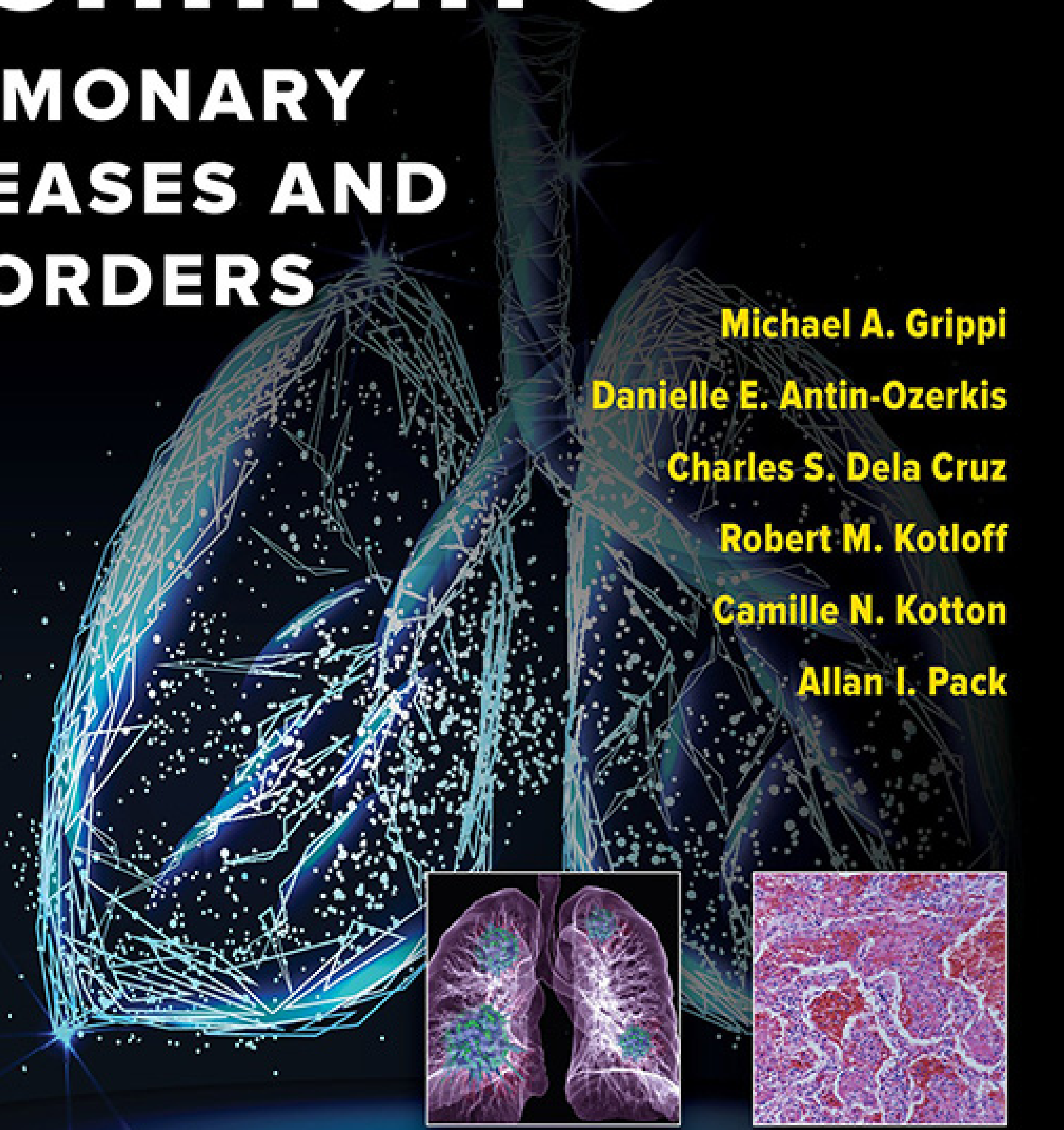
SIXTH EDITION

Fishman's

PULMONARY DISEASES AND DISORDERS



Michael A. Grippi
Danielle E. Antin-Ozerkis
Charles S. Dela Cruz
Robert M. Kotloff
Camille N. Kotton
Allan I. Pack

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Fishman's Pulmonary Diseases and Disorders

Volume 1

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Fishman's Pulmonary Diseases and Disorders

Sixth Edition

Volume 1

EDITOR-IN-CHIEF

Michael A. Grippi, MD

Pulmonary, Allergy, and Critical Care Division
Department of Medicine
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania

EDITORS

Danielle E. Antin-Ozerkis, MD

Medical Director, Yale Center for Interstitial Lung Diseases
Associate Professor of Medicine
Section of Pulmonary, Critical Care and Sleep Medicine
Yale School of Medicine
New Haven, Connecticut

Charles S. Dela Cruz, MD, PhD

Associate Professor of Medicine
Section of Pulmonary, Critical Care and Sleep Medicine
Associate Professor of Microbial Pathogenesis
Director, Center of Pulmonary Infection Research and Treatment
Yale School of Medicine
New Haven, Connecticut

Robert M. Kotloff, MD

Craig and Elaine Dobbin/Nancy P. Blumenthal
Professor of Advanced Lung Disease
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania

Camille Nelson Kotton, MD

Associate Professor, Harvard Medical School
Clinical Director, Transplant and Immunocompromised Host
Infectious Diseases
Infectious Diseases Division, Massachusetts General Hospital
Boston, Massachusetts

Allan I. Pack, MBChB, PhD

John Miclot Professor of Medicine
Division of Sleep Medicine
Department of Medicine
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania

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DEDICATION

This book is dedicated to the many clinicians worldwide who have devoted themselves to caring for those affected by SARS-CoV-19 and to the scientists who developed vaccines and therapeutic modalities directed against the virus.

MAG: To my wife, Barbara, and to our daughters, Kristen and Amy, for their steadfast support over the years, and to their families—Emily, Ali, Sawyer, Sophie, Levi, and Kieran.

DAO: To my husband, Eric, and our daughters, Orly and Daya. If you are going to spend a pandemic with anyone, you might as well laugh a lot. And to my patients, from whom I learn every day.

CDC: I would like to thank my family, friends, and all the mentors in pulmonary and critical care medicine who helped support me throughout my career. I would also like to thank my patients, from whom I have learned so much and who have been the motivation for my current work.

RMK: To my wife, Debbie, and my sons, Eric, Brian, and Ethan, for their unwavering love and support. And to the memory of my parents, Jean and Leon Kotloff, for instilling in me the principles by which I live my life and practice my profession.

CNK: Thanks to my husband, Darrell Kotton, and to our wonderful sons, David and Benjamin, for their thoughtfulness and support, especially as we navigated our family through the peaks of the COVID-19 pandemic. And thanks to my patients over the years, who have taught me so much about medicine, but also about resilience, optimism, and hope.

AIP: To my very supportive wife, Frances; my long-collaborating Administrative Assistant, Daniel Barrett; my four children, Alison, Angela, Andrew, and Allan Junior; and our 11 grandchildren.

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CONTRIBUTORS

Gerald F. Abbott, MD, FACR
Department of Radiology
Division of Thoracic Imaging & Intervention
Massachusetts General Hospital
Associate Professor, Harvard Medical School
Boston, Massachusetts
Chapter 117

Abass Alavi, MD, PhD (hon.), DSci (hon.)
Professor of Radiology and Neurology
Perelman School of Medicine at the University of Pennsylvania
Pennsylvania University Hospital
Philadelphia, Pennsylvania
Chapter 30

Timothy E. Albertson, MD, MPH, PhD
Chair, Internal Medicine, Distinguished Professor of Medicine
Pharmacology & Toxicology, Anesthesia & Emergency Medicine
Department of Internal Medicine
Division of Pulmonary, Critical Care and Sleep Medicine
University of California
Department of Emergency Medicine, University of California, Davis, Sacramento
Veterans Administration Northern California Health Care System, Department of Medicine
Mather, California
Chapter 66

John S. Albin, MD, PhD
Instructor, Harvard Medical School
Assistant in Medicine, Division of Infectious Diseases
Massachusetts General Hospital
Boston, Massachusetts
Chapter 131

Micheala A. Aldred, PhD
Professor of Medicine
Catherine and Lowe Berger and Pauline L. Ford Chair of Pulmonary Medicine
Department of Medicine
Division of Pulmonary, Critical Care, Sleep & Occupational Medicine
Indiana University School of Medicine
Indianapolis, Indiana
Chapter 7

Timothy Craig Allen, MD, JD, FCAP
Professor and Chair
Department of Pathology
The University of Mississippi Medical Center
Jackson, Mississippi
Chapter 67

Konstantinos-Dionysios Alysandratos, MD, PhD
Assistant Professor of Medicine
The Pulmonary Center and Department of Medicine
Boston University School of Medicine
Attending Physician
Department of Medicine
Boston Medical Center
Boston, Massachusetts
Chapter 8

Brian J. Anderson, MD, MSCE
Assistant Professor of Medicine
Department of Medicine
Division of Pulmonary, Allergy & Critical Care Medicine
Hospital of the University of Pennsylvania
Philadelphia, Pennsylvania
Chapter 146

Danielle E. Antin-Ozerkis, MD
Medical Director, Yale Center for Interstitial Lung Diseases
Associate Professor of Medicine
Section of Pulmonary, Critical Care and Sleep Medicine
Yale School of Medicine
New Haven, Connecticut
Chapter 52

Reuben J. Arasaratnam, MD, MPH
Staff Physician, Section of Infectious Diseases
VA North Texas Health Care System
Assistant Professor of Medicine
Division of Infectious Diseases and Geographic Medicine
UT Southwestern Medical Center
Dallas, Texas
Chapter 137

Silvia Asioli, MD
Team Leader of Haematopathology and Consultant
Department of Anatomic Pathology
Ospedale GB Morgagni
Forlì, Italy
Chapter 119

Olga I. Astapova, MD, PhD
Assistant Professor, Department of Medicine
Division of Endocrinology
University of Rochester Medical Center
University of Rochester School of Medicine and Dentistry
Rochester, New York
Chapter 62

Joshua H. Atkins, MD, PhD, FASA
Associate Professor of Anesthesiology & Critical Care
Department of Anesthesiology and Critical Care
Perelman School of Medicine at the University of Pennsylvania
Attending Physician, Co-Chair Airway Safety Committee
Director of Anesthesia for Head and Neck Surgery
Medical Director In-situ Simulation
Department of Anesthesiology and Critical Care
Hospital of the University of Pennsylvania
Philadelphia, Pennsylvania
Chapter 145

Marwan M. Azar, MD
Assistant Professor of Medicine/Infectious Diseases
Section of Infectious Diseases
Department of Internal Medicine
Yale University School of Medicine
Department of Laboratory Medicine
Yale University School of Medicine
New Haven, Connecticut
Chapter 134

Tara M. Babu, MD, MSCI
Acting Assistant Professor
Department of Medicine
Division of Allergy & Infectious Diseases
University of Washington
Seattle, Washington State
Chapter 137

Nathan C. Bahr, MD
Associate Professor
Department of Internal Medicine
Division of Infectious Diseases
University of Kansas Medical Center
Kansas City, Kansas
Chapter 133

AL GRAWANY

Stephen R. Baldassarri, MD, MHS
Department of Internal Medicine
Section of Pulmonary, Critical Care, and Sleep Medicine
Yale School of Medicine
New Haven, Connecticut
Chapter 41

Debasree Banerjee, MD, MS
Assistant Professor, Department of Medicine, Brown University
Director, Critical Care Consult, Rhode Island Hospital
Providence, Rhode Island
Chapter 96

Tami J. Bang, MD
Assistant Professor
Department of Radiology, Division of Cardiothoracic Imaging
University of Colorado—Anschutz Medical Campus
Aurora, Colorado
Chapter 61

Eduardo J. Mortani Barbosa Jr., MD
Assistant Professor of Radiology
Director of Thoracic CT modality
Department of Radiology
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania
Chapter 28

Peter J. Barnes, DM, DSc, FRCP, FCCP, FMedSci, FRS
Professor of Thoracic Medicine
National Heart & Lung Institute, Imperial College London
London, United Kingdom
Chapter 45

Sonja D. Bartolome, MD
Professor, Department of Internal Medicine, University of Texas Southwestern Medical Center
Dallas, Texas
Chapter 97

Cynthia M. Beall, PhD
Professor, Anthropology
Case Western Reserve University
Cleveland, Ohio
Chapter 91

Matthew C. Bell, MD
Assistant Professor of Medicine and Pediatrics
Department of Pediatrics
Division of Allergy & Immunology
University of Arkansas for Medical Sciences
Arkansas Children's Hospital
Little Rock, Arkansas
Chapter 43

Seth A. Bellister, MD
Department of Trauma and Acute Care Surgery
Christus Mother Frances Hospital
Tyler, Texas
Chapter 104

Ghada Bourjeily, MD
Professor of Medicine
Warren Alpert Medical School of Brown University
Associate Chief for Academic Advancement and Research in Women's Services
Women's Medicine Collaborative of Lifespan
Department of Medicine
The Miriam Hospital
Providence, Rhode Island
Chapter 96

James P. Bridges, PhD
Associate Professor
Department of Medicine
National Jewish Health
Denver, Colorado
Chapter 5

Carl D. Britto, MBBS, DPhil
Clinical Fellow in Pediatrics, Harvard Medical School
Resident in Pediatrics, Department of Pediatrics
Boston Children's Hospital
Boston, Massachusetts
Chapter 124

Clemente J. Britto, MD
Assistant Professor of Medicine
Associate Director, Yale Adult Cystic Fibrosis Program
Department of Internal Medicine
Division of Pulmonary, Critical Care and Sleep Medicine
Yale University School of Medicine
New Haven, Connecticut
Chapter 19

Nathan E. Brummel, MD, MSCI, FCCM
Associate Professor of Medicine
Department of Internal Medicine
Division of Pulmonary, Critical Care, and Sleep Medicine
The Ohio State University Columbus, Ohio
Chapter 151

A. Cole Burks, MD
Assistant Professor of Medicine
Division of Pulmonary and Critical Care Medicine
University of North Carolina at Chapel Hill
Interventional Pulmonology, University of North Carolina Medical Center
Chapel Hill, North Carolina
Chapter 112

William W. Busse, MD
Emeritus Professor of Medicine
Department of Medicine
Division of Allergy, Pulmonary and Critical Care Medicine
University of Wisconsin School of Medicine and Public Health
Madison, Wisconsin
Chapter 43

Marcus W. Butler, MD, FRCPI
Associate Professor
University College Dublin School of Medicine
Consultant Respiratory Physician
St. Vincent's University Hospital
Dublin, Ireland
Chapter 24

Hilary C. Cain, MD, MS
Associate Professor of Medicine
Section of Pulmonary, Critical Care and Sleep Medicine
Yale School of Medicine
New Haven, Connecticut
Section Chief, Pulmonary Medicine
VA Connecticut Healthcare System
West Haven, Connecticut
Chapter 65

Jeffrey P. Callen, MD, FACP, MAAD, MACR
Professor of Medicine (Dermatology)
Chief, Division of Dermatology
University of Louisville School of Medicine
Louisville, Kentucky
Chapter 27

Edward J. Campbell, MD
Heredilab, Inc.
Salt Lake City, Utah
Chapter 18

Wellington V. Cardoso, MD, PhD
Professor of Medicine and Genetics & Development
Columbia Center for Human Development
Department of Medicine
Columbia University Medical Center
New York, New York
Chapter 4

Brenna Carey, MS, PhD
Assistant Professor of Medicine
Department of Pediatrics, University of Cincinnati
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio
Chapter 70

Laurie L. Carr, MD
Associate Professor of Medicine
Division of Oncology
National Jewish Health and University of Colorado
Denver, Colorado
Chapter 114

Rodrigo Cartin-Ceba, MD, MSc
Professor of Medicine, Mayo Clinic College of Medicine and Science
Consultant, Department of Medicine
Division of Pulmonary Medicine, Mayo Clinic
Phoenix, Arizona
Chapter 74

David M. Center, MD
Gordon and Ruth Snider Professor of Pulmonary Medicine
Associate Provost for Translational Research
Professor of Medicine
Department of Medicine
Boston University
Chief, Pulmonary, Allergy, Sleep and Critical Care Medicine
Boston Medical Center
Boston, Massachusetts
Chapter 20

Georgios Chamilos, MD
Professor of Medicine
Department of Internal Medicine
School of Medicine, Stavrakia, Voutes
University of Crete Heraklion
Crete, Greece
Chapter 132

Giuliana Cerro Chiang, MD
Fellow in Pulmonary & Critical Care Medicine
Department of Medicine
Cedars-Sinai Medical Center
Los Angeles, California
Chapter 54

Edward S. Chen, MD
Assistant Professor
Division of Pulmonary and Critical Care Medicine
Johns Hopkins University School of Medicine
Attending Physician, Department of Medicine
Division of Pulmonary and Critical Care Medicine
Johns Hopkins Hospital
Baltimore, Maryland
Chapter 53

James A. Chenoweth, MD, MAS
Assistant Professor, Emergency Medicine
Department of Emergency Medicine
University of California, Davis
Sacramento, California
Veterans Administration Northern
Department of Medicine California Health Care System
Mather, California
Chapter 66

Asha N. Chesnutt, MD
The Oregon Clinic
Pulmonary, Critical Care & Sleep Medicine
Portland, Oregon
Chapter 140

Humberto K. Choi, MD
Assistant Professor of Medicine of Lerner College of Medicine of Case Western Reserve University
Respiratory Institute, Cleveland Clinic
Cleveland, Ohio
Chapter 109

David C. Christiani, MD, MPH, MS
Elkan Blout Professor of Environmental Genetics
Department of Environmental Health
Harvard T.H. Chan School of Public Health
Professor of Medicine
Harvard Medical School
Physician, Pulmonary and Critical Care Division
Department of Medicine
Massachusetts General Hospital
Boston, Massachusetts
Chapter 88

Jason D. Christie, MD, MSCE
Professor of Medicine and Epidemiology
Division of Pulmonary, Allergy, and Critical Care
Department of Medicine
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania
Chapter 141

Geoffrey L. Chupp, MD
Professor of Medicine
Yale School of Medicine
Director, Yale Center for Asthma and Airway Disease
Director, Pulmonary Function Laboratory, Yale New Haven Hospital
New Haven, Connecticut
Chapters 43 and 46

Andrew Churg, MD, PhD
Professor of Pathology, University of British Columbia Pathologist
Vancouver General Hospital
Vancouver, British Columbia, Canada
Chapter 37

Brian J. Clark, MD
Assistant Professor, Section of Pulmonary, Critical Care and Sleep Medicine
Yale School of Medicine
New Haven, Connecticut
VA Connecticut Healthcare System
West Haven, Connecticut
Chapter 71

Lauren Cohn, MD
Associate Professor
Department of Medicine, Section of Pulmonary, Critical Care and Sleep Medicine
Yale School of Medicine, New Haven, Connecticut
VA Connecticut Healthcare System
West Haven, Connecticut
Chapters 23 and 71

Gregory P. Cosgrove, MD
Associate Professor
Department of Medicine
Division of Pulmonary Sciences and Critical Care Medicine
University of Colorado—Anschutz Medical Campus
Denver, Colorado
Chapter 58

Gerard Joseph Criner, MD
Chair and Professor of Thoracic Medicine and Surgery
Department of Thoracic Medicine and Surgery
Lewis Katz School of Medicine at Temple University
Philadelphia, Pennsylvania
Chapter 84

Megan Rose Curtis, MD, MS
Research Fellow, Harvard Medical School
Associate Physician, Division of Infectious Diseases,
Brigham and Women's Hospital
Boston, Massachusetts
Chapter 122

AL GRAWANY

James B. Cutrell, MD
Associate Professor of Internal Medicine
Program Director, Infectious Diseases Fellowship Program
Director, Antimicrobial Stewardship, Clements University Hospital and UTSW Health Systems
Department of Internal Medicine
Division of Infectious Diseases and Geographic Medicine
University of Texas Southwestern Medical Center
Dallas, Texas
Chapter 136

Erin DeBiasi, MD
Assistant Professor of Medicine
Department of Internal Medicine
Section of Pulmonary,
Critical Care, and Sleep Medicine
Yale School of Medicine
New Haven, Connecticut
Chapters 47 and 64

Malcolm M. DeCamp, MD, FACS
Professor and Chair, Division of Cardiothoracic Surgery
University of Wisconsin Hospitals and Clinics
Madison, Wisconsin
Chapter 81

Roy H. Decker, MD, PhD
Professor, Department of Therapeutic Radiology
Yale School of Medicine
Radiation Oncologist
Yale New Haven Hospital
New Haven, Connecticut
Chapter 57

Marc Decramer, MD, PhD
Emeritus Professor of Medicine
University of Leuven
Laboratory of Respiratory Diseases and Thoracic Surgery (BREATHE)
Department of Chronic Diseases and Metabolism (CHROMETA), KU-Leuven
Leuven, Belgium
Chapter 3

Charles S. Dela Cruz, MD, PhD
Associate Professor of Medicine
Section of Pulmonary, Critical Care and Sleep Medicine
Associate Professor of Microbial Pathogenesis
Director, Center of Pulmonary Infection Research and Treatment
Yale School of Medicine
New Haven, Connecticut
Chapters 19 and 108

Horace M. DeLisser, MD
Associate Professor of Medicine
Department of Medicine
Associate Dean for Diversity and Inclusion
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania
Chapters 105 and 152

Bradley M. Dennis, MD
Associate Professor of Surgery
Division of Acute Care Surgery,
Vanderbilt University School of Medicine
Trauma Medical Director, Vanderbilt University Medical Center
Associate Chief of Staff, Vanderbilt University Hospital
Nashville, Tennessee
Chapter 104

Jessy Deshane, PhD
Associate Professor
Department of Medicine
Division of Pulmonary Allergy and Critical Care Medicine
University of Alabama at Birmingham
Birmingham, Alabama
Chapter 25

Himanshu Deshwal, MD
Fellow in Pulmonary Disease and Critical Care Medicine
Division of Pulmonary, Critical Care, and Sleep Medicine
New York University Grossman School of Medicine
New York, New York
Chapter 105

Joshua M. Diamond, MD, MSCE
Associate Professor of Medicine
Department of Medicine
Division of Pulmonary, Allergy and Critical Care Medicine
University of Pennsylvania
Philadelphia, Pennsylvania
Chapter 121

David M. DiBardino, MD
Assistant Professor of Clinical Medicine
Section of Interventional Pulmonology
Division of Pulmonary, Allergy and Critical Care
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania
Chapter 33

Burton F. Dickey, MD
Clifton Howe Distinguished Professor of Pulmonary Medicine
University of Texas MD Anderson Cancer Center
Houston, Texas
Chapter 6

John D. Dickinson, MD, PhD
Assistant Professor of Medicine
Department of Internal Medicine
Division of Pulmonary, Critical Care, and Sleep Medicine
University of Nebraska Medical Center
Omaha, Nebraska
Chapter 6

Jennifer J. Dorsch, MD
Assistant Professor of Clinical Medicine
Perelman School of Medicine at the University of Pennsylvania
Division of Sleep Medicine,
The Hospital of the University of Pennsylvania
Associate Director, Sleep Non-Invasive Ventilation Program
Philadelphia, Pennsylvania
Chapter 142

Jonathan E. Dowell, MD
Professor of Internal Medicine
Division of Hematology/Oncology
UT Southwestern
Dallas, Texas
Chapter 116

Mark T. Dransfield, MD
Professor of Medicine, Endowed Chair in Pulmonary Disease
Division of Pulmonary, Allergy, and Critical Care Medicine
Lung Health Center
University of Alabama at Birmingham
Birmingham VA Medical Center
Birmingham, Alabama
Chapter 38

Benjamin J. Drapkin, MD, PhD
Assistant Professor of Internal Medicine
Division of Hematology/Oncology
UT Southwestern
Dallas, Texas
Chapter 116

M. Bradley Drummond, MD, MHS
Associate Professor of Medicine
Division of Pulmonary Diseases and Critical Care Medicine
University of North Carolina at Chapel Hill
Attending Physician
University of North Carolina at Chapel Hill Medical Center
Chapel Hill, North Carolina
Chapter 40

Hilary M. DuBrock, MD
Assistant Professor, Department of Internal Medicine
Mayo Clinic
Rochester, Minnesota
Chapter 97

Daniel G. Dunlap, MD
Assistant Professor of Medicine
Division of Pulmonary, Allergy, and Critical Care Medicine
University of Pittsburgh
Pittsburgh, Pennsylvania
Chapter 34

Ghassan El-Haddad, MD
Section Head, Radionuclide Therapy Program
Associate Member, Interventional Radiology
Associate Member, Cancer Physiology
H. Lee Moffitt Cancer Center and Research Institute
Associate Professor of Radiology and Oncologic Sciences
University of South Florida
Tampa, Florida
Chapter 30

Davide Elia, MD
Unità di Pneumologia e Terapia Semi-Intensiva Respiratoria
Servizio di Fisiopatologia Respiratoria ed Emodinamica Polmonare
Ospedale San Giuseppe, MultiMedica IRCCS
Milano, Italy
Chapter 59

Richard I. Enelow, MD
Professor of Medicine, and of Microbiology and Immunology
Geisel School of Medicine at Dartmouth
Dartmouth-Hitchcock Medical Center
Lebanon, New Hampshire
Chapter 56

Kyle B. Enfield, MD, MS
Associate Professor of Medicine
Section Chief, Critical Care
Department of Medicine
Division of Pulmonary and Critical Care Medicine
University of Virginia School of Medicine
Associate Chief Medical Officer for Critical Care UVA Health
Charlottesville, Virginia
Chapter 127

Perenlei Enkhbaatar, MD, PhD, FAHA
Professor, Department of Anesthesiology
Director, Translational Intensive Care Unit
Charles Robert Allen Professor in Anesthesiology
The University of Texas Medical Branch
Galveston, Texas
Chapter 93

Gary R. Epler, MD
Clinical Associate Professor
Harvard Medical School
Pulmonary and Critical Care Medicine
Brigham and Women's Hospital
Boston, Massachusetts
Chapter 49

Rodolfo A. Estrada, MD
Assistant Professor of Medicine
Division of Pulmonary and Critical Care
UT Health San Antonio/University of Texas Health Science
Center San Antonio
San Antonio, Texas
Chapter 79

Peter F. Fedullo, MD
Clinical Professor of Medicine
University of California San Diego Health
Division of Pulmonary, Critical Care, and Sleep Medicine
San Diego, California
Chapter 73

David Feller-Kopman, MD
Professor of Medicine, Department of Medicine, Geisel School of Medicine
Chief, Pulmonary and Critical Care Medicine,
Dartmouth Hitchcock Medical Center
Lebanon, New Hampshire
Chapter 76

Thomas W. Ferkol, MD
Alexis F. Hartmann M.D. Professor of Pediatrics
Department of Pediatrics
Professor, Department of Cell Biology and Physiology
Washington University School of Medicine
St. Louis Children's Hospital
St. Louis, Missouri
Chapter 6

Timothy M. Fernandes, MD, MPH
Associate Clinical Professor of Medicine
University of California, San Diego School of Medicine
Division of Pulmonary, Critical Care and Sleep Medicine
La Jolla, California
Chapter 73

Barry G. Fields, MD, MSEd
Associate Professor of Medicine
Division of Pulmonary, Allergy, Critical Care, and Sleep Medicine
Emory University School of Medicine
Sleep Physician, Sleep Medicine Center, Atlanta VA Health Care System
Atlanta, Georgia
Chapter 98

Michael C. Fishbein, MD
Distinguished Professor of Pathology and Medicine
Department of Pathology and Laboratory Medicine
David Geffen School of Medicine at UCLA
Ronald Reagan Medical Center
Los Angeles, California
Chapter 68

Christopher Gange, MD
Assistant Professor, Radiology and Biomedical Imaging
Yale University School of Medicine
Thoracic Radiologist
Yale New Haven Hospital
New Haven, Connecticut
Chapter 63

David E. Gerber, MD
David Bruton, Jr. Professorship in Clinical Cancer Research
Departments of Internal Medicine and Population and Data Sciences
Division of Hematology/Oncology
UT Southwestern
Dallas, Texas
Chapter 116

Ghislaine Gayan-Ramirez, PhD
Professor at University of Leuven
Laboratory of Respiratory Diseases and Thoracic Surgery (BREATHE)
Department of Chronic Diseases and Metabolism (CHROMETA),
KU-Leuven
Leuven, Belgium
Chapter 3

Subha Ghosh, MD, MBA
Assistant Professor, Lerner College of Medicine of Case
Western Reserve University
Staff Physician
Imaging Institute, Section of Thoracic Imaging
Cleveland Clinic Foundation
Cleveland, Ohio
Chapter 105

Timothy D. Girard, MD, MSCI, ATSF
Associate Professor of Critical Care Medicine
Department of Critical Care Medicine
University of Pittsburgh
Pittsburgh, Pennsylvania
Chapter 151

AL GRAWANY

Mark T. Gladwin, MD
Vice President for Medical Affairs, UM Baltimore
John Z. and Akiko K. Bowers Distinguished Professor and Dean, University of Maryland School of Medicine
Baltimore, Maryland
Chapter 95

Stanley Goldfarb, MD
Former Associate Dean for Curriculum
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania
Chapter 17

Michael A. Grippi, MD
Pulmonary, Allergy, and Critical Care Division
Department of Medicine
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania
Chapters 1, 10, 27, 31, 102, and 139

Marco Guazzi, MD, PhD
Professor of Cardiology,
University of Milano School of Medicine
Head of Cardiology Division
San Paolo University Hospital
Milano, Italy
Chapter 32

Mridu Gulati, MD, MPH
Associate Professor
Departments of Internal Medicine
Section of Pulmonary, Critical Care and Sleep Medicine
Yale School of Medicine
New Haven, Connecticut
Chapter 55

Akash Gupta, MD
Instructor, Harvard Medical School
Assistant in Medicine, Department of Medicine
Division of Infectious Diseases
Massachusetts General Hospital
Boston, Massachusetts
Chapter 130

Nishant Gupta, MD, MS
Associate Professor
Division of Pulmonary, Critical Care and Sleep Medicine
University of Cincinnati
Cincinnati, Ohio
Chapter 61

Indira Gurubhagavatula, MD, MPH, FAASM
Associate Professor of Medicine, Division of Sleep Medicine
Perelman School of Medicine at the University of Pennsylvania
Corporal Michael Crescenz VA Medical Center
Philadelphia, Pennsylvania
Chapter 100

Jacob Gutsche, MD
Associate Professor
Department of Anesthesiology and Critical Care
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania
Chapter 149

Duc M. Ha, MD, MAS
Assistant Professor of Medicine
Department of Medicine
University of Colorado Anschutz Medical Campus
Staff Physician, Section of Pulmonary and Critical Care
Rocky Mountain Regional Veterans Affairs Medical Center
Aurora, Colorado
Chapter 42

Andrew R. Haas, MD, PhD
Associate Professor of Medicine
Director, Section of Interventional Pulmonary and Thoracic Oncology
Pulmonary, Allergy, and Critical Care Division
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania
Chapter 34

Ramsey R. Hachem, MD
Professor of Medicine
Division of Pulmonary and Critical Care Medicine
Department of Medicine
Washington University in St. Louis
Medical Director of Lung Transplantation
Barnes-Jewish Hospital
St. Louis, Missouri
Chapter 106

Chadi A. Hage, MD, ATSF
Professor of Medicine
University of Pittsburgh
Pulmonary, Allergy, and Critical Care Medicine
McGowan Institute for Regenerative Medicine
Medical Director, Lung Transplant
University of Pittsburgh Medical Center
Pittsburgh, Pennsylvania
Chapter 133

Kelly M. Hager, MD, MPH
Fellow, Yale Occupational and Environmental Medicine
Department of Medicine, Yale University School of Medicine
New Haven, Connecticut
Chapter 55

Stephen R. Hammes, MD, PhD
Professor and Chief, Division of Endocrinology
Department of Medicine
University of Rochester School of Medicine and Dentistry
Rochester, New York
Chapter 62

Sergio Harari, MD
Professor of Internal Medicine
University of Milan
Unità di Pneumologia e Terapia Semi-Intensiva Respiratoria
Servizio di Fisiopatologia Respiratoria ed Emodinamica Polmonare
Ospedale San Giuseppe, MultiMedica IRCCS
Department of Medical Sciences, San Giuseppe Hospital
MultiMedica IRCCS
Department of Clinical Sciences and Community Health
Università degli Studi di Milano
Milan, Italy
Chapter 59

Howard M. Heller, MD, MPH
Assistant Professor of Medicine, Harvard Medical School
Infectious Disease Division, Massachusetts General Hospital
Boston, Massachusetts
Chapter 138

Michael J. Herriges, PhD
Post-doctoral Fellow
Center for Regenerative Medicine (CReM) of Boston
University and Boston Medical Center
Boston, Massachusetts
Chapter 8

Søren Hess, MD
Chief Physician, Head of Section (Nuclear Medicine & PET)
Department of Radiology and Nuclear Medicine
Hospital South West Jutland
Esbjerg, Denmark
Clinical Associate Professor, Head of Research (Imaging)
Research Unit for Radiology and Nuclear Medicine
Department of Regional Health Research, Faculty of Health Sciences
University of Southern Denmark
Odense, Denmark
Chair, Danish Society of Clinical Physiology and Nuclear Medicine
Aarup, Denmark
Chapter 30

Janet Hilbert, MD
Associate Professor of Clinical Medicine
Medical Director of Yale Noninvasive Ventilation Program
Division of Pulmonary and Critical Care Medicine
Yale University
New Haven, Connecticut
Chapter 148

Robert J. Homer, MD, PhD
Professor of Pathology
Yale University School of Medicine
New Haven, Connecticut
Chapter 63

Gary B. Huffnagle
Department of Internal Medicine
Department of Molecular Cell and Developmental Biology
Division of Pulmonary and Critical Care Medicine
University of Michigan Medical Center
Ann Arbor, Michigan
Chapter 120

Rocio M. Hurtado, MD
Assistant Professor of Medicine, Harvard Medical School
Director, Mycobacterial Center, Division of Infectious Diseases
Massachusetts General Hospital
Boston, Massachusetts
Chapter 131

Louise C. Ivers, MD, MPH
Professor of Medicine, Professor of Global Health and Social Medicine, Harvard Medical School
Director, Center for Global Health, Massachusetts General Hospital
Boston, Massachusetts
Chapter 135

Karen R. Jacobson, MD, MPH
Associate Professor of Medicine
Section of Infectious Diseases
Boston University School of Medicine and Boston Medical Center
Boston, Massachusetts
Chapter 130

Frank J. Jacono, MD
Virginia Hubbell Chair in Pulmonary and Critical Care and Tenured Professor of Medicine
Case Western Reserve University School of Medicine
Division Chief, Pulmonary, Critical Care & Sleep Medicine
University Hospitals Cleveland Medical Center
Cleveland VA Medical Center, VA Northeast Ohio Health System
Cleveland, Ohio
Chapter 11

Tulip Ajit Jhaveri, MBBS
Assistant Professor of Medicine, University of Mississippi School of Medicine
Attending Physician, Division of Infectious Diseases, University of Mississippi Medical Center
Jackson, Mississippi
Chapter 122

David H. Johnson, MD
R. Ellwood Jones, M.D. Distinguished Professorship in Clinical Education
Department of Internal Medicine
Division of Hematology/Oncology
UT Southwestern
Dallas, Texas
Chapter 116

Austin J. Jolly
MD/PhD Student, Department of Medicine
University of Colorado Anschutz Medical Campus
Aurora, Colorado
Chapter 90

Christopher M. Kapp, MD
Clinical Instructor of Medicine, Department of Medicine,
University of Illinois at Chicago College of Medicine
Interventional Pulmonologist and Pulmonary Critical Care Medicine Physician, Department of Medicine, University of Illinois Hospital
Chicago, Illinois
Chapter 76

Joel D. Kaufman, MD, MPH
Professor
Departments of Environmental & Occupational Health Sciences
University of Washington
Medicine, and Epidemiology
Seattle, Washington
Chapter 89

Joshua B. Kayser, MD, MPH, MBE, FCCM
Professor of Clinical Medicine and Medical Ethics & Health Policy
Department of Medicine
Department of Medical Ethics & Health Policy
Perelman School of Medicine University of Pennsylvania
Philadelphia, Pennsylvania
Chapter 152

Michael P. Keane, MD, FRCP, FRCPI
Professor of Medicine
Dean and Head of School of Medicine
University College Dublin
Consultant Respiratory Physician
St. Vincent's University Hospital
Dublin, Ireland
Chapter 24

Andrea Kelly, MD MSCE
Attending Physician, Division of Endocrinology and Diabetes
Children's Hospital of Philadelphia
Professor of Pediatrics
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania
Chapter 48

Jeffrey A. Kern, MD
Professor of Medicine
National Jewish Health
University of Colorado, Denver
Chief, Oncology Division
Vice-Chair, Department of Medicine
National Jewish Health
Denver, Colorado
Chapter 107

Nick H. Kim, MD
Professor of Medicine
Section Chief, Pulmonary Vascular Medicine
Medical Director, Pulmonary Thromboendarterectomy Program
Pulmonary, Critical Care, and Sleep Medicine
University of California San Diego
La Jolla, California
Chapter 72

Corrine R. Kliment, MD, PhD
Assistant Professor
Department of Medicine
Division of Pulmonary, Allergy and Critical Care Medicine
University of Pittsburgh
University of Pittsburgh Medical Center
Pittsburgh, Pennsylvania
Chapter 18

Robert A. Klocke, MD
Emeritus Professor of Chairperson
Department of Medicine
Jacobs School of Medicine and Biomedical Sciences
University at Buffalo
Buffalo, New York
Chapters 15 and 16

Marin H. Kollef, MD
Director, Critical Care Research
Director, Respiratory Care Services Barnes-Jewish Hospital
Virginia E. and Sam J. Golman Chair in Respiratory Intensive Care Medicine
Professor of Medicine
Division of Pulmonary and Critical Care Medicine
Washington University School of Medicine
St. Louis, Missouri
Chapter 129

AL GRAWANY

Dimitrios P. Kontoyiannis, MD, ScD, FACP, FIDSA
Frances King Black Endowed Professor, Infectious Diseases
Deputy Head
Division of Internal Medicine
The University of Texas MD Anderson Cancer Center
Adj Professor Baylor College of Medicine
Adj Professor University of Houston
Houston, Texas
Chapter 132

Robert M. Kotloff, MD
Craig and Elaine Dobbin/Nancy P. Blumenthal
Professor of Advanced Lung Disease
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania
Chapters 94 and 103

Darrell N. Kotton, MD
David C. Seldin Professor of Medicine
The Pulmonary Center and Department of Medicine
Boston University School of Medicine
Director, Center for Regenerative Medicine (CReM) of Boston
University and Boston Medical Center
Attending Physician
Department of Medicine
Boston Medical Center
Boston, Massachusetts
Chapters 8 and 39

Mary Elizabeth Kreider, MD, MSCE
Professor of Clinical Medicine
Vice Chief for Education and Faculty Development
Fellowship Program Director
Director, ILD Program
Division of Pulmonary and Critical Care Medicine
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania
Chapter 86

Arnold S. Kristof, MDCM, FRCPC
Associate Professor of Medicine
Meakins-Christie Laboratories and Translational Research in Respiratory
Diseases Program
Research Institute of the McGill University Health Centre
Departments of Critical Care and Medicine, McGill University
Montreal, Quebec
Chapter 60

Meir Kryger, MD, FRCPC
Professor, Pulmonary, Critical Care, and Sleep Medicine
Yale School of Medicine
New Haven, Connecticut
Chapters 47 and 101

Ricardo M. La Hoz, MD
Director, Solid Organ Transplant Infectious Diseases
Associate Professor of Internal Medicine
Department of Internal Medicine
Division of Infectious Diseases and Geographic Medicine
University of Texas Southwestern Medical Center
Dallas, Texas
Chapter 136

James H. Laird, MD
Resident Physician
Department of Therapeutic Radiology
Yale School of Medicine
Resident Physician
Yale New Haven Hospital
New Haven, Connecticut
Chapter 57

Daniel Langer, PT, PhD
Professor of Rehabilitation Sciences and Physiotherapy
Department of Rehabilitation Sciences
Research Group for Cardiovascular and Respiratory Rehabilitation
KU-Leuven
Respiratory Rehabilitation and Respiratory Division
University Hospital Leuven
Leuven, Belgium
Chapter 3

Kathleen A. Lee-Sarwar, MD, MS
Instructor, Harvard Medical School
Physician, Department of Medicine, Brigham and Women's Hospital
Boston, Massachusetts
Chapter 44

Andrew T. Levinson, MD, MPH
Associate Professor of Medicine, Clinician Educator
Program Director, Critical Care Medicine Fellowship
Warren Alpert Medical School of Brown University
Department of Medicine
Miriam Hospital and Rhode Island Hospital
Providence, Rhode Island
Chapter 96

Erik E. Lewis, MD
Fellow, Division of Cardiothoracic Surgery, University of Wisconsin
Hospitals and Clinics
Madison, Wisconsin
Chapter 81

Howard Y. Li, MD
Associate Professor
Department of Internal Medicine
Division of Pulmonary Disease and Critical Care Medicine
Virginia Commonwealth University
Director, Lung Cancer Screening
Medical Service
Section of Pulmonary and Critical Care Medicine
Hunter Holmes McGuire Veterans Affairs Medical Center
Richmond, Virginia
Chapter 107

Shu-Yi Liao, MD, MPH, MS, ScD
Assistant Professor of Medicine
Department of Medicine
National Jewish Health
Assistant Professor of Medicine
Department of Medicine
University of Colorado Anschutz Medical Campus
Physician
Department of Medicine
Division of Environmental & Occupational Health Sciences
National Jewish Health
Denver, Colorado
Chapter 88

Augusto A. Litonjua, MD, MPH
Professor of Pediatrics and Medicine
Department of Pediatrics and Department of Medicine
University of Rochester School of Medicine and Dentistry
Division Chief of Pediatric Pulmonary Medicine
Physician, Department of Pediatrics, Golisano Children's Hospital
Department of Medicine, Strong Memorial Hospital, University of
Rochester Medical Center
Rochester, New York
Chapter 44

Leslie A. Litzky, MD
Professor, Pathology and Laboratory Medicine
Perelman School of Medicine at the University of Pennsylvania
Chief of Surgical and Medical Pathology
Subspecialty Director, Thoracic Pathology
Hospital of the University of Pennsylvania
Philadelphia, Pennsylvania
Chapters 78 and 111

Jining Lu, PhD
Program Director
Division of Lung Diseases
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland
Chapter 4

Natalie S. Lui, MD
Assistant Professor of Cardiothoracic Surgery
Stanford University School of Medicine/Stanford Cancer Institute
Stanford, California
Chapter 82

Joseph P. Lynch, III, MD, FCCP, FERS
Holt and Jo Hickman Endowed Chair of Advanced Lung Disease and Lung Transplantation
Distinguished Professor of Clinical Medicine
Division of Pulmonary and Critical Care Medicine,
Clinical Immunology, and Allergy
David Geffen School of Medicine at UCLA
Los Angeles, California
Chapter 68

Kevin C. Ma, MD
Assistant Professor of Clinical Medicine
Section of Interventional Pulmonology and Thoracic Oncology
Division of Pulmonary, Allergy, and Critical Care
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania
Chapter 77

Roberto F. Machado, MD
Dr. Calvin H. English Professor of Medicine
Chief, Division of Pulmonary, Critical Care, Sleep, and Occupational Medicine
Department of Medicine
Indiana University
Indianapolis, Indiana
Chapter 95

Mitchell Machtay, MD
Professor of Radiation Oncology
Department of Radiation Oncology
Penn State University College of Medicine and Cancer Institute
Hershey, Pennsylvania
Chapter 115

Atul Malhotra, MD
Peter C. Farrell Presidential Chair and Tenured Professor of Medicine
University of California San Diego
Division of Pulmonary, Critical Care & Sleep Medicine
La Jolla, California
Chapter 10

Joshua Malo, MD
Associate Professor of Medicine, Clinical Scholar
Associate Director, Internal Medicine Residency Program—Tucson Campus
Tucson, Arizona
Chapter 133

Scott Manaker, MD, PhD
Professor of Medicine
University of Pennsylvania
Hospital of the University of Pennsylvania
Philadelphia, Pennsylvania
Chapter 144

Jess Mandel, MD, MACP, ATSF
Kenneth M. Moser Professor of Medicine
Chief, Division of Pulmonary, Critical Care, and Sleep Medicine
Vice-Chair for Education, Department of Internal Medicine
UC San Diego School of Medicine
La Jolla, California
Chapter 72

Keshav Mangalick, MD
Resident Physician, Department of Medicine
New York University Grossman School of Medicine
Resident Physician, Department of Medicine
New York University Langone Health
New York, New York
Chapter 78

Patrick Mangialardi, DO
Senior Fellow, Pulmonary, Critical Care and Sleep Medicine
Department of Internal Medicine
Division of Pulmonary, Critical Care and Sleep Medicine
University of California, Davis, Sacramento
Veterans Administration Northern California Health Care System
Department of Medicine
Mather, California
Chapter 66

Nathaniel Marchetti, DO
Professor of Thoracic Medicine and Surgery
Department of Thoracic Medicine and Surgery
Lewis Katz School of Medicine at Temple University
Philadelphia, Pennsylvania
Chapter 84

Paul E. Marik, MD, FCCP, FCCM
Professor, Pulmonary and Critical Care Medicine
Department of Internal Medicine
Eastern Virginia Medical School
Norfolk, Virginia
Chapter 69

Fernando J. Martinez, MD, MS
Chief, Division of Pulmonary and Critical Care Medine
Joan and Sanford Weill Department of Medicine
Weill Cornell Medicine
NY Presbyterian Hospital
New York, New York
Chapter 50

Fiore Mastroianni, MD
Attending Intensivist and Pulmonologist
Department of Intensive Care and Pulmonary Medicine
Mather Hospital
Northwell Health
Port Jefferson, New York
Chapter 29

Aditi Mathur, MD
Attending Pulmonary Physician
Summit Health, Department of Pulmonary, Critical Care & Sleep Medicine
Hackensack University Medical Center
Montclair, New Jersey
Chapter 52

Michael A. Matthay, MD
Professor, Departments of Medicine and Anesthesia
Senior Associate Cardiovascular Research Institute
University of California San Francisco
Associate Director, Critical Care Medicine
University of California, San Francisco Medical Center
San Francisco, California
Chapter 140

Daniel N. Maxwell, MD
Fellow of Infectious Disease and Critical Care, UT Southwestern
Fellow of Infectious Disease and Critical Care
Parkland Hospital, Clements Hospital, North Texas VA Hospital
Dallas, Texas
Chapter 137

Paul H. Mayo, MD, FAACP
Professor of Clinical Medicine at the Donald and Barbara Zucker School of Medicine at Hofstra/Northwell
Academic Director of Critical Care
Division of Pulmonary, Critical Care, and Sleep Medicine
Department of Medicine
Northwell Health
New Hyde Park, New York
Chapter 29

Jeffrey Mazer, MD
Director of Pulmonary and Critical Care
Lovelace Medical Group
Albuquerque, New Mexico
Chapter 96

Peter J. Mazzone, MD, MPH
Section Head, Thoracic Oncology
Respiratory Institute
Cleveland Clinic
Cleveland, Ohio
Chapter 109

Cormac McCarthy, MD, PhD
Associate Professor of Medicine
School of Medicine, University College Dublin
Consultant Respiratory Physician, St. Vincent's University Hospital
Dublin, Ireland
Chapter 70

Daniel P. McCarthy, MD, MBA, MEM
Assistant Professor, Division of Cardiothoracic Surgery
University of Wisconsin Hospitals and Clinics
Madison, Wisconsin
Chapter 81

F. Dennis McCool, MD
Professor of Medicine, Warren Alpert Medical School of Brown University
Division of Pulmonary Critical Care and Sleep Medicine
Rhode Island Hospital
Providence, Rhode Island
Chapter 83

John E. McGinniss, MD
Assistant Professor of Medicine
Department of Medicine
Division of Pulmonary, Allergy, and Critical Care Medicine
Hospital of the University of Pennsylvania
Philadelphia, Pennsylvania
Chapter 121

Paul McLoughlin, MB, BCh, MRCPI, PhD
Professor of Physiology
University College Dublin
School of Medicine
Conway Institute of Biomedical and Biomolecular Research
St. Vincent's University Hospital
Dublin, Ireland
Chapter 24

Robert E. Merritt, MD, FACS
Professor of Surgery
Director, Division of Thoracic Surgery
Medical Director of Inpatient Services
The James Comprehensive Cancer Center
The Ohio State University Wexner Medical Center
Columbus, Ohio
Chapter 35

Joseph A. Miccio, MD
Assistant Professor of Radiation Oncology
Department of Radiation Oncology
Penn State University College of Medicine and Cancer Institute
Hershey, Pennsylvania
Chapter 115

Joseph P. Mizgerd, ScD
Jerome S. Brody, MD, Professor of Pulmonary Medicine
Professor of Medicine, Microbiology, and Biochemistry
Director, Pulmonary Center
Pulmonary Center, Boston University School of Medicine
Boston, Massachusetts
Chapter 20

Takudzwa Mkorombindo, MD
Division of Pulmonary, Allergy, and Critical Care Medicine
Lung Health Center
University of Alabama at Birmingham
Birmingham VA Medical Center
Birmingham, Alabama
Chapter 38

Edmund K. Moon, MD
Medical Director
Cell & Gene Therapy
Oncology R&D
Collegeville, Pennsylvania
Chapter 78

Richard E. Moon, MD, FACP, FCCP
Professor of Anesthesiology
Professor of Medicine
Duke University Medical Center
Durham, North Carolina
Chapter 92

Jorge I. Mora, MD
Associate Professor of Clinical Medicine
Perelman School of Medicine at the University of Pennsylvania
Associate Chief for Clinical Affairs and
Medical Director Division of Sleep Medicine
Hospital of the University of Pennsylvania
Director, Sleep Non-Invasive Ventilation Program
Philadelphia, Pennsylvania
Chapter 99

Alice Moroni, MD
Resident in Cardiology
University of Milano school of Medicine
Milano, Italy
Chapter 32

Joel Moss, MD, PhD
Senior Investigator, Pulmonary Branch
National Heart, Lung, and Blood Institute, National Institutes of Health
Clinical Center, National Institutes of Health
Bethesda, Maryland
Chapters 59, 60, and 62

Prerna Mota, MD
Assistant Professor of Medicine
Geisel School of Medicine at Dartmouth
Dartmouth-Hitchcock Medical Center
Lebanon, New Hampshire
Chapter 56

Susan Murin, MD, MBA
Professor and Associate Dean
Department of Internal Medicine
Division of Pulmonary, Critical Care and Sleep Medicine
University of California
Davis, Sacramento
Department of Medicine
Veterans Administration Northern California Health Care System
Mather, California
Chapter 66

Robert Naeije, MD, PhD
Professor of Physiology
Department of Physiology
Erasme Campus of the Free University of Brussels
Brussels, Belgium
Chapter 13

Girish B. Nair, MD, MS, FACP, FCCP
Division of Pulmonary and Critical Care
Beaumont Health
Associate Professor of Medicine
OUWB School of Medicine
Royal Oak, Michigan
Chapter 125

Camille Nelson Kotton, MD
Associate Professor, Harvard Medical School
Clinical Director, Transplant and Immunocompromised Host
Infectious Diseases
Infectious Diseases Division, Massachusetts General Hospital
Boston, Massachusetts
Chapters 123 and 138

Natalia Neparidze, MD
Associate Professor
Research DART Leader, Multiple Myeloma and Gammopathies Program
Section of Hematology
Department of Internal Medicine and Yale Cancer Center
Yale University School of Medicine
New Haven, Connecticut
Chapter 63

Nikolaus C. Netzer, MD, PhD
Prof. Prof.(Hon)/Director Hermann Buhl Institute for Hypoxia and Sleep Medicine Research
University Innsbruck
Innsbruck, Austria
Scientific Medical Director, Terra X Cube
Institute of Mountain Emergency Medicine
Eurac Research
Bozen, Italy
Chapter 91

Michael S. Niederman, MD, MACP, FCCP, FCCM, FERS
Professor of Clinical Medicine
Division of Pulmonary and Critical Care Medicine
New York Presbyterian/Weill Cornell Medical Center
Weill Cornell Medical College
New York, New York
Chapter 125

Paul W. Noble, MD
Professor of Medicine and Chair, Department of Medicine
Vera and Paul Guerin Family Distinguished Chair in Pulmonary Medicine
Medical Director, Women's Guild Lung Institute
Cedars-Sinai Medical Center
Los Angeles, California
Chapter 54

Eliezer Zachary Nussbaum
Fellow in infectious diseases
Department of infectious disease
Massachusetts General Hospital
Boston, Massachusetts
Chapter 134

Matthias Ochs, MD
Professor and Chair, Institute of Functional Anatomy, Charité—Universitätsmedizin Berlin, Germany
Chapter 2

Philip G. Ong, MD
Associate Professor of Medicine, Division of Pulmonary and Critical Care
UT Health San Antonio/University of Texas Health Science Center San Antonio
San Antonio, Texas
Chapter 79

David E. Ost, MD, MPH
Professor of Medicine, Department of Pulmonary Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas
Chapter 110

Gustavo Pacheco-Rodriguez, PhD
Staff Scientist, Pulmonary Branch
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland
Chapter 62

Allan I. Pack, MBChB, PhD
John Miclot Professor of Medicine
Division of Sleep Medicine
Department of Medicine
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania
Chapters 10 and 12

Henry S. Park, MD, MPH
Assistant Professor, Department of Therapeutic Radiology
Yale School of Medicine
Radiation Oncologist
Yale New Haven Hospital
New Haven, Connecticut
Chapter 57

John E. Parker, MD
Professor of Pulmonary Critical Care and Sleep Medicine
Department of Medicine
West Virginia University
Morgantown, West Virginia
Chapter 87

Nicholas J. Pastis, MD
Professor of Medicine
Director of Interventional Pulmonology
Interventional Pulmonology Fellowship Program Director
The Ohio State University Wexner Medical Center
Columbus, Ohio
Chapter 118

Susheel P. Patil, MD, PhD
Clinical Associate Professor of Medicine
Pulmonary, Critical Care, and Sleep Medicine
University Hospitals Cleveland Medical Center
Cleveland, Ohio
Chapter 100

Tyler J. Peck, MD
Instructor of Medicine, Harvard Medical School
Physician, Division of Pulmonary, Critical Care, and Sleep Medicine
Beth Israel Deaconess Medical Center
Boston, Massachusetts
Chapter 75

Jay I. Peters, MD
Professor of Medicine, Division of Pulmonary and Critical Care
UT Health San Antonio/University of Texas Health Science Center San Antonio and the South Texas Veterans Health Care System
San Antonio, Texas
Chapter 79

Steve G. Peters, MD
Professor of Medicine
Division of Pulmonary/Critical Care Medicine
Mayo Clinic
Rochester, Minnesota
Chapter 94

Sara Piciucchi, MD
Team Leader of Thoracic Radiology and Consultant
Department of Radiology
Ospedale GB Morgagni
Forlì, Italy
Chapter 119

Grace W. Pien, MD, MSCE
Program Director, Sleep Medicine Fellowship Program
Assistant Professor of Medicine
Pulmonary and Critical Care Division
Johns Hopkins School of Medicine
Baltimore, Maryland
Chapter 98

Gerald B. Pier, PhD
Professor of Medicine (Microbiology and Immunology)
Department of Medicine, Harvard Medical School
Senior Investigator, Department of Medicine
Brigham and Women's Hospital
Boston, Massachusetts
Chapter 124

Venerino Poletti, MD
Professor of Pulmonary Medicine, Dipartimento di Medicina Specialistica e Sperimentale (DIMES)
Università di Bologna
Bologna, Italy
Honorary Professor of Pulmonary Medicine
Department of Clinical Medicine
Aarhus University Hospital
Aarhus, Denmark
Head & Professor, Department of Pulmonology, Ospedale GB Morgagni
Forlì, Italy
Chapter 119

Jennifer D. Possick, MD
Associate Professor of Medicine
Department of Internal Medicine
Section of Pulmonary,
Critical Care, and Sleep Medicine
Yale School of Medicine
Director, Winchester Center for Lung Disease
Yale-New Haven Hospital
New Haven, Connecticut
Chapter 64

Niall T. Prendergast, MD
Research Fellow, Division of Pulmonary,
Allergy, and Critical Care Medicine
Attending Physician, Department of Medicine
University of Pittsburgh Medical Center
University of Pittsburgh
Pittsburgh, Pennsylvania
Chapter 151

Gregory P. Priebe, MD
Associate Professor of Anaesthesia, Harvard Medical School
Senior Associate in Critical Care Medicine
Department of Anesthesiology, Critical Care and Pain Medicine
Associate in Pediatrics
Department of Pediatrics, Division of Infectious Diseases
Boston Children's Hospital
Boston, Massachusetts
Chapter 124

Benjamin A. Raby, MD, CM, MPH
Professor of Pediatrics
Division of Pulmonary Medicine
Boston Children's Hospital
Harvard Medical School
Boston, Massachusetts
Chapter 9

Christopher H. Rassekh, MD, FACS
Professor of Clinical Otorhinolaryngology: Head and Neck Surgery
Department of Otorhinolaryngology: Head and Neck Surgery
Perelman School of Medicine at the University of Pennsylvania
Attending Physician, Co-Chair Airway Safety Committee
Director of Risk Reduction, Professional Practice, and
Salivary Gland Center
Department of Otorhinolaryngology: Head and Neck Surgery
Hospital of the University of Pennsylvania
Philadelphia, Pennsylvania
Chapter 145

John P. Reilly, MD, MSCE
Assistant Professor of Medicine
Division of Pulmonary, Allergy, and Critical Care
Department of Medicine
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania
Chapter 141

Stephen I. Rennard, MD
Internal Medicine, Division of Pulmonary, Critical Care, Sleep & Allergy
University of Nebraska Medical Center
Omaha, Nebraska
Chapter 41

Alejandro Restrepo, MD
Clinical Assistant Professor
Department of Medicine
UTMB Health
League City, Texas
Chapter 137

Scott I. Reznik, MD
Associate Professor
Department of Cardiovascular and Thoracic Surgery
University of Texas Southwestern Medical Center
Dallas, Texas
Chapter 113

Andrew L. Ries, MD, MPH
Professor of Medicine and Public Health
Associate Vice Chancellor for Health Sciences Academic Affairs
University of California, San Diego
San Diego, California
Chapter 42

M. Patricia Rivera, MD
C. Jane Davis & C. Robert Davis Distinguished
Professor in Pulmonary Medicine
Chief, Division of Pulmonary and Critical Care Medicine
University of Rochester
Associate Director of DEI, Wilmot Cancer Center
University of Rochester Medical Center
Rochester, New York
Chapter 112

Kenneth B. Roberts, MD
Professor, Department of Therapeutic Radiology
Yale University School of Medicine
Attending Physician, Department of Radiation Oncology
Yale-New Haven Health System
New Haven, Connecticut
Chapter 57

Matthew B. Roberts, MBBS, MPH&TM, FRACP
Infectious Diseases Physician, Infectious Diseases Unit
Royal Adelaide Hospital
Adelaide, South Australia
Chapter 123

Carolyn L. Rochester, MD
Professor, Section of Pulmonary, Critical Care and Sleep Medicine
Yale School of Medicine
New Haven, Connecticut
VA Connecticut Healthcare System
West Haven, Connecticut
Chapter 71

Karen Rodriguez, MD
Department of Radiology
Division of Thoracic Imaging & Intervention
Massachusetts General Hospital
Instructor, Harvard Medical School
Boston, Massachusetts
Chapter 117

Josanna M. Rodriguez-Lopez, MD
Instructor of Medicine, Harvard Medical School
Physician, Division of Pulmonary and Critical Care Medicine
Massachusetts General Hospital
Boston, Massachusetts
Chapter 75

William N. Rom, MD, MPH
Sol and Judith Bergstein Professor, Emeritus
Department of Medicine
Division of Pulmonary, Critical Care, and Sleep Medicine
NYU Grossman School of Medicine
Research Scientist
NYU School of Global Public Health
New York, New York
Chapter 85

AL GRAWANY

Ilene M. Rosen, MD, MSCE
Assistant Dean for Graduate Medical Education
Vice Chair for Education, Department of Medicine
Associate Professor of Medicine
Division of Sleep Medicine
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania
Chapter 98

Leonid Roshkovan, MD
Department of Radiology
Hospital of the University of Pennsylvania
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania
Chapter 28

Andrew T. Roth, MD
Fellow
Department of Medicine
Division of Pulmonary and Critical Care Medicine
Washington University School of Medicine
St. Louis, Missouri
Chapter 129

Ami Rubinowitz, MD
Associate Professor of Radiology & Biomedical Imaging
Yale School of Medicine
Thoracic Imaging Section
Yale-New Haven Hospital
New Haven, Connecticut
Chapter 55

Lisa Ruvuna, MD
Fellow, Division of Pulmonary Sciences and Critical Care Medicine
University of Colorado Anschutz Medical Campus
University of Colorado School of Medicine
Denver, Colorado
Chapter 36

Edward T. Ryan, MD
Professor of Medicine, Harvard Medical School
Professor of Immunology and Infectious Diseases
Harvard T.H. Chan School of Public Health
Director, Global Infectious Diseases, Massachusetts General Hospital
Boston, Massachusetts
Chapter 135

Coralynn Sack, MD, MPH
Assistant Professor
Departments of Medicine and Environmental &
Occupational Health Sciences
University of Washington
Seattle, Washington
Chapter 89

Moiz Salahuddin, MD
Interventional Pulmonary fellow, Interventional Pulmonology
MD Anderson Cancer Center
Houston, Texas
Chapter 110

Amali E. Samarasinghe, MS, PhD
Plough Foundation Endowed Chair of Excellence
Director of the Pediatric Asthma Research Center
Associate Professor, Department of Pediatrics, Division of Pulmonology
University of Tennessee Health Science Center
Le Bonheur Children's Hospital
Children's Foundation Research Institute
Memphis, Tennessee
Chapter 21

Rahul G. Sangani, MD
Associate Professor, Section of Pulmonary, Critical Care and Sleep Medicine
West Virginia University Department of Medicine
Morgantown, West Virginia
Chapter 87

Thomas F. Scanlin, MD
Chief, Division of Pediatric Pulmonary Medicine and
The Cystic Fibrosis Center
Professor, Department of Pediatrics,
Rutgers, Robert Wood Johnson Medical School
New Brunswick, New Jersey
Chapter 48

Edward S. Schulman, MD
Professor of Medicine
Division of Pulmonary, Critical Care and Sleep Medicine
Director, Allergy and Asthma Research Center
Drexel University College of Medicine
Philadelphia, Pennsylvania
Chapter 21

Richard J. Schwab, MD
Professor of Medicine
Perelman School of Medicine at the University of Pennsylvania
Chief, Division of Sleep Medicine
The Hospital of the University of Pennsylvania
Philadelphia, Pennsylvania
Chapter 99

David A. Schwartz, MD
Distinguished Professor of Medicine and Immunology
Anschutz Medical Campus
University of Colorado Denver
Aurora, Colorado
Chapter 90

Bernardo Selim, MD
Associate Professor of Medicine
Medical Director of Respiratory Care Unit
Division of Pulmonary and Critical Care Medicine
Mayo Clinic
Rochester, Minnesota
Chapter 148

Mithu Sen, MD, FRCPC, DABSM, ABIM, FCCP, FCCM, FAASM
Professor of Medicine, University of Western Ontario
Schulich School of Medicine & Dentistry
Department of Medicine
Division of Respirology, Critical Care, & Sleep Medicine
London, Canada
Chapter 101

David S. Seres, MD
Professor of Medicine in the Institute of Human Nutrition
Director of Medical Nutrition
Associate Clinical Ethicist
Department of Medicine
Columbia University Irving Medical Center
New York, New York
Chapter 150

Hari M. Shankar, MD
Assistant Professor of Clinical Medicine
Department of Medicine
Division of Pulmonary, Allergy & Critical Care Medicine
Hospital of the University of Pennsylvania
Philadelphia, Pennsylvania
Chapter 146

Adrian Shifren, MBBCh, FCCP
Associate Professor of Medicine
Washington University School of Medicine
St. Louis, Missouri
Chapters 15 and 16

Joseph B. Shrager, MD
Professor of Cardiothoracic Surgery
Chief, Division of Thoracic Surgery
Director, Thoracic Oncology CCP
Stanford University School of Medicine/Stanford Cancer Institute
Stanford, California
Chapter 82

Costi D. Sifri, MD
Becton, Dickinson and Company Endowed Chair of Infectious Diseases and International Health Division of Infectious Diseases and International Health Department of Medicine, University of Virginia School of Medicine
Attending Physician and Director, Hospital Epidemiology/Infection Prevention & Control UVA Health
Charlottesville, Virginia
Chapter 127

Gerard A. Silvestri, MD, MS
Hillenbrand Professor of Thoracic Oncology
Senior Vice-Chair of Faculty Development
Department of Medicine
Medical University of South Carolina
Charleston, South Carolina
Chapter 118

Kimberly A. Smith, PhD
Research Associate
Department of Pediatrics
Northwestern University
Chicago, Illinois
Chapter 72

Nilam J. Soni, MD
Professor of Medicine, Academic Hospitalist
UT Health San Antonio/University of Texas Health Science Center San Antonio and the South Texas Veterans Health Care System
San Antonio, Texas
Chapter 79

Akshay Sood, MD, MPH
Professor, Department of Internal Medicine
University of New Mexico School of Medicine
Albuquerque, New Mexico
Chapter 36

Shweta Sood, MD, MS
Assistant Professor of Clinical Medicine
Medical Director of Perelman Harron Lung Center
Division of Pulmonary and Critical Care Medicine
The Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania
Chapter 86

Ulrich Specks, MD
Professor of Medicine, Mayo Clinic College of Medicine and Science
Consultant, Department of Medicine
Division of Pulmonary and Critical Care Medicine
Mayo Clinic
Rochester, Minnesota
Chapter 74

Peter H.S. Sporn, MD
Professor of Medicine
Cell and Developmental Biology, and Medical Education
Northwestern University Feinberg School of Medicine
Chicago, Illinois
Chapter 21

Theodore J. Standiford, MD
Professor of Medicine
Chief, Division of Pulmonary and Critical Care Medicine
University of Michigan Medical Center
Ann Arbor, Michigan
Chapter 120

Robert C. Stansbury, MD
Associate Professor
Department of Medicine
Section of Pulmonary, Critical Care and Sleep Medicine
West Virginia University
Morgantown, West Virginia
Chapter 87

Daniel H. Sterman, MD, FCCP, ATSF, DAABIP
Thomas & Suzanne Murphy Professor of Pulmonary & Critical Care Medicine
Departments of Medicine and Cardiothoracic Surgery
Director, Division of Pulmonary, Critical Care & Sleep Medicine
Director, Multidisciplinary Pulmonary Oncology Program
Principal Investigator, NYU Pulmonary Oncology Research Team (NYU PORT)
NYU Grossman School of Medicine/NYU Langone Health
New York, New York
Chapters 33, 34, and 78

Kingman P. Strohl, MD
Professor, Medicine and Physiology & Biophysics
Case Western Reserve University
Cleveland, Ohio
Chapter 91

Erik R. Swenson, MD
Professor of Medicine and Physiology
Division of Pulmonary, Critical Care and Sleep Medicine
University of Washington School of Medicine
Attending Physician
Pulmonary, Critical Care and Sleep Medicine
VA Puget Sound Health Care System
Seattle, Washington
Chapter 143

Flora K. Szabo, MD, PhD
Assistant Professor of Pediatrics
Department of Pediatrics
Division of Gastroenterology, Hepatology and Nutrition
Children's Hospital of Richmond, VCU
Richmond, Virginia
Chapter 48

Nichole T. Tanner, MD, MSCR
Professor of Medicine
Co-Director, Hollings Lung Cancer Screening Program
Division of Pulmonary, Critical Care, Allergy and Sleep Medicine
Medical University of South Carolina
Core Investigator
Health Equity and Rural Outreach Innovation Center (HEROIC)
Ralph H. Johnson Veterans Affairs Hospital
Charleston, South Carolina
Chapter 118

Lynn T. Tanoue, MD, MBA
Professor of Medicine and Vice-Chair for Clinical Affairs
Department of Internal Medicine
Yale School of Medicine
Director, Lung Screening and Nodule Program
Yale Cancer Center, Yale New Haven Hospital
New Haven, Connecticut
Chapters 64 and 108

Kelan G. Tantisira, MD, MPH
Professor of Pediatrics
Chief, Department of Pediatrics
Division of Pediatric Respiratory Medicine
University of California San Diego and Rady Children's Hospital
San Diego, California
Chapter 9

Luis F. Tapias, MD
Assistant Professor of Surgery
Mayo Clinic College of Medicine and Science
Thoracic Surgeon, Mayo Clinic
Rochester, Minnesota
Chapter 80

Tachira Tavarez, MD, MSc
Clinical Associate, Neurosciences Critical Care
NIH T32 Post-Doctoral Research Fellow in Critical Care
Departments of Neurology, Anesthesiology & Critical Care Medicine
The Johns Hopkins University School of Medicine
Baltimore, Maryland
Chapter 150

Abdellatif Tazi, MD, PhD
Professor of Pulmonology, Medical School, Université Paris Cité, INSERM UMR 976
Human Immunology Pathophysiology and Immunotherapy
Head of Respiratory Department, National Reference Center for Histiocytoses
St. Louis Hospital, AP-HP
Paris, France
Chapter 59

Victor J. Thannickal, MD
Professor and Harry B. Greenberg Chair
John W. Deming Department of Medicine
Tulane University School of Medicine
New Orleans, Louisiana
Chapters 25 and 26

Sritika Thapa, MD
Clinical Instructor, Pulmonary, Critical Care, and Sleep Medicine
Yale School of Medicine
New Haven, Connecticut
Chapter 101

Jeffrey C. Thompson, MD, MTR
Assistant Professor of Medicine
Section of Interventional Pulmonology and Thoracic Oncology
Division of Pulmonary, Allergy, and Critical Care
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania
Chapter 77

Gregory Tino, MD
Associate Professor of Medicine
Perelman School of Medicine at the University of Pennsylvania
Chief, Department of Medicine
Penn Presbyterian Medical Center
Philadelphia, Pennsylvania
Chapters 31 and 51

Karen J. Tietze, PharmD
Professor of Clinical Pharmacy
Department of Pharmacy Practice
Philadelphia College of Pharmacy
St. Joseph's University
Philadelphia, Pennsylvania
Chapter 144

Martin J. Tobin, MD
Professor of Medicine
Division of Pulmonary and Critical Care Medicine
Loyola University of Chicago Stritch School of Medicine and Hines VA Hospital
Chicago, Illinois
Chapter 147

Kevin P. Toole
College of Science
University of Notre Dame
Notre Dame, Indiana
Chapter 58

Katrina E. Traber, MD, PhD
Assistant Professor of Medicine
Boston University
Pulmonary, Allergy, Sleep and Critical Care Medicine
Boston Medical Center
Boston, Massachusetts
Chapter 20

Bruce C. Trapnell, MD
Professor, Departments of Medicine and Pediatrics, University of Cincinnati
Attending Physician, Department of Medicine University of Cincinnati Medical Center
Attending Physician, Department of Pediatrics, Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio
Chapter 70

John Treanor, MD
Emeritus Professor of Medicine
University of Rochester Medical Center
Rochester, New York
Chapter 126

Jun-Chieh J. Tsay, MD, MSc
Assistant Professor, Department of Medicine
Division of Pulmonary, Critical Care, and Sleep Medicine
NYU Grossman School of Medicine
Department of Medicine
VA New York Harbor Healthcare System
New York, New York
Chapter 85

Homer L. Twigg III, MD
Professor of Medicine
Department of Medicine
Division of Pulmonary, Critical Care, Sleep, and Occupational Medicine
Indiana University
Indianapolis, Indiana
Chapters 22 and 63

George E. Tzelepis, MD
Professor of Medicine
National and Kapodistrian University of Athens Medical School
Athens, Greece
Chapter 83

Asad Ali Usman, MD, MPH
Instructor of Anesthesiology and Critical Care
University of Pennsylvania
Hospital of the University of Pennsylvania
Philadelphia, Pennsylvania
Chapter 149

Omar S. Usmani, MBBS, PhD, FHEA, FRCP, FERS
Professor of Respiratory Medicine
National Heart and Lung Institute, Imperial College London
Royal Brompton Hospital and St. Mary's Hospital London
London, United Kingdom
Chapter 45

Anil Vachani, MD, MS
Associate Professor of Clinical Medicine
Section of Interventional Pulmonology
Division of Pulmonary, Allergy and Critical Care
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania
Chapter 33

Judith A. Voynow, MD
Edwin L. Kendig Jr. Professor of Pediatric Pulmonary Medicine
Department of Pediatrics
Virginia Commonwealth University School of Medicine
Children's Hospital of Richmond at VCU
Richmond, Virginia
Chapter 48

Peter D. Wagner, MD
Emeritus Distinguished Professor of Medicine and Bioengineering
Department of Medicine, University of California San Diego
La Jolla, California
Chapter 14

James M. Walter, MD
Assistant Professor
Department of Internal Medicine
Division of Pulmonary and Critical Care Medicine
Northwestern University Feinberg School of Medicine
Chicago, Illinois
Chapter 128

Tisha S. Wang, MD
Professor of Clinical Medicine
UCLA Department of Medicine
UCLA Division of Pulmonary, Critical Care, and Sleep Medicine
Ronald Reagan Medical Center
Los Angeles, California
Chapter 68

John K. Waters, MD
Assistant Professor
Department of Cardiovascular and Thoracic Surgery
University of Texas Southwestern Medical Center
Dallas, Texas
Chapter 113

Timothy E. Weaver, PhD
Professor of Pediatrics (retired)
Division of Pulmonary Biology
Cincinnati Children's Hospital Medical Center
Department of Pediatrics
University of Cincinnati College of Medicine
Trout Run, Pennsylvania
Chapter 5

Andrew Weber, MD
Attending Intensivist and Pulmonologist
Department of Intensive Care and Pulmonary Medicine
Mather Hospital
Northwell Health
Port Jefferson, New York
Chapter 29

Scott T. Weiss, MD, MS
Professor of Medicine, Harvard Medical School
Physician, Department of Medicine, Brigham and Women's Hospital
Boston, Massachusetts
Chapter 44

Matthew Wemple, MD
Clinical Associate Professor of Medicine
Division of Pulmonary, Critical Care and Sleep Medicine
University of Washington School of Medicine
Intensivist, Medical Director, MICU
Pulmonary, Critical Care and Sleep Medicine
VA Puget Sound Health Care System
Seattle, Washington
Chapter 143

Jeffrey A. Whitsett, MD
Kindervelt Professor of Pediatrics
Co-Director, Perinatal Institute
Chief, Division of Neonatology and Pulmonary Biology
Cincinnati Children's Hospital Medical Center
University of Cincinnati College of Medicine
Cincinnati, Ohio
Chapter 5

Kathryn A. Wikenheiser-Brokamp, MD, PhD
Professor, Department of Pathology & Laboratory Medicine
Cincinnati Children's Hospital Medical Center and University of Cincinnati
Cincinnati, Ohio
Chapter 61

Andrew A. Wilson, MD
Associate Professor of Medicine
The Pulmonary Center and Department of Medicine
Boston University School of Medicine
Director, The Alpha-1 Center of Boston University and
Boston Medical Center
Attending Physician
Department of Medicine
Boston Medical Center
Boston, Massachusetts
Chapter 39

Christopher E. Winstead-Derlega, MD
Undersea & Hyperbaric Fellow
Department of Emergency Medicine
The Outer Banks Hospital
Nags Head, North Carolina
Chapter 92

Robert A. Wise, MD
Professor of Medicine
Johns Hopkins University School of Medicine
Attending Physician
Johns Hopkins Hospital
Johns Hopkins Bayview Medical Center
Baltimore, Maryland
Chapter 40

Christine Won, MD, MS
Associate Professor of Medicine
Section of Pulmonary, Critical Care and Sleep Medicine
Yale University School of Medicine
Chapter 47

Cameron D. Wright, MD
Professor of Surgery, Harvard Medical School
Thoracic Surgeon, Massachusetts General Hospital
Boston, Massachusetts
Chapter 80

Joanne L. Wright, MD, FRCP(C)
Professor of Pathology, University of British Columbia
Pathologist, St. Paul's Hospital
Vancouver, British Columbia, Canada
Chapter 37

Richard G. Wunderink, MD
Professor of Medicine
Department of Medicine
Division of Pulmonary and Critical Care
Northwestern University Feinberg School of Medicine
Medical Director, Medical Intensive Care Unit,
Northwestern Memorial Hospital
Chicago, Illinois
Chapter 128

Hemang Yadav, MBBS
Assistant Professor of Medicine
Division of Pulmonary and Critical Care Medicine
Mayo Clinic
Rochester, Minnesota
Chapter 94

Henry K. Yaggi, MD, MPH, BA
Professor of Internal Medicine
Vice Chief of Research in Pulmonary, Critical Care & Sleep Medicine
Associate Director of Yale Pulmonary Critical Care Fellowship Program
Director of Yale Centers for Sleep Medicine
Division of Pulmonary and Critical Care Medicine
Yale University
New Haven, Connecticut
Chapter 148

Ying Yang, PhD
Columbia Center for Human Development
Department of Medicine
Columbia University Medical Center
New York, New York
Chapter 4

Jason X.-J. Yuan, MD, PhD
Professor and Director, Department of Medicine
University of California, San Diego
La Jolla, California
Chapter 72

Tanzira Zaman, MD
Assistant Professor of Medicine, Department of Medicine
Medical Director, Interstitial Lung Disease Program
Cedars-Sinai Medical Center
Los Angeles, California
Chapter 54

Yong Zhou, PhD
Associate Professor
Department of Medicine
University of Alabama at Birmingham
Birmingham, Alabama
Chapter 26

PREFACE

This, the 6th edition of *Fishman's Pulmonary Diseases and Disorders*, represents a major update of the prior edition. The book continues to incorporate broad and authoritative discussions of topics relevant to pulmonary physicians and those interested in sleep medicine and associated disorders; it also includes core topics of importance to the practice of critical care medicine. As in previous editions, the 6th relies heavily upon expert presentations of many basic science areas that, in the Editors' opinions, constitute an important substrate for clinically based discussions. The clinical sections of the book have been extensively revamped and expanded.

Notable content additions include important information on the respiratory effects of vaping, more detailed discussion of the idiopathic interstitial pneumonitides, an expanded presentation on the imaging and work-up of lung nodules, consideration of immunotherapy in the treatment of lung cancer, information on COVID-19–related lung disease and its management, and comprehensive discussion of noninvasive ventilation, including its use in ambulatory and ICU settings. In addition, new chapters on cystic lung disease, lung cancer screening, the lung microbiome, developmental lung disorders, nocardiosis and actinomycosis, and application of ECMO have been included. The work is extensively referenced, with more than 22,000 citations.

Remarkably, all the material presented was prepared during an unprecedented global pandemic caused by the coronavirus, SARS-CoV-2. At the time of the 6th edition's publication, more than 6.3 million deaths due to COVID-19 had been reported worldwide. The impact that the pandemic has had on all aspects of society, including health care, has been extraordinary. The fact that this edition was orchestrated during a time when those most engaged in its preparation were also heavily involved in caring for patients with coronavirus-related respiratory disease is noteworthy. The dedication of the scientists and clinicians globally who contributed to the volume during this time is duly recognized and greatly appreciated. In fact, the 6th edition is the result of contributions from 328 authors from many countries around the world, reflecting expertise that is truly global in nature; 141 are new to the publication.

Illustrations remain a pivotal component of the book, with nearly 2500 included in the book and online on *AccessMedicine.com.*

Preparation of this edition required the work of many. The Editors wish to express their sincere gratitude to the clinicians and scientists who contributed content. They are among the leading authorities on the topics on which they have written. The Editorial group itself includes three new members. Each has stepped up to the challenge and has invested considerable time and energy in helping to prepare the work. On a personal note, I'd like to express my sincere gratitude to all my Editor colleagues who collaborated in the book's development.

Finally, the Editors wish to thank key individuals on the McGraw-Hill staff who played important roles during the project, including Jason Malley, Executive Editor, Medical Publishing; Christie Naglieri, Senior Project Development Editor; and Leah Carton, Associate Editor.

Michael A. Grippi, M.D.

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PART 1

Perspectives

1 **Milestones in the History of Pulmonary Medicine** 2

CHAPTER 1

Milestones in the History of Pulmonary Medicine*

Michael A. Grippi

Clinical, scientific, and technologic aspects of medicine have evolved over more than 2000 years, and the study of lung function and pulmonary diseases has been an integral part of its growth and development. About 3 centuries ago, progress toward scientific medicine accelerated markedly, and it has continued to gain speed ever since. In the 17th century, research and experimentation began to tilt clinical medicine toward the exact sciences; by the 18th century, pathology had become an integral part of clinical medicine, and clinical–pathologic correlations succeeded empiricism, dogmatism, and metaphysics. The age of the great clinicians dawned in Europe in the early 19th century, when autopsies became legal and socially acceptable, and when physicians who cared for patients actually *performed* the autopsies.

The road to our current understanding and practice of pulmonary medicine and science has been somewhat convoluted.[1–3] However, it is possible to retrace the scientific trail by examining iconic figures and addressing milestones (Table 1-1). This chapter traces the course of scientific pulmonary medicine over the last two millennia. By necessity, what follows constitutes a limited overview of *selected* aspects of the history of the field, including alveolar–capillary gas exchange, lung volumes, mechanics of breathing, control of breathing, ventilation–perfusion relationships, and scientific advancements impacting clinical medicine, including chest imaging, lung transplantation, bronchoscopic techniques, and advances in critical care. Indeed, much of the content of the book addresses the many advances in respiratory disorders achieved over the last 50 years.

ALVEOLAR–CAPILLARY GAS EXCHANGE

In reflecting on the history of the science and thinkers largely responsible for our current understanding of the central role of the lungs in gas exchange, the following are considered: the ancient Greeks, William Harvey and the Oxford physiologists, the "phlogiston theory," theories of blood gas diffusion and "secretion" of oxygen, and the physical chemistry of blood gas transport.

Ancient Greek Medicine

The beginnings of scientific medicine can be traced to ancient Greece in the sixth century BC. At that time, natural philosophers speculated that air, or an essential ingredient in air, was inspired to generate a "vital essence" for distribution throughout the body.

Hippocrates, the "father of medicine," is as much a symbol of the Greek physician of the fifth and fourth centuries BC as the name of a real figure (Fig. 1-1). As an individual, he exemplified the caring physician who kept accurate records, made cautious inferences, and relied more on nature, rest, and diet than on drugs for treatment. His name has been immortalized by affixing it to three major components of Greek medicine, even though none appears to be the work of a single individual.

The first is the *Hippocratic corpus*, a collection of about 70 works that includes case reports, textbooks, lectures, and notebooks. The collection contains a description of Cheyne–Stokes respiration and the use of *Hippocratic succussion* for the diagnosis of fluid and air in the pleural space. The second is a collection of aphorisms—a compilation of brief generalizations related to medicine. The third, which is more likely attributable to Pythagoras (c. 530 BC) than Hippocrates (who lived about a century later), is the *Hippocratic oath*, which not only represents the spirit of the physician of ancient Greece, but which has endured to modern times as a reflection of the physician's code of ethics.

Another Greek, Aristotle, not only had an enduring influence on the intellect of humankind in his own time, but also for two millennia thereafter. Not until the 17th century were Aristotle's doctrine of the four elements (earth, air, fire, and water) and that of Hippocrates (blood, phlegm, yellow bile, and black bile) laid to rest, thereby clearing the way for modern scientific medicine.

Soon after Aristotle, in about 300 BC, an extraordinary medical school was founded at Alexandria in Egypt. One of the first teachers at the school, Erasistratus, postulated that the "pneuma," or spirit essential for life, is generated from interplay between air and blood.

About four centuries after Erasistratus, Galen (Fig. 1-2) drew upon the medical, philosophic, and anatomic knowledge of his day to fashion a remarkable physiologic schema.[3,4] His construct was largely teleologic. Unfortunately, it was so convincing that even though it was ultimately proved to be fanciful, it sufficed to retard scientific progress for a millennium and a half. Galen was a talented individual who was well educated, well read, and well positioned in society to popularize his beliefs. Moreover, his concepts fit well into the tenets of Christianity, which was then in its ascendency; to controvert his authority was tantamount to blasphemy. Among his long-lasting, albeit erroneous, postulates were the following: invisible pores in the ventricular septum that enabled the bulk of the blood to flow from the right ventricle to the left ventricle, thereby bypassing the lungs; a diminutive pulmonary circulation that served only to nourish the lungs; and two-way traffic in the pulmonary veins that enabled inspired air and "effluent waste vapors" to go their respective ways (Fig. 1-3).

Voices raised in protest to Galen's theories were without lasting effect. In the 13th century, Ibn al-Nafis, writing in his *Canon of Avicenna*, objected that blood does not traverse the ventricular septum from right to left, as Galen had proposed. However, this insight attracted little attention. Three hundred years later, Vesalius voiced similar misgivings. In the 16th century, Michael Servetus, a polymath trained in theology, geography, and anatomy, pictured the pulmonary circulation as the vehicle by which the "inhaled spirit" could be distributed throughout the body. In his theologic treatise, *Christianismi Restitutio*, he pointed out that blood could not traverse the septum between the right and left ventricles, and that the lumen of the pulmonary artery was too large for a nutrient vessel. He became a hunted heretic, wanted for execution by both the Catholic Church and Calvin. He was warned by Calvin to stay out of Geneva. Both Servetus and Calvin then behaved predictably: Servetus showed up at a church where Calvin was preaching, and Calvin had him captured and burned at the stake. In 1559, Realdus Columbus of Cremona, a pupil of Vesalius, rediscovered the pulmonary circulation, as did Andreas Caesalpinus in 1571. Despite these challenging observations, Galen's schema was to last for more than another half century—until the physiologic experiments of William Harvey.

William Harvey and the Oxford Physiologists

William Harvey's (Fig. 1-4) discovery of the circulation of the blood[5] was preceded by anatomic observations on the valves in systemic veins made by his mentor, Fabricus ab Aquapedente. Harvey's

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*This chapter is a revision of the original chapter written by Alfred P. Fishman.

AL GRAWANY

TABLE 1-1 Landmark Figures in the Evolution of Modern Pulmonary Medicine

Alveolar–Capillary Gas Exchange

Ancient Greek Medicine

- Hippocrates of Cos (c. 460–359 BC)
- Aristotle (384–322 BC)
- Erasistratus of Chios (c. 300–250 BC)
- Galen of Pergamon (AD 129–99)
- Ibn al-Nafis (c. 1210–1288)
- Leonardo da Vinci (1452–1519)
- Miguel Servetus (1511–1553)
- Andreas Vesalius of Brussels (1514–1564)
- Realdus Columbus of Cremona (1516–1559)
- Andreas Caesalpinus of Pisa (1519–1603)

William Harvey and the Oxford Physiologists

- Galileo Galilei (1564–1642)
- William Harvey (1578–1657)
- Giovanni Alfonso Borelli (1608–1679)
- Marcello Malpighi (1628–1694)
- Robert Boyle (1627–1691)
- Richard Lower (1631–1691)
- Robert Hooke (1635–1703)
- John Mayow (1640–1679)

Phlogiston: The Rise and Fall

- Georg Ernst Stahl (1660–1734)
- John Black (1728–1799)
- Joseph Priestley (1733–1804)
- Carl Wilhelm Scheele (1742–1782)

Respiration and Metabolism

- Antoine Laurent Lavoisier (1743–1794)
- John Dalton (1766–1844)
- Julius Robert von Mayer (1814–1878)
- Carl von Voit (1831–1908)
- Nathan Zuntz (1847–1920)

The Blood Gases

- Joseph Black (1728–1799)
- John Dalton (1766–1844)
- Heinrich Gustav Magnus (1802–1870)
- Felix Hoppe-Seyler (1825–1895)
- Paul Bert (1833–1886)
- Christian Bohr (1855–1911)
- John Scott Haldane (1860–1936)
- August Krogh (1874–1949)

Diffusion or Secretion of Oxygen

- Joseph Barcroft (1872–1947)
- Marie Krogh (1874–1943)

The Physical–Chemical Synthesis

- Lawrence J. Henderson (1878–1942)

Mechanics of Breathing

- John Hutchinson (1811–1861)
- Karl Ludwig (1816–1895)
- Franciscus Cornelius Donders (1818–1889)
- Fritz Rohrer (1888–1926)
- Wallace Osgood Fenn (1893–1971)

Control of Breathing

The Central Respiratory Centers

- Thomas Lumsden (1874–1953)
- Hans Winterstein (1878–1963)
- Merkel Henry Jacobs (1884–1970)

The Peripheral Chemoreceptors

- Ewald Hering (1834–1918)
- Joseph Breuer (1842–1925)
- Cornelius Heymans (1892–1968)

Scientific Basis of Clinical Medicine

Pathologic Anatomy

- Gioranni Battista Morgagni (1682–1771)
- Leopold Auenbrugger (1727–1809)
- Jean Nicolas Corvisart (1755–1821)
- René Théophile Hyacinthe Laënnec (1781–1826)

Microbiology

- Robert Koch (1843–1910)

Physiology of the Pulmonary Circulation

- Claude Bernard (1813–1878)
- Auguste Chauveau (1827–1917)
- Étienne Jules Marey (1830–1904)
- Dickinson W. Richards (1895–1973)
- André Frederic Cournand (1895–1988)
- Werner Forssmann (1904–1979)

Thoracic Imaging

- Wilhelm Conrad Roentgen (1845–1923)
- Godfrey N. Hounsfield (1919–2004)

Bronchoscopy

- Gustav Killian (1860–1921)
- Chevalier Jackson (1865–1958)
- Shigeto Ikeda (1925–2001)

Lung Transplantation

- Vladimir P. Demikhov (1916–1998)
- James D. Hardy (1918–2003)
- Joel D. Cooper

small book, *De Motu Cordis*, published in 1628, not only corrected a self-perpetuating error in Galenical teaching, but also marked the birth of modern physiology. The time, however, was not yet ripe to relate the function of the heart to the physiology of breathing. To his dying day, Harvey clung to the idea that the main function of breathing was to cool the heart. Moreover, since he made no use of the microscope, he could not picture how the pulmonary arteries made connections with the pulmonary veins. Galileo invented the compound microscope in 1610. In 1661, using the compound microscope, Marcello Malpighi reported that alveoli were covered by capillaries and that blood and air were kept separate by the continuous alveolar–capillary barrier.

Figure 1-1 The Hippocrates of Ostia. This damaged bust is believed to represent Hippocrates as perceived in antiquity. It was found in a family tomb in excavations near Ostia. *(Reproduced with permission from Dr. Dickinson W. Richards.)*

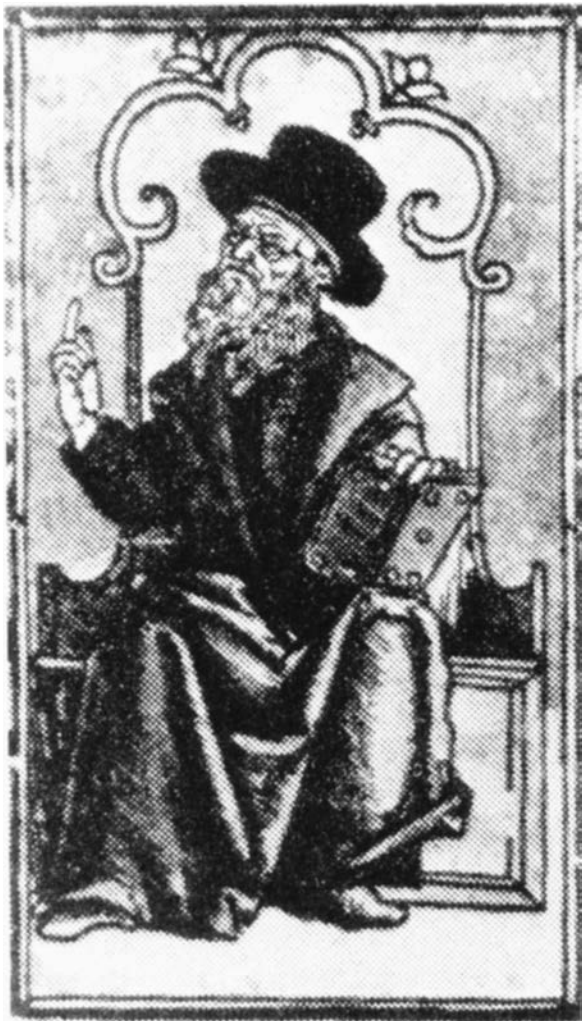

Figure 1-2 Galen of Pergamon as depicted in medieval times. No authentic reproduction exists of Galen in ancient times. *(Reproduced with permission from Galen's Therapeutica, published in Venice in 1500.)*

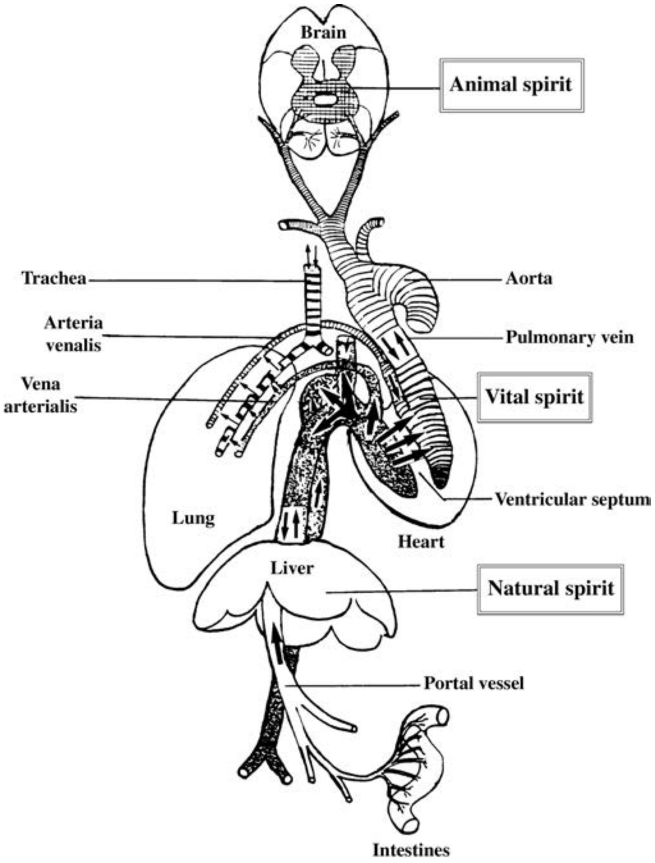
Brain
Animal spirit
Trachea
Aorta
Arteria venalis
Pulmonary vein
Vena arterialis
Vital spirit
Ventricular septum
Lung
Heart
Liver
Natural spirit
Portal vessel
Intestines

Figure 1-3 Galen's scheme of the circulation. The diagram shows the source and distribution of the three types of spirits. The validity of this scheme depended on invisible pores in the ventricular septum, two-way traffic in the pulmonary vein, and selective permeability of the mitral valve for sooty wastes but not for spirit-containing blood. Vena arterialis, pulmonary vein; arteria venalis, pulmonary artery. *(Modified with permission from Singer C. A Short History of Scientific Ideas to 1900. London: Oxford University Press; 1959.)*

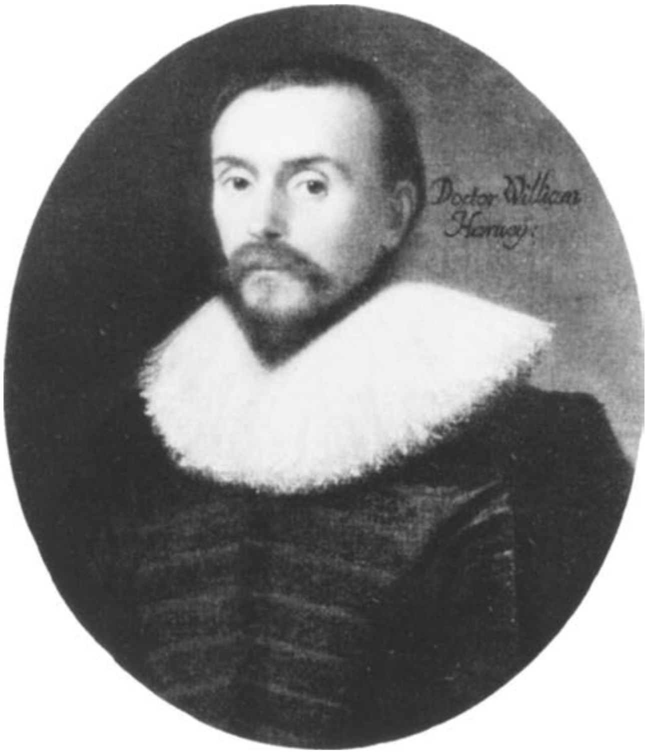

Figure 1-4 William Harvey (1578–1657). This portrait of William Harvey is part of a family group in which William Harvey and his five brothers are gathered around their father, William Harvey.

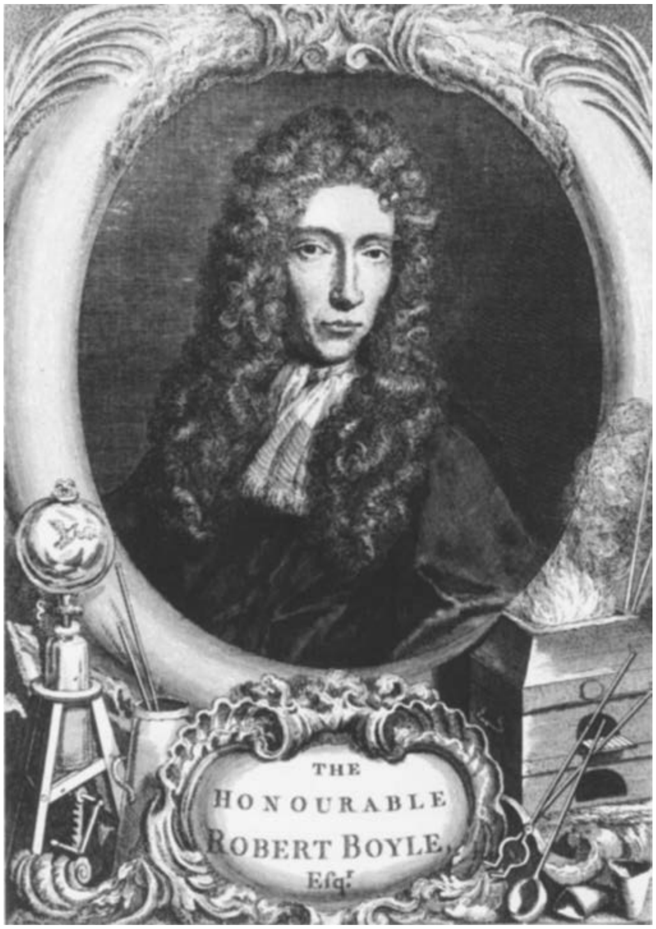
THE HONOURABLE ROBERT BOYLE, Esq.r

Figure 1-5 Robert Boyle (1627–1691). This engraving, from an original painting by Johann Kerseboom, hangs in the Royal Society, London. Boyle's invention of a pneumatic air pump and his publications concerning "the spring of air and its effect" stimulated considerable research on the physical properties of air and its role in respiration and combustion. He strongly influenced Hooke, Lower, and Mayow at Oxford.

Harvey's description in 1628 of the circulation of the blood had three major consequences for pulmonary medicine: (1) it oriented pulmonary medicine toward the basic sciences and away from philosophy and empiricism; (2) it demolished the Galenic concept of the movement of the blood; and (3) it set the stage for an upcoming generation of physiologists at Oxford University to explore breathing in chemical and physical terms.

The physiologists working at Oxford in the 1660s were greatly impressed by Harvey's disciplined approach to scientific inquiry. Many were medical practitioners who conducted research as a sideline. Four, in particular, began the systematic study of air and its constituents, thereby laying the foundations for contemporary respiratory physiology and medicine: Robert Boyle (Fig. 1-5), Robert Hooke, Richard Lower, and John Mayow.

In 1660, Robert Boyle proved by means of his air pump that air is necessary for life. In 1667, Robert Hooke showed that insufflation of the lungs with air while breathing movements were arrested could keep an open-chest animal alive; that is, that movement of the lungs was not essential for life. Richard Lower, the first to practice blood transfusion, took advantage of Hooke's continuously inflated lung preparation in the dog to observe that dark venous blood becomes bright red as it traverses lungs insufflated with air. In 1674, Mayow interpreted the change in the color of blood from venous to arterial as due to the uptake of "nitroaerial particles" (later to be called "oxygen") from the air.

■ Phlogiston: the Rise and Fall

Unfortunately, the discoveries and insights of the Oxford physiologists went largely unnoticed during the century that followed, overshadowed by the "phlogiston theory" of combustion. The theory, advanced by Stahl, postulated that all combustible materials were composed of two ingredients: phlogiston, a principle that transformed into fire when heated, and an ash that was left behind after the fiery phlogiston escaped. The phlogiston theory was sufficiently malleable to accommodate almost every new discovery that could have overthrown it, including the rediscovery of carbon dioxide in 1754 by John Black, and the independent discoveries of oxygen by Priestley and Scheele. Although the respiratory gases had been discovered by the end of the 18th century and many of their properties characterized, the discoveries were misapplied to support, rather than destroy, the phlogiston theory. The phlogiston theory was finally undone by the experiments of Lavoisier.

■ Respiration and Metabolism

From the time of Hippocrates until early in the 20th century, debate had continued about the site of heat production in the body. In 1777, Lavoisier suggested that air was composed of one respirable gas (which he later named "oxygine") and another (nitrogen) that remained unchanged in the course of respiration. Between 1782 and 1784, Lavoisier and Laplace concluded, on the basis of calorimetric experiments on guinea pigs, that "respiration is therefore a combustion, admittedly very slow, but otherwise exactly similar to that of charcoal" (Fig. 1-6). The similarity between respiration and combustion had previously been recognized by the Oxford physiologists, especially Mayow.[6] By 1783, Lavoisier was accumulating evidence against the phlogiston theory and began to replace it with an entirely new system of chemistry.

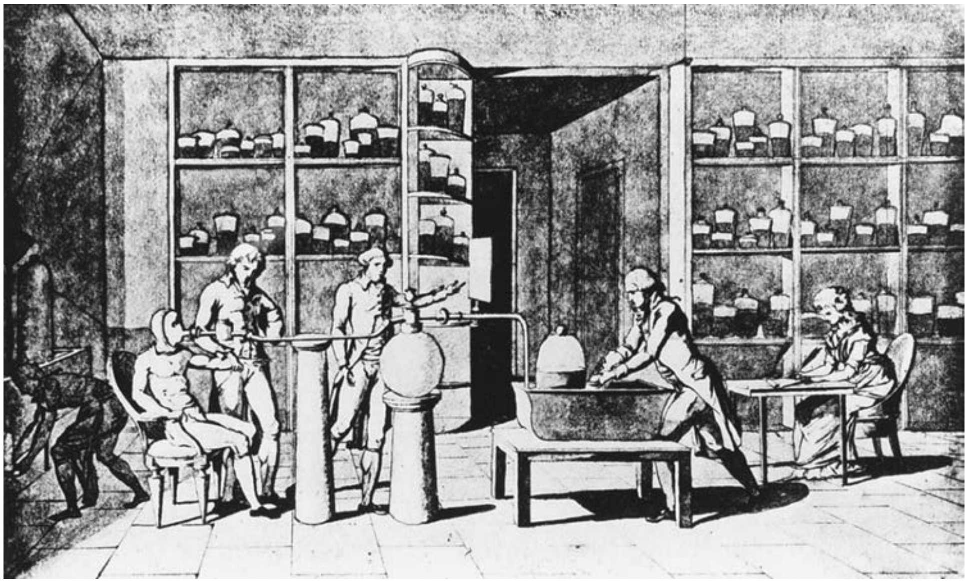

Figure 1-6 Scene from the laboratory of Antoine Laurent Lavoisier (1743–1794). His wife is acting as his assistant, and Sequin is the subject. Studies such as this led to the conclusion that respiration and combustion are similar processes.

As noted previously, the ancients pictured the heart as the heat generator. Lavoisier favored the lungs. Others held that combustion occurred in the blood. Although Spallanzani had shown in the 18th century that isolated tissues take up oxygen and evolve carbon dioxide, the idea that combustion occurred in the tissues was slow to gain acceptance. However, the hypothesis gained strength through the work of Pflüger in 1878. He measured oxygen consumption and carbon dioxide production in dogs and calculated respiratory quotients. His research substantiated a concept that had been enunciated, but not named, by Lavoisier.[7]

Once the idea that oxidation occurred in the tissues had become generally accepted, investigators delved into the processes involved in utilization of foodstuffs by the tissues, energetics, growth, and repair. Carl von Voit and Max von Pettenkofer, using a respiration chamber, drew upon chemical balances and respiratory quotients in humans to distinguish the nature of the foodstuffs being burned and to show that the amounts of fat, protein, and carbohydrate burned varied with the mechanical work done by the subject. Between 1842 and 1845, Julius Robert von Mayer formulated the law of conservation of energy. Subsequently, Max Rubner showed that the law applied to the living body, and Herman von Helmholtz showed that its relevance to metabolism could be demonstrated experimentally. Application of these principles at the bedside was greatly facilitated by the development of a portable metabolic apparatus by Nathan Zuntz. Pioneering bedside studies of metabolic states were conducted by a succession of distinguished investigators, including Magnus-Levy, Graham Lusk, F. G. Benedict, and Eugene F. DuBois.

■ The Blood Gases

The Oxford physiologists set the stage for the discovery of the blood gases. Using his vacuum pump, Robert Boyle extracted "air" from blood. John Mayow came close to discovering oxygen by showing that only a portion of air was necessary for life—the "nitroaerial spirits"—which were removed both by respiration and fire (combustion). One of his famous experiments entailed enclosing a mouse and a lighted lamp in an airtight container; the lamp went out first and then the mouse died. However, Mayow did not realize that the "nitroaerial spirits" could be isolated as a gas.[6]

One hundred years after Mayow, Joseph Priestley (Fig. 1-7) exposed a mouse to the gas released from heated mercuric oxide and found that the gas supported life better than air did; he also noticed that a flame burned more vigorously in this gas than in air. Priestley was not alone in his preoccupation with flame. In 1773, about a year before Priestley had obtained oxygen by heating mercuric oxide, Scheele discovered oxygen independently because of his interest in fire, and he designated oxygen as "fire air."

In 1662, Van Helmont, a Capuchin friar and talented chemist, as well as a mystic with a drive to quantify, discovered carbon dioxide, coined the word *gas*, and called carbon dioxide "wild gas" ("gas sylvestre"). In 1755, Joseph Black rediscovered carbon dioxide. He showed that calcium carbonate (limestone) and magnesium carbonate (magnesia alba) lost weight on heating, releasing "fixed air" (CO_2) in the process. This fixed air extinguished both flame and life. Lavoisier knew of the observations of Black and of Priestley

JOSEPHUS PRIESTLEY
C. G. HANCOCK F.

Figure 1-7 Joseph Priestley (1733–1804), the discoverer of oxygen. This figure shows a silver medal struck in his honor in 1783. A Presbyterian minister, he was radical in his religious and political beliefs, inventive in science, and conservative in the interpretation of his findings. *(Reproduced with permission from Fishman AP, Richards DW. Circulation of the Blood: Men and Ideas. New York, NY: Oxford University Press; 1964.)*

Figure 1-8 Christian Bohr (1855–1911). At work in his laboratory, Bohr *(far right)* and his associates systematically explored the interplay between the respiratory gases and hemoglobin that led to the discovery of the “Bohr effect.” *(Reproduced with permission from Fishman AP, Richards DW. Circulation of the Blood: Men and Ideas. New York, NY: Oxford University Press; 1964.)*

and Scheele. He decided in 1778 that the gas obtained from heating mercuric oxide was not “fixed air” or “common air,” but “highly respirable air” (oxygen).

The story of hemoglobin, the essential element in the transport of the respiratory gases by the blood, begins with Hoppe-Seyler, who, between 1866 and 1871, crystallized hemoglobin, explored its chemical properties, and assigned it a proper role in the transport of oxygen by the blood. At the turn of the 19th century, Dalton reported his experiments with the respiratory gases, which led to the development of his atomic theory. In 1872, taking advantage of Dalton’s law, Paul Bert published the first oxygen dissociation curve, that is, oxygen content at different barometric pressures; he pictured the curve as hyperbolic. Christian Bohr (Fig. 1-8) subsequently identified its s-shaped contour, and in 1904, together with Hasselbach and August Krogh, showed that increasing carbon dioxide tension in blood drives out oxygen, that is, the “Bohr effect.” Shortly thereafter, the influence of various factors, for example, temperature and electrolytes, on the affinity of oxygen for hemoglobin (and, consequently, on the position of the oxygen dissociation curve) was explored in detail by Barcroft and associates. In 1914, Christiansen, Douglas, and Haldane reported that an increase in the oxygen tension of the blood drives out carbon dioxide, that is, the “Haldane effect.” In 1967, a new dimension was added to the understanding of the position and configuration of the oxygen dissociation curve by the demonstration that diphosphoglycerate, a chemical constituent of red cells, regulates the release of oxygen from oxyhemoglobin.

■ Diffusion or Secretion of Oxygen

Bohr is a central figure as an investigator and mentor in respiratory physiology.[8] In 1904, he raised a troublesome issue that was not easily resolved, primarily because of limitations in methodology at the time. He postulated that even though diffusion could account for oxygen uptake at rest, it could not suffice during strenuous exercise, particularly at altitude. He held that oxygen *secretion* had to be involved.[9] He clung to this misconception during his lifetime, a conviction supported by two major lines of evidence. The first was indirect: Oxygen secretion by the swim bladder of fish showed by extrapolation that active transport of oxygen in the lungs was possible. The second was based on observations made during Bohr’s expedition to Pike’s Peak in 1912, during which it was erroneously demonstrated that with exercise at altitude, arterial oxygen tension exceeded alveolar oxygen tension.

However, even before the report from high altitude, Bohr’s former assistant, August Krogh, and his wife, Marie Krogh (Fig. 1-9) had marshaled new evidence to show that “the absorption of oxygen and the elimination of carbon dioxide in the lungs takes place by diffusion and diffusion alone.” The final blow to the secretion theory was delivered by Marie Krogh.[10] Based on the single-breath carbon monoxide method for determining diffusing capacity that she and her husband had developed in 1910,[11] she was able to account for oxygen uptake in the lungs by diffusion alone, even during strenuous exercise under conditions of low oxygen tension. Refinements in the carbon monoxide method by Roughton and others extended

Figure 1-9 August and Marie Krogh in 1922, at the time of their first visit to the United States so that August Krogh could deliver the Silliman Lecture at Yale. They demonstrated that diffusion, without secretion, could account for the transfer of O_2 and CO_2 across the alveolar–capillary membranes of the lungs. *(Reproduced with permission of their daughter, Dr. Bodil Schmidt-Nielsen.)*

Figure 1-10 Two founders of contemporary respiratory physiology in 1936. Sir Joseph Barcroft (1872–1947) *(left)* proved, in experiments on himself, that diffusion was the mechanism for gas exchange in the lungs and pioneered current understanding of the respiratory functions of the blood. Lawrence J. Henderson (1878–1942) *(right)* provided a mathematical analysis of blood as a physiochemical system and stimulated research on the complex interplay involved in respiratory gas exchange during exercise. *(Reproduced with permission from Fishman AP, Richards DW. Circulation of the Blood: Men and Ideas. New York, NY: Oxford University Press; 1964.)*

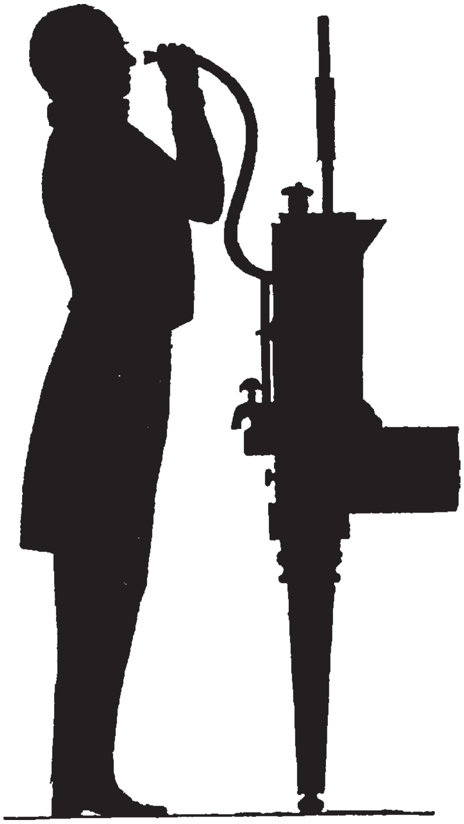

Figure 1-11 John Hutchinson's illustration of a subject about to undergo measurements of lung volumes. *(Reproduced with permission from Hutchinson J. On the capacity of the lungs, and on the respiratory functions, with a view of establishing a precise and easy method of detecting disease by the spirometer. Med Chir Trans. 1846;29:137–252.)*

its clinical applicability and provided further evidence against the secretion theory.[12] Despite these observations, Haldane would not let go. Throughout his life, despite mounting evidence to the contrary, he adhered to the idea that oxygen was secreted by the alveolar membrane.

The issue was finally settled by Joseph Barcroft (Fig. 1-10). Using a chamber to reproduce the circumstances of hypoxia and strenuous exercise assessed during the Pike's Peak expedition, he found that under all conditions, the oxygen saturation of arterial blood was less than that of arterial blood exposed to a sample of alveolar gas obtained at the same time. He subsequently confirmed these results by experiments done at high altitude at Cerro de Pasco (1921–1922).

■ The Physical–Chemical Synthesis

Lawrence J. Henderson undertook the herculean task of depicting the reactions of oxygen and carbon dioxide in blood, not as cause and effect, but as interplay among physiochemical variables and functions (Fig. 1-10). His theoretical considerations and practical applications in the Fatigue Laboratory at Harvard University were greatly abetted by close collaboration with Van Slyke, Wu, and McLean at the Rockefeller Institute in New York, who were exploring the exchanges of blood constituents between red cells and plasma. In 1828, Henderson presented his synthesis in the form of a d'Ocagne nomogram that displayed changes in the various elements that entered into the exchange of the respiratory gases between alveolar gas and blood: plasma; the red cell; hemoglobin; and chloride, bicarbonate, and hydrogen ions. He presented nomograms not only for the normal subject at rest and during exercises, but also for individuals with anemia, nephritis, diabetic coma, and other major clinical entities. Henderson dealt with steady-state observations. Roughton and associates enlarged the physiochemical horizons further by discovering carbonic anhydrase in the red cell and addressing transient phenomena related to transport of respiratory gases and carbon monoxide in blood.

LUNG VOLUMES

Although Humphrey Davy had determined his own lung volume using hydrogen as the test gas in 1800,[13] it was not until the 1840s that John Hutchinson laid the groundwork for modern pulmonary function testing. He devised a spirometer and used it to determine the subdivisions of the lung in a large number of healthy subjects, relating the measurements to height and age (Fig. 1-11). The many refinements since then are too numerous for mention in this chapter. A big step forward was the invention of the body plethysmograph many years later, which made possible the determination of the thoracic gas volume and airway resistance.

MECHANICS OF BREATHING

The ancients wondered how air moved into and out of the lungs; as far back as the time of Erasistratus, the diaphragm was recognized as involved in breathing. Galen was aware that the lungs fill the chest cavity and are moved by the actions of the thorax, and that the large airways enlarge and lengthen during inspiration. He marveled at the long course of the nerves to the diaphragm and the innervation of the intercostal muscles. After Galen, interest in the mechanics of breathing waned except for sporadic observations and experiments by anatomists, notably Leonardo da Vinci and Andreas Vesalius. Interest in respiratory mechanics resumed in the 16th century, largely as a result of progress in physics and mathematics, as exemplified in the works of Borelli and Galileo.

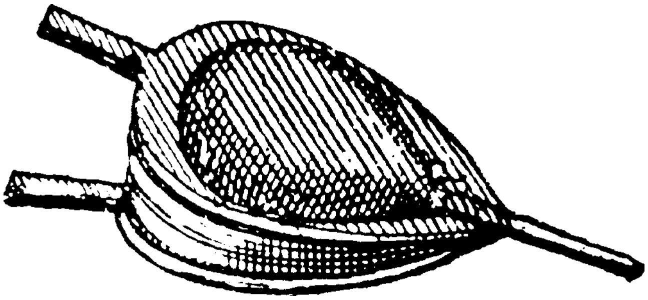

Figure 1-12 Mayow's model of the chest and lungs. The bellows encloses a bladder, the neck of which opens to the outside. A glass window on the upper side makes it possible to observe the bladder during inflation and deflation. *(Reproduced with permission from Mayow J: Medico-Physical Works, Crum A, Brown, Dobbin L [trans]. Edinburgh, Alembic Club, Reprints, no 17, 1957. [Translated from Tractatus quinque medico-physics, 1674.])*

■ The Respiratory Muscles

Mayow, one of the Oxford physiologists, drew heavily on the work of colleagues, including Boyle and Hooke, to develop considerable insight into the mechanics of breathing. He also built the first model on record of the chest as a bellows, which contained a bladder within it (Fig. 1-12). He understood that air moved into the lungs as the chest expanded because of the pressure and elasticity of ambient air; he also appreciated that the chest expands because of the action of the intercostal muscles (internal and external), that the diaphragm is the primary muscle of inspiration, and that normal expiration is passive. After Mayow, little research was done on the role of the respiratory muscles in breathing until the mid-19th century, when Donders distinguished between the respective roles played by the inspiratory muscles and elastic forces.

■ Elastic Properties of Lungs and Chest Wall

Until the 20th century, observations on the elastic properties of the lungs and chest wall in humans were fragmentary. Access to the pleural space was the major limiting factor. With few exceptions—notably Neergaard and Wirz, who used pleural pressures to determine elastic recoil in normal human subjects, and Christie, who recorded pleural pressures to demonstrate loss of pulmonary elasticity in emphysematous patients—measurements in humans were largely confined either to therapeutic interventions, for example, induction of a pneumothorax or aspiration of pleural fluid, or experiments done at autopsy. The number of observations on the mechanical properties of the lungs increased dramatically when it was shown by Buytendijk, in 1949, and again by Dornhurst and Leathart, in 1952, that esophageal pressures provided an accurate measure of pleural pressures.

The role of alveolar surface tension in determining the elastic forces in the lungs began to be widely appreciated in the late 1950s, although the stage had been set long before. In 1812, Laplace had published the law of surface tension. The implication of this law for the lungs was appreciated initially in 1929 when Neergaard compared pressure–volume curves of lungs filled with air with those filled with fluid. He concluded that unopposed surface tensions would favor alveolar collapse. Then, between 1954 and 1960, a remarkable outpouring of papers from different laboratories showed that a unique surfactant lined the alveoli, and that this material was absent in premature infants with hyaline membrane disease (and alveolar collapse); these papers prompted extensive research on the chemical and physical properties of surfactant and on its sites of formation and removal.

■ Airway Resistance

A giant step forward occurred in 1916 when Rohrer, as part of his doctoral dissertation, presented a conceptual framework for determining flow and resistance in airways. His equations were based on precise anatomic measurements of airway dimensions in a human cadaver, coupled with aerodynamic principles. During the following decade, he and his coworkers, Neergaard and Wirz, applied Poiseuille's law for laminar flow and his equations to the determination of airway resistance. Use of Fleisch's pneumotachograph, coupled with periodic interruptions of airflow, permitted measurement of alveolar pressure. Clinically useful measurements of alveolar pressure became available in 1956 with the introduction by DuBois and associates of the whole-body plethysmograph, which they coupled with the application of Boyle's law.

■ Synthesis of Mechanics

During the decade between 1915 and 1926, Rohrer and his colleagues provided a remarkably comprehensive synthesis of respiratory mechanics that included a description of the static pressure–volume characteristics of the respiratory system and the work of breathing; they also developed the principle of optimal frequencies of breathing to minimize respiratory work. Together with von Neergaard and Wirz, Rohrer developed and tested, experimentally, concepts involving pressures, flows, and volumes. The full significance of Rohrer's work was not appreciated until the publications by Fenn and his group at the University of Rochester, starting in the 1940s. The contributions of W. O. Fenn, H. Rahn, and A. B. Otis to our present understanding of the mechanics of breathing are significant, and there is little doubt that this group shaped much of the contemporary thinking of respiratory physiologists and pulmonary physicians.[14–17]

CONTROL OF BREATHING

The control of breathing is a complex process that depends on the integrity of the entire respiratory system—lungs, airways, circulation, and control systems.[18] Two dominant control systems exist. One is in the central nervous system; the other is outside the brain. Control mechanisms in the central nervous system are influenced by the state of wakefulness or alertness and are subject to voluntary control. These mechanisms are also influenced reflexively by a variety of peripheral receptors.

■ Localization of the Central Respiratory Centers

In 1812, Legallois, apparently intrigued by the gasping movements of the head after decapitation, identified an area in the medulla that was essential for life. In 1923, Lumsden systematically explored the effects of serial sectioning of the brain stem on respiration, marking the beginning of the era of contemporary research on rhythmic breathing. He designated an area in the caudal pons responsible for a sustained inspiratory drive as the "apneustic center," and an area in the rostral and lateral portions of the pons that presumably inhibited the apneustic drive as the "pneumotaxic center"; sectioning of the vagi exaggerated the inhibition of the apneustic drive by the pneumotaxic center. Sixteen years later, Pitts et al.,[19] using stereotactic stimulation of the cat medulla, identified inspiratory and expiratory centers and proposed a theory that could account for both rhythmic breathing and apneusis.

■ Chemical Stimulation of the Respiratory Centers

The chemical stimuli to breathing have been known for more than a century. In 1885, Miescher-Ruesch showed in humans that ventilation at rest is primarily regulated by carbon dioxide. Between 1887 and 1901, cross-perfusion experiments by Leon Fredericq underscored the role of carbon dioxide. However, it was not until 1905 to 1909 that Haldane, Priestley, and Douglas paved the way to the modern understanding of the role of carbon dioxide under a variety of experimental conditions.[20] In their experiments on humans, they relied heavily on the Haldane gas analyzer and an alveolar gas sampler of their own invention. However, their experiments did not distinguish clearly between CO_2 and H^+ in the stimulation of the respiratory centers. Winterstein, and later Gesell,[21] advanced the idea that the chemical regulation of respiration is determined by the concentration of hydrogen ions within the respiratory centers.

The Winterstein theories[22] provide a good example of the evolution of ideas prompted by new discoveries and inventions. The original theory in 1911 attributed increments in ventilation caused by hypoxic or hypercapnic inspired mixtures to a single mechanism, that is, acidification of arterial blood by either carbonic acid or lactic acid. In 1921, Jacobs' demonstration of the rapid diffusion of carbon dioxide into starfish eggs implicated acidity within the respiratory centers,[23] as well as arterial blood acidity, as the sites of stimulation. To account for the stimulation of breathing by hypoxia (the peripheral chemoreceptors had not yet been discovered), he invoked the release of asphyxiating substances *(Erstickungsstoffen)* within the respiratory centers themselves. A third theory, postulated in 1949, attempted to incorporate the discovery of the peripheral chemoreceptors, and it finally gave way in 1955 to his fourth theory, which explained the effects of acid or hypoxia on both the central and peripheral chemoreceptors.

A major consequence of Winterstein's research was an impetus to subsequent exploration of the chemical control of breathing. These studies led to the identification of central chemoreceptors, distinct from mechanoreceptors, on the ventral surface of the medulla, and clarification of the role of hydrogen ion activity as the central stimulus to breathing. The studies also prompted a search for a unifying theory for the chemical control of breathing.

■ The Reflex Regulation of Breathing

A considerable and diverse number of peripheral receptors can influence breathing reflexively by supplying information to respiratory centers located in the brain. These include pain receptors, stretch receptors in the muscles and distensible thoracic structures, and organs and chemoreceptors in major systemic arteries.

■ Mechanoreceptors

Until the work of Hering and his student, Breuer, little was known about the role of afferent impulses to the central control mechanisms in the control of breathing, other than the fact that electrical stimulation of the vagus nerves influenced respiration.[24] In 1868, Hering and Breuer reported that inflation of the lungs stopped respiration in expiration and promoted expiration, and that, conversely, a decrease in lung volume ended expiration and promoted inspiration. They inferred that inflation mechanically stimulated nerve endings in the lungs and that the resulting impulses ascending the vagi were inhibitory to inspiration.

■ Peripheral Chemoreceptors

In 1841, Volkmann suggested the existence of chemoreceptors in the systemic circulation that were sensitive to blood-borne stimulants to respiration. In 1927, J. F. Heymans and C. Heymans first showed that the aortic bodies served this function, and in 1930, C. Heymans and Bouckaert demonstrated the peripheral chemoreceptive function of the carotid bodies. These were physiologic observations that tallied well with the observations of F. De Castro, a student and later a colleague of Ramón y Cajal, who was sufficiently impressed by the histologic structure, location, and rich innervation of the carotid body to propose that it might be stimulated by blood-borne substances (Fig. 1-13).[25]

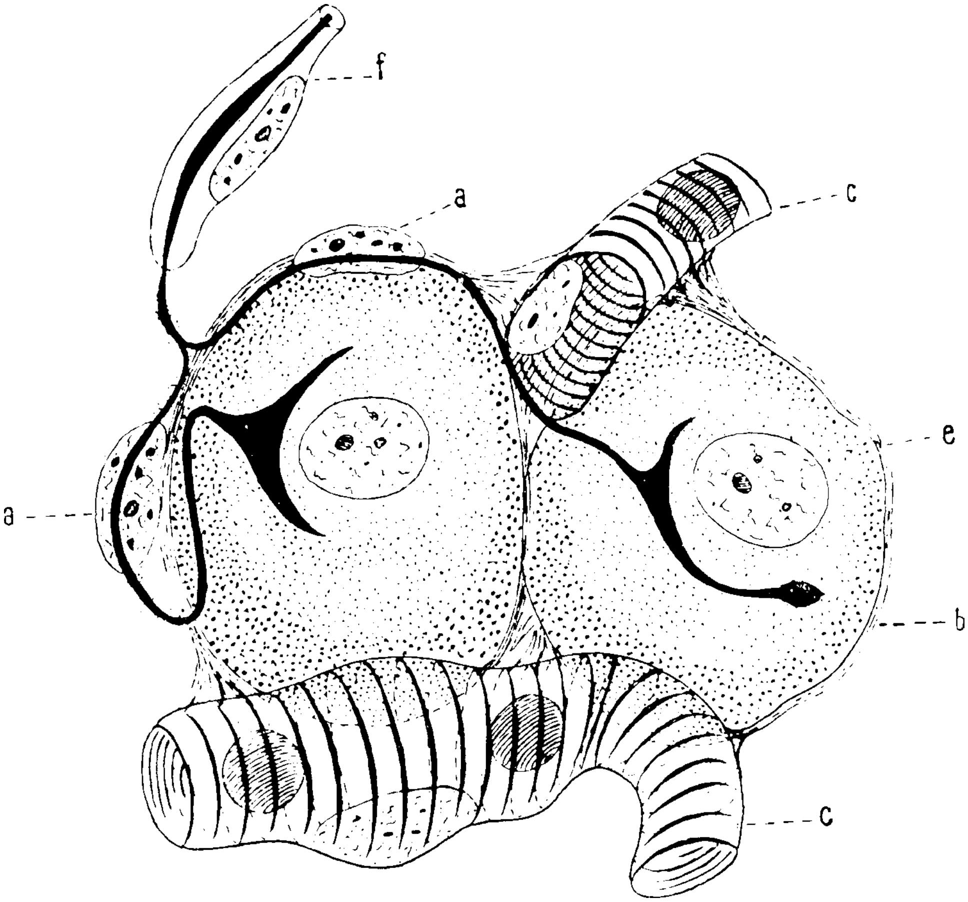

Figure 1-13 Drawing by De Castro showing the structure of the chemoreceptor. The glomus cells (*e*) present an ample cytoplasmic surface for contact with the perfusing blood delivered by the capillary (*c*); sensory nerve fiber (*f*) with sheath of myelin; Schwann cells (*a*) surround the unmyelinated fibers which form the terminal menisci; cell membrane (*b*). *(Reproduced with permission from De Castro F: Sur la structure de la synapse dans les chemocepteurs: leur mécanisme d'Excitation et R™ le dans la circulation sanguine locale. Acta Physiol Scand. 1951;22(1):14–43.)*

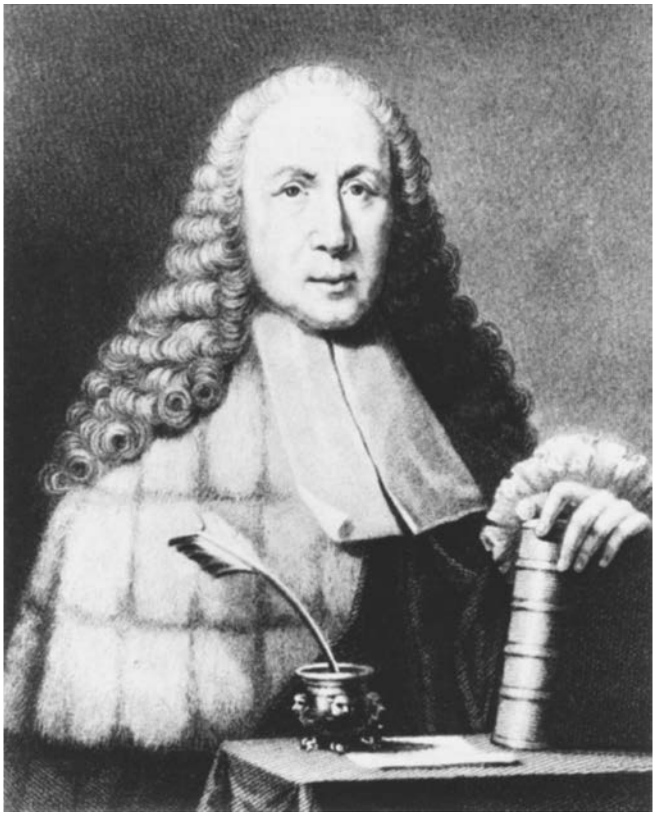

Figure 1-14 Giovanni Battista Morgagni (1682–1771). The five volumes of his *De Sedibus* contain the clinical and pathologic descriptions of approximately 700 cases. *(Reproduced with permission from the Library of the College of Physicians of Philadelphia.)*

VENTILATION–PERFUSION RELATIONSHIPS

In 1946, William Dock attributed the apical localization of tuberculosis to hypoperfusion of well-ventilated alveoli in the lung apices in the upright position.[26] Shortly thereafter, ventilation–blood flow relationships were described in quantitative terms in papers by two separate groups: Rahn and Fenn[27] and Riley and Cournand.[28–30]

SCIENTIFIC BASIS OF CLINICAL PULMONARY MEDICINE

Five remarkable figures serve to illustrate different stages in the evolution of the scientific basis of pulmonary medicine: Morgagni, Laënnec, Koch, Cournand, and Richards. They represent key scientists in the areas of pathologic anatomy, microbiology, and physiology.

■ Pathologic Anatomy

Morgagni and Laënnec, almost a century apart, made major contributions to the field of pathologic anatomy. Morgagni (Fig. 1-14), who lived in the 18th century and was a student of Valsalva, veered away from the undisciplined case reports of his predecessors. Instead, he adopted a logical system for relating findings at autopsy to their clinical manifestations. At age 79, he published a compilation of his lifelong experience in his famous work, *De Sedibus et Causis Morborum per Anatomen Indagatis. De Sedibus* includes about 700 cases. The clinical–pathologic correlations in this work benefited greatly from the fact that Morgagni was both a seasoned clinician and a pathologist. One of the compilation's five books is devoted to diseases of the thorax. Among his descriptions were those of a tubercle undergoing liquefaction and the hepatization stage of pneumonia.

René Théophile Laënnec is, perhaps, best known for inventing the stethoscope in 1816 (Fig. 1-15).[31,32] At that time, clinical medicine in Europe, especially in France, was turning from metaphysical concepts and doctrinal systems to pathology as its scientific foundation. Eminent physicians, such as Bichat, Bayle, and Corvisart in France, and William and John Hunter and Baillie in England, were turning to anatomic findings at autopsy to understand the signs and symptoms of their patients. Percussion had been rediscovered by Corvisart. Although Auenbrugger had reported in Latin his "new invention" in 1761, the idea had not caught on until Corvisart—eminent clinician and teacher and personal physician to Napoleon—published a translation in French in 1808. Corvisart's approach to medicine strongly influenced Laënnec. Laënnec applied the stethoscope and Corvisart's "sounding of the chest" to study individual patients with diseases of the lungs and heart throughout their clinical course, along with anatomical examination at autopsy. This was no simple matter. Since there were no pathologists in those days, the physician not only had to provide continuous care during the patient's lifetime, but he also had to arrange for, and perform, the autopsy; he then had to gather all that he had seen and learned and prepare it for publication.

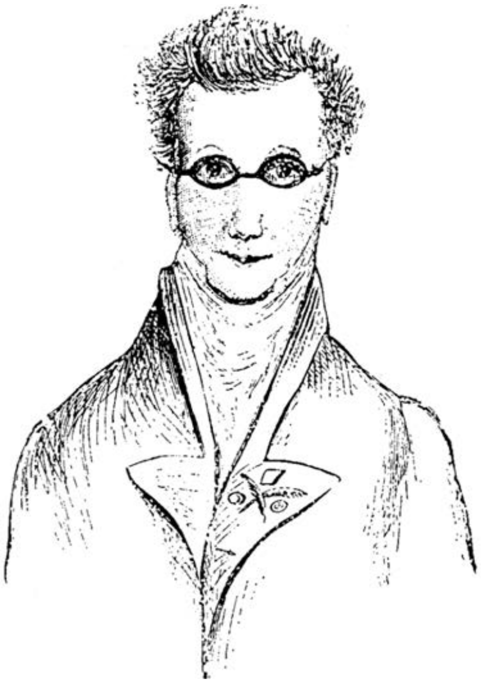

Figure 1-15 Rene T.H. Laënnec (1781–1826). *(Drawn from life in 1825 by Charles James Blasius Williams (1805–1889) and reproduced in his autobiography, Memoirs of Life and Work, London: Smith, Elder & Co; 1884.)*

In 1819, two years after the invention of the stethoscope, Laënnec published his famous monograph, *De l'Auscultation médiate*, which drew lessons from carefully documented cases that were studied throughout their clinical course and at autopsy. In this work, Laënnec built upon the monumental tome of Morgagni, who, a generation before, had related the clinical features of the diseases he described to the morbid anatomy, but who had not been able to take the next step of relating the clinical course of individual patients to the anatomic findings after death.

Laënnec's monograph contains descriptions of physical signs, clinical–pathologic correlations for tuberculosis, pneumonia, bronchiectasis, emphysema, and cancer of the lung, and instructions for the treatment of these conditions. The descriptions of tuberculosis were an outstanding contribution to the field and were reported prior to Koch's discovery of the causative agent.

■ Microbiology

Tuberculosis provides a remarkably illuminating example of the impact of a novel basic science on clinical medicine.[33–35] The disease can be traced back to the ancients, who were familiar with the diverse clinical syndromes that we now take for granted as due to tuberculosis; however, they had no way to relate them to a common etiologic agent. A synthesis by Morton in 1685 of all that was then known about tuberculosis focused on cavitary lesions, emaciation ("consumption"), and the tubercle, but it was shrouded in Galenic humors. An understanding of the disease accelerated in the 18th century when clinicians, such as William Cullen, began to sort out the various syndromes relating to phthisis, including hemoptysis, empyema, catarrh, and asthma.

The tempo of discovery increased dramatically in the 19th century after the French Revolution. During the Napoleonic era, distinguished Parisian clinicians, including Bichat, Bayle, Louis, Broussais, and Laënnec, reported clinical–pathologic correlations of tuberculosis. (Notably, both Bayle and Laënnec died of tuberculosis.) However, little advance was made in understanding the pathogenesis of tuberculosis until Villemin, who, impressed by the analogy between glanders and syphilis on the one hand, and tuberculosis on the other, and the fact that two of the three diseases had been shown to be infectious in origin, undertook experiments demonstrating that tuberculosis was an infectious disease that could be transmitted from humans to animals, and from animals to animals.

Koch

In 1876, Koch was a general practitioner in the German township of Wollestein in the province of Posen, where he was responsible for the health care of 4000 inhabitants (Fig. 1-16). Between obstetrical deliveries and satisfying the medical and surgical needs of patients of all ages, he managed to conduct research on the microbial causes of communicable diseases. His laboratory was homemade—based in either the barn or his living room; his major instrument was a microscope used to examine bacteriologic and tissue specimens. In pursuing his research, he kept in mind the dictum of Jacob Henle, one of his teachers in medical school, who counseled that, "before microscopic organisms can be regarded as the cause of contagion in man, they must be found constantly in the contagious material, they must be isolated from it and their strength tested." This lesson was to become the keynote of the future "Koch postulates."

In 1876, Koch, the busy medical practitioner, sent a letter to Professor Ferdinand Cohn, director of the Botanical Institute in Breslau, indicating that he had discovered "the process of development of bacillus anthracis" and requesting permission to present his findings to Professor Cohn, "the foremost authority on bacteria." Koch had discovered the spores of anthrax bacilli. Cohn arranged for him to present his results before a room full of formidable, distinguished scientists, including Julius Cohnheim, Carl Weigert, Moritz Traube, Ludwig Lichtheim, and Leopold Auerbach. Koch's demonstration of the complete life history of the anthrax bacillus, including sporulation, was entirely convincing to these scientists. After the meeting, Cohnheim, upon his return home, announced to his colleagues, "This man has made a splendid discovery which is all the more astonishing because Koch has had no scientific connections and has worked entirely on his own initiative and has produced something absolutely complete. There is nothing more to be done. I consider this the greatest discovery in the field of bacteriology."

During the next 2 years, Koch described novel procedures for the examination, preservation, and photography of bacteria and demonstrated the role of microorganisms in traumatic infections, while continuing his dual existence as a country doctor and an independent investigator. In 1880, Cohn and Cohnheim arranged for him to move to Berlin as a member of the Imperial Sanitary Commission. The move freed more time for research. By 1881, he made another breakthrough—the pour-plate method for isolating pure cultures. The opportunity that this technique afforded to produce transparent solid media, coupled with Koch's invention of new staining methods, paved the way for him to tackle the microbial cause of tuberculosis.

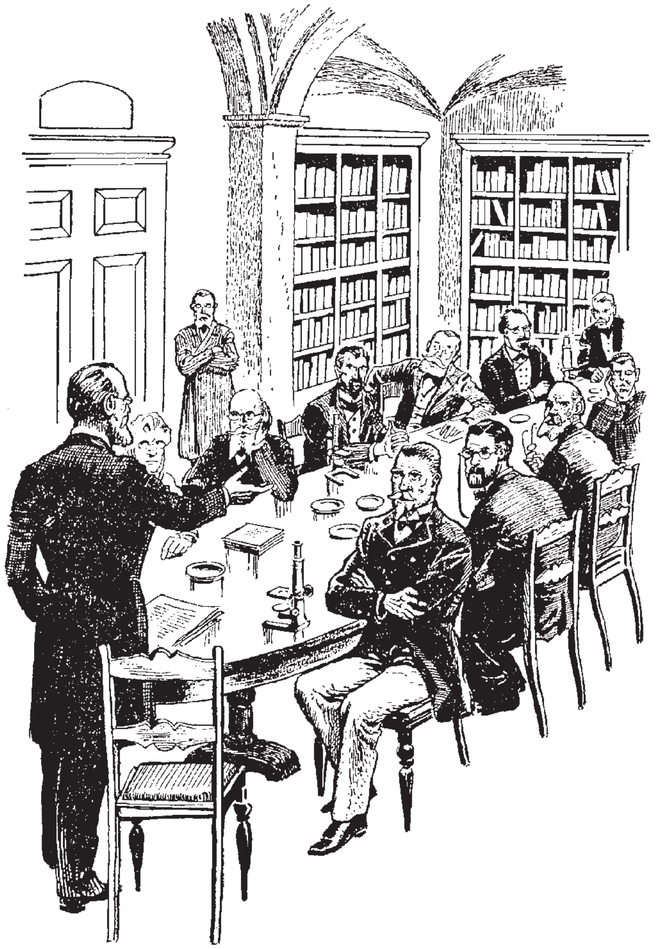

Figure 1-16 Robert Koch (1843–1910), announcing his discovery of the tubercle bacillus as the cause of tuberculosis, Berlin, March 28, 1882. *(Reproduced with permission from Knight D: Robert Koch: Founder of Bacteriology. New York, NY: Franklin Watts, Inc; 1961.)*

Koch's scientific approach, which has been immortalized as "Koch postulates," consisted of four essential steps: (1) To prove that a microbe is the cause of a disease, it must be present in all cases of the disease. (Koch showed this for the tubercle bacillus using methylene blue and a counter stain.) (2) The microbe must be grown outside of the body in pure culture. (Koch devised blood-serum jelly as a culture medium for the slow-growing tubercle bacillus.) (3) The pure culture must be capable of causing the disease in healthy animals. (Koch proved this initially by inoculation and, subsequently, by allowing animals to breathe contaminated air.) (4) The same microbe must then be isolated from the inoculated (infected) animal and grown outside of the body in pure culture.

Koch's discovery of the tubercle bacillus and its modes of transmission revolutionized the treatment of tuberculosis. Before the discovery, tubercular patients were treated in sanitaria, which offered fresh air and altitude. Those who ran the sanitaria did not know that tuberculosis was a contagious disease: Sanitation was unregulated, and neither sterilization nor fumigation was practiced; diagnostic capabilities were limited. Koch's discovery of the tubercle bacillus revolutionized therapy. For the rest of his life, while pursuing the causes of other diseases around the world—rinderpest in South Africa, Texas fever, tropical malaria, blackwater fever, and bubonic

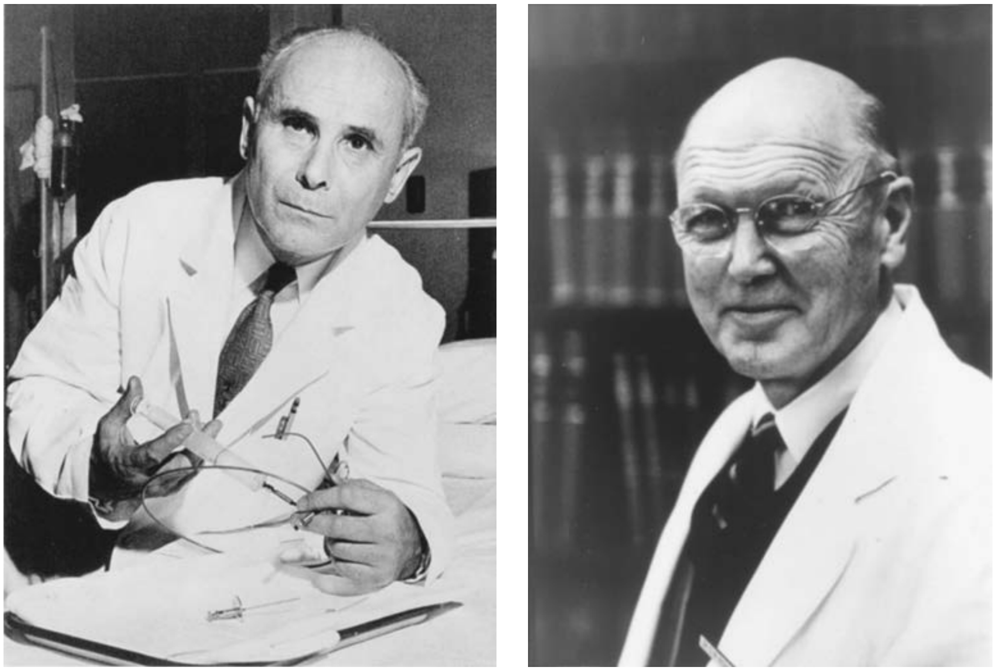

Figure 1-17 André Frederic Cournand (1895–1988) and Dickinson W. Richards (1895–1973). After Forssman's report of the uneventful catheterization of his own right heart, Cournand and Richards pioneered the use of cardiac catheterization for the study of the normal and the abnormal pulmonary circulation and the standardization of pulmonary function tests.

plague in Bombay—Koch maintained his interest in tuberculosis. This interest, however, led him into a major mistake—advocacy of tuberculin as a vaccine instead of as a diagnostic test. In 1905, he was awarded the Nobel Prize. On April 7, 1910, the year of his death, he delivered a final address on the epidemiology of tuberculosis before the Berlin Academy of Sciences.

■ Physiology of the Pulmonary Circulation

Starting with William Harvey,[5] studies of the pulmonary circulation have gone hand in hand with advances in pulmonary physiology and medicine. For many years, research on the pulmonary circulation was confined to animal experimentation. A giant step forward was made with the introduction of cardiac catheterization in humans.

Accurate measurement of pulmonary blood flow is a sine qua non for assessing pulmonary and cardiac performance in health and disease. The use of nitrous oxide in humans by Krogh and Lindhard was an important beginning in this direction, but not until mixed venous blood could be sampled for application of the Fick principle could reliable determinations of pulmonary blood flow be made.

Claude Bernard in 1846, and Chauveau and Marey in 1861, had catheterized the right side of the heart in animal experiments. Whether this technique could be used safely in humans was not known until 1929, when Werner Forssmann, a young surgeon in Germany, introduced a ureteral catheter into his own right atrium. In the 1940s, Cournand, Richards, and their colleagues resorted to right heart catheterization to obtain mixed venous blood for the determination of cardiac output by application of the Fick principle (Fig. 1-17). The technique opened the way not only to the accurate determination of cardiac output, but also to exploration of the heart and lungs in a wide variety of clinical disorders.

Until 1946, when von Euler and Liljestrand reported the effects of hypoxia and hypercapnia on the pulmonary circulation in an open-chest preparation of an anesthetized cat (Fig. 1-18),[36] there was little understanding of the regulation of the pulmonary circulation. However, these studies, coupled with the proposition of local control of the pulmonary circulation by local concentrations of the respiratory gases, paved the way to understanding pulmonary hypertension and the behavior of the pulmonary circulation in normal individuals at rest, after birth, during exercise, and at altitude, and in individuals with heart or lung disease.

The interposition of the pulmonary circulation between the right and left sides of the heart is a prerequisite for gas exchange. However, it also serves a variety of other functions, for example, a mechanical role, as a filter for particulate matter in blood returning to the heart, and a metabolic role, effecting the synthesis, uptake, and breakdown of biologic compounds. Extensive studies have been

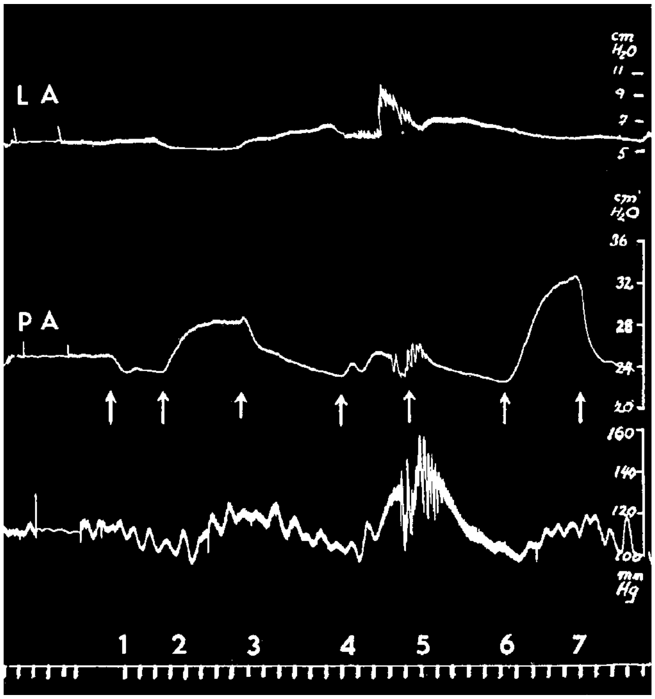

Figure 1-18 Effects of the blood gases on pulmonary arterial pressure in the open-chest cat, artificial respiration. LA, left atrial pressure; PA, pulmonary arterial pressure; lower trace, systemic arterial blood pressure. Numbers along the baseline represent the administration of test gases: 1, O_2 (from air); 2, 6.5% CO_2 in O_2; 3, O_2; 4, 18.7% CO_2 in CO_2; 5, O_2; 6, 10.5% O_2 in N_2; 7, O_2. *(Reproduced with permission from Von Euler US, Liljestrand, G: Observations on the pulmonary arterial blood pressure in the cat. Acta Physiol Scand. 1946;12(4):301–320.)*

conducted in recent decades on the nonrespiratory functions of the lungs. From these studies has emerged considerable understanding of the diverse functions served by the branching pulmonary circulation and its components, including the endothelium and smooth muscle and their interplay.

TECHNOLOGIC ADVANCES THROUGH THE EARLY 20TH CENTURY

The road to contemporary pulmonary medicine could be just as easily traced by using technologic advances as landmarks, instead of people and discoveries. For example, the introduction of the manometer for pressure recording, the use of chambers to simulate high altitude, the development of accurate blood gas analyzers, and the application of sophisticated optical systems for viewing the lumens of the airways and the inside of the chest cavity are all notable milestones. However, probably no better example exists than the discovery of radiographs and the application of this discovery to the diagnosis, prevention, and management of pulmonary tuberculosis.

Wilhelm Conrad Roentgen discovered radiographs in 1895 while experimenting with cathode ray tubes in his physics laboratory at the University of Wurzburg. Although others before him had seen radiographs as early as 1890, Roentgen was apparently the first to grasp the full significance of the discovery, and his publication, quite unpretentious, immediately attracted worldwide attention because of its prospects for the study of anatomic structures and pathologic changes.

Within 2 years after Roentgen's discovery, fluoroscopy of the chest had been introduced into clinical practice, and its value in the early detection of tuberculosis and the diagnosis of pleural effusions was appreciated. In 1901, an atlas of chest radiographs was published, and the use of chest radiography increased greatly with each subsequent improvement in hot cathode radiograph tubes and intensifying screens. The radiographic evaluation of tuberculosis was superior to physical examination for diagnosis and characterization of the disease. By 1910, all patients admitted to sanatoriums had a chest radiographic examination, and by 1917 tuberculosis was classified according to radiographic findings.

MAJOR DEVELOPMENTS SINCE THE MID-20TH CENTURY

Many notable developments have occurred over the last 60 years in pulmonary medicine and the related field of critical care. Measured against the metric of having a broad and deep impact on clinical care, several are particularly noteworthy: advances in thoracic imaging, lung transplantation, bronchoscopy and interventional bronchoscopic techniques, and advances in management of the critically ill, including those infected with COVID-19 (SARS-CoV-2).

Advances in Thoracic Imaging

Following Roentgen's discovery of the x-ray at the turn of the 20th century, another major diagnostic leap forward in pulmonary medicine occurred with development of computerized tomography (CT) in the 1960s.[37–39] In 1967, the first experimental CT scan was generated, with computer reconstruction of an image of a mouse taking 9 days to complete. The first human application was a head CT that demonstrated a brain tumor (Fig. 1-19). In 1973, Dr. Godfrey Hounsfield published a description of CT scanning in the British Journal of Medicine. Along with Dr. Allan Cormack, Hounsfield (Fig. 1-20) was awarded a Nobel Prize in 1979.

Application of CT to lung imaging arose in the mid-1970s; high-resolution techniques were developed in the 1980s. Multi-slice CT scanning now permits rapid acquisition of high-resolution images from which multiplanar reconstructions can be derived (Fig. 1-21). Elegant characterization and classification of a variety of interstitial and airway diseases is now possible using CT. In addition, when coupled with intravenous contrast injection (CT angiography),

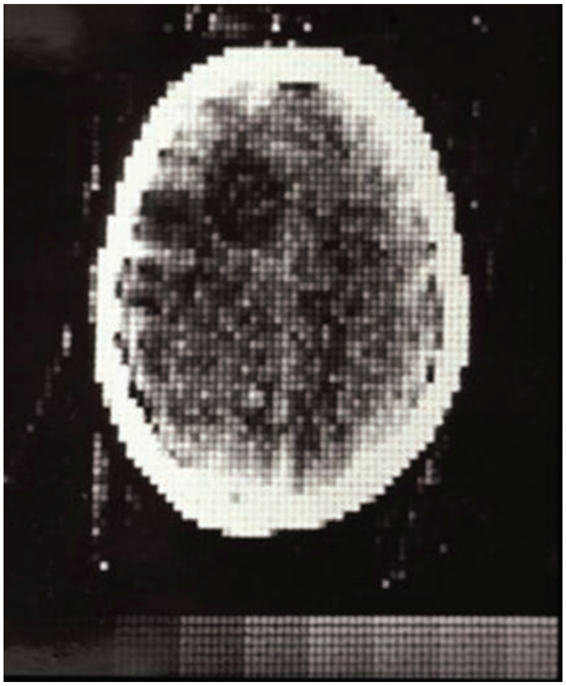

Figure 1-19 The first clinical CT scan, obtained in 1971. The grainy image shows a brain tumor in a frontal lobe (*left side* of image). Advances in image quality over the last four decades have been dramatic. *(Reproduced with permission from impactscan.org.)*

Figure 1-20 Dr. Godfrey Hounsfield, inventor of computerized tomography (CT). Along with Dr. Allan Cormack, Hounsfield was awarded a Nobel Prize in 1979. *(Reproduced with permission from Visible Proofs, National Library of Medicine, National Institutes of Health.)*

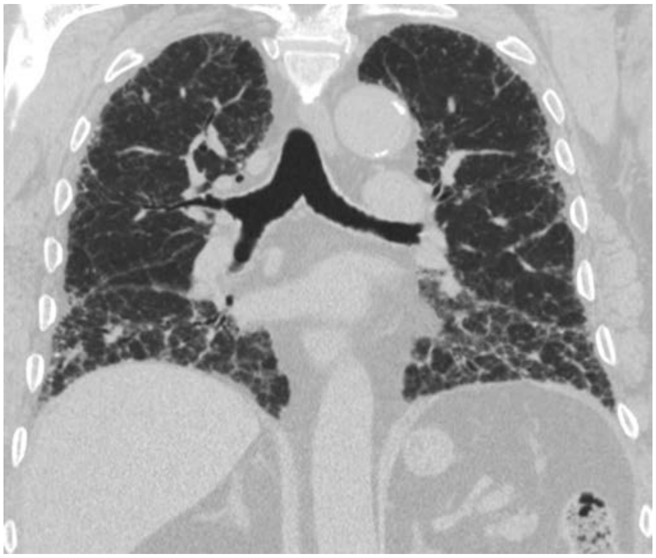

Figure 1-21 A modern-day, coronal reconstruction of the chest using CT in a patient with idiopathic pulmonary fibrosis (IPF). Current scanners are capable of rapidly generating high-resolution images from which a variety of computer-generated reconstructions can be derived. *(Reproduced with permission from Dr. Eduardo J. Mortani Barbosa, Jr.)*

rapid, high-resolution scanners provide for the very accurate diagnosis of pulmonary embolism[40] and other pulmonary vascular disorders. Advances in multi-slice techniques (e.g., 320-slice scanners) offer extremely high-quality imaging.

Aligning the anatomic detail provided by CT with functional images afforded by positron emission tomography (PET) has generated useful information on the staging and clinical assessment of bronchogenic carcinoma, particularly non–small-cell carcinoma.[41–45] Positively charged electrons (positrons), emitted from injected radionuclides, are destroyed by electrons and, in the process, produce photons that are detected and imaged by the PET scanner. Malignant cells, by virtue of having increased numbers of cell membrane–based glucose transporters compared with normal cells, accumulate greater levels of the radionuclide, ^{18}F-fluorodeoxyglucose (F-FDG), which cannot be metabolized further and is trapped within the cells. The tracer-enriched collection of malignant cells stands out against the background of normal tissue. Coupling of the PET-based and CT images provides precise localization of the area of abnormality (Fig. 1-22). PET/CT imaging has been used to evaluate solitary pulmonary nodules, assess local extent of disease (particularly mediastinal and pleural involvement) in lung cancer, and evaluate distant anatomic sites for metastatic disease.

■ Lung Transplantation

Following on the heels of pioneering animal experimentation conducted by Vladimir Demikhov,[46] the first reported human lung transplantation was conducted by Dr. James Hardy and colleagues in 1963.[47,48] However, it was not until the 1980s that clinically meaningful outcomes were achieved by Dr. Joel Cooper and colleagues with single-lung[49] and bilateral-lung[50] transplantation.

Since the advent of lung transplantation, approximately 70,000 procedures have been performed worldwide. Survival of recipients has improved from 4.0 years in the late 1980s and early 1990s to 5.8 years in the last decade. Contemporary, overall survival rates are 85% at 1 year and 59% at 5 years.[51,52] Lung transplantation is associated with improvements in lung function, exercise tolerance, and hemodynamic parameters. Currently, the primary diagnoses for which lung transplantation is most commonly conducted include idiopathic pulmonary fibrosis (IPF), chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), and other disorders, including alpha-1-antitrypsin deficiency, sarcoidosis, non-CF bronchiectasis, lymphangioleiomyomatosis (LAM), and primary pulmonary hypertension.[53,54]

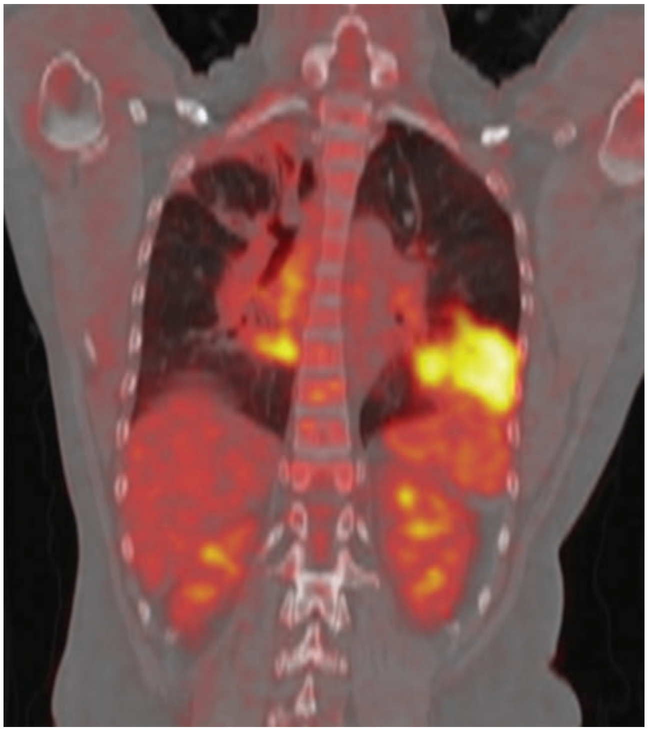

Figure 1-22 A coronal PET/CT image demonstrating metastatic lung cancer, evident as bright areas (in *yellow*) at the left base and the right hilum. The PET and CT images are aligned ("in register") to create precise anatomic localization of the heightened metabolic activity noted in the PET image. *(Reproduced with permission from Dr. Eduardo J. Mortani Barbosa, Jr.)*

Despite tremendous advances in the field, complications of lung transplantation are common and include primary graft dysfunction (noncardiogenic pulmonary edema without other apparent cause occurring in the first 72 hours following transplantation); bronchial stenosis developing at the anastomotic site; a broad array of infectious complications, including CMV infection; acute rejection (occurring in over one-third of recipients); and chronic allograft dysfunction due to bronchiolitis obliterans.[53]

Improved surgical techniques in lung transplantation have been important. However, critical to advances in solid organ transplantation, including lung transplantation, has been development of effective immunosuppressive regimens. The earliest regimens included a limited repertoire of drugs, for example, corticosteroids and azathioprine. Development of calcineurin inhibitors, including cyclosporine in 1977 and tacrolimus in 1983, substantially advanced the field.[55]

While technical and pharmacologic advances in lung transplantation afford many patients with advanced lung disease improved quality of life, a limited supply of suitable donor organs persists. Various approaches have been employed in an attempt to ameliorate the continuous shortage. In addition to obtaining organs from brain-dead donors as the primary source, more recently, many transplant programs have embarked on the somewhat controversial program of donation after cardiac death (DCD) or donation from "non–heart-beating donors," who undergo controlled withdrawal of life support in an operating room. In addition, new technologic developments in organ "reconditioning" offer hope for enlarging the supply of transplantable lungs.[56–58]

Figure 1-23 Gustav Killian (1860–1921), the father of bronchoscopy. *(Reproduced with permission from Klaus D. Peter, Wiehl, Germany. Released to the public domain, via Wikimedia Commons.)*

Bronchoscopy and Interventional Bronchoscopic Techniques

Application of bronchoscopic techniques, both rigid and flexible, has revolutionized the field of pulmonary medicine, from both diagnostic and interventional perspectives. Credit for invention of the rigid bronchoscope is given to Gustav Killian (Fig. 1-23) in Germany in the late 19th century;[59] in the United States, the field of rigid bronchoscopy was pioneered by Chevalier Jackson in Philadelphia (Fig. 1-24).[60] The next major wave in bronchoscopy arose with development of the flexible fiberoptic technique by Shigeto Ikeda in Japan.[61,62] Since then, significant advances in optics, digital technology, and a variety of interventional techniques, including those based on the fiberoptic method, have been reported.

Figure 1-24 Chevalier Jackson (1865–1958), a pioneer in American bronchoesophagology. *(Reproduced with permission from Thomas Jefferson University.)*

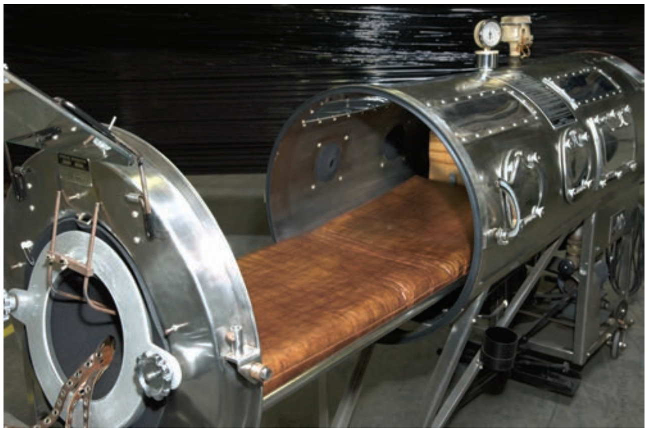

Figure 1-25 An "iron lung." The patient was placed in the hollow cylinder before the device was sealed, with his or her head protruding from one end. *(Reproduced with permission from CDC/GHO/Mary Hilpertshauser. Photo contributor: Jim Gathany.)*

Advances in Critical Care

In parallel with the previously noted advances in imaging, transplantation, and bronchoscopy, significant progress in the management of critically ill patients has occurred over the last several decades. One of the most notable is application of mechanical ventilation.[63–65]

The era of the "iron lung," the first widely used negative pressure ventilator, dates back to 1928 (Fig. 1-25).[66–68] Restricted access to the patient was a major limitation to use of the device. The advent of positive pressure ventilators, dramatically evident during the polio epidemic in Copenhagen in 1952, ushered in the "modern" era of mechanical ventilation.[69] Indeed, the clustering of paralyzed patients needing ventilatory support paved the way for development of medical intensive care units. Subsequent invention of the Bennett valve, a result of efforts to establish a means of facilitating high-altitude flight for military purposes, further enhanced clinical use of positive pressure ventilation.[70–73] Many additional refinements in mechanical ventilation, including microprocessor-controlled functions, have evolved over the last quarter century. One noteworthy development in the field deserves special consideration: use of the "low-stretch protocol."

Based on recognition that application of traditionally used tidal volumes of 10 to 15 mL/kg body weight may cause stretch-induced injury in patients with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS), a multicenter prospective trial was undertaken to address whether use of smaller tidal volumes (6 mL/kg), that is, a "low-stretch protocol," would improve outcomes. Indeed, in a landmark study published in 2000, an approximate 25% reduction in mortality using a low-stretch protocol was demonstrated.[74] Additional refinements, including use of higher levels of positive end-expiratory pressure (PEEP)[75] and the so-called "lung recruitment maneuvers"[76] have been added to the contemporary ventilator management scheme for these patients.

In addition to advances in mechanical ventilation, other notable recent refinements in critical care include recognition of the value of venous thromboembolism prophylaxis, prophylaxis against gastrointestinal bleeding, semierect patient positioning to minimize aspiration risk, good (but not excessive) glycemic control, application of spontaneous breathing trials and sedation interruption, and early patient mobilization. However, one particular development warrants special mention: use of early goal-directed therapy (EGDT) in sepsis.

Sepsis is a severe, systemic response to infection and is associated with high mortality. A reflection of the systemic inflammatory response syndrome (SIRS), sepsis may progress to severe sepsis (end-organ dysfunction in the setting of documented or suspected infection) or septic shock (severe sepsis with hypotension unresponsive to intravenous fluid administration). An important study published in 2000 addressed the value of EGDT in the management of septic patients. Such therapy focuses on early and aggressive fluid administration titrated to a goal central venous pressure (CVP), mean arterial blood pressure (MAP), and target central venous oxygen saturation (Scv_{O2}), and incorporates use of vasoactive agents and transfusion of packed red blood cells as necessary. Application of EGDT has been shown to reduce mortality by as much as one-third[77] and constitutes one of the cornerstones of management of critically ill patients with sepsis, as comprehensively discussed in the "Surviving Sepsis Campaign Guidelines for Management of Severe Sepsis and Septic Shock."[78]

Acute Lung Injury Related to COVID-19

In late 2019, a cluster of cases of pneumonia due to a novel coronavirus emanating from Wuhan, China, was reported.[79] The World Health Organization designated the disease as COVID-19, the causative organism of which is SARS-CoV-2 (Fig. 1-26). We now know that the major morbidity and mortality due to this infection is acute viral pneumonia that may evolve to ARDS.[80,81]

The pandemic has stimulated rapid evaluation of a variety of modalities related to management of the critically ill patient with diffuse lung injury, including prone positioning,[82,83] use of high-flow oxygen therapy and noninvasive mechanical ventilation prior to consideration of intubation, use of adjunctive agents, including corticosteroids,[84] and an alternative to a low-stretch ventilator protocol, based on data suggesting that the disturbed lung mechanics in COVID-19-related ARDS are different from those of other causes of ARDS.[85,86]

The social and economic consequences of COVID-19 pandemic have been extraordinary. With well over 250 million infections and more than 5 million deaths worldwide, the impact of the pandemic has triggered debate over the preparedness of nations globally for dealing with future pandemics. As the world struggles with containing COVID-19, attention has been intensely focused on development of effective vaccines and therapeutics.

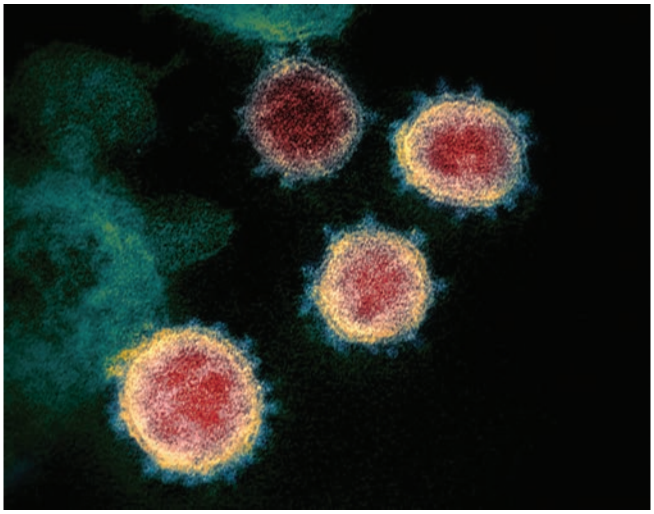

Figure 1-26 Transmission electron microscope image of SARS-CoV-2, the virus that causes COVID-19. The image shows virus particles emerging from laboratory-cultured cells. Spikes on the surface of the virus, appearing as a crown, account for the name, "coronavirus." *(Reproduced with permission from NIH Research Matters: Novel coronavirus structure reveals targets for vaccines and treatments. Bethesda, MD: U.S. Department of Health & Human Services; March 2020.)*

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PART 2

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CHAPTER 2

Functional Design of the Human Lung for Gas Exchange*

Matthias Ochs

INTRODUCTION

At the end of a deep breath, about 80% of the lung volume is air, 10% is blood, and only the remaining 10% is tissue. Because this small mass of tissue is spread over an enormous area—nearly the size of a tennis court—the tissue framework of the lung must be extraordinarily delicate. It is indeed remarkable that the substance of the lung manages to maintain its integrity in the face of the multitude of insults that inevitably accompany a lifetime of exposure to ambient air and the complex necessity of keeping air and blood in intimate contact, but separate, for the sake of gas exchange.

Part of this success is undoubtedly attributable to the unique design of the lung, which ensures mechanical stability as well as nearly optimal conditions for the performance of the lung's primary function: to supply the blood with an adequate amount of oxygen even when the body's demands for oxygen are particularly high, as during heavy work.

THE LUNG AS AN ORGAN

At total lung capacity, the lung fills the entire chest cavity and can reach a volume, in the adult human, of some 5 to 6 L, largely depending on body size. Upon expiration, the lung retracts, most conspicuously from the lower parts of the pleural cavity, the posterior bottom edge of the lung moving upward by some 4 to 6 cm. This preferential lifting of the bottom edge is caused by retraction of the tissue throughout the entire lung, the surfaces of which are freely movable within the thoracic cavity.

The structural background for this mobility of a healthy lung is the formation, during morphogenesis, of a serosal space that is lined on the interior of the chest wall and on the lung surface by a serosa, the parietal and visceral pleurae, respectively (Fig. 2-1). However, this serosal space is minimal, since the visceral pleura is closely apposed to the parietal pleura, with only a thin film of serous fluid intercalated as a lubricant between the two surfaces.[1] Both pleural surfaces are lined by a squamous epithelial layer, often called *mesothelium* (due to its mesodermal origin), whose surface is richly endowed with long microvilli. The apical microvilli increase the surface area available, suggesting that pleural mesothelial cells are capable of participating in active transserosal transport of solutes. The total volume of pleural fluid is about 15 to 20 mL, with approximately 1700 cells/mm^3 (75% macrophages, 23% lymphocytes, 1% mesothelial cells). The volume and composition of the pleural fluid have to be tightly controlled to ensure an efficient mechanical coupling between chest wall and lung. Pleural fluid originates from pleural capillaries through microvascular filtration. Drainage occurs partly via lymphatic stomata in the parietal pleura. Transcytosis through mesothelial cells in both directions represents another mechanism involved in pleural fluid homeostasis.[2–6]

The connective tissue of the visceral pleura consists of three layers. A superficial layer of predominantly elastic fibers follows the mesothelium, thereby forming an elastic "bag" that enwraps each lobe. A deep sheet of fine fibers follows the outline of alveoli and extends into the depth of the lung. Between these sheets lies a bed of loose connective tissue, containing free cells (histiocytes, plasma cells, and mast cells), that is often close to lymphatics and systemic arterial branches from the bronchial arteries.

The lung is maintained in a stable position within the chest by the hilum, where airways and blood vessels enter from the mediastinum, and by the pulmonary ligament, a long, narrow band of attachment between visceral and mediastinal pleura that extends downward from the hilum. Because of these attachments, a pneumothorax causes the lung to retract and form a lump of tissue that is attached to the mediastinal wall of the thoracic cavity.

The shape of the lung is congruent with that of the fully expanded pleural cavity. This shape is preformed in lung tissue and is hence also evident if an excised lung is inflated, revealing its three faces: the convex thoracic face apposed to the rib cage, the concave diaphragmatic face modeled by the diaphragmatic dome, and the mediastinal face, on which the contours of the heart are impressed beneath the hilum.

As the lung retracts during deflation, the acute edges between the thoracic face and the diaphragmatic and (anterior) mediastinal faces of the lung withdraw; the thoracic and diaphragmatic leaflets

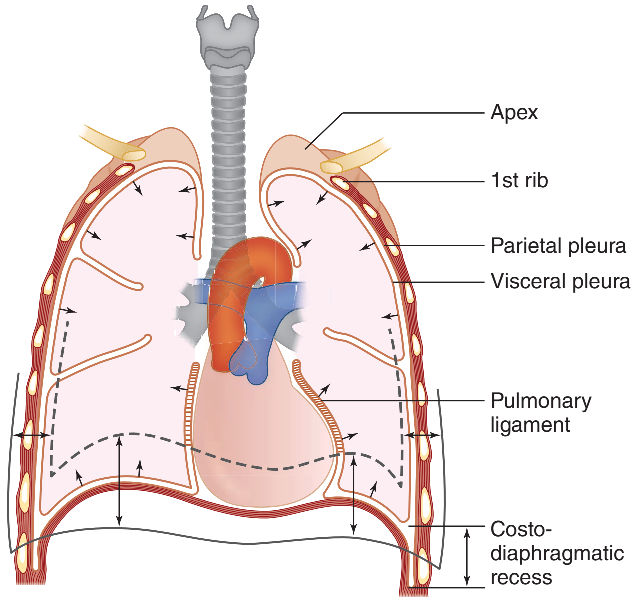

Figure 2-1 Frontal section of chest and lung showing pleural space. *Single arrows* indicate retractive force. *Double arrows* show the excursion of the lung bases and periphery between deep inspiration and expiration.

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*The author would like to acknowledge the major contribution of Ewald R. Weibel (1929–2019) to previous versions of this chapter.

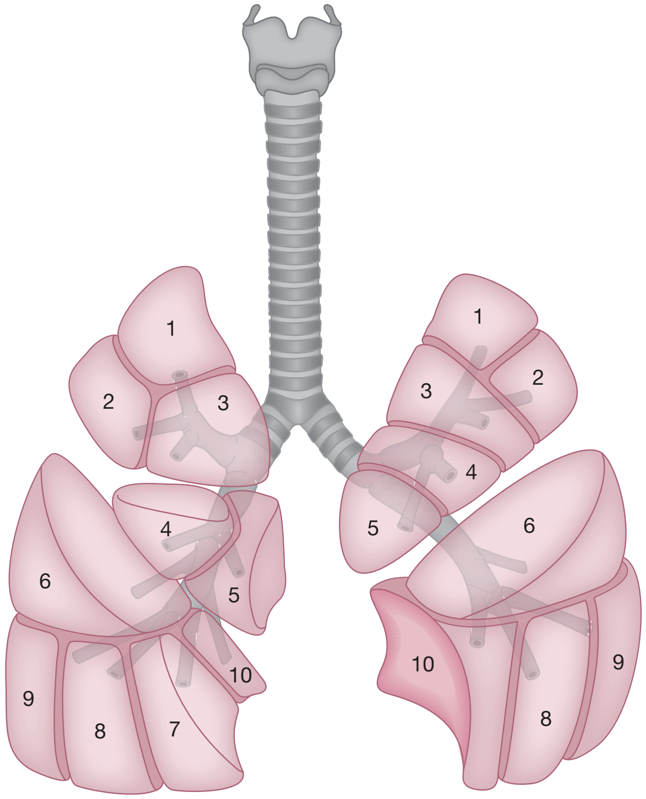

Figure 2-2 Bronchopulmonary segments of human lung. Left and right upper lobes: (1) apical, (2) posterior, (3) anterior, (4) superior lingular, and (5) inferior lingular segments. Right middle lobe: (4) lateral and (5) medial segments. Lower lobes (6): superior (apical), (7) medial–basal, (8) anterior–basal, (9) lateral–basal, and (10) posterior–basal segments. The medial–basal segment (7) is absent in the left lung. (Note: The lungs are represented as turned inward slightly to display part of the lateral face.)

of the parietal pleura become apposed, thereby forming a costodiaphragmatic recess on each side (Fig. 2-1). Similarly, as the ventral edge of the lung retracts, the costal and mediastinal pleurae form a recess on each side, corresponding topographically to the borders of the sternum.

The port through which airways and blood vessels enter the lung is the hilum, that is, the attachment of lung tissue to the mediastinum (Fig. 2-1). The airways reach the two hili by the mainstem, or principal, bronchi (Figs. 2-1 and 2-2). The left mainstem bronchus is longer than the right because it must pass under the aortic arch before it reaches the lung. The two principal bronchi course downward and begin to divide sequentially shortly after entering the lung, first releasing the lobar bronchus to the upper lobe (Fig. 2-2). Since a middle lobe is formed only on the right side, there is no middle lobe bronchus on the left; instead, the corresponding parts form the lingula, which receives its airways from the superior bronchus of the upper lobe (Fig. 2-2). The last branch of the stem bronchus goes to the lower lobe.

The branching pattern of the human bronchial tree and of the pulmonary artery and veins are shown in a resin cast in Fig. 2-3. The pulmonary artery joins the bronchi while still in the mediastinum (Fig. 2-4A); its trunk lies to the left of the ascending aorta, and the right pulmonary artery turns dorsally to course between ascending aorta and right principal bronchus. In the hilum, the right pulmonary artery lies anterior to the right principal bronchus; the left pulmonary artery, however, "rides" on the principal bronchus and crosses over the superior lobar bronchus to the posterior side. From there on, the pulmonary artery branches in parallel with the bronchi; characteristically, each bronchus is associated with one closely apposed pulmonary artery branch, and this relationship is strictly maintained to the periphery, that is to the respiratory bronchioles.

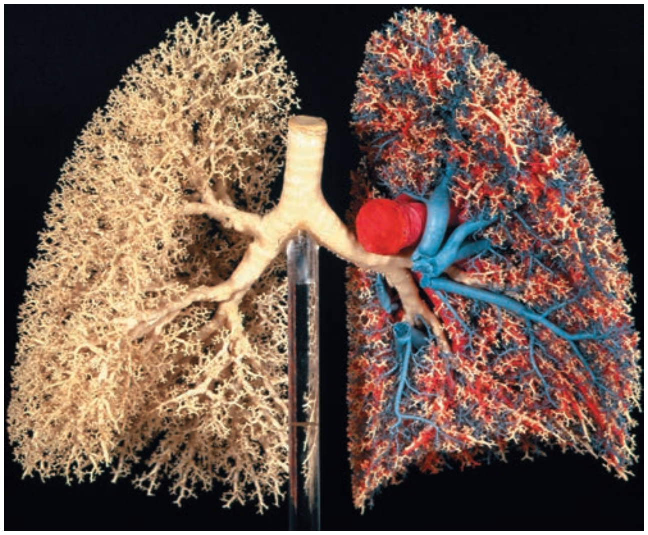

Figure 2-3 A resin cast of the human airway tree shows the dichotomous branching of the bronchi from the trachea and the systematic reduction of airway diameter and length with progressive branching. In the left lung the pulmonary arteries *(red)* and veins *(blue)* also are shown.

In contrast, the pulmonary veins (Fig. 2-4B) follow a course independent of the bronchial tree; rather, they lie about midway between two pairs of bronchi and arteries; this position is maintained to the periphery of the airway system. In the hilum, these veins are collected into at least two main veins on either side, which lead into the left atrium located at the back of the heart.

The airways systematically branch over an average of 23 generations of dichotomous branching,[7,8] ending eventually in a blind sac (Fig. 2-5). The last nine generations of these airways are connected to tightly packed alveoli, airway chambers in which gas exchange takes place, whereas the central airways serve the function of conducting the air to the gas-exchange parenchyma. In such a system of sequential branching, the unit of lung parenchyma could be defined according to the portion of parenchyma that is supplied by a particular branch of the bronchial tree, and it is possible to conceive of as many types of units as there are generations unless clear definitions for such units are proposed. However, two units appear to be natural:

1. The lobes, which are demarcated by a more or less complete lining of pleura. There are three lobes on the right (superior, middle, and inferior lobes), and two on the left (superior and inferior lobes).
2. The acinus, which is defined as the parenchymal unit in which all airways have alveoli attached to their wall and thus participate in gas exchange. Along the airway tree, the acinus begins with a transitional bronchiole (Fig. 2-5).[9,10]

Since all other units are somewhat arbitrarily defined, it is not surprising that some ambiguity exists in the literature about their meanings. Nonetheless, a certain convention has been adopted with respect to the following:

1. The lung segments, which are considered as the first subdivisions of lobes. Figure 2-2 shows the location and distribution of the segments to the various lobes. The symmetry is imperfect because on the left the two segments corresponding to the right middle lobe are incorporated into the superior lobe as the lingula (segments 4 and 5) and because the medial–basal segment of the lower lobe is generally missing on the left (segment 7).

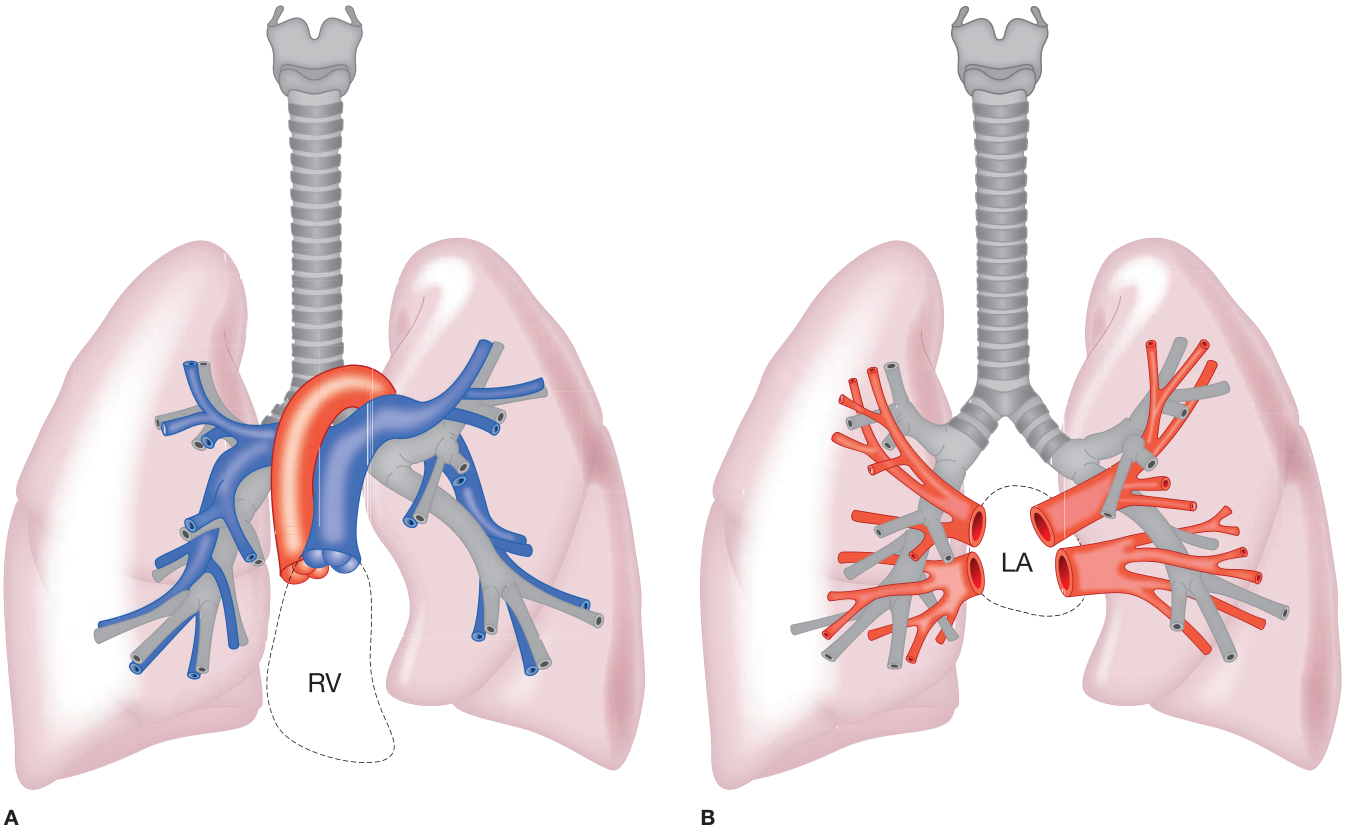

Figure 2-4 Schematic diagrams of the relation of the main branches of pulmonary arteries (**A**) and pulmonary veins (**B**) to the bronchial tree. The arteries follow the airways. Two mainstems of pulmonary vein penetrate independently into the lung on each side. LA, left atrium; RV, right ventricle.

2. The secondary lobule, an old anatomic unit. It was introduced in the 19th century because "lobules" of about 1 cm^3 are visible on the surface of the lung. These lobules are delineated by connective tissue septa that are connected to the pleura. The secondary lobule is difficult to define in terms of the bronchial tree, but it does seem to comprise about a dozen acini. With reference to radiologic imaging techniques, secondary lobules are supplied by airway branches that are about 1 mm in diameter.

The pulmonary blood vessels show a characteristic relationship to these units (Figs. 2-3 and 2-4). The pulmonary arteries, following the airways, course through the centers of the units and finally fan out into the capillaries located in the delicate alveolar septa of lung parenchyma. In contrast, the veins lie in the boundary between units and collect the blood from at least two or three adjacent units. This arrangement applies to acini and secondary lobules as well as to lung segments.

Therefore, it is evident that the units of lung parenchyma are bronchoarterial units, which share their venous drainage with neighboring units. This architecture has important functional and practical consequences. Except for the lobes, none of the units is separated from each other by complete connective tissue septa.

ORGANIZATION OF LUNG TISSUE

Lung tissue is a complex structure. Its individual components are discussed below.

Basic Structural Elements

While looking at the tissue organization of the lung, we must first consider that the airways and the blood vessels each have their own lining by an uninterrupted cell layer. These layers extend all the way out to the gas-exchange region, but they show different properties in conducting as compared with respiratory structures. Likewise, the connective tissue forms a continuum throughout the lung all the way out to the pleura, but it, too, will be differently organized in the different functional zones; whereas it is reduced to a minimum in the alveolar walls, it contributes a number of different ancillary structures to the wall of conducting airways and blood vessels, such as smooth muscle sheaths or cartilage. This connective tissue space also houses the nutritive vessels and nerves as well as the elaborate defense system related to lymphatic vessels. In the gas-exchange region, however, very few of these accessory structures are found.

The complexity of lung structure is also reflected at the cell biologic level. There is no such thing as a standard "lung cell." Instead, based on morphologic criteria, some 40 different cell types, which are highly specialized, both structurally and functionally, can be found in the lung.[11–13]

A word of caution is also necessary with respect to the extrapolation of structural findings in experimental animals, especially rodents, to the human lung. Noteworthy species differences include the bronchial circulation, the presence of respiratory bronchioles, the ultrastructural composition and distribution of nonciliated bronchiolar epithelial cells (club cells) and their protein expression pattern, the frequency of certain cell types like alveolar brush cells and lipid-containing interstitial cells (lipofibroblasts), and the ultrastructural organization of lamellar bodies in type II alveolar epithelial cells. All these structural elements have features characteristic of the human lung that are not found in rodents.[14]

Wall Structure of Conducting Airways

The wall of conducting airways consists of three major components (Figs. 2-6 and 2-7): (1) a mucosa composed of an epithelial and a connective tissue lamina; (2) a smooth muscle sleeve; and (3) an enveloping connective tissue tube partly provided with cartilage.[15]

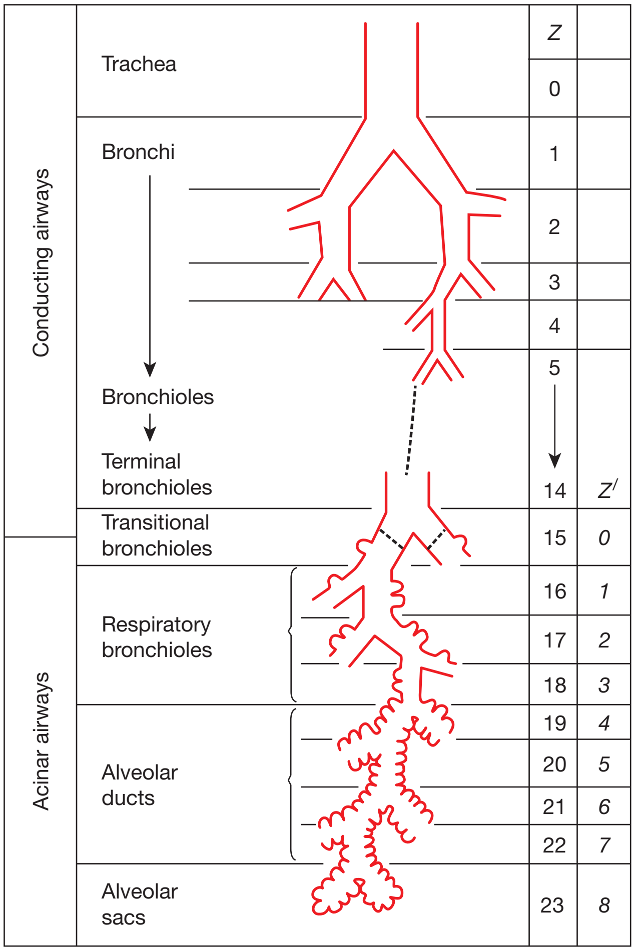
Conducting airways
Acinar airways
Trachea
Bronchi
Bronchioles
Terminal bronchioles
Transitional bronchioles
Respiratory bronchioles
Alveolar ducts
Alveolar sacs
Z
0
1
2
3
4
5
14
15
16
17
18
19
20
21
22
23
Z'
0
1
2
3
4
5
6
7
8

Figure 2-5 Model of airway branching in human lung by regularized dichotomy from trachea (generation z = 0) to alveolar ducts and sacs (generations 19–23). The first 14 generations are purely conducting; transitional airways (generation 15) lead into the acinar airways with alveoli that branch over 8 generations (z′). *(Modified with permission from Weibel ER: Morphometry of the Human Lung. Heidelberg: Springer-Verlag; 1963.)*

Epithelium

Although derived from the same anlage,[16,17] the airway epithelium modifies its differentiation characteristics as we proceed from large bronchi over bronchioles to the alveolar region (Fig. 2-6). A simple epithelium exists as a lining of smaller bronchioles: As we move upward toward larger bronchi, the epithelium becomes higher and some basal cells appear, making the epithelium pseudostratified. At the point of transition into the gas-exchange region—that is, at the entrance into the complex of alveoli—the epithelium abruptly becomes extremely thin. Figure 2-6 also shows that the epithelium is not made of a uniform cell population but that it is, at each level, rather a mosaic of at least two cell types, in that secretory cells as well as some rarer special cells are interspersed into the complex of lining cells.[15,18]

If we first have a closer look at the epithelium of larger conducting airways, we see that the lining cells are provided with a tuft of kinocilia at their apical cell face, whereas the secretory cells are goblet cells that produce and discharge to the surface a sticky mucus (Figs. 2-7–2-9). This mucus spreads out as a thin blanket on top of the cilia, which are embedded in a periciliary layer containing a dense network of mucins and mucopolysaccharides tethered to the cilia.[19] The mucus layer is capable of trapping dust particles that are still contained in the air entering the lung. Kinocilia (Fig. 2-10) are motile cell extensions that are known to beat rhythmically in a given direction and at a frequency of about 12 to 20 Hz.[20,21] In the airway epithelium, the cilia are oriented in such a fashion that their beat is directed outward. It is interesting that the cilia of airway epithelia develop at their tip fine claws with which they can grasp the mucus blanket in the phase of their forward beat, whereas on their return to the upright position they glide past the mucus blanket. The result of this is that the mucus blanket, together with trapped foreign material, moves outward or "up the airways" in a steady stream, a feature appropriately called the *mucociliary escalator*. Since the lining by ciliated cells is uninterrupted from the bronchioles, up the bronchi, to the trachea, this mucociliary escalator ends at the larynx, so that the normal fate of bronchial mucus is to be steadily discharged into the pharynx, whence it is swallowed, usually unnoticed. Only when an excessive amount of mucus accumulates in the trachea or in larger bronchi do we have to assist the system by coughing.

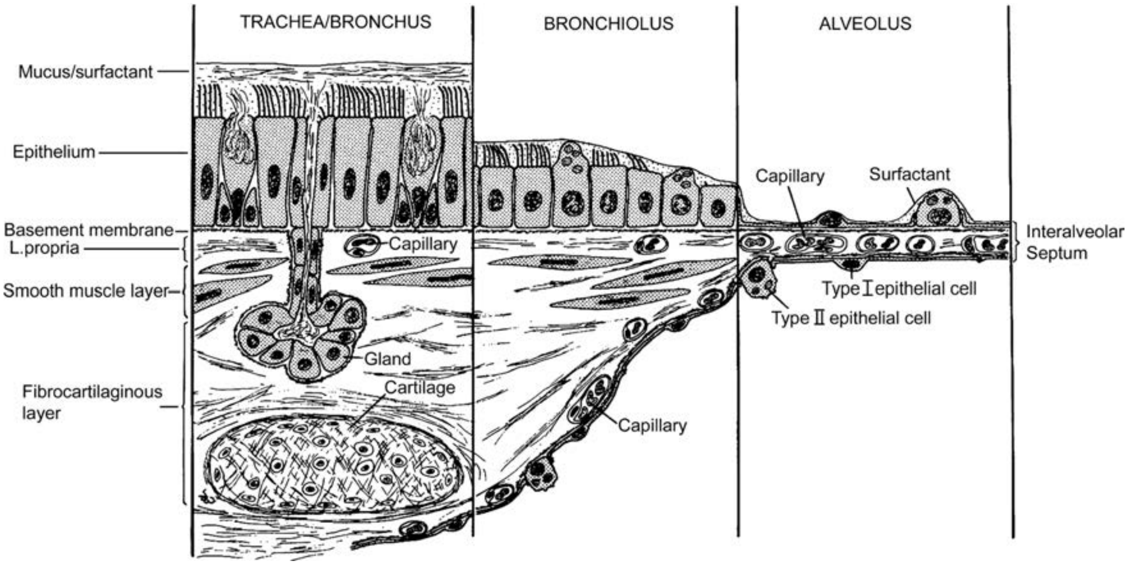
TRACHEA/BRONCHUS
BRONCHIOLUS
ALVEOLUS
Mucus/surfactant
Epithelium
Basement membrane
L.propria
Smooth muscle layer
Fibrocartilaginous layer
Capillary
Gland
Cartilage
Capillary
Capillary
Surfactant
Interalveolar Septum
Type I epithelial cell
Type II epithelial cell

Figure 2-6 Airway wall structure at the three principal levels. The epithelial layer gradually becomes reduced from pseudostratified to cuboidal and then to squamous but retains its organization as a mosaic of lining and secretory cells. The smooth muscle layer disappears in the alveoli. The fibrous layer contains cartilage only in bronchi and gradually becomes thinner as the alveolus is approached.

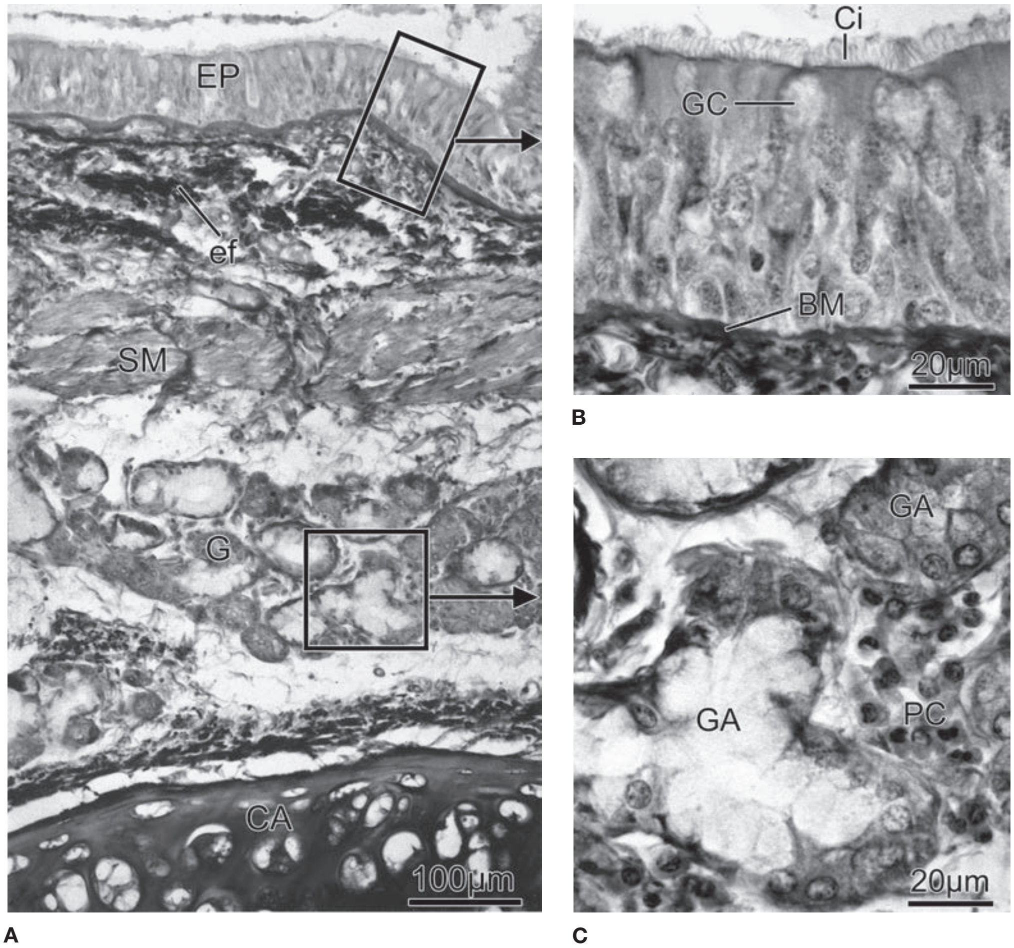

Figure 2-7 Light micrographs of bronchial wall. **A.** The layers from epithelium (EP) to cartilage (CA) with elastic fibers (ef), smooth muscle bundles (SM), and glands (G). **B.** Higher power of pseudostratified epithelium with cilia (Ci). **C.** Details of gland with acini (GA) associated with groups of plasma cells (PC). BM, basement membrane; GC, goblet cell.

The secretory cell population shows a number of specialized features. In the bronchi of all sizes and in larger bronchioles, one finds goblet cells interspersed between the ciliated cells; they form the mucus in their endoplasmic reticulum and Golgi complex, store it as droplets in their apical part, and discharge it in bulk (Figs. 2-8 and 2-9). In larger bronchi, one finds, in addition, small mucus glands located in the connective tissue; they are connected to the bronchial surface by long and narrow ducts (Figs. 2-6 and 2-7). In the normal bronchus, the glandular acini are relatively small and composed of serous and mucus cells; enlargement of the acini and a relative increase of mucus cells are characteristics of chronic bronchitis.

Finally, a special nonciliated secretory cell appears in the smaller bronchioles, the club cell (Fig. 2-11).[22,23] This cell population is very heterogeneous, thus displaying both interspecies and intraspecies variations.[24–28] In the human lung, club cells account for about 11%

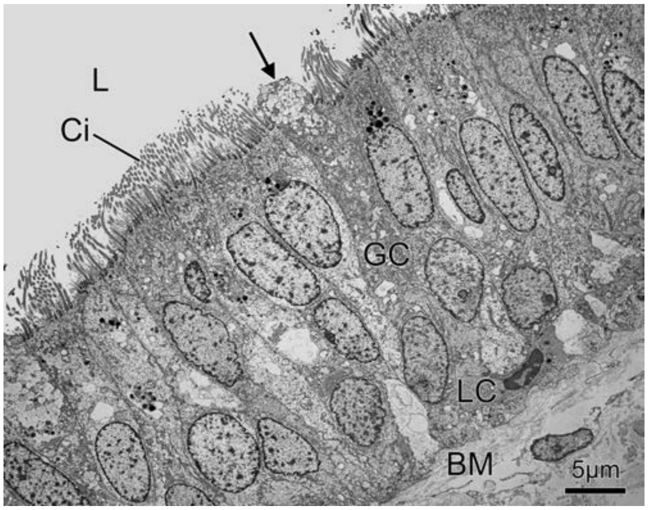

Figure 2-8 Electron micrograph of section across human bronchial epithelium made of high-columnar cells, most of which are ciliated (Ci). A goblet cell (GC) is cut lengthwise; note mucus droplets in process of accumulating at cell apex *(arrow)* and leukocyte (LC) caught in epithelium in process of diapedesis. BM, basement membrane; L, lumen.

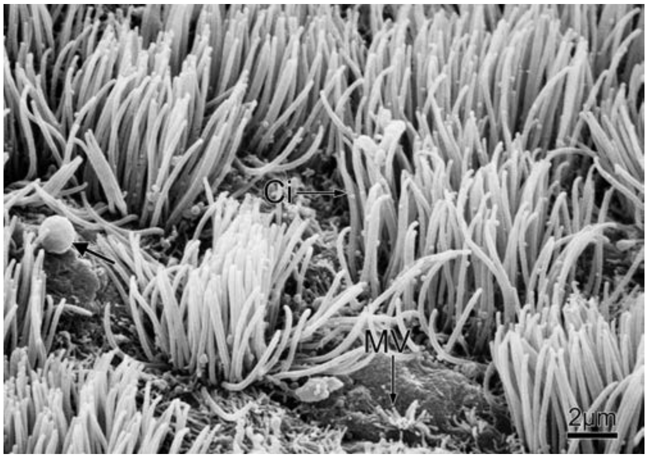

Figure 2-9 Surface view of bronchiolar epithelium shows tufts of cilia (Ci) forming on individual ciliated cells and microvilli (MV) on other cells. Note secretion droplet in process of release from goblet cell *(arrow)*.

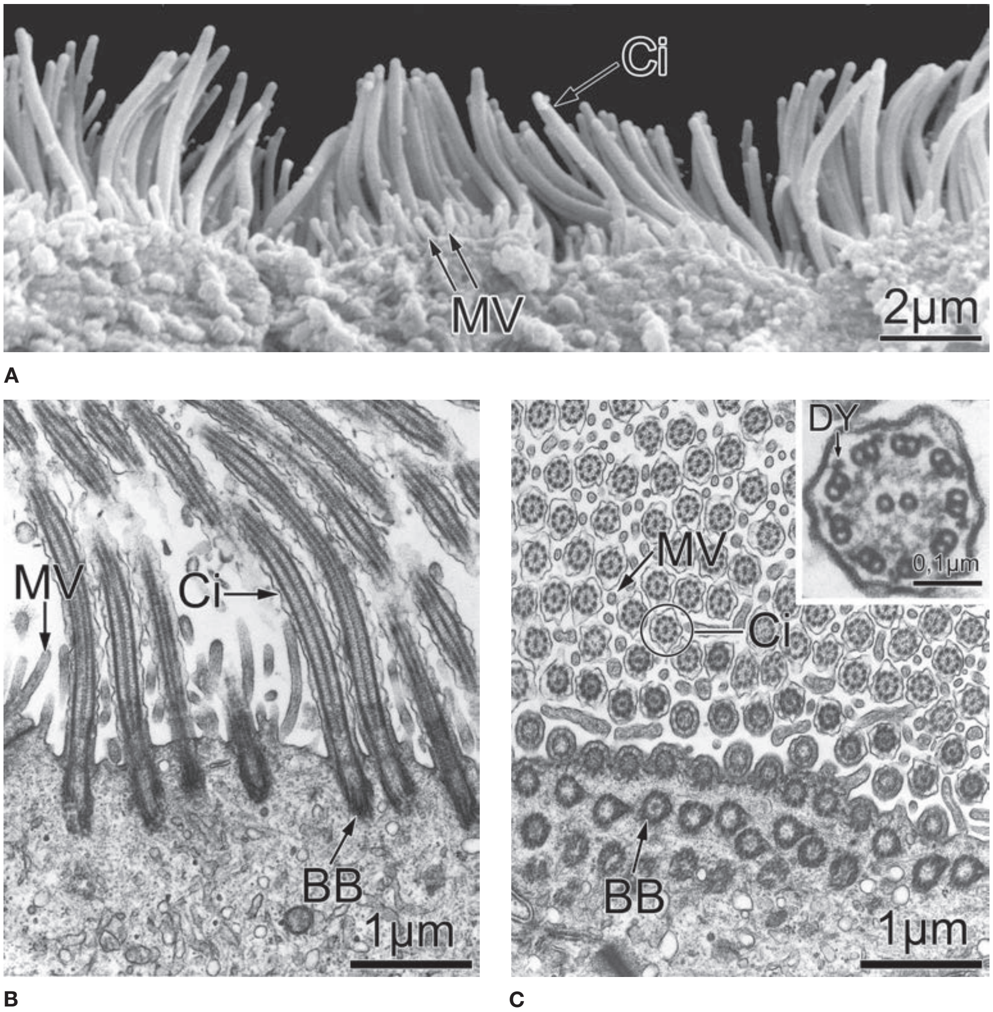

Figure 2-10 Cilia (Ci) from human bronchial epithelium seen on sections of epithelial cells in scanning electron micrograph (**A**), and on thin sections in longitudinal (**B**), and oblique cross section (**C**). They are implanted in the epithelial cell by a basal body (BB). Cross-sectioned cilium at high power (*inset*, **C**) reveals its membrane, which is enveloping a typical set of two axial tubules and nine peripheral duplex tubules with dynein arm (DY) attached. Note abundant short microvilli (MV) interspersed between cilia.

and 22% of the total epithelial cell number in terminal and respiratory bronchioles, respectively.[29] Besides the absence of cilia, club cells in conventional preparations are characterized by their dome-shaped apex that protrudes into the airway lumen. In contrast to that in rodents, where this cell is rich in smooth endoplasmic reticulum, club cells in the human lung lack significant amounts of smooth ER. They possess short lateral cytoplasmic extensions while their basal surface that rests on the basement membrane is practically free of infoldings. Membrane-bound electron-dense granules of about 500 to 600 nm diameter are present, which underlines their secretory activity. Our understanding of the functions of club cells is still incomplete. In many aspects, they appear to be functionally related to the secretory cell type of the alveoli, the type II alveolar epithelial cell; ultrastructural features and expression patterns of lung adenocarcinoma cells show characteristics of both club and type II cells. Club cell secretions add to the lining layer of the distal lung. Club cells synthesize and secrete the club cell secretory protein (CCSP),[22] which has been shown to be structurally similar to rabbit uteroglobin. The exact function of CCSP in the human lung still remains to be elucidated. CCSP levels in BAL fluid are decreased in smokers and in patients with COPD or interstitial lung diseases.[30] Animal studies suggest immunomodulatory functions for CCSP.[28] Within the lung, the club cell is the primary site of cytochrome P450 monooxygenase activity. Thus, they are heavily involved in detoxification of xenobiotics. Normal bronchiolar epithelial homeostasis is maintained by proliferation of club cells, whereas a cell population termed "variant Clara cells" or "variant CCSP-expressing cells," which is associated with neuroepithelial bodies or localized at bronchioloalveolar duct junctions, appears to act as progenitor cells for the bronchiolar epithelium under certain pathologic conditions.[28,31]

There are also some additional rarer cells. Neuroendocrine cells are capable of secreting mediators (amines and neuropeptides) into subepithelial capillaries. Prior to secretion, the bioactive substances are stored in dense-cored vesicles (Fig. 2-12). Occasionally, but only rarely in the adult human lung, these cells are organized in extensively innervated groups, and then termed "neuroepithelial bodies." Although it seems clear that neuroepithelial bodies have sensory, most likely oxygen-sensing, properties, their exact physiologic function is still poorly understood.[32–36] Another rare cell type of the airway epithelium is the brush cell (sometimes also referred to as "tuft cells"). These cells are characterized by the presence of an apical tuft of blunt, broad, and straight microvilli with root-like structures composed of filaments extending into the cytoplasm (Fig. 2-13). Glycogen granules, vesicles, and smooth endoplasmic reticulum are usually present as well. There is species variation in the occurrence of brush cells. While common in rodents (in rats even present in the proximal alveolar epithelium[37]) they are only rarely found in the human lung. Their function is only partly explored. Owing to their ultrastructure and their strategic localization in the airways and at alveolar duct bifurcations, sensory/chemoreceptor as well as sentinel/immune surveillance functions have been proposed.[38,39] Evidence suggests that brush cells "taste" the chemical composition of the airway lining fluid.[40,41] Based on single cell sequencing data, ionocytes have been identified as another rare cell type of the airway epithelium.[42,43] They express chloride channels, including cystic fibrosis transmembrane conductance regulator (CFTR).

Interstitium

The layer of connective tissue in the bronchial mucosa consists predominantly of elastic fibers that are oriented longitudinally;

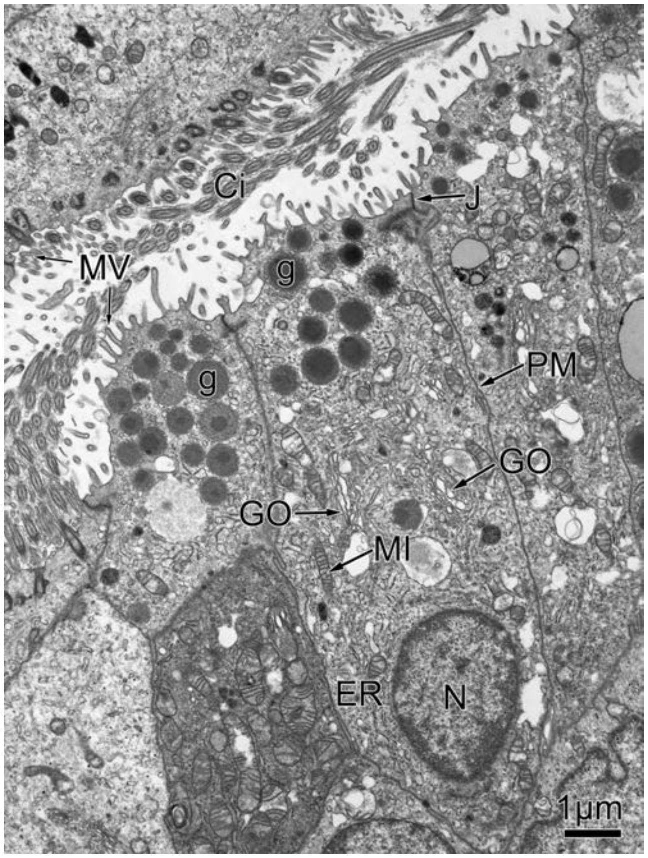

Figure 2-11 Club cells from human bronchiolar epithelium contain dense secretion granules (g) at apex. Note abundant cytoplasmic organelles such as mitochondria (MI), Golgi complex (GO), or endoplasmic reticulum (ER) as well as microvilli (MV) at surface. Cell membranes are closely apposed and form tight junctions (J) at apical edge. Ci, cilia; N, nucleus; PM, plasma membrane.

these fibers serve to maintain a smooth outline of the longitudinal profile of the bronchial lumen no matter how much the bronchi are stretched as the lungs are inflated. In this connective tissue lamina there are foci of lymphoid cells; often they form small lymphoid follicles.[44] However, bronchus-associated lymphoid tissue (BALT) is usually absent in normal adult human lungs and develops only after stimulation when inducible BALT might organize local immune responses.[45–48]

Smooth muscle bundles form a continuous sleeve in the connective tissue underlying the epithelial tube that extends from the major bronchi to the respiratory bronchioles; beyond the respiratory bronchioles, the bundles extend into the wall of alveolar ducts where the muscle fibers lie in the alveolar entrance rings. The bundles have an oblique course and encircle the mucosal tube in a crisscross pattern; hence, their contraction results primarily in a narrowing of the lumen.

In the small bronchioles there is little else to the airway wall; the smooth muscle layer is ensheathed by a layer of delicate connective tissue that is in direct contact with adjacent alveoli (Fig. 2-6). In the larger bronchioles and even more in the bronchi, the outer connective tissue sheath forms a strong layer of fibers; in the bronchi, rings or plates of cartilage are incorporated into this layer.

The wall structure in the respiratory bronchioles is identical to that of terminal bronchioles except that in some regions the cuboidal epithelium is replaced by an alveolar epithelium of squamous cells (type I cells) closely apposed to capillaries. Very often, these single alveoli constitute outpouchings in these regions; sometimes simple “respiratory patches” form in the bronchiolar wall (see below).

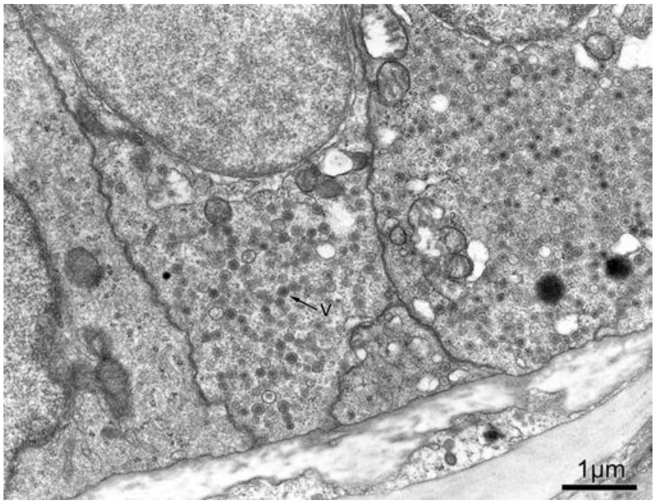

Figure 2-12 Basal part of neuroendocrine cell of human bronchiolar epithelium showing dense-cored vesicles (v). *(Reproduced with permission from Fishman A, Fisher AB: Handbook of Physiology. Section 3: The Respiratory System. vol 1. Bethesda, MD: American Physiological Society; 1985.)*

■ Wall Structure of Conducting Blood Vessels

The endothelial lining of pulmonary arteries and veins differs from that of capillaries by some site-specific structural and functional differences.[49–51] The endothelium of conducting blood vessels is thicker, and parts of its cytoplasm are richly endowed with organelles of various kinds (Fig. 2-14). Clearly, these cells are metabolically more active than those of the capillary endothelium. They are particularly rich in membrane-bound rod-shaped granules termed *Weibel–Palade bodies*,[52,53] which represent the regulated secretory organelles of endothelial cells (Fig. 2-14). The lumen of Weibel–Palade bodies

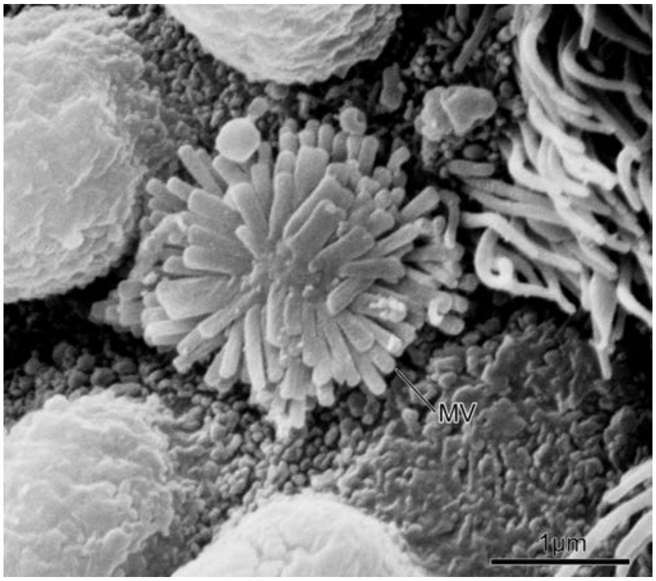

Figure 2-13 Brush cell from small bronchiole of rat lung containing broad microvilli (MV). *(Reproduced with permission from Fishman A, Fisher AB: Handbook of Physiology. Section 3: The Respiratory System. vol 1. Bethesda, MD: American Physiological Society; 1985.)*

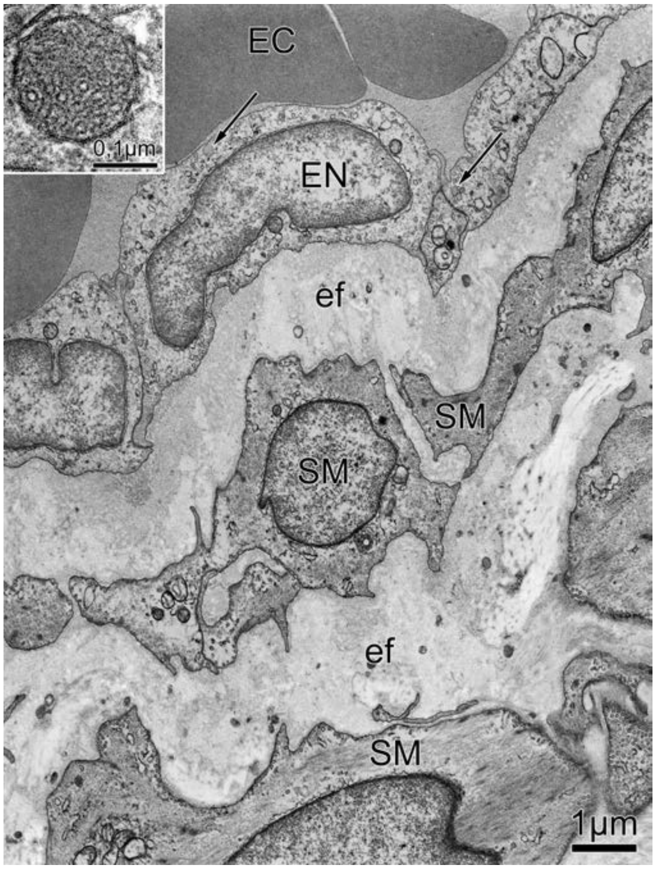

Figure 2-14 Part of wall of pulmonary artery from human lung. Endothelial cells (EN) form thick layer; their cytoplasm is rich in organelles. Specific granules of endothelium *(arrows),* a cross-section of one of which is shown at high power in the inset, are enveloped by a membrane and contain tubules. The arterial wall is of the elastic type, formed of alternating layers of smooth muscle (SM) and elastic fibers (ef). EC, erythrocyte.

is filled with longitudinally arranged tubules. These tubules represent von Willebrand factor,[54] packed in a highly organized spiral that allows rapid secretion into the blood. Other components of Weibel–Palade bodies include tissue-type plasminogen activator, endothelin 1, the leukocyte adhesion receptor P-selectin, interleukin 8, the tetraspanin CD63/LAMP-3, and the small GTPase Rab27a. Thus, Weibel–Palade bodies are actively involved in hemostasis as well as in vasoactive and inflammatory responses.[55–58]

Many of the nonrespiratory metabolic functions of the lung—particularly the transformation of certain bioactive substances, such as angiotensin and prostaglandins—are performed in endothelial cells. Caveolae (or plasmalemmal vesicles) have been implicated in these processes.[59,60] Caveolae are plasma membrane invaginations and associated vesicles with an outer diameter of about 50 to 70 nm. Depending on fixation, the shape of these invaginations appears omega- or cup-like.[61] Their structural framework consists of members of the caveolin family of proteins associated with cholesterol and sphingolipids. Caveolae perform transport and signaling functions and are involved in membrane organization. All endocytic activity mediated by caveolae (thereby bypassing the clathrin-coated vesicle pathway) is pooled under the term potocytosis.[62–65]

Accessory structures develop in the wall in accord with the functional properties of the vessels. Thus, the walls of the major pulmonary arteries that are close to the heart, and therefore exposed to the pressure oscillations of large amplitude prevailing in the outflow tract of the right ventricle, are of the elastic type—that is, layers of elastic lamellae are interconnected with smooth muscle cells as in the aorta; the tone of the smooth muscle regulates the elastic modulus of the vessel wall, thereby controlling the shape of the pulse wave. In the pulmonary arterial tree, this pattern prevails out to branches of about 1 mm diameter.

In contrast, branches less than 1 mm in diameter are of the muscular type, that is, the smooth muscle fibers encircle the vessel lumen; they can modify the vessel's cross-section and can thus regulate blood flow through this vessel. Compared with systemic arteries, the thickness of the pulmonary arterial wall is reduced about in proportion to systolic pressure, that is, by about a factor of 1:5; in pulmonary hypertension, the wall becomes thicker. Although arterioles are a well-defined entity in the systemic vascular bed, where they constitute the major site of arterial resistance, pulmonary arterioles are more difficult to locate and define. A single muscle layer—the histologic definition of an arteriole—does occur in branches about 100 µm in diameter, but the arterial bed continues out to the precapillaries, which consist of vessels 20 to 40 µm in diameter that are enwrapped by an incomplete smooth muscle sheath. This poverty of smooth muscle contributes importantly to the low resistance to blood flow that is normally afforded by the pulmonary arterial tree.

The structure of pulmonary veins is similar to that of systemic veins in the upper half of the organism. Their walls are rich in connective tissue and contain irregular bundles of smooth muscle. Larger veins contain a large amount of elastic tissue. More extensive in rodents, but to a certain degree also in humans, cardiac muscle tissue from the left atrial myocardium forms sleeves in the adventitia of pulmonary veins where they overlap with the smooth muscle of the venous wall. The arrangement of the myocardial sleeves correlates with the distribution of foci of ectopic beats initiating atrial fibrillation.[66–69]

■ Nutritive Vessels and Nerves

The tissue of lung parenchyma is very well supplied with blood; the fact that it is venous is of no disadvantage, because O_2 is easily obtained from the air. Thus, nutrient supply from pulmonary arteries combined with O_2 supply from air appears to suffice not only for the parenchyma but also for bronchioles and the smaller pulmonary vessels, whose outer surface is almost directly exposed to air. The thicker-walled bronchi, with their glands and cartilage, require a nutrient blood supply from bronchial arteries.[15,70,71] These derive in part directly from anterior branches of the aorta and partly from the upper intercostal arteries. They course alongside the esophagus and penetrate on both sides into the hilum. The bronchial arteries extend to the most peripheral bronchi but not into the walls of bronchioles. On the other hand, some branches supply large pulmonary vessels as vasa vasorum, whereas others course along larger septa to reach the pleura. Some bronchial arteries form anastomoses with peripheral branches of the pulmonary arteries. There have been long discussions about the role that such anastomoses may play. It seems that in the normal lung their importance has been overrated. However, in certain pathologic conditions, such as bronchiectasis and tumors, the bronchial arteries and perhaps the bronchopulmonary anastomoses appear to play an important role. They also enlarge to form a collateral circulation when branches of the pulmonary artery are obliterated. The peribronchovascular space around larger pulmonary artery branches and bronchi with its capillaries from the bronchial circulation also has been proposed as a unique compartment since it is a preferential site of leukocyte infiltration and edema formation under pathologic conditions.[72] Furthermore, the bronchial circulation attenuates ischemia–reperfusion lung injury. Consequently, interruption of the bronchial circulation without revascularization during lung transplantation often leads to bronchial anastomotic complications.

Except for a few bronchial veins in the hilar region, the bronchial system does not have its own venous drainage into the systemic veins. Instead, the bronchial veins, which begin as a

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peribronchial venous plexus, drain into pulmonary veins; this drainage seems to constitute one source of normal venous admixture to arterial blood.

The lung is innervated by the autonomic nervous system. The parasympathetic fibers are derived from the vagal nerves and the sympathetic fibers from the upper thoracic and cervical ganglia; together they form the pulmonary nervous plexus in the region of the hilum before entering the lung. The fiber bundles follow the major bronchi and blood vessels, finally penetrating into the acini; some nerves also supply the pleura. In addition, motor nerves influence the smooth muscle tone of airways and blood vessels, and sensory nerves are involved in reflex functions (e.g., cough reflex, Hering–Breuer reflex). Moreover, the secretory function of glands as well as of secretory epithelial cells is at least partly under control of this nervous system. Nerve fibers are easily found in the wall of bronchioles and bronchi, where they often follow the course of bronchial arteries. However, fibers in alveolar septa are small and scarce.

THE CELLS OF THE ALVEOLAR REGION

The alveolar region of the lung is the region where gas exchange occurs. Its fundamental design and cellular components are discussed below.

Basic Design of the Gas-Exchange Barrier

Efficient gas exchange in the lung depends on a very thin barrier of very large surface between air and blood.[16,73] Actually, the barrier is so thin that it cannot be resolved into its constituents by light microscopy. Nevertheless, this barrier must be built of the three minimal tissue layers: an endothelium lining the capillaries, an epithelium lining the airspaces, and an interstitial layer to house the connective tissue fibers. The guiding principle in designing these cells must evidently be to minimize thickness and maximize extent. However, there is definitely a limit to this, set by the need to make the barrier and its constituent cells strong enough to resist the various forces that act on it: capillary blood pressure, tissue tension, and surface tension, in particular. Furthermore, the barrier must remain intact for a lifetime, and this requires continuous repair and turnover of the cells and their components. As a result, about half of the surface of the air–blood barrier is optimized for gas exchange in that the thin epithelial and endothelial cell extensions are only separated by a fused basement membrane. These areas are termed the thin parts of the air–blood barrier. Cell nuclei and connecting tissue fibers are concentrated in the so-called thick parts of the air–blood barrier.

In spite of this delicacy of tissue structure, we find that three-quarters of all the lung cells by volume or weight are contained in the lung parenchyma (Table 2-1). We also note that epithelium and endothelium make up about one-quarter each of the tissue barrier in the alveolar walls, whereas interstitial cells amount to 35%; the interstitial space with the connective tissue fibers makes up no more than 15% of the barrier.[11,74]

Alveolar Epithelium

The alveolar epithelium is a mosaic of different cell types. The vast majority of the total surface is lined by a single layer of squamous cells; the remaining fraction—only about 3% (Table 2-2)—is occupied by cuboidal secretory cells; one usually calls the squamous lining cells type I and the secretory cells type II alveolar epithelial cells or pneumocytes. Type I and II cells occur with a numeric frequency of about 1:2. A very rare third cell type, the brush cell, can be found in some specific regions near the entrance of the acinus (see above).

The fine structural details of the different types of alveolar epithelial cells can be fully visualized only by electron microscopy, whereas molecular markers selective for either type I or II cells or some of their constituents can be detected and localized by light microscopy (Fig. 2-15; Table 2-3).

TABLE 2-1 Estimated Cell Volumes in the Human Lung

Cell or Tissue	Volume (mL)	Percent Septal Tissue
Tissue (excl. blood)	284	—
Nonparenchyma	99	—
Alveolar septa	185	—
Cells	213	—
Nonparenchyma	50	—
Alveolar septa	163	—
Parenchymal cells	163	—
Alveolar epithelium type I	23	12.6
Alveolar epithelium type II	18	9.7
Capillary endothelium	49	26.4
Interstitial cells	66	35.8
Alveolar macrophages	7	3.9

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Type I Alveolar Epithelial Cells

At first glance, the squamous type I cells show rather simple design features (Fig. 2-16). Their small, compact nucleus is surrounded by a slim rim of cytoplasm, where one finds a modest basic set of organelles, a few small mitochondria, and some cisternae of endoplasmic reticulum, seemingly the picture of a quiescent cell with no great metabolic activity.[11,75]

At the edge of the perinuclear region, a very attenuated cytoplasmic leaflet emerges (Fig. 2-16) and spreads out broadly over the basal lamina. This leaflet is made essentially of the two plasma membranes forming the apical and basal cell face, respectively, with a very small amount of cytoplasmic ground substance interposed (Fig. 2-17). Here one rarely finds any organelles except for the numerous plasmalemmal vesicles implied in the transcellular

TABLE 2-2 Morphometric Characteristics of Cell Population in Human Pulmonary Parenchyma

Cell Population	Percent of Total Cell Number[a]	Average Cell Volume (μm^3)	Average Apical Cell Surface (μm^2)
Alveolar epithelium			
Type I	8	1764	5098
Type II	16	889	183
Endothelium	30	632	1353
Interstitial cells	36	637	—
Alveolar macrophages	10	2492	—

[a] *Total cell number in human lung 230×10^9.*

Data from Crapo JD, Barry BE, Gehr P, et al. Cell number and cell characteristics of the normal human lung. Am Rev Respir Dis. 1982;125:332–337.

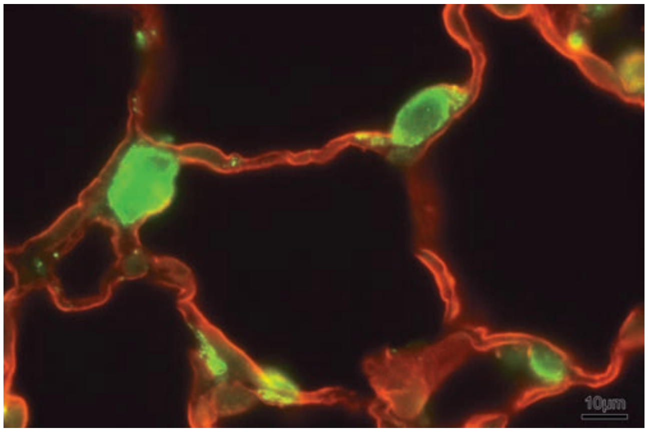


Figure 2-15 Immunofluorescent double labeling of alveolar epithelial cells. Type I cells are stained for Lycopersicon esculentum lectin *(red)*, type II cells are stained for SP-D *(green)*. Compare with Table 2-3. *(Micrograph reproduced with permission from H. Fehrenbach.)*

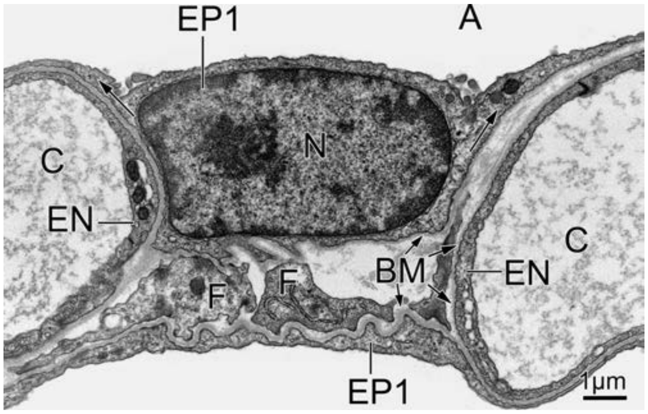


Figure 2-16 A type I alveolar epithelial cell (EP1) from human lung. The nucleus (N) is surrounded by very little cytoplasm, which extends as thin leaflets *(arrows)* to cover the capillaries (C). Note the basement membranes (BM) of the epithelium and endothelium (EN), which become fused in a minimal barrier. Interstitial space contains fibroblast processes (F).

transport of molecules. In fact, besides capillary endothelial cells, type I alveolar epithelial cells are among the richest in caveolae.

The surface covered by one type I epithelial cell is about 4000 to 5000 μm^2. In some texts one may find the type I cell called the "small alveolar cell" because of its small nucleus; clearly this is a misnomer, as the type I cell is a rather large cell indeed, with respect to both surface and cell volume (Table 2-2). Terminal bars are formed where the cytoplasmic leaflets of epithelial cells meet (Fig. 2-18). If one looks at the surface of the alveolar epithelium in scanning electron micrographs (Fig. 2-19), one notes that the patches covered by single type I cells are variable in size and that even the largest are much smaller than the 4000 to 5000 μm^2 given earlier, a number derived by dividing the total alveolar surface by the total number of type I cell nuclei. Why is this? There seem to be three to four times as many type I cell domains encircled by terminal bars as there are nuclei. Indeed, this observation was already made some 130 years ago by Albert Kölliker; his interpretation was that part of the alveolar surface was lined by "nonnuclear" cytoplasmic plates rather than by complete cells. It turns out that an alternative explanation is possible. One finds that type I cells are not simple squamous cells but rather branched cells with multiple apical faces, as shown diagrammatically in Fig. 2-20. Thus, what appears as nonnucleated plates are cytoplasmic domains connected to the perinuclear region by a stalk, spreading out on one side of the alveolar wall or the other; it is evident that several such domains may share a nucleus.[76–78]

Although type I cells cover about 97% of the alveolar surface area, they have long been neglected as being "silent," providing solely a barrier function. Although their overall function in the human lung

TABLE 2-3 Markers for Alveolar Epithelial Cells

Type I Cell	Type II Cell
HTI-56 (human)	Surfactant proteins:
T1α/RTI-40 (rat, mouse)	SP-A
Aquaporin 5	SP-B
Caveolin 1	SP-C
Receptors for advanced glycation end products (RAGE)	SP-D
	ABCA3
Carboxypeptidase M	HTII-280 (human)
Lectins:	RTII-70 (rat)
Lycopersicon esculentum	MMC4 (rat)
Bauhinia purpurea	Alkaline phosphatase
Ricinus communis 1	CD44
	Lectins:
	Maclura pomifera

These markers allow a selective distinction between type I and type II alveolar epithelial cells and can be visualized at a light microscopic level by immunohistochemistry, enzyme histochemistry, or lectin histochemistry. However, other cell types of the distal bronchiolar and alveolar region, e.g., club cells, capillary endothelial cells, or alveolar macrophages, also might stain positive for some of these markers. Data from Fehrenbach H. Alveolar epithelial type II cell: defender of the alveolus revisited. Respir Res. 2001;2:33–46; Griffiths MJD, Bonnet D, Janes SM. Stem cells of the alveolar epithelium. Lancet. 2005;366:249–260; Gonzales RF, Allen L, Gonzales L, Ballard PL, Dobbs LG. HTII-280, a biomarker specific to the apical plasma membrane of human lung alveolar type II cells. J Histochem Cytochem. 2010;58:891–901.

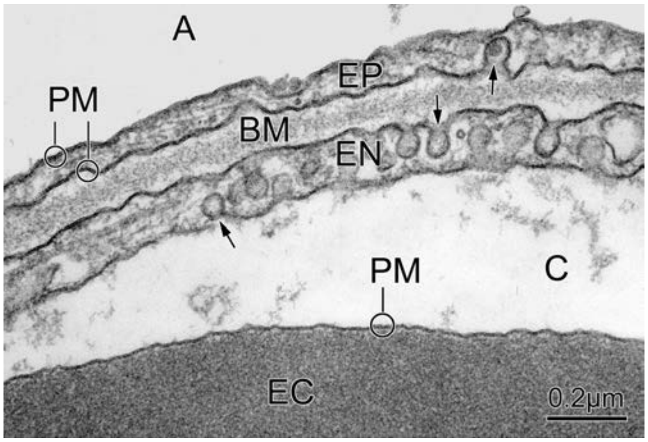


Figure 2-17 Thin, minimal tissue barrier between alveolar air (A) and capillary blood (C) is made of cytoplasmic leaflets of epithelium (EP) and endothelium (EN), joined by fused basement membranes (BM). Note that the epithelial and endothelial leaflets are bounded by plasma membranes (PM), as is the erythrocyte (EC). *Arrows* point to pinocytotic vesicles/caveolae. *(The Pathway for Oxygen: Structure and Function in the Mammalian Respiratory System by Ewald R. Weibel, M.D., Cambridge, Mass.: Harvard University Press, Copyright © 1984 by the President and Fellows of Harvard College. Used by permission. All rights reserved.)*

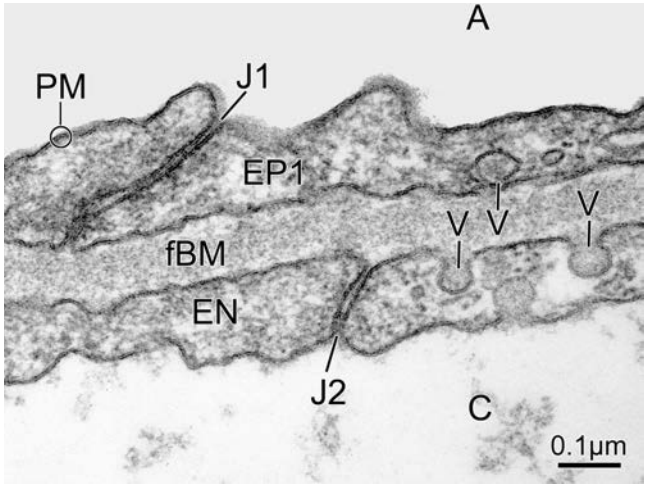


Figure 2-18 Minimal barrier part showing intercellular junctions. Between type I epithelial cells, a "tight" junction (J1) is formed by close apposition of the cell membranes over a comparatively wide band; the junction between endothelial cells (J2) is "leaky" because membranes become apposed over a narrow strip only. Note trilaminar structure of plasma membranes (PM), the occurrence of pinocytotic vesicles/caveolae (V) in both epithelium and endothelium (EN), and the fused basement membranes (fBM). A, alveolus; C, capillary; EP1, type I epithelial cell.

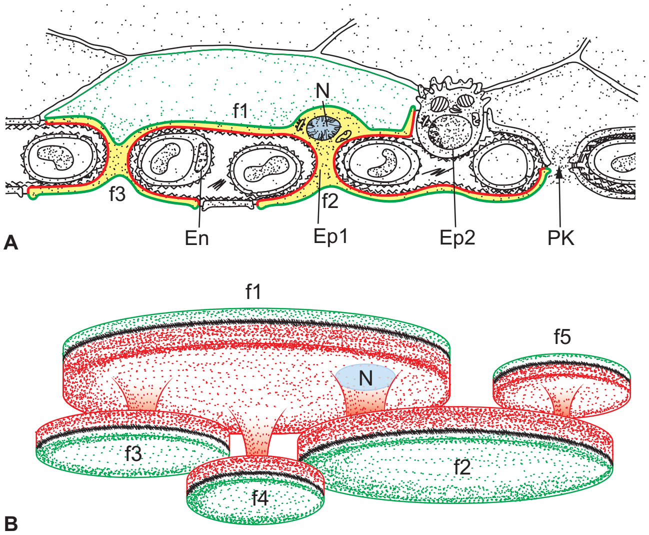


Figure 2-20 **A.** Diagram of section of alveolar septum with branched type I cell (yellow) forming the cytoplasmic plates: f1 (comprising the nucleus) and f2 plus f3 (connected with stalks to the nuclear area). The apical cell membrane is shown in green and the basal cell membrane in red, separated by the terminal bar (black dots). **B.** Topological diagram of this type I cell, in bottom-up view, showing the connection of the apical cytoplasmic facets (f2 to f5) by stalks to f1 and the nucleus (N). Note that the basal cell membrane (red) is a continuum, whereas the apical membrane (green) is fragmented into facets. The black bands represent the terminal bars on the lateral surfaces. En, endothelial cell; Ep1, type I epithelial cell; Ep2, type II epithelial cell; PK, pore of Kohn.

remains to be determined, animal and in vitro studies strongly suggest that type I cells are actively involved in alveolar ion and fluid homeostasis.[79–81]

Type I cells are easily damaged, particularly because of their extensive surface area and their complex branching architecture. However, there is an additional problem: one finds that type I cells are not capable of multiplying by mitosis in vivo, neither during lung growth when more cells are needed to coat the expanding alveolar surface nor upon damage in the adult lung when cells need to be replaced. In both instances new type I cells are made by mitotic division and transformation of type II cells, a process that takes about 2 to 5 days.

This seems to work under normal circumstances. There are, however, conditions where this repair mechanism is too slow to cope with excessive damage, so that a syndrome of severe respiratory failure, acute respiratory distress syndrome (ARDS), develops, which requires intensive care treatment. In such patients one finds large parts of the type I cell lining of the alveolar surface to be destroyed. As a consequence, the barrier has become leaky and the alveoli fill with alveolar edema, so that they can no longer take part in gas exchange.[82,83]

With proper medical care, this alveolar edema can often be resolved within a few days. The alveoli become again filled with air, but in spite of this, gas exchange does not improve. What has

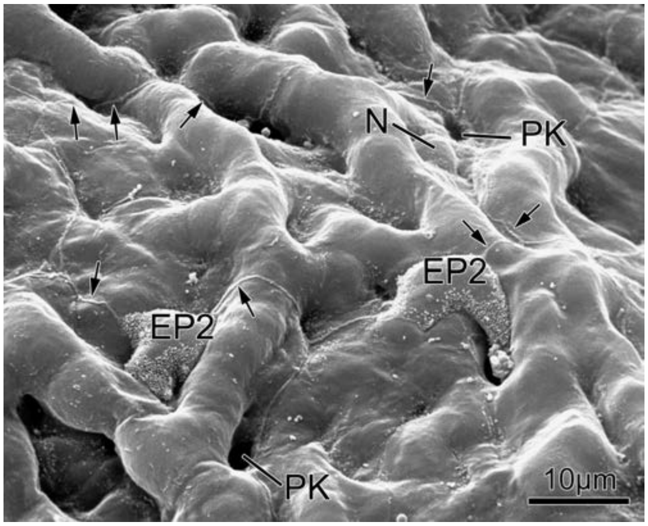


Figure 2-19 Surface of the alveolar wall in the human lung seen by scanning electron microscopy reveals a mosaic of alveolar epithelium made of type I and type II (EP2) cells. *Arrows* indicate boundary of the cytoplasmic leaflet of the type I cell which extends over many capillaries. Note the two interalveolar pores of Kohn (PK). N, nucleus of type I cell.

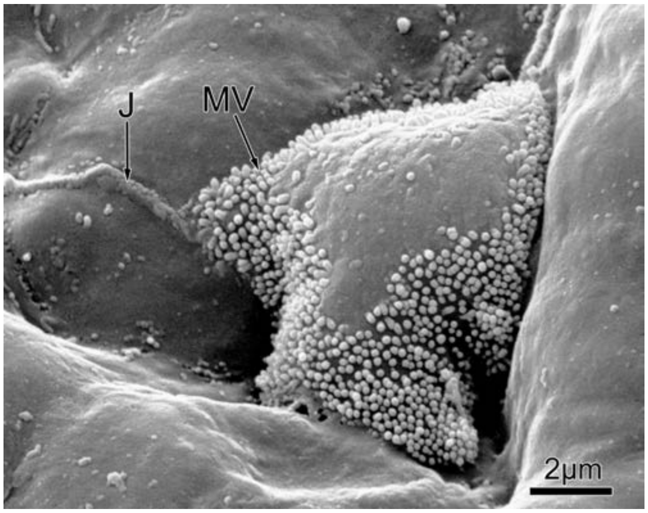


Figure 2-21 Higher magnification of a type II cell reveals a "crown" of short microvilli (MV) and a central "bald patch." Note junction lines of type I cells (J) meeting with the type II cell.

happened is that the repair of the severely damaged alveolar epithelium requires a lot of new cells to be made by division of type II cells.[84] These form a rather thick cuboidal lining of the barrier surface, a phenomenon termed *cuboidal metaplasia*, and this thick barrier offers a high resistance to O_2 flow. It takes several weeks until a thin barrier is restored by transformation of the cuboidal cell lining into delicate type I cells. During this process, the cells go through intermediate stages where they are often positive for both type II and type I cell markers.[85,86]

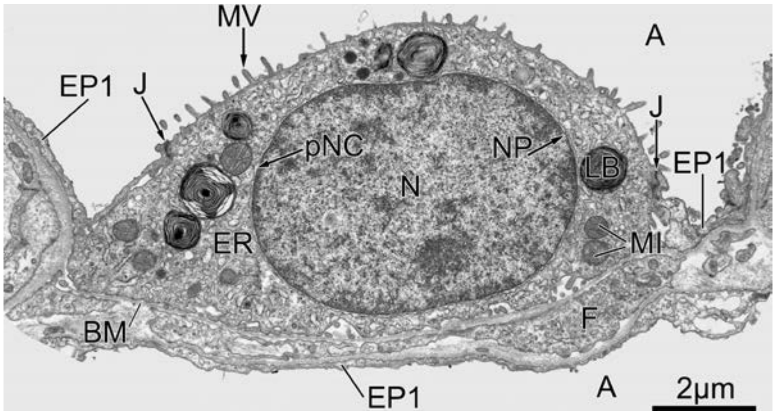


Figure 2-22 A type II epithelial cell from the human lung forms junction (J) with type I epithelial cells (EP1). Its cytoplasm contains osmiophilic lamellar bodies (LB) and a rich complement of organelles: mitochondria (MI), endoplasmic reticulum (ER), and so on. The nucleus (N) is surrounded by a perinuclear cisterna (pNC) which is perforated by nuclear pores (NP). A, alveolus; BM, basement membrane; F, fibroblast; MV, microvilli.

Type II Alveolar Epithelial Cells

The type II alveolar epithelial cell is a conspicuous but in fact relatively small cell whose mean volume is less than half that of the type I cell (Table 2-2), although it is often called the "large alveolar cell."[11] Its shape is cuboidal, the apical cell surface bulges toward the lumen and is provided, mostly around its periphery, with a tuft of microvilli (Figs. 2-21 and 2-22). Often, type II cells seem to be preferentially located in the corners of alveoli or in close proximity to interalveolar pores of Kohn. They are usually found as solitary cells; only in cases of alveolar epithelial damage, proliferation of type II cells leads to focal clusters during the repair process. Occasionally, a single type II cell might supply two or even three adjacent alveoli with its apical surface. The basement membrane beneath type II cells is occasionally interrupted. Through these apertures, foot processes of type II cells can extend to the interstitium and come in close proximity to interstitial cells.[87]

Type II cells contain a wealth of cytoplasmic organelles of all kinds (Fig. 2-22): mitochondria, a lot of endoplasmic reticulum with ribosomes, and a well-developed Golgi complex surrounded by a set of small lysosomal granules among which so-called *multivesicular bodies*—membrane-bounded organelles containing a group of small vesicles—stand out (Fig. 2-23). In addition, one finds the characteristic lamellar bodies, larger membrane-bounded secretory organelles that contain densely packed phospholipid lamellae. There are notable species differences in the ultrastructural organization of lamellar bodies. In rodents, the lamellae are mostly arranged in parallel stacks whereas in humans, concentrically arranged lamellae are mostly found, which are attached to a projection core consisting of randomly arranged short stacks of densely packed membrane segments (Fig. 2-24).[88] The periodicity of the lamellae is in the range of 4 to 6 nm. One human type II cell contains between 200 and 500 lamellar bodies, making up a total volume of about 2 cm^3 in the entire lung. With a diameter of approximately 1 μm, lamellar bodies are among the largest secretory organelles of all cells in the body. Owing to their equipment with lysosomal enzymes (e.g., acid phosphatase, cathepsins) and proteins (e.g., members of the lysosomal membrane protein [LAMP] family) and their acidic pH of about 5.5, lamellar bodies are regarded as secretory lysosome-related organelles.[89]

Type II cells have two main functions: they serve as the cellular source of pulmonary surfactant and they contribute to the regeneration of the alveolar epithelium under physiologic and pathologic conditions. These properties form the basis of the concept of the type II cell as the "defender of the alveolus."[90–92]

Surfactant prevents alveolar atelectasis by a surface area–dependent reduction of the alveolar surface tension (see below).[93–96] Another function of surfactant as a result of the reduction of alveolar surface tension is to prevent the formation of intra-alveolar edema.[97] In addition, certain surfactant components have important immunomodulatory functions in the innate host defense system.[98,99] Taken together, the main functions of surfactant might be summarized as to keep alveoli open, dry, and clean. Surfactant is composed of around 90% lipids, mainly saturated phosphatidylcholine, and around 10% proteins, including the surfactant apoproteins termed SP-A, SP-B, SP-C, and SP-D. Besides its biochemical complexity, surfactant is also morphologically very heterogeneous, consisting of different surfactant subtypes with highly organized structure that represent different stages in metabolism (Figs. 2-24–2-26).[88,100]

The alveolar epithelium (including interalveolar pores of Kohn) is lined by a thin but apparently continuous fluid layer inserted between the apical cell membrane and the surface film, thus forming a duplex lining layer.[101,102] Surfactant functions in and on this layer. It is synthesized, stored, secreted, and to a large extent recycled by type II cells.[88,91,103] Therefore, an intracellular surfactant pool present

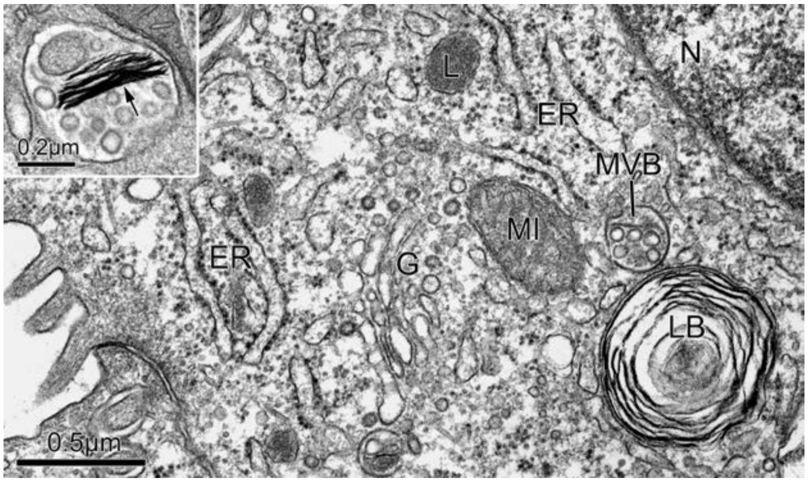


Figure 2-23 Cytoplasmic organelles of the type II cell implicated in the synthesis of surfactant are the endoplasmic reticulum (ER), Golgi complex (G), lysosomes (L), multivesicular bodies (MVB), and finally lamellar bodies (LB). The *inset* shows a large composite body with a stack of phospholipid lamellae *(arrow)*. N, nucleus. *(The Pathway for Oxygen: Structure and Function in the Mammalian Respiratory System by Ewald R. Weibel, M.D., Cambridge, Mass.: Harvard University Press, Copyright © 1984 by the President and Fellows of Harvard College. Used by permission. All rights reserved.)*

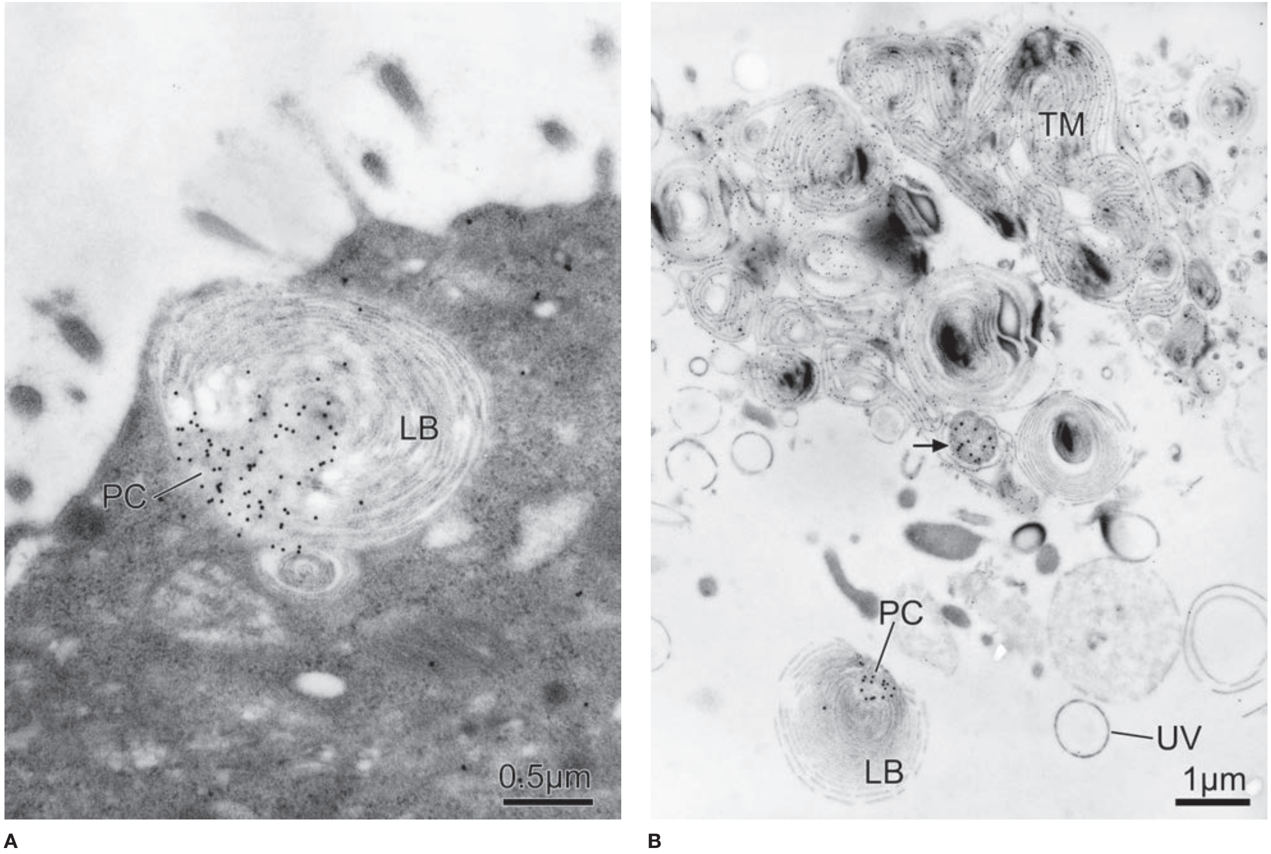


Figure 2-24 Immunogold labeling for SP-A (5-nm gold particles) and SP-B (15-nm gold particles) in the human lung. **A.** Within type II cells, SP-B is localized in the projection core (PC) of lamellar bodies (LB). **B.** In the alveolar lumen, SP-A is associated with tubular myelin figures (TM) whereas SP-B is found in the projection core (PC) of freshly secreted lamellar bodies (LB) and dense core particles *(arrow)* close to tubular myelin. UV, unilamellar vesicle.

in type II cells and an intra-alveolar surfactant pool present at the surface of the fluid alveolar lining layer as well as within its hypophase can be distinguished. The intracellular storage form of surfactant is represented by lamellar bodies. Prior to storage, the synthesis of surfactant material involves endoplasmic reticulum, (at least partly) Golgi complex, and multivesicular bodies. In type II cells, multivesicular bodies participate in the posttranslational processing of surfactant proteins as well as in endocytosis and subsequent recycling and/or degradation of surfactant material; thus, most probably representing the junction point between the biosynthetic and endocytotic pathway. In addition, transitional forms between multivesicular bodies and lamellar bodies, termed *composite bodies*, have been described. Surfactant material present in lamellar bodies is secreted into the alveolar lumen via exocytosis (Figs. 2-25 and 2-26).

Most surfactant components are assembled in lamellar bodies prior to secretion (Figs. 2-24–2-26)—at least the lipid fraction and the hydrophobic surfactant proteins, SP-B and SP-C, whereas the hydrophilic surfactant proteins SP-A and SP-D seem to be secreted independently via a constitutive pathway bypassing the regulated exocytosis of lamellar bodies. Lamellar body secretion starts with the fusion of its limiting membrane with the apical plasma membrane, followed by formation of a fusion pore, and finally the slow release of surfactant material through the pore. The diameter of the pore is considerably smaller than that of the lamellar body. Thus, surfactant seems to be squeezed through the pore.[104] The mechanisms that regulate surfactant secretion in vivo are still not fully elucidated. It seems that, among the various stimuli that can act via several different signaling pathways, mechanical stretch during ventilation—either as a direct effect on

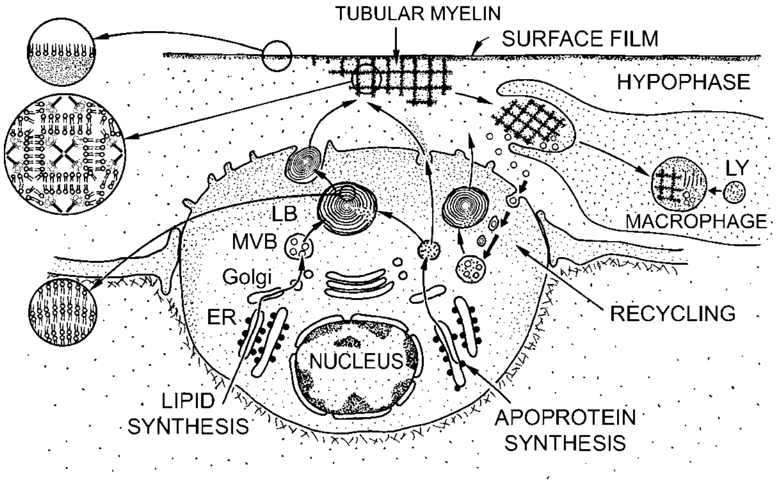


Figure 2-25 Schematic diagram of pathways for synthesis and secretion of surfactant lipids and apoproteins by a type II cell, for their recycling by type II cells, and for their removal by macrophages. Note the arrangement of phospholipids and apoproteins in the lamellar bodies, in tubular myelin, and in the surface film. *(The Pathway for Oxygen: Structure and Function in the Mammalian Respiratory System by Ewald R. Weibel, M.D., Cambridge, Mass.: Harvard University Press, Copyright © 1984 by the President and Fellows of Harvard College. Used by permission. All rights reserved.)*

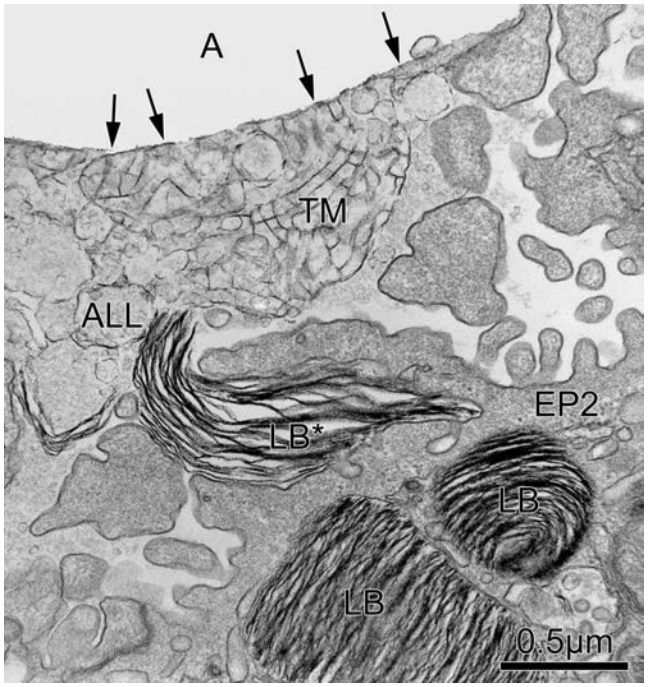


Figure 2-26 Apical part of type II cell (EP2) with lamellar bodies (LB); one of these (LB*) is seen in the process of being secreted into the alveolar surface lining layer (ALL). The free surface of the lining layer is covered by a thin black film of lipids *(arrows)*, which is connected with tubular myelin (TM) in the hypophase. *(Reproduced with permission from West JB: Bioengineering Aspects of the Lung. New York, NY: Springer-Verlag; 1977.)*

type II cells or indirectly via type I cells or capillary endothelial cells which may act as "strain sensors"—is the physiologically most relevant.[91,103,105,106]

Intra-alveolar surfactant consists of several subtypes, namely freshly secreted lamellar body-like forms, tubular myelin, the surface film, and small unilamellar vesicles. After secretion, lamellar body-like forms in the hypophase associate with SP-A, which is separately secreted by type II cells,[107] and undergo a major structural transformation into tubular myelin figures with a unique lattice-like structure.[108] The precise physiologic function of tubular myelin, however, is still unclear. Tubular myelin is thought to be the immediate precursor of the surface film, although the existence of an additional multilayered surface-associated surfactant reservoir underneath the surface film has been suggested.[100,109] "Spent" surfactant components are found in the hypophase as small unilamellar vesicles. The major route of surfactant clearance is reuptake by type II cells. Within type II cells, surfactant material can either be recycled or degraded. Other routes of surfactant clearance include ingestion and lysosomal degradation by alveolar macrophages and clearance via the airways.

After differential centrifugation of intra-alveolar surfactant material harvested by bronchoalveolar lavage, surface active large aggregates (LA), ultrastructurally largely corresponding to lamellar body-like forms and tubular myelin, and inactive small aggregates (SA), ultrastructurally largely corresponding to unilamellar vesicles, can be distinguished. Thus, the SA/LA ratio can be used to assess the biophysical activity of surfactant.[94,95]

A surfactant film, most likely mainly transported upward from the alveoli, is also present in the airways. Here, surfactant prevents collapse of smaller airways, prevents transepithelial fluid influx, enhances mucociliary transport, and interacts with inhaled pathogens and particles. At least some of the surfactant proteins are also synthesized and secreted by club cells. Club cells express SP-B, but not SP-C, which is exclusively expressed by type II cells. There is some controversy regarding whether club cells express SP-A and SP-D. Although this is obviously the case in rodents, club cells in the normal adult human lung most likely express very low or no SP-A and SP-D.[107,110,111] It seems that club cells are not involved in reuptake or recycling of surfactant components.[112] However, their overall role in surfactant biology is not yet defined.

The surfactant apoproteins as the "smart molecules in the surfactant system"[113] have important functions in surfactant subtype assembly, surfactant biophysics, surfactant homeostasis, and innate immunity.[114–118] The hydrophilic proteins SP-A and SP-D belong to the collectin protein family involved in innate immunity. In addition, SP-A, together with SP-B, is important for tubular myelin formation, thus stabilizing active surfactant forms, whereas the hydrophobic proteins SP-B and SP-C and, in conjunction, SP-A enhance the adsorption of phospholipids into the surface film. SP-A might also inhibit surfactant secretion and stimulate surfactant reuptake by type II cells.

Differences in the ultrastructural organization of intracellular and intra-alveolar surfactant subtypes between humans and rodents are also reflected by a different distribution of surfactant proteins (Fig. 2-24).[88] In the human lung, SP-A within type II cells is mainly found in small vesicles and multivesicular bodies and only rarely at the periphery of lamellar bodies. In the alveolar lumen, SP-A is associated with peripheral membranes of lamellar body-like forms in close proximity to tubular myelin, in the corners of the tubular myelin lattice structure, and partly at the surface film and unilamellar vesicles.[107] SP-B in the human lung is localized in the projection core of lamellar bodies within type II cells and in dense core particles associated with tubular myelin in the alveolar lumen.[119]

The crucial role of the surfactant system for the maintenance of the functional integrity of the lung is clearly demonstrated by surfactant dysfunction disorders, which can be caused either at birth by developmental deficiency (owing to lung immaturity or mutations affecting surfactant synthesis or secretion) or later by acquired dysfunction (owing to damage of type II cells or inhibition/inactivation of intra-alveolar surfactant).[94,95,120] A primary deficiency of surfactant in the immature lungs causes the respiratory distress syndrome of premature neonates (RDS). Surfactant dysfunction mutations causing either acute respiratory failure or chronic lung disease after birth have been identified in the genes encoding for SP-B, SP-C, and the ATP-binding cassette transporter ABCA3, which is present at the limiting membrane of lamellar bodies. Impairment of an originally intact surfactant system is involved in the pathogenesis of a variety of other lung diseases, such as acute lung injury/ARDS as well as obstructive, infectious, and interstitial lung diseases. Mechanisms leading to impaired surfactant activity include apoptotic or necrotic cell death of type II cells, damage of surfactant proteins and lipids by reactive oxygen and nitrogen species, and enzymatic damage by phospholipases or neutrophil elastase. In addition, plasma proteins entering the alveolar space during edema formation also are known to inactivate surfactant.

With a turnover time of about 4 to 10 hours and only a rather small intracellular surfactant reserve available for secretion onto the large alveolar surface, the ability to cope with a lack of active surfactant during lung injury is limited. Hence, there is a rationale to supplement the surfactant material available in cases of surfactant deficiency or damage. One of the major advances in neonatology in our time has been the development of surfactant replacement therapy for the treatment of RDS. The story of the treatment of premature babies with exogenous surfactant is indeed a paradigmatic example in which discoveries from basic research were successfully applied to an important clinical problem.[95,121–123] The indications for surfactant replacement therapy have widened in recent years, with promising results in forms of respiratory failure not caused by a primary deficiency of endogenous surfactant but rather by impairment of an originally intact surfactant system. In these cases, however, the efficacy of exogenous surfactant therapy very much depends on the ability of the surfactant preparation to resist the inhibition/inactivation that caused alterations of the endogenous system.

■ Capillary Endothelium

The alveolar septa of the adult lung contain a single capillary network. The capillary endothelium is of the continuous (non-fenestrated) type. Alveolar capillaries are provided with pericytes, but they are rarer and less densely branched than pericytes of the systemic circulation.[124] Pericytes are related to vascular smooth muscle cells in that they both are contractile perivascular cells. Thus, pericytes protect microvessel wall integrity by providing some mechanical support. However, in contrast to vascular smooth muscle cells, pericytes are embedded within the endothelial basement membrane, frequently forming contacts with capillary endothelial cells. They seem to contribute components to the capillary basement membrane and extracellular matrix and secrete vasoactive substances. In addition, pericytes are thought to be involved in the regulation of endothelial cell proliferation and differentiation and to act as progenitor cells for other cell types.[125–129]

Capillary Endothelial Cells

At first glance, capillary endothelial cells resemble type I alveolar epithelial cells, but in contrast to type I cells with their complex branching architecture, capillary endothelial cells form simple sheets (Fig. 2-27).[59] Moreover, compared with the tight occluding junctions between alveolar epithelial cells that constitute a powerful seal of the intercellular cleft, the occluding junctions between capillary endothelial cells are rather leaky, allowing a nearly uninhibited exchange of water, solutes, and even some smaller macromolecules between the blood plasma and the interstitial space (Fig. 2-18). Occluding junctions between capillary endothelial cells are often located at the transition of the thin to the thick part of the air–blood barrier and are often covered by pericytes.

There is another notable and important difference between the two basically similar lining cells on the epithelial and endothelial side of the gas-exchange barrier: their size. Although the capillary surface is some 10% to 20% smaller than the alveolar surface, the capillary endothelial cells are about four times more numerous than type I cells[74]; this means that the surface covered by one type I epithelial cell must be about four times larger, namely 4000 to 5000 μm^2, compared with about 1000 μm^2 in endothelial cells (Table 2-2).

Numerous caveolae are found in capillary endothelial cells (Figs. 2-17 and 2-18). However, at the bulging part of the capillaries, some parts of the endothelial cell extensions are free of caveolae and are thinned down to a thickness of about 20 to 30 nm, basically consisting of the two plasma membranes with only a minute amount of cytoplasm in between. These areas, rarer in human lungs than in rodents, are termed the *avesicular zone* of the alveolar capillary endothelium.[11,59] In contrast to the endothelium of conducting vessels, Weibel–Palade bodies are missing in capillary endothelial cells, thereby underscoring the structural and functional differences between alveolar and extra-alveolar endothelial cells.[11,51,129,130] There is even specialization among alveolar capillary endothelial cells: Those at the thick parts of the air-blood barrier are similar to endothelial cells in capillaries of other organs. They function as progenitor cells, whereas those at the thin parts cover a larger surface area and are more widely ramified.[131]

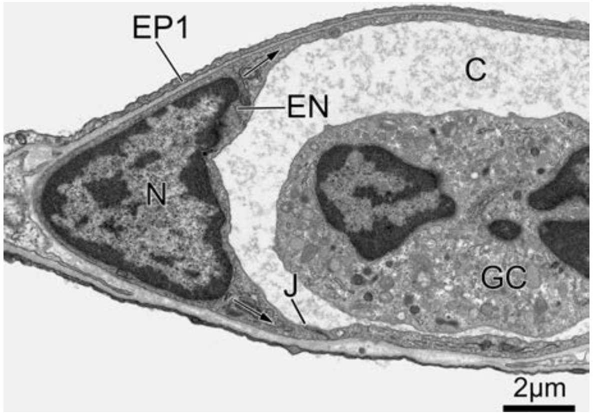


Figure 2-27 An endothelial cell (EN) of capillary (C) is similar in basic structure to a type I epithelial cell (EP1). The nucleus is enwrapped by little cytoplasm but thin leaflets extend as capillary lining *(arrows)*. Note the intercellular junction (J) and a white blood cell/granulocyte (GC), in the capillary. *(The Pathway for Oxygen: Structure and Function in the Mammalian Respiratory System by Ewald R. Weibel, M.D., Cambridge, Mass.: Harvard University Press, Copyright © 1984 by the President and Fellows of Harvard College. Used by permission. All rights reserved.)*

■ Interstitium

The interstitium of the alveolar septum is for the most part extremely thin. At the thick parts of the air–blood barrier where epithelial and endothelial basement membranes are separated, one finds elastic fibers and bundles of collagen fibrils in the extracellular matrix as well as interstitial cells, mainly fibroblasts, the cells responsible for production of extracellular matrix components (Figs. 2-28 and 2-29). The

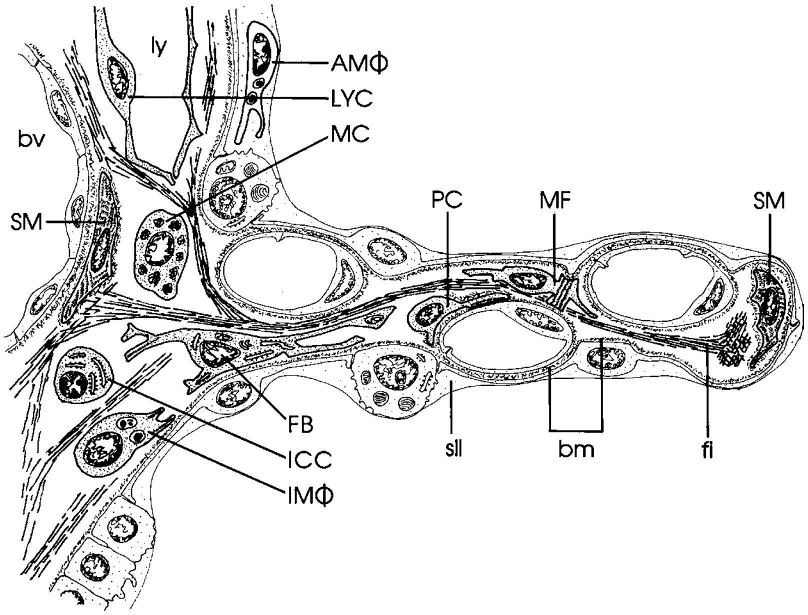


Figure 2-28 Schematic diagram of the structural organization of the alveolar interstitium. The alveolar septum extends between a free edge *(right)* and a perivascular connective tissue sleeve *(left)*, enwrapping a blood vessel (bv). Basement membranes (bm) are associated with epithelium and endothelium, and they bound the interstitial space. Fiber strands (fi) form a continuum. Interstitial cells include: fibroblasts (FB), myofibroblasts (MF), smooth muscle cells (SM), pericytes (PC), various kinds of immune competent cells (ICC), mast cells (MC), lymphatic endothelial cells (LYC), and histiocytes or interstitial macrophages (IMΦ). Alveolar macrophages (AMΦ) are submerged in the alveolar surface lining layer (sll)., ly, lymphatic capillary. *(Reproduced with permission from Crystal RG, West JB, Weibel ER, et al: The Lung: Scientific Foundations, 2nd ed. New York, NY: Lippincott-Raven; 1997.)*

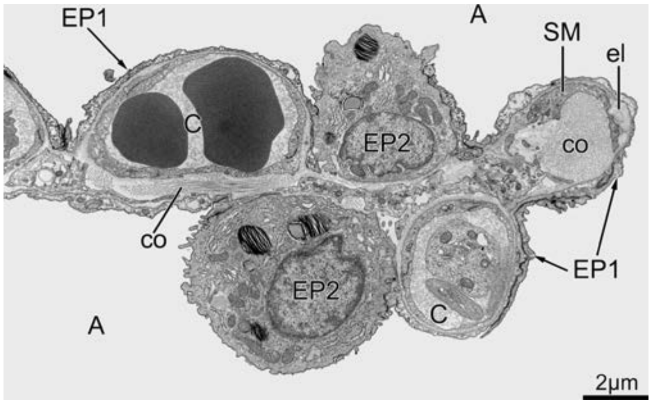


Figure 2-29 Alveolar septum with free edge *(right)* showing reinforced entrance ring with elastic fibers (el), collagen fibrils (co), and smooth muscle cell (SM). The two capillaries (C) are on different sides of the septum, as are the two type II cells (EP2). A, alveolar space; EP1, type I cell. *(Reproduced with permission from West JB: Bioengineering Aspects of the Lung. New York, NY: Springer-Verlag; 1977.)*

precise arrangement of the connective tissue fibers will be discussed later in relation to the mechanical properties of the lung.

Interstitial Cells

The resident interstitial cells of the alveolar septum comprise fibroblasts and contractile cells (myofibroblasts, lipofibroblasts, smooth muscle cells, and pericytes) (Fig. 2-28). Free interstitial cells are part of the defense system usually found in the juxta-alveolar connective tissue sleeves (see below) and include interstitial macrophages (histiocytes), mast cells, and under certain conditions, lymphocytes, plasma cells, and granulocytes.

Fibroblasts are a heterogeneous cell population. Many fibroblasts have notable contractile properties; therefore, they have been termed *myofibroblasts*. Myofibroblasts contain bundles of microfilaments anchored in patches beneath the plasma membrane. These filament bundles span the entire width of the cell. At the places where the microfilament bundles are connected to the plasma membrane, attachments to the epithelial and/or endothelial basement membrane exist.[11,132,133] Through holes in the basement membranes, myofibroblasts directly link alveolar epithelial and capillary endothelial cells.[87]

Some contractile fibroblasts are equipped with nonmembrane–bound lipid bodies, thus termed *lipid interstitial cells* or *lipofibroblasts*.[134,135] These cells are more common in rodent than in human lungs and occur particularly during alveolar development and growth. Lipid bodies consist of an osmiophilic rim of amphipathic phospholipids, glycolipids, sterols and specific proteins, and a hydrophobic core of neutral lipids. In many cell types, lipid bodies represent specialized domains for the synthesis of eicosanoid mediators.[136] Pulmonary lipofibroblasts seem to be related to the lipid-containing perisinusoidal cell (Ito cell) in the liver in that they might serve as a storage depot for retinoids.[135,137] Under certain conditions, lipofibroblasts might provide fatty acid substrates for surfactant synthesis in type II cells.[135]

The occurrence of smooth muscle cells in the alveolar septa is mostly restricted to the free septal edges where they contribute to the network of alveolar entrance rings (Figs. 2-28 and 2-29). Pericytes abut alveolar capillaries (see above).

STRUCTURAL ASPECTS OF THE DEFENSE SYSTEM OF THE LUNG

The large and delicate alveolar surface is constantly challenged by inhaled microorganisms and particulate matter. Thus, normal lung function critically depends on an efficient defense system.[98,117,138–141]

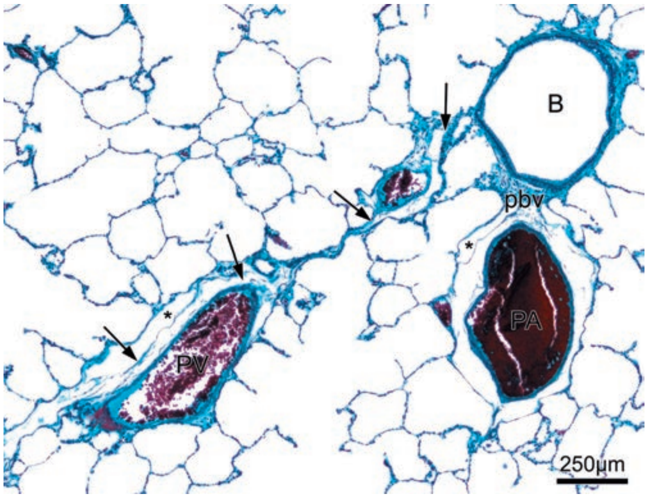


Figure 2-30 Light micrograph of human lung showing connective tissue sleeve *(arrows)* extending from the peribronchovascular space (pbv) around branch of pulmonary artery (PA) and bronchiolus (B) to pulmonary vein branch (PV). Asterisks, lymphatic.

At the alveolar level, the primary defense barrier is the alveolar lining layer. Here, alveolar macrophages are the sentinel phagocytic cells of the innate immune system, as we shall discuss later. In addition, protein components of the innate immune system, including the lung collectins SP-A and SP-D as well as a variety of other antimicrobial peptides (e.g., lysozyme, lactoferrin, defensins, cathelicidins), are present in the alveolar lining layer.

Another set of macrophages forms a second defense line just beneath the alveolar epithelium; that is, in the interstitial space of the lung parenchyma. In the normal lung, these interstitial macrophages (histiocytes) are not found in alveolar septa; instead, they occur only in the connective tissue sleeves at the periphery and in the center of acini where the peripheral fiber system connects with the adventitial sheath of bronchioles and pulmonary arteries (Fig. 2-30). Thus, they are found in regions where lymphatics begin their course toward the major airways in the hilar region where lymph nodes are found. In these juxta-alveolar regions of connective tissue, we usually find the common elements of the defense system (Figs. 2-30 and 2-31). These include lymphatic vessels and several mobile cells. Interstitial macrophages are constantly being

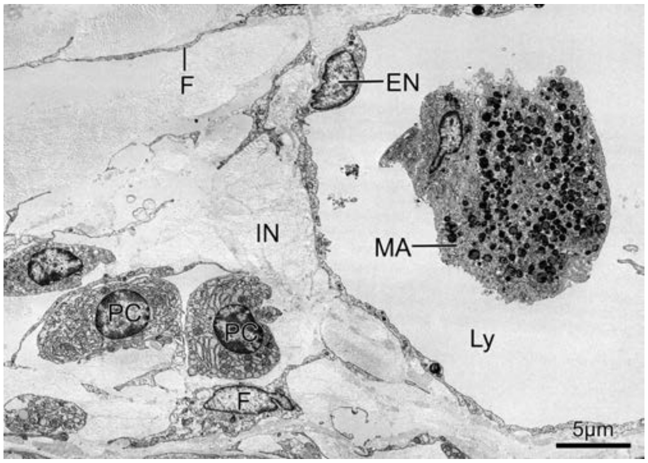


Figure 2-31 Perivascular connective tissue with lymphatic (Ly) containing a macrophage (MA) with heterogeneous population of "lysosomal" granules. Interstitium (IN) contains fibroblasts (F) and plasma cells (PC). EN, lymphatic endothelium.

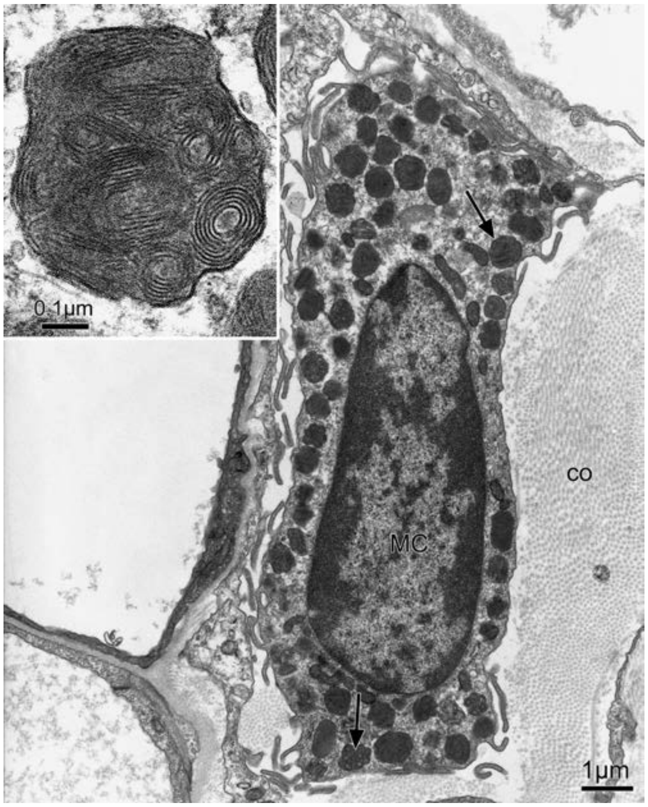


Figure 2-32 Mast cell from human lung containing granules *(arrows)* with scroll-like substructure. *Inset:* Scroll-like substructure of mast cell granule at higher magnification. Co, collagen fibrils. *(Reproduced with permission from Fishman A, Fisher AB: Handbook of Physiology. Section 3: The Respiratory System. vol 1. Bethesda, MD: American Physiological Society; 1985.)*

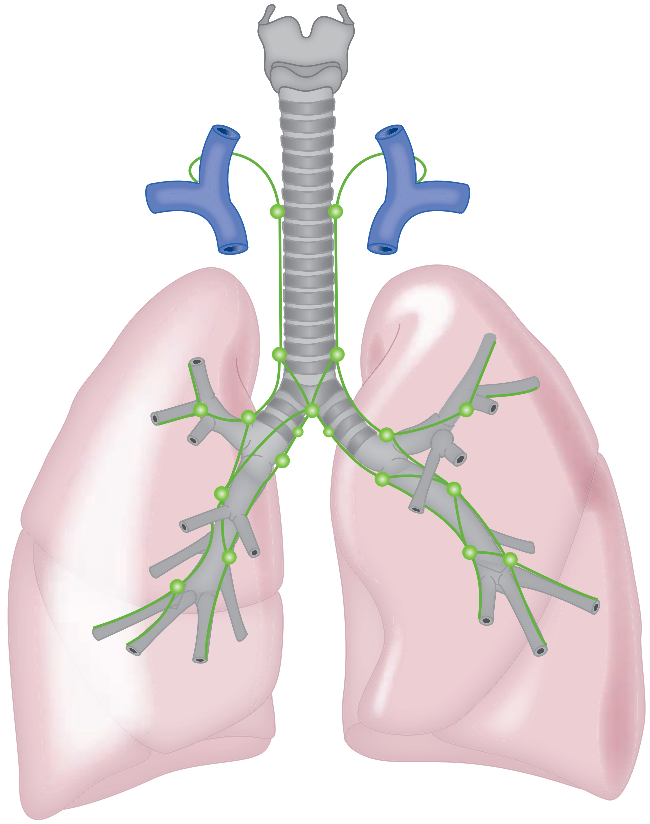


Figure 2-33 Schematic diagram of distribution of lymph nodes and main lymphatic channels along bronchial tree.

replenished by blood monocytes migrating into the interstitial space. Sometimes they become permanent residents in the form of storage cells for "indigestible" foreign matter, such as carbon particles and silicates. The relationship between interstitial macrophages and dendritic cells (see below) is under discussion.[142,143] Lymphocytes are less common and are mostly present as T cells whereas B cells and natural killer cells are rare in the normal lung. Granulocytes (neutrophils, eosinophils, and basophils) are present in the human lung, but they also are very rare. Mast cells contain granules storing heparin and histamine as well as peptidases such as tryptases and chymases[144] that, in the human, show a characteristic scroll-like substructure (Fig. 2-32) as well as lipid bodies. According to their anatomic location, they show site-specific characteristics, thus displaying considerable heterogeneity.[145] Antigen-presenting dendritic cells possess long branched dendritic cell processes (hence, their name) and an irregular, folded nucleus. Phagolysosomes are absent. Once activated, dendritic cells migrate to lymph nodes where they induce the proliferation of antigen-specific T cells, thus providing a link between innate and adaptive immunity. In addition to their presence within the lung parenchyma, dendritic cells are found within the tracheal and bronchial epithelium where they seem to form a network comparable to the Langerhans cells in the epidermis. Like Langerhans cells, airway dendritic cells are characterized by pentalaminar platelike organelles (Birbeck granules).[146–148] In the ciliated epithelium of bronchi and bronchioles diapedesis is seen—that is, lymphocytes and other leukocytes in the process of penetrating the epithelium to reach the mucus blanket. Plasma cells occur in relatively high numbers around the acini of the seromucous glands of bronchi (Fig. 2-7); hence, it is likely that antibodies are being secreted into the mucus blanket by these glands by a process similar to that occurring in the salivary glands or in the glands of the nasal mucosa.

The third defense line is constituted by the lymph nodes, which are arranged along the major bronchi and extend to subsegmental bronchi about 5 mm in diameter (Fig. 2-33). The most peripheral lymph nodes are tiny, a mere 1 to 2 mm in diameter, but closer to the hilum they become larger, reaching 5 to 10 mm in diameter in the region of the tracheal bifurcation and along the trachea. The lymph nodes from adult human lungs often appear gray or even black because of deposition in the medullary cords of large numbers of macrophages loaded with carbon pigment. This material entered the lung via the airways, primarily as smoke, soot, or coal dust; depending on the size of the particles, they either were deposited on the surface of conducting airways or reached the alveoli. The further down the deposition, the greater the likelihood that this material cannot be eliminated while in the airways, that is, within the mucus blanket. The only exit from the lung parenchyma then is via the lymphatics, but this exit ultimately leads to the blood, a circumstance that is obviously to be avoided. Filtering the lymph in lymph nodes and providing a depository in the medullary cords protects the blood and hence the entire organism from dissemination of indigestible foreign matter and also, in most instances, of infective agents.

Thus, the lymphatic "circulation" in the lung plays an important defense role.[6,44] It is unidirectional. It begins as interstitial fluid that seeps from the capillaries and is efficiently drained along the connective tissue fibers toward those connective tissue sleeves in the center and at the periphery of acini where lymph capillaries begin. From there, lymphatic vessels, endowed with valves and an irregular smooth muscle wall, course in septal structures, in the pleura, and peribronchial and perivascular sheaths toward the hilar region (Fig. 2-33). Lymph nodes are intercalated in the course of the lymphatics, which lead the lymph toward the tracheal bifurcation and then along the trachea into the right and left mediastinal lymph

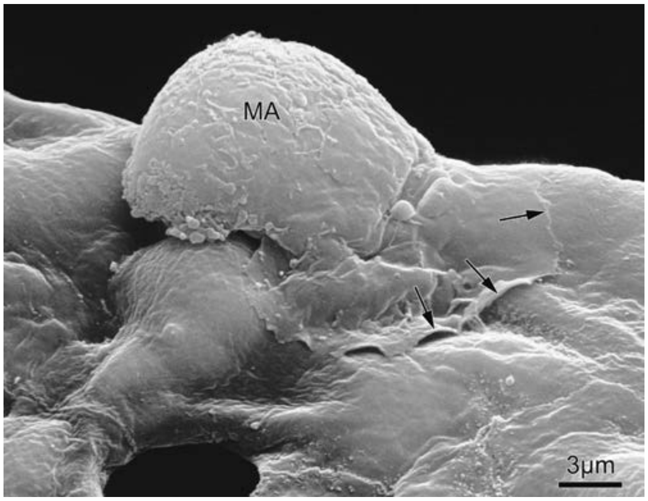


Figure 2-34 Alveolar macrophage (MA) seen sitting on epithelial surface of human lung. Note cytoplasmic lamella *(arrows)* which represents the advancing edge of the cell.

channels. The right channel drains into the right subclavian vein; the left, together with the thoracic duct, into the left subclavian vein. Because of the many anastomoses connecting parallel lymphatics, a particular lymph node receives lymph from various lung regions, but the closest regions tend to predominate.

■ Alveolar Macrophages

Lung macrophages can be differentiated into several populations according to the compartment in which they are found: intravascular, interstitial, airway, and alveolar macrophages.[149–152] Of these, the alveolar macrophages, the cell population of the surface lining layer, are of particular importance. They are free cells, endowed with a high phagocytic capacity, which are transiently attached to the surface of the alveolar epithelium by pseudopodia and can crawl over this surface by amoeboid movement (Fig. 2-34). Occasionally, alveolar macrophages can be observed during the passage through an interalveolar pore of Kohn. However, they are submerged beneath the surface film of phospholipids (Fig. 2-35) and, therefore, are part of the surface lining layer of alveoli, more specifically of its hypophase. Alveolar macrophages exert their phagocytic activity within the surface lining layer (Fig. 2-25). Hence, it is not surprising that their vacuoles contain large amounts of ingested surfactant material, in part even tubular myelin. The importance of alveolar macrophages for surfactant removal is underscored by the acquired form of pulmonary alveolar proteinosis, where a defect in surfactant catabolism by alveolar macrophages caused by autoantibodies against granulocyte/macrophage colony-stimulating factor (GM-CSF) leads to an accumulation of surfactant material in the alveoli.[153]

Alveolar macrophages are initially derived from monocytes—indirectly, therefore, from hematopoietic cells—and probably reach the alveoli in two steps: first, by settling in the pulmonary interstitial tissue, and second, by migration from the interstitial tissue into the alveoli where they constitute a partly self-reproducing cell population. Under certain circumstances, e.g., during inflammation, this resident pool can be supplemented by alveolar macrophages freshly recruited from circulating monocytes.[154,155] Their removal seems to involve two different pathways: (1) some of the macrophages undoubtedly move up the bronchial tree in the mucus blanket and eventually appear in the sputum; and (2) others possibly return into the interstitial space. In the normal lung, however, the second path seems to occur exclusively in those alveoli that abut the connective tissue sleeves around larger vessels and conducting airways or on interacinar septa; that is, where the lymphatic capillaries are located. A preferred location appears to be in the respiratory bronchioles at the entrance into the acinus or in the center of the acinus, where one often finds congregations of dust-laden macrophages; this may be at the origin of centroacinar damage observed in smokers, which leads to progressive emphysema. In these places, macrophages either settle as carbon pigment-loaded histiocytes, or they leave the lung parenchyma via lymphatics (Fig. 2-31) to settle in the lymph nodes. The way in which macrophages and/or their ingested material are transferred from the alveolar surface to the interstitial space is still unknown.

FUNCTIONAL DESIGN OF THE LUNG

From the preceding section it has become apparent that the lung is built of a multitude of cells and tissue elements that all serve specific functions in support of the lung's main function: the exchange of oxygen and carbon dioxide between the air and the blood. But it takes more than cells to make a good lung.[156] The lung's multiple component structures must be integrated to make an efficient and stable gas exchanger, and this demands a blueprint for the integral architecture of the human lung.[7] This must first ensure that the airways and blood vessels are adequately correlated topologically and quantitatively to allow well-matched ventilation and blood flow. It must also realize a complex organization that allows air ventilation, blood perfusion, and gas exchange to function in the most efficient manner. The design principles that govern the architecture of the human lung toward that goal can be characterized as *Complexity, Correlativity,* and *Connectivity*. Complexity means that the microscopic gas-exchange units are an integral part of the macroscopic airways and vessels; their architectural correlation determines the efficient approximation of air and blood in the gas exchanger; and connecting all the parts into a whole is achieved with a fiber continuum that pervades the entire lung. The implementation of these principles during development is decisive for "making a good lung."

■ Design of the Branching Airway Tree

The entrance to the lung's airways is the trachea (Fig. 2-3), a single tube. The gas-exchange elements where air and blood are brought into close contact are contained in several million units. Between entrance and periphery lies a meticulously designed system of branching airways that serve to conduct the inspired air into those peripheral channels that carry alveoli in their walls and can thus contribute to the exchange of gases between air and blood (Fig. 2-5).[8]

In the mammalian and human lung the airways are built as dichotomous trees.[157] This is the result of lung morphogenesis where the end bud of each airway tube gives rise to two daughter branches. In the human lung this goes on for 23 generations, on average, and, since the number of branches doubles with each generation, there are 2^{23} or about 8 million end branches, generally called *alveolar sacs*.[8] This is an average value; in reality the number of branching generations needed to reach the alveolar sacs is quite

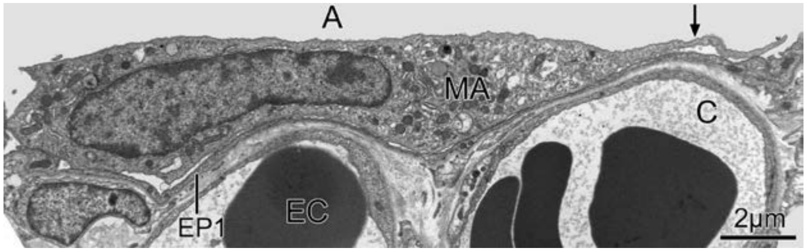


Figure 2-35 Alveolar macrophage (MA) fixed in its natural position of "flat" attachment to the alveolar epithelium. *Arrow* points to advancing cytoplasmic leaflet.

AL GRAWANY

variable, ranging from about 18 to 30. This variability results from the fact that the airways form a space-filling tree (Fig. 2-3) whose endings must be homogeneously distributed in space and reach into every corner and into every gap in the available space, determined by the form of the chest cavity into which the lung develops. Some spaces are filled rapidly and the airways cannot continue to divide, whereas in other places more branches are needed to fill the space.

This branching process is accompanied by growth in length and diameter of the airway segments, the tubes between the branching nodes. The length of the tubes is adjusted to cover the distances needed to fill the space homogeneously with endings, whereas the diameter is, grossly speaking, made proportional to the volume of peripheral lung that is supplied by this branch.

Figure 2-36 shows a portion of a cast of the airway tree from a human lung. It is evident that the airways branch by dichotomy and that the length and the diameter of the tubes become gradually reduced with each generation. At first sight, the airway branching seems quite regular, but there is a certain degree of asymmetry in the sense that the two daughter branches differ in length and diameter; in animal lungs asymmetry is more pronounced than in human lungs.

Despite asymmetric branching some general rules govern the progression of dimensions along the tree. The diameter of daughter branches is smaller than that of the parent in the sense that the diameter reflects the volume of peripheral lung it supplies with air: larger airways serve larger lung units, smaller airways smaller units. The progression of airway diameters follows the law of Hess (1917)[158] and Murray (1926)[159] that, in a dichotomous tree, the diameters of the daughter branches, d_1 and d_2, are related to the parent branch d_0 as:

$$d_0^3 = d_1^3 + d_2^3$$

a law that predicts optimization of the airway diameters for convective air flow, providing lowest resistance for lowest dead space.

For a symmetric tree in which $d_1 = d_2$ this becomes:

$$d_1 = d_0 \cdot 2^{-1/3}$$

which means that the airway diameter becomes reduced by a factor of cube root of 1/2 or about 0.79 with each generation. Considering the progression of airway dimensions along the tree, this law should apply to all successive generations so that we predict the average diameter in generation z to be:

$$d(z) = d_0 \cdot 2^{-z/3}$$

Figure 2-37 shows that this is approximately the case for the first 14 generations of conducting airways.

However, a closer look at the airways of the human lung shows that this is only approximately correct.[160] It appears that the smaller bronchioles (beyond generation 10) are provided with some safety factor in that the diameter is reduced by a factor of 0.83 rather than the physically optimal 0.79. This allows regulation of airway cross-section by contraction of the bronchiolar muscle sleeve without unduly increasing flow resistance which is very low in small airways (Fig. 2-38).[161] Design optimization is limited in favor of physiologic robustness.

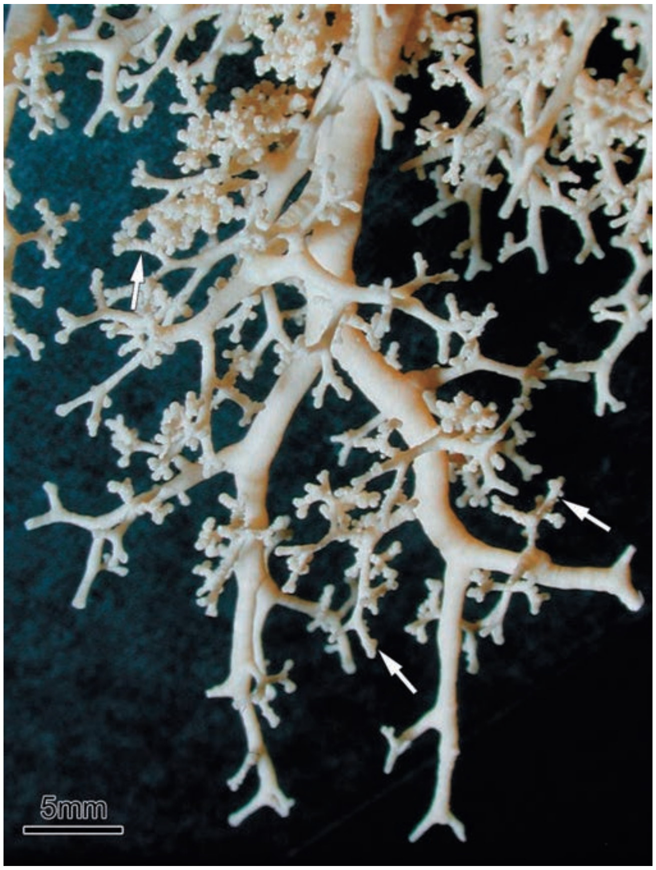


Figure 2-36 Peripheral portion of cast of human airway tree reaching out to the transitional bronchioles and some respiratory bronchioles *(arrows)*.

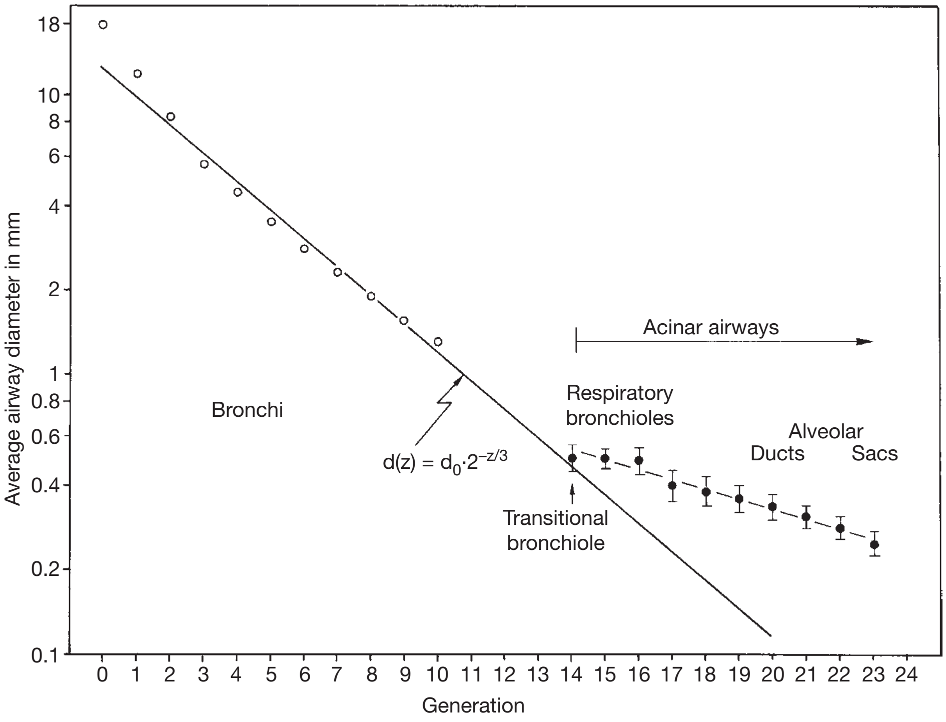


Figure 2-37 Average diameter of airways in human lung plotted by generations of regularized dichotomous branching. *(Reproduced with permission from Haefeli-Bleuer B, Weibel ER: Morphometry of the human pulmonary acinus. Anat Rec. 1988;220(4):401–414.)*

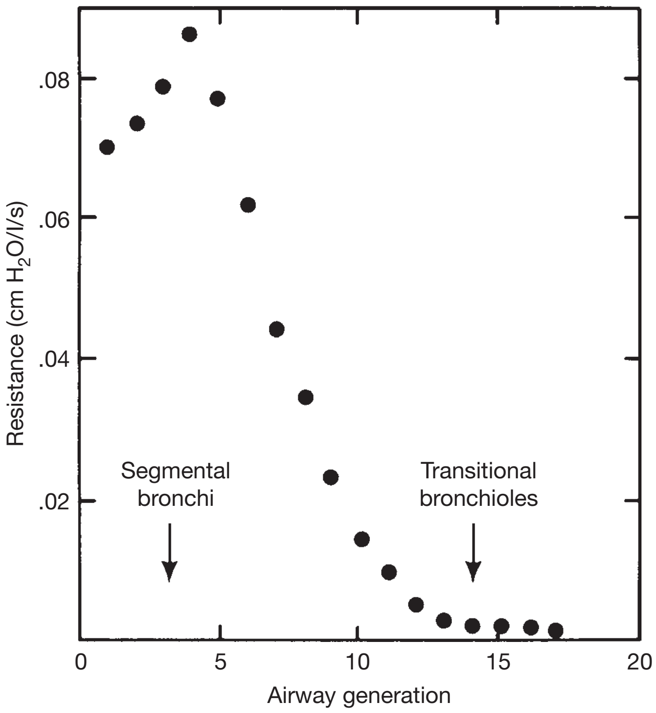


Figure 2-38 Airway resistance to mass air flow is located mostly in the conducting airways and falls rapidly toward the periphery. *(Reproduced with permission from Pedley TJ, Schroter RC, Sudlow MF. The prediction of pressure drop and variation of resistance within the human bronchial airways, Respir Physiol. 1970;9(3):387-405.)*

This symmetric airway model reflects the typical pathway along the airway tree. It has been very useful in modeling the basic rules governing the distribution of air flow as well as the deposition of particles entering the lung. However, it disregards the effects of asymmetric branching. It is possible to construct models that take into account irregularities in branching, for example by considering the number of airways of a given diameter, d_u, that exist in each generation, and the length of the bronchial pathway that intervenes between the larynx and particular airways (Fig. 2-39).[8,162]

An alternative approach is to regard the airways as a system of tubes converging from the periphery, the acinus, toward the center, the trachea.[163] By using an ascending ordering system that is employed in analyzing rivers (Strahler system), branches are grouped into orders according to the sequence of convergence, beginning with the smallest most peripheral branches, designated as order l. This ordering pattern is particularly well adapted to a system of irregular dichotomy because the size of branches in one order varies less than with the generations-down model. This approach does not really account for the asymmetry of branching, however; it rather represents an attempt at extracting average data with less variability in each order. The degree of asymmetric branching is reflected in the branching ratio determined as the ratio of the number of branches in order μ to that in order $\mu + 1$. Remarkably, the progression of diameters through the various orders is again roughly proportional to the cube root of the branching ratio. Hence, from a functional point of view both models yield comparable results.

The general conclusion drawn from this type of analysis is that the diameters of the conducting airways are such as to assure optimal conditions for airflow but relaxing physical optimality conditions in the interest of physiologic robustness; the airways of the lung are thus well designed. The total volume of the conducting airways down to generation 14 (the anatomic dead space) is about 150 mL; it is rapidly flushed by simple gas flow in the course of inhaling 500 mL of fresh air during quiet inspiration. Therefore, for the larger airways, optimization for flow and its distribution to peripheral units are essential for good design.

These are the characteristics of the proximal airways built as smooth-walled tubes to distribute convective air flow into the lung. This design ends more or less abruptly when the airways reach lung parenchyma, the complex of alveoli that are arranged around peripheral airways (Fig. 2-40). The airway tree is thus subdivided into two major functional zones (Fig. 2-5): the first about 14 to 16 generations, on average, are designed as conducting airways where air flow is by convection; this is followed by about 8 generations of acinar airways where an axial channel, called *alveolar duct*, is enwrapped by a sleeve of alveoli with gas-exchange tissue on their surface.

In the human lung the transition is not abrupt. At some point the smooth bronchiolar wall becomes interrupted by one or two alveoli (Fig. 2-41). This so-called *transitional bronchiole* (Fig. 2-5) marks the entrance into an acinus.[9] It is followed by some three generations of respiratory bronchioles where an increasing fraction of the wall surface is occupied by alveoli, until the alveolar ducts are reached where the central air duct is completely surrounded by alveoli (Fig. 2-42). These acinar airways continue to branch by dichotomy. Their length and diameter decrease with each generation, but the slope does not follow the law of reduction by the cube root of 1/2; the diameters of respiratory bronchioles and alveolar ducts change very little with each generation.[9] Does this arrangement imply less than an optimal design? On the contrary, the cube-root-of-1/2 law relates to optimizing mass flow of a liquid or air. In the most peripheral airways, mass airflow is only part of the means of transporting O_2 toward the air–blood barrier. Since the airways are blind-ending tubes and since a sizable amount of residual air remains in the lung periphery after expiration, O_2 molecules must move into the residual air by diffusion (Fig. 2-43). However, diffusion of O_2 in the gas phase is best served by establishing as large an interface as possible between residual air and the fresh air that flows in from the trachea.[16] In fact, since the airway diameter remains nearly unchanged, the total airway cross section nearly doubles with each generation beyond generation 14.

The dimensions of the airway tree influence the ventilatory flow of air in a number of ways. First of all, airflow velocity falls along the airway tree because the total cross-sectional area of the airways increases with every generation (Fig. 2-44); whereas the cross-sectional area of the trachea is about 2.5 cm^2, that of the 1024 airways in the 10th generation taken together is 13 cm^2, and as we approach the acinar airways, the total cross section reaches 300 cm^2. However, since the same air volume flows through all generations, the flow velocity falls by more than 100-fold from the trachea to the acini: at rest, the mean flow velocity on inspiration is about 1 m s^{-1} in the trachea and less than 1 cm s^{-1} in the first-order respiratory bronchioles. In exercise, the flow velocities are up to 10 times greater, in proportion to the increased ventilation. This is discussed further when considering the relative importance of convection and diffusion in bringing O_2 to the alveolar surface for gas exchange.

The size of airways also determines the resistance to airflow. However, the overall resistance is rather small; it is given by the reciprocal of the ratio of ventilatory airflow to the pressure difference between the mouth and alveoli, which is normally no greater than about 1 cmH$_2$O (mbar) or less than 1 mm Hg. It is large enough, however, to potentially affect the distribution of ventilation to the many gas-exchange units. Because, in laminar flow, the resistance is inversely proportional to d^4 the distribution of air flow depends on a delicate balance of the size of parallel airway tracts. Even a slight narrowing of one of the two daughter branches at

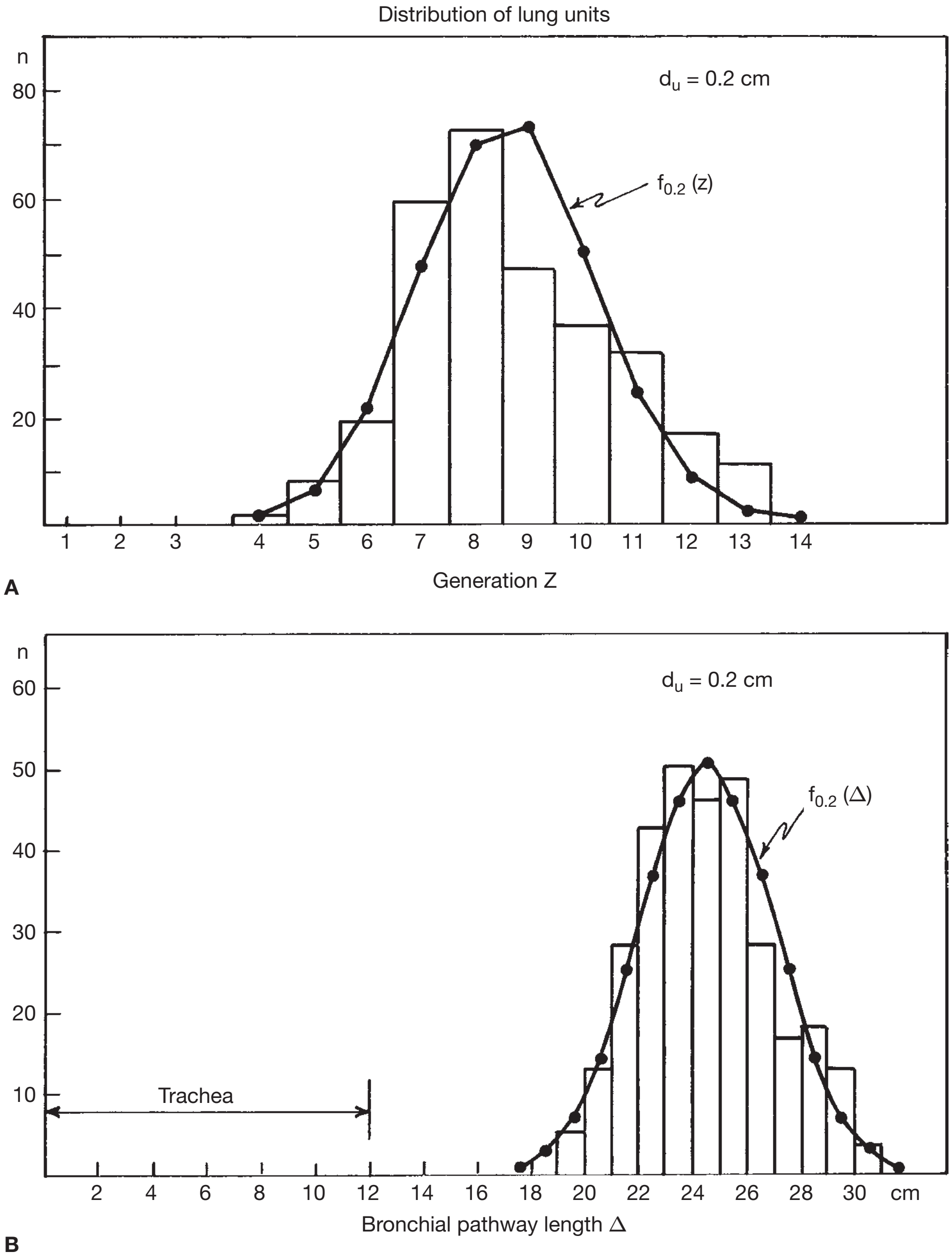


Figure 2-39 Distribution of airways of diameter d_u = 2 mm with respect to (**A**), generations of branching and (**B**), bronchial pathway lengths. *(Reproduced with permission from Weibel ER: Morphometry of the Human Lung. Heidelberg: Springer-Verlag; 1963.)*

a branch point will cause disproportionate air flow to the other branch and thus result in ventilation inhomogeneity.

Since the diameter of airways decreases as they branch (Fig. 2-37), one would suspect that their resistance increases toward the periphery. Apparently, this is not the case, as the major pressure drop along the airways occurs in medium-sized bronchi; because the airway diameter decreases with a factor larger than the optimal 0.79, resistance becomes very low in the small bronchioles (Fig. 2-38).[161] This is further accentuated by the fact that the thin-walled bronchioles become widened as the lung expands on inspiration because they are subject to the tissue tensions in the coarse fiber system of the lung. Therefore, airway resistance is seen to fall as lung volume increases. When this effect of tissue tension is disturbed, as in emphysema, some small bronchioles may collapse. This causes ventilation of the peripheral lung units to become highly uneven.

This biophysical way of looking at the significance of the progression of airway dimensions has recently been complemented by the alternative notion that the airway and vascular trees could be determined by the laws of fractal geometry.[164] Fractal trees are formed by repeating the branching pattern from one generation to the next. If the proportion between parent and daughter branches remain the same this is called *self-similar branching*. In a dichotomous tree the diameter is ideally reduced by a factor of $2^{-1/D_f}$ where D_f is the fractal dimension. Since the airway tree is nearly space-filling $D_f \sim 3$, which means that the Hess–Murray law also follows from fractal geometry as a rule of optimal design, but because the reduction factor is somewhat larger than $2^{-1/3}$ it follows that the actual fractal dimension of the airway tree is a bit larger than 3; this is possible because the tree is "cut off" at the entrance to the acini and the "space" becomes filled with alveoli.[165,166]

■ Design of the Vascular Tree

In many ways, the course and pattern of dimensional changes in the pulmonary blood vessels resemble those of the airways. Figure 2-3 shows that the pulmonary arteries follow the airways closely, out to the smallest branches; together they form the axis of lung parenchymal units of varying order: acinus, lobule, segment,

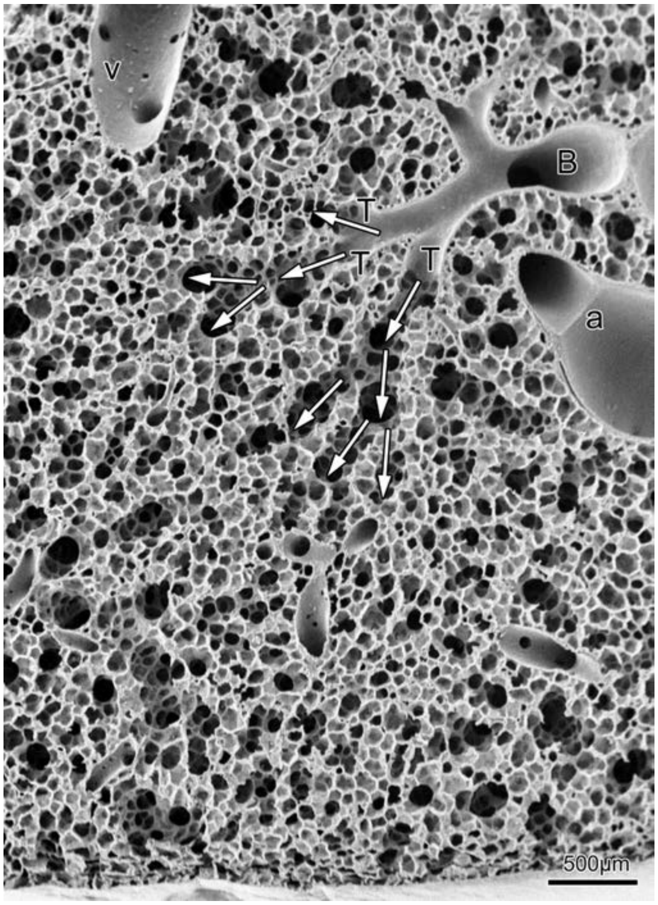


Figure 2-40 Scanning electron micrograph of lung shows branching of small peripheral bronchiole (B) into transitional bronchioles (T), from where the airways continue into respiratory bronchioles and alveolar ducts *(arrows)*. Note the location of the pulmonary artery (a) and vein (v) as well as visceral pleura *(bottom)*.

lobe. As indicated, the veins are differently disposed, lying in the boundary between two or three adjacent units (Figs. 2-30 and 2-45).

The diameter of each pulmonary artery branch also approximates closely that of the accompanying bronchus (Fig. 2-45A). Therefore, it is evident that the diameter law presented earlier for airways must also hold for the first 10 to 16 generations of pulmonary arteries (Fig. 2-37). However, the pulmonary arteries divide more frequently than the airways; very often, small branches leave the artery at right angles and supply blood to the parenchymal units adjacent to the bronchus (Fig. 2-45B). From a count of precapillaries, it seems that the pulmonary arteries divide, on the average, over 28 generations, as compared with 23 for the airways. The diameter of these terminal vessels is about 20 to 50 µm; if this range is plotted onto an extension of the graph of Fig. 2-37 to generation 28, it falls on the curve that is obtained by extrapolation from the major branches[8,16]:

$$d(z) = d_0 \cdot 2^{-z/3}$$

This suggests that the pulmonary arteries abide to the cube-root-of-1/2 law from beginning to end. Evidently, the blood is transported to the capillary bed by mass flow only. Therefore, there is no reason to deviate from this fundamental law of design, which minimizes the loss of energy caused by blood flow.

In a thorough analysis of the pulmonary vascular trees[167] conceived as fractal structures it has been shown that the fractal dimension of both arteries and veins is 2.71, thus somewhat less than 3.

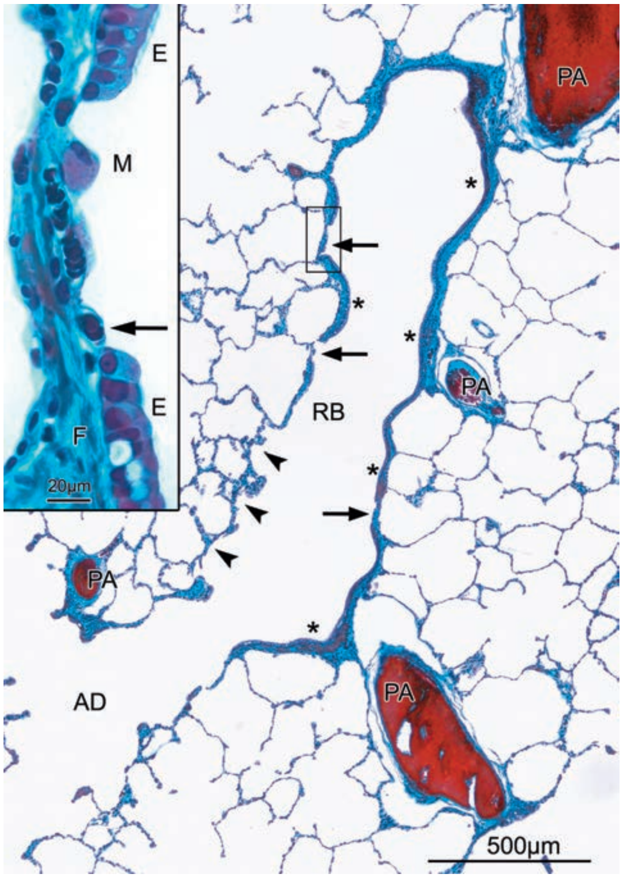


Figure 2-41 Respiratory bronchiole (RB) from human lung cut along its axis toward the transition to alveolar ducts (AD). Note lining by cuboidal airway epithelium *(asterisks)* and the occurrence of respiratory patches *(arrows)* before alveoli proper *(arrowheads)* appear. PA marks branches of pulmonary artery. *Inset:* Higher magnification of one of the respiratory patches in the wall of the respiratory bronchiole with capillaries *(arrow)* and alveolar macrophage (M). The cuboidal epithelium (E) with cilia is replaced by thin squamous epithelium of alveolar type 1 cell. Note thick fibrous layer (F) with smooth muscle cells.

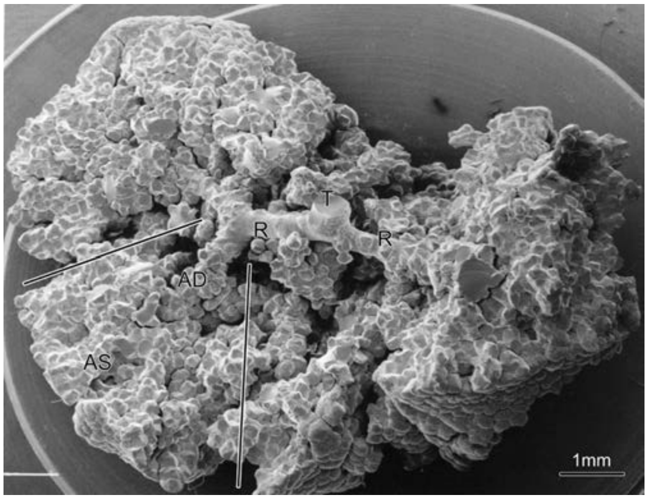


Figure 2-42 Scanning electron micrograph of a complete acinus from a silicon rubber cast of a human lung partly dissected to show transitional (T) and respiratory (R) bronchioles as well as alveolar ducts (AD) and alveolar sacs (AS). Lines mark approximate boundary of 1/8 subacinus. *(Reproduced with permission from Haefeli-Bleuer B, Weibel ER: Morphometry of the human pulmonary acinus. Anat Rec. 1988;220(4):401–414.)*

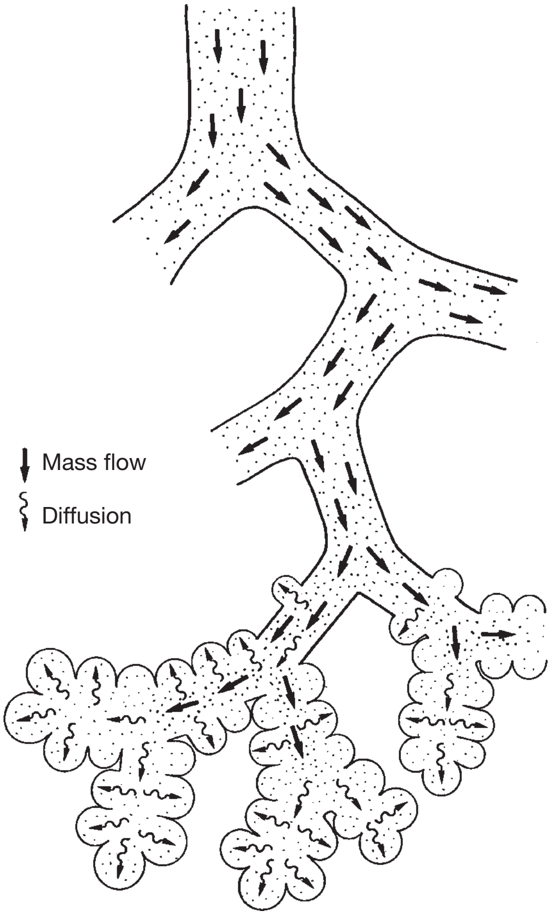


Figure 2-43 Oxygen molecules reach alveoli by combined mass airflow and molecular diffusion, the importance of diffusion increasing toward the periphery.

The diameter reduction factor is therefore slightly smaller than cube-root-of-1/2, and the diameters follow the regression:

$$d(z) = d_0 \cdot 2^{-z/2.71}$$

Therefore, in contrast to the airways, the resistance to blood flow increases along the pulmonary arteries and is highest in the most peripheral branches or arterioles. The resistance profile of the pulmonary arteries is thus the same as in the systemic circulation.

The alveolar capillary network of the lung is very different from that of the systemic circulation. Whereas in muscle, for example, long capillaries are found to be joined in a loose network, the capillaries of the alveolar walls form dense meshworks made of very short segments (Fig. 2-46).[8,168] The meshes are so dense that some people believe blood flows through the alveolar walls like a sheet rather than through a system of interconnected tubes. In this sheet-flow concept,[169] the sheet is bounded by two flat membranes, the air–blood barrier, connected by numerous "posts." When blood flows through this sheet, it is not channeled in a given direction but has freedom to move in a tortuous way between the posts. Although this concept oversimplifies the actual structural conditions, it does provide a useful description of the pattern of blood flow through the alveolar walls and explains why blood flow is not interrupted when some parts of the capillary bed become squashed flat at high inflation levels (see Fig. 2-58); the capillaries that remain open in the corners are simply some channels of this broad sheet. Furthermore, it is important to note that the capillary network or sheet is continuous through many alveolar walls (Fig. 2-46), probably at least throughout the entire acinus, if not for greater distances.[168] Consequently, it is not possible to isolate microvascular units. One finds, rather, that arterial end branches simply feed into this broad sheet at more or less even distances and that the veins drain these sheets in a similar pattern. However, now we must remember that the arteries reach the acinus along the airways, whereas the veins are in a peripheral location (Fig. 2-45). In principle, therefore, blood flows through the acinar capillary sheet from the center to the periphery of the acinar gas-exchange unit.

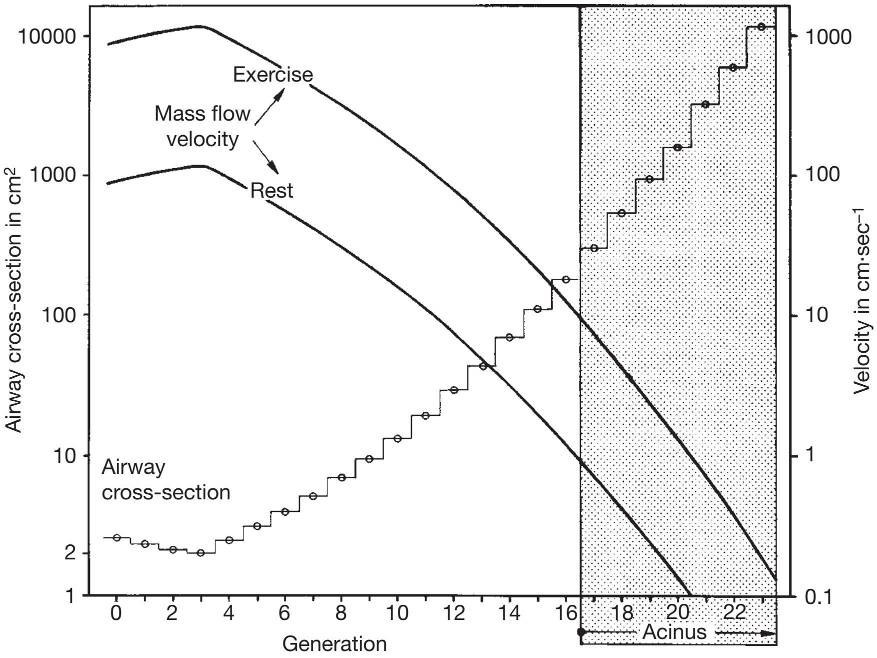


Figure 2-44 As total airway cross-section increases with the generations of airway branching, the mass flow velocity of inspired air decreases rapidly, falling below the molecular velocity of O_2 diffusion in air as we enter the acinus (see Fig. 2-66). *(The Pathway for Oxygen: Structure and Function in the Mammalian Respiratory System by Ewald R. Weibel, M.D., Cambridge, Mass.: Harvard University Press, Copyright © 1984 by the President and Fellows of Harvard College. Used by permission. All rights reserved.)*

DESIGN OF PULMONARY PARENCHYMA

The pulmonary parenchyma is a complex structure, the design of which is considered below.

■ Alveoli and Capillaries

The airspaces and blood vessels of lung parenchyma are designed to facilitate gas exchange between air and blood. To this end a very large area of contact between air and blood must be established; for the human lung it is sometimes compared with the area of a tennis court in size. Furthermore, the tissue barrier separating air and blood must be kept as thin as possible—it is found to be about 50 times thinner than a sheet of airmail stationery. This is important, because less than 1 second is available for loading O_2 onto the erythrocytes as they flow through the lung's gas-exchange region.[170]

The first design feature to this end is the formation of alveoli in the walls of all airways within the acinus—that is, in the ventilatory gas-exchange units beginning with a transitional bronchiole (see above) (Fig. 2-40). In the human lung, one estimates that there are about 30,000 acini,[9] and 400 million alveoli[171]

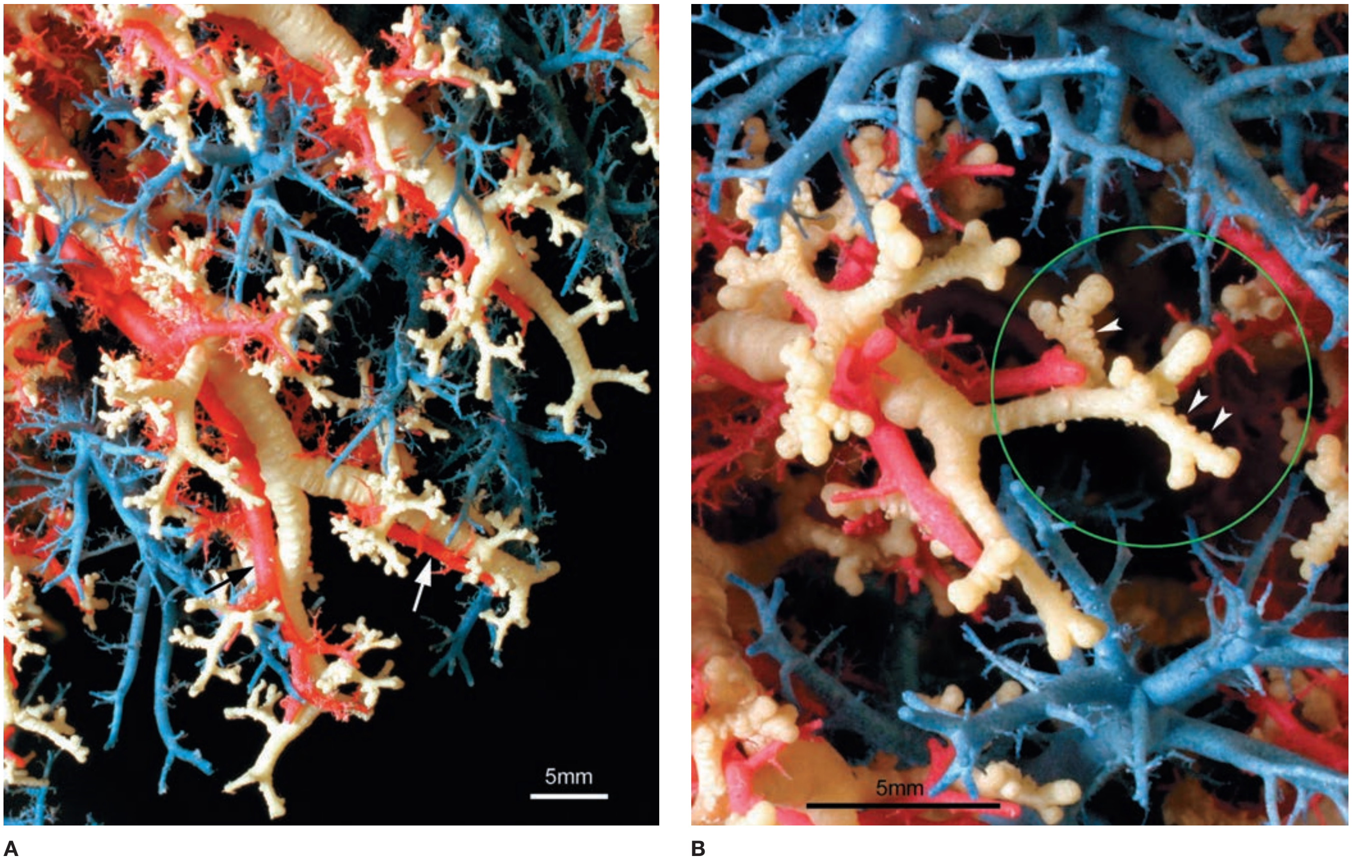


Figure 2-45 Casts of airways and blood vessels of human lung. **A.** shows how the pulmonary artery *(red)* closely follows the airways *(yellow)* to the periphery, whereas the pulmonary vein branches *(blue)* lie between the units. Note that the diameter of the pulmonary arteries is similar to that of the accompanying airway, but becomes relatively smaller toward the periphery *(arrow)*; small supernumerary arteries take off at right angles. **B.** Higher power view of group of acini *(circle)*, corresponding about to a secondary lobule, shows how artery penetrates into center of gas-exchange unit with veins collecting the blood around the periphery. *Arrowheads* point to alveolar pouches on transitional and respiratory bronchioles.

so that each of the ventilatory gas-exchange units contains some 13,000 alveoli, on average, connected to about seven to nine generations of acinar airways, respiratory bronchioles, and alveolar ducts.[9]

The alveoli are so densely packed that they occupy the entire surface of alveolar ducts; they are separated from each other by delicate alveolar septa that contain the capillary network (Fig. 2-47). About half the space of the septum is taken up by blood, which is thus exposed to the air in two adjacent alveoli (Fig. 2-48A). Although the barrier separating air and blood is extremely thin, we find the capillaries to be provided with a complete endothelial lining, as the alveolar surface of the septum is lined by an epithelium.[11] We have seen earlier that these two cell linings are very much attenuated over the greatest part of the surface.

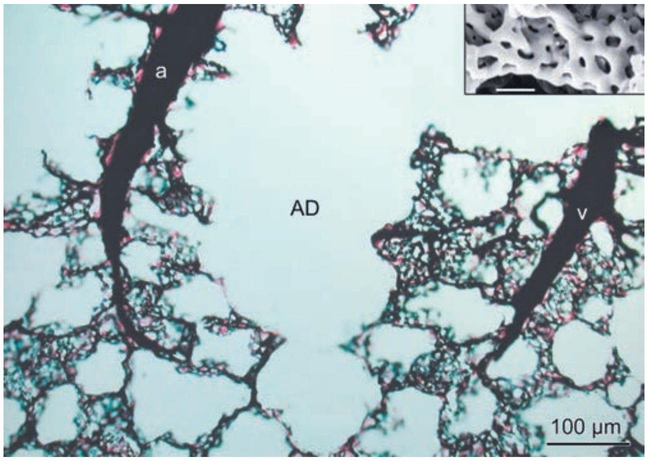


Figure 2-46 Alveolar capillary network demonstrated with gold labeling of blood plasma in a physiologically perfused preparation of a rabbit lung. The dense capillary network spans between end branches of pulmonary artery (a) and vein (v) and extend through many alveolar septa around alveolar duct (AD). *Inset:* Plastic cast shows the dense meshes of the network. Scale bar = 20 µm. *(Inset reproduced with permission from P. Burri.)*

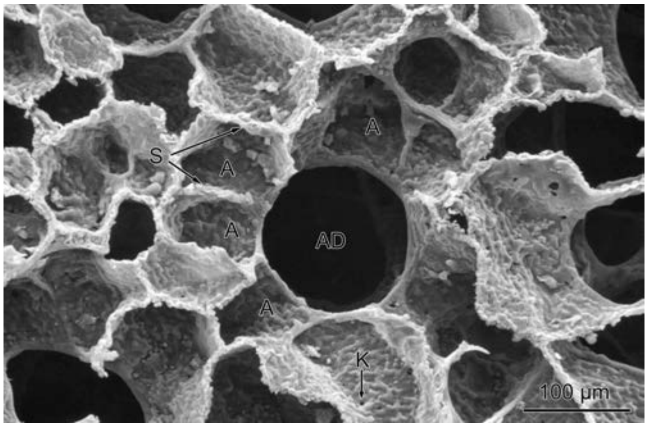


Figure 2-47 Scanning electron micrograph of human lung parenchyma. Alveolar ducts (AD) are surrounded by alveoli (A), which are separated by thin septa (S). K, interalveolar pore of Kohn.

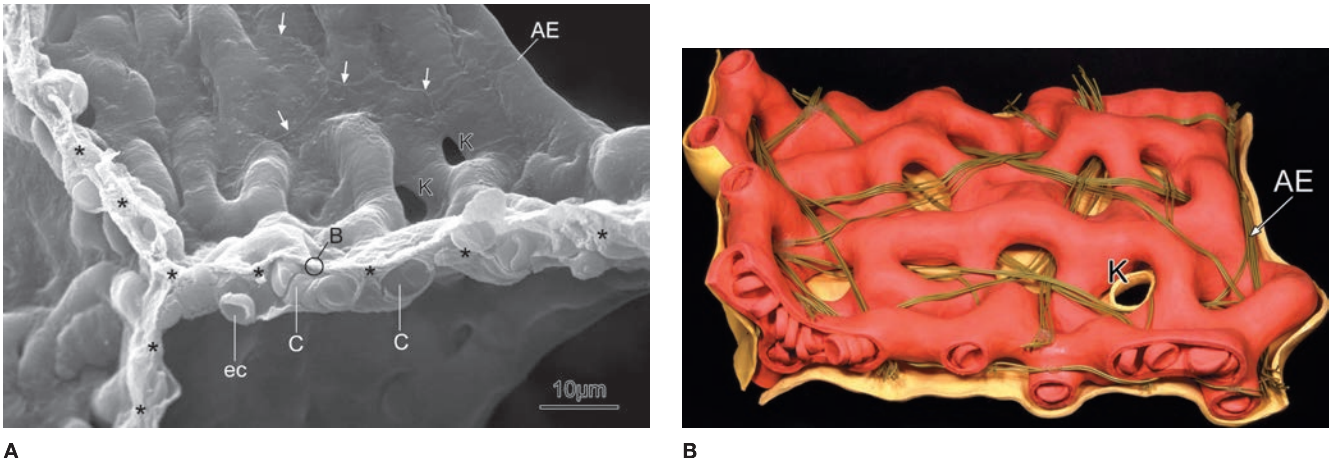


Figure 2-48 In the alveolar wall, shown in (**A**) in a scanning electron micrograph from a human lung, the capillary blood (C) with its erythrocytes (ec) is separated from the air by a very thin tissue barrier (B). *Short arrows* mark intercellular junctions of alveolar epithelium that course toward interalveolar pores of Kohn (K). The model (**B**) shows the capillary network *(red)* to be interwoven with the meshwork of septal fibers *(green)*, the course of which is marked by asterisks in (**A**). The epithelial lining *(yellow)* that crosses the septum at interalveolar pores (K) is removed on the upper surface of the septum to show the capillary. The septal fibers are anchored on the strong fiber bundle marking the free edge of the septum or the alveolar entrance ring (AE). *(The Pathway for Oxygen: Structure and Function in the Mammalian Respiratory System by Ewald R. Weibel, M.D., Cambridge, Mass.: Harvard University Press, Copyright © 1984 by the President and Fellows of Harvard College. Used by permission. All rights reserved.)*

To make the barrier very thin, the interstitial structures must also be reduced to the minimum required (Fig. 2-49). The septal interstitium contains very few cells, mostly slim fibroblast with long extensions; these contain fine bundles of contractile filaments that serve an as yet unknown mechanical function. The septal interstitium usually does not contain cells of the defense system or lymphatics.

■ Internal Support of Parenchymal Structures: The Pulmonary Fiber Continuum

This extraordinary reduction of the tissue mass in the alveolar septa inevitably introduces a number of major problems. How is it possible to secure the mechanical integrity of the system if we consider that several forces act on the septal tissue with a tendency to disrupt it? The thin barrier must not only withstand the distending pressure of the capillary blood due to both hemodynamic forces and gravity, particularly in the lower lung zones, but must also keep the capillary bed expanded over a very large surface—a task that is made difficult because surface forces that act on the complex alveolar surface would tend to collapse alveoli and capillaries (see further below). This requires a very subtle, economical design of the fibrous support system.[172,173]

The problem of supporting the capillaries on connective tissue fibers with as little tissue as possible has been solved ingeniously: we find that the fiber network is interlaced with the capillary network.[174] Figure 2-48B shows that when the fibers are taut, the capillaries weave from one side of the septum to the other. This arrangement has a threefold advantage: (1) it allows the capillaries to be supported unit by unit directly on the fiber strands without the need of additional "binders"; (2) it causes the capillaries to become spread out on the alveolar surface when the fibers are stretched; and (3) it optimizes gas-exchange conditions by limiting the presence of fibers, which must interfere with O_2 flow, to half the capillary surface. The thin section of a capillary shown in Fig. 2-49 reveals that an interstitial space with fibers and fibroblasts exists on only one side of the capillary, whereas on the other the two lining cells, endothelium and epithelium, become closely joined with only a single common basement membrane interposed. Therefore, over half the surface of the capillary blood is separated from the air merely by a minimal tissue barrier made of epithelial and endothelial cytoplasmic sheets with their basement membranes fused leaving no interstitial space that could enlarge with interstitial pulmonary edema (Fig. 2-17).

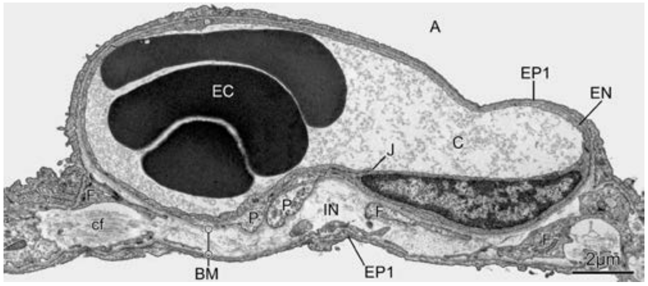


Figure 2-49 Alveolar septum from human lung lined by type I epithelium (EP1) with capillary lined by endothelial cell (EN) that is associated with processes of pericytes (P). Substantial interstitial space (IN) with collagen and elastic fibers (cf) and fibroblasts (F) occurs on one side only, whereas minimal air–blood barrier is formed on other side by fusion of basement membranes (BM) of endothelium and epithelium.

The principal structural "backbone" of the lung is a continuous system of fibers anchored at the hilum and put under tension by the negative intrapleural pressure that tugs on the visceral pleura.[173] The general construction principle follows from the formation of the mesenchymal sheath of the airway units in the developing lung; as the airway tree grows, its branches remain separated by layers of mesenchyme within which blood vessels form. When fiber networks develop within this mesenchyme, they enwrap all airway units and extend from the hilum right to the visceral pleura. The pulmonary fiber system hence forms a three-dimensional fibrous continuum that is structured by the airway system and is closely related to the blood vessels. By virtue of the design of this fibrous continuum, the lung becomes, in fact, subdivided into millions of little bellows that are connected to the airway tree, as represented schematically in Fig. 2-50; these structures expand with expansion of the chest because the tension exerted on the visceral pleura by the negative intrapleural pressure becomes transmitted to the bellows' walls through that fiber system.

To try to put some order into this fiber system, we can first single out two major components that can be identified easily (Fig. 2-50).

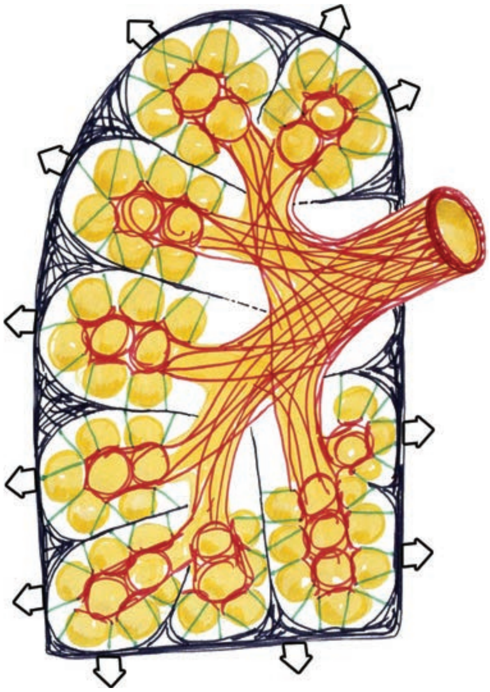


Figure 2-50 The lung's fiber continuum: axial fibers *(red)* extend from airways into the alveolar ducts as a network of entrance rings into alveoli *(yellow)*; peripheral fibers *(black)* extend from the pleura to interlobular septa; the septal fibers *(green)* in the alveolar walls are anchored in peripheral and axial fibers. *Arrows* indicate the traction on the pleura exerted by thorax and diaphragm. *(Reproduced with permission from Weibel ER: Looking into the lung: What can it tell us? Am J Roentgenol. 1979;133(6):1021–1031.)*

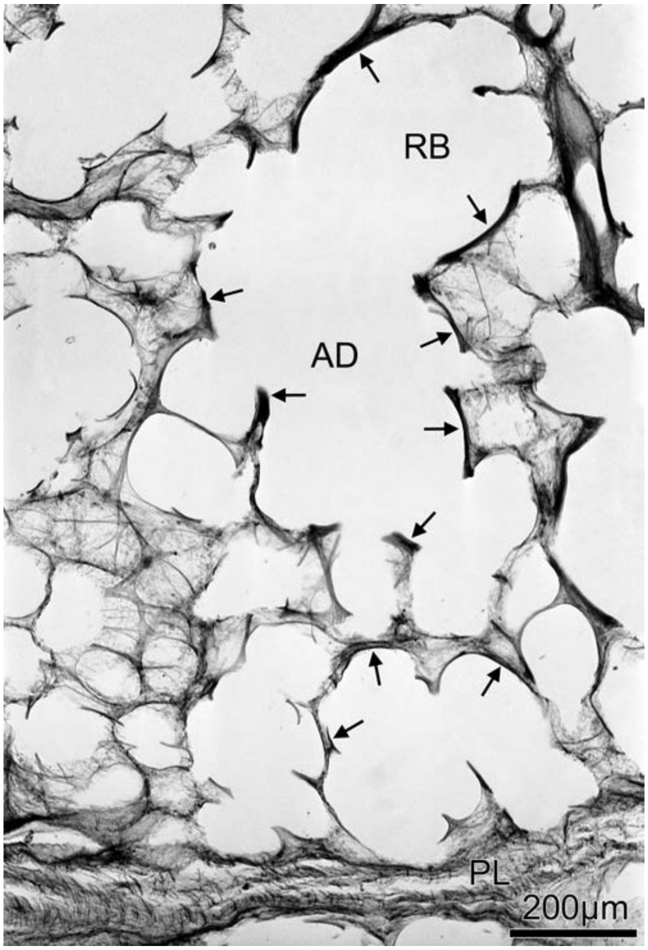


Figure 2-51 Connective tissue stain reveals the strong fiber rings *(arrows)* that demarcate the alveolar ducts (AD) and respiratory bronchioles (RB). Pleura (PL) extends as peripheral fibers into parenchyma. *(The Pathway for Oxygen: Structure and Function in the Mammalian Respiratory System by Ewald R. Weibel, M.D., Cambridge, Mass.: Harvard University Press, Copyright © 1984 by the President and Fellows of Harvard College. Used by permission. All rights reserved.)*

First, we find that all airways—from the mainstem bronchus that enters the lung at the hilum out to the terminal bronchioles and beyond—are enwrapped by a strong sheath of fibers. These fibers constitute the axial fiber system; they form the "bark" of the tree whose roots are at the hilum and whose branches penetrate deep into lung parenchyma, following the course of the airways. A second major fiber system is related to the visceral pleura, which is made of strong fiber bags enwrapping all lobes. We then find connective tissue septa penetrating from the visceral pleura into lung parenchyma, separating units of the airway tree. We call these fibers the peripheral fiber system because they mark the boundaries between the units of respiratory lung tissue.

The peripheral fiber system subdivides the lung into a number of units that are not simple to define because they form a continuous hierarchy in accordance with the pattern of airway tree branching. However, as we have seen, two such units appear to be natural: the lobes, which are demarcated by a more or less complete lining by visceral pleura with a serosal cleft interposed (Fig. 2-1); and the acinus, the parenchymal unit in which all airways participate in gas exchange.

The acinus is the functional unit of the pulmonary parenchyma. The airway that leads into the acinus, the transitional bronchiole, continues branching within the acinus for about 6 to 10 additional generations (Figs. 2-5 and 2-40). These intra-acinar airways, called *respiratory bronchioles* and *alveolar ducts*, also carry in their wall relatively strong fibers of the axial fiber system, which extend to the end of the duct system. However, since the walls of intra-acinar air ducts are densely settled with alveoli, these fibers are reduced to a kind of delicate network that constitutes the "wall" of the alveolar ducts. The meshes of this network that encircle the alveolar mouths are generally called *alveolar entrance rings*; it is this fiber network that allows alveoli to be formed as open chambers with free edges of the alveolar septa (Figs. 2-47 and 2-51).[156] These fiber rings are associated with some smooth muscle cells (Fig. 2-29), and they serve as a scaffold for a network of finer fibers that spread within the alveolar septa (Figs. 2-48B and 2-51). However, in a fiber system there may be no loose ends. Accordingly, the septal fiber system must be anchored at both ends—on the network of axial fibers around the alveolar ducts, and on extensions of the peripheral fibers that penetrate into the acinus from interlobular septa. Thus, the fiber system of the lung becomes a continuum that spans the entire space of the lung, from the hilus to the visceral pleura (Fig. 2-50). It is put under varying tension as the pleural bag is expanded by the chest wall and diaphragm. It thus functions as a tensegrity structure where structural integrity is maintained only if the fiber continuum is under tension and undisrupted.[175,176]

The continuous nature of a well-ordered fiber system is an essential design feature of the lung.[156] This becomes evident in emphysema. When some fibers are disrupted, they cannot be kept under tension. They retract and larger airspaces form as the fiber system is rearranged near the damage. Small foci of emphysema form in most lungs in the course of time.

The fiber system serves mainly as a mechanical support for the blood vessels, with which it is intimately associated in an orderly fashion.[156] The pulmonary artery branches in parallel with the airway tree, but it is not related to the axial fiber system. Like the pulmonary veins the pulmonary arteries are associated with those parts of the peripheral fiber system that form an adventitial sheath on the larger vessels of both types and also form a boundary sheath on the outer surface of bronchi where alveolar complexes touch on the bronchial wall. Therefore, it is justified to characterize the connective tissue surrounding bronchi and pulmonary arteries as a peribronchovascular space, which houses the lymphatics as well as the systemic bronchial arteries and their branches. In fact, this space is continuous with the septal connective tissue that enwraps the pulmonary veins (Fig. 2-30) and is continuous with the visceral pleura. However, whereas the arteries penetrate into the acinus, the veins remain at the periphery and are thus located between the airway units (Fig. 2-45). In the alveolar septa, the capillary network spreads out as a broad sheet of vessels whose paths are continuous throughout the system of interconnected alveolar septa (Fig. 2-46). We have seen that these capillaries are intimately related to the septal fiber system (Fig. 2-48B).

Parenchymal Mechanics and Tissue Design

As in all connective tissue, the fibers of the lung are composed of collagen and elastic fibers.[172] The collagen fibers are bundles of fibrils bound together by proteoglycans; they are practically inextensible (less than 2%) and have a very high tensile strength; they rupture at loads of 50 to 70 dyn/cm^{-2}, which means that a collagen fiber of 1-mm diameter can support a weight of over 500 g. In contrast, elastic fibers have a much lower tensile strength but a high extensibility. They can be stretched to about 130% of their relaxed length before rupturing.

In the fiber system of lung parenchyma, collagen and elastic fibers occur in a volume ratio of about 2.5:1, whereas this ratio is 10:1 for the visceral pleura. In a relaxed state, one finds the collagen fibers to be longer than the accompanying elastic fibers, so that they appear wavy. Because of the association between "rubber-like" elastic and "twine-like" collagen fibers, the connective tissue strands behave like an elastic band. They are easy to stretch up to the point where the collagen fibers are taut, but from there on they resist stretching very strongly.

The elastic properties of the lung's fiber system can be studied by filling the airways with fluid so as to eliminate the effects of surface tension. This reveals that the lung's fiber system has a high compliance until high levels of inflation are reached, and that the retractive or recoil force generated by the fiber system amounts to no more than a few millibars at physiologic inflation levels. The actual recoil force in the air-filled lung, reflected by the negative pressure in the pleural space, is appreciably higher, but this is caused by surface tension rather than the retractive force of the fibers.

Surface tension arises at any gas–liquid interface because the cohesive forces between the molecules of the liquid are much stronger than those between the liquid and gas.[177] As a result, the liquid surface tends to become as small as possible. A curved surface, such as that of a bubble, generates a pressure that is proportional to the curvature and the surface tension coefficient γ. The general formula of Gibbs relates this pressure, P_s, to the mean curvature $\overline{K}$:

$$P_s = 2\gamma \cdot \overline{K}$$

In a sphere, the curvature is simply the reciprocal of the radius r (Laplace's law):

$$P_s = \frac{2\gamma}{r}$$

The most critical effect of surface tension is that it endangers stability of the airspace, because a set of connected "bubbles," the alveoli, is inherently unstable: The small ones should contract and the large ones expand. Since the 400 million alveoli are all connected with each other through the airways, the lung is inherently unstable: Why do the alveoli not all collapse and empty into one large bubble? There are two principal reasons.[16,178,179]

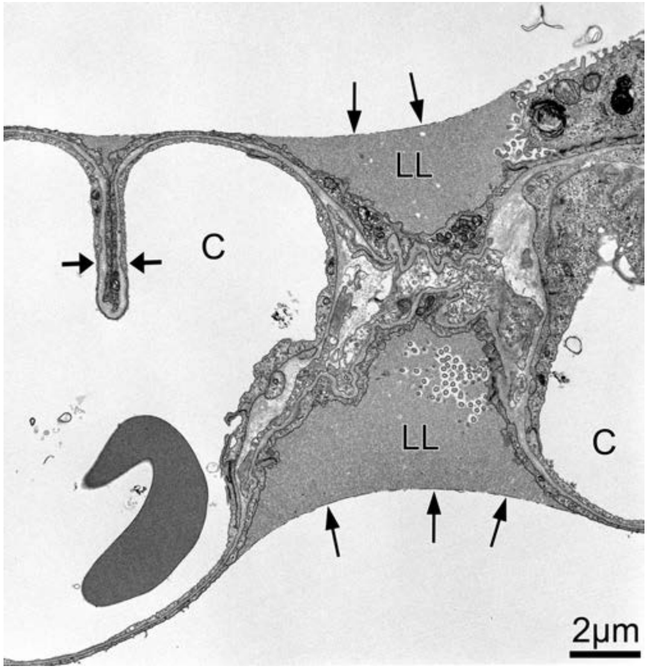


Figure 2-52 Alveolar septum of human lung fixed by perfusion through blood vessels shows alveolar lining layer (LL) in crevices between capillaries (C) topped by surfactant film that appears as a fine black line *(arrows)*. Note the type II cell with lamellar bodies and the fold in thin tissue barrier *(bold arrows)*. *(Reproduced with permission from M. Bachofen and G. Wolff Basel.)*

The first reason is one of tissue structure. The alveoli are not simply soap bubbles in a froth. Rather, their walls contain an intricate fiber system, as we have seen. Thus, when an alveolus tends to shrink, the fibers in the walls of adjoining alveoli are stretched, preventing the alveolus from collapsing altogether. Alveoli are said to be "mechanically interdependent" and, hence, stabilized.

The second reason is related to the fact that the alveolar surface is not simply water exposed to air but is lined by surfactant[180] (Figs. 2-25 and 2-52), which has peculiar properties in that its surface tension coefficient γ is variable.[177,181] From a large volume of evidence, it is now established that surface tension falls as the alveolar surface becomes smaller, and that it rises when the surface expands. Because of this feature, which is due to the phospholipoprotein nature of alveolar surfactant (see above), alveoli do not behave like soap bubbles whose surface tension remains constant. When an alveolus begins to shrink, the surface tension of its lining layer falls and the retractive force generated at the surface is reduced or even abolished. Combined with interdependence, this property of surfactant allows the complex of alveoli to remain stable.[178]

Which of the two factors for stabilizing lung structure is now the most important: interdependence or surfactant properties? It turns out that both are essential. If one depletes the lung of its surfactant lining by washing with a detergent, the pressure–volume curve changes dramatically[182] (Fig. 2-53). On deflation, lung volume falls rapidly. If we look at samples from lungs fixed at the same volume (60% total lung capacity) but derived from either normal or detergent-rinsed lungs, we find that surfactant depletion causes the alveoli to collapse. However, this causes the alveolar ducts to enlarge, stretching the strong fiber nets at the mouths of the collapsed alveoli. The ducts do not collapse because of interdependence between adjacent units.

In the normal air-filled lung, surfactant properties and interdependence owing to fiber tension both contribute to stabilizing

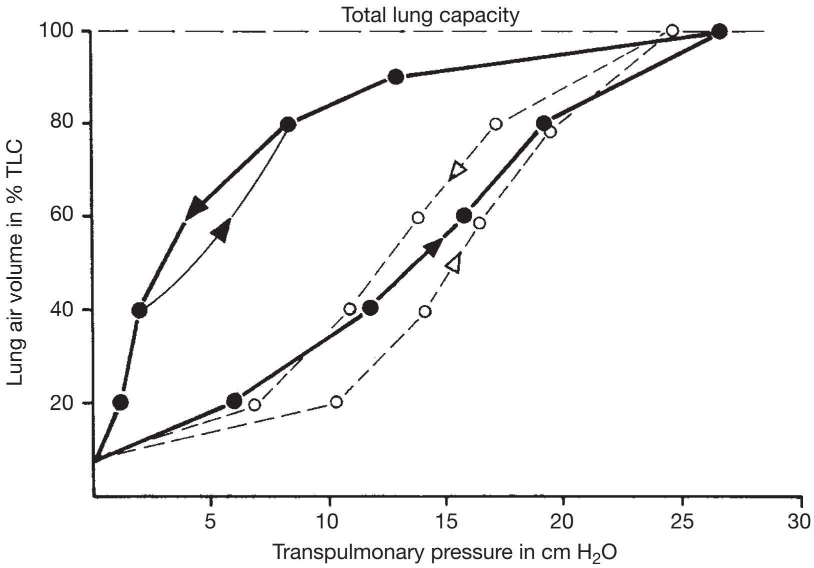


Figure 2-53 Comparison of pressure–volume curve of a normal air-filled rabbit lung *(heavy line)* with that of a surfactant-depleted lung *(broken line)*. The thin line with *paired arrows* represents small hysteresis when breathing between 40% and 80% TLC along the deflation curve.

the complex of alveoli and alveolar ducts.[183] To understand this, let us examine Fig. 2-54, which shows a highly simplified diagram of a parenchymal unit. Interdependence is established by the continuum of axial, septal, and peripheral fibers. Surface tension exerts an inward pull in the hollow alveoli, where curvature is negative. However, over the free edge of the alveolar septa, along the outline of the duct, the surface tension must push outward because there the curvature is positive.[16] The latter force must be rather strong, because the radius of curvature is very small on the septal edge; but this force is counteracted by the strong fiber strands, usually provided with some smooth muscle cells, that we find in the free edge of the alveolar septum (Figs. 2-29, 2-47, and 2-51). Thus, interdependence is an important factor in preventing the complex hollow of the lung, where negative and positive curvatures coexist, from collapsing. However, its capacity to do so is limited and requires low surface tensions, particularly on deflation when the fibers tend to slack. If surface tension becomes too high, the lung's foam-like structure will partly collapse in spite of fiber interdependence.

This is of considerable physiologic importance. It is sometimes claimed that alveoli pop open when the lung is inflated, collapsing on deflation. That is correct when starting with a deflated lung (Fig. 2-53): collapsed alveoli open up along the inflation curve. But that is not the way we breathe. The normal breathing cycle operates on the deflation slope of the pressure–volume curve (Fig. 2-53) with small hysteresis, a state that is maintained by taking a deep sigh intermittently up to TLC. In this condition the surface tension is kept low because the surfactant lining is spread out[181] and alveoli do not collapse. When we breathe in and out between 80% and 40% of total lung capacity, the range of normal breathing in exercise, alveoli change their size very little. In contrast to the twofold change in air volume the alveolar surface area changes by only about a factor of 1.2.[183] The reason for this is that the main change in air volume does not occur in alveoli, but predominantly in the alveolar ducts as shown in Fig. 2-55, and this is very favorable for acinar ventilation. This differential volume change can be explained by the effect of surface forces: at 40% TLC surface tension γ is nearly 0 but it increases to 12 $mN{\cdot}m^{-1}$ at 80% TLC 2. As the lung inflates this causes the positive surface force to become strong on the free edge of alveolar septa (Fig. 2-54), thus causing the duct cross section to widen, while shrinking when the forces decrease on deflation (Fig. 2-55). In this process the alveolar septa become stretched on inflation by only a small degree, a mere 20% in area. The acinus is thus well ventilated whereas the gas-exchange surface is little affected by varying air volume.[156]

■ Micromechanics of the Alveolar Septum

Finally, we must consider the mechanical factors that shape the alveolar septum in the air-filled lung. As we have seen, the alveolar septum is made of a single capillary network that is interlaced with fibers (Fig. 2-48). When the fibers are stretched, the capillaries bulge alternatingly to one side or the other, and this causes pits and crevices to occur in the meshes of the capillary network.

This irregular surface is to some extent evened out by the presence of an extracellular layer of lining fluid, which is rather thin over the capillaries but forms little pools in the intercapillary pits (Fig. 2-52).[184] This lining consists of an aqueous layer of variable thickness, called the *hypophase*, and surfactant, which forms a film on the surface of the hypophase. The hypophase seems to contain considerable amounts of reserve surfactant material, which occurs in a characteristic configuration called *tubular myelin* (Figs. 2-25 and 2-26).

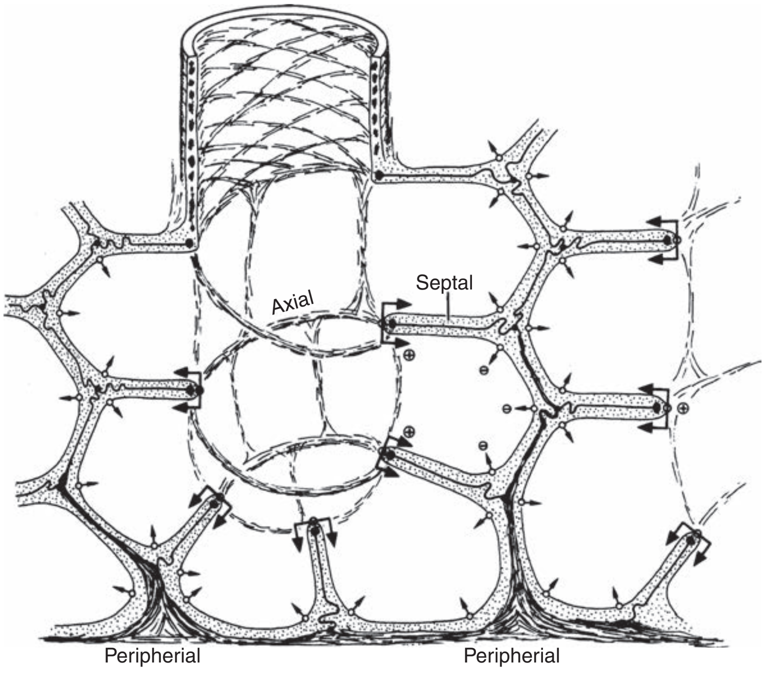


Figure 2-54 Model of the disposition of axial, septal, and peripheral fibers in an acinus showing the effect of surface forces *(arrows)*. *(The Pathway for Oxygen: Structure and Function in the Mammalian Respiratory System by Ewald R. Weibel, M.D., Cambridge, Mass.: Harvard University Press, Copyright © 1984 by the President and Fellows of Harvard College. Used by permission. All rights reserved.)*

AL GRAWANY

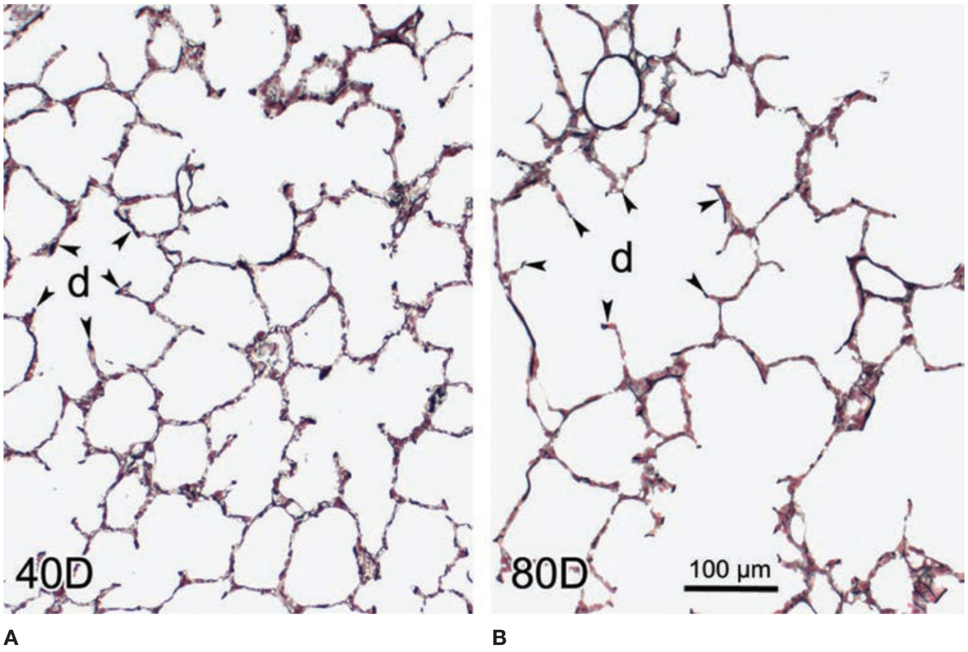


Figure 2-55 Light micrographs of sections of lung parenchyma in rabbit lungs perfusion fixed on deflation to 40% TLC (**A**), and 80% TLC (**B**), respectively (compare Fig. 2-53). Note that the size of the alveolar ducts (d) is markedly enlarged in 80D due to the surface forces acting on the free edges of alveolar septa *(arrowheads). (Reproduced with permission from H. Bachofen, University of Bern.)*

In the alveolar septum, the tissue structures are extremely delicate, as we have seen. Therefore, its configuration is not exclusively determined by structural features but results from the molding effect of various forces that must be kept in balance. Figure 2-56 shows how the three principal mechanical forces—tissue tension, surface tension, and capillary distending pressure—interact in the septum.[16] The fibers of the alveolar septum are under a tension whose magnitude depends on the level of lung inflation. This tends to straighten out the fibers, so that a force (pressure) normal to the fiber axis results, which is responsible for shifting the capillaries to one side of the septum or the other (Figs. 2-48B and 2-56). The walls of the capillaries are exposed to the luminal pressure, which is the result of blood pressure in pulmonary arteries and veins but also depends on gravity, for one finds wider capillaries at the bottom of the lung than at the top. If this distending pressure acts homogeneously over the circumference of the capillary, it will push against the fibers on one side but will cause the thin barrier on the opposite side to bulge outward. This effect is to some extent counteracted by surface tension, which exerts a force normal to the surface (Fig. 2-56). This force depends on two factors. Its direction depends on the orientation of curvature, acting toward the alveolar space over concave regions (negative curvature) and toward the tissue over convexities (positive curvature); and its magnitude depends on the degree of curvature and on the value of the surface tension coefficient γ.

The alveolar septum achieves a stable configuration when all these interacting forces are in balance.[185] Combined forces tend to squash the capillary flat; this happens at high levels of lung inflation when the fibers are under high tension and the surface tension coefficient of surfactant reaches its highest value because of expansion of the surface. On deflation, the fibers are relaxed, and surface tension falls drastically. The capillary distending pressure now exceeds both the tissue and the surface forces, with the result that the slack fibers are bent, weaving through the capillary network, whereas the capillaries bulge slightly toward the airspace. Surface tension is apparently so low as to permit a considerable degree of surface "crumpling" to persist (Fig. 2-57).

The importance of the balance between the forces that act on the septum is also shown in Fig. 2-58.[186] The specimen of panel B was fixed under zone 3 perfusion conditions, where capillary pressure is larger than alveolar pressure, and all the capillaries are wide, partly bulging toward the airspace, as in Fig. 2-57. This is different in panel A, which was fixed under zone 2 conditions where capillary pressure is close to alveolar pressure. In the flat part of the septum, the capillaries are squashed flat, because the surface and tissue forces now exceed the vascular distending pressure. However, it is interesting that the capillaries remain wide in the corners where three septa come together. The distribution of surface forces causes the internal pressure to be lower in the region of these corners, as we can see intuitively from Fig. 2-54.

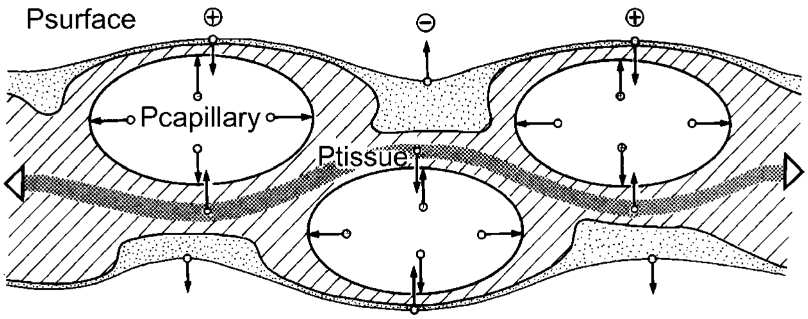


Figure 2-56 Model showing the micromechanical forces of surface tension, tissue tension, and capillary distending pressure that shape the alveolar septum. *(The Pathway for Oxygen: Structure and Function in the Mammalian Respiratory System by Ewald R. Weibel, M.D., Cambridge, Mass.: Harvard University Press, Copyright © 1984 by the President and Fellows of Harvard College. Used by permission. All rights reserved.)*

■ The Lung as Gas Exchanger

The structures discussed so far are designed to ultimately serve the lung's main function, gas exchange between air and blood, in relation to the body's varying O_2 needs.[187,188] These are set by the energetic demands of the cells and their mitochondria when these produce ATP by oxidative phosphorylation to allow the cells to do work. This process requires a flow of O_2 to be maintained from the lung to the cells, as will be discussed later. It proceeds along the respiratory system through various steps: into

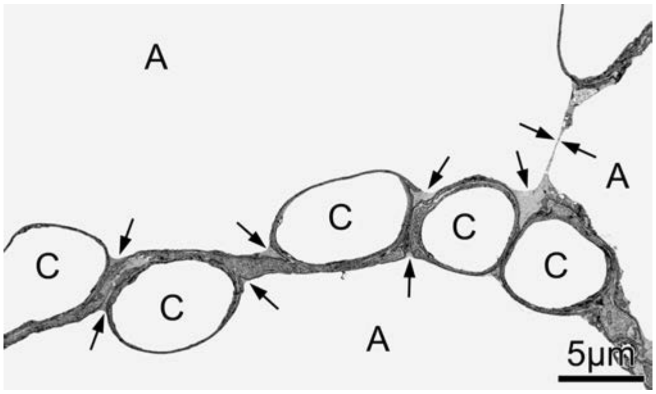


Figure 2-57 Alveolar septum of air-filled rabbit lung perfusion fixed at 60% TLC shows empty capillaries (C), which bulge toward the alveolar airspace (A). Note pools of surface lining layer in the crevices between capillaries *(arrows)* and film spanning across alveolar pore *(double arrows). (Reproduced with permission from Gil J, Bachofen H, Gehr P, et al. Alveolar volume-surface area relation in air- and saline-filled lungs fixed by vascular perfusion. J Appl Physiol Respir Environ Exerc Physiol. 1979;47(5):990–1001.)*

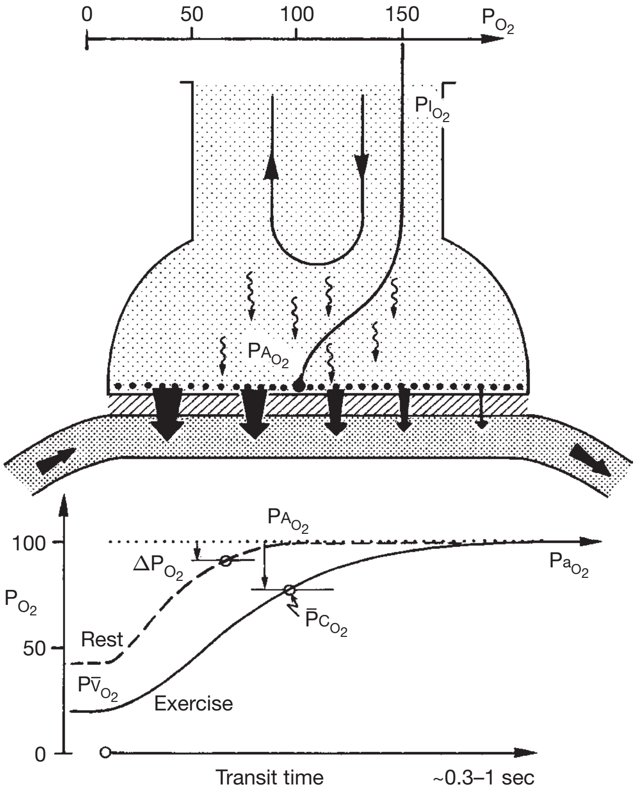


Figure 2-59 Model of gas exchange showing gradual rise of capillary P_{O_2} ($P_{c_{O_2}}$) as blood flows through capillary until it approaches alveolar P_{O_2} ($P_{A_{O_2}}$). *(The Pathway for Oxygen: Structure and Function in the Mammalian Respiratory System by Ewald R. Weibel, M.D., Cambridge, Mass.: Harvard University Press, Copyright © 1984 by the President and Fellows of Harvard College. Used by permission. All rights reserved.)*

the lung by ventilation, to the blood by diffusion, through the circulation by blood flow, from the blood capillaries by diffusion to the cells and mitochondria, where it disappears in the process of oxidative phosphorylation.[16] A number of basic features characterize this system[189]: (1) under steady-state conditions the O_2 flow rate, $\dot{V}_{O_2}$ is the same at all levels, that is, O_2 uptake in the lung is equal to O_2 consumption in the tissues; (2) the basic driving force for O_2 flow through the system is a cascade of O_2 partial pressure which falls from inspired P_{O_2} down to near zero in the mitochondria; (3) the O_2 flow rate at each step is the product of a partial pressure difference and a conductance which is related to structural and functional properties of the organs participating in O_2 transfer, as will be discussed below in detail.

With respect to gas exchange in the lung (Fig. 2-59), the O_2 flow rate is determined by the Bohr equation:[190]

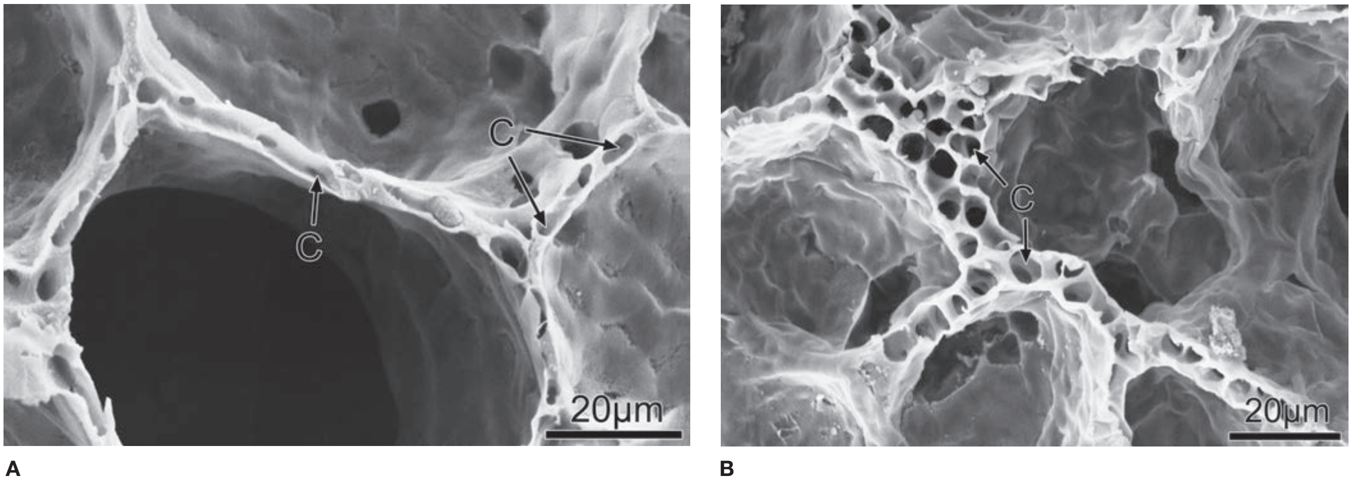
$$\dot{V}_{O_2} = (P_{A_{O_2}} - P\bar{c}_{O_2}) \cdot D_{L_{O_2}}$$

where

$P_{A_{O_2}}$ = P_{O_2} in alveoli,

$P\bar{c}_{O_2}$ = the mean P_{O_2} in pulmonary capillaries, and

$D_{L_{O_2}}$ = the pulmonary diffusing capacity or the lung's O_2 conductance



A **B**

Figure 2-58 Scanning electron micrographs of alveolar walls of rabbit lungs fixed under (**A**), zone 2 and (**B**), zone 3 conditions of perfusion. Note that capillaries (C) are wide in zone 3 and slit-like in zone 2, except for "corner capillaries," which are wide in either case. *(Reproduced with permission from Bachofen H et al. Morphometric estimates of diffusing capacity in lungs fixed under zone II and zone III conditions. Respir Physiol. 1983;52(1):41–52.)*

The important point is now that all parameters to the right of this equation may be significantly affected by design features. We will see that DL_{O_2} is largely determined by the surface area and the thickness of the air–blood barrier. The O_2 partial pressure difference is established by ventilation and perfusion of the gas-exchange units, and this may be affected by the design of the airway and vascular trees, particularly in the acinus.[187]

■ Pulmonary Diffusing Capacity

In the equation mentioned earlier, DL_{O_2} is the total conductance of the gas exchanger for O_2 diffusion from the alveolar air into the capillary erythrocytes until it is bound to hemoglobin. It can be estimated physiologically if we can measure O_2 uptake $\dot{V}_{O_2}$ and estimate the effective P_{O_2} difference between alveolar air and capillary blood, not a trivial undertaking as the change in capillary P_{O_2} as O_2 is being taken up must be integrated (Fig. 2-59). On the other hand, the conductance is a physical characteristic. Therefore, it should be possible to calculate a theoretical value of DL_{O_2} from the physical properties of the gas exchanger, its dimensions and material properties.[191,192] To do that we must consider the geometry of the structures involved, alveoli, tissue barrier, and capillary blood, in setting up a physical model of DL_{O_2}. In the first step, we can break the process into two steps (Fig. 2-60):[193] (1) O_2 flow across the barrier or what has been called the *membrane conductance* DM_{O_2} and (2) O_2 binding to hemoglobin in the red blood cells or the conductance of capillary blood De_{O_2}. These two conductances are in series. Accordingly, their overall effect on O_2 flow is obtained by adding their resistances or the reciprocal of the conductance:

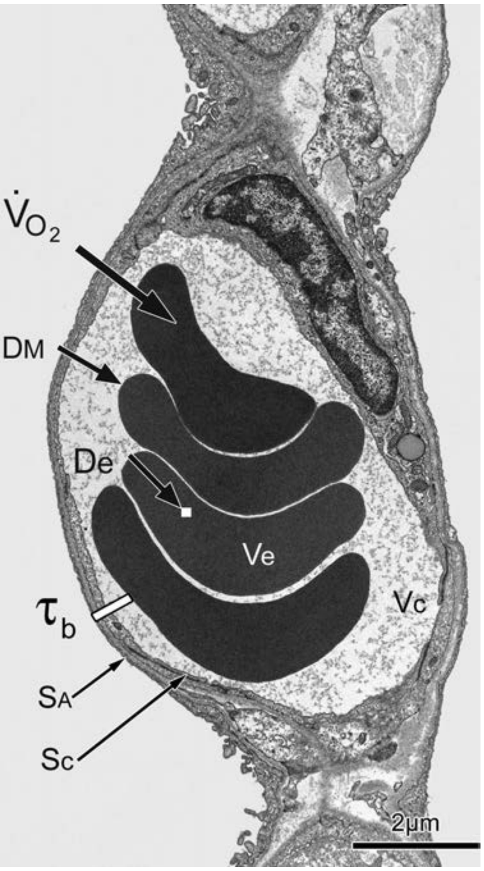


Figure 2-60 Morphometric model for calculating diffusion capacity, DL. Its two components are: (1) the membrane conductance DM, which extends from the alveolar surface (SA) to the nearest erythrocyte membrane traversing the tissue barrier, the capillary surface (Sc), and the plasma layer over the distance τ_b; and (2) the conductance of the erythrocyte interior, De, that depends on the capillary and the erythrocyte volume, Vc and Ve. (See text.)

$$1/DL_{O_2} = 1/DM_{O_2} + 1/De_{O_2}$$

The two conductances DM_{O_2} and De_{O_2} are of very different natures. DM_{O_2} is the conductance of a diffusion barrier that offers "passive" resistance to diffusion and thus depends essentially on the material properties of the barrier, estimated by a diffusion coefficient K, and on the dimensions of the barrier. The larger the surface area S and the thinner the barrier thickness τ the greater DM_{O_2}, according to the formula $DM_{O_2} = K \cdot S/\tau$. In contrast, De_{O_2} is related to a more complex process that involves, besides diffusion, the binding of O_2 to hemoglobin, which is a nonlinear process.

The Membrane Conductance (DM_{O_2})

The structural characteristics of the membrane conductor are seen in Fig. 2-60. It is made of the two layers that separate air in alveoli from the erythrocytes in the capillary: the tissue barrier and the layer of blood plasma. In addition, an alveolar lining layer of varying thickness spreads over the epithelial surface. Even though these layers have distinct characteristics; in effect they act as a single diffusion barrier.[192]

As discussed earlier in this chapter, the tissue barrier is a complex structure. Its two bounding surfaces are formed by independent cell layers, epithelium and endothelium, and they are related to two independent functional spaces, alveoli and capillaries. The two surfaces are not perfectly matched, and the thickness of the barrier varies considerably (Fig. 2-60). Over about half the surface the tissue barrier shows minimal thickness compatible with an intact structure: The thin cytoplasmic leaflets of type I epithelial cells are joined to the thin extensions of endothelial cells by the fused basement membranes leaving no interstitial space. In this region we also find the surface lining layer to be very thin. Over the other half the barrier is thicker because of the occurrence of supporting connective tissue fibers (Fig. 2-49) and the presence of cell bodies of epithelial and endothelial cells as well as fibroblasts, and the lining layer can form deeper pools (Fig. 2-52).

The plasma layer shows even greater variation in its thickness and distribution. Since erythrocytes are of about the same dimension as the capillaries, the plasma layer that separates them from the endothelium can be vanishingly thin where the red cell nearly touches the wall. However, erythrocytes are corpuscular particles and there are "plugs" of plasma of varying size that separate them in the direction of blood flow. Also, their distortable disk shape causes the plasma layer between erythrocyte and capillary surface to be quite variable.[194] Furthermore, occasional leukocytes function like plasma plugs in regard to O_2 diffusion to the red cells. Therefore, the diffusion distance from the capillary wall to the red cell membrane can vary from a few nm to several μm.

Strictly speaking, these two layers of the barrier offer O_2 diffusion different resistances so their conductances should be calculated separately. However, this distinction does not appear to be important under normal conditions. Indeed, it is more reasonable to treat them as a single barrier. For one, the flow velocity of the plasma layer is much lower than the diffusion of O_2 so that plasma is quasistatic with respect to diffusion. Furthermore, under normal conditions the surface areas of alveoli, capillaries, and erythrocytes do not differ much, and the diffusion coefficients of tissue and plasma also are quite similar. Therefore, we prefer now to estimate the membrane diffusing capacity by considering O_2 diffusion from the alveolar surface to the erythrocyte membrane as:[192]

$$DM_{O_2} = K_b \cdot S(b)/\tau_{hb} = K_b \cdot (S(A) + S(c))/2 \cdot \tau_{hb}$$

where K_b is Krogh's permeation coefficient estimated at 3.3×10^{-8} $cm^2\ min^{-1}\ mm\ Hg^{-1}$, τ_{hb} is the harmonic mean distance from the alveolar surface to the nearest erythrocyte membrane, and S(b) is the surface area of the barrier that we estimate as the mean of the alveolar and capillary surface areas, S(A) and S(c), respectively, the two most robust measures of the area of air–blood contact. These parameters can be estimated on sections of properly sampled lung tissue by stereologic methods.[195–197]

We should also mention that the presence of a surface lining layer in the living lung may modify the geometry of the barrier as we see it on electron micrographs with the consequence that both the barrier thickness and the alveolar surface are reduced to a similar degree because some thicker parts of the barrier become shifted beneath the surfactant pools (Fig. 2-52).[186] Therefore, the effect on the estimate of DL_{O_2} is negligible.

Erythrocyte Conductance (De_{O_2})

As mentioned, the erythrocyte conductance is of a different nature in that it involves two coupled events,[193] that is, diffusion of molecular oxygen and oxyhemoglobin within the red blood cell as well as the chemical reaction of O_2 with hemoglobin. A way out of this is to obtain an empirical estimate of the rate at which O_2 is bound to whole blood, θ_{O_2}, and to express the erythrocyte conductance De_{O_2} as:

$$De_{O_2} = \theta_{O_2}\,Vc$$

where Vc is the total capillary blood volume, which can again be estimated on sections by stereologic methods.

The coefficient θ_{O_2} is estimated in vitro on whole blood, but this is difficult because of the effect of variable unstirred layers around the red cells.[198,199] In addition, θ_{O_2} depends on the hematocrit or hemoglobin concentration, and it is not a constant as it falls with increasing O_2–hemoglobin saturation; recent studies have shown that, as blood moves through alveolar capillaries, θ_{O_2} falls gradually from about 4 to 1 mL O_2 mL^{-1}, $torr^{-1}$ so that the correct value can only be found after Bohr integration of capillary P_{O_2}. For normal human lungs and a hemoglobin content of 15 g/100 mL of blood, a value $\theta_{O_2} = 1.8$ $mLO_2 \cdot mL^{-1}$ is a reasonable estimate, but if the actual hemoglobin concentration [Hb] varies a corrected value can be obtained by multiplying this standard value with a factor c = [Hb]/15.

Morphometry of the Human Lung and Diffusing Capacity

With this model in hand, we can now attempt to estimate the diffusing capacity of the human lung on the basis of morphometric data, as listed in Table 2-4. These data, obtained by electron microscopic morphometry on seven young adults,[200] reveal the alveolar surface area to amount to 130 m^2 and the capillary surface to be about 10% smaller. These values are higher than those most commonly quoted in textbooks derived from light microscopic studies, which did not adequately resolve the alveolar surface texture. The harmonic mean thickness of the tissue barrier is 0.6 μm, whereas the total barrier, from alveolar to red cell surface (Fig. 2-60), measures 1.11 μm.[192] The capillary volume is estimated at about 200 mL. With these data we calculate DL_{O_2} for the adult human lung to be about 150 to 200 mL O_2 min^{-1} mm Hg^{-1}, the variation depending on the choice of θ_{O_2}.

These data also allow us to ask how the resistance to O_2 diffusion is distributed between the diffusion barrier and the red cells. Table 2-4 shows that the diffusion conductance of the "membrane" and that of the red cells are very similar, which means that the resistance to O_2 uptake is nearly equally divided between membrane and red cells.

These morphometric estimates of the diffusing capacity are based on model assumptions that are considered reasonable. The test of their validity must be to compare them with physiologic estimates. The standard physiologic value of DL_{O_2} in a healthy adult at rest is about 30 mL O_2 min^{-1} mm Hg^{-1}; thus, considerably less than what we find on the basis of morphometric estimates. However, this is not a valid comparison, because, under resting conditions, we take up only one-tenth the amount of O_2 that our lungs are capable of absorbing under conditions of heavy work. There have been a number of estimates of DL_{O_2} in exercising humans,[201] and these have yielded values of the order of 100 mL O_2 min^{-1} mm Hg^{-1}. This estimate should come closer to the "true capacity" of the lung for O_2 transfer to the blood than the value obtained at rest. The fact that this is only about 50% lower than the morphometric estimate is not disturbing, for we do not know whether the "true diffusing capacity" is completely exploited even in heavy exercise. Inhomogeneities in the distribution of ventilation and perfusion would, for example, limit the degree to which "true" DL_{O_2} can be exploited. One aspect of this type of limitation is discussed in the following when we consider the effect of the acinus design on gas exchange.

TABLE 2-4 Morphometric Estimate of DL_{O_2} for Young, Healthy Adult Humans of 70-kg Body Weight, Measuring 175 cm in Height

Morphometric data (mean ± 1 SE)			
Total lung volume (60% TLC)	4340	±285	mL
Alveolar surface area	130	±12	m^2
Capillary surface area	115	±12	m^2
Capillary volume	194	±30	mL
Air–blood tissue barrier thickness			
Arithmetic mean	2.2	± 0.2	μm
Harmonic mean	0.62	±0.04	μm
Total barrier harmonic mean thickness	1.11	± 0.1	μm
Diffusing Capacity (mL/min/mm Hg)			
Membrane	DM_{O_2}	350	
Total	DL_{O_2}	158	

Reproduced with permission from Gehr P, Bachofen M, Weibel ER. The normal human lung: Ultrastructure and morphometric estimation of diffusion capacity. Respir Physiol. 1978;32:121–140 and Weibel ER. Symmorphosis: on form and function in shaping life. Cambridge, MA: Harvard University Press; 2000.

To test whether the morphometric estimate of DL_{O_2} is reasonable we performed, some years ago, a combined physiologic and morphometric estimation of pulmonary diffusing capacity on four species of canids ranging from 4 to 30 kg in body mass.[202]

Because it is difficult to estimate mean capillary P_{O_2} reliably, most physiologic measurements of the diffusing capacity use carbon monoxide (CO) as a tracer gas; CO binds to hemoglobin so avidly that, for practical purposes, the Pb_{CO} is zero, so that it suffices to measure CO uptake and alveolar CO concentration. It is also possible to revise the morphometric model of diffusing capacity to estimate the conductance for CO instead of O_2 by appropriately changing the permeability coefficients and the rate of CO binding to erythrocytes, θ_{CO}, whereas the morphometric parameters are not changed. In a study on dogs and on other canids, the calculated morphometric value of DL_{O_2} was found to be larger than the physiologic estimate by less than a factor of 1.5, thus confirming the observation made with respect to human lungs.

Therefore, we conclude that the pulmonary gas exchanger is designed with a certain amount of redundancy or excess capacity, but this is by no means unreasonable from an engineering point of view. Indeed, to design the pulmonary gas exchanger with a certain degree of redundancy may make a lot of sense. The lung forms the interface to the environment and its functional performance will thus depend on environmental conditions, such as the prevailing O_2 partial pressure, which falls as we go from sea level to higher altitudes. It has been shown that goats, whose DL_{O_2} is about twice as large as seemingly required, can maintain their maximal level of exercise-induced $\dot{V}_{O_2}$ even under hypoxic conditions whereas the dogs that have very small excess DL_{O_2} cannot. It has also been suggested that human athletes exercising at high altitude may fully exploit their DL_{O_2}. This suggests that the apparent redundancy in DL_{O_2} may be a safety factor to protect the good functioning of the pulmonary gas exchanger even when environmental conditions are not optimal. Recent studies with partial pneumonectomy in dogs have shown that the lung can achieve 85% of its maximal O_2 uptake even when 40% of lung tissue is removed after left pneumonectomy, making use of some of this reserve capacity; but when right pneumonectomy removes 60% of lung tissue, adequate function can be achieved only after compensatory growth of the residual lung tissue to restore diffusing capacity.[203–206]

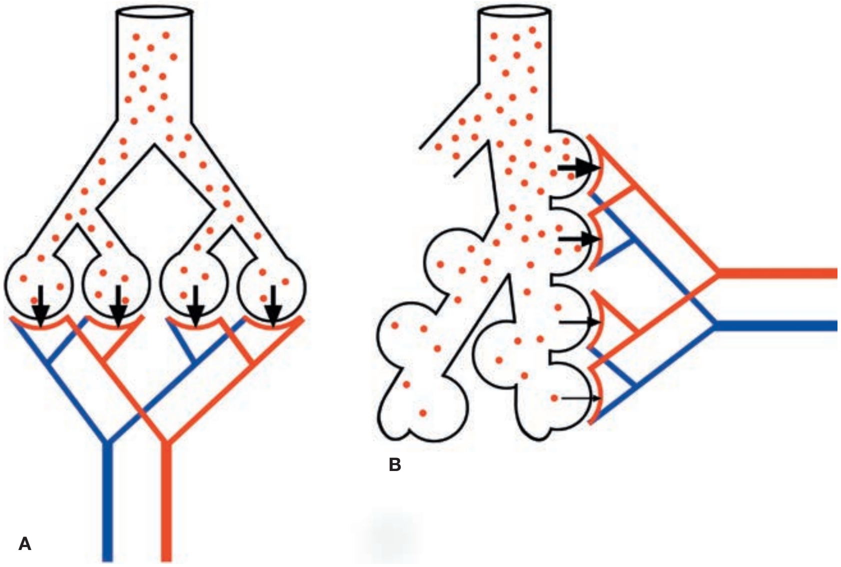


Figure 2-61 Models of ventilation–perfusion relationship in the mammalian pulmonary gas exchanger. **A.** Parallel ventilation/parallel perfusion. **B.** Serial ventilation/parallel perfusion. *(Reproduced with permission from Sapoval B, Filoche M, Weibel ER. Smaller is better, but not too small: A physical scale for the design of the mammalian pulmonary acinus. Proc Natl Acad Sci USA. 2002;99(16):10411–10416.)*

■ Design of the Acinus and Gas Exchange

The preceding section considered the overall size of the gas exchanger of the entire lung to compare it with the global performance of this organ. In reality, the surface the size of a tennis court is subdivided into some 400 million gas-exchange units. These are individually perfused with blood because they correspond to the unit capillary network that spans between pulmonary arteriole and venule (Fig. 2-46). The diameter of such a roughly disk-shaped unit is about 500 μm and has a surface area that corresponds approximately to that of an alveolus, even though alveoli and the capillary unit are not congruent as the latter spans over several alveoli and each alveolus is in contact with several capillary units.[170]

These gas-exchange units are arranged along the terminal generations of the airway tree that form the pulmonary acinus (Fig. 2-61B). Note that this arrangement of gas-exchange units to the airway system differs from the common representation of the alveolar–capillary unit as a terminal "bubble" (Fig. 2-61A). This has potential functional consequences because ventilation of alveoli occurs in two steps:[207] (1) upon inspiration oxygen-rich air flows through the airways into the acinus carrying along O_2; (2) in the peripheral airways flow velocity slows down because the airway cross-section increases, and O_2 now moves toward the periphery by diffusion in the air phase, driven by the P_{O_2} gradient that becomes established as O_2 is absorbed at the alveolar surface (Fig. 2-62). Thus, in the peripheral airways diffusion along the airways is combined with diffusive permeation of O_2 into the alveoli and across the tissue barrier to the blood, the actual process of gas exchange. Whereas all capillary network units are individually perfused with venous blood the alveoli are not independent in terms of their O_2 supply, which depends on their location along the airway tree. Therefore, the design of the acinus has significant effects on the gas-exchange conditions.

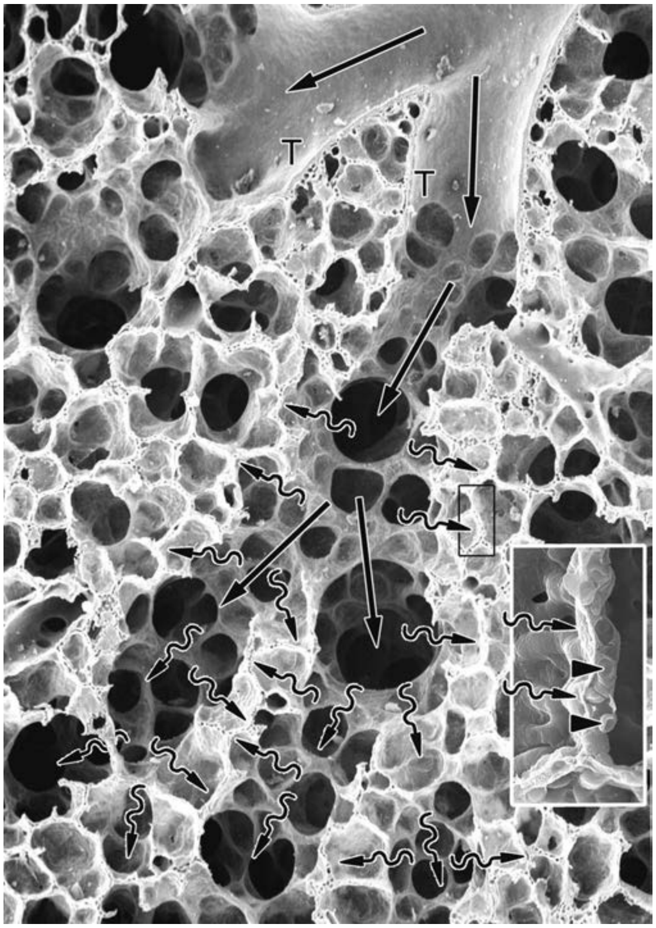


Figure 2-62 Central part of the acinar airways beginning with transitional bronchiole (T) and leading into the branched alveolar ducts. On inspiration air flows in by convection *(straight arrows)*, but as flow velocity falls diffusion of O_2 *(wiggly arrows)* becomes the dominant mechanism for bringing O_2 to the gas-exchange surface. All along acinar airways O_2 is absorbed by the capillary blood in the septa *(inset, arrowheads)*.

■ The Acinar Airway System Connected to the Gas Exchanger

In a systematic study of human lungs[9] the mean volume of acini was found to be 187 mm^3 with a standard deviation of 79 mm^3. The branching pattern for an average-size human acinus is shown in Fig. 2-63. The segment lengths have been drawn to scale, and

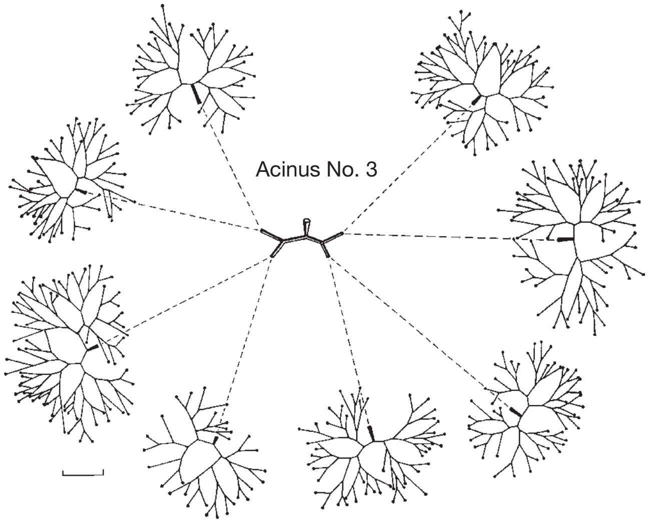


Figure 2-63 Graphic representation of branching pattern of acinar airways in one human acinus of 183 mm^3 volume with the segment lengths drawn to scale. The airways are separated at the third generation thus displaying the branching pattern within each 1/8 subacinus. *(Reproduced with permission from Haefeli-Bleuer B, Weibel ER: Morphometry of the human pulmonary acinus. Anat Rec. 1988;220(4):401–414.)*

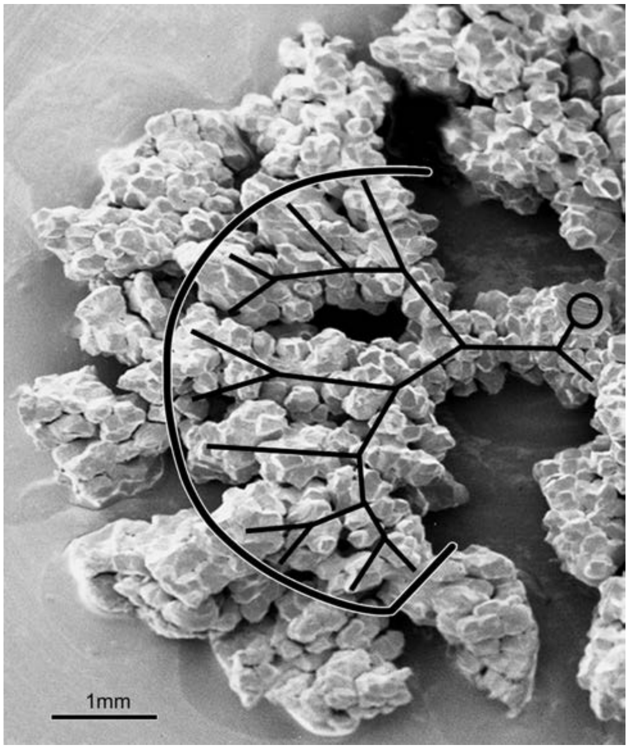


Figure 2-64 Airways of 1/8 subacinus of human lung beginning with generation 18 alveolar duct (circle). The silicon rubber cast has been spread out to show the course of the subsequent branchings. The curved line marks the approximate boundary to the last generation to show that this generation of alveolar sacs (see Fig. 2-5) comprises over half the gas-exchange area of the acinus.

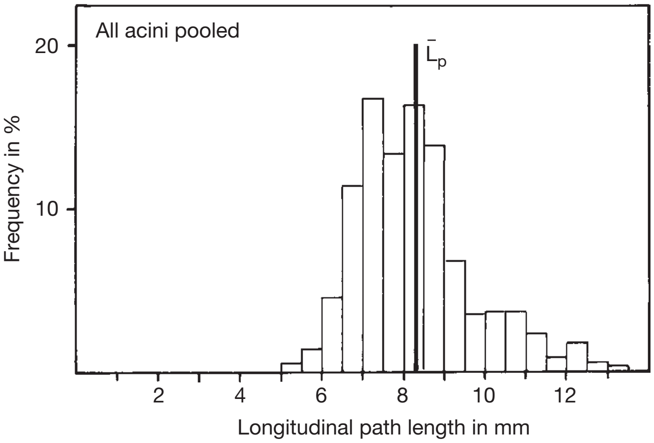


Figure 2-65 Frequency distribution of longitudinal path length from the transitional bronchiole to the alveolar sacs in the human lung. *(Reproduced with permission from Haefeli-Bleuer B, Weibel ER: Morphometry of the human pulmonary acinus. Anat Rec. 1988;220(4):401–414.)*

the terminal clusters of alveoli of the alveolar sacs are marked by a dot. This acinus has been subdivided into eight subacini whose substems are located in the third generation of acinar airways. The first three generations of acinar airways following on the transitional bronchiole are respiratory bronchioles, where there are only a few alveoli. In contrast, the alveolar ducts that follow are completely and densely lined with alveoli (Fig. 2-64). The 1/8 subacinus is a unit of functional significance, as we shall see. The intra-acinar airways branch by irregular dichotomy; terminal sacs are located in generations 6 to 11 so that the intra-acinar airways branch over an average of 8 generations (Fig. 2-5).

The morphometry of the intra-acinar airways of the human lung shows a number of characteristic traits. The inner diameter (d_{in}) that characterizes the cross-section of the duct tube decreases from about 490 μm at the transitional bronchiole to 270 μm in the last generations.[9] When this is plotted onto the graph relating airway diameter to generations of branching (Fig. 2-37), we note that this diameter falls less steeply than the cube-root-of-1/2 law we have observed for conducting airways. This is a significant finding in terms of the ventilation of alveoli by O_2 diffusion.

An important morphometric characteristic of acinar airways is the total path length for O_2 diffusion from the entrance at the transitional bronchiole to the terminal cluster of alveoli at the alveolar sac (Fig. 2-5). This path length is determined by two factors: the number of generations and the segment length. The length of alveolar ducts gradually decreases from 1330 to 640 μm in the peripheral generations, the alveolar sacs being a little bit longer. Since the number of branching generations varies somewhat, we can expect the path length to vary even within one acinus. In the human lung, the average longitudinal path length measures 8.3 ± 1.4 mm (Fig. 2-65).[10] Because of the decreasing length of acinar ducts 3.4 mm of this total path length are for the first three generations of respiratory bronchioles, whereas the path length of alveolar ducts and sacs comprised in the 1/8 subacinus (Fig. 2-64) averages 4.7 ± 0.88 mm.

Typical Path Model of Human Acinus

In view of assessing the effect of these structural features on the functional performance of the pulmonary gas exchanger we can attempt to develop what we may call a typical path model for an average human acinus[9,10]; the relevant morphometric data are given in Table 2-5. Such an acinus has a volume of 187 mm^3. Its airways branch over an average of eight generations to reach the terminal alveolar sacs. With each generation the number of branches doubles to end with some 256 terminal alveolar sacs in an average acinus (Fig. 2-63). Locating the transitional bronchiole ($z' = 0$) in generation 14 (Fig. 2-5) the terminal air sacs are in generation 23 of the typical path airway tree. From the estimates of the lengths and inner diameters of the airway segments we can derive

TABLE 2-5 Typical Path Model of Human Acinus

Generation		Segments			Dimensions per Generation			Path Length
Airways z	Acinus z′	N(z′)	l mm	d_{in} mm	$A_d(z')$ mm^2	$V_d(z')$ mm^3	$S_{alv}(z')$ mm^2	$L_p(z')$ mm
15	0	1	1.4	0.50	0.20	0.32	7	1.4
16	1	2	1.33	0.50	0.39	0.52	23	2.73
17	2	4	1.12	0.49	0.75	0.84	67	3.85
18	3	8	0.93	0.40	1.00	0.93	129	4.78
19	4	16	0.83	0.38	1.81	1.50	219	5.61
20	5	32	0.70	0.36	3.26	2.28	349	6.31
21	6	64	0.70	0.34	5.81	4.07	661	7.01
22	7	128	0.70	0.31	9.11	6.38	1204	7.71
23	8	256	0.70	0.29	16.9	13.47	2720	8.41

Modified with permission from Haefeli-Bleuer B, Weibel ER: Morphometry of the human pulmonary acinus. Anat Rec. 1988;220(4):401–414.

overall parameters of functional significance, such as the total airway cross-section per generation, $A_d(z')$, which is a determinant of air flow velocity (Fig. 2-44). Finally, we can also estimate the distribution of alveolar surface area to the different generations in proportion to the duct surface $S_d(z')$, adjusting for the fact that only part of this surface is associated with alveoli in the respiratory bronchioles (generations $z' = 1–3$). For an estimated alveolar surface of 130 m^2 in the human lung (Table 2-4), there would be about 54 cm^2 of gas-exchange surface per average acinus. It is seen that half this gas-exchange surface is in the last generation (see also Fig. 2-64). A final check of this model is that the path length from the entrance into the transitional bronchiole to the end of the alveolar sacs is 8.4 mm, which agrees well with the mean path length estimated in the human acini (Fig. 2-65).

Implications of Acinar Design for Gas-Exchange Function: The Phenomenon of Diffusion Screening

The gas exchange in the pulmonary acinus involves several physicochemical phenomena that occur within the complex acinar geometry described in the preceding section.[207] As mentioned, in the distal regions of the lung, oxygen is transported toward the alveolar membrane by both convection and molecular diffusion. Oxygen then diffuses through the tissue membrane into the blood, where it is bound by hemoglobin. Several physical parameters govern oxygen uptake at the acinar level, such as air flow velocity, diffusion coefficient of oxygen in air, alveolar membrane permeability, blood hemoglobin content, and its reaction rate with oxygen. Conversely, carbon dioxide is discharged from the blood to the alveolar gas through diffusion across the membrane. It then diffuses backward along the airways to the zone, where convection becomes dominant, and is lastly expelled from the lung. In all these processes, the morphology of the system plays an essential role.

Since oxygen uptake into the blood is driven by the O_2 partial pressure at the alveolar surface we must ask whether this driving force is the same throughout the acinus or whether there could be differences between its central and peripheral parts. Some earlier studies had shown that concentration gradients may exist as a consequence of efficient capture of oxygen by hemoglobin. More recently,[207] we have come to realize that such gradients are strongly influenced by the finite permeability of the membrane that plays a dominant role in the effective properties of the acinus as the ventilatory gas-exchange unit. O_2 molecules entering the unit where diffusion prevails have a larger probability to hit the surface of the alveolar membrane near the entrance than in the more distal regions. If the membrane permeability is large, O_2 molecules are absorbed at the very first hits. As a consequence, O_2 is absorbed into the blood in the first parts of the acinar pathway, a process called *diffusional screening,* so that the gas-exchange units in the deeper part of the acinus would receive less O_2 (Fig. 2-61) or perhaps even not enough for gas exchange to occur. Blood perfusing these regions would not be oxygenated and would thus appear as a shunt. In contrast, if the permeability is small, molecules will be absorbed only after many collisions with the wall. They then have a fair chance to reach the deeper regions and the entire acinar surface can be effective for gas exchange.

To put this into the perspective of structure–function relations this process is related to the balance between two conductances:[207] a diffusion conductance Y_{cross} for O_2 to *cross* the barrier from alveolar air to capillary blood, and a diffusion conductance Y_{reach} for O_2 to *reach* the surface through the airspaces. Both these conductances are determined by the product of (a) a physical parameter (the permeability coefficient for O_2 in tissue, and the diffusion coefficient for O_2 in air, respectively); and (b) a morphometric parameter (the gas-exchange surface, and the distance along the acinar airways, respectively). The physical coefficients are given quantities, except that the tissue permeability is also affected by the thickness of the tissue barrier, a parameter that varies very little between species. On the other hand, the size and surface of the acinus can be varied during evolution and growth to adjust the two conductances. We can predict that the design of the acinus is optimized if Y_{cross} and Y_{reach} are about equal, as this means that both the gas-exchange surface and the acinar air volume, or the diffusion distance, are matched. If Y_{cross} were much smaller than Y_{reach} the low permeability of the gas exchanger would need to be compensated by a larger gas-exchange surface, and this would inevitably entail a larger volume of the acinus to accommodate the surface and by that a longer diffusion distance.

The morphometric study of acini in various mammalian species[9,207,208] revealed that the size of the acini is such that $Y_{cross} \sim Y_{reach}$ so that their morphology seems to be at least partially adapted to minimize the effects of screening. Note that the problem of screening occurs in that part of the acinus where O_2 moves to the surface by diffusion only (Fig. 2-62), in what is called the *diffusion cell.* The transition between convection and diffusion is determined by the Peclet number (Fig. 2-66), essentially the ratio between air flow and diffusion velocities[207]; diffusion is more effective than convection when the Peclet number is smaller than 1. In the human lung, under resting conditions, this transition occurs in generation 18 and that is the entrance to the 1/8 subacinus (Fig. 2-63); accordingly, the diffusion cell corresponds to the 1/8 subacinus. In exercise, where O_2 consumption as well as ventilation is increased, convective transport

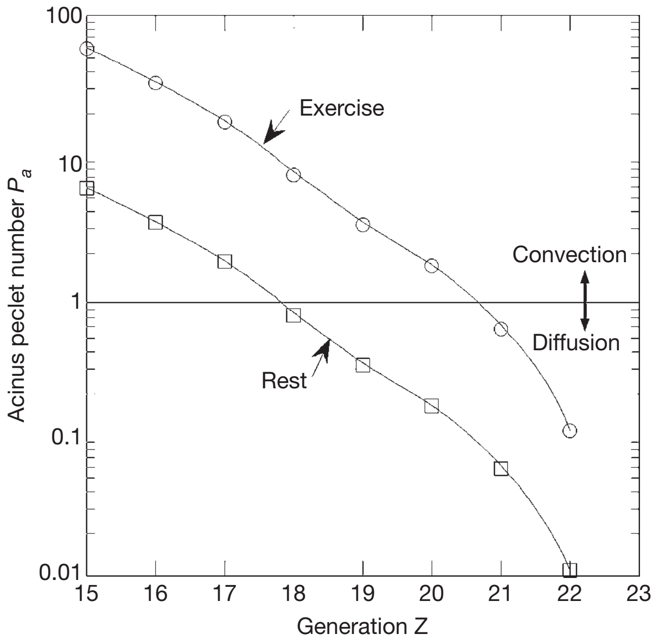


Figure 2-66 In the human acinus the Peclet number, reflecting the relation between convective flow velocity and diffusion velocity of O_2, falls as the airway cross-section increases. Below 1 diffusion becomes the dominant mechanism of alveolar ventilation. This transition point is about in generation 18 at rest and extends out to generation 21 in heavy exercise. *(Reproduced with permission from Sapoval B, Filoche M, Weibel ER. Smaller is better, but not too small: A physical scale for the design of the mammalian pulmonary acinus. Proc Natl Acad Sci USA. 2002;99(16):10411–10416.)*

of O_2 is effective out to generation 21 (Fig. 2-66). So in exercise there are only two to three generations of acinar airways that act as diffusion cell, but that is still highly significant because these generations accommodate 75% of the gas-exchange surface (Fig. 2-64 and Table 2-5).

Note that what has been discussed so far relates essentially to about half the respiratory cycle, namely, inspiration when fresh O_2-rich air is actively brought into the acinus. During expiration things are in a way reversed: CO_2 that has diffused from the blood into the acinar air now dilutes O_2 and the convection–diffusion front is moved toward the bronchi. For this reason, the effective duty cycle of the gas-exchange system is smaller than 1, particularly under the conditions of high O_2 uptake rate in exercise. This must be considered when modeling gas exchange. Recent refined model studies using the same morphometric data together with reasonable assumptions on the physiologic conditions revealed that the size of the human pulmonary acinus is such as to avoid negative effects of diffusional screening.[209]

The Lung as Part of the Pathway for Oxygen

The lung's main function, gas exchange between air and blood, serves the body's varying O_2 needs as they are set by the energetic demands of the cells and their mitochondria when these produce ATP by oxidative phosphorylation to allow the cells to do work. This process requires a flow of O_2 to be maintained from the lung to the cells[16] which proceeds along the respiratory system through various steps from the lung to the blood, by circulatory blood flow to the cells and mitochondria (Fig. 2-67). A number of basic features characterize this system: (1) under steady-state conditions the O_2 flow rate, $\dot{V}_{O_2}$, is the same at all levels; (2) the basic driving force for O_2 flow through the system is a cascade of O_2 partial pressures, which fall from inspired P_{O_2} down to near zero around the mitochondria; (3) the O_2 flow rate at each step is the product of an O_2 partial pressure difference and a conductance G, which is related to structural and functional properties of the organs participating in O_2 transfer. In the preceding section we have seen that the principal design features of the lung that determine one of the key conductances, the pulmonary diffusing capacity, are sized to just yield a conductance that allows the O_2 uptake required to satisfy the demands of the whole-body cell system at work, with a small margin of safety under normal conditions. Therefore, the lung appears designed to serve the body's needs efficiently and economically. The question we may now ask is whether the other parts of the respiratory system, from the heart to the mitochondria, also are designed for economic functional performance.[210]

Let us first look at the overall functional performance of the system. We first note that O_2 consumption is highly variable, increasing by about a factor of 10 between resting conditions and heavy exercise when 90% of the O_2 is consumed in the locomotor muscles. Figure 2-68 shows that the oxygen consumption in muscle is proportional to the energy output,[211] measured for example as running speed, and that it reaches a limit $\dot{V}_{O_2max}$ beyond which the running speed can still be increased, but the additional energy required by the higher speed is then supplied through glycolysis or anaerobic ATP production with the result that lactic acid concentration in the blood gradually increases. It is now interesting to note that $\dot{V}_{O_2max}$ is a characteristic of the work capacity of an individual: well-trained athletes reach their $\dot{V}_{O_2max}$ at a higher running speed and a higher level of oxygen consumption, and lactic acid concentration in the blood also begins to increase at the higher performance levels corresponding to $\dot{V}_{O_2max}$ (Fig. 2-68).

One may now raise the question whether this variable limitation of oxidative metabolism is a result of variable functional constraints affecting the regulation of metabolic rate and circulatory transport, or whether it could be set by variations in design constraints characterizing the structural components of the pathway, one possible candidate being the pulmonary diffusing capacity. The answer to this question depends on an integrated study of structure and function of the respiratory system. For this we need a quantitative model of the oxygen pathway that identifies all the functional variables and the design parameters at the four levels of the system[212]: the lung,

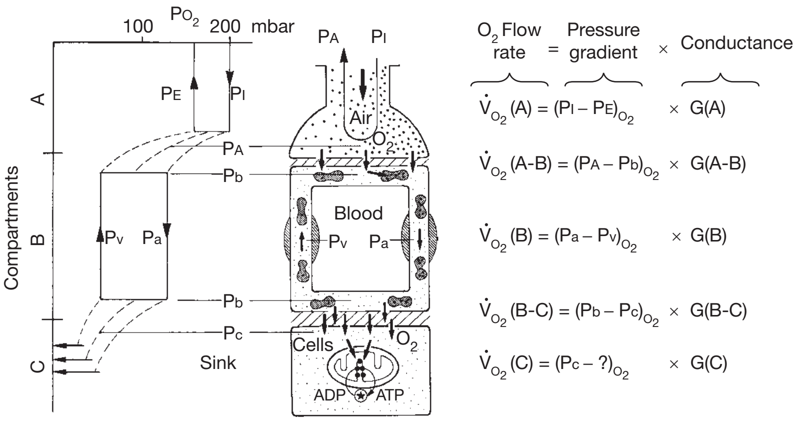

100
P_{O_2}
200 mbar
A
B
C
Compartments
PE
PI
PA
Pb
Pv
Pa
Pb
Pc
Sink
PA
PI
Air
O_2
Blood
Pv
Pa
Cells
O_2
ADP
ATP
O_2 Flow rate = Pressure gradient × Conductance
$\dot{V}_{O_2}(A) = (P_I - P_E)_{O_2} \times G(A)$
$\dot{V}_{O_2}(A\text{-}B) = (P_A - P_b)_{O_2} \times G(A\text{-}B)$
$\dot{V}_{O_2}(B) = (P_a - P_v)_{O_2} \times G(B)$
$\dot{V}_{O_2}(B\text{-}C) = (P_b - P_c)_{O_2} \times G(B\text{-}C)$
$\dot{V}_{O_2}(C) = (P_c - ?)_{O_2} \times G(C)$

Figure 2-67 Model of the respiratory system from the lung to the cells. Oxygen flow is driven through the system by a cascade of P_{O_2} ranging from inspired to near zero at the mitochondria. At each level the flow rate is determined by a partial pressure difference and a conductance. *(Modified with permission from Taylor CR, Weibel ER: Design of the mammalian respiratory system. I. Problem and strategy, Respir Physiol. 1981;44(1):1–10.)*

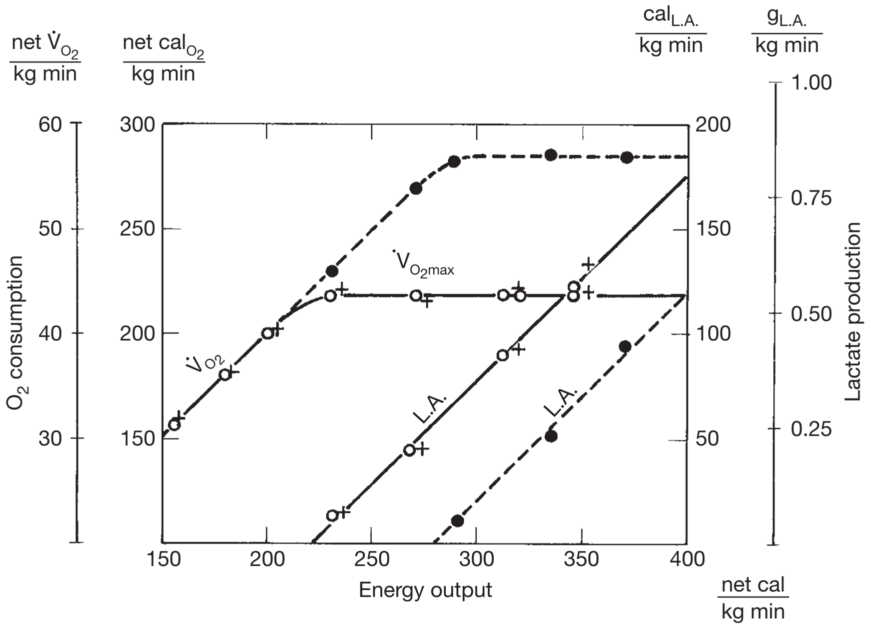


Figure 2-68 Rate of O_2 consumption *(left ordinate)* and lactic acid production *(ordinate at right)* in exercise are plotted as a function of the work intensity and, therefore, of the energy requirement *(abscissa)*. Oxygen consumption increases linearly up to a point corresponding to an energy requirement of 220 cal/kg min^{-1}; if work is pushed beyond that there is no further increase in O_2 consumption ($\dot{V}_{O_2max}$ is reached) but glycolysis now generates the required energy resulting in an increase in lactic acid production. The broken lines refer to athletes (middle- and long-distance runners) whose maximum oxygen consumption is higher; the line of the lactic acid for these subjects is correspondingly shifted to the right. *(Reproduced with permission from Margaria R, Cerretelli P, Diprampero PE, et al. Kinetics and mechanism of oxygen debt contraction in man. J Appl Physiol. 1963;18:371–377.)*

circulation of blood with the heart, capillaries, and mitochondria (Table 2-6). This model is a further development of the one shown in Fig. 2-67 in the sense that, at each level, the equation describing oxygen flow rate sorts out the parameters of functional regulation and those of structural design. These are distinguished in the following sense: Functional variables are regulated according to need with short time constants (seconds), whereas structural design parameters are genetically determined static elements that can be adjusted to a certain extent, for example, by training, but with time constants of weeks to months.

Thus, design variables set the capacity of the system because they are determined by structures whose quantitative properties cannot be adjusted at short notice. If the system were designed according to the principle of symmorphosis we would predict that the design variables are adjusted to $\dot{V}_{O_2max}$ at all levels from the lung to the mitochondria.

The experimental test of this hypothesis requires the integrated measurement of $\dot{V}_{O_2max}$ of the relevant functional parameters, and of all the design parameters, which must then be correlated on the basis of the model of Table 2-6. This cannot be easily done in the human, so that is where we can learn from studies in comparative physiology. We know that $\dot{V}_{O_2max}$ is highly variable among mammals. Some species such as dogs, horses, or pronghorn antelopes have a much higher level of $\dot{V}_{O_2max}$ than "normal" species of the same size such as goats or cows; this is called *adaptive variation*.[213] On the other hand body size matters so that small animals have a higher metabolic rate per unit body mass than large species, which is called *allometric variation*.[210] These are genetically determined variations, the result of evolution and selection by fitness, in contrast to the changes in overall work capacity and $\dot{V}_{O_2max}$ induced by exercise training in human athletes, which are epigenetic variations.[214,215] In all these cases we can ask how and to what extent the structural design parameters are adjusted to meet the different requirements for O_2 to cover the energetic need at the limit of the aerobic work capacity. If there is a bottleneck, then there will be one and only one parameter whose variation is perfectly matched to the variation in the limit of O_2 flow, $\dot{V}_{O_2max}$, whereas all the parameters that are overdesigned would appear in haphazard relations to the flow limit. On the other hand, if the limiting resistances are distributed all steps would have to be matched to the varying $\dot{V}_{O_2max}$. If we take the bold view that the organisms are economically designed we would predict that the structural parameters at all levels should be sized to the maximal total O_2 flow requirement with no unnecessary excess capacity because that would be a waste. We have called this design principle *symmorphosis*, meaning that there should be no more structure built into the system than required to serve the functional needs.[189]

TABLE 2-6 Model of Structure–Function Relations in Pathway for Oxygen Separating Functional and Structural Parameters in the Equations Defining O_2 Flow Rate Through Four Levels

FUNCTION • DESIGN
$\dot{V}_{O_2}$ (lung) = $(P_{A_{O_2}} - Pb_{O_2})\{t_c, \theta_{O_2}\} \bullet D_{L_{O_2}}\{S(A), S(c), V(c), \tau_{hb}\}$ (1)
$\dot{V}_{O_2}$ (heart) = $(\sigma_a \cdot Pa_{O_2} - \sigma_{\bar{v}} \cdot P\bar{v}_{O_2}) \cdot f_H \bullet Vs\{V(LV)\} \ldots V_v\,(ec)$ (2)
$\dot{V}_{O_2}$ (caps) = $(Pb_{O_2} - Pc_{O_2})\{tc\theta_{O_2}\} \bullet D_{T_{O_2}}\{S(c), V(c), V_v\,(ec), \delta(c,mi)\}$ (3)
$\dot{V}_{O_2}$ (mito) = $\dot{V}_{O_2}\{\dot{m}_{ATP}\} \bullet V(mi)\{S_V\,(im,mi)\}$ (4)

The O_2 flow rate $\dot{V}_{o_2}$ is expressed as the product of functional and design parameters; parameters that affect the factors are shown in italics and placed in braces {.}. The functional parameters include: O_2 partial pressures (P_{O_2})*, coefficients of "hematocrit-specific" O_2 capacitance (σ) which depend on O_2-hemoglobin dissociation, O_2 binding rate* (θ)*, heart frequency (f_H), capillary transit time* (tc)*, and mitochondrial O_2 consumption rate as function of ATP flux* ($\dot{V}_{o_2}\{\dot{m}_{ATP}\}$)*. Design parameters include: diffusion conductances* (D) *of lung and tissue gas exchangers which depend on alveolar and capillary exchange surface areas* (S(*A*), S(c))*, capillary volumes* (V(c))*, hematocrit* (V_V(ec))*, harmonic mean barrier thickness* (τ_{hb})*, capillary-mitochondrial diffusion distance* (δ(c,mi))*, and mitochondrial volume* (V(mi)) *with inner membrane surface density* (S_V(im,mi)).
Data from Weibel ER: Symmorphosis: on form and function in shaping life. Cambridge, MA: Harvard University Press; 2000.

Testing the Hypothesis of Symmorphosis

To test such a hypothesis, we can first compare mammals that greatly differ in terms of their maximal O_2 consumption. The first type of this variation is found in comparing normal with athletic species, such as dogs with goats or horses with steers.[213] It has been found that such athletic animals can achieve a $\dot{V}_{O_2max}$ that is about 2.5 times higher than that of normal species of the same size. This is much more than

TABLE 2-7 Comparison of Morphometric and Physiologic Parameters of Muscle Mitochondria and Capillaries, and of Heart, Blood and Lung with Variation of $\dot{V}_{O_2max}$ in Three Pairs of Athletic and Sedentary Species. Data per Unit Body Mass

	Mitochondria		Blood	Capillaries		Heart			Lung
Design Function	$\dot{V}_{O_2max}/M_b$ mL·min^{-1}·kg^{-1}	V(mt)/Mb mL·kg^{-1}	V_V(ec)	V(c)/Mb mL·kg^{-1}	V(ec)/Mb mL·kg^{-1}	fH min^{-1}	Vs/M_b mL·kg^{-1}	$\dot{Q}$(ec)/Mb mL·min^{-1}·kg^{-1}	D_{LO_2}/Mb mL·min^{-1}·mm Hg^{-1} kg^{-1}
25–30 kg									
Dog	137.4	40.6	0.50	8.2	4.10	274	3.17	434.3	424.8
Goat	57.0	13.8	0.30	4.5	1.35	268	2.07	166.4	288.0
D/G	2.4	2.9	1.68[a]	1.8[a]	3.0	1.02[a]	1.53[a]	2.61	1.48[a]
150 kg									
Pony	88.8	19.5	0.42	5.1	2.14	215	2.50	225.7	284.4
Calf	36.6	9.2	0.31	3.2	0.99	213	1.78	117.5	180.0
P/C	2.4	2.13	1.35[a]	1.6[a]	2.16	1.02[a]	1.40[a]	1.92	1.57[a]
450 kg									
Horse	133.8	30.0	0.55	8.3	4.57	202	3.11	345.5	388.9
Steer	51.0	11.6	0.40	5.3	2.12	216	1.52	131.3	194.4
H/S	2.6	2.6	1.4[a]	0.94[a]	2.16	2.1[a]	2.0[a]	2.63	2.0[a]
Ath/Sed[b]	2.5	2.5	1.5[a]	1.7[a]	2.44	1.0[a]	1.7[a]	2.39	1.7[a]

[a] *These ratios are significantly different from that for $\dot{V}_{O_2max}$.*

[b] *This line presents overall ratios for athletic/sedentary species.*

Data from Taylor, CR, Karas, RH, et al: (1987) Respir. Physiol. 69, 1–127; Jones, JH, Longworth, KE, Lindholm, A et al: (1989) J. Appl. Physiol. 67, 862–870; Constantinopol, M, Jones, JH, Weibel, ER, et al: (1989) J. Appl. Physiol. 67, 871–878; Hoppeler, H, Jones, JH, Lindstedt, SL, et al: (1987) in Equine Exercise Physiology II, eds. Gillespie, JR & Robinson, (Edward Brothers, Ann Arbor, MI), 278–289; Hoppeler, H, Kayar, SR, Claassen, H, et al: (1987) Respir. Physiol. 69, 27–46; Conley JE, Kayar SR, Rosler K, et al: (1987), Respir Physiol 69, 47–64; Karas, RH, Taylor, CR, Rosler, K, et al: (1987) Respir. Physiol. 69, 65–79; Weibel, ER, Marques, LB, Constantinopol, M, et al: (1987) Respir. Physiol. 69, 81–100.

what human athletes can achieve. The relevant morphometric data on such species are shown in Table 2-7 for three species pairs.[216] If we go through the respiratory system, beginning at the bottom with the mitochondria, we note that their total volume in the locomotor muscles is also 2.5 times greater in the athletic species with the result that, at $\dot{V}_{O_2max}$ the unit volume of mitochondria consumes the same amount of oxygen in all these six species, namely about 5 mL O_2 per minute and mL mitochondria. In the next level up, the muscle capillaries, we note that the capillary volume is only 1.7 times greater in the athletic species. However we note that in the athletes the hematocrit, that is, the concentration of erythrocytes in the blood, is larger so that as a result the capillary erythrocyte volume, the product of capillary volume with hematocrit, is 2.44 times greater, thus well matched to the mitochondrial O_2 demands. Note that this is what counts because oxygen is delivered exclusively from the capillary red blood cells. When we look at the determinants of total blood flow the heart is the central element. We notice that athletic species have larger hearts resulting in a larger stroke volume Vs, but that the maximal heart frequency is not different between the species pairs so that cardiac output is determined by the stroke volume. This is only 1.7 times greater in the athletic species. However, note that, here again, the hematocrit plays an important role as it determines the amount of O_2 that can be transported to the capillaries. If we calculate the cardiac erythrocyte output $\dot{Q}$ (ec) we find that it is again 2.4 times greater in the athletic species. Thus, the design parameters of the internal steps of the O_2 transport cascade are quantitatively adjusted to the needs for O_2 flow under limiting conditions. Thus, it appears that the resistance to O_2 flow is distributed to all levels.

When we then consider the design of the pulmonary gas exchanger, we note that the O_2 diffusing capacity of the lung of athletic species is only 1.7 times greater than that of normal species. Considering that we found that the human lung may have some excess capacity by about a factor of 1.5, this may signify that normal sedentary species such as goats or cows have a greater excess capacity than athletic species. Indeed, this can be shown to be the case in two ways:[217] (1) when one calculates the progression of O_2 loading on capillary blood (Bohr integration, Fig. 2-59) one finds that dogs reach saturation just before the blood leaves the capillaries into arterial blood, whereas the goats have some 30% reserve capacity; (2) when goats are run on a treadmill while breathing hypoxic air one finds that they can maintain their $\dot{V}_{O_2max}$ in contrast, dogs cannot run at their established $\dot{V}_{O_2max}$ under such conditions. We concluded from this observation that athletic species have designed a lung to match the requirements for maximal O_2 uptake with no excess capacity while normal sedentary species apparently allow for a certain safety margin that allows them to perform well also under unfavorable hypoxic conditions. If this is now applied to our observations on the human lung this may mean that the excess capacity of the normal lung may just be sufficient to allow athletes to increase their $\dot{V}_{O_2max}$ by training by a factor 1.5, just about what they can achieve (Fig. 2-67).

One has also found that highly trained athletes do not tolerate heavy exercise at very high altitudes as they cannot achieve O_2 saturation of their arterial blood. Thus, it seems that the pulmonary gas exchanger is now the limiting factor for O_2 transfer to the working muscles. The reason for this is that the lung of the adult cannot enlarge its gas-exchange surfaces to match the increased demands of trained muscles. So an athlete must make do with the lung she or he has developed during growth. This contrasts with the changes induced by exercise training in muscle with an increase in mitochondria and capillaries, and in the heart by enlargement of the ventricles, all well matched to the maximal O_2 demands.[212] Therefore, it is fortunate—and perhaps a sign of good design—that the lung is designed with some excess diffusing capacity to allow the lower, internal, levels of the respiratory system to exploit their capacity to adapt to increased energetic needs.

AL GRAWANY

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CHAPTER 3

The Respiratory Muscles

Ghislaine Gayan-Ramirez
Daniel Langer
Marc Decramer

INTRODUCTION

The respiratory muscles constitute a complex pump system. Several muscles constitute this system, represented schematically in Figure 3-1. Breathing under all circumstances requires a coordinated contraction of different respiratory muscles. The most important inspiratory muscle is the diaphragm. The conditions under which this respiratory muscle system weakens and eventually will fail are addressed in other chapters. This chapter focuses on structural and functional properties of the respiratory muscles, respiratory muscle action, and respiratory muscle interaction.

STRUCTURAL AND FUNCTIONAL PROPERTIES OF RESPIRATORY MUSCLES

The respiratory muscles are skeletal muscles, and, in essence, their structural and functional properties are within the range of other skeletal muscles located in the limbs. Adaptations to their specific function, however, make them distinctly different from other skeletal muscles in a number of respects. First, limb muscles are essentially designed to produce movements, and hence, primarily work against inertial loads. Respiratory muscles mainly have to overcome resistive and elastic loads.

Second, peripheral muscles contract rhythmically during movements, whereas respiratory muscles contract rhythmically and continuously, and they are the only skeletal muscles on which life depends. These vital muscles thus have to be well equipped to sustain continuous rhythmic contraction. These adaptations include high fatigue resistance, high oxidative capacity, greater capillary density, and greater maximal blood flow, and they depend upon structural and functional properties of the muscles.

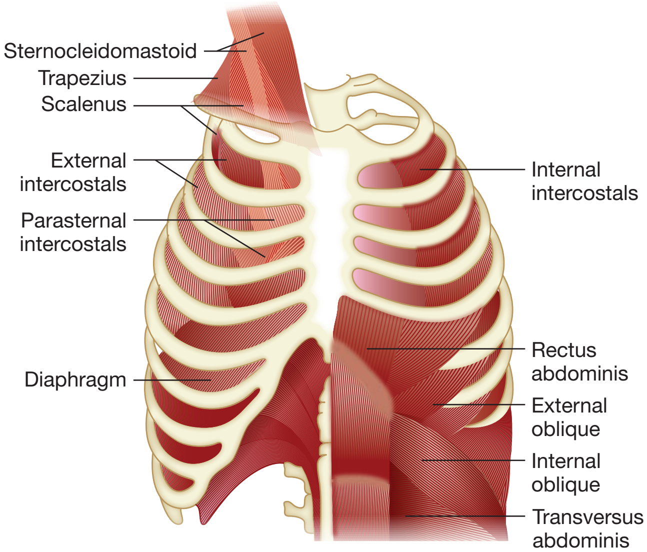

Figure 3-1 Idealized drawing of the respiratory muscles.

Structural Properties

Structural properties of muscles in general, and respiratory muscles in particular, depend upon fiber types present in the muscle, morphologic characteristics of the fibers, and motor unit organization.

Fiber Types

Four types of muscle fibers are usually present in skeletal muscles. They are distinguished on the basis of the myofibrillar myosin adenosine triphosphatase (ATPase) activity and its pH dependence and pretreatment with paraformaldehyde.[1,2] Thus, after acid preincubations at pH 4.5, type I fibers are stained dark, and type IIa fibers are stained lighter than type IIb and type IIx fibers. In addition, pretreatment with paraformaldehyde after alkaline preincubation at pH 10.4 further allows the distinction between type IIb fibers staining lighter than type IIx fibers. Alternatively, muscle fibers may be distinguished through myosin heavy chain gene expression using electrophoresis and western blotting or via immunostaining.[3] This latter technique has the advantage of revealing the presence of coexpression of different myosin heavy chain isoforms within the same muscle fiber. It has also been revealed that myosin heavy chain 2b is not expressed in human muscle.[4] Type I fibers, or slow oxidative fibers, have a slow contraction profile but are high in endurance and rich in oxidative enzymes.[5] Type II fibers are fast-twitch fibers that develop tension rapidly. They either are fatigue resistant or glycolytic oxidative (IIa), or fatigable or glycolytic (IIb),[5] whereas resistance to fatigue for the type IIx fibers is intermediate between the IIa and IIb fibers. Type II fibers develop greater forces than do type I fibers. Muscles primarily composed of type I fibers have high endurance capacity, whereas those primarily composed of type IIb fibers are designed to develop high forces but have low endurance capacity.[5] Type IIa fibers are intermediate and combine relatively high force development with relatively long endurance.[5] In general, type I fibers have the smallest cross-sectional area, and type IIb fibers tend to have the largest.

The respiratory muscles are mixed muscles containing both fast-twitch and slow-twitch fibers. The human diaphragm contains about 55 ± 5% type I fibers, 21 ± 6% type IIa fibers, and 23 ± 3% type IIx fibers. Other respiratory muscles (i.e., intercostal muscles, abdominal muscles, sternomastoids, scalenes) contain at least 60% highly oxidative fibers.[6,7] The respiratory muscles thus are generally well equipped to sustain continuous rhythmic contraction.

Morphologic Characteristics of the Fibers

The respiratory muscles consist of muscle bundles oriented in a parallel fashion. These bundles consist of hundreds of muscle fibers, each of which in turn consists of hundreds of myofibrils. These myofibrils are made up of hundreds of sarcomeres arranged in series, each sarcomere consisting of a number of myosin (thick filaments) and twice the number of actin (thin) filaments. The capacity of the muscle to produce forces depends upon the number of myofibrils in parallel, since the forces developed by all these myofibrils are additive, whereas the displacement and velocity of shortening depend upon the number of sarcomeres in series. Indeed, the displacements of these sarcomeres arranged in series are additive.

The density of mitochondria in each of the four fiber types tends to be greater than in the same fiber types in limb muscles.[5,8] In addition, in humans, the diaphragm is composed of about 80% oxidative fibers compared with 36% to 46% in the limb muscles of untrained men.[5,8] As a consequence, the volume density of mitochondria in the diaphragm is twofold greater than in the limb muscles.[5,8] Therefore, the oxygen uptake capacity of the diaphragm is considerably greater than that of limb muscles because of the high oxidative fiber content and the greater mitochondrial density.[5,8] Moreover, the maximal blood flow also considerably exceeds that of limb muscles because of the greater capillary density, which is about twice the capillary density in the limb muscle. The diaphragm is thus well equipped to sustain rhythmic contraction at rest through its type I and IIa fibers: The type IIa fibers permit additional recruitment in power and rate during exercise, and the few type IIx fibers permit high power outputs necessary for sneezing and coughing.

Motor Unit Organization

Muscle fibers are organized by their innervations in motor units that vary in their mechanical and fatigue properties. In adults, all muscle fibers within a motor unit are the same fiber type. The muscle fibers within a given motor unit are broadly dispersed throughout a region of the diaphragm. Dispersion occurs both horizontally across the surface of the diaphragm and vertically with fibers at different depths. The innervation ratio (number of fibers supplied by a single motoneuron) is approximately 400 in rat diaphragm[9] compared with an estimated value of 2500 in humans.[10] There are four types of motor units in the respiratory muscles: a motor unit with slower contraction times and resistance to fatigue (type S) and three types of motor units displaying faster contraction times, with various degrees of fatigue resistance. The type S comprises fibers that express the slow isoform of myosin heavy chain. Fast motor units that are fatigue resistant (type FR) comprise muscle fibers expressing the myosin heavy chain 2a; those that are highly fatigable (type FF) comprise muscle fibers expressing myosin heavy chain 2b; and those that are fatigue intermediate (type FInt) comprise muscle fibers that express the myosin heavy chain 2x. Motor units composed of fast fibers are large and develop forces in the range of 110 millinewtons (mN). These, however, are considerably smaller than in limb muscles. Motor units composed of slow fibers are smaller and develop forces in the range of 30 to 60 mN. The recruitment pattern of the diaphragm follows the size principle with the smallest motor units being recruited first.

■ Functional Properties

There are different ways to assess functional properties of respiratory muscles. Respiratory muscle strength is usually assessed by maximal static pressures measured at the mouth.[11] Validated reference values are available. Respiratory muscle strength can also be evaluated by determining esophageal, gastric, and transdiaphragmatic maximal pressures, although there is a lack of widely accepted reference equations.[11] Non-volitional maneuvers, obtained through electrical or magnetic stimulation, can be employed in patients unable to cooperate.[11] Muscle endurance also can be assessed, generally using repeated submaximal maneuvers until exhaustion, but no validated reference values are available yet.[11] Evaluation of contractile properties of respiratory muscle using ultrasound imaging also has gained popularity as a clinical tool in recent years.[11] There are also several techniques available to evaluate respiratory muscle neurophysiology, but mainly for research purposes. Applications and technical specifications of these techniques include (1) electromyography (EMG) to measure the output of the respiratory motor neurons, (2) electroencephalography (EEG), which tests the involvement of motor and premotor areas, and (3) transcranial magnetic stimulation (TMS), which assesses the neural pathways to the respiratory muscles (described in more details elsewhere).[12] Finally, near infrared spectroscopy has recently gained popularity as a technique to evaluate local respiratory muscle perfusion and metabolism.[13]

Functional properties of muscles are generally described in terms of force–length relationships, time-dependent characteristics of the twitch, force–frequency, force–velocity, and power–frequency relationships.

The force–length characteristics of the diaphragm are, in essence, similar to other muscles. Maximal tension is generated at the optimal length. Three aspects of the force–length curve of the diaphragm are potentially relevant to clinical medicine. First, with hyperinflation, the diaphragm shortens and its capacity to generate force is concomitantly reduced.[14] Second, when hyperinflation occurs chronically, adaptation occurs in the muscle. This adaptation consists of dropout of sarcomeres such that muscle shortening is then accommodated by a reduced number of sarcomeres rather than alterations in filament overlap within the sarcomeres.[15] As a consequence, the force-generating capacity is restored, at least in part, at foreshortened length.[15] This adaptation is summarized in Figure 3-2. The consequences of this adaptation to patients with hyperinflation are discussed in the section "Physiologic Conditions Affecting Respiratory Muscle Interaction." Third, although less-than-optimal filament overlap is the primary reason for a reduction in force with muscle shortening, calcium deactivation due to T-tubular failure also plays a role.[16] This is potentially significant for treatment, since inotropic agents restore T-tubular function in foreshortened muscle.[17] Accordingly, inotropic agents exert much greater effects on foreshortened diaphragm than on diaphragm placed at its optimal length.[18] This concept opens up new perspectives for respiratory muscle pharmacotherapy in patients with severe hyperinflation. The length–tension curves of other respiratory muscles and their adaptation to hyperinflation have not been systematically studied.

A particularly interesting question is the relationship between the in situ operational length of the respiratory muscles and the optimal length in vitro. For the diaphragm, the length at functional residual

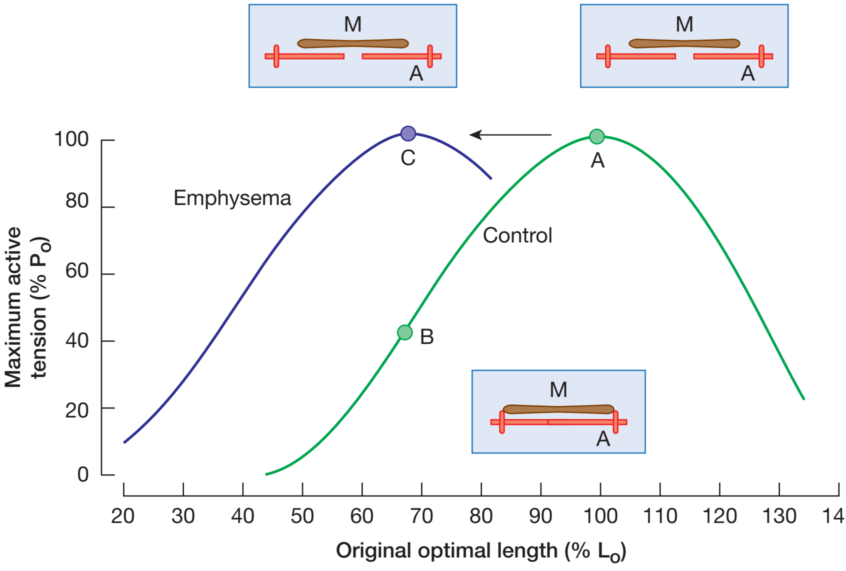

Figure 3-2 Diaphragmatic length–tension curve in normal hamsters and hamsters with elastase-induced emphysema. Tension is expressed as a percentage of maximum tetanic tension, P_o, and length is expressed as a percentage of original optimal length, L_o. The degree of filament overlap among actin (A) and myosin (M) filaments in control (**A**), acute (**B**), and chronic hyperinflation (**C**) is shown. Note that due to sarcomere adaptation in chronic hyperinflation, the degree of filament overlap is the same at a considerably shorter length. *(Reproduced with permission from Farkas G: Functional characteristics of the respiratory muscles. Sem Respir Crit Care Med. 1991;12(4):247–257.)*

capacity (FRC) comes close to the optimal length.[19,20] The length changes undergone by the diaphragm over the vital capacity range are large, 30% to 40%.[21,22] These length changes are considerably smaller for the parasternal intercostals, the scalenes, and the sternocleidomastoids.[23–25] For the parasternal intercostals, the length at FRC is clearly longer than optimal in supine dogs, so that with hyperinflation, the parasternal intercostals move toward their optimal length.[25,26] Subsequent experiments, however, indicate that the fall in pleural pressure caused by stimulation of the parasternal intercostals in dogs is reduced with increasing lung volume.[27] This discrepancy was shown to result from changes in orientation and motion of ribs with hyperinflation. The scalenes and sternocleidomastoids appear to operate on the ascending limb of their length–tension curves in supine dogs.[24] How hyperinflation in patients affects the force-generating capacity of these muscles remains unclear. According to an analysis, the changes in length during passive inflation are proportional to the mechanical advantage of a particular respiratory muscle.[28] In keeping with this analysis, the mechanical advantage of the diaphragm would be considerably greater than the mechanical advantage of other inspiratory muscles (see in the section "Physiologic Conditions Affecting Respiratory Muscle Interaction").

The force developed by a muscle increases with increasing frequency of stimulation. The increase in force is considerably steeper for a slow muscle in which fusion occurs at lower frequency because of the longer relaxation time than for a fast muscle. The diaphragm is intermediate, so that at in vivo stimulation frequencies (10–30 Hz), a fused tetanic contraction occurs. Particularly interesting is the effect of acute shortening on the force–frequency curve. Since acute shortening is associated with a downward shift of the force–frequency curve, the detrimental effect of acute shortening on the force-generating capacity of the diaphragm appears to be twofold.[14] With muscle shortening there is a clear reduction in maximal tetanic force. However, the decrease in force at submaximal stimulation frequencies is disproportionately greater (Fig. 3-3).

The force–velocity curve of the diaphragm is shown in Figure 3-4. With increasing loads, the velocity of contraction is reduced. The velocity of contraction is a direct function of myosin ATPase activity, and, hence, the force–velocity curve is primarily determined by the muscle fiber composition. The diaphragm is intermediate between the force–velocity curve of a fast and a slow muscle (Fig. 3-4).[6] The production of airflow into the lungs requires power output by the respiratory muscles. Power may be calculated as the product of the values of velocity and force according to the force–velocity relationship (Fig. 3-4). Instantaneous peak power occurs at 30% of maximal force and at 30% of maximal velocity. The frequency–isometric force relationship, frequency–shortening force, and frequency–power relationships show a similar dependency of force and power upon frequency of stimulation.

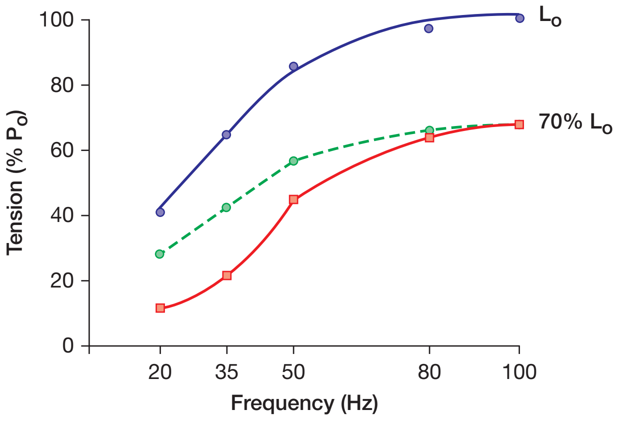

Figure 3-3 Force–frequency curve of human diaphragm at optimal length (L_O) and 70% L_O. Force is expressed as a percentage of maximal tetanic tension, P_O, and frequency is expressed in Hz. *Dashed line* is the predicted line at 70% L_O, whereas the *solid line* is the observed line. The predicted line is based on the assumption that a 30% change in length produces a 35% drop in force at all stimulation frequencies, as is observed for maximal tetanic force. Note that the decrease in force at lower stimulation frequencies is considerably greater than theoretically predicted. *(Reproduced with permission from Farkas G: Functional characteristics of the respiratory muscles. Sem Respir Crit Care Med. 1991;12(4):247–257.)*

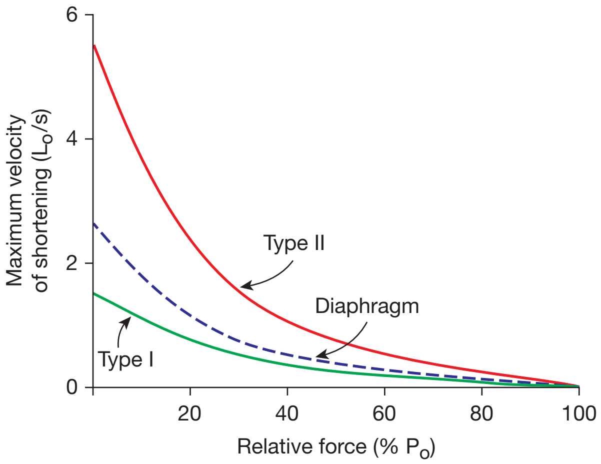

Figure 3-4 Force–velocity curve of human diaphragm *(dashed line)*, which is intermediate between the force–velocity curve of a typical slow muscle (type I) and a typical fast muscle (type II). Maximum velocity is expressed in optimal length (L_O), per second and relative force is expressed as a percentage of maximum tetanic force, P_O.

Fatigue also affects profoundly the force–length, force–frequency, force–velocity, and power–frequency characteristics of the diaphragm. The diaphragm, however, is more resistant to developing fatigue than limb muscles in vivo and in vitro.[29] Of note, the inspiratory muscles recover from fatigue 10 times faster than the elbow flexors performing a similar task.[30] The effects of fatigue on functional properties of the respiratory muscles are discussed in Chapters 84 and 103. The factors determining the development of respiratory muscle fatigue also are discussed in these chapters.

ACTIONS OF RESPIRATORY MUSCLES

Below we consider the actions of individual respiratory muscles or groups of muscles, beginning with the diaphragm.

The Diaphragm

The diaphragm is the most important inspiratory muscle. It is innervated by the phrenic nerves supplied by the cervical nerve roots C3 to C5 in humans. It consists of two distinct parts, the costal and crural parts, which have separate actions on the rib cage, separate segmental motor innervations, and a different embryologic origin. In respiratory activities, however, the diaphragm frequently operates as a functional unit, and in the following its action is described as such. Diaphragmatic action is schematically represented in Figure 3-5. Diaphragmatic contraction increases chest wall dimensions because of three distinct reasons. First, diaphragmatic descent increases the craniocaudal dimensions of the thorax. Diaphragmatic descent is tightly coupled to outward motion of the free abdominal wall.

Second, diaphragmatic contraction increases the dimensions of the lower rib cage because of the increase in abdominal pressure that it causes. This increase in abdominal pressure acts through the zone of apposition (i.e., the zone in which the diaphragm is immediately apposed to the rib cage) to expand the lower rib cage. This action is

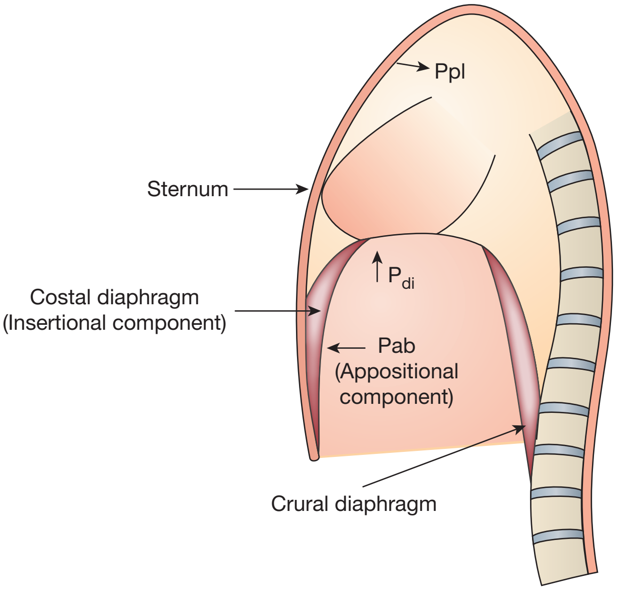

Figure 3-5 Diagram illustrating diaphragmatic action. Lateral view of the thorax. Ppl, pleural pressure; Pab, abdominal pressure; P_{di}, transdiaphragmatic pressure. The costal and the crural diaphragm are shown. See text for further explanation.

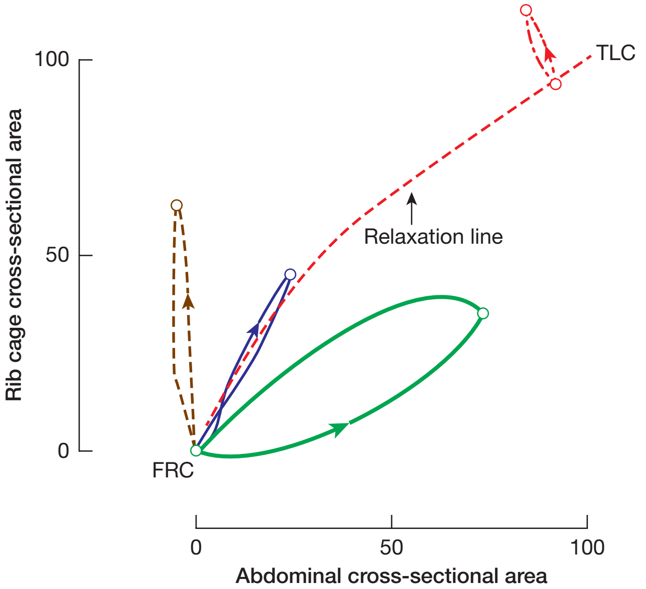

Figure 3-6 Konno–Mead diagram illustrating chest wall motion during quiet breathing *(thin loop)*, diaphragmatic pacing or quiet breathing in tetraplegic patient *(thick loop)*, breathing with diaphragm paralysis *(dash loop)*, and breathing at severely elevated end-expiratory volume *(dash–dot loop)*. Rib cage and abdominal cross-sectional areas are expressed as a percentage of inspiratory capacity. *Dashed line* is the relaxation line obtained during expiration with muscles relaxed.

the appositional component of diaphragmatic action (Fig. 3-5).[31,32] The magnitude of the appositional component is determined by the magnitude of the zone of apposition, about 25% to 30% of the total internal surface area of the rib cage at FRC in standing humans, and by the magnitude of the increase in abdominal pressure caused by diaphragmatic contraction.[32]

Third, diaphragmatic contraction further increases lower rib cage dimensions because of its insertions into the lower rib cage. The diaphragmatic fibers are oriented axially, and their contraction causes pull on the lower rib cage in an axial direction, leading to cephalad motion and outward rotation of the lower rib and hence, to lower rib cage expansion. This is the *insertional component* of diaphragmatic contraction (Fig. 3-5).[31]

When the diaphragm acts in isolation during diaphragmatic contraction or pacing in high quadriplegics, in whom all inspiratory muscles, except for sternocleidomastoids, are paralyzed,[33,34] it exerts an expiratory effect on the upper rib cage during inspiration.[33,35] These data point out that in normal subjects, quiet inspiration is not accomplished by the diaphragm alone but rather results from the coordinated activity of the diaphragm with the rib cage inspiratory muscles and the abdominal muscles. Indeed, the pattern of chest wall motion in quadriplegics shown in Figure 3-6 indicates that diaphragmatic contraction alone cannot be responsible for the pattern of chest wall motion observed during quiet breathing (see in the section "Physiologic Conditions Affecting Respiratory Muscle Interaction") and hence, that other muscles assist the diaphragm in moving the chest wall during quiet breathing.

The Intercostal Muscles

The functional anatomy of intercostal muscles is schematically represented in Figure 3-7. Between the chondral portions of the ribs only one layer of intercostal muscles, the parasternal intercostals, is present. Between the osseous portions of the ribs, two layers are present. The outermost layer runs obliquely downward and forward and is called the *external intercostal*. The innermost layer runs obliquely downward and backward and is called the *internal intercostal* (Fig. 3-7, left panel). Note that the internal intercostals and parasternal intercostals have the same fiber orientation. Dorsally only an external intercostal is present. Finally, the fusiform muscle running from the lateral border of the transverse processes of the thoracic vertebra and inserting caudally into the rostral border of the rib below is called the *levator costae* (Fig. 3-7, right panel).

The parasternal portion of the intercostal musculature, the "parasternals," is consistently active during quiet breathing both in animal and human subjects,[23,36] and is the most important inspiratory portion of the intercostal musculature. The parasternal intercostals have the greatest mechanical advantage, and their contraction produces about 60% of the cephalad motion of the rib during inspiration.[37,38]

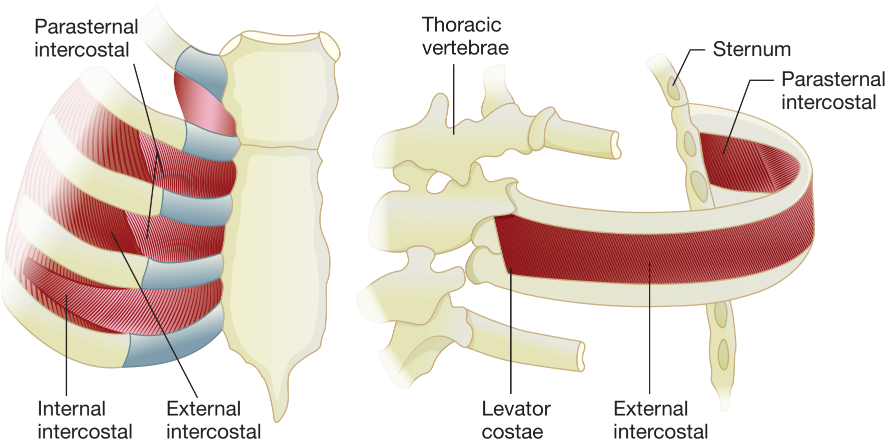

Figure 3-7 Diagram of the functional anatomy of the intercostal muscles, at their anterior *(left)* and posterior *(right)* aspects. Notice the parasternal, internal, and external intercostals, and the levator costae.

Within the parasternal intercostals, the medial fibers have a greater mechanical advantage and are activated more consistently and before the middle and lateral fibers.[39]

The action as well as the respiratory role of the interosseous intercostals remain the subject of a longstanding debate. The most commonly accepted view on intercostal muscle action is based on a theory of intercostal muscle fiber orientation and rib geometry. This theory states that the external intercostals are inspiratory in action, and the internal intercostals are expiratory in action.[40] Numerous experiments do not fit with this theory, although a finite element analysis largely confirmed these actions.[40] It is commonly believed that the interosseous intercostals constitute a reserve system that may be recruited with increased ventilatory load. The external intercostals are recruited predominantly during inspiration, primarily in the upper interspaces, whereas the internal intercostals are recruited predominantly during expiration primarily in the lower interspaces.[40] Wilson et al.[38] demonstrated by the application of the reciprocity theorem of Maxwell that the external intercostals in the dorsal portion of the costal interspaces have a large inspiratory mechanical advantage. This advantage decreases in the ventral and caudal directions such that in the ventral portion of the caudal interspaces it is reversed in an expiratory mechanical advantage.[40] Conversely, the internal intercostals in the caudal interspaces have a large expiratory mechanical advantage, but this advantage decreases in the cranial and ventral directions.[40] Because of this pattern of topographic distribution the pattern of neural activation is crucial for the function of these muscles.[40] This pattern was shown to match the pattern of distribution of mechanical advantage, such that the external intercostals have an inspiratory function and the internal intercostals have an expiratory function.[40]

Without question, the levator costae have an inspiratory action on the rib. It is frequently activated even during quiet inspiration in supine dogs.[41] The levator costae's contribution to inspiratory motion of the ribs during quiet breathing, however, appears substantially smaller than that of the parasternal intercostals. This contribution may further increase when the inspiratory motion of the ribs is appreciably increased.

■ The Scalenes

The scalenes run between the transverse process of the five lower cervical vertebrae and the upper margin of the first (scalenus anterior) and second (scalenus medius and posterior) ribs. The action of these muscles is to raise the first two ribs. The orientation of their axis in the neck causes upward motion of these ribs ("pump handle" motion). Moreover, the scalenes are consistently active during quiet breathing in normal individuals and contribute to chest wall expansion.[42] They may be very important in the case of spinal cord injury. When the injury is below C4 to C8, the scalenes' function is entirely or partially preserved, and they contribute importantly to upper rib cage motion in these patients.[43]

■ The Sternocleidomastoids

The sternocleidomastoids run between the mastoid processes of the temporal bone and the manubrium sterni and medial portion of the clavicle. The pressure-generating ability of the sternocleidomastoid muscle in normal humans is about the same as that of the scalene muscles. In humans, these muscles are electrically silent during quiet breathing, but they may be recruited with increased ventilatory load. These muscles are particularly important in high quadriplegics in whom they preserve their function because they are innervated by the 11th cranial nerve and spinal nerves C1 to C2.[33,44] Through training the sternocleidomastoids may develop marked hypertrophy and contribute to several hours of ventilator independence in these patients.[44] They also may be recruited in patients with poliomyelitis and diaphragmatic dysfunction. These muscles are thought to be important in moving the upper rib cage in patients with chronic obstructive pulmonary disease (COPD), even though a clinical experimental study failed to demonstrate consistent activity in these muscles in these patients.[45]

■ The Shoulder Girdle and Neck Muscles

Several shoulder girdle and neck muscles may contribute to inspiration under particular circumstances. Most of these muscles run from the rib cage to an extrathoracic extension. When the rib cage is fixed in the lean-forward position—a position commonly employed by patients with COPD—these muscles contribute to expansion of the rib cage during inspiration. Muscles that may contribute to inspiration include the trapezius, latissimus dorsi, pectoralis major and minor, erector spinae, teres major, serratus anterior, platysma, mylohyoid, and sternohyoid. Since these muscles commonly contribute to inspiration in patients with severe airflow obstruction, their further use for other activities (e.g., hair combing), may considerably increase dyspnea in these patients.[46]

■ The Clavicular Head of Pectoralis Major

The clavicular head of the pectoralis major runs laterally and caudally from the medial half of the clavicle and manubrium sterni to the humerus. If the arms are fixed and braced, contraction causes downward motion of the ribs and sternum, increase in pleural pressure and, hence, expiration. Simultaneously, the lower rib cage and the abdomen move outward. Tetraplegics use this expiratory action when all other expiratory muscles are paralyzed.[47]

■ The Triangularis Sterni

The triangularis sterni is the most important expiratory muscle of the rib cage.[48] The muscle runs at the inside of the thorax between the inner aspect of the sternum and the inner aspect of the five lower ribs (Fig. 3-8), and its action is to lower the ribs relative to the sternum and thus to cause expiration. The triangularis sterni is electrically silent in humans breathing quietly,[48] but it is recruited during expiration below FRC.[48] Its neural activation is also coupled with that of the abdominal muscles.[48] Its recruitment threshold is low, lower than the recruitment threshold of most other expiratory muscles.

■ The Abdominal Muscles

The abdominal muscles are composed of four different muscle layers (Fig. 3-1). Ventrally, a muscular sheet running between the

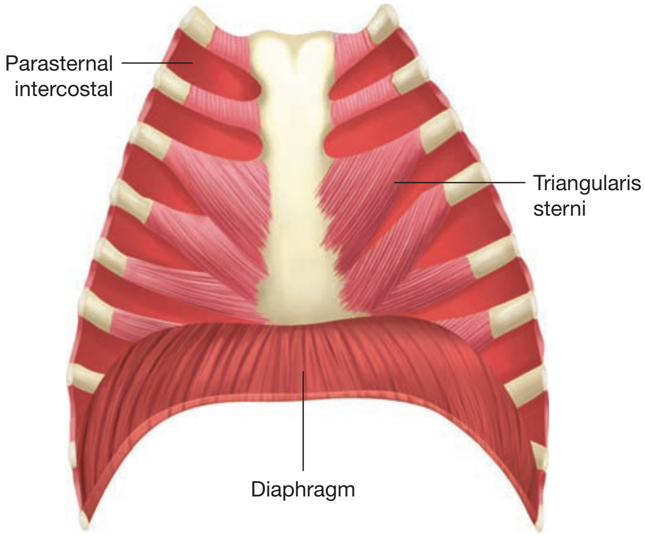

Figure 3-8 Diagram illustrating the functional anatomy of the parasternal intercostal muscles, the triangularis sterni, and the diaphragm.

AL GRAWANY

lower costal cartilages and the sternum and the pubis represents the rectus abdominis. This muscle is enclosed in a sheath formed by the aponeuroses of the other three muscles. Laterally, an oblique muscle runs obliquely downward and forward between the lower eight ribs and the iliac crest, inguinal ligament, and linea alba medially, the external oblique. At the inner surface of this muscle lies the internal oblique with a fiber orientation, which is 90 degrees perpendicular to the external oblique. These muscles are homologous to the external and internal intercostals. The innermost layer is the transversus abdominis, a circular muscular sheet surrounding the abdomen, with a fiber orientation that is parallel to the ribs. The transversus abdominis originates from the inner surface of the lower six ribs, where it interdigitates with the costal insertions of the diaphragm. It runs from this origin and the lumbar fascia, iliac crest, and inguinal ligament, circumferentially around the abdominal visceral mass to terminate ventrally in the rectus sheet. These muscles all have an expiratory action, by virtue of the inward pull of the abdomen they cause and of the insertions they have in the rib cage. In addition, however, rib cage expansion may occur with contraction of some of these muscles through the increase in abdominal pressure accompanying their contraction.[49]

The abdominal muscles are electrically silent during quiet breathing. Usually, however, tonic activity is present in the abdominal muscles in upright position, particularly in the upper segments.[31] During inspiratory loading, CO_2-induced hyperventilation, exercise, and forced expiration, these muscles are recruited. The transversus abdominis appears to have the lowest recruitment threshold.[50,51]

RESPIRATORY MUSCLE INTERACTION

Important interactions among respiratory muscles during quiet breathing are discussed in the following section.

■ Respiratory Muscle Interaction During Quiet Breathing

Respiratory muscle interaction is traditionally studied by means of a Konno–Mead diagram, relating rib cage diameter or cross-sectional area to abdominal diameter or cross-sectional area (Fig. 3-6). First, this relationship is determined in the absence of muscle contraction, during a relaxed expiration, yielding a relaxation line. During quiet breathing in the upright position, the chest wall moves along this relaxation line, which means that proportional expansion of rib cage and abdomen is occurring. In the supine position, abdominal movement is proportionally greater than rib cage movement. Since isolated diaphragmatic contraction in quadriplegics causes abdominal movement without rib cage motion or even inward movement of the upper rib cage (upper rib cage paradox), diaphragmatic contraction alone cannot be responsible for the pattern of motion occurring during quiet breathing (Fig. 3-6). Therefore, this motion requires concomitant contraction of other muscles (i.e., the parasternal intercostals and scalenes). These muscles actively contribute to chest wall motion and cause upper rib cage expansion, whereas diaphragmatic contraction alone would cause upper rib cage paradox. During quiet breathing, the diaphragm probably contributes about 60% to 70% of the tidal volume, and the parasternal intercostals and scalenes contribute the rest.[52]

Posture alters the interaction between the respiratory muscles. For the diaphragm, the resistance of the abdominal contents on diaphragmatic descent is the principal determinant of its action on the rib cage. When changing from a seated to a supine posture in humans, there is a marked increase in abdominal compliance[53] and changes in the diaphragm shape result in less rib expansion. The influence of posture on the lung-expanding action of the diaphragm has been confirmed in patients with upper cervical cord transaction. Indeed, when these patients were supine, the paced diaphragm was able to generate an adequate tidal volume but the latter was progressively and markedly reduced when the patients were gradually tilted head up.[33] The abdominal muscles[54,55] and also the triangularis sterni[48,56,57] are silent in the supine posture in healthy individuals, and while the tonic activity of the abdominal muscles in the standing posture is not related to the phases of the respiration, the activity of the triangularis sterni is confined to expiration.[57] Active use of these two sets of expiratory muscles in the standing posture compensates for the adverse effect of this posture on the inspiratory muscles, in particular the diaphragm.

Sleep affects respiratory muscle function negatively but in healthy individuals these physiologic changes are not clinically significant. Sleep is associated with a generalized postural muscle hypotonia that is most profound during the phasic events of rapid eye movement (REM) sleep.[58] Therefore, respiratory muscles with a dual respiratory and postural function like the intercostals lose activity during REM sleep.[59] However, the diaphragm, which exhibits respiratory and postural function, maintains and even increases its activity to maintain tidal volume during REM sleep.[59] In severe COPD patients where rib cage motion is mainly produced by the inspiratory muscles of the rib cage as the diaphragm is mechanically impaired by hyperinflation, the substantial decrease in the activity of the scalene and sternocleidomastoid muscle during REM sleep is expected to decrease inspiratory pressure development and to lead to hypoventilation.[60]

PHYSIOLOGIC CONDITIONS AFFECTING RESPIRATORY MUSCLE INTERACTION

Respiratory muscle interaction present during quiet breathing and the chest wall motion resulting from it may be altered in a number of physiologic circumstances in which ventilatory load is affected. Indeed, the respiratory muscles participate in tasks that, although not strictly ventilatory in nature, serve important respiratory functions. These tasks of daily life include speech, laughter, swallowing, gagging, vomiting, and coughing. In addition, the interaction of the respiratory muscles is also modified during non-ventilatory tasks.

Speech and laughing require the coordination of respiration and structures involved in producing sound features. Spontaneous speech occurs primarily at volume levels below spontaneous end expiration.[61] There is, therefore, a successive recruitment of muscles of expiration to empty the rib cage: first the triangularis sterni muscle[48,61] and the internal intercostal muscles, then the external oblique and other muscles of the lateral abdominal wall, and finally the rectus abdominis.[50,62,63] At the very end of expiration, the latissimus dorsi is active too.[62,63] Abdominal contraction during speech can optimize the inspiratory function of the diaphragm obliged to contract rapidly between phrases, and will also prevent dissipation of the pressure developed by the rib cage muscles on paradoxical abdominal displacement.[61]

Laughing is a natural maneuver triggered by emotion necessitating the coordination of the laryngeal and respiratory systems to produce a characteristic sound pattern and phasic lung pressure variations superimposed on an active expiratory effort. Laughter generally takes place when lung volume is low, near FRC, and is terminated near residual volume.[64] It is characterized by sudden repetitive expiratory efforts leading to a decrease in lung volume due to sudden and sustained increase in gastric and esophageal pressures. The triangularis sterni muscle is recruited during laughing.[48] Higher transdiaphragmatic pressure at the end of the consecutive expiratory efforts indicates that the diaphragm actively prevents part of the increase in abdominal pressure from being transmitted to the chest wall cavity, thereby protecting intrathoracic structures from further mechanical stress and compression.[64] A pilot study suggests that the pattern of diaphragm activation during laughter is different from that induced by coughing or sneezing.[65]

For swallowing, respiration needs to be interrupted. During swallowing, the passive expiration of the diaphragm is interrupted by static activity aimed at preserving respiratory volume for expiration after swallowing.[66] Abdominal activity increases throughout pre- and post-swallowing expiration.[66]

Vomiting that is produced by changes in thoracic and abdominal pressures is generated by the coordinated action of the major respiratory muscles. During vomiting, the diaphragm and the external intercostal (inspiratory) muscles co-contract with abdominal (expiratory) muscles in a series of bursts of activity culminating in expulsion while the internal intercostal (expiratory) muscles contract out of phase with these muscles during retching and are inactive during expulsion.[67] Finally, the portion of the diaphragm surrounding the esophagus relaxes during expulsion, presumably to facilitate rostral movement of the gastric content.[67]

Coughing, sneezing, and gagging represent complex acts involving both inspiratory and expiratory phases during which most of the respiratory muscles are recruited. Importantly, during those maneuvers, the maximal diaphragm force is reached.[68,69] Voluntary cough in humans is associated with a coordinated activation of the expiratory and accessory muscles. A graded increase in activity and burst duration proportional to cough flow rates is observed. Low cough flow rates are essentially produced by the activation of the expiratory muscles, whereas accessory muscles become involved sequentially and increasingly with the production of higher flow rates.[70] The triangularis sterni muscle is actively recruited during coughing[48,71] and during sneezing.[71]

Finally, understanding the level of muscle recruitment may be particularly relevant when testing respiratory muscle force to evaluate the degree of impairment in some diseases. Indeed, in untrained normal subjects, maximal inspiratory effort against a closed shutter (Müller maneuver or the maximal inspiratory pressure) mainly activates the intercostal muscle and the diaphragm as well as the sternomastoid.[72] The same holds true for the sniff maneuver through the nose.[72] The combined maneuver consisting in a maximal inspiratory maneuver combined with a maximal expiratory effort also activates the expiratory muscles (rectus abdominis) and produces the highest level of diaphragmatic strength as assessed by measuring transdiaphragmatic pressure.[72] The maximal electrical activity of the diaphragm is reached during the sniff maneuver.[72] These data indicate that the pressure generated by these maneuvers reflects a complex interaction between several groups of muscles.

All the above-mentioned effects pertain to ventilatory aspects of the respiratory muscles but, in addition to their respiratory role, the respiratory muscles also contract during postural tasks. The costal and the crural diaphragm are active with a single rapid movement of the contralateral upper limb in humans.[73] Electromyographic activity of the diaphragm increases prior to the onset of the activity of the muscle responsible for movement. This occurs irrespective of the phase of respiration[73] and is associated with an increase in transdiaphragmatic pressure with an initial reduction in length of the costal diaphragm. Similarly, during trunk rotation external and internal intercostal muscles show increased inspiratory activity superimposed on their postural tone[74,75] as do the parasternal intercostals.[76] During repetitive movement, the diaphragm contracts tonically throughout the respiratory cycle and phasic modulation of diaphragm activity at the frequency of limb movement is superimposed on its respiratory and tonic activation.[77] This was also observed in the transversus abdominis muscle.[77] Modulation of the intra-abdominal pressure that occurs through coordinated activity of the diaphragm, abdominal muscles, and pelvic floor muscles may be important for the control of spinal stability when the limbs move.[73,77] When respiratory demand is increased, the activity of the diaphragm and the transversus abdominis associated with movement of an arm is reduced or even abolished, and the associated changes in gastric pressure are reduced.[78] In humans, the postural role of the diaphragm may also be impaired with specific fatigue of the inspiratory muscles.[79] The human triangularis sterni muscle also contracts during postural maneuvers such as head flexion, trunk rotation, and leg lift.[48]

PATHOLOGIC CONDITIONS AFFECTING RESPIRATORY MUSCLE INTERACTION

Respiratory muscle interaction is profoundly affected by a number of pathologic conditions, including hyperinflation and reduction in or loss of muscle activity.

Hyperinflation is a functional abnormality of lung diseases in which airflow obstruction or loss of elastic recoil are features. Hyperinflation may be particularly severe in patients with COPD, in whom the FRC often exceeds predicted total lung capacity (TLC). An overwhelming amount of evidence shows that hyperinflation reduces the diaphragmatic effectiveness as a pressure generator and reduces diaphragm contribution to chest wall motion. The contribution of the intercostal muscles and scalenes is likely to be increased, such that chest wall motion becomes exclusively or predominantly rib cage motion (Fig. 3-6). The ineffectiveness of the diaphragm may result from diaphragmatic shortening, geometric alterations, alterations in diaphragm–rib cage interaction, alterations in mechanical arrangements among the costal and crural parts of the diaphragm, and reduction in the zone of apposition.[80] Among these, diaphragmatic shortening appears to be the most important. Indeed, with inflation from FRC to TLC, the diaphragm shortens about 30% to 40%,[21,22] whereas the parasternal and upper external intercostal muscles shorten by only 10%,[23,81] the scalene by 2%,[82] and the sternomastoid muscle by 6%.[82] For the diaphragm, this shortening is expected to reduce significantly its pressure-generating capacity. Several studies indicate that diaphragmatic geometry is not affected significantly by hyperinflation, pointing out that the length–force properties of the diaphragm represent the most important factor for the pressure-generating capacity of this muscle.[83,84] The appositional component of diaphragmatic action is reduced substantially due to a reduction in the zone of apposition.[32] The insertional component is affected so that diaphragmatic contraction causes inward retraction of the lower rib cage. This may be noticed clinically in patients with severe hyperinflation.[85,86] The mechanical arrangement between the costal and crural parts of the diaphragm changes from a parallel arrangement at FRC to a series arrangement at TLC.[21] This is likely to further compromise the pressure-generating capacity of the diaphragm independently of its force–length characteristics.

Hyperinflation also impairs the pressure-generating capacity of the inspiratory intercostal muscles (the parasternals and the external intercostals). This effect is mainly related to the orientation and motion of the ribs.[27] The synergistic interaction between the diaphragm and the inspiratory intercostal muscles becomes prominent at high lung volumes.[27] The force-generating capacity of the neck muscles like the scalene and the sternomastoid muscle is maintained with hyperinflation.[82] During exercise, dynamic hyperinflation brings end inspiratory lung volume close to total lung capacity and reduces inspiratory reserve volume. Consequently, patients develop a rapid and shallow breathing pattern. Impairments in dynamic respiratory muscle function might further exacerbate the rapid and shallow breathing of these patients during exercise by promoting further restriction of tidal volume expansion.[87] With increasing lung hyperinflation in COPD patients, the inspiratory muscles of rib cage and accessory respiratory muscles are increasingly recruited even at relatively low work rates.[88] It has also been observed that during exercise, there is a progressive increase in total inspiratory pressure contribution from rib cage and accessory muscles relative to that of the diaphragm, and the magnitude of this increase appears to depend on the non-diaphragmatic muscle reserves during resting breathing.[89] These alterations in respiratory muscle recruitment pattern might contribute to exercise limitation and might necessitate the application of specific therapeutic strategies.[90] It has been suggested that in severe COPD patients, improving rib cage and accessory inspiratory muscle function should be a priority.[88] It has been demonstrated that respiratory muscle resistance training can provide a strong training stimulus specifically to the rib cage and accessory inspiratory muscles in these patients, with diaphragm activation being similar to that during exercise hyperpnea.[91] In dogs, hyperinflation induces lengthening of the abdominal muscles, particularly the transverse abdominis and internal oblique muscle.[92] Consequently, the rise in abdominal pressure obtained by selective stimulation of the abdominal muscles at TLC is greater than that obtained at FRC.[93] This also happens in normal humans during magnetic stimulation of the abdominal muscles.[92]

It should be emphasized, however, that the above pertains to acute hyperinflation. In chronic hyperinflation, the diaphragm adapts to the chronically foreshortened state by dropping out of sarcomeres.[15] As a consequence, the filament overlap within each sarcomere is restored toward optimal overlap. This adaptation is shown in Figure 3-2. This adaptation, however, only partially restores diaphragmatic function—first, because part of the reduction in force with shortening is due to compression of the T-tubular system, blocking exit-electrolyte flow and impeding excitation–contraction coupling.[16] Whether adaptations in T-tubular function also occur with chronic foreshortening remains to be investigated. Second, sarcomere adaptation adapts only to the loss in diaphragmatic function associated with diaphragmatic shortening and not to the loss in function due to geometric alterations, alterations in diaphragm–rib cage interaction, changes in mechanical arrangement among different parts of the diaphragm, or loss of zone of apposition. Third, although sarcomere adaptation restores the force-generating capacity of a foreshortened diaphragm, it reduces the number of sarcomeres in series. Consequently, sarcomere adaptation compromises the capacity of the diaphragm to undergo changes in length and, hence, its capacity to produce volume changes, presumably its most important function. The fiber length of the parasternal intercostal muscles[94] and of the scalenus muscle[95] are, however, not affected by chronic hyperinflation in animals.

Interventions aimed at reducing hyperinflation such as lung volume reduction surgery (LVRS) and lung transplantation improve diaphragmatic function.[96] The effects of LVRS are primarily due to an increase in the zone of apposition, lengthening of the diaphragm, and improved neuromechanical coupling.[97] To what extent complete sarcomere adaptation is present in patients with COPD and extreme hyperinflation is not clear from the clinical studies with LVRS. After lung transplantation the radius of curvature and the zone of apposition of the diaphragm are restored. This is primarily due to mediastinal displacement toward the graft.[96]

Expiratory muscle recruitment is frequently observed in COPD patients with severe airflow obstruction both at rest and during exercise.[98,99] The transversus abdominis is frequently recruited. Expiratory muscle recruitment may contribute to the intrinsic positive end-expiratory pressure ($PEEP_i$) that is frequently observed in these patients. $PEEP_i$ is primarily caused by impaired pulmonary mechanics and consequent dynamic hyperinflation.[100] The functional significance of this expiratory muscle activation is poorly understood. Indeed, in severe airflow obstruction, expiratory flow limitation is frequently present. In the presence of expiratory flow limitation, recruitment of expiratory muscles no longer contributes to expiratory flow. Whether excessive expiratory muscle activation during exercise might contribute to symptoms and exercise limitation in these patients is still a matter of debate.[99,101]

In patients with pulmonary disease in general and COPD in particular, several factors may contribute to generalized muscle weakness, in which the respiratory muscles partake. These include hypoxemia and hypercapnia, malnutrition, cardiac failure, corticosteroid treatment, infection, electrolyte disturbances, and inactivity with consequent disuse atrophy.[102] There is consensus that COPD exacerbations contribute to the development of this muscle weakness.[103] Of particular importance appears to be treatment with corticosteroids in repetitive bursts, which is often inadvertently administered to COPD patients. Typically, this causes a myopathic pattern characterized by scattered necrotic fibers with an increased number of central and subsarcolemmal nuclei, and generalized muscle fiber atrophy as seen on muscle biopsy[104] instead of selective type IIb fiber atrophy as is seen in animal studies.

The continuous patterns of motor activity associated with respiration make the diaphragm the most active muscle in the body. The daily duty cycle (ratio of active to inactive time) of the diaphragm in most species is about 45% compared to 2% for the extensor digitorum muscle (predominantly composed of type IIb fibers) and 14% for the soleus muscle (mainly a type I muscle).[105] Given that the diaphragm is highly active, it is expected to be particularly sensitive to inactivity. It is therefore not surprising that serious diaphragm dysfunction develops rapidly during controlled mechanical ventilation, a situation in which the diaphragm is totally inactive.[106–108] Perturbations in respiratory muscle interaction are also marked in patients with cervical spinal cord injuries. In these patients, the intercostal and abdominal muscle contribution to respiratory function is lost. Diaphragm inspiratory capacity is also often compromised when injury is located at the C3 to C5 levels. During quiet breathing, tetraplegic subjects with injuries at C4 to C7 use their scalene[43,109] that becomes hypertrophied.[109] Patients with high tetraplegia use several neck muscles[44] in addition to the sternocleidomastoids and trapezii to breathe.[33] Quadriplegics are also predisposed to the development of inspiratory muscle fatigue because of reduced muscle strength and endurance.[110] Inspiratory muscle training in these patients increases both strength and endurance and protects against fatigue.[110] Diaphragm contracting alone through phrenic nerve pacing in subjects with upper cervical cord transaction or during spontaneous breathing in subjects with traumatic lower cervical cord transaction exerts both an expiratory action on the upper rib cage and an inspiratory action on the lower rib cage.[33,35,43] Finally because abdominal and expiratory rib cage muscles are paralyzed in subjects with tetraplegia, their ability to raise intrathoracic pressure is markedly reduced. Despite active use of the clavicular portion of the pectoralis major to deflate the rib cage during forced expiration,[47,111,112] cough is ineffective, and the clearance of airway secretion is markedly impaired. Strength training of the pectoralis major improves expiratory function,[113] an effect that is expected to increase the effectiveness of coughing that might reduce the prevalence of bronchopulmonary infections in these subjects.

CONCLUSIONS

The act of breathing requires the coordinated action of a number of muscle groups. During quiet breathing, chest wall motion results from the action of the diaphragm but also from the other inspiratory muscles such as the parasternal intercostals and the scalenes in addition to the expiratory muscles. Those respiratory muscles are all well equipped to sustain continuous rhythmic contraction. Respiratory muscle interaction is affected by posture and sleep but also in a number of physiologic circumstances in which ventilatory load is altered, such as during speech, laughter, swallowing, gagging, vomiting, and coughing. In addition to their respiratory role, the respiratory muscles also contract during postural tasks such as limb muscle movement, leg lift, trunk rotation, and head flexion. Finally, several pathologic conditions including hyperinflation, reduced or loss of activity caused by undernutrition, medical treatment (in particular corticosteroids), mechanical ventilation, or spinal cord injury also may affect the function and the interaction of the respiratory muscles. Strategies consisting of reducing hyperinflation (e.g., LVRS, lung transplantation) or improving muscle function through muscle training may help to some extent in restoring respiratory muscle function.

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CHAPTER 4

Molecular Regulation of Lung Development

Wellington V. Cardoso
Ying Yang
Jining Lu

INTRODUCTION

This chapter focuses on the mechanisms that control the development of the respiratory system from specification of the progenitors of the primordial lung to the formation of the definitive alveoli. The respiratory system is characterized not only by its major diversity in cellular phenotypes, but also by its complex 3D architecture in both the airway and alveolar compartments designed to conduct air and facilitate gas exchange. Its network of conduits comprises the trachea and extrapulmonary and intrapulmonary airways formed by multiple generations of branching epithelial tubules.

Development of the respiratory system encompasses prenatal and postnatal life, but timing and duration of specific events can vary substantially among species. Lung development starts much earlier in humans than in mice and rats; alveolar formation initiates in the human lung by late gestation in contrast to the murine lung, in which it is a postnatal process (Fig. 4-1). As an organ of exceptional structural and functional complexity, the lung is formed by a contribution of all embryonic layers, including the endoderm (epithelium), mesoderm (mesenchyme), and ectoderm (innervation).

Based essentially on histologic criteria, lung development has been traditionally described in four stages: (1) *Pseudoglandular*: corresponding to the initial period of formation of the bronchial tree, when the lung exhibits a gland-like morphology with epithelial tubules separated by a thick mesenchymal layer; (2) *Canalicular*: when airway branching is nearly finished and distinct columnar and cuboidal epithelial cells are seen in proximal (large) and distal (small) airways, respectively. The epithelial tubules are then separated by a thinner mesenchyme containing blood vessels; (3) *Saccular*: primitive saccules are seen at the distal end of bronchial tree with widening of the lumens and the appearance of flat-shaped type I (AT1) and cuboidal, surfactant-producing type II (AT2) cells. The intimate approximation of the type I cell to the vascular structures (primitive alveolo-capillary barrier) allows gas exchange during the immediate postnatal period; and (4) *Alveolar*: when these primitive saccules undergo secondary septation to form numerous smaller mature alveolar structures to increase the gas-exchange surface.[1,2]

HOW RESPIRATORY PROGENITORS ARISE

The lung originates from the anterior portion of the gut tube (foregut), which also gives rise to organs, such as the thyroid, stomach, liver, and pancreas.[3,4] Respiratory progenitors of the lung and trachea arise from the ventral foregut endoderm in mice at around embryonic day 9 (E9.0, mid-gestation) and in humans around the 4th week of gestation. These cells can be readily recognized even before a lung primordial bud forms by the expression of Nkx2-1 (Ttf1, thyroid transcription factor 1); this gene, however, is not lung-specific, and it labels progenitor cells of the thyroid located in more anterior (cranial) regions of the foregut (Fig. 4-2).[5] An Nkx2-1 lineage tracing study reveals that these Nkx2-1+ progenitors at E9.0 give rise to the vast majority of lung epithelial cells.[6] Nkx2-1 is essential for the lung, as disruption of this gene in mice results in severely hypoplastic cystic lungs and inability of airways to form branches. Importantly, in mutants there is no evidence of epithelial cells expressing surfactant protein or other differentiation markers typically found in the lung.[5] It is unclear whether these mutants' lung progenitors are never specified or just cannot be maintained in the absence of Nkx2-1.

How are these progenitors specified? In vivo and in vitro studies in different species point to an interplay between multiple endodermal and mesodermal signals in the foregut, but notably WNT is found to be crucial in this process. Both WNT2 and WNT2B are present in the foregut mesoderm while β-CATENIN (CTNNB1) is present in both mesoderm and endoderm at the prospective site of lung formation. Loss of canonical WNT signaling prevents the appearance of Nkx2-1-expressing lung progenitor cells.[7,8] The significance of this pathway

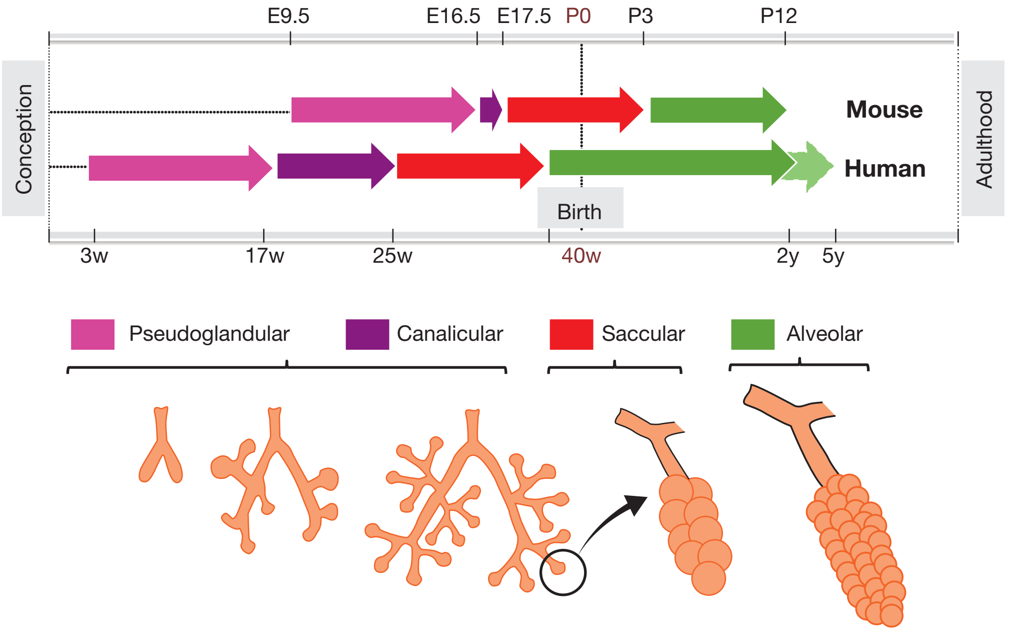

Figure 4-1 Timeline for the developmental stages of mouse and human lungs and diagram of representative stages. Mouse (E, embryonic or P, postnatal days); humans (w, gestation week; y, year).

is further confirmed by the expansion of the Nkx2-1 lung domain to more posterior sites when WNT/β-CATENIN signaling is overactivated in the foregut endoderm.[7,8] Sonic hedgehog (SHH), a member of the hedgehog family of proteins, and its transducing molecules Patched (PTC) and GLI1/2/3, also are present in the lung domain of foregut in the endoderm and mesoderm, respectively. Gli2/3 double knockout results in failed induction of respiratory progenitors.[9] Moreover, there is a role for bone morphogenetic protein (BMP) signaling in regulating the expression of Sox2, which is required for proper foregut patterning and the expansion of Nkx2-1-expressing lung progenitors.[10]

Interestingly, the vitamin A derivative retinoic acid (RA) serves as a core signal bridging WNT, SHH, and BMP pathways. RA synthesis and receptor (RAR) activity are prominent in the E8.5–9.5 mouse foregut.[11] The importance of RA in lung development has been recognized for decades from lung agenesis and developmental abnormalities due to vitamin A deficiency or due to genetic disruption of key components of the RA pathway.[12–15] There is accumulated evidence that lung agenesis is due to the inability to specify and expand the lung progenitors in the absence of RA signaling. RA was shown to be required for lung specification through a mechanism that involves RA induction of SHH, which then acts in the foregut mesoderm inducing WNT2/2B.[16]

FORMATION OF THE LUNG AND TRACHEAL PRIMORDIA

Once specified, these Nkx2-1-expressing respiratory progenitors are subsequently expanded to generate the tracheal and the lung primordia. The primordial lung is identified in human embryos at the beginning of gestation (4th week), much earlier compared with mice (mid-gestation at E9.5). Lung buds arise as lateral outgrowth of the ventral foregut endoderm and fuse at the midline, where the tracheal primordium forms (Fig 4-2B–D). From then on, the trachea and the

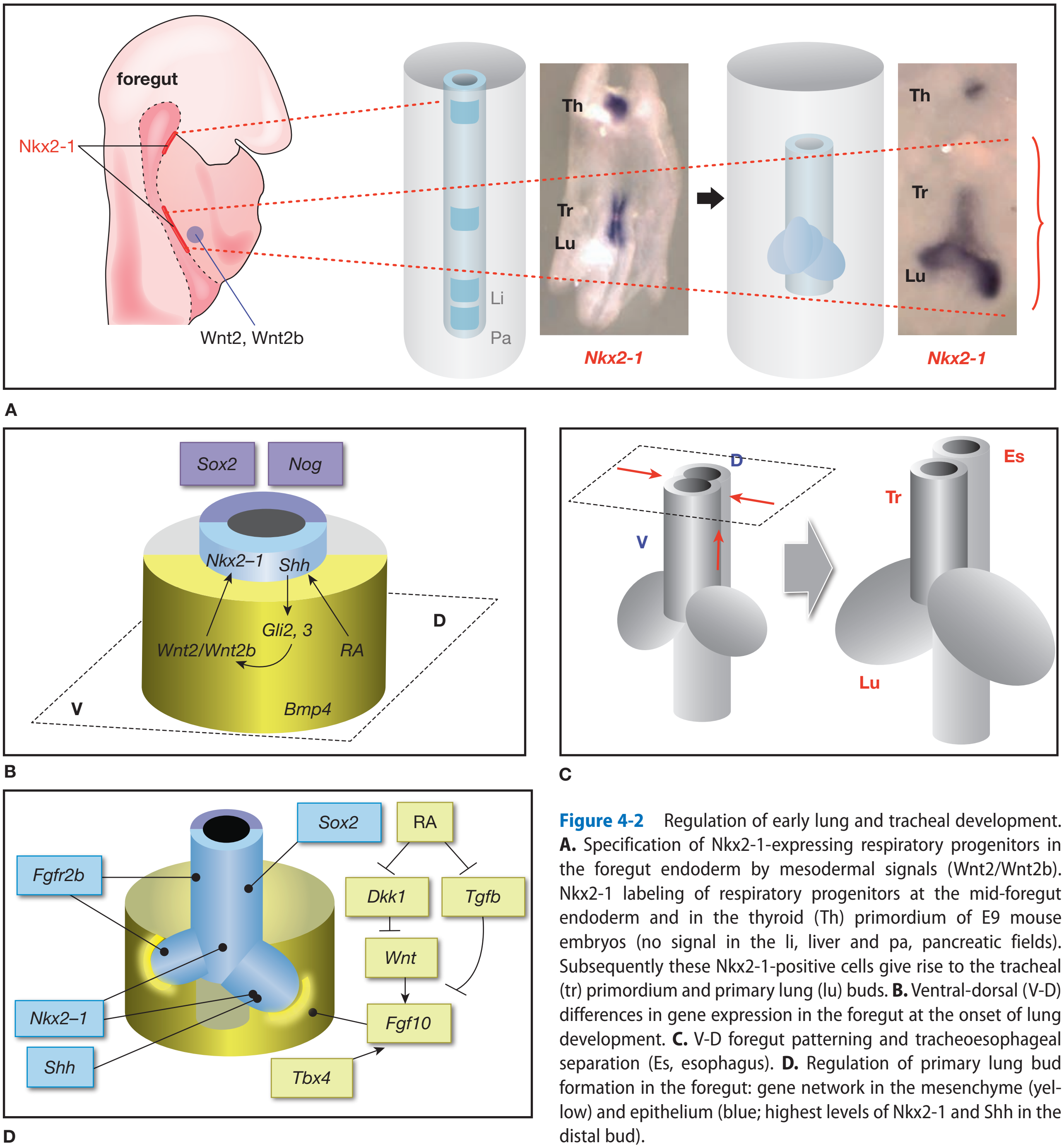

Figure 4-2 Regulation of early lung and tracheal development. **A.** Specification of Nkx2-1-expressing respiratory progenitors in the foregut endoderm by mesodermal signals (Wnt2/Wnt2b). Nkx2-1 labeling of respiratory progenitors at the mid-foregut endoderm and in the thyroid (Th) primordium of E9 mouse embryos (no signal in the li, liver and pa, pancreatic fields). Subsequently these Nkx2-1-positive cells give rise to the tracheal (tr) primordium and primary lung (lu) buds. **B.** Ventral-dorsal (V-D) differences in gene expression in the foregut at the onset of lung development. **C.** V-D foregut patterning and tracheoesophageal separation (Es, esophagus). **D.** Regulation of primary lung bud formation in the foregut: gene network in the mesenchyme (yellow) and epithelium (blue; highest levels of Nkx2-1 and Shh in the distal bud).

digestive tube separate through a mechanism still poorly understood that involves formation of a tracheo-esophageal septum.[17,18] Primary lung bud formation is crucially dependent on the local expression of Fgf10 in the foregut mesoderm.[19,20] FGF10 diffuses to the nearby endoderm at the prospective lung region and activates FGFR2b signaling in Nkx2-1-expressing progenitor cells, leading to epithelial proliferation and migration toward the FGF10 source.[21,22] Fgf10 null mice fail to form lungs and die at birth. Interestingly, the trachea still forms in these mutants, suggesting that Nkx2-1-expressing progenitors from the lung and trachea have different requirements for FGF10 signaling for expansion or survival.[19,20]

Evidence suggests that RA signaling is highly active in the foregut at the onset of lung development, integrating multiple pathways that control Fgf10 expression to form the lung primordium. RA ensures proper levels of FGF10 in the lung region by balancing the activity of WNT and TGF-β in the foregut mesoderm. RA controls expression of the WNT inhibitor Dkk1, thus allowing WNT induction of FGF10.[23,24] This is further supported by the inability of Wnt2a/Wnt2b null mice to induce FGF10 in the foregut.[7] Moreover, RA prevents the widespread activation of TGF-β signaling in the foregut mesoderm, which suppresses Fgf10 expression (Fig. 4-2D). Thus, the disruption of WNT/TGF-β/FGF10 interactions represents an additional mechanism to explain the failure to form the lungs classically reported in vitamin A deficiency.

Members of the T-box family of transcription factors (Tbx2–Tbx5) have been reported in the developing foregut and lung mesenchyme.[25] Studies in chick embryo show that Tbx-4 is co-expressed with Fgf10 in the foregut at the onset of lung development. Notably, Tbx4 can induce Fgf10 expression and consequently expand the domain of Nkx2-1-expressing respiratory progenitors at the onset of lung development.[26] Moreover, genetic studies in mice showed a dose-dependent activity of Tbx4 and Tbx5 in regulating primary bud formation, likely through regulation of FGF10 and WNT.[27]

VENTRAL-DORSAL (V-D) PATTERNING AND TRACHEOESOPHAGEAL SEPARATION

Differences in V-D cell fate are already obvious in the foregut at the onset of lung development (Fig. 4-2). The ventral endoderm (respiratory progenitors) expresses Nkx2-1 while the dorsal endoderm (esophageal progenitors) maintains high levels of SOX2 (SRY-box-containing gene 2).[5,28] However, SOX2 inhibition leads to expansion of the NKX2-1 domain and respiratory fate dorsally, towards the esophageal domain.[28] A proper balance between BMP4, expressed ventrally, and its antagonist NOGGIN, expressed dorsally in the foregut, also significantly influences V-D patterning.[10] Conditional deletion of both Bmpr1a and Bmpr1b leads to expansion of a dorsal cell population marked by Sox2 at the cost of the ventral population of NKX2-1-positive cells.[10] NOGGIN has been proposed to protect the dorsal endoderm from the ventralizing effects of BMP4.[29]

An initially single-lumen foregut starts to separate into the ventral trachea and dorsal esophagus as early as E9.5, and it is completed by E11.5. A "splitting and extension model" has been proposed based on live imaging of foregut cultures. The separation initiates from the site of lung bud outgrowth with a saddle-like structure moving anteriorly and a nascent trachea and esophagus extending posteriorly. This mechanism ultimately separates the respiratory from the digestive tract.[30] Alternative models include the fusion of endodermal ridges in the midline[18] and extension of a tracheoesophageal septum by formation of a mesenchymal condensation.[31] The precise mechanisms regulating these events await further in vivo evidence and genetic analyses. A midline epithelial population that co-expresses Sox2, Nkx2-1, and the LIM Homeobox 1 (Isl1) has been recently characterized as a key player in controlling tracheoesophageal separation. These triple-positive cells locate at the dorsal–ventral boundary, and they contribute to both tracheal and esophageal epithelium during the separation.[32] Failure of this separation results in tracheoesophageal fistula, a relatively frequent condition in neonates with high morbidity. This defect has been observed as part of the phenotype of several mouse mutants. Examples include the Shh$^{-/-}$, Nkx2-1$^{-/-}$, Sox2-conditional mutants, Isl1$^{-/-}$ and Gli2$^{-/-}$; Gli3$^{+/-}$ and the RARα$^{-/-}$; RARβ$^{-/-}$ mice.[5,9,28,33,34]

BRANCHING MORPHOGENESIS: FORMATION OF THE BRONCHIAL TREE AND PATTERNING

The bronchial tree forms through a reiterative process of growth and budding of the epithelial tubules collectively termed *branching morphogenesis*. This process initiates after secondary buds form from the lung primordium in mice at E10.5. At this time the pattern of lobation of the right and left lungs also is established. The lungs are asymmetric with respect to their right and left axis and their number of lobes varies according to the species. For example, mouse lungs have one left lobe and four right lobes. It is thought that this asymmetry is regulated by left–right (L–R) determinants as part of an early global program of axis specification. Among the signals involved in this process are TGF-β-related molecules, such as activin receptor II, Lefty1 and 2, and growth differentiation factor 1 (Gdf1), as well as paired-like homeodomain transcription factor 2 (Pitx2).[35–39] Loss of left-right asymmetry resulting in equal number of lobes in both sides is called pulmonary isomerism and is found in several human conditions such as primary ciliary dyskinesia (Kartagener Syndrome).[40,41]

Analysis of the three-dimensional branching pattern of embryonic mouse lungs suggests that the bronchial tree is generated by three geometric branching modes: domain branching, planar bifurcation, and orthogonal bifurcation, following three sequential orders.[42] All modes are used concurrently during development of the bronchial tree and strongly suggest that distinct genetically encoded pathways control each branching model. It is likely that these branching modes are also used in the developing human lungs, but this has not been yet demonstrated.

The mechanism generating new buds during branching morphogenesis is similar to that of primary bud morphogenesis and relies on local epithelial activation of FGFR2b signaling by mesenchymal FGF10 at the sites of budding.[21,22] Perturbations in levels or distribution of FGF10 have a major impact in airway morphogenesis and result in smaller than normal hypoplastic lungs. Reduced number of branches, among other patterning abnormalities, is found in Fgf10 hypomorphic mice (Fgf10$^{lacZ/-}$).[43] During branching morphogenesis Fgf9 expressed from the pleura and transiently from the distal epithelium expands a population of Fgf10-expressing distal mesenchyme (Fig. 4-3A). Mice deficient in Fgf9 have reduced mesenchymal cell population and Fgf10 expression. This leads to disruption of branching morphogenesis and hypoplastic lungs.[44] Recent studies challenge the paradigm that bud formation is strictly dependent on the localized expression of Fgf10. Budding occurs in mesenchyme-free cultures despite the uniform widespread availability of FGF10 in the culture media.[45] Additionally, expression of an Fgf10 transgene in the mesenchyme of Fgf10 knockout mice in vivo partially rescues branching morphogenesis despite its ubiquitous distribution, suggesting a permissive rather than an instructive role for FGF10 signaling.[46]

The size and shape of the growing buds is controlled dynamically by feedback loops established by FGF activity within the epithelium or by exchange of signals between the bud epithelium and the adjacent mesenchyme. For example, high FGFR2 activity in the emerging bud induces expression of its target Sprouty 2 (Spry2) in the distal epithelium. SPRY2, a highly conserved cysteine-rich protein, negatively regulates the FGF-mediated activation of receptor tyrosine kinase signaling in the epithelial bud and thus inhibits bud growth (Fig. 4-3A).[47–50]

Several molecules have been implicated in epithelial-mesenchymal crosstalks that control lung budding. For example, in the developing lung Shh is expressed predominantly at the tip bud epithelium, acting in the lung mesenchyme via Patched (PTC)/

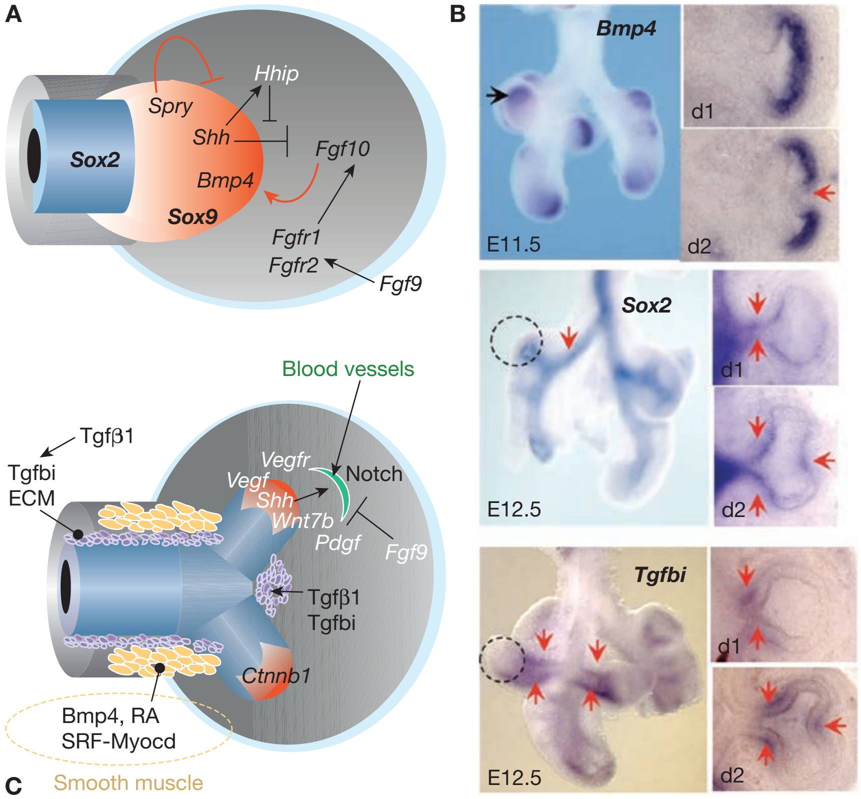

Figure 4-3 Regulation of lung branching morphogenesis, proximal-distal (P-D) patterning and differentiation. **A.** Gene network regulating lung bud elongation. Bud outgrowth is restricted by Fgf10 induction of Bmp4 and Spry2; Spry2 inhibits epithelial Fgf signaling; Bmp4 inhibits epithelial proliferation; Shh inhibits Fgf10 expression through activation of Ptc/Smo signaling. Shh signaling is inhibited by Hhip through a feedback loop. **B.** ISH of Bmp4, Sox2, and Tgfβi during branching (E11.5–E12 in vivo and in lung cultures 24–48 h). Bmp4 labels distal epithelial buds while Sox2 marks the epithelium in stalk and non-branching proximal regions; Tgfβi labels newly formed stalks and proximal mesenchyme. **C.** Airway branching and differentiation of mesenchymal components. Localized Tgfβ activity promotes local ECM deposition and cleft formation. Airway and vascular SM requires the input of Shh, Wnt, Vegf, Pdgf, Notch, and Fgf.

Smoothened (SMO)/GLI (1,2,3) proteins critical for survival of mesenchymal cells.[51–53] However, SHH signaling also has a key role as a negative regulator of Fgf10 expression,[51,54] in distal mesenchymal cells, inhibiting bud outgrowth during airway branching (Fig. 4-3A). In Shh null mice, there is increased expression of Fgf10 transcripts and generalized activation of FGFR2b in the lung epithelium, resulting in severely disrupted branching morphogenesis and cyst-like lungs.[33,53] Increased FGF10-FGFR2 signaling in distal buds is responsible for the high local expression of Shh through activation of Etv transcription factors (Etv4 and Etv5), downstream targets of FGF, establishing an FGF-SHH feedback loop.[55] The high SHH activity in the lung mesenchyme can be negatively controlled by induction of the SHH target Hhip1 (Hedgehog interacting protein) (Fig. 4-3A). HHIP1 binds to and sequesters SHH ligand preventing it from activating signaling in the mesenchyme to repress Fgf10. In Hhip1 null mice, SHH activity is aberrantly increased, leading to decreased Fgf10 expression and disruption of branching morphogenesis.[56] Moreover, FGF10 protein distribution and receptor binding can be modulated by FGF interactions with heparan sulfate (HS) proteoglycans. Disrupting HS expression or altering HS sulfation prevents FGF10 from inducing local responses and can markedly alter lung pattern formation in lung explant cultures.[57,58]

Another mechanism contributing to airway branching is cleft formation. Here extracellular matrix (ECM) is deposited at branch points, accumulating in the epithelial-mesenchymal interface and preventing local expansion of the epithelium. Clefting has been classically associated with local activity of TGF-β signaling in the distal lung (Fig. 4-3). Members of the TGF-β subfamily TGF-β1, 2 and 3, and their receptors (TGFBR1 and TGFBR2) and transducing proteins (SMAD 2, 3), are expressed in different compartments and in a complex pattern during branching morphogenesis. TGF-β1 transcripts are distributed throughout the lung mesenchyme; however, TGF-β1 protein accumulates in regions between buds and along proximal airways, where ECM components (collagen I and III and fibronectin), which are also TGF-β targets, are abundant.[59] The dynamic activity of TGF-β during branching is best visualized by expression of its target gene Tgfbi (Tgfb-induced or BigH3) in the mesenchyme associated with stalk region of growing buds[60] (Fig. 4-3B–C). Treatment of embryonic lungs in culture with TGF-β1 dramatically inhibits branching morphogenesis.[54,61,62] Epithelial activation of TGF-β signaling represses growth and differentiation. Moreover, TGF-β1 exerts important effects in the lung mesenchyme, where it induces expression of ECM components and inhibits Fgf10 expression.[54,63,64] Analysis of organogenesis in TGF-β1-null mice has been largely inconclusive apparently due to rescue by maternal transfer of Tgfb1.[65] The importance of TGFBβ signaling for lung morphogenesis has been demonstrated in Tgfbr2-deficient mice.[66] Both TGF-β2 and TGF-β3 are expressed in the developing lung but neither one seems to be required prenatally. By contrast, mice deficient in these genes die postnatally with collapsed lungs.[67,68]

There is evidence that small non-coding regulatory RNAs are part of the regulatory networks controlling lung development. miRNAs are endogenous small noncoding RNAs that regulate target gene expression post-transcriptionally and play important roles in diverse biological processes.[69–72] Individual miRNAs may target multiple mRNAs; conversely, individual mRNAs may contain sequences complementary to multiple miRNA family members.[73] The importance of the miRNA pathway in lung development was demonstrated by the epithelial deletion of Dicer, the key enzyme that processes microRNA precursors into mature miRNAs. Loss of Dicer in the mouse lung epithelium results in drastic arrest of branching morphogenesis and increased epithelial cell death.[74] The increased levels of FGF10, BMP4, and SPRY-2 in these mutant lungs suggested that the miRNA pathway represses expression of these genes during epithelial–mesenchymal interaction.[74] In humans, Dicer mutation has been linked to pleuropulmonary blastoma, a rare pediatric tumor that arises during fetal lung development.[75] Loss of Dicer1 in the developing lung epithelium alters miRNA-dependent regulation of diffusible growth factors, specifically the miR-140-FGF9 pathway, which promotes proliferation of both epithelial and mesenchymal cells.[76]

AL GRAWANY

ESTABLISHMENT OF PROXIMAL-DISTAL (P-D) CELL FATE

During lung development, the appearance of distinct fates in epithelial progenitors along the P-D axis is tightly coupled with branching morphogenesis. This process is highly dynamic and establishes a SOX9+ distal and a SOX2+ proximal domain to become later the alveolar and airway compartments, respectively. Lineage tracing analyses of epithelial progenitors in the distal compartment (SOX9+ also identified by ID2) shows that they are actually multipotent and able to generate cell types of both the alveolar and the SOX2+ intrapulmonary airways.[77,78] By contrast, extrapulmonary airways, including the trachea, originate from a different progenitor, labeled by p63, a transcription factor from the p53 family of genes.[79]

Canonical WNT and BMP signaling have been implicated as major regulators of P-D cell fate in the lung epithelium. WNT ligands, receptors (Frizzled), and β-catenin are widely expressed in the developing lung but show distinctive distribution in both epithelium and mesenchyme (*web.stanford.edu/group/nusselab/cgi-bin/wnt/*).[80–82] High activity of WNT signaling reporter (TOPGAL), nuclear-localized β-CATENIN, and TCF/LEF transcripts is found in the distal lung buds undergoing branching.[83,84] Targeted disruption of β-catenin or overexpression of the WNT inhibitor Dickkopf 1 (Dkk1) in the distal lung epithelium inhibits distal cell fate and bud formation and proximalizes the lung, a phenotype characterized by proximal epithelial phenotypes extending ectopically to distal sites.[85,86] Conversely, activation of canonical WNT signaling throughout the lung epithelium inhibits Sox2 expression and leads to the appearance of distal fates in proximal airways.[87,88] Thus, canonical WNT plays a key role in the establishment and maintenance of distal cell fates.

Distal epithelial cell fate is also crucially dependent on the BMP pathway. Transgenic mice expressing BMPR antagonists (Xnoggin, Gremlin) in lung epithelial progenitors fail to properly form the distal lung and show proximalization.[89,90] During branching morphogenesis, Bmp4 is expressed in epithelial progenitors at the tip of growing buds and acts locally through autocrine activation of BMPR-SMAD signaling.[91] In lung bud tip organoid cultures, SMAD activation by exogenous BMP4 and TGF-β1 promotes specification of P63+ airway progenitors.[92] BMP4 has been shown to antagonize the proliferative effects of FGF10 in the distal epithelium.[93] and TGF-β1 inhibits Id2 to facilitate differentiation in airway progenitors.[94] BMP4 levels are increased by FGF10-FGR2b and WNT/β-catenin signaling in distal buds.[93] The availability of BMP4 protein in these buds is controlled by Cathepsin H (Ctsh), a cysteine protease induced by FGFR2 in the embryonic lung. Inhibiting CTSH activity markedly accumulates BMP4 protein, interfering with branching morphogenesis.[95] Additional regulators of BMP4 during P-D patterning include histone deacetylases (Hdac1/2)[96] and HOX5-WNT2/2b.[97]

The mechanisms by which distal epithelial buds (SOX9+ ID2+) give rise to epithelial progenitors of the airway compartment (SOX2+) are still poorly understood. There is evidence that this process is under the control of the Hippo-YAP pathway. The transcriptional co-regulator Yap (Yes-associated protein) is a key modulator of cell fate and proliferation during development. YAP transcriptional activity is dependent on its phosphorylation status, determined by the Hippo serine/threonine kinases (such as MST1/2, LATS1/2), which regulate YAP subcellular localization. Unphosphorylated YAP is maintained in the nucleus, where it activates downstream targets through binding to TEA-domain (Tead) family transcription factors.[98] In the developing lung epithelium, nuclear YAP has been reported predominantly in SOX9+ distal progenitors while cytoplasmic phospho-YAP was shown in SOX2+ proximal progenitors. Disruption of Yap in epithelial progenitors at the onset of lung development results in severely impaired branching morphogenesis with reduction in the SOX2+ airway progenitors and expansion in the SOX9+ distal compartment.[99] Another study of compartment-specific YAP functions reveals that nuclear YAP in distal progenitors is essential for lung branching, while cytoplasmic YAP is required for proper differentiation.[100] These studies suggest that YAP controls the specification of airway progenitor cells at the transition zone between the SOX9-SOX2 domains, presumably by rendering epithelial cells competent to respond to proximalizing signals.[99,101] Disruption of Lats1/2 using similar genetic strategy also results in dramatic impairment of branching morphogenesis, but both SOX9 and SOX2 compartments are equally affected.[102]

miRNAs also play a significant role in lung P-D patterning. For example, the miR-17-92 cluster is expressed during early lung development; gain of function selectively in the developing lung epithelium of transgenic mice results in increased cell proliferation.[103] Conversely, miR-17-92 cluster knockout mice have hypoplastic lungs.[104] In an independent study, miR-17 family members were shown to modulate FGF10-FGFR2b downstream signaling by targeting STAT3 and MAPK14.[105] miR-302/367, a direct target of GATA6, coordinates the balance between proliferation and differentiation of lung epithelium by directly regulating the expression of Rbl2 and Cdkn1a. Overexpression of miR-302/367 leads to expansion of both proximal and distal lung progenitors and regulates epithelial apical-basal polarity.[106]

FORMATION OF THE VASCULAR AND OTHER MESENCHYMAL COMPONENTS OF THE LUNG

Besides playing a crucial role in epithelial development, the lung mesenchyme gives rises to the vascular, cartilage, and other stromal components of the lung. Lineage tracing studies reveal that a multipotent cardiopulmonary progenitor population marked by Wnt2, Gli1, and Isl1 generates the mesodermal progenitors that give rise to the cardiac inflow tract and the lung vasculature, except for the distal alveolar capillary endothelium, which is derived from a VE-CADHERIN+ population.[107] In turn, expansion and differentiation of mesenchymal progenitors into these different components require diffusible signals from the epithelial and mesothelial (pleural) layers. Pulmonary veins arise from cardiac progenitors migrating from the neighbor atria. VEGF signaling plays a major role in vascular development by promoting endothelial cell differentiation[108] (Fig. 4-3). VEGFA is found predominantly in the distal lung epithelium but also in the mesenchyme at early stages and signals through VEGFR2 (Flk1) and VEGFR1 (Flt1) in the mesenchyme.[109–111] Among the several VEGF isoforms, VEGF164 is the most active in the lung.[111] Development of lymphatic vessels is still poorly understood. Studies in mice show that VEGF-C and VEGF-D acting through their receptor VEGFR-3 promote lymphangiogenesis.[112,113] Vegfr-3 null mice fail to proper develop lymphatic vessels.[114]

Smooth muscle (SM) is an integral component of vascular and airway epithelium of the lung (Fig. 4-3). Vascular SM develops by contribution from mesenchymal precursors through signals derived from the epithelium but also from pleural cells migrating to the vascular structures during blood vessel assembly.[115] Shh signaling from the anterior foregut endoderm affects proliferation and differentiation of lung mesenchymal cells, and it is required for SM development.[116,117] A signaling cascade involving SHH, miR-206, and BDNF (brain-derived nerve growth factor) coordinates innervation and formation of the airway SM layer.[118] Moreover, miR-29, abundantly expressed in SM cells associated with distal vessel walls during postnatal lung development, suppresses the expression of Klf4 and extracellular components and promotes the maturation of vessel walls.[119] WNT7b, acting through its receptors FZD1 and FZD10 and its co-receptor LRP5 (low-density lipoprotein receptor-related protein 5), is an important epithelial signal required for vascular SM development and the integrity of blood vessels.[120] Wnt7b null mice show hemorrhagic lungs resulting from rupture of the blood vessels due to SM structural defects.[121] GPR177, which regulates WNT secretion, is essential for vascular SM development and maintenance.[122]

Assembly of the pulmonary arterial wall occurs through controlled migration of SM cells from the inner to the outer layers in a process mediated mostly by PDGFB.[123] In addition, vascular SM formation depends on BMP and NOTCH signaling.[124,125] Bmp4 and Bmpr2 are expressed in SM precursors, and disruption of BMP signaling is associated with increased SM cell proliferation. This phenotype is reminiscent of the excessive SM growth reported in pulmonary hypertension patients with mutations in the Bmpr2 gene.[126–128] Disruption of canonical NOTCH signaling interferes with specification of arterial SM cells.[125] NOTCH3 dysregulation is associated with structural changes in the pulmonary artery postnatally and has been implicated in the pathogenesis of adult pulmonary hypertension.[129,130] The importance of having a precisely matched airway–vascular development is well illustrated by the role of Foxm1, a transcription factor expressed in the lung mesenchyme. Foxm1 null mice show pulmonary hemorrhage and perinatal death due to misalignment of epithelial and vascular structures.[131] This phenotype closely reminds the abnormalities seen in human congenital alveolar dysplasia.

During development, airway SM is responsible for phasic contractility of airways and growth factor production, contributing to maintain normal lung growth. Previous studies have ascribed a role for airway peristalsis in epithelial branching.[132,133] However, a more recent analysis of a myocardin (Myocd) conditional mouse model in which airway SM differentiation was disrupted showed no branching defect.[134] Airway SM originates from mesenchymal cells of the developing lung when the initial airway starts to branch, preceding the appearance of the lung vascular SM. A lineage tracing study using Fgf10-CreERT2 suggests that FGF10+ cells at the early pseudoglandular stage serve as the progenitors for both myogenic and adipogenic lineages, and later no longer give rise to SM cells.[135] The FGF10+ mesenchymal progenitors, initially surrounding the distal buds, expand and migrate proximally to enwrap the proximal airways.[136,137] This myogenic program is likely to be triggered by high levels of BMP4 and SHH present at the bud tips[51,91] (Fig. 4-3). Canonical WNT signaling is required for the expansion of the SM progenitors in developing airways.[138] Proper differentiation of the airway SM requires input from pathways, including FGF and TGF-βR, as well as physical stretch transduced by tension-induced proteins such as TIP1.[139,140] FGF9-FGFR1/2 signaling suppresses airway SM differentiation through inhibition of Myocd expression.[141,142]

Analysis of models in vivo and in vitro provide evidence that endogenous RA is active in the mesenchyme associated with distal buds of branching airways. At these sites RA transiently inhibits SM differentiation, preventing precocious and excessive formation of SM. These sites of RA activation coincide with sites where SM differentiation signals, such as TGF-β and MYOCD, are dynamically active.[143] RA downregulates TGF-β signaling in the developing lung. Maternal vitamin A deficiency results in aberrantly increased and ectopic formation of SM in fetal airways. The effect can be similarly reproduced by disrupting RA signaling in lung explant cultures. This is relevant since vitamin A deficiency in utero, even for a short period, can have deleterious consequences during postnatal life. Indeed, administration of a vitamin A–deficient diet to pregnant mice for only 4–5 days with subsequent normal levels to adulthood leads to offspring with markedly thick airway SM layer and airway hyperresponsiveness.[143] Interestingly, the effect of RA deficiency in the SM program is not seen in blood vessels, suggesting different molecular regulation of SM differentiation within the same organ.

Cartilage rings present in trachea and proximal airways develop from the precursors in ventral mesenchyme. Proper formation and patterning of cartilage primordia require signaling by WNT-NOTUM (Notum being a target of WNT/β-CATENIN pathway that attenuates WNT signaling), retinoic acid (particularly RARγ-mediated), FOXF1, and SHH, among others.[144–147] Airway SM and cartilage develop coordinately and complementarily: genetic inactivation of Srf leads to loss of airway SM and increase in cartilage, while inactivation of Sox9 leads to loss of cartilage and increase in SM.[148]

AIRWAY DIFFERENTIATION

As the epithelial tubules form and branch, they initiate a program of cell fate choice and differentiation that ultimately gives rise to the various airway epithelial cell types. Airway epithelial cells are collectively marked by expression of Sox2, which extends from the developing trachea and branching tubules to the stalks of the growing buds[149] (Fig. 4-4). By the middle of the pseudoglandular period (~E12.5–E14.5 in mice) airway lineages progressively start to be specified in secretory, multiciliated, and neuroendocrine precursors, as seen by expression of Scgb3a2, Foxj1, and Ascl1, respectively. These phenotypes arise from a process of cell fate selection in the SOX2+ progenitors crucially dependent on cell–cell interactions mediated by NOTCH signaling. Notch receptors (Notch 1, 2, 3) and ligands (Jag1, Jag2, Dll1, Dll4) are expressed in the developing lung. Cells in which NOTCH is activated assume a secretory fate; otherwise they commit to a multiciliated or neuroendocrine fate.[125,150–152]

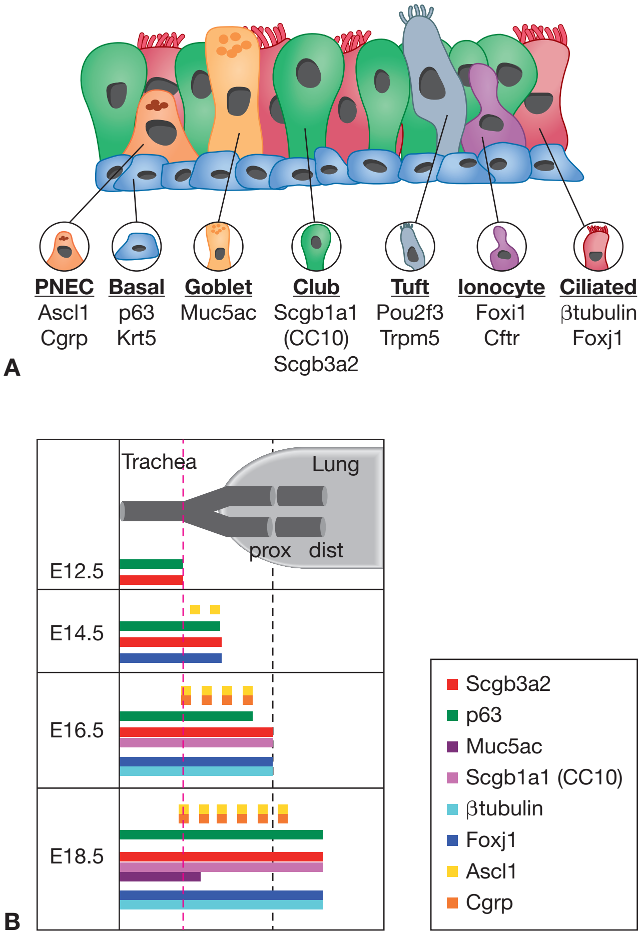

Figure 4-4 Epithelial differentiation in conducting airways. **A.** Cell types and markers associated with or required for the differentiation of specific cells in adult airways. **B.** Time course of appearance of gene markers associated with different cell lineages in trachea, and proximal and distal airways of the developing mouse lung.

Different Notch receptors and ligands play distinct roles in airway development.[153,154] NOTCH3 is required at early stage for the generation of parabasal cells in extrapulmonary airways, which then activate NOTCH1 or 2 for ciliated-secretory fate selection.[155] JAG ligands regulate the balance of basal, ciliated, and secretory cells, while DELTA ligands restrict the NEB microenvironment.[154] Downregulation of NOTCH pathway components has been identified in patients with chronic obstructive pulmonary disease (COPD).[156]

Formation of multiciliated cells in the airways depends on the activity of MULTICILIN and its transcriptional effector E2F4. In the absence of these regulators, airways have no multiciliated cells.[157] E2F4 is essential to induce a transcriptional program of centriole biogenesis that allows large-scale centriole multiplication from which cilia emerge. Interestingly, once this program is initiated, E2F4 undergoes nucleocytoplasmic shuttling and acts as an apical organizing center for assembly of deuterosomes to ultimately form centrioles.[158] Apical docking of centrioles to initiate multiciliogenesis depends on FOXJ1. Foxj1 null mice are unable to form multiciliated cells.[159] miR-449 has been shown to promote the differentiation of multiciliated cells by targeting Notch1 and Dll1 in human airway epithelial cells.[160]

Secretory cell precursors are identified initially by SCGB3A2+ cells at around E12.5 and subsequently acquire additional markers, such as CC10 (Scgb1a1),[161,162] as they differentiate into Club cells. Lineage tracing using CC10-CreERT2 provides evidence that Club cells are the progenitor/stem cells in intrapulmonary airways. They are shown to self-renew and generate multiciliated cells during development and homeostasis and in injury repair.[163] However, this population is heterogeneous. For example, those associated with neuroendocrine cells express a few distinct genes and are considered as immature (or variant) Club cells in the adult lung, since they can survive exposure to an environmental agent (naphthalene) and repopulate the damaged epithelium.[164–166]

Mucin-secreting (MUC5ac+) goblet cells are relatively rare in developing mouse airways, occurring mostly postnatally in trachea and proximal airways. Their abundance is increased in adult mice during exposure to environmental agents or infection.[167] By contrast in humans, goblet cells are seen throughout the airway epithelium. NOTCH signaling is critical for the lineage balance of different cell types in the airways.[150] Disruption of NOTCH signaling in mice results in loss of secretory (Club) cells and airways overpopulated by multiciliated and NE cells.[125,150,153,168] Conversely, constitutive activation of NOTCH in the embryonic lung epithelium leads to a decrease in number of multiciliated cells and increase in secretory goblet cells.[152] Goblet cell differentiation is also controlled by transcription factors, such as Spdef (SAM-pointed domain-containing Ets transcription factor) and Foxa2.[169–171]

Neuroendocrine cells are relatively rare, and their lineage marker Ascl1 is first expressed in developing airways around E12.5 in scattered airway cells in proximal regions. There is evidence that these NE progenitors assemble into clusters (bodies, thus the term *NEB*) at the branchpoints of intrapulmonary airways through a "slithering" migratory activity.[172] The ability to cluster is dependent on ROBO-SLIT pathway. NEBs are important in the regulation of neuropeptide production and immune response to environmental agents.[173] Mice deficient in Ascl1 do not form NE cells or NEB, and they exhibit substantially impaired immune response and goblet-cell hyperplasia, suggesting essential roles of NE cells as sensory and neuroimmunologic modulators in airways.[174,175] Within NEB, rare NE cells serve as reserve stem cells, which are activated by injury and reprogrammed to other airway lineages surrounding the NEB for regeneration. These even rarer stem NE cells might serve as tumor initiating cells for small cell lung cancer (SCLC).[176] NE cells recently have been discovered in mouse trachea, and although rare, they are heterogeneous in expression of neuropeptides and TUBB3.[177,178] It remains unclear how basal cells generate tracheal NE cells as well as how intrapulmonary NE cells are specified during development. Addressing these questions will probably shed light on the pathogenesis of pulmonary diseases associated with NE hyperplasia, like neuroendocrine hyperplasia in infancy (NEHI) and sudden infant death syndrome (SIDS).

Basal cells are considered the principal source of almost all the epithelial lineages in extrapulmonary airways of the adult mouse lung. Lineage studies using Krt5-CreERT2 and p63-CreERT2 suggest that prenatal basal cells, specified at E13.5, function as progenitors to both ciliated and secretory cells during development, similar to their postnatal counterparts.[79,179] p63 null mice do not form basal cells in the lung or other tissues to undergo pseudostratification in the tracheal epithelium or stratification in other tissues.[30,180–183]

Recent single-cell RNA sequencing studies chart the comprehensive epithelial landscape in adult airways and reveal rare cell types, including Tuft cells, ionocytes, and hillock cells. Although constituting less than 1% of total epithelial population, these rare cell types play important roles in immunologic, neuronal, and chemosensory functions.[177,184–186] These cells are also associated with pulmonary diseases: ectopic Tuft cells were identified in H1N1 influenza virus–induced dysplastic epithelium and may contribute to eosinophil recruitment and mucous hyperplasia after severe lung injury.[187] Ionocytes express Cftr transcripts and may contribute to the pathogenesis of cystic fibrosis. Hillock cells exhibit higher turnover rate and express squamous cell markers, potentially related to metaplastic changes in the airway epithelium.[177,183] Notably, the developmental origin of these cell types remains so far elusive and await further exploration.

FORMATION OF THE GAS EXCHANGE REGION OF THE LUNG

Once branching morphogenesis is completed, distal epithelial buds undergo sacculation. During this morphogenetic process, the lumen of epithelial tubules enlarges at their distal ends to form primitive saccules and AT1 and AT2 cells differentiate. During formation of AT1 cells the progenitors undergo flattening and folding[188] to cover the large area occupied by these saccules. The mesenchyme becomes thinner, and the epithelium comes into intimate contact with the capillary network of the primitive saccules to form the primitive alveolar-capillary barrier.[189] AT2 cells remain cuboidal and produce surfactant to reduce surface tension and facilitate breathing postnatally.

Single-cell RNA sequencing and lineage tracing analyses have suggested that AT1 and AT2 cells originate from a common distal bipotent progenitors present at the onset of sacculation.[190] However, a more recent study shows that AT1 and AT2 lineages are already specified as early as E13.5 when airways are still actively branching.[191] The balance of AT1 versus AT2 lineages is tightly controlled. One key regulator of this balance is the Hippo/YAP/TAZ pathway. Notably, during sacculation nuclear Yap signaling is activated in the progenitors differentiating selectively into AT1 cells, while Yap is kept largely cytoplasmic in those differentiating into AT2 cells. Yap knockout in the lung epithelium prevents AT1 cells from forming. Conversely, constitutive expression of nuclear Yap transgene increases the AT1 number.[100,102] At late gestation fetal breathing-induced mechanical forces contribute to promote flattening of progenitors differentiating into AT1 cells, while FGFR2-ERK activation in differentiating AT2 cells by local mesenchymal FGF10 prevents flattening, maintaining their cuboidal shape[192] (Fig. 4-5). Interestingly, AT1 cells are found to be highly plastic and can give rise to AT2 cells during repair after hyperoxic injury during the neonatal period.[193] However, this mechanism is not efficient as seen in the adult lung when both AT1 and AT2 can function as progenitor cells.[189,194–197,199] Whether this developmental fate choice is due to plasticity of AT1/AT2 cells or bipotential progenitors remains to be investigated further. Defects in sacculation have been reported in several gene knockout mouse mutants. These include mutants

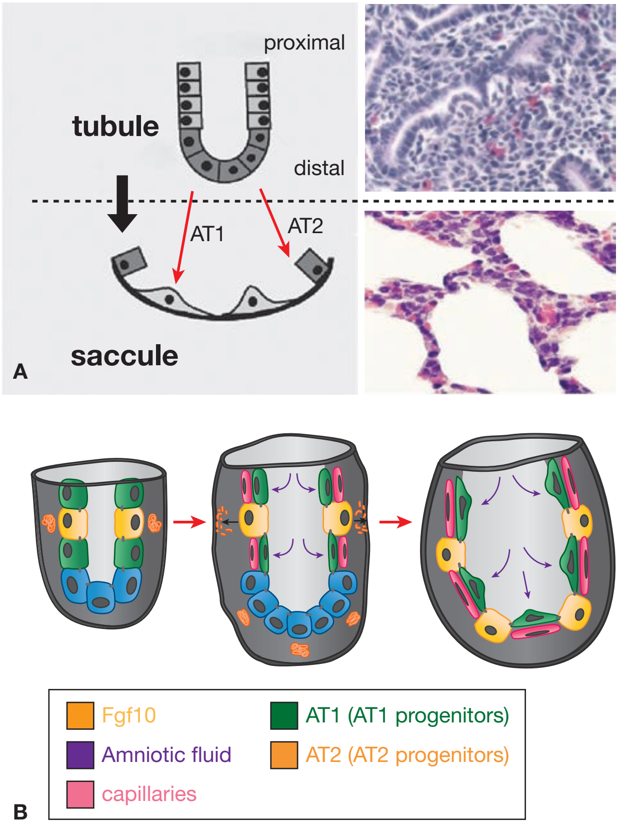

Figure 4-5 Sacculation. **A.** Distal epithelial tubules expand their lumens and form primitive saccules lined by alveolar type I and type II cells. **B.** During transition from canalicular to saccular stage, distal epithelial progenitors start to protrude toward the mesenchyme through local activation of Fgf10-Fgfr2 signaling and later become AT2 cells. Non-protruded cells are flattened by increased intraluminal pressure with inhaled amniotic fluid, and differentiate into AT1 cells.[192]

for T1α,[198] Nfib (nuclear factor I/B),[199] Erk3 (extracellular signal-regulated kinase 3), and Foxm1.[200]

By late gestation in humans or postnatally in mice the primitive saccules subdivide into smaller units to form the mature alveoli, which greatly increases the surface area for gas exchange (Fig. 4-5). Development of the mature alveoli (alveologenesis or alveolarization) involves formation of secondary septa, which greatly increases the surface area for gas exchange (Fig. 4-5). This process (alveologenesis or alveolarization) has been thought to involve formation of secondary septa from the saccule wall, which protrude into the lumen pushed by myofibroblasts. Interestingly, recent 3D reconstruction analysis shows a continuous network of myofibroblasts and elastin forming "cables" underlining the nascent septae. This suggests a very different mechanism in which these "cables" act as anchor points that form the alveolar ridges as the septal walls are pushed out by airway pressure from breathing movements, resulting in subdivisions of the original saccule (mature alveoli).[201]

Alveolar formation requires tight control of elastin levels by signals such as PDGF, FGFR3/4, and MFAP5 (Fig. 4-6).[202–204] This process is also controlled by many other signals, including VEGF-FLT1,[205] FOXN4,[206] VEGFA,[188] UPR (unfolded protein response) pathway,[207] HOX5,[208] and IGF1R.[209] Disruption of these signals can lead to immature lungs with decreased alveolar septation.

FINAL REMARKS

A wealth of information has been generated over the past decades on how growth factors, transcription factors, and matrix components influence lung development. Many of these studies suggest that alterations in developmental pathways reported in animal models are relevant to understand the pathogenesis of human lung conditions. There is also increasing evidence that developmental regulators are recruited in different contexts to mediate normal and aberrant injury-repair responses in the adult lung. Further understanding of these issues will be invaluable in discovery of different therapeutic targets and in the new field of lung regenerative medicine.

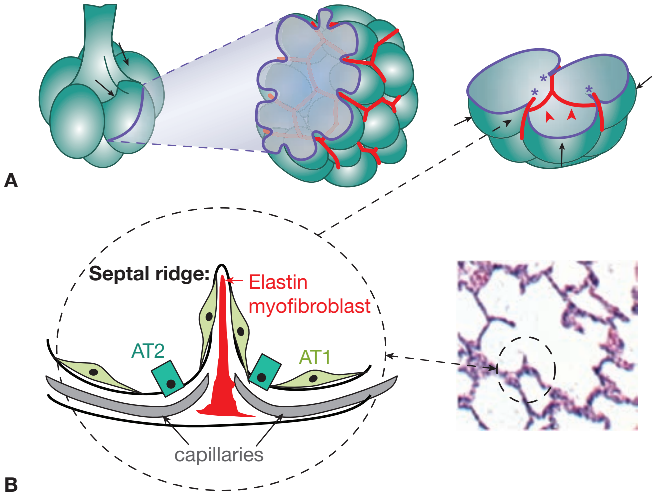

Figure 4-6 Alveolar formation. Diagram from 3D reconstruction of distal lung undergoing alveolarization. Myofibroblasts and elastin (in red) form "cables" that serve as anchor points (septal ridges) while the septal walls are pushed away by airway pressure from breathing movements **(A)** resulting in subdivision of the saccules in multiple alveoli **(B)**.[201]

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CHAPTER 5

Pulmonary Surfactant and Disorders of Surfactant Homeostasis

Jeffrey A. Whitsett
James P. Bridges
Timothy E. Weaver

INTRODUCTION

Pulmonary surfactant is a complex mixture of phospholipids and proteins that creates a unique interface separating alveolar gas and liquids at the alveolar cell surface, reducing surface tension, and maintaining lung volumes at end expiration. Reduction of the surface tension at the air-liquid interface is a requirement for respiratory function following birth and throughout life. Deficiency of pulmonary surfactant causes respiratory failure in premature infants, or infantile respiratory distress syndrome (IRDS). The adequacy of pulmonary surfactant is maintained by unique and highly regulated systems mediating the synthesis, secretion, reutilization, and catabolism of surfactant. Loss of pulmonary surfactant later in life occurs in the adult respiratory distress syndrome (ARDS), a significant cause of morbidity and mortality following infection, shock, or trauma. Mutations in genes regulating surfactant homeostasis, including *SFTPA*, *SFTPB*, *SFTPC*, *ABCA3*, *NKX2-1*, and *CSF2RA/B* cause acute and/or chronic lung disease in newborn infants, children, and adults. Disorders of GM-CSF signaling inhibit surfactant lipid and protein catabolism by alveolar macrophages causing pulmonary alveolar proteinosis (PAP). This chapter reviews the biology of the surfactant system and its implications for the pathogenesis, diagnosis, and treatment of respiratory disease in premature infants and adults. Reviews of these topics are suggested.[1–7]

PHYSICAL FORCES AT THE AIR-LIQUID INTERFACE

In 1929, Van Neergard recognized the critical role of surface tension as a “retractile force” in the lung, observing the markedly increased pressures required to inflate the air- versus water-filled lung. Avery and Mead associated the lack of a lipid-rich material in the lungs of infants dying from IRDS with alveolar collapse and respiratory failure.[8] In the absence of pulmonary surfactant, molecular forces at the air-liquid interface create a region of high surface tension because intermolecular forces between water molecules are unopposed at the air-liquid interface, and an area of high retractile force at the surface is created. Forces of 70 dyn/cm^2 are generated at the air-water interface; if unopposed in the alveolus, such forces lead to alveolar collapse and respiratory failure. A surface film composed of multilayered sheets of phospholipids creates a distinct phase separating air and liquid, reducing surface tension to nearly zero and maintaining residual lung volume at end expiration. Complex interactions between surfactant phospholipids and proteins are required to maintain the surfactant film throughout life. Pulmonary surfactant lipids and proteins are synthesized and secreted by alveolar type 2 (AT2) cells into the alveoli, where they form multilayered lipid rich films that reduce surface tension to maintain ventilation (Figs. 5-1 and 5-2).

COMPOSITION OF PULMONARY SURFACTANT

Pulmonary surfactant isolated by lung lavage consists of highly heterogeneous forms of phospholipid-protein aggregates of distinct sizes, structural characteristics, and composition. Tubular myelin is the most abundant form of alveolar phospholipid and consists of large, relatively dense aggregates (termed *large aggregate surfactant*) composed of phospholipids and surfactant proteins. Tubular myelin is a highly organized form of surfactant phospholipid, forming square tubular arrays. Tubular myelin represents an extracellular pool of surfactant lipids that rapidly moves to the air-liquid interface and re-organizes to form multilayered sheets that reduce surface tension in the alveolus (Fig. 5-2). Large lamellated structures, with lipid composition similar to that of tubular myelin, are seen within the alveolus and likely represent newly secreted lamellar bodies that unravel to form tubular myelin in the alveoli. The phospholipid composition of lamellar bodies, the intracellular storage form of surfactant, tubular myelin, and lamellated forms present in the alveolus are virtually identical. Smaller, less dense particles (small aggregate surfactant) also are present within the alveolar space, representing remnants or catabolic forms of surfactant that have relatively poor surface activity. Small aggregate surfactant is destined for uptake, reutilization, or catabolism by AT2 cells and catabolism by alveolar macrophages.[2,3]

■ Surfactant Phospholipids and Proteins

The composition of surfactant lipids is similar in all of the structural forms of surfactant isolated from mammalian lungs, with phospholipids generally representing 80% to 90% of the mass of

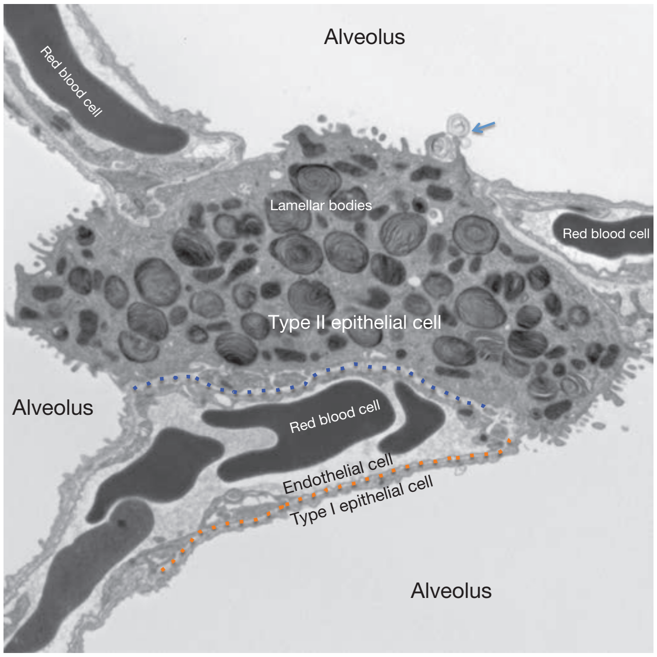

Figure 5-1 Pulmonary alveolar ultrastructure. The air-blood barrier comprises the capillary endothelium (above the dotted orange line) and the closely apposed type I epithelial cell (below the dotted orange line). The dotted blue line delineates the interstitial space between endothelial cells and AT2 cells with their specialized secretory lipid organelles (lamellar bodies). AT2 cells form tight junctions with type I cells and serve as alveolar progenitor cells. Surfactant lipids and proteins are secreted as lamellar membranes (arrow) into the alveolar space forming tubular myelin and lipid membrane multilayers that reduce surface tension, preventing alveolar collapse.

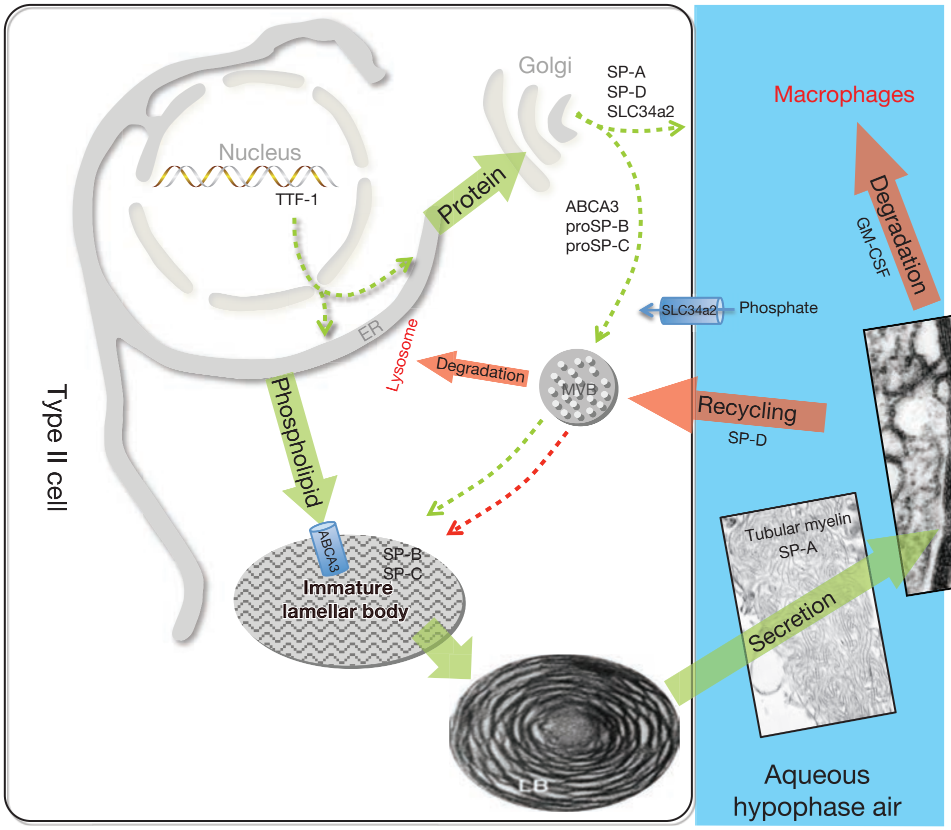

Figure 5-2 Surfactant metabolism. Newly translated surfactant proteins (proSP-B and proSP-C) and lamellar body (ABCA3) proteins traffic from the endoplasmic reticulum (ER) to the Golgi and subsequently to the multivesicular body (MVB). Fusion of the MVB with the lamellar body (LB) is accompanied by proteolytic processing of SP-B and SP-C proproteins to their mature peptides. Surfactant phospholipids (DPPC, PG) are likely transported directly from the ER to the LB by lipid transfer proteins. The contents of the LB are secreted into the alveolar space where they interact with SP-A to form tubular myelin and, ultimately, a phospholipid-rich film (surfactant) at the air-liquid interface. Alveolar surfactant lipids and proteins are cleared through a GM-CSF-dependent pathway that regulates alveolar macrophage differentiation and function. Surfactant remnants are also taken up by the AT2 cell and recycled to the LB, via the MVB, for resecretion, while a portion is degraded in lysosomes. SP-D plays an important role in regulating alveolar surfactant pool size likely by enhancing its reuptake by AT2 cells. The MVB serves to integrate surfactant synthesis, secretion, recycling, and degradation pathways in the AT2 cell. TTF-1 is a transcription factor critical for differentiation of AT2 cells and regulation of expression of Abca3, Slc34a2, and the surfactant proteins. Synthetic pathways are shown in green and catabolic pathways are shown in red.

pulmonary surfactant.[3] In the adult lung, phosphatidylcholine (PC) and phosphatidylglycerol (PG) are the most abundant phospholipids, representing approximately 70% to 80% and 5% to 10%, respectively, of the lipid mass. Dipalmitoyl phosphatidylcholine (DPPC) is the most abundant species of PC. Lesser amounts of phosphatidylserine, phosphatidylethanolamine, sphingomyelin, neutral lipids (mostly cholesterol), and glycolipids also are present in surfactant. The fetal lung content of surfactant phospholipids increases markedly with advancing gestation, regulated by a complex signaling and transcriptional network that controls AT2 cell differentiation, lipid synthesis, and surfactant protein gene expression. Lamellar bodies are secreted into the fetal amniotic fluid. PC, lamellar body counts, DPPC content, and increased lecithin (PC) to sphingomyelin (L/S) ratio, correlate with postnatal respiratory function. These tests are used to predict pulmonary maturity prior to the birth of preterm infants. Lung maturation and synthesis of surfactant components are induced by maternal administration of glucocorticoids, used clinically to prevent respiratory distress prior to premature birth.[9] Proteins represent approximately 5% to 15% of the mass of pulmonary surfactant and include serum proteins and proteins that are synthesized and secreted by AT2 cells. In addition to its specific interaction with SP-B, the anionic phospholipid PG may also play an important role in innate defense. PG constitutes 10 mole% of surfactant lipid, with palmitoyl-oleoyl-PG (PoPG) being the most common species in human surfactant. PoPG specifically suppresses LPS-induced inflammatory responses and prevents infection of epithelial cells by binding RSV or influenza A virus (IAV).[10] Phosphatidylinositol (PI), a minor anionic phospholipid species in the pulmonary surfactant, also inhibits RSV and IAV infection in mice.[11,12] Thus, the unique enrichment of PoPG and PI in the distal airspaces may be important components of host defense against inhaled pathogens. Four surfactant proteins (SP), SP-A, SP-B, SP-C, and SP-D, are produced by respiratory epithelial cells, each playing specific roles in surfactant homeostasis and innate host defense.[2,3,13,14]

Surfactant is uniquely enriched in disaturated DPPC. The saturated C16 acyl chains pack densely at an air-liquid interface, reducing tension at the surface. However, dense and stable packing of DPPC occurs at a phase transition of 41°C, far above physiologic temperatures. Thus, at 37°C, pure DPPC maintains a semicrystalline or gel phase that is incapable of moving rapidly with the expansion and compression of the alveoli during the respiratory cycle. The capability of DPPC pulmonary surfactant to move rapidly to the alveolar interface at 37°C and to maintain low surface tension during dynamic compression is conferred by the surfactant-associated proteins SP-B and SP-C. Phosphatidylcholine synthesis in the lung is controlled by genes encoding choline phosphate cytidyltransferase

(PCYTLA and CHKA), which are required for surfactant lipid synthesis and lung function at birth. A transcriptional network, controlled by sterol-response element binding proteins (SREB), regulates a number of key enzymes involved in phospholipid synthesis by AT2 cells.[15] DPPC is synthesized in AT2 cells via both a de novo pathway and remodeling of lysoPC. The enzyme LPCAT1 (lysoPC acyltransferase) mediates reacylation during surfactant lipid biosynthesis, enhancing the abundance of saturated PC.[16,17] Surfactant lipids, synthesized in the endoplasmic reticulum (ER), are transferred via a Golgi-independent pathway to lamellar bodies, the major intracellular storage site of surfactant (Fig. 5-2). Transfer of lipids in AT2 cells occurs via nonvesicular transport, and uptake into lamellar bodies requires the ABCA3 transporter, which selectively transports PC and PG. In contrast, surfactant proteins SP-B and SP-C traffic from the ER to the Golgi and subsequently to multivesicular bodies and lamellar bodies completing proteolytic processing of the proproteins. Ultimately, multivesicular bodies are incorporated into lamellar bodies with surfactant lipids prior to secretion into the alveoli by AT2 cells.[3]

Structure and Function of Surfactant Proteins

Four distinct surfactant associated proteins have been isolated from surfactant obtained by lung lavage. Their cDNAs, genes, and structures have been identified and are well characterized (Table 5-1).[13,14] The surfactant proteins are expressed in a relatively lung epithelial cell–selective manner and are secreted into the airspaces, where they influence the structure, metabolism, and function of surfactant. Two classes of proteins have been distinguished on the basis of their structures. SP-A and SP-D are relatively abundant, hydrophilic, structurally related proteins and are members of the calcium-dependent lectin family of proteins that have similar amino-terminal collagenous and C-terminal lectin domains.[18] SP-A and SP-D have few "surfactant"-like qualities but are able to bind complex carbohydrates, lipids, and glycolipids, including those on the surface of cells, bacteria, viruses, fungi, and other lung pathogens. SP-A and SP-D influence the structural forms and metabolism of surfactant lipids in the alveolus. They act as opsonins, activate alveolar macrophages, and play important roles in innate host defense in the lung. In contrast, SP-B and SP-C are small, hydrophobic proteins that play critical roles in enhancing the rate of spreading and stability of surfactant phospholipids needed to optimally reduce surface tension.[14] SP-B and SP-C are the sole protein components of the animal-derived surfactant replacement preparations used for the treatment of IRDS at present.[14] Mutations in the genes encoding SP-A, SP-B, and SP-C cause diffuse pulmonary disease affecting infants and older individuals.[19,20]

Surfactant Protein B (SP-B)

Surfactant protein SP-B is a hydrophobic, amphipathic 8.8-kDa protein produced from a single gene (*SFTPB*, OMIM 178640) located on human chromosome 2 (Table 5-1). The SP-B mRNA is expressed in non-ciliated bronchiolar cells and AT2 cells and is translated to produce a 40- to 42-kDa precursor that is proteolytically processed in the secretory pathway of AT2 cells to form the active 79-amino-acid peptide found in alveolar surfactant. In combination with lipids, SP-B can reconstitute most of the surface activity of natural lung surfactant. SP-B contains two regions, (Trp$_9$-Pro$_{23}$) and (Ile$_{56}$-Pro$_{67}$), predicted to form amphipathic α-helices that interact with the surface of lipid films. Almost 50% of the protein is in an α-helical conformation; the amphipathic domains of SP-B interact with surfactant lipids, and PG in particular, to promote lipid incorporation into and stabilization of the surface film. SP-B contains three intramolecular disulfide bonds that confine the amphipathic helices of SP-B in an antiparallel configuration. The SP-B monomer is assembled into a higher order hydrophobic ring, consisting of 6 covalently linked dimers, that is anchored to the surface of secreted surfactant membranes via the helical domains;[21] stacking of SP-B rings connects adjacent surfactant membranes to form a multilayer reservoir of phospholipids in the airspaces.[22] The membrane-perturbing properties of SP-B promote reorganization of surfactant membranes and facilitate transfer of phospholipids to the alveolar air-liquid surface film.

ProSP-B is synthesized in the endoplasmic reticulum and proteolytically processed in multivesicular and lamellar bodies by cathepsins and other intracellular proteases. The active SP-B peptide is packaged with SP-C and surfactant lipids in lamellar bodies prior to secretion into the alveolus. In the alveoli, the positively charged amino acid residues of SP-B selectively interact with the negatively charged phospholipid DPPG. In a mixed DPPC/DPPG monolayer, SP-B is believed to purify the DPPC monolayer by removal of DPPG. SP-B increases order in the lipid head groups with little effect on order in the lipid membrane interior. The ability to order

TABLE 5-1 Genetic Causes of Disorders of Surfactant Homeostasis

Genes/Locus	Functions	Inheritance	Presentation	Age at Presentation
ABCA3 16p13.3	Lipid transport, surfactant packaging/function	AR	RDS ILD	Newborns, children
SFTPB 2p12	Surfactant packaging/function	AR	RDS	Newborns
SFTPC 8p21	Surfactant function	AD	ILD > RDS	Infants, children, adults
SFTPA 10q22.2	Tubular myelin, host defense	AD	ILD/lung cancer	Adults
TTF-1 14q13	Lung, thyroid, CN morphogenesis, surfactant regulation	AR haploinsufficiency	Thyroid/lung/CNS malformations, ILD	Newborns, infants
GMCSFRα 22.32	Alveolar macrophage function	AR	PAP	Children
GM-CSF 15q31	Alveolar macrophage function	Autoimmune	PAP	Adults

Abbreviations: RDS, respiratory distress syndrome; ILD, interstitial lung disease; PAP, pulmonary alveolar proteinosis; AR, autosomal recessive; AD, autosomal dominant.

the lipid head group region is located in the amino- and carboxy-terminal regions of SP-B (1-20) and (53-78), which contain the predicted amphipathic helices. Synthetic peptides that contain these two regions have surface tension–lowering activity similar to that of native SP-B, and peptide mimics have been developed for therapy of respiratory distress in infants. SP-B enhances the insertion (fusion) of phospholipid vesicles into a preformed DPPC/DPPG monolayer, particularly in the presence of divalent cations. SP-B causes lipids in solution to form discoid particles often appearing as stacks or sheets. Together with SP-A, lipids, and Ca^{2+}, SP-B reconstitutes the characteristic ultrastructural features of tubular myelin, producing multilamellar aggregates and square lattice configurations. Recent findings support a potential role for SP-B in the secretion of lamellar bodies from AT2 cells, mediated in part by enhancing Ca^{2+}-dependent purinoreceptor signaling and exocytosis.[23]

■ SP-B Is Required for Survival After Birth

Mutations in the gene encoding SP-B (*SFTPB*, OMIM 265120) cause acute respiratory failure at birth related to surfactant dysfunction.[24,25] Similarly, deletion of *Sftpb* in the developing lung or its conditional deletion in adult mice causes acute respiratory distress associated with alveolar capillary leak and surfactant deficiency.[26] Pathologic findings of patients with lung disease related to *SFTPB* mutations are similar to those in mice in which the *Sftpb* gene is deleted.[26,27] SP-B deficiency is associated with failure to form lamellar bodies, accumulation of abnormal multivesicular bodies within the AT2 cells, and failure to form tubular myelin or functional surfactant films after secretion into the alveoli.

■ Hereditary SP-B Deficiency Causes Respiratory Failure at Birth

SP-B deficiency is inherited in an autosomal recessive pattern, and most affected infants develop respiratory failure shortly after birth. While lung morphogenesis proceeds normally in utero, the lack of SP-B results in acute atelectasis and respiratory distress, usually presenting as full-term infants with signs and symptoms of diffuse alveolar collapse after birth. More than 40 distinct *SFTPB* mutations in patients with SP-B deficiency have been identified.[25,27] The disorder is refractory to surfactant replacement therapy, and most patients die from respiratory failure within several months after birth, requiring oxygen and ventilatory support throughout their clinical course. Lung transplantation has been offered to some patients. SP-B deficiency disrupts the formation of lamellar bodies and tubular myelin and interferes with the processing of proSP-C to the active peptide. Thus, most SP-B deficient patients lack both SP-B and SP-C peptides in the alveolus. In patients with *SFTPB*-related disease, proSP-C accumulates in the airspaces, contributing to an alveolar proteinosis–like syndrome. Pathologic diagnoses include desquamating interstitial pneumonitis, chronic pneumonitis of infancy or infantile alveolar proteinosis, and histologic changes being influenced by age and supportive therapies (Fig. 5-3).[28] The definitive diagnosis is made by identification of *SFTPB* gene mutations, enabling prenatal diagnosis and genetic counseling. While various missense, nonsense, frameshift, and splice variants have been identified, mutation 121ins2 in exon 4 is the most common.[24] In most affected infants, SP-B is lacking in bronchoalveolar lavage fluid and the abnormal proSP-C peptide accumulates in the alveoli, findings that can be verified by immunohistochemistry. Patients with SP-B deficiency do not respond to surfactant replacement and generally succumb from chronic respiratory failure early in infancy in spite of intensive care. A number of SP-B-deficient infants have been treated successfully by lung transplantation. Recent published data demonstrated efficacy of adeno-associated virus (AAV)-mediated gene rescue of SP-B deficiency in a transgenic mouse model.[29] These data, coupled with multiple ongoing clinical trials for AAV-mediated gene therapy approaches for other genetic diseases, pave the way for potential gene therapy approaches for SP-B-deficient patients in the future.

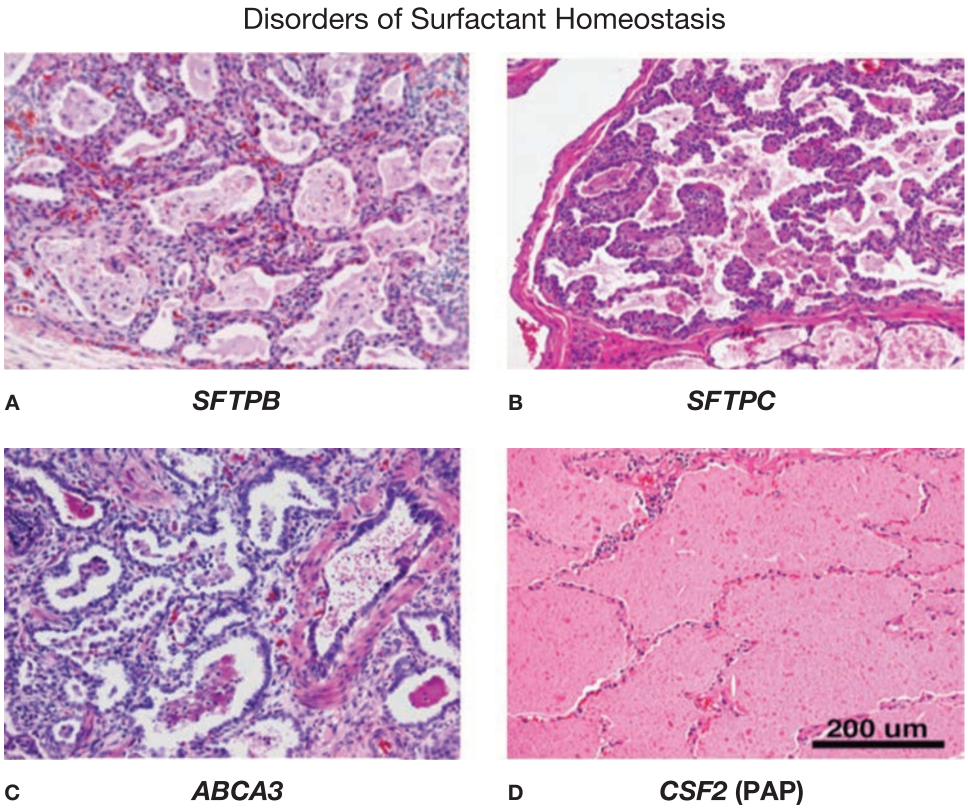

Figure 5-3 Pulmonary histopathology associated with disorders of surfactant homeostasis. Pathologic findings in neonates with mutations in *SFTPB*, *SFTPC*, and *ABCA3* are consistent with varying pathologic diagnoses, e.g., childhood interstitial pneumonitis (CIP), non-specific interstitial pneumonitis (NSIP), desquamating interstitial pneumonitis (DIP), or interstitial alveolar proteinosis (IAP). Severe alveolar remodeling, alveolar loss, macrophage infiltration, varying degrees of alveolar proteinosis, and stromal thickening are observed. In contrast, auto-antibodies against GM-CSF or mutations in the GM-CSF receptor (*CSFR2A*) are associated with pulmonary alveolar proteinosis (PAP) in which surfactant lipids and proteins accumulate in the alveolus. Alveolar structure is generally well maintained in PAP. *(Reproduced with permission from Whitsett JA, Wert SE, Trapnell BC. Genetic disorders influencing lung formation and function at birth. Hum Mol Genet. 2004;13(suppl 2):R207–R215.)*

Surfactant Protein C (SP-C)

In humans, SP-C is encoded by a single gene (*SFTPC*, OMIM 178620), located on human chromosome 8.[2,14] SP-C mRNA is expressed exclusively in AT2 cells in the lung and is translated to produce a 22-kDa precursor that is palmitoylated and proteolytically processed during intracellular transport to form the active, hydrophobic peptide of 35 amino acids stored in lamellar bodies.[2,3] After secretion, SP-C enhances the surface-active properties of lipid mixtures, lowering surface tension during compression and enhancing adsorption rate of lipid films at the air-water interface. Both SP-C and SP-B enhance the speed of formation and stability of lipid films. A mixture of surfactant lipids and proteins SP-B and SP-C improves lung inflation and compliance and is useful for treatment of respiratory distress syndrome in newborn infants. SP-C is palmitoylated on cysteine residues near the NH_2 terminus. The surface activity of depalmitoylated SP-C is somewhat less than that of palmitoylated SP-C, likely related to reduced stability of the α-helical domain that anchors the peptide within the lipid bilayer. Although the orientation of the palmitoyl groups in a lipid environment is not currently known with certainty, the lipid moiety on SP-C enhances the hydrophobicity of the amino-terminal region enabling its close contact with multilayered lipid films and likely serves to stabilize the α-helical, hydrophobic domain of SP-C. SP-C enhances the uptake of lipids by AT2 cells and plays an important role in lipid homeostasis in the alveoli.

In a lipid bilayer, the orientation of the α-helical segment of SP-C is closely parallel with the lipid acyl chains, implying a transbilayer orientation. In a surface monolayer, SP-C has a preferential orientation parallel to the interface, as observed by circular dichroism of monolayer films. The positive charges near the NH_2 terminus of SP-C may promote binding of phospholipid vesicles to the monolayer, a step required for insertion of phospholipids into the monolayer. SP-C forms well-defined domains within DPPC/DPPG films below the phase transition temperature of the bulk lipid. SP-C alters the size and shape of lipid vesicles, disrupting vesicular structures, causing the formation of larger vesicles and discoid particles.

Surfactant lipid films fold as a consequence of dynamic compression during the respiratory cycle in a process enhanced by SP-C and SP-B, each interacting with lipids in distinct ways. Interactions among SP-B and SP-C and disordered lipid phases enhance the surface tension–lowering properties of surfactant lipids. SP-B serves to stabilize the membrane-to-membrane interactions between the folded lipid layers to create multilayers.[3]

Role of SP-C in the Pathogenesis of Pulmonary Disease

Deletion of *Sftpc* in transgenic mice perturbed surfactant function and caused severe interstitial lung disease with advancing age.[30] While *Sftpc*$^{-/-}$ mice survive after birth,[31] the mice develop emphysema, pulmonary inflammation, and abnormal lipid accumulations in alveolar macrophages, epithelial, vascular, and stromal cells. Surfactant lipid spreading and stability are only modestly perturbed in the absence of SP-C in vivo. The severity of pulmonary disorder related to SP-C deficiency in mice is strongly influenced by genetic strain, age, and other injuries, indicating that both genetic and environmental factors influence lung structure and function in the absence of SP-C. SP-C binds bacterial endotoxin, supporting a role in innate host defense in the lung. SP-C-deficient mice are susceptible to viral and bacterial pathogens and develop severe pulmonary injury in mouse models of pulmonary fibrosis. The finding that "*Sftpc* gene deleted" mice develop an interstitial pulmonary disorder is consistent with findings in humans, wherein *SFTPC* mutations cause both acute and chronic lung disease.

Mutations in SFTPC Cause Severe Interstitial Lung Disease in Humans

Mutations in *SFTPC* represent a rare cause of acute and chronic lung disease in humans.[32,33] *SFTPC* mutations are generally inherited as an autosomal-dominant gene that has been causally linked to acute respiratory disease in newborn infants and, more commonly, to chronic interstitial lung disease in infants, children, and adults. De novo mutations in the *SFTPC* gene have been reported. The diagnosis of *SFTPC*-related lung disease (OMIM 610913) is usually made during infancy but can present later in life, the severity of disease varying in a single extended family.[33] Most mutations occur in the C-terminal BRICHOS domain of proSP-C that serves as an intramolecular chaperone for the metastable membrane-spanning helical domain.[34] The mutant proSP-C protein is misfolded and/or misrouted, resulting in intracellular accumulation and cell injury. Most mutations result in the lack of synthesis of the active SP-C peptide that may influence the pathogenesis of lung disease. Various forms of interstitial lung disease have been associated with the disease, including acute respiratory distress (RDS) in newborns, chronic pneumonitis of infancy (CPI), non-specific interstitial pneumonitis (NSIP), and other forms of idiopathic pulmonary fibrosis (IPF) (Fig. 5-3).[28] Lung histopathology associated with *SFTPC* mutations is likely influenced by age, duration and severity of the disease, treatment, and both genetic and environmental factors. Infants with *SFTPC* mutations often present with severe respiratory signs and symptoms following viral infections. Definitive diagnosis is made by identification of mutations in the *SFTPC* gene. The onset and severity of pulmonary disease in humans is highly variable, even in the same kindreds, indicating that genetic and environmental factors strongly influence the disorder. At present, there is no effective therapy for SP-C-related disease. Lung transplantation has been offered for treatment of hereditary *SFTPC* deficiency in patients with respiratory failure. Mutations in *SFTPC* are a rare cause of acute and chronic interstitial lung disease. More than 50 distinct mutations in *SFTPC* have been associated with clinical lung disease and include missense, frameshift, splice, insertions, and deletions that generally disrupt the structure of the C-terminal BRICHOS domain leading to rapid degradation of proSP-C by the proteasome. The most common mutation, I73T, is located in the linker domain (the region between the BRICHOS and transmembrane domains) and occurs in approximately one-third of patients. Unlike mutations in the BRICHOS domain, linker domain mutations do not lead to misfolding of proSP-C but rather alter intracellular trafficking and subsequent processing of the proprotein. Accumulation of proSP-C in a late endosomal compartment is associated with impaired autophagy that, in turn, may limit the ability of AT2 to respond to further injury.[35]

Expression of allele variants encoding SP-C has been linked to cytotoxicity and pathogenesis in several mouse models. Acute induction of an L188Q *SFTPC* transgene in adult mouse lung was associated with decreased repair capacity following lung injury.[36] Prenatal expression of a Δexon4 *SFTPC* transgene[37] or the C121G *Sftpc* allele[38] resulted in AT2 cell death, disrupted lung morphogenesis, and neonatal lethality. These mouse models confirmed in vitro findings of mutant SP-C toxicity but failed to model the human disease, which is not typically associated with postnatal lethality. Acute induction of expression of the I73T[39] or C121G *Sftpc* allele in adult lung resulted in interstitial lung disease marked by alveolitis, aberrant remodeling, and restrictive lung disease. These mouse models strongly linked expression of the mutant *Sftpc* allele to development of fibrotic lung disease and model the acute exacerbation phase of disease.

ABCA3 Mutations Cause Respiratory Failure at Birth

ABCA3 is a large, membrane-spanning transport protein that is present in the limiting membrane of lamellar bodies in AT2 cells (Fig. 5-2). More than 140 different mutations associated with severe lung disease in newborn infants have been identified, *ABCA3* mutations (OMIM 610921) representing the most common genetic cause of neonatal respiratory failure.[1,4,34,40] While expressed in many tissues, patients with mutations in *ABCA3* present with isolated lung disease, and abnormalities in other organ structures or functions have not been observed. Pathologic findings in newborn infants with respiratory failure are similar to those in mice wherein the *ABCA3* gene has been genetically deleted. *ABCA3* gene–related lung disease is generally inherited as an autosomal recessive disorder (Table 5-1). Affected infants present with severe respiratory failure characteristic of surfactant deficiency within the first days of life. Their lung disease is refractory to conventional therapies, resulting in respiratory failure and death within the first months of life. Pathologic findings are similar to those in *SFTPB*-related disease and include alveolar proteinosis, lipoidal pneumonia, cuboidal epithelial cell hyperplasia, interstitial thickening, loss of normal alveolar structures, and features of desquamating interstitial pneumonitis (DIP) (Fig. 5-3).[28] Older children present with features of NSIP (non-specific interstitial pneumonitis). In newborn infants, respiratory failure is not responsive to surfactant replacement. Lung transplantation has been successful for treatment of some patients with *ABCA3*-related diseases. ABCA3 is a member of the ATP-dependent Walker domain containing proteins that constitute a family of membrane-associated transport proteins that includes the CFTR (cystic fibrosis transmembrane conductance regulator). ABCA3 mediates phosphatidylcholine and phosphatidylglycerol transport into lamellar bodies. The diagnosis of ABCA3-related lung disease is confirmed by nucleotide sequencing of the gene in infants and children with refractory pulmonary disease. While most mutations cause respiratory failure in infancy, the E292V mutation is associated with less severe lung disease, and these patients often present with ILD later in childhood. Ultrastructural analysis of lung tissue from patients with *ABCA3* mutations usually demonstrates the presence of small, atypical lamellar bodies in AT2 cells and the absence of tubular myelin in the airways, indicating an abnormality in both intracellular and extracellular lipid homeostasis. The processing of proSP-B is disrupted in some patients with ABCA3-related lung disease.[25]

NKX2-1 in Surfactant Homeostasis

NKX2-1, encoding the homeodomain-containing nuclear transcription factor TTF-1 (thyroid transcription factor-1), plays a critical role in lung morphogenesis and the expression of surfactant proteins.[41,42] TTF-1 is expressed in the central nervous system, thyroid, and lung and is required for lung formation during embryonic development.[42] TTF-1 regulates the transcription of surfactant protein genes (*SFTPA*, *B*, *C*, and *D*), *ABCA3*, and *SLC34a2*, all expressed in AT2 cells.[41] *SLC34a2* is a phosphate transporter associated with the disease pulmonary alveolar microlithiasis.[43] Mutations in *NKX2-1* are linked to disorders of the central nervous system, thyroid, and lung (OMIM 600635), and more than 150 patients have been reported to date.[44,45] *NKX2-1* gene–related lung disorders are generally inherited as heterozygous mutations resulting in lung dysfunction of varying severity, ranging from disordered alveolar morphogenesis, surfactant deficiency with respiratory failure in neonates and infants, and interstitial lung disease in older patients. The majority of patients with *NKX2-1* mutations present with severe lung disease, approximately half of which have a spectrum of brain, thyroid, and lung disease. Histologic findings vary greatly, with severe abnormalities in the alveoli and variable loss of surfactant proteins and lipids. Pulmonary disease associated with *NKX2-1* mutations is frequently accompanied by congenital hypothyroidism. The severity of *NKX2-1*-related CNS, thyroid, and pulmonary disease varies widely. Diagnosis is made by identification of mutations in the *NKX2-1* gene. Heterozygous mutations in the *NKX2-1* gene have been associated with neuroendocrine hyperplasia.[46]

The Pulmonary Collectins (SP-A and SP-D)

The collectins SP-A and SP-D are critical components of the pulmonary surfactant system. The collectins are a group of highly conserved proteins expressed in many tissues that share functional domains, including helical collagenous and C-type lectin domains that bind to complex carbohydrates on pathogens and their products. A number of recent reviews summarize the roles of acquired immunity.[6,47] SP-A and SP-D bind and aggregate microbial pathogens, enhancing mucociliary clearance and opsonization by alveolar macrophages, serving to inhibit damaging inflammatory responses. Both proteins play important roles in surfactant homeostasis in the alveoli, interacting with lipids and proteins to regulate surfactant structures and pool sizes. SP-A and SP-D interact with a diversity of cells in the alveolus including macrophages, neutrophils, and eosinophils to regulate inflammation. SP-A and SP-D bind to and influence signaling via CD14, TLR2, LAIR-1, and SPR-210 to regulate phagocytosis or in professional immune cells.

Surfactant Protein A (SP-A)

SP-A is an abundant hydrophilic 26-kDa (monomer) glycoprotein that functions in the host defense and regulation of extracellular surfactant lipid structure. SP-A mRNA is expressed in non-ciliated bronchiolar and AT2 cells in the lung, being transcribed from two genes (*SFTPA1* and 2) located on chromosome 10 in the human.[2,13,18] SP-A in combination with SP-B and SP-C enhances formation of a surface lipid film in the presence of divalent ions but is not critical for surfactant activity in the alveoli. The amino-terminal third of SP-A is arranged in a collagen-like triple helix, while a carboxy-terminal region has structural similarity to mammalian lectins including SP-D, serum mannose-binding lectin (MBL), and C1q. Protein-protein interactions among SP-A molecules are mediated by the collagen-like domains via intermolecular disulfide bonds that are necessary for SP-A-mediated aggregation of lipids and formation of tubular myelin. SP-A trimers further oligomerize to form octadecamers that enhance cooperative interactions with glycoproteins and glycolipids on the surface of microbial pathogens. Binding and uptake of SP-A by AT2 cells and alveolar macrophages are mediated by specific cell-surface receptors; however, the precise nature of the SP-A receptors and their intracellular functions remain unclear.[48] Both collagenous and noncollagenous domains of SP-A bind to isolated AT2 cells and immune cells. SP-A increases the association of lipids with AT2 cells but does not appear to increase internalization of lipid. Deletion of the SP-A gene (*Sftpa*) in mice does not alter survival or lung function after birth. While tubular myelin is absent, surfactant function, uptake, and secretion are not strongly influenced by deletion of *Sftpa* in mice.[49] Nevertheless, $Sftpa^{-/-}$ mice are highly susceptible to lung infections by bacterial, viral, and fungal pathogens, indicating that SP-A plays an important role in innate host defense of the lung.[2,13,18]

Usual Interstitial Pulmonary (UIP) Disease Caused by Mutations in SFTPA2

Missense mutations in the genes encoding SP-A (*SFTPA1* and *SFTPA2*) have been linked to pulmonary fibrosis pathologically diagnosed as UIP (OMIM 178642), generally presenting as interstitial lung disease (ILD) in the 4th and 5th decade of life.[50,51] Increased risk of pulmonary adenocarcinoma was observed at more advanced ages. This rare disorder is inherited as an autosomal dominant mutation in which the oligomerization and intracellular trafficking of SP-A is disturbed, resulting in the unfolded protein response and chronic alveolar cell injury. Transgenic knock-in mice expressing the human *SFTPA1* mutation associated with ILD resulted in spontaneous fibrosis associated with necroptosis of AT2 cells[52] demonstrating a causal relationship between *SFTPA1* mutations and ILD.

Surfactant Protein D (SP-D)

Surfactant protein D is a collagenous Ca^{2+}-dependent carbohydrate-binding protein that is structurally related to SP-A and other C-type lectins.[18] SP-D is encoded by a single gene (*SFTPD*) located near the *SFTPA* genes on human chromosome 10.[2,13,18] SP-D is synthesized by AT2 cells and non-ciliated bronchiolar cells in the lung, but it is also expressed in many other tissues. SP-D trimers form larger oligomers that bind carbohydrates and glycolipids on the surface of bacteria, fungi, and viruses. The interaction of SP-D with microbial pathogens is Ca^{2+}- and carbohydrate-dependent.[18] In contrast to other surfactant proteins (SP-A, SP-B, and SP-C), SP-D is not strongly associated with surfactant lipids in the alveolus but plays an important role in determining surfactant structure and homeostasis.

■ Functions of SP-D In Vivo

Deletion of *Sftpd* in mice has provided insight into its important role in surfactant and alveolar homeostasis. *Sftpd*$^{-/-}$ mice survive after birth but develop severe pulmonary disease associated with macrophage activation, airspace enlargement, and marked accumulation of surfactant lipids in the alveoli.[53,54] SP-D regulates alveolar pools of large and small aggregate surfactant, influencing surfactant particle size and its uptake by AT2 cells. Addition of SP-D to surfactant lipid extracts enhances surfactant stability in vitro and protects the preterm lung from endotoxin-induced injury. Infiltration with lipid-laden macrophages, and the induction of synthesis of metalloproteinases 2, 9, and 12 by alveolar macrophages, may contribute to the spontaneous airspace remodeling seen in the *Sftpd*$^{-/-}$ mice. *Sftpd*$^{-/-}$ mice are highly susceptible to pulmonary infections and inflammation associated with viral (respiratory syncytial and influenza virus), bacteria and endotoxin, or fungal exposures, indicating that SP-D plays a critical role in innate host defense of the lung.[2,13,18] SP-D binds bacterial, fungal, and viral pathogens, enhancing their opsonization and their killing by alveolar macrophages. Levels of SP-D are low in preterm infants and in infants and older patients with chronic lung disease. SP-D influences immunologic responses to allergens, interacting with alveolar macrophages and lymphocytes in the innate immune system. Thus, SP-D plays an important role in the regulation of surfactant lipid homeostasis, innate host defense of the lung, and prevention of inflammation and alveolar remodeling. Susceptibility to influenza A viral infections has been linked to specific *SFTPD* alleles, but to date, mutations in *SFTPD* have not been directly linked to acute or chronic lung disease. Serum SP-D levels are increased in COPD, PAP, and other chronic and acute lung diseases and have been utilized in clinical settings to monitor disease progression and response to therapy.[55]

RECYCLING AND CATABOLISM OF SURFACTANT LIPIDS AND PROTEINS

Pulmonary surfactant is taken up rapidly in the lung, and much of the lipid is reutilized (Fig. 5-2). After intratracheal administration, labeled lipid appears in AT2 cells and alveolar macrophages, but is not found in type I cells, indicating that the AT2 cells actively take up surfactant lipids from the alveolus for recycling or catabolism. Isolated epithelial AT2 alveolar cells internalize H-PC and re-secrete the internalized material or degrade it with subsequent reincorporation into other lipids. Isolated primary AT2 cells endocytose SP-C and SP-B. SP-A also binds to AT2 epithelial cells and is endocytosed by receptor-mediated mechanisms. While a number of candidate SP-A and SP-D receptors and binding proteins have been identified, whether the proteins are efficiently recycled and the mechanisms by which they signal to influence surfactant homeostasis remain unclear.

Pulmonary surfactant as isolated from lavage fluid exists in several forms that can be fractionated based on density. In vivo labeling indicates that phospholipid is initially secreted in the heaviest forms, followed by conversion into distinct heavy and light forms. The densest or ultraheavy form contains lamellar bodies and tubular myelin. Small aggregate forms are comprised of small unilamellar vesicles. While their lipid composition is similar to that of large aggregates, small aggregates are depleted of SP-A, SP-B, and SP-C, and lack surfactant function. SP-A and SP-D play important roles in the maintenance of the large aggregate surfactant structures. Cycling surfactant by expansion and contraction of a surface film in vitro converts lipids from large to small aggregates that are likely remnants destined for catabolism or recycling.[3]

REGULATION OF SURFACTANT PRODUCTION

The synthesis of pulmonary surfactant is subject to precise regulatory controls both during development and postnatally.[56] Surfactant phospholipid synthesis increases markedly in late gestation and is enhanced by a variety of hormones, including glucocorticoids in the fetal lung. Lung phospholipid content increases in the latter two-thirds of gestation in preparation for respiratory adaptation at birth. Prenatal glucocorticoids are routinely used to induce lung maturation and surfactant synthesis in infants at risk for preterm delivery.[9] Glucocorticoids reduce the risk of IRDS, enhancing the structural maturation of the alveoli and the efficacy of surfactant replacement therapy after birth. Like surfactant phospholipids, the surfactant proteins are highly regulated, increasing in the latter two-thirds of gestation in the mammalian species studied. Expression of surfactant proteins is regulated in complex ways by a variety of hormonal agents. The levels of surfactant protein mRNA increase in the perinatal period in association with increased surfactant synthesis and secretion required for postnatal respiratory adaptation. Expression of the surfactant proteins is regulated at both transcriptional and posttranscriptional levels, maintaining steady-state protein concentrations within tight constraints in the adult lung. Surfactant production is, in general, enhanced by glucocorticoids, in a process mediated by lung fibroblasts, epidermal growth factor (EGF), and cyclic adenosine monophosphate (cAMP) but inhibited by tumor necrosis factor alpha (TNF-α), transforming growth factor beta (TGF-β), and insulin, depending on experimental conditions. Transcriptional control of the surfactant genes is modulated by a number of nuclear transcription factors, e.g., thyroid transcription factor 1 (TTF-1), cyclic AMP–responsive binding protein (CREBPα), members of the forkhead family transcription factors (FOXA2), retinoic acid receptors (RARs), sterol responsive element binding protein (SREBP), GATA binding proteins, Krupple factor 5 (KLF-5), NFATC3, and co-activators associated with the transcription factor.[57] In the lung, surfactant proteins A, B, and D are expressed in non-ciliated bronchiolar and AT2 cells, while SP-C is expressed exclusively in AT2 cells in the lung. Transcriptional, epigenetic, and posttranscriptional mechanisms influence the synthesis of surfactant proteins and lipids, regulating surfactant concentrations in the airspace during development and repair.

■ Surfactant Secretion

Lamellar bodies containing surfactant proteins SP-B and SP-C and lipids are secreted into the alveoli in a process mediated by activation of β-adrenergic receptors and P2X7R purinergic receptors that regulate intracellular cAMP and calcium homeostasis to influence cytoskeletal organization and secretion.[58] SP-B may regulate surfactant secretion mediated by Ca^{2+} and purinoreceptor activation.[23] Recent studies support a role for the orphan G protein–coupled receptor GPR116 in the regulation of surfactant secretion. Loss of GPR116 results in increased surfactant secretion, decreased surfactant uptake by AT2 cells, and increased alveoli surfactant pool sizes.[59] While secretion of surfactant lipids SP-B and SP-C occurs via lamellar bodies, secretion of surfactant-associated proteins SP-A and SP-D occurs via a distinct, secretory pathway (Fig. 5-2). Interactions of SP-A and SP-D with lipids occur after their secretion into the alveoli.

GM-CSF Signaling Regulates Surfactant Clearance

Mutations in the genes encoding GM-CSF receptors (*CSFR2A* and *CSFR2B,* OMIM 13899) and autoantibodies against CSF2 (GM-CSF) have been associated with early-onset pulmonary alveolar proteinosis in children and in adults, respectively.[5,60] While less than 10% to 15% of surfactant lipids is cleared by catabolism in alveolar macrophages, this pathway is critical in controlling steady-state surfactant concentrations in vivo. Granulocyte macrophage colony-stimulating factor (GM-CSF or *CSF2*) and GM-CSF receptors are required for normal surfactant catabolism by alveolar macrophages.[5,61] Surfactant protein and lipid clearance are decreased in *Csf2*, *Csfr2a*, and *Csfr2b* gene-deleted mice, causing pulmonary alveolar proteinosis in which surfactant proteins and phospholipids accumulate in the lung. Findings in the mouse models led to the discovery that GM-CSF signaling abnormalities cause idiopathic pulmonary alveolar proteinosis (PAP).[5,62] Clinical studies demonstrate that idiopathic PAP in adults is usually caused by autoantibodies against GM-CSF.[60] Similar abnormalities in surfactant homeostasis and alveolar macrophage morphology and function are observed in patients with PAP, whether caused by mutations in GM-CSF receptors or by neutralization of GM-CSF by autoantibodies. While surfactant components are taken up by alveolar macrophages in PAP, lipid metabolic products, in particular cholesterol and cholesterol esters, accumulate in AMs causing cell toxicity. Lung lavage and GM-CSF, given systemically or by aerosol, have been successfully used to treat adults with PAP (see Chapter 70).

SURFACTANT HOMEOSTASIS AND REPLACEMENT IN INFANTILE RESPIRATORY DISTRESS SYNDROME (IRDS)

Infantile respiratory distress syndrome is associated with prematurity, the risk increasing as gestational age decreases. In addition to the morphologic immaturity of the respiratory tract, lung phospholipid content and surfactant secretion are decreased in preterm infants. While functional surfactant can be isolated from infants with IRDS, surfactant pool sizes are markedly decreased in the preterm compared to the term infant, and the surface activity of surfactant from infants with IRDS is decreased. Alveolar-capillary leak of blood or serum proteins inactivates surfactant function. Decreased alveolar surfactant activity associated with pulmonary immaturity causes atelectasis, alveolar collapse, pulmonary hemorrhage, and hypoxemia in preterm infants. A schematic representing factors influencing the pathogenesis of IRDS is provided in Fig. 5-4.[63]

Supplemental oxygen and mechanical or assisted ventilation is routinely used to treat IRDS. Widespread use of exogenous surfactant has ameliorated the morbidity and mortality associated with IRDS in preterm infants. Exogenous surfactants—in the form of synthetic mixtures of phospholipids and extracts of lung or surfactant containing bovine or porcine surfactant proteins B, C, and phospholipids—have been used extensively for prevention and therapy of RDS in newborn infants.[64] Surfactant replacements with preparations containing surfactant proteins B and C act rapidly, increasing lung volumes and compliance and decreasing the requirements for positive-pressure ventilation and oxygen. Morbidity and mortality from IRDS have been markedly reduced since the application of surfactant replacement for preterm neonates, decreasing lung injury, pneumothorax, and mortality. Surfactant replacement is given intratracheally, resulting in improved lung function and oxygenation. Treatment with protein-containing surfactants was effective in decreasing morbidity and mortality from IRDS in clinical studies. Animal-based surfactant preparations containing SP-B and SP-C are now standard treatment for IRDS. The effectiveness of surfactant therapy is likely related to the immediate surface tension–reducing properties and to the reuptake and reutilization of the exogenous surfactant lipids by the respiratory epithelium. Following preterm birth, production of endogenous surfactant lipids and proteins by the respiratory epithelium is rapidly induced; therefore surfactant replacement is primarily utilized in the first few days following birth. Surfactant replacement has been used off-label in the treatment of meconium aspiration and pneumonia in neonates.

SURFACTANT HOMEOSTASIS IN ADULT RESPIRATORY DISTRESS SYNDROME (ARDS)

Adult respiratory distress syndrome occurs in association with trauma, sepsis, long bone fractures, thermal burns, and injury to the lung from aspiration of gastric contents, pneumonia, inhalation of toxic gases, and infection (see Chapter 140). In ARDS, increased permeability of the microvasculature permits leakage of protein and fluid into the lung, inactivating surfactant. Epithelial cell injury also may contribute to surfactant deficiency in ARDS. Various non-surfactant proteins and lipids present in elevated concentrations in the lung in ARDS have been implicated in reducing surface activity of pulmonary surfactant; these include immunoglobulins, albumin, fibrinogen, fatty acids, lyso-phosphatidylcholine, and C-reactive protein. The mechanisms causing the decrease in surfactant activity in ARDS include competition of the proteins for the air-liquid interface, sequestration and dilution of surfactant in non-surface-active particles, and inhibition of surfactant protein and lipid synthesis and secretion. Alterations in surfactant composition occur during ARDS and may precede the development of respiratory failure.[65] Phospholipid, SP-A, and SP-B concentrations are decreased, and the minimum surface tension of surfactant tested in vitro is increased in patients at risk for ARDS. In ARDS, total phospholipid, phosphatidylcholine, phosphatidylglycerol, and surfactant proteins SP-A and SP-B are decreased and the ratio of small to large aggregates is significantly increased compared with that in non-ARDS patients. Thus, ARDS leads to both a deficiency in pulmonary surfactant

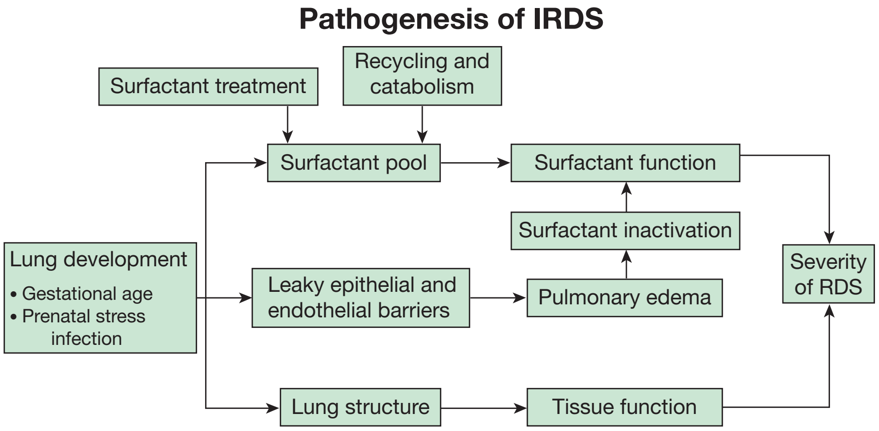

Figure 5-4 Factors influencing the pathogenesis of idiopathic respiratory distress syndrome (IRDS). The pathogenesis of IRDS is multifactional. Immaturity of AT2 cells results in decreased surfactant pools. Lung collapse and injury are caused by surfactant deficiency. Alveolar damage causes leakage of serum proteins and edema that inactivate surfactant, increasing the severity of respiratory distress. Surfactant treatment reduces surface tension, restores phospholipid pool sizes, and improves alveolar-capillary leak to maintain surfactant function. *(Reproduced with permission from Dr. Alan Jobe.)*

constituents and inhibition of the activity of the remaining surfactant. While exogenous surfactant has been effective in decreasing ARDS severity in laboratory experiments, to date, clinical studies have not supported the routine use of surfactant replacement for RDS in adult patients. In contrast, application of careful ventilatory support and prone positioning of patients has improved outcomes in ARDS.

INHIBITION OF SURFACTANT ACTIVITY DURING LUNG INJURY

Phospholipases A2 and C and their products, fatty acids, lysoPC, and dipalmitin inhibit surface activity in vitro. These molecules may be released or produced during lung injury. Inhibitory effects of oleic acid may be related to its miscibility with phospholipids, disrupting the interfacial surfactant film, rather than by competition for the interface. The inhibition by PAF, lysoPC, and oleic acid is not reversible, suggesting that their direct interaction with surfactant lipids disrupts lipid organization required for stable film formation. In contrast, palmitic acid improves surfactant function of preparations used for therapy of IRDS. The surface activity of pulmonary surfactant is readily destroyed by phospholipase A_2 or phospholipase C. Oxygen therapy, used routinely for ARDS and IRDS, may influence surfactant homeostasis and function in the alveolus. The rate of synthesis of surfactant lipids and clearance of radiolabeled surfactant extracts decreased in rabbits exposed to 100% O_2 for 64 h. In contrast, exposure of adult rats to 85% O_2 increased expression of surfactant proteins SP-A, SP-B, and SP-C and phospholipids. Oxidants are also released locally in the lung by activated immune cells. Activated alveolar macrophages secrete NO and superoxide, which can then react to form peroxynitrite that can oxidize and inactivate proteins and lipids. Peroxynitrite inhibited the surface activity of surfactant, damaging both lipids and surfactant proteins.

■ Plasma Proteins Inactivate Pulmonary Surfactant

Edema fluid leaks into the airspace in both ARDS and IRDS. Edema fluid obtained from hyperoxia-exposed rabbits contains serum proteins capable of inhibiting surface activity of surfactant extracts, as evaluated in the pulsating bubble apparatus. Thus, edema fluid may interfere with surfactant therapy, although the concentration dependence of the inhibition suggests that increased doses of surfactant may aid in overcoming the inhibitory effects of edema fluid. Serum albumin, globulin, and fibrinogen reduce the rate of adsorption, increase the minimum surface tension of the surfactant film, and reduce the hysteresis area between compression and expansion curves in vitro. The mechanism by which plasma proteins inhibit the activity of pulmonary surfactant is likely to be one of competition for the interface, because higher surfactant lipid concentrations overcome albumin inhibition even at high albumin concentrations. Inhibition by C-reactive protein, fibrinogen, and other plasma proteins is reversible. Addition of SP-A and organic surfactant extracts reverses inhibition caused by soluble proteins but not by lysoPC. Both SP-C and SP-B increase the ability of a phospholipid mixture to resist inhibition of surface activity by plasma proteins. SP-B is more effective than SP-C at resisting inhibition by fibrinogen. Optimal resistance to surfactant inhibition by serum protein was observed when both SP-C and SP-B were present.

REDUCTION OF SURFACTANT SYNTHESIS IN ARDS

In addition to the inactivation of pulmonary surfactant by proteins and lipids in edema fluid, a reduction of synthesis of surfactant may contribute to the decreased surfactant activity in ARDS. *Escherichia coli* endotoxin inhibited surfactant synthesis in lung organ cultures. Synthesis of surfactant proteins is also influenced by inflammatory responses following lung injury or infection. TNF-α decreased de novo synthesis of SP-A, SP-B, and SP-C mRNA and caused respiratory distress when administered intratracheally to the mouse. TGF-β1, produced during lung injury, decreased the expression of SP-A and SP-C in vitro. Thus, sepsis or lung injury may reduce both the synthesis and functions of surfactant lipids and proteins.

SUMMARY

Pulmonary surfactant is required for air breathing after birth and for protection of the lung from microbial pathogens and toxicants. Surfactant homeostasis requires the integrated functions of surfactant proteins and lipids to reduce surface tension in the alveolus. Decreased production or inactivation of pulmonary surfactant has been associated with both IRDS and ARDS. Mutations in genes mediating surfactant synthesis or catabolism (*ABCA3*, *SFTPA*, *SFTPB*, *SFTPC*, *NKX2-1*, and *CSFR2A/B* receptors) are rare genetic causes of acute or chronic lung diseases.[1–5,27,66] Identification of the genes and proteins mediating alveolar homeostasis provides the knowledge and tools to diagnose and treat rare lung diseases caused by disorders of surfactant homeostasis.

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CHAPTER 6

Mucociliary Clearance

Thomas W. Ferkol
John D. Dickinson
Burton F. Dickey

INTRODUCTION

Mucus forms an essential barrier that protects the lungs from inhaled particles, pathogens, and toxicants. However, excessive mucus accumulation contributes to the pathogenesis of all the common diseases of the airways. Therefore, understanding airway mucus function and dysfunction is important for pulmonary medicine. The airway mucus barrier is mobile, continually propelled in a proximal direction by ciliary beating. Ciliary dysfunction causes disease both because of the failure to clear xenobiotics from the lungs and by causing mucus accumulation. Mucus and ciliary biology will be considered together in this chapter as they interact to achieve, or fail to achieve, airway clearance.

MUCOCILIARY CLEARANCE IN HEALTH

Below we consider the roles of airway surface liquid, surface epithelial cells, submucosal glands, and mucociliary and cough clearance in healthy individuals.

■ Airway Surface Liquid (ASL)

Liquid in the airway lumen is distributed between two distinct layers—a mobile mucus layer and a stationary periciliary layer (Fig. 6-1). Secreted polymeric mucins are the principal macromolecular components of the mucus layer, whereas membrane-tethered mucins and non-mucin glycoconjugates are the principal macromolecular components of the periciliary layer.

Mucus Layer

Normal mucus has physical characteristics on the border between a viscous fluid and a soft elastic solid. Its physical state can vary with the extent of hydration and other conditions as described below. Mucus is formed by a dilute network of mucin polymers in aqueous solution, with water accounting for $\sim$98% of the mass, salts $\sim$0.9%, globular proteins $\sim$0.6%, and mucins only $\sim$0.5%. Mucins are exceedingly large glycoproteins (monomeric masses up to 3×10^6 Da) that link up to form long chains and branched networks. MUC5AC and MUC5B are the major secreted mucins in the airways.[1–4] They exhibit similar molecular weights and primary structure (Fig. 6-2A) but differ in function (see "Secretory Cells," below) and polymer structure. Whereas MUC5B forms end-to-end polymers (Fig. 6-2B), emerging data suggest that MUC5AC forms branched covalent networks. They have characteristic regions rich in serine and threonine residues linked by their hydroxyl side groups to sugar chains (*O*-glycosylation) that account for 50% to 90% of the mass of mucins.

Mucins are packaged dehydrated in secretory granules. After secretion, they rapidly adsorb several hundred fold their mass of water, so it is critical there be sufficient airway surface liquid.[5] Insufficient liquid results in formation of a gel that is too viscoelastic and adhesive to be readily cleared by ciliary motion or cough. Once immobile mucus plaques are formed, they swell only very slowly if subsequently exposed to additional liquid because of the high degree of entanglement of the mucin polymers. Besides the need for sufficient surface liquid, determined mostly by the amount of chloride and sodium in the ASL, adequate bicarbonate must also be present to bind calcium and allow proper mucus swelling. In secretory granules, calcium organizes the folding of mucin polymers and must dissociate to allow mucus expansion.[6–8] Chloride and

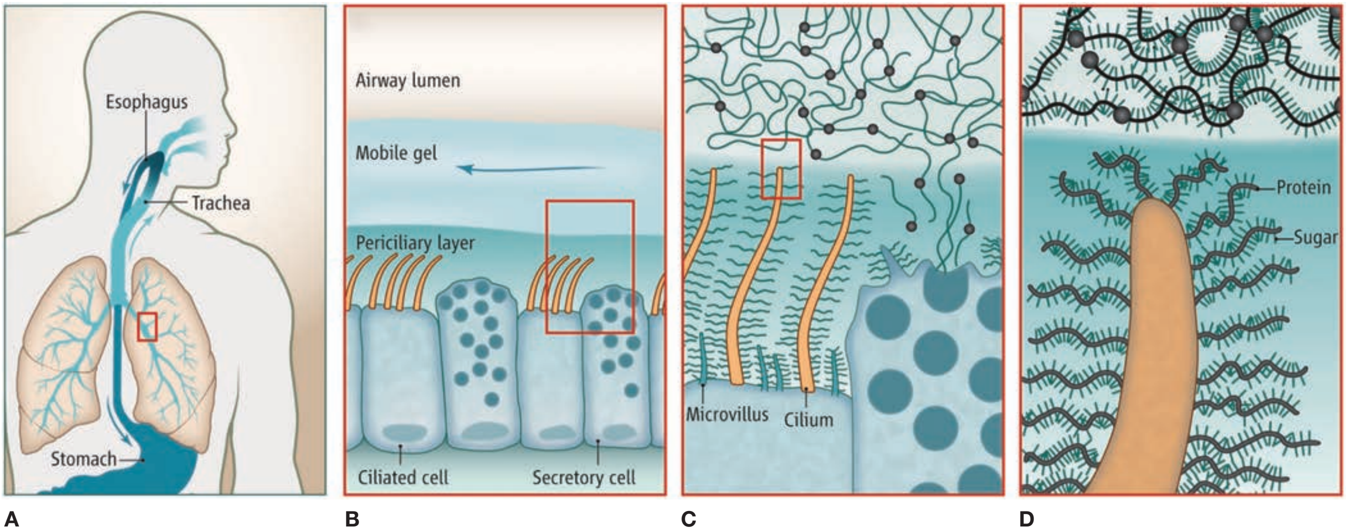


Figure 6-1 Airway surface liquid layers. **A.** Mucus is continuously produced in the conducting airways of the lungs, and swept by ciliary action from distal to proximal airways. After passing through the larynx, mucus is swallowed. **B.** The mobile mucus layer *(light blue)* glides over a periciliary layer of higher osmotic modulus *(dark blue)*. **C.** Airway secretory cells synthesize and secrete mucin polymers that interact with water to form the mobile mucus layer. Ciliated cells are covered by a dense glycocalyx containing glycosaminoglycans, membrane-tethered mucins, and other glycoconjugates that give the periciliary layer its high osmotic modulus. **D.** Mucin polymers are illustrated in the mucus layer with the protein core shown in *black*, sugar side chains in *blue*, and sites of end-to-end polymerization as *black circles*. Membrane-tethered mucins are shown densely coating cilia, while other glycoconjugates are not illustrated. *(Reproduced with permission from Dickey BF: Biochemistry. Walking on solid ground, Science. 2012;337(6097):924–925.)*

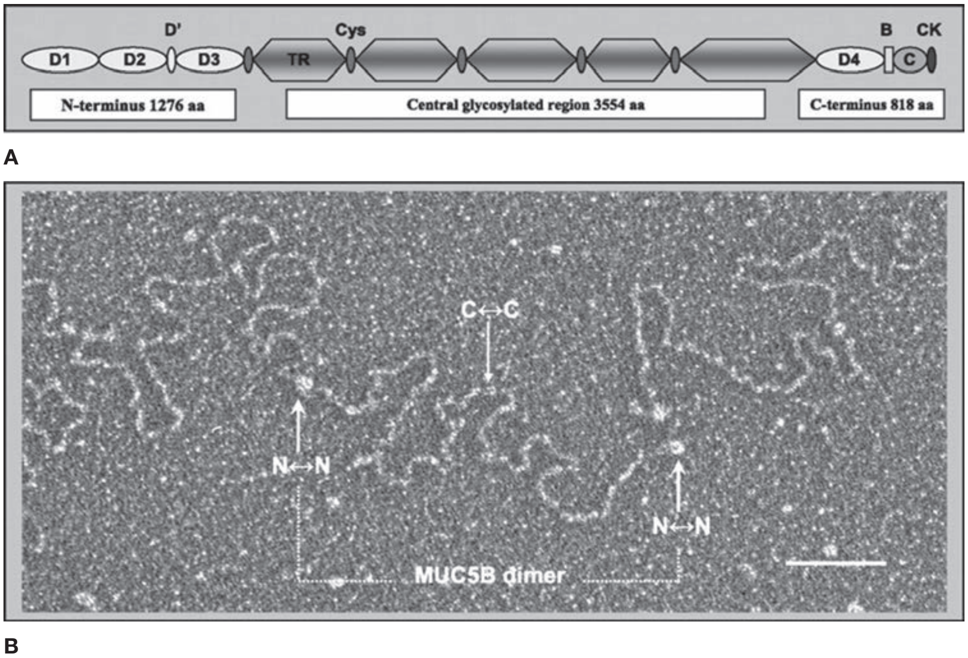


Figure 6-2 The structure of MUC5B. **A.** Structural domain representation of the MUC5B monomer. MUC5B has Von Willebrand factor (VWF)-like domains at NH_2 and COOH-terminal regions (D, B, C, and CK domains). The central region contains five heavily glycosylated, tandem repeat (TR), mucin domains, and five small cysteine-rich (Cys) regions. **B.** Electron microscopy image of a conformationally relaxed, linear MUC5B molecule. The MUC5B intact molecule in mucus is assembled from disulfide bond-mediated interactions between COOH-terminal domains of monomers to form dimers, and subsequent interactions between NH_2-terminal domains to form higher order polymers. The assignment of the structure as a dimer (dotted bar) is made on the basis of the length (850 nm), which is greater than that obtainable by a single MUC5B monomer. The N↔N terminal region and C↔C terminal region can be identified by their size. Scale bar, 100 nm. *(Reproduced with permission from Kesimer M1, Makhov AM, Griffith JD, et al. Unpacking a gel-forming mucin: a view of MUC5B organization after granular release. Am J Physiol Lung Cell Mol Physiol. 2010;298(1):L15–L22.)*

bicarbonate are both secreted into the airway lumen by the cystic fibrosis transmembrane conductance regulator (CFTR). Since the airway epithelium is quite water-permeable, water follows these anions into the airway lumen.[9] Additional hydration can be provided by other chloride channels as described below in the sections on Secretory Cells, Asthma, and Treatment.

Polymeric mucins are produced both in the superficial epithelium and in submucosal glands (Fig. 6-3). In the superficial epithelium, mucins are produced throughout the conducting airways down to the level of the smallest bronchi and the larger bronchioles, but not in terminal or respiratory bronchioles (Fig. 6-4A). Bronchioles lack submucosal glands, and overall, it is estimated that two-thirds of total airway mucus is produced by surface epithelial cells and one-third by submucosal glands in primates[10,11] (Fig. 6-4B). In the most distal airways, the mucus layer is vanishingly thin, but it becomes increasingly thick as it travels proximally, both because additional production adds to its bulk and because the total cross-sectional area of the airways progressively narrows. In the trachea, the mucus gel layer is approximately 50 μm thick. Besides mucus acting as a simple physical barrier in defense of the airway, the mucin sugar side chains act as a combinatorial library to bind particles and pathogens, and a thicker mucus layer has been shown to protect against infection.[12]

Periciliary Layer

It was widely believed until recently that cilia beat in a watery layer of lower density than the overlying mucus layer. However, recent data indicate that the periciliary layer has a higher density than the mucus layer due to a high concentration of membrane-tethered mucins (MUC 1, 4 and 16) and mucopolysaccharides (also called glycosaminoglycans).[13–15] This finding has several important implications for airway function:[4,16] (1) It helps to explain how distinct layers form because dense packing of the grafted glycoconjugates of the periciliary layer tends to exclude the unattached polymeric mucins of the mucus layer (Fig. 6-1C). (2) Charged polymers are highly effective lubricants in an aqueous environment, providing low friction between the periciliary and gel layers, and allowing low friction ciliary beating despite the high density of grafted glycoconjugates. (3) Spatial impingement by grafted glycoconjugates may physically couple neighboring cilia to coordinate their beating (Fig. 6-1C). (4) Glycoconjugates are grafted with increasing density from the top of the periciliary layer to the bottom, propelling exogenous particles and pathogens out of the periciliary layer for removal by the mobile mucus layer. (5) The higher density of water-avid glycoconjugates in the periciliary layer and their grafting to the cell surface results in a nearly constant amount of liquid in this layer except under conditions of severe underhydration. In conditions of overhydration, liquid is transferred to the mucus layer, which is generally well tolerated except with extreme dilution as some degree of viscoelasticity is required for cilia to move mucus against gravity.[17]

■ Airway Epithelial Cells

The surface airway epithelium is mostly a mosaic of two major cell types—secretory and ciliated cells (Figs. 6-1, 6-5, and 6-8). In addition, basal cells that do not contact the airway lumen serve as progenitors in the proximal airways, and scattered throughout the airways are neuroendocrine cells that secrete basolaterally toward sensory neurons, tuft cells that sense odorants, and ionocytes that express high levels of CFTR.[18] Secretory and ciliated cells have a tall columnar shape with a pseudostratified appearance in proximal airways but become progressively shorter in distal airways until they reach a cuboidal shape in bronchioles with a simple single-layer

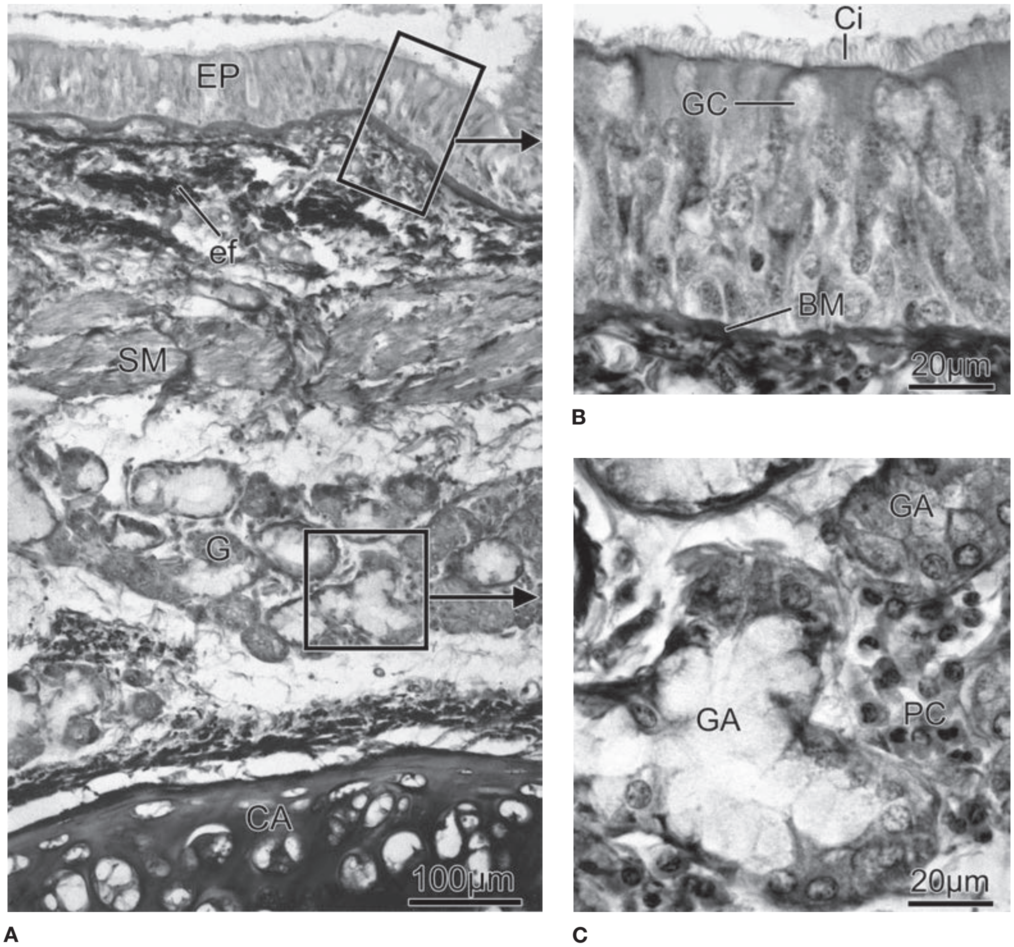


Figure 6-3 Light micrographs of bronchial wall. **A.** The layers from epithelium (EP) to cartilage (CA) with elastic fibers (ef), smooth muscle bundles (SM), and glands (G). **B.** Higher power view of pseudostratified epithelium with ciliated cells (Ci), goblet cells (GC), and basement membrane (BM). **C.** Details of gland acini (GA) associated with groups of plasma cells (PC).

appearance. Ciliated cells are more abundant than secretory cells in proximal airways, whereas secretory cells are more abundant in distal airways.

Secretory Cells

Subsets of airway secretory cells have been given different names based upon differences in their microscopical appearances, including goblet and club (Clara) cells. However, molecular techniques reveal overlap between these subsets, such as the presence of CCSP (SCGB1A1) in cells with a goblet morphology that express mucin, and the presence of MUC5B in cells with a club morphology.[11,19–21] The identity of secretory cells is unified by the stable expression of a regulated exocytic machinery at the apical surface[22,23] (Fig. 6-6), whereas the presence of secretory products such as mucins and secretoglobins varies along the proximal-distal axis and with exposure to extracellular signals that acutely regulate their expression and secretion. Therefore, it is simplest to refer to these cells generically as airway secretory cells, while further specifying their appearance, airway level, and gene expression profile as appropriate. Recently it has been found that CFTR is expressed in surface epithelial secretory cells throughout the airways.[24] Thus, these cells are “secretory” in the sense of apical secretion of both macromolecules and salt.

Secretory cells in bronchi and proximal bronchioles constitutively express MUC5B (Figs. 6-4 and 6-5), whereas secretory cells in terminal and more distal bronchioles do not express MUC5B either constitutively or inducibly.[1,11,19,25] The same secretory cells that express MUC5B can also express MUC5AC, with MUC5AC expressed constitutively in a small number of cells in proximal airways, but inducibly in large numbers of cells in both proximal and distal airways.[11] Mice with deletion of MUC5B often die postnatally from upper and lower respiratory tract inflammation and infection.[26] In contrast, mice with deletion of MUC5AC are healthy at baseline but have an impaired ability to trap parasitic worms transiting their lungs,[27] and induced expression of MUC5AC in rat lungs increases worm trapping.[22] Thus, MUC5B appears to be the principal mucin functioning in baseline clearance of particles and microbes from the airways, while MUC5AC appears to function principally in parasite defense. Notably, the level of expression of MUC5B in mice is limiting for particle clearance such that heterozygous mice have an approximately 50% rate of bead clearance, and MUC5B expression and bead clearance decline in parallel with age.[28] The relevance of these observations from mice for human pathophysiology is indicated by the occurrence of bronchiectasis, repeated airway infections with *Staphylococcus aureus*, and impaired lung function in two siblings with biallelic loss of MUC5B expression, subclinical abnormalities of lung function in two siblings with monoallelic loss of MUC5B expression, and genetic evidence of constraint against monoallelic loss-of-function variation in the general population.[29]

The effector function of MUC5AC in parasite defense dovetails well with the central role of IL-13 in parasite defense and the ability of IL-13 to strongly induce expression of MUC5AC (>100-fold in cultured human airway cells and 40-fold in mice in vivo).[30–32] Other cytokines that promote mucin gene expression include IL-1β, -4, -6, -9, -23, and -25. Among these, IL-1β has a central role in CF and COPD,[33] but whether the other cytokines signal directly or indirectly through IL-13 is not yet clear.[1] Complement protein C3a, epinephrine, and γ-aminobutyric acid signaling interact with IL-13 signaling to augment MUC5AC expression.[1] ClCa1 is a secreted protein that signals in an autocrine and paracrine fashion in response to IL-13 to increase MUC5AC expression.[30] A

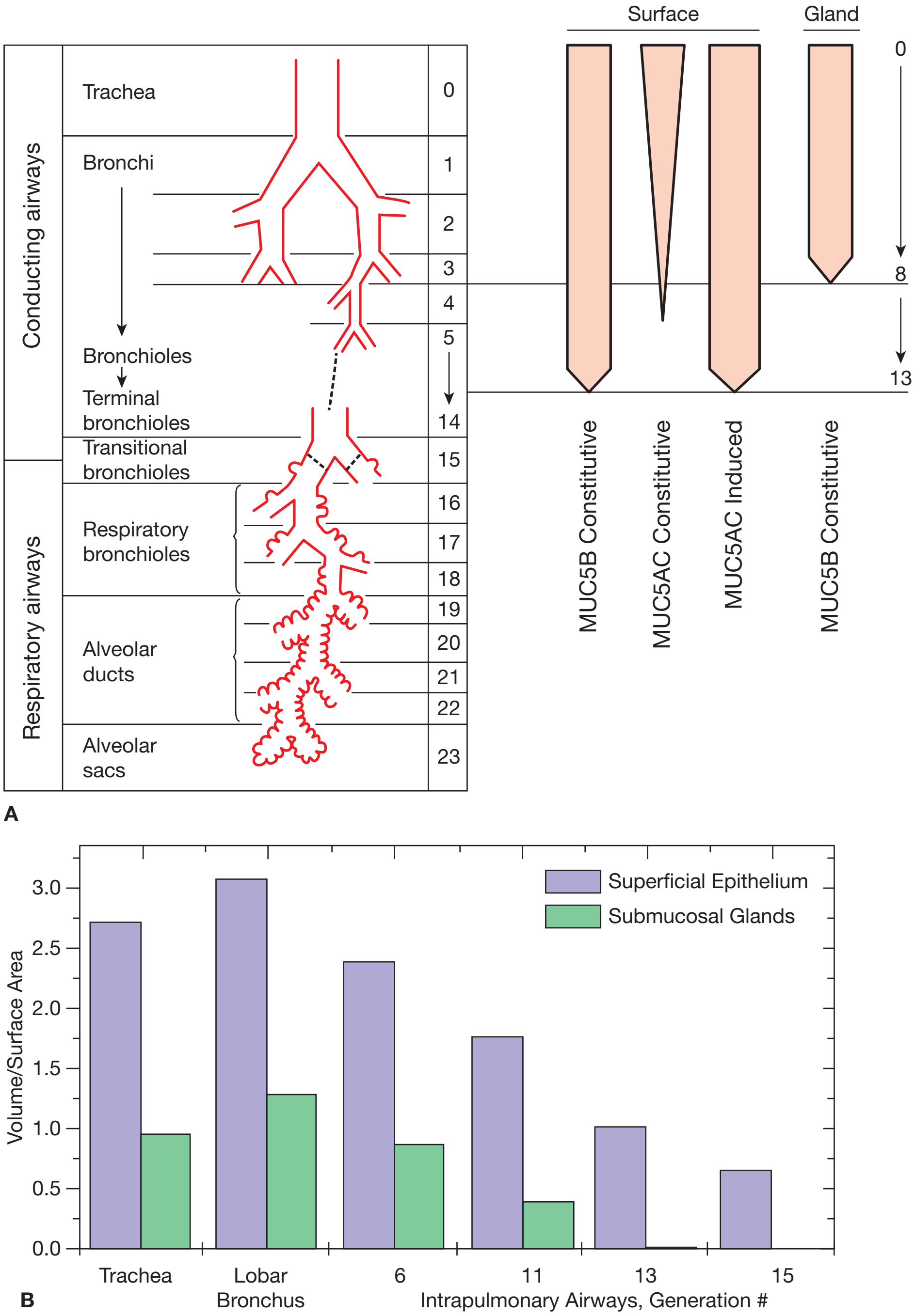


Figure 6-4 Mucin production in conducting airways. **A.** MUC5B is produced constitutively by surface epithelium down to the level of bronchioles proximal to terminal bronchioles, and by submucosal glands present in the trachea and bronchi but not bronchioles. MUC5AC is produced constitutively by surface epithelial cells with a goblet morphology in more proximal airways, and its production can be induced in nongoblet secretory cells that produce MUC5B down to the level of preterminal bronchioles. Airway generation is listed numerically in the third column. **B.** The relative amount of mucin produced by surface epithelium and submucosal glands has been estimated by morphometric analysis of the airways of rhesus monkeys stained with Alcian blue/PAS, expressed as the ratio of volume of stained material ($mm^3 \times 10^{-3}$) per unit area of basal lamina (mm^2). *(**A:** Modified with permission from Weibel ER: Morphometry of the Human Lung. Heidelberg: Springer-Verlag; 1963; **B:** Reproduced with permission from Plopper CG, Heidsiek JG, Weir AJ, et al. Tracheobronchial epithelium in the adult rhesus monkey: a quantitative histochemical and ultrastructural study, Am J Anat. 1989;184(1):31–40.)*

network of transcription factors has been identified that regulates MUC5AC expression, including STAT6, SPDEF, Foxa2, Foxa3, Notch, β-catenin, and XBP-1. While some components of the signaling pathways connecting extracellular ligands with transcriptional regulation are known, such as the key roles of STAT6 downstream of IL-13 and MAPK13 downstream of ClCa1,[30,34] other details remain to be elucidated. The regulation of MUC5B expression was less well studied until recently, reflecting its stable expression relative to MUC5AC. However, the discovery of MUC5B overexpression in interstitial lung diseases led to intensive analysis of its transcriptional control[35] (see "Interstitial Lung Diseases," below). Besides a core Sp1-dependent promoter,[36] there is a strong enhancer that interacts with FOX transcription factor family members and SPDEF, and is regulated epigenetically.[37] Along with production of the polymeric mucins themselves, specialized enzymes required for glycosylation (e.g., GalNAc-T),[38] folding and polymerization (e.g., AGR2),[39] and other aspects of mucin processing are produced by airway secretory cells.

Mucins are secreted into the airway lumen at a low basal rate and a high stimulated rate. A regulated exocytic mechanism mediates both rates as indicated by abnormal phenotypes in both basal and stimulated secretion when Munc13-2, a sensor of second messengers, is deleted in mice.[20] Additional molecular components of the exocytic mechanism have been identified and their functions studied (Fig. 6-6).[22,23,40,41] Of particular interest are the Munc18 proteins because Munc18a participates primarily in basal secretion whereas Munc18b participates primarily in stimulated secretion, indicating that distinct molecular machines mediate mucin secretion at low and high rates.[42] The rate of mucin secretion is regulated by the second messengers, calcium and diacylglycerol, which are generated by a signaling cascade downstream of G protein–coupled receptors that include the $P2Y_2$ purinergic and A3 adenosine receptors.[22,43,44] ATP is released in

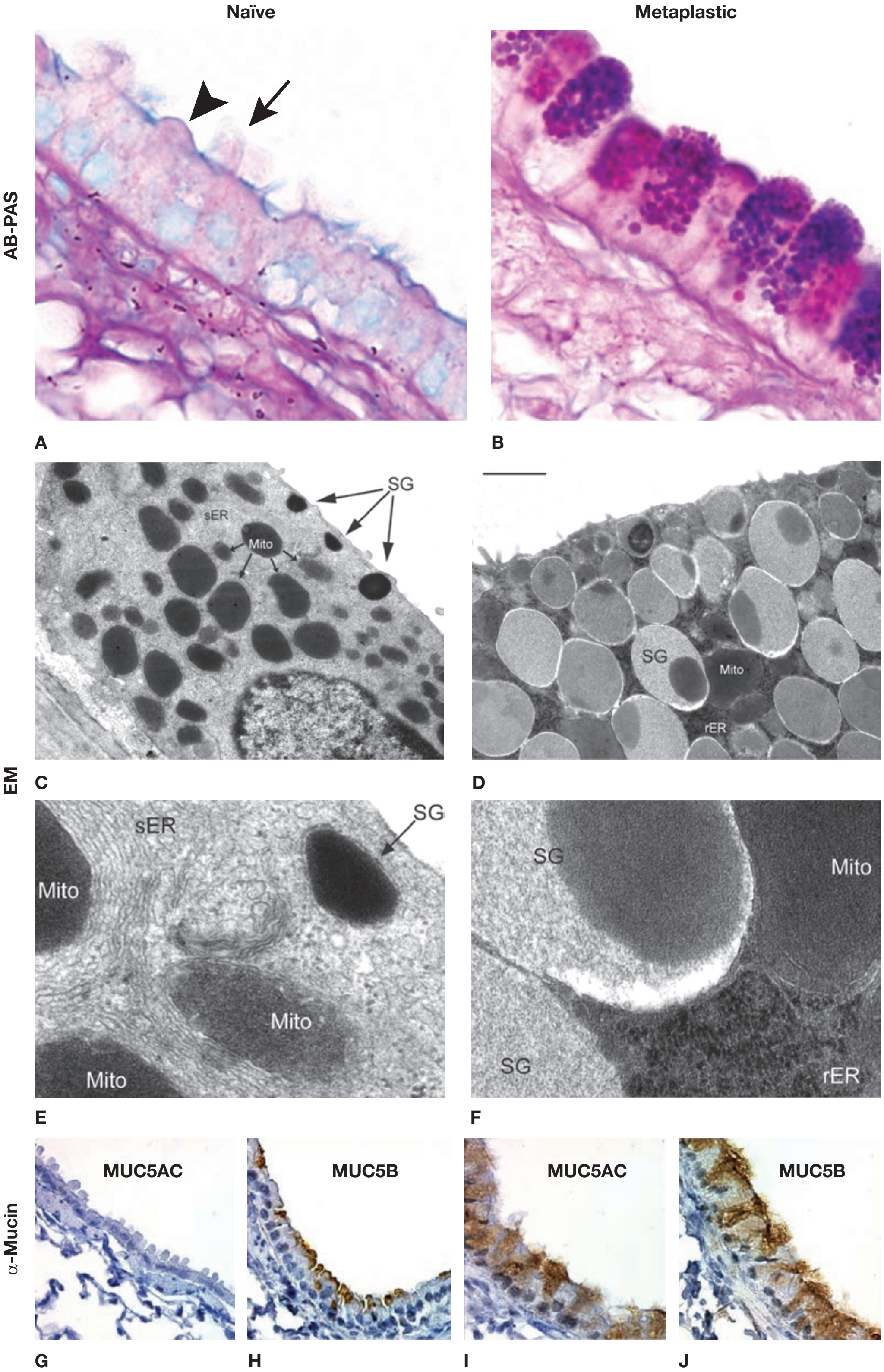


Figure 6-5 Airway epithelial mucus metaplasia. Light micrographs with AB-PAS staining (**A, B**), electron micrographs (EM) (**C–F**; low and high magnification), and immunohistochemical images using mucin-specific antibodies (**G–J**). On the left are images from the airway of a healthy mouse without airway inflammation (naïve), and on the right are images from the airway of a mouse with mucus metaplasia 3 days after the onset of allergic inflammation, as described by Evans et al.[19] Cells in the top row on the left show alternating ciliated *(arrow)* and domed secretory *(arrowhead)* cells, and on the right show prominent mucin granules in secretory cells. Cells in the EM images on the left show small numbers of electron-dense secretory granules (SG) near the apical membrane, numerous mitochondria (Mito), and abundant smooth endoplasmic reticulum (sER). Cells in the EM images on the right show numerous electron-lucent SG containing mucins and an electron-dense core, and abundant rough ER (rER). Images in the bottom row show that MUC5B is present in naïve airways even though it is not apparent by insensitive AB-PAS staining, and that both MUC5AC and MUC5B are present in the thickened metaplastic epithelium. Scale bar in the right middle panel is 10 μm for top row, 1 μm for second row, 150 nm for third row, and 30 μm for bottom row.

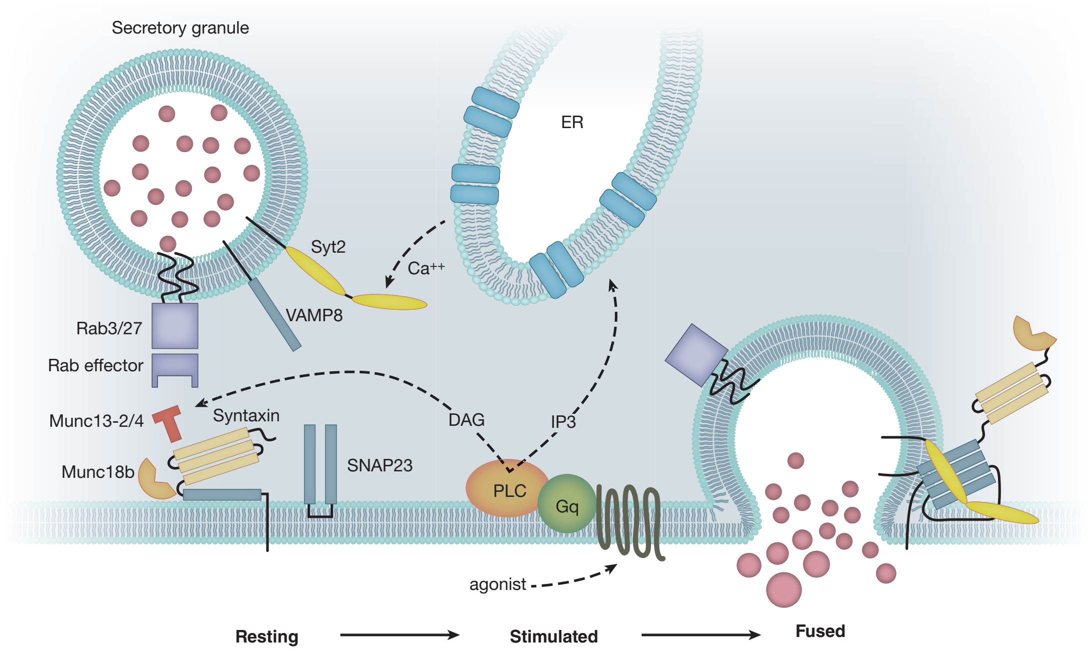


Figure 6-6 Airway mucin secretion. Initially, mucin granules become tethered to the plasma membrane by Rab proteins and their effectors in the vicinity of the exocytic SNARE proteins (VAMP8, SNAP23, and an unknown Syntaxin, shown as blue bars) *(Left)*. Activation of heptahelical receptors such as those for ATP (P2Y$_2$) and adenosine (A3R) leads to activation of the trimeric G-protein, Gq, and phospholipase C (PLC), resulting in generation of the second messengers diacylglycerol (DAG) and inositol trisphosphate (IP$_3$). Diacylglycerol activates the priming protein Munc13-2, and IP$_3$ induces the release of calcium from apical ER to activate Synaptotagmin-2 (Syt2) *(Center)*. Activation of the regulatory Munc13 and Syt proteins leads to full coiling of the SNARE proteins to induce fusion of the granule and plasma membranes. The interactions of the SNARE proteins take place on a scaffold provided by Munc18b *(Right)*. *(Adapted with permission from Davis CW, Dickey BF: Regulated airway goblet cell mucin secretion, Annu Rev Physiol. 2008;70:487–512.)*

autocrine and paracrine fashion, whereupon it activates P2Y$_2$ receptors and is metabolized to adenosine that actives A3 receptors. It is possible that additional ligands such as histamine and acetylcholine act as secretagogues during inflammation, although they may act indirectly by causing smooth muscle contraction and nucleotide release. Besides their release from intracellular stores by exocytic secretion, mucins can be degraded by autophagy upon cytokine withdrawal.[45]

Since secreted mucins must adsorb large volumes of water to yield mucus of normal viscoelasticity, it is important that adequate airway luminal water be available. The autocrine/paracrine ligands ATP, adenosine and ClCa1 regulate the expression and/or activity of CFTR, the calcium-activated chloride channel (CaCC) TMEM16A, and solute carrier family 26, member 9 (SLC26A9) to control chloride secretion.[30,43,46] Since these same ligands regulate mucin production and/or secretion as described above, mucin release is coordinately regulated with water translocation. Furthermore, recognition that CFTR is expressed predominantly in secretory cells in superficial epithelia suggests that mucin and ion secretion are coordinately regulated within a single cell,[24] with additional anion secretion in proximal airways provided by scattered ionocytes and submucosal glands. In small airways, longitudinal folds open and close during inspiration and expiration (Fig. 6-7). Mucin and ion

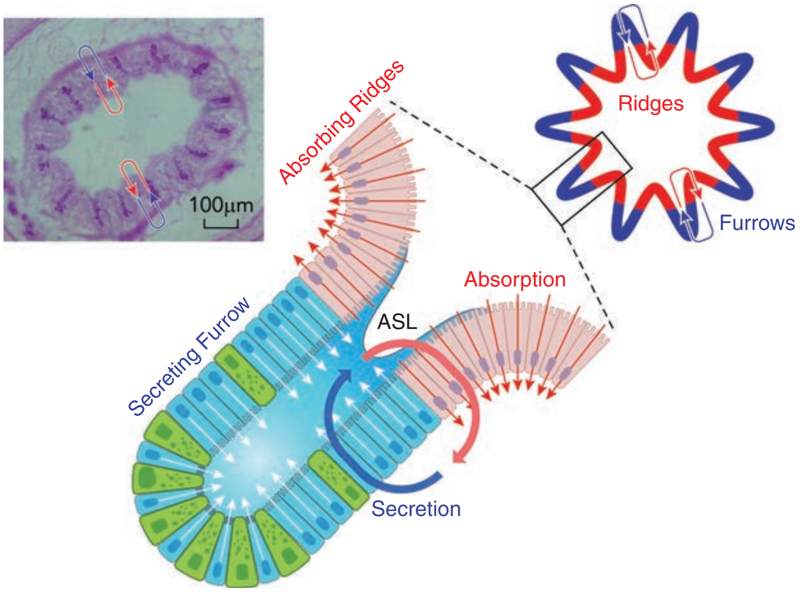


Figure 6-7 Fluid secretion and absorption in small airway folds. **(Top left)** Micrograph of a cross-section of a small airway stained with H&E and AB-PAS, showing numerous folds with mucin predominantly expressed at the base of furrows. Blue arrows indicate fluid secretion in the furrows, and red arrows indicate fluid absorption in the ridges. **(Top right)** Diagram schematizing the distribution of fluid secretion and absorption as in the micrograph. **(Bottom)** High magnification diagram of the same scheme as top right, with mucin secreting cells illustrated in green. *(Reproduced with permission Quinton PM. Both ways at once: keeping small airways clean. Physiology. 2017;32(5):380–390.)*

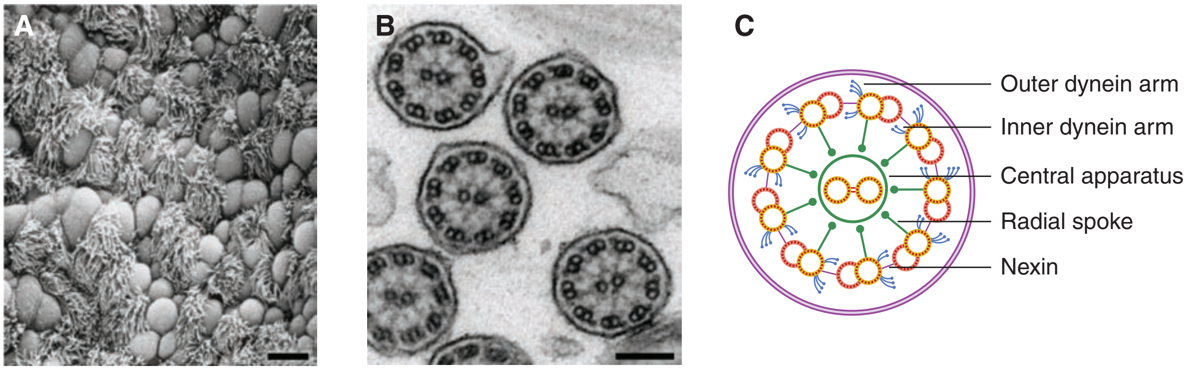


Figure 6-8 Cilia structure. **A.** Scanning electron micrograph of human tracheobronchial epithelial cells grown in primary culture, showing a mosaic of ciliated and secretory cells. Scale bar = 5 μm. **B.** Transmission electron micrograph through airway cilia of a cell in the same culture, showing the structure of the axonemes. Scale bar = 100 nm. **C.** Schematic diagram of the structural elements of a normal ciliary axoneme. *(Reproduced with permission from Thomas W. Ferkol, MD.)*

(with concomitant water) secretion are concentrated at the base of these furrows to form mucus of low viscoelasticity, while ion absorption is concentrated at the top of the ridges to prevent small airway flooding.[47] Identification of ion-secreting cells can be made either by expression of CFTR, which localizes to the apical membrane,[24] or by expression of the Na-K-Cl cotransporter, NKCC1, or the Na-HCO_3 cotransporter, NBC1, which localize to the basolateral membrane,[47] as these apical and basolateral ion conductances function in tandem.

Besides their role in mucin production and secretion, airway secretory cells serve as progenitors of both secretory and ciliated cells,[18,48] and express components of the cytochrome P450 system that inactivates toxic inhaled organic compounds by oxidation.[49] They also secrete antimicrobial peptides and reactive oxygen species at low levels constitutively, and are capable of sensing pathogens and responding by augmentation of their intrinsic antimicrobial defenses and signaling to leukocytes.[50]

Ciliated Cells

Motile cilia on the apical surface are the defining structural and functional feature of airway ciliated cells (Fig. 6-8) (Video 6-1). They are evolutionarily conserved and share homologous features with flagella of unicellular eukaryotes and mammalian sperm tails. Respiratory cilia have a “9+2” axonemal (microtubular) structure, which is composed of 9 peripheral doublets surrounding a central pair.[51,52] The outer doublets are linked together by proteins that form the dynein regulatory complex (“nexin link”), and radial spokes extend from the doublets to the central pair.[53] Taken together, these axonemal components provide the framework for generation of a complex ciliary waveform. The key components for driving ciliary movement are the inner and outer dynein arms, which are repetitive units present at regular intervals of 96 and 24 nm, respectively, along the length of the peripheral microtubules (doublets) and contain enzymes for ATP hydrolysis to generate force for dynein arm movement. Each cilium contains >300 different proteins and is rooted in the airway epithelial plasma membrane by a modified centriole, the basal body. Mutations in genes encoding many parts of the axonemal structure, or functional components of motile cilia, or components necessary for the biogenesis of cilia, including cytoplasmic proteins, can result in disease, including primary ciliary dyskinesia (PCD), as described below.

The function of normal motile cilia is to provide mucociliary clearance in the conducting airways, an important innate defense mechanism of the lungs.[54] Cilia provide the coordinated motive force for mechanically clearing mucus containing infectious agents, particles, and toxic substances from the conducting airways. ATP hydrolysis in the dynein arms produces sliding of adjacent axonemal structures and generates the complex ciliary waveform that occurs in human airways.[51,52] Approximately 200 cilia per cell beat in a coordinated fashion on and between cells. This coordinated vectorial synchrony results from the planar orientation that occurs during ciliogenesis, the tight packing of cilia in relation to large glycoproteins that coat their surfaces, longitudinal furrows in airways, and existing cilia-driven fluid flow.[13,47,55,56] The ciliary forward (power) stroke is more rapid and extends a bit more into the mucus layer than the recovery stroke.[55] Cilia beat at ~6–12 Hz, and propel mucus proximally at 1–5 mm/min. The regulation of ciliary beat frequency involves a variety of signaling molecules and multiple feedback mechanisms.[51,57] In brief, ciliary beat frequency and mucociliary clearance do not operate at full capacity under basal conditions but can be stimulated by several intracellular signaling mechanisms including cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) dependent phosphorylation of axonemal components, as well as changes in intracellular calcium and pH. In contrast, protein kinase C downregulates ciliary beat frequency. Infection or smoke exposure can negatively impact ciliary beating.[58]

Besides their role in moving the mucus layer, ciliated cells play additional crucial roles in airway homeostasis. They regulate mucin and fluid secretion by sensing multiple mechanical forces, including shear stress from airflow, stretch and compressive forces during inspiration and expiration, and cilial strain from interactions with overlying mucus of varying viscoelasticity.[59] Sensing these forces results in graded release of ATP from pannexin channels, which signals in a paracrine manner to neighboring secretory cells, both directly via $P2Y_2$ purinergic receptors and indirectly after metabolism via A2B and A3 adenosine receptors.[60] In addition, despite their terminal differentiation status, ciliated cells are capable of flattening to cover epithelial gaps when secretory cells are injured.[61]

Video 6-1 Lateral view of normal ciliary activity, using high-speed video microscopy. Note the full range of motion (forward and backward) and coordination of ciliary beating within and across ciliated cells. *Video available on AccessMedicine.com.*

■ Submucosal Glands

In bronchial airways, submucosal glands contribute to the secretion of mucins and liquid. The body of the gland is located between

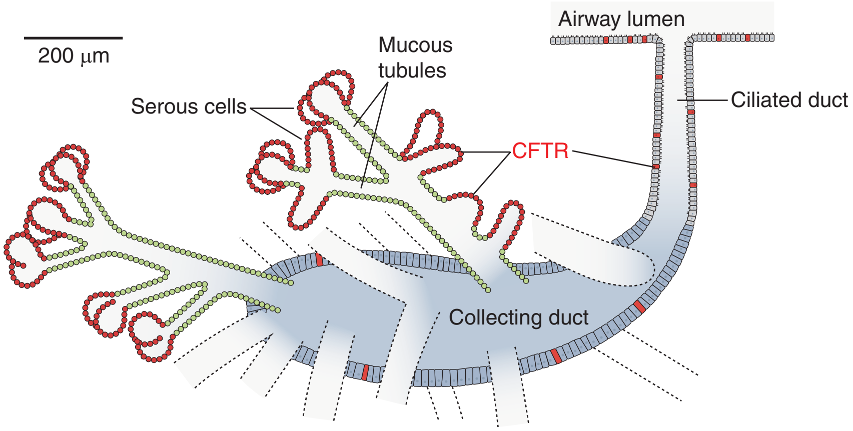


Figure 6-9 Diagram of a human bronchial submucosal gland. A single gland was reconstructed from serial cross sections. Only two of thirteen secretory tubules are illustrated, with the positions of the proximal portions of the others indicated by dotted lines. In the secretory tubules, serous cells expressing CFTR are shown in red, mucous cells are shown in green, and in the collecting duct, occasional ionocytes expressing CFTR are also shown in red. *(Reproduced with permission from Widdicombe JH, Wine JJ. Airway Gland Structure and Function. Physiol Rev. 2015;95(4):1241–1319.)*

spiral bands of smooth muscle and cartilage plates in the airway wall (Fig. 6-3). Each gland is connected to the airway lumen by a superficial ciliated duct that propels secretions outward and a deeper non-ciliated collecting duct[62] (Fig. 6-9). The body of the gland is composed of multiple mucous tubules that empty into the collecting duct, with serous cells that secrete fluid and antimicrobial peptides located in more distal acini. This spatial arrangement allows mucous cells, which constitute ~60% of the gland volume, to secrete mucins into a dilute, bicarbonate-rich liquid provided by serous cells, which constitute ~40% of the gland volume. Further anion secretion is provided by scattered ionocytes that express CFTR at high levels in the ducts.[24] Glandular mucous cells express MUC5B almost exclusively, with little or no expression of MUC5AC.[1,62] In pathologic states such as chronic obstructive pulmonary disease (COPD) and cystic fibrosis (CF), the volume and number of submucosal glands can increase several-fold while maintaining a normal ratio of mucous and serous cells.[63,64]

The rate of submucosal gland secretion can be greatly increased by cholinergic, adrenergic, and peptidergic stimulation. Recent work shows that mucus is released in strands from submucosal glands, and that these strands help clear large particles from the airway surface.[65,66] The importance of submucosal glands to mucociliary clearance of large particles and to defense against bacterial infection is indicated by studies in pigs that lack submucosal glands due to targeted deletion of ectodysplasin and to the presence of airway disease in humans who lack glands due to spontaneous mutation of genes in the ectodysplasin signaling pathway.[67] Besides their roles in clearance and antimicrobial defense, submucosal glands provide a protected niche for myoepithelial stem cells at the base of serous acini that can repopulate the surface epithelium as well as the submucosal gland after severe airway injury.[68]

■ Mucociliary and Cough Clearance

Mucus rises in the trachea by ciliary beating, then normally leaves the lungs by passing through the vocal cords to enter the pharynx and be swallowed (Fig. 6-1A). The vocal cords are covered by squamous epithelium that cannot provide a propulsive surface, but the posterior commissure is covered by mucociliary epithelium and is ideally situated adjacent to the esophagus.

Approximately 30 mL of respiratory mucus is normally propelled out of the lungs daily, carrying inhaled particles and pathogens that are excreted in the gastrointestinal tract.[69] Notably, mucins are required to provide sufficient viscoelasticity for cilia to propel the mobile airway surface liquid layer against gravity because an isotonic salt solution slides downward rather than rising upward.[17]

The rate of mucociliary clearance can be measured in different animal species by a wide variety of techniques. In rodents, the clearance from the lungs of polystyrene beads instilled through the trachea or measurement of the movement of beads in excised tracheas have been commonly used.[26,28] In pigs, the movement of inhaled tantalum microdisks in central airways has been observed by computed tomographic imaging.[70] In human subjects, direct bronchoscopic observation of the movement of instilled particles and external imaging of the movement of radiolabeled particles (scintigraphy) have been used. From a practical standpoint, only the latter is performed commonly, as follows. Small, radiolabeled particles, such as sulfur colloid labeled with technicium-99m, are inhaled, followed by serial imaging with a planar gamma camera.[69,71] The movement of labeled particles from peripheral to central lung regions over the course of several hours is then measured. This technique is used for the evaluation of both disease pathophysiology and the efficacy of therapeutic interventions.[71] Mucus velocity is highest in the trachea and decreases in more distal airway generations.[69] Different techniques yield different velocities, but these center around a mucus velocity of ~5 mm per minute in the trachea of a healthy young adult.

Cough clearance provides an important backup mechanism when mucociliary clearance is impaired. The effectiveness of cough depends upon sufficient muscle strength, glottic function, and airway caliber to generate high-velocity airflow.[72] Mucus can then be mobilized by the resulting shear force, either by overcoming adhesive bonds between mucus and the epithelial surface or by fracturing mucus cohesive bonds, though both mechanisms depend heavily on mucus concentration.[73] In small airways, airflow velocity is not sufficient to generate adequate shear force to mobilize mucus, consistent with the persistence of mucus plugs in small airways for years on CT imaging.[74–77] As can be done for mucociliary clearance, the rate of cough clearance in central airways can be measured by scintigraphy using standardized protocols of controlled coughs.[71]

Effective mucociliary clearance depends upon a mucus layer of appropriate viscoelasticity, a periciliary layer of sufficient depth, and effective ciliary beating. When these components are interacting optimally, particles and pathogens suspended in the 10,000 liters of air that are inspired daily are cleared from the lungs with minimal impact on the underlying epithelium. However, failure of any of these components can lead to cascading dysfunction that causes symptoms and contributes to disease pathogenesis.

MUCOCILIARY DYSFUNCTION IN DISEASE

The principal symptoms of mucociliary dysfunction are dyspnea and cough. Dyspnea is caused by reduction of the total cross-sectional area of the conducting airways from mucus occlusion. This occurs most commonly from diffuse plugging of small airways but may also occur when a central airway becomes obstructed by mucus due to an underlying anatomic abnormality. Cough is caused by the stimulation of vagal afferents in the intrapulmonary airways or larynx and pharynx. Patients often infer that laryngopharyngeal stimulation, described as "a tickle in the throat," results from postnasal drip because they recognize that mucus descends from the nasopharynx by gravity but are unaware it also ascends from the lungs by ciliary action. Physical signs of impaired mucus clearance include cough, bronchial breath sounds, rhonchi, and wheezes. Radiographically, retained mucus may appear as localized atelectasis or linear and branched opacities. It is important to recognize the role of retained mucus in disease presentation so that symptoms can be relieved and its contribution to disease progression addressed.

■ Asthma

The central role of diffuse airway obstruction by luminal mucus in fatal asthma (Fig. 6-10) has been recognized by pathologists for more than 100 years and confirmed in multiple subsequent autopsy case series.[78,79] Mucus occlusion is particularly dangerous in asthma because smooth muscle contraction around the luminal plugs further constricts airflow. The principal underlying cause of mucus dysfunction in asthma is mucin overproduction. This is usually driven by allergic inflammation mediated by IL-13,[80] although IL-17 also can cause mucin overproduction and airway hyper-responsiveness.[81–83] IL-13 can increase the production of MUC5AC in human airway epithelial cells in vitro 100-fold,[30,31] and the production of MUC5AC in the lungs of mice in vivo 40-fold.[32] In contrast, the production of MUC5B increases minimally or may even decrease.[32,84]

Mucus plugs in asthma often have a rubbery quality, suggesting that the large quantities of mucins that are produced overwhelm the available airway surface liquid when they are suddenly secreted in response to inflammatory stimuli. This abnormality can occur despite the additional hydration provided by SLC26A9 and ClCa1-dependent CaCC activity that are coordinately upregulated with MUC5AC production by IL-13.[30,46] Additional contributors to abnormal rheologic properties of asthmatic mucus are a high concentration of plasma proteins resulting from increased microvessel density and permeability in the airway wall,[85,86] and the presence of granule, cytoplasmic, and nuclear macromolecules from eosinophils and other leukocytes.

Recent work using CT imaging reveals a high prevalence of mucus plugs in distal airways associated with eosinophilia and airflow obstruction.[74] Remarkably, these plugs can persist for many months. The therapeutic focus in addressing mucus dysfunction in asthma should be reducing mucin overproduction and plasma extravasation through use of anti-inflammatory drugs. Corticosteroids have been the mainstay of treatment, but immunotherapies directed at IgE, IL-13, IL-5, and other inflammatory mediators play increasing roles. Mucin overproduction in non-eosinophilic asthma remains poorly understood and with inadequate treatment options. Further discussion of the pathogenesis and therapy of asthma is found in Chapters 43–45.

■ Cystic Fibrosis

Complications from the impaired clearance of airway mucus dominate the clinical course of patients with cystic fibrosis (CF).[4,87,88] An autosomal recessive disorder, CF is caused by mutations in CFTR, a 180-kDa anion channel (see Chapter 48). CFTR is expressed throughout the conducting airways on the apical surface of secretory cells, and in proximal airways it is also expressed at a high level in ionocytes.[24] In submucosal glands, it is expressed in serous cells and ductal secretory cells[24,62] (Fig. 6-9).

More than 1900 pathogenic CFTR variants have been described. These mutations cause an imbalance between salt and water absorption mediated by the epithelial sodium channel (ENaC) and secretion mediated by CFTR (Fig. 6-11), resulting in insufficient airway surface liquid and the formation of excessively concentrated mucus.[89] Defective CFTR function also causes deficient bicarbonate secretion that results in impaired mucin unfolding and reduced activity of antimicrobial peptides secreted by airway epithelial cells.[90] It causes deficient secretion of thiocyanate, which is normally oxidized by lactoperoxidase to form isothiocyanate, an antimicrobial effector of the innate immune system that is variably reduced in CF.[91]

Retained luminal mucus is apparent pathologically in small airways and glandular ducts early in life.[59] Biophysical properties of mucus scale with the third power of mucin concentration,[4] so seemingly modest increases in mucin concentration in CF result in dramatic increases in mucus viscoelasticity and adhesivity that impair ciliary and cough clearance.[92] Unlike asthma, in which increased MUC5AC predominates, the expression of both secretory

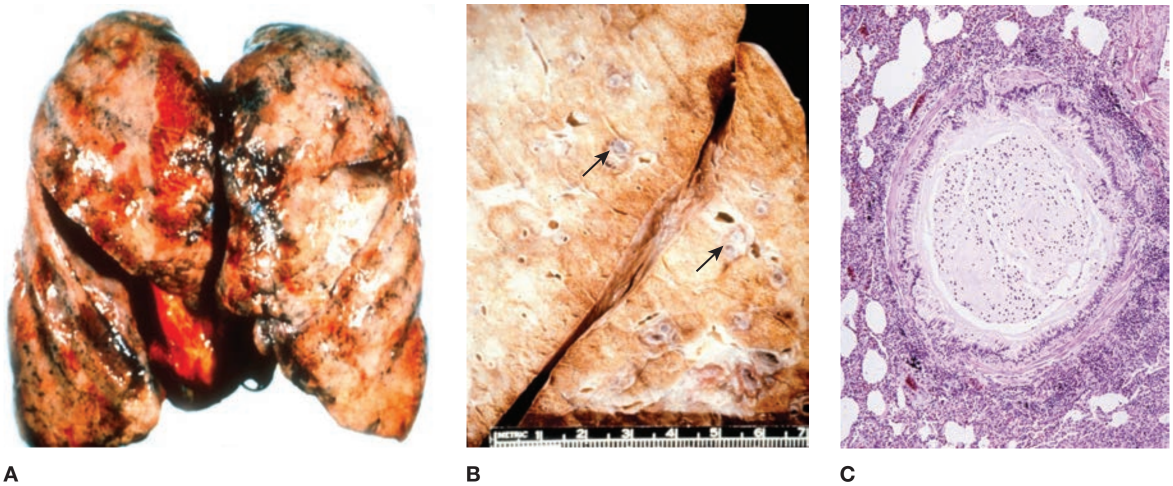


Figure 6-10 Airway obstruction by mucus in asthma. **A.** Lungs removed at autopsy from a patient who died from asthma. The lungs did not spontaneously collapse as they normally do because the airways were obstructed by lumenal mucus and bronchoconstriction. **B.** Cut surface of the lungs from the same patient showing mucus plugs *(arrows)* filling the large airways. **C.** Light microscopic image of a small airway from another patient who died from asthma showing infiltration of the airway wall and the lumenal mucus by inflammatory cells. *(**A, B:** Reproduced with permission from James C. Hogg, University of British Columbia; **C:** Reproduced with permission from Martha L. Warnock, University of California, San Francisco.)*

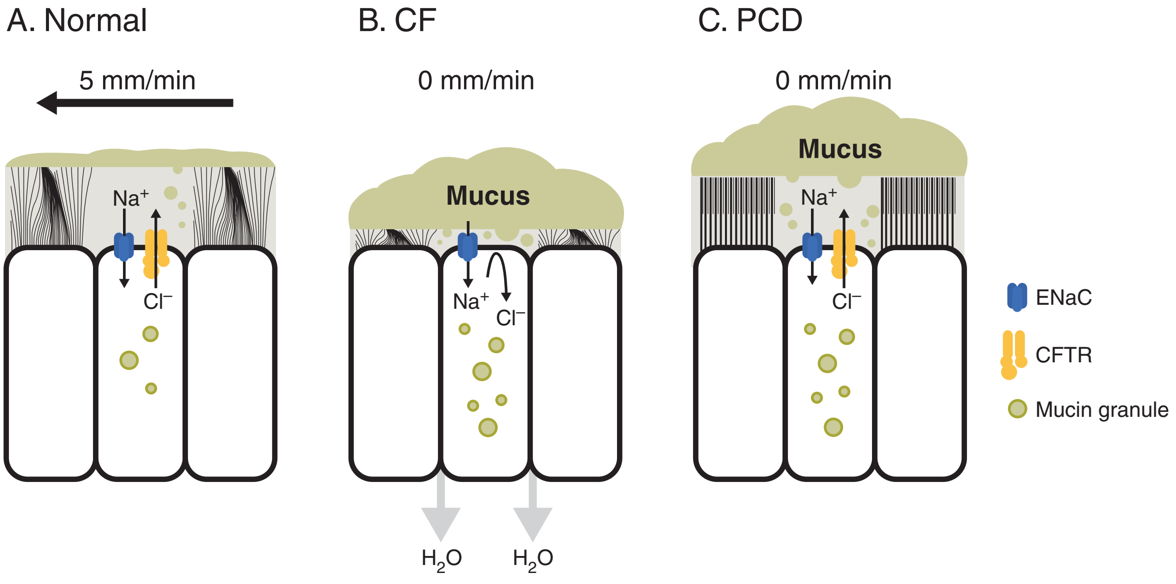


Figure 6-11 Mucus dysfunction in cystic fibrosis and primary ciliary dyskinesia. **A.** In a normal airway, balanced secretion of Cl^- and absorption of Na^+ result in a periciliary layer ~7 µm in depth, with motile cilia propelling overlying mucus towards the throat. **B.** In cystic fibrosis (CF), reduced secretion of Cl^- and increased absorption of Na^+ result in a periciliary layer of reduced depth such that cilia cannot propel overlying mucus, which accumulates and becomes adherent. **C.** In primary ciliary dyskinesia (PCD), cilia do not move normally and fail to propel overlying mucus. CFTR: cystic fibrosis transmembrane regulator; ENaC: epithelial sodium channel. *(Reproduced with permission from Thomas W. Ferkol, MD.)*

mucins, MUC5B and MUC5AC, is increased in the CF airway, driven by the inflammatory cytokine, IL-1β.[33] In addition, the presence of substantial amounts of DNA in CF mucus from necrotic neutrophils impairs ciliary clearance because the higher rigidity of DNA compared to mucins increases mucus viscosity even at low concentrations.[56] As disease progresses, the concentrated mucus layer draws water from the periciliary layer (Fig. 6-11), compressing cilia and making ciliary beating impossible.[13,16]

A porcine model has shown that tethered strands of mucus secreted by submucosal glands limits mucociliary clearance in the proximal airway.[93] These strands form because inadequate bicarbonate transport by mutant CFTR results in impaired mucin unfolding as it exits the gland duct.[6,8] Data from the newborn CF pig suggest that early defects in mucociliary clearance fail to clear inhaled bacteria even before the onset of airway inflammation.[94] This failure of mucociliary clearance results in airway colonization with bacteria and fungi, and paradoxically, the mucus gel layer and glandular secretions that evolved to protect the lungs from infection instead provide a protected environment for microbial growth.[4,87]

Aerosolized hypertonic saline solution, DNase, and antibiotics have become mainstays of CF therapy, while more recently, oral small molecule CFTR potentiators and correctors have had a dramatic effect in preventing disease progression.[1,4,87] Further discussion of the genetics, pathogenesis, and evolving therapy of CF is found in Chapter 48.

■ Primary Ciliary Dyskinesia and Other Motile Ciliopathies

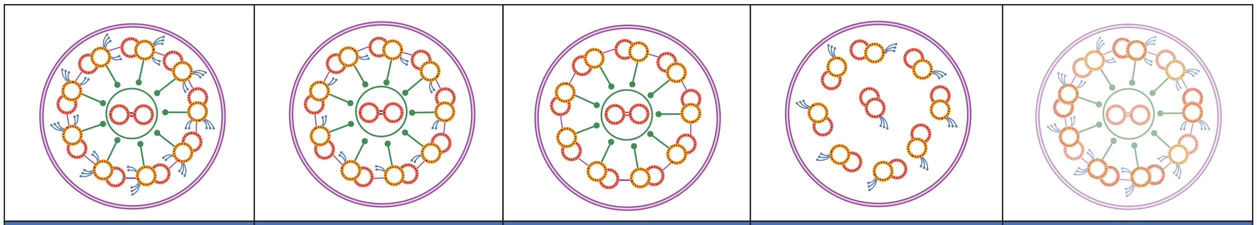
Primary ciliary dyskinesia (PCD) is a rare, genetically heterogeneous disease with an estimated prevalence of 1 in 10,000–20,000 live-born children.[95] It typically presents early in life, with many affected children presenting within 24 hours of birth and requiring supplemental oxygen or mechanical ventilation for days or weeks.[96] Most patients with PCD have daily, year-round "wet" or productive cough.[96] Abnormal lung function develops early, and intrathoracic airway obstruction can worsen with increasing age.[97] In contrast to CF, cough clearance is relatively preserved in PCD, which partially compensates for defective ciliary clearance (Fig. 6-11). However, the lower airway is still chronically infected, and bronchiectasis is common with predilection for the right middle lobe and lingula.[98]

Upper airway involvement is common, manifested as daily, nonseasonal rhinosinusitis with watery nasal discharge that begins under 6 months of age.[96] Middle ear involvement is nearly universal, with chronic otitis media with effusion, often associated with conductive and sensorineural hearing loss.[99] Roughly half of all people with PCD have left-right laterality abnormalities, including *situs inversus totalis* and heterotaxy syndromes that can be associated with congenital heart disease.[100] Male and female subfertility are other non-respiratory complications, related to sperm dysmotility and ciliary dysfunction in the fallopian tubes, respectively.[101] Rarer manifestations of PCD include prenatal hydrocephalus and blindness due to *RPGR* gene mutations.[102] Patients with PCD also have a higher prevalence of pectus excavatum and scoliosis.[103]

Historically, the diagnosis of PCD has been challenging due to limitations of diagnostic tests, but newer tools have emerged during the past decade. Nevertheless, clinicians should only perform testing in patients who have a clinical phenotype compatible with the disease.[95] When combined with established clinical criteria, nasal nitric oxide (nNO) measurement is an effective screening tool in patients 5 years and older.[104] Reduced nNO concentrations alone are never sufficient to make the diagnosis, as individuals with CF or primary immunodeficiencies can also have lower nNO levels.[105]

Transmission electron microscopy evaluation of the ciliary axoneme for ultrastructural defects has been used for over four decades, although this diagnostic approach can no longer be considered the "gold standard" because people with PCD can have "normal" axonemal structure. Four ultrastructural patterns have consistently been described in PCD: outer dynein arm defects (Video 6-2); inner and

Video 6-2 Lateral view of defective ciliary function in primary ciliary dyskinesia (PCD) associated with defective outer dynein arms (ODAs). Note the very limited range of motion, which gives the appearance of the cilia being "stiff." *Video available on AccessMedicine.com.*



Normal ultrastructure	ODA defect	ODA and IDA defect	IDA defect and MTD	Oligocilia
DNAH1	*DNAH5*	*DNAAF1 (LRRC50)*	*CCDC39*	*CCNO*
DNAH9	*DNAI1*	*DNAAF2 (KTU)*	*CCDC40*	*MCIDAS*
DNAH11	*DNAI2*	*DNAAF3*		*RPGr*[†]
DNAH17	*DNAL1*	*LRRC6*		*FOXJ1*[‡]
LRRC56	*NME8 (TXNDC3)*	*DNAAF5 (HEATR2)*		
HYDIN	*CCDC114*	*ZMYND10*		
CFAP221	*CCDC151*	*DYX1C1*		
SPEF2	*ARMC4*	*SPAG1*		
STK36	*TTC25*	*CFAP300 (C11orf70)*		
CCDC164 (DRC1)	*CCDC103*	*CFAP298 (C21orf59)*		
CCDC65 (DRC2)		*PIH1D3*[†]		
GAS8 (DRC4)				
RSPH1				
RSPH3				
RSPH4A				
RSPH9				
DNAJB13				
CFAP53 (CCDC11)				
TTC12				
OFD1				
GAS2L2[*]				
NEK10[§]				

[*] Disoriented cilia
[§] Shortened cilia
[†] X-linked
[‡] Autosomal dominant

Figure 6-12 Genes linked to motile ciliopathies and their associated ultrastructural findings. IDA: inner dynein arm; MTD: microtubule disorganization; ODA: outer dynein arm. *(Reproduced with permission from Thomas W. Ferkol, MD.)*

outer dynein arm defects; microtubular disorganization with inner dynein arm defects; and radial spokes and central apparatus defects (Figs. 6-8 and 6-12). Inner dynein arm defects alone are often artefactual and rarely associated with disease, leading to false-positive diagnoses. Approximately 30% of persons with primary ciliary dyskinesia can have normal or only subtle changes in axonemal structure.[106] Adopted by many European centers, high-speed video microscopy has become a diagnostic approach, in which motile ciliary beat frequency and patterns in freshly excised or cultured ciliated epithelia are qualitatively assessed. However,[106] this technique has not been fully standardized.[107]

Advances in gene discovery have transformed genetic testing, and it has become a viable, first-line diagnostic tool. Several molecular diagnostic companies offer commercially available gene panels. Primary ciliary dyskinesia is primarily an autosomal-recessive disease, but autosomal-dominant and X-linked inheritance patterns have been described. To date, nearly 50 genes have been linked to disease,[108] most encoding proteins involved in ciliary structure, regulation, or assembly (Fig. 6-12). More than 70% of all patients tested have biallelic mutations within one of these genes. PCD exists as a clinical spectrum, and genotype-phenotype associations have emerged. For example, studies have shown that children who have *CCDC39* or *CCDC40* mutations have more rapid pulmonary function decline, whereas people with *RSPH1* defects tend to have milder lung disease.[109,110]

New understanding of cilia genetics has also revealed motile ciliopathies distinct from classical PCD. For instance, people with biallelic mutations in *CCNO* have clinical features similar to PCD but lack cilia on airway epithelial cell surface.[111] Single mutations in *FOXJ1*, a transcription factor that regulates cilia gene expression, similarly reduce the number of motile cilia, and are clinically associated with hydrocephalus, recurrent respiratory infections, and laterality defects.[112]

While the pathogenesis of PCD has classically been considered purely a problem of mucus propulsion (Fig. 6-11), sputum from patients with PCD is hyperconcentrated, similar to CF. This suggests that strain-induced release of ATP by ciliated cells, which normally induces fluid secretion by secretory cells, also is defective, promoting mucus plaque and plug formation.[4] Also similar to CF, the airway microbiota is dominated early in the course of disease by anaerobes, with subsequent acquisition of classic bronchiectatic pathogens such as *Staphylococcus aureus*, *Haemophilus influenzae*, and *Pseudomonas aeruginosa*.[4]

Finally, no treatment has been shown to correct cilia function in patients with PCD. Management has largely been extrapolated from those used to treat other diseases with abnormal mucociliary clearance, like CF, relying on airway clearance techniques and systemic antibiotics to mobilize secretions and reduce the bacterial burden of the lower respiratory tract, especially during acute respiratory exacerbations.[113] A recent, multicenter clinical trial showed that thrice-weekly azithromycin resulted in modest reduction in frequency of respiratory exacerbations.[114] Otherwise, the effectiveness of inhaled antimicrobials, hypertonic saline, and mucolytics has not been adequately studied thus far.

■ Chronic Obstructive Pulmonary Disease (COPD)

A role for mucus dysfunction in COPD has long been recognized in the syndrome of chronic bronchitis, defined as a persistent cough that produces sputum for at least 3 months per year in 2 consecutive years. The productive cough probably results from mucus overproduction in proximal airways due to surface epithelial mucous metaplasia and submucosal gland expansion, combined with ciliary dysfunction.[1,115] More recently a second role for mucus dysfunction in COPD has been recognized in the widespread obstruction of small airways identified in pathologic analysis of resected surgical specimens[116,117] and by CT scan.[77]

The extent of small airway mucus occlusion correlates with the degree of airflow obstruction, occurs even in patients with an emphysematous phenotype, and predicts longevity. These two mucus phenotypes in COPD—productive cough and airflow obstruction—correlate only weakly.[115] These findings suggest that individuals have differential susceptibility to the effects of cigarette smoke on different aspects of mucociliary clearance, as well as reflecting the independent roles of emphysema and small airway fibrosis in airflow obstruction in COPD. Notably, smokers with preserved pulmonary function who nonetheless have symptoms of productive cough and dyspnea experience exacerbations and activity limitation and show CT evidence of airway disease.[118]

A unifying feature of the pathogenesis of muco-obstructive lung diseases, including COPD, is that mucus hyperconcentration results in a failure of transport and in mucus adhesion to airway surfaces.[4] In the mucus of subjects with severe COPD, the concentration of MUC5AC is increased 10-fold and the concentration of MUC5B is increased 3-fold.[119]

Mucus overproduction and ciliary dysfunction both result from exposure to toxic products in cigarette smoke and environmental pollutants. Among these products, acrolein is a particularly potent inducer of MUC5AC production.[68] In addition to increased mucin production resulting from acute extracellular signaling, surface epithelial progenitors epigenetically committed to a mucous metaplastic phenotype overgrow the airways of COPD subjects.[120] In ciliated cells, cigarette smoke causes both structural and functional changes.[121] Besides these effects, cigarette smoke also decreases airway surface liquid by reducing CFTR function and increasing ENaC function.[122] As is the case in CF, impaired mucociliary clearance results in persistent airway infection, particularly with unencapsulated *Haemophilus influenzae*. Further discussion of the pathogenesis and therapy of COPD is found in Chapters 38–40.

■ Interstitial Lung Diseases

A link between mucus dysfunction and interstitial lung disease was not suspected until a genome-wide association study in 2011 found genetic linkage between a polymorphism in the MUC5B promoter and both familial interstitial pneumonia (FIP) and idiopathic pulmonary fibrosis (IPF). The promoter variant was found in 50% to 60% of individuals with FIP or IPF compared with 19% of unaffected individuals and increased the risk of disease 7-fold in heterozygotes and 21-fold in homozygotes.[35] Subsequent studies have extended the association to other idiopathic interstitial pneumonitides[123] and subclinical radiographic interstitial abnormalities.[124]

The presence of the promoter variant is associated with improved survival among patients with IPF,[125] presumably because it is a less severe driver of disease than other susceptibility genes. The promoter variant causes substantial overexpression of MUC5B (up to 20-fold), particularly in distal airspaces including honeycomb cysts. Whether disease ensues because of mucus dysfunction in the airway lumen, an epithelial stress response induced by the demands of synthesizing such a large and complex molecule, or some other mechanism is not yet known with certainty.

The risk allele is almost exclusively found in Caucasians, and there is evidence of positive selection, possibly by protection against a respiratory infection, consistent with the finding that a thicker mucus layer due to transgenic MUC5AC expression protects mice against challenge with influenza virus.[12] Further discussion of the pathogenesis and therapy of IPF is found in Chapter 54. The same MUC5B overexpressing risk allele is found in other interstitial lung diseases, including those associated with collagen-vascular diseases and hypersensitivity pneumonitis. These are further described in Chapters 52, 56, and 58.

■ Other Diseases

As discussed below, a variety of other diseases are characterized by alterations in mucociliary clearance, including idiopathic bronchiectasis, allergic bronchopulmonary aspergillosis, viral respiratory infections, panbronchiolitis, localized anatomic abnormalities of the airways, and disorders notable for retained mucus.

Idiopathic Bronchiectasis

Idiopathic bronchiectasis is a morphologic term that describes irreversibly dilated bronchi in the absence of a monogenic airway disease such as CF or PCD.[126,127] It is most commonly a sequela of lung infection but may also be associated with a defect in host defense such as immunoglobulin deficiency, or an inflammatory disorder such as a connective tissue disease. While it is most commonly identified by dilated bronchi on a CT scan, pathologic studies have identified severe small airway disease with bronchiolectasis, mucus plugging, and inflammation, consistent with the airflow impairment that is commonly observed.[4] Similar to CF and PCD, persistent airway infection and retained purulent secretions dominate the clinical course. In addition to antibiotic therapy during exacerbations, treatment with aerosolized hypertonic saline has been shown to improve lung function and quality of life.[128] In contrast, inhaled recombinant human DNase resulted in greater pulmonary function decline and more pulmonary exacerbations.[129] Bronchiectasis is covered in further depth in Chapter 51.

Allergic Bronchopulmonary Aspergillosis (ABPA)

ABPA is an inflammatory complication of chronic airway diseases, such as asthma and CF. It manifests clinically with wheezing and cough refractory to standard therapies, and with migratory radiographic lung infiltrates. It is characterized by an intense immunologic response to surface colonization with the fungus *Aspergillus fumigatus*, and florid MUC5AC overproduction induced by the persistent fungal infection leads to mucus impaction, atelectasis, and central bronchiectasis. The diagnosis is based on typical clinical features, elevated serum quantitative immunoglobulin E concentrations, positive skin test to *Aspergillus fumigatus*, and elevated in vitro *Aspergillus*-specific IgE and IgG levels or precipitins. ABPA is addressed in greater detail in Chapter 46.

Viral Respiratory Infections

Viral respiratory infections commonly lead to acute mucociliary dysfunction because of a combination of injury to ciliated cells, increased mucin production, and reduced airway surface liquid from ENaC activation by proteases.[4] Moreover, an acute respiratory viral infection can induce chronic lung disease through persistent overexpression of MUC5AC resulting from an IL-33—IL-13 signaling loop.[130] Viral infections of the respiratory tract are further discussed in Chapter 126 and in the previously noted chapters on asthma, COPD, and CF.

Panbronchiolitis

Panbronchiolitis is a syndrome of small airway inflammation and mucus obstruction that occurs predominantly in Asian subjects. It was reported to be associated in some cases with a polymorphism in the MUC5B promoter,[131] although a molecular mechanism of mucin gene dysfunction has not been identified. Further discussion of bronchiolitis can be found in Chapter 49.

Localized Anatomic Abnormalities

Localized anatomic abnormalities of the airways, such as the presence of a stricture, a surgical anastomosis, or a therapeutic stent, can result in mucus accumulation, obstruction, and atelectasis. It may be possible to remove the localized mucus accumulation by flexible or rigid bronchoscopy, and instillation of sodium bicarbonate solution may partially dissolve the mucus. Interventional bronchoscopy is reviewed in detail in Chapter 34.

Retained Mucus

Retained mucus is a common problem in intubated patients and those in whom lung mechanics are disrupted as a result of paralysis, immobilization, or surgery.[1] Atelectasis and pneumonia are frequent complications in such patients. Endotracheal and tracheostomy tubes impede generation of the high intrathoracic pressures required for effective cough clearance, endotracheal tubes block the path for normal mucociliary clearance through the posterior commissure of the glottis, and both types of tubes damage the mucosa and cause inflammation.[72] Effective endotracheal suctioning and subglottic secretion drainage can help prevent atelectasis and pneumonia, as discussed in Chapter 129 on Nosocomial Pneumonia, Including Ventilator-Associated Pneumonia.

In patients who have ineffective cough due to central nervous system injury or progressive neuromuscular disease, manually or mechanically assisted coughing is very helpful.[132,133] The roles and details of these techniques are further reviewed in Chapter 84. Postoperatively, early mobilization and deep breathing exercises or incentive spirometry are widely used despite the low quality of existing evidence of effectiveness.[134] These and other perioperative considerations are further discussed in Chapter 102.

■ Treatment

Therapies for mucus dysfunction can be classified into those that address mucin production, mucin secretion, mucin autophagy, mucus clearance, or airway infection.[1,135] Validated therapies in current use are described in the sections on specific diseases, above. Here, we review strategies in development.

Mucin Hyperproduction

Mucin hyperproduction is currently treated with agents designed to treat upstream signaling pathways, particularly in allergic asthma as described above. Additional signaling pathways under investigation are Notch and MAPK13.[135] Targeting mucin gene expression directly is under preclinical and clinical investigation. In view of the generally pathologic role of MUC5AC and the generally homeostatic role of MUC5B, strategies that selectively target MUC5AC production are attractive. Nonetheless, limited reduction of MUC5B overexpression in IPF or CF could also have therapeutic value. For both MUC5AC and MUC5B, careful assessment of their pathologic and protective roles will be required to optimize the therapeutic ratio of any intervention. Besides these pharmacologic strategies, ablation of mucous metaplastic surface epithelial cells by physical techniques including abrasion, cryospray, and pulsed electrical fields is under investigation.[136]

Mucin Secretion

Inhibiting mucin secretion may seem to be an obvious strategy to treat combined overproduction and secretion ("mucus hypersecretion"). However, it may not be possible to selectively target secretion of MUC5AC because it is packaged together with MUC5B in mucin granules. Nonetheless, the therapeutic value of selectively targeting stimulated mucin secretion, which causes airway occlusion, while leaving basal secretion intact, which mediates protective mucociliary clearance, has been demonstrated in mice.[42]

Autophagy

Recently, it was demonstrated that hyperproduced mucins can be degraded intracellularly by autophagy rather than being secreted.[45] Since autophagy can be activated by mTOR inhibition using drugs that are currently available, such as sirolimus and other rapamycin analogs, this presents another strategy that could reduce mucus hypersecretion.

Mucus Clearance

Treatments that promote mucus clearance include physical measures to remove retained secretions and pharmacologic agents to improve mucus rheology. Historically, physical measures were used extensively in CF, but perhaps less with the advent of highly effective CFTR potentiators and correctors. Physical measures remain in use to aid in the clearance of retained mucus as described above. Drugs that effectively improve mucus rheology in specific settings include inhaled dornase alfa, inhaled hypertonic saline solution, and systemic CFTR modulators, as indicated in the sections on specific diseases above. In addition, inhibitors of ENaC and potentiators of chloride channels other than CFTR are being developed.[135]

Mucolytics reduce mucus viscoelasticity by reducing disulfide bonds within and between mucin monomers. In the past, multiple trials of N-acetylcysteine failed to show benefit, probably reflecting its low reducing power and its cellular toxicity at therapeutic concentrations. However, these limitations are being overcome by multiple drugs in development that hold great promise.[135,137] Another strategy to reduce mucus viscoelasticity is by altering mucin ionic interactions.[138]

Antibiotics

For the treatment of infected airway mucus, a variety of inhaled, oral, and intravenous antibiotic regimens have been shown to have utility in specific situations, particularly in CF, PCD, COPD, and idiopathic bronchiectasis.[1,4]

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CHAPTER 7

The Genetic Basis of Respiratory Disorders

Micheala A. Aldred

INTRODUCTION

The field of genetics and genomics continues to advance at an incredible pace since the completion of the Human Genome Project. Now, thanks to rapid advances in sequencing technology and bioinformatics, we have sequenced hundreds of thousands of genomes from around the world, uncovering great genetic diversity and challenging us to understand the biologic relevance. Sequencing the exome (the protein-coding parts of the genome) of a patient with an undiagnosed condition as part of their clinical evaluation is now commonplace, although distinguishing the causative genetic change from the myriad other nonpathogenic variants remains challenging. As other technologies develop, we increasingly look beyond our DNA sequence to understand the regulation and function of the resulting RNA (transcriptome) and proteins (proteome) it encodes, integrating these layers to understand complex biological networks in health and disease. Even beyond human genetics, genomic technologies are making an enormous impact on pulmonary disease. In 2020, as the COVID-19 pandemic emerged, the SARS-CoV-2 virus was quickly sequenced and shared, in the spirit of open science pioneered by the Human Genome Project. Existing bioinformatic networks that already tracked other pathogens, such as influenza, were repurposed to disseminate the latest knowledge on the evolution of the virus as it spread around the world. Knowing the sequence, understanding its relation to other coronaviruses, and modeling the structure of viral proteins has been pivotal in enabling the development of vaccine candidates in record time. Against this backdrop, this chapter on the genetics of lung diseases could easily be out of date before it is even in print. Thus, it does not seek to be encyclopedic, but rather gives the reader a grounding in the principles of human genetics, an overview of current knowledge in Mendelian lung diseases, and a summary of recent progress in understanding genetic factors contributing to common lung conditions. The chapter outlines some of the emerging roles of epigenetic modifications and aims to give a vision of where the field is moving, concluding with exciting advances and prospects for genetically targeted therapies.

PRINCIPLES OF HUMAN GENETICS

The sections below review the basics of genome organization, structure, and mutations; basic principles of inheritance; and mitochondrial mutations.

Genome Organization

The term *genome* refers to the genetic makeup of an organism (Table 7-1). Mammalian genomes are composed of deoxyribonucleic acid (DNA) and can be subdivided into a nuclear genome—DNA within the nucleus of each cell—and a separate circular genome housed within each mitochondrion. DNA has a double-helix structure. Each strand comprises four constituent bases—adenine (A), cytosine (C), guanine (G), and thymine (T)—that pair together, A with T and G with C. DNA needs to be replicated every time a cell divides. This strict base pairing ensures accurate copying of the DNA code.

The human genome is approximately 3.3 billion base pairs in size. This large amount of DNA is wound around proteins known as histones, then packaged into higher-order structures called chromosomes that can be visualized under a light microscope. Most cells of the body contain two copies of each chromosome, one inherited from each parent, and are termed *diploid*. Diploid cells contain 23 pairs of chromosomes. During meiosis, these pairs of chromosomes are separated, giving rise to oocytes and sperm that contain a single copy of each chromosome (termed *haploid*). Thus, fusion of two haploid gametes gives rise to a new diploid organism, preserving the correct copy number of DNA through the generations. Sex is determined by a pair of sex chromosomes, X and Y; females have two copies of the X chromosome, whereas males have one each of X and Y. The other 22 pairs of chromosomes are known as the autosomes. Genetic diseases are mainly caused by mutations in autosomal or X chromosome genes; the Y chromosome harbors only a few genes, and these are mainly involved in determining male characteristics.

Gene Structure

Only about 1% to 2% of the human genome actually encodes for proteins. The noncoding portion was originally considered to be junk DNA, but it is now increasingly clear that some of it has important regulatory functions. The protein-coding units are called genes. The DNA within a gene is first transcribed into ribonucleic acid (RNA). RNA has a similar base structure to DNA, but it is single stranded, it has a slightly different sugar backbone, and thymine (T) is replaced by uracil (U). Genes are typically divided into coding exons and intervening noncoding introns. The intronic sequences are spliced out of the initial RNA transcript to produce the mature messenger RNA (mRNA) molecule. Some genes have alternative splicing patterns that can give rise to slightly different variants ("isoforms") of the protein. The mRNA is then translated into protein by ribosomes. Ribosomes read the RNA code as a triplet of bases or "codon" and add the corresponding amino acid to the growing protein chain. There is some redundancy in the genetic code, and amino acids may be encoded by several different codons. Four codons have a special function: AUG encodes methionine and always marks the initiation site for protein translation, while UGA, UAG, and UAA are stop signals that lead to termination of translation. The DNA flanking the coding region of a gene is not translated but contains important regulatory elements, including the promoter region that regulates transcriptional activity.

Classes of Mutations

Alterations in the DNA sequence occur when there is an error in DNA replication prior to cell division or DNA damage occurs through environmental exposures such as UV radiation or tobacco smoke. Such mutations may affect a single base (known as a point mutation) or may involve the insertion or deletion of multiple bases. Cells have an extensive DNA repair mechanism that will correct most of these mutations, but any that escape may lead to a permanent change in the sequence that is propagated to daughter cells. Mutations in noncoding regions of the genome often have no detrimental effect, and over time they may become quite common in the population. Variants that are present at a frequency of greater than 1% are known as polymorphisms and have been widely used in genetic mapping studies. Thus, the two copies of a gene in any individual are subtly different at the DNA sequence level. These variant forms are known as "alleles." However, mutations that occur in the introns of genes may lead to disease, especially if they disrupt the highly conserved splicing signals immediately flanking an exon.

TABLE 7-1 Glossary of Genetic Terms

Genome	The complete genetic makeup of an organism, including all coding and noncoding DNA
Gene	A discrete protein-coding unit within the genome. Genes are typically subdivided into exons (blocks of protein-coding DNA), introns (intervening noncoding DNA), and flanking regulatory regions
Exome	The entire sequence of all exons within the genome
Somatic	Relating to any cell of the body other than the germ cells. Mutations in somatic cells cannot be passed on to the next generation
Chromosome	A higher-order structure into which DNA is packaged. Humans have 23 pairs of chromosomes, 22 autosomes, and a pair of sex chromosomes, X and Y, that determine sex
Telomere	The cap at the ends of each chromosome, composed of hundreds of copies of the repeat sequence TTAGGG
Diploid	Containing a full complement of 23 chromosome pairs. All normal somatic cells are diploid
Haploid	Having only a single copy of each chromosome. Mature gametes are haploid, ensuring that a new zygote has the correct chromosome complement
Aneuploid	Cells that have a nondiploid number of chromosomes due to gain or loss of one or more chromosomes during cell division. Aneuploidy commonly occurs in cancer cells, which may become highly abnormal as the tumor progresses
Mutation	Strictly, any change that occurs in the DNA sequence; in relation to genetic diseases, the term is mainly used to refer to changes that have a deleterious clinical effect
Polymorphism	A genetic variant present at a frequency of at least 1% in a given population, often used synonymously with mutations that have no adverse effect
SNP	Single nucleotide polymorphism: a polymorphism resulting from a single DNA base substitution
Allele	Referring to a specific version of a gene, often used to distinguish between the copies inherited from each parent, or between wild-type and mutant copies
Heterozygote	An individual with one wild-type allele and one variant
Homozygous	An individual with two copies of the same variant allele. In autosomal recessive diseases where an individual inherits two different mutations, one from each parent, the term "compound heterozygote" is used
Genotype	The genetic sequence of the two alleles at a particular gene location
Phenotype	The clinical manifestation of genetic change
Dominant	A mutation that exerts a phenotypic effect in heterozygous form
Recessive	A mutation that is masked by the wild-type allele in a heterozygote and only results in a phenotype when wild-type function is lost
Penetrance	The likelihood that an individual with a mutation will develop clinical disease
Heterogeneity, allelic	The presence of different pathogenic mutations in same gene across different individuals. Most genetic diseases show allelic heterogeneity, unless they are caused by gain of an abnormal function that is only conferred by one specific mutation (e.g., sickle cell disease)
Heterogeneity, genetic	Diseases for which a mutation in one of several different genes can lead to the same clinical phenotype
Heritability	The proportion of trait variance that can be attributed to genetic factors versus the environment
Haplotype/haplogroup	A specific combination of SNPs on a contiguous piece of DNA. *Haplotype* is used when defining the arrangement of SNPs on an individual chromosome; *haplogroup* refers to groups of ancestrally related variants in mitochondrial genome
Genetic anticipation	A phenomenon in which the age of onset of an autosomal dominant disease becomes earlier with each successive generation. It is most often observed in a group of neuromuscular diseases caused by a unique class of DNA-repeat mutations, but also occurs in familial pulmonary fibrosis associated with telomerase mutations
Imprinting	Epigenetic silencing of an allele based on its parental origin. Relatively few genes are imprinted, but those that are give rise to unusual patterns of inheritance, as the mutation is masked when present on the silenced allele

Within the coding region of a gene, the consequence of a point mutation depends on whether it alters the genetic code (Fig. 7-1). Most redundancy lies in the third base of the codon, so, for example, a change from GGG to any of GGA, GGC, or GGU still encodes glycine and would not change the sequence of the protein. Such changes are usually silent and may become common polymorphisms. Mutations that lead to an amino acid substitution, for example UGU (cysteine) to UAU (tyrosine), are known as missense mutations. Their effect on protein function depends much on the specific structure and function of that protein. In general, missense mutations in regions that are functionally critical, such as the catalytic domain of an enzyme, will be highly deleterious. These regions are often highly conserved across species, indicating that mutations have not been tolerated during evolution. Missense mutations that affect residues important in secondary structure and protein folding also are likely to have adverse effects, whereas mutations in linker regions may be less critical. Thus, interpreting the consequences of genetic changes requires an in-depth knowledge of the protein concerned.

Mutations that lead to premature truncation of a protein are highly likely to be pathogenic and are a major cause of inherited diseases. Several different types of mutation can lead to premature protein truncation. Nonsense mutations result from a single base change that introduces a stop codon earlier than the natural translation endpoint, for example, AGA (arginine) to UGA (stop). Small insertions and deletions also can introduce premature stop codons because if the number of bases added or lost is not a multiple of three, the reading frame for the triplet codon is offset and it is read incorrectly. This is known as a frameshift mutation

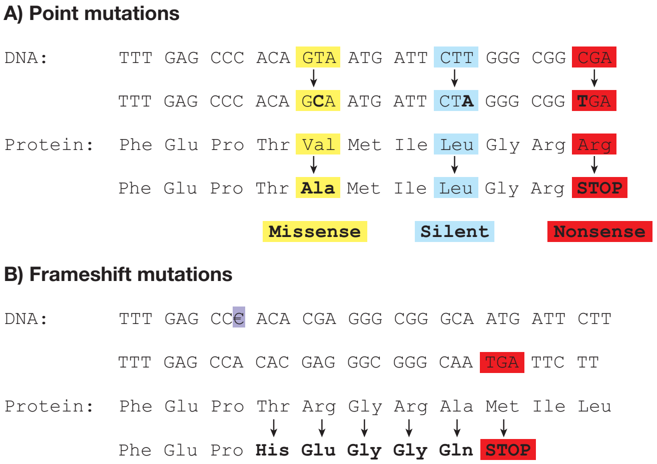
A) Point mutations
DNA: TTT GAG CCC ACA GTA ATG ATT CTT GGG CGG CGA
TTT GAG CCC ACA GCA ATG ATT CTA GGG CGG TGA
Protein: Phe Glu Pro Thr Val Met Ile Leu Gly Arg Arg
Phe Glu Pro Thr Ala Met Ile Leu Gly Arg STOP
Missense
Silent
Nonsense
B) Frameshift mutations
DNA: TTT GAG CCG ACA CGA GGG CGG GCA ATG ATT CTT
TTT GAG CCA CAC GAG GGC GGG CAA TGA TTC TT
Protein: Phe Glu Pro Thr Arg Gly Arg Ala Met Ile Leu
Phe Glu Pro His Glu Gly Gly Gln STOP

Figure 7-1 Classes of genetic mutations. **A.** Single base changes within an exon may lead to premature protein truncation (nonsense mutation, shaded in red), or an amino acid substitution (missense mutation, yellow), or there may be no change due to redundancy in the genetic code (silent, blue). **B.** Insertions or deletions lead to frameshift mutations if the number of bases involved is not divisible by three. This almost invariably leads to premature protein truncation downstream of the mutation site. In this example, deletion of a single G (shaded gray) changes the amino acid sequence and quickly ends with a STOP codon.

(Fig. 7-1). Splice-site mutations can lead to retention of an intron, which does not normally code for a protein and, therefore, often contains a stop codon. Alternatively, splice-site mutations can lead to exon skipping and again, if the size of the missing exon is not a multiple of three bases, this leads to a downstream frameshift, in addition to losing a whole exon of sequence. The presence of a premature stop codon often triggers a process known as nonsense-mediated mRNA decay (NMD), which leads to degradation of the nonsense-containing mRNA transcript, preventing translation of a truncated protein. This protects the cell from potentially adverse effects of an abnormal protein product. The mechanisms underlying NMD are not fully understood, and some transcripts are degraded more efficiently than others. Nonsense mutations in the last exon of a gene do not trigger NMD, due to their proximity to the natural stop codon, whereas mutations in the first exon, close to the translation initiation codon, may lead to re-initiation at a downstream ATG site.

The last major class of mutation is gene rearrangements, large deletions, or duplications that affect one or more exons. These mutations can be missed by sequence-based methods of DNA analysis and require specialized methods that measure the copy number of DNA across the gene. They typically lead to major disruption of the gene structure, and any protein that may be produced is likely to be nonfunctional.

■ Modes of Inheritance

The pattern of inheritance of a genetic disease within a family is determined by the location of the mutation—on an autosome, the X-chromosome, or in the mitochondrial genome—and whether a clinical effect (phenotype) is evident when only one copy of the gene is mutated. When mutation of a single allele is sufficient to cause disease, it is known as dominant because the mutation is sufficient to overcome the positive effect of the remaining wild-type allele. Genes that are affected by dominant mutations are typically very sensitive to the 50% reduction in gene dosage that results from inactivating one allele. Alternatively, the mutation may cause an abnormal gain of function, or create an abnormal protein that in turn interferes with the function of the wild-type protein, an effect known as dominant negative. In contrast, recessive mutations have no detrimental effect when only one allele is mutated. The remaining wild-type allele is sufficient to maintain normal gene function, and a clinical phenotype is apparent only when both alleles are inactivated, and the gene function is completely lost. Individuals with a personal or family history of genetic disease should be offered genetic counseling to help them understand their risks and options, and to facilitate appropriate genetic testing.

Autosomal Dominant

Autosomal dominant mutations result in a strong pattern of disease in each generation of a family (Fig. 7-2A). An individual with such a mutation has a 50% chance of passing the disease on to each of their children. The hallmarks of autosomal dominant inheritance are approximately equal proportions of males and females affected by the disease and the presence of male-to-male transmission. However, several factors can complicate this model. Some dominant diseases may skip a generation, due to reduced penetrance (Fig. 7-2B). The penetrance of a mutation is defined as the likelihood that someone with the mutation actually develops the disease. If the penetrance is less than 100%, then an individual who inherits the mutation may escape the disease themselves, while still being at 50% risk of passing it on to their children. Independently, the gender ratio may be skewed by environmental and/or genetic modifying factors. The most extreme example is inherited diseases affecting sex-specific organs. For example, ovarian cancer may be inherited in an autosomal dominant manner, but only females with the mutation actually develop the disease.

Autosomal Recessive

The pattern of inheritance of autosomal recessive diseases is quite different. Individuals with a single copy of the mutation are known as carriers or heterozygotes. Since there is no clinical effect, such individuals are usually unaware of their status. However, when both parents are carriers, each has a 50% chance of passing on the mutation, meaning there is a 25% chance that a child will inherit two copies of the mutation and be affected by the disease. Consequently, autosomal recessive diseases often appear "out of the blue" in a family with no previous history of the condition (Fig. 7-2C). The incidence of recessive diseases largely depends on the heterozygote frequency in the population, but the risk increases in consanguineous families.

X-Linked Inheritance

X-linked diseases are caused by mutations in genes on the X-chromosome. Most are recessive, but the different sex-chromosome constitution between females and males, XX versus XY, leads to a unique pattern of inheritance. Males who inherit an X-linked mutation have no wild-type allele on the Y-chromosome to mask its effect, and consequently they develop the disease. Female carriers are generally unaffected, as for autosomal recessive diseases. Thus X-linked diseases are passed through the female line and typically affect only males (Fig. 7-2D). A female carrier has a 50% chance of an affected son. Importantly, males cannot pass the mutation to their sons, so evidence of male-to-male transmission rules out X-linked inheritance; however, all their daughters will be carriers.

Females only have a single X-chromosome active in any given cell, due to a process of X-inactivation in early embryonic development that adjusts the dosage of X-linked genes to be the same as in males. If X-inactivation is random, approximately half of cells in a carrier will express the wild-type allele and half express the mutation, meaning that female carriers usually have no phenotype or are only mildly affected. However, if X-inactivation is highly skewed toward expression of the mutant allele, then female carriers may be as severely affected as males. Rarely, X-linked mutations may be dominant, meaning that all females who inherit the mutation will be affected. Such mutations are often lethal in males. Examples of X-linked recessive conditions that affect the lung include X-linked agammaglobulinemia, an immunodeficiency that can lead to chronic lung disease, and X-linked severe combined immunodeficiency caused by mutations in the *IL2RG* gene that encodes a subunit of the receptor for multiple interleukins.

■ Mitochondrial Mutations

The mitochondrial genome is a small circular molecule, approximately 16,500 bases long. It encodes some of the proteins required for oxidative phosphorylation and electron transport, together with multiple transfer RNAs and ribosomal RNAs. Mutations in mitochondrial genes adversely affect energy production and thus the clinical consequences are greatest in tissues with high-energy requirements, such as heart, brain, and skeletal muscle.

Two characteristics make the inheritance of mitochondrial gene mutations unique. First, mitochondria are almost exclusively transmitted through the maternal lineage; sperm only have mitochondria in the tail for motility and do not enter the oocyte at fertilization. Thus, the pattern of inheritance within a family is similar to X-linked inheritance, with no male-to-male transmission, but it differs in that females and males are equally likely to be affected (Fig. 7-2E). In theory, all children born to an affected mother would

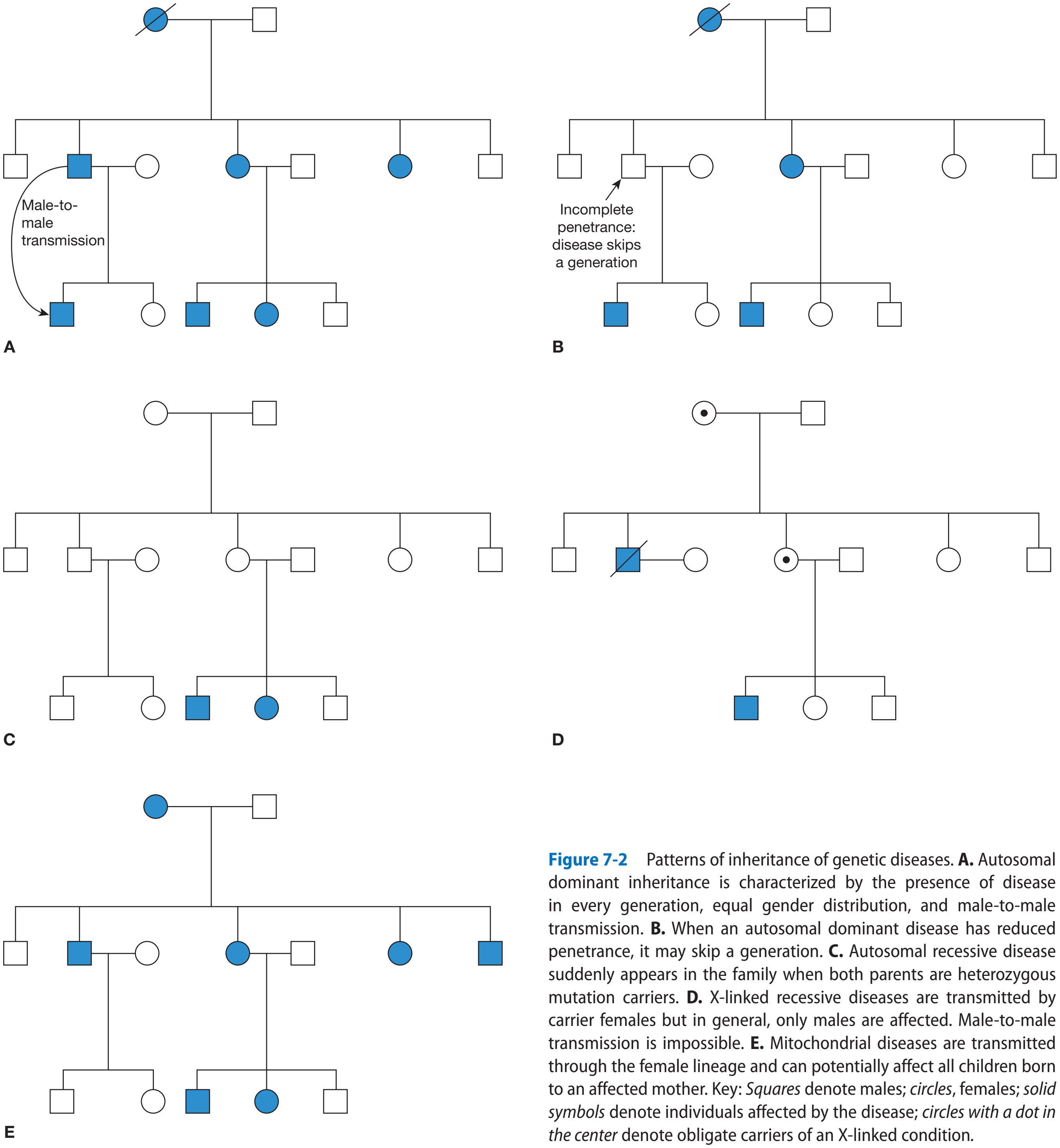
Male-to-male transmission
A
Incomplete penetrance: disease skips a generation
B
C
D
E

Figure 7-2 Patterns of inheritance of genetic diseases. **A.** Autosomal dominant inheritance is characterized by the presence of disease in every generation, equal gender distribution, and male-to-male transmission. **B.** When an autosomal dominant disease has reduced penetrance, it may skip a generation. **C.** Autosomal recessive disease suddenly appears in the family when both parents are heterozygous mutation carriers. **D.** X-linked recessive diseases are transmitted by carrier females but in general, only males are affected. Male-to-male transmission is impossible. **E.** Mitochondrial diseases are transmitted through the female lineage and can potentially affect all children born to an affected mother. Key: *Squares* denote males; *circles*, females; *solid symbols* denote individuals affected by the disease; *circles with a dot in the center* denote obligate carriers of an X-linked condition.

inherit the mutation and develop the disease. However, there are many copies of the mitochondrial genome per cell, and each cell has a mixture of wild-type and mutant mitochondria (*heteroplasmy*). The segregation of these mitochondria during cell division is random, so, by chance, an oocyte may have a high or low number of mitochondria carrying the mutation. This random drift continues throughout embryonic development and beyond, generating considerable variability in the severity of disease and the tissues that are affected, even among individuals in the same family.

Pulmonary involvement is not a major feature of most mitochondrial diseases, but several case reports link pulmonary hypertension with mutation in mitochondrial genes or a nuclear-encoded mitochondrial protein.[1–11] Pulmonary complications of mitochondrial disease are most likely to present as part of a multiorgan syndrome that may also include cardiac and/or skeletal myopathy, neuropathy, retinopathy, renal problems, or metabolic abnormalities.

Another fascinating property of the mitochondrial genome is its high degree of polymorphic variation. Clusters of variants, or "haplogroups," have been used to plot early human migration patterns across the globe. As new variants arose, they were propagated to offspring in the immediate geographic area but were not present in other populations that had already migrated to different regions. Some of these variants confer subtle functional differences and may have been selectively enriched by helping adaptation to a new environment. They may also modulate risk of disease, particularly for conditions where there is oxidative stress. Data concerning lung diseases are currently limited, but associations with different haplogroups and or mitochondrial DNA copy number have been reported for atopy and asthma, chronic obstructive pulmonary disease (COPD), high-altitude pulmonary edema, pulmonary hypertension, and lung cancer risk.[12–19]

SOMATIC MUTATIONS AND CANCER

Not all the genetic changes that contribute to disease are inherited. This is particularly true in cancer where, although there may be an inherited predisposition, most genetic changes are somatic and confined to the tumor itself. A later chapter is devoted to the molecular basis of lung cancer, so here we will briefly review the types of somatic changes observed in cancer cells and their relevance to benign lung conditions.

Two major classes of genes may be mutated in cancer: oncogenes and tumor suppressor genes. Oncogenes promote tumorigenesis when they are expressed at an abnormally high level or are inappropriately expressed in tissues where the gene should normally be silent. This may occur due to amplification (extra copies) of the gene, overactivation by upstream transcription factors, a chromosome rearrangement that brings the gene under the control of a strong promoter, or loss of DNA methylation as described in the following section on epigenetics. Alternatively, the gene may be mutated in a way that gives the protein a novel gain of function—for example, mutation of a ligand-dependent receptor such that, once activated, it cannot be switched off and continues to signal in the absence of the ligand. These types of oncogenic mutations are usually dominant missense mutations at specific amino acid sites within the protein.

Tumor suppressor genes (TSGs) are like the brakes on the cell; they control cell growth, differentiation, and apoptosis. When their function is lost, the cell proliferates uncontrollably or evades programmed cell death. TSGs are predominantly inactivated by nonsense and frameshift mutations, large gene deletions, or loss of an entire chromosome. They may also be silenced by hypermethylation of their promoter, as described in the next section. In contrast to oncogenes, TSG mutations are often recessive at the cellular level and both copies of the gene must be inactivated before the full cancer-promoting effect is seen. Both mutations may occur as somatic changes in the cell that initiates the cancer, or the first mutation may be inherited, predisposing the individual to the risk of cancer, a model that was first proposed by Alfred Knudson.[20]

As tumors proliferate, their genome may become highly disorganized. Abnormal segregation of the chromosomes during mitosis can lead to aneuploidy, with gains and/or losses of entire chromosomes. There may also be translocations, where segments of different chromosomes are inappropriately joined together, and localized deletions or duplications of large segments of DNA. Such large rearrangements will clearly affect many different genes and can contribute to the activation of oncogenes and/or loss of TSG function.

The study of somatic mutations requires tissue from the affected area and ideally entails comparison with normal tissue from the same patient, as well as normal tissue from unrelated controls. Due to the difficulty of obtaining such tissues for benign lung diseases, somatic changes have mainly been studied in the context of cancer, but the same approach has recently been applied to pulmonary arterial hypertension (PAH). In addition, somatic epigenetic changes described below are common both in cancer and in several chronic lung diseases, emphasizing the importance of acquiring tissue from the site of disease when this is ethically possible.

EPIGENETICS

The term *epigenetics* refers to factors that influence gene expression without altering the underlying base sequence. Both DNA and histones, the proteins around which DNA is wound, may be epigenetically modified. These changes are usually reversible and play important roles in regulating gene expression and genome stability.

■ DNA and Histone Modifications

The most common DNA modification is methylation of cytosine residues. The promoters of many genes contain a CpG island, a region with a high density of CG dinucleotides. Methylation of CpG sites in these islands leads to a closed chromatin conformation that makes the DNA inaccessible to transcription factors, turning off expression of the gene. Conversely, when most of the cytosines are unmethylated, the DNA is open and actively transcribed. DNA methylation, therefore, plays a critical role in regulating tissue-specific patterns of gene expression. Patterns of DNA methylation are controlled by DNA methyltransferases (DNMTs). DNMT3A and 3B are responsible for de novo methylation of residues that were previously unmethylated. Established patterns of methylation are then maintained by DNMT1. Further fine tuning of gene regulation comes through methylation and acetylation of histones. Acetylation mainly occurs on lysine residues and relaxes the interaction between histone and DNA, leading to increased gene transcription. Deacetylation reverses this and leads to a more tightly closed chromatin conformation. Histone acetylation patterns are controlled by histone acetyltransferases (HATs) and deacetylases (HDACs).

Within noncoding regions of the genome, DNA methylation and chromatin condensation act to suppress repetitive elements that could otherwise recombine and cause structural alterations. In cancer, there is often a global loss of methylation, which can lead to activation of mobile and repetitive elements, predisposing to the genomic instability that is the hallmark of many cancers. Loss of methylation at gene promoters can also activate oncogenes that in turn accelerate the growth of the tumor. At the same time, there may be hypermethylation of specific gene promoters, causing loss of expression of TSGs.

It is increasingly clear that more subtle epigenetic changes likely contribute to variation in normal lung function and lung diseases, including idiopathic pulmonary fibrosis (IPF), pulmonary hypertension, and COPD.[21–24] Unlike the DNA sequence, epigenetic modifications can change dynamically with age and are influenced by dietary factors such as folate intake. There is also mounting evidence that airborne pollutants, such as small diesel particulates and tobacco smoke, can directly mediate epigenetic changes.[25,26] Thus, the lung may be particularly susceptible to epigenetic changes caused by repeated exposure to these environmental modulators, influencing disease susceptibility and severity.[27–29] Importantly, though, some adverse epigenetic changes are reversible with time, for example, smoking-induced changes in DNA methylation gradually revert after quitting.[30] Also, the anti-inflammatory action of corticosteroids is, in part, epigenetic, recruiting HDAC2 to the site of acetylated (activated) inflammatory genes.[31] Characterizing the role of epigenetics in lung disease is challenging because it requires access to affected and control lung tissues. It may also be difficult to distinguish which changes are causative of disease and not just a reaction to the disease state. However, considerable progress has already been made under the auspices of the NIH Roadmap Epigenomics Consortium and other focused research initiatives.

■ Noncoding RNAs

Noncoding RNAs can directly regulate gene expression at the RNA level without being translated into a protein product. The best characterized family is the microRNAs (miRs), first studied in plants but now also recognized to be important throughout the animal kingdom. Primary miR transcripts are transcribed in the same manner as regular protein-coding genes. In some cases, the miR gene may be within an intron of a protein-coding gene and is controlled by the promoter of the "parent" gene. In other cases, miRs may be encoded as separate genes, individually or in a cluster, with their own promoter. The primary miR transcript is then processed into a pre-miR, about 70 to 80 nucleotides in length (Fig. 7-3). The ends of the pre-miR are highly homologous, causing the molecule to loop back on itself in a hairpin-like conformation. This double-stranded RNA structure is then exported from the nucleus into the cytosol, where it is cleaved by the enzyme Dicer into a mature single-stranded miR, approximately 18 to 22 nucleotides long (Fig. 7-3). The mature miR negatively regulates gene expression by binding to the 3′-untranslated region of its target mRNA, which either leads to degradation of the mRNA or inhibits protein synthesis. The seed sequence that initiates binding between the miR and its mRNA target is very short, typically around seven nucleotides, and does not require perfect base pairing. As a consequence, a single miR can potentially target tens or even hundreds of genes.

miRs have been widely studied in cancer, and several, such as miR-21, have been dubbed "oncomiRs" because their overexpression promotes tumorigenesis by downregulating tumor suppressor pathways.[32–35] In comparison, relatively little is known about the role of miRs in benign lung diseases. However, it is now an intense area of research and recent data highlight important roles in IPF and PAH, as detailed in the disease-specific sections that follow. The miR pathway is often considered to be an epigenetic mechanism, yet it can be influenced by changes in DNA sequence, either through mutation affecting the miR gene itself, or through mutations and polymorphisms that alter the seed sequence in the mRNA target.

Another major class of noncoding RNAs is the long noncoding (lnc) RNAs, greater than 200 bases long. lncRNA transcripts can be thousands of bases in length and, unlike miRs, they may be encoded

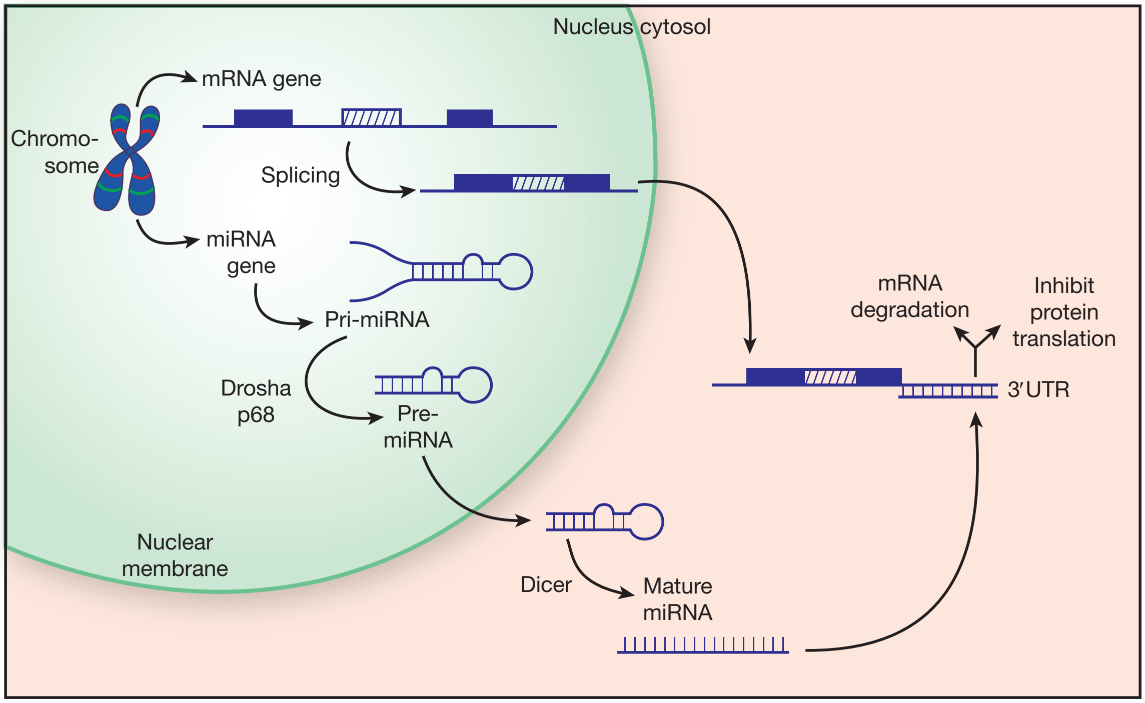

Figure 7-3 microRNA biogenesis. microRNAs that are encoded by independent genes are transcribed by RNA polymerases (mainly RNA pol II) into a primary miRNA transcript with a 5′-cap and 3′-polyadenylation. The primary miRNA molecule is cleaved by a protein complex, including Drosha and p68, into a double-strand hairpin RNA known as the pre-miRNA. For a subset of microRNAs, recruitment to the p68-Drosha complex is stimulated by activation of the bone morphogenetic protein and transforming growth factor-beta pathways,[85,86] a process that is disrupted by some mutations that cause pulmonary arterial hypertension.[68] Alternatively, some miRNA genes are embedded within the introns of mRNA genes, in which case they are transcribed along with the host gene and the pre-miRNA is generated during mRNA splicing. The pre-miRNA is then exported to the cytosol, where the Dicer complex converts it to the mature single-stranded miRNA molecule. Mature microRNAs negatively regulate expression of their target genes by binding to the 3′-untranslated region of the mRNAs, which either leads to degradation of the mRNA or blocks protein translation.

TABLE 7-2 Mendelian Inherited Lung Diseases

Disease	OMIM	Mode of Inheritance	Gene(s)	Chromosome	Comments
Cystic fibrosis	219700	Autosomal recessive	*CFTR*	7	ΔF508 accounts for ~75% of mutations; many other mutations described at a frequency of 5% or less
Alpha-1 antitrypsin deficiency	613490	Autosomal recessive	*SERPINA1*	14	Z allele (E342K) associated with severe disease, S allele (E264V) is intermediate
Sickle cell disease	603903	Autosomal recessive	*HBB*	11	Predominantly caused by a single mutation, E6V, which leads to an abnormal hemoglobin molecule (HbS)
Pulmonary arterial hypertension	178600	Autosomal dominant, reduced penetrance	*BMPR2* *SMAD9* *ACVRL1* *ENG* *CAV1*	2 13 12 9 7	6% to 10% of patients have a family history and an additional 15% to 20% of patients with sporadic idiopathic disease carry a mutation in one of these genes. *BMPR2* mutations account for about 80% of all families and more than 200 different mutations have been described. Several more genes have recently been identified by whole genome sequencing, as referenced in the text
Idiopathic/familial pulmonary fibrosis	614742 614743 178500 610913	Autosomal dominant, variable penetrance	*TERT* *TERC* *SFTPA2* *SFTPC*	5 3 10 8	Mutations in *TERT* or *TERC* lead to shortened telomeres. The severity of disease is inversely correlated with telomere length, and the age of onset decreases with each succeeding generation (genetic anticipation)
Surfactant metabolism dysfunction	265120 610921 614370 300770	Autosomal recessive X-linked	*SFTPB* *ABCA3* *CSF2RB* *CSF2RA*	2 16 22 X	Disease presentation can range from severe respiratory distress in neonates, through childhood or adult-onset interstitial lung disease. *SFTPC* mutations, listed above under IPF, can also lead to neonatal or childhood surfactant metabolism dysfunction
Alveolar capillary dysplasia	265380	Usually de novo	*FOXF1*	16	Caused by de novo heterozygous mutations or deletions of maternal origin; gene is imprinted; occasionally transmitted as a dominant trait by an unaffected mother
Primary ciliary dyskinesia	Multiple	Autosomal recessive	Multiple	Multiple	Highly heterogeneous disorder with at least 15 different genetic loci
Agammaglobulinemia	300300	X-linked	*BTK*	X	Rare B-cell disorder; recurrent respiratory tract infections
Severe combined immunodeficiency	300400	X-linked	*IL2RG*	X	Rare, affects at least two immune cell types; more severe than agammaglobulinemia; also several autosomal recessive forms

OMIM, Online Mendelian Inheritance in Man; http://omim.org/.

by large multiexon genes that undergo splicing in the same manner as most protein-coding genes. Well-known examples of lncRNAs are *XIST*, which coats the inactive X-chromosome in female cells, and *TERC*, part of the telomerase complex that maintains the ends of the chromosomes (telomeres). Currently, relatively little is known about the role of lncRNAs in human disease, the notable exception being *TERC* mutations, one of several causes of IPF described below.

INHERITED LUNG DISEASES

This section provides an overview of the genetic basis of inherited conditions that include lung disease as a major component (Table 7-2). These brief summaries cannot provide exhaustive reviews of current knowledge, but the reader is referred to entries in Online Mendelian Inheritance in Man (OMIM) and other web resources listed at the end of this chapter for in-depth information.

■ Cystic Fibrosis

Cystic fibrosis (CF; OMIM 219700) is the most common autosomal recessive disorder in Northern European Caucasians, with a carrier frequency of 1 in 20 to 1 in 25. It is caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene on chromosome 7, which encodes a transmembrane channel protein important for chloride transport[36] (see Chapter 48). The most common mutation in Northern Europeans, accounting for about 75% of all CFTR mutations, is a deletion of three base pairs of DNA encoding phenylalanine at codon 508, denoted F508del. The frequencies of other mutations are all much lower, each accounting for less than 5% of the total. Thus, approximately 56% of individuals with CF are homozygous for F508del, and the majority of others are compound heterozygotes for two different mutations. In Southern Europeans, F508del is somewhat less common, and the mutation spectrum is markedly different in the Ashkenazi Jewish population. Many countries now perform newborn screening for the most common CF mutations, enabling early diagnosis and treatment.

CF mutations can be subdivided into several categories, based on their molecular consequences.[37] Class I mutations, including most nonsense, frameshift, and splice-site mutations and large gene deletions, result in loss of CFTR protein. Class II mutations encode stable proteins that are abnormally processed, leading to retention of the mutant protein in the endoplasmic reticulum. F508del is an example of a class II mutation. Class III and IV mutations localize correctly to the membrane but they either fail to activate or are inefficient at transporting chloride ions. Class V mutations reduce the rate of CFTR synthesis. Some of these mutations retain a degree of residual function and can mitigate the severity of clinical phenotype.[37,38] Understanding the molecular consequences of these different mutations has been instrumental to developing new therapeutic approaches that seek to correct these defects, as described in the concluding section of this chapter.

Most genetic diseases show variability in the extent and severity of clinical disease, even for individuals with identical mutations. Just as common SNPs may confer risk or protection for common disease, they may also act as genetic modifiers in Mendelian traits. CF is a multisystem disease and with a large enough cohort of patients, it has been possible to identify polymorphisms that modify different aspects of the disease, including pulmonary function (FEV_1), bacterial colonization, meconium ileus, and diabetes.[39,40] One particularly interesting polymorphism involves a run of thymine residues in intron 8 of CFTR, commonly present as 9T, 7T, or 5T alleles. These bases are just upstream of exon 9 of the gene and are part of an important signal to regulate mRNA splicing. The shorter alleles splice less efficiently; in particular, the 5T allele can lead to abnormal splicing that excludes exon 9 from a proportion of the transcripts. Since some full-length CFTR is still made, this is not a severe CF mutation. However, it can lead to a partial phenotype in combination with other mutations and is, therefore, an intragenic modifier. Embryonic development of the vas deferens in males is especially sensitive to the amount of CFTR protein, and the 5T allele can contribute to congenital bilateral absence of the vas deferens, even in individuals with little or no lung disease.[41]

■ Alpha-1 Antitrypsin Deficiency

Alpha-1 antitrypsin deficiency (AATD; OMIM 613490) is an autosomal recessive disease caused by mutations in the *SERPINA1* gene on chromosome 14, which encodes the protease inhibitor alpha-1 antitrypsin (AAT) (see Chapter 39). AATD was one of the earliest genetic diseases to be understood at the molecular level, since the variant alleles could be identified by protein gel electrophoresis (isoelectric focusing) before the advent of DNA-based genetic testing. Consequently, the alleles are denoted by letters assigned for their relative position on the gel. The wild-type allele is designated M. The most common deficiency allele is Z, a missense mutation that changes glutamic acid to lysine at codon 342 (E342K). Its frequency is highest in Northern European populations.

AATD is likely underdiagnosed, and the true prevalence may be higher than CF in some countries.[42–44] ZZ homozygotes have low plasma AAT concentrations and are at highest risk for developing lung disease. Accumulation of the mutant protein in the liver can also lead to liver damage. The other most common allele, denoted S (amino acid change E264V), is intermediate in respect to both the level of AAT and disease risk. It is highly prevalent in Southern European populations, with frequencies of 15% to 20% in Spain and Portugal.[44] Clinically, the S allele is of greatest concern in SZ compound heterozygotes, but the severity of lung disease is generally less than for ZZ homozygotes. Individuals with the MZ, MS, or SS genotypes may have slightly impaired lung or liver function. Thus, while overt AATD is considered a recessive condition, the alleles are codominant in their influence on AAT levels and associated risk of disease. There is also a strong gene–environment interaction with tobacco smoking, which can inactivate AAT, further decreasing the level of active protein and greatly increasing the risk of lung disease in susceptible genotypes.

Testing for the S and Z alleles may be performed by isoelectric focusing or DNA-based testing. Isoelectric focusing has the advantage that it will pick up other rare alleles that lead to altered protein mobility, whereas the DNA-based tests target only the two known mutations. However, both methods fail to detect rare null mutations that lead to complete loss of protein and, therefore, it is also important to measure the level of AAT in the plasma. This may be followed up with sequencing of the entire *SERPINA1* gene if rare alleles are suspected. Recommendations for genetic testing have been developed by a joint task force of the American Thoracic Society and European Respiratory Society.[45]

■ Pulmonary Arterial Hypertension

PAH (OMIM 178600) may be idiopathic (IPAH) or associated with an underlying condition, such as connective tissue disease, congenital heart defect, or HIV infection (APAH) (see Chapter 72). About 6% of IPAH patients have a family history. PAH is inherited as an autosomal dominant trait with reduced penetrance; on average, only about 27% of mutation carriers develop symptomatic disease. It is more common in females than males, and the gender-specific penetrances are estimated at 42% and 14%, respectively.[46] Initial suggestions of genetic anticipation have now been disproved.[46]

Mutations in the bone morphogenetic protein receptor type II (*BMPR2*) gene account for approximately 80% of familial PAH.[47,48] These are predominantly nonsense, frameshift, or splice-site mutations that lead to premature protein truncation or NMD.[49] Larger gene rearrangements also are frequent.[50,51] Mutations triggering NMD may cause less severe disease than missense mutations resulting in a stable dominant-negative protein, although data from different centers are conflicting in this regard.[52,53] *BMPR2* mutations are also found in 11% to 40% of IPAH patients without a family history.[54–56] The revised classification of PAH agreed at the fourth World Symposium created a new category—heritable PAH (HPAH)—that encompasses all patients with a detectable mutation, irrespective of family history.[57,58] *BMPR2* mutations have also been identified in patients with pulmonary veno-occlusive disease[50,59] and in PAH associated with anorexigen exposure,[60,61] congenital heart disease[62] but not in connective tissue disease.

Other genes within the bone morphogenetic protein pathway also can predispose to PAH. Mutations in the type I receptor ALK1 and its accessory protein endoglin (*ENG*) predominantly cause hereditary hemorrhagic telangiectasia (HHT). However, PAH has been reported in a number of families and may precede the onset of signs or symptoms of HHT.[63–66] Patients with HHT may also develop pulmonary arteriovenous malformations. Several mutations have also been identified in the *SMAD9* gene, which encodes Smad8, a downstream mediator of bone morphogenetic protein signaling,[67–70] and in *GDF2*, which encodes BMP9, one of the ligands that bind to the ALK1-BMPRII receptor complex.[70,71] Recent exome and genome sequencing efforts have led to the identification of numerous additional PAH genes.[70,72–75] One notable finding is that the mutation spectrum in children with PAH differs from adults, with enrichment for mutations in *TBX4,* a gene that plays a crucial role in lung development and is also associated with small patella syndrome.[76–78]

The low penetrance of PAH mutations suggests that additional genetic and/or environmental factors also play a role. The proliferative vascular changes share many features with cancer,[79–81] and analysis of affected lung tissues provides molecular support for this hypothesis, with evidence of somatic mutations, microsatellite instability, and aneuploidy.[82–84] miRs likely play an important role in PAH pathogenesis. The bone morphogenetic protein pathway regulates expression of a subset of miRs by promoting processing of the primary miR transcripts.[85,86] This pathway is attenuated in patients with *BMPR2* or *SMAD9* mutations,[68] whereas several other miRs also have been implicated in PAH, independent of mutation status.[87–92]

There is now considerable evidence for abnormalities in DNA damage and repair in PAH lung vascular cells, as well as the role and therapeutic potential of epigenetic modifications. These are too numerous to detail here; we refer the reader to several recent reviews.[24,93,94] Overall, despite the progress in understanding HPAH, relatively little is known about the genetic factors that may influence other forms of pulmonary hypertension, particularly non-Group 1, and the heterogeneous nature of the disease remains a challenge. Newer omics studies, such as proteomics and metabolomics, show promise as diagnostic biomarkers and for risk prediction and are likely to provide considerable new insight as these technologies mature.[95–97]

Heritable pulmonary veno-occlusive disease (PVOD) and pulmonary capillary hemangiomatosis (PCH) are rare and pathologically distinct forms of PAH, inherited in an autosomal recessive pattern. Biallelic mutations in *EIF2AK4*, a gene encoding eukaryotic translation initiation factor 2 alpha kinase 4, were identified as a cause of PVOD/PCH in families, and up to 25% of sporadic cases.[98,99] Whole genome sequencing in a large cohort of PAH patients identified biallelic *EIF2AK4* mutations in approximately 1%, indicating that genetic testing can be beneficial to refine the diagnosis in patients who have been misclassified.[100] This is especially important for PVOD/PCH, where response to standard PAH therapies is poor, and early lung transplantation should be considered.[101]

Idiopathic Pulmonary Fibrosis

The genetics of IPF (OMIM 178500, 614742, 614743) (see Chapter 54) parallels that of PAH in many respects. A small proportion of cases are familial, and the only significant difference in clinical presentation is an earlier age of onset. The pattern of inheritance is autosomal dominant with variable penetrance.

Familial pulmonary fibrosis (FPF) is genetically heterogeneous, but the genes involved do not all fall in a common pathway. About 3% of families have mutations in either surfactant protein A2 (*SFTPA2*) or surfactant protein C (*SFTPC*) genes, but a much larger proportion of families have mutations affecting telomerase.[102–104] Telomeres are like protective caps on the ends of chromosomes, important in maintaining genome stability. Their DNA sequence comprises many hundreds of copies of the repeat TTAGGG. Due to its position at the end of the chromosome, this sequence cannot be fully replicated and over time the number of repeats gets progressively shorter. Indeed, telomere shortening is believed to be one of the major molecular factors underlying aging. To counteract this, proliferative cells express telomerase, which catalyzes the addition of telomeric DNA. It is especially important in stem cells and germ cells but is turned off in most differentiated cells. Cancer cells frequently reactivate telomerase. Telomerase is a heteromeric complex composed of a protein with reverse transcriptase activity, encoded by the gene *TERT*, and a lncRNA (*TERC*) that provides the template for synthesizing new telomeric DNA.

The link between IPF and telomerase first came from the identification of genes causing dyskeratosis congenita, a rare multisystem genetic disorder. Patients with dyskeratosis congenita have shortened telomeres and a high incidence of pulmonary fibrosis, prompting analysis of telomere-related genes in FPF.[105] About 18% of families have now been identified with heterozygous mutations in *TERT* and about 1% with *TERC* mutations.[103,104] The average length of the telomeres modifies disease severity, and, since the telomeres become progressively shorter with each generation, families with these mutations demonstrate increasingly earlier onset of disease in successive generations, a phenomenon known as "genetic anticipation." Patients with very short telomeres are also at risk for developing aplastic anemia or dyskeratosis congenita.[104] Other genes within the telomere maintenance pathway that are mutated in IPF include *PARN*, *RTEL1*, and *DKC1*.[106–108]

For patients with IPF (i.e., without a family history), approximately 3% have a *TERT* mutation and less than 1% surfactant protein mutations. However, 25% have a telomere length below the 10th percentile in the general population, suggesting that shortened telomere length is a major risk factor for pulmonary fibrosis, even in the absence of an identifiable mutation.[109] Genomic studies of IPF lung tissue have already yielded considerable insight into the genetic changes contributing to lung fibrosis,[110] including distinct changes in gene expression,[111–113] DNA methylation patterns,[114–116] and miR expression,[117–120] although these have not as yet been translated in new therapeutic approaches.

Surfactant Metabolism Dysfunction

Genetic disorders of surfactant metabolism (OMIM 265120, 300770, 610913, 610921, 614370) range from severe neonatal respiratory distress and congenital pulmonary alveolar proteinosis to interstitial lung disease presenting in childhood or adulthood. It is important to note that acquired pulmonary alveolar proteinosis is a distinct autoimmune disorder (see Chapter 70). Autosomal recessive forms of surfactant metabolism dysfunction are caused by mutations in surfactant protein B gene (*SFTPB*)[121] or the transporter gene *ABCA3*.[122–124] Both lead to severe neonatal respiratory distress. Recessive forms of pulmonary alveolar proteinosis can also be caused by mutations in the granulocyte-macrophage colony-stimulating factor receptor subunits *CSF2RA*, which is X-linked recessive, or *CSF2RB*, autosomal recessive. *SFTPC* mutations are inherited as an autosomal dominant trait with variable penetrance. The phenotype may range from severe neonatal or childhood-onset interstitial lung disease to adult-onset pulmonary fibrosis.[125,126]

Alveolar Capillary Dysplasia

Alveolar capillary dysplasia (ACD; OMIM 265380) with misalignment of the pulmonary veins is a rare condition caused by heterozygous mutation or deletion of the *FOXF1* gene on chromosome 16.[127] It is usually lethal in infancy and, therefore, mutations are not inherited from an affected parent; rather, they occur de novo in the oocyte or sperm or in the very early embryo. However, one family has been described in which the mother had five affected children and was found to carry a missense mutation in *FOXF1,* despite being unaffected herself.[128] The mutation had arisen de novo on her paternally derived chromosome 16. The authors proposed that *FOXF1* is imprinted on the paternal allele, meaning that it is only expressed from the maternal allele. Thus, when the mutation first arose on the paternal allele, its effect was masked because only the normal, maternally derived allele was expressed; however, when the mother passed the mutation to her children, it was now on a maternally derived chromosome and was expressed, leading to ACD and multiple congenital anomalies. Subsequently, however, transmission of a paternally derived mutation has been documented, with a variable phenotype in his three children.[129] Furthermore, *FOXFI* was found to be expressed from both parental alleles in lung tissue, with no evidence of differential methylation, suggesting that it is *not* imprinted.[130]

Overall, the pattern of tissue-specific methylation and imprinting in this region of chromosome 16 is complex, and parent-of-origin effects in ACD may be due to differential methylation of the *FOXF1* enhancer region, rather than the gene itself.[131] Single nucleotide variants in this enhancer region also may modulate the ACD phenotype.[132] Lastly, a small number of families have been reported where multiple affected babies are born to parents who have no evidence of a mutation in their blood DNA by standard genetic testing methods. This situation may arise due to gonadal mosaicism, in which the mutation has arisen post-zygotically in the parent and is present in a proportion of germ cells. Highly sensitive mutation detection methods may pick up a low level of mutant molecules in blood DNA, helping to accurately counsel the parents as to their recurrence risk.[133]

Primary Ciliary Dyskinesia

Primary ciliary dyskinesia (PCD; numerous OMIM numbers) is predominantly an autosomal recessive disorder, with occasional X-linked recessive inheritance, in which abnormalities of the cilia lead to frequent respiratory infections and chronic lung disease (see Chapter 6). Other manifestations of the condition may include situs inversus and infertility. PCD is genetically very heterogeneous; mutations in more than 40 different genes have so far been identified.[134] Many of these genes encode critical structural components of cilia, such as axonemal dynein, or affect the assembly or motility of cilia. A significant proportion of cases still have no identifiable mutation and, thus, it is expected that more genes will be identified. This very high level of genetic heterogeneity represents a significant challenge, but the ability to sequence the entire exome of affected individuals is improving the ability to identify additional genes and is enabling genotype-phenotype correlations to be made.[135,136]

■ Sickle Cell Disease

Sickle cell disease (OMIM 603903) is the most common autosomal recessive disease in individuals of African ancestry (see Chapter 95). Although primarily a blood disorder, it can give rise to significant pulmonary complications, including acute chest syndrome, emboli, and pulmonary hypertension. It is caused by a single A>T mutation in the beta-globin gene that leads to substitution of valine in place of glutamic acid at codon 6. The resulting hemoglobin molecule has reduced solubility compared to the wild-type protein, an example of a mutation that causes gain of an abnormal function. Heterozygous carriers of the mutation have increased resistance to malaria, which is believed to account for the high frequency of the mutation in regions where malaria is or was previously endemic.

Persistence of fetal hemoglobin (HbF) beyond infancy can ameliorate the severity of sickle cell disease. This observation underlies the rationale for treatment with hydroxyurea, which boosts HbF levels, reducing pain crises, the need for blood transfusions, and the incidence of acute chest syndrome.

HbF levels are genetically determined by polymorphisms at several loci, and these SNPs also associate with the frequency of pain crises.[137] One of these genes, *BCL11A*, is a transcription factor that normally silences HbF expression. Deletion of *BCL11A* leads to persistence of fetal hemoglobin, and this gene is now the target of some exciting clinical trials testing gene therapy approaches for sickle cell disease. One study uses CRISPR-Cas9 gene editing to disrupt an erythroid-specific enhancer of *BCL11A* in patients' own hematopoietic stem cells, which are then transplanted back into the patient, with the potential for long-term engraftment and expression of HbF.[138] Initial results from the first patient, followed for more than a year, show a high level of HbF expression and a reduction in pain crises. By boosting HbF levels, rather than attempting to correct to the sickle cell mutation, this approach is also being trialed for beta-thalassemia.[138] A similar approach using posttranscriptional silencing of *BCL11A* by RNA interference also has shown promising results in early clinical trials.[139]

GENETIC BASIS OF COMMON LUNG DISEASES

Common lung diseases such as asthma and COPD are not inherited as strong Mendelian traits. However, they may show evidence of familial clustering, suggesting that there is a genetic component to their etiology. The proportion of variation that is estimated to come from genetic factors is termed the "heritability" of the trait, high heritability indicating a strong genetic component.

Since common complex diseases do not show clear segregation patterns within families, traditional model-based (parametric) mapping studies cannot be used. Instead, nonparametric methods have been employed across large collections of small family groupings, such as affected sib pairs. Early studies used a candidate gene approach. More recently genome-wide association studies (GWAS) have been used in very large case-control cohorts. Both types of study utilize some of the millions of polymorphic genetic variants throughout the genome and look for a statistically significant association between these genetic markers and the trait of interest. Single nucleotide polymorphisms (SNPs) are now the most commonly used genetic variants, as microarray technology enables simultaneous analysis of more than one million SNPs on a single array. Correlations can also be tested with clinical parameters and biomarkers such as exhaled nitric oxide, serum IgE, and FEV_1, both for genetic and epigenetic markers.[23,140]

Analyzing so many variants across thousands of samples raises the problem of multiple testing, whereby the large number of comparisons between cases and controls greatly increases the likelihood that differences will be identified just by chance. To reduce the number of false-positive results, stringent correction for multiple testing is required. Also, cases and controls must be carefully matched to ensure there is no hidden population stratification that might distort allele frequencies.

It is important to note that many of these SNPs are in noncoding regions of the genome and do not directly affect gene regulation or protein function. Rather, they are markers that tag a nearby sequence that may modulate disease risk. In comparison to Mendelian diseases, where mutations confer a high risk of developing the condition, the relative risks for loci identified in GWAS are generally quite small. They have little or no predictive value and so in this respect their clinical utility is limited; the value of these studies is in identifying new pathways and targets for therapeutic intervention.[141] Significant resources have been invested in GWAS in a wide range of diseases, and the challenge is to identify the functional variants and fully realize the translational potential of this research. A new and powerful approach is systems biology, which aims to integrate multiple types of "omics" data, such as GWAS, genome-wide expression data, miRs, and epigenomics into networks that identify new pathways and biologic connections. Furthermore, the advent of polygenic risk scores—which combine the effects of individual SNPs into an aggregate odds ratio—will likely improve the clinical utility of GWAS results in the future.

The literature on GWAS in common lung diseases is large and continues to expand rapidly. In this brief space, it is not possible to discuss these studies in any detail, especially given the complexities of racial and ethnic differences in SNP frequencies and the many subphenotypes that have been studied. Therefore, only a brief overview of some of the major candidate loci will be provided; the reader is referred to reviews that can be used as a starting point for in-depth reading.

■ Asthma

Asthma (see Chapters 43–45) has a high heritability and, therefore, has been a good candidate for GWAS. Some of the strongest loci identified thus far include HLA-DQ, Orosomucoid-like 3 (*ORMDL3*), and several interleukins and interleukin receptors.[142,143] *ORMDL3* is inducible in the bronchial epithelium and, in mice, it has been shown to regulate metalloproteinases and several cytokines.[144] Residing in the endoplasmic reticulum (ER), *ORMDL3* has also been linked to ER stress, as well as to playing a critical role in sphingolipid biosynthesis.[145,146] SNPs in the same region also modulate expression of a neighboring gene, gasdermin-B (*GSDMB*), part of a family of genes implicated in regulating epithelial cell apoptosis. The *ORMDL3/GSDMB* locus, originally identified in cohorts of European origin, was also validated as a critical asthma susceptibility locus in African-American children.[147,148]

African genomes can help to refine candidate genetic regions, since regions of linkage disequilibrium—where SNPs travel together through the generations without being separated by recombination—are smaller than in European genomes. In the case of *GSDMB*, this approach pinpointed a single causative SNP that directly affects splicing of *GSDMB*.[148,149] Several genes are also associated with response to bronchodilators.[150]

Hispanic and African American populations have a higher incidence of severe asthma but are understudied in comparison to Caucasians and represent an important research priority. As described above, trans-ethnic studies can be very helpful in refining the localization of candidate loci that are in common between different races. However, distinct loci also exist, both in disease susceptibility and response to therapy, underlining the importance of inclusive research to address health disparities.[151–153] Ultimately, translating GWAS hits to functional biology is one of the biggest challenges of studying the role of genetic variants in common diseases; however, high throughput functional screening assays are increasingly effective as way of validating findings from GWAS and whole genome sequencing studies.[154]

Environmental factors, such as air pollution and smoking, are known to be important modulators of asthma risk.[29] This may be mediated, at least in part, through epigenetic changes affecting DNA methylation, histone acetylation, and miR expression.[22] Changes in DNA methylation directly regulate the arginase–nitric oxide pathway,[26,155] and distinct methylation profiles have been identified in asthmatic children compared to controls.[156] Expression studies of the effect of PM2.5 on nasal airway epithelial cultures identified significant transcriptomic changes, including drivers of mucus metaplasia and mucociliary clearance that may contribute to respiratory disorders such as asthma and COPD.[157]

■ Chronic Obstructive Pulmonary Disease

As described previously, the strongest genetic risk factor for COPD (see Chapters 37 and 38) is a mutation in the *SERPINA1* gene that encodes AAT, a risk that is further heightened by tobacco smoke exposure. More common variants with smaller effect size include the nicotine receptors *CHRNA3* and *CHRNA5*, hedgehog-interacting protein (*HHIP*), and *FAM13A*.[158] Smoking is a major risk factor for COPD and as mentioned previously, induces many epigenetic changes in the lung. Altered DNA methylation patterns have been identified in COPD patients in comparison with controls[159] and may be related to response to therapy,[160] while histone deacetylase activity is decreased.[161] Importantly, methylation changes associated with cigarette smoking are reversible with time after quitting,[30] and epigenetic changes offer promising targets for drug therapy.[31]

■ Sarcoidosis

Relatively little is known about genetic susceptibility to sarcoidosis (see Chapter 53), and despite its prevalence in African Americans, early studies were mainly conducted in cohorts of European ancestry.[162,163] Surprisingly, emerging data suggest common risk loci across multiple different ethnic groups,[164–166] a marked contrast from the heterogeneity in GWAS data for some other diseases. Key loci identified from these studies include the *ANXA11* gene and several HLA subtypes, with complement C4A or C4B deficiency also suggested.[167]

TARGETED THERAPIES FOR GENETIC DISEASE

The completion of the human genome project led to high expectations (and in some cases, hype) of a new era of personalized medicine. The first arena in which this has been realized is in the treatment of cancer. Drugs such as imatinib (for chronic myeloid leukemia) and trastuzumab (in breast cancer) target specific gene rearrangements or amplifications that occur within the tumor. Several drugs are approved to target epidermal growth factor receptor (EGFR) in non–small-cell lung cancer. Targeted lung cancer therapies are discussed in detail in chapter 114. Progress in other fields has been slower, but some recent advances show great promise, especially for CF.

Initial hopes for gene replacement therapy in CF failed to live up to expectations, but detailed characterization of the types of mutations and their functional consequences are now translating into new therapies. One approach is to promote read-through of nonsense mutations with a small molecule called ataluren (PTC124).[168] This reduces the recognition of a premature stop codon and allows the ribosome to translate a full-length protein. The same approach has been tried previously with aminoglycoside antibiotics, but ataluren is more potent and has fewer adverse effects.[169] In theory it should work for any nonsense mutation, but in practice some mutant transcripts are rapidly degraded by nonsense-mediated decay. Logically, therefore, the approach has proved to be most effective for mutations that are relatively stable and not subject to NMD.[170] After positive results in mouse models of CF and Duchenne muscular dystrophy, ataluren was given orphan drug designation by the U.S. Food and Drug Administration (FDA) and showed promising results in phase 2 CF clinical trials.[171] However, subsequent studies have failed to show a statistically significant difference in lung function or pulmonary exacerbations.[172,173] The drug is approved in Europe for the treatment of Duchenne muscular dystrophy and has shown promising in vitro results against nonsense mutations in PAH vascular cells.[174]

In cases where a full-length CFTR protein is made, but either mislocalizes (class II) or is an inefficient chloride transporter (classes III and IV), drugs are being tested that could improve trafficking to the membrane and improve transporter function. Ivacaftor (VX-770) was found to be effective in rescuing channel gating function of the G551D mutation,[175] a class III mutation with a frequency of 3% to 5%. A randomized placebo-controlled trial of ivacaftor produced exciting results, with highly significant improvements in FEV_1, sweat chloride levels, weight, and quality of life scores.[176] However, therapies to help the majority of patients with CF who are homozygous for F508del were still needed.

The next agent developed was tezacaftor (VX-661), which rescues the mislocalization of F508del and restores it to the cell membrane. Tezacaftor is known as a CFTR corrector, whereas ivacaftor is a potentiator of channel function. The two drugs in combination were shown to be effective in patients with F508del/F508del and F508del/G551D genotypes.[177] However, in some patients, either the second mutation leads to lack of protein production, or the mutant protein fails to respond to tezacaftor/ivacaftor. These are dubbed “minimal function” mutations.

The latest addition to this remarkable therapeutic family is elexacaftor (VX-445), also a CFTR corrector. In combination with tezacaftor and ivacaftor, elexacaftor significantly improved lung function and reduced pulmonary exacerbations in patients with one copy of F508del and a minimal function mutation.[178] This triple combination therapy—known as Trikafta—has since been approved by the FDA for the treatment of CF patients with at least one copy of F508del. This covers at least 90% of patients in most populations. While this is an incredible success story, a small proportion of patients remain who do not benefit from the current combinations of drugs.

These therapies also do not address some of the extrapulmonary manifestations of CF, such as meconium ileus in newborns, and may not reverse existing lung damage. Nevertheless, the message is that careful study of the effects of specific genetic mutations can ultimately translate into novel therapies that directly target the underlying molecular defect.

Other lung diseases are lagging compared with CF, although many do not have the benefit of more than two decades of research on a single gene. However, new therapeutic targets are starting to emerge from some of the research summarized earlier, particularly at the epigenetic level. Several approaches to improving BMPR2 signaling in HPAH are being studied.[174,179–183] In particular, Sotatercept, a soluble TGF-beta/BMP ligand trap, has shown promising results in early clinical trials.[184] At the epigenetic level, histone deacetylase inhibitors and bromodomain and extraterminal domain (BET) inhibitors have been proposed as a possible therapy in PAH,[24,185] whereas corticosteroid-resistant COPD may benefit from increasing HDAC2 activity.[31] Meanwhile, as discussed previously, the potential for therapeutic uses of gene editing is being realized in sickle cell disease. As our understanding of the effect of specific genetic mutations and epigenetic modifications continues to deepen, the future for targeted therapeutic intervention is bright.

WEB RESOURCES

GeneReviews (current expert-authored disease descriptions of inherited diseases): *http://www.ncbi.nlm.nih.gov/books/NBK1116/*
Genetic Testing Registry: *http://www.ncbi.nlm.nih.gov/gtr/*
Mitochondrial genome database: *http://www.mitomap.org/MITOMAP*
NIH Epigenomics Roadmap Consortium: *http://www.roadmapepigenomics.org/*
Online Mendelian Inheritance in Man (OMIM): *http://omim.org/*

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CHAPTER 8

Stem Cells and Respiratory Disease: Prospects for the Future

Konstantinos-Dionysios Alysandratos*
Michael J. Herriges*
Darrell N. Kotton*

INTRODUCTION

Advances in stem cell research offer unprecedented opportunities to develop new treatments, disease models, and drug screens for previously untreatable conditions. These discoveries have captivated the imagination of the lay press and have inspired hope in patients, clinicians, and scientists. Inevitably, in an emerging new field, there are false starts that accompany promising discoveries. If rigorous researchers in the field have difficulty discerning hype from hope, what is a busy clinician to do when confronted with basic questions, such as: "Is stem cell therapy available for my lung disease?" or "Shall I bank my baby's cord blood in case he/she develops cystic fibrosis or emphysema?" This chapter is designed to describe the quickening pace of stem cell and regenerative medicine research related to lung disease and to place the latest discoveries in a historic context, before discussing future prospects.

Stem cells have been found in an increasing number of tissues whose biology is characterized by rapid turnover of differentiated cells. In these tissues, for example, blood, skin, and intestine, a stem cell hierarchy has been described where rare stem cells proliferate occasionally, giving rise to stem cell daughters or to progenitors that can proliferate rapidly and differentiate into mature cells required for the function of that tissue. These properties of self-renewal and differentiation are the classic hallmarks of stem cells, and their importance in homeostatic maintenance of the blood, skin, and intestine are well accepted.[1–3] These features also make stem cells attractive vehicles for clinical applications such as the reconstitution of injured or diseased tissues. Several decades of research, including the seminal bone marrow transplantation work of Till and McCullough,[4] has rigorously proved that the hematopoietic stem cell, a cell that constitutes 1 in 10,000 bone marrow cells, can be delivered to a recipient by simple intravenous infusion, reconstituting all cells of the bone marrow and circulating blood for the lifetime of the recipient.[1]

Given the virtually unlimited self-renewing capacity and blood differentiation repertoire of hematopoietic stem cells, most pulmonologists are surprised to learn that cells of similar capacity have not been reproducibly proven to exist in the lung and may not be necessary for the homeostasis of an organ with a quiescent epithelium that contrasts with the rapidly self-renewing epithelia of intestine and skin.

LUNG EPITHELIAL RESPONSES TO INJURY

Because the unperturbed adult lung epithelium displays remarkably slow cell turnover, the post-injury or disease responses of human or animal lung have been studied to elucidate both the proliferation potential and differentiation repertoire of various lung cell types. These injury models have been used to search for potential specialized lung cells that might exhibit stem cell properties, such as self-renewal and multipotent differentiation (reviewed by Rawlins and Hogan).[5] In the lung many types of functionally mature cells appear to be endowed with the ability to proliferate, if needed, and to subsequently differentiate, with the responding cell type depending on the type and severity of injury. In this way, the biology of the lung epithelium may be more akin to that of other quiescent endoderm-derived tissues, such as the liver and pancreas, whose tissues have less turnover and may be repaired by proliferating mature cells or facultative progenitors, depending on the type of injury.[6] Beginning in the 1970s, morphologic studies of human and animal lungs defined subsets of lung epithelia with proliferative capacity, revealing basal and secretory (club) cells (previously called Clara cells) of the proximal airway, and alveolar epithelial type 2 cells of the distal lung parenchyma all had the capacity to enter cell cycle in response to lung injury.[7–15] More recently, thymidine-labeling techniques have been replaced by newer methods of identifying proliferating cells or tracking their progeny. These studies have emphasized that most lung epithelial cells, except for airway ciliated cells or alveolar epithelial type 1 cells, can proliferate after injury in a remarkably resilient organ where many differentiated epithelial subtypes contribute to tissue repair.[5,16–20]

Beyond assessing the proliferation of cells in the adult lung, the classic developmental biologist's method of "lineage tagging" cells has allowed investigators to follow the origin of lung epithelial cells during development, and to assess where they go upon aging or after injury.[16,21–23] It is now well established that the many types of epithelial cells in the adult lung arise during development from a few progenitor cells in the embryonic foregut endoderm.[24] The concept has become generally accepted that a limited number of lung epithelial cell types are specified during embryonic development and sustain their committed differentiated state throughout life.[23] In the nascent field of stem cell research, most investigators agree that multipotent, bona fide lung epithelial progenitors exist, if only fleetingly early in embryonic development.[24,25] It remains unclear, however, whether any specialized progenitors or stem cells similar to these embryonic endodermal precursors remain in the lung postnatally or are rederived after injury.

EVOLVING STUDIES IN THE SEARCH FOR LUNG STEM CELLS

With so many proliferation-competent epithelial cells in the adult lung able to participate in post-injury repair, some investigators have begun to wonder which of these cells are responsible for functional epithelial repair. The search for specialized reparative lung cells in recent years has been propelled by the emergence of specific and sensitive molecular biology tools and laboratory instruments that can refine our previous understanding of lung biology (Fig. 8-1). New studies suggest that a much greater diversity exists within the previously identified broad classifications of lung airway and alveolar epithelial cells.[26] For example, the response of mouse lung to recover from naphthalene exposure, an injury that depletes the lung of most secretory cells (identified by the marker secretoglobin family 1A member 1 [SCGB1A1], also known as club cell secretory protein [CCSP or CC10]), revealed a small subset of airway progenitors, called "variant club cells" (v-club cells; previously variant Clara cells).[27–29] These cells expressed *Scgb1a1*, but they lacked expression of the cytochrome P450 2F2 isoenzyme (encoded by *Cyp2f2*) that is responsible for generation of the toxic naphthalene metabolites that kill other secretory cells, rendering them resistant to naphthalene injury. These

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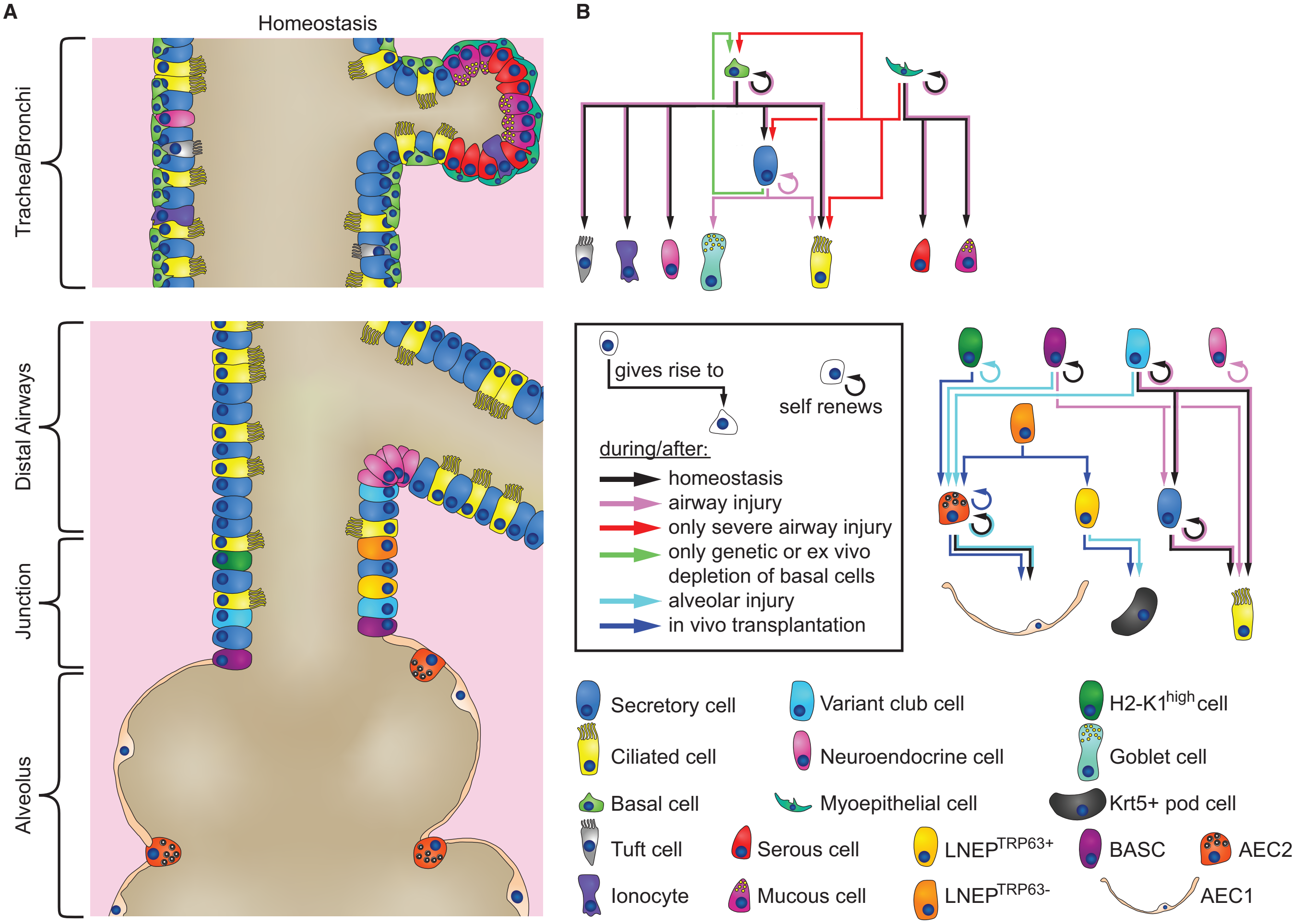
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Ionocyte
Mucous cell
LNEP^{TRP63-}
AEC1

Figure 8-1 Epithelial cell types of the murine lung and their progenitor capacity. **A.** The murine lung contains a diverse population of epithelial lineages that are each restricted to specific compartments of the respiratory system. **B.** While the lung is largely quiescent during homeostasis, many of these lineages may serve as facultative progenitors capable of self-renewal and differentiation following injury or transplantation. AEC1, alveolar epithelial type 1 cell; AEC2, alveolar epithelial type 2 cell; BASC, bronchioalveolar stem cell; LNEP, lineage negative epithelial progenitor. *(Reproduced with permission from Alysandratos KD, Herriges MJ, Kotton DN. Epithelial stem and progenitor cells in lung repair and regeneration. Annu Rev Physiol. 2021;83:529–550.)*

cells survived and rapidly reconstituted both secretory and ciliated populations of the injured airway. Most intriguing was the observation that this rare subset of *Scgb1a1+* cells appeared to reside in two specialized microanatomic locations or niches: adjacent to neuroepithelial bodies of the airways and at bronchioalveolar duct junctions. This observation remains one of the most convincing examples to date, suggesting the lung contains progenitor niches, or microanatomic cell compartments with specialized stem or progenitor cells.

A remarkable study by Kim et al. proposed that some rare *Scgb1a1+* progenitors located at the bronchioalveolar duct junction in mice may possess the capacity to reconstitute both airway and alveolar epithelia, suggesting the rodent lung contains rare, multipotent, "bronchioalveolar stem cells" (BASCs).[30] Until recently, the existence of BASCs was contested in experimental work by Hogan et al.[21] using *Scgb1a1*-lineage tracing, which should label the putative BASC population. These investigators found that during development and injury repair these cells gave rise only to conducting airway but not alveolar epithelia. In contrast, after bleomycin induced lung injury in later publications, *Scgb1a1+* lineage traced cells were capable of generating alveolar epithelial cells, although their contribution was limited and they did not appear to expand significantly.[22,31] Two recent studies using novel lineage tracing approaches provided more convincing evidence that BASCs are indeed a rare but distinct population of cells residing at the mouse bronchioalveolar duct junction and are capable of giving rise to both airway and alveolar epithelia to some degree following injury.[32–34] The relevance of these emerging murine BASC studies to human lung biology remains uncertain given that the anatomy of the most distal airways differs between the two species, and the anatomic equivalent of the murine bronchioalveolar duct junction is not present in the human terminal airways, which end as sequentially tapering terminal bronchioles, respiratory bronchioles, and alveolar ducts.[35,36]

In the more proximal airways, such as the mouse trachea or human bronchi, investigators have also found remarkable subsets of basal cells that contain extensive proliferative potential and a multipotent differentiation repertoire consisting of the capacity to give rise to basal cells, secretory cells, ciliated cells, neuroendocrine cells, ionocytes, and tuft cells.[37–43] With the advent of modern flow cytometry, these cells can now be sorted to purity, allowing the cataloging of protein markers (such as Trp63, NGFR, KRT5, or KRT14) that identify these cells as well as the delineation of their global transcriptome by microarray analysis or single-cell RNA sequencing.[37,42–44] The capacity to purify, expand in culture, and differentiate basal cells has resulted in a number of publications in recent years with important implications for those searching for lung stem or progenitor cells.[37,42–45] First, these studies have confirmed that heterogeneity within the previously limited subsets of lung epithelial cells is indeed much greater than was appreciated a decade ago.[26,46] Second, the studies have revealed the impressive proliferative potential and differentiation repertoire of some subtypes of single lung epithelial cells (such as basal cells), which can expand almost indefinitely in vitro, similar to classically studied stem cells of the skin.[37–45]

The surface epithelium of the conducting airways of humans and other mammals and of the proximal trachea of mice, forms crypts where the submucosal glands reside.[47–49] These glands are composed of luminal epithelial cells as well as basally located myoepithelial cells and have long been identified as airway niches that harbor proliferative cells able to give rise to surface airway epithelial cells following severe airway injury, providing additional epithelial progenitors able to participate in airway repair.[50–53]

Taken together, this body of work supports the concept that basal cells can function as tissue-specific stem cells of the conducting airway epithelium, secretory lineages can serve as facultative progenitors after certain injuries, and, following severe injury of the surface airway epithelium, the submucosal gland epithelial cells also can serve as a facultative progenitor cell population.

While there is a quickly growing list of stem/progenitor candidate cells able to reconstitute the conducting airway epithelium, the alveolar epithelial type 2 cell to date remains the best accepted progenitor of the lung alveolus;[54] however, the question of whether all alveolar type 2 cells or an "elite" minority are capable of functioning as progenitor cells remains unresolved.[55–57] Adding further complexity to this question, a growing number of recent reports suggest that, depending on the extent and type of injury to the alveolar epithelium, several alternative subsets of distal airway epithelial cells might serve as facultative progenitors that can also contribute to regeneration of the alveolar epithelium following injury. The first of these reports suggested that cells expressing airway basal cell markers in mice (TRP63+/KRT5+/KRT14+) following severe influenza injury undergo rapid proliferation and expand in regions of the distal lung as discrete KRT5+ clusters of cells, termed "pods".[45] Although the authors concluded that KRT5+ pods subsequently express alveolar markers such as the alveolar type 1 cell marker PDPN, the contribution of KRT5+ pods directly to the alveolar epithelium remains in doubt because (1) lineage tracing of *Krt14+* cells was induced following the initiation of injury, thus limiting the interpretation of the in vivo differentiation repertoire of these cells; (2) subsequent reports have not validated differentiation of *Trp63+/Krt5+* cells into alveolar cells;[58–60] and (3) PDPN is not an alveolar type 1 cell-specific marker, as it is also expressed in TRP63+ airway basal cells, limiting its use as an alveolar marker. Separate work by Chapman and colleagues has suggested that an alternative subpopulation of mouse epithelium, presumably in the airway, expressing the integrins alpha6 and beta4 ($\alpha6\beta4$), but little or no SFTPC, is capable of proliferating in response to lung injury, and after purification from mouse lungs displayed remarkable potential for multipotent airway and alveolar differentiation.[61] A subsequent study from this group showed that cells residing in the mouse distal airways, termed *lineage negative epithelial progenitors (LNEPs)*, proliferated following influenza injury and were a major cell type contributing to the previously described KRT5+ pods.[62] Orthotopic transplantation of LNEPs into influenza-injured mice demonstrated their multipotent differentiation to both airway and alveolar cell fates.[62] A follow-up study determined that LNEPs are composed of both *Trp63+* and *Trp63-* cells and that local hypoxia through hypoxia-inducible factor 1a (HIF1a) is responsible for the Notch signaling mediated expansion of KRT5+ basal-like cells. A recent study by the same group determined that an H2-K1^{high} subset of *Scgb1a1*-traced cells, quiescent in normal murine lungs, was capable of expanding in vivo after bleomycin-induced lung injury and gave rise to alveolar and airway lineages in vitro. Transplantation of FACS purified H2-K1^{high} cells into bleomycin-injured mice resulted in differentiation into alveolar lineages and improved oxygenation in the recipients.[60] These H2-K1^{high} cells appeared to be distinct from BASCs based on their absence of *Sftpc* expression and were distinct from the previously described *Trp63+* LNEPs. H2-K1^{high} cells expanded only following bleomycin and not influenza injury, suggesting that the type of progenitor cells that mobilize to regenerate the alveolar epithelium depends on the nature of the injury. In summary, an extensive literature dating back to the 1970s has established alveolar epithelial type 2 cells as the predominant facultative progenitors of the distal lung in both mice and humans,[63–65] but an emerging recent literature, based almost entirely on mouse studies, suggests there may be alternative rare progenitors with alveolar epithelial competence that can be harnessed after specific injuries (reviewed in Alysandratos et al.).[20]

PRELIMINARY ATTEMPTS TO HARNESS LUNG PROGENITORS FOR ENGRAFTMENT OR BIOENGINEERED LUNG TISSUE

While the therapeutic application of these progenitor populations remains years away, it is already clear that the lessons learned from studying the biology of progenitor cells in both mouse models and humans with lung disease can be applied to clinical settings. For example, many publications now demonstrate that communications between some of the best-studied lung epithelial progenitors and their neighbors, either in the epithelium or surrounding lung mesenchyme, helps to regulate the fine balance between progenitor self-renewal and differentiation.[18,46,66–71] Perturbations in these communications, controlled by familiar developmental signaling molecules (such as Wnt, Notch, FGF, retinoic acid, and TGFβ) disturb the balance of lung epithelial homeostasis[72] and contribute to the disordered histopathology and physiology of many lung diseases, including cystic fibrosis, emphysema, idiopathic pulmonary fibrosis, and asthma.[46,73,74] The increased understanding provided by studying the basic biology of lung progenitors and epithelial–mesenchymal interactions has thus allowed a more complete understanding of clinical disease[73,75] and already is being applied for the development of new pharmaceuticals designed to modulate the above signaling pathways. The long-term goal of achieving sophisticated drug therapies for a variety of lung diseases is likely to ultimately involve activation of endogenous lung progenitors or mature epithelia to accomplish reparative reepithelialization to avoid pathologic lung remodeling.[83]

Common to most of the aforementioned studies evaluating the differentiation repertoire of purified lung progenitor candidates is the suggestion that if an effective technique for grafting these cells into injured lungs were available, these progenitors might be used to regenerate injured epithelia in patients. In recent years, a number of studies have reported data supporting the capacity of transplanted epithelial progenitor[60,62,76–81] or mature cells[82] to survive in injured mouse lungs and express lung epithelial markers. Despite use of the term *engraftment* in several of the above studies, it remains unclear whether these cells are truly "engrafted" as this will require proof that the donor cells are long-lived as well as structurally and functionally integrated into recipient lungs. Importantly, physiologic improvement of injured mouse lungs after cell transplantation, as described in some of the above reports, might be explained by paracrine effects or transient secondary reparative effects on recipient lung tissue rather than by direct, durable replacement of the epithelium with functional cells. Furthermore, due to the lack of competitive repopulation assays it remains unclear which of the several candidate populations would have the highest potential to reconstitute the injured epithelium following transplantation. The contribution of the exogenously delivered cells relative to surviving intrinsic progenitors also is unknown. Furthermore, translation of these experimental mouse therapies to humans will be required if this approach is to be clinically applied in the future.

The prospect of engineering entirely new bioartificial lungs from these cells has also been proposed to meet the needs of growing numbers of patients with end-stage lung diseases who require lung transplantation. Pioneering studies in tissue engineering[84,85] have attempted to develop methods for preparing lung scaffolds or bioartificial lungs that might surmount this highest hurdle in our field: a method for delivering candidate progenitors or lung reparative cells in vivo for engineered lung regeneration. For example, the laboratories of Harald Ott and Laura Niklasson in 2010 both published a technique of engineering bioartificial lungs through the method of detergent-based decellularization of rodent lungs. This method leaves the 3D architecture of the lung matrix intact while stripping away rodent cells. This matrix then served as a scaffold upon which rodent or human cells were adhered to generate "recellularized" lung tissue able to carry out gas exchange in vitro or even in vivo after transplantation.[84,85] More recently, Dorrello et al. developed a rat model of epithelial-only decellularization, which maintains the vasculature and basement membrane integrity. The resulting grafts were recellularized with human adult pulmonary cells and pluripotent stem cell–derived alveolar progenitors.[86] Although the complexity of human lung has made the generation of a functional bioengineered whole lung a daunting task, the combination of targeted decellularization and recellularization of the lung epithelium and ex vivo lung perfusion are promising early steps toward achieving the goal of increasing the availability of acceptable donor lungs.[87]

CONTROVERSIAL CLAIMS OF PARADIGM-SHIFTING STEM CELL RESEARCH DISCOVERIES

These aforementioned studies of lung epithelial injury, proliferation, and regeneration are slowly defining and refining our understanding of candidate lung epithelial progenitors, but there are occasional studies that challenge earlier paradigms of lung development and repair after injury. In the 1990s and early 2000s, for example, a wave of publications claimed that cells within the bone marrow, such as mesenchymal stromal cells (also known as mesenchymal stem cells [MSCs]) or hematopoietic stem cells, could circulate to the lung and give rise to almost any type of differentiated lung epithelial or vascular endothelial cell. Similar findings were reported when examining injured hearts, brains, livers, and other organs, creating understandable excitement (reviewed by Weiss et al. and Wagers and Weissman[46,89]). Clinical trials were rapidly planned to expose patients to injections of bone marrow–derived cells in the hope of reconstituting degenerative or injured tissues. The opportunity for financial profit inspired companies to promote the banking of cord blood from babies, with glossy pamphlets suggesting to expectant parents that umbilical cord blood containing "stem cells" (now more appropriately called HSCs and MSCs) had the potential to treat diabetes, cystic fibrosis, Parkinson's disease, strokes, or a myriad of other diseases. These diseases might be treated with banked cord blood if, indeed, circulating blood or bone marrow–derived cells could form reconstituting cells for each relevant organ. In hindsight, the launch of some clinical trials and the promotion of cord blood as a panacea was premature as it was based on a first wave of controversial published literature. Advances in laboratory instruments and follow-up laboratory studies begun in 2000 slowly revealed that artifacts, such as autofluorescence, nonspecific antibody labeling, and the fusion of marrow-derived myeloid cells with recipient tissues were actually responsible for the bulk of initial observations and misinterpretations of bone marrow–stem cell engraftment.[88,89] Yet today, several for-profit clinics continue to promote their unproven, direct-to-consumer "stem cell" interventions based on the now-debunked stem cell plasticity literature from the 1990s to early 2000s.[88,90] Such businesses have been taking advantage of the confusion regarding the identity and properties of MSCs from various sources[91] and administer autologous, often crude cell preparations such as the adipose tissue–derived stromal vascular fraction, for a variety of indications, including respiratory diseases.[92] Culture-expanded MSCs after transplantation may induce potentially important indirect, paracrine, or immunomodulatory effects on injured lung tissues that need to be demonstrated in well-designed and powered clinical trials. Nevertheless, in the view of these authors, existing evidence does not support their use in approaches designed to directly regenerate the lung epithelium.[93–95]

ONE CELL TO RULE THEM ALL: PLURIPOTENT STEM CELLS

Because it remains controversial whether an endogenous or transplanted lung cell possesses broad multipotency or the capacity to produce every type of lung cell, some investigators have chosen to focus their research on the de novo derivation of lung lineages in vitro from pluripotent stem cells (PSCs), such as embryonic stem cells (ESCs), which have well-established potential to generate all cell types in the body,[96] including all lung cells (at least after injection into mouse embryos). The controversy over human ESC research, unlike other stem cell fields, has not been focused on the differentiation potential of the cells, but rather on the ethical debate over whether it is permissible to utilize for research cells that are derived from a preimplantation human blastocyst embryo (typically those unused from fertility clinics) and whether PSCs that are biologically similar to ESCs might be derived from postnatal patients. Solutions to these controversies and questions were provided in the remarkable discovery of reprogramming technology by Dr. Shinya Yamanaka in 2006. Yamanaka's work revealed that four transcription factors (Oct4, Klf4, Sox2, and cMyc) transferred into cells could reset the epigenetic state of somatic cells, such as skin fibroblasts, into an embryonic-like state virtually indistinguishable from ES cells.[103] Reproduction and refinement of this discovery established reprogramming as an accepted technique to engineer induced pluripotent stem cells (iPSCs) from dermal fibroblasts or from peripheral blood cells, such as those obtained from simple skin punch biopsies, or banked blood (reviewed by Stadtfeld and Hochedlinger[104]). Like ESCs, the broad differentiation repertoire of iPSCs suggests their potential to form any desired somatic cell type, including lung epithelium.[97] In contrast to ESCs, iPSCs are genetically identical to the individual from whom they are derived, raising the prospect of utilizing iPSCs for autologous cell-based therapies without risk of rejection. Yamanaka, together with his predecessor, Sir Jon Gurdon, who discovered reprogramming approaches in tadpoles 50 years earlier, were awarded the 2012 Nobel Prize in Physiology or Medicine for their paradigm-shifting discoveries.[105]

The key advance that enabled the derivation of lung progenitors from PSCs (ESCs and iPSCs) came with the discovery by Keller et al. that the soluble growth factor activin A (hereafter activin) induced the differentiation of these PSCs into the germ layer, definitive endoderm.[100] Since the lung develops from this germ layer, emerging from the anterior foregut endoderm by budding and then branching, the derivation of definitive endoderm from ESCs was a key milestone on the way to generating lung epithelial cells from PSCs.[102] Keller's discovery was based on a careful study of how the embryo develops in vivo. Secreted nodal protein from the node of the embryo is known to differentiate embryonic cells of the epiblast into primitive streak and then into definitive endodermal progenitors within the anterior region of this primitive streak. Since activin binds similar receptors to nodal protein, Keller et al. found that ESC cultures exposed to activin differentiated efficiently into definitive endoderm. It was not until the cellular and molecular pathways responsible for definitive endoderm induction[100] and its subsequent patterning to anterior foregut endoderm[97] were discovered that efficient generation of lung epithelial lineages was made possible.[97–99,106,107] Using expression of the *Nkx2-1* (also known as thyroid transcription factor-1 [TTF1 or

Titf1]) locus as a marker of lung lineage specification from foregut endodermal progenitors, a number of studies identified that the temporal activation of Wnt, BMP, and RA signaling is essential for lung lineage specification in vivo and can be harnessed to generate lung epithelium in vitro from PSCs.[107–111] Again, these discoveries of how to differentiate stem cells into lung progenitors through activating a sequence of developmental milestones was made possible by mimicking the published inductive signals known to be active during in vivo embryonic endoderm and lung development.[101,102] Additional studies have developed methods for further differentiating human PSC-derived NKX2-1+ progenitors into the developing cells of the proximal airways or distal alveoli, including their progeny of varying functionally mature stages. For example, 3D culture systems have now been developed for the efficient generation of functional alveolar epithelial type 2 cells that are transcriptomically and ultrastructurally similar to primary alveolar type 2 cells and capable of producing surfactant proteins and phospholipids.[112–114] In addition, airway progenitors have been generated from primordial NKX2-1+ lung progenitors and can be propagated in 3D spheres producing secretory and ciliated cells,[115,116] or most recently airway basal-like cells.[117] These studies have also highlighted the importance of better understanding the temporal relationship of developmental signaling pathways involved in lung lineage specification, differentiation, and maturation.

To establish clinically relevant pluripotent stem cell platforms for lung disease research, some investigators have developed new reprogramming technologies able to derive “clinical grade” iPSCs from human skin or blood[104] and have successfully applied these technologies to generate banks of “lung disease–specific” iPSC lines from patients with a variety of end-stage lung diseases.[118] There are an increasing number of publications demonstrating how these cells are being applied to model lung disease. For example, iPSCs generated from patients with cystic fibrosis have been differentiated into endodermal or more mature airway epithelial cells expressing the *CFTR* gene responsible for cystic fibrosis, thus modeling *CFTR* dysfunction using cells of each patient’s own genetic background and studying the effects of a pharmaceutical product designed to correct *CFTR* chloride ion flux.[117,119–121] In addition, an emerging literature has also utilized iPSCs to produce in vitro distal lung disease models by generating alveolar type 2–like cells that reveal pathogenetic mechanisms associated with children’s interstitial lung disease (chILD) due to surfactant mutations[112,122] or pulmonary fibrosis associated with Hermansky-Pudlak syndrome.[123,124] Many other groups are now focused on utilizing patient-specific iPSC lines (and ESCs) to model additional lung diseases in vitro, to screen drugs and gene therapy approaches, and to derive de novo replacement lung epithelia and endothelial cells that may one day be transplanted back into the patients from whom they have been derived (Fig. 8-2). The lessons learned from the failed attempts to deliver bone marrow–derived cells to the injured lung epithelium have taught us that delivery of iPSC-derived lung cells (or any other lung cell) in vivo will not be easy or straightforward. Still, precedent has already been set in initial clinical trials involving the transplantation of ESC- or iPSC-derived retinal pigmented epithelial cells to treat macular degeneration or dopaminergic neurons to treat Parkinson’s disease.[125,126] Animal models of Parkinson’s disease and mouse models of sickle cell disease paved the way for these new clinical trials after iPSC-derived replacement neurons or hematopoietic stem cells, respectively, resulted in clinical improvement when technology for effective differentiation and transplantation of these cells was carefully developed (reviewed in Stadtfeld and Hochedlinger[104]).

In almost any field of research where cells reminiscent of the early embryo are employed, such as iPSCs or ESCs, recapitulating the milestones of early development of that tissue lineage has proven to

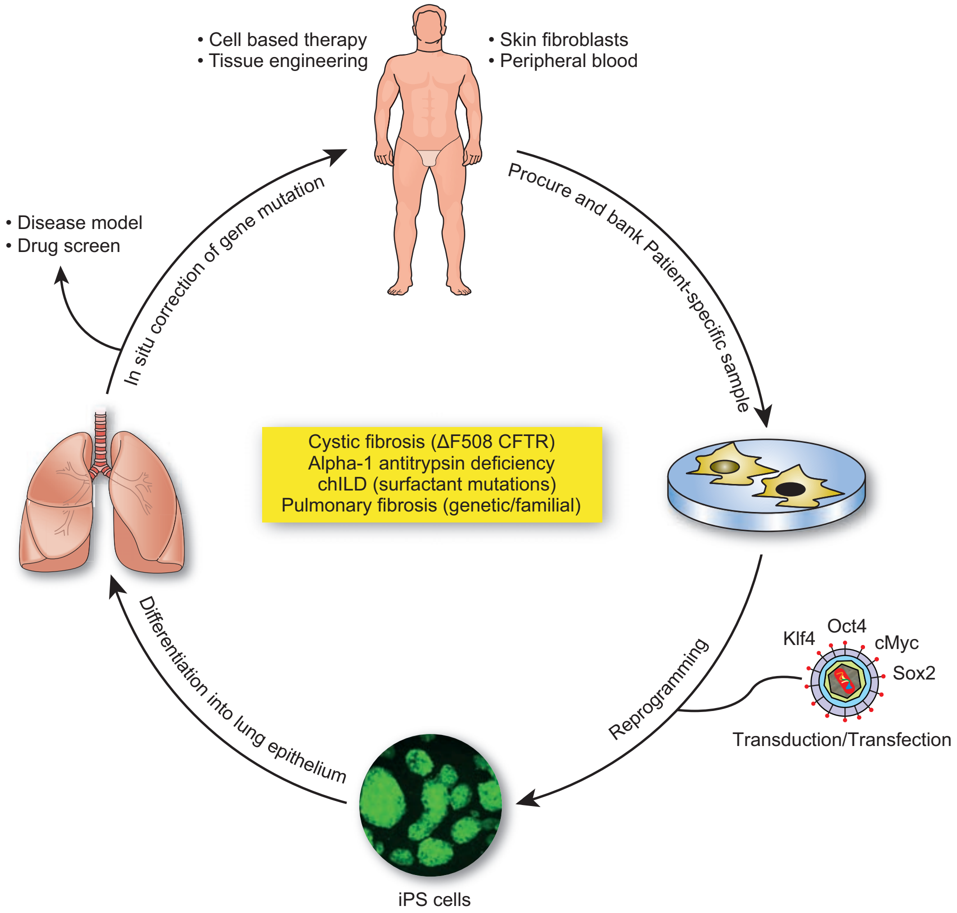
• Cell based therapy
• Tissue engineering
• Skin fibroblasts
• Peripheral blood
Procure and bank Patient-specific sample
• Disease model
• Drug screen
In situ correction of gene mutation
Cystic fibrosis (ΔF508 CFTR)
Alpha-1 antitrypsin deficiency
chILD (surfactant mutations)
Pulmonary fibrosis (genetic/familial)
Klf4
Oct4
cMyc
Sox2
Transduction/Transfection
Reprogramming
Differentiation into lung epithelium
iPS cells

Figure 8-2 Schematic indicating approach for generating patient-specific or disease-specific induced pluripotent stem cells (iPSCs) from humans with lung disease. Peripheral blood cells or skin fibroblast cells harvested from a patient with lung disease, are reprogrammed into iPSCs using defined transcription factors. The resulting iPSCs undergo in vitro “directed differentiation” into lung epithelial or other lung lineages. These lineages can be employed for in vitro studies of disease pathogenesis modeling or high-throughput screening of drugs to predict efficacy. The cells may also undergo correction of any disease-causing gene mutations (such as ΔF508 CFTR) using various genome editing technologies. Correction may be performed in the undifferentiated state or (as shown) following directed differentiation into lung lineages. For future studies, corrected cells may be employed to tissue engineering bioartificial lungs or to develop cell-based therapy by transplantation back into the patient from whom they have been derived. Alternatively, drugs passing in vitro screening can be administered to the patient as personalized medicine.

be the most effective and most efficient way to derive desired differentiated lineages in vitro.[96] Unfortunately, little is known about many stages of embryonic lung development, a deficit that limits progress in deriving de novo mature lung epithelia from pluripotent stem cells (be they ESCs or iPSCs) in vitro and hampers our ability to properly understand and modulate repair after lung injury.

FUTURE PROSPECTS FOCUSED ON THE CLINICAL APPLICATIONS OF STEM CELLS

Given that safe clinical applications of most of the aforementioned exciting stem cell advances remain years away, how is a pulmonologist able to answer questions and respond to the pleas of patients desperate for stem cell therapies? One resource designed to help both physicians and patients access reliable information is the International Society for Stem Cell Research (ISSCR) webpage, which features a downloadable free "Patient Handbook" designed to educate the public about the promise and perils of stem cell research (*www.closerlookatstemcells.org*). The American Thoracic Society webpage equivalent also helps to objectively caution patients that most stem cell trials charging fees for claimed "treatments" have not been reviewed or substantiated by experts (*https://www.thoracic.org/patients/patient-resources/resources/stem-cell-therapy.pdf*).

At the time of publication of this chapter, a number of clinical trials are listed at clinicaltrials.gov for evaluating various cell-based therapies for several lung diseases (reviewed by Weiss et al.[46] and Ikonomou et al.[95]). Infusions of MSCs to treat patients suffering from COPD, bronchopulmonary dysplasia, bronchiolitis obliterans, asthma, idiopathic pulmonary fibrosis (IPF), pulmonary hypertension, acute respiratory distress syndrome (ARDS), or more recently acute lung injury from coronavirus infection are planned, underway, or completed.[95] Additional clinical investigations, not listed on this website, have also targeted IPF with cell-based therapy.

It is still too early to determine whether any of these trials will prove efficacious, but accumulating data from >100 MSC clinical trials (mostly phase 1 or 2) registered on clinicaltrials.gov for treating diseases affecting other organs suggest that, at least for MSCs, there appears to be little safety risk to participants.[127] There is also little reason to believe that these trials will result in regeneration of lung tissue for participants, as the bulk of basic mechanistic studies in animals suggest the infused cells work mostly via paracrine or immunomodulatory effects on recipient lung tissue, as detailed above.[46] Thus, these trials might be viewed as evaluations of cell-based immunomodulatory drug delivery rather than attempts to regenerate lung tissue.[128] Infused endothelial progenitor cells (EPCs), which are investigated as a potential treatment for pulmonary hypertension, also appear to have paracrine and perhaps angiogenic effects on recipient tissue,[46] but their capacity to directly form replacement endothelial cells in the lung remains in doubt. When viewed with these results in mind, the term "stem or progenitor cell"—used to refer to the cells being infused in the trials to date—risks misleading clinicians and participants attracted by the promise that these terms imply. The dream of delivering truly regenerative or reconstituting cells to the lung, such as endogenous lung progenitors, ESCs, or iPSCs, will need to be appropriately delayed while these cell populations are fully evaluated in laboratory animals. The impressive differentiation and proliferation potential of the newly described PSC-derived populations also makes them potentially risky and teratogenic in human trials, if deployed before their biology is more fully understood.

All indicators suggest that we are at the onset of realizing the promise of lung regenerative medicine propelled by the quickening pace of stem cell research. Endogenous lung stem or progenitor cell populations, such as basal cells, are already revealing the mechanisms that control their biology in careful studies at the lab bench.[42,44,66,129–131] New bioartificial lungs generated in the laboratory have already been successfully transplanted into rat recipients,[84,85] and human iPSCs generated from patients with alpha-1 antitrypsin (AAT) deficiency have undergone successful gene correction in vitro followed by hepatic transplantation into rodents.[132] Early studies of approaches for transplanting epithelial progenitors into animal lungs following injury[60,62,76–82] also imply that a similar approach may one day be feasible for reconstituting the lung epithelium by transplantation of gene-edited lung progenitors derived from either iPSCs or endogenous sources.

How will the emerging studies focused on lung stem cells impact future clinical care of patients with lung disease? Treatment approaches are likely to involve one or more of several approaches based on the growing literature on endogenous lung progenitors and the recently described lung lineages developed from exogenous PSC sources, such as iPSCs. First, an improved understanding of the pathways that regulate endogenous lung progenitors and control their cell fate decisions to self-renew or differentiate is likely to result in pharmaceutical approaches designed to regulate the behavior of these cell populations during disease pathogenesis. For example, if syndromes such as bronchiolitis obliterans result from an inability to maintain bronchiolar epithelial homeostasis, then an improved understanding of the biology of progenitors of the airways should with time lead to drug approaches for regulating the behavior of these cells toward improved maintenance of homeostasis, epithelial–mesenchymal crosstalk, or epithelial barrier integrity. Second, gene therapies aimed at correcting monogenic lung diseases, such as cystic fibrosis or alpha-1 antitrypsin deficiency, likely will involve gene editing[61] or gene correction of lung progenitors or stem cells. A key hurdle limiting progress in lung gene therapy has been the inability to accomplish gene transfer into enough cell numbers. Stem cells provide a potential solution to this problem, since correction of just one stem cell may be sufficient if that cell can self-renew (either in vitro or after engraftment in vivo) extensively enough to reconstitute large numbers of lung epithelial cells via its progeny. Hence, methods for the translation of the aforementioned mouse transplantation therapies to humans will be required in order for this hope to come to fruition.

iPSCs are likely to impact lung disease treatments in several ways in the future. First, personalized therapeutic drug regimens can be screened in vitro using lung lineages derived from each patient's iPSCs, potentially predicting effective individualized drug regimens for each individual, rather than the globalized approach currently used to treat disease, where treatments for disease targets are chosen based on trial data from heterogeneous cohorts of patients. If approaches for engrafting or reconstituting human lung tissue with exogenously delivered cells are ever successfully developed, iPSC-derived cells are one potential source of autologous cell derivatives for potential reconstituting therapies. A particularly attractive, yet far-off, goal of some stem cell researchers is the engineering of tissues from stem cells, including the tissue engineering of a whole, functioning, transplantable lung.[84,85] Several groups are working to optimize this approach using iPSCs to derive lung lineages for recellularizing these grafts to optimize tissue engineering of bioartificial lungs for transplantation in the future.

While some prospects for employing stem cell–based therapies will take many years to come to fruition, this exciting field of research raises many potential avenues for achieving the long-sought goal of lung regenerative therapies. Perhaps at this, the most optimistic time in a century of basic science research, we would be most wise to re-emphasize that many of the miraculous advances being made in this field are based on basic science research discoveries realized by investigators who originally had no practical clinical translation in mind. Those who simply wondered what made the Drosophila fly's wing notched, or made the jellyfish glow green, for example, paved the way for today's stem cell discoveries. In 1976, Comroe and Dripps found that the top 10 clinical advances in cardiac and pulmonary medicine derived from 529 key articles, 61.7%

of which were classified as "basic science research" and 42% were not clinically oriented at the time the work was done, leading the authors to conclude that "basic science research" pays off in terms of key discoveries.[133] Their report from 45 years ago potentially provides a guide for realizing the full promise of lung-related stem cell research in the years ahead.

SUMMARY

Research discoveries in the fields of stem cell biology and regenerative medicine are beginning to advance and refine an understanding of lung injury and repair. While these emerging studies offer unprecedented opportunities to develop novel therapies for a variety of lung diseases, realization of these therapies will take time and clinical application remains predominantly a future prospect rather than a clinical trial–ready treatment. Given the increasing number of questions from patients about how stem cell research will impact their care, this chapter provides an overview for the clinician or clinician-researcher of the latest advances in lung-related stem cell research and places the new discoveries in a historic context. Established, lineage-restricted, epithelial progenitors of the conducting airways and gas-exchanging alveoli are briefly reviewed, and controversial, newly proposed, tissue-specific candidate lung stem/progenitor cells with broader differentiation repertoire are introduced. Exogenous derivation of lung epithelia from ESCs or iPSCs is also presented as an alternative method for engineering lung tissue de novo in culture.

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CHAPTER 9

Personalized Pulmonary Medicine

Benjamin A. Raby
Kelan G. Tantisira

INTRODUCTION

Since the first draft sequences of the human genome were completed in 2001,[1,2] medical research has increasingly focused on the utilization of genetic and genomic profiling in the prediction of disease susceptibility and natural history, as well as drug response and drug development. Personalized medicine, aka "precision" medicine, can be defined as an approach to medicine in which medical decisions are tailored to the individual patient. In theory, in patients with established disease, personalized medicine will make health care more efficacious, more affordable, and safer by avoiding costly and prolonged trial-and-error approaches, unwanted therapeutic side effects, and diminished treatment efficacy. In preclinical settings where an individual's molecular profile could be used to estimate their risk of disease, precision medicine can be used to triage patients for more vigilant screening to identify disease presence before clinical indications and symptoms appear or to initiate preventative therapies. Thus, personalized medicine enhances the focus on preventive medicine at the primary, secondary, and tertiary levels. Fully realized, personalized medicine has the potential to facilitate early diagnosis and/or prevention of disease and selection of optimal therapeutic choices with minimal attendant side effects for established disease states. The potential benefits, from both a financial and quality of life perspective, are enormous.

Much of the efforts to adopt personalized medicine into clinical practice have centered on genetic approaches, as sequence changes in deoxyribonucleic acid (DNA) have been closely associated with a wide range of disease susceptibilities and therapeutic responses. However, the "omics" era includes enhanced focus on cellular and metabolic changes downstream of DNA sequence variation including genomics or transcriptomics (the analysis of gene expression), proteomics (the analysis of protein changes), and metabolomics (the analysis of end products of cellular metabolism). Adding to genomic complexity are the so-called epigenetic changes, the study of changes in gene expression or cellular phenotype caused by mechanisms other than changes in DNA sequence, such as DNA methylation, post-translational modification of gene expression, and microRNA (see Chapter 7). Many of these modalities are already being used as biomarkers in a personalized medicine context, and all have the potential to do so. In this chapter we review the foundations of personalized pulmonary medicine and the current approaches being used to develop personalized diagnostic and treatment strategies for pulmonary disorders, including specific examples of personalized approaches currently being implemented in clinical practice. We provide overviews of human genetics, personalized pulmonary diagnostic testing, pharmacogenomics, biomarkers, and future implementation as they relate to personalized respiratory medicine.

DETERMINANTS OF THE CLINICAL UTILITY OF A GENETIC TEST

The predictive power of a genetic test is a function of four interdependent estimable parameters: (1) the *heritability* of the trait; (2) the *penetrance* of the tested genetic variant; (3) *allelic heterogeneity*; and (4) the variant *allele frequency*.

Heritability can be defined as the proportion of disease risk that is explained by genetic determinants. Heritability is highest (~100%) among monogenic diseases like cystic fibrosis, and more modest (30%–60%) for common diseases such as asthma or obstructive sleep apnea, where a substantial proportion of disease risk is due to environmental factors. The heritability for many commonly measured pulmonary quantitative traits is also modest (Table 9-1).

Penetrance is defined as the likelihood of manifesting phenotype (i.e., disease or trait) among individuals who carry the risk genotype (Fig. 9-1). Penetrance is highest for variants implicated in rare monogenic disorders, approaching 100% for the ΔF508 mutation in cystic fibrosis (CF) and is lowest for more prevalent genetic variants associated with common diseases. The range of reported penetrance in pulmonary disease is broad, from 90% for FLCN mutations in Birt-Hogg-Dubé syndrome (BHD)[3] to 20% to 50% for *BMPR2* mutations in familial pulmonary hypertension[4] and the *MUC5B* promoter polymorphism in familial pulmonary fibrosis.[5] Penetrance is phenotype-dependent. For example, in BHD, although ~90% of patients with *FLCN* mutations have radiographic evidence of parenchymal lung cysts, penetrance is lower for dermatologic findings (seen in ~60%) and spontaneous pneumothorax (observed in 38% of patients).[3] Similarly, although virtually all PiZ homozygotes have markedly reduced circulating levels of α1-antitrypsin levels, only a subset of these individuals manifests symptomatic emphysema.[6]

Allelic heterogeneity refers to the existence of more than one disease-causing allele at different locations in the same disease-causing gene. Although one variant may predominate as the most prevalent disease allele (for example, the Z allele in 85% in α1-antitrypsin deficiency), numerous pathogenic variants are typically described, including more than 20 *SERPINE1* mutations in α1-antitrypsin, 50 *FLCN* mutations in BHD, and more than 120 pathogenic *CFTR* variants in cystic fibrosis. Allelic heterogeneity must be distinguished from *locus heterogeneity*, where the same phenotype can manifest through mutations in different genes. For example, familial bronchiectasis resulting from primary ciliary dysfunction has been mapped to no fewer than 34 separate genes that code for distinct proteins of the ciliary apparatus.

TABLE 9-1 Heritability Estimates in Pulmonary Medicine

Trait	Heritability Estimates
Pulmonary diseases	
Cystic fibrosis	1.0
Asthma	0.36–0.72
COPD	0.40–0.77
Pulmonary fibrosis	
Sarcoidosis	0.60–0.70
Obstructive sleep apnea	0.33–0.52
Quantitative traits	
FEV_1	0.38–0.77
FVC	0.54–0.91
FEV_1/FVC	0.44–0.46
Airways responsiveness	0.30–0.66
D_{LCO}	0.39–0.46
IgE levels	0.40–0.60

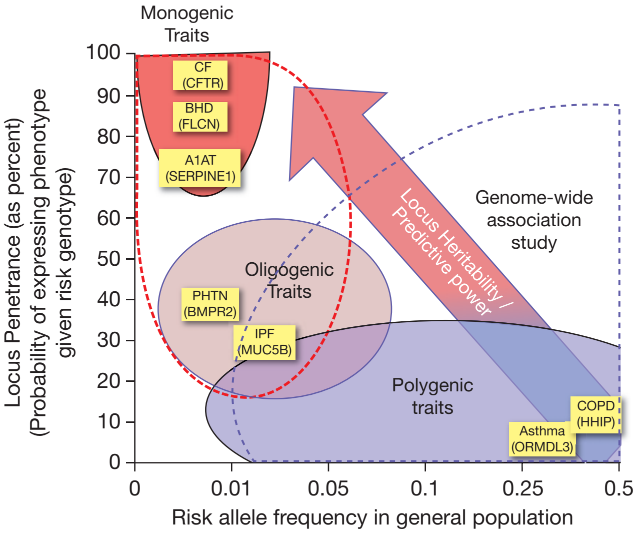

Figure 9-1 The relationship between allele frequency, locus heritability, predictive power, and genetic mapping strategies. Monogenic diseases, such as cystic fibrosis (CF), Birt-Hogg-Dubé syndrome (BHD), and α1-antitrypsin deficiency (A1AT) are caused by highly penetrant, deleterious causal mutations that can be detected by parametric linkage analysis. Polygenic, complex traits, such as asthma and COPD, are caused by numerous genes (dozens to hundreds) harboring variants of much weaker genetic effect. Genome-wide association studies can identify the subset of these variants, but their individual predictive value is low. Oligogenic traits, like familial forms of pulmonary hypertension (PHTN) and idiopathic pulmonary fibrosis (IPF), are caused by variants in a handful of genes with both intermediate frequencies and intermediate penetrance functions.

The influence of variant *allele frequency* on the predictive power of a genetic test is complex, and it depends largely on the strength of the genetic effect conferred (the locus heritability) and the disease prevalence. Rare monogenic lung diseases typically result from highly penetrant, low-frequency (<1%) variants situated in highly conserved protein-coding sequences. Most common disease susceptibility variants reported are of high frequency (>5% in the general population) but individually are of weak effect. In many instances, the population risk allele frequency exceeds the population disease prevalence (such as the asthma-associated *ORMDL3/GSDMB* risk haplotype, frequency of 62% in asthmatics). In these cases, the specificity of the variant is quite weak. In contrast, rare variants of high penetrance implicated in common disease will have high specificity, yet their low population prevalence diminishes their clinical predictive value, as sensitivity and negative predictive values will be poor.

GENETIC TESTING

All the major classes of genetic variation—including single nucleotide substitutions, insertions and deletions, copy number variants, and larger, more complex structural variants—have been described in pulmonary disease (Table 9-2), and no single technology has been developed that can reliably survey all these forms simultaneously. The rapid pace of technological advancement and the vast number of technologies in current use preclude comprehensive review of all available genetic diagnostic platforms here. Instead, we focus on next-generation sequencing, which is emerging as an efficient, reliable, and increasingly affordable diagnostic platform in many clinical contexts.

■ Whole-Genome Sequencing

Next-generation sequencing (NGS) platforms enable DNA sequencing in a highly paralleled fashion by generating short sequence reads (30 to 135 bases in length) sampled randomly from across the target sequence. With these methods, sequencing of nearly all genomic regions (i.e., "whole genome") is now feasible and is being widely implemented for both research and clinical purposes. The massive parallel nature of these techniques, and their lack of reliance on Sanger chemistries, have resulted in dramatic reductions in cost (now less than $1000) for whole-genome sequence.

The major technical challenge, and an important determinant of cost, is achieving sufficient base-calling accuracy. Given the very large numbers of both the bases being called (billions) and polymorphisms per genome (~3–4 million), accuracies of >99.9% are needed to limit the number of spurious findings (both false positive and negative). Such accuracy can be achieved by ensuring high read depth—the number of times a given base is sequenced. For clinical purposes, minimum average read depths of 30–40 times provide reasonable accuracies. For whole genomes, such coverage can be achieved only by performing multiple sequencing runs, increasing costs considerably. Despite this, however, the more expensive elements of whole-genome sequencing are the downstream data analysis costs, which include sequence quality assessment, sequence alignment and annotation, and variant classification (see below).

Additional costs are often incurred from the current clinical guidelines that mandate independent technical validation of all actionable (clinically relevant, reportable) variants by Sanger sequencing. Thus, while the technical cost continues to fall, current total charges (often exceeding $10,000 per clinical genome) have limited widespread adoption of whole-genome sequencing at present. Moreover, because all people carry thousands of functional variants, many of which are disease causing, physicians ordering whole-genome sequence should anticipate identifying incidental findings (including unsuspected actionable variants in genes unrelated to pulmonary disease) of which the patient would need to be informed. Thus, we recommend judicious use of whole-genome sequencing, with appropriate pretest counseling with the assistance of an experienced provider and genetic counselor.

■ Targeted Sequencing Panels

While use of whole-genome sequencing in clinical practice remains modest, there is increasing use of focused, targeted NGS of selected genes or gene regions, which is achieved by "pulling down" DNA segments of interest using oligonucleotide filters (i.e., probe sets that bind complementary sequence). These filters can be customized to target specific sequences, ranging from a handful of genes to all gene-coding regions (i.e., whole exome filters). This approach markedly reduces the size of targeted sequence length (for example, an exome sequence is only 3% of the total genome sequence), with numerous advantages for clinical implementation. The marked reduction in target size accommodates clinically reliable read depths in one sequence run, reduces analytic costs (as there is less sequence to annotate), and reduces follow-up validation costs. Panel testing also sharply limits the potential for incidental findings, greatly simplifying both pre- and posttest counseling.

■ Pulmonary-Specific Sequencing Panels

Targeted sequencing panels of selected genes that cause pulmonary disease are available commercially through several companies and clinical laboratories. The services provided differ from each other primarily in their gene content, which are frequently organized in discrete gene panels. Most panels are designed to assess limited sets of genes implicated in disorders typified by a particular clinical or radiographic manifestation (i.e., a pulmonary fibrosis panel) or a shared molecular defect (i.e., ciliopathy panel). The largest panels available are those for workup of pulmonary fibrosis and bronchiectasis. Due to technical limitations and the constant pace of novel disease-gene discovery, few

TABLE 9-2 Types of Genetic Variation and Their Relative Contribution to Disease Phenotype

Genetic Variation	Definition	Phenotypic Variation %[a]	Example	Pulmonary Manifestation
Chromosomal abnormalities				
Numerical abnormalities	Variations in chromosome number			
Polyploidy	Additional genome copies		69 XXY	Fetal loss
Aneuploidy	Variable number of single chromosome	<1%	Trisomy 21: Down syndrome	Obstructive sleep apnea and pulmonary hypertension
		<1%	Monosomy XO: Turner syndrome	No common pulmonary phenotype
Structural abnormalities	Variations in chromosome structure			
Gross rearrangements	Visible by karyotype/FISH	1%	del(4)(q12): FIP1L1-PDGFRA gene fusion	
Translocations	Aberrant exchange of DNA sequence between two different chromosomes		T(9;22)—Philadelphia chromosome of chronic myelogenous leukemia	Somatic translocations commonly seen in lung cancer tumors
Inversions	Altered sequence orientation		900-kb inversion on 17q21	Glucocorticoid pharmacogenetic response
Copy number variants	Gains or losses of DNA sequence spanning 500 bp or more	9%	GSTM1 null variant	Smoking-related lung function decline
Sequence variants				
Single nucleotide polymorphism	Single base pair substitutions			
Nonsense/missense	Variant introduces stop codon/amino acid substitution	55%	FLCN R4496X: Birt-Hogg-Dubé SERPINE1 Glu366Lys (Z) allele	Spontaneous pneumothorax, α1-antitrypsin deficiency, emphysema
Splicing	Variant alters normal intron splicing pattern	9.20%	DNAI1 IVS1+3insT: Primary ciliary dyskinesia	Bronchiectasis
Regulatory	Variant alters mRNA transcription or protein translation	2%	17q21 rs12936231 variant alters ORMDL3/GSDMB expression	Asthma
Insertion/deletion (Indel)	Gain or loss of one or more nucleotides	23%	CFTR ΔF508	Cystic fibrosis
Short tandem repeat	Repetitive element that varies in copy number	0.30%	PHOX2B exon 3 polyalanine repeat expansion	Primary central hypoventilation syndrome

[a] *Percent of total variation listed in Human Gene Mutation Database (http://www.hgmd.cf.ac.uk/ac/), accessed May 30, 2013.*

panels can be considered fully comprehensive. Yet, most offer coverage of the most commonly implicated genes being considered clinically. Even for large panels (40 or more genes), the costs of panel sequencing are comparable to those of other genetic tests routinely used in practice (cytogenetics) and typically only 2–3 times the cost of single-gene sequencing. Thus, when more than one gene is clinically suspected, or for diseases with known locus heterogeneity, diagnostic panels offer greater sensitivity and cost efficiency over single gene testing.

More broad sequencing panels may have particular value in the evaluation of patients with more complex presentations (for example, patients presenting with a combination of bronchiectatic and fibrotic features, or with parenchymal lung disease disproportionate to the degree of concomitant pulmonary hypertension). When a genetic basis is suspected, massively paralleled sequencing across multiple disease panels may help narrow the differential diagnosis to one or two disorders. One such solution, available through some sequencing providers, is a sequential, hierarchical analysis approach, where analysis/interpretation of a whole exome sequence is initially limited to the panel deemed most likely to harbor mutation and then extended to increasingly less probable panels (and eventually whole exome) as needed. For example, evaluation of idiopathic bronchiectasis may begin with a bronchiectasis panel (∼40 genes, including CFTR, PCD genes, and SERPINA1), with reflex testing of immunodeficiency panels (often greater than 150 genes). Although possibly more cost-effective over current diagnostic strategies, the value of such an approach to the workup of patients with complex presentations remains unclear.

■ Interpreting Genetic Test Results

The American College of Medical Genetics has developed guidelines for the classification of variants based on their probability of pathogenicity.[7] This classification schema and the criteria for variant classification (Table 9-3) have been broadly adopted by clinical laboratories and are included routinely in test reports. There are five variant categories: “pathogenic,” “likely pathogenic,” “variant of unknown significance (VUS),” “likely benign,” and “benign.” Variants classified as pathogenic are those firmly implicated as disease-causing due to their demonstrated functional impact, their localization to a highly conserved functional genomic sequence, their presence in affected individuals only, and their strong segregation with disease. Likely pathogenic variants have many, but not all, of these features. Benign variants are those that are common

TABLE 9-3 American College of Medical Genetics Standards and Guidelines for Variant Reporting

	Strength of Evidence (Odds of pathogenicity[a])					
	Benign			Pathogenic		
	Strong (−18.7)	Supporting (−2.08)	Supporting (2.08)	Moderate (4.33)	Strong (18.7)	Very Strong (350.0)
Population allele frequencies	High allele frequency/ presence in controls inconsistent with penetrance			Absent in databases	Prevalence in cases > controls	
Computational and predictive analysis		Multiple lines of evidence support benign effect Missense variant in gene with only disease-causing are LOF	Multiple lines of evidence support deleterious effect	Missense in gene with other missense/ truncating	Same amino acid change	Null variant in gene where LOF is pathogenic
Functional studies	Studies show no deleterious effect		Missense in gene with low missense rate	Mutational hot spot in well-studied functional domain	Studies confirm deleterious effect	
Segregation in families	Segregation in healthy individuals		Co-segregation with multiple affected individuals	⟶	Increasing segregation data ⟶	⟶
De novo				De novo (paternity uncertain)	De novo (paternity certain)	
Allelic information		Observed with pathogenic variant		For recessive disease, found in trans with pathogenic variant		
Other databases		Reputable source	Reputable source			
Other		Found in cases with alternate cause	Phenotype or family history highly specific for gene			

[a]As reported by Strande et al.[109] Assumes a prior probability of 0.10 for a single-gene analysis.

Reproduced with permission from Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology, Genet Med. 2015;17(5):405–424.

among healthy controls, have no demonstrable function, and do not segregate with disease in families. Counseling of patients regarding these three classes of variants is often unambiguous: the finding of pathogenic or likely pathogenic variants in a gene known to cause phenotypes consistent with those of the patient often confirm or establish diagnosis and can inform management decisions, while finding only benign variants can, in the appropriate clinical context, provide reassuring information by excluding specific disorders. In contrast, VUS variants fall into a grey zone: either they do not have a sufficient number of features to firmly classify in one category, or they meet criteria for both benign and pathogenic that are contradictory. Given that most disease-causing variants are rare (often private to one family or ethnic group) and are thus unlikely to have been studied experimentally for functional impact or disease association, the likelihood of detecting a VUS is high and increases as the number of genes tested is increased. Providers and patients must understand the possibility of such findings and their implications on subsequent workup and management.

■ Clinical Indications for Genetic Testing

Table 9-4 lists the most common uses of genetic information in clinical practice, for both the patient and at-risk family members. Diagnostic genetic testing is of greatest value when knowledge of the specific gene or mutation will directly impact clinical management. In these cases, genetic testing should be offered to patients in whom the possibility of defining an actionable variant is high, including those with specific disease presentations compatible with the diagnosis of interest, at-risk family members of patients with confirmed molecular diagnoses, and subjects with strong family histories. Examples include:

- Confirmation of α1-antitrypsin deficiency in patients with emphysema and lung function decline identifies a small subset of COPD patients who may benefit from replacement therapy.
- Characterizing CFTR genotypes in patients with cystic fibrosis to determine likelihood of responsiveness to modulator therapy.[8,9]
- Differentiating molecular forms of familial idiopathic pulmonary fibrosis: (1) Patients with *SFTPC* mutations may benefit from hydroxychloroquine treatment;[10] (2) TERC and TERT mutations help identify patients with short telomere syndrome (STS) at risk of marrow and liver failure, including during the post–lung transplant period; (3) Hermansky-Pudlak syndrome (HPS) can often be overlooked clinically due to subtle neurologic (nystagmus) and dermatologic (albinism) features, although these patients are at risk for a potentially severe but treatable (with DDAVP) bleeding diathesis.

TABLE 9-4 Utility of Genetic Information in Clinical Practice

Activity	Paradigmatic Example	Current/*Potential* Utility in Pulmonary Medicine
Preimplantation screening	Tay-Sachs disease	*Primary ciliary dyskinesia*
In utero diagnosis	Trisomy 21	*Congenital diaphragmatic hernia*
Newborn screening	Phenylketonuria	Cystic fibrosis
Diagnostics		LAM versus Birt-Hogg-Dubé syndrome
Prognostics	Expansion length and age of onset in Huntington's disease	*MUC5B as positive prognostic in IPF*
Presymptomatic interventions	BRCA1 and prophylactic mastectomy/oophorectomy	*BMPR2 and vasodilator therapy*
Surveillance strategies	APC mutations and familial adenomatous polyposis	FLCN mutations and renal cancer screening in Birt-Hogg-Dubé syndrome
Replacement therapies	Gaucher's disease	A1-antitrypsin deficiency
Mutation-directed therapies	Tyrosine kinase inhibition in EGFR+ tumors	Ivacaftor in G551R-positive cystic fibrosis
Pharmacogenetics	Warfarin dosing	*Polygenic model of inhaled corticosteroid response in asthma*
Gene replacement therapy	X-linked severe combined immunodeficiency	*Surfactant gene replacement in infantile pulmonary fibrosis*

For highly penetrant monogenic diseases, the implications of a positive test result are often profound, even in instances where gene- or mutation-specific therapies are not yet available. Examples include preclinical identification of patients at risk for malignancy (for example, in BHD or LAM), accelerated lung function decline (in LAM, familial fibrosis), cerebrovascular complications (in hereditary hemorrhagic telangiectasia), or pulmonary hypertension, who can be more closely followed enabling earlier intervention, and who can be more vigorously counseled regarding the benefits of tobacco smoke avoidance or other risk modification. An illustrative example is provided in Fig. 9-2, depicting the value of testing in a family pedigree with BHD. For autosomal dominant diseases of variable penetrance, and for recessive disease, genetic testing offers the ability to identify at-risk carriers prior to the onset of symptoms, providing opportunities for early diagnosis.[11] Negative test results are also of value, providing reassurance to relatives that they are not at risk of developing an illness they may have witnessed afflicting their relatives.

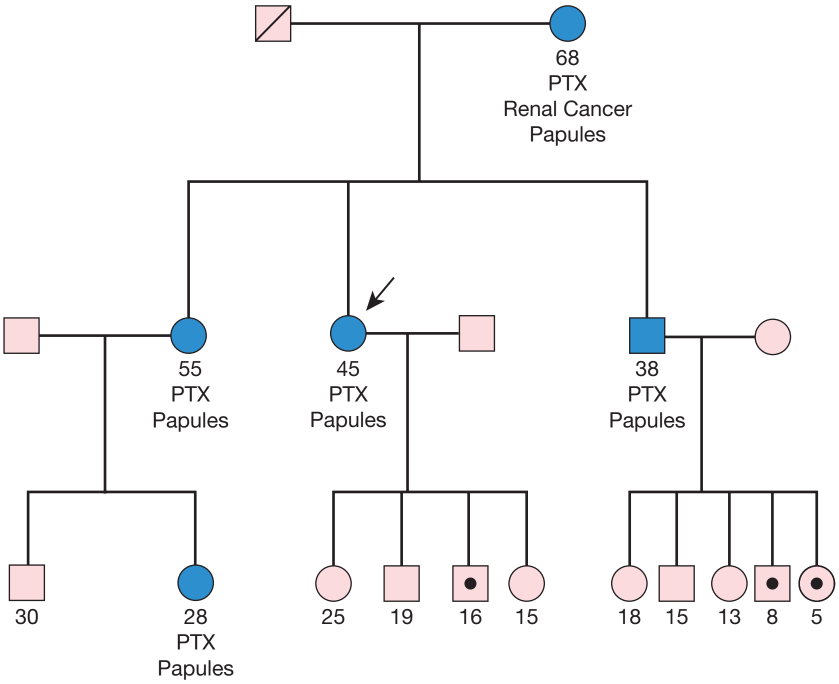

Figure 9-2 Birt-Hogg-Dubé (BHD) syndrome. Index patient (*arrow*) confirmed to harbor a pathogenic FLCN gene mutation. The maternal history of renal cancer places other mutation carriers in this family at risk of both renal and other malignancies. In this pedigree, the large number of reportedly unaffected offspring of two carriers is unusual, given a 50% probability of transmission from carrier to offspring. More likely, the mutation was passed on (hypothetically denoted by dot), but these carriers have not yet developed clinical manifestations, possibly due to their younger age. Such individuals would be at risk of eventually developing BHD, including malignancy. Therefore, confirmation of carrier status among at-risk, but seemingly unaffected, family members is warranted.

■ Genetic Counseling in Pulmonary Medicine

The inherently predictive, personal, and irreversible nature of an individual's genetic code distinguishes genetic from other forms of clinical testing. The psychological impact of genetic test results, whether positive or negative, cannot be underestimated. Feelings of inadequacy or imperfection, a sense of inevitable doom, and therapeutic nihilism due to a genetic "fate" are not uncommon with a confirmed genetic diagnosis. Conversely, negative results can lead to a false sense of invincibility, leading to unhealthy behaviors (for example, continuing to smoke). Inherently, the potential impact of genetic testing extends beyond the patient, implicating all blood relatives. Moreover, test results can impact family dynamics and the way in which individual family members react to their test results. For example, although most at-risk family members will be relieved by a negative test result, some experience a deep sense of guilt ("survivor's guilt") in relation to their affected family members. In addition, despite legislation at state and federal levels protecting patients from genetic discrimination in the workplace and in access to health care insurance, patients must be informed regarding this risk in other contexts (for example, the impact on eligibility for life insurance policies). Lastly, we emphasized that, prior to ordering expansive tests (panels, exomes, genomes), patients must be made aware that broad surveys increase the likelihood of identifying variants of unknown clinical significance (so-called VUS). Patients must be counseled pre-test regarding the uncertainty these findings may impart.

For all these reasons, it is advised that expanded genetic testing be offered only by, or in consultation with, experienced providers familiar with these issues, including certified genetic counselors, who can adequately address the medical, psychological, and familial implications of test results. We recommend initiating these discussions prior to testing ("pretest counseling"), so that patients are empowered to provide truly informed consent. Patients should be made aware of the medical implications of both positive and negative results and should be advised regarding the impact these results may have on them and their family members. Genetic pretest counseling should also address the potential identification of variants of unclear significance, as well as the potential impact of positive test results on both the cost of, and eligibility to obtain, life or long-term disability insurance. This approach can mitigate the development of patient stress and regret, even when returning potentially distressing results.[12]

MUTATION-SPECIFIC THERAPIES IN MONOGENIC LUNG DISEASE

One of the primary goals of genetic classification of disease is the development of mutation-specific treatment strategies. Such activities have traditionally focused on the development of replacement therapies for loss-of-function recessive diseases (e.g., recombinant human α1-proteinase inhibitor replacement therapies for α1-antitrypsin deficiency). Newer pharmacologic approaches, including small molecule screens and others informed by the functional impact of specific mutations, are emerging.

Tyrosine Kinase Inhibition for Hypereosinophilic Syndrome

Imatinib was identified as a therapy for chronic myelogenous leukemia (CML). However, once the functional mechanisms underlying its therapeutic effects were elucidated other therapeutic indications were identified, including its use in the treatment of hypereosinophilic syndrome (HES). Subsets of HES patients harbor a chromosome 4q interstitial deletion that results in the creation of a fusion of the *FIP1L1* and *PDGFRA* genes. The resultant fusion protein has tyrosine kinase activity similar to that of the BCR-ABL fusion protein in CML (the target of imatinib), and HES patients positive for the *FIP1L1-PDGFRA* rearrangement respond positively to imatinib therapy.[13,14] *FIP1L1-PDGFRA*-negative HES patients do not. Similar to CML, mutations of the tyrosine kinase binding site have been reported upon HES relapse.

Mutation-Specific Therapies for Cystic Fibrosis

In 2011, positive results of a randomized clinical trial of a novel therapy for G551D-positive cystic fibrosis were reported[8] (Fig. 9-3). This oral agent—ivacaftor—"potentiates" CFTR activity by prolonging channel opening times and augmenting transmembrane chloride transportation in individuals with class III CFTR mutations, the most common of which is G551D. In a randomized, double-blind, placebo-controlled trial, cystic fibrosis patients with at least one G551D mutation treated with ivacaftor demonstrated significant improvements in FEV_1, fewer respiratory exacerbations, improved quality of life, and a positive weight gain compared with those receiving placebo. The ~50% reduction in sweat chloride levels to those approaching those observed in asymptomatic *CFTR* mutation carriers (i.e., heterozygotes) serves as an elegant molecular-clinical correlate, suggesting selective effect on the G551D+ channel, but not ΔF508+ channels. Class III mutations are found in only ~6% of patients. Subsequently, two additional compounds have been developed that improve function of other CFTR channel classes, including ΔF508 and ~90% of all CF-causing variants. The efficacy of combined triple therapy (elexacaftor-tezacaftor-ivacaftor) was established in two large, randomized, placebo-controlled trials that demonstrated clinically significant improvements in lung function and quality of life and marked reductions in exacerbation and hospitalization rates (Fig. 9-3D). The advent of this novel treatment strategy provides motivation for the development of additional agents that target other *CFTR* mutation classes (including the most common *CFTR* mutation—ΔF508) and the application of similar strategies for the treatment of other genetic diseases. This example also illustrates the increasing importance of classifying patients by genotype status, as there remain 10% of CF patients—those with mutations that preclude CFTR protein production (class I mutations)—who are not responsive to triple therapy. Alternative approaches to address these patients' needs are in development, including the prospect of so-called read-through therapies.

INTRODUCTION TO DIAGNOSTIC TESTING

Given the increase in biomarkers with an emphasis on precision medicine, a brief review of quantifiable diagnostic measures of accuracy is warranted. Importantly, poorly designed studies, or studies limited to a specific disease stratum or subgroup, may generate false estimates of the test accuracy or severely limit generalizability of the results. The classic metrics of diagnostic accuracy as it applies to the patients receiving the test include sensitivity, the proportion of disease subjects with a positive test (TP, see Table 9-5) in a total group of subjects with the disease: TP/(TP + FN). Sensitivity thus represents the probability of getting a positive result in a patient with the disease and relates directly to the ability of a test to recognize the ill, i.e., the true positive rate. Specificity is the proportion of subjects without the disease with a negative test result (TN) in a total group of subjects without the disease: TN/(TN + FP). That is, specificity represents the probability of getting a negative test result in a healthy subject (i.e., the true negative rate); it relates to the ability of a diagnostic procedure to recognize the healthy. In the ideal world, every diagnostic test would have a sensitivity and a specificity of 1.0 (100%), but no test is perfect. While sensitivity and specificity are not dependent on disease prevalence, their discriminative ability may increase with disease severity. When combined and plotted for different values of sensitivity and 1–specificity (one minus specificity), these two measures generate a receiver operator curve (ROC), in which the area under the ROC curve (AUROC) can vary from 0.5 (no discriminatory ability) to 1.0 (perfect diagnostic test).

While sensitivity and specificity are informative with regard to using patients with known disease to comment on test accuracy, often the clinical question centers around the converse, "How certain can we be about the disease status of a subject given a positive (or negative) test result?" To answer this question, predictive values are used. Positive predictive values (PPV) represent the proportion of diseased patients with a positive test result in a total group of subjects with a positive result: TP/(TP + FP) (see Table 9-5), whereas negative predictive values (NPV) are defined as the proportion of subjects without the disease and with a negative test result in a total group of subjects with a negative test result: TN/(TN + FN). Notably, both PPV and NPV depend on disease prevalence, with PPV increasing and NPV decreasing with an increase in the prevalence of a disease in a given population.

Currently, the most pervasive biomarker tests directly related to pulmonary medicine are the ones linked to COVID-19, which makes for an interesting use case scenario. More than 160 COVID-19 tests

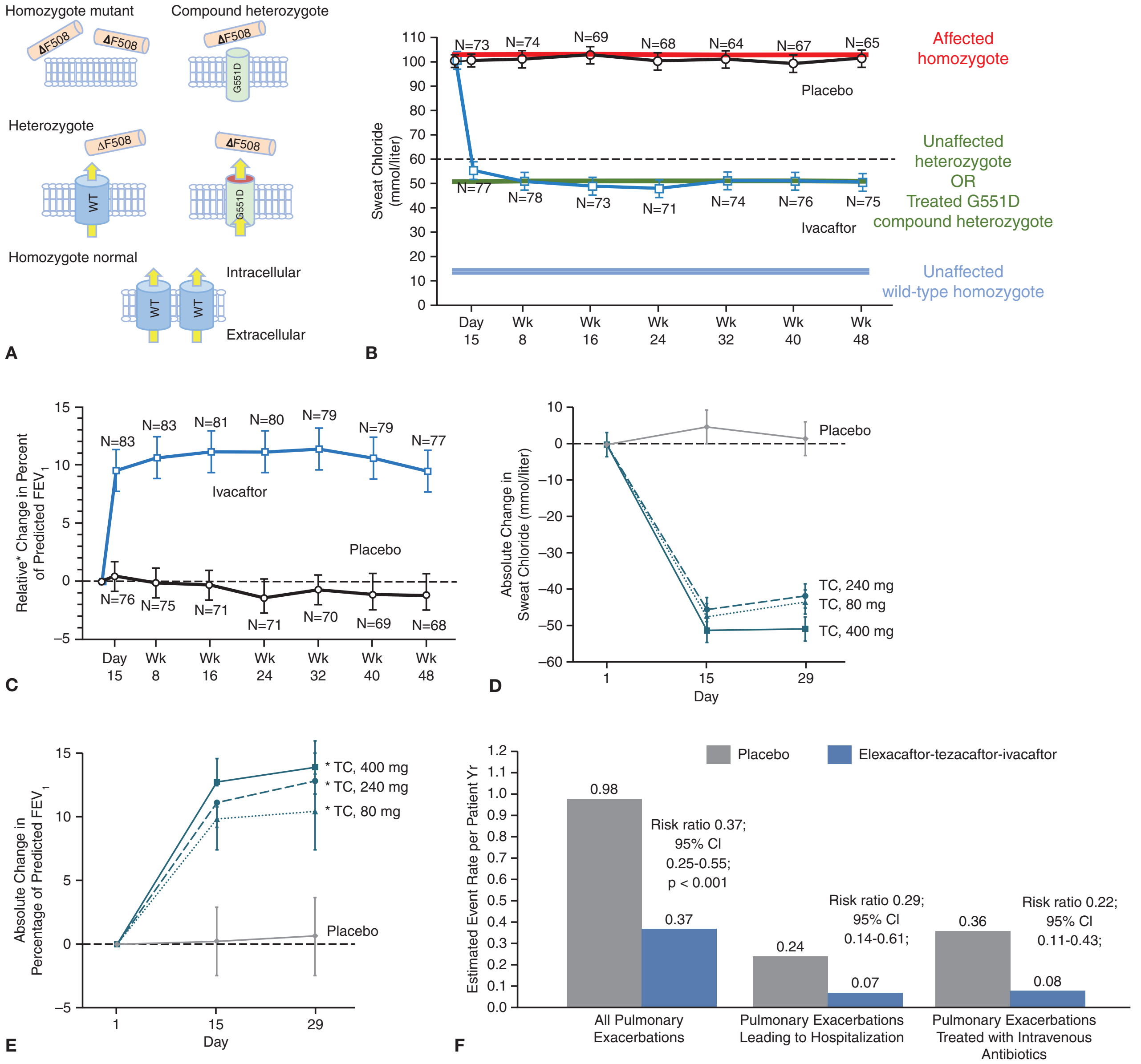

Figure 9-3 Mutation-specific therapeutic action of CFTR modulators in cystic fibrosis. **A, B.** The additive effect of CFTR mutations on epithelial chloride efflux and sweat chloride levels, and the effect of ivacaftor. Individuals with 2 normal alleles have normal chloride efflux (yellow arrows), and a corresponding normal sweat chloride test (blue double line). Individuals with two mutated alleles demonstrate markedly reduced chloride efflux and elevated sweat chloride (red line). Heterozygotes with ~%50 normal functional chloride channels on epithelial cell surfaces manifest intermediate reductions in both chloride efflux and sweat chloride responses (orange line). G551D compound heterozygotes treated with ivacaftor (red disc) demonstrate sweat chloride levels similar to heterozygote carriers. **C.** Therapeutic efficacy of ivacaftor: Patients randomized to ivacaftor demonstrated improvements in relative change in percent of predicted FEV_1 over 48 weeks, in addition to improvements in body weight, symptoms and in quality of life scores (not shown). (Original report erroneously labeled figure as absolute [not relative] change in percent of predicted FEV_1.) **D–F.** Therapeutic efficacy of triple modulator therapy: Panels **D** and **E** demonstrate improvements in sweat chloride and absolute change of FEV_1 over 29 days in patients randomized one of three doses of triple therapy compared to placebo. Panel **F** demonstrates clinical meaningful reductions in all pulmonary exacerbations (63% reduction), those leading to hospitalization (71% reduction), and those treated with intravenous antibiotics (78% reduction) among those treated with triple therapy compared to placebo. *(**B** and **C** Reproduced with permission from Ramsey BW, Davies J, McElvaney NG, et al. A CFTR Potentiator in Patients with Cystic Fibrosis and the G551d Mutation. New Engl J Med. 2011;365(18):1663–1672, **D** and **E** Reproduced with permission from Davies JC, Moskowitz SM, Brown C, et al. VX-659-Tezacaftor-Ivacaftor in Patients with Cystic Fibrosis and One or Two Phe508del Alleles. N Engl J Med. 2018;379(17):1599–1611, and **F** Reproduced with permission from Middleton PG, Mall MA, Dřevínek P, et al. Elexacaftortezacaftor-ivacaftor for cystic fibrosis with a single Phe508del allele. N Engl J Med. 2019;381(19):1809–1819.)*

have been authorized in the United States.[15] While there is no "gold standard" for test performance, estimates of sensitivity have been made, with one study reporting sensitivities of 32%, 63%, 72%, and 93% for throat swabs, nasal swabs, sputum, and BAL fluid, respectively.[16] Given that these sensitivities were reported in hospitalized populations at high risk, sensitivities in the community setting are likely far lower. One meta-analysis demonstrated an overall sensitivity of 70% and specificity of 95% for RT-PCR test performance.[17] A second meta-analysis, limited to respiratory sampling in symptomatic patients, demonstrated an overall summary sensitivity

TABLE 9-5 Contingency Table for Diagnostic Testing

	Subject with Disease	Subject Without Disease	Total
Test—positive	TP	FP	TP + FP
Test—negative	FN	TN	FN + TN
Total	TP + FN	FP + TN	

TP, true positive; FP, false positive; FN, false negative; TN, true negative.

of 89.1% (95% credible interval [CR], 84.0–92.7) and specificity 98.9% (95% CR, 98.0–99.4).[18] Finally, a recent Cochrane review noted that SARS-CoV-2 diagnostic testing varied considerably across studies and test type.[19] For antigen tests the sensitivity varied from 0% to 94%; the average sensitivity was 56.2% (95% confidence interval [CI], 29.5–79.8) and average specificity was 99.5% (95% CI, 98.1–99.9 based on 8 evaluations in 5 studies on 943 samples). In contrast, the sensitivity of rapid molecular assays showed less variation compared to antigen tests (from 68% to 100%); for the rapid molecular assays, average sensitivity was 95.2% (95% CI, 86.7–98.3) and specificity 98.9% (95% CI, 97.3–99.5) based on 13 evaluations in 11 studies of on 2255 samples. Thus, different tests exhibit markedly different test characteristics.

Understanding of variability of test characteristics is clearly important in the care of patients. For instance, using the Cochrane data above (with a sensitivity of 95% and specificity of 99%), a hypothetical cohort of 1000 people with suspected COVID-19 infection (with a prevalence of 10%) would be predicted to result in 105 positive test results including 10 false positives (positive predictive value 90%), and 895 negative results including 5 false negatives (negative predictive value 99%). Incumbent on the pulmonary practitioner is the additional knowledge of how a higher prevalence (or pretest likelihood) for a presenting individual or a lower prevalence for a susceptible larger population may be have substantial implications related to test interpretation. For example, a busy emergency room physician who develops fever, cough, and fatigue following a run of local SARS-CoV-2 infections has an initial COVID-19 negative test. However, given a pretest likelihood of disease of 90%, with a test specificity of 95%, that physician still has a 74% chance of having COVID-19.[20] In contrast, if one tests a large metropolitan area of 5 million people with a disease prevalence of only 1% and a COVID-19 test with 98% sensitivity and 99% specificity, 1000 SARS-CoV-2 positive cases would be missed (false negative), increasing the risk of spread, and 49,500 people would receive false positive results, potentially burdening the public health system.[15]

BIOMARKERS IN PULMONARY MEDICINE

Biomarkers have been defined as "biological characteristics that can be objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention."[21] Ideal biomarker characteristics have been espoused (Table 9-6).[22] There are two major types of biomarkers applicable to clinical medicine: (1) biomarkers of exposure, which are used in risk prediction; and (2) biomarkers of disease, which are used in the screening, diagnosis, and monitoring of disease progression, as well as response to therapy. Thus, biomarkers have the potential to support clinical decisions, from diagnosis to treatment planning; to improve tailored treatment strategies; to avoid over- or under-treatment and adverse side effects; and to enhance prognosis and cost effectiveness.

While a number of biomarkers have been evaluated in a wide range of pulmonary conditions—including MMP-7, ICAM-1, and IL-8 for interstitial lung disease,[23] procalcitonin for community acquired pneumonia,[24,25] exhaled nitric oxide for asthma and other inflammatory lung disease,[26,27] and RAGE, ICAM-1, and SP-D for ARDS[28]—few are recommended for routine clinical use. This stems largely from their relatively weak predictive power. For instance, at a 5% false positive rate (specificity 95%), a relative odds of 3.0 between the 1st and 5th quartile of a biomarker gives only a 20% detection rate.[29] As a clinical example, a recent meta-analysis evaluating the value of procalcitonin for bacterial pneumonia in children yielded an overall sensitivity of 0.64 (95% CI, 0.53–0.74), a specificity of 0.72 (95% CI, 0.64–0.79), and an AUROC of 0.74 (95% CI, 0.70–0.78).[30] As such, this and other current biomarkers cannot directly substitute for other clinical parameters in clinical evaluation but can be used as adjuncts to support clinical judgment.

TABLE 9-6 Ideal Biomarker Characteristics

- Easy to measure
- Safe to measure
- Low cost to measure
- Consistent across gender, age, race
- Cost of follow-up tests is reasonable
- Proven therapy to modify biomarker
- Modification of biomarker is proven to protect against disease or outcome

An example of a biomarker in prominent routine use in pulmonary medicine is the D-dimer and its role in the diagnosis of acute pulmonary embolism (Fig. 9-4). The quantitative rapid enzyme-linked immunosorbent assay (ELISA) has a sensitivity of 95%. In patients with low pretest clinical probability (i.e., 4% to 15%), a normal D-dimer rapid ELISA substantially reduces the posttest probability of pulmonary embolism to 0.7%–2%.[31] Therefore, these

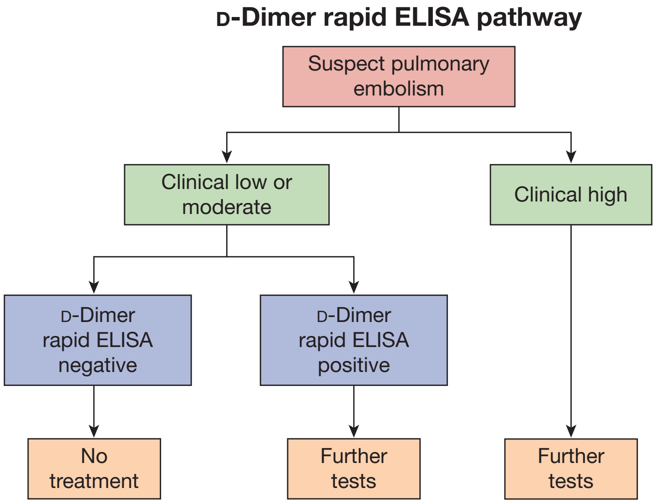
D-Dimer rapid ELISA pathway
Suspect pulmonary embolism
Clinical low or moderate
Clinical high
D-Dimer rapid ELISA negative
D-Dimer rapid ELISA positive
No treatment
Further tests
Further tests

Figure 9-4 Use of D-dimer as a biomarker in the exclusion of pulmonary embolism. The quantitative rapid enzyme-linked immunosorbent assay (ELISA), with a sensitivity of 95%, showed the most clinically useful values among the various D-dimer assays. When used in combination with a low probability objective clinical assessment, which ranges from 4% to 15%, the posttest probability of pulmonary embolism ranges from 0.7% to 2% with a normal D-dimer rapid ELISA. No further testing is required if D-dimer is normal in a patient with a low probability clinical assessment. *(Reproduced with permission from Stein PD, Woodard PK, Weg JG, et al. Diagnostic Pathways in Acute Pulmonary Embolism: Recommendations of the Pioped II Investigators. Am J Med. 2006;119(12):1048–1055.)*

patients can safely be excluded from further evaluation.[31–34] Notably, the D-dimer is still used adjunctively to clinical judgment, as both the predictive ability falls in patients with intermediate to high pretest clinical likelihood of pulmonary embolism and the relatively poor specificity (of about 27%)[35] of the D-dimer limit its usefulness outside of low probability cases.

More recently, pulmonary embolism guidelines have increasingly focused on using age-adjusted D-dimer cutoffs to assist with exclusion of pulmonary embolism, as D-dimer increases with normal aging.[36,37] One suggested modification is patient's age multiplied by 10 ng/mL for patients older than 50 years.[37]

The recent SARS-CoV-2 pandemic has seen an accompanying increase in the incidence of pulmonary embolism.[38,39] D-dimer admission levels, combined with D-dimer increment and fibrinogen, appears to have good prognostic ability for symptomatic pulmonary embolism cases (AUROC, 0.865; 95% CI, 0.822–0.907).[38]

PHARMACOGENETICS

The response to pharmacologic agents varies tremendously between individuals. For instance, the plasma level of a given medication can vary more than 1000-fold between two individuals having the same weight when treated with the same drug dosage.[40] On average for a given drug, 30% of patients show beneficial effects, 30% fail to improve, 10% experience only side effects, and 30% are noncompliant (which may be related to either lack of efficacy or side effects).[41] Therefore, as many as 70% of all patients are unnecessarily exposed to the potential to develop adverse drug reactions (ADRs).[42–44] In the United States, more than 2 million hospitalizations due to serious ADRs and more than 100,000 fatal ADRs were noted in 1994, ranking ADRs between the 4th and the 6th leading cause of death.[45] Worldwide, the prevalence of hospitalizations due to ADRs was recently estimated at a median of 5.3% (interquartile range [IQR], 2.7–9.0), as based on prospective cohort studies of more than 100,000 admissions.[46] Overall, the cost of drug-related morbidity and mortality in the United States exceeded $177.4 billion in 2000,[47] a figure more than double the estimate from 1995.[48] As enormous as these figures are, the burden due to lack of therapeutic response to drug therapy is likely to be much greater.[49]

Pharmacogenetics is the study of variability in drug response due to heredity. Pharmacogenetic variability in drug absorption, drug metabolism, and drug action at the receptor level is well known. Overall, it is estimated that genetics can account for 20% to 95% of variability in drug disposition and effects.[50] Ideally, pharmacogenetics will allow for "individualized therapy" based upon an individual's genetic makeup that will maximize the potential for therapeutic benefit, while minimizing the risk of adverse effects. The potential for cost savings and for decreasing morbidity and mortality is immense.

■ Pharmacogenetic Response Categories

The heritability of many therapeutic agents has been formally established via genetic studies, including the twin studies of Vessel and Page.[51–55] Barring formal genetic studies, the response distribution can also strongly suggest a heritable response. The inter-individual response distribution may be either multimodal or unimodal (Fig. 9-5). A multimodal distribution suggests distinct population subgroups of response, thereby directly supporting a pharmacogenetic basis for response. A unimodal drug response distribution still supports the concept of inter-individual variation, with subjects demonstrating both "good" and "poor" responses. The combination of wide inter-individual response with high repeatability (the likelihood of a subsequent beneficial/poor response to a drug given a prior response) supports the plausibility of a pharmacogenetic effect.[56]

Pharmacogenetics has traditionally been divided into four categories based upon the effects of genetic variability on the pharmacologic properties of a drug. For instance, one genetic variant can alter the

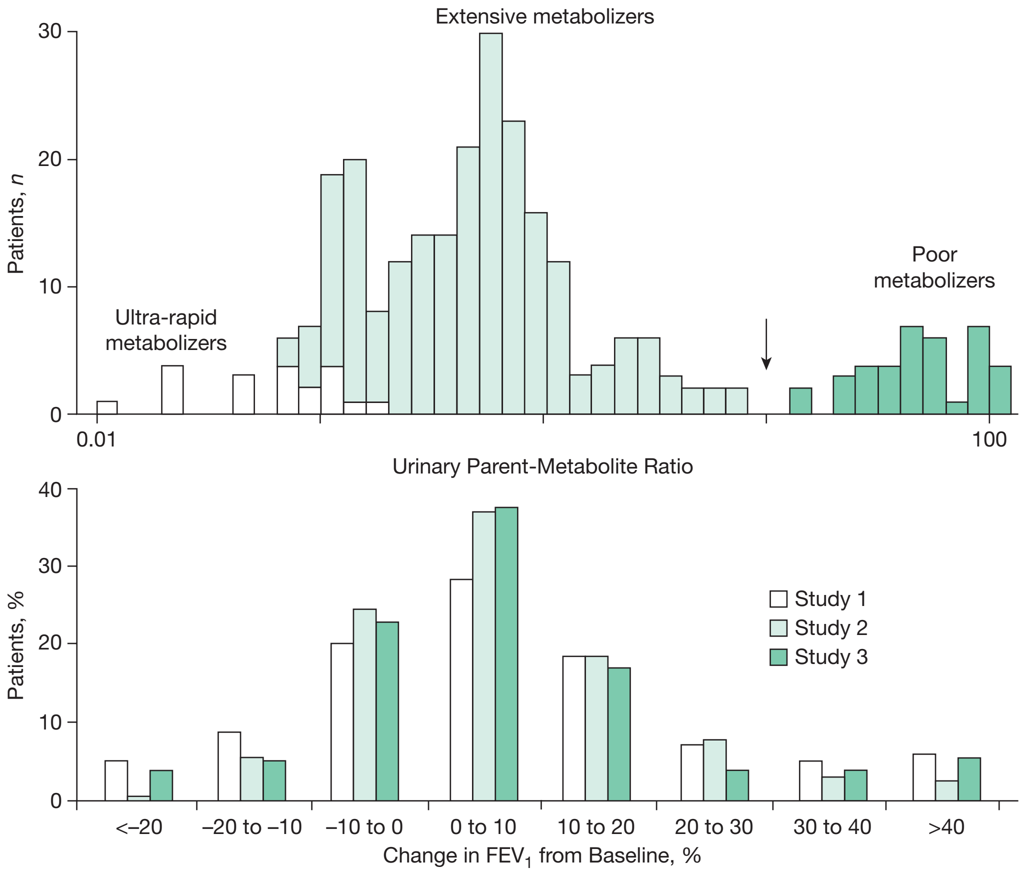

Figure 9-5 Patterns of variation in drug response. **Top.** multimodal response common to many drug metabolizing enzymes. **Bottom.** Unimodal, yet highly variable, response noted in complex trait drug response. In this case, studies 1–3 refer to three independent clinical trials that measured inhaled corticosteroid response over time. *(Reproduced with permission from Roden DM, Altman RB, Benowitz NL, et al. Pharmacogenomics: Challenges and Opportunities. Ann Intern Med. 2006;145(10):749–757.)*

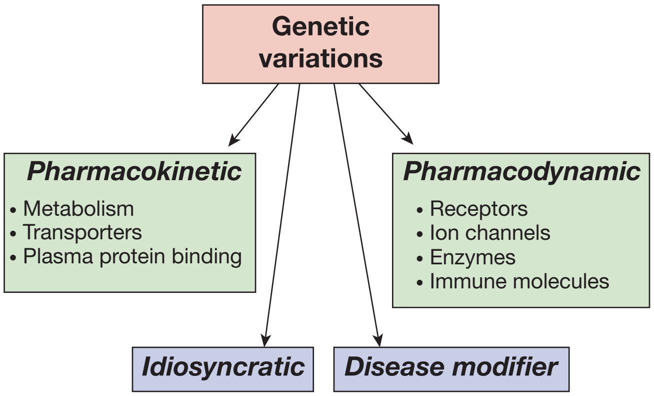

Figure 9-6 Categories of pharmacogenetic response, based upon site of activity of the genetic variant of interest.

rapidity of drug metabolism (thereby altering bioavailability), whereas another genetic variant can affect binding to a drug receptor (thereby decreasing therapeutic efficacy). The four categories include variation related to pharmacokinetics, pharmacodynamics, idiosyncratic reactions, and disease pathogenesis[57] (Fig. 9-6). Each of these categories will be discussed below, followed by a known example or examples pertinent to pulmonary medicine. Clinical implementation guidelines for several of these examples have been developed.[58–62] Additional examples likely to be encountered by the respiratory practitioner and labeled by the U.S. Food and Drug Administration (FDA) are listed in Table 9-7. *Pharmacokinetics* studies the effect of the body upon an administered drug, including the absorption, distribution, tissue localization, biotransformation, and excretion of drugs.[63] Common drug metabolizing enzymes implicated in pharmacogenetics and their estimated effect on drug dosing are shown in Fig. 9-7. The cytochrome p450 enzymes (*CYP*s) encode for ∼60%–70% of all phase I (i.e., structural transformation)-dependent metabolism and have been the classic examples of drug metabolizing enzymes. The clinically most important *CYP*s are *CYP2C9*, *CYP2D6*, and *CYP3A4*, with *CYP2C9* discussed in the context of warfarin administration below. *CYP* genotypes generally result in three metabolic phenotypes, ultra-rapid metabolizers, extensive (normal) metabolizers, and poor metabolizers (Fig. 9-5).

An example of polymorphic phase II (i.e., drug conjugation) drug metabolizing enzymes is the metabolism of azathioprine by thiopurine-*S*-methyltransferase (*TPMT*).[64] Azathioprine, which is commonly used in the therapy of interstitial lung disease and pulmonary vasculitides, is converted to the active 6-mercaptopurine, which is then metabolized by *TPMT* or converted into 6-thioguanine nucleotides. Decreased *TPMT* activity, as mediated through genetic variation, occurs in about 10% of individuals at intermediate levels, while ∼0.3% (1 in 300) have low to absent activity. Clinically, this results in drug-related myelosuppression in 5%, severe leukopenia in 1.2%, and mortality in 0.3% of subjects taking azathioprine.[65] Both clinical phenotyping (pre-drug assessment of *TPMT* activity) and genotyping assays are available. Such testing has been noted to be cost effective in a variety of diseases,[66–68] including modeling of azathioprine use in interstitial pulmonary fibrosis.[69] Clinical pharmacogenomic implementation guidelines have been published.[58,61]

Genetics can also influence drug transporters affecting drug absorption, distribution, and excretion. As an example, the solute carrier organic anion transporter family member 2B1 (*SLCO2B1*) mediates the Na(+)-independent transport of organic anions such as leukotriene C4. A nonsynonymous *SLCO2B1* polymorphism (rs12422149) has been associated with significantly reduced plasma concentration and differential response to therapy with montelukast as assessed by change in baseline Asthma Symptom Utility Index scores.[70]

Pharmacodynamics is the study of the biochemical and physiologic consequences of the administration of a drug and its mechanism of action,[63] i.e., the effect of a drug at its therapeutic target. Genetic variation may lead to response differences despite appropriate concentrations of a drug at its intended target. This category is especially pertinent to pulmonary medicine, since many conditions are treated with inhaled medications that bypass first-pass metabolism by the liver, thereby limiting the effect of pharmacokinetic variants.

Warfarin is the most commonly prescribed anticoagulant medication worldwide and in respiratory medicine is commonly used for the treatment of pulmonary embolism. For warfarin, cytochrome p450 2C9 (*CYP2C9*) is the primary enzyme involved in its metabolism, while vitamin K epoxide reductase complex, subunit 1 (*VKORC1*) is its primary therapeutic target, responsible for the conversion of vitamin K-epoxide to vitamin K. FDA labeling of warfarin includes consideration for testing of variants involved in both pharmacokinetics and pharmacodynamics. "High" and "low" dose risk variants of the *VKORC1* gene, as well as variants of the *CYP2C9* gene, have been identified.[71] Overall, *VKORC1* variants account for ∼25% of variability in warfarin dosing, with *CYP2C9* adding an additional 6% to 10%.

Multiple early studies supported the ability to predict initial warfarin dosing using a genotype-stratified approach.[71–75] Initial guidelines for the clinical implementation of warfarin pharmacogenetics have been detailed.[60,76] In two[77,78] of three initial published clinical trials comparing use of a pharmacogenetic algorithm to a clinical dosing strategy, no significant benefit was noted in terms of percentage of time spent within the therapeutic international normalized ratio (INR) range, with the third[79] demonstrating only a modest (67.4% to 60.3%) benefit to pharmacogenetics. While disappointing from a pharmacogenetic dosing standpoint, these studies were not powered to address the more important issue of bleeding and thrombotic complications. One study comparing a current genotyped cohort with historic controls demonstrated 31% fewer hospitalizations overall (adjusted hazard ratio [HR], 0.69; 95% CI, 0.58–0.82) and 28% fewer hospitalizations for bleeding or thromboembolism (HR, 0.72; 95% CI, 0.53–0.97) based upon pharmacogenetic dosing.[80] More recently, both the ENGAGE AF-TIMI 48 study and the GIFT study reported significant benefit in terms of time spent at therapeutic dosing and decreased risk of major bleeding events from pharmacogenetic testing for warfarin.[81,82] These outcomes are further supported by recent meta-analyses.[83,84]

Pharmacogenetic tests aimed at combining multiple genetic predictors will likely continue to be a focus going forward. For instance, variants in *CRHR1* and *GLCCI1* have been associated with lung function response to inhaled corticosteroids in multiple asthmatic populations.[85,86] However, these each account for just a small proportion of the variability in response to these medications. Nonetheless, combining two variants in the *CRHR1* and *GLCCI1* genes significantly improves the ability to predict response in a replicable fashion.[87]

The *idiosyncratic* category of pharmacogenetic response to drugs includes the individuals that experience an ADR to a therapeutic agent that could not be anticipated based upon the known drug target. Examples of the idiosyncratic category include some compounds that are metabolized by arylamine-*N*-acetyltransferase 2 (*NAT2*). Genetic differences in *NAT2* have been associated with predisposition to the development of peripheral neuropathy in certain individuals taking isoniazid[88] and hypersensitivity reactions to trimethoprim/sulfamethoxazole (including rash, granulocytopenia, and abnormal liver function tests).[88,89] Interestingly, the *NAT2* acetylator phenotype (based upon metabolized level of drugs) may correlate poorly with *NAT2* genotype,[90,91] suggesting that factors other than drug level may explain these idiosyncratic reactions associated with genetic variation.

TABLE 9-7 Common Pulmonary Medications FDA Labeled for Pharmacogenomic Effects

Drug	Therapeutic Area	Genotype(s)	Variant Genotype Effect	FDA-Labeled Sections
Afatinib	Oncology	*EGFR*	*EGFR* mutations are biomarker of afatinib efficacy in lung cancer	Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies
Arformoterol	Pulmonary	*CYP2D6, UGT1A1*	Direct glucuronidation of arformoterol is mediated by UGT1A1 and is the primary elimination route; O-demethylation is a secondary route catalyzed by CYP2D6 and CYP2C19	Clinical Pharmacology
Azathioprine	Interstitial lung disease	*TPMT, NUDT15*	Increased potential for bone marrow suppression	Dosage and Administration, Warnings, Precautions, Adverse Reactions, Clinical Pharmacology
Cisplatin	Oncology	*TPMT*	Children with variants may have an increased risk of ototoxicity	Adverse Reactions
Codeine	Analgesics, cough suppression	*CYP2D6*	Decreased pain relief in poor metabolizers	Boxed Warning, Warnings and Precautions, Use in Specific Populations, Patient Counseling Information
Dapsone	Anti-infective	*G6PD*	Hemolytic anemia	Precautions, Adverse Reactions, Overdosage
Erlotinib	Oncology	*EGFR*	EGFR-TK mutation is biomarker of erlotinib efficacy in lung cancer	Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies
Formoterol	Pulmonary	*CYP2D6, CYP2C19*	Metabolized by O-demethylation, which is catalyzed by CYP2D6 and CYP2C19	Clinical Pharmacology
Gefitinib	Oncology	*EGFR, CYP2D6*	EGFR-TK mutation is biomarker of gefitinib efficacy in lung cancer; reduced function of CYP2D6 leads to gefitinib-induced rash and has been associated with hepatotoxicity when CYP3A4 also is inhibited	Indications and Usage, Dosage and Administration, Clinical Studies
Imatinib	Pulmonary hypertension	*KIT*	cKIT mutations may exhibit decreased efficacy	Indications and Usage, Dosage and Administration, Clinical Studies
Indacaterol	Pulmonary	*UGT1A1*	UGT1A1 metabolizes indacaterol to the phenolic O-glucuronide	Clinical Pharmacology
Irinotecan	Oncology	*UGT1A1*	Increased potential for severe diarrhea and fatal neutropenia	Dosage and Administration, Warnings and Precautions, Clinical Pharmacology
Isoniazid	Anti-infective	*NAT1; NAT2*	Increased risk of peripheral neuropathy with *NAT1* variation; attenuated with pyridoxine administration; *NAT2* influences drug level	Clinical Pharmacology
Ivacaftor	Pulmonary	*CFTR (G551D)*	G551D genotype is one benefitting from actions of ivacaftor	Indications and Usage, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies
Lansoprazole	Gastroenterology	*CYP2C19*	Increased efficacy (higher intragastric pH) vs. extensive (normal) metabolizers	Drug Interactions, Clinical Pharmacology
Mercaptopurine	Oncology	*TPMT, NUDT15*	Increased potential for bone marrow suppression	Dosage and Administration, Warnings and Precautions, Adverse Reactions, Clinical Pharmacology
Mycophenolic acid	Transplantation	*HPRT1*	Should be avoided in patients with hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase (*HPRT1*) such as Lesch-Nyhan and Kelley-Seegmiller syndromes.	Warnings and Precautions
Omeprazole	Gastroenterology	*CYP2C19*	Increased efficacy (higher intragastric pH) vs. extensive (normal) metabolizers	Drug Interactions, Clinical Pharmacology
Umeclidinium	Pulmonary	*CYP2D6*	Umeclidinium is metabolized by CYP2D6	Clinical Pharmacology
Voriconazole	Antifungals	*CYP2C19*	Possible risk of subtherapeutic voriconazole concentrations, and subsequently of treatment failure	Clinical Pharmacology
Warfarin	Hematology	*CYP2C9; VKORC1*	Higher warfarin levels and increased potential for adverse effects	Dosage and Administration, Drug Interactions, Clinical Pharmacology

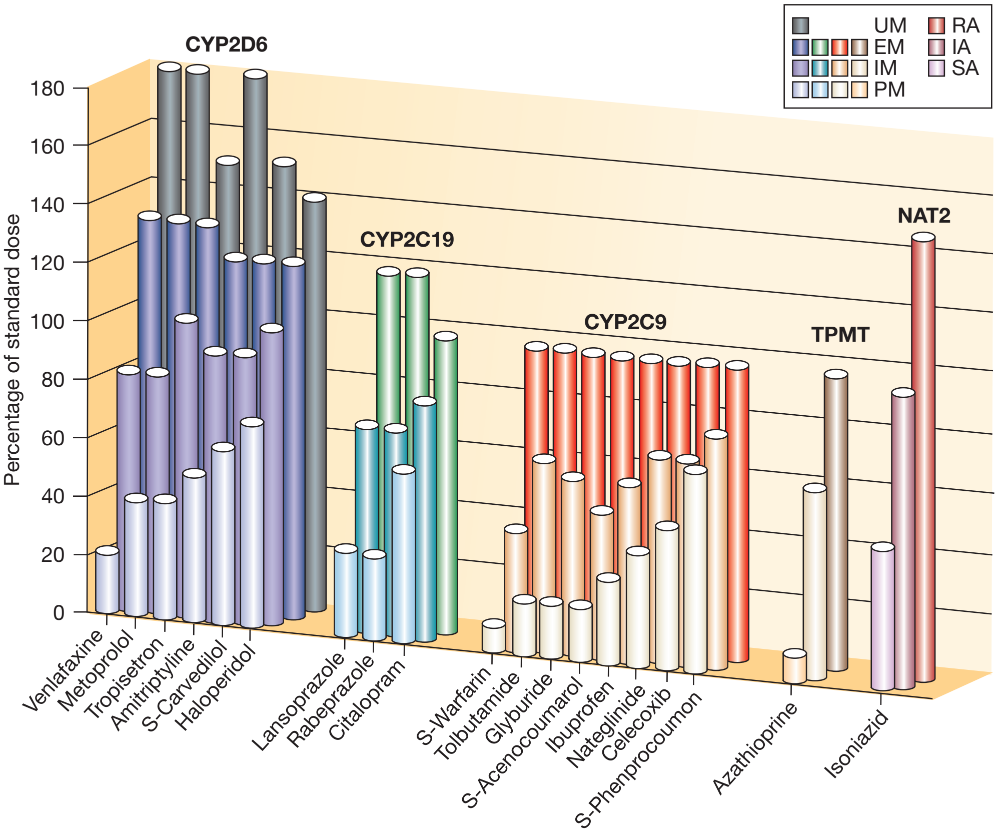

Figure 9-7 Common drug metabolizing enzymes and their standardized effect on drug dosing, according to the difference in pharmacokinetic parameters from clinical studies. Substantial adjustments need to be made to drug dose to achieve the same level of drug exposure in individuals with different genotypes. EM, extensive metabolizer; IA, intermediate acetylator; IM, intermediate metabolizer; PM, poor metabolizer; RA, rapid acetylator; SA; slow acetylator; UM, ultra-rapid metabolizer. *(Reproduced with permission from Kirchheiner J, Fuhr U, Brockmoller J. Pharmacogenetics-Based Therapeutic Recommendations Ready for Clinical Practice? Nat Rev Drug Discov. 2005;4(8):639–647.)*

The final pharmacogenetic category is that of genetic factors influencing *disease pathogenesis.* By modifying the underlying biology/severity of the disease, these genetic factors can also influence which therapies will work or how effective a given medication might be. As a brief example, in cystic fibrosis, the *CFTR*ΔF508 variant has been associated with earlier colonization with *Pseudomonas aeruginosa*,[92] whereas the G551D mutation has a milder clinical phenotype with later *P. aeruginosa* colonization.[93] Therefore, *CFTR* genotype would affect both severity of disease and frequency of antibiotic dosing.

In addition to pharmacogenetics, which focuses on DNA variants, pharmacogenomic drug response studies have begun to focus on the influence of other genomic data types. As an example, our group recently noted that, following small RNA sequencing in a large asthma cohort, two microRNAs with the ability to modify glucocorticoid-mediated transrepression of NfκB (the primary immunosuppressive mechanism for corticosteroid medications), miR-155-5p and miR-532-5p, were able to predict long-term lung function response to inhaled corticosteroids (AUROC, 0.86). The rapidly increasing availability of large-scale “omic” technologies that permit large scale profiling of the transcriptome, epigenome, proteome, metabolome, and microbiome at unprecedented levels of detail, such as single-cell RNA sequencing, will serve to dramatically increase the number of precision pulmonary studies in the near future.

PERSONALIZED PULMONARY MEDICINE: THE CHALLENGE

Though the use of genetics in clinical practice is gradually being adopted for the evaluation of rare lung diseases, the same is not true for more common lung disease. Despite the availability of personalized diagnostic panels, labeling changes implemented by regulatory agencies (e.g., the FDA), and an ever-increasing compilation of genetic, biomarker, and pharmacogenetic studies in the literature, actual translation of personalized pulmonary testing for common lung diseases from the bench to the bedside has been slower than expected, and the existing available tests may still be suboptimal. There are several of reasons for this delay. In the preceding sections, we have outlined how low heritability, variable penetrance, and the need for large effect sizes may affect test performance. Other implementation issues include (1) limitations in the design of published studies, (2) regulatory and ethical concerns, (3) lack of cost effectiveness analyses, and (4) need to educate both patients and providers.

■ Study Design Limitations

Despite the availability of numerous reported genetic and pharmacogenetic associations in the literature, many have not been reproduced in subsequent studies.[94,95] False-positive initial associations may be due to the fact that many pharmacogenetic studies are “spin-offs” from clinical trials or for improperly designed case-control studies and, thus, are underpowered for genetic association. The nature of clinical trials (for pharmacogenetics) and of individualized cohorts (for genetic association) may also result in multiple distinct clinical phenotypes, which vary from study to study. This “phenotypic heterogeneity” combined with “genotypic heterogeneity” (interrogating disparate markers within the same gene) may also contribute to failure to replicate initial findings. These issues were detailed in an evaluation of the pharmacogenetic associations of the β2-adrenergic receptor (*ADRB2*) gene[96] with β_2-agonist response in asthma.

Overall, in 21 studies that focused on the two most common *ADRB2* coding variants (Arg16Gly and Gln27Glu), there were large differences in study design for both genotype definition (e.g., single variant vs. haplotype) and phenotypic outcome. Of a total of 487 interrogated associations, only two associations were probed in at least five of the studies, for the same endpoint, time of assessment, type of intervention, and genetic group. Not surprisingly, no definitive conclusions have been made regarding the utility of *ADRB2* variants to guide asthma therapy. Clearly, a continued focus on appropriate phenotypes and more precise replication of existing data are needed.

While beyond the scope of this chapter, two additional topics related to study design should be mentioned. The first relates to systems biology and personalized medicine. Given that multiple genetic and environmental factors impact the majority of respiratory disease susceptibility and treatment response, systems approaches seek to integrate data both at the level of data type (e.g., epistasis or gene-gene interactions) and across data types (e.g., integration of biomarker, gene expression, and SNP data) to formulate predictive models.[97–101] While young, this approach is promising with regard to complex trait test development. The second additional point is the ongoing controversy regarding study design and whether prospective, genotype-stratified trials are necessary prior to implementation of pharmacogenetic testing. One perspective is that dosing and administration of drug changes warrant such trials, while the other perspective argues that genotypes are invariant (since people are born with them) and therefore precede even retrospective studies. A potential compromise might be in the use of adaptive clinical trials, with pharmacogenomics and other biomarkers included as part of the main trial adaptations.[102,103]

■ Regulatory and Ethical Concerns

As noted above, the FDA has been proactive in terms of pharmacogenetics, with pharmacogenetic information included on about 10% of labels for drugs approved by the FDA. Nevertheless, questions regarding the regulation of genotyping tests and the extent to which pharmacogenetic analyses should be incorporated into new drug development before or after large clinical trials, remain.[104] While beyond our current scope, one detailed perspective on how pharmacogenetic testing might be included in each phase of clinical drug development has been recently published.[105] Another potential boon to genetic test development is the recent ruling by the U.S. Supreme Court that genes cannot be patented.[106,107]

From an ethics perspective, the long-standing concern has been whether genetic variants could result in stigmatization (e.g., denied insurance).[104] A major step in the protection of individuals' rights came with the passage of H.R. 493, the Genetic Information Nondiscrimination Act of 2008. This law protects Americans against discrimination based on their genetic information in matters related to health insurance and employment and should translate into increased acceptance of personalized testing by the public in the future.

■ Lack of Cost-Effectiveness Analyses

Despite the multitude of pharmacogenetic association studies in the literature, relatively few cost-effective analyses have been performed. These studies will be crucial prior to the availability of widespread reimbursement for routine personalized pulmonary testing. Circumstances that favor cost effectiveness of a genetic test include the following: a high prevalence of the genetic variant of interest in the target population, good correlation between phenotype and genotype, satisfactory diagnostic test criteria, disease associated with significant morbidity or mortality if left untreated or undiagnosed, and, for pharmacogenetic variants, significant reduction in adverse drug reactions resulting from testing.[108]

■ Need to Educate Both Patients and Providers

Pharmacogenetics and the promise of personalized medicine have been frequently mentioned in the popular lay press. It is therefore incumbent upon both the developers of a given test, as well as health care professionals responsible for ordering the test, to be cognizant of the test characteristics and interpretation and to be able to effectively disseminate that information to patients. In turn, in the era of personalized medicine, the need for educating health care providers in both the broad array of potential predictive tools (in addition to genetic variants, genomic, proteomic, and other molecular biomarkers will be increasingly available), as well as the strengths and weakness of each of these approaches, will be needed. The context for these educational efforts is not yet clear. Given available tests, providers will potentially need a diagnostic step to determine which drug is best suited to each patient. Of paramount importance, providers will need to be reassured and cognizant that these tests will not and cannot replace sound clinical judgment.

CONCLUSION

Variation in the susceptibility to disease and response to drugs within pulmonary medicine has a significant heritable component. Although many challenges remain, testing of personalized pulmonary medicine, biomarkers, and pharmacogenetics has begun in earnest. Given the rapidity of new genetic, genomic, and other biomarker knowledge, we are making progress toward the goal of individualized medicine.

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SECTION 2 Physiological Principles of Normal Lung Function

CHAPTER 10

Pulmonary Mechanics*

Allan I. Pack
Michael A. Grippi

OVERVIEW

"Arterialization" of venous blood requires matching of the distribution of air and blood within the lung, thereby ensuring effective gas exchange across the alveolar–capillary membrane. Arterialization comprises a series of interrelated processes that begin with the mechanical performance of the ventilatory apparatus—that is, the lungs and the chest wall, including the rib cage, diaphragm, and abdominal wall. Ventilation is critical for replenishing fresh air to the lungs for gas exchange. Although the function of each component of the lung and of the chest bellows can be deranged by injury or disease, the design of the ventilatory apparatus provides for considerable reserve. As a result, mechanical derangements are usually quite severe by the time clinical symptoms appear or arterial blood-gas levels become abnormal.

In many clinical instances, characterization of the mechanical abnormality provides insight into disease pathogenesis and affords a quantitative measure of severity. This is true in a variety of settings, including management of ventilator-dependent patients in the intensive care unit.[1]

During breathing, the lungs and chest wall operate in unison. The lungs fill the chest cavity so that the visceral pleurae are in contact with the parietal pleurae of the chest wall. The two pleural surfaces are separated by only a thin liquid film, which interconnects the lungs and chest wall.

At the end of a normal exhalation, when the respiratory muscles are at rest, the ventilatory apparatus is in a state of mechanical equilibrium. The pressure along the entire tracheobronchial tree from the airway opening to the alveoli is equal to atmospheric pressure ("zero gauge pressure"). The tendency of the lung is to deflate, however, and lung elastic recoil is directed inwardly toward the center of the chest cavity (i.e., centripetally). This is counterbalanced by the elastic recoil of the chest wall, which is directed outwardly (i.e., centrifugally) to favor an increase in volume. These opposing forces generate a subatmospheric pleural pressure of about -5 cmH$_2$O (Fig. 10-1A). The tendency for the lung to recoil inward and for the chest wall to recoil outward is illustrated by the observation that when the chest is opened at autopsy, the lungs collapse to a nearly airless state, and the thorax expands.

Although conventionally pleural pressure is considered a single, mean value that reflects mechanical events within the entire ventilatory apparatus, this is clearly an oversimplification on several accounts: (1) pleural pressure is not directly determinable because normally there is only a potential space between the visceral and parietal pleura; (2) on conceptual grounds, distinctions exist between surface and liquid pleural pressures; (3) pleural pressures are not uniform over the surface of the lungs, since they are strongly affected by gravity; and (4) transmission of pleural pressures at the surface to alveoli located at different depths and loci with the lungs depends on the structural interplay among supporting structures in the alveolar walls ("interdependence"), which resists any inclination of individual alveoli or even a lobule to collapse.[2] Nonetheless, the concept of *mean pleural pressure*, as generally used in considerations of respiratory system mechanics, has proved to be of great practical value.[3]

Contraction of the muscles of inspiration produces the forces that permit the flow of gas along the tracheobronchial tree and lung and chest wall expansion. The movement of air into the lungs requires a pressure difference between the airway opening and the alveoli sufficient to overcome the resistance to airflow of the tracheobronchial tree. Additionally, a pressure difference across the alveolar walls (i.e., between the alveoli and pleural space) must be generated to overcome elastic recoil and inflate the lungs. During spontaneous breathing, the action of the inspiratory muscles causes an increased outward pull on the chest wall.[4] As a result, the pleural pressure becomes more subatmospheric. This pressure change is transmitted to the interior of the lungs, so alveolar pressure also becomes subatmospheric (Fig. 10-1B). In contrast, during artificial ventilation with a positive-pressure ventilator, a supra-atmospheric pressure applied at the inlet to the airways creates a pressure gradient between the airway opening and alveoli to create airflow.

Expansion of alveoli depends on the achievement of an adequate distending pressure across alveolar walls. This distending pressure, or *transpulmonary pressure*, is the difference between alveolar (P_A) and pleural (P_{pl}) pressures. As shown in Fig. 10-1A, the transpulmonary pressure at end expiration ($P_A - P_{pl}$) is 5 cmH$_2$O. At end-inspiration (Fig. 10-1C), the lungs contain more air, and the distending pressure, which also represents the recoil pressure, is greater.

The energy used during inspiration to overcome the elastic resistance of the lungs is stored. Expiration occurs when these forces are released. When the inspiratory muscles relax, the recoil of the lungs causes the alveolar pressure to exceed the pressure at the mouth, and air flows out of the lungs. Although expiration during quiet breathing is passive, with high ventilatory requirements (e.g., during exercise), the expiratory muscles engage to assist movement of air out of the lungs.

LUNG VOLUMES

The lung volumes and capacities (Table 10-1) are also considered elsewhere in this book (see Chapter 31). The end-expiratory position of the lungs, known as *functional residual capacity* (FRC), is the major reference point for the subdivisions of lung volume. This position is set by the opposing recoil forces of the lungs and chest wall when the respiratory muscles are at rest.

Total lung capacity (TLC), which is the total volume of air contained in the lungs after a maximal inhalation, is determined by the balance between the force-generating capacity of the inspiratory muscles and the opposing elastic recoil forces of the lungs and chest wall.[5] Weakness of the muscles of inspiration or increased stiffness of the lungs reduces TLC. Loss of retractive forces exerted by the lung, as seen in emphysema, increases TLC.

Residual volume (RV), defined as the volume of air remaining in the lungs after a complete exhalation, is set by the balance between the actions of the expiratory muscle and the recoil forces of the lungs, which act to decrease lung volume, and the outward recoil

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*The authors wish to acknowledge that this chapter was previously written by Murray D. Altose.

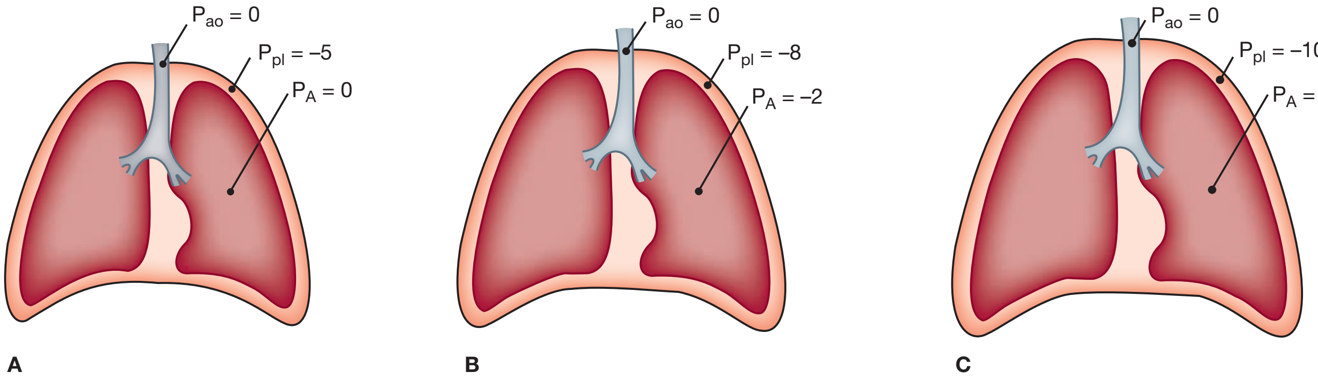

Figure 10-1 Respiratory pressures during a breathing cycle. **A**. End expiration. **B**. During inspiration. **C**. End inspiration. P_{pl}, pleural pressure; P_A, pressure in the alveoli; P_{ao}, pressure at the airway opening.

forces of the chest wall, which favor lung expansion. In middle-aged and older individuals, closure of airways at low lung volumes and resulting air trapping is an important determinant of RV.[6]

STATIC MECHANICAL PROPERTIES OF THE RESPIRATORY SYSTEM

Assessment of the elastic properties of the respiratory system is best assessed by evaluating the elastic properties of the lungs and chest wall separately. Elastic properties are conventionally determined over a fixed range of volumes during periods of no airflow.

■ Elastic Properties of the Lungs

The change in transpulmonary pressure required to effect a given change in the volume of air in the lungs is a measure of the distensibility, or *compliance*, of the lungs. Pulmonary compliance is calculated as the ratio of the change in lung volume to the change in transpulmonary pressure:

$$C = \frac{\Delta V_L}{\Delta(P_A - P_{pl})}$$

where

C = lung compliance
$\Delta(P_A - P_{pl})$ = change in transpulmonary pressure
P_A = alveolar pressure and P_{pl} = pleural pressure
ΔV_L = change in lung volume

TABLE 10-1 Lung Volumes and Subdivisions

The *functional residual capacity* (FRC) is the volume of air that remains in the lungs at the end of a normal expiration.
The *tidal volume* (TV) is the volume of air that is drawn into the lungs during inspiration from the end-expiratory position (and also leaves the lungs passively during expiration) in the course of quiet breathing.
The *expiratory reserve volume* (ERV) is the maximum volume of air that can be forcibly exhaled after a quiet expiration has been completed (i.e., from the end-expiratory position).
The *residual volume* (RV) is the volume of air that remains in the lungs after a maximal expiratory effort.
The inspiratory capacity (IC) is the maximum volume of air that can be inhaled from the end-expiratory position. It consists of two subdivisions: tidal volume and the *inspiratory reserve volume* (IRV).
The *total lung capacity* (TLC) is the total volume of air contained in the lungs at the end of a maximum inspiration.
The *vital capacity* (VC) is the volume of air that is exhaled by a maximum expiration after a maximum inspiration.

Compliance denotes distensibility, i.e., the ease of stretch or inflation. The inverse of compliance is known as *elastance* and refers to the stiffness or the tendency to resist distortion and to return to the original configuration when the distorting force is removed.

In practice, pulmonary compliance is determined by relating the changes in transpulmonary pressure to the changes in lung volume during interruptions in airflow in the course of an expiration following a maximal inspiration (i.e., starting from TLC).

The pressure–volume characteristics of the lung are nonlinear. As lung volume increases, the elastic elements approach their limits of distensibility, and a given change in transpulmonary pressure produces progressively smaller increases in lung volume.[7,8] Thus, the compliance of the lung is least at high lung volumes and greatest as RV is approached (Fig. 10-2). Elastic recoil forces favoring collapse of the lung can be demonstrated throughout the range of the vital capacity, even at low lung volumes approaching RV. If the opposing forces of the chest wall on the lungs are eliminated—for instance, by removing the lungs from the thorax or by opening the chest—the

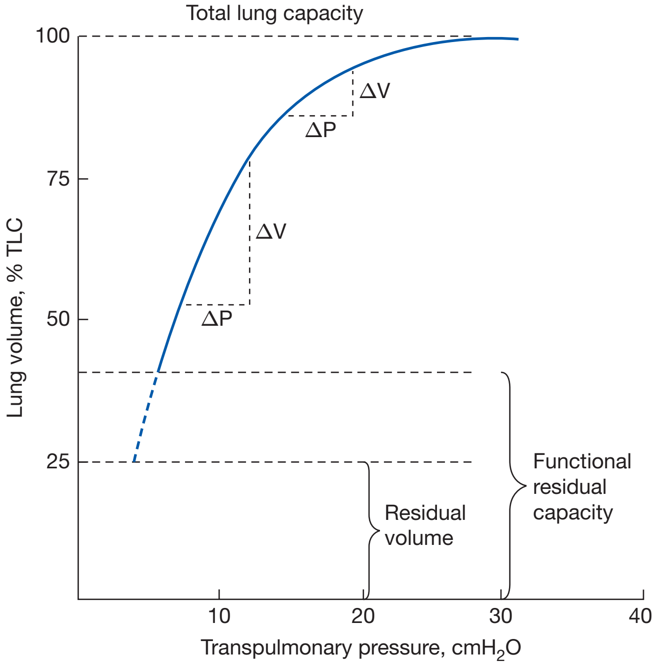

Figure 10-2 Pressure–volume curve of the lung. The static elastic recoil pressure of the lung is approximately 5 cmH_2O at FRC and 30 cmH_2O at TLC. The compliance of the lung (ΔV/ΔP) is greater at low lung volumes than at high lung volumes.

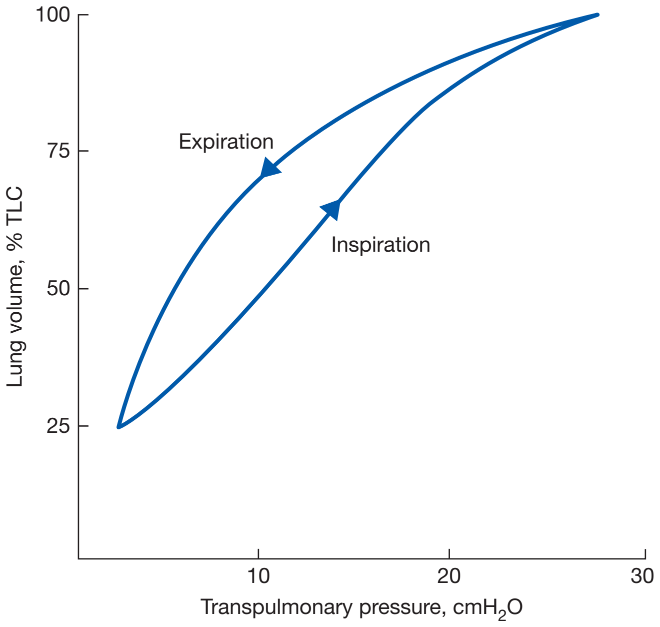

Figure 10-3 Pressure–volume curves of the lung during inspiration and expiration.

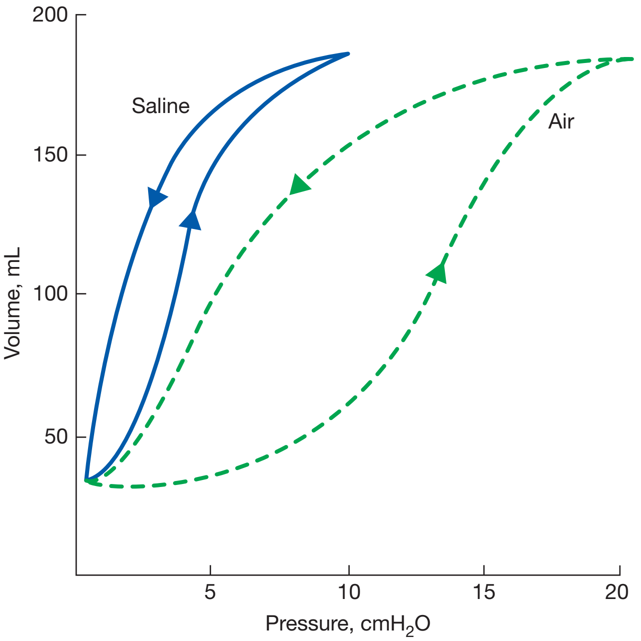

Figure 10-4 Comparison of pressure–volume relationships of air- and saline-filled excised lungs. *Arrows* directed upward indicate inflation; those directed downward indicate deflation. Since saline eliminates surface forces at the liquid–air interface without affecting tissue elasticity, the difference in pressure between the two curves, at any lung volume, is that required to overcome surface forces. To maintain a small lung volume, a large proportion of the pressure is used to overcome surface forces. In contrast, at high lung volumes a greater fraction of the pressure is used to overcome tissue elasticity.

lung collapses to a near-airless state. A minimal volume of air does remain in the lungs because of closure of small airways resulting in the trapping of air in more distal airspaces.

If static measurements of transpulmonary pressure are made during lung inflation, rather than deflation, the pressure–volume curve has a different configuration (Fig. 10-3). This indicates that the elastic recoil of the lung depends not only on the lung volume at which the determination is made, but also on the "volume history" of the lung,[9] known as *hysteresis*, as described below.

Hysteresis

Differences in the pathways of the static pressure–volume curve during inspiration (when force is applied) and expiration (when force is withdrawn) are designated as hysteresis, which is a property of all elastic structures. In the lungs, it is due to the surface forces and the properties of the surface material lining the alveolar walls, as well as the elastic properties of the tissues. The tissues of the lungs are also subject to stress adaptation whereby, over time, the pressure required to maintain a given lung volume declines.[10] An additional factor relates to the closure of small airways at low lung volumes. Once these airways close, the lung units that they serve will not expand during inspiration until a critical opening pressure has been exceeded; only then will the closed units inflate. Recruitment of additional lung units as increasing transpulmonary pressure expands the lungs from low lung volume contributes to the hysteresis of the pressure–volume curve.

The elastic behavior of the lung depends on two factors: the physical properties of the lung tissue, per se, and the surface tension of the film lining the alveolar walls.

Surface Forces

The interior surfaces of the alveoli are lined by a thin liquid layer of osmophilic material. The surface tension at the air–liquid interface of the alveoli, in addition to the elastic properties of the parenchyma, contributes importantly to the elastic recoil of the lungs and acts to decrease lung compliance.[11] The cohesive forces between the molecules of the liquid lining of the alveoli are stronger than those between the film and alveolar gas, thereby causing the film to shrink to its smallest surface area. The behavior of this surface film has been examined in experimental animals by comparison of pressure–volume relationships of air-filled lungs with those of saline-filled lungs; saline eliminates the liquid–air interface without affecting elastic properties of the tissue. A lung distended with saline requires a lower transpulmonary pressure to maintain a given lung volume than a lung that is inflated with air.[12] Also, hysteresis is less in the saline-filled lung. The greater hysteresis in the air-filled lung is explained by the surface tension of the film lining the alveoli, which is higher during inflation as the film expands than it is during deflation as the film is compressed (Fig. 10-4).

By considering the alveolus to be a sphere, Laplace's law can be applied. Laplace's law states that the pressure inside a spherical structure—for example, the alveolus—is directly proportional to the tension in the wall and inversely proportional to the radius of curvature:

$$\text{Alveolar pressure} = \frac{2T}{r}$$

where

T = tension (dyn/cm)
r = radius

Abolition of the liquid–air interface by the instillation of saline into the alveolar spaces eliminates surface forces, thereby reducing the transpulmonary pressure required to maintain a given lung volume.

The surface film lining the alveoli of the lung is termed *surfactant*.[13] The superficial layer of the film facing the alveolar air is made up of surface-active phospholipids, notably dipalmitoyl lecithin. The deeper layer, termed the hypophase, consists of surface-active phospholipids linked to protein. Surfactant is generated by type II alveolar cells and undergoes a continuous cycle of formation, removal, and replenishment.[14]

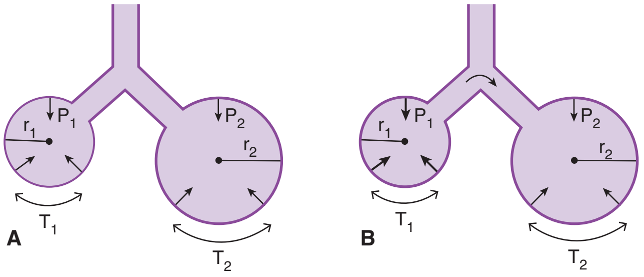

Figure 10-5 The effects of surfactant in maintaining alveolar stability. **A.** Surfactant lowers the tension of the alveolar walls at low lung volumes. Consequently, the transpulmonary pressure (P) of large and small communicating airspaces is the same. $r_1 < r_2$, $T_1 < T_2$, $P_1 = P_2$. **B.** Without surfactant, the surface tension remains constant as lung volume changes, and the recoil pressure of small airspaces exceeds that of larger ones. As a result, small alveoli tend to empty into larger ones. $r_1 < r_2$, $T_1 = T_2$, $P_1 > P_2$.

Surfactant serves several important functions. The surface tension of surfactant is inherently low and decreases even further at low lung volumes when the surface area of the film is reduced. The minimization of surface forces, particularly at low lung volumes, minimizes the adherence of the walls of distal airways that tend to close at low lung volumes and increases the compliance of the lung and decreases the work required to inflate the lungs during the next breath. The automatic adjustment of surface tension as lung volume changes also promotes stability of alveoli at low lung volumes; if the surface tension were to remain constant instead of changing with lung volume, the transpulmonary pressure required to keep an alveolus open would increase as the radius of curvature diminished with decreasing lung volume. Therefore, small alveoli would empty into the larger ones with which they communicate, and atelectasis would be a regular occurrence (Fig. 10-5). Surfactant dysfunction, as occurs with acute lung injury, i.e., acute respiratory distress syndrome (ARDS), results in marked increases in surface tension causing stiffening and instability of alveoli and leads to alveolar collapse (see Chapters 140 and 141).

Interdependence and Collateral Ventilation

The low surface tension of surfactant is not the most important determinant of alveolar stability. In reality, the alveoli form a froth rather than individual bubbles.[15] The walls of each alveolus are shared in common with those of adjacent alveoli so that contiguous airspaces attached by their connective tissue framework are tethered to one another and are not free to move independently. The tendency of any one alveolus to collapse is opposed by the traction exerted by the surrounding alveoli. This mechanical interdependence of adjacent airspaces resists the collapse of individual alveoli and serves as a stabilizing influence and ensures uniform inflation.[16] Even when a distal airway is completely obstructed, the alveoli served by the airway can still be ventilated through collateral channels between alveoli (*pores of Kohn*) and from bronchioles to alveoli (*canals of Lambert*). This collateral ventilation also prevents alveolar collapse and enhances the uniformity of ventilation, particularly in patients with lung disease.[17]

Physical Properties of Lung Tissue

A variety of tissue components contribute to lung elasticity. The pleura, the intralobular septa, peripheral airway smooth muscle tone, and pulmonary vasomotor tone, as well as the tissues of the alveolar walls, play a role in shaping lung elastic recoil.

The major connective-tissue elements of the alveolar walls are the collagen and elastin fibers.[18] Elastin fibers in the alveolar walls and surrounding the bronchioles and pulmonary capillaries have a low tensile strength but can be stretched to over twice their resting length. Elastin fibers are thought to bear most of the stress in the lung at low volumes. Collagen fibers have high tensile strength but are poorly extensible and probably act to limit expansion at high lung volumes.[19] Like a stretched nylon stocking, expansion of the lungs appears to entail an unfolding and geometric rearrangement of the fibers and only slight elongation of individual fibers.

As a result of alterations in the elastin and collagen fibers in the lung, the distensibility of the lungs (measured as compliance) increases with age.[8] This is part of the normal aging process. Pulmonary compliance is also increased by the destruction of alveolar walls and the enlargement of alveolar spaces that characterize pulmonary emphysema. In contrast, the distensibility of the lungs is reduced by pulmonary fibrosis, which stiffens its interstitial tissues.[7]

■ Elastic Properties of the Thorax

The elastic recoil of the chest wall is such that if it were unopposed by the lungs, the chest would enlarge to approximately 70% of TLC. This position represents its equilibrium or resting position.[20] In this position (when the respiratory muscles are completely relaxed), the pressure difference across the chest wall—that is, the difference between pleural pressure and the pressure at the surface of the chest—is zero. If the chest were forced to enlarge beyond its equilibrium position by an increasingly positive pleural pressure or by the application of subatmospheric pressure at the body surface, it would, like the lung, recoil inward, resisting expansion and favoring return to its equilibrium position. Conversely, at volumes less than 70% of TLC, the recoil of the chest is opposite that of the lung and is directed outward (Fig. 10-6).[21]

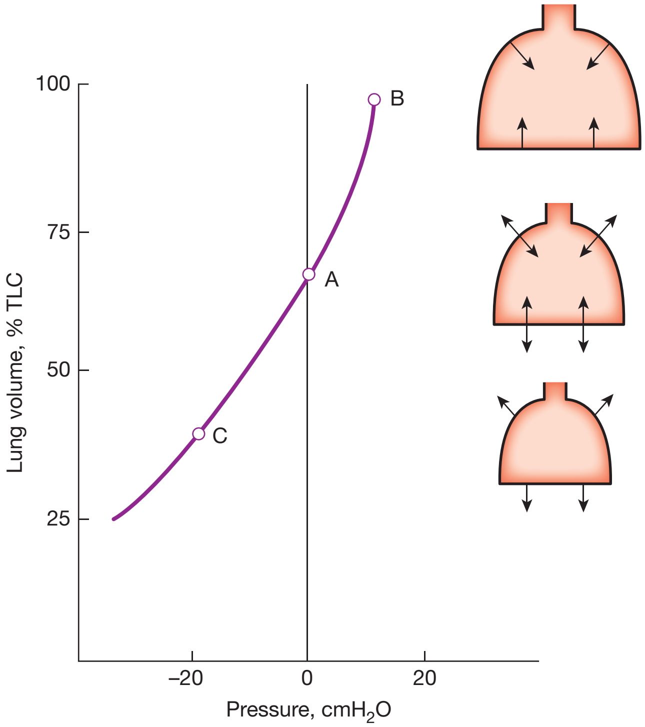

Figure 10-6 Pressure–volume relationships of the isolated chest wall. The direction of the recoil forces across the chest wall is represented by the *arrows*. The equilibrium position of the chest wall at point A, unopposed by the lungs, is approximately 70% of the total lung capacity. In this position, the pressure difference across the chest wall is zero. At larger volumes (B), there is inward recoil of the chest wall; at volumes below the equilibrium position (C), the recoil of the chest wall is directed outward, favoring expansion.

The chest wall can also be represented as a two-compartment system consisting of the rib cage and the abdomen, and volume changes can be partitioned between the two compartments.[22] Changing from the upright to the supine position at a constant overall lung volume produces a shift in volume from the abdominal to the rib cage compartment. The compliance of the rib cage is similar in the supine and upright positions, but the compliance of the abdominal compartment—particularly at high volumes—is greater in the supine position.[23]

The elastic recoil properties of the chest wall play an important role in determining the subdivisions of lung volume. They may be seriously deranged by disorders affecting the chest wall, such as marked obesity,[24] kyphoscoliosis, and ankylosing spondylitis.

■ Elastic Properties of the Respiratory System as a Whole

During breathing, the lung and the chest wall move together and operate mechanically in series. At any given lung volume, the elastic recoil pressure of the total respiratory system (P_{rs}) can be calculated as the algebraic sum of the pressures exerted by the elastic recoil of the lung (transpulmonary pressure) and the elastic recoil of the chest wall.[25]

Since the elastic recoil of the lung is determined (under static conditions of arrested airflow) as the difference between alveolar pressure (P_A) and pleural pressure (P_{pl})—that is, $P_A - P_{pl}$—and the elastic recoil of the chest wall is determined (while the respiratory muscles are completely at rest) as the difference between pleural pressure and the pressure at the external surface of the chest (P_{bs})—that is, $P_{pl} - P_{bs}$, the elastic recoil of the entire respiratory system can be expressed as the sum of the two:

$$P_{rs} = (P_A - P_{pl}) + (P_{pl} - P_{bs}) = P_A - P_{bs}$$

Thus, a measure of the elastic recoil of the respiratory system is supplied by the alveolar pressure, provided that the respiratory muscles are completely at rest and the pressure of the body surface is at atmospheric levels. In the absence of airflow into or out of the lung and when the glottis is open, alveolar pressure corresponds to the pressure at the mouth.

Relaxation Pressure–Volume Curve

The elastic properties of the entire respiratory system can be determined from the relaxation pressure–volume curve (Fig. 10-7). FRC represents the equilibrium position of the lung–chest wall system while the respiratory muscles are relaxed. At this point, the opposing recoils of the lung and chest wall are of equal magnitude, and the recoil pressure of the entire respiratory system is zero. With increases in lung volume above FRC, the recoil pressure of the entire system becomes positive, owing to the combination of an increase in centripetal elastic recoil of the lungs and a decrease in the centrifugal recoil of the chest wall. The net effect favors a decrease in lung volume, and lung volume can be maintained with the airway open to the atmosphere only by the action of the inspiratory muscles. As lung volume exceeds 75% of TLC, the recoil of the chest wall also becomes centripetal, and the recoil pressure of the chest wall adds to the inward forces acting to diminish lung volume. TLC represents the lung volume at which the inward passive elastic recoil pressure of the respiratory system reaches the maximum force that can be generated by the inspiratory muscles.

At lung volumes below FRC, when the centrifugal recoil of the chest wall exceeds the reduced centripetal recoil of the lungs, the relaxation pressure is negative, and this net effect favors an increase in lung volume. Lung volumes below FRC are achieved and maintained by the muscles of expiration.

A switch from the sitting to the supine position decreases FRC because of the effects of gravity. In the upright position, gravity pulls the abdominal contents away from the chest wall. In contrast, in the supine position, the push of the abdominal contents against the diaphragm decreases the centrifugal recoil of the chest wall. The chest wall pressure–volume curve—and, consequently, the pressure–volume curve of the entire respiratory system—is displaced to the right.

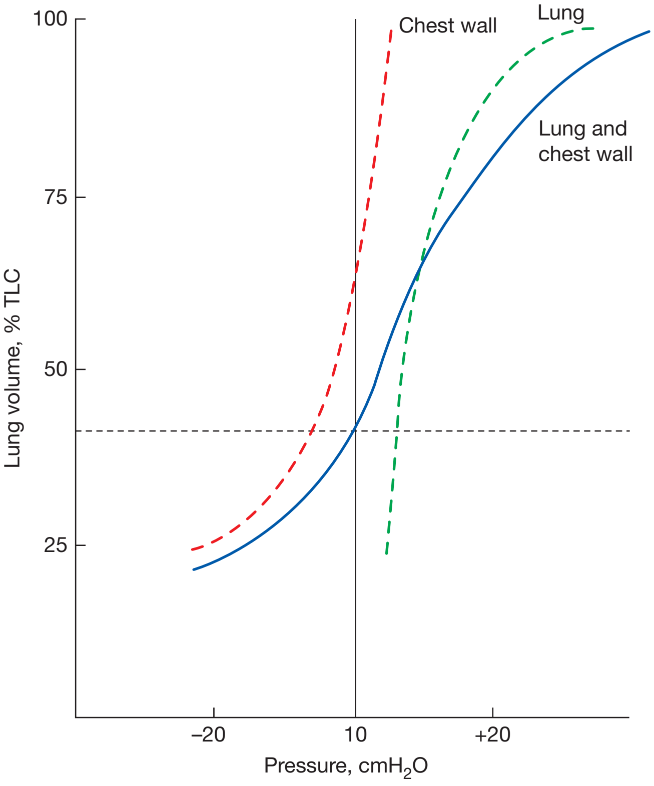

Figure 10-7 Relaxation pressure–volume curves. The lungs and the chest wall function mechanically in series so that the elastic recoil pressures of the total respiratory system, represented by the *solid line*, is the algebraic sum of the separate recoil pressures of the lung and chest wall. At the volume represented by the horizontal *dashed line*, the recoil pressures of the lung and chest wall are equal but in opposite directions. Consequently, the net recoil pressure is zero, and the respiratory system is in a position of equilibrium.

DYNAMIC MECHANICAL PROPERTIES OF THE RESPIRATORY SYSTEM

The total nonelastic resistance of the lungs consists of the resistance of the airways to airflow (airway resistance), defined in terms of the driving pressure and the resulting rate of airflow, and the frictional resistance of the lung tissues to displacement during breathing (tissue resistance). Normally, tissue resistance makes up only 10% to 20% of the total pulmonary nonelastic resistance, but in diseases of the pulmonary parenchyma, it may increase considerably.

■ Airway Resistance

Much of our understanding of the physics of airflow and airway resistance dates back to the early part of the 20th century.[26] A large fraction of the resistance to airflow is in the upper respiratory tract, including the nose, mouth, pharynx, larynx, and trachea. During nasal breathing, the nose constitutes up to 50% of total airway resistance. During quiet mouth breathing, the mouth, pharynx, larynx, and trachea constitute 20% to 30% of the airway resistance, but they account for up to 50% of the total airway resistance when minute ventilation increases—during vigorous exercise, for example. Most of the remainder of airway resistance is in medium-sized lobar, segmental, and subsegmental bronchi up to about the seventh generation of airways.[27,28] Additional branching distally causes a progressive increase in the number of airways in any generation. While the caliber of individual airways in daughter branches compared to the parent branch is reduced, the total cross-sectional area of all airways in a given generation increases tremendously with successive generations along the tracheobronchial tree. Consequently, in the normal lung, the small peripheral airways, particularly those less than 2 mm in diameter, constitute only about 10% to 20% of the total airway resistance.[29]

Airway Caliber

The airways, like the pulmonary parenchyma, exhibit elasticity and can be compressed or distended. Therefore, the diameter of an airway varies with the transmural pressure applied to that airway—that is, the difference between the pressure within the airway and the pressure surrounding the airway. The pressure surrounding intrathoracic airways approximates pleural pressure, since these airways are tethered to the parenchymal tissue and are exposed to the expansive forces that are active in overcoming the elastic recoil of the lung.[1]

Airway resistance varies inversely with lung volume. As the lung volume increases, the elastic recoil forces of the lung increase; the traction applied to the walls of the intrathoracic airways also increases, widening the airways and decreasing their resistance to airflow. Conversely, at low lung volumes, the transmural airway pressure is lower and airway resistance increases.[30,31] If the elastic recoil of the lung is reduced—by destruction of alveolar walls in pulmonary emphysema, for instance—the transmural airway pressure at any given lung volume decreases correspondingly; the airways are narrower and airway resistance is greater even though there is no disease of the airways per se.

The effects of a change in transmural pressure on airway caliber depend on the compliance of the airways—which, in turn, is determined by their structural support. The trachea, for example, is almost completely surrounded by cartilaginous rings, which tend to prevent complete collapse even when the transmural pressure is negative. The bronchi are less well supported by incomplete cartilaginous rings and plates, whereas the bronchioles lack cartilaginous support. All airways can be stiffened, albeit to different degrees, by contraction of smooth muscle in their walls.

In patients with airway disease, mucosal edema, hypertrophy and hyperplasia of mucus glands, increased elaboration of mucus, and hypertrophy of smooth muscle further compromise airway caliber and increase airway resistance.

Neural pathways and humoral mechanisms also are important in controlling airway smooth muscle tone and regulating airway caliber. Cholinergic parasympathomimetic stimulation originating from the vagus nerve and mediated through the release of acetylcholine causes airway smooth muscle contraction and airway narrowing. Noncholinergic parasympathetic activity may play a role in airway smooth muscle relaxation through the release of vasoactive intestinal peptide and the subsequent production of nitric oxide.[32] Beta-adrenergic receptors in bronchial smooth muscle activated by various sympathomimetic agents promote airway smooth muscle relaxation and airway dilatation.[33]

Pressure–Flow Relationships: Theoretical Considerations

In the lungs, pressure–flow relationships are extremely complicated because the airways consist of a system of irregular branching tubes that are neither rigid nor perfectly circular. For purposes of simplification, pressure–flow relationships in rigid tubes are generally regarded as a model for those in the airways.

The driving pressure that produces flow of air into and out of the lung must suffice to overcome friction and to accelerate the air. Acceleration in the lungs is of two types: local (i.e., changes in the rate of airflow with time when flow is initiated) and convective (i.e., acceleration of molecules of air over distance while flow is constant). The driving pressure required for convective acceleration is proportional to the gas density and to the square of the flow rate. It is important during expiration because, as air moves downstream from the alveoli toward the airway opening, the total cross-sectional airway diameter decreases; therefore, molecules of air must accelerate through the converging channels even though the overall flow rate remains unchanged. Also, the driving pressure that produces high expiratory flow rates at large lung volume serves for convective acceleration rather than for overcoming friction.[34,35]

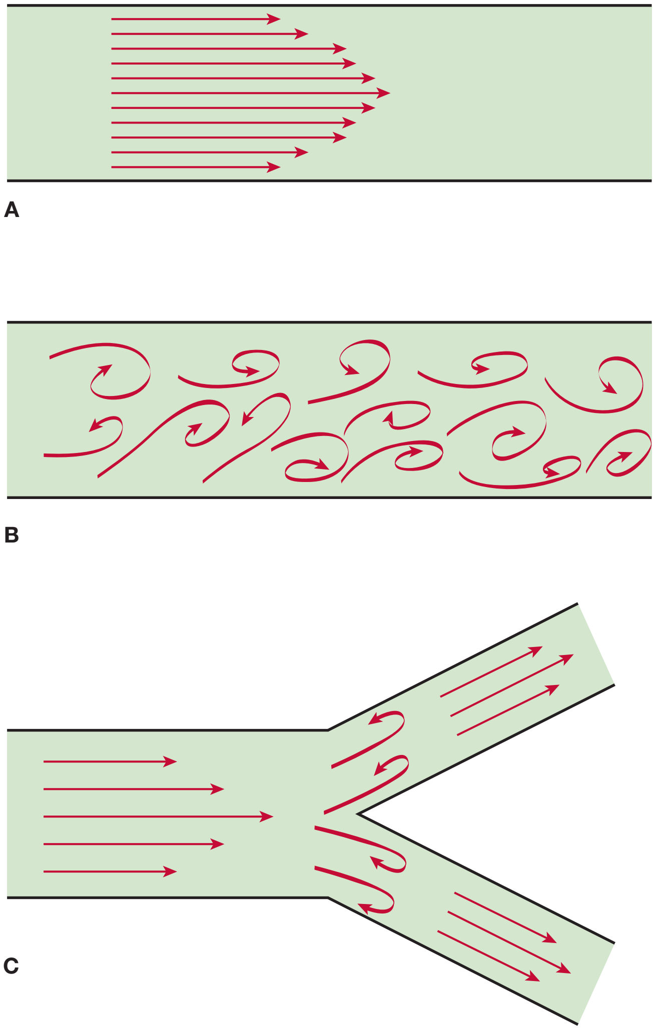

Figure 10-8 Patterns of airflow. **A.** Laminar flow. **B.** Turbulent flow. **C.** Transition flow that occurs at bifurcations.

The driving pressure required to overcome friction depends on the rate and the pattern of airflow. Two major patterns of airflow warrant special consideration: *laminar* and *turbulent*. Laminar flow is envisioned as streamlines of gas that flow parallel to the sides of the tube and "slide" over one another. Also, because the streamlines at the center of the tube move faster than those closest to the walls, the flow profile is parabolic (Fig. 10-8). The pressure–flow characteristics of laminar flow depend on the length (l) and the radius (r) of the tube, as well as the viscosity of the gas (η) according to Poiseuille's equation:

$$\Delta P = \frac{\dot{V} 8 \eta l}{\pi r^4}$$

where

ΔP = the driving pressure (pressure drop between the beginning and the end of the tube)
$\dot{V}$ = the flow rate that the driving pressure produces
r = the radius of the tube

The critical importance of tube radius in determining the driving pressure for a given flow is apparent in the previously mentioned equation. If the radius of the tube is halved, the pressure that is required to maintain a given flow rate must be increased 16-fold. Laminar flow patterns occur only in small peripheral airways, where, because of the enormous overall cross-sectional area, flow through the individual airways is exceedingly slow.

Turbulent flow occurs at high flow rates and is characterized by a complete disorganization of streamlines, so that the molecules of gas move laterally, collide with each other, and change velocities. Under these circumstances, pressure–flow relationships change. In contrast to laminar flow, the rate of turbulent airflow is no longer proportional to the driving pressure. Instead, the driving pressure to produce a given rate of airflow is proportional to the square of flow and is dependent on gas density. Turbulent flow predominates in the trachea.

At lower flow rates during expiration—particularly at branches in the tracheobronchial tree, where flow in two separate tubes comes together into a single channel—the parabolic profile of laminar flow becomes blunted, the streamlines separate from the walls of the tube, and minor eddy formation develops. This is referred to as a mixed, or *transitional*, flow pattern. In a mixed pattern of airflow, the driving pressure for a given flow depends on both the viscosity and the density of the gas.

Whether airflow is laminar or turbulent is predictable from the Reynolds number (Re), a dimensionless number that depends on the average velocity ($\bar{v}$), the density of the gas (ρ), the viscosity of the gas (η), and the diameter of the tube (D), so that

$$\mathrm{Re} = \frac{\bar{v}\,\mathrm{D}\rho}{\eta}$$

In straight, smooth, rigid tubes, turbulence occurs when the Reynolds number exceeds 2000. Therefore, turbulence is most apt to occur when the average velocity is high, gas density is high, gas viscosity is low, and the tube diameter is large. Since most of the resistance to airflow in the normal lung is in large airways, where airflow is largely turbulent and where resistance is density dependent, breathing a mixture of 80% helium and 20% oxygen (a mixture that is 64% less dense than air) reduces the Reynolds number, favoring a conversion from turbulent to laminar flow. Consequently, airflow increases at a given driving pressure and airway resistance falls.[27]

Calculation of Airflow Resistance

The driving pressure along the tracheobronchial tree—that is, the difference between alveolar pressure and the pressure at the airway opening (mouth) that is required to produce a given rate of airflow into the lungs—provides a measure of the flow resistance of the airways, according to the equation

$$\mathrm{R_{aw}} = \frac{\mathrm{P_A} - \mathrm{P_{ao}}}{\dot{\mathrm{V}}}$$

where

$\dot{\mathrm{V}}$ = airflow (L/s)
$\mathrm{P_A}$ = alveolar pressure ($\mathrm{cmH_2O}$)
$\mathrm{P_{ao}}$ = airway-opening pressure ($\mathrm{cmH_2O}$)
$\mathrm{R_{aw}}$ = airway resistance ($\mathrm{cmH_2O/L/s}$)

Flow–Volume Relationships

Considerable insight into the flow-resistive properties of the airways can be obtained from the relationship between airflow and lung volume during maximal expiratory and inspiratory maneuvers.[36] In practice, a person inhales maximally to TLC; then exhales as forcefully, rapidly, and completely as possible to RV; and then returns to TLC by a rapid, forceful inhalation (Fig. 10-9). During the maximal expiration, the rate of airflow peaks at a lung volume that is close to the TLC; as the lung volume decreases and intrathoracic airways narrow, airway resistance increases, and the rate of airflow decreases progressively.

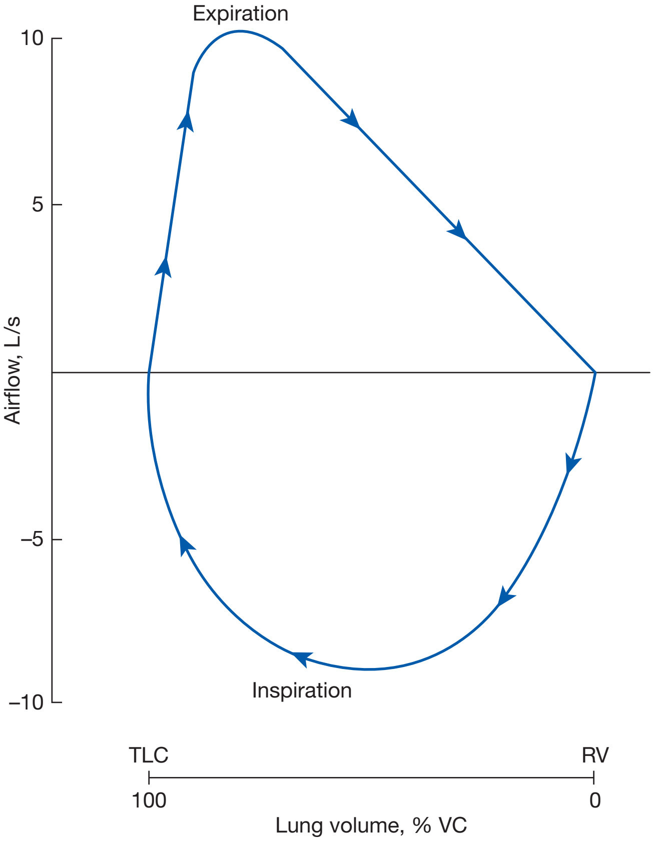

Figure 10-9 Maximal expiratory and inspiratory flow–volume loop.

During maximal inspiration, the pattern of airflow is different. Because of the markedly negative pleural pressure and large transmural airway pressure, the bronchi are wide, and their calibers increase further as lung volume increases. Consequently, inspiratory flow becomes high while the lung volume is still low and remains high over much of the vital capacity, even though the force generated by the inspiratory muscles decreases as they shorten.

A family of flow–volume loops is produced by repeating full expiratory and inspiratory maneuvers over the entire range of the vital capacity using different levels of effort (Fig. 10-10). The greater the effort exerted during inspiration, the greater is the rate of airflow over the entire range—that is, from RV to TLC. Similarly, during expiration, the rate of airflow increases progressively with increasing effort at large lung volumes close to TLC. At intermediate and low lung volumes, the rate of expiratory airflow reaches a maximum while the effort expended is only moderate; thereafter, airflow does not increase further despite increasing expiratory efforts.

Isovolume Pressure–Flow Curves

Separation of the effects of increasing effort from those of changes in lung volume on the rate of airflow during expiration can be accomplished by using isovolume pressure–flow curves (Fig. 10-11). During repeated expiratory maneuvers performed with varying degrees of effort, simultaneous measurements are made of airflow rate, lung volumes, and pleural pressure. For each lung volume the rate of airflow is plotted against the pleural pressure, as an index of the degree of effort.[37]

As expiratory effort is increased at any given lung volume, the pleural pressure increases toward, and then exceeds, atmospheric pressure; correspondingly, the rate of airflow increases. At lung

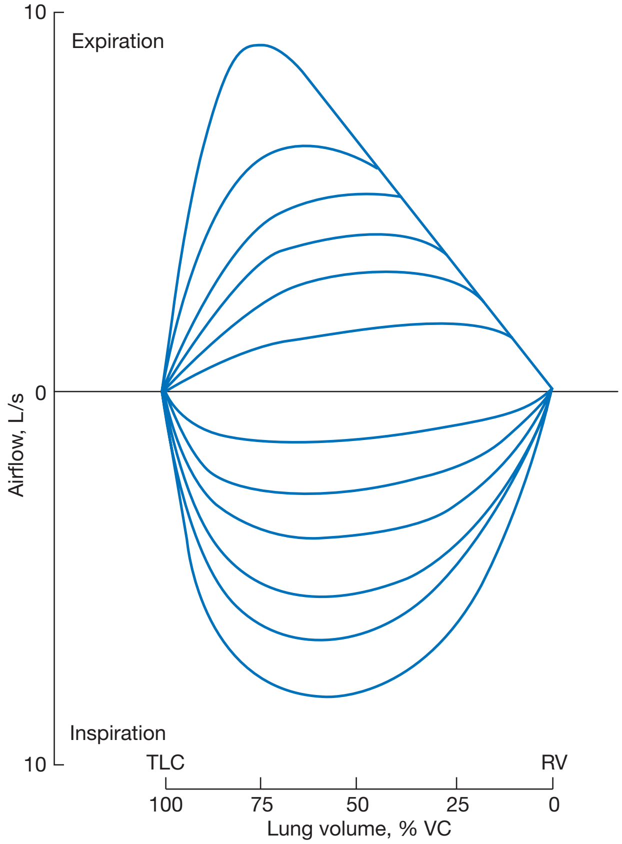

Figure 10-10 Series of flow–volume loops constructed from complete inspiratory and expiratory maneuvers repeated at different levels of effort.

volumes above 75% of the vital capacity, airflow increases progressively as pleural pressure increases; it is considered "*effort dependent*." In contrast, at lung volumes below 75% of the vital capacity, the rate of airflow levels off as the pleural pressure exceeds atmospheric pressure and becomes fixed at a maximum level. Thereafter, further increases in effort, and in pleural pressure, effect no further increase in the rate of airflow; at these lower lung volumes, airflow is considered "*effort independent*." Since the rate of airflow remains constant despite increasing driving pressure, it follows that the resistance to airflow must be increasing in direct proportion to the increase in driving pressure. This increase in resistance is attributed to compression and narrowing of large intrathoracic airways.

■ Equal Pressure Point Theory: Dynamic Compression of Airways

To illustrate the mechanisms that normally limit airflow during a maximal expiratory maneuver, it is useful to consider a model of the lung where the alveoli are represented by an elastic sac and the intrathoracic airways by a compressible tube, both enclosed within a pleural space (Fig. 10-12).[38]

At a given lung volume, when there is no airflow (as during breath holding with the glottis open), pleural pressure is subatmospheric, counterbalancing the elastic recoil pressure of the lung. The alveolar pressure (P_A), which is the sum of the recoil pressure of the lung and pleural pressure (P_{pl}), is zero (Fig. 10-12A). Since airflow has ceased, the pressure along the entire airway also is atmospheric.

At the same lung volume during a quiet expiration, pleural pressure is less subatmospheric. Since lung volume and the elastic recoil pressure of the lung are unchanged, alveolar pressure is now positive with respect to atmospheric pressure; airflow occurs. The alveolar pressure is gradually dissipated along the airway in overcoming resistance so that the pressure at the airway opening (P_{ao}) is zero.

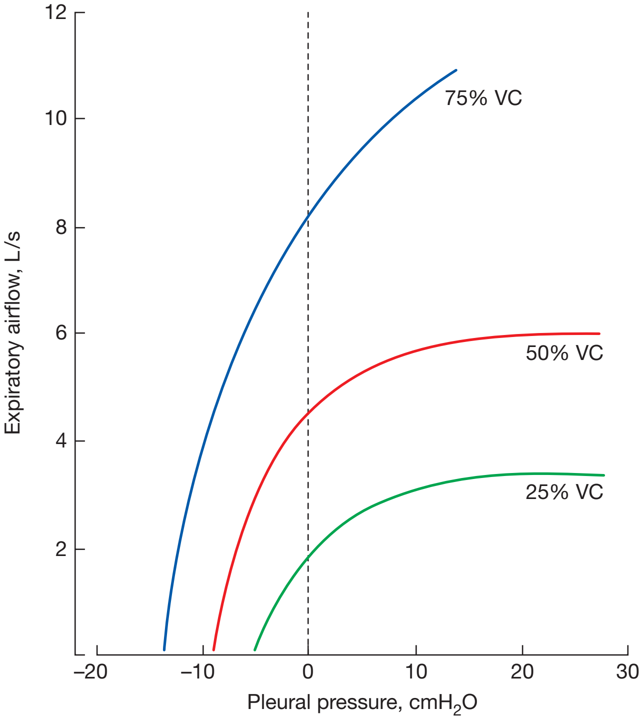

Figure 10-11 Isovolumetric pressure–flow curves. At lung volumes greater than 75% of the vital capacity, airflow is effort dependent; that is, airflow increases progressively with increasing effort. At lower lung volumes, airflow is effort independent—that is, airflow becomes fixed at a maximum level and does not increase despite further increases in effort.

All along the airway, however, the airway pressure exceeds pleural pressure, and the transmural pressure is positive; the airways remain open, and flow continues (Fig. 10-12B).

A forceful expiration raises pleural pressure above atmospheric pressure and further increases alveolar pressure (Fig. 10-12C). Airway pressure again falls progressively from the alveolus toward the airway opening. But at some point along the airway—the *equal pressure point*—the drop in airway pressure is equal to the recoil pressure of the lung; intraluminal pressure and the pressure surrounding the airways are equal and the same as pleural pressure. Downstream (i.e., toward the airway opening) the transmural pressure is negative, because the intraluminal airway pressure is less than pleural pressure; the airways are subjected to dynamic compression.

The equal pressure point divides the airways into two components arranged in series: an *upstream segment*, from the alveoli to the equal pressure point, and a *downstream segment*, from the equal pressure point to the airway opening. With increasing expiratory effort, as the pleural pressure becomes more and more positive with respect to atmospheric pressure, the equal pressure point moves upstream. Once maximum expiratory flow is achieved, the position of the equal pressure point becomes fixed in the region of the lobar or segmental bronchi. Further increase in pleural pressure by increasing expiratory force simply produces more compression of the downstream segment without affecting airflow through the upstream segment.

The driving pressure of the upstream segment—that is, the pressure drop along the airways of that segment—is equal to the elastic recoil of the lung. The maximum rate of airflow during forced expiration ($\dot{V}_{max}$) can be expressed in terms of the elastic recoil pressure of the lung (P_L) and the resistance of the upstream segment (R_{us}), as follows:

$$\dot{V}_{max} = \frac{P_L}{R_{us}}$$

Measurements of the rate of airflow during force expiration form the basis of many tests used to assess the flow-resistive properties of

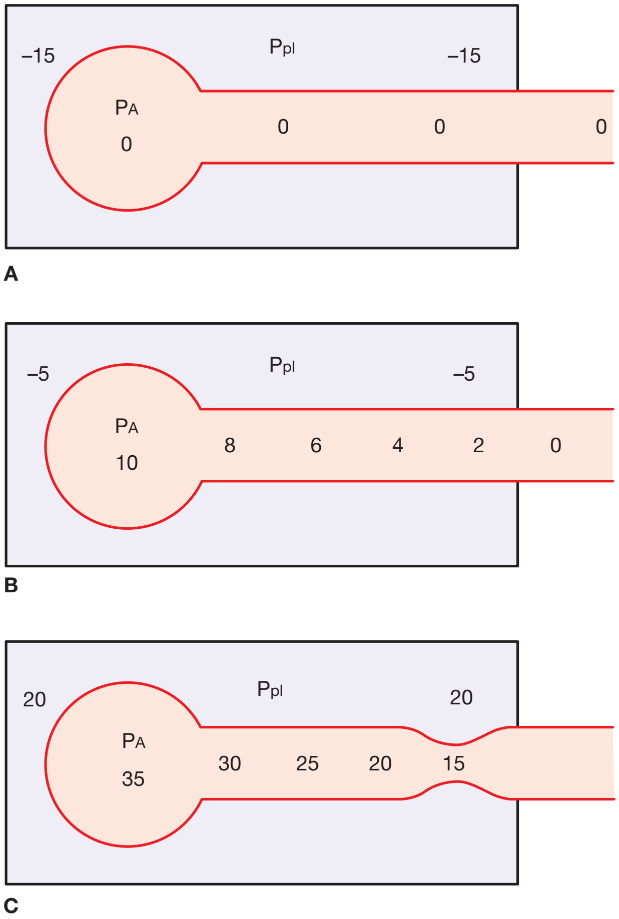

Figure 10-12 Schema of the distribution of pleural, alveolar, and airway pressures at rest and during expiration, illustrating the equal pressure point concept. **A.** End expiration. **B.** Quiet expiration. **C.** Forced expiration.

the lung. It is evident, however, that the maximum rate of expiratory airflow depends on many factors: The lung volume at which airflow is determined; the force of expiration (particularly at high lung volumes [i.e., above 75% of vital capacity]); the elastic recoil pressure of the lung; the cross-sectional area of large airways; the collapsibility of large intrathoracic airways; and the resistance of small peripheral airways.

■ Wave Speed Limitation Theory

An alternative explanation for airflow limitation during forced expiration is based on principles of wave speed theory.[39] The wave speed theory proposes that flow is limited by the velocity of propagation of pressure waves along the wall of the tube. The velocity of propagation (v) varies proportionally with the cross-sectional area of the tube (A) and with airway stiffness. At a site where the linear velocity of gas molecules equals the velocity of propagation of pressure waves, that is, wave speed, a choke point develops, preventing further increases in flow rate. The flow rate at wave speed is a function of the cross-sectional area of the tube at the choke point (A) and the stiffness of the choke segment (dP/dA), where P is the transmural airway pressure. Where choke points occur in the tracheobronchial tree depends on the lung volume: at large lung volumes, a choke point is situated in the vicinity of the lower trachea; at lower lung volumes, choke points develop more upstream along the bronchial tree. Extension of the neck exerts longitudinal tension and stiffens the trachea, increases wave velocity, and increases maximum expiratory flow rates at large lung volumes.[40]

MECHANICAL DETERMINANTS OF REGIONAL VENTILATION

The lung is not homogeneous, and the mechanical properties of all airways in a given generation and of all alveoli are not the same. This results in important nonuniformities of regional ventilation.

Pleural pressure in the upright person is more subatmospheric at the apex than at the base of the lung, because of the effects of gravity and the weight of the lung.[41] Pleural pressure topography and regional lung expansion are also determined by the shape of the chest wall and by the forces required for the lung to conform to the thoracic cavity shape.[9,42] The rate of increase in pleural pressure from top to bottom is approximately 0.25 cmH_2O per centimeter of vertical distance. Consequently, the transpulmonary pressure—that is, alveolar pressure minus pleural pressure—is greater at the top than at the bottom of the lung. Therefore, at most lung volumes, the alveoli at the lung apexes are larger (more expanded) than those at the lung bases (Fig. 10-13).

Because of regional variations in lung compliance, ventilation is not uniform, even in the normal lung. With the use of external scanners after the inhalation of a radioactive gas, such as ^{133}xenon, it has been demonstrated that within the range of normal tidal volume, lung units are better ventilated, and ventilation per alveolus is greater, at the bottom than at the top of the lung.[43] This is because alveoli near the top of the lung are positioned on the upper, flatter part of the pressure–volume curve and are less compliant than alveoli at the lung bases positioned on the lower, steeper portion of their pressure–volume curves.

At low lung volumes (i.e., near the RV), pleural pressure at the bottom of the lung actually exceeds airway pressure and leads to closure of peripheral airways (Fig. 10-13). During a breath taken from RV, air that enters the lungs first is preferentially distributed to the lung apexes.

The distribution of ventilation within the lungs and the volume at which airways at the lung bases begin to close can be assessed by the single-breath N_2 washout test[44] (see Chapter 31). This test requires a maximum expiration into an N_2 meter after a maximal inspiration of pure O_2 from RV; the changing concentration of nitrogen is plotted against expired lung volume (Fig. 10-14). Because the inspiration starts at the RV, the initial portion of the breath containing dead-space gas, rich in nitrogen, is distributed to alveoli in the upper lung zones. The rest of the breath, which contains only O_2, goes preferentially to lower lung zones. Consequently, the concentration of nitrogen is lower in the alveoli at the lung bases than in the alveoli at the apexes of the lungs.

During expiration, the initial portion of the breath consists of O_2 remaining in the large airways; it contains no N_2 (phase I). As alveolar gas containing N_2 begins to be washed out, the concentration of N_2 in the expired air rises to reach a plateau. The portion of the curve where the concentration of N_2 rises steeply is phase II. The plateau is phase III. Phase III depends on the uniformity of the distribution of ventilation in the lung. If gas enters and leaves alveoli throughout the lung synchronously and equally, phase III is flat. But when the distribution of ventilation is nonuniform, so that gases coming from different alveoli have different N_2 concentration, phase III slopes upward.

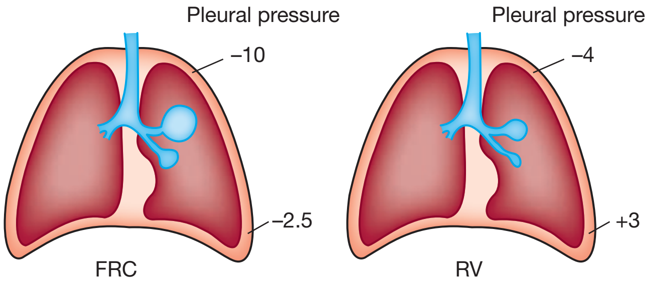

Figure 10-13 Pleural pressure gradients in the upright lung at FRC (left) and at RV (right). The effect of the gradient on alveolar volumes is shown schematically for each case.

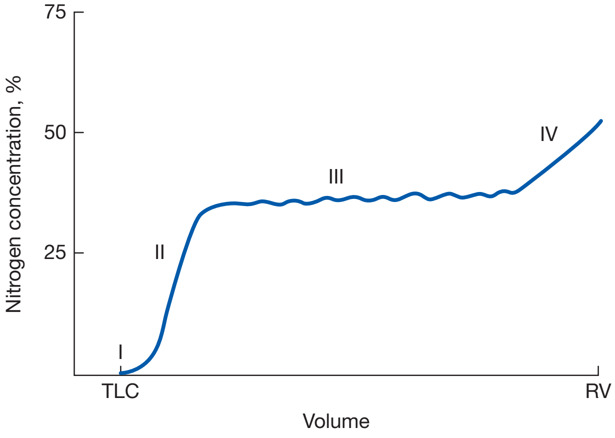

Figure 10-14 Tracing of expired nitrogen concentration during a slow expiration from TLC to RV after a full inspiration of pure O_2. The four phases are indicated. For further details, see text.

At low lung volumes, airways at the lung bases close; only alveoli at the top of the lung continue to empty. Since the concentration of N_2 in the alveoli of upper lung zones is higher than in the alveoli at the lung bases, the slope of the N_2–volume curve increases abruptly, marking the start of phase IV. The volume, above RV, at which phase IV begins is termed the *closing volume*.[45]

The closing volume increases with advancing age. With diseases of the peripheral airways closing volume may rise to levels above FRC. This results in lung units that are perfused but poorly ventilated leading to reductions in arterial oxygenation.[46,47]

■ Dynamic Compliance of the Lungs

The relationship between changes in volume and changes in pleural pressure during a normal breathing cycle is shown in Fig. 10-15. Airflow momentarily ceases at the end of expiration (A) and at the end of inspiration (C); the change in pleural pressure between these two points reflects the increasing elastic recoil of the lung as the volume of air in the lungs increases. The slope of the line connecting the end-expiratory and end-inspiratory points (AEC in the figure) on a pressure–volume loop provides a measure of the dynamic compliance of the lungs.

In normal persons, dynamic compliance closely approximates inspiratory static lung compliance and remains essentially unchanged even when breathing frequency is increased up to 60 breaths per minute. This indicates that lung units that are parallel with each other normally fill and empty uniformly and synchronously, even when airflow is high and the change in lung volume is rapid. The rate of filling and emptying of a lung unit depends on its time constant—that is, the product of its resistance and compliance. Lung units with high resistance and high compliance take longer to fill and empty more slowly compared to units with low resistance and low compliance. For the distribution of ventilation in parallel lung units to be independent of the rate of airflow, the resistance and compliance of these units must be matched so that the time constants of individual units throughout the lungs are approximately the same. The time constants of lung units distal to airways 2 mm in diameter are approximately 0.01 second, and fourfold differences in time constants are necessary to cause dynamic compliance to become frequency dependent.[29]

Patchy narrowing of small peripheral airways produces regional differences in time constants. At low breathing frequencies, when the rate of airflow is low, ventilation is fairly evenly distributed. As the breathing frequency increases, however, ventilation tends to be distributed to areas that offer the least resistance to airflow. Therefore, lung units fed by narrowed airways receive proportionally less ventilation than do areas of the lung where the airways remain normal; the change in pleural pressure required to effect the same change in overall lung volume increases. As a result, the dynamic compliance falls.

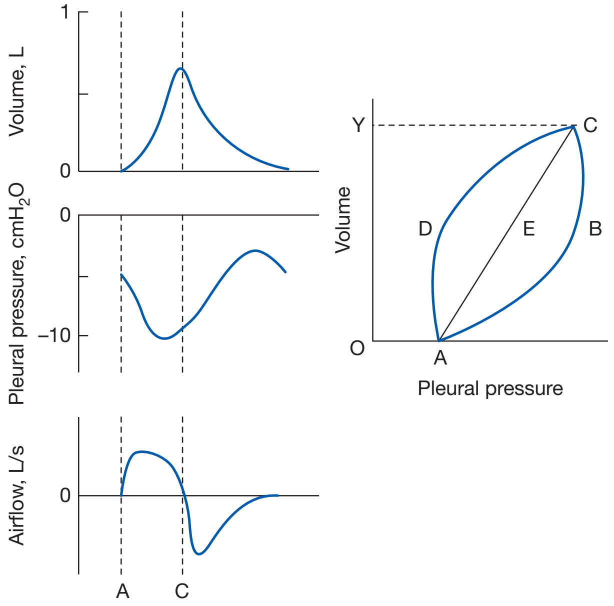

Figure 10-15 Individual tracings of tidal volume, pleural pressure, and airflow, taken simultaneously during a single complete breath, are shown on the left. The relationship between volume and pleural pressure is illustrated by the dynamic pressure–volume loop on the right. Dynamic compliance is determined as the slope of the line AEC. The work of breathing during inspiration to overcome the elastic forces of the lung is represented by the area of the trapezoid OAECY, and the work required to overcome nonelastic forces is represented by the area of the loop ABCEA. The loop AECDA represents the work required to overcome airflow resistance during expiration.

Measurements of frequency dependence of dynamic compliance are time-consuming and technically difficult. The test was thought to be potentially useful in the diagnosis of obstruction in small peripheral airways when results of other conventional tests of lung mechanics are still within normal limits.[48] However, it is rarely performed in pulmonary function laboratories.

WORK OF BREATHING

During breathing, the respiratory muscles work to overcome the elastic, flow-resistive, and inertial forces of the lungs and chest wall.[49] The elastic work of breathing is done to overcome the elastic recoil of the lungs and chest wall; the resistive work is done in overcoming the resistance of airways and tissues. The mechanical work of breathing can be determined by relating the pressure exerted across the respiratory system to the resulting change in volume, since the product of pressure (P) and volume (V) has the dimension of work, according to the equation:

$$\text{work} = \int P\,dV$$

Recordings of pleural pressure and lung volume changes during spontaneous breathing can be used to measure the work of breathing; the work of breathing performed on the lungs can be determined from the area of the dynamic pressure–volume loop (Fig. 10-15) and fractionated into its elastic and resistive components. During inspiration, the work done to overcome the elastic forces of the lung is determined from the area of the trapezoid OAECY (Fig. 10-15). The area of the loop ABCEA is the work in overcoming nonelastic forces during inspiration, and the area of the loop OABCY is the total work of breathing during inspiration.

Expiration during quiet breathing is passive since the elastic recoil of the lung suffices to overcome the expiratory airflow resistance. Some of the stored elastic energy is also used to overcome inspiratory muscle activity that persists into the expiratory phase of breathing. At high levels of ventilation and when airway resistance is increased, additional mechanical work during expiration is required to overcome nonelastic forces. Under these circumstances, the pleural pressure exceeds atmospheric pressure, and the loop AECDA extends beyond the confines of the trapezoid OAECY (Fig. 10-15).

The work of breathing at any given level of ventilation depends on the pattern of breathing. Large tidal volumes increase the elastic work of breathing, whereas rapid breathing frequencies increase the work against flow-resistive forces. During quiet breathing and during exercise, people tend to adjust tidal volume and breathing frequency to values that minimize the force and the work of breathing.[50] Similar adjustments are also seen in patients with pulmonary disorders. Patients with pulmonary fibrosis, which is characterized by an increased elastic work of breathing, tend to breathe shallowly and rapidly; those with airway obstruction and increased nonelastic work of breathing usually breathe more deeply and slowly.

The work done on the chest wall during breathing is calculated by subtracting the work performed on the lung from the total mechanical work of breathing. The total mechanical work of breathing cannot be readily measured during spontaneous breathing because the respiratory muscles that perform the work also make up part of the resistance offered by the chest wall. But the total mechanical work can be determined during artificial ventilation by using either intermittent positive airway pressure or negative pressure applied to the chest, provided that the respiratory muscles are completely at rest. For this determination, the change in lung volume is related to the pressure difference across the respiratory system—that is, differential pressure between the mouth and the body surface. Disturbances of the chest wall, such as kyphoscoliosis and obesity, increase the work of breathing severalfold.

■ Oxygen Cost of Breathing

To perform their work, the respiratory muscles require O_2. The O_2 cost of breathing, which reflects the energy requirements of the respiratory muscles, provides an indirect measure of the work of breathing.[51,52] The O_2 cost of breathing is assessed by determining the total O_2 consumption of the body at rest and at an increased level of ventilation produced by voluntary hyperventilation or CO_2 breathing. Provided there are no other factors acting to increase O_2 consumption, the added O_2 uptake is attributed to the increased metabolism of the respiratory muscles.

The O_2 cost of breathing in normal subjects is approximately 1 mL/L of ventilation and constitutes less than 5% of the total O_2 consumption. At high levels of ventilation, however, the O_2 cost of breathing becomes progressively greater. There is a dramatic increase in the O_2 cost of breathing at high levels of ventilation in some diseases of the lung, such as pneumonia, pulmonary fibrosis, and emphysema, and in disorders of the chest wall, such as obesity and kyphoscoliosis. The increase in the energy requirement of the respiratory muscles during increased ventilation, concomitant with a decrease in O_2 supply secondary to arterial hypoxemia, contributes to muscle fatigue, thereby limiting the amount of exertion that these patients can sustain.[3]

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CHAPTER 11

Control of Ventilation

Frank J. Jacono
Atul Malhotra

INTRODUCTION

Breathing is a rhythmic motor act that is under both conscious and automatic control. The respiratory control system maintains numerous controlled variables within their homeostatic ranges but is also responsible for rapidly changing ventilation in response to often unpredictable stimuli. We will discuss the anatomy and physiology of the ventilatory control system, then address integrated responses and illustrative examples of adaptation and dysfunction in the setting of selected disease states.

ANATOMY AND PHYSIOLOGY

The respiratory control system, broadly speaking, comprises a controller, sensors, and a plant (Fig. 11-1). This hierarchical structure, in which there is central processing of afferent input, is important for coordinating respiratory movements with behaviors such as eating, speaking, and moving.[1] The controller is a neuronal network within the central nervous system (CNS), which is responsible for generating and modulating individual breaths and the overall breathing pattern. Often referred to as the respiratory central pattern generator (rCPG), the controller comprises reciprocally connected neuronal populations in the medulla and pons.[2,3] Neural output from the rCPG drives the activity of various motor neuron pools. Motor neurons in the spinal cord (e.g., phrenic and intercostal) innervate the respiratory pump muscles, while brain stem motor neurons innervate upper airway muscles. The so-called "plant" is an important component of breathing control and includes the CO_2 stores, which are made up of lung stores and circulating blood volume including hemoglobin. Closed loop feedback to the controller is supplied by chemoreceptors and mechanoreceptors.

The consistent cycling of the ventilatory pattern is generated spontaneously from the spatial and functional architecture of the rCPG. Intrinsic membrane properties of rhythmically active neurons within the rCPG are capable of producing automatic periodicity.[4] In addition, reciprocal (excitatory and inhibitory) synaptic connections between neuronal populations in the medulla and pons are believed to be critical for the automatic generation of the respiratory rhythm.[2,3]

The neural respiratory cycle comprises three phases (Fig. 11-2).[5] Inspiration (I) involves ramp-like increases in inspiratory motor neuron firing, which drive phrenic nerve activity throughout this phase. The first phase of expiration (E_1) is often called post-inspiration because inspiratory motor neurons are still active. Persistent inspiratory motor activity during E_1, which declines throughout this phase, acts to slow the exit of air from the lungs. Finally, during the second phase of expiration (E_2), expiratory muscles are typically electrically silent. During this phase of passive relaxation, gas is expelled as the lungs and chest wall return to their equilibrium state (i.e., functional residual capacity). However, under conditions where respiratory drive is increased, expiratory muscles including the internal intercostal and abdominal muscles become active during E_2. This notion is an example of how the central controller, influenced by sensory feedback, modulates and alters the integrated motor response of the system.

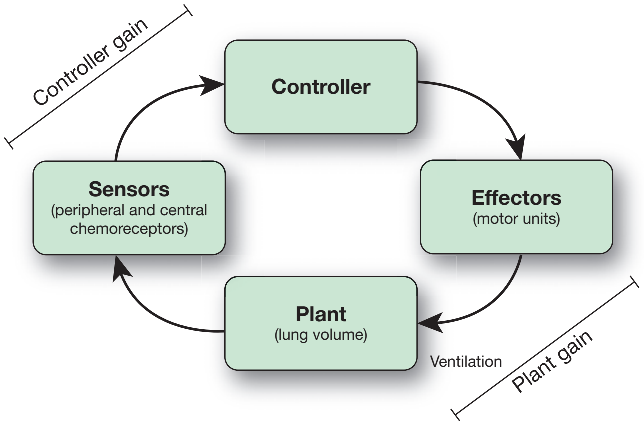

Figure 11-1 Block diagram of the respiratory control system.

■ Brain Stem

Within the medulla and pons, interconnected neuronal populations constitute a network that is considered necessary for the generation of the respiratory rhythm (Fig. 11-3).[2,3,6] This bilateral pontomedullary respiratory network, which is also responsible for control of the ventilatory pattern, contains the ventral respiratory column (VRC) and the pontine respiratory group (PRG). Afferent signals from lung mechanoreceptors and peripheral chemoreceptors enter the pontomedullary network via the nucleus of the solitary tract (nTS) in the dorsal respiratory group (DRG). The nTS has projections to both pontine and ventral medullary components of the central respiratory network. Taken together, the VRC, DRG, and PRG constitute the brain stem rCPG. The rhythmic output of the rCPG drives the activity of spinal phrenic, intercostal, and lumbar motor neuron pools that innervate the muscles of respiration. Other brain stem motor neurons exhibit respiratory modulation and control muscles of the upper airway. Finally, the rCPG is influenced by higher CNS structures, which allows for conscious control of the ventilatory pattern.

Several regions of rhythmically active neurons in the VRC represent the core circuitry of the rCPG. The pre-Bötzinger complex (pre-BötC) within the VRC is believed to be the main source of rhythmic excitation driving inspiratory premotor neurons and other brain stem circuits. Furthermore, the pre-BötC has been shown to manifest intrinsic rhythmic activity.[4] However, the mechanisms responsible for rhythmic inspiratory pattern generation are complex given the large number of modulatory inputs that converge on the pre-BötC compartment and are likely to manifest as the result of network properties. Neuronal populations in the Bötzinger complex (BötC) are the major source of expiratory network activity during normal breathing. Thus, BötC neurons are important for control of the transition between inspiratory and expiratory activities in the rCPG and maintenance of the rhythmicity of normal breathing.

Neurons within the PRG are critical for formation of normal resting breathing patterns. Functional connections between the pons and the rest of the rCPG modulate phase switching (onset and termination of inspiration). For example, the dorsolateral pons (dlPons) is a region within the PRG with respiratory-modulated neurons whose activity varies depending on the presence of vagal afferent feedback. In particular, eupneic breathing patterns are dependent on excitatory drive from pontine neurons to the VRC, emphasizing the importance of the spatial and functional architecture of the brain stem respiratory network. Medullary raphe nuclei likely represent a system of intermediate relays for signaling between the PRG and the

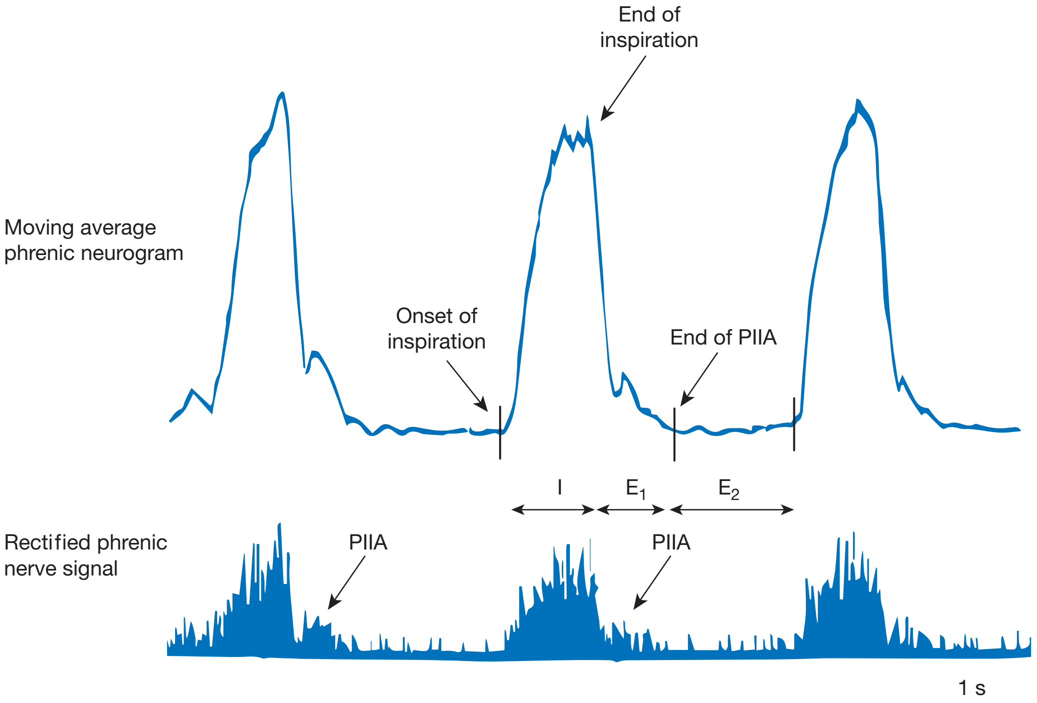

Figure 11-2 Recording of phrenic nerve activity (below) and its moving average (above), which highlights the three phases of the respiratory cycle: (1) Inspiration (I), (2) post-inspiratory activity (expiration, phase 1, E_1), and (3) late expiration (expiration, phase 2, E_2). PIIA, post-inspiratory inspiratory activity.

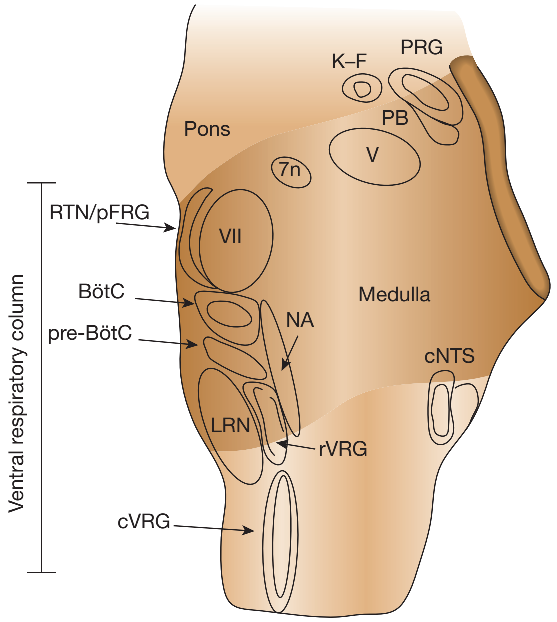

Figure 11-3 Overview of the respiratory central pattern generator (rCPG) within the brain stem. The ventral respiratory column (VRC) is orientated in the rostral-to-caudal direction. The VRC extends from the retrotrapezoid nucleus (RTN) adjacent to the rostral facial nucleus (VII) superiorly, to the caudal ventral respiratory group (cVRG) near the spinomedullary junction inferiorly. The main areas of rhythmically active VRC respiratory neurons are in the Bötzinger complex (BötC), pre-Bötzinger complex (pre-BötC), rostral ventral respiratory group (rVRG), and cVRG. The parafacial respiratory group (pFRG) overlaps anatomically with the RTN, and together these regions include intrinsically bursting neurons that may contribute to rhythm generation. Peripheral chemo- and mechanosensory inputs are transmitted to the nucleus of the solitary tract (nTS) in the dorsal respiratory group (DRG). The pontine respiratory group (PRG) includes the Kölliker–Fuse (K–F) and the parabrachial (PB) nuclei, which contain respiratory-modulated neurons. See text for additional details.

VRC. Transmission of an efference copy of ventilatory drive from the VRC is an example of one of these reciprocal connections. These medullary circuits may serve to maintain an overall level of rCPG activity. In addition, certain (particularly rostral) regions within the medullary raphe are chemosensitive, responding to local changes in carbon dioxide or pH, as well as exhibiting altered activity with stimulation of peripheral chemoreceptors.

The rostral ventral respiratory group (rVRG) region within the VRC comprises excitatory neurons that drive spinal phrenic and intercostal inspiratory motor neurons. This group of neurons is inhibited by the BötC during expiration and excited by the pre-BötC during inspiration. These rhythmically alternating influences, along with modulatory inputs from other areas of the pontomedullary network, are responsible for shaping and controlling the pattern of inspiratory rVRG activity. In contrast, the cVRG is thought to be the expiratory counterpart to rVRG activity.

Peripheral chemo- and mechanosensory inputs are transmitted to the nTS, which contains second-order neurons critical for reflex respiratory responses. For example, carotid body chemoreceptor and baroreceptor afferents terminate in the medial and lateral subnuclei of the nTS. Lung mechanoreceptors have projections to "pump cells" in the nTS, resulting in rhythmic activity of these cells which is modulated by lung inflation. The retrotrapezoid nucleus (RTN) is a site of central chemoreception. Chemoresponsive neurons within this region project to other areas of the rCPG and provide excitatory drive to the VRC and PRG. These sensory afferents, and the way in which they modulate breathing, will be discussed in subsequent sections. As part of the respiratory neural network, the nTS modulates breathing via projections to both pontine and ventral medullary components of the central respiratory network. In addition, neurons within the nTS receive inspiratory drive from the VRC and reciprocal pontine projections gate neuronal activity in the nTS.

■ Chemoreceptors

The carotid and aortic bodies are bilateral sensory organs that detect changes in arterial oxygen. Although very small in size, the reflexes initiated by these tissues (particularly the carotid bodies) are critical for evoking stimulation of breathing during hypoxemia.[7]

Stimulation of the carotid body by hypoxia (O_2 sensing) involves stimulus transduction and afferent nerve activation. Carotid bodies are composed of two cell types: type I and type II. Type I cells (also referred to as glomus cells) are of neural crest origin and are the putative oxygen-sensing cells. Glomus cells express a variety of neurotransmitters that play critical roles in sensory transmission of hypoxemia. Afferent nerve endings, whose cell bodies lie in the petrosal ganglion, form synaptic contacts with glomus cells and are responsible for afferent signaling to the CNS. The type II cells (also referred to as sustentacular cells) resemble glial cells, and they are thought to act primarily as supporting cells.

There are two main pathways by which the carotid body senses hypoxia, although which mechanism is primary remains an area of debate.[8–10] The first main pathway for oxygen sensing involves heme-containing proteins in the glomus cell (metabolic hypothesis). First proposed by Mills and Jobsis, and later supported by studies using exogenous carbon monoxide (CO), there is evidence that mitochondrial cytochrome(s) may act as potential O_2 sensors. Further, several nonmitochondrial heme proteins that are expressed in glomus cells, including NADPH oxidases and heme oxygenase-2 (HO-2), have been proposed as potential oxygen sensors. Finally it has been suggested that hypoxia leads to the formation of iron-containing compounds via chelation as part of the transduction process, although the putative proteins and downstream signaling pathways responsible for afferent nerve activation are not well defined.

The second general mechanism by which hypoxia leads to depolarization of glomus cells is via inhibition of an O_2-sensitive, membrane-bound K^+ channel. This pathway for sensory transduction is based on the neuronal phenotype of the glomus cells and is referred to as the membrane hypothesis. Glomus cells express a variety of O_2-sensitive K^+ channels including outward rectifiers, Ca^{2+}-activated K^+ channels, human-ether-a-go-go (hERG), and twin pore-acid–sensitive K^+ (TASK) channels.[11] There is published evidence supporting and refuting aspects of both the metabolic and membrane hypotheses. Most likely, both pathways complement each other and work in concert to facilitate oxygen sensing by glomus cells. For example, it has been proposed that with increasing severity of hypoxemia, additional pathways are activated, allowing the carotid body to respond to a wide range of arterial oxygen levels.

Regardless of the mechanism(s) involved, hypoxic sensing ultimately leads to a Ca^{2+}-dependent release of neurotransmitters from glomus cells. These signaling molecules activate nerve endings in the carotid sinus nerve leading to an increase in afferent nerve activity (sensory transmission). The carotid body expresses several classes of neurotransmitters, including (1) biogenic amines (acetylcholine [Ach], dopamine, norepinephrine, and 5-hydroxytryptamine), (2) neuropeptides (enkephalins, substance P, and endothelins), (3) adenosine triphosphate (ATP), (4) amino acids (e.g., GABA), and (5) gas transmitters (CO and nitric oxide, NO). Some of the transmitters (e.g., ACh, substance P, ATP) stimulate whereas others (e.g., dopamine, enkephalins) inhibit carotid sinus nerve activity. Identifying which transmitters are primarily responsible for hypoxia-induced afferent nerve activation under physiologic conditions remains an area of active research, and it is possible that corelease of multiple molecules, acting in concert, may ultimately be responsible for sensory excitation by hypoxia. While the carotid body is the primary peripheral chemoreceptor responsible for oxygen sensing, carbon dioxide also stimulates the carotid body, but the mechanisms are not fully understood. Finally, the interaction of the central and peripheral chemoreceptors is still debated, but recent evidence supports a hyperadditive model whereby the gain of one group of chemoreceptors can increase the responsiveness of the other (e.g., carotid body stimulation increases the gain of the central chemoreceptors).[12]

■ Mechanoreceptors

The lung, chest wall, and respiratory muscles all contain mechanoreceptors, which provide closed-loop feedback to the rCPG. This afferent input regulates minute ventilation independent from chemical drive. In addition, mechanoreceptor reflexes modulate the respiratory pattern on a breath-by-breath basis by enhancing or terminating inspiration. Afferent axons from lung mechanoreceptors are contained within the vagus nerve, but the importance of these receptors to control of respiration in awake, adult humans is likely small. Additional mechanoreceptors in the respiratory muscles and chest wall have central projections that travel in spinal nerves and the spinal cord. These receptors are important to coordinating the breathing pattern during trunk twisting and during movement between the upright and supine positions.

Several broad categories of mechanoreceptors are relevant to ventilatory control.

Lung stretch receptors are present in the airway smooth muscle of the distal airways. These slowly adapting receptors are stimulated by lung inflation. Afferent signaling following activation of these receptors tends to terminate inspiration without altering the slope of the inspiratory ramp, as well as to promote expiratory activity. Slowly adapting receptors in the lung are the afferent fibers responsible for the Hering–Breuer reflex, which describes the termination of inspiration (promotion of inspiratory-to-expiratory phase switching) that occurs as a result of lung inflation. In addition, expiratory prolongation and occasional apneas that occur with large and sustained inflation of the lung are a manifestation of this reflex.

Rapidly adapting receptors respond to changes in airway mechanical properties that accompany lung inflation and deflation and become more active as the rate of airflow increases. These receptors are also activated by stimuli that induce bronchospasm, edema, or mucus secretion. For example, they produce cough and laryngeal narrowing in response to stimulation by dust, ammonia, histamine, and other agents, as well as in response to increases in inspiratory airflow. These lung mechanoreceptors are primarily located in the epithelial and submucosal layers of the larger airways, accounting for their sensitivity to inhaled agents. Finally, rapidly adapting receptors lead to increased respiratory frequencies at low lung volumes, due to afferent signaling that increases inspiratory neural activity during lung deflation.

Bronchial J receptors are named for their juxtacapillary location. These lung mechanoreceptors project centrally through unmyelinated (in contrast to the first two types) fibers and respond to pulmonary vascular congestion associated with increases in pulmonary artery and capillary pressure. Stimulation contributes to the increase in respiratory frequency and a decrease in tidal volume in response to pulmonary edema.

Bronchial C receptors are named for their sensitivity to capsaicin and are located in the airway wall. Similar to type J receptors, these lung receptors project centrally through unmyelinated-fibers. Activation of C fibers with capsaicin or bradykinin produces cough and a rapid, shallow breathing pattern. Unlike other lung receptors described here, bronchial C receptors are relatively insensitive to mechanical stimulation and changes in lung volume.

Muscle spindles transduce muscle length. The diaphragm has few if any muscle spindles, but these mechanoreceptors are plentiful in the intercostal muscles. Muscle spindles tend to augment breathing when activated.

Muscle tendon organs are located in series with muscle fibers in the tendon and are activated as muscle fibers generate force. Thus, these mechanoreceptors sense the efficiency of force generation and inhibit breathing when activated. The central tendon of the diaphragm contains tendon organs, as do the tendons of accessory muscles of respiration.

The rib cage joints and upper airways (larynx, pharynx, and nasal cavity) also contain receptors that impact control of ventilation. For example, cold air stimulation of the pharynx initiates the cough reflex and can reduce the ventilatory response to carbon dioxide.

Upper Airway and Pump Muscles

The upper airway muscles are described more completely elsewhere but are addressed briefly here for completeness. The pharyngeal dilator muscles can be broadly classified into those with phasic activity (burst with inspiration) and tonic activity (constant activity throughout the respiratory cycle). The genioglossus is a frequently studied muscle as it is a representative phasic muscle that is readily accessible for intramuscular recordings and is controlled by the hypoglossal motor nucleus. The genioglossus is a major dilator muscle, which serves to protrude the tongue and protect pharyngeal patency in the face of collapsing perturbations. The tensor palatini, in contrast, is a representative tonic muscle controlled by trigeminal motor branches. Recent insights from recordings of single motor units have defined the complexity of these various muscles and provided insights into brain stem control in humans.[13] Although robust activity of the pharyngeal dilator muscles has been observed in obstructive sleep apnea patients during wakefulness, the fall in activity of these muscles at sleep onset likely contributes to a propensity to upper airway collapse in susceptible individuals. Some data also support evidence of structural neural remodeling and reinnervation of genioglossus muscle fibers, suggesting that neural injury also may be present in patients with sleep apnea.[14] Given the recent realization that sleep apnea has multiple underlying mechanisms, there is likely a subset of OSA patients who have dysfunction in upper airway muscles as a major pathogenic factor. Various approaches are being considered to augment upper airway dilator muscle activity, including the possibility of pharmacologic manipulation of hypoglossal output or electrical stimulation of the hypoglossal nerve. Pharmacologic targets are being defined through careful studies of premotor inputs to the hypoglossal motor nucleus, although, as yet, no human trials have shown clear augmentation of genioglossus activity with pharmacotherapy. While the role of hypoglossal nerve stimulation in treating sleep apnea remains incompletely defined, recent work highlights the clinical promise of this approach.[15,16]

STABILITY OF VENTILATORY CONTROL: LOOP GAIN

Loop gain is an engineering term that is used to define the stability or instability of a negative feedback control system. Overall loop gain can be thought of as the integration of controller and plant factors and is thus the product of controller gain and plant gain (Fig. 11-1). A system with a high loop gain is prone to instability, whereas a system with low loop gain is intrinsically stable. The concept of loop gain can be considered in the context of the thermostat analogy, which is a common example of a negative feedback control system designed to regulate room temperature. Situations that lead to oscillations in room temperature can be considered analogous to situations in humans in which CO_2 levels fluctuate. For example, a highly sensitive thermostat is one that responds to trivial fluctuations in room temperature with major changes in output from the air conditioner or furnace; thus, a very sensitive thermostat will lead to marked fluctuations in room temperature. By analogy, exquisite sensitivity of chemoreceptors will contribute to marked fluctuations in CO_2 levels. Another example of elevated loop gain is a furnace that is too powerful such that a minor drop in room temperature leads to major elevations in room temperature as a result of the output of the furnace. By analogy, if a minor increase in Pa_{CO_2} led to major increases in ventilation yielding marked reductions in Pa_{CO_2}, the system would be considered unstable—that is, elevated loop gain. Thus, situations that lead to fluctuations in room temperature can be considered to understand the factors underlying CO_2 fluctuations in the human.

In the case of ventilation, the propensity for CO_2 fluctuations is a function of an individual's loop gain. That is, an individual with a high loop gain is prone to developing periodic breathing or Cheyne–Stokes respiration (CSR), even with minimal perturbation. On the other hand, an individual with low loop gain will maintain relatively stable breathing patterns even with major perturbations. The mechanism underlying a high loop gain can be highly varied but can generally be considered due to an elevation of either controller gain or plant gain. Controller gain is also known as chemoresponsiveness, which includes chemosensitivity (i.e., how much chemoreceptors fire with a given CO_2 stimulus) in addition to the actual change in ventilation for a given CO_2 stimulus (e.g., which includes upper airway patency). In addition, plant gain describes the efficiency of CO_2 excretion, that is, how much the CO_2 actually changes for a given change in ventilation. Individuals with congestive heart failure are at risk of CSR likely due to elevated chemoreflex gain as well as elevated plant gain compared with matched controls.

The delay in the circulation, sometimes defined by a mixing gain, also is an important factor in determining breathing pattern. The ability for the human ventilatory control system to develop instabilities is a result of chemoreceptors being located in the brain stem and carotid bodies rather than in the lung. Circulatory delay can also contribute to an unstable breathing pattern, although most studies suggest that marked prolongation of circulatory delay is not present in CSR patients with congestive heart failure compared to heart failure patients without CSR. In classic Guyton experiments, several-minute delays were occasionally required to induce periodic breathing in dogs; such circulatory delays are beyond the range of what occurs in humans even in pathologic states (e.g., end-stage congestive heart failure). Thus, circulatory delay is considered necessary but not sufficient to induce periodic breathing or CSR. Some interventional studies suggest improvements in sleep apnea with reduction in circulatory delay, emphasizing the importance of this variable in some individuals.[17]

The measurement of loop gain is cumbersome currently, as it requires overnight experimental measurements and considerable expertise. However, the concepts are useful in a qualitative manner even if quantitative data are not available. In addition, efforts are ongoing to simplify the loop gain measurement to determine expeditiously which patients may respond to particular interventions.[18] The importance of loop gain is receiving increasing attention given the recognition of its importance in obstructive sleep apnea,[19] central sleep apnea,[20] periodic breathing at high altitude, and other conditions. Indeed, manipulation of loop gain using interventions such as oxygen or acetazolamide can lead to improvements in sleep apnea in small physiologic studies.[21,22] Thus, further work on ventilatory loop gain is required to define the optimal diagnostic and therapeutic approaches.

CONTROL OF VENTILATION IN HEALTH AND DISEASE: ILLUSTRATIVE EXAMPLES

The afferent, efferent, and central neural systems described earlier respond to a variety of challenges that affect both normal individuals and patients with respiratory disease. These pathophysiologic changes will affect the level of ventilation, the respiratory rhythm, or both. The impact of ventilatory control on specific disease states is addressed as appropriate in relevant sections elsewhere in this text. Following are illustrative examples that are considered to highlight how the respiratory control system adapts in clinically important conditions.

Ventilatory Acclimatization to Oxygen Disturbances

There are many pathophysiologic mechanisms that cause hypoxemia, and it has been well known for more than a century that hypoxia stimulates the respiratory and cardiovascular systems.[23] Heymans et al., among others, demonstrated the importance of carotid body chemoreceptors for the hypoxic ventilatory response.[22,25] Comroe and Mortimer[6] established the idea that arterial chemoreceptors are the dominant O_2-sensitive chemoreceptors for cardiopulmonary control. Elimination of the carotid and aortic body chemoreceptors elicits hypoventilation and essentially obliterates the acute ventilatory response to hypoxemia.[26] Therefore, it has been assumed that central O_2 sensitivity may not play a major role in this response.[27] In fact, chronic hypoxia reportedly has a depressive effect on the brain, limiting its response to further hypoxia. This hypoxic depression spreads rostrocaudally in the brain; and it may be the result of slowed removal of inhibitory neurotransmitters like GABA during hypoxia due to the buildup of lactic acid in the brain. However, in some experimental preparations, hypoxia continues to stimulate ventilation and the cardiovascular system in the absence of carotid body chemoreceptors, suggesting that other arterial chemoreceptors or sites in the CNS must be sensitive to hypoxia.[6] Focal hypoxia produced by cyanide in the medulla excites sympathoexcitatory neurons,[28] and experimental evidence supports central O_2 sensitivity in the C1 sympathoexcitatory region of the rostral ventrolateral medulla, the posterior hypothalamus, the preBötC, and the nucleus tractus solitarius.[26]

Hypoxic Ventilatory Response

The hypoxic ventilatory response is characterized by discrete, time-dependent mechanisms that depend on the severity, duration, and pattern of hypoxic exposure. A reduction in the partial pressure of oxygen produces an immediate increase in ventilation mediated through the peripheral chemoreceptors.[29] While the ventilatory response to hypoxia is independent of the source of hypoxemia, the brain has multiple time domains of O_2 sensitivity that can elicit different ventilatory responses to acute versus chronic hypoxia. Furthermore, this ventilatory response has several unique forms of respiratory plasticity.[30]

Acute and Chronic Exposure to High Altitude

The hypoxic and hypobaric environment encountered at high altitude results in a reduction in the available inspired oxygen (inspiratory partial pressure of O_2 [$P_{I_{O_2}}$]). Acute exposure to altitude results in hypoxemia, which produces an immediate increase in minute ventilation mediated through the peripheral chemoreceptors and characterized by an increase in frequency (respiratory rate) and amplitude (tidal volume). With ongoing exposure, ventilation continues to increase for several days resulting in a sustained gradual decrease in arterial P_{O_2}. Chronic exposure to high altitude, lasting from several hours to months, results in acclimation. This adaptation to high altitude is characterized by a gradual rise in minute ventilation with a time course depending on the altitude. In humans, at very high altitudes (~8000 m), this process may take at least 30 days. At less extreme altitudes, complete adaptation may be achieved in less than 10 days. However, in one study, ventilation and arterial oxygenation were noted to be greater than during the initial ascent to 3800 m after 8 weeks.[31] In addition, there is an increase in CO_2 sensitivity with exposure to altitude. In people living in high altitude for long periods of time, the P_{CO_2} falls to the lower level of normal or even less (Fig. 11-4).[31]

A number of physiologic mechanisms of ventilatory acclimation to hypoxia have been identified. They include (1) plasticity in O_2 sensitivity of the carotid body chemoreceptors, (2) the CNS integration of peripheral O_2-sensitive reflexes (e.g., carotid body chemoreflex), (3) plasticity of CNS mechanisms of acute O_2 sensing, and (4) the CNS integration of other nonchemoreflex ventilatory control pathways such as reflexes from pulmonary vagal chemoreceptors or respiratory rhythm generators.[26,32,33] For example, hypoxia-inducible factor-1 (HIF-1) is a key regulator of O_2-sensitive gene expression in the brain, and increases in HIF-1 have been identified in respiratory nuclei of the CNS as soon as 1 hour after hypoxemia. Hence, O_2 sensing by HIF-1α could be involved in the ventilatory acclimation to high altitude by increasing the expression of genes with products known to modulate the hypoxic ventilatory response (see Chapter 91 for further discussion).[34]

■ Oxygen-Induced Hypercapnia in Chronic Obstructive Pulmonary Disease

In severe chronic obstructive pulmonary disease (COPD), transient falls in ventilation and respiratory acidosis have been reported with breathing 100% oxygen for 20 minutes.[35–37] Initially CO_2 retention with oxygen treatment was thought to result from the suppression of the hypoxic drive mediated by carotid chemoreceptors.[38] Subsequently, additional mechanisms have been shown to contribute to oxygen-induced hypercapnia in COPD as follows:

(1) The increase in oxygen tension in lung units with low ventilation/perfusion (V/Q) ratios can blunt hypoxic pulmonary vasoconstriction in these low-V/Q lung units, thus diverting perfusion away from high-V/Q lung units yielding higher dead space; (2) the Haldane effect, which refers to the reduction in hemoglobin affinity for CO_2 with the binding of oxygen to hemoglobin. With increased

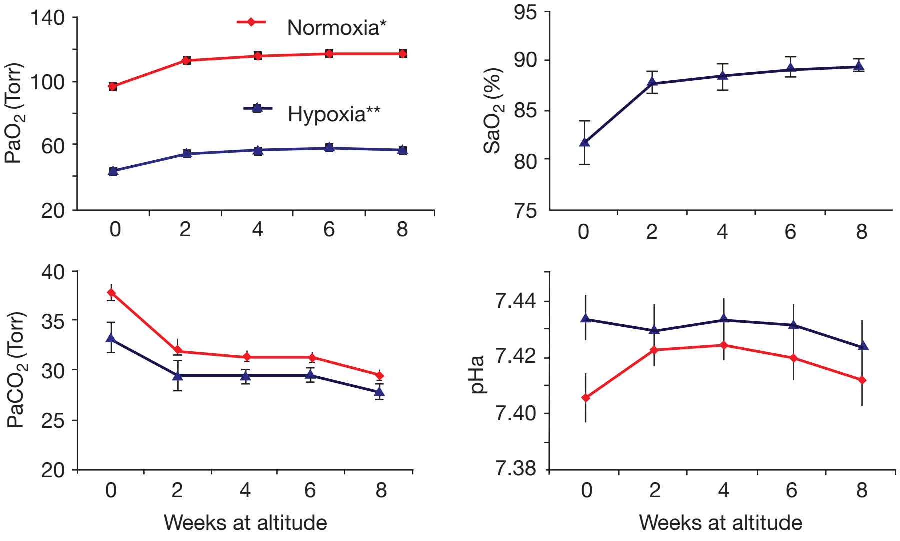

Figure 11-4 Arterial oxygenation increases and arterial CO_2 decreases during time at altitude. These changes persist in normoxia, indicating hyperventilation. pHa is partially compensated during acclimatization. *Normoxia is from data collected breathing at sea level. **Hypoxia is from data collected breathing at 3800-m altitude. *(Data from Hupperets MD, Hopkins SR, Pronk MG, et al. Increased hypoxic ventilatory response during 8 weeks at 3800 m altitude. Respir Physiol Neurobiol. 2004;142(2–3):145–152.)*

blood oxygen levels, the Haldane effect promotes dissociation of carbon dioxide from hemoglobin and leads to a small increase in Pa_{CO_2}; (3) suppression of hypoxic drive as mentioned above—data on P_{CO_2} recruitment threshold in intubated COPD patients support a change in sensitivity of the CNS to CO_2 during hyperoxia; (4) some patients with acute exacerbations of COPD are susceptible to the development of severe hypercapnia due to sleep deprivation that is common in acute illness; patients with associated obstructive sleep apnea might be susceptible since they have high sleep drive and are likely to lose the wakefulness drive to breathe at sleep onset upon initiation of therapy—for example, patients during acute exacerbations of COPD will commonly be sleep deprived and will typically fall asleep once they receive the anxiolytic and antidyspnea effects of oxygen therapy[37,39]; and (5) increases in Fi_{O_2} that occur as minute ventilation falls when supplemental oxygen is delivered noninvasively via conventional, low-flow nasal cannula. Actual delivered Fi_{O_2} is a function of inspiratory flow demand and room air entrainment; thus, higher oxygen tensions result as ventilatory drive falls for any reason. Occasionally vicious cycles can occur whereby supplemental oxygen leads to a rise in CO_2 level, which contributes to a further increase in oxygen level due to a resultant decrease in inspiratory flow with reductions in room air entrainment.

Understanding these mechanisms has clinical implications, as maintaining the arterial oxygen saturation between 87% and 92% may be a safer approach in patients with a history of respiratory disease and is unlikely to compromise tissue oxygen delivery.

■ Responses to External Mechanical Loads and Bronchoconstriction

In response to external mechanical loads, several compensatory factors act to maintain ventilation:[40] (1) *Responses intrinsic to the respiratory muscles*. The force that the muscle develops for a fixed electrical input depends on the length of the muscle (the force–length relationship). As the muscle shortens, less force is developed. The generated force also decreases as the velocity of shortening increases (force–velocity relationship). With external mechanical impediments (loading), both the magnitude and the velocity of shortening tend to decrease. (2) *Reflex effects.* At the spinal level, less shortening of the inspiratory muscles increases the signal from muscle spindles that, in turn, augments contraction of these muscles. During loading, afferent information from pulmonary mechanoreceptors also changes. Since tidal volume is depressed, inspiratory duration tends to be prolonged (Hering–Breuer inspiratory terminating reflex), but this mechanism is of little importance in humans. (3) *Conscious responses.* Loads increase neuromuscular output even in the face of a constant chemical drive. The magnitude of the increase is related to the severity of the mechanical load. This aspect of load compensation is abolished by anesthesia. Furthermore, the intensity of this load-compensating mechanism is variable, and it is reduced in some chronic lung disease like COPD.

While external loading is used experimentally, major differences exist between the neural responses to bronchoconstriction and external loading. In particular, inspiratory muscle activity increases during bronchoconstriction, even in anesthetized animals. Bronchoconstriction increases breathing frequency via reflex changes in respiratory timing. Expiratory duration (especially the second phase of expiration) shortens more than inspiratory duration. In asthma-induced bronchoconstriction, rapidly adapting receptors are stimulated by mechanical changes in the airways and by substances such as histamine and bradykinin.

■ Response to Exercise

The exercise ventilatory response is the most frequently engaged ventilatory response in everyday life.[30] Despite the increase in CO_2 production and O_2 utilization during exercise, ventilatory control mechanisms normally keep arterial P_{CO_2} and $[H^+]$ remarkably constant over a wide range of metabolic rates.[41] This pattern is achieved by graded increases in minute ventilation ($\dot{V}_E$) as the rate of CO_2 production increases and acts to minimize acidosis that would impair cellular function. This response is tightly controlled; respiratory alkalosis does not typically develop during moderate exercise in normal subjects, although it occasionally occurs in pathophysiologic states. With increased intensity of exercise, oxygen demand outstrips oxygen supply, anaerobic pathways start to operate, and blood lactate levels increase. With exertion above this anaerobic threshold, the exercise-induced metabolic acidosis becomes more marked due to a net increase in lactic acid production. As a result, high-level exercise results in a large increase in ventilation to enhance carbon dioxide excretion and minimize acidemia (see Chapter 32 for additional discussion).

The minute ventilation required to maintain acid–base equilibrium during exercise is defined by (1) the amount of carbon dioxide produced as a result of metabolism ($\dot{V}_{CO_2}$), (2) physiologic dead space, and (3) the set point at which P_{CO_2} is regulated by the respiratory control system. There is an incomplete understanding of the reflexes responsible for controlling how pulmonary ventilation matches the increases in metabolic demand during exercise without appreciable changes in arterial blood gas composition. The magnitude of oscillations in ventilation is directly related to metabolic CO_2 production. Thus, it has been proposed that a blood-borne signal helps in the coupling of metabolic production of CO_2 and ventilation. Neurally mediated signals from exercising muscles and from higher brain centers are also likely important in the ventilatory response. Finally, this response is responsible for meeting the increased need for oxygen consumption by exercising limb and respiratory muscles.

The initial phase of the exercise response is a rapid increase in ventilation. Proposed sources include signals arising from the cortex (so-called feedforward control), temperature increases, afferent signals arising as a result of muscle contraction (locomotor muscle afferents and respiratory muscle metaboreflex), accumulation of catecholamines, and increases in potassium in the venous blood.[42] There is also evidence that the abrupt initial increase in ventilation at the onset of exercise is a learned response. That is, the primary drive to breathe at the start of exercise will augment respiration in anticipation of impending metabolic needs based on past exercise experiences.[43] Chemoreceptor feedback may act in concert with the feedforward stimulus to minimize disruptions in homeostasis as the intensity of exercise increases. In addition, there is capacity for modulation and plasticity of the mechanisms controlling breathing during exercise. For example, serotonergic modulation of descending drive is a mechanism for long-term modulation of exercise hyperpnea, which may be important in individuals with underlying cardiorespiratory disease.[44]

■ Disturbances of Respiratory Rhythm

Congenital central hypoventilation syndrome (CCHS), occasionally referred to as *Ondine's curse*, is a rare neurologic disorder characterized by inadequate breathing during sleep and, in more severely affected individuals, also during waking periods. Patients congenitally lack or have poor chemosensitivity to both hypercapnia and hypoxia and suffer from inadequate ventilation. More than 90% of patients with CCHS have an increased polyalanine repeat expansion mutation (PARM) in the paired-like homeobox 2B (PHOX2B) gene. Other cases of CCHS are the result of non-PARM mutations of the PHOX2B gene. Most cases are the result of a de novo mutation, although patients may have a family history of the disorder. There is a correlation with the number of polyalanine repeat expansion genotype and the need for continuous ventilatory support. The disease typically presents in childhood, but rare adult-onset cases have

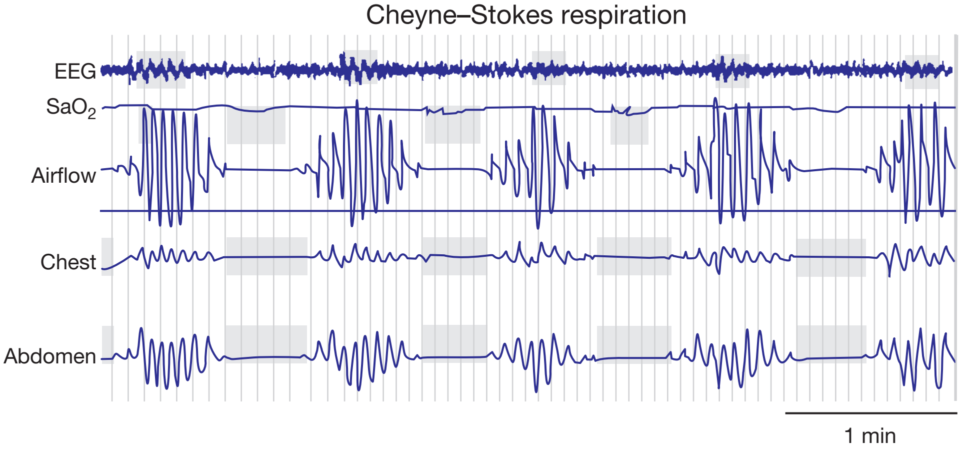

Figure 11-5 An example respiration in a patient with Cheyne–Stokes breathing. Note the characteristic crescendo/decrescendo pattern of breathing, long circulation time (each oxygen desaturation corresponds to the previous apnea), and arousal occurring at the peak of respiratory effort.

been reported.[45] A number of conditions are associated with CCHS and reflect the autonomic nervous system dysregulation, including Hirschsprung disease (about 20% of cases) and tumors of neural crest origin (neuroblastomas). While PHOX2B is considered to be the disease-defining gene in CCHS, these patients may have other protein-altering mutations including mutations in the *RET* gene which encodes the RET receptor tyrosine kinase, as well as the genes encoding, brain-derived neurotrophic factor (BDNF), endothelin 1 and endothelin 3.

Rett syndrome is a neurodevelopmental disorder that occurs almost exclusively in females. After a period of initially normal development, affected patients experience loss of speech and purposeful hand use, stereotypic hand movements, gait abnormalities, and breathing abnormalities among others. Most cases result from mutations in the gene encoding methyl-CpG-binding protein 2 (Mecp2). Loss of Mecp2 function is associated with an irregular breathing pattern. The implicated mechanism has not been established but may be related to widespread hyperexcitability in respiratory-related regions in the brain stem. Apnea that occurs during wakefulness is typically central, although it may be obstructive. These events may be isolated or precede or follow hyperventilation. During apneic episodes, the child may stare quietly ahead or smile and appear happy with no evidence of distress, despite severe cyanosis.

Cheyne–Stokes breathing is one form of periodic breathing characterized by a cyclic rise and fall in ventilation with recurrent periods of apnea or near apnea (Fig. 11-5). It was first observed in patients with cardiac or CNS disease, but it has since been reported in seemingly normal humans. The appearance of Cheyne–Stokes breathing can occur during wakefulness, although often masked by behavioral influences, but is more common during nonrapid eye movement (NREM) sleep. The period of the oscillations in ventilation in Cheyne–Stokes breathing often averages 60 to 90 seconds. Cycle length is related to the circulation time measured from the lung to a systemic artery and increases when circulation time is prolonged. Arousal tends to occur during the hyperpneic phase of the respiratory pattern, a finding that is often associated with paroxysmal nocturnal dyspnea in patients with heart failure.

Cheyne–Stokes breathing has not been consistently produced in animals by lesions in the CNS, but it has been shown to follow manipulations that are likely to produce unstable feedback control of breathing. Cheyne–Stokes breathing is seen in chronic heart failure, as well as in stroke and traumatic brain injury. A similar breathing pattern with a shorter cycle time (~15–30 seconds), often referred to as periodic breathing at high altitude, can occur in otherwise healthy individuals at high altitude during the acclimation period.

Sleep-Related Abnormalities of Ventilatory Control

Abnormal ventilatory patterns that can emerge during sleep are increasingly appreciated, including their associations with adverse neurocognitive and cardiovascular consequences. Ventilatory control instability may contribute to both central and obstructive sleep apnea. Indeed, sleep promotes breathing instability because it unmasks a highly sensitive dependence of the respiratory control system on chemoreceptor input. For example, the CO_2 reserve (i.e., the difference between the eupneic Pa_{CO_2} and that required to induce apnea) is labile during sleep and is reduced by hypoventilation, predisposing patients to the development of apneas.[46] Transient cortical arousals promote ventilatory overshoots, upper airway dilator muscle tone is reduced, and airway collapsibility is enhanced.[47] In addition, depending on the prevailing pharyngeal mechanics, anatomic factors may cause or contribute to sleep-related disorders. Thus, both basic and clinical investigators have focused on mechanisms that influence upper airway patency during wakefulness and sleep, along with ventilatory control stability during sleep (see Chapters 98–101 for further discussion).

There are a number of changes in ventilatory control that occur during sleep; however, most of the same basic mechanisms active during wakefulness are also relevant during sleep. During sleep, there is an elevation of the CO_2 set point (~45 mm Hg as opposed to 40 mm Hg during wakefulness), associated with reduced alveolar ventilation during sleep. In all stages of sleep, there is decreased ability to respond to increments in resistance–load and the work of breathing. Thus, narrowing of the upper airway during sleep is a factor contributing to the rise in Pa_{CO_2}.

Other ventilatory control mechanisms also are affected. Sleep apnea results in recurrent episodes of hypoxemia, which alter the hypoxic ventilatory response resulting in respiratory long-term facilitation (LTF).[48] LTF is a form of neuronal plasticity that is induced by exposure to intermittent hypoxia and causes a persistent increase in ventilation even when normoxia is restored.[30,49] Phrenic (innervating the diaphragm) and hypoglossal (innervating upper airway muscles) nerve activities are both increased. Whereas the impact of LTF on ventilatory stability remains uncertain in the context of sleep apnea at this time, experiments in preclinical animal models suggest that LTF has the potential for both stabilizing and destabilizing influences on breathing that warrant further investigation.[21,50,51]

Apnea is a cessation of airflow for at least 10 seconds and is probably the most common respiratory rhythm abnormality. Apneas occur often in premature infants and occasionally during sleep in healthy humans. Central apneas arise from complete or partial reductions in central neural outflow to the respiratory muscles during sleep (Fig. 11-6). In contrast to obstructive apneas, in which

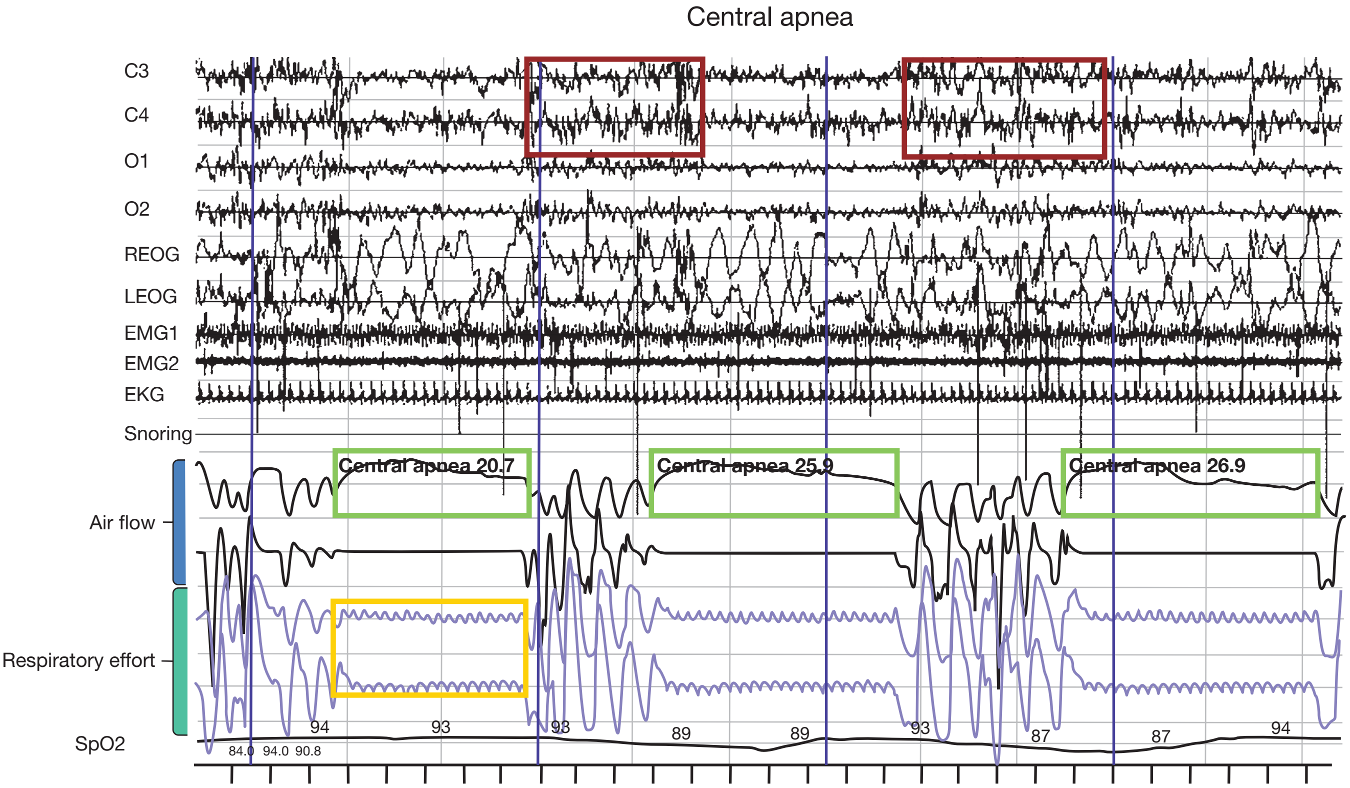

Figure 11-6 An example of respiratory pattern in a patient with central apneas. Note the typical characteristics of central apneas including absence of air flow by both nasal cannula pressure transducer and nasal–oral thermistor (durations in seconds), absence of respiratory effort measured with piezoelectric bands of the thorax and abdomen (orange box), associated oxygen desaturation corresponding to the previous apnea measured by pulse oximeter, and EEG arousal (red box) occurring after an apneic event. EEG channels (C3, C4, O1, O2); electrooculogram channels (REOG, LEOG), chin electromyogram (EMG1), bilateral tibialis anterior EMG2, EKG, snoring microphone.

inspiratory efforts are made against the occluded upper airway, no respiratory effort is generated during central apneas due to cessation of respiratory drive. Thus central apneas are distinguished from obstructive apneas by the absence of respiratory effort, which can be detected by routine monitoring techniques such as respiratory inductive plethysmography combined with assessment of nasal pressure.[20] Mechanisms that can produce central apneas include (1) reduced excitation of chemoreceptors as a consequence of hypocapnia and hyperoxia; (2) functional or actual structural medullary damage, which may result in a pattern of grossly irregular ataxic breathing; (3) loss of nonspecific respiratory excitatory stimulation (noise, light, tactile stimuli) in the absence of adequate chemical drive; and (4) active suppression of breathing by respiratory inhibitory reflexes, which is observed in a number of clinical situations including pharmacologic therapy with methadone and other opiate medications. Reflex inhibition may arise from the cardiovascular system, from the lung and chest wall, or from somatic and visceral afferents. For example, excitation of receptors located in the upper airway can, via the superior laryngeal nerve, trigger an apnea. Stimulation of J receptors in the lungs by inhaled irritants may produce temporary apnea.

Complex sleep apnea syndrome describes the appearance and persistence of central apneas or hypopneas in patients with obstructive sleep apnea upon successful restoration of airway patency. Patients with complex sleep apnea syndrome present with features of obstructive sleep apnea syndrome. However, when instability of upper airway tone is treated with positive airway pressure therapy, these patients exhibit unstable, chemosensitive ventilatory control leading to repetitive central apneas or periodic breathing during sleep.[52] Adaptive servo-ventilation, which provides both a minimum pressure to hold the airway open as well as a ventilatory assist to minimize persistent cycles of hypo- and hyperventilation, has emerged as an effective treatment in patients with normal systolic heart function. Noninvasive ventilation using bi-level positive airway pressure in the spontaneous-timed mode also may normalize ventilation in some patients.[53]

Central apneas may also occur in critically ill patients as a result of artificial ventilatory support. Application of positive pressure mechanical ventilation may result in a loss of respiratory drive and associated apneas both during and after periods of ventilatory support. This may occur despite normocapnic conditions and is more frequent during NREM sleep.[53] It is unclear whether these inhibitory effects are dependent on increases in tidal volume (e.g., Hering–Breuer mechanism) or are caused by a resetting of the inherent respiratory rhythm by the externally imposed ventilator frequency.[54,55] In addition, hypocapnia, oversedation, and the presence of CNS disease also will impact the prevalence of apneas during mechanical ventilation.

■ Dyspnea and Breathlessness

Dyspnea is defined as a subjective sensation of difficulty breathing, frequently termed “shortness of breath.” Under normal conditions, breathing is not noticeable. However, with increased demands (e.g., during exercise or with progressive cardiopulmonary disease), respiratory movements and forces become more perceptible. When sufficiently intense, respiratory efforts result in symptoms of dyspnea, and patients with lung disease may complain of dyspnea even at rest. The development of dyspnea is a warning signal that likely serves to protect the body from harm, but since dyspnea itself can become an incapacitating symptom, considerable attention has been given to its etiology.[56–61] Experiments using breath-holding techniques showed that hypercapnia and hypoxia decrease breath-holding times, supporting the idea that increased levels of chemical drive promote dyspnea. In contrast, increased lung volume (increased oxygen stores) lengthened breath-holding time. Other investigations identified that combined blockade of the phrenic and vagus nerves extends the time apnea can be voluntarily maintained, suggesting that signals from respiratory muscles contribute to the sense of dyspnea. Dyspnea also seems to be related to the effort (as a percentage of maximal capacity) required during breathing. In particular, dyspnea increases as the pressures required for tidal breathing grow greater or the maximal inspiratory pressure decreases (e.g., respiratory muscle paresis or fatigue). Taken together, these data suggest dyspnea may manifest as a sense of air hunger (breath holding) and/or as a sense of excessive effort (breathing against a resistance); it has been proposed that the two types of dyspnea are produced by different mechanisms with different anatomic pathways. In addition, cognitive and affective factors that determine the relative pleasantness and intensity of sensations may affect the level of dyspnea. A corollary discharge hypothesis has emerged whereby dyspnea is related to a mismatch between the central respiratory output and the actual achieved ventilation. During exercise, dyspnea is not profound since elevations in respiratory drive are associated with increases in the achieved minute ventilation. However, in situations where respiratory mechanics are impaired, for example, airway obstruction, dyspnea can be profound since high drive does not translate into high minute ventilation.

SUMMARY

Considerable progress has occurred in the area of control of breathing, both in terms of the basic underlying mechanisms as well as the clinical implications of the applied physiology. Given the ubiquitous nature of the associated diseases and conditions, further efforts into the basic and clinical aspects of this field will likely allow new therapeutic strategies to emerge.

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CHAPTER 12

Sleep and Circadian Rhythms

Allan I. Pack

INTRODUCTION

Sleep and circadian rhythm are highly coupled processes. In the original formulation they were considered independent but interacting. Borbely and colleagues[1–4] posited that the circadian process (Process C) had a 24-hour rhythm that interacted with the sleep drive system (Process S) (Fig. 12-1). Process S is envisaged to be like an old-fashioned egg timer. The drive for sleep is at a very low level following the major sleep bout and increases progressively as wakefulness proceeds, i.e., the drive to sleep is related to the duration of prior wakefulness. Humans are programmed to sustain wakefulness for 16 hours but beyond this develop progressive performance impairments. During the day the drive to sleep is counteracted by an alertness signal from the clock. When this alertness signal declines later in the evening, the sleep drive is unopposed, and sleep ensues. During sleep the drive to sleep progressively declines, i.e., the egg timer is flipped, and the sands recover (Fig. 12-1). The situation is actually more complex than this since sleepiness occurs at two times of day, i.e., siesta time in early afternoon and late in the evening. While these processes were initially considered independent, they are not at a molecular level.[5,6] Core clock molecules increase their expression in brain when sleep is deprived.[7] Moreover, mutations of a clock-associated gene—DEC2, now called BHLEH41—result in short sleep in humans (<6 hours) without evidence of daytime performance impairment.[8,9]

In this chapter the basis of the clock is described, and the point made that the lung itself has a clock. Sleep is discussed and recent evidence reviewed that sleep alters gene transcription in the lung. The reader will get a background in sleep that will facilitate understanding the cardiopulmonary changes during sleep (Chapter 100) and sleep-disordered breathing (Chapter 98).

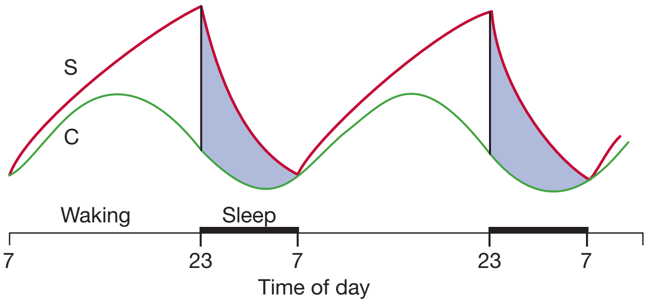

Figure 12-1 Two-process model of sleep/wake control. Behavioral state is controlled by the interaction between two processes: process C, the biological clock, and process S, the sleep homeostatic drive. The dark bar from 2300 to 0700 is the lights-off period. For further details, see text. *(Reproduced with permission from Kryger MH, Roth T, Dement WC: Principles and Practice of Sleep Medicine, 5th ed. Philadelphia, PA: Elsevier; 2011.)*

MOLECULAR MECHANISMS OF THE CLOCK

The fundamental principles of how the clock ticks are conserved across species, although the specific details, i.e., genes involved, vary between species.[10,11]

The original concept that the clock involves a distinct molecular mechanism came from identification of mutant fruit flies (*Drosophila*) with long circadian periods, flies with short circadian periods, and flies with no circadian rhythm.[12] Subsequently it was determined that these different flies had different mutations in the same gene, which was given the name period (per), i.e., the first clock molecule identified.[13] Later forward genetic studies identified another clock molecule in *Drosophila*, i.e., timeless.[14] The first mammalian clock gene was also identified by forward genetic studies, i.e., studying mice that had received a chemical mutagen—ENU—and had an abnormal circadian period.[15] This clock molecule is Clock and is a transcription factor.

In both *Drosophila* and rodents, the major mechanism of oscillation is a negative feedback loop (for mammalian model, see Fig. 12-2). There are also positive feedback loops. In mammals the main clock proteins are the 3 period proteins (per1, per2, and per3) and the two cytochrome proteins (cry1 and cry2). These proteins form a complex in the cytoplasm that enters the nucleus where they inhibit their own transcription that is controlled by the clock/BMAL1 complex (see Fig. 12-2). The degradation of the PER and CRY proteins is important in setting the period of the clock. The PER proteins are phosphorylated by enzymes such as casein kinase 1e and CKII. Once phosphorylated, the PER proteins are targeted for ubiquitination and degradation. In humans mutations in PER2, in the site in which it is phosphorylated[16] and also in CK1 delta,[17] lead to familial phase advance syndrome.[18] Individuals with this have marked phase advance going to sleep at 7:30 PM and waking up at 4:00 AM.

The other core feedback loop involves the orphan nuclear-receptor genes—Rev-Erbα/β and RORα/β. RORs activate BMAL1 while REV-ERBs repress BMAL1 and clock RORs and REV-ERBs are themselves targets of CLOCK-BMAL1 and are negatively regulated by the repressors CRY1 and 2 and PER, particularly PER2.

Thus, the clock is a cell-autonomous process and individual cells show circadian oscillation and clock mechanisms can be studied in vitro with cells in culture. The investigators who described this molecular mechanism in *Drosophila*—Jeff Hall, Michael Rosbash, and Michael Young—were awarded the Nobel Prize for this discovery.

SUPRACHIASMATIC NUCLEUS—THE MASTER CLOCK[19]

The master clock is in the suprachiasmatic nucleus (SCN) of the hypothalamus. It contains approximately 20,000 neurons. Destruction of this nucleus by lesioning results in the animal becoming arrhythmic, i.e., with no obvious circadian period.[20,21] The intrinsic period of the clock is not exactly 24 hours, and the clock is entrained each day to 24 hours by environmental cues. For the SCN, the main entrainment is by light/dark signals. There is a direct track from the retina to the SCN—the retino-hypothalmic tract. Moreover, there is a separate light-sensing mechanism in the eye for entrainment of the clock. This was identified in knockout mice that lacked rods and cones in the retina. While they were blind, there was normal entrainment of the circadian system to light/dark.[22,23] Subsequently, the basis of this light sensing mechanism was identified.[24,25] It is the pigment, melanopsin, that is in retinal ganglion cells scattered across the retina.[26–28] This pigment is particularly sensitive to light in the blue color range.[29] This has led to development of blue light boxes, blue light glasses, and glasses that filter out blue light to manipulate the light input to the clock. Following time zone change the output of the master clock is entrained to the new time zone by altered light/dark input. However, this re-entrainment is relatively slow with the clock adjusting only about 1 hour/day.

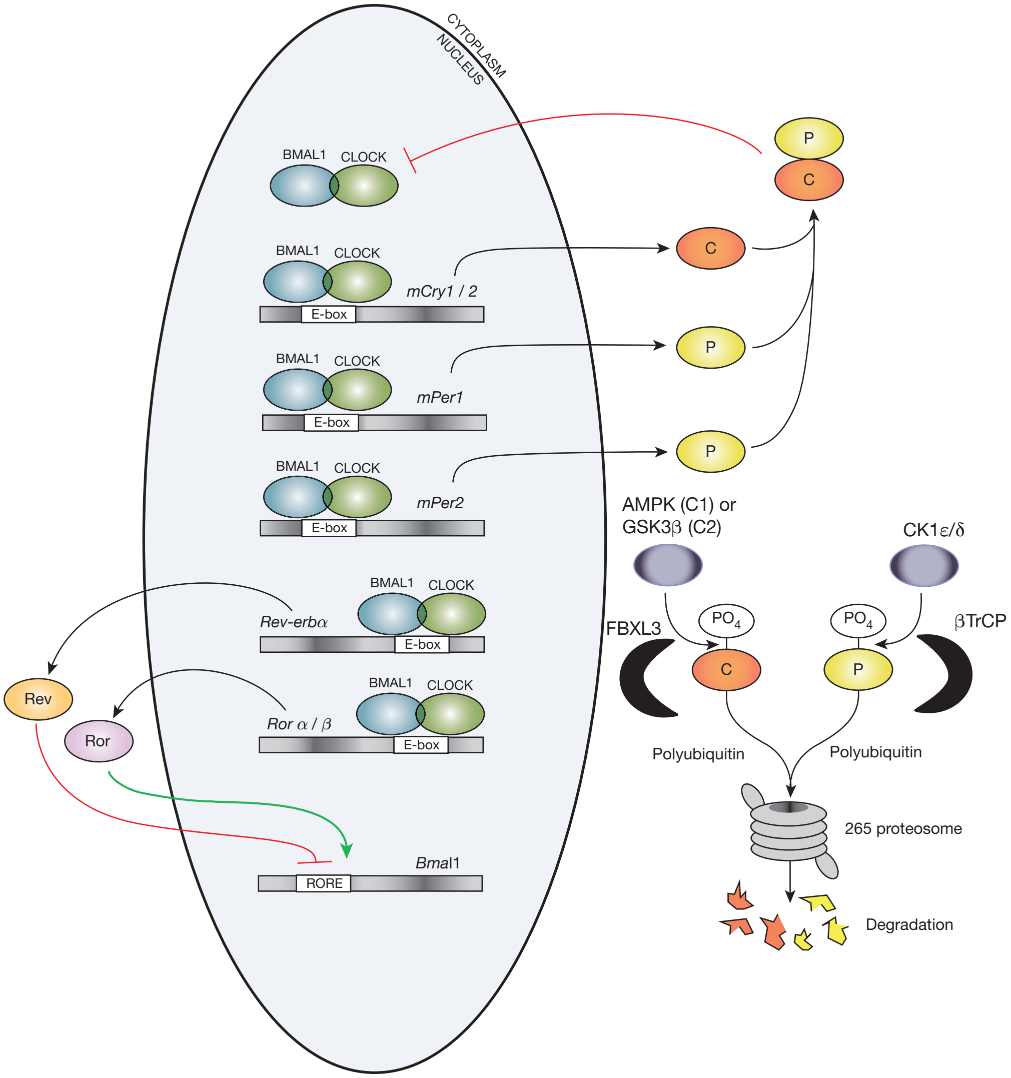
CYTOPLASM
NUCLEUS
BMAL1
CLOCK
P
C
BMAL1
CLOCK
mCry1 / 2
E-box
C
BMAL1
CLOCK
mPer1
E-box
P
BMAL1
CLOCK
mPer2
E-box
P
AMPK (C1) or
GSK3β (C2)
CK1ε/δ
BMAL1
CLOCK
Rev-erbα
E-box
FBXL3
PO4
PO4
βTrCP
C
P
BMAL1
CLOCK
Rev
Ror
Ror α / β
E-box
Polyubiquitin
Polyubiquitin
265 proteosome
Bmal1
RORE
Degradation

Figure 12-2 The major mechanisms that result in diurnal oscillation of clock genes. For further details, see text. *(Reproduced with permission from Buhr ED, Takahashi JS. Molecular components of the Mammalian circadian clock. Handb Exp Pharmacol. 2013;(217):3–27.)*

PERIPHERAL CLOCKS[11,30]

Once clock molecules were identified in mammals, the surprising result was that they were expressed in all tissues. It is now realized that there are functioning clocks in all tissues. These peripheral clocks are synchronized with signals from the master clock in the SCN. These peripheral clocks result in rhythmic expression of genes in each tissue, and some 3% to 10% of all mRNAs show rhythmic expression in different issues.[31] (The precise number of genes oscillating depends on the mathematical definition of oscillation such that some estimates of the number of mRNAs oscillating are higher than this.) Thus, there are substantial changes in the molecular functions of different organs at different times of day. The lung is no exception in this regard (see further below).

Peripheral clocks are not only controlled by signals from the master clock but also by signals that occur locally in the particular tissue (Fig. 12-3). Important signals include changes in autonomic nerve activity, body temperature, glucocorticoids and feeding pattern (see Fig. 12-3). Phase shifting of peripheral clocks occurs much more rapidly than for the SCN. Altering the feeding pattern of mice can produce large phase shifts in liver clocks without any effect on the rhythmic expression in genes in the SCN.[32,33]

There is also a molecular clock, not surprisingly, in the lung.[34,35] There is a clock in the Clara cells of the mouse bronchial epithelium.[36] As in other organs, there are a large number of genes that show diurnal changes in expression including genes involved in

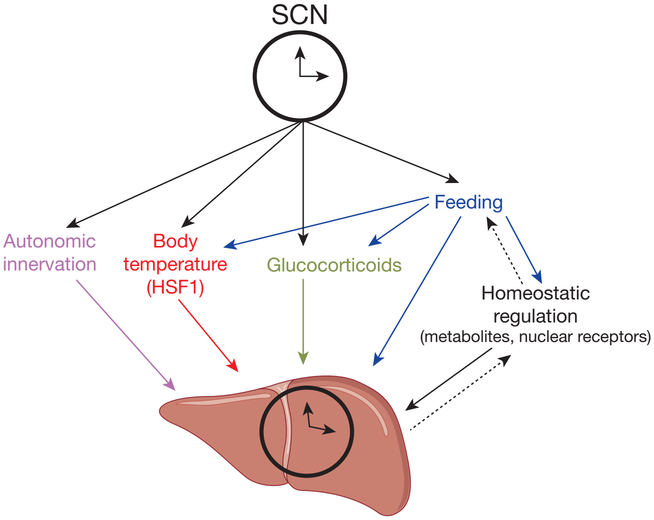
SCN
Feeding
Autonomic innervation
Body temperature (HSF1)
Glucocorticoids
Homeostatic regulation
(metabolites, nuclear receptors)

Figure 12-3 There are peripheral clocks in all organs. This diagram is for liver, but there are also clocks in the lung (see text). The "master" clock is in the suprachiasmatic nucleus (SCN) of the hypothalamus. It sends signals to peripheral clocks to synchronize them. There is also local control of clocks by metabolites, etc. *(Reproduced with permission from Mohawk JA, Green CB, Takahashi JS. Central and peripheral circadian clocks in mammals. Annu Rev Neurosci. 2012;35:445–462.)*

extracellular matrix, cell cycle, and apoptosis.[37] Genes encoding inflammatory molecules such as chemokine ligands also show diurnal oscillation.[37] The immune response, which is such a critical function of the lung, is under circadian control.[38] Circadian rhythm of other functions of the lung are known to occur, including in FEV_1.[39] Circadian variation also occurs in asthma symptoms,[39] as do changes in the cellular content of bronchoalveolar lavage fluids in patients with mild asthma.[40]

The lung clock and, indeed, other peripheral clocks, are affected by hypoxia.[41] The transcriptional response to hypoxia is dependent on time of day. Exposure to hypoxia phase shifts clocks in a tissue-specific fashion, leading to asynchrony of rhythms of the clock in different tissues.[41]

The functioning of the lung clock is particularly relevant to lung cancer and to the immune response in the lung. A wide range of core clock molecules are epigenetically altered in a variety of lung tumors.[42] Moreover, disruption of the circadian rhythm promotes tumor growth in the lung.[43] This has been shown in a mouse model with lung adenocarcinoma. Physiologic perturbations to simulate jet-lag promoted growth of the lung tumor.[43]

The immune system in the lung has a circadian rhythm.[44] This applies to both innate and adaptive immune responses. The role of the clock in immune responses was the topic of a recent NIH workshop.[45] Different aspects of the immune response are regulated by the circadian system. The best-documented aspect is the regulation of pro-inflammatory cytokines.[46] Trafficking of myeloid and lymphocyte subsets are also regulated by the clock.[47] The clock is also involved in the differentiation and maturation of specific subsets of immune cells.[48,49]

CLOCK GENES AND PHARMACOLOGY[50,51]

Given that a large part of the genome is regulated by clocks, it is not surprising that clock mechanisms can affect actions of drugs. The absorption of many commonly used drugs shows time-of-day effects, as do drug metabolism and drug excretion.[50,51] For example, there is a circadian variation in gene expression of several members of the cytochrome P450 system, the main system for drug oxidation, in liver.[31] Protein levels of cytochrome P450 also oscillate across the day,[52] and there is a circadian rhythm of the activity of all cytochrome P450 enzymes.[53]

Thus, efficacy of specific drugs can vary with time of day. The anticoagulant effect of heparin, for example, varies with time of day.[54] When heparin is administered by constant intravenous infusion, the anticoagulant effect varies at different times of day.[54]

The concept of *chronopharmacology* is most developed for cancer therapy. Levels of plasma 5-fluorouracil vary across the day when the drug is delivered at the same rate.[55–57] There is a circadian variation of the pharmacokinetics of 5-fluorouracil.[58] Clinical trials show that treatment efficacy and toxicity of a chemotherapeutic regimen for metastatic colorectal cancer are enhanced using appropriate chronotherapy compared to constant infusion.[59]

Thus, time of day circadian effects need to be considered in pharmacology. There is a developing interest in this aspect when considering optimal drug regimens.

SLEEP AND ITS STAGES

It is now realized that sleep is universal. While definitions of sleep in mammalian species are based on the electroencephalogram, behavioral criteria[60,61] have led to identification of sleep in many species. In particular, a sleep state has now been identified in *Drosophila*,[62,63] zebrafish,[64] and most recently in the worm *C. elegans*.[65] Thus, all model systems are available to study sleep. There are already data showing that molecular mechanisms regulating sleep are conserved across species.[66]

While there is a suggestion that there are different stages of sleep in *Drosophila*,[67] rapid eye movement (REM) sleep has been recognized in mammals and birds. There is recent demonstration of a REM sleep state in zebrafish.[68] In mammals sleep is divided into two major types—non-REM (NREM) sleep and REM sleep.[69] REM sleep is a stage with the following: the brain is quite active with flurries of activity resulting in rapid eye movements; individuals waking from REM sleep recall their dreams; there is active paralysis of muscles apart from the diaphragm such that normal individuals do not live out their dreams. (Individuals with REM behavior disorder do enact their dreams since the atonia of REM sleep is no longer in place. This is a synucleinopathy, and a high percentage of individuals with REM behavior disorder go on to develop Parkinson's disease.[70]) There is also in REM autonomic instability with variations in heart rate and breathing pattern [see Chapter 100].) NREM sleep is divided into stages based on the electroencephalogram (Fig. 12-4). Originally four stages of NREM sleep were identified,

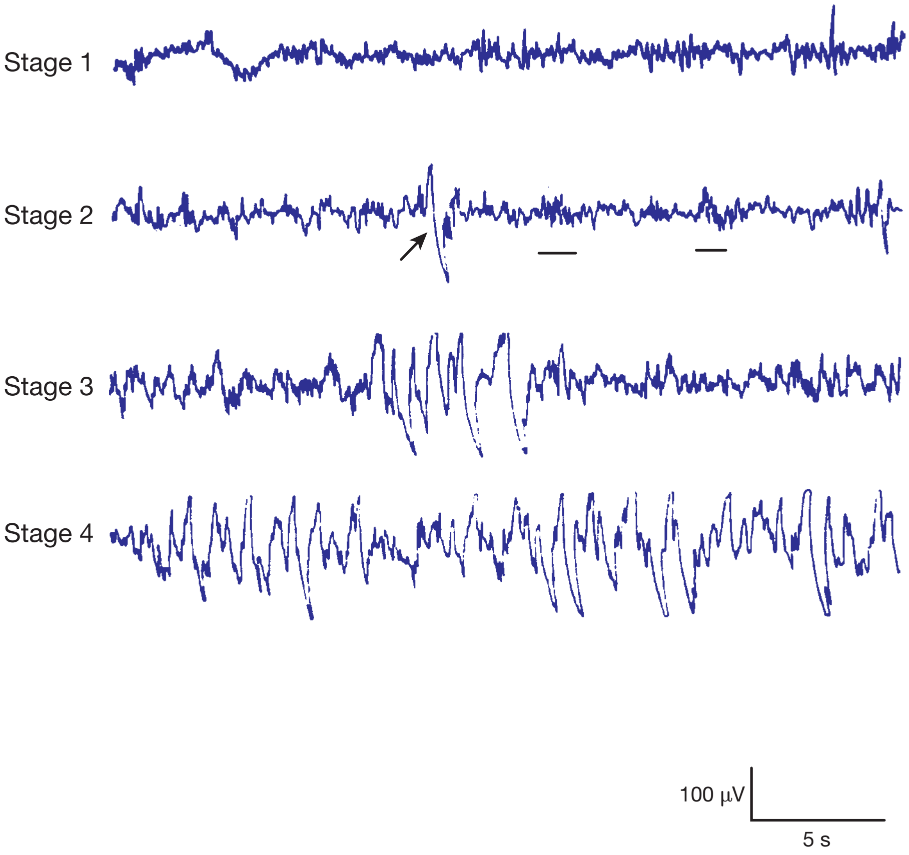

Figure 12-4 Electroencephalographic tracings recorded from a normal young adult demonstrating the four stages of NREM sleep. In the stage 2 recording, the arrow points to a characteristic K complex and the underlining to sleep spindles.

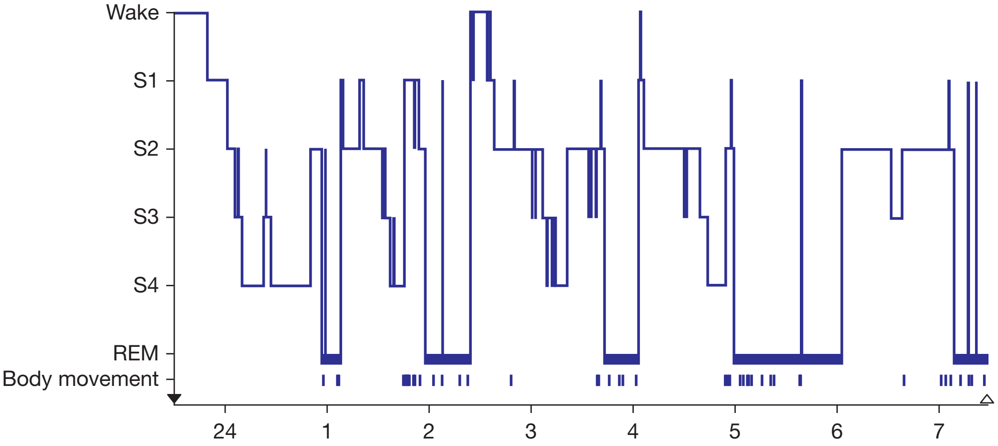

Figure 12-5 The progression of sleep stages across a single night's sleep of a normal young adult. The histogram was drawn on the basis of continuous recordings scored in 30-s epochs.

but recently stage 3 and stage 4 NREM sleep have been collapsed into one stage—N3. In this stage there is synchronized oscillatory firing of cortical neurons that generate large slow waves that are detected on the electroencephalogram (see Fig. 12-4). In all mammalian species there is distinct cycling of the different sleep stages, although the periods of these cycles vary between species. In humans the cycles have approximately a 90-minute duration, with episodes of REM sleep occurring every 90 minutes (Fig. 12-5). In the first part of the night individuals cycle down into stage 3 sleep; slow wave sleep occurs early in the sleep period. Episodes of REM sleep get longer and indeed more phasic, i.e., more eye movements etc., as the night progresses. Thus, typically humans are waking up out of REM sleep in the morning. There are major differences in the behavior of the cardiopulmonary system in these different sleep stages. These are discussed in Chapter 100.

MECHANISMS CONTROLLING SLEEP

Sleep is a circuit property. There is no evidence that single neurons sleep, although the intensity of "sleep" may vary across the brain—i.e., *local* sleep; slow waves in NREM sleep are particularly marked over brain regions that have been very active during wakefulness as a result of their involvement in specific tasks.[71,72] Much work over the last two to three decades has identified the neuronal basis for sleep/wake control.[69,73] Many neuronal groups have increased firing during wakefulness, reduced firing during NREM sleep, and virtually absent firing during REM sleep. These include the following: cholinergic cells in basal forebrain; orexin (hypocretin) cells in lateral hypothalamus; histamine cells in posterior hypothalamus; dopamine cells in peri-aqueductal grey; noradrenaline cells in locus coeruleus; and serotonin cells in brainstem raphe nuclei. While these neurons are all more active in waking, they are likely to have different functions during wakefulness. For example, it has been shown that orexin (hypocretin) neurons respond to emotions, e.g., positive emotions that result in pleasure increase the level of hypocretin.[74]

While all these neurons show similar differences in firing between wake and sleep states, there is a different pattern for cholinergic neurons in the pedunculopontine tegmentum (PPT) and lateral-dorsal tegmentum (LDT) in the brainstem. These neurons have reduced firing in NREM sleep compared with wakefulness but higher firing in REM sleep.[69] Thus, REM sleep is thought of as a time with higher cholinergic activity.[69]

While many neurons show increased firing during wakefulness, there is a more limited number of neurons that increase their activity during sleep. These neurons are in the ventro-lateral preoptic (VLPO)[75] and medial preoptic (MPO)[76] area of the hypothalamus. The VLPO has been called the sleep switch.[75] Neurons active during sleep contain the inhibitory neurotransmitter GABA and the neuropeptide galanin. Recently new neuronal groups that promote sleep have been identified such as GABA cells in the parafacial region.[77] Recent comprehensive reviews of the circuits controlling wake, NREM, and REM have been published.[78,79]

Since control of wake, sleep, and its stage is a circuit property, it has been proposed that behavioral state is controlled by a flip-flop[73] (Fig. 12-6). It is posited that wake-active neurons inhibit sleep-active cells during wakefulness but there are state-dependent changes such that a flip occurs and now sleep cells inhibit wake neurons during sleep. There is a secondary flip-flop that controls oscillation between NREM and REM sleep.[80]

In this proposed mechanism orexin cells play a critical role in stabilizing the flip-flop, i.e., preventing too many state transitions. Orexin cells play an important role in narcolepsy. Following the description of this new neuropeptide by two groups—one of which called the neuropeptide *hypocretin*[81] while the other called it *orexin*[82]—it was quickly recognized that it played a key role in narcolepsy. Dogs with a mendelian recessive genetic form of narcolepsy had mutations in the orexin-2 receptor that made it nonfunctional[83] while mice with orexin knockout showed key features of human narcolepsy.[84] Postmortem studies have shown that patients with narcolepsy and cataplexy have loss of orexin (hypocretin) neurons.[85] Thus, narcolepsy is likely to be an autoimmune disorder in which the main pathogenetic mechanism is destruction of orexin neurons.[86]

FUNCTIONS OF SLEEP

Although much effort has been made to understand the neuronal basis of sleep, an equally if not more important question is what the functions of sleep are. We spend about one-third of our lives sleeping. The question is what benefit do we obtain? Is the benefit just for the brain or do other organs, such as the lung, also obtain benefit?

While theories as to the functions of sleep have been proposed for decades, the concepts that have been articulated recently have in large part, although not exclusively, come from studies comparing gene expression (initially with microarrays; recently with RNA sequencing) between sleeping and awake animals (often enforced with sleep deprivation) sacrificed at the same time of day. The major focus, not surprisingly, has been on the functions of sleep for the brain. The proposed functions of sleep for the brain are discussed below.

■ Energy Restoration Hypothesis[87,88]

One of the concepts that has been proposed is the Benington-Heller hypothesis.[87] It posits that energy stores in brain—primarily glycogen in glia—are depleted during wakefulness and are restored during sleep. There are some data to support this.[89] However, the situation is more complex.[88] There is upregulation of key components of

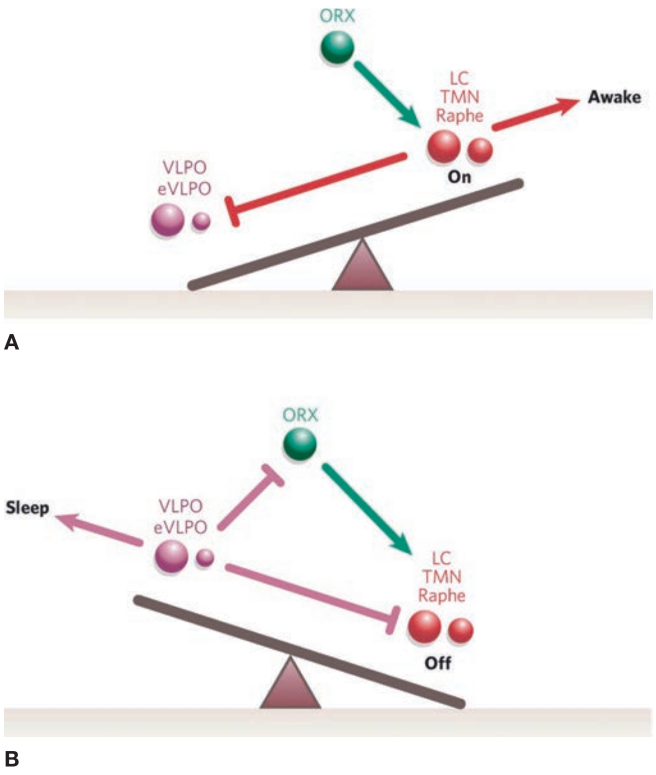

Figure 12-6 A schematic diagram of the flip-flop switch model. During wakefulness **(A)**, the monoaminergic nuclei inhibit the ventrolateral preoptic nucleus (VLPO), thereby relieving the inhibition of the monoaminergic cells, and that of the orexin (ORX) neurons, the cholinergic pedunculopontine (PPT), and the laterodorsal tegmental nuclei (LDT). Because the VLPO neurons do not have orexin receptors, the orexin neurons serve primarily to reinforce the monoaminergic tone, rather than directly inhibiting the VLPO on their own. During sleep **(B)**, the firing of the VLPO neurons inhibits the monoaminergic cell groups, thereby relieving their own inhibition. This also allows it to inhibit the orexin neurons, further preventing monoaminergic activation that might interrupt sleep. The direct mutual inhibition between the VLPO and the monoaminergic cell groups forms a classic flip-flop switch, which produces sharp transitions in state but is relatively unstable. The addition of the orexin neurons stabilizes the switch. eVLPO, extended ventrolateral preoptic nucleus.

the electron transport chain during wakefulness.[90] This is presumably to make ATP to provide increased energy resources during wakefulness with higher neuronal firing rates.

■ Synaptic Homeostasis Theory[91]

Expression of genes involved in synaptic upscaling such as BDNF and ARC are upregulated during wakefulness and downregulated during sleep.[92] This has led to the concept that there is synaptic upscaling during wakefulness and downscaling during sleep.[91] There are data to support this hypothesis. In *Drosophila* there are increased amounts of synaptic proteins detected during wakefulness and less during sleep.[93]

There is, however, contradictory evidence. In developing animals there is evidence that synaptic plasticity is enhanced during sleep (not wakefulness).[94] It is conceivable, of course, that this phenomenon is specific to the developmental period. Sleep is a critical period for brain development.[95] It is also conceivable that changes in synaptic plasticity with sleep/wake are different in different brain regions.[96] Thus, much remains to be determined and it is likely that the situation is more complex than simply strengthening of synapses during wakefulness and downscaling during sleep.

■ Macromolecular Biosynthesis[97]

Microarray studies also suggest that sleep is a stage of macromolecular biosynthesis. Among classes of genes whose expression is increased in cerebral cortex and hypothalamus during sleep compared with wakefulness are genes involved in macromolecular biosynthesis.[98] These gene classes are very overrepresented among genes whose expression is increased during sleep.[98] This involves pathways for multiple molecules, e.g., all genes in the cholesterol synthesis pathway, six of seven genes in heme synthesis pathway, and genes involved in protein synthesis. Thus, sleep and wake may be part of a metabolic cycle.[99] Energy resources during wakefulness are used for neural activity, e.g., ion pumps, but during sleep they are used for macromolecular biosynthesis. Thus, sleep is a stage where new molecules are made to restore membranes, vesicles, etc., i.e., to prepare for subsequent wakefulness.

■ Oxidative Stress and DNA Repair[100]

As described above, there is upregulation of the various components of the electron transport chain during wakefulness.[90] This will result in increased production not only of ATP but also free radicals. During sleep there is upregulation of expression of antioxidant enzymes in different brain regions.[98] Studies in *Drosophila* find a bidirectional relationship between sleep and oxidative stress.[101] Specifically, overexpression of genes for antioxidant enzymes in neurons reduces the amount of sleep.[101] There are data indicating that an oxidative byproduct regulates the electrical activity of key neurons in *Drosophila* that respond to sleep need.[102] Thus, the "flip" from wake to sleep may in part be determined by oxidative changes.

Increased free radicals also lead to DNA damage.[103] There is evidence that DNA repair mechanisms are upregulated during sleep[100,104] (Fig. 12-7). Studies in zebrafish show reduction in double-strand DNA breaks during sleep.[105] Moreover, in zebrafish administration of a molecule that leads to double-strand breaks increased sleep.[105] Thus, the need for sleep may be coupled to the amount of DNA damage that accumulates during wakefulness. Upregulation of expression of DNA repair genes during sleep is attenuated in older mice compared with young,[106] i.e., the molecular functions of sleep are attenuated with age.

■ Recovery from ER Stress[107]

Another concept that arose from microarray studies is that prolonged wakefulness leads to endoplasmic reticulum (ER) stress with protein misfolding.[107,108] This was suggested by the observation that the molecular chaperone, BiP, the master regulator of the unfolded protein response,[109,110] is upregulated in multiple brain regions in multiple species with sleep loss.[107,108] The unfolded protein response is a ubiquitous protective mechanism that is activated when stress occurs in the ER with misfolding of proteins.[109,110] The UPR results in helping misfolded proteins to fold properly, chaperoning those not folded out for degradation and inhibition of protein translation to reduce protein production.[109,110] All components of the unfolded protein response are activated in mouse cerebral cortex following 6 hours of sleep loss.[111] Inhibiting protein translation by administration of the drug salubrinal, a modulator of the ER stress response, enhances slow wave sleep and activates sleep promoting neurons in the medial pre-optic area.[112]

■ Clearance of Compounds from Brain[113]

The brain is unique among organs in that it has a limited lymphatic system. Thus the question: How are compounds cleared from the

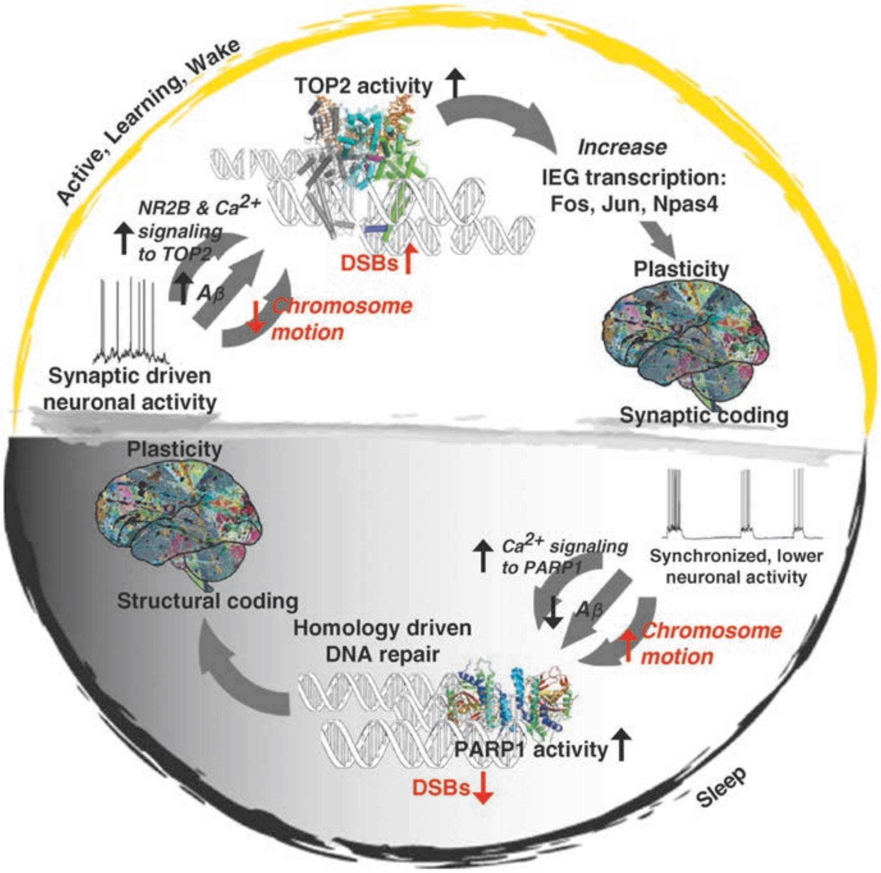

Figure 12-7 Sleep and DNA repair. There are increasing DNA double-strand breaks during wakefulness. DNA repair occurs during sleep. *(Reproduced with permission from Mourrain P, Wang GX. Sleep: DNA Repair Function for Better Neuronal Aging? Curr Biol. 2019;29(12):R585–R588.)*

brain? This has led to the intriguing concept of glia-lymph, i.e., glial cells in brain are responsible for clearance of compounds. Compounds are much more rapidly cleared during sleep than during wakefulness.[113] Studies with fluorescent-labeled compounds show that there is substantially more convective flux across the brain in sleeping compared with waking animals.[113] The precise mechanism that allows this increased transport to occur during sleep is unknown, although it seems to be a result of lower levels of the neurotransmitter noradrenaline during sleep.[113] A compound that is cleared more rapidly during sleep is beta-amyloid, which plays a key role in the pathogenesis of Alzheimer's disease. Thus, disturbances of sleep might accelerate Alzheimer's pathology. This has been shown experimentally in mice since sleep loss over many days accelerates plaque development in a mouse model of the disease.[114] Moreover, sleep apnea is now recognized as an independent risk factor for mild cognitive impairment and dementia.[115]

■ Memory Consolidation[116,117]

All the above indicates that at a molecular level sleep is an active state with several specific functions. It is not only an active state at a molecular level but also with respect to cognition and memory consolidation. Performance or tasks that require identification of a "hidden rule" are enhanced following sleep, i.e., sleep allows the brain to continue to process information and enhances insight.[118] Memory tasks are enhanced after sleep. This is not simply a matter of time since repeating the task several hours later during wakefulness does not result in this enhancement. Enhancement of performance in some tasks is correlated with the amount of slow-wave sleep while for other tasks the correlation is with the amount of REM sleep.[116,117] It has been proposed that REM sleep enhances procedural and emotional memories, while slow wave sleep enhances declarative memories.[117] Sleep enhancement of memory is reduced with aging.[119]

Thus, sleep seems to have many functions for brain rather than simply one. This is not surprising since it seems logical to ensure maximal benefit from "downtime." The discussion of functions of sleep largely treats sleep as a single entity. We know, however, as described above, that there are specific stages of sleep. Thus, it is conceivable that slow-wave sleep and REM sleep have different functions (see discussion above about memory consolidation). One of the challenges to elucidating function of different stages of sleep is that in mouse models REM sleep episodes are extremely short—on the order of minutes. They are so short that if REM sleep has particular functions, they cannot be at the transcriptional level but are likely to be related to post-translational modifications. It is of interest to consider what the impact of fragmented sleep, such as occurs in obstructive sleep apnea (see Chapter 99), will have on the functions described. This has not, however, been studied and is an area of research need and opportunity.

DOES THE LUNG SLEEP?

One of the fundamental tenants of sleep biology is that sleep is by the brain and for the brain—a title of a provocative article in *Nature*.[120]

Again, data from studies of gene expression challenge this tenet. Comparing gene expression between sleeping and awake animals sacrificed at the same time of day shows that there are common pathways downregulated in both lung and heart during sleep. As in brain, these pathways are those involved in ER stress, molecular chaperones, and heat shock molecules.[121] There is remarkable similarity in the changes in gene expression in both organs with sleep and sleep deprivation in key genes in these pathways (Fig. 12-8). This suggests that there must be a common signaling mechanism that leads to these dynamic changes in expression of these genes in different tissues in a coordinated way. The nature of this mechanism is unknown. While there

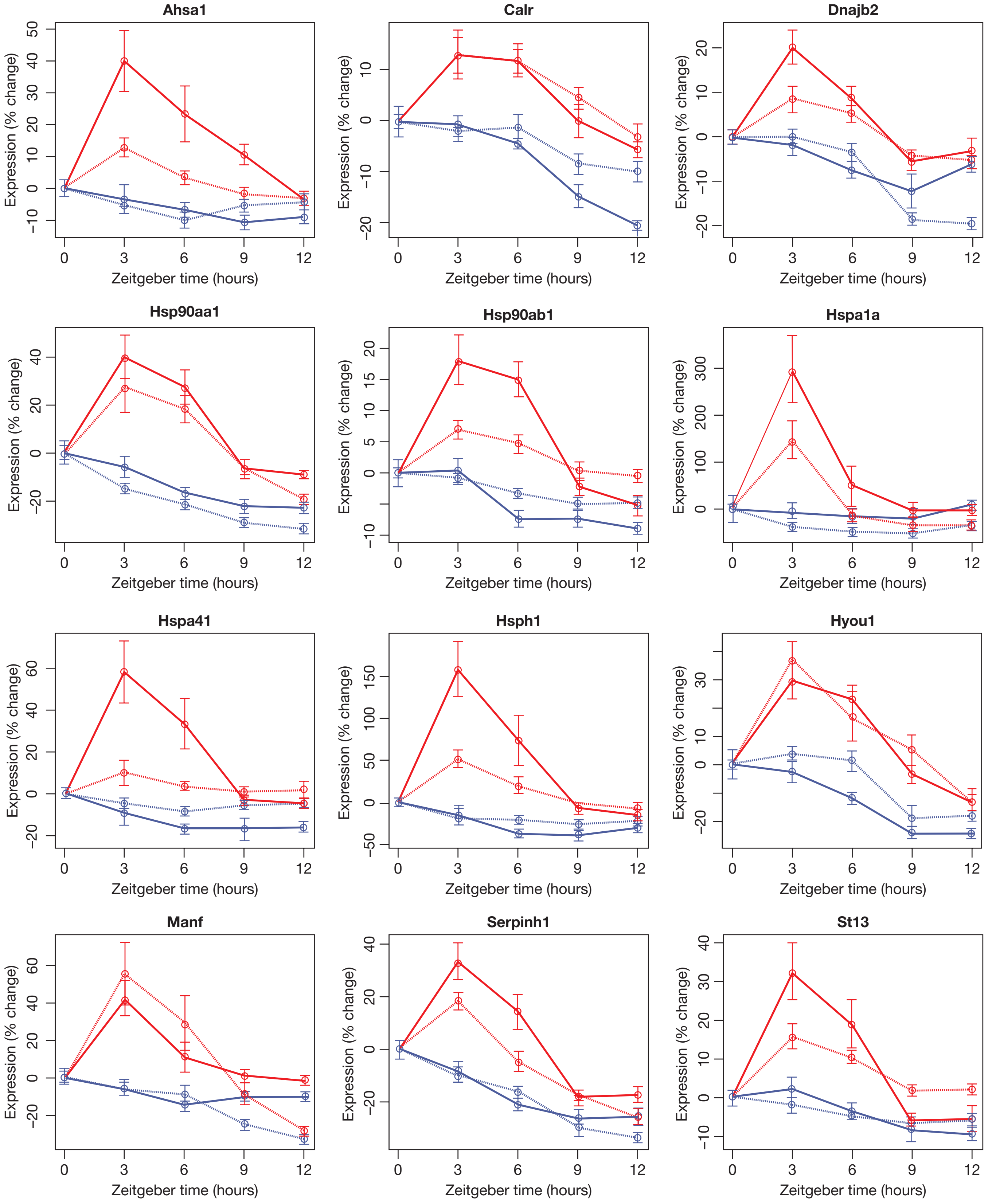

Figure 12-8 Transcript profiles of sleep-repressed genes involved in the unfolded protein response. Temporal profiles of expression for select sleep-responsive genes with annotations relating to protein processing and endoplasmic reticulum (ER) stress. Changes in gene expression from the baseline condition (lights on) are plotted as a percent of baseline expression levels. Maroon curves show data from experimentally sleep-deprived animals, and blue curves show data from spontaneously sleeping animals. Data from heart tissue are connected with dashed lines. Data from lung tissue are connected by uninterrupted lines. All genes shown here met statistical criteria for sleep specific repression in both tissues. Data shown represent mean ± standard error for 8 or 9 biological replicates. *(Reproduced with permission from Anafi RC, Pellegrino R, Shockley KR, et al. Sleep is not just for the brain: transcriptional responses to sleep in peripheral tissues. BMC Genomics. 2013;362.)*

AL GRAWANY

are common gene pathways downregulated in sleep in lung and heart, upregulated pathways with sleep are different between organs. In the lung there is upregulation of certain genes for antioxidant enzymes. Thus, is sleep a time for clearing the free radicals produced in the lung during the day? This is similar to the concept described above for brain. There is a need for more in-depth exploration of the changes in the lung during sleep. These recent data would lead to the conclusion, however, that the lung does indeed sleep.

CONCLUSION

Sleep and circadian biology are dynamic areas of research. New concepts are emerging, and some of the fundamental mechanisms are being elucidated. From the point of view of the pulmonologist, there are two major issues. First, both circadian rhythm and sleep have direct effects on molecular mechanisms in the lung. Second, disturbances of sleep like those produced by sleep-disordered breathing or jet lag will have adverse consequences at a molecular level on the functions of sleep, including in the lung itself.

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CHAPTER 13

The Pulmonary Circulation

Robert Naeije

INTRODUCTION

The discovery of the pulmonary circulation was reported in the 13th century by Ibn al-Nafis (1213–1288) in the "Commentary on Anatomy in Avicenna's Canon" and, probably independently, in the 16th century by Michael Servetus (1511–1553) in the "The Restoration of Christianity."[1] The pulmonary circulation as a separate high-flow low-pressure system is the end result of an evolutionary process aimed at the optimization of gas exchange of endothermic birds and mammals.[2] Evolution from ancestors of fishes to amphibians, reptiles, and finally birds and mammals has led to progressively greater oxygen consumption requiring thinner pulmonary blood gas barrier. The alveolo-capillary membrane in mammals is a vulnerable structure only 0.3 μm thick. Preservation of the integrity of this barrier requires complete separation of the pulmonary circulation from the systemic circulatory systems, which is accompanied by a progressive unloading and reshaping of the right ventricle as a thin-walled flow generator.

The extreme possible physiologic stresses on the pulmonary circulation are exercise and hypoxia. Exercise increases oxygen uptake and carbon dioxide output up to some 20-fold above resting values and increases cardiac output up to some 6-fold. Strenuous exercise may eventually alter gas exchange because of excessive capillary filtration and stress failure, or expose the right ventricle to excessive loading resulting in a limitation of maximum cardiac output. Hypoxia adds the burden of further increase in pulmonary vascular pressures due to hypoxic pulmonary vasoconstriction.

PULMONARY VASCULAR PRESSURES AND RESISTANCE

Pulmonary blood flow is determined by the driving pressure in the pulmonary circulation and resistance to flow, as discussed below.

■ Normal Relationships

Pulmonary blood flow (CO) is driven by a pressure difference between an inflow pressure, or mean pulmonary artery pressure (mPAP), and an outflow pressure, or mean left atrial pressure (LAP). From these measurements, resistance to flow in the pulmonary circulation can be approximated by a single number, pulmonary vascular resistance (PVR), which depends on the ratio between (mPAP − LAP) and CO:

$$\text{PVR} = (\text{mPAP} - \text{LAP})/\text{CO}$$

In clinical practice, measurements of pulmonary vascular pressures and pulmonary blood flow are performed during a catheterization of the right heart with triple-lumen, fluid-filled balloon- and thermistor-tipped catheter technology introduced by Swan, Ganz, and Forrester in the 1970s.[3,4]

As illustrated in Fig. 13-1, the procedure allows for the estimation of LAP from a balloon-occluded or wedged PAP (PAOP or PAWP). Wedged or occluded PAP are usually grouped under the term PAWP, as a discrepancy may occur only in case of an increase in large pulmonary vein resistance, which is very rare. The fractal structure of the pulmonary arterial and venous trees allows for a stop-flow phenomenon downstream of occlusion and de facto extension of the fluid-filled lumen of the catheter to same diameter pulmonary veins. A left heart catheterization allows for the measurement of left ventricular (LV) end-diastolic pressure (EDP) to estimate LAP in the absence of mitral stenosis. With injection of 5 to 10 mL cooled saline into a lumen opening into the right atrium, a temperature change over time in the pulmonary artery is registered and CO is calculated from the thermal dilution curve. Cardiac output can also be calculated by the so-called "direct Fick method" or ratio between oxygen uptake ($\dot{V}O_2$) and the arterio-mixed venous oxygen content difference ($CaO_2 - C\dot{v}O_2$).

$$\text{CO} = \dot{V}O_2/(CaO_2 - C\dot{v}O_2)$$

But this also requires systemic arterial blood sampling, measurements of inspired and expired oxygen concentrations, and a steady state, which is sometimes difficult to attain.[5]

■ Methodologic Aspects

Fluid-filled thermodilution catheter measurements of pulmonary vascular pressures and CO are accurate (i.e., no bias by Bland and Altman analysis), but may suffer from an inherent lack of precision (i.e., large limits of agreement by Bland and Altman analysis).[6] Errors in the measurements of PAP with fluid-filled catheters compared with gold standard, high-fidelity micromanometer-tipped catheters range from −8 to +8 mm Hg.[7] Errors in the measurement of thermodilution CO when compared with the gold standard direct Fick method range from −1 to +1 L/min.[8] Reported errors in the estimation of LVEDP from PAWP in large series of patients range from −15 to +12 mm Hg.[9,10] Accurate but imprecise measurements are suitable for population studies, but they are to be used cautiously for individual decision-making.[6]

Fluid-filled catheters measure vascular pressures with an external manometer, which requires zero levelling. For this purpose, the best reference is at the cross-section of three trans-thoracic planes: mid-chest frontal, transverse through the fourth intercostal space, and sagittal.[11] This is close to the hydrostatic indifference point, located at the tricuspid valve, where pressure is independent of body position.[12]

Pulmonary vascular function is affected by changes in lung volumes and in intrathoracic pressures. PVR is minimal at functional residual capacity (FRC). Lung volumes below or above FRC are associated with increased PVR, because of predominant increased in alveolar vessel resistance at high lung volumes and increased extra-alveolar vessel resistance at lower lung volumes.[13] Pleural pressure is slightly subatmospheric, on average, at −3 mm Hg at FRC. Pleural pressure decreases at inspiration and increases at expiration. Pulmonary vascular pressures, systolic and diastolic right heart pressures, and diastolic, but not systolic, left heart pressures follow the changes in pleural pressure.[14] Expiration may be associated with dynamic hyperinflation, increased FRC, and positive alveolar pressures, which are transmitted to pleural pressure. Respiratory swings of pulmonary vascular pressures are illustrated in Fig. 13-2. During normal breathing, pulmonary vascular pressures are, therefore, best averaged over several respiratory cycles.[15]

Adequate measurement of a PAWP requires attention to wave morphology. For the estimation of LAP or LVEDP, which are identical in diastole, reading the tracing at the nadir preceding the c wave, or using a QRS-gated approach (130–160 ms after the Q) and omitting of course the V wave, which is systolic, is recommended.[15] However, for the estimation of the outflow pressure of the pulmonary circulation and calculation of PVR, it is preferable to average the reading

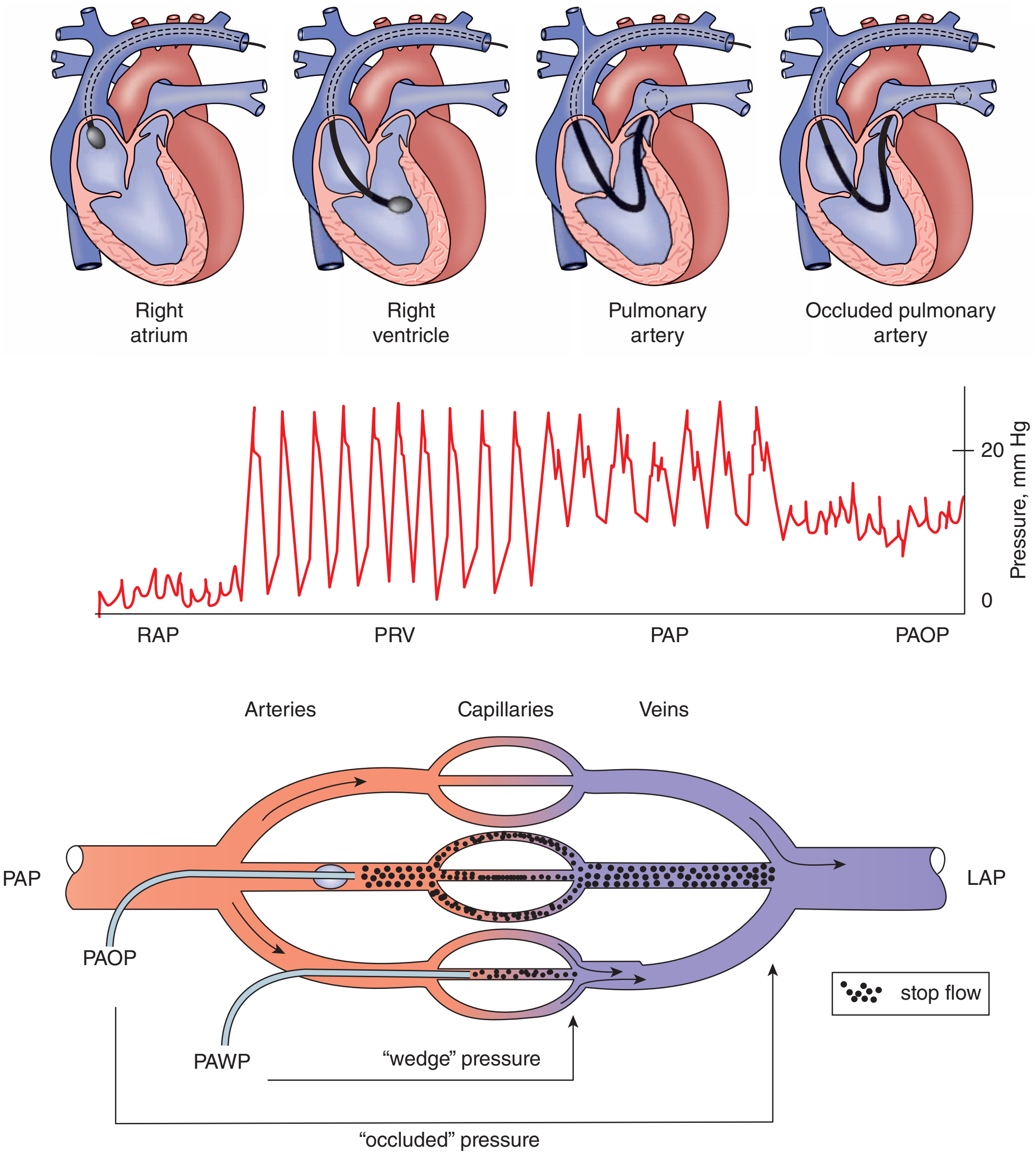

Figure 13-1 Right heart catherization with flow-directed balloon-tipped catheter with successive measurements of right atrial pressure (RAP), right ventricular pressure (PRV), pulmonary artery pressure (PAP), and occluded PAP (PAOP). Because of the fractal structure of the arterial and venous branching of the pulmonary vascular tree, occluded or wedged PAP (PAWP) prolongs the fluid column of the catheter until same diameter pulmonary vein, which is a satisfactory estimate of left atrial pressure (LAP) or left ventricular end-diastolic pressure.

of a PAWP tracing over the cardiac cycle, as the V wave pressure is transmitted upstream to PAP. Omission of the V wave could markedly overestimate PVR. Reading a PAWP, while taking into account cardiac cycle and respiratory cycle variability, is illustrated in Fig. 13-2.

Sometimes a measurement of LVEDP or PAWP cannot be obtained, and a *total* PVR (TPVR) is calculated as:

$$\text{TPVR} = \text{mPAP/CO}$$

Since LAP is not negligible with respect to mPAP, TPVR is larger than PVR, and this difference may be flow-dependent. Thus, TPVR is not a correct characterization of the flow-resistive properties of the pulmonary circulation when LAP is increased. On the other hand, TPVR may be a more realistic estimate of right ventricular (RV) afterload. The RV is exposed to PAP, and not to the difference between PAP and LAP.

■ Pulmonary Capillary Pressure

While wedged or occluded PAP measurements are acceptable estimates of LAP, micropuncture studies have shown that pulmonary capillary pressure (PCP) is higher than PAWP, lying about halfway between arterial and venous pressures.[16] Thus, wedged or occluded PAP should not be called "capillary" or "capillary-wedge" pressure. Estimates of PCP can be obtained from the analysis of PAP decay curves after arterial occlusion (Fig. 13-3).[17]

Pulmonary artery pressure decay curves present with a first rapid portion, corresponding to the interruption of flow through arterial resistance, and then a slow capillary-venous portion corresponding to the emptying of pulmonary capillary compliance through venous resistance. The inflection point of the pressure decay curve defines PCP.[17]

Based on measured distribution of resistances in perfused normal lungs, assuming 60% arterial resistance and 40% capillary plus

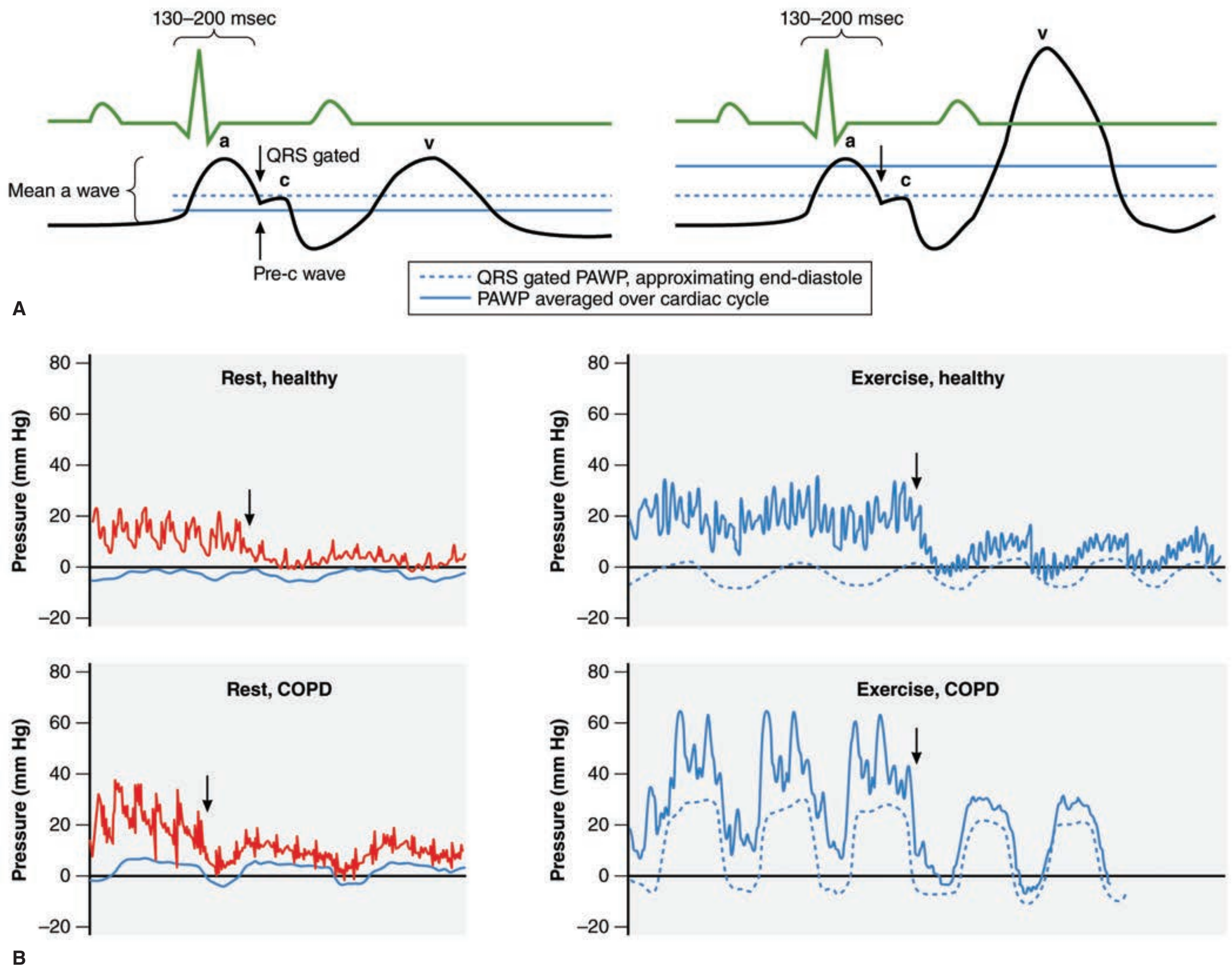

Figure 13-2 Impact on respiratory and cardiac cycle timing on pulmonary artery wedge pressure (PAWP). **A.** Pulmonary arterial wedge pressure tracing. Measurements that approximate end-diastole (mean a wave, pre-c wave, and QRS gated assessment at 130–160 ms from the onset of QRS to allow time delay between PAWP and left atrial pressure, shown in gray) should provide the closest approximation of left ventricular end-diastolic pressure (LVEDP). This value is usually slightly higher than the PAWP averaged over the cardiac cycle (solid line). However, the reverse occurs in the setting of a large V wave (right panel). **B.** Pulmonary arterial pressure and wedge pressure tracing at rest (red) and with exercise (blue), with pleural pressures shown below (dashed lines). Pulmonary vascular pressure changes follow pleural pressure changes, which are more pronounced in chronic obstructive pulmonary disease (COPD). *(Reproduced with permission from Naeije R, Chin K. Differentiating Precapillary From Postcapillary Pulmonary Hypertension. Circulation. 2019;140(9):712–714.)*

venous resistance, PCP can be estimated from a simple equation proposed by Gaar et al.:[19]

$$\text{PCP} = \text{PAWP} + 0.4 \times (\text{mPAP} - \text{PAWP})$$

Measurements of PCP by single PA occlusion in healthy volunteers show an average PCP of 10, ranging from 8 to 12 mm Hg.[18]

■ Limits of Normal

The limits of normal of the human pulmonary circulation derived from invasive measurements reported in 47 studies on a total of 1187 individuals, of whom 225 were identified as women and 717 as men,[20] are shown in Table 13-1.

■ Calculation of PVR

A vascular resistance calculation derives from the physical law that governs laminar flows of Newtonian fluids through nondistensible, straight cylindric tubes, originally proposed by the French physician Poiseuille and later put in mathematical equation by the German physicist Hagen. Poiseuille showed experimentally that flow was inversely related to the fourth power of the internal radius, and he confirmed previous demonstrations that arterial pressure remains high in arteries down to 2 mm in diameter, while venous pressure is low in animals. The Hagen-Poiseuille law states that resistance, R, to flow of a single tube is equal to the product of the length, l, of the tube and viscosity, η, and a constant, 8, divided by the product of π and the fourth power of the internal radius, r. More generally, R can be calculated as the ratio of pressure drop, ΔP, to flow, Q:

$$R = l \bullet \eta 8/\pi \bullet r^4 = \Delta P/Q$$

The ratio of pressure drops to flow through an entire vascular bed accounts for the resistances in series and in parallel of the individual vessels. The fact that r in the equation is to the fourth power explains why R is exquisitely sensitive to small changes in caliber of these small vessels (e.g., a 10% change in radius results in an almost

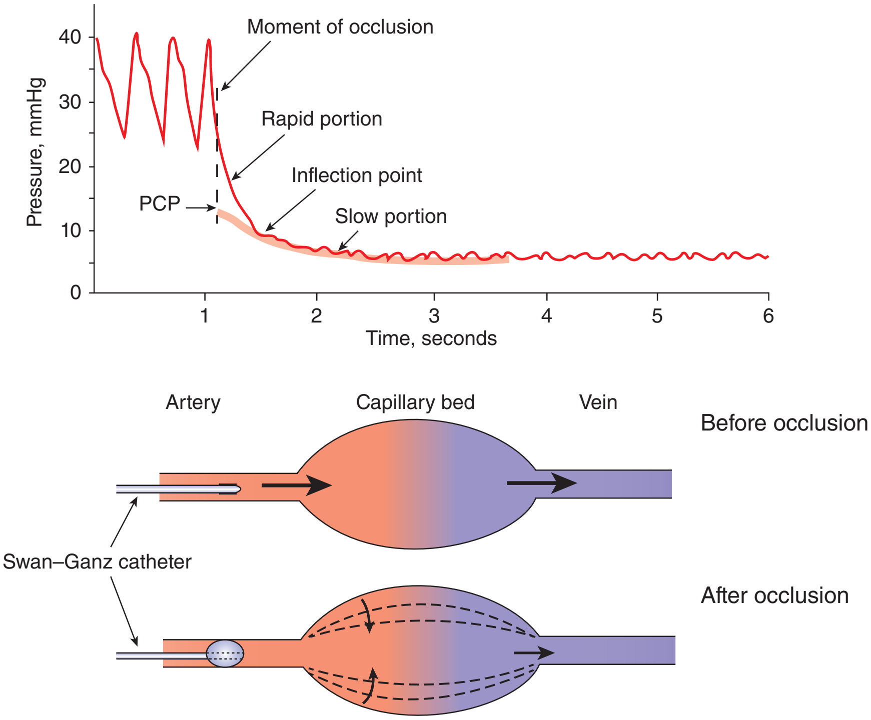

Figure 13-3 Analysis of the pressure transient after pulmonary arterial occlusion for the estimation of pulmonary capillary pressure (PCP) either by the intersection of the fast and the slow components of the pressure decay curve, or by the extrapolation of the exponential fitting of the slow component of the pressure decay curve to the moment of occlusion.

50% change in resistance). Accordingly, PVR is a good indicator of the state of constriction or dilatation of pulmonary resistive vessels and is useful for detecting changes in arteriolar vessel caliber due to changes in tone or structure.

■ Effects of Age, Sex, and Body Position

Generally, women are of smaller body size than men. Accordingly, cardiac output is lower and PVR higher in women.[20] However, there are no sex differences in pulmonary hemodynamics after correction for body dimensions. Aging is associated with an increase in PVR. This is due to a slight increase in mPAP and a more important decrease in cardiac output, leading to a doubling of PVR over five decades of life.[21,22] However, measurements in healthy old individuals are few; hence, the exact limits of normal of the pulmonary circulation as a function of age are not exactly known.

Body position affects PVR through associated changes in systemic venous return. In the upright position, LAP, right atrial pressure (RAP), and CO are lower than in the supine position. This results in a de-recruitment of pulmonary vessels, and mPAP remains essentially the same. Accordingly, PVR is increased at rest in the upright position.[23,24] When cardiac output is increased during an incremental exercise test, body position does not affect the slope of pulmonary vascular pressure-flow relationships.[23,24] The effects of body position on PVR at rest and during exercise, as in reported data from 96 healthy subjects,[25] is illustrated in Fig. 13-4.

TABLE 13-1 Limits of Normal of Pulmonary Vascular Pressures and Pulmonary Blood Flow at Rest

Variables	Mean	Limits of Normal
CO, L/min	7.3	5.0–9.5
HR, bpm	76	50–100
PAP systolic, mm Hg	21	13–29
PAP diastolic, mm Hg	9	3–15
PAP, mean, mm Hg	14	8–20
PAWP, mm Hg	8	2–14
PCP, mm Hg	10	8–12
RAP, mm Hg	5	1–8
PVR, Wood units	0.9	0.2–1.8

■ Limits of Normal and Definition of Pulmonary Hypertension

Currently expert consensus defines pulmonary hypertension (PH) as a mPAP >20 mm Hg, precapillary PH as a mPAP >20 mm Hg with PAWP ≤15 mm Hg and PVR ≥3 Wood units (WU), and postcapillary PH as a mPAP >20 mm Hg with PAWP >15 mm Hg and PVR <3 WU.[26] Data from large population registries show that a mPAP >20 mm Hg and a PVR >2 WU are independently associated with a decreased life expectancy.[27,28] A PVR at the upper limit of normal of 2 WU can be modeled to correspond to 20%–25% obstruction of the pulmonary circulation at a normal cardiac output.[29]

■ Effects of Pulmonary Blood Flow

The inherent assumption in a PVR calculation is that the mPAP-flow relationship is constant and crosses the pressure axis at a value equal to LAP (such that when flow is zero, theoretically, mPAP =

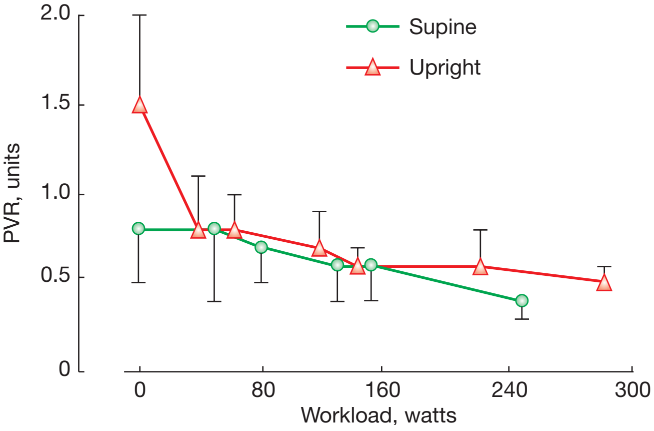

Figure 13-4 Pulmonary vascular resistance (PVR) at rest and during progressively increased workload in healthy volunteers in the upright (triangles) vs. the supine position (circles). Resting PVR was higher in the upright position. As soon as at moderate workload, upright and supine PVR converge, with mild further decline with increasing levels of exercise. Vertical bars indicate SDs. *(Data from Weir EK, Reeves JT: Pulmonary Vascular Physiology and Physiopathology. New York, NY: Marcel Dekker; 1989.)*

LAP). Then, PVR is constant, independent of the absolute pressure or flow.

The relationship between (mPAP − LAP) and CO has been shown to be reasonably well described by a linear approximation over a limited "physiologic" range of flows, with a zero extrapolated pressure intercept in well-oxygenated lungs in supine resting intact animals, including humans, suggesting complete recruitment and minimal distension of the normal well-oxygenated pulmonary circulation. However, hypoxia and a number of cardiac and respiratory diseases increase both the slope and the extrapolated intercepts of multipoint mPAP-CO.[30]

While an increase in the slope of mPAP-Q is easily understood as being caused by a decreased cross-sectional area of pulmonary resistive vessels, the non-zero and, typically, positive extrapolated pressure intercept has inspired various explanatory models.

■ The Starling Resistor Model of the Pulmonary Circulation

To explain the non-zero and positive pressure intercept, Permutt et al. conceived a vascular "waterfall" or "Starling resistor" model made of parallel collapsible vessels with a distribution of non-zero and positive closing pressures.[31] The waterfall analogy refers to the fact that the flow rate (CO) over a waterfall is independent of its height (the pressure difference between upstream and downstream). Instead, an "external" factor (in the case of a waterfall, fluid momentum) controls the flow rate. The Starling resistor itself was actually a device: a collapsible tube inside of a closed chamber that could be pressurized, thus providing an "external" control over the flow rate through the collapsible tube. Starling used this device in the circuit of his heart-lung preparation to control blood pressure.

Permutt et al. postulated that in the pulmonary circulation, as flow decreased, arteries would be progressively de-recruited, accounting for a low-flow mPAP-CO curve that is concave to the flow axis and intercepts the pressure axis at the lowest closing pressure needed to be overcome to generate a flow. At higher flows, complete vessel recruitment and negligible distension account for a linear mPAP-CO curve, with an extrapolated pressure intercept representing a weighted mean of closing pressures. In this model, the mean closing pressure is the effective outflow pressure of the pulmonary circulation. At higher flows, LAP is equal to the mean closing pressure. However, at lower flows, LAP is less than the mean closing pressure and becomes irrelevant to flow, analogous to the height of water below a waterfall (Fig. 13-5).

A characteristic typical of a vascular system made up of collapsible vessels is the functional dissociation between inflow, outflow pressures, and flow rate when the closing pressure is higher than the (apparent) outflow pressure (Fig. 13-6).

The functional dissociation of inflow and outflow outflow pressures is a feature of de-recruited upright upper lung zone I described by West.[32] It has been reported in pulmonary hypertension on acute lung injury[33,34] and in occasional cases of pulmonary hypertension on terminal heart failure, after cardiac transplantation.[35] An increased closing pressure possibly explains positive extrapolated pressure intercepts on mPAP-CO plots in idiopathic pulmonary arterial hypertension (PAH).[36,37] However, experimental data have been accumulated that cannot be explained by the Starling resistor model of the pulmonary circulation in embolic pulmonary hypertension[29,38,39] or increased hematocrit,[40] and the assumption that recruited vessels are not distensible is not correct.[41] Therefore, distensibility models at variable hematocrit have been developed.

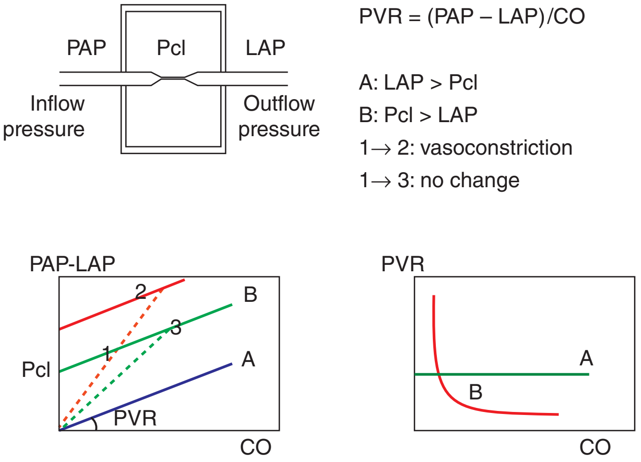

Figure 13-5 Starling resistor model of the pulmonary circulation as a collapsible tube within a pressure chamber. Pulmonary artery pressure (PAP) is the inflow pressure, left atrial pressure (LAP) is the apparent outflow pressure, and the pressure in the chamber Pcl is a closing pressure. Pulmonary vascular resistance (PVR) is a pressure difference vs. flow (CO) relationship, with either PAP – Pcl or PAP – LAP as a driving pressure depending on whether Pcl is greater than LAP. The pressure difference vs. flow relationship is linear. Low-flow convexity to the pressure axis is explained by vascular recruitment. When Pcl > LAP, PVR decreases when flow increases. *(Reproduced with permission from Naeije R. Pulmonary vascular resistance. A meaningless variable? Intensive Care Med. 2003;29(4):526–529.)*

■ Distensible Models of the Pulmonary Circulation

Zhuang modeled the feline pulmonary circulation, taking into account not only morphometry but also mechanics (i.e., distensibility) of the pulmonary vascular tree and rheologic properties of each of its branched segments.[42] The authors predicted mPAP-CO curves with a slight curvilinearity concave to the flow axis over physiologic ranges

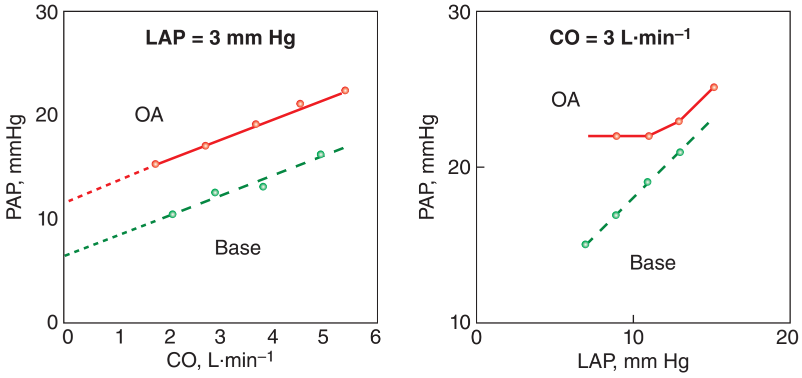

Figure 13-6 Mean pulmonary artery pressure (mPAP) vs. cardiac output (CO) at constant left atrial pressure (LAP) (left panel), and mPAP vs. LAP at constant CO (right panel) before and after induction of oleic acid (OA) lung injury in an anesthetized dog. Oleic lung shifts the linear mPAP-CO relationship in parallel to higher pressure, with an extrapolated pressure intercept higher than LAP, suggesting an increased closing pressure, which is confirmed by a functional dissociation between mPAP and LAP at low LAP on mPAP-LAP relationship. The inflection point of the mPAP-LAP relationship after OA lung injury is equal to the extrapolated pressure intercept on mPAP-CP plots. *(Reproduced with permission from Leeman M, Lejeune P, Closset J, et al. Nature of pulmonary hypertension in canine oleic acid pulmonary edema. J Appl Physiol (1985). 1990;69(1):293–298.)*

of flow that was progressively enhanced at decreasing flow. This curvilinearity was generated via arterial, capillary, and venous distensibility based on experimental data with no need to invoke a closing pressure.

The distensible or compliant model of Zhuang has been shown to predict parallel shifts of mPAP-CO plots to higher pressures, induced by various interventions such as embolism, changes in lung volume, and hypoxia, and even a functional dissociation between PAP and LAP at constant CO.[29,43,44]

Linehan et al. reasoned that previously reported compliant models were too complex, requiring a large number of parameters not identifiable from pressure and flow measurements alone, so that many investigators persisted in using the simpler Starling resistor model of the pulmonary circulation, with its dependence on only two parameters, despite mounting evidence of its inability to model key features of pulmonary pressure-flow relationships.[45] Accordingly, he developed a simpler distensibility model based on only two parameters as well, and showed its adequacy to describe mPAP vs. CO relationships at variable hematocrits in perfused dog lung lobes by the equation:

$$\text{mPAP} = \{[(1 + \alpha \text{PAWP})^5 + 5\alpha \cdot R_0 \cdot \text{CO}]^{1/5} - 1\}/\alpha$$

where the variable hematocrit is captured in the total pulmonary vascular resistance at rest, R_0, and the vessel distensibility α (expressed in % increase in diameter D_0 per mm Hg increase in pressure) is constant throughout the pulmonary vasculature (as has been demonstrated on in vitro mounted vessels):[41]

$$D = D_0 + \alpha \cdot P$$

Nelin et al. showed that Linehan's equation accounted perfectly for measurements of multipoint mPAP vs. CO in isolated pig lungs under normoxic and hypoxic conditions.[46]

An interesting application of this equation is that α can be calculated from the best fit of mPAP, PAWP, and CO measurements obtained during exercise.[47] Invasive and noninvasive studies have shown that a so-calculated α is normally between 1% and 2% per mm Hg higher in young healthy women, and decreases with aging or chronic hypoxic exposure.[48–51] Noninvasive studies have also shown that α is decreased in male subjects of Sub-Saharan African ascendance compared with Caucasian controls,[52] in adolescents conceived by in vitro fertilization,[53] and in healthy subjects exposed to diesel exhaust.[54]

Although α is a small number and the curvilinearity of multipoint mPAP vs. CO plots is slight, a normal value of 2% per mm Hg is associated with a marked decreased in mPAP at high cardiac outputs, such as during strenuous exercise.[50] This is illustrated in Fig. 13-7.

The improved PVR equation has been used to show decreased resistive vessel distensibility in early or latent pulmonary vascular disease.[55] In the study demonstrating these findings, α was, on average, 0.25% per mm Hg in patients with overt PH and pulmonary vascular disease, 0.45% per mm Hg in patients with abnormal lung scintigraphy but no PH, and 1.40% per mm Hg in no-PH controls. Interestingly, α discriminated pulmonary vascular disease with no PH from normal hemodynamics with a sensitivity of 88% and a specificity of 100%. In another study, α was shown to be decreased to an average of 0.4% per mm Hg in PAH and 0.8%–0.9% per mm Hg in heart failure compared with 1.4% per mm Hg in age-matched controls.[56] These results have been independently confirmed.[57] A low α has been shown to be independently associated with a decreased exercise capacity, an altered coupling of right ventricular function to the pulmonary circulation, and a shorter survival.[56,57]

■ Prediction of Vascular Obstruction from Hemodynamic Measurements

The distensibility model of Linehan can be used to estimate the effects of pulmonary vascular obstruction on mPAP over a wide range of cardiac outputs, as shown in Fig. 13-8. At a cardiac output of 5 L/min, mPAP reaches 20 mm Hg at 20%–25% of obstruction and 25 mm Hg at 50% obstruction of the pulmonary circulation.

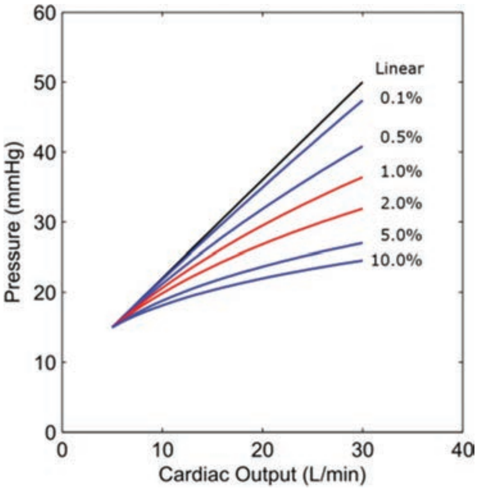

Figure 13-7 Modeled mean pulmonary artery pressure vs. cardiac output relationships at progressively increased distensibility factor α from 0 to 10% per mm Hg. At high flows, slight increases α to 1%–2% (red curves) decreases considerably pulmonary artery pressure, thereby unloading the right heart. *(Reproduced with permission from Naeije R, Vanderpool R, Dhakal BP, et al. Exercise-induced pulmonary hypertension: physiological basis and methodological concerns, Am J Respir Crit Care Med. 2013;187(6):576–583.)*

■ Viscosity

Several equations have been reported to define the relationship between resistance to blood flow, hematocrit, and blood viscosity. The first was reported by Whittaker and Winton in 1933 and was

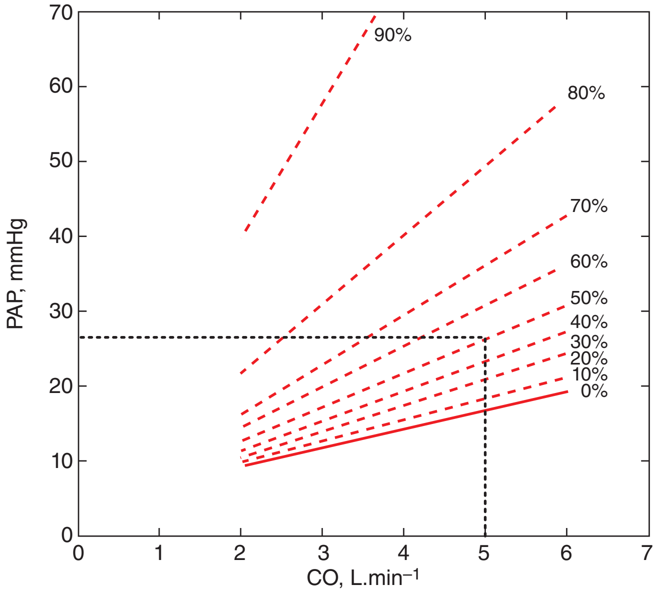

Figure 13-8 Mean pulmonary artery pressure (mPAP)–cardiac output (CO) relationships predicted by the viscoelastic model of Linehan at increasing levels of angiographically determined embolic obstruction. An increase in mPAP above 25 mm Hg corresponding to the definition of pulmonary hypertension occurs after approximately 50% obstruction of the pulmonary vascular bed (see stippled lines). A mPAP of 50 mm Hg as seen in severe pulmonary hypertension corresponds to 80% obstruction. These estimates are for a CO of 5 L/min as the mPAP-obstruction relationship is flow-dependent.

based on measurements on perfused canine hindlimbs at various hematocrits.[58] In these experiments, total resistance (i.e., inflow pressure/flow) at a given hematocrit (R_{HCT}) increased exponentially from plasma perfusate resistance (R_{plasma}) as a function of hematocrit (ϕ):

$$R_{HCT}/R_{plasma} = 0.24/(1 - \phi^{1/3})$$

Linehan et al. repeated the experiments on isolated-perfused lungs of dogs and derived a more pulmonary specific different but still exponential relationship:[45]

$$R_{HCT}/R_{plasma} = \exp(a_1 \cdot \phi)$$

The equations of Whittaker and Winton or Linehan et al. have been shown to yield essentially the same resistance vs. hematocrit relationships. In addition, PVR at a normal hematocrit can be predicted in patients with variable degrees of anemia or polycythemia in a PAWP-dependent manner.[59] A diagram allowing for the prediction of PVR at the normal hematocrit of 45% in anemic or polycythemic patients at PAWP equal either to 5 or 15 mm Hg (taken as extremes of lower and upper limits of normal) is presented in Fig. 13-9.

Because of the exponential relationship between PVR and hematocrit, the impact of hematocrit on PVR increases at high hematocrits or PVR. Furthermore, the increased PAWP makes the PVR vs. hematocrit relationship steeper. For example, a PVR at 1.5 WU at a hematocrit of 20% becomes 3.0 or 4.1 WU at PAWP values of 5 and 15 mm Hg, respectively, at a hematocrit of 45%. At a hematocrit of 70%, PVR becomes approximately 5.5 or 8.4 WU at PAWP values of 5 and 15 mm Hg, respectively.

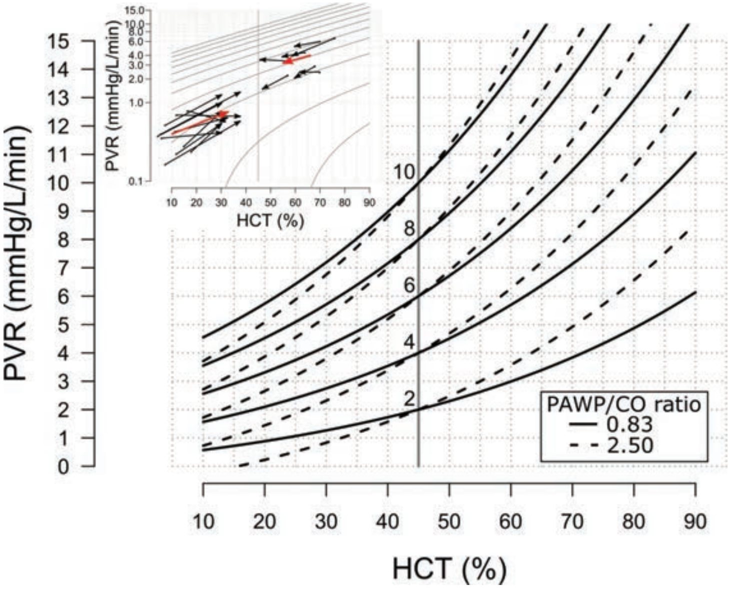

Figure 13-9 Pulmonary vascular resistance (PVR) as a function of hematocrit (HCT). The graphical representation is derived from an exponential relationship previously determined from isolated perfused lung experiments.[52] Iso-PVR lines allow for a prediction of PVR "normalized" for a hematocrit at 45% in anemic or polycythemic patients, at pulmonary artery wedge pressures (PAWP) of 5 mm Hg (full lines) and 15 mm Hg (stippled lines). The window shows log changes in PVR (black arrows, with mean responses as red arrows) previously reported in polycythemic patients after isovolemic hemodilution and in anemic patients after blood cell transfusion. The impact of hematocrit on PVR increases with PVR, PAWP, or hematocrit. Changes in PVR after correction of excessively low or high hematocrit agree on average with the model predictions. *(Reproduced with permission from Vanderpool RR, Naeije R. Hematocrit-corrected Pulmonary Vascular Resistance. Am J Respir Crit Care Med. 2018;198(3):305–309.)*

■ Pulmonary Arterial Compliance

While the distensibility coefficient, α, defines the steady-flow distensibility of small pulmonary resistive vessels, pulmonary arterial compliance (PAC) provides an estimation of pulsatile-flow distensibility of the entire pulmonary vascular bed. Pulmonary arterial compliance (PAC) is usually calculated as a ratio between stroke volume (SV) and pulse pressure (PP), or the difference between systolic and diastolic PAP.

$$PAC = SV/PP$$

This simple equation assumes that the SV is buffered in the large elastic arteries in systole, without any peripheral outflow. However, there is a continuous flow toward the periphery, and the volume increase during ejection is only a fraction of SV. Therefore, SV/PP is a theoretical maximum for pulmonary vascular compliance and overestimates true PAC.

The best method to calculate PAC is based on a two-element Windkessel model: flow waveform and resistance are used as inputs to estimate the compliance value that optimally predicts systolic and diastolic pressures.[60] It has been shown in intact experimental animals at various severities of induced PH that SV/PP overestimates PAC by 60% to 80%.[61]

The afterload of the right ventricle is determined by a dynamic interplay between PVR, PAC, and wave reflections.[62] PAC decreases as a function of increased pulmonary vascular pressures.[63,64] Magnetic resonance imaging–determined proximal arterial compliance amounts to approximately 20% of PAC.[65]

■ The Time Constant of the Pulmonary Circulation

The PAP decay curve in diastole is determined by the product of PVR by PAC. The unit of this product is time and, therefore, is called the arterial time-constant (RC-time).

The inverse hyperbolic relationship between PVR and PAC was first reported in 1971.[66] It is illustrated in Fig. 13-10 and derives from measurements in an anesthetized dog before and after an increase in PVR induced by either embolization with micro-beads or proximal PA ensnarement.[7]

A series of studies have shown that the RC-time is constant over a wide range of severities, etiologies, and treatments of PH.[65–68] The constancy of RC-time implies that PAC becomes a more important

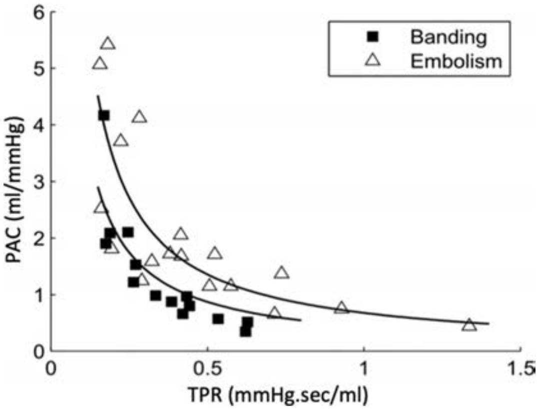

Figure 13-10 Pulmonary arterial compliance (PAC) as a function of total pulmonary vascular resistance (TPR) in dogs with pulmonary hypertension induced either by an ensnarement of the pulmonary arteries (banding, proximal obstruction) or the injection of micro-beads (embolism, (distal obstruction). The time constant PAC × TPR is shorter with proximal obstruction. *(Reproduced with permission from Pagnamenta A, Vanderpool R, Brimioulle S, et al. Proximal pulmonary arterial obstruction decreases the time constant of the pulmonary circulation and increases right ventricular afterload. J Appl Physiol (1985). 2013;114(11):1586–1592.)*

determinant of RV afterload than PVR when PAP and PVR are only modestly elevated,[69] that the pulsatile component of RV hydraulic load is relatively constant,[70] and that the impact of wave reflection on RV afterload is negligible.

The RC-time decreases with proximal PA obstruction, for example in purely proximal thromboembolism[7] or when PAWP increases in patients with HF.[64] This means that PAC decreases out of proportion with increased PVR, and that, accordingly, the oscillatory component of hydraulic load on the RV increases.

Measuring the RC-time is difficult because it is a small number exposed to amplification of errors on measurements of both PAC and PVR. As already mentioned, PAC calculated as SV/PP is almost twice the PAC calculated by the more valid pulse pressure method. On the other hand, PVR is misleading because of the unmet assumptions of linearity and proportionality of the relationships between mPAP and CO and PAWP. Not surprisingly, therefore, RC-times reported in the literature present with considerable variation, casting doubt as to the clinical interest of the measurement in the diagnostic workup of PH.[71]

It has been proposed that the stability of RC-time of the pulmonary circulation may explain the reported tight correlation between systolic, diastolic, and mean PAP (sPAP, dPAP, and mPAP) in normal subjects and in patients with PH of all possible etiologies and severities.[72] The sPAP/mPAP and mPAP/dPAP ratios are, indeed, remarkably stable[73,74] and match actually the golden ratio,[75] with PP equal to mPAP and mPAP predicted from sPAP by the formula:

$$\text{mPAP} = 0.6 \times \text{sPAP} + 2$$

Whether the constancy of RC-time is a satisfactory explanation for the pulmonary circulation's golden ratio remains debated, as the PVR × PAC product shows as much variability as mPAP.[73]

However, the constant proportionality between sPAP and mPAP is useful in clinical practice, as sPAP is easily determined noninvasively from the maximum velocity of tricuspid regurgitation measured by Doppler echocardiography.[76]

■ Pulmonary Vascular Pressure Gradients

The transpulmonary gradient (TPG) or numerator of the PVR equation has traditionally been used for the diagnostic workup of PH:[77,78]

$$\text{TPG} = \text{mPAP} - \text{PAWP}$$

The TPG elucidates the resistive properties of the pulmonary circulation, much like the PVR, when pulmonary blood flow remains within limits of normal. A high cardiac output will spuriously increase the TPG and decrease PVR, while a low cardiac output will have opposite effects.

The limits of normal TPG are not exactly known. The upper limit of normal of TPG was thought to be 10 mm Hg until the 1970s[79] but has since drifted upward to 12 mm Hg,[77] or even, most recently, to 15 mm Hg.[78]

The TPG is sensitive to SV and to PAC. This was modeled in the early 1970s[63] and more recently revisited with a focus on heart failure.[80]

The diagnosis of pulmonary vascular disease is preferably based on the gradient between dPAP and PAWP, or the diastolic pulmonary pressure gradient (DPG). A progressive increase in PAWP would be normally expected to decrease DPG (or TPG) because of vascular distensibility. However, the entire pulmonary vascular tree gets stiffer with increased PAW, thereby increasing TPG while leaving the DPG essentially unchanged or more slightly increased.[80] Thus, a progressive increase in PAWP inevitably increases sPAP, mPAP, and dPAP, with preservation of their relationships. The increase in dPAP is proportionally less than the increase in mPAP (Fig. 13-11).

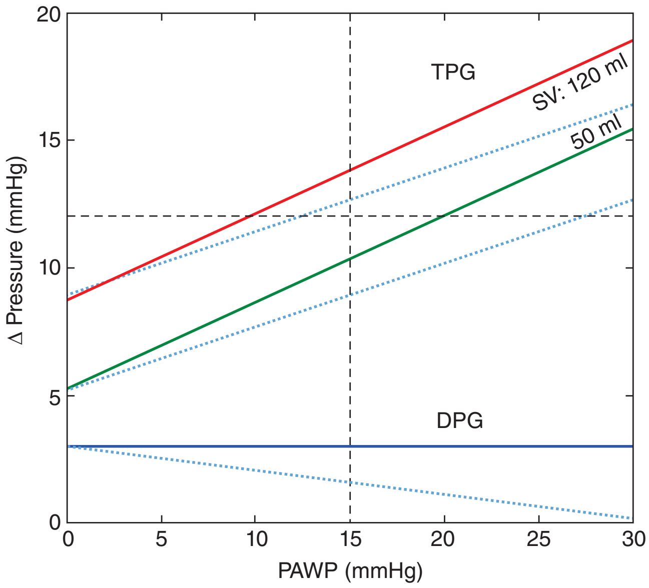

Figure 13-11 Effects of increased pulmonary artery wedge pressure (PAWP) on systolic, diastolic, and mean pulmonary artery pressures (sPAP, dPAP, mPAP) showing progressive increase of the transpulmonary pressure gradient mPAP – PAWP (TPG) with unchanged or decreased (stippled lines) diastolic pressure gradient dPAP – PAWP (DPG). *(Adapted with permission from Naeije R, Vachiery JL, Yerly P, et al. The transpulmonary pressure gradient for the diagnosis of pulmonary vascular disease. Eur Respir J. 2013;41(1):217–223.)*

The DPG was used in the 1970s in combination with PAWP, cardiac output (or arterio-venous oxygen content difference), and blood pressure measurements for the differential diagnosis of cardiac and pulmonary causes of acute respiratory failure.[81] The upper limit of normal of DPG was assumed to be 5 mm Hg,[63] derived from measurements in healthy, athletic young adults. The true upper limit of normal over the entire age range and levels of fitness and ages is probably a few mm Hg higher. A DPG >7 mm Hg has been shown to be associated with a decreased survival in patients with pulmonary hypertension due to left heart conditions.[82]

The diagnosis of pulmonary vascular disease in heart failure best relies on a combination of higher-than-normal PVR and DPG.[83] However, the DPG is difficult to measure, particularly when it is low-normal, prompting clinicians to lose confidence in its diagnostic relevance. A component or precapillary PH that develops on postcapillary PH can then be identified by a PVR calculation alone, albeit with loss of diagnostic accuracy.[84]

■ Gravity

Pulmonary blood flow increases almost linearly from nondependent to dependent lung regions. This inequality of pulmonary perfusion is best demonstrated in an upright lung.[32] The vertical height of a lung averages about 30 cm. The difference in pressure between the extremities of a vertical column of blood of the same size amounts to 23 mm Hg, which is large compared to the mean perfusion pressure of the pulmonary circulation. Accordingly, the physiologic inequality of the distribution of perfusion of a normal lung can be explained by a gravity-dependent interplay between arterial, venous, and alveolar pressures.

At the apex of the lung, alveolar pressure (P_A) is higher than mPAP and pulmonary venous pressure (PVP). In this *zone 1*, flow may be present only during systole, or not at all. Zone 1 is extended in clinical situations of low flow, such as hypovolemic shock, or increased alveolar pressure such as during ventilation with a positive end expiratory pressure. Further caudal in the lung is *zone 2* where

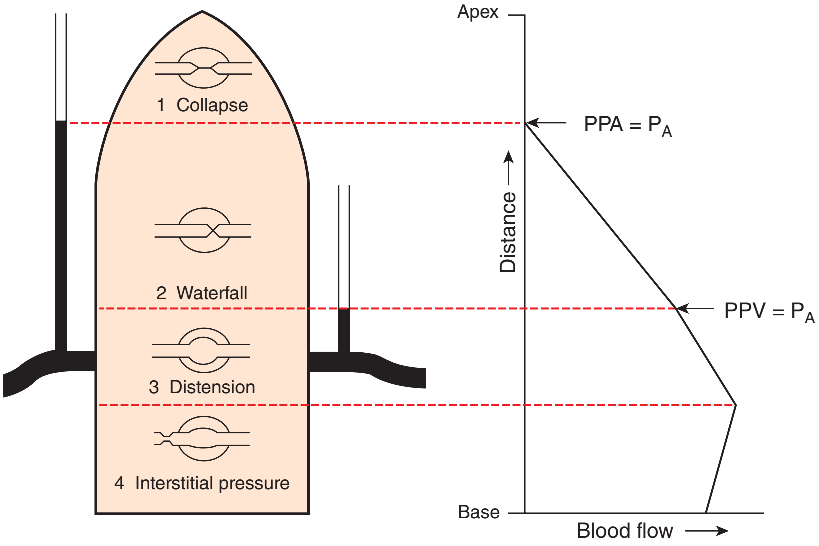

Figure 13-12 Zonal distribution of pulmonary perfusion in an upright lung as determined by the interrelationships between arterial (PAP), alveolar (P_A), and venous pressures (PVP), explaining a gravity-determined progressive increase in perfusion from zones I and II to III. There is a zone IV of decreased perfusion at the most dependent part of the lung. *(Adapted with permission from Hughes JM, Glazier JB, Maloney JE, West JB. Effect of lung volume on the distribution of pulmonary blood flow in man. Respir Physiol. 1968;4(1):58–72.)*

PAP > P_A> PVP. In zone 2, alveolar pressure is an effective closing pressure, and the driving pressure for flow is the gradient between mean mPAP and P_A. As noted previously, such a flow condition can be likened to a waterfall, since PVP, the apparent outflow pressure, is irrelevant to flow, as is the height of a waterfall. In the most caudal portions of the lung, *zone 3*, PVP is higher than P_A, so that the driving pressure for flow is mPAP – PVP. These so-called “West zones” are illustrated in Fig. 13-12.

At the most dependent regions of upright lung, there is an additional region where flow decreases.[85] This *zone 4* has been attributed to an increase in the resistance of extra-alveolar vessels, because it expands when lung volume is reduced or in the presence of lung edema. Active tone may be an additional explanation for zone 4, as it is also reduced by the administration of vasodilators.

The vertical height of lung tissue in a supine human subject is much reduced compared with the upright position. Accordingly, the normal lung constitutes nearly all zone 3; however, there remains a measurable increase in flow from nondependent to dependent lung regions.

Three-dimensional reconstructions using single-photon-emission computed tomography have shown that there is also a decrease in blood flow from the center of the lung to the periphery.[86] High-resolution methods and fractal modeling of the pulmonary circulation have actually led to the notion of a predominantly non-gravity-dependent distribution of pulmonary blood flow.[87] Subtle differences in arterial branching ratios may, indeed, influence flow distribution with increased heterogeneity as the scale of the inquiry narrows, corresponding to the “what is the length of the coastline” effect.[88] However, the overwhelming evidence remains in favor of the thesis that gravity is the single most important determinant of pulmonary blood flow distribution.[88] Vascular geometry–related small-unit heterogeneity of pulmonary blood flow distribution has not been shown to be relevant to gas exchange.

■ Hypoxia

An active intrapulmonary control mechanism is able, to some extent, to correct the passive gravity-dependent distribution of pulmonary blood flow: a decrease in PO_2 increases pulmonary vascular tone. Hypoxic pulmonary vasoconstriction was first demonstrated by von Euler and Liljestrand,[89] who proposed a functional interpretation that can still be considered valid. In lung tissue, PO_2 is determined by a ratio between O_2 carried to the lung by alveolar ventilation ($\dot{V}_A$) and O_2 carried away from the lung by blood flow ($\dot{Q}$):

$$PO_2 = \dot{V}A/\dot{Q}$$

In contrast, with hypoxic vasodilation in systemic tissue local PO_2 is determined by the ratio flow of O_2 carried to the tissues ($\dot{Q}$) and local O_2 consumption ($\dot{V}O_2$):

$$PO_2 = \dot{Q}/VO_2$$

The attributes of hypoxic pulmonary vasoconstriction have been recently extensively reviewed.[90] The hypoxic pulmonary pressor response is universal in mammals and in birds, but with considerable interspecies and interindividual variability. It is intense in pig, horse, and cow, moderate in rodents and humans, and very low in dog, guinea pig, yak, and llama. Chronic hypoxia induces pulmonary hypertension in proportion to initial vasoconstriction. Initial hypoxic vasoconstriction is a quasi-immediate response, with subsequent modulation depending on the experimental model or preparation. Hypoxic vasoconstriction strengthens during the first few hours of hypoxic exposure in humans. The temporal sequence of hypoxia-induced remodeling is less well known. After 6 hours of hypoxic exposure, re-oxygenation immediately decreases PVR without, however, a complete return to normal.[91] The reversibility of increased PVR with re-oxygenation is largely lost after 24 to 48 hours exposure to hypoxia.[18]

Hypoxic vasoconstriction is observed in lungs devoid of nervous connections and, indeed, also in isolated pulmonary arterial smooth muscle cells.[90] The response is enhanced by acidosis, a decrease in mixed venous PO_2, repeated hypoxic exposure (in some experimental models), perinatal hypoxia, decreased lung segment size, cyclooxygenase inhibition, nitric oxide inhibition, and by certain drugs or mediators, which include almitrine and low-dose serotonin. The response is inhibited by alkalosis, hypercapnia, an increase in pulmonary vascular or alveolar pressures, vasodilating prostaglandins, nitric oxide, complement activation, low-dose endotoxin, calcium channel blockers, β_2 stimulants, nitroprusside, and, paradoxically, by peripheral chemoreceptor stimulation. The hypoxic pressor response is biphasic, with a progressive increase as PO_2 is progressively decreased to approximately 35 to 40 mm Hg, followed by a decrease (“hypoxic vasodilatation”) in more profound hypoxia.

The hypoxia-induced increase in PVR is mainly caused by a constriction of precapillary small arterioles.[90] Small pulmonary veins also constrict in response to hypoxia, but this does not normally contribute to more than 20%–30% of the total change in PVR.[92]

While hypoxic pulmonary vasoconstriction has been shown to be an only moderately efficient feedback mechanism,[93,94] it may still produce substantial improvements in arterial oxygenation of patients with inhomogeneous lungs, such as in chronic obstructive

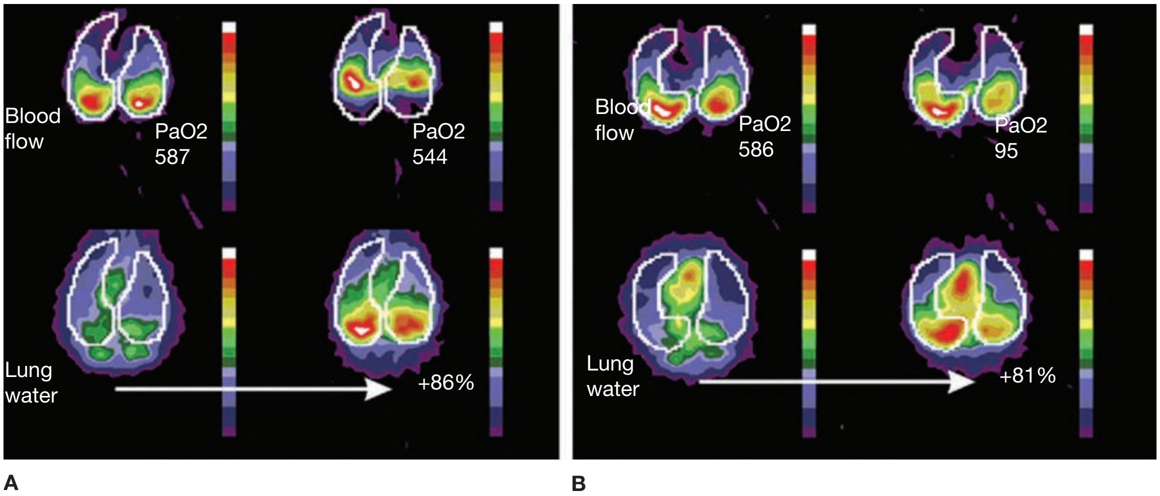

Figure 13-13 PET scan measurements of blood flow and lung water in a supine dog before and after induced of acute lung injury, with preserved hypoxic vasoconstriction (**A**) or without hypoxic vasoconstriction (**B**). In the normal lung, blood flow and water increase to the most dependent lung regions (from blue to red). Acute lung injury approximately doubles lung water, but arterial PO_2 (PaO_2) is preserved because of a hypoxic vasoconstriction redirecting flow to better-aerated lung regions. Prevention of hypoxic vasoconstriction increases flow to the dependent edematous lung regions, and this is associated with a marked decrease in PaO_2. *(Reproduced with permission from Gust R, Kozlowski J, Stephenson AH, et al. Synergistic hemodynamic effects of lowdose endotoxin and acute lung injury. Am J Respir Crit Care Med. 1998;157(6 Pt 1):1919–1926.)*

pulmonary disease (in which hypoxemia is explained mainly by low V_A/Q ratios) or in the acute respiratory distress syndrome, ARDS (in which hypoxemia is explained mainly by V_A/Q ratios equal to zero, i.e., shunt).[95]

Topographic blood flow distribution (assessed with PET scanning) and arterial PO_2 can be shown to conform to the expected functional effects of hypoxic pulmonary vasoconstriction in experimental acute lung injury models, as an inhibition of the response prevents redistribution of blood flow to nondependent lung regions and markedly aggravates shunt and arterial hypoxemia.[96] This is illustrated in Fig. 13-13 in an experiment that also shows the predominant effects of gravity on the distribution of pulmonary blood flow and its relevance to gas exchange.

The biochemical mechanism of hypoxic pulmonary vasoconstriction remains incompletely understood.[90] Current thinking is that a decrease in PO_2 inhibits smooth muscle cell voltage-gated potassium channels, resulting in membrane depolarization, influx of calcium, and cell shortening. However, the nature of the low PO_2 sensing mechanism remains elusive. Mitochondria and nicotinamide adenine dinucleotide phosphate oxidases are discussed as oxygen sensors. Reactive oxygen species, redox couples, and adenosine monophosphate–activated kinases are candidate mediators. The reversal of hypoxic vasoconstriction by profound hypoxia is due to an activation of ATP-dependent potassium channels.

Normal and abnormal pulmonary vascular tone have been shown to be modulated by a series of endothelium-derived and circulating mediators.[90] Endothelium-derived relaxing factors include nitric oxide, prostacyclin, and the endothelium-derived hyperpolarizing factor. The major endothelium-derived contracting factor is endothelin. These observations have been at the basis of efficient treatments of pulmonary arterial hypertension using prostacyclin derivatives, phosphodiesterase-5 inhibitors to enhance nitric oxide signaling, and endothelin receptor blockers.

Hypoxic pulmonary vasoconstriction serves to limit the perfusion of fetal lungs. That hypoxic pulmonary vasoconstriction matters to the outcome of lung diseases has not been demonstrated. Persistent whole-lung hypoxic vasoconstriction at high altitudes may be a cause of "fixed" pulmonary hypertension in proportion to initial pressor response.[97] High altitude is generally mild or borderline in the human species[98] and, thus, of uncertain clinical relevance.

■ Autonomic Nervous System Control

The pulmonary circulation is richly innerved by the autonomic nervous system, which includes adrenergic, cholinergic, and nonadrenergic noncholinergic signaling systems.[99] However, the role played by the autonomic nervous system in the control of pulmonary vascular tone remains incompletely understood. Sympathetic nervous system activation does not affect PVR but stiffens the proximal pulmonary arterial tree.[100]

Distension of the proximal pulmonary arterial tree causes distal vasoconstriction, which can be inhibited by chemical or surgical sympathectomy.[101,102] This pulmonary reflex is believed to contribute to high fetal PVR and to slow postnatal pulmonary vasodilation and the associated risk of lung edema. It has been invoked to explain reverse pulmonary vascular remodeling after pulmonary artery banding in infants born with congenital left-to-right cardiac shunts.[103] It offers rationale for current attempts at treating PH by PA denervation.[104]

■ Exercise

Exercise is associated with an increase in cardiac output in response to increased oxygen uptake ($\dot{V}O_2$). Therefore, pulmonary blood flow CO is increased during exercise. This is necessarily associated with an increase in PAP and, to a lesser extent, PAWP. However, exercise is also associated with increased ventilation, changes in lung volumes, and sympathetic nervous system activation with systemic hemodynamic changes, all of which affect pulmonary vascular pressure-flow relationships.[105]

The stress of exercise on the pulmonary circulation is mediated by an increase in cardiac output. This is true for dynamic exercise such as cycling, running, or swimming. Resistive or static exercise, such as weightlifting and handgrip strengthening, is associated with increases in cardiac output too small to stress the pulmonary circulation[106] and may, furthermore, be associated with confounding effects of increased intrathoracic pressure and systemic blood pressure.[107]

Exercise stress testing of the pulmonary circulation to diagnose latent or early pulmonary vascular disease has to conform to a series of methodologic constraints. Body position does not matter, as the same maximum $\dot{V}O_2$ and cardiac output are measured during incremental cardiopulmonary exercise testing in supine or semirecumbent positions.[24] Maximum workload is actually lower semirecumbent, but this is not relevant to the pulmonary vascular function as defined by pulmonary vascular pressure-flow relationships.[24] Measurements should be done during, not after, the exercise stress, as post-exercise recovery of vascular pressures and flows normally occurs within minutes.[108] Exercise stress should be incremental.[49,50,105] Prolonged steady-state exercise may be associated with a progressive decrease in pulmonary vascular pressures in relation to a decreased pulmonary blood volume, as the systemic circulation adapts and does not offer the improved accuracy of a range of pressure-flow coordinates to define pulmonary vascular function.[109,110]

Since CO, workload, and $\dot{V}O_2$ are (quasi-) linearly related as long as CO is not too high, and cardiac output measurements during exercise are challenging, either workload[111,112] or $\dot{V}O_2$[113] are sometimes used as surrogates for CO to describe pulmonary vascular function. Equations to predict CO have been derived from linear regressions on measurements during exercise in healthy volunteers:[24]

$$\text{CO (L/min)} = 0.34 \times \dot{V}O_2\ \text{(mL/kg/min)} + 5.4$$
$$\text{CO (L/min)} = 0.06\ \text{Workload (W)} + 6.5$$

However, CO vs. workload and CO vs. $\dot{V}O_2$ relationships tend to plateau at high levels of exercise, and interindividual variability of these relationships alters the reliability of the prediction.[24] For example, at a $\dot{V}O_2$ of 20 mL/kg/min or a workload of 100 W, CO may vary between 8 and 16 L/min, making estimation of CO excessively imprecise.[24,48–50]

Noninvasive exercise stress testing of the pulmonary circulation using Doppler echocardiography is acceptable, as exercise measurements are probably accurate[48–50] even though this has been rigorously demonstrated for all the components of the PVR equation only in resting conditions.[114] Echocardiographic estimates of PAP from the maximum velocity of tricuspid regurgitation during exercise have recently been shown to be accurate, but with limited precision.[112]

Doppler echocardiography may underestimate cardiac output during exercise.[111] Another concern is the possible occurrence of a gradient between systolic RV and PAP, particularly at high cardiac output and in the upright position.[115,116] This will need to be confirmed with high-fidelity micro-manometer-tipped catheters.

Exercise is associated with increased ventilation and pleural pressure–dependent pulmonary vascular pressure swings, which make the interpretation of pulmonary vascular pressure curves difficult. Averaging vascular pressures over several respiratory cycles instead of reading them at end-expiration largely allows cancelling out the influence of negative inspiratory and positive expiratory pleural pressures.[11,15] Zero leveling in different body positions may be a challenge. Computed tomography has offered easy-to-implement, three-dimensional guidance.[11] Zero leveling is not a problem for echocardiographic estimates of systolic PAP from recalculated trans-tricuspid gradients.

Most of the information from a set of pulmonary vascular pressure pressure-flow coordinates during exercise is captured by the slope of a linear adjustment.[49,50,105,117] Invasive, as well as noninvasive, studies have shown that slopes on mPAP-CO relationships in healthy subjects are, on average, about 1.5 mm Hg/L/min; limits of normal range from 0.5 to 3 mm Hg/L/min.[49,50,105,117,118] These values correspond to a maximum exercise total PVR (TPVR) of no more than 3 Wood units, or a mPAP of 30 mm Hg at a CO <10 L/min. Combining all these criteria actually strengthens the discrimination between normal and abnormal responses.[117]

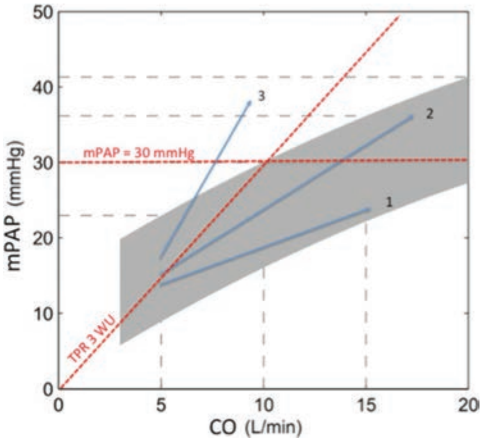

Figure 13-14 Mean pulmonary artery pressure (mPAP) as a function of cardiac output (CO) in 3 subjects (arrows): 1 and 2 are normal, even if 2 has exercise mPAP >30 mm Hg, and 3 has an abnormal response suggesting exercise-induced pulmonary hypertension. Limits of normal are within the shaded area. *(Reproduced with permission from Lewis GD, Bossone E, Naeije R, et al. Pulmonary vascular hemodynamic response to exercise in cardiopulmonary diseases. Circulation. 2013;128(13):1470–1479.)*

Theoretical normal and abnormal linearized mPAP vs. CO relationships in individuals with normal resting mPAP are illustrated in Fig. 13-14.

The upper limit of normal of PAWP during exercise is generally considered to be between 15 and 20 mm Hg, but higher values can be recorded in athletes and in elderly subjects.[20,49,50] A higher cutoff value of 25 mm Hg has been proposed for the diagnosis of heart failure.[119–121] A flow-corrected measure may be more appropriate.[50] Given the average proportional difference between mean mPAP vs. CO and PAWP vs. CO relationships, a slope of 2 mm Hg/L/min is the upper limit of normal of PAWP vs. CO.[105] This cutoff value has been confirmed in studies on young and old male and female healthy volunteers[122] and patients with heart failure compared with healthy controls.[123]

■ Pulsatile Flow Pulmonary Hemodynamics

The study of the pulmonary circulation as a steady-flow system is a simplification. Pulmonary pulse pressure, or the difference between sPAP and dPAP, is on the order of mPAP, as compared with less than half the value in the systemic circulation. Instantaneous pulmonary blood flow varies from a maximum at mid-systole to around zero in diastole.

The morphology of pulmonary pressure and flow waves changes with the development of pulmonary hypertension. In patients with severe PH, the RV pressure wave is characterized by a sharp initial upstroke, followed by a short plateau and by a late systolic peaking; the PA pressure wave is characterized by a huge pulse pressure and a late systolic peaking, as well,[124] while the pulmonary flow wave presents a shortened acceleration time and late or midsystolic deceleration.[125] In the most severe forms of PH, the PAP appears "ventricularized."[124] These morphologic aspects are entirely explained by the combined effects of decreased compliance[126] and wave reflection.[127]

A complete evaluation of pulmonary vascular function relies on the calculation of the relationship between pulsatile pressure and flow or pulmonary vascular impedance (PVZ), instead of the relationship between mean pressure and flow as used in the PVR equation.

Pulmonary vascular impedance, PVZ, is calculated from a spectral analysis of the pulmonary arterial pressure and flow waves.[128] This analysis is possible because the pulmonary circulation behaves nearly linearly. This means that a purely sinusoidal

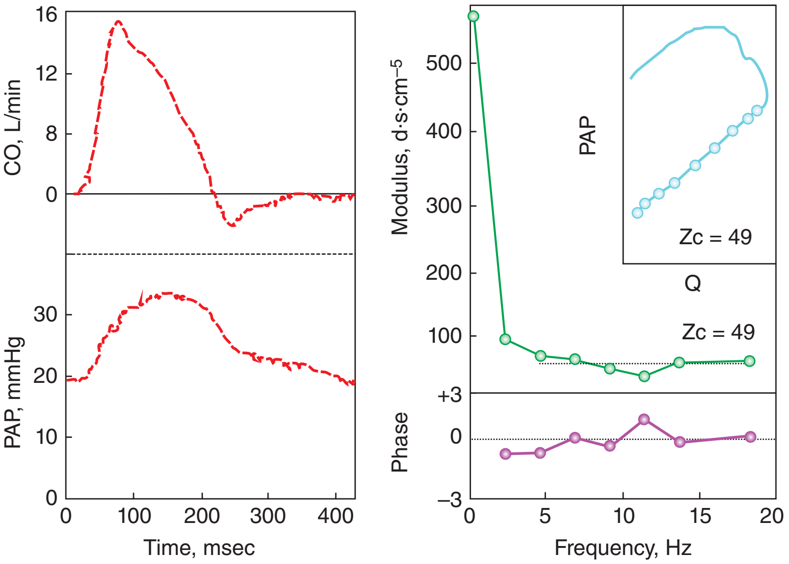

Figure 13-15 Pulmonary artery flow (CO) and pressure (PAP) waves (left panel) and pulmonary arterial input impedance spectrum (right panel). At 0 Hz the total PVR is obtained (mean pressure over mean flow). Between 0 and 4 Hz the impedance is determined mainly by total arterial compliance. The averaged input impedance for high frequencies, usually taken between 4 and 8 Hz, equals the characteristic impedance (Zc). The oscillation of the impedance about the characteristic impedance results from wave reflection. Zc is also the slope of early systolic PAP-flow relationship.

flow oscillation produces a purely sinusoidal pressure oscillation of the same frequency. The sinusoidal pressure and flow waves can be related by the ratio of their amplitudes (modulus) and the difference in their phases (phase angle). A typical PVZ spectrum is illustrated in Fig. 13-15.

Pulmonary arterial impedance at zero Hz, Z_0, (the ratio of mean pressure to mean flow, mPAP/Q) corresponds to TPVR. This parameter is mainly determined by the small resistance vessels, as well as LAP. As frequency increases, the impedance is affected by more proximal elements of the arterial tree. The modulus of the impedance decreases rapidly from Z_0 to a first minimum at 2–3 times the heart rate and then oscillates about a constant value. The impedance phase increases from a negative value at low frequencies, indicating that flow leads pressure to zero at higher frequencies. The precipitous fall in modulus and the negative phase of the impedance are a measure of pulmonary artery compliance. At high frequencies the rather constant modulus and nearly zero phase angle are a measure of the proximal arterial compliance.

The impedance modulus at high frequencies, when impedance phase is nearly zero and, therefore, wave reflections can be ignored, is the characteristic impedance Z_C. It is typically measured as the average modulus at higher frequencies (usually 10–20 times the heart rate). It can also be measured as the slope of the early systolic pulmonary artery pressure-flow relationship in the time domain.[129]

The oscillations of the impedance modulus about its mean value result from distinct wave reflections. Increased magnitude of these oscillations implies increased reflections. A shift of the first minimum of modulus to higher frequencies indicates an increased wave velocity or a decreased distance to the dominant reflection site.

Distal small vessel obstruction, such as that caused by microembolism, hypoxia, or PAH increase Z_0 but have limited effects on the PVZ spectrum; some shift may be noted of first minimum and maximum of PAP/Q to higher frequencies, along with unchanged or, sometimes, even a decrease in Zc.[130–132] Proximal vessel disease, such as that mimicked by experimental proximal ensnarement of the pulmonary arteries or clinical chronic thromboembolic pulmonary hypertension (CTEPH), shifts the entire PVZ spectrum to higher ratios of pressure and flow moduli.[130] Very high PAP due to major peripheral small vessel obstruction also increases Z_c because of extreme stiffening of the pulmonary arteries and increased reflected wave speed.[131,132]

Exercise has been reported in an animal study to decrease PVR but to shift the PVZ spectrum to higher pressure and flow moduli at all frequencies with an increase in Zc, a shift of the first minimum of the ratio of pressure, and flow moduli to higher frequencies and more negative phase angle.[133] The increase in Zc is explained by a decreased area compliance of the proximal pulmonary arterial tree because of increased distending pressure related to increased flow, with a possible contribution of exercise-associated sympathetic nervous system activation. Exercise has been reported to be associated with unchanged Zc in a small human study.[134] Exercise is also associated with a greater decrease in PAC than in PVR, which results in a decreased RC-time and increased RV hydraulic load.[135] The apparent discrepancy between changes in Zc and PAC is explained by the sensitivity of Zc to proximal stiffness and dimensions, while PAC integrates the distensibility of the entire pulmonary circulation.

■ Right Ventricular Function

The RV is functionally coupled to the pulmonary circulation. Because of the normally low pulmonary vascular pressures taking the entire cardiac output, the RV acts as a thin-walled flow generator. The structural and functional characteristics of the RV allow for the accommodation of large increases in flow, less so small increases in afterload. However, the basic laws of the heart remain applicable, i.e., rapid beat-to-beat heterometric adaptations (Starling's law of the heart) and otherwise progressive structural and inotropic homeometric adaptations (Anrep's law of the heart) to changes in loading conditions. Thus, RV adaptation to pulmonary hypertension is homeometric with increased contractility, eventual hypertrophy, and preserved dimensions. Failure of this mechanism, depending on rate of onset and magnitude of increase in PAP, requires heterometric adaptation, with increased RV dimensions and systemic congestion.[136,137]

Right Ventricular Hydraulic Load

Increased PAP requires increased RV hydraulic power to sustain adequate forward flow. Hydraulic power is made of two components: the energy per unit time (power) to produce steady flow, which is the product of mPAP and SV, and the power to produce the pulsatile component of PAP and SV.[138] The latter can be calculated from the difference between the product of the integrations of instantaneous PAP and SV waves and the product of mPAP and SV.

Since mean flow determines oxygen transport, mean power may be considered useful, whereas oscillatory power is "wasted." As a consequence, the ratio of oscillatory (W_{OSC}) to mean (W_{MEAN}) power, or W_{OSC} to total (W_{TOT}), should preferably be small.

Because of the proportional relationship between systolic, diastolic, and mPAP, the ratio of W_{OSC} to W_{TOT} should remain constant. This was indeed reported by Saouti et al.[70] in a total of 49 patients with pulmonary hypertension of variable severity. Total power increased with severity of pulmonary hypertension, but the ratio of W_{OSC} to W_{TOT} remained at 23%. Accordingly, the authors proposed that W_{OSC} should be equal to 1.3 times W_{MEAN} in all circumstances.

$$W_{TOT} = 1.3 \times \text{mPAP} \times \text{SV}$$

Extremes of reported RC-times, ranging from 0.2 to 1.0 s, affect the proportionality constant between W_{TOT} and W_{MEAN} from only 1.2 to 1.4.[139] Thus, changes in PAC at any given level of PVR have a minimal effect on the oscillatory component of RV hydraulic load.

Right Ventriculo-Arterial Coupling

The calculation of power includes a measurement of cardiac output and, thus, depends not only on the mechanical properties of the pulmonary circulation but also on ventricular function. It has been suggested that power transfer and ventricular efficiency are near maximal in normal subjects. A simplified approach to test this has been given by Sunagawa et al.[140] and Suga et al.[141] These authors proposed a graphical analysis based on the ventricular pressure-volume diagram and a characterization of the arterial system by means of its arterial elastance.

The diagram allows for the determination of maximal or end-systolic ventricular elastance (Ees) as a load-independent measurement of contractility, and of arterial elastance (Ea) as a measurement of afterload as it is “seen” by the ventricle, as well as calculation of an Ees/Ea ratio as a measurement of the coupling of ventricular to arterial function. This analysis is equally valid for the RV and the LV.[141,142]

Mathematical modeling shows that the optimal matching of systolic ventricular and arterial elastances occurs at an Ees/Ea ratio around 1.5. An isolated increase in Ea or decrease in Ees, or a decrease the Ees/Ea ratio, indicates uncoupling of the ventricle from its arterial system. If all other measurements are the same, a decrease in Ees/Ea is necessarily accompanied by a decrease in SV. On the other hand, an isolated increase in preload is associated with an increase in SV with unaltered ventriculo-arterial coupling.

The complex geometry of the RV makes functional evaluations with measurement of instantaneous volume changes technically difficult, and the determination of Ees may be unreliable because of the particular shape of the RV pressure-volume loop and non-coincidence of end-ejection and end-systole. This problem can be overcome by measuring pressure-volume loops at several levels of preload,[142] but bedside manipulations of venous return are too invasive to be ethically acceptable. In addition, when applied to intact beings, changes in venous return are associated with reflex sympathetic nervous system activation, which affects the ventricular function that is measured.

These concerns have been addressed by a single beat method allowing for a direct quantification of the coupling of the RV to the pulmonary circulation.[143] The approach had been initially proposed for the left ventricle.[144] In its principle, the method avoids absolute volume measurements and related technical complexities in calculating Ees and Ea from instantaneous RV pressure and flow output measurements. As shown in Fig. 13-16, a Pmax is estimated from a nonlinear extrapolation of the early and late systolic isovolumic portions of the RV pressure curve. This estimated Pmax has been shown to be tightly correlated with Pmax directly measured during a non-ejecting beat.[143] A straight line drawn from Pmax to the RV pressure versus relative change in volume curve allows for the determination of Ees. A straight line drawn from the Ees point to the end-diastolic relative volume point determines Ea (Fig. 13-16).

The Ees/Ea ratio as determined by the single beat method has been shown to be decreased by propranolol and increased by dobutamine and maintained in the presence of increased Ea due to hypoxic pulmonary vasoconstriction.[143] In fact, Ees increases adaptively to increased Ea in hypoxia, even in the presence of adrenergic blockade, which is compatible with the notion of homeometric adaptation of RV contractility.

Kuehne et al. used cardiac magnetic resonance (CMR) imaging together with RV pressure measurements with Pmax calculations to generate pressure-volume loops and Ees and Ea determinations in patients with PAH.[145] As compared with controls, Ees was almost doubled, but Ees/Ea was decreased, indicating insufficient homeometric adaptation and pending RV failure.

The Right Ventricular Pump Function Graph

An alternative approach was developed by Elzinga and Westerhof in 1978.[146] The authors described RV pump function curves by plotting mean RV pressure as a function of SV. As shown in Fig. 13-17, the pump function curve is built from measurements of mean RV pressure and SV, a calculated maximum pressure at zero SV, and a parabolic extrapolation to a zero pressure SV. In this representation, an increase in preload shifts the curve to greater SV with no shape change, while an increased contractility leads to a higher maximum pressure with no change in maximum SV. This analysis has been used to explain more severe RV failure in the face of lower mPAP in PH associated with systemic sclerosis, as explained by myocardial involvement by the disease process.[147]

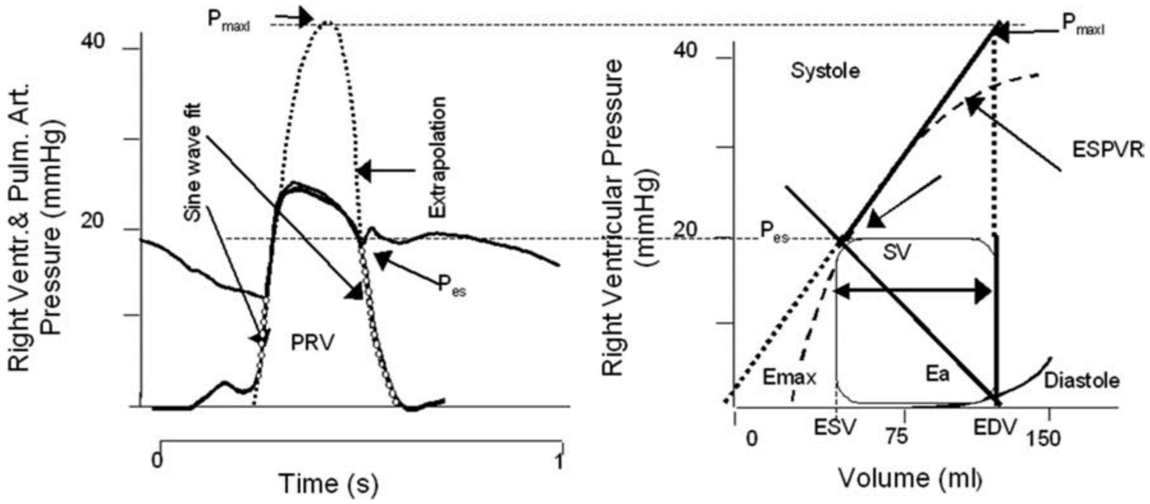

Figure 13-16 Single beat method to measure right ventriculoarterial coupling. A maximum pressure (*P*max) is calculated from nonlinear extrapolation of early and late isovolumic portions of the right ventricular pressure curve. A straight line is drawn from *P*max and the end-diastolic volume (EDV) to *P*es (end-systolic pressure) and the end-systolic volume, thus *E*max (maximum or end-systolic elastance) = (*P*max −*P*es)/SV, where SV is the stroke volume. The arterial elastance *E*a is defined by the ratio *P*es/SV.

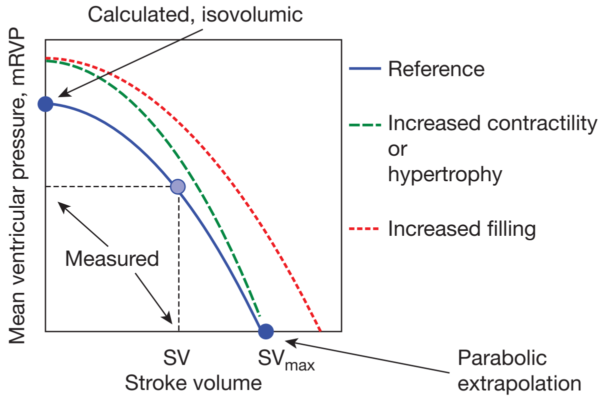

Figure 13-17 Pump function curve defined by mean right ventricular pressure as a function of stroke volume. The zero-stroke volume point is calculated from a maximum pressure determination (see Fig. 13-16). The zero pressure point results from a parabolic extrapolation, from measured and zero stroke volume points. *(Data from Elzinga G, Westerhof N. The effect of an increase in inotropic state and end-diastolic volume on the pumping ability of the feline left heart. Circ Res. 1978;42(5):620–628.)*

Simplified Estimates of Right Ventriculo-Arterial Coupling

Both the ratio of end-systolic to arterial elastance and the pump function graph are not readily clinically applicable. Therefore, clinicians use simplified bedside estimates of RV-arterial coupling.

Ees/Ea may be simply expressed as a ratio of volumes. Sanz et al. reported on assessment of RV-arterial coupling estimated by the ratio of SV to end-systolic volume (ESV), as measured by CMR in 139 patients referred for PH. The resulting volume-determined Ees/Ea or SV/ESV was shown to decrease progressively with increasing severity of PH.[148]

Since ESV is equal to end-diastolic volume (EDV) minus SV, the SV/ESV ratio is necessarily related to ejection fraction (EF) or SV/EDV:[149]

$$\text{Ees/Ea} = \text{SV/ESV} = \text{EF}/(1 - \text{EF})$$

Another manipulation of the Ees/Ea equation allows for the calculation of EV/ESV or EF from an RV pressure curve:

$$\text{Ees/Ea} = \text{Pmax/mPAP} - 1$$
$$\text{EF} = 1 - \text{mPAP/Pmax}$$

where mPAP approximates end-systolic pressure.[150,151]

A progressive decrease in either EF or SV/ESV is inevitably associated with increased ESV and end-diastolic volume EDV. This is modeled to occur at an EF <35% or SV/ESV ratio <52% when SV is preserved.[149] High-fidelity measurements of pressures and volumes using conductance catheter technology have confirmed that the coupling of the RV to the pulmonary circulation has a lot of reserve, as RV Ees/Ea or EF decrease to critical values of approximately 0.8 or 35% before RV dimensions increase above normal and symptoms of systemic congestion appear.[152,153]

Measurements of RV-PA coupling by gold standard methodology[152] are demanding, and pressure or volume surrogates rely on assumptions that may alter their clinical relevance.[153] Accordingly, entirely noninvasive surrogates, such as the tricuspid annular plane systolic excursion (TAPSE) to estimate contractility, and systolic PAP to estimate afterload (both of which are easily assessed during a transthoracic echocardiographic evaluation[154]) have been validated[155,156] and shown to be of great prognostic relevance in heart failure,[83,154,155] PAH,[157] and PH in chronic lung diseases.[158]

SUMMARY

The pulmonary circulation is a high-flow and low-pressure circuit, with an average resistance of 1 mm Hg·min·L^{-1} in young adults that increases to 2.5 mm Hg·min·L^{-1} over 4–6 decades of life. Pulmonary vascular mechanics are best described by pulmonary vascular pressure-flow relationships conforming to distensible vessel models with a correction for hematocrit. The product of pulmonary arterial compliance and resistance is constant, but it decreases slightly as a cause of increased pulsatile hydraulic load in the presence of increased venous pressure or proximal pulmonary arterial obstruction. Left atrial pressure is transmitted upstream to pulmonary artery pressure in a less than 1:1 ratio in steady flow conditions, but in a higher than 1:1 ratio in pulsatile flow conditions. The distribution of pulmonary perfusion is mainly determined by the effects of gravity and corrected to some extent by hypoxia-induced vasoconstriction to preserve matching to regional decrease in ventilation. Exercise is associated with a decrease in pulmonary vascular resistance. Right ventricular function is coupled to the pulmonary circulation, with an optimal ratio of end-systolic to arterial elastance of 1.5–2.

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CHAPTER 14

Ventilation, Pulmonary Blood Flow, and Ventilation–Perfusion Relationships

Peter D. Wagner

This chapter presents the physiologic basis of normal pulmonary gas exchange. Gas exchange occurs by an integrated series of gas transport steps between the environmental air we breathe and the Hb molecule of the red cells passing through the pulmonary capillaries. These transport steps are of two types—diffusive and convective—and a number of conceptually separate diffusive as well as convective processes interact to accomplish the gas exchange mission. This is true both for gases that are taken up from the environment into the blood (i.e., O_2 and occasional toxic gases or volatile anesthetics) and for gases that are eliminated from the body (i.e., CO_2 and volatile anesthetic agents).

This chapter deals principally with the convective processes and Chapter 16 with those involving diffusion. However, since the two types of process occur simultaneously, they are closely linked.

BASIC OUTLINE OF THE GAS EXCHANGE PATHWAY

This section dwells on O_2, being the gas of principal physiologic interest. However, the pathway components are of course identical for all gases and furthermore do not depend on whether the gas is being taken up (O_2) or eliminated (CO_2). On the other hand, distinct quantitative differences in the uptake or elimination patterns of different gases exist, but those are readily explained by differences in their fundamental physical or chemical properties, and not by transport pathway differences.

To understand the gas transport pathway one must first appreciate the anatomy of the lungs, laid out in detail in Chapter 2. The salient functional features are presented in Fig. 14-1.

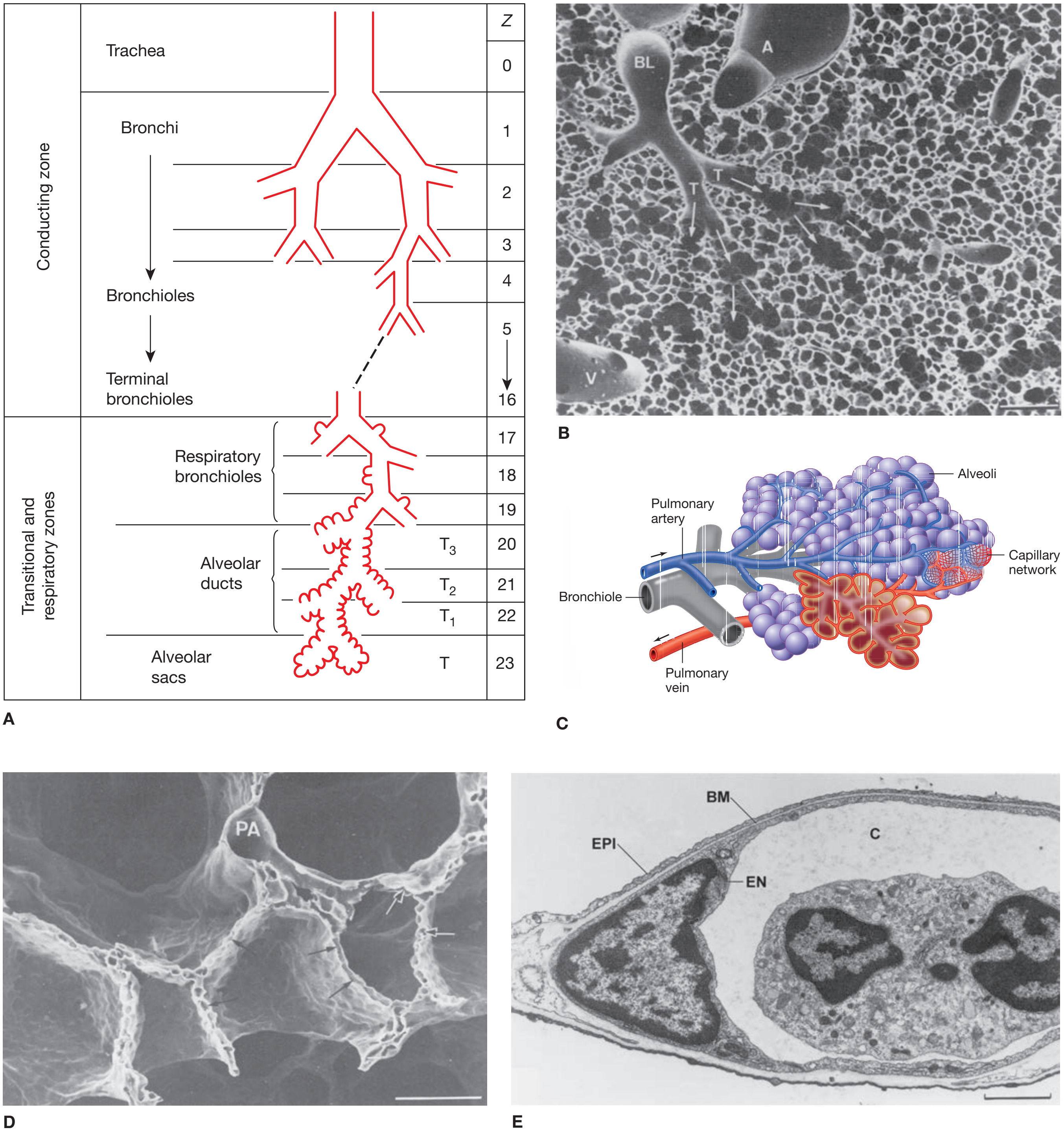
The chest wall (rib cage and diaphragm) contains muscles that on contraction expand the volume of the chest cavity and thus reduce the hydrostatic pressure of the pleural space, expanding the lungs with air drawn in via the mouth and nose. Although there is but a single air passage in the neck (i.e., the trachea), this soon branches into right and left main bronchi. These also divide many times, essentially dichotomously. There are some 16 such orders of branching of these bronchi, resulting in a structure that resembles an inverted deciduous tree without its leaves in winter.[1] With each successive branch the airways become shorter and narrower, but ever greater in number, usually doubling at each branching. Thus, although the cross-sectional area of any one airway becomes smaller with each branching, the greater number of airways more than makes up for loss of individual cross-sectional area such that the sum of cross-sectional areas of all airways of a given generation rises essentially exponentially with each branching (Fig. 14-2). The total volume of gas in these 16 conducting airway generations is called the anatomic or conducting airway dead space and approximates 1 mL per pound of body weight. After these 16 or so successive branches, the tubular, purely conducting airways begin to show alveolar units in their wall (generations 17–19 or so) and these finally give way to fully alveolated structures (in succession: alveolar ducts, alveolar sacs, and alveoli). There are some 500 million alveoli, each about 300 μm in diameter. They are blind structures so that ventilation has to be accomplished by a tidal, in-and-out process (rather than a flow-through process as for pulmonary blood flow). The alveoli can be seen in Fig. 14-1, from a different perspective. For gas exchange to occur, O_2 must be moved from the mouth all the way to the alveoli—it is only within alveoli that gas exchange occurs.

Each alveolus is densely covered in a capillary network, seen from various perspectives in Fig. 14-1. This network is closely applied to the alveolar gas space as Fig. 14-1 shows, with on average only about 1/2 μm of cellular and interstitial tissue between the blood inside the capillary and the alveolar gas outside.[2] The capillary network is fed by the pulmonary arterial tree which branches alongside the airways in a very similar pattern as the airways. The capillaries then drain into venules that join to form larger and larger vessels, eventually becoming the pulmonary veins that drain oxygenated blood into the left atrium. This coalescence of venous vessels forms a similar branching tree to the pulmonary arteries and airways, but in reverse. The right ventricle is responsible for unidirectional pumping of blood through this vascular system.

The gas exchange pathway from the lips to the left atrium is therefore highly complex structurally; understanding how gases pass along the pathway requires following the events an O_2 molecule must participate in between the lips and the left atrium.

1. The first step is inspiration of air into the trachea via mouth and nose. Accomplished by inspiratory chest wall muscle contraction that reduces intrathoracic pressure, this step is convective (like water flowing from a region of high to low pressure along a garden hose). All the respired air must pass the trachea but at the first branch point some air goes to the right lung, the rest to the left. At each successive branch point, similar mass-conserving distribution of air must occur between the daughter branches of each parent pathway. Remembering that there are some 23 total branchings from the mouth to the 300 million alveoli, there is a very real risk of quite uneven distribution of that inspired air amongst those alveoli.[3] The principal determinants of how air is distributed at branch points (i.e., between daughter branches) are the mechanical properties of the respiratory system: the compliance (elastic properties), the resistance, and the inertial properties. These concepts are more fully treated in Chapter 10.
2. During normal resting inspiration, flow is laminar in most of the airways. Thus, inspired gas develops a parabolic profile due to higher molecular velocities in the center than periphery of the airway (Fig. 14-3). The parabolic "tongue" of inspired gas in Fig. 14-3 moves down an airway, while around the tongue is gas remaining from the previous expiration. The tongue therefore has O_2 at a concentration of 21% and essentially no CO_2. The gas around the tongue, having undergone gas exchange during the preceding breath, has about 14% O_2 and 5% CO_2. Consequently, during forward motion of this tongue toward the alveoli, O_2 will diffuse from the tongue to its surrounding gas while CO_2 will diffuse in the opposite direction. This is called Taylor dispersion[4] and it reduces the forward transport of O_2 produced by the onward convective movement of the tongue. This effect however is considered quite small and is generally not of significance to overall gas exchange.

   Note that if inspiration occurs at high rates as in exercise, such laminar flow may not occur in the larger airways—it may be turbulent and then Taylor dispersion is essentially noncontributory, as the turbulent mixing evens gas concentrations across the airway lumen.


Z
Trachea
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Terminal bronchioles
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Conducting zone
Respiratory bronchioles
17
18
19
Alveolar ducts
T3
20
T2
21
T1
22
Alveolar sacs
T
23
Transitional and respiratory zones
A
BL
A
T
T
V
B
Alveoli
Pulmonary artery
Capillary network
Bronchiole
Pulmonary vein
C
PA
D
BM
EPI
C
EN
E

Figure 14-1 Principal anatomic features of the lung related to gas exchange. **A** shows the organization of branching airways, mirrored by a photograph of a lung slice showing terminal and respiratory bronchioles and the alveolar parenchyma (see also **B**). **C** shows how the capillaries are wrapped around alveoli, and **D** is a scanning electron micrograph indicating the rich capillary networks in the alveolar walls (PA, pulmonary artery). **E** is a transmission electron micrograph showing the capillaries (C) and the three layers of the blood–gas barrier (EN, endothelium; BM, basement membrane; and EPI, epithelium). (***A.*** *Modified with permission from Weibel ER: Morphometry of the Human Lung. Heidelberg, Springer-Verlag; 1963.)* (***B, D,*** *and* ***E.*** *The Pathway for Oxygen: Structure and Function in the Mammalian Respiratory System by Ewald R. Weibel, M.D., Cambridge, Mass.: Harvard University Press, Copyright © 1984 by the President and Fellows of Harvard College. Used by permission. All rights reserved.)*

3. Figure 14-2 shows the exponential increase in airway cross-sectional surface area as one proceeds deeper and deeper into the lungs. The significance of this curve is that since the mass flow rate of inspired gas is the same at every generation (because the airways are simply a conducting system), the forward velocity of O_2 molecules falls (since flow rate is the product of velocity and cross-sectional area). As it happens, by about generations 17 to 19, where the alveoli are just beginning to appear, this forward velocity has become so low that passage of O_2 from here on out to the alveoli is heavily dependent on simple gaseous diffusion, not just on continuing convective flow.
4. If alveoli are not equally ventilated with gas (and equally perfused with blood), their alveolar O_2 concentration will differ, as explained later in this chapter. Because adjacent alveoli are

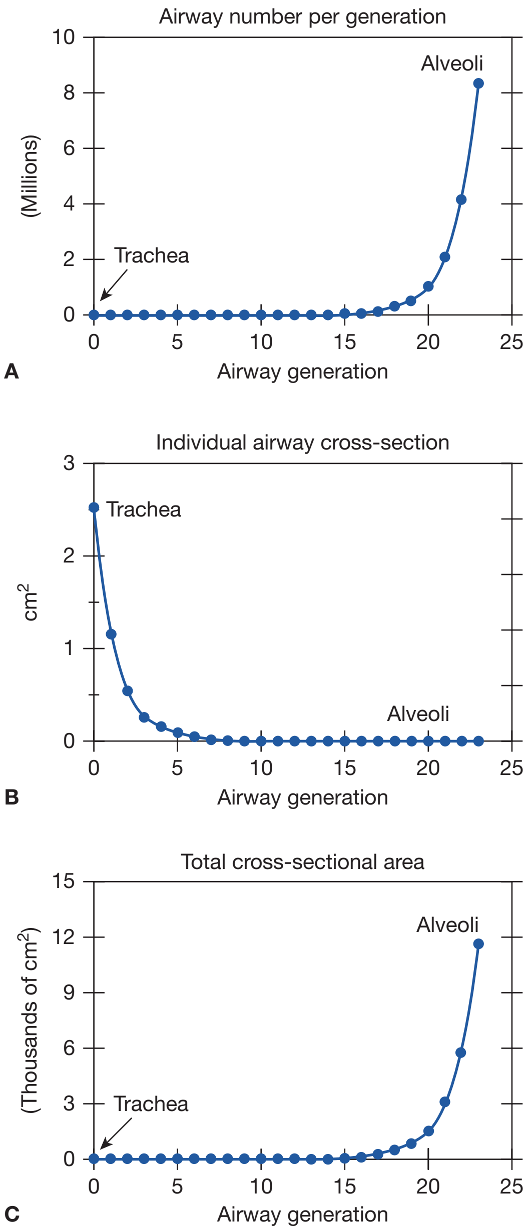

Figure 14-2 Relationship between number (**A**) and cross-sectional area (**B**) of the airways at a given generation. Note that total airway cross-sectional area (**C**) increases extremely rapidly beyond airway generation 15 or so, the beginning of the respiratory zone for gas exchange.

so physically close, there can be considerable diffusion of O_2 between such alveoli when their O_2 levels are different. This passive process tends to reduce concentration differences between these alveoli. However, although it can be detected experimentally, it is of probably minor clinical significance. Step 3 (and to some extent, Step 4) are responsible for most of the alveolar gas mixing that must occur for gas exchange to take place—that is, the mixing of each breath of newly inspired gas with alveolar gas still present from prior breaths.

5. The heart acts as a massaging pump to further enhance gas mixing into the alveolar gas spaces. Alternate filling and emptying of the cardiac chambers respectively facilitate exhaling and inhaling of airway gas into those alveoli physically close to the heart,[5] but have little effect on more distant alveoli. Although a well-known and easily demonstrated phenomenon, this so-called cardiogenic mixing is probably also of minimal physiologic impact for gas exchange.

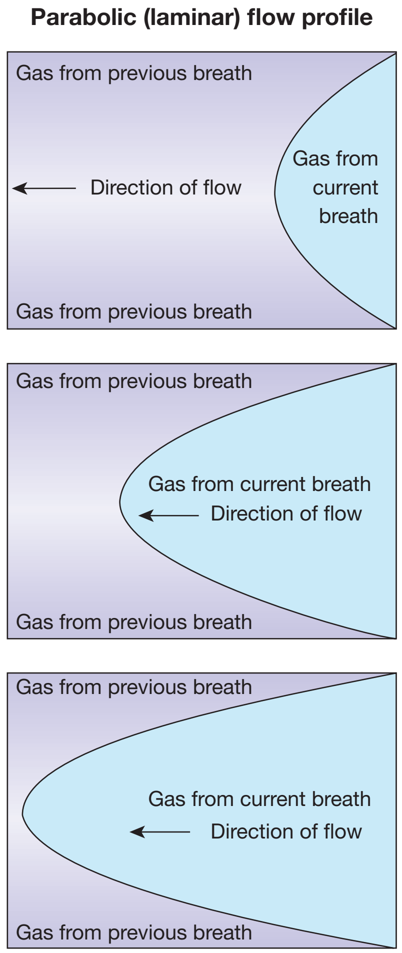

Figure 14-3 The parabolic profile of laminar flow. The three panels indicate sequential points in time during a single inspiration proceeding from right to left. Because the gas remaining from the previous breath has a low oxygen concentration and high CO_2 concentration relative to that of the inspired gas in the current breath, there will be diffusive exchange between the parabolic tongue and the surrounding gas (Taylor dispersion).

6. Once the dominant convective and diffusive gas transport steps have brought O_2 from the lips to the alveolar gas spaces, O_2 physically dissolves in the tissues separating alveolar gas from capillary blood, the blood–gas barrier (Fig. 14-1). O_2 then moves by diffusion through the blood–gas barrier and into the plasma. Over 98% of these O_2 molecules diffuse further, that is, into the red cell interior, and then bind rapidly to hemoglobin. The remaining 2% or so remain physically dissolved in the plasma and red cell water.

   This transport process from alveolar gas to hemoglobin is accomplished passively by simple diffusion: No convective forces or active transport processes are involved. The diffusion process is discussed more fully in Chapter 16. In normal lungs at rest, this process is very rapid and causes no O_2 transport limitation.

7. Finally, the red cells are transported convectively by cardiac pumping action out of the pulmonary capillaries and into the pulmonary veins and then to the left atrium, and left ventricle, finally reaching the various body tissues.

POTENTIAL DISRUPTIONS OF THE GAS TRANSPORT PATHWAY

If all the above elements of the transport pathway mentioned previously were functionally perfect, the partial pressure of O_2 (and other gases) would be identical in the gas of all 500 million alveoli and equal to that in systemic arterial blood. The system comes close to perfection in health,[6] but there is never complete equivalence of alveolar and arterial pressures, even in healthy young, normal people. Aging further leads to a progressive impairment of the pathway, with arterial P_{O_2} falling from 95 to 100 mm Hg at age 20 to 75 to 80 mm Hg at age 80 or thereabouts.[7] However, alveolar P_{O_2} tends to be invariant with age. Thus, the difference between alveolar and arterial P_{O_2} steadily increases from about 5 to 10 mm Hg to about 20 to 25 mm Hg over this age range. Pulmonary diseases such as asthma, emphysema and bronchitis, fibrosis, pneumonia, and many others can greatly disrupt gas transport to the point of causing death from insufficient tissue O_2 supply.

Consequently, it is essential to have a good understanding of the O_2 transport pathway and what may affect it even in health, in order to appreciate the problems seen in pulmonary diseases.

A traditional view of how to consider abnormalities of the transport pathway has evolved over the years and is very useful as a framework for discussion. It is based upon the end result of gas exchange—the arterial P_{O_2}—and there are different reasons why this variable can fall below normal values.

Four principal potential mechanisms of failure of the O_2 transport pathway can lead to a reduced arterial P_{O_2} (i.e., to arterial hypoxemia): (1) hypoventilation, (2) diffusion limitation, (3) shunt, and (4) ventilation–perfusion ($\dot{V}_A/\dot{Q}$) inequality. These are the so-called "intrapulmonary" factors that directly cause hypoxemia. Modulating "extrapulmonary" factors also are important. These include changes in inspired O_2 concentration, in total cardiac output, in overall metabolic rate, and in Hb concentration. The four "intrapulmonary" factors are now defined and discussed.

Hypoventilation

Normal levels of ventilation produce a tightly regulated arterial P_{CO_2} at 40 ± 2 mm Hg in normal subjects with several control systems in place to ensure this (for details, see Chapter 11). However, if overall ventilation is reduced for any reason, alveolar P_{CO_2} ($P_{A_{CO_2}}$), and therefore arterial P_{CO_2}, must rise to maintain constant the elimination of metabolically produced CO_2. Reciprocally, alveolar P_{O_2} ($P_{A_{O_2}}$), and hence arterial P_{O_2}, will fall (and by relatively similar amounts as P_{CO_2} will rise). The alveolar gas equation[8] quantitatively relates $P_{A_{O_2}}$ and $P_{A_{CO_2}}$, and is used to calculate how much $P_{A_{O_2}}$ will change for a change in $P_{A_{CO_2}}$:

$$P_{A_{O_2}} = P_{I_{O_2}} - \frac{Pa_{CO_2}}{R} + P_{A_{CO_2}} \cdot F_{I_{O_2}} \cdot \frac{(1 - R)}{R} \tag{1}$$

$P_{I_{O_2}}$ and $F_{I_{O_2}}$ are inspired O_2 partial pressure and fractional concentration, respectively, and R is the respiratory exchange ratio, normally 0.8.

Hypoventilation represents a failure of step 1 of the gas transport pathway (see above) and can occur for several reasons: (1) the control centers in the nervous system that regulate ventilation could malfunction due to trauma, diseases, drugs, or anesthetics; (2) there could be neuronal or neuromuscular dysfunction of the nerves supplying the chest wall muscles of respiration; (3) the chest wall muscles could be fatigued, damaged, or paralyzed; or (4) the airways or chest wall could be disrupted from trauma or other mechanical derangement such as compression, or in the case of airways, obstruction.

Conceptually this type of problem is usually thought of as a whole-lung issue, usually with obvious causes, and can be reversed by recognizing the cause and taking appropriate reparative and/or ventilatory supportive steps.

Diffusion Limitation

Whereas diffusive transport plays a recognizable, if small, role within the airways and alveolar gas (see above), the concept of diffusive limitation affecting arterial P_{O_2} is more usually associated with transport step 6—diffusion of O_2 from alveolar gas into the capillary and red cell.

This topic is specifically the focus of Chapter 16 and is not dealt with here. Indeed, the ensuing discussion of other factors sets aside diffusion limitation of O_2 transport for the sake of simplicity and assumes that the diffusive exchange of O_2 (and CO_2) between alveolar gas and capillary blood proceeds to completion within a single red cell's passage through the pulmonary microcirculation. This is reasonable under most conditions. Diffusion limitation in health is seen at sea level in some but not all athletes,[9] but only at or near maximal exercise. It is universally seen in normal subjects exercising at altitude.[10,11]

Shunt

A shunt is a blood pathway that does not allow any contact between alveolar gas and red cells, so that no gas exchange occurs in the affected region. Consequently, blood passes through a shunt maintaining a mixed venous blood composition. When this blood reaches pulmonary veins, the left atrium, and eventually arterial blood, it mixes with other blood that has undergone alveolar gas exchange. The result is a fall in arterial P_{O_2} and potentially an increase in arterial P_{CO_2}. (Arterial P_{CO_2} may not increase if the patient raises his or her level of ventilation, but hypoxemia will persist.)

Classic pathophysiologic scenarios giving rise to shunts are: (1) pulmonary edema, which fills alveoli with fluid, thereby abolishing their ventilation and any gas exchange; (2) alveolar filling with cellular and micro-organismal debris as in pneumonia, with the same result as in edema; (3) collapse of a region of lung due to pneumothorax, gas absorption distal to a fully obstructed airway, or external compression; (4) rarely, the presence of abnormal arteriovenous vascular channels in the lungs, that can occur in, for example, hepatic cirrhosis; and (5) direct right-to-left vascular communications at the level of the heart or great (extrapulmonary) blood vessels.

Ventilation–Perfusion ($\dot{V}_A/\dot{Q}$) Inequality

The exquisite and complex branching architecture of the airways and of the blood vessels makes the lungs very susceptible to the potential problem of nonuniform distribution of alveolar ventilation and of pulmonary blood flow. Whenever alveoli are ventilated at less than average rates, for example if their feeding airways become partially obstructed for any reason, the ratio of ventilation to blood flow ($\dot{V}_A/\dot{Q}$ ratio) will fall (assuming their blood flow does not fall similarly). In certain other conditions, lung regions may suffer a reduction in local blood flow rather than ventilation, so that the $\dot{V}_A/\dot{Q}$ ratio rises above the average value in those areas.

Whenever there is a range of $\dot{V}_A/\dot{Q}$ ratios in a lung such that the $\dot{V}_A/\dot{Q}$ ratio is not identical everywhere, it is said that $\dot{V}_A/\dot{Q}$ inequality exists. The pathologic cause of $\dot{V}_A/\dot{Q}$ inequality does not matter in this definition, nor whether the problem originates in the airways or blood vessels. The principal concept is that, compared with a lung having the same total alveolar ventilation and blood flow, a lung that has $\dot{V}_A/\dot{Q}$ inequality will exchange (all) gases in an inefficient manner.[12] The result is hypoxemia and, potentially, hypercapnia (raised arterial P_{CO_2}). A large section of this chapter presents the physiologic reasons for this effect of $\dot{V}_A/\dot{Q}$ inequality.

Understanding of $\dot{V}_A/\dot{Q}$ inequality can be demanding, but no matter what its pathologic origins, the concepts are similar. $\dot{V}_A/\dot{Q}$ inequality can occur at many different scales. Not uncommonly, it can manifest on a large scale as differences between the right and left lungs. Classic examples of this include unilateral atelectasis, pneumothorax, pulmonary embolus, or pneumonia. All these are relatively common phenomena that can lead to severe gas exchange disturbances. At the other end of the scale, there can be $\dot{V}_A/\dot{Q}$ ratio differences between essentially adjacent alveoli. However, research has shown that small groups of contiguous alveoli can maintain functional homogeneity of $\dot{V}_A/\dot{Q}$ ratios via rapid gas diffusion rates, possibly augmented by collateral ventilation and/or blood flow.[13] It is likely that all alveoli distal to individual respiratory (or perhaps terminal) bronchioles can retain functional homogeneity for gas exchange through these mechanisms.[14]

In between these two extremes of scale, vascular or airway obstruction at all levels will produce $\dot{V}_A/\dot{Q}$ inequality that, depending on how widespread it is, causes hypoxemia and potentially hypercapnia.

Even the young normal lung usually contains $\dot{V}_A/\dot{Q}$ inequality, which explains the 5– to 10–mm Hg P_{O_2} difference between alveolar gas and arterial blood generally observed in healthy young subjects.[15] There are several mechanisms for the existence of such $\dot{V}_A/\dot{Q}$ inequality.

Gravity-Based Inequality

Ventilation, and, even more so, blood flow are unevenly distributed in a manner systematically influenced by gravity.[6,16] This is due respectively to the weight of the lungs and of the blood in the blood vessels. Thus, dependent lung regions receive far more blood flow than nondependent regions, a finding that is in concept independent of body position. It turns out that the gravitational gradient in blood flow considerably exceeds that of ventilation. As a result, the nondependent lung regions are of higher than average $\dot{V}_A/\dot{Q}$ ratio, and the dependent regions are of lower than average $\dot{V}_A/\dot{Q}$ ratio.[6] Average $\dot{V}_A/\dot{Q}$ ratio is about 1.0, because total alveolar ventilation and blood flow are similar. At the apex of the upright human lung, the $\dot{V}_A/\dot{Q}$ ratio is about 3; at the base it is about 0.6, 5-fold lower. There is a smooth gradation between the two extremes as depicted in Fig. 14-4. This large-scale apex-to-base gradient in $\dot{V}_A/\dot{Q}$ ratios does not produce more than about a 4 mm Hg drop in arterial P_{O_2} (compared with expectations in the absence of this phenomenon), and thus a 4 mm Hg alveolar–arterial P_{O_2} difference.[6]

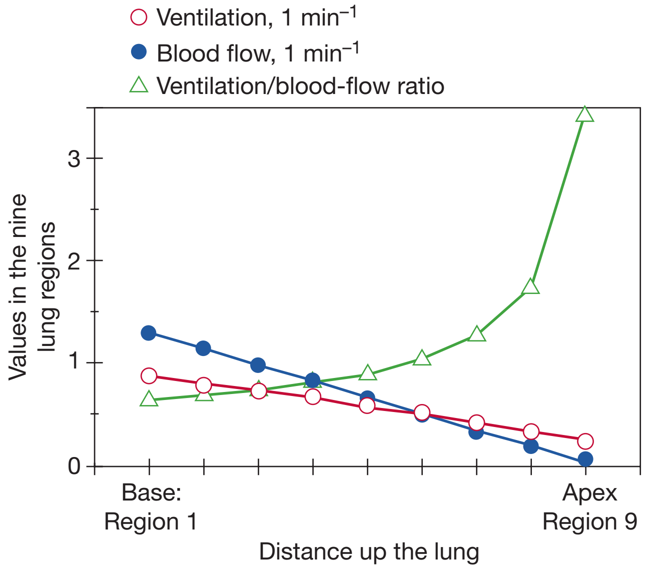

Figure 14-4 Topographic relationships between ventilation and blood flow as a function of distance up and down the upright lung (divided into nine contiguous regions). Although both ventilation and blood flow are higher at the base than at the apex, the ventilation–perfusion ratio ($\dot{V}_A/\dot{Q}$) rises exponentially from the bottom to the top of the lung. *(Adapted with permission from West JB. Ventilation/blood flow and gas exchange, 5th ed. Chicago, IL. Blackwell Scientific Publications; 1990.)*

Fractally Based $\dot{V}_A/\dot{Q}$ Inequality

The branching airway and blood vessel structure of the lung constitutes a fractal system that is innately susceptible to $\dot{V}_A/\dot{Q}$ inequality independent of gravity.[17] A fractal system is one in which the geometric pattern (e.g., of airway branching) is repeated at ever smaller scales. In the case of the airway tree it means in essence that the division of an airway into two "daughter" branches is a repeating feature from the large to the small airways. With some 23 sequential orders of branching, very small random inequalities in gas or blood flow distribution repeated at each branch point of the system can rapidly escalate into very significant degrees of nonuniform ventilation or blood flow. To illustrate, consider a branching system of just 16 dichotomous sequences—at each of the 16 branch points, air is not precisely split 50/50 between each daughter pair. Rather, suppose a 49%/51% split—a nonuniform effect of trivial proportions at any one airway branch. The most poorly ventilated regions (receiving 49% of the split at every one of the 16 branchings) end up with only about half as much ventilation as the best-ventilated regions that receive 51% of the split at each branch.

Unless the fractal structure somehow distributes both ventilation and blood flow in a correlated manner to preserve $\dot{V}_A/\dot{Q}$ ratios (even as $\dot{V}_A$ or $\dot{Q}$ individually vary), significant hypoxemia could result. Understanding the consequences of the fractal nature of the lung is a topic of much current interest. It appears that there must be correlation of $\dot{V}_A$ with $\dot{Q}$ since the large potential for fractally based hypoxemia is not generally realized.

Longitudinally Based Inequality

As airways and blood vessels progressively narrow with each branch point, resistance to gas and blood flow increases. Not all alveoli receive gas or blood from airways that have gone through the exact same number of branchings. Hence, some alveoli will be more, and some will be less, distant from the mouth. Such simple principles suggest the possibility of reduced $\dot{V}_A$ and/or $\dot{Q}$ of those alveoli further from the mouth compared to more proximal alveoli, and therefore the chance of a central to peripheral, or longitudinal, gradient in ventilation and blood flow. Although not universally observed, there is a fair amount of evidence that such inequality exists,[18] but its contribution to gas exchange is hard to establish. To the extent that similar physical principles apply to both gas and blood flow in the present context, one can theorize that more distant alveoli have both less ventilation and blood flow, so that again there is a natural tendency to preserve the $\dot{V}_A/\dot{Q}$ ratio between central and peripheral regions.

Anatomically Based Inequality

Another potential reason for nonuniform gas or blood flow distribution is intrinsic anatomic differences between lung regions. Perhaps the best example is in the dog and horse where, independent of body position in relation to gravity, the dorsal regions of the lower lobes often can be shown to have an unduly high share of total pulmonary perfusion. This tendency, presumably based on the overall branching architectural differences between lobes or within lobes, becomes important in concept when patients are moved from one body position to another, in order to best understand consequent changes in gas exchange.[19]

■ Collateral Ventilation and Blood Flow

To this point, a picture has been painted of a branching architecture that has no lateral connections between either adjacent airways or blood vessels at any level of branching. Such lateral connections can exist at several airway levels from large airways down to alveoli.[13,20] This is a species-dependent phenomenon, so that while the pig has little or no such collateral pathway structures, the dog has extensive collateral ventilatory channels. Humans are somewhere between these extremes.

Whatever the evolutionary pressure for collateral channel development, the ability to move gas around obstructions in airways by the use of collateral channels appears to be a useful property of human lungs. This is because total airway obstruction in the absence of collateral channels often leads to rapid alveolar gas absorption into the blood from the alveoli distal to the obstructed airway, and this in turn leads to atelectasis and therefore vascular shunts and hypoxemia. Remarkably, chronic human lung diseases typified by airway obstruction—chronic obstructive pulmonary disease (COPD), asthma—produce $\dot{V}_A/\dot{Q}$ inequality due to presence of poorly ventilated areas, but only uncommonly lead to true shunts.[21,22] The likely explanation for the paucity of shunts in COPD and asthma is the existence of collateral ventilation.

Collateral ventilation in humans therefore appears to be a naturally occurring structural phenomenon that can to some extent counteract the gas exchange consequences of diseases.

Collateral perfusion must also occur in the alveolar capillary network. This is deduced simply from the richly interconnecting microvascular network that has the potential to allow blood to flow easily around microvascular obstructions into adjacent vessels. Just how much collateral blood flow potential exists at a larger scale is not clear, being difficult to study. However, well-documented connections occur between the bronchial and pulmonary circulations,[23] creating a different kind of collateral circulatory network. The importance of this connection is evident when the pulmonary artery is either absent or embolized. Then, the bronchial circulation expands considerably and can support function of the affected lung regions long term.

■ Reactive Vasoconstriction and Bronchoconstriction

The distribution of ventilation or blood flow in the lung can be modified by vasoreactive or bronchoreactive functional changes that appear triggered by changes in alveolar gas composition. The most well-documented phenomenon is that of hypoxic pulmonary vasoconstriction.[24,25] Here, in response to local alveolar hypoxia produced by locally reduced ventilation, local pulmonary arterial constriction reduces blood flow in the hypoxic region. Whether this system developed to counteract disease or to cope with intrauterine life and the abrupt transition to air-breathing is arguable, although most people favor the latter explanation.

Irrespective of the reasons, the effect of hypoxic vasoconstriction is to help return the local ratio of ventilation to blood flow towards normal. This automatic effect (mediated by O_2-sensitive potassium channels in pulmonary arterial smooth muscle cells) is rarely able to fully restore $\dot{V}_A/\dot{Q}$ ratios to normal, but even partial improvements in $\dot{V}_A/\dot{Q}$ ratio facilitate gas exchange significantly. The negative aspect of hypoxic vasoconstriction is a rise in pulmonary vascular resistance. If this is substantial and protracted over time, pulmonary arterial hypertension can develop, eventually leading to right heart failure. However, factors other than hypoxic vasoconstriction are then also generally present—microvascular destruction and alveolar distortion—and these may be more important to heart failure than hypoxia per se. However, hypoxic vasoconstriction has provided a rationale for enriched O_2 therapy in patients with chronic disease to reduce the severity, or to delay the progression, of pulmonary hypertension.

To a much less obvious extent, a counterpart to hypoxic vasoconstriction occurs in the airways: hypocapnic bronchoconstriction.[26] Here, especially when pulmonary embolism occurs, the $\dot{V}_A/\dot{Q}$ ratio in the embolized area rises due to loss of blood flow from vascular obstruction. This increase in $\dot{V}_A/\dot{Q}$ ratio leads to a lower local P_{CO_2} (see below), which causes bronchoconstriction in the local area. This reduces local ventilation and thus tends to normalize the local $\dot{V}_A/\dot{Q}$ ratio. Radioactive tracer ventilation scans may show evidence of this as a modest reduction in the ventilation of embolized regions.

THE $\dot{V}_A/\dot{Q}$ RATIO AND GAS EXCHANGE

To this point, much space has been given to the concepts underlying the distribution of ventilation ($\dot{V}_A$), blood flow ($\dot{Q}$), and hence their ratio, $\dot{V}_A/\dot{Q}$. The reason for this lies in the importance of $\dot{V}_A/\dot{Q}$ ratios to the basic function of the lung—to exchange O_2 and CO_2 between the blood and the air. $\dot{V}_A/\dot{Q}$ inequality, no matter what its physiologic basis or pathologic cause, interferes with gas exchange and causes hypoxemia and sometimes hypercapnia.

The following section will explain the relationship of $\dot{V}_A/\dot{Q}$ inequality to gas exchange. The subject is complex and must be considered at several "concentric" levels. To start, we will consider how the $\dot{V}_A/\dot{Q}$ ratio in a small local lung region controls local P_{O_2} and P_{CO_2}, and therefore how much O_2 and CO_2 are exchanged in that region. This isolated approach requires at first some key assumptions. Removing the restrictions of these assumptions is the next "concentric" step in understanding $\dot{V}_A/\dot{Q}$ relationships. A final outer shell of modifying factors that can further affect gas exchange forms a third level of the analysis.

■ The $\dot{V}_A/\dot{Q}$ Ratio of a Small Homogeneous Unit of Lung and Gas Exchange

How the $\dot{V}_A/\dot{Q}$ ratio determines gas exchange is best explained by considering the flux of O_2 from the environment into and out of the alveolus with each breath as well as from the alveolar gas into the capillary blood. Equations that describe these processes and follow the fundamental principle of mass conservation must be used. Original descriptions of these appeared more than 70 years ago.[8,27–30] Figure 14-5 provides a model of the lung and specifies the total ventilation ($\dot{V}_A$) and blood flow ($\dot{Q}$) of this model together with the key locations of the relevant O_2 levels. It can be used to consider a small homogeneous unit of lung.

Convention has long considered ventilation over a period of time as a constant in spite of the tidal nature of breathing. This is in fact a very reasonable approximation that has stood the test of time. Similarly, blood flow is considered constant, and this too has proved reasonable. If $\dot{V}_A$ and $\dot{Q}$ are therefore considered as alveolar minute ventilation and blood flow of a small homogeneous unit respectively, the following simple mass conservation equations can be written for O_2:

$$\dot{V}_{O_2} = \dot{V}_I \cdot F_{I_{O_2}} - V_A \cdot F_{A_{O_2}} \qquad (2)$$

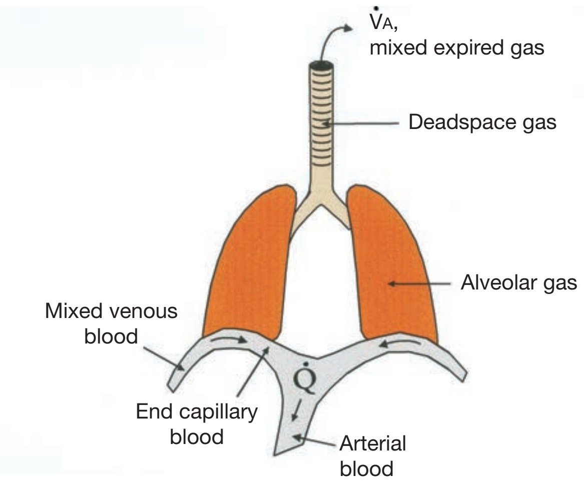

Figure 14-5 Conceptual model of the lungs indicating main sites in which oxygen and carbon dioxide partial pressures are different, together with the principal convective processes accomplishing gas exchange, ventilation ($\dot{V}_A$), and blood flow ($\dot{Q}$).

and

$$\dot{V}_{O_2} = Q \cdot Cc'_{O_2} - \dot{Q} \cdot C\bar{v}_{O_2} \qquad (3)$$

In these equations, $\dot{V}_{O_2}$ is amount of O_2 transferred from the environment into the blood per unit time and, given the assumption of steady state conditions, this, when summed over all such units in the lungs, equals metabolic rate. $\dot{V}\mathrm{I}$ and $\dot{V}\mathrm{A}$ are, respectively, the inspired and expired volumes of gas respired per minute, less the amount remaining in the conducting airways. As anticipated, $\dot{V}\mathrm{I}$ and $\dot{V}\mathrm{A}$ are close to being identical, otherwise the lungs would blow up or collapse in a short period of time. However, $\dot{V}\mathrm{I}$ does not generally equal $\dot{V}\mathrm{A}$ because slightly more O_2 is consumed per minute than is CO_2 produced (i.e., the respiratory quotient is in general not 1.0). Thus, $\dot{V}\mathrm{A} = \dot{V}\mathrm{I} - \dot{V}O_2 + \dot{V}_{CO_2}$. Mostly, the inequality of $\dot{V}\mathrm{I}$ and $\dot{V}\mathrm{A}$ can be ignored because the difference is only about 1%—if $\dot{V}\mathrm{I}$ is 6 L/min and $\dot{V}O_2$ is 300 mL/min with $\dot{V}_{CO_2}$ at 240 mL/min, $\dot{V}\mathrm{A} = 5.94$ L/min. Although this small difference is not ignored in research applications, it can be for the present purposes, so that $\dot{V}\mathrm{I}$ is replaced by $\dot{V}\mathrm{A}$ in Equation (2), simplifying the analysis. In Equation (2), $F\mathrm{I}_{O_2}$ and $F\mathrm{A}_{O_2}$ are the fractional concentrations (F) of O_2 in inspired (I) and exhaled alveolar (A) gas, respectively, from a small unit in Fig. 14-5. In Equation (3), Cc'_{O_2} and $C\bar{v}_{O_2}$ are the O_2 concentrations (C) in the oxygenated end capillary blood leaving (c′) and the deoxygenated blood entering ($\bar{v}$) the vasculature respectively. The abbreviation c′ stands for end capillary blood, and $\bar{v}$ for mixed venous (pulmonary arterial) blood.

Since Equations (2) and (3) both describe the same O_2 flux rate ($\dot{V}O_2$) they may be set equal to each other:

$$\dot{V}\mathrm{A}\,[F\mathrm{I}_{O_2} - F\mathrm{A}_{O_2}] = \dot{Q}\,[Cc'_{O_2} - C\bar{v}_{O_2}] \qquad (4)$$

and rearranged so that:

$$\dot{V}\mathrm{A}/\dot{Q} = [Cc'_{O_2} - C\bar{v}_{O_2}]/[F\mathrm{I}_{O_2} - \mathrm{A}_{O_2}] \qquad (5)$$

It should further be noted that because diffusion equilibration of O_2 transfer across the alveolar–capillary membrane is assumed to be complete, alveolar P_{O_2} and end capillary P_{O_2} are identical. Hence, the relationship between $F\mathrm{A}_{O_2}$ and Cc'_{O_2} is uniquely dictated by the O_2-Hb dissociation curve such that knowing $F\mathrm{A}_{O_2}$ allows us to determine directly Cc'_{O_2} (or vice versa).

Equation (5) is very revealing and explains directly the role of the $\dot{V}\mathrm{A}/\dot{Q}$ ratio in governing alveolar gas exchange. This equation states that for a given set of what may be called boundary conditions (i.e., composition of inspired gas and mixed venous blood, represented here by $F\mathrm{I}_{O_2}$ and $C\bar{v}_{O_2}$, respectively) and for a known O_2–Hb dissociation curve, alveolar (and thus end capillary) P_{O_2} is uniquely determined by the ratio of alveolar ventilation ($\dot{V}\mathrm{A}$) to blood flow ($\dot{Q}$).

Under the given assumptions, summarized as (1) continuous and constant ventilation and blood flow; (2) steady state conditions; (3) diffusion equilibration of alveolar–capillary exchange; and (4) equality of inspired and expired ventilation, equations identical in construct to Equation (5) can be written for any gas being exchanged by the lung.

For CO_2, this produces Equation (6):

$$\dot{V}\mathrm{A}/\dot{Q} = [C\bar{v}_{CO_2} - Cc'_{CO_2}]/[F\mathrm{A}_{CO_2} - F\mathrm{I}_{CO_2}] \qquad (6)$$

The order of bracketed terms on the right is reversed to maintain positive numbers, since CO_2 is being eliminated from the blood. Of course, $F\mathrm{I}_{CO_2}$ is essentially zero and thus drops out of the equation.

Unfortunately, neither Equation (5) nor (6) is amenable to simple quantitative solutions, because of the complexity of the O_2 and CO_2 dissociation curves. The equations are however readily explored by appropriate computerized numerical analyses.[31–35] Using such programs, one can explore the relationship between $\dot{V}\mathrm{A}/\dot{Q}$ ratio and alveolar P_{O_2} and P_{CO_2}, and this is done in Fig. 14-6. These relationships are important because they indicate what degrees of $\dot{V}\mathrm{A}/\dot{Q}$ abnormality are required to affect gas exchange for both O_2 and CO_2. The four panels of Fig. 14-6 show alveolar P_{O_2} and P_{CO_2} as well as end capillary O_2 and CO_2 concentrations. The latter better reflect total gas exchange as a function of $\dot{V}\mathrm{A}/\dot{Q}$ ratio. Specific conditions for Fig. 14-6 are that mixed venous blood P_{O_2} is 40 mm Hg and P_{CO_2} 45 mm Hg, normal resting values. Also, inspired gas is room air, and [Hb] is 15 g/dL. In each panel, the three solid circles are positioned at the normal $\dot{V}\mathrm{A}/\dot{Q}$ ratio (of about 1.0) and at $\dot{V}\mathrm{A}/\dot{Q}$ ratios 10 times greater and less. All four relationships are highly nonlinear. Focusing on the two lower panels, it is evident for O_2 that a 10-fold reduction in $\dot{V}\mathrm{A}/\dot{Q}$ greatly reduces local O_2 transport, whereas a 10-fold increase barely improves it. Furthermore, as $\dot{V}\mathrm{A}/\dot{Q}$ falls even lower than 0.1, there is little further loss in O_2 transport. There is however little protection against a fall in $\dot{V}\mathrm{A}/\dot{Q}$ below 1.0, because the curve is very steep below a $\dot{V}\mathrm{A}/\dot{Q}$ of 1.0, as the lower left panel shows. For CO_2, the curves are opposite in slope (P_{CO_2} falls as $\dot{V}\mathrm{A}/\dot{Q}$ increases). However, unlike the case for O_2, there is little difference between a $\dot{V}\mathrm{A}/\dot{Q}$ of 1.0 and a 10-fold reduction, whereas an increase in $\dot{V}\mathrm{A}/\dot{Q}$ considerably reduces alveolar P_{CO_2} and end capillary CO_2 concentration. The reason for the differences between O_2 and CO_2 lies mainly in the slopes of their dissociation curves: that for CO_2 is about 10-fold greater than that for O_2. It has been shown that the higher the slope of the dissociation curve (or equivalently for an anesthetic gas, its solubility) the more it is sensitive to areas of high $\dot{V}\mathrm{A}/\dot{Q}$. The lower the slope or solubility, the more the gas is affected by areas of low $\dot{V}\mathrm{A}/\dot{Q}$. Consequently, areas of low $\dot{V}\mathrm{A}/\dot{Q}$ predictably cause more reduction in arterial P_{O_2} than increase in arterial P_{CO_2}. Although Fig. 14-6 is true strictly only for the stated "boundary" conditions (i.e., mixed venous blood and inspired gas

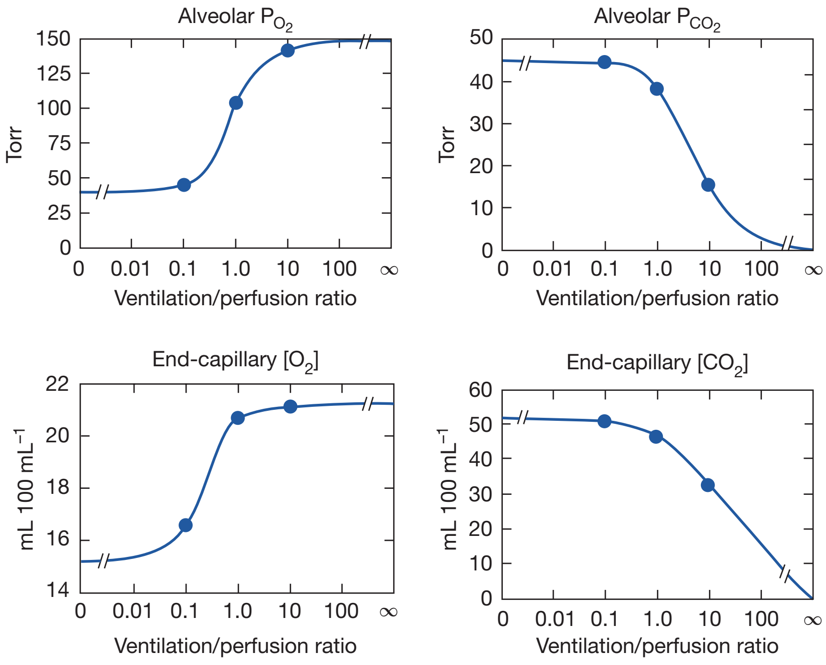

Figure 14-6 Calculated relationships between alveolar P_{O_2} and P_{CO_2} and the ventilation–perfusion ratio (*top panels*) and their corresponding end-capillary blood concentrations (*lower panels*). The three solid circles in each case represent values for ventilation–perfusion ratios of 0.1, 1.0, and 10. (See text for further details.)

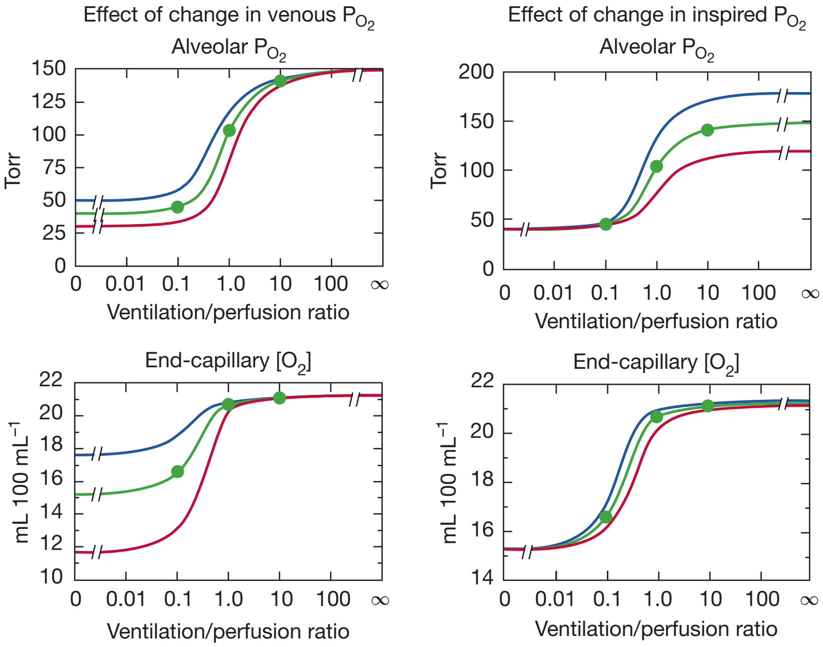

Figure 14-7 Effects of changes in mixed venous P_{O_2} (*left panels*) or inspired P_{O_2} (*right panels*) on alveolar P_{O_2} and associated end-capillary oxygen concentrations. Note that changes in venous P_{O_2} mostly affect values associated with low ventilation–perfusion ratios, whereas changes in inspired P_{O_2} affect units throughout the $\dot{V}_A/\dot{Q}$ range, especially those with medium to high $\dot{V}_A/\dot{Q}$ ratios.

composition), the principles hold even for different such conditions, as shown in Fig. 14-7 for O_2. The left panels illustrate how changes in mixed venous P_{O_2} alone will affect alveolar P_{O_2} and end capillary $[O_2]$ via Equation (4). The right panels correspondingly show how change in inspired P_{O_2} affects O_2. Venous P_{O_2} is selected at 30, 40, and 50 mm Hg, and inspired P_{O_2} is chosen to be 120, 150, and 180 mm Hg. Changes in venous P_{O_2} dramatically affect P_{O_2} and $[O_2]$ in unventilated and poorly ventilated regions as well as regions approaching normal but have no real effect on high $\dot{V}_A/\dot{Q}$ alveoli. Altering inspired P_{O_2} (but not venous) has the converse effect if P_{O_2} is examined (top right panel), but, due to the nonlinear shape of the O_2–Hb dissociation curve, effects on $[O_2]$ are minimal in high $\dot{V}_A/\dot{Q}$ areas, small in very low $\dot{V}_A/\dot{Q}$ areas, and more significant between $\dot{V}_A/\dot{Q}$ ratios of 0.1 and 1.0 (bottom right panel). This figure shows how the inspired and mixed venous "boundary conditions" alter the magnitude (but not basic patterns) of alveolar gas exchange.

If one returns to the normal boundary conditions ($P\bar{v}_{O_2} = 40$ mm Hg, $PI_{O_2} = 150$ mm Hg), one can explore the consequences of $\dot{V}_A/\dot{Q}$ inequality on gas exchange. In reality, the complex structure of the lungs defies a simple analysis but conceptually even a two-compartment model is an invaluable aid to understanding this conceptually difficult area.

Figure 14-8 shows such a simple two-compartment model in three configurations: (1) each compartment equally ventilated and perfused such that there is no $\dot{V}_A/\dot{Q}$ inequality; (2) the left compartment hypoventilated due to airway obstruction, causing $\dot{V}_A/\dot{Q}$ inequality; and (3) the left compartment hypoperfused from vascular obstruction. Table 14-1 shows the corresponding O_2 and CO_2 calculations for each compartment. Specific assumptions common to all three models are the mixed venous P_{O_2} remains at 40 mm Hg; inspired P_{O_2} is constant at 150 mm Hg; total alveolar ventilation summed over both compartments is constant as is total blood flow, both taken to be 6 L/min; [Hb] is constant at 15 g/dL. Further, airway obstruction reduces L-hand compartmental ventilation from 3.0 to 0.3 L/min, redistributing the balance to the R-hand compartment. Vascular obstruction is of the same order as the right panel of the figure shows. Note that for both obstructive models, one compartment has developed a $\dot{V}_A/\dot{Q}$ ratio less than average and the other a $\dot{V}_A/\dot{Q}$ ratio greater than average, irrespective of the location of the obstruction.

Using the curves of Fig. 14-6, for $P\bar{v}_{O_2} = 40$ mm Hg and $PI_{O_2} = 150$ mm Hg, $P\bar{v}_{CO_2} = 45$ mm Hg and $PI_{CO_2} = 0$ mm Hg, alveolar P_{O_2} and P_{CO_2} are listed for each compartment of Fig. 14-8 in Table 14-1.

In Table 14-1, alveolar diffusion equilibration is assumed to be complete such that alveolar P_{O_2} (PA_{O_2}) equals end capillary P_{O_2} (Pc'_{O_2}); the same holds for P_{CO_2}. In each obstructive model, the low $\dot{V}_A/\dot{Q}$ compartment has a lower-than-average P_{O_2} and higher-than-average P_{CO_2} as Fig. 14-6 dictates. The converse is seen for the compartment of high $\dot{V}_A/\dot{Q}$ ratio. Corresponding end capillary O_2 and CO_2 concentrations also are listed in Table 14-1.

The question is what will the mixed arterial blood and mixed expired gas O_2 and CO_2 levels change to as a result of obstruction of one compartment, and how will this affect the ability of the total system to exchange O_2 and CO_2? To answer these questions, one applies

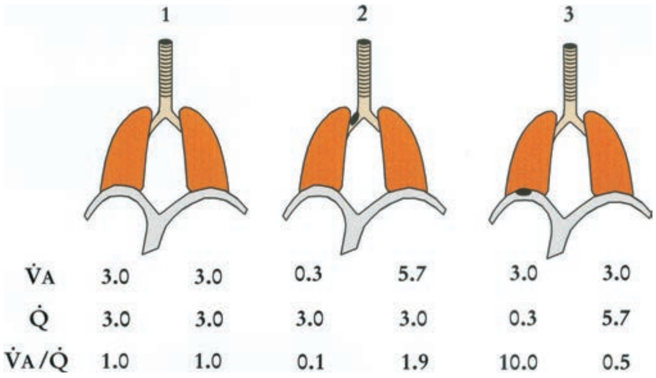
1
2
3
$\dot{V}_A$ 3.0 3.0 0.3 5.7 3.0 3.0
$\dot{Q}$ 3.0 3.0 3.0 3.0 0.3 5.7
$\dot{V}_A/\dot{Q}$ 1.0 1.0 0.1 1.9 10.0 0.5

Figure 14-8 Three two-compartment models of ventilation–perfusion relationships. *Model 1* represents an ideal lung without ventilation–perfusion mismatch. *Model 2* represents a lung in which one compartment has a 90% reduction in its alveolar ventilation due to airway obstruction, and *Model 3* is a lung in which one compartment has a 90% reduction in capillary blood flow due to vascular obstruction. Ventilation, blood flow, and ventilation–perfusion ratio of each compartment are indicated. Total ventilation and total blood flow remain the same among the three models. (See text for further details.)

TABLE 14-1 O_2 and CO_2 Calculations for the Models of Figure 14-8

	Normal		Airway Obstruction Model		Vascular Obstruction Model	
	Left	Right	Left	Right	Left	Right
PA_{O_2}, Pc'_{O_2}, mm Hg	103.0	103.0	45.0	120.0	142.0	77.0
PA_{CO_2}, Pc'_{CO_2}, mm Hg	38.8	38.8	44.9	32.5	15.5	42.7
Cc'_{O_2}, $mL \cdot dL^{-1}$	20.7	20.7	16.7	20.9	21.1	20.1
Cc'_{CO_2}, $mL \cdot dL^{-1}$	46.9	46.9	50.8	43.9	32.5	48.8
Ca_{O_2}, $mL \cdot dL^{-1}$	20.7		18.8		20.1	
Ca_{CO_2}, $mL \cdot dL^{-1}$	46.9		47.5		48.0	
Pa_{O_2}, mm Hg	103.0		55.0		77.0	
Pa_{CO_2}, mm Hg	38.8		39.0		40.9	
$P\bar{A}_{O_2}$, P_{O_2}, mm Hg	103.0		118.0		110.0	
$P\bar{A}_{CO_2}$, P_{CO_2}, mm Hg	38.8		33.7		29.2	
Total O_2 exchange, $mL \cdot min^{-1}$	328.0		212 (65%)		294 (90%)	
Total CO_2 exchange, $mL \cdot min^{-1}$	270.0		234 (87%)		203 (75%)	
$P\bar{A}_{O_2}'-PA_{O_2}$, mm Hg	0.0		63.0		33.0	
$PA_{CO_2}-P\bar{A}_{CO_2}$, mm Hg	0.0		5.0		11.7	

simple mixing questions to the two individual compartments (left [L] and right [R]):

For O_2:

$$P\bar{A}_{O_2} = (PA_{O_{2L}} \cdot \dot{V}A_L + PA_{O_{2R}} \cdot \dot{V}A_R)/(\dot{V}A_L + \dot{V}A_R)$$

$$Ca_{O_2} = (Cc'_{O_{2L}} \cdot \dot{Q}_L + Cc'_{O_{2R}} \cdot \dot{Q}_R)/(\dot{Q}_L + \dot{Q}_R) \qquad (7)$$

For CO_2, identical equations apply. These mixing equations conserve mass and use the principle that the two gas or blood streams combine in a manner proportional to their relative ventilation and blood flow, respectively. Table 14-1 lists the results of these calculations, giving mixed alveolar partial pressure ($P\bar{A}_{O_2}$, $P\bar{A}_{CO_2}$) and mixed arterial concentrations (Ca_{O_2}, Ca_{CO_2}). From the blood–gas concentration, corresponding arterial partial pressures (Pa_{O_2}, Pa_{CO_2}) are read directly off the O_2 and CO_2 dissociation curves. Finally, whole-lung computations of O_2 and CO_2 exchange rates (mL/min) are determined using either Equation (2) or (3) and the mixed alveolar or arterial data respectively, and the mixed alveolar to arterial partial pressure differences expressed for each gas.

The results are very instructive. Both obstructive models result in hypoxemia and slight hypercapnia, but the effects on arterial P_{O_2} and on the alveolar–arterial P_{O_2} difference greatly exceed those for CO_2 due to both shape and slope differences between the dissociation curves of the two gases. Airway obstruction produces more hypoxemia but *less* hypercapnia than the identical degree of vascular obstruction. This reflects the 10-fold greater dissociation curve slope of CO_2 compared to O_2, rendering O_2 relatively more susceptible to the lower $\dot{V}A/\dot{Q}$ areas seen in the airway obstruction model (0.1 vs. 0.5) (Fig. 14-8) and CO_2 relatively more susceptible to the higher $\dot{V}A/\dot{Q}$ areas of vascular obstruction (10.0 vs. 1.9) (Fig. 14-8) as Fig. 14-6 would predict.

Both models have impaired overall O_2 and CO_2 exchange (recall that venous blood, inspired gas, total ventilation, and blood flow were all considered fixed and identical for all three models) as a result of the development of $\dot{V}A/\dot{Q}$ mismatch. In keeping with the differential sensitivity of O_2 and CO_2 to regions of low and high $\dot{V}A/\dot{Q}$ discussed earlier, total O_2 transport is diminished to a greater extent in the airway obstruction model than in the vascular obstruction model (Table 14-1). The converse is true for CO_2, also shown in Table 14-1.

The principal effects of $\dot{V}A/\dot{Q}$ inequality as they apply to O_2 and CO_2 exchange may thus be listed.

$\dot{V}A/\dot{Q}$ inequality:

a. Affects both gases, no matter what the pathologic basis of the inequality.
b. Causes arterial hypoxemia and hypercapnia.
c. Causes usually more severe hypoxemia than hypercapnia.
d. Affects O_2 more than CO_2 when very low $\dot{V}A/\dot{Q}$ regions develop.
e. Affects CO_2 more than O_2 when very high $\dot{V}A/\dot{Q}$ regions develop.
f. Impairs total O_2 and CO_2 exchange by the lung.
g. Creates alveolar–arterial differences for both gases.

COMPENSATION FOR THE EFFECTS OF $\dot{V}A/\dot{Q}$ MISMATCH

The preceding analysis shows that if no changes in total ventilation, blood flow, mixed venous blood, or inspired gas composition occur, O_2 and CO_2 transfer across the lung is compromised. This is not viable in the steady state: the lungs must find a way to restore total O_2 and CO_2 transfer to levels equal to metabolic use of O_2 and production of CO_2. This leads to the next concentric level of consideration of $\dot{V}A/\dot{Q}$ inequality referred to at the start of this section.

Here we ask what compensatory mechanisms exist to achieve restoration of O_2 and CO_2 transfer, assuming that the initial pathophysiologic insults have persisted unchanged. The same models as in Fig. 14-8 and Table 14-1 will be used.

■ Changes in Mixed Venous Blood

The only possible short-term compensatory changes are in mixed venous blood, total ventilation, and cardiac output. (Hb change in response to tissue hypoxia requires days to weeks to develop and then is by no means always observed; changing inspired P_{O_2} is not usually an option until the patient seeks medical attention.) To reduce complexity, changes in venous blood alone are first addressed.

If it is assumed that there is no limit to how much O_2 can be extracted from the arterial blood by the peripheral tissues, it is evident that $\dot{V}A/\dot{Q}$ inequality will passively lead to a reduced venous P_{O_2} and increased venous P_{CO_2}. This is deduced simply from the

TABLE 14-2 Gas Exchange Effects of Passive Changes in Mixed Venous Blood—Gas Values Required to Restore $\dot{V}O_2$ and $\dot{V}CO_2$ to Normal in the Models of Figure 14-8

	Airway Obstruction Model		Vascular Obstruction Model	
	Before Change	After Change	Before Change	After Change
$P\bar{v}_{O_2}$, mm Hg	40.0	30.4	40.0	39.5
$P\bar{v}_{CO_2}$, mm Hg	45.0	50.7	45.0	62.4
Pa_{O_2}, mm Hg	55	46	77	67
Pa_{CO_2}, mm Hg	39.0	44.5	40.9	55.6
$\dot{V}_{O_2}$, mL·min^{-1}	212.0	328 (normal)	294.0	328.0 (normal)
$\dot{V}_{CO_2}$, mL·min^{-1}	234.0	270 (normal)	203.0	270.0 (normal)

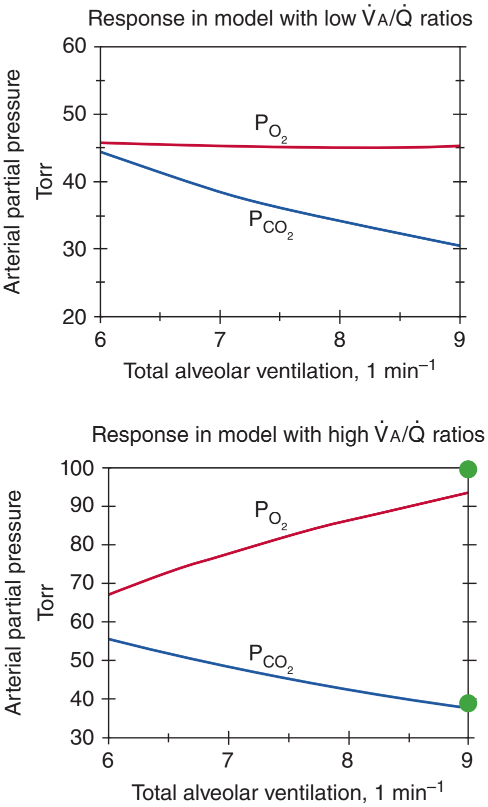

Figure 14-9 Effect of increasing alveolar ventilation on arterial P_{O_2} and P_{CO_2} in the two models with ventilation–perfusion inequalities in Figure 14-8. *Top panel* is that for Model 2 and *bottom panel* is that for Model 3. Increasing ventilation is ineffective in restoring arterial P_{O_2} in the low $\dot{V}\mathrm{A}/\dot{Q}$ Model 2, but much more effective in the high $\dot{V}\mathrm{A}/\dot{Q}$ Model 3. Both models respond in terms of P_{CO_2}.

hypoxemia and hypercapnia initially produced by the $\dot{V}\mathrm{A}/\dot{Q}$ insult, together with the need to extract the same amount of O_2 from (and add CO_2 to) each mL of blood perfusing the tissues as before the $\dot{V}\mathrm{A}/\dot{Q}$ insult developed.

If venous P_{O_2} falls (and P_{CO_2} rises), Fig. 14-7 indicates that alveolar P_{O_2} will fall in each $\dot{V}\mathrm{A}/\dot{Q}$ compartment (as will P_{CO_2} rise). Thus, a circle of events is set up such that if a single red cell were followed around the circulation, at each passage through the lungs and then tissues, P_{O_2} would fall progressively with each circuit of the body.

Although not intuitively obvious, this reduction in both arterial and venous P_{O_2} will not "bottom out" at zero (or in the case of CO_2 rise toward infinity) unless the $\dot{V}\mathrm{A}/\dot{Q}$ insult was fatally overwhelming in the first place. Both arterial and venous P_{O_2} will restabilize at new lower values (P_{CO_2} values will be higher) than were present immediately after the $\dot{V}\mathrm{A}/\dot{Q}$ insult developed. In so doing, $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ will have been restored to normal values.

To explore this quantitatively, we will continue on with the models of Fig. 14-8 and Table 14-1 to show just what changes in venous and arterial P_{O_2} and P_{CO_2} must occur as a result of this process in order to restore pulmonary O_2 and CO_2 exchange to normal. The values are shown in Table 14-2. For the airways obstruction model, the passive blood gas changes are greater for O_2 than CO_2, consonant with the greater initial decrement in O_2 exchange caused by airway obstruction in the first place. For the vascular obstruction model, the effects are more marked for CO_2, for corresponding reasons. To restore $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ in the airway obstruction model, hypoxemia is now more severe, but hypercapnia is mild. However, with vascular obstruction, hypoxemia remains mild while hypercapnia is severe. In both cases, the lung is meeting the original healthy requirement of transferring 328 and 270 mL/min of O_2 and CO_2, respectively.

The speed of passive venous blood composition changes is very rapid, taking place in seconds to minutes as the blood moves continuously around the vascular system between lungs and tissues. The principal effects of the changes can be summarized as follows:

a. Following development of $\dot{V}\mathrm{A}/\dot{Q}$ mismatch, and a fall in $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ at the lungs, mixed venous P_{O_2} will fall and mixed venous P_{CO_2} will rise to restore pulmonary $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ to equal the original metabolic requirements for O_2 and CO_2 transport.
b. As a result, there will always be a further fall in arterial P_{O2} and rise in arterial P_{CO_2}, compared to conditions prior to mixed venous blood changes.
c. When the $\dot{V}\mathrm{A}/\dot{Q}$ insult primarily involves development of extremely low $\dot{V}\mathrm{A}/\dot{Q}$ areas, those effects are more marked for O_2 than for CO_2.
d. When the $\dot{V}\mathrm{A}/\dot{Q}$ insult primarily consists of high $\dot{V}\mathrm{A}/\dot{Q}$ areas, CO_2 is affected more than O_2.

■ Changes in Total Ventilation

When either low or high $\dot{V}\mathrm{A}/\dot{Q}$ areas develop and the mixed venous and arterial adjustments occur as described earlier, there is hypoxemia and hypercapnia. Either or both may well stimulate an immediate increase in total ventilation,[36] which will alleviate to some extent both the hypoxemia and hypercapnia. Figure 14-9 shows for the same two examples used earlier how increases in alveolar ventilation (distributed in the same proportions as in each of the two $\dot{V}\mathrm{A}/\dot{Q}$ models of Fig. 14-8) variably improve arterial P_{O_2} and P_{CO_2}. In the low $\dot{V}\mathrm{A}/\dot{Q}$ (airways obstruction) model, a 50% increase in total alveolar ventilation from the normal value of 6 to 9 L/min drops arterial P_{CO_2} to almost 30 mm Hg, well below the normal standard value of 40 mm Hg. Arterial P_{O_2}, however, is not affected at all. This is because even a 50% increase in ventilation of the very poorly ventilated unit fails to significantly increase end capillary P_{O_2} of that unit (Fig. 14-6), whereas in the better ventilated unit of that model, Hb in the end capillary blood was already virtually fully saturated before the increase in ventilation.

For the model with vascular obstruction, a 50% increase in alveolar ventilation returns both P_{O_2} and P_{CO_2} to near-normal values (Fig. 14-9, lower panel). The difference in the two model responses

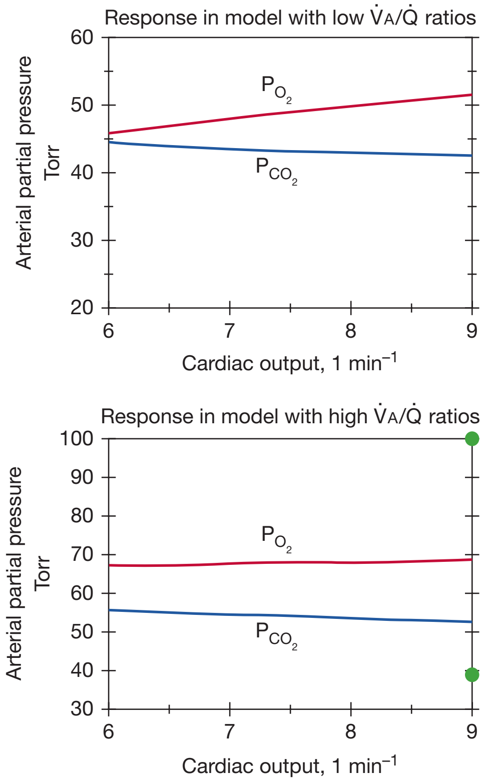

Figure 14-10 Effects of increases in cardiac output on arterial P_{O_2} and P_{CO_2} in Models 2 and 3 of Fig. 14-8. Cardiac output produces a significant rise in P_{O_2} in the presence of regions of very low ventilation–perfusion ratio (*top panel*) but has little influence in the presence of higher ventilation–perfusion ratios (*bottom panel*). P_{CO_2} is affected only minimally in either case.

to ventilation reflects the original $\dot{V}A/\dot{Q}$ ratios of the two compartments—that is, where they lie on the curves of Fig. 14-6.

Changes in Cardiac Output

One final compensatory adjustment is possible—an increase in cardiac output. Adrenergic stimulation by arterial hypoxemia can raise cardiac output by 50% or more, and this will also tend to improve arterial blood gases by raising mixed venous P_{O_2} (and lowering mixed venous P_{CO_2}). Figure 14-10 shows the effects on arterial P_{O_2} and P_{CO_2} of such increases, as was done for ventilation in Fig. 14-9, again assuming that the relative distribution of blood flow remains unaltered between the two compartments as total blood flow is increased. For a lung with airway obstruction causing very low $\dot{V}A/\dot{Q}$ regions (upper panel), an increase in cardiac output significantly improves arterial oxygenation—more so than does the same relative increase in ventilation. However, arterial P_{CO_2} is only slightly improved. In stark contrast, increases in cardiac output barely alter arterial P_{O_2} and P_{CO_2} in the high $\dot{V}A/\dot{Q}$ ratio model, especially when it is recalled (Fig. 14-9) how effective an increase in ventilation is in restoring arterial P_{O_2} and P_{CO_2}.

When both ventilation and cardiac output are simultaneously increased, there is no real synergistic effect (Fig. 14-11): P_{O_2} and P_{CO_2} are improved as predicted from the individual changes (i.e., as shown in Figs. 14-9 and 14-10).

In all the calculations depicted in Figs. 14-9 to 14-11, the two-compartment models are exchanging the necessary amounts of O_2 and CO_2 to sustain normal metabolism. Depending on (a) the ventilatory and cardiovascular responses to the original insult causing $\dot{V}A/\dot{Q}$ mismatch and (b) the fundamental pattern of $\dot{V}A/\dot{Q}$ mismatch (i.e., the preponderance of low and/or high $\dot{V}A/\dot{Q}$ areas), it is possible to observe hypercapnia, normocapnia, or hypocapnia. However, it is very uncommon for arterial P_{O_2} to be fully normalized by the compensatory mechanisms, and the observed degree of hypoxemia can be extremely variable. As an important clinical corollary, it becomes difficult to establish the severity of the $\dot{V}A/\dot{Q}$ insult per se when the extent of compensating mechanisms cannot be easily established, since these two aspects are so intertwined in their resulting effect on gas exchange.

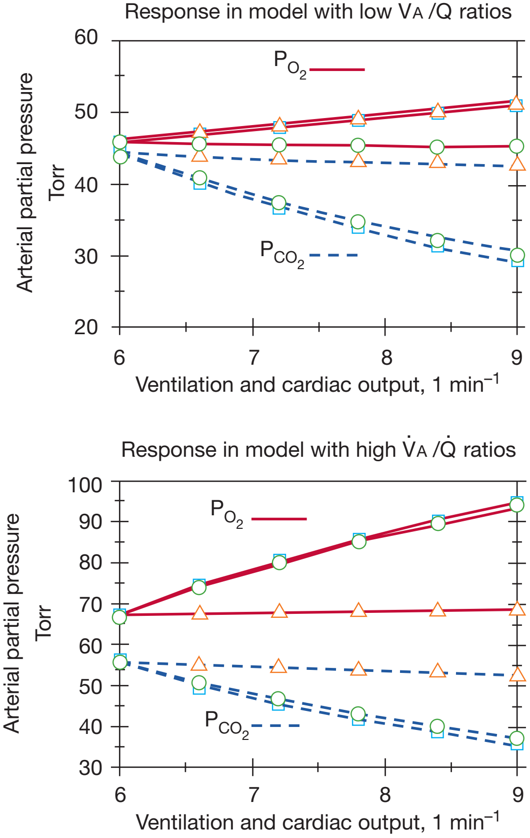

Figure 14-11 Responses to simultaneous increases in ventilation and cardiac output (compared with responses to individual increases as shown in Figs. 14-9 and 14-10). Simultaneous increases do not provide for significantly more improvement than with either alone. o-o, response to increased ventilation only; △—△, response to increased cardiac output only; □-□, response to simultaneously increased ventilation and cardiac output.

ASSESSMENT OF VENTILATION–PERFUSION INEQUALITY

Whereas the preceding discussion highlights the complexity of how $\dot{V}A/\dot{Q}$ inequality impairs gas exchange, there is a need for methods to assess the extent of such mismatch in the clinical setting. The multiple inert gas elimination technique was developed expressly for this purpose.[37,38] Although the technique provides the necessary descriptions of the extent and pattern of inequality, it remains a complex technique that is not well suited to routine clinical use. Several traditional quantifying indices of $\dot{V}A/\dot{Q}$ mismatch remain useful on a daily basis. They all make use of O_2 and CO_2 as indicator gases:

1. The first is the alveolar–arterial P_{O_2} difference, PA_{O_2}– Pa_{O_2}. This is the difference between alveolar P_{O_2} (PA_{O_2}, calculated from the alveolar gas equation presented subsequently) and the measured arterial P_{O_2} (PA_{O_2}). The PA_{O_2} − Pa_{O_2} is therefore given by

$$PI_{O_2} - Pa_{CO_2}/R + Pa_{CO_2} \cdot FI_{O_2} \cdot (1 - R)/R - Pa_{O_2} \qquad (8)$$

Use of this equation requires knowledge of inspired P_{O_2} and $[O_2]$, the respiratory exchange ratio R, and the ideal alveolar P_{CO_2}, which is the P_{CO_2} that would be observed in alveolar gas of a homogeneous lung having the R value of the patient's actual lung at the time. Three problems arise with the application of this equation: First, the result is very dependent on PI_{O_2} even when the amount of $\dot{V}A/\dot{Q}$ inequality does not change as PI_{O_2} is varied. Second, the value of R is generally not known and must be assumed. Suppose $P_{CO_2} = 40$ mm Hg and $Pa_{O_2} = 90$ mm Hg for a subject breathing sea level air. If R were 0.7, $PA_{O_2} - Pa_{O_2}$ would be 7 mm Hg (Equation 8). But if R were 1.0, $PA_{O_2} - Pa_{O_2}$ would be 20 mm Hg, a quite different value. Third, in some cases, the usual substitution for the ideal alveolar P_{CO_2}, the measured arterial P_{CO_2}, leads to a systematic error because arterial P_{CO_2} can be significantly higher than the ideal alveolar value. However, $PA_{O_2} - Pa_{O_2}$ remains a very useful index of $\dot{V}A/\dot{Q}$ inequality providing these limitations are kept in mind.

2. The second index is simply the ratio of arterial P_{O_2} to FI_{O_2}, which in a perfectly normal lung is virtually insensitive to PI_{O_2}, a major advantage. However, even that is an over-simplification, because this ratio may not be as constant as hoped for depending on the pattern of $\dot{V}A/\dot{Q}$ inequality present.
3. A third index is venous admixture (QSQT) or, equivalently, physiologic shunt. This is a parameter that expresses what magnitude shunt would have to be present in a particular case to explain a patient's arterial P_{O_2} if that shunt were the sole cause of hypoxemia. The formula is:

$$\%QsQ_T = 100 \cdot [Cc'_{O_2} - Ca_{O_2}]/[Cc'_{O_2} - C\bar{v}_{O_2}] \qquad (9)$$

   where Cc'_{O_2} is the calculated end capillary $[O_2]$ of blood perfusing a hypothetical alveolus exchanging gas at the overall respiratory exchange ratio of the patient's actual lungs. Ca_{O_2} is arterial and $C\bar{v}_{O_2}$ mixed venous $[O_2]$, respectively. This parameter, working in the O_2 concentration domain (rather than the partial pressure domain of the $PA_{O_2} - Pa_{O_2}$), better reflects the degree of the gas exchange defect but requires knowledge of the ideal alveolar conditions to calculate Cc'_{O_2}, as well as [Hb]. It also is sensitive to PI_{O_2} in that when $\dot{V}A/\dot{Q}$ inequality is present, its contribution to QsQT diminishes progressively as PI_{O_2} is raised. The most limiting aspect of this parameter however is the need to know the value of $C\bar{v}_{O_2}$, reflecting mixed venous blood. If this must be assumed rather than measured, the value of QsQT will be only as good as the assumption, which may be extremely misleading if changes in $C\bar{v}_{O_2}$ in fact occur but are not accounted for in the QsQT calculation.
4. Finally, as a fourth index, using the arterial and mixed expired partial pressures of CO_2 (Pa_{CO_2} and $P\bar{E}_{CO_2}$, respectively), a very similar calculation to QSQT can be performed to compute the percentage of total ventilation that is wasted on non-gas-exchanging ("deadspace") areas of the lungs. As for QsQT, the calculation determines the magnitude of the deadspace that would have to be present to dilute the alveolar P_{CO_2} down to the mixed expired level if that deadspace were the only abnormality in ventilation. Expressed as deadspace (VD)/tidal volume (VT) percentage,

$$\%V_D/V_T = 100 \cdot [Pa_{CO_2} - P\bar{E}_{CO_2}]/[Pa_{CO_2}] \qquad (10)$$

This parameter is independent of PI_{O_2} but is weakened by the fact that the normal airway conducting volume is included in the computed result. Thus, it may be difficult to separate how much the VD/VT value represents this normal anatomic deadspace as opposed to reflecting $\dot{V}A/\dot{Q}$ inequality amongst the alveoli. This problem is amplified because even normally VD/VT is very dependent on the size of the tidal volume even if the deadspace volume itself is essentially constant. Thus, for a deadspace volume of 150 mL and a tidal volume of 500 mL, VD/VT is 30%, but if tidal volume were to drop to 400 mL, VD/VT now becomes 38%—not because $\dot{V}A/\dot{Q}$ inequality has developed, but simply because smaller breaths are being taken.

In summary, no index of $\dot{V}A/\dot{Q}$ inequality is without potentially significant limitations, both quantitative and qualitative. However, if these limitations are recognized and the data interpreted accordingly, they remain very useful indices of clinical gas exchange function.

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CHAPTER 15

Blood Gas Transport

Adrian Shifren
Robert A. Klocke

OXYGEN TRANSPORT

Oxygen is relatively insoluble in aqueous solutions such as blood. Dissolved oxygen alone is insufficient to meet the demands of tissue metabolism. Therefore, an alternate means of transporting oxygen is essential. Oxygen binds reversibly to hemoglobin, enabling the transport of large amounts of oxygen—approximately 20 mL/100 mL of blood at a hemoglobin concentration of 15 g/100 mL.

■ Oxygen Dissociation Curve

The oxygen dissociation curve represents the relationship between the oxygen content of blood and the partial pressure of oxygen to which it is exposed (Fig. 15-1).[1] Oxygen content is expressed as the volume of oxygen contained in 100 mL of blood but may also be expressed as either volumes % or mL/dL. The standard oxygen dissociation curve (Fig. 15-1) demonstrates the effects of oxygen–hemoglobin interaction at standard pH (7.40), temperature (37°C), and atmospheric pressure (760 mm Hg). The blue line at the bottom of the graph in Fig. 15-1 shows the amount of oxygen dissolved in blood, and the red line shows the total amount of oxygen in blood at any given oxygen tension. Almost the entire quantity of oxygen transported in blood is bound to hemoglobin. However, the role of dissolved oxygen cannot be ignored. Oxygen diffuses across the alveolar-capillary membrane, enters the plasma, traverses the red cell membrane, and enters the erythrocyte interior—all while dissolved in aqueous solutions. It then combines with hemoglobin enabling the transport of large amounts of oxygen to the metabolizing tissues. Dissolved oxygen, although present in very low concentration in blood, is a critical component of the process of O_2 exchange because hemoglobin cannot traverse endothelial and erythrocytic membranes.

Changes in the quaternary structure of hemoglobin that accompany oxygen binding result in a sigmoid, rather than hyperbolic, oxygen dissociation curve. The S-shaped dissociation curve is the result of changes in oxygen affinity of unbound heme groups following the binding of oxygen to another heme group in the same hemoglobin molecule. As illustrated in Fig. 15-1, once the partial pressure of oxygen reaches 90 to 100 mm Hg, hemoglobin is almost completely saturated with bound oxygen. There is little additional oxygen binding even at higher oxygen tensions. The relatively flat nature of the curve in this range of arterial oxygen tension is an advantage because reductions in arterial P_{O_2} (as might be caused by lung disease) will still allow for a relatively normal arterial O_2 content as long as arterial P_{O_2} remains ≥60 mm Hg. The normal partial pressure of oxygen in mixed venous blood at rest is ~40 mm Hg with an oxygen content of ~75% of maximum oxygen capacity. Thus, at rest only one-quarter of the oxygen delivered to body tissues is extracted from blood. However, oxygen extraction varies widely in different tissues. In addition, oxygen utilization changes appreciably during states of increased metabolism. In the tissues, the steep slope of the oxygen dissociation curve between 20 and 60 mm Hg facilitates the release of large amounts of oxygen with relatively moderate decrease in oxygen tension. This permits maintenance of blood oxygen tensions that promote diffusion of oxygen from the capillary blood into metabolizing tissues.

The maximum quantity of oxygen transported in blood is dependent upon hemoglobin concentration, which may vary moderately in normal circumstances but substantially in disease states. To facilitate comparison of oxygen dissociation curves with different hemoglobin concentrations, the ordinate of the curve can be normalized by expressing oxygen content as a percentage of the maximum possible oxygen content. This approach substitutes % saturation of hemoglobin for oxygen content, as illustrated in Fig. 15-2. Using this format, all normal oxygen dissociation curves are superimposable, regardless of differing hemoglobin concentrations.

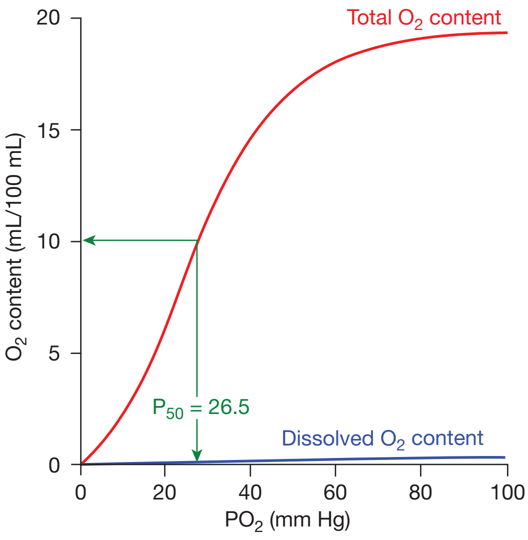

Figure 15-1 Oxygen dissociation curve. Relationship between oxygen content and pressure in normal human blood. The total oxygen content of blood as a function of the partial pressure of oxygen is indicated by the *red line*. The *blue line* indicates the content of dissolved oxygen resulting from changes in P_{O_2}. The partial pressure of oxygen (P_{50}) necessary to saturate one-half of hemoglobin in blood is indicated in *green*.

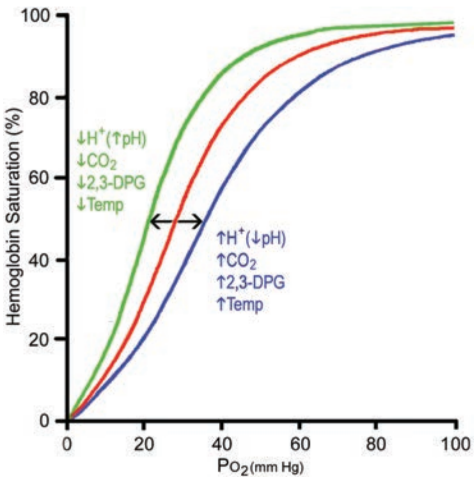

Figure 15-2 Oxygen dissociation curve. The ordinate is % saturation, the percentage of the maximum possible oxygen content. The normal oxygen dissociation curve is shown in *red*. The *green curve* is shifted to the left of the normal curve (increased oxygen affinity of hemoglobin) as a result of decreased blood hydrogen ion, decreased carbon dioxide, and 2,3-DPG concentrations or decreased temperature. The *blue curve* is shifted to the right (decreased oxygen affinity) of the normal curve caused by increases of these factors. The *black arrows* indicate the changes in P_{50}.

Alterations of Oxygen Affinity

The relationship between oxygen content and pressure can be affected by several factors. Increases in temperature, carbon dioxide tension, hydrogen ions (decreased pH), and 2,3-diphosphoglycerate (2,3-DPG) all shift the oxygen dissociation curve to the right.[1] This results in a decrease in the affinity of hemoglobin for oxygen, i.e., a greater oxygen tension is required to bind the same amount of oxygen to hemoglobin (Fig. 15-2). Conversely, decreases in temperature, carbon dioxide tension, hydrogen ions (increased pH), and 2,3-DPG shift the curve to the left, i.e., increase the affinity of hemoglobin for oxygen.[1] The degree of shift of the oxygen dissociation curve is described by the P_{50}, the partial pressure of oxygen required to achieve 50% oxygen saturation of hemoglobin. The normal P_{50} for human blood is 26.5 mm Hg (Fig. 15-1). The basic sigmoid nature of the relation between oxygen and hemoglobin does not change with alterations in the P_{50}. Rather, the curve is uniformly either stretched or compressed along the P_{O_2} axis.

The human erythrocyte contains large quantities of 2,3-DPG, an organic phosphate that is a product of glycolytic metabolism inside the erythrocytes. 2,3-DPG binds to the hemoglobin tetramer and decreases the O_2 affinity of hemoglobin.[1] The normal concentration of 2,3-DPG in erythrocytes is approximately 5 mM. However, this concentration can change significantly, thereby altering the P_{50}. There is a substantial change in the configuration of the hemoglobin tetramer between the oxygenated and deoxygenated states. The β-chains of the hemoglobin tetramer are more widely separated in the deoxygenated state than in the oxygenated state and have positive charges surrounding the central cavity of the hemoglobin tetramer. The widened gap between the β-chains of the deoxygenated molecule enables the highly negatively charged 2,3-DPG molecule to enter the space between the β-chains and bind electrostatically to four positively charged amino acids of the hemoglobin molecule. This tends to stabilize the hemoglobin molecule in the deoxygenated configuration. Higher pressures of oxygen are thus required to force the change in molecular configuration to the oxygenated form, resulting in a shift of the dissociation curve to the right along the P_{O_2} axis.

Most abnormal hemoglobins have normal oxygen equilibrium curves despite differences in amino acid sequences. Some relatively rare mutant hemoglobins are exceptions to this rule and exhibit increased O_2 affinity that is accompanied by erythrocytosis. Previously, measurements of P_{50} were advocated to investigate erythrocytosis, but identification of mutant hemoglobins with molecular techniques is far more likely to identify this rare cause of erythrocytosis.

Large quantities of carbon monoxide (CO) bound to hemoglobin can increase the affinity for oxygen of the remaining unbound sites on hemoglobin. The adverse effects of CO poisoning are twofold: (1) Binding of CO to hemoglobin interferes with oxygen binding and produces a functional anemia; and (2) binding of CO to hemoglobin also increases the affinity of hemoglobin for oxygen, thereby shifting the oxygen equilibrium curve to the left. This increased affinity hinders the release of oxygen in the tissues but is not as important as the functional anemia caused by CO binding.

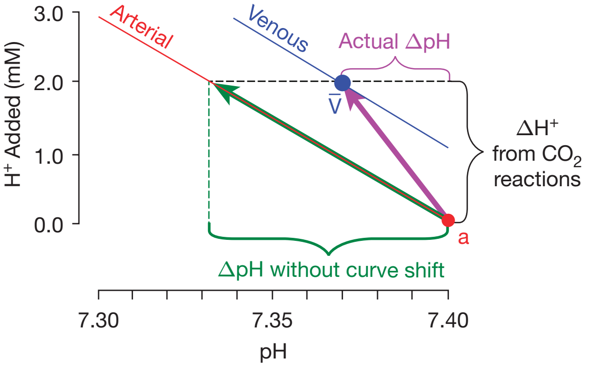

Figure 15-3 Buffer curves (change in pH produced by binding of hydrogen ions) of normal arterial (a) and mixed venous (v) blood. With release of oxygen bound to hemoglobin in tissues, buffering sites on the hemoglobin molecule increase their affinity for hydrogen ions, thereby shifting the buffer curve upward. The quantity of hydrogen ions (ΔH^+) added to blood by production of CO_2 in normal metabolizing tissues at rest is indicated by the *black bracket*. The figure shows the change in pH (*green bracket*) that would occur if buffering occurred only along the arterial buffer curve (*green arrow*). The actual, much smaller change in pH (*purple bracket*) that accompanies buffering (*purple arrow*) is due to the upward shift of the arterial buffering curve to the venous relationship that accompanies release of oxygen in the tissues. *(Reproduced with permission from Klocke RA: Encyclopedia of Respiratory Medicine. Philadelphia, PA: Elsevier; 2007.)*

Bohr Effect

The right shift of the oxygen dissociation curve produced by increases in P_{CO_2} and hydrogen ion concentration is known as the Bohr effect, named after the individual who first described the negative effect of increased P_{CO_2} on the oxygen affinity of hemoglobin. Both hydrogen ions and carbon dioxide bind at sites on the hemoglobin molecule that differ from the oxygen-binding sites.[2] However, there are many more sites that bind hydrogen ions than bind CO_2 molecules. Importantly, as the tertiary and quaternary configurations of the hemoglobin molecule change with release of oxygen, 16 of these hydrogen binding sites (14 histidine and 2 terminal amino groups) change their physiologic buffering capacities due to alterations in their acidic equilibrium constants (pKa).[3] The change in molecular configuration of hemoglobin causes some groups to increase their pKa and others to decrease their pKa. Two of the 16 Bohr buffering groups (one β-chain terminal amino group and one histidine [Lys82β] group) only contribute buffering activity during oxygen release when 2,3-DPG is bound to the hemoglobin molecule.[3] This is the usual situation inside the erythrocyte during normal circumstances. The net effect of the multiple changes in pKa increases the buffering power of hemoglobin at physiologic pH as bound oxygen is released from the hemoglobin tetramer. This is known as the alkaline Bohr effect. This effect minimizes the decrease in blood pH by buffering hydrogen ions released in CO_2 metabolism. Figure 15-3 illustrates the buffering curves of normal arterial and venous blood. Both exhibit effective, but parallel, buffering curves. As hemoglobin is deoxygenated, its buffering curve shifts upward (becomes greater), and significant amounts of hydrogen ion can be buffered with a smaller change in pH.[2] At rest, the decrease in blood pH accompanying tissue metabolism is reduced by one half due to buffering by the Bohr groups. Approximately half of the hydrogen ions released in aerobic metabolism are buffered in this manner (see "Haldane Effect," below).

It has been speculated that the increased carbon dioxide tension and hydrogen ion content in blood facilitate the release of oxygen bound to hemoglobin by shifting the oxygen dissociation curve to the right.[4] However, quantitative analysis indicates that this mechanism results in minimal augmentation of oxygen release in tissues at rest (2%–3%) because of the minute difference in pH between arterial and venous blood (0.03–0.05 pH units).[5] This effect becomes more significant during strenuous exercise with the production of lactic acid in anaerobic metabolism in heavily exercising muscle.[6] However, the main physiologic benefit of the Bohr effect is the increased buffering capacity of hemoglobin that accompanies release of oxygen from the hemoglobin molecule.[2,4]

Changes in Oxygen Affinity in Disease

Anemia or exposure to altitude impairs the ability to deliver oxygen to body tissues. The normal compensatory response to these situations is to increase 2,3-DPG concentration within the erythrocytes. This decreases the oxygen affinity of hemoglobin, thereby shifting the oxygen dissociation curve to the right. The loss of oxygen uptake at high oxygen tensions present in the lungs is small in this scenario because the right-shifted curve is very close to the normal curve at normal arterial oxygen tensions (Fig. 15-2). However, oxygen is released at a higher tension at the capillary level with a right-shifted curve. Since the P_{O_2} in the metabolizing mitochondria is close to zero, release of oxygen in the capillary at a higher P_{O_2} increases the oxygen tension gradient between the capillary and mitochondria. This augments diffusion of oxygen from the capillary to the site of its utilization. This is especially critical during elevated oxygen requirements or reduced organ perfusion.

Efforts have been made to produce shifts of the dissociation to the right in certain diseases or circumstances to improve oxygen delivery.[7] For example, the P_{50} of bank blood, even though stored at low temperature, can decrease dramatically after as little as 7 days of storage as a result of degradation of intraerythrocytic 2,3-DPG. Although stored blood is useful to expand intravascular volume, it may not be optimal in situations where oxygen delivery is impaired. This has prompted use of fresh blood in certain situations when large quantities of blood are needed, such as with open-heart surgery. To date there have been no definitive studies that have tested this hypothesis, largely due to the difficulty of determining the 2,3-DPG levels in transfused cells in a complex clinical setting. In normal, healthy humans with type A blood, it is possible to determine the level of 2,3-DPG in transfused type O cells essentially depleted of all 2,3-DPG by 35 days of storage.[8] Seven hours after transfusion, 2,3-DPG levels in type O transfused cells rise to approximately 50% of the level present before storage. In this study 2,3-DPG levels in the transfused cells reach 95% of the original levels prior to storage by 48 hours after trasfusion.[8]

In contrast to efforts to improve oxygen delivery to tissues by increasing P_{50}, recent work has suggested that decreasing P_{50} in patients with sickle cell disease may be clinically beneficial. When erythrocytes become sickled, the sickled cells may cause vaso-occlusive disease and are more likely to hemolyze, leading to substantial anemia. Voxelotor is a relatively small molecule (MW 337.4) that penetrates erythrocytes and binds reversibly to the N-terminal amino acid of the α-chain of hemoglobin.[9] The distribution of voxelotor between red cells and plasma is approximately 150:1, and the binding of voxelotor to hemoglobin decreases the P_{50}. This increases blood oxygen saturation in vivo, thereby decreasing red cell sickling in metabolizing tissues.

Vichinsky et al.[10] reported a randomized, double-blind study of 274 anemic patients with sickle cell disease (hemoglobin of 8–9 gm/dL) randomized in 1:1:1 ratio to treatment with either daily doses of 1500 mg or 900 mg of voxelotor or placebo. The primary endpoint was an increase of hemoglobin greater than 1.0 gm/dL after 24 weeks of therapy. Patient percentages reaching this goal were 51% in the 1500-mg group ($p = 0.001$) and 33% in the 900-mg group, compared with 7% in the control group. The change in the 900-mg group did not quite reach statistical significance. Laboratory measures of hemolysis provided evidence of decreased hemolysis in the patients treated with high-dose voxelotor. There was no evidence of reduced vaso-occlusive crises in any of the three groups. There were no adverse events reported with voxelotor in this study, although the possibility of tissue hypoxia secondary to reduction of the P_{50} was only monitored with usual clinical observations.

CARBON DIOXIDE TRANSPORT

Carbon dioxide (CO_2) is the primary by-product of aerobic metabolism. It is also generated through the buffering of hydrogen ions (H^+) released from organic acids, such as lactic acid and ketoacids. This buffering occurs through chemical reaction of H^+ ions with intracellular and extracellular bicarbonate ions (HCO_3^-). The CO_2 produced by these reactions diffuses into capillary blood and is carried in both chemical combination and physical solution to the lungs, where it is eliminated through expired ventilation. Similar to O_2 transport, most CO_2 in blood is not carried as dissolved gas, but rather as bicarbonate or bound to hemoglobin as carbamate.

Carbon Dioxide Dissociation Curve

Carbon dioxide is transported in three forms in blood: dissolved CO_2, bicarbonate ions, and carbamate compounds. The relationship between the blood content and partial pressure of CO_2 differs substantially from that of O_2. The total quantity of CO_2 contained in arterial blood is more than twice that of O_2 despite the lower partial pressures of CO_2. The CO_2 dissociation curve is very steep (Fig. 15-4). As a result, the difference in partial pressures of CO_2 between arterial and venous blood is small when compared to the large arterial–venous differences in blood P_{O_2}.[11] The total content of blood CO_2, that is, the vertical axis of the CO_2 dissociation curve, is the sum of all three forms of CO_2 (dissolved CO_2, bicarbonate, and carbamate).

Dissolved CO_2

Carbon dioxide is 20 times more soluble in aqueous solution than oxygen. However, this increased solubility is insufficient to facilitate transport of all the CO_2 produced by metabolism. Approximately

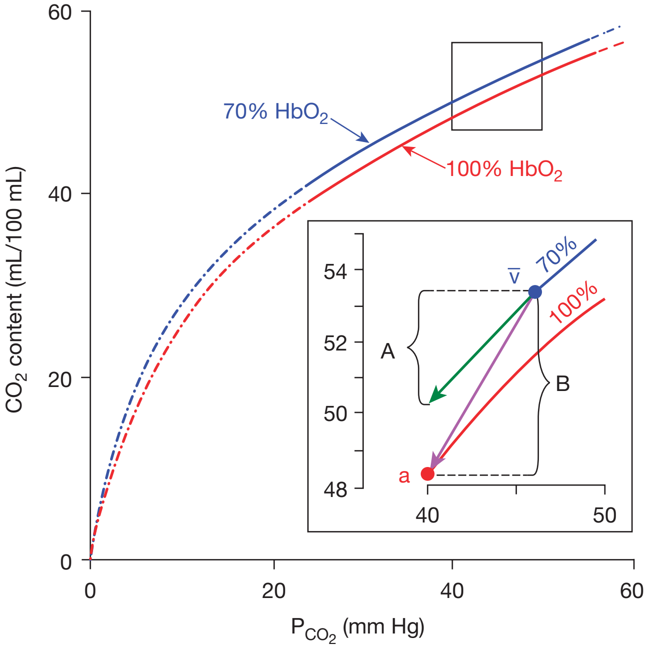

Figure 15-4 The Haldane effect showing the carbon dioxide dissociation curves of blood with 70% (*blue*) and 100% (*red*) oxygen saturations. The portions of the curves most commonly involved in gas exchange are drawn with *solid lines*. The P_{CO_2} and CO_2 contents of mixed venous ($\bar{v}$) and arterial blood (a) normally present at rest are shown in the enlarged inset. If there were no change in the CO_2 dissociation curve with oxygenation in the lung, the decrease in P_{CO_2} would take place along the venous curve (*green arrow*). This would produce a decrease in blood CO_2 content indicated by the vertical bracket A. The course of CO_2 exchange between arterial and mixed venous points is shown by the *purple arrow*. The enhanced CO_2 exchange produced by the Haldane effect is indicated by the greater vertical height of bracket B.

5% of total CO_2 content in blood exists as dissolved CO_2 in plasma and red cell water. Despite this, dissolved CO_2 has a critical role in gas exchange since only dissolved CO_2 crosses the alveolar–capillary membrane. Therefore, regardless of how CO_2 is transported in blood, each molecule must be converted into the dissolved form for excretion through ventilation. The quantity of dissolved CO_2 is directly proportional to the partial pressure of carbon dioxide in blood.

■ Bicarbonate

Carbon dioxide combines with water to form carbonic acid (H_2CO_3), which dissociates into a hydrogen and a bicarbonate ion.

$$CO_2 + H_2O \xleftrightarrow{\text{CA}} H_2CO_3 \leftrightarrow H^+ + HCO_3^- \qquad (1)$$

Because the pKa of carbonic acid is approximately 4.1, the actual concentration of carbonic acid in blood is minuscule. The overall pKa for reaction (1), including hydration of CO_2 and dissociation of carbonic acid to bicarbonate, is 6.1. The natural rate of formation of carbonic acid from CO_2 and water is very slow and takes seconds to minutes to reach completion in simple aqueous solutions. Under the influence of the carbonic anhydrase (CA) enzyme in the cytosol of erythrocytes, this reaction is increased by an overall factor of approximately 13,000.[11] CA inside red cells occurs as two isoenzymes. CA I is present in high concentrations in erythrocytes, but its activity is inhibited by intracellular chloride ions. CA II is present at one-sixth the concentration of CA I within red cells, but it is not inhibited by chloride ion and has a sevenfold greater intrinsic activity than CA I. Therefore, CA II is responsible for almost all the CO_2–bicarbonate catalysis in vivo.[11]

The presence of large, charged macromolecules on one side of a semipermeable membrane failing to distribute evenly across the membrane leads to an uneven distribution of charge across the membrane. This affects the distribution of small, permeable ions across the same membrane and is known as the Donnan effect. Hemoglobin and 2,3-DPG are both negatively charged and are confined to the red cell interior, leading to greater concentrations of permeable anions in plasma, principally chloride and bicarbonate, to maintain electroneutrality across the erythrocytic cell membrane. When bicarbonate is formed through the production and dissociation of carbonic acid (Equation 1), the intracellular concentration of bicarbonate rises leading to movement of bicarbonate from the red cell into the plasma. This disturbs the electroneutrality across the red cell membrane and is balanced by an equal movement of chloride into the red cell from the plasma in exchange for the exiting bicarbonate. Most anionic movement across the erythrocyte membrane is far too slow to achieve equilibrium during capillary transit time, but rapid exchange of the two anions is achieved via an exchanger located in the erythrocytic membrane.[12,13]

■ Carbamate

Carbon dioxide is also transported as carbamate compounds. Less than 10% of all exchanged CO_2 in blood binds to hemoglobin as carbamates, which are salts of carbamic acid formed by the reaction of CO_2 with amino groups on hemoglobin. CO_2 combines with uncharged terminal amino groups on the α and β chains of hemoglobin:

$$R - NH_3^+ \rightarrow H^+ + R - NH_2 \qquad (2)$$

$$R - NH_2 + CO_2 \rightarrow R - NHCOOH \rightarrow R - NHCOO^- + H^+ \qquad (3)$$

where R represents an N-terminal amino group of either the α or β chains of hemoglobin.[11] While any NH_2 group on hemoglobin can potentially bind CO_2 as a carbamate compound, only the N-terminal amino groups of hemoglobin participate in CO_2 exchange. At the pH present inside red cells, carbamic acid (R-NHCOOH) dissociates almost completely into a carbamate ion and a hydrogen ion. These H^+ ions, like those liberated by the formation of bicarbonate ions, are buffered substantially by hemoglobin (see "Haldane Effect," below).

Changes in the quaternary structure of hemoglobin accompanying binding and release of oxygen affect the pKs of reactions (2) and (3), altering the equilibrium between the NH_2 and NH_3^+ forms of the terminal amino groups. Because deoxygenated hemoglobin binds more CO_2 than oxygenated hemoglobin, more CO_2 can be carried as carbamate in venous blood at any given P_{CO_2} than in oxygenated arterial blood. The change in CO_2 binding between oxygenated and deoxygenated hemoglobin accounts for approximately one-eighth of the difference between the arterial and venous CO_2 contents during normal gas exchange. The physiologic importance of this process would be twice as great but is reduced by interactions between DPG and hemoglobin that limit carbamate formation.[11] Binding of the highly negatively charged DPG molecule to hemoglobin increases the number of N-terminal amino-NH_2 moieties to the positively charged amino-NH_3^+ forms that do not bind CO_2 as carbamate.

■ Haldane Effect

Oxygenated blood at any partial pressure of CO_2 contains less total CO_2 content than deoxygenated blood at the same partial pressure (Fig. 15-4). This is known as the *Haldane effect* after one of the investigators who first described the phenomenon.

Transport of CO_2 in blood as bicarbonate or carbamate is altered by blood oxygenation. These changes are described as "oxylabile" since they are dependent upon the state of hemoglobin oxygenation.[11] Changes in configuration of the hemoglobin molecule accompanying the release of oxygen facilitate binding of CO_2 to hemoglobin as carbamate, that is, *oxylabile carbamate formation*. This increases the total CO_2 content in deoxygenated blood compared with oxygenated blood.[14]

Formation of both bicarbonate ions and carbamate compounds releases large quantities of hydrogen ions. It is essential to buffer these hydrogen ions effectively to promote CO_2 transport. Deoxygenation of hemoglobin also results in a shift of the buffering curve of hemoglobin since deoxygenated hemoglobin is a stronger base than oxyhemoglobin. This shift permits binding of a greater number of hydrogen ions (Fig. 15-3). This *oxylabile buffering*, in turn, facilitates formation of larger quantities of carbamate and bicarbonate.[14]

The synergistic effects of oxygen and carbon dioxide transport result in a change in the carbon dioxide dissociation curve as oxygen is bound and released.[15] Approximately equal changes in bicarbonate and carbamate concentrations are responsible for the Haldane effect. Without the change between the oxygenated and partially deoxygenated CO_2 dissociation curves (the Haldane effect), the difference between arterial and venous CO_2 tensions would be approximately twice the normal value, thereby increasing tissue P_{CO_2}. Model calculations and in vitro data suggest that the Haldane effect accounts for 40% to 50% of total CO_2 exchange in the lung under normal conditions.[11,14,15]

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CHAPTER 16

Diffusion, Chemical Reactions, and Diffusing Capacity

Robert A. Klocke
Adrian Shifren

INTRODUCTION

Uptake of oxygen and excretion of carbon dioxide require rapid, efficient exchange in the lung. The quantities of exchanged gases are staggering. For example, an 1800-calorie diet requires absorption of 375 L of oxygen per day, as well as excretion of a slightly smaller volume of carbon dioxide. Because blood remains in the pulmonary capillary bed for a limited time, the process of exchange must be accomplished in less than 0.75 s at rest and 0.5 s during exercise. This rapid, high-volume exchange occurs efficiently despite numerous interacting processes of diffusion and chemical reaction that occur in the lung. The rates of these processes are not only affected by intrinsic characteristics of blood but also determined by a host of other factors, including inspired oxygen fraction, alveolar gas tensions, cardiac output, and metabolic activity. The ease of exchange of respiratory gases belies the complexity of the overall process.

DIFFUSION

The concentration (C) of a gas dissolved in fluid depends upon its partial pressure (P) and solubility (α)

$$C = \alpha P \qquad (1)$$

Gases diffuse from a higher to a lower partial pressure, not necessarily from a higher to a lower concentration. This fact is especially pertinent when a gas diffuses between two phases, as occurs when O_2 and CO_2 are exchanged between alveolar gas and blood. For example, dissolved CO_2 diffuses down a partial pressure gradient from blood (46 mm Hg) into the alveolus (40 mm Hg), even though its actual concentration (millimoles of molecular CO_2 per liter of gas or blood) is greater in alveolar gas (2.5) than it is in venous blood (1.4).

Influence of Physical Properties

The rate of a gas diffusing through an aqueous membrane such as that separating alveolar gas and capillary blood is influenced by five factors. The rate is directly proportional to the surface area of the membrane, but inversely proportional to the thickness of the membrane. The rate increases in direct proportion to the difference in gas pressure between alveolar gas and capillary blood and with increases in diffusion and solubility coefficients of the gas in the membrane.

The diffusion coefficient of a gas in the alveolar–capillary membrane is largely a function of the size of the gas molecule, which is inversely proportional to the square root of its molecular weight (MW). Oxygen (MW 32) has a slightly greater diffusion coefficient than carbon dioxide (MW 44) in the alveolar membrane. However, the solubility of CO_2 in water, the major component of tissue composing the membrane, is much greater than the solubility of O_2. This difference far outweighs the effect of the slightly smaller size of the oxygen molecule. Thus, the rate of CO_2 transfer across the alveolar membrane is approximately 20 times greater than that of O_2 when both gases diffuse under the same partial pressure gradient. As a result, a much greater P_{O_2} gradient across the membrane is required to maintain O_2 transfer equal to that of CO_2.

On the other hand, the rate of carbon monoxide (CO) transfer is very similar to that of oxygen when both gases diffuse across the alveolar–capillary membrane under the same partial pressure gradient. CO (MW 28) is a slightly smaller molecule than oxygen, so its diffusion coefficient is slightly greater. This diffusive advantage is offset by a slightly lower aqueous solubility of CO compared to oxygen. As a result, CO and O_2 transfer across the membrane have approximately equal rates at the same transmembrane partial pressure gradient.

The rate of diffusion of a substance is affected by the viscosity of the medium through which diffusion occurs. Diffusion of a gas in air occurs at a rate that is four orders of magnitude greater than diffusion in water. Diffusion coefficients in tissues are only moderately less than those in water since most tissues are composed primarily of water. The interior of the erythrocyte is an exception to this general rule. As a consequence of the high concentration of hemoglobin inside the red cell, the viscosity of the cell contents is substantially greater than that of water. This greater viscosity reduces the diffusion coefficient for oxygen to one-third of its aqueous coefficient. The combination of increased viscosity and the large size of the hemoglobin molecule decreases the diffusion coefficient of hemoglobin within the red cell to less than 10% of its diffusion coefficient in a dilute aqueous solution. As a result, significant diffusion gradients are thought to exist within the red cell even though the distance between the cell membrane and the innermost portion of the cell is only a few microns.

Effect of Different Capacitances

The alveolar–capillary membrane provides a barrier to diffusion of gases between the alveoli and the capillaries. The rate of approach to diffusion equilibrium of a gas in the lung is dependent on the capacitances of the gas in the alveoli and blood relative to its solubility in the alveolar–capillary membrane. Normal ventilation of alveoli results in a large reservoir of oxygen with a pressure of ~100 mm Hg to promote diffusive transfer across the alveolar–capillary membrane. The ability of hemoglobin to bind O_2 increases the oxygen capacity of blood by two orders of magnitude compared with that of the alveolar–capillary membrane. This large capacitance for oxygen in blood requires substantial oxygen transfer across the membrane to reach diffusion equilibrium. Because the solubility of oxygen in the membrane is small relative to the large capacitances in alveolar gas and blood, oxygen exchange across the membrane requires 0.2 to 0.4 s to reach equilibrium.[1] Fortunately, this delay in reaching equilibrium is less than the average of 0.75 s that blood remains in the pulmonary capillary bed under resting conditions. These same conditions are present during carbon monoxide transfer. The large capacitance and the low aqueous solubility of CO lead to similar impediments in gas exchange.

In contrast to oxygen and carbon monoxide, the solubility of carbon dioxide in the membrane is sufficiently great compared to the capacitances of CO_2 in blood and alveoli to permit rapid equilibration of CO_2 across the alveolar–capillary membrane. CO_2 exchange requires a finite time for completion, but this delay is the result of the time needed to complete chemical and transport processes in blood and is not the result of slow diffusive transport across the alveolar–capillary membrane.

Gases transported in blood only in dissolved form are exchanged almost instantaneously across the alveolar–capillary membrane. As long as gas solubilities in the membrane and blood are similar, diffusion equilibrium between alveolar contents and blood is reached within 0.01 s because the normal alveolar–capillary membrane is extremely thin (median thickness of 0.3 μm). Only gases such as oxygen and carbon monoxide that have large alveolar and blood capacitances and reduced solubility in the alveolar–capillary membrane will require a finite time to reach diffusive equilibrium.

EXCHANGE OF OXYGEN AND CARBON MONOXIDE

Transport of respiratory gases entails numerous chemical reactions with the components of blood. Like diffusive transport of oxygen, these chemical reactions are not instantaneous and require finite periods of time to reach completion. It is commonly thought that diffusion provides the greatest time-dependent impediment to pulmonary gas exchange, but in actuality, chemical processes, especially those occurring in combination with diffusion or other chemical reactions, are more likely to slow rates of O_2 and CO_2 exchange.

From a stoichiometric viewpoint, the successive binding of O_2 to the heme moieties of hemoglobin is described by successive steps, each with separate association and dissociation rate constants. If the heme rings acted independently, these constants would be the same for each heme ring and the resulting dissociation curve would have a hyperbolic shape. However, binding of oxygen to one of the heme rings on the hemoglobin tetramer affects the affinity for O_2 of the remaining heme moieties of the molecule, leading to the familiar sigmoid shape of the oxygen dissociation curve.

Reactions of oxygen and hemoglobin during capillary transit are further complicated by the rate of oxygen diffusion through the viscous interior of the red cell. The chemical reactions of oxygen and hemoglobin occur quite rapidly in dilute hemoglobin solutions but proceed more slowly in red cell suspensions. Because of the large size of the hemoglobin molecule and increased viscosity of the red cell contents, hemoglobin molecules remain relatively immobile inside the red cell. As the red cell enters the pulmonary capillary, oxygen molecules bind to reduced hemoglobin molecules just inside the erythrocyte membrane. As these hemoglobin molecules become saturated, subsequent oxygen molecules entering the red cell must diffuse more deeply into the interior of the cell to reach reduced hemoglobin molecules. This combination of diffusion and chemical reaction causes oxygen uptake to occur as an "advancing front" that proceeds at a rate that is an order of magnitude slower than O_2 uptake in well-mixed, dilute hemoglobin solution. This combined process is complex and not easily described from a theoretical standpoint. As a result, the rate of oxygen uptake by hemoglobin contained in red cells is described by a single overall descriptive parameter, θ_{O_2}, which incorporates all the processes into a single phenomenologic value. The same approach is used to describe carbon monoxide uptake in blood. The rate at which CO replaces bound O_2 in blood is described by θ_{CO}.

The rates of O_2 and CO uptake by erythrocyte suspensions are determined in vitro and assumed to be representative of the rates of gas exchange in vivo. However, measurements of these rate constants in red cell suspensions in vitro may be affected adversely by methodologic artifacts. The actual rates of combination of O_2 and CO with red cells in vivo have not been measured and this leads to uncertainties in our complete understanding of exchange of these two gases in the lung.

SOURCES OF CO_2 EXCHANGED IN THE LUNGS

CO_2 is transported in blood as dissolved molecular CO_2, bicarbonate ion, and carbamate ion.[2] The relative contributions of each form of CO_2 content to the quantity of CO_2 excreted during gas exchange in the lung are not exactly proportional to their blood contents. Analysis of the differences between arterial and venous blood CO_2 contents can be used to calculate the amounts of each form of carbon dioxide content excreted in expired ventilation.[2] This analysis of differences between arterial and venous blood CO_2 contents is shown in Fig. 16-1.

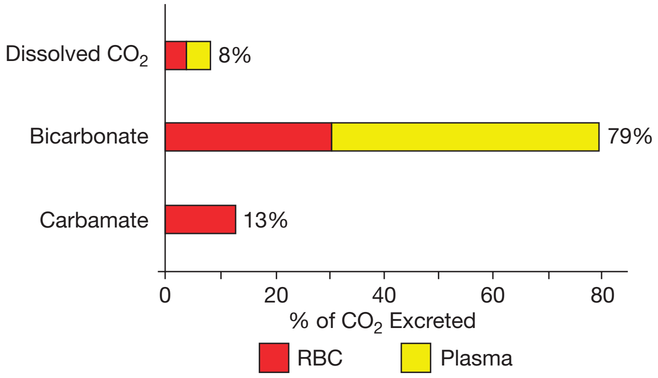

Figure 16-1 Sources of carbon dioxide excreted during passage of blood through the lungs in resting humans. The bars indicate the quantities of the different sources of CO_2 leaving blood from red cells *(red)* and plasma *(yellow)*. Bicarbonate contributes the overwhelming majority of CO_2 to the expired ventilation. As indicated in the figure, the majority of excreted bicarbonate enters the lung in plasma and is exchanged for chloride to reach carbonic anhydrase and hemoglobin buffering capacity within the red cell. *(Data from Farhi LE, Tenney SM: Handbook of Physiology. Section 3, The Respiratory System, vol 4. Bethesda, MD: American Physiological Society; 1987.)*

Dissolved CO_2 Exchange

Because CO_2 is more soluble than O_2 in the alveolar–capillary membrane, it often is assumed that overall CO_2 exchange occurs much more rapidly than O_2 exchange. As blood enters the pulmonary capillary bed, dissolved CO_2 immediately diffuses into the alveoli and capillary blood P_{CO_2} falls to the level present in the alveolar gas. However, this is a minimal amount of the total carbon dioxide that must be excreted in expired ventilation. The vast remainder of CO_2 is transported as bicarbonate and carbamate and the conversion of these forms to dissolved CO_2 limits the rate of CO_2 exchange.[2,3] As a result, CO_2 exchange proceeds more slowly than oxygen exchange. This is illustrated in Fig. 16-2, *Upper Panel*, when a bolus of dissolved CO_2 and an inert gas such as acetylene is injected into an isolated lung perfused with saline buffer. CO_2 is rapidly exchanged, similar to the inert gas acetylene. In contrast, when a bicarbonate bolus and dissolved acetylene is injected into the same preparation (Fig. 16-2, *Lower Panel*), CO_2 exchange lags behind acetylene excretion for a finite period of time until bicarbonate is converted into dissolved CO_2 that can cross the alveolar–capillary membrane.[4]

Bicarbonate Exchange

Bicarbonate ion combines with hydrogen ion extremely rapidly to form carbonic acid (H_2CO_3). The natural rate of dehydration of carbonic acid to CO_2 and water is a slow process, requiring 60 to 90 s to reach completion. However, this reaction is catalyzed inside the red cells by a factor of ~13,000 by the large concentration of carbonic anhydrase (CA) contained in red cells.[2]

$$HCO_3^- + H^+ \rightarrow H_2CO_3 \xrightarrow{CA} CO_2 + H_2O \qquad (2)$$

The substantial buffering capacity of hemoglobin inside the erythrocyte, augmented by the simultaneous conversion of reduced to oxygenated hemoglobin (Bohr Effect), provides the hydrogen ions required for this reaction. The dissolved CO_2 formed by this reaction inside the red cell leaves the blood and enters the alveoli, but continuing excretion of CO_2 is still dependent upon continuing conversion of bicarbonate to CO_2. Inside the red cell, the catalyzed formation of dissolved CO_2 rapidly (~0.1 s) depletes the concentration of intracellular bicarbonate and the production of CO_2 slows substantially.[1,5]

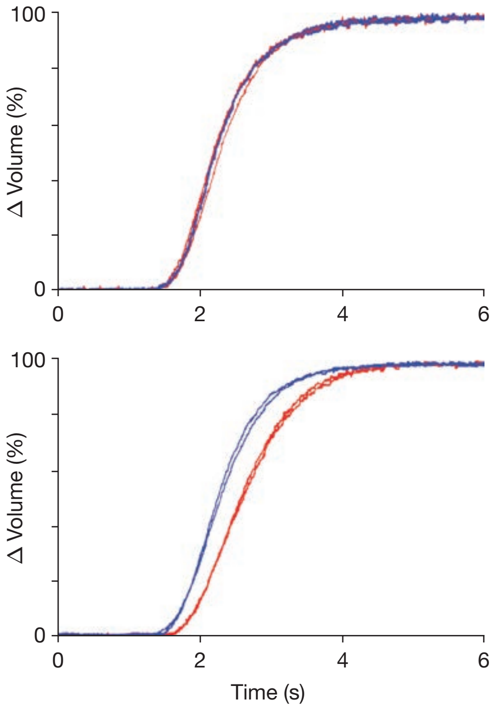

Figure 16-2 Rates of acetylene *(blue curves)* and CO_2 *(red curves)* excretion after two pairs of injections into the pulmonary artery of a single isolated lung preparation perfused with buffer. Volume changes are normalized to facilitate comparison. *Upper Panel*: The excretion of both acetylene and CO_2 proceeds at the same rate after injections of buffer containing either dissolved CO_2 or acetylene. Differences in mean transit times for CO_2 and acetylene were essentially the same (−0.027 s for first pair and +0.022 s for second pair of injections). Thus, dissolved CO_2 crosses the alveolar–capillary membrane at the same rapid rate as the inert gas acetylene. *Lower Panel*: The excretion of CO_2 generated from injections of bicarbonate *(red curves)* lags substantially behind the excretion of dissolved acetylene (*blue curves*) (+0.301 s in the first set of paired injections and +0.312 s in the second set of paired injections). This slower excretion of CO_2 is caused by the time required to convert bicarbonate to CO_2 with catalysis in this experiment provided by carbonic anhydrase localized to the capillary endothelium. *(Reproduced with permission from Schünemann HJ, Klocke RA. Influence of carbon dioxide kinetics on pulmonary carbon dioxide exchange. J Appl Physiol (1985). 1993;74(2):715–721.)*

Bicarbonate accounts for the majority (~79%) of the CO_2 excreted in the lungs under resting conditions (Fig. 16-1). Of this 79%, 30% entered the lung inside the erythrocytes and 49% in the plasma. There is a minimal amount of CA attached to the interior surface of the pulmonary capillaries, but its activity is ~1% of the erythrocytic enzyme. As a result, little or no conversion of bicarbonate to dissolved CO_2 occurs in the plasma during the short pulmonary capillary transit time (0.75 s at rest, 0.5 s during exercise). The quantity of bicarbonate transported in plasma is much greater than that carried within the red cells for three reasons. First, plasma volume constitutes 55% and erythrocytes only 45% of the total blood volume. Second, bicarbonate is present only in the volume of water in each component; plasma water content (95%) is substantially greater than erythrocyte water content (72%). Third, because of the Donnan distribution of anions across the erythrocyte membrane (see Chapter 15), bicarbonate concentration inside the red cell is only 63% of the plasma concentration.

As the intracellular concentration of bicarbonate decreases, plasma bicarbonate enters the cell in exchange for intracellular chloride. Bicarbonate–chloride movement across the erythrocyte membrane occurs in an electrically neutral, one-for-one exchange that is facilitated by an anion exchange protein present in the erythrocyte membrane.[2] Despite the presence of approximately one million anion exchangers with an extremely rapid turnover (50,000 ions per second) in each red cell membrane, bicarbonate–chloride exchange requires 0.3 to 0.4 s to reach completion.[6] This ionic exchange permits the continuing production of dissolved CO_2 from bicarbonate that entered the lung capillary bed in the plasma compartment of blood.

The delay between acetylene and CO_2 excretion shown in the lower panel of Fig. 16-2 illustrates the lag in CO_2 excretion that occurs if any chemical reaction or transport process is required to convert bicarbonate or carbamate into dissolved CO_2 to be excreted in the lungs. In the experimental data shown in the figure, bicarbonate conversion to CO_2 is catalyzed by a small amount of carbonic anhydrase located on the capillary endothelium. If red cells were present, the conversion to dissolved CO_2 inside the red cell would occur much more rapidly (~0.1 s) because of the large quantity of carbonic anhydrase inside red cells. However, as described above, the majority of bicarbonate entering the pulmonary capillary bed in plasma first has to enter the red cell to access intraerythrocytic carbonic anhydrase, a relatively slow process compared to exchange of dissolved CO_2 in the lung. Thus, although dissolved carbon dioxide entering the pulmonary capillaries is exchanged extremely rapidly, the CO_2 exchange derived from bicarbonate conversion is delayed by chemical and transport processes.

■ Carbamate Exchange

Besides exchange of dissolved CO_2 and bicarbonate, a modest amount of CO_2 excretion results from release of CO_2 bound to hemoglobin as carbamate.[2] The latter is a salt of a carbamic acid formed by reaction of CO_2 with terminal amino groups of the four chains of the hemoglobin molecule. The release of CO_2 bound as carbamate is caused by the alteration of the molecular conformation of hemoglobin that accompanies oxygenation. This change in configuration favors formation of the charged amino group that does not bind CO_2 (see Equations 2 and 3, Chapter 15). The carbamate reaction is complete in 0.2 to 0.3 s but cannot occur until hemoglobin is first oxygenated. The process of oxygenation further delays conversion of carbamate to dissolved CO_2. As a result, conversion of carbamate is a relatively time-consuming process that slows its actual excretion as dissolved CO_2.

In summary, exchange of CO_2 in the lung is thought to require at least ~0.4 to 0.5 or more seconds because of the series of processes that are necessary to convert CO_2 transported as bicarbonate and carbamate to dissolved CO_2.[1,5] In fact, computational models of CO_2 exchange suggest that in some circumstances total chemical and transport processes do not quite reach equilibrium prior to blood leaving the pulmonary capillary.[1,5] Even in the worst case, the degree of disequilibrium is small and a minimal increase in ventilation can easily compensate for a slight impairment of the rate of CO_2 exchange.

GASES USED TO MEASURE DIFFUSING CAPACITY

The pulmonary diffusing capacity (DL) of a gas provides an estimate of its rate of transfer from the alveoli into capillary blood. Initially investigators thought that only diffusion of gas across the alveolar-capillary membrane limited exchange. This is the case for inert gases and, as noted earlier, equilibrium of these gases is achieved rapidly even in disease. However, transfer of gases that combine with hemoglobin are limited both by diffusion across the alveolar membrane and by the rate of reactions inside red blood cells. The only gases that have measurable diffusing capacities are those with low solubility in the pulmonary membrane and high capacitance in blood as a result of binding to hemoglobin. These gases include oxygen (O_2), carbon monoxide (CO), and nitric oxide (NO).

OXYGEN DIFFUSING CAPACITY (DL_{O_2})

The diffusing capacity is calculated as the volume of gas absorbed by pulmonary blood per unit time ($\dot{V}$) divided by the pressure gradient between alveolar gas (PA) and pulmonary capillary blood (Pcap).

For oxygen,

$$DL_{O_2} = \frac{\dot{V}_{O_2}}{PA_{O_2} - Pcap_{O_2}} \tag{3}$$

Measurement of DL_{O_2} is difficult because, in addition to diffusion, O_2 transfer may be limited by other mechanisms, such as ventilation–perfusion mismatching and shunting. The measurement is further complicated by a changing capillary P_{O_2} during capillary transit that cannot be accurately determined. These difficulties have led investigators to abandon attempts to measure the diffusing capacity of oxygen.

CARBON MONOXIDE DIFFUSING CAPACITY (DL_{CO})

Carbon monoxide provides an excellent alternative to measuring diffusing capacity because CO normally is present in minimal amounts in blood and binds to hemoglobin, similar to O_2. Because capillary P_{CO} is extremely low in usual circumstances, it can be assumed to be negligible and DL_{CO} is calculated by dividing CO uptake ($\dot{V}_{CO}$) by alveolar P_{CO}.

Measurement of the Single-Breath Diffusing Capacity

Several different techniques can be used to measure the carbon monoxide diffusing capacity. The steady-state and rebreathing methods of determining DL_{CO} are employed in relatively few clinical laboratories. The steady-state method usually is performed in subjects who are exercising on a treadmill or stationary bicycle, thereby limiting its clinical application in some patients. The rebreathing methodology requires rapid-responding gas analyzers and has technical requirements that are not available in most clinical laboratories. The single-breath technique is the method utilized in clinical pulmonary function laboratories because of its relative technical ease and the ability of patients to perform the respiratory maneuvers. The patient performs a maximum expiration to residual volume followed by a maximum inspiration to the total lung capacity of a gas mixture of 0.3% carbon monoxide, 21% oxygen, an inert tracer gas with low aqueous solubility (usually helium or methane), and balance nitrogen. After the inspiration of this gas mixture, the breath is held for 10 s followed by a maximum expiration. After the expired volume is sufficient to clear the volume of the tracheobronchial dead space in which gas exchange does not occur, a gas sample is obtained. Analysis of the CO and tracer gas concentrations in the expired gas permits calculation of the diffusing capacity.

The volume of CO absorbed in the lungs can be calculated from the alveolar volume and the initial and final concentrations of CO in alveolar gas. The rate of CO uptake during the breath-hold is a function of the alveolar PA_{CO}, which falls exponentially during the breath-hold. Capillary CO pressure is assumed to be equal to zero. The single-breath diffusing capacity is calculated by:

$$DL_{CO} = \frac{60 VA}{t_{bh}\,(PB - 47)} \ln \frac{FA_{CO\ \text{initial}}}{FA_{CO\ \text{final}}} \tag{4}$$

where

60 = the number of seconds per minute
VA = the alveolar volume of gas (mL_{STPD}) present in the lung during the breath-hold
t_{bh} = the duration of the breath-hold (seconds)
$PB - 47$ = the barometric pressure (mm Hg) – water vapor pressure at 37°C
FA_{CO} = the alveolar fraction of carbon monoxide at the initial and final times of the breath-holding period

The minimally soluble inert gas included in the inspired volume is not significantly absorbed in capillary blood and is diluted in the lung volume present at the start of the maximal inspiration. Alveolar volume (VA) is calculated from the dilution of the tracer (helium in this example) and the inspired volume (VI):

$$VA = VI\frac{FI_{He}}{FA_{He}} \tag{5}$$

where

FI_{He} and FA_{He} = the inspired and alveolar helium concentrations

The alveolar fraction of helium and the final alveolar CO fraction are obtained by measuring CO and He concentrations in the expired alveolar gas sample. The initial alveolar CO fraction (FA_{CO}) is calculated from the dilution of the inspired CO in the volume of gas present in the lung during the breath-hold,

$$FA_{co} = FI_{co}\frac{VI}{VA} \tag{6}$$

where

FI_{CO} = the inspired CO fraction

Calculation of the diffusing capacity is based on the assumption that the lung is homogeneous, that is, all portions of the lung have the same relative ventilation, perfusion, alveolar volume, and diffusing capacity.

The single-breath method requires patient cooperation to perform the necessary respiratory maneuvers. A patient with an extremely reduced lung volume may not have a vital capacity large enough to sufficiently clear the dead space and provide a sufficient sample for analysis of alveolar gas concentrations. The ability to hold the breath for 10 s also limits applicability to some patients. Finally, this method can be employed only in the resting state since few patients can hold their breath during exercise. Despite these limitations, the single-breath DL_{CO} is the most practical and widely used method for measuring DL_{CO}. The technical aspects of the test have been standardized so that the same methodology is utilized in different laboratories.[7]

Measurement of Dm and V_c

Similar to oxygen, CO uptake is limited both by diffusion across the alveolar–capillary membrane and by chemical reaction of CO with intracellular hemoglobin. As described by Roughton and Forster,[8] DL_{CO} can be viewed as a composite of two elements:

$$\frac{1}{DL_{CO}} = \frac{1}{Dm_{CO}} + \frac{1}{\theta_{CO} V_C} \tag{7}$$

where

Dm_{CO} = the diffusing capacity of the alveolar–capillary membrane for CO
θ_{CO} = the rate of displacement of O_2 from red cell hemoglobin by CO
V_C = the volume of blood in the pulmonary capillary bed

Because O_2 and CO compete for binding sites on hemoglobin, CO binding is inhibited by increases in P_{O_2}. Thus, DL_{CO} and θ_{CO} vary inversely with P_{O_2}. Using in vitro values of θ_{CO} and two measurements of DL_{CO} at normal and elevated inspired O_2 concentrations, Equation (7) can be solved to provide values of both Dm_{CO} and V_C. In most clinical circumstances, only DL_{CO} breathing gas with a normal oxygen concentration is measured because of the requirement to perform two diffusing capacities with different fractions of inspired oxygen in patients needed to measure Dm and V_C.

Unfortunately, there is uncertainty regarding the actual values of θ for any gas that binds to hemoglobin contained in erythrocytes in humans in vivo. In vitro measurements of θ have utilized rapid reaction techniques that may be flawed due to unstirred layers of fluid surrounding red cells in a dilute suspension used in the experimental apparatus. This artifact is greater the more rapidly that the gas reacts with hemoglobin ($NO > O_2 > CO$). Furthermore, the rate of gas uptake by erythrocytes may be influenced by the ability of the red cells to be deformed during passage through the pulmonary capillaries, a factor not present during in vitro measurements of θ. Mathematical models suggest that the rate of uptake of gases also depends on erythrocyte orientation and spacing within capillaries. Since the characteristics of erythrocyte transit in the capillary bed have not been defined, extrapolation of in vitro measurements to the in vivo situation introduces uncertainties in the data. Despite these reservations, solution of Equation (7) using values of θ_{CO} determined in vitro yields values of Dm_{CO} and V_C that agree fairly well with independent estimates of these variables using alternative experimental techniques such as morphometry. These calculations indicate pulmonary capillary blood volume (V_C) at rest of 75 to 100 mL for men and slightly less for women.

NITRIC OXIDE DIFFUSING CAPACITY ($D_{L_{NO}}$)

Nitric oxide binds to hemoglobin at the same sites as O_2 and CO, but the rate of NO binding is much more rapid. Since NO binds to hemoglobin in solution two orders of magnitude faster than the rate of CO binding, it has been postulated that θ_{NO} is much greater than θ_{CO} and approaches a value of infinity. If this is the case, then the term $1/\theta_{NO}V_C$ (analogous to Equation (7) for CO) approaches zero and the diffusing capacity measured with NO should reflect only the resistance to gas transfer provided by the alveolar–capillary membrane, that is, the Dm_{CO} component of the CO diffusing capacity.

Unfortunately, there is uncertainty regarding the actual values of θ_{NO} that binds to hemoglobin contained in erythrocytes in humans in vivo.[9] In vitro measurements of θ_{NO} have utilized rapid reaction techniques that may be flawed due to unstirred layers of fluid surrounding red cells in a dilute suspension used in the experimental apparatus. This artifact is greater the more rapidly that the gas reacts with hemoglobin.

Furthermore, the rate of gas uptake by erythrocytes may be influenced by the ability of the red cells to be deformed during passage through the pulmonary capillaries, a factor not present during in vitro measurements of θ_{NO}. In addition, calculations of Dm and V_C using simultaneous CO and NO diffusing capacity measurements often provide substantially different values. As a result of these issues, it is premature to speculate on the potential clinical value of measurements of $D_{L_{NO}}$ until these underlying problems are clarified. In addition, measurement of $D_{L_{NO}}$ requires sophisticated equipment and technical expertise that only are present in research settings.

FACTORS INFLUENCING THE DIFFUSING CAPACITY

The CO diffusing capacity originally was thought to reflect the resistance of the alveolar–capillary membrane to transfer of CO from the alveoli to capillary blood. The classic work of Roughton and Forster[8] elucidated the influence of chemical reactions on transfer of CO. $D_{L_{CO}}$ may be a measure of decreased gas transfer caused by abnormal diffusion, but also can reflect reduction in hemoglobin concentration, nonuniform distribution of physiologic properties throughout the lung, or loss of lung tissue. Because multiple factors in addition to diffusion can affect $D_{L_{CO}}$, in Europe this test is often termed the CO transfer factor, rather than the CO diffusing capacity. If correction for factors that affect measured $D_{L_{CO}}$ are performed, the predicted values, not the measured values, of $D_{L_{CO}}$ should be adjusted.[7]

Hemoglobin Concentration

Capillary blood volume (V_C) is a prime variable in the diffusing capacity. Its importance is due to the quantity of hemoglobin available to combine with CO within the capillary bed. The calculated value of V_C can be reduced directly by diseases that decrease capillary volume, but also can vary with the concentration of hemoglobin in blood. For this reason, the predicted $D_{L_{CO}}$ can be corrected for alterations in hemoglobin concentration.[7] For adult males and adolescents:

$$\begin{aligned}&\text{Predicted } D_{L_{CO}} \text{ (Corrected)}\\ &= \text{Predicted } D_{L_{CO}}\ (1.7\ \text{Hb}/(10.22 + \text{Hb}))\end{aligned} \tag{8}$$

where

Hb = hemoglobin concentration expressed in g/dL

For adult women and children less than age 15, the factor of 10.22 in Equation (8) is replaced by a factor of 9.38. Unfortunately, most clinical laboratories do not correct the predicted value of $D_{L_{CO}}$ for abnormal hemoglobin values.

Partial Pressure of Alveolar Oxygen

As indicated previously, the actual value of θ_{CO} depends on P_{O_2}. Increased alveolar P_{O_2} will reduce measured $D_{L_{CO}}$. Therefore, measured $D_{L_{CO}}$ will be lowered if patients receive supplemental oxygen prior to the actual measurement. Conversely, reduced alveolar P_{O_2} will lead to an increment in measured $D_{L_{CO}}$. This has led to the suggestion to correct predicted $D_{L_{CO}}$ if the measurement was made with an altered inspired oxygen fraction or at altitude.

Body Position

$D_{L_{CO}}$ is 5% to 15% greater in the supine position than in the erect position. Blood volume shifts from the lower trunk and legs to the lungs when in the supine position. Most of the increase in $D_{L_{CO}}$ appears to be due to a 13% to 27% increase in V_C accompanying the fluid shift. However, there is also a minimal increase in Dm_{CO} in the supine position, possibly the result of recruitment of capillaries by the increased intravascular volume. The effect of posture on $D_{L_{CO}}$ decreases with age, but the reasons underlying this observation remain unknown.

Exercise

$D_{L_{CO}}$ can increase as much as twofold during exercise. This increase is attributed to proportionally equal increases in both Dm and V_C. Both alveolar–capillary surface area and capillary volume are recruited by the increase in cardiac output that accompanies exercise. The transit time through the capillary bed decreases, but not to the same degree as would be predicted in a vascular bed with fixed resistance. The potential reduction in transit time is partially offset by recruitment and distention of the pulmonary capillary bed.

Theoretically, $D_{L_{CO}}$ must have a maximum that cannot be exceeded when the entire pulmonary capillary bed and alveolar surface have been recruited. This should lead to a plateau in measured $D_{L_{CO}}$ even though the level of exercise continues to increase. This has not been observed in humans. Using a unique animal model of conscious greyhounds exercising on a treadmill, Carlin et al.[10] could not demonstrate a plateau in $D_{L_{CO}}$ with increasing exercise even though oxygen uptake reached a level of approximately 120 mL/kg/min. This level of O_2 uptake is almost twice that seen in highly trained humans. Thus, it seems unlikely that the diffusing capacity in humans reaches a plateau during maximal exercise, but this does not rule out the possibility that oxygen exchange is limited by diffusion in this circumstance. Disequilibrium may occur before maximum recruitment of the diffusing capacity because capillary transit time may be less than the time required for O_2 exchange to be completed. Evidence in humans suggests that blood may leave the capillary bed without attaining complete equilibrium between alveolar P_{O_2} and capillary

P_{O_2} at sea level in some highly trained athletes during maximal exercise. This also can occur in normal individuals at extreme altitude, which results in a marked reduction in the inspired P_{O_2}.

■ Alveolar Volume

DL_{CO} decreases with reduction in alveolar volume due to accompanying decreases in DL_{CO} and V_C. This occurs with an inadequate inspiration to total lung capacity in persons with normal lungs, or with maximal inspiration in patients whose total lung capacities have been reduced by disease. In an effort to correct for alterations in alveolar volume rather than a true loss of diffusing capacity, some clinicians and investigators normalize DL_{CO} by dividing the observed DL_{CO} by the alveolar volume present during the measurement. This ratio of DL_{CO}/VA will be a useful index only if two assumptions are valid. First, there must be an approximately linear relation between DL_{CO} and VA. This assumption is reasonable at lung volumes greater than 50% of total lung capacity, but not at lower lung volumes. Second, the relation between DL_{CO} and VA must be directly proportional (i.e., a graph of DL_{CO} vs. VA must pass through the origin of the graph). This clearly is not the case. DL_{CO}/VA is not constant in normal persons and varies as alveolar volume changes.[11] Although frequently used, the DL_{CO}/VA ratio alone does not provide a valid index of the effect of changes in alveolar volume.[7,11,12]

■ Nonuniform Distribution of Physiological Properties

Calculation of DL_{CO}, regardless of the method used to make the measurement, implicitly assumes that the lung is completely uniform with regard to ventilation, alveolar volume, perfusion, and diffusive properties. This requires that each gas exchange unit possesses the same relationship among all these physiologic properties, an assumption that is not completely valid even in normal, healthy persons. The most important factor determining CO uptake is the relationship of local diffusing capacity to local blood flow, the ratio of DL_{CO}/Q. Nonuniform distribution of important physiologic variables throughout the lung produces a decrease in diffusing capacity and, by analogy, a reduced ability to transfer oxygen from the inspired air to capillary blood. Transfer is further complicated by the nonlinear nature of the processes involved. For example, the oxygen dissociation curve of hemoglobin has a sigmoid shape, and a change in alveolar P_{O_2} may have a large or a minimal effect on the quantity of O_2 exchanged depending on the absolute value of the P_{O_2}. Disruptions of these complex relationships among physiologic parameters have variable effects on O_2 transfer. The contributions of individual pathophysiologic deviations cannot be assessed by a global measurement such as the diffusing capacity. Thus, DL_{CO} provides a means of assessing overall oxygen exchange but does not indicate specific defects in gas exchange.

TECHNICAL CONSIDERATIONS

Measurements of DL_{CO} have greater variation than spirometric observations such as the forced vital capacity (FVC) or forced expiratory volume in 1 s (FEV_1). Criteria for acceptable measurements of DL_{CO} have been based upon relative or absolute differences between repeated measurements. The European Respiratory Society/American Thoracic Society (ERS/ATS) consensus statement[7] recommends reporting the average of two measurements, both of which agree within 2.0 mL/min/mm Hg or within 10% of the higher measured value. Punjabi et al.[13] reported that an absolute difference of 2.5 mL/min/mm Hg between duplicate measurements could be achieved in 96% of patients. This criterion was deemed more reasonable than a percentage variation because it remained constant over a wide range of measured values in contrast to a changing percentage criterion. The strength of this study is in its size (more than 6000 patients) and its performance during routine pulmonary testing in a single clinical setting. A drawback to its universal application is that three or more determinations of DL_{CO} were required in one-half of patients to meet criteria of acceptability. It is important to note that some clinical laboratories will perform only a single diffusing capacity measurement and report this value rather than reporting the mean of at least two acceptable determinations. This obviously increases the variability of reported values and lessens the ability to compare measurements over a period of time.

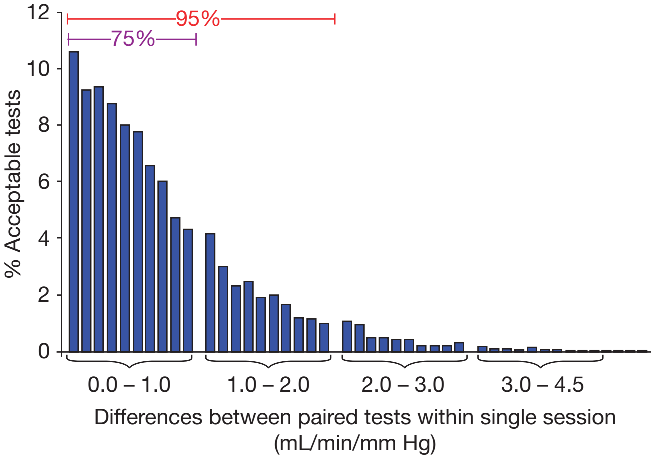

Figure 16-3 Differences between pairs of DL_{CO} measured within a single session in 4732 patients who had acceptable DL_{CO} efforts. The bars in the figure include differences in 75% of paired measurements *(purple)* and the differences in 95% of paired measurements *(red). (Data from Wise RA, Teeter JG, Jensen RL, et al. Standardization of the single-breath diffusing capacity in a multicenter clinical trial. Chest. 2007;132(4):1191–1197.)*

There is considerable variation in measurements of DL_{CO} among different clinical laboratories. These differences can be overcome by following strict technical protocols. In a carefully controlled multicenter (33 sites) clinical trial, Wise et al.[14] reported that 75% and 95% of the differences between duplicate DL_{CO} determinations with acceptable subject efforts (4797 pairs) were within <1 and <2 mL/min/mm Hg, respectively (Fig. 16-3). Acceptable criteria included inspired volume >90% of the FVC and a breath-hold time of 9–11 s.

The time of the breath-holding maneuver in the single-breath method requires patient cooperation. Because of nonuniform distribution of physiologic variables, CO uptake does not occur in a strictly exponential fashion even in some healthy persons. As a result, measured DL_{CO} decreases slightly with prolonged breath-hold in normal subjects. This decrement can be substantially greater in patients with lung disease. The empirical breath-holding time of 10 s was chosen as a practical compromise to permit measurable CO uptake but still be feasible for patients to perform. Many laboratories set a breath-hold range of 9 to 11 s as acceptable, although the ERS/ATS consensus report[7] stipulates a range of 8 to 12 s. Patients with lung disease often cannot perform rapid respiratory maneuvers mandated by the single breath DL_{CO} measurement. Slower flow rates prolong the time required for inspiration and expiration. As a result, instantaneous, uniform mixing of alveolar contents assumed in the calculation of DL_{CO} is not achieved. This may lead to a decrement in the reported measurement.

Most laboratories request that patients refrain from smoking for variable periods of time prior to measurement of DL_{CO} to avoid accumulation of CO in blood. Significant elevation of carboxyhemoglobin reduces measured DL_{CO} in two ways. First, the presence of carboxyhemoglobin produces a functional anemia, lessening the capacity of hemoglobin to bind O_2 or CO. This reduces the $\theta_{CO}V_C$ component of DL_{CO}. Second, calculation of DL_{CO} assumes that the back pressure of

CO in the capillary is zero, and the gradient for CO transfer is equal to PA_{CO}. The presence of carboxyhemoglobin in blood produces an actual alveolar-capillary P_{CO} gradient less than that assumed in the calculation, thereby leading to a lower calculated value of DL_{CO}. Graham et al.[15] measured the effect of experimental elevation of carboxyhemoglobin in normal individuals. Values of DL_{CO} obtained with the usual single-breath calculation decreased approximately 1.5% from the true value for each 1.0% elevation of blood carboxyhemoglobin. Although algorithms are available to correct observed DL_{CO} for carboxyhemoglobin effects, it is preferable to make the measurement without a significant elevation of carboxyhemoglobin. At a minimum, 12 hours of abstinence from smoking is advisable in patients who smoke extensively because carboxyhemoglobin levels as great as 6% to 12% are observed immediately following tobacco usage.

Measurement of DL_{CO} has been improved by the development of new equipment in recent years.[7] Previously the expired gas sample was obtained after a variable volume of expiration to clear the dead space. This sample was then analyzed for CO and tracer gas off-line. Newer equipment utilizes online rapidly responding analyzers that provide a record of expired tracer gas and CO concentrations as a function of inspired and expired volumes throughout the entire study. The record of the expired tracer gas as a function of lung volume allows an accurate measurement of the dead space, indicating the proper point to utilize the CO data to calculate DL_{CO}. While this has little value in normal individuals, it provides more accuracy in determining the point in expiration to sample gas volumes in patients, particularly in those with obstructive lung diseases. This may improve accuracy of DL_{CO} measurements by 8%–15%.[7] Although the current equipment does not use this data for other improvements, the authors of the ERS/ATS standards point out that this will improve the reproducibility of the measurements and may provide estimates of gas mixing and variation of the diffusing capacity throughout the lungs.[7]

UNCERTAINTIES IN INTERPRETATION OF DL_{CO}

As noted previously, DL_{CO} is affected by a number of circumstances. Alveolar P_{O_2} and body position do not present significant problems since a standard inspired P_{O_2} and the sitting position are utilized during measurements in almost all clinical laboratories. Equations to correct for alterations of alveolar P_{O_2} are available if needed. Empirical equations also can adjust the predicted value of DL_{CO} to compensate for anemia or polycythemia.

Variability in cardiac output and the alveolar volume present during the measurement provides more significant problems. The increases in DL_{CO} observed during exercise are the result of increases in cardiac output. Increasing cardiac output together with enlargement of the capillary bed not only increases V_C but also increases Dm because capillary volume and surface area of the alveolar–capillary membrane are related variables. Clinical measurements of DL_{CO} are accomplished under resting conditions, minimizing but not obviating variability in cardiac output. In addition, disease can alter the distribution of blood flow in the lung in patterns that do not match the distribution of diffusive properties. Measurements of pulmonary blood flow and its distribution are not measured in usual clinical laboratories. As a result, the effect of cardiac output on DL_{CO} cannot be appreciated in routine determinations. The only practical alternative is to minimize conditions that might alter cardiac blood flow.

Reduction in alveolar volume by disease is a large potential source of error in interpreting DL_{CO}. Correction for the effect of reduced alveolar volume has been attempted by reporting the ratio of DL_{CO}/VA. However, this attempt to normalize measurements by alveolar volume leads to errors because DL_{CO}/VA does not remain constant as alveolar volume changes. Stam et al.[11] reported values of DL_{CO} and DL_{CO}/VA obtained at several alveolar volumes in normal subjects. They recommend using predicted values of DL_{CO} or DL_{CO}/VA for patients with reduced alveolar volumes equal to values in normal subjects measured at the same reduced alveolar volume. This assumes that disease processes that reduce alveolar volume in patients produce the same changes in DL_{CO} as voluntary reduction in alveolar volume in normal subjects. However, other reports in different clinical conditions suggest that some diseases may not affect DL_{CO} in the same manner as voluntary changes in normal subjects. Uncertainties have led to questions regarding the value of the ratio DL_{CO}/VA.[7,11]

Measurements of Dm_{CO} and V_c can be useful in a carefully controlled research setting, but there is little value of using isolated measurements of these two parameters to aid in diagnosis and clinical management. Calculation of Dm_{CO} and V_c involves both a number of assumptions and extrapolations of data in the literature to a specific clinical setting. Even more cogent is the lack of sufficient data to validate the value of these measurements in clinical practice.

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CHAPTER 17

Acid–Base Balance

Stanley Goldfarb

INTRODUCTION

Regulation of $[H^+]$ is of crucial importance for maintenance of normal cellular functions. The normal $[H^+]$ is maintained at about 40 nEq/L. When there is even a small change in the $[H^+]$, intracellular proteins gain or lose H^+ ions resulting in alterations in charge distribution that may affect molecular structure and protein function. The hydrogen ion concentration in bodily fluids is largely regulated by the ratio of the concentrations of carbon dioxide and bicarbonate. This is predicated upon the relationship demonstrated in the Henderson–Hasselbalch equation:

$$\text{pH} = \text{pKa} + \frac{[\text{HCO}_3^-]}{0.03\text{P}_{\text{CO}_2}} \qquad (1)$$

where $\text{pH} = -\log[H^+]$ (the H^+ concentration measured in moles per liter) and $\text{pKa} = 6.10$. The lungs are responsible for modulating arterial P_{CO_2}, whereas the kidneys are primarily responsible for modulating the concentration of bicarbonate in plasma. In concert, these organs maintain a stable extracellular acid–base milieu that is readily assessed by measuring arterial pH.

The normal internal environment is maintained within narrow limits: The arterial blood pH is kept remarkably close to 7.40, the bicarbonate concentration is maintained around 24.5 mEq/L, and the P_{CO_2} is maintained at about 40 mm Hg. Deviations of the pH with accompanying changes in the P_{CO_2} and $[HCO_3^-]$ result in the four major categories denoted in Table 17-1. Metabolic acidosis is characterized by acidemia (pH <7.35) that is due to reduced plasma $[HCO_3^-]$. Metabolic alkalosis is characterized by an alkalemia (pH >7.45) that results from an elevation in the plasma $[HCO_3^-]$. Respiratory acidosis is due to hypoventilation resulting in a net increase in P_{CO_2} (hypercapnia) and a concomitant fall in pH. Respiratory alkalosis is due to primary hyperventilation leading to a fall in P_{CO_2} (hypocapnia) and a rise in pH.

In this chapter, the basic physiologic roles that the kidneys and lungs play in maintaining acid–base balance is reviewed before discussion of their adaptation in primary acid–base disorders. The following section then focuses on clinical application of physiologic concepts in analyzing acid–base problems as encountered by the clinician.

BASIC PHYSIOLOGY OF THE KIDNEY IN ACID–BASE BALANCE

Normal metabolism generates large quantities of volatile acid (CO_2) and nonvolatile acid daily. The complete metabolism of carbohydrates and fats generates 15,000 mmol of CO_2 daily. This leads to acid generation as the CO_2 combines with H_2O to form carbonic acid (H_2CO_3). As the volatile fraction is excreted by the lungs during respiration, acid accumulation does not occur. The nonvolatile or "fixed" fraction is produced at a rate of 1 mEq/kg per day. The major source of the nonvolatile acid fraction is the oxidation of sulfur-containing proteins from the diet to sulfuric acid. If this amount of nonvolatile acid is not excreted, life-threatening metabolic acidosis ensues; therefore, for a normal individual to maintain acid–base balance, 50 to 100 mEq of nonvolatile acid must be excreted daily by the kidneys.

The addition of 50 to 100 mEq of acid requires initial buffering before it can be excreted. Whole-body buffering capacity is composed of interacting buffer systems: the bicarbonate and nonbicarbonate buffers (Buf^-), consisting primarily of hemoglobin, proteins, and phosphates. The sum of the buffer anions $[HCO_3^-]$ and $[\text{Buf}^-]$ is the total buffer base and defines total-body buffering capacity. Since all body buffer systems are in equilibrium, a change in the serum $[HCO_3^-]$ reflects concurrent changes in the other body buffer systems. The importance of bicarbonate in buffering is due to its relationship with CO_2. As H^+ ions are buffered by HCO_3^-, there is a decrease in the $[HCO_3^-]$ and a concurrent increase in the dissolved $[CO_2]$. As the $[CO_2]$ can be excreted by the lungs to maintain a constant $[CO_2]$, this substantially increases the buffering capacity of bicarbonate. Since the kidney plays a major role in controlling the $[HCO_3^-]$ and $[HCO_3^-]$ is easily measured in serum, the HCO_3^- anion is a useful parameter to evaluate the renal response to an acid load.

The H^+ ions released from the dissociation of sulfuric acid are titrated by blood bicarbonate and nonbicarbonate buffers.

$$H_2SO_4 + 2NaHCO_3 \rightarrow Na_2SO_4 + 2H_2CO_3 \rightarrow 2H_2O + CO_2 \qquad (2)$$

Although the added H^+ is excreted via CO_2 elimination by the lungs, this occurs at the cost of depletion of $[HCO_3^-]$. To *replenish* the consumed base, bicarbonate is reabsorbed by the kidneys and returned to the blood. This process does not accomplish the replacement of consumed base, since continuous metabolic production of acid will ultimately decrease the available base present. The process of renal *regeneration* of base requires the urinary excretion of acid or H^+ ions in the absence of any urinary bicarbonate. For every H^+ ion excreted, a bicarbonate is returned to the body. If there is any bicarbonate in the urine, there will be a net gain of H^+. Therefore, the kidney has two major functions in this context: (1) Reabsorption of all the filtered bicarbonate; this takes place primarily in the proximal tubule, and (2) The base consumed by metabolism must be

TABLE 17-1 Patterns of P_{CO_2} and HCO_3 Changes in Acid–Base Disorders

Primary Disturbance	Initial Abnormality	Compensatory Response	Expected Compensation
Metabolic acidosis	Decreased pH, decreased $[HCO_3^-]$	Decreased P_{CO_2}	$P_{CO_2} = 1.5 \times [HCO_3^-] + 8 \pm 2$ (Winter's formula)
Metabolic alkalosis	Increased pH, increased $[HCO_3^-]$	Increased P_{CO_2}	P_{CO_2} increases 0.6 mm Hg per mEq/L rise in $[HCO_3^-]$
Respiratory acidosis	Decreased pH, increased P_{CO_2}	Increased $[HCO_3^-]$	Acute: $[HCO_3^-]$ increases 1 mEq/L per 10 mm Hg rise in P_{CO_2} Chronic: $[HCO_3^-]$ increases 3.5 mEq/L per 10 mm Hg rise in P_{CO_2}
Respiratory alkalosis	Increased pH, increased P_{CO_2}	Decreased $[HCO_3^-]$	Acute: $[HCO_3^-]$ falls 2 mEq/L per 10 mm Hg fall in P_{CO_2} Chronic: $[HCO_3^-]$ falls 5 mEq/L per 10 mm Hg fall in P_{CO_2}

generated in the process of urinary acid excretion; this takes place in the distal portions of the nephron, the distal collecting tubule, and the collecting ducts.

■ Bicarbonate Reclamation

The proximal tubule is responsible for reclaiming 70% to 90% of the filtered bicarbonate. This may occur either by direct bicarbonate absorption at the proximal tubule or via proton secretion into the lumen of the tubule. The latter mechanism appears to be the predominant pathway.[1] Acid excretion across the apical membrane of the proximal tubule occurs by an Na^+/H^+ antiporter (NHE3)[2] and to a lesser extent by a proton pump. The secreted proton enters the tubular fluid and combines with filtered bicarbonate ions leading to carbonic acid formation. Under the influence of carbonic anhydrase, carbonic acid is then split into CO_2 and H_2O. The CO_2 diffuses into the cell where it is rehydrated to carbonic acid and then again split into protons and bicarbonate. The bicarbonate ion exits from the cell through the basolateral membrane into the interstitium via a $3HCO_3/Na$ (NBCe1) symporter, while the proton is secreted into the lumen. The basolateral membrane Na^+/K^+ ATPase antiporter, maintaining a low intracellular sodium concentration, further enhances the NHE3 activity.

In summary, reabsorption of bicarbonate is a cyclic phenomenon and requires carbonic anhydrase and is strictly associated to sodium reabsorption.

Biochemical studies show that total NHE3 and NBCe1 protein abundance are upregulated by chronic respiratory acidosis.[3] However, the main mechanism responsible for the elevation in serum bicarbonate is the increased excretion of titratable acid and ammonium, which are stimulated by persistently elevated P_{CO_2} (Fig. 17-1).[4] It is important to understand that this process reclaims filtered bicarbonate but does not result in a net gain of bicarbonate. At the end of the proximal tubule there is a lowering of the luminal pH from 7.26 to 6.70, and the bicarbonate concentration is lowered from 24 mEq/L to 8 mEq/L.[5] The fluid delivered to the distal tubule is essentially the same with respect to pH and bicarbonate concentration as that which leaves the proximal tubule. The reclamation of the remaining bicarbonate occurs in the thick ascending limb and in the outer medullary collecting tubule. At the collecting tubule, H^+ secretion occurs primarily by an H^+ ATPase pump at the luminal membrane, and bicarbonate entry to the blood is via a Cl^-/HCO_3^- exchanger at the basolateral membrane.[6]

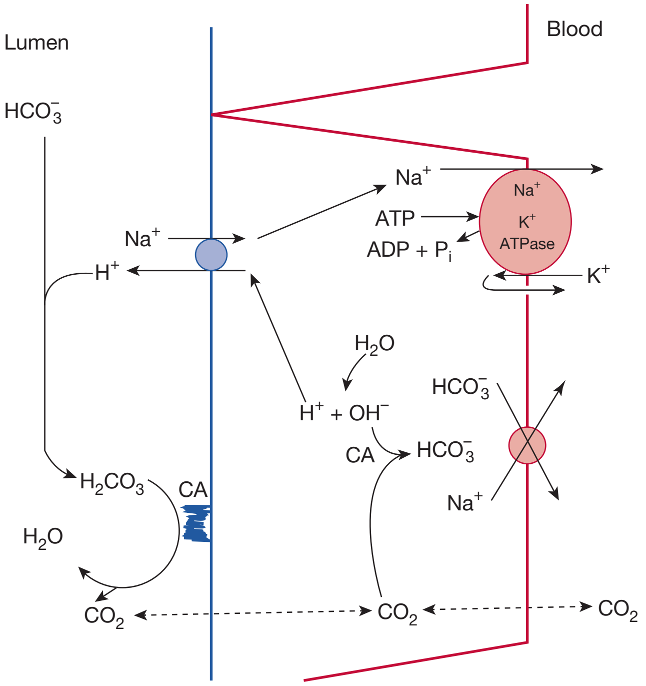

Figure 17-1 Schematic representation of proximal tubular reclamation of filtered bicarbonate. In the lumen, filtered bicarbonate reacts with secreted H^+, generating carbonic acid, which is dehydrated by carbonic anhydrase, CA, located on the brush border. The cell secretes H^+ by a process that exchanges H^+ for filtered Na^+. The source of secreted H^+ is water, which in turn generates OH^- and subsequently bicarbonate because of the presence of intracellular CA. Bicarbonate exits the basolateral side of the cell linked in some fashion with Na^+; sodium is also actively pumped out of the cell.

The crucial role of carbonic anhydrase is demonstrated by the fact that carbonic anhydrase inhibitors, that is, acetazolamide, result in bicarbonate wasting and the generation and maintenance of metabolic acidosis. The most physiologically important regulators of reclamation of bicarbonate are the pH, the P_{CO_2}, and the extracellular volume status of the patient. In states of acidosis, there is enhanced luminal Na^+/H^+ exchange that may be mediated by an increase in intracellular H^+ ions and by increasing the number of new exchangers and increased activity of the Na^+/HCO_3^- cotransporter at the basolateral membrane. Elevation of the P_{CO_2} will promote higher proximal tubular concentration of CO_2 and lead to intracellular acidosis, giving rise to further secretion of H^+ ions and reclamation of bicarbonate. If there is volume depletion, there will be avid Na^+ reabsorption at the proximal tubule in exchange for H^+ and thus greater reabsorption of bicarbonate. Other factors that are important include the luminal bicarbonate concentration, the tubular flow rate, and the serum potassium.

■ Net Renal Acid Excretion

Net excretion of acid occurs primarily in the distal nephron and is largely mediated by the active secretory pumps, H^+-K^+ ATPase and H^+ ATPase. The latter appears to be linked in some way to Cl^- reabsorption to preserve electroneutrality. By definition, to produce net H^+ excretion the secreted H^+ will have to be excreted in processes that do not consume bicarbonate.

To achieve net secretion of protons in the luminal fluid of the distal nephron requires association of the protons with urinary buffers other than bicarbonate. Although secreted protons lower the urinary pH to 4.5 resulting in a 3-pH-unit differential from arterial pH (a 1000-fold increase in H^+ concentration), the quantity of acid excreted as free H^+ is trivial. For example, daily excretion of 2 L of urine with a pH of 5 would result in excretion of only 0.02 mEq of dissociated H^+ ions in contrast to the 50 to 100 mEq of H^+ generated each day from dietary sources. The nonbicarbonate buffers present in the urine that carry out the role of net acid excretion are the titratable buffers, primarily phosphate, which accounts for 40% of net acid excretion, and ammonia, which accounts for the remainder.

The ability of phosphate to act as proton acceptor in the urine is based on its pKa of 6.8. As the urine pH is lowered below the pKa of 6.8, there is conversion of HPO_4^- to H_2PO_4. This transfer continues until the urine pH reaches 5.5, at which point almost all the phosphate present is in the associated form, H_2PO_4. Other components of this system are uric acid (pKa = 5.75) and creatinine (pKa = 4.97). Although the titratable buffers account for a sizable fraction of net basal acid excretion, they cannot increase in amount to enhance acid excretion in settings of acid loading since phosphate excretion depends on phosphate intake and not on synthesis as is the case for ammonia excretion.

The rate of ammonium (NH_4^+) production and excretion can, however, be varied according to physiologic needs. Ammonia (NH_3) combines with H^+ to form ammonium, which is trapped in the collecting tubule lumen and excreted in the urine. The pKa for

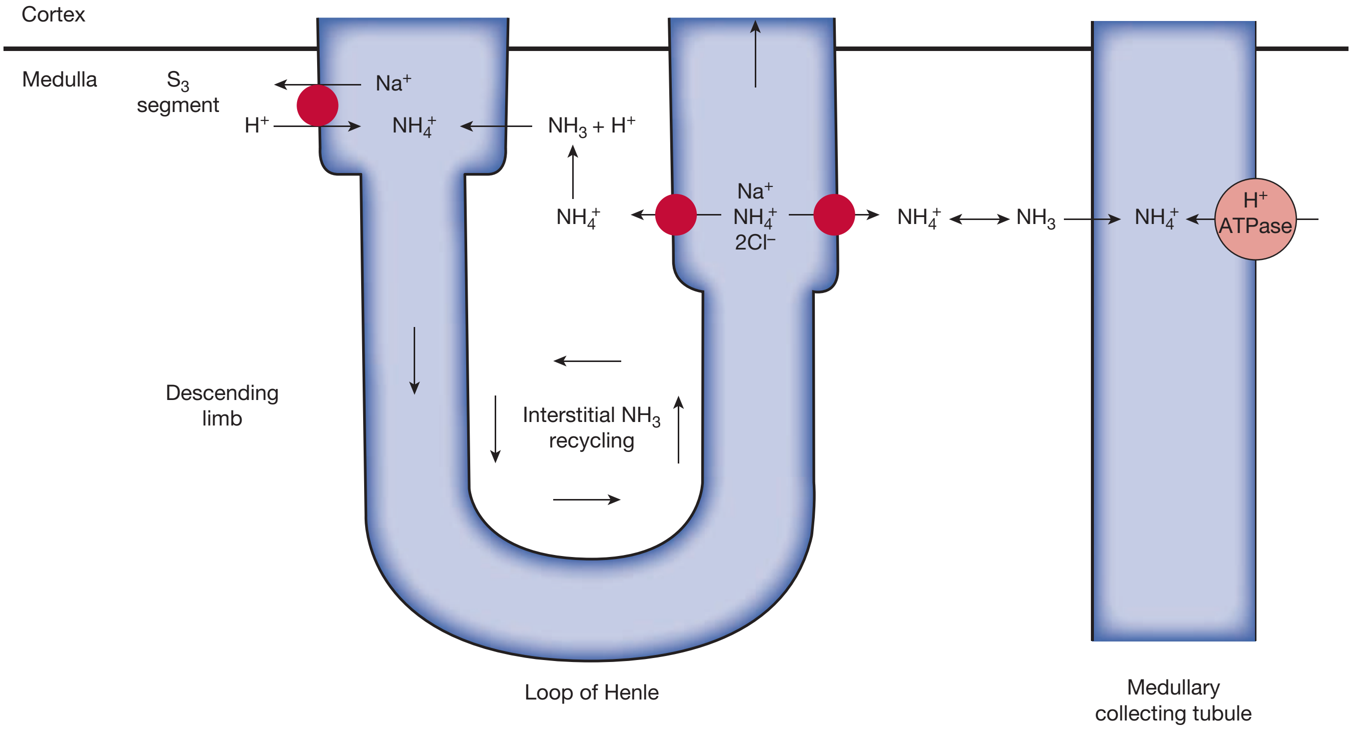

Figure 17-2 Schematic representation of ammonia recycling within the renal medulla. Although NH_4^+ production occurs predominantly in the proximal tubule, most of the NH_4^+ is then reabsorbed in the thick ascending limb, apparently by substitution for K^+ on the Na^+-K^+-$2Cl^-$ carrier in the luminal membrane. Partial dissociation into NH_3 and H^+ then occurs in the less acid tubular cell. The NH_3 diffuses into the medullary interstitium, where it reaches relatively high concentrations; it then diffuses back into those segments that have the lowest pH and therefore have the most favorable gradient: the S_3 segment of the late proximal tubule and, more important, the medullary collecting tubule, where the secreted NH_3 is trapped as NH_4^+ and then excreted. *(Reproduced with permission from Rose B. Clinical Physiology of Acid-Base and Electrolyte Disorders, 4th ed. New York, NY: McGraw Hill; 1994.)*

this reaction is 9.0. The majority of ammonia is synthesized in the proximal tubular cell by the enzymatic breakdown of glutamine. Glutamine is actively taken up by the proximal tubule at the apical and basolateral membranes and transported to mitochondria.[1] Deamidation by glutaminase forms ammonium and glutamate. The latter is further metabolized by glutamate dehydrogenase to form ammonium and α-ketoglutarate. Metabolism of α-ketoglutarate to bicarbonate in the liver leads to return of bicarbonate to the systemic circulation (Fig. 17-2).

The ammonium that is formed is transported into the proximal tubular lumen via the Na^+-H^+ antiporter, working in this case as an Na^+–NH_4^+ antiporter. The ammonium is then reabsorbed in the thick ascending limb by substitution of NH_4^+ for K^+ on the Na^+–K^+–$2Cl^-$ carrier. The intracellular ammonium in the thick ascending limb cell is then dissociated into ammonia and H^+. The ammonia accumulates in the medullary interstitium and is finally secreted into the lumen of the medullary collecting tubule. At this site, due to the low lumen pH (4.5–5) the ammonia accepts an H^+ and is trapped in the lumen and excreted in the urine as NH_4Cl.

The importance of the ammonia system is that it can be regulated by the systemic acid–base state. An acid load initially leads to an increase in ammonium excretion within 2 hours due to formation of a more acidic urine, which enhances ammonia diffusion into the lumen at the collecting duct. After 5 to 6 days there is maximal NH_4^+ excretion due to increased glutamine uptake and enhanced activity of phosphate-dependent glutaminase and glutamate dehydrogenase to produce more ammonium in the proximal tubule.[6] This is presumably mediated by intracellular acidosis of the proximal tubular cell. The net effect is that NH_4^+ excretion can increase from about 30 mEq/d to as much as 300 mEq/d in severe metabolic acidosis. The plasma potassium is an important regulator of ammonia synthesis, as hyperkalemia will result in a transcellular influx of K^+ in exchange for H^+ resulting in lowering of the intracellular H^+ concentration, thus causing an intracellular alkalosis with consequent inhibition of ammonia synthesis. Hypokalemia would have the opposite effect. Urinary acidification also is very important, since an inability to lower urinary pH will result in a reduction in NH_3 trapping in the collecting duct lumen and a subsequent inhibition of the degree of ammonium formation. Inadequate acidification of the urine will also inhibit H_2PO_4 formation.

RESPIRATORY CONTRIBUTION TO ACID–BASE BALANCE

The major roles of the lungs in acid–base balance are to excrete the CO_2 produced daily by aerobic metabolism and to compensate for primary metabolic acid–base disturbances by altering the rate and depth of ventilation. The CO_2 generated by the tissues diffuses into the plasma, at the peripheral capillaries, and is present in the blood in three compartments. Part of the CO_2 remains in the gas phase, but the amount is limited by the solubility coefficient of CO_2 (0.03 mM/mm Hg). CO_2 may also react with amino groups of proteins and form carbamino compounds. The majority of the CO_2 is carried within red blood cells.[7] The red cells contain carbonic anhydrase, which hydrates the CO_2 and thus forms carbonic acid, which dissociates to H^+ and HCO_3^-. The protons are buffered by hemoglobin which has an increased affinity for H^+ at the low oxygen tension present in the peripheral capillaries and venous blood. The bicarbonate produced in the red cell leaves the cell in exchange for chloride. This chloride shift is a characteristic response to elevation of CO_2 in the blood resulting in an acute elevation of bicarbonate in exchange for a drop in serum chloride. When the blood enters the pulmonary circulation, the enhanced oxygenation of hemoglobin promotes release of bound H^+. The H^+ and HCO_3^-, via carbonic anhydrase, combine to reform CO_2, which passively diffuses from the blood into the pulmonary interstitium where the CO_2 tension is very low. Subsequently, CO_2 is lost into the alveolar space.

The rate of minute ventilation is controlled by two sets of chemoreceptors: those in the respiratory center in the brain stem and those in the carotid and aortic bodies located at the bifurcation of the carotid arteries and in the aortic arch, respectively. The central chemoreceptors are stimulated by an increase in the P_{CO_2} or by metabolic acidosis, both of which appear to be sensed by a fall in the pH of the surrounding cerebral interstitial fluid. The peripheral chemoreceptors are primarily stimulated by hypoxemia, although they may also respond to acidemia. The level of alveolar or effective ventilation varies in accord with the total minute ventilation. Level of total ventilation changes as a function of metabolic demand. Under normal circumstances, P_{CO_2} is well controlled between 38 and 42 mm Hg according to the relationship:

$$P_{CO_2} = \frac{\dot{V}_{CO_2}}{\dot{V}_A} \qquad (3)$$

where $\dot{V}_{CO_2}$ is CO_2 production (reflecting metabolic rate) and $\dot{V}_A$ is alveolar ventilation (reflecting CO_2 clearance).

Under basal conditions the volatile acid production or CO_2 that is metabolically generated is completely eliminated by the lungs. The mechanism of the central stimulation of respiration in response to an elevated CO_2 is a topic of intense debate and will not be focused upon in this section (see further details in Chapter 11). However, intracranial adjustments to pH have been consistently observed and have interesting parallels to the effects of acidosis on the proximal tubular cell in the kidney. Increased concentrations of CO_2 in the cerebrospinal fluid (CSF) result in intracellular acidosis, an increase in CSF bicarbonate concentration, and an equimolar reduction in CSF chloride concentration.[7] As brain cells increase their bicarbonate concentration, there is increased buffering, and intracellular brain pH is returned toward normal. The major group of cells within the central nervous system (CNS) responsible for acid–base regulation are the glial cells and the cells of the choroid plexus.[7,8] These cells contain carbonic anhydrase,[9] which converts intracellular CO_2H_2O to H^+ and HCO_3^-. The H^+ is exchanged for Na^+ on the blood side, allowing the intracellular pH to increase. The administration of acetazolamide into the cerebral ventricles blocks the expected increase in CSF bicarbonate in response to hypercapnia.[8] In addition to changes in bicarbonate concentration in the CSF in response to hypercapnia, there are also changes in the levels of ammonia.[10] Brain and CSF ammonia increase in hypercapnia; ammonia acts to enhance H^+ buffering thereby preventing a fall in the bicarbonate concentration.

ACUTE AND CHRONIC ADAPTATION TO RESPIRATORY ACIDOSIS

Figure 17-3 depicts the acute steady-state relationships among P_{CO_2}, plasma bicarbonate concentration, and plasma hydrogen concentration during graded degrees of acute hypercapnia.[11,12] These observations were obtained by sequentially exposing unanesthetized normal human volunteers to increasing concentrations of inspired carbon dioxide in a large environmental chamber. Increasing degrees of hypercapnia are associated with a curvilinear rise in plasma bicarbonate concentration, with higher levels of P_{CO_2} resulting in lesser incremental changes in bicarbonate concentration. This acute rise in bicarbonate is largely due to the chloride shift as described earlier. As a result of the modest increment in bicarbonate, the average rise in plasma $[H^+]$ is limited to 0.75 nEq/L per mm Hg rise in P_{CO_2} rather than the 1-nEq/mm Hg rise that would have occurred if the plasma bicarbonate concentration did not change.[13]

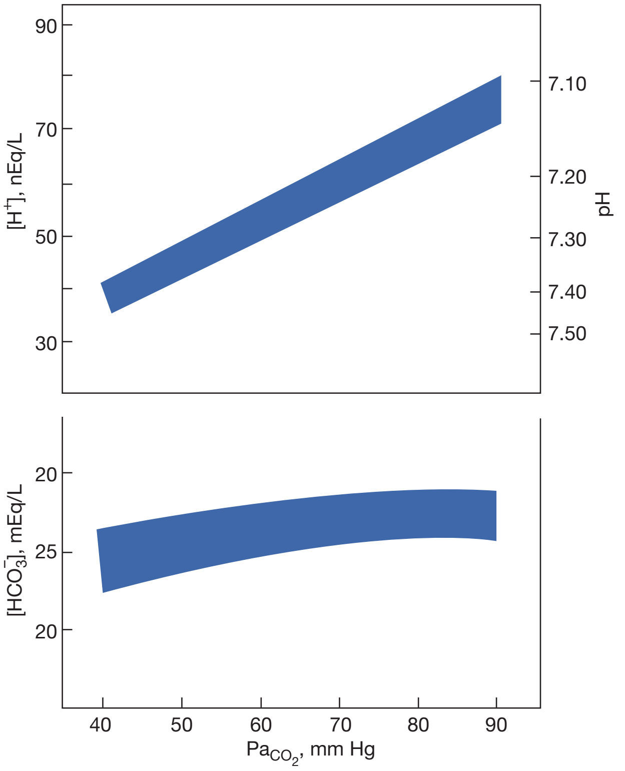

Figure 17-3 Ninety-five percent confidence bands for plasma hydrogen ion and bicarbonate concentrations during acute hypercapnia in normal humans. *(Adapted with permission from Brackett NC Jr, Cohen JJ, Schwartz WB. Carbon dioxide titration curve of normal man. Effect of increasing degrees of acute hypercapnia on acid-base equilibrium. N Engl J Med. 1965;272:6–12.)*

The quantitative aspects of the adaptive response to acute hypercapnia are influenced markedly by the baseline acid–base status. Acute hypercapnia induces a larger increment in both plasma bicarbonate and H^+ ion concentrations in animals with pre-existing hypobicarbonatemia (whether from metabolic acidosis or from chronic respiratory alkalosis) than in animals with pre-existing hyperbicarbonatemia (whether from metabolic alkalosis or from chronic respiratory acidosis).[14] This points out that the factor controlling the amount of bicarbonate generated from an acute rise in P_{CO_2} is not only the initial pH but also the initial bicarbonate concentration. Although the rise in bicarbonate in response to hypercapnia limits the fall in pH acutely, to excrete the gain of H^+ produced from the rise in P_{CO_2} requires renal compensatory mechanisms.

During the initial period of respiratory acidosis, renal compensation takes about 3 to 5 days, during which time there is enhanced reabsorption of proximal tubular bicarbonate, enhanced secretion of H^+, and increased ammonia production.[15]

These processes will lead to an increase of the serum bicarbonate concentration and a rise in the systemic pH toward normal. However, when a steady state is achieved and a stable P_{CO_2} is present, there is no longer an increase in ammonia production. As filtered bicarbonate is increased, there is enhanced proximal secretion of H^+ and a normalization of intracellular pH removing the stimulus for ammonia synthesis.[15]

RENAL ADAPTATION TO RESPIRATORY ALKALOSIS

The adaptive responses to respiratory alkalosis occur in two distinct steps, in close analogy with respiratory acidosis. Hypocapnia reduces the carbonic acid concentration and causes a prompt fall in H^+.[16] Acutely, this alkalemia is ameliorated by a secondary, adaptive reduction in plasma bicarbonate concentration that stems principally from titration of nonbicarbonate body buffers.[17] During protracted hypocapnia, renal adaptive mechanisms yield a further and larger secondary reduction in plasma bicarbonate that results in still greater amelioration of the alkalemia.[17]

In acute uncomplicated respiratory alkalosis the plasma bicarbonate concentration falls by approximately 0.2 mEq/L for each mm Hg reduction in P_{CO_2}. Thus, a reduction in plasma bicarbonate of 3 to 4 mEq/L occurs within minutes after P_{CO_2} is lowered to 20 to 25 mm Hg. The resulting change in plasma H^+ concentration is approximately 0.75 mEq/L for each mm Hg fall in P_{CO_2}, similar to the relationship between P_{CO_2} and H^+ in acute hypercapnia.

When hypocapnia persists beyond the acute phase, the additional decrement in plasma bicarbonate concentration is a consequence of renal adaptive responses and reflects a damping of hydrogen ion secretion by the renal tubule.[5] As a result, a transient suppression of net acid excretion occurs, largely manifested by a fall in ammonium excretion and by an increase in net bicarbonate excretion. These changes lead, in turn, to a positive hydrogen ion balance and a reduction in the body's bicarbonate stores. Persistence of the resulting hypobicarbonatemia is explained by the continued inhibition of tubular hydrogen ion secretion and suppression of bicarbonate reabsorption.

The adaptive retention of acid during chronic hypocapnia is normally accompanied by a loss of sodium into the urine; the resultant decrease in the extracellular volume promotes chloride retention and the typical hyperchloremia of chronic respiratory alkalosis.[18] Upon reaching a new steady state, the net excretion of acid returns to control levels, and the altered anionic concentration of the extracellular fluid (ECF), namely hypobicarbonatemia and hyperchloremia, is maintained by a reduced bicarbonate reabsorption and enhanced chloride reabsorption. On average, the combined effect of cell buffers and renal compensation results in a new steady state in which the plasma HCO_3^- concentration falls approximately 4 mEq/L for each 10-mm Hg reduction in the P_{CO_2}.[19] The renal adaptation to persistent hypocapnia appears to be mediated by some direct effect of P_{CO_2} itself, not the systemic pH. In animals in which plasma bicarbonate was reduced by HCl loading prior to adaptation to sustained hypocapnia, the renal response to a primary reduction in P_{CO_2} was the same as in normal individuals, even though the net effect of this adaptation was an overt fall in pH.

RESPIRATORY ADJUSTMENT TO METABOLIC ACIDOSIS

Metabolic acidosis stimulates both central and peripheral chemoreceptors to increase alveolar ventilation and decrease P_{CO_2} to limit the fall in pH. Although peripheral chemoreceptors appear to play a small role, in animal experiments the same degree of respiratory compensation occurs with intact and with ablated peripheral chemoreceptors. The increase in ventilation begins within 1 to 2 hours and reaches its maximal level at 12 to 24 hours. The stereotype is Kussmaul breathing in acute diabetic ketoacidosis, in which tidal volume is characteristically large with minute ventilation increasing by as much as 35 L. On average, studies in otherwise normal patients with metabolic acidosis reveal that the P_{CO_2} will fall 1.2 mm Hg for every 1.0-mEq/L reduction in plasma HCO_3^- down to a minimum P_{CO_2} of 10 to 15 mm Hg.[20]

On the other hand, failure to mount the expected ventilatory response to metabolic acidosis is an important indicator of respiratory decompensation. Daniel et al.[21] in 140 critically ill trauma patients with metabolic acidosis applied the traditional formula derived from patients with chronic metabolic acidosis. Those whose Pa_{CO2} exceeded the predicted Pa_{CO_2} by 2 mm Hg or more were 4.2 times more likely to be intubated and compensation status was an independent predictor of intubation as early as 60 minutes after episodes of significant hypotension.

RESPIRATORY ADJUSTMENT TO METABOLIC ALKALOSIS

The development of metabolic alkalosis is sensed by the respiratory chemoreceptors resulting in a decline in alveolar ventilation and an elevation of the P_{CO_2}. On average, the P_{CO_2} rises 0.7 mm Hg for every 1.0-mEq/L increment in the plasma HCO_3^- concentration.[18] Values significantly different from the predicted value represent superimposed respiratory acidosis or alkalosis. However, it is unclear whether this response significantly protects the pH from rising. In experimental animals, the rise in P_{CO_2} in metabolic alkalosis increases net H^+ excretion leading to an increase in the HCO_3^- concentration. The effect after several days is that the arterial pH is the same as it would have been if there had been no respiratory compensation.[6,18]

Ventilation may be strongly affected by influences other than acid–base balance. Among these influences are body temperature, increases in circulating catecholamines, changes in cerebral blood flow, changes in systemic blood pressure, and changes in metabolic activities of different organs (e.g., liver), as well as the physiologic state of the lung itself. Perhaps for teleologic reasons, the defense of chronic metabolic acid–base imbalances by ventilatory compensation is not of major importance.

ALTERNATIVE CONCEPTS OF ACID–BASE BALANCE

The preceding discussion has tacitly assumed that the systemic pH is the final control that affects the renal and respiratory response to an acid–base disorder; however, this issue is certainly not settled. The proximal tubular cell of the kidney can often have effects that are more predictably based on the P_{CO_2} rather than the arterial pH. If P_{CO_2} is elevated, the proximal tubular cells act to secrete protons and reabsorb bicarbonate whether or not there is systemic alkalosis or acidosis. This may be explained if an elevation in P_{CO_2} results in intracellular acidosis and the cell is responding appropriately to its internal milieu.[6,18] Similarly, in the central control of respiration, it is controversial as to whether it is CSF pH, interstitial pH, P_{CO_2}, or the bicarbonate concentration that stimulates compensatory changes in ventilation.[7]

In addition to the previously mentioned observations, it is also known that changes in salt and water balance may affect acid–base status. For example, Schwartz's group[18] found that a low dietary sodium chloride intake in dogs with a stable amount of water intake results in hypoventilation, increased P_{CO_2}, and increased HCO_3^- concentration. Studies in dogs have demonstrated that increasing dietary NaCl with a fixed water intake increases the acidity of body fluids, whereas decreasing the NaCl in diet with a fixed water intake decreases the acidity of body fluids.[22]

An alternative view to understanding acid–base disorders and the regulatory response of the lungs and kidneys is offered by the theories initially proposed by Stewart.[23,24] Based on physicochemistry, Stewart emphasized the important principle that H^+ and HCO_3^- as well as the acidic and anionic forms of weak acids are actually dependent variables in a solution. The three independent variables, P_{CO_2}, the strong ion difference (SID), and the total weak anion concentration, can be manipulated externally and serve to determine the concentration of the dependent variables, H^+ and HCO_3^-. The major components of the weak anions in plasma are the albumin and inorganic phosphate concentrations. The SID is the difference between the sums of all strong cations and all strong anions:

$$[\mathrm{SID}] = [\mathrm{Na}^+] + [\mathrm{K}^+] + [\mathrm{Ca}^{2+}] + [\mathrm{MG}^{2+}] - [\mathrm{CL}^-] - [\text{Other Strong Anions}] \qquad (4)$$

This equation is based on the principles of: (1) electroneutrality, (2) dissociation equilibria of all incompletely dissociated substances, and (3) conservation of mass. This concept appears to better explain the basis for renal and ventilatory response in a variety of states, which also affects acid–base balance. Practically, it is observed that the plasma SID is regulated primarily by the kidneys, whereas the P_{CO_2} is regulated by alveolar ventilation. The weak anion concentration is generally not regulated and may often be assumed to be stable.

This concept has primarily been used by investigators in relation to the study of central regulation of ventilation.[7] As albumin and other proteins are not present in the CSF, it is the SID and P_{CO_2} that determine the concentration of weakly dissociating electrolytes, H^+, OH^-, and HCO_3^-. In analyzing various acid–base disturbances, it appears that the change in CSF SID can predict the concentration of CSF bicarbonate.[7]

In evaluating acid–base balance in many species, there is a consistent inverse relationship between the pH and body temperature, whereas the CO_2 content remains stable.[4,25] To explain this relationship Reeves and his coworkers provided evidence that the imidazole ring structure of histidine is responsible for the pH–temperature relationship.[26] This is because imidazole has a pKa in the physiologic range (7.00), is relatively ubiquitous, and has total energy of ionization (7 kcal/mol). To integrate acid–base regulation with receptor function and control of respiration, Reeves and Rahn[4] have proposed the hypothesis that it is not the arterial or intracellular pH that is being regulated per se but rather the constancy of the fractional dissociation of the imidazole moiety of histidine contained in proteins throughout the body.

α-Imidazole is defined as the ratio of the absolute amount of unprotonated imidazole (Im) to total imidazole (HIm + Im):

$$\alpha\text{-Imidazole} = \frac{\text{Im}}{\text{HIm} + \text{Im}} \tag{5}$$

α-Imidazole regulation (alphastat regulation) would have the effect of maintaining cellular protein charge states and enzymatic functions constant. It would also maintain the OH^-/H^+ ratio constant in all compartments. There is also evidence that alphastat regulation directly influences ventilatory status. For example, application of an imidazole blocker to the chemosensitive area of the medulla in cats blocked increases in ventilation caused by local application of acid.[27] Thus, changes in P_{CO_2}, reflecting alveolar ventilation, may be determined by alphastat regulation, which maintains the OH^-/H^+ ratio constant in membranes of the cells in the chemosensitive areas of the medulla.

The difficulty with using these concepts lies in the practical measurement of the relevant molecules. For example, although the imidazole moiety of histidine is considered the most important of the intracellular buffers,[26] its pKa and total energy of ionization may vary widely due to the influence of the local configuration of molecules into which they are incorporated. Thus, even in lower animals such as fish under different temperatures, calculations based on the alphastat model do not accurately predict the acid–base disturbance, since the pKa and enthalpy of ionization vary with temperature and are difficult to measure.

Similarly, measurement of the plasma SID is problematic and is often replaced by the "SID effective," which is roughly equal to the bicarbonate concentration plus albumin and inorganic phosphate.[23] Calculation of the anion gap (see below) accounts for the roles of the strong ions Na^+ and Cl^- as well as bicarbonate but does not account for the role of inorganic phosphate or plasma proteins. Although the bicarbonate concentration may not be, strictly speaking, an independent variable, the AG calculation does indicate the quantity of unmeasured anions and hence is an indirect measure of the SID. If one considers the impact of serum proteins and inorganic phosphate in the unmeasured anion pool, the AG gives a very useful parameter in evaluating acid–base disturbances. Many studies have compared the utility of SID versus corrected AG (corrected for the level of serum albumin) and found that it was no more accurate in making a diagnosis. One study of patients in an intensive care unit reported that Stewart's method diagnosed underlying metabolic acidosis in 22 patients (of the total of 152 patients in the study) with normal plasma bicarbonate level. However, when the AG was corrected for hypoalbuminemia, it was elevated in all of the samples with normal bicarbonate showing the effectiveness of the traditional approach.[28] In another study of 935 ICU patients, the Stewart method detected metabolic acidosis in 14% patients with normal bicarbonate levels, whereas the traditional method made a similar diagnosis in 13% of patients.[29] A recent study in patients with septic shock and liver transplantation found an excellent correlation between SID and corrected AG.[30]

Thus, as will be described in more detail in the following section, the use of the AG is still the most clinically useful tool to determine the contribution of different metabolic etiologies of metabolic acidosis.

APPROACH TO PATIENTS WITH AN ACID–BASE DISTURBANCE

In this section, a diagnostic approach to disorders of acid–base balance is outlined, with a particular emphasis on the ventilatory response and its role in mitigating or exacerbating acid–base disorders. The approach to the patient with complex acid–base disorders also is reviewed.

Analysis of Clinical Information

Table 17-1 summarizes the pattern of abnormality of arterial blood acid–base parameters in the four classic acid–base disorders. It also indicates the physiologic or compensatory response induced in pulmonary or renal function in response to the initial disturbance.

Base Excess and Base Deficit Notations

Base excess and *base deficit* are terms applied to an analytic method for determination of the appropriateness of responses to disorders of acid–base metabolism.[31] The base excess or deficit is determined by measuring blood pH against ambient P_{CO_2} and against a P_{CO_2} of 40 mm Hg. If the calculated HCO_3^- is below 25 when the P_{CO_2} is 40 mm Hg and the original pH is low, a base deficit is indicated. The magnitude of the deficit is expressed as the number of mEq of bicarbonate needed to restore the serum bicarbonate to 25 mEq/L at a P_{CO_2} of 40 mm Hg compared to that at the ambient P_{CO_2}. The use of notations for base excess and deficit has been debated in the medical literature. This notation is favored in the evaluation of acid–base status in the operating room because acute changes in P_{CO_2} and in HCO_3^- can be simply evaluated by this approach. However, this notation can be misleading in chronic respiratory alkalosis or acidosis, since the patient with chronic respiratory alkalosis will be categorized as suffering from a base deficit because of the low serum bicarbonate induced as compensation for the reduced P_{CO_2}. In fact, a "base deficit" is a normal physiologic response to the chronic reduction in P_{CO_2}. Unfortunately, lack of familiarity with the complete analytical paradigm used for this analysis of acid–base disorders has led some to focus on the designations "base deficit" and "base excess" as guides to bicarbonate or acid therapy in chronic respiratory disorders. In addition, discrepancies between the buffering characteristics of plasma, blood, and whole body have also been cited as potential weaknesses in a system for assessing acid–base disorders that relies on in vitro CO_2 titration methods. We therefore recommend that the physiologic evaluation of the patient be the mode of analysis of acid–base disorders rather than an emphasis on derived formulae.

Use of Nomograms

As indicated earlier, the body buffers and the kidneys respond in a predictable fashion to a change in P_{CO_2}, whereas ventilatory

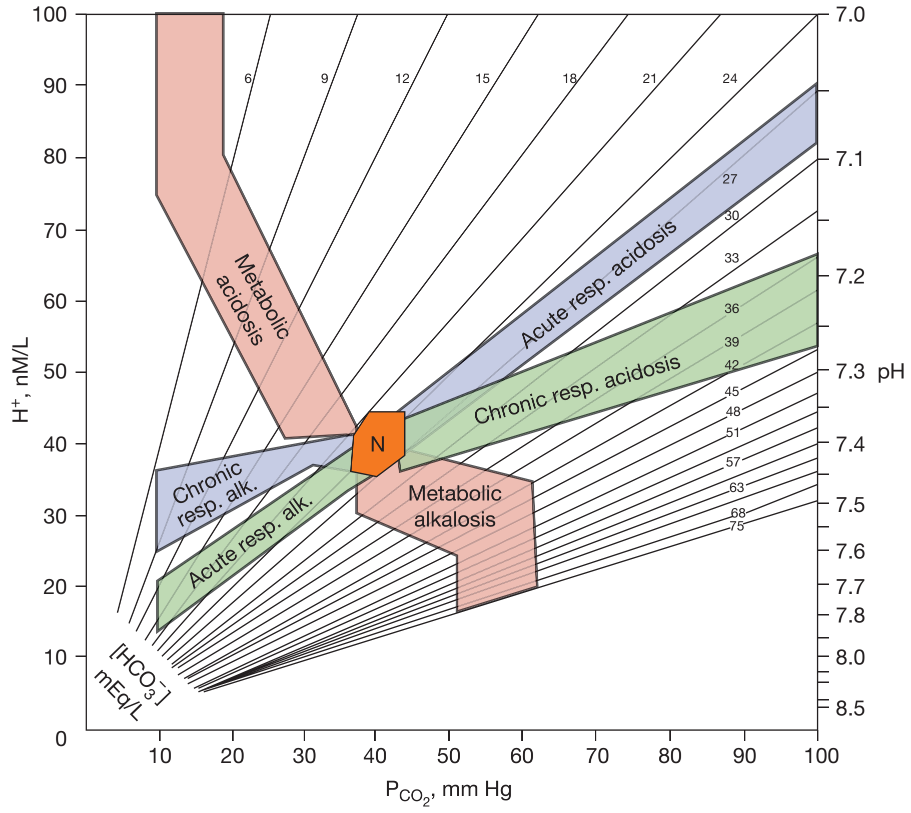

Figure 17-4 Acid–base map showing the normal range (N) and the confidence bands for acute or chronic respiratory and metabolic acid–base disturbances. The ordinates are the partial pressure of CO_2 and the hydrogen-ion activity given in nmol/L and pH units. Isopleths for bicarbonate concentration, in mEq/L, are also shown. *(Reproduced with permission from Goldberg M, Green SB, Moss ML, et al. Computer-based instruction and diagnosis of acid-base disorders. A systematic approach. JAMA. 1973;223(3):269–278.)*

response to changes in [HCO_3^-] also is predictable. Also, the resulting changes in bicarbonate and pH are time dependent so that a larger change occurs in several days than in the first hours. The confidence bands for changes in P_{CO_2} or HCO_3^- in response to primary disturbances are shown in Fig. 17-4.[7] Any deviation can be interpreted as a reflection of processes other than a compensatory response. For example, in a patient with chronic obstructive airways disease, other factors affecting the acid–base status are the concentration of potassium in the plasma, the size of ECF volume, chloride depletion, diuretics, renal hypoperfusion, and coexisting renal disease. The special case of posthypercapnic alkalosis is discussed in the next section.

In evaluating an acid–base disorder, the history and physical examination are invaluable in focusing attention on potential pathologic processes.[32] The composition of blood, with respect to serum electrolytes and blood gases, is then examined for consistency with clinical impressions. However, in using the acid–base map (Fig. 17-4), remember that the map is based on data from individuals who had a single disorder. Therefore, the map does not take into account the possibility of multiple disorders. For example, in a patient with chronic obstructive airways disease whose sputum has turned purulent and who develops nausea and vomiting, the possibility arises of coexistent metabolic alkalosis and acute respiratory acidosis. However, ill-advised application of the arterial blood-gas values from this patient (e.g., pH = 7.25 and $P_{CO_2} = 75$ mm Hg) to the acid–base map would lead to the erroneous conclusion that a chronic respiratory acidosis is present. Thus, the clinician needs to integrate laboratory data with clinical assessments to properly analyze clinical disorders of acid–base balance.

■ Approach to the Patient with Metabolic Acidosis

An increase in the H^+ concentration of the ECF will result in a series of predictable responses that allow the clinician to ascertain the appropriateness of organized homeostatic responses to the perturbation.[20] The pathophysiologic basis for the initiation of metabolic acidosis and homeostatic responses in the defense of systemic pH have been defined earlier in descriptions of the buffering of newly introduced acid [see Equation (1)] and in the demonstration of the normal confidence band for the ventilatory response to metabolic acidosis as detailed in the acid–base nomogram (Fig. 17-4).

A key clinical distinction in the pathogenesis of metabolic acidosis is whether the production of the acidosis is rapid or slow. If the etiology of the metabolic acidosis is merely the continued ingestion of a diet that generates a variety of fixed acids such as H_2SO_4 [see Equation (2)] from the metabolism of methionine residues, then the serum HCO_3^- will fall slowly as only that fraction of the 50 to 100 mEq of H^+ generated from diet that is not excreted would be added to the body fluids each day. However, if the addition occurs because of an acute increase in the acid load such as may occur with lactic acidosis, the kidney capacity can be rapidly overwhelmed, and serum bicarbonate may fall precipitously. See Table 17-2 for the common causes of metabolic acidosis.

Utility of the Anion Gap

As seen in Equation (6), the buffering of mineral acids will result in the production of the salt of the acid, NaA.

$$\mathrm{NaHCO_3 + HA \rightarrow NaA + H_2CO_3^- + H^+ \rightarrow CO_2 + H_2O + NaA} \quad (6)$$

If the kidney is able to excrete this salt or, in the case of the production of the salts of organic acids such as lactic acid, if the liver can metabolize the anion to HCO_3^-, then there will be no accumulation of the anion in the ECF. Typically, anions associated with strong organic acids are not measured with routine electrolyte determinations and contribute to the so-called anion gap (AG). Determination of the plasma AG is primarily used in the differential diagnosis of metabolic acidosis. However, the AG also changes in other conditions, a finding that may be of diagnostic importance.

TABLE 17-2 Causes of Metabolic Acidosis (Common)

Failure to generate new bicarbonate to replace that consumed in buffering dietary acid load
Diminished NH_4^+ production and excretion
Reduced renal mass
Chronic hyperkalemia
Chronic aldosterone deficiency
Decreased H^+ ion secretion (primary)
Distal renal tubular acidosis
Increased H^+ ion production
Lactic acidosis
Ketoacidosis
Toxic ingestion
Bicarbonate or equivalent losses from body fluids
Renal–proximal RTA, carbonic anhydrase inhibitors
GI—diarrhea, villous adenoma, fistula

The plasma AG is calculated from the following formula based on routine laboratory determination[33]:

$$AG = (\text{cations}) - (\text{anions})$$

Since Na^+ is the primary measured cation and Cl^- and HCO_3^- are the primary measured anions:

$$AG = [Na^+] - ([Cl^-] + [HCO_3^-]) \qquad (7)$$

The normal value is 12 ± 2 mEq/L.

An increase in the AG can be produced by an increase in unmeasured anions or by a reduction in unmeasured cations. Hypokalemia, hypocalcemia, or hypomagnesemia can only raise the AG by a few mEq/L, since these ions can only deviate from normal by a mEq/L or less and maintain a physiologic condition. The predominant extracellular unmeasured anion is actually albumin with many negative charge sites per molecule. Hence, a mild elevation in the AG can occur in conditions in which the albumin concentration or the charge characteristics of albumin are altered, for example, in metabolic alkalosis. In that instance, a number of factors may contribute to the increment, including a rise in the plasma albumin concentration due to extracellular volume depletion and contraction of plasma constituents, an increase in the number of negative charges per albumin molecule induced by the rise in extracellular pH titrating protons off the albumin molecule, and a tendency for systemic alkalemia to induce an increase in lactate production. This latter response serves a homeostatically beneficial function.

In forms of metabolic acidosis in which there is buffering of excess hydrochloric acid by extracellular bicarbonate, then

$$HCl + NaHCO_3 \rightarrow NaCl + H_2CO_3 \rightarrow CO_2 + H_2O \qquad (8)$$

Bicarbonate is replaced on an equimolar basis by chloride, and there is no change in the AG; this disorder is also called a *hyperchloremic acidosis* because of the rise in the plasma chloride concentration. Both diarrhea and type 2 (proximal) renal tubular acidosis can lead to the loss of $NaHCO_3$. The kidneys compensate by retaining NaCl in an attempt to preserve volume, with the net effect being a mEq-for-mEq exchange of chloride for bicarbonate.

If the retained acid is not HCl but an organic acid whose anion is not routinely measured such as lactic acid, then the increase in the unmeasured lactate anion will raise the AG. It is important to emphasize that the acidosis is due to the retained proton; the anion is irrelevant to the change in acid–base status or systemic pH but is important as a diagnostic tool. The major causes of a high-AG metabolic acidosis include those listed in Table 17-2 under disorders of increased H^+ production. Although renal failure produces an acidosis because of failure of H^+ excretion and bicarbonate production, most patients with severe renal failure retain both hydrogen and anions, such as sulfate, phosphate, and urate and, hence, demonstrate a high AG.

The diagnostic utility of a high AG is greatest when the AG is above 20 mEq/L; in this setting, renal failure, lactic acidosis, or evidence of a toxic ingestion will almost always be present. When the AG is less than 20 mEq/L, identifying the anions that contribute to the mild elevation[33] is often impossible.

Urine AG

Estimation of the urinary ammonia content may be a useful clue to the etiology of metabolic acidosis, as the value will increase in diseases in which kidney function affecting acid–base balance is completely intact but in which bicarbonate is lost from the body fluids.[13] The calculation of the urinary AG is shown in Equation (9):

$$\text{Urine AG} = (\text{Urine }[Na^+] + \text{Urine }[K^+]) - \text{Urine }[Cl^-] \qquad (9)$$

The usual value will be negative, between −25 and −50 mEq/L, as the ammonium content of the urine is typically in this range, and ammonium accounts for the apparent discrepancy between the level of cations and anions in the urine. In states of metabolic acidosis due to diarrhea or to chronic acid ingestion, the value will be >50 mEq/L as ammonium production is stimulated.

In some conditions, the urine AG will be very low or even positive in the face of metabolic acidosis. In all forms of renal insufficiency, ammonia production by the kidney will be deficient and significantly contribute to a reduced urinary AG and to metabolic acidosis. In type I distal RTA, inability to maintain a steep gradient for protons in the distal tubular lumen and in the collecting duct results in a deficiency in ammonia trapping in the luminal fluid and therefore a decreased excretory rate for ammonia. This in turn leads to metabolic acidosis, a low ammonia excretion, and an abnormally low urinary AG. Finally, type IV RTA, a condition in which hyperkalemia and mild renal insufficiency are found, hyperkalemia suppresses renal ammonia production, and a low urinary AG is found.

In any condition associated with hypokalemia, increased intracellular proton accumulation (which results from the exchange of cellular potassium for extracellular protons) will lead to an exaggerated ammonia production in the kidney. Hence, the use of the AG in the urine will be particularly useful to differentiate classic type I RTA from hypokalemia and acidosis due to diarrhea. The former will show a very low urine AG. Typically, a careful history will elicit the crucial information, and measurement of the urine AG will be confirmatory.

■ Clinical Assessment of Metabolic Acidosis

In approaching a patient with metabolic acidosis, the clinician should first assess the history and clinical circumstances. For example, patients with renal failure or with uncontrolled diabetes may be presumed to have a metabolic acidosis until disproved by laboratory analysis. The next step is to evaluate the serum electrolytes to determine the level of the serum HCO_3^- and the presence of an AG of greater than 12 ± 2 mEq/L. If both are present, then one must consider the possibility of a metabolic acidosis secondary to increased acid production as listed in Table 17-2. If the HCO_3^- is reduced but the serum AG is normal, then one is dealing with either a respiratory alkalosis or a metabolic acidosis due to reduced renal

TABLE 17-3 Causes of Metabolic Alkalosis

- Gastrointestinal hydrogen loss
  - Removal of gastric secretions
- Renal hydrogen loss
  - Primary mineralocorticoid excess
  - Loop or thiazide diuretics
  - Posthypercapnic alkalosis
- Intracellular shift of hydrogen
  - Hypokalemia
- Alkali administration
- Contraction alkalosis

capacity to generate replacement HCO_3^- to compensate for that lost as a result of decreased acid excretion or increased HCO_3^- loss.

At this point arterial blood gases should be assessed to determine the pH and the ventilatory response. Finding a low pH establishes the diagnosis of metabolic acidosis. Reference to the acid–base nomogram (Fig. 17-4) will verify whether the clinical response is consistent with a simple metabolic acidosis with a normal ventilatory response or whether some other disturbance in ventilation is present.

■ Approach to the Patient with Metabolic Alkalosis

Two separate processes are involved in metabolic alkalosis: an excess load of base that is generated either endogenously or exogenously (see Table 17-3) and maintenance of an abnormally high concentration of bicarbonate in the plasma.[5] During hypercapnia, the load of base is the result of renal compensation and de novo bicarbonate generation; in posthypercapnic alkalosis, the key abnormality is maintaining the bicarbonate level in plasma at inordinately high levels, as will be discussed below.

Generation of Metabolic Alkalosis

Causes of metabolic alkalosis are predominantly events that remove H^+ ions from the body but also include circumstances in which excess base is added to the body fluids. Hydrogen loss can occur from the gastrointestinal tract or in the urine. Each mEq of hydrogen lost generates 1 mEq of bicarbonate, as the source of hydrogen ions in cells that produce and secrete protons is:

$$H_2O \rightarrow H^+ + OH^- + OH^- + CO_2 \rightarrow HCO_3^- \qquad (10)$$

When vomiting or tube drainage prevents stomach acid from reaching the duodenum and combining with HCO_3^- released from pancreatic secretions, the net balance of bicarbonate in body fluids becomes positive, and serum HCO_3^- begins to rise.

Increased renal acid losses may result from enhanced distal hydrogen secretion. Aldosterone acts both by directly stimulating the secretory H^+ ATPase pump and, via the stimulation of sodium reabsorption, by making the lumen more electronegative, thereby favoring hydrogen ion secretion. Increased distal nephron delivery and reabsorption of sodium further stimulates hydrogen ion secretion as the accompanying anion is less avidly reabsorbed than is sodium, and the lumen of the distal nephron becomes more negatively charged. Excess secretion of mineralocorticoids can lead to metabolic alkalosis by this pathway. In patients treated with loop-active or thiazide diuretics, enhanced distal delivery of sodium and increased secretion of aldosterone are usually present, thereby enhancing renal bicarbonate production as a result of enhanced hydrogen ion secretion. This pattern commonly leads to the development of metabolic alkalosis.

Chronic respiratory acidosis leads to a secondary increase in renal hydrogen secretion, as the subsequent rise in the plasma bicarbonate concentration will restore the pH toward normal as a compensatory response. If the patient undergoes a therapeutic maneuver such as rapid lowering of the P_{CO_2} by mechanical ventilation, a posthypercapnic form of metabolic alkalosis will ensue as the patient is left with an elevated plasma bicarbonate concentration.

Hypokalemia is a frequent finding in patients with metabolic alkalosis and may not only be the consequence of some of the disorders that lead to the initiation of metabolic alkalosis but may also actually induce an alkalotic tendency. Gastric drainage, diuretics, and mineralocorticoid excess all induce potassium as well as hydrogen losses through the GI tract and kidney, respectively. Hypokalemia also induces a transcellular shift in which potassium is exchanged in an electroneutral fashion for hydrogen ions in the ECF. This exchange directly raises the extracellular pH, lowers the intracellular pH, and mitigates the hypokalemia. Intracellular acidosis in renal tubular cells promotes hydrogen secretion and therefore bicarbonate reabsorption (see “Bicarbonate Reclamation,” above).

Administering large amounts of alkali does not maintain metabolic alkalosis in normal individuals because of rapid urinary excretion, but it may induce the initiation stage of metabolic alkalosis if factors are active to sustain a high rate of renal HCO_3^- reabsorption. A form of metabolic alkalosis termed *contraction alkalosis* occurs when there is loss of relatively large volumes of bicarbonate-free fluid. Administration of a loop diuretic to induce rapid fluid removal in a markedly edematous patient is the most common cause of a contraction alkalosis. The plasma bicarbonate concentration rises in this setting because there is contraction of the extracellular volume around a relatively constant quantity of extracellular bicarbonate. The degree to which this occurs is in part minimized by intracellular buffering, as the release of hydrogen ions from cell buffers lowers the plasma bicarbonate concentration toward the baseline value. Even this form of alkalosis is probably critically dependent on increases in renal bicarbonate production for its manifestation, since the diuretics promote excess renal hydrogen ion secretion as noted earlier.

Maintenance Phase of Metabolic Alkalosis

Maintenance of metabolic alkalosis requires an increase in the reabsorption of bicarbonate by the renal tubule.[27] Four factors are known to be important in the maintenance phase of metabolic alkalosis: extracellular volume depletion, chloride depletion, hypokalemia, and mineralocorticoid excess.[34]

A reduction in ECF volume and possibly a fall in the glomerular filtration rate (GFR) secondary to extracellular volume depletion are major stimuli for increasing the proximal reabsorption of bicarbonate. The enhanced proximal tubular bicarbonate reabsorption is likely the most important factor. This reabsorption is stimulated by extracellular volume depletion, which is a frequent accompaniment of metabolic alkalosis. Enhanced proximal tubular reabsorption of sodium ions is a major factor in the enhanced rate of proton secretion, a key factor in the proximal tubular reabsorptive pathway for bicarbonate. Enhanced activity of the sodium–proton exchanger in the luminal membrane of the proximal tubule is an important component of the transport system.

In addition, an important role is played by the distal nephron in maintaining metabolic alkalosis by way of the secondary phenomena of chloride depletion, extracellular volume depletion, and hypokalemia.[35] Cells of the cortical collecting tubule can either reabsorb or secrete bicarbonate depending on homeostatic requirements. For example, during excess bicarbonate ingestion, the secretory process predominates, and excess bicarbonate is lost into the urine. Chloride depletion enhances the bicarbonate reabsorptive pathway by reducing chloride availability at an anion exchange site on the luminal membrane of the type A intercalated cell. This exchange process normally allows bicarbonate entry into the urine in exchange for chloride absorption. Chloride depletion thus blocks bicarbonate loss.

Hypokalemia acts to stimulate bicarbonate reabsorption through several mechanisms. First, loss of potassium from the ECF leads to a shift of protons into the cell as potassium leaves the cell. Hence, intracellular pH falls, driving enhanced tubular bicarbonate reabsorption. Also, severe potassium depletion produces a defect in tubular fluid chloride reabsorption, thus mimicking a chloride depletion state. Finally, excess mineralocorticoid hormone, either as a result of primary overproduction or due to a variety of secondary hyperreninemic states, stimulates H^+ secretion in the cortical collecting tubule and thereby stimulates increased renal tubular bicarbonate production and helps maintain metabolic alkalosis.

Typically, all four components coexist in patients with metabolic alkalosis secondary to vomiting or gastric drainage following gastric intubation. If any of the factors is present in a patient with metabolic alkalosis, therapy will be only partially successful until all the factors have been eliminated.

Depression of ventilation in metabolic alkalosis is a normal physiologic response to the elevation in serum bicarbonate but is difficult to assess clinically and may not be found in many patients as detailed earlier.[36]

Posthypercapnic Metabolic Alkalosis

In response to sustained hypercapnia, the increased excretion of hydrogen ion in the urine and the increased bicarbonate generated by the acid secretory process increase the concentration of bicarbonate in the plasma, as described earlier. During this process, the total sodium content of the body remains stable, as does the ECF volume (unless there is a separate reason for a volume abnormality, e.g., right ventricular failure and the use of diuretics). If correction of hypercapnia occurs, for example, through the use of mechanical ventilation without simultaneous replacement of sodium chloride, the urinary loss of sodium bicarbonate may lag for several hours or days. This is particularly true if there is concomitant depletion of the ECF volume. This leads to an increase in the reabsorption of solute, including sodium bicarbonate, by the proximal tubule, sustaining the high bicarbonate concentration in blood. This process is similar to the maintenance phase of metabolic alkalosis described earlier; the other processes outlined also could pertain to this posthypercapnic state and produce a persistent metabolic alkalosis following correction of hypercapnia.[37]

■ Approach to the Patient with a Mixed Acid–Base Disorder

The approach to patients with mixed acid–base disorders, that is, more than one disturbance in acid–base metabolism, is particularly challenging because no nomogram, calculation of base excess or deficit, or other formula can allow the clinician to parse the pathophysiologic disorders and allow a rational therapeutic plan.[18] Rather, it is the combination of clinical assessment, application of expected compensatory responses, assessment of the AG, and application of principles of physiology that together allow a successful analysis.

To determine the presence of a mixed or complex acid–base disorder, the clinician must follow a rigorous approach that integrates clinical observation with assessment of a variety of laboratory parameters. No single nomogram or other shortcut device will suffice. The initial step is to perform a history and physical examination to seek processes that could contribute to acid–base disorders. For example, any patient who has vomited has the potential for developing a metabolic alkalosis, and any patient with chronic renal failure surely has metabolic acidosis as an ongoing process for which compensation will be necessary. Moreover, many clinical conditions are typically characterized by the presence of more than one concurrent disorder. Patients with severe liver failure will usually experience respiratory alkalosis as a consequence of hepatic encephalopathy so that any other conditions associated with abnormalities of acid–base balance that may develop in these patients will result in mixed acid–base disorders. Septic shock is associated with the mixed disorders of respiratory alkalosis and metabolic acidosis due to lactic acid production. Immediately, following cardiac arrest, patients will have both a respiratory and a metabolic acidosis. Patients with renal failure who undergo gastric drainage will manifest both metabolic alkalosis and metabolic acidosis as a result of the underlying conditions. The clinician must consider these expected abnormalities in acid–base balance when addressing laboratory results.

The second step in the process is to evaluate a venous blood sample for determination of the electrolytes, blood urea nitrogen (BUN), creatinine, and other parameters indicative of liver function. Here, the evaluation of the $[HCO_3^-]$ and analysis of the AG is invaluable. Decrements or elevations of $[HCO_3^-]$ will point toward a disturbance in the body's buffering system. The AG measurement, if elevated, will clarify whether a metabolic acidosis is present, as described earlier. Also, analyzing the AG together with the venous $[HCO_3^-]$ can provide important information. Because the anions that accumulate in most forms of organic acidosis (lactic acidosis, ketoacidosis, many toxic ingestions) can be metabolized in the liver to bicarbonate through the Krebs cycle, adding the unmeasured anion concentration to the current plasma HCO_3^- concentration indicates the level of $[HCO_3^-]$ prior to the onset of the metabolic acidosis.

ILLUSTRATIVE CASES

The following cases illustrate the clinical approach to the patient with acid–base disturbances.

■ Metabolic Acidosis

A 75-year-old patient presented with a 7-day history of intermittent diarrhea and a 5-lb weight loss. The rest of the history was unrevealing. Physical examination only revealed signs of volume depletion. Laboratory values were as follows:

$$[BUN] = 18 \text{ mg/dL}$$
$$[Na^+] = 138 \text{ mEq/L}$$
$$[K^+] = 3.0 \text{ mEq/L}$$
$$[Cl^-] = 110 \text{ mEq/L}$$
$$[HCO_3^-] = 13 \text{ mEq/L}$$

At this point, the lack of an elevated AG (12 mEq/L) and the reduced bicarbonate concentration together suggest the possibility of either respiratory alkalosis or metabolic acidosis of the non-AG variety, that is, in which the chloride concentration has risen as bicarbonate has been utilized in buffering reactions or has been lost from body fluids. The history of diarrhea strongly suggests that a metabolic acidosis is the culprit in the disorder. The relatively low BUN supports the theory that diarrhea, and not renal insufficiency, is the main etiologic factor.

Arterial blood gases are then obtained:

$$pH = 7.24$$
$$P_{CO_2} = 27 \text{ mm Hg}$$
$$P_{O_2} = 100 \text{ mm Hg}$$
$$[HCO_3^-] = 13 \text{ mEq/L}$$

The low serum bicarbonate in association with a low arterial blood pH indicates that the patient has a metabolic acidosis. Finding that the rate of ventilation produces a P_{CO_2} of 27 is consistent with the expected P_{CO_2} of 27.5 ± 2 mm Hg calculated from Winter's formula (see Table 17-1). Reference to the acid–base nomogram (see Fig. 17-4) reveals the graphical equivalent of this calculation as the values for pH, P_{CO_2}, and $[HCO_3^-]$ fall in the confidence band for metabolic acidosis. Other possible etiologies for this form of non-AG metabolic acidosis would include mild renal insufficiency, wherein the decline of GFR has not reached a level where the unmeasured anions such as SO_4^{2-} would begin to accumulate in plasma, and the ingestion of salts such as ammonium chloride which are metabolized in the liver to urea and hydrochloric acid. Urinary electrolyte analysis confirms the diagnosis:

$$\begin{aligned}[Na^+] &= 50 \text{ mEq/L}\\ [K^+] &= 20 \text{ mEq/L}\\ [Cl^-] &= 140 \text{ mEq/L}\\ \text{Urine volume} &= 2 \text{ L}\\ \text{Urinary AG} &= -70 \text{ mEq/L}\end{aligned}$$

The discrepancy between the sum of urine cations and anions in the negative range indicates that an unmeasured cation, in this case ammonium, is being excreted into the urine.[13] It is the excretion of protons in association with ammonia that allows the renal excretion of the accumulated acid load and the attempted regeneration of body HCO_3^- stores. If this value was not greater than −20 to −50 mEq/L, a defect in ammonia production or excretion such as could be found in renal insufficiency or in renal tubular acidosis could be present. In this case, the large urinary cation gap suggests that diarrhea is the culprit.

Metabolic Alkalosis

A 65-year-old patient experienced severe and unremitting vomiting for 4 days. He has had a history of peptic ulcer disease, but he decided to medicate himself with an antacid, which he could not keep from vomiting. There was no other significant past medical history. Physical examination showed a moderate degree of orthostatic hypotension as blood pressure fell from 100/70 mm Hg supine to 90/60 mm Hg when seated. The rest of the examination was not remarkable except for some abdominal tenderness.

Laboratory results revealed the following:

$$\begin{aligned}[BUN] &= 28 \text{ mg/dL}\\ [Na^+] &= 43 \text{ mEq/L}\\ [K^+] &= 3.0 \text{ mEq/L}\\ [Cl^-] &= 85 \text{ mEq/L}\\ [HCO_3^-] &= 39 \text{ mEq/L}\end{aligned}$$

The elevation in HCO_3^- content is consistent with either metabolic alkalosis or with chronic respiratory acidosis with renal compensation. The clinical circumstances strongly imply that metabolic alkalosis will be found, since the patient has been vomiting and has therefore been generating new alkali in the body fluids as gastric hydrochloric acid is lost. Also, the vomiting-induced deficit in ECF volume and in body fluid chloride content will likely act to help sustain the metabolic alkalosis by stimulating a high rate of renal bicarbonate transport by the proximal tubule and inhibiting distal nephron bicarbonate secretion.

Arterial blood gases are then obtained:

$$\begin{aligned}\text{pH} &= 7.52\\ P_{CO_2} &= 46 \text{ mm Hg}\\ [HCO_3^-] &= 36 \text{ mEq/L}\end{aligned}$$

These confirm the diagnosis. Note that the hypoventilatory response is modest, probably because of the degree of hypokalemia, which tends to acidify the intracellular fluid and stimulate ventilation. Correction of this abnormality will require both replacement of fluid with sodium and chloride and adequate intake of potassium to fully restore acid–base balance to normal.

Mixed Acid–Base Disturbance

An insulin-dependent diabetic patient with several days of vomiting developed diabetic ketoacidosis. The following set of electrolytes is obtained:

$$\begin{aligned}[Na^+] &= 140 \text{ mEq/L}\\ [K^+] &= 5 \text{ mEq/L}\\ [Cl^-] &= 90 \text{ mEq/L}\\ [HCO_3^-] &= 15 \text{ mEq/L}\\ \text{Anion gap (AG)} &= 35 \text{ mEq/L}\end{aligned}$$

Since the normal AG is 12 ± 2 mEq/L, this individual has utilized 23 mEq/L of HCO_3^- to buffer the ketoacids. If the production of ketoacids ceases and hepatic metabolism is restored through insulin administration, then 23 mEq/L of HCO_3^- could be added to body fluids. The new set of electrolytes would be:

$$\begin{aligned}[Na^+] &= 140 \text{ mEq/L}\\ [K^+] &= 5 \text{ mEq/L}\\ [Cl^-] &= 90 \text{ mEq/L}\\ [HCO_3^-] &= 38 \text{ mEq/L}\\ \text{Anion gap (AG)} &= 12 \text{ mEq/L}\end{aligned}$$

By assessing the value—(AG increment above 12 mEq/L) + (serum $[HCO_3^-]$)—and finding a value greater than 30, one can infer that some process has previously raised the bicarbonate content above normal even if the ambient total CO_2 level is subnormal at the current moment. Hence either metabolic alkalosis or respiratory acidosis is a component process of the acid–base disorder. Conversely, finding a value less than 20 suggests that the patient had a pre-existent metabolic acidosis or a respiratory alkalosis prior to the onset of the organic acidosis. Finally, the clinician may assess the alveolar–arteriolar O_2 gradient to determine the effectiveness of oxygenation as an initial assessment of respiratory gas exchange efficiency.

At this point the clinician is able to ascertain a tentative diagnosis and perform an arterial blood gas determination to conclude the process. Measurement of the blood gas will show whether the respiratory response to a metabolic disturbance (metabolic alkalosis or metabolic acidosis) or the metabolic (renal) response to a respiratory disturbance is as expected. The acid–base disorder could still be labeled a simple disturbance if the initial assessment of the clinical condition and the AG support that conclusion. Consulting the acid–base map (see Fig. 17-4) will provide the expected compensatory response to each disturbance. In the previously mentioned case of a patient with diabetic ketoacidosis and an initially increased (AG + total CO_2) concentration, the following arterial blood gases were obtained:

$$\begin{aligned}\text{pH} &= 7.18\\ P_{CO_2} &= 38 \text{ mm Hg}\\ [HCO_3^-] &= 15 \text{ mEq/L}\end{aligned}$$

In pure metabolic acidosis the ventilatory response to an $[HCO_3^-]$ lowered to 15 mEq/L would be a P_{CO_2} of 25 mm Hg (see Table 17-1 and Fig. 17-4). In this example, the patient shows a P_{CO_2} that is higher than the expected value of 25 for a patient with pure metabolic acidosis and a depressed HCO_3^- value of 15 mEq/L. Hence this patient demonstrates a so-called triple disturbance: a metabolic acidosis (low HCO_3^-, high AG), a metabolic alkalosis ($[HCO_3^- +$ AG increment above 12] >30 mEq/L), and a respiratory acidosis (P_{CO_2} higher than expected value given the lowering of

HCO_3^- level as determined from the acid–base nomogram or the formula for expected compensation). Therapy for this patient will require awareness of these various processes, since removal of one of multiple disturbances can induce a more severe expression of the still-present abnormality.

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CHAPTER 18

Aging of the Respiratory System

Edward J. Campbell
Corrine R. Kliment

INTRODUCTION

The fastest growing segment of the U.S. population consists of individuals of age 65 and older. In the 2018 census, this segment comprised 52 million individuals or 16% of the population. Since the 1950s, the median age of the U.S. population has increased by 20 years.

The largest decrements in age-adjusted death rates have been occurring in older patients. With the increasing longevity of human population, it is necessary to understand the effects of aging on the respiratory system in healthy people. Perhaps, more importantly, because the age-related decrements in respiratory system function can be unmasked by disease, it is critically important to point out that the aged: (1) have an enhanced predisposition to lung disease; (2) have a decreasing reserve of respiratory system function that decreases their ability to cope with the stresses of illness, injury, and surgery; and (3) may have differing responses to therapy when compared with their younger counterparts.

Even in individuals who enjoy apparently good health, there are measurable decrements in function of the respiratory system with age. These changes occur progressively as a healthy individual grows older and are most marked beyond 60 years of age. Cross-sectional studies show clear differences between elderly and young persons with regard to the structure and function of the components of the respiratory system (Table 18-1). As we will see, however, caution must be exercised in ascribing observed changes to age alone. It is also necessary to be aware that longitudinal studies of "healthy" individuals followed to old age are essentially not available. Where appropriate, methodologic problems in the available cross-sectional studies are described.

Although age-associated changes can be measured easily by objective testing, it is important to note that the routine activities of healthy elderly persons are not limited by the decreasing respiratory system function. However, whereas youthful persons have a marked excess of functional capacity over the amount required to meet metabolic needs at rest or with stress (physiologic reserve), the respiratory system draws on this reserve as its function declines with age. Thus, the physiologic reserve, especially for alveolar gas exchange, is reduced with aging. This leaves elderly individuals vulnerable to stresses, diseases, and injuries that are weathered much more easily in the young.

ARE CHANGES IN THE RESPIRATORY SYSTEM CAUSED BY AGING OR RELATED TO AGE IN OTHER WAYS?

For decades, the phenomena explained purely by aging have been required to satisfy specific principles. Roughly according to Hayflick,[1] the changes must be: (1) intrinsic (as opposed to environmentally mediated); (2) universal; (3) progressive; and (4) usually detrimental to the organism. Developing an understanding of changes to the lung over time is complicated by the fact that the lung is an open system that is exposed to environment. As such, it is assaulted by respiratory infections and by a constant barrage of particulates and other air pollutants. In addition, the lungs are commonly exposed to tobacco smoke, to occupational dusts and fumes, and to effects of aspiration. At times, environmental influences are inextricably involved in the changes that are observed in the respiratory system over time. However, it is important to draw a distinction between alterations purely related to aging and those associated with older individuals. Purely age-related changes are biologic phenomena and irreversible. Other alterations associated with increasing age have the potential to be preventable, treatable, and/or reversible.

CHANGES IN THE UPPER AIRWAY

There is a clearly increased risk of aspiration in the elderly that is thought to be a consequence of a number of age-related factors, including comorbid illnesses and debility, medications, and the aging process itself. With regard to purely age-related changes, attention has been focused upon the cough and swallowing reflexes, both of which are protective against aspiration. In the past, these reflexes have been thought to be controlled primarily by the brainstem, but there is now evidence that cortical and subcortical structures play critical roles in their control.[2] By their nature, reflexive cough and swallowing activate both sensory and motor areas in the cortex. The sensory component, including the sensory cortex

TABLE 18-1 Respiratory System: Functional Divisions and Changes with Aging

Functional Division	Components	Function	Change(s) with Aging
Conducting airways	All airways not involved in gas exchange (mouth to terminal bronchioles)	Gas movement between environment and alveolar space	Slight changes in size; calcification; glandular hypertrophy
Lung parenchyma	Gas-exchanging airways and vessels; connective tissue framework	Gas exchange between alveolar space and capillary blood	Enlarged terminal airspaces; ventilation/perfusion mismatching
Bellows apparatus	Chest wall and muscles of respiration	Provide mechanical forces for ventilation	Increased rigidity of chest wall; decreased respiratory muscle strength
Ventilatory control	Respiratory control center (pons and medulla); carotid and aortic bodies	Maintaining homeostasis by altering ventilation to match metabolic needs	Markedly decreased responses to hypercapnia and hypoxemia
Cardiovascular system	Heart and systemic vasculature	Blood transport and tissue exchange of respiratory gases	Decreased maximal heart rate and cardiac output; decreased responsiveness to hypoxemia

in reflexive circuits, seems to be more vulnerable to aging than the motor component, including the motor cortex. Therefore, strategies to restore effective cough and swallowing reflexes should be focused upon compensations of sensory components.

Variable amounts of aspiration of both oropharyngeal contents (food particles, saliva, and oropharyngeal organisms), and also gastric contents (food particles and gastric secretions including gastric acid), are increasingly common with aging. Aspiration is particularly common in the very old. Because of the sensory alterations discussed earlier, aspiration in elderly individuals can be associated with few, or no, symptoms.[3]

A potentially important contributor to aspiration is gastroesophageal reflux. In accordance with the earlier discussion of sensory impairments, reflux esophagitis severity increases with age while heartburn severity decreases with age.[4] Consequences of gastroesophageal reflux may be exacerbated by esophageal motor abnormalities associated with aging. Recurrent aspiration of gastric contents in the elderly can lead to airway inflammation, bronchiectasis, and pneumonia.

STRUCTURAL CHANGES IN THE LUNG

Studies of the aging lung have shown changes in shape, with increase in anteroposterior diameter that leads to a "rounding" shape of the lung. These changes are presumably secondary to changes in the shape of the surrounding thoracic cage that are very common after the age of 75. In a study of 100 chest radiographs from individuals ranging in age from 75 to 93 years, 25% had severe kyphosis (>50 degrees) and 43% had moderate kyphosis (35–50 degrees) from vertebral fractures.[5]

■ Conducting Airways

The conducting airways consist of the air passages from mouth to the level of respiratory bronchioles. Their volume comprises the anatomic dead space, and their geometry is a primary determinant of airway resistance. The larger cartilaginous airways show a modest increase in size with age, resulting in slight but probably functionally insignificant increase in anatomic dead space. Although calcification of cartilage in the walls of the central airways and hypertrophy of bronchial mucus glands is seen in advanced age, these changes in the extraparenchymal conducting airways appear to have little or no physiologic significance.

Ciliary motility of both the upper and lower airways is important in normal lung clearance. Several studies have shown that ciliary function is significantly reduced with aging in the lung[6–8] and nasal tissue.[9] This reduction in ciliary function is often compounded by noxious stimuli such as cigarette smoke that reduce ciliary beat frequency. Dysfunctional ciliary beating likely further increases the risk of lower respiratory infections and inflammation in the elderly population.

■ Lung Parenchyma

After the age of 30 or 40, the respiratory bronchioles and alveolar ducts undergo progressive enlargement (Fig. 18-1). This change has been termed "ductectasia" because of the prominent finding of enlargement of alveolar ducts.[10] The proportion of the lung made up of alveolar ducts increases, and alveolar septa become shortened, leading to a "flattened" appearance of the alveoli. With the change in geometry, the distance between alveolar walls (known to morphologists as the mean linear intercept, or MLI) increases, while the surface-to-volume ratio of the lung decreases.[11] The age-related enlargement of the terminal respiratory units also produces a decrease in the percentage of parenchymal air contained within the alveoli.[12] The net result of these structural changes is that the alveolar surface area decreases by approximately 15% by age 70.

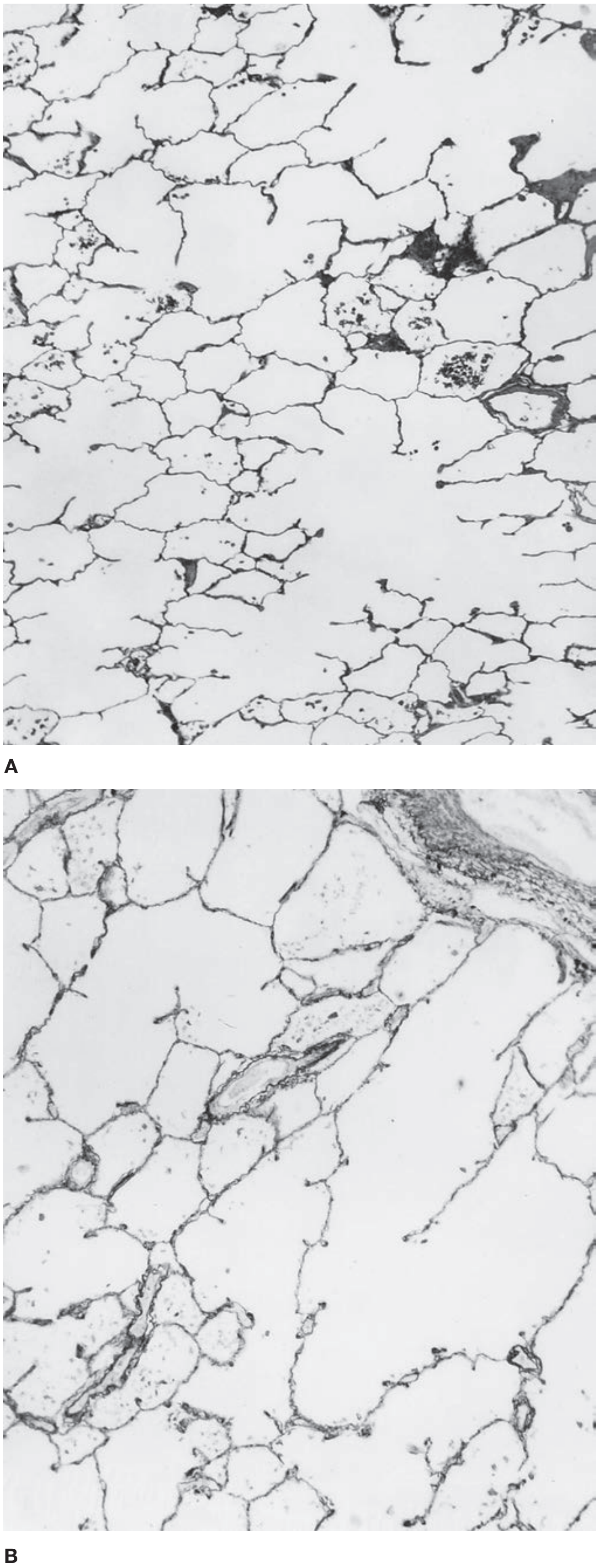

Figure 18-1 Histologic changes in the aging lung. **A.** Normal lung of a 36-year-old woman. **B.** Lung of a 93-year-old woman. In (**B**), the alveolar ducts are dilated, and shortening of inter-alveolar septa is observed. *(Reproduced with permission from Mayo Foundation; photomicrographs reproduced with permission from Charles Kuhn III, MD.)*

Pulmonary emphysema also is characterized by an increase in the size of terminal airspaces, an increase in MLI, and a decrease in surface area; however, destruction of alveolar septa with fusion of terminal airspaces is a defining characteristic of emphysema. There have been some reports of emphysematous lesions in aged lungs, but it is not certain that smokers were excluded from these studies. Since the fate of individual alveolar septa during the aging process has been somewhat controversial, some have referred to the histologic changes in aged lungs as "senile emphysema." A National Heart, Lung, and Blood Institute workshop on the definition of emphysema[13] weighed the available evidence and decided not to include age-related changes in the lung parenchyma under the definition of *emphysema*. To simplify terms and avoid confusion, they recommended use of the term *aging lung* to apply to the uniform airspace enlargement that develops with increasing age. Despite the continued use of "senile emphysema," this term should be avoided.

Computed tomography of the chest in individuals more than 75 years of age has shown a surprising prevalence (60%) of a subpleural basilar reticular pattern that was absent from images from a control population that was less than 55 years old. Lung cysts were seen in 25% of the elderly subjects, but none of the controls.[14] These findings are usually associated with interstitial lung disease, but in the elderly they seem not to reflect a clinically relevant disease process. Caution must be exercised to avoid overreacting to similar image findings in older patients.

CHANGES IN MECHANICAL PROPERTIES OF THE LUNGS

Both the lungs and chest wall are elastic. The resting volume of excised lungs is smaller than that contained within an intact thoracic cage, because the lungs are held at an increased volume by the outward recoil forces of the chest wall. Thus, in the intact thoracic cage, the lungs exert an inward recoil force. The retractile force of the lungs, or the "elastic recoil," can be measured during life by estimating the pleural pressure with an esophageal balloon at progressively decreasing lung volumes from total lung capacity to functional residual capacity (FRC), when the airways are open and there is no air flow. The negative pleural pressure is generated by the lungs' elastic recoil forces.

The pressure measurements may be displayed on a pressure–volume diagram (Fig. 18-2). Figure 18-2 compares, at the same volume, the elastic recoil pressures of a young man, a normal elderly adult, and a patient with emphysema. The normal elderly individual and the patient with emphysema both have a greater decrease in elastic recoil pressure than does a young person.[15] This is reflected in the leftward shift of their pressure–volume curves.[16–19] This loss of elastic recoil is the physiologic hallmark of emphysema. However, emphysema is characterized by a much greater loss of elastic recoil than is caused by aging alone.

There has been some disagreement regarding the effects of aging on lung compliance (Δ volume/Δ pressure; that is the slope of the pressure–volume relationship, Fig. 18-2). The question is whether there is a parallel leftward shift of the pressure–volume curve with aging (no change in compliance), or, instead, a steeper slope in addition to a shift (indicating an increase in compliance), as seen in emphysema. In aged individuals, the static pressure–volume curve is slightly steeper and is more concave in relation to the pressure axis. However, there is a general agreement that changes in lung compliance with aging are not physiologically significant.

Two forces in the lung parenchyma are responsible for producing the elastic recoil of the lungs. The greatest part of the elastic recoil forces is provided by the surface tension at the curved air–fluid interface of the small airways and alveoli. The second retractive force is that produced when the fibrous skeleton of the lung (primarily the elastic fibers) is stretched.

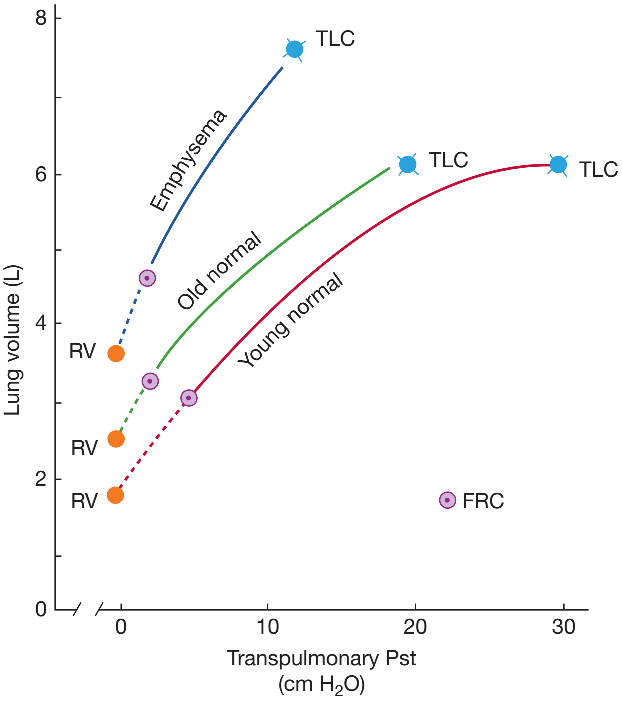

Figure 18-2 Static pressure–volume curves of the lungs. Static recoil pressure, expressed as transpulmonary pressure measured at various lung volumes, is plotted against lung volume on the ordinate. Note that at any lung volume, the recoil pressure is less in the aged individual than in the young, normal control, resulting in a pressure–volume curve that is shifted upward and to the left. For comparison, a curve for a patient with emphysema is shown. In emphysema, recoil pressures are reduced much more, and lung compliance (the slope of the pressure–volume relationship) is clearly abnormal. *(Reproduced with permission from Pride NB. Pulmonary distensibility in age and disease. Bull Physiopathol Respir. 1974;10(1):103–108.)*

■ Changes in Surface Forces

Most of the loss in lung recoil with age is likely to be related to the decrease in lung surface area. The loss of surface area that accompanies aging can be expected to reduce the area of gas–liquid interface, resulting in a decrease in the surface tension forces and, ultimately, a decrease in the total elastic recoil of the lung. Whether it is due to loss of air–liquid interface or to changes in lung structural macromolecules, the reduced elastic recoil has important consequences for the function of the intraparenchymal airways and, ultimately, on alveolar gas exchange and forced expiratory flow (see "Pulmonary Function Tests," below).

■ Changes in Structural Macromolecules

Weibel has produced elegant studies of the "integral fiber continuum" that extends from the hila to the pleura. This consists of axial fibers extending to the alveolar septae, and septal fibers extending to the pleura.[20] Although most proteins in the lung turn over relatively rapidly, the structural proteins, elastin and collagen, in the lung fibrous network provide a very stable, long-lived skeletal structure for the lung.

Elastic fibers consist in large part of an extremely hydrophobic, highly cross-linked, and very elastic macromolecule (elastin). These fibers are thought to contribute substantially to lung elasticity. Analysis of whole lungs has revealed that the elastin content actually increases (rather than decreases) with age. More recent evidence indicates that the increase in lung elastin with age is accounted for by an increase in pleural elastin; parenchymal elastin does not change.

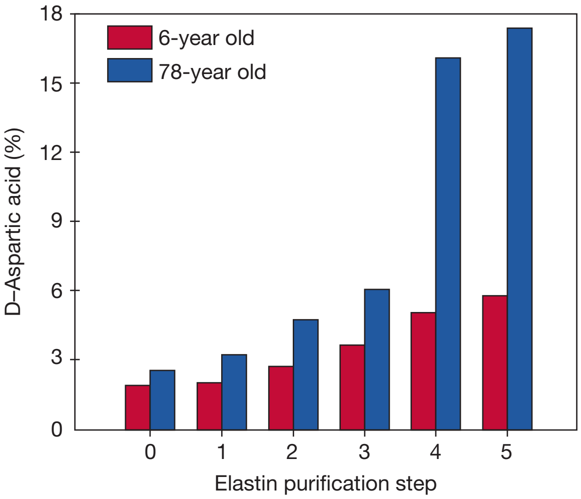

Figure 18-3 Longevity of human lung parenchymal elastin, as evidenced by in vivo racemization of aspartic acid. Each pair of bars shows results from two individuals with greatly differing ages at time of death. Step 0 of elastin purification represents whole lung parenchyma, while step 5 is purified elastin. D-aspartic acid detected in the 6-year-old specimen can be attributed to racemization that occurs during the analytical procedures, whereas, the difference in prevalence of D-aspartic acid between the young and old individual has resulted from racemization in vivo. Note that results from whole-lung hydrolysates (step 0) are similar for both specimens, reflecting their composition of proteins, having predominantly rapid turnover. However, purified elastin from the oldest specimen has racemized extensively in vivo, indicating that it was synthesized many decades before death. These data for elastin agree well with results for other very long–lived proteins. *(Reproduced with permission from Shapiro SD, Endicott SK, Province MA, et al. Marked longevity of human lung parenchymal elastic fibers deduced from prevalence of D-aspartate and nuclear weapons–related radiocarbon. J Clin Invest. 1991;87(5):1828–1834.)*

Careful studies of the elastic fibers in the lung parenchyma have shown that they are remarkably stable following postnatal lung growth. Certain biochemical changes in very long-lived proteins (change of amino acids into their mirror-image structures, or racemization) provide a type of "biological clock" that permits an estimate of the time that has elapsed since the proteins were synthesized. Because of the constraints of the protein synthetic mechanisms, only L-amino acids are incorporated into newly synthesized proteins. With the passage of years at body temperature, however, there is a readily measurable accumulation of D-aspartic acid. When all of the lung proteins are examined together, minimal D-aspartic acid is found. In purified lung elastin, however, there is an age-related accumulation of D-aspartic acid,[21] indicating that lung elastin is turning over very slowly if at all (Fig. 18-3). It has also been possible to estimate lung elastin turnover by measurement of the incorporation into elastic fibers of carbon 14 (^{14}C) from atmospheric nuclear weapons testing. For example, individuals who completed their postnatal lung growth prior to the nuclear age show no excess ^{14}C in their lung elastin, indicating absence of new elastin synthesis. In contrast, an appropriate excess of ^{14}C is found in the lung elastin of individuals whose lungs were growing in the post–weapons testing era. Modeling of the radiocarbon data indicates that the "mean carbon residence time" in elastin is 74 years.

Taken together, the amino acid racemization and radiocarbon data indicate that lung parenchymal elastin is stable over the human life span, and it appears that the elastin content of the lung parenchyma not only does not change with age, but the individual fibers persist for at least many decades.

Other studies of lung elastic fibers have shown changes in the location and orientation of individual fibers with age as well as changes in the cross-linking of elastin. Thus, some authors have suggested that remodeling of the lung architecture may occur without replacement of elastic fibers. In any case, at the present time, the age-related changes in connective tissue do not provide a sufficient explanation for the decrease in elastic recoil forces observed in the elderly.

Studies of collagen in alveolar walls of humans, as measured by hydroxyproline, have failed to show a consistent change in its quantity during aging.[22] Although human studies have not been done, studies in rodents and birds suggest that lung collagen fibers, like elastic fibers, are very long-lived.[23] Finally, although some qualitative changes in collagen during aging have been described (decreases in solubility and increases in intermolecular cross-links), these appear to have no relationship to changes in lung elastic recoil.

Although convincing evidence for very slow compensatory human lung growth (over many years) has been provided following pneumonectomy,[24] under more ordinary circumstances it appears that the lung adapts to changing dimensions of thorax by realignment of its fibrous skeleton rather than by molecular remodeling.

■ Changes in the Chest Wall

There is good evidence that the chest wall becomes more rigid with advancing age.[25] As may be seen in Fig. 18-4, the static pressure–volume curve of the chest wall is shifted to the right and is less steep

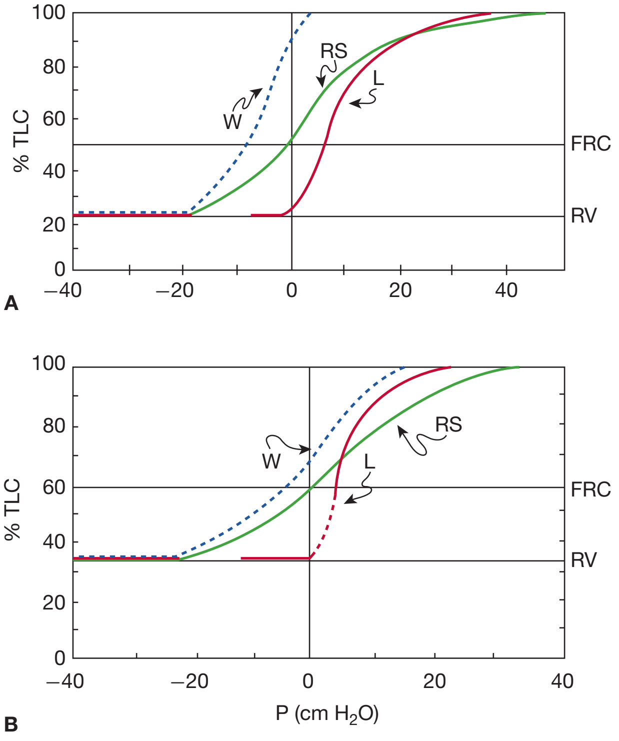

Figure 18-4 Static compliance relationships of the components of the respiratory system. (L, lungs; W, chest wall; RS, total respiratory system.) **A.** A 20-year-old man. **B.** A 60-year-old man. Note that the static compliance of the chest wall is substantially decreased (reduced slope) in the older individual, while functional residual capacity (the resting volume of the respiratory system, or the point at which the pressure gradient across the respiratory system is zero) increases. As in Fig. 18-2, it is also apparent that the static recoil pressure of the lungs is reduced in the older subject. *(Data from Mittman C, Edelman NH, Norris AH, et al. Relationship between chest wall and pulmonary compliance and age. J Appl Physiol. 1965;20:1211–1216; and Turner JM, Mead J, Wohl ME. Elasticity of human lungs in relation to age. J Appl Physiol. 1968;25:664–671.)*

with increasing age. The articulations of the ribs with the sternum and the spinal column may become calcified, and the compliance of the rib articulations decreases. The changes in rib articulations may be compounded by the development of kyphosis due to osteoporosis. The decreasing compliance of the chest wall demands greater work from the respiratory muscles. For example, in a 70-year-old person, approximately 70% of the total elastic work of breathing is expended on the chest wall, whereas this value is 40% in a 20-year-old person.

Figure 18-4 also demonstrates that the compliance of the total respiratory system decreases with age because the decrease in lung elastic recoil is outweighed by the changes in the mechanical properties of the chest wall.

CHANGES IN MUSCLES OF RESPIRATION

Age-related changes in non-respiratory skeletal muscle include decreased work capacity due to alterations in the efficiency of muscle energy, metabolism, atrophy of motor units, and electromyographic abnormalities. Based upon lessons learned with other skeletal muscles, it appeared likely that age-related abnormalities in respiratory muscles also would be found.

An early study by Black and Hyatt appeared to confirm age-related decrements in respiratory muscle function by measuring maximal inspiratory pressure ($P_{I_{max}}$) and maximal expiratory pressure ($P_{E_{max}}$) in 120 normal individuals (both smokers and nonsmokers) between the ages of 20 and 70.[26] Maximal respiratory pressures in females were 65% to 70% of those in males. No significant age-related changes were observed in individuals under the age of 55. Trends toward reduced maximal respiratory pressures with age were seen in both genders and with both $P_{I_{max}}$ and $P_{E_{max}}$. With the number of males studied, the change with age in $P_{I_{max}}$ was not statistically significant for male gender.

More recently, McElvaney and coworkers came to a different conclusion in a similar study of 104 healthy individuals over the age of 55.[27] They found a large variation in maximal respiratory pressures from individual to individual (as by Black and Hyatt), but no significant correlation with age. In contrast, in a third population of 160 healthy individuals who ranged in age from 16 to 75 years, Chen and Kuo found significant gender differences in maximal respiratory pressures as well as trends toward decrements with age for $P_{I_{max}}$ and $P_{E_{max}}$ in both genders. The age-related change in $P_{E_{max}}$ in males was not statistically significant with the sample size studied. When the 40 individuals of both genders in the youngest age group (16–30 years) were compared with the 40 individuals in the oldest group (61–75 years), the decrement in $P_{I_{max}}$ was 32% to 36%, while the decrement in $P_{E_{max}}$ was 13% to 23%.[28] Representative findings for maximal respiratory pressures in women are illustrated in Fig. 18-5.

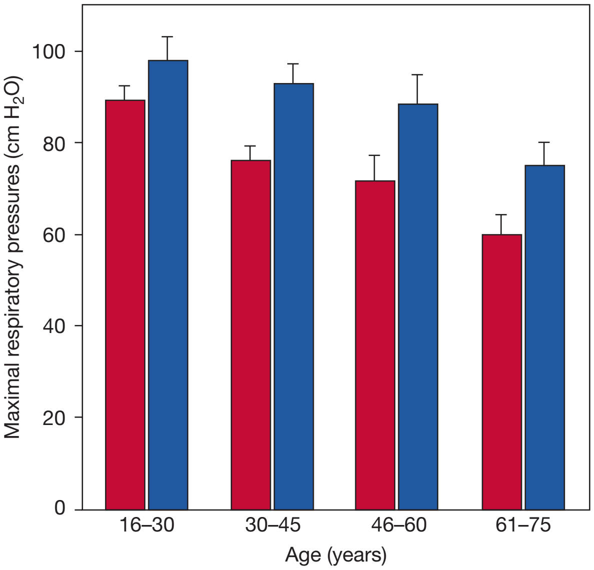

Figure 18-5 Representative variations in maximal respiratory pressures with age among women. Inspiratory and expiratory measurements were made at residual volume and total lung capacity, respectively. Maximal inspiratory pressure *(open bars)* and maximal expiratory pressure *(hatched bars)*. Error bars are standard errors of the mean. Although quantitatively moderate, variations with age were statistically significant for both measurements. *(Data from Chen H-S, Kuo C-S. Relationship between respiratory muscle function and age, sex, and other factors. J Appl Physiol. 1989;66(2):943–948.)*

Chen and Kuo also measured inspiratory muscle endurance against a resistive load and found significant decrements with age. Physically active men had greater inspiratory muscle endurance than sedentary men.

In summary, it appears that when populations of healthy individuals of widely differing ages are studied, moderate age-related decrements in respiratory muscle strength and endurance can be found. These studies usually define *healthy* only by the absence of disease and do not control for physical activity. They are complicated by marked interindividual variability, and longitudinal studies have not been reported. Continuous respiratory muscle activity may have a training effect that leads to better preservation of respiratory muscle function when compared with other skeletal muscles. Finally, physical activity may have an additional training effect that enhances inspiratory muscle endurance in all age groups.

CONTROL OF BREATHING

In young individuals, minute ventilation is matched with metabolic demands. As a result, arterial blood gas values remain stable throughout a wide range of activities from rest to strenuous exertion, while oxygen consumption and carbon dioxide production are varying widely. Similarly, when the efficiency of gas exchange is diminished by lung disease or congestive heart failure, appropriate increases in minute ventilation minimize the resulting hypercapnia and/or hypoxemia in healthy young individuals. The ventilatory control system is described in detail in Chapter 11.

Ventilatory control mechanisms are typically tested by stressing the respiratory system, by inducing either hypoxemia or hypercapnia while monitoring ventilatory parameters (and often cardiac parameters as well). Such tests have shown striking differences between young and elderly individuals in both ventilatory and cardiac responses.

■ Diminished Ventilatory Response to Hypercapnia

Kronenberg and Drage compared the ventilatory responses to hypercapnia in eight young (mean age, 25.6 years) and eight elderly (mean age, 69.6 years) individuals.[29] During the tests, the subjects were asked to rebreathe 5% CO_2, while their $P_{A_{O_2}}$ was held above 200 mm Hg by supplemental oxygen to eliminate hypoxic ventilatory drive. Measurements were made while $P_{A_{CO_2}}$ was allowed to rise to 65 mm Hg. Although there was considerable individual variation and some overlap between the groups, the elderly individuals had a significantly diminished ventilatory response to hypercapnia, measured as the slope of the relationship between ventilation and $P_{A_{CO_2}}$.

■ Diminished Ventilatory Response to Hypoxia

When Kronenberg and Drage measured the ventilatory response to hypoxia at constant CO_2, they found even more striking differences between the young and elderly subjects (Fig. 18-6). For example, the ventilatory response to a $P_{A_{O_2}}$ of 40 mm Hg was uniformly smaller in the older subjects, and there was no overlapping between the groups.[29] The mean minute ventilation at a $P_{A_{O_2}}$ of 40 mm Hg was 40.1 and 10.2 L/min in the young and old groups, respectively.

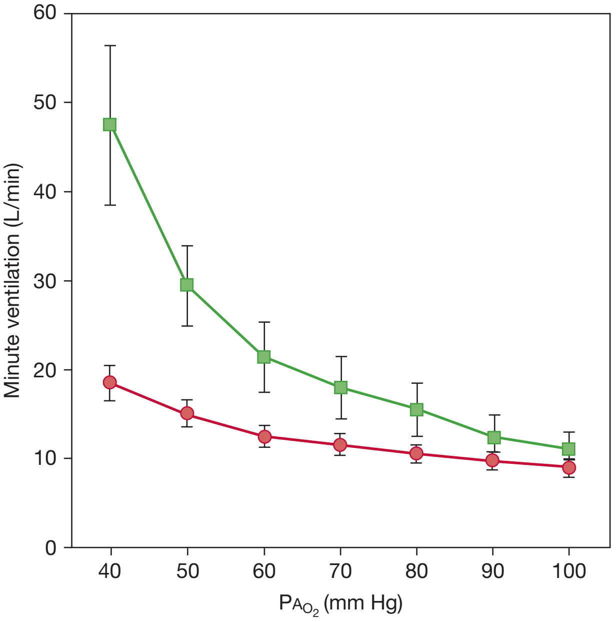

Figure 18-6 Variations with age in ventilatory responses to hypoxia. Eight normal men aged 64 to 73 *(circles)* and eight controls aged 22 to 30 *(squares)* were subjected to isocapnic progressive hypoxia by a rebreathing method. Data values are means, with standard errors of the mean shown by the error bars. Note that the ventilatory responses differ strikingly between the elderly individuals and the controls. *(Reproduced with permission from Kronenberg RS, Drage CW. Attenuation of the ventilatory and heart rate responses to hypoxia and hypercapnia with aging in normal men. J Clin Invest. 1973;52(8):1812–1819.)*

Diminished Occlusion Pressure Responses

Peterson et al. confirmed the previously discussed observations and have shown that the differences in responses of elderly subjects to both hypercapnia and hypoxia are due to a lesser increase in tidal volume while the ventilatory rate increases normally. Since this observation could be caused by differences in respiratory muscle strength or increases in chest wall stiffness, the authors also measured airway occlusion pressures, which are valuable indices of respiratory drive that are not affected by respiratory muscle strength or respiratory mechanics.[30] The measurement (P_{100}) is the negative pressure at the mouth, measured 100 ms after the start of inspiration against an occluded airway. The occlusion pressure responses to both hypoxia and hypercapnia (Fig. 18-7) were significantly reduced in the 10 elderly subjects studied by Peterson (mean age, 73.3 years) when compared with nine young control subjects (mean age, 24.4 years). Although the elderly individuals had reduced respiratory muscle strength (mean, 24% lower maximal static inspiratory pressure), the differences in occlusion pressure persisted when normalized for these differences.

The previously mentioned seminal studies of ventilatory control have been discussed in some detail out of respect for their groundbreaking conceptual importance. Subsequent studies have created some confusion that appears likely to be due to methodologic differences, ages of subjects, and small sample sizes. However, in 14 of 16 studies reviewed by Lalley, ventilatory responses in the elderly were found to be abnormal.[31]

In summary, the reduced responsiveness in tidal volume to either hypoxemia or hypercapnia with age is apparently due to a reduced responsiveness of ventilatory drive or neural output from the respiratory center. It has not been determined whether the diminished ventilatory drive results from altered chemoreceptor function or from altered function of the respiratory center. Kronenberg and Drage favored altered receptor function based on their observation that elderly subjects responded to an alveolar oxygen tension of 40 torr with only an 11% increase in heart rate, whereas the young subjects responded with a 34% increase.

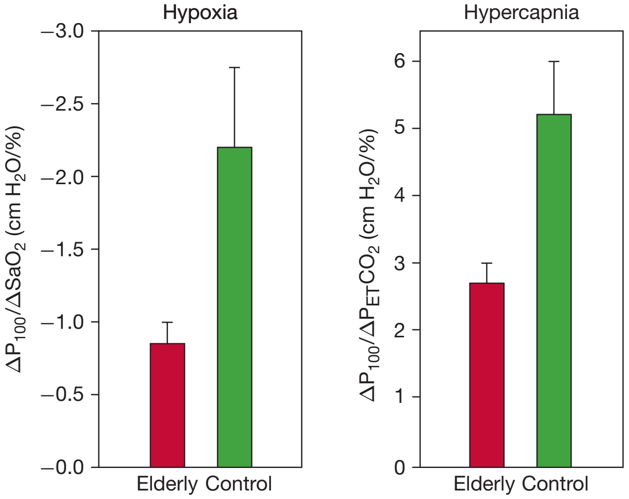

Figure 18-7 Variations with age in occlusion pressure responses to hypoxia and hypercapnia. Data shown are slopes of relationships between occlusion pressure responses and either Sa_{O_2} or end-tidal P_{CO_2}; error bars are standard errors of the mean. Elderly individuals had significantly diminished occlusion pressures in response to both hypoxia and hypercapnia. Both differences were significant, with $p < 0.01$. *(Reproduced with permission from Peterson DD, Pack AI, Silage DA, et al. Effects of aging on the ventilatory and occlusion pressure responses to hypoxia and hypercapnia. Am Rev Respir Dis. 1981;124(4):387–391.)*

Respiratory Load Compensation and Dyspnea

Reflex compensation is a response that maintains constant ventilation during a change in respiratory mechanical load, as occurs in lung disease, changes in posture, and mouth versus nose breathing. Akiyama et al. measured responses to inspiratory flow-resistive loading in young and elderly individuals and found significant differences.[32] In the young control group, inspiratory loading resulted in an increase in P_{100} at each level of induced hypercapnia, such that inspiratory loading did not change the ventilatory response to hypercapnia when compared with unloaded responses. In marked contrast, the P_{100} in the elderly group did not change when an inspiratory load was applied. In the absence of a compensatory change in ventilatory drive, ventilatory responses to hypercapnia were reduced during inspiratory loading in the elderly group.

At each level of P_{CO_2}, the intensity of perceived dyspnea in response to inspiratory loading was greater in the elderly than in the control group. Thus, the sensation of dyspnea was intact or enhanced in the elderly subjects, while their compensatory responses were reduced. This suggests the possibility that elderly individuals may complain of a greater dyspnea than younger individuals with similar pathophysiologic deterioration.

Sensitivity to Respiratory Depression by Opioids and Sedatives

Older individuals are substantially more sensitive to respiratory depression by opioids and sedatives. This phenomenon demands extra vigilance when these medications are prescribed in non-intubated elderly patients. The enhanced drug effect has been shown to be multifactorial, and the various mechanisms involved are beyond the scope of this chapter.[33–35] However, the dangers associated with higher levels and more prolonged effects of these drugs are real and potentially catastrophic.

PULMONARY CIRCULATION

Invasive physiologic studies of pulmonary artery catheterization have typically been biased by including only subsets of patients whose signs and symptoms led to referral for heart catheterization and who, therefore, may not be representative of a "healthy" cohort. Further, age-related changes in the pulmonary circulation are difficult or impossible to separate from changes due to heart disease or age-related changes in cardiac function.

Ehrsam et al. reported a retrospective analysis of right heart catheterization studies performed in 125 asymptomatic subjects who ranged from 14 to 68 years of age.[36] Small increases in right atrial, pulmonary artery, and pulmonary artery wedge pressures observed in the highest age group disappeared when values were adjusted for sex, weight, and height. No significant age-related changes were found in cardiac output, stroke volume, or oxygen uptake. Age explained 10% or less of the total variation in the hemodynamic and pressure variables when assessed by multiple regressions. During supine exercise with a bicycle ergometer, however, pulmonary artery and wedge pressures increased with age, particularly in subjects over the age of 45. The changes were highly significant with age accounting for 12% to 30% of the total variation when assessed by multiple regressions. Finally, pulmonary artery resistance showed a highly significant increase with age, whether measured at rest or during exercise, with age contributing 12% to 27% to the total variation in pulmonary artery resistance. Although the cohort studied were all asymptomatic and ambulatory, it is possible that silent coronary artery disease was present in some of the subjects, and the prevalence of coronary artery disease can be expected to increase with age. Moreover, younger patients tended to be referred for evaluation of a heart murmur, whereas the older patients were referred for "pulmonary investigation" that included coin lesions, hilar lymphadenopathy, "previous pulmonary infiltrates," and smoke inhalation. Cigarette smoking history was not discussed. Thus, it is not certain that the younger and older patients were strictly comparable.

Davidson and Fee reported the results of right-heart catheterization at rest in 47 normal subjects (smokers were included) who were free of coronary disease and had normal left ventricular systolic function.[37] The investigators found highly significant but quantitatively modest age-related increases in mean pulmonary artery pressure, pulmonary vascular resistance, and pulmonary/systemic vascular resistance ratio, but they found no age-related differences in pulmonary artery wedge pressure. The authors felt that the most likely explanation for the age-related changes in pulmonary artery pressure and pulmonary vascular resistance was a primary abnormality of the pulmonary vascular bed, but they could not exclude the effects of subtle abnormalities in left ventricular function.

In summary, studies of pulmonary hemodynamics with aging are limited by retrospective design, bias in patient selection, and potential effects of smoking. Minor increases in pulmonary vascular resistance and age-related increases in pulmonary artery wedge pressure during exercise have been reported. These age-related changes may not be physiologically significant.

PULMONARY FUNCTION TESTS

Lung function and exercise capacity decline with age in concert with numerous other physiologic, morphologic, and biochemical changes. Descriptions of "normal" age-related changes are confounded by an increasing prevalence of disease, chronic illness, medication use, and an increasingly sedentary lifestyle. Further, chronologic age only approximates physiologic age; the two often differ significantly. Chronologic age is, therefore, an imperfect measure for indexing changes with senescence. While it would be desirable to isolate the effects of biologic aging (aging in the absence of disease), it is essentially impossible to do so. The best studies to do so are longitudinal, tracing change with time, because they avoid the obvious biases of cross-sectional studies. Longitudinal studies, however, have methodologic problems and biases of their own, the most obvious being that the healthy elderly represent a healthy survival population. If, as a group, they have better than average lung function, they would not represent the general population of elderly people well.

■ Lung Volumes

Figure 18-8 illustrates typical lung volume changes with aging based on cross-sectional studies. With the exception of vital capacity, the effect of aging on lung volumes is based on cross-sectional rather than longitudinal data because there are almost no longitudinal studies of static lung volumes. Total lung capacity (TLC), the volume of air in the lungs at the end of a maximal inspiration, is marked by the point at which the recoil pressure exerted by the respiratory system is exactly counterbalanced by the maximal inspiratory pressure generated by the respiratory muscles. Since both the compliance of respiratory system (lung and chest wall combined) and maximum inspiratory pressure fall with aging, TLC might also be expected to fall. However, in seven cross-sectional studies of TLC summarized by the European Coal and Steel Community, four of the studies in men and three of those in women did not find a significant age coefficient.[38] The remaining studies found only small declines in TLC with age, on the order of −8 to −19 mL/year. When these study results were combined into average equations, no significant age coefficients were reported for either men or women. McClaran et al. measured lung volumes twice in 18 healthy, fit men.[39] The first measurement was at a mean age of 67 and the second was 6 years later. Although average TLC fell 25 mL/year, the change was not statistically significant. The study was small and the interval was short.

In summary, current cross-sectional studies suggest that TLC either does not decline with age or declines very slowly. It is interesting to speculate on the possibility that cross-sectional studies of TLC might be confounded because they typically index TLC to both age and height. Height declines with aging, and maximum height during a life span appears to increase with successive generations. The

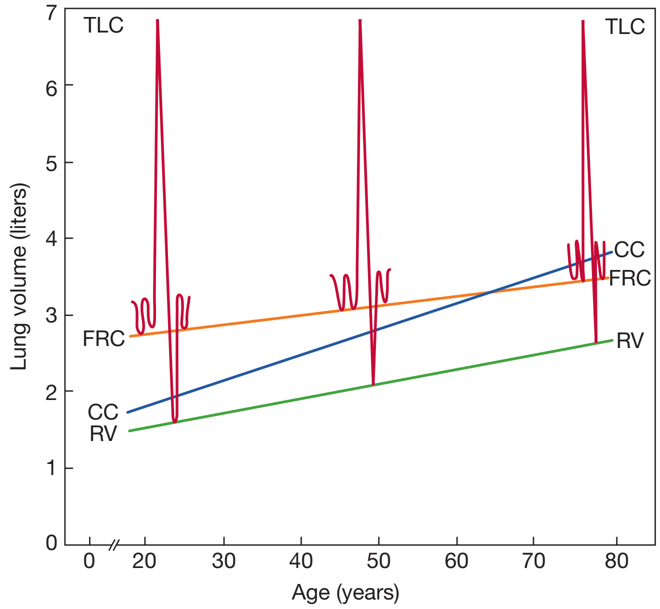

Figure 18-8 Schematic illustration of lung volume changes with age based on cross-sectional studies in seated individuals. (CC, closing capacity; FRC, functional residual capacity; RV, residual volume.) Although not labeled, vital capacity (VC) is TLC, total lung capacity; TLC minus RV. The most consistent changes are an increase in RV and a decrease in VC. *(Reproduced with permission from Fishman AP: Pulmonary Diseases and Disorders. New York, NY: McGraw Hill; 1992.)*

authors believe that longitudinal studies of TLC with age are likely to show small but significant declines with age.

Both slow and forced vital capacity (FVC) decline with age, more rapidly in men than in women. Average decrements in vital capacity per year vary considerably; in cross-sectional studies, declines range from 21 to 33 mL/year in men and 18 to 29 mL/year in women. Theoretically, longitudinal studies should provide better estimates of the effect of aging on lung function. Ware et al., in a study containing both longitudinal and cross-sectional computations, found cross-sectional falls in FVC for men and women to be −34 and −27.8 mL/year, respectively.[40] The longitudinal estimates were −40 mL and −31.3 mL/year, respectively. This study contradicts the generally held concept that longitudinal studies show smaller declines in FVC than cross-sectional studies. Currently, it is not certain whether longitudinal studies are all that much different from cross-sectional studies in describing declines in FVC and forced expiratory volume in 1 s (FEV$_1$). Longitudinal studies tend to show an acceleration in the rate of loss in FVC and FEV$_1$ as age advances.

Cross-sectional studies of residual volume (RV) and the RV/TLC ratio consistently show increases with age. In the young, RV, the volume of air in the lungs at the end of a maximal expiration, is the volume at which the outward static recoil pressure of the respiratory system is counterbalanced by the maximal pressure exerted by the expiratory muscles. In older subjects, expiratory flow never completely reaches zero and the determination of RV is made partly by the length of time an individual can maintain expiratory effort.[41] Other factors leading to an increased RV with aging include loss of lung recoil, decreased chest wall compliance, decreased expiratory muscle force, and increased small airway closure (air trapping) in dependent lung zones. Time of exhalation and increase in air trapping are probably more important than changes in lung and chest wall compliance in explaining the increase in RV with aging.

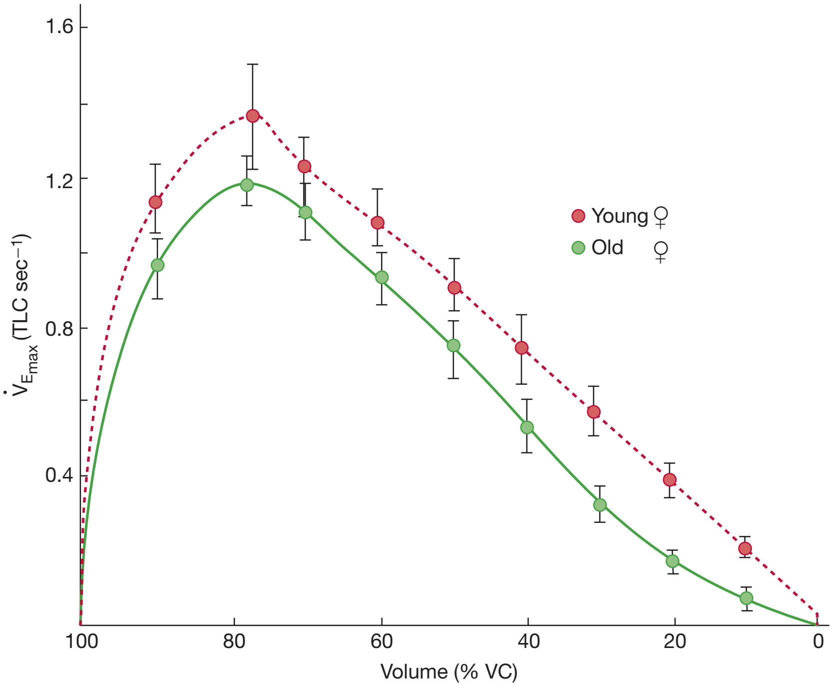

Figure 18-9 Illustrative maximal flow–volume curves for healthy “elderly” women (mean age, 63 years) and healthy young women (mean age, 25 years). Although all flows tend to be reduced with aging, the reduction in flow is most evident at lower lung volumes, where the flow–volume curve is clearly concave to the volume axis. *(Reproduced with permission from Fishman AP: Pulmonary Diseases and Disorders. New York, NY: McGraw Hill; 1992.)*

FRC is also determined by the balance of the elastic recoil forces of the lung and chest wall—but, in this instance, the equilibrium occurs at the end of a quiet (unforced) exhalation. Since lung recoil falls and the chest wall stiffens with age, one would expect FRC to increase. Cross-sectional studies, however, show inconsistent results, with most showing no change in FRC with aging. Studies that find an increase in FRC with aging show a small positive age coefficient on the order of 7 to 16 mL/year. McClaran’s longitudinal study found FRC to increase 40 mL/year, but again, the change was not significant.[39] Despite the conflicting data, it is generally believed that FRC increases with aging.

Loss of lung recoil also changes the volume at which airway closure occurs. When adults exhale fully, small airways close in the region of the terminal bronchioles in dependent lung zones. The lung volume at which this closure begins is measured as closing volume or, if it is added to RV, closing capacity. Closing volume increases linearly with age from about 5% to 10% of TLC at age 20 to about 30% of TLC at age 70.[16] The loss of lung elastic recoil, a possible decrease in the recoil of the intra-pulmonic airways, and decreases in small airway diameter probably explain most of the changes in CV.

Closing volume encroaches on tidal volume by about age 44 when subjects are supine and about age 65 when they are seated (Fig. 18-8). Airway closure during tidal breathing explains most of the decrease in arterial oxygen tension ($P_{A_{O_2}}$) observed with aging[42,43] and may contribute to an aging-related increased frequency dependence of compliance.

■ Airflow

While essentially all expiratory flows measured during a maximum expiratory maneuver decrease with age, the declines are most evident at lower lung volumes (Fig. 18–9). Nunn and Gregg, in a study of 225 male and 228 healthy female nonsmokers,[44] reported a modest, nonlinear decrease in peak expiratory flow (PEF) with aging (Fig. 18-10), which reached a high point at age 30 to 35; a decline became evident at about age 45. After age 50, the average decline was about 4 L/min per year in men, about 2.5 L/min per year in women.

Figure 18-11, from Paoletti et al., illustrates changes in FEV$_1$ during growth, maturation, and senescence.[45] Changes in FVC are similar. In one model of aging, FVC and FEV$_1$ increase progressively during the growth phase until about age 12. In the maturation phase (during adolescence), there is an acceleration of these increases. Increases in FVC and FEV$_1$ are seen up to about 20 years in women and about 25 years in men; increases in lung volumes occur even after somatic growth ceases. There appears to be a plateau phase where there is little or no change in FVC or FEV$_1$ prior to the onset of a decline. However, Robbins et al. demonstrated that, while the plateau correctly represents average data, lung function is often increasing or decreasing in individuals (Fig. 18-12). Their study confirms the suspicion that the “plateau” phase represents the merging of slower maturation-related increases in FVC and FEV$_1$ in some subjects, with subtle decreases in others.[46] In the decline phase, there appears to be acceleration in the rate of loss of FVC and FEV$_1$ as age progresses. An accelerated rate loss at older ages is, however, not found in all studies. The rate of decline in FVC and FEV$_1$ with age tends to be greater: (1) in men; (2) in taller individuals; (3) in

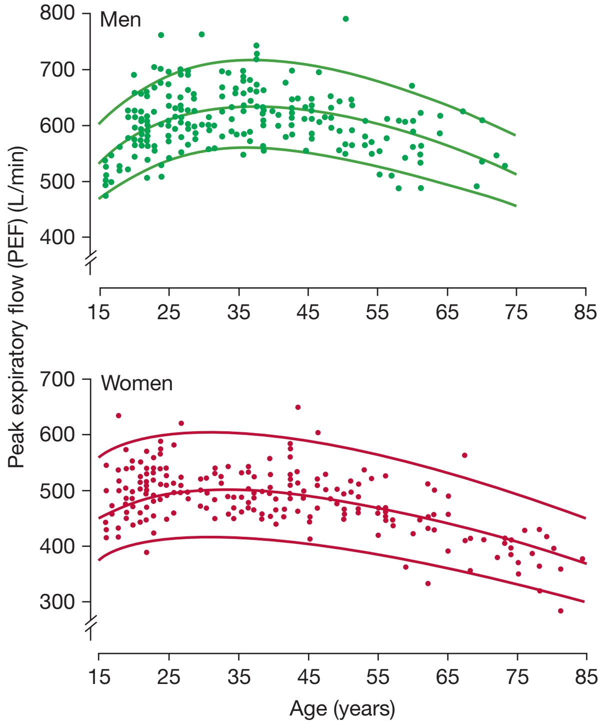

Figure 18-10 Changes in peak expiratory flow in 225 males and 228 females who were healthy nonsmokers. The *center line* is a regression curve representing mean data and the boundaries are 90% confidence intervals. *(Reproduced with permission from Nunn AJ, Gregg I. New regression equations for predicting peak expiratory flow in adults. Br Med J. 1989;298(6680):1068–1070.)*

individuals with larger baseline values; and (4) in individuals with increased airway reactivity.

■ Airways Resistance

Total airway resistance measured at FRC does not change with aging. Since upper airways increase and smaller airways decrease in size with aging, it is likely that peripheral airway resistance increases and central airway resistance decreases. That total airway resistance does not change with aging may be a function of the counterbalancing of these two opposite changes. However, since about 90% of total airway resistance resides in the upper airways, significant changes in peripheral airway resistance might not be readily reflected in total airway resistance. Significant increases in peripheral airway resistance with age also would be consistent with the more dramatic decreases in maximum flow observed at low lung volumes.

■ Gas Exchange

The carbon monoxide diffusing capacity (DL$_{\text{CO}}$), also known as transfer factor (TL$_{\text{CO}}$), declines with age. Earlier cross-sectional studies report a linear decline in DL$_{\text{CO}}$ of about −0.2 mL CO/min per mm Hg per year for men and −0.15 mL CO/min per mm Hg per year for women. These declines are roughly 0.5% per year. In a large representative sample of U.S. adult men, Neas and Schwartz found an almost linear fall in DL$_{\text{CO}}$.[47] In women, however, they found a nonlinear, quadratic decline in DL$_{\text{CO}}$ with age. After age 47, the nonlinear component was not significant and the decline in DL$_{\text{CO}}$ was identical to that in the earlier studies. The decline in DL$_{\text{CO}}$ with age did not vary with race.

The decline in DL$_{\text{CO}}$ with age is not explained by increased inhomogeneity of gas distribution. Measured DL$_{\text{CO}}$ falls as alveolar P_{O_2} increases, and venous hemoglobin concentration falls. Neither alveolar P_{O_2} nor hemoglobin concentration varies enough with age to explain the aging decline in DL$_{\text{CO}}$. The magnitude of the decline in DL$_{\text{CO}}$ corresponds fairly well to the magnitude of the known aging-related decrease in the internal surface area of the lung.

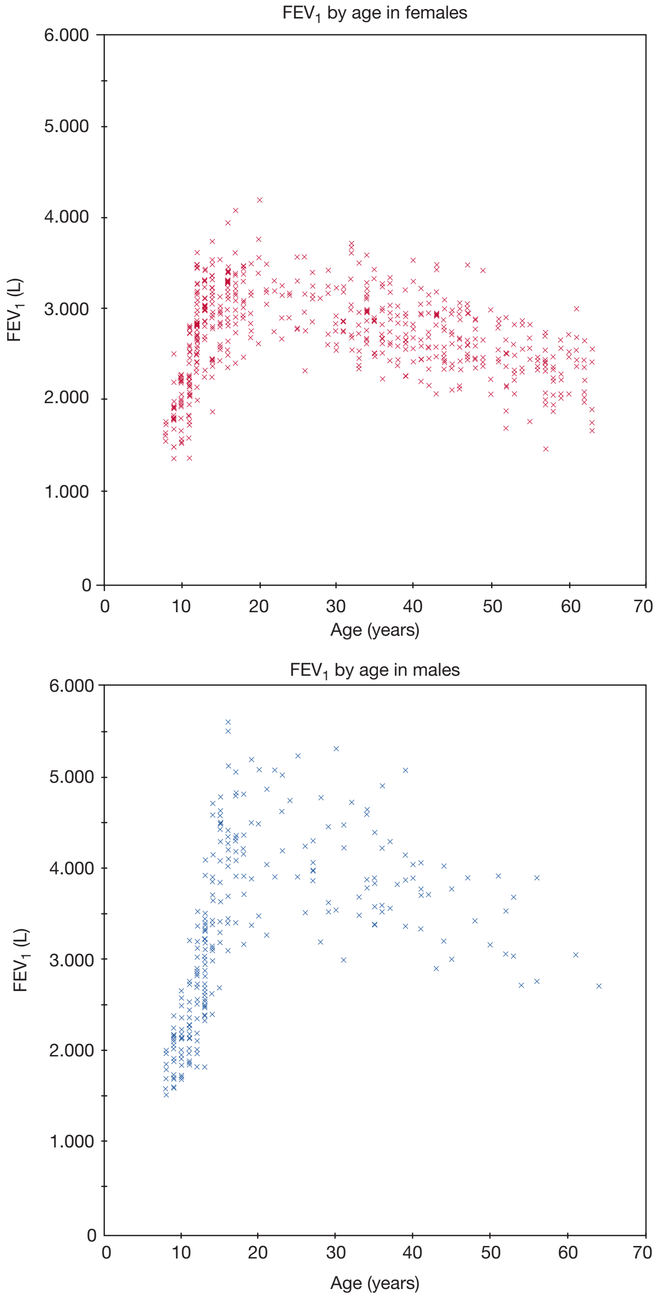

Figure 18-11 Change in FEV$_1$ with age from a cross-sectional study of 538 females and 263 males selected as "normal" from a larger study of 3289 subjects. Changes in FVC are similar. *(Reproduced with permission from Paoletti P, Pistelli G, Fazzi P, et al. Reference values for vital capacity and flow-volume curves from a general population study. Bull Eur Physiopathol Respir. 1986;22(5):451–459.)*

The components of DL$_{\text{CO}}$ are membrane diffusing capacity (Dm) and pulmonary capillary blood volume (Vc). Both Dm and Vc decrease with age. In a cross-sectional reference value study of 54 male and 36 female healthy nonsmokers, the decline in Dm and Vc with age were found to be linear.[48] Membrane diffusing capacity fell at about 0.6% per year in both men and women. Pulmonary capillary blood volume fell at about 0.3% per year.

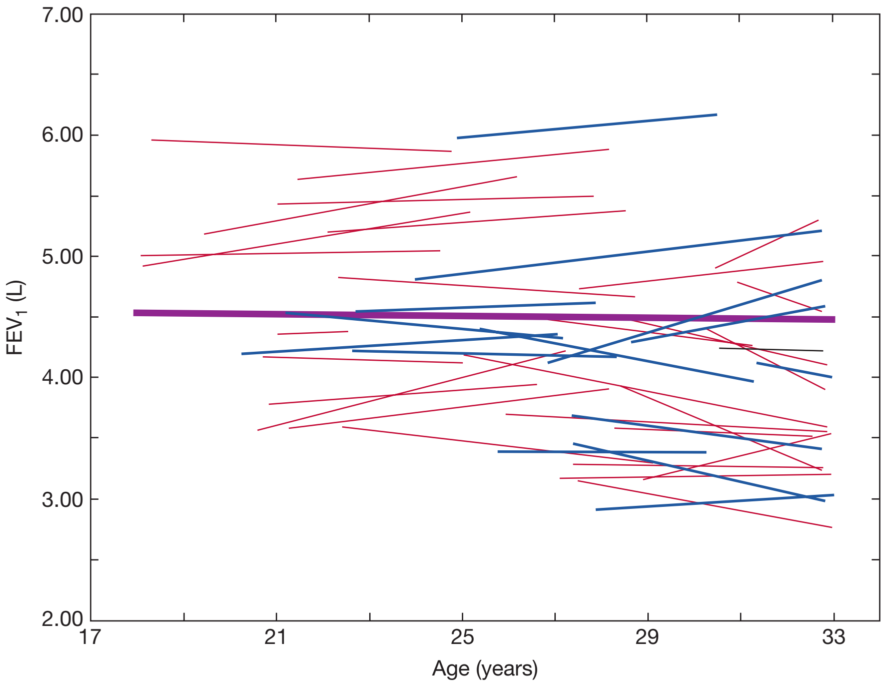

Figure 18-12 Predicted FEV_1 trajectories from 44 men based on linear regressions of longitudinal data. Nonsmokers *(fine lines)* and smokers *(dashed lines)*. The heavy line is based on the entire group's data. While the group's data show no change with age, data for individuals show both increases and declines with age during this time period, when a plateau in lung function was theorized to occur. *(Reproduced with permission from Robbins DR, Enright PL, Sherrill DL. Lung function development in young adults: Is there a plateau phase? Eur Respir J. 1995;8(5):768–772.)*

Although alveolar oxygen pressure (PA_{O_2}) remains constant with age, arterial P_{O_2} (Pa_{O_2}) decreases and the alveolar–arterial oxygen tension gradient ($PA - Pa_{O_2}$) increases with aging (Fig. 18-13).[49] The decline in Pa_{O_2} with aging is more pronounced when subjects are studied in a recumbent as contrasted with an upright position. The most likely explanation for the decline in Pa_{O_2} with aging is increased mismatching of ventilation to blood flow ($\dot{V}E/\dot{Q}$) as airway closure begins to occur during tidal breathing. Increased ($\dot{V}E/\dot{Q}$) mismatching with aging is also associated with an increase in physiologic dead space.[50,51] Hypoventilation does not contribute to the age-related fall in Pa_{O_2}, since Pa_{CO_2} and pH do not change with age (Fig. 18-13).

EXERCISE CAPACITY

Peak $\dot{V}_{O_2}$ ($\dot{V}_{O_2\,peak}$) and maximum work capacity decrease with aging in both sedentary and active individuals.[52] $\dot{V}_{O_2\,peak}$ (L/min) increases until about age 20. Declines are evident at about age 25 in both men and women and continue at about 1% per year (Fig. 18-14). If one expresses $\dot{V}_{O_2\,peak}$ as a function of body weight (L/kg per min), the decline is evident much earlier, perhaps in the first decade of life. The magnitude of the decline in $\dot{V}_{O_2\,peak}$ tends to be greater in longitudinal than in cross-sectional studies and occurs roughly twice as fast in sedentary than in physically active persons. Most, but not all, studies report linear declines in $\dot{V}_{O_2\,peak}$ with age, even though a nonlinear decline would be expected based on the number and type of variables that affect exercise capacity.

The decline in exercise capacity with age occurs as a result of normal aging but is accelerated by lifestyle issues. Aging is associated with significant changes in body configuration. Specifically, there is an increase in total body weight, primarily representing an increase in fat mass, since fat-free mass (mostly muscle mass) decreases with aging. The changes are most pronounced in sedentary persons. Muscle mass decreases, with a preferential atrophy of type II muscle fibers, and is associated with a decrease in muscle capillarization and oxidative activity. Muscle strength decreases on the order of 2%/year from ages 20 to 70. Variables associated with loss of exercise capacity with aging are listed in Table 18-2.

While exercise capacity declines with aging, it is also clear that the ability to respond to exercise conditioning is well maintained even at very advanced ages. Elderly individuals respond to both endurance and resistive training with improvements similar in magnitude

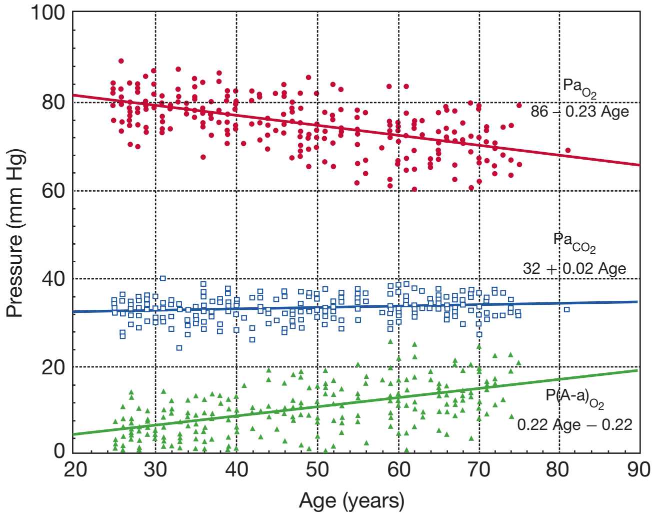

Figure 18-13 Change in Pa_{O_2}, Pa_{CO_2} and A-a gradient $P(A-a)_{O_2}$ with age. Data were obtained from 200 healthy men and women living in Salt Lake City, UT (altitude = 1400 m). Sea-level data would be similar, with a small upward shift in Pa_{O_2} and Pa_{CO_2}.

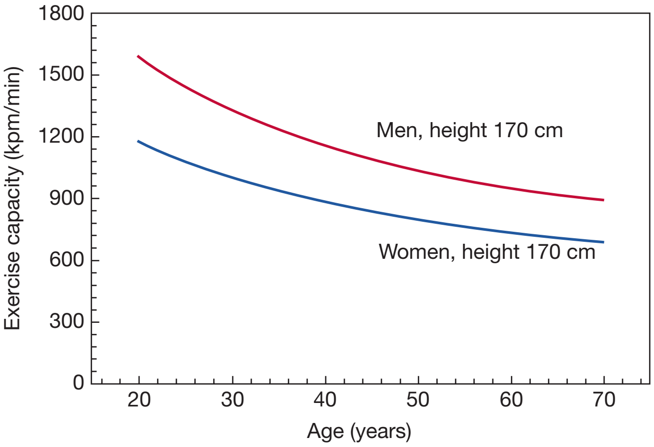

Figure 18-14 Decline in maximum exercise capacity with age. Exercise capacity declines nonlinearly with age. Maximum work capacity correlates strongly with peak oxygen uptake. *(Reproduced with permission from Jones NL, Summers E, Killian KG. Influence of age and stature on exercise capacity during incremental cycle ergometry in men and women. Am Rev Respir Dis. 1989;140(5):1373–1380.)*

TABLE 18-2 Variables Associated with a Decline in Exercise Capacity with Age

Variable	Comment
Decreased muscle mass	These changes especially affect $\dot{V}_{O_2}$ calculated per kg of body weight
Increased fat mass	
Decreased tissue oxygen delivery	As a result of the decreased cardiac output and maximal $C(a-\bar{v})_{O_2}$, delivery and extraction are reduced; decreased cardiac output is a major contributor to the age–related decline in exercise capacity
Decreased maximal heart rate	
Decreased stroke volume	
Decreased maximal $C(a-\bar{v})_{O_2}$ difference	
Maximum voluntary ventilation	
Increased ventilation at each workload	At each workload, older individuals breathe more and work harder for each breath than younger persons; however, the effect is small and contributes little to the decline in exercise capacity with aging
Increased oxygen cost of breathing	
Sedentary lifestyle	Lifestyle issues play a large role in the rate at which exercise capacity is lost with age; the good news is that, like other deconditioned groups, the elderly respond very well to exercise training
Decreased training intensity in active persons	
Decreased willingness to work to maximal level during tests	

to those seen in the young.[52–54] There are equivalent increases in $\dot{V}_{O_{2\,peak}}$, muscle mass, capillarization of muscle tissue, muscle oxidative activity, and general muscle strength.

LUNG PARENCHYMAL AND AIRWAY INFLAMMATION

Chronic low-level inflammation has been linked to aging of tissues, including in the lung.[55] In recent years, there has been considerable interest in the presence and control of lung inflammation in elderly individuals, and this has become a confusing subject. A variety of quantitative abnormalities in mediators of inflammation have been described in elderly individuals that have mostly been in the direction of increased lung parenchymal and airway inflammation. However, these differences from younger subjects must be viewed in the context that elderly individuals have impaired cough, increased evidence of gastroesophageal reflux, and decreased effectiveness of the ciliary escalator. All of these abnormalities can be expected to lead to an increased load of particulates and microorganisms in the lower respiratory tract, and/or recurrent episodes of aspiration. As a striking example of studies of airway inflammation, the mean quantity and percentage of neutrophils in broncho-alveolar lavage fluid have been found to be increased in elderly individuals, but many of the studied elderly subjects were indistinguishable from young normal subjects.[56] The increased mean values in the elderly were strongly influenced by outlying high values in a subpopulation, and thus presumably did not result from a direct effect of aging.

Significant changes to immune cell function occur with aging. The innate immune system, such as neutrophils, macrophages, and dendritic cells, is the rapid, initial line of defense against invading pathogens, while the adaptive immune system (T- and B-cells) is a slower-onset response designed for specificity and long-term responses. Intrinsic cellular dysfunction occurs with both arms of the immune system. Immunosenescence describes the decline in immune cell function, reduced pathogen recognition, signaling, and clearance. For example, neutrophils and macrophages have impaired migration to sites of injury, phagocytic function, and bacterial killing function in both aging patients and those with COPD.[57] In elderly individuals, B-cells have reduced antibody responses to influenza vaccination.[58] A second process termed *inflammaging* describes an increase in chronic inflammatory cells in tissues that occurs with aging, albeit with ineffective function of these cells. These age-related changes and dysfunction of the immune system likely have important impacts on lung function, chronic disease development, and treatment responses.

SLEEP

Sleep complaints from elderly patients present a difficult problem for the clinician, who must determine whether the complaints are related to the normal aging process, sleep hygiene issues, or the presence of pathology.[59,60] Problems with sleep are widespread among elderly persons, with 25% to 40% complaining about sleep difficulties. There is no evidence to confirm the widely held belief that the need for sleep declines with age. However, sleep quality decreases, and the frequency of various primary sleep disorders increases. The most common age-related change in sleep pattern is a striking increase in the number of nocturnal awakenings, resulting in lower total sleep time and lower sleep efficiency (total sleep time/time in bed). Whether sleep latency changes with aging is equivocal. The amount of time spent in stage 1 nonrapid eye movement (NREM or light) sleep tends to increase with age. The decrease in total sleep time at night is associated with an increase in unwanted daytime naps. Disrupted sleep in the elderly is, in large part, explained by medical and psychological issues and the lack of structured physical and social activity during the day. Chronic illnesses, nocturia, medication and alcohol use, periodic leg movements, bereavement, and depression also play a role. Not surprisingly, the elderly are more likely to use sedatives or hypnotics; their use is more frequent in elderly women than in elderly men. While hypnotics and sedatives are occasionally necessary, their chronic use may contribute to sleep disruption and aggravate certain sleep disturbances, such as sleep apnea. Increased autonomic activity, increased sensitivity to external stimuli (which may increase arousals as a result of environmental factors), decreased exposure to outdoor light, inactivity, and daytime napping also play a role in sleep disruptions in the elderly. Alterations in endogenous circadian rhythms for variables like temperature and cortisol or thyroid-stimulating hormone (TSH) levels also may contribute to sleep disruption in the elderly.

The neural system that regulates sleep is, like most other systems, subject to the aging process, and sleep disruption occurs in the elderly in the absence of any pathologic process. The amount of stage 3 and 4 sleep (slow- or delta-wave sleep) declines with aging, although some argue that the aging decline is mostly a technical issue related to how delta-wave amplitude is defined. Changes in slow-wave sleep appear to be evident early, perhaps by 20 years of age. Arguments have been made both for and against declines in the amount of REM sleep with age. The persistent controversy about REM sleep and aging suggests that if REM sleep does change with aging, the magnitude of decline is so small that it does not overwhelm the confounding factors in studies.

Sleep disorders such as sleep apnea and restless limb syndrome, with periodic limb movements, appear to be more prevalent in older persons, and they are also marked more among nursing home residents than the independent elderly. For example, using an apnea index of five per hour as a threshold, one study found evidence of sleep apnea in 42% of elderly nursing home residents, in contrast to 24% of the independent elderly. A community-based study of individuals aged 71 to 87 showed a 55% prevalence of sleep-disordered breathing that was documented by polysomnography, including 38% obstructive sleep apnea and 17% central sleep apnea.[61] However, longitudinal follow-up of these individuals did not show an independent correlation with either cardiovascular disease or mortality.

INTERPRETING PULMONARY FUNCTION TESTS IN THE ELDERLY

Several issues complicate the interpretation of lung function tests in the elderly, as reviewed by Vaz Fragoso and Gill.[62] The elderly are not well represented in most reference value reports; the number of subjects usually falls off significantly after age 60. The number of subjects over age 80 is usually so small that mean values calculated from regression equations are essentially an extrapolation of the data for younger persons. This means that the average or "predicted" value may not be as representative for the elderly as it is for middle-aged persons. The fall in sample size with aging likely reflects the reduced total number of candidates for participation and the larger number of individuals who fail screening criteria. In reference value studies, individuals are screened so as to be free of symptoms and illnesses that alter lung function. These selection criteria may eliminate more older, than younger, candidates because of their increased prevalence of illness. Also, test quality is carefully standardized. Cognitive impairment may compromise test quality. As a result, older individuals may have more difficulty meeting test quality criteria, increasing their likelihood of exclusion and potentially increasing the variability of reference data for the elderly. In summary, the selection processes may make the older individuals who participate in reference studies less representative of the individuals who present for clinical lung function testing.

These same issues also affect the limits applied to determine whether a tested individual is within the "normal" range. Limits are often defined assuming that the distribution of data is Gaussian. Although tests of this assumption are sparse, there is reason to suspect that it is more likely to fail in the elderly. Even when the "normal" range is defined using methods that avoid assumptions about data distribution, data from the elderly are often lumped with those of the younger subjects. The result may be an erroneous "normal" range. All these reference value issues suggest that increased caution should be used in interpreting lung function tests in the elderly. This caution is especially important for those over age 80 and in any elderly person whose data lie near the limits of a "normal" range.

UNRAVELING THE BIOLOGY OF THE AGING LUNG

Many questions remain about how the lung ages and how this affects the development of chronic age-related disease (such as pulmonary fibrosis and COPD). The National Institutes of Health and interest groups have named seven "pillars of research" in the biology of aging including inflammation, adaptation to stress, epigenetics, cellular metabolism, macromolecular damage, proteostasis, and stem cells/regeneration.[63] Model organisms (such as yeast, worms, and flies) and vertebrate models (primarily mice) have begun to address these key aspects clarifying what factors accelerate or protect against aging and how aging drives lung disease pathogenesis that will likely result in clinical impact. To connect molecular and cellular changes that occur within the aging lung, Angelidis et al. integrated single cell transcriptomic and proteomic data of a mouse lung aging model (3 months vs. 24 months old), showing an increase in proinflammatory pathways, reduction in mitochondrial function, and altered extracellular matrices.[64] Modeling of aging is important in preclinical testing and comparative studies of human disease. Ongoing research efforts are critical to model development and understanding lung aging.

CONCLUSIONS

As the aging population grows, it becomes increasingly important to understand the aging lung and its function. At the cellular level, the processes central to aging are thought to include inflammation, adaptation to stress, epigenetics, cellular metabolism, macromolecular damage, proteostasis, and stem cells/regeneration. Pathologic changes in these homeostatic processes result in changes to airway and parenchymal structure and abnormal respiratory system physiology. Understanding normal aging in the lung may potentially inform management and treatment of diseases of accelerated aging such as COPD and pulmonary fibrosis.

As this chapter is being written, the world is gripped by a pandemic caused by a novel respiratory coronavirus, SARS-CoV-2 (COVID-19). There are marked disparities in risk of symptomatic, severe, critical, and fatal disease among people with various comorbidities and ethnicities. Chief among the determinants of risk is age (and, particularly, advanced age). Many factors may contribute to the age-related risk. Additional investigation is necessary to increase our understanding of how these specific factors impact disease pathogenesis and improve our treatment and control of current and future respiratory disease outbreaks.

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CHAPTER 19

Innate and Adaptive Immunity in the Lung

Clemente J. Britto
Charles S. Dela Cruz

INTRODUCTION

The lung is constantly exposed to environmental nonpathogenic and pathogenic moieties in ambient air. These moieties include infectious agents or their products, allergens, irritants, and other inhaled antigens capable of eliciting an immune response. The first line of defense in the interactions between environmental exposures and the respiratory tract is a barrier composed of a mucus layer, airway surface liquid, cilia, and the airway epithelium. This barrier is supported by a complex network of immune defense mechanisms that are both innate and adaptive.[1,2] The immune response must recognize and react to a wide variety of stimuli. It must also identify and eliminate unwanted pathogens to keep pulmonary structures free from infection. On the other hand, this response must be closely regulated to maximize pathogen clearance while minimizing excessive inflammation and tissue injury. An adequate balance between immune response and its resolution is essential to preserve normal pulmonary architecture, especially the highly vascular and fragile alveolar epithelial surface required for gas exchange. The disruption of these lung protective mechanisms contributes to the pathogenesis of many pulmonary diseases. Therefore, understanding innate and adaptive immune responses in the lung is important to understand the pathophysiology and to improve the management of respiratory diseases. These anatomic and immune defenses are reviewed below.

ANATOMIC MECHANISMS

The lung's extensive surface area creates an opportunity for frequent and numerous inhaled environmental challenges that include infectious agents, irritants, and fine particulate matter (Fig. 19-1). The alveolar and capillary membranes are critical for gas exchange and must be defended from the noxious effects of these challenges and the immune response they elicit. Unchecked, these exposures can cause excessive inflammation, tissue injury, and the propagation of infection. In turn, unchecked inflammation and tissue damage can lead to anatomic distortion, functional impairments, and abnormal fibrotic repair that compromise gas exchange. Air is inhaled through the nose or the mouth into the extrathoracic portion of the trachea before it enters the thorax. The air is filtered of large particulates by vibrissae (nasal hairs) in the nasal passages and subsequently warmed and humidified as it flows through the nasal turbinates. The nasal secretions lining the airway mucosa contain immunoglobulins (such as secretory immunoglobulin A, sIgA), mucins, and host defense peptides and proteins that facilitate mucociliary clearance, inactivate invading pathogens, and modulate innate immune responses. For example, sIgA accounts for 15% of the total protein in upper airway secretions and plays a significant role in neutralizing and preventing epithelial attachment of invading viruses and bacteria, while host defense proteins and peptides such as lysozyme, cathelicidins, and defensins perform antibacterial, antiviral, and immunomodulatory roles.[3] The airway mucosa is coated, with viscous fluid and mucus secreted by Clara cells, goblet cells, and bronchial glands (Fig. 19-1). This fluid makes up an important airway surface lining that protects the bronchial epithelium and forms a barrier between the environment and the lung parenchyma.

INNATE IMMUNITY IN THE LUNG

The innate immune response is an evolutionarily conserved system of host defense present in multicellular organisms. The purpose of the innate immune system is to provide a rapid response, in contrast to the adaptive immune system, which provides a more specific response but takes longer to respond (discussed later). Because humans breathe approximately 10,000 L of air per day (12 to 15 breaths per minute ×~500 mL tidal volume), we are constantly exposed to pathogens (e.g., viruses, bacteria, and fungi), allergens (e.g., house dust mites, dander), and toxins (e.g., cigarette smoke, pollutants). The innate immune system allows humans to respond to these stimuli even if they have not been primed for a specific response.

Similar to other mucosal surfaces (e.g., gut and skin), innate immune responses must be sequential and balanced. Ideally, this sequence should include: (1) pathogen recognition, (2) initiation of an appropriate response, typically manifested by inflammation, and (3) resolution of inflammation. An inappropriately regulated innate response contributes to the pathogenesis of lung diseases as diverse as asthma, chronic obstructive pulmonary disease (COPD), and interstitial lung disease.

The most important property of the innate immune system is its response to pathogens regardless of whether there has been a prior exposure. Thus, acquired immunologic memory against the pathogen is not required. The anatomic and antimicrobial structures that prevent infection and injury noted above can be thought of as part of this innate response. Therefore, one of the most important roles of the lung innate immune system is its function as a barrier to inhaled pathogens.[4,5] The tight junctions formed between neighboring cells create a barrier that prevents pathogen entry (Fig. 19-1). In addition to this barrier function, the epithelium has a coordinated system for the removal of inhaled pathogens and cellular debris. Goblet cells and secretory glands produce mucus that traps pathogens. A coordinated system of ciliated cells moves mucus up the mucociliary escalator to be expectorated during coughing. A disturbance in these essential functions may lead to pathology. In primary ciliary dyskinesia (PCD), ciliary function impairments result in bronchiectasis and recurrent bacterial infection.[6,7] In cystic fibrosis (CF), abnormal epithelial chloride and bicarbonate transport disrupts airway surface liquid homeostasis, preventing effective mucus clearance that leads to chronic inflammation, bronchiectasis, and recurrent bacterial infections.[8–11]

The mucociliary escalator is particularly effective for large particles, but smaller particles (<5 μm) can travel to the distal alveolar epithelium. Here, instead of mucociliary clearance, particles encounter secreted surfactant proteins (specifically SP-A and SP-D; also known as pulmonary collectins) that act as opsonins and assist resident macrophages in phagocytosis.[12] Finally, throughout the respiratory tract the epithelium secretes numerous innate immune antimicrobial molecules with their own antimicrobial, ion transport, and immunomodulatory activity that modulate cellular responses to infection.[13,14]

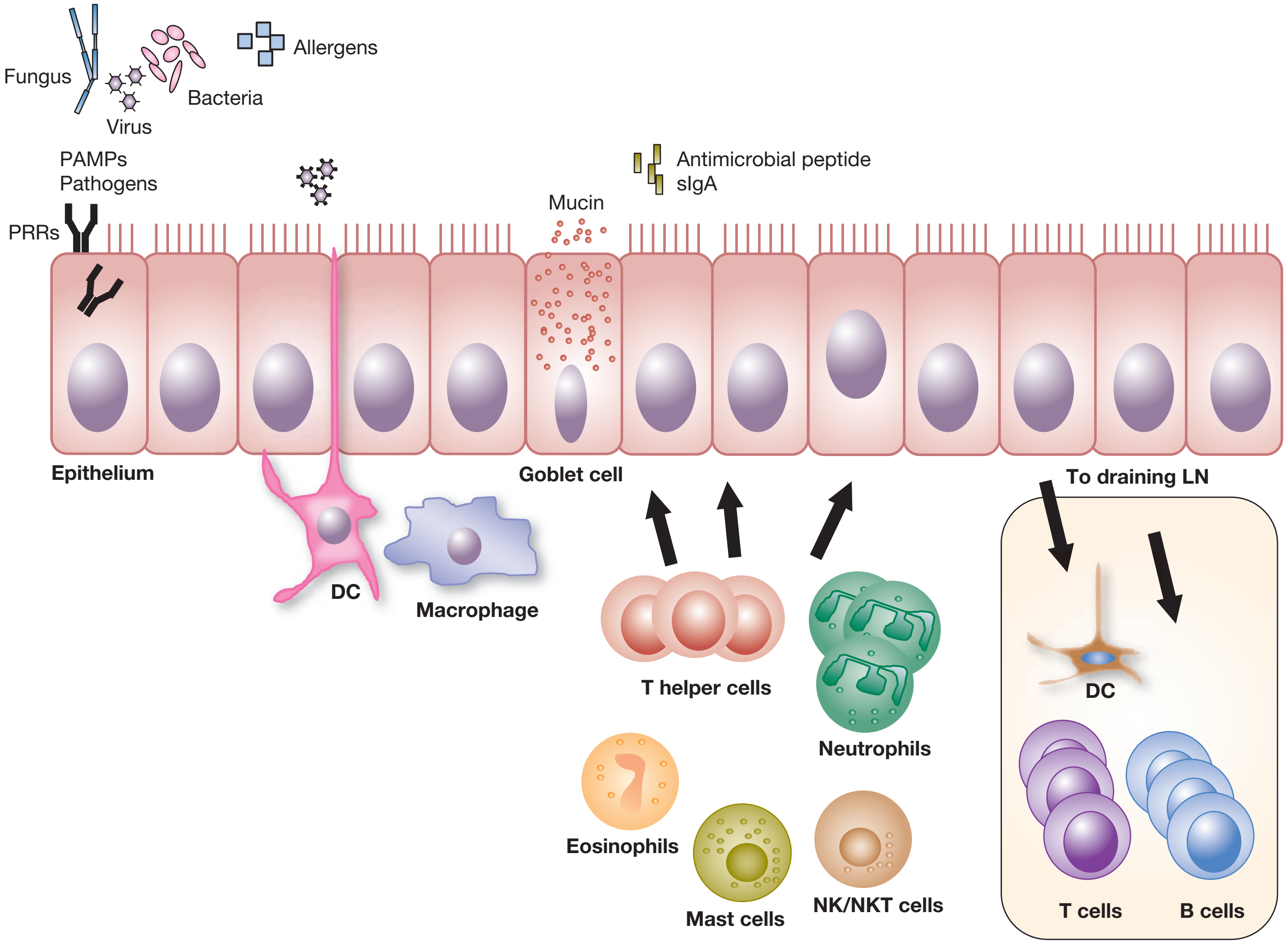

Figure 19-1 Innate recognition of pathogen or PAMPs on airway epithelium. Pathogens such as fungus, virus, or bacteria (or their associated pattern-associated molecular proteins, [PAMPs]) and environmental allergens are first detected by membrane-bound, cytosolic, and/or endosomal innate sensors or pattern recognition receptors (PRRs). The respiratory epithelial cells provide a physical barrier between the airway luminal antigens and the underlying respiratory tissues in their control of immune defense and tolerance. Specialized epithelial cells can have cilia, produce a mucus layer, and secrete antimicrobial proteins and secretory IgA (sIgA) that limit pathogen exposure to the epithelial cells. Dendritic cells (DCs) interdigitating between and lying near the epithelium, as well as tissue macrophages, are well positioned to sample and ingest incoming antigen. Recognition of the antigen by the innate immune receptors leads to production of proinflammatory cytokines and chemokines, which recruit immune cells such as neutrophils, T cells, NK cells, NKT cells, eosinophils, or mast cells. Activated DCs that have taken up the inhaled antigen migrate to nearby draining lymph nodes. In the lymph nodes, the DCs help integrate the signals from the inhaled substance and the innate immune response into signals that direct cells of the adaptive immune system. The DCs encounter appropriate naïve CD4$^+$ T cells where factors such as the phenotype of the antigen-presenting cells (APCs) and cytokine milieu modulate differentiation of CD4$^+$ T cell subsets with their characteristic cytokine and functional profiles. These immune cell functions and cytokine production determine whether an activating or a tolerant response will develop.

PATHOGEN RECOGNITION

The innate immune response enables the host to respond to a wide array of pathogens. Foundational discoveries in the field of innate immunity suggested that the host detects and responds to these pathogens through receptors that recognize conserved sequences called pathogen-associated molecular patterns (PAMPs), which exist in pathogens and are not present in the host (Fig. 19-2).[15,16] Experiments in *Drosophila* (fruit flies) in 1996 identified pattern recognition receptors (PRR) that recognized PAMPs and supported the concept of innate receptors.[17] Subsequently, PRR were identified in humans,[18] and more recently, additional PRRs have been shown to recognize not only exogenous PAMPs, but also endogenous molecules released from damaged cells, referred to as damage-associated molecular patterns (DAMPs).[19,20] The major types of PRR are described below.

■ Toll-like Receptors

The mammalian Toll-like receptor (TLR) family received its name from the *Drosophila* Toll gene. Early studies that involved the genetic manipulation of Toll resulted in dramatic defects in innate immune responses.[17,21] Since this discovery, the TLRs are appreciated to be the prototypical PRR molecules.[18,22] TLRs are present on the cell surface, in cytoplasm, or in endosomes (intracellular vesicles). As a group, they are characterized by N-terminal leucine-rich repeats that recognize pathogens, a transmembrane region, and a cytoplasmic domain that is highly homologous to the interleukin 1 (IL-1) receptor and the IL-18 receptor.[23] To date, 10 TLRs have been identified in humans, with different TLRs recognizing distinct PAMPs.[24,25] In general terms, TLR recognition of PAMPs is based upon cellular compartmentalization. Recognition of viral RNA and DNA occurs in intracellular vesicles by TLR3, TLR7, TLR8, and TLR9. In addition,

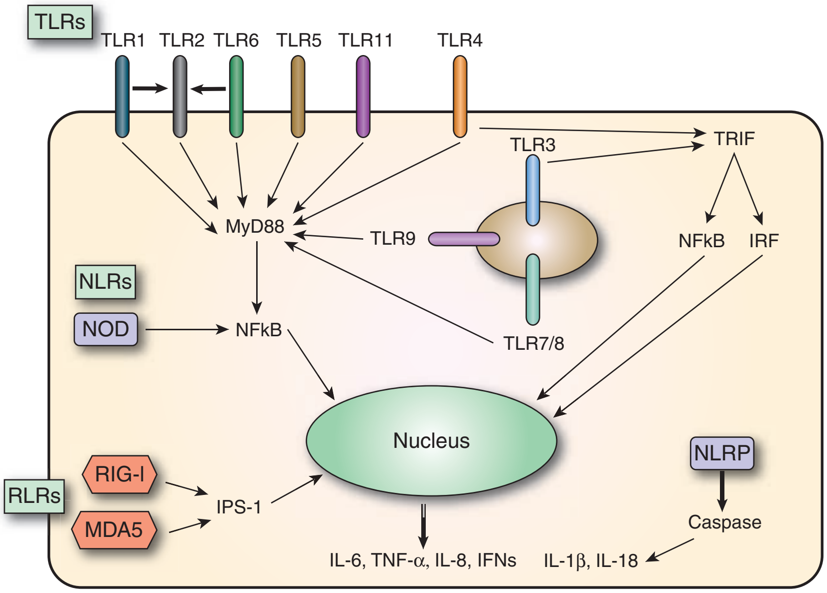

Figure 19-2 Pattern recognition receptors (PRRs). Classes of PRRs include Toll-like receptors (TLRs), retinoid acid–inducible gene-I-like receptors (RLRs), and nucleotide oligomerization domain–like receptors (NLRs). Not shown are C-type lectin receptors (CLRs). TLRs, RLRs (e.g., RIG-I, MDA5, other sensors), and NLRs (e.g., NOD1, NOD2, NLRP3) are innate immune sensors that recognize danger signals derived from pathogens (PAMPs), damaged cells (DAMPs), or associated nucleic acids at the cell surface, in endolysosomes, or in the cytoplasm. Signaling by these sensors promotes either the activation and nuclear translocation of transcription factors (IRFs, NFκB, and AP-1) that drive expression of cytokines (IFN-α/β, TNF, and pro-IL-1β), or the assembly of the caspase-1 inflammasome and subsequent maturation of IL-1β from pro-IL-1β. IFN, interferon; IL, interleukin; IRFs, interferon regulatory factors; MDA5, melanoma differentiation-associated gene-5; NFκB, nuclear factor κB; NLRP, NLR with a pyrin domain; NOD, nucleotide oligomerization domain; RIG-I, retinoid acid–inducible gene-I; TNF, tumor necrosis factor; TRIF, TIR-domain-containing adapter-inducing interferon-β.

TLR7 and TLR9 recognize RNA and DNA, respectively from bacteria, protozoa, and fungi. One unique characteristic of TLR4 is its localization on the cell surface and in endosomes,[26] and thus TLR4 recognizes viral proteins in addition to bacteria, protozoa, and fungi. TLR2, which is present on the cell surface, also recognizes viral proteins. TLR2 and the remaining TLRs, which are also surface receptors, recognize bacteria, parasite, fungi, and host proteins (e.g., DAMPs) (Table 19-1; Fig. 19-2).[25,27–29]

TABLE 19-1 Toll-like Receptors (TLRs)

TLRs	PAMP	Cellular Location
TLR1	Lipoprotein (bacteria)	Plasma membrane
TLR2	Lipoprotein (e.g., bacteria, viruses, parasites, host damage)	Plasma membrane
TLR3	dsRNA	Endosome
TLR4	LPS (bacteria, virus, host damage)	Plasma membrane
TLR5	Flagellin (bacteria)	Plasma membrane
TLR6	Lipoprotein (bacteria, virus)	Plasma membrane
TLR7 (human TLR8)	ssRNA (virus, bacteria, host damage)	Endosome
TLR9	CpG-DNA (virus, bacteria, protozoa, host damage)	Endosome
TLR10	Unknown	Endosome
TLR11	Profilin-like molecule (protozoa)	Plasma membrane

TLR Signaling Pathways

PAMP recognition by TLRs stimulates signaling pathways that ultimately lead to transcriptional activation and protein synthesis. The responses that are elicited can be cell type specific. They also utilize two distinct pathways based on which of two adaptor molecules they employ: (1) myeloid differentiation primary response gene 88 (MyD88) and (2) TIR-domain-containing adapter-inducing interferon β (TRIF).[30,31] With the exception of TLR3, MyD88 is activated for the downstream signaling of TLRs. MyD88 interacts with the IL-1R-associated kinase (IRAK)-4, and other IRAK family members, before they dissociate from MyD88 and interact with TNFR-associated factor 6 (TRAF6). IκB kinase (IKK)-β and MAP kinases are then activated, leading to another complex of IKK molecules that are degraded and release nuclear factor kappa light chain enhancer of activated B cells (NF-κB). NF-κB is a critical transcription factor for TLR-induced genes in inflammation. In addition, activation of the MAP kinase cascade leads to another transcription factor, AP-1, which is associated with activation of cytokines. TRIF-dependent signaling is responsible for TLR3 signaling and in endosomal TLR signaling.[32] TRIF interacts with TRAF3 and TRAF6 and leads to tumor necrosis factor (TNF) receptor (R)-associated death domain protein (TRADD), ultimately leading to activation of NF-κB. Downstream from TRIF is activation of interferon regulatory factors (IRFs) that induce the expression of interferons and interferon-stimulated genes.

RIG-I-Like Receptors

The RIG-I-like receptor (RLR) family presently includes three members: retinoic acid-inducible gene I (RIG-I), melanoma differentiation-associated factor 5 (MDA5), and laboratory of genetics and physiology 2 (LGP2) (Table 19-2).[33,34] RLRs are constitutively expressed by all nucleated cells, suggesting a central role in innate immune recognition and response to viral infection. A measure of their importance can be seen in the evolution of viral mechanisms to evade or suppress RLRs.[35–37] In the 1950s, interferons (IFNs) were discovered to be a critical antiviral innate immune response to viral infection produced by infected cells, and important in the recruitment and activation of lymphocytes (e.g., NK and CD8+ T cells) that recognize and kill virus-infected cells.[38] While the presence of an intracellular TLR receptor for dsRNA was hypothesized in 1969,[39] and subsequently identified, the discovery of RLRs introduced a

TABLE 19-2 RIG-I-like Receptors (RLRs)

RLRs	PAMP	Cellular Location
RIG-I	Short dsRNA	Cytoplasm
MDA5	Long dsRNA	Cytoplasm
LGP2	Unknown	Cytoplasm

second family of PRRs that are cytoplasmic sensors of viral nucleic acids that contribute to antiviral host defense by inducing interferon production. RIG-I was initially discovered in 1997 as a gene induced in acute promyelocytic leukemia cells after stimulation with retinoic acid.[40,41] Several years later, RIG-I was found to be activated by interferon.[42] Similarly, MDA5 was identified in 1999[43] and was later found to be induced by interferon.[44] LGP2 was suggested to function as a RIG-I inhibitor, exerting a regulatory role on antiviral innate immune responses.[45] Additional experiments suggest that LGP2 may modify viral RNA to assist RIG-I and MDA5 recognition of dsRNA.[24] Three genes encode RLRs in mice and humans, and all share a conserved helicase domain. Structurally, RIG-I and MDA5 are composed of two N-terminal caspase recruitment domains (CARDs), a central DEAD box helicase/ATPase domain, and a C-terminal regulatory domain.[46] LGP2 retains the helicase domain but lacks the CARD domain.[46] Their cytoplasmic location allows for recognition of dsRNA viruses and dsRNA intermediates generated during ssRNA viral replication. In addition, ssRNA from common respiratory viruses (e.g., influenza virus, respiratory syncytial virus, and human metapneumovirus) also may be detected by RLRs.[47] An important adaptation to protect the host from unwanted RLR-induced inflammation and injury is the ability of eukaryotic cells to avoid self-activation of RLRs by RNA in mitochondria, and RNA released into the cytosol through packaging that avoid RLR recognition.[35]

In the human lung, RLRs have been found to respond to a range of respiratory viruses, from rhinovirus to influenza virus. In response to viruses, activation of intracellular signaling ultimately leads to interferon production and the activation of interferon-stimulated genes.[47] RLR signaling is dependent on CARDs, which interact with the interferon-β-promoter stimulator 1 (IPS-1, also known as MAVS, CARDIF, or VISA). IPS-1 is localized on the mitochondrial membrane. IPS-1 activates TRAF3 and TRADD, which are adapter molecules for IFN-inducible gene expression.[24] In addition, NF-κB signaling may also be triggered by RLR-nucleic acid interactions.[48]

NOD-Like Receptors

Nucleotide-1 oligomerization domain (NOD)-like receptors (NLRs) are another family of cytoplasmic pathogen sensors that were discovered in the 1990s.[49] There are more than 20 NLR receptors in this family, which share structural similarity (Table 19-3).[50] Their molecular structure includes: (1) C-terminal leucine-rich repeats, which function to detect microbial patterns; (2) a central NOD domain that initiate self-oligomerization; and (3) the N-terminal effector domain.[51] Based upon this N-terminal structure, the NLRs are subsequently classified into four groups (NLRA, NLRB, NLRC, NLRP).[50] NLRs activate important signaling pathways mediated by NF-κB and MAP kinases and activate caspases. The result is activation of diverse signaling pathways that induce innate immune responses.[52,53]

NOD1 and NOD2 identify bacterial PAMPs by recognition of peptidoglycan from Gram-negative bacteria, Gram-positive bacteria, and mycobacteria.[50] The importance of NLRs was highlighted by the evidence that NOD polymorphisms are associated with increased severity of atopy, eczema, and asthma,[54] as well as other inflammatory diseases (e.g., Crohn's disease,[55] tuberculosis,[56] and lung cancer[57]). This suggests that a defect in bacterial clearance may influence the host microbiome and subsequent pathophysiology of disease. Distinct from NOD1 and NOD2 are a group of NLRs that activate caspases such as caspase-1. Caspase-1 is the prototypical caspase required for cleavage and processing of inflammatory cytokines (IL-1β, IL-18) into their active forms.[58] This signaling pathway is now commonly referred to as the "inflammasome," and has been shown to be critical for effective innate immune responses against a wide range of microbial pathogens, cancer, and inflammatory, metabolic, and autoimmune diseases.[59] Specific to the lung, the inflammasome is critical for responses to important pathogens such as influenza A virus,[60,61] *Streptococcus*,[62,63] *Pseudomonas aeruginosa*,[64] and *Mycobacterium tuberculosis*.[65] In addition, activation of the inflammasome has been suggested to contribute to the pathogenesis of asthma,[66] chronic obstructive pulmonary disease (COPD),[67] cystic fibrosis,[68] and pulmonary fibrosis.[69]

TABLE 19-3 NOD-like Receptors (NLRs)

NLRs	PAMP	Cellular Location
NOD1	Gram-negative > Gram-positive bacteria	Cytoplasm
NOD2	Gram-negative, Gram-positive bacteria, mycobacteria	Cytoplasm
NLRP 1–14	Viruses, bacteria, mycobacteria	Cytoplasm

C-type Lectin Receptors

The C-type lectin receptors (CLRs) were identified in the early 1900s and represent a diverse family that includes more than 1000 members.[70] The CLRs were initially characterized as Ca^{2+}-dependent (C-type) carbohydrate-binding (lectin) proteins[70] but, subsequently, some CLRs were found to not bind carbohydrate ligands or require Ca^{2+}-dependent signaling.[71] Currently, CLRs have been classified into 17 groups.[71] Structurally, CLRs are characterized by a carbohydrate-recognition domain (CRD) that is highly conserved.[70] Despite this conserved CRD structure, CLRs are involved in cell functions as diverse as adhesion, repair, endocytosis, and phagocytosis, as well as innate immune pathogen recognition.[72] CLRs recognize a wide variety of pathogens including viruses, bacteria, and fungi. Several of the canonical CLRs include dectins, mannose-binding lectin receptors, and surfactant protein. Dectin-1 and Dectin-2 are important PRRs for recognition of fungi.[73] Upon recognition of fungal PAMPs, intracellular signaling pathways involve activation of NF-κB and MAP kinases.[74]

Mannose-binding lectin (MBL) receptors function as PRRs by recognizing carbohydrate motifs on pathogens, which leads to complement activation.[23] MBLs recognize diverse pathogens that include Gram-positive and Gram-negative bacteria, yeast, parasites, mycobacteria, and viruses.[75] Surfactant protein (SP) was first identified as a critical phospholipid for decreasing alveolar surface tension to prevent atelectasis.[76] However, in the 1980s after the discovery of MBLs, sequencing of SP revealed significant structural similarities.[77] In accord with these similarities, SP-A and SP-D, secreted by alveolar epithelium, are considered collectins, and have been shown to function as agglutinins, opsonins, and inflammatory modulators[12] in response to viruses, bacteria, mycobacteria, and fungi.[78,79]

PATHOGEN-INDUCED INNATE IMMUNE RESPONSES

Inhaled pathogens may circumvent the mucociliary escalator on the airway epithelium, which, along with mucus and airway host defense proteins, form the first barrier against respiratory pathogens by virtue of their location and distribution. Antigen-presenting cells (APCs) such as dendritic cells (DCs) serve a critical role for pathogen recognition by extending projections into the airway between epithelial cells to sample the environment. On both airway epithelium and DCs, there is a wide repertoire of PRR that recognize pathogens.[80] Upon PAMP recognition, PRRs activate signaling pathways that lead to subsequent inflammatory responses. An important component of this inflammatory response is the production of chemokines to recruit immune cells (e.g., neutrophils, eosinophils, macrophages, and lymphocytes including natural killer [NK] and NKT cells) that are critical effectors for the initiation and resolution of inflammation. In addition to chemokine production, PRR activation stimulates the production of cytokines (e.g., TNF-α, IL-1β, IL-6, transforming growth factor β [TGF-β], IL-10) that activate effector cells and contribute to the regulation of innate and adaptive responses in the lung.[80] PRR activation influences the balance of oxidation and proteases present in the lung. Importantly, dysregulation of oxidation has been shown to contribute to the pathogenesis of COPD,[81] while defective antiprotease activity, best exemplified by α-1 antitrypsin deficiency, is a significant risk factor for the development of asthma, bronchiectasis, and emphysema.[82]

Human host defense (or antimicrobial) peptides and proteins such as cathelicidins, defensins, lysozyme, cystatin, PLUNCs, and others, are also produced by epithelial cells and recruited immune cells, in response to PRR activation (Fig. 19-1).[83] In humans, two significant groups of host defense peptides are the cathelicidins[84] and defensins.[83] These small cationic peptides have antimicrobial activity against Gram-negative and Gram-positive bacteria, fungi, parasites, and viruses.[85] Epithelial cells and immune cells (e.g., neutrophils) produce both cathelicidins and defensins, and in addition to their antimicrobial properties, these peptides participate in immune modulation, influencing adaptive immune responses and wound repair.[84,85] Therefore, host defense peptides and proteins are an excellent example of an innate immune response, initiated by PRR recognition of pathogens or PAMPs, which results in a protective response, regulates inflammation, and bridges innate and adaptive immunity.

CELLULAR RESPONSES IN THE LUNG

When pathogens bypass the initial lung mucosal barriers, the host's immune system responds with a coordinated defense program that involves specialized cells that target the threat, neutralize it, and dispose of remnants that may cause tissue injury. Macrophages are phagocytes that engulf pathogens (viable and nonviable microorganisms), as well as apoptotic and necrotic cells that have undergone physiologic and pathologic cell death.[86] Ultimately, the lung must perform these tasks in a selective manner in order to avoid unnecessary inflammation that can cause continued tissue destruction. The innate immune system, as described above, is made up of a humoral arm (lactoferrins, lysozyme, secretory IgA, surfactant proteins, mannose-binding lectins, and defensins) as well as a cellular arm (alveolar macrophages, dendritic cells, neutrophils, ILCs, etc.) that express numerous PRRs and or phagocytic receptors important for their diverse functions. Details of these critical components are provided below.

■ Macrophages

Macrophages are large mononuclear phagocytic cells. They play an important role in host defense based on their ability to phagocytize inhaled moieties, maintain tissue homeostasis, and function as antigen-presenting cells (APCs), which are important in adaptive, humoral, and cell-mediated responses.[87] Macrophage precursors arise from committed hematopoietic stem cells in the bone marrow and are released into the circulation as monocytes before they differentiate into macrophages and dendritic cells as they migrate into the lung. Tissue-resident macrophages form a specialized population based on their local anatomic location. Once called dust cells for their ability to engulf particulates, alveolar macrophages (AMs), named for their presence in the pulmonary alveolus, frequently contain granules of various exogenous materials.[88] One example is particulate matter such as the black carbonaceous granules seen in lungs from smokers and long-term city dwellers. Routine bronchoalveolar lavage will identify these resident airway and alveolar macrophages. However, pulmonary interstitial macrophages from lung tissue can only be collected by tissue dispersion techniques.[89] Of note, the antigen-presenting properties of AMs are inferior compared to those of DCs.[90]

AMs secrete numerous products (e.g., cytokines, chemokines, peptides) and directly interact with other cells and molecules through surface receptors.[91] AMs have multiple functions that include phagocytosis of cells undergoing apoptosis and necrosis, clearance of ingested pathogens or particulates, routine clearance of surfactant, and suppressing inappropriate inflammation and immune responses to harmless inhaled antigens. Macrophages ingest and phagocytose microbial or environmental particulate matter, which is then enclosed in intracellular vesicular phagosomes that undergo fusion with primary or secondary lysosomes to form phagolysosomes. In these AM vacuoles, intracellular killing takes place through mechanisms that include host defense proteins, degradative enzymes, oxidation, reactive oxygen intermediate generation, and "respiratory burst" known as nicotinamide adenine dinucleotide phosphate (NADPH) oxidase degradation. Macrophages facilitate innate recognition functions through expression of diverse PRRs (e.g., TLRs, NLRs, CLRs) to assist host defense in combating invading pathogens. The recognition and clearance of invading pathogens can also occur via opsonin-mediated phagocytosis through the Fcγ receptors. These receptors allow macrophages to be selective in their response to phagocytosed antigen, minimize damaging effects on normal cells, and limit responses to harmless moieties encountered in the airway.

While AMs have greater respiratory burst capacity than other phagocytes,[92] certain organisms have evolved to evade AMs to improve their growth and survival. For example, mycobacteria prevent the fusion of phagosomes and lysosomes, escaping lysosomal hydrolases, and thus becoming resistant to the effects of macrophages. Some inhaled pathogens such as *Mycobacterium tuberculosis* and environmental particulates such as silica are resistant to AM degradation and remain in intracellular lysosomal vacuoles for the duration of the macrophage lifespan. Macrophages also produce inflammatory cytokines and chemokines to recruit other specialized cells to assist in PRR recognition and host defense, in turn, helping to shape the adaptive immune response that follows.

Lung resident AMs continuously sample inhaled particles and pathogens because of their unique position in the alveolar lumen (Fig. 19-1). Because of this location and the potential to cause harm to surrounding delicate and sensitive lung structures (e.g., alveolar epithelium), alveolar macrophages remain in a quiescent state to limit unnecessary inflammation and injury to nearby structural type I and surfactant-producing type II pneumocytes when they encounter harmless antigens. Compared to AMs, DCs are less capable phagocytes with lower levels of expression of phagocytic receptors such as CD11b. In contrast, AMs generate a less robust proinflammatory cytokine response and can suppress adaptive immunity through their effects on neighboring DCs and T cells. It has been shown that depletion of AMs can lead to exuberant lung inflammation in response to otherwise innocuous antigens.[93] These AMs, when co-cultured with DCs in vitro, can suppress T cell function through the release of factors such as nitric oxide, IL-10, TGF-β, and various prostaglandins.[94] Subpopulations of lung macrophages have been identified in lung and disease using cell markers by flow cytometry and RNA sequencing that are likely to have context-specific roles according to anatomical distribution (airway, interstitial, alveolar), maturity, and immune activation profiles.[95–97] These phenotypic approaches can identify interstitial macrophages (IMs) in well-characterized animal models. There is evidence that AMs and IMs are distinct cell populations with differing functions and that each population contributes to different inflammatory and immune responses in the lung.[98] Because IMs are in direct contact with the lung matrix and other pulmonary connective tissue components, the release of mediators or enzymes by these cells may have greater biologic and/or pathologic effects than those released by macrophages in the alveolar compartment.

Dendritic Cells (DC)

In addition to nonspecific mechanisms of the innate immune system, a complex network of DCs is responsible for mobilizing the adaptive immune response, especially against invading pathogens and unwanted antigens.[90,99] DCs are also important phagocytic cells and, in general, are better APCs than macrophages.[90,100] DCs are critical at bridging innate and adaptive immunity because of their extensive interdigitating extensions that reach between cells to provide a tight surveillance network within intraepithelial and subepithelial structures of the respiratory tract. Through this network, DCs continuously sample the lung microenvironment. Because of their distribution, they are ideally positioned to participate in determining whether an inhaled moiety results in pulmonary immunity or tolerance. DCs express MHC and accessory molecules such as CD80, CD86, and CD40, making them excellent professional APCs to incoming naïve T cells.[101,102] They also express a number of innate immune receptors including TLRs, NLRs, and CLRs for the recognition of various patterned motifs from inhaled antigen and pathogens. Lung DCs also express prostaglandin receptors that affect migratory behavior and cell maturation. They also express receptors that detect DAMP proteins such as uric acid, ATP, and high-mobility group box (HMGB)-1. Their ability to sense, take up, and process incoming molecules, and to migrate to nearby draining lymph nodes for antigen presentation, allows DCs to bridge innate and adaptive immunity in the lung.[100] In the lymph nodes, DCs present MHC peptide antigen complexes to T cell receptors on naïve T cells and, in the appropriate context of co-stimulatory molecules on their cell surface and cytokines in the local microenvironment, naïve T cells are activated and proliferate. In the absence of appropriate co-stimulation or cytokines, DC and T cell interaction can lead to tolerance to an antigen, a mechanism that likely helps to avoid harmful immunologic response to harmless inhaled antigens.

DCs have been divided into several subsets based on their cell surface protein expression, origin, location, and specialized function.[103,104] In mice, three major subsets of DCs have been described: resident conventional DCs (cDCs), plasmacytoid DCs (pDCs), and inflammatory DCs. The resident cDCs express CD11c markers and have been divided into those that express CD11b, and those that are CD11b-negative. At baseline, cDCs expressing MHC and CD11c line the conducting airways and can extend their dendrites into the airway lumen between tight junctions. In murine models, these cDCs can also express langerin (a CLR) and the mucosal integrin CD103. cDCs have good antigen-presentation function. A migratory cDC subset migrates to nearby lymph nodes after capturing inhaled antigen in the airway lumen, while lymphoid tissue–resident cDCs reside in the lymph nodes and spleen and respond to antigen delivered via the draining lymphatics. pDCs are characterized by the expression of the surface marker Siglec-H (a bone marrow stromal antigen 1) and abundance of endosomal innate receptors TLR7 and TLR9, which make pDCs particularly important antiviral effectors because of their type I interferon production in response to viruses and bacterial DNA. Residing in the alveolar space are alveolar DCs, which classically express MHCII and CD11c, and can have CD103 subsets. These alveolar DCs resemble human Langerhans cells.[105]

In response to innate and inflammatory stimuli, DCs increase their numbers with rapid recruitment. These DCs have similar abilities to undergo antigen processing, to migrate to draining lymph nodes, and to modulate naïve T cells for either activation or tolerance. The inflammatory cDCs are normally not present in the lung. However, in the setting of inflammation and or infection, circulating monocyte-derived CD11b$^+$ DCs upregulate CD11c, retain Ly6C, and can rapidly be recruited to the lung as inflammatory cDCs to respond to the stimulus. Comparable subsets of DCs in human lungs have been described such as myeloid types of DC that express both blood dendritic cell antigen (BDCA) 1 or BDCA3 and HLA-DR and plasmacytoid DCs that express BDCA2 and CD123.[104,106–109]

Overall, DCs rely on neighboring structural cells, such as the airway epithelial cells, to influence their type of antigen-specific immune response.[110] This epithelial–DC interaction in the lung plays an important role in immune homeostasis as well as the initiation and transition of innate immunity towards antigen-specific adaptive immunity. Some have proposed that extracellular matrix surrounding epithelial cells and DCs contains chemokines that allow for the activation properties of DCs.[111] Antigen presentation by APCs such as macrophages and DCs is a required priming event for T cell activation to occur.

Neutrophils

Neutrophils are derived from the bone marrow and require granulocyte colony-stimulating factor (G-CSF) for their proliferation and differentiation into their mature form. In times of stress or infection, neutrophils are mobilized from the bone marrow into the blood stream and eventually to sites of inflammation such as the lungs.[112] During this process, neutrophils become activated, generate free radicals, release granule contents such as neutrophil elastases and proteases, and participate in phagocytosis and degradation of invading microbes.[113] Neutrophils are one of the first phagocytes recruited to sites of acute lung disease, but they have a limited life span after their release from the bone marrow and within hours they may be cleared along with the resolution of inflammation or disease process. Lungs are a reservoir of neutrophils under steady state. With infection or injury, the neutrophils are promptly activated and recruited to the alveolar compartment as well as the airways.

In chronic lung diseases, neutrophils can be persistently recruited to the lung. Recruited tissue neutrophils are thought to live substantially longer, up to several days, compared with circulating neutrophils.[114] These neutrophils, which are modulated by the local microenvironment, are important for antipathogen responses, but they can cause significant lung tissue damage when they accumulate over longer time periods and release granule contents in an uncontrolled manner.[115,116] Neutrophils can respond to a number of particulate and soluble stimuli. They also have the ability to be primed prior to exposure to stimuli.[117] For example, neutrophils can be primed, or preactivated, by stimuli such as IL-8, granulocyte macrophage colony-stimulating factor, platelet activating factor, and reactive oxygen species. This process helps prepare neutrophils for subsequent contact with pathogens by extending their life span, upregulating cell surface integrins (such as CD11b), optimizing NADPH oxidase assembly, and prolonging neutrophil functional longevity.[118–120]

Neutrophils play an important role in innate immune responses to infection, as these phagocytic cells also possess an impressive array of microbicidal weapons against invading pathogens that include toxic oxygen radical species and proteolytic enzymes. Local infiltration and tissue accumulation of neutrophils are mediated by chemokines secreted by inflamed tissues. At sites of inflammation, mediators such as IL-1 or TNF-α induce or augment the expression of adhesion molecules on endothelial cells and circulating granulocytes. Intravascular circulating neutrophils undergo significant transcriptomic and functional adaptations as they roll along, anchor on the endothelium, and transmigrate to the lung interstitium and subsequently the alveolar space.[120] Ultimately, inflammation will cease, and with successful containment of pathogens, resolution of inflammation often follows. This resolution of inflammation requires wound healing and restoration of the lung's normal structure and function.[121–123] Mechanisms for resolution of tissue inflammation are not as well established, but include substances such as sphingosine-1-phosphate for restoring endothelial barrier and vascular permeability after endotoxin injury, or natural mediators derived from essential fatty acids such as ω-3 fatty acids with their anti-inflammatory and pro-resolving properties.[124] Cytokines such as IL-10, TGF-β, and IL-1 receptor antagonist also have been implicated as important mediators of inflammatory resolution. An inability to resolve inflammation can lead to chronic inflammation in the lung as seen in a number of pulmonary diseases.

■ Innate Lymphoid Cells

Recently a group of innate immune cells, known as innate lymphoid cells (ILCs), have been recognized to lack specific antigen receptors but can produce an array of effector cytokines.[125,126] These ILCs have morphologic characteristics of lymphoid cells and can respond to a variety of signals and play an important role in immunity against microorganisms, tissue homeostasis, and damaged tissue repair. ILCs have been identified and categorized into the following subsets: ILC1s include IL-15-dependent natural killer cells; ILC2s are characterized by their production of T helper 2 cytokines (IL-5 and IL-13); and ILC3s express the nuclear hormone receptor retinoic acid receptor related receptor (Ror)γt and produce cytokines such as IL-17 and IL-22.[125,127] These ILCs are important in innate immunity and very likely will be discovered to contribute to the development of effective adaptive responses. The function and plasticity of these ILCs have an essential role in tissue homeostasis and disease.[128]

ADAPTIVE IMMUNE RESPONSES IN THE LUNG

An essential prerequisite for a successful host immune response is the ability to discriminate between self and non-self.[129,130] Adaptive immune responses, which can also be described as acquired, refer to antigen-specific immunity that often takes several days to mature and to develop a targeted response to a specific antigen.[131] Ultimately, the goal of this adaptive response is to react with, and subsequently remove, a specific antigen. This type of immunity is one that develops throughout life and is the premise behind vaccination for pulmonary infections caused by pathogens such as influenza virus and *Streptococcus pneumoniae*.[132,133] Classically from an immunologic standpoint, an antigen is defined to be a substance that reacts to antibody molecules or antigen receptors on lymphocytes. For example, B cells recognize antigen through specific B cell receptors (BCRs) (and in this case immunoglobulin), while T cells recognize antigen through specific T cell receptors (TCRs). This recognition is through specific epitopes on the antigen being recognized. For T cells to recognize antigenic epitopes through TCRs, cells recognize peptide epitopes from antigen only when presented by antigen-presenting cells (e.g., dendritic cells, macrophages) in the context of appropriate MHC molecules.

Adaptive immune responses are often divided into two major branches: humoral immunity and cell-mediated immune responses. Humoral immune responses rely on the production of antibodies in response to encountered antigens and are mediated by B lymphocytes. Cell-mediated immune responses involve various immune cells such as T lymphocytes, cytotoxic T lymphocytes, activated macrophages, and/or activated NK cells. Activated macrophages and NK cells destroy intracellular pathogens and stimulate nearby structural cells to secrete cytokines that influence other cells of the immune system. Cytotoxic T lymphocytes (often CD8$^+$ cells) can destroy host cells that display foreign antigens on the cell surface, such as cells infected with viruses or intracellular bacteria, or cancer cells that display tumor antigens.

The adaptive arm of the immune response relies on specific recognition of antigens by B and T lymphocytes. These cells are highly equipped to be specific because of their receptors; thus the immune system can recognize a large number of antigens. The functionality of adaptive immunity is based on specific gene rearrangement that results in the generation of more than 10^{11} different species of antigen receptors on the cell surface of T and B cells.[134–136] In addition to adaptive immune responses, this defense system targets pathogens that have evolved mechanisms to evade or to counteract innate immune responses. Therefore, the adaptive immune response builds upon, is shaped by, and itself shapes innate immune responses resulting in a strong interplay between the innate and adaptive arms of our immune system.[137]

Adaptive immunity helps protect the lungs against not only a range of pathogens, but also environmental inhalants, such as cigarette smoke and dusts, as well as allergens. The adaptive immune response is quite versatile, relies on exquisite specificity, and takes advantage of robust memory. This is especially evident when it comes to countering airborne antigens. It is estimated that our human body can recognize 10^7 or more different epitopes and can make up to 10^9 different antibodies, each with different specificity. These epitopes are antigenic determinants that are part of the antigen that is recognized by the antibodies generated by B cells, or by receptors on B and T cells. To recognize the immense number of different epitopes, the human body produces 10^7 or more distinct clones of both B and T lymphocytes, each with their unique BCR or TCR, respectively.[114,138] Among the large variety of BCRs and TCRs, there is bound to be at least one that has the epitope-binding site capable to recognize any antigen the immune system eventually encounters. Thus, the body can recognize any conceivable antigen it may eventually encounter, allowing for an adaptive immune response. However, only a few B and/or T cells can recognize any one epitope, and these cells require an appropriate stimulus to allow for rapid proliferation. This process typically takes several days to occur. During this time, to achieve an effective and mature adaptive immunity, the invading pathogen could cause considerable damage, which is why innate immune responses are important at the early stage of infection, unless the host has already encountered the antigen before and has developed a specific adaptive immune response against the antigen. In this situation, during a repeated encounter with an antigen, adaptive immunity, which already has an established memory response, will take a shorter period to mobilize the adaptive effector cells to counter the invading antigen.

Most T cells express TCR with αβ variable chains, which permits them to recognize the short peptide epitope of an antigen. Typically, precursor αβ T cells are recruited out of the bone marrow to the thymus. In the thymus, they undergo the process of positive and then negative selection to assure that the resultant T cells appropriately respond to peptide in the context of self-MHC, but not strong enough to cause potentially damaging autoreactivity. It is also during this thymic maturation that the T cells acquire the expression of either CD4 (allowing it to recognize peptide in the context of class II MHC) or CD8 (allowing it to recognize peptide in the context of class I MHC). Of note, only a small fraction, <5% of all precursor T cells, complete this process of thymic education and maturation. These cells become naïve T cells that circulate throughout the host to encounter their specific antigen for antigenic stimulation. Thymus-independent T cells do exist and have been identified in the gut but are less well understood in the lung. However, these cells are limited in their diversity and recirculatory capacity and cannot compensate for the lack of thymus-dependent T cells.[139]

T cell development occurs in the thymus where bone marrow–derived premature naïve T cell precursors congregate.[140–142] These T cells start off as double-negative cells (CD4 and CD8 negative). Upon acquisition of successful rearrangement of α and β TCRs, as well as expression of both CD4 and CD8 (making them double-positive cells), these developing T cells undergo positive and negative selection. Since TCRs recognize antigen only in the context of MHC molecules, T cells must be "educated" to first recognize host MHC. During positive selection, double-positive T cells that can recognize self-MHC are selected for proliferation, and those T cells that do not recognize self-MHC are removed through apoptotic cell death pathways. Positive selection also assures that the appropriate TCR selection will associate with the appropriate CD4 or CD8. For example, TCRs specific for MHC II need to retain CD4 and lose CD8. If the reverse occurs, they will die via apoptosis. The same is true for T cells that are specific for MHC I, which need to retain CD8 and lose CD4. Single-positive thymocytes (either $CD4^+$ or $CD8^+$) undergo negative selection to remove potential autoreactive cells. Those T cells that have high affinity for binding self-proteins presented on self-MHCs are induced to upregulate genes that drive apoptosis, eliminating them in the thymus. However, if they escape this elimination process, they may subsequently react against self-antigens, which can result in autoimmunity.[143] Positive selection identifies T cells that react with self-MHC and self-antigen.[144] Negative selection eliminates those that react strongly with self-MHC and self-antigen. Therefore, a successful T cell differentiation selects for MHC restricted TCRs with low affinity for self-antigens.

The underlying premise of the adaptive immune response that allows the system to recognize an unlimited scope of antigens that the host ultimately can encounter is the generation of antigen receptor diversity through gene translocation and recombination processes.[145] This process helps shape each receptor [either T cell receptors on T cells or B cell receptors, or the immunoglobulins (Ig) on B cells]. The TCRs have α and β chains, where there are many different V and J genes that can make up the TCR α chain, and many V, D, and J genes that can recombine to form the variable TCR β chain. Similarly, BCR undergoes similar gene recombination, including junctional diversity and somatic hypermutation that help generate a wide scope of BCR diversity. In the end, each T or B cell will exhibit a unique receptor capable of recognizing its unique antigen. For B cells, the BCR (Ig) recognizes specific epitopes of the antigen. For T cells, $CD8^+$ or $CD4^+$ T cells will express a unique cognate complementary-shaped peptide that is bound to either MHC class I or MHC class II molecules, respectively.

GENERATION OF AN IMMUNE RESPONSE

Upon cognate recognition of T cells with antigen/peptide presented on MHC molecules on antigen-presenting cells, the activated lymphocytes rapidly proliferate to produce large clonal populations (Fig. 19-3). Circulating memory T cells have the capacity to persist in the host for a long time and become mobilized and reactivated during a repeat encounter with the same antigen. This subsequent exposure of antigen leads to a more rapid and persistent production of effector cells in a process called clonal expansion. This allows the limited T cell number, with the appropriate antigen recognition and specificity, to expand and proliferate when necessary. During adaptive immunity, pathogens encountered in the mucosal surfaces, the lung, and the airway mucosa are transported to draining lymphoid organs where antigen is recognized by naïve B and T lymphocytes, which leads to cell activation. These activated B and T cells proliferate and differentiate into effector cells.

Naïve T cells undergo development and maturation in the thymus and circulate out of the thymus to mucosal surfaces and lymph nodes to encounter antigens.[146,147] APCs, such as macrophages and DCs from the innate immune system, present endocytosed foreign antigen to naïve T cells at local draining lymph nodes. APCs present MHC class II associated peptides processed from pathogens to CD4 T cells that express specific TCR against the particular antigen peptide/MHC complex. The TCR-CD3 complex binds to the antigen peptide MHC complex on APC, and this interaction triggers intracellular signaling pathways that provide the first signal, "signal 1," of T cell activation. Upon a subsequent encounter with the same antigen, memory T cells are reactivated using these same TCR pathways.[146] A second signal, "signal 2," is required to ensure that naïve T cells are responding to foreign antigen. This process involves binding

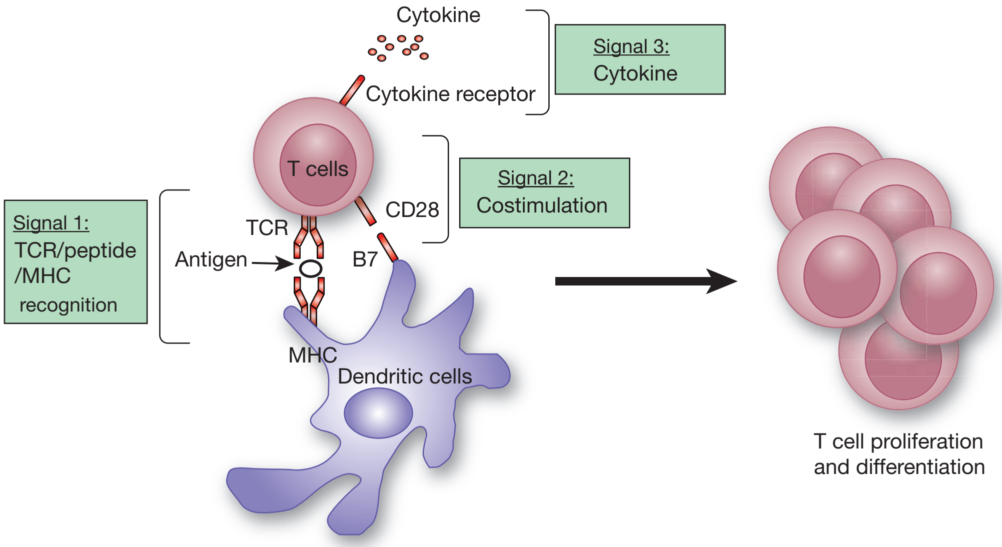

Figure 19-3 Generation of an immune response. Dendritic cells (DCs) and other antigen-presenting cells (such as macrophages) link the innate and adaptive immune response. DCs from the innate immune system present their antigen to naïve T cells at local draining lymph nodes; in the case of the respiratory tract, these are the mediastinal draining lymph nodes. T cell receptor (TCR) ligation to MHC molecules associated with peptides processed from antigen (e.g., pathogen, allergen, toxin) by DCs provides "signal 1." The binding of co-stimulatory molecule CD28 on lymphocyte to CD80 and CD86 expressed by dendritic cells ("signal 2") leads to T cell activation and cell lineage differentiation. "Signal 3" is provided by the polarizing cytokine signals from nearby innate immune cells and local tissue environment. Depending on the type of antigen that is presented and the nature of cytokines in the microenvironment, innate DC cells direct the development of various T helper lymphocyte lineages that play crucial roles in the adaptive immune system.

of CD28 on lymphocytes to co-stimulatory molecules CD80 and CD86 that are expressed only by activated APCs. “Signal 2” leads to T cell lineage differentiation. Without “signal 2,” during the initial antigen exposure, T cells become anergic and are unable to respond to subsequent antigen encounters, a process that avoids or minimizes production of autoreactive cells, and thus autoimmunity against self-antigens. Once T cells are activated by the two signals, only “signal 1” is required for subsequent future activation; an example of this is seen with memory T cells providing a faster immune response. After two-signal activation, T helper cells proliferate and produce multiple cytokines, and this includes IL-2 production for autocrine activation by upregulation of the IL-2 receptor, CD25. “Signal 3” involves polarizing cytokine signaling from innate immune cells that allow for the development of specific types of immune responses.[148] Inflammatory cytokines such as IL-12 can act directly on naïve T cells to provide a third signal, along with antigen and IL-2, to optimally activate differentiation and clonal expansion. CD4$^+$ T helper cells play an important role in mediating various types of immune responses through their cytokine release. There are also other CD4-expressing T cells that are not T helper cells; these include some cytotoxic T cells, NKT cells, and regulatory T cells.

■ Activation of Naïve Helper T Cells

CD4$^+$ T cells play an important role in adaptive immune responses. Proliferating helper T cells that develop into effector T cells can differentiate into one of several lineages (Fig. 19-4).[149] Depending

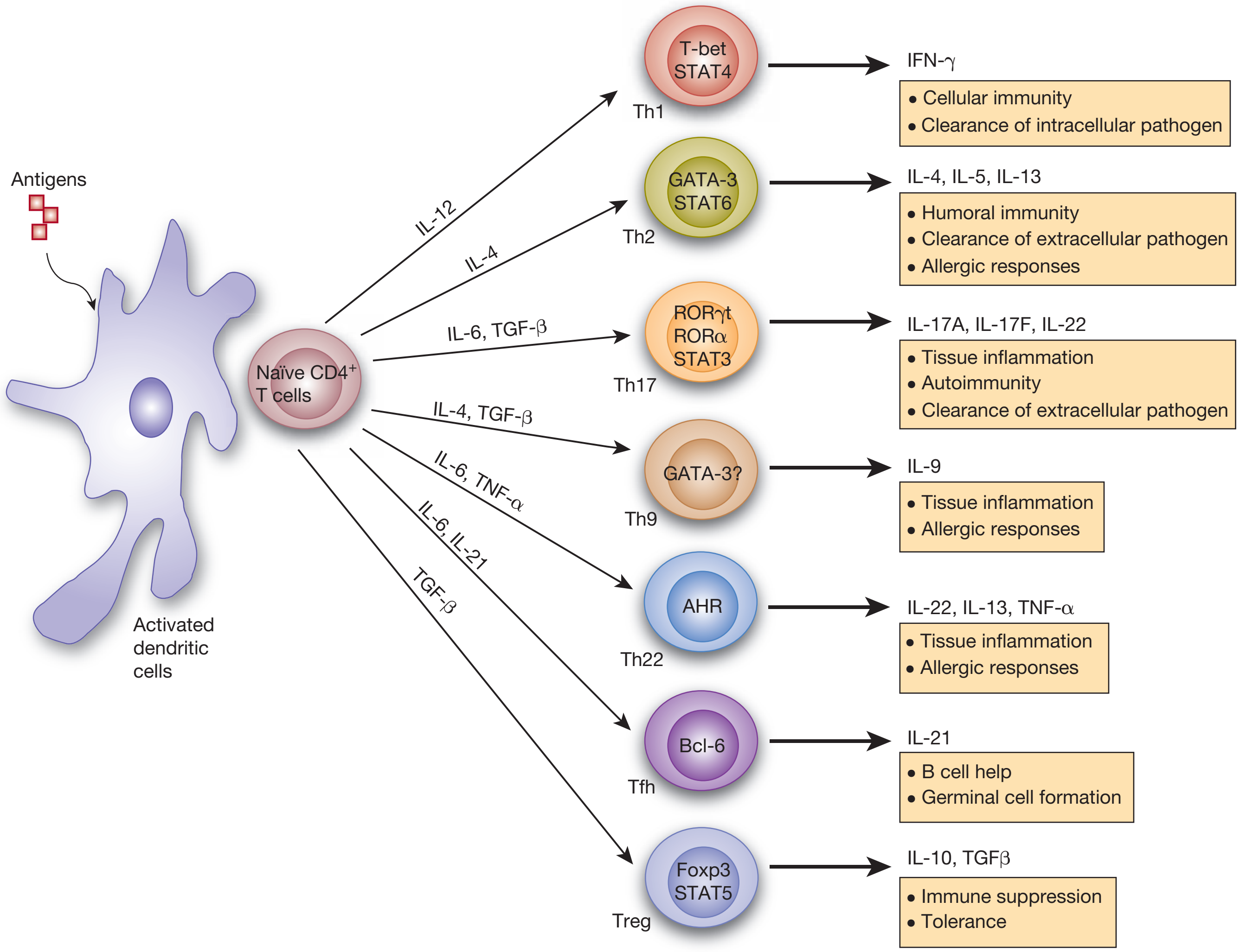
Antigens
Activated
dendritic
cells
Naïve CD4$^+$
T cells
IL-12
IL-4
IL-6, TGF-β
IL-4, TGF-β
IL-6, TNF-α
IL-6, IL-21
TGF-β
T-bet
STAT4
Th1
IFN-γ
• Cellular immunity
• Clearance of intracellular pathogen
GATA-3
STAT6
Th2
IL-4, IL-5, IL-13
• Humoral immunity
• Clearance of extracellular pathogen
• Allergic responses
RORγt
RORα
STAT3
Th17
IL-17A, IL-17F, IL-22
• Tissue inflammation
• Autoimmunity
• Clearance of extracellular pathogen
GATA-3?
Th9
IL-9
• Tissue inflammation
• Allergic responses
AHR
Th22
IL-22, IL-13, TNF-α
• Tissue inflammation
• Allergic responses
Bcl-6
Tfh
IL-21
• B cell help
• Germinal cell formation
Foxp3
STAT5
Treg
IL-10, TGFβ
• Immune suppression
• Tolerance

Figure 19-4 T cell differentiation. Naïve CD4$^+$ T cells differentiate into one of several T helper (Th) cell lineage based on signals from innate immune cells induced by antigenic and inflammatory stimuli as presented by activated DCs. The resultant products of differentiated T cells subsequently help tailor the immune response to various encountered antigen scenarios. T helper cell differentiation is classically regarded as a dichotomy between two main cell types, Th1 and Th2. Th1 cells produce IFN-γ as the signature cytokine and are predominantly involved in cell-mediated immunity against intracellular pathogens. In contrast, Th2 cells do not produce IFN-γ and instead produce IL-4, IL-5, and IL-13. Th2 cells are effective activators of B cell proliferation and antibody production, mediating humoral immunity essential for the eradication of extracellular pathogens as well as mediating allergic-type inflammation. Th17 cells have been described as a distinct T helper subset characterized by the production of IL-17A, IL-17F, and IL-22, contributing to host defense against extracellular pathogens particularly on mucosal surfaces, as well as in the pathogenesis of autoimmune diseases. Recently, more T helper cell subsets have been described, such as Th9 and Th22 cells that participate in allergic-type immune responses. Other stimuli cause CD4$^+$ T cells to become regulatory T (Treg) cells that help dampen immune responses. Other stimuli allow CD4$^+$ T cells to reside in lymph nodes, differentiate into follicular helper T (Tfh) cells, and provide help to B cells. The various T helper subsets require activation of specific master regulator transcription factors such as T-bet, Gata3, Rorγt, Bcl-6, and Foxp3, as well as various STAT molecules for their differentiation as indicated in the diagram. Bcl-6, B cell lymphoma-6; Foxp3, forkhead box p3; ROR, retinoid-related orphan receptor; AHR, aryl hydrocarbon receptor; STAT, signal transducer and activation of transcription.

on the type of antigen that is presented, the strength of the TCR signal, and the nature of cytokines in the microenvironment, innate antigen-presenting cells (typically DCs) direct the development of various T helper lymphocyte lineages. The differentiation of each CD4$^+$ T cell subset is associated with the expression of specific transcription factors that lead to production of an array of cytokines that help orchestrate a specific host response. CD4$^+$ T helper cells, based on their cytokine production, help dictate this type of response. The most studied and established T helper subset is the dichotomy between type 1 and type 2 responses, often called T helper 1 (Th1) and T helper 2 (Th2) responses.

Th1 cells promote cell-mediated immune responses and are required for host defense against viral and intracellular bacterial pathogens. Th1 responses can be characterized by the secretion of IFN-γ, IL-12, IL-10, and TNF-α/β, and stimulation of classically activating macrophages to tackle intracellular pathogens.[150] These cytokines promote macrophage activation, nitric oxide production, and cytotoxic T lymphocyte proliferation, leading to phagocytosis and destruction of microbial pathogens. Th1 responses in the lung are important because alveolar macrophages encounter antigens to activate these specific effector responses. IL-27 signaling in naive CD4$^+$ T cells induce STAT1-dependent expression of the Th1-specific transcription factor, T-bet, which promotes expression of IFN-γ and IL-12 receptors. Subsequent activation stimulates STAT4-dependent IFN-γ production and Th1 differentiation. While Th1 cells are critical for the clearance of intracellular pathogens, exaggerated Th1 responses can result in lung pathology (e.g., autoimmune disease, interstitial lung disease, COPD).

Th2 responses are characterized by production of IL-4, IL-5, IL-9, IL-13, and IL-25, and these cytokines favor antibody production and class switching to IgE and IgG. Th2 cells are required for humoral immunity and play an important role in coordinating immune responses to extracellular pathogens.[151] Th2 differentiation occurs in the presence of IL-4 and either IL-2, IL-7, or thymic stromal lymphopoietin (TSLP). IL-4 stimulates naive CD4$^+$ T cells to induce STAT6-dependent expression of GATA-3, the transcriptional regulator of Th2 cells, which promotes IL-5 and IL-13 expression, and stimulates the expansion of Th2 cells, while suppressing the differentiation of other T cell subtypes. In addition to IL-4-induced activation of GATA-3, IL-2, IL-7, or TSLP is required during Th2 differentiation to activate STAT5, which cooperates with GATA-3 to promote T cell production of IL-4. IL-4 regulates clonal expansion of Th2 cells and, along with IL-13, promotes B cell production of IgE and alternative macrophage activation. Th2 cells also produce IL-5 to stimulate eosinophil activation and survival, or IL-9 to promote mast cell activation. Th2 responses are typically important host immune responses to extracellular pathogens such as parasites or helminths. However, excessive Th2 signaling has been implicated in the development of chronic allergic inflammation and asthma.

T helper 17 (Th17) cells are involved in the immune response against specific fungi and extracellular bacteria.[152] Th17 cells develop from naive CD4$^+$ T cells in the presence of TGF-β and IL-6, cytokines that induce STAT3-dependent expression of IL-21 and the transcription factor RORγt. IL-21 and IL-23 help establish, regulate, and develop (via clonal expansion) Th17 cells. RORγt-induced gene expression leads to the secretion of IL-17A, IL-17F, and IL-22. Cytokines secreted by Th17 cells stimulate chemokine secretion by resident cells, leading to the recruitment of neutrophils and macrophages to sites of inflammation. These cells produce additional cytokines and proteases that further augment immune responses. For human Th17 differentiation, Th17 polarization requires IL-1β, IL-6, IL-21, and IL-23, and is less dependent upon TGF-β. While Th17 cells play a central role in eliminating harmful microbes, persistent secretion of Th17 cytokines can promote chronic inflammation and has been implicated in lung diseases such as COPD, sarcoidosis, and granulomatous diseases. The role of cytokine polarization in lung diseases has been studied in transgenic animal modeling systems where specific cytokines are overexpressed, or cytokine receptors or transcriptional factors such as GATA-3 and T-bet are modified. These studies have helped to elucidate the effector function of individual cytokines and their pathophysiologic consequences in the lung.[153]

T helper 9 (Th9) cells secrete high levels of IL-9, CCL17, CCL22, and, in mouse, IL-10. Th9 cell differentiation requires the presence of TGF-β and IL-4, which induce transcription factors PU.1/Spi-1 and interferon regulatory factor (IRF) 4 that regulate IL-9.[154] Cytokines such as IL-1β, IL-6, IL-21, and type I interferons all enhance Th9 differentiation, and IL-2 and IL-25 promote IL-9 secretion. Different from Th2 cells, Th9 cells do not express IL-4, IL-5, or IL-13. Th9 cells are important for host defense against parasitic and helminthic infections, but they are also associated with the development of chronic allergic inflammation, airway remodeling, and autoimmune diseases.[154,155] T helper 22 (Th22) cells primarily secrete IL-22, IL-13, and TNF-α. Similar to Th17 cells, Th22 cells express IL-22, but in contrast, they express several fibroblast growth factors (FGFs) and do not express IL-17, IL-4 (Th2 marker), or IFN-γ (Th1 marker).[156] Th22 cells differentiate in the presence of IL-6 and TNF-α, and their differentiation is inhibited by TGF-β.[157] Th22 cells can be regulated by the aryl hydrocarbon receptor (AHR) transcription factor. IL-22 secreted by Th22 cells primarily affects epithelial and stromal cells rather than other hematopoietic cells, which lack a functional IL-22 receptor. Th22 cells contribute to allergic inflammation in the lung, but their role in skin immunity is better established.

Another subset of CD4$^+$ helper cells are follicular helper T cells (Tfh), which regulate the development of antigen-specific B cell immunity.[158,159] These Tfh cells help B cells generate antibody-producing plasma cells and long-lived memory B cells. Tfh cells are identified by Bcl-6 (a transcriptional repressor) expression and IL-21 secretion. IL-6 and autocrine IL-21 signaling induce helper T cells to express Bcl-6, which controls Tfh cell differentiation and suppresses differentiation of Th1, Th2 and Th17 cells. These Tfh cells have been implicated in several autoimmune diseases, including systemic lupus erythematosus and Sjögren's syndrome.

The actions of T helper cells are balanced by regulatory T (Treg) cells, a subpopulation of CD4-expressing cells that specializes in suppression of T cell-mediated immune responses.[160,161] Treg cells are identified by their expression of CD25 and the transcription factor Foxp3. Treg cells can regulate and suppress immune responses. They produce cytokines such as TGF-β and IL-10 that have immune suppressive activities. Of note, failure to activate an appropriate T cell response can lead to chronic infection, while exaggerated T cell responses can cause excessive tissue damage and are associated with inflammatory and autoimmune diseases. During lung infections, Th1 may mediate lung damage in response to infection. Thus, downregulation of such Th1 responses may help preserve lung integrity. Th2 responses are known to be important during the wound healing process, but if this response is prolonged and uncontrolled, it can worsen the injury and contribute to fibrosis.

Considering the diverse and important roles helper T cells play in the immune system, it is not surprising that these cells influence the immune response in many pulmonary diseases (more is discussed in other chapters). Helper T cells can make occasional mistakes or generate responses that would be considered harmful. In the worst-case scenario, helper T cell responses may be disastrous and prove fatal to the host. Fortunately, this is a very rare occurrence. The adaptive immune system must achieve a balance of sensitivity in order to respond appropriately to foreign antigens, without responding to host antigens and damaging self. When the immune system responds to very low antigen levels that it should not respond to, a hypersensitivity response, such as seen in airway allergies and autoimmune lung diseases, ensues. There are four general types of hypersensitivity reactions that have been described: Type 1 reactions, such as in asthma and allergic lung diseases, involve IgE antibodies and a Th2 response; type 2 and type 3 hypersensitivity responses involve the role of autoimmune and low-affinity antibodies (and, in some instances, it is felt that Th2 cytokines promote such disorders); and type 4 reactions, also known as delayed-type hypersensitivity, are the result of chronic inflammation and activation of lymphocytes and macrophages, typically a Th1 cytokine response.

■ T Cell Subsets with Innate Immunity Properties

While most conventional T cells have reactivity to specific complexes of major histocompatibility (MHC) molecules and antigen peptides, many other T cells do not fit this paradigm. These innate T cell subsets include natural killer (NKT) cells, γδ T cells, and mucosa-associated invariant T (MAIT) cells.[162,163]

NKT cells are innate T cells that are restricted through the glycolipid α-galactosylceramide when it is presented on MHC class I–like CD1d. These NKT cells express both conventional T cell markers such as αβ TCRs and NK cell markers. These cells are only 0.1% to 0.2% of the circulating lymphocyte population in humans. Two types of NKT cells have been described: invariant NKT (iNKT) cells that express specific invariant Vα-Jα α chain paired with certain Vβ chains, and the more diverse NKT cells that display a diverse αβ TCR pairings. NKT cells can readily produce various cytokines upon encounter with various environmental stimuli that have important roles in mucosal lung immunity.[164,165]

γδ **T cells** are enriched in mucosal and epithelial surfaces such as the respiratory tract and can represent from 8% to 20% of resident pulmonary lymphocytes in the lung and 1% to 5% of the circulating blood lymphocytes.[166–168] These T cells have TCR with γδ chains, rather than the conventional TCR chains. These cells recognize antigens via γδ TCR mediated signaling and can recognize stress ligands such as MIC-A, MIC-B, or ULBP through NKG2D receptors. γδ T cells can also be activated by peptide antigen derived by isoprenoid pathway used by certain microorganisms or by mevalonate pathways in infected cells. γδ TCRs have more limited repertoire diversity, and are considered, at times, invariant because they are only able to recognize limited types of antigens. These γδ T cells have been shown to be important in maintaining normal airway responsiveness or tone, as well as in their immunoregulatory role in numerous infectious and noninfectious diseases in the lung.[166,169] Their role includes maintaining lung tissue homeostasis, providing protective immunity against invading pathogens, tissue healing, and epithelial cell maintenance.

Mucosa-associated invariant T (MAIT) cells are a subset of innate-like T cells that express evolutionarily conserved T cell receptor α chain that is restricted by the nonpolymorphic MHC class I related protein MR1.[170] These cells can be activated by microbial riboflavin metabolite–derived antigens presented by MR1, which distinguishes them from other T cells with αβ. Because the riboflavin pathway is unique to microbes, these metabolites can be considered to be comparable to other microbial molecular patterns.[171] For example, MAIT cells secrete TNFα, IFN-γ, and IL-17 when stimulated with various microbial pathogens, and lacking MR1 (and thus MAIT cells), they have impaired control of lung infections. These cells function to promote monocyte differentiation into dendritic cells during infection that bridges innate to adaptive immunity.[172] Their role in the contribution to human lung diseases is beginning to be described.[173,174]

CONCLUSIONS

The lung is a vast organ comprised of conducting airways, alveoli, and tissue parenchyma that is highly specialized to sample the diverse antigens that we breathe in. The lung is equipped with a well-orchestrated immune system to clear particulate debris and to eliminate inhaled pathogens and toxins to protect the delicate capillary-alveolus barrier system that is critical for gas exchange. The immune system in the lung has evolved complex and diverse innate and adaptive immune responses to accomplish these critical functions of lung homeostasis and host defense.

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CHAPTER 20

Macrophages and Lymphocytes in the Lung

Katrina E. Traber
Joseph P. Mizgerd
David M. Center

INTRODUCTION

This chapter describes the macrophage and lymphocyte populations present in the lung, in both the absence and presence of inflammatory stimuli. This distinction may be artificial, as the lung actively interfaces with the aero-environment and thus is constantly exposed to stimuli. While we describe the phenotypes themselves, other chapters cover the inflammatory processes and migratory stimuli that change the inflammatory cell complexion in the lung in disease states. Of greatest importance is to note that there is marked heterogeneity of cell surface markers, secretory products, and macrophage and lymphocyte functions in the lung that, together, represent the overall responses to stimuli and pathogens and the resolution of inflammation. We defer discussion of disease states to other chapters, only peripherally referring to unique roles of specific macrophage or lymphocyte subtypes when important to understanding the phenotypes. Our approach is to divide the chapter into descriptions of leukocyte subtypes of the innate (macrophages and lymphocytes) and adaptive (lymphocytes) immune systems, recognizing that there are many other ways to classify the inflammatory cell populations in the lung. Innate and adaptive immunity are described in detail in other chapters.

LUNG LEUKOCYTES IN THE INNATE IMMUNE SYSTEM

A variety of macrophages and lymphocytes are found in the lung and are discussed below.

■ Macrophages

Macrophages are large mononuclear cells with phagocytic capability that are found throughout the lung airspaces and parenchyma at baseline and during inflammation.[1] These cells are key components of innate immune responses in the lung and manifest diverse functions that are associated with cell location, cell stimuli, and cellular origin. Their functions include: (1) phagocytic clearance of inhaled particles, pathogens, and apoptotic cells; (2) immunologic surveillance, raising an immunologic alarm in the presence of pathogenic but not innocuous stimuli; (3) immune regulation by interfacing with other members of innate and adaptive immune responses; and (4) promoting resolution and repair pathways after an injurious insult. No single macrophage effects all these disparate roles. Rather, macrophage populations are diverse and dynamic; they originate from multiple cell types and retain a remarkable degree of functional plasticity over their potentially long life.[2] Because of this diversity, many classification schemas have been developed to categorize macrophages, based on surface markers, location, and function.[3]

In recent years, especially with the emergence of single cell-based analytic techniques, it has become clear that many of these systems inadequately describe the full breadth of macrophage heterogeneity. Here, we describe lung macrophage population based on primary location—airspace/alveolar vs. interstitial/tissue-resident macrophages—and describe the current understanding of subcategories in each of these regions. This is a rapidly evolving field, and our understanding will likely be further refined in the future.

Alveolar Macrophages

Alveolar macrophages (AMs) are defined primarily by their location in the alveolar space (Fig. 20-1) and their accessibility via bronchoalveolar lavage. Their readily accessible location has made them

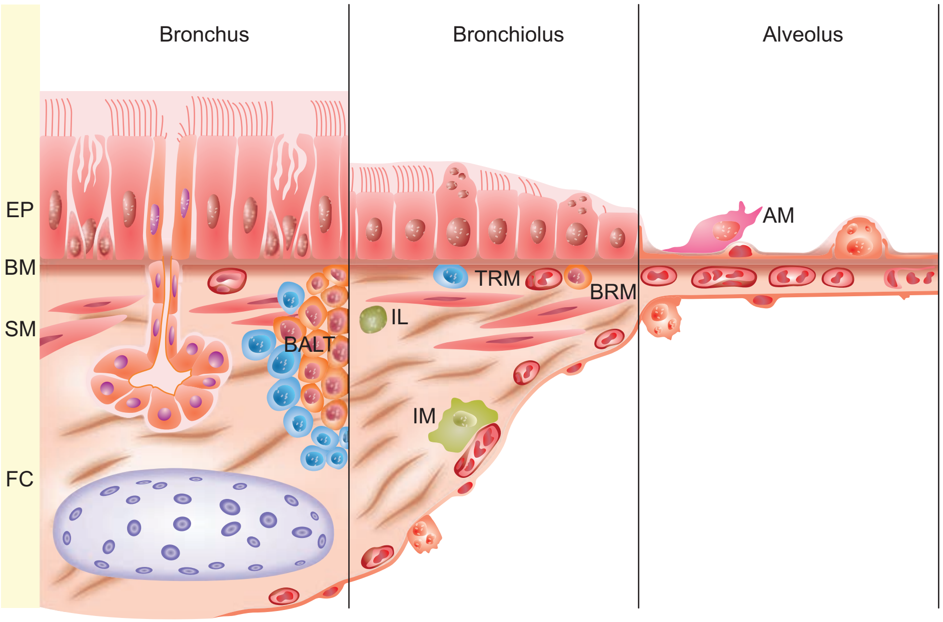

Figure 20-1 Macrophages and lymphocytes are typical components of most lungs. The conducting airways including bronchi and bronchioles are surrounded by loose connective tissue containing diverse leukocytes as well as mesenchymal cells and blood vessels. When organized into tertiary lymphoid structures, lymphocyte aggregates form bronchus-associated lymphoid tissue (BALT) containing both B cells (orange) and T cells (blue), as well as supportive elements like high endothelial venules, fibroblastic reticular cells, and follicular dendritic cells (not depicted). Resident memory T (T_{RM}) cells, including both CD8$^+$ T cells and CD4$^+$ T cells, resident memory B (B_{RM}) cells, and innate lymphocytes (IL), including multiple types of innate T cells and of innate lymphoid cells, are dispersed in these loose connective tissues, often but not always near the columnar epithelial cells and/or blood vessels. Distinct subsets of interstitial macrophages (IM) are found near nerves or blood vessels in the connective tissue. In the parenchyma, alveolar macrophages (AM) are apposed to alveolar epithelial cells on the luminal side. This network of lung leukocytes is key to pulmonary innate and adaptive immune responses to lower respiratory system challenges by infection, allergens, pollutants, or other. (*Modified with permission from Bergofsky EH. The lung mucosa: a critical environmental battleground. Am J Med. 1991;91(4A):4S–10S.*)

TABLE 20-1 Leukocytes of the Innate Immune System: Macrophages

Location	Surface Phenotype[a]	Function	Secretory Products
Alveolar Macrophages Self-renewed; monocyte derived (after infections and injuries)	$CD11b^{-}CD11c^{+}CD64^{+}F4/80^{+}$ $CD24^{-}MHCII^{var}SiglecF^{+}$ various TLR and cytokine receptors; autofluorescent	Direct microbicidal activity; clearance of lipids and cellular debris	Varied; see below
Proinflammatory M1	PAMPs, IFNs, and TLR receptors	Amplification of the anti-infectious inflammatory response	TNF-α, IL-6, IL-1β, chemotactic cytokines for neutrophils and lymphocytes
Proinflammatory M2	IL-4, IL-13 receptors	Amplification of the allergic type response	Arginase, chitinase like proteins, CD36, CD206
Regulatory	IL-10, various proinflammatory stimuli	Control of the local inflammatory response	IL-10, TGF-β, prostaglandins, resolvins
Interstitial Macrophages (IM)	$MerTK+CD64+CD11b+SiglecF^{-}$	Immunomodulatory>>inflammatory	IL-10>IL-6
IM1	$CD11c^{lo}$ $Lyve1^{hi}MHCII^{lo}$ $CD206^{+}$	Subset-specific function not defined, fibrogenic	Poorly defined
IM2 (subset of IM1?)	$(CD11c^{lo}MHCII^{hi})$	Subset-specific function not defined	Poorly defined
IM3	$CD11c^{+}$ $Lyve1^{lo}MHCII^{hi}$ $CD206^{-}$	Subset-specific function not defined	Poorly defined

[a] Surface markers of macrophages vary across species. Table 20-1 highlights mouse data since these macrophage subsets are best characterized in that species.

a well-studied population of lung macrophages in both humans and animal models. In addition, during homeostasis, alveolar macrophages can be identified based on surface marker profiles (Table 20-1) as $CD11b^{-}$ $CD11c^{+}$ $CD64^{+}$ $F4/80^{+}$ $CD24^{-}$ $MHCII^{var}$ $SiglecF^{+}$ autofluorescent cells from mouse lungs[4] or $CD11b^{+}$ $HLA\text{-}DR^{++}$ $CD206^{++}$ $CD169^{+}$ cells from human lungs.[5] However, the specific populations of macrophages residing in the alveolar space vary with inflammatory state of the lung, prior inflammatory experience, and age.

The lungs are populated with macrophages through multiple pathways during embryonic development and early postnatal periods. Much of our knowledge of macrophage origins is the result of fate-mapping and parabiosis techniques. The first macrophages to arrive in the developing lungs are derived from erythromyeloid progenitor cells (EMPs) in the yolk sac.[6,7] These cells widely populate the developing lung, maturing into macrophages without a monocytic intermediate.[7] EMPs also seed the early fetal liver, developing into monocytes that subsequently populate the developing lung.[6] These fetal liver–derived monocytes in the lung migrate to the alveolar space, becoming alveolar macrophages, replacing yolk sac–derived macrophages.[8,9] Development of alveolar macrophages from fetal liver monocytes requires TGF-β[10] and GM-CSF signaling through PPAR-γ.[9,11]

Once established, alveolar macrophages are largely self-renewing.[12] However, in the setting of severe lung injury and significant loss of viable AMs, this population can be renewed by circulating monocytes, as discussed below. Therefore, over a lifetime of stimuli and injury, the pool of AMs gradually and persistently transitions from an initial dominance by cells of embryonic origin towards ever larger fractions of cells derived from marrow-origin monocytes.[13] Distinguishing developmental origins of AMs in humans is difficult, but studies of transplant patients have been revealing. Transplanted lungs retain a large proportion of donor alveolar macrophages for years after transplant,[14,15] establishing their ability to persist without replacement by monocytes. However, in the setting of allogenic bone marrow transplant, where the recipient's alveolar macrophages are ablated, these cells become replaced by monocyte-derived macrophages from the donor, and these cells take on AM surface markers and phenotypes.[16]

The average human cycles thousands of liters of air through the lung daily, which includes particulate matter, innocuous organisms, and potential pathogens. Because of their location at the interface between external air and lung epithelium, a major role of AMs is to clear particulate matter, surfactant, and cell debris. In fact, abnormal AM development secondary to interruption of GM-CSF signaling underlies pulmonary alveolar proteinosis (PAP), which is characterized by progressive respiratory dysfunction secondary to an accumulation of surfactant.[17] In addition, AMs are well positioned to function as the primary immunologic sentinel of the lungs. This process is largely immunologically silent because the bulk of stimuli are nonpathogenic, and inflammatory responses to all of these stimuli would have damaging consequences.

Several mechanisms function to limit AM activation, including the soluble mediators IL10 and TGF-β, surfactant-mediated inhibition of TLR2 and TLR4 signaling, and direct interactions between AMs and epithelial cells.[18] In aggregate, these factors have a much greater effect on AM function than developmental origin of the cells. Of note, adoptive transfer of peritoneal macrophages (PMs) to the alveolar space or AMs to the peritoneal space results in alteration of macrophage phenotype consistent with transfer site.[19] More recently, transcriptomic studies of embryonic derived AMs and monocyte-derived macrophages within the same lungs demonstrated that very few genes differ between these two cell populations.[20] After transfer into the air spaces of the lung, myeloid progeny from induced pluripotent stem cells differentiate to resemble AMs and are sufficient to correct models of pulmonary alveolar proteinosis,[21,22] confirming the cellular plasticity of myeloid cells and the significance of the pulmonary microenvironment in driving the AM phenotype.

Consistent with their role as airway sentinel, AMs must rapidly react to pathogens or other injurious stimuli. Although, as discussed previously, AMs have tonic mechanisms in place to limit activation, AMs also possess an array of surface receptors able to recognize pathogens and inflammatory cytokines. To move AMs into a fully activated state, multiple disrupting events are likely required, such as a decrease in inhibitory signaling after epithelial destruction, plus binding of activating factors to surface receptors.[18] However once activated, AMs play multiple essential roles in pathogen defense (Table 20-1).

First and foremost, AMs can directly clear pathogens through phagocytosis and phagolysosomal killing.[23] AMs also have a significant impact on other members of the innate immune response via the release of proinflammatory cytokines, such as TNF-α, IL-1α, IL-1β, IL-6, and chemokines.[24] These signals lead to the recruitment and activation of several cell types, including monocyte-derived macrophages, to the alveolar space. These monocyte-derived macrophages have a proinflammatory phenotype, producing high levels of TNF-α, neutrophil chemokines, and lysosomal proteases.[25] Alveolar macrophages and monocyte-derived macrophages have distinct transcriptomes and functions in the inflamed lung.[26–28]

Equally important to their role in host-defense, AMs are critical to resolution and repair. After the acute event has been managed, AMs actively stimulate resolution through the phagocytosis of apoptotic neutrophils and injured cells (*efferocytosis*) and the production of anti-inflammatory (e.g., IL-10 and TGF-β) and proresolving (e.g., resolvins, protectins, and maresins) protein and lipid mediators.[29] Monocyte-derived macrophages can undergo apoptosis and be cleared by resident AMs, or they can further differentiate and develop a phenotype nearly indistinguishable from the resident AMs.[20,29] As a result, the overall proportion of embryologically derived AMs is decreased from pre-event levels. Furthermore, these AMs in the resolved lung are reprogrammed, with new baselines and responses to subsequent pulmonary challenges that persist long after the earlier challenges are removed.[28,30,31]

Steady-state alveolar macrophages are long-lived and largely self-renewing, even during inflammation and injury.[32] However, during acute inflammatory events, there is a dramatic influx of monocyte-derived macrophages with a proinflammatory phenotype. Some authors have classified these macrophages as M1 (“classically activated” and stimulated by IFN-γ and LPS, microbicidal, producing TNF-α, IL-6, and reactive oxygen and nitrogen intermediates) vs. M2 (“alternatively activated” and stimulated by IL-4 and IL-13, expressing arginase 1, chitinase-like proteins, CD36, and CD206).[3] However, this classification, while a helpful initial guide to the spectrum of macrophage function, does not apply well to lung macrophage populations.[2,33] Recent, single-cell RNA sequencing analysis of alveolar macrophages before, during, and after an acute inflammatory event demonstrated that while there are subsets of macrophages, they do not conform to the M1 vs. M2 dichotomy, as many cells express markers of both groups.[27]

Interstitial Macrophages (IMs)

In addition to the lung lumen, macrophages are also found in the interstitium of the lung, between the epithelium lining the air spaces and the endothelium lining the blood vessels (Fig. 20-1). Nearly 80% of lung IMs are within alveolar septae, with the remainder residing in connective tissues around conducting airways and vasculature.[34] IMs have been less studied than AMs because they are not readily accessible by lavage.

The early stages of IM development are shared with AMs, as discussed previously, with primitive yolk sac–derived macrophages initially populating the lung, and subsequently replaced by fetal liver monocyte–derived macrophages. Shortly after birth, a final population of macrophages, originating from bone marrow hematopoietic precursors, arrives in the lung and become IMs.[8] Subsequent turnover of IMs appears to be a combination of direct IM replication, and continual seeding from circulating monocytes, which differentiate into IMs.[8,35]

The study of IM function has been limited due to the cells’ location. Until recently, IM function has been studied by stimulating these cells ex vivo, analysis of which can be limited by experimental artifact. However, similar to AMs, IMs are capable of phagocytosis, carry receptors for PAMPs and cytokines on their surface, and are capable of secreting both immunosuppressive (IL-10) and immunostimulatory (IL-6) cytokines.[36,37] Overall, it appears that IMs may have a more immunoregulatory phenotype, secreting higher levels of IL-10, both at baseline and with stimulation (Table 20-1). However, comprehensive studies of IM function in vivo remain forthcoming.

Detailed analysis of IM subsets has become possible in recent years through the combination of advanced flow cytometric techniques that allow for discrimination of IMs and single cell–based methods, such as single-cell RNAseq (Table 20-1). There may be three[38,39] (or two)[40,41] distinct populations of IMs based on current schema. For division of mouse lung IMs (all $\text{MerTK}^+\text{CD64}^+\text{CD11b}^+\text{SiglecF}^-$) into three subsets, CD11c and MHCII levels serve to subdivide ($\text{CD11c}^{\text{lo}}\text{MHCII}^{\text{lo}}$ [IM1]; $\text{CD11c}^{\text{lo}}\text{MHCII}^{\text{hi}}$ [IM2]; and $\text{CD11c}^+\text{MHCII}^{\text{hi}}$ [IM3]). Humans have similar subsets of IMs based on transcriptomes, albeit with divergent surface markers from mice.[39] Other single-cell transcriptomic studies of mouse lungs independently identified two IM subsets: $\text{Lyve1}^{\text{lo}}\text{MHCII}^{\text{hi}}$ vs. $\text{Lyve1}^{\text{hi}}\text{MHCII}^{\text{lo}}$[40] and CD206^- vs. CD206^+.[41] When considered together, all these IM subsets show substantial overlap (IM3; $\text{Lyve1}^{\text{lo}}\text{MHCII}^{\text{hi}}$; CD206^- compared with IM1/IM2; $\text{Lyve1}^{\text{hi}}\text{MHCII}^{\text{lo}}$; CD206^+[41]), suggesting that these studies are detailing comparable subsets of IMs. While all IMs are found in connective tissue (Fig. 20-1), the $\text{Lyve1}^{\text{lo}}\text{MHCII}^{\text{hi}}$ IMs tend to reside near nerves whereas the $\text{Lyve1}^{\text{hi}}\text{MHCII}^{\text{lo}}$ cells tend to be near blood vessels.[40] The latter contribute to fibrotic responses in mouse models,[40] but there remains much to be learned about the unique niches in the tissue, dynamics during inflammation, and distinct functional roles of IM subsets in the lung.

■ Lymphocytes

Growing attention has been paid to subsets of lymphocytes that have antigen receptors of limited diversity or lack antigen receptors entirely and that, instead, respond to stereotypical pathogen products or host-generated alarm signals. Because these cells do not require clonal expansion prior to response, they can respond quickly to stimulus, often with the production of activating cytokines. As a group, these cells are known as *innate lymphocytes* (Fig. 20-1), and they play a crucial role in interaction with other innate effector cells (such as macrophages and neutrophils), as well as adaptive immune responses mediated by T cells, B cells, and dendritic cells. The innate lymphocytes can further be divided into T cells with limited antigen receptor diversity (γδ T cells, iNKT cells, and MAIT cells) and those with lymphocyte morphology, but without antigen receptors (innate lymphoid cells—NK cells, ILC1, ILC2, ILC3, and LTi cells) (Table 20-2).

Innate T Cells

Below we will consider innate lymphocytes that express a T-cell receptor, but of limited diversity, collecively known as innate T cells.

γδ T Cells As suggested by their name, γδ T cells express T cell receptor (TCR) heterodimers containing gamma and delta chains (Table 20-2). While these TCR chains do undergo RAG-directed recombination, the diversity of products is quite limited compared with the αβ TCR. γδ T cell subsets express Vγ1, Vγ4 and Vγ7, in combination with a variety of Vδ chains.[42,43] γδ T cell development branches off from the common thymocyte pathway at the DN2 DN3 stage; therefore, these cells do not express CD4 or CD8.[44]

During lung infections, γδ T cells act as early responders to pathogens. These cells can be stimulated by direct binding of antigen to TCR, binding of PAMPs and DAMPs to TLRs, or direct cytokine stimulation.[45] Activation of γδT cells leads to production

TABLE 20-2 Leukocytes of the Innate Immune System: Lymphocytes

Common Name	Surface Markers	Stimulus	Functions	Products	Location
γδ T cell	Limited γδ TCR CD4$^-$CD8$^-$	Antigen PAMP/DAMP Cytokines	Rapid responders Granuloma formation Protection from injury	IFN-γ IL-17A IL-4	Mucosal barriers
Invariant NKT cell	CD1d; Invariant αTCR Limited βTCR	Lipid antigens (α-Gal-Cer)	Rapid responder Cytokine production Cytotoxic	See subsets below	Marginated in vasculature and interstitium
	Regulator		**Functions**	**Products**	**Location**
iNKT1	PLZF, T-bet		Type 1 responses	IFN-γ	Liver and spleen
iNKT2	PLZF, GATA-3		Type II responses	IL-4	Lung
iNKT17	PLZF, RORγt		IL-17 responses, neutrophils	IL-17	Lung
Mucosal-associated invariant T cells (MAIT)	MR1 Restricted αβ TCR	Riboflavin metabolites IL-18	Rapid responder Cytokine production Cytotoxic	IFNγ or IL-17 or IL-22	Mucosal tissues and vasculature
	Regulator		**Functions**	**Products**	**Location**
MAIT1	PLZF, T-bet		Type I response	IFN-γ	Liver and spleen
MAIT17	PLZF, RORγt		IL-17 response	IL-17, IL-22	Lung
Innate lymphoid cells (ILCs)	No TCR No lymphoid or myeloid markers	Danger and stress signals	Varied	Varied	Varied
	Surface Marker	**Regulator**	**Function**	**Products**	**Location**
NK	CD127$^-$ NKp46$^+$ Eomes$^+$	T-bet	Cytotoxic Effector cell recruitment FAS-mediated apoptosis	Perforin, granzyme, variety of pro- and anti-inflammatory cytokines	Lung parenchyma and airspaces
ILC1	CD90$^+$ CD127$^+$ RORγt$^-$GATA3^{int} Eomes$^-$ NKp46$^+$	Tbet	IL-22, IL-18 receptors	IFN-γ, GM-CSF	Low numbers in resting lung
ILC2	CD90$^+$ CD127$^+$ RORγt$^-$ GATA3^{hi}	GATA-3	“Helper type” Protect against helminths Maintain barrier integrity	IL-5, IL-13	Diffuse; mucosa
ILC3	CD90$^+$ CD127$^+$ RORγt$^+$ GATA3^{int}	RORγt	TH17-type response	IL17, IL22	Non-lung mucosa
LTi	RORγt	RORγt	Induce development of lymphoid tissue	IL17, IL22	Fetal lymphoid tissue

of IL17A and IFN-γ, which have important downstream results, such as effector cell recruitment (macrophage, neutrophil), granuloma formation, and Th17 immune responses. Multiple models of pulmonary infection have demonstrated that γδ T cells increase numbers during acute infection,[46–49] likely due to expansion rather than recruitment.[48] However, experimental depletion of γδ T cells has mixed results, with decreased IFN-γ production and inability to clear pathogen in *Klebsiella*,[50] pneumococcus,[46] and BCG[51] infections, but improved pathogen clearance and increased IFN-γ in a cryptococcus model.[47]

The role of γδ T cells in allergic lung disease has been the subject of investigation. Initial studies in both human asthma and mouse models produced conflicting data regarding whether γδ T cells promoted or inhibited allergic inflammation.[52–54] It now appears that subsets of γδ T cells in the lungs produce IL-4, which leads to enhanced Th2 responses,[55] IL-17, which leads to suppressed Th2 inflammation,[56] or IFN-γ, which inhibits antigen specific IgE. Alteration of the balance of these subsets of γδ T cells, specifically an increase in IL-4-producing and decrease in IFN-γ-producing γδ T cells, was found in patients with allergic asthma[57] or after segmental allergen challenge.[58]

Invariant Natural Killer T Cell (iNKT) Cell Natural killer T cells (NKT cells) are defined by their response to lipid antigens presented by an MHC class I–like molecule, CD1d (Table 20-2). Invariant NKT cells (iNKT, also known as classic or type I NKT cells) express an αβ TCR with invariant α TCR (Vα14-Jα18 in mice, Vα24-Jα18 in humans), combined with one of three β chains (Vβ8.2, Vβ7, or Vβ2 in mice and Vβ11 in humans).[59] Other NKT subsets have been identified, but less is known about them as cell-specific genetic models are lacking and human studies are limited. Hence, we focus the remainder of this section on type I (iNKT) cells.

In mice, iNKT cells make up about 1% to 3% of circulating T cells in mice, and approximately 2% to 5% of lung resident T cells, largely as marginated cells in the vasculature and in the interstitium.[60,61] iNKT cells respond to lipid antigens presented by CD1d, specifically the glycosphingolipid (GSL) alpha-galactosylceramide (α-Gal-Cer).[62] α-Gal-cer-loaded CD1d has become a useful way to identify and study both human and mouse NKT cells.[63] iNKT cells also respond to a variety of microbial- and host-derived lipids, allowing them to respond to a wide range of pathogens.[64] In addition, iNKT cells respond directly to cytokine stimulation, including IL-12, IL-1β, IL-18, IL-23, and IFN-β.[65,66]

Specific sub-populations of iNKT cells (NKT1, NKT2, and NKT17) have been defined based on the repertoire of cytokines produced. NKT1 cells produce IFN-γ and express the transcription factor T-box 21 (T-bet).[67,68] NKT2 cells produce IL-4, express PLZF,[68] and depend on PLZF, Gata3, and Irf4 for development.[68,69] Finally, NKT17 cells produce IL-17 and express RORγt.[68,70] Lungs are particularly enriched for NKT17 cells, with NKT17 cells located in the lung parenchyma, and NKT1 and NKT2 cells in the marginated vascular pool.[71]

Given the rapidity and potential diversity of their response, iNKT cells play a critical role in the defense against multiple lung pathogens. In bacterial pneumonia, iNKT cells are required for a robust response to infection. Lack of iNKT cells in mice (Jα18–/– mice) results in increased mortality and decreased bacteria clearance in *Streptococcus pneumoniae*,[72] *Pseudomonas aeruginosa*,[73] *Mycobacterium tuberculosis*,[74] and *Chlamydia pneumoniae* models of pneumonia. These studies also show an interaction between iNKT cells, neutrophils, and alveolar macrophages via chemokine (CXCL2) and cytokine (IFNγ) production.[72,73] iNKT cells also play an important role in pulmonary viral infections. Influenza virus–infected DCs stimulate iNKT cells, resulting in rapid production of IL-22.[75] iNKT cells are protective against influenza through modification of the activities of myeloid-derived suppressor cells[76] and proinflammatory monocytes.[77]

Data supporting a role for iNKT cells in chronic inflammation, such as asthma and reactive airways disease, are mixed. Murine studies have shown that mice lacking iNKT cells do not develop airway hyperreactivity in response to OVA treatment.[78] However, germ-free mice demonstrate an accumulation of iNKT in colon and lung and increased morbidity in asthma models.[79] In humans, some studies of iNKT cells in asthmatics show significant alterations in numbers, while other similar studies show no change in iNKT cells.[80–83]

Mucosal-Associated Invariant T (MAIT) Cells Similar to iNKT cells, mucosal-associated invariant T cells (MAIT cells) have a restricted TCR, with humans expressing Vα7.2-Jα33 and Vβ2 or Vβ3,[84–86] while mice express Vα19-Jα33 and Vβ8.1, Vβ8.1, or Vβ6.[87] However, these cells do not respond to CD1d; rather, they are stimulated by the MHC class I–related (MR1) receptor (Table 20-2). This molecule presents riboflavin (vitamin B_2) metabolites,[88,89] which occur in diverse bacterial[90–92] and yeast species.[93,94] In addition, MAIT cells can be stimulated by TCR-independent pathways, including from IL-18.[95,96]

Similar to iNKT cells, MAIT cells develop in the thymus and are regulated by many of the same signaling pathways.[97,98] MAIT cells can also be subdivided by the cytokines that they produce. Thus far, MAIT1 (IFN-γ producing) and MAIT17 (IL-17 and IL-22 producing) have been identified. Unlike iNKT cells, a subset of MAIT cells producing type 2 cytokines has not been identified. MAIT cells display heterogeneity in response to microbes and may function to distinguish between pathogen and commensal.[85,98] Furthermore, MAIT cell numbers are reduced in germ-free mice, in contrast to iNKT cells, which are increased in these mice.[99]

At baseline, MAIT cell numbers in lungs of mice are low. However, cell numbers dramatically expand with infection by intracellular bacteria, including *Salmonella typhimirum*,[100] *Francisella tularensis*,[101] and *Legionella*. MAIT cell number is negatively correlated with disease severity and *P. aeruginosa* infection in cystic fibrosis.[102] Furthermore, studies with MR1$^{-/-}$ mice demonstrate that MAIT cells protect against *E. coli* and *M. abscessus*.[93] In humans, MAIT cells are higher in peripheral blood of patients recovered from than died from severe influenza.[96]

The evidence for MAIT cell involvement in asthma and COPD is limited, but suggestive. In humans, the number of MAIT cells is approximately 5- to 10-fold higher than in mice. In an inner-city asthma study, higher numbers of MAIT cells in circulation at age 1 predicted protection from asthma at age 7.[103] Conversely, lower numbers of MAIT cells in peripheral blood and BAL were associated with more severe asthma.[104] In contrast to the deleterious effects of iNKT cells in mouse models of asthma, these data suggest that MAIT cells may be protective.

Innate Lymphoid Cells

Innate lymphoid cells (ILCs) are defined by a lack of RAG-dependent antigen receptor, an absence of cell-surface markers associated with other lymphoid and myeloid lineages, and a lymphoid morphology.[105] Similar to the other innate-like lymphocytes discussed, parabiosis studies have demonstrated that ILCs are largely tissue resident and do not recirculate.[106] Because these cells do not have antigen receptors, they instead respond to direct stimulus by danger and stress signals. The first of these types of cells to be identified were natural killer (NK) cells and lymphoid tissue inducer (LTi) cells. Additional types of innate lymphoid cells have since been identified and, together with NK and LTi cells, categorized by the constellation of cytokines they produce, namely ILC1 producing type I cytokines (IFN-γ and TNF), ILC2 producing type II cytokines (IL-4, IL-5, IL-9, and IL-13), and ILC3 producing IL-17 and IL-22. The contribution each of these cell types to lung immunity is described further below and in Table 20-2.

Natural Killer Cells (NK) NK cells make up the largest proportion of ILCs in the lungs.[107] They are defined by surface markers CD127$^-$NKp46$^+$Eomes$^+$ and require the transcription factor T-bet.[108] NK cells express a wide variety of activating and inhibitory surface receptors that enable tuning of NK responses based on the combination of binding ligands.[109,110] In the presence of activation signals, NK cells can directly kill target cells (Table 20-2) through the release of perforin and granzyme, recruit additional effector cells by the secretion of cytokines and chemokines, or induce target cell apoptosis through the expression of apoptosis-inducing ligands such as FasL or TRAIL.[110,111] Conversely, NK cells can also produce anti-inflammatory cytokines. In the lung, where over-exuberant action of NK cells could be particularly deleterious, NK cells have a higher proportion of inhibitory to activating receptors, and tightly regulated activation.[112]

ILC1 ILC1s are defined by markers CD90$^+$CD127$^+$RORγt$^-$GATA3^{int}Eomes$^-$NKp46$^+$ and require the transcription factor Tbet.[108] They are very similar in overall surface marker repertoire and function to NK cells, except that they lack direct cytotoxic function (Table 20-2); there are very few ILC1s resident in the lungs of either humans or mice.[108] Although initially thought to be a subset of NK cells, recent lineage data suggest the cells originate from a separate ILC precursor in bone marrow.[105] They respond to stimulation by IL-22 and IL-18, resulting in the production of IFN-γ and GM-CSF.[108]

ILC2 ILC2 are the second most populous ILC in the lungs, after NK cells, and are defined by the markers CD90$^+$CD127$^+$RORγt$^-$GATA3^{hi}.[108] They have been characterized as a "helper-type" ILC (Table 20-2) and function in defense against helminth infection, as well as maintaining barrier integrity in the lung.[110] They are activated in response to IL-1β, prostaglandin D2, IL-22, IL-25, and TLSP and, once activated, upregulate GATA3 to produce IL-5 and IL-13.[108] In the lungs, ILC2 play an important role in lung immunology. Their ability to secrete large quantities of type 2 cytokines gives them an important role in responding to viral and helminth infections, as well as in the pathogenesis of allergic asthma.[113]

ILC3 In general, ILC3 are abundant at mucosal sites but are not commonly found in lungs. They are defined by the markers CD90$^+$CD127$^+$RORγt$^+$GATA3^{int}.[108] They function to promote immunity to extracellular bacteria and fungi (Table 20-2). They respond to IL-1β and IL-23 via the transcription factor RORγt and production of the cytokines IL-17 and IL-22.[110] ILC3 can be further subset based on their production of NKp46(mice) or NKp44 (humans).[105]

Lymphoid Tissue Inducer (LTi) Cells These innate lymphoid cells are similar to ILC3 in that they are dependent on the transcription factor RORγt and produce IL-17 and IL-22 (Table 20-2). However, their main function occurs during fetal development with generation of secondary lymphoid organs, such as lymph nodes and Peyer's patches. Currently, their role in adults is unclear.[110]

LUNG LEUKOCYTES IN THE ADAPTIVE IMMUNE SYSTEM

In addition to the macrophages and innate lymphocytes detailed above, healthy human lungs contain distinct populations of adaptive immunity lymphocytes.[114] While diverse phenotypes are present, a preponderant majority of the T cells from human lungs display surface marker characteristics (most prominently CD69 to inhibit S1P-mediated trafficking) that identify them as resident memory lymphocytes and differentiate them from effector memory, central memory, and other memory lymphocytes.[115,116] In this chapter, we concentrate on resident memory cells (Table 20-3).

Resident memory lymphocytes are functionally defined by their tendency not to re-enter the lymphatics or blood for recirculation, although this may not be insurmountable.[115] Parabiosis experiments in mice demonstrate that lung resident memory lymphocytes are stably retained in the tissue, rather than recirculating with lung-homing propensity; human lung transplant recipients maintain donor resident memory lymphocytes in their lungs without evidence of donor lymphocytes appearing in the blood.[117] Thus, healthy lungs are a niche for a distinct compartment of immunologic memory, which modulates the timing, type, and degree of inflammation in the lungs.

While lungs of human infants contain predominantly naïve and regulatory cells, from later childhood years through adulthood the lungs are stocked with resident memory phenotype lymphocytes.[118–120] Laboratory animals for which pathogen exposures can be carefully controlled reveal that the presence of resident memory lymphocytes is predominantly determined by experiences such as a prior history of infections, rather than age.[24,121] The biology of lung resident memory lymphocytes and their influences on inflammation in the lung are rapidly evolving areas of investigation.

■ Lung Resident Memory CD8$^+$ T Cells

CD8$^+$ resident memory T (T_{RM}) cells are the most studied and best understood of lung resident memory lymphocytes (Table 20-3). CD8$^+$ T_{RM} cells are abundant in adult human lungs, as well as in laboratory mouse lungs that have recovered from respiratory viral infections.[114,118,120–122] They are primarily near conducting airways and pulmonary vasculature (Fig. 20-1), often in clusters but sometimes distributed dispersedly.[123] A subset of CD8$^+$ T_{RM} cells are marked by CD103, which is the αE chain of an integrin that binds E-cadherin on epithelial and other cells. In both mouse and human lungs, CD103$^+$CD8$^+$ T cells are preferentially found among columnar epithelial cells of the airways.[122] CD8$^+$ T_{RM} cells consistently express CD49a, which is the a_1 chain of an integrin that binds to collagens including the collagen IV of basement membranes as well as the type I collagen of connective tissue. CD103$^-$CD49a$^+$CD8$^+$ T cells are found near basement membranes of the airways and in the bronchovascular interstitium, where CD49a facilitates T cell crawling on collagen within tissue.[122] CD49a is essential for retention of CD8$^+$ T_{RM} cells in the lung and for effective memory defense against heterotypic respiratory infection.[122,124]

Lung CD8$^+$ T_{RM} cells arise from a combination of cues. Inflammation to recruit T cells plus local antigen presentation to activate them there can be sufficient to generate CD8$^+$ T_{RM} cells in settings when neither alone can, establishing a satisfying set of rules for their establishment.[125] After severe influenza virus infection, CD8$^+$ T_{RM} cells are present in the lung specifically where injury leads to keratin-5$^+$ epithelial cells that express α_V integrins that activate TGF-β.[126] Unlike in nonpulmonary tissues, formation of CD8$^+$ T_{RM} cells in the lung requires the transcription factor Blimp-1 but not Hobit.[127] Maintenance of CD103$^+$CD8$^+$ T_{RM} cells in the lungs requires Notch signaling in these cells.[128] Antigen specificity of naturally occurring human lung CD8$^+$ T_{RM} cells is only beginning to be detailed. Analyses of T cell receptor (TCR) repertoires reveals limited overlap of lung CD8$^+$ T_{RM} cells with splenic memory CD8$^+$ T cells, suggesting clonal segregation within the tissue likely

TABLE 20-3 Leukocytes of the Adaptive Immune System: Resident Lymphocytes

Common Name	Phenotype/Surface Markers	Functions	Products	Location
T cells				
Resident memory CD8$^+$ T cells (CD8$^+$$T_{RM}$)	Variable TcR; CD8$^+$, CD49a$^+$ CD103$^+$ and CD103$^-$ BLIMP-1 dependent	Cytotoxic Suppressor Activated by antigens, cytokines, and neurotransmitters	Direct cytotoxic proteins: granzyme, perforin IFN-γ, TNF-α, PGs	CD103$^+$ in columnar epithelium; CD103$^-$ basement membrane, interstitium
Resident memory CD4$^+$ T cells (CD4$^+$$T_{RM}$)	Variable TcR; CD4$^+$ Multiple other receptors depending on function and TH type Lung residence maintained by IL-7 produced by lymphatic endothelial cells Responsive to antigens, cytokines depending on subset and neurotransmitters	Extensive helper, cytotoxic, proinflammatory, and regulatory functions reviewed in disease specific chapters; memory responses to infections	TH cytokines, cytotoxic proteins, prostaglandins	Airways, interstitium, BALT
B Cells				
Lung-resident memory B cells (B_{RM})	Variable BcR/Ig receptors CD20, CD69, CD27, B220	Ig synthesis, memory responses to infections of II types; helper and suppressor cytokines, antigen presentation	Ig, extensive list of type I and type II cytokines, regulatory factors	Airways, interstitium, iBALT

resulting from locally relevant antigen encounters.[129] Compared to extrapulmonary memory T cells, influenza-reactivity is overrepresented in the lung CD8$^+$ T$_{\text{RM}}$ cells.[123,130,131] Remarkably, the influenza virus antigens recognized by CD8$^+$ T$_{\text{RM}}$ cells include peptide epitopes conserved across influenza A, B, and C viruses,[132] demonstrating that lung-localized lymphocytes can accomplish a previously unanticipated breadth of antiviral defense. Lung CD8$^+$ T$_{\text{RM}}$ cells may be enriched for specificities against many or most respiratory viral pathogens.

In addition to providing cytolytic activity typical of cytotoxic T lymphocytes (CTL), lung CD8$^+$ T$_{\text{RM}}$ cells help direct inflammation in the lungs. By pre-populating the tissue, they do not require time for recruitment like other memory cells do. In addition, CD8$^+$ T$_{\text{RM}}$ cells are in a poised state at rest. They contain more transcripts for cytokines (like IFN-γ and TNF-α) and cytotoxic proteins (like granzyme B) than do memory CD8$^+$ T cells from the blood.[128] These transcripts are not translated to protein until the T$_{\text{RM}}$ cells are activated, but this enables lung CD8$^+$ T$_{\text{RM}}$ cells to secrete their mediators more quickly compared to systemic counterparts.[128,133]

Lung CD8$^+$ T$_{\text{RM}}$ can also rapidly proliferate upon heterotypic lung infection by respiratory viruses,[134,135] amplifying local sources of inflammatory mediators. The daughter progeny of CD103$^+$CD8$^+$ T$_{\text{RM}}$ cells are more prone to being polyfunctional (and simultaneously producing diverse cytokines) than are those from other memory CD8$^+$ cells.[123] The transcriptomes of lung CD8$^+$ T$_{\text{RM}}$ cells reveal that both proinflammatory and anti-inflammatory intermediates are abundant,[128,129] but their net effect seems to be consistently proinflammatory in experimental settings where these cells are selectively depleted or added. A general truism for lungs that contain abundant CD8$^+$ T$_{\text{RM}}$ cells is that their triggering results in more rapid ramping up of inflammation upon infection of the tissues with a heterotypic microbe or an inflammatory stimulus that causes bystander activation. Because speed of the response is so key for defense against microbes in the lungs,[24] these CD8$^+$ T$_{\text{RM}}$ cells often contribute to improved immune resistance in the lung.

Beyond their canonical activation through TCR recognition of antigen, lung CD8$^+$ T$_{\text{RM}}$ cells can also become activated in a bystander fashion, more like the innate lymphocytes detailed above. For example, influenza-elicited lung CD8$^+$ T$_{\text{RM}}$ cells produce IFN-γ after activation by IL-12 secreted by dendritic cells responding to unrelated bacterial stimuli; this amplifies inflammation and improves antibacterial defense in these lungs.[136] The IFN-γ released from influenza-elicited CD8$^+$ T$_{\text{RM}}$ cells after bystander cytokine activation can skew pulmonary inflammation away from Th2 responses and help curb allergic airways disease.[137] Human lung T$_{\text{RM}}$ cells may likely be the CD8$^+$ T cells that respond rapidly to bystander histamine or serotonin with rapid secretion of chemotactic and regulatory cytokines.[138–140] Consequently, lung CD8$^+$ T$_{\text{RM}}$ cells can influence pulmonary inflammation in broad fashion, unrelated to the antigen specificity of the original stimuli that resulted in their establishment.

Lung CD8$^+$ T$_{\text{RM}}$ cells may also contribute to inflammatory pulmonary pathophysiology. To our knowledge, this has yet to be demonstrated in human settings. However, precedent is firmly established with mouse models of incomplete recovery after severe influenza virus infections. Such lungs contain diverse subpopulations of lung CD8$^+$ T$_{\text{RM}}$ cells, one of which (nucleoprotein-specific and PD-1$^{\text{high}}$) receives persistent MHC-I antigen presentation and develops a T cell exhaustion phenotype.[141] Blockade of PD-1 in such mice results in a CD8$^+$ T$_{\text{RM}}$ cell–driven increase in chronic pulmonary inflammation and lung fibrosis.[141] In this same mouse model, aging lungs accumulate increased amounts of CD8$^+$ T$_{\text{RM}}$ cells compared with younger lungs, perhaps via excess pulmonary TGF-β generation.[142] In addition to being overabundant, the older CD8$^+$ T$_{\text{RM}}$ cells are aberrant, clustering distinctly after single cell sequencing, with compromised IFN-γ production and less capability to provide defense against a heterotypic infection.[142] These excessive and aberrant CD8$^+$ T$_{\text{RM}}$ cells contribute to chronic inflammation and diseases, and their depletion is sufficient to reduce fibrosis, monocytes, and neutrophils in the post-influenza lungs.[142] Thus, dysregulated activities of CD8$^+$ T$_{\text{RM}}$ cells may contribute to chronic lung inflammation underlying pulmonary disease.

Lung CD8$^+$ T$_{\text{RM}}$ cells stray from textbook depictions of memory CTL. They do not recirculate through the blood and secondary lymphoid organs, looking for antigen-presenting cells. They can be triggered by a wider than usually envisioned range of stimuli, including antigens that are heterotypic and very broadly conserved, as well as by inflammatory cytokines and neurotransmitters generated by innate immunity. In addition to eliminating infected cells, they are important sources of local cytokines that modulate inflammatory responses in the lung.

■ Lung Resident Memory CD4$^+$ T Cells

CD4$^+$ T$_{\text{RM}}$ cells (Table 20-3) are less well characterized, but more abundant in human lungs, than are CD8$^+$ T$_{\text{RM}}$ cells.[118] Many features of lung CD8$^+$ T$_{\text{RM}}$ cells apply to lung CD4$^+$ T$_{\text{RM}}$ cells.[114] They are tissue-resident, rather than tissue-homing, as demonstrated in parabiosis studies in mice.[143–154] They are found in the interstitial connective tissues near airways and blood vessels[131] (Fig. 20-1). CD4$^+$ T$_{\text{RM}}$ cells derive from effector T cells recruited to the lungs and are maintained there by continuous local production of IL-7, from sources that include lymphatic endothelial cells.[144] Their generation, including IL-7 responsiveness, requires IL-2 receptor signaling to the T cells,[146–148] activated in part by IL-15 produced in the infected lung.[148] They accumulate preferentially in previously infected lung regions.[149] They tend to be polyfunctional, generating multiple cytokines together.[129,149]

CD4$^+$ T$_{\text{RM}}$ cells share transcriptome similarities to CD8$^+$ T$_{\text{RM}}$ cells, and these transcriptome profiles distinguish them from systemic CD4$^+$ memory counterparts found in the spleen.[129] In further similarity to CD8$^+$ T cells and distinct from circulating CD4$^+$ T cells, memory CD4$^+$ T cells in the lungs resemble CTL in their production of perforin and granzymes and their ability to kill infected cells directly.[147] Unlike CD8$^+$ T$_{\text{RM}}$ cells, CD103 is found on CD4$^+$ T$_{\text{RM}}$ cells only rarely. However, the small subset of lung CD4$^+$ T$_{\text{RM}}$ cells that does have CD103 shows similar characteristics to CD8$^+$ T$_{\text{RM}}$ cells, including the absence of Hobit protein, a transcriptional signature reflecting Notch signaling and resting levels of proinflammatory mediators and cytotoxic proteins.[129,150]

CD4$^+$ T$_{\text{RM}}$ cells provide strong protection against respiratory infection. Using adoptive transfer, memory CD4$^+$ T cells from the lungs of mice recovered from influenza infection are far superior to splenic counterparts with identical antigen specificity in conferring defense against subsequent infection.[143] Thus, they are sufficient to provide effective immunologic memory against respiratory pathogens. After recovery from lobar pneumococcal pneumonia, the previously infected lobe has superior protection against subsequent heterotypic pneumococcal infections compared with contralateral lobes, despite the fact that systemic immunity including circulating memory T cells and plasma antibodies should have equal access to all lobes;[149] in this setting, CD4$^+$ T$_{\text{RM}}$ cells localize to the previously infected lobe and their depletion compromises subsequent defense.[149,151] These CD4$^+$ T$_{\text{RM}}$ cells accelerate neutrophil recruitment compared to infections in naïve lungs,[149] which they do by instructing epithelial cells to ramp up production of a neutrophil-attracting chemokine.[151] These data suggest that resident lung CD4$^+$ T$_{\text{RM}}$ cells are essential for effective immunologic memory against respiratory pathogens, and that hastening inflammation in the lungs is a major role of pulmonary CD4$^+$ T$_{\text{RM}}$ cells.

Whether, when, and how $CD4^+$ T_{RM} cells influence pulmonary pathophysiology is only now beginning to be considered. In mouse models of house dust mite allergy-driven airways disease, both circulating and resident $CD4^+$ T cells contribute to inflammation and sequelae, but distinctly.[145,146,152] While circulating cells amplify the perivascular recruitment of eosinophils and T cells, the lung $CD4^+$ T_{RM} cells are responsible for the mucus metaplasia, airway hyperresponsiveness, and activation of recruited eosinophils.[145,146,152] $CD4^+$ T_{RM} cells are also induced and responsible for airway hyperreactivity in a more reductionist model involving ovalbumin (OVA)-induced allergic responses in the lung.[153] These data implicate $CD4^+$ T_{RM} cells in driving the deleterious pulmonary inflammation in asthmatic airways. $CD4^+$ T_{RM} cells may be involved in the pulmonary inflammation of additional lung diseases, but further studies are needed.

Again, resident memory T cells stray from textbook depictions. Lung $CD4^+$ T_{RM} cells do not recirculate through the blood and secondary lymphoid organs, looking for antigen-presenting cells. Instead, they reside in the lungs and influence local immunity. They are capable of being cytotoxic T cells that eliminate infected cells, and they are important sources of local cytokines that modulate inflammatory responses in the lung.

■ Lung-Resident Memory B Cells

The concept of lung-resident memory B (B_{RM}) cells has been established recently,[154] based largely on studies of mice recovering from influenza infection. The lungs of such mice contain increased numbers of memory B cells.[155–157] These cells are in extravascular compartments;[157,158] they express the CD69 marker that distinguishes T_{RM} cells from other resting T cells;[157–159] and they do not recirculate based on parabiosis studies.[157] Upon adoptive transfer to naïve mice, memory B cells from the lung provide superior protection compared with their counterparts from the spleen.[159] Lung memory B cells produce multiple isotypes of antibodies against influenza when stimulated;[156,157] the lung, in particular, harbors memory B cells with immunoglobulin B cell receptors capable of recognizing heterotypic strains of influenza.[158] In concert, these data support the concept that, like T_{RM} cells, B_{RM} cells populate lung tissues after recovery from pulmonary challenge and improve protection against respiratory infection (Table 20-3).

While mouse models of recovery from influenza infection are instructive, they involve persistent pulmonary pathology that includes bronchus-associated lymphoid tissue (BALT) and dysplastic epithelial structures.[160,161] B_{RM} cells also arise in lungs of mice that recovered from pneumococcal pneumonia, displaying neither BALT nor dysplastic epithelium.[162] These lung B_{RM} cells are in the loose connective tissue of bronchovascular bundles (Fig. 20-1), often near $CD4^+$ T_{RM} cells.[162] They produce antibodies against heterotypic strains of pneumococcus.[162] In addition to CD69, they are characterized by surface expression of PD-L2, CD73, and/or CD80, and depletion of $PD\text{-}L2^+$ B cells from the lungs renders recovered mice more susceptible to pneumonia caused by heterotypic pneumococci.[162] Collectively, these data suggest that B_{RM} cells in histologically normal lungs are essential for optimal protection against heterotypic respiratory infection.

Healthy human lungs contain B cells, but they are far less abundant than T cells.[118] Memory ($CD27^+$) B cells in human lungs have CD69, but not CD38 or CD83 on their surface,[162] suggesting that they are resident rather than recently activated memory B cells. Memory B cells recognizing influenza virus are found in the lungs (as well as secondary lymphoid organs) and have an increased presence compared with peripheral blood.[163] The specificities and functions of lung B_{RM} cells, including their contributions to immunologic memory and to inflammation in the lungs, are still largely unknown and constitute important knowledge gaps requiring further investigation.

LUNG TERTIARY LYMPHOID STRUCTURES

When exposures are chronic or fail to resolve, immunologic remodeling becomes more pronounced[164–166] and can result in organized aggregates of lymphocytes, variously called *bronchus-associated lymphoid tissue* or BALT (Fig. 20-1), inducible BALT (iBALT), tertiary lymphoid organs (TLO), or tertiary lymphoid structures (TLS). Defining features for such organized structures are the clustering of T cells and of B cells into anatomically segregated, but adjacent, areas and the presence of high endothelial venules expressing peripheral node addressin (PNAd). Additional distinguishing features are the presence of fibroblastic reticular cells and follicular dendritic cells, as well as evidence of B cell germinal center reactions, class switching, and activation-induced cytidine deaminase (AID) expression for somatic hypermutation. True BALT includes all the above components, recapitulating elements of secondary lymphoid organs within the tissue of the lung. Such organized structures are observed in smokers and patients with pulmonary disease but are atypical for healthy lungs.[164–166]

Although often portrayed as a dichotomy between healthy, BALT-free and diseased BALT-containing states, the ways in which adaptive immunity lymphocytes accumulate and interact in healthy lungs may more accurately reflect a continuum between these extremes. While the naïve lungs of infants contain in effect no immunologic memory,[119] and while fully formed BALT establishes an aberrant new lymphoid organ within the lung,[164–166] the T_{RM} cells and B_{RM} cells described above are characteristic of normal lung tissue.[114,118,120,162,163] These lymphocytes likely interact with each other and with other immune and stromal cells of the lung, even when organized anatomic structures are imperceptible.[167]

Immune cell organization may be dynamic and context dependent. Biological pathways upstream and downstream of BALT[164–166] may apply to normal, healthy lungs, and the T_{RM} cells and B_{RM} cells of normal, healthy lungs may be predecessors or remnants of more organized lymphoid structures. There is two-way communication between pulmonary inflammation and these aggregates of lymphocytes with varying degrees of organization. Regardless of how organized, lymphocyte clusters and their interactions provide an immunologic "tone" to the lower respiratory tract. The importance of BALT in immunologic tone has become more evident in the era of lung transplantation. Donor lungs have greater survival if they contain BALT with abundant regulatory T cells which appears dependent upon IL-22.[168–170] These results, combined with observations of BALT governing lung immune activities during acute respiratory infections and chronic pulmonary diseases,[164–166] reveal that lung TLOs have myriad and profound effects influencing integrated immune responses within the lower respiratory tract.

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CHAPTER 21

Mast Cells and Eosinophils

Edward S. Schulman
Peter H.S. Sporn
Amali E. Samarasinghe

INTRODUCTION

Hematopoietic stem cells that differentiate into common myeloid stem cells give rise to granulocytes that include mast cells (MC), eosinophils, basophils, and neutrophils. In addition to the shared heritage, granulocytes share physical and functional similarities. MCs and eosinophils are popularly known for their presence and function during allergic diseases. Because physicians have noted a clear connection between mast cell activation and the subsequent appearance of eosinophils both within the circulation and in tissues for over a century, MCs and eosinophils are considered together in this chapter.

Both cell types were discovered in the 1870s by the same observer, Paul Ehrlich, who noted that some cells stained in a peculiar fashion when incubated with standard aniline dyes such as toluidine blue and alcian blue. He used the term *metachromasie* or metachromasia to describe the peculiar color modifications that occurred and the term *Mastzellen*, meaning "well fed" or "fattened" in German, to describe what we now call MC. Interestingly, this latter term is now known to be a misnomer, since MC cytoplasmic granules are not phagocytized but rather synthesized during cell growth and again during regranulation. Ehrlich also noted that some cells stained intensely when incubated with the acidic dye eosin. As a result, these cells were called *eosinophils* to mean "eosin lovers." Both cell types have been evolutionarily conserved (albeit with some differences among species), underscoring their importance to the immune system. Studies of these two cell types, over the ensuing years, have provided great insight into their roles in biology both in health and in disease.

MAST CELLS

The capacity of strategically localized MCs to rapidly release an assortment of powerful chemical mediators makes this cell a unique member of the body's immune response network. Although most frequently discussed in the context of hypersensitivity immune responses, MCs are also known to participate in normal physiologic processes including gastric acid secretion,[1] angiogenesis,[2,3] lipid clearance,[4–8] and host defense.[9,10] MCs also participate in nonallergic pathophysiologic processes such as inflammatory bowel disease,[11,12] arthritis,[13] scleroderma,[14,15] tumors, interstitial pulmonary fibrosis,[16–19] envenomation,[3,20–23] and atherosclerosis.[4,5,24,25] Over the years, basophils have been confused with MC in a number of contexts.[26] This confusion is due, in part, to a number of similarities between the cells, including the shared expression of FcεRI (high-affinity receptor for Fc fragment of immunoglobulin E, IgE), release of preformed histamine, and metachromatic staining. However, MCs are mononuclear cells and are almost exclusively localized to tissues. In contrast, basophils are circulating polymorphonuclear cells that are found occasionally in tissue reactions, including the late-phase allergic response. In addition, significant differences in these two cell populations exist in their cell lineage, ultrastructure, mediator release biochemistry, mediator profiles, pharmacology, and surface antigenicity.

Origins of Mast Cells

MCs are believed to be derived from pluripotent hematopoietic stem cells.[27–29] Tryptase-negative MC colony–forming cells leave the bone marrow and circulate with a surface phenotype that is Lineage$^-$, CD (cluster of differentiation) 34$^+$, c-kit (CD117)$^+$, CD13$^+$, CD135$^+$, CD45RA$^-$, and CD14$^-$.[30] MC progenitors express the α4β1 integrin (VLA-4), which regulates adhesion to activated endothelial cells.[31] The agranular mononuclear monocyte progenitors home in a tissue-specific manner where they complete differentiation, maturation, and synthesis of granule proteases in response to microenvironmental factors, including the matrix and chemokines from fibroblasts, endothelial cells, airway smooth muscle cells, and possibly T cells. Lung inflammation-induced recruitment of progenitors requires both α4β7 and α4β1.[27] The microenvironmental factor most critical in chemotaxis, differentiation, adhesion, proliferation, maturation, and survival is stem cell factor (SCF) which is the ligand for c-kit tyrosine kinase receptor. This receptor is expressed on the MC surface throughout its life span.[32,33]

Morphology

All MCs are round/elongated mononuclear cells ranging from 8 to 20 μm in size with heterogeneous cytoplasmic granules (Fig. 21-1).[34,35] Cell membranes are outlined by short, narrow surface folds.[36–39] A variety of granule-filling patterns that can be affected by cross-sectioning occur within individual cells: scrolls, crystals, particles (the least seen in pure form), and combinations (mixed). Each MC may contain up to 1000 secretory granules that range from 200 to 800 nm in diameter and outlined by a perigranular membrane.[40]

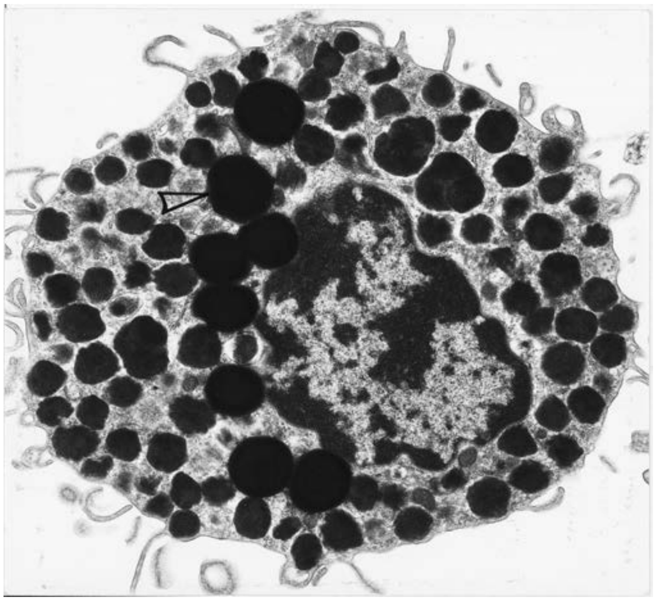

Figure 21-1 Ultrastructure of the human lung mast cell after purification. The mast cell is a mononuclear cell packed with multiple dense cytoplasmic granules that vary in size and shape. Eight electron-dense lipid bodies *(open arrow)* are bunched near the nucleus (×15,000). *(Reproduced with permission from Galli SJ, Austen KF: Mast Cell and Basophil Differentiation and Function in Health and Disease. New York, NY: Raven; 1989.)*

Mast Cell Heterogeneity

Striking differences in the morphology, T cell dependence, resident proteoglycans, and responsiveness to secretagogues and drugs have been described in human MC.[34,41–47] The ontogeny of this heterogeneity, as well as the differing roles these MC play in physiology and disease remain speculative.

The most common classification of human MC is based on the expression of protease profiles as determined by immunohistochemical staining using monoclonal antibodies. According to this system, the serine proteinase tryptase (T) is expressed in virtually all human MC, and a subset, predominantly in the submucosa of the gut and in the skin and within asthmatic airway smooth muscle also express chymase (C) and multiple other proteases including carboxypeptidase A3 (CPA3) and cathepsin G. Mast cells that express tryptase alone are classified as the MCT type, and those with additional proteases as the MCTC type.[48–50] Because significant numbers of both types can be found in the same organ (e.g., lung), tissue location cannot dictate the protease type. In the lung, only 8% to 35% of MCs are MCTC, 1% is MCC, and the remainder are MCT. The protease system does follow some rules of distribution and function. MCT are preferentially localized in bronchi, bronchioles, mucosal surfaces, alveolar parenchyma, lamina propria, and areas of T cell infiltration, and they are reduced in immunodeficiency syndromes. The MCTC phenotype does not appear immune related and is more prevalent in pulmonary vessels and pleura. As detected by immunohistochemical staining, the MCTC subtype more selectively expresses interleukin 4 (IL-4) (85% MCTC vs. 15% MCT). IL-5 and IL-6 are almost exclusively restricted to the MCT subtype. Within human lung, different compartments appear to show site-specific expression of FcεRIα, IL-9 receptor, histidine decarboxylase (higher in MCT of bronchi than MCT of alveoli), 5-lipoxygenase, leukotriene (LT)C$_4$ synthase, vascular endothelial growth factor (VEGF), basic fibroblast growth factor (FGF),[51] and renin.

Human lung mast cell (HLMC) diameters vary between 8 and 18 μm with the majority being 12 to 15 μm. Histamine contents of 2.5 to 10.0 pg/MC vary directly with cell diameter. HLMC densities vary from 1.053 to 1.123 g/mL with the majority (67%) between 1.077 g/mL and 1.088 g/mL These diameter- and density-based subtypes also are distinct with respect to mediator content and function. MC location also subserves function: airway and parenchymal MC differ in their granule secretion. Finally, at least two types of proteoglycans are present in HLMC: chondroitin sulfates, predominantly chondroitin sulfate E, and heparin. HLMCs are both positive and negative for the heparin-sensitive dye berberine sulfate, whereas stomach MCs synthesize exclusively chondroitin sulfate E and not heparin.[52,53]

Anatomic Localization

MCs are present in all organs but are particularly abundant in the nose, skin, gastrointestinal tract, and lung. They reside primarily near blood vessels, within the adventitia of arteries, and near lymph vessels and nerves.[54–56] HLMC are estimated to range from 500 to 4000 per mm^3 of tissue. In non-asthmatics, HLMCs localize to submucosal connective tissues and not epithelium or smooth muscle. Although data in asthmatics are conflicting as to whether the numbers MCs are increased versus non-asthmatics, MCs localize to three critical sites: bronchial epithelium,[57] airway mucus glands,[58] and within smooth muscle.[59–62] Mediator release from the small numbers of HLMCs within the epithelium may subserve initial antigen recognition and also be strategically placed to respond to nonantigenic signals, including hyperosmolarity,[63] as well as "endogenous" mediators, including extracellular adenosine and adenosine 5′ triphosphate (ATP).[64–66] In the case of aeroallergens, permeabilization resulting from epithelial MC mediators enhances further antigen penetration to deeper airway smooth muscles and mucus glands, which in turn, promotes bronchoconstriction and mucus secretion, respectively. The finding of HLMC within the smooth muscle layer appears to be a common and critical finding in asthmatics. It is an uncommon finding in non-asthmatics and in patients with eosinophilic bronchitis. Other than MC localization to alveolar smooth muscle, the latter condition has virtually identical structural remodeling changes to asthma but is not associated with obstruction or airway hyperresponsiveness (AHR).[59,67] In the lung periphery, abundant MCs reside within small airways and in the alveolar septa, within a few microns of the alveolar lumen.[65] The small numbers of MC in bronchoalveolar lavage (BAL) fluid (≤0.1% of all cells) likely result from epithelial shedding.[55,68]

Perivascular MC are also important in the initiation and unfolding of lung hypersensitivity responses. Recently, a novel mode of antigen delivery to pulmonary perivascular MC has been described. Intravascular projections from perivascular dendritic cells continuously sample blood for antigens. Dendritic cells then rapidly feed antigen-bearing microvesicles to neighboring immune cells including mast cells.[69]

Activation

Immunologic allergic activation of MC is the mechanism most studied.[70] It results from allergen cross-linking of allergen-specific cell surface IgE molecules and subsequent aggregation of IgE-high-affinity receptors (FcεRI) to which they are attached.[71,72] Receptor dimerization is the minimum cross-linkage requirement for initiation of IgE-mediated activation. In vitro, immunologic MC activation can be achieved using animal-derived or monoclonal antibodies directed against human IgE or the FcεRI-receptor itself. The mechanism(s) involved in chronic HLMC activation characteristic of asthma are not known but likely reflect low-level allergen activation. Monomeric IgE alone, in the absence of antigen, has been reported to induce prolonged mediator release, a mechanism that may be operative within the asthmatic airway.[73] Many mast cell-related reactions are triggered by non-IgE mechanisms. These reactions have been termed "pseudo-allergic" reactions or "nonallergic anaphylaxis."[74] These triggers include opioid drugs, calcium ionophores, hyperosmolar stimuli, "histamine-releasing activities" derived from human alveolar macrophages and other cells,[75–78] basic compounds (e.g., 48/80), neuropeptides (e.g., substance P and hemokinin-1), and cationic ligands including many U.S. Food and Drug Administration (FDA)-approved drugs (e.g., atracurium, ciprofloxacin) (reviewed by Thapaliya et al.[79]). In general, the profile of agents that degranulate MC from human intestine and synovium is similar to that of HLMC but different from skin MC. Even within lung compartments, responsiveness to triggers may vary. Compound 48/80 is reported to degranulate BAL MC, whereas those from lung parenchyma are minimally responsive. Bee venom phospholipase (PLA)2 and antigens from dust mites, cockroaches, pollens, and fungal spores contain phospholipases and proteases, which can lead to MC release through the protease-activated receptor (PAR) 2.[80,81]

The MC receptor responsible for mediating effects of compound 48/80, substance P, hemokinin 1, and cationic drugs recently was identified as MRGPRX2 (MAS-related G protein–coupled receptor X2) in humans and the mouse ortholog as MRGPRB2.[82] Human dermal mast cells have markedly higher transcript levels of MRGPRX2 than HLMC, which explains the relative in vitro unresponsiveness of HLMC to 48/80 and neuropeptides.[83,84] However, HLMC upregulation of MRGPRX2 has been reported in asthma-related deaths vs. non-asthma related deaths.[85] Neutrophil cathelicidin (LL-37), eosinophil major basic protein, and peroxidase and epithelial β-defensins, all implicated in asthma, activate human MC via MRGPRX2. The purified anaphylatoxin C5a, an active trigger of human basophils and dermal MC, is generally inactive in HLMC,[86,87] although CD88, the receptor for C5, has been reported in the MCTC.[88]

IgG/antigen immune complexes via FcγR can trigger MC-induced anaphylaxis in high-dose antigen reactions (e.g., intravenous administration of drug). The immune complexes can also act by blocking low-dose antigen access to IgE and interacting with the inhibitory receptor FcγRIIB. Thus, this dual role IgG can play is dependent on antibody and antigen concentrations.[89]

In both mouse MC and human progenitor–derived MC, several innate pathogen-associated molecular pattern recognition receptors (PAMPs), including Toll-like receptors (TLRs), have been reported. TLR-2 and -4 have been reported in HLMC.[90–92] The expression of TLR and effects on activation of HLMC remain poorly defined. Human peripheral blood–derived cultured MCs are reported to express TLR-1, TLR-2, TLR-4, TLR-5, TLR-6, TLR-7 and TLR-9. They also produce type I IFNs following exposure to double-stranded RNA and or virus, the former confirming functional TLR-3 expression.[90]

Finally, the immunoglobulin superantigens protein A of *Staphylococcus aureus* and protein L of *Peptostreptococcus magnus* can directly induce HLMC mediator release.[93] The superantigens bind to the variable regions of either the heavy (V_H3) or light chain (κ) of IgE. Angiogenic (VEGF-A) and lymphangiogenic (VEGF-C) factors also were rapidly in 30 minutes released along with histamine, a response enhanced after prolonged (12 hour) HLMC preincubation in IL-33.[93]

Modulators of Activation

Although not acting as direct release triggers, several endogenous chemicals in the MC microenvironment and/or their receptors can influence activation. Extracellular adenosine triphosphate (ATP) and its breakdown product, adenosine, are potent modulators of HLMC degranulation, although neither directly activates HLMC degranulation in vitro.[64–66,94,95] Adenosine exhibits a bimodal effect on IgE-mediated HLMC challenge: enhancing histamine release at 10^{-6} to 10^{-4} M and inhibiting release at 10^{-3} M. ATP (10^{-4} M), at local concentrations achievable in vivo, consistently enhanced anti-IgE–induced histamine release. The adenine nucleotides consistently enhanced anti-IgE–induced histamine release; the rank order for this action was ATP > 2mSATP (2-methyl-thio-ATP) >α,βmATP (α,βmethylene-ATP) >β,γmATP (β,γmethylene-ATP), suggesting mediation by a P2Y-purinoceptor subtype. P2X7, strongly expressed on the HMC-1 cell line and mouse mast cell models, is not expressed in freshly isolated and purified HLMC. In asthmatics, aerosolized adenosine induces bronchoconstriction, an effect not observed in other groups of pulmonary patients or normals.[96] The ability of antihistamines to inhibit this response has directly implicated activation of allergically primed airway MC by adenosine.[97,98] Components of the local connective tissue matrix such as fibronectin also modulate MC reactivity.[99]

Airway challenge with allergens, viruses, and irritants can trigger release of epithelial alarmins such as IL-33, IL-25, and thymic stromal lymphopoietin (TSLP).[100] IL-33 primarily binds to the IL-1 receptor family member ST2. IL-33/ST2 complex assembles with the IL-1 receptor accessory protein (IL-1RAcP), which is needed for signal transduction. ST2 is highly expressed on Th2 cells and group 2 innate lymphocytes. In lung samples from patients with severe asthma, IL-33 expression was higher than in those with mild asthma. Peripheral blood CD34+ precursor-derived mast cells and HLMCs pretreated with IL-33 showed enhanced degranulation responses.[93,101] HLMCs robustly express ST2 both intracellularly and on their surface. Expression is markedly enhanced within 2 hours of IgE-mediated stimulation. In a purified HLMC microarray analysis, ST2 is the fourth most expressed cytokine-related gene only preceded by granulocyte macrophage-colony stimulating factor (GM-CSF), IL-8, and IL-3.[102] It should be noted that these most abundantly expressed HLMC cytokines (GM-CSF and IL-3) appear to be vital to create an asthmatic milieu in a “next-generation” humanized mouse model, IL-3/GM-CSF or IL-3/GM-CSF/IL-5 transgenic (Tg) NOD/Shi-*scid*-IL2rγ^{null}(NOG) mouse. This GM-CSF/IL-3 milieu produces a human type-2 allergic immune response in which human myeloid cells including mast cells, basophils, and eosinophils differentiate and maturate.[103]

In human peripheral blood– or cord blood–derived MC, TSLP alone does not trigger degranulation, but in combination with IL-1β or TNF-α it releases several cytokines and chemokines.[104,105] Human lung biopsies demonstrate expression of TSLP in bronchial and submucosal mast cells. Asthmatic airways have a higher percentage of MCs expressing TSLP compared to non-asthmatic controls. Both airway smooth muscle and mast cells embedded within express TSLPR.[106]

Human bone marrow–derived MC produce IL-25 following IgE-mediated stimulation.[107] HLMC express IL-25 mRNA transcripts constitutively and levels increase within 2 hours of IgE-mediated stimulation.[102]

Although most research in MC has been performed on receptors that mediate activation, MC responses can involve cross talk with inhibitory signals. A number of the MC inhibitory receptors contain **i**mmunoregulatory **t**yrosine **i**nhibition **m**otifs (ITIMs). Following inhibitory receptor activation, these regions are phosphorylated and then recruit phosphatases that dephosphorylate key signaling molecules.[108] ITIM-containing MC inhibitory receptors include platelet-endothelial cell adhesion molecule 1 (PECAM-1,CD31), Fc-gamma-RIIb,[89] CD300a,[109] the c-lectin mast cell function–associated antigen (MAFA),[110] and sialic acid–binding immunoglobulin-like lectins (Siglecs). The latter are expressed on MC and eosinophils (see “Eosinophils,” below).[111] HLMCs express mRNA for Siclec-6 but not Siglec-8.

Biochemical Analysis of HLMC Activation

Elegant studies defining the biochemical events following IgE-mediated activation have been performed in rodent MCs or cell lines.[112,113] Evaluations of similarities and differences in HLMC activation await future investigations. Two receptors for IgE have been identified. The FcεRI on MC and basophils is expressed in a tetrameric form (αβγ2). On platelets, neutrophils, monocytes, eosinophils, smooth muscle, and antigen-presenting cells the IgE receptor is present in a trimeric form (αγ2). The Fc fragment of IgE binds to the α-chain of FcεRI. Expression of the β-chain amplifies signaling. A low-affinity IgE receptor (FcεRII; CD23) is present on B cells but not on MC or basophils.[114] Serum IgE levels correlate with basophil expression of FcεRI, likely indicating a role for IgE in stabilizing the FcεRI on the cell surface. As noted earlier, receptor dimerization is the minimum cross-linkage requirement for antigen-mediated allergen activation through the FcεRI. Following receptor aggregation, multiple signal transduction pathways are activated. Since FcεRI possesses no inherent tyrosine kinase activity, critical to the sequential activation are two tyrosine kinases: Lyn, which is associated with the β chain, and Syk. Lyn binds to the β-chain–associated immunoreceptor tyrosine-based activation motifs (ITAMs), which are phosphorylated after FcεRI aggregation. For degranulation to proceed, Syk then binds to the γ-chain–linked ITAMs, which are also phosphorylated after receptor aggregation. The Lyn:Syk-driven pathway directly or indirectly stimulates tyrosine phosphorylation of several adapter proteins, including the transmembrane adaptor molecule linker for activation of T cells (LAT) among others. These events lead to the generation of inositol triphosphate (IP3), which induces Ca^{2+} mobilization from intracellular rough endoplasmic reticulum stores. Phospholipase C-γ1 and PLC-γ2 are also activated.[115–123] In this context, at 2 min following FcεRI aggregation, extracellular calcium influx occurs through CRACM channels (Ca^{2+} release–activated Ca^{2+} [CRAC] modulator 1),[124,125] which is a prerequisite for degranulation to proceed over the next 5 to 20 min. Other “early-phase” granule-associated and lipid mediators (e.g., arachidonate metabolites) also are released over 20 min. Over the ensuing 1 to 24 h, mRNAs for select cytokines are generated followed by their protein synthesis and release.

Morphology of Degranulation and Regranulation

Following IgE-mediated (anaphylactic) activation of HLMC, granules swell and their perigranular membranes fuse to form canaliculi that open through multiple pores to the cell exterior. Within 20 minutes of activation, granular matrix materials solubilize within these intracytoplasmic channels and empty. In HLMC, only rarely is extrusion of non-solubilized granules observed. Lipid bodies (LBs), which are electron-dense non-membrane-bound organelles,[126–129] remain adjacent to these channels. They appear to serve as repositories of arachidonic acid and occasionally release lipid into the degranulation channels. In vivo, a process termed *piecemeal degranulation* (PMD) is more frequently observed than anaphylactic degranulation.[130] This process involves the budding of small vesicles from granule membranes and their movement to the cell surface. PMD may be more typical of the ongoing MC release observed in chronic asthma.

Depending on the extent to which an individual cell has degranulated, one of two predominant types of regranulation are observed individually or in combination. In partially degranulated cells, the channel (formerly perigranular) membranes are reutilized, and regranulation events resemble degranulation in reverse. In cells with more complete degranulation, the channel membranes are placed in continuity with the plasma membrane and externalized. This results in the appearance of elongated, activated cell surface folds. These excessive folds can be internalized or shed. Shedding results in cells that are initially small (7 μm) but then enter a rapidly expanding recovery cycle to produce a fully mature cell.

Chemical Mediators

The clinical expression of MC-mediated responses may reflect the individual mediators or, in certain instances, the interplay of the multiple mediators these cells release (Table 21-1). The temporal sequence of their release appears critical to the development of both the early- and late-phase responses after antigen challenge (Fig. 21-2). Certain mediators are virtually unique to MC (e.g., tryptase, chymase, heparin), and others are shared with one or more other cells (e.g., histamine, LTC_4, and IL-5).

Mediators released within minutes after activation are divided into preformed, or secretory, granule-associated mediators (e.g., histamine) and non-preformed, or newly synthesized mediators (e.g., lipids). It is now known that tumor necrosis factor alpha (TNF-α) may be both preformed and newly synthesized. Other cytokine mediators, including IL-5 and IL-13, are detected over hours and may be critical to the evolution of the "late-phase" response.

Preformed Mediators

Below we discuss a number of preformed mediators, including histamine, proteoglycans, chemotactic factors, and proteases.

Histamine

Histamine is produced by several cell types that express the enzyme histidine decarboxylase that synthesizes histamine from histidine. The cells that can secrete histamine but cannot store it include neutrophils, macrophages, monocytes, and keratinocytes. MCs and basophils can both store and secrete histamine.

Histamine measurements have served as a classic marker of MC-mediated events. The pleiotropic effects of histamine are mediated through the differential expression, regulation, and distinct intracellular signals evoked by four distinct receptors, H1, H2, H3, and H4. Only the H4 receptor has been reported to be both expressed and functional (chemotaxis) in HLMC.[131] The actual role of histamine in asthma remains less clear, although levels in BAL fluid are many-fold higher in asthmatics and plasma levels rise three- to five-fold following airway antigen challenge. Most histamine-induced allergic respiratory reactions are mediated via the H1 histamine receptor subclass, producing enhancement of vascular permeability, mucus production, initiation of neurogenic reflexes, and bronchial smooth muscle contraction. The reasons for the marginal value of the H1 receptor–blocking drugs in asthma may be due to high local tissue concentrations of histamine that exceed the inhibitory capacity of these agents and/or the redundancy of histamine actions with the multiple other mediators that are released.

TABLE 21-1 Human Mast Cell and Eosinophil Mediators

	Mast Cells	Eosinophils
Granule-associated (preformed) mediators	Histamine	MBP
	Heparin	ECP
	Chondroitin-sulfate E	EDN
	TNF-α	EPO
		CLC protein
Enzymes	Tryptase	EPO
	Chymase	ECP, EDN
	Cathepsin G	Collagenase
	Elastase	MMP-9
	Carboxypeptidase-A	Indoleamine 2,3-dioxygenase
Acid hydrolases	β-hexosaminidase	β-glucuronidase
	β-glucuronidase	Arylsulfatase B
	Arylsulfatase	
Lipid mediators (non-preformed)	PGD_2	LTC_4
	LTC_4	15-HETE
	LTB_4	5-oxo-ETE
	PAF	PAF
	Thromboxane-A_2	
Cytokines	IL-4, IL-5, IL-13	IL-1α, IL-2, IL-3
	IL-6, IL-8	IL-4, IL-5, IL-6, IL-8
	TNF-α	IL-10, IL-12, IL-13
	TGF-β	IL-16, IL-17
	bFGF	GM-CSF
		TNF-α
		TGF-α
		TGF-β
		SCF
		NGF
		PDGF
		VEGF
Chemokines		CCL3
		CCL5
		CCL13
		CCL11
Reactive oxygen products	None detected	$O_2\bullet^-$, H_2O_2, OH HOBr, HOCl

Proteoglycans

MC proteoglycans serve as the major determinant for the metachromatic tinctorial properties of the cell and form the granule backbone to which other preformed mediators, including histamine and neutral proteases, are bound. HLMCs synthesize heparin

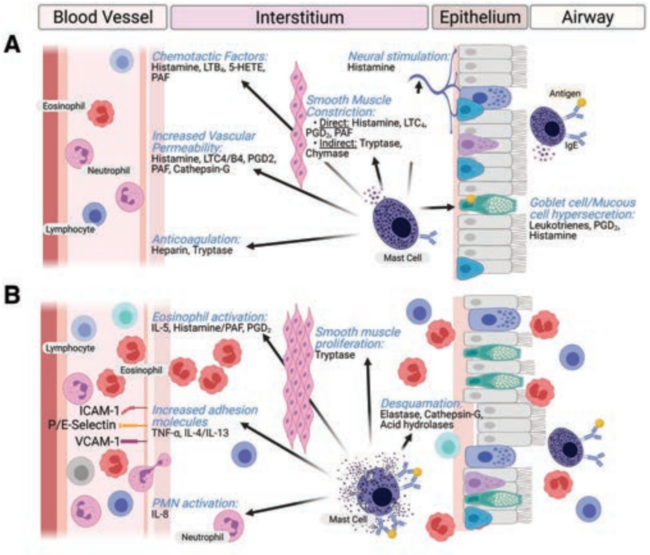
Blood Vessel
Interstitium
Epithelium
Airway
A
Chemotactic Factors:
Histamine, LTB$_4$, 5-HETE, PAF
Neural stimulation:
Histamine
Eosinophil
Smooth Muscle Constriction:
• Direct: Histamine, LTC$_4$, PGD$_2$, PAF
• Indirect: Tryptase, Chymase
Antigen
IgE
Increased Vascular Permeability:
Histamine, LTC4/B4, PGD2, PAF, Cathepsin-G
Neutrophil
Goblet cell/Mucous cell hypersecretion:
Leukotrienes, PGD$_2$, Histamine
Lymphocyte
Anticoagulation:
Heparin, Tryptase
Mast Cell
B
Eosinophil activation:
IL-5, Histamine/PAF, PGD$_2$
Smooth muscle proliferation:
Tryptase
Lymphocyte
Eosinophil
Desquamation:
Elastase, Cathepsin-G, Acid hydrolases
ICAM-1
P/E-Selectin
VCAM-1
Increased adhesion molecules
TNF-α, IL-4/IL-13
PMN activation:
IL-8
Mast Cell
Neutrophil

Figure 21-2 Effects of mast cell mediators in the early- and late-phase responses following airway allergen challenge. **A.** Early phase: Mediators are released within minutes following antigen cross-linking of allergen-specific IgE on the cell surface. Mechanisms of the initial airflow obstruction that persists for 30 to 60 minutes include smooth muscle constriction, edema formation due to increased vascular permeability, nerve stimulation, and mucus hypersecretion from both goblet cells and submucosal glands. **B.** Late phase. Within hours, the effects of newly synthesized and released cytokine mediators along with delayed effects of early-phase mediators produce recurrent airway obstruction. Mast cell mediators and cytokines can increase the expression of adhesion molecules on endothelial cells, both recruit and activate leukocytes (particularly eosinophils), contribute to epithelial desquamation, and stimulate smooth muscle proliferation.

and chondroitin sulfate E proteoglycans in roughly a 2:1 ratio.[52] In humans, heparin appears to be unique to MC. In addition to anticoagulant activity, heparin possesses both anti-inflammatory and immunoregulatory properties.[132–134] Heparin may limit allergic responses in the skin, nose, and lung and exert protective effects on exercise-induced asthma (EIA). The inhibitory effects may be related to the extracellular binding and inhibition of multiple mediators, including histamine and cytokines.

Chemotactic Factors

Within hours of MC activation, airway inflammation (the late-phase response) at the tissue level is characterized by the infiltration of leukocytes. This response is principally eosinophilic but also contains neutrophils and, over time, lymphocytes. Chemotactic mediators may be derived directly from MC and/or other cells through secondary stimulation. Early-phase MC-derived eosinophilic chemotactic activities include LTB$_4$, platelet-activating factor (PAF), and histamine.[135] HLMCs robustly express CXCL8 (also known as IL-8), which along with LTB4, attracts neutrophils. MCs are responsive to chemokines released from other cells. Airway smooth muscle secretes a number of chemotactic factors including CXCL-8, CXCL-10 (also known as interferon gamma–induced protein, IP-10), CXCL-11 (also called interferon-inducible T cell alpha chemoattractant, I-TAC), and CXCL-12 (also known as stromal cell–derived factor 1, SDF1). It appears that the CXCR3/CXCL10 axis predominantly mediates the HLMC migration into the airway smooth muscle observed in asthmatic airways.[136,137]

Proteases

Large quantities of neutral proteases are contained within MC and constitute the predominant protein component of the secretory granule. The proteases include tryptase, chymase, cathepsin G, carboxypeptidase A3, and elastase.[48–50,138]

Tryptase is the predominant neutral protease of the MC granule. Within the MC granule, tryptase is a tetramer that is stabilized by its association with heparin proteoglycan. The concentration of tryptase in pulmonary MC is 11 pg per MC. Since the concentration of tryptase in circulating basophils is more than 100 times lower than in MCs, responses characterized by the presence of histamine but not tryptase at a reaction site or in the circulation implicate mediation by basophils and not MC.

Two genes produce tryptase: *TPSAB1*, which can encode alpha (α)- and beta (β)-protryptase; and *TPSB2,* which encodes only β-protryptase. All humans appear to produce β-protryptase; α-protryptase is lacking especially in those of Asian (10%), European (23%), or African (41%) ancestry.[139] The amount of protryptase protein expression can vary dependent on the number of gene copies of each (e.g., 1 to 5 copies). Further, their ratios can result in an α- vs. β-tryptase “dosage effect.” This ratio can have clinical consequences.[140,141] Resting MCs continuously, spontaneously, and without activation release large portions of synthesized α- and β-protryptases into the circulation. Therefore, the basal “total” tryptase level from a blood draw is genetically determined.

A fraction of protryptases are converted to proteolytically active mature tryptase, which spontaneously forms donut-shaped tetramers and are stored in secretory granules in unstimulated MCs. Following activation, such as in IgE-mediated allergic reactions, the tetramers are released complexed to heparin proteoglycan and result in acutely elevated tryptase levels. If all four components of the tetramer are α- (α- homo-tetramer) the tryptase is proteolytically inactive; β- homo-tetramers and α/β— hetero-tetramers are both proteolytically active. The α/β— hetero-tetramer has altered substrate specificities from β- tryptase homo-tetramers. Only α/β-tryptase has been shown to induce vibration-triggered degranulation in both dermal and HLMC. This results from cleavage of the α subunit of the EGF-like module–containing mucin-like hormone receptor-like 2 (EMR2) mechanosensory receptor. The α/β-tryptase if present can selectively activate protease-activated receptor-2 (PAR2), which is expressed in smooth muscle, neurons, and alveolar endothelium. Released extracellular tetrameric tryptase dissociates over time into inactive monomers as its natural mechanism of inactivation.

Postulated roles for β-tryptase in pathophysiology remain to be established. Described actions include the degradation of the neuropeptide vasoactive intestinal peptide (VIP) and of muscle-relaxing neuropeptides, mitogenic effects on smooth muscle and epithelial cells, and inactivation of procoagulant proteins. Increased levels of tryptase in BAL fluid correlated to asthma severity, with severe asthma patients exhibiting the highest levels. While there were no differences in plasma tryptase levels between healthy volunteers and mild to moderate asthma patients, levels were significantly elevated in severe asthma patients and uncoupled from type 2 biomarker levels.[142]

Chymase is a serine protease that is essentially confined to MC. It is associated with heparin in a manner like tryptase. Although many activities continue to be reported in different pathophysiologic settings, the role of chymase in asthma and other airway disorders is not clearly defined.[143] Chymase may play a role in tissue remodeling. Substrates include angiotensin I, converting it to angiotensin II, VIP (inactivates), substance P, bradykinin, and kallidin (inactivates). Other activities include activation of matrix metalloprotease and stimulation of tissue neutrophilia and eosinophilia.[144]

Cathepsin G is a neutral protease with chymotryptic specificities. The concentration of cathepsin G in HLMC is roughly 100 to 700 ng/10^6 cells.[138] An elastase released from HLMC appears to be identical to human neutrophil elastase.[138] A measurement of 40 to 170 ng/10^6 cells assumes all HLMCs contain this enzyme, although it may be localized to an HLMC subset. Among carboxypeptidases, the MC carboxypeptidase A3 (CPA3), a zinc metallo-exopeptidase, is unique.[145] In eosinophilic type 2 asthma, CPA3 has recently been prominent in multiple gene signature studies.[146,147]

Granule-associated acid hydrolases include β-hexosaminidase, β-glucuronidase, and arylsulfatase.

■ Non-Preformed Mediators

Arachidonic acid metabolites are generated within minutes of MC activation and play a crucial role in the early phases of the asthmatic response. Cyclooxygenase metabolism in MC generates large quantities of prostaglandin (PG) D_2 and a small quantity of thromboxane A2.[65,148] PGD_2 can be produced by a number of cell types through the hematopoietic prostaglandin D2 synthase (H-PGDS). These cells include lung endothelial cells megakaryocytes, platelets, monocytes, T helper type 2 (T_H2) cells, and dendritic cells, although MCs are the predominant source of PGD_2. A lipocalin-type PGDS type is present in CNS and cardiac cells. PGD_2 is the most potent bronchoconstrictor of the cyclooxygenase metabolites. Additional actions of PGD_2 include induction of chemotaxis in eosinophils, basophils, and T_H2 cells, and increase in capillary permeability and vasodilation.

Although all tissue MCs generate PGD_2, not all generate significant quantities of 5-lipoxygenase products (e.g., lung >> skin). The major 5-lipoxygenase pathway products of HLMC are LTC_4, and LTB_4, with lesser quantities of 5-HETE. In IgE-mediated human lung challenges, HLMCs constitute the major source of released LTC_4,[149] although the LTC4 synthase is present in other cells including eosinophils, basophils, monocytes, macrophages, and dendritic cells. Cells such as neutrophils lack the ability to make LTC4 but can synthesize and secrete LTA4 to adjacent LTC4 synthase-competent cells to make LTC4. Released LTC4 is converted to LTD4 and LTE4. LTC4, D4 and E4 exert their effects through via three G protein–coupled receptors: CysLT1R, CysLT2R, and CysLT3R.[150] HLMCs express CysLT3R/GPR99[95], which is the high-affinity receptor for LTE4.[151] The consequences of LTE4 stimulation of HLMC are unknown but may prove important, as LTE4 is the most abundant of the leukotrienes in vivo due to its stability.

PAF is an early-phase phospholipid bronchoconstrictor that consists of a family of molecules. In contrast to the other lipid mediators, MCs appear to retain PAF intracellularly or demonstrate rapid reuptake of any that may be released. IgE-mediated activation of MCs induces the release of PAF, which plays an important role in inflammation and can be pathologic if left unchecked. PAF induces histamine release, Ca^{2+} mobilization, and chemotaxis in MCs.[152] MCs are also a source of PAF-acetyl hydrolase, which degrades extracellular PAF as an autocrine regulatory mechanism.[153]

HLMCs synthesize and release T_H2-type cytokines, including IL-5 and IL-13, which are felt to be central to the evolution of the late-phase response.[154,155] Additional multifunctional cytokines, including IL-3, IL-6, IL-8, transforming growth factor beta (TGF-β), basic fibroblast growth factor (bFGF), and TNF-α, also are synthesized by HLMCs. In general, cytokine protein products are released over a 1- to 24-hour period following allergic activation. IL-4, a cytokine that virtually defines T_H2 immunity, is immunolocalized to HLMCs, which are rich in surface IL-4 receptors. However, generation of IL-4 mRNA and protein release by HLMCs has been reported by some, but not all, investigators.[154,156] TNF-α, stored preformed within MC granules, is in a unique position to exert diverse host defense effects in allergy and innate immunity.[157] Some studies suggest that increased expression of TNF-α within HLMCs may play a role in asthmatic airway inflammation and correlates with asthma severity.[158,159]

Amphiregulin, a member of the epidermal growth factor family, is secreted following FcεRI-mediated activation. Its effects include increasing mucin gene expression, which may contribute to the epithelial cell metaplasia and mucus hypersecretion of asthma.[160]

■ Pharmacologic Modulation of Mast Cell Function

Only a limited number of pharmacologic agents have been tested in vitro on HLMC activation–secretion. In general, these agents have been tested on human parenchymal MCs rather than those in bronchi or resident in BAL.[64,65,161] Moreover, inhibitory potency has been evaluated with anaphylactic degranulation rather than PMD, the latter being more characteristic of asthma.[162,163] Several receptors that inhibit MCs activate ITIMs (see above). The common classes of anti-allergic and/or anti-asthmatic drugs used in clinical practice have received most evaluation. To date, the β-agonist pharmacologic agents, as typified by fenoterol and salmeterol, are reported to be among the most potent global inhibitors of HLMC mediator release with concentrations that inhibit histamine release by 50% (IC_{50}) of $\leq 10^{-8}$ M. Less effective inhibitors include the theophylline-like phosphodiesterase inhibitor isobutylmethylxanthine (IC_{50} = 0.5 mM) and PGE_2 ($IC_{50} = 10^{-5}$ M). Although widely touted as "MC stabilizers," disodium cromoglycate and nedocromil sodium, which have been shown as agonists at G protein–coupled receptor 35 (GPR35),[164] poorly inhibit purified HLMC histamine release.[43,165] Inhibition of BAL MC activation by these agents is reportedly more striking.[166]

The effects of glucocorticosteroids on MCs are diverse, including both stimulatory and inhibitory effects on the transcription of select genes. Release of early-phase mediators (e.g., histamine, LTC_4) in vitro and acute airway responses in vivo are unaffected by short pretreatment (up to 24 h) with these drugs. In contrast, IgE-mediated generation of TH2-type late-phase cytokine mRNA and protein (e.g., IL-5, IL-13) are suppressed ($IC_{50} = 10^{-8}$–10^{-9} M).[167]

FK-506, a macrolide that binds to a specific binding protein, inhibits HLMC mediator release at low concentrations (0.1–300 nM). Cyclosporin A, which binds to cyclophilin, and auranofin, an orally absorbable gold compound, both inhibit HLMC mediator release.

Specific inhibitors of LT generation include direct 5-lipoxygenase enzyme inhibitors, such as A-60477 (Zileuton), and indirect inhibitors, such as MK-886, which bind to a protein termed 5-lipoxygenase–activating protein (FLAP). Interestingly, PGD_2 release is markedly enhanced by FLAP inhibition. This phenomenon has been termed a "reverse shunt effect." Generally, 5-lipoxygenase pathway inhibitors do not affect HLMC histamine release. Cyclooxygenase-1 inhibition plays a critical role in a certain subset of "aspirin-sensitive" asthmatic patients. Agents such as indomethacin potently inhibit HLMC PGD_2 generation (IC50 = 5.5×10^{-10} M) while producing significant enhancement of LTC_4 release.

Stem cell factor and its receptor c-kit are critical for MC homeostasis. The drug imatinib inhibits multiple tyrosine kinases including c-kit. Severe asthmatics treated for 6 months with imatinib, a drug that has been used in chronic myeloid leukemia, showed diminished MCs in endobronchial biopsies, reduced AHR, and decreased serum tryptase compared with severe asthmatic controls.

These results support the crucial role MC and c-kit contribute to severe asthma pathogenesis.[168]

Omalizumab, a humanized monoclonal antibody, prevents binding of free IgE to the FcεRI-receptor on MC and basophils and inhibits surface FcεRI expression.[169] It is indicated in moderate to severe allergic asthma where it improves symptoms and quality of life and decreases exacerbations.[170]

Mast Cells in Pulmonary Disease

MCs have been implicated in a variety of pulmonary disorders based, to a great extent, on their presence in increased numbers and/or percentages in diseased tissues and the recovery of increased concentrations of MC-derived mediators, particularly histamine, in BAL fluid.[171,172] Implicated pulmonary disorders include asthma, idiopathic pulmonary fibrosis, sarcoidosis, hypersensitivity pneumonitis, pulmonary hypertension, cystic fibrosis, and chronic bronchitis.[47,173–176] The impact of MCs in common pulmonary diseases is highlighted below.

Asthma

MCs within airway epithelium are in an ideal sentinel position to be exposed to inhaled inciting stimuli. Intraepithelial MCs (IEMCs) produce tryptase but seldom chymase except in severe asthma[55,57] and were traditionally thought to represent the classic MCT phenotype. More recent reports assert that intraepithelial MCT in "T_H2-high" asthma also expresses CPA3, which had previously been identified only in association with MCTC.[145,177] A similar pattern is noted in asthmatic sputa, which more often show gene expression signatures for tryptase and CPA3 compared with healthy controls.[178] At baseline, even very mild asthmatics show evidence of continuous MC degranulation in bronchial mucosa and increased histamine content in BAL. Analysis of BAL in allergen-challenged atopic subjects and asthmatics demonstrates increased release of histamine, tryptase, and PGD_2. Increased numbers of luminal MC are also noted and correlate with mediator content, airflow obstruction, eosinophil numbers, and bronchial hyperresponsiveness. In general, asthmatic MCs exhibit ultrastructural evidence of degranulation. In nonfatal asthma, there is a significant increase of MCs within airway smooth muscle and mucosal gland stroma.[58] Multiple redundant MC mediators likely contribute to increased mucus gland secretion and smooth muscle constriction. Following chronic corticosteroid treatment, allergic reactions are diminished in association with depletion of MCs in both the epithelium and submucosa.

Although much attention has been given to IgE-mediated mechanisms of asthmatic airway activation, it is likely that multiple other MC-triggering mechanisms operate under a variety of immunologic, occupational, and environmental conditions. One mechanism proposed for EIA relates to airway cooling and the generation of hyperosmolarity on the dried airway surface leading to MC degranulation.

Up to 10% of asthmatics are intolerant of aspirin and other non-structurally related nonsteroidal anti-inflammatory drugs (NSAIDs). In vitro pretreatment of human airway tissues with indomethacin results in increased LTC_4 generation following IgE-mediated stimulation. MCs are the principal cells expressing LTC_4 synthase in the airways of aspirin-exacerbated asthmatics,[179] and these patients have increased Cox-2-expressing bronchial MC numbers.[180]

Pulmonary Fibrosis

The cellular composition of diffuse fibrotic reactions includes striking increases in MC numbers. MCs synthesize and release important mediators of fibrosis, including TGF-β and bFGF.[16–19,181] Most bFGF$^+$ cells in lung interstitium are HLMCs, a finding most prominent in idiopathic pulmonary fibrosis. Also, their distribution matches that of extracellular matrix deposition. The hypothesis that MCs and their mediators are critical to the development of fibrotic reactions is supported by animal models in which MC hyperplasia has been a constant finding in pulmonary fibrosis induced by bleomycin, ionizing radiation, and asbestos. Bronchial remodeling with subepithelial fibrosis is also a prominent feature of the asthmatic airway. It is not clear whether MC proliferation and activation drive and/or are secondary to the fibrotic process. The latter mechanism could be affected through fibroblast generation of SCF, producing MC proliferation, chemotaxis, and inhibition of apoptosis.

Respiratory Infections

Recently, novel functions for MCs as regulators of immune responses to infections have been elucidated. Like other innate immune leukocytes, MCs express a gamut of both surface and cytoplasmic pattern recognition receptors that afford the capability to recognize fungi, viruses, and bacteria.

Fungi make up the most abundant class of eukaryotic organisms found in the environment, and fungal antigens are the most common aeroallergen that trigger allergies. Environmental fungi such as *Aspergillus fumigatus* and *Alternaria alternata* are common allergens thought to play a role in asthma pathogenesis.[182] Although fungal interaction with the host is most commonly on the mucosal surfaces where MCs are localized, MC functions during fungal contact or infection are poorly understood and under-investigated. While *A. fumigatus* directly triggers MC activation in vitro[183] the possibility that MCs are triggered directly in vivo has not been fully elucidated. Fungi induce IL-33 production in the lungs, and airway epithelial cells are prominent producers of this cytokine that activates MCs.[184–187]

The respiratory tract is bombarded with environmental agents both innocuous and pathogenic. Viruses are common culprits that threaten the physiology of the respiratory tract and can cause life-threatening disease in patients. Influenza A virus (IAV), rhinovirus, coronavirus, respiratory syncytial virus (RSV), adenovirus, parainfluenza virus, and bocavirus are common circulating viruses that can cause mild to severe disease in humans. Early-life infection with RSV can cause asthma development in later life.[188] RSV can directly interact with MCs, inducing their degranulation in addition to causing their activation through epithelial cell infection.[189] Excessive MC activation/degranulation has been linked to severe pathologies associated with influenza and dengue viruses.[190,191] Host protective roles for MCs during respiratory virus infections have recently been elucidated wherein viral RNA activation of TLR3 promotes the production of type I and III interferons by MCs[192] and helps recruit CD8$^+$ T cells.[193] As MCs express TLR2 and TLR4 on the cell surface, in addition to complement receptors that bind opsonized complement proteins, MCs can be activated by bacteria both directly and indirectly, and can play a role in bacterial containment and killing.[194,195]

Murine Mast Cells

Like in the human, mice have MCs that take up primary residence in the respiratory mucosa where MC recruitment increases after allergenic or viral triggers.[196] Mouse MCs are phenotypically and physiologically comparable to human MCs and can be visualized in both hematoxylin and eosin stains as well as toluidine blue stains. Figure 21-3 shows several MCs in the connective tissue around the upper airways of a mouse subjected to an *Aspergillus fumigatus*–induced asthma model.[197] MC progenitors (Lin$^-$Kit$^+$Sca-1$^-$Ly6c$^-$FcεRIα$^-$CD27$^-$β7$^+$ST2$^+$) have been identified in the adult mouse bone marrow[198] to support the ability to generate MCs as needed in adult animals. The availability of MC-deficient mice (*Kit*$^{W/Wv}$,

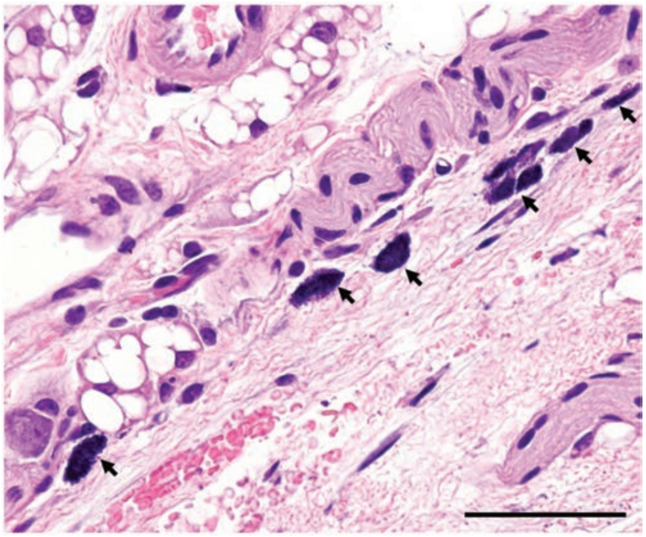

Figure 21-3 Localization of mast cells in mouse upper respiratory tract. C57BL/6J mice that were sensitized with *Aspergillus fumigatus* antigen and challenged with live airborne *A. fumigatus* conidia exhibit characteristics of fungal allergic asthma. *Arrows* point at mast cells localized to the upper airway connective tissue in this hematoxylin and eosin–stained lung tissue section. Scale bar = 50 μm. *(Unpublished work from A. E. Samarasinghe's laboratory. Photomicrograph reproduced with permission from Veterinary Pathologist, Dr. Peter Vogel at St. Jude Children's Research Hospital, Memphis, TN.)*

$Cpa3^{Cre/+}$, and *Mcpt5-Cre*) has aided investigation of the role and immunoregulatory functions of MCs in health and disease.[199–201]

MAST CELL–EOSINOPHIL INTERACTIONS

Since shortly after their discovery, it has been recognized that MC and eosinophils home to many of the same tissues, particularly in the setting of allergic and other inflammatory conditions. Not surprisingly, therefore, researchers have identified a variety of crosstalk between these two cell types that involves both soluble and physical cellular interactions.[202] For example, eosinophil granule proteins can trigger histamine, PGD$_2$, and cytokine release from human MC.[203,204] Eosinophils also produce important MC survival and activation factors, such as SCF and nerve growth factor (NGF).[205] Conversely, in human lung IgE-mediated hypersensitivity reactions, the major cellular source of the "lifeblood" of eosinophils, IL-5, is the HLMC.[154] PGD2 activates the eosinophil PGD2 receptor 2 (DP2; previously CRTH2) producing chemotaxis.[206] Histamine also activates eosinophils through the H3 receptor[206] and also what is now known as the histamine H4 receptor.[207] Histamine and PGD$_2$ have been shown to augment synthesis of LTC$_4$ in human eosinophils.[206] MC-derived TNF-α induces eosinophil GM-CSF release and autocrine survival enhancement,[208] and MC tryptase induces eosinophil IL-6 and IL-8 secretion.[206,209] In addition, MC chymase suppresses eosinophil apoptosis and increases adhesion molecule expression, chemokinesis, and cytokine and chemokine release by human eosinophils.[210] Not all MC–eosinophil interactions are proinflammatory, however, as it has been shown that MC tryptase can cleave and inactivate the eosinophil chemokines CCL5 and CCL11.[211] The opposing charges of each cell's granule contents, mast cells having a relative negative charge while eosinophil granule proteins are positively charged, also is considered to afford the relative blockage of effector functions of each cell.[212] Additionally, MC enzyme β-tryptase can cleave eosinophil chemoattractants[211] to limit eosinophil migration into mucosal tissue. Thus, MCs and eosinophils communicate bidirectionally in complex ways that may amplify or potentially modulate the inflammatory response.

EOSINOPHILS

While eosinophils are considered leukocytes, like MCs, they in fact reside primarily in the tissues. Indeed, the ratio of tissue to blood eosinophils is estimated to be 100:1 or greater. Under normal circumstances, the major resident population of eosinophils is in the lamina propria of the gastrointestinal tract. Eosinophils are also present in the thymus, as well as the uterus and developing mammary gland in females. In the absence of disease, very few eosinophils are found in the lung (although resident eosinophil populations have recently been identified in mouse lungs). On the other hand, large numbers of eosinophils traffic to the lungs and other tissues in the setting of allergic diseases, helminthic parasite infections, and certain other pathologic states.

■ Eosinophil Origins and Development

Eosinophils have been evolutionarily conserved, with eosinophil-like cells identified in invertebrates and in early order vertebrates. Eosinophils develop in the bone marrow from hematopoietic stem cell precursors. The immediate eosinophil precursor is a common eosinophil–basophil progenitor. Specific differentiation to the eosinophil lineage involves coordinated expression of the transcription factors, GATA-1, PU.1, and C/EBP. Among these, GATA-1 plays a central role, since mice with deletion of a high-affinity GATA-binding site in the GATA-1 promoter (ΔdblGATA1 mice) lack mature eosinophils, without loss of other hematopoietic lineages.[213] $CD34^+$ stem cells that are $CD38^+IL5RA^+IL3RA^+CD45RA^-$ give rise to eosinophils exclusively.[214,215] The cytokines IL-3, GM-CSF, and IL-5 stimulate growth and differentiation of eosinophils in the bone marrow, and IL-5 plays an essential role in stimulating bone marrow production of eosinophils and triggering their release into the circulation.[216] A common basophil–eosinophil progenitor cell population that expresses low levels of CD133 on the cell surface also has been identified circulating in the blood.[217,218]

IL-5 is produced by lymphocytes and endothelial cells in the bone marrow, as well as by lymphocytes and parenchymal cells in the lung and other tissues. The importance of IL-5 in eosinophilopoiesis is demonstrated by the fact that transgenic mice overexpressing IL-5 develop profound blood and tissue eosinophilia.[219] IL-5 production by resident B cells in the bone marrow, spleen, and Peyer's patches likely support the presence of resident eosinophils in these tissues at baseline.[220] IL-5 knockout mice have markedly reduced numbers of eosinophils at baseline, and they fail to develop eosinophilia in response to allergen sensitization and challenge.[221] These and other findings have provided the impetus for the development of IL-5 and IL-5 receptor–targeted monoclonal antibodies as therapeutics for asthma and other eosinophilic diseases, as discussed below.

■ Morphology and Structure

The mature human eosinophil has a diameter of 12 to 17 μm, slightly larger than the neutrophil. The nucleus is usually bilobed, and the cytoplasm contains characteristic granules that stain pink with eosin. The distinctive features of eosinophil granules can be seen clearly by electron microscopy (Fig. 21-4). Primary granules, which appear during the promyelocytic stage of development, are round, membrane-limited structures that contain Charcot–Leyden crystal (CLC) protein.[222] Secondary (also termed specific or cytoplasmic crystalloid) mature granules appear later during eosinophil differentiation,[223] are more numerous, and appear as oval or elongated trilaminar membrane-bound structures with a dense crystalline core and less dense matrix.[222] The mature granule core contains major basic protein (MBP), while other granule proteins (eosinophil

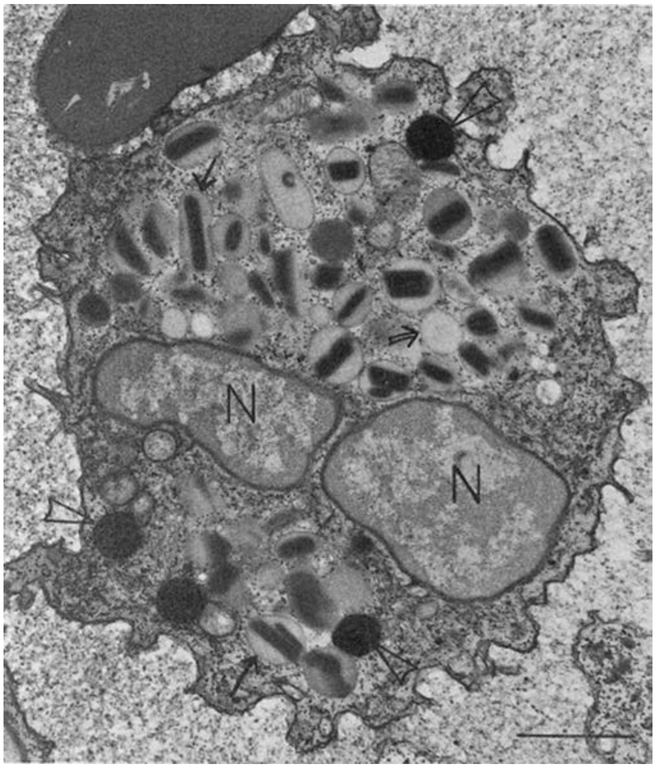

Figure 21-4 Ultrastructure of a mature human blood eosinophil. The bilobed nucleus (N), specific granules *(closed arrows)*, primary granules *(open arrow)*, lipid bodies *(open arrowheads)*, mitochondria, and irregular surface processes are seen. Dark cytoplasmic particles represent glycogen. *(Reproduced with permission from Harris JR: Megakaryocytes, Platelets, Macrophages, and Eosinophils. New York, NY: Plenum Press; 1991.)*

cationic protein [ECP], eosinophil-derived neurotoxin [EDN], and eosinophil peroxidase [EPO]) are in the matrix. A plethora of premade cytokines and chemokines also are stored within the granule matrix. Intriguingly, in resting eosinophils, approximately 8% of the eosinophil granules are found in various stages of the emptying process. The number of emptying granules increases significantly when eosinophils are activated.[224]

Eosinophil LBs were misidentified as granules in the past due to technical limitations. Based on TEM images, they are now recognized to be electron-dense, round organelles of varying size, without a true bilayer-membrane demarcation.[225] These lipid-rich organelles localize arachidonic acid–metabolizing enzymes and serve as sites of eicosanoid synthesis,[226] as well as storage of some cytokines like TNF-α.[227] The number and size of LBs increase with eosinophil activation. Eosinophil LBs associate with the endoplasmic reticulum, suggesting that they may play a role in protein synthesis.[225]

■ Eosinophil Recruitment

Current knowledge about the mechanisms of eosinophil recruitment into tissues is based largely on studies of asthma and allergic diseases, but these mechanisms may operate in other eosinophilic disorders as well. The initial step in eosinophil recruitment involves priming, which converts the resting cell to an adhesive, migratory, and activation-sensitive phenotype. Priming likely results from exposure to IL-3, IL-5, GM-CSF, and chemokines such as CCL11 (eotaxin-1), particularly in allergic individuals, in whom these factors are elevated in the circulation.[228–231] TNF-α, LTs, and other inflammatory mediators may prime eosinophils as well. Once primed, eosinophils make contact with the blood vessel wall and undergo rolling, mediated by E- and P-selectins on endothelial cells, which can be upregulated by IL-1 and TNF-α, and L-selectin that is constitutively expressed on the eosinophil.[232–235] Rolling activates eosinophil integrins, which mediate tight adhesion through high-affinity binding to endothelial cell adhesion molecules. The eosinophil integrins, VLA-4 ($\alpha 4\beta 1$ or CD49d/CD29) and CD11b/CD18, and their respective endothelial counter-ligands VCAM-1 and ICAM-1, constitute the most important binding pairs responsible for firm adhesion to the vessel wall. IL-4 and IL-13 increase VCAM-1 expression on endothelial cells.[236,237] Because VLA-4 (binding partner for VCAM-1) is highly expressed on eosinophils, but not neutrophils, this represents a mechanism for selective eosinophil recruitment to sites of allergic inflammation.[233,238] Integrin-mediated firm adhesion is followed by diapedesis, or transmigration across the endothelium. Eosinophils are further activated by endothelial transmigration, which also increases their ability to survive.[239] Based on in vitro studies, eosinophils can probably survive in tissues for two weeks or longer.

Upon entering tissue, eosinophils shift from β1- to β2-integrin–dominated interactions under the influence of chemokines such as CCL24 (eotaxin 2),[240] and migrate along chemoattractant gradients. Multiple factors are known to be chemotactic for eosinophils, including PAF, LTB_4, complement factors C3a and C5a, GM-CSF, IL-3, IL-5, IL-16, and the chemokines CCL3 (MIP-1α), CCL5, CCL7 (MCP-3), CCL11, CCL24, CCL26 (eotaxin 3), and CXCL8 (IL-8). Among these, IL-5 and the eotaxins (CCL11, CCL24, and CCL26) are the most highly selective for eosinophils, making them attractive as therapeutic targets. Indeed, monoclonal antibodies directed against IL-5 and the IL-5 receptor are now approved for treatment of severe eosinophilic asthma. In addition, a variety of agents that block CCR3, the receptor for eotaxins and several other eosinophil-active chemokines, are currently in clinical trials for treatment of eosinophilic asthma. The results of some of these studies are discussed at the end of this chapter.

■ Heterogeneity and Localization

Phenotypic and physiologic differences have been observed in peripheral blood eosinophils and tissue localized eosinophils. Eosinophil density (granularity), potential for respiratory burst, metabolism, surface expression of markers, and the ability to regulate other leukocytes vary based on locale.[241–243] Most tissue localization occurs neonatally or during early postnatal days. Thymic eosinophils have an activated phenotype with low CD62L and high CD69 expression, and they are considered to participate in T cell selection and education.[244] Intriguingly, the female reproductive tract and mammary glands are sites of high tissue localization for eosinophils where they are considered to play roles in uterine and mammary duct development and remodeling.[245–247] Eosinophils are also located in mucosal tissue at homeostasis, where they are hypothesized to play regulatory functions. For example, eosinophils in the gastrointestinal tract mucosa may regulate the functions of Paneth cells, goblet cells, and B cells.[248] While IL-5 is the major attractant for eosinophils to take up residence at these sites, infiltration and residence can occur even in the absence of IL-5. Mouse models have been of extreme importance in delineating eosinophils functions during disease, as tissue eosinophils are difficult to access in human patients. Mouse eosinophils closely resemble human eosinophils in phenotype, physical characteristics, and functions.[249] As shown in Fig. 21-5, mouse eosinophils marginate the peribronchial spaces in a fungal model of allergic asthma, similar to observations in human asthmatics.

■ Eosinophil Activation and Degranulation

The priming process required for eosinophil recruitment also represents the initial phase of eosinophil activation. IL-5 is the most

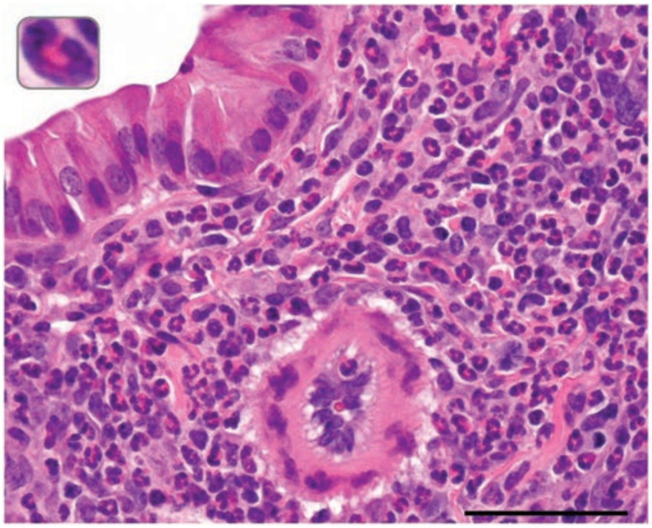

Figure 21-5 Localization of mouse eosinophils around the airways after allergen provocation and challenge. *Aspergillus fumigatus* antigen–sensitized C57BL/6J mice challenged via inhalation of airborne *A. fumigatus* live conidia result in peribronchovascular inflammation with eosinophil dominance. Inset is of a magnified eosinophil from the cross section shown. Scale = 50 μm. *(Image is from laboratory of A. E. Samarasinghe. Photomicrograph reproduced with permission from Veterinary Pathologist, Dr. Peter Vogel at St. Jude Children's Research Hospital, Memphis, TN.)*

important cytokine for priming of eosinophils in vivo.[229,250] IL-5 binds to heterodimeric receptors on the eosinophil surface, consisting of a ligand-specific α chain and common β chain that is also found in the receptors for IL-3 and GM-CSF. Binding of IL-5 to its receptor triggers a variety of intracellular signaling cascades, which enhance multiple eosinophil functions, including the response to chemotactic factors, integrin-mediated adhesion, agonist-stimulated LTC_4 and superoxide generation, phagocytosis, and helminthotoxic activity.[229,231,251–254] IL-3 and GM-CSF stimulate these functions on eosinophils as well. As noted earlier, IL-5, IL-3, and GM-CSF also enhance eosinophil survival. The effects of all three cytokines are antagonized by glucocorticoids, which induce eosinophil apoptosis.[255,256]

Eosinophils are primed in the circulation of patients with asthma and hypereosinophilic states, resulting in greater functional responses when blood eosinophils from such individuals are studied in vitro, in comparison to cells from normal controls.[229] In vivo priming also has been demonstrated in eosinophils obtained by BAL following antigen instillation into the lungs of allergic subjects (segmental allergen challenge).[257] Intriguingly, eosinophils within the airways can be activated by respiratory viruses, evidenced by upregulation of eosinophil survival marker IL-5Rα in addition to CD69 and adhesion molecules.[258,259]

Eosinophils express a number of surface receptors that can mediate cell activation. These include receptors for immunoglobulins (IgA, IgG, and IgE), complement components (C3a and C5a), eicosanoids (LTB_4, cysteinyl LTs, and PGD_2), and PAF, as well as numerous cytokines and chemokines. Priming can upregulate cell surface expression and/or activation of specific receptors,[260] and may induce new expression of receptors not normally present on resting eosinophils, such as the high-affinity IgE receptor FcεRI.[261] Ligand binding to many of these receptors triggers responses that include degranulation, lipid mediator synthesis, and generation of reactive oxygen species. Various ligands activate distinct signaling cascades within the cell, resulting in stimulus-specific differential activation of eosinophil effector functions.

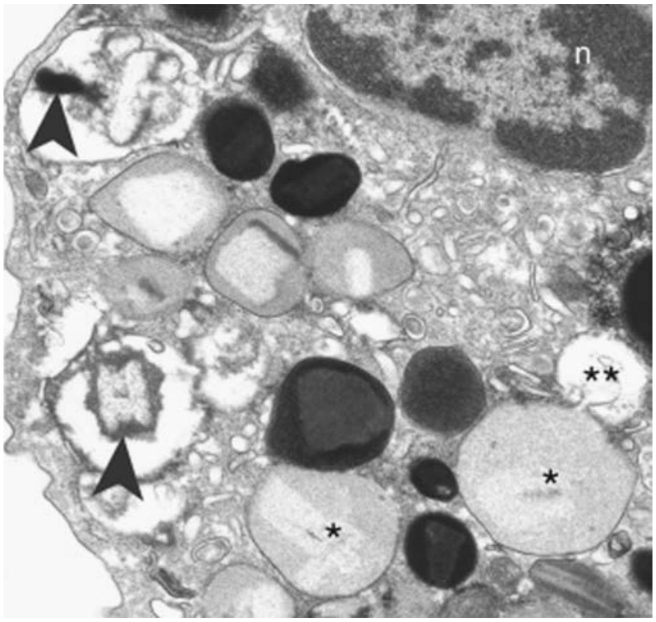

Figure 21-6 Ultrastructure of a human blood eosinophil activated in vitro with CCL11 (eotaxin). Specific granules undergoing piecemeal degranulation exhibit lucent areas in their cores, matrices, or both. Granules with residual cores *(arrowheads)*, reduced internal electron density (*) and membrane empty chambers (**) are shown. *(Reproduced with permission from Melo RCN, Perez SAC, Spencer LA, et al. Intragranular vesicotubular compartments are involved in piecemeal degranulation by activated human eosinophils. Traffic. 2005;6(10):866–879.)*

As in MCs, the principal mode by which granule-associated proteins are released from human eosinophils is PMD.[223,224,262,263] This process involves secretion of specific granule contents in discrete packets, without granule-to-granule or granule-to-plasma membrane fusion. An eosinophil undergoing PMD in vitro is illustrated in Fig. 21-6. Electron microscopic studies reveal that PMD is associated with the development of complex vesicotubular networks within emptying granules.[262,263] Interestingly, intracellular cytokine receptors within granules and secretory vesicles play a key role in transporting and guiding selective secretion of their cognate cytokines, allowing for stimulus-specific, selective, and sequential release of cationic granule proteins and stored cytokines and chemokines.[264] In addition, receptors for cysteinyl LTs have been demonstrated on eosinophil granule membranes, where they may mediate secretion of granule contents from intact cells in response to endogenously generated LTC_4 or secretion from cell-free granules triggered by extracellular LTD_4.[265] Intriguingly, mouse eosinophils undergo PMD after contact with respiratory viruses,[266,267] although the clinical relevance of this phenomenon remains to be determined.

Besides PMD, eosinophil granules may be emptied through classic or compound exocytosis pathways. In classic exocytosis, the granule membrane fuses with the plasma membrane, releasing granule contents into the extracellular space. In compound exocytosis, several granules fuse intracellularly prior to fusing their membranes with the plasma membrane. These two processes have not typically been observed in vivo.[268] Compound exocytosis involves SNARE family transport docking and vesicle fusion proteins.[269] Finally there is also cytolytic degranulation, leading to the appearance of cell-free eosinophil granules in tissue in certain eosinophilic diseases.[223] Whether this is a regulated process or the result of eosinophil necrosis at sites of inflammation is not known.

■ Eosinophil Granule Proteins

Eosinophils contain a variety of cationic granule proteins that have toxic effects on parasitic helminths and RNA viruses, as well as on

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host cells. In addition, a variety of other proteins, including enzymes and cytokines, are stored in and released from eosinophil granules. MBP, a highly basic protein that accounts for more than half of eosinophil granule protein mass, is found in the crystalline core of specific granules.[270] MBP is synthesized as a preproprotein, which is cleaved to a 13.8-kDa highly cationic molecule during eosinophil maturation. The pro-peptide, which is anionic, is thought to protect the developing eosinophil from the toxic effects of the highly cationic mature MBP. Low levels of MBP are expressed in basophils, consistent with their close lineage relationship to eosinophils. MBP is directly toxic to larvae of *Schistosoma mansoni*, *Trichinella spiralis*, and other helminths, supporting a role in host defense against parasites.[271] Several lines of evidence have suggested that MBP could be an important mediator of asthma. MBP inhibits ciliary function and is toxic to respiratory epithelial cells.[272,273] When administered to the airways of nonhuman primates, MBP caused transient bronchoconstriction followed by persistent bronchial hyperresponsiveness.[274] In addition, MBP was shown to bind to and inhibit M2 muscarinic receptors, increasing vagally mediated bronchoconstriction in guinea pigs.[275] On the other hand, mice deficient in MBP showed no attenuation of airway histopathologic changes or airway hyperreactivity in an allergen-induced asthma model,[276] suggesting that MBP does not play an essential role in allergic airway disease, at least in the mouse. While the effect MBP has on respiratory viruses is yet to be fully elucidated, MBP trapped in eosinophil extracellular traps may have antibacterial properties.[277]

Both ECP and EDN are highly basic proteins found in the matrix of specific granules. ECP and EDN are homologous proteins (67% amino acid sequence identity), the result of gene duplication, that are also similar to human pancreatic ribonuclease (RNase) A.[271] Indeed, both ECP and EDN are active RNases, with the ability to inactivate RNA viruses such as RSV and IAV.[259,271] EDN was initially described as a neurotoxin that causes severe damage to myelinated neurons, a property possessed by ECP as well. This activity may account for the neurologic abnormalities seen in patients with hypereosinophilic syndrome (HES) and cerebrospinal fluid eosinophilia. Like MBP, ECP and EDN are both helminthotoxic.[271] Levels of ECP are elevated in blood, BAL fluid, and sputum in patients with asthma, and have been found to correlate with disease severity.[278] For this reason, ECP levels in blood or sputum are often monitored in asthma clinical trials as a means of assessing response to treatment.

Similarly, EPO is also a highly basic protein found in the matrix of specific granules. EPO is a unique peroxidase expressed only in eosinophils. In the presence of H_2O_2, EPO oxidizes halide ions to form highly reactive hypohalous acids. Bromide is the preferred substrate, leading to hypobromous acid (HOBr), an extremely potent oxidant that damages DNA and other critical cellular targets. EPO plus H_2O_2 and halide ions can kill parasites, bacteria, and mycobacteria, as well as MCs and tumor cells.[279] The potential role of EPO in allergic airway disease has been explored in mice with targeted deletion of the EPO gene. In this study, despite a marked reduction in bromo-oxidation of lung proteins, EPO deficiency did not result in any attenuation of allergen-induced airway inflammation or bronchial hyperresponsiveness,[280] indicating that EPO is not essential for development of allergic pulmonary pathology in the mouse. The combination of ECP, EDN, and EPO affords eosinophils antipathogenic effector functions against several classes of pathogens.[277]

CLC protein localizes to the primary eosinophil granule and is also expressed in basophils. The protein readily crystalizes to form bipyramidal CLCs, often seen in affected tissues and considered a hallmark of eosinophil-associated diseases in humans. Previously thought to possess lysophospholipase activity, CLC protein has been shown to belong to the galactose-binding lectin family (galectins) and to avidly bind mannose sugar.[281] Despite the long-recognized association of CLCs with eosinophil infiltration of tissues, the role of CLC protein in eosinophil-related pathology is unknown.

Eosinophils also contain within their granules various other enzymes, including β-glucuronidase, arylsulfatase B, and matrix metalloproteinase-9 (MMP-9), as well as a plethora of preformed cytokines and chemokines, which can be released in regulated fashion when stimulated.

■ Other Eosinophil Contents

A variety of chemical and immune mediators are pre-stored in eosinophil granules and LBs and some may be synthesized de novo upon stimulation. In addition to eosinophil-specific granule proteins, these additional eosinophil contents allow them to crosstalk with other members of the immune system and regulate immune functions.

Lipid Mediators

Upon stimulation, eosinophils produce large quantities of the 5-lipoxygenase–derived eicosanoid, LTC_4. Synthesis of LTC_4 in eosinophils occurs at the nuclear membrane[251,282] and in cytoplasmic LBs.[283] Following secretion, LTC_4 is converted extracellularly to LTD_4 and LTE_4. These cysteinyl leukotrienes act through cysLT1 and cysLT2 receptors to cause bronchoconstriction, stimulate mucus secretion, promote synthesis of T_H2 cytokines, and contribute to airway remodeling.[284] The ability to block these effects underlies the beneficial actions of cysLT receptor antagonists and LT synthesis inhibitors in asthma. Other biologically active lipids produced in substantial quantities by eosinophils include 15-HETE, 5-oxo-ETE, and PAF. However, the roles of these products in asthma and other eosinophil-associated diseases remain unclear.

Cytokines and Chemokines

Classically, eosinophils were considered terminal effector cells of inflammatory responses, acting by secretion of granule proteins and the acute release of other mediators. However, it is now recognized that eosinophils synthesize a wide array of cytokines and chemokines, equipping them to participate in the regulation of immune and inflammatory responses. The major cytokines and chemokines expressed in eosinophils are listed in Table 21-1. Interestingly, a number of these factors have autocrine or paracrine effects on eosinophils themselves. Most notably, IL-3, GM-CSF, and IL-5, which are produced by activated T lymphocytes and other cells, including MCs and eosinophils themselves, enhance eosinophil survival and activate eosinophil function in vitro and in vivo.[251–253,257,285–289] In another example, IL-16, a product of eosinophils and other cells, triggers rapid eosinophil release of CCL5 (RANTES), which generates autocrine signals that augment release of LTC_4 and IL-4.[290] A number of cytokines and chemokines synthesized by eosinophils are stored within granules. When the cells are stimulated, these preformed cytokines are released by PMD.

Eosinophil-derived cytokines likely contribute to the regulation of inflammatory responses in eosinophil-associated diseases and drive specific pathophysiologic responses. For example, elaboration of T_H2 cytokines amplifies allergic responses, and is likely important in host defense against parasites and tissue remodeling and repair. TGF-α released by eosinophils is a potent stimulus for synthesis of mucins by airway epithelial cells,[291] which contributes to asthma and other eosinophilic airway diseases. Also, accumulating evidence implicates eosinophil-derived TGF-β as a driver of airway remodeling in asthma[292] and suggests a link to pulmonary fibrosis as well.[293]

Eosinophil involvement in local immunity and or remodeling or repair (LIAR), as proposed by Lee and colleagues in 2010, posits that eosinophils are recruited into tissues that are undergoing alterations in response stimulus and engage in regulatory processes that lead to resolution of inflammation and repair processes.[294] Eosinophil-derived cytokines are also important in the regulation of female reproductive development, adipose tissue maintenance, and B cell regulation.[295] A clearer understanding of the roles of eosinophil-related cytokines in human diseases will emerge as additional therapeutic agents designed to target specific cytokines, their receptors, and downstream signaling pathways are tested in clinical trials.

Reactive Oxygen Metabolites

Like neutrophils, eosinophils synthesize superoxide anion ($O_2\bullet^-$) and H_2O_2 through the action of NADPH oxidase. Notably, NADPH oxidase components are more highly expressed and more readily activated in eosinophils than neutrophils, endowing stimulated eosinophils with a greater capacity to produce $O_2\bullet^-$ and H_2O_2.[296] As discussed previously, eosinophils produce HOBr through the action of EPO on bromide and H_2O_2.[279] In a reaction involving HOCl and $O_2\bullet^-$, EPO also catalyzes formation of hydroxyl radical ($\bullet$OH), the most reactive of all oxygen metabolites. As noted, EPO-derived oxidants kill parasites and other microorganisms, and thus may be important for host defense. By contrast, EPO appears not to play a key role in allergic airway disease in mice.[276,280]

In addition to reactive oxygen species, eosinophils also generate nitric oxide through nitric oxide synthase activity to react with superoxide anions to form highly cytotoxic compound peroxynitrite. These reactive nitrogen species play a role in antiviral defense mechanisms during RSV and parainfluenza virus infections.[297,298] The importance of eosinophil-derived oxidants in human health and disease is at present uncertain and requires further study.

Immunoregulatory Capacity of Eosinophils

Recent investigations have demonstrated that human and mouse eosinophils can process antigen, express major histocompatibility complex II (MHC-II) and co-stimulatory molecules, and function as "professional" antigen-presenting cells.[299,300] In mice, eosinophils within the airway lumen can migrate to regional lymph nodes where they stimulate antigen-specific T cell proliferation.[301] In addition, eosinophils synthesize, store, and secrete T_H2 cytokines and chemokines, granting them the capacity to initiate T_H2 differentiation of $CD4^+$ T cells as well as recruit T_H2 cells to sites of infection or allergen deposition, as demonstrated in several mouse models of allergen-induced airway disease and parasitic infection.[302] Thus, there is now substantial evidence, largely from murine models, that eosinophils play a central role in directing the T_H2 immune response. Additionally, eosinophils can support B cell differentiation to plasma cells, interact with plasmablasts, and promote the generation of long-lived plasma cells.[303,304] These findings emphasize that, beyond their cytotoxic and destructive potential, eosinophils contribute in complex ways to host defense and the pathophysiology of allergic disease. Mouse eosinophils also perform a putative antigen-presenting function during IAV infection, through upregulation of MHC-I and co-stimulatory marker expression, elevating migratory molecules and trafficking to draining lymphoid organs, and stimulating virus-specific $CD8^+$ T cell responses.[259,267] Whether eosinophils perform a similar function in human influenza infection remains to be elucidated.

Eosinophils and Host Defense

Many years ago, histopathologic evidence of eosinophils surrounding dying helminths in tissue biopsy specimens led to the hypothesis that eosinophils play a role in the immune response to multicellular parasites. Subsequently, it was demonstrated that, in the presence of antibodies or complement, eosinophils can kill parasites in vitro, as can purified eosinophil granule proteins.[305] Further support of a role for eosinophils in host defense against helminths came from epidemiologic studies that correlated high eosinophil counts with resistance to posttreatment reinfection with *Schistosoma* spp. in humans.[306] Moreover, studies of experimental helminth infections in mice depleted of eosinophils by IL-5 neutralization or gene targeting have indicated that IL-5 and eosinophils are important for protective innate immunity against a variety of parasites,[307–309] although the results are not all consistent.[310] Other studies of mice deficient in CCL11 or treated with a monoclonal antibody targeting the eotaxin receptor CCR3 have also demonstrated that eosinophils are important for clearance of parasites in vivo.[311,312] A recent study using mice made eosinophil-deficient by expressing the diphtheria toxin A gene under control of the EPO promoter (*PHIL* mice),[313] as well as mice lacking either MBP or EPO, showed that eosinophils kill parasite larvae during primary *Strongyloides stercoralis* infection by a mechanism dependent on MBP.[314] A consistent finding in a number of these studies is that eosinophils play an important role in host defense during primary parasite infection, whereas they appear not to be essential for adaptive responses leading to protective secondary immunity.[309,311,312,314] Interestingly, other recent studies showed that survival of *Trichinella spiralis* was actually reduced in mice genetically ablated of eosinophils, and that parasite growth and survival were restored when the mutant mice were reconstituted with eosinophils by intravenous transfer; in this model, eosinophils enhanced parasite survival by promoting accumulation of T_H2 lymphocytes and preventing induction of inducible NO synthase in macrophages and neutrophils at sites of disease.[315,316] Thus, while substantial evidence indicates that eosinophils are protective in the innate immune response to many parasites, the roles they play in helminthic infections are complex and depend on interactions with other immune cells.

As noted earlier, human ECP and EDN are both RNases, and can inactivate RSV in vitro.[271] Mouse eosinophils express a diverse array of eosinophil-associated RNases (EARs) with the ability to inactivate pneumonia virus of mice (PVM),[317] a major pathogen in rodents that is closely related to RSV. More recently, it has been demonstrated that hypereosinophilic IL-5 transgenic mice exhibit enhanced virus clearance when infected with RSV,[318] and that activated eosinophils recruited to the lung in a model of allergen-induced airway disease are profoundly antiviral and promote survival in an otherwise lethal PVM infection.[266] Eosinophils also function as antigen presenters that activate $CD8^+$ T cells promoting their priming, activation, and cytokine production through epigenetic regulation during IAV infection.[258,267] Viral-induced damage to the respiratory epithelial cell barrier is a significant effect of IAV infection. Although eosinophil products can be cytotoxic,[319] eosinophils protect the respiratory epithelium from IAV-induced cytopathology,[259] indicating that eosinophil functions at the mucosa are complex and multifaceted. Parainfluenza virus infectivity is directly reduced by eosinophils through nitric oxide generation.[298] Thus, while they contribute to the pathophysiology of allergic airway disease, activated eosinophils have the capacity to mediate effective antiviral host defense in the mouse. Further studies are needed to define the role of eosinophils in the immune response to viral infection in humans.

Human MBP and ECP also possess bactericidal activity, and various bacteria can induce degranulation of human eosinophils in vitro.[271] In addition, human eosinophils are able to kill *Escherichia coli* by a mechanism involving NADPH oxidase- and EPO-generated oxidants in vitro.[271] Similar to neutrophil extracellular DNA traps, eosinophils release DNA to form traps that serve as a scaffold for their cationic granule proteins to limit bacterial growth and dissemination.[320–322] Despite these observations, few data exist to implicate a role for eosinophils in host defense against bacterial infections in vivo. Eosinophil responses to respiratory pathogens have been reviewed in depth elsewhere.[277] Cumulatively, ascribed functions

TABLE 21-2 Eosinophilic Lung Diseases

Asthma
Allergic bronchopulmonary aspergillosis/mycosis
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)
Simple pulmonary eosinophilia
Chronic eosinophilic pneumonia
Acute eosinophilic pneumonia
Helminthic infections
Drug hypersensitivity reactions
Hypereosinophilic syndrome

of eosinophils at the pathogen interface further support the LIAR hypothesis that eosinophils are not necessarily tissue destructive.[294]

Eosinophil–Disease Associations

Peripheral blood eosinophilia and eosinophilic lung inflammation are common in a variety of pulmonary conditions, including those listed in Table 21-2. The clinical manifestations and treatment of these disorders are discussed in detail elsewhere in this textbook.

Among eosinophilic lung diseases, asthma is by far the most common and most well studied. Over the years, much evidence has accumulated supporting a key role for eosinophils in the pathogenesis of asthma. Among the numerous animal studies addressing this question, most compelling are those involving genetically eosinophil-deficient (ΔdblGATA1 and *PHIL*) mice, which are protected against allergen-induced airway hyperresponsiveness, allergic airway inflammation, mucus hypersecretion, and peribronchiolar collagen deposition.[213,313,323,324] In humans with asthma, eosinophils and their specific products (e.g., ECP) increase in the airway lumen and airway wall during spontaneous exacerbations and following experimental allergen challenge.[287,325,326] Sputum eosinophil numbers and ECP levels also correlate with asthma severity.[278] When asthma improves, either spontaneously or in response to treatment, eosinophils and their products decline.[327,328] Corticosteroids, the most effective therapy for asthma, have potent anti-eosinophil effects.[329] Also, an inhaled corticosteroid treatment strategy directed specifically at reducing sputum eosinophils resulted in significantly better asthma control than treatment based on standard asthma guidelines.[330] Finally, as discussed in the next section, specific eosinophil-targeted therapy with an IL-5-neutralizing monoclonal antibody has been shown to reduce exacerbations and facilitate steroid tapering in patients with severe, oral corticosteroid–dependent asthma with high eosinophils.[331,332] It should however be emphasized that eosinophilia is primarily associated with “T2 high” asthma endotypes, and that in “non-T2” asthma, neutrophils, rather than eosinophils, likely play a key pathogenetic role.

HES is a rare disorder characterized by persistent marked blood eosinophilia (>1500/µL) or prominent tissue eosinophilia and eosinophil-induced organ damage or dysfunction, in which secondary causes of eosinophilia, such as parasitic or viral infections, allergic diseases, drugs, and hypoadrenalism have been excluded.[333] Pulmonary involvement is seen in 50% of cases. HES is classified as either myeloproliferative or lymphocytic, based on pathophysiology. The myeloproliferative form, exemplified by patients bearing the FIP1L1-PGDFRA fusion gene, which produces a constitutively active tyrosine kinase that drives eosinophil hyperproliferation, represents a type of myeloproliferative neoplasm. The tyrosine kinase inhibitor, imatinib mesylate, is useful in treatment of these patients. In lymphocytic HES, eosinophil proliferation is driven by T-cell overproduction of IL-5 and/or other eosinophil hematopoietins. Corticosteroids are the first line of treatment for these patients. The anti-IL-5 monoclonal antibody mepolizumab has also been shown to be effective in steroid-requiring lymphocytic HES.[334,335]

In addition to the disorders listed in Table 21-2, eosinophils may play a role in the pathogenesis of several pulmonary diseases not normally thought of as eosinophilic in origin. Among these is idiopathic pulmonary fibrosis, in which elevated numbers of eosinophils in BAL fluid have in some studies been associated with a poor prognosis.[336] This is consistent with in vitro and animal data demonstrating the ability of eosinophils to promote tissue fibrosis. Another example is cystic fibrosis, in which increased levels of cationic eosinophil granule proteins correlate with worse pulmonary function, presumably due to toxic effects of these proteins on lung cells.[337]

Pharmacologic Modulation of Eosinophils

Corticosteroids have been the mainstay of pharmacotherapy for eosinophilic disorders for many years. Corticosteroids induce apoptosis of eosinophils, both directly and by inhibiting formation of the prosurvival cytokines IL-5, IL-3, and GM-CSF.[255,256,329] This leads to rapid reductions of circulating and tissue eosinophils and clinical improvement in the majority of treated patients. Leukotriene receptor antagonists and the anti-IgE monoclonal antibody omalizumab are two other classes of drugs used to treat asthma and allergic diseases that have been shown to reduce circulating eosinophil counts and cause eosinophil apoptosis.[327,338] Of course, these classes of drugs are not specific for eosinophils, so the degree to which their anti-eosinophil activities contribute to their beneficial effects is uncertain.

More recently, several highly selective anti-eosinophil therapeutics have been developed, tested in clinical trials, and approved for clinical use in the United States. The best studied of these new agents is the anti-IL-5 monoclonal antibody mepolizumab, which is highly effective in reducing circulating eosinophil levels in asthma. Although it did not improve clinical endpoints in mild to moderate asthma,[339] mepolizumab has been shown to reduce exacerbation rates, facilitate corticosteroid tapering, and improve asthma-related quality of life in patients with severe, oral steroid–dependent asthma and increased sputum eosinophils.[331,332,340] As noted earlier, mepolizumab also facilitated oral steroid tapering and reduced flare-ups in randomized trials of patients lymphocytic HES.[334,335] Similarly, mepolizumab increased the rate of remission and facilitated steroid tapering in eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome).[341] Reslizumab,[342,343] another anti-IL-5 monoclonal antibody, and benralizumab,[344] which targets the IL-5 receptor α chain, have benefits similar to mepolizumab and are also approved for treatment of severe eosinophilic asthma. Dupilumab, a monoclonal directed against the common IL-4/IL-13 receptor α chain, also reduced exacerbations and improved pulmonary function and symptom control in severe eosinophilic asthma.[345]

Other eosinophil-selective therapies in clinical development include monoclonal antibodies, antisense oligonucleotides, and small molecule inhibitors targeting CCL11, CCR3, and IL-1.[346] An intriguing anti-eosinophil strategy in early clinical development involves targeting Siglec-8, a sialic acid–binding immunoglobulin-like lectin expressed on the surface of human eosinophils and MCs. Engagement of Siglec-8 with cross-linking antibody or glycan ligands triggers selective apoptosis of eosinophils and inhibits inflammatory mediator synthesis and release by MCs (without affecting their survival), suggesting the possibility that activators of Siglec-8 signaling might be particularly effective therapeutic agents by their ability to target two major cell types that drive allergic respiratory disease.[347,348] Indeed, a monoclonal antibody directed against siglec-8 triggered NK cell–mediated antibody-dependent depletion of asthmatic sputum eosinophils and inhibited activation of MC in human lung tissue.[349] The anti-Siglec-8 monoclonal antibody also depleted tissue eosinophils and improved symptom scores in patients with eosinophilic gastritis and duodenitis.[350]

Ongoing and future investigations involving these novel eosinophil-targeted therapies listed earlier, as well as others yet to be devised, will hopefully lead to safe and even more effective new treatments for eosinophilic respiratory disorders. Such studies will also almost certainly yield new and unexpected insights into the complex mechanisms that eosinophils play in human health and disease.

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CHAPTER 22

Antibody-Mediated Lung Defenses and Humoral Immunodeficiency

Homer L. Twigg III

INTRODUCTION

Antibody-mediated, or humoral, immunity is essential for host defense against respiratory pathogens. Defects in humoral immunity are common and frequently underappreciated. From a respiratory perspective, patients with impaired humoral immunity are susceptible to recurrent bacterial sinopulmonary infections and bronchiectasis. Antibody responses are also the principal mechanism behind the efficacy of vaccination against respiratory pathogens. This chapter focuses on our understanding of the normal B cell environment in the lung, generation of appropriate antibody responses after antigenic challenge, disease states associated with impaired lung humoral immunity, and the pulmonary response to vaccination.

OVERVIEW OF B CELL DEVELOPMENT (ONTOGENY)

The primary cell responsible for generating humoral immunity is the B lymphocyte. There are two phases in the development of antibody responses. The first phase is antigen independent and is called lymphopoiesis. As with the generation of other immune cells, the process begins with a multipotent stem cell in the bone marrow that undergoes multiple maturation steps leading to mature but antigen-naïve B lymphocytes (Fig. 22-1) that express IgM and IgD on the cell surface.[1] This process occurs entirely within the bone marrow (or liver during fetal development). Important cytokines in this process include interleukin 7 (IL-7),[2] *ckit*-ligand (stem cell factor),[3] and IL-11.[4] Mature B cells express surface the receptors CD19, CD20, CD21, and CD72.[5,6] CD20 is especially relevant as it is the target of the monoclonal antibody rituximab, which is used to deplete B lymphocytes in B cell lymphoproliferative disorders[7] and autoimmune disorders characterized by the production of pathogenic autoantibodies.[8]

At the completion of lymphopoiesis, IgM-expressing B cells traffic to various lymphoid organs, including lymph nodes in the lung, to await antigenic challenge and enter immunopoiesis.[9,10] Thus, unlike lymphopoiesis, immunopoiesis is antigen dependent. The end result of immunopoiesis is the generation of antibody-secreting plasma cells[1] and long-lived memory B cells, which secrete immunoglobulin only upon re-exposure to antigen.[11] During immunopoiesis class switch, recombination and somatic hypermutation occur resulting in the generation of IgA- and IgG-secreting cells out of IgM precursors, which will be discussed in detail below. Immunopoiesis is most efficient in the presence of antigen-activated T cells, which provide “help” to B cells in the form of cytokines and cell surface activation signals. The latter signal most critical is the interaction between CD40 on B cells and CD40L on activated T cells. The importance of CD40–CD40L in signaling in antibody generation is highlighted by recent efforts to block this interaction in the treatment of various cancers[12] and autoimmune diseases.[13] However, early in B cell development this interaction is crucial, and in the absence of such signaling (e.g., due to genetic mutations in CD40 or CD40L) class switching fails to occur, resulting in the accumulation of IgM-secreting cells and the hyperimmunoglobulin M syndromes, discussed later in this chapter.

IMMUNOGLOBULIN DEVELOPMENT AND STRUCTURE

Below are considered the structure of immunoglobulins, their formation, and immunoglobulin subtypes.

■ Basic Structure

Immunoglobulin (Ig) molecules expressed are made up of two identical protein heavy chains and two identical kappa (κ) or lambda (λ) light chains.[14,15] Immunoglobulin heavy-chain genes reside on chromosome 14 and immunoglobulin light chains are derived from

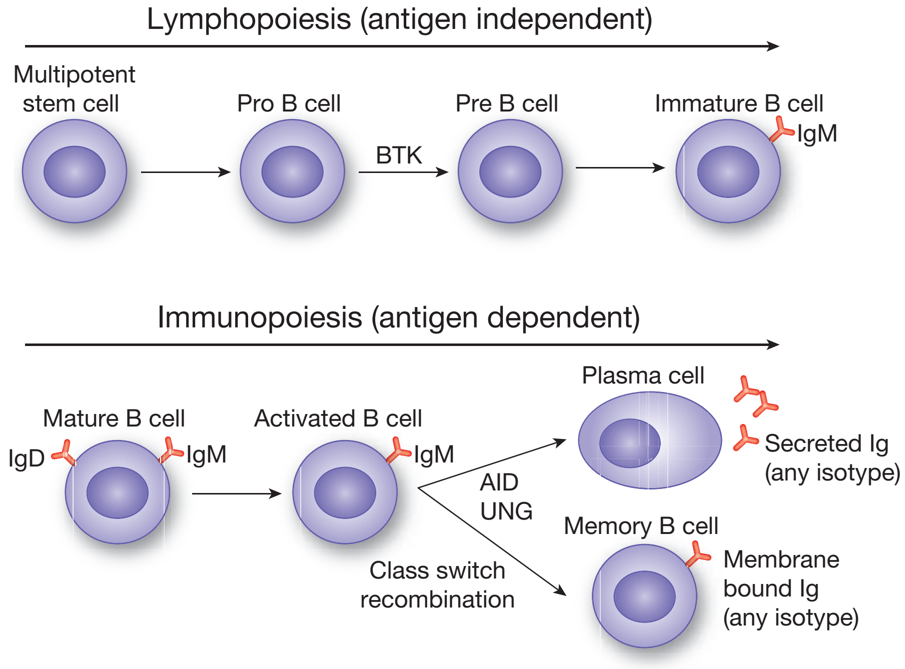
Lymphopoiesis (antigen independent)
Multipotent stem cell
Pro B cell
BTK
Pre B cell
Immature B cell
IgM
Immunopoiesis (antigen dependent)
Mature B cell
IgD
IgM
Activated B cell
IgM
AID
UNG
Class switch recombination
Plasma cell
Secreted Ig (any isotype)
Memory B cell
Membrane bound Ig (any isotype)

Figure 22-1 Overview of B cell ontogeny. Lymphopoiesis, occurring in the bone marrow or fetal liver, is an antigen-independent process that begins with a multipotent stem cell and ends with an IgM-expressing immature B cell that will migrate to lymphoid tissues. Immunopoiesis begins with antigen stimulation (hence antigen dependent) and results in antibody-secreting plasma cells and antibody-expressing memory B cells. Class switch recombination leads to the generation of different immunoglobulin subtypes (IgG, IgA, IgE) from activated IgM-expressing B cells. AID, activation-induced cytidine deaminase; BTK, Bruton’s tyrosine kinase; UNG, uracil-N-glycosylase.

either the Igκ-locus on chromosome 2 or the Igλ locus on chromosome 22. Immunoglobulin heavy chains contain both a variable region that will ultimately contribute to antigen binding, and a constant region that binds to cell Fc receptors and complement. Mature immunoglobulin light chains also contain variable and constant regions. Within each variable region there are hypervariable regions, which represent the actual antigen-binding site, and less variable regions, which make up the *framework region*.

The variable domain of the heavy chain is encoded by three sets of genes, the variable (V), diversity (D), and junctional (J) genes, which must be physically rearranged to result in expression of immunoglobulin heavy-chain protein.[16] Similarly, the variable region of the immunoglobulin light-chain protein is encoded by two sets of genes, the V and J genes, which are likewise rearranged to allow transcription of functional protein.[15,16] The rearrangement of DNA to join V, D, and J heavy-chain genes and V and J light-chain genes also results in elimination of unused V, D, and J sequences and noncoding stretches of DNA or introns. The many possible variable regions resulting from these random rearrangements confer a broad range of potential antigen specificities to the mature immunoglobulin molecules.

■ Class Switching

Once immunopoiesis is initiated B cells alter the isotype of antibody that is produced via *isotype switching*.[16,17] This occurs in *switch regions* on immunoglobulin heavy chains through a process called *class switch recombination*. By translocation of the IgM variable region to switch regions adjacent to one of the constant regions coding for IgG, IgA, or IgE, the B cell can maintain antigen specificity and, at the same time, generate different immunoglobulin subtypes with different functional capabilities. Class switch recombination requires an enzyme called activation-induced cytidine deaminase (AID). AID is also critical for *somatic hypermutation*, a process where rapidly proliferating activated B cells have a high rate of point mutations in genes encoding the variable region, leading to production of antibodies with different antigen-binding affinities.[18] This results in a greatly expanded repertoire of B cells expressing surface IgG of different affinities for the triggering antigen. B cells expressing high-affinity antibody on their surface (and thus binding greater amount of antigen) have a survival benefit over B cells coated with weaker affinity to antigen, where less signaling through antigen recognition results in B cell apoptosis. In this way, the antibody response moves toward production of higher affinity and more specific immunoglobulin. The importance of AID is reflected in the development of one of the hyperimmunoglobulin M syndromes in patients with defects in this enzyme.[19] The structure of the various immunoglobulin classes is shown in Fig. 22-2.

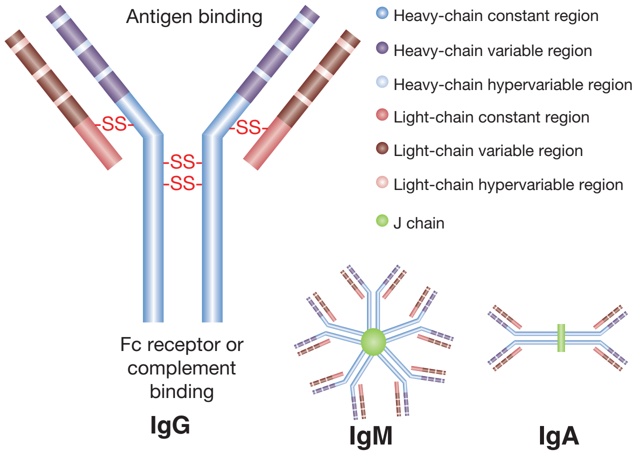
Antigen binding
-SS-
-SS-
-SS-
-SS-
Fc receptor or complement binding
IgG
IgM
IgA
● Heavy-chain constant region
● Heavy-chain variable region
● Heavy-chain hypervariable region
● Light-chain constant region
● Light-chain variable region
● Light-chain hypervariable region
● J chain

Figure 22-2 Basic immunoglobulin structure. Immunoglobulin molecules consist of two identical protein heavy chains and two identical light chains joined by disulfide bonds. Both heavy and light chains contain a constant and a variable region. Within each variable region there are hypervariable regions that represent actual antigen-binding sites. IgM typically exists as a pentamer and IgA as a dimer.

■ Lung Immunoglobulins

In the lung, immunoglobulins constitute the second largest class of proteins present in bronchoalveolar lavage (BAL) fluid after albumin.[20] IgG is the major immunoglobulin in the lower respiratory tract.[21] In contrast, IgA is the most abundant immunoglobulin in secretions from the upper respiratory tract, exceeding the concentration of IgG by a ratio of 2.5:1. Smaller amounts of IgE are consistently found in the BAL fluid of normal subjects.[20]

IgG

IgG is the major circulating immunoglobulin found in the vascular compartment. In normal subjects, the amount of IgG measured in BAL (usually expressed as an immunoglobulin/albumin ratio) is in the same proportion as serum, suggesting that under resting conditions most IgG in the lung represents transudation from the vascular compartment.[20] This is further supported by the relatively small size of IgG (150,000 D). There are four IgG subclasses found in BAL fluid in approximately the same proportions as found in serum. IgG1 represents approximately 60% to 70% of the IgG present in BAL fluid, IgG2 20% to 25%, and IgG3 and IgG4 are present only in small amounts (<5%).[21] Responses to protein antigens predominantly reside in the IgG1 and IgG3 subclasses, while polysaccharide antigens predominantly give rise to IgG2 antibodies.[22,23]

The major function of IgG is to opsonize pathogens and target them for clearance either through uptake by phagocytic cells or by fixing complement. In this regard, IgG1 and IgG3 fix complement more avidly than IgG2.[24] Antibody also binds to Fc receptors on phagocytic cells to facilitate uptake. The three primary Fc receptors are FcRI, FcRII, and FcRIII. IgG1 and IgG3 bind FcRIII receptors on phagocytic cells equally well and more potently than IgG2.[25] IgG1 binds to the other Fc receptors more avidly than the other IgG subclasses. Binding of antigen–antibody complexes to Fc receptors is potentially a double-edged sword. On the one hand, not only is uptake of opsonized pathogens through Fc receptors more efficient, so is the intracellular digestion of organisms in phagolysosomes. For example, uptake of opsonized *Mycobacterium tuberculosis* through the Fc receptor results in intracellular killing of the organism, while uptake through other receptors (e.g., the mannose receptor) allows the organism to escape digestion.[26] On the other hand, uptake of opsonized pathogens through Fc receptors represents an "inflammatory clearance" mechanism that is associated with release of potentially harmful inflammatory mediators into the lung environment.[27]

IgA

In contrast to IgG, IgA is likely locally produced based on an elevated IgA/albumin ratio in BAL compared with serum.[28] IgA can exist as monomeric and polymeric proteins. The latter is usually found as dimeric IgA, characterized by two monomers connected by a J chain.[29] Most IgA in the lung is in dimeric form, with features of secretory IgA (sIgA) characterized by the presence of a J chain and secretory component (SC).[30] The large size of dimeric IgA (385,000 Da) also argues against simple transudation of IgA from the vascular compartment into the lung. Finally, the presence of secretory component in BAL is another argument for the local production of IgA in the lung.[31]

IgA has two subclasses: IgA1 and IgA2.[29] IgA1 constitutes nearly 80% of serum IgA. In contrast, IgA2 appears to be important in mucosal immunity and nearly half of the IgA present in secretions is IgA2. IgA exerts its protective effect through three mechanisms.[32]

First, it serves as an immunologic barrier, inhibiting binding of organisms to mucosal surfaces. Second, the normal movement of IgA from the basilar to apical region of epithelial cells suggests that it may be effective in neutralizing intracellular pathogens. Finally, pathogens bound to IgA may be taken up by airway macrophages through the phagocytic process.

IgM

IgM is present only in very low amounts in respiratory secretions from normal subjects.[20] It exists as a pentamer, and the resulting very large size (900,000 Da) limits transudation into the lung under normal conditions. Nevertheless, IgM in BAL is greater than would be expected for simple diffusion, suggesting some local production.[33] Furthermore, in some disorders characterized by lower respiratory tract inflammation, IgM can be detected. However, in this setting, it is almost certainly largely derived from serum transudation as part of the inflammatory process.

IgE

Under normal conditions, the amount of IgE in BAL is lower than IgG, IgA, or IgM.[33] When present, the IgE/albumin ratio suggests local production.[33] IgE-antigen complexes bind the high-affinity receptor for IgE (FcRI) on mast cells, basophils, and eosinophils leading to immediate hypersensitivity responses.[34,35] IgE is important for host defense against parasites mediated by eosinophils.[36] However, in developed countries, the main role of IgE in pulmonary immunity is in the pathogenesis of allergic and asthmatic disease.[37,38] The severity of disease is correlated with serum IgE in asthma and allergic patients. The importance of this molecule in the pathogenesis of asthma has led to the development of anti-IgE antibodies for patients with resistant IgE-mediated disease.[39] Interestingly, when IgE binds to the low-affinity FcRII receptor, it inhibits IgE synthesis and reduces inflammation.[40] Thus, IgE may also have a role in downregulating the immune response.

■ Cellular Interactions Leading to Antibody Secreting Cells

Important considerations in development of antibody secreting cells are discussed below.

■ B1 and B2 Cells

B lymphocytes constitute 1% to 10% of the lung lymphocyte population and can be separated into two main classes. Plasma cells constitutively secrete IgG and other immunoglobulin subclasses.[1,11] In contrast, memory B cells produce immunoglobulin only in response to re-exposure to particular antigens.[11] B cells can be further classified into B1 and B2 cells, although recent studies suggest there is plasticity between the two subtypes.[41] B1 cells were first described in the gastrointestinal tract. These cells are IgM+, CD5+ cells that do not require T cell help for development.[42] In the lamina propria, B1 cells undergo class switching to an IgA secretory cell. B1 cells home to peritoneal and pleural cavities, respond to common bacterial antigens, and are felt to be very important in the production of IgM and IgA against bacterial pathogens at mucosal sites.[43] As such, they are thought to be important in innate immunity against conserved bacterial antigens. Because of their autonomous ability to secrete antibody, they are also felt to contribute to autoimmune diseases.[44] These cells are difficult to demonstrate in normal lung. As stated above, T cells are not necessary for B1 cells to produce antibody, although the presence of T cells appears to augment the immune response.[45–47]

In contrast to B1 cells, B2 cells require T cell help, mainly through secretion of the cytokines IL-4, IL-6, IL-7, and IL-10, along with interferons,[48] as well as ligation between CD40 on B cells and CD40L on T cells.[49] T cell–dependent antibody responses begin with uptake of antigen by accessory cells (AC) and presentation to T cells. AC function can be carried out by mononuclear phagocytes (monocytes, macrophages) or dendritic cells. Submucosal dendritic cells are likely the principal accessory cell in the lung.[50] B cells themselves can also serve as the accessory cell leading to T cell activation.[51] B cells in the lung express surface IgG and IgM. Crosslinking of surface IgG or IgM by antigen results in partial activation of B cells leading to expression of IL-2 receptors and MHC class II molecules,[1] which allows them to serve as accessory cells in T cell activation. With appropriate T cell help, activated B cells eventually differentiate into short-lived antibody-producing plasma cells or memory B cells, the latter being characterized by the co-expression of CD20 and CD27.[52] Other surface markers indicating B cell activation and differentiation include CD69, CD80, and CD86.[1] The latter two interact with CD28 and CTLA4 on T cells, respectively, thereby enhancing proliferation of helper T cells. Activation results in production of CD38+ CD138+ plasma cells, which secrete IgM (primary response) or other immunoglobulin isotypes (secondary immune responses).[53] IL-21 is critically important in the terminal differentiation and expansion of plasma cells.[54]

■ Cognate versus Noncognate Responses

Activated T cells can prove cognate and noncognate B cell help. Cognate B cell help is antigen- and MHC-restricted and occurs after helper T cells have been activated through T cell receptor (TCR)-MHC class II/antigen complex mechanisms. It was initially thought that B cells were the obligate accessory cells for cognate responses since B cell–T cell contact was occurring through MHC class II/antigen complexes on activated B cells and the TCR on T cells. In contrast, when T cells are stimulated by accessory cells other than B cells or activated in an accessory cell–independent manner (e.g., with immobilized anti-CD3), T cells can induce immunoglobulin production in many B cells in a non-MHC- or antigen (noncognate)-restricted manner. This latter phenomenon results in stimulation of both antigen specific as well as "bystander" B cells, leading to a polyclonal antibody response. Subsequent work has shown that this bystander response is present when T cells providing B cell help are highly activated and/or differentiated and is dependent on both B and T cell contact through CD40–CD40L receptor interactions as well as cytokine secretion from activated T cells.[55] Additional work has shown that the bystander effect can also be mediated by transfer of the B cell receptor from antigen-stimulated B cells to neighboring B cells, thereby greatly increasing the number of antigen-specific B cells available to stimulate T cells to provide help.[56]

■ Cytokine Secretion

Resting T cells provide poor B cell help. T cells that have been stimulated by antigen can be loosely divided into Th1 (T helper 1) and Th2 (T helper 2) cells based on the cytokine profile they secrete.[57] Th1 cells secrete predominantly interferon γ (IFN-γ) and IL-2 and are involved primarily in cellular immunity. Th2 cells secrete IL-4, IL-5, and IL-10 and drive humoral immunity. Th2 cells that provide B cell help are called "effector" cells. Signals from T cells to B cells are in two forms: direct cell-to-cell contact and cytokine secretion. While direct B cell–T cell contact is required for induction of antibody production, both Th1 and Th2 cell membranes can provide this signal.[58] What differentiates these two T cell populations is the cytokine profile they secrete. In particular, IL-4 seems to be an early competence factor that increases the number of B cells responsive to T cell help.[58,59] In contrast, IL-6 is a late factor that promotes continued B cell proliferation and immunoglobulin secretion.[59] IFN-γ downregulates most immunoglobulin secretion.[60] Thus, Th2 cells secrete a more favorable cytokine pattern for immunoglobulin production. The one exception is IgG2, which is dependent on IFN-γ secretion.[60]

Specific B Cell and T Cell Receptor Interactions and Downregulation of B Cell Responses

Tight regulation of antibody production and secretion is necessary to turn off the response when it is no longer needed and to prevent production of unwanted autoantibodies. This control is mediated through a combination of signaling pathways between T cells and B cells (Fig. 22-3). CD40L is an activation-induced molecule on CD4 T cells that delivers signals to B cells through its counterreceptor CD40, which is constitutively expressed on B cells. Highly activated T cells express increased CD40L. CD40 on B cells in turn downregulates CD40L on activated T cells.[61] These cells are subsequently unable to stimulate resting B cells. Thus, this may represent an attempt to downregulate noncognate immunoglobulin production. However, CD40 ligation is still critically important for cognate interactions. Crosslinking of surface immunoglobulin on B cells results in apoptosis of the B cell unless simultaneous binding of CD40 by CD40L occurs.[62] Interestingly, CD40 binding alone induces Fas expression on B cells, an effect that is not inhibited even in the presence of B cell tropic factors such as IL-2, IL-4, and IL-10.[63] Thus, ligation of CD40 acts to co-stimulate B cells that have been activated by binding of specific antigen while simultaneously increasing sensitivity to apoptosis in B cells not crosslinked by antigen. This drives an antigen-specific antibody response.[62]

The role of Fas/FasL interactions in modulating immune responses is well established. Activation of T cells upregulates expression of both Fas and FasL. This is seen as a mechanism to control chronic T cell activation.[64] Fas/FasL interactions are also important in modulating B cell responses.[65] As stated above, B cells stimulated through CD40 increase expression of Fas. Thus, these cells are susceptible to apoptosis mediated by FasL expressed by activated T cells. B cell apoptosis induced by FasL is blocked if there is simultaneous crosslinking of surface immunoglobulin by antigen, thereby preserving secretion of protective antibody in the presence of persistent pathogen exposure.

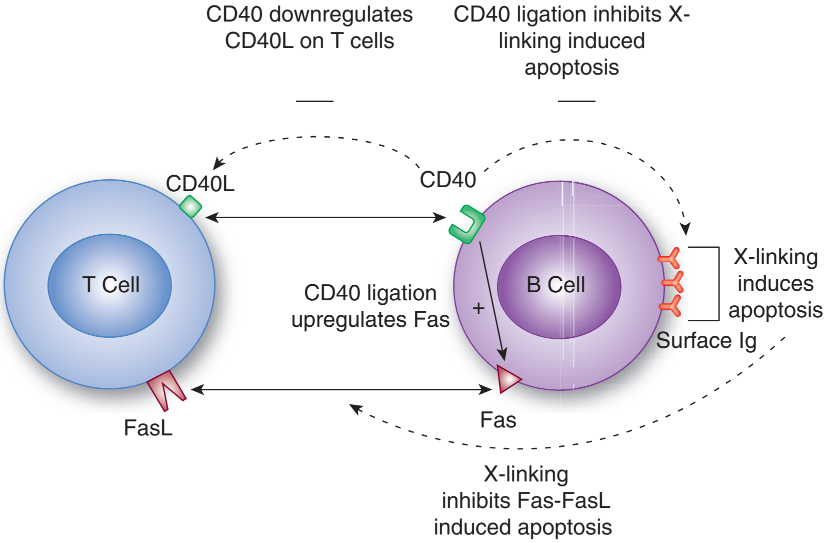
CD40 downregulates CD40L on T cells
—
CD40 ligation inhibits X-linking induced apoptosis
—
CD40L
CD40
T Cell
B Cell
CD40 ligation upregulates Fas
+
X-linking induces apoptosis
Surface Ig
FasL
Fas
X-linking inhibits Fas-FasL induced apoptosis

Figure 22-3 Interaction between T cells and B cells during the generation of a humoral response. Multiple signals occur between T cells and B cells. Depending on the presence or absence of crosslinking of surface immunoglobulin on B cells, T cells can either promote B cell growth or induce apoptosis.

Pulmonary Antibody Production in Response to Antigen Exposure

Pulmonary immunity to pathogens can be divided into innate and acquired responses. Most pathogens gaining access to the alveolar space are handled by phagocytosis by alveolar macrophages, the principal form of innate immunity. If phagocytosis of pathogens occurs in the absence of opsonizing antibody, this usually results in "non-inflammatory clearance," with minimal release of inflammatory mediators and preservation of lung structure and function.[66] If phagocytosis is overwhelmed, a specific acquired immune response occurs. This involves the interaction of B and T lymphocytes to produce an antigen-specific cellular and humoral immune response. In the lung, the acquired response has three distinct phases (Fig. 22-4)—afferent antigen processing and transport to regional lymph nodes,[67] presentation to naïve lymphocytes, and efferent migration of activated T lymphocytes and mature B cells back to

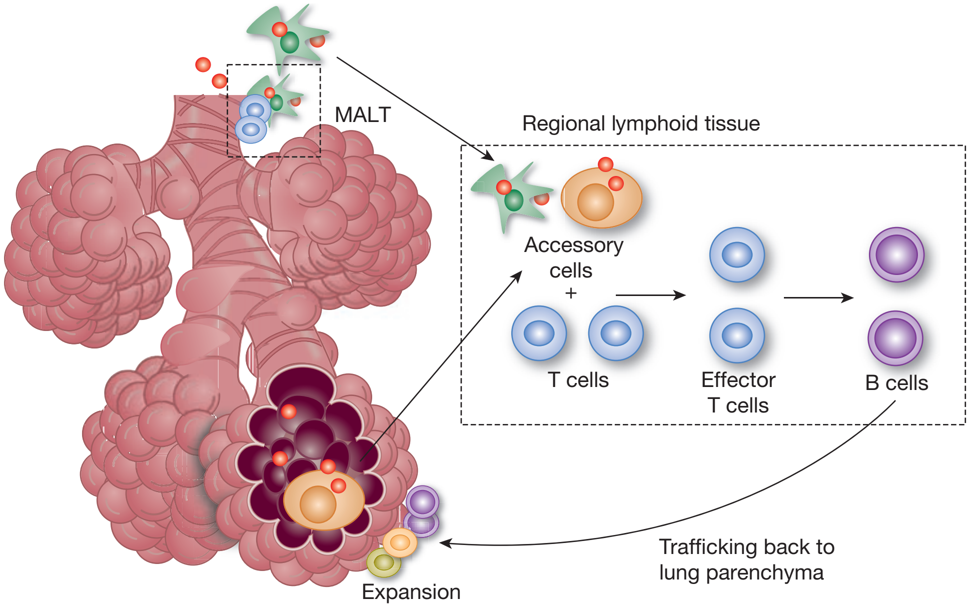

Figure 22-4 Pathway for generation of antigen-specific immune responses in the lung. Foreign antigen is taken up by antigen-presenting cells and transported to regional lymph nodes where the primary cellular and humoral immune response is generated. Effector cells then traffic back to the lung to the site of initial antigen challenge. B cells will become antibody-secreting plasma cells, while others will become memory B cells. This circuit is significantly shorter in the presence of mucosal-associated lymphoid tissue (MALT).

the site of initial antigenic challenge in the lung.[68] This results in the presence of antigen-specific immunoglobulin in the lung lining fluid and consequent increased effectiveness of professional phagocytes such as alveolar macrophages and neutrophils.[69]

This general pathway is similar for IgG and IgA production, although the length of the "circuit" is likely much less for IgA. Rather than having the antigen travel to regional lymph nodes, in mucosal immunity, IgA can be generated in specialized lymphoid tissue just beneath the mucosal surface, called mucosal-associated lymphoid tissue (MALT). This suggests that IgA-secreting plasma cells are produced locally, and IgA can readily diffuse back into the airspaces. Such submucosal lymphoid tissue in the upper airway, called nasal-associated lymphoid tissue (NALT), is seen in most animal species, including humans.[70] In contrast, in the lower respiratory tract bronchus-associated lymphoid tissue, or BALT, is readily demonstrable in mice[70] but has been more difficult to find in normal human airways.[71] Studies claiming that humans have BALT have generally been in subjects with an inflammatory pulmonary process.[72] To address these conflicting studies, the concept of inducible bronchus-associated lymphoid tissue, or iBALT, has been introduced. In mice, iBALT is clearly found in multiple infection models, including those lacking secondary lymphoid tissues (spleen, lymph nodes),[73] and is associated with robust B cell responses.[74] Similar pulmonary inflammatory conditions can induce iBALT in humans.[75] Thus, collections of antigen-presenting cells, B cells, and T cells in the submucosa, which are thought to collectively represent BALT, may be readily detectable only during times of antigenic challenge.

Once antibody producing B cells are formed in secondary lymphoid tissue or MALT, they must traffic back to the original point of entry of the pathogen. This trafficking of lymphocytes back to mucosal sites has been intensely studied, giving rise to a four-step model. The first step is tethering. L-selectin on lymphocytes interacts with addressins on endothelial cells to slow down the movement of lymphocytes through capillaries. In NALT, the responsible endothelial receptor is PNAd,[76] while in the lung, adhesion is mediated by ICAM-1.[77] Tethering leads to lymphocyte activation mediated by chemokines and their receptors and subsequent firm adhesion to the endothelium. The latter is mediated by LFA-1 binding to ICAM-1 and $\alpha_4\beta_7$ integrin binding to MADCAM-1.[78] Finally, diapedesis through the mucosa occurs, a process that probably involves all the above receptor–counter receptor interactions.

The end result of this process is the accumulation of antibody-secreting plasma cells at the site of initial challenge. Once the invading pathogen has been cleared, plasma cells disappear and are replaced by memory B cells. The great majority of B cells in the normal lung are mature memory B cells. This mirrors the predominance of memory T cells in the lung,[79] suggesting that the lung is primed to respond quickly to antigenic challenges. IgG-, IgM-, and IgA-secreting B cells are present in normal subjects; however, poor correlations exist between the numbers of Ig-producing BAL cells and the levels of Ig in BAL fluids.[20,80] In BAL fluid from nonsmokers IgG is present in the same proportion as in serum, leading to speculation that most IgG enters via transudation from the plasma compartments.[20,81] These two observations fit in well with the primary presence of memory B cells in the lung, suggesting that under resting conditions very little local antibody is made. Only after antigenic challenge is local production increased. In support of this is the finding of increased ratios of specific to total antibody in BAL fluid after pneumococcal infection, suggesting that local antibody production can be increased after relevant exposures.[82]

As will be discussed below, immunoglobulin deficiencies primarily lead to an increase in bacterial infections, including pneumonia. IgG seems to be particularly important in host defense against bacterial pneumonia. However, there appears to be an increased role for IgA protection in viral infections, likely due to the fact they are usually initially encountered at mucosal surfaces. Very recent studies exploring the pulmonary immune response to the SARS-CoV-2 demonstrate that both IgG and IgA are generated during infection and can be found in bronchoalveolar lavage and saliva in addition to serum.[83] Furthermore, IgA possessed more viral neutralizing capacity than IgG and persisted longer in saliva.[83] Similar observations have been observed in response to influenza infection,[84] suggesting that IgA is a critical component of host defense against viral pneumonia.

DISORDERS OF HUMORAL IMMUNITY AND LUNG DISEASE

In general, defects in humoral immunity result in an increased susceptibility to bacterial infections, including recurrent sinusitis, bronchitis, pneumonia, otitis media, and even meningitis. In particular, patients are susceptible to infection with encapsulated organisms, such as *Hemophilus influenzae*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Neisseria* species. Chronic diseases such as bronchiectasis and obstructive lung disease can result from recurrent infections. Antibody defects can be either quantitative (an absolute decrease or loss of antibody) or qualitative (poor antigenic specificity and or poor opsonic function). In addition, the presence of antibodies against host antigens can lead to autoimmune lung disease. Figure 22-5 shows some of the known molecular defects causing immunoglobulin deficiency. The cause of most of the selective immunoglobulin deficiencies described below is unknown.

■ Quantitative Defects

Isolated *IgA deficiency* is the most common primary immunodeficiency in humans, occurring in roughly 1 in 500 individuals.[85,86] The presence of selective IgA deficiency is defined by a serum IgA level of less than 7 mg/dL and normal levels of other immunoglobulins. Asthma, IgE-mediated allergic disease, and autoimmune diseases are more common in patients with IgA deficiency.[87,88] Potential explanations for these observations include the inability to clear allergic antigens[89] and dysbiosis of the gut and lung microbiome.[90,91] Only about a third of patients with IgA deficiency develop recurrent sinus, pulmonary, and gastrointestinal tract infections, usually with encapsulated bacteria. In the absence of an associated IgG subclass deficiency the development of structural lung disease is rare. These patients almost never require immunoglobulin replacement therapy. However, the coexistence of IgA and IgG subclass deficiency is extremely important to document since the latter may require immunoglobulin infusions. IgA-deficient patients are at increased risk for anaphylactic reactions after blood product infusions, including immunoglobulin preparations, because of the presence of IgG anti-IgA antibodies in up to 60% of individuals.[92] As such, when the decision is made to give immunoglobulin infusions to an IgG-deficient patient with a coexisting low IgA level, immunoglobulin preparations low in IgA must be used.

In contrast to IgA deficiency, patients with *IgG subclass deficiencies* frequently exhibit recurrent sinus and respiratory tract infections with encapsulated organisms regardless of whether it is associated with IgA deficiency.[93] Recurrent infections in IgG subclass deficiency can lead to chronic bronchiectasis, and assessment of immunoglobulin deficiency should be part of the standard evaluation of patients with unexplained recurrent infections with destructive lung disease. Decreased IgG2 is the most common IgG subclass deficiency and results primarily in an impaired ability to respond to polysaccharides.[22] As such, their response to the standard polysaccharide pneumococcal vaccine is poor, and they have an increased susceptibility to infections with encapsulated bacteria.[94] When IgG subclass deficiency is combined with IgA deficiency, the resultant lung disease is more severe than with either deficiency alone.

More severe disease occurs when there are multiple immunoglobulin defects. The most common immunodeficiency in this group is *common variable immunodeficiency (CVID).* Present in 1 in 25,000 individuals, this disease is characterized by hypogammaglobulinemia,

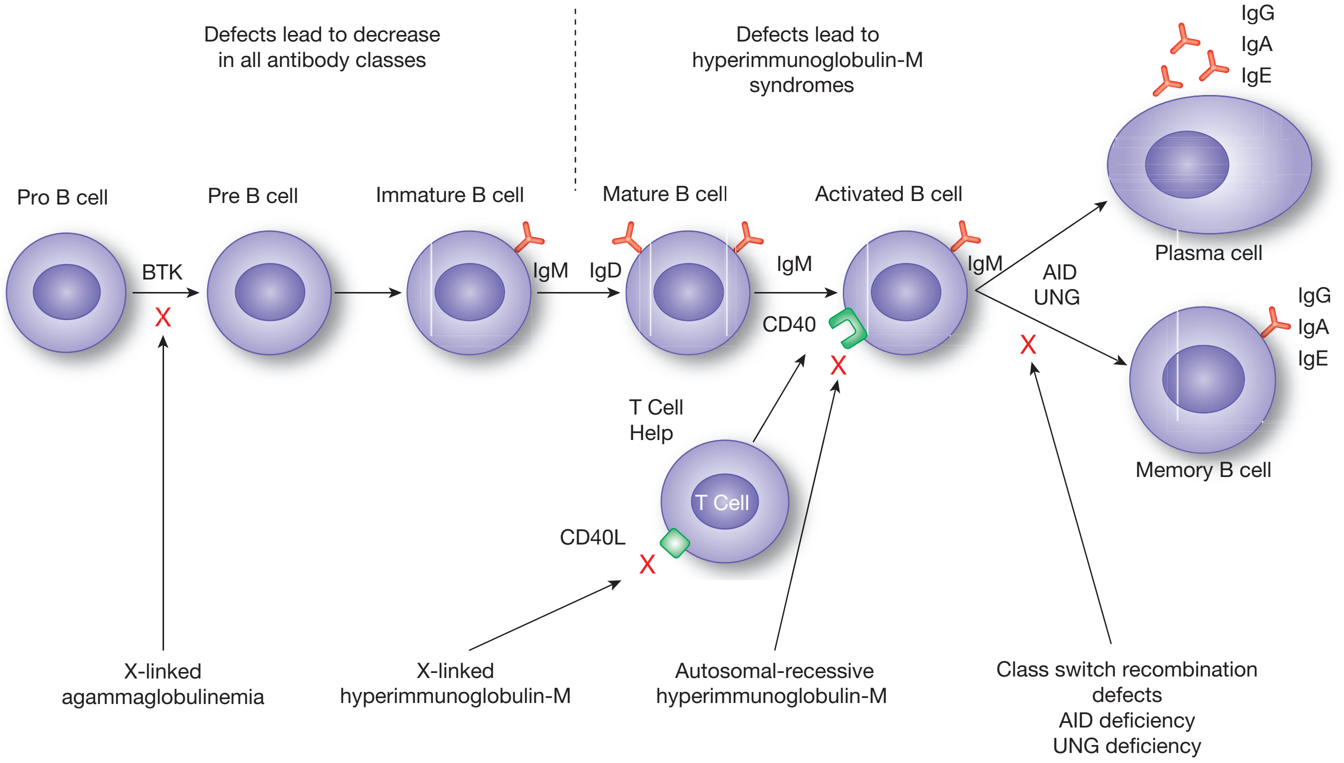
Defects lead to decrease in all antibody classes
Defects lead to hyperimmunoglobulin-M syndromes
Pro B cell
Pre B cell
Immature B cell
Mature B cell
Activated B cell
Plasma cell
Memory B cell
BTK
X
IgM
IgD
IgM
IgM
CD40
X
AID
UNG
X
IgG
IgA
IgE
IgG
IgA
IgE
T Cell Help
T Cell
CD40L
X
X-linked agammaglobulinemia
X-linked hyperimmunoglobulin-M
Autosomal-recessive hyperimmunoglobulin-M
Class switch recombination defects
AID deficiency
UNG deficiency

Figure 22-5 Known sites of molecular defects leading to immunoglobulin deficiency. Note defects that occur past the mature B cell stage tend to lead to hyperimmunoglobulin-M syndromes, while defects prior to this stage lead to loss of all immunoglobulin classes. AID, activation-induced cytidine deaminase; BTK, Bruton's tyrosine kinase; UNG, uracil-N-glycosylase.

decreased antigen-specific antibody responses, and recurrent sinopulmonary infections, frequently leading to chronic lung disease.[95] IgG levels are usually below 300 mg/dL and are accompanied by low IgA and IgM levels as well. Specific antibody responses to common antigens such as tetanus toxoid and pneumococcus are usually very low. Cellular immune defects, primarily lymphopenia with a normal or decreased CD4:CD8 ratio, also may be present. Thus, patients may present with infections typically associated with T cell defects (fungi, mycobacteria) in addition to infections caused by encapsulated bacteria. Proliferation of B cells and T cells in response to strong mitogens is impaired as well. While the cause of most cases of CVID is unknown, some patients have been found to have either intrinsic B cell genetic defects or defects affecting the ability of T cells to provide B cell help,[95,96] resulting in failure of B cells to class switch or terminally differentiate. Defects in immunity also impair immunosurveillance, leading to an increased incidence of autoimmune disease and malignancies in patients with CVID.[97,98]

Patients with *X-linked agammaglobulinemia (Bruton's agammaglobulinemia)* demonstrate a generalized defect in the ability to make all immunoglobulin classes. This is due to a deficiency of Bruton's tyrosine kinase (BTK), which is essential for early lymphopoiesis.[99] These individuals present in early childhood with recurrent middle ear, sinus, pulmonary, joint, bone, and CNS infections. They almost always develop chronic lung disease including bronchiectasis, pulmonary fibrosis, and pulmonary hypertension.[100,101] IgG levels are below 200 mg/dL and the other Ig subclasses may be absent. In contrast to patients with CVID, lymphoid tissue is hypoplastic in these patients.

Hyperimmunoglobulin M syndrome refers to several diseases characterized by low concentrations of IgG, IgA, and IgE, and a normal or elevated IgM level.[102] As might be expected based on our understanding of normal B cell development, these syndromes result from failure of IgM-secreting B cells to undergo class switching. The most common disorder is X-linked hyperimmunoglobulin M syndrome, which arises from a deficiency in the important T cell co-stimulatory molecule CD40L.[103] Deficiency in the B cell CD40 molecule also has been described, although this is rare.[104] Patients with either of these disorders have severely impaired T cell–dependent antibody production. Other hyperimmunoglobulin M disorders are caused by genetic mutations in the enzymes required for class switching, such as activation-induced cytidine deaminase[105] and uracil nucleoside glycosylase.[106]

Immunoglobulin replacement therapy can prevent recurrent infection and ameliorate some of the long-term sequelae of IgG deficiency.[107,108] Replacement therapy has also been reported to reduce the incidence of malignancies in patients with CVID.[98] However, it is important to base treatment decisions on the inability to make specific antibody, not just on an isolated low IgG (or IgG subclass) level. When immunoglobulin deficiency is suspected, total IgG, IgA, IgM, and IgG subclass concentrations are checked. A lymphocyte phenotype panel should also be obtained to look for low T and B cell numbers. If low antibody titers are detected, then one should measure common specific antibody titers. Usually, tetanus toxoid and pneumococcal antibody titers are assessed because this assesses both the ability to respond to protein (tetanus) and polysaccharide (pneumococcal) antigens. If specific antibody titers are low the patient should be given the tetanus or pneumococcal vaccine and repeat antibody titers obtained 4 weeks later. Failure to increase antibody titers into a "protective" range is indicative of immunoglobulin deficiency and warrants consideration of immunoglobulin replacement therapy. There are several immunoglobulin preparations available. As mentioned above, if IgA deficiency is present, a preparation that contains very low IgA should be used to minimize the risk of anaphylaxis.[92] The typical dose of immunoglobulin is 400 mg/kg given once a month, with a goal trough immunoglobulin immediately before the next infusion of 500 mg/dL.

Qualitative Defects

Once antibody is produced in the lung, it must be effective in promoting clearance of the offending pathogen. Only having a vigorous antibody response is insufficient. There are several diseases characterized by poor functioning antibody.

Specific antibody deficiency (SAD) is characterized by poor antibody responses to polysaccharide antigens despite normal IgG, IgG subclass, IgM, and IgA concentrations.[109] While many of the primary immunodeficiency diseases described above are associated with poor responses to polysaccharide antigens, SAD should be reserved for patients with only this specific defect. SAD is one of the most common immunodeficiencies, occurring in 5% to 10% of older children and adults presenting with recurrent sinopulmonary infections.[110,111] As with other immunoglobulin deficiencies, these patients also have an increased incidence of atopic disease. Since SAD is a diagnosis of exclusion, normal IgG, IgG subclass, IgM, and IgA levels must be demonstrated. To demonstrate polysaccharide unresponsiveness, baseline pneumococcal titers are measured and then the 23-valent polysaccharide pneumococcal vaccine is administered.[112] Four weeks later pneumococcal titers are repeated. An appropriate response is indicated by an antibody titer of 1.3 μg/mL or greater in 70% of the serotypes tested.[112] Some patients have an appropriate response to vaccination, but this is followed by a rapid loss of antibody titers over 6 months. These patients fall within the spectrum of patients with SAD. One of the main reasons for establishing the diagnosis of SAD versus other immunodeficiencies is the differences in treatment. Patients with SAD should be administered the 13-valent conjugated pneumococcal vaccine, which is more immunogenic due to the presence of a protein carrier attached to polysaccharide antigens, which acts as a hapten.[86,113] Prophylactic antibiotics are also frequently used in patients who have recurrent respiratory infections.[114] Unlike in more severe humoral immunodeficiencies, immunoglobulin replacement therapy is needed only in a minority of patients with SAD and should be reserved for those who fail vaccination strategies and prophylactic antibiotics.[109]

While *HIV infection* is most notably characterized by profound defects in cell-mediated immunity, antibody defects also are present. In fact, the occurrence of recurrent bacterial pneumonia remains an AIDS-defining illness in children and adults.[115] Pneumococcal infections are especially problematic in the HIV-infected population,[116] suggesting these patients have an especially profound defect in the ability to respond to polysaccharide antigens. Indeed, studies suggest that HIV-infected subjects have a relative defect in IgG2[117] and that this may be due to impaired T cell help toward IgG2 antibody-secreting cells.[118] The result is an antibody repertoire that is skewed towards pneumococcal proteins rather than polysaccharides.[119] These studies have been primarily performed on blood and various mucosal sites. Studies from the lower respiratory tract are more limited and demonstrate that there is an increased amount of total and pneumococcal-specific antibody in the alveolar space.[82,120] For example, in HIV-infected Malawians, a population with a high incidence of invasive pneumococcal infection, BAL contains four times the amount of pneumococcal-specific IgG compared with non-HIV-infected subjects. Capsule-specific IgG levels were highest in a group of HIV infected patients with recent invasive pneumococcal disease, suggesting that despite polyclonal IgG responses in HIV-infected adults, appropriate responses to infection also were present.[82] However, the ability of highly purified BAL IgG from HIV-infected subjects to bind pneumococci is impaired compared with BAL IgG from non-HIV-infected subjects.[121] This parallels the work of other investigators who have demonstrated impaired immunoglobulin opsonic function in HIV infected subjects, including activity against pneumococcus.[122,123] Thus, HIV-infected subjects appear to have dysfunctional pneumococcal antibody in the alveolar space. These findings highlight the fact that better correlates are needed for assessing the host response to natural infection or vaccination besides simple measurement of antibody concentrations.[124]

Pulmonary Disease Associated with Autoantibodies

There are many well-described lung diseases associated with the presence of autoantibodies. Classically these have been described in patients with vasculitic processes such as Goodpasture's syndrome, granulomatosis with polyangiitis, and various connective tissue diseases. A discussion of these disorders is beyond the scope of this chapter. However, a great deal of interest is now turning toward the potential role of autoantibodies in some of the more commonly encountered lung diseases.

Chronic obstructive pulmonary disease (COPD) is increasingly being thought of as an autoimmune disease.[125] Multiple reports demonstrate increased evidence of B cell activation in patients with emphysema.[126–128] While early reports of increased anti-elastin antibodies in patients with COPD[129] have not been uniformly supported,[130,131] investigations continue to demonstrate increased general autoantibodies[132] as well as more specific antibodies against collagen V,[131] cytokeratin,[133] and epithelial and endothelial antigens.[134,135] Furthermore, lymphoid follicles consisting of B cells and follicular dendritic cells with adjacent T cells are present in the parenchyma and in bronchial walls of patients with emphysema, suggesting that at least some these antibodies may be locally produced.[136] This is further supported by detailed studies demonstrating that the B cells in these aggregates have a limited (oligoclonal) repertoire.[136] That these autoantibodies may be pathogenic is suggested by the presence of immune complex and C3 deposition in the lungs of patients with emphysema[134] and strong relationships between evidence of B cell activation and the severity of radiographic emphysema.[128] In animal models, smoking is able to induce autoantibodies against extracellular matrix proteins in mice,[137] and adoptive transfer of anti-endothelial antibodies can cause emphysema in rats.[138] This discussion would suggest immunosuppressive medications may be effective in COPD. Indeed, systemic and inhaled corticosteroids result in decreased lymphoid aggregates in the lungs of humans with COPD.[139] Trials are currently underway examining whether anti–B cell therapies have a role in slowing the progression of COPD.[140] Whether reduction in lung B cell immunity is ultimately helpful or harmful will depend on the balance between secretion of destructive autoantibodies or protective antibodies against microbes that have colonized the airway of these patients.

Another lung disease in which autoantibodies may contribute to pathogenesis is *pulmonary fibrosis*. The current paradigm for the pathogenesis of pulmonary fibrosis starts with lung epithelial and or microvascular injury leading to an exaggerated inflammatory and fibrotic response. While extensive literature exists on the inflammatory and fibrotic response, much less is known about the inciting event. In pulmonary fibrosis associated with connective tissue disease, numerous autoantibodies have been described and in patients presenting with fibrotic lung disease, screening should include testing for antinuclear antibodies (ANA is nonspecific; but, if positive, should prompt search for systemic lupus erythematosus, mixed connective tissue disease, systemic sclerosis, and CREST syndrome), anti-Jo-1 (inflammatory myopathies and anti-synthetase syndrome), SSA and SSB (Sjögren's Syndrome), rheumatoid factor and cyclic citrullinated peptide antibodies (rheumatoid arthritis), and antineutrophil cytoplasmic antibodies (microscopic polyangiitis and other ANCA-associated vasculitis).[141] Many of these antibodies are also found in patients with idiopathic pulmonary fibrosis (IPF) but without overt signs of autoimmune disease,[142] but whether they are pathogenic is not known. Antibodies to alveolar epithelial cells and components or their tight adhesion junctions have been found in patients with IPF and correlate with disease severity.[143,144] More recently, antibodies to modified proteins (citrullinated, acetylated,

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carbamylated) have been found in patients with IPF and rheumatoid arthritis associated pulmonary fibrosis,[145–147] suggesting that inflammation-induced protein damage may lead to autoimmunity capable of perpetuating the fibrotic response. These same considerations have led to questions of whether the presence of autoantibodies in pulmonary fibrosis is causative or just an epiphenomenon.[148]

Dysregulated humoral immunity also plays a role in *lung transplant rejection.*[149] B cells are a prominent finding in areas of the lung demonstrating obliterative bronchiolitis, the pathologic hallmark of lung rejection.[150] Furthermore, recent work has demonstrated that blocking the development of B cell lymphoid follicles can prevent lung transplant rejection in a murine model.[151] Like most cases of organ rejection, the classic response is felt to be donor-specific antibodies against donor HLA antigens.[152] However, there is also ample evidence that autoantibodies against collagen V and K-alpha 1 tubulin also play an important role, especially in chronic rejection.[153] In fact, there is increased collagen V expression in obliterative bronchiolitis lesions and the presence of collagen V antibodies in the lungs of patients who had lung transplant rejection.[154] Furthermore, the presence of circulating anti–collagen V antibody predicts primary graft dysfunction after transplant.[155] That autoantibodies may have a pathogenic role in lung transplant rejection is further supported by studies demonstrating that anti–B cell targeted therapies such as rituximab or intravenous immunoglobulin therapy reduce the concentration of the autoantibody and reduce the severity of rejection.[156]

PULMONARY ANTIBODY RESPONSES TO VACCINATION

The pulmonary antibody response to a variety of vaccinations, including pneumococcal and influenza vaccinations, is an important clinical consideration, as discussed below.

■ Systemic versus Mucosal Vaccination

Vaccination against pulmonary pathogens is a common and effective practice against many diseases. However, mechanisms behind their effectiveness are not always clear. Both IgG and IgA have a role in protection after vaccination, providing systemic and mucosal protection, respectively. Mucosal immunity is especially important for pulmonary pathogens,[157] where the mucosal barrier needs to be breached to cause disease. The presence of pathogen-specific IgA should decrease colonization of the respiratory tract by limiting attachment to respiratory epithelium. Since airway colonization is usually the first step in the development of bacterial or viral pneumonia, decreased colonization should lead to a decreased incidence of pneumonia. When pathogens manage to reach the alveolar space, IgG takes on a greater role as an opsonin in the phagocytosis of organisms. Thus, the most effective immunity against infections should involve both IgG and IgA responses. Nonetheless, the vaccine delivery mechanism impacts the type of immune response generated. In general, systemic administration of an antigen results in the generation of circulating IgG, some of which will diffuse into the epithelial lining fluid. In contrast, mucosal antigenic challenge results in a more vigorous IgA response locally at the site of challenge.[157] Whether systemic immunization can induce effective mucosal immunity is controversial and an intense area of study.[158] While there is no question systemic vaccination can ameliorate pulmonary disease as discussed below, there are two factors that theoretically favor attempts to induce mucosal immunity. First, mucosal immunity can be induced through exposure of vaccines to mucosal surfaces and thus alleviate the need for needles, thereby improving tolerance and acceptability.[159] Second, by preventing the initial binding of pathogens to mucosal surfaces, mucosal immunity can actually prevent disease rather than just decrease its severity.[160] In fact, vaccination efforts to eliminate disease have generally used mucosal approaches, the eradication of polio and smallpox being prime examples.[161,162]

Despite the recognition that local antibody may be important in pulmonary host defense, there is remarkably little information on humoral responses in the respiratory tract after systemic immunization, the standard approach to most vaccine strategies. In a mouse model of mucosal immunity against *Mycoplasma pulmonis*, it has been demonstrated that the site of antigen deposition greatly influences the antibody response and subsequent protective immunity.[163] Intranasal challenge resulted in an increase in IgA antibody–forming cells in the nasal submucosa and an increase in mycoplasma-specific IgA in nasal washes. Low numbers of IgA antibody–forming cells and IgA concentrations were seen in the lung after isolated nasal challenge, but were increased significantly if animals received both nasal and pulmonary immunization. Both nasal and nasal-pulmonary vaccine exposures resulted in equivalent antigen-specific IgA and IgG in the systemic circulation. Both forms of immunization also significantly reduced the ability of mycoplasma to colonize the nasal passages after experimental exposure to a mycoplasma inoculum. However, animals receiving nasal-pulmonary immunization had significantly fewer organisms in the lungs compared with animals that received only nasal immunization. Since serum mycoplasma-specific IgA and IgG were similar after both types of immunization, this suggests that circulating antibody is less effective in protection against pulmonary pathogens compared to locally produced antibody.

In another animal immunization model against a different pulmonary pathogen, *Moraxella catarrhalis*, the site of specific antibody production and protection after intranasal and subcutaneous challenge was examined.[164] Intranasal administration of *M. catarrhalis* surface proteins resulted in antigen-specific IgA and IgG in both nasal washes and BAL. IgA concentrations far exceeded IgG concentrations in both sites. IgA was significantly higher in BAL and nasal washes than in serum, whereas IgG was higher in serum than both mucosal sites. Immunization was associated with a marked increase in bacterial clearance after intranasal challenge with live *M. catarrhalis* organisms. As might be predicted, subcutaneous administration of the same vaccine resulted in production of far greater antigen-specific IgG compared to IgA, especially in the lung, where *Moraxella*-specific IgG in BAL was nearly 20 times greater than that found in nasal washes. Subcutaneous vaccination induced a marked systemic IgG response, but virtually no antigen-specific IgA in serum, BAL, or nasal washes. Interestingly, despite the brisk systemic and pulmonary IgG response after subcutaneous immunization, intranasal immunization promoted significantly greater bacterial clearance after intranasal challenge with the organisms. These data further support the general premise that while systemic vaccination results in antigen-specific IgG that may passively diffuse into the epithelial lining fluid in the lung, better protection will be afforded if local IgA immune responses also are induced.

The effect of the intranasal and intramuscular polysaccharide pneumococcal vaccine has also been studied in a mouse model.[165] Intranasal vaccination, when accompanied by IL-12 administration (which increases IFN-γ production), resulted in increased serum IgG2a anti-pneumococcal antibody, consistent with the known stimulatory effect of IFN-γ on IgG2a production.[60] This regimen also resulted in increased pneumococcal-specific IgA in BAL fluid. The serum antibody response was functional in opsonophagocytosis assays. Interestingly, intramuscular vaccination afforded more protection against subsequent intraperitoneal pneumococcal challenge compared with intranasal vaccination. In contrast, intranasal vaccination was more effective in reducing nasopharyngeal colonization after nasal challenge of the organism compared with intramuscular vaccination, despite the higher serum IgG response after the latter. Finally, using IgA knockout mice, these investigators demonstrated that IgA was responsible for reducing pneumococcal colonization after vaccination and intranasal challenge.[165] These early findings using the pneumococcal polysaccharide vaccine have been confirmed more recently by two studies using pneumococcal surface protein A vaccines.[166,167] Both these studies demonstrated greater mucosal anti-pneumococcal IgA and better protection against pneumococcal challenge after intranasal vaccination compared with subcutaneous vaccination. Similar findings were observed when systemic versus mucosal vaccination against influenza was studied in mice.[168]

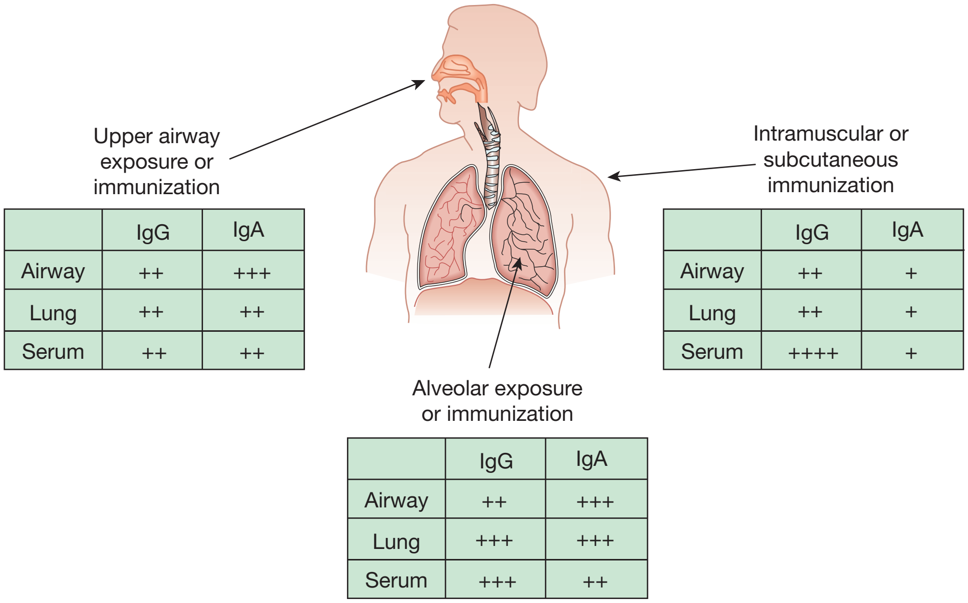
There are significantly fewer studies on the pulmonary response to vaccines in humans. One study compared oral and nasal administration of a cholera toxin B subunit vaccine.[169] Nasal immunization resulted in fivefold increases in the levels of specific IgA antibodies in BAL fluid. No significant specific IgA responses were seen after oral immunization. Specific IgG antibody concentrations increased eightfold in BAL fluid in the nasally vaccinated subjects, although this was felt to be from transudation from serum rather than local production. Several studies have examined systemic and salivary pneumococcal-specific antibody titers after systemic vaccination in children. Infants given the 7-valent conjugated pneumococcal vaccine at 1, 2, and 3 months followed by the 23-valent polysaccharide vaccine at 9 months developed significant IgG and IgA titers in saliva up to 18 months of age.[170] Other investigators have shown that salivary anti-pneumococcal IgA, especially IgA1, can persist for 4 to 5 years in saliva after vaccination;[171] interestingly in this study, there was no difference in antibody titers between vaccinated and unvaccinated children at this time point, suggesting that natural environmental exposure also results in mucosal immunity. Finally, immunization with the pneumococcal polysaccharide vaccine has been shown to lead to an increase in salivary pneumococcal-specific IgG and IgA in adults as well.[172]

In total, these studies suggest that in general systemic vaccination induces primarily an IgG response whereas mucosal vaccination induces primarily an IgA response (Fig. 22-6). While it is clear systemic immunization can result in some local lung IgA production, the strongest mucosal immunity is induced when antigen is introduced directly into the respiratory tract. Intranasal and inhaled vaccines offer advantages in addition to the potential for improved local immunity, including the ability to immunize large populations at less cost.[173] However, despite all the theoretical benefits of mucosal vaccination, systemic vaccination remains the most prominent form today for several reasons.[174] First, mucosal vaccines typically require far greater amounts of antigen to ensure adequate absorption, and amounts needed vary by mucosal site.[175] Thus, production and quality control become more difficult. Second, mucosal vaccines are frequently live attenuated forms of the original pathogen. As such, they have the potential either to cause disease in immunosuppressed subjects or subjects with immature immune systems, as is the case for the inactivated influenza vaccine,[176] or to mutate and cause vaccine strain–related disease, as is the case for the oral poliovirus vaccine.[177] Finally, while mucosal vaccination can prevent disease at mucosal sites, it is often site-specific and potentially less effective at preventing systemic disease.[178]

Vaccination Against Pneumococcal Disease

There are currently two active vaccines against pneumococcal disease: the 23-valent pneumococcal polysaccharide vaccine (23-PPV) and the 13-valent pneumococcal conjugate vaccine. Because the conjugated vaccine contains protein linked to various polysaccharides, it is theoretically more immunogenic by virtue of its ability to induce T cell help for antibody secretion. The 23-PPV comprises capsular polysaccharide from 23 of the 92 serotypes of *Streptococcus pneumoniae*. Cross-reactivity between serogroups and the epidemiology of disease suggest that this vaccine should be effective against 80% to 90% of strains world-wide.[179] Interestingly, there is some suggestion that active vaccination strategies that reduce carriage of vaccine component serotypes may lead to replacement by nonvaccine serotypes, thereby reducing vaccine coverage.[180,181] In a recent study the 23-valent and 13-valent pneumococcal vaccines covered only 66% and 56.8%, respectively, of pneumococcal serotypes isolated from patients with pneumococcal pneumonia.[182]

While many studies suggest the pneumococcal vaccine is effective in reducing the morbidity and mortality of pneumococcal disease,[183–185] this is not a universal finding. Some studies and meta-analyses suggest the benefit is modest at most and most evident in preventing severe disease.[186–188] There are likely many reasons for these discrepant studies. Certainly study endpoints are important, and several studies suggest that pneumococcal vaccination is more effective in preventing severe systemic disease than pneumonia.[186,187] This is not surprising given the discussion above on vaccine delivery and subsequent immune responses. Since current pneumococcal vaccines are administered intramuscularly, one would predict they have greater protection against severe systemic disease than pneumonia or colonization, which is more responsive to mucosal vaccination strategies. Second, given the changing nature of serotype coverage in different parts of the world, it is likely that in some negative studies pneumococcal disease was being


Upper airway exposure or immunization
Intramuscular or subcutaneous immunization
Alveolar exposure or immunization

	IgG	IgA
Airway	++	+++
Lung	++	++
Serum	++	++

	IgG	IgA
Airway	++	+
Lung	++	+
Serum	++++	+

	IgG	IgA
Airway	++	+++
Lung	+++	+++
Serum	+++	++

Figure 22-6 Summary of IgG and IgA concentrations at various sites after upper airway, lower airway, or systemic exposure to bacteria, either as a pathogen or in a vaccine.

caused by serotypes not found in vaccines. In support of this, a comprehensive review of pneumococcal vaccine effectiveness found that the greatest benefit was in preventing disease caused by serotypes found in the vaccine.[189]

The effect of pneumococcal vaccination on respiratory tract antibody concentrations is not clearly defined. Most studies assessing the immune response to the pneumococcal vaccine focus on serum and salivary antibody titers. Only a few studies have tried to analyze the pulmonary response after vaccination. One study found no difference in the opsonic function of BAL IgG against pneumococcus 1 and 6 months after systemic immunization with the conjugate pneumococcal vaccine.[190] In another study the effect of intramuscular administration of the 23-valent vaccine was compared with inhalation of the same preparation.[191] Bronchoalveolar lavage was performed on month after vaccination. Intramuscular administration resulted in significant increases in serum and BAL pneumococcal-specific IgG titers. Pneumococcal-specific IgA1 titers increased in serum, but not in BAL. This observation supports the concept that mucosal exposure is needed to generate local IgA responses. No change was seen in any serum or BAL measurement in subjects who inhaled the vaccine. Similarly, nasal inoculation with two live pneumococcus serotypes induced local pneumococcal specific IgG and IgA in nasal washes and bronchoalveolar lavage, but did not affect serum anti-pneumococcal titers.[192] This contrasts with two other studies that found a mild systemic IgG response to inhaled pneumococcal vaccine.[193,194] Lung-specific measurements were not assessed in these latter two studies. Thus, studies to date suggest that while mucosal vaccination against pneumococcus may offer advantages in preventing pneumonia, effective immunization against pneumococcus still requires systemic (intramuscular) immunization, especially with regard to preventing severe invasive disease.

■ Vaccination Against Influenza

Vaccination against influenza is generally effective in preventing morbidity and mortality.[195,196] Effectiveness varies from year to year due to the constantly changing genetic makeup of circulating viruses. For example, a recent analysis from the CDC showed that from years 2004 to 2020 influenza vaccine effectiveness ranged from 10% in the 2004–2005 season to 60% during the 2011–2012 season. Each year world experts meet to determine the upcoming vaccine composition.[176] There are two currently available routes for influenza vaccination in humans. The most common are intramuscularly administered trivalent (made up of three strains) or quadrivalent (made up of four strains) killed (inactivated) vaccines. Depending on the manufacturer, vaccines may contain either whole killed viruses or further purified viruses to isolate the immunodominant neuraminidase and haemagglutinin antigens, which give rise to the classic “H” and “N” nomenclature used for influenza virus. A second formulation consists of a live attenuated influenza vaccine and is given intranasally. Because it is a live vaccine it is not used in individuals with underdeveloped or impaired immunity. Thus candidates for the nasal vaccine are individuals between the age of 2 and 49 with no existing potentially immunosuppressive condition, including pregnancy.[176]

Because there are systemic and mucosal vaccination options for influenza, more is known about the pulmonary immune response to these vaccines.[197] In one study, comparison of inactivated intramuscular and live intranasal influenza vaccines in young children undergoing primary immunization demonstrated that the intranasal preparation induced longer-lasting protective antibody concentrations.[198] Nasal secretory IgA developed almost exclusively in nasally vaccinated individuals, whereas nasal IgG was detected in both nasal and intramuscular vaccine recipients. In general, studies show that influenza intramuscular vaccinations result in a strong IgG response but minimal mucosal influenza-specific IgA. In contrast, the nasal live attenuated vaccine gives a stronger mucosal IgA response. Furthermore, because it results in low-level infection, the intranasal formulation also induces a specific cellular (cytotoxic T cell) response.[199] Studies that have directly compared the clinical efficacy of the two vaccine strategies have generally found that intramuscular injection of inactivated influenza virus is generally slightly superior to use of the live attenuated intranasal virus in adults,[200,201] whereas the intranasal approach may be more effective in children.[202]

Newer vaccine strategies are being developed to enhance population vaccination strategies and improve immunogenicity in individuals with poor antibody responses. Studies comparing high-dose versus standard-dose influenza vaccination in subjects over 65, a population known to have a poorer vaccine response, demonstrate that high-dose vaccination is more effective.[203] Novel adjuvants are also being developed to augment the immune response to influenza vaccines.[204] Another innovative approach is to target more conserved influenza antigens, which would obviate the need for yearly vaccination.[205,206] However, many conserved epitopes are poorly immunogenic, indicating that novel delivery methods will be necessary to elicit broad immune responses. Nanoparticles are being studied in vaccine formulations because of their ability to enhance antigen stability and immunogenicity and provide a mechanism for targeted delivery and slow release.[207] Newer animal models are exploring the use of adenovirus vectors to immunize with conserved influenza vaccines.[208] Thus, recent advances in vaccine strategies offer hope that newer influenza vaccines will generate broader antigenic coverage, induce both humoral and cellular immunity, and provide longer-lasting and better protection against this worldwide pathogen.

CONCLUSION

The humoral immune response is essential for host defense against pathogens. After exposure to infectious microbes, antibody responses in the respiratory tract can occur either quickly through activation of resident memory B cells if there has been prior pathogen exposure, or more slowly through the induction of both systemic and local mucosal immunity if the host is naïve to the organism. The resulting production of antigen-specific IgG and IgA acts to help clear the invading pathogen and reduce subsequent colonization of respiratory epithelium. The type and concentration of antibody produced is dependent on the site of exposure. Upper airway exposure results in primarily an IgA response. Organisms that reach the lung after passing through the upper airway induce a more systemic response, including increased production of pathogen-specific IgG. The importance of an effective pulmonary antibody response is highlighted by the significant morbidity associated with diseases characterized by deficient or defective antibody production. Increasing evidence is also pointing toward a key role of autoantibodies in many common lung diseases. Finally, vaccination against respiratory pathogens is dependent on an intact humoral immune system. Systemic vaccination against respiratory pathogens, while effective in generating systemic IgG responses and some mucosal IgA responses, may be less effective than vaccination through mucosal surfaces, which induce a brisk IgA and IgG response both locally and systemically depending on the site of vaccine deposition. Future studies should provide further insight on the pulmonary humoral host response to microbial challenge and optimal vaccine regimens to minimize the burden of respiratory disease caused by these organisms.

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CHAPTER 23

T Cell Responses in the Lung

Lauren Cohn

INTRODUCTION

The lung is a major site of exposure to the outside world in air-breathing species. Lung immunity has developed to recognize pathogens and activate appropriate responses, to temper inflammation in response to nonpathogenic exposures, and to turn off immune responses when danger signals have been shut down. T lymphocytes play a major role in lung immunity predominantly as CD4+ and CD8+ T cells involved in adaptive immunity. A number of smaller subsets of T lymphocytes also play critical roles in early immune responses to pathogens and to stimulate adaptive immune responses. Long-lived memory CD4+ and CD8+ T cells are crucial for host protection from pathogens, but they also may drive chronic disease states such as asthma. This chapter reviews the basic biology of T lymphocytes and their relevance in the lung in health and disease.

T LYMPHOCYTE SUBSETS

Lymphocytes make up approximately 10% of leukocytes in the blood and nearly 70% of leukocytes in the normal human lung.[1] In both sites, a majority of lymphocytes are T lymphocytes. Lymphocytes include T and B cells and are small, mononuclear cells with a characteristic large nucleus-to-cytoplasm ratio in the resting state. T lymphocytes have their origin in the thymus. T lymphocytes are essential for adaptive immune responses, the type of immunity that develops over a period of days to weeks and fine-tunes an immune response to limit a specific pathogen or insult. The majority of T lymphocytes express alpha-beta (α/β) T cell antigen receptors (TCRs) on the cell surface. The α/β TCR consists of two polypeptide chains with a variable region that binds to antigen, a constant region, and an anchor to the cell membrane. During development in the thymus, T cells undergo TCR gene rearrangement to generate a receptor that has an antigen-binding structure. Each mature T cell bears only this TCR with its unique specificity for antigen binding. Approximately 10^6 different TCRs develop and allows an individual to respond to an extraordinary range of antigens throughout life. After exposure to a new antigen, TCRs expressed on conventional CD4- and CD8-expressing T lymphocytes develop even finer antigen-binding capabilities through a process called affinity maturation.

There are also unconventional subsets of T lymphocytes that express T cell receptors with restricted diversity and include NKT and MAIT cells that express an α/β TCR, and gamma-delta (γ/δ) TCR-expressing cells. These populations of T lymphocytes are typically fewer in number and more prominent at sites of pathogen exposure, such as the mucosal surfaces. They express preformed receptors that bind to common pathogen components. This preset ability to bind and react to pathogens allows them to respond quickly, leading to early release of cytokines. NKT, MAIT, and γ/δ T cells are part of the early immune response to pathogens and other insults and provide signals to initiate and direct CD4 and CD8 T cell activation in the adaptive immune response.

T lymphocytes that express α/β TCR most commonly also express a co-receptor CD4 or CD8. CD4-expressing T cells are called T helper (Th) cells because of their ability, through production of cytokines, to instruct and activate other cells. Another subset, CD4 regulatory T cells (Treg), downregulate immune responses. CD8-expressing T cells, traditionally called cytotoxic T cells (Tc), release preformed effector molecules that destroy infected cells. They also produce cytokines that aid in local immunity. TCRs on CD4+ T cells recognize peptide antigens that bind to domains on MHC class II molecules that are present on the surface of antigen-presenting cells (APCs). CD8+ T cells recognize endogenously derived antigens bound to MHC class I molecules. MHC class I molecules are present on the surface of all nucleated cells, whereas MHC class II molecules are only present on APCs, including dendritic cells, B cells, and macrophages. Exogenous protein antigens, such as extracellular pathogens and environmental substances, are taken up by APCs and processed into peptides in endocytic vesicles, which are presented on the cell surface bound to MHC II molecules. Endogenous antigens, such as those of intracellular pathogens, including viruses, are processed and presented by class I MHC molecules.

CD4+ T CELLS

Below are selected aspects of CD4+ T cell activation and differentiation, as well as elements of CD4+ effector/memory and regulatory cells.

CD4+ T Cell Activation

Mature, naïve CD4+ T cells are released from the thymus into the circulation and enter the lymph node through specialized blood vessels, the high endothelial venules (HEVs). Expression of L-selectin (CD62L) on the naïve CD4 T cell along with chemokine signals produced by stromal cells within lymphoid tissues permits attachment and transit through the HEVs into the lymph node.[2,3] In the lung, this occurs in the lymph nodes that drain the trachea, bronchi, and lung parenchyma.

Antigens or pathogens that enter the lung are taken up by APCs in the airways and alveoli. DC are the major APC of the mucosal surfaces. DC in the airway walls and alveoli form a dense network just beneath the epithelium with processes that extend to the air-spaces, designed to catch foreign antigens.[4] Macrophages in the airways and lungs also engulf large particles and pathogens through phagocytosis, but they are typically poor stimulators of adaptive immune responses, and likely eliminate antigens or induce regulatory responses, rather than activate immunity. After antigen uptake, APCs break down antigens into peptide fragments in endocytic vesicles, where the peptides are loaded onto class II MHC proteins and transported to the cell surface. Concurrent with antigen presentation, the APC increases expression of co-stimulatory molecules and migrates to the lung-draining lymph nodes.

In the T cell area of the lymph node, naïve CD4+ T cells move past antigen-expressing APCs, permitting the interaction of TCR and MHC class II-peptide. When the TCR on a CD4+ T cell interacts with its specific antigen on an APC, it ceases to migrate further. T cell activation is initiated upon (1) TCR recognition of MHC class II peptide and (2) co-stimulatory signaling from the APC (Fig. 23-1). The principal co-stimulatory molecules expressed on the surface of APCs are CD80 (B7-1) and CD86 (B7-2), which both interact with

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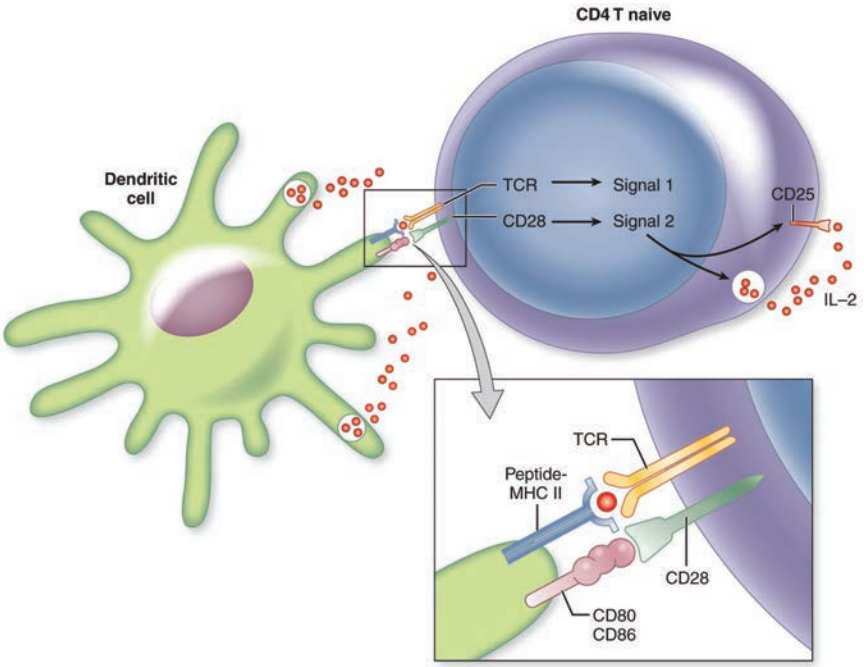

Figure 23-1 Two-signal mechanism of CD4 T cell activation. An antigen-presenting cell (APC) takes up a protein antigen and processes it into peptide fragments that are presented by class II major histocompatibility complex (MHC) molecules. A naïve CD4 T cell and APC interact with **Signal 1**, which is engagement of the T cell antigen receptor (TCR) and class II MHC-peptide complex, and **Signal 2**, the interaction of CD28 on the T cell with CD80 or CD86 on the APC, termed co-stimulation. These signals stimulate interleukin-2 (IL-2) production and IL-2 receptor (IL-2R) expression, and they induce CD4 T cell proliferation.

CD28 on the T cell.[5] If both signal 1 and signal 2 are received, the T cell goes into G1 phase of the cell cycle, begins to produce interleukin-2 (IL-2), and undergoes clonal expansion. This gives rise to a population of effector cells with the identical TCR specificity to the parental cell.

■ CD4+ Helper T Cell Differentiation

The primary immune response and molecular mechanisms of CD4+ Th cell differentiation are considered below.

Primary Immune Response

Antigen-activated CD4+ T cells differentiate into effector cells of different subsets defined by the cytokines they produce and expression of lineage-defining molecules (Table 23-1).[6] *T helper type 1* (Th1) cells are a subset of CD4+ T cells that secrete the macrophage activating factor interferon gamma (IFN-γ), as well as lymphotoxin (LT or TNF-β), and express the molecule t-bet. Th1 cells stimulate strong cell-mediated immune responses, particularly against intracellular pathogens.

TABLE 23-1 T Lymphocyte Subsets, Signals and Functions

		Signals to Activate/Differentiate			
T Lymphocyte		Cytokine	Transcription Factor	Cytokines and Mediators Produced	Major Functions
CD4 Activated by peptide- MHC class II	Th1	IFN-γ, IL-12	T-bet	IFN-γ, lymphotoxin	Antiviral and -mycobacterial effects, activation of macrophages to kill intracellular pathogens
	Th2	IL-4	GATA-3	IL-4, IL-5, IL-13	Antiparasitic responses Stimulation of IgE and other antibody production, increased mucus production, promotion of eosinophilia
	Th17	IL-6, TGF-β1, IL-1β (human)	RORγt	IL-17A, IL-17F, IL-22	Antibacterial and -fungal effects, recruitment and activation of PMNs
	Treg	TGF-β1, IL-10	FoxP3	TGF-β1, IL-10	Suppression of T cell activation, inhibition of APC function
	Tfh	IL-6	BCL6	IL-21, IL-4 (and crucial signaling molecules incl. CD40-ligand)	Promote antibody production by B cells in germinal center
CD8		Peptide-MHC class I		IFN-γ, TNF-α Granzyme, perforin	Cytotoxicity of cells infected with virus or bacteria
iNKT		Glycolipids		Extensive range of pre-formed cytokines that are rapidly released	Shaping adaptive immunity against pathogens
MAIT		Vitamin B metabolites		IFN-γ, TNF-α, IL-17, granzyme	Antimicrobial responses
γ/δ		Mycobacterial lipids, heat-shock proteins, lipid antigens		Extensive range of pre-formed cytokines that are rapidly released	Antimicrobial responses, immunosurveillance

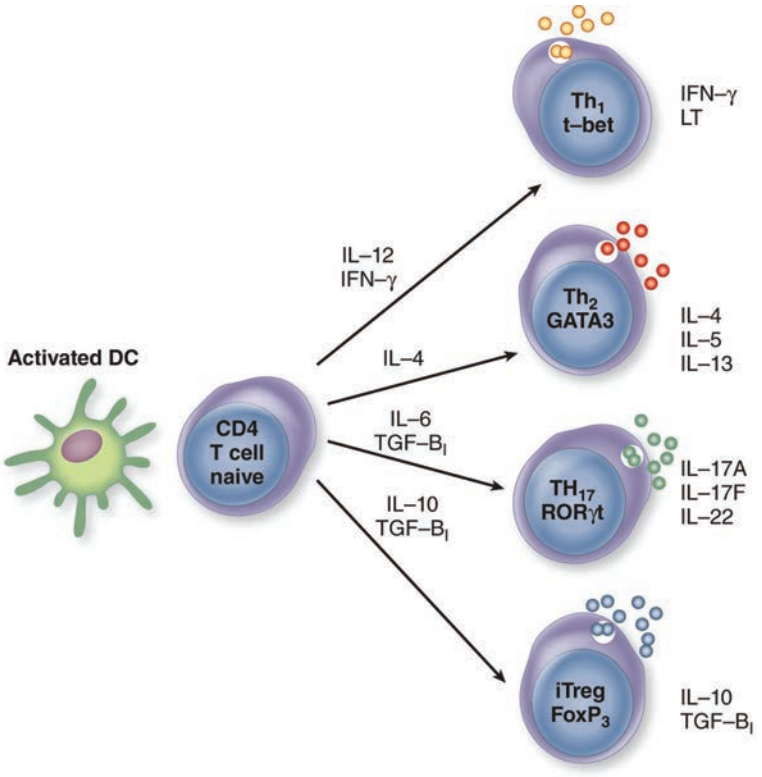

Figure 23-2 Generation of T helper types 1, 2, and 17 (Th1, Th2, Th17) and regulatory T (Treg) cells from a naïve CD4+ T cell. A naïve CD4+ T cell secretes very low levels of cytokines. Differentiation along the Th1, Th2, Th17, and Treg pathways is triggered when antigen is presented to the T cell receptor in the context of the major histocompatibility complex (MHC) by the appropriate antigen-presenting cell (APC) and a second signal imparted by ligation of co-stimulatory molecules CD80/CD86 and CD28. Dendritic cells (DCs) represent the key APCs for naïve T cells. Cytokines produced in innate immune responses activate DC to produce cytokines that direct differentiation of Th subsets leading to induction of critical lineage-determining molecules, T-bet for Th1 cells, GATA-3 for Th2 cells, RORγt for Th17 cells, and FoxP3 for inducible (i)Treg. Naïve CD4 T cells can also differentiate into Tfh cells that promote B cell antibody production.

T helper type 2 (Th2) cells produce IL-4, IL-5, and IL-13 and express the transcription factor GATA-3. Th2 cells, through the production of IL-4 and IL-13, are potent activators of B cell antibody production, particularly immunoglobulin E (IgE). IL-5 secretion by Th2 cells is critical for eosinophil differentiation and maturation. Th2 cells are elicited in immune responses that require a strong humoral component and in antiparasitic responses.

T helper type 17 (Th17) cells produce IL-17A, IL-17F, and IL-22 and express the transcription factor RORγt. Th17 cells stimulate neutrophil mobilization and recruitment, promote release of antimicrobial peptides, and serve critical host defense functions at mucosal surfaces. IL-10, an anti-inflammatory cytokine, was originally defined as a Th2 cytokine, but it is now recognized that it can be synthesized by all Th cell subsets upon appropriate activation.[7]

Regulatory CD4+ T cells (Treg) produce IL-10 and/or TGF- β1 and express the transcription factor FoxP3.

CD4+T follicular helper cells (Tfh) provide help to B cells within the germinal centers of the secondary lymphoid tissues to facilitate antibody production. Tfh produce IL-21 and express the transcription factor BCL6.[8] An effective immune response to a pathogen commonly results in the induction of a balance of Th1, Th2, Th17, and Tfh cells to provide strong cellular and humoral immunity.

CD4+ Treg cells comprise subsets of cells generated in the thymus (natural Treg) or induced in the secondary lymphoid tissues (inducible Treg) that produce IL-10 and/or TGF-β1 and express the transcription factor FoxP3. They are often identified by their high expression of CD25 and Foxp3.[9] CD4+ Treg inhibit the development of Th1, Th2, and Th17 subsets through actions on APCs, naïve T, cells and effector T cells.[10] Treg exert their suppressive effects by secreting cytokines, including TGF-β1 and/or IL-10, by cell contact leading to cytotoxicity or metabolic disruption or by suppression of APCs.[11]

Molecular Mechanisms of CD4+ Th Differentiation

Differentiation of a naïve CD4+ T cell into Th1, Th2, Th17, or Treg requires the coordinate action of multiple molecular signals induced by stimulation of the TCR, co-stimulatory molecules, and cytokine receptors (Fig. 23-2). These actions lead to expression of lineage-determining molecules that promote T cell differentiation, simultaneous inhibition of the opposing Th cell phenotypes, T cell proliferation, epigenetic remodeling to modify the chromatin structure and cytosine methylation, and expression of key transcription factors.

T-bet is one of the lineage-determining molecules required for Th1 differentiation. It belongs to the T-box family of transcription factors that regulate multiple developmental processes. T-bet is upregulated in Th1 cells, through effects of IL-12 and activation of STAT4, and IFN-γ and activation of STAT1.[12] Induced expression of t-bet in vitro and in vivo leads to IFN-γ production;[13] thus t-bet drives Th1 development. T-bet also promotes Th1 induction through negative regulation of GATA-3.[14]

The transcription factor GATA-3 is an essential regulator of Th2 differentiation.[15,16] Whereas GATA-3 is expressed at low levels in naïve CD4+ T cells,[15] it is markedly upregulated in cells differentiating along the Th2 lineage and is downregulated in cells differentiating along the Th1 pathway.[15] The differentiation of a naïve CD4+ T cell along the Th1 or Th2 pathway is accompanied by extensive reorganization of chromatin structure around the IFN-γ or IL-4/IL-5/IL-13 locus, respectively.[17] GATA-3 appears to be the critical downstream regulator of chromatin remodeling around the IL-4 locus.

The orphan nuclear receptor RORγt induces differentiation of naïve CD4+ T cells into Th17 cells.[18] RORγt is required for the expression of IL-17 and the related gene IL-17F in response to IL-6 and TGF-β1 in mice or IL-1β in humans.

Cytokines, by stimulating production of critical lineage-determining molecules, are the primary factors that affect CD4+ Th generation.[19,20] Cytokines produced in innate immune responses modulate how the adaptive immune response will develop. IFN-γ and IL-12 promote Th1 cell development. IL-4 and IL-13 drive Th2 cell generation. IL-10 enhances Th2 cell development by inhibiting Th1 cell induction. IL-6, IL-1β, IL-23, and TGF-β1 promote Th17 development.

Other factors that influence CD4+ T cell differentiation into Th subsets affect the quality of the signal through the TCR. The dose and structure of the antigen affect the APC-TCR interaction and have been shown to drive Th differentiation along distinct pathways.[21] If peptide-MHC class II complex on the APC has a high-affinity interaction with the TCR, then a Th1-predominant response results, whereas a weaker-affinity interaction leads to a Th2-like response. Very low doses of soluble protein antigen tend to stimulate Th2-predominant responses, and at higher antigen doses, Th1 responses, suggesting that the antigen dose affects the APC–T cell interaction. This may have important implications in allergy, since it has been estimated that exposure to common allergens is so small that it does not exceed 1 μg per year. Another line of investigation suggests that high-affinity interactions lead to preferential generation of Th2 cells.[22] Other studies show that the fate of Th differentiation is an effect of both antigen dose and TCR-MHC class II binding.[23] Ultimately, the integration of signals—including TCR binding, costimulatory signals, and cytokines in the environment—activates transcriptional networks that lead to expansion and differentiation of a naïve CD4 T cell.

■ Effector/Memory CD4 T /Cells

It takes 4 to 5 days of proliferation in the lymph node for a naïve CD4+ T cell to differentiate into an effector cell. Associated with differentiation is a change in expression of cell surface selectins, integrins, and chemoattractant receptors that permit exit from the lymph node and recruitment to sites of inflammation. With differentiation there is loss of expression of the lymph node homing receptor CD62L and gain of function of tissue homing receptors. Trafficking to different tissues is controlled by expression of a combination of selectins, chemokine receptors, and integrins on the lymphocyte surface, akin to area codes, and ensures that T cells accumulate where they are needed, at sites of inflammation.[24,25] Skin and gut effector CD4+ T cells each have ligands that confer their localization to that tissue through binding to vascular endothelial cells (skin, cutaneous lymphocyte-associated antigen [CLA]; small intestine, integrin α4β7), but such a lung-specific surface marker has not been identified. Human lung effector CD4+ T cells are enriched for expression of CCR5, CCR6, chemokine (C-X-C motif) receptor 3 (CXCR3), and the integrins VLA1 (α1β1), CD103 (αEβ7), and VLA4 (α4β1).[26]

In addition to expression of receptors that respond to specific signals to direct them to the tissue, subsets of effector CD4+ Th cells express different panels of chemokine receptors so they can be recruited to perform necessary duties. In response to a specific injury or invading pathogen, mediators are released to recruit appropriate populations of CD4+ Th cells to manage the problem. Th1 cells typically express CCR5 and CXCR3, Th17 cells express CCR6, and Th2 cells express CCR4, CCR8, and the prostaglandin D2 chemoattractant receptor DP_2 (CRTH2) in humans.[26]

CD4+ effector Th cells arrive at an inflammatory site in the lung where they proliferate and produce cytokines. The major function of CD4+ T cells is to produce cytokines to recruit other inflammatory cells that modulate local host-protective responses. Following this robust immune response, most activated effector CD4+ T cells die, either by apoptosis or necrosis. A small population of CD4+ T cells persists as memory cells for the life of the host. CD4+ memory T cells, upon re-exposure to specific antigen, respond quicker with a stronger response of longer duration. Subsets of CD4+ memory T cells have been identified that have specific tissue localization and circulation patterns guided by cell surface markers. Together these memory T cell subsets function to provide long-lasting immunity against pathogens in the peripheral tissues and blood, as well as a mechanism to replace dying cells.[27–29]

■ CD4+ Regulatory T Cells

CD4+ regulatory T cells (Treg) cells comprise subsets of cells generated in the thymus (natural Treg) or induced in the secondary lymphoid tissues (inducible Treg) that produce IL-10 and/or TGFβ1 and exhibit high expression of CD25 and the transcription factor FoxP3.[30] They make up 5% to 10% of the peripheral CD4+ T cell population. Cytokines produced by CD4+ Treg inhibit the development of Th1, Th2, and Th17 subsets through actions on APCs and naïve and effector T cells.[10] CD4+ Treg are critical for suppressing primary immune responses to self, as indicated by mice and humans deficient in a functional FoxP3 protein who develop autoimmune diseases.[31,32] Tregs exhibit additional diverse mechanisms to achieve immune suppression in different inflammatory milieu.[33]

CD8+ T CELLS

Pathogens that enter the lung activate tissue-resident DCs and migrate to lymph nodes where they activate naïve CD8+ T cells. CD8+ T cells are activated to differentiate into effector cells through interactions with DCs and provision of two required activation signals, antigenic peptide presented by MHC class I molecules and co-stimulatory signals. Viruses and intracellular bacteria are classic activators of CD8+ T cells. Cytokines secreted by dendritic cells drive proliferation and differentiation of CD8+ T cells to acquire the ability to become effector CD8+ T cells that most commonly secrete IFN-γ and TNF-α and have cytotoxic capabilities through production of granzyme B and perforin.[34] Effector CD8+ T cells may also differentiate into subsets of Tc2 cells that secrete IL-4, IL-5, and IL-13 and Tc17 cells that produce IL-17.[35] After pathogen clearance, the majority of antigen-specific CD8+ T cells die by apoptosis and about 10% develop into CD8+ memory cells. Similar to CD4+ T cells, multiple signals through the TCR, co-stimulatory molecules, and the local inflammatory milieu including metabolic factors coordinate the fate of CD8+ T cells.[36,37]

CD4+ AND CD8+ MEMORY T LYMPHOCYTES

Memory CD4+ and CD8+ lymphocytes allow the host to respond more quickly and effectively to reencounter with pathogens. Memory cells are more abundant than their naïve counterparts in order to provide wide-ranging host surveillance, and they populate peripheral tissues where they are poised to immediately proliferate and execute their functions. To integrate the need for tissue surveillance and self-renewal, there are subsets of memory cells with distinct functions and circulation patterns based on expression of different combinations of surface homing molecules. Tissue-resident memory T cells (T_{RM}) are responsible for barrier protection, exhibit the activation marker CD69, and can be activated locally in the tissue, without trafficking to the lymph node, to provide expedient control of infection.[38] T_{RM} remain in the tissue compartment in which they were initially activated, and do not recirculate. Most CD4+ and CD8+ T cells in nonlymphoid tissues, such as the skin and mucosal tissues, including the lung, are T_{RM} lymphocytes. In the lung, a majority of CD4+ and CD8+ T lymph are T_{RM}. A subset of lung CD8+ T_{RM}, and a smaller proportion of CD4+ T_{RM}, express the integrin CD103 (αEβ7) that binds to E-cadherin on epithelial cells, thus positioning and retaining T_{RM} in the lung and airways.[29] TRM are affected by O_2, pH, and blood supply and serve other surveillance functions including the ability to sense changes in metabolism, inflammation, cancer, and wound repair.[28]

Two subsets of circulating memory cells participate in protective immune responses by acting as reinforcements to T_{RM} or protecting sites that were not challenged in the initial infection. Effector memory cells (T_{EM}) circulate in the blood and in nonlymphoid tissues, such as liver and lung, and unlike naïve T cells, they do not enter uninflamed lymph nodes. They arrive within hours to days at a site of infection to help restrict pathogen replication and spread.[39] Central memory T cells (T_{CM}) recirculate through secondary lymphoid organs, lymphatics, and blood.[38] T_{CM} have high proliferative capacity and produce IL-2, rather than effector cytokines, which allows them to expand and replenish other memory cell compartments. More detailed phenotyping of memory cell populations suggests there are additional T lymphocyte memory cell subpopulations and heterogeneity within the populations described above, and this highlights ongoing research to understand the complexities of T cell memory in immunosurveillance.[40]

"UNCONVENTIONAL" T LYMPHOCYTE POPULATIONS

iNKT, MAIT, and g/d T cells are subsets of T lymphocytes that accumulate in the lung and other sites and have less diverse TCRs compared with traditional α/β CD4+ and CD8+ T cells. They also respond to different antigens. Their numbers in tissues are low, but due to their reduced diversity, more of them will respond to a single antigen. As described below, some "unconventional" T lymphocyte populations may be activated by cytokines through an antigen-independent process. These lymphocytes are already primed to respond; therefore, they can be activated quickly. These three T cell populations participate in the early immune response and may expand and adapt to exposures. Thus, these T lymphocytes subsets bridge innate and adaptive immunity and have been termed "adaptate."[41] There are two small populations of α/β T cells, iNKT cells and mucosal-associated invariant T (MAIT) cells that have semi-invariant α-chains. Thus, they have undergone somatic mutation in the thymus to generate a TCR, but they have limited diversity due to fewer possible TCR combinations. Both iNKT and MAIT cells are found in high frequencies in mucosal tissues. γ/δ T cells are the better-known "unconventional" T cell population.

Natural Killer T Lymphocytes

Type I or invariant (i) NKT cells are a small subpopulation of α/β T cells that express a narrow repertoire of TCRs due to invariant expression of the TCR variable (V) α chain and limited TCR Vβ chains. In humans Vα24-Jα18 pairs almost exclusively with Vb11, whereas in mice Vα14-Jα18 pairs with a limited number of Vβ chains. iNKT cells respond to glycolipids presented on the MHC-like molecule CD-1d, which is a member of a family of nonpolymorphic proteins that bind to lipids, rather than peptide antigens. In the lung, CD-1d is expressed on populations of DCs and alveolar macrophages.[42]

iNKT cells leave the thymus upon maturation and are already antigen-experienced when they migrate into tissues. Mirroring CD4+ T cell subsets, iNKT1 secrete IFN-γ, iNKT2 secrete IL-4, and iNKT17 secrete IL-17. Each iNK T cell subset has distinct combinations of surface receptors including chemokine receptors and integrins that direct their localization to different tissue sites.[42] iNKT cells have important functions in various lymphoid and nonlymphoid tissues, but they are best characterized in lung, liver, adipose, and intestine. In the BAL of normal human subjects, iNKT cells constituted less than 1% of the lymphocyte population.[43] In mice, iNKT cells constituted 5% to 10% of the lung lymphocytes.[44] Murine studies show that iNKT cells are resident in the lung interstitium and, for the most part, do not recirculate to other organs.[45] iNKT cells reside in the lung microvasculature in the resting state and upon exposure to inhaled lipids, become activated, and extravasate into the lung parenchyma where they contribute to lung inflammation.

Upon activation by lipid-CD1d or by cytokines, iNKT cells rapidly elaborate cytokines to activate an immune response. In mice, iNKT cells contain disease in pulmonary infections with bacteria, parasites, viruses, and fungi by reducing pathogen burden and increasing inflammation, particularly neutrophilia.[42] Pathogens activate iNKT cells in tissues early in an immune response, and the elaboration of cytokines is important in shaping the appropriate adaptive immune response.

MAIT Cells

Mucosal-associated invariant T (MAIT) cells are another small subpopulation of α/β T lymphocytes that express TCRs with limited diversity. MAIT cells express a semi-invariant α/β chain, Vα7.2-Jα33, that pairs with a limited number of Vβ chains. MAIT cells are present in humans in the peripheral blood and in mucosal tissues and liver, and constitute about 4% of T lymphocytes in the lung in humans.[46] Signal 1 for MAIT cell activation is TCR interaction with APCs expressing the nonpolymorphic MHC I-like molecule MR-1 bound to vitamin B2 and B9 precursor metabolites. Only certain bacteria, fungi, and yeast synthesize these B vitamins; therefore a limited number of pathogens can activate MAIT cells.[46,47] MAIT cells can also be activated independent of the TCR by IL-12 and/or IL-18 in synergy with other cytokines.[46] Activation of MAIT cells leads to release of cytokines, including IFN-γ, TNF-α, and IL-17, as well as granule exocytosis leading to apoptosis and delivery of antimicrobial peptides.[48,49] MAIT cells have direct antimicrobicidal effects and stimulate antipathogen CD4+ and CD8+ adaptive immune responses through effects on DC activation.[46] In the lung, MAIT cells are enriched in infections, such as tuberculosis, where they were increased five-fold compared with the blood.[50] MAIT cells also provided protection in animal models of influenza A where they were triggered rapidly by the cytokines IL-18, IFN-a, and IL-12.[51] MAIT cells serve in mucosal tissues as intermediary cells that bridge innate and adaptive responses, and potentiate protective antimicrobial immunity.

Gamma/Delta T Cells

Gamma/delta (γ/δ) cells are a subset of T cells that have a TCR comprised of γ and δ chains. The γ/δ TCR is generated by VDJ recombination during thymic maturation, but unlike the α/β TCR, γ- and δ-chain recombination results in a less diverse repertoire of TCRs. γ/δ T cells are the first T lymphocytes released from the thymus during fetal life, and they migrate to and expand in epithelial and mucosal tissues, including lung, skin, intestine, and uterus.[52] There they are considered a first-line defense against pathogens. Most γ/δ T cells are activated in an MHC-independent manner by nonpeptide phosphorylated metabolites of microbes, markers of cellular stress like heat shock proteins, or lipid antigens presented on CD1 molecules.[53] γ/δ T cells have a broad range of functions including production of cytokines, particularly IFN-γ, IL-17, and TNF-α and production of chemokines, many of which are preformed and quickly produced, to recruit other inflammatory cells. γ/δ T cell are capable of cytolysis of infected or transformed cells in an MHC-unrestricted manner. This suggests that γ/δ T cells play a role in surveillance and protection from infection, and possibly a role in cancer immunosurveillance. Their narrow TCR diversity in a tissue compartment, and ability to respond quickly to stimulation, allows for rapid clonal activation without the need for expansion, highlighting their role as a bridge between innate and adaptive immune responses.

T LYMPHOCYTES IN THE LUNG

The distribution of lymphocytes in the normal lung and their role in infection and in a variety of disease states is considered below.

T Lymphocyte Distribution in the Lung

In the normal human lung, T lymphocytes are found in the airways and alveolar spaces, lung parenchyma, pulmonary intravascular spaces, and lymph nodes, and their numbers differ in each of these compartments. In adult humans, lymphocytes in the lung are not typically organized into lymphoid structures, such as bronchus-associated lymphoid tissue (BALT), whereas BALT is more common in healthy children, smokers, and those with chronic infections and inflammatory diseases, as well as normal animals such as rabbits and rats.[54,55] Lymphocytes are not randomly distributed in each lung compartment, but are organized at sites of pathogen entry.[56] T lymphocytes have a multidimensional organization in the lung, including close associations with dendritic, epithelial, and mast cells, but these structural interactions are not yet well defined.

Lymphocytes, including T and B cells, make up about 7% of leukocytes isolated from the nondiseased human lung. It has been estimated that $2–4 \times 10^8$ lymphocytes reside in the airways and alveolar spaces. Twenty-fold more are estimated to make up the pool of lymphocytes in the lung parenchyma in the normal human lung.[57,58]

Lymphocytes isolated from the lung parenchyma consist of large populations within the interstitium and the intravascular spaces.[59]

In the lung parenchyma, T lymphocytes are the predominant lymphocyte population, a majority of which are CD4+ T cells (T:B ratio 15:1, CD4:CD8 2:1).[60] Memory CD4+ T cells make up a majority of CD4+ T cells in the lung and at other mucosal sites. CD8+ memory cells make up half of the CD8+ T cell population in the lung. With age, the number of lymphocytes and the proportion of lymphocytes with a memory phenotype increase. In the BAL, CD4+ T cells constitute about 4% of leukocytes in young adults and 20% in older adults.[61–63] In lung parenchyma, memory CD4+ T cells constitute 65% of the CD4+ T cell population in young adults and almost 80% in older adults.[60] Thus, the proportion of antigen-experienced CD4+ T cells increases with age in the lung and likely reflects an individual's accumulated respiratory exposure over time.

■ T Lymphocytes in Lung Infection

T lymphocytes play critical roles in host defense against bacteria, viruses, and fungi that enter the host through the respiratory tract. This essential function of T lymphocytes is illustrated in HIV infection, in which individuals lack functional T cell subsets leading to susceptibility to pulmonary infection with bacteria, including *Staphylococcus aureus*, *Streptococcus pneumonia*, *Haemophilus influenzae*, and mycobacterial species, viruses such as influenza, and fungi such as *Pneumocystis jirovecii*, *Histoplasma capsulatum*, and *Cryptococcus neoformans*.[64]

The immunocompetent individual responds to pathogen invasion through activation of NKT, MAIT, and γ/δ T cells along with other first responders, including macrophages, neutrophils, and epithelial cells. These innate immune cells are rapidly activated to secrete cytokines and other mediators that help to contain the pathogen directly and indirectly by shaping the necessary adaptive immune response through stimulation of populations of CD4+ and CD8+ T cell subsets. In a primary response to a pathogen, antigen-specific CD4+ and CD8+ effector T cells begin to arrive from the secondary lymphoid organs in the lung within days after the initial infection.

In lung infection, the primary function of CD4+ T lymphocytes is to produce cytokines that ultimately lead to elimination of pathogens. CD8+ T cells produce cytokines and have the additional capacity to kill infected cells. A primary infection results in the development and recruitment of a range of pathogen-specific T cell subsets, including CD4+ Th1, Th2, and Th17 cells, and CD8+ T cells. Each subset serves a specific purpose in the complex antimicrobial immune response. Yet, in some infections, one subset is essential for antipathogen immunity. Th1 cells are absolutely required for elimination of a number of pathogens, and this reflects Th1 production of IFN-γ. IFN-γ is essential for immunity to respiratory infections because of its myriad antimicrobial functions including macrophage activation, stimulation of microbicidal effectors, and stimulation of antiviral enzymes.[65] Th1 cells are essential for host defense against all mycobacterial species, other intracellular pathogens such as *Chlamydia pneumonia* and *Francisella tularensis*, virus infections including influenza and RSV, gram-negative bacterial infections with *Klebsiella pneumoniae*, and fungal infections including *Coccidioides*, cryptococcosis, and *Histoplasma*.[66] Th2 cells are required for immunity to helminth parasites, and Th17 cells are essential to eliminate the gram-negative bacteria *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*, chlamydia, and *Mycoplasma pneumoniae* and for immunity to various fungal infections including *Candida*.

After a primary infection, pathogen-specific memory CD4+ and CD8+ T cells develop. Some are retained in the lung as T_{RM}, and the population is retained in the lung through the life of an individual. Animal studies show that maintenance of the memory CD4+ T cell population in the lung in the first year after primary infection requires recruitment of new cells from the circulating pool.[56,67] And it is likely that a dynamic process like this sustains a population of memory T cells in the lung long after infection.

The population of memory T_{RM} are retained in the lung by surface expression of tissue-specific homing molecules.[68,69] Animal studies show that in different species memory CD4+ and CD8+ T lymphocytes isolated from the lung returned to the lung when re-injected systemically into another animal. One such localization signal is CD103, which is expressed on antigen-specific T cells.[38,70] In both mice and humans, CD69 expression characterized CD4+ and CD8+ memory T cells that were retained in the lung, rather than those that recirculated.[56] Influenza-specific CD4+ and CD8+ T_{RM} were compartmentalized in bronchovascular bundles surrounding the airways.[56] Thus, CD4+ T_{RM} may be retained adjacent to the tight web of dendritic cells just below the epithelial surface, where they can be quickly activated by specific antigen.[71] Virus-specific memory CD8+ T cells were observed in or near capillaries in the lung in association with epithelial cells, and this process was chemokine-dependent.[67,72] This juxtaposition in the lung at sites of exposures ensures that CD4+ and CD8+ T_{RM} can be activated locally.[38,56] T_{RM} produce the type-1 cytokines IFN-γ and IL-2 upon activation,[60] thus safeguarding that both antimicrobial and proliferative cytokines are released at the site of pathogen entry. This ensures that T_{RM} in the lung are rapidly reactivated, undergo proliferation, and stimulate recruitment of an appropriate inflammatory response upon pathogen re-exposure.

■ T Lymphocytes in Lung Diseases

T lymphocytes serve essential functions in host defense as they respond to specific antigens and are retained in the lung as memory cells, but they may also drive chronic disease when immune responses are generated against nonpathogens such as allergens or self-antigens. The development of immunity against nonpathogenic aeroallergens in allergic asthma is an example of immune dysregulation. Long-lived memory T lymphocyte populations may drive chronic diseases. While asthma is the most extensively studied T lymphocyte–driven lung disease, many other chronic pulmonary diseases may be caused and/or perpetuated by T lymphocytes, including sarcoidosis, hypersensitivity pneumonitis, autoimmune lung diseases, idiopathic pulmonary fibrosis, pulmonary hypertension, and others. In lung cancer, T lymphocyte activation using checkpoint inhibitors can lead to tumor cell death and improved survival. T lymphocyte subsets and the factors that cause these diseases will be addressed in other chapters. Here, we will consider the many T cell subsets that have been implicated in asthma pathogenesis and persistence.

T Lymphocytes in Allergic Asthma

The roles of a variety of T lymphocytes in allergic asthma are discussed below.

CD4+ T Helper Type 2 Cells in Asthma In asthmatic patients, CD4+ T cells are the predominant lymphocyte population infiltrating the airways, and they express markers of activation. CD4+ T cells producing IL-4, IL-5, and IL-13 have been identified in bronchoalveolar lavage (BAL) and airway biopsies and are secreted in the airways of patients with mild or asymptomatic asthma.[73] GATA-3 expression was increased in airways of asthmatic patients compared with those in control subjects, indicating the presence of Th2 cells.[74] Inhaled allergen challenge in allergic asthmatic patients led to an increase in Th2 lymphocytes in the airways.[75] In asthmatic patients, airway hyperreactivity (AHR) and airway eosinophilia correlated with airway CD4+ T cells that produced IL-4 or IL-5 or expressed GATA-3.[74] In conjunction with known effects of IL-4, IL-5, and IL-13, these studies support the hypothesis that Th2 cells drive the characteristic inflammatory response that results in asthma.

Animal studies show that activation of CD4+ Th2 cells in the airways leads to pathophysiologic manifestations of asthma. Eosinophilic airway inflammation and AHR have both been shown to be dependent on CD4+ T cells.[76] Studies that employed adoptive transfer of CD4+ T cells from animals with antigen-induced AHR resulted in airway inflammation and hyperresponsiveness in recipient mice, indicating that CD4+ T cells can control many aspects of the disease. CD4+ Th2 cells induced airway eosinophilia, mucus hypersecretion, and AHR, whereas Th1 cells caused a neutrophil-predominant inflammatory response without any of these features of asthma.[76]

Gene association studies also support a role for Th2 cells in asthma. Strong linkages have been identified to flanking markers of the human cytokine gene cluster on chromosomes 5q31 and 16p12, which include genes for IL-4, IL-13, and IL-4Rα.[77] Variants in the IL-4 promoter region are associated with atopy, as are polymorphisms of IL-4Rα, a component of both the IL-4 and IL-13 receptors, and a variant IL-13R.[78] Thus, modifications of IL-4 and/or IL-13 or their signaling, increasing Th2 cell functions, are associated with atopy and asthma.

CD4+ T Helper Type-1 Cells in Asthma Th1 cells are also present in the airways of asthmatic patients. CD4+ Th1 cells may serve a protective or pathogenic function in asthma. IFN-γ was elevated in the airways of some severe asthmatics, and it was reduced in subsets of other asthmatics.[79,80] Some studies show that Th1 cell activation inhibits allergic airway inflammation, whereas other studies suggest that Th1 cells potentiate the inflammatory response in asthma due to the proinflammatory effects of Th1 cytokines.[76,81]

Human and animal studies suggest that enhancing Th1 cytokines in the lung before or early in the generation of a Th2 response may protect against the development of allergic asthma. IFN-γ-dominated immune responses to viral or mycobacterial infection in childhood are associated with a reduced incidence of asthma.[82] Attendance at day care and exposure to other siblings was protective against wheezing in childhood, which is hypothesized to be from beneficial exposures to respiratory infections. Also, mice immunized in the presence of a Th1-stimulating environment exhibited a reduction in antigen-induced eosinophilic airway inflammation and AHR.[83] Thus, reducing the generation of Th2 cells appears to decrease allergic inflammation. However it is also apparent that a high frequency of virally induced wheezing in early life is a strong predictor for the subsequent development of asthma in children,[84] thus suggesting that timing and nature of infections in early life may be crucial.

Th1 cells can also inhibit the effects of ongoing Th2 cell responses. Th1 cells, through the production of IFN-γ, have been shown to inhibit Th2 cell cytokine production and Th2 cell proliferation in vitro.[85] In mice the Th1 cytokine IFN-γ has inhibitory effects on Th2-induced airway eosinophilia and AHR. When administered before inhaled antigen challenge, IFN-γ reduced the number of CD4+ T cells in the respiratory tract or reduced Th2 cytokine secretion.[86] These effects may result from inhibition of Th2 cell recruitment by IFN-γ. Once Th2 cells are present in the respiratory tract, IFN-γ promotes the resolution of airway eosinophilia and suppresses Th2 cytokine production.[87] Th1 cells, through the production of IFN-γ, can inhibit airway eosinophilia, mucus production, and AHR without an increase in airway inflammation.[88] Although many studies support Th1 cells and IFN-γ as inhibitors of Th2-type responses, other studies show that Th1 cells enhance inflammation and do not ameliorate disease.[89] The proinflammatory effects of Th1 cells are supported by the association of viral respiratory infections, which tend to induce Th1 responses, and exacerbation of symptoms in asthmatic patients. Ultimately, the influence of Th1 cells on allergic airway inflammation may depend on the timing of Th1 relative to Th2 cell activation and the sub-phenotype of the asthmatic.

CD4+ T Helper Type 17 Cells in Asthma Th17 cells, IL-17A, and IL-17F are increased in the airways, sputum, and blood of subjects with asthma.[90] Given the heterogeneity of asthmatic airway inflammation and the effects of IL-17A and IL-17F on neutrophil recruitment, it was hypothesized that Th17 cells would be pathogenic in neutrophilic, non-atopic asthma. Yet, there was a positive association of IL-17 and IL-5, and IL-17 with atopic, but not non-atopic, asthma.[91] As expected, IL-17A levels were associated with sputum neutrophils and not eosinophils,[92] suggesting that Th17 cells may drive disease in a subset of neutrophilic asthmatics.[93]

Studies to determine the function of CD4+ Th17 cells have not established a definitive role of Th17 and IL-17A in animal models of asthma. A number of laboratories have shown that Th17 cells, IL-17A, and IL-17 receptors are critical for optimal Th2 cell function, AHR, and eosinophilic inflammation. Furthermore, IL-17A was a major determinant in the development of AHR in mice with susceptibility compared to mice with resistance to develop AHR.[94] Yet, other investigators showed neutralization of IL-17 leads to worse disease.[32,95] The complex interplay of Th17 and Th2 cells is highlighted by studies showing that IL-13 inhibits IL-17A production and IL-17A production inhibits IL-25 that drives Th2 function. These studies suggest that disease pathogenesis in asthma may result from a disruption in a critical balance of cytokines that includes IL-17.

Regulatory T Cells in Asthma Foxp3+ Treg likely determine early sensitization to allergen, as suggested by studies of the rare **i**mmune dysregulation, **p**olyendocrinopathy, **e**nteropathy, **X**-linked syndrome (IPEX), which is caused by mutations in the *Foxp3* gene on the X chromosome. This results in markedly reduced or absent Foxp3+ Treg cells. Young boys with this condition suffer from both severe autoimmune and allergic symptoms.[31] T cells from these patients show skewing toward a Th2 phenotype. Mice with a mutation in the Foxp3 gene also demonstrate intense multiorgan inflammation, including allergic airway disease, high levels of IgE, eosinophilia, and dysregulated Th1 and Th2 cytokine responses, but they do not exhibit Th2 skewing, as observed in humans with IPEX.[96] FoxP3+ Treg also exert immunosuppressive actions on cells involved in asthma and allergy, including limiting mast cell activation by limiting IgE signaling through Fcε receptor 1 and suppressing ILC2 cells.[97]

Studies to assess the numbers of CD4+CD25+ T cells in the peripheral blood of healthy, compared to allergic, subjects have not consistently shown differences.[10,98] However, the methodologies used to detect Treg improved over time, and newer data show impaired CD4+CD25^{high} Foxp3 Treg in allergic disease. In asthmatic children there were reduced numbers of CD4+CD25^{high} T cells in BAL, but not blood, compared to control children with chronic cough.[99] A lower level of Foxp3 mRNA was reported in asthmatic children. CD4+CD25^{high} T cells in the airways of the asthmatic children correlated with clinical parameters such as lung function and were restored following corticosteroid treatment. A similar increase in Foxp3 mRNA was reported in the peripheral blood of adult asthma patients following inhaled corticosteroid treatment.[100] Foxp3-expressing Tregs are also important negative regulators of asthma and allergic disease in animal models. Treg expressing either IL-10, TGF-β1, or both were required to limit airway inflammation in numerous models of tolerance induction.[101–104] Overall, it appears that impaired Treg responses may contribute to the development of asthma and allergic diseases.

CD8+ T Cells in Asthma In atopic asthmatics there were increased CD8+ T cells in airway biopsies when compared to biopsies in non-asthmatic, atopic, and normal subjects.[105] Furthermore, the number of CD8 T cells in airway biopsies of atopic asthmatics was associated with a decline in FEV1.[106] During asthma exacerbations and in death from status asthmaticus, there were increased CD8+ T cells in the respiratory tract.[107] These observations suggest that CD8+ T cells are detrimental in asthma. Animal studies both support these observations and show that CD8+ T cells inhibit allergic airway disease through the production of IFN-γ and induction of IL-12 production. Most likely, CD8+ T cells have varying effects in different individuals and under different circumstances.

CD8+ T cells recognize endogenous antigens, like viral peptides, rather than inhaled allergens. Asthma exacerbations are most commonly caused by viral respiratory infections and, in response, virus-specific CD8 T cells are recruited and retained in the lung. Tissue-resident CD8+ T memory cells are present near the airways and poised to respond to reinfection, and the numbers of CD8+ T cells rise in asthmatic lungs after infection. CD8+ T cells, like CD4+ T cells, can be polarized into subsets. Cytotoxic type 1 (Tc1) T cells are activated in viral infections and generally produce IFN-γ and lymphotoxin. These are classic CD8+ T cells. Smaller subsets of CD8+ T cells can make other panels of cytokines. For example, when activated in the presence of IL-4, CD8+ T cytotoxic type 2 (Tc2) cells can be induced to produce IL-4, IL-5, and IL-13. Animal studies show that Tc2 cells retain their cytotoxic function, stimulate recruitment of eosinophils, provide B cell help for IgE production, and promote airway hyperresponsiveness.[107] It has been theorized that some respiratory infections may stimulate CD8+ Tc2 responses, thus initiating or exacerbating local allergic responses. Furthermore, CD8+ T cell effects may be pronounced after exacerbations in asthmatics because they are more resistant to corticosteroids and may persist in the lung for longer than CD4+ T cells.[108]

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CHAPTER 24

Chemokines, Adipokines, and Growth Factors in the Lung

Marcus W. Butler
Paul McLoughlin
Michael P. Keane

INTRODUCTION

The normal development of organ systems—including the lungs in utero, their subsequent maturation to adulthood, and maintenance of health throughout life—requires intricate signals to be exchanged among various tissues, capable of permitting diversity and adaptation in differing cellular and extracellular contexts, while being robust to onslaughts from ever-changing environmental stimuli. Among the mediators involved in such complex cellular signaling, and relevant in the setting of many pulmonary disorders, are chemokines and growth factors. There has been further complexity added with increasing recognition of adipose tissue as a source of systemic bioactive mediators, called adipokines, that impact on lung health. While some of these mediators are implicated in the development of disease states, they are more often than not also critical to tissue homeostasis and are challenging target systems for therapeutic manipulation. Nonetheless, we are now in an era of exciting developments in targeted biologic therapies that offer the potential for substantial progress in the fight against difficult-to-treat pulmonary disorders characterized by pathogenic processes including acute and chronic inflammation, fibrosis, vascular remodeling, and neoplasia.

CHEMOTACTIC CYTOKINES AND THE INFLAMMATORY RESPONSE

The salient feature of inflammation is leukocyte infiltration. These recruited leukocytes contribute to the pathogenesis of chronic inflammation and promote fibrosis via the elaboration of a variety of cytokines. Maintenance of leukocyte recruitment during inflammation requires the expression of cell-surface adhesion molecules, and the production of chemotactic molecules, such as chemokines.[1] The chemokines can be divided into four families—CXC, CC, C, and CXXXC—which behave as potent chemotactic factors for neutrophils, eosinophils, basophils, monocytes, mast cells, dendritic cells, NK cells, and T and B lymphocytes (Table 24-1). There is approximately 20% to 40% homology between the members of the four chemokine families.[2] Chemokines are produced by an array of cells, including monocytes, alveolar macrophages, neutrophils, platelets, eosinophils, mast cells, T- and B-lymphocytes, NK cells, and various structural cells, including keratinocytes, mesangial cells, epithelial cells, hepatocytes, fibroblasts, smooth muscle cells, mesothelial cells, and endothelial cells. Specific chemokines can form heterodimers that differentially dictate their functional activity, for example, obligate CC-type heterodimers can drive acute lung injury.[3] Production of chemokines by both immune and nonimmune cells supports the contention that these cytokines may play a pivotal role in orchestrating chronic inflammation.[4]

CXC Chemokines

CXC chemokines can be further divided into two groups on the basis of a structure and function domain consisting of the presence or absence of three amino acid residues (Glu-Leu-Arg; ELR motif) that precede the first cysteine amino acid residue in the primary structure of these cytokines. ELR+CXC chemokines are chemoattractants for neutrophils and act as potent angiogenic factors. In contrast, ELR–CXC chemokines are highly induced by interferons, are chemoattractants for mononuclear cells, and are potent inhibitors of angiogenesis[5] (Table 24-2).

CXC Chemokine Receptors

Chemokine activities are mediated through G protein–coupled receptors. Seven CXC chemokine receptors have been identified (Table 24-3). The ELR+ chemokines bind to CXCR1 and CXCR2 receptors, which are found on neutrophils, T lymphocytes, monocytes/macrophages, eosinophils, basophils, keratinocytes and mast cells, and endothelial cells.[6] CXCR3 is the receptor for CXCL9, CXCL10, and CXCL11, and is expressed on activated T lymphocytes. CXCR3 is also expressed on HUMVEC in a cell cycle–dependent fashion. CXCR4 is the specific receptor for CXCL12 and is the cofactor for lymphotropic HIV-1. In contrast to CXCR3, CXCR4 appears to be expressed on resting T lymphocytes.[6] Two other chemokine receptors have been identified that bind chemokines without a subsequent signal-coupling event. The DARC receptor is similar to other chemokine receptors, and it binds both CXC and CC chemokines without apparent signal coupling. This receptor was originally found on human erythrocytes and was thought to represent a "sink" for chemokines.[7] The second nonsignaling chemokine receptor is the D6 receptor, which binds several CC chemokines with high affinity, including CCL2, CCL4, CCL5, and CCL7.[8]

CXC Chemokines in Pulmonary Inflammation

CXC chemokines play a significant role in mediating neutrophil infiltration in the lung parenchyma and pleural space in response to endotoxin and bacterial challenge. CXCL8 is in the bronchoalveolar lavage of patients with community-acquired pneumonia and nosocomial pneumonia and a variety of animal models of pneumonia. In a model of *Aspergillus fumigatus* pneumonia, neutralization of TNF resulted in marked attenuation of the expression of CXCL1 and CXCL2/3 that was paralleled by a reduction in the infiltration of neutrophils and associated with increased mortality.[9] Administration of a TNF agonist peptide to animals that had been intratracheally inoculated with *Klebsiella pneumoniae* led to markedly elevated levels of CXCL2/3 associated with increased neutrophil infiltration.[10] Studies have shown that ventilator-induced lung injury is secondary to stretch-induced chemokine release with a subsequent inflammatory response and neutrophil recruitment.[11] CXCR2$^{-/-}$ mice are also protected from hyperoxia-induced lung injury. In other studies, the production of CXCL5 in the lung was correlated with the presence of neutrophil-dependent lung injury, and passive immunization with neutralizing CXCL5 antibodies resulted in significant attenuation of lung injury.[12] Lung neutrophils have been shown by single-cell RNA sequencing in mouse models of allergic asthma to transiently activate in the presence of a pro-allergic, low-dose lipopolysaccharide environment, with upregulated expression of CXCR4 on the neutrophil surface, necessary for subsequent release of neutrophil extracellular traps (NETs), potentiating the uptake of house dust mite by dendritic cells to promote early triggering of type 2 allergic airway inflammation.[13]

AL GRAWANY

TABLE 24-1 The Human C, CC, CXC, and CXXXC Chemokine Families of Chemotactic Cytokines

Systemic Name	Human Ligand Name
C Chemokines	
XCL1	Lymphotactin
XCL2	SCM-1β
CC Chemokines	
CCL1	I-309
CCL2	Monocyte chemotactic protein 1 (MCP-1)
CCL3	Macrophage inflammatory protein 1 alpha (MIP-1α)
CCL4	Macrophage inflammatory protein 1 beta (MIP-1β)
CCL5	Regulated on activation normal T cell expressed and secreted (RANTES)
CCL7	Monocyte chemotactic protein 3 (MCP-3)
CCL8	Monocyte chemotactic protein 2 (MCP-2)
CCL9	Macrophage inflammatory protein 1 delta (MIP-1δ)
CCL11	Eotaxin
CCL13	Monocyte chemotactic protein 4 (MCP-4)
CCL14	HCC-1
CCL15	HCC-2
CCL16	HCC-4
CCL17	Thymus and activation-regulated chemokine (TARC)
CCL18	DC-CK-1
CCL19	Macrophage inflammatory protein 3 beta (MIP-3β)
CCL20	Macrophage inflammatory protein 3 alpha (MIP-3α)
CCL21	6Ckine
CCL22	MDC
CCL23	MPIF-1
CCL24	MPIF-2
CCL25	TECK
CCL26	Eotaxin-3
CCL27	CTACK
CCL28	MEC
CXC Chemokines	
CXCL1	Growth-related oncogene alpha (GRO-α)
CXCL2	Growth-related oncogene beta (GRO-β)
CXCL3	Growth-related oncogene gamma (GRO-γ)
CXCL4	Platelet factor 4 (PF4)
CXCL5	Epithelial neutrophil–activating protein 78 (ENA-78)
CXCL6	Granulocyte chemotactic protein 2 (GCP-2)
CXCL7	Neutrophil-activating protein 2 (NAP-2)
CXCL8	Interleukin 8 (IL-8)
CXCL9	Monokine induced by interferon γ (MIG)
CXCL10	Interferon γ–inducible protein (IP-10)
CXCL11	Interferon-inducible T cell alpha chemoattractant (ITAC)
CXCL12	Stromal cell–derived factor 1 (SDF-1)
CXCL13	B cell–attracting chemokine 1 (BCA-1)
CXCL14	BRAK/Bolekine
CXCL16	
CXXXC Chemokine	
CXC3CL1	Fractalkine

TABLE 24-2 The CXC Chemokines That Display Disparate Angiogenic Activity

CXC chemokines that contain the ELR motif	
CXCL1	Growth-related oncogene alpha (GRO-α)
CXCL2	Growth-related oncogene beta (GRO-β)
CXCL3	Growth-related oncogene gamma (GRO-γ)
CXCL5	Epithelial neutrophil–activating protein 78 (ENA-78)
CXCL6	Granulocyte chemotactic protein 2 (GCP-2)
CXCL7	Neutrophil-activating protein 2 (NAP-2)
CXCL8	Interleukin 8 (IL-8)
CXC Chemokines that lack the ELR motif	
CXCL4	Platelet factor -4 (PF4)
CXCL9	Monokine induced by interferon γ (MIG)
CXCL10	Interferon γ–inducible protein (IP-10)
CXCL11	Interferon-inducible T cell alpha chemoattractant (ITAC)
CXCL12	Stromal cell–derived factor 1 (SDF-1)

The B lymphocyte chemokine CXCL13 is a key mediator in development of tertiary lymphoid follicles, a histologic hallmark of COPD progression.[14] CXCL13 expression within these structures in resected lungs of COPD patients and cigarette smoke–exposed mice is increased, and anti-CXCL13 antibodies prevented pulmonary lymphoid follicle formation in mice, attenuating alveolar wall destruction and BALF inflammation.[14]

CXCL8 is chemotactic for neutrophils via high-affinity binding to CXCR2, a receptor also activated by CXCL1 and CXCL5, ligands that rise from baseline expression in lung-derived tissues during COPD exacerbations.[14] This initially led to clinical development, since discontinued for lack of efficacy, of three different oral CXCR2 small molecule antagonists in neutrophilic airways diseases such as COPD and neutrophilic asthma.[15–17]

Several studies have demonstrated that CXCL8 levels correlate with the development and mortality of acute respiratory distress syndrome (ARDS). Early increases in CXCL8 in bronchoalveolar lavage fluid correlated with an increased risk of subsequent development of ARDS, and also demonstrated that alveolar macrophages were an important source of CXCL8 prior to neutrophil influx.[11] Furthermore, there is an imbalance in the expression of ELR+ (CXCL1, CXCL5, CXCL8) as compared with ELR-CXC (CXCL10, CXCL11) chemokines from BALF of patients with ARDS compared with controls. This imbalance correlated with angiogenic activity and both procollagen I and procollagen III levels in BALF.[18] These findings suggest that CXC chemokines have an important role in the fibroproliferative phase of ARDS via the regulation of angiogenesis. In sterile ARDS such as severe trauma or hemorrhagic shock, lung injury has been thought to be due to excessive recruitment of activated neutrophils into pulmonary vasculature. Many activated neutrophils may in fact physiologically arrive in the lung in a preprogrammed homeostatic pathway, having performed key repair functions at extrapulmonary injured tissue sites, then selectively migrate via CXCR4 to the bone marrow from the “pit-stop” in the lungs, a “reverse migration” process that may be dysregulated in ARDS.[19,20]

■ The Role of CXC Chemokines in Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF) is characterized by the progressive deposition of collagen within the interstitium and subsequent destruction of lung tissue.[21,22] The mechanisms of cellular injury and the role of classic inflammatory cells remain unclear. Several CXC chemokines are elevated in the BAL of IPF patients, including CXCL5, CXCL8, and CXCL17.[23,24] CXCL8 is significantly elevated in IPF, as compared with either normal or sarcoidosis patients, and correlates with BALF presence of neutrophils. The alveolar macrophage is an important cellular source of CXCL8 in IPF.[25] In addition, BALF levels of CXCL8 in IPF may correlate with a worse prognosis.[26] CXCL4 may be a useful biomarker as the predominant circulating protein secreted by plasmacytoid dendritic cells in systemic sclerosis, and predicts risk and progression of the pulmonary fibrosis and pulmonary arterial hypertension as well as response to immunosuppressive therapy in systemic sclerosis–related interstitial lung disease.[27,28]

TABLE 24-3 The CXC Chemokine Receptors

Receptor	Ligand
CXCR1	CXCL6, CXCL7, CXCL8
CXCR2	CXCL1, CXCL2, CXCL3, CXCL5, CXCL6, CXCL7, CXCL8
CXCR3A	CXCL9, CXCL10, CXCL11
CXCR3B	CXCL4, CXCL9, CXCL10, CXCL11
CXCR4	CXCL12
CXCR5	CXCL13
CXCR6	CXCL16
CXCR7	CXCL11, CXCL12

■ Vascular Remodeling in Pulmonary Fibrosis: The Role of CXC Chemokines

The existence of neovascularization in IPF was originally identified in 1963 by Turner-Warwick, who demonstrated that within areas of pulmonary fibrosis there was extensive neovascularization with anastomoses between the systemic and pulmonary microvasculature.[29] Further evidence of neovascularization during the pathogenesis of pulmonary fibrosis has been demonstrated in a rat model of bleomycin-induced pulmonary fibrosis.[30] An imbalance in the levels of angiogenic chemokines (CXCL5, CXCL8), as compared with angiostatic chemokines (CXCL9, CXCL10, CXCL11), favoring net angiogenesis has been demonstrated in both animal models and tissue specimens from patients with IPF (Fig. 24-1).[31] Renzoni have demonstrated vascular remodeling in both IPF and fibrosing alveolitis associated with systemic sclerosis.[32] Cosgrove et al. provided further support for the concept of vascular remodeling in IPF when they demonstrated a relative absence of vessels in the fibroblastic foci of IPF. This appeared to correlate with increased expression of pigment epithelium–derived factor in the fibroblastic foci. Interestingly, they also noted significant vascularity in the areas of fibrosis around the fibroblastic foci, with numerous abnormal vessels in the regions of severe architectural distortion.[33] These findings are similar to those of Renzoni and support the concept of regional heterogeneity of vascularity in IPF. This heterogeneity is not surprising, as usual interstitial pneumonia, which is the pathologic description of IPF, is defined by its regional and temporal heterogeneity.[34] CXCR7, expressed on pulmonary capillary endothelial cells (PCECs), appears to play a role in ameliorating lung fibrosis in a bleomycin or hydrochloric acid mouse model, but is downregulated by such repetitive lung injury when PCECs are activated, resulting in Jagged 1 (JAG1)-mediated Notch signaling activation in lung perivascular fibroblasts and recruitment of vascular endothelial growth factor receptor 1 (VEGFR1)-expressing perivascular macrophages. Agonism of CXCR7 reduces JAG1 expression in PCECs, reducing fibrosis and promoting alveolar repair, and such CXCR7 agonists are a potential therapeutic target.[35]

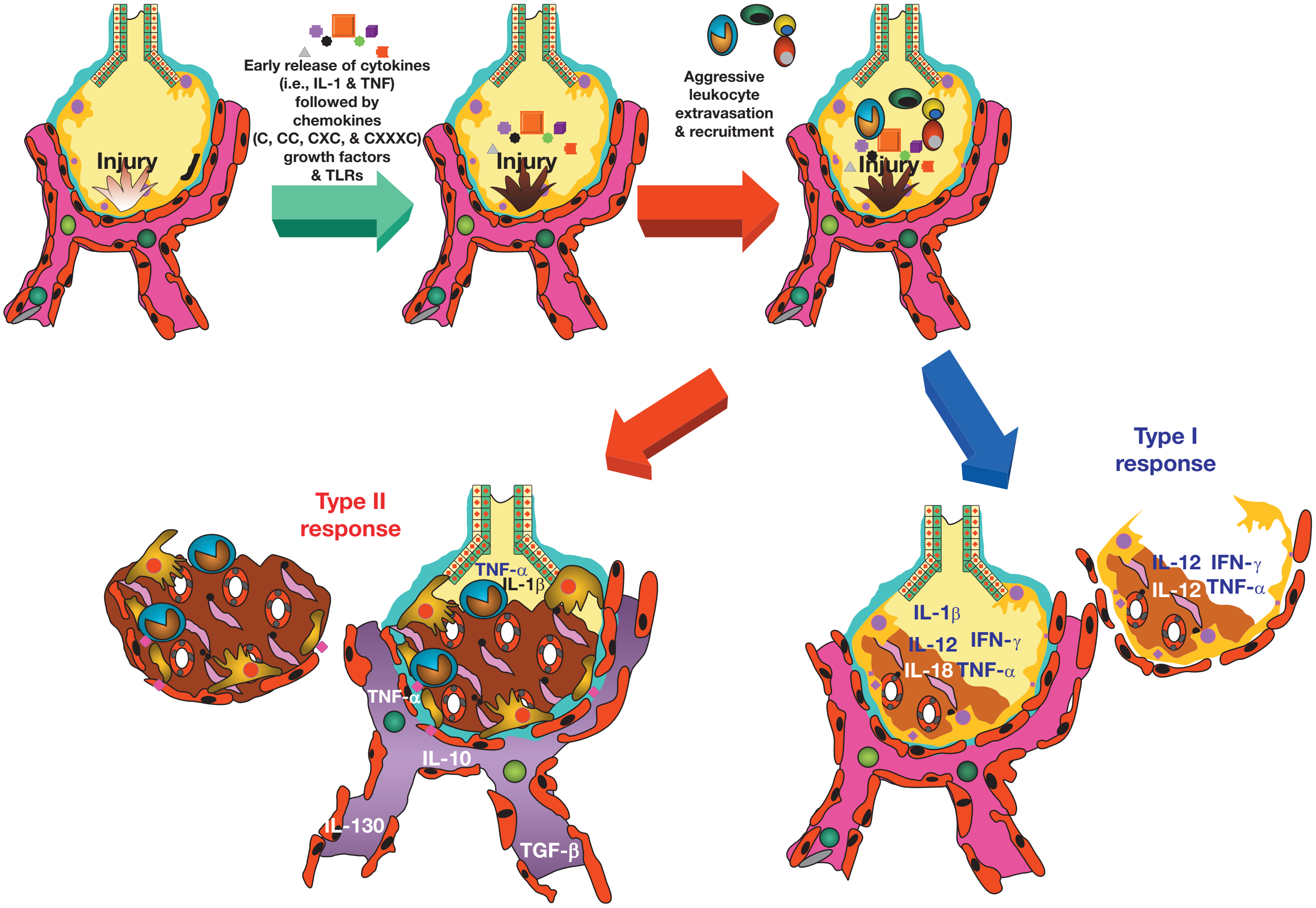

Figure 24-1 The inflammatory response to lung injury. The cytokine profile that is secreted by inflammatory cells during lung injury determines the ultimate outcome following injury. Polarization of the inflammatory response toward a type I response is associated with resolution of lung injury or infection. In contrast, chronic infections (e.g., tuberculosis) and chronic inflammatory diseases (e.g., idiopathic pulmonary fibrosis) are associated with a type II profile.

■ CXC Chemokines in Pulmonary Hypertension

The potential role of the CXCL12/CXCR4/CXCR7 axis in pulmonary hypertension was first suspected when it was reported that CXCR7 expression increased in the lungs of hypoxic hypertensive mice and in the lungs of patients with IPAH.[36] Subsequently, CXCL12 was found to be elevated in the peripheral plasma of patients with PAH, although in a separate study this increase was not observed.[37,38] Increased expression of CXCL12 in remodeled vessels and particularly in the plexiform lesions in explanted IPAH lungs also has been shown.[39]

CXR7 was most prominently expressed in the endothelium of the explanted lungs of hypertensive subjects and, in addition to its well-established role in leucocyte chemotaxis, was shown to play a central role in stimulating endothelial proliferation, whereas CXCR4 was required for endothelial cell chemotaxis.[37] Recruitment of progenitor cells to the remodeled pulmonary vessels is a prominent feature in PAH lungs.[39,40] In vivo blockade of CXCR4 in hypoxic mice reduced the recruitment of progenitor cells to the remodeled vasculature of hypertensive lungs, whereas blockade of CXCR7 did not affect this behavior.[38,40,41]

In rodents models inhibition of CXCL12 action using function blocking antibodies, or separate selective inhibition of CXCR4 signaling or CXCR7 signaling, attenuates the development of hypoxic pulmonary hypertension.[38,41,42] There is a greater attenuation of established pulmonary hypertension through CXCL12 neutralization ligands than via CXCR4 blockade in the monocrotaline (MCT) and Sugent5416/hypoxia (SuHx) rat models of severe PAH.[43] Taken together these data suggest an important role of CXCL12 signaling, requiring both its cognate receptors, in the pathogenesis of pulmonary hypertension.

■ Chemokines and the Trafficking of Fibrocytes to the Lung

Fibrocytes present in the peripheral circulation were first identified in 1994, constitute a minor component of the circulating pool of leukocytes (<1%), and express a characteristic pattern of markers, including collagen (Col) I and CD45.[44] Subsequent studies have revealed that circulating fibrocytes express chemokine receptors such as CXCR4 and CCR7 and extracellular matrix proteins, such as procollagen I and procollagen III. Fibrocytes migrate in response to CXCL12 and traffic to the lungs in a model of bleomycin-induced pulmonary fibrosis. Treatment of bleomycin-exposed animals with specific neutralizing anti-CXCL12 antibodies inhibits intrapulmonary recruitment of fibrocytes and attenuated lung fibrosis. Levels of circulating CD45+ Col1+ cells are elevated in stable IPF patients versus controls, are transiently higher during an exacerbation and predicted survival.[45] Although fibrocytes are not an essential source of type I collagen during lung fibrosis, the licensed antifibrotic medication nintedanib inhibits the differentiation of fibrocytes from human mononuclear cells and the growth factor–induced migration of fibrocytes and their accumulation in fibrotic lesions in a bleomycin mouse model.[46,47] These findings challenge the dogma that fibroblasts and myofibroblasts arise from an intrapulmonary pool of tissue fibroblasts.[48]

The CC Chemokines

CC chemokines (Table 24-1) are chemoattractants for monocytes, T and B lymphocytes, NK cells, dendritic cells, basophils, mast cells, and eosinophils.[49] The CC chemokines are produced by an array of cells, including monocytes, alveolar macrophages, neutrophils, platelets, eosinophils, mast cells, T cells, B cells, and NK cells, as well as structural cells such as keratinocytes, mesangial cells, epithelial cells, hepatocytes, fibroblasts, smooth muscle cells, mesothelial cells, and endothelial cells.[50]

CC Chemokine Receptors

CC chemokine receptors are structurally homologous and have been identified to have specific ligand-binding profiles (Table 24-4).[50] Naïve T cells express CXCR4 and CCR7 and migrate in response to CXCL12 and CCL19. CXCR3, CXCR6, and CCR5 are expressed at higher levels on type I cells than type II, whereas CCR3, CCR4, and CCR8 are more characteristic of type II cells.[51]

CC Chemokines in Pulmonary Inflammation

The CC chemokines, CCL2, CCL3, CCL4, CCL5 have been implicated in mediating the innate host defense in animal models of *pulmonary infection.*[52,53] These studies have demonstrated that CC chemokine ligand/receptor biology plays a critical role in innate host defense and development of pulmonary inflammation that is important in eradication of microorganisms.

Mehrad et al. have shown that CCL3 and the recruitment of mononuclear cells play an important role in the eradication of invasive pulmonary aspergillosis. They demonstrated that in both immunocompetent and neutropenic mice CCL3 is induced in the lungs in response to intratracheal inoculation of *Aspergillus fumigatus.*[54] These studies indicate that CCL3 and elicitation of mononuclear cells are crucial in mediating host defense against *Aspergillus fumigatus* in the setting of neutropenia.[55]

Eosinophilic pulmonary infiltration is central to the type 2 inflammation of asthma and a subset of COPD patients, orchestrated by cytokines such as interleukins (IL-4, IL-5, IL-9, and IL-13), but also trafficked by CCL5, CCL11, CCL13, CCL17, CCL22 and CCL24.[56,57] Such eosinophilic inflammation and compensatory tissue repair in murine allergic asthma models are further dynamically regulated by subsets of lung dendritic cells and regulatory T cells via altered expression of CCL11, CCL17, CCL22, and CCL24.[58,59]

TABLE 24-4 The CC Chemokine Receptors

Receptor	Ligand
CCR1	CCL2, CCL3, CCL3LI, CCL4, CCL5, CCL7, CCL8, CCL13, CCL14, CCL15, CCL16, CCL23
CCR2	CCL2, CCL7, CCL8, CCL13, CCL16
CCR3	CCL5, CCL7, CCL8, CCL11, CCL13, CCL15, CCL16, CCL24, CCL26, CCL28
CCR4	CCL17, CCL22
CCR5	CCL3, CCL3LI, CCL4, CCL5, CCL7, CCL8, CCL11, CCL13, CCL14, CCL16
CCR6	CCL20
CCR7	CCL19, CCL21
CCR8	CCL1
CCR9	CCL25
CCR10	CCL27, CCL28

CC Chemokines in Pulmonary Fibrosis

Animal models, such as bleomycin-induced pulmonary fibrosis, have demonstrated the presence and contribution of CC chemokines to the pathogenesis of fibrosis. CCL2 is an important cofactor for the stimulation of fibroblast collagen production and induction of the expression of TGF-β_1. Inhibition of CCL2 or CCL3 resulted in a reduction of infiltrating cells into the lungs of bleomycin-treated animals.[60,61]

Furthermore, it has been shown that CCL2 can stimulate IL-4 production, indicating that it might be involved in type II polarization.[62] IL-13 promotes bleomycin-induced fibrosis through the elaboration of CCL6.[63] Both CCL17 and CCL22 and their receptor, CCR4, are significantly elevated in the bleomycin model, and neutralization of CCL17 attenuates pulmonary fibrosis.[64] Thus, chemokines may have an important role in the switch toward a profibrotic type II phenotype.

Both CCR1 and CCR2 have been shown to play an important role in the pathogenesis in the mouse model of bleomycin-induced pulmonary fibrosis. Treatment with antibodies to CCR1 leads to a reduction in both inflammatory cell infiltrates and the development of fibrosis.[65] Similarly, CCR2$^{-/-}$ mice are protected from pulmonary fibrosis in response to bleomycin.[66] Furthermore, alveolar epithelial cells from CCR2$^{-/-}$ mice suppress fibroblast proliferation more than AECs from wild-type mice.[67] CCL2 and CCR2 have an important role in suppression of PGE2, thereby promoting fibroproliferation. Similarly, an important role for CCR2 has been seen in murine model of obliterative bronchiolitis, in which the fibrotic response associated with this disorder was attenuated in CCR2$^{-/-}$ mice.[68] Similarly, CCL2 and CCL3 are elevated in BALF and lung tissue of ILD patients.[69,70] Accordingly, targeting chemokine receptors may be an efficient way to inhibit pulmonary fibrosis.

Choi et al. described enhanced expression of the chemokines CCL7 and CCL22 in lung tissue of patients with IPF compared with nonspecific interstitial pneumonia and non-idiopathic interstitial pneumonia.[71] Furthermore, they describe increased expression of CCL5 in nonspecific interstitial pneumonia compared with usual interstitial pneumonia. Interestingly, CCL5 protein was identified in nonspecific interstitial pneumonia more prominently than usual interstitial pneumonia. This is all the more interesting as CCL5 is a major stimulus for the production of CCL7 through its interactions with CCR5. These findings raise the possibility that there is a continuum from nonspecific interstitial pneumonia to usual interstitial pneumonia with higher levels of CCL5 in nonspecific interstitial pneumonia leading to subsequent increased CCL7 expression as the disease progresses to usual interstitial pneumonia. There is considerable controversy as to whether nonspecific interstitial pneumonia is an earlier lesion of usual interstitial pneumonia.[72] Several studies have demonstrated the presence of usual interstitial pneumonia and nonspecific interstitial pneumonia patterns in the same patients, which suggests that these are overlapping processes.[72–74] The findings suggest a transition from a predominance of CCL5 to CCL7 and further support this notion. Of further interest is the previous description that CCL7 can act as a natural antagonist at the CCR5 receptor, which raises the possibility that CCL7 may play a role in regulating its own production.[75]

ADIPOKINES AND PULMONARY INFLAMMATION

With the emergence of obesity as a major epidemic linked to systemic metabolic dysfunction, concerted efforts have been made to gain a fuller understanding of the varied functions of adipose tissue, beyond that of being an energy storage organ, and leading to the discovery of various factors that are secreted by adipocytes.[76] These mainly proteinaceous endocrine factors were initially termed adipocytokines, and later, adipokines,[77] and possess pro- and anti-inflammatory activities, potentially of relevance in the context of pulmonary disorders associated with body mass index, including asthma, obstructive sleep apnea syndrome, chronic obstructive pulmonary disease, pulmonary arterial hypertension, various pulmonary infections, and lung cancer.[78] While the main source of adipocytes in the body is from deposits of subcutaneous and visceral adipose tissue, the development of obesity can give rise to collections of adipose tissue in other locations including the heart, kidneys, bone marrow, the adventitia of major blood vessels, and within the lungs. There is evidence that differential adipokine secretion and functional outcomes can occur at different sites of adiposity within the body, following the stimulus of dietary modification.[79] White adipose tissue, the major form in humans, is predominantly composed of lipid-laden adipocytes, but also adipocyte precursor cells, fibroblasts that generate extracellular matrix scaffolding, vascular (smooth muscle and endothelial) cells that provide systemic access for secreted adipokines, and macrophages and T cells that influence the immune phenotype.[80] The cellular composition of adipose tissue can vary in conditions of altered body mass, and macrophages in particular seem to traffic in larger numbers to adipose tissue under conditions of increased obesity with associated capillary rarefaction and adipose tissue hypoxia.[81]

■ Pro-inflammatory Adipokines

Beyond the “pure” effects of uncomplicated obesity upon respiratory mechanics, pulmonary gas exchange, ventilatory drive and work of breathing, there is increasing evidence of an association among obesity, adipokines and pulmonary disease states that are characterized by inflammation.[78] Most of the adipokines identified to date are pro-inflammatory in their effects (Table 24-5). Some important adipokines that are better known for their other roles, such as TNF-α, IL-6, CCL2, and CXCL5, will not be discussed here.

Leptin

Leptin, coded for by the *ob* gene on chromosome 17, is a 16-kDa protein hormone, mainly secreted by adipocytes,[82] and regulated principally by food intake, whereby fasting reduces leptin levels, and food consumption transiently increases *ob* gene expression, with leptin being initially regarded as a satiety hormone.[83,84] It is also expressed in human peripheral lung tissue, including alveolar type II pneumocytes, alveolar macrophages, and bronchial epithelial cells,[85,86] and is known to be modulated by gender, sepsis, catecholamines, glucocorticoids, and insulin.[87,88] It is now clear that leptin has pleiotropic effects, which include stimulating TNF and IL-6 production by monocytes, stimulating production of CCL3-5 by macrophages, and stimulating reactive oxygen species production, cell proliferation, and migration. In addition, leptin may have a role in lung development,[76] as it is differentially expressed by fetal rat lung fibroblasts during the time of alveolar differentiation,[89] and capable of stimulating fetal rat surfactant protein synthesis in vitro,[90] although contradictory in vivo findings were observed in fetal sheep and mice lungs.[91]

There have been extensive efforts to relate leptin to respiratory disorders, most notably with obstructive sleep apnea–hypopnea syndrome (OSAHS), chronic obstructive pulmonary disease (COPD), asthma, pneumonia, and other pulmonary infections. Some data suggest leptin has a stimulatory effect on ventilation; for example, the mutant *ob/ob* mouse, which lacks functional leptin and has a phenotype of obesity, hyperphagia, and a low resting metabolic rate, displays an elevated arterial $PaCO_2$ independent of obesity onset, which is acutely reversible through exogenous leptin replacement.[92] It has been speculated that OSAHS is a leptin-resistant state, but progress in this field has been hampered by conflicting results of leptin and leptin receptor candidate gene association studies[93,94] and trials of nasal continuous positive airway pressure.[95,96]

In chronic obstructive pulmonary disease, it has been hypothesized that the known link between the cachexia of COPD and increased mortality might somehow be related to leptin function. There appears to be an absence of the usual circadian rhythm of circulating leptin in cachectic COPD patients, as opposed to normal-weight COPD patients, with associated heart rate variability changes that raise the possibility of a role for leptin in the pathophysiology of COPD cachexia,[97] although further data are needed. The reproducible finding of elevated serum leptin levels during acute exacerbations of COPD, that track markers of the systemic inflammatory response, points to disturbance of the normal leptin feedback loop regulating food intake and energy balance, due to the influence of the acute inflammatory response and systemically administered glucocorticoids, as a possible contributing mechanism to cachexia in COPD.[98] Wild-type mice exposed chronically to cigarette smoke have increased leptin expression in bronchial epithelial cells and pneumocytes compared with air-exposed controls. *Ob/ob* mice (lacking functional leptin) that are then exposed acutely or chronically to cigarette smoke exhibit higher neutrophils and CD4+, CD8+, and dendritic cells in BAL and lung tissue than smoke-exposed wild-type mice, compatible with modulation of innate and adaptive immune cell recruitment by leptin in response to smoke.[99] Within human airways, leptin expression is increased in bronchial epithelial cells and alveolar macrophages of ex-smokers with or

TABLE 24-5 Adipokines Linked to Pulmonary Disease States

Adipokine	Pulmonary Source	Receptor	Lung Disease State
Proinflammatory Adipokines			
Leptin	Alveolar type II pneumocytes, alveolar macrophages, bronchial epithelial cells, lung endothelial cells	Leptin receptor	OSAHS, OHS, COPD, asthma, NSCLC, PAH
Apelin	Lung endothelial cells	Apelin receptor	PAH
Nampt	Lung endothelial cells	Unknown	ALI
Resistin	Unknown	Unknown	Asthma
Anti-inflammatory Adipokines			
Adiponectin	Bronchial epithelial cells	Adiponectin receptors 1 and 2, T-cadherin	COPD, asthma, ALI, PAH

OSAHS, obstructive sleep apnea-hypopnea syndrome; OHS, obesity hypoventilation syndrome; COPD, chronic obstructive pulmonary disease; NSCLC, non–small-cell lung cancer; PAH, pulmonary arterial hypertension; ALI, acute lung injury.

without severe COPD compared to never-smokers, and leptin can induce phosphorylation of the transcription factor STAT3 in lung epithelial cells, supporting the notion of a functioning leptin signaling pathway in these cells.[85]

Obesity is believed to be a risk factor for asthma, but some controversy still surrounds whether obesity is a central cause or a confounding comorbidity of asthma.[100,101] Notably, unbiased clustering approaches in severe asthma subjects have identified an obesity-related clinical asthma phenotype typified by obese female patients with late-onset asthma and lacking in eosinophilic T_H2-mediated inflammation.[102] *Ob/ob* mice appear to have elevated pulmonary resistance and increased responses to ozone and methacholine, although this could be mechanical bias from the low lung size of these mutant mice.[88] Interestingly, when a cohort of obese asthmatic women and obese female controls were studied in the setting of bariatric surgery, leptin expression and macrophage inflammation were both increased in visceral adipose tissue of asthmatics independent of BMI, and correlated with airway reactivity, but there was no association with airway inflammation measurements even though the airway epithelial cells expressed receptors for leptin, suggesting that leptin exerts a direct effect on airway epithelium (and not indirectly via enhancing airway inflammation) that is important in the pathogenesis of asthma in obesity.[103] These observations run counter to the hypothesis that leptin is merely a marker for airway inflammation in poorly controlled asthma.[104]

NAMPT (PBEF/visfatin)

The gene *NAMPT* codes for a cytokine called pre-B-cell colony stimulating factor (PBEF), also known as visfatin. Confirmatory studies of the potential receptors for extracellular NAMPT (eNAMPT), Toll-like receptor 4 (TLR4), and CCR5 are awaited.[105,106] It is now known to be produced by various cell types including adipocytes, and especially by visceral as opposed to subcutaneous fat, and has gained greater interest by the rediscovery of PBEF as NAMPT, the rate-limiting enzyme in the biosynthesis of the essential redox cofactor NAD. NAMPT is inducible in neutrophils and lung microvascular endothelial cells by endotoxin, TNF-α, and IL-1β, and in monocytes, it induces production of IL-1β, TNF-α, and IL-6, as well as the surface expression of co-stimulatory molecules CD54, CD40, and CD80.[107,108] Against this background of catalyzing the respiratory burst, and its proinflammatory and immunomodulatory capabilities, NAMPT has been found at higher concentrations in serum and BAL fluid from patients with acute lung injury.[109] Investigators have found inhibition of NAMPT ameliorates ventilatory and ischemic acute lung injury.[110,111] There have also been a number of independent candidate gene association studies that support a role for NAMPT promoter genetic variants in acute lung injury (ALI) pathogenesis.[109,112,113]

■ Anti-inflammatory Adipokines

An important anti-inflammatory adipokine is adiponectin, which is discussed below.

Adiponectin

The most intensely studied of the anti-inflammatory adipokines, and with notable evidence of a role in inflammatory lung disorders, is adiponectin, which shares some structural similarity with complement factor C1q and forms trimers that can go on to form stable hexamers or a high-molecular-weight form, all of which are detectable in blood.[80] Circulating adiponectin levels are decreased in obesity, particularly in visceral obesity, nonalcoholic fatty liver disease, and type 2 diabetes, being inversely related to insulin resistance. The adipokine is inhibited by proinflammatory factors such as TNF, IL-6, hypoxia, and oxidative stress.[76] There has been considerable interest concerning the involvement of adiponectin in pulmonary disease states. Three described adiponectin receptors (AdipoR1, AdipoR2, and T-cadherin) are expressed in the lungs, with AdipoR1 expressed by lung epithelial cells, and importantly, the baseline phenotype of mice following targeted disruption of the adiponectin gene shows evidence of emphysema-like dilated airspaces and activation of alveolar macrophages.[114,115] These same adiponectin-deficient mice develop pulmonary hypertension with evidence of perivascular inflammation,[116] as well as an exaggerated form of LPS-inducible acute lung injury that is abrogated by adiponectin.[117]

As further evidence of anti-inflammatory functionality, adiponectin can bind to apoptotic cells and facilitate their phagocytosis by macrophages, analogous to other members of the collectin family, such as C1q and surfactant proteins A and D.[118] In keeping with this intuitive role in airways disease pathobiology, a number of groups have reported increased levels of circulating adiponectin in COPD.[115,119] Adiponectin was found to be elevated in BALF of COPD patients, being highly expressed in their airway epithelium, and the adiponectin receptor AdipoR1 on lung epithelial cells was shown to be functional, releasing IL-8 in the presence of adiponectin.[115] Animal and human data suggest that short-term exposure to cigarette smoke downregulates adiponectin whereas the COPD disease state elevates its expression.[115] Higher plasma adiponectin levels were independently associated with radiologic emphysema in multiple regression analysis in a substudy of the COPDGene cohort including more than 600 current/former smokers with or without COPD.[120] In contrast, AdipoR2 is more highly expressed in the airway epithelium of obese asthma patients versus obese control subjects, and the opposite to what is observed for T-cadherin expression.[103] In mice, allergen challenge appears to decrease the pulmonary expression of all three adiponectin receptor types, and T-cadherin may play a role in transporting adiponectin into the lungs.[121] In an atopic adult study, co-exposure to diesel exhaust and allergen extract resulted in a potentially protective bronchoalveolar lavage adiponectin/leptin ratio in subjects with normal airway responsiveness, but not in those with baseline hyperresponsiveness.[122] The exact role of adiponectin signaling in asthma will require further study.

■ Adipokines and Pulmonary Hypertension

The high prevalence of pulmonary hypertension in obese subjects has previously been attributed to hypoxemia resulting from associated obstructive sleep apnea or obesity hypoventilation syndrome.[123–125] However, more recently, evidence has shown that alterations in three specific adipokines (adiponectin, apelin, and leptin) may directly contribute to pulmonary vascular dysfunction.

Adiponectin concentrations are paradoxically reduced in the plasma of obese subjects despite the expansion of adipose tissue.[126] Mice in which adiponectin has been deleted spontaneously develop elevated pulmonary arterial pressure, vascular remodeling, and perivascular inflammation as they grow older.[116] Conversely, constitutive overexpression of adiponectin in mice protects against the development of both hypoxia-induced and inflammation-induced (ovalbumin challenge) pulmonary hypertension.[127] These suggest that reduced adiponectin concentrations contribute directly to the development of pulmonary vascular dysfunction in obesity due to a loss of its normal vascular homeostatic action.

Apelin is produced and secreted by adipocytes and acts by binding to the apelin receptor.[128] It is also expressed by a wide variety of other tissues including the pulmonary vasculature.[128] Plasma apelin concentrations are increased in obese individuals.[129] Apelin-null mice develop more severe hypoxic pulmonary hypertension than wild-type mice, which is associated with endothelial dysfunction.[130] Leptin concentrations are elevated in patients with both idiopathic

PAH and scleroderma-associated PAH and in the pulmonary endothelium from these patients.[131,132] In mice, inhibiting the leptin/receptor axis can ameliorate hypoxia-induced pulmonary hypertension by targeting pulmonary artery smooth muscle cell proliferation and perivascular monocyte-derived cellular accumulation.[133] However, the exact role of apelin and leptin in the pulmonary circulation in obese humans remains to be determined.

■ Adipokines and Pulmonary Fibrosis

The elevated leptin levels observed in obese patients with type 2 diabetes mellitus has been postulated to play a role in an apparent reduction in development of and mortality from acute lung injury/acute respiratory distress syndrome (ALI/ARDS) in this patient population.[134,135] Leptin has been implicated in fibrogenesis pathways in lung tissues, as well as liver and kidney, and augments TGF-β1 signaling in lung fibroblasts by inhibiting peroxisome proliferator-activated receptor γ.[135–137] Mice with leptin resistance are protected from hyperoxia-induced acute lung injury.[138] Serum leptin is elevated in never-smokers who have subclinical interstitial lung abnormalities and lower forced vital capacity in a subset of a large multi-ethnic community-based cohort.[139] In Asian patients with acute exacerbation of idiopathic pulmonary fibrosis, plasma leptin levels are elevated and are an independent predictor of survival.[140–142] Leptin may promote pulmonary fibrosis by promoting epithelial mesenchymal transition and by inhibiting autophagy through a PI3K/Akt/mTOR pathway, but these observations need to be replicated in broader populations.[142]

GROWTH FACTORS

A variety of growth factors have been described in the lung and are described in the following sections.

■ Transforming Growth Factor β

Mammalian transforming growth factor beta (TGF-β) belongs to a superfamily of genes and exists as three closely homologous (72%–80%) dimeric isoforms: TGF-β_1, TGF-β_2, and TGF-β_3. Although the three isoforms of TGF-β appear to have overlapping biologic activity, the predominant isoform of TGF-β is TGF-β_1. There are three TGF-β receptors, and signal transduction to the nucleus is via the Smad group of proteins. Smad 1, 2, 3, 4, 5, 8, and 9 are activating signals, whereas Smad 6 and 7 are inhibitory signals of TGF-β_1 signaling.[143]

TGF-β is produced by a variety of cells, including platelets, neutrophils, eosinophils, mononuclear leukocytes, fibroblasts, and endothelial cells.[144,145] TGF-β is a pleiotropic cytokine that can modulate inflammatory and immune responses, and orchestrate fibrosis and tissue repair.[146] TGF-β is a potent immunosuppressive agent that inhibits IL-1–dependent lymphocyte proliferation.

TGF-β is chemotactic for fibroblasts and can indirectly induce their proliferation via the expression and autocrine and paracrine activity of PDGF-B. TGF-β is perhaps the most potent and efficacious promoter of extracellular matrix production–inducing gene expression and protein production of many of the constituents of extracellular matrix. Furthermore, it inhibits the generation of metalloproteinases and augments the expression of tissue inhibitors of metalloproteinases (TIMP).[144,147]

Transient overexpression of active TGF-β_1 results in prolonged and severe interstitial and pleural fibrosis.[148] Transfer of TNF-α or GM-CSF to rat lung induces pulmonary fibrosis, due in part to induction of TGF-β_1.[149] Furthermore, transient expression of IL-1β using an adenoviral vector can lead to progressive fibrosis that is associated with a sustained increase in levels of TGF-β_1.[150] Smad 3 –/– mice developed less fibrosis in response to bleomycin compared with wild-type controls.[151] In contrast, IL-7 downregulates TGF-β production and inhibits bleomycin-induced pulmonary fibrosis, and this is mediated via Smad 7 signaling.[152]

In IPF, increased expression of TGF-β has been found in bronchiolar epithelial cells, epithelial cells of honeycomb cysts, and hyperplastic type II pneumocytes. BALF from patients with IPF induces apoptosis in cultured bronchiolar epithelial cells, and this effect is attenuated using anti TGF-β_1 antibodies.[153] In the bleomycin model, in vivo administration of TGF-β_1 enhanced Fas-mediated epithelial cell apoptosis and lung injury.[153] The antifibrotic medication pirfenidone, which slows the progression of IPF and possibly also unclassifiable progressive forms of pulmonary fibrosis, has been demonstrated to inhibit TGF-β_1 synthesis and signaling among other pleiotropic, incompletely understood effects that include inhibition of fibroblast proliferation and differentiation into myofibroblasts, as well as modulation of epithelial-mesenchymal transition.[154–156] These studies support the contention that TGF-β is an important mediator of human pulmonary fibrosis.

■ TGF-β Superfamily Members and Pulmonary Hypertension

Disturbance of signaling by members of the TGF-β superfamily plays a key role in pulmonary hypertension.[157–160] The bone morphogenetic proteins (BMPs) and their receptors form part of the TGF-β superfamily, whose activities include important proangiogenic and vascular remodeling effects in endothelial and vascular smooth muscle cells.[36,161] The BMPs, like all ligands of the TGF-β superfamily, bind to transmembrane cell surface receptors formed from heterodimerization of a type 1 and type 2 receptor, many of which are expressed in the normal lung and can form a large number of different heteromeric receptor combinations binding with particular BMP ligands. BMP signaling is further modulated modified by a family of secreted extracellular glycoproteins, accessory proteins that bind directly to BMPs and prevent or enhance their interactions with BMPRs.[162,163]

The requirement for normal BMP function to maintain a healthy pulmonary circulation was first demonstrated by the identification of heterozygote inheritance of loss-of-function mutations in the gene encoding BMPR2 as the underlying cause in the rare heritable form of pulmonary arterial hypertension (HPAH) and in a significant proportion (10%–40%) of patients with IPAH without a previous family history.[164–166] These mutations cause attenuation of the normal cellular responses to the BMPs in the lung, where BMP2 and BMP4 signaling through BMP type 1 receptor (BMPR1) and BMPR2 heterodimers play particularly important roles in normal vascular homeostasis, and result in pulmonary hypertension.[160,167–171] Experimentally induced loss-of-function BMPR2 mutations in mice, or expression of dominant negative BMPR2 constructs, were sufficient to cause the development of pulmonary hypertension alone or increased susceptibility to other well-known causes of PH.[169,171–173] Conversely, overexpression of BMPR2 in the endothelium protected mice against the development of hypoxic pulmonary hypertension.[174] These data show that reduced BMP signaling in the lung either causes pulmonary hypertension or increases susceptibility to other causes of PH. Further evidence for the important role of impaired BMP signaling in the development of pulmonary hypertension has been provided by the discovery that pathogenetic mutations in GDF2, which encodes BMP9, also cause PAH by reducing plasma BMP9 and thus impairing signaling through BMPR2.[175,176]

Later studies reported that reduced BMP signaling was found in many of the common forms of pulmonary hypertension, including hypoxic pulmonary hypertension,[160,170,177] although it was not clear what mechanisms cause reduced BMP signaling in these conditions. Further work has shown that the glycoprotein BMP antagonist gremlin 1 is markedly and selectively increased in the hypoxic mouse lung and in human lungs with PAH.[36] Genetically manipulated mice with reduced gremlin 1 expression (haplodeficient) are partially protected against the development of hypoxic pulmonary hypertension.[162,178] Investigation of the mechanisms of the incomplete penetrance of PAH caused by BMPR2 mutations (~20%) shows that family members with the mutation who develop PAH have higher endothelial expression and secretion of gremlin 1 than other family members who also carry the mutation but do not develop the disease, suggesting that upregulation of gremlin 1 with a consequent further reduction in BMP signaling contributes to the pathogenesis of pulmonary vascular disease in those patients.[179]

Furthermore, the basal normoxic expression of gremlin 1 is higher in the lung than in any other organ, potentially rendering it more vulnerable to any loss of BMP signaling and may help to explain why the vascular abnormality in hereditary PAH is restricted to the pulmonary circulation even though the expression of mutant BMPR2 is ubiquitous in all vascular beds.[180] ACTRIIA-Fc, which traps ligands (activin, growth and differentiation factors GDF8, GDF11) that share receptors and effectors with BMP and TGF-β, has helped reveal a significant role for GDF8/11 and activin in attenuating pulmonary hypertension and rebalancing BMP signaling.[181]

TGF-βs are also expressed in the lung as are their type 1 receptors (TGF-β R1) ALK1 and ALK5, and TGF-β receptor type 2 (TGF-β R2) and increased TGF-β signaling has been observed in some forms of pulmonary hypertension.[157–160] Furthermore, pulmonary arterial hypertension develops in a subset of hereditary hemorrhagic telangiectasia patients who have heterozygous mutations in one of the TGF-β type 1 receptors, the ALK1 (activin receptor–like kinase 1).[182,183] Heterozygous mutations in the endoglin (ENG) gene, which codes for a TGF-β co-receptor, also are associated with the spontaneous development of pulmonary arterial hypertension.[182] Eng$^{+/-}$ mice developed pulmonary hypertension associated with loss of peripheral vasculature in adulthood but not in early postnatal life.[184] Taken together, these data indicate a requirement for normal TGF-β signaling to prevent the development of pulmonary hypertension.

■ Epidermal Growth Factor

Epidermal growth factor (EGF) is the prototype member of a family of polypeptide ligands that interact with the ERBB family of four tyrosine kinase receptors (ERBB1–4, also known as human epidermal growth factor receptor, HER1–4).[185,186] All 13 of the EGF extracellular ligands described to date, which include transforming growth factor α (TGF-α), heparin-binding (HB)-EGF, amphiregulin, epiregulin, and betacellulin among others, contain a conserved EGF domain and are made as a transmembrane protein that is then cleaved by cell surface proteases (ectodomain shedding) to release mature growth factors that bind ERBB, such as the case with EGF which binds to HER1/EGFR.[187] EGF motifs are also found in unrelated proteins including extracellular matrix and cell adhesion proteins, blood coagulation factors, and immune response proteins.[188] Control of ERBB family signaling occurs at many levels, including specific cellular patterns of ligand and receptor expression, subcellular segregation of ligands and receptors, and the diversity of intracellular receptor binding proteins that can amplify or attenuate receptor signaling and transcription factor activation, leading to varying cellular outputs of cell proliferation, adhesion, migration, differentiation, or apoptosis.[185] Dysfunctional EGF-ERBB signaling in the lung has consequently been implicated in lung tumorigenesis and lung injury.[189]

EGFR (ERBB1/HER1) is overexpressed in a large number of non–small-cell lung cancers (NSCLC), and its expression has been correlated with a poor prognosis.[190] NSCLCs will also often express EGFRs cognate ligands EGF and TGF-α, leading to receptor hyperactivity in an autocrine fashion.[191] The tyrosine kinase inhibitors gefitinib, erlotinib, and afatinib target the EGF-ERBB complex by acting as competitive inhibitors of ATP binding at the active site of the kinase. It became apparent that drug-responsive cases were enriched for somatic activating mutations in the EGFR kinase domain, with these mutations occurring at a greater frequency in nonsmokers, women, those of Asian genetic ancestry, and those with adenocarcinoma.[192] The third-generation EGFR tyrosine kinase inhibitor osimertinib selectively targets activating EGFR mutations, as well as the most common resistance mechanism to earlier TKIs, the T790M mutation in exon 20, which sterically interferes with binding of earlier-generation TKIs to the ATP-binding site of EGFR.[193]

There is overlap between the signaling events that orchestrate the proliferation, migration, and differentiation of the developing lung epithelia, and those events that are active during lung injury and repair. The importance of EGF motif signaling in lung development is apparent from the HB-EGF –/– mouse hypoplastic lung phenotype, characterized by fewer alveoli and less surfactant. Similarly, the EGFR knockout mice display alveolar collapse, reduced alveolarization, and loss of surfactant expression, resulting in a phenotype similar to the neonatal respiratory distress syndrome,[194] and exogenous EGF can rescue EGFR –/– fetal lambs from such a phenotype.[195] Later in life, there is evidence implicating EGFR signaling in an in vitro model of alveolar epithelial wound repair[196] and bronchial epithelial repair in asthma.[197] A body of evidence has also implicated EGFR signaling in the pathogenesis of pulmonary fibrosis: for example TGF-α –/– mice are protected from bleomycin-induced fibrosis,[198] as are wild-type mice exposed to bleomycin but administered gefitinib.[199] Given that ERBB tyrosine kinase inhibitors can also cause interstitial lung disease in clinical use,[200] it remains to be seen how best the complex ERBB signaling pathways can be therapeutically manipulated in the lung fibrosis arena.

■ Vascular Endothelial Growth Factor

Initially described as a growth factor for endothelial cells, vascular endothelial growth factor (VEGF) is highly expressed in many different lung cell types, and has important roles in lung development and maintenance of lung tissue integrity, through its angiogenic, lymphangiogenic, and hematopoietic roles.[201] VEGF is produced by endothelial cells, fibroblasts, neutrophils, PBMCs, and macrophages, and exists as any of five family members, VEGFA, B, C, D and placenta growth factor (PLGF); further diversity in biologic activity arises from various alternatively spliced isoforms of family members,[202] including VEGFA121, VEGFA145, VEGFA165, VEGFA189, and VEGFA206, named after the number of coded amino acids. Transcription of VEGF is induced by hypoxia, IL-1β, and many growth factors including platelet-derived growth factor, TGF-α and -β, insulin growth factor 1, fibrocyte growth factor, and FGF7 (keratinocyte growth factor). The VEGF family members have three different VEGF receptors, with VEGFA binding to VEGFR-1 and VEGFR-2. VEGFR-2 –/– mice have lethal defects in vasculogenesis and angiogenesis.[203] The role of VEGF in lung development is complex and can be highlighted by a number of observations. When embryonic murine lungs are cultured, VEGF expression, initially diffuse, is restricted over time and space to subepithelial matrix in the branching tips of the developing airways.[204] Furthermore, aberrant lung morphology has been shown to arise from targeted overexpression or underexpression of VEGF.[205,206] In bronchopulmonary dysplasia, the disease of prematurity and its attending interventions including supplemental oxygenation there was a demonstrable reduction in lung expression of VEGF, VEGFR-1 and Tie-2 associated with disrupted pulmonary vasculature.[207]

There is some evidence to suggest that VEGF may play a protective role in emphysema. Partial and transient inactivation of VEGF gene in murine lungs using an adeno-associated *Cre* recombinase virus and conditional VEGF knockout mice, VEGF*loxP*, resulted in apoptosis of alveolar and bronchial cells with ensuing air space enlargement and reduced elastic recoil, reminiscent of emphysema.[208] The low levels of VEGF expressed in human emphysematous lung[209] may be due to upstream factors that cause a reduction in expression of the major controller of VEGF expression, hypoxia-inducible factor (HIF)-1α in COPD lungs.[210]

VEGF and Pulmonary Hypertension

VEGF levels have been variably reported as increased, reduced, or unchanged in pulmonary hypertension with no consistent pattern emerging. However, studies directly examining the effect of inhibiting or stimulating VEGF receptors have produced a coherent picture. Blockade of VEGFR2 using small molecule inhibitors in rats aggravated hypoxic pulmonary hypertension, reduced pulmonary VEGFR2 expression, and increased endothelial cell apoptosis, suggesting that VEGFR2 was essential for maintaining and expanding the vascular bed in the hypoxic lung.[211] Moreover, even following return to normoxia and withdrawal of VEGFR2 blockade the pulmonary hypertension was progressive and ultimately fatal. After extended time periods in this model, complex plexiform-like lesions similar to those found in human PAH are observed.[212] Mice also show aggravation of hypoxic pulmonary hypertension in the presence of VEGFR2 blockade.[213] A mouse model of endothelial cell–specific ablative VEGFR-2 (*Kdr*) knockout in chronic hypoxic conditions led to pulmonary arterial wall thickening, muscularization, and VEGFR-3$^+$ endothelial cells obliterating the pulmonary artery vessel lumen.[214] Interestingly, pulmonary hypertension has occasionally been reported in patients receiving VEGF inhibitors such as bevacizumab as part of a cancer chemotherapy treatment program, where pulmonary vascular lesions similar to the Kdr-knockout have been seen.[214,215]

Overexpression of VEGFA in the rat lung using adenoviral vectors protected against the development of pulmonary hypertension, although no analysis of the capillaries and small intra-acinar vessels (<50 μg) was carried out so it is not possible to know if this protection was accompanied by angiogenesis.[216] Louzier et al. found that overexpression of VEGFB in the hypoxic rat lung using an adenoviral vector strategy protected against the development of hypertension and increased vessel density within the lung.[217] Thus, it is clear that the balanced actions of agonist and inhibitory members of the VEGF family are essential for normal adaptation of the pulmonary circulation to hypoxia, although the precise role of the VEGF pathway in human pulmonary hypertension is at present unclear.

■ Fibroblast Growth Factor

The fibroblast growth factor (FGF) family consists of 18 secreted polypeptide ligands that bind to one of four target cell-surface FGF receptors (FGFR), that are tyrosine kinase receptors (FGFR1–4), and that have many isoforms as a result of exon skipping and alternative splicing, the latter being generally tissue specific.[218] FGF subfamilies are grouped for their shared sequence homology and phylogeny. FGFs regulate diverse biologic processes including angiogenesis and organogenesis including proliferation, cell migration, and paracrine effects on tissue patterning. Two of the FGF ligands have particular relevance to the lung, both within the FGF subfamily including FGF7 (keratinocyte growth factor, KGF) and FGF10.[218,219]

FGF7 is expressed specifically by mesenchymal cells, including fibroblasts and vascular smooth muscle cells, and binds exclusively to the epithelial receptor FGFR2-IIIb, suggesting a paracrine loop effect in its epithelial–mesenchymal interactions. The use of a dominant-negative mutant to inhibit FGFR2-IIIb resulted in an absence of branching morphogenesis within the developing murine lung,[220] and FGF7 overexpression resulted in enlarged bronchial airspaces and papillary cystadenomas.[221] A variety of experimental data have indicated that FGF7 expression increases following acute lung injury and that FGF7 is protective, principally when used as a pretreatment, in the face of injury caused by varied insults including hyperoxia, radiation, graft-versus-host-disease following allogeneic bone marrow transplant, acid, and bleomycin,[219,222–224] but FGF7 may also partially prevent loss of barrier function in airway epithelium when given after an inciting exposure, potentially making FGF7 a more attractive therapeutic intervention were it so.[225,226] Notably, recombinant FGF7 (palifermin), which improves wound healing through cellular proliferation, is FDA-approved for the treatment of chemoradiation-induced oral mucositis.[227] In addition to FGF7, FGF10 plays a critical role in lung development, given that FGF10 −/− mice have defects in branching morphogenesis in lungs and other organs.[228] FGF10 overexpression attenuates bleomycin-induced pulmonary fibrosis in mice.[229] The triple angiokinase inhibitor nintedanib (BIBF 1120) inhibits VEGFR(1–3), platelet-derived growth factor receptors α and β, and FGFR1–3, and it slows decline in forced vital capacity—leading to its use in IPF, systemic sclerosis–associated interstitial lung disease, and other chronic fibrosing interstitial lung diseases with a progressive phenotype.[230,231]

■ Granulocyte Macrophage-Colony Stimulating Factor

Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a glycosylated secreted protein produced by a variety of cells including macrophages, endothelial cells, T cells, natural killer cells, mast cells, and fibroblasts. It is defined by its ability to expand in vitro bone marrow precursor cells, via proliferation and differentiation, into colonies of mature myeloid cells, and to act as a proinflammatory cytokine.[232–234] Interest from the pulmonary field grew with the initial observation that mice lacking GM-CSF had no major perturbation of hematopoiesis, but had an unexpected finding of compromised maturation of alveolar macrophages resulting in a phenotype of pulmonary alveolar proteinosis (PAP), with defective clearing of surfactant by alveolar macrophages.[235] The major form of human PAP is classified as autoimmune (or primary) PAP, accounting for about 90% of all PAP cases.[236] Autoimmune PAP is characterized by abnormally elevated levels of GM-CSF IgG autoantibodies, which bind GM-CSF with high affinity and neutralize GM-CSF functionality, and it results in persistence of dysfunctional alveolar macrophages that are less efficient, with associated neutrophil dysfunction leading to opportunistic infections.[237] A heritable component to autoimmune PAP has been linked in Japanese subjects to HLA-DRB1*08:03, which is associated with increased levels of anti–GM-CSF antibody.[238] While whole-lung lavage remains the cornerstone of therapy for PAP, nebulized recombinant GM-CSF modestly improves lung function and functional health status and may facilitate some clearance of GM-CSF–antibody complexes from lung tissue.[239]

■ Connective Tissue Growth Factor

Connective tissue growth factor (CTGF) is a member of the structurally related CCN (*CTGF/CYR61/NOV*) gene family, which contains six genes: *CTGF*, *CYR61*, *NOV*, *ELM1*, *COP1*, and *WISP3*.[240] CTGF I is produced by vascular smooth muscle cells, fibroblasts, endothelial cells, and epithelial cells, and is activated by a number of factors, particularly TGF-β.[240] CTGF has in vitro activities that include fibroblast proliferation, fibroplasia, and extracellular matrix production.[240–242] Furthermore, its presence has been documented in skin lesions of systemic sclerosis, keloids, scar tissue, and eosinophilic fasciitis and in BALF from patients with IPF and sarcoidosis, and it induces ECM in asthmatic airway smooth muscle.[240–243] Transient overexpression of CTGF in a rat model leads to a moderate but reversible pulmonary fibrosis that is associated with increased levels of TIMP-1.[244] Overexpression of TGF-β leads to a concomitant increase in CTGF and TIMP-1, suggesting that CTGF may be a cofactor for the development of fibrosis.[244] CTGF may be responsible for some of the downstream actions of TGF-β and is a potential therapeutic target for the treatment of interstitial lung disease, now being targeted in IPF by the recombinant anti-CTGF antibody pamrevlumab in phase 3 clinical trials due to favorable tolerability and efficacy data to date in slowing disease progression.[245]

CONCLUSIONS

Chemokines, adipokines, and growth factors are now recognized to play fundamental roles in lung development, the lifelong maintenance of lung health, and the development of pulmonary disorders characterized by inflammation and/or fibrosis, some of which are modulated by body mass. The generation of complex, overlapping signaling networks is necessary for both the pathogenesis and resolution of a variety of acute and chronic lung diseases, as these mediators are fundamental to the initiation, maintenance, and final resolution of the inflammatory response. Studies that illuminate the mechanistic role of chemokines, adipokines, and growth factors in mediating lung inflammation are beginning to lead to novel targeted forms of therapies, which will significantly aid in treating enigmatic lung disease.

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CHAPTER 25

Redox Signaling and Oxidative Stress in Lung Diseases

Jessy Deshane
Victor J. Thannickal

INTRODUCTION

Molecular oxygen is a prerequisite to life of all aerobic organisms. With its large surface area and extensive blood supply the human lung is engineered for its primary function in gas exchange. While oxygen is essential for its many roles in human physiology, high concentrations of oxygen or its metabolites, commonly referred to as reactive oxygen species (ROS), have the potential to cause cellular injury and contribute to disease pathogenesis. The most damaging forms of ROS are free radicals. A free radical, by definition, refers to any chemical species containing one or more unpaired electrons in their atomic or molecular orbitals. These unpaired electrons give considerable reactivity to free radical species, which can trigger chemical reactions that damage cellular constituents of living organisms. Molecular oxygen (dioxygen) is itself a radical based on the presence of unpaired electrons in its outermost orbital; however, their parallel spin retrains its reactivity. O_2 can form the superoxide anion radical ($O_2^{\bullet-}$) upon addition of an electron, thus overcoming this restraint and making $O_2^{\bullet-}$ a highly reactive species.[1,2] The photodynamic activation of oxygen can result in the formation of singlet oxygen, and its reductive activation results in the formation of hydrogen peroxide (H_2O_2) or the highly reactive hydroxyl radical ($^{\bullet}OH$).[3,4] When two free radicals share their unpaired electrons, nonradical species of lower reactivity are generated. Thus, ROS constitute both free radicals and nonradicals.

Nitric oxide ($NO^{\bullet}$) is another small gaseous molecule that serves as an important signaling molecule in diverse physiologic processes, including vasorelaxation and immune regulation during chronic inflammation in the lung.[5,6] The regulated production of $NO^{\bullet}$ by lung cells is critical for homeostasis of the lung. However, in some contexts, the reaction of $NO^{\bullet}$ with $O_2^{\bullet-}$ to form reactive nitrogen species (RNS), such as peroxynitrite ($ONOO^-$), may contribute to the pathophysiology of chronic lung diseases.[7–9]

ROS and RNS together play important roles in regulation of cell proliferation, differentiation, and survival.[10–12] ROS/RNS can inactivate enzymes including antiproteases, induce apoptosis, regulate cell proliferation, and modulate the immune-inflammatory system in the lungs and other tissues.[13–16] ROS/RNS have been implicated in initiating inflammatory responses in the lungs through the activation of transcription factors, protein kinase pathways, chromatin remodeling, and gene expression of proinflammatory mediators.[13–16] Under normal physiologic conditions, the balance between generation and elimination of ROS/RNS maintains the functional integrity of redox-sensitive signaling cascades regulating cellular phenotypes. In this context, it is important to differentiate the roles of ROS/RNS in "oxidative stress" from "redox signaling." Paradoxically, it appears that nature has co-opted the chemical reactivities of ROS/RNS to function as signaling molecules in homeostasis and normal cellular physiology.

Redox homeostasis of cells/tissues is maintained by the regulated balance of oxidant production and antioxidant systems, both enzymatic and non-enzymatic. However, an increase in oxidant generation in excess of the capacity of cells/tissues to detoxify or scavenge reactive species leads to oxidative stress.[10,17,18] Oxidative stress typically causes damage to cellular components in an indiscriminate manner. Such states are accelerated in the presence of transition metals, such as iron and copper, and/or specific monooxygenases or oxidases.[13,15,16] It is also important to recognize that aberrations in redox signaling or oxidative stress may contribute to the pathogenesis of lung diseases. In this chapter, we review the physiology of ROS and RNS; cellular antioxidant systems; and the role of oxidative stress and redox signaling in disease development and progression of selected chronic lung diseases.

METABOLISM OF REACTIVE OXYGEN/NITROGEN SPECIES (ROS/RNS)

Metabolism of reactive oxygen and nitrogen species includes consideration of enzymatic and non-enzymatic sources of ROS and RNS, mechanisms to detoxify these species, and a variety of cellular sources and regulation of ROS and RNS.

■ Enzymatic and Non-Enzymatic Sources of ROS

The primary ROS include superoxide anion ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), and hydroxyl radical ($^{\bullet}OH$), which can be generated from both enzymatic and non-enzymatic sources. The human lung is constantly exposed to ambient air, which may contain environmental toxins capable of inducing ROS generation.[13,19] ROS may be also be generated by electron transfer reactions in the mitochondria and endoplasmic reticulum (ER), from xenobiotics, and a range of metabolic enzymes that catalyze oxidation reactions.[19] The major endogenous ROS/RNS and the primary mechanisms for their generation are summarized in Table 25-1.

TABLE 25-1 Key Reactive Oxygen and Nitrogen Species

Reactive Species	Formula	Chemical Reaction		
Superoxide	$O_2^{\bullet-}$	$NADPH + 2O_2$	$\longleftrightarrow$	$NADP+ + 2O_2^{\bullet-} + H^+$
		$2O_2^{\bullet-} + H+$	$\longrightarrow$	$O_2 + H_2O_2$
Hydrogen peroxide	H_2O_2	$Hypoxanthine + H_2O + O_2$	$\rightleftarrows$	$Xanthine + H_2O_2$
		$Xanthine + H_2O + O_2$	$\rightleftarrows$	$Uric\ acid + H_2O_2$
Hydroxyl radical	$^{\bullet}OH$	$Fe^2 + H_2O_2$		$Fe^{3+} + OH^- + {}^{\bullet}OH$
Hypochlorous acid	HOCl	$H_2O_2 + Cl^-$	$\longrightarrow$	$HOCl + H_2O$
Peroxyl radicals	$ROO^{\bullet}$	$R^{\bullet} + O_2$	$\longrightarrow$	$ROO^{\bullet}$
Peroxynitrite	$ONOO^-$	$O_2^{\bullet} + NO$	$\longrightarrow$	$ONOO^-$
		$H_2O_2 + NO_2^-$	$\longrightarrow$	$ONOO^- + H_2O$

The highly reactive $O_2^{\bullet -}$ formed by the addition of an electron to molecular oxygen is unstable, with a half-life of milliseconds. The major site for producing $O_2^{\bullet -}$ is the mitochondria, which is also the primary site for ATP generation in any cell. During mitochondrial electron transport, there is an estimated leak of 1%–3% of electrons to oxygen resulting in the formation of $O_2^{\bullet -}$.[16] $O_2^{\bullet -}$ generated in the mitochondria, due to its negative charge, does not cross membranes and is released into the mitochondrial matrix where it targets proteins with heme moieties or iron sulfur clusters to cause loss of protein or enzymatic function.[20] The steady-state levels of intramitochondrial $O_2^{\bullet -}$ concentrations are maintained at very low levels by detoxifying enzymes. ER is another intracellular compartment in which enzymes detoxify lipid-soluble drugs and other toxic metabolites, and reduce molecular O_2 to produce $O_2^{\bullet -}$ and/or H_2O_2, while oxidizing unsaturated fatty acids and xenobiotics.[19,20]

The NADPH oxidase (NOX) gene family encompasses enzymes, the primary function of which is the regulated generation of ROS. NOX enzymes form a membrane-bound multi-component complex that is present in phagocytes and nonphagocytic cells in the lung.[15,16,18] NOX enzymes play crucial roles in host defense, signal transduction, and hormone synthesis in eukaryotes. There are seven mammalian NOX homologs constituting NOX1–5 and DUOX1 and DUOX2.[21–24] The best-characterized NOX isoform is NOX2, which is essential for microbicidal killing activity of phagocytes. NOX2, upon activation, generates ROS by coordinated assembly and activation of the NOX2 enzymatic complex, which is composed of the membrane-associated flavocytochrome b558 ($gp91^{phox}$), $p22^{phox}$, and the various cytosolic cofactors ($p47^{phox}$, $p67^{phox}$, and $p40^{phox}$, and the GTPase Rac1). This complex then mediates the transmembrane electron transfer electrons from NADPH to molecular O_2 to generate $O_2^{\bullet -}$ or H_2O_2.[15,16,18]

Similar to NOX2, activation of NOX1 and NOX3 also requires association with $p22^{phox}$ and assembly with Rac 1 and cytosolic cofactors ($p47^{phox}$ and $p67^{phox}$ or their homologs, NOX organizer 1 [NOXO1] and NOX activator 1 [NOXA1]). NOX4 also requires $p22^{phox}$ but is constitutively active and is activated independently of other cofactors.[16,21–24] Expression of NOX1 and NOX4 in fibroblasts results in increased levels of both $O_2^{\bullet -}$ and H_2O_2, implying that these, unlike the phagocytic NOX2, possess intrinsic basal activity. NOX5 and DUOX1/2 differ from the other NOX homologs and contain additional intracellular Ca^{2+}-binding EF-hand domain regions, and are regulated by Ca^{2+} signaling.[16,21–24] The dual oxidases, DUOXs, are composed of the NOX-like region at the C-terminal half, two EF-hands, a membrane-spanning region, and a peroxidase-like domain at the N-terminus. DUOXs do not require cytosolic regulatory components for their activity.[16,21–24] However, the transmembrane maturation factors DUOXA1 and DUOXA2 are essential for ER-to-Golgi transition, maturation, and targeting DUOXs to the plasma membrane as functional complexes. Although initially identified in the thyroid gland, DUOX1 and DUOX2 are the primary sources of H_2O_2 production in the airway epithelium.[25] The NOX/DUOX isoforms are expressed widely in the lung extending from the proximal trachea and large airways to terminal bronchioles and alveoli[16,21–25] (Table 25-2).

TABLE 25-2 Enzymatic Sources for ROS and RNS

Enzyme	Distribution in Lung	Lung Cell Types
DUOX1, DUOX2, NOX2, NOX4	Trachea and upper airways	Airway epithelial cells
NOX1, NOX2, NOX4	Pulmonary vasculature	Pulmonary artery endothelial cells
NOX4	Pulmonary vasculature	Pulmonary artery smooth muscle cells
DUOX1, DUOX2, NOX2, NOX4	Lower airways/ alveolus	Airway epithelial cells
NOX3	Airway alveolus	Endothelial cells
NOX4	Airway alveolus	Myofibroblasts
NOX2, NOX4	Alveolar space/ blood	Monocytes, macrophages, neutrophils, eosinophils
NOS1 (neuronal)	Trachea, bronchus, airways	Airway epithelial cells Neutrophils Neurons
NOS2 (inducible)	Airways, alveolus, alveolar space/ blood	Airway and vascular smooth muscle cells Type II pneumocytes Fibroblasts Macrophages Monocytes Neutrophils Eosinophils Mast cells
NOS3 (endothelial)	Airways, pulmonary vasculature	Airway epithelial cells Type II pneumocytes Pulmonary artery smooth muscle cells Endothelial cells Macrophages

In biologic systems, dismutation reaction of $O_2^{\bullet -}$ generates H_2O_2, either spontaneously or by enzymatic catalysis by superoxide dismutases (SODs). $O_2^{\bullet -}$ can be generated by molybdenum hydroxylase reactions involving xanthine, sulfite and aldehyde oxidases, dihydroorotate and flavoprotein dehydrogenases, and tryptophan dioxygenases, as well as arachidonic acid metabolism.[26,27] Certain oxidases such as monoamine and amino acid oxidases can generate H_2O_2 directly without the intermediate formation of $O_2^{\bullet -}$.[17] During chronic inflammation in the lung, H_2O_2 is produced by both resident and inflammatory cells of the lung.[26,27] The oxidizing potential of H_2O_2 is amplified by inflammatory cell–derived heme peroxidases such as myeloperoxidase (MPO) and eosinophil peroxidase (EPO).[28–32] The hydroxyl radical, $^{\bullet}OH$, is the neutral form of the hydroxide ion, which is highly reactive towards cellular constituents, more so than $O_2^{\bullet -}$ or H_2O_2. This radical contributes to most of the reactivity by $O_2^{\bullet -}$ and H_2O_2 in a series of reactions that are catalyzed by transition metal ions. Excess $O_2^{\bullet -}$ targets Fe-S cluster-containing enzymes and catalyzes production of $^{\bullet}OH$ from H_2O_2 by reducing free iron (Fe^{3+} to Fe^{2+}) in a Fenton chemistry reaction (see Table 25-1). MPO and EPO enzymes represent an alternate pathway for $^{\bullet}OH$ formation in vivo. MPO uses Cl^- as substrate to generate hypochlorous acid, while EPO uses Br^- to generate brominating species. The hypohalous acids then generate $^{\bullet}OH$ by reaction with $O_2^{\bullet -}$.[33–38] Both these enzymes can accelerate oxidative modifications of proteins, in particular bromination and chlorination.

■ Enzymatic and Non-Enzymatic Sources of RNS

An important RNS in the lung is nitric oxide ($NO^{\bullet}$), which is endogenously generated by specific nitric oxide synthases (NOS). These NOS enzymes metabolize L-arginine to $NO^{\bullet}$ and L-citrulline via a five-electron oxidation reaction.[6,39–48] This reaction requires a dimeric enzyme, oxygen, NADPH, and the co-factors flavin adenine dinucleotide (FAD), flavin mononucleotide (FMN), tetrahydrobiopterin (BH_4), calmodulin, and iron protoporphyrin. Active NOS enzymes exist in the dimeric form with each monomer consisting of an N-terminal oxygenase domain that binds heme, BH_4, and substrate L-arginine. The cofactors FAD, FMN, and NADPH bind the C-terminal end of the NOS monomer. There are three different NOS isoforms, all of which are expressed in the lung, the inducible form iNOS or NOS2, neuronal NOS or NOS1, and the endothelial NOS enzyme NOS3 (Table 25-2).

The NOS1 and NOS3 enzymes are calcium dependent and produce picomolar levels of NO, while nanomolar levels are generated by the calcium-independent iNOS. $NO^\bullet$ synthesis by iNOS is regulated by the availability of the substrate L-arginine and cofactor BH_4. Transfer of electrons occur from the carboxy-reductase domain to the heme iron of the oxygenase domain, which then binds oxygen and oxidizes L-arginine to generate the end-products, $NO^\bullet$ and citrulline.[6,39–48] Uncoupling of NOS enzymes can contribute to the formation of $O_2^{\bullet-}$ from NADPH oxidation under low arginine conditions. Arginase, an enzyme that competes with the NOSs for L-arginine, decreases the arginine availability for NOS. Arginase is a critical enzyme in the urea cycle and converts arginine to ornithine, and then to urea; it can promote uncoupling of NOSs to generate $O_2^{\bullet-}$.[49,50] About 40% of the highly reactive and highly diffusible $NO^\bullet$ is consumed in chemical reactions and, when metabolized, gives rise to reactive intermediates. $NO^\bullet$ reacts with O_2 yielding nitrite (NO_2^-), and recycling of nitrite causes regeneration of bioactive $NO^\bullet$. NO_2^- is also a substrate for the heme peroxidases MPO and EPO, which oxidize nitrite to nitrogen dioxide radical ($NO_2^\bullet$). $NO^\bullet$ is also oxidized to methemoglobin and NO_3^- by reaction with oxyhemoglobin. $NO^\bullet$ reacts with $O_2^{\bullet-}$ to form peroxynitrite ($ONOO^-$), which mediates tyrosine nitration that may result in either the loss or gain of function of proteins.[7–9,51]

In acidic environments, the protonation of $ONOO^-$ results in the formation of ONOOH (peroxynitrous acid), which is then decomposed to both NO_3^- via intermediate $^\bullet OH$ and NO_2.[52] ONOOH can also react with thiol residues to form S-nitrosothiols, and the reaction is referred to as S-nitrosation or S-nitrosylation. A wide variety of proteins including kinases, ion channels, and transcription factors are susceptible to S-nitrosylation. S-nitrosothiols (SNOs) are important molecules in the signaling of $NO^\bullet$ bioactivity in the respiratory system.[53–57] SNOs are present in the airway epithelial lining fluid in μmol concentrations, can influence airway tone, and possess substantially greater half-lives than $NO^\bullet$ in the lung. It has also been reported that iNOS can specifically bind to cyclooxygenase 2 (COX-2) and S-nitrosylate COX-2, upregulate its catalytic activity, and enhance prostaglandin E2 production. Thus, S-nitrosylation represents an important signaling pathway for $NO^\bullet$.[53–57] Under physiologic conditions, interaction with metal centers of enzymes and S-nitrosylation are the major mechanisms for biologic actions of $NO^\bullet$. In biologic systems, the levels of $O_2^{\bullet-}$ are in the 10^{-11} to 10^{-10} M range, while that of NO is 10^{-9} to 10^{-7} M. Under these conditions, $ONOO^-$ is formed at a low rate by the reaction of $NO^\bullet$ with $O_2^{\bullet-}$ with a 1:1 stoichiometry.[7–9,51,53–57] However, under pathophysiologic conditions, $ONOO^-$ and its derivatives are formed at high levels and may cause irreversible damage to the mitochondrial electron transport chain, inhibit ATP synthesis, and induce cytochrome c release and caspase-dependent apoptosis. RNS also mediate lipid peroxidation, protein oxidation and nitration, enzyme inactivation, and even cell necrosis.[7–9,51,53–57]

■ Mechanisms to Detoxify ROS/RNS

ROS/RNS play a key role in the initiation, amplification, and persistence of inflammation associated with chronic lung diseases.[15–18,58,59] Similar to the formation of ROS/RNS, the removal or detoxification of these species may involve enzymatic and non-enzymatic mechanisms. Non-enzymatic systems constitute the first line of defense against ROS/RNS.

The low-molecular-weight non-enzymatic antioxidants in the lung include glutathione, vitamins C and E, beta-carotene, uric acid, thiols, and taurine. The larger-molecular-weight antioxidants include lactoferrin, albumin, ceruloplasmin, and transferrin; these molecules mediate their antioxidant function primarily by binding heavy metals, making them unavailable for participation in the Fenton reaction to produce free radicals such as hydroxyl radical.[15,18,26,59,60] Non-enzymatic antioxidant activities may also include hydrophilic quenching of free radicals and protection of critical sulfhydryl groups on proteins to inhibition of lipid peroxidation.

Although non-enzymatic antioxidants are the first line of defense against different ROS, several enzymatic antioxidants work in concert with non-enzymatic antioxidants to form a tightly regulated antioxidant network. The major components of the pulmonary enzymatic antioxidant defense systems are SODs, catalase, and glutathione peroxidases. Peroxiredoxins, thioredoxins, glutaredoxins, heme oxygenases, and reductases also are involved in cellular adaptation and protection against oxidative stress in the lung. The enzymatic reactions that catalyze the elimination of ROS/RNS are summarized in Fig. 25-1.

Superoxide Dismutases

The $O_2^{\bullet-}$ radical is a primary oxidant in chronic lung inflammation.[15,17,61] It participates in the generation of other reactive metabolites, H_2O_2, $^\bullet OH$, and $ONOO^-$. SODs represent a key defense against reactive species generated during normal metabolism or inflammatory states. SODs are ubiquitous enzymes that catalyze the dismutation of $O_2^{\bullet-}$ radical to the weaker oxidant, H_2O_2 (see Fig. 25-1). The function of SOD extends beyond its catalysis of $O_2^{\bullet-}$ dismutation to its participation in the regulation of normal cellular homeostasis. H_2O_2 formed from the SOD-catalyzed reaction may function as a signaling molecule at low concentrations. By reducing steady-state concentrations of $O_2^{\bullet-}$, which reacts with $NO^\bullet$ to form $ONOO^-$, SOD may serve to promote vasoreactivity and reduce inflammation.[15,61]

There are three mammalian SOD isozymes: the intracellular copper-zinc SOD (CuZn-SOD), the mitochondrial manganese SOD (Mn-SOD), and extracellular SOD (EC-SOD).[61] The structural and catalytic characteristics of these SOD isozymes are highlighted in Table 25-3.[62–65] Given the complexity of the human lung with its plethora of different cell types, it is conceivable that these isozymes are expressed differentially in specific lung cells with subcellular compartmentalization, as summarized in Table 25-4.[66–79]

$$\begin{aligned}
2O_2^{\bullet-} + 2H^+ &\xrightarrow{\text{Superoxide dismutase}} H_2O_2 + O_2 \\
2H_2O_2 &\xrightarrow{\text{Catalase}} O_2 + 2H_2O \\
H_2O_2 + 2\ GSH &\xrightarrow{\text{Glutathione peroxidase}} GSSG + 2H_2O \\
ROOH + 2\ GSH &\xrightarrow[\text{peroxiredoxin}]{\text{Glutathione peroxidase}} ROH + GSSG + H_2O \\
ONOO^- + 2\ GSH &\xrightarrow{\text{Glutathione peroxidase}} ROH + GSSG + H_2O \\
GSSG + NADPH + H^+ &\xrightarrow{\text{Glutathione reductase}} 2\ GSH + NADP^+ \\
TrxS_2 + NADPH + H^+ &\xrightarrow{\text{Thioredoxin reductase}} Trx(SH)_2 + NADP^+ \\
H_2O_2 + Trx(SH)_2 &\xrightarrow{\text{Peroxiredoxin}} 2H_2O + TrxS_2 \\
RX + GSH &\xrightarrow{\text{Glutathione transferase}} HX + R\text{-}S\text{-}GSH \\
Heme + 3O_2 + 3\ NADPH &\xrightarrow{\text{Heme oxygenase}} CO + Fe_2^+ + Biliverdin
\end{aligned}$$

Figure 25-1 Enzymatic mechanisms to detoxify reactive oxygen and nitrogen species.

TABLE 25-3 Characteristics of Superoxide Dismutases

SOD	Structure	Metal Ions	Type of Enzymatic Activity	Intracellular SOD Activity
Mn-SOD	Homotetramer	Mn and Zn	$O_2^{\bullet -}$ Dismutation	10%
CuZn-SOD	Homodimer	Cu and Zn	$O_2^{\bullet -}$ Dismutation Peroxidation Nitration	90%
EC-SOD	Homotetramer	Cu and Zn	$O_2^{\bullet -}$ Dismutation Peroxidation	0%

Aside from dismutating $O_2^{\bullet -}$ radical by the cyclic oxidation-reduction of its metal ion Cu^{2+}, CuZn-SOD exhibits peroxidase activity.[65] At high levels, H_2O_2 may reduce the Cu^{2+} to either Cu^{+}-O or Cu^{2+}-OH that may oxidize the histidine residue in the monomer and inactivate or oxidize lung proteins.[80–82] CuZn-SOD also nitrates tyrosine residues in proteins via peroxynitrite[83–87] and catalyzes the release of NO from nitrosothiols.[88] Although Mn-SOD has similar dismutase activity, it does not elicit peroxidation or nitration, and it is inactivated by tyrosine nitration but not by hydrogen peroxide or cyanide.

EC-SOD is the primary extracellular SOD in the lung.[72,89,90] The EC-SOD has an active site that can be inhibited by H_2O_2 and cyanide, similar to CuZn-SOD.[74–76] EC-SOD has an arginine- and lysine-rich heparin/matrix binding domain at its C-terminal region.[91–94] Its extracellular localization is maintained by the interaction of this domain with heparin and heparin sulfate proteoglycans on diverse lung cell types and in the extracellular matrix (ECM) of the lung. This heparin/matrix binding polybasic region is sensitive to proteolysis, leading to reduced affinity of EC-SOD for ECM and increased release of EC-SOD in plasma.[72,91–97] EC-SOD is abundant in the lung at both the mRNA and protein levels.[91–94] As indicated in Table 25-4, the wide cellular distribution of EC-SOD is consistent with robust EC-SOD activity in the human lung (8-fold > liver, 6-fold > brain, 2- to 3-fold > heart, and 1- to 2-fold > kidney).[61] In comparison, CuZn-SOD and Mn-SOD activities are much lower. The lower activities of CuZn-SOD and Mn-SOD in the lung suggest that cytoplasmic production of $O_2^{\bullet -}$ is lower in lung cells, compared with the metabolically more active cells of the liver and kidney. The dense airway and vascular network in the lung and the higher potential for extracellular inflammatory events resulting from direct exposure of the lung to the external environment may account for high EC-SOD levels in the lung. Even with its high lung localization, EC-SOD is not present at sufficient concentrations to justify its role as the sole scavenger of $O_2^{\bullet -}$ across the entire extracellular space. While CuZn-SOD and Mn-SOD function mainly as bulk scavengers of the $O_2^{\bullet -}$ radicals, the relatively high levels of EC-SOD in the lung and its binding specificity to the ECM components provide protection for the lung matrix.[14,98]

The lack of abnormalities in CuZn-SOD-deficient mice suggest that pathologic consequences of mutations are perhaps due to gain of compensatory functions of the enzyme, including its peroxidase or nitration reactions, and not associated only with the complete loss of SOD activity.[97,99] EC-SOD-overexpressing mice were only partially protected from hyperoxia-induced lung injury, influenza, bleomycin, and hemorrhagic shock,[14,61,98] suggesting that EC-SOD may not be sufficient to attenuate oxidative stress in pathologic states in which

TABLE 25-4 Enzymatic Mechanisms to Detoxify or Remove ROS/RNS

Antioxidant Enzymes	Acronym	Expression of Antioxidant Enzymes in Lung Cell Types	Cellular Distribution
Superoxide Dismutase	SOD		
MnSOD		Alveolar type II epithelial cells, septal tip of the alveolar duct, arterioles near the airways, aveolar macrophages	Mitochondria
EC-SOD		Bronchial epithelium, alveolar epithelium, epithelial cells lining intrapulmonary airways, ECM, endothelial cells lining arteries and veins, alveolar macrophages	Plasma membrane
CuZnSOD		Bronchial epithelium, alveolar epithelium, mesenchymal cells, fibroblasts, arterioles, capillary endothelial cells	Cytosol, nucleus, lysosome, peroxisomes
Catalase	CAT	Airway and alveolar epithelial cells, type II pneumocytes, alveolar macrophages	Peroxisomes, mitochondria
Glutathione peroxidase 1	GSH-Px	Airway epithelial cells, bronchial epithelial cells, alveolar macrophages	Cytosol, mitochondria
Thioredoxin	TRX1 & 2	Bronchial epithelium, alveolar epithelium, macrophages	Cytosol, mitochondria
Thioredoxin peroxidase	TRXPrx	Bronchial epithelial cells, type II pneumocytes, macrophages	Cytosol
Thioredoxin reductase	TRR	Bronchial epithelium, alveolar epithelium, macrophages	Cytosol, mitochondria
Glutaredoxin	Glrx	Bronchial epithelium, alveolar macrophages	Plasma membrane, cytoplasmic vacuoles, nucleus
Glutathione S transferase	GST	Bronchiolar Clara and alveolar type II cells, bronchial epithelial cells	Plasma membrane, cytosol, microsomes, mitochondria
Peroxiredoxin	PRX	Bronchial epithelium, alveolar epithelium, macrophages	Cytosol, nuclear matrix, peroxisomes, mitochondria
Heme oxygenase	HO	Alveolar type II cells, lung fibroblasts, monocytes, alveolar macrophages	Microsomes, mitochondria, endoplasmic reticulum

the EC-SOD system is overwhelmed. Under hyperoxia, mice lacking EC-SOD show shortened survival and extensive lung damage.[14,61,98] Thus, although other antioxidant enzymes may compensate for the loss of EC-SOD under homeostatic conditions, during inflammatory stress, EC-SOD is essential for protecting the lung and limiting injury. More than 90 genetic polymorphisms have been identified in CuZn-SOD, several in association with neurodegenerative diseases.[62] The Arg 213-gly polymorphism in EC-SOD (R213G) is found in 4% to 6% of the human population and influences chronic obstructive pulmonary disease[100,101] and acute lung injury.[102]

Catalase

H_2O_2 is reduced to water by catalase (CAT) and the glutathione peroxidases (Fig. 25-1). CAT is a metalloprotein oxidoreductase enzyme widely expressed in lung cells[103–107] (see Table 25-4). In the presence of excess H_2O_2, CAT undergoes alternate divalent oxidation and reduction at its heme-containing active site. Catalase degrades H_2O_2 to O_2 and water.[103–107] Although catalase is the principal scavenger of H_2O_2, it is unable to metabolize large molecular peroxides including lipid peroxides. The gene for catalase is not induced by oxidant stress. However, post-translational tyrosine phosphorylation of CAT upregulates its activity,[108] whereas oxidation of tyrosine residues inhibits CAT activity.[8]

Glutathione Peroxidases

Glutathione peroxidases (GSH-Pxs) are selenocysteine-containing tetrameric enzymes that utilize reduced glutathione (GSH), a low-molecular-weight tripeptide, as an electron donor and catalyze the biotransformation of various organic and inorganic peroxides, including H_2O_2 and lipid peroxides, to their corresponding alcohols. The detoxification of peroxides by GSH-Pxs occurs via bidirectional second-order kinetics and is a saturation-limited process.[26,109] GSH-Px1, GSH-Px2, GSH-Px3, and GSH-Px4 are the four glutathione peroxidases.[26,109] GSH-Px1 is a ubiquitous intracellular form and is the predominant isoform that catalyzes the removal of inorganic peroxides and lipid peroxides hydroperoxides.[26,109–112] GSH-Px-2 is localized to the gastrointestinal epithelia with substrate specificities similar to that of GSH-Px1. GSH-Px3 is a secreted form able to reduce lipid hydroperoxides.[111,112] This extracellular isoform accounts for 57% of the GSH-Px activity in the epithelial lining fluid, and GSH-Px-1 contributes 40%.[111,112] The fourth isoform, GSH-Px-4, is an intracellular peroxidase that preferentially catalyzes the peroxidation of phospholipid hydroperoxides.[110]

Thioredoxins

Thioredoxins (TRXs), which contain an active site cysteine, serve as redox sensors while also reducing H_2O_2.[113,114] H_2O_2 oxidizes the reduced dithiol group (-SH HS-) in TRX to a disulfide bridge (-S-S-). TRXs can reduce protein disulfides (-SH) and protein sulfenic acid intermediates (-SO_3H) by cysteine thiol-disulfide exchanges.[10,11] Two human TRXs are expressed widely in various lung cell types (see Table 25-4). In addition to its direct antioxidant function, TRX, in cooperation with peroxiredoxins, augments gene expression of other antioxidant enzymes, including SOD.[115–119] TRXs also participate in refolding of oxidized proteins and activate transcription factors by reducing cysteines present in the DNA binding site.[120] TRX can be activated by hypoxia, lipopolysaccharide, H_2O_2, microbial infections, and photochemicals. Thus, TRXs are powerful redox modulators, protect cells against oxidative stress, and participate in cell proliferation and survival.[115–119]

Glutaredoxins

Glutaredoxins (GRX) are thiol-disulfide oxidoreductases with antioxidant capacity in human lung[18,121–124] (see Table 25-4). GRX regulates cellular redox state and redox-dependent signaling pathways via modulation of protein glutathionylation; it regulates the intracellular and extracellular homeostasis of glutathionylated proteins and GSH.[18,121–125] These enzymes use glutathione as a cofactor and catalyze the reversible exchange of glutathione with protein thiol groups (see chemical reactions, Table 25-2). GRX enzymes are dependent on GSH/GSSG concentrations.[126]

Glutathione-S-Transferases

Glutathione-S-transferases (GSTs) are detoxification enzymes that require intracellular GSH for their catalytic activity. These antioxidant enzymes inactivate secondary metabolites, such as unsaturated aldehydes, epoxides, and hydroperoxides.[127] Three major families of GSTs have been described: the cytosolic GST, mitochondrial GST, and membrane-associated microsomal GST[60] (see Table 25-4). GSTs regulate eicosanoid and glutathione metabolism.[60,128] Under conditions of oxidative stress, cytosolic GST interacts with peroxiredoxins.[127] GST family enzymes are expressed in normal lung, mainly in the airways. They protect cells against a number of oxidizing species. GSTs have high genetic variability and are implicated in the development of smoking-related nonmalignant and malignant diseases.[60,129–132]

Peroxiredoxins

Peroxiredoxins (PRXs) are broad-spectrum peroxidases that detoxify or reduce H_2O_2, peroxynitrite, and organic hydroperoxides (ROOH).[133,134] These are nonseleno-peroxidases whose antioxidant properties are dependent on redox-active cysteines.[134] Six different PRXs have been found in human lung[135,136] (see Table 25-4). These PRXs differ widely in their specificities for H_2O_2 and lipid and phospholipid hydroperoxides.[135–139] PRX V and VI function as peroxynitrite reductases and are protective in ROS/RNS-mediated lung injury.[135–137,140,141] PRXs also regulate peroxide-mediated signaling cascades related to cell proliferation, differentiation, and apoptosis by modulating cytokine-mediated induction of H_2O_2.[18,134,138,139]

Heme Oxygenases

Heme oxygenase (HO) catalyzes the breakdown of pro-oxidant heme to generate equimolar amounts of carbon monoxide, ferrous iron, and biliverdin (Fig. 25-1). Biliverdin is then converted by biliverdin reductase to bilirubin, the antioxidant end-product of the HO reaction.[142–145] CO transported to the lung has vasodilatory and antiapoptotic properties.[146–151] Iron is used for heme synthesis in the cells required for heme-containing proteins or transported to the bone marrow and other tissues.[18,142,145,152,153] There are three isoforms of HO: the inducible HO-1 and the constitutive forms, HO-2 and HO-3. During oxidative stress, transcriptional activation results in rapid induction of HO-1.[142,145,146] This adaptive response of HO-1 confers protection during inflammation and oxidative stress. HO-1 is expressed widely in the lung (see Table 25-4). Consistent with the antioxidant properties of HO-1, mice deficient in HO-1 are more susceptible to oxidative stress.[154,155] Overexpression or induction of HO-1 suppresses inflammation in several models of chronic lung disease.[18,142,145,152,153]

■ Cellular Sources and Regulation of ROS/RNS

Cellular sources of ROS/RNS include immune cells, epithelial cells, endothelial cells, and fibroblasts.

Immune Cells

Inflammation is an adaptive response to infectious and noninfectious tissue injury. Recruited inflammatory cells emigrate from the pulmonary microcirculation into the airspaces where they become activated to generate ROS/RNS.

$NO^\bullet$ participates in pathogen killing by macrophages.[156] $NO^\bullet$ also delays fusion of phagosomes with lysosomes to form a functional phagolysosome, which enhances antigen processing/presentation of macrophages. Macrophages scavenge endogenous dying cells. Phagocytosis of dying cells requires the secretion of alarmins by dying cells to attract and pre-activate phagocytes; these signals by dying cells ensure specific recognition and phagocytosis/efferocytosis, all of which involve redox regulation.[157,158]

Beyond the chemical interactions of $NO^\bullet$ and ROS that cooperatively eradicate pathogens, these redox-active biomolecules regulate cellular metabolism, inflammation, and tissue repair functions. Cellular supply of substrates/cofactors for iNOS activity, including arginine, is required for $NO^\bullet$ production. However, in the absence of arginine or BH4, uncoupled NOS becomes a $O_2^{\bullet-}/H_2O_2$ generator. The flavin-binding sites of the reductase domain of iNOS, eNOS, and nNOS are a source of $O_2^{\bullet-}$ generation in the absence of arginine.[156,159–162] Therefore, metabolic pathways that control arginine and BH4 play a role in determining $NO^\bullet$ – $O_2^{\bullet-}$ balance. Cellular arginine levels are dependent on uptake and transport mechanisms and the activation of NOS-arginase enzymatic systems that use arginine. Arginase activation produces ornithine, a starting metabolite for the production of polyamines that are critical molecules supporting DNA stabilization, ion channel transport, and cell proliferation.[156,159–162] Arginase is regulated by NOS and NOX activities; N-hydroxyarginine, a product of NOS, inhibits arginase, while $O_2^{\bullet-}$ increases arginase activity.[156,159–162] High arginase activity is associated with elevated ROS and low $NO^\bullet$ fluxes. $NO^\bullet$ antagonizes NOX2 assembly through the activation of PPARγ, which, in turn, inhibits expression of the p47 subunit required for NOX2 activation.[156,159–162] Thus, $O_2^{\bullet-}$ production is suppressed when NOS activity and $NO^\bullet$ levels are high. $NO^\bullet$ also inhibits COX2 activity, reducing COX2-dependent ROS production.[163] Thus, as $NO^\bullet$ levels decline, ROS generation may increase via multiple mechanisms.

The balance between $NO^\bullet$ and ROS may play a key role in the orchestration and resolution of inflammation. RNS and ROS actively control innate and adaptive immune signaling. This aspect of redox function is evident in cells of myeloid lineage, such as monocytes, macrophages, and neutrophils. RNS and ROS produced by these cells participate in induction, maintenance, and/or termination of proinflammatory and anti-inflammatory signaling. Similar to the effect of $NO^\bullet$ on pathogen eradication, the temporal and spatial concentration profiles of $NO^\bullet$ are key determinants of immune-mediated processes.[156,159–162] A relationship between increasing steady-state levels of $NO^\bullet$ has been linked to regulation of expression of tumor suppressor gene p53 and apoptosis in murine and human macrophage cell lines.[164,165] Concentration- and time-dependent changes in the functional profiles of $NO^\bullet$ are evident from NO-mediated regulation of cell survival protein signaling cascade.[166–170]

Macrophages rely primarily on the NOX2 complex to produce ROS,[5,17,158,169] although the oxidative burst of macrophages is less intense than that of neutrophils. Induction of the proinflammatory phase of an innate immune response is an early response in the immune activation process. This is defined as "classic activation" in macrophages (also called M1 macrophages) and is associated with the production and release of proinflammatory cytokines, proteases including MMP-9, and transcription factors such as NF-κB, as well as RNS and ROS, including $NO^\bullet$ and $O_2^{\bullet-}$. In addition to a role in pathogen eradication, the localized levels of ROS/RNS may dictate integrated signaling and the type of immune activation and determination of cellular phenotypes; ROS/RNS may also regulate cross-talk between proinflammatory and resolution pathways. Classic (proinflammatory) activation of macrophages is followed by an anti-inflammatory healing/tissue repair phase, which is the ideal outcome of a successful innate immune response. These phases of the innate immune response are initiated by the pathogens or tissue injury, but are rapidly re-enforced by the actions of anti-inflammatory cytokines released from macrophages that function in an autocrine manner.[158,159,171–173] These cytokines initiate downregulation of the proinflammatory phase and induction of the repair or tissue remodeling phase.

$NO^\bullet$ also affects function of T lymphocytes.[156,174–177] Low $NO^\bullet$ concentrations promote differentiation of IFN-γ-producing Th1 (T helper 1) in mice and humans, mediated by cGMP activation.[178] During the immune repair/restoration phase, the collective activity of IL-4, IL-13, IL-10, and TGF-β suppress iNOS expression, thereby decreasing $NO^\bullet$ and shifting in favor of ROS.[156,174–178] A $NO^\bullet$-independent role for arginase has been identified in the differentiation of alternatively activated macrophages. Although arginase expression in macrophages is prominently associated with Th2 responses, part of its function is to sequester arginine away from effector T cells resulting in a reduced Th2 response; reconstitution with exogenous arginine blocks this reduced Th2 response. In general, low $NO^\bullet$ favors Th2 responses, and high $NO^\bullet$ augments Th1 responses, suggesting that a $NO^\bullet$/ROS balance may be a critical determinant of immune polarity.[156,179,180] Naïve lymphocytes exposed to high-μM concentrations of $NO^\bullet$, however, regulate the expansion and proliferation of regulatory T cells within lymphoid tissue.[156]

This concentration-dependent regulation by $NO^\bullet$ is seen in immunosuppression by heterogeneous immature myeloid cells called myeloid-derived suppressor cells (MDSCs).[181,182] Free radical–producing subsets of these MDSCs are critical regulators of allergic airway inflammation.[183,184] $NO^\bullet$-producing cells suppress T cell proliferation and airway hyper-responsiveness (AHR), while $O_2^{\bullet-}$ enhances T cell proliferation and exacerbates AHR.[183,184] Immunosuppression by MDSCs also occurs in the tumor microenvironment, in which $NO^\bullet$-mediated increase in cGMP activation facilitates their binding to cytotoxic lymphocytes to reduce their proliferation.[185,186] Peroxynitrite and H_2O_2 are produced by the combined and cooperative activities of NADPH oxidase, arginase, and iNOS in different MDSC subsets. These drive several molecular blocks in T cells, including the loss of TCRζ-chain expression, interference with IL-2 receptor–mediated signaling and nitration, and subsequent desensitization of the TCR.[185,186] Signal transducer and activator of transcription 3 (STAT3) is a critical regulator of MDSC. STAT3-mediated upregulation of the NADPH oxidase and ROS levels enhances the suppressive potential of MDSCs.[156,185,186]

Inflammasome activation is an innate immune response to pathogens, but it also accompanies the development of autoimmune and chronic inflammatory diseases. Inflammasomes are multicomponent platforms that sense a variety of danger signals, including bacteria, viruses, and pathogenic crystals; they aggregate through a family of Nod-like receptors and consist of caspase 1 to process proinflammatory cytokines for activation.[187–189] Inflammasome activation starts with a priming signal followed by an activation signal. Studies with ROS scavengers suggest a role of ROS in inflammasome activation.[187–191]

Epithelial Cells

The epithelium of the airways and the alveoli is exposed to high levels of oxygen and to other environmental oxidizing species. Although inflammatory cells are major producers of RNS/ROS, resident lung cells such as epithelial cells possess enzymatic systems for regulated production of RNS and ROS. DUOX enzymes are the primary contributors of H_2O_2 in the airway epithelium.[25,192] DUOXs are expressed in ciliated surface cells, but not in nonciliated cells or basal cells of the upper airway. The levels of expression of DUOX1 and DUOX2 are selectively regulated by cytokines, with Th1 cytokines regulating DUOX2 and Th2 cytokines regulating DUOX1.[19,21,193,194] The highly inducible DUOX2 mediates host responses to infection and inflammation, while DUOX1 is constitutively expressed in non-inflamed airways; DUOX2 plays a role in innate immunity, cell signaling, and mucus production.[19,21,193,194] The airway epithelium participates in innate immune response through the secretion of immune effectors such as mucin, antimicrobial peptides, and ROS to entrap or kill invading microbes. Epithelial cells use microbial pattern recognition receptors for innate immune system recognition to discriminate self from non-self.[19,21,193,194] The release of cytokines/chemokines by the epithelium induces neutrophil recruitment and the activation of transcription factors augmenting the inflammatory response. Lactoperoxidase (LPO), a heme-containing peroxidase, in concert with DUOX-generated H_2O_2 generates hypohalous acids that kill pathogens.[25,195] A functional difference between the airway DUOX/LPO system and the phagocytic NOX2/MPO system is that the phagocytic system is active only during the respiratory burst, whereas DUOX generates H_2O_2 continuously.[19,21,193,194]

Endothelial Cells

Endothelial cells (ECs) also participate in innate immunity and crosstalk with immune cells. The importance of ECs in inflammation-induced vascular dysfunction is dependent on their ability to produce and respond to ROS and RNS. Inflammation may alter the balance between $NO^\bullet$ and $O_2^{\bullet-}$ within and surrounding ECs, which is necessary for normal vascular function. ROS produced by the endothelium play an important role in vascular pathology.[196,197] ROS can quench $NO^\bullet$ and mediate proinflammatory signaling. Targeting ROS-quenching enzymes catalase and SOD in ECs alleviates toxic effects of excessive ROS and suppresses proinflammatory mechanisms, including endothelial cytokine activation and barrier disruption.[198–200] Pulmonary EC-derived ROS play a pivotal role in EC activation and function. Alterations in EC phenotype contribute to vascular tone, permeability, and inflammatory responses and, thus, have been implicated in lung diseases, including pulmonary hypertension, ischemic-reperfusion injury, and adult respiratory distress syndrome.[201–203] Contrasting effects of NOS isoforms occur during ischemia reperfusion (IR) injury, where eNOS appears to be protective and iNOS detrimental. Under homeostatic conditions, the low NO flux generated by eNOS prevents leukocyte recruitment and associated tissue damage through scavenging of ROS. However, when iNOS expression increases, $NO^\bullet$ levels rise and induce tissue injury.[201–203] Thus, the beneficial effects of specific NOS isoforms depend on the type of primary damaging event.

Fibroblasts

Fibroblasts and fibroblast-like mesenchymal cells participate in innate immunity and in tissue repair. Such cells are typically resident within the adult human lung;[204] however, studies have reported fibroblast-like cells derived from bone marrow cells[205] or epithelial cells, the latter in a process known as epithelial-to-mesenchymal transition (EMT).[206] EMT is a process that allows epithelial cells to lose their polarity and specialized junctional structures, to undergo cytoskeletal reorganization, and to acquire morphologic and functional features of mesenchymal cells. Myofibroblasts are the primary "effector" cells in tissue remodeling and pulmonary fibrosis.[207–209] Activation of the NADPH oxidase isoform, NOX4, mediates generation of H_2O_2, myofibroblast differentiation, contractility, and extracellular matrix production in response to TGF-β1.[210] Additionally, NOX4 may play a profibrotic role by inducing apoptosis of lung epithelial cells, while myofibroblasts themselves acquire an apoptosis-resistant phenotype. Epithelial cell death may also be mediated indirectly by the paracrine secretion of H_2O_2 by activated myofibroblasts, supporting the concept that NOX4 may be responsible for both myofibroblast activation and epithelial cell disrepair.[211]

OXIDATIVE STRESS IN VARIOUS LUNG DISORDERS

Below we consider oxidative stress in a variety of common clinical disorders, including asthma, emphysema, pulmonary fibrosis, pulmonary hypertension, and acute respiratory distress syndrome (ARDS) (Fig. 25-2).

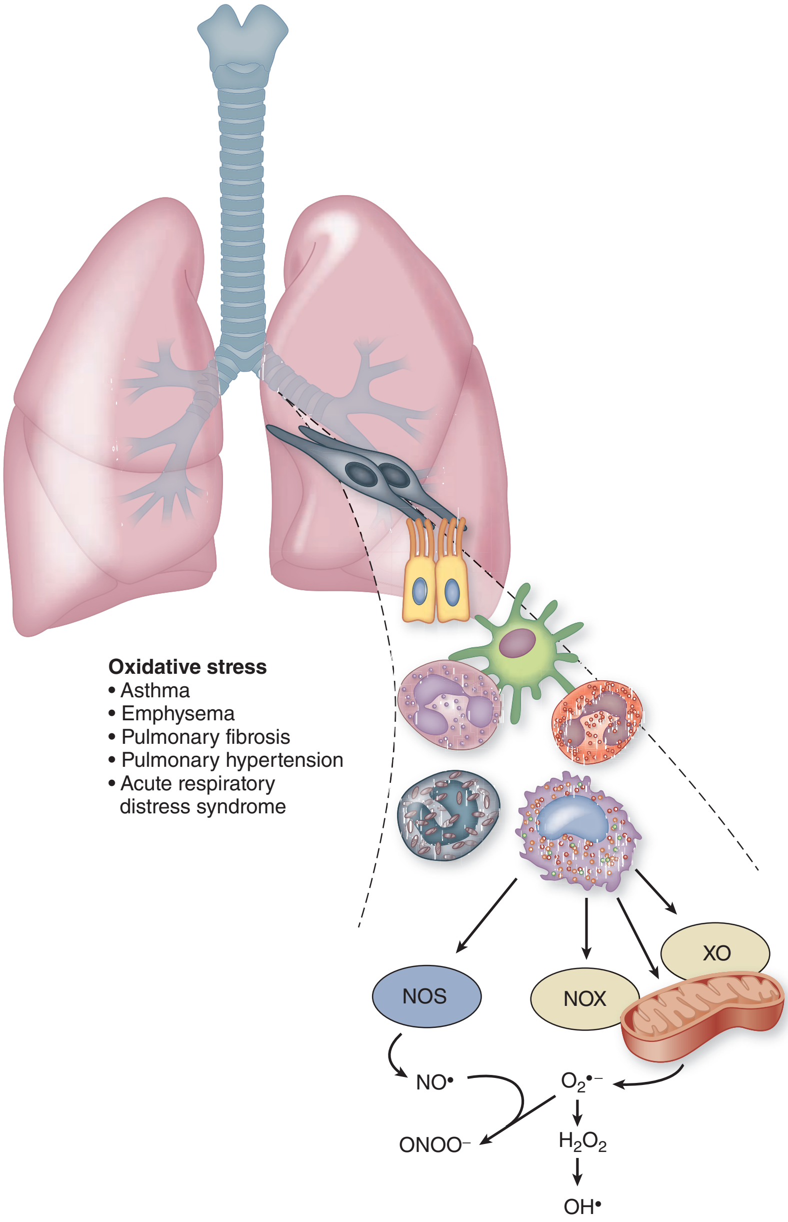

Figure 25-2 Oxidants initiate a number of pathologic processes with a multitude of complex mechanisms that contribute to pathogenesis of both acute and chronic inflammatory diseases of the lung. Resident lung cells and recruited inflammatory cells together orchestrate these multilevel processes by regulating enzymatic pathways to balance the generation and metabolism of oxidants.

Asthma

Asthma is a chronic inflammatory airway disease.[212,213] ROS and RNS have been implicated in the pathogenesis of asthma.[20,214–217] Dysregulation in pathways that leads to oxidative stress or its defense may contribute to the initiation and severity of asthma.[8,20,214–219] Recruitment of inflammatory cells and ROS production have been documented in the airways of asthmatic subjects.[20,113,215,220–223] $O_2^{\bullet -}$ generation was observed highest in airspace cells at the sites of antigen challenge.[214] Leukocyte activation with induction of NADPH oxidase and production of $O_2^{\bullet -}$ and H_2O_2 correlate negatively with FEV_1 in asthmatic subjects.[223] Besides airway macrophages and eosinophils, blood eosinophils and monocytes also are major sources of ROS in asthmatic patients.[214,219,224]

Airway inflammation–associated oxidative stress in asthma may induce oxidative modifications of proteins or lipids.[89,90,225] Increased numbers of eosinophils and neutrophils, in association with higher expression of peroxidases and other markers of eosinophil activation, are found in BAL and bronchial tissues of asthmatics.[226,227] Oxidant products of neutrophil/eosinophil activation, 3-bromotyrosine, and MPO-mediated oxidants such as chlorotyrosine are increased in asthmatics compared with control subjects; these have been implicated in the pathophysiology of severe asthma.[228,229] Other reactive products including malondialdehyde, thiobarbituric acid reactive products, and 8-isoprostane, a biomarker of lipid peroxidation, also are elevated in exhaled breath condensates of adults and children with asthma.[230–235] The precise mechanisms by which ROS exacerbate asthma are not known, but they may involve effects on airway smooth muscle, mucin secretion, and T cell responses.[59,236] ROS can decrease β-adrenergic function in lungs and sensitize airway smooth muscle to acetylcholine-induced contraction.[103,237] H_2O_2 activates mitogen-activated kinases in tracheal myocytes and stimulates contraction of tracheal smooth muscle cells.[236] ROS also stimulates mucin secretion,[103,237] contributes to Th2 cell differentiation,[180] and promotes T cell proliferation via arginase and NADPH oxidase pathways.[183,184] Proinflammatory cytokines are elevated during airway inflammation, which activate oxidases leading to increases in ROS, the targets of which include receptor kinases, phosphatases, phospholipids, or nonreceptor tyrosine kinases.[16,238,239]

RNS metabolism, in particular that involving $NO^{\bullet}$, is dysregulated in asthma. Exhaled $NO^{\bullet}$ is increased in asthmatics and is associated with airway inflammation.[54,55,240] Despite the expression and distribution of all three NOS enzymes in the airway, it is primarily iNOS that contributes to exhaled $NO^{\bullet}$. Induction of iNOS is observed at both transcriptional and translational levels principally in steroid-naïve patients.[41–43] In mild asthmatics, $NO^{\bullet}$, nitrate, and S-nitrosothiols (SNO) are enhanced in the lower airways.[54] Following antigen challenge, levels of $NO^{\bullet}$ decrease, while nitrate increases without perturbing levels of nitrite and SNO.[54] Decreasing $NO^{\bullet}$ levels correlate with increased nitrotyrosine formation from reaction of $NO^{\bullet}$ with $O_2^{\bullet -}$.[54] Peroxynitrite, thus formed during inflammation, is toxic to microbes; however, it can also cause airway hyperresponsiveness. Nitrate can be generated from peroxidase-mediated RNS production.[54,241] S-nitrosothiols are primarily formed during the late asthmatic response.[54,241] Thus, persistent increases in ROS and $NO^{\bullet}$ lead to RNS formation and subsequent oxidation and nitration of proteins, which contributes to the dysregulation of airway inflammation in asthma.[15] $NO^{\bullet}$ synthesis can reduce airway resistance mediated by increased production of the bronchodilator S-nitrosoglutathione (GSNO).[242–246]

Two mechanisms to co-opt beneficial effects of $NO^{\bullet}$ signaling are (1) shifting $NO^{\bullet}$ to a more stable species, such as GSNO, or (2) reducing the local concentrations of ROS, potentially by augmenting the concentration of antioxidant enzymes in the extracellular space. Elevated $NO^{\bullet}$ has also been attributed to the greater catabolic breakdown of the storage pools of GSNO during changes in the redox state of the lungs.[242–244] GSNOR, a glutathione-dependent formaldehyde dehydrogenase, reduces GSNO to hydroxylamine, which is converted to NO by catalase.[246–248] GSNOR-deficient mice are protected from methacholine hyperreactivity following allergen sensitization and challenge, implicating GSNO in controlling airway hyperreactivity.[246–248]

High levels of ROS may overwhelm antioxidant defenses, causing significant loss of antioxidant activity in asthma.[8,67,70,214,218] Global loss of SOD activity, due to SOD deficiency, loss of circulating SOD activity, or inactivation of SOD via oxidative modification, reflects the increased oxidative stress in asthmatics patients.[8,67,70,214,218] Oxidative modification–mediated reduction of catalase activity also is observed in asthmatics.[8] Although airway glutathione is increased in asthmatic patients, the ratio of oxidized to reduced glutathione is elevated, reflecting an oxidizing microenvironment. Inhalation of exogenous ROS and RNS from exposures to environmental pollutants including ozone, diesel exhaust particles, and oxidant components of tobacco smoke all contribute to additive oxidative stress, airway hyperreactivity, and inflammation in asthma.

In addition to airway inflammation and bronchial hyperresponsiveness, pathologic airway remodeling is associated with asthma.[222,249–251] In fact, airway remodeling has been shown to be responsible for the rapid decline in lung function in treatment-resistant asthmatics compared with non-asthmatics.[252,253] The proliferation of resident airway smooth muscle (ASM) cells and persistent activation of fibroblasts[254] contribute to increase in ASM mass and subepithelial fibrosis, the key cellular and structural features of asthmatic airway remodeling.[255] The TGF-β-induced activation of the ROS-generating enzyme NOX4, which induces myofibroblast differentiation,[210] is implicated in ASM proliferation and hypercontractility in asthma,[256,257] as well as in epithelial ciliary dysfunction in neutrophilic asthma. Ciliary dysfunction is increased in neutrophilic asthma associated with increased NOX4 expression and is attenuated by NOX inhibition.[258] NOX4 expression has been shown to be higher in both ASMs and fibroblasts in asthmatics compared with non-asthmatics.[256,257,259,260] NOX4 small interfering RNA knockdown and the pharmacologic inhibitors diphenyleneiodonium and apocynin abrogated the agonist-induced increased contraction in primary ASM from bronchial biopsies of asthmatics.[256] These data suggest a role for NOX4 overexpression in the promotion of oxidative stress and consequent airway smooth muscle hypercontractility in asthma, and they implicate NOX4 as a potential novel target for asthma therapy. Recent studies also show that a mechanosensitive ion channel mediates lung fibroblast differentiation and house dust mite–induced airway remodeling via a novel interaction of the channel TRPV4, which integrates TGFβ1 and ROS signaling through NOX4.[259] This TRPV4–NOX4 interaction may be amenable to therapeutic targeting of lung remodeling associated with asthma.

Emphysema

Emphysema is a dominant phenotype of chronic obstructive pulmonary disease,[261–264] defined pathologically by airspace enlargement and destruction of alveolar septae.[261–264] Important contributing factors to the pathobiology of emphysema include inflammation, alveolar epithelial cell injury/apoptosis, and protease-antiprotease and oxidant-antioxidant imbalances.[263–268] Inflammatory cells are recruited to the alveolar environment where they release elastases, cytokines, and oxidants that may then perpetuate the cycle of epithelial injury and inflammation.[263–268] In addition to inflammation, oxidative stress caused by cigarette smoke inhalation contributes to the pathogenesis of emphysema. Cigarette smoke contains $O_2^{\bullet -}$, ${}^{\bullet}OH$, and H_2O_2.[269] ROS are also generated by the chronic inflammation characteristic of emphysema, which persists even after smoking cessation. Activated macrophages and neutrophils, present in high numbers in the emphysematous lung, are major producers of ROS.[270–275] The cytoplasmic redox changes and cellular damage caused by cigarette smoke may in part be mediated by ROS generated by NOX enzymes, including NOX4 in conjunction with the decrease in cellular antioxidant enzymatic defenses.[260] The expression of the ROS-generating enzymes, specifically NOX4, is increased also in primary ASM of COPD and healthy controls with >20 pack-year history compared to control subjects without a significant smoking history.[276] The generation of hydrogen peroxide–induced reactive oxygen species by these ASMs in COPD was markedly attenuated by NOX4 inhibition.[276]

Oxidative stress originating from constituents of cigarette smoke or products of inflammatory cells can overcome the antioxidative capacity of lung tissues and diminish antiprotease defenses.[277,278] A major consequence of oxidative stress is the activation of the transcription factor nuclear factor-κB (NF-κB), which activates transcription of proinflammatory cytokines.[264,277–279] Cigarette smoke also inhibits histone deacetylase, further promoting the release of proinflammatory cytokines.[280] Therefore, oxidant injury and lung inflammation act in concert to increase alveolar destruction or compromise maintenance and repair of alveolar structures. Antioxidant defenses are determinants of susceptibility to emphysema. A protective role for Nrf2, a transcription factor that regulates multiple critical antioxidant enzymes, has been identified in pulmonary emphysema.[281–284] SOD mimetics abrogate alveolar cell apoptosis and emphysema in mouse models,[285] further supporting the link between oxidative stress and apoptosis.[286,287]

■ Pulmonary Fibrosis

Pulmonary fibrosis may result from a number of infectious and noninfectious injuries; by far, the most lethal form is idiopathic pulmonary fibrosis (IPF). IPF is characterized by exuberant extracellular matrix deposition, tissue contraction, and apoptosis-resistance of (myo)fibroblasts, alongside apoptosis-prone and aberrantly differentiated alveolar type 2 cells.[18,288] This loss of epithelial-mesenchymal homeostasis and communication is central to the pathogenesis of IPF.[207,209] Myofibroblasts are key effector cells in tissue remodeling and fibrosis, typically contained in fibroblastic foci, which are a pathologic hallmark of IPF. Chronic inflammation, aberrant wound healing, and degenerative aging processes have all been proposed as contributing to the pathogenesis of IPF.[289] Oxidative stress is common to these processes and is implicated in IPF pathogenesis.[290–292] Lung tissues and bronchoalveolar lavage fluid from IPF patients demonstrate a signature profile of oxidatively damaged proteins.[293–296]

NOX enzymes are a major source of ROS production in pulmonary fibrosis.[208,297–300] Several NOX isoforms, including NOX1,[301–303] NOX2,[304–307] and NOX4,[210,299,308] have been implicated in tissue fibrosis. In addition to NOX enzymes, another potential source of ROS implicated in fibrosis is the mitochondria.[309,310] Epithelial cell death is a prominent feature in the IPF lung.[299,311,312] During acute lung injury in mice, NOX1-mediated ROS generation by endothelial and epithelial cells induces cell death.[313,314] NOX4 is expressed in hyperplastic alveolar type II cells in the lungs of IPF patients[308] and may mediate fibrogenic effects by promoting alveolar epithelial cell death.[215] NOX4-deficient mice are protected from bleomycin induced pulmonary fibrosis with reduced levels of epithelial cell apoptosis in vivo.[215] EMT has been proposed to contribute to the accumulation of myofibroblasts in lung fibrosis.[315,316] ROS has also been shown to promote EMT.[317,318] A role for NOX4 in mediating myofibroblast differentiation and lung fibrosis has been identified.[210] NOX4 mRNA expression is induced by a profibrotic cytokine, transforming growth factor β1 (TGF-β1), while other NOX/DUOX isoforms were unaffected. NOX4-dependent generation of ROS, specifically H_2O_2, is required for TGF-β1-induced myofibroblast differentiation, ECM generation, and contractility of lung myofibroblasts.[210] Genetic or pharmacologic targeting of NOX4 attenuates lung fibrogenesis in murine models of lung injury. Myofibroblasts from IPF patients also produce high levels of H_2O_2 in response to TGF-β1.[211] Additionally, NOX4 may also contribute to pulmonary vascular remodeling associated with IPF.[319]

ROS generation from alveolar inflammatory cells, primarily neutrophils and macrophages, may promote alveolar epithelial cell injury in IPF.[290,320] Mice deficient in NOX2 are protected from bleomycin-induced lung injury and fibrosis, suggesting a role for inflammatory injury in this model.[321] The protection in $p47^{phox-/-}$ mice was accompanied by enhanced neutrophilic inflammation and MMP-9 activity.[321] Interestingly, airway neutrophils isolated from IPF patients exhibit elevated expression of $p47^{phox}$ and $p67^{phox}$,[322] supporting roles for the NOX2 isoform and neutrophilic inflammation in IPF. MMPs and tissue inhibitors of matrix metalloproteinases play a role in homeostasis and turnover of the ECM. In IPF, oxidation of the cysteine switch of MMPs by ROS activates the latent forms of MMPs.[211,290,323] ROS also regulates MMPs at the transcriptional level.[211,290,323] Thus, oxidative stress, from exogenous sources and multiple endogenous enzymatic sources, contributes to altered cellular homeostasis, including resident cells, recruited inflammatory cells, and their activated products.

Several clinical trials testing therapies for IPF have not demonstrated efficacy. The use of the antioxidant N-acetylcysteine (NAC) was initially suggested to benefit patients with IPF by reducing oxidative stress in the lung.[324] But NAC as a monotherapy or as triple therapy—a three-drug regimen consisting of azathioprine, prednisone, and acetylcysteine—has not demonstrated efficacy in slowing the progression of IPF.[325,326] The antifibrotic drugs pirfenidone, a pyridine derivative, and nintedanib, a potent intracellular inhibitor of tyrosine kinases, have been associated with significant slowing of respiratory deterioration in IPF and perhaps prolonged survival.[327–329] However, the responses to these antifibrotic treatments are heterogeneous and are limited by side effects and tolerability. Novel therapeutic approaches, including combination therapies and the development of novel compounds, are being actively pursued.

Numerous potential molecular targets of novel therapeutic agents are currently being explored in early clinical trials. Recently, a small molecule NOX4/NOX1 dual inhibitor has been developed, showing good oral bioavailability and tolerability when administered orally in an animal model of pulmonary fibrosis.[298] GKT137831 (setanaxib) is an orally available, small organic molecule of the pyrazolopyridine dione chemical class; it is a selective inhibitor of NOX4/1 and the first drug in this class of NOX inhibitors to enter clinical trials. A phase 2, placebo-controlled, multicenter, randomized trial to test GKT137831 in ambulatory patients with IPF is currently ongoing (NCT03865927). In the past, several attempts to therapeutically target activated myofibroblast-like cells referred to as cancer associated fibroblasts (CAFs) in the tumor microenvironment have been unsuccessful and, possibly, compounded by poor understanding of the heterogeneity of cells and lack of specific CAF targets.

Recent studies have shown that the NOX4/1 inhibitor GKT13783 not only prevents differentiation of CAFs but normalizes them to a quiescent state of activation.[330] These studies reveal the CAF dependency on continuous NOX4-dependent ROS generation and provide proof of concept for specific targeting of NOX enzymes to overcome the exclusion of T cells and reshaping the CAF-regulated immune microenvironment. Thus, combination approaches utilizing direct targeting of NOX4 activity in CAFs and immunotherapy are predicted to provide improvement of clinical outcomes for CAF-rich tumors that respond poorly to checkpoint immunotherapy. Such treatment strategies with NOX4 inhibitors may have beneficial outcomes for IPF, as recent epidemiologic evidence also supports an association between IPF and lung cancer; such association of two lethal diseases carries a very poor outcome.[331–334] In IPF patients, lung tumors develop adjacent to fibrotic areas and are different histologically from non-IPF-associated lung tumors. There is a higher prevalence of lung cancer in the combined IPF and emphysema syndrome compared with fibrosis only.[331–334]

■ Pulmonary Hypertension

Pulmonary arterial hypertension (PAH) is a disorder of the pulmonary circulation characterized by endothelial dysfunction and intimal and smooth muscle proliferation.[335,336] Increased expression of ROS-generating enzymes, uncoupling of NOS enzymes, and mitochondrial dysfunction all contribute to the oxidative stress in PAH.[335,336] Upstream dysregulation of ROS/$NO^{\bullet}$ redox homeostasis impairs vascular tone, which then triggers the activation of antiapoptotic and mitogenic pathways, leading to cell proliferation and obliteration of the vasculature.[335,336]

ROS derived from the NOX2 and NOX4 isoforms contribute to the long-term responses of the pulmonary vasculature to hypoxia.[337–340] Increased NOX4 expression in pulmonary artery smooth muscle cells (PASMCs) has been linked to hypoxia-dependent PAH in mice.[340] Levels of the NOX1 and -2 regulatory proteins, $p47^{phox}$ and Rac1, are increased in both the endothelial and SMC layers of pulmonary arteries[341–343] and accompanied by an increase in NOX-derived $O_2^{\bullet-}$.[341–343] NOX-derived ROS is associated with medial thickening, disordered proliferation and migration, impaired angiogenesis, and disturbed fibrinolysis.[341–345] Another source of vascular ROS is xanthine oxidoreductases (XOR), including xanthine dehydrogenase (XD) and xanthine oxidase (XO). In PAH, XO activity dominates over XD activity and is a significant source of ROS production. XO is increased in idiopathic PAH patients compared with healthy controls.[345]

In a rat model of chronic hypoxia–induced PAH, lung XO activity was enhanced and inhibition of XO activity with allopurinol reduced right ventricular hypertrophy and pulmonary vascular thickening.[341–344,346] Clinical studies have also demonstrated alterations of TGF-β1 expression in adult PAH patients.[347] In hypoxia-dependent PAH in mice, hypoxia increases the expression of TGF-β1 and NOX4 expression.[339,340] TGF-β-induced NOX4 expression and NOX4-mediated ROS production have been implicated in PASMC proliferation.[348,349] TGF-β1 also induces proangiogenic effects by upregulating VEGF.[350] In PASMCs, cyclic stretch induces VEGF expression, at both the mRNA and protein levels;[351] this is preceded by both increased expression and secretion of TGF-β1 and an increase in ROS generation by the activation of NOX enzymes.[348,349] In models of spontaneously developing PAH, mitochondrial dysfunction and hyperpolarization are associated with reduction in ROS production.[352,353] Decreases in ROS inhibit an $O_2^{\bullet-}$ sensitive K^+ channel leading to pulmonary vascular constriction.[352–354]

Nitrosative stress with increased nitrated eNOS is an early contributor to the development of PAH.[341,355–358] The vasodilatory effects of cGMP are mediated through protein kinase G (PKG).[341,355–358] However, nitration of PKG attenuates the kinetic activity of PKG, impairs vasodilation, and increases smooth muscle proliferation.[359] This nitration-dependent reduction in PKG activity is observed in lungs of patients with PAH.[359] Nitration of carnitine acetyl transferase, an enzyme that maintains normal mitochondrial function, is another indicator of early nitrosative stress in PAH.[360]

Alterations in arginine metabolism also have been noted in models of PAH,[342] where the activity of arginase, which catalyzes the hydrolysis of L-arginine to L-ornithine and urea, is increased[159,342,361,362] and the activity of the caveolar enzymes involved in the recycling of L-citrulline and other L-arginine byproducts back to L-arginine is attenuated.[159,342,361,362] Further, increased arginase activity is associated with formation of polyamines and L-proline, which promote smooth muscle cell growth and collagen synthesis. Additionally, uncoupling of NOS enzymes occurs when L-arginine becomes limited, resulting in the production of ROS.[343,363–365] Therefore, high arginase activity may promote aberrant pulmonary vascular remodeling and neointima formation in PAH.[159,361,362]

■ Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome (ARDS) is a severe form of acute lung injury and a syndrome of acute pulmonary inflammation.[366,367] ARDS is characterized by sudden onset, impaired gas exchange, and an increase in pulmonary capillary permeability.[366–368] Oxidative damage by ROS and RNS has been implicated in the pulmonary vascular endothelial damage that characterizes ARD. Several factors contribute to the intracellular and extracellular oxidant stress in ARDS patients.[366–368] The high inspiratory concentrations of oxygen required to achieve adequate arterial oxygenation, infection, or extrapulmonary inflammation lead to increased ROS production. This, combined with decreased antioxidant capacity of tissues resulting from consumption of the natural antioxidants, leads to cellular damage and loss of vasomotor control.[366–368] Measurements of antioxidant concentrations have revealed an oxidant-antioxidant imbalance in ARDS patients. The production of toxic levels of ROS and RNS not only leads to damage of key molecules in cells but can signal changes in cellular responses such as proliferation, apoptosis, and necrosis.[366–368] H_2O_2 has been detected in the exhaled breath, while myeloperoxidase and oxidized α1-antitrypsin have been detected in BAL of ARDS patients.[366–368]

Nitration and oxidation of alveolar space proteins including the surfactants have been identified ex vivo in patient samples with ARDS.[366–368] Although the nature of these oxidized proteins has not been well defined, recent studies indicate the potential aggregation and cross-linking of extracellular matrix proteins, specifically fibronectin, in the presence of an inflammatory microenvironment that includes inflammatory cell infiltration and heme peroxidases.[369] Overabundance of ROS also induces adhesion molecules and cytokines that contribute to endothelial injury.[370–372]

CONCLUSION

Oxidative stress is implicated in the pathogenesis of both acute and chronic inflammatory and fibrotic lung diseases, some of which are discussed here. The lungs are exposed to exogenous oxidants from the environment, in addition to endogenous generation of ROS/RNS from resident and recruited inflammatory cells. Several measures of oxidative stress have been used to estimate oxidative stress within the lungs;[373–379] however, current approaches do not adequately differentiate between different oxidative mechanisms. Further investigations are needed to discover oxidative stress biomarkers that correlate and differentiate between various types of oxidative injury. While progress has been made to delineate mechanisms through which oxidants initiate and propagate cell and tissue damage, specific signaling pathways and mechanisms of activation are not well understood. Elucidation of these mechanisms may provide strategies for intervention to prevent or protect from disease pathogenesis or progression. A better understanding of factors that influence individual susceptibility will also be useful in risk stratification of patients. Investigations on how early life exposures to oxidants impact airway morphology, immune function, and the airway epigenome may aid in determining susceptibility, disease expression, and progression.

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CHAPTER 26

Fibroblasts in Lung Homeostasis and Disease

Yong Zhou
Victor J. Thannickal

INTRODUCTION

Fibroblasts are the primary cellular source responsible for synthesis and remodeling of the extracellular matrix (ECM). These cells are in communication with the surrounding microenvironment and play a key role in lung homoeostasis. Following lung injury, fibroblasts are activated and undergo myofibroblast differentiation. Myofibroblasts are key effector cells for lung repair following injury. In addition to fibroblasts, perivascular pericytes and mesenchymal stem cells (MSCs) of bone marrow (BM) origins contribute to myofibroblast population. There is evidence that type II alveolar epithelial cells can differentiate into myofibroblasts in vitro through a process known as epithelial-mesenchymal transition (EMT); however, the role of EMT in fibrogenesis in vivo remains controversial. Myofibroblasts express α—smooth muscle actin (α-SMA), develop robust actin filaments (stress fibers), and acquire contractile activity. The function and behavior of myofibroblasts are regulated by both biochemical and physical cues in the surrounding microenvironment. The fate of myofibroblasts is a key determinant of whether an injury-repair response will resolve or progress into fibrosis. Destruction and aberrant remodeling of the ECM is a common feature of many lung diseases, including pulmonary fibrosis, asthma, chronic obstructive pulmonary disease (COPD), and lung cancer. Targeting myofibroblasts and tissue remodeling may provide a novel and effective strategy for treating a number of chronic lung diseases.

FIBROBLAST BASICS

The following discussion focuses on a description of fibroblasts and their functions.

What Are Fibroblasts?

Fibroblasts were described as early as in the late 19th century, based on their location and their microscopic appearance.[1] These cells are elongated cells that display a spindle-shaped morphology with extended cell processes.[2] Fibroblasts are ubiquitous in tissues and organs throughout the body and communicate with other cells such as epithelial cells (Fig. 26-1). Despite its discovery over a century, a reliable and specific molecular marker that identifies the fibroblast is currently lacking. Many indicators of fibroblast phenotype have been suggested in the previous studies (e.g., fibroblast-specific protein 1, vimentin, prolyl-4-hydroxylase, procollagen-Iα2, etc.).[3] However, none is specific to fibroblasts or present in all fibroblasts. Currently, fibroblasts are identified by their ability to adhere to plastic and their lack of markers that indicate other cell lineages. Identification of better cellular markers with absolute specificity for fibroblasts will aid in the study of sources, differentiation, and phenotypic plasticity of fibroblasts.

Tissue-Specific Fibroblasts and Fibroblast Heterogeneity

Fibroblasts isolated from different tissues display a considerable degree of heterogeneity in phenotype and activity.[4] Such diversity is evident by divergent and specific gene expression patterns among fibroblasts isolated from distinct anatomical locations.[5] For example, fetal skin fibroblasts express high levels of collagen types I and V, whereas fetal lung fibroblasts lack collagen I and V expression.[5] Instead, fetal lung fibroblasts exclusively express lung-specific forkhead family transcription factors FOXF1 and FOXP1.[5] Tissue-specific fibroblasts may provide location-specific signaling for a given anatomic origin as well as important positional cues for wound healing and tissue regeneration. Besides the differences in fibroblasts from different anatomic sites, fibroblasts derived from a single tissue are often composed of subsets of different fibroblasts.[6] Fibroblast subpopulations isolated from lung differ in expression of surface markers such as Thy-1, cytoskeletal composition, lipid content, and cytokine profile.[7,8] Fibroblasts isolated from lungs with active fibrotic disease such as in the fibroblastic foci of human idiopathic pulmonary fibrosis (IPF) are morphologically and functionally distinct from fibroblasts isolated from normal lungs,[9] suggesting that selective expansion of specific fibroblast subsets is associated with the pathogenesis of this disease.

With the advent of new technologies including transgenic lineage tracing and single-cell RNA sequencing (RNAseq), significant

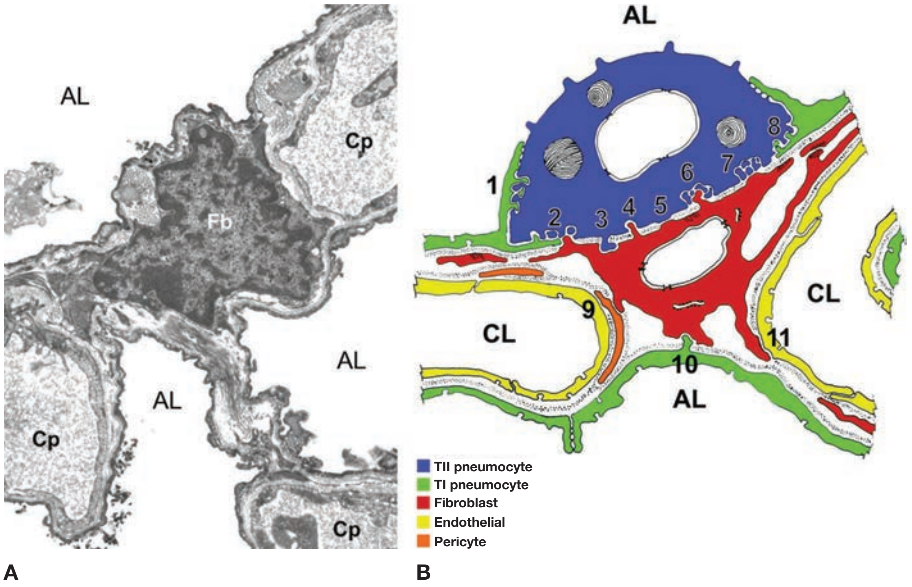

Figure 26-1 An interstitial fibroblast in the alveolar wall. **A.** Transmission electron microscopic image showing the structural organization of the alveolar wall in canine lung. AL: alveolar lumen, Cp: capillary, Fb: fibroblast. **B.** Summary of fibroblast (red) relationships with type I (green) and type II (purple) alveolar epithelial cells, capillary endothelial cells (yellow), and pericytes (orange) in human and rabbit alveolar walls. *(Reproduced with permission from Burns AR, Smith CW, Walker DC. Unique structural features that influence neutro phil emigration into the lung. Physiol Rev. 2003;83(2):309–336.)*

advances have been made to characterize fibroblast heterogeneity. For example, clonal cell labeling strategies with multicolor reporters identified a diversity of mesenchymal populations with different locations, patterns of migration, recruitment mechanisms, and lineage boundaries in the developing mouse lung.[10] Single-cell and population-based RNA sequencing revealed functionally distinct myofibrogenic mesenchymal cell type (Axin2$^+$) as well as mesenchymal alveolar niche cell type (Pdgfra$^+$Axin2$^-$) that is critical for alveolar epithelial cell growth and self-renewal.[11] Similarly, single-cell analyses found distinct mesenchymal niches that drive airway (Lgr6$^+$) and alveolar (Lgr5$^+$) differentiation.[12] More recent transcriptomic analyses conducted at single-cell resolution demonstrated a novel profibrotic mesenchymal population (Pdgfrb^{hi}) along with known mesenchymal cell subtypes in bleomycin injury–induced mouse lung fibrosis.[13] The existence of different fibroblast lineages may contribute to the functional heterogeneity of fibroblasts, resulting in fibroblasts that may respond differently to environmental stimuli or signals.

■ Fibroblast Functions

The important functions of fibroblasts include deposition of ECM, regulation of inflammation, and wound healing.[14] Fibroblasts produce ECM-degrading proteases such as matrix metalloproteinases (MMPs) and their inhibitors, tissue inhibitors of metalloproteinases (TIMPs), supporting their crucial roles in regulating ECM turnover and homeostasis.[15]

ECM Production

One of the major functions of fibroblasts is the production of ECM. The ECM in the lung provides an essential scaffold on which cells can proliferate and differentiate. It also provides the lung with tensile strength and elasticity that are essential for ventilation. Lung ECM is composed of fibrillar proteins, glycoproteins, proteoglycans, and polysaccharides, each of which has distinct biochemical and biomechanical properties; these include collagens, elastin, fibronectin, proteoglycans (PGs), hyaluronan (HA), laminin, vitronectin, and thrombospondin.[16] Type I and type III collagens are the most abundant collagens in the lung interstitium (ratio 3–6:1). Collagen IV is mainly localized to basement membranes. A fibroblast is estimated to synthesize approximately 3.5 million procollagen molecules/cell/day.[17,18] Depending on tissue type and age, 10% to 90% of synthesized procollagens are intracellularly degraded by lysosomal enzymes (e.g., cathepsins B, D, and L). It is postulated that regulation of procollagen degrading rate may provide an important mechanism for rapid secretion of collagen in response to injury without de novo synthesis of new proteins.

Secretion of Proteolytic Enzymes and Inhibitors

The ECM is a dynamic structure that undergoes constant remodeling. Remodeling of the ECM is regulated by complex mechanisms including stimulatory and inhibitory mediators derived from resident cells in the local environment.[18] Fibroblasts synthesize a variety of proteolytic enzymes and inhibitors that enable them to control the assembly and turnover of the ECM. MMPs are either secreted by fibroblasts as inactive zymogens or anchored to the cell surface. Activation of MMPs occurs by disruption of interactions between the prodomain and the catalytic domain through either the proteolytic cleavage or the conformational change of the proenzymes.[19] MMPs function as proteinases that degrade most ECM proteins. Proteolysis of the ECM macromolecules by MMPs results in the release of cryptic fragments and neo-epitopes that promote angiogenesis and cellular migration.[20,21] MMPs also have critical roles in the post-translational regulation of other proteins including latent growth factors stored within the ECM, membrane receptors, and other proteases.[22] Hence, MMPs impact cell behavior both through modulation of cell-matrix interactions and through regulation of other signaling molecules. MMPs themselves are regulated by their endogenous inhibitors TIMPs. TIMPs block MMP activity by noncovalently binding to the MMP active site. A tight balance between MMP proteolysis and TIMP expression is required for maintaining lung homeostasis.[23]

Innate Immune Function

Fibroblasts are capable of synthesizing many inflammatory cytokines that are initially thought to be exclusively produced by inflammatory cells.[24] Fibroblast-derived cytokines play an important role in the amplification and perpetuation of the immune response. Fibroblasts generate constitutive and cytokine-induced C-C and C-X-C chemokines that recruit inflammatory and immune cells to the injured cites.[25] Lung fibroblast–derived granulocyte macrophage-colony stimulating factor promotes the survival of eosinophils, which contributes to the fibrotic response in the lung.[26,27] Direct contacts between fibroblasts and T cells promote the production of adhesion molecules and cytokines by the T cells.[28] Interactions between fibroblasts and mast cells facilitate de novo production of eotaxin, a potent eosinophil chemattractant.[29] Interactions between fibroblasts and inflammatory cells are bidirectional. Th2 cells produce IL-4 that recognizes specific receptors on fibroblasts and modulates fibroblast proliferation and biosynthetic capacity.[30] Eosinophils release mitogens that augment fibroblast proliferation and collagen production.[31,32] Fibroblasts are the main producers of ECM proteins. Since ECM components affect multiple functions and properties of inflammatory and immune cells,[33,34] it suggests a further regulatory role of fibroblasts in innate immune response by the effects on the ECM.

Regulation of Tissue Interstitial Fluid Pressure and Microhemodynamics

Fibroblasts regulate tissue interstitial fluid volume, pressure, and microcirculation hemodynamics by generation of actomyosin-derived forces and transmission of the forces to the ECM via transmembrane integrins.[35] Such mechanical interactions between fibroblasts and matrix are subjected to modulation by soluble factors, such as PDGF that results in increased interstitial fluid pressure, and TNF-α that leads to decreased interstitial fluid pressure.[36,37] Fibroblasts express ecto-5′-nucleotidase (CD73) and soluble guanylyl cyclase (cGC) that affect hemodynamics,[38] suggesting a role of fibroblasts in the regulation of the microcirculation.

Fibroblasts Support Epithelial Stem Cell Niches

Normal structure and function of the lung is maintained in homeostasis and reconstituted following diverse injuries by regionally defined stem/progenitor cells.[39–51] Stem cells reside in unique tissue microenvironments, known as the stem cell "niche," which constitutes stem cell progeny, other niche-support cells including mesenchymal/stromal cells (fibroblasts, smooth muscle cells, endothelial cells, immune cells), and the surrounding extracellular matrix (ECM).[11,12,52–57] The stem cell niche provides instructive cues for stem cell self-renewal and differentiation.[58–61] Lipofibroblasts (LIFs) are adipocyte-like fibroblasts located close to AT2 stem cells,[62,63] representing a special niche for AT2 stem cells. LIFs contribute to the maturation of alveolar epithelial cells and the formation of surfactant, a phospholipoprotein complex produced by AT2 cells involved in the reduction of surface tension.[64] The growth of AT2 stem cells in Matrigel to form alveolosphere-like structures, known as organoids, is drastically enhanced when co-cultured with LIFs.[41,65] Pdgfrα$^+$ lung fibroblast population has been defined as an AT2 niche in mouse lungs[11,41,66] (Fig. 26-2). Pdgfrα$^+$ fibroblast

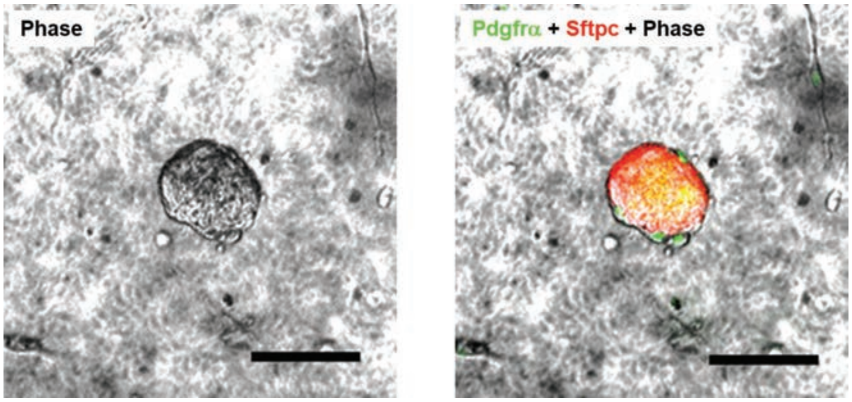

Figure 26-2 An alveolar organoid formed in 3D Matrigel. Pdgfrα$^+$ lung mesenchymal niche cells (green) were co-cultured with Sftpc$^+$ AT2 cells (red) in Matrigel. Images were taken at day 11. Scale bar: 100 µm

lineage contributes to the lipofibroblast pool of the lung.[67] Discrete lung stem cell niches along the proximal-distal axis of the respiratory tree regulate the reparative and regenerative function of region-specific lung stem cells.[54,68–70] In addition to Pdgfrα$^+$ LIFs and AT2, other fibroblast lineages, including EpCAM$^-$Sca-1$^+$, Axin2-Pa$^+$, Lgr6$^+$, Lgr5$^+$, and Gli2$^+$Gli1$^-$Hh^{low} support lung epithelial stem cells located in the airway and bronchoalveolar duct junctions (BADJ) that participate in repair/regeneration of injured lungs.[11,12,71,72]

MYOFIBROBLASTS: EFFECTOR CELLS IN TISSUE REPAIR

Below we consider a number of functional aspects of myofibroblasts, after first reviewing some historic context. Included are a discussion of the origin of myofibroblasts, factors that influence the cell's activity and differentiation, the cell's role in tissue homeostasis and repair, and the fate of the myofibroblast.

■ Historic Context

Myofibroblasts were first identified as fibroblastic cells with a strong muscle cell–like contractile filamentous apparatus in the granulation tissue of healing wounds.[73] These cells are present in organs with increased remodeling, such as in development, inflammation, fibrosis, cancer invasion, and metastasis.[74] Myofibroblasts display prominent cytoplasmic actin microfilaments (stress fibers) (Fig. 26-3). They are connected to one another with adherens and gap junctions as well as to the ECM with focal adhesion complexes (FAs).[75]

Myofibroblasts may be further classified into subtypes based on the presence or absence of vimentin, desmin, and/or α smooth muscle actin (α-SMA) in cytoskeletal filaments. Expression of these proteins varies upon tissue types and is subjected to the regulation by environmental factors.[76] Alternatively, myofibroblasts can be simply classified into two subpopulations, proto-myofibroblasts and mature myofibroblasts.[77] Proto-myofibroblasts are partly differentiated myofibroblasts that contain α-SMA-negative actin stress fibers, whereas mature myofibroblasts possess extensive networks of α-SMA-positive stress fibers and large FAs (termed supermature FAs). α-SMA has been the most widely used marker for identification of myofibroblasts (Fig. 26-3). However, a study of fibrosis in multiple organs found that only a minority of collagen-producing cells co-expressed α-SMA in the fibrotic lung and kidney,[78] suggesting non-myofibroblasts are important contributors to the deposition of collagen in the fibrotic ECM. Additionally, myofibroblasts themselves are heterogeneous with a number of other markers and modulators (Table 26-1). Heterogeneity among fibroblasts and

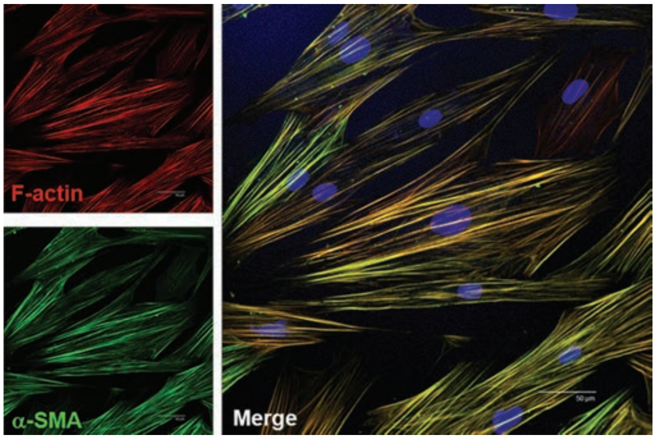

Figure 26-3 Myofibroblasts are characterized by de novo synthesis of α-SMA synthesis and incorporation of α-SMA into filamentous actin stress fibers. Scale bar: 50 µm

TABLE 26-1 Myofibroblast Markers

Marker	Cellular Overlap
Cytoskeletal component	
α-SMA[251]	Smooth muscle cells
Desmin[252]	Hepatic stellate cells, cardiomyocytes
Cofilin[253]	Smooth muscle cells
GB 42-antigen[254]	Smooth muscle cells
Palladin 4Ig[255]	Smooth muscle cells
Tropomyosin 1[256]	Cardiomyocytes
Cell membrane receptor	
Angiotensin II type 1 receptor (AT1R)[257]	Cardiomyocytes, smooth muscle cells
Integrin $\alpha_{11}\beta_1$[258]	Musculoskeletal cells
Thy 1[199]	Lipofibroblasts
Endosialin[259]	Cardiomyocytes, smooth muscle cells, adipocytes
Cadherin 11[260]	Tenocytes, endothelial cells, mesenchymal cells
Frizzled 2[261]	Smooth muscle cells
CD82[262]	T cells
AOC3[263]	Vascular smooth muscle cells
CKAP4[264]	Bladder epithelial cells
Extracellular protein	
Collagen I, III, IV, V, VI[265]	Various cells
Tenascin C[266]	Smooth muscle cells
Fibronectin ED-A[267]	Smooth muscle cells
Osteopondin[268]	Osteoblasts, osteocytes, chondrocytes
Periostin[269]	Preosteoblasts, cardiac myocytes

myofibroblasts remain an important area for future investigations, as the behavior and fate of these cells may differ, and potentially determine, pathologic states.

Origin of Myofibroblasts

The precise origin of myofibroblasts remains unsolved at present. Studies have suggested that local fibroblasts, perivascular pericytes, bone marrow (BM)-derived mesenchymal stem cells (MSCs), tissue MSCs, and epithelial/endothelial cells (through epithelial/endothelial-mesenchymal transition) are among potential cellular sources for myofibroblast population.

Resident Fibroblasts-Mesenchymal Stem Cells

Fibroblasts are the most widely accepted origin for myofibroblasts.[79,80] Fibroblasts influx into injured sites from the surrounding tissue and differentiate into myofibroblasts in response to extracellular stimuli including biochemical and physical cues.[81] These stimuli induce intrinsic changes in gene expression and stress fiber formation that characterizes myofibroblast differentiation.

MSCs that reside in tissues lack hematopoietic and leukocyte markers, but may express α-SMA.[82] Tissue MSCs have been described in the dermal sheath that surrounds the hair follicle facing epithelial stem cells.[83] These MSCs are involved in papilla regeneration and differentiate into myofibroblasts in response to environmental insults. It has been reported that MSCs from subcutaneous fat are responsible for collagen accumulation in scars.[84] Following lung injury, myofibroblasts were found to originate from perivascular and peribronchial sources.[85] It is likely that there are tissue MSCs in the human adult lung,[86] which become activated and undergo myofibroblast differentiation in response to lung injury. In support of this notion, a previous study has provided evidence for isolation of postnatal MSCs from different organs including liver, kidney, and lung.[87]

Pericytes

Pericytes are perivascular cells located on the abluminal side of endothelial cells in microvasculature.[88] These cells share developmental origins with fibroblasts, but they differ from fibroblasts by the fact that pericytes anatomically connect with endothelial cells through cell processes within capillary basement membrane, whereas fibroblasts do not directly interact with endothelial cells.[89] The normal function of pericytes includes the regulation of vascular tone and blood flow through expression of contractile microfilaments (actin, myosin) and intermediate filaments (desmin, vimentin).[90] Microvascular pericytes differentiate into myofibroblasts in diffuse cutaneous systemic sclerosis, providing a link between microvascular damage and skin fibrosis.[91] Recent studies using the genetic fate-mapping approach have clearly demonstrated that pericytes are a major cellular source of myofibroblasts in animal models of acute injury to muscle, dermis and kidney.[92,93] In addition, hepatic stellate cells, pericyte-like cells in the liver, are the primary myofibroblast progenitors in mouse models of alcoholic and toxic liver fibrosis.[94]

Bone Marrow–Derived Mesenchymal Cells

BM-derived MSCs are self-renewable, multipotent progenitor cells with the capacity to differentiate into lineage-specific cells that form bone, cartilage, fat, tendon, and muscle.[95] Compared with hematopoietic stem cells, MSCs are more radio-resistant and reside mostly in BM stroma. BM-derived MSCs do not express hematopoietic markers and can be isolated as Lin^- $CD45^-$ $CD31^-$ $CD34^-$ $CD133^-$ Sca-1+ Vitamin A^- cells.[96] In vitro evidence for a BM origin of myofibroblasts was first presented more than four decades ago. By plating BM cells on culture dishes, colonies consisting of cells exhibiting elongated or polygonal cytoplasm and clear nuclei were formed.[97] Transplantation studies using Y chromosome or green fluorescent protein (GFP) as a marker of donor cells provide in vivo evidence that (myo)fibroblasts in wounded skin, lung fibrosis, and intestinal fibrosis may derive from the BM.[98] There is evidence that monocytes may represent the major BM-derived cell population that contributes to myofibroblasts in fibrotic lesions, at least in some contexts.[99]

Circulating fibrocytes express markers of hematopoietic cells (CD34), leukocytes (CD11b, CD13, and CD45) and fibroblast products (collagens I and III, fibronectin). These cells are distinguished from monocytes/macrophages, dendritic cells, and B cells by their lack of expression of specific markers for these cell lineages. Circulating fibrocytes migrate into injured tissues and have been identified in a number of fibrotic conditions.[100] Studies have identified the potential for fibrocytes to participate in wound healing and pathologic scarring.[100,101] However, the direct contribution of fibrocytes to myofibroblast population during wound healing and fibrosis remains controversial. Evidence for and against fibrocyte-to-myofibroblast differentiation exist.[98,102] It is likely that instead of direct differentiation into myofibroblasts, circulating fibrocytes contribute to fibrosis by production of profibrogenic paracrine mediators that target resident cells.

Epithelial-to-Mesenchymal Transition

Epithelial-to-mesenchymal transition (EMT) refers to as a process through which fully differentiated epithelial cells lose their epithelial characteristics (e.g., apico-basal polarity, polygonal cell shape, tight and adherens junctions) and acquire properties of mesenchymal cells (e.g., elongated cell shape, increased motility, contractility). Epithelial cells undergoing EMT are characterized by downregulation of epithelial markers (e.g., E-cadherin, ZO-1) and concomitant upregulation of mesenchymal markers (e.g., FSP1, α-SMA) in the injured epithelium.[103] There is overwhelming evidence that primary epithelial cells cultured in vitro undergo EMT in response to a stimulatory input of soluble growth factors (e.g., TGF-β, EGF, HGF) and/or ECM components (e.g., collagen).[104] However, the concept of in vivo fibrogenic EMT has been challenged by new epithelial lineage tracking studies in a variety of models of kidney, lung, and liver fibrosis in animals.[105]

Factors Regulating Fibroblast Activation and Myofibroblast Differentiation

Fibroblasts isolated from the site of a healing wound or from fibrotic tissue secrete higher levels of ECM constituents and proliferate more than their normal counterparts isolated from healthy organs.[106] Such increased activity is referred to as "fibroblast activation." Activated fibroblasts express α-smooth-muscle actin, leading to the term "myofibroblasts." Fibroblast activation and differentiation into myofibroblasts are regulated by various stimuli, including biochemical factors, biophysical cues from the ECM, and epigenetic modifications.

Growth Factor and Cytokine-Mediated Activation

Fibroblasts become activated by stimulation with cytokines such as TGF-β1, PDGF, and FGF-2, which are released from injured epithelial cells, infiltrating mononuclear cells such as monocytes and macrophages as well as the ECM.[107–110] TGF-β1 is a pluripotent cytokine that plays a central role in the development of fibrosis. TGF-β1 is sequestered in a latent form (termed latent TGF-β1) in the ECM.[111] Latent TGF-β1 becomes activated in a spatially and temporally regulated fashion in response to injury.[111] Active TGF-β1 binds to its membrane receptors (TGF-βRI and TGF-βR2) which signal through both Smad-dependent canonical pathway and Smad-independent noncanonical pathway that promote fibrotic gene expression.[77] Active TGF-β1 also increases the assembly of stress fibers and focal adhesions that are required for the development of cellular contractility.[77] In addition, prototypic cytokines produced by CD4+ T cells such as interleukin (IL)13/IL4 and IL17 exert profibrotic effects on fibroblasts and play a crucial role in the development of fibrosis.[112,113]

Components of Vascular/Coagulation System

Coagulation proteases such as factor Xa and thrombin activate fibroblasts through receptor-mediated effects elicited by a high-affinity thrombin receptor, proteinase-activated receptor (PAR)-1.[114] PAR-1 signaling promotes fibroblast proliferation via the autocrine production of PDGF and CTGF, and drives fibroblasts differentiation into myofibroblasts via αvβ5-dependent TGF-β activation.[115,116] Thrombin upregulates expression of the fibrinolysis inhibitor plasminogen activator inhibitor (PAI)-1, resulting in increased fibrin matrix.[117] Fibrin matrix inhibits surfactant function and contributes to alveolar collapse and traction of remaining airspaces (honeycombing).[114] Lysophosphatidic acid (LPA), a platelet-derived molecule during blood coagulation, promotes fibroblast activation and pulmonary fibrosis by activation of latent TGF-β1 through LPA receptor.[118] Endothelin 1 (ET-1), an activator of extrinsic coagulation cascade, exerts potent mitogenic and profibrotic effects on fibroblasts.[119] Transgenic mice expressing human ET-1 transgene have been shown to develop progressive pulmonary fibrosis.[119]

Reactive Oxygen Species

Accumulating evidence indicates that oxidative stress and reactive oxygen species (ROS) production, mainly in the form of superoxide and hydrogen peroxide, play a significant role in myofibroblast differentiation.[120] The NAD(P)H oxidases of the Nox family have been identified as the enzyme system that is primarily responsible for ROS generation by fibroblasts in response to injury and are recognized as key mediators of myofibroblast differentiation and matrix accumulation in lung fibrosis.[121] Nox4, the most abundant Nox isoform in the lung, has been characterized as a "constitutively active" enzyme, meaning that the enzymatic activity of Nox4 is primarily regulated at the level of gene expression. TGF-β1 increases Nox4 expression and ROS production in lung fibroblasts, which mediates TGF-β1-dependent myofibroblast differentiation.[121] A similar mechanism for myofibroblast differentiation has been demonstrated in cardiac fibroblasts, renal fibroblasts, and mesangial cells.[122,123] Nox4 is also associated with TGF-β1-induced cellular contractility in lung myofibroblasts and cytoskeletal remodeling in vascular smooth muscle cells as well as endothelial cells.[121,124,125] Together, these results indicate that Nox-derived ROS regulate fibroblast morphology, contractility, and differentiation.

Mechanical Stress

Fibroblasts respond to mechanical cues, including externally applied forces, interstitial fluid flow, and matrix rigidity sensed through internally generated forces. Externally applied forces such as stretch provoke diverse fibroblast signaling responses, including activation of mitogen-activated protein (MAP) kinases,[126] Akt,[127] and focal adhesion kinase (FAK). It has been shown that stretch augments TGF-β release and signaling, and promotes the myofibroblast phenotype.[128,129] The continuous interactions between cell-generated forces and the resistance of matrix to cellular forces strengthen cell-matrix contacts and develop α-SMA-positive stress fibers characterizing myofibroblast differentiation.[77,130] Normal lung fibroblasts grown on polyacrylamide gels with a stiffness grade similar to fibrotic lungs undergo myofibroblast differentiation.[131] The effects of matrix stiffening on myofibroblast differentiation may occur through TGF-β-dependent intrinsic and/or TGF-β-independent extrinsic mechanotransduction[131,132] (see below). Interstitial fluid flow induces fibroblast proliferation, collagen alignment, and fibroblast-to-myofibroblast differentiation in the absence of exogenous mediators.[133,134] $\alpha_1\beta_1$ integrin appears to play an important role in the specific response to interstitial fluid flow.[133] Taken together, these results suggest that fibroblasts are mechanosensitive and are programmed for matrix production, contraction, and differentiation in the presence of mechanical stimuli.

Metabolic Regulators

Emerging evidence indicates that lung fibroblasts undergo dramatic metabolic reprogramming in lung fibrosis in both human and mice. These metabolic reprogramming events are critical to fibroblast proliferation, transition from quiescent to activated states, and synthetic activities.[135–139] A hallmark feature of these metabolic reprogramming events is the elevation of aerobic glycolysis. It has been found that rate-limiting enzymes involved in glycolysis are dramatically upregulated in activated lung fibroblasts, which is associated with a marked increase in glycolytic flux.[139,140] An augmented glycolysis is thought to meet increasing energy demands of activated lung fibroblasts. Although glycolysis is considered an inefficient means for generating ATP (two ATP molecules by glycolysis vs. 36 ATP by oxidative phosphorylation), aerobic glycolysis can produce ATP at a faster rate than oxidative phosphorylation. Aerobic glycolysis also generates byproducts, such as lactate, that could be important for fibroblasts. Lactate production serves as an energy source for neighboring cells, and its conversion to lactic acid may potentially result in activation of latent TGF-β1 by lowering extracellular pH.[141,142] Additionally, aerobic glycolysis may favor anabolic metabolism and promote proliferative/activated states by diverting glycolytic intermediates involved in the synthesis of nucleotides, lipids, or amino acids. Glucose-6-phosphate is an essential substrate for the pentose phosphate pathway (PPP), producing ribose-5-phosphate for the synthesis of nucleotides (ATP and GTP) and NADPH for the de novo synthesis of lipids.[137,143]

Along with an increase in glycolysis, glutaminolysis is also increased in activated lung fibroblasts.[144,145] It has been reported that glutaminase levels were significantly increased in both TGF-β1-stimulated mouse lung fibroblasts and fibroblasts from patients with IPF.[144] Succinate, a byproduct of glutaminolysis, has been found to stabilize HIF1α expression, thereby augmenting levels of glycolytic enzymes and enhancing metabolic reprogramming.[140]

Epigenetic Regulation

The findings that specific signatures of gene profile in myofibroblasts are "memorized" over passages suggest that epigenetic modifications may be involved in the regulation of myofibroblast differentiation.[146] Epigenetic regulation of myofibroblastic phenotype involves DNA methylation, histone modification, and sequence-specific microRNAs (miRNAs). DNA methylation at CpG islands is associated with expression of myofibroblast marker α-SMA in lung cells. Type II alveolar epithelial cells that do not express α-SMA exhibit high levels of methylation at the three CpG islands in the regulatory regions of ACTA2 gene encoding α-SMA protein, whereas lung (myo) fibroblasts exhibit significantly low levels of DNA methylation at these sites.[147] Inhibition of DNA methyltransferase (DNMT) induces α-SMA expression, whereas overexpression of DNMT suppresses α-SMA expression in lung fibroblasts.[147] Inhibition of DNA methylation activates PPARγ and NF-κB, transcription factors known to suppress ACTA2 gene expression,[148] suggesting that modifications of DNA methylation may also indirectly regulate α-SMA expression by inactivation of PPARγ and NF-κB. Histone acetylation has been shown to regulate myofibroblast differentiation. It has been shown that histone deacetylase (HDAC)4 is an essential epigenetic regulator of TGF-β1-induced skin fibroblast-to-myofibroblast differentiation.[149] HDAC8 binds to α-SMA, and the binding is likely to regulate actin cytoskeleton-derived cellular contractility.[150]

miRNAs are single-stranded RNA molecules that target multiple mRNAs and induce silencing of multiple transcripts. It has been shown that miR-21 mediates TGF-β1-induced lung myofibroblast differentiation by targeting Smad7, a major inhibitor of TGF-β signaling.[151] In contrast, downregulation of miRNA let-7d expression by TGF-β results in increased mesenchymal gene expression (e.g., ACTA2) in multiple epithelial cell lines, indicative of EMT.[152]

miR-132 inhibits MeCP2 and PPARγ expression, resulting in enhanced α-SMA expression in lung fibroblasts.[148]

Other Factors

Wnt ligands induce fibroblast activation and collagen synthesis.[153] β-catenin, a transcription factor and a downstream signal transducer of Wnt signaling, was found to accumulate in the nuclei of cells located in the fibroblastic foci of IPF lungs.[154] Selective inhibition of β-catenin-mediated transcription attenuates lung fibrosis in a bleomycin-induced mouse model.[155] These studies suggest a crucial role of the Wnt/β-catenin signal in fibroblast activation and lung fibrosis. Integrins have been implicated in the differentiation of protomyofibroblasts into mature myofibroblasts.[156] Integrin $\alpha_5\beta_1$ is associated with α-SMA expression in differentiating myofibroblasts.[156] Large clusters of $\alpha_5\beta_1$ are present in the FAs of mature myofibroblasts.[156] Additionally, environmental stimuli including hypoxia and hyperglycemia, as well as direct contacts between fibroblasts and leukocytes, have been reported to be associated with fibroblast activation.[157,158]

■ Mechanical Aspects of Myofibroblasts

Important in detailing myofibroblast function is consideration of the cell's mechanical properties.

Myofibroblast Contractility

Acquisition of contractility similar to smooth muscle cells is a defining feature of myofibroblasts. Myofibroblasts generate intracellular contractile forces by ATP-powered sliding of actin–myosin filaments.[159] Compared with Ca^{2+}-regulated rapid and reversible contraction in smooth muscle cells, myofibroblast contraction is relatively slow, sustained, and nonreversible.[160] Myofibroblast contractility is primarily regulated by the Rho family of small GTPases (Rho, Rac, and Cdc 42) and their downstream targets, primarily myosin light chain kinase (MLCK) and myosin light chain phosphatase (MLCP).[77] α-SMA expression and incorporation of α-SMA into stress fibers contribute to myofibroblast contractility.[161] However, the mechanism by which α-SMA regulates myofibroblast contractile force formation is not clear. Myofibroblast contractility facilitates a normal wound healing process by limiting and closing the exposed surface area of the wound. Myofibroblasts disappear from the wound site when a normal repair process is successfully completed. The persistence of myofibroblasts is associated with aberrant wound repair and leads to tissue fibrosis/scarring. Increasing evidence suggests that myofibroblast contractility may provide a feed-forward mechanism (known as mechanotransduction, see below) that sustains fibrosis. Inhibiting myofibroblast contractility by targeting Rho/Rho kinase (ROCK)/actin cytoskeleton signal pathway selectively activates mitochondria-dependent intrinsic apoptotic pathway in myofibroblasts and ameliorates bleomycin-induced mouse lung fibrosis.[162] Disruption of myofibroblast contraction interrupts septa formation,[163] supporting a critical role for myofibroblasts in normal alveologenesis.

Sensing Matrix Stiffness

The ECM in healthy organs has well-defined mechanical properties that fall within a physiologic range.[164] Changes in matrix stiffness that occur in pathologic states, such as fibrosis and cancer, have profound effects on cell morphology, proliferation, migration, and gene expression.[164] Characterization of the mechanical properties of normal and fibrotic lung matrix demonstrates increased matrix rigidity in both human IPF and experimental models of lung fibrosis.[165,166] It is believed that protein cross-linking enzymes such as lysyl oxidase (LOXL2) and tissue transglutaminase (TG2) and/or matrix degrading enzymes such as MMPs regulate the stiffness of ECM, although the precise mechanisms remain to be determined. Fibroblasts sense changes in matrix stiffness by cell-matrix adhesions.[167] Transmembrane integrins at FAs act as direct mechanosensors on the cell membrane by providing a physical link between intracellular actin cytoskeleton and the ECM. The cytoplasmic domain of integrins interacts with signaling molecules at the FA sites (e.g., FAK and c-Src). Thus, integrins also act as indirect mechanosensors to regulate cell function and behavior by modulating FA signals.[168] Matrix stiffness sensing depends largely on cellular contractility and actin cytoskeleton integrity. Fibroblast contractility generates cytoskeletal tension that serves to transmit mechanical information from the ECM. Disruption of actin cytoskeleton-mediated contractility blocks matrix stiffening–induced myofibroblast differentiation.[131]

Mechanotransduction in Myofibroblasts

Mechanotransduction is a process in which cells sense mechanical stimuli and convert mechanical signals into biochemical signals. Recent studies suggest that mechanotransduction in myofibroblasts with prolonged survival/resistance to apoptosis may provide a feed-forward mechanism for progression of fibrosis, as in IPF. It has been reported that lung myofibroblast contraction promotes latent TGF-β activation, the most potent fibrogenic cytokine characterized to date, in the extracellular compartment[132,169] (Fig. 26-4). In this process, the actomyosin apparatus in myofibroblasts generates contractile forces that are transmitted across the cell membrane to the ECM. The force transmission results in a conformational change of the ECM-bound latent TGF-β1 complex, resulting in the release/exposure of active TGF-β1 from the latent complex. The finding suggests an extrinsic mechanotransduction pathway in which mechanical forces derived from intracellular stress fibers are transduced to the extracellular matrix and converted into TGF-β1 fibrogenic signal capable of regulating fibrosis.

In contrast to TGF-β-mediated extrinsic mechanotransduction pathway, an intrinsic mechanotransduction pathway in which the myofibroblast contractile signal is converted into a nuclear signal by transcription factor co-activator megakaryocytic leukemia protein (MKL) 1 (also known as MAL/MRTF-A) also has been identified[131]

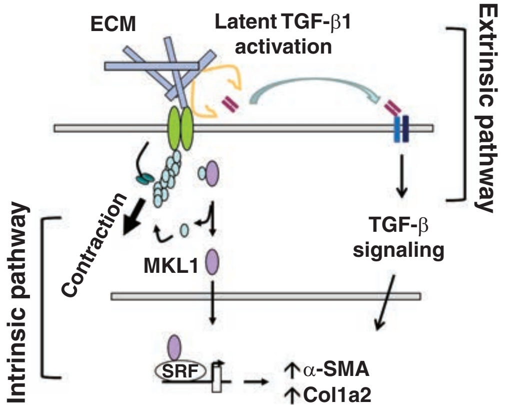

Figure 26-4 Contractile forces promote myofibroblast differentiation via intrinsic and extrinsic mechanotransduction pathways. In the intrinsic mechanotransduction pathway, mechanical stimuli from stiff/fibrotic ECM promote G-actin polymerization into F-actin. This results in the release of MKL1 and its nuclear translocation. MKL1 binds to SRF in the nucleus to form a transactivation complex and activates fibrotic gene expression that specifies myofibroblast differentiation. In the extrinsic mechanotransduction pathway, actomyosin-generated contractile forces pull against stiff/fibrotic ECM. This results in a conformational change of latent TGF-β1 complex, which releases active TGF-β1 from the latent molecule. Active TGF-β1 then binds to its receptors on the cell membrane and initiates TGF-β signaling that promotes fibrotic gene expression.

(Fig. 26-4). MKL1 is a serum response factor (SRF) co-activator that constitutively binds to monomeric G-actin in the cytoplasm.[170] In response to matrix stiffening, normal lung fibroblasts undergo extensive actin cytoskeletal remodeling and develop contractile forces. This changes actin cytoskeletal dynamics that favors G-actin polymerization into F-actin. Polymerization of G-actin into F-actin results in the release of MKL1 from G-actin. The liberated MKL1 enters into nucleus, where it binds to SRF and targets to the CArG sequence in the promoter region of ACTA2 gene and COL1A2 gene, leading to gene activation.[171] TGF-β neutralizing antibody does not block MKL1-mediated α-SMA expression,[131] suggesting that MKL1-mediated intrinsic mechanotransduction is independent of TGF-β-dependent extrinsic mechanotransduction. In addition to sensing mechanical stimuli, integrins are important mechanotransducers that allow bi-directional transduction and conversion of external forces into intracellular response (outside-in signaling) and internal forces (e.g., stress fiber–derived contractile forces) into extracellular and/or FA signals (inside-out signaling).[77,172] Besides integrins, stretch-activated ion channels, receptor tyrosine kinases (RTKs), CD44, and syndecan-4 are potential mediators of mechanotransduction as well.[173–176] However, mechanical stress may also regulate gene expression in fibroblasts through mechanotransduction-independent mechanisms. It has been shown that cyclic strain increases the mRNA level of tenascin-C within 1 h in cultured fibroblasts,[177] and this induction does not require synthesis of new proteins.[178]

■ Myofibroblasts in Tissue Homeostasis and Repair

Myofibroblasts play a role in the regulation of differentiation and homeostasis of adjacent epithelia. Such mesenchymal–epithelial interactions are crucial for morphogenesis and organogenesis.[179] Myofibroblasts regulate epithelia by secretion of soluble growth factors and production of basement membrane molecules.[180]

Myofibroblasts play important roles in both normal and aberrant wound repair. As mentioned above, myofibroblast contractility facilitates wound closure. During the resolution phase, myofibroblasts produce MMPs and TIMPs that change the local microenvironment from a balance favoring ECM deposition to matrix degradation.[181] Interconnected gap junctions of myofibroblasts allow the electrical signals created by cyclic ion movements to be transmitted through the syncytium and the length of the resident organ.[182] Myofibroblasts sustain their activated state in fibrosis/hypertrophic scarring even when the initial insults have regressed. Myofibroblasts in such a sustained state of activation continue to secrete ECM constituents, growth factors, and cytokines. These result in a self-perpetuating autocrine loop that further stimulates myofibroblast differentiation and prevents normal resolution of tissue injury. In addition to fibrosis/hypertrophic scars, diseases associated with myofibroblastic phenotype include inflammatory pseudotumors, cancer metastasis, and neoplastic transformation of the myofibroblasts themselves.

■ The Fate of Myofibroblasts

The fate of myofibroblasts is a key determinant between normal repair and fibrosis. In normal wound healing, myofibroblasts gradually disappear after wounds are closed. Persistent myofibroblast differentiation is associated with pathologic wound healing and fibrosis. Understanding of the physiologic clearance of activated fibroblasts is particularly important for developing therapeutic strategies for persistent/progressive fibrosis such as IPF.

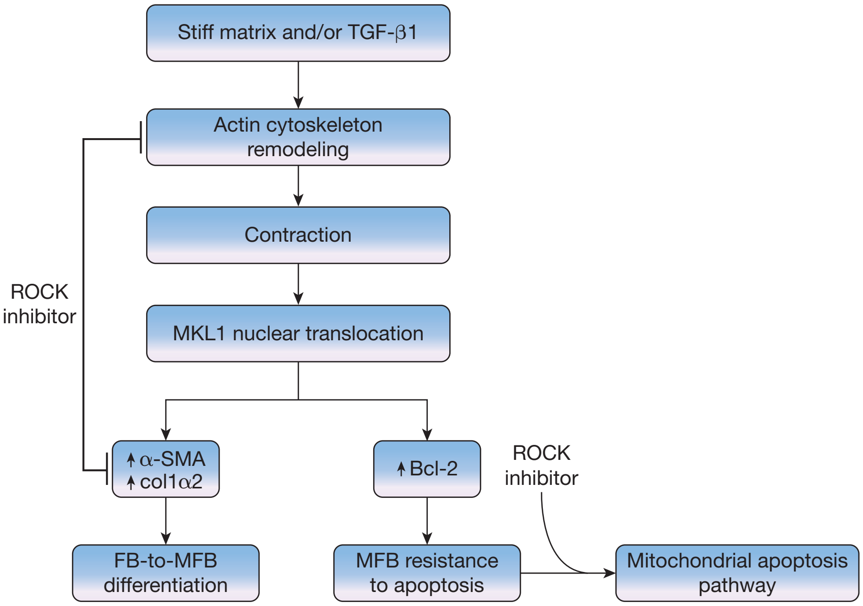
Stiff matrix and/or TGF-β1
Actin cytoskeleton remodeling
Contraction
ROCK inhibitor
MKL1 nuclear translocation
↑α-SMA
↑col1α2
↑Bcl-2
ROCK inhibitor
FB-to-MFB differentiation
MFB resistance to apoptosis
Mitochondrial apoptosis pathway

Figure 26-5 Mechanosensitive signaling in myofibroblasts as a target for antifibrotic therapy. In response to extracellular biomechanical and biochemical stimuli, such as matrix stiffness and active TGF-β1, lung fibroblasts undergo actin cytoskeleton remodeling and activation of the actomyosin contractile system, which result in MKL1 translocation from cytoplasm to nucleus, where it activates fibrotic genes that specify myofibroblast differentiation. Inhibition of ROCK blocks actin cytoskeletal reorganization, fibroblast acquisition of contractile activity, and MKL1 nuclear translocation, preventing fibroblast-to-myofibroblast differentiation. On the other hand, ROCK inhibition disrupts actin cytoskeleton required for myofibroblast contractility in pre-existing myofibroblasts. This deactivates constitutively activated MKL1 nuclear signal in myofibroblasts, resulting in downregulation of the antiapoptotic protein Bcl-2 and activation of the intrinsic apoptotic pathway.

Apoptosis

Apoptosis has been suggested as an intriguing possibility for the elimination of myofibroblasts from healing wounds and reversible fibrosis.[183] An earlier study has observed that myofibroblasts undergo apoptosis in granulation tissue on which a vascularized skin flap is grafted.[184] Reduced growth factor and increased MMP expression appear to link to myofibroblast cell death.[185] Disruption of cell-matrix interactions using RGD peptides or soluble fibronectin promotes myofibroblast anoikis, a type of apoptosis that is induced by inadequate or inappropriate cell-matrix interactions.[186] In reversible liver fibrosis, hepatic stellate cell (HSC)-derived myofibroblasts undergo apoptosis in parallel to the reduction of the total number of HSCs in the recovery phase.[187] Hepatic myofibroblast apoptosis appears to occur by a Fas ligand (APO-1/CD95)-mediated extrinsic pathway.[187] Pharmacologic inhibition of ROCK, such as with fasudil, inhibits actin polymerization and downregulates constitutive expression of the antiapoptotic protein Bcl-2 in IPF lung myofibroblasts; this results in release of cytochrome *c* from mitochondria, triggering the mitochondria-dependent intrinsic apoptosis pathway. Furthermore, fasudil-induced myofibroblast apoptosis ameliorates bleomycin-induced lung fibrosis in mice.[162] This study indicates that targeting mechanosensitive signaling in myofibroblasts may offer an effective approach for treatment of fibrotic disorders (Fig. 26-5).

Interestingly, mitochondria in stiff matrix-activated lung myofibroblasts were found to load with proapoptotic BH3 proteins, thus increasing their mitochondrial priming. Myofibroblasts in this "primed for death" state were prone to undergo apoptosis and became reliant on antiapoptotic proteins for their survival. This creates a therapeutic opportunity to treat lung fibrosis by inducing myofibroblast apoptosis with BH3 mimetics, which have been shown to be effective in experimental models of lung fibrosis.[188]

Dedifferentiation

A recent study showed that HSC-derived myofibroblasts regress to a more quiescent state upon the removal of the fibrogenic stimuli in a carbon tetrachloride-induced mouse model of liver fibrosis.[94] The finding suggests that reversion of myofibroblasts to a more quiescent phenotype may be a second possibility folsis,[94] suggesting that myofibroblast regression may be an intermediate step towards the resolution of fibrosis. Although regression to an inactive precursor cell may limit the activity of myofibroblasts, this does not appear to completely eliminate the potential for re-activation. In large skin wounds, myofibroblasts can generate lipid-filled adipocytes that regenerate hair follicles.[189] It has been suggested that myofibroblasts undergo a dedifferentiation event that is controlled by mitogen(s)/ERK/MAPK/CDKs, as opposed to TGF-β1/ALK5/MyoD-dependent myofibroblast differentiation during fibrosis formation.[190] The reversibility of the fibrotic response in mouse lungs triggered by bleomycin administration was used to investigate the fate of myofibroblasts following fibrosis resolution. Results show that a subset of activated myofibroblasts transitioned to a lipofibroblast-like phenotype,[191] supporting the myofibroblast dedifferentiation as an essential process in fibroblast resolution.

Senescence

Cellular senescence is associated with the loss of the ability of cells to replicate their genome and enter permanent growth arrest in the G1/G0 cell-cycle phase.[192] Although senescent fibroblasts do not respond to mitogens, they remain metabolically active and are resistant to apoptosis. Cellular senescence often occurs by telomere shortening and subsequent activation of p53 and p21 and/or inactivation of pRB and activation of p16.[192] Senescence may also be triggered by other forms of cellular damage, including oxidative stress, DNA damage and oncogene activation.[192] Myofibroblast senescence has been proposed as an antifibrotic mechanism by limiting the proliferative capacity of fibrogenic fibroblasts and/or by modulating the cellular microenvironment.[193,194] However, this basic assertion is inconsistent with the clinical observation of an increased risk of fibrotic disease with advancing age. This highlights the complexities of cellular senescence in tissue injury repair processes, and supports the concept that the plasticity and fate of senescent cells may be altered with aging which, ultimately, determines the outcome of the tissue repair response.

MYOFIBROBLASTS IN LUNG DEVELOPMENT AND DISEASE

Important considerations in any discussion of myofibroblasts include their role in alveogenesis and in a variety of disease states, including pulmonary fibrosis, asthma, emphysema, and non–small-cell lung cancer.

Alveologenesis

Lung development is a complex process involving reciprocal interactions between mesoderm-derived mesenchyme and endoderm-derived epithelium. Alveolar myofibroblasts are present during alveologenesis but absent in the adult lung.[195] Myofibroblasts surround the distal lung epithelial tubules and buds in the pseudoglandular stage of lung development. The absence of alveolar myofibroblasts is associated with deficient secondary septation and the failure of alveolar development.[196] Although alveolar myofibroblasts play an essential role in the morphogenesis of pulmonary alveolar septa, mechanisms involved in the regulation of alveolar myofibroblast survival and clearance in the process of alveologenesis are poorly understood and need further investigation.

Pulmonary Fibrosis

Pulmonary fibrosis is characterized by excessive synthesis and deposition of ECM proteins in the lung parenchyma, resulting in deficient gas exchange. IPF is the most common and lethal diffuse fibrosing lung disease, with a mortality rate that exceeds that of many cancers. Currently, there is no FDA-approved pharmacologic therapy for patients with IPF. The pathogenesis of IPF remains elusive. The current paradigm posits that repeated alveolar epithelial injury and persistent myofibroblast activation are central to the progression of IPF.[197] Regardless of the origins, myofibroblasts isolated from IPF lungs have increased migratory activity, ability to deposit ECM, and prolonged survival/resistance to apoptosis compared to their normal conterparts.[197] Abnormal myofibroblast survival is a key determinant of whether fibrosis will progress or resolve.[198] The survival of IPF myofibroblasts has been found to be regulated by multiple antiapoptotic signals.[199] These include enhanced responsiveness to growth factors and fibrotic cytokines; impaired cyclooxygenase-2 expression and consequential reduction in prostaglandin E2 production; decreased caveolin 1 (CAV1) and PTEN expression; and increased antiapoptotic protein expression, as well as signals from the extracellular microenvironment. Myofibroblasts isolated from fibrotic lungs induce cytotoxic effects on epithelial cells. Co-culturing of myofibroblasts with lung epithelial cells results in epithelial cell apoptosis by FAS–Fas ligand (FAS–FasL)-dependent and -independent mechanisms.[200,201] Epithelial cell apoptosis can cause further lung injury that augments lung fibrosis. Myofibroblasts produce cytokines and growth factors that signal to the epithelium, resulting in damage to the alveolar basement membrane that prevents re-epithelialization.[202] Myofibroblast-produced chemokines promote the recruitment of immune cells and fibrocytes that actively participate in fibrotic progression.[203,204]

Asthma

Airway remodeling in patients with asthma encompasses the structural alterations that lead to persistent airflow limitation. Both smooth muscle cells and (myo)fibroblasts have been implicated in the pathogenesis of airway remodeling in asthmatic airways. In asthmatic patients, susceptibility to injury and aberrant repair responses result in fibroblast activation and myofibroblast differentiation, leading to subepithelial fibrosis.[205] Reduced airway remodeling in anti-leukotriene therapy is due, in part, to diminished myofibroblasts in asthmatic airways.[206] Viral infections are major triggers of acute asthma exacerbations.[207] The susceptibility to viral infections in asthmatic patients is not limited to epithelial cells. Rhinoviruses have been detected in subepithelial cells including fibroblasts, likely due to the disrupted and inflamed epithelium.[208] Fibroblasts from asthmatic patients have enhanced abilities for replication of rhinoviruses and subsequent production of IL-6 and IL-8, resulting in vigorous proinflammatory responses.[209] TGF-β augments rhinovirus replication in fibroblasts isolated from asthmatic patients.[210]

Emphysema

Emphysema is characterized by the progressive destruction of pulmonary alveoli. A vast majority of cases of pulmonary emphysema are associated with chronic lung injury induced by cigarette smoke. Chronic smoke exposure induces inflammation, protease/

antiprotease imbalance, oxidative stress, and death of bronchiolar and alveolar epithelial and endothelial cells.[211] Cigarette smoke reduces lung fibroblast proliferation and migration and induces fibroblast apoptosis.[212,213] In addition to the cytotoxic effects, cigarette smoke inhibits elastin synthesis and cross-linking in fetal lung fibroblasts.[214,215] Interactions between fibroblasts and alveolar epithelial cells are greatly reduced in the emphysematous lung,[216] suggesting that the repair and regeneration function of fibroblasts are impaired. Emphysema fibroblasts display features of myofibroblast differentiation and senescent phenotype characterized by enlarged morphology and cell cycle arrest.[217,218]

■ Non–Small-Cell Lung Cancer (NSCLC)

Carcinoma-associated fibroblasts (CAFs) constitute a major portion of reactive tumor stroma. CAFs express α-SMA and high levels of collagens and ED-A FN, indicating that these cells are of myofibroblast characteristics.[219] CAFs are responsible for dense ECM deposition around tumors and thus have been considered as a defense mechanism for tumor growth. In established tumors, CAFs synthesize cytokines/growth factors (e.g., TGF-β1) and ECM-degrading proteases (e.g., MMPs) that promote angiogenesis, recruitment of inflammatory cells, cancer cell proliferation, invasion, and metastasis.[3] CAF-associated prognostic factors have been identified in NSCLC. In adenocarcinomas, carbonic anhydrase IX expression has been found a better prognostic predictor in CAFs than in cancer cells.[220] Expression of podoplanin, a lymphatic endothelial cell marker, in CAFs is associated with shorter survival in patients with NSCLC.[221] In squamous cell carcinomas, MMP-2 expression in CAFs is found to be a significant unfavorable prognostic factor.[222] While expression of PDGF-B, PDGF-C, and PDGFR-α in cancer cells is associated with a negative prognosis, expression of PDGF-A, PDGF-B, PDGF-D, and PDGFR-α in CAFs is a favorable prognostic indicator.[223] Additionally, it has been found that stromal expression of PDGF-B, PDGF-D, and PDGFR-α is associated with less nodal metastasis.[224] Clinical prognostic values of TGF-β and FGF in NSCLC have been evaluated in the previous studies.[225–228] Due to the conflicting results, the prognostic roles of TGF-β and FGF2 in NSCLC remain uncertain.

TARGETING MYOFIBROBLASTS AND MATRIX REMODELING FOR LUNG DISEASE THERAPIES

Tissue remodeling in response to injury is a common pathologic feature observed in many lung diseases including IPF. Dysregulation of fibroblast function and matrix metabolism are crucial to the aberrant injury repair in IPF lungs. Currently, there are no treatments that specifically target myofibroblast-associated pathologies in IPF. Pirfenidone is an FDA-approved drug for IPF treatment. It inhibits fibroblast proliferation and collagen synthesis.[229,230]

PDGF is a potent mitogen and chemoattractant for fibroblasts and induces procollagen production by fibroblasts in vitro. Targeting PDGF receptor with imatinib mesylate, a tyrosine kinase inhibitor, has been shown to prevent bleomycin-induced mouse lung fibrosis.[231] However, a randomized, placebo-controlled trial showed that imatinib does not improve survival or lung function in patients with mild to moderate IPF.[232]

TGF-β1 is the most potent inducer of fibroblast ECM production characterized to date and promotes fibroblast to myofibroblast differentiation. Several types of pharmacotherapy to block TGF-β have been developed including antibodies, soluble receptors, intracellular signaling pathway inhibitors, and agents that target the cell surface receptors for TGF-β (TGF-βRI/II).[233,234] A phase 1 clinical trial with TGF-β neutralizing antibody has begun in patients with IPF. Orally active TGF-βRI kinase inhibitors have been shown to attenuate bleomycin-induced mouse lung fibrosis.[235] Since TGF-β has important homeostatic functions in the regulation of immune response and tumor suppression, therapeutic strategies that directly block TGF-β may yield undesirable side effects. Alternatively, targeting latent TGF-β activation has become a more favorable approach for antifibrotic therapy. Integrins are important mediators for in vivo activation of latent TGF-β.[236] $\alpha_v\beta_6$ integrin plays the primary role in regulating epithelial latent TGF-β1 activation.[237] Mouse studies have shown that inhibition of $\alpha_v\beta_6$ integrin blocks bleomycin- and radiation-induced lung fibrosis, and this integrin is also abnormally regulated in human fibrotic diseases.[237] BG00011, a humanized monoclonal antibody to integrin $\alpha_v\beta_6$, demonstrated TGF-β suppression in phase 2A clinical trial in IPF. $\alpha_v\beta_5$ integrin regulates mechanical tension-induced latent TGF-β1 activation in lung (myo) fibroblasts.[132] This integrin is co-expressed with α-SMA positive myofibroblasts, but absent on hyperplastic epithelial cells in the fibroblastic foci in IPF.[238] The GPI-linked Thy-1 blocks mechanical tension–induced latent TGF-β1 activation, presumably by disruption of the binding of latent TGF-β1 with $\alpha_v\beta_5$ integrin.[169]

Emerging preclinical evidence suggests that targeting metabolic pathways could be effective in the treatment of pulmonary fibrosis. Pharmacologic or genetic approaches to inhibiting the glycolytic enzyme 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3) reduced fibroblast activation in vitro and dramatically ameliorated the severity of pulmonary fibrosis in mice.[140] It remains to be determined whether chronic use of glycolytic inhibitors will be safe in animals or, more importantly, in humans. Pharmacologic (CB-839 or BPTES) and genetic approaches to inhibiting glutaminolysis can significantly suppress collagen gene transcription in lung fibroblasts.[144,145] Inhibition of amino acid biosynthesis might be effective in reducing fibrotic responses.[239,240] AMPK functions to restore energy balance by inhibiting processes that consume ATP and by stimulating processes the lead to the production of new ATP. AMPK activation is reduced in lungs of mice during pulmonary fibrosis. Treatment of mice with the AMPK activator metformin markedly improved fibrosis resolution capacity in the bleomycin injury model.[241]

Inhibition of excess ECM generation, deposition, and stabilization, and increasing matrix degradation, have become important targets for pharmacologic therapy. Cytokines including CTGF, PDGF, ET1, and IGF can induce fibroblast/myofibroblast activation and regulate matrix production. Inhibition of all of these cytokines can inhibit pulmonary fibrosis in a variety of in vivo models of fibrosis.[112,242–244] MMPs, including MMP 1, 3, and 7, among others, have been implicated in the pathogenesis of pulmonary fibrosis,[245] although the exact role of the MMPs in the pathogenesis of pulmonary fibrosis remains not known. Matrix cross-linking enzymes are responsible for the regulation of ECM stabilization. Cross-linking makes matrix potentially more resistant to degradation and may favor fibrosis progression. TG2 induces the cross-linking of collagen and fibronectin, resulting in stabilization of the matrix.[246] TG2 is elevated in many forms of human and murine pulmonary fibrosis.[246] Inhibition of the extracellular cross-linking function of TG2 results in inhibition of ECM generation and cross-linking in the lung.[246] Irreversible inhibitors of TG2 have been developed and are available from several commercial sources. LOXL2, another matrix cross-linking protein, catalyzes the first step in the formation of cross-links in collagens and elastin.[247] LOXL2 cross-links fibrillar collagen, making it more resistant to homeostatic turnover. LOXL2 is induced by TGF-β and is upregulated in IPF.[248,249] Administration of a monoclonal anti-LOXL2 antibody (AB0023) in either a prophylactic manner or a therapeutic manner significantly attenuates bleomycin-induced fibrosis in mice.[249]

Drug targeting systems for delivering therapeutic agents to myofibroblasts utilize cell surface targets. As a general targeting strategy, ligands such as peptides, antibodies, aptamers, or other moieties are designed against receptors overexpressed by myofibroblasts.[250]

These ligands are either directly conjugated to the therapeutic molecule or to a (nano)carrier incorporating a therapeutic agent. Drug targeting to subpopulations of myofibroblasts will be a highly appealing approach since it allows to specifically hamper the disease-inducing functions of myofibroblasts while leaving the rest unaffected. To achieve this would require the identification of specific surface markers delineating myofibroblast subpopulations.

CONCLUSION AND PERSPECTIVES

An understanding of the physiology and pathophysiology of fibroblasts has greatly advanced in the past few decades. It has become increasingly clear that fibroblasts and myofibroblasts play important roles in human health and disease. Despite this, many fundamental questions remain to be answered. The origins of myofibroblasts remain to be clarified. It is not known whether myofibroblasts of various origins exhibit different characteristics and functions in the injury and repair process. Identification of specific markers for fibroblasts will allow their specific isolation and more precise characterization, both in vitro and in vivo. Additionally, specific markers could facilitate genetic animal studies allowing the specific targeting of these cells. The independent and interactive roles of cytokines, ECM, and mechanical forces in the regulation of the structure and function of fibroblasts and myofibroblasts need to be characterized.

The identification of myofibroblasts as key cells and potential targets in fibrotic diseases such as IPF has led to the concept that targeting these cells may be a promising approach for disease therapy. Interesting approaches that target myofibroblasts and the ECM include termination of myofibroblast persistence by inducing their apoptosis or their reversion to nonfibrogenic cell phenotypes; interference with collagen cross-linking and ECM stiffening by controlling the activities of protein cross-linking enzymes and nonenzymatic crosslinking mediators such as advanced glycation end products (AGEs); and the use of miRNAs and metabolic modulators as potential therapeutic strategies. We believe that these novel approaches will eventually lead to more effective treatments for patients with fibrotic lung diseases.

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PART 3

Symptoms and Signs of Respiratory Disease

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CHAPTER 27

Approach to the Patient with Respiratory Symptoms

Michael A. Grippi
Jeffrey P. Callen

The most common respiratory complaints prompting medical evaluation are shortness of breath and cough. Less frequent are hemoptysis and thoracic pain. As in any medical assessment, a detailed history and thorough physical examination are of paramount importance. Use of plain chest radiography for routine screening, once popular in the hope of uncovering silent disease amenable to therapy, is not routinely employed, as it has not been proven to decrease mortality or to be cost-effective. Chest radiography is now usually reserved for patients who have clinical manifestations of thoracic disease; serial chest radiographs often provide invaluable clues regarding the underlying problem. More sophisticated imaging techniques, including computed tomography (CT),[1,2] along with tests of lung function, help complete the clinical picture.

HISTORY

Although seasoned clinicians may be adept at quickly spotting telltale diagnostic clues, a comprehensive medical history is central to patient evaluation. The history should include a detailed inventory of exposure to airborne substances that may result in lung injury. One of the most common offenders is cigarette smoke. An attempt should be made to quantify the exposure.

Often, the workplace is the site where toxic air is inhaled. An almost forgotten exposure to a toxic inhalant 20 years ago may explain certain types of pulmonary or pleural diseases. Symptoms that appear to improve during weekends or other periods away from work may be a clue to an occupational exposure that causes a respiratory ailment. A newly installed home humidifier or an air conditioning system that incorporates stagnant pools of water can point the way to resolving a mysterious illness. Brief residence in an area where either cryptococcosis (southwestern United States) or histoplasmosis (southern and midwestern United States) is endemic may help clarify the nature of an illness that mimics tuberculosis. A recent visit to a South or Central American country may bring into focus a more remote possibility (e.g., South American blastomycosis) (Fig. 27-1).

The history should include a thorough evaluation of prior and current medical problems. Rheumatologic disorders, such as systemic sclerosis (scleroderma), may be associated with interstitial lung disease, aspiration pneumonia due to esophageal involvement, or pulmonary vascular disease. Certain malignancies often metastasize to the lung (e.g., breast or colon carcinoma), or predispose to development of venous thromboembolism (e.g., pancreatic carcinoma). Infection with the human immunodeficiency virus (HIV) should not be overlooked, since pulmonary complications are often the initial presentation of acquired immunodeficiency syndrome (AIDS). Other causes of immunodeficiency, such as hematologic malignancy, or prior administration of chemotherapeutic agents, should heighten suspicion of infection as the cause of respiratory symptoms, as well as potential pulmonary drug toxicity.

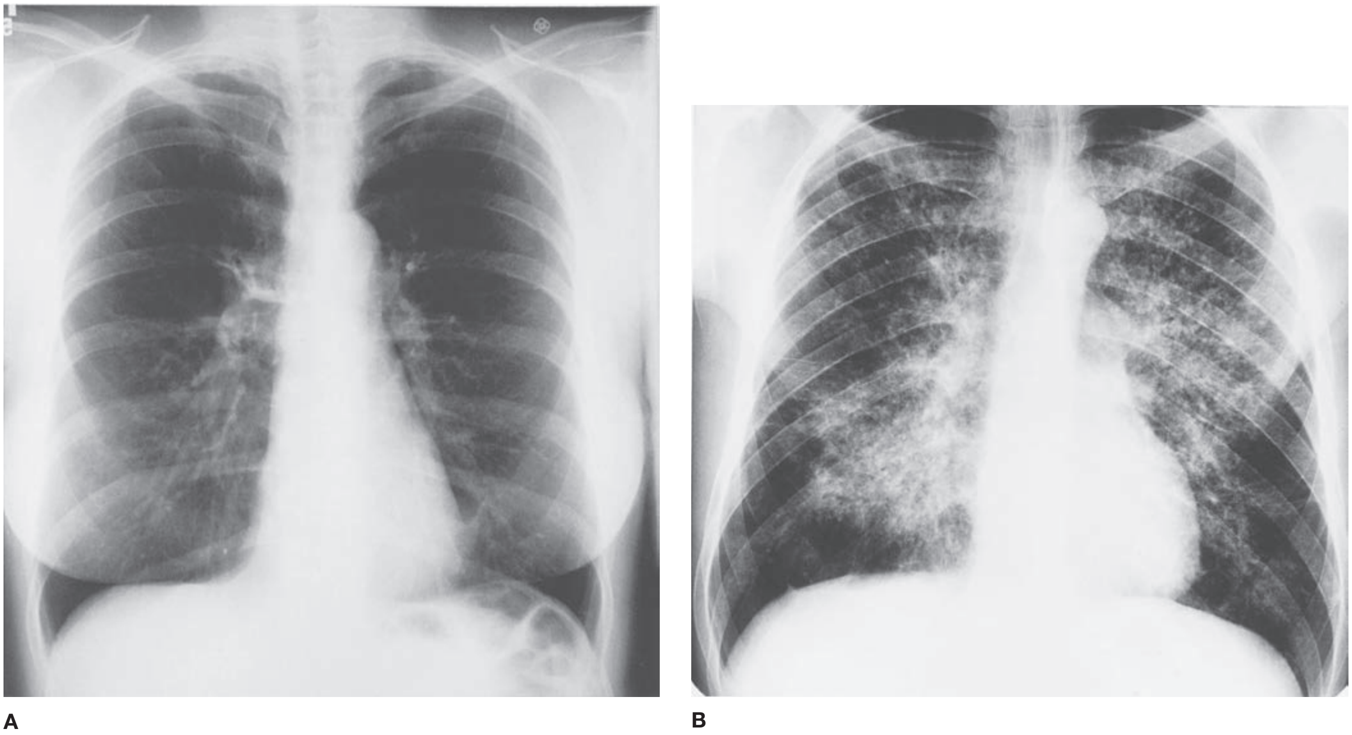


Figure 27-1 Exposure in an endemic area. **A.** Clear lung fields. **B.** South American blastomycosis. *(Reproduced with permission from Dr. Nelson Porto.)*

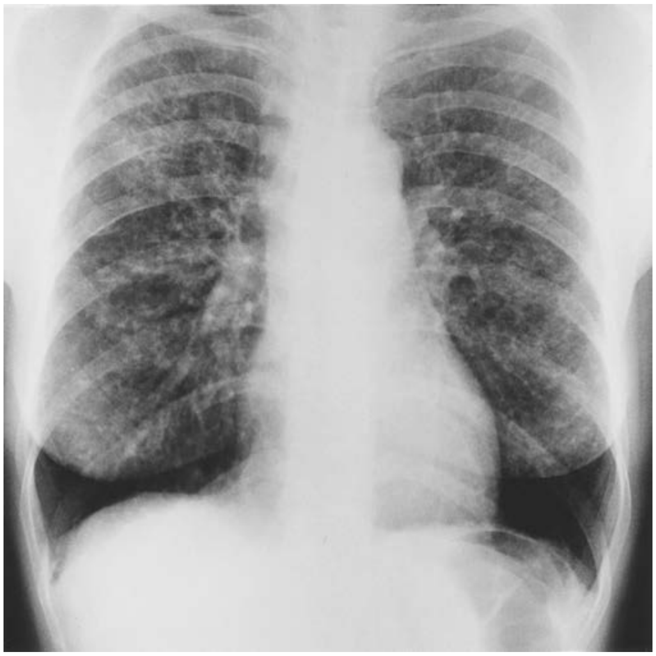


Figure 27-2 Nitrofurantoin hypersensitivity pneumonitis. The ingestion of nitrofurantoin was accompanied by the appearance of patchy interstitial and alveolar changes throughout both lungs.

Indeed, many pharmacologic agents, including chemotherapeutic and nonchemotherapeutic agents, have a propensity for inflicting lung damage (see Chapters 65 and 66). Classic examples include bleomycin, nitrofurantoin, and methotrexate (Fig. 27-2), but the number of drugs implicated in producing lung injury has grown exponentially in recent years. Beta blockers, administered as part of a cardiac regimen, may evoke bronchoconstriction. Even a common medication, such as aspirin, may, on rare occasion, cause a severe pulmonary disorder (e.g., pulmonary edema).

Finally, the family history is an essential ingredient of the medical inventory. This history can uncover a heritable disease of the lungs (e.g., cystic fibrosis [CF], α_1-antitrypsin deficiency, alveolar microlithiasis, hereditary telangiectasia).

PHYSICAL EXAMINATION

Before the widespread use of chest radiography, physical examination, along with the history, played a pivotal role in the diagnosis of pulmonary disease. The advent of chest radiography and chest CT imaging has de-emphasized the value of the physical examination. Nonetheless, the physical examination remains a valuable diagnostic measure in the appraisal of chest disease.[3,4]

■ General Aspects

Important clues are often available before examination of the chest. For example, neglected pyorrheal teeth raise the prospect of necrotizing aspiration pneumonia. A lacerated tongue suggests that a convulsive episode may have led to aspiration (Fig. 27-3). Pursing of the lips during expiration ("pursed-lip breathing") may be seen in patients with chronic obstructive pulmonary disease (COPD). Subtle changes in consciousness or coordination may signal that metastasis has occurred to the brain from a primary carcinoma of the lung. In the patient with COPD, a clouded sensorium or a disturbed personality can signify acute elevation in arterial P_{CO_2}.

Inspection of the skin often provides clues to diseases of the chest; a more detailed discussion of notable cutaneous manifestations in respiratory disorders is provided later in this chapter. Evidence to support the diagnosis of pulmonary sarcoidosis may be found in the eyes and skin. Petechiae, purpura, necrosis, and/or ulceration of the skin may reflect a systemic vasculitis. The skin lesions of neurofibromatosis type 1 (von Recklinghausen disease) may signify that a solitary pulmonary nodule in the paraspinal region may be a neurofibroma. A minute skin abscess may turn out to be the source of multiple lung abscesses. Distinctive scars over the antecubital veins of a drug addict can help to clarify the etiology of old lesions in the lungs, as well as of a newly discovered lung abscess. Erythema nodosum (EN) is frequently due to sarcoidosis, but may also occur in patients with tuberculosis, histoplasmosis, or coccidioidomycosis. Skin papules in Birt–Hogg–Dubé syndrome

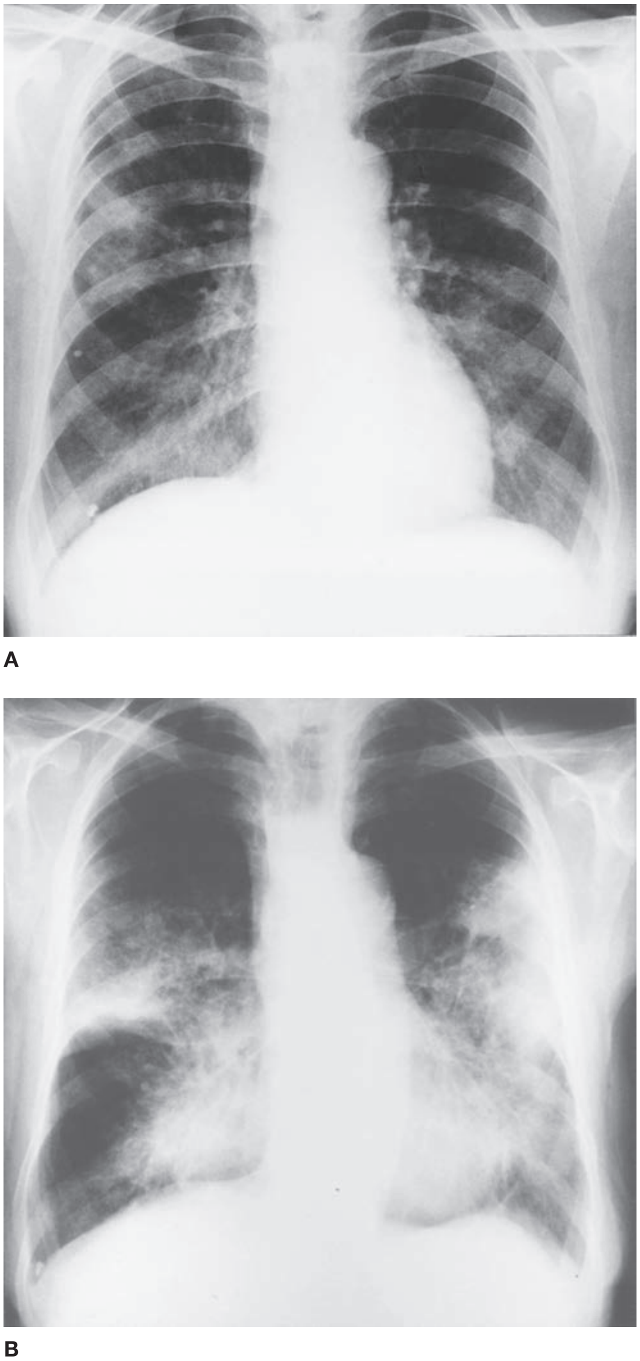


Figure 27-3 Chronic aspiration pneumonia. **A.** Chronic aspiration pneumonia in a 72-year-old man hospitalized for repair of hernia. Patchy infiltrates bilaterally. No pulmonary symptoms. Initiating cause was achalasia of esophagus. **B.** Eighteen months later. Persistent cough and breathlessness.

TABLE 27-1 Clinical Disorders Commonly Associated with Clubbing of Digits

Pulmonary and thoracic
Primary lung cancer
Bronchiectasis
Cystic fibrosis
Lung abscess
Pulmonary fibrosis
Pulmonary arteriovenous malformations
Empyema
Mesothelioma
Neurogenic diaphragmatic tumors
Cardiac
Congenital
Subacute bacterial endocarditis
Gastrointestinal and hepatic
Hepatic cirrhosis
Chronic ulcerative colitis
Regional enteritis (Crohn's disease)

(see "Pulmonary-Cutaneous Syndromes," below) may antedate the pulmonary manifestations of cystic lung lesions and pneumothorax by decades.[5]

A variety of endocrine syndromes may accompany carcinoma of the lung. An altered mental status may be due to hyponatremia caused by the syndrome of inappropriate antidiuretic hormone (SIADH). Clubbing of the digits may accompany various clinical disorders, including idiopathic pulmonary fibrosis, bronchiectasis, and certain carcinomas of the lung (Table 27-1).[6] A puffy face, neck, and eyelids, coupled with dilated veins of the neck, shoulder, thorax, and upper arm (i.e., superior vena cava syndrome) may constitute the first clinical evidence of obstruction of the superior vena cava by a neoplasm of the lung. Although the causes of superior vena cava syndrome are many and diverse, at least 80% are attributable to a primary carcinoma of the lung (Fig. 27-4). In the patient in whom a neoplasm has evoked acute signs and symptoms of increased systemic venous pressure that progresses rapidly (e.g., to laryngeal edema), early diagnosis and prompt treatment of the neoplasm can be lifesaving. The presence of Horner syndrome—unilateral ptosis, miosis, and anhidrosis—in a patient with a carcinoma of the lung suggests a pulmonary sulcus tumor with involvement of the ipsilateral sympathetic pathway within the thorax (Fig. 27-5).

■ Inspection of the Chest

Observation of the chest from the foot of the bed can be informative: a visible lag in expansion of one side of the thorax localizes a pleural effusion, pulmonary infection, or paralyzed diaphragm. The respiratory pattern may be informative: patients with severe airflow obstruction often take slow, deep breaths, whereas rapid and shallow breaths are often seen with restrictive processes, such as interstitial lung disease or kyphoscoliosis. Inspection of the chest and abdomen in the supine position may reveal paradoxical inward movement of the abdomen, indicative of respiratory muscle weakness.[7]

■ Palpation of the Chest

Over the years, the role of palpation in examination of the chest has been considerably devalued. Nonetheless, palpation may provide helpful diagnostic clues as well as confirmatory evidence for other

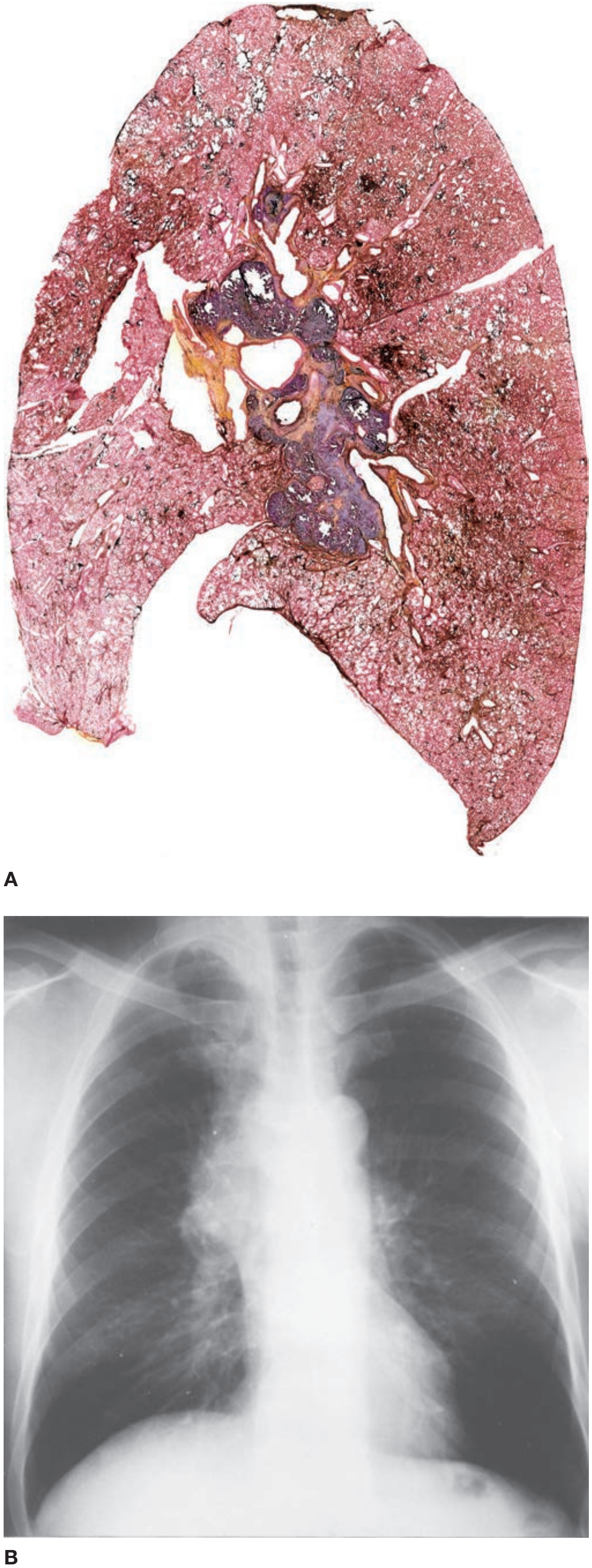


Figure 27-4 Local invasiveness of carcinoma of the lung. **A.** Sagittal section of the lung illustrating a carcinoma *(blue)* of the lung in the vicinity of the hilus. **B.** Chest radiograph showing right hilar mass.

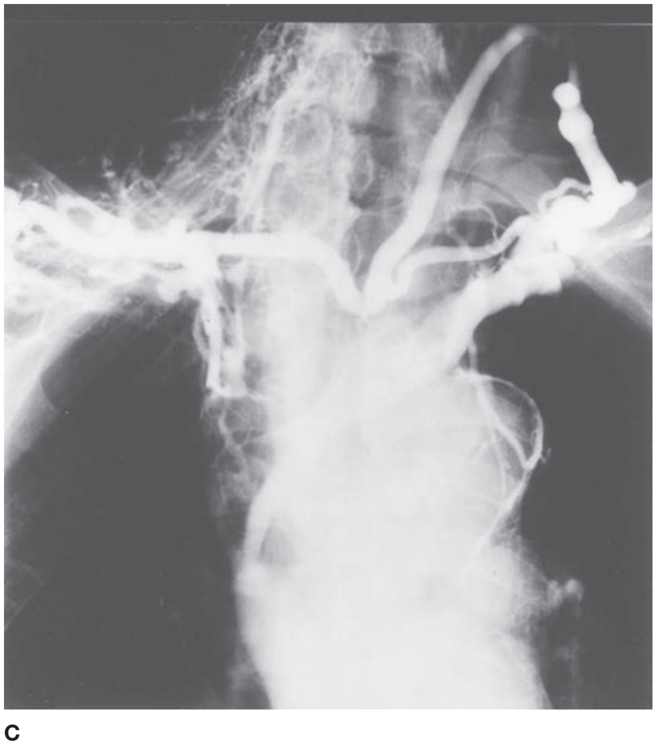


Figure 27-4 *(Continued)* **C.** Angiogram showing obstruction and extensive collateral circulation.

physical signs. For example, the position of the trachea determined by palpation in the suprasternal notch may be helpful in detecting a lateral displacement of the upper mediastinum. Displacement of the apical impulse and of cardiac dullness may be useful indices in detecting shift of the lower mediastinum. Tenderness over a rib may reflect a fracture, metastasis, or underlying pleuritis. Enlargement of the right ventricle can be readily detected by palpation in the subxiphoid region. *Hoover sign* may be useful in disclosing a unilateral lag in motion of one side of the chest due to pleuritis or a pleural effusion. The sign is elicited by comparing the displacement from the midline during a patient's deep inspiration of the examiner's hands, each placed lightly over one hemithorax, with thumbs touching beneath the xiphoid at the start of the breath.

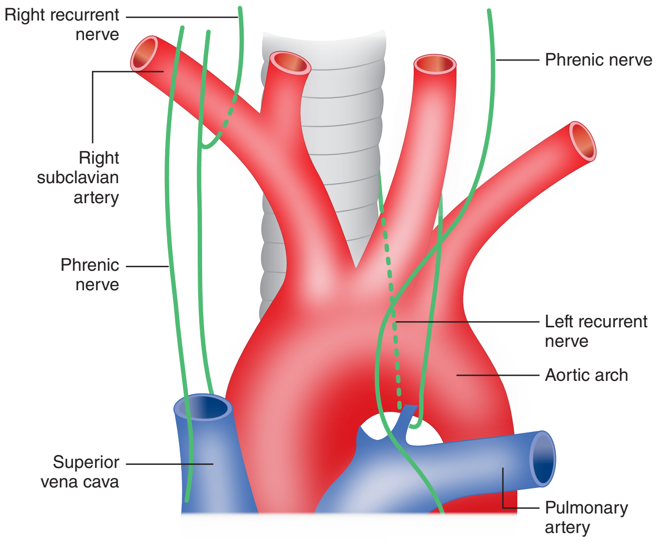


Figure 27-5 Courses of the recurrent laryngeal nerves. Invasion or compression of a nerve by a carcinoma of the lung causes paralysis of the vocal cord.

An abnormal mass or fullness palpated in the supraclavicular space may be a clue to a neoplasm or an involved lymph node and suggests a convenient location to obtain a biopsy for diagnosis.

Consolidation of the lung, which causes increased transmission of sound, can be detected as fremitus (i.e., as a palpable vibration) over the affected area while the patient repeatedly vocalizes the traditional "one, two, three" as the examiner moves his or her palms systematically over the two hemithoraces. Conversely, impairment of sound transmission, as by a pleural effusion, diminishes vocal fremitus. In some instances, a pleural friction rub is palpable.

■ Percussion of the Chest

Percussion as part of the physical examination follows Auenbrugger sounding of beer barrels to determine their fluid levels. The response to percussion is impaired whenever something other than air-filled lung lies directly beneath the chest wall. Common causes of dullness to percussion are consolidation or atelectasis of the lung, fluid in the pleural space, pleural thickening, and a large mass at the surface of the lung. Widespread hyperresonance may be elicited in emphysema, and circumscribed hyperresonance over a pneumothorax or large bulla.

■ Auscultation of Lungs

Ever since the time of Laennec, physicians have applied a stethoscope to the chest in search of sounds of disease.[8] Attention is focused on the intensity and quality of the sounds, as well as on the presence of abnormal (often called "adventitious") lung sounds.[9] Other devices have been used to assess sounds generated by breathing.[10,11] Web sites providing access to audio files demonstrating normal and adventitious breath sounds are available (e.g., www.easyauscultation.com/lung-sounds).[12] The advent of bedside ultrasonography has greatly augmented clinical assessment of patients with respiratory complaints (see Chapter 29).

Changes in the Intensity and Duration of Lung Sounds

The generation of lung sounds requires an ability to move air through patent airways. A global decrease in the intensity of breath sounds over the thorax or a hemithorax may be due to a variety of abnormalities: impaired movement of air due to airways disease (e.g., in emphysema), paralysis of a diaphragm, or complete obstruction of a bronchus. A decrease in audible breath sounds may also occur when the transmission of sounds to the chest wall is impaired (e.g., by a pleural effusion, pleural thickening, or a pneumothorax). A bulla gives rise to a more circumscribed diminution in breath sounds. In a patient with COPD, regional variations in breath sounds correspond to the distribution of ventilation. With adequate pressure of the diaphragm of the stethoscope, it is possible to auscultate the lungs as effectively through thin clothing as over bare skin; of course, this approach hinders inspection and percussion.[13]

An abnormal increase in intensity of breath sounds is accompanied by a change in their character. (The sounds become either harsh or bronchial.) The abnormal sounds are heard over consolidated, atelectatic, or compressed lung as long as the airway to the affected portion of the lung remains patent. Consolidated lung is presumed to act as an acoustic conducting medium that, unlike normal lung, does not attenuate transmission of tracheal sounds to the periphery.

Noting the duration of the inspiratory and expiratory phases of breathing may be useful. Inspiration is normally audible for a longer period, with little, if any, expiratory noise. A prolongation of expiration, often longer than inspiration, is found with obstructed airways.

Changes in the Transmission of Lung Sounds

Changes in voice sounds are often easier to appreciate than changes in breath sounds. Large pleural effusions, pneumothorax, and bronchial occlusion produce distant or inaudible breath sounds. Transmission of voice sounds is enhanced by consolidation, infarction, atelectasis, or compressions of lung tissue. Accompanying the increased transmission is a change in the character of the voice sounds that causes them to be higher pitched and less muffled than normal *(bronchophony)*. When bronchophony is extreme, spoken words assume a nasal or bleating quality *(egophony)* and the sound "ee" is heard through the stethoscope as "ay."[14] Egophony is most common when consolidated lung and pleural fluid coexist; sometimes it is heard over an uncomplicated lobar pneumonia or pulmonary infarction. Transmission of whispered voice sounds with abnormal clarity *(whispered pectoriloquy)* has the same significance as bronchophony.

Changes in the Quality of Lung Sounds

Normal breath sounds have a smooth, soft quality and are described as *vesicular*. Abnormal, or adventitious, lung sounds have traditionally been resistant to meaningful clinical classification. However, a rational, clinically useful set of definitions based on acoustic analysis of tape recordings and the nomenclature introduced by Forgacs is commonly employed (Table 27-2). Using this approach, lung sounds are categorized as continuous (*wheezes*, *rhonchi*, or *stridor*) or discontinuous *(crackles)*.

Wheezes, rhonchi, and stridor are musical adventitious sounds. Wheezes originate in airways narrowed by spasm, thickening of the mucosa, or luminal obstruction. Although wheezes are more apt to occur during forced expiration (which further narrows airways), they may occur during both inspiration and expiration in asthma. Wheezes presumably originate through a combination of limitation to airflow and vibrations in the walls of the airways. Rhonchi are due to the presence of liquid or mucus in the airways; the quality and location may be readily changed by asking the patient to cough, thus moving the secretions. Stridor is predominantly inspiratory and best heard over the neck. Common causes of stridor are a foreign body in the upper intrathoracic airway or esophagus, an acquired lesion of the airway (e.g., carcinoma in adults), or a congenital lesion in children.

TABLE 27-2 Classification of Common Lung Sounds

Acoustic Characteristics	American Thoracic Society Nomenclature	Common Synonyms
Discontinuous, interrupted explosive sounds; loud, low in pitch	Coarse crackle	Coarse rale
Discontinuous, interrupted explosive sounds; less loud than above and of shorter duration; higher in pitch than coarse crackles or rales	Fine crackle	Fine rale, crepitation
Continuous sounds longer than 250 ms, high-pitched; dominant frequency of 400 Hz or more, hissing sound	Wheeze	Sibilant rhonchus
Continuous sounds longer than 250 ms, low-pitched; dominant frequency about 200 Hz or less, snoring sound	Rhonchus	Sonorous rhonchus

Adapted with permission from Loudon R, Murphy RLH. Lung sounds. Am Rev Respir Dis. 1984;130(4):663–673.

Crackles are generally attributed to a rapid succession of explosive openings of small airways that closed prematurely during the previous expiration.[15] Crackles have been subdivided according to their timing during inspiration (early or late) and by differences in their quality ("wet" or "dry"); at times they have been termed "*rales*." Noting differences in timing has been advocated as a way of distinguishing between possible causes (e.g., "dry" crackles in the fibrosis of interstitial lung disease vs. "wet" crackles in pulmonary edema).[16] Unfortunately, wide variation in the interpretation of these sounds generally renders such attempts at classification of little value and often a cause of confusion. Crackles may accompany alterations in the elastic recoil of airways (emphysema), the presence of secretions (bronchitis or pneumonia), inflammation or fibrosis (interstitial lung disease), or fluid (pulmonary edema). Crackles may also be due to atelectasis, as noted in bedridden patients, and may clear with sequential deep breaths.

Pleural Rub

A pleural friction rub is a coarse, grating, or leathery sound that is usually heard late in inspiration and early in expiration; most often a pleural friction rub is audible low in the axilla or over the lung base posteriorly. The rub sounds close to the ear and usually is not altered by coughing.

DYSPNEA

Dyspnea is the medical term for breathlessness or shortness of breath.[17] The American Thoracic Society has published a comprehensive discussion of the topic.[18] For the patient, dyspnea involves an experience of discomfort in breathing. It is alarming to most and may arouse great concern about a potential dire cause, making it one of the most frequent complaints prompting patients to seek medical evaluation.

In the extensive medical, physiologic, and psychological literature, dyspnea is used variously to designate a variety of sensations, ranging from awareness of breathing on the one hand to respiratory distress on the other. The wide range of meanings is understandable on several counts: (1) dyspnea is a subjective complaint without consistency in objective signs such as tachypnea; (2) few physicians have experienced the respiratory discomfort associated with chest disease, so that most interpretations of the complaint represent extrapolations from normal breathlessness (e.g., after strenuous exercise); (3) most experimental observations relating to dyspnea are based on the study of normal subjects or animals under artificial circumstances; and (4) most physicians apply the term loosely, based on their experience with the predominant patient population that they serve (e.g., patients with COPD or asthma). Despite this variability, in clinical medicine, the complaint of dyspnea almost invariably implies respiratory discomfort.

Because of its subjective nature, the sensation of dyspnea is an amalgam of two components. The first is the sensory input to the cerebral cortex, which consists of information from specialized receptors, predominantly mechanoreceptors, at various sites in the respiratory apparatus (predominantly the upper airways) and face (Fig. 27-6). The different sites of stimulation may contribute to disparities in the sensation. Furthermore, no specific area in the central nervous system (CNS) has been identified as the sensory locus for dyspnea. The input—from airways, lungs (via the vagus nerves), respiratory muscles, chest wall, and chemoreceptors—is processed at consecutive levels of the nervous system (i.e., spinal cord and supraspinal regions en route to the sensorimotor cortex). Additional sensory input, triggered by inadequate oxygen delivery or utilization, is poorly understood. The second component is the perception

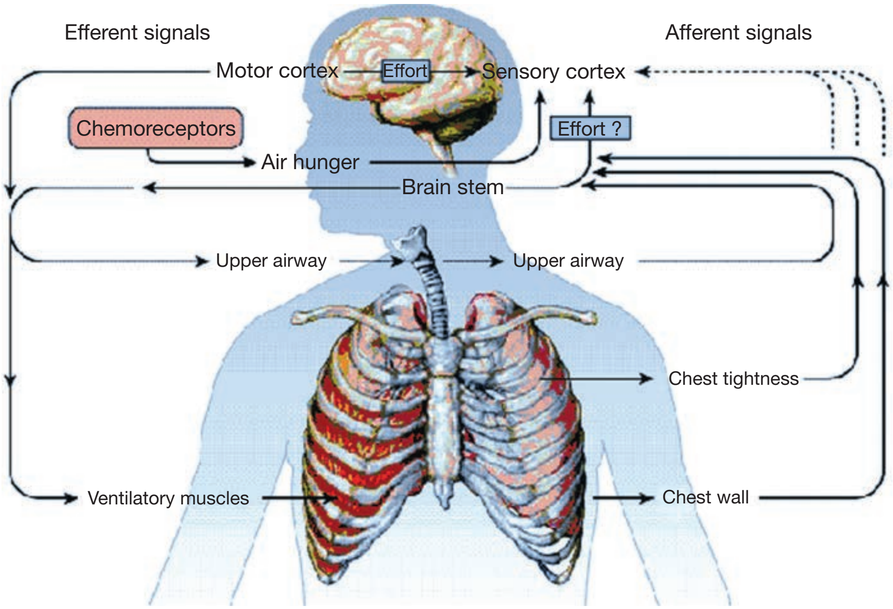


Figure 27-6 Pathways to the sensation of breathlessness. Respiratory effort is believed to originate as a signal transmitted from the motor cortex simultaneously to the sensory cortex and to the motor command to ventilatory muscles. The brain stem may also contribute to the sense of effort. The perception of air hunger is believed to arise, in part, from increased respiratory activity within the brain stem, whereas the sensation of chest tightness probably results from stimulation of vagal irritant receptors. Although afferent information from airway, lung, and chest-wall receptors most likely passes through the brain stem before reaching the sensory cortex, the *dashed lines* indicate uncertainty about whether some afferents bypass the brain stem and project directly to the sensory cortex. *(Reproduced with permission from Manning HL, Schwartzstein RM. Pathophysiology of dyspnea. N Engl J Med. 1995;333(23):1547–1553.)*

of the sensation, which rests heavily on the interpretation of information arriving at the sensorimotor cortex. The interpretation depends greatly on the psychological makeup of the person.

A variety of influences may modify the psychological component of dyspnea. During "Kussmaul breathing" (see below), "air hunger" may seem obvious to the observer, even though the patient does not feel short of breath. In contrast, patients with congestive heart failure or COPD frequently volunteer the complaint of "air hunger." Blunting of the sensorium, as by narcotics or by acute hypercapnia, can eliminate the sensation of breathlessness, even though the abnormal breathing pattern remains. Anxiety may heighten the sense of breathlessness. Indeed, anxiety may be responsible for the clinical syndrome of psychogenic dyspnea, in which the patient experiences "breathing discomfort" that eludes explanation on the basis of a somatic cause. Ill-defined sensations may accompany a full-blown hyperventilation syndrome, consisting of lightheadedness, tingling of the hands and feet, tachycardia, inversion of T waves on the electrocardiogram, and even syncope. Breathing discomfort at rest that decreases with activity is often seen when anxiety or other psychological issues are the cause and is a distinctly unusual pattern for dyspnea due to a cardiopulmonary abnormality.

The quality of dyspnea can vary greatly. In normal persons, as well as in those with chest disease, dyspnea may simply signify the transition from an effortless process that is ordinarily conducted at a subconscious level to the awareness that muscular effort is being expended in breathing.[19] The healthy athlete completing a sprint experiences breathlessness that can be exhilarating, rather than uncomfortable. The asthmatic often interprets breathlessness in terms of "tightness in the chest." The patient with COPD often complains of less severe breathlessness than would be expected from the degree of airway obstruction, possibly reflecting adaptation, either to the chronic obstructive airway disease or to CO_2 retention.

Patients may use different terms to describe breathing discomfort due to various causes.[20–25] In some instances these descriptors may be useful in establishing a differential diagnosis and in assessing the response to therapy.[26] Patients with asthma or myocardial ischemia often refer to "chest tightness."[27] Patients with pulmonary edema may suffer a sensation of "air hunger" or "suffocation."[28] Patients with COPD and hyperinflation of the chest often note an inability to take a deep, satisfying breath. Individuals who are deconditioned may complain of "heavy breathing." Unfortunately, no descriptor has sufficient sensitivity or specificity to be used alone in establishing the cause of a patient's dyspnea. Ethnic and gender differences in the descriptors and perceptions related to dyspnea have been reported.[29,30]

Clinical Presentations

Dyspnea may be acute, chronic, or paroxysmal (Table 27-3).

TABLE 27-3 Common Causes of Acute and Chronic Dyspnea[a]

Acute
Pulmonary edema
Asthma
Injury to chest wall and intrathoracic structures
Spontaneous pneumothorax
Pulmonary embolism
Pneumonia
Adult respiratory distress syndrome
Pleural effusion
Pulmonary hemorrhage
Foreign body aspiration
Vocal cord dysfunction
Chronic, progressive
Chronic obstructive pulmonary disease
Left ventricular failure
Diffuse interstitial fibrosis
Asthma
Pleural effusions
Pulmonary thromboembolic disease
Pulmonary vascular disease
Psychogenic dyspnea
Anemia, severe
Postintubation tracheal stenosis
Hypersensitivity disorders

[a] *Many chronic processes (e.g., left ventricular failure, asthma, and COPD) may have acute exacerbations.*

Acute Dyspnea

The usual causes of acute dyspnea in children differ from those in adults. In children, upper airway infection (e.g., epiglottis, laryngitis, or acute laryngotracheobronchitis) is a common cause. In adults, the causes of acute dyspnea are much more varied (Table 27-3). Among the most common are acute left ventricular failure, pulmonary thromboembolism, pneumonia, and spontaneous pneumothorax. Less common, but not unusual, is massive collapse of one lung due to inability to clear the airways of thick, tenacious secretions (e.g., in chronic bronchitis or asthma) or the first attack of asthma.

Chronic Dyspnea

Chronic dyspnea is almost invariably progressive. As a rule, this type of dyspnea begins with breathlessness on exertion—which, in time, progresses to dyspnea at rest. Pulmonologists encounter dyspnea in patients who have COPD; cardiologists more often deal with dyspnea in patients who are in chronic congestive heart failure. Especially in older patients, distinction between the heart and lungs in the etiology of dyspnea, or the relative contributions of each, can be difficult to establish.

Asthma is a common cause of recurrent bouts of dyspnea, which are usually accompanied by cough and wheezing. Cardiac dysfunction is another cause of acute bouts of bronchospasm, especially in middle-aged or elderly persons.

■ Physiologic Correlates of Dyspnea

Historically, attempts to understand the physiologic basis of dyspnea have evolved along four separate lines: ventilatory performance, the mechanics of breathing, chemoreception, and exercise testing. Exercise testing is presented in Chapter 32.

Ventilatory Performance

Early investigations related the sensation of dyspnea to the level of minute ventilation. Dyspnea was found to correlate with excessive minute ventilation relative to the level of oxygen uptake. Most of the increase in ventilation was accounted for by an increase in respiratory rate, especially in patients with stiff lungs. In patients who continued to ventilate excessively for the level of oxygen uptake (e.g., those with chronic left ventricular failure), the sensation of breathlessness gradually diminished, suggesting adaptation to the continued stimulus.

A second ventilatory measurement that proved to correlate well with dyspnea is the maximum voluntary ventilation (MVV). MVV is decreased by diseases of the lungs, airways, or chest wall. The smaller the MVV, the more likely is dyspnea to occur.

A third time-honored approach to measurement is the "breathing reserve." This value is determined as the difference between the MVV and the actual minute ventilation. In principle, the sensation of breathlessness during the performance of any ventilatory task may be related to the fraction of the maximum breathing capacity (i.e., the MVV) that is used for force generation by the respiratory apparatus. Thus, the closer the minute ventilation is to the maximum breathing capacity, the more likely is the subject to complain of breathlessness. Indeed, when the actual level of ventilation reaches 30% to 40% of the maximum breathing capacity, dyspnea is inevitable. Unfortunately, the breathing reserve correlates better with the dyspnea of normal subjects during exertion than with the dyspnea of chronic bronchitis and COPD or of left ventricular failure. Thus, in COPD the minute ventilation may be a very large fraction of the MVV (>50%) without eliciting dyspnea. In contrast, in acute left ventricular failure, a mild increase in ventilation and a nearly normal MVV may be associated with considerable breathlessness.

Mechanics of Breathing

One teleologic way to regard dyspnea is as a sensation that prompts an unconscious effort to minimize the work, energy cost, or force of breathing. In this light, dyspnea protects the respiratory apparatus from overwork and inefficient operation. This approach has led to exploration of the relationships between dyspnea and the work or oxygen cost of breathing.

Work, Oxygen Cost, and Efficiency of Breathing

It has not been possible to identify a critical level for the work of breathing at which dyspnea will occur. However, a breakdown of the work of breathing into its elastic, resistive, and inertial components has helped to relate physiologic disturbances to particular diseases. For example, in chronic mitral stenosis with pulmonary congestion, the elastic work is greatly increased (Fig. 27-7), whereas in obstructive airway disease, resistive work predominates. Moreover, such observations have reinforced the concept that patterns of breathing are automatically adjusted to minimize the work done by the respiratory muscles in breathing.

The relationship between ventilation and O_2 consumed by the respiratory muscles is curvilinear (Fig. 27-8). This O_2 cost of breathing may increase extraordinarily in patients with COPD or with abnormalities of the chest wall. Indeed, in patients with COPD, the quantity of O_2 delivered to the respiratory muscles during the large ventilatory effort may fail to satisfy their aerobic needs, leading to anaerobic metabolism and lactic acidosis. Although the greater the O_2 cost of breathing the greater the likelihood of dyspnea, the determination of O_2 cost provides no more useful insight into the mechanism of dyspnea than does the work of breathing. Calculation of the efficiency of breathing (i.e., the work of breathing related to energy cost) provides no further clarification.

Length–Tension Inappropriateness

The concept of "length–tension inappropriateness" explains dyspnea as a mismatch between the central motor command to the respiratory muscles (i.e., the motor signal emitted from the brain) and the suboptimal ("inappropriate") shortening of the respiratory muscles elicited by this command (e.g., suboptimal thoracic expansion for any level of central motor command).[31] In essence, this concept pictures a decrease, instead of an increase, in the pressure-generating capacity of the respiratory muscles in the face of the increased need arising from the heightened respiratory drive.

Chemoreception

Chemoreceptors in the medulla respond to changes in pH and Pa_{CO_2} (see Chapter 11). Peripheral receptors in the aortic arch and carotid body also respond to alterations in Pa_{O_2}. Acute hypoxia, hypercapnia, and acidosis are the traditional stimuli for ventilation. For example, upon ascent to altitude, acute hypoxia can stimulate ventilation to the level of awareness that may progress to discomfort during exertion. The effects of these stimuli on breathing decrease if they continue unabated. In addition, side effects, such as blunting of the sensorium during chronic CO_2 retention, diminish the likelihood of dyspnea, even if the level of ventilation is increased. In patients with abnormal pulmonary mechanics, the onset of abnormalities in blood gas composition, as during exercise, may aggravate or contribute to dyspnea. In general, acute hypercapnia is a stronger stimulus for dyspnea than is acute hypoxia.

■ Scaling

A variety of scaling methods have been devised to quantify dyspnea during exercise and various experimental settings. Some, such as the Borg Category Scale (Table 27-4), use numbers and descriptive terms to depict a change in the intensity of the stimulus ("threshold stimulus detection methods"). Others rely on visual analog scales, which are straight lines, usually 10 cm long, that extend from "not breathless" at one end to "extremely breathless" at the other. The

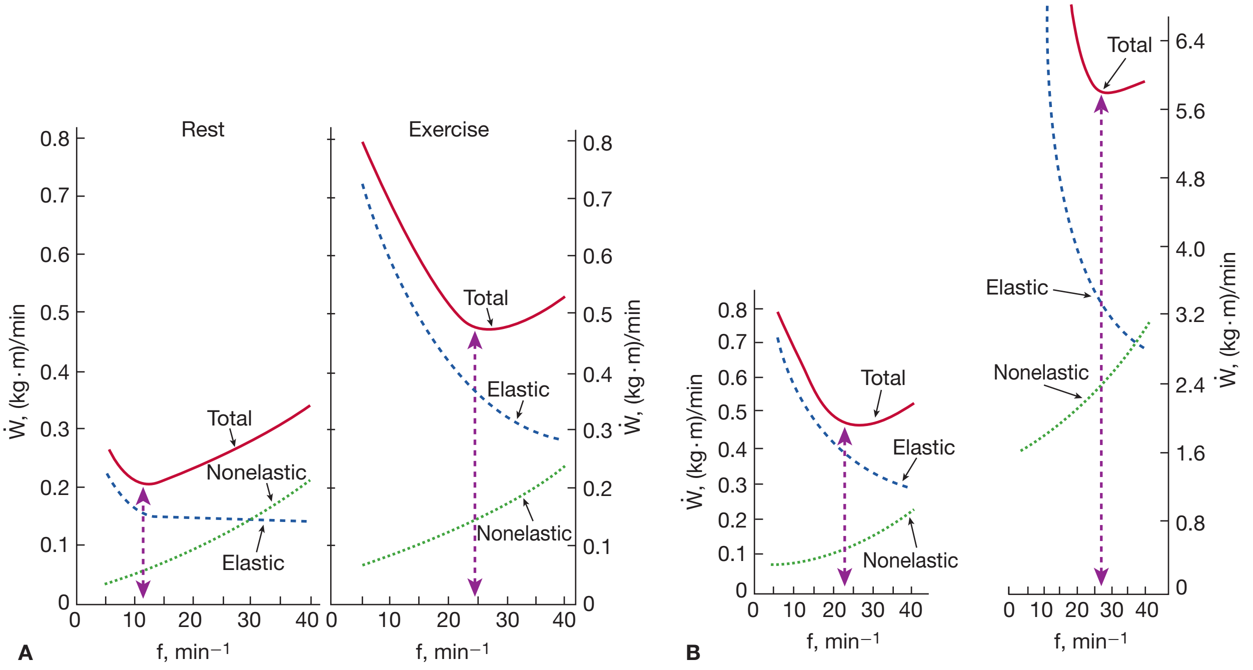


Figure 27-7 Partition of the work of breathing in pulmonary congestion and edema at rest and during exercise. **A.** Normal. The minimal work of breathing at rest was at a respiratory frequency of 12 breaths/min; during exercise, the minimal work was done at a higher frequency (25 breaths/min). **B.** Mitral stenosis. At rest, the frequency for least respiratory work was abnormally high (22 breaths/min); during exercise it increased further (to 28 breaths/min). The *dashed vertical line* (capped by *arrowheads*) in each frame indicates the respiratory frequency at which respiratory work was minimal. f, respiratory frequency. *(Reproduced with permission from Christie RV. Dyspnea in relation to the visco-elastic properties of the lung. Proc R Soc Med. 1953;46(5):381–386.)*

patient marks on the line the intensity of respiratory discomfort elicited by external stimuli, such as resistive loads or exercise testing. The score is measured as the length of the line between "not breathless" and the mark made by the patient. The Shortness of Breath Scale issued by the American Thoracic Society (Table 27-5) and the Medical Research Council (MRC) Dyspnea Scale have also been used in one form or another, particularly in epidemiologic studies. A method of quantifying dyspnea severity that utilizes patient descriptors appears to be applicable and reproducible in a variety of disorders.[32]

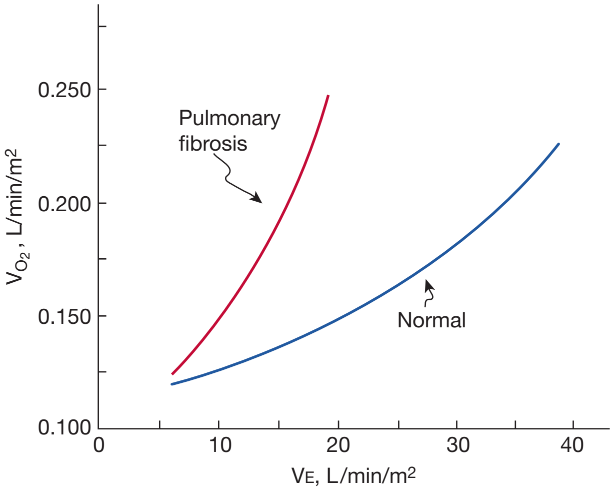


Figure 27-8 Oxygen cost of breathing in restrictive lung disease. Relationship between ventilation and O_2 consumption in pulmonary fibrosis. At each level of ventilation, the patient with pulmonary fibrosis does more work and expends more energy in breathing than does the normal subject.

DYSPNEA IN OBSTRUCTIVE AND RESTRICTIVE PULMONARY DISORDERS

Two common pathophysiologic categories of pulmonary disease in which dyspnea features prominently are chronic obstructive airway disease and restrictive pulmonary disorders.

Chronic Obstructive Airway Diseases

Several chronic obstructive airway diseases associated with dyspnea are well recognized, including COPD and asthma.

COPD

COPD refers to a spectrum of airway diseases in which obstruction to airflow is the common denominator (Chapters 39 and 40). Cigarette

TABLE 27-4 Modified Borg Category Scale

Rating	Intensity of Sensation
0	Nothing at all
0.5	Very, very slight (just noticeable)
1	Very slight
2	Slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

TABLE 27-5 American Thoracic Society Shortness of Breath Scale

Descriptions	Grade	Degree
Not troubled by shortness of breath when hurrying on the level or walking up a slight hill	0	None
Troubled by shortness of breath when hurrying on the level or walking up a slight hill	1	Mild
Walks more slowly than people of the same age on the level because of breathlessness or has to stop for breath when walking at own pace on the level	2	Moderate
Stops for breath after walking about 100 yards or after a few minutes on the level	3	Severe
Too breathless to leave the house; breathless on dressing or undressing	4	Very severe

smoking is the leading cause of COPD (Chapter 41). The outer limits of the spectrum are marked by chronic bronchitis at one end and emphysema at the other. Most patients with COPD fall into categories between those limits (i.e., they manifest mixtures of chronic bronchitis and emphysema, which vary in degrees) (Fig. 27-9).

Patients with COPD suffer from disturbances in the mechanics of breathing, abnormal lung volumes, and derangements in gas exchange. The minute ventilation, which may be only slightly increased at rest, constitutes an abnormally large fraction of the maximum breathing capacity (i.e., the "breathing reserve" is low).

Abnormalities in the mechanics of breathing dominate the scene: resistance to airflow is high; the thorax assumes a hyperinflated position, placing the inspiratory muscles at mechanical disadvantage; the work of breathing is greatly increased. The O_2 cost of breathing is correspondingly high. Derangements in dead space ventilation and in alveolar–capillary gas exchange add to the afferent stimuli. As a result of the disturbances in mechanics and gas exchange, swings in pleural pressure (a measure of force applied to the lungs) are large, and a considerable muscular effort is expended in breathing; instead of the normal increase of about 1 mL of O_2 uptake per liter of ventilation per minute, the O_2 uptake increases enormously (up to 25 mL/min). Should O_2 delivery to the overworked respiratory muscles be insufficient, fatigue and exhaustion may send nervous and chemical signals of their own to the brain. Finally, if the patient accumulates excess water in the lungs, the juxtacapillary ("J") receptors provide additional sensory input to the central integrating mechanism. As noted above (see "Length–Tension Inappropriateness"), the convergence of these diverse stimuli upon the sensorimotor cortex may generate an inordinate motor command to the respiratory muscles, which cannot mobilize the thorax sufficiently to generate the pleural pressures needed for adequate ventilation.

One enigma is why patients with COPD maintain different levels of ventilation despite equal abnormalities in conventional pulmonary function tests. The "CO_2 retainer," with respiratory acidosis and arterial hypoxemia, often breathes less than does the non–CO_2 retainer in whom blood gas levels are near normal. One teleologic explanation is that the lower ventilation in the CO_2 retainer causes less dyspnea. However, this explanation affords no insight into the physiologic mechanism.

Treatment of the patient with COPD is directed at diminishing airways resistance and restoring arterial blood gases toward normal. Unfortunately, bronchodilators generally have only modest effects, and the basic abnormalities in the mechanics of the lungs and airways remain. Consequently, the load on the respiratory muscles is not readily alleviated by medical management. Management strategies also include consideration of ways in which the performance of the respiratory muscles can be improved. These have generally taken the form of training exercises to facilitate adaptive changes and to increase both muscle strength and endurance. Exercise reconditioning in patients with COPD has been shown to diminish breathlessness, possibly owing to three interactive mechanisms: (1) increased mechanical efficiency of the exercising muscles, which decrease ventilatory requirements; (2) improved function of the respiratory muscles; and (3) increased tolerance of the "dyspneagenic" sensory input to the brain. Attempts to rest the respiratory muscles have no lasting effect on dyspnea.

Asthma

Asthma constitutes a different entity, not only in its clinical expressions but also because it is usually episodic and is often related to allergic manifestations, and generally affects younger individuals (Chapters 43 to 45).

The mechanisms described previously for COPD apply as well to asthma. However, these mechanisms do not account for the sensation of "tightness in the chest" or the inordinate sense of labored breathing that accompanies the breathlessness in asthma.

■ Restrictive Ventilatory Defects

Restrictive ventilatory defects are due to a variety of causes, ranging from lung disorders to diseases that affect the pleural space, as well as neuromuscular diseases that affect the function of the thorax (Table 27-6). Diffuse interstitial disease has many different etiologies and may be either acute or chronic (Table 27-7). Characteristically, in widespread interstitial disease the diffusing capacity is low and is accompanied by a considerable decrease in total lung capacity and in vital capacity, as well as lesser decrements in functional residual capacity and residual volume (see Chapter 31). Similar findings occur in severe kyphoscoliosis or encasement of the lung by pleural thickening (Fig. 27-10). In contrast, in pulmonary vascular disease, such as idiopathic pulmonary arterial hypertension, a low diffusing capacity may be accompanied by normal lung volumes. Neuromuscular disease that affects the inspiratory muscles sufficiently to diminish maximum inspiratory pressures may decrease vital capacity and total lung capacity, leaving functional residual capacity and residual volume increased.

Patients with widespread pulmonary fibrosis breathe faster and maintain a higher minute ventilation than do normal subjects, both at rest and during exercise. The work and oxygen cost of ventilating the stiff lungs are increased. Dyspnea is attributable to the

TABLE 27-6 Common Causes of Restrictive Ventilatory Defects

Cause	Example
Interstitium	
Interstitial fibrosis and/or infiltration	Usual interstitial pneumonitis/ idiopathic pulmonary fibrosis
Pulmonary edema	Left ventricular failure
Pleura	
Pleural disease	Fibrothorax
Thoracic cage and abdomen	
Neuromuscular disease	Poliomyelitis
Skeletal abnormalities	Severe kyphoscoliosis
Marked obesity	Grossly overweight

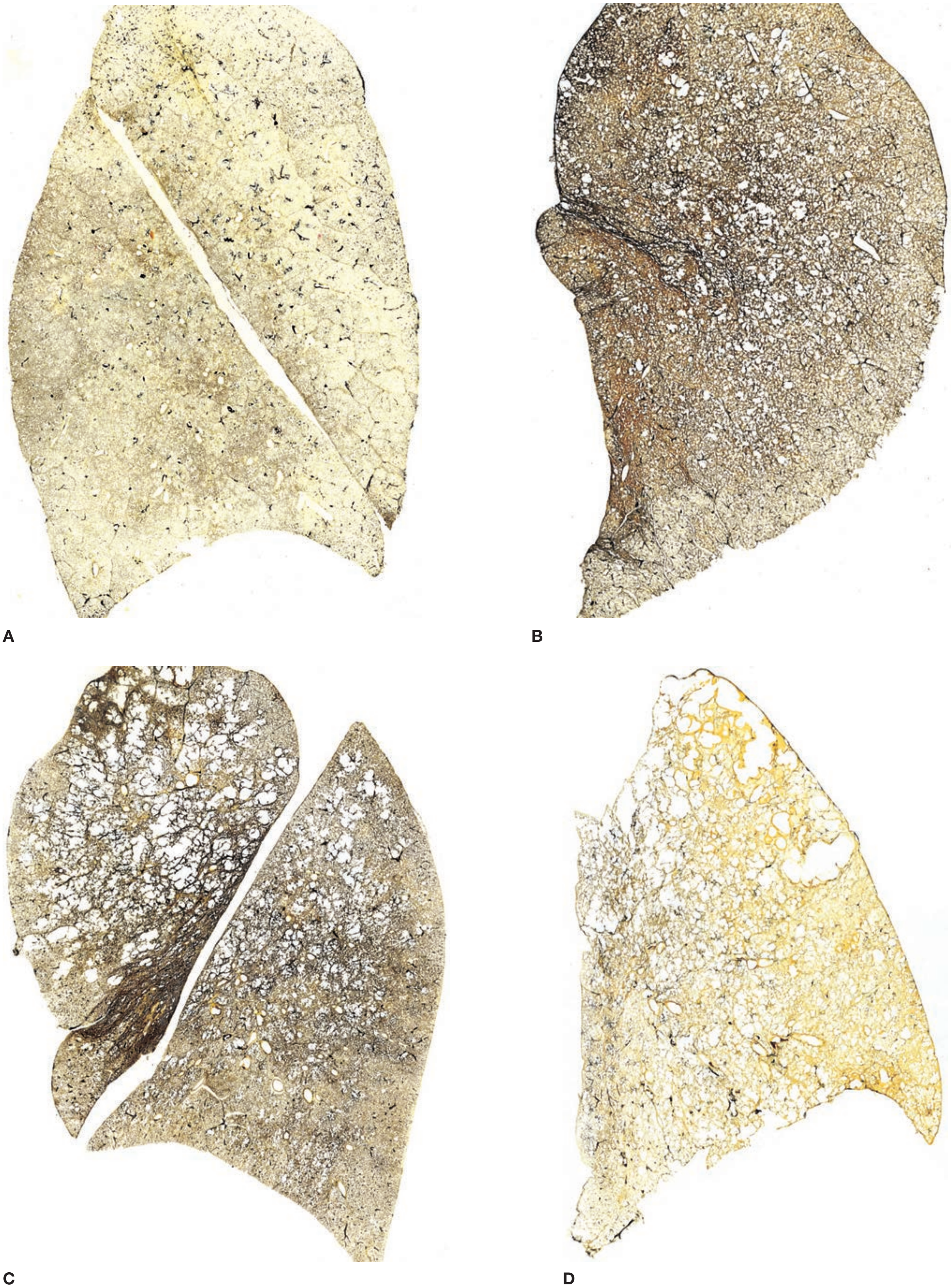


Figure 27-9 Chronic obstructive pulmonary disease (COPD). Sagittal sections showing patterns of emphysema. **A.** Normal lung from a patient who died of unrelated causes. **B.** Predominantly centrilobular emphysema. **C.** Predominantly centrilobular and panlobular emphysema. **D.** Predominantly panlobular emphysema. Centrilobular emphysema is less marked. The three patients with emphysema (**B, C, D**) also had clinical manifestations of chronic bronchitis confirmed by histologic sections.

TABLE 27-7 Some Types of Diffuse Interstitial Diseases

Etiology	Example	Common Features
	Acute	
Infections	Miliary tuberculosis, histoplasmosis *Pneumocystis*, cytomegalic inclusion virus, fungi	Opportunity for exposure to organism Immunosuppression
Pulmonary edema	Narcotic overdosage, nitrogen dioxide (silo-filler's disease), uremia	Distinctive history
Inhalation	Byssinosis	Monday morning asthma and fever
Aspiration	After loss of consciousness	History of alcoholism or epilepsy
Immunologic	Goodpasture syndrome	Renal and pulmonary involvement
Carcinoma of lung	Adenocarcinoma in situ or minimally invasive adenocarcinoma (previously known as alveolar cell carcinoma)	
	Chronic	
Inhalation	Pneumoconioses	History of exposure to inorganic dust
Radiation therapy	After mastectomy	Gradual evolution after treatment
Lymphangitic spread	Carcinoma of breast, lung, stomach, pancreas	Evidence of primary carcinoma
Medications	Bleomycin, busulfan, cyclophosphamide	History, suggestive chest radiograph
Systemic disorders	Sarcoidosis, connective tissue disorders, eosinophilic granuloma, amyloidosis, tuberous sclerosis	Multiorgan involvement; biopsy
Idiopathic	Idiopathic pulmonary fibrosis	Exclusion of known causes

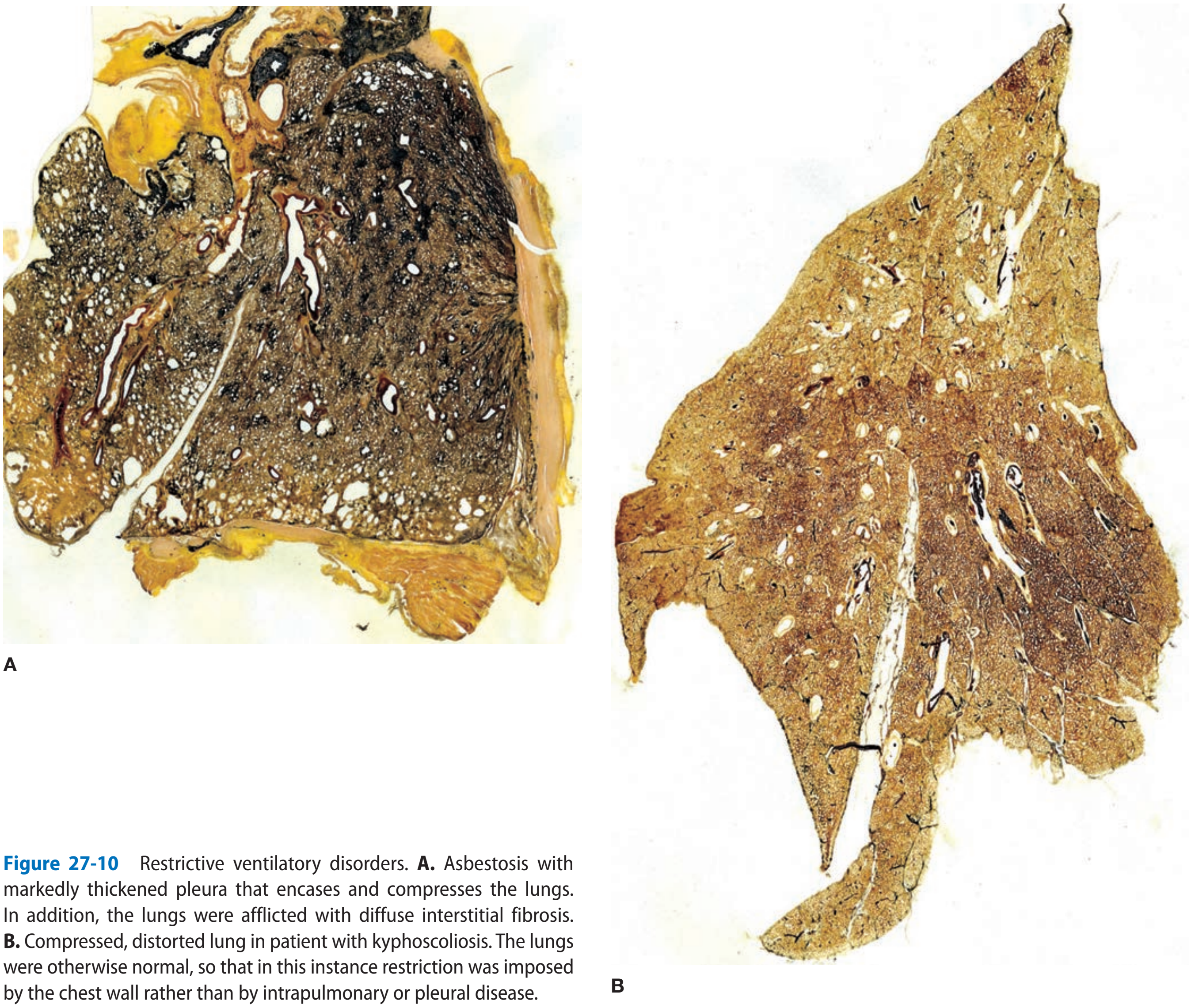


Figure 27-10 Restrictive ventilatory disorders. **A.** Asbestosis with markedly thickened pleura that encases and compresses the lungs. In addition, the lungs were afflicted with diffuse interstitial fibrosis. **B.** Compressed, distorted lung in patient with kyphoscoliosis. The lungs were otherwise normal, so that in this instance restriction was imposed by the chest wall rather than by intrapulmonary or pleural disease.

considerable effort by the respiratory muscles in ventilating the stiff lungs and in sustaining the high ventilatory rate. During exercise, dyspnea may become intolerable.

DYSPNEA IN CHRONIC CARDIAC DISEASE

The mechanisms responsible for dyspnea in cardiac disease vary with the extent to which the lungs are stiffened.

Dyspnea occurs in many forms of heart disease that are not associated with congestion of the lungs. Uncomplicated pulmonic stenosis is an excellent example. The symptom is probably related to an inadequate cardiac output during exercise. In tetralogy of Fallot, dyspnea is sometimes severe and often relieved by assuming a squatting position. In this and other forms of cyanotic heart disease, both dyspnea and fatigue appear during exertion when the arterial oxyhemoglobin saturation decreases appreciably below the resting level.

Cardiac dyspnea is associated with an increase in blood and water content of the lungs. It is a common occurrence in left ventricular failure and mitral stenosis, both of which are accompanied by increases in pulmonary venous and capillary pressures. The engorged pulmonary circulatory bed, coupled with interstitial and alveolar edema, stiffens the lungs (i.e., decreases their compliance) and stimulates the ventilation via "J" receptors. In chronic left ventricular failure, pulmonary fibrosis, consequent to long-standing interstitial edema, contributes to the stiff lungs. Edema of the tracheobronchial mucosa increases airway resistance.

As a result of the stiff lungs and increased airway resistance, swings in pleural pressure during the respiratory cycle are large and the work and energy cost of breathing are increased. Arterial hypoxemia, generally mild, may add to the ventilatory drive. Exercise exaggerates the pulmonary congestion and edema, promotes arterial and mixed venous hypoxemia, and increases the dyspnea.

In patients with pulmonary congestion and edema, tachypnea is a regular feature at rest and increases during exercise. Although tachypnea is consistent, its degree is generally modest and probably not entirely responsible for the dyspnea. Fatigue is a common concomitant of low cardiac output and may stem from diminished O_2 delivery to the respiratory muscles, contributing to respiratory discomfort.

Orthopnea and Other Positional Forms of Breathlessness

Orthopnea signifies dyspnea in the recumbent, but not in the upright or semi-upright, position; it is usually relieved by two or three pillows under the head and back. *Platypnea* signifies dyspnea induced by assuming the upright position and relieved by recumbency.[33]

Platypnea may be seen when, due to gravity, increased blood flow worsens right-to-left shunting of blood through arteriovenous malformations at the lung bases; it may be accompanied by *orthodeoxia*—desaturation of arterial blood when the patient is upright.

Orthopnea is a hallmark of pulmonary congestion that stiffens the lungs (i.e., decreases their compliance). The decrease in compliance on lying flat is attributable to the fact that more of the lung is located at or below the level of the heart. During recumbency, the swings in pleural pressure, the work of breathing, and the respiratory frequency increase. The increase in respiratory frequency appears to be automatically adjusted to minimize the work of ventilating the more rigid lungs.

Some patients with chronic lung disease or asthma are also intolerant of lying flat. Their discomfort is attributed to the greater difficulty of performing vigorous movements of the chest bellows in the recumbent position.

Finally, patients with asymmetric lung disease may experience *trepopnea*—dyspnea when the affected side of the chest is in the dependent position, thereby promoting ventilation–perfusion mismatch (Chapter 14) and resultant hypoxemia.

Paroxysmal Nocturnal Dyspnea

In an episode of paroxysmal nocturnal dyspnea (PND), the patient is aroused from sleep, gasping for air, and must sit up or stand to catch his or her breath; sweating may be profuse. Sometimes the patient opens a room window in an attempt to relieve the oppressive sensation of suffocation. The chest tends to become fixed in the position of forced inspiration. Both inspiratory and expiratory wheezes, often simulating typical asthma, are heard. In some instances, overt pulmonary edema occurs, accompanied by inspiratory crackles. Attacks occasionally recur several times a night, forcing the patient to sleep upright in a chair.

An episode of PND represents precipitous failure of the left ventricle caused by the factors that produce orthopnea (see above), abetted by pulmonary hypervolemia caused by a surge in systemic venous return. Mobilization of peripheral edema from the periphery as the extremities are elevated from the dependent position may contribute to the increase in systemic venous return. The acute increase in pulmonary blood volume increases pulmonary capillary pressures, thereby promoting pulmonary edema, while the surge in venous return imposes an additional burden on the left ventricle.

A variety of factors may trigger an episode of PND: coughing, abdominal distention, the hypercapnic phase of Cheyne–Stokes respiration (see below), a startling noise, or anything that causes a rise in heart rate and further increases the pulmonary capillary and venous pressures. Usually the attack is terminated by assumption of the erect position and a few deep breaths. Cough, an important manifestation of pulmonary congestion, frequently occurs during the attack.

Cardiac Asthma

Asthmatic wheezes, often audible in patients with pulmonary congestion, have given rise to the term *cardiac asthma.* The wheezes are a manifestation of tracheobronchial edema and often are accompanied by overt signs of pulmonary edema. In addition to the reduction in the lumen of the airways and thickening of bronchial walls by edema, the high intrathoracic pressures, which are required to overcome the obstruction during expiration, tend to narrow the airways even further. The resistance to airflow is increased during both inspiration and expiration, and the compliance of the lungs is greatly reduced, reaching values as low as one-tenth of normal. Upon recovery from the acute episode of pulmonary edema, airway resistance and pulmonary compliance return toward normal unless previous episodes have left a residue of pulmonary fibrosis.

DYSPNEA IN ANEMIA

Shortness of breath during exercise or excitement is a common complaint in severe anemia (e.g., hemoglobin concentration under 6–7 g/dL). It is more common in acute than in chronic anemia. Often the dyspnea is associated with dizziness or faintness, and invariably the patient manifests signs of a high cardiac output and low peripheral resistance (i.e., bounding pulse, warm skin, and systolic cardiac murmurs). Although the pathogenesis of the dyspnea is not clear, inadequate oxygen delivery to the respiratory muscles has been proposed.

METABOLIC ABNORMALITIES AND DRUGS

Increases in CO_2 production demand a concomitant rise in ventilation to dispose of the metabolic load and, hence, may result in dyspnea. To prevent acidemia, patients with diabetic ketoacidosis may require an enormous increase in minute ventilation in order to reduce Pa_{CO_2}. Thyrotoxicosis, fever, infection, and pregnancy can also cause an increased minute ventilation, as can drugs, such as aspirin and progesterone.

MISCELLANEOUS DISORDERS

Breathlessness is not uncommon in patients with musculoskeletal disorders. The usual explanation is the heightened motor drive that is needed to activate the weakened respiratory muscles. In the intensive care unit, inadequate ventilator settings for flow and tidal volume may fail to satisfy the intrinsic ventilatory drive of the patient, generating the sensation of breathlessness.

ABNORMAL BREATHING PATTERNS

An important clue to the nature of a clinical problem in pulmonary disease is sometimes provided by bedside observation of a patient's breathing pattern. The pertinent features are the rate, regularity, depth, and apparent effort being expended in breathing. A normal person at rest breathes about 12 to 15 times per minute, with a tidal volume of 400 to 800 mL. As a result, minute ventilation is normally greater than 5 L/min. The pattern is quite regular except for an occasional slow, deep breath, and the respiratory movements appear effortless.

Severe skeletal deformity, as well as massive obesity, can limit chest excursions to cause alveolar hypoventilation (Chapter 83). Neuromuscular weakness, as in myasthenia gravis or Guillain–Barré syndrome, may do the same, not only by diminishing ventilatory excursions as a result of generalized weakness of the respiratory muscles, but also by causing overload of respiratory muscles (e.g., residual effects of poliomyelitis) (Chapters 83 and 84). Unilateral involvement of one pleural space by pneumothorax, effusion, or fibrothorax limits excursions on the affected side. Massive chest trauma may cause flail chest.

In COPD, a slow respiratory rate and large tidal volumes are characteristic. This pattern presumably serves to minimize the work of breathing. Pursed-lip breathing, a self-induced type of positive-pressure breathing, is often part of the picture. In contrast, persons with restrictive ventilator disorders adopt a breathing pattern that is characterized by small tidal volumes and a rapid respiratory rate, often with little apparent effort. This pattern is seen in patients with a decrease in the distensibility of the lung or chest wall or with reduction of the vital capacity from any other cause. During exercise, minute ventilation increases inordinately with respect to the level of O_2 uptake, and respiratory frequency increases more than tidal volume.

Fatigue of the diaphragm and intercostal muscles, sufficient to disturb their coordinated contractions, may give rise to paradoxical breathing, which heralds the onset of respiratory failure.

■ Cheyne–Stokes Respiration

In the fourth century BC, in a preterminally ill person with fever, sweats, and black urine, Hippocrates described a pattern of breathing in which "the respiration throughout [was] like that of a man correcting himself, and rare and large." Presumably he had observed Cheyne–Stokes breathing, which was described more graphically by William Stokes two millennia later (in 1854) as follows:

"The symptom in question (previously described by Dr. Cheyne) consists in the occurrence of a series of inspirating, increasing to a maximum, and then declining in force and length, until a state of apparent apnea is established. In this condition the patient may remain for such a length of time as to make his attendants believe that he is dead, when a low inspiration, followed by one more decided, marks the commencement of a new ascending and descending series of inspirations."

Cheyne–Stokes breathing is characterized by alternating periods of hypoventilation and hyperventilation (Fig. 27-11). In its typical form, an apneic phase, which lasts for 15 to 60 seconds, is followed by a phase during which tidal volume increases with each successive breath to a peak level and then decreases in a progressive fashion to the apneic phase. At the onset of apnea, CO_2 tension in brachial or femoral arterial blood is at its lowest. As apnea persists, CO_2 tension gradually increases, and respiration is stimulated. CO_2 tension continues to increase until maximum hyperventilation is attained, after which ventilation decreases until apnea again occurs. The arterial oxyhemoglobin saturation varies in an inverse manner, being highest at the onset of apnea and lower during mid-hyperpnea. During the cycle, CO_2 tension varies by as much as 14 mm Hg and oxyhemoglobin saturation by as much as 18%.

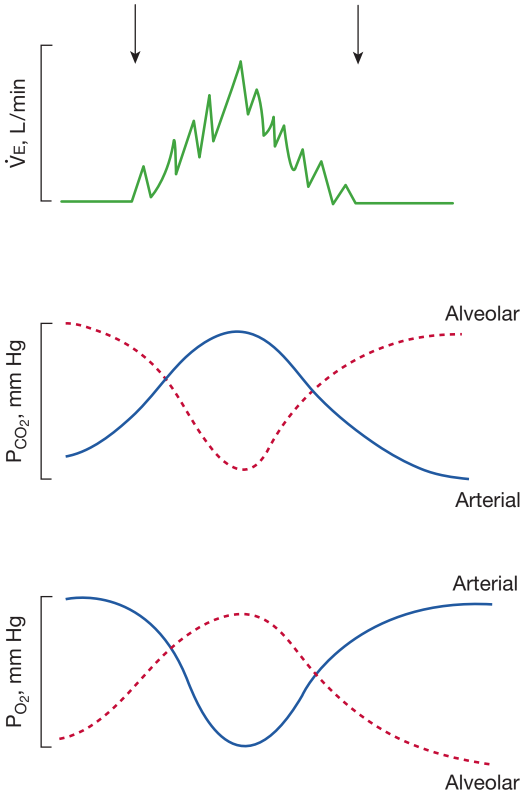


Figure 27-11 Cheyne–Stokes breathing, illustrating the relationship between the ventilation and the blood and alveolar gas tensions during the periods of apnea and hyperpnea. *(Reproduced with permission from Cherniack NS, Fishman AP. Abnormal breathing patterns. Dis Mon. 1975:1–45.)*

In patients with congestive heart failure, the respiratory oscillations are attributable to slowing of the circulation so that the blood gases reaching the respiratory centers in the brain are 180 degrees out of phase with those in pulmonary capillary blood. This mechanism has been verified experimentally by eliciting Cheyne–Stokes breathing in dogs by prolonging the circulation time from heart to brain by way of an extracorporeal circuit.

Fluctuations in mental state and electroencephalographic patterns, and evidence of nervous system dysfunction, may occur during Cheyne–Stokes breathing because of swings in cerebral blood flow. In neurologic disorders, Cheyne–Stokes breathing may be due to supramedullary dysfunction, particularly in patients who have destructive lesions in the tegmentum of the pons.

Less common than in heart failure or neurologic disorders is the occurrence of Cheyne–Stokes respiration in normal infants, in healthy elderly persons, and in normal persons at high altitude. It is also seen occasionally after the administration of respiratory depressants (e.g., morphine), often accompanied by an increase in intracranial pressure, uremia, or coma. At one time, the respiratory center was believed to be depressed in Cheyne–Stokes respiration. This hypothesis has been proved to be in error, since it has been shown that the respiratory response to inhalation of CO_2 is greater than normal in individuals with Cheyne–Stokes respiration. Respiratory alkalosis is common and the arterial P_{CO_2} remains subnormal in both the apneic and hyperpneic phases.

Kussmaul Breathing

In 1874, Kussmaul described three patients with diabetic ketoacidosis who manifested “air hunger”: they were breathing with large tidal volumes and so rapidly that there was virtually no pause between breaths. In essence, they were breathing at rest as though they were exercising; breathing was accomplished with little apparent effort. Since then, this pattern of breathing has been observed in other types of severe metabolic acidoses (e.g., alcoholic ketoacidosis). The usual sequence leading to this type of breathing is renal failure with a progressive decrease in plasma bicarbonate and resultant acidosis. The “compensatory” increase in ventilation that Kussmaul described mitigates the fall in systemic pH caused by the fall in plasma bicarbonate (see Chapter 17).

Other Abnormal Patterns

Gasping respirations are characteristic of severe cerebral hypoxia. The pattern consists of irregular, quick inspirations associated with extensions of the neck and followed by a long expiratory pause. It is commonly seen in shock or in other conditions associated with severe reduction in cardiac output.

Hyperventilation is commonly seen in anxious patients without structural disease of the lungs. In some of these patients, striking deep sighs dominate the ventilatory pattern.

DIAGNOSTIC TESTING IN THE EVALUATION OF DYSPNEA

Attention to the history and physical examination findings, as described in the preceding sections, will help to focus the initial approach to diagnosis.[34] In most cases, the initial diagnostic impression can be confirmed or excluded with only a few tests, and appropriate therapy instituted or the hunt for a cause continued (Table 27-8).

A plain chest radiograph is useful in demonstrating changes suggestive of COPD (chest hyperinflation, bullous changes). Vascular engorgement, an enlarged cardiac silhouette, increased interstitial markings, and pleural effusions may indicate left heart failure.

Spirometry is useful in identifying airways obstruction; improvement in values may be noted following administration of a bronchodilator. The measurement of lung volumes or the diffusing capacity may be reserved for when there is suspicion of an interstitial process or other cause of restriction (e.g., muscle weakness). Measurement of arterial oxyhemoglobin saturation both at rest and with exertion is important. While oxyhemoglobin desaturation will not indicate the etiology of the problem, its presence is always an important indicator of the severity of the disease. An echocardiogram can be used to assess ventricular or valvular cardiac function and to estimate pulmonary arterial pressures.

A complete blood count may reveal anemia or suggest an infection. Measurement of serum electrolytes may indicate the presence of an acidosis or renal dysfunction. Measurement of brain natriuretic peptide (BNP) has been useful in helping to exclude heart failure as an acute cause of dyspnea.[35]

Additional testing is usually not required unless the cause of dyspnea remains unclear following basic studies. Further tests often include CT of the chest, which may reveal changes of emphysema or an interstitial process not suggested by plain radiographs or lung function testing. The CT may additionally help to better

TABLE 27-8 Common Tests in the Evaluation of Dyspnea

Test	Some Possible Abnormalities	Some Possible Diagnoses
Plain Chest Radiograph	Cardiac enlargement	Congestive heart failure
	Vascular enlargement	Pulmonary hypertension
	Abnormal interstitial markings	Pulmonary fibrosis
	Pleural effusions	Malignant pleural effusion
	Hyperinflation	COPD
	Nodules/masses	Neoplastic process
Pulmonary function tests		
Spirometry	Obstructive ventilation defect (decreased FEV$_1$/FVC, %)	Asthma
		COPD
	Restrictive ventilatory defect	Interstitial lung disease
Diffusing capacity	Decreased	Interstitial lung disease
		Pulmonary vascular disease
	Increased	Alveolar hemorrhage
Inspiratory and expiratory pressures	Decreased values	Respiratory muscle weakness
Computed tomography	Abnormal interstitial markings	Interstitial lung disease
	Cystic changes	Bullous lung disease
	Lymphadenopathy	Sarcoidosis
	Vascular filling defects	Pulmonary embolism
	Ground-glass opacities	Neoplastic disease
Blood tests	Elevated white blood cell count	Infection
	Anemia	Anemia
	BNP	Heart failure
	Cr	Renal failure
		Respiratory or metabolic acidosis
	ABG	Acidoses or alkaloses (respiratory or metabolic)

COPD, chronic obstructive pulmonary disease; FEV$_1$/FVC, forced expiratory volume in 1 s/forced vital capacity; BNP, brain natriuretic peptide; Cr, creatine; ABG, arterial blood gas.

characterize an interstitial process identified on plain radiographs. Cardiopulmonary exercise testing (Chapter 32) may be helpful in differentiating between cardiac and respiratory causes of dyspnea, or in excluding a significant abnormality of either system and suggesting deconditioning as the culprit. Arterial blood gas measurements may be necessary to characterize the level of blood oxygenation or to identify hyperventilation or hypercapnia. More invasive testing, including cardiac catheterization or lung biopsy (by either bronchoscopy or surgery), is reserved for situations when the diagnosis remains unsettled and the results will be helpful in guiding therapy or discussions of prognosis.

COUGH

Cough is one of the most frequent causes of visits to the doctor's office.[36,37] Patients are frequently anxious about the possibility of a serious underlying cause. They may also be troubled by the complications of cough, including chest pain from intercostal muscle strain or even a fractured rib. They may be embarrassed by cough-induced urinary or fecal incontinence. Social isolation may also arise from the frequent fear of others that the patient's cough is infectious and communicable.

A cough is an explosive expiration that protects the lungs against aspiration and promotes the movement of secretions and other airway constituents upward toward the mouth. It is a critical element in the self-clearing and protective mechanisms of the lungs—a reflex act that usually, but not invariably, arises from stimulation of the bronchial mucosa somewhere between the larynx and the second-order bronchi. On rare occasions the cause is remote: impacted cerumen in the external auditory canal[38] or an inflammatory process of the pleura (see "Mechanism," below) (Fig. 27-12). The stimuli that may elicit a cough are diverse: inhaled particles, mucus that has been elaborated by the lining of the airways, inflammatory exudate in airways or parenchyma, a new growth or foreign body in an airway, or pressure on the external wall of the bronchus.

A cough may be voluntary, involuntary, or a combination of the two if the subject attempts to control an involuntary cough. Three categories of stimuli are commonly at work in producing an involuntary cough: mechanical, inflammatory, and psychogenic. Mechanical and chemical causes range from inhalation of irritants, such as smoke or dust, to distortions of the airways produced by pulmonary fibrosis or atelectasis. Most often, cough is due to tracheobronchial inflammation. The cigarette smoker is particularly vulnerable to exacerbation of cough by inhaled particles and fumes because of underlying chronic pharyngitis, laryngitis, and tracheobronchitis. As a rule, cough represents organic disease. But on occasion, psychogenic influences are responsible for a dry cough that is related to anxiety. Psychogenic stress can aggravate cough due to organic causes.[39] Cough may also be caused by certain pharmacologic agents, including, most notably, angiotensin-converting enzyme (ACE) inhibitors.

The site of origin and significance of a cough may sometimes be ascertained from telltale signs and symptoms (Table 27-9). For example, the cough of acute tracheitis is often associated with retrosternal "burning." Acute laryngitis is usually associated with hoarseness and sore throat, as well as cough. Tuberculosis of the larynx is associated not only with painful swallowing but also with unequivocal evidence of pulmonary tuberculosis. In asthma, cough is part of a constellation of airway obstruction.

Interpretation of the significance of a cough depends on the clinical features with which it is associated. It has to be viewed in context: Is it acute or chronic? Is it productive or nonproductive? How long has it lasted? What is the general condition of the patient, and what comorbidities are present? For example, the acute onset of a hacking, nonproductive cough accompanied by coryza, sore throat, malaise, sweating, and fever generally heralds a viral upper respiratory infection. An episode of asthma may begin with cough and wheezing. In contrast, a persistent cough, even if virtually ignored by the patient, may be a harbinger of serious disease (e.g., carcinoma of the lung). In a cigarette smoker, a change in the nature of the cough from nonproductive to productive may signify the onset of a serious tracheobronchial infection or pneumonia.

A cough that is productive of purulent sputum is generally a reliable indication of infection in the tracheobronchial tree or lungs. When this symptom is associated with an acute illness, the characteristics of the sputum can be of considerable diagnostic help. Rust-colored sputum, which has a distinctive coloration from the even dispersion of blood in yellow, purulent sputum, was previously seen often in pneumococcal pneumonia; it is less commonly seen today due to the widespread use of antibiotics. The classic description of sputum in *Klebsiella* pneumonia is a resemblance to currant jelly; it also contains blood, but it is bright red and more translucent and viscid than the sputum of pneumococcal pneumonia. Purulent sputum with a foul odor usually indicates an anaerobic infection, commonly due to streptococci or *Bacteroides* in a lung abscess. A persistent cough that is productive of purulent sputum occurs in chronic bronchitis, bronchiectasis, and a variety of other suppurative disorders. Sputum that is mucoid may be a consequence of any long-standing bronchial irritant. Copious sputum production *(bronchorrhea)* may be a sign of adenocarcinoma in situ (AIS) or minimally invasive adenocarcinoma (MIA), previously known as bronchoalveolar carcinoma.

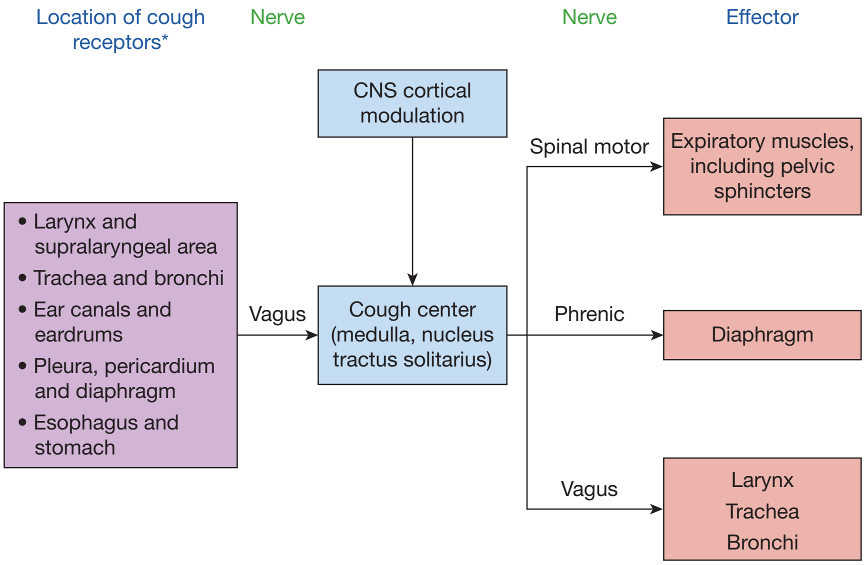

Location of cough receptors*
Nerve
Nerve
Effector
CNS cortical modulation
Spinal motor
Expiratory muscles, including pelvic sphincters
• Larynx and supralaryngeal area
• Trachea and bronchi
• Ear canals and eardrums
• Pleura, pericardium and diaphragm
• Esophagus and stomach
Vagus
Cough center (medulla, nucleus tractus solitarius)
Phrenic
Diaphragm
Vagus
Larynx
Trachea
Bronchi

Figure 27-12 Signaling pathways in the development of cough. CN, cranial nerve. *(Copyright ©2022 UpToDate, Inc. and its affiliates and/or licensors. All rights reserved.)*

TABLE 27-9 Some Causes and Characteristics of Cough

Cause	Characteristics
Sinusitis or nasopharyngitis	Cough following an upper respiratory syndrome or sinus symptoms; sensation of a need to clear the throat; postnasal drip
Acute infections of lungs	
Tracheobronchitis	Cough associated with sore throat, running nose, and eyes
Lobar pneumonia	Cough often preceded by symptoms of upper respiratory infection; cough dry, painful at first; later becomes productive
Bronchopneumonia	Cough dry or productive, usually begins as acute bronchitis
Mycoplasma and viral pneumonia	Paroxysmal cough, productive of mucoid or blood-stained sputum associated with flulike syndrome
Exacerbation of chronic bronchitis	Cough productive of mucoid sputum becomes purulent
Chronic infections of lungs	
Bronchitis	Cough productive of sputum on most days for more than 3 consecutive months and for more than 2 y Sputum mucoid until acute exacerbation, when it becomes mucopurulent
Bronchiectasis	Cough copious, foul, purulent, often since childhood; forms layers upon standing
Tuberculosis or fungus	Persistent cough for weeks to months, often with blood-tinged sputum
Parenchymal inflammatory processes	
Interstitial fibrosis and infiltrations	Cough nonproductive, persistent, depends on origin
Smoking and inhalation of irritants	Cough usually associated with injected pharynx; persistent, most marked in morning, usually only slightly productive unless succeeded by chronic bronchitis
Tumors	
Bronchogenic carcinoma	Cough nonproductive to productive for weeks to months; recurrent small hemoptysis common
Adenocarcinoma *in situ* or minimally invasive adenocarcinoma	Cough similar to that with bronchogenic carcinoma except in occasional instances, when large quantities of watery, mucoid sputum are produced
Benign tumors in airways	Cough nonproductive; occasionally hemoptysis
Mediastinal tumors	Cough, often with breathlessness, caused by compression of trachea and bronchi
Aortic aneurysm	Brassy cough
Gastrointestinal	
Gastroesophageal reflux disease (GERD)	Nonproductive cough often following meals or with recumbency; may (or may not) be accompanied by other symptoms of GERD (e.g., heartburn, a bitter oral taste, belching)
Foreign body	
Immediate, while still in upper airway	Cough associated with progressive evidence of asphyxiation
Later, when lodged in lower airway	Nonproductive cough, persistent, associated with localizing wheeze
Cardiovascular	
Left ventricular failure	Cough intensifies while supine, along with aggravation of dyspnea
Pulmonary infarction	Cough associated with hemoptysis, usually with pleural effusion
Medication-induced	
Angiotensin-converting enzyme (ACE) inhibitors	Nonproductive cough, more common in women, may occur at any time (following soon after drug initiation or with years of use)

■ Mechanism

A cough begins with a rapid inspiration, followed, in rapid sequence, by closure of the glottis, contraction of the abdominal and thoracic expiratory muscles, abrupt increase in pleural and intrapulmonary pressures, sudden opening of the glottis, and expulsion of a burst of air from the mouth (Fig. 27-13). The high intrathoracic pressures, which often exceed 100 to 200 mm Hg, increase the velocity of airflow through the airways, hastening the propulsion of the offending particles and producing the sound of a cough by setting into vibration airway secretions, the tracheobronchial walls, and the adjacent parenchyma (Fig. 27-14).

Afferent stimuli for a cough originate in irritant receptors and are conveyed centrally by the vagus, glossopharyngeal, trigeminal, and phrenic nerves (Fig. 27-12). In subjects with an idiopathic, persistent, nonproductive cough, increased sensitivity of the afferent nerves of the airways due to neuropeptides stored in them has been proposed.

The vagus nerve carries impulses not only from the larynx, trachea, and bronchi, but also from the pleura and stomach. Receptors in the airways are most concentrated in the larynx, diminish in density in the conducting airways, and are absent from the distal airways, enabling the pooling of secretions in the periphery. The glossopharyngeal nerve carries stimuli from the pharynx; the trigeminal nerve, from the nose and paranasal sinuses; the phrenic nerve, from the pericardium and diaphragm. The motor pathways are even more extensive, comprising not only the cranial and phrenic nerves but also the nerves to the muscles of the rib cage and the accessory muscles. Additional impulses from chemoreceptors are located in the esophagus and carried by the phrenic nerve.

The effectiveness of a cough is strongly influenced by the lung volume at which it occurs. As indicated elsewhere in this volume, cough only removes particles toward the mouth ("downstream" from the "equal pressure points"). In healthy persons at high lung volumes, the equal pressure points are located in the larger airways; they move

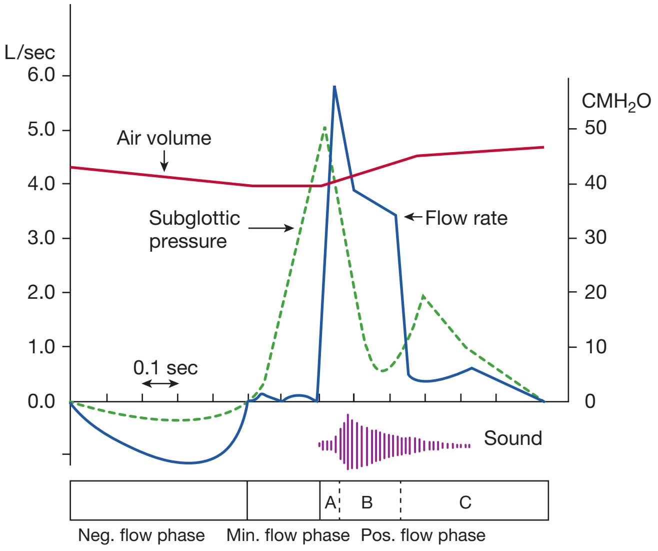


Figure 27-13 Sequence of events during a cough. Simultaneous recordings obtained during a single explosive cough by a normal subject. The three phases of a cough are identified by the boxes at the bottom of the figure. They correspond to (1) a deep initial inspiration, (2) compression of air in the lungs and airways by forceful contraction of the expiratory muscles coupled with tight closure of the glottis and opening of the larynx, and (3) sudden explosive expiration followed by narrowing of the glottis and return of the larynx to its normal inspiratory position. *(Reproduced with permission from Yanagihara N, Von Leden H, Werner-Kukuk E. The physical parameters of cough: the larynx in a normal single cough. Acta Otolaryngol. 1966;61(6):495–510.)*

toward the alveoli ("upstream") as lung volume decreases. A series of coughs without any intervening inspiration moves the equal pressure points even closer to the small airways, helping to clear the depths of the lungs.

The cough reflex may be impaired by interrupting or blunting any step in the sequence. Irritant receptors can be damaged by a local destructive process (e.g., bronchiectasis), or their sensitivity can be diminished by narcotics or anesthetics.

The reflex pathways may be damaged as part of a neurologic disease. Tracheostomy, which eliminates glottic closure, decreases peak intrapulmonary pressures. Contraction of the respiratory muscles may be impaired by weakness due to illness, age, or neuromuscular disease. In general, as long as the patient can achieve maximum expiratory pressures greater than about 60 cm H_2O, the peak flow will suffice to produce effective coughs.

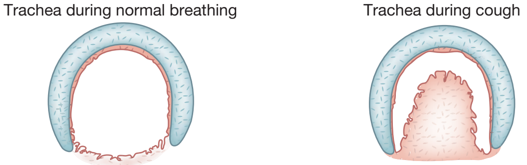
Circulatory Consequences

The increase in intrathoracic pressure that is part of the cough mechanism exerts considerable circulatory effects. However, because the increase in intrathoracic pressure is accompanied by an equal rise in vascular (and cerebrospinal fluid) pressures, distending pressures on the vessels of the heart, lungs, and other vital organs are unaltered, so they are normally spared the ill consequences of marked swings in transmural pressures.

The increase in intrathoracic pressure is accompanied by reflex vasodilation of systemic arteries and veins. Both of these effects contribute to a decrease in cardiac output. In patients with cor pulmonale and right heart failure, cough impedes systemic venous return and may result in syncope.

Posttussive Syncope

Over 100 years ago, Charcot recognized the syndrome of posttussive syncope in individuals without underlying cardiopulmonary disease.



Intrathoracic pressure, cm H_2O	– 4	+ 150
Cross-sectional area, cm^2	1.5	0.25
Volume flow, L/sec	1	7
Linear velocity, cm/sec	667	28,000

Figure 27-14 Effects of tracheal narrowing during a cough. The forced expiratory effort during coughing causes invagination of the noncartilaginous part of the intrathoracic trachea by the high intrathoracic pressure. Air rushing with a high linear velocity through the exceedingly narrow trachea dislodges the material to be dispelled and propels it into the throat. *(Reproduced with permission from Comroe JH: Physiology of Respiration. St. Louis, MO: Mosby-Year Book; 1965.)*

Originally conceived of as a form of epilepsy or a consequence of a laryngeal reflex, it is now attributed to the same circulatory consequences of raised intrathoracic pressures that coughing evokes in a normal person. However, the patient with cough syncope probably coughs more forcefully and longer than does a normal person.

The syncope usually develops within a few seconds after the onset of a paroxysm of coughing and ends quickly once the coughing has stopped. Return to consciousness is without sequelae unless the subject falls and is injured during the faint. Posttussive syncope nearly always occurs in men, probably because they generate a higher intrathoracic pressure and much more profound decrease in cardiac output than do women. It is not clear why this type of fainting occurs in the supine, as well as the upright, position; this occurrence suggests that the reduction in cerebral blood flow during posttussive syncope reflects more than interference with cardiac output. The extent to which intense reflex vasodilation contributes to posttussive syncope is unclear. It is important to distinguish cough syncope from epilepsy and cataplexy.

Etiology

The most common causes of chronic cough and sputum (defined as lasting longer than 8 weeks) are postnasal drip, gastroesophageal reflux disease (GERD), and asthma.[40,41] In most cases, the etiology can be determined, and more than one cause may be present.

In patients treated with angiotensin-converting enzyme (ACE) inhibitors, the drug is very often the cause of a chronic cough (even one developing after years of uncomplicated use). The association of cough and ACE inhibitors may be different among various ethnic groups.[43]

A deliberate evaluation can identify the cause of cough in the vast majority of patients. Usually, the diagnosis is established only by the resolution of the cough following a specific intervention (Fig. 27-15). For example, cough that disappears after antihistamines and inhaled nasal corticosteroid treatment for allergic rhinitis can logically be attributed to postnasal drip. Similarly, cough may disappear after interventions for GERD (e.g., use of H_2-blockers) or asthma (use of inhaled bronchodilators and steroids). A cough that resolves after discontinuation of an ACE inhibitor was presumably caused by the drug. Although the causes of chronic cough are usually benign, a chest radiograph is warranted at the beginning of the evaluation of a chronic cough to assess for serious causes.

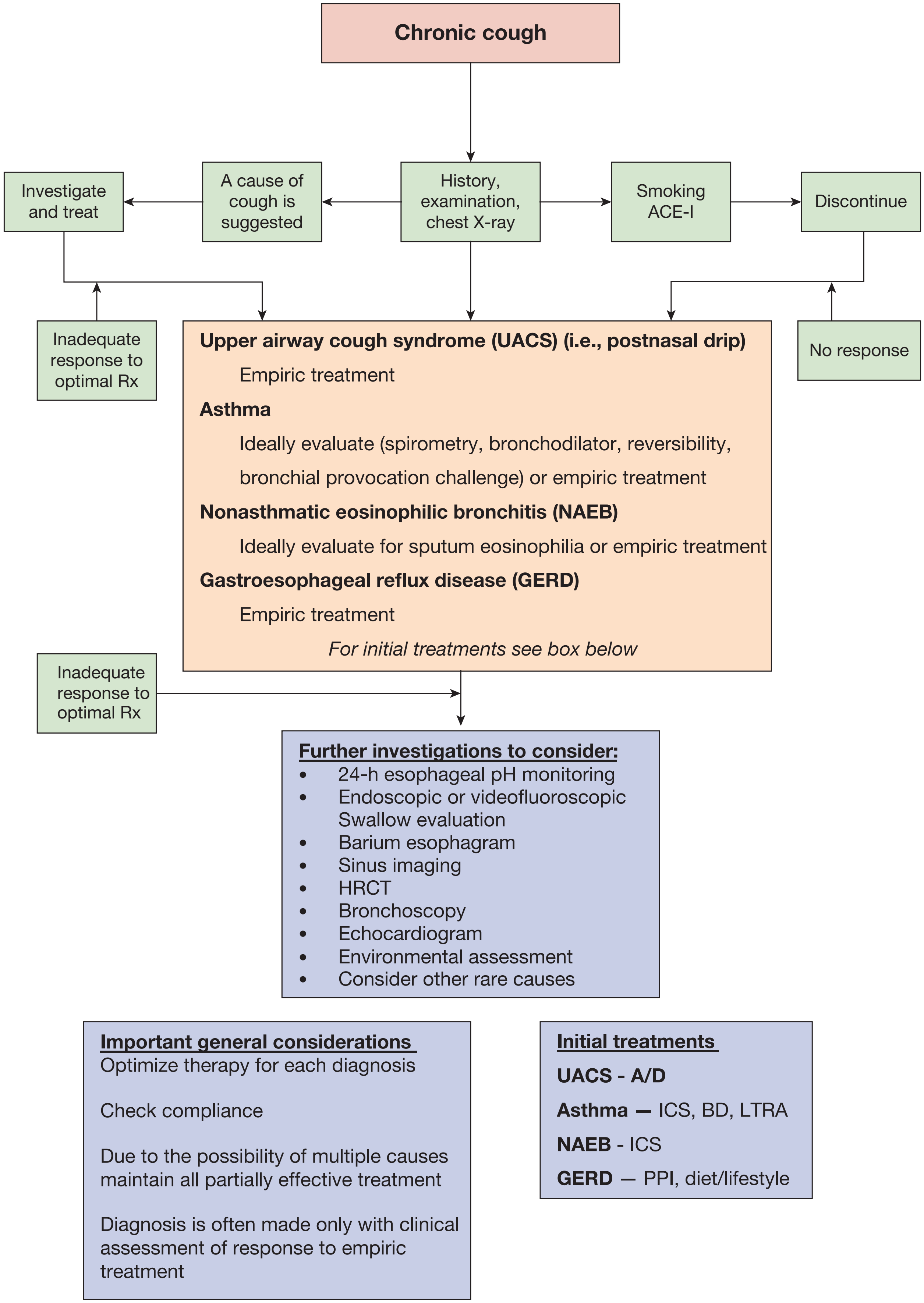

Chronic cough
Investigate and treat
A cause of cough is suggested
History, examination, chest X-ray
Smoking ACE-I
Discontinue
Inadequate response to optimal Rx
No response
Upper airway cough syndrome (UACS) (i.e., postnasal drip)
Empiric treatment
Asthma
Ideally evaluate (spirometry, bronchodilator, reversibility, bronchial provocation challenge) or empiric treatment
Nonasthmatic eosinophilic bronchitis (NAEB)
Ideally evaluate for sputum eosinophilia or empiric treatment
Gastroesophageal reflux disease (GERD)
Empiric treatment
For initial treatments see box below
Inadequate response to optimal Rx
Further investigations to consider:
• 24-h esophageal pH monitoring
• Endoscopic or videofluoroscopic Swallow evaluation
• Barium esophagram
• Sinus imaging
• HRCT
• Bronchoscopy
• Echocardiogram
• Environmental assessment
• Consider other rare causes
Important general considerations
Optimize therapy for each diagnosis
Check compliance
Due to the possibility of multiple causes maintain all partially effective treatment
Diagnosis is often made only with clinical assessment of response to empiric treatment
Initial treatments
UACS - A/D
Asthma — ICS, BD, LTRA
NAEB - ICS
GERD — PPI, diet/lifestyle

Figure 27-15 Algorithm for the evaluation of chronic cough lasting 8 weeks in adults. ACE-I, ACE inhibitor; A/D, antihistamine/decongestant; BD, bronchodilator; HRCT, high-resolution computed tomography; ICS, inhaled corticosteroid; LTRA, leukotrienes receptor antagonist; PPI, proton pump inhibitor. *(Reproduced with permission from Irwin RS, Baumann MH, Bolser DC, et al. Diagnosis and management of cough executive summary: ACCP evidence-based clinical practice guidelines. Chest. 2006;129(1 Suppl):1S–23S.)*

HEMOPTYSIS

The coughing up of blood is termed *hemoptysis.*[44] The material and amount produced varies from mere blood streaking of expectorated sputum to massive volumes of pure blood. Massive hemoptysis has been variably defined according to the volume, but its presence implies a potentially life-threatening process requiring immediate evaluation and treatment.

An initial decision faced by the physician who is told that blood has been coughed up is whether to conclude that the blood is coming from the respiratory tract. Any portion of the respiratory tract can be the source of bleeding including a main bronchus, the lungs, or the nose or throat. On occasion, blood from the nose and throat is inhaled and then expectorated. As long as this possibility is kept in mind, bleeding that originates in the nose, throat, or larynx is not apt to be overlooked.

An additional consideration is distinguishing hemoptysis from hematemesis (vomited blood). Even if the blood is aspirated and then coughed up, the patient can usually tell if the blood originated in the respiratory or alimentary tract. The appearance of the bloody material also helps to distinguish between hemoptysis and hematemesis: blood that originates in the airways is usually bright red, is mixed with frothy sputum, has an alkaline pH, and contains alveolar macrophages that are laden with hemosiderin; in contrast, blood from the stomach usually is dark, has an acid pH, contains food particles, and often occurs in patients with a long history of gastric disease.

Blood arising from the bronchial arteries is more often the source of massive hemoptysis, owing to its higher perfusion pressure, than blood from the pulmonary circulation. The bronchial circulation may be the source of life-threatening bleeding, for example, in patients with bronchiectasis in whom the vessels frequently become distorted and easily ruptured. Dieulafoy's disease of the bronchus, in which there is a submucosal fistula between bronchial and pulmonary arteries, is a rare cause of massive hemoptysis.[45]

The differential diagnosis of hemoptysis includes disorders arising within the airways and the pulmonary parenchyma. Inflammatory processes (e.g., bronchitis and bronchiectasis) and neoplasms are the most common causes of blood arising within the airways. Within the pulmonary parenchyma, common causes are infections, such as tuberculosis, pneumonia, *Aspergillus*, or lung abscess. Inflammatory processes that involve the lung, such as granulomatosis with polyangiitis (formerly known as Wegner's granulomatosis) or Goodpasture syndrome, also are important causes of hemoptysis (Fig. 27-16). Bleeding may be iatrogenic, as for example, after a lung biopsy or when chemotherapy for bone marrow transplantation evokes diffuse alveolar hemorrhage. Vascular disorders, including pulmonary embolism, arteriovenous malfunctions, and mitral stenosis, are also to be considered in the differential diagnosis. Unexplained hemoptysis occurs in COPD and usually is not recurrent.[46]

The causes of hemoptysis are numerous and diverse (Table 27-10). The clinical setting is usually helpful in identifying the cause. Hemoptysis before middle age usually brings to mind infections; after 40 to 45 years of age, or if there is a history of smoking, bronchogenic carcinoma heads the list. In patients left with a pulmonary cavity after pulmonary disease that has healed (e.g., tuberculosis), and in regions of the country where pulmonary fungal diseases are prevalent, a bout of hemoptysis is occasionally the first sign of the disease. In patients who have a predisposing cause, such as oral contraceptives or chronic heart failure, pulmonary embolism must be considered.

TABLE 27-10 Some Causes of Hemoptysis

Infections
Bronchitis
Tuberculosis
Fungal infections
Pneumonia
Lung abscess
Bronchiectasis
Neoplasms
Bronchogenic carcinoma
Bronchial adenoma
Cardiovascular disorders
Pulmonary infarction from thromboembolism
Mitral stenosis
Trauma
Foreign body
Hematologic/immunologic
Disorders of hemostasis
Goodpasture syndrome

The evaluation of hemoptysis involves a careful history, physical examination, and a chest radiograph. Initial studies also include a complete blood count. The degree of anemia may influence the rapidity of further testing, and thrombocytopenia may be a contributing factor to hemoptysis. Rapid correction of anemia, thrombocytopenia, or coagulopathy with the transfusion of appropriate blood products may be required promptly depending upon the clinical status and degree of abnormality. Similarly, measurement of coagulation parameters is important. Studies of renal function and a urinalysis may be indicated when a systemic process, which causes a pulmonary-renal syndrome is a possibility. Sputum should be collected and, depending on the circumstance, microbiologic cultures and stains or cytologic examination should be performed. Depending on whether a cause is identified, and the risk factors for a serious cause of bleeding, the evaluation next involves additional studies to search for a source.

Because hunting for the cause and the source of bleeding is generally uncomfortable for the patient and often expensive, the intensity of the search depends on the circumstances. For example, rarely is a search for the bleeding site needed in a patient with acute bronchitis, pneumonia, or bronchopulmonary suppuration. But as a rule, unless the cause is evident, a full-scale investigation is mandatory.

Patients with hemoptysis and a history of tobacco smoking, individuals who are more than 40 years of age, or those who experience hemoptysis that lasts for more than 1 week are at greater risk for a worrisome cause and warrant additional studies. A chest CT scan is usually the next step if the patient has no history of tobacco use or if the plain chest radiograph suggests a parenchymal abnormality, such as bronchiectasis or arteriovenous malformation. Patients with a history of tobacco use or other risk factors for a malignancy warrant fiberoptic bronchoscopy (Chapter 33). In practice, CT scanning and bronchoscopy are often complementary for visualizing abnormalities that are not apparent on plain chest radiographs. Patients with chronic bronchitis and who are at low risk for malignancy, or in whom the chest radiograph is normal or identifies the cause of hemoptysis (e.g., pneumonia) can usually be treated initially for bronchitis with follow-up appraisals to show prompt resolution of hemoptysis. However, should hemoptysis recur, further evaluation is required.

■ Neoplasms

Nonmassive hemoptysis (<500 cc/24 h) is common in bronchogenic carcinoma; less frequently carcinoma is the cause of massive hemoptysis. The likelihood of a neoplastic cause of hemoptysis is greatly increased in a cigarette smoker. Usually a troublesome cough and vague chest pain precede and accompany the hemoptysis. For hemoptysis to occur, the lesion must communicate with the airways. Most often the bleeding is a consequence of ulceration caused by an

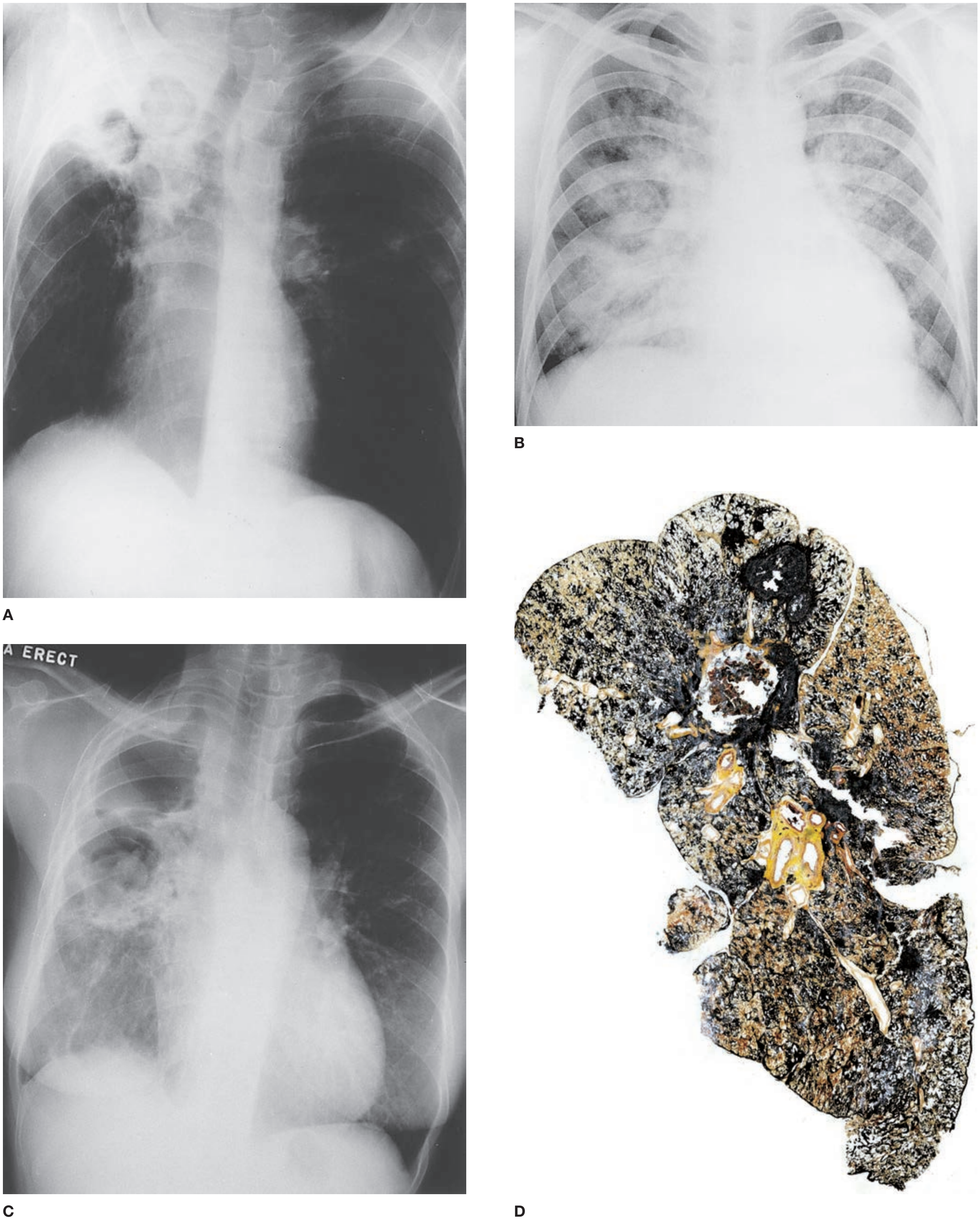


Figure 27-16 Causes of hemoptysis. **A.** Old tuberculosis cavities in right apex. They were removed surgically to control hemoptysis. **B.** Goodpasture syndrome. **C.** Fungus ball in coal miner's pneumoconiosis. **D.** Sagittal section of lung. Fungus ball due to aspergillosis in old tuberculosis cavity. Recurrent hemoptysis was treated with surgical removal of right upper lobe. *(**C.** Reproduced with permission from J. Gough.)*

expanding tumor; sometimes it is due to a pneumonic process or to an abscess in the lung behind an obstructive lesion. Hemoptysis rarely complicates metastatic tumors of the lungs.

Not only malignant, but also benign, tumors of the lung cause bleeding. The classic example is bronchial carcinoid.

Hemoptysis may accompany a severe infection occurring anywhere from the top to the bottom of the respiratory tract. It is uncommon in the usual viral or bacterial pneumonia. Conversely, it is not uncommon in the pneumonia that complicates bronchogenic carcinoma.

The infecting organism determines the appearance and composition of the material that is expectorated with the blood. As indicated previously, in pneumococcal lobar pneumonia, the sputum at the onset is classically described as rusty-looking, but sometimes it is faintly or grossly bloody. In staphylococcal pneumonia, the blood is mixed with pus. In *Klebsiella* pneumonia, the bloody sputum is historically described as resembling currant jelly. Brisk bleeding is common in lung abscess; the blood is mixed with copious amounts of foul-smelling pus. In lung gangrene, blood is associated with necrotic lung tissue.

Bleeding is common in bronchiectasis. Because it usually originates in a bronchial artery, bleeding is often brisk. While most episodes stop spontaneously, the hemoptysis tends to recur and may be life-threatening.

Fungal infections of the lungs may cause hemoptysis (Fig. 27-16). As in tuberculosis, hemoptysis is generally a consequence of a continuing necrotizing and ulcerating inflammatory process or of bronchiectasis. The most common fungal disorder associated with hemoptysis is a "fungus ball" that resides either in a healed tuberculous or bronchiectatic area or in a cystic residue of sarcoidosis. *Aspergillus* is the usual fungal agent; less often another fungus (e.g., *Mucor*) is the cause.

At one time, the most common source of hemoptysis was an active tuberculosis cavity. Despite the increasing frequency of tuberculosis, hemoptysis is uncommon because of effective antituberculous therapy. If tuberculosis is allowed to progress to the point of extensive fibrosis and cavitation, or becomes complicated by bronchiectasis, hemoptysis can be troublesome and persistent. Hemoptysis may arise from a *Rasmussen aneurysm*, which is an erosion of a small- or medium-sized pulmonary artery into an adjacent tuberculosis cavity.

The "right middle lobe syndrome" is frequently associated with hemoptysis. It is due to a partial or complete obstruction of the right middle lobe bronchus, resulting in atelectasis or pneumonitis in the right middle lobe. The obstruction is more often caused by scarring or inflammation than by physical compression of the lumen by an enlarged lymph node. The cause is usually infectious; the infection may be tuberculosis.

In parts of the world where amebiasis is endemic, hemoptysis follows perforation into the airways of an amebic lung abscess. The sputum resembles anchovy sauce.

■ Cardiovascular Disorders

Pulmonary congestion and alveolar edema sometimes produce blood-tinged sputum. In chronic pulmonary congestion secondary to left ventricular failure or to mitral valve disease, alveolar macrophages in the sputum are often laden with hemosiderin ("heart failure cells"). In severe congestion and edema, the sputum is often pink and frothy. Usually there is no difficulty in recognizing that inadequate performance of the left ventricle is the cause of the bloody sputum.

Pulmonary thromboembolism may produce hemoptysis when associated with infarction (Fig. 27-17). The hemoptysis of pulmonary infarction is usually associated with pleuritic pain and, often, with a small pleural effusion because of the peripheral location of the infarct.

Historically, tight mitral stenosis was sometimes first manifested by a bout of brisk, bright-red hemoptysis that is difficult to control. The source of the bleeding is the submucosal bronchial veins, which proliferate considerably in this disorder. Massive hemoptysis due to mitral stenosis is not frequently seen in modern times.

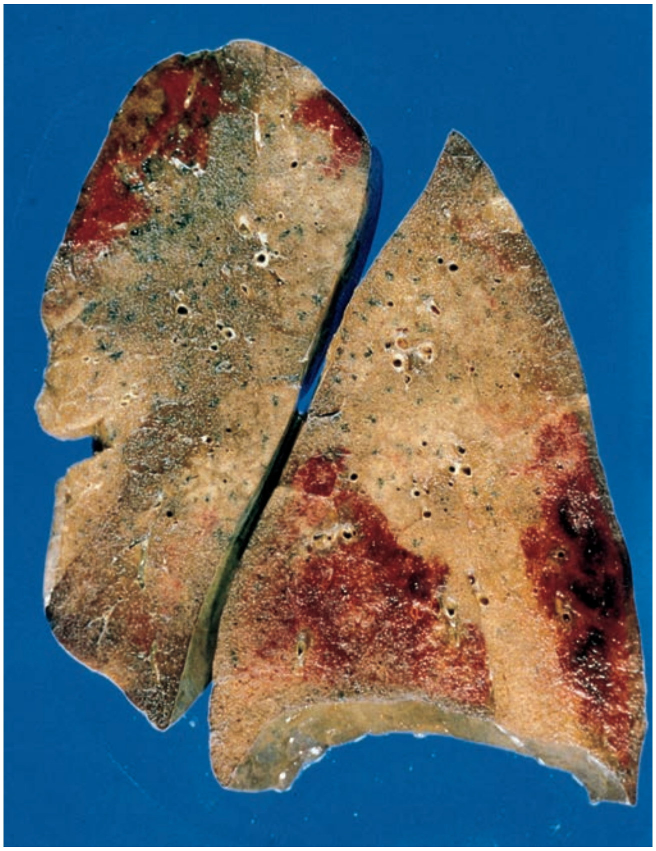


Figure 27-17 Hemorrhagic pulmonary infarcts. Several subpleural areas of infarction are clearly demarcated.

Hemoptysis from other circulatory disorders should be noted. Occasionally, an aortic aneurysm penetrates into the tracheobronchial tree, causing death by exsanguination and asphyxiation. An extraordinary event is the communication of an arteriovenous fistula with a small airway, causing bleeding that is exceedingly difficult to arrest.

■ Trauma

Hemoptysis follows a variety of chest injuries: puncture of a lung by a fractured rib, contusions of a lung by severe blunt trauma to the chest, and necrosis of the lining of the tracheobronchial tree by inhaled fumes or smoke. Blunt trauma from the steering wheel during an automobile collision sometimes lacerates or fractures the tracheobronchial tree. Stab or gunshot wounds often tear the lungs or airways. On occasion, mucosal lacerations in the course of severe coughing evoke hemoptysis.

After lobectomy, or now, much less commonly, pneumonectomy, a large hemothorax occasionally empties into the airways. This is an alarming and ominous event. Its imminent occurrence is often heralded by the expectoration of blood-stained sputum after a paroxysm of coughing. The hemothorax must be promptly evacuated and the bronchus surgically repaired. Hemoptysis within a few weeks to months after lung resection has different implications: recurrence of tumor, granulation tissue, or bronchial sutures. Prompt bronchoscopy is necessary for accurate appraisal of the situation.

■ Miscellaneous

Other causes of hemoptysis are listed in Table 27-10. They vary greatly in severity, urgency, and prognosis. Sometimes the cause is obscure, as in the occasional instance of hemoptysis that accompanies menstruation (*catamenial hemoptysis*). An aspirated foreign body produces bleeding by damaging the mucosa on impact; if allowed to remain in place, it sometimes causes bronchiectasis, which, in turn, may cause bleeding. Pulmonary calcific foci, either in the pulmonary parenchyma or in lymph nodes, sometimes cause hemoptysis by ulcerating into a bronchus.

Thrombocytopenic purpura and hemophilia and the therapeutic use of anticoagulants are occasional causes of hemoptysis.

Hemoptysis in Goodpasture syndrome (Fig. 27-16) or in idiopathic hemosiderosis is life-threatening.

Management of Massive Hemoptysis

The first priority in the care of a patient with life-threatening hemoptysis is to protect the airway and prevent asphyxiation.[47] Intubation should be contemplated and consideration given to selective intubation of one lung in order to protect it from spillage of blood from the other. When the site of bleeding is known, one simple, initial bedside maneuver is to place the involved side in a dependent position in order to protect the uninvolved lung. Bronchoscopy should be performed promptly in order to identify the source (Chapter 33). This may also allow bronchoscopic interventions, such as the placement of a balloon catheter to isolate the involved segment, lavage with iced saline, or the application of topical epinephrine. Bronchoscopic localization may help to guide attempts at arresting the bleeding by angiographic embolization. If these modalities fail to stop the bleeding, surgical exploration may be required. Not surprisingly, emergency procedures are accompanied by a high mortality. None of the approaches has been rigorously studied, and the choice is frequently dictated by the urgency, local experience, and availability of bronchoscopy.

CYANOSIS

Cyanosis refers to a bluish discoloration of the skin that is caused by increased amounts of reduced hemoglobin in the subcapillary venous plexus. The discoloration is most apparent in the lobes of the ears, the cutaneous surfaces of the lips, and the nail beds. In patients with dark skin, the mucus membranes and the retina are important sites to examine for cyanosis. Unless flow through the skin is slowed, as in heart failure, cyanosis implies arterial hypoxemia. Cyanosis does not appear in carbon monoxide poisoning or in severe anemia, even though arterial O_2 content is extremely low. This is because there is an insufficient amount of reduced hemoglobin present for the cyanotic discoloration to be visible. The presence of abnormal pigments in blood, such as methemoglobin or bilirubin, complicates the detection of cyanosis.

Capillary O_2 Content

An increase in the amount of reduced hemoglobin in the capillaries of the skin, as elsewhere, results from inadequate oxygenation of arterial blood, excessive removal of O_2 from capillary blood (as when the circulation through a region is slowed by vasoconstriction or a very low cardiac output), or from a combination of the two. The concentration of reduced hemoglobin in the skin capillaries must reach about 5 g/dL before cyanosis becomes discernible. Thus, in severe anemia, when hemoglobin concentrations are exceedingly low (on the order of 3–4 g/dL), although virtually all the hemoglobin can be reduced in traversing the skin capillaries, an insufficient amount of reduced hemoglobin remains to produce a visible discoloration. On the other hand, the polycythemic patient develops cyanosis at a higher arterial O_2 saturation than does the normal individual.

Causes of Cyanosis

Several types of cyanosis are usually identified according to the underlying mechanism. They include peripheral cyanosis, cyanosis arising from pulmonary disease, cyanosis from venous admixture, and cyanosis due to abnormal pigments in the blood.

Peripheral Cyanosis

This type of cyanosis is secondary to abnormally large extraction of O_2 from blood flowing through peripheral capillaries. The most common cause is a diminished cardiac output associated with peripheral vasoconstriction. Not only the hands and feet, but also the tip of the nose become blue in severe heart failure. Indeed, in patients with intractable heart failure, necrosis occasionally develops at the tip of the nose.

Peripheral vasoconstriction per se, as in Raynaud's disease, also produces cyanosis of the nail beds.

Cyanosis in Pulmonary Disease

Patients with chronic bronchitis and emphysema characteristically manifest derangements in ventilation–perfusion relationships. In some, arterial hypoxemia results. In patients with diffuse interstitial fibrosis, normal arterial oxygenation at rest is succeeded by arterial hypoxemia, and sometimes, by cyanosis, during exercise. Another cause of arterial hypoxemia is the syndrome of alveolar hypoventilation in patients with normal lungs. In any of these situations, cyanosis is intensified if heart failure supervenes and slows blood flow through the skin (i.e., is associated with decreased O_2 delivery).

Cyanosis Due to Venous Admixture

In patients with intracardiac right-to-left shunts, cyanosis arises from a mixture of venous and arterial blood. The effect of venous admixture is particularly striking if the O_2 content of mixed venous blood is inordinately low, as in some types of congenital heart disease and in severe heart failure. Often, secondary polycythemia contributes to the cyanosis. On occasion, regional cyanosis is diagnostic. For example, in patent ductus arteriosus with reversal of blood flow, the lower extremities are deeply cyanotic, whereas the upper extremities are virtually normal in color.

Cyanosis Due to Abnormal Pigments in Blood

Methemoglobinemia is an occasional cause of cyanosis. Methemoglobinemic blood is chocolate brown, and spectrophotometric examination of blood reveals the characteristic pigment. Arterial blood examination discloses a normal P_{O_2}.

The cause of methemoglobinemia may be hereditary (i.e., due to the presence of hemoglobin M or a deficiency in methemoglobin reductase) or, more often, acquired (e.g., by exposure to chemical agents such as aniline dyes, chlorates, nitrates, and nitrites); methemoglobinemia may also result from drugs, such as dapsone, nitroglycerin, phenacetin, or primaquine. Nitrates are a common cause of methemoglobinemia. Nitrates are reduced to nitrites by bacteria in the intestinal tract. Excessive use of nitroglycerin, an organic nitrate, leads to methemoglobinemia.

In methemoglobinemia, the ferrous iron is oxidized to ferric iron, rendering the hemoglobin molecule incapable of binding O_2 or CO_2. Methemoglobin is formed continuously in the normal erythrocyte, but its level within the cell is kept low (<2%) by intracellular reductive mechanisms. High levels of methemoglobin result from hereditary abnormalities (e.g., a deficiency in methemoglobin reductase) or from exposure to drugs or chemicals that increase the rate of oxidation beyond the reductive capacity of the erythrocytes. Clinical manifestations of methemoglobinemia vary with the blood levels. Concentrations of methemoglobin between 10% and 25% usually cause asymptomatic cyanosis. When these levels are exceeded, dizziness, fatigue, and headache appear.

CLUBBING

Clubbing of the digits is a classic finding in medicine that dates back to Hippocrates' awareness of the association between characteristic changes in the fingertips and empyema. Occasionally, it constitutes a valuable clue to clinically inapparent disease of the lungs and pleura.

Clubbing of the fingers designates the selective bulbous enlargement of the distal segments of the digits due to an increase in soft tissue (Fig. 27-18). Although most often it is painless, clubbing remains an important finding, as its presence should signal an evaluation for potential serious causes.

When full-blown, clubbing is easy to recognize: (1) the nails, particularly the index finger, become abnormally curved in the longitudinal and coronal planes; (2) the hyponychial angle, viewed in profile, becomes blunted, often in conjunction with softening and sponginess of the base of the nail; and (3) the undersurface of the

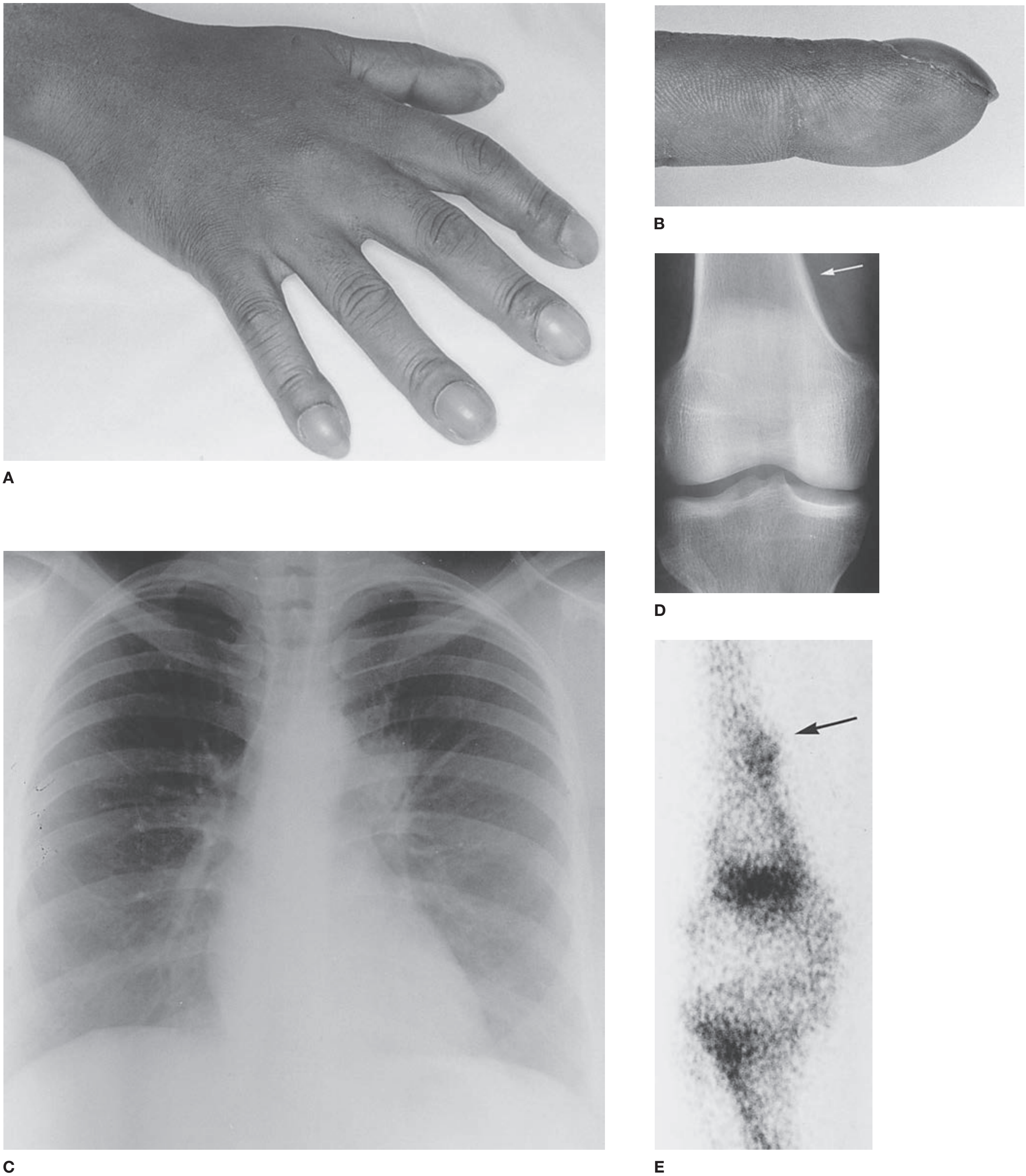


Figure 27-18 Clubbing of the digits and hypertrophic osteoarthropathy. A 40-year-old woman developed swelling and tingling of the fingertips in association with painful swelling of both knees. She was a heavy smoker (36 pack-years) and had an 8-month history of a dry cough. **A.** Clubbing of all fingers. **B.** Index finger. **C.** Left hilar mass that proved to be a primary adenocarcinoma of the lung. **D.** Subperiosteal formation of new bone on the medial aspect of the diaphysis of the femur. **E.** Bone scan, using ^{99m}Tc methylene diphosphonate. An abnormal accumulation of isotope is seen in the area of new bone *(arrow)*.

terminal digit becomes large and bulbous. Early stages of clubbing are subtle and generally difficult to diagnose. Clubbing often has to be distinguished from simple curvature of the nails and, occasionally, from chronic paronychia and Heberden nodes. A variety of methods have been proposed for quantifying clubbing (e.g., measuring casts of the fingertips), but none has become popular.

Clubbing is generally acquired, but it may be hereditary. Acquired clubbing is seen in a wide variety of disorders, both extrathoracic and thoracic (Table 27-1).

It is important to recognize that clubbing is not caused by all forms of chronic lung disease. COPD, for example, does not cause clubbing. The presence of clubbing in a patient with COPD should alert the clinician to the possibility of a second process, commonly lung cancer. As a rule, clubbing is bilaterally symmetrical, affecting hands and feet; on occasion, local factors, such as injury of a finger or of the median nerve, may cause clubbing that is confined to a single finger. Rarely, clubbing may be confined to the digits of one hand (e.g., in an ipsilateral pulmonary sulcus tumor that has invaded the brachial plexus or following hemiplegia). In certain types of congenital heart disease, a telltale distribution of clubbing is of considerable diagnostic value. For example, in patent ductus arteriosus associated with reversal of shunt through the ductus, clubbing affects only the toes.

■ Pathogenesis

The pathogenesis of clubbing is unknown, and no suitable animal model of clubbed fingers has yet been developed, largely because so few species other than primates have fingers. A common denominator in the pathogenesis of clubbing appears to be vasodilation of vessels in the fingertip, including formation of the arteriovenous connections. As a result, hydrostatic pressures increase in the capillaries and venules, promoting the transduction of fluid into the interstitium. The reason for this preferential vasodilation is unclear. A popular notion is that a humoral substance escapes normal deactivation by pulmonary capillaries. This theory could account for clubbing in cyanotic congenital heart disease, in various pulmonary diseases in which proliferation of the bronchial circulation occurs, and in hepatic cirrhosis in which pulmonary arteriovenous anastomoses and right-to-left shunts are common. However, it is difficult to relate this theory to the high incidence of clubbing in subacute bacterial endocarditis.

At present, a single hypothesis that would account for the clubbing that occurs in such diverse disorders as subacute bacterial endocarditis, carcinoma of the lung, hemiplegia, chronic mountain sickness, and purgative abuse is not possible. Indeed, it seems likely that clubbing of the digits is a stereotyped consequence of diverse influences that have in common the capacity to induce marked digital vasodilation and interstitial edema of the soft tissue.

HYPERTROPHIC OSTEOARTHROPATHY

Occasionally, clubbing of the digits is accompanied by hypertrophic osteoarthropathy (HOA), a separate clinical and radiographic entity. Clinically, HOA is manifested by pain and swelling of the soft tissues over the distal ends of the long and tubular bones. Radiographically, the distinctive feature of HOA is the formation of new bone beneath the periosteum of the distal diaphyses of the long bones of the extremities (Fig. 27-18).

The most common disorder associated with HOA is carcinoma of the lung. The incidence is about 5% and is unrelated to the cell type of the cancer, except that small-cell carcinoma is rarely implicated; a peripheral carcinoma of the lung is slightly more common than a central one. Joint symptoms precede the local signs of tumor in about one-third of the cases; the interval is sometimes as long as 2 years. Pulmonary metastases rarely cause HOA. Pulmonary tuberculosis is seldom, if ever, associated with HOA. CF and idiopathic pulmonary fibrosis may be accompanied by HOA. Pregnancy may rarely be a cause of HOA, with symptoms resolving promptly with delivery.

As in the case of clubbing of the digits, theories about pathogenesis tend to focus on humoral factors generated elsewhere. However, a neurogenic theory has also been advanced on the basis of two types of observations: (1) in a few patients, vagotomy has relieved the symptoms of inoperable carcinoma of the lung and led to regression of the bony lesions; and (2) in keeping with the observations on the few patients, vagotomy in dogs is usually followed by a decrease in blood flow to the limbs.

In contrast to clubbing of the digits, which is rarely painful, HOA associated with carcinoma of the lung often causes severe rheumatic symptoms. These symptoms vanish after resection of the carcinoma, even though clubbing usually remains. In patients who are treated with radiotherapy for unresectable carcinoma, pain in the vicinity of the joints usually decreases greatly and usually does not recur even if metastases develop in the lungs or elsewhere.

CHEST PAIN

Pain in the chest is a common clinical problem. It may arise from within the thorax (the heart, pericardium, lungs, pleura, chest wall) or be referred from elsewhere (e.g., from below the diaphragm). Characteristic patterns and associations may help to clarify the source of the pain.

First thoughts about chest pain almost invariably turn to the pain of myocardial ischemia. However, cardiac pain is often distinguishable from other types of chest pain because of its viselike nature; its characteristic radiation to the left arm, shoulder, or neck; and its lack of relation to breathing. Extracardiac painful sensations can arise from various sites within the thorax, most often from the pleura, the lungs, or the chest wall. Pain may also be referred to the thorax as a result of GERD.[48–50] In the primary care setting, in stable patients it is usually possible to exclude as the basis for pain cardiac, gastrointestinal, or pulmonary diseases.[51,52]

■ Pleuritic Pain

The most characteristic pain associated with the respiratory apparatus is pleural pain. It originates in the parietal pleura and endothoracic fascia; the visceral pleura is insensitive to pain. In contrast to the deep, oppressive substernal pain of myocardial infarction, pleuritic pain is identified by the patient as being close to the thoracic cage. It is predominantly an inspiratory pain, reflecting the stretching of inflamed parietal pleura during movement of the thorax; coughing or laughing is distressing; the patient often clutches the chest to minimize its excursion. The pain is usually local, but sometimes it spreads along the course of the intercostal nerves that supply the affected area. Irritation of the diaphragmatic pleura by an inflammatory process either below or above the diaphragm often causes ipsilateral shoulder pain when the central portion of the diaphragm is involved; sometimes the pain is referred to the abdomen when the outer diaphragmatic pleura is irritated.

As a rule, pleural pain is part of a syndrome of pleural inflammation that includes malaise and fever; an important exception to this generalization is the pleural pain of pulmonary infarction, which is often unassociated with any premonitory signs. In addition to inflammation and malignant etiologies, pleuritic pain occurs with pneumothorax.

■ Pulmonary Pain

A second distinctive type of respiratory chest pain accompanies a tracheitis or tracheobronchitis. The pain is searing and is most pronounced after cough. Invariably, this central chest pain is associated with evidence of upper respiratory infection. It is aggravated by cough. Cold air may be intolerable.

An uncommon type of chest pain is associated with pulmonary hypertension. It is usually absent at rest and appears during exertion. The pain is substernal and is associated with dyspnea; it subsides

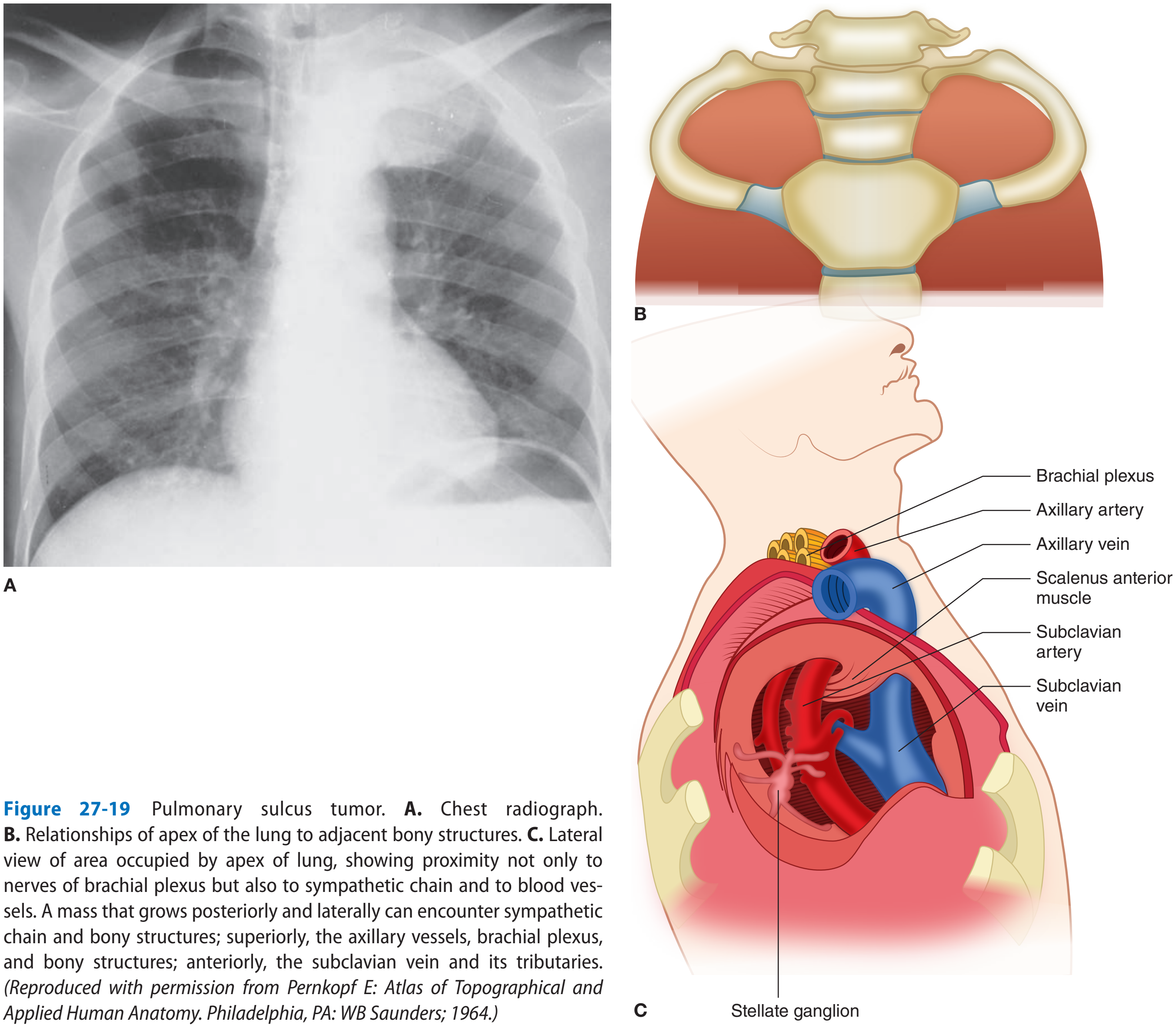


Figure 27-19 Pulmonary sulcus tumor. **A.** Chest radiograph. **B.** Relationships of apex of the lung to adjacent bony structures. **C.** Lateral view of area occupied by apex of lung, showing proximity not only to nerves of brachial plexus but also to sympathetic chain and to blood vessels. A mass that grows posteriorly and laterally can encounter sympathetic chain and bony structures; superiorly, the axillary vessels, brachial plexus, and bony structures; anteriorly, the subclavian vein and its tributaries. *(Reproduced with permission from Pernkopf E: Atlas of Topographical and Applied Human Anatomy. Philadelphia, PA: WB Saunders; 1964.)*

promptly when exercise stops. It is often mistaken for classic angina until the presence of pulmonary hypertension is uncovered. It may be due to right ventricular strain and ischemia.

■ Chest-Wall Pain

Musculoskeletal pain arising in the chest that is also aggravated by breathing may be confused with pleuritic pain. It is rarely severe and incapacitating, is often bilateral, and generally is intensified by changes in body position or flexing the thorax. The affected muscles are often tender to gentle pressure. A fractured rib is often identified as the source of pain by a history of a fall, injury, or trauma. Additional clues are point tenderness and crepitus of the affected area, reproduction of the pain upon manual compression of the chest, or radiographic evidence of a broken rib.

The pain of a pulmonary sulcus tumor, or "Pancoast tumor," (Fig. 27-19) is quite distinctive. This unusual location of a carcinoma of the lung was originally described by Pancoast in 1932. Pain due to the tumor occurs along the distribution of the eighth cervical and first and second thoracic nerves. In addition, Horner syndrome, local destruction of bone by the tumor, and atrophy of hand muscles may be observed. The chest radiograph is distinctive in showing a small, sharply defined shadow at one apex. Destruction of one or more of the upper three ribs posteriorly and of their adjacent transverse processes may also be seen.

■ Cardiac Pain

Attention was called above to the pain of myocardial ischemia. Another type of cardiac pain is that of pericarditis. Pericardial pain is often aggravated by deep breathing and, almost invariably, is accompanied by a telltale rub that is synchronous with the heartbeat. The discomfort may be relieved by leaning forward.

The *postcommissurotomy* or *postpericardiotomy syndrome* is characterized by chest pain that develops within a few days to weeks after cardiac surgery or pericardiotomy. The pain is usually sudden in onset and substernal, with radiation to the left side of the neck; often it is aggravated by deep breathing. Low-grade fever and a high erythrocyte sedimentation rate are regular concomitants.

Chest pain may also be troublesome in patients who have undergone cardiac transplantation. The diagnosis is usually self-evident when account is taken of the antecedent history of cardiac surgery. Indeed, confusion is more apt to arise with the pain of myocardial infarction than with respiratory causes of chest pain.

Miscellaneous Causes of Pain

Other structures in the mediastinum may be the source of chest pain. Noteworthy are the types of pain arising from the esophagus (peptic esophagitis) and dissection of the aorta. Their patterns and intensity help to distinguish them from respiratory pain. Esophageal disease is typically accompanied by a burning pain, frequently after eating. Acid reflux may worsen with recumbency. Aortic dissection is often described with a sharp, tearing sensation of acute onset, with radiation to the shoulder; these are often signs of impending cardiovascular collapse.

Arthritis of the cervical spine is a common cause of thoracic pain. Usually the cause is quite clear because of the characteristic distribution of the pain. Cervical spondylosis occasionally causes severe pain in the chest and arms, but it is more apt to mimic myocardial infarction than is respiratory pain. A metastatic tumor to the thoracic spine often causes bilateral symmetric pain; there is often discomfort to palpation over the affected area. Unilateral pain, along the distribution of an intercostal nerve, is characteristic of herpes zoster before the appearance of the skin eruption and is often described as an intense burning sensation.

Anxiety may produce or intensify chest pain. Usually, pain related to anxiety is accompanied by dyspnea and hyperventilation. Manifestations of vasomotor instability, such as excessive palmar sweating, flushing, and tachycardia, may accompany the complaint of chest pain due to anxiety. Rarely does the pain conform to a characteristic or consistent pattern. Anxiety also interferes with the quantification of pain originating in a somatic lesion and with its management.

FEVER

In the patient with lung disease, fever usually, but not invariably, signifies infection. When the lung disease is chronic, as in bronchitis and emphysema, a bout of acute bronchitis usually elicits only a modest fever, even though the sputum turns purulent. In contrast, an acute pneumonia or lung abscess may be associated with high fever.

The possibility that fever is due to infection lends urgency to the situation. The wide range of pulmonary infections is considered elsewhere in this book.

Neoplasms are also associated with fever. In certain neoplasms, such as carcinoma within a bronchus, the fever is generally a secondary effect attributable to infection distal to obstruction; necrosis within the tumor is a less common cause. In others, such as hypernephroma, fever and chills are striking, even though evidence of infection is absent. A mesothelioma of the pleura is often associated with fever. Presumably, in patients with neoplasms who have no evidence of infection, necrosis within the tumor leads to the elaboration of fever-producing factors within and around the tumor.

Acute hypersensitivity pneumonitis (extrinsic allergic alveolitis) is sometimes accompanied by fever.

In contrast to the pulmonary disorders in which fever is a characteristic feature, pulmonary sarcoidosis is uncommonly associated with fever unless there is extrapulmonary involvement, such as lymphadenopathy or erythema nodosum. Pneumoconiosis is usually not associated with fever unless complicated by necrosis in the midst of conglomerate fibrosis or by superimposed tuberculosis. Among the other many disorders of the lungs that cause no fever (and few systemic complaints) are idiopathic pulmonary fibrosis, lymphangitic carcinomatosis, multiple pulmonary metastases, alveolar proteinosis, idiopathic pulmonary hemosiderosis, and alveolar microlithiasis.

PULMONARY-CUTANEOUS SYNDROMES

Examination of the skin may provide important clues in the diagnosis and treatment of patients with pulmonary disease. Some skin lesions either accompany pulmonary disease or complicate its treatment; occasionally, systemic diseases that affect both skin and lung present first with cutaneous manifestations.

This section focuses on processes in which there are prominent cutaneous manifestations that might impact the care of the patient with pulmonary disease. The diagnosis and development of a differential diagnosis of cutaneous lesions is beyond the scope of this chapter and can be found in general dermatology textbooks.[53–55]

Atopic Dermatitis

Atopy refers to a group of disorders, including asthma, allergic rhinitis, and atopic dermatitis, in which immune and pharmacologic responses are abnormal. The atopic person usually has a family history of one or more of these disorders. Atopic dermatitis is a common disorder, affecting 1% to 3% of the population in the United States. In 85% of affected subjects, the skin lesions appear before 5 years of age.[56] The dermatitis may resolve as the patient reaches adulthood; in the adult, either the skin lesions or respiratory systems may predominate although there is a wide range of individual variability.

In infants, the skin lesions often begin as dry, erythematous plaques on the cheeks; excoriations and scaling may be prominent. In older children, the lesions localize in flexures; lichenification and excoriated papules are prominent features (Fig. 27-20). In adults, the lesions favor the hands and extremities. Atopic subjects also manifest prominent folds of the lower eyelids, periorbital hyperpigmentation with facial pallor, generalized dry skin, and white dermatographism. At any age, pruritus may be prominent, leading to secondary bacterial infection (bacterial impetigo) within the lesions.

The cause of atopic dermatitis is unknown. In all likelihood, the pathogenesis is multifactorial, probably including disordered immune regulation as a causative factor. Patients with atopic dermatitis often have elevated levels of IgE; may have abnormalities of CD30, macrophage-derived chemoattractant, interleukins (IL)-12, -16, -18, and -31, and thymus and activation-regulated chemokine; and have mutations of the filaggrin gene. The use of any of these biomarkers has not yet been demonstrated to be diagnostic or of prognostic value.[56] In persons with atopic dermatitis, abnormalities in cell-mediated immunity and lymphocyte function increase the risk of disseminated viral disease, particularly herpes simplex. The role of food or environmental antigenic challenge in flares of atopic dermatitis is unsettled, but it is known that asthma can be precipitated by such challenges.

The relationship between atopic dermatitis and lung disease is imperfect. Although hyposensitization is useful for asthma, it is either not helpful or is detrimental in atopic dermatitis. In addition, the use of omalizumab, while beneficial for asthma, has

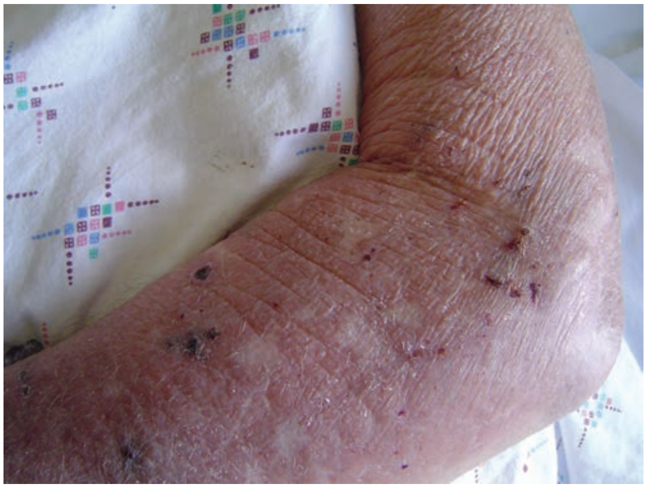


Figure 27-20 Atopic dermatitis is characterized by lichenification, excoriations, and slight scale.

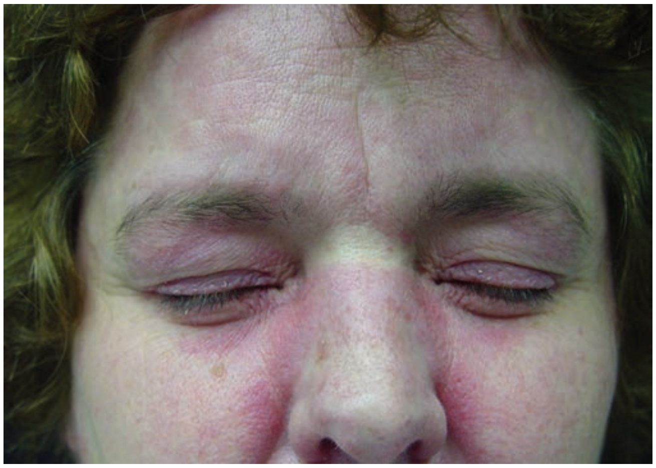


Figure 27-21 Heliotrope eruption of dermatomyositis.

demonstrated mixed results for patients with atopic dermatitis. Recent evidence suggests that the use of dupilumab, an IL-4, IL-13 antagonist, might be useful for atopic dermatitis, as well as for the associated asthma.[57] In addition, there is active clinical investigation using JAK inhibitors and other biologic agents for atopic dermatitis (ClinicalTrials.gov accessed December 29, 2021).

Collagen Vascular Disorders

Common collagen vascular disorders warrant discussion in relation to possible coexisting pulmonary manifestations, especially dermatomyositis (DM) and scleroderma.

Dermatomyositis (DM)

DM is one of the idiopathic inflammatory myopathies. DM characterized by proximal, symmetrical, progressive muscle weakness, and characteristic cutaneous lesions.[58,59] The pathognomonic skin lesions include a heliotrope eruption, which consists of erythematous to violaceous periorbital changes that may be accompanied by edema (Fig. 27-21), and Gottron papules, which consist of erythematous papules over the bony prominences on the dorsal hands (Fig. 27-22). Patients may also manifest a photodistributed poikiloderma (Fig. 27-23), nail-fold changes, and an erythematous to violaceous scaly alopecia. Patients with DM frequently complain of marked itching.

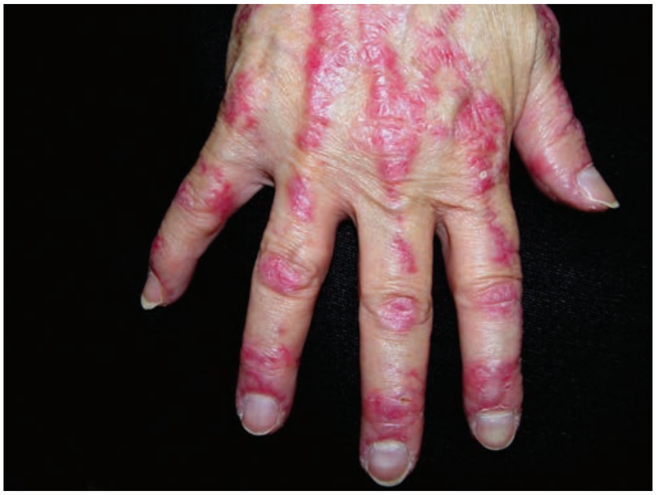


Figure 27-22 Gottron papules in dermatomyositis: Erythematous to violaceous lesions are most prominent over the joints. In addition, this patient demonstrates cuticular and periungual changes that are frequent in dermatomyositis.

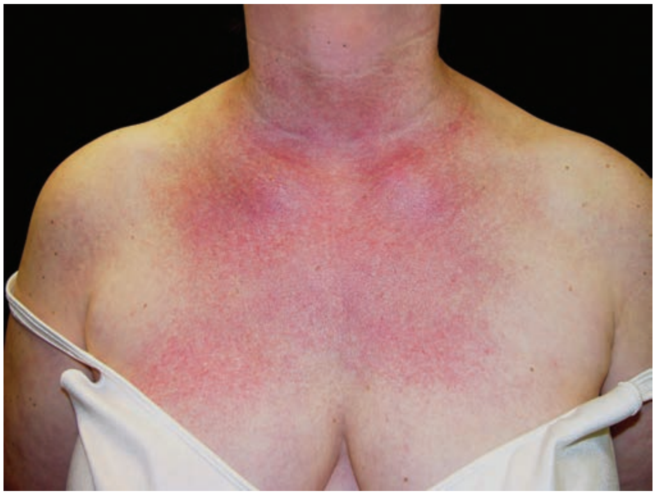


Figure 27-23 Photodistributed poikiloderma in a patient with dermatomyositis.

Patients with DM may also have other systemic manifestations, including arthritis, esophageal disease, and cardiopulmonary disease; some have a malignancy. A variant of DM is known as clinically amyopathic dermatomyositis (CADM). CADM is manifest by skin lesions in the absence of muscle weakness; muscle-derived enzymes are not elevated.

Pulmonary disease occurs in classic DM and in CADM in approximately 15% to 65% of patients. Interstitial pneumonitis is a primary process in DM/polymyositis.

Pulmonary involvement is more frequent in patients with esophageal dysfunction. Lung disease may also occur as a direct complication of the muscle disease, for example, hypoventilation or aspiration in patients with dysphagia, or may be a result of treatment, such as opportunistic infections or drug-induced hypersensitivity pneumonitis.

Pulmonary disease appears to be more prominent in patients in southeast Asia, China, and Japan; however, there are many reports of patients in the United States with varying ethnicities who have developed pulmonary disease, particularly interstitial fibrosis, as well as rapidly progressive and, at times, fatal disease.[60] Patients with polymyositis and lung disease tend to have antisynthetase antibodies, particularly the Jo-1 antibody. However, Jo-1 is rarely found in patients with dermatomyositis. In addition, some of the patients with CADM, specifically those with the myositis-specific antibody, melanoma differentiating antibody 5 (MDA5), are associated with an elevated risk of interstitial lung disease. Further, many of the MDA5+ CADM patients with lung disease have a rapidly progressive course and a high mortality rate. These patients are best treated aggressively, beginning with pulsed intravenous corticosteroids and with intravenous cyclophosphamide and either a calcineurin inhibitor or mycophenolate mofetil. Those who respond may be transitioned to corticosteroids with a traditional immunosuppressive, such as mycophenolate mofetil or azathioprine. Those without a good response might be treated with rituximab and, eventually, lung transplantation.[61]

Scleroderma

Scleroderma refers to hard skin. This process may be localized to the skin or may be part of a systemic disease.[62,63] Localized cutaneous scleroderma may occur as limited plaques of morphea, generalized morphea, deep morphea, or linear scleroderma. Interstitial pneumonitis is an extremely rare complication of morphea or linear scleroderma.

Two principal forms of progressive systemic sclerosis (PSS) have been described: limited scleroderma (acrosclerosis) and diffuse

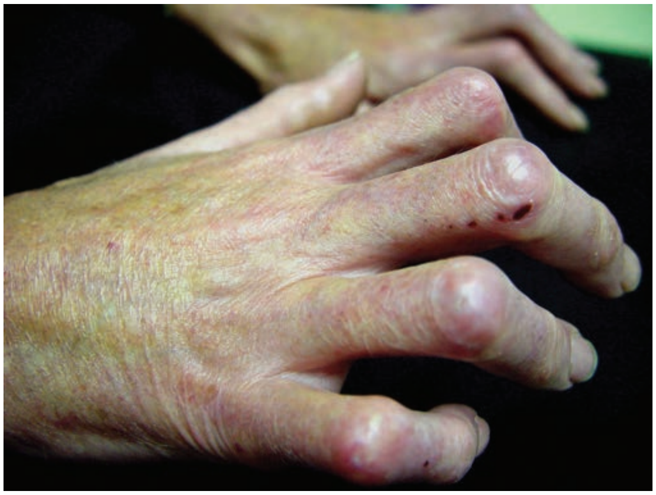


Figure 27-24 Acrosclerosis characterized by marked contractures and sclerodactyly.

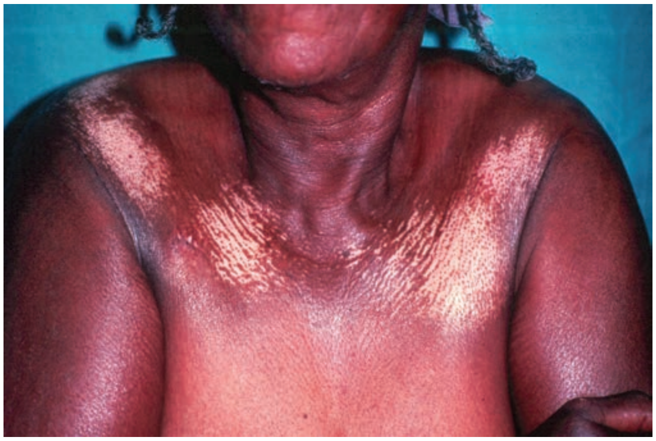


Figure 27-26 Vitiligo-like dyspigmentation associated with progressive systemic sclerosis.

scleroderma. Acrosclerosis is the more common of the two and is characterized by sclerosis of the skin of the fingers (sclerodactyly) (Fig. 27-24) and Raynaud's phenomenon (Fig. 27-25). A variant (CREST syndrome) includes calcinosis, Raynaud's syndrome, esophageal dysmotility, sclerodactyly, and telangiectasia.

In contrast, patients with diffuse scleroderma have widespread sclerosis beyond the acral areas of sclerodactyly. The prognosis for patients with diffuse scleroderma is poorer than those with acrosclerosis. Both types of scleroderma are often preceded by Raynaud's phenomenon, diffuse arthralgias, or arthritis. The skin manifestations begin with transient, recurrent swelling of the hands, and progress to tapered fingers with shiny, hidebound skin (sclerodactyly). The feet, chest, face, and scalp are often involved in the sclerotic process. In time, the skin becomes taut, leading to contractures of the large and small joints that culminate in a claw-like deformity of the hand.

A variety of pigmentary disturbances may occur in scleroderma, including generalized hyperpigmentation that resembles adrenal insufficiency, focal hyperpigmentation or hypopigmentation, and areas of perifollicular pigmentation that resemble vitiligo (Fig. 27-26). Raynaud's phenomenon leads to small pitted scars at the fingertips or frank ulceration, with or without gangrene of the fingertips, toes, knuckles, and ankles, especially the malleoli.

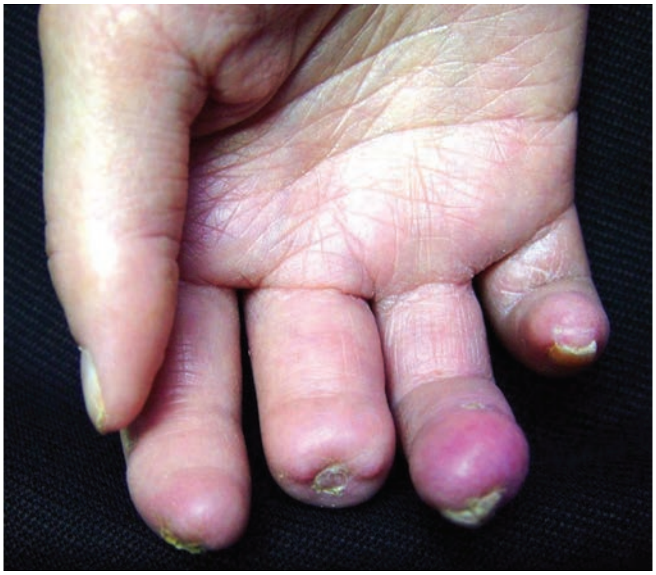


Figure 27-25 Raynaud's phenomenon in this patient was so severe that autoamputation of the distal digits occurred.

The face often undergoes distinctive changes, leading to a fixed stare and inability to wrinkle the forehead. As the facial tissues shrink, the nose becomes pinched, the cheeks sunken, the mouth narrowed, and the lips thinned. In diffuse scleroderma, cutaneous sclerosis, accompanied by a yellowish-brown hue, spreads from the chest to the head and extremities. Sharply delineated, broad telangiectatic macules appear on the face, buccal mucosa, lips, and hands.

PSS is associated with interstitial pneumonitis. This is more common in patients with diffuse disease than in patients with limited disease. Pulmonary hypertension has been reported to occur in patients with CREST syndrome (see Chapter 72).

Treatment of ILD associated with scleroderma is potentially difficult and includes the use of immunosuppressive medications, as well as antifibrotic agents, including nintedanib. Management recommendations are an evolving process, and combinations of therapies might prove effective in the near future.

■ Infections

A variety of infections involving the lungs may have cutaneous involvement.[64] Prototypical examples are described below.

Blastomycosis

Skin lesions are as common as pulmonary lesions in patients with blastomycosis. Cutaneous disease usually represents dissemination from a pulmonary focus that is often small and may be inapparent. The typical presentation is as a solitary nodule or multiple papules or nodules on the face, wrists, hands, or feet, which subsequently ulcerate and discharge pus (Fig. 27-27). The lesions grow eccentrically at the periphery and atrophy centrally over a period of months, eventually forming an arciform or serpiginous contour with sharply elevated and verrucous borders. Miliary abscesses occur along the borders of the lesions. In addition to the cutaneous involvement, osteolytic lesions may occur.

Coccidioidomycosis

Coccidioidomycosis is usually manifest as a pulmonary infection. In its acute form, it is often associated with cutaneous symptoms; roughly 20% of patients develop erythema nodosum (EN). EN is often accompanied by fever, arthritis, and eosinophilia. In patients with progressive pulmonary disease and eventual disseminated disease, the skin may be affected; subcutaneous granulomatous eruptions

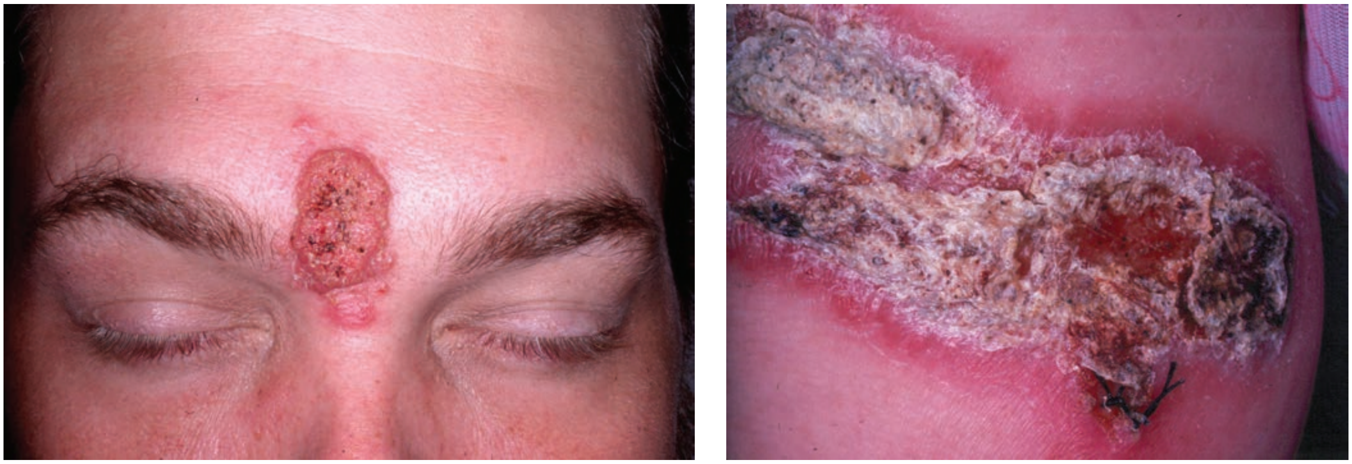


Figure 27-27 **A, B.** Blastomycosis: verrucous lesions on the face (**A**) and trunk (**B**).

form and undergo necrosis and ulceration. After several months, the lesions tend to become verrucous. A third form is primary cutaneous disease, which occurs in farmers and laboratory workers as a chancriform lesion with sporotrichotic spread. This variant is extremely rare.

Actinomycosis

The thoracic form of this disease presents as a pulmonary parenchymal process that sometimes forms multiple draining sinus tracts.[65] Diagnosis is often difficult, but identification of sulfur granules in the draining exudates is helpful.

Tuberculosis

Cutaneous involvement results from direct inoculation with the tubercle bacillus via either the skin or mucus membranes, or as a consequence of widespread organ involvement that begins in the respiratory tract.

When the tubercle is introduced via the skin or mucus membranes by a contaminated syringe or a wound in a previously unexposed host, a nodule usually develops at the site of injury. Within several weeks, the nodule evolves into a chancre, a well-circumscribed ulcer. Particularly if host defenses are impaired, these chancriform lesions, which are typically located on the extremities, develop associated regional lymphadenitis, followed by systemic dissemination of the organism.

A person who was previously infected with *Mycobacterium tuberculosis* is apt to develop *tuberculosis verrucosa cutis* after receiving a cutaneous inoculation. The characteristic lesion in a sensitized person is a papule or a pustule, which becomes verrucous. On occasion, this disorder produces plaque-like lesions of the extremities, consisting of verrucoid-indurated papules surrounded by an erythematous halo.

Lupus vulgaris is the most common form of cutaneous postprimary tuberculosis that follows inoculation or lymphatic or hematogenous spread of *M. tuberculosis.*[66] Patients with this disorder typically present with reddish-brown plaques surrounded peripherally by yellowish nodules, especially on the neck or extremities. The skin lesions tend to spread centrifugally as the center becomes atrophic. Papillary growths also occur in the nasal, buccal, and conjunctival mucosa. Histologically, lupus vulgaris generally shows epithelioid tubercles with caseation necrosis. Chronic cutaneous eruptions tend to involute, leaving considerable scarring. Treatment with antituberculosis drugs is effective in treating these skin manifestations.

Disseminated miliary tuberculosis may result in macules, papules, or vesicles. In children, especially those who are debilitated, subcutaneous nodules or gummas appear, ulcerate, and eventually develop draining sinus tracts, especially in the extremities and trunk. *Scrofuloderma,* which occurs following the necrosis of cervical nodules, is associated with fistula and sinus tract formation in the overlying cutaneous tissues.

Tuberculids are skin lesions that are considered to represent either a hypersensitivity reaction to *M. tuberculosis* or an embolic response to atypical *Mycobacteria.* EN also occurs in association with primary tuberculosis.

HIV Infection

Early in the epidemic of HIV infection, the incidence of Kaposi's sarcoma (KS) increased. However, since the advent of HAART therapy, KS has become less common.[67,68] KS can occur in any immune-suppressed individual, whether the immune dysfunction is due to HIV infection, age, or iatrogenic immunosuppression in transplant recipients.

Human herpesvirus 8 (HHV-8) has been identified and linked to all forms of KS. In addition, HHV-8 viremia is associated with progression on KS in both classic and endemic forms. In the elderly population, KS has an indolent course and occurs primarily on the lower extremities. At the outset, the lesions are dark-blue, purplish, or reddish papules, macules, and nodules (Fig. 27-28). After months to years, plaques evolve in association with thickening of the skin from mid-tibia to ankle and lymphedema. In patients with immune dysfunction, including AIDS, KS is more aggressive and is often widespread in its cutaneous manifestations.

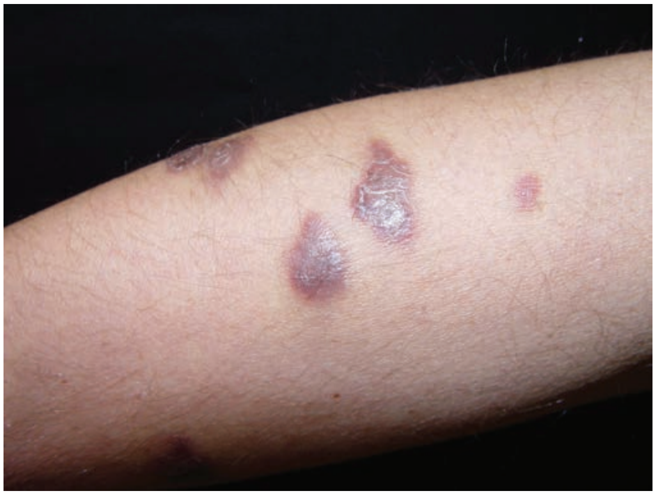


Figure 27-28 Kaposi's sarcoma in an HIV-positive patient.

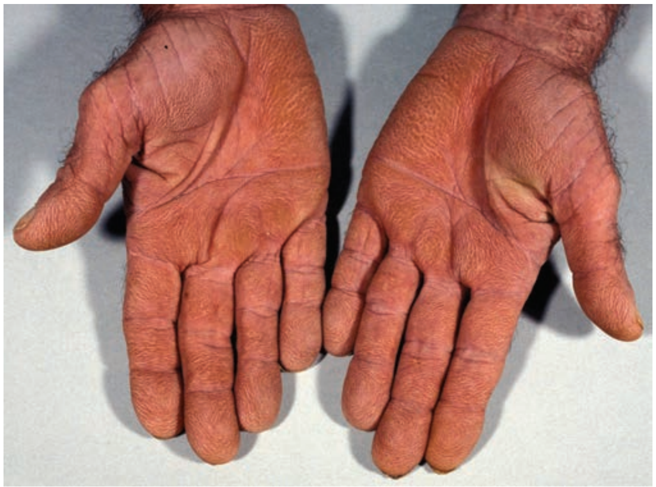


Figure 27-29 Tripe palms. *(Reproduced with permission from Dr. Jon Dyer.)*

The respiratory tract is second only to the gastrointestinal tract in frequency of systemic involvement. Tumors may involve the larynx, trachea, bronchi, pulmonary parenchyma, and pleura. Accordingly, local manifestations of respiratory tract involvement range from hoarseness, signs of airway obstruction, cough, and hemoptysis, to dyspnea. When the parenchyma of the lung is affected, chest radiographs usually show many small nodules; occasionally, parenchymal infiltration of the lung is massive. On bronchoscopic examination, bronchial and tracheal lesions appear as small bluish nodules. Bloody pleural effusions are rare.

■ Lung Cancer

Several paraneoplastic syndromes may occur in patients with lung cancer.[69] In most instances the dermatosis is not specific for lung cancer; other sites may be involved. The following are some of the more ominous manifestations of potential pulmonary malignancy.

Tripe palms is a paraneoplastic condition that is manifest as rugose thickening of the palms and, occasionally, the soles (Fig. 27-29).[70] Patients often have coexistent acanthosis nigricans (AN). Patients with tripe palms and AN usually have adenocarcinomas of the gastrointestinal tract; however, when tripe palms occur in the absence of AN, patients often have squamous cell carcinoma of the lung.

Patients with *Bazex syndrome (acrokeratosis paraneoplastica)* develop an erythematous to violaceous psoriasiform eruption primarily on acral surfaces[71] (Fig. 27-30). The ears, nose, cheeks, hands, feet, and knees are most often affected, but the nails may become dystrophic, and the palms and soles may develop a keratoderma in later stages of the disease. The disorder may develop in stages and is associated primarily with carcinomas of the upper respiratory and digestive tracts (larynx, pharynx, trachea, bronchus, and/or upper esophagus); the malignancy is often detected concurrently. If the tumor is effectively treated the eruption may resolve, but it may return with tumor recurrence.

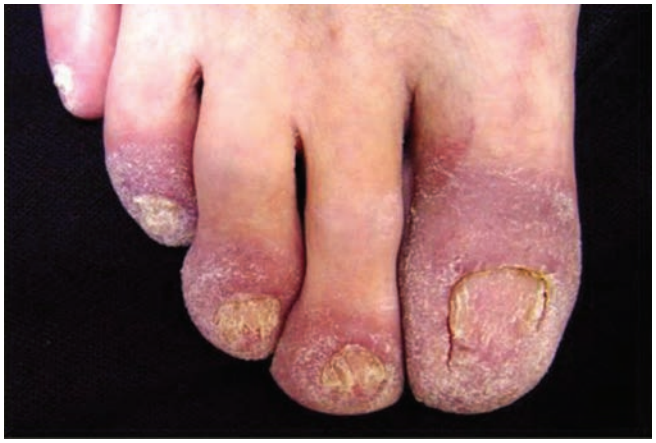


Figure 27-30 Acrokeratosis paraneoplastica (Bazex syndrome). This patient was thought to have psoriasis prior to the diagnosis of a squamous cell carcinoma of the tonsillar pillar.

Ectopic ACTH-producing tumors cause many of the typical signs and symptoms of Cushing syndrome. Intense hyperpigmentation, present in only 6% to 10% of patients with Cushing disease, is especially common in association with ectopic ACTH production and should alert the clinician to the possibility of a hormone-secreting tumor. Although the cause of the hyperpigmentation is unclear, it may be related to tumor production of the peptide β-lipotropin, which contains within its sequence of 91 amino acids the 22-amino-acid sequence of β-MSH. A myasthenia gravis–like syndrome, including profound proximal muscle weakness, may be a striking clinical feature and may reflect either underlying hypokalemia or polymyositis. Small-cell carcinoma of the lung is the tumor most often associated with ectopic ACTH production, although other malignancies have been reported.

The *carcinoid syndrome* is another example of a hormonal syndrome associated with a nonendocrine tumor. The disorder is probably most often caused by the release of the enzyme kallikrein from tumor cells, with subsequent conversion of kininogen to vasoactive kinin peptides, including bradykinin; in addition, increased blood levels of histamine may be important in the rare metastatic gastric carcinoid. The most striking cutaneous manifestations are episodes of flushing, initially lasting 10 to 30 minutes and involving only the upper half of the body; as the flush resolves, gyrate and serpiginous patterns may be noted. With successive attacks more extensive areas may be affected and the redness takes on a cyanotic quality, eventually leading to a more permanent facial cyanotic flush with associated telangiectasia, resembling rosacea. Persistent edema and erythema of the face may result in leonine facies. A pellagra-like picture, which has been noted in some patients, may be due to abnormal tryptophan metabolism. Systemic symptoms associated with the cutaneous flushing include abdominal pain with explosive watery diarrhea, shortness of breath, and hypertension.

Carcinoid tumors are usually found in the appendix or small intestine; extraintestinal carcinoid tumors may arise in the bile ducts, pancreas, stomach, ovaries, or bronchi.[72] The carcinoid syndrome occurs primarily when an intestinal carcinoid tumor metastasizes to the liver or with extraintestinal tumors; flushing attacks can be provoked by palpation of hepatic or abdominal metastases or by alcohol ingestion, enemas, emotional stress, or sudden changes in body temperature. When the syndrome is associated with bronchial adenomas of the carcinoid variety, the flushing is more prolonged and often associated with fever, marked anxiety, disorientation, sweating, salivation, and lacrimation.

Migratory superficial thrombophlebitis and multiple deep venous thromboses have been noted in patients with cancer, especially those with tumors arising in the pancreas, lung, stomach, prostate, or hematopoietic system. The neck, chest, abdominal wall, pelvis, and limbs are most frequently affected.

■ Lymphomatoid Granulomatosis

Lymphomatoid granulomatosis (LYG) is a rare Epstein-Barr virus–associated B cell lymphoproliferative disorder. LYG universally involves the lungs with other common sites, including the skin, the central nervous system, the liver, and the kidneys. It may occur more frequently in patients with immunologic diseases undergoing therapy with immunosuppressive agents, particularly thiopurines and methotrexate. The skin is the most commonly affected extrapulmonary site, occurring in 40% to 50% of patients.[73,74]

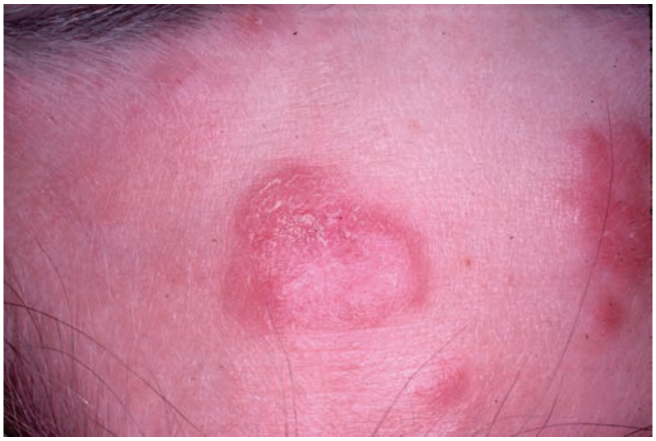


Figure 27-31 Lymphomatoid granulomatosis. This young woman developed the acute onset of multiple erythematous plaques on her face, accompanied by dyspnea and fever. She died within a month from pulmonary disease.

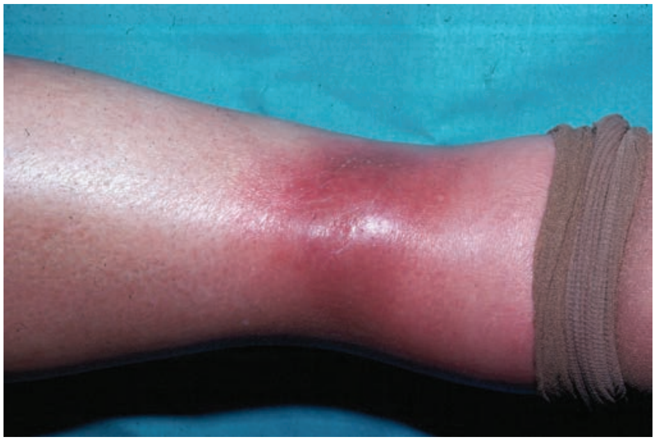


Figure 27-32 Erythema nodosum. Red tender subcutaneous nodule on the leg.

In 10% to 25% of patients, the skin lesions are the first clinical evidence of the disorder; the skin lesions precede involvement of the lungs by 2 weeks to 9 years. Because of the frequent occurrence of skin lesions, ease of performing a skin biopsy, and characteristic histology of the disease, careful dermatologic examination should be carried out in patients suspected of having lymphomatoid granulomatosis.

The characteristic cutaneous lesions are 1- to 4-cm erythematous to purplish dermal papules, or subcutaneous nodules, with or without ulceration.[75]

The lesions generally occur over the buttocks, thighs, and lower extremities (Fig. 27-31), but they may occur anywhere. Healing is often accompanied by scarring and hyperpigmentation.

The skin histopathology is similar to that observed in the lungs and is characterized by a marked angiocentric and angiodestructive lymphohistiocytic infiltrate composed predominantly of CD4-positive T cells. EBV-positive B cells are often present.

Reactive Dermatoses

Two disorders in this category warrant mention: pachydermoperiostosis and EN.

Pachydermoperiostosis is a syndrome in which hypertrophic osteoarthropathy (HOA) is associated with cutaneous changes of the face and extremities that are similar to those that occur in patients with acromegaly. Although this disorder is generally benign, it is occasionally associated with bronchogenic carcinoma.

EN is a relatively common process and is usually acute and self-limited.[76] The typical clinical presentation is the sudden onset of one or more, tender, erythematous nodules on the anterior legs, which are more easily palpated than visualized (Fig. 27-32). The eruption is often preceded by a prodrome of fever, malaise, or arthralgias. As the lesions age, they may develop an ecchymotic appearance. They heal over a 4- to 6-week period, usually without scar formation. Ulceration of the primary process is rare. Although EN is usually acute, patients with chronic or recurrent disease have been described using such terms as "chronic EN," "EN migrans," "subacute nodular migratory panniculitis" (Vilanova's disease), or "septal granulomatous panniculitis." Chronic or recurrent EN most commonly occurs in middle-aged women. The disease is often present for several years and is most common on the legs.

Etiologic or associated conditions are present in about 50% of patients with EN. The associated conditions can be divided into three broad categories: infections, drugs, or systemic diseases (usually inflammatory disorders). The infectious agents associated with EN tend to primarily affect the respiratory or gastrointestinal tract and are most often bacterial or fungal in origin. The most common drugs are antibiotics and oral contraceptives. Pregnancy, particularly in its second trimester, is a known association, and the EN will recur with subsequent pregnancies or with the administration of oral contraceptives. EN-like lesions may occur in Behçet disease and are accompanied by oral and genital ulcerations, pathergy, uveitis, or CNS disease or other systemic manifestations.

A specific variant of sarcoidosis associated with EN is known as Löfgren syndrome.[77] This is an acute, self-resolving process in which EN occurs with bilateral hilar lymphadenopathy, polyarthritis, and anterior uveitis. Granulomatous colitis (Crohn disease), regional enteritis, and ulcerative colitis have been associated with EN. In patients with inflammatory bowel disease, it appears that the EN parallels the activity of the bowel disease. At least half of the cases of EN are not found to have an associated or underlying process.

Neutrophilic Dermatoses: Sweet Syndrome and Pyoderma Gangrenosum

Sweet syndrome (Fig. 27-33) and pyoderma gangrenosum (Fig. 27-34) are distinct dermatoses, but they share common associations and are often managed using similar therapies.[78,79] In addition, a condition

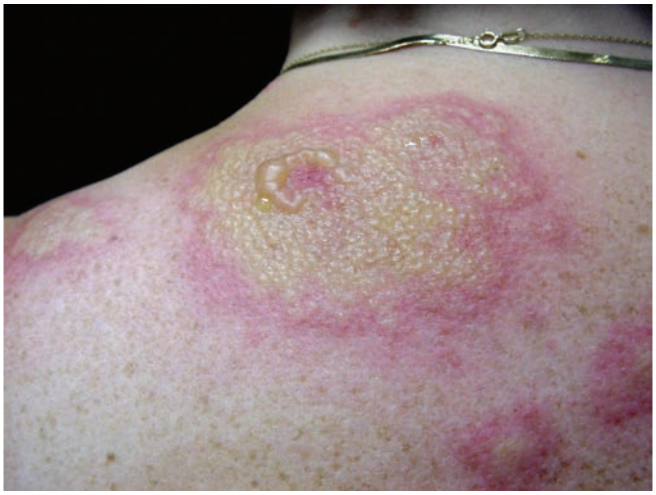


Figure 27-33 Acute febrile neutrophilic dermatosis (Sweet syndrome): erythematous plaque with what appears to be vesiculation on the surface.

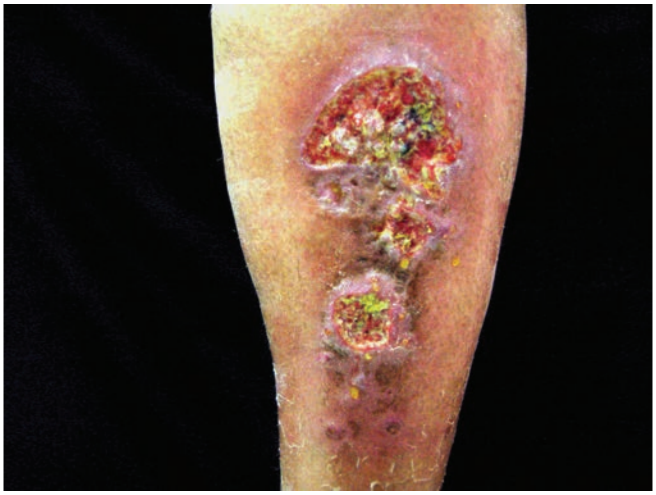


Figure 27-34 Pyoderma gangrenosum: large ulceration on the leg with a violaceous, undermined border. This patient had active Crohn's disease.

known as neutrophilic dermatosis of the dorsal hands (Fig. 27-35) often has characteristics that overlap between a superficial variant of pyoderma gangrenosum (also termed atypical pyoderma gangrenosum) and Sweet syndrome.[79] The associated diseases include inflammatory bowel disease, rheumatoid arthritis, and myelogenous malignancy and premalignancy. Extracutaneous neutrophilic inflammation has been reported in multiple organs, but the lungs are most frequently involved. The inflammatory reaction may cause pulmonary infiltrates, including cavitary disease. It is critical that infectious diseases be excluded with appropriate cultures before initiating therapy with corticosteroids or other immunosuppressive therapy.

■ Pruritus

Pruritus is a symptom that accompanies many dermatoses, but it may also accompany systemic diseases.[80] Patients without an obvious cause for their itching require a systemic evaluation, which usually includes a chest x-ray. Causes for pruritus are not commonly found, but Hodgkin disease and other malignancies might be uncovered during the evaluation. Effective treatment of an underlying malignancy will result in a disappearance of the pruritus.

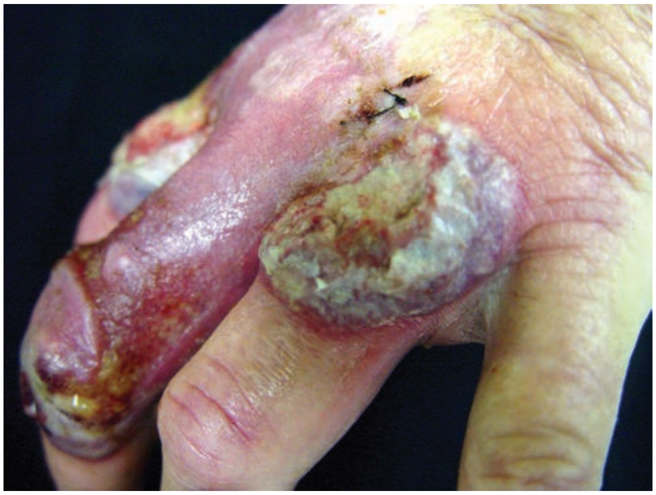


Figure 27-35 Neutrophilic dermatosis of the dorsal hands (also known as atypical pyoderma gangrenosum). Such patients often have a hematologic malignancy or premalignant process.

■ Urticaria

Urticaria is a reactive cutaneous disease manifested by transient urticarial skin lesions. Acute urticaria is almost always due to the ingestion of a food or medication and usually subsides within several days. The presence of chronic urticaria requires a thorough evaluation and, at times, pulmonary evaluation may reveal an infectious, inflammatory, or neoplastic cause (<25% of patients).

■ Vasculitic Syndromes

Important vasculitic syndromes with cutaneous and pulmonary (Chapter 58) involvement are discussed below: granulomatous polyangiitis with eosinophilia (formerly known as Churg–Strauss syndrome), granulomatous polyangiitis (formerly known as Wegener granulomatosis), polyarteritis nodosa, and urticarial vasculitis.

Granulomatous Polyangiitis with Eosinophilia

The clinical picture of allergic rhinitis, asthma, peripheral eosinophilia, and pulmonary infiltrates occurring with systemic vasculitis has been designated the granulomatous polyangiitis with eosinophilia.[81] However, the histologic finding of necrotizing granulomas and tissue eosinophilia is not unique to this clinical syndrome. Indeed, the same histologic appearance may be seen in a wide variety of systemic diseases, including allergic granulomatosis, granulomatosis polyangiitis (see below), rheumatoid arthritis, and lymphoproliferative disease.

One or more types of skin lesions develop in 70% of patients with granulomatous polyangiitis with eosinophilia. Most common is palpable purpura of the extremities; histologically, the lesions show necrotizing vasculitis without granuloma formation. In one-third of patients, the cutaneous lesions are nonspecific—that is, erythematous and urticarial. In another one-third, however, the skin lesions are distinctive—that is, tender, red to violaceous, indurated nodules, measuring 0.5 to 2 cm, which develop central crusting or become infarcted. These nodules occur most often over the scalp or symmetrically over the extensor surfaces of the extremities. These nodules are the ones most likely to have the histologic picture of necrotizing granulomatous vasculitis and eosinophilic infiltration; immunofluorescence staining may show vascular deposition of fibrin and complement.

Granulomatous Polyangiitis

About 45% of patients with granulomatous polyangiitis have cutaneous manifestations, most often small vessel vasculitis manifest as palpable purpura or livedo reticularis.[82] Occasionally, biopsy of the skin lesions reveals usually reveals a small vessel vasculitis and only rarely is a granulomatous process observed. In addition, the presence of cutaneous disease is usually indicative of active systemic involvement; therefore, such patients should be carefully evaluated and aggressively treated.

Polyarteritis Nodosa

Patients with polyarteritis nodosa frequently have cutaneous lesions. The skin disease may represent small vessel vasculitis as in granulomatosis with polyangiitis or may represent medium-sized vessel involvement. In the latter case, the manifestation is livedo reticularis or ulceration.

Urticarial Vasculitis

Urticarial lesions may occur in patients as a manifestation of small vessel vasculitis. Urticarial vasculitis was first described in four patients with recurrent attacks of erythematous urticarial and hemorrhagic skin lesions associated with synovitis and, sometimes, abdominal distress. The patients did not have systemic lupus erythematosus or paraproteinemia, but they did have hypocomplementemia; two had nephritis.

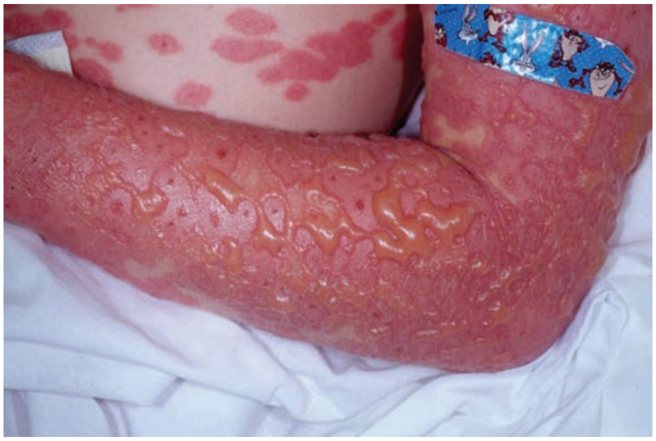


Figure 27-36 Stevens–Johnson syndrome/toxic epidermal necrolysis.

Urticarial lesions may also be an early clinical manifestation of lesions that become typical palpable purpura. The spectrum of urticarial vasculitis has also grown in recent years to include the presence of lung disease, characterized by asthma or obstructive lung disease. Patients with hypocomplementemic urticarial vasculitis often have or develop obstructive pulmonary disease, whereas most patients with normal complement levels, chronic urticarial, and vasculitis have little or no systemic involvement.[83]

Patients are often treated with corticosteroids or other immunosuppressive drugs. Although these agents are useful in controlling the cutaneous lesions, they do not appear to have any impact on progression of the pulmonary disease.

■ Toxic Epidermal Necrolysis

Toxic epidermal necrolysis (TEN) is one of the true dermatologic emergencies.[84] This disorder is most often due to drug administration and develops acutely. Patients often have a prodrome followed shortly by widespread skin involvement with a superficial blistering (Fig. 27-36). Multiple mucosal surfaces are affected (Fig. 27-37). Prognosis is dependent upon the extent of the blistering, age, and the presence of comorbid diseases.

Lung involvement in TEN is unusual, but affected patients often are treated in an intensive care unit or burn unit and frequently become ventilator-dependent. Infections, particularly pneumonia, are a frequent complication and may result in death.

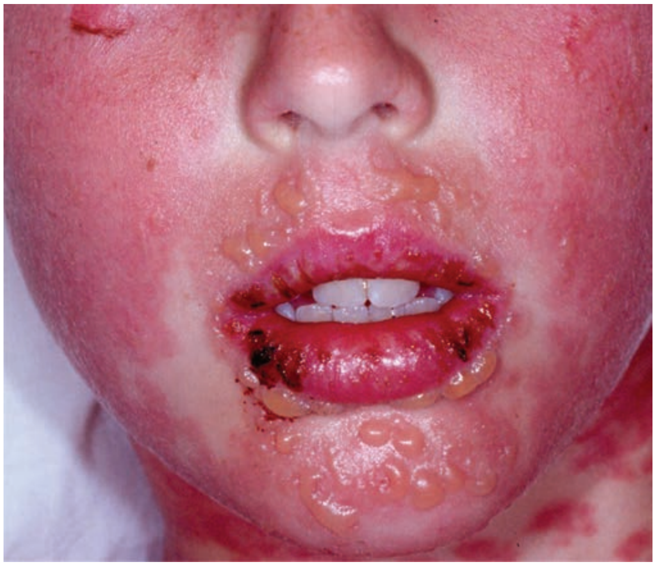


Figure 27-37 Mucosal lesions of Stevens–Johnson syndrome/toxic epidermal necrolysis.

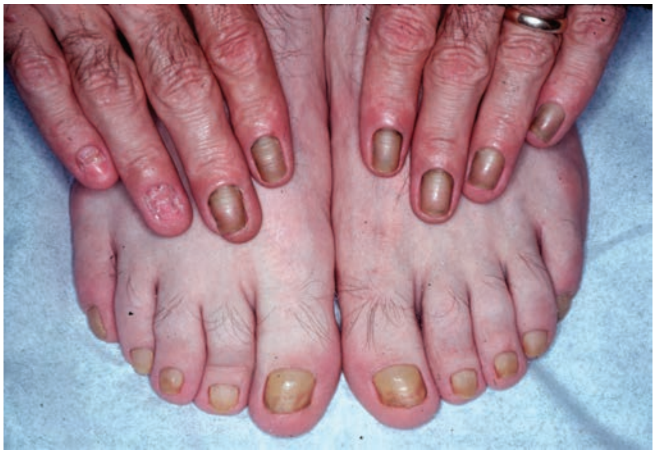


Figure 27-38 Yellow nail syndrome. All 20 nails were affected in this patient.

■ Yellow Nail Syndrome

Thick, yellow discoloration of all 20 nails occurs in the yellow nail syndrome[85] (Fig. 27-38). The nails are thick, but there is no onycholysis and no subungual debris, allowing clinical differentiation from onychomycosis. The nails are not clubbed, and there are no underlying bony abnormalities. This disorder is almost always associated with pulmonary abnormalities, including pleural effusions, lymphoma, and sleep apnea. There is no known therapy for the nail changes in this disorder, but improvement of the associated pulmonary disease may result in improvement of the nails.

■ Miscellaneous Disorders

Pulmonary-cutaneous syndromes include a number of inherited congenital and developmental disorders.

α_1-Antitrypsin Deficiency

α_1-Antitrypsin deficiency is regularly associated with pulmonary (Chapters 39 and 40) or hepatic disease. Cutaneous manifestations may also occur in some patients with this inherited disorder and most commonly manifest as panniculitis or, rarely, as a cutaneous vasculitis.[86,87] Although the panniculitis is a lobular panniculitis, in contrast to the septal panniculitis that is found in EN, the clinical disease is similar except that these patients' lesions may ulcerate.

Cutis Laxa

Cutis laxa is caused by a disorder in the formation of elastin that is transmitted as a dominant hereditary trait.[88] In children with this disorder, skinfolds of the abdomen and face are large and pendulous. The pulmonary manifestations of cutis laxa include emphysema and pulmonary artery stenosis.

Cystic Fibrosis and the Skin

CF is an inherited disorder that frequently affects the lungs and results in premature death (Chapter 48). Some patients with CF have skin disease.[89] Specifically, cutaneous vasculitis seems to be more frequent in CF patients, probably due to the frequent formation of circulating immune complexes.

Ehlers–Danlos Syndrome

The most important disorder of collagen affecting the skin and lungs is Ehlers–Danlos syndrome (cutis hyperelastica), a hereditary

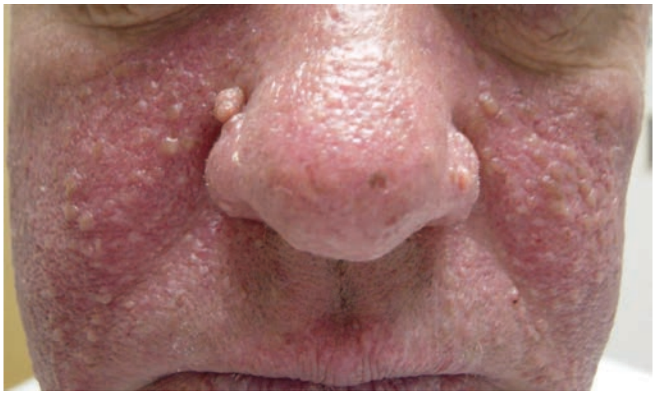


Figure 27-39 Flesh-colored central facial papules in a patient with Birt–Hogg–Dubé syndrome.

disorder of collagen in which the skin and blood vessels are unduly elastic and fragile and the joints are hyperextensible. The skin is smooth, rubbery, and bruisable; the joints are hypermobile. Associated systemic abnormalities include megaesophagus, megacolon, dissecting aortic aneurysm, and diaphragmatic and inguinal hernias. Among the pulmonary disorders are spontaneous pneumothorax, arteriovenous fistulas, megatrachea, and bronchial ectasia.[90]

Birt–Hogg–Dubé Syndrome

Birt, Hogg, and Dubé described an autosomal dominant condition that is manifested by multiple facial flesh-colored papules characterized histologically as trichodiscomas.[91] BHD is due to heterozygous mutations in the folliculin (FLCN) gene located on chromosome 17, which encodes a highly conserved tumor suppressor protein (Fig. 27-39). Affected patients frequently develop renal cell carcinomas, particularly oncocytomas. In addition, multiple lung cysts and development of spontaneous pneumothorax at a young age are common. Although there is no known therapy, recognition of affected patients may lead to discovery of renal tumors prior to metastasis and assessment of family members.

Hereditary Hemorrhagic Telangiectasia

Hereditary hemorrhagic telangiectasia (HHT), also known as Osler–Rendu–Weber syndrome, is an autosomal dominant disorder that is manifested by vascular ectasia in various organs, including the skin and mucus membranes (Fig. 27-40). HHT often is first manifested as nosebleeds. Eventually lesions affect the lips, tongue, nasal mucosa, palate, and palms. Patients with HHT may have arteriovenous malformations in the lungs or CNS. Epistaxis, melena, and hemoptysis are common in adults.

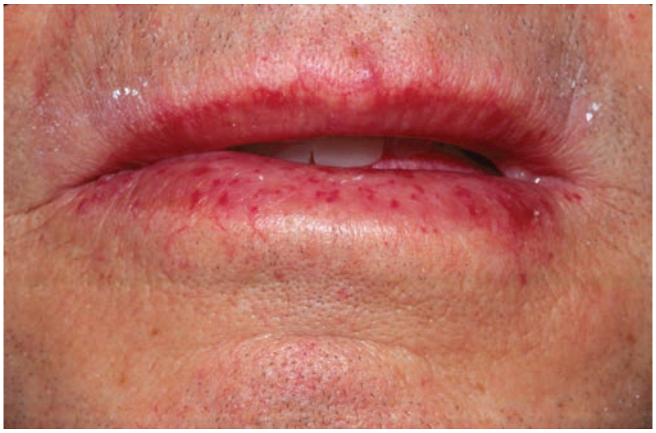


Figure 27-40 Mucosal telangiectasia in a patient with hereditary hemorrhagic telangiectasia.

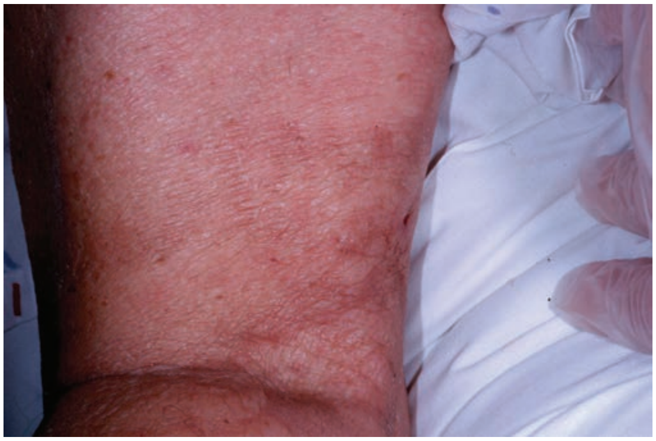


Figure 27-41 Peau d'orange changes in a patient with nephrogenic systemic fibrosis.

Nephrogenic Systemic Fibrosis

Nephrogenic systemic fibrosis is a disorder of the skin in which a rapid onset of skin hardening (Fig. 27-41) occurs in patients with some form of renal disease.[92] Often the onset of the fibrosis is preceded by anasarca. The disease has been linked to gadolinium deposition in tissue following its use for MRI or MRA. Initial descriptions of the disease focused on the cutaneous findings, but it has become evident that patients may also have systemic fibrosis, including pulmonary fibrosis. There is no known effective therapy for these patients, but with time the fibrosis does seem to lessen.

Paraneoplastic Pemphigus

Paraneoplastic pemphigus (PNP) is a severe mucocutaneous disease with a specific pattern of immunofluorescence. It is a rare vesiculobullous disorder. Patients with PNP often present with severe oral erosions and polymorphous cutaneous lesions, including targetoid lesions, bullae, and erosions (Fig. 27-42). Patients with PNP often have a lymphoproliferative disorder with a high prevalence of Castleman disease. In addition to the mucocutaneous disease, these patients frequently have bronchiolitis obliterans.[69]

Sarcoidosis

Sarcoidosis is a multisystem disorder with protean manifestations (Chapter 53). Skin lesions occur in about 25% of patients and may

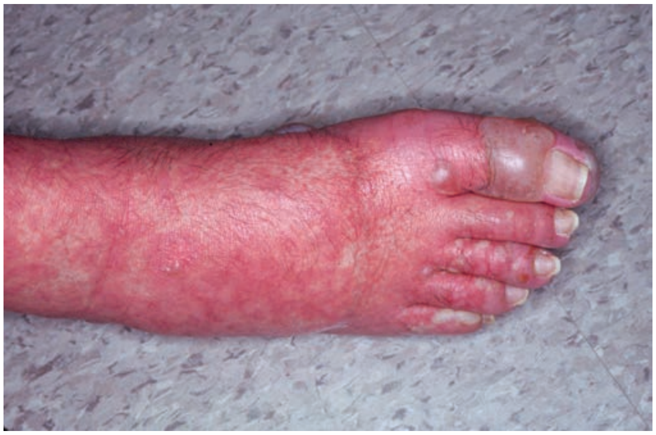


Figure 27-42 Paraneoplastic pemphigus.

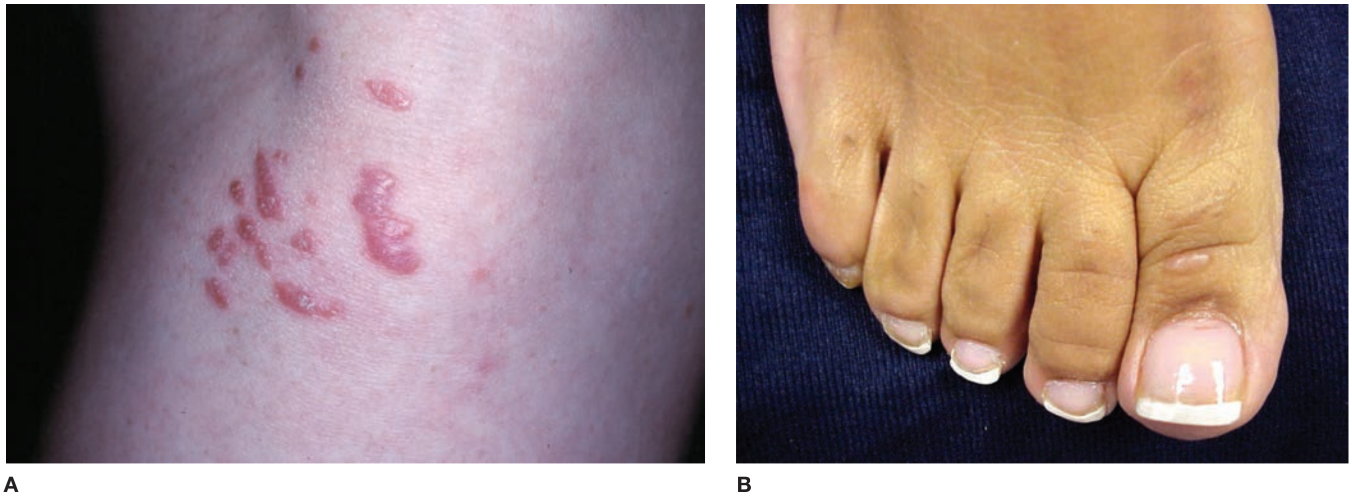


Figure 27-43 **A, B.** Sarcoidosis: acute onset of papular lesions (**A**) on the knees and feet (**B**) were associated with a self-limited course in these patients.

be "histopathologically specific" or "nonspecific." The most common nonspecific manifestation is EN (see above). Histopathologically specific lesions are manifestations of granulomatous inflammation in the skin. Although associated with chronic disease in the past, it now appears that there are many patients with self-limiting granulomatous disease of the skin. Skin lesions are most commonly papules, plaques, or nodules. Rarely is there a great deal of surface change, and ulceration is uncommon.

Several clinical variants are worth noting. Papular lesions on the knees (Fig. 27-43) are commonly associated with EN and are self-limiting. Lesions on the nasal ala (Fig. 27-44) are frequently associated with sarcoidosis of the upper respiratory tract (SURT), and a thorough otolaryngologic evaluation is indicated. Erythematous to violaceous plaques on the face are known as lupus pernio (Fig. 27-45); residual scarring in this disorder is possible. In addition, patients tend to have accompanying chronic disease in the lungs. Finally, lesions of sarcoidosis frequently occur within scars or tattoos (Fig. 27-46). In this circumstance it may be difficult to distinguish sarcoidosis from foreign body granulomas.

Tuberous Sclerosis

Tuberous sclerosis is a hereditary disorder characterized by mental retardation, epilepsy, and skin lesions, including adenoma sebaceum (Fig. 27-47), periungual and subungual fibromas (Fig. 27-48), Shagreen patches, and ash leaf macules. Also seen as part of this disorder are retinal phakomas, calcification of basal ganglia, and ungual fibromas. Approximately 9% of patients with visceral tuberous sclerosis have pulmonary manifestations; some of the pulmonary lesions are cystic and may be associated with recurrent spontaneous pneumothorax and hamartomas. Certain, poorly understood diseases, such as fibrocystic pulmonary dysplasia, may represent a forme fruste of tuberous sclerosis.

MEDICATION TOXICITY

Cutaneous toxicity may arise from therapy given for pulmonary disease. In addition, pulmonary toxicity may develop in the setting of treatment of dermatologic disorders.

■ Dermatologic Toxicity from Agents Used to Treat Pulmonary Disease

Two examples of dermatologic injury from agents used to treat lung disease are described below: epidermal growth factor receptor inhibitors and immunosuppressive agents.

Epidermal Growth Factor Receptor Inhibitors

Epidermal growth factor receptor inhibitors are now being used for the treatment of solid tumors, including lung cancers. These agents

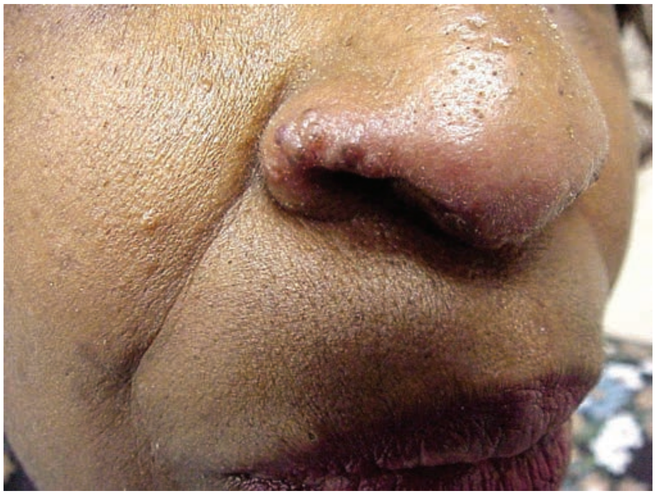


Figure 27-44 Sarcoidosis affecting the nasal ala is regularly associated with granulomatous disease in the upper respiratory tract (SURT).

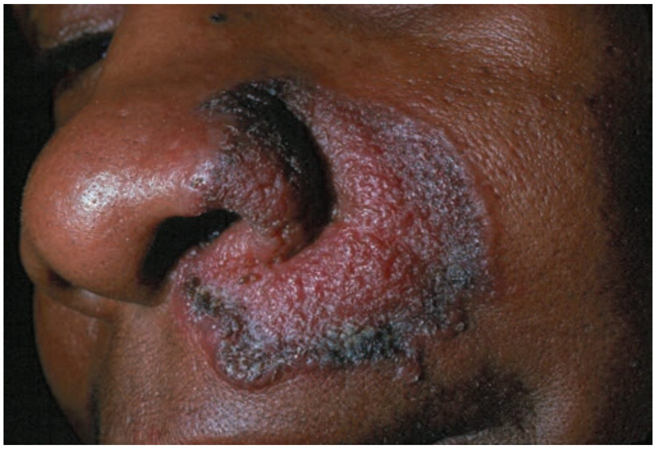


FIGURE 27-45 Lupus pernio (sarcoidosis).

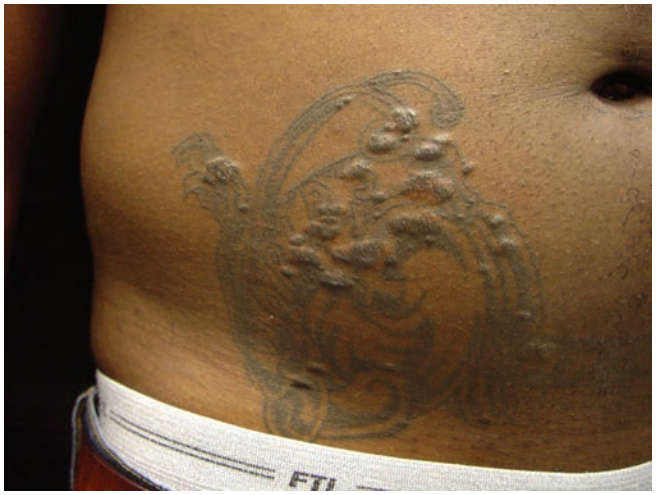


Figure 27-46 Sarcoidosis within tattoos.

are regularly associated with development of an acneiform eruption on the face.[93] The presence and severity of the eruption appear to correlate with survival.

Immunosuppressive Therapy in Lung Transplant Recipients

Patients who are organ recipients are regularly treated with corticosteroids in combination with various immunosuppressive agents. Therapy with corticosteroids has well-known dermatologic consequences, including striae, steroid-acne, or folliculitis, and an increased risk of superficial fungal infections. The intensity of the immunosuppression and duration of therapy are associated with increasing risk of cutaneous malignancy, specifically nonmelanoma skin cancer (NMSC) and KS. Squamous cell carcinoma is overrepresented in comparison with basal cell carcinoma; in addition, the tumors appear to be more aggressive in the presence of immunosuppressive therapy. Therefore, in patients who develop multiple squamous cell carcinomas immunosuppressive therapy should be less intense, if possible, or substitution of cyclosporin and azathioprine by other “less” toxic agents should be considered.

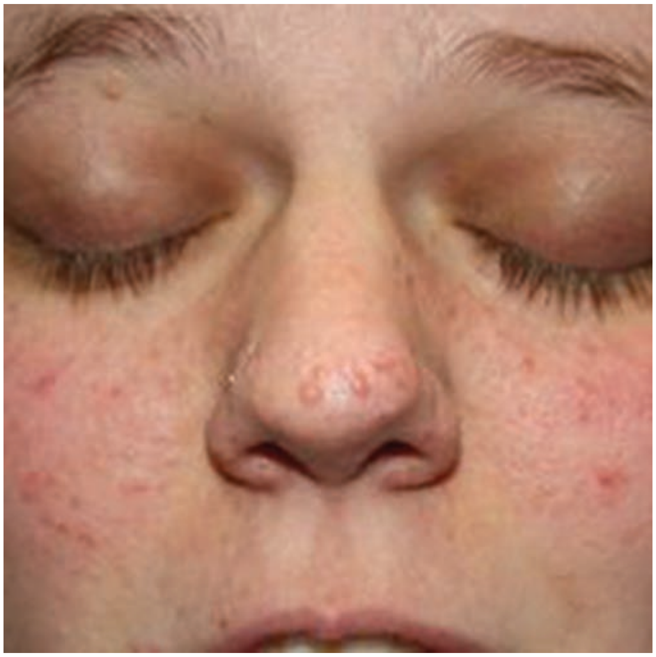


Figure 27-47 Tuberous sclerosis. Fibrous papules on the nasal tip and central face.

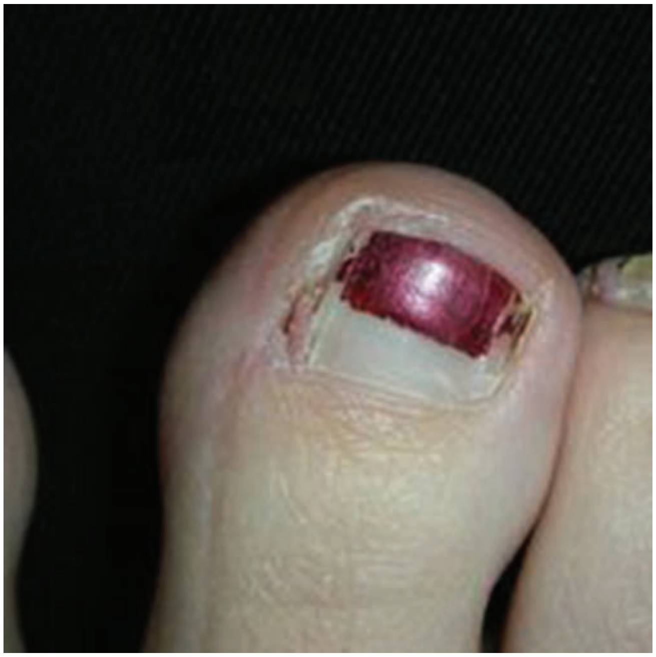


Figure 27-48 Tuberous sclerosis. Periungual fibromas.

■ Pulmonary Toxicity from Dermatologic Therapies

Two examples of pulmonary toxicity arising from agents used to treat dermatologic disorders are described below: methotrexate and tumor necrosis factor-α inhibitors.

Methotrexate

Methotrexate is a common systemic therapy for patients with psoriasis. In addition, it is regularly used for cutaneous dermatomyositis, cutaneous sarcoidosis, and cutaneous lymphomas. Pulmonary toxicity is not common and is believed to be idiosyncratic. Most of the dermatologic use is for psoriasis vulgaris and psoriatic arthritis; fortunately, pulmonary disease appears to be quite rare in these patients. No specific monitoring is recommended.

Biologics and Small Molecules

A growing number of tumor necrosis factor (TNF) antagonists are available, including infliximab, etanercept, adalimumab, golimumab, and certolizumab. In addition, IL 12/23, IL 23, IL 17, and JAK inhibitors are additional therapeutic considerations. These therapies have revolutionized our approach to psoriasis, psoriatic arthritis, inflammatory bowel disease, and rheumatoid arthritis. All have been associated with an increased risk of infection, particularly pneumonia and tuberculosis.

SUMMARY

The diagnostic approach to a patient with suspected pulmonary disease begins with a thorough history and physical examination. Elements of the family history, along with determination of work and other environmental exposures, are important components of the history. Many times, characteristic cutaneous findings shed light on an underlying pulmonary diagnosis. The clinical examination is complemented by radiographic studies, assessment of pulmonary and cardiac function, and routine and specialized laboratory studies, as warranted.

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AL GRAWANY

and Alfred P. Fishman, Approach to the Patient with Respiratory Symptoms.

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CHAPTER 28

Modern Approach to Thoracic Imaging Diagnosis

Eduardo J. Mortani Barbosa Jr.
Leonid Roshkovan

INTRODUCTION

This chapter is not intended to provide a comprehensive review of the entire scope of thoracic imaging; dedicated textbooks in radiology serve this purpose well. Moreover, the chapter does not provide a comprehensive guide to the interpretation of thoracic imaging studies. Rather, the focus is on what modern thoracic imaging can provide to empower clinicians to diagnose and manage common clinical scenarios in the third decade of the 21st century. The goal is to present a strategic approach to thoracic imaging, which starts with broad clinical categories of disease and addresses the following central clinical questions: What is the differential diagnosis and how can a specific diagnosis be confirmed? What is the prognosis and how can disease progression and therapeutic effectiveness best be monitored?

In each subsection, organized initially by imaging technique, and subsequently, by broad diagnostic categories, the authors aim to answer these questions by providing a practical, logical, and evidence-based approach that emphasizes which imaging tests to order and what to expect from each test. Often, imaging findings are either pathognomonic or highly characteristic of a diagnosis in the appropriate clinical context and, therefore, will suffice for clinical diagnosis and management. However, when this is not the case, tissue sampling or additional laboratory tests may be required for diagnostic confirmation; these scenarios are outlined and options discussed for tissue sampling, including image-guided percutaneous biopsy, bronchoscopy, and surgical biopsy. In addition, the ways in which modern functional and quantitative radiographic techniques may impact the field of thoracic imaging in the near future will be considered, and validated clinical applications differentiated from promising research applications that may evolve into useful clinical tools in the next several decades.

Finally, since radiology and, in particular, thoracic imaging, play such a major and central role in modern medicine, our ultimate goal is to enable the practicing pulmonologist to use imaging resources consistently, wisely, efficiently, and effectively.

SUMMARY OF TECHNIQUES: DIAGNOSTIC AND INTERVENTIONAL

The inception of the field of radiology dates back to 1895 with Wilhelm Röentgen's serendipitous discovery of x-rays and subsequent production of the first radiograph. Within only a few years, radiology became established as a new medical field. Chest radiography, although one of the first clinical applications and currently over 100 years old, is still the most frequently performed imaging test worldwide and the cornerstone of initial imaging assessment of most patients with thoracic diseases. Nonetheless, over the last four decades we have witnessed an explosion of technical innovation and developments, with the introduction of ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and hybrid scanners (PET/CT and PET/MRI), which have greatly expanded the ability of modern imaging to accurately diagnose even the smallest or earliest disease processes and revolutionized the practice of medicine.

More recently, the widespread impact that computers have made on the acquisition, distribution, visualization, and post-acquisition processing of medical images has consolidated the central role of radiology. In the future, we hypothesize that major trends will include quantitative and functional imaging, molecular diagnosis, clinical utilization of radiomic and artificial intelligence tools, and value assessment with regard to generating better patient outcomes. In the following sections we present current clinical applications, advantages, and disadvantages of each modality, as well as appropriateness criteria for ordering each test, according to the clinical scenario.

CHEST RADIOGRAPHY

Two basic types of chest radiographic examinations are available—bedside portable AP (anteroposterior) and the combination of PA (posteroanterior) and lateral projections. Supplementary views include oblique, lordotic, lateral decubitus, and expiratory radiographs. For most clinical scenarios, the evaluation should begin with a chest radiograph, as this study remains the most cost-effective imaging test for diagnosing a variety of common clinical conditions (Figs. 28-1 and 28-2). Moreover, chest radiographs are universally available and can be obtained even in patients who cannot be moved to an advanced scanner (e.g., patients in the ICU setting). Nonetheless, in many clinical scenarios, additional advanced imaging will be required to clarify radiographic findings or obtain more

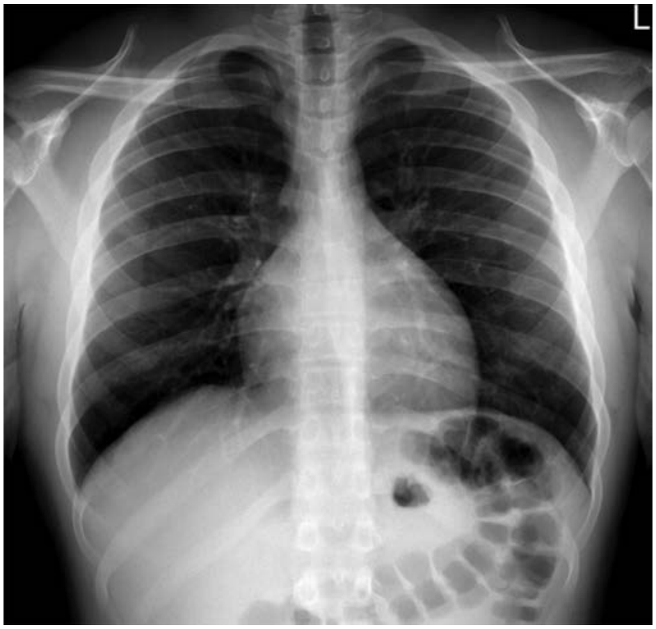


Figure 28-1 Normal PA radiograph.

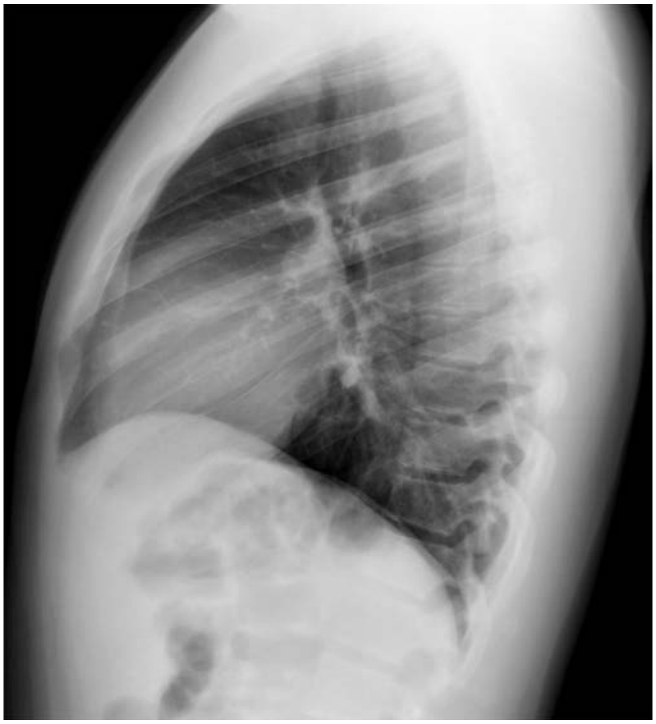


Figure 28-2 Normal lateral radiograph.

accurate characterization of disease pattern and severity (Figs. 28-3 to 28-6).

Whereas the basic physical principles of radiography have not changed in over a century, the quality and clinical availability of chest radiographs have been greatly enhanced in recent decades due to the transition from analog to digital technology. Digital imaging provides better image contrast, reduces the number of suboptimal or nondiagnostic examinations, and permits more immediate examination availability using image transfer and display software.

Currently, two standards for digital radiography exist: computed radiography (CR) and digital radiography (DR), which differ in the process of imaging acquisition. CR utilizes a photostimulable phosphor cassette, just as does the film-screen analog technique; however, the latent image is read by a laser and converted from an analog to digital signal, rather than being transferred to film. DR bypasses this step and utilizes flat panel detectors that directly transform the x-ray signal to a digital image via integrated, thin-film, transistor readout systems. From a practical perspective, DR images are often sharper, with better spatial resolution and, consequently, better visualization of detail. In addition, DR streamlines workflow for routine images and offers the possibility of tailoring the radiation dose.

Most modern facilities use a combination of CR and DR units, due to cost considerations. The principal benefit of CR and DR technology is the ability to process the acquired images to emphasize specific anatomic areas (e.g., lung parenchyma, soft tissues, bones), thereby greatly reducing the need to repeat examinations due to over- or under-penetration by the x-ray beam.[1] Digital methods to "remove" the ribs from the image are now available using either post-processing bone-suppression software or dual-energy acquisition techniques (Figs. 28-7 and 28-8). These approaches can provide an unobstructed view of the lungs for improved detection of nodules and other pulmonary findings. In addition, computer-aided diagnostic techniques and use of artificial intelligence[2] may now assist the radiologist in the detection of subtle lung lesions.

The PA view obtained in the erect position is the standard radiographic examination and demonstrates the anatomy and most thoracic pathologic processes. In particular, the PA view allows evaluation of pulmonary masses and consolidation, diffuse lung disease, pleural effusion, pneumothorax, mediastinal abnormalities, and disorders of the rib cage and scapular girdle.

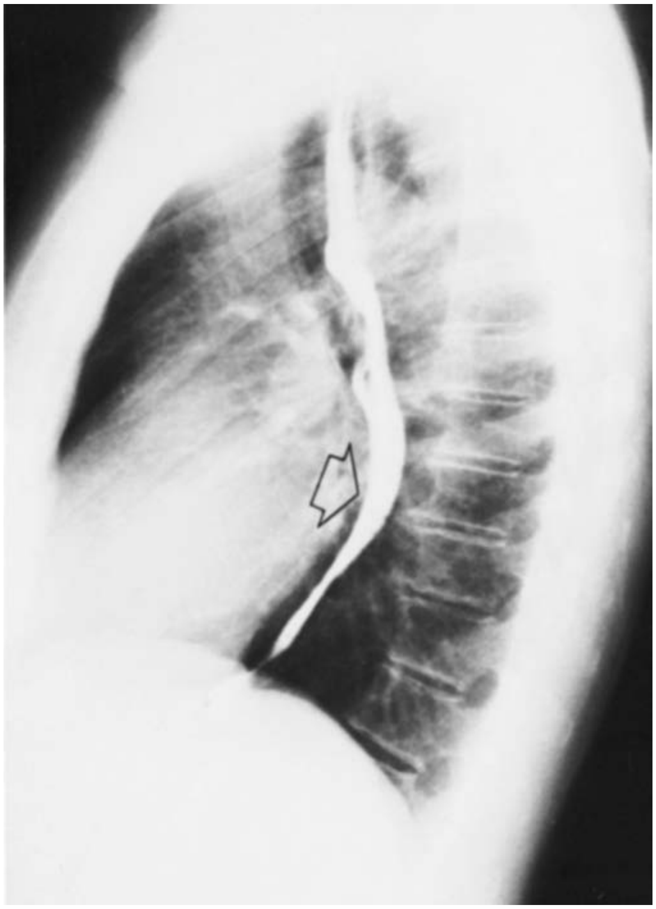


Figure 28-3 Lateral chest radiograph following barium contrast swallow. Not only is this technique very useful for evaluating the esophagus, it is also able to demonstrate left atrial enlargement, with consequent posterior displacement of the contrast column *(arrow)*.

The lateral view provides additional information by better depicting the posterior diaphragms and posterior lung bases, retrocardiac left lung base, anterior mediastinum, and thoracic spine.

The AP view provides similar information to the PA view, but it is limited by lower spatial and contrast resolution and by magnification of the mediastinal structures. In addition, it is less sensitive for detection of small pneumothoraces and pleural effusions. The AP view is often performed in the supine position in bedridden patients, particularly those who are postoperative or in the ICU. AP portable chest radiographs can be very helpful in assessing the position of support lines, tubes, and medical devices. Medical devices can also be enhanced using newer digital image-processing algorithms.

Supplementary views are not routinely performed, unless there is a specific clinical question. In the past, lordotic views were obtained to better visualize the lung apices by displacing the clavicle and first rib shadows superiorly. However, their role has been largely replaced by CT. Expiratory views may be more sensitive in detecting small pneumothoraces, particularly in the setting of recent lung interventional procedures. Lateral decubitus views, although used less frequently than in the past, may be helpful in determining if a pleural opacity seen on standard views is a freely mobile effusion or a loculated effusion or pleural mass. When the patient is imaged with the pleural opacity on the dependent side, a freely mobile pleural effusion conforms to the most dependent region of the

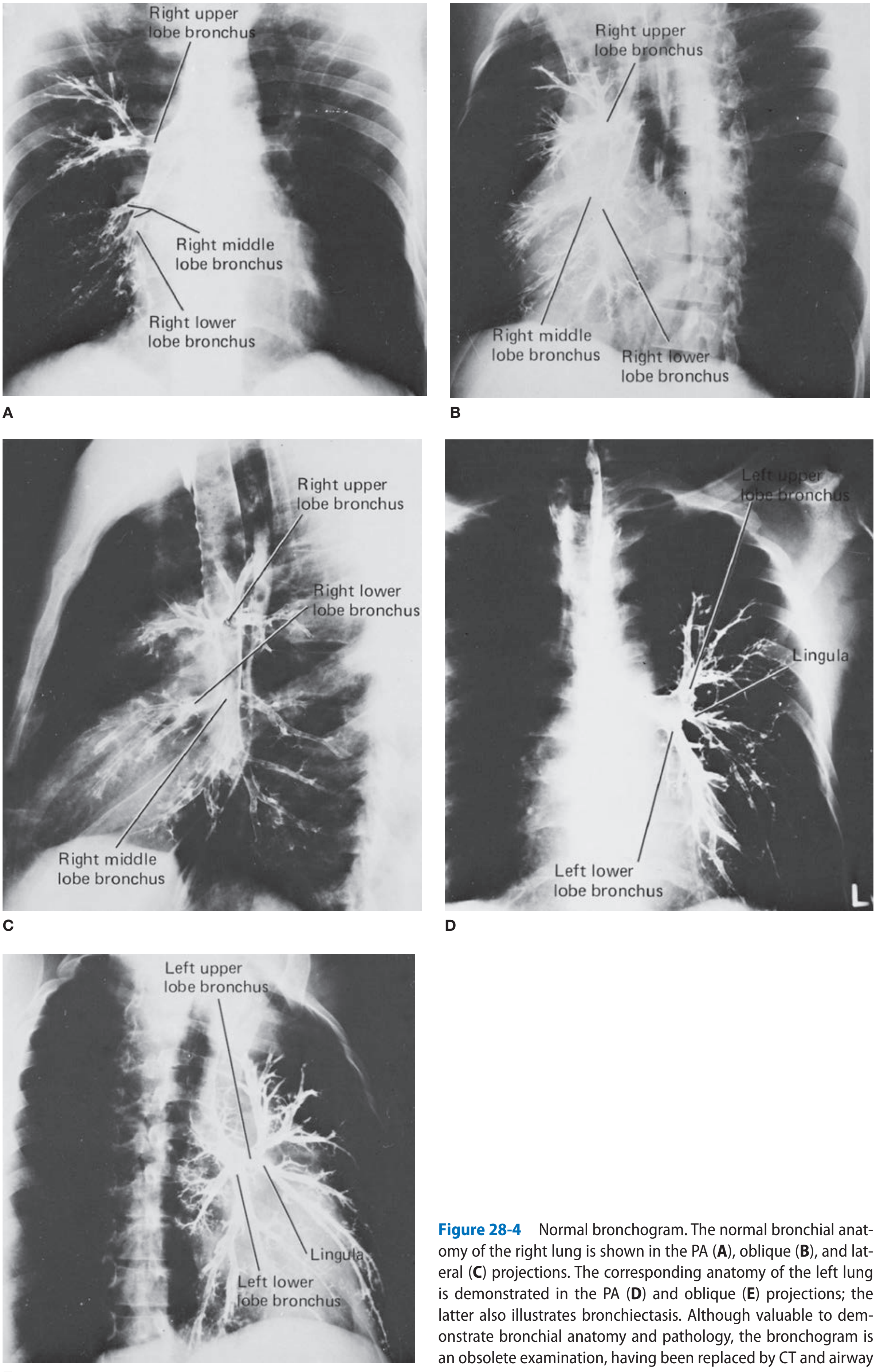

Right upper lobe bronchus
Right middle lobe bronchus
Right lower lobe bronchus
A
Right upper lobe bronchus
Right middle lobe bronchus
Right lower lobe bronchus
B
Right upper lobe bronchus
Right lower lobe bronchus
Right middle lobe bronchus
C
Left upper lobe bronchus
Lingula
Left lower lobe bronchus
L
D
Left upper lobe bronchus
Lingula
Left lower lobe bronchus
E

Figure 28-4 Normal bronchogram. The normal bronchial anatomy of the right lung is shown in the PA (**A**), oblique (**B**), and lateral (**C**) projections. The corresponding anatomy of the left lung is demonstrated in the PA (**D**) and oblique (**E**) projections; the latter also illustrates bronchiectasis. Although valuable to demonstrate bronchial anatomy and pathology, the bronchogram is an obsolete examination, having been replaced by CT and airway reconstruction techniques.

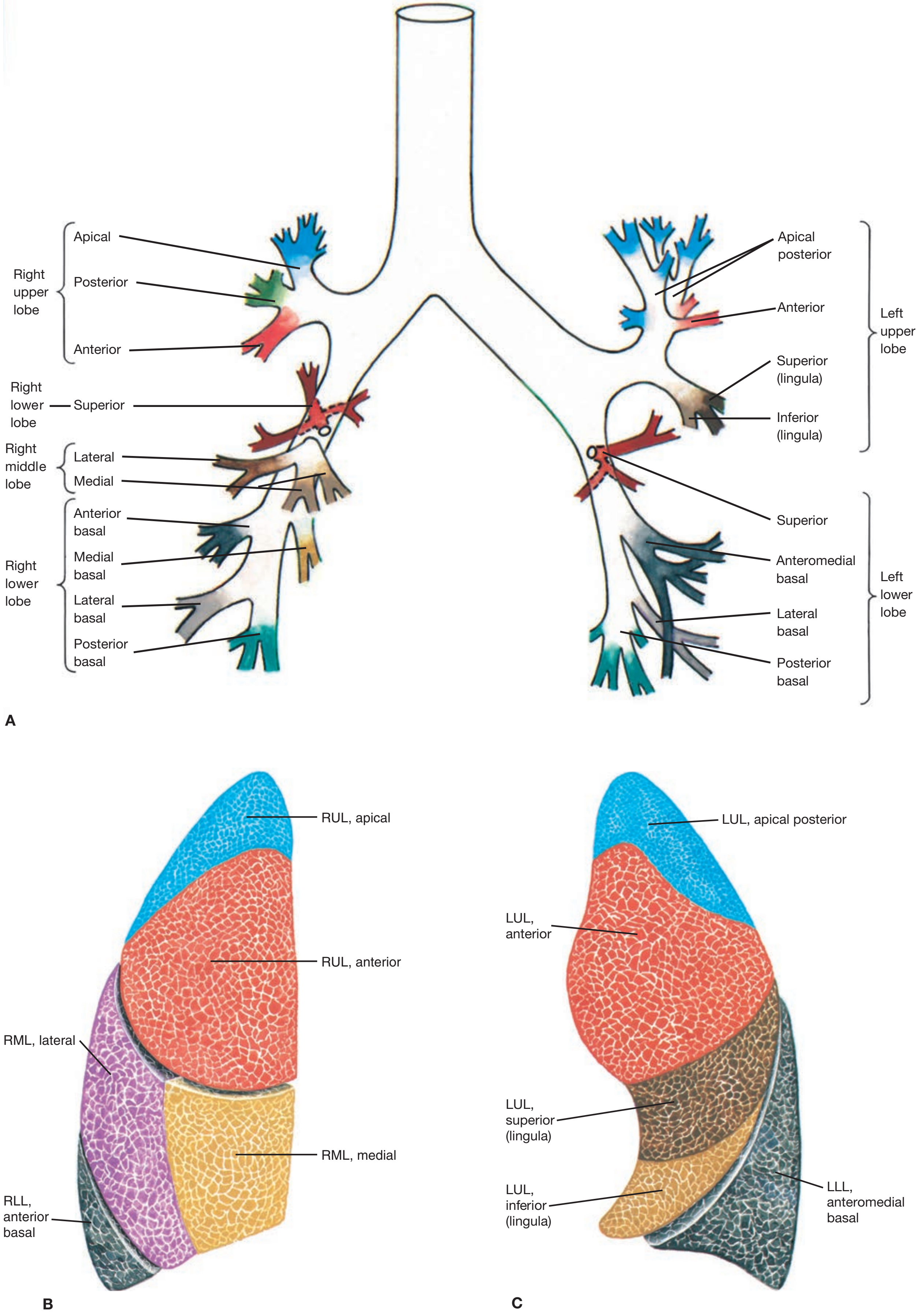

Right upper lobe
Apical
Posterior
Anterior
Right lower lobe
Superior
Right middle lobe
Lateral
Medial
Right lower lobe
Anterior basal
Medial basal
Lateral basal
Posterior basal
Apical posterior
Anterior
Superior (lingula)
Inferior (lingula)
Left upper lobe
Superior
Anteromedial basal
Lateral basal
Posterior basal
Left lower lobe
A
RUL, apical
RUL, anterior
RML, lateral
RML, medial
RLL, anterior basal
B
LUL, apical posterior
LUL, anterior
LUL, superior (lingula)
LUL, inferior (lingula)
LLL, anteromedial basal
C

Figure 28-5 Topographic anatomy of the tracheobronchial tree and respective pulmonary subsegments. **A.** Tracheobronchial tree. **B.** Right lung segments. **C.** Left lung segments. Currently, CT is the best modality for accurate anatomic delineation of pulmonary airway segmentation. LLL, left lower lobe; LUL, left upper lobe; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe.

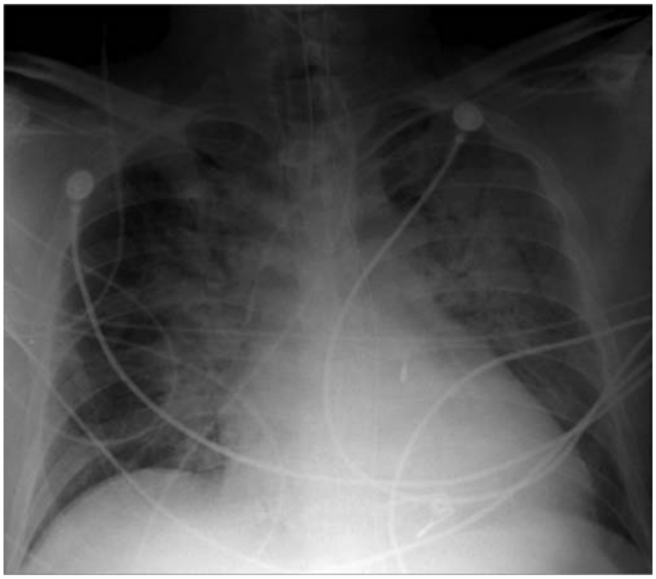


Figure 28-6 Portable anteroposterior (AP) projection chest radiograph, in a patient in the ICU, demonstrating multiple support tubes and lines and the typical configuration of cardiogenic pulmonary edema, with symmetrical bilateral consolidations with perihilar predominance.

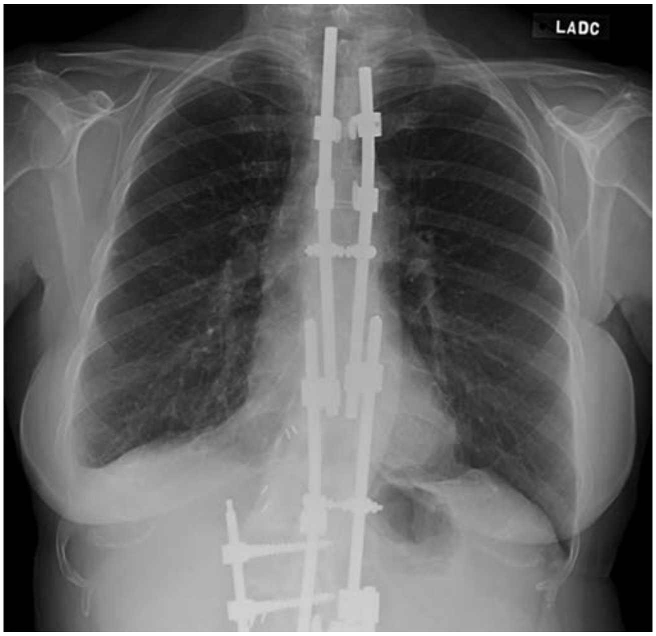


Figure 28-7 Dual-energy PA radiograph without post processing.

hemithorax and a sharp horizontal level demonstrated due to gravity. If a nondependent lucency is seen in the chest or abdomen, in conjunction with a sharp horizontal level delineating it from normal anatomical structures, the diagnosis of a small pneumothorax or pneumoperitoneum may be made. Finally, oblique views are helpful in determining if a questionable radiographic abnormality seen on the frontal view is real or artifactual, as well as in determining its location in the thorax. Performed properly, supplementary views can increase the diagnostic accuracy and clinical utility of chest radiography, sometimes obviating the need for chest CT with its attendant higher cost and radiation exposure.

Many radiographic techniques that were widely used in the past (e.g., laminography, bronchography, air contrast studies, fluoroscopy) have been made obsolete by other techniques and are of historic interest only. The exception is focused fluoroscopy for evaluation of diaphragmatic motion ("sniff test"), in which the patient is imaged during quiet breathing, deep breathing, and forceful inspiration ("sniff"). A paralyzed hemidiaphragm moves paradoxically upward with forceful inspiration. Fluoroscopy in conjunction with barium swallow may also be used to assess esophageal diseases, assessing for both structural and, to a lesser degree, functional abnormalities.[3]

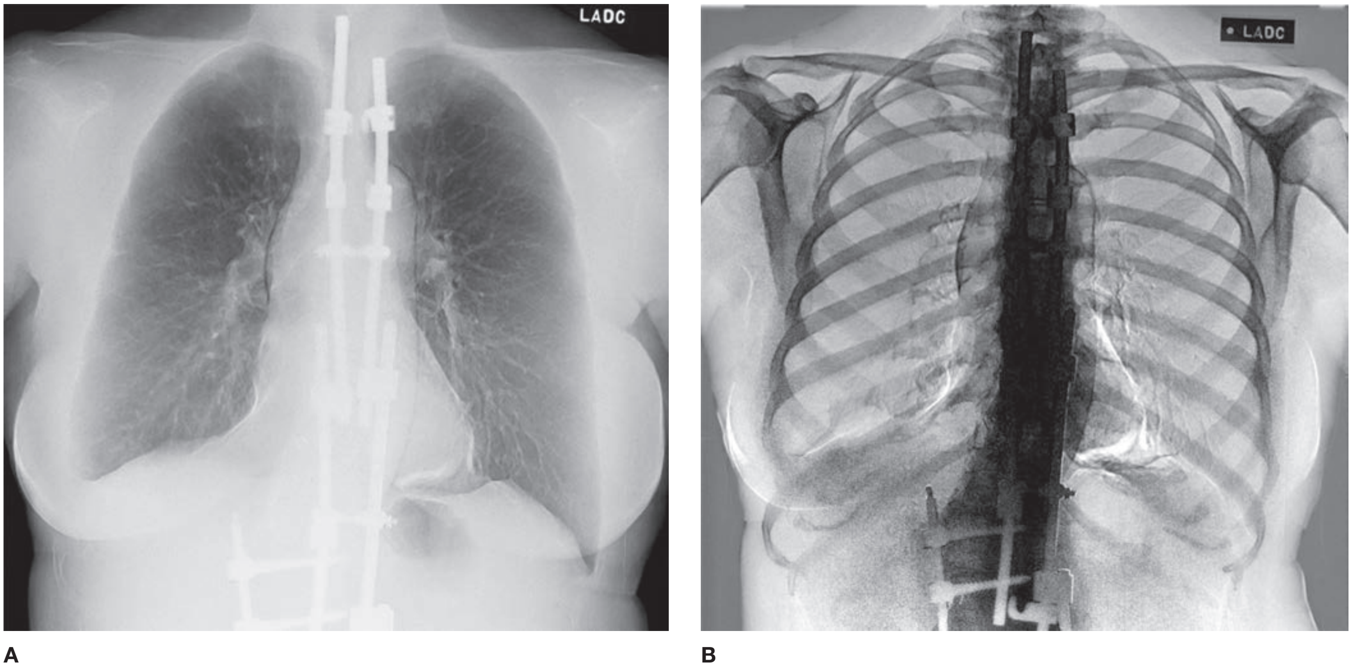


Figure 28-8 **A.** PA radiograph with bone subtraction. **B.** PA radiograph with lung and soft tissue subtraction. This technique may allow detection of subtle disease patterns otherwise obscured on a regular radiographic image.

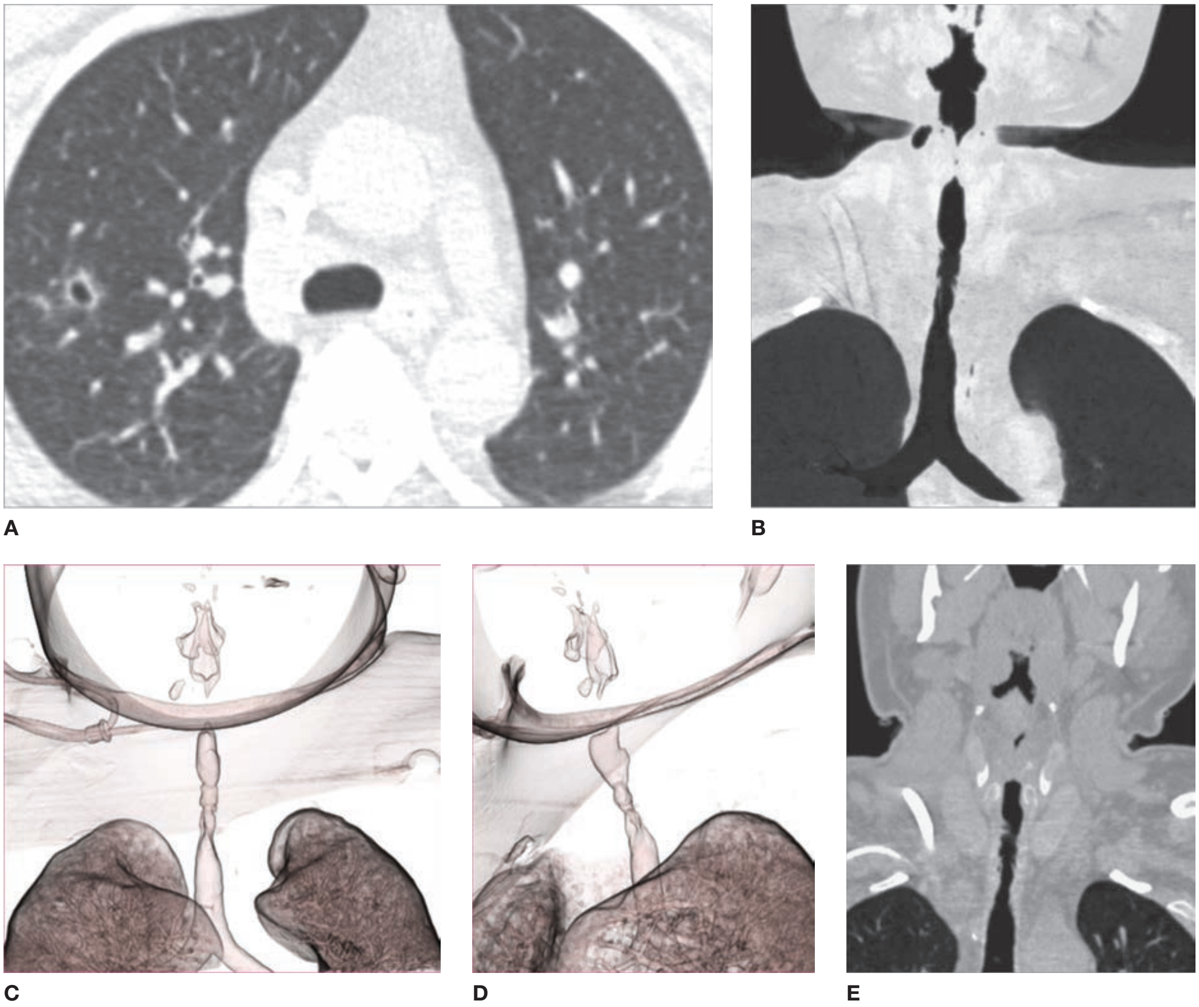


Figure 28-9 CT offers the best imaging evaluation of the pulmonary parenchyma and airways, and advanced postprocessing techniques can provide exquisite views of disease distribution and extension. Granulomatosis with polyangiitis (formerly known as Wegener granulomatosis) affecting the lung and airways. **A.** Cavitary nodule in the right upper lobe; (**B**) minimum intensity projection image demonstrating irregular, long segment narrowing of the upper and middle trachea; (**C**) and (**D**) two different projections of a 3D volume rendering airway reconstruction demonstrating the complex configuration of the stenotic tracheal segment; (**E**) coronal reformatted image depicting tracheal wall thickening associated with stenosis.

CHEST CT

CT is the current cornerstone of advanced thoracic imaging. It is a digital cross-sectional imaging technique that utilizes a rotating x-ray source around the patient, coupled to diametrically positioned sodium iodide detectors in a circular configuration. As the scanner gantry rotates, multiple projections are generated at different angles with different x-ray beam attenuations, depending on which part of the patient's anatomy was traversed. Following scan acquisition, through a mathematical procedure (filtered back projection or, more recently, iterative reconstruction), the sum of projections is transformed into an image in which the relative density of each small volume of the patient's anatomy (voxel) is proportional to its x-ray absorption coefficient and normalized from a scale of –1000 to >+1000 HU (Hounsfield units, zero representing the absorption coefficient of water, –1000 of air). Because it eliminates the main drawback of radiographic techniques, that is, the projection of a three-dimensional (3D) structure into a two-dimensional image, CT allows very accurate localization of pathologic processes. Moreover, the superior contrast resolution of CT allows detailed evaluation of mediastinal and chest wall soft tissue attenuation structures, which are poorly assessed radiographically. CT is also superior to chest radiographs for detection of small pulmonary lesions, as well as for their characterization (Figs. 28-9 and 28-10).

Early CT scanners had a single row of detectors and a single x-ray source, acquiring one axial image at a time before the scanner table was moved to acquire the next image. This process could take more than 30 minutes for a single thoracic CT examination. Most modern scanners have between 64 and 320 rows of detectors, one or two x-ray tubes (dual-source CT scanners), extremely fast and continuous gantry rotation, and simultaneous table translation, resulting in helical image acquisition and the ability to scan the entire chest in less than 1 second. Modern CT scanners are able to produce high-quality, submillimeter, isotropic resolution images that can be reconstructed in any arbitrary plane without loss of detail. Postprocessing techniques utilizing computational algorithms also allow 3D reconstructions, such as volume rendering and maximal-intensity projection images, which can be utilized to demonstrate complex 3D vascular or airway anatomy and pathology. A new generation of commercially available CT scanners called dual-energy scanners (utilizing both high- and low-energy kV settings while scanning) offer additional advantages compared to routine CT scanners based on their ability to perform advanced material decomposition—e.g.,

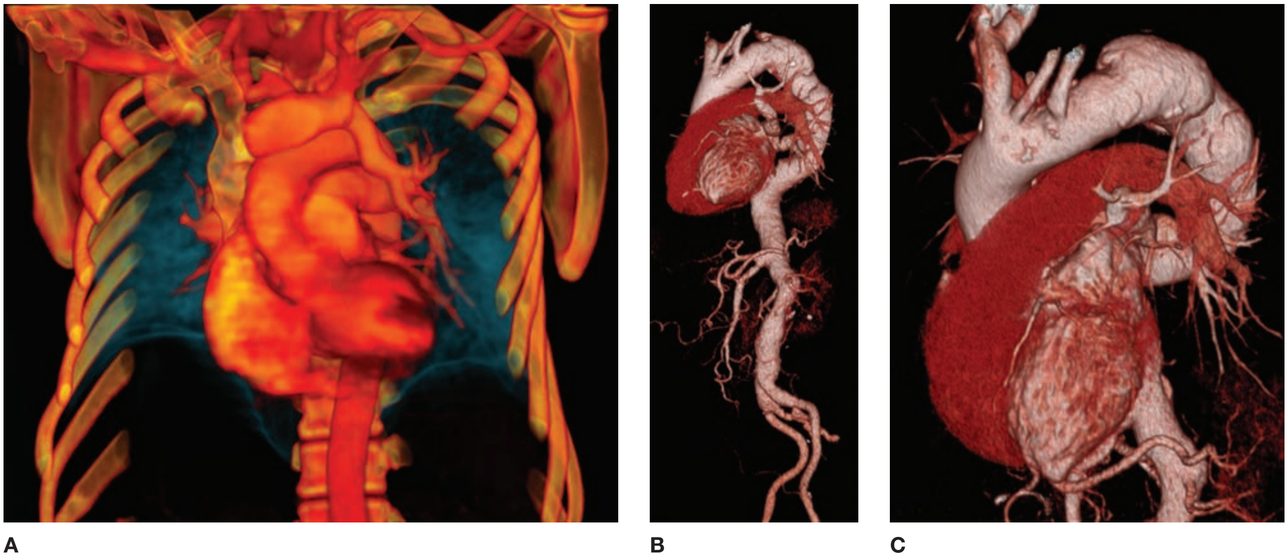


Figure 28-10 CT allows acquisition of isotropic volumetric images, in which advanced 3D postprocessing can be performed to demonstrate complex disease processes with a high level of detail. **A.** Volume rendering (VR) reconstruction demonstrating partial anomalous pulmonary venous connection of the left upper lobe to the left brachiocephalic vein; (**B**) and (**C**) VR reconstructions at different degrees of rotation, demonstrating the complex configuration of a thoracic aortic aneurysm. These images are invaluable for treatment planning.

the ability to quantitate iodine distribution in the lung parenchyma as a reflection of pulmonary blood volume; reconstruction of virtual unenhanced images obtained from contrast-enhanced studies; and detection of bone marrow edema (Fig. 28-11).[4]

An important concept is that of high-resolution CT ("HRCT") of the thorax. Historically, when early CT scanners were limited to the acquisition of relatively thick axial slices (7 to 10 mm) in the thorax, the only way to adequately assess lung parenchymal detail was to acquire serial, thin (1 mm) anatomic images utilizing an axial, rather than helical, mode; this required noncontiguous (i.e., slices with an interslice gap, typically 20 mm wide), rather than contiguous, slices. These images were also reconstructed using a high spatial frequency algorithm, sharpening edges and allowing improved visualization of fine detail. The result was a set of higher-spatial-resolution, thin-section images that sampled the lung parenchyma and provided excellent insight into certain pulmonary disorders. This was termed "high-resolution CT" or "HRCT" of the chest, differentiating it from the "standard" chest CT scan, in which thicker sections were acquired through the entire chest in a contiguous helical mode (i.e., without interslice gaps). Generally, a choice had to be made as to which of these two types of scans to perform, since both studies could not be performed simultaneously. Standard CTs were ordered for a general assessment of larger pulmonary lesions, as well as mediastinal, bone, and chest wall pathology. High-resolution chest CTs were ordered to assess pulmonary parenchymal disease, such as bronchiectasis, interstitial diseases, and micronodular diseases.

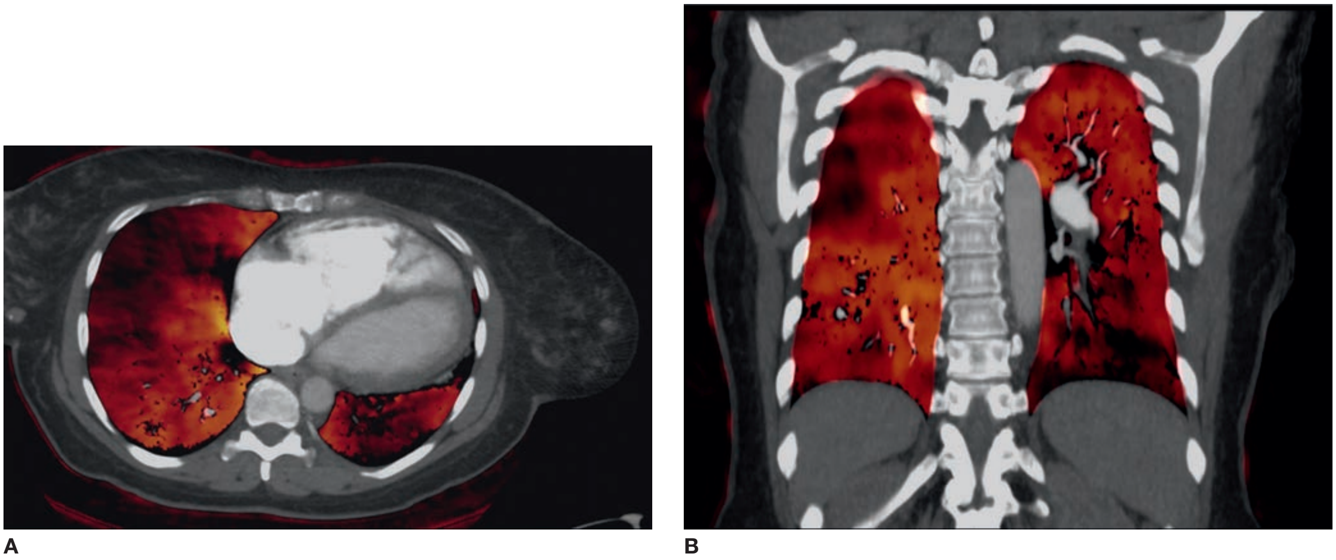


Figure 28-11 Dual-energy CT provides additional functional information with regards to iodine distribution in lung parenchyma thus allows characterization of pulmonary blood volume. This ability results in superior detection of pulmonary embolism in both acute and chronic setting. (**A**) Axial and (**B**) coronal reconstruction of pulmonary blood volume map in a patient with chronic thromboembolic disease demonstrates a chronic filling defect in a segmental artery to the left lower lobe with associated decrease in pulmonary blood volume consistent with decreased circulation in the affected region.

Video 28-1 **A.** Axial cine images using lung window and inspiratory acquisition. This CT airway examination demonstrates bronchiectasis, mosaic attenuation, and faint peribronchial opacities, compatible with a diagnosis of bronchiolitis obliterans. Inspiratory acquisitions should ideally reflect the lung appearance at TLC (total lung capacity). **B.** Same patient as in Video 28-1A. Axial cine images on lung window/level, expiratory acquisition, in this CT airway examination, demonstrating same findings earlier, plus dynamic partial collapse of the trachea and central bronchi, compatible with tracheobronchomalacia superimposed on bronchiolitis obliterans. Note the value of expiratory imaging to establish the diagnosis of tracheobronchomalacia and to increase the conspicuity of the mosaic attenuation pattern reflecting small airway disease. Expiratory acquisitions should ideally reflect residual volume (RV). *Video available on AccessMedicine.com.*

With advances in CT technology, however, it is currently feasible to acquire volumetric, isotropic, thin-section (1 mm) images throughout the entire thorax in a single breath-hold, and to reconstruct them in any arbitrary plane (typically, axial, sagittal, and coronal) using soft tissue and high-resolution algorithms. Consequently, every chest CT is now effectively both a standard, as well as a high-resolution, CT, combining the advantages of each in a single study. This simplifies the ordering process for clinicians. Currently, when ordering a chest CT, there are only two decisions that the clinician needs to make: (1) whether to include expiratory imaging; and (2) whether to perform the study with or without intravenous contrast (as discussed in detail below).

The first important decision is whether to perform expiratory images, noting that normally, a chest CT is acquired in full inspiration. The reason to avoid performing expiratory images for every patient is to decrease medically unnecessary radiation exposure. Typically, an expiratory CT is ordered if there is a clinical concern for an obstructive lung disease (e.g., asthma, COPD, or small airway disease) or if there is a risk of developing bronchiolitis obliterans (e.g., related to lung or bone marrow transplantation) **(Video 28-1A, B)**. Expiratory CT may also be ordered to assess for large airway diseases, such as tracheobronchomalacia. Expiratory CT is currently the best imaging test to demonstrate small airway air trapping and, therefore, is a very useful tool to evaluate potential causes of a "mosaic attenuation pattern" on CT (as discussed in detail in the following sections addressing specific diseases).

The second important decision is whether to perform the study with or without intravenous contrast administration. For the sake of decreasing medically unnecessary radiation exposure, there are very few indications for combined chest CT (i.e., with and without intravenous contrast); these are discussed below. The vast majority of chest CT is performed either with or without intravenous contrast. Generally, to assess the lung parenchyma and airways, no intravenous contrast is required. Assessment of bone lesions also usually does not benefit from intravenous contrast administration. On the other hand, vascular and cardiac assessment is greatly enhanced by intravenous contrast. Moreover, mediastinal and hilar pathology (including lymphadenopathy) and cervical and chest wall masses are more conspicuous and better evaluated using intravenous contrast. For certain thoracic neoplasms and pleural diseases, the enhancement pattern adds information to their diagnostic characterization. Finally, it is worth noting that if dual-energy CT is available, it is possible to produce virtual unenhanced images from an enhanced scan, thus minimizing radiation exposure.

It is important to emphasize that since iodinated CT intravenous contrast is excreted primarily by the kidneys, substantially impaired renal function may preclude intravenous contrast administration and may increase the risk of nephrotoxicity. Additional risks associated with intravenous contrast administration include local effects related to contrast extravasation at the injection site and anaphylactoid reactions, ranging from clinically insignificant symptoms to life-threatening airway or cardiovascular collapse; the latter is very rare with the low-osmolar contrast material currently utilized.

When performing chest CT with intravenous contrast, it is important to inform the radiologist of the clinical indication. Broadly, three different basic protocols can be utilized: (1) standard contrast-enhanced CT; (2) CT angiography (CTA) for visualization of the aorta or coronary arteries; and (3) CTA for visualization of the pulmonary arteries ("pulmonary embolism [PE] protocol").

For a standard contrast-enhanced CT, the injection rate and imaging acquisition relative to the contrast injection are tailored for maximum enhancement of parenchymal organs and soft tissues; consequently, the images are acquired during the venous or equilibrium phase of contrast distribution. This is the standard approach for routine, contrast-enhanced chest CT.

CTA of the aorta and CTA of the coronary arteries are dedicated examinations that are tailored for maximum enhancement of these systemic vessels and are not covered further in this chapter. In particular, cardiac CTA is a thriving application that is usually performed in conjunction with ECG gating to compensate for cardiac motion. CTA of the pulmonary arteries is a well-established application and the current reference standard for the diagnosis of PE **(Video 28-2A, B)**. With this CT technique, contrast injection and imaging acquisition are optimized for maximum enhancement of the pulmonary arteries. This requires a high rate of injection (4–6 mL/s, as opposed to 2 mL/s for regular contrast-enhanced CT) through a large-caliber peripheral IV access (ideally larger than 20G) and very fast volumetric imaging acquisition, usually using contrast bolus tracking to maximize the probability of scanning the patient at the peak of opacification of the pulmonary arteries. When optimally performed, this study allows confident diagnosis of PE in even small subsegmental vessels via direct visualization of vascular filling defects. It also allows accurate assessment of pulmonary vascular caliber and distribution to diagnose pulmonary hypertension, chronic thromboembolic disease, and vasculitides.

CTA of the pulmonary arteries has supplanted conventional pulmonary angiography (except for therapeutic applications) and largely supplanted ventilation–perfusion scanning, although the latter still has an important role in specific clinical settings, such as pregnancy, young patients with normal chest radiographs, or patients with renal insufficiency. This advanced CTA technique not only allows the diagnosis of PE and possible complications, such as pulmonary infarcts, but also accurately reflects the overall clot burden and signs of right ventricular strain, both important prognostic indicators.[5]

An additional, specific advanced application of CT in the chest is the evaluation of the airways. The imaging protocol for CT of the

Video 28-2 **A.** Axial cine images using soft tissue window, demonstrating a massive saddle embolus straddling the bifurcation of the main pulmonary artery. Note that the clot extends to the bilateral lower lobes; oligemia of the right lower lobe is demonstrated. Also note right ventricular enlargement and leftward deviation of the interventricular septum, findings compatible with right ventricular strain. **B.** Same patient as in Video 28-2A. Full-color, coronal, 3D VR (volume rendering) thick slab cine (anterior to posterior), emphasizing cardiovascular structures. This type of reconstruction provides exquisite detail of vascular anatomy and extent of massive pulmonary embolism. *Video available on AccessMedicine.com.*

Video 28-3 Full-color, coronal 3D VR (volume rendering) with 360 degrees of rotation about the long axis of the trachea, emphasizing central airways. **A.** Lower magnification with vertical and horizontal axis for spatial orientation. **B.** Higher magnification without axis. The images demonstrate an irregular, long region of segmental stenosis involving the upper trachea. The patient also presented with multiple pulmonary nodules, at least one of which was cavitary. A diagnosis of granulomatosis with polyangiitis or GPA (previously known as Wegener granulomatosis) was established on tracheal biopsy. *Video available on AccessMedicine.com.*

airways utilizes thin-section (1 mm), volumetric, isotropic images, both in full inspiration and end-expiration. The images are acquired from the base of the tongue to the basilar segmental bronchi to include the entire tracheobronchial tree and larynx. Postprocessing 3D techniques are routinely utilized—that is, volume rendering, minimal intensity projections, and virtual bronchoscopy (Video 28-3A, B). The result is accurate depiction of global, regional, and local large airway disorders, including tracheobronchomalacia, airway stenoses, infiltrative and obstructive neoplasms, and inflammatory conditions.

An important consideration recently receiving much attention is the issue of medical radiation exposure in CT. CT, as any imaging modality that utilizes x-rays, exposes the patient to ionizing radiation, which is a known carcinogen due to stochastic effects, and which, at very high doses, can have deterministic detrimental effects. To understand the true magnitude of the risks associated with radiation exposure related to diagnostic chest CT, it is critical to have a basic understanding of the ways in which radiation dose is measured, as well as how to quantitatively estimate risk based on best available evidence.

Ionizing radiation dose equivalent (which takes into account energy absorbed (J/kg) and the biologic effects of the specific type of radiation) is measured in Sieverts (Sv). Every human is exposed to approximately 3 mSv/year of background radiation from natural and man-made sources. In contrast, a chest radiograph delivers 0.1 to 0.2 mSv, whereas a chest CT performed using standard protocols delivers between 5 and 20 mSv. Deterministic effects are extremely rare below 2000 mSv of acute exposure. Although it is difficult to quantify the magnitude of stochastic effects, the International Commission of Radiological Protection (ICRP) estimates the risk coefficient (additional cancers due to radiation exposure) as 0.00005 per mSv of exposure (i.e., ∼5% per 1000 mSv). In summary, CT delivers a low, but nonnegligible, radiation dose that is unlikely to cause detrimental biologic effects if used in a prudent and medically justifiable manner.

Notwithstanding the relatively small risks, radiologists, engineers, and physicists have made substantial strides to develop reconstruction algorithms and protocol optimization techniques that decrease the radiation dose of thoracic CT to the lowest attainable level and that allows diagnostic-quality images. Among the recent dose-reduction methods that have become widely available are iterative reconstruction techniques, combined with tube current and voltage modulation. The combined effects can generate markedly reduced radiation dose, down to sub-mSv (<1 mSv) levels. This is particularly useful for low-dose screening CT, which is discussed in detail later (see "Lung Cancer Evaluation," below).[6,7]

Finally, CT has a major role for guidance of thoracic interventional procedures, which is described in detail below.

CHEST MRI

MRI is another advanced cross-sectional technique utilized in thoracic imaging. The physics behind MRI are complex and beyond the scope of this chapter. Fundamentally, MRI uses a very strong static magnetic field (main field) generated by superconducting coils in combination with a radiofrequency radiation pulse sequence and variable magnetic field (gradients) to cause oscillation of hydrogen proton nuclear spins. The result is generation of a radiofrequency signal, which is detected and measured. The signal can be also spatially localized to generate an image that can be obtained in any arbitrary plane. Image contrast with MRI depends on the physical properties of the tissue being imaged, as well as on the specific pulse sequence utilized (Fig. 28-12).

MRI has advantages and disadvantages with respect to CT. The main advantage of MRI is the lack of ionizing radiation. CT utilizes high-energy x-rays, whereas MRI utilizes low-energy radiofrequency radiation that has minimal biologic effects and no ionization potential. MRI also has better contrast resolution than CT and is exquisitely

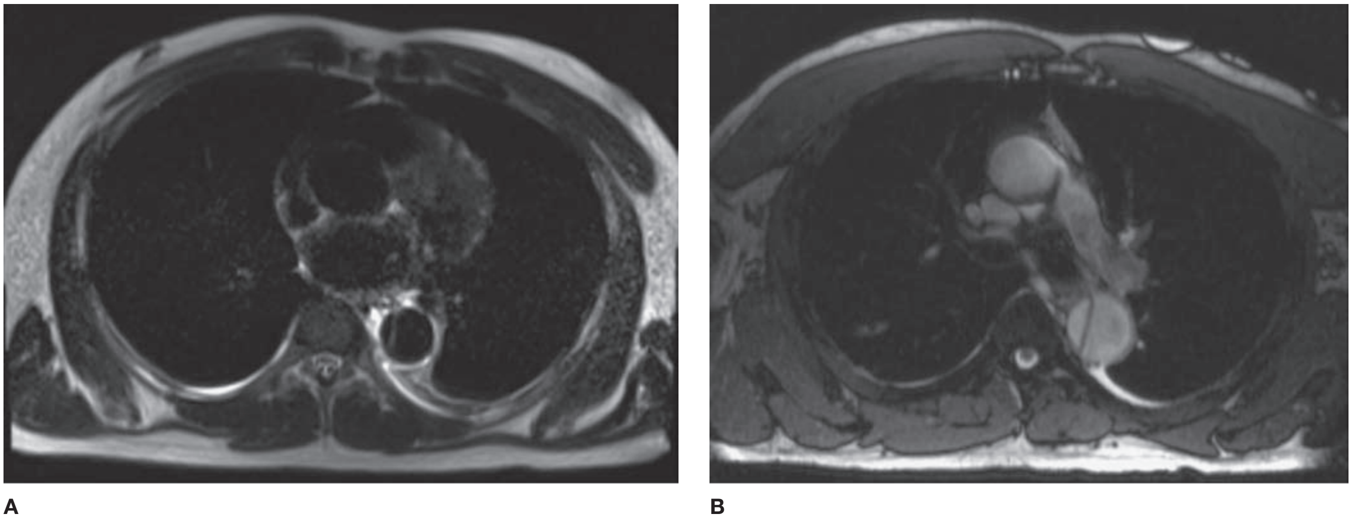


Figure 28-12 MR offers lower spatial resolution than CT; however, it allows better contrast resolution and tissue characterization through utilization of varied pulse sequences that emphasize specific aspects of tissue composition. For example, (**A**) and (**B**) demonstrate a dissection of the descending thoracic aorta. **A.** The blood pool appears black and this is, therefore, termed a "black blood" sequence (typically, spin echo sequence). In contrast (**B**) demonstrates the blood pool to be bright and is, therefore, termed a "bright blood" sequence (typically, steady-state free precession gradient echo sequence). (*continued*)

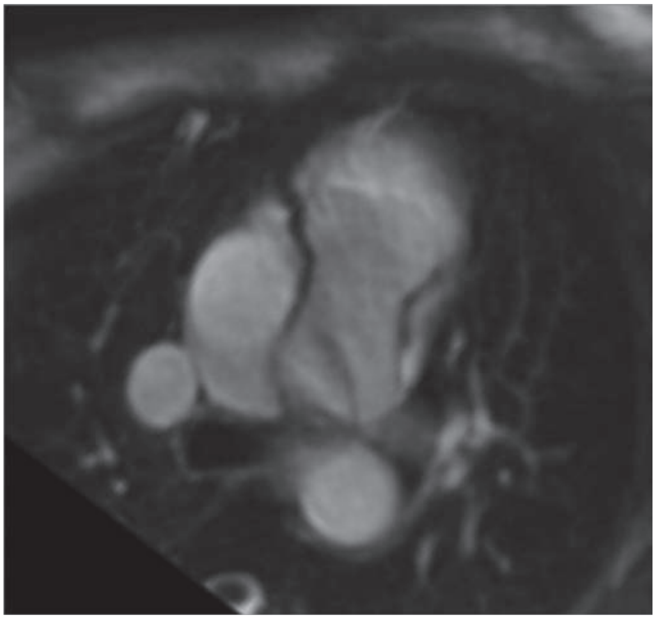


Figure 28-12 (*Continued*) **C.** Different patient with a patent ductus arteriosus (PDA), which causes a linear flow artifact (dark band from the aorta to the left PA).

sensitive in the detection of water and fat. MRI thus provides a greater degree of soft tissue characterization than is possible with CT. Examples of this greater resolution of soft tissue densities include identification of proteinaceous fluid in bronchogenic cysts (Fig. 28-13), which can appear solid on CT, and the presence of fat in confirming thymic hyperplasia as a cause for an anterior mediastinal mass, thereby enabling differentiation from lymphoma. Another advantage of MRI over CT is that iodinated contrast material is not used, obviating the potential problem of CT contrast allergy (Fig. 28-14). In the past, MRI also had the advantage of intrinsic multiplanar imaging, but modern multidetector-based CT now demonstrates similar capability.

The disadvantages of MRI include longer examination time, greater susceptibility to artifacts, lower spatial resolution, and generally very low signal-to-noise ratio in the lung parenchyma, traditionally making it less suitable than CT for optimal pulmonary parenchymal evaluation. However, it should be noted that use of better scanners and newer MRI sequences such as parallel imaging, respiratory gating, Half-Fourier acquisition, and ultra-short echo times are promising for the evaluation of patients who need to undergo multiple serial imaging studies and in whom cumulative radiation exposure is of particular concern, such as in young patients with cystic fibrosis, and for multiple imaging indications in the pediatric population.[8,9]

From a clinical perspective, MRI is still not the first-line modality for assessment of pulmonary diseases, but it is a well-established technique for evaluation of the heart and great vessels, for tissue characterization of mediastinal and chest wall masses, and for dynamic assessment of thoracic wall and diaphragmatic motion. Current applications of MRI, in addition to those mentioned earlier, include evaluation of the brachial plexus, local staging of superior sulcus tumors, evaluation of neurogenic tumors and lesions involving the thoracic spine, and cardiac or paracardiac masses, with early evidence showing promising results in evaluation of lung parenchyma.[10–12]

Recently, considerable interest has arisen in the use of hyperpolarized gases, including helium-3 and xenon-129, for MRI of the lungs. Hyperpolarized gas MRI can provide detailed images of pulmonary ventilation, as well as information on lung microstructure, beyond the resolution of CT. The latter includes measurements of alveolar

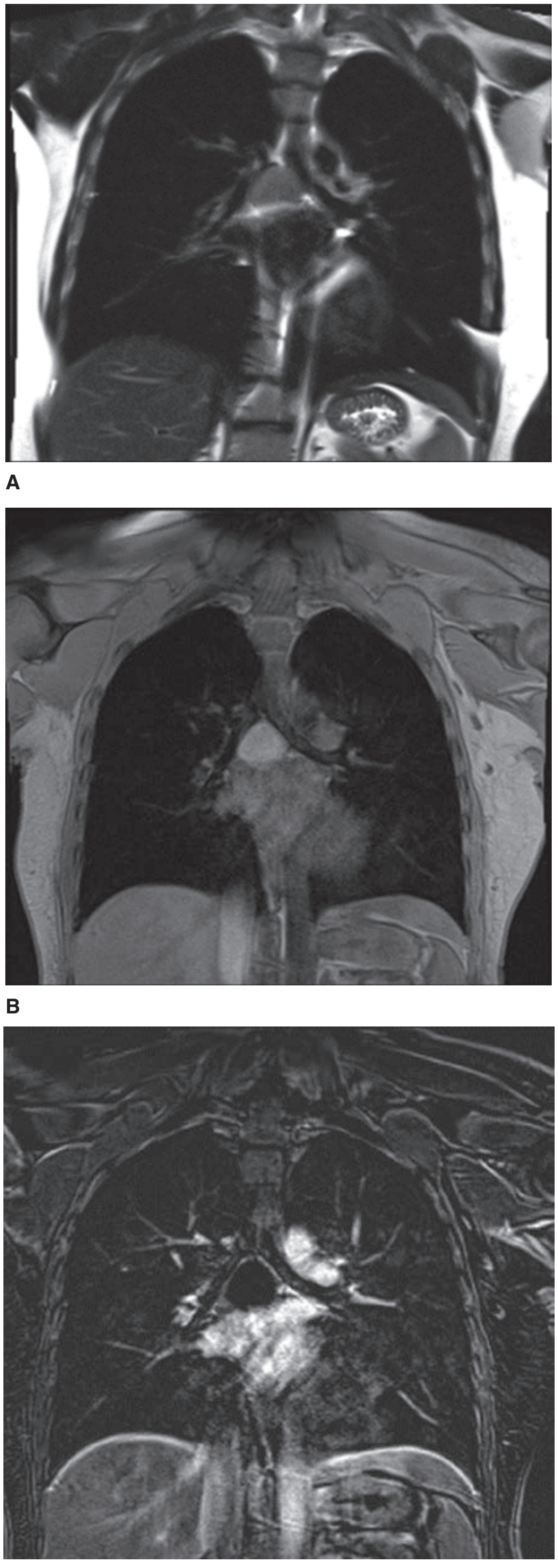


Figure 28-13 The superior contrast resolution of MRI allows for confident characterization of complex cystic lesions that are indeterminate on CT due to overlapping tissue density with solid lesions. An indeterminate mediastinal lesion detected on a chest CT in a 21-year-old female demonstrates intermediate T2 signal intensity on coronal T2 HASTE sequence (**A**), high T1 signal intensity on coronal T1 sequence before contrast injection (**B**), and no internal enhancement on T1 post contrast subtraction images (**C**), consistent with protein containing bronchogenic cyst.

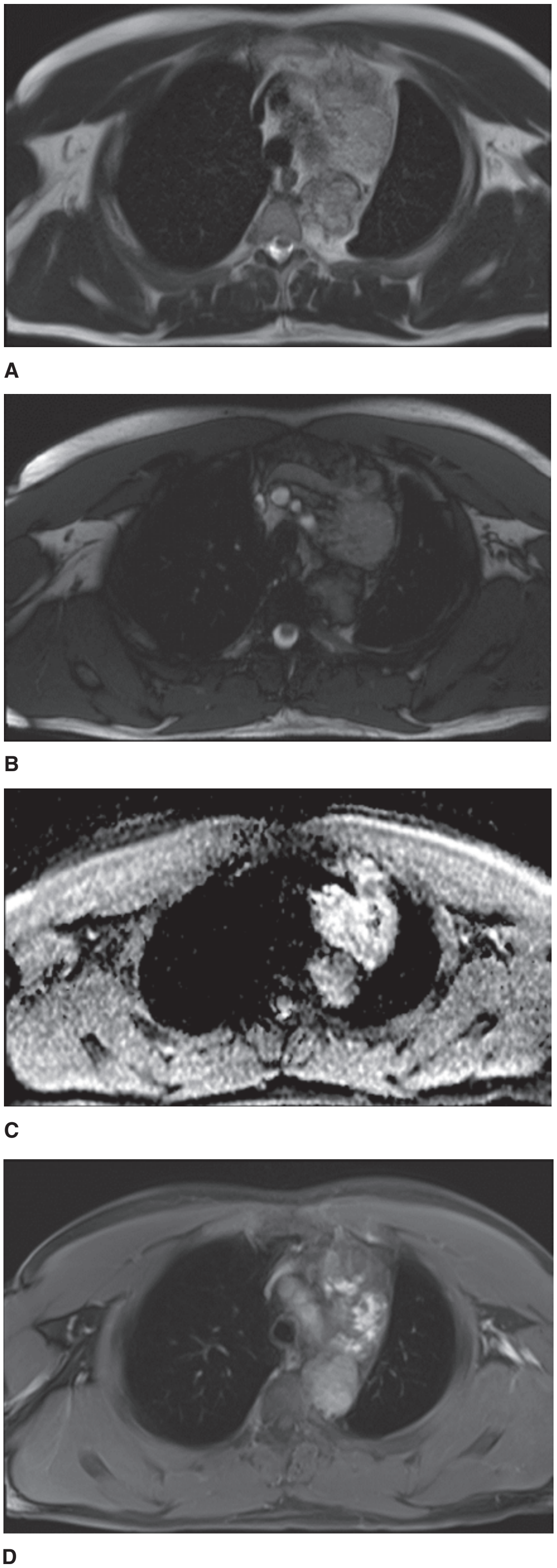


Figure 28-14 As opposed to CT, MRI allows acquisition of contrast enhanced images at multiple time points without the additional radiation exposure. Additionally, diffusion-weighted imaging allows characterization of cellular density thus facilitating better tissue characterization. A young patient with a large soft tissue mediastinal lesion demonstrating high signal on both T2 (**A**) and bright blood steady-state free precession (**B**) images without significant restricted diffusion on apparent diffusion coefficient (ADC) sequence (**C**) and showing gradual slow filling of the lesion on contrast-enhanced sequences (**D**) allowing a confident diagnosis of benign hemangioma.

size and alveolar–capillary membrane thickness. Nonetheless, to date, hyperpolarized gas MRI remains investigational.

PET, PET/CT, AND PET/MRI

PET is a nuclear medicine emission tomographic technique (see Chapter 30), in which an intravenously administered radionuclide that decays via positron emission (most often ^{18}F coupled to deoxyglucose [FDG]), generates an annihilation event (when a positron collides with an electron and two antiparallel 511-keV photons are simultaneously generated). The event is registered by coincidence detectors, allowing localization of the origin inside the body. Because FDG is very similar to glucose in biodistribution and pharmacokinetics, it effectively concentrates in tissues that have a high metabolic rate and, therefore, increased glucose uptake—namely, the brain, heart (in the non-fasting state), and many neoplasms; in addition, FDG is concentrated where it is metabolized and excreted: the liver, kidneys, and urinary collecting system. FDG-PET images essentially map the biodistribution of glucose in the body. CT and MRI may be performed almost simultaneously with PET in dedicated hybrid scanners (PET/CT and, more recently, PET/MRI). The higher spatial resolution of these modalities is helpful for localization of the abnormal PET signals in fused imaging analysis (Fig. 28-15).

It is a common misconception that PET/CT is specific for cancer diagnosis. In reality, it is not. Many normal tissues and inflammatory or infectious processes have a high metabolic rate and high glucose uptake and, therefore, are also avid on PET images. Moreover, many cancers are not highly metabolically active or are not FDG avid, and these may not be detectable by PET imaging. A typical example in the chest is an indolent adenocarcinoma in situ (AIS), formerly called bronchioloalveolar cell carcinoma (BAC), or certain subtypes of carcinoid tumors.

The strength of PET/CT relies on its ability to accurately stage malignancy if the primary neoplasm is FDG-avid. In this context, it is superior to CT or MRI because it may demonstrate small metastases in normal-sized structures, particularly lymph nodes, which would not be detectable by CT or MRI. PET/CT is, therefore, routinely employed for staging of malignancies such as lung cancer, lymphoma, head and neck carcinoma, and esophageal carcinoma.[13] Additionally, PET/CT increasingly plays a role in detection of inflammatory disorders such as detection of myocarditis, myocardial sarcoidosis, or large vessel vasculitis.[14]

ULTRASOUND

Ultrasound (US) has a more limited but evolving role in thoracic imaging. The primary limiting factor is that both the thoracic cage and the lungs act as reflecting interfaces that block penetration of the US mechanical wave. However, US has been shown to be useful for specific applications, such as detection of pneumothorax or pneumonia, as well as in evaluation of pleural effusions and chest wall pathology (Fig. 28-16) especially with increasing availability of hand-held devices, resulting in increased use in emergency departments, in intensive care units, in the setting of trauma, and in places with limited imaging resources. In addition, it is useful in guiding imaging interventions.[15] Thoracic US is discussed in detail in Chapter 29.

IMAGE-GUIDED INTERVENTIONS

Image-guided interventions have dramatically changed the diagnosis of thoracic diseases that require tissue sampling for pathologic confirmation. They have also impacted the treatment of many benign and malignant diseases. Increasingly, image-guided biopsy procedures are being performed for tumor genotyping to guide more targeted, personalized therapies. Half a century ago, surgical procedures were necessary to obtain tissue from the lungs, mediastinum, or chest wall. Surgical biopsies may require hospitalization, are costlier, and carry small but measurable rates of morbidity and

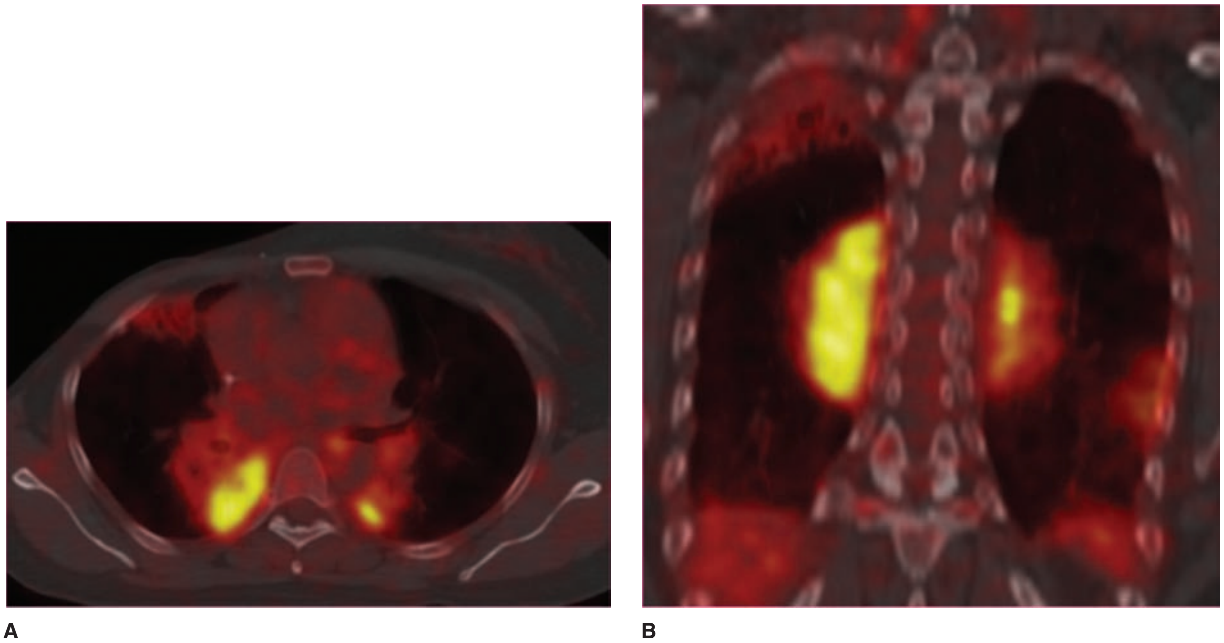
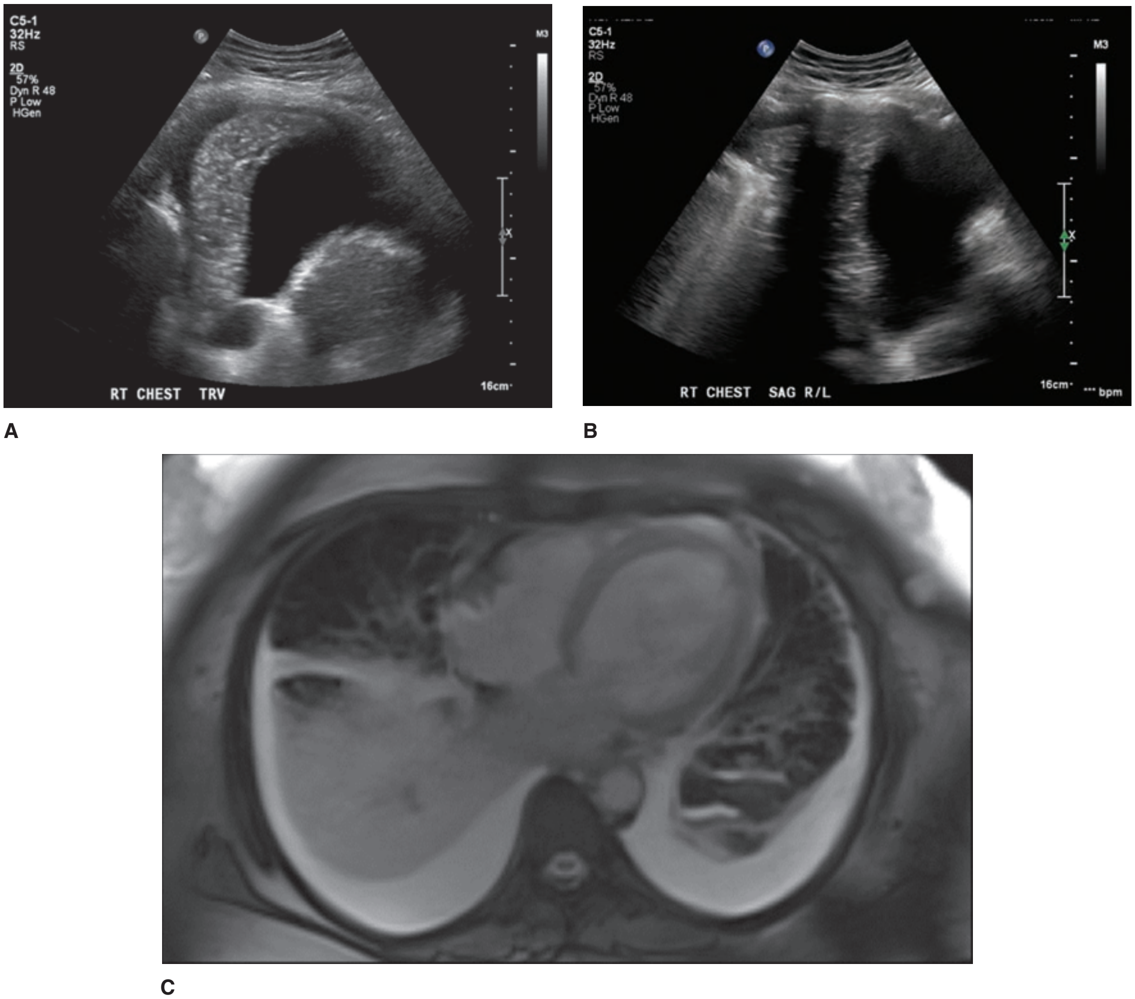


Figure 28-15 Fusion images combining CT and PET data in a patient with multifocal MALT pulmonary lymphoma. (**A**) Axial and (**B**) coronal images demonstrate that the areas of consolidation in the posterior medial lungs also demonstrate high FDG uptake, thus appearing bright yellow in this color scheme, a typical feature of metabolically active lymphomas.


C5-1
32Hz
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2D
57%
Dyn R 48
P Low
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M3
RT CHEST TRV
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RS
2D
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Dyn R 48
P Low
HGen
M3
RT CHEST SAG R/L
16cm
bpm
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C

Figure 28-16 US allows detection of even small amounts of pleural effusion and adjacent lung atelectasis. Transverse (**A**) and sagittal (**B**) views of the lower thoracic pleural space demonstrate moderate amount pleural effusion with adjacent passive atelectasis. A subsequently obtained steady free precession MRI (**C**) one day later demonstrates similar findings.

mortality. Currently, most diagnostic procedures can be performed percutaneously or via bronchoscopy in a minimally invasive fashion. Bronchoscopy and endobronchial interventions are described in Chapters 33 and 34 (Fig. 28-17).

Percutaneous transthoracic biopsy (PTB) may be performed via a variety of imaging guidance systems, most commonly CT, but also fluoroscopy or US (Videos 28-4 and 28-5A, B). Different

Video 28-4 4D cine using custom window. The images are acquired sequentially at the same level and used for guidance in performing a transthoracic fine-needle aspiration (TTNA). The needle was advanced to perfectly engage a small RUL nodule (9 × 7 mm). Final diagnosis was primary adenocarcinoma. *Video available on AccessMedicine.com.*

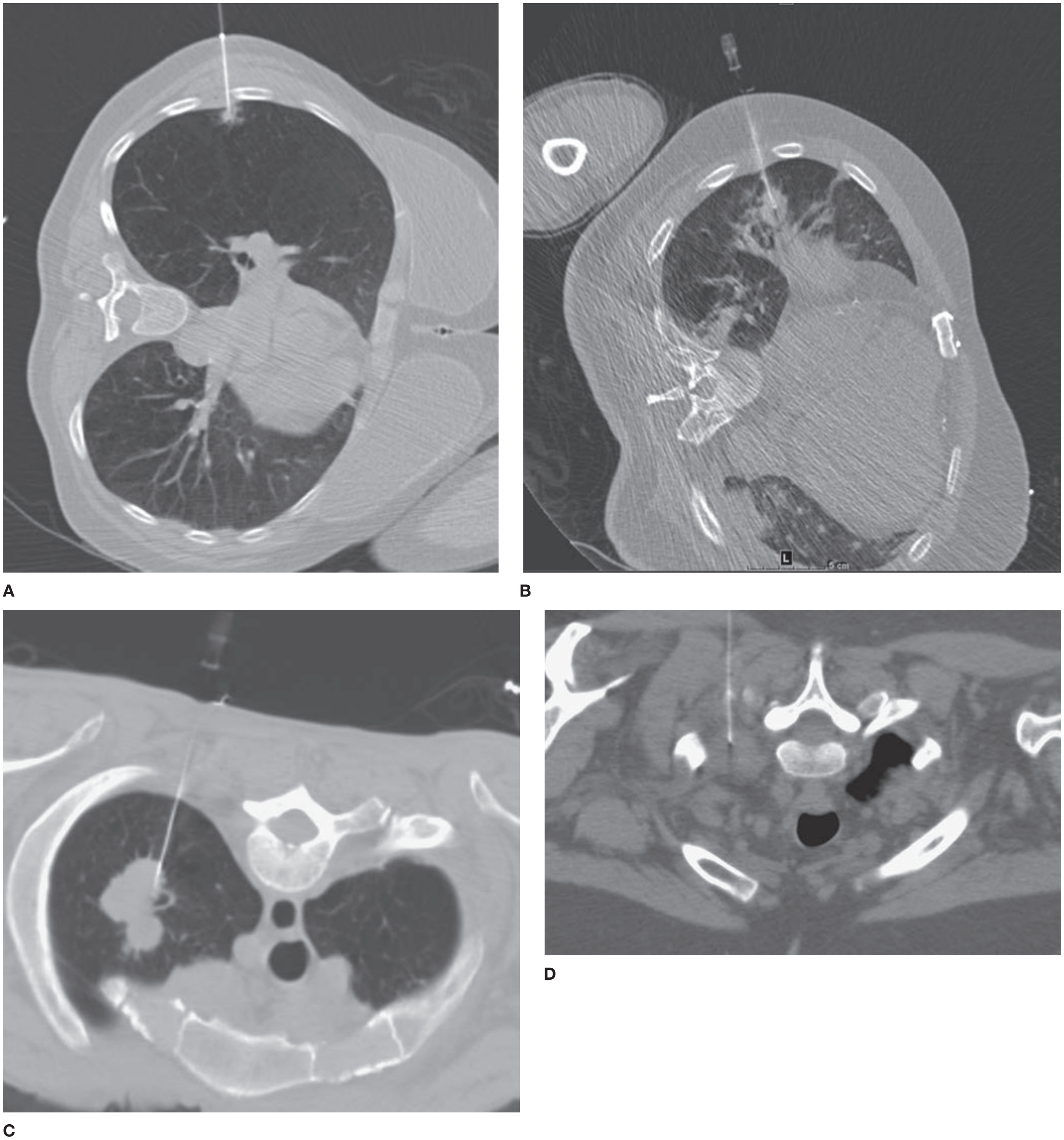


Figure 28-17 CT offers accurate, near–real-time localization of lesions for image-guided percutaneous small-needle biopsy. **A.** CT-guided biopsy of a small (0.8 cm) RUL spiculated nodule, a biopsy-proved adenocarcinoma; (**B**) CT-guided biopsy of a larger (1.8 × 2.2 cm) RML nodule, biopsy-proved small cell carcinoma; (**C**) CT-guided biopsy of a lobulated LUL mass (3.0 × 4.2 cm), biopsy-proved adenocarcinoma; (**D**) CT-guided biopsy of a soft tissue mass in the left superior sulcus, biopsy-proved malignant neurogenic neoplasm.

Video 28-5 4D cine using custom window. **A.** Lung window. **B.** Reversed lung window. The images are acquired sequentially at the same level and used for guidance in performing a transthoracic fine-needle aspiration (TTNA). The needle was advanced to perfectly engage a 14- × 13-mm LUL nodule. Final diagnosis was metastasis from RCC (renal cell carcinoma). *Video available on AccessMedicine.com.*

needle types, lengths, and calibers may be chosen according to the clinical question and lesion characteristics. As a general rule, superficial chest wall lesions can be accessed via US or CT; pleural, pulmonary, and anterior mediastinal lesions are accessed via CT; central hilar lesions and deep mediastinal masses are not accessible via PTB.

There are two basic types of PTB: fine-needle aspiration (FNA) and automated core needle biopsy (CNB). In FNA, a small-caliber needle (25–22G) is inserted through the chest wall into the lesion via CT guidance. The tip of the needle is positioned inside the lesion. Negative pressure (suction) is applied via a syringe, and fluid or clusters of cells are aspirated. The material obtained via FNA is processed using cytopathology techniques, and specific stains and molecular tests can be performed.

In contradistinction, CNB uses a larger coaxial system in which a 19G introducer (outer core) hollow needle is advanced to the pleura or close to the edge of the lesion, followed by introduction of a 20G automated inner core biopsy needle, which is advanced to the lesion. An automated mechanism is then activated, rapidly moving the needle forward and filling the needle trough, or shallow receptacle, with cylindrical "cores" of tissue. The outer sheath instantly moves forward to cut the tissue and keep it in the trough. This process is repeated several times as multiple tissue cores are obtained. The material obtained via CNB is processed using surgical pathology techniques. Both FNA and CNB provide material for microbiology studies, including stains and cultures.

From a diagnostic perspective, FNA is almost equally accurate to CNB for diagnosis of malignant diseases, although CNB is superior for diagnosis of benign diseases. FNA sensitivity for diagnosis of lung cancer is 80% to 95%, and the rate is higher if onsite cytopathology is available and the procedure is approved and performed by experienced radiologists. Limitations of FNA include diagnosis of indolent or low-grade malignancies (for which more tissue or histoarchitecture is required for confident pathologic diagnosis) and inflammatory or infectious diseases—scenarios in which CNB is superior. The advantage of FNA over CNB is a lower complication rate and the capacity to engage and sample very small lesions that would otherwise be inaccessible.

Lesion location, lesion size, and patient body habitus are major determinants utilized by the radiologist in deciding the optimal biopsy technique. All other factors being equal, large pulmonary masses (>3 cm), pleural masses, chest wall masses, and large anterior mediastinal masses are best sampled via CNB. On the other hand, small pulmonary nodules (as small as 0.8 cm), pulmonary nodules in highly mobile regions (posterior or anterior lung bases), and small lymph nodes are best approached using FNA.

Complications related to PTB are relatively infrequent, but occasionally can be life-threatening. For mediastinal, chest wall, and pleural biopsies, the major risk is hemorrhage, with infection and postprocedural pain following in incidence. Major vascular injury is rare, but it has been reported following biopsies of mediastinal masses. For lung biopsies, the major risk is pneumothorax, followed by hemorrhage, infection, and, rarely, air embolism. While air embolism is the rarest complication, with a reported frequency of 0.05% to 0.10%, it is potentially the most life-threatening, due to its unpredictable nature and difficult treatment. Pneumothorax rate varies widely according to institution, and estimates from 5% to 50% have been reported. Most postprocedural pneumothoraces are small and not clinically significant; however, in up to 5% to 10% of patients, a large or symptomatic pneumothorax requires chest tube placement.

The following precautions are advised to minimize the risks associated with PTB: (1) critical appraisal of the clinical need for biopsy and whether PTB is the best approach; (2) thorough preprocedural laboratory assessment to ensure normal platelet count and function and normal coagulation profile. Anticoagulants and antiplatelet medications should be discontinued after conferring with the referring physician; (3) performance or supervision of the procedure by an experienced radiologist; (4) careful preprocedural planning, choosing a patient position and needle trajectory that minimizes the risk of vascular injury and decreases the distance to the lesion; (5) proper biopsy technique with purposeful, fast, accurate needle motion, confirming with imaging the needle location, depth, and relationship to the lesion prior to, and after, each needle movement; (6) minimization of the effects of patient motion by tracking chest wall movement and advancing the needle in a consistent phase of the respiratory cycle; and (7) intraprocedural maneuvers such as introduction of saline solution into the outer core of the biopsy needle during exchanges, to provide a water seal, and positioning the patient in a lateral decubitus position with the biopsied lung in dependent position.[16–20]

Therapeutic, percutaneous, image-guided techniques also have been increasingly accepted and utilized. These range from percutaneous chest tube or drain placement to preoperative localization of lung lesions and ablation of neoplasms utilizing microwave or cryoablation techniques. The same principles of imaging guidance described for PTB apply for percutaneous therapeutic interventions. Given their complexity and the availability of alternative treatment options (such as surgery or radiation therapy), their use is best reserved for selected patients following discussion with multidisciplinary healthcare teams.

OBSTRUCTIVE LUNG DISEASES, WITH EMPHASIS ON COPD

Pulmonary ventilation, as is the case for pulmonary perfusion, is not homogeneous; it is affected by gravity, airway caliber, and chest wall mechanics. Ventilation is greater at the bases in the erect position due to greater regional changes in lung volume with inspiration, but the apical–basal ventilation gradient is smaller than the perfusion gradient (noting that perfusion is also greater at the bases). Therefore, the ventilation–perfusion ratio ($\dot{V}/\dot{Q}$) is greater at the apices in the erect patient. A similar pattern occurs in the supine patient between the dependent posterior and the nondependent anterior lungs, albeit to a lesser extent. Changes in relative ventilation affect the relative volume and average density of the lung parenchyma and, therefore, can be depicted by imaging.

Chronic obstructive pulmonary disease (COPD) is a complex group of disorders characterized by chronic, progressive airflow limitation that is not fully reversible and is associated with a range of pathologic changes in the lungs (Chapters 37 and 38). In addition, significant extrapulmonary effects caused by chronic inflammation and structural changes are observed. The chronic airflow limitation is caused by a mixture of small airway disease (obstructive bronchiolitis) and parenchymal destruction (emphysema). In addition, large airway inflammation, with increased sputum production and cough, is the hallmark of chronic bronchitis, part of the spectrum of COPD. The relative contributions of these components vary substantially from patient to patient. The presence and extent of each component has the potential to affect clinical presentation, disease severity, prognosis, and therapeutic response. COPD is strongly related to smoking. It has emerged as the third leading cause of death in the United States.

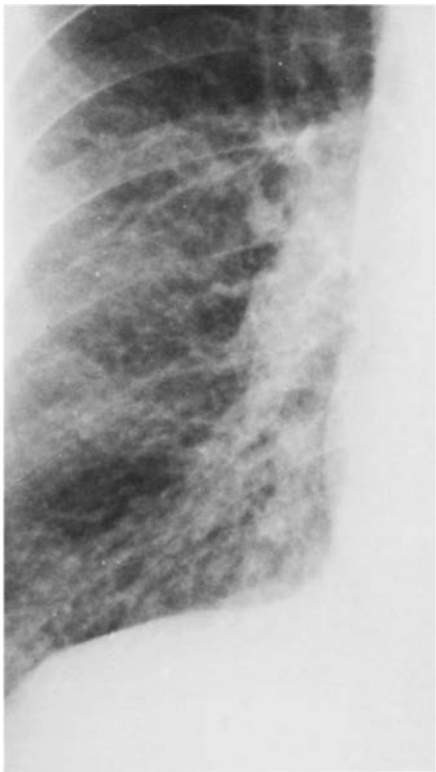


Figure 28-18 Detail view of the lung parenchyma in a PA radiograph, demonstrating increased bronchovascular markings, which are particularly prominent throughout the central lung fields. The patient has COPD with predominant chronic bronchitis. Hyperaeration is minimal.

Another clinically prevalent obstructive lung disease is asthma, which is an inflammatory condition affecting mainly small airways, with increased mucus production, airway wall inflammation, and reduced luminal caliber (Chapters 43–45). Asthma differs from COPD from an imaging standpoint in that the clinical manifestations are usually intermittent and reversible, and the degree of hyperinflation tends to be mild, except in severe, long-standing disease.[21,22]

Chest radiographs are not particularly useful in diagnosing obstructive lung disease. In early disease, these are generally normal, as is the case with most asthmatic patients. In more severe or advanced disease, hyperinflation ensues and can be detected radiographically. The classic radiographic appearance of hyperinflation is manifested by increased radiolucency of the lungs; low, flat diaphragms; exaggerated verticality of the heart; increased AP diameter of the chest; and widening of the retrosternal lucent space. Of all these criteria, diaphragmatic flattening is probably the most reliable in supporting a diagnosis of COPD, as it is likely associated with severe emphysema. Care must be taken in making a diagnosis, however, as hyperinflation can be simulated radiographically when a healthy person exerts a maximal inspiratory effort. The lungs also appear hyperinflated in very slender persons. Therefore, it is unwise to make the diagnosis of emphysema solely on the basis of the radiographic finding of hyperinflation (Figs. 28-18 and 28-19).

Radiographic evaluation of the pulmonary vessels may also support a diagnosis of emphysema. Two distinctly different vascular patterns have been identified in patients with chronic bronchitis and emphysema: arterial deficiency and increased lung markings. Patients who show the arterial deficiency pattern often have panlobular emphysema and manifest the clinical syndrome of the "pink puffer." Those who have the pattern of increased lung markings often have centrilobular emphysema and manifest the "blue bloater" syndrome. Notably, these radiographic findings occur relatively late in the clinical course of emphysema. Moreover, these findings are not specific and must be considered in the clinical context provided.

Similarly, the diagnosis of chronic bronchitis is a clinical one, based upon a history of chronic cough and sputum production and supplemented by characteristic abnormalities in pulmonary function tests. The radiograph rarely provides substantive help. Vascular markings throughout the lung fields are sometimes prominent, but this finding is nonspecific.

CT, on the other hand, is capable of demonstrating the pathologic changes associated with COPD, including large and small airway inflammation and parenchymal destruction (emphysema). Three

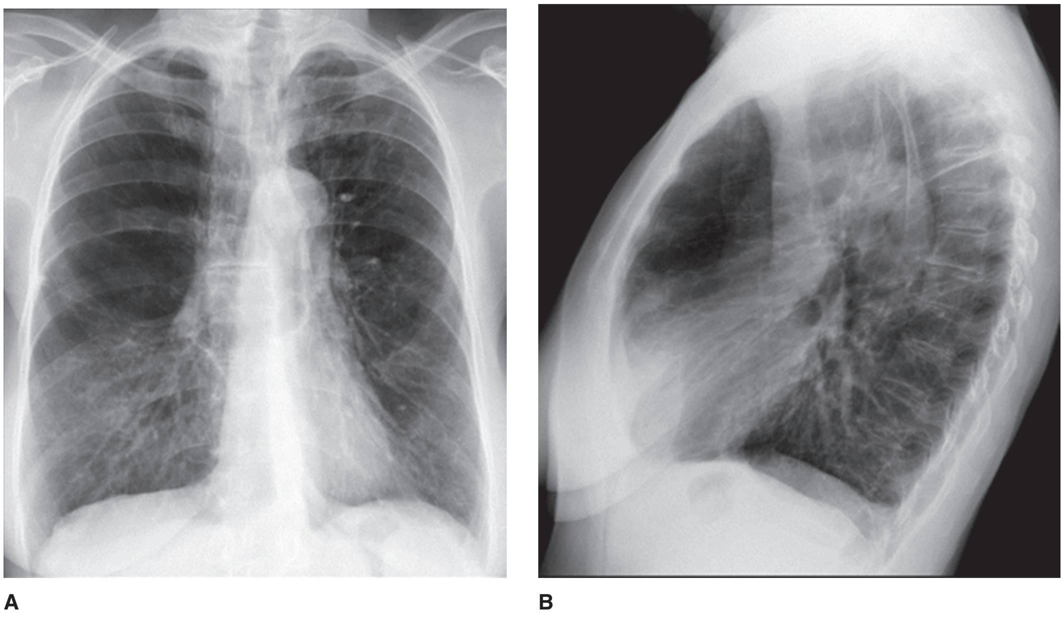


Figure 28-19 (**A**) PA and (**B**) lateral of a patient with severe emphysema-predominant COPD. Salient features are upper lobe predominant hyperinflation (denoted by flattening of the diaphragms and increased craniocaudal and anteroposterior diameters of the chest), hyperlucency of the parenchyma, and increased interstitial markings.

basic types of emphysema can be detected by CT—centrilobular, paraseptal, and panlobular.

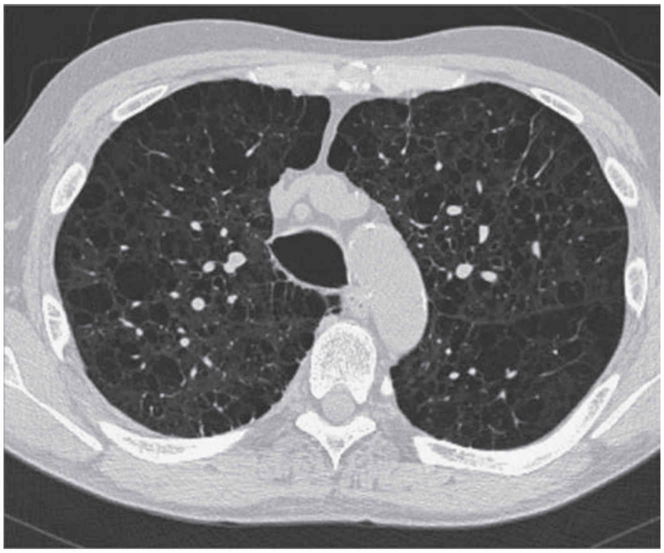
Centrilobular emphysema is characterized by focal areas of lucency within the centers of secondary pulmonary lobules and without perceptible walls. The lobular arteries and bronchi are maintained, appearing as small dots within the involved secondary lobules. These features help to differentiate the holes of centrilobular emphysema from the cysts of cystic lung disease, as the latter have thin walls and are devoid of internal structure.

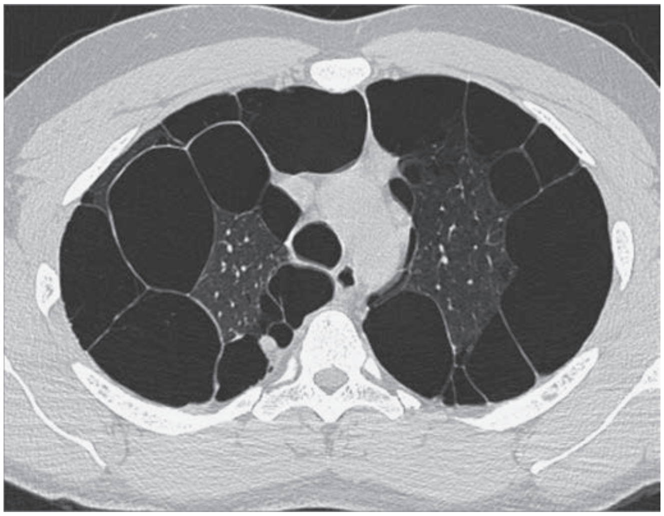
Paraseptal emphysema occurs peripherally, adjacent to the visceral pleura, and adjacent to the bronchovascular interstitium. Centrilobular and paraseptal emphysema are both associated with smoking and, therefore, tend to coexist, although the contribution of each form for the total amount of emphysema varies substantially. There is generally upper lung predominance, except in very severe disease. The extreme form of paraseptal emphysema is evident as bullous disease, in which the cystic spaces may become large enough to compromise lung mechanics due to their mass effect.

Finally, panlobular emphysema is a distinct entity in which there is diffuse hyperlucency, hypovascularity, and a paucity of interstitial markings, often with a basilar predominance. These important findings can be overlooked, even in patients with marked panlobular emphysema, since there are no discrete holes, as is the case in centrilobular emphysema. This form of emphysema is less likely associated with smoking, and more likely associated with α1-antitrypsin deficiency, a genetic condition that can be exacerbated by smoking (Figs. 28-20 and 28-21).[23–25]

Large airway inflammation as a manifestation of chronic bronchitis may be suggested by the presence of airway wall thickening, the diagnosis of which is somewhat subjective, although several studies have described computer-assisted quantitative measurement methods. Mucoid impaction is a reliable indicator of airway inflammation, but it is not specific for COPD, as it can be seen in the setting of asthma, acute bronchitis, or bronchopneumonia.

Small airway inflammation was previously the most difficult component of COPD to diagnose by imaging. While it is still not possible to directly image inflammation of the very distal airways, expiratory CT now provides the best technique to indirectly diagnose small airway disease. The presence of small airway disease may be inferred by the presence of expiratory air trapping. Normally, the average CT attenuation of aerated lung parenchyma increases in expiration due to volume averaging of voxels that contain less air. In contrast, with air trapping, the increased lung attenuation with expiration is not observed. Thus, in the presence of small airway disease,





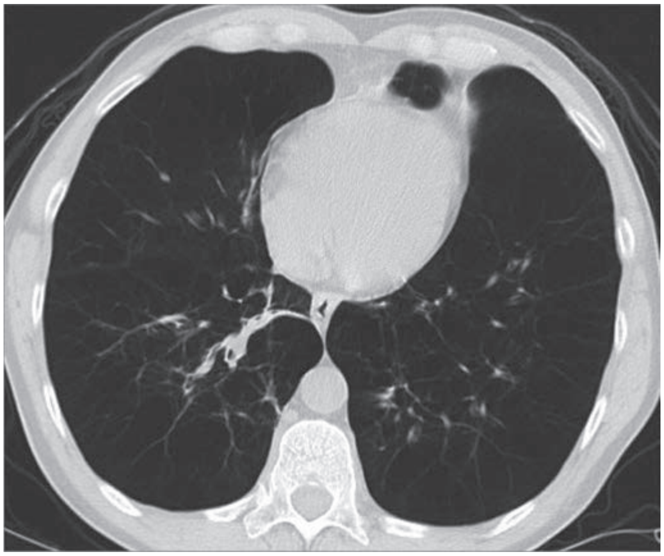


Figure 28-20 Three different phenotypes of emphysema. **A.** Centrilobular. **B.** Paraseptal. **C.** Panlobular. The images demonstrate different configurations and anatomic distribution of parenchymal destruction. (**A**) and (**B**) are typically smoking-related, whereas the patient in (**C**) had α1-antitrypsin deficiency.

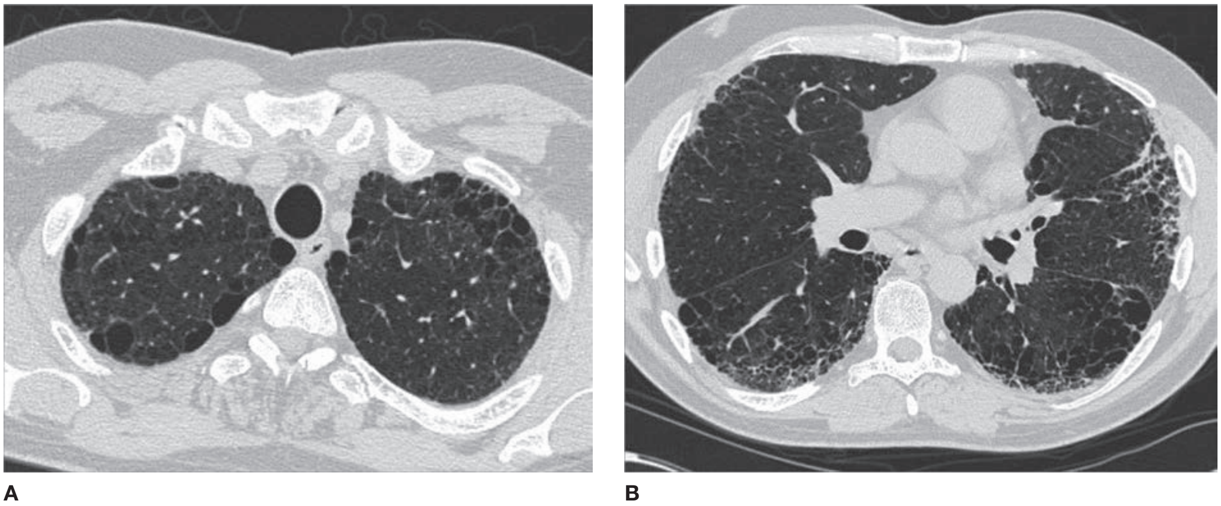


Figure 28-21 Severe emphysema and pulmonary fibrosis in a long-term smoker. **A.** Paraseptal and centrilobular emphysema involving the upper lung fields; (**B**) Additional presence of traction bronchiectasis, peripheral reticulation and honeycombing—features of fibrosis. Smoking-related pulmonary fibrosis is associated with COPD and resembles UIP from an imaging standpoint.

a "mosaic attenuation pattern" is demonstrated on CT images obtained in end expiration, with the darker (lower attenuation) areas corresponding to areas of regional air trapping. Up to 25% of the lung may show air trapping in healthy subjects (typically at the lung bases); higher degrees of air trapping correlate with decreases in functional parameters assessed with pulmonary function testing, such as residual volume (RV) or functional residual capacity (FRC) (Figs. 28-22 and 28-23).

A major trend in the imaging of COPD is the development of semi-quantitative approaches and quantification techniques for COPD phenotyping. In 2015, a semi-quantitative analysis was proposed in a statement by the Fleischner Society, aiming to better define the phenotypic abnormalities that can be identified on CT in subjects with COPD. The goal of the statement is to categorize COPD into distinct structurally and functionally defined subtypes, thereby allowing a personalized approach to treatment. The statement defines emphysema on imaging as the presence of >6% of pixels measuring <–950 HU by quantitative CT and/or visual identification. Airway-predominant subtypes of COPD are defined by evidence of obstructive physiology on pulmonary function testing, with <6% of pixels measuring <–950 HU by quantitative CT. Quantitative CT analysis can be used to determine the severity of emphysema and the magnitude of expiratory gas trapping. Associated features that may affect prognosis or risk of exacerbations also are emphasized, including interstitial abnormalities and pulmonary arterial enlargement.[26] These categories are summarized in Table 28-1.

For quantitative imaging, strict standardization of the scanning technique is required. Sophisticated computer algorithms are also required to accurately separate the lung parenchyma, central airways, central vasculature, mediastinum, and chest wall structures, based upon attenuation characteristics and geometric constraints; the algorithms employ thin-section, isotropic volumetric data sets primarily obtained using CT. A variety of computational methods can then be applied to detect several disease patterns and characterize their extent and distribution. These methods can be used for both diagnosis and disease quantification, as well as for assessment of prognosis and response to therapy.[27–29]

It has been established that "attenuation masks" that separate all low-attenuation voxels in the segmented lung parenchyma (e.g., areas of <–950 HU), not including central airways, can accurately quantify the volume of emphysema compared with the reference

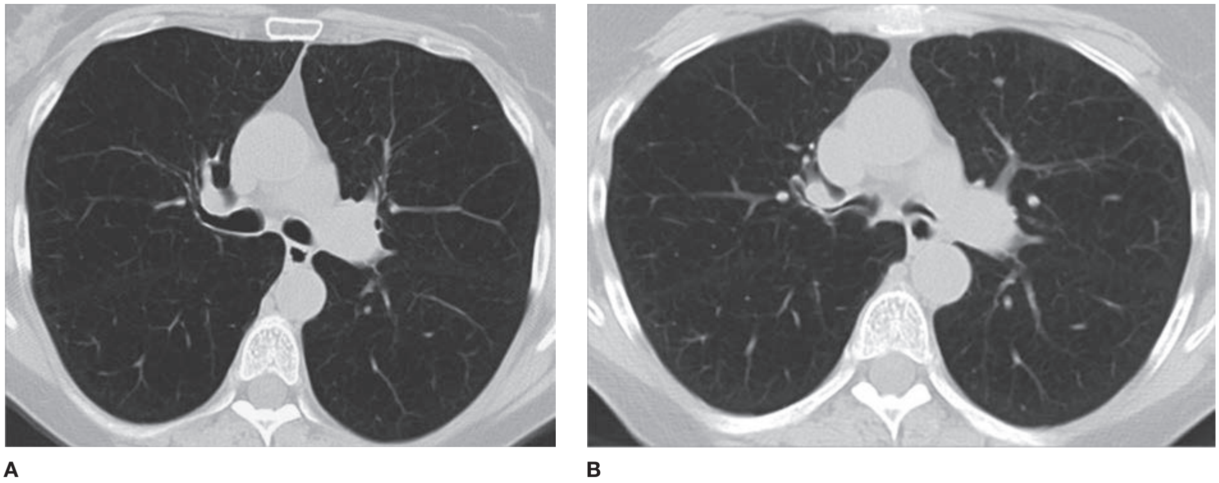


Figure 28-22 (**A**) Inspiratory and (**B**) expiratory CT images at the level of the mainstem bronchi, demonstrating dynamic expiratory collapse of the central airways, indicative of bronchomalacia, a common association with COPD.

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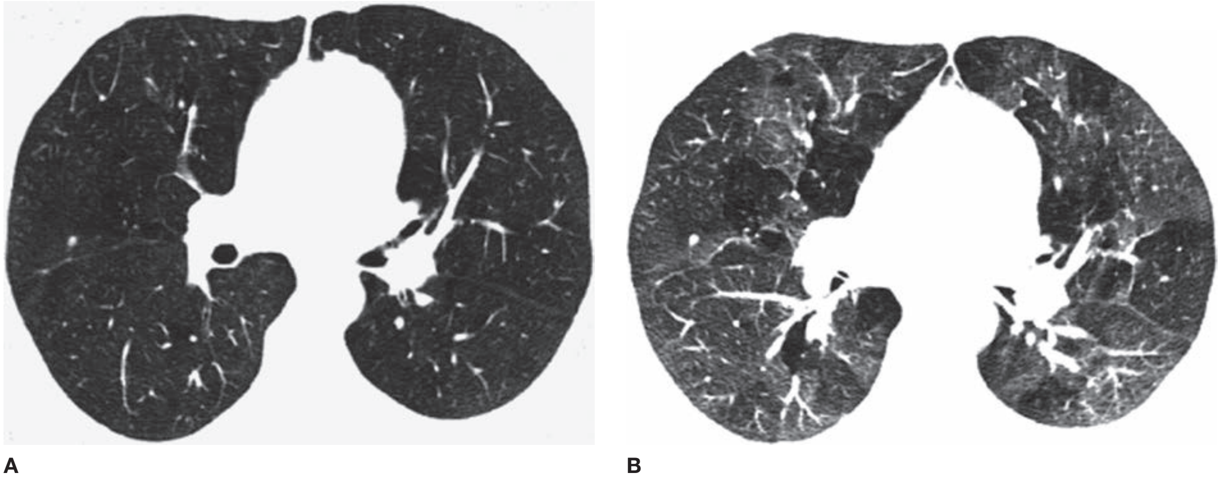


Figure 28-23 (**A**) Inspiratory and (**B**) expiratory CT images demonstrate the presence of mosaic attenuation (i.e., geographic areas of low parenchymal attenuation interspersed within normal, higher-attenuation areas in expiration), characteristic of air trapping. This patient had a diagnosis of bronchiolitis obliterans.

TABLE 28-1 Phenotypes of Emphysematous Destruction and Airway Changes Seen in COPD Patients on CT Imaging Defined by the Fleischner Society

Emphysema

1. Centrilobular
    a. Trace-minimal amount of lucencies involving <0.5% of the lung
    b. Mild-scattered lucencies involving 0.5%–5% of the lung
    c. Moderate: lucencies involving >5% of the lung
    d. Confluent: coalescent lucencies that may span several secondary lobules without hyper-expansion of secondary pulmonary lobules or distortion of lung architecture
    e. Advanced destructive emphysema: panlobular lucencies with hyperexpansion of secondary pulmonary lobules and distortion of lung architecture
2. Panlobular emphysema—lower lobe predominant with generalized acinar destruction, most commonly associated with α1-antitrypsin deficiency
3. Paraseptal
    a. Mild: juxta-pleural or peri-fissural small lucencies measuring <1 cm
    b. Substantial: juxta-pleural or peri-fissural large lucencies measuring >1 cm

Airway disease—may be associated with emphysema or present as the predominant expression of COPD

1. Bronchial disease—segmental or subsegmental wall thickening
2. Small airway disease (SAD)—inflammatory SAD, identified by the presence of peripheral centrilobular micronodular opacities; obstructive SAD, identified by gas trapping on expiratory CT in the absence of significant emphysema

Associated features

1. Large airway disease—presents with tracheobronchomalacia, saber sheath trachea, or tracheobronchial diverticula
2. Interstitial abnormality—patchy ground glass or presence of subpleural reticulation
3. Pulmonary arterial enlargement—a sign suggestive of pulmonary hypertension
4. Bronchiectasis

standard of pathologic assessment. Such CT measures of emphysema demonstrate strong correlation with functional metrics that denote obstruction (e.g., FEV1/FVC, %). Moreover, it is possible to measure the thickness of the central airways (to the fifth or sixth generation) as a quantitative metric in chronic bronchitis. In addition, small airway disease can be indirectly measured using quantification of expiratory air trapping, which can be accomplished via several different techniques. The simplest method uses attenuation masks in expiration. Voxels measuring less than −856 HU on expiratory CT are considered areas of air trapping. This attenuation threshold has been validated in multiple publications. More sophisticated techniques take into account how much each voxel varies in attenuation between full inspiration and end expiration (at FRC). The latter approach requires mathematical, nonrigid registration techniques that track individual voxel motion and regional volume changes between data acquired at two different time points, allowing for a one-on-one correspondence between lung voxels in inspiration and expiration.[30–32]

While these sophisticated, quantitative applications are still largely investigational, they will likely reach the clinical realm in this decade. Studies continue to validate the superiority of quantitative imaging over standard qualitative assessment of thoracic imaging studies, demonstrating improved correlations with disease severity and functional impairment. Such quantitative imaging will ultimately provide better tools to estimate prognosis and monitor the efficacy of therapy.

INTERSTITIAL LUNG DISEASE

Interstitial lung disease (ILD) is a broad and complex topic, with many distinct and unrelated clinical entities potentially contributing to a single imaging pattern. Their detailed pathophysiology is described elsewhere. The focus of this discussion is the contribution of imaging to the differential diagnosis of ILD, emphasizing the most common and clinically relevant diseases.

The chest radiographic pattern of interstitial disease differs from the pattern of alveolar disease in that with interstitial disease, the imaging pattern tends to be discrete and sharp, rather than fluffy and irregular; the lesions tend to be diffuse, rather than localized. In addition, coalescence is not a typical feature in ILD, and the small opacities are characteristically nodular, reticular, or linear. Large masses or consolidations are not characteristic of the interstitial pattern (Fig. 28-24).

In and of itself, the recognition of an interstitial pattern on chest radiographs is not specific for a particular diagnosis. Most often a CT is necessary for further characterization. However, two

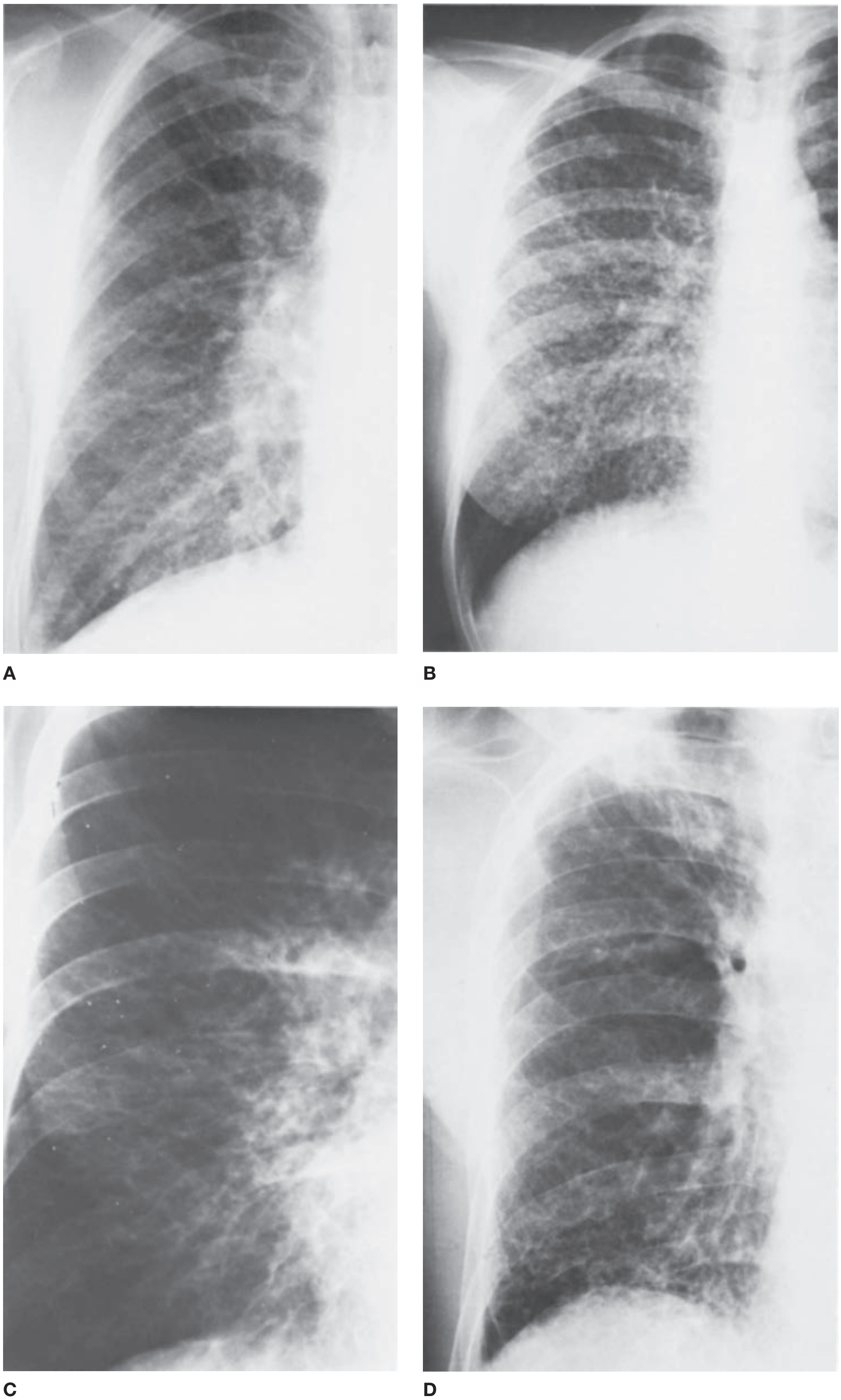


Figure 28-24 Radiographic patterns of interstitial disease. **A.** Linear interstitial pattern produced by interstitial pulmonary edema. The pattern is caused by fluid in the axial and septal interstitial spaces of the lungs, particularly in interlobar septae. **B.** Nodular interstitial pattern due to sarcoidosis. Multiple small, discrete nodules involve both lung fields diffusely. Adenopathy is absent. **C.** Lymphangitic spread of neoplasm. The linear interstitial pattern was caused by metastatic carcinoma of the pancreas. **D.** Reticular interstitial lung pattern. The pattern is most marked at the bases and is characteristic of idiopathic pulmonary fibrosis or collagen vascular disease, particularly scleroderma (as in this patient).

observations that may provide useful insight into the likely diagnosis are the temporal course and distribution of disease.

Most interstitial diseases have a chronic, progressive course. Therefore, recognition of an acute interstitial pattern, that is, development and rapid evolution over hours or a few days, is strongly suggestive of interstitial pulmonary edema. This is even more likely if ancillary findings indicative of congestive heart failure or volume overload are present, such as cardiomegaly, pleural effusions, and widening of the vascular pedicle in the mediastinum. Occasionally, a rapidly changing interstitial pattern represents atypical pneumonia due to *Pneumocystis jiroveci*, cytomegalovirus, or *Mycoplasma*. The acute interstitial disorders typically cause a radiographic linear or reticular pattern, which is characterized by prominent Kerley lines throughout the lungs.

In his original description in 1951, Kerley associated thin, radiographic parenchymal opacities with left ventricular failure.

Initially, Kerley lines were thought to represent swollen pulmonary lymphatics. It is now recognized that Kerley lines usually represent edematous septae within the pulmonary interstitium. Three patterns exist. Kerley type B lines are the most familiar and are particularly prominent at the lung bases, where they appear as straight, thin, peripheral lines approximately 1 cm long and oriented parallel to the diaphragm. Kerley type A lines represent septae deep within the substance of the lungs; they radiate from the hili, but they are thinner than central vessels. Kerley type C lines probably represent coalescence of A and B lines and are difficult to recognize.

Chronic ILDs may be caused by a wide variety of diseases, including idiopathic interstitial pneumonias, connective tissue diseases, pneumoconiosis, sarcoidosis, lymphangitic spread of malignancy, infections, Langerhans cell histiocytosis (LCH), and lymphangioleiomyomatosis (LAM). Of note, LCH and LAM are not interstitial diseases per se, but rather cystic lung diseases that can present as an interstitial pattern on chest radiography; they are better characterized as cystic diseases on CT.

Characterization of the pattern of interstitial disease as nodular, reticular, or linear on chest radiograph may help in differential diagnosis, since many of the ILDs have a predilection for one of these three patterns. However, beyond that, the radiographic findings are not sufficient for a specific diagnosis. Nonetheless, separation of the distribution of disease into two broad categories can be helpful—upper lung predominant versus basilar predominant.

Upper lung–predominant distribution favors airway-related pathology, with inhalational diseases such as infections, LCH, and pneumoconiosis predominating in this group. Moreover, sarcoidosis is also typically upper lung predominant, a finding compatible with the hypothesis that the disease is triggered by an inhaled agent, although its exact cause remains elusive. On the other hand, basilar-predominant distribution favors idiopathic interstitial pneumonias and connective tissue diseases, in which increased blood flow and greater regional volume changes may play a role in explaining the lower lung predominance. Following such radiographic assessment, CT is generally the next diagnostic step.[33,34]

CT has been validated as the optimal imaging technique for evaluating chronic ILDs. CT can often identify interstitial disease that is not seen on chest radiography, and it provides better disease pattern characterization to enable identification of the underlying etiology, as well as better qualitative or quantitative assessment of severity. CT patterns of ILD follow, to some degree, the patterns seen on the chest radiograph; however, CT allows distinction of reticular, linear, and nodular patterns much more confidently. In addition, it permits evaluation of ancillary findings, such as honeycombing, traction bronchiectasis, ground-glass opacities, and cystic changes, all of which may be very challenging or impossible to recognize on chest radiographs. Important to emphasize is that, as previously discussed, every chest CT performed using current protocols on modern scanners may serve as a high-resolution examination. Therefore, the distinction between standard and high-resolution chest CT is obsolete, and detailed interstitial disease characterization can be performed on all current chest CT studies.[35,36]

Careful analysis of the CT in evaluating ILD can be described as comprising three steps.

The first step in the diagnostic approach of ILD on CT is to exclude interstitial pulmonary edema as the cause. An acute course and ancillary findings of cardiomegaly, bilateral pleural effusions, and central vascular engorgement strongly suggest interstitial pulmonary edema. CT findings include symmetric bilateral axial (peribronchovascular) and interlobular septal thickening, with central and basilar predominance. Ground-glass opacities may be present, denoting concomitant alveolar edema. It is important to remember that lymphangitic spread of neoplasm may present with a similar CT pattern; however, the temporal course is not acute, and the findings are often asymmetric and more nodular, with additional features of malignancy present, such as pulmonary masses and hilar or mediastinal lymphadenopathy.[37,38]

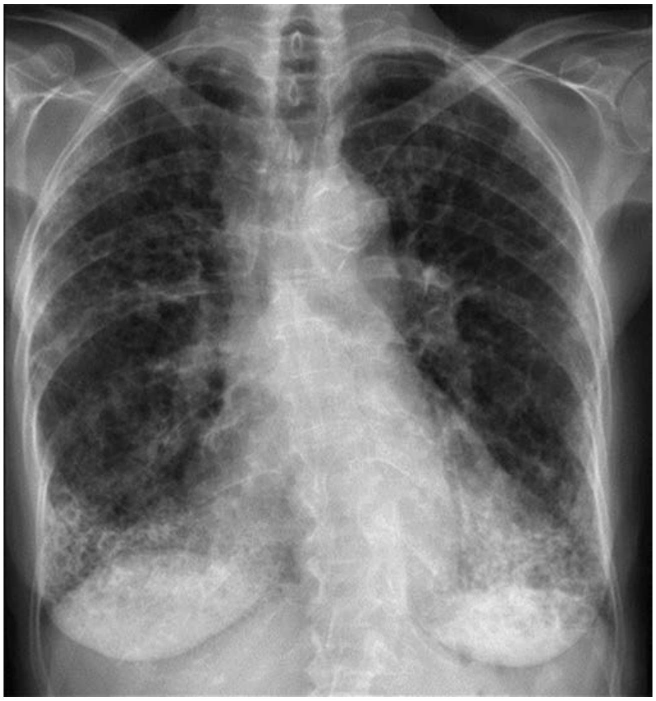


Figure 28-25 PA chest radiograph demonstrating typical changes of UIP pattern with increased basilar predominant reticulations and microcystic changes in a female patient with IPF.

The second step is to decide whether usual interstitial pneumonia (UIP) is the most likely cause of the pattern (Fig. 28-25).

UIP is the pathologic correlate of idiopathic pulmonary fibrosis (IPF), although it may also be associated with connective tissue disorders and asbestosis, with both needed to be excluded to establish diagnosis of IPF. The latter should be considered if other findings that correlate with asbestos exposure, such as pleural plaques, are present. It is important to recognize UIP because it generally has a much worse prognosis than other causes of ILD. Multiple recent consensus statements and clinical guidelines have been published in an effort to standardize the description of imaging description and a clinical approach to diagnosis. A Fleischner Society white paper, published in 2018, suggests four categories of diagnostic confidence, as summarized in Table 28-2.

In the setting of a typical UIP pattern on CT, most authorities do not recommend surgical biopsy. Even in patients with a probable UIP pattern on CT, a surgical lung biopsy may not be necessary, since 82% to 94% of these patients have a UIP histopathologic pattern on surgical biopsy. Thus, a biopsy should be reserved for cases falling in the “indeterminate” or “inconsistent with UIP” categories.

Additionally, strong emphasis is currently placed on the importance of a multidisciplinary approach to diagnosis, based on a team comprising a pulmonary clinician, radiologist, and pathologist with interest and experience in ILD. The team should discuss clinical and radiologic findings to define when a biopsy can be of value, especially in cases where imaging and or clinical features do not provide a confident diagnosis. A multidisciplinary approach can be also of value in cases where the longitudinal course is discordant with the clinical diagnosis, or in establishing an appropriate clinical approach after a biopsy is performed—based on the cumulative experience of all team members (Video 28-6).[39–41]

Many patients with an idiopathic interstitial pneumonia (IIP) have clinical features that suggest an underlying autoimmune disease

TABLE 28-2 Diagnostic Categories of UIP on CT Imaging Recommended by the Fleischner Society

	Typical UIP CT Pattern	Probable UIP CT Pattern	CT Pattern Indeterminate for UIP	CT Features Most Consistent with Non-IPF Diagnosis
CT distribution	Basal (occasionally diffuse) and subpleural predominant. Distribution is often heterogeneous.	Basal and subpleural predominant. Distribution is often heterogeneous.	Variable or diffuse.	Upper- or mid-lung predominant fibrosis. Peribronchovascular predominance with subpleural sparing.
CT features	Honeycombing. Reticular pattern with peripheral traction bronchiectasis/bronchiolectasis.[a] Absence of features to suggest an alternative diagnosis.	Reticular pattern with peripheral traction bronchiectasis/bronchiolectasis.[a] Honeycombing is absent.	Evidence of fibrosis, with some inconspicuous features suggestive of non-UIP pattern.[a]	Any of the following: predominant consolidation, extensive pure ground-glass opacity (without acute exacerbation), extensive mosaic attenuation with extensive sharply defined lobular air trapping on expiration, diffuse nodules or cysts.

[a] Reticular pattern is superimposed on ground glass opacity and, in these cases, is usually fibrotic. Pure ground glass opacity, however, would not support the diagnosis of UIP/IPF and would suggest acute exacerbation, hypersensitivity pneumonitis, or other conditions.

process, but that do not meet established criteria for any connective tissue disease (CTD). The current term for this subgroup is *interstitial pneumonia with autoimmune features (IPAF)*. In 2015, criteria for imaging and clinical features describing these patients were proposed by an Official European Respiratory Society/American Thoracic Society research statement. The radiologic patterns included in the IPAF criteria are nonspecific interstitial pneumonia (NSIP), imaging features of which are described below; organizing pneumonia (OP); and NSIP with OP, which includes basal predominant consolidation, often peri-diaphragmatic, with associated features of fibrosis and lymphoid interstitial pneumonia (LIP). These patterns are commonly found in CTD-ILD, and their presence should raise the suspicion for an underlying autoimmune process.

Additional thoracic manifestations are often encountered among patients with CTD and include unexplained airways disease (e.g., airflow obstruction, bronchiolitis, bronchiectasis), vascular abnormalities (e.g., several categories of pulmonary hypertension), and pleural or pericardial abnormalities (e.g., presence of serositis and effusion).[42]

Other common causes of fibrotic lung disease include fibrotic nonspecific interstitial pneumonia (NSIP), end-stage sarcoidosis, and chronic hypersensitivity pneumonitis (CHP). Fibrotic NSIP is favored over UIP if there is central, rather than peripheral, predominance, sometimes accompanied by subpleural sparing. The fibrosis is more uniform, and honeycombing is usually absent. Inflammatory opacities (ground-glass) may or may not be present, and, if present, reflect active inflammation. Moreover, the early phase of NSIP may manifest as multifocal bilaterally symmetric ground-glass opacities without fibrotic features or consolidation, denoting early inflammatory changes (cellular NSIP) (Video 28-7). Untreated cellular NSIP generally progresses to fibrotic NSIP, although cellular NSIP tends to respond to anti-inflammatory drugs, such as steroids. Nonetheless, significant overlap occurs between fibrotic NSIP and atypical manifestations of UIP. Both may be idiopathic or associated with connective tissue disorders. Clinical correlation and laboratory tests usually are required to exclude a connective tissue disorder. Of note, the presence of a patulous esophagus may be a clue to the diagnosis of CREST syndrome or systemic sclerosis (Figs. 28-26 and 28-27).[43,44]

Video 28-6 Axial cine images using lung window, demonstrating a typical usual interstitial pneumonia (UIP) pattern of fibrosing interstitial lung disease—in this case, idiopathic (and, therefore, classified as IPF, or idiopathic pulmonary fibrosis). *Video available on AccessMedicine.com.*

Video 28-7 Axial cine images using lung window, demonstrating mild interstitial lung disease characterized by basilar-predominant ground-glass opacities without overt fibrotic features, likely reflecting cellular nonspecific interstitial pneumonia (NSIP). In this case, the findings were attributed to connective tissue disease (likely due to scleroderma). *Video available on AccessMedicine.com.*

Sarcoidosis is suspected when there is a combination of upper lung–predominant disease that is bilaterally symmetric, axial, and accompanied by interlobular septal interstitial thickening, multiple diminutive nodules with perilymphatic distribution (see "Pulmonary Nodules and Lung Cancer," below), and associated mediastinal and hilar lymphadenopathy. Mosaic air trapping also may be present. The presence of fibrotic features denotes end-stage disease (radiographic stage IV). The differential diagnosis includes interstitial pulmonary edema and lymphangitic spread of neoplasm, with interlobular septal thickening as the unifying theme for these three entities. Nuclear imaging, and specifically PET-CT, can play a supplementary role in diagnosis and management of lung involvement by sarcoidosis by directing biopsy to areas of increased FDG uptake. Additionally, the technique serves as a tool to assess inflammatory activity in patients with pulmonary fibrosis, as well as prognostic marker of future pulmonary function. In the heart, both MRI (which may demonstrate myocardial function, scarring, and edema) and PET-CT (demonstrating abnormal FDG uptake) have been shown to be valuable in the detection of disease, in assessment of response to therapy, and as a prognostic tool.[45–47]

IIPs are frequently confused with hypersensitivity pneumonitis, except when the environmental exposure is readily apparent. The imaging features of chronic HP have been more accurately defined in recent publications, helping to separate these cases from the IIPs, particularly IPF and NSIP. HRCT findings suggesting HP include centrilobular/peribronchial nodules, mosaic attenuation due to air-trapping that is accentuated on expiratory imaging (denoting heterogeneous small airway disease), and upper lobe–predominant distribution. The presence of air trapping is somewhat specific for CHP in the setting of pulmonary fibrosis that does not conform to typical UIP or show features of sarcoidosis, unless the patient has superimposed asthma or COPD (Figs. 28-28 and 28-29).[48–50]

Pneumoconioses, particularly silicosis and berylliosis, may present with interstitial interlobular septal and axial thickening, as well as with perilympathic nodules—a pattern that can be indistinguishable from sarcoidosis. The presence of calcified nodules and mediastinal or hilar lymph nodes support the diagnosis of pneumoconiosis,

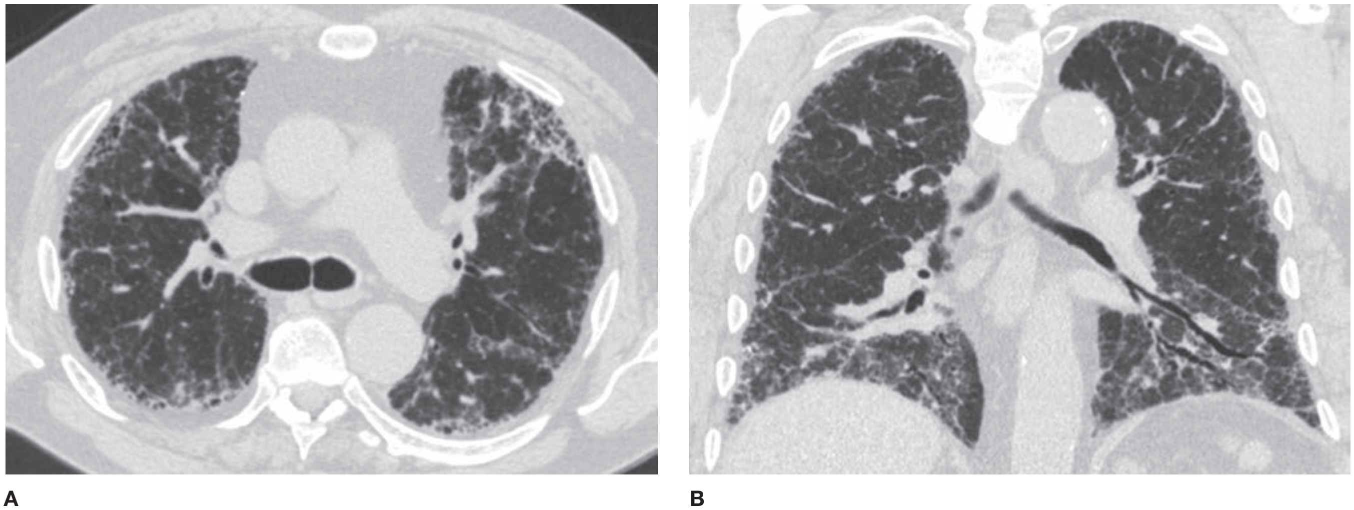


Figure 28-26 (**A**) Axial and (**B**) coronal CT images demonstrate a classic usual interstitial pneumonia (UIP) pattern, depicting symmetric, basilar- and peripheral-predominant reticulation, traction bronchiectasis, and honeycombing. A UIP pattern confers the worst prognosis among interstitial diseases and is associated with the clinical diagnosis of idiopathic pulmonary fibrosis (IPF).

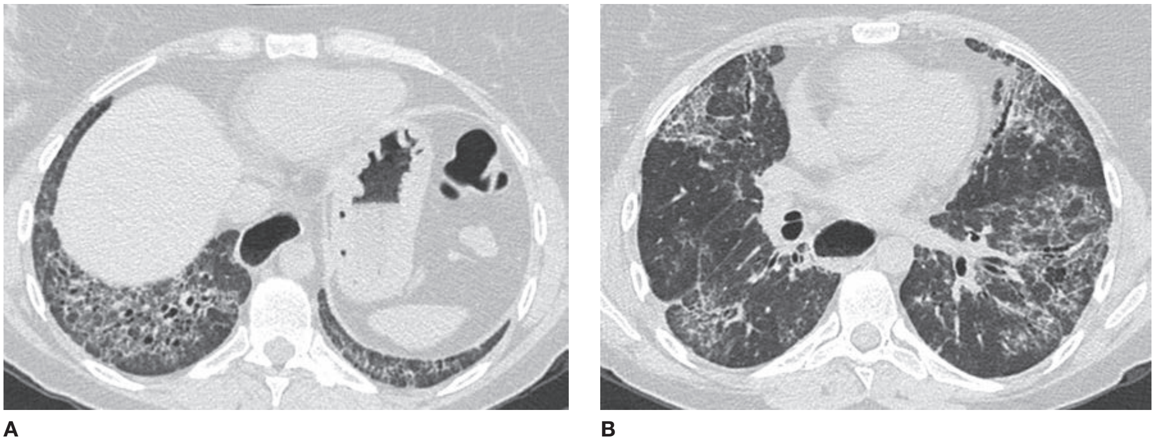


Figure 28-27 (**A**) Axial basilar and (**B**) axial midlung CT images in a patient with nonspecific interstitial pneumonia (NSIP) pattern. This pattern is distinguished from UIP by the absence of honeycombing and the more central (or peribronchovascular) distribution of reticulation denoting fibrosis. Traction bronchiectasis is also noted. The patient had a clinical diagnosis of scleroderma.

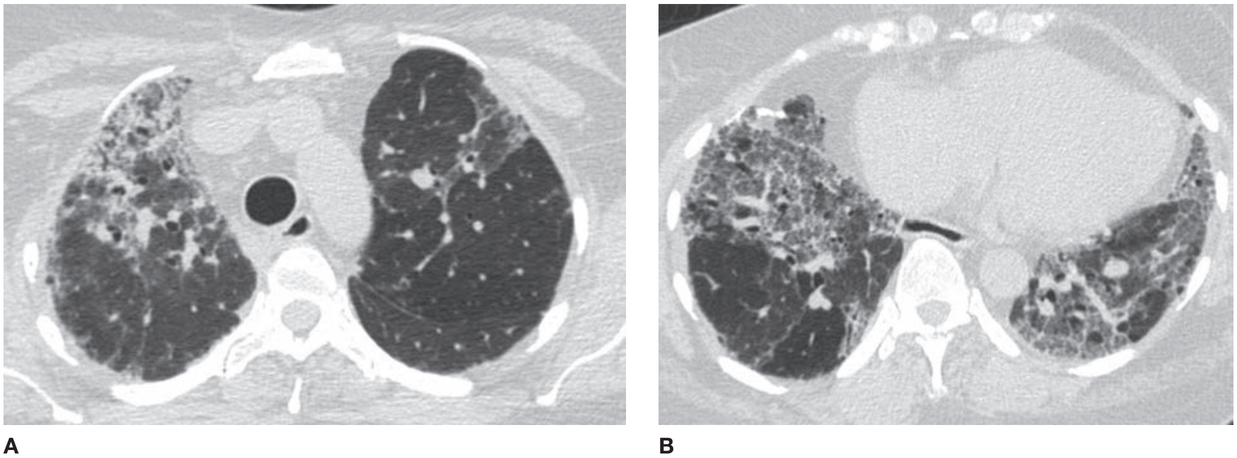


Figure 28-28 (**A**) and (**B**) are axial apical and axial basilar CT images in a patient with biopsy-proved CHP (chronic hypersensitivity pneumonitis);

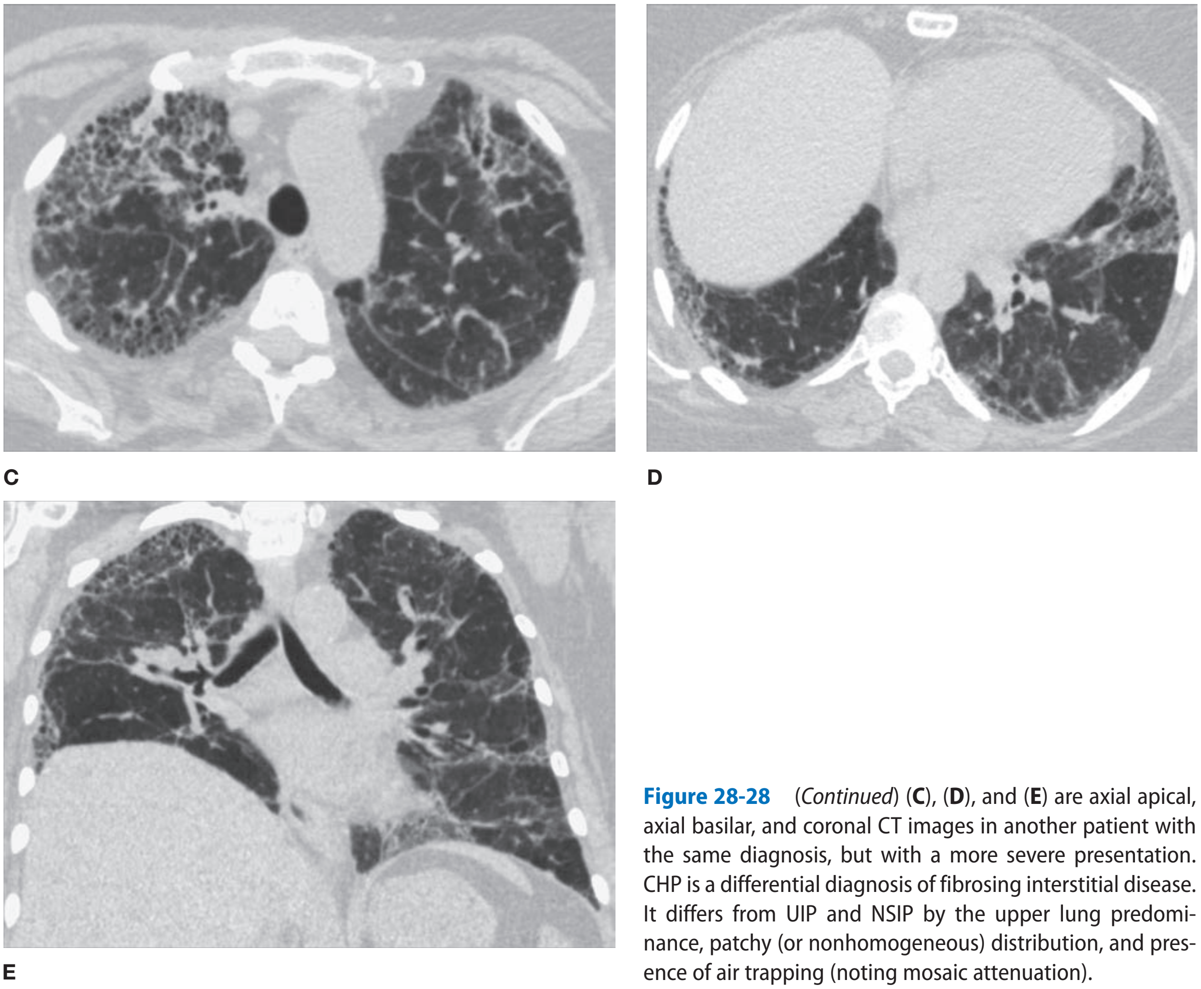


Figure 28-28 (*Continued*) (**C**), (**D**), and (**E**) are axial apical, axial basilar, and coronal CT images in another patient with the same diagnosis, but with a more severe presentation. CHP is a differential diagnosis of fibrosing interstitial disease. It differs from UIP and NSIP by the upper lung predominance, patchy (or nonhomogeneous) distribution, and presence of air trapping (noting mosaic attenuation).

but these findings may also be seen with sarcoidosis. Specific environmental exposure history is, of course, central in suggesting the diagnosis of pneumoconioses.

Currently, severity of ILD is assessed routinely via subjective analysis of disease extent on CT, along with evaluation of the degree of restriction on pulmonary function testing. Ongoing research has shown the promise of computational quantitative imaging techniques, which allow not only accurate diagnosis based upon pattern, but also quantification of the individual contributions of each pattern feature (e.g., ground-glass opacities and septal thickening) to the overall disease extent. This approach offers the potential for better tools for monitoring disease progression, refining prognosis, and developing quantitative, surrogate imaging biomarkers for future medication trials.[51,52]

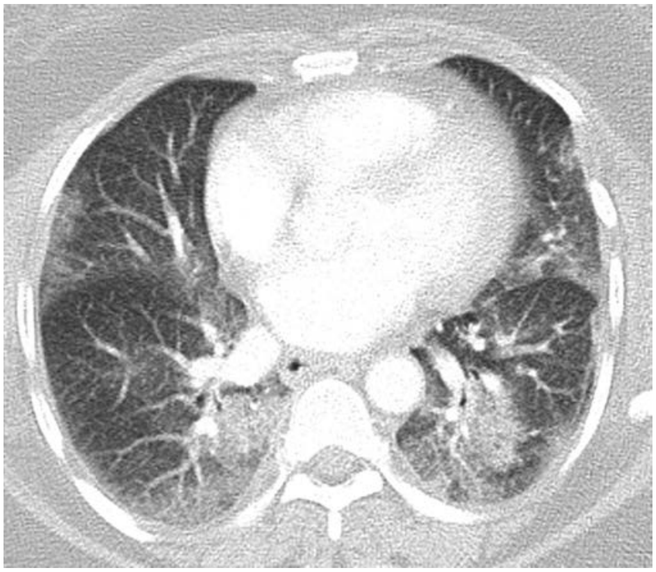
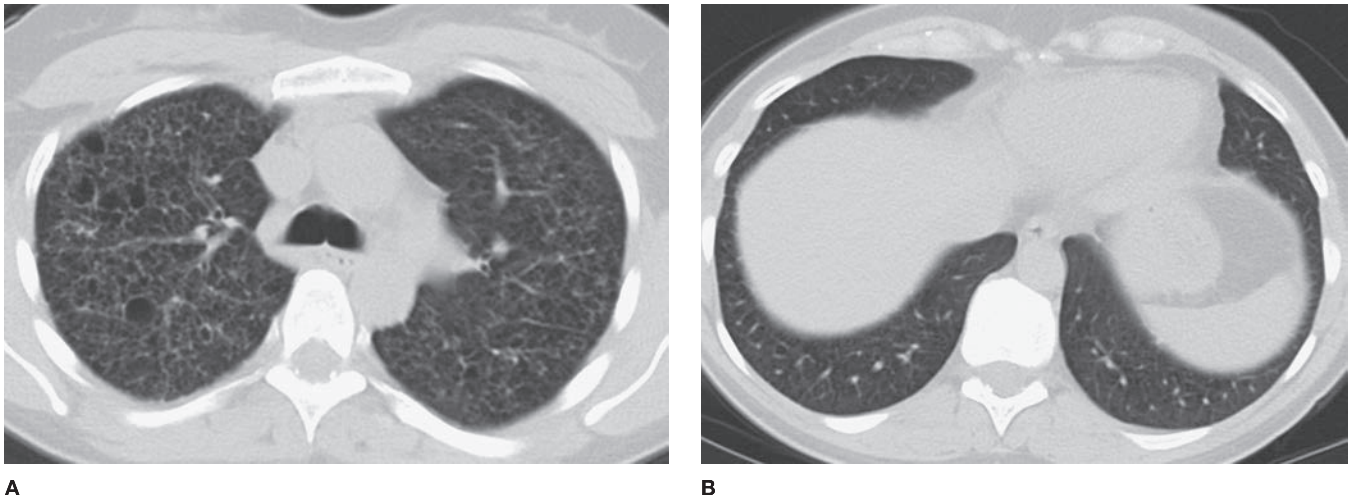


Figure 28-29 Multifocal airspace consolidation and ground-glass opacities in a patient with cryptogenic organizing pneumonia (COP). Infection is the most common differential diagnosis.

PULMONARY NODULES AND LUNG CANCER

Pulmonary nodules are exceedingly common and may be noted in up to 50% of CT examinations performed in hospital settings. Furthermore, the differential diagnosis is extremely broad and the imaging findings often nonspecific. Therefore, management of pulmonary nodules can be very challenging. We aim here to present a practical, evidence-based approach that is centered on answering four key questions: (1) Is the nodule likely malignant? If so, what is the best approach to tissue sampling? (2) If not, does the nodule need to be followed? If so, how often and for how long? (3) If it is not likely malignant, is the nodule likely to be a manifestation of an infectious or inflammatory process that requires pathologic confirmation for proper management? (4) Does the nodule have any features that allow either a specific diagnosis or a confident diagnosis of benignity? The reader is also referred to Chapter 110 for further discussion.

The discussion of pulmonary nodules starts with their definition, which is not always straightforward. While there is no question that well-circumscribed round or ovoid opacities should be characterized as nodules, the distinction of nodules from focal consolidations


A

B

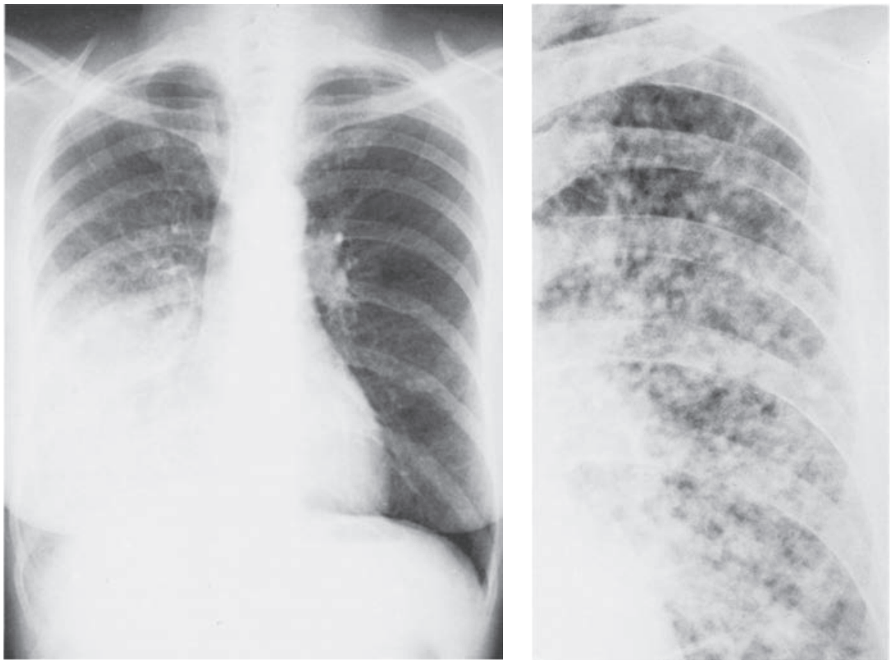
Figure 28-30 (**A**) and (**B**) are axial apical and axial basilar CT images in a patient with Langerhans cell histiocytosis (LCH). Although LCH is not considered an interstitial lung disease proper (instead, it is classified as a cystic lung disease), this disease does cause an interstitial pattern on chest radiographs. Key features are cysts with upper lung predominance, occasional nodules, and associated hyperinflation. A strong smoking history is often elicited.

and interstitial opacities can sometimes be cloudy, particularly when ill-defined or ground-glass nodules are taken into account. As a general rule, any opacity that has mostly convex borders and a shape that can be described as round or ovoid should be classified as a nodule. This has implications for differential diagnosis (Figs. 28-30 and 28-31).

From an imaging perspective, the following descriptors are important in assigning a nodule to a particular differential diagnostic category: number (solitary versus multiple), size, border, CT attenuation, and distribution (if multiple). Below, each category is described and a strategic approach to diagnosis and management discussed, emphasizing a combination of clinical and CT findings.[53,54]

To answer the first question, that is, is the nodule likely to be malignant, one must be cognizant of the pretest clinical probability. Age is important; the older the patient, the more likely that a lung nodule is malignant. Smoking history and COPD are major risk factors for lung cancer and should be taken into account. A history of prior lung cancer or a known diagnosis of malignancy also places the patient at a higher risk of an additional lung cancer and pulmonary metastases, respectively.

Nodule features on CT are of considerable importance in suggesting malignancy. For a solitary nodule, the larger its size, the more likely it is malignant and represents a primary bronchogenic carcinoma. Ill-defined borders are also more highly associated with primary bronchogenic carcinoma than benign etiologies, although infectious processes, such as fungal pneumonia, also have to be considered in the proper clinical setting. Mixed-attenuation nodules, that is, subsolid nodules with coexistence of solid and ground-glass components, are highly associated with a diagnosis of primary bronchogenic carcinoma. Multiple nodules that are well circumscribed, vary in size, and are basilar predominant are strongly suggestive of metastatic disease (Figs. 28-32–28-41).


A

B

Figure 28-31 Radiographic patterns of adenocarcinoma. **A.** Large area of consolidation in the right lower lobe. The alveolar pattern suggests pneumonia, but it failed to improve with antibiotic treatment and was discovered to be an adenocarcinoma. **B.** Multiple ill-defined nodules. The nodules have irregular or fuzzy margins that are characteristic of alveolar, rather than interstitial, nodulation, in this patient with metastatic adenocarcinoma.

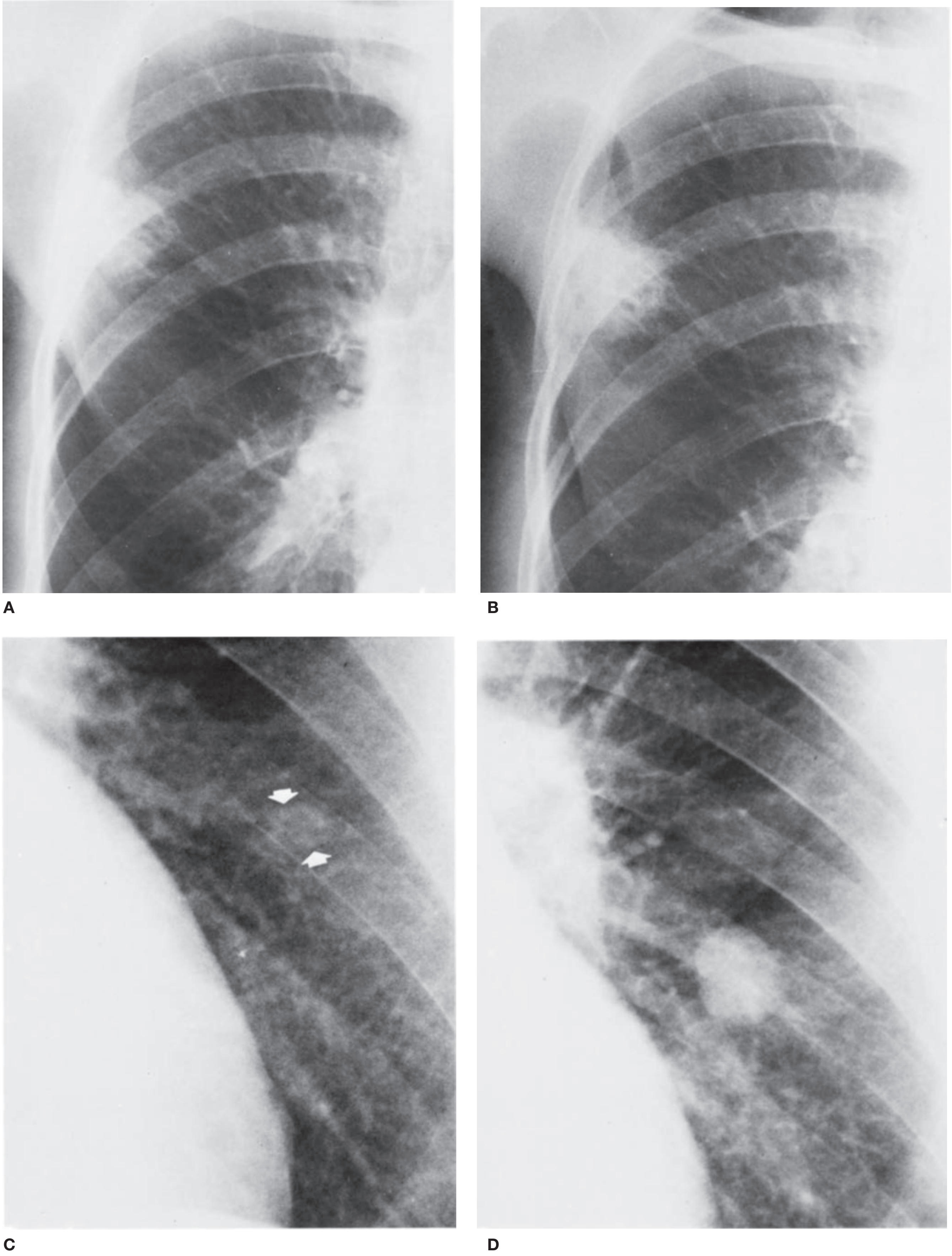


Figure 28-32 *Top:* Carcinoma of the lung with a long doubling time. An interval of 18 months elapsed between (**A**) and (**B**). The right upper lobe lesion, which enlarged minimally during that time, proved to be primary squamous cell. *Bottom:* Carcinoma of the lung with a short doubling time. An interval of 4 months elapsed between (**C**) and (**D**). The nodule was not detected on the first radiograph (**C**). It proved to be a primary small cell carcinoma.

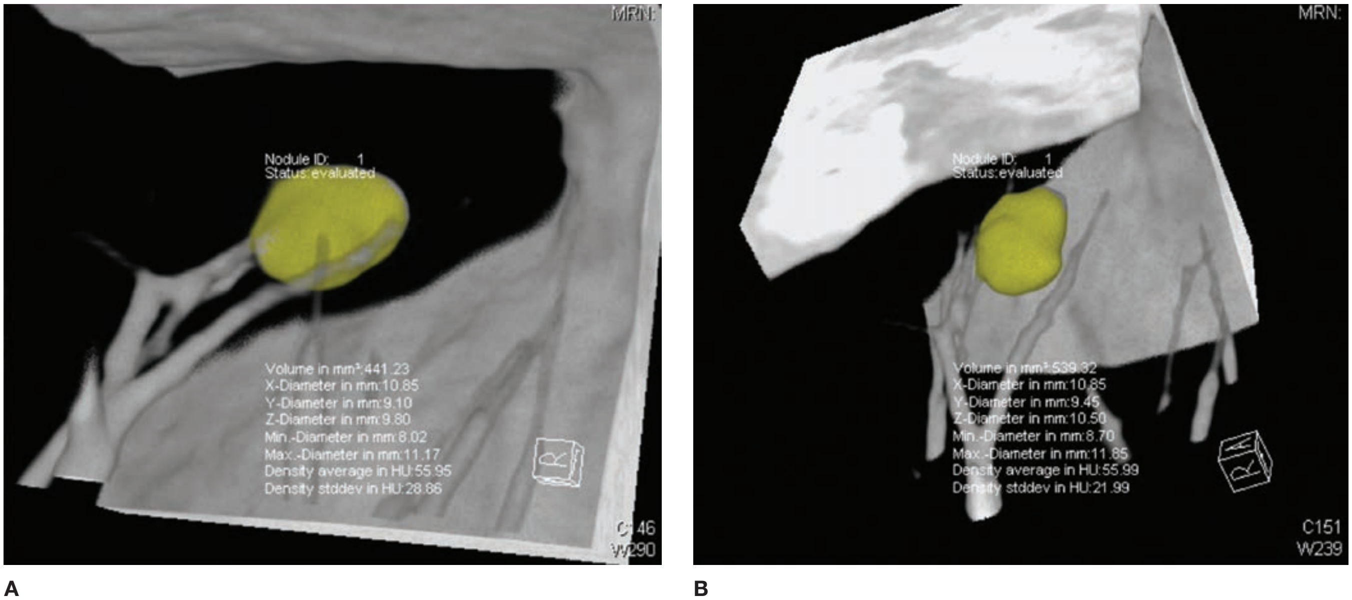

MRN:
Nodule ID: 1
Status:evaluated
Volume in mm³:441.23
X-Diameter in mm:10.85
Y-Diameter in mm:9.10
Z-Diameter in mm:9.80
Min.-Diameter in mm:8.02
Max.-Diameter in mm:11.17
Density average in HU:55.95
Density stddev in HU:28.86
R
C146
W290
A
MRN:
Nodule ID: 1
Status:evaluated
Volume in mm³:539.32
X-Diameter in mm:10.85
Y-Diameter in mm:9.45
Z-Diameter in mm:10.50
Min.-Diameter in mm:8.70
Max.-Diameter in mm:11.85
Density average in HU:55.99
Density stddev in HU:21.99
A
R
C151
W239
B

Figure 28-33 CT allows accurate volumetric measurement, which is not possible with chest radiographs, with the use of postprocessing software for nodule segmentation and volume calculation. This nodule grew from 441 mm^3 (**A**) to 539 mm^3 (**B**) in 7 months, an increase of 19%; it was later confirmed as metastasis from colon cancer.

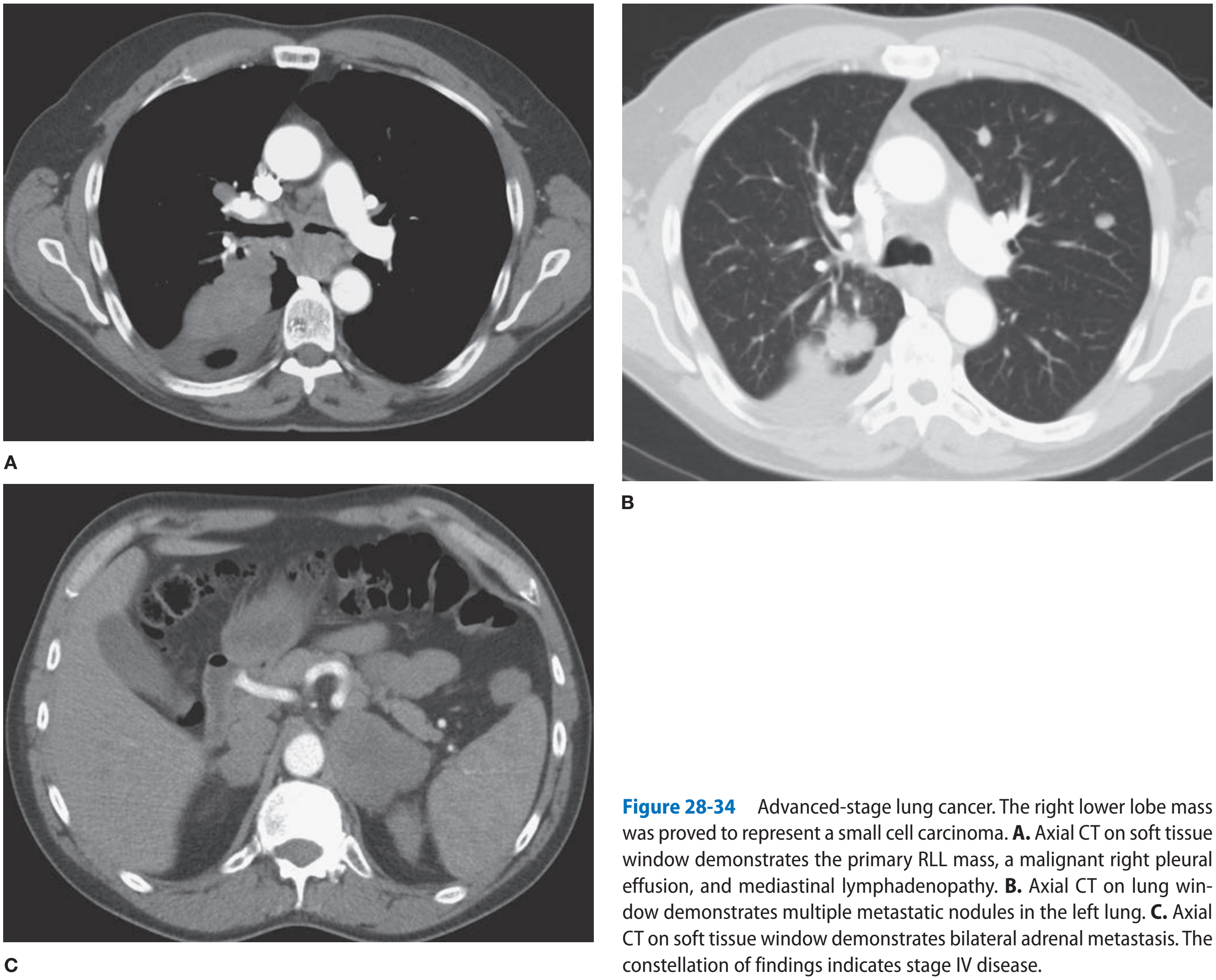


Figure 28-34 Advanced-stage lung cancer. The right lower lobe mass was proved to represent a small cell carcinoma. **A.** Axial CT on soft tissue window demonstrates the primary RLL mass, a malignant right pleural effusion, and mediastinal lymphadenopathy. **B.** Axial CT on lung window demonstrates multiple metastatic nodules in the left lung. **C.** Axial CT on soft tissue window demonstrates bilateral adrenal metastasis. The constellation of findings indicates stage IV disease.

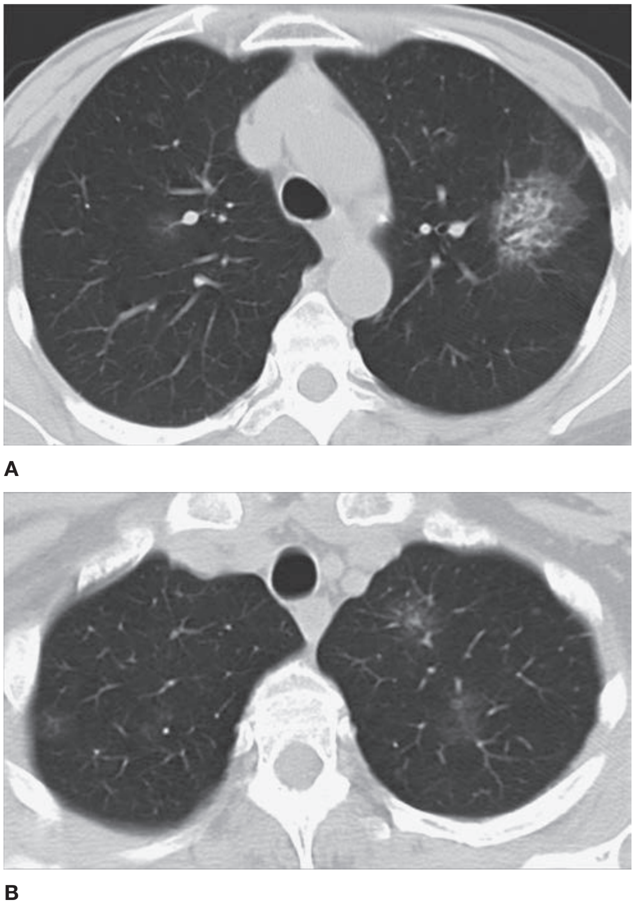


Figure 28-35 Spectrum of pulmonary adenocarcinoma. **A.** Axial CT image demonstrates a dominant, mixed-attenuation left upper lobe nodule, with solid and ground-glass components, which was resected and characterized as an adenocarcinoma. **B.** Axial CT image at a higher level demonstrates multiple smaller nodules, some of them mixed, most of purely ground-glass attenuation, which are compatible with multiple lesions in the spectrum of atypical adenomatous hyperplasia (AAH), adenocarcinoma in situ (AIS), and minimally invasive adenocarcinoma (MIA). In the past, all of these lesions would have been classified as BACs (bronchoalveolar carcinomas), a terminology that should no longer be utilized, as discussed in the text.

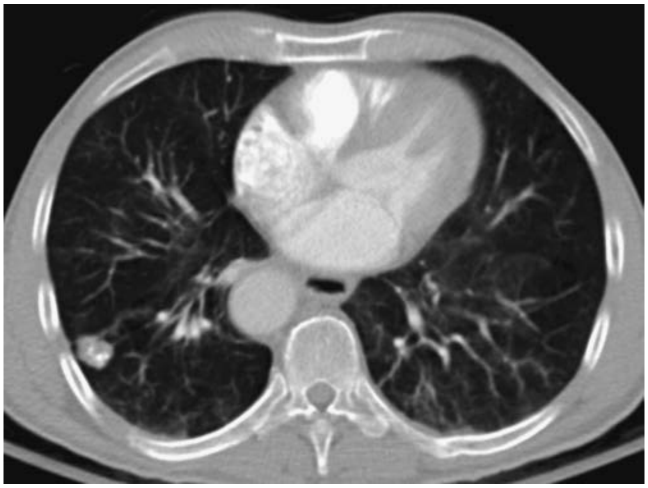


Figure 28-37 Right lower lobe nodule with coarse calcification, typical of a benign pulmonary hamartoma. Incidentally noted is a right-sided descending thoracic aorta.

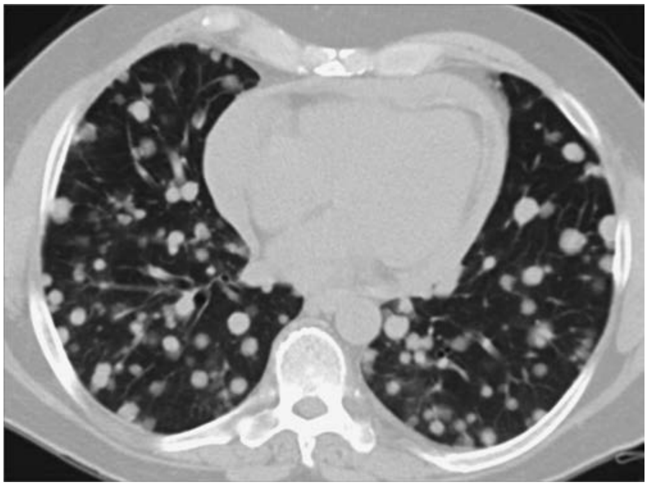


Figure 28-38 Differential diagnosis of multiple pulmonary nodules: axial CT image showing multiple well-circumscribed nodules, of varying size, characteristic of pulmonary metastases, in this case from renal cell carcinoma.

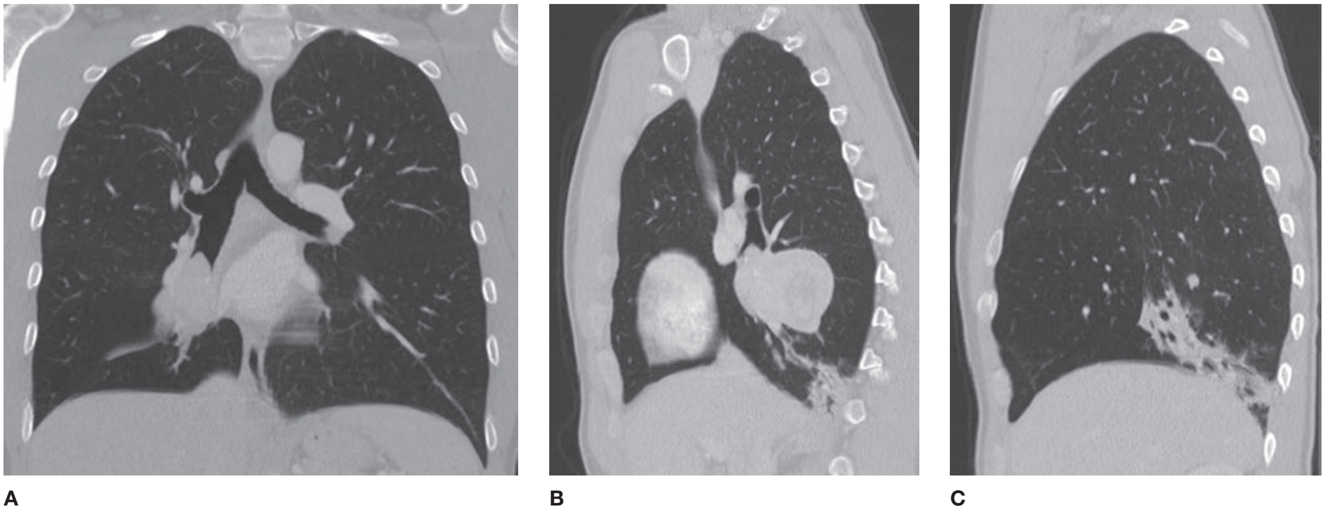


Figure 28-36 Coronal (**A**) and two sagittal CT images (**B**) and (**C**) showing a large endobronchial mass obstructing the RLL and growing concentrically into the lung parenchyma, with well-circumscribed borders. Note the associated atelectasis of the RLL basilar posterior segment. This mass was a carcinoid neoplasm.

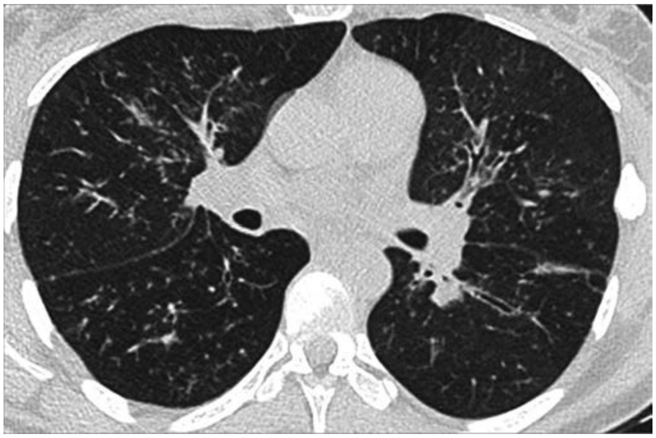


Figure 28-39 Differential diagnosis of multiple pulmonary nodules: axial CT image demonstrating very numerous, very small (1–2 mm) pulmonary nodules with a perilymphatic distribution (along the septal and axial interstitial compartments), typical of sarcoidosis—the diagnosis in this patient. This pattern can also be seen in lymphangitic carcinomatosis.

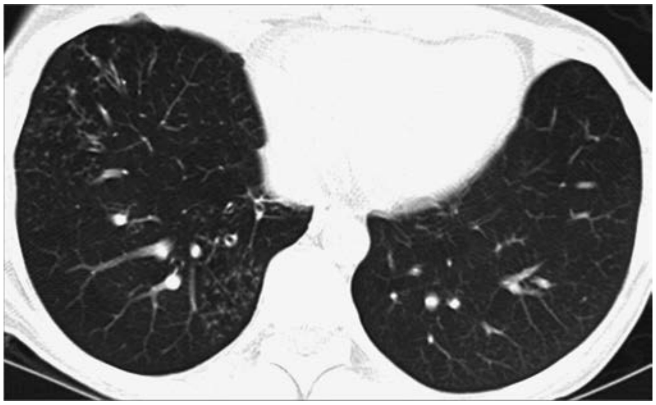


Figure 28-40 Differential diagnosis of multiple pulmonary nodules: axial CT images demonstrating multiple clusters of small nodules (measuring <2–3 mm each) in the RLL and RML, with centrilobular distribution and tree-in-bud configuration. This pattern is typical of infection and usually represents bronchiolitis. In this case, it was due to nontuberculous mycobacterial infection.

Several prediction models were developed for malignant risk estimation in individuals with lung nodules and utilize the above described clinical and imaging components. Several notable ones include the Brock University, Mayo Clinic, and Peking University People's models. The Brock University model was developed in the screening setting, while the latter two arose in a standard clinical setting (incidental nodules). The models vary in the components incorporated, and they have been shown to have an area under the curve of 0.80 and higher for assessing lung nodules in both the screening setting and for incidentally noted nodules. The Brock university model has been shown to be slightly superior to other models.[55–59]

The best evidence-based guidelines for management of solid pulmonary nodules are those published in 2017 by the Fleischner Society.[60] Although originally described only for solitary solid nodules, the guidelines are now also applied to sub-solid, as well as multiple, nodules.

The Fleischner Society guidelines stratify the risk of malignancy and recommend imaging follow-up intervals according to nodule size and clinical risk factors (Table 28-1). Nodules measuring <6 mm in a low-risk patient do not require follow-up, whereas larger nodules in higher-risk patients require follow-up at progressively shorter intervals (between a maximum of 18 months and a minimum of 3 months for solid nodules, and up to 24 months for sub-solid nodules). Most nodules measuring more than 8 mm and lacking definitive benign imaging characteristics or confirmation of temporal stability are potentially malignant and, therefore, require more aggressive evaluation. Evaluation may include short-term interval CT follow-up, PET imaging, and often, tissue sampling, which can

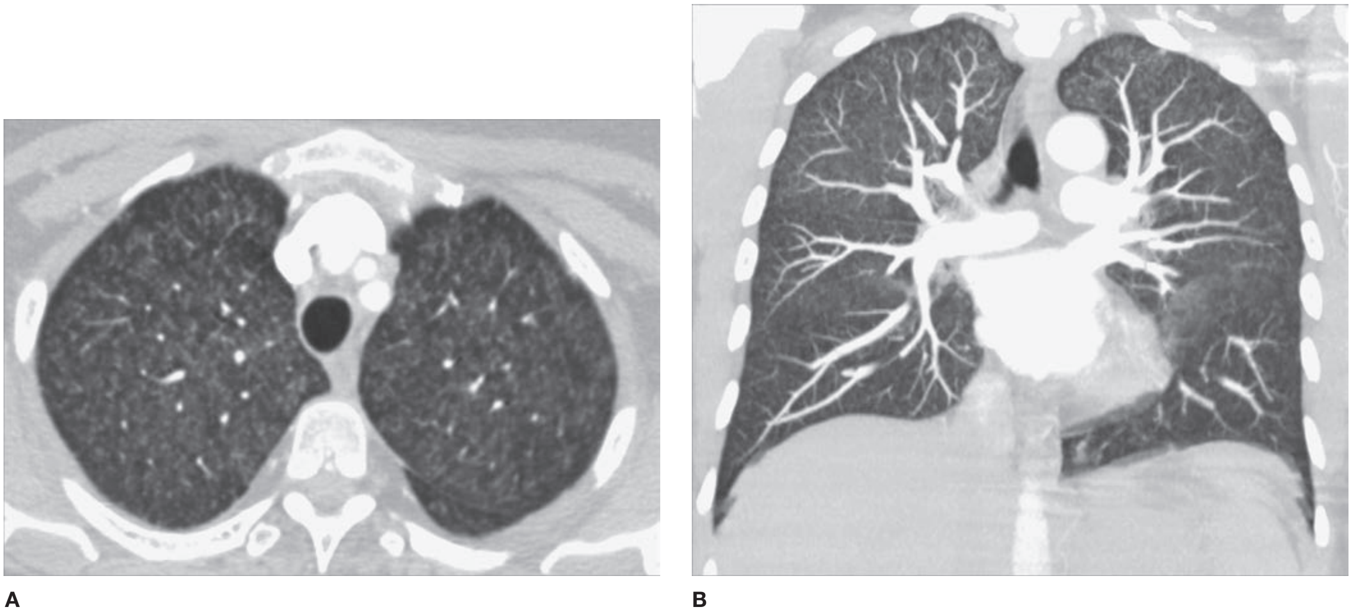


Figure 28-41 Differential diagnosis of multiple pulmonary nodules: (**A**) axial and (**B**) coronal MIP (maximum intensity projection) images demonstrate very numerous, very small (1–2 mm) pulmonary nodules with centrilobular distribution, low attenuation, and indistinct contours. Also noted is symmetric upper lung field predominance. The diagnosis is acute hypersensitivity pneumonitis. In a smoker, the differential diagnosis includes respiratory bronchiolitis.

TABLE 28-3 Solid Nodule Recommendations

Size	Follow up		
<6 mm (<100 mm^3)	Single	Low risk	No routine follow-up
		High risk	Optional CT at 12 months
	Multiple	Low risk	No routine follow-up
		High risk	Optional CT at 12 months
6–8 mm (100–250 mm^3)	Single	Low risk	CT at 6–12 months, then consider 18–24 months
		High risk	CT at 6–12 months, then 18–24 months
	Multiple	Low risk	CT at 3–6 months, then consider 18–24 months
		High risk	CT at 3–6 months, then 18–24 months
>8 mm (>250 mm^3)	Single	All	Consider CT at 3 months, PET/CT or biopsy
	Multiple	Low risk	CT at 3–6 months, then consider 18–24 months
		High risk	CT at 3–6 months, then 18–24 months

be accomplished via minimally invasive transthoracic CT-guided or bronchoscopic techniques, or rarely, via surgical biopsy. As a general rule, peripheral and smaller nodules are more accurately sampled using transthoracic CT-guided techniques, whereas central or larger masses are more safely approached via bronchoscopic techniques (Table 28-3). It is important to note that these guidelines are not intended for use in patients with known primary cancers who are at risk for metastases, nor are they intended for use in immunocompromised patients who are at risk for infection; in these patients, treatment should be based on the specific clinical situation. Also, because lung cancer is rare in children and adults younger than 35 years, these guidelines are not appropriate for such patients, in whom management decisions should be made on a case-by-case basis.

It has been shown that only two CT features generally allow confident diagnosis of benignity for solid nodules: (1) a benign pattern of calcification, and (2) absence of growth for at least 2 years.

A benign pattern of calcification includes any of the following: central, concentric, diffuse, or coarse ("popcorn" calcification). On the other hand, punctuate or eccentric calcifications are considered indeterminate, as both benign and malignant nodules may demonstrate these findings. Recognition of a benign pattern of calcification is, therefore, very important, as it may obviate the need for imaging follow-up or intervention, alleviating patient and clinician anxiety.

As noted, the second benign feature is interval stability for 2 years as measured by CT, following the Fleischner Society guidelines. The feature is based on the concept of doubling time, which is the time required for a nodule to double in volume. A very fast doubling time (<1 month) is most characteristic of inflammatory or infectious nodules. An extremely slow doubling time (>24 months) is more typical of benign processes, such as granulomas, hamartomas, intraparenchymal lymph nodes, or pulmonary arteriovenous malformations. Intermediate doubling times (>1 month but <24 months) are observed with most malignancies, as well as some indolent infections. In this indeterminate range of growth rate, tissue sampling should be strongly considered to exclude primary or metastatic malignancy.

A CT finding of low-attenuation areas compatible with macroscopic fat in an otherwise well-circumscribed pulmonary nodule is strongly suggestive of a benign pulmonary hamartoma and can obviate the need for more aggressive workup. Care must be taken, however, in differentiating true fat from noise on thin-section CT performed with high-resolution ("HRCT") reconstruction kernels. The use of soft tissue kernels may help in making a more confident diagnosis of fat.[61]

Finally, a note should be made concerning perifissural and juxtapleural nodules that exhibit a triangular or oval form on transverse images, and a flat or lentiform configuration in sagittal or coronal reconstructions and a fine, linear septal extension to the pleura. Multiple publications have addressed the invariably benign nature of these findings; they should not be routinely followed, even if the average dimension exceeds 6 mm.

Cavitation is a useful finding in narrowing the differential diagnosis, although it is not specific for malignancy. A cavitary nodule suggests a necrotizing malignancy, particularly primary or metastatic squamous cell carcinoma. However, a number of benign entities may present with cavitary nodules, most typically septic emboli (if multiple), granulomatous infections (including mycobacterial and fungal), bacterial abscesses, and granulomatosis with polyangiitis (GPA, formerly known as Wegener granulomatosis).

Ancillary findings on chest CT that support a diagnosis of malignancy include hilar and mediastinal lymphadenopathy, unilateral pleural effusion, pleural nodules, and hepatic, osseous, or adrenal metastases.

MULTIPLE PULMONARY NODULES

Most of the prior discussion applies to solitary or few pulmonary nodules, which should be approached similarly. In the setting of numerous, usually small (subcentimeter) pulmonary nodules, a different diagnostic approach must be utilized, emphasizing the distribution of the nodules. Two characteristics of the spatial distribution of nodules are relevant: (1) upper lung–predominant versus basilar predominant versus widespread; and (2) centrilobular versus perilymphatic versus random. The otherwise very long differential diagnosis can be substantially narrowed by correctly recognizing the distribution.

As discussed previously, an upper lung–predominant distribution suggests inflammatory or infectious etiologies, in which the inciting factor is inhaled; the exception is primary bronchogenic carcinomas that are more likely in the upper lungs, but uncommonly multiple. A lower lung–predominant distribution suggests hematogenously disseminated disease processes, such as hematogenous metastasis or hematogenous infectious processes. Diffuse distribution comprises a combination of both differential diagnoses and is the least specific.

The centrilobular distribution implies that the majority of nodules are in or near the center of the secondary pulmonary lobule. Such a distribution suggests small airway and acinar disease, indicative of endobronchial spread. This distribution can be further subclassified into two groups: (1) centrilobular nodules in which the nodules are fuzzy, ill-defined, and often of ground-glass attenuation—findings indicative of small airway inflammatory diseases, as can be seen with respiratory bronchiolitis–interstitial lung disease (RB-ILD) and subacute hypersensitivity pneumonitis; and (2) centrilobular nodules in which the nodules are sharp, well defined, and measure less than 2 mm—findings associated with distal bronchiolar filling, a pattern referred to as "tree-in-bud." A tree-in-bud pattern strongly suggests infectious bronchiolitis of bacterial, viral, or mycobacterial etiology. Least commonly, the centrilobular distribution may indicate small vessel disease, such as pulmonary vasculitides or capillary hemangiomatosis. Among the vasculitides, eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome) and microscopic polyangiitis are primary considerations.

A perilymphatic distribution implies that the majority of nodules are within the septal and bronchovascular interstitial compartments. A perilymphatic distribution is associated with diseases with lymphatic system involvement. Such a distribution suggests a narrow differential diagnosis, including pulmonary interstitial edema, sarcoidosis, or lymphangitic spread of neoplasm ("lymphangitic

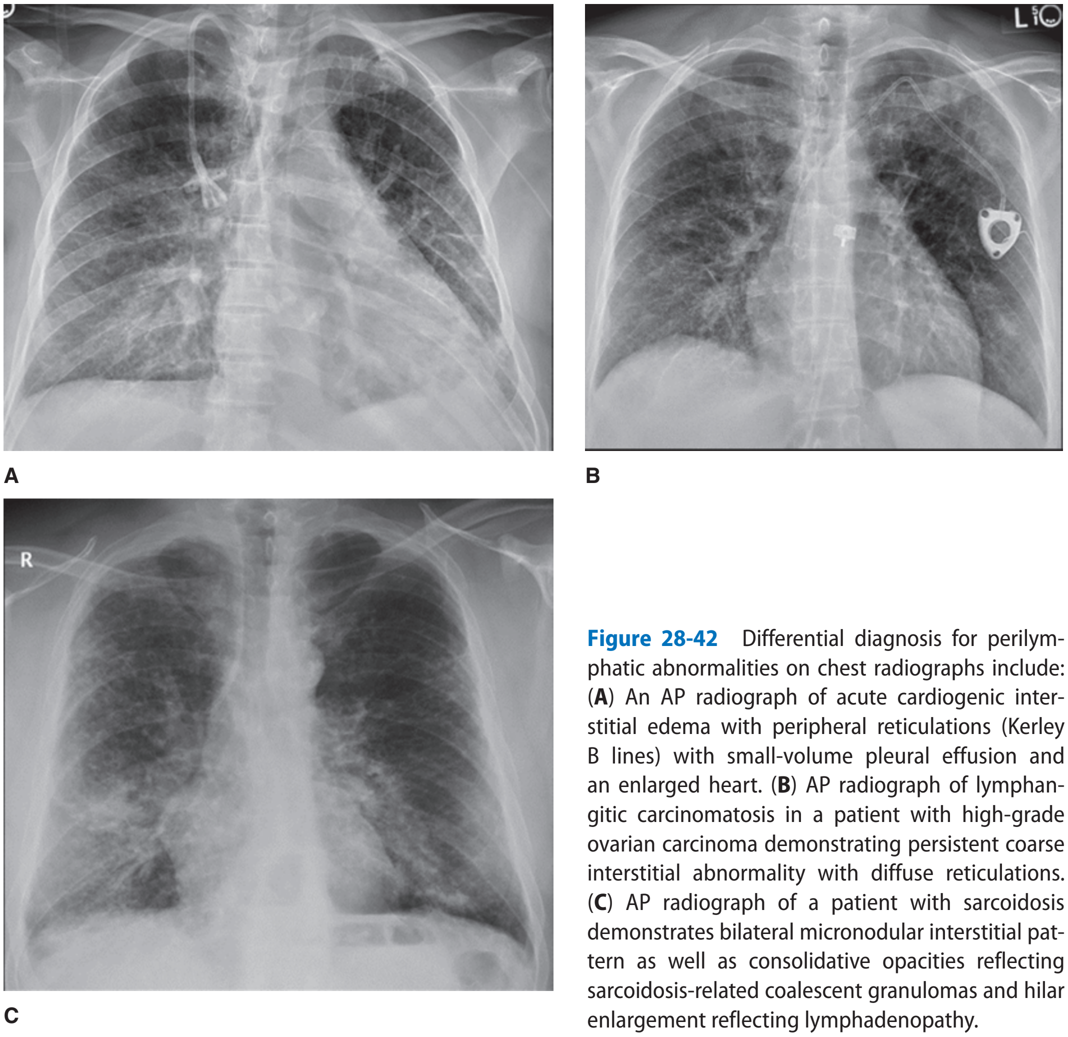


Figure 28-42 Differential diagnosis for perilymphatic abnormalities on chest radiographs include: (**A**) An AP radiograph of acute cardiogenic interstitial edema with peripheral reticulations (Kerley B lines) with small-volume pleural effusion and an enlarged heart. (**B**) AP radiograph of lymphangitic carcinomatosis in a patient with high-grade ovarian carcinoma demonstrating persistent coarse interstitial abnormality with diffuse reticulations. (**C**) AP radiograph of a patient with sarcoidosis demonstrates bilateral micronodular interstitial pattern as well as consolidative opacities reflecting sarcoidosis-related coalescent granulomas and hilar enlargement reflecting lymphadenopathy.

carcinomatosis”) (Fig. 28-42). The latter two diagnoses are more likely if there is nodular interstitial thickening.

A random distribution usually implies hematogenous dissemination of metastases or infection. The archetypal infectious process with numerous random nodules is miliary tuberculosis, although miliary fungal infections can be indistinguishable. Patients with miliary infectious are often immunocompromised and may present with bacteremia or fungemia.

GROUND-GLASS PULMONARY NODULES

Ground-glass nodules deserve separate consideration, as their pathophysiology, differential diagnosis, biologic behavior, and management strategies differ considerably from solid pulmonary nodules.

Ground-glass attenuation is defined as increased attenuation of the lung parenchyma, although the attenuation is not as high as soft tissue attenuation and, therefore, is insufficient to obscure adjacent pulmonary vessels. From a pathology perspective, ground-glass attenuation implies partial filling of the distal airspaces (acini) at a scale below the spatial resolution of CT, causing volume averaging of gas, acinar structures, and material partially filling the alveoli. It is often associated with the lepidic growth pattern, that is, cellular proliferation along the walls of the alveoli, rather than the more common hilic (radial) growth pattern characteristic of most neoplasms.

Multiple ground-glass nodules were described previously, and the rationale for their imaging assessment is included in the description of multiple pulmonary nodules.

Solitary or few ground-glass-attenuation nodules carry a different implication from solid nodules. The differential diagnosis is essentially limited to nonspecific infectious or inflammatory processes versus indolent primary bronchogenic adenocarcinoma or premalignant lesions. Therefore, these lesions must be followed to assess their persistence and chronicity. Most nonspecific infectious or inflammatory processes resolve spontaneously within 3 months. Therefore, lesions that persist on a 3-month follow-up chest CT are suspicious for malignancy.

Ground-glass nodules include a spectrum of premalignant to low-grade malignant diseases, which correlate pathologically with the diagnoses of atypical adenomatous hyperplasia (AAH) (a premalignant precursor to adenocarcinomas), AIS, and minimally invasive adenocarcinoma (MIA). These specific diagnoses cannot be differentiated accurately by CT imaging findings or by small biopsies; surgical biopsy is generally necessary. Nonetheless, CT features suggest a specific diagnosis. Namely, smaller lesions (particularly those $\leq$5 mm) with pure ground-glass attenuation are more likely AAH, whereas the larger the lesion and the more complex its structure (particularly if solid or cystic areas are noted), the more likely it represents AIS (formerly called bronchioloalveolar carcinoma, BAC) or MIA. Large ($\geq$5 mm) or progressive solid components are strongly associated with invasive adenocarcinomas.

The Fleischner Society originally published in 2013 a statement with evidence-based recommendations for management of ground-glass (subsolid) nodules and incorporated a revised version of the recommendations into a unified statement in 2017.[62,63] The statement is mostly based on the revised classification of pulmonary adenocarcinoma proposed in 2011 by the International Association

TABLE 28-4 Part-Solid Nodule Recommendations

Ground glass	<6 mm	No routine follow-up indicated
	≥6 mm	CT at 6–12 months to confirm persistence, then CT at 3 and 5 years
Part solid	<6 mm	No routine follow-up indicated
	≥6 mm	CT at 3–6 months to confirm persistence, then CT annually for 5 years
Multiple	<6 mm	CT at 3–6 months, if stable follow at 2 and 4 years
	≥6 mm	CT at 3–6 months; subsequent management based on the most suspicious nodule

for the Study of Lung Cancer (IASLC), the American Thoracic Society (ATS), and the European Respiratory Society (ERS).[64] In the same spirit as the original recommendations for solid nodules, subsolid nodules are stratified according to size, and different follow-up intervals are proposed. However, unlike the guidelines for solid nodules, those for ground-glass nodules do not differentiate between low- and high-risk groups because of the incidence of subsolid lesions in younger and nonsmoking patients.

The algorithm for subsolid lesions is more involved, also accounting for multiplicity of nodules and the fact that many subsolid nodules are inflammatory (Table 28-4). For example, a subsolid nodule measuring <6 mm does not need any follow-up. If it is >6 mm, then an initial follow-up chest CT should be obtained at 6 to 12 months to determine persistence. If persistent, then CT at 3 and 5 years is recommended. (Many institutions, including our own, pursue longer surveillance.) If a subsolid nodule >6 mm demonstrates a solid component measuring more than 6 mm that is persistent after 3 to 6 months, then tissue sampling, PET-CT, and/or resection is recommended, as these nodules have a very high probability of representing AIS or MIA. The size of the solid component correlates with the likelihood of an invasive component being present.

For multiple ground-glass opacities measuring >6 mm, the algorithm is similar, and management is dictated by the CT characteristics of the most suspicious nodule; in multiple nodules measuring <6 mm, an initial 3- to 6-month follow-up is recommended to exclude infectious etiologies, after which 2- and 4-year follow-up intervals are suggested, as infectious or inflammatory etiologies become far more likely in that setting. Important caveats are the limited usefulness of PET/CT for evaluation of subsolid nodules, since most are not substantially metabolically active (therefore, a negative PET/CT can be misleading), the need to obtain clinical correlation, and the requirement for a meticulous evaluation protocol that includes thin-section (1 mm) volumetric images and consistent use of low-radiation-dose CT technique.[62]

A comprehensive management algorithm for both solid and subsolid pulmonary nodules was published by the American College of Chest Physicians in 2013.[65] The algorithm commences with identification of a new nodule on chest CT and proceeds with follow-up recommendations according to size, risk factors for malignancy, and surgical risk. The recommendations emphasize the need for tissue sampling for most nodules larger than 8 mm and compare the advantages and disadvantages of surgical biopsy, CT-guided percutaneous biopsy, and bronchoscopy with biopsy. The specific recommendations for nodules measuring <8 mm are in line with the 2005 Fleischner Society guidelines.

LUNG CANCER

The classification, pathophysiology, epidemiology, and management of lung cancer are described elsewhere (Chapters 112–118). This chapter focuses on the contributions of imaging to lung cancer screening, initial diagnosis, and staging.

Lung cancers are typically initially identified on chest radiography or are noted incidentally on chest CT performed for another clinical indication (except in the context of lung cancer screening). Most lung cancers present as pulmonary nodules or masses. Hilar or mediastinal lymphadenopathy and overt signs of metastatic disease are indicative of more advanced stages of disease. Central masses may cause obstructive atelectasis or consolidation.

At initial presentation, the clinical aim is to confirm the diagnosis pathologically, for which tissue sampling is required. In the past, surgical biopsies were the only available options, but in the last three decades, minimally invasive biopsies performed either percutaneously using CT guidance, or transbronchially with bronchoscopic techniques, have been strongly favored for their better risk/benefit ratio, lower complication rate, faster patient recovery, and high diagnostic accuracy. As a general rule, most peripheral lesions (i.e., those within 3 cm of a costal pleural surface) are better accessed percutaneously using CT guidance, whereas central lesions, particularly if an airway visible on CT leads to the lesion, are better accessed via bronchoscopy.[64,66]

Once the diagnosis of lung cancer is pathologically confirmed and fully characterized, staging is of paramount importance to determine the extent of disease and, therefore, the management approach. The most current staging system for lung cancer is the eighth edition of the TNM classification, which was published in 2016. Several references depict visual maps of the T, N, and M criteria and tables with the detailed revised classification.[67–70]

In summary, the most important aspects of staging are the size and location of the primary tumor (T), the presence of abnormally enlarged lymph nodes and their location and distribution (N), and the presence of distant metastasis (M). By combining the T, N, and M scores, a specific stage from I to IV is obtained, and management strategies are tailored for the type of cancer (histology and genotypic profile) and the staging classification. It cannot be overemphasized that imaging, particularly CT, plays an overarching role not only in tumor detection, but also in tumor staging. It is the primary method for obtaining TNM staging information. PET/CT is also valuable, particularly for nodal staging and identification of distant metastasis. Finally, nodal metastasis may be evaluated using endobronchial US combined with transbronchial biopsies of suspicious lymph nodes.

LUNG CANCER SCREENING

A discussion of the role of modern imaging in the diagnosis of lung cancer would not be complete without mention of the current status of lung cancer CT screening (Fig. 28-43).

The 20.0% decrease in mortality from lung cancer observed with implementation of low-dose computed tomography (LDCT) screening in the National Lung Screening Trial (NLST) has led to approval of annual screening in the United States as a benefit covered by both private insurers and by Medicare (Centers for Medicare and Medicaid Services).[71] Lung cancer screening guidelines in the United States are based mainly on the same criteria for which participants in the NLST study were chosen and include patients with history of heavy smoking, defined as 30 pack-years or more; who smoke currently or have quit within the past 15 years; and who are between 55 and 80 years of age. The Lung CT Screening Reporting and Data System (Lung-RADS 1.1) is the most used system for classification and management of screened patients.

Eligibility requirements exist for the interpreting radiologist(s), as well as the imaging facilities that perform LDCT screening. The

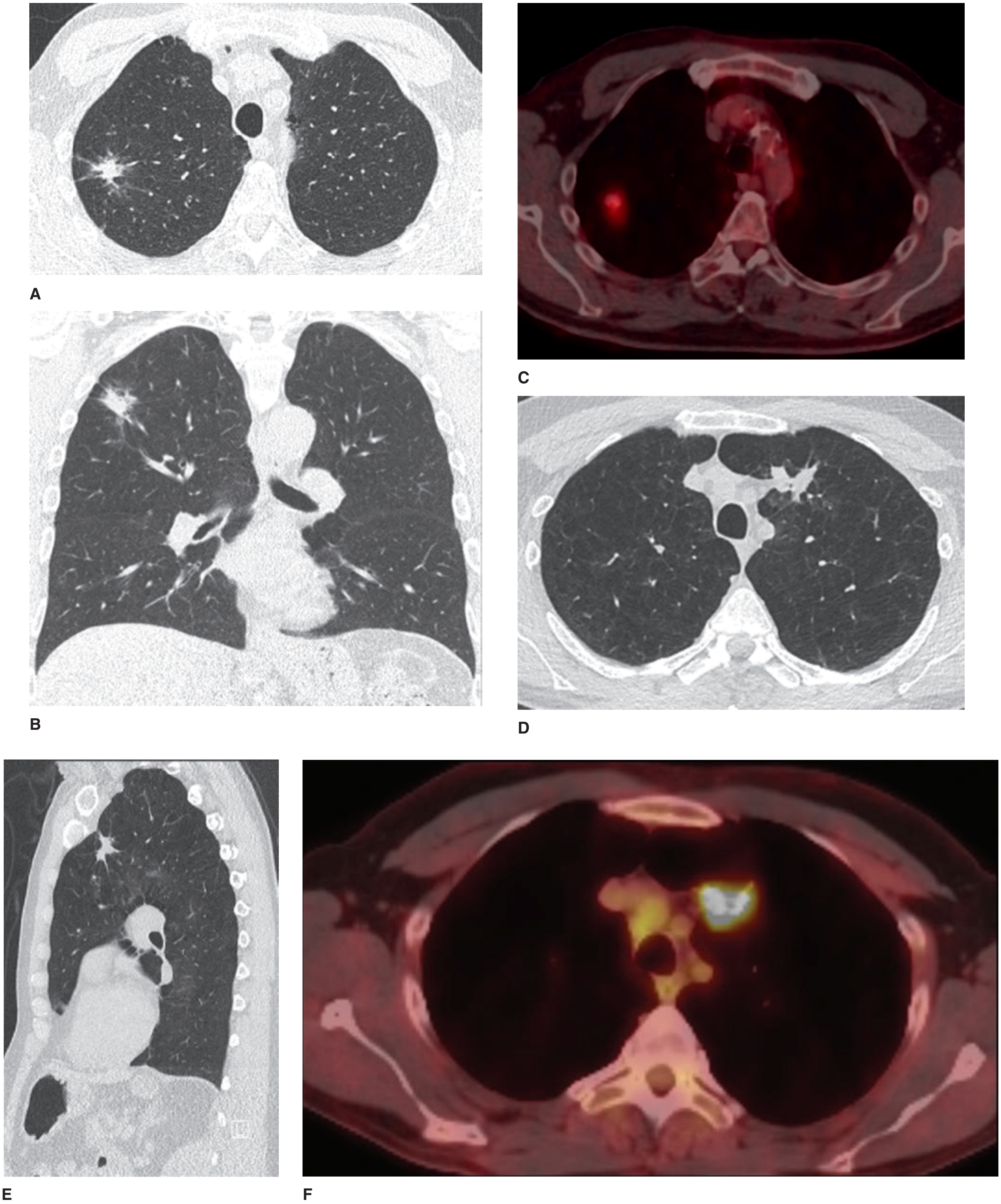


Figure 28-43 Category 4X finding on first lung screening CT examination. Axial (**A**) and coronal (**B**) reconstructions CT images demonstrate a spiculated irregular right upper lobe lung nodule with pleural tagging highly suspicious for primary lung malignancy. Fused images (**C**) from a subsequently obtained PET-CT demonstrate FDG uptake in the lesion, which was later confirmed to represent a primary lung adenocarcinoma. A similar-appearing lesion identified on a screening exam of another patient in a left upper lobe demonstrating spiculations and mediastinal tagging on axial (**D**) and sagittal (**E**) CT images as well as marked FDG uptake on fused PET-CT images (**F**). This lesion was subsequently resected, with pathology revealing necrotizing granuloma without evidence of malignancy.

latter include: (a) performing LDCT with a volumetric CT dose index (CTDIvol) of <3 mGy; (b) using a standardized lung nodule identification, classification, and reporting system, such as the American College of Radiology (ACR) Lung-RADS; (c) making smoking cessation interventions available for current smokers; and (d) collecting and submitting screening data to a CMS-approved registry for all LDCT screening examinations, including those covered by private insurers.[72]

The American College of Radiology has developed a quality-assurance tool, Lung-RADS 1.1 (Table 28-5), with the aim of standardizing the reporting of LDCT screening results. Lung-RADS defines positive examinations on lung-cancer screening CT and is designed to decrease the false-positive rate, with a minimum effect on test sensitivity; it includes management recommendations. Applying Lung-RADS retrospectively has been shown to substantially reduce the false-positive rate when compared to NLST criteria; however, a decrease in detection sensitivity has been noted.[73]

Additional methods of nodule evaluation and nodule detection that are gaining recognition and have the potential to assist radiologists to decrease the rate of missed lung nodules are nodule volumetry and computer-assisted detection (CAD). These tools were recommended as the preferred evaluation tools for nodule assessment by the 2015 European Society of Radiology white paper on lung cancer screening. Although volumetric analysis is less widely practiced in the United States than in the Europe, it has the potential to improve measurement accuracy in positive screening examinations, leading to lower false-positive rates, as well as to reduce variability in size assessment. The advantages of nodule volumetry are that size measurements make use of all voxels representing the nodule, not a single cross-sectional subset, and that three-dimensional volumes can be viewed at any angle, which is advantageous in asymmetrically growing nodules, increasing the likelihood of detecting subtle growth over time.

Moreover, CAD has the potential to enhance radiologist productivity in clinical settings; it can automatically detect lung nodules and calculate both two-dimensional and volumetric measurements of lung nodules using standard CT images. Using those measures, nodule progression can more accurately be tracked over time by assessing its growth rate, a very important metric in predicting biologic behavior and malignant potential. The advantage for the clinical workflow is potentially to increase radiologist efficiency and produce more repeatable results for nodule follow-up.

Recent studies have demonstrated the ability of CAD to detect lung cancer at an earlier stage and to improve detection of small or subtle nodules.

Another hallmark study, the Nederlands-Leuvens Longkanker Screenings Onderzoek (NELSON), conducted in the Netherlands and Belgium and launched in 2003, compared low-dose CT against no screening. NELSON differed from the NLST in many important aspects, including the serial imaging protocol utilized and patient selection criteria.[74]

Similar to the NLST trial, NELSON demonstrated that lung-cancer mortality was significantly lower among those who underwent volume CT screening compared with those who underwent no screening.

The interval between LDCT studies is a main subject of debate regarding the optimization of lung cancer screening. This topic was assessed in NELSON, which showed similar performance of annual and biennial screening intervals. However, an interval longer than 2 years was discouraged by recent results of the fourth round of NELSON; there was a reported excess of interval cancers associated with a screening interval of 2.5 years.

A white paper published in 2015 by the European Society of Radiology (ESR) and the European Respiratory Society (ERS) encouraged lung cancer screening using LDCT, either in clinical trials or in routine clinical practice at certified multidisciplinary medical centers. The ESR/ERS recommendations include specific selection of high-risk patients, based on several pretest parameters (e.g., age 55–80 years, smoking history ≥30 pack-years and having stopped smoking within <15 years, a dedicated comprehensive risk model, biologic profiling) and adaptation of screening intervals based on refined risk predictive models. The ESR/ERS recommendations encourage inclusion of additional CT findings, such as chronic obstructive pulmonary disease (COPD) and vascular calcification, which can be used along with nodule records for posttest refinement of cardiovascular and general mortality risk, in addition to lung cancer risk.[75]

PULMONARY INFECTIONS

Pulmonary infections constitute a very broad group of diseases caused by a wide variety of viruses, bacteria, and fungi. The imaging findings are helpful to establish a diagnosis of pneumonia, but they are virtually never specific as to etiology. Therefore, most patients with suspected pulmonary infections are treated empirically, based upon epidemiologic considerations. Subgroups of vulnerable patients (particularly very ill or immunocompromised patients) may require etiologic confirmation, which can be obtained by sampling the abnormalities via percutaneous or bronchoscopic techniques and requesting microbiologic testing of the material.

The imaging approach to a suspected pulmonary infection involves identifying the imaging patterns that are more likely associated with an infectious etiology, as well as recognizing the more likely associations with a specific pattern. The most typical pattern of pneumonia is focal or multifocal consolidation, denoted by dense, conspicuous alveolar opacities that obscure vascular contours on CT and which may or may not be associated with air bronchograms. Other patterns include focal or multifocal ground-glass opacities (which can be difficult to recognize on chest radiographs and require CT for adequate evaluation); peribronchovascular patchy opacities (bronchopneumonia pattern); centrilobular nodules with tree-in-bud configuration (bronchiolitis pattern); multiple nodules or masses (cavitary or not); solitary cavitary nodule or mass; and nodules or masses associated with calcifications or ground-glass halo. None of these patterns is specific for infection; they are even less specific for a particular infectious etiology. Nonetheless, some imaging patterns allow a narrower differential diagnosis in the proper clinical setting and are worth recognizing.[76–83]

Notable radiographic patterns include: (1) Focal or multifocal consolidation, which favors typical bacterial infection (e.g., *Streptococcus pneumoniae*). A bronchopneumonia pattern can be seen in a variety of bacterial and viral infections. (2) Focal or multifocal ground-glass opacities favor atypical infections, including *Pneumocystis jiroveci* and hematogenously disseminated bacterial and viral infections (e.g., CMV pneumonitis).[84–86] (3) A bronchiolitis pattern may be seen in community-acquired viral infections, including influenza, parainfluenza, and adenovirus. If associated with air trapping, respiratory syncytial virus (RSV) should be considered. (4) Multiple cavitary nodules or masses suggest septic emboli or virulent infections, such as those due to *Staphylococcus aureus*. (5) A solitary cavitary mass suggests a pulmonary abscess; anaerobic infections related to aspiration are primary considerations, although if in the upper lobes, reactivation tuberculosis must be excluded.[87] (6) Calcified nodules or masses suggest granulomatous infectious, typically chronic, and favor mycobacterial (tuberculous and nontuberculous) or fungal etiologies.[88–90] (7) Nodules or masses with ground-glass halo are suggestive of opportunistic fungal infection, particularly invasive aspergillosis, in the setting of immunocompromised hosts who are neutropenic.

TABLE 28-5 Lung-RADS 1.1: Standardizing the Reporting of LDCT Screening Results

Category Descriptor	Lung RADS Score	Findings	Management	Risk of Malignancy	Est. Population Prevalence
Incomplete	0	Prior chest CT examination(s) being located for comparison Part or all of lungs cannot be evaluated	Additional lung cancer screening CT images and/or comparison to prior chest CT examinations is needed	N/A	1%
Negative No nodules and definitely benign nodules	1	No lung nodules Nodule(s) with specific calcifications: complete, central, popcorn, concentric rings, and fat-containing nodules	Continue annual screening with LDCT in 12 months	<1%	90%
Benign appearance or behavior Nodules with a very low likelihood of becoming a clinically active cancer due to size or lack of growth	2	Perifissural nodule(s) <10 mm (524 mm^3) Solid nodule(s): <6 mm (<113 mm^3) new <4 mm (<34 mm^3) Part-solid nodule(s): <6 mm total diameter (<113 mm^3) on baseline screening Non-solid nodule(s) (GGN): <30 mm (<14,137 mm^3) *or* ≥30 mm (≥14,137 mm^3) and unchanged or slowly growing Category 3 or 4 nodules unchanged for ≥3 months			
Probably benign Probably benign finding(s)—short-term follow-up suggested; includes nodules with a low likelihood of becoming a clinically active cancer	3	Solid nodule(s): ≥6 to <8 mm (≥113 to <268 mm^3) at baseline *or* new 4 mm to <6 mm (34 to <113 mm^3) Part-solid nodule(s): ≥6 mm total diameter (≥113 mm^3) with solid component <6 mm (<113 mm^3) *or* new <6 mm total diameter (<113 mm^3) Non-solid nodule(s) (GGN): ≥30 mm (≥14,137 mm^3) on baseline CT or new	6-month LDCT	1%–2%	5%
Suspicious Findings for which additional diagnostic testing is recommended	4A	Solid nodule(s): ≥8 to <15 mm (≥268 to <1767 mm^3) at baseline *or* growing <8 mm (<268 mm^3) *or* new 6 to <8 mm (113 to <268 mm^3) Part-solid nodule(s): ≥6 mm (≥113 mm^3) with solid component ≥6 mm to <8 mm (≥113 to <268 mm^3) *or* with a new or growing <4-mm (<34-mm^3) solid component Endobronchial nodule	3-month LDCT; PET/CT may be used when there is a ≥8-mm (≥268-mm^3) solid component	5%–15%	2%
Very suspicious Findings for which additional diagnostic testing and/or tissue sampling is recommended	4B	Solid nodule(s): ≥15 mm (≥1767 mm^3) *or* new or growing, and ≥8 mm (≥268 mm^3)	Chest CT with or without contrast, PET/CT, and/or tissue sampling depending on the probability of malignancy and comorbidities; PET/CT may be used when there is a ≥8-mm (≥268-mm^3) solid component; for new large nodules that develop on an annual repeat screening CT, a 1-month LDCT may be recommended to address potentially infectious or inflammatory conditions	>15%	2%
	4B	Part-solid nodule(s) with a solid component ≥8 mm (≥268 mm^3) *or* a new or growing ≥4 mm (≥34 mm^3) solid component			
	4X	Category 3 or 4 nodules with additional features or imaging findings that increases the suspicion of malignancy			
Other clinically significant or potentially clinically significant findings (non–lung cancer)	S	Modifier—may add to category 0–4 coding	As appropriate to the specific finding	N/A	10%

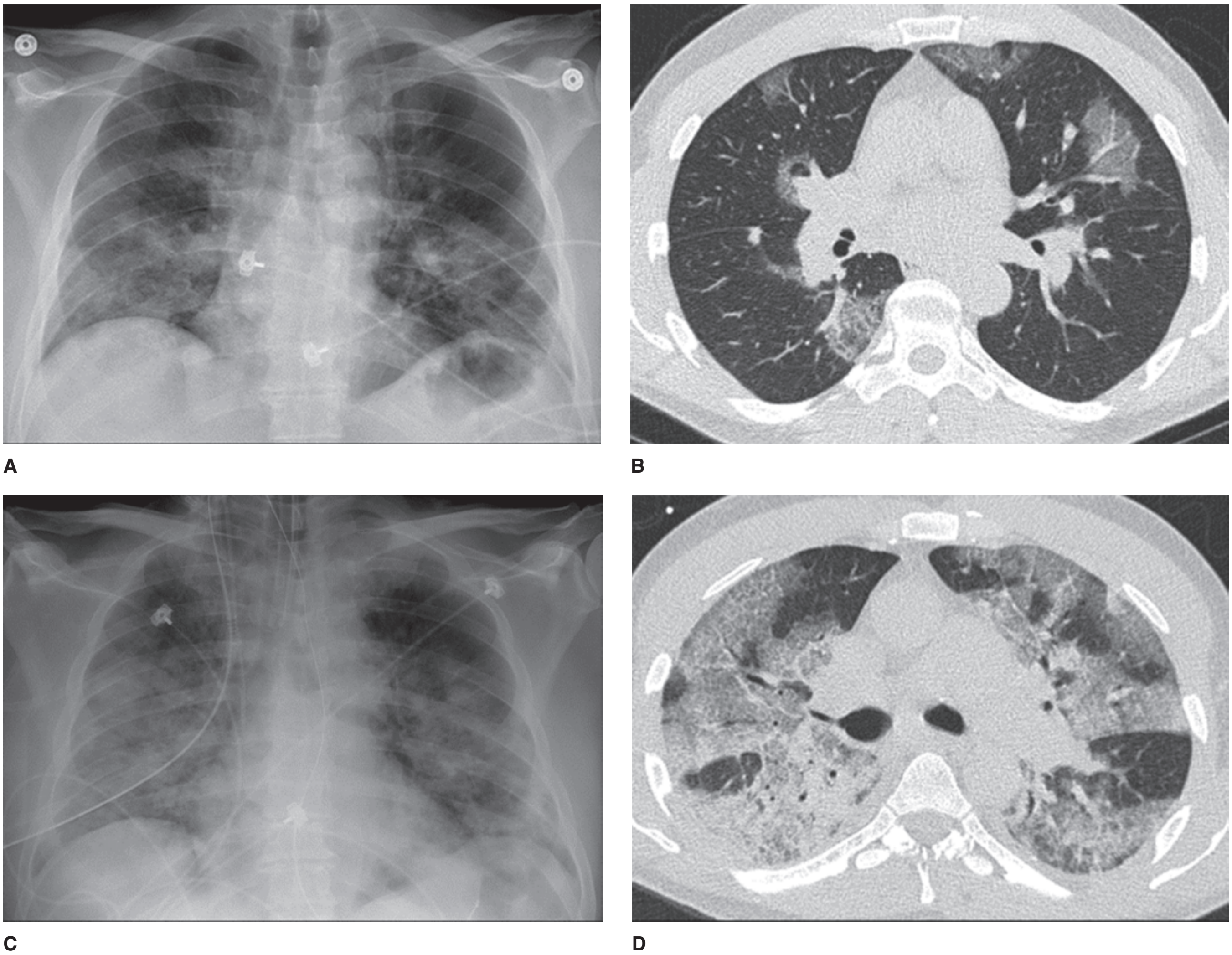


Figure 28-44 Characteristic imaging features of evolving COVID-19 pneumonia. **A.** AP view chest x-ray demonstrates lower lung zone predominant patchy opacities without sizable pleural effusions in a patient presenting with 5 days of respiratory symptoms. **B.** Axial CT image obtained 7 days after initial presentation reveals typical peripheral predominant ground glass opacities. With worsening symptoms, an AP view chest x-ray (**C**) and axial CT–obtained image (**D**) demonstrate progressive disease with more extensive radiographic opacities and correlating bilateral, confluent mixed-density consolidations and ground glass opacities some with associated interlobular septal thickening forming what is called a "crazy paving" pattern.

Special note should be made of pneumonia due to COVID-19, an illness caused by a novel SARS-CoV2 coronavirus that rapidly progressed to a global pandemic starting in early 2020. This virus has typical, but not specific, imaging characteristics, manifest most commonly as bilateral, lower lobe–predominant ground-glass opacities mimicking the imaging appearance and distribution of organizing pneumonia (Fig. 28-44). The specificity of these findings is directly linked with local prevalence of the virus. Although the primary diagnosis is based upon PCR testing for detection of viral RNA in nasal, nasopharyngeal, or oral secretions, CT imaging has gained an established role in patient care. A 2020 Fleischner Society guideline on imaging in COVID-19 disease recommended that it be used only in the setting of moderate or severe symptoms, in the setting of worsening respiratory status in patients with confirmed disease, or if alternative diagnoses are sought.[91,92]

With regard to localized alveolar disease, the very important distinction between atelectasis and consolidation needs to be clarified. Patchy opacification of airspaces without a decrease in the volume of the affected area suggests consolidation, while opacification of airspaces associated with a decrease in the volume of the affected area suggests atelectasis. The differential diagnosis depends largely on the extent to which lung volume is decreased. However, assessment of the magnitude of volume loss is not always useful. For example, while pneumonia usually is associated with minimal or no volume loss, occasionally, volume loss is considerable. On the other hand, atelectasis usually has moderate or severe loss of volume, but in some instances, there may be little volume loss (Figs. 28-45–28-49).

Consolidations are statistically likely to represent pneumonias, especially in the acute setting, whereas atelectasis indicates airway obstruction (obstructive atelectasis), adjacent mass effect (compressive atelectasis), or, more rarely, surfactant deficiency or scarring (adhesive atelectasis). For practical purposes, focal airspace opacities, particularly if lobar, are considered consolidations if the degree of volume loss is negligible or mild, and atelectasis if the degree of volume loss is substantial. The various patterns of lobar atelectasis are important to recognize, since this radiographic finding is a very common manifestation of carcinoma of the lung or, occasionally, some other endobronchial neoplasm.

Atelectasis is also common in the postoperative patient ("dependent atelectasis"), presumably because of hypoventilation of

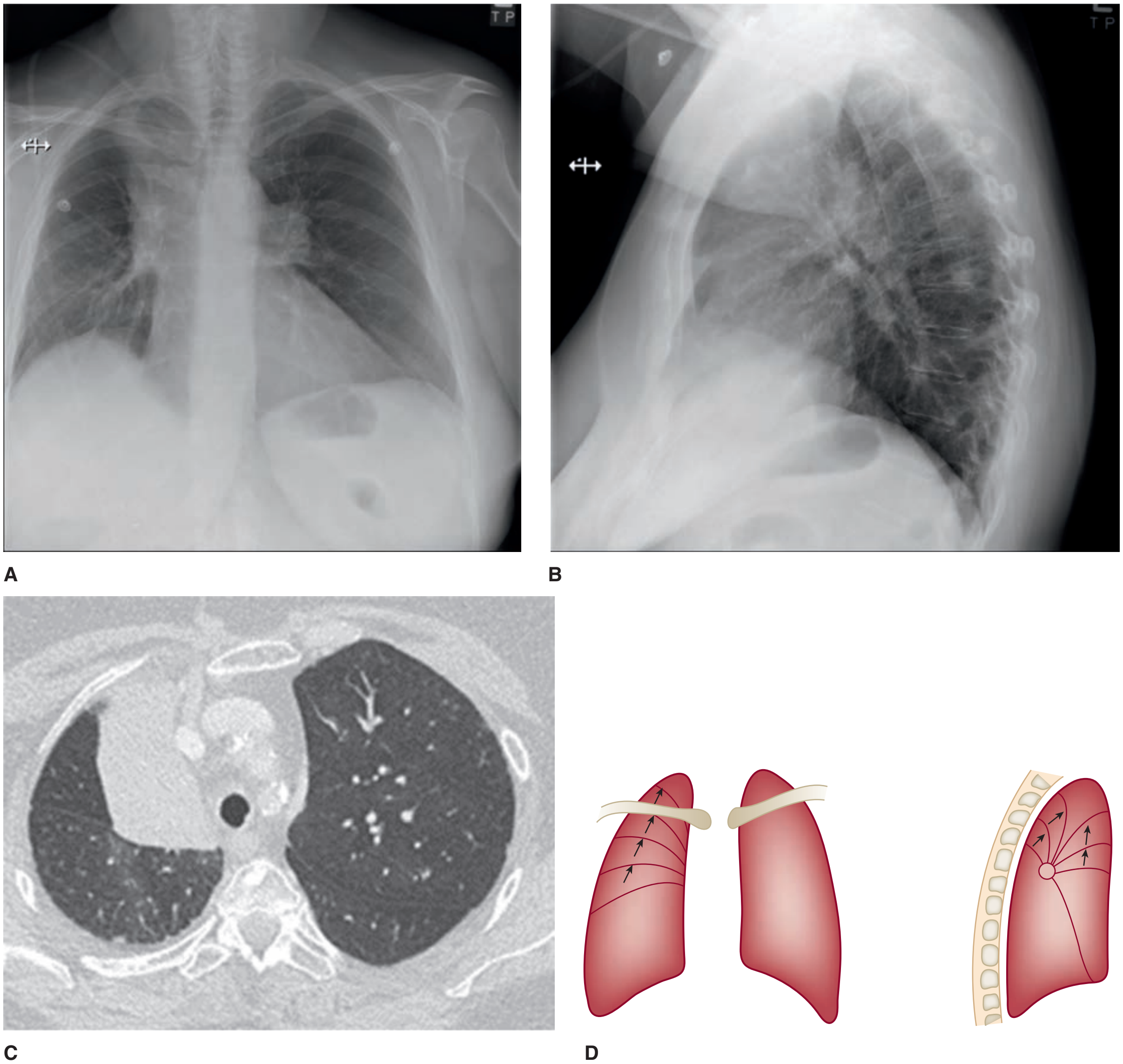


Figure 28-45 Right upper lobe atelectasis secondary to bronchogenic carcinoma. **A.** PA view. The minor fissure is elevated. **B.** Lateral view. Increased anterior opacity with the major fissure is displaced anteriorly. **C.** Axial CT image demonstrating partial RUL collapse with a central density with convex borders reflecting the obstructing mass. **D.** Schematic representation of atelectasis of the right upper lobe.

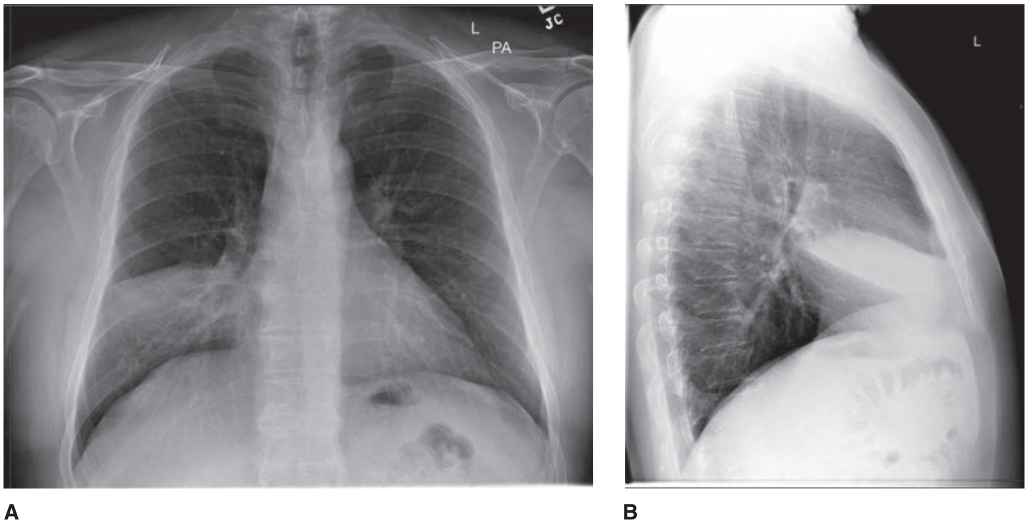


Figure 28-46 Right middle lobe atelectasis secondary to calcified lymph node eroding into and obstructing the RML bronchus. **A.** PA view. The middle lobe is collapsed against the right side of the heart. **B.** Lateral view. The major and minor fissures are drawn together, creating an opacity that overlies the cardiac shadow.

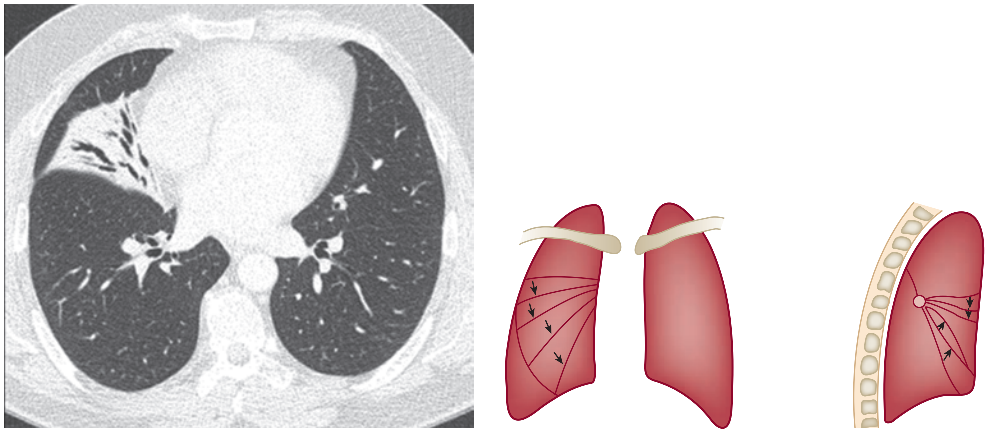

C D

Figure 28-46 (*Continued*) **C.** Axial CT image demonstrating near complete RML collapse **D.** Schematic representation of right middle lobe atelectasis.

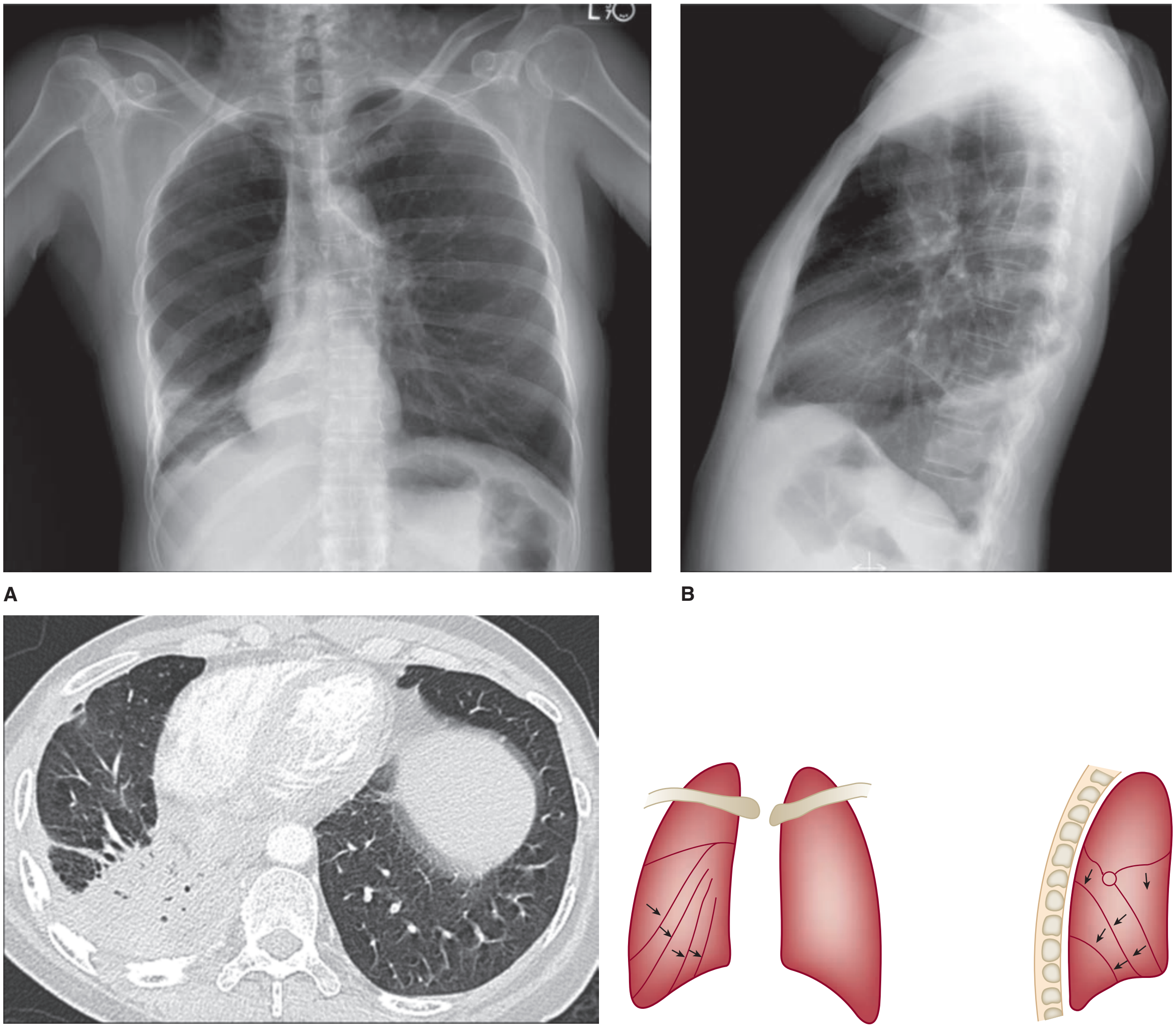

A B C D

Figure 28-47 Atelectasis (severe) of the right lower lobe due to chronic radiation changes for primary lung malignancy. **A.** PA view. Secondary signs of atelectasis are present in the right lung: small hemithorax, hyperlucent lung, and small hilus. In this instance, these secondary signs are important in suspecting atelectasis. In addition, the collapsed lower lobe can be seen (poorly) through the right heart border. **B.** Lateral view. The entire right lower lobe appears only as a diffuse opacity overlying the spine. The posterior portion of the right hemidiaphragm cannot be identified (silhouette sign). **C.** Axial CT image demonstrates a complete RLL collapse. **D.** Schematic representation of collapse of right lower lobe.

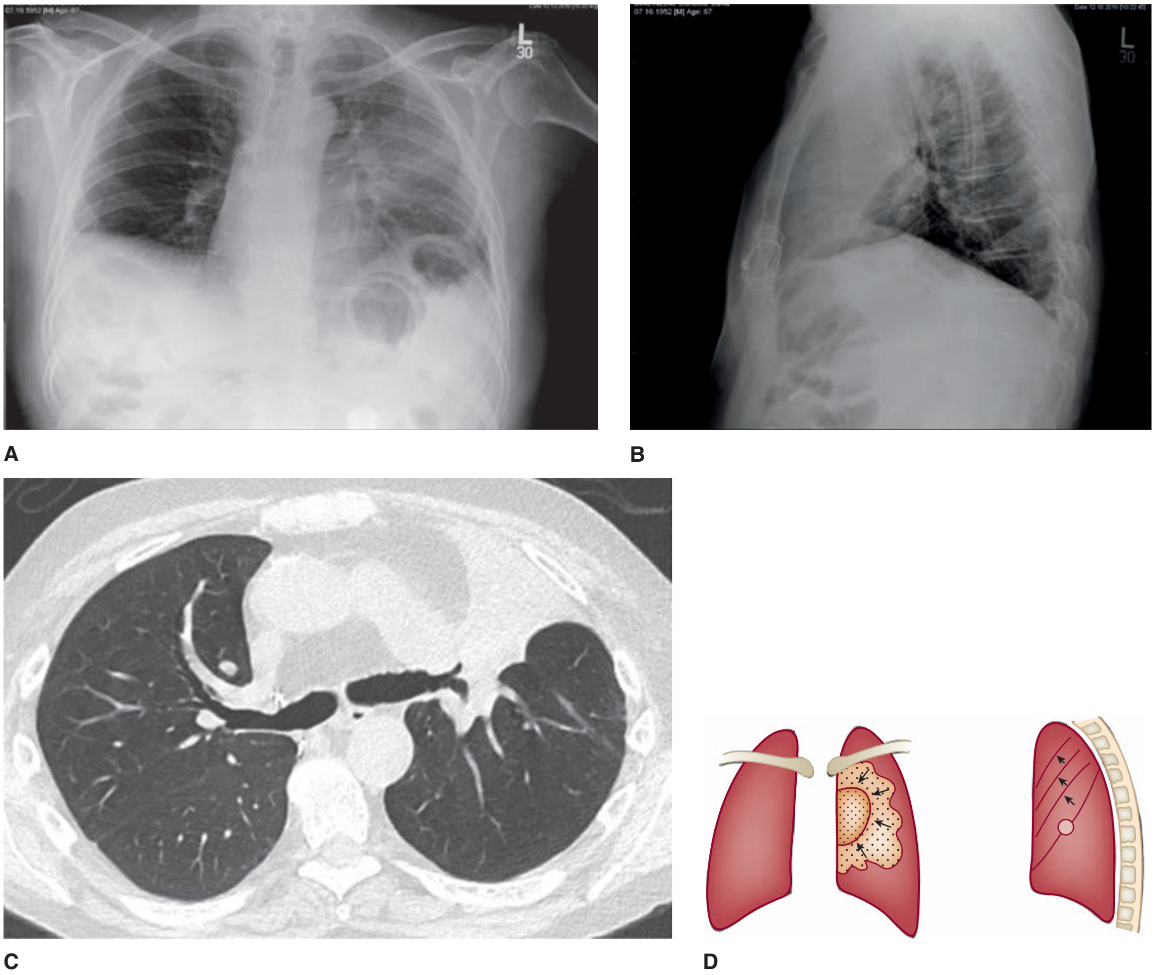


Figure 28-48 Left upper lobe atelectasis secondary to chronic bronchial occlusion in a transplanted lung. **A.** PA view. Increased hazy opacity at the left hemithorax; the left side of the heart is indistinct due to collapse of the left upper lobe. Hyperinflation of superior segment of the left lower lobe between the left upper lobe and the aorta, resulting in a sickle-shaped lucency medially (luftsichel sign) **B.** Lateral view. The collapsed lung is seen as an opacity anterior to the major fissure, which is displaced anteriorly. **C.** Axial CT image demonstrates a complete LUL collapse. **D.** Schematic representation of collapse of left upper lobe.

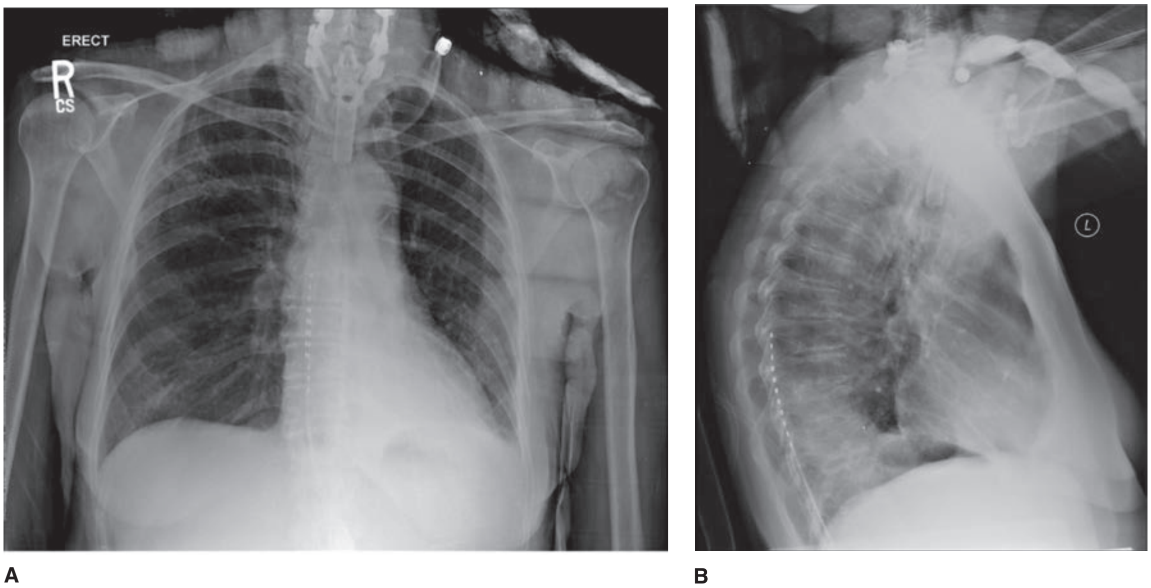


FIGURE 28-49 Left lower lobe atelectasis due to aspiration. **A.** PA view. The collapsed left lower lobe is seen as a straight line behind the left heart border. No vasculature can be seen through the heart shadow, and the medial border of the left hemidiaphragm is obscured by the collapsed left lower lobe. **B.** Lateral view. Opacity over the spine and absence of left posterior diaphragm. This is difficult to differentiate from a pleural effusion.

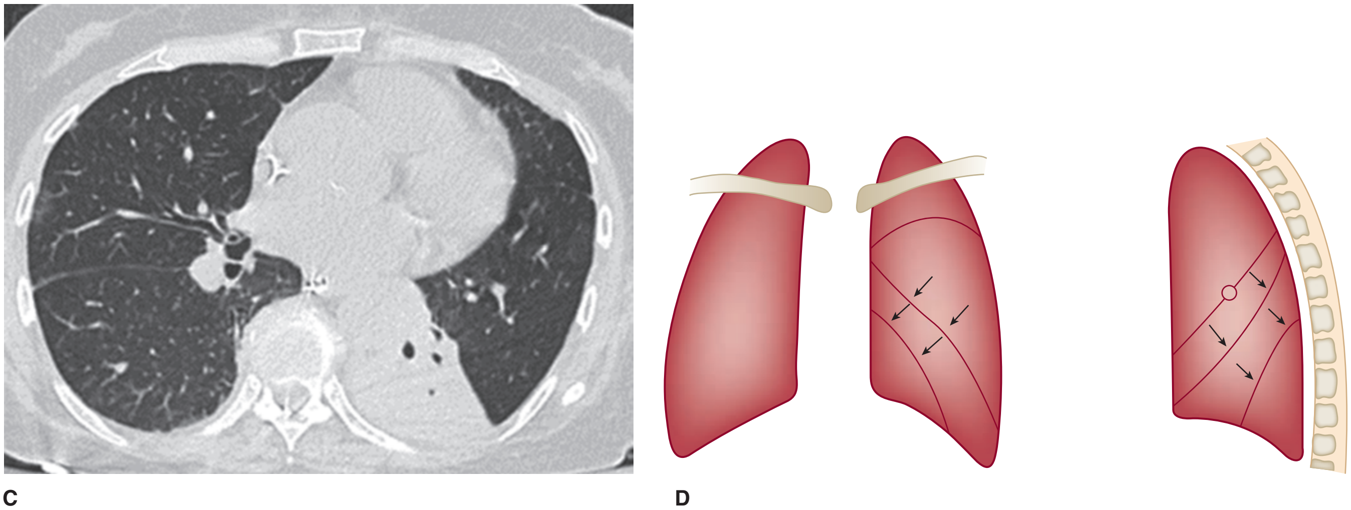


Figure 28-49 (*Continued*) **C.** Axial CT image demonstrates a complete LLL collapse. **D.** Schematic representation of collapsed left lower lobe.

dependent parts of the lungs and inadequate clearing of respiratory secretions. In this instance, loss of volume may be mild or absent. Atelectasis may also occur as a consequence of inflammatory disease of the airways or aspiration of a foreign body. Atelectasis also invariably accompanies pleural effusions and pneumothorax. With pleural effusions, atelectasis is greatest in the vicinity of the pleural effusion. Rounded atelectasis is a subtype characterized by ovoid peripheral opacity, associated with underlying chronic pleural disease (manifested by loculated effusion or pleural thickening). Architectural distortion and convergence of the bronchovascular structures supplying the area of rounded atelectasis ("comet tail sign") are seen. It is important to recognize the typical features of rounded atelectasis, as it can be confused with pulmonary neoplasms.

In non-immunocompromised hosts, most acute consolidations reflect bacterial pneumonias and should improve to complete resolution with treatment, generally within 4 to 6 weeks; radiographic clearance lags a few weeks behind clinical improvement. Therefore, in adult patients it is important to obtain chest radiographs at the end of this time frame to demonstrate complete resolution of the consolidation. Any consolidation that persists (>1 month) in spite of optimal empirical treatment should be considered potentially neoplastic; the differential diagnosis includes pulmonary mucinous adenocarcinoma (formerly classified as BAC), pulmonary lymphoma (of the MALT type, denoting low-grade extranodal lymphomas), or hemorrhagic metastasis (such as from breast, renal cell carcinoma, or melanoma primaries). In addition, atypical infectious processes (such as fungal or mycobacterial infection) may present as persistent consolidations, as well as several noninfectious or inflammatory processes, such as cryptogenic organizing pneumonia (COP), eosinophilic pneumonia, and granulomatous vasculitides (e.g., granulomatosis with polyangiitis). Most chronic consolidations ultimately require chest CT and tissue sampling (via transthoracic or bronchoscopic approaches) for final diagnosis (Figs. 28-50–28-55).

PULMONARY EDEMA: CARDIOGENIC AND NONCARDIOGENIC

Imaging offers a comprehensive display of the anatomy of the cardiopulmonary system and its function. Chest radiographs can demonstrate the heart size and configuration, the width of the vascular pedicle, and the caliber and distribution of the pulmonary arteries and veins. Pulmonary arteries and veins can generally be distinguished on chest radiographs by their anatomic location, with the pulmonary veins more horizontal, more inferior, and more lateral to the pulmonary arteries in relationship to the hila. The distinction is, nonetheless, seldom useful radiographically and, therefore, the generic terms *pulmonary vessels* and *pulmonary vasculature* are used. CT and MRI more readily depict the pulmonary arteries and veins. The pulmonary arteries arise from the main pulmonary artery trunk, while the pulmonary veins enter the left atrium and are readily distinguished on cross-sectional imaging even without intravenous contrast. Moreover, CT and MRI can accurately evaluate cardiac structure and function, particularly cardiac MRI, providing quantitative metrics to assess ventricular and valvular function.

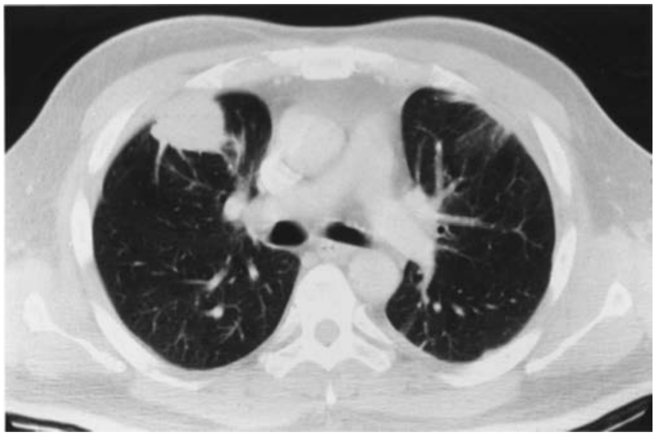


Figure 28-50 Axial CT image showing rounded atelectasis. A mass with a "tail" can be seen in the anterior segment of the right upper lobe. Pleural thickening is seen on the left side, with transpulmonary bands extending into the left upper lobe. The mass on the right represents rounded atelectasis, a finding usually associated with asbestos exposure or chronic pleural disease. The changes on the left probably represent an early stage in the development of rounded atelectasis.

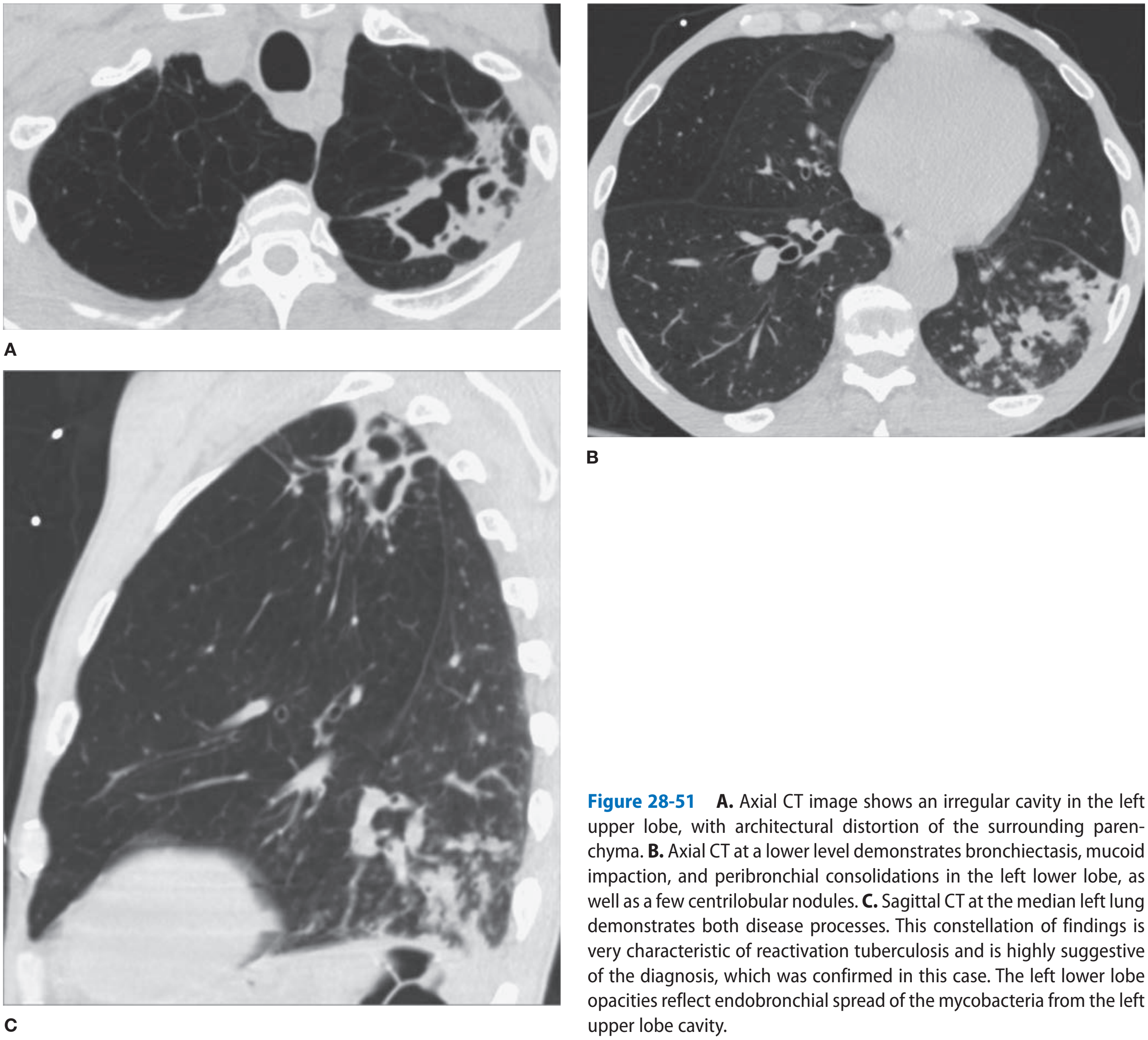


Figure 28-51 **A.** Axial CT image shows an irregular cavity in the left upper lobe, with architectural distortion of the surrounding parenchyma. **B.** Axial CT at a lower level demonstrates bronchiectasis, mucoid impaction, and peribronchial consolidations in the left lower lobe, as well as a few centrilobular nodules. **C.** Sagittal CT at the median left lung demonstrates both disease processes. This constellation of findings is very characteristic of reactivation tuberculosis and is highly suggestive of the diagnosis, which was confirmed in this case. The left lower lobe opacities reflect endobronchial spread of the mycobacteria from the left upper lobe cavity.

Congestive heart failure is a common clinical condition characterized by systolic and/or diastolic dysfunction of the left ventricle, leading to increasing diastolic filling pressure, increasing left atrial pressure, and fluid retention. Ultimately, left ventricular failure leads to right ventricular failure. The heart is almost invariably enlarged, and the central pulmonary vasculature appears prominent and indistinct. These changes are easier to recognize on PA and lateral views than on portable chest radiographs.

A rational progression of chest radiographic findings in congestive heart failure can be fully appreciated on PA and erect radiographs and is strongly correlated with increases in pulmonary capillary wedge pressure (PCWP, reflecting left atrial pressure), indicating progressive pulmonary venous congestion.

The first stage is correlated with a PCWP of 13 to 18 mm Hg and is characterized by increased width of the vascular pedicle and vascular redistribution in the erect patient; the caliber of the upper lung vessels is increased relative to the lower lung vessels (cephalization), and cardiomegaly is present.

The second stage is correlated with PCWP of 18 to 25 mm Hg and is characterized additionally by the presence of pulmonary interstitial edema—which is manifested on chest radiography as Kerley lines, thickened fissures, and peribronchial cuffing with indistinct contour of the central vessels. Kerley B lines, as previously described, represent small (1–2 cm), thin, linear opacities that are seen peripherally perpendicular to a pleural surface, reflecting edema involving interlobular septae.

Finally, the third stage is correlated with PCWP >25 mm Hg and is characterized by the additional presence of alveolar edema, manifested as fluffy (cotton-wool appearance), symmetric airspace consolidation with mid and lower lung field predominance. Pleural effusions are often present in stages II or III and may be present earlier if there is a substantial component of right ventricular dysfunction or central volume overload, such as in patients with pulmonary hypertension or superimposed chronic renal or liver disease.

Pleural effusions often accompany biventricular heart failure. However, while the pulmonary congestion usually clears rapidly in response to therapy, the pleural effusions often remain after the pulmonary vessels have returned to normal size and require a longer time to resolve. Pleural effusions in congestive heart failure may be unilateral or bilateral, although they are most often bilateral. The effusions are nearly always transudates. Therefore, the presence of

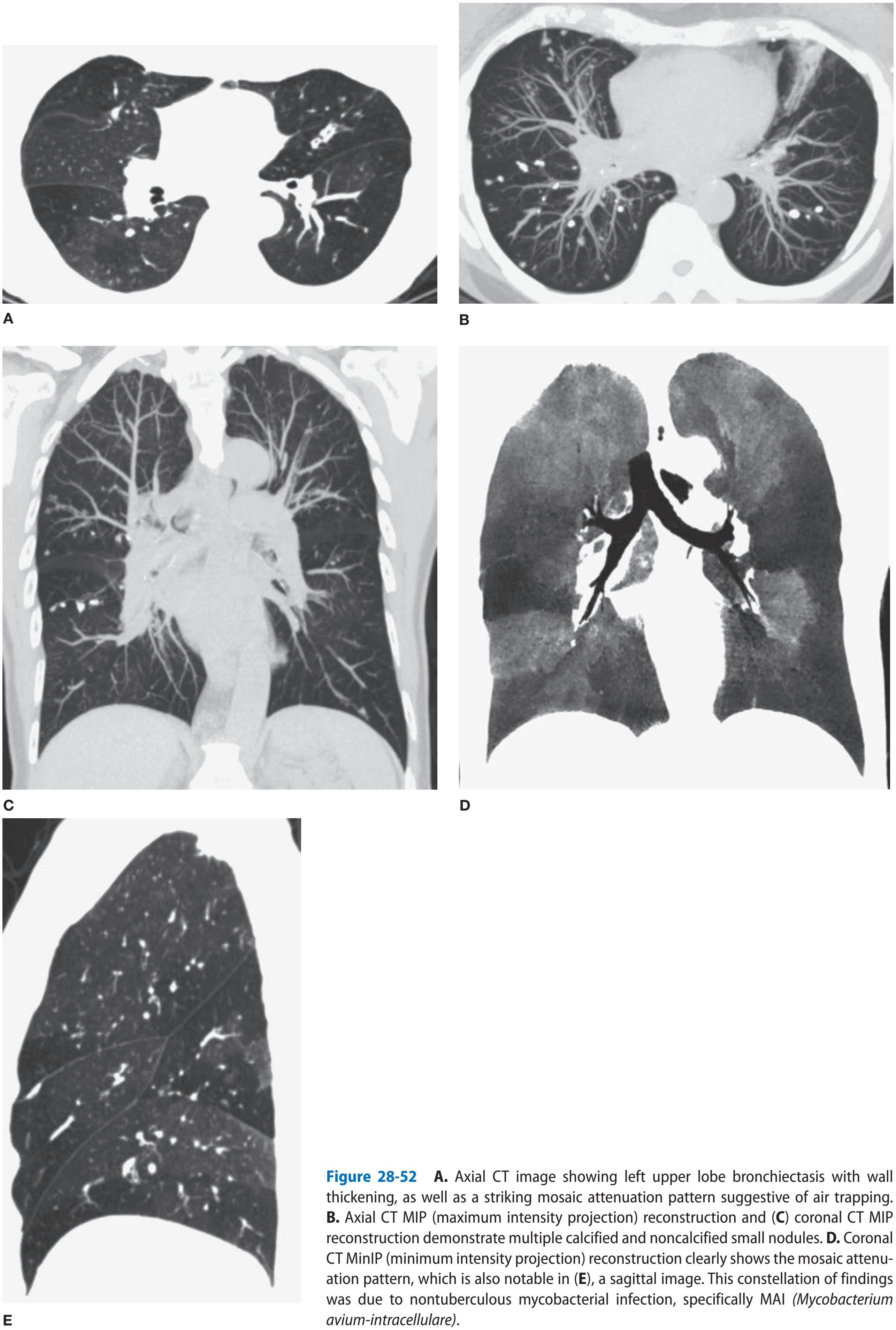


Figure 28-52 **A.** Axial CT image showing left upper lobe bronchiectasis with wall thickening, as well as a striking mosaic attenuation pattern suggestive of air trapping. **B.** Axial CT MIP (maximum intensity projection) reconstruction and (**C**) coronal CT MIP reconstruction demonstrate multiple calcified and noncalcified small nodules. **D.** Coronal CT MinIP (minimum intensity projection) reconstruction clearly shows the mosaic attenuation pattern, which is also notable in (**E**), a sagittal image. This constellation of findings was due to nontuberculous mycobacterial infection, specifically MAI *(Mycobacterium avium-intracellulare)*.

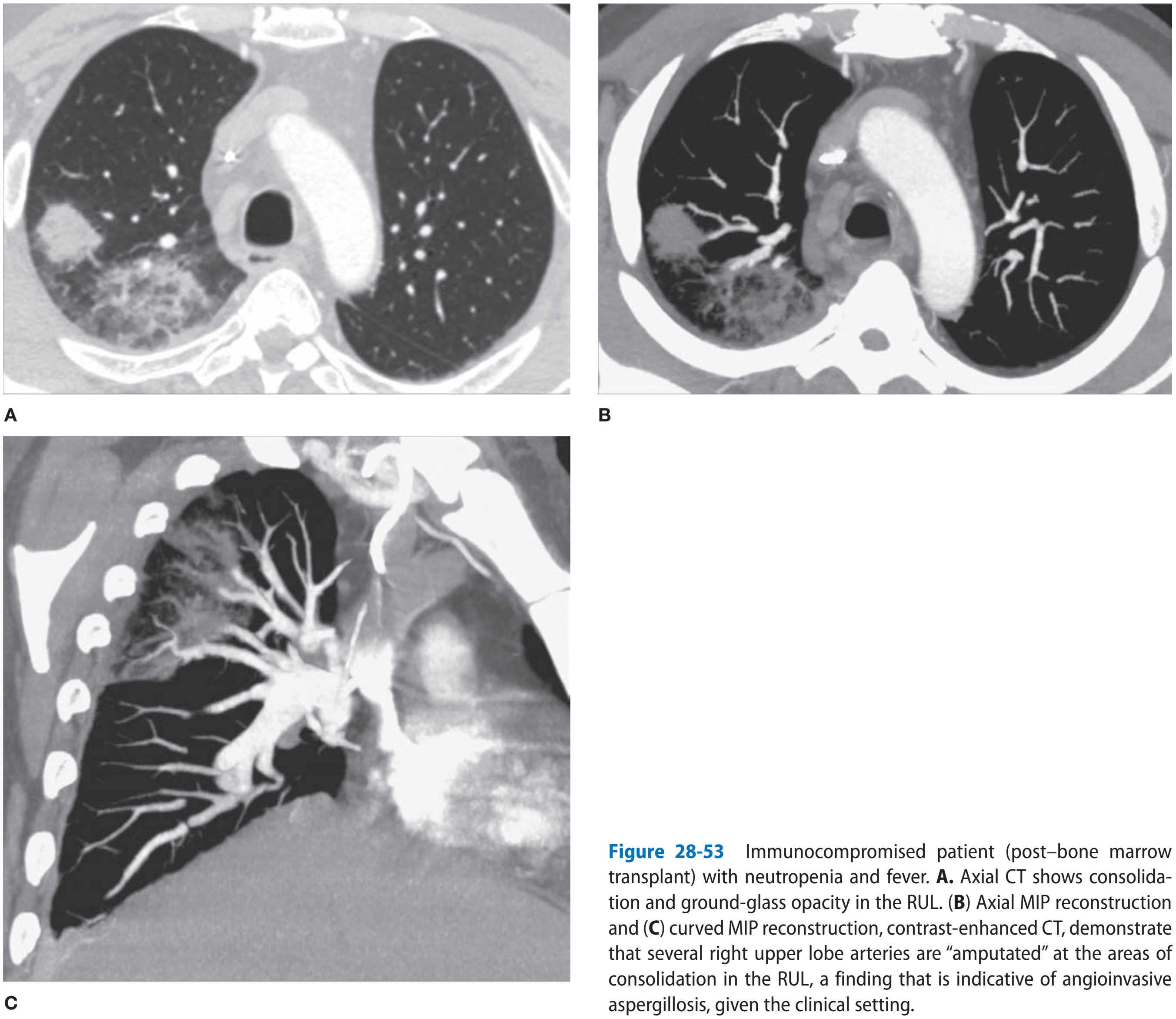


Figure 28-53 Immunocompromised patient (post–bone marrow transplant) with neutropenia and fever. **A.** Axial CT shows consolidation and ground-glass opacity in the RUL. (**B**) Axial MIP reconstruction and (**C**) curved MIP reconstruction, contrast-enhanced CT, demonstrate that several right upper lobe arteries are "amputated" at the areas of consolidation in the RUL, a finding that is indicative of angioinvasive aspergillosis, given the clinical setting.

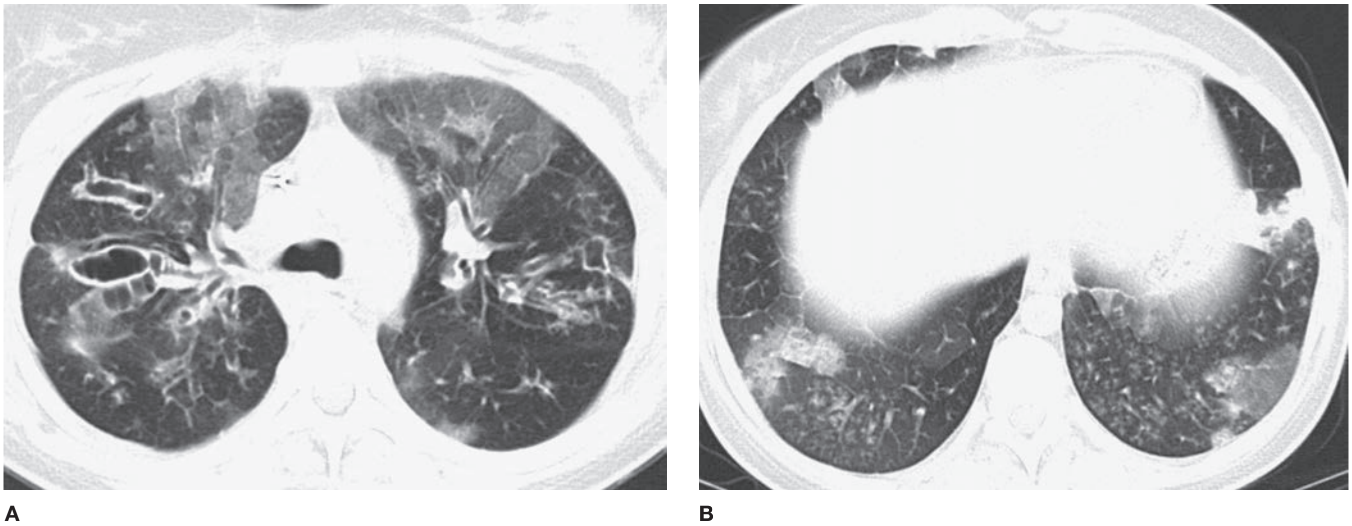


Figure 28-54 **A.** Axial CT through the level of the carina demonstrates extensive bronchiectasis. **B.** Axial CT at a lower level demonstrates multiple areas of consolidation and numerous centrilobular nodules. This patient had a diagnosis of cystic fibrosis, complicated by superinfection by *Pseudomonas aeruginosa*.

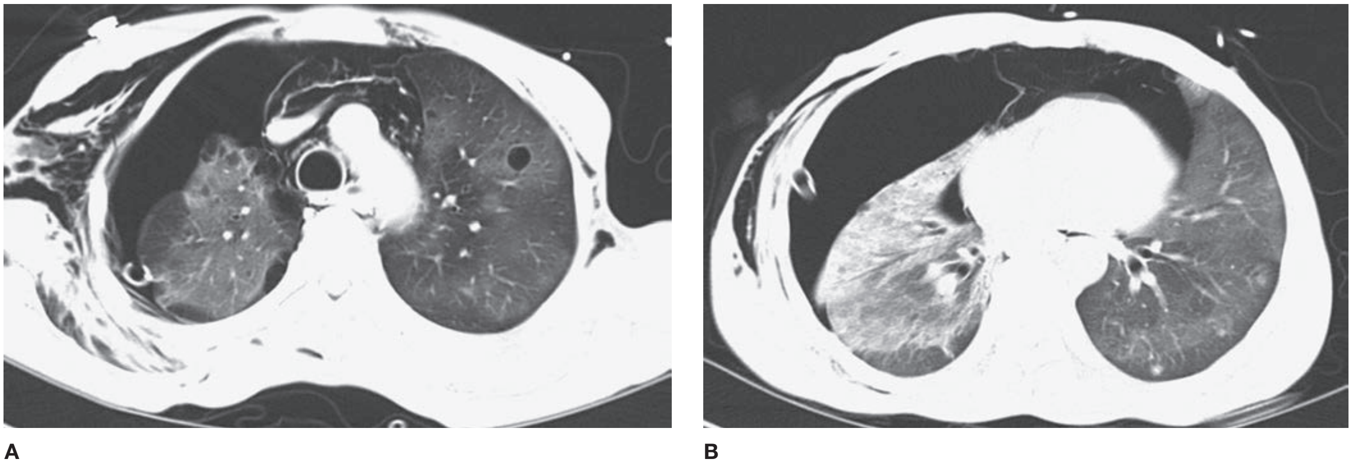


Figure 28-55 **A.** Axial CT through the upper lung fields demonstrates a large right-side pneumothorax with a chest tube partially visualized. The lung parenchyma demonstrates diffuse, but nonhomogeneous, ground-glass opacities, as well as scattered cysts. **B.** Axial CT at a lower level demonstrates diffuse ground-glass opacities, small nodules, and patchy areas of consolidation. This patient had AIDS complicated by *Pneumocystis jiroveci* pneumonia. Spontaneous pneumothorax is a known complication of this disease.

a unilateral effusion, particularly an isolated left effusion, should prompt consideration of a diagnostic thoracentesis. If the effusion is an exudate, an alternate cause, such as malignancy or infection, should be considered (Figs. 28-56 and 28-57).

CT may demonstrate the same findings and the same pattern of progression according to the degree of left heart dysfunction and PCWP increase. Nonetheless, it allows better assessment of cardiac chamber size, vascular caliber, and presence of pulmonary interstitial or alveolar edema. Nonetheless, because the combination of clinical, laboratory, and radiographic findings generally suffices for the diagnosis of congestive heart failure, CT is not routinely obtained in patients in this setting, although it is not uncommon to establish the diagnosis on CT studies performed for other reasons.

As previously discussed, pulmonary interstitial edema presents on CT as axial (peribronchovascular) and septal interstitial thickening (interlobular and intralobular); the findings are usually symmetric, smooth, and lower lung field predominant. The differential diagnosis, especially if the pattern of interstitial thickening is nodular, upper lung predominant, or asymmetric, includes sarcoidosis and lymphangitic spread of neoplasm. Pulmonary alveolar edema is demonstrated as airspace opacities (ground-glass or consolidation), with fluid-filled acinar structures; the opacities are symmetric, ill-defined, confluent, and central and lower lung field predominant. Findings of pulmonary alveolar edema often coexist with pulmonary interstitial edema, but not vice-versa. The exception is flash pulmonary edema, in which alveolar edema develops so rapidly that there is not enough time for interstitial edema to manifest. Flash pulmonary edema may occur with sudden changes in intravascular volume, such as following resuscitation in trauma patients or with sudden changes in cardiac function, as occurring with cardiac arrhythmias or myocardial infarction.

Finally, US findings in pulmonary edema include the presence of B-lines, which reflect the presence of an interstitial abnormality and in the setting of cardiogenic edema reflect extravascular lung fluid.

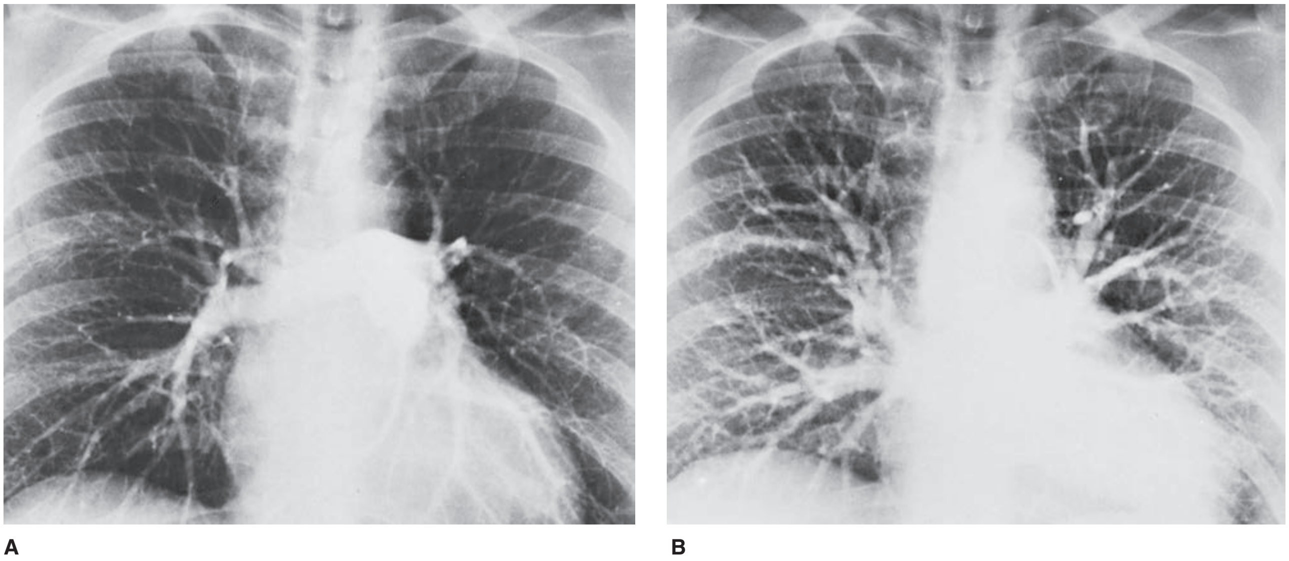


Figure 28-56 Pulmonary arteries and veins: **A.** The early phase of the pulmonary angiogram depicts the normal course and caliber of the pulmonary arteries. **B.** The late phase shows the normal course and caliber of the pulmonary veins. The veins have a more horizontal course than the arteries and enter the hila below the arteries.

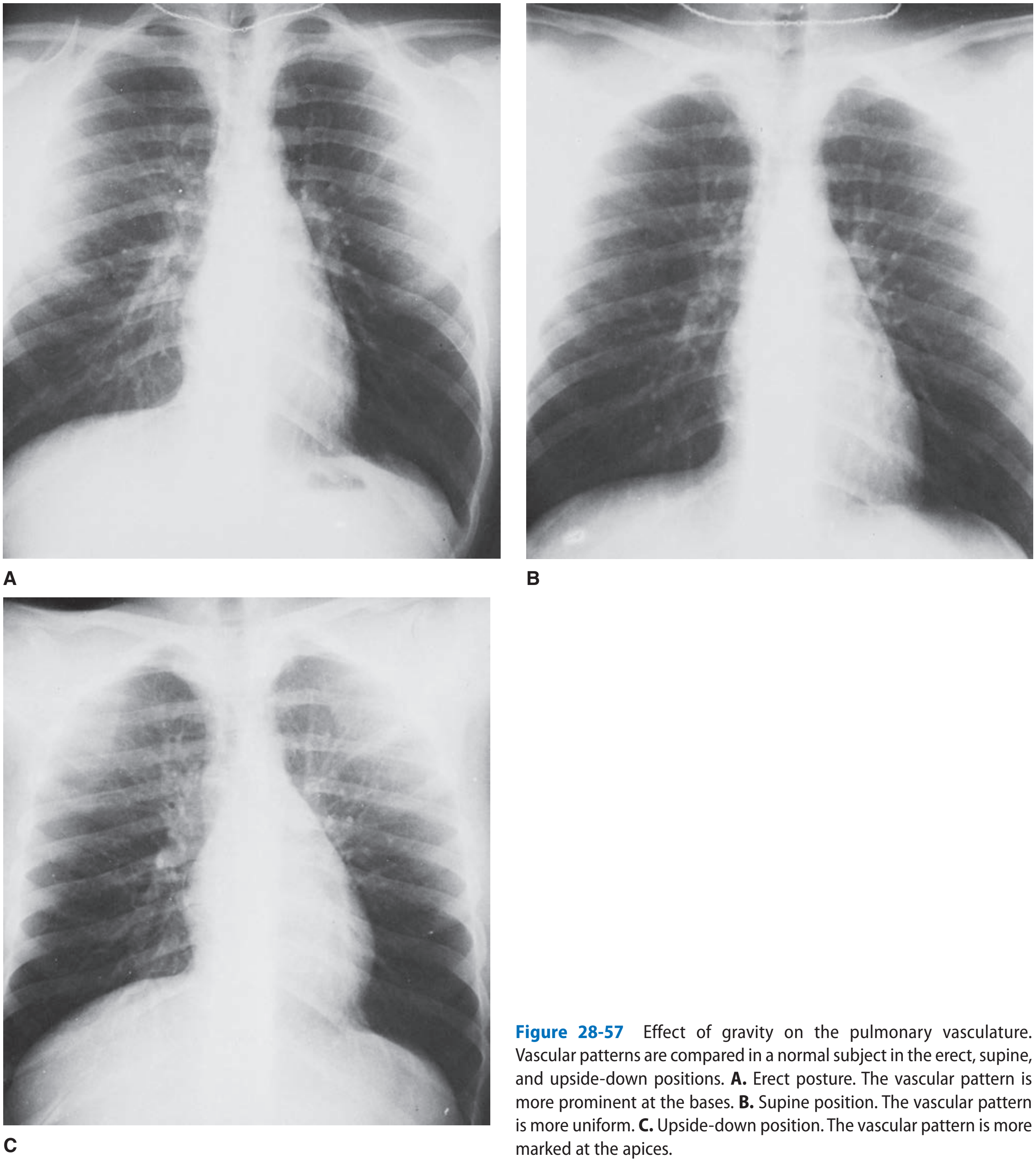


Figure 28-57 Effect of gravity on the pulmonary vasculature. Vascular patterns are compared in a normal subject in the erect, supine, and upside-down positions. **A.** Erect posture. The vascular pattern is more prominent at the bases. **B.** Supine position. The vascular pattern is more uniform. **C.** Upside-down position. The vascular pattern is more marked at the apices.

Moreover, US has high sensitivity to the presence of pleural effusion, which exceeds the sensitivity of chest radiography. Although findings are nonspecific, US can help guide therapy and monitor response to therapy in the appropriate clinical setting. Echocardiography has a well-established role in the assessment of cardiac function and, when used in combination with lung US, can help differentiate cardiogenic from noncardiogenic causes of edema.[93–95]

Pulmonary edema is the prototype of diffuse lung disease. Etiologically, it can be broadly separated into cardiogenic and noncardiogenic causes. Cardiogenic edema is caused by congestive heart failure.[96,97] Noncardiogenic edema is a manifestation of increased permeability of the pulmonary capillaries in which cardiac function is relatively preserved. Major differential diagnoses include acute hypersensitivity reactions, inhaled toxins, near-drowning, sepsis, and several processes that lead to the pathologic diagnosis of diffuse alveolar damage (DAD), most notably acute respiratory distress syndrome (ARDS).[98–102] From an imaging perspective, cardiogenic edema is more likely associated with cardiomegaly and functional impairment of the ventricles and tends to clear rapidly following administration of diuretics and drugs that optimize cardiovascular status. Noncardiogenic edema tends to resolve slowly and often requires clinical and laboratory correlation for etiologic characterization (Figs. 28-58 and 28-59). The definitions for ARDS were updated in 2011 to include the following criteria: (1) Timing: Respiratory symptoms must have begun within 1 week of a known clinical

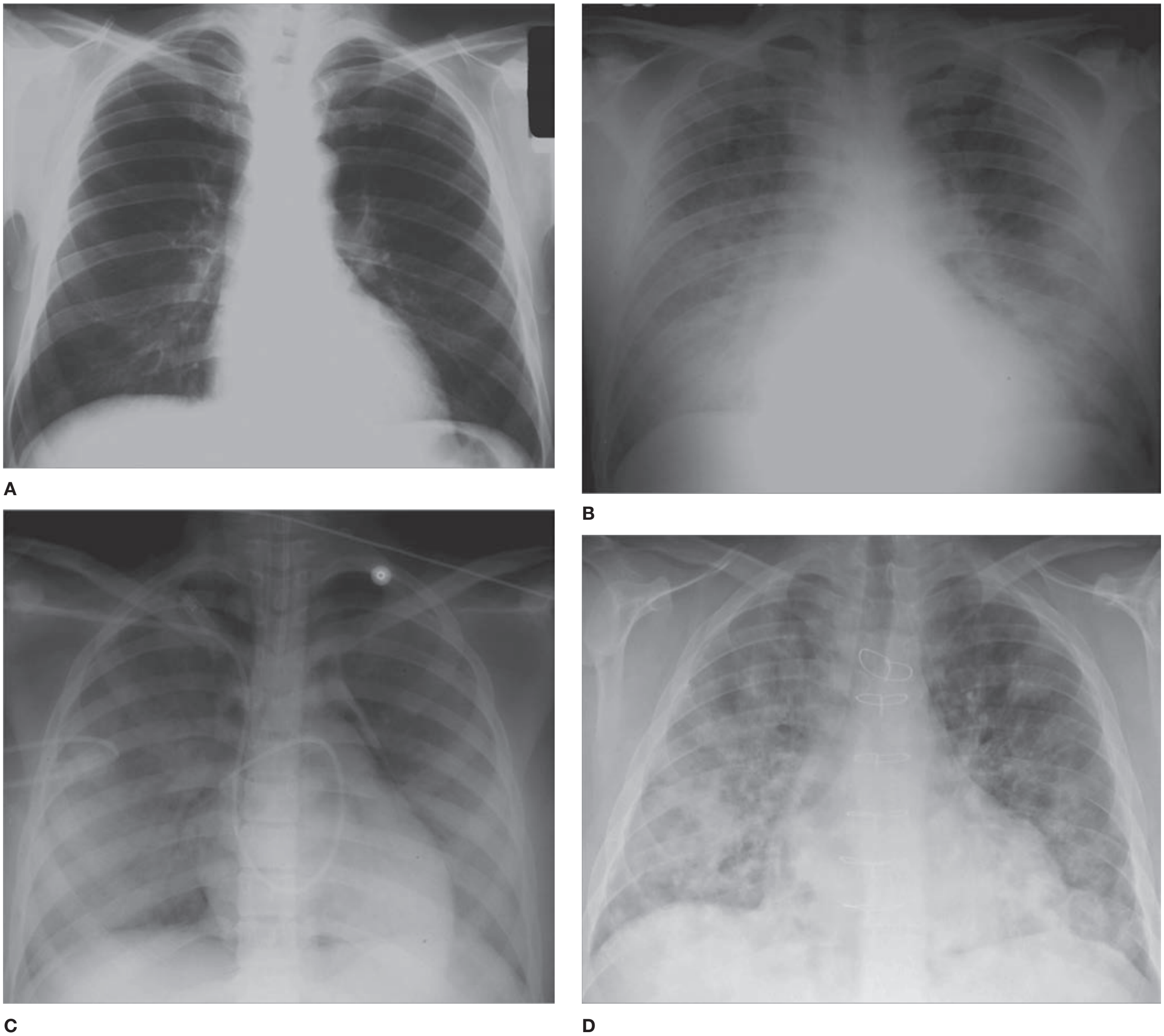


Figure 28-58 Patterns of diffuse alveolar disease. **A.** Normal PA chest radiograph, for comparison. **B.** Cardiogenic edema, with severe, symmetric, basilar-predominant airspace opacities, associated with cardiomegaly and likely small effusions. **C.** Noncardiogenic edema, with severe, symmetric, more diffuse airspace opacities; however, the cardiac size is normal and no pleural effusions are present. This patient has ARDS. **D.** Diffuse alveolar hemorrhage (DAH)—patchy, but fairly diffuse, airspace opacities are noted, with borderline heart size. This patient had systemic lupus erythematosus. Note that this pattern can be difficult to distinguish from diffuse pneumonia or pulmonary edema—clinical correlation is often needed.

insult, or the patient must have new or worsening symptoms during the past week. (2) Chest imaging: Bilateral opacities consistent with pulmonary edema must be present on a chest radiograph or CT scan, which is not fully explained by pleural effusions, lobar collapse, lung collapse, or pulmonary nodules. (3) Origin of edema: The patient's respiratory failure must not be fully explained by cardiac failure or fluid overload. An objective assessment (e.g., using echocardiography) to exclude hydrostatic pulmonary edema is required if no risk factors for ARDS are present. (4) Oxygenation: A moderate to severe impairment of oxygenation must be present, as defined by the PaO_2/FiO_2 ratio. The severity of the hypoxemia defines the severity of the ARDS, and increasing severity better correlates with patient mortality using these criteria compared with the older criteria.[103]

In the proper clinical setting, diffuse alveolar opacities represent pulmonary edema until proven otherwise. If standard therapy for congestive heart failure fails to clear the opacities, and if clinical and laboratory findings exclude noncardiogenic pulmonary edema, other diagnostic entities must be considered. The most important is a diffuse pneumonia, which can be caused by several bacterial and viral agents, including, most notably, influenza. Other differential diagnostic considerations for diffuse lung disease include diffuse alveolar hemorrhage, pulmonary alveolar proteinosis, extensive multifocal mucinous adenocarcinoma, acute hypersensitivity pneumonitis—for example, that due to drug toxicity[104]—sarcoidosis, NSIP, and desquamative interstitial pneumonia (DIP). These entities are described in Chapters 54–66 (Figs. 28-60 and 28-61).

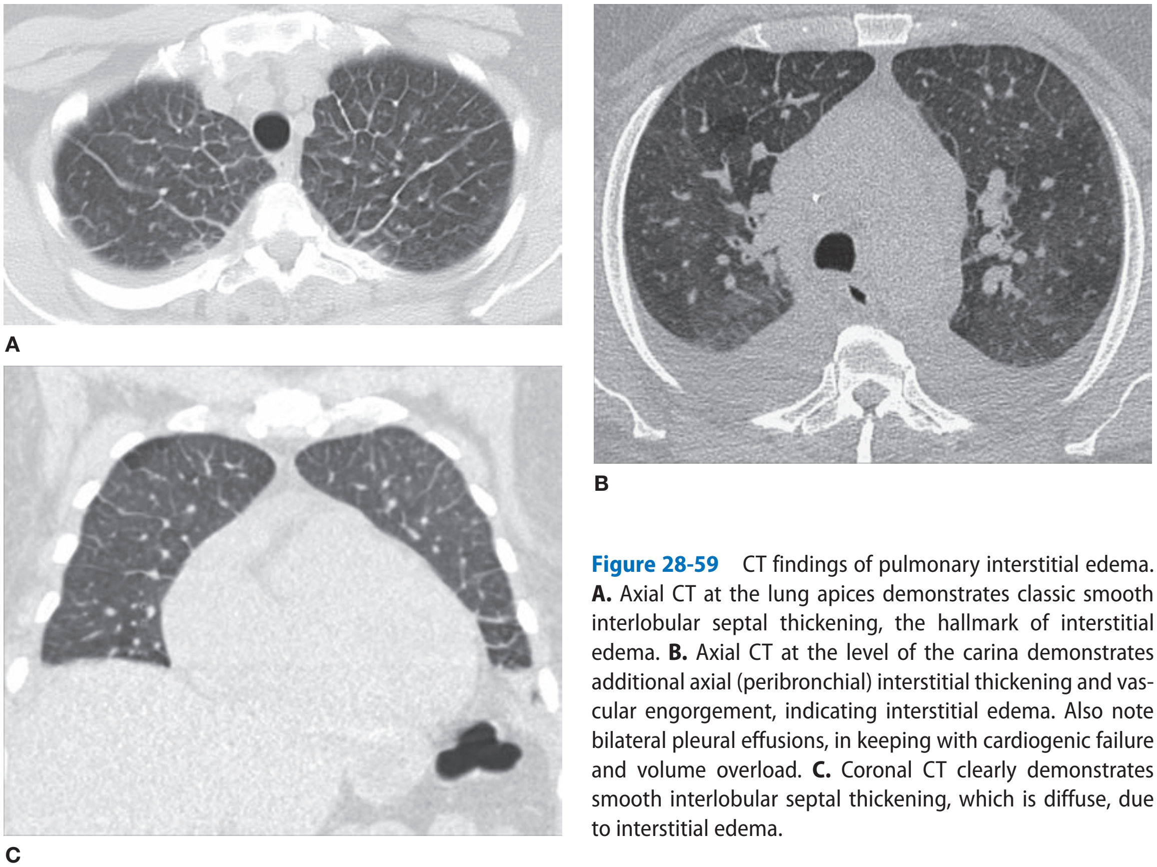


Figure 28-59 CT findings of pulmonary interstitial edema. **A.** Axial CT at the lung apices demonstrates classic smooth interlobular septal thickening, the hallmark of interstitial edema. **B.** Axial CT at the level of the carina demonstrates additional axial (peribronchial) interstitial thickening and vascular engorgement, indicating interstitial edema. Also note bilateral pleural effusions, in keeping with cardiogenic failure and volume overload. **C.** Coronal CT clearly demonstrates smooth interlobular septal thickening, which is diffuse, due to interstitial edema.

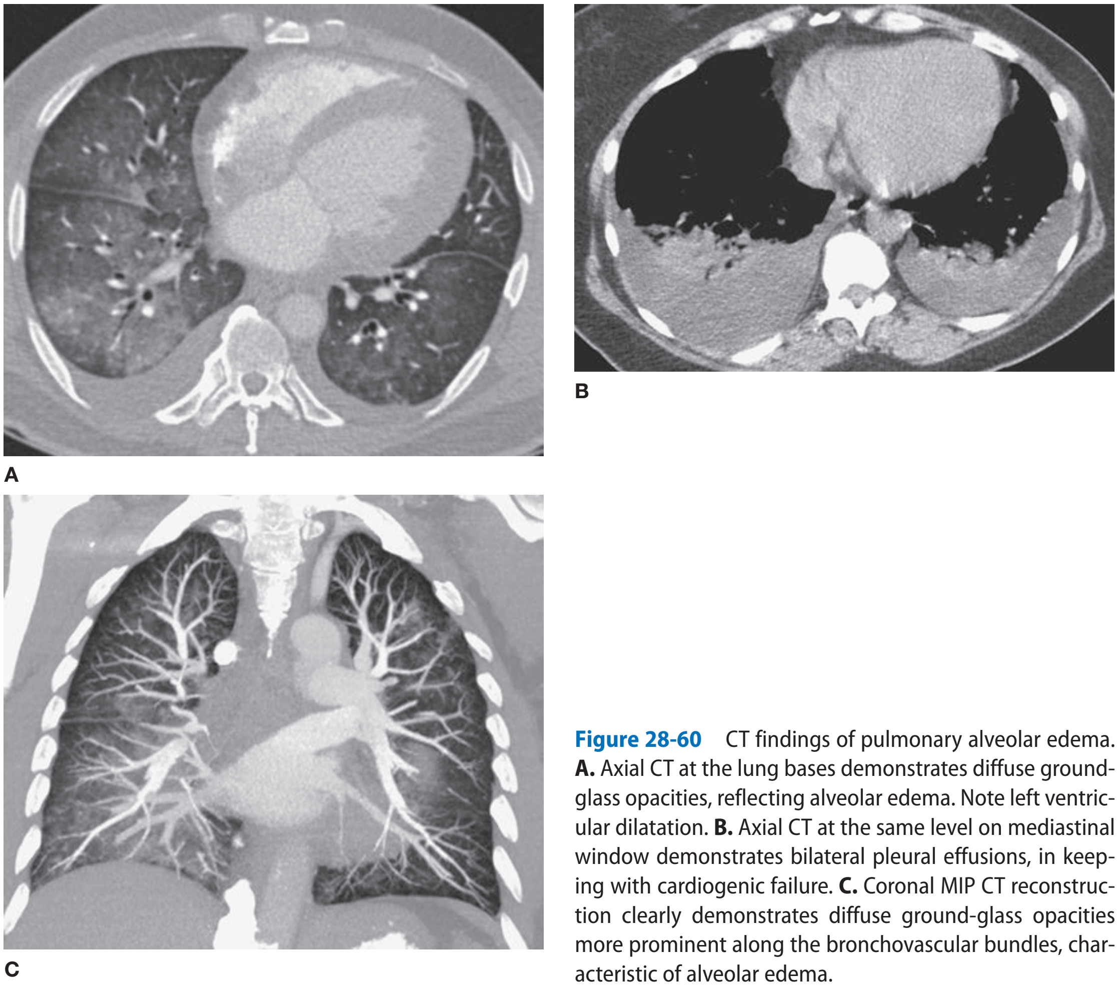


Figure 28-60 CT findings of pulmonary alveolar edema. **A.** Axial CT at the lung bases demonstrates diffuse ground-glass opacities, reflecting alveolar edema. Note left ventricular dilatation. **B.** Axial CT at the same level on mediastinal window demonstrates bilateral pleural effusions, in keeping with cardiogenic failure. **C.** Coronal MIP CT reconstruction clearly demonstrates diffuse ground-glass opacities more prominent along the bronchovascular bundles, characteristic of alveolar edema.

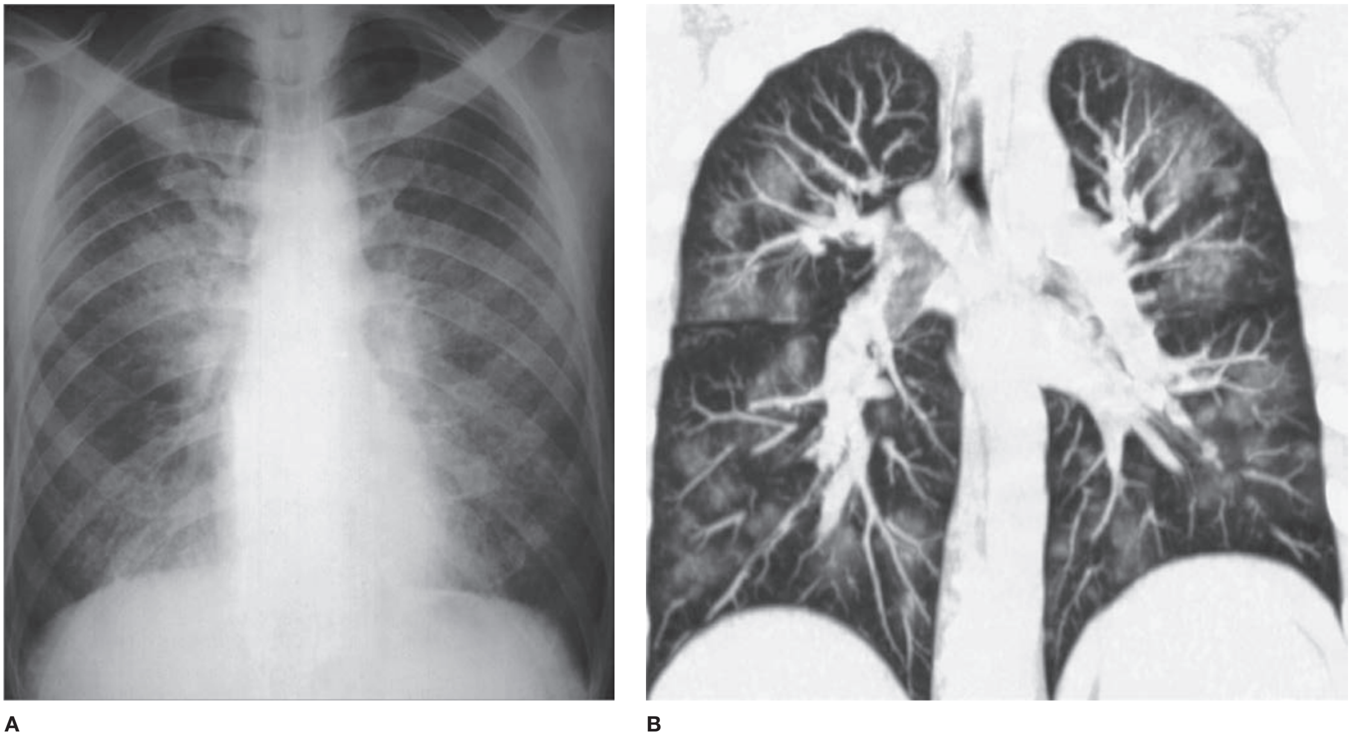


Figure 28-61 CT findings of diffuse alveolar hemorrhage (DAH). **A.** PA chest radiograph demonstrates patchy, but predominantly perihilar, alveolar opacities. **B.** Coronal MIP CT reconstruction better demonstrates the patchy, but widespread, ground-glass opacities, more prominent along the bronchovascular bundles. This patient had a diagnosis of DAH due to Goodpasture syndrome. This pattern can be indistinguishable from pulmonary edema or diffuse infection. Clinical correlation is often needed to narrow the differential diagnosis.

PULMONARY EMBOLISM AND PULMONARY HYPERTENSION

Two critically important clinical entities involving the pulmonary vasculature can be assessed using imaging: pulmonary embolism (PE) and pulmonary hypertension. Each is discussed subsequently.

Pulmonary Embolism

Contrast-enhanced, multidetector chest CT provides a powerful and readily available technique for the evaluation of PE and has become the current reference standard for the diagnosis of acute and chronic pulmonary thromboembolic disease. Not only does CT enable direct visualization of clots, it also can provide alternative diagnoses to explain symptoms in the many patients who do not prove to have PE. Moreover, CT may facilitate diagnosis of associated right heart strain when present, a finding of prognostic importance. While CT may be limited in detecting small, peripheral, subsegmental clots, particularly if the study is not of optimal quality, it has a very high negative predictive value for PE. CT may also be combined with CT venography of the pelvis and lower extremities in selected cases, when clinically indicated.

The major disadvantage of CT relative to ventilation–perfusion scanning is the breast radiation dose, which is of concern in young women and pregnant patients. The problem is further heightened by the current overutilization of CT PE studies, manifested by a yield of positive cases that is generally under 10%. Technical methods to reduce the CT radiation dose continue to be introduced. However, the best approach to radiation dose reduction is to improve the appropriate utilization of CT. Better clinical pretest assessment of risk factors for PE is required. Such assessment, using the Wells, Simplified Geneva, and PERC scores are frequently not used. Other more objective and easily implemented scoring systems have been advocated.

D-dimer measurement is a very useful screening test that carries a high negative predictive value for PE; measurement is particularly useful in the emergency room setting. A negative D-dimer in combination with a low or intermediate clinical suspicion for PE may obviate the need for CT in approximately 50% of outpatients and 20% of inpatients. Its major disadvantage, however, is its lack of specificity in conditions such as pregnancy or recent surgery, which may result in increased values.

Young patients with normal chest radiographs (and without a history of asthma or COPD) may undergo radionuclide perfusion scans as an alternative to CT; the diagnostic yield of perfusion scans in this setting is high, and the breast dose is significantly lower than with CT. More extensive use of ventilation/perfusion ($\dot{V}/\dot{Q}$) scans are limited by their poor specificity and a high rate of nondiagnostic tests, as demonstrated in the hallmark PIOPED study.[105]

Single photon-emission computed tomography (SPECT) $\dot{V}/\dot{Q}$ and SPECT with low-dose CT overcome many of the limitations of a planar $\dot{V}/\dot{Q}$ scan by introducing tomographic image acquisition, instead of only the two-dimensional views obtained using planar techniques. As a result, better characterization of the appearance and location of filling defects, as well as detection of other pathologies, are noted.[106]

Patients with coexisting symptoms and/or signs of DVT should have Doppler US of their lower extremities as the initial test.[107–109]

MRI is not considered a first-line modality for PE, as earlier studies demonstrated an unacceptably high proportion of technically inadequate or nondiagnostic scans. With continued evolution of scanning technique and MRI hardware, more recent studies and meta-analyses show promising results, including improved diagnostic capabilities and a lower number of nondiagnostic studies. Hence, MRI may be an attractive alternative to other imaging modalities, especially in younger patients and those with compromised renal function.[110,111]

The imaging workup of suspected PE in pregnancy presents several unique challenges, as both fetal and maternal breast radiation

Video 28-8 **A.** Full-color, coronal 3D VR (volume rendering) thick slab cine (anterior to posterior) emphasizing cardiovascular and pulmonary parenchymal structures and demonstrating marked ectasia of the central pulmonary arteries, compatible with pulmonary hypertension. (In this patient, mean pulmonary artery pressure was 100 mm Hg.) Also note asymmetry of arterial caliber, with relative oligemia of the left lower lobe and ectatic right upper lobe arteries, attributed to chronic thromboembolic pulmonary hypertension. **B.** Same patient. Coronal, minimum intensity projection (minIP) thick slab cine (anterior to posterior). This type of reconstruction provides excellent assessment of mosaic attenuation, which in this case is due to mosaic perfusion secondary to chronic thromboembolic pulmonary hypertension. The brighter areas of the lung parenchyma are relatively hyperperfused, whereas the darker areas are oligemic, and correlate with areas of diminished regional vascular caliber. *Video available on AccessMedicine.com.*

doses must be considered. Moreover, D-dimer is generally positive in pregnancy and, thus, not of diagnostic value. In addition, there are no useful pretest clinical risk assessment scoring systems for pregnancy. Published national guidelines recommend use of ventilation–perfusion scans in pregnant women with normal chest radiographs (and without COPD or recently active asthma) and CT in the setting of chest radiographic abnormalities that do not provide an alternative diagnosis to PE.[112,113]

Acute and chronic pulmonary thromboembolic disease can be distinguished on CT imaging by the morphology of the pulmonary arterial filling defects. Acute emboli are usually more centrally located within the vessel lumen and may be occlusive. The nonopacified pulmonary arterial branches tend to be dilated in the setting of acute thromboembolic disease. In contrast, chronic clots are more likely eccentric along the vessel wall, nonocclusive, and sometimes calcified (if long-standing). The involved vessels tend to be smaller than normal. Moreover, chronic thromboembolic disease tends to present with associated dilated central pulmonary arteries, indicating pulmonary hypertension, whereas acute emboli generally present with normal-caliber central pulmonary arteries, unless there is pre-existing pulmonary hypertension (Video 28-8A). Other findings suggesting chronic thromboembolic disease include a mosaic perfusion pattern and the presence of dilated bronchial or other systemic collateral vessels (Video 28-8B).

Given the immense functional reserve of the normal pulmonary vasculature, it is uncommon for acute PE to cause pulmonary hypertension and right ventricular dysfunction. Nonetheless, in the setting of large embolic burden, as measured by an obstruction index of the pulmonary arterial circulation of 40% or higher on helical chest CT, poor clinical outcomes are associated with right ventricular dysfunction. This situation generally only occurs with massive saddle emboli in the large proximal pulmonary arteries, or with a large number of relatively smaller emboli occluding the more distal segmental or subsegmental arteries. Chronic pulmonary thromboembolism, on the other hand, is far more prone to be associated with pulmonary hypertension, even in the absence of a substantial thromboembolic burden, due to molecular adaptation mechanisms that lead to remodeling of the pulmonary vasculature, including medial hypertrophy and in situ small vessel thrombosis.[114–116] Ventilation-perfusion lung scan is currently the preferred initial imaging test for chronic thromboembolic pulmonary hypertension (CTEPH) screening, with a normal scan essentially excluding the presence of disease.

More recently, dual-energy CT has been proposed as a method for the combined assessment of acute and chronic emboli, pulmonary vascular anatomy, pulmonary parenchymal abnormalities, and pulmonary perfusion. Pulmonary perfusion, in particular, is obtained via dual-energy CT's capacity to derive iodine maps. Identification of pulmonary perfusion defects can increase the sensitivity and specificity of CT for clot detection. Dual-energy CT has also been used for quantitative perfusion in chronic thromboembolic PE, given the strong correlation of dual-energy CT–derived perfusion parameters with subjective assessment of a mosaic attenuation pattern. Consequently, contrast-enhanced chest CT has been shown to be a useful diagnostic modality for diagnosing chronic thromboembolic pulmonary hypertension and has a comparable diagnostic performance to ventilation-perfusion scans (Figs. 28-62–28-65).[117–121]

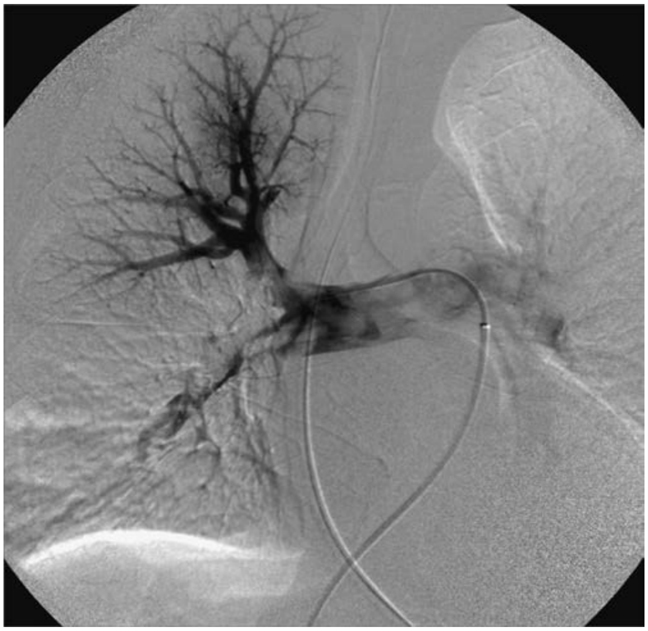


Figure 28-62 Pulmonary angiogram, arterial phase. Note normal caliber of the pulmonary arteries, with multiple filling defects in the right main, right interlobar, and proximal right upper lobar arteries, diagnostic of acute pulmonary embolism.

Pulmonary Hypertension

Because of its dual vascular supply (systemic and pulmonary, in series), the lungs effectively receive slightly greater than 100% of the cardiac output (100% via the pulmonary circulation and 1% to 2% via the systemic bronchial circulation arising from the aorta), far more than the brain, heart, liver, or kidneys (which constitute the group of highly perfused organs). In addition, the pulmonary circulation is a low-pressure, low-impedance, high-flow system that demonstrates some remarkable physiologic adaptations, such as vasoconstriction whenever there is tissue hypoxia (the opposite response of arteries elsewhere in the body, which normally vasodilate in response to hypoxia), and the ability to adapt to major changes in flow with minimal changes in pressure. Because the caliber and distribution of pulmonary vessels provide insight into the pathophysiology of the cardiopulmonary system, imaging methods can be used to study pulmonary vascular diseases.

Pulmonary blood flow is not uniform in the normal, upright human. Moreover, the blood flow pattern shifts with changes in posture, during exercise, and in a variety of heart and lung diseases. In the normal pulmonary circulation, gravity and distance from the heart are the predominant determinants of the pattern of blood flow, given that pulmonary vascular impedance is relatively uniform throughout the lungs (1/10 of average systemic vascular impedance). Assuming a normal average pulmonary arterial pressure of

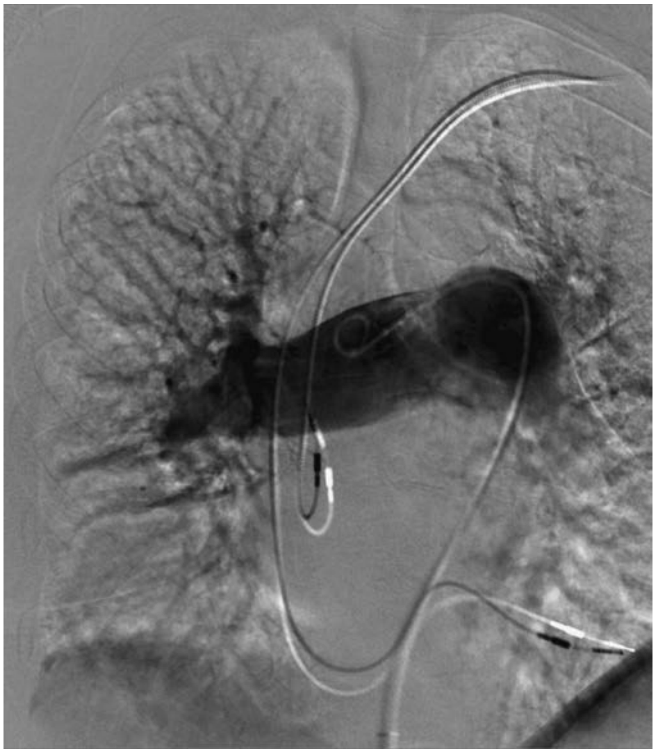


Figure 28-63 Pulmonary angiogram, arterial phase. Note marked dilatation of the pulmonary arteries, without occlusive filling defects, but with overall poor delineation of the arteries, suggesting semiocclusive defects and increased contrast transit time. The constellation of findings indicates chronic thromboembolic pulmonary hypertension (CTEPH).

15 mm Hg, in an adult patient in the erect position a gradient of 22 to 23 mm Hg exists between the apex (2–3 mm Hg) and the bases (25 mm Hg). Given that vascular impedance in the lungs is uniformly low, flow to the bases is approximately 10 times greater than flow to the apices. These differences are greatly reduced in supine position, in which there is a much smaller pressure gradient between the posterior and anterior lungs; consequently, flow is far more uniform in the supine position. In the healthy patient, exercise may increase cardiac output and pulmonary blood flow fivefold, with minimal changes in pressure due to decreased pulmonary vascular impedance. The decline in pulmonary vascular impedance is secondary to capillary recruitment and increased vascular distension.

In pathologic conditions in which pulmonary arterial or venous pressures are increased, or in which alveolar pressure is elevated, the importance of gravity as the major determinant of pulmonary flow is diminished. Furthermore, impaired gas exchange and ventilation may cause alveolar hypoxia that further interferes with pulmonary blood flow via hypoxic vasoconstriction of small arterioles.

The concept of lung "perfusion zones" is based on functional compartmentalization of the lung into three zones according to the relationships among pulmonary arterial, pulmonary venous, and alveolar pressures. In zone 1, average alveolar pressure > arterial pressure > venous pressure, and perfusion is minimal. In zone 2, average arterial pressure > alveolar pressure > venous pressure, and perfusion is pulsatile. In zone 3, average arterial pressure > venous pressure > alveolar pressure, and perfusion is continuous. Normal healthy subjects do not manifest zone 1 physiology; however, patients on mechanical ventilation with high positive end-expiratory pressure (PEEP) or patients with COPD and air trapping may develop large areas of zone 1 physiology. Moreover, heart diseases characterized by left ventricular dysfunction demonstrate increased left atrial and, consequently, increased pulmonary venous pressure. In the short term, this may cause vascular redistribution (with cephalization of the pulmonary vasculature) or pulmonary edema (if acute and more severe). In the long term, adaptation mechanisms of the pulmonary arterial circulation and right ventricle, including increased vascular impedance and right ventricular hypertrophy and dilatation, ultimately result in increased pulmonary arterial pressure; pulmonary hypertension ensues. Understanding the underlying pathophysiology is important for interpreting the imaging findings of pulmonary hypertension.

In its broadest sense, pulmonary hypertension is a pathophysiologic condition in which pulmonary hemodynamics are altered, including an increase in pulmonary vascular impedance and a consequent increase in mean pulmonary arterial pressure above 25 mm Hg (current diagnostic criteria). The pathophysiology, current WHO classification, and treatment of pulmonary hypertension are described in Chapter 72.

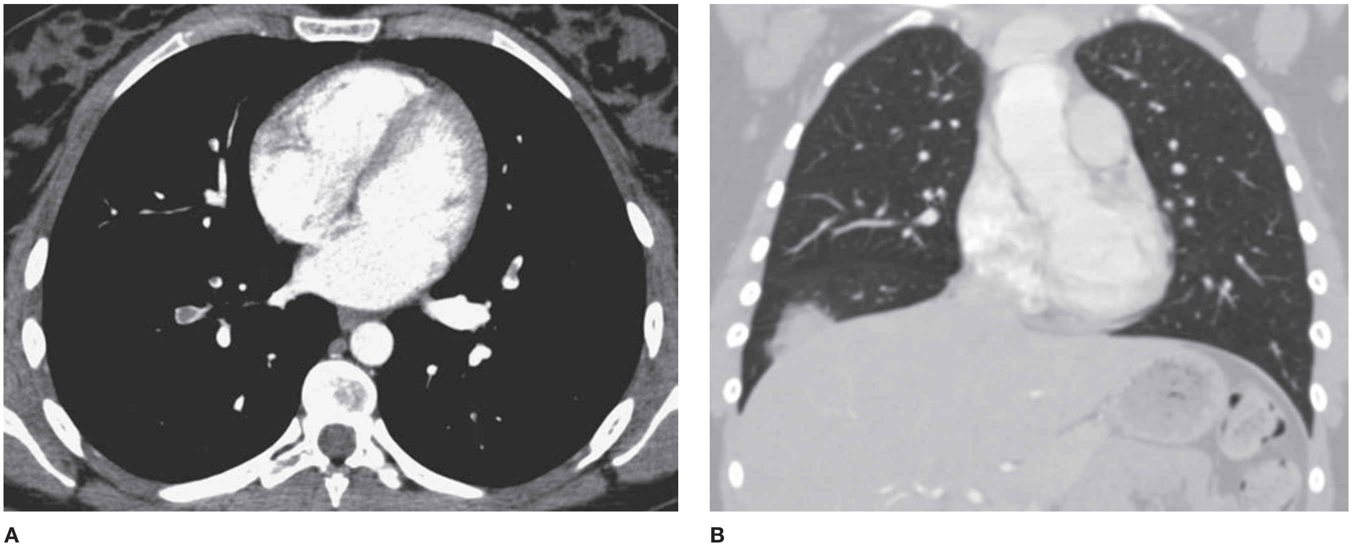


Figure 28-64 Acute pulmonary embolism. **A.** Axial CT at the lung bases demonstrates filling defects in the right lower lobe segmental arteries and left lower lobe anterior segmental artery, compatible with acute PE. **B.** Coronal CT image demonstrates a peripheral RLL consolidation, compatible with pulmonary infarct.

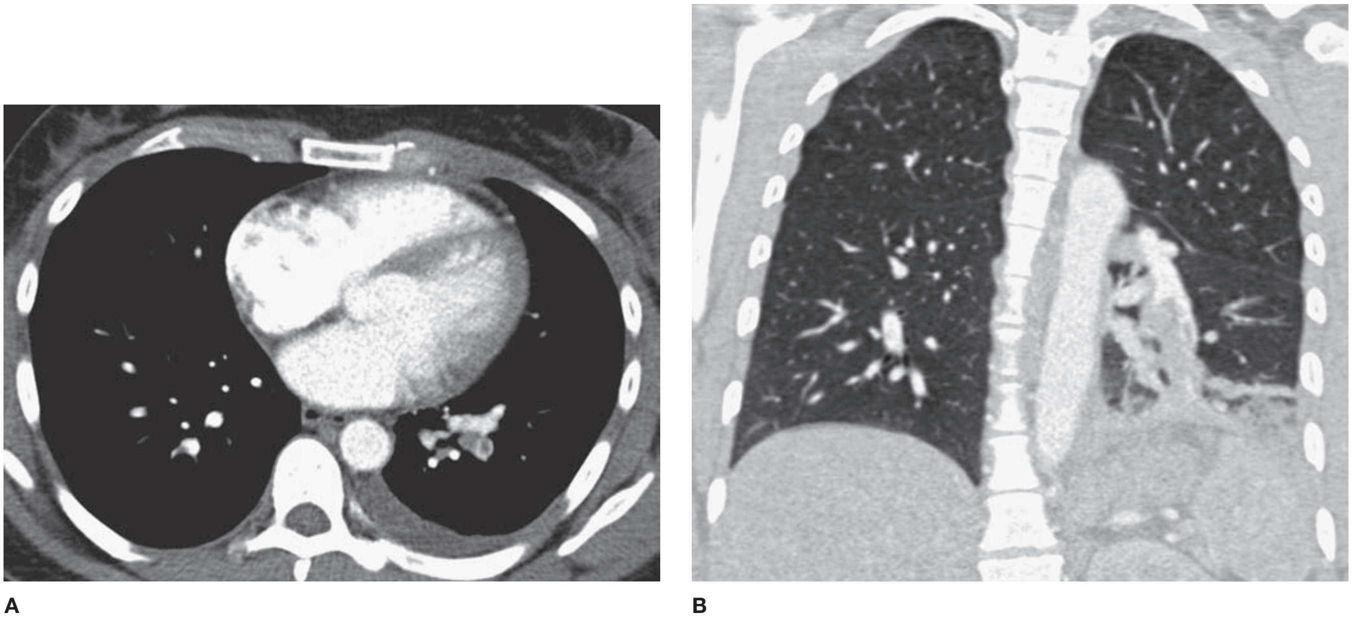


Figure 28-65 Acute pulmonary embolism. **A.** Axial CT at the lung bases demonstrates filling defects in the left lower lobe segmental arteries, compatible with acute PE. Note small left pleural effusion. **B.** Coronal CT image demonstrates a peripheral LLL consolidation, compatible with pulmonary infarct.

The reference standard for diagnosis of pulmonary hypertension is right heart catheterization, an invasive diagnostic modality that allows direct measurement of right ventricular pressure and pulmonary arterial pressure, as well as indirect measurement of pulmonary venous pressure throughout the cardiac cycle. Noninvasive imaging tests cannot measure pressure directly, although echocardiography can be used to estimate pulmonary arterial pressure via Doppler techniques that measure the velocity of the regurgitant jet through the tricuspid valve during systole. The right atrial pressure is usually assumed to be 7 to 8 mm Hg plus the central venous pressure, as estimated by physical evaluation of neck vein distention. These pressures cannot be directly measured by Doppler ultrasonography.

From a diagnostic standpoint, imaging tests may, nonetheless, provide important insight into the possible presence and potential etiology of pulmonary hypertension. The hemodynamic distinction between precapillary pulmonary hypertension (defined by mean pulmonary arterial pressure >25 mm Hg and PCWP <15 mm Hg) and postcapillary pulmonary hypertension (defined by mean pulmonary arterial pressure >25 mm Hg and PCWP >15 mm Hg) can generally be made by advanced imaging. Precapillary pulmonary hypertension includes pulmonary arterial hypertension, pulmonary hypertension due to lung parenchymal diseases, chronic thromboembolic pulmonary hypertension, and miscellaneous causes (WHO classes I, III, IV, and V). Postcapillary pulmonary hypertension includes pulmonary venous hypertension associated with left heart disease (WHO class II).

Imaging studies are important in separating pulmonary arterial hypertension from pulmonary hypertension related to pulmonary parenchymal diseases, left ventricular failure, and chronic thromboembolic pulmonary disease, since the management of these entities differs substantially.

Chest radiographs are helpful in the initial assessment of suspected pulmonary hypertension, although they are not sensitive for early diagnosis. Given their low cost and universal availability, chest radiographs can provide an assessment of cardiac size and pulmonary vasculature caliber and distribution, as well as suggest findings of congestive heart failure or diffuse lung parenchymal disease. Published studies suggest that on erect PA examinations, if PCWP is >13 but <18 mm Hg, there is usually vascular redistribution with relative hypervascularity of the upper lung fields; if between 18 and 25 mm Hg, there is also interstitial pulmonary edema; if >25 mm Hg, there is usually alveolar edema and often pleural effusions. If pulmonary hypertension is present in these clinical settings, strong consideration should be given to left ventricular failure as a causal factor.

Several radiographic findings have been described as suggestive of, but not specific for, the presence of pulmonary hypertension. These include: (1) right heart enlargement, suggested by a distance of >44 mm from the midline to the prominent right heart border on a PA film, indicating right atrial enlargement; (2) a right descending pulmonary artery (RDPA) ≥ 16 mm in diameter; (3) a left descending pulmonary artery (LDPA) ≥ 18 mm in diameter; and (4) peripheral vascular pruning on the PA film. The size of the right ventricle is better assessed on the lateral view, where filling of the usually lucent retrosternal space is indicative of enlargement.[122]

Chest CT and, increasingly, MRI have been proposed as diagnostic tests that can provide pertinent detailed information regarding the pulmonary parenchyma, cardiac anatomy and function, and the status of the pulmonary vasculature, with minimum patient risk.

Chest CT has a major role in evaluating patients with suspected pulmonary hypertension. It is the best imaging test to demonstrate lung parenchymal disease. A normal appearance of the lung parenchyma on chest CT in the setting of pulmonary hypertension effectively eliminates the possibility of COPD or ILD significantly contributing to the pulmonary hypertension and should prompt search for alternative etiologies.

Furthermore, chest CT is also useful for direct assessment of the pulmonary arteries in the setting of suspected pulmonary arterial hypertension. It has been reported that a main pulmonary artery caliber >29 mm, when measured 2 cm from the pulmonary valve, has a sensitivity of 84%, a specificity of 75%, and a positive predictive value of 97% for the presence of pulmonary arterial hypertension, as confirmed by invasive imaging. Moreover, if the main pulmonary artery has a maximum transverse diameter greater than that of the proximal ascending thoracic aorta, there is a sensitivity of 70%, specificity of 92%, and positive predictive value of 96% for the presence of pulmonary arterial hypertension. One should be mindful first to determine that the ascending aorta is not aneurysmal when performing these measurements.

An additional chest CT finding suggesting pulmonary arterial hypertension is enlargement of the segmental arteries >1.25 times the caliber of the adjacent bronchus. A combination of positive findings increases diagnostic confidence. For instance, the presence of enlarged main pulmonary artery (>29 mm) and concomitant enlargement of three out of four segmental arteries (arterial/bronchial diameter >1.25) provides a very high specificity (100%) for the diagnosis of pulmonary arterial hypertension. However, if pulmonary fibrosis or emphysema is present, the correlation between pulmonary artery dimension and severity of pulmonary hypertension is substantially weaker. In these clinical settings, a combination of findings is warranted to suggest the diagnosis.

A prospective study comparing right heart catheterization and chest CT demonstrated that CT-derived measurement of the main pulmonary artery diameter (MPAD) correlates more strongly with the presence of pulmonary hypertension in patients without ILD (MPAD >31.6 mm associated with a PPV of 90.0% and an NPV of 58.3%) than in patients with ILD (MPAD >25 mm associated with a PPV of 46.3% and an NPV of 83.8%), although in both groups the MPAD was significantly greater in patients with pulmonary hypertension than in those without. One conclusion is that pulmonary hypertension is more likely to be present even with normal-caliber pulmonary arteries if the underlying diagnosis is ILD. The presence of bronchial artery hypertrophy >1.5 mm also has been implicated in pulmonary arterial hypertension, although this sign is probably far more common in chronic pulmonary thromboembolic disease.

Several pulmonary parenchymal findings are associated with pulmonary arterial hypertension, although they are not individually sensitive or specific enough to warrant the diagnosis. The first is mosaic attenuation, which is more commonly seen in the setting of pulmonary hypertension due to chronic pulmonary thromboembolic disease, but which can also be seen in the presence of small airway disease without pulmonary hypertension, among other possibilities. Widespread tiny centrilobular ground-glass nodules also may be present, similar to those observed in hypersensitivity pneumonitis, but pathologically deemed to represent cholesterol granulomas or large plexogenic arterial lesions, which have been described in 7% to 47% of patients with pulmonary arterial hypertension.[123–125]

MRI is currently the reference standard for assessment of congenital heart diseases, as it accurately delineates structural changes, cardiac situs, intracardiac shunts, atrial–ventricular and ventriculoarterial relationships, and vascular dimensions, along with wall motion and valvular abnormalities. It is the most useful modality for assessing right ventricular anatomy and function, which is a critical prognostic determinant in pulmonary hypertension. Furthermore, contrast-enhanced MRI, through demonstration of delayed enhancement, uniquely enables detection of the presence and extent of myocardial scarring related to prior infarction, myocarditis, or infiltrative disease in the myocardium—findings that may be associated with left ventricular dysfunction and pulmonary venous hypertension. MRI, similar to Doppler echocardiography, can be used to quantitatively measure flow velocity using phase contrast imaging, allowing for estimation of arterial and intracardiac pressures. However, a major strength of MRI when compared with echocardiography is that arbitrary planes can be set without limitation by available acoustic windows, providing for greater accuracy and reproducibility. Further developments in MRI techniques will increase the clinical usefulness of this modality. In the future, it is conceivable that the combination of advanced CT and MRI techniques will be able to provide a thorough anatomic and functional assessment of the heart–lung unit in patients with suspected pulmonary hypertension, obviating the need for invasive right heart catheterization in selected patients (Figs. 28-66–28-68).[126–128]

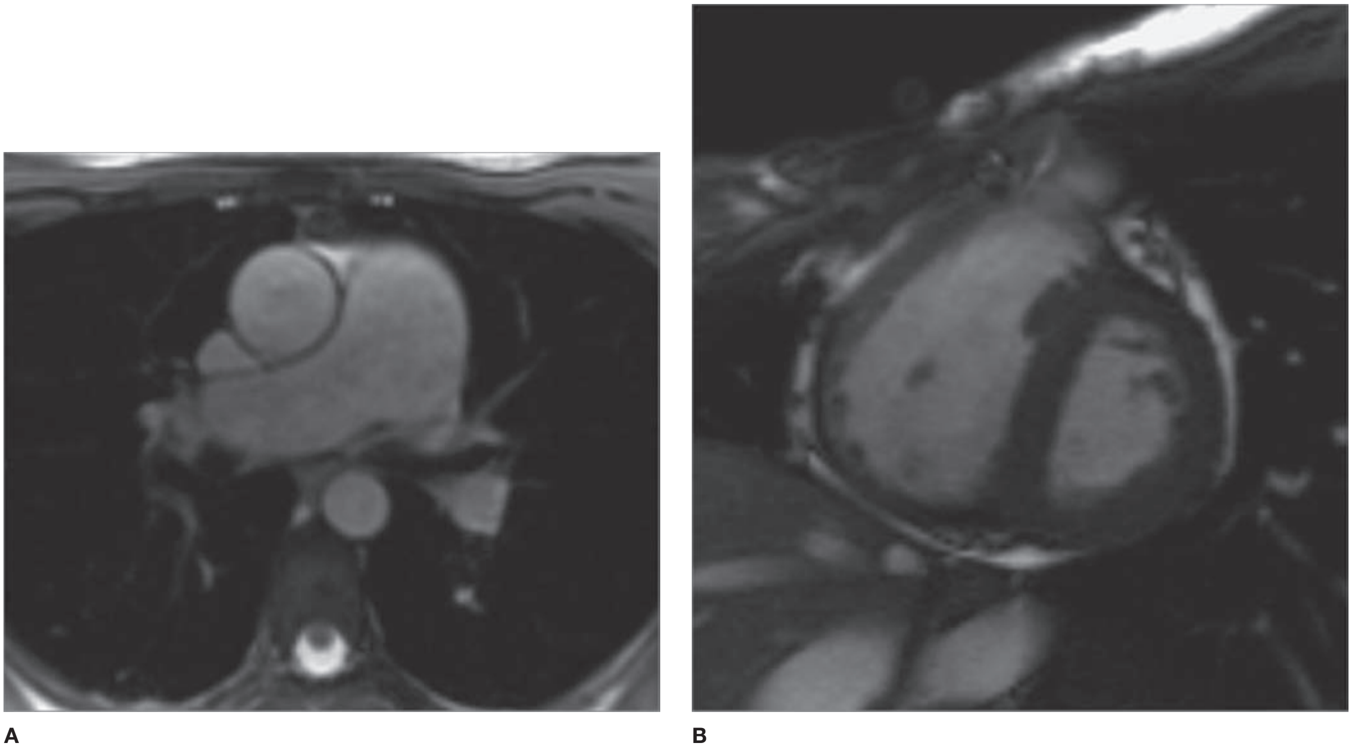


Figure 28-66 Pulmonary hypertension and right ventricular strain. **A.** Steady-state, free precession axial (SSFP) MR image ("bright blood") demonstrates dilatation of the central pulmonary arteries, with the main PA larger than the ascending aorta, compatible with pulmonary arterial hypertension. **B.** SSFP MR image, short axis of the heart, demonstrates right ventricular dilatation and straightening of the interventricular septum, indicative of right ventricular strain. The septum is normally convex toward the RV, due to normally higher LV pressure.

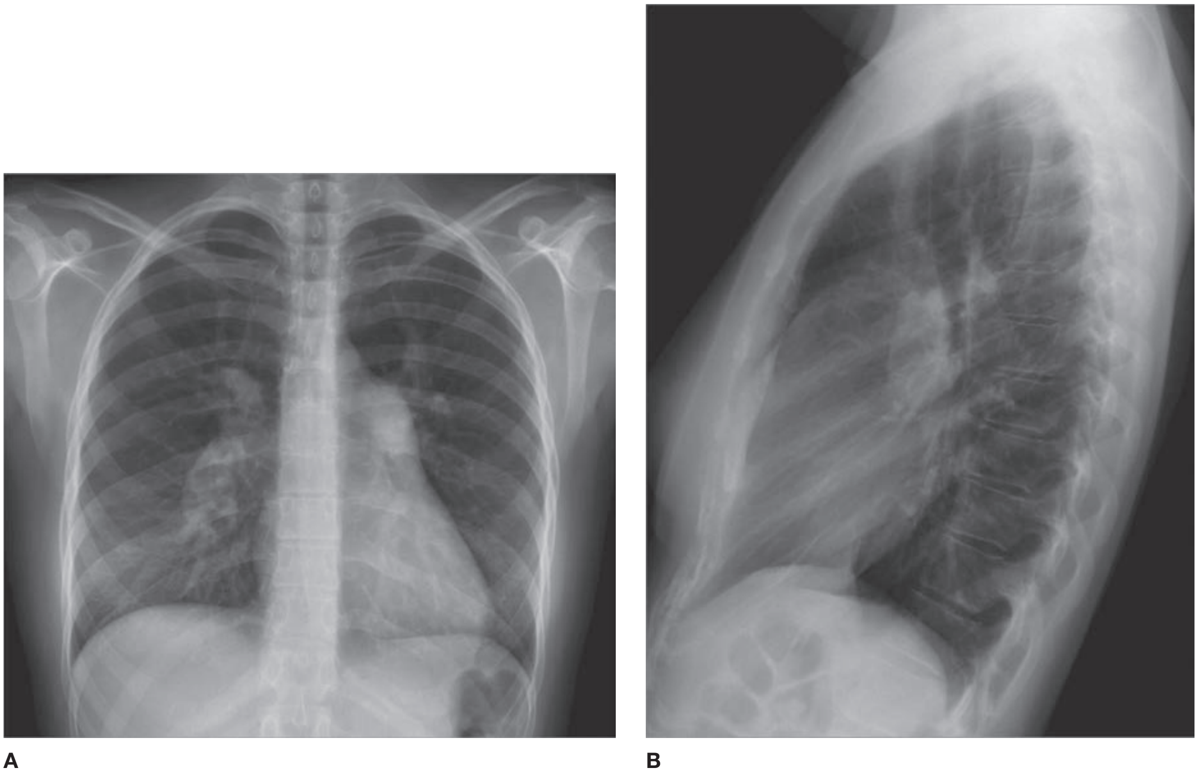


Figure 28-67 Pulmonary hypertension due to cardiac shunt. (**A**) PA, (**B**) lateral chest radiographs demonstrate moderate dilatation of the central pulmonary arteries, secondary to a long-standing uncorrected atrial septal defect (ASD).

PLEURAL, DIAPHRAGMATIC, AND CHEST WALL DISEASES

Radiographic imaging of the pleural space, diaphragm, and chest wall plays an important role in the diagnosis and evaluation of common, clinically important disorders involving these structures.

■ Pleural Diseases

Pleural pathology can be broadly classified, for imaging purposes, into three major categories: pneumothoraces; pleural effusions; and pleural thickening, nodules, or masses. These are described in the subsections that follow.

Pneumothorax

Even though generally placed within the subgroup of pleural pathology, pneumothorax, characterized as the presence of gas within the pleural cavity separating the parietal from the visceral pleura, is rarely related to a disease process of the pleura itself (see Chapter 79). Rather, it is associated with pulmonary or chest wall lesions. Nonetheless, pneumothorax

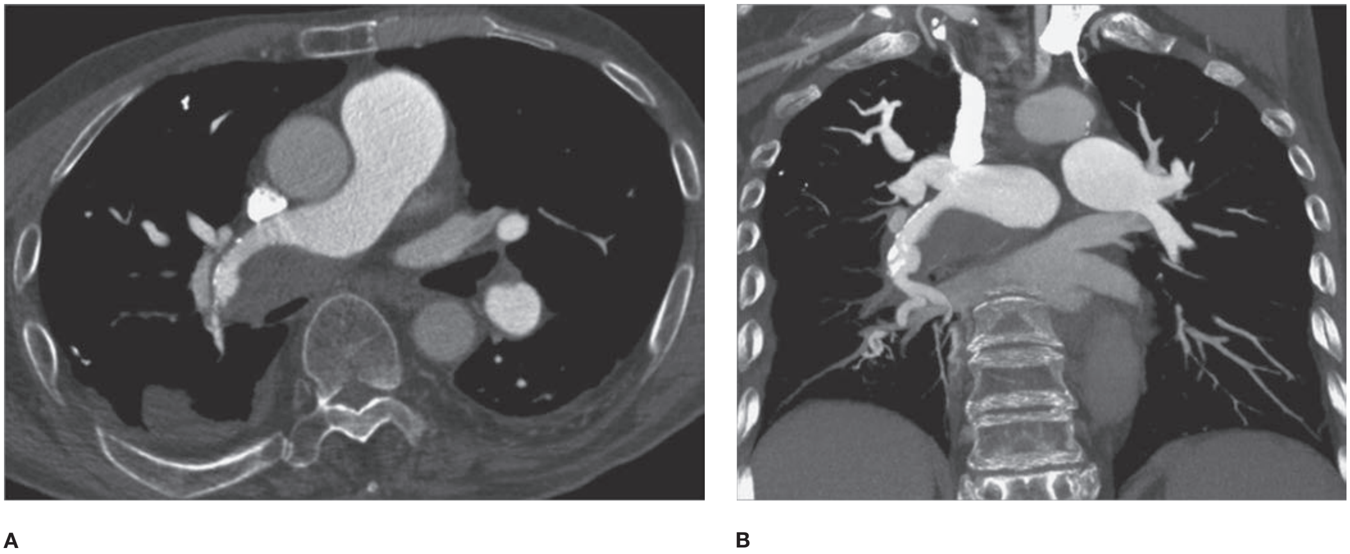


Figure 28-68 Chronic thromboembolic pulmonary hypertension (CTEPH): (**A**) axial CT image and (**B**) coronal MIP CT image demonstrating marked dilatation of the central pulmonary arteries, partially occlusive filling defect in the right main pulmonary artery, and tortuosity of the pulmonary arteries, with asymmetric vascular caliber. The constellation of findings reflects CTEPH.

is a very important clinical diagnosis, since it can lead to substantial morbidity or mortality if undetected or not properly treated.

Imaging is generally extremely accurate in the diagnosis of pneumothorax. The only exception is a portable chest radiograph obtained in a supine position, which is relatively insensitive for detection of small pneumothoraces. In this scenario, a pneumothorax should be suspected if there is increased lucency in the least dependent portion of the hemithorax (the anterolateral costophrenic angle in supine position), known as the "deep sulcus sign." This finding should prompt a lateral decubitus film, with the patient positioned with the suspected pneumothorax in the nondependent side; findings include a sharply marginated lucency along the lateral nondependent hemithorax.

On the other hand, erect PA radiographs are very sensitive and can detect even very small pneumothoraces, which are identified as crescentic-shaped lucencies lateral and superior to the apex of the lung and delineated from the lung parenchyma by a thin visceral pleural line. If there is doubt regarding the presence of a very small pneumothorax, an expiratory view may help by increasing the conspicuity of the pneumothorax, as the lung volumes will be reduced while the pneumothorax volume remains constant, resulting in an increase in the percent volume of the hemithorax occupied by the pneumothorax. In addition, lung parenchymal attenuation will be slightly increased relative to the pneumothorax.

Thoracic ultrasound (see Chapter 29), especially as a bedside study performed in the emergency department or ICU, has a reported higher sensitivity, and similar specificity, as chest radiography for detection of pneumothorax. A combination of lack of pleural movement and presence of a "lung point" (where parietal and visceral pleura split and lung parenchyma separates from the chest wall) have been described as the most specific findings for diagnosis.[129]

Finally, CT is the most accurate modality for detecting pneumothorax and can demonstrate even minuscule pneumothoraces (<1%) that cannot be detected by standard radiographic techniques.

Special cases include tension and loculated pneumothoraces. Tension pneumothorax is a critical diagnosis that requires emergent treatment. A tension pneumothorax manifests on imaging as substantial lung collapse, contralateral mediastinal shift, and downward ipsilateral diaphragmatic displacement. It is generally associated with respiratory and cardiovascular compromise and requires prompt decompression. Loculated pneumothorax occurs when there are inflammatory or neoplastic adhesions between the parietal and visceral pleura, causing gas to accumulate in the pleural space in unusual locations and geometric configurations that do not respect gravitational gradients.

Imaging can also be performed to monitor a pneumothorax, for example, to decide if and when to place a chest tube, and also to investigate the etiology. Most pneumothoraces are either traumatic (in the setting of rib fractures or pulmonary lacerations) or iatrogenic (in the setting of pulmonary, mediastinal, or chest wall interventional procedures, which may be percutaneous, bronchoscopic, or surgical). CT is the best imaging modality to demonstrate rib fractures and pulmonary lacerations. Occasionally, a patient presents with a spontaneous pneumothorax. Most often these are related to rupture of pulmonary blebs or bullae, which may occur in patients with COPD or cystic lung diseases; in some cases, no specific cause can be demonstrated.[130]

A chronic pneumothorax usually occurs in association with pleural effusion, resulting in a hydropneumothorax. Hydropneumothoraces are generally associated with surgical procedures, malignancy, or severe infections, such as empyema. A chronic pneumothorax strongly suggests the presence of a bronchopleural fistula, as gas-forming infection in the pleural space is rare (Figs. 28-69 and 28-70).[131]

Pleural Effusions

Fluid in the pleural cavity appears radiographically as a homogeneous opacity that generally occupies a dependent position. A small pleural effusion that is barely perceptible or is overlooked on the PA view is often readily apparent on the lateral radiograph as blunting of the posterior costophrenic sulcus. The best non-CT radiographic study for demonstrating small quantities of pleural fluid is the lateral decubitus view, with the suspected pleural effusion on the dependent side. Using this technique, as little as 25 mL of fluid can be detected. Larger pleural effusions usually blunt the lateral costophrenic sulcus on the PA radiograph as well.

US is highly sensitive to the presence of pleural effusions and can identify as little as 5 mL of free pleural fluid; the technique is also useful in assessing the fluid for degree of complexity (i.e., the presence of septations and loculations).[132]

Occasionally, pleural fluid remains between the diaphragm and the lung, that is, infra-pulmonary or subpulmonic, displacing the lung upward so that the lateral costophrenic angle remains sharp. The presence of a subpulmonic accumulation of fluid should be suspected if the diaphragm appears elevated, particularly along its lateral aspect on the frontal radiograph; if the costophrenic sulcus is blunted posteriorly; or if the gastric gas bubble is separated from the dome of the apparent left hemidiaphragm by more than a few millimeters. (The last finding is frequently normal, however.) CT is especially sensitive in identifying even the smallest of pleural effusions, which may be undetectable on chest radiographs. In the intensive care unit, where many portable radiographs are obtained in supine patients, CT imaging is particularly helpful in the diagnosis of pleural effusions, often revealing sizable effusions that are unsuspected.

Pleural effusions can be classified into two major categories: transudates and exudates. Transudates are characterized by low protein concentration relative to the plasma, and very low cellularity; exudates are characterized by higher protein concentration and cellularity, as discussed in detail elsewhere (Chapters 76 and 77). Transudative pleural effusions are commonly caused by congestive heart failure, volume overload in the setting of renal dysfunction, or ascites in the setting of hepatic failure. Rarely, they are due to connective tissue disease or metastatic neoplasm. Broad causes of exudative effusions include parapneumonic collections, pulmonary infarction, malignancy (metastatic or due to primary pleural neoplasms), connective tissue disorders, subdiaphragmatic inflammatory processes, and infections (including empyema). Obtaining a specific diagnosis usually requires extensive evaluation that includes CT or MRI, thoracentesis, and, possibly, pleural biopsy (Fig. 28-71).

Imaging modalities, particularly CT, may suggest, but not confirm, that an effusion is more likely a transudate or an exudate, thereby guiding patient management. Most transudates are bilateral, simple, non-loculated effusions occurring in dependent locations. Many exudates are unilateral, loculated effusions. A loculated effusion usually conforms to an unusual shape, commonly ovoid or with geometric edges, and sometimes along the fissures. Loculated effusions may resemble pulmonary masses on chest radiographs, although the pleural location can be readily ascertained on CT. The differential diagnosis of pleural effusions is one scenario in which US can be used to provide additional information beyond CT. For example, US may demonstrate internal septations within an effusion, a finding that can be difficult to demonstrate using CT and that is highly associated with exudative effusions. Furthermore, US can be used therapeutically to provide real-time guidance for thoracentesis and chest tube placement.[133–135] Conversely, US may occasionally fail to detect exudative pleural effusions, including empyemas, which are echogenic, and which are readily detected by CT.

Pleural Thickening, Nodules, and Masses

Pleural diseases that cause diffuse thickening or localized nodularity may be separated into three broad etiologic categories: inflammatory, infectious, and neoplastic (both benign and malignant). Specific subgroups that are commonly encountered, but rarely clinically relevant, include apical pleural thickening (apical capping),

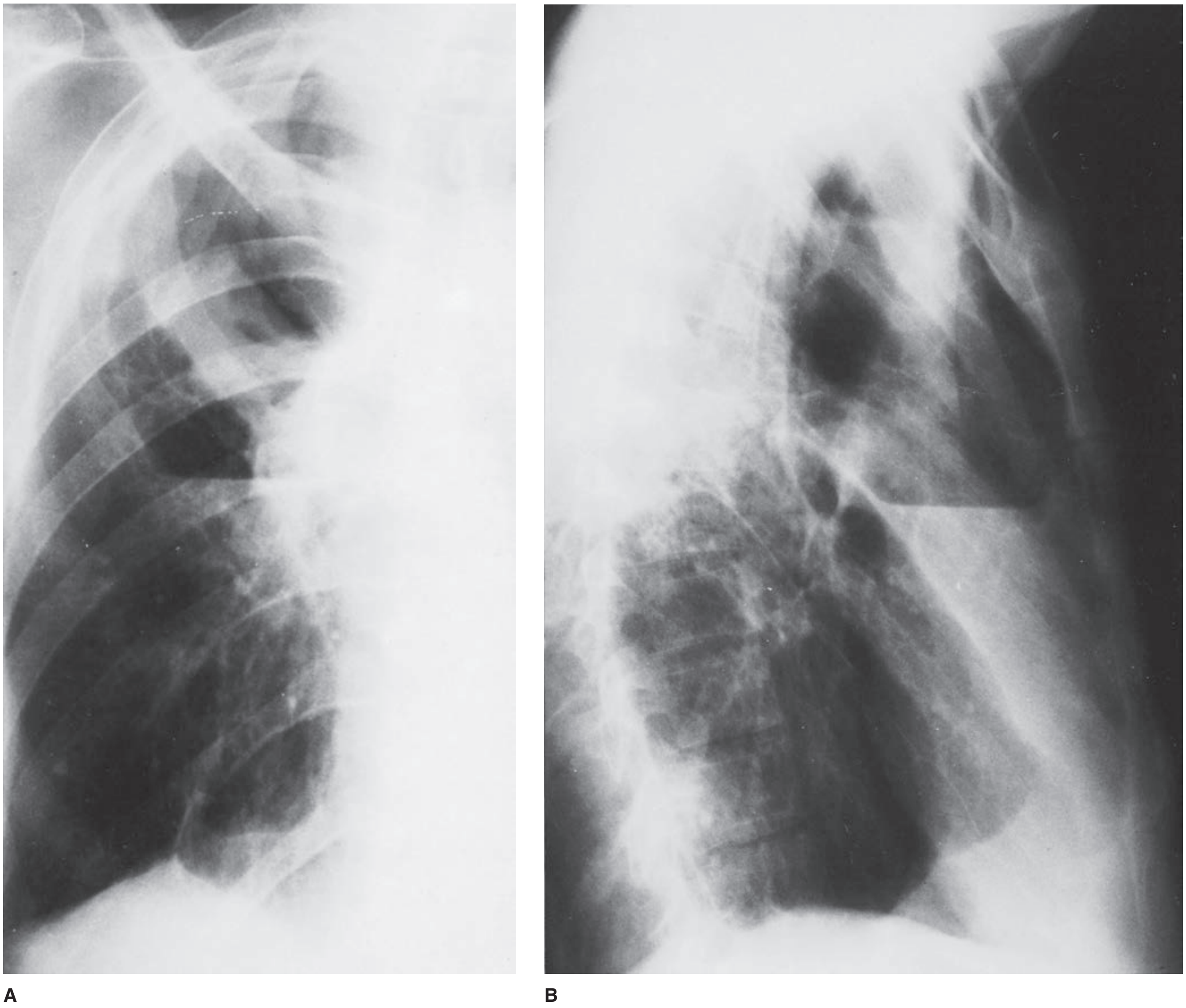


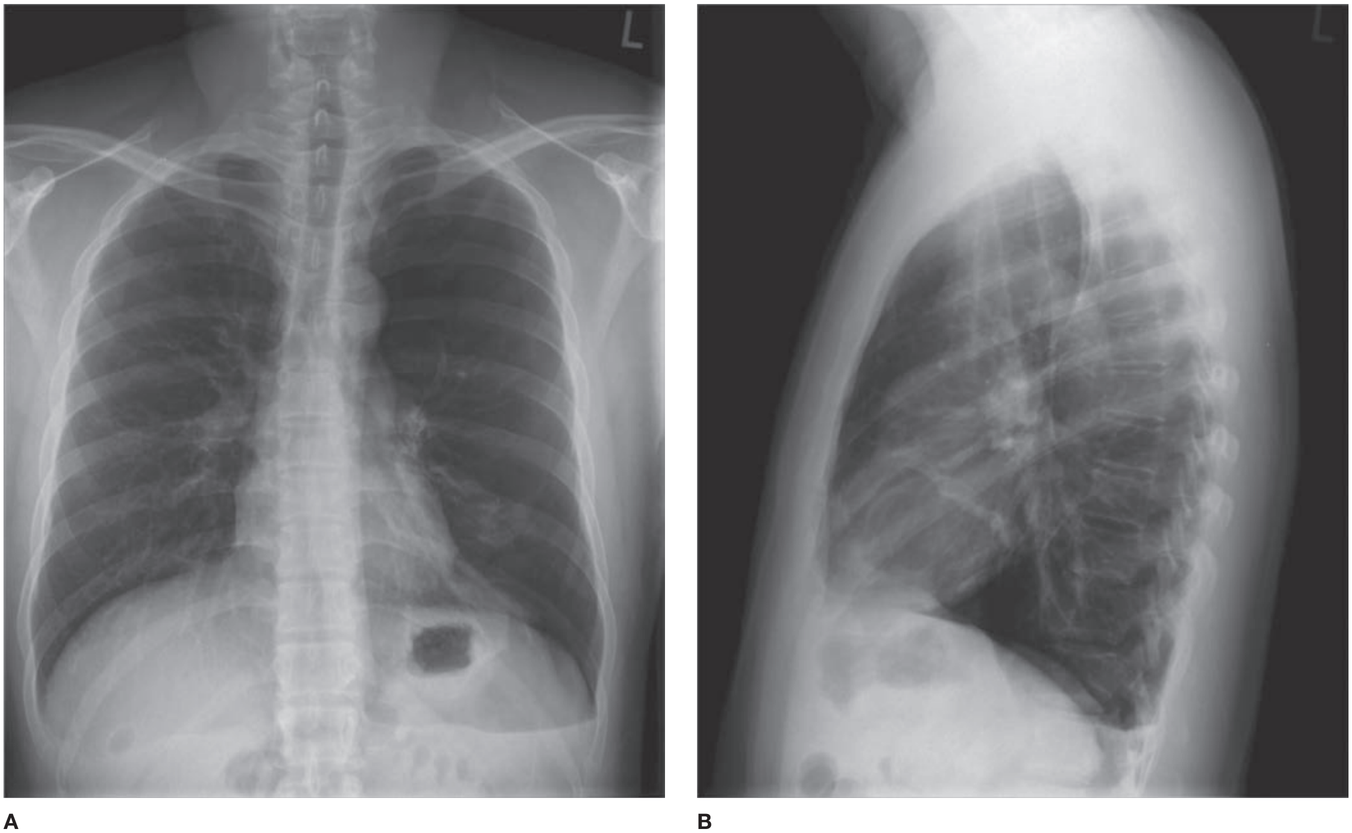
Figure 28-69 Hydropneumothorax. **A.** PA view. A distinct air–fluid level is seen overlying the right hilus. **B.** Lateral view. The fluid and air are anterior to the hilus. The findings are difficult to differentiate from a lung cavity, but the very thin edge suggests localization in the pleural space. This was a hydropneumothorax and was secondary to a postoperative bronchopleural fistula.

which is usually bilateral and age-related and usually idiopathic (attributed to age-related ischemic changes); however, apical capping may potentially be associated with sequelae of granulomatous infections, particularly if accompanied by apical parenchymal scarring. Blunting of the lateral costophrenic angle on the PA view with sparing the posterior costophrenic angle on the lateral may be attributed to post-inflammatory pleural thickening. Radiographic follow-up is helpful in excluding a focal mass. Multifocal pleural plaques, which are smoothly marginated, localized areas of pleural thickening, and which are often associated with calcifications, are common late manifestations of prior asbestos exposure. Frequently, they are the sole imaging manifestation of past asbestos exposure. CT is the optimal modality for their detection and characterization.

Diffuse pleural thickening involving both hemithoraces is more likely of inflammatory etiology, although bilateral pleural metastases can definitely occur and should be considered. Smooth pleural thickening measuring <5 mm in thickness with sparing of the mediastinal pleura is more suggestive of benign etiology. Unilateral, extensive pleural thickening is more suspicious for a malignant etiology, either pleural metastases or primary malignancy, such as pleural mesothelioma. Nodular thickening of the mediastinal pleura and involvement of the interlobar fissures are particularly correlated with a malignant etiology; as a rule, the more nodular the pleural thickening appears, the more likely a malignant process is its cause. The differential diagnosis includes empyema, particularly tuberculous empyema, which may be indistinguishable from mesothelioma based on imaging appearance. Imaging cannot distinguish mesothelioma, pleural metastases, and tuberculous empyema; tissue sampling and correlation with other clinical and laboratory findings are required.[136–139]

A special case to consider is extensive pleural thickening associated with calcifications and diminished volume of the adjacent lung parenchyma—a fibrothorax. Most fibrothoraces reflect sequelae of prior substantial pleural inflammation caused by empyema or hemothorax, and their clinical significance is due to their potential to impair chest wall mechanics and restrict lung expansion.

A localized pleural nodule suggests a benign pleural neoplasm, such as a solitary fibrous tumor of the pleura or lipoma. The nodule may be difficult to distinguish from a localized area of pleural thickening, but generally it is larger and more symmetric in contour. On CT, these nodules usually have a characteristic appearance: Their



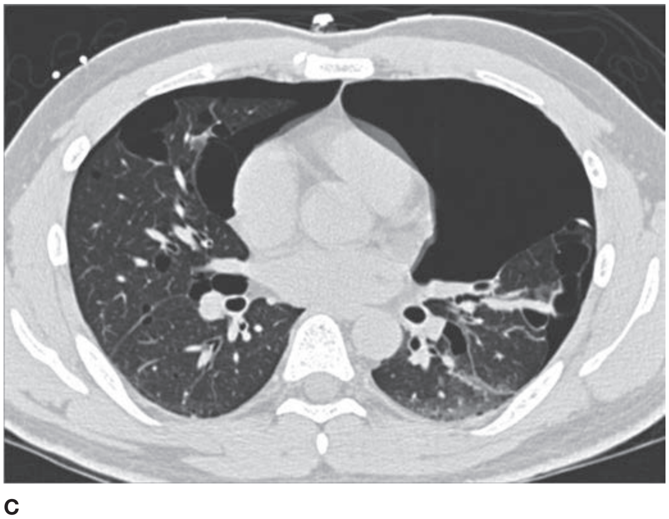


Figure 28-70 Bilateral pneumothoraces. (**A**) PA and (**B**) lateral chest radiographs demonstrate bilateral pneumothoraces, approximately 20% on the right and 40% on the left. The patient presented with spontaneous pneumothoraces. **C.** Axial CT at the lung bases confirms bilateral pneumothoraces and also indicates the etiology, demonstrating multiple pulmonary cysts. The patient was found to have Birt–Hogg–Dubé syndrome, a genetic disease that causes pulmonary cysts and predisposes the patient to recurrent spontaneous pneumothorax.

shape is ovoid with their largest diameter parallel to the chest wall, and their edges are flat and tapering. The appearance is similar to the extrapleural sign on chest radiographs, which is defined as a shadow that has smooth margins, has tapering edges with obtuse angles with the chest wall, and is generally seen well in only one of the two standard views of the chest. Occasionally, a peripheral nerve sheath tumor (e.g., schwannoma or neurofibroma) arising from an intercostal nerve may mimic a pleural nodule. These lesions, however, tend to cause indentation of adjacent ribs due to long-standing mass effect, helping to suggest the diagnosis.

Rarely, solitary or multiple pleural nodules without associated effusion may represent a malignant process; the classic example is the so-called "drop" metastases from thymic neoplasms.

DIAPHRAGMATIC DISEASES

Diaphragmatic evaluation can be performed initially via chest radiographs, ideally PA and lateral views. The normal hemidiaphragm has smooth contours and gentle curvature, with its dome near its center and no focal protrusions, with the left hemidiaphragm slightly lower than the right. The most common diaphragmatic abnormality is an eventration, in which there is focal weakness of the muscle, correlated with focal protrusion or bulge. Diaphragmatic paralysis should be suspected when an entire hemidiaphragm is elevated, typically >2 cm in comparison to the normal side. To confirm diaphragmatic paralysis, the standard test is a fluoroscopic dynamic evaluation ("sniff test"), in which the patient is imaged during shallow breathing, deep breathing, and forceful inspiration ("sniff"). The normal hemidiaphragm moves downward with the sniff maneuver, while a paralyzed hemidiaphragm will demonstrate paradoxical upward motion.

Diaphragmatic hernias can be classified into three broad categories: hiatal, congenital, and traumatic. Hiatal hernias occurring through the centrally placed esophageal hiatus are the most common, and usually contain a portion of the stomach, although very large

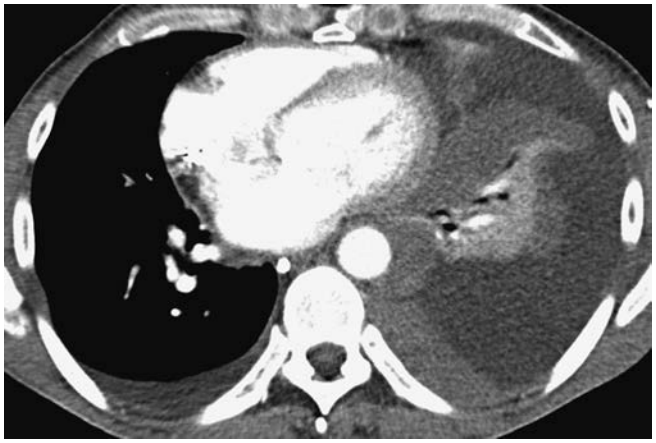


Figure 28-71 Malignant pleural effusion. Axial CT image demonstrates bilateral pleural effusions. The left effusion is associated with enhancing pleural masses, better visualized at the posterior medial costophrenic angle and adjacent to the descending thoracic aorta. This is characteristic of a malignant effusion. The patient was later diagnosed with mesothelioma.

hernias can contain small or large bowel loops as well. Congenital hernias are usually through the paired foramina of Morgagni (anterior and medial) or the paired foramina of Bochdalek (posterior and central). The latter are more frequent and are usually small, incidental hernias containing fat. When large, these congenital hernias can contain viscera, either bowel loops (Morgagni) or retroperitoneal structures such as the kidney (Bochdalek), but these are virtually always diagnosed in infancy. Traumatic hernias should be suspected in patients who had blunt trauma and present with a newly elevated hemidiaphragm. These are more common on the left, as the liver usually prevents herniation on the right except in very large defects. Traumatic diaphragmatic ruptures may occur in the setting of trauma without detectable herniation, and the actual herniation of abdominal viscera into the thorax may occur days, months, or even years later. Inquiry regarding a history of remote trauma is thus important in the evaluation of diaphragmatic hernias. Multiplanar coronal and sagittal CT or MRI images allow accurate assessment of diaphragmatic contour abnormalities and are the reference standard for the diagnosis of diaphragmatic rupture. MRI offers the additional advantage of functional assessment, with fast-gradient echo cine sequences optimally demonstrating diaphragmatic motion (Figs. 28-72 and 28-73).[140–144]

CHEST WALL MASSES

Chest wall masses may extend into the pleura and cause pleural nodularity or masses. These are very difficult to detect radiographically unless they cause bone destruction or substantial mass effect. US plays an important role in detection and characterization of superficial lesions, especially by differentiating cystic from noncystic lesions, as well as by assisting performance of percutaneous biopsies. CT or MRI provide a more comprehensive assessment. CT excels in assessment of lung and osseous structure involvement, while MRI offers superior contrast resolution of soft-tissue tumors, hematomas, and abscesses. Tissue sampling is generally necessary for accurate diagnosis. The differential diagnosis of chest wall masses includes soft-tissue infection (e.g., cellulitis, phlegmon, abscess), which is generally associated with trauma and surgical procedures; hematoma, also often associated with trauma or surgical procedures; extension of infection arising from the lung, the classic example of which is actinomycosis; and rarely, neoplasms, such as soft-tissue sarcomas, lymphomas, metastatic disease, and malignant nerve sheath tumors.[145,146]

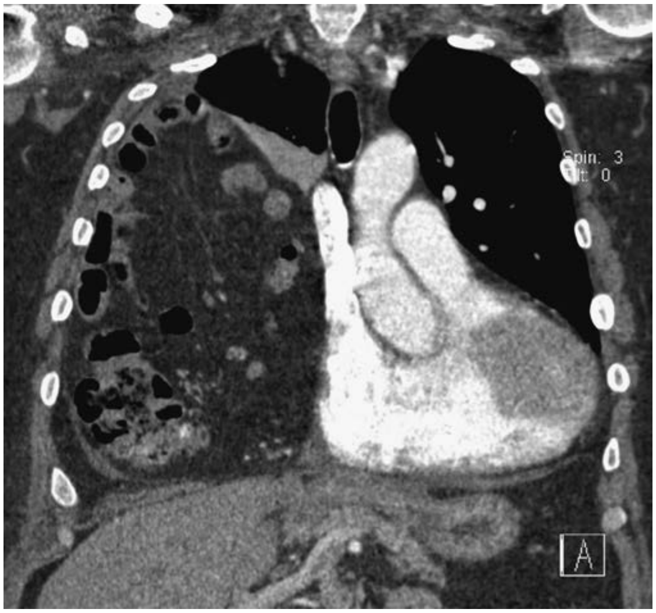


Figure 28-72 Diaphragmatic hernia. Coronal CT image demonstrates a wide defect in the right hemidiaphragm. The right lung is nearly completely collapsed, and the right hemithorax is nearly completely occupied by small and large bowel loops with associated mesenteric fat. This is diagnostic of diaphragmatic hernia, in this case due to blunt trauma to the abdomen.

MEDIASTINAL DISEASES

Mediastinal diseases encompass multiple systems, organs, and a vast array of differential diagnoses. Before discussing mediastinal diseases, it is necessary to define the contents of the mediastinum and its boundaries.

The anatomic delineations of "compartments" of the mediastinum are not defined consistently throughout the medical literature. For radiographic diagnosis, a simple classification has been employed: (1) The *anterior compartment*, which extends from the sternum anteriorly to the heart, aorta, and brachiocephalic vessels posteriorly, comprises only the thymus, fat tissue, and a few lymph nodes. (2) The *middle* or *visceral compartment* contains the heart,

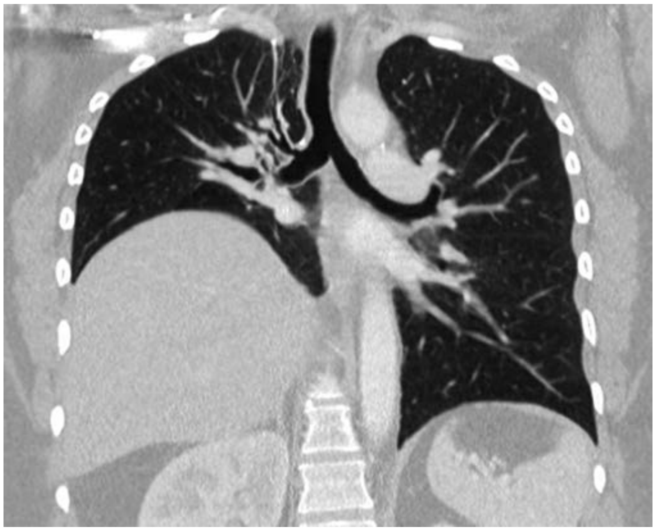


Figure 28-73 Diaphragmatic paralysis. Coronal CT image shows marked elevation of the right hemidiaphragm. Fluoroscopic examination confirmed a paralyzed right hemidiaphragm.

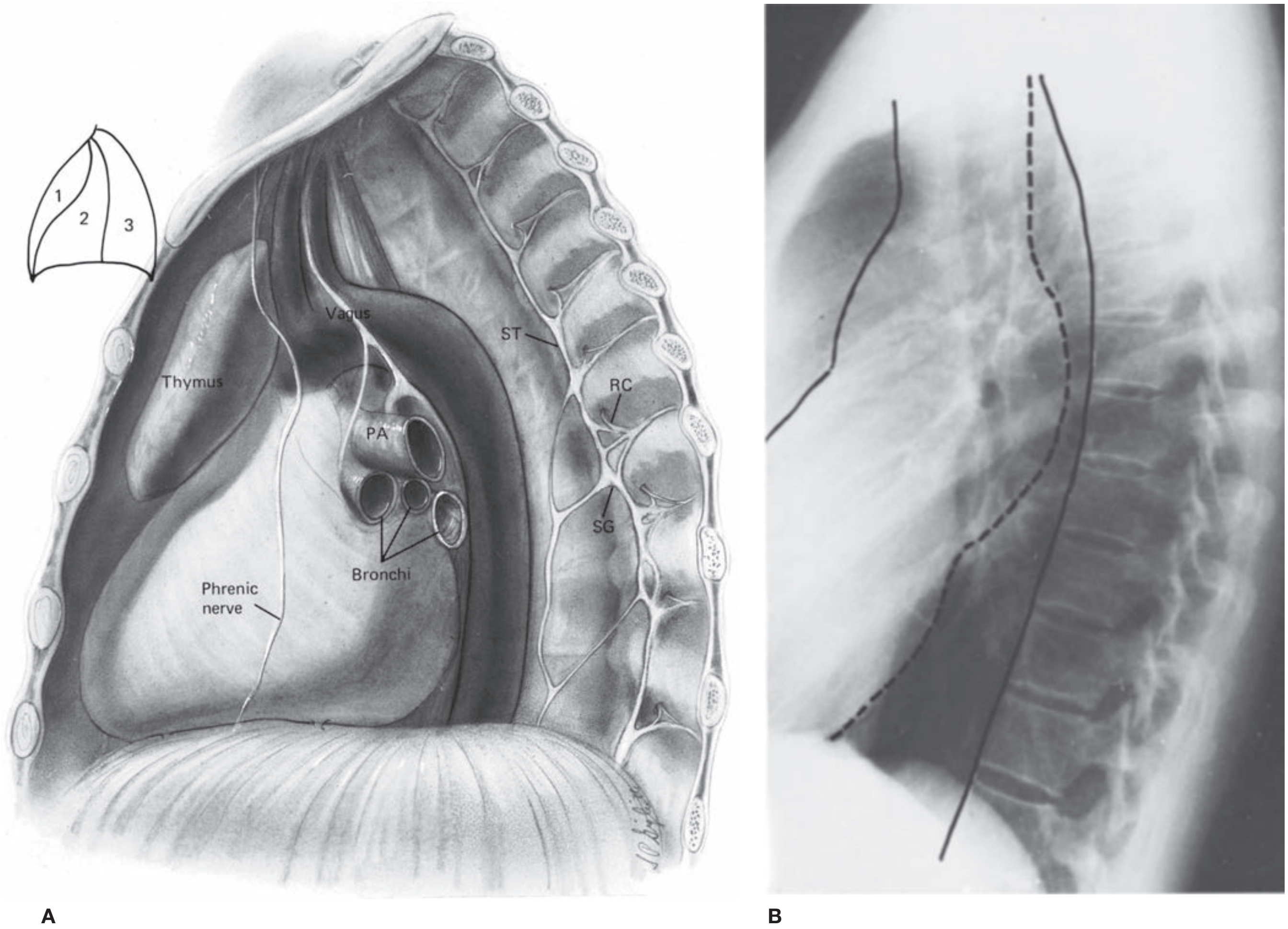


FIGURE 28-74 Compartments of the mediastinum: **A.** Anatomic view of the compartments of the mediastinum. The subdivisions (1, anterior; 2, middle; 3, posterior) in the small schematic *(top left)* correspond to those designated by the *solid black lines* in **B.** PA, pulmonary artery; RC, ramus communicans; SG, sympathetic ganglion; ST; sympathetic trunk. **B.** Radiographic division of the mediastinum. The *closed lines* delineate the anterior, middle, and posterior compartments. The *dashed line* represents the division of the middle and posterior mediastinum that is conventionally used by anatomists. ***(A:** Reproduced with permission from Fishman AP: Pulmonary Diseases and Disorders. New York, NY: McGraw Hill; 1980.)*

great vessels, trachea and its branches, esophagus, and descending aorta. It extends from the posterior border of the anterior compartment to the anterior border of the vertebral column. These boundaries differ from the anatomist's classification, which relegates portions of the esophagus and the descending aorta to the posterior mediastinum. (3) The *posterior compartment* contains the vertebrae and paravertebral sulci.

More recently, the International Thymic Malignancy Interest Group (ITMIG) has introduced a classification system based on CT anatomy, in which the mediastinum is also considered to have three compartments, with the thoracic inlet forming the superior border and the diaphragm representing the inferior border. These compartments are known as the perivascular, visceral, and paravertebral compartments. This classification scheme offers a more accurate approach to anatomic characterization of pathology (Figs. 28-74 and 28-75).[147,148]

This section focuses on diseases of the lymph nodes and thymus. Cardiac and systemic vascular diseases are beyond the scope of this textbook and will be mentioned only briefly. Pulmonary vascular diseases have been described previously. Esophageal diseases and spinal or paraspinal diseases are briefly discussed (Fig. 28-76).

Before a discussion on mediastinal neoplasms, it is important to emphasize the role of CT for evaluation of suspected mediastinal infections in the postoperative patient.

Mediastinitis is a catastrophic complication of multiple types of cardiothoracic surgeries and, if unrecognized and not treated aggressively, often leads to a fatal outcome. In the immediate postoperative period, after cardiac, central vascular, major pulmonary, or esophageal surgery, the presence of a small amount of gas and fluid in the mediastinum is an expected occurrence. The findings tend to subside within hours or a few days. While there is no absolute rule to apply to the time frame over which a pneumomediastinum or mediastinal fluid collection becomes clearly pathologic, some general guidelines are helpful in guiding management decisions: (1) It is expected that any postoperative fluid or gas collection will decrease in size over time, and any increase in size is suspicious for an evolving mediastinitis. (2) Large fluid and gas collections (those measuring >2 cm in the smallest diameter) are almost always pathologic. (3) Any persistent mediastinal fluid or gas collection >1 week following surgery is suspicious, and the index of suspicion rises if the patient is clinically worsening, if there are laboratory signs to support infection (e.g., leukocytosis with a left shift), and if there are CT features suggesting active inflammation, such as rim enhancement in the boundaries of the collection. Any of these findings should prompt aggressive management with percutaneous or surgical drainage of the collection and institution of broad-spectrum antibiotics.

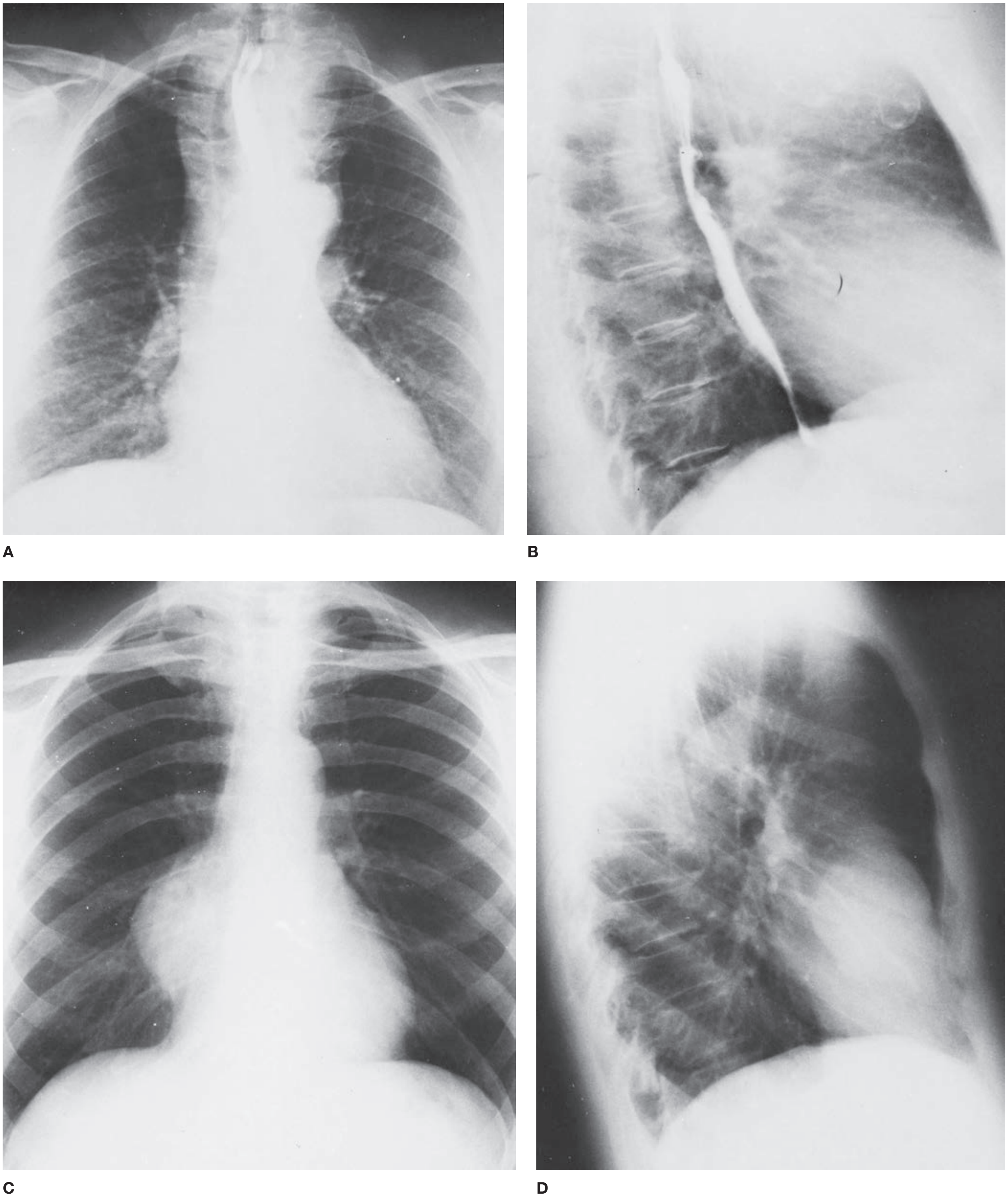


Figure 28-75 Radiographic spectrum of mediastinal masses: Substernal thyroid. **A.** PA view. A large mass in the neck extends below the clavicle. The trachea and esophagus are displaced to the right. **B.** Lateral view. The trachea and esophagus are also displaced posteriorly. Several calcifications are present within the mass. **C.** PA view. A discrete mass (thymoma) lies along the right heart border. **D.** Lateral view. The mass also overlies the anterior portion of the cardiac shadow. Despite being radiographically well circumscribed, the mass may be either invasive or noninvasive thymoma. CT is required for further characterization.

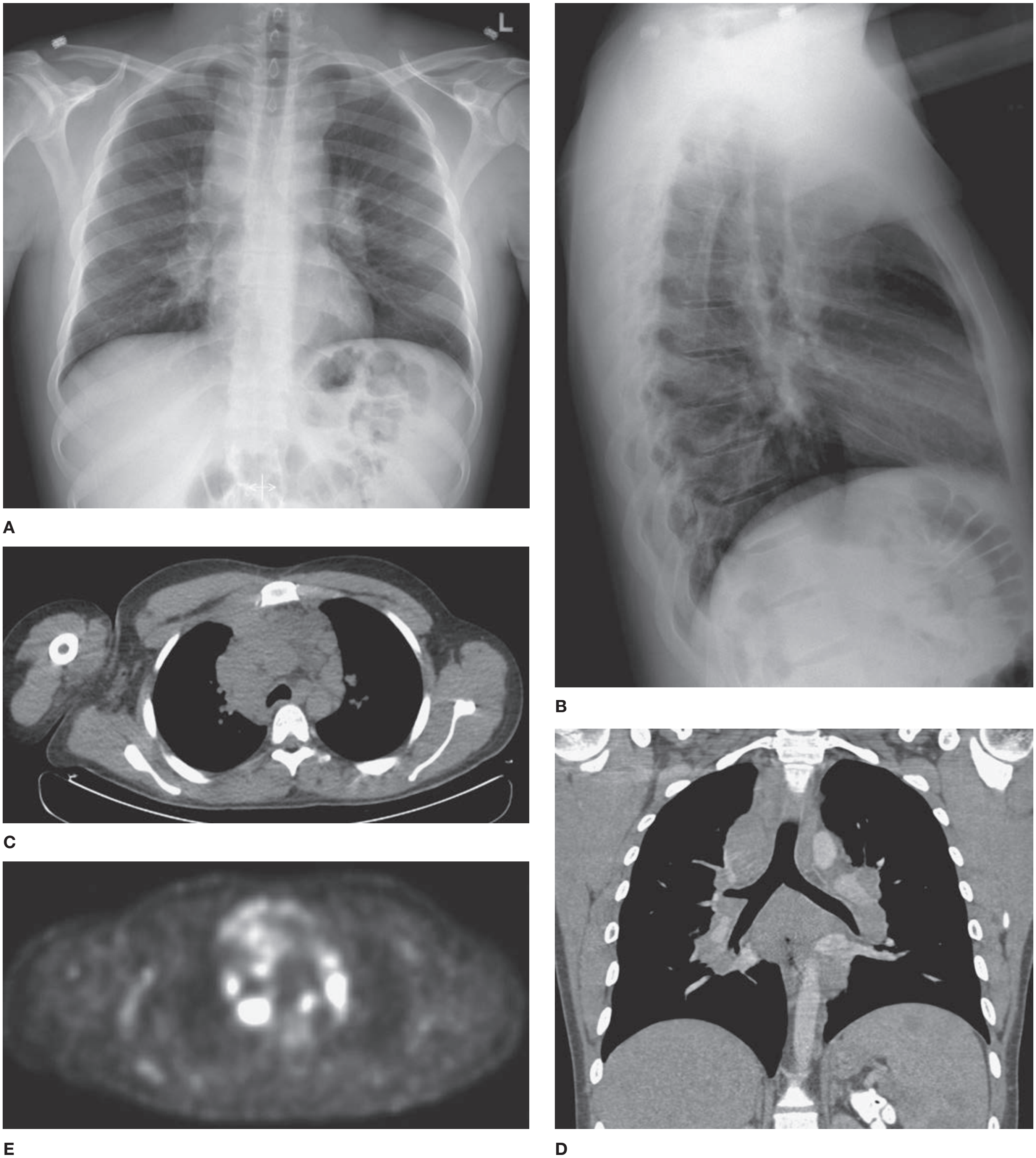


Figure 28-76 Lymphadenopathy: (**A**) PA and (**B**) lateral chest radiographs demonstrate marked widening of the bilateral paratracheal stripes and mild prominence of the bilateral pulmonary hila, compatible with mediastinal and hilar lymphadenopathy. (**C**) Axial noncontrast CT and (**D**) Coronal contrast-enhanced CT better demonstrate the extent of mediastinal and hilar lymphadenopathy. Pathology confirmed a large B cell lymphoma. **E.** Axial FDG-PET at the level of the upper lung fields demonstrates increased glucose uptake within the enlarged mediastinal lymph nodes, indicative of increased metabolic activity. This study can be performed to monitor treatment response.

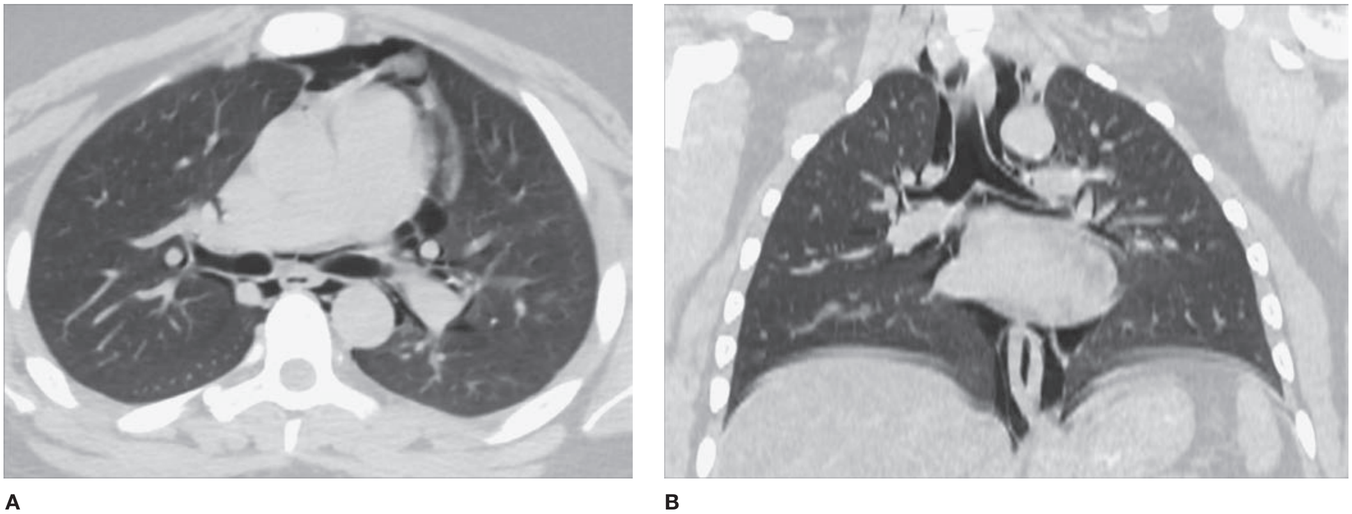


Figure 28-77 Pneumomediastinum. **A.** Axial CT at the level of the mainstem bronchi demonstrates gas within the anterior, middle, and posterior mediastinal compartments, compatible with pneumomediastinum. **B.** Coronal CT demonstrates the full extent of the pneumomediastinum. Note absence of pneumothorax. There is also subtle pulmonary interstitial emphysema, denoted by linear lucencies parallel to the proximal airways. This patient had barotrauma related to a severe asthma exacerbation.

A spontaneous pneumomediastinum has different clinical implications, as it may be a sign of an ominous condition, such as esophageal perforation (which warrants urgent surgical treatment), or a relatively benign condition when associated with barotrauma and tear of the distal airways or acini. Clinical correlation and careful clinical observation are very important to distinguish these etiologies (Fig. 28-77).[149,150]

The classic differential diagnosis of masses in the anterior compartment includes enlarged lymph nodes, substernal goiter or thyroid neoplasm, thymic hyperplasia and thymic neoplasms, and germ cell neoplasms. Distinction among these can be made on the basis of the patient's age and clinical presentation, their position within the anterior mediastinum, and the appearance on CT or MRI.

Thyroid masses invariably lie high in the anterior or middle mediastinum and often displace or compress the trachea and esophagus. On CT, the thyroid has characteristic high attenuation on unenhanced images due to its iodine content, and multinodular goiter often presents with a very heterogeneous texture containing cystic and calcified opacities within a background of dense thyroid parenchyma. Ultimately, any high anterior mediastinal mass with these imaging characteristics and unequivocal contiguity with the thyroid gland on CT or MRI is deemed to represent a thyroid neoplasm or multinodular goiter, until proved otherwise.[151]

If an anterior mediastinal mass does not arise from the thyroid, the differential diagnosis of germ cell neoplasm, thymoma, and lymphoma can be challenging using imaging; tissue sampling is almost always necessary. Nonetheless, some clinical and imaging features may suggest a specific diagnosis. For example, germ cell neoplasms tend to occur in younger patients and are often heterogeneous—in particular, CT demonstration of fat and calcification within an anterior mediastinal mass is diagnostic of a teratoma.[152] Teratomas may also contain cystic components. Thymic hyperplasia or neoplasms tend to conform to the triangular shape of the thymus (particularly benign thymomas, although invasive thymomas and thymic carcinomas may have a more irregular configuration). Thymomas tend to occur in older patients and may be associated with the diagnosis of myasthenia gravis. Because of the presence of intracellular lipids in the normal thymus, thymic hyperplasia can be distinguished from thymomas and infiltration by lymphoma using proton chemical-shift MRI; signal loss is noted in out-of-phase sequences (Fig. 28-78).

Noncomplex thymic cysts measure fluid attenuation and are smoothly marginated with thin walls and no internal IV enhancement or solid components on CT. MRI offers superior contrast resolution and confident characterization of complex cystic thymic lesions, which can appear of soft tissue density on CT due to proteinaceous or hemorrhagic component.

The histologic classification of thymic epithelial tumors was updated in 2015 by the World Health Organization (WHO). In addition, a TNM/AJCC classification was published in 2017, establishing a staging system for thymic neoplasms (including thymoma, thymic carcinoma, thymic neuroendocrine tumors, and combined thymic carcinoma). Several imaging features were suggested to better characterize and stage thymic malignancy. On CT and MRI, the presence of lobulated or irregular contours, as well as cystic or necrotic areas within the tumor, was found useful in differentiating early from advanced disease. Advanced imaging techniques utilizing perfusion characteristics on MRI and dual-energy CT, as well as iodine content on dual-energy CT and diffusion-weighted MRI sequences, enable differentiation of low- and high-grade neoplasms.[153,154]

Finally, lymphomas occur over a wide age range (with Hodgkin disease having a bimodal distribution) and are generally homogeneous on CT and MRI, unless previously treated (Figs. 28-79 and 28-80).[155,156]

In cases where imaging does not provide a definitive diagnosis, tissue sampling should be considered. Surgical biopsies offer the highest accuracy (approaching 100%) but are also associated with a significant complication rate (approaching 15%). If visible by US, a guided percutaneous biopsy has been shown to be a safe and efficient method to obtain tissue, and it has a reported accuracy of >90%. Furthermore, reported complication rates are lower compared with CT-guided biopsies. CT provides better visualization of deeper compartments, with an approximate reported overall accuracy of 90%. It is the most common method of image-guided biopsy in most institutions.[157–159]

Lymphadenopathy in the thorax has an extremely broad differential diagnosis, and its presence is best assessed using CT or MRI. Anatomically, the largest lymph nodal chains in the thorax can be divided into axillary, supraclavicular (which includes lower cervical chains), mediastinal, and bilateral hilar chains. Smaller chains include internal thoracic (mammary), anterior cardiophrenic (or paracardiac), and retrocrural. Mediastinal lymph node stations are further subdivided into prevascular, paratracheal (upper and lower,

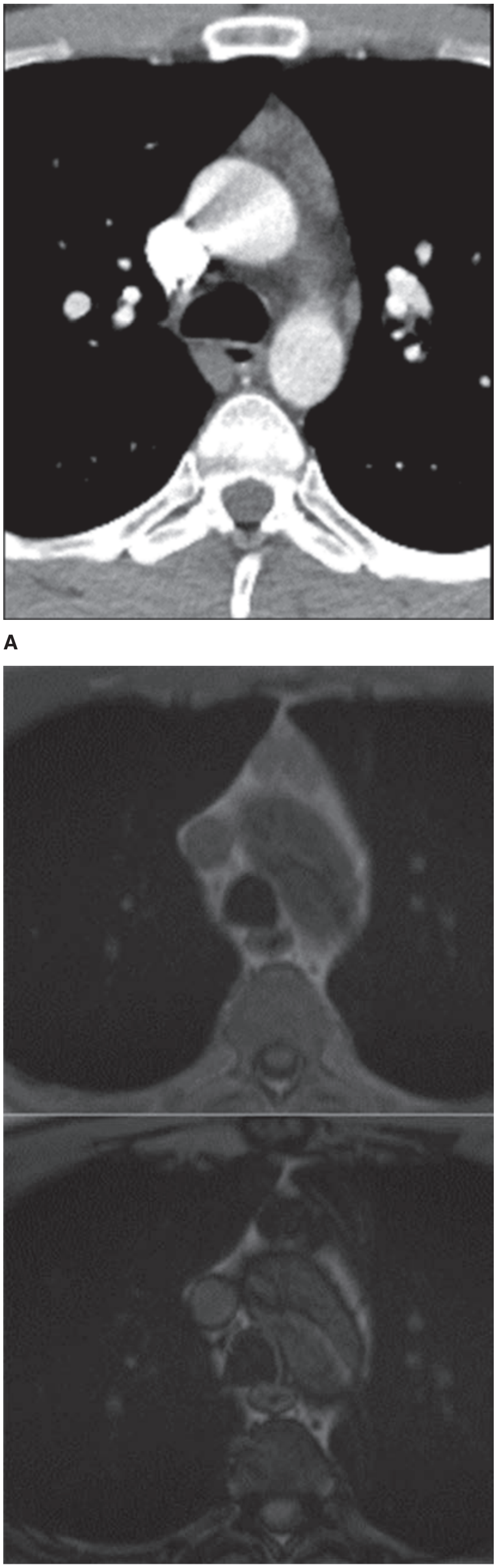


Figure 28-78 MRI allows confident diagnosis of an indeterminate anterior mediastinal lesion identified on axial CT image (**A**) using chemical shift MRI sequence (**B**). The lesion had an intermediate intensity on the in-phase MRI image (upper image) with subsequent >20% loss of intensity on the out-of-phase image (lower image) consistent with intracellular fat found in benign thymic hyperplasia.

right and left), subaortic (or AP window), subcarinal, para-aortic, and paraesophageal.

A normal lymph node on CT or MRI has an ovoid, reniform shape ("kidney shape") and a fatty hilum and measures <1 cm in its smallest diameter. An abnormal lymph node is frequently rounded, loses the delineation of the hilum, and measures >1 cm in its smallest diameter. It is important to emphasize that early neoplastic or infectious disease may be associated with "normal" lymph nodes on CT or MRI, but "abnormal" lymph nodes on CT or MRI are virtually never normal from a pathologic standpoint, even if the diagnosis is not clinically significant.

From an imaging perspective, establishing the etiology of mediastinal lymphadenopathy implies assessing the size, configuration, number, and location of the enlarged lymph nodes. Enhancement patterns on CT or MRI have a limited role, and FDG uptake on PET/CT may identify pathologic lymph nodes that do not meet pathologic size criteria on CT or MRI. The presence of calcification is also an important sign in narrowing the differential diagnosis.

The following guidelines should be utilized in the general assessment of mediastinal and thoracic lymphadenopathy.[160–162]

Very large (measuring >2–3 cm), confluent, conglomerate lymphadenopathy is malignant until proven otherwise. Considerations include nodal metastasis and lymphoma, particularly high-grade, large B cell lymphomas or Hodgkin disease. An anterior mediastinal, prevascular location favors lymphoma. Distribution of disease may help elucidate the origin of the primary neoplasm, in case the diagnosis is not obvious or previously established if one is cognizant of the typical lymphatic drainage pathways. For example, lung carcinomas present more frequently with ipsilateral hilar, subcarinal, and paratracheal lymphadenopathy; head and neck squamous cell carcinomas more often involve supraclavicular lymph nodes; breast carcinomas frequently involve ipsilateral axillary and internal thoracic lymph nodes; hepatocellular carcinomas usually involve anterior cardiophrenic lymph nodes (paracardiac nodes).

An increased number of nodes in disseminated lymphadenopathy, symmetric distribution involving multiple nodal stations, and moderately or substantially enlarged nodes suggest a low-grade lymphoproliferative disease, particularly chronic lymphocytic leukemia/small lymphocytic lymphomas (CLL/SLL). Note that early disease may present with only mildly enlarged lymph nodes.

Mild or moderately enlarged lymph nodes with a bilateral hilar and lower paratracheal distribution suggest the diagnosis of sarcoidosis.

Mild, bilateral, predominantly axillary lymphadenopathy can be seen in the setting of connective tissue diseases, such as systemic lupus erythematosus.

Mild disseminated lymphadenopathy can be seen in systemic infections, particularly "mono-like" syndromes caused by mononucleosis, CMV, and related infections.

Necrotizing lymphadenopathy may be seen in the setting of infectious lymphadenitis (particularly mycobacterial) but is also commonly seen in nodal metastasis.

Coarsely calcified lymph nodes, particularly mediastinal and hilar, suggest sequelae of granulomatous inflammation, including sarcoidosis and mycobacterial or fungal infection; however, treated malignancy and pneumoconiosis also should be considered in the differential diagnosis in the proper clinical setting.

Mild lymphadenopathy can be ascribed to a "reactive" etiology, including prior infections, congestive heart failure, or ILDs. Reactive lymphadenopathy is a diagnosis of exclusion.

Additional structures of the middle mediastinal compartment are the heart and central vessels. Aortic or aortic branch aneurysms can be suggested on chest radiographs by the presence of mediastinal widening and prominence of the aortic contours. Diagnostic confirmation and full characterization require CT or MRI, typically with intravenous contrast. Duplication cysts of the foregut may arise

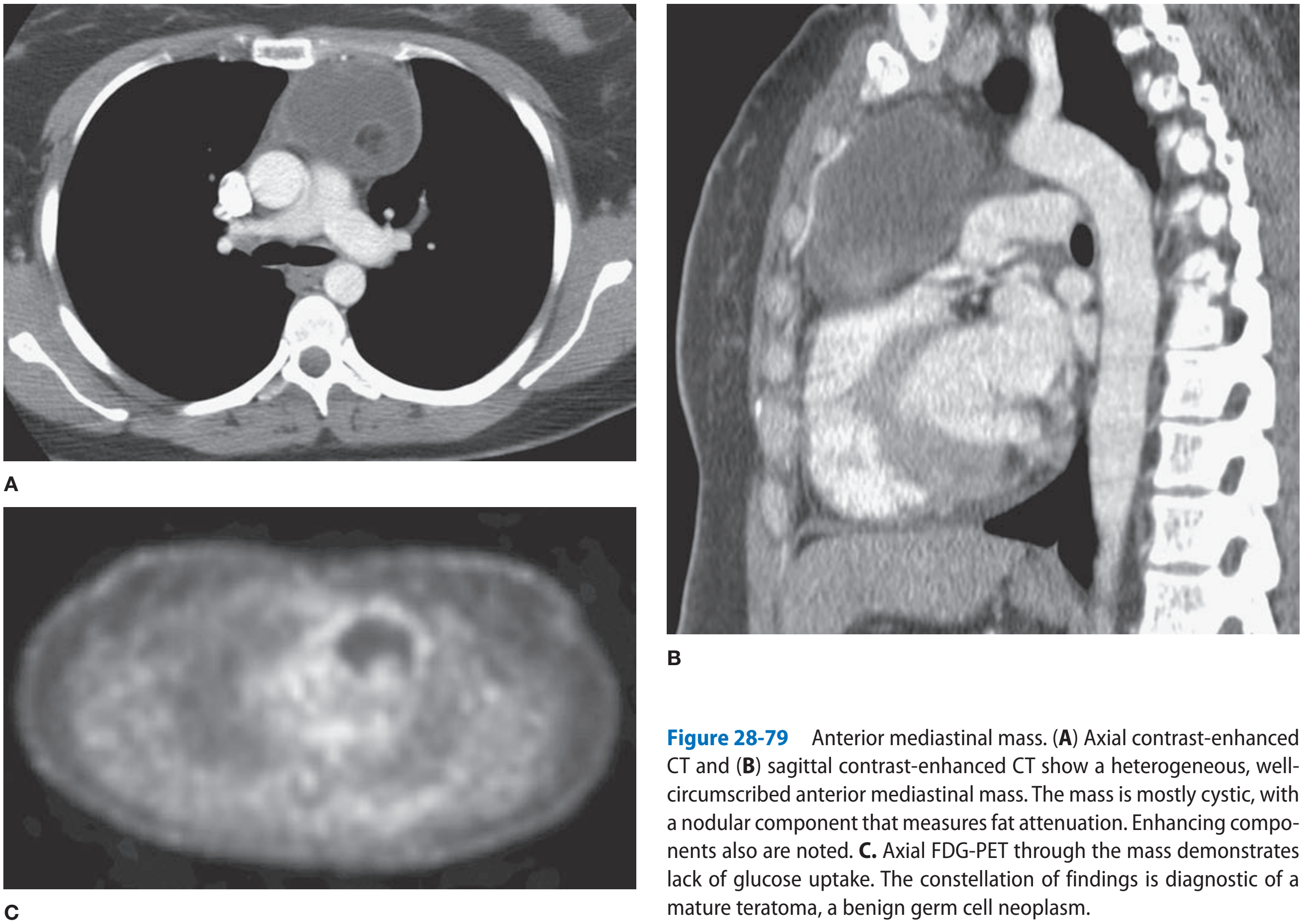


Figure 28-79 Anterior mediastinal mass. (**A**) Axial contrast-enhanced CT and (**B**) sagittal contrast-enhanced CT show a heterogeneous, well-circumscribed anterior mediastinal mass. The mass is mostly cystic, with a nodular component that measures fat attenuation. Enhancing components also are noted. **C.** Axial FDG-PET through the mass demonstrates lack of glucose uptake. The constellation of findings is diagnostic of a mature teratoma, a benign germ cell neoplasm.

from the esophagus or tracheobronchial tree and are also common in the middle compartment. These localized masses are smooth and well circumscribed; generally, they do not contain air, and their attenuation is low on CT (generally of simple fluid density) without contrast enhancement. However, duplication cysts containing highly proteinaceous fluid may have CT densities comparable to soft tissue, thus mimicking solid masses. As indicated earlier, MRI is useful in characterizing proteinaceous fluid and, thus, may be diagnostic in these cases. Bronchogenic cysts commonly occur at the tracheal carina or paratracheal region, whereas esophageal duplication cysts are characteristically located near the distal esophagus. However, esophageal and bronchogenic cysts may occur anywhere within the middle compartment.

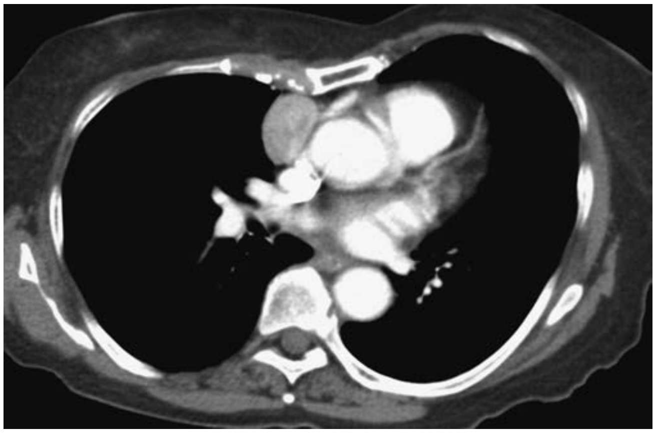


Figure 28-80 Anterior mediastinal mass. Axial contrast-enhanced CT demonstrates a homogeneous, enhancing, well-circumscribed anterior mediastinal mass along the anterior right heart border. Pathology confirmed a thymoma.

A dilated (patulous) esophagus is sometimes seen on the chest radiograph as a long tubular mass in the middle compartment and is readily identified by CT. The significance of a patulous esophagus is its association with dysmotility disorders, such as achalasia, CREST syndrome, and presbyesophagus. Neoplasms of the esophagus or trachea may also present as more localized mediastinal masses by chest radiograph; usually, CT is required for recognition. Early esophageal neoplasms may involve primarily the mucosa and may not be well seen on the CT, even if clearly demonstrated on a barium swallow study or endoscopy. Hiatal hernias are readily diagnosed using CT. The presence of esophageal wall thickening is usually clinically relevant. Smooth and concentric wall thickening favors esophagitis, particularly reflux esophagitis; irregular and eccentric wall thickening is concerning for esophageal carcinoma.[163]

In the posterior (paraspinal) compartment, the most common radiographic abnormalities are neurogenic neoplasms. However, neoplasms or infections of the vertebral column may also present as masses in the posterior compartment. CT or MRI usually distinguishes between a neurogenic neoplasm, which is unilateral and paraspinal in location, and lesions that erode or destroy the vertebrae and are generally present on both sides of the vertebral column. MRI is the best modality to diagnose a neurogenic neoplasm (Figs. 28-81 and 28-82).[164,165] Other considerations in the posterior compartment include paraspinal hematoma in the setting of trauma, and rarely, extramedullary hematopoiesis in patients with hemoglobinopathies, myeloproliferative disorders, or bone marrow infiltration.

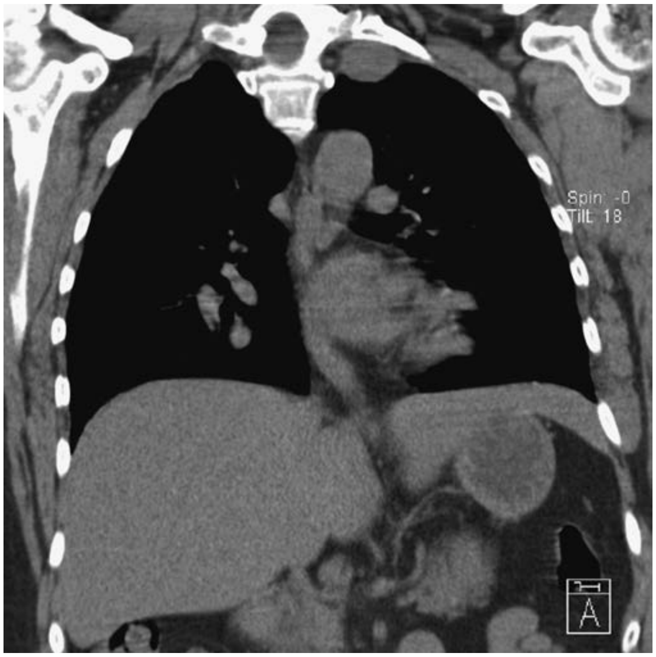


Figure 28-81 Posterior mediastinal mass. Coronal noncontrast CT shows a homogeneous, well-circumscribed posterior mediastinal mass in the left superior sulcus medially. Note absence of aggressive features by CT. Pathology confirmed a neurogenic neoplasm (schwannoma).

OUTLOOK FOR THE FUTURE

This chapter provides a modern, evidence-based overview of the wide scope and central role imaging plays in the diagnosis and management of thoracic diseases. Currently, it is inconceivable to imagine practicing thoracic medicine and surgery without the constant support of radiologist consultants and their armamentarium of basic and advanced imaging modalities.

Predicting the long-term future is most often a futile endeavor. However, there are clear trends that allow us to attempt to forecast likely innovations and changes in the field of thoracic imaging over the next decade.

The most important trend is demonstrating that imaging-based diagnostic and therapeutic approaches are beneficial to patient care, improving morbidity and mortality, while decreasing the overall cost of care. This trend is imposed by the current global economic environment and the mandate to increase the efficiency of healthcare systems by diminishing waste and redundancy and eliminating procedures that do not positively impact patient outcomes. Future clinical trials will emphasize what imaging can offer to empower practitioners to diagnose thoracic diseases earlier, faster, and in a less invasive manner. In addition, studies will address delivery of therapeutic approaches that will be more effective and less costly and contribute to better patient outcomes and quality of life.

The introduction of artificial intelligence (AI) has heavily influenced research trends in radiology in the last decade. Early clinical applications of AI in imaging generally, and thoracic imaging specifically, have already been implemented across the globe. Efforts have been made to develop automatic and semiautomatic methods to detect and characterize imaging pathology. In addition, the building of predictive imaging tools to streamline patient care using deep learning have resulted in early detection of pulmonary nodules and interstitial lung disease on CT, or pneumothorax on chest radiography. The evolving field of radiomics offers the possibility of identifying imaging features not visible to the human eye, and using them to predict treatment response in lung cancer or assessment of the aggressiveness of subsolid pulmonary nodules noted on CT. The field of AI will likely continue to evolve and become a useful tool in the radiologist's toolbox in improving patient care and outcomes.[166,167]

Another important trend is combining functional and anatomic information within a single imaging modality. PET/CT already offers this capability by coupling anatomic and metabolic imaging. CT, when performed with 4D cine sequences, may provide insight into chest wall, central airway, and lung mechanics, and may detect air trapping related to small airway disease. Dual-energy CT can provide further insight regarding perfusion dynamics and material characterization of lesions. It is likely that with continuous advancement of MRI hardware and sequences, MRI will finally become an integral part of imaging of lung parenchyma, noting that improving quality of DWI sequences will likely contribute to functional assessment of mediastinal and lung pathology.

We expect that increasing availability of hand-held US devices will impact the way patients are evaluated, particularly in the emergency department, where US may possibly surpass chest radiography as the main imaging tool for certain situations, e.g., evaluation

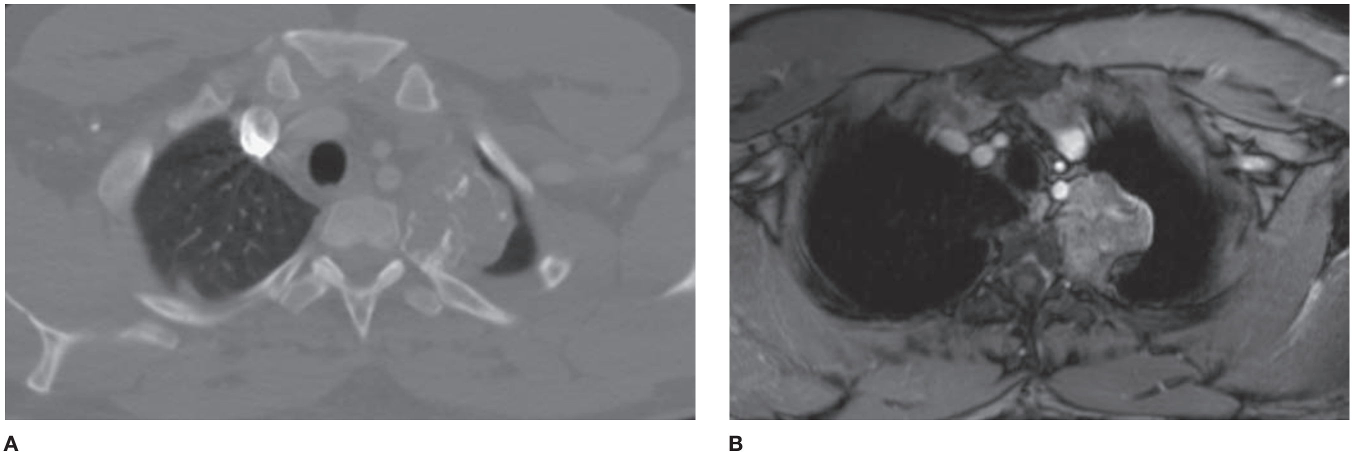


Figure 28-82 Posterior mediastinal mass. **A.** Axial noncontrast CT demonstrates a large left posterior mediastinal mass that appears to arise from the left posterior second rib, which demonstrates expansion and cortical destruction. Note irregular calcifications within the mass. **B.** Axial T1-weighted postcontrast MR shows moderate enhancement throughout the lesion. The constellation of findings suggests a primary bone neoplasm with chondroid differentiation. Pathology confirmed a chondrosarcoma.

of pleural pathology and detection of peripheral parenchymal lung disease.

Thoracic oncology will greatly benefit from new molecular imaging agents that target important cellular and subcellular biochemical pathways associated with carcinogenesis. Furthermore, molecular imaging will allow in vivo real-time assessment of the genetic and epigenetic processes underlying a number of pathologic conditions in the heart, lungs, and mediastinum, leading to more targeted, individualized, and, ultimately, effective therapeutics.

Quantitative imaging will be another trend that aims to provide a much better assessment of disease severity, particularly for diffuse lung diseases, such as COPD and ILD. Instead of simply reporting the presence of a specific disease and, at most, subjectively classifying the severity of the disease, radiologists will utilize computational image analysis tools to provide accurate disease quantification that reflects, and highly correlates with, physiologic metrics. Quantitative imaging utilizing computer-assisted detection and quantification of disease-specific imaging patterns on CT, MRI, and PET/CT will, therefore, allow development of biomarkers that will reflect disease prognosis and response to therapies far more accurately and earlier then currently possible. Future drug trials will particularly benefit from this approach.

Finally, it is of interest to consider what role plain chest radiography will play in the future, if any. Practical and economic considerations suggest that chest radiographs will not disappear soon, given their low cost, very low radiation dose, universal availability, portability, and capacity to address basic clinical questions. As we already witnessed during the COVID-19 pandemic, the information extracted from chest radiographs will likely be enhanced by AI, thereby adding value to differential diagnosis, prognostication, and patient management.

Beyond the technologic advancements in imaging, computer hardware, and software, an ongoing trend of simplifying patients' access to their medical information and better understanding of the imaging reports, by both the patient and referring physician, will continue to be emphasized in the near future. Actionable structured radiology reports that (1) integrate relevant clinical and laboratory data, (2) compare current to prior findings and convey the findings of the examination accurately and clearly lead to the appropriate intervention and/or follow up examination in a safe and timely manner, and (3) are integrated into the electronic medical record are now recommended by both the American College of Radiology and major European societies. With better IT support and widespread access to electronic medical records, this type of reporting will likely become the standard of care.

Irrespective of the many uncertainties, challenges, and exciting prospects for the future, it is undeniable that thoracic imaging will continue to be an indispensable companion to the practicing physician caring for patients with thoracic disorders and a central component of modern pulmonary medicine.

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CHAPTER 29

Thoracic Ultrasonography

Andrew Weber
Fiore Mastroianni
Paul H. Mayo

INTRODUCTION

Thoracic ultrasonography is a readily available, noninvasive imaging method that is useful for pulmonary and critical care specialists. The technique is easy to learn and has multiple applications related to lung and pleural disease. The ease of use and portability of ultrasonography allows physicians to perform point-of-care imaging and reduce dependence on other thoracic imaging techniques, such as chest computed tomography (CT) and standard radiography (CXR).

This chapter focuses on use of ultrasonography for diagnosis and management of pleural and lung diseases that are of particular interest to the pulmonary specialist. The chapter is written with the understanding that the pulmonary consultant will personally perform image acquisition, interpret the image, and apply results at the bedside; this is a paradigm that is different from standard thoracic imaging, which requires the pulmonary specialist to rely on the radiology service to acquire and interpret the imaging study. While point-of-care thoracic ultrasonography (POCUS) is advantageous regarding cost and clinical efficiency, it requires acquisition of additional technical skills and knowledge by the pulmonary specialist. An advantage of clinician-performed POCUS is that it couples imaging results with the clinician's overall knowledge of the case. Thoracic ultrasonography is not performed in isolation; rather, it is combined with other key elements of clinical evaluation, such as the history, physical examination, and laboratory analysis, and it can be performed serially with ease.

TRAINING IN THORACIC ULTRASONOGRAPHY

The goal of thoracic ultrasonography training is to establish clinical competence in performing and interpreting ultrasonographic images. The Statement on Competence in Critical Care Ultrasonography provides a well-defined description of training goals in pleural and lung ultrasonography.[1] The Statement is a good starting point for pulmonary specialists who seek training in the field, and the competencies outlined should be their initial learning objectives.

No definitive literature is available to guide the optimal duration of training or the minimal number of studies to be performed and interpreted to achieve competence in thoracic ultrasonography; several professional societies offer formal training. Compared with the training required in cardiac and abdominal ultrasonography, training in thoracic ultrasonography is more straightforward. The authors have experience in training fellows and attending physicians in thoracic ultrasonography and have found that a motivated learner will achieve skill in the basic elements of pleural and lung ultrasonography with several hours of formal teaching. Training should include practice at image acquisition, initially focused on healthy human models and then on patients at the bedside. In addition, training should include the review of a comprehensive image set of normal and abnormal studies, enabling the learner to recognize a wide range of findings when they encounter them at the bedside. The cognitive elements of the field may be learned through reading chapters or review articles.[2–4] For more advanced training, comprehensive textbooks are available.[5,6] It is useful for the learner to identify a local expert who is able to help with bedside training and image review.

EQUIPMENT NEEDS

Thoracic ultrasonography may be performed using a wide variety of ultrasonography machines. Machines that are used for cardiac or abdominal ultrasonography generally provide adequate image quality. A probe designed for cardiac ultrasonography, employing a frequency range of 3.5 to 5.0 MHz, works well. The small footprint of the probe allows for easy placement between rib interspaces, and frequency selection allows for adequate penetration to enable imaging the deeper structures of the thorax. The larger curvilinear abdominal probe provides adequate images as well. A linear vascular probe, using a frequency range of 7.5 to 10.0 MHz, is required for detailed imaging of the pleural surface. The higher frequency improves the resolution, but at the sacrifice of signal penetration.

Every machine has its own performance characteristics. The operator must adapt machine setup to optimize image quality. What works well using one machine may not work well when using another. Some machines have presets for thoracic ultrasonography, but they may not necessarily be the optimal setup for thoracic imaging. Consequently, the operator must be prepared to alter machine settings from standard cardiac, abdominal, or thoracic presets. For instance, high-end cardiac echocardiography machines give excellent cardiac image quality, but they often yield poor near-field images. Many modern portable machines have acceptable thoracic imaging capability and provide the additional advantage that they are designed specifically for point-of-care scanning. In recent years, low-cost, pocket-sized, ultraportable machines with internet connectivity have become available. The authors have observed that some these models yield serviceable thoracic ultrasonography images.

SCANNING TECHNIQUE

For the pulmonary specialist, thoracic ultrasonography may be performed with the patient in a seated position. The supine scanning position is more typical for the critically ill patient, but it has the disadvantage of concealing the posterior chest from interrogation. The standard transducer orientation is with the transducer indicator oriented in a cephalad position, defining the primary scanning plane in a longitudinal axis. With the screen indicator placed to the left of the screen, images on the left side of the screen represent cephalad structures.

Machine control is integral to good-quality image acquisition; hence total, near, and far field gains must be adjusted for optimization of the image. Depth should be set to place the structure of interest in the middle of the screen, and the focal point should be adjusted for optimal image quality of the target structure. Using adequate ultrasonography coupling gel and application of firm pressure, the transducer is applied perpendicular to the chest wall and adjusted to examine the rib interspace. Adjacent interspaces are examined by sliding the transducer to the next interspace. In this way, the examiner performs a scan line while the transducer is moved over the chest wall. In an orderly fashion, multiple adjacent scan lines are performed so that the entire chest wall can be imaged. Using this approach, the examiner obtains multiple, two-dimensional, tomographic ultrasonography planes of the thorax, in effect developing a three-dimensional model of the thorax. If a focal abnormality is identified, the examiner performs a more detailed examination of the area.

Aerated lung blocks ultrasonography, whereas the liver and spleen do not. Consequently, to visualize the peridiaphragm area, the transducer may be angled such that the scanning plane passes through the liver or spleen to obtain an adequate image window. Bone also blocks ultrasonography. So, when an abnormality lies deep to a rib, the transducer may need to be angled to look over or under the rib for proper visualization. Pleural effusions and consolidated lung each transmit ultrasonography. Their presence may yield a window for examination of the heart, mediastinum, or, in the case of pleural effusion, the lung. While the standard scanning plane is longitudinal, a transverse plane may be utilized on occasion. This may be required when examining the pleura for a "lung point" or to establish an optimal angle for needle insertion for access to a lung mass.

PLEURAL ULTRASONOGRAPHY

Ultrasonography is particularly effective for identifying pleural fluid, since fluid is either anechoic or hypoechoic relative to adjacent soft tissue. While physical examination is neither specific nor sensitive for detection of pleural effusion,[7] a pleural effusion as small as 5 cc may be identified with ultrasonography.[8] Pleural ultrasonography is superior to standard chest radiography in identifying pleural effusions and in differentiating a pleural effusion from pleural thickening or lung consolidation.[7,9] Compared with chest CT, pleural ultrasonography demonstrates 93% sensitivity and specificity for identification of pleural effusion.[10] When a patient has complete opacification of one hemithorax on CXR, ultrasonography has 95% sensitivity for identification of pleural effusion.[9]

■ Identification of Pleural Fluid

The pulmonary specialist will generally examine the patient in the seated position. Pleural fluid, unless loculated, distributes by gravitational effect to the most dependent part of the thorax. Therefore, the ultrasonography examination focuses on the lower dependent area of the posterior thorax.

The examiner seeks to identify three characteristic findings indicating the presence of a pleural effusion: (1) An anechoic or hypoechoic space that is surrounded by typical anatomic boundaries defines the pleural effusion (Video 29-1). (2) The typical anatomic boundaries, including the chest wall, lung surface, and diaphragm (Fig. 29-1). The heart may form an anatomic boundary on the left side. Recognition of the diaphragm requires definitive identification of the subdiaphragmatic organs such as the liver, spleen, and kidneys in order to distinguish pleural effusion from ascites (Video 29-2) (Fig. 29-2). (3) The dynamic changes typical of a pleural effusion, such as lung movement, diaphragm movement, and mobility on echogenic elements within the effusion (Video 29-3).

Video 29-1 Typical anatomic boundaries that surround a hypoechoic pleural effusion: chest wall, surface of lung, and diaphragm. The image was obtained using a 3.5-MHz transducer. The transducer was in longitudinal orientation and placed perpendicular to the chest wall to scan through the seventh intercostal space in the right midaxillary line. *Video available on AccessMedicine.com.*

Video 29-2 Pleural effusion above the diaphragm, subphrenic ascites below the diaphragm superior to liver, hepatorenal space, and kidney. These structures must be positively identified before proper identification of a pleural effusion, subphrenic ascites, or both can be made. The image was obtained using a 3.5-MHz transducer. The transducer was in longitudinal orientation and placed perpendicular to the chest wall to scan through the eighth intercostal space in the right midaxillary line. *Video available on AccessMedicine.com.*

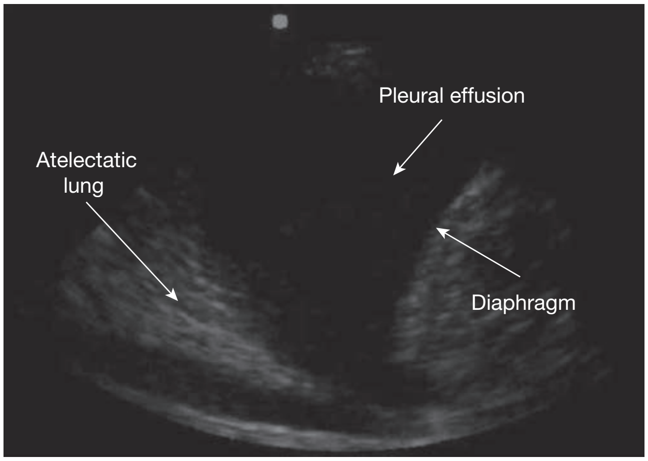

Figure 29-1 Typical anatomic boundaries that surround a hypoechoic pleural effusion. The image was obtained using a 3.5-MHz transducer. The transducer was in longitudinal orientation and placed perpendicular to the chest wall to scan through the seventh intercostal space in the right midaxillary line.

Usually, pleural fluid is hypoechoic relative to the liver or spleen. However, complex pleural effusions may demonstrate echogenicity similar to these organs. The chest wall, as a "stationary" structure, does not show dynamic changes with respiration. Lung that is adjacent to, or surrounded by, pleural fluid is compressed by the pleural effusion and is consequently airless. The atelectatic lung, which is of tissue density and presents a pattern of alveolar consolidation on ultrasonography examination, is visualized as "floating" in the pleural fluid. It moves in both a cardio- and respirophasic fashion. This is one of the typical dynamic changes useful for identification of pleural effusion. Other typical dynamic changes include those of swirling debris or fibrin strands agitated by respiratory or cardiac motion. On occasion, a highly cellular pleural effusion may develop an echogenic layer as more and less dense components separate over time and with immobility.

Inadvertent subdiaphragmatic device insertion into the spleen or liver is a dangerous complication of thoracentesis, so identification of the diaphragm is required for localizing a pleural effusion

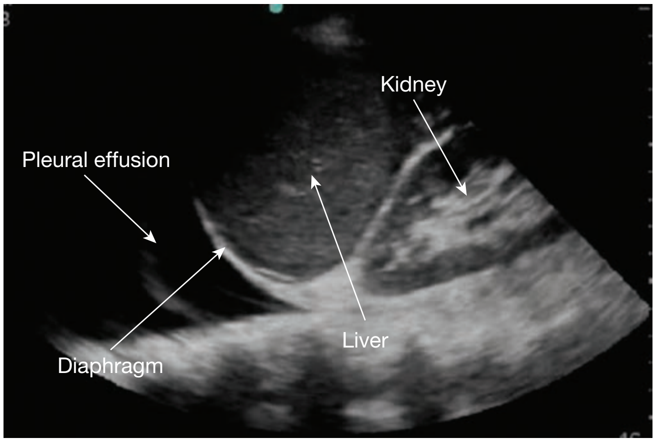

Figure 29-2 Pleural effusion above the diaphragm, liver, hepatorenal space, and kidney. These structures must be positively identified before thoracentesis to avoid inadvertent subdiaphragm device insertion. The image was obtained using a 3.5-MHz transducer. The transducer was in longitudinal orientation and placed perpendicular to the chest wall to scan through the eighth intercostal space in the right midaxillary line.

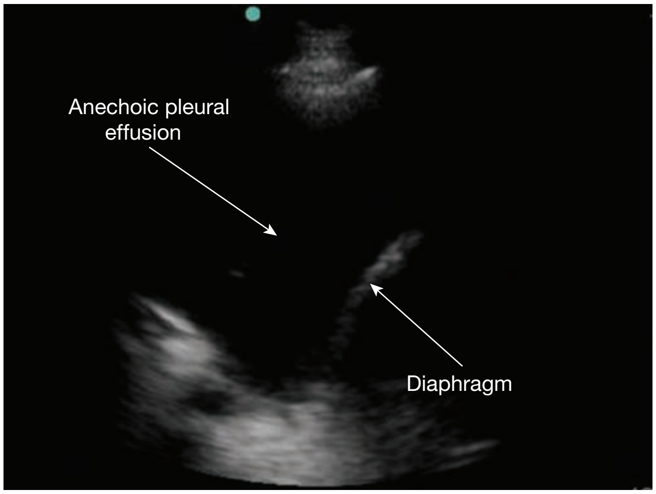

Figure 29-3 Anechoic pleural effusion, likely a transudate. The image was obtained using a 3.5-MHz transducer. The transducer was in longitudinal orientation and placed perpendicular to the chest wall to scan through the sixth intercostal space in the right midaxillary line.

and enabling safe performance of thoracentesis. The diaphragm, having respirophasic movement, is a hyperechoic curvilinear structure superior to the liver and spleen. The inexperienced operator may mistake the hepatorenal or splenorenal space for the diaphragm, as they are hyperechoic curvilinear structures. The overlying spleen or liver may then be mistaken for an echogenic pleural effusion. This may result in inadvertent subdiaphragmatic device insertion while attempting a thoracentesis, with potentially catastrophic consequence to the patient. It is helpful to identify the kidney when scanning below the diaphragm to avoid this dangerous pitfall. Identification of the chest wall allows measurement of the depth required for needle penetration when planning thoracentesis. Identification of the underlying lung allows the operator to limit the depth of needle insertion to avoid visceral pleural laceration.

■ Characterization of the Pleural Effusion

Ultrasonography may have utility in distinguishing transudative from exudative effusions; however, it is not sufficiently reliable to distinguish between the two.[11] Transudates often lack constituents that are ultrasonographic reflectors and are, therefore, anechoic (Video 29-1) (Fig. 29-3). Some pleural effusions may have a complex, non-septated pattern with slow flowing movement of ill-defined heterogeneous elements within a hypoechoic effusion, referred to as *swirling*.[12] These swirling effusions may be observed with a transudate; however, their presence suggests an exudative cellular effusion that can be associated with malignancy or infection.[13]

Video 29-3 Dynamic findings typical of a pleural effusion, including movement of homogenous echogenic elements within the effusion. The image was obtained using a 3.5-MHz transducer. The transducer was in longitudinal orientation and placed perpendicular to the chest wall to scan through the sixth intercostal space in the right midaxillary line. *Video available on AccessMedicine.com.*

Video 29-4 Multiseptated pleural effusion. This pattern is consistent with a complex parapneumonic effusion or empyema that will likely require fibrinolytic treatment or surgical drainage. The image was obtained using a 3.5-MHz transducer. The transducer was in longitudinal orientation and placed perpendicular to the chest wall to scan through the fourth intercostal space in the left midaxillary line. *Video available on AccessMedicine.com.*

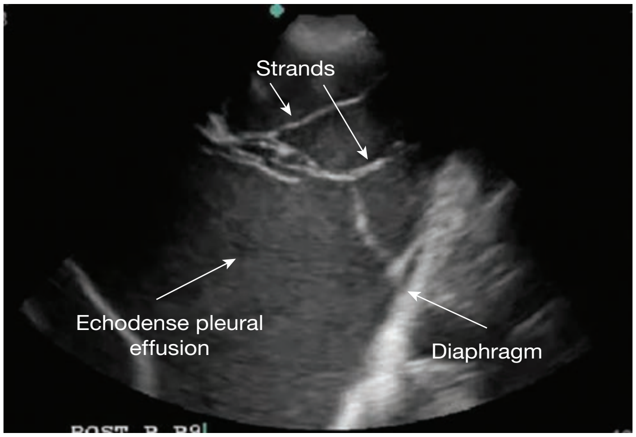

Figure 29-4 Pleural effusion with a homogeneously echogenic pattern and mobile strands suggestive of an exudate. Thoracentesis showed a hemothorax. The image was obtained using a 3.5-MHz transducer. The transducer was in longitudinal orientation and placed perpendicular to the chest wall to scan through the sixth intercostal space in the right midaxillary line.

A heterogeneously echogenic pattern, with swirling debris, septations, fronds, or strands is typically observed with exudates with a positive predictive value of 90%.[11] Highly cellular exudates, such as empyema or hemothorax, may demonstrate homogeneous echogenicity[14] (Video 29-3) (Fig. 29-4). Exudates can be echogenic, but are occasionally anechoic. The presence of strands, debris, or septations is characteristic of a parapneumonic effusion or empyema[15] (Fig. 29-5).

The presence of a septated effusion on ultrasonography suggests the need for fibrinolytic therapy or surgical intervention, prolonged chest tube drainage, and longer hospital stay when compared with effusions lacking such complexity[16] (Video 29-4). Pleural ultrasonography is superior to CT scanning in detecting pleural fluid complexity.[17]

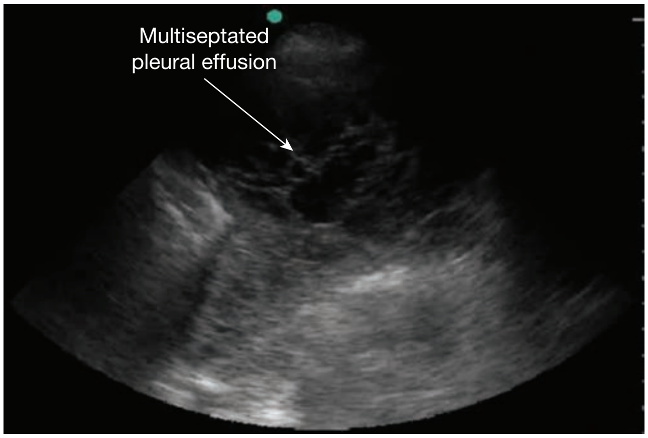

Figure 29-5 Multiseptated pleural effusion. The pattern is consistent with a complex parapneumonic effusion or empyema that will likely require fibrinolytic treatment or surgical drainage. The image was obtained using a 3.5-MHz transducer. The transducer was in longitudinal orientation and placed perpendicular to the chest wall to scan through the fourth intercostal space in the left midaxillary line.

By making a number of defined measurements, the volume of a pleural effusion may be estimated using ultrasonography.[18] For clinical purposes, it generally suffices to characterize the effusion as small, moderate, or large. Pleural effusions may become loculated collections, which characteristically develop in nondependent positions and fail to move with changes in body position. The loculum may be thick-walled and often has internal hyperechoic complexity.

Performance of Thoracentesis

Pleural ultrasonography facilitates safe performance of thoracentesis. When compared with physical examination combined with standard chest radiography, ultrasonography is superior in identifying a safe site for needle insertion.[7] A meta-analysis supports the use of ultrasonography to guide thoracentesis to reduce the risk of pneumothorax.[19] As needle insertion is required not only for simple thoracentesis, but also for a wide variety of pleural procedures requiring use of guidewires and device placement, pleural ultrasonography is an essential component of interventional practice.

Thoracic ultrasonography allows for identification of a safe site, depth, and angle for needle insertion. Using the technique of scan lines described previously, the operator identifies the pleural effusion and establishes the best site and trajectory for needle insertion while avoiding injury to structures that surround the fluid collection. In selecting a site, the operator is aware that the lung may move in a respirophasic fashion. Safe site selection is predicated on the absence of intermittent respirophasic movement of lung into the needle path. When such movement is observed, constituting the so-called "curtain sign," needle insertion is contraindicated at that point. Examination of the planned needle insertion trajectory with the vascular probe adds an additional element of safety to the procedure by identifying aberrantly positioned intercostal vessels that can be avoided by changing the access site.[20] Once a safe site is found, it is marked by indentation of the skin. Just prior to sterile skin preparation, the operator rescans to confirm site selection, depth of needle penetration required, and the angle of insertion. The procedure is then performed using an angle of insertion of the needle and syringe assembly that duplicates the angle of the transducer employed at the time of the final scan. Patient position should not change between the final scan and needle insertion, as this may cause movement of the fluid within the thorax.

For the pulmonary specialist, thoracentesis is usually performed with the patient in the seated position. For more complex procedures requiring tunneling of a catheter or chest tube insertion, the patient may be supine or in lateral decubitus position. Using the same scan line technique as utilized for the upright patient, the operator identifies the pleural effusion based on the previously described ultrasonography criteria. The site is marked. The angle and depth for safe needle insertion are determined. Immediately before final skin preparation, the operator rescans to confirm the safety of the site for device insertion and, without patient movement, proceeds with device insertion and advancement.

While ultrasonography facilitates pleural access, pitfalls exist. Although pneumothorax is a rare occurrence with ultrasonography-assisted thoracentesis, the operator checks for pneumothorax before and after the procedure by examining the superior anterior chest for lung sliding (see "Lung Ultrasonography," below). The presence of sliding lung rules out pneumothorax. The most common cause of pneumothorax following ultrasonography-assisted thoracentesis is the presence of nonexpandable lung, rather than visceral pleural laceration.[21]

In performing ultrasonography-assisted thoracentesis, several causes may account for failure of fluid aspiration, despite good site selection. In edematous or obese patients, the operator may press the probe into the skin surface with some force, causing a compression artifact. As the measurement for depth of needle penetration is made when the skin is compressed by the probe, once the skin has rebounded, the distance of needle penetration required may be greater than that predicted during initial measurement.

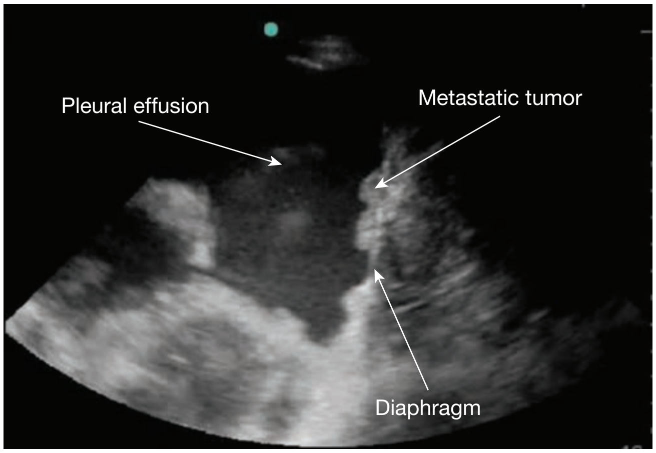

Figure 29-6 Pleural effusion with pleural masses on the diaphragm caused by metastatic breast cancer in the pleural space. The image was obtained using a 3.5-MHz transducer. The transducer was in longitudinal orientation and placed perpendicular to the chest wall to scan through the fifth intercostal space in the left midaxillary line.

In performing the procedure in patients with loose skin, the operator may place tension on the skin at the time of mark placement, displacing the skin from the underlying soft tissue. When the tension is released, the mark may displace to a new position on the chest wall that is not appropriate for needle insertion. This underlies the importance of a final scan, post position marking, and prior to needle insertion.

While it is not necessary to use real-time needle guidance in performing ultrasonography-assisted thoracentesis, failure of needle insertion to yield fluid may warrant rescanning to confirm appropriate site selection. Occasionally, a "dry" tap results from tissue impaction in the needle during insertion or because of septations occluding the needle.

Pleural Pathology

In addition to identification of pleural fluid, ultrasonography allows visualization of a variety of pleural pathologies. A number of pleural diseases cause echogenic abnormalities within the pleural space. Some of these solid pleural abnormalities may coexist with pleural effusions. For example, metastatic pleural disease often occurs with a coexisting pleural effusion, such that the pleural effusion acts as an acoustic window that allows easy observation of the metastatic disease (Fig. 29-6). Metastatic tumors are usually hyperechoic and are often multiple (Video 29-5). They may demonstrate a variety of different sizes and shapes, such as nodular, hemispheric, or circular. The tumors may be broad-based or have frond-like protrusions. Chest wall or diaphragm invasion may cause disruption of normal tissue interfaces and direct extension of tumor into adjacent structures, each of which is visible with ultrasonography.

Video 29-5 Pleural effusion with pleural masses on the diaphragm. The patient had metastatic breast cancer in the pleural space. The image was obtained using a 3.5-MHz transducer. The transducer was in longitudinal orientation and placed perpendicular to the chest wall to scan through the sixth intercostal space in the left midaxillary line. *Video available on AccessMedicine.com.*

Video 29-6 Complex multiloculated pleural effusion with thick septations caused by an empyema. The transducer was in longitudinal orientation and placed perpendicular to the chest wall. The examiner moved the transducer over several intercostal spaces to show the extent of the fluid collection. The scan line is in right midaxillary line. *Video available on AccessMedicine.com.*

Ultrasonography is superior to chest CT for the diagnosis of transpleural chest wall invasion.[22]

Benign pleural tumors, such as benign mesothelioma, chondroma, lipoma, or thoracic sclerosis, are uncommonly found during pleural ultrasonography. They are usually hyperechoic, have a distinct capsule, and do not demonstrate invasion through adjacent tissue planes. Ultrasonographic morphology is not sufficiently diagnostic, but the technique may be used to guide biopsy. Primary pleural malignancy, such as malignant mesothelioma, has ultrasonographic features that include pleural thickening with unclear and irregular borders, nodularity, and evidence of chest wall or diaphragm invasion.

Inflammatory diseases that involve the pleural space are usually caused by infection. Both parietal and visceral pleura are thickened and hyperechoic, while the underlying lung may demonstrate an alveolar consolidation pattern. Within the pleural fluid collection, linear mobile echogenic elements float freely. Over time, the elements may thicken and divide the effusion into multiple fluid-filled cavities that have variable echogenicity. Eventually, the infected space becomes a multiseptated conglomerate of thick-walled cavities (Video 29-6). A homogeneously echogenic empyema may be so dense that no dynamic findings are discernible within the pleural collection (Fig. 29-7). This makes differentiation from the underlying liver or spleen difficult and may even complicate delineation of the diaphragm, which is a key element in identifying a safe site for device insertion. Occasionally, a chest CT may be required to fully characterize a complex pleural space infection.

Pleural fibrosis shows variable echogenicity, so it may be difficult to differentiate fibrosis from an adjacent pleural effusion. Color-flow Doppler is helpful in distinguishing between the two.[23] Color-flow Doppler signals are generally absent from areas of fibrosis but are present in pleural effusions due to small ultrasonography reflectors moving within the fluid.

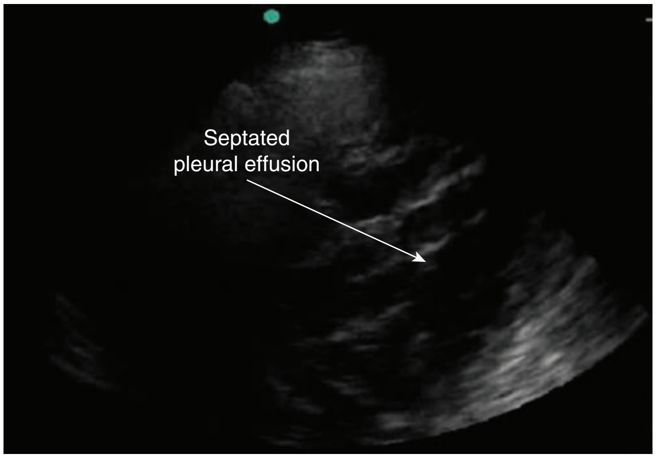

Figure 29-7 Complex, multiloculated pleural effusion with thick septations caused by an empyema. The transducer was in longitudinal orientation and placed perpendicular to the chest wall to scan through the sixth intercostal space in the right midaxillary line.

DIAPHRAGM ULTRASONOGRAPHY

Diaphragm ultrasonography is noninvasive and without ionizing radiation. It is feasible, reproducible, repeatable, and affordable when compared with other techniques to assess diaphragm dysfunction (DD). DD can be either partial (weakness) or complete (paralysis) and is often clinically underdiagnosed due to nonspecific presentations.[24] When the pulmonologist has suspicion for DD, the diaphragm can be imaged utilizing ultrasonography to acquire qualitative and quantitative measurements to guide further management. Diaphragm excursion is determined using the cardiac or abdominal probe using the liver or spleen as acoustic windows, as described above (Fig. 29-8). Best visualization is from an anterior midclavicular subcostal view or lower lateral mid-axillary view.[25]

■ Diaphragm Thickening

Diaphragm thickening is determined using the high-frequency linear vascular probe from the lateral lower midaxillary view of the zone of apposition. The examiner observes a three-layer structure consisting of two outer hyperechoic membranes with a singular

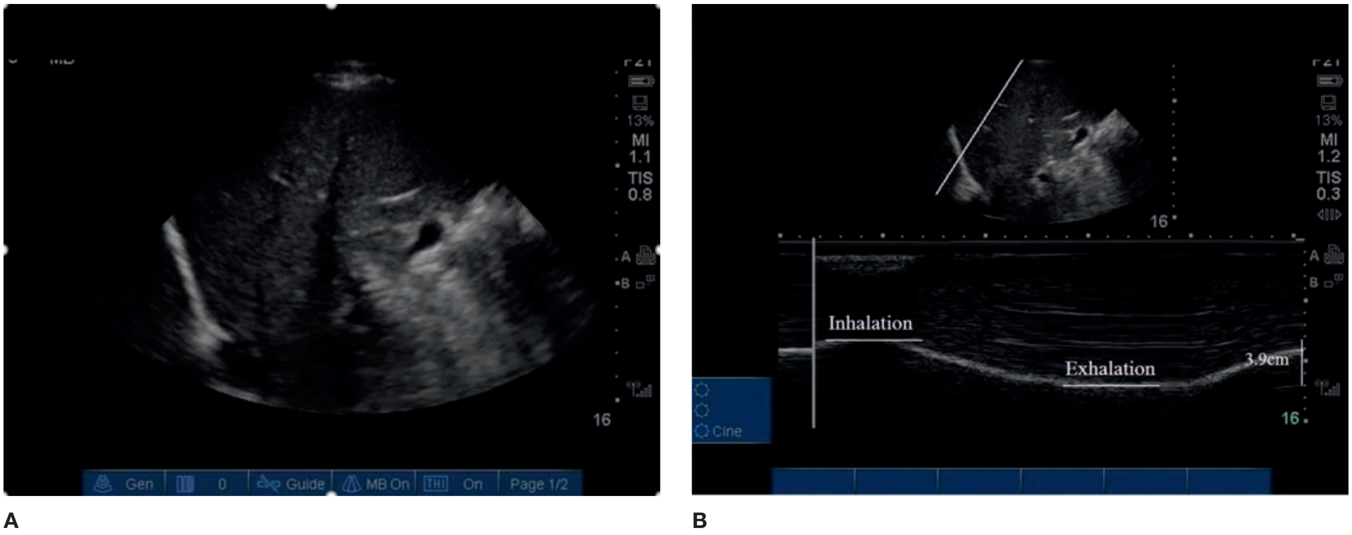

Figure 29-8 **A.** Hepatic hemidiaphragm visualized from the lateral position. **B.** Diaphragm excursion measured using M-mode. The image was obtained using a 3.5-MHz transducer. The transducer is in longitudinal orientation and placed perpendicular to the chest wall to scan through the 6th intercostal space at the mid axillary line.

Video 29-7 This video demonstrates the three-layer structure consisting of two outer hyperechoic membranes (pleura and peritoneum) with a singular hypoechoic inner muscle (diaphragm) during a respiratory cycle. The image was obtained using a 7.5-MHz vascular transducer. The transducer is in longitudinal orientation and placed perpendicular to the chest wall to scan through the 8th intercostal space in the midaxillary line. *Video available on AccessMedicine.com.*

Video 29-8 Demonstration of diaphragm excursion using B-mode. M-mode can then be applied as perpendicular to the diaphragm as possible and activated to obtain a quantitative value. The image was obtained using a 3.5-MHz transducer. The transducer is in longitudinal orientation and placed perpendicular to the chest wall to scan through the 6th intercostal space at the mid axillary line. *Video available on AccessMedicine.com.*

hypoechoic inner muscle (Video 29-7), the visualization of which allows measurement of the thickening of the diaphragm during inspiration and expiration. Thickening quantification is obtained by measuring the distance between the two hyperechoic structures during end inspiration and expiration (Fig. 29-9).[26,27]

Diaphragm Excursion

Diaphragm excursion (DE) is measured through the anterior or lateral views or with M-mode during quiet breathing during deep breathing, and during voluntary sniffing[28] (Video 29-8). Diaphragm paralysis can be diagnosed by identifying the absence of mobility during quiet and deep breathing together with paradoxical motion during voluntary sniffing.[29] Diaphragm weakness can be diagnosed by identifying reduced DE with or without paradoxical motion during voluntary sniffing.[30]

Diaphragm Thickness and Thickening Fraction

Thickness of the diaphragm (Tdi) and the thickening fraction (TF) are used to evaluate diaphragm atrophy and contraction, respectively. These measurements are obtained using the high-frequency linear probe visualizing the diaphragm at the zone of apposition. This acoustic window is found by placing the transducer between the eighth and ninth intercostal spaces in the midaxillary line using a longitudinal scanning plane. The diaphragm is identified as the hypoechoic inner muscular layer encased by two hyperechoic membranes as previously described (pleura and peritoneum).[26] Tdi is measured from the center of the pleural line to the center of the peritoneum during both end-inspiration (Tdi-insp) and end-expiration (Tdi-exp). The TF is calculated as follows:

$$[(\text{Tdi-insp} - \text{Tdi-exp})/\text{Tdi-exp}] \times 100.$$[31]

Chronic diaphragm paralysis is characterized by a thin, atrophic structure that does not demonstrate inspiratory thickening.[32] Acute or subacute diaphragm paralysis may have a normal Tdi; however, the TF is diminished.[30]

LUNG ULTRASONOGRAPHY

Lung ultrasonography is performed using the same equipment and scanning techniques as used for pleural ultrasonography. As the pulmonary specialist performs the imaging at point of care, results are immediately available for integration into the standard tools of patient evaluation, including the history, physical examination, and laboratory analysis. Lung ultrasonography is designed to be used in a goal-directed fashion at the point of care.

Basic Findings of Lung Ultrasonography

Several important, useful findings in lung ultrasonography include lung sliding, A lines, B lines, and evidence of lung consolidation, which are described below.

Lung Sliding

When the transducer is placed perpendicular to the chest wall and orientated to enable imaging through rib interspaces, the pleural

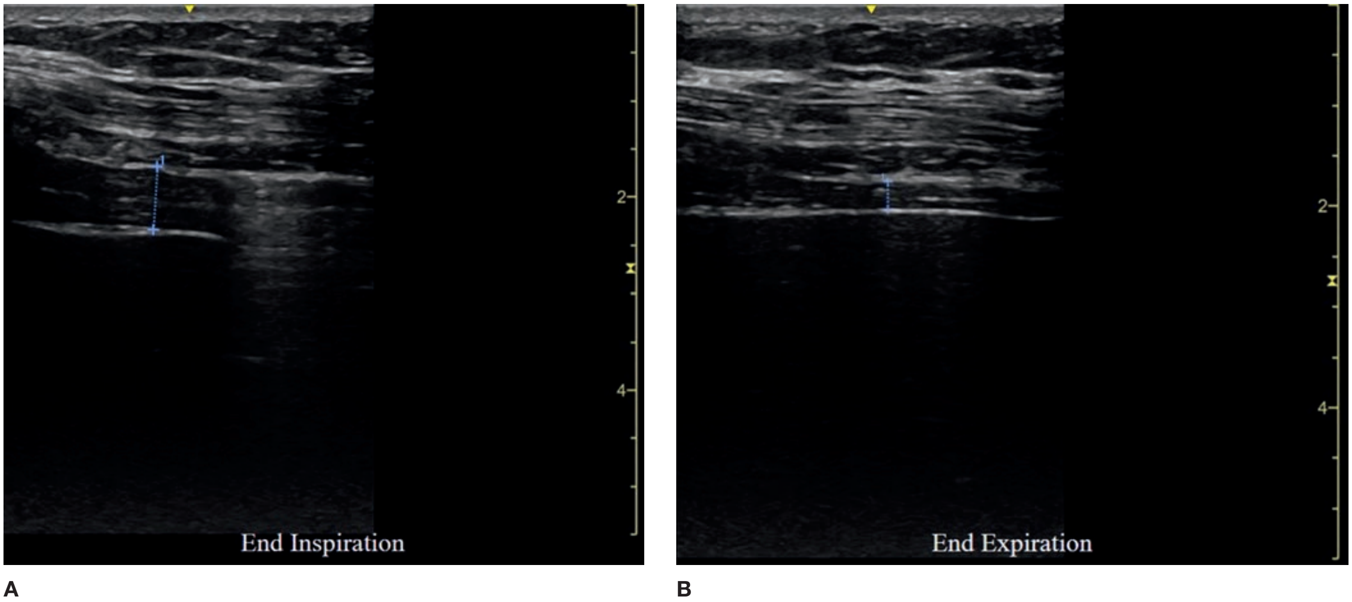

Figure 29-9 The three-layer structure consisting of two outer hyperechoic membranes (pleura and peritoneum) with a singular hypoechoic inner muscle (diaphragm) during a respiratory cycle. **A.** Measurement of diaphragm thickness during end inspiration. **B.** Measurement of diaphragm thickness during end expiration. The image was obtained using a 7.5-MHz vascular transducer. The transducer is in longitudinal orientation and placed perpendicular to the chest wall to scan through the 8th intercostal space in the midaxillary line.

Video 29-9 This video demonstrates the presence of lung sliding. The image is obtained using a 7.5-MHz vascular transducer. The transducer is in longitudinal orientation and placed perpendicular to the chest wall to scan through the second intercostal space in the midclavicular line. The resolution of the 7.5-MHz transducer is superior to that of the 3.5-MHz transducer at the expense of reduced penetration (see also Chapter 79). *Video available on AccessMedicine.com.*

line is visualized approximately 5 mm deep to the rib periosteum. The normal pleural line demonstrates a shimmering respirophasic to-and-fro movement called *lung sliding*, which is caused by movement of the visceral pleura against the parietal pleura during breathing (Video 29-9).

The presence of lung sliding indicates that, at that point of examination, no pneumothorax is present, as the lung is apposed to the chest wall.[33] Lung sliding can be detected rapidly over the anterior upper chest by moving the probe over multiple interspaces. Since a loculated pneumothorax is uncommon, in the supine or upright patient, examination of several anterior interspaces suffices to rule out pneumothorax; free air in the pleural space rises to the nondependent part of the thorax, unlike fluid, which is dependent. Lung sliding is generally more prominent at the base of the lung because of the effect of diaphragm movement on lung inflation, so lung sliding may be more difficult to detect at the lung apex. To optimize visualization of lung sliding, the ultrasonography machine gain is decreased, and depth adjusted to place the pleural line in center of the screen.

A finding related to lung sliding is *lung pulse*. If a normal subject suspends respiration, lung sliding is temporarily absent; however, cardiophasic movement of the pleural line continues due to the lung movement that derives from transmission of cardiac contraction. The finding of lung pulse has the same implication as lung sliding; when noted, there is no pneumothorax at the site of the examination (Video 29-10).

While lung sliding and lung pulse, when present, rule out pneumothorax, their absence is less helpful (Video 29-11). The absence of lung sliding indicates the possibility of pneumothorax. Other causes for absence of lung sliding include pleurodesis, apnea, mainstem bronchial obstruction, giant lung bullae, and severe parenchymal lung disease. The absence of lung sliding should be correlated with the clinical context. For example, if a patient demonstrates lung sliding before an ipsilateral thoracentesis or central-line insertion, the absence of lung sliding following the procedure suggests an extremely high probability of a procedure-related pneumothorax. On the other hand, the patient who has had prior pleurodesis will lack lung sliding.

Video 29-10 This video demonstrates the presence of lung pulse in a tachycardic patient. Note the absence of lung sliding with perception of cardiac activity near the meeting of the parietal and visceral pleural line. The image was obtained using a 7.5-MHz vascular transducer. The transducer was in longitudinal orientation and placed perpendicular to the chest wall to scan through the second intercostal space in the midclavicular line. The resolution of the 7.5-MHz transducer is superior to that of the 3.5-MHz transducer, although depth of penetration is reduced (see also Chapter 79). *Video available on AccessMedicine.com.*

Video 29-11 Absence of lung sliding and lung pulse. The image was obtained using a 7.5-MHz vascular transducer. The transducer was in longitudinal orientation and placed perpendicular to the chest wall to scan through the second intercostal space in the midclavicular line. The resolution of the 7.5-MHz transducer is superior to that of the 3.5-MHz transducer, although depth of penetration is reduced (see also Chapter 79). *Video available on AccessMedicine.com.*

Video 29-12 Lung point. A pneumothorax has caused partial deflation of the lung. Respirophasic movement of the partially deflated lung's visceral pleura into the pneumothorax space is seen. The image was obtained using a 7.5-MHz vascular transducer. The transducer was in transverse orientation and placed perpendicular to the chest wall to scan through the fifth intercostal space in the right anterior axillary line (see also Chapter 79). *Video available on AccessMedicine.com.*

While the absence of lung sliding is only indicative of the possibility of pneumothorax, it is possible to positively diagnose a pneumothorax using lung ultrasonography based on identification of a *lung point*.[34] Most pneumothoraxes result in only partial collapse of the affected lung; hence, the partially deflated lung is, at some point, still apposed to the chest wall. Under these circumstances, when the transducer is placed into an anterior interspace, no lung sliding will be noted—as the lung is not inflated against the inside of the chest wall. More laterally, lung sliding may become apparent if there is partial collapse of the lung. At the interface between the aerated lung and the pneumothorax space, the lung will be seen to enter the scanning plane in a respirophasic manner (Video 29-12). This interface is called the lung point. Identification of a lung point is diagnostic of pneumothorax and allows for an estimate of pneumothorax size. While a lung point is 100% specific for pneumothorax, its sensitivity depends on the skill of the examiner; furthermore, a large pneumothorax will not have a lung point. High-frequency vascular probes are useful in examining for lung point.

A Lines

Once the pleural line has been examined, the depth setting on the machine is increased to examine deeper structures within the thorax. The normal lung reveals *A lines,* which are one or more horizontally oriented lines visible deep to the pleural line (Video 29-13). When multiple, they are equidistant; their separation distance corresponds to the distance between the chest wall and pleural line (Fig. 29-10). A lines are reverberations of the pleural line caused by echoes reflecting off the air just deep to the pleural line, which then reflect off of the probe face. When this reflection returns to the probe, it appears on the screen as an ultrasonographic interface similar to the pleural line, but twice as far away. A lines may be single or multiple, but they are always separated by the same distance. In the presence of sliding lung, A lines indicate normally aerated lung at the site of probe application to the chest. When present without lung sliding, they suggest the possibility of a pneumothorax. A lines correlate with a normal aeration pattern seen on a CT scan.[35]

B Lines

Using standard scanning technique and a depth set to visualize deeper structures, *B lines* may be observed instead of A lines (Fig. 29-11). B lines have several distinct characteristics: (1) They are hyperechoic;

Video 29-13 A lines. The image was obtained using a 3.5-MHz transducer. The transducer was in longitudinal orientation and placed perpendicular to the chest wall to scan through the second intercostal space in the midclavicular line (see also Chapter 79). *Video available on AccessMedicine.com.*

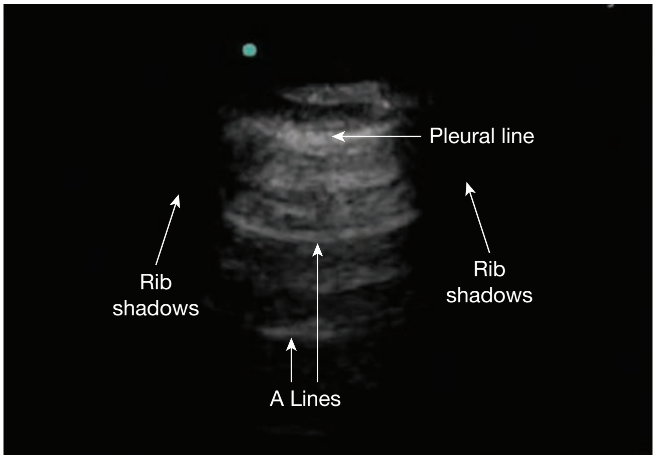

Figure 29-10 Pleural line, A lines, and adjacent rib shadows. The image was obtained using a 3.5-MHz transducer. The transducer was in longitudinal orientation and placed perpendicular to the chest wall to scan through the second intercostal space in the midclavicular line.

(2) the originate at the pleural interface; (3) they extend to the bottom of the device screen in vertical orientation; (4) they fan out; (5) they move with the pleural interface (if it is mobile); and (6) they efface A lines where A lines and B lines intersect (Video 29-14). The presence of B lines correlates with alveolar or interstitial abnormalities encountered on CT scanning (reticular pattern or ground-glass abnormality).[36]

B lines result from of any interstitial infiltrative process, such as inflammation, neoplasm, fibrosis, hemorrhage, or edema.[37–41] B lines may be focal, scattered, or profuse in distribution, based on the underlying disease process.

As with any radiographic abnormality, clinical correlation is required to determine the cause of B lines. For example, healthy individuals often have one or two B lines on examination of the lateral lower rib interspaces, which are not pathologic. More than two B lines in a single field is considered abnormal. Pneumonia may manifest with focal B lines detected over the involved lobe or segment. Pulmonary fibrosis results in scattered B lines, whereas cardiogenic pulmonary edema yields profuse bilateral B lines. Pleural morphology may be useful in distinguishing B lines related to elevation of left atrial pressure from those caused by an inflammatory process. Typically, the B lines noted in cardiogenic pulmonary edema are associated with a smooth pleural surface, while those seen in primary lung injury manifest an irregular pleural surface.[41] As B lines originate from the area of the visceral pleura, their presence rules out pneumothorax.

Video 29-14 B lines. The image was obtained using a 3.5-MHz transducer. The transducer was in longitudinal orientation and placed perpendicular to the chest wall to scan through the second intercostal space in the midclavicular line (see also Chapter 79). *Video available on AccessMedicine.com.*

Consolidation

Consolidated lung manifests as tissue density on ultrasonography.[42] Its echogenicity is similar to that of the liver (sonographic hepatization of lung). Consolidation may be localized to a specific lobe or segment of the lung and may also be observed in the lung periphery as a small consolidation pattern. Within the consolidated lung, punctate, hyperechoic foci are often visible (Fig. 29-12). These foci represent air retained within the bronchi. If they move in a respirophasic manner, the finding indicates patency of the bronchus supplying that portion of the lung[43] (Videos 29-15 and 29-16). Demonstration of consolidation on lung ultrasonography correlates strongly with results of chest CT scanning.[35]

As with chest radiography and CT scanning, the finding of alveolar consolidation on lung ultrasonography does not give the clinician a specific diagnosis. While pneumonia may result in alveolar consolidation, so will atelectasis (compressive, resorptive, or cicatricial). Severe pulmonary edema, with complete filling of the alveolar compartment, and infiltrative processes, such as tumor, may result in the ultrasonographic finding of lung consolidation. While lung ultrasonography identifies consolidation, the pulmonary specialist determines its cause.

LIMITATIONS OF THORACIC ULTRASONOGRAPHY

A specific limitation of lung ultrasonography relates to the physics of the technique. Due to the mismatch of acoustic impedance

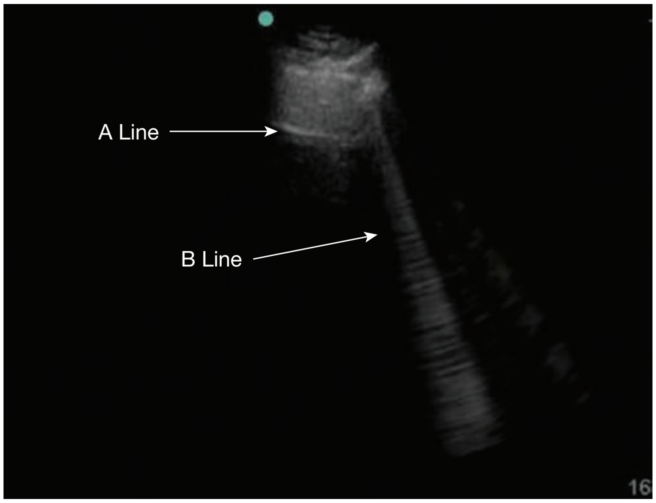

Figure 29-11 B lines. The image was obtained using a 3.5-MHz transducer. The transducer was in longitudinal orientation and placed perpendicular to the chest wall to scan through the second intercostal space in the midclavicular line.

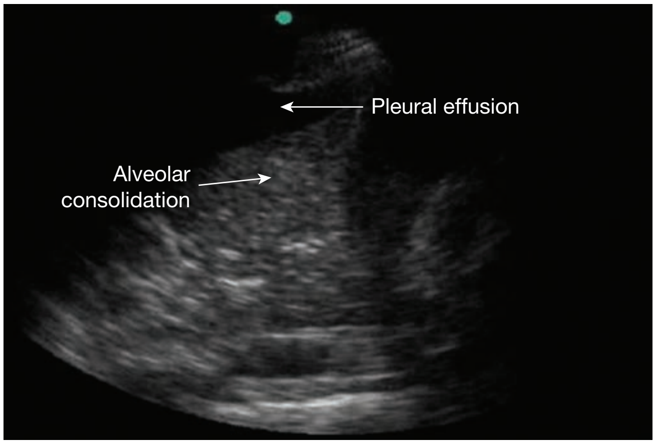

Figure 29-12 Alveolar consolidation of the left lower lobe and pleural effusion. The image was obtained using a 3.5-MHz transducer. The transducer was in longitudinal orientation and placed perpendicular to the chest wall to scan through the sixth intercostal space in the left posterior axillary line.

Video 29-15 Mobile air bronchograms in an area of alveolar consolidation. The gain was turned down to bring out the punctate hyperechoic mobile foci that have respirophasic movement. The foci represent air within the bronchi surrounded by alveolar consolidation. The image was obtained using a 3.5-MHz transducer. The transducer was in longitudinal orientation and placed perpendicular to the chest wall to scan through the sixth intercostal space in the right midaxillary line. *Video available on AccessMedicine.com.*

Video 29-16 Alveolar consolidation of the right lower lobe without dynamic air bronchograms. Punctate hyperechoic foci can be seen; however, the appearance of movement demonstrated derives from translational artifact and is not from respirophasic movement. The image was obtained using a 3.5-MHz transducer. The transducer was in longitudinal orientation and placed perpendicular to the chest wall to scan through the sixth intercostal space in the left posterior axillary line. *Video available on AccessMedicine.com.*

between the soft tissue of the chest wall and underlying aerated lung, there is complete reflection of ultrasonography at the interface of the two, so aerated lung is not visible as a discrete structure. Any disease process resulting in focal abnormality that is surrounded by aerated lung will not be visible with ultrasonography examination. For example, a lung mass that is surrounded by aerated lung will not be visible using ultrasonography. Similarly, mediastinal structures are not visible using surface ultrasonography unless there is a convenient acoustic window related to lung consolidation or pleural effusion.

A major limitation of thoracic ultrasonography in the critical care unit relates to the difficulty in scanning the posterior thoracic area in the unstable patient who is in supine position and encumbered by life support devices. The pulmonary specialist is advantaged as he or she will be able perform the scan with the stable patient in the sitting position, thereby allowing imaging of the posterior thorax. However, obesity, heavy musculature, subcutaneous emphysema, or surgical dressings may degrade image quality in some patients (Video 29-17). In the case of ambiguous results obtained with thoracic ultrasonography, the pulmonary specialist may revert to CXR or chest CT.

Documentation of the results of lung ultrasonography is challenging compared with CXR and chest CT scanning, for which results can be stored indefinitely in a durable format, and for which serial studies can be compared. The need for documenting the results of thoracic ultrasonography requires that the clinician have a reliable and convenient means of storing the results in a durable digital format—requirements for both clinical and billing purposes.[44]

By definition, thoracic ultrasonography is performed at the point of care by the pulmonary specialist. This requires the clinician to commit time to training to become competent, to have immediate access to a capable portable machine, and to have an easy method of saving the results of the study. These factors are barriers and, therefore, constitute limitations to use of thoracic ultrasonography in clinical practice. The clinician who decides to adopt thoracic ultrasonography as a primary imaging modality is prepared to meet these challenges, with the intent of improving patient care and reducing reliance on CXR and chest CT.

Video 29-17 Hypoechoic pleural effusion without definite septations and an adjacent translobar consolidation in a morbidly obese patient. Due to heavy musculature, connective tissue, rib shadowing artifact, and skin folding, identification of ultrasound findings can be obscured, rendered challenging, or be uninterpretable. The image was obtained using a 3.5-MHz transducer. The transducer was in longitudinal orientation and placed perpendicular to the chest wall to scan through the sixth intercostal space in the right posterior axillary line. *Video available on AccessMedicine.com.*

ADVANCED LUNG ULTRASONOGRAPHY

A wide variety of additional lung ultrasonography findings have been described. Mastery of the basic findings is the first step of training for the pulmonary specialist. The reader is referred to standard texts for a complete review of the subject.[5]

CONCLUSION

Thoracic ultrasonography is a useful imaging modality for the pulmonary specialist. Thoracic ultrasonography is easy to learn and has multiple applications as a point-of-care tool. The technique provides the pulmonary specialist information of immediate clinical relevance at the point of care.

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CHAPTER 30

Physiologic and Metabolic Assessment of Pulmonary Disorders Using Conventional Imaging Techniques and Positron Emission Tomography

Ghassan El-Haddad
Søren Hess
Abass Alavi

INTRODUCTION

Since the mid-1950s, use of radiopharmaceuticals has made it possible to assess a variety of pulmonary disorders. In 1955, ^{133}Xe was introduced for the study of regional pulmonary ventilation.[1] Shortly thereafter, it became possible to evaluate regional pulmonary blood flow using inhaled carbon dioxide containing radioactive ^{15}O^{2} or intravenous injection of ^{133}Xe dissolved in saline solution.[3] In 1964, intravenous injection of ^{131}I-macroaggregated albumin made it feasible to obtain perfusion scans of the lungs.[4] Although these techniques rapidly gained wide acceptance as tests of regional abnormalities in ventilation and pulmonary blood flow, the main practical application was as a ventilation–perfusion lung scan ($\dot{V}/\dot{Q}$ scan) in the diagnostic evaluation of patients with suspected pulmonary embolism. Over the years, the role of nuclear medicine in respiratory medicine expanded to include such indications as preoperative assessment of lung function, mucociliary clearance, alveolar-capillary membrane permeability, inflammatory lung disease, and lung cancer. The last two indications were facilitated by the more widespread availability of positron emission tomography (PET) and integrated PET/CT (computed tomography) that has provided powerful tools to aid in the diagnosis, staging, and management of patients.

RADIOPHARMACEUTICALS AND TECHNIQUES IN VENTILATION–PERFUSION LUNG SCANNING

Perfusion lung scans are routinely utilized to examine patients with suspected pulmonary embolism. The overall principle is simple: radiolabeled microembolic particles are injected intravenously and transported to the pulmonary vasculature where they lodge uniformly and reversibly in the smallest blood vessels proportional to the perfusion. If a part of the vasculature is blocked by an embolus, a corresponding, often wedge-shaped, downstream area of the lung devoid of perfusion and injected radiolabeled microemboli appears photopenic on subsequent gamma camera examination.

Perfusion imaging is sensitive but, unfortunately, not specific for diagnosing pulmonary embolism. Virtually all lung diseases (including tumors, infections, asthma, and chronic obstructive pulmonary disease) may cause decreased pulmonary arterial blood flow in the affected lung zones. Therefore, combined use of perfusion and ventilation studies improves the diagnostic specificity of lung scanning for pulmonary embolism (Fig. 30-1). Pulmonary embolism almost always causes abnormal perfusion, while ventilation is preserved *(mismatched defects)* (Fig. 30-2). In contrast, in parenchymal pulmonary disorders, decreased ventilation and perfusion are noted in the same lung region, as perfusion is reduced secondary to ventilation disturbances due to regional hypoxic pulmonary vasoconstriction *(matched defects)*.[5] Sometimes ventilation abnormalities appear even larger than the perfusion abnormality *(reverse mismatch)*, for example, due to airway obstruction, mucus plug, atelectasis, or pneumonia.[6]

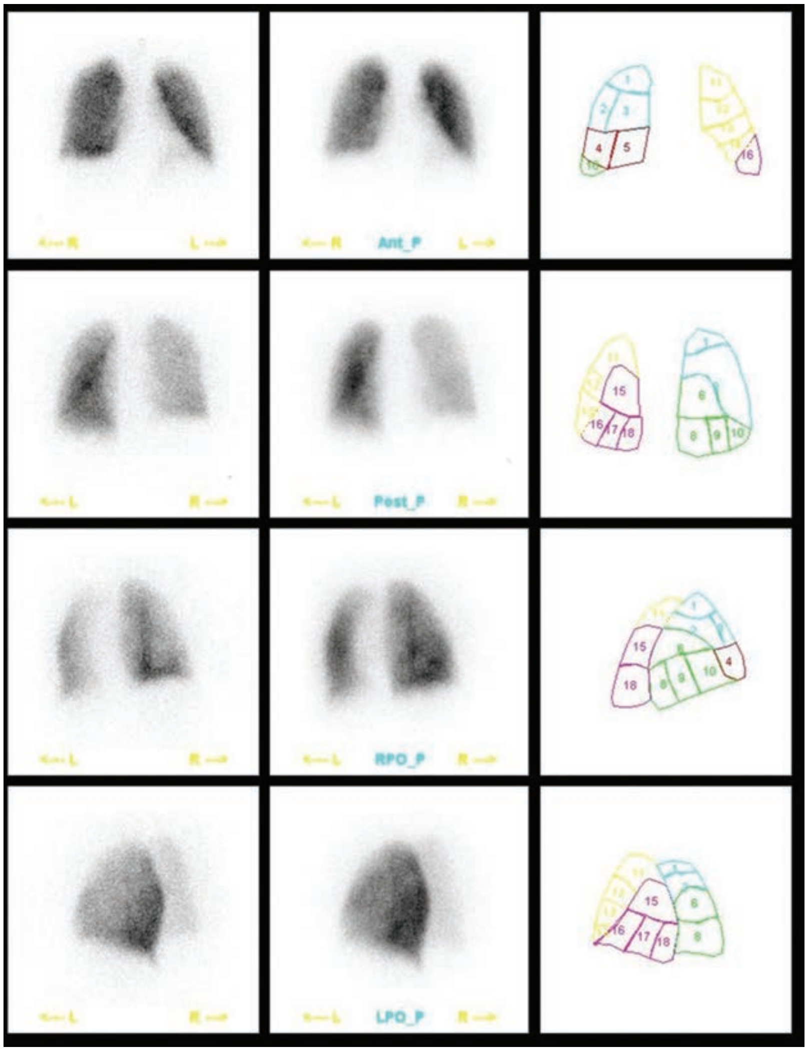


Figure 30-1 Normal ventilation–perfusion lung scanning. Ventilation scan using ^{99m}Tc Technegas aerosol (left column): Uniform distribution of the aerosol throughout both lungs. Perfusion scan using ^{99m}Tc MAA (middle column): Uniform distribution of particles throughout both lungs.

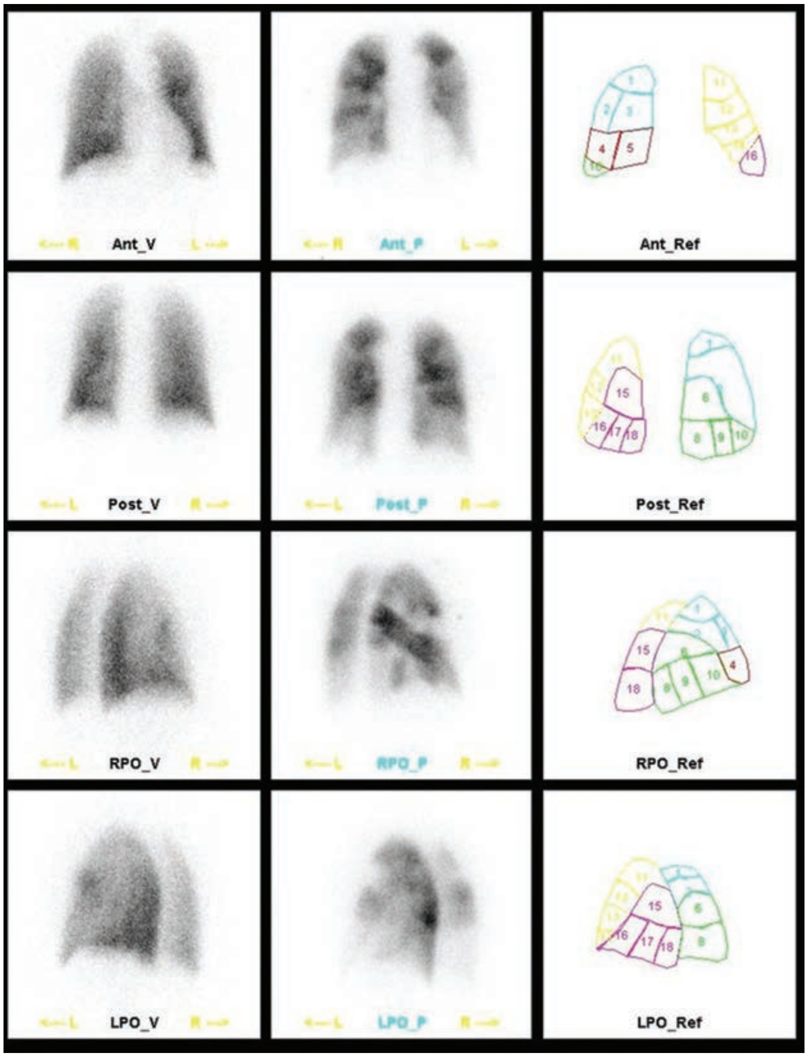


Figure 30-2 High-probability scan for pulmonary embolism. Ventilation scan using ^{99m}Tc Technegas aerosol (left column) is within normal limits. Perfusion scan using ^{99m}Tc MAA (middle column) shows large segmental defects in both lungs. This combination of findings *(mismatch)* is consistent with pulmonary embolism.

■ Perfusion Agents and Techniques

Clinical application of perfusion lung scanning was first described in 1964, when iodine 131–labeled macroaggregates of albumin were utilized in the evaluation of pulmonary perfusion.[4] Currently, the agent of choice in clinical practice is technetium 99m–labeled macroaggregated albumin (^{99m}Tc MAA) because of its availability, short residence time in the lungs, and relatively low cost.[7,8] The distribution of radiolabeled particles in the lungs is proportional to regional pulmonary blood flow at the time of injection. These particles should be injected intravenously while the patient is supine to limit the effect of gravity on regional pulmonary arterial blood.[9]

Following the administration of ^{99m}Tc MAA, particles mix uniformly with venous blood flowing to the heart; MAA particles range in size from 10 to 100 μm and lodge in precapillary arterioles and pulmonary capillaries of the lungs (usual caliber <15 μm), obstructing <0.1% of their total number. The usual administered dose of radioactivity is 40–150 MBq (1 to 4 mCi) in adults, typically 200,000 to 700,000 particles.

The blockage of pulmonary precapillary arterioles by ^{99m}Tc MAA is transient; the biologic half-life in the lung ranges between 2 and 8 h. The physical half-life of ^{99m}Tc is 6 h. The MAA particles are cleared by enzymatic hydrolysis forming smaller particles, which are phagocytized by reticuloendothelial cells. The usual administered activity and number of particles should be reduced in pediatric patients, pregnancy, (suspected) pulmonary hypertension, poor respiratory function, prior pneumonectomy or single lung transplant (to reduce blockage), and (suspected) right-to-left shunt (to avoid systemic emboli).[5,7,8,10,11]

■ Ventilation Agents and Techniques

Historically, ^{133}Xe was the agent used to determine regional ventilation.[1,12] ^{133}Xe has a physical half-life of 5.24 days and a low gamma energy emission of 81 keV compared with 140 keV of ^{99m}Tc; furthermore, the three-phase examination is somewhat laborious. Thus, other tracers, such as ^{81m}Kr and the ^{99m}Tc–labeled aerosols, have been gradually replacing it.[7,8,10]

^{81m}Kr is a noble gas that has a very short physical half-life (13 s), which allows generation of images of the lungs in multiple projections to match the perfusion images. ^{81m}Kr is produced from a rubidium 81 generator. The parent radionuclide has a physical half-life of 4.7 h, which limits the useful lifetime of the generator to only 1 day, so daily delivery is necessary at a relatively high cost. On the other hand, imaging with ^{81m}Kr may be performed simultaneously with the perfusion scan due to higher energy than ^{99m}Tc; due to a very low radiation exposure, it is particularly suitable for children.

A radioaerosol is produced by nebulizing radiopharmaceuticals into a fine mist, which is subsequently inhaled. Two ^{99m}Tc-labeled aerosols are widely available: ^{99m}Tc DTPA (diethylene triamine penta-acetic acid) and ^{99m}Tc Technegas. The advantages of ^{99m}Tc aerosols are that they are readily available, are inexpensive, and have a 140-keV energy photopeak, which is ideal for gamma camera imaging. ^{99m}Tc-labeled radioaerosols have particles between 0.5 and 2 μm in size and are produced by utilizing commercially available nebulizers.[13] The patient generally breathes from the nebulizer (with oxygen at 8 to 10 L/min) for 3 to 5 min or until 37 MBq (1 mCi) of radioactivity is deposited in the lungs. Only 2% to 10% of administered radioactivity goes to the lungs. The regional distribution of radioactivity in the lungs is proportional to local ventilation.

^{99m}Tc-labeled radioaerosol studies are generally performed before perfusion imaging. Although less desirable, the ventilation study can be performed following the perfusion scan, but the dose placed in the nebulizer should be increased to at least 1665 MBq (45 mCi) instead of the usual 1110 MBq (30 mCi) in order to overwhelm the activity present in the lungs from ^{99m}Tc MAA. Ventilation studies using ^{99m}Tc-labeled radioaerosols require some patient cooperation but can be performed at the bedside and on patients who are on ventilators. Disadvantages of ^{99m}Tc-labeled radioaerosols include the central deposition of radioactivity in patients with chronic obstructive pulmonary disease (COPD) or airway obstruction; use of ^{99m}Tc Technegas has significantly improved this deficiency.[7,8,10]

One limitation of ^{99m}Tc DTPA is its relatively rapid absorption across the pulmonary capillaries into the blood in the presence of inflammation, including that caused by smoking. (The typical ^{99m}Tc DTPA aerosol biologic half-life is about 80 min compared with ~20 to 30 min in smokers.) However, since ^{99m}Tc DTPA aerosol is cleared from the alveoli by transepithelial diffusion, the clearance rate may be used as an index of alveolar epithelial membrane integrity.[7]

LUNG SCANNING IN THE DIAGNOSIS OF ACUTE PULMONARY EMBOLISM

Pulmonary embolism (PE) is a common and potentially fatal disorder for which treatment is highly effective in decreasing mortality and morbidity if initiated soon after the event. The accurate and expeditious diagnosis of acute PE can be difficult because of the nonspecificity of clinical, laboratory, and radiographic findings.[14] Despite diagnostic advances, delays in diagnosis of PE are still common and represent an important clinical issue.[15]

Venous thromboembolism and PE are no longer considered a one-time only event, as they have a high recurrence and mortality rate.[16] Although the incidence of PE has increased over the past two decades, the overall mortality rate from PE has decreased substantially, which has been attributed to more effective therapy and better adherence to guidelines. However, trends toward overdiagnosis also have been reported, which may contribute to falsely lowering the case fatality rate by inflating the population with alleged PE.[17] Although prompt anticoagulation therapy has remained the cornerstone of PE treatment, as it is effective and reduces mortality, it is not without risks, specifically hemorrhagic complications. Therefore, accurate diagnosis of PE is essential, not only to prevent death from recurrent embolism, but also to avoid complications related to unnecessary anticoagulant therapy.

During the past half century various imaging modalities have come and gone, and the modality of choice remains controversial; however, the choice in contemporary clinical practice has been narrowed to radioisotope-based $\dot{V}/\dot{Q}$ scan and pulmonary CT-based angiography (CTA).[5,17]

The first major study that utilized perfusion lung scanning as a screening test for the diagnosis of PE was the Urokinase Pulmonary Embolism Trial (UPET).[18] Despite suboptimal radiopharmaceutical and imaging equipment, this study established the potential of perfusion lung scanning in screening for PE and assessing restoration of pulmonary blood flow. Approximately 75% to 80% of perfusion defects resolved by 3 months; the remainder persisted to some extent after 1 year, indicating that most patients either completely lyse the thrombi or partly recanalize the pulmonary artery clots. This finding is corroborated by clinical experience and may prompt follow-up scans after 6 to 12 months to obtain a new baseline in patients with persisting risk factors for PE recurrence.[5]

■ Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) Study

Subsequent studies acknowledged the need for supplemental ventilation images and the added value of combined $\dot{V}/\dot{Q}$ scans, and much work was invested in establishing the best possible interpretation criteria. To date, the most comprehensive prospective investigation addressing the role of ventilation–perfusion scanning in the diagnosis of PE remains the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study. This multi-institutional study was designed to evaluate the efficacy of various conventional methods for diagnosing acute PE. In particular, PIOPED focused on the sensitivity and specificity of planar $\dot{V}/\dot{Q}$ scans in the diagnosis of acute PE.

Although the clinical diagnosis of PE is not definitive, results from PIOPED emphasize the importance of incorporating clinical assessment in evaluating patients suspected of having acute PE. As expected, combining clinical assessment with lung scan interpretation improves diagnostic accuracy of the imaging technique. Of patients with PE in PIOPED, 92% had at least one of the following risk factors: immobilization and recent surgery (two most common risks), underlying malignancy, history of DVT or PE, estrogen use, and pre-existing cardiac disease. Of patients diagnosed with PE, more than 90% had dyspnea, tachycardia, or pleuritic chest pain. Similarly, although chest radiographic findings alone are not sensitive or specific for PE, they are essential for diagnosing conditions that can mimic PE clinically. The most common radiographic finding in patients with PE was atelectasis and/or parenchymal opacity. Furthermore, chest radiographic findings heavily influence the criteria utilized for estimating the probability of PE based on lung scan patterns. For example, in patients with COPD, the sensitivity of a high-probability $\dot{V}/\dot{Q}$ scan is significantly lower than in patients with no cardiopulmonary disease. The worse the underlying cardiopulmonary disease, the higher the likelihood of the $\dot{V}/\dot{Q}$ scan to be of intermediate probability. Intermediate probability occurred in 60% of patients with COPD in PIOPED, compared with only 13% of patients with normal chest x-ray.[19] The sensitivity, specificity, and positive predictive value from PIOPED of ventilation–perfusion lung scans in detecting acute PE are presented in Table 30-1.

TABLE 30-1 Sensitivity, Specificity, and Positive Predictive Value of Lung Scans in Detecting Pulmonary Embolism in Patients Enrolled in PIOPED

Lung Scan Interpretation (Probability)	Sensitivity	Specificity	Positive Predictive Value
High	40%	98%	87%
High, intermediate	82%	64%	49%
High, intermediate, low	98%	12%	32%

All patients enrolled in PIOPED were to undergo $\dot{V}/\dot{Q}$ scan and pulmonary arteriogram. However, a large number of patients with low probability or normal $\dot{V}/\dot{Q}$ scan did not undergo pulmonary arteriogram to avoid additional risks. Therefore, there was a selection bias toward patients with intermediate or high probability for PE, leading to an overestimation of the sensitivity, but underestimation of the specificity, of $\dot{V}/\dot{Q}$ scan. In an analysis of the angiography results in PIOPED, PE occurred more frequently on the right than on the left, and more commonly in the lower lung zones.

One of the limitations of $\dot{V}/\dot{Q}$ scan in PIOPED was the interobserver variability in scan interpretation. As expected, agreement among readers was excellent for normal, high-probability, and very low-probability $\dot{V}/\dot{Q}$ scan (92%–95%), but it was not as good for intermediate and low probability.[19] Use of anatomic lung segment reference charts has been shown to reduce interobserver disagreement when interpreting scans. Other interpretative pitfalls include false-negative and false-positive readings. False-negative interpretations (i.e., low-probability read with PE present) do occur, and patients who have a recent history of immobilization (bed rest for 3 days), recent surgery, trauma to the lower extremities, or central venous instrumentation are particularly at risk. In patients with low- or very low-probability scans who have none of the aforementioned risk factors, the prevalence of PE was only 4.5%. Conversely, in patients with low- or very low-probability scans and one or more of the risk factors, the prevalence of PE was 12% and 21%, respectively (Table 30-2). Patients with false-negative lung scans tend to have nonocclusive subsegmental thrombi and a low pulmonary clot burden. The prognostic value of a low-probability scan is excellent, particularly in patients with a low clinical pretest likelihood of disease or negative lower leg ultrasound.[20]

The most common cause of $\dot{V}/\dot{Q}$ mismatch in patients who do not have acute PE is chronic or unresolved PE. Other causes include compression of the pulmonary vasculature (e.g., from mass lesions, lymphadenopathy, or mediastinal fibrosis), vessel wall abnormalities (e.g., pulmonary artery tumors or vasculitis), nonthromboembolic

TABLE 30-2 Risk Factors and Prevalence of Pulmonary Embolism in Patients with Low-Probability and Very Low-Probability Lung Scans Enrolled in PIOPED

	Patients with 0 Risk Factors (%)[a]	Patients with 1 Risk Factor (%)[a]	Patients with ≥2 Risk Factors (%)[a]	Total
PE positive	14 (2.2%)	19 (2.9%)	37 (5.7%)	70
PE negative	301 (46.4%)	136 (21.0%)	142 (21.9%)	579
Prevalence of PE	4.5%	12.2%	20.7%	10.8%

[a] *Risk factors include immobilization, trauma to lower extremities, surgery, and central venous instrumentation within 3 months of enrollment.*

intraluminal obstruction (e.g., tumor emboli or foreign body emboli), and congenital vascular abnormalities (e.g., pulmonary artery agenesis or hypoplasia). In patients who have unilateral V̇/Q̇ mismatch (hypoperfusion or absent perfusion) within an entire lung or in multiple contiguous segments and normal perfusion in the contralateral lung, extrinsic compression of the pulmonary vasculature, congenital abnormalities, or proximal PE should be considered. Patients with a suspected false-positive scan or unilateral V̇/Q̇ mismatch often require further imaging using CTA, even though emboli are frequently multiple (in 90%) and bilateral (in 85% of cases), and unilateral decreased/absent perfusion to one lung is uncommonly the result of pulmonary embolism.

Shortly after the PIOPED study, helical CTA was introduced.[21] This led to PIOPED II, which is the largest multicenter, prospective, outcome-based study to date that was designed to assess the accuracy of CTA in the evaluation of acute PE in comparison with composite reference standard.[22] In PIOPED II, for the detection of acute PE, CTA had a sensitivity, specificity, PPV, and NPV of 83%, 96%, 86%, and 95%, respectively.[22] The results of PIOPED II suggested that the predictive value of CTA is highly concordant with the pretest clinical probability of PE using Wells' criteria, but highly dependent of vascular segment involved.[23]

The PPV of PE with a positive CTA was 97% for main or lobar artery, 68% for segmental vessel, and 25% for subsegmental branch. The probability of false-negative chest CTA is minimal in large PE, but false-negative findings may occur in the small group of patients with PE limited to subsegmental arteries. PPV of PE in patients with positive CTA and high, intermediate, or low clinical probability was 96%, 92%, and 58%, respectively. NPV of PE in patients with negative CTA and low, intermediate, or high clinical probability was 96%, 89%, 60%, respectively. The limitations of this study included use of 4- to 16-slice multidetector CT devices (mostly 4), and application of a noninvasive diagnostic test as the reference standard.

In contrast to original PIOPED population, which included 68% of inpatients, PIOPED II included only 11% inpatients. Inpatients are more likely to have abnormalities on chest radiographs, which would potentially interfere with optimal V̇/Q̇ scan reading.[24] The accuracy of CTA would also be lower if patients with inconclusive interpretations of CT (51 patients or 6%) were included, giving an overall sensitivity and specificity of 78% and 90%, respectively. The overall PPV of 86% and NPV of 95% are values comparable to V̇/Q̇ results. The combination of CT venography with CTA increased the sensitivity to detect PE to 90% from 83% when using CTA alone. CT venography, however, showed similar results in diagnosing or excluding DVT as compression ultrasound.[25]

Finally, PIOPED III, a multicenter collaborative investigative trial, was designed to determine the diagnostic accuracy of gadolinium-enhanced magnetic resonance angiography (Gd-MRA) of the pulmonary arteries in combination with magnetic resonance venography (MRV) of the veins of the thighs in patients with clinically suspected acute PE. In PIOPED III, most centers had difficulty in obtaining adequate-quality MR pulmonary angiograms, which were inadequate in 25% of patients.[26] This varied from 11% to 52% between centers. Adequate-quality images were obtained in 91% in main or lobar pulmonary arteries, 87% in segmental pulmonary arteries, and 73% in subsegmental branches. Technically adequate MRA had a sensitivity of 78% and specificity of 99%. This led the PIOPED III investigators to conclude that MRA should be considered only at centers that routinely perform it well, and for patients who have contraindications to other standard tests.

V̇/Q̇ Scan Interpretation and Modifications to Original PIOPED Criteria

Several diagnostic schemes have been suggested for interpretation of V̇/Q̇ scans. The original PIOPED criteria were developed to interpret the scans generated from the study based upon experience gathered over the preceding decade.

A PE is characterized by V̇/Q̇ mismatch, which is an area of normal ventilation corresponding to a segmental wedge-shaped area of decreased or absent perfusion extending to the pleural surface. The segmental defect should correspond to vascular anatomy. The probabilistic, categoric interpretation scheme resulted in either high sensitivity or high specificity, but never both in a dichotomous setting; if only high-probability scans were considered positive for PE (and all other categories were considered negative), sensitivity was only 41%, but specificity 96%; conversely, if only normal scans were considered negative for PE (and all other considered positive), sensitivity reached 97%, but with specificity of only 10%.

Due to the high number (44%) of intermediate-probability V̇/Q̇ scans in PIOPED[27] and interobserver disagreements, several revisions and modifications have been made to the original criteria. Some of the V̇/Q̇ scan interpretation nuances include the "Gestalt interpretation," which is based on an experienced nuclear medicine physician's subjective estimate of the likelihood of PE (without using specific interpretation criteria). This interpretation takes into account various published lung image interpretation algorithms, clinical data, ancillary findings, and pathophysiologic features of PE, which are integrated with the individual case presentation. The Gestalt interpretation has been shown to correlate well with the fraction of patients with angiographic evidence of PE in the PIOPED study, with good to excellent intra- and interobserver variability.[28,29] Thus, experienced readers (such as the PIOPED investigators) can provide an accurate estimate of the probability of PE based on clinical, radiographic, and scintigraphic findings.

Other nuances include the so-called "triple match," that is, matching perfusion, ventilation, and chest x-ray abnormalities. Based on the PIOPED data, the prevalence of PE in the presence of a triple match varies depending on the location, that is, 11% to 12% in the upper or middle lung (low probability for PE), but 33% in the lower lung zones and, therefore, intermediate probability.[30] Another nuance to the intermediate category is single defects; for example, a single moderate-sized V̇/Q̇ mismatch was found to harbor PE in 36% of cases,[31] whereas a single matched V̇/Q̇ defect of any size corresponded with PE in 26% of cases. Thus, both should be classified as intermediate probability.[31]

The limitations of the original PIOPED criteria led the investigators to revise the original interpretation criteria for easier application and better integration of clinical pretest probability of PE. Modifications to original PIOPED interpretation criteria were used in the PIOPED II trial[32] (Table 30-3), which decreased the number of intermediate scan readings (73.5% of patients had V̇/Q̇ scans with

TABLE 30-3 Revised PIOPED Criteria for Interpretation of Lung Scans[a]

High probability (≥80%)	
	≥2 Large segmental perfusion defects (>75% of a segment) without corresponding ventilation or radiographic abnormalities
	1 Large segmental perfusion defect and ≥2 moderate segmental perfusion defects (25%–75% of a segment) without corresponding ventilation or radiographic abnormalities
	≥4 Moderate segmental perfusion defects without corresponding ventilation or radiographic abnormalities
Intermediate probability (20%–79%)	
	1 Moderate to <2 large segmental perfusion defects without corresponding ventilation or radiographic abnormalities
	Corresponding ventilation-perfusion defects and radiographic parenchymal opacity in lower lung zone
	Single, moderate, matched ventilation-perfusion defects with normal radiographic findings
	Corresponding ventilation-perfusion defects and small pleural effusion
	Difficult to categorize as normal, low, or high probability
Low probability (<19%)	
	Multiple matched ventilation-perfusion defects, regardless of size, with normal radiographic findings
	Corresponding ventilation-perfusion defects and radiographic parenchymal opacity in upper or middle lung zone
	Corresponding ventilation-perfusion defects and large pleural effusion
	Any perfusion defects with substantially larger radiographic abnormality
	Defects surrounded by normally perfused lung (stripe sign)
	>3 Small segmental perfusion defects (<25% of a segment) with a normal radiograph
	Nonsegmental perfusion defects (cardiomegaly, aortic impression, enlarged hila)
Very low probability	
	≥3 Small segmental perfusion defects (<25% of a segment) with a normal radiograph
Normal probability	
	No perfusion defects; perfusion outlines the shape of the lung seen on the radiograph

[a] *Criteria generated after completion of prospective study.*

definitive interpretation) and provided a more accurate assessment of angiographically proven PE than the original criteria (increased sensitivity of 83% compared with the original criteria, with virtually unchanged specificity of 96%).

In another attempt to avoid the clinically problematic intermediate probability category, which in some series accounted for half of the results and contributed to the reputation of planar $\dot{V}/\dot{Q}$ scan as an equivocal examination, the Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis (PISA-PED)[33] introduced criteria (Table 30-4) for interpretation of perfusion-only lung scan. Instead of size, number, and match or mismatch, criteria were based on shape and anatomy. Thus, PE was considered present when there was one or more wedge-shaped perfusion defects and absent when there was normal perfusion, nonsegmental perfusion defects smaller than radiographic lesions, or non-wedge-shaped defects. All other findings were called nondiagnostic. When the PISA-PED study[33] utilized perfusion scanning alone in conjunction with the chest radiograph, the sensitivity and specificity of scintigraphy were 92% and 87%, respectively. The prevalence of PE was high (39%). When considered in conjunction with clinical assessment of the likelihood of PE (very likely, possible, or unlikely), the positive predictive value (PPV) of a perfusion scan was 99%; the combination of a near-normal or abnormal perfusion scan without segmental defects and low clinical likelihood of PE had a negative predictive value (NPV) of 97%. Using standardized clinical assessment and perfusion lung scanning, the authors were able to accurately diagnose or exclude PE (PPV, 96%; NPV, 98%). CT angiography was required in only a minority of cases having discordant clinical and scintigraphic findings. Thus, although results from the PISA-PED study have never been reproduced and relied heavily on skilled interpretations of chest x-ray, they at least suggest that perfusion-only images may be a viable option in patients incapable of completing ventilation images.[5]

Along the same lines, modified PIOPED II criteria (Table 30-4) were established in 2008, diagnosing PE when the equivalent of ≥2 large segmental perfusion scan-chest radiograph mismatches were observed. (Findings could include 1 large and 2 moderate segmental mismatches or 4 moderate segmental mismatches.)[34] PE was considered absent when there was normal or near-normal perfusion, and the perfusion defect was nonsegmental and non-wedge-shaped.[34] All other scans were called nondiagnostic.

When perfusion scans obtained in PIOPED II were reinterpreted using composite reference standard (all PIOPED II patients were eligible for this study if they had a CTA or digital subtraction angiography [DSA] diagnosis, an interpretable perfusion scan and chest radiographs, and a Wells' score), investigators found only 21% of patients with nondiagnostic results using revised PIOPED II criteria.[34] Only 11% patients had nondiagnostic perfusion scans among the 72% of patients with normal or near normal chest radiograph. The prevalence of PE in the sample was 19%. Using the modified PIOPED II criteria, and after excluding the nondiagnostic perfusion scans, the sensitivity of "PE present" reached 85%, and the specificity of "PE absent" was 93%. When using PISA-PED criteria, none had nondiagnostic perfusion scans; the sensitivity of a "PE present" scan was 80%, and the specificity of "PE absent" scan was 97%. Based on these findings, it was postulated that perfusion scintigraphy combined with chest radiography can provide diagnostic accuracy similar to CT angiography at a lower cost and, more importantly, at a lower radiation dose.[34]

Older data from prospective and large studies have reported outcome-based results of $\dot{V}/\dot{Q}$ scans combined with clinical assessment and noninvasive leg testing.[23,35] In patients with suspected PE with nonhigh probability or nondiagnostic $\dot{V}/\dot{Q}$ scan, normal cardiorespiratory reserve, and negative serial noninvasive leg tests for proximal venous thrombosis (as determined by serial impedance plethysmography), PE at 3-month follow-up occurred in only 0.6% of cases while the patients were not on anticoagulation.[35] Among patients with suspected PE but a low-probability clinical assessment and negative serial noninvasive leg tests, as well as a nondiagnostic $\dot{V}/\dot{Q}$ scan, PE at 3-month follow-up occurred in 0.5% of patients.[23] When the probability for clinical assessment was intermediate, PE occurred in only 0.4% of patients.[23] These studies determined that anticoagulation could be safely withheld in patients with adequate cardiorespiratory reserve who did not have high-probability ventilation–perfusion scans or proximal venous thrombosis, since the incidence of recurrent PE is very low. Unfortunately, the criteria used in these studies to categorize the probability of PE (normal, nondiagnostic, or high) were different than those used in the PIOPED study, and direct comparison is not possible.

■ Imaging Protocols for the Evaluation of Pulmonary Embolism

All of the aforementioned interpretation criteria are based on planar images, that is, static, two-dimensional images in various projections. A routine planar perfusion scan should include at least six

TABLE 30-4 Modified PIOPED II and PISA-PED Criteria for Interpretation of Perfusion Scans

	Modified PIOPED II	PISA-PED
PE present	• High probability (≥2 segments of perfusion scan—chest radiograph mismatch. May be ≥2 large segmental mismatches, or 1 large and 2 moderate mismatches, or 4 moderate segmental mismatches)	• ≥1 Wedge-shaped perfusion defects
PE absent	• Normal perfusion • Near normal • Contour defect (caused by enlarged heart, mediastinum, or diaphragm) • Perfusion defect, not wedge-shaped	• Normal perfusion • Very low probability • Nonsegmental lesion (e.g., prominent hilum, cardiomegaly, elevated diaphragm, linear atelectasis, costophrenic angle effusion with no other perfusion defect in either lung) • Perfusion defect smaller than radiographic lesion • 1–3 Small segmental defects • Solitary CXR-Q matched defect in the mid or upper lung zone confined to a single segment • Stripe sign present around the perfusion defect (best tangential view) • Pleural effusion ≥1/3 the pleural cavity with no other perfusion defect in either lung
Not diagnostic	• Cannot classify as PE-positive or PE-negative	• All other findings

Modified with permission from Sostman HD, Miniati M, Gottschalk A, Matta F, Stein PD, Pistolesi M. Sensitivity and specificity of perfusion scintigraphy combined with chest radiography for acute pulmonary embolism in PIOPED II. J Nucl Med. 2008;49(11):1741–1748.

views of the lungs: anterior, posterior, right and left lateral, and right and left posterior oblique views, using a large-field-of-view high-resolution gamma camera. Right and left anterior oblique views may be helpful in selected cases. Ventilation images are obtained in multiple projections, which correspond to those obtained during the perfusion study. However, despite imaging in multiple projections, two-dimensional images of three-dimensional organs may underestimate abnormalities. For instance, a solitary segmental perfusion defect within the medial basal segment of the right lower lobe is completely surrounded by normal lung. Consequently, a perfusion defect in this segment will not be detected on planar perfusion imaging. Also, interpretation may be equivocal, as some anatomic structures may appear suspicious on planar images due to overlapping activity or artefact (e.g., interlobar fissures).

Thus, in recent years the use of single-photon emission computed tomography (SPECT) imaging has increased generally.[36] Technologic advances have also been made with SPECT in PE-imaging, including use of new radiopharmaceuticals like ^{99m}Tc Technegas,[37] which is currently not available in the United States (Figs. 30-3 and 30-4). Total acquisition time for the SPECT $\dot{V}/\dot{Q}$ exam is 20 to 30 min for a dual-headed camera; it generally increases specificity and reduces the number of equivocal results.[7,10,38]

SPECT has several advantages over planar imaging, including higher contrast resolution and avoidance of overlapping small perfusion defects by normal tissue, resulting in better sensitivity and/or specificity with SPECT compared to planar images. In a pivotal proof-of-concept animal study using artificial emboli, the sensitivity of planar $\dot{V}/\dot{Q}$ lung scan was 67% compared with 93% for SPECT.[39] Later clinical studies found similar results, that is, more and better delineated mismatched defects, better quantification, and less interobserver variation.[40] One study found 53% more mismatched regions with SPECT, and another noted an increase in specificity from 78% to 96% at similar sensitivities. Finally, one study found increases in sensitivity (76% to 97%) and specificity (85% to 91%) with SPECT compared to planar images.[7]

A recent meta-analysis summarized the current literature on SPECT $\dot{V}/\dot{Q}$ scan, including the results from a few other

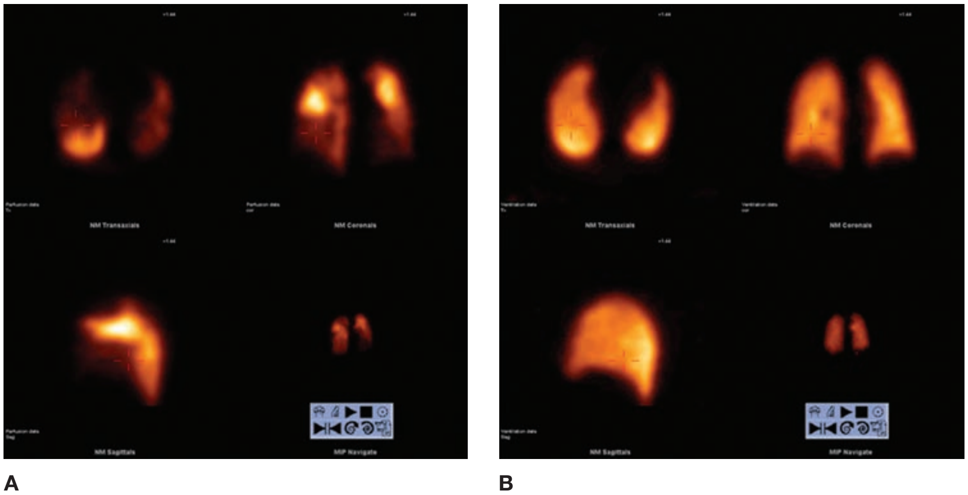
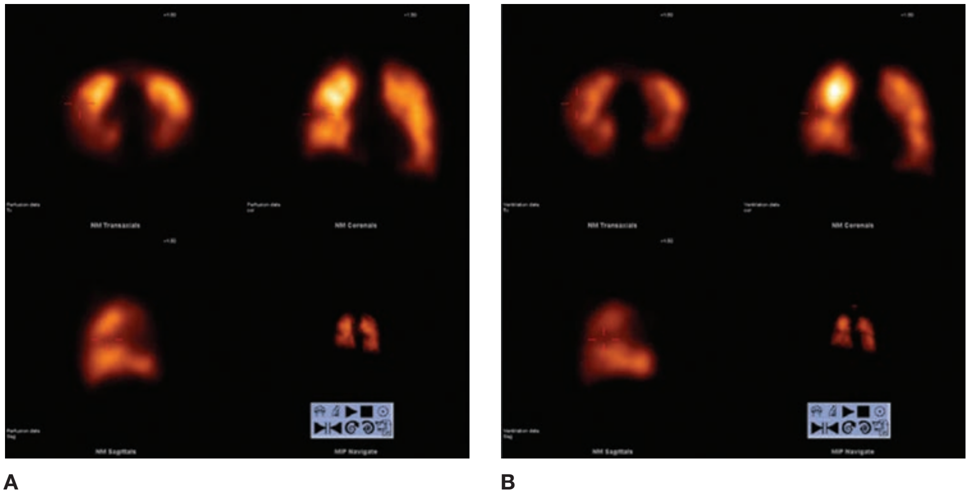


Figure 30-3 High-probability $\dot{V}/\dot{Q}$ SPECT scan for pulmonary embolism. Ventilation scan using ^{99m}Tc Technegas aerosol in transaxial, sagittal, and coronal views (**B**) is within normal limits. Perfusion scan using ^{99m}Tc MAA in transaxial, sagittal, and coronal views (**A**) shows large segmental defects in both lungs. This combination of findings *(mismatch)* is consistent with pulmonary embolism.

FIGURE 30-4 V̇/Q̇ SPECT scan for pulmonary embolism. Ventilation scan using ^{99m}Tc Technegas aerosol in transaxial, sagittal, and coronal views (**B**) and perfusion scan using ^{99m}Tc MAA in transaxial, sagittal, and coronal views (**A**) show *matched* defects.



meta-analyses. Although the data were relatively sparse, the sensitivity of V̇/Q̇ SPECT was generally better than CTA with comparable specificity (Table 30-5).[38] Some investigators have also suggested the use of combined SPECT V̇/Q̇ scan and low-dose CT scan to further improve accuracy in diagnosing PE and to help provide a differential diagnosis in those patients with V̇/Q̇ scan results negative for PE.[41] The interpretation criteria, however, for SPECT V̇/Q̇ scan are not yet clearly defined or universal. It seems that the classic PIOPED or PISA-PED criteria cannot simply be transposed from planar to SPECT V̇/Q̇ scanning.[38] Instead, much simpler criteria (Table 30-6) have been proposed and propagated in the latest guidelines. Perhaps the most important advantage of SPECT V̇/Q̇ scans is a significant reduction in equivocal scans; that is, most investigators report a ≤3% nondiagnostic rate.[10,38,42] Despite the many advantages of SPECT, the substitution of planar V̇/Q̇ by SPECT V̇/Q̇ scan has been considered controversial.[24,43,44] However, according to the latest guidelines on V̇/Q̇ scans from the European Association of Nuclear Medicine, SPECT or SPECT/CT is now considered the method of choice.[10]

Interest has arisen in “positive” imaging based on antibody fragments and radiolabeled peptides directed against components of thromboemboli and glycoprotein IIb/IIIa receptors on the surface of activated platelets.[45] ^{99m}Tc-labeled apcitide is a synthetic peptide that binds with a high affinity and specificity to the glycoprotein IIb/IIIa receptor on the membrane of activated platelets.[46] The main advantage of the agent is its ability to distinguish between acute and chronic DVT.

Several ^{99m}Tc-labeled peptides directed against activated platelets are currently under investigation in the evaluation of patients with suspected pulmonary embolism. Radiolabeled peptide imaging has the potential to serve as a single, comprehensive modality in the evaluation of patients with venous thromboembolism.

TABLE 30-5 Comparative Diagnostic Values of CT Angiography and V̇/Q̇ SPECT

Modality	Sensitivity	Specificity	PPV	NPV
CT angiography	82%–88%	95%	94%	85%
V̇/Q̇ SPECT	93%–96%	93%	88%	96%

Data from Hess S, Frary EC, Gerke O, et al. State-of-the-Art Imaging in Pulmonary Embolism: Ventilation/Perfusion Single-Photon Emission Computed Tomography versus Computed Tomography Angiography—Controversies, Results, and Recommendations from a Systematic Review. Semin Thromb Hemost. 2016;42(8):833–845.

Another agent is the ^{99m}Tc-labeled anti–D-dimer (DI-80B3) monoclonal antibody Fab′ fragment that binds specifically to thromboemboli. In a small, prospective, multicenter study to investigate the sensitivity and specificity of ^{99m}Tc DI-80B3/SPECT in patients with suspected acute PE, ^{99m}Tc-DI-80B3/SPECT had a sensitivity of 76.2% and a specificity of 90.5%.[47] Several preclinical studies are underway to investigate the role of fibrin and platelet imaging for thrombus detection.[48] At the current time, most results are limited to the preclinical setting, and translation to clinical results is not warranted.

■ Recommendations for the Use of V̇/Q̇ Scan and CT Angiography in Suspected Pulmonary Embolism

Over the past decade, there have been significant technical improvements in both CTA and V̇/Q̇ scanning. However, usage of chest CTA in patients with suspected PE has increased significantly and markedly surpassed the usage of V̇/Q̇ scan.[49] Studies show equivalent outcomes-based results, and a recent meta-analysis actually found V̇/Q̇ SPECT superior to CTA.[38] However, the ready availability of CTA, particularly after regular work hours, and the bias towards anatomic, rather than functional, imaging has made CTA the favored diagnostic test for PE.[17]

In a large, prospective, randomized study with high pretest probability and/or positive D-dimer levels, the false-negative rates for V̇/Q̇ scan and CTA were very close at 1% and 0.4%, respectively.[50]

TABLE 30-6 New V̇/Q̇ SPECT Diagnostic Criteria for Pulmonary Embolism (PE)

PE	• Wedge-shaped V̇/Q̇ mismatch (≥1 segment or 2 subsegments)
No PE	• Normal perfusion pattern in keeping with the anatomic boundaries of the lungs • Only matched or reversed-mismatched V̇/Q̇ defects of any size, shape, or number • Mismatch that does not follow a lobar, segmental, or subsegmental pattern
Nondiagnostic	• Widespread V/P abnormalities not typical of specific diseases

Adapted with permission from Bajc M, Schumichen C, Gruning T, et al. EANM guideline for ventilation/perfusion single-photon emission computed tomography (SPECT) for diagnosis of pulmonary embolism and beyond. Eur J Nucl Med Mol Imaging. 2019;46(12):2429–2451.

Despite the fact that CTA in some studies detects more emboli than $\dot{V}/\dot{Q}$ scanning,[50] the risk of recurrent PE and death have not decreased during the CTA era.[51] In fact, the ability of sophisticated multidetector CT scans to detect emboli in subsegmental branches of the pulmonary arteries created a healthcare problem by encouraging clinicians to treat patients who have incidental, asymptomatic pulmonary emboli whose natural history and optimal management are currently unknown (except in cancer patients in whom these emboli carry a poor prognosis).[52,53] The scans are usually ordered in the emergency department with no particular pretest diagnosis; this may represent a double-edged sword.

Recent reports of overutilization of imaging for suspected PE is probably due to a combination of increased awareness of PE and widespread availability of advanced imaging. However, the result is a significant drop in confirmed PE diagnoses in patients undergoing a workup for suspected PE; that is, the incidence of a positive diagnosis has dropped from 50% in the 1980s to 5% at present.[54] The same may be true with SPECT $\dot{V}/\dot{Q}$ scanning, as it is not yet clear whether treating a small peripheral PE confers an outcome benefit unless patients have significant clot burden and limited cardiovascular reserve.[27]

In patients with a normal chest radiograph, the ventilation–perfusion lung scan is an effective, noninvasive initial study. However, in patients with significant chest radiographic abnormalities, CT angiography is more likely to provide a definitive diagnosis of PE or an alternative diagnosis, as well as risk assessment of PE based on the evaluation of right ventricular size and function.[55,56] Furthermore, the combination of CT angiography and CT venography has the potential to provide a single, comprehensive evaluation of patients with suspected venous thromboembolism (VTE), albeit with increased radiation exposure.

$\dot{V}/\dot{Q}$ scanning remains an important alternative to CTA in patients with contrast allergy or renal failure. On the other hand, $\dot{V}/\dot{Q}$ scanning may be the modality of choice to evaluate patients with chronic thromboembolic disease, and for follow-up of PE after therapy.[24] Additionally, concern exists regarding the high radiation exposure, particularly to the female breast, that is associated with chest CTA.[57,58] Despite dose-reduction schemes, CTA may deliver significant radiation doses of 20 mGy (2.0 rad) to the breasts of an average-sized woman;[59] in contrast, breast irradiation with $\dot{V}/\dot{Q}$ scan is approximately 0.28 to 0.9 mGy.[60]

In general, there is great concern that the increasing use of CTA may result in an increased incidence of radiation-related cancer in the future.[57] However, the potential latent carcinogenic effects of such radiation exposure at this time remain unknown. As part of the Choosing Wisely campaign initiated in 2013 by the American Board of Internal Medicine, which focused on questioning medical tests and procedures that may be unnecessary, and in some instances can cause harm, the Society of Nuclear Medicine and Molecular Imaging (SNMMI) has recommended to avoid using a CTA to diagnose PE in young women with a normal chest radiograph and to consider a $\dot{V}/\dot{Q}$ study instead.[61]

Finally, there is considerable debate about the radiation doses received by the fetus from pulmonary CTA compared with $\dot{V}/\dot{Q}$ scanning.[62] During pregnancy, when only a perfusion scan with 50 MBq of ^{99m}Tc MAA is used, the fetal absorbed dose is 0.1 to 0.2 mGy. It is estimated that a 16-slice MDCT scan gives an absorbed fetal dose of 0.24 to 0.66 mGy during the first trimester.[63] The advantages and disadvantages of CTA and $\dot{V}/\dot{Q}$ scan in the evaluation of PE are summarized in Table 30-7.

TABLE 30-7 Comparison of CTA and $\dot{V}/\dot{Q}$ Scan in the Evaluation of PE

	Advantages	Disadvantages
CTA	• Accuracy • Interobserver agreement • Provides alternative diagnosis, and risk assessment based on the evaluation of right ventricular size and function • After-hours availability • High speed in image acquisition • Suitable for unstable patients • Binary reports ("PE" or "no PE")	• Radiation exposure • Contrast allergy • Nephrotoxicity • Relative cost • Potential overdiagnosis of non–clinically relevant peripheral PE
$\dot{V}/\dot{Q}$ scan	• High NPV in low pretest probability • High PPV in high pretest probability • Low radiation • Relative cost • Serial follow-up	• Low overall specificity • Low interobserver agreement • After-hours availability • Slower speed in image acquisition • Unsuitable for unstable patients • Limited in providing alternative diagnosis • Unpopular probabilistic reports

Data from Reid JH, Coche EE, Inoue T, et al. Is the lung scan alive and well? Facts and controversies in defining the role of lung scintigraphy for the diagnosis of pulmonary embolism in the era of MDCT. Eur J Nucl Med Mol Imaging. 2009;36(3):505–521.

■ Use of $\dot{V}/\dot{Q}$ Scan in the Era of COVID-19

On February 11, 2020, the World Health Organization (WHO) gave the official name of COVID-19 for a 2019 novel coronavirus (SARS-CoV-2) that caused a global pandemic.[64] COVID-19 is caused by a highly transmittable and pathogenic viral infection that is believed to be transmitted via respiratory droplets and fomites.[64] Most people who contracted COVID-19 had mild symptoms, but the disease also caused severe illnesses and even death, especially in older people and patients with underlying medical conditions.[65]

Patients who contract COVID-19 have a high risk of PE and DVT.[66] A recent systemic review and meta-analysis found the pooled incidence rate of PE and DVT to be 16.5% and 14.8%, respectively, with more than half of PE patients lacking a DVT.[67] Due to the risk of transmission of COVID-19 to patients and staff alike, the SNMMI and European Association of Nuclear Medicine (EANM) issued warnings in March 2020 about use of lung ventilation studies with aerosolized agents.[68,69] In view of the unknown risk of transmission of COVID-19 and ability to disinfect the ventilation systems, early during the pandemic most institutions used perfusion-only studies when other imaging modalities, such as CTA, could not be obtained. Ventilation images were acquired rarely, and only if necessary, to make the diagnosis of acute PE after patients tested negative for COVID-19 using xenon (^{133}Xe) gas in the United States or krypton (^{81m}Kr) gas or ^{99m}Tc Technegas where available. Since Technegas does not release aerosolized particles, it has the potential to allow institutions to resume full $\dot{V}/\dot{Q}$ scans. Technegas is still under review by the U.S. Food and Drug Administration (FDA) as a ventilation agent.

Although there is a paucity of data supporting lung perfusions studies only,[70] it is likely that data on use of PISA-PED criteria in the era of COVID-19 will grow in the foreseeable future. This is particularly important since COVID-19 can also cause renal injuries,[71] thereby limiting use of intravenous contrast agents. Since this is a new disease, many questions remain unanswered about the best imaging modality for patients with COVID-19 suspected to have a PE.

Summary of Conclusions Regarding V̇/Q̇ Scanning

In summary, based on results from prospective and outcome-based studies, the following conclusions can be drawn regarding use of V̇/Q̇ scan and CTA in evaluating patients with suspected PE:

- Proper pretest clinical probability scoring is important, irrespective of the imaging modality used. When imaging results for either V̇/Q̇ scan or CTA are discordant with the pretest probability, the alternative test should be recommended.
- Whenever possible, SPECT or SPECT/CT V̇/Q̇ scanning should be performed instead of planar V̇/Q̇ scanning.
- Whenever possible, V̇/Q̇ scans should be interpreted as either "positive for PE," "nondiagnostic study," or "no evidence of PE."
- A normal V̇/Q̇ scan excludes the diagnosis of clinically significant PE.
- Patients with very low- or low-probability scans and a low clinical likelihood of PE have a low (<5%) prevalence of PE and generally do not require CTA or anticoagulation.
- Patients with very low- or low-probability scans, intermediate or high clinical likelihood of PE, and negative serial noninvasive venous studies of the lower extremities generally do not require anticoagulation. In selected cases, CTA is helpful in excluding PE and providing an alternative diagnosis.
- Clinically stable patients with an intermediate-probability scan require noninvasive venous studies of the legs; if negative, CTA is required for definite diagnosis of PE.
- A clinically stable patient with a high-probability scan and high clinical likelihood of PE requires treatment; no further diagnostic tests are required to confirm the diagnosis.
- Clinically stable patients with a high-probability scan and a low clinical likelihood of PE require noninvasive venous studies of the legs; if negative, CTA may be required for definitive diagnosis.
- V̇/Q̇ scanning has a high negative predictive value and should be used particularly when a low radiation dose is desirable, for example, in young females with normal chest radiograph, outpatients with low clinical probability plus normal chest radiograph, patients with high clinical probability plus normal chest radiograph, patients with prior contrast allergy, or patients with renal failure.
- To minimize radiation to the fetus in a pregnant patient, a 1- to 2-day protocol is suggested. Perfusion-only scans should be performed on day 1, using a reduced dose of ^{99m}Tc MAA. If normal, ventilation images are not required.
- V̇/Q̇ scanning is preferred over pulmonary CTA for follow-up of PE and investigating the etiology of pulmonary hypertension.
- If after-hours imaging is not available, and a clinically stable patient has a high clinical suspicion of PE, a reasonable approach includes administering a single dose of low-molecular-weight heparin and imaging the patient the next morning. This strategy may be particularly advisable for performing V̇/Q̇ scanning in young women in order to avoid the excessive breast radiation exposure associated with CTA.
- If there is a contraindication to V̇/Q̇ scanning or CTA, MRA of the pulmonary artery may be performed in centers that perform it well. Caution is advised if contraindications are present related to poor renal function, as nephrogenic systemic fibrosis/nephrogenic fibrosing dermopathy occurs rarely after gadolinium-containing contrast material.[72,73]
- In regions where COVID-19 numbers are high or increasing, or if there is inadequate testing, it may be appropriate to perform perfusion-only studies. If a ventilation study is still necessary to help diagnose airway and vascular diseases, it should be performed following local and institutional protective protocols for aerosol-generating procedures. A perfusion-only study is unlikely to benefit patients with COVID-19 infection who have an abnormal chest x-ray, as ^{99m}Tc MAA distribution will probably be abnormal. The use of pretest probability for PE assessment and D-dimer level measurement are paramount in these scenarios.

EVALUATION OF CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

Chronic thromboembolic pulmonary hypertension (CTEPH) is defined as the persistence of pulmonary hypertension (defined as a mean pulmonary artery pressure >25 mm Hg) after a single or recurrent PE. CTEPH is a serious underdiagnosed disease and the only cause of pulmonary hypertension that can be potentially cured by pulmonary endarterectomy (PEA). Estimates are that between 0.5% and 3.8% of patients eventually develop CTEPH after an acute PE; CTEPH occurs in up to 10% of those with a history of recurrent PE.[74,75]

It is not entirely clear why some patients with a history of acute PE go on to develop CTEPH. The risk of developing CTEPH increases in patients with a history of prior PE, presentation at a younger age, larger perfusion defects, and idiopathic pulmonary embolism at presentation.[74] Diagnosis is the key to survival in CTEPH, as without appropriate treatment, long-term prognosis is poor. There is a positive correlation between increased mean pulmonary artery pressure and mortality.[76] Unfortunately, the clinical features, laboratory studies, chest radiograph, electrocardiogram, and echocardiogram are often unreliable in distinguishing CTEPH from primary and nonthromboembolic secondary pulmonary hypertension. In most centers, conventional pulmonary angiography remains the gold standard imaging study to confirm the diagnosis of CTEPH and to determine whether surgical intervention is indicated; chest CTA and MRA provide complementary information if needed.

V̇/Q̇ scanning is a safe, noninvasive technique that facilitates selection of patients with pulmonary hypertension for pulmonary angiography to confirm the diagnosis of chronic PE. V̇/Q̇ scanning remains one of the most important diagnostic tests to help distinguish CTEPH from other forms of pulmonary hypertension. In a retrospective analysis, V̇/Q̇ scanning had a sensitivity of 97.4% for the detection of chronic thromboembolic disease, while CT angiography was only 51% sensitive.[77]

Patients with CTEPH usually have at least one, and often several, segmental or larger, mismatched perfusion defects.[78] In order to prevent potential adverse hemodynamic effects when performing V̇/Q̇ scans in patients with pulmonary hypertension, the number of ^{99m}Tc MAA particles administered should be reduced. V̇/Q̇ scanning may underestimate the magnitude of central vascular occlusion by chronic emboli, as determined at conventional pulmonary angiography and/or thromboendarterectomy.[79]

Most patients with primary or secondary nonthromboembolic pulmonary hypertension have low-probability scans. The distribution of ^{99m}Tc MAA particles within the lungs is diffuse and nonhomogeneous. Patients with CTEPH rarely, if ever, have normal or very low-probability scans. Thus, a low-probability ventilation-perfusion scan effectively excludes chronic thromboembolism as the cause of pulmonary hypertension.

Even though SPECT is more sensitive than planar perfusion lung scanning for identifying obstructed segments in CTEPH, it still underrepresents the true extent of the vascular occlusions in CTEPH.[80] Although CTA and MRA may provide complementary information, they often miss the eccentric lesions of CTEPH. Any patient with unexplained pulmonary hypertension should be evaluated for the presence of CTEPH, and a V̇/Q̇ scan remains the recommended screening method of choice.[81]

QUANTITATIVE VENTILATION–PERFUSION LUNG SCANNING

In patients undergoing pulmonary resection, bronchoscopic lung volume reduction surgery, or lung transplantation, quantitative ventilation–perfusion lung scanning is a useful method for determining regional lung function and predicting postoperative pulmonary function.[82–85] Currently, the presurgical assessment to predict response to lung volume reduction surgery (LVRS) in patients with emphysema is mainly performed using chest CT scan, which provides an anatomic diagnosis of emphysema, delineates its extent and distribution, and detects any other incidental findings that may represent a contraindication to the procedure.[86,87]

$\dot{V}/\dot{Q}$ scanning can provide additional and important information concerning the heterogeneity and distribution of the functional disruption caused by emphysema; patients with advanced upper lobe–predominant emphysema derive the most benefit from LVRS.[83,87,88] Rectangular regions of interest over the anterior and posterior scintigraphic images of each lung are divided into upper, middle, and lower zones of equal craniocaudal height, and the geometric mean for a given zone is obtained and presented as the percent perfusion to that zone.[89]

In patients being considered for lung cancer surgical resection, $\dot{V}/\dot{Q}$ scan can predict postoperative pulmonary function and assess the risk of surgery for patients with borderline pulmonary function.[90] The predicted postoperative forced expiratory volume in 1 s (ppo FEV_1) is calculated by multiplying the preoperative value by the ratio of the counts in the remaining lung to total lung activity[91,92] (Fig. 30-5).

Lung perfusion scintigraphy can quantify the degree of right-to-left shunting due to patent foramen ovale, atrial septal defect, elevated right heart pressures, or hepatopulmonary syndrome (HPS). HPS is defined as the triad of liver disease, pulmonary gas exchange abnormalities leading to hypoxemia, and intrapulmonary vascular dilatations leading to right-to-left intrapulmonary shunting.[93,94] The number of injected ^{99m}Tc MAA particles should be reduced in patients with suspected right-to-left shunt. Normally, there is $<5\%$ of ^{99m}Tc MAA uptake in the brain, but in HPS, fewer MAA particles are entrapped in pulmonary vasculature and are able to enter the systemic circulation and lodge in different organs (thyroid, spleen, liver, kidneys, and brain), leading to $>6\%$ uptake in the brain (Fig. 30-6). The major disadvantage of perfusion scintigraphy is that it cannot distinguish intracardiac from intrapulmonary right-to-left shunt. Estimation of the right-to-left shunt fraction is calculated using the equation: $100 \times (\text{TBC} - \text{TLC})/(\text{TBC})$ where TBC is total body count and TLC is total lung count. A less precise alternative method of right-to-left shunt quantification derives an estimate of total body counts from the measurement of renal and/or cerebral activity.

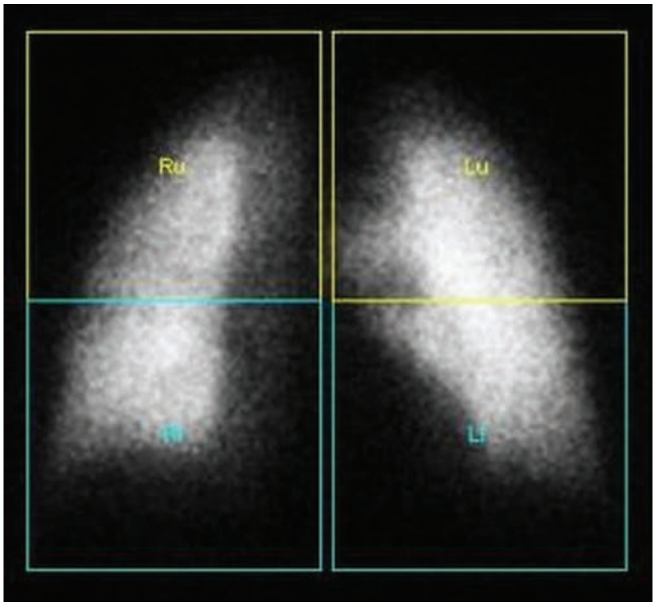


Figure 30-5 Quantitative perfusion lung scan. Regional perfusion can be quantified by outlining regular or irregular regions of interest and generating ratios that correspond to percentage of total pulmonary function. Images shown were analyzed by dividing each lung into two equal rectangles.

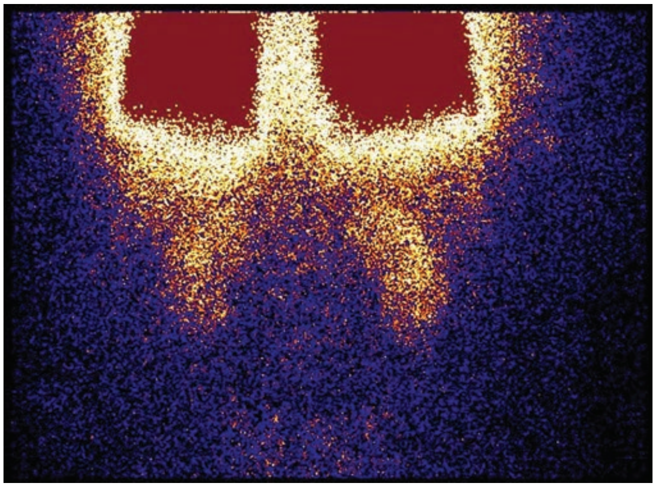


Figure 30-6 Right-to-left shunt in a patient with hepatopulmonary syndrome. Perfusion scan using ^{99m}Tc MAA is showing particles in the systemic circulation lodged in the kidneys.

ASSESSMENT OF ALVEOLAR-CAPILLARY MEMBRANE PERMEABILITY AND MUCOCILIARY CLEARANCE

The clearance rate of inhaled ^{99m}Tc DTPA aerosol from the lungs can be measured using a gamma camera and used as an index of lung epithelial permeability.[95] Aerosols of relatively small aerodynamic diameter (e.g., ^{99m}Tc DTPA) are deposited largely within the small airways and alveoli; the normal half-time of ^{99m}Tc DTPA washout from the lungs is about 80 min.[96] In the presence of epithelial alveolar damage, the clearance of ^{99m}Tc DTPA is accelerated.[95] Such injuries are noted in amiodarone toxicity, inhalation damage in fire victims, pneumoconiosis, idiopathic pulmonary fibrosis, collagen vascular diseases, sarcoidosis, acute respiratory distress syndrome, and pneumocystis pneumonia.[95,97] Cigarette smoking or physiologic factors, such as posture and exercise, also influence epithelial lung clearance.[95,98] Since increased alveolar-capillary membrane permeability is relatively nonspecific, ^{99m}Tc DTPA aerosol clearance studies have been utilized only to assess the effects of therapy in patients with known pulmonary diseases.

Mucociliary clearance is the primary physiologic defense mechanism that protects the lungs from damage caused by inhaled particles and microorganisms. Determination of mucociliary clearance may be obtained after inhalation of relatively large, aerosolized particles, followed by measurement of the rate of clearance with a gamma camera. The rate of mucociliary clearance depends on several factors, including ciliary activity and mucus production.[99,100]

Inhaled particles, such as ^{99m}Tc MAA or ^{99m}Tc sulfur colloid, tend to be deposited within the proximal airways.[101] The normal mucociliary clearance half-time is approximately 24 h. Delayed mucociliary clearance is seen in patients with airway inflammation (e.g., cystic fibrosis, COPD, asthma, or viral respiratory tract infections), following bronchial surgery, or after irradiation. Scintigraphic assessment of alveolar-capillary membrane integrity and mucociliary clearance has not gained wide clinical use, and only a few centers worldwide use it routinely in a clinical context.[97,99] It has been employed in the development of orally inhaled drugs administered by inhalation by assessing their deposition patterns and the extent of delivery and the depth of penetration in the lungs.[102] Also, quantification of the impact of new drugs on the rate of mucociliary clearance is a key biomarker for products in development for the treatment of respiratory diseases.[103]

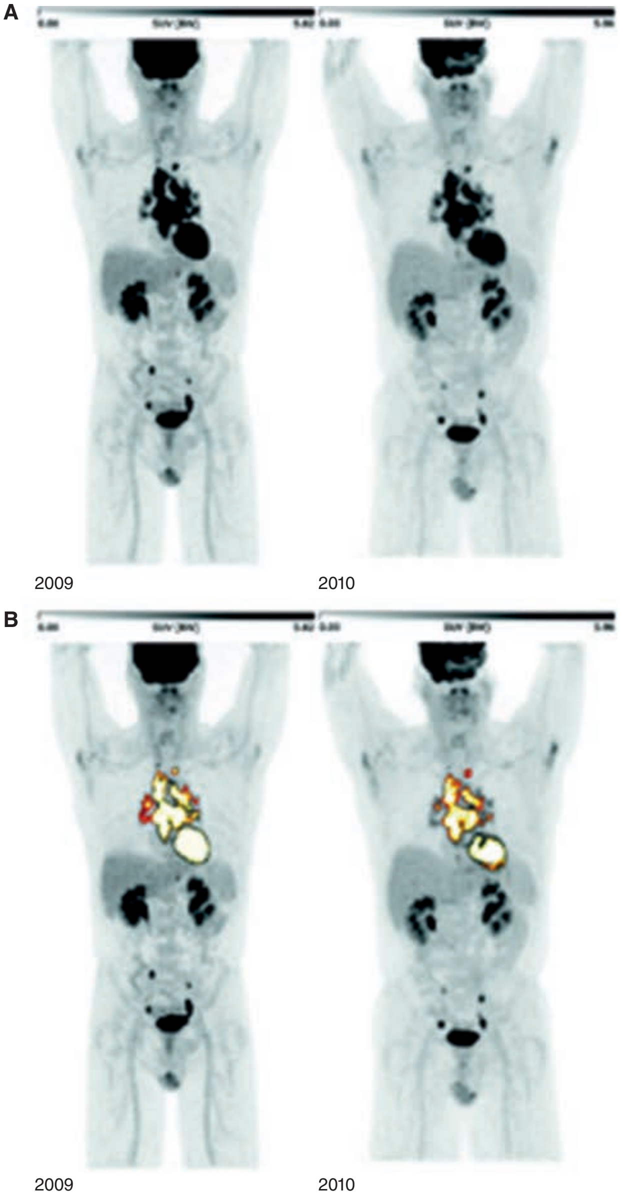
POSITRON EMISSION TOMOGRAPHY: BASIC PRINCIPLES

Positron emission tomography (PET) is a nuclear medicine imaging modality that provides a 3D image of molecular processes in the body. A PET scan detects gamma rays emitted by positron-emitting tracers. The most commonly used radiopharmaceutical in clinical PET today is 2-[^{18}F] fluorodeoxy-D-glucose (FDG), a fluorine-labeled glucose analogue with a favorable, 110-min half-life. FDG competes with glucose for transport into the cell and for enzymatic phosphorylation by hexokinase. Unlike glucose, once phosphorylated to FDG-6-phosphate, it does not undergo further metabolism and is trapped inside the cell—a net accumulation that allows for detection by PET.[104] FDG uptake is proportional to the metabolic activity of the cells that have undergone malignant transformation, and as such, have increased glucose transport and metabolism and increased hexokinase activity. FDG accumulation also depends on various factors, including cell mitotic rates, level of hypoxia (hypoxia-inducible factor 1-α upregulates glucose transport receptors), and the degree of cell differentiation (well-differentiated tumors have low FDG uptake).[105] In addition, inflammatory cells share many of the same features as malignant cells; therefore, FDG-PET imaging can be employed to assess infectious and inflammatory processes and diseases. FDG-PET imaging is performed in the fasting state to minimize competitive inhibition of FDG uptake by the circulating glucose in the plasma. (Hyperglycemia can result in decreased FDG accumulation in either malignant or inflammatory cells.)

A key feature of PET compared to conventional imaging techniques is the possibility of accurate quantification of the ongoing metabolic activities in normal or diseased states. The most common means used for this purpose is measurement of the *standardized uptake value* (SUV), a semiquantitative expression of the intensity of FDG accumulation in a region of interest (ROI) assigned on the PET scan. SUV normalizes the amount of FDG accumulation in a ROI to the total injected dose and the patient's body weight. It is calculated by dividing the mean activity within a selected region (or volume) of interest (in mCi/mL) by the injected dose (in mCi/kg). SUV_{max} is derived from the single voxel showing the highest uptake within a defined ROI, which typically represents the most metabolically active part of a tumor or inflammatory process.[106,107] However, it is important to note that several factors can impact SUV, including extravasation of the compound administered, hyperglycemia, exercise, nonfasting state, respiratory motion, time from injection, and size of ROI.[108]

During the past decade, efforts have been made for accurate quantification of focal, as well as diffuse, pulmonary diseases and disorders in the lung.[109] PET/CT imaging allows for precise assessment of disease activity compared to what is achievable by CT or other structural imaging techniques.[110] Significant efforts have been made for accurate quantification of focal lesions due to disorders, such as malignancies, as well as inflammatory processes in the lung (Fig. 30-7).[111] Over the years, these techniques have become readily available and can be adopted in the community for routine daily application. Partial volume correction for accurate quantification of focal lesions is a necessary step for assessing the true degree of aggressiveness of either benign or malignant disorders.[112] Furthermore, employing PET imaging for global disease assessment has become a necessity for determining and quantifying overall disease activity during the course of benign or malignant processes.[113–116]

Today, a mainstay of PET imaging is integrated PET/CT scanners, which allow combining metabolic and structural imaging modalities and have been shown to be superior to images generated from



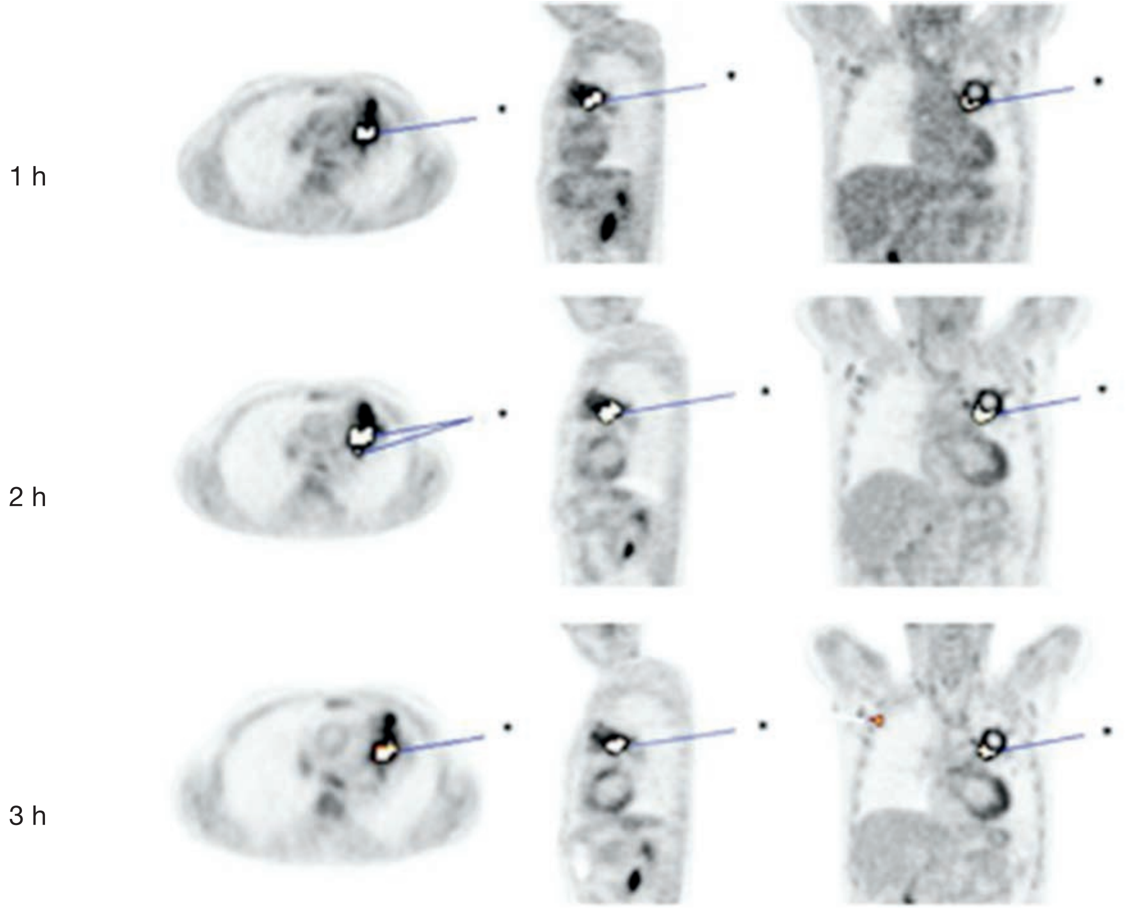
	Volume	SUV_{max}	SUV_{mean}	$\text{cSUV}_{\text{mean}}$	MVP	cMVP
2009	216.08	11.98	6.17	13.34	1333.73	2882.24
2010	131.40	10.59	5.30	12.29	690.75	1615.87

Figure 30-7 **A.** Comparison of MIP FDG-PET images of a patient with sarcoidosis performed in 2009 (*left*) and 2010 (*right*) reveals no significant difference in the extent and degree of FDG uptake in the thoracic structure. In fact, SUV of a comparable lesion in the mid-mediastinum was 5.83 and 5.75, respectively, which is almost identical. **B.** The same images with segmentation using an iterative thresholding algorithm (region of interest visualization, evaluation and registration [ROVER]; ABX, Radeberg, Germany) permits generating significant data with regard to the size of the lesions and their metabolic activities. These include the volume, SUV_{max}, SUV_{mean}, partial volume corrected SUV_{mean} ($\text{cSUV}_{\text{mean}}$), metabolic volume product (MVP), and corrected MVP as recorded above. These values clearly demonstrate a substantial reduction in the overall metabolic burden of the disease, which was not apparent from standard approach. MIP, maximum intensity projection; SUV, standardized uptake value. *(Reproduced with permission from Basu S, Saboury B, Werner T, et al. Clinical utility of FDG-PET and PET/CT in non-malignant thoracic disorders. Mol Imaging Biol. 2011;13(6):1051–1160.)*

separate PET and CT scans.[117] Current PET/CT scanners contain a state-of-the-art multidetector CT machine and time-of-flight PET technologies that reconstruct high-quality images with low FDG doses and short scan times, especially in large patients.[118]

PET/CT has some limitations related to attenuation artifacts leading to false-positive results on corrected images; motion and misregistration between PET and CT images can also result in major artifacts in regions adjacent to the heart and diaphragm.[119]

The newest technologic advances in PET include larger fields of view, including a total-body scanner[120] that can cover the entire human body. This allows very short single data acquisition without any movement,[121] better signal-to-noise ratio, smaller amounts of radioactivity injected, and the ability to perform kinetic analysis.[122] These instruments have significantly reduced the time required to image the body and improved the overall quality of the images.[123,124] Furthermore, these new PET scanners allow for delayed imaging over several hours in patients with lung cancer and other malignancies. Based on experience gained over the years, it has been established that delayed imaging allows for accurate determination of the extent of various malignancies, particularly lung cancer (Fig. 30-8). Therefore, it is conceivable that delayed imaging by these new PET scanners will eliminate unnecessary surgeries in patients with lung cancer.[125] Also, combined early and delayed imaging allows determination of tumor biology and, therefore, degree of aggressiveness of the cancer,[126] which may radically change management of patients with this common and potentially fatal disease.



Left Lung Tumor (*)	MTV	SUV$_{max}$	SUV$_{mean}$	pvcSUV$_{mean}$	TLG	pvcTLG
1 h	7.8	18.3	10.9	18.4	85.1	144.1
2 h	7.9 (1.28%)	23.6 (28.96%)	14.2 (30.28%)	23.4 (27.17%)	111.8 (31.37%)	184.8 (28.24%)
3 h	8.4 (7.69%)	26.7 (45.9%)	15.7 (44.04%)	26 (41.3%)	132.5 (55.7%)	218.8 (51.84%)

Figure 30-8 Multiple-time-point FDG-PET of a patient with left upper lobe malignancy. Sagittal, axial, and coronal PET scans of the patient at the first, second, and third hours are shown in the top three rows. The left upper lobe tumor (asterisks) is segmented using a commercial tool, and PET parameters including MTV, TLG, SUV$_{max}$, SUV$_{mean}$, pvcSUV$_{mean}$, and pvcTLG are quantified in the bottom chart. There is an increasing trend of FDG uptake in various parameters over time. MTV, metabolic tumor volume; pvcSUV, partial volume corrected standardized uptake value; pvcTLG, partial volume corrected total lung glycolysis; SUV, standardized uptake value; TLG, total lesion glycolysis. *(Reproduced with permission from Houshmand S, Salavati A, Segtnan EA, et al. Dual-time-point Imaging and Delayed-time-point Fluorodeoxyglucose-PET/Computed Tomography Imaging in Various Clinical Settings. PET Clin. 2016;11(1):65–84.)*

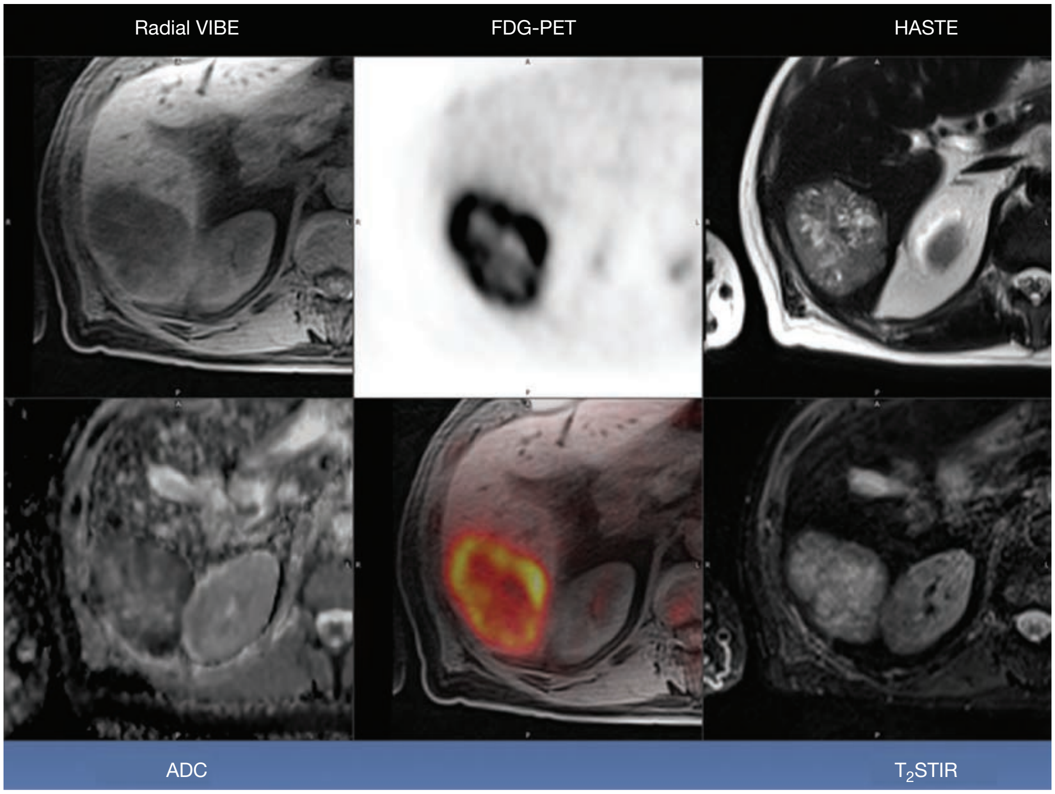


Figure 30-9 72-year-old male with lung cancer and liver metastases. Multisequence PET/MR of the liver demonstrates excellent co-registration of PET and multiple MRI sequences. Simultaneous acquisition maximizes accuracy of image registration and facilitates voxel-to-voxel correlations to support quantitative imaging. *(Reproduced with permission from Dr. Kent Friedman, Department of Radiology, Nuclear Medicine Section, New York University School of Medicine, New York, NY, USA.)*

Combined PET/MRI systems are now commercially available, but their added potential clinical benefit is still not fully validated,[127] particularly in thoracic disorders. There are early data on the value of diffusion-weighted MRI in assessing early response to chemotherapy in patients with lung cancer.[128] Tumor cellularity and proliferation can be evaluated using the "apparent diffusion coefficient" (ADC), and changes can be detected before tumor size reduction.[129] One of the main advantages of combined PET/MRI systems is the large amount of data obtained, allowing for quantitative studies (Fig. 30-9). Some limitations of MRI include issues related to the presence of implanted devices, claustrophobia, large body habitus, and cost. However, continued technologic advances aim to reduce those barriers.

ROLE OF POSITRON EMISSION TOMOGRAPHY IN THROMBOEMBOLISM, PULMONARY INFLAMMATION, AND INFECTION

PET can be used in evaluating patients with a variety on nonmalignant conditions, including suspected venous thromboembolism, suspected lung infection in the immunocompromised host, and noninfectious inflammatory lung diseases.

■ Potential Role for FDG-PET in Evaluating Suspected Venous Thromboembolism

In recent years, FDG-PET/CT has been explored in many inflammatory conditions, given the increased FDG uptake by activated inflammatory cells resulting from increased cell surface glucose transporters after cellular stimulation by various cytokines.[130] This is also the case with venous thromboembolism (VTE). Based on our own experience and the literature,[131] PET may be of value in assessing VTE for several reasons. Current imaging techniques, which are based on structural detection of thrombi, are limited in detecting thrombi throughout the body; deep venous thrombosis (DVT) and pulmonary embolism (PE) are only two manifestations of VTE, which may occur in parts of the venous vasculature not easily accessible by conventional methods (e.g., the pelvis). This also applies to the detection of any occult disease (i.e., cancer), which is often a key factor in developing VTE (Fig. 30-10). Additionally, structural imaging techniques cannot differentiate among different phases of thrombus formation, which may hold therapeutic implications.

Many of these shortcomings may be overcome by using FDG-PET/CT. Several case reports have addressed the incidental detection of VTE using FDG-PET in patients with cancer and bacteremia.[132,133] Inflammatory processes also play a key role in nonmalignant, noninfectious VTE in the setting of local vessel wall inflammation and inflammatory components, like activated leukocytes, in the thrombus itself.

In a small, prospective proof-of-concept series,[134] both DVT and PE were visible on FDG-PET/CT. All patients with proven acute lower-extremity DVT had marked FDG uptake along the venous wall at the site of thrombus. Diagnosis was established by positive compression ultrasound in patients with symptoms less than a week in duration; no history of cancer, infection, or prior DVT; and a high clinical probability according to Wells' DVT score. Conversely, none of the control patients with suspected, but disproven, DVT had FDG uptake in any part of the venous vasculature (patients with negative compression ultrasound; symptoms less than a week in duration; no history of cancer, infection, or prior DVT; and a low clinical probability according to Wells' DVT score. Results were more equivocal in PE, with some patients with high-probability $\dot{V}/\dot{Q}$ scans showing no FDG uptake in the pulmonary arteries. However, this may be attributed to significantly longer symptom duration (i.e., months) in some patients. It may, in fact, be that FDG-PET/CT was truly negative for active thrombi, since recent data suggest a significant decrease in FDG avidity over time.

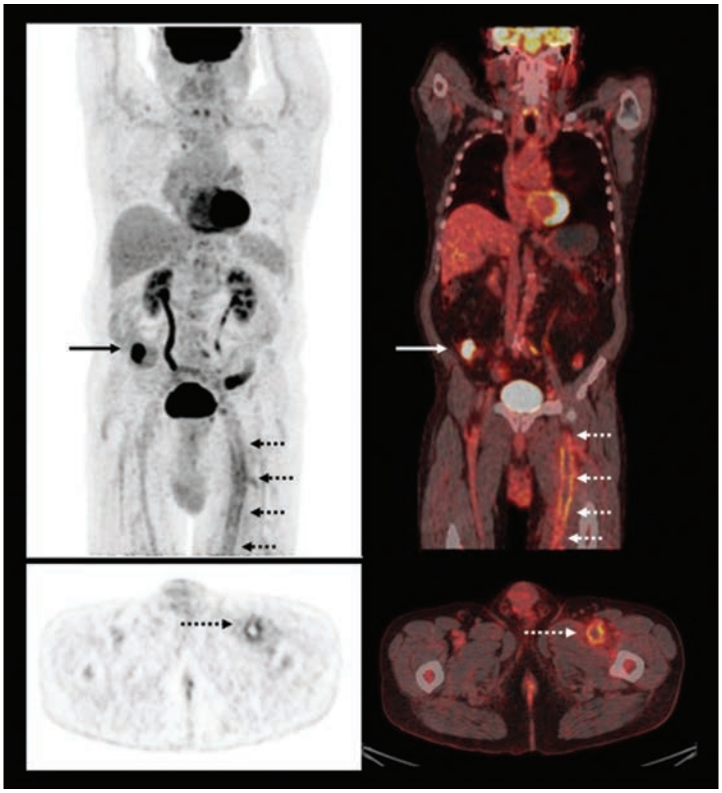


Figure 30-10 Incidental left femoral venous thrombosis on FDG-PET/CT scan. Coronal PET scan (***top left***), transaxial PET scan (***bottom left***), fused coronal PET/CT scan (***top right***), and fused transaxial PET/CT scan (***bottom right***) in a patient who underwent an FDG-PET/CT for malignancy of unknown etiology. Increased FDG uptake is seen along the acutely thrombosed vein *(interrupted arrows)*, and focally increased FDG uptake is seen in the cecum *(solid arrows)* corresponding to a biopsy-proven colon cancer.

In a pivotal study of 12 patients with confirmed proximal thrombosis in the lower extremity, the authors found a specificity of 87.5% to 100% and sensitivity of 87.5% to 100%, depending on SUV_{max} threshold used. In addition, they noted a steady decrease in SUV_{max} and possible complete normalization within 3 months.[135] This is in accordance with VTE pathophysiology. The thrombus may be classified as acute when inflammatory cells and mediators are abundant, subacute with subsiding inflammation and increasing fibrosis, and chronic with recanalization and loss of inflammation. These distinctions have significant clinical implications, since active thrombi require therapy, while unresolved old clots require no treatment. However, a substantial fraction of VTE patients experience symptoms of recurrence, and in as many as half, the morphologic features suggestive of the diagnosis remain for years after the first event.[131] FDG-PET/CT likely will differentiate new, active clots from old, inactive ones and facilitate an individualized therapeutic approach.

Although the literature is sparse, the role of FDG-PET/CT imaging appears to be promising in select patients suspected of VTE. The technique may contribute to detection of clots at any location throughout the body, establishment of an early diagnosis of underlying malignancy, and differentiation of acute from chronic thrombi.

Imaging of the Thorax in the Immunocompromised Host

^{67}Ga-citrate and white blood cells labeled with ^{111}In or ^{99m}Tc were once considered appropriate agents for imaging pulmonary infection and inflammation. However, due to poor image quality, laborious labeling techniques, and the requirement for imaging several days after injection, imaging with either ^{67}Ga-citrate or radiolabeled white blood cells is now considered obsolete in these settings. In recent years, these methods have been largely replaced by FDG-PET/CT in the evaluation of suspected infection or inflammation in many anatomic locations. This is certainly true in the lungs, where FDG-PET/CT is employed for suspected pulmonary infections, fever of unknown origin in the immunocompromised host (Fig. 30-11), and assessment of opportunistic infections in patients with HIV (Fig. 30-12) and a multitude of inflammatory disorders.[136]

FDG-PET/CT is also emerging as a potential diagnostic tool in tuberculosis and for establishing disease extent, especially extrapulmonary tuberculosis. A meta-analysis suggested that FDG-PET might be helpful in determining treatment response in patients with tuberculosis.[137] The high sensitivity of FDG-PET allows for the detection of response within weeks after initiating treatment, contrary to structural imaging using CT, which is of limited value for this purpose.[138] This approach will be particularly important in detecting drug resistance in this population. Similar to its role in the management of patients with tuberculosis, FDG-PET has become an important tool in assessing patients with other mycobacterial infections (Fig. 30-13).

Noninfectious Inflammatory Lung Diseases

^{67}Ga citrate lung imaging has been used to quantify the degree of alveolitis in various interstitial lung diseases, particularly sarcoidosis and idiopathic pulmonary fibrosis. However, pulmonary accumulation of ^{67}Ga in idiopathic pulmonary fibrosis proved not to be reliable in predicting response to treatment with corticosteroids or prognosis.[139] FDG-PET/CT appears to be substantially superior to ^{67}Ga.

Additionally, even with sparse reports in the literature, the evidence points toward a correlation between the

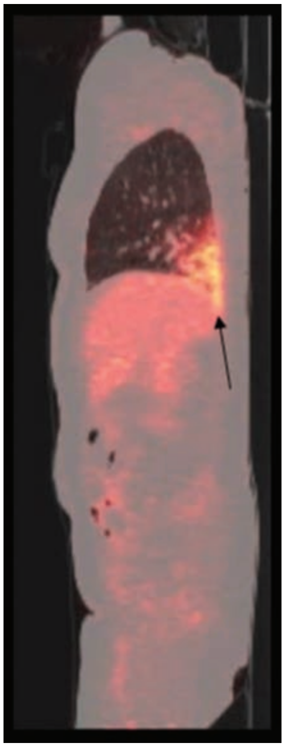


Figure 30-11 Fever of unknown origin in an immunocompromised patient with a kidney transplant. Conventional chest x-ray was non specific. Fused sagittal FDG-PET/CT image shows characteristically increased FDG uptake in the right lower lung *(arrow)* consistent with lobar pneumonia.

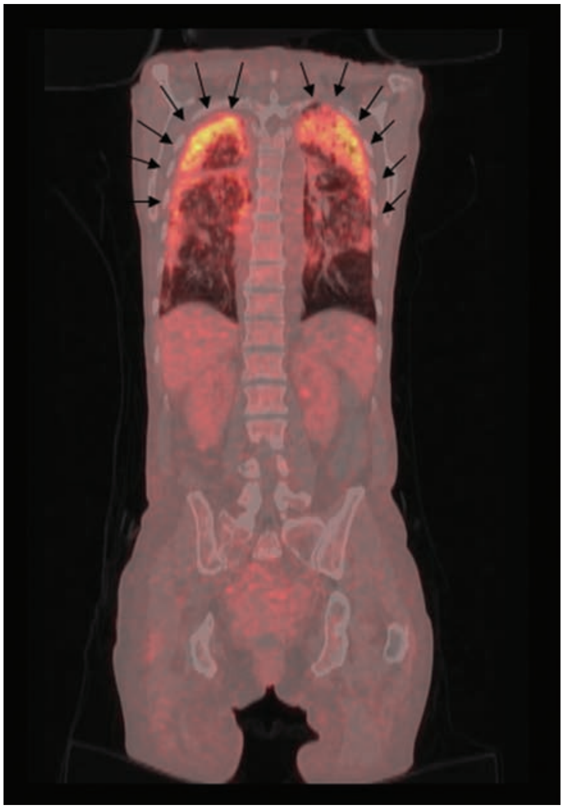


Figure 30-12 *Pneumocystis jirovecii* pneumonia. Diffuse, markedly increased FDG lung uptake bilaterally *(arrows)* in a patient with human immunodeficiency virus.

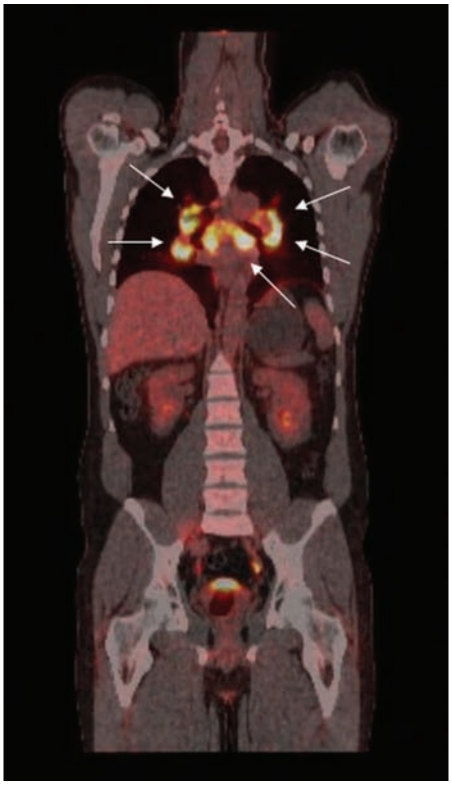


Figure 30-14 Sarcoidosis. Typical presentation of sarcoidosis on FDG-PET/CT with markedly increased FDG uptake in mediastinal and hilar lymph nodes *(arrows)*. Similar patterns are seen in patients with lymphoma.

distribution and severity of emphysema and the degree of FDG uptake.[140]

Over the past two decades, FDG-PET has been proven to be very effective for the detection of inflammation, and as such, it has been adopted for assessing many infectious and inflammatory disorders.[141,142] The technique has proved to be of great value, due to both its sensitivity and accurate quantification of various inflammatory processes.

Sarcoidosis is a multisystem inflammatory granulomatous disease that involves the lungs in 90% of patients; however, it can affect almost any organ. Historically, scintigraphy using ^{67}Ga citrate was used for assessment of disease activity in pulmonary sarcoidosis, but its use has been overshadowed by FDG-PET.

FDG-PET has several advantages to ^{67}Ga citrate scintigraphy, including lower radiation exposure, shorter time interval between injection and imaging, higher image quality, better interobserver agreement, and better detection of intra- and extrathoracic lesions.[143–146] Hilar and mediastinal lymph nodes (as well as any other soft tissues) harboring active granulomas due to sarcoidosis accumulate FDG (Fig. 30-14). Although FDG-PET cannot distinguish

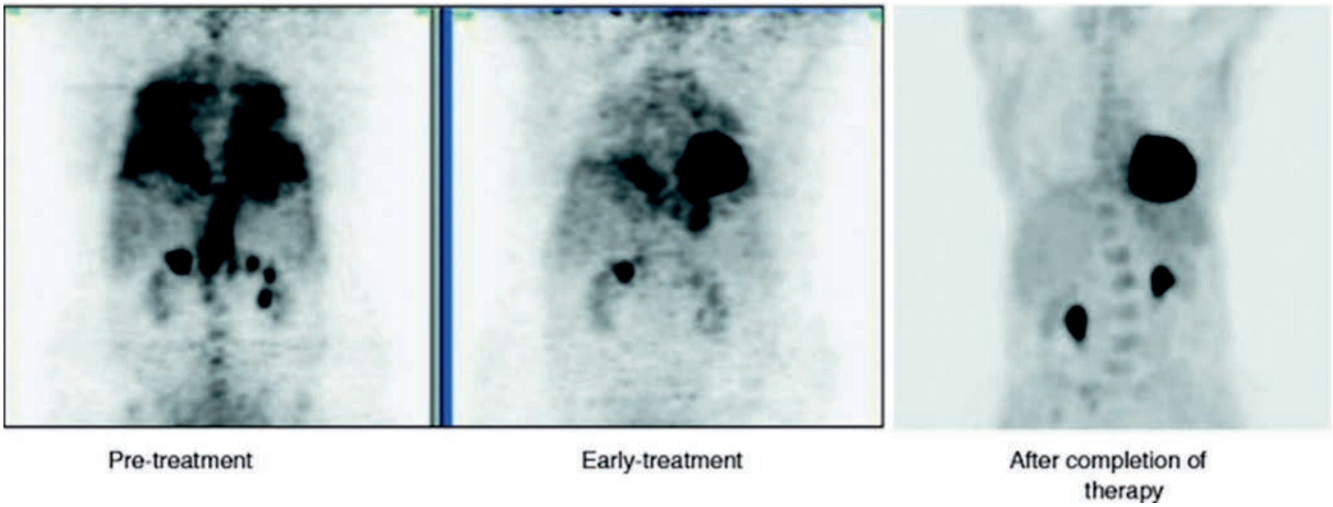


Figure 30-13 FDG-PET maximum-intensity projection images (antero-posterior view) demonstrating the FDG uptake during the treatment course in a patient with *Mycobacterium avium–intercellulare* (MAI) infection. *(Reproduced with permission from Basu S, Saboury B, Werner T, et al. Clinical utility of FDG-PET and PET/CT in non-malignant thoracic disorders. Mol Imaging Biol. 2011;13(6):1051–1160.)*

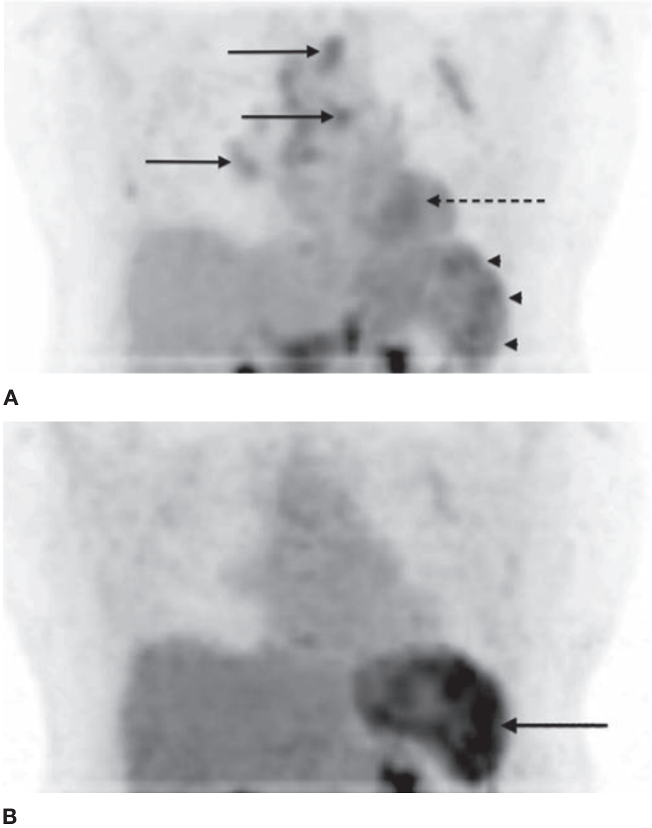


Figure 30-15 **A.** FDG-PET/CT images of the thorax and upper abdomen reveal increased metabolic activity in hilar lymph nodes *(solid arrow)*, myocardium *(interrupted arrow)*, and spleen *(arrow heads)* secondary to involvement with sarcoidosis. **B.** Following successful treatment, there is substantial response in the affected sites within the myocardium and lymph nodes. However, there is significantly increased FDG uptake in the splenic lesions *(solid arrow)*, which demonstrates the complexity of the biologic behavior of sarcoidosis in various organs during the course of the disease.

sarcoidosis from other diseases, such as Hodgkin's or non-Hodgkin's lymphomas, it is quite effective in guiding an appropriate site for biopsy and staging after an initial diagnosis is made. Increasingly, this technology is employed for determining the extent of sarcoidosis in the lung, as well as its presence and extent in other organs, particularly in the heart.[147,148] More importantly, FDG-PET provides a means for assessing response to treatment (Fig. 30-15).[138,149] High FDG uptake in the involved lung parenchyma correlates with disease severity[150] as revealed by bronchoalveolar lavage (BAL).[151] In a study on 90 patients with chronic sarcoidosis and persistent symptoms, FDG-PET/CT proved helpful in detecting active inflammatory sites, especially in patients with normal angiotensin-converting enzyme (ACE) levels, thereby influencing adjustment of therapy.[152] On the other hand, total-lesion glycolysis (TLG) by FDG-PET as an index of lung inflammation in 87 patients with positive uptake failed to correlate with clinical symptoms, functional impairment, or need for therapy.[153]

Finally, FDG-PET may be useful in evaluating pneumoconiosis. Pneumoconioses may be progressive, even after dust exposure has ceased. The inhaled particles activate pulmonary macrophages that secrete cytokines that mediate an inflammatory reaction, inducing fibroblast proliferation and collagen deposition. FDG is taken up by both fibroblasts and alveolar inflammatory cells. The intensity of pulmonary FDG uptake in pneumoconioses depends on whether active inflammation (increased uptake) or end-stage fibrosis (reduced uptake) predominates at the time of the scan.[154] In addition, progressive massive fibrosis has been shown to be associated with increased FDG accumulation.[155]

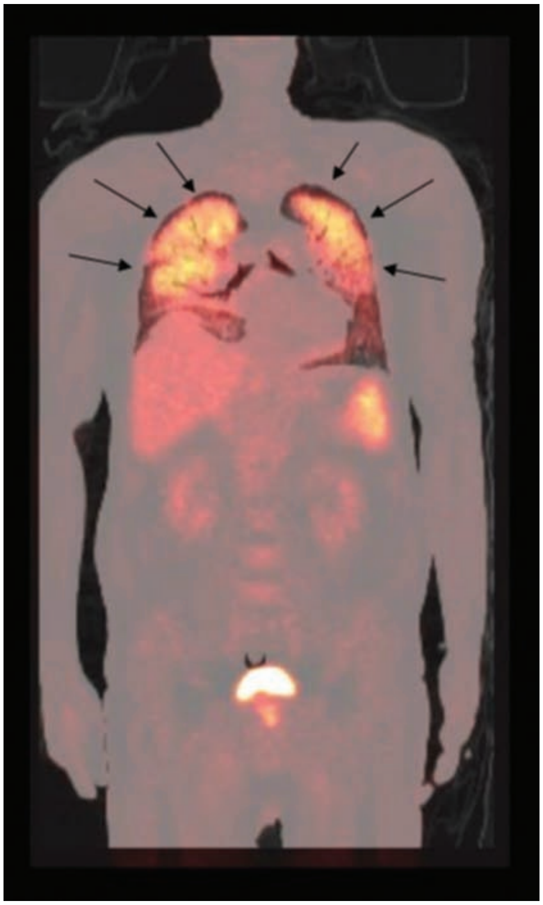


Figure 30-16 Interstitial lung disease. The patient presented with dyspnea and intermittent fever and the PET/CT showed diffusely increased FDG uptake in both lungs *(arrows)*.

The findings from FDG-PET have direct clinical implications, as therapeutic interventions are ineffective in end-stage fibrosis. Interstitial lung disease may also be FDG-avid, but there are limited data on the use of FDG-PET in this setting (Fig. 30-16). In a small prospective study of 21 patients, FDG-PET did not allow differentiation of idiopathic from nonidiopathic pulmonary fibrosis.[156] However, dual-timepoint FDG-PET with early and delayed imaging might help in the differential diagnosis and predict disease progression in idiopathic interstitial pneumonia.[157] Early preclinical and human studies are underway to investigate the role of new PET tracers to determine disease activity in IPF and response to therapy. One such radiotracer is ^{64}Cu-DOTA-ECL1i, which tracks the C-C motif CCR2 (chemokine receptor 2) expressing monocytes and interstitial macrophages, which are active in IPF and play a central role in fibrosis.[158]

ROLE OF POSITRON EMISSION TOMOGRAPHY IN THE ASSESSMENT OF THE SOLITARY PULMONARY NODULE AND LUNG CANCER

Current clinical indications for FDG-PET imaging in malignant lung disease include evaluation of a solitary pulmonary nodule, staging of lung cancer (non–small-cell, small-cell, mesothelioma), and planning and monitoring response to therapy.

Evaluation of a Solitary Pulmonary Nodule

A solitary pulmonary nodule (SPN) is defined as a round or oval radiographic opacity in the lung parenchyma that measures up to 3 cm in size and is not accompanied by mediastinal adenopathy or atelectasis.[159] SPNs are among the most common incidental thoracic imaging findings on chest radiographs or CT scans.[160] In the United States, about 1 million new SPNs are detected each year, and approximately 40% to 50% of such lesions are malignant. Of the malignant SPNs, adenocarcinoma is the most common (47%), followed by squamous cell carcinoma (22%) and small-cell lung cancer (4%).[161] An early and accurate diagnosis is essential for timely intervention, as lung cancer remains, by far, the leading cause of cancer death among both men and women in the world, and survival depends on the stage of the cancer when diagnosed (Fig. 30-17).[162]

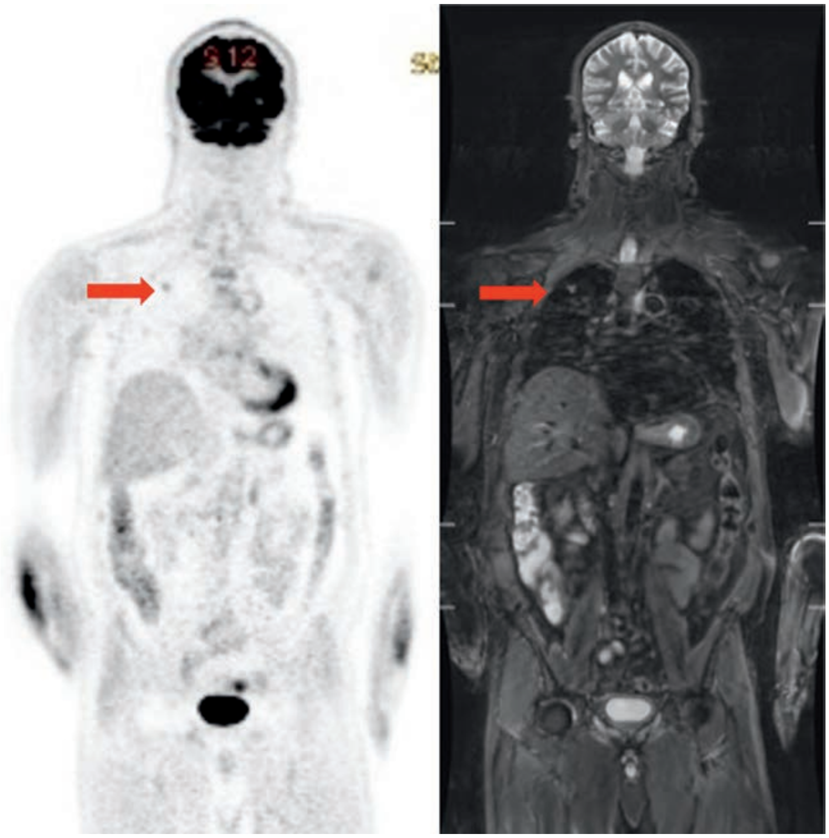


Figure 30-17 Coronal FDG-PET/MRI demonstrating a hypermetabolic right upper lobe solitary pulmonary nodule with no evidence of metastatic disease. *(Reproduced with permission from Dr. Andrei Iagaru, Department of Radiology, Nuclear Medicine Division, Stanford University, Stanford, CA.)*

Of SPNs that are benign, about 80% are caused by infectious granulomas.[159] While a number of benign etiologies for SPNs may have a characteristic appearance on CT, many cannot be characterized accurately using CT and often require further invasive assessment for accurate diagnosis. Certain factors, including the history of smoking, characteristics of the nodule (e.g., size, edge irregularity and spiculation, appearance as a pure ground glass opacity, absence of calcification) and patient age when detected are features that determine the probability of malignancy. However, there is considerable overlap in the appearance of benign and malignant lesions[163] in spite of radiographic and other clinical criteria employed for this purpose. CXR and CT scan are not accurate in differentiating benign from malignant, noncalcified pulmonary nodules that range 1 to 3 cm in diameter; benign patterns of calcification and morphologic stability over 2 years are the most reliable signs of benignity.[163]

FDG-PET provides a highly accurate, noninvasive diagnostic assessment of solid SPNs >8 mm, without the morbidity and costs associated with invasive tissue sampling.[164,165] In a prospective multicenter trial designed to determine the ability of FDG-PET to discriminate between benign and malignant pulmonary nodules, the sensitivity and specificity of FDG-PET ranged from 80% to 100% and 60% to 95%, respectively.[164] False-positive studies are seen with active granulomas due to aspergillosis, tuberculosis, or sarcoidosis.[130] False-negative results are noted with hyperglycemia, malignancies that have a low metabolic activity (e.g., bronchoalveolar carcinoma or carcinoid tumors[166]), and nodules <8 mm in diameter.[167]

In an early meta-analysis of 40 studies that included 1474 pulmonary lesions studied with FDG-PET, the technique had an average sensitivity of 97% and specificity of 78%.[168] Optimal visual criteria for malignancy were greater than mediastinal uptake for nodules >1 cm and any FDG uptake for smaller nodules. A meta-analysis done 7 years later reported a similar sensitivity of 95%, specificity of 82%, PPV of 91%, and NPV of 90%.[169]

A more recent systematic review and meta-analysis of 12 studies including a total of 1297 patients and 1301 pulmonary nodules found significant heterogeneity among the studies included, but reported a pooled sensitivity and specificity of FDG-PET/CT of 82% (95% confidence interval [CI], 0.76–0.87) and 81% (95% CI, 0.66–0.90), respectively.[170] As expected, the lowest heterogeneity and the best results for sensitivity (0.90; 95% CI, 0.68–0.86) and accuracy (0.93; 95% CI, 0.90–0.95) were seen in prospective studies.[170] These results were in line with a large meta-analysis that included 70 studies reporting a total of 8511 nodules, 60% (5105) of which were malignant; however, the accuracy of FDG-PET for diagnosing lung nodules was extremely heterogeneous.[165]

Pretest probability and Bayesian analysis can be used to stratify risk (based on clinical information and imaging characteristics) and guide management of SPN.[171,172] In areas with a high incidence of infectious diseases and a low incidence of lung cancer, the specificity of FDG-PET/CT is low.[165] However, even in that scenario, FDG-PET/CT can safely guide tissue diagnosis to confirm or exclude malignancy. In a prospective study that evaluated 341 patients comparing the diagnostic accuracy of FDG-PET/CT–guided lung biopsy (216 patients) to CT-guided biopsies (125 patients), no difference was noted in complication rates; however, there were fewer inconclusive results leading to a second biopsy in the PET group (5 of 216 [2.3%]) than in the CT group (13 of 125 [10.4%]).[173]

The optimal SUV cut-off point to distinguish benign from malignant lesions is yet to be determined. An SUV_{max} >2.5 has been shown to be very sensitive and specific for differentiating malignant from benign lesions.[167,174] However, several studies have shown that no significant differences between use of a semiquantitative analysis of FDG uptake with SUV and a qualitative visual assessment.[168,175,176] With this approach, FDG uptake in the lesion that is greater than that in the liver or mediastinum (typically, an SUV of about 2.0) is considered indicative of malignancy.[164] Visual analysis may be more sensitive for nodules that are smaller than 1.5 cm in diameter, but the approach results in a lower specificity.[164] In a prospective study of 344 patients for whom a definitive diagnosis was known (prevalence of malignancy, 53%; average size of nodule, 16 mm), FDG-PET had a sensitivity of 92% compared with 96% for CT; however, the specificity of PET was markedly better than that of CT (82% vs. 41%).[177]

The low accuracy of FDG-PET in assessing nodules having a "ground-glass" or "mixed" appearance on CT scanning is likely related to the cell types that predominate in these lesions, including pure bronchioalveolar cell cancer or adenocarcinomas with bronchioalveolar features.[178] In "ground-glass" SPNs, FDG-PET/CT demonstrates a sensitivity and specificity of only 10% and 20% for detecting malignancy, respectively.[176] Therefore, nonsolid SPNs are better assessed using thin-section CT.[179,180]

The sensitivity of FDG-PET is affected by lesion size and the degree of respiratory motion. The threshold of 8 mm for SPN is based on the limited spatial resolution of PET. In one study addressing this issue, the technique's sensitivity in detecting malignancy was 69% for nodules ranging from 5 to 10 mm in diameter and 95% for nodules >10 mm in diameter.[181] Therefore, PET is not recommended for SPN <8 mm.[167] One method aimed at compensating for this limitation is based on using lesion size measured on CT imaging to correct the underestimated SUV with conventional measurements.[112] Data in the literature are based on assigning standard ROIs to the lesions visualized by FDG-PET. Unfortunately, because of the limited spatial resolution of PET imaging, along with respiratory motion of pulmonary lesions, this approach results in substantially underestimated values for SUV, which are proportional to the size of the lesion and the degree of respiratory motion.

The physical factors described are known as partial volume effect and, as such, introduce substantial errors to the quantitative data from PET studies, particularly those related to pulmonary nodules.[112] Therefore, methodologies that can correct for partial volume effect should be employed for accurate measurement of metabolic activity of the lesions assessed. By adopting this approach, significant changes will be noted in the SUV in most clinical settings. Therefore, total reliance on what has been described in the literature will result in significant mismanagement of patients with solitary pulmonary nodules.[182] In particular, we wish to point out that adopting the SUV of 2.5 as a threshold for separating malignant and benign lesions is fraught with error and should be abandoned altogether in the future. Many lesions that are smaller than 3 or 4 cm in size will be prone to such errors.

Errors in the interpretation of PET/CT can occur from misregistration of PET and CT images, since CT images are obtained in a single breath-hold, while FDG is obtained during quiet breathing. This occurs more frequently for SPNs close to the diaphragm and heart. Different respiratory gating techniques have been employed to synchronize PET and breathing with encouraging results;[183] however, the results come at the cost of a longer scan time, thereby increasing the likelihood of patient movement.

The data acquired by simultaneous performance of PET and CT has significantly improved the diagnostic accuracy of PET or CT alone. In a small retrospective study of 42 patients with known pathology of an SPN, PET/CT outperformed (sensitivity and specificity of 97% and 85%, respectively) CT alone (sensitivity and specificity 93% and 31%, respectively) and PET alone (sensitivity of 69% and 85%, respectively).[184] With whole-body FDG-PET/CT, areas beyond the lungs are evaluated, which can facilitate the diagnosis of SPN. Neither intravenous nor oral contrast is necessary for the evaluation of SPN by FDG-PET/CT. The average effective radiation doses are 8.19 ± 0.83 mSv and 13.44 ± 5.14 mSv for PET and CT, respectively.[185]

While most infectious or inflammatory pulmonary disorders generally have a lower FDG uptake than malignancies, overlap exists, and false positives can occur, especially in cases of pneumonia, mycobacterial disease, sarcoidosis, or rheumatoid nodules. Based on the observation in animal and human studies that FDG uptake by malignant tumors increases over time, while that of inflammatory tissue decreases, dual-timepoint FDG-PET scanning has been proposed as a potentially useful means of improving discrimination between benign and malignant diseases.

Using dual-timepoint FDG-PET scanning, images are obtained at 1 h and at a later time following administration of FDG. In one study in which an SUV cut-off value of 2.5 and a 10% increase in SUV were used to indicate malignancy, the sensitivity and specificity of FDG-PET were 80% and 94%, respectively, for the single-timepoint method, and 100% and 89%, respectively, for the dual-timepoint technique.[111] There are no standard protocols or strict guidelines for dual time imaging, specifically with regard to the optimal time between scans.

A meta-analysis comparing diagnostic performance in evaluating SPN showed that dual-timepoint FDG-PET/CT is more specific than single-timepoint FDG-PET/CT.[186] Dual-timepoint imaging is not required in lesions with a baseline SUV of <1.0, since these lesions have a very high likelihood of being benign; dual-timepoint imaging may result in false-positive examinations.[111] Even for nodules with an SUV_{max} <2.5, dual-timepoint imaging may not discriminate accurately between benign and malignant lesions, particularly in areas with a high incidence of granulomatous disease, as false-positive exams have been reported in association with granulomatous inflammation.[187] In two meta-analyses conducted in 2012 and 2013, the overall diagnostic accuracy of dual-timepoint imaging was similar to single-timepoint PET scanning.[186,188]

In a study comparing the accuracy of FDG-PET/CT scanning to dynamic CT scanning for pulmonary nodule characterization, FDG-PET/CT scanning was found to be more sensitive and accurate than dynamic CT scanning. The sensitivity, specificity, and accuracy for malignancy with dynamic CT scanning were 81%, 93%, and 85%, respectively, whereas the values for PET/CT scanning were 96%, 88%, and 93%, respectively.[189]

Guidelines form the American College of Chest Physicians (ACCP) recommend use of FDG-PET/CT in patients where the probability of cancer is intermediate (5%–60%) and an indeterminate nodule measures at least 8 mm.[167] Current National Comprehensive Cancer Network (NCCN) guidelines for lung cancer screening recommend considering FDG-PET/CT for the diagnosis of a solid SPN >8 mm on initial screening with low-dose CT.[190] PET/CT scan is not recommended as a screening tool for healthy individuals, as the likelihood of finding cancer is extremely low, and an increased risk of detecting harmless findings may lead to more tests or invasive procedures.[61,190]

■ Use of Positron Emission Tomography in Lung Cancer

PET has been used extensively in the evaluation and staging of lung cancer, including non–small-cell lung cancer, small-cell lung cancer, and mesothelioma.

Non–Small-Cell Lung Carcinoma

Principal types of lung cancer include the most common variety, non–small-cell lung cancer (adenocarcinoma, squamous cell carcinoma, and large cell carcinoma), which accounts for about 84% of lung cancers.[162] About 13% of lung cancers are small-cell carcinoma, which tends to spread quickly, and 1% to 2% of lung cancers are neuroendocrine (carcinoid) tumors, which tend to grow slowly and rarely spread.[162] FDG-PET scanning has assumed a central role in the staging of non–small-cell lung cancer (NSCLC).[191]

Correct lung cancer staging is important because the treatment options and prognosis vary significantly by stage. FDG-PET imaging can have a significant impact on patient management by identifying unsuspected sites of disease (Fig. 30-18) and by guiding selection of a biopsy site (Fig. 30-19). Similarly,

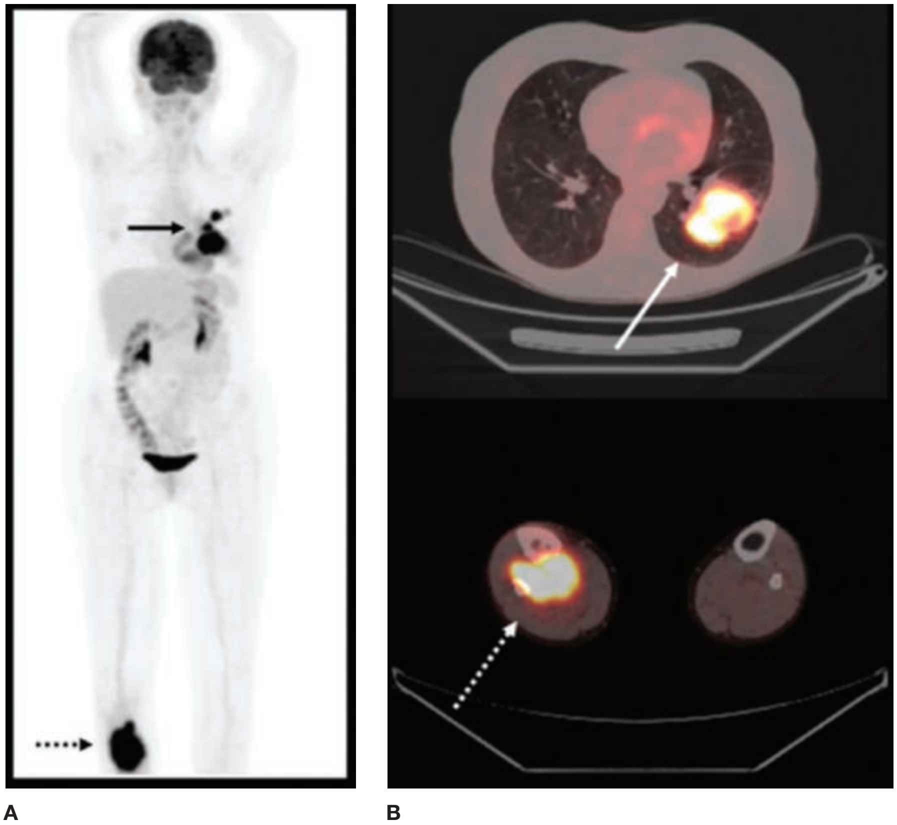


Figure 30-18 Lung cancer. Preoperative evaluation of a patient with a lung cancer in the left lower lobe intended for curative surgery. Whole-body coronal PET (**A**) and fused transaxial PET/CT *(***B** *top and bottom right)* show increased FDG uptake in the lung tumor *(solid arrows)*, and unexpected focal FDG uptake in a soft tissue mass in the left proximal tibia *(interrupted arrows)*. Biopsy showed metastasis from the lung cancer, obviating surgery.

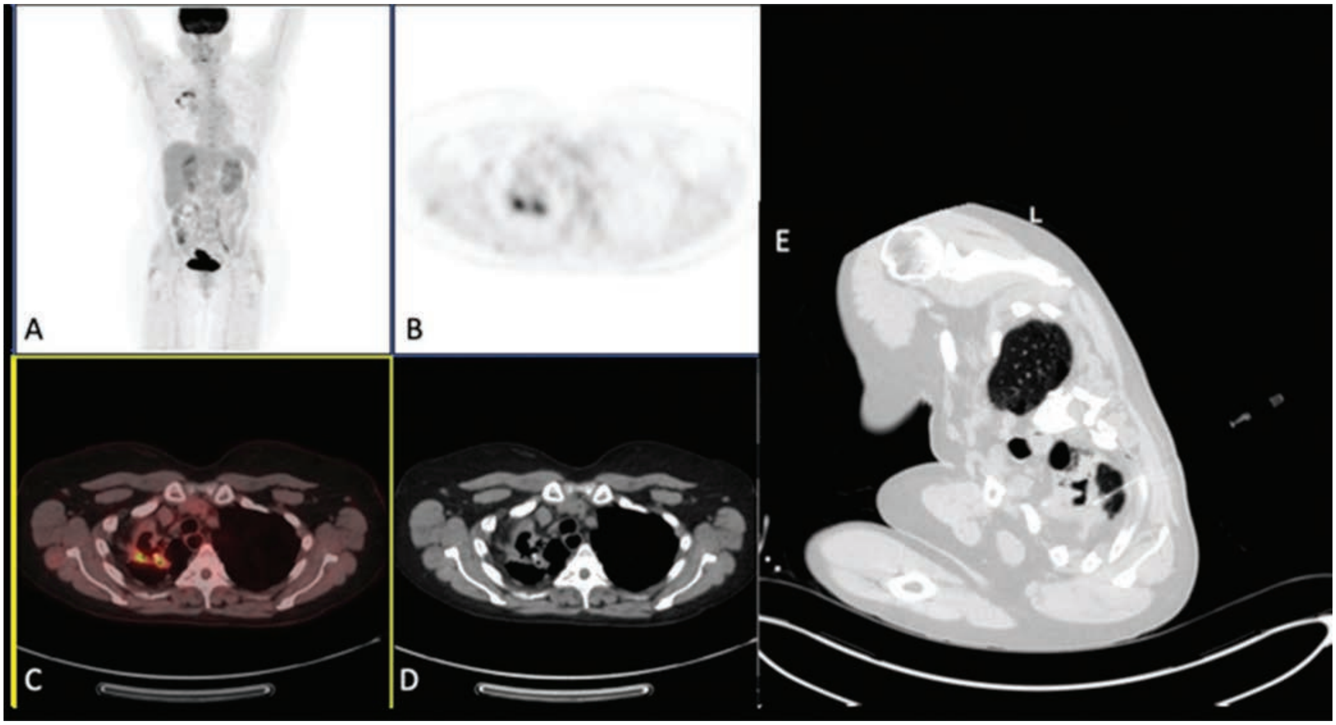


Figure 30-19 FDG-PET/CT guiding a percutaneous biopsy. Maximal-intensity projection PET (**A**), axial PET (**B**), fused axial PET/CT (**C**), and axial CT (**D**) of patient with a cavitary right upper lobe lung lesion. Using the data from PET, a percutaneous CT-guided biopsy targeted the most metabolically active part of lesion yielding non–small-cell lung carcinoma. Without the information from FDG-PET, it would be impossible for the interventional radiologist to determine which part of the lesion will have the best diagnostic yield.

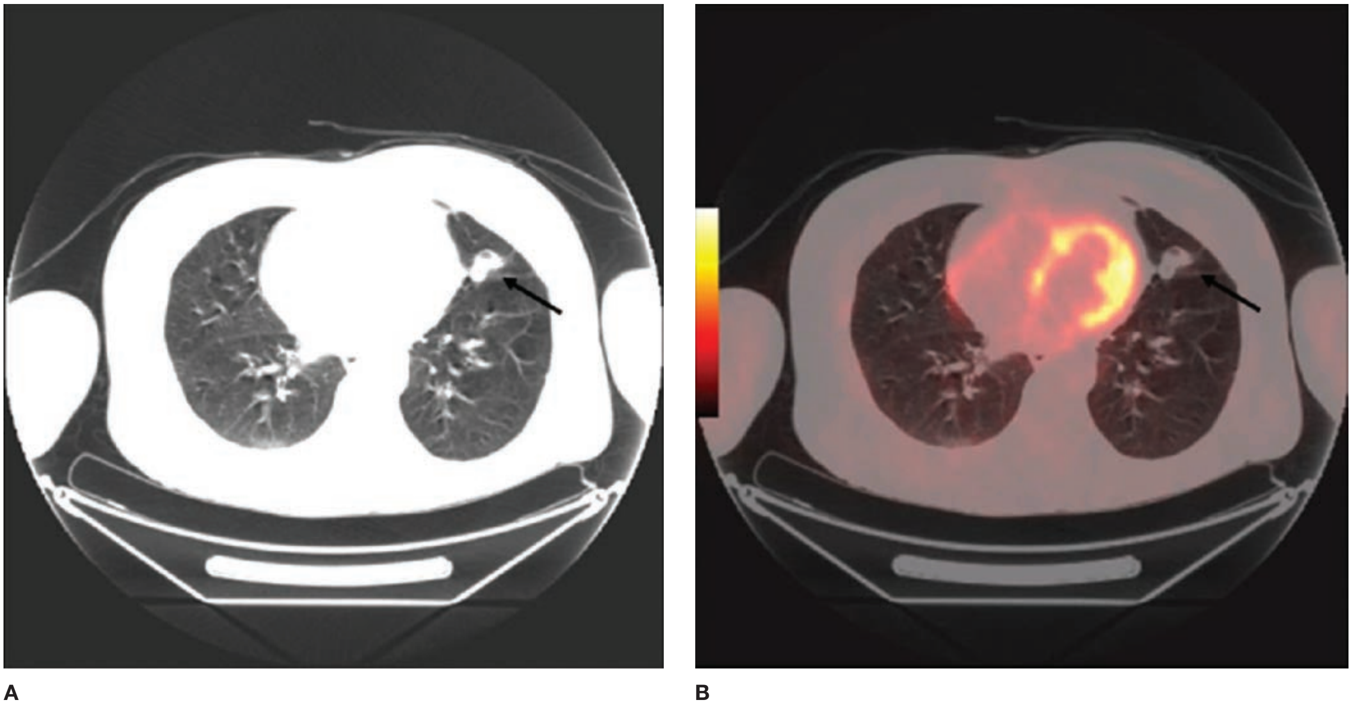


Figure 30-20 Suspected lung cancer. CT scan (**A**) shows a consolidation/mass in the lingula suspected of malignancy *(arrow)*. Transaxial fused PET/CT (**B**) shows no abnormal FDG uptake in the lesion *(arrow)*, consistent with a benign etiology.

a negative FDG-PET scan indicates a low likelihood for malignancy[177] and supports the use of conservative management and follow-up (Fig. 30-20). When used in staging, FDG-PET/CT scanning has to be done within a month from the surgical evaluation.[191] Patients with stage I or II NSCLC are typically referred for surgical resection, while those with stage III or IV disease are almost never surgical candidates; they may benefit from chemotherapy, radiation therapy, or both. The basis for staging NSCLC is the TNM system.[192]

Tumor Staging

For T (tumor) staging, CT and MRI remain the best imaging modalities to demonstrate the local extension of the tumor and its relationship to adjacent organs and vessels. FDG-PET/CT is limited for T staging due to its inability to accurately define tumor limits. However, FDG-PET/CT has demonstrated a clear advantage in T staging of certain cases, especially in areas of post-obstructive atelectasis[193] or low CT density variation; in the future it may replace CT and MRI alone for this purpose.[194,195]

In a prospective study of 50 patients with NSCLC, integrated PET/CT provided additional diagnostic information in 41% of patients and was significantly more accurate in TNM disease staging than either PET or CT alone.[196] Integrated PET/CT provides important clinical information by virtue of accurate localization of known disease and identification of lesions that do not consistently accumulate FDG, such as carcinoid tumors and bronchioloalveolar carcinoma.[196] PET/CT without contrast-enhanced CT is unable to distinguish confined, centrally located tumors from those producing direct invasion of mediastinal structures. Therefore, clinicians may still rely on contrast-enhanced CT scans to help define mediastinal vascular invasion.

From a prognostic point of view, FDG uptake in NSCLC has been correlated with tumor growth rate, aggressiveness, and proliferation capacity, and it is has been found to be an independent prognostic factor correlated with survival in patients with NSCLC, especially in early-stage disease.[197] A meta-analysis of 13 studies showed that tumor SUV$_{max}$ pre- and post- radiotherapy is an independent prognostic indicator for NSCL; higher FDG uptake in the primary tumor is associated with less local control and shorter overall survival.[198] New volumetric parameters have been proposed to better assess the overall metabolic activity of tumors, such as total-lesion glycolysis (TLG) that is defined as the product of the metabolically active tumor volume (MATV) and the SUV$_{average}$ (average SUV of each voxel within the tumor volume). In a group of 214 patients from the multicenter prospective study of the American College of Radiology Imaging Network (ACRIN) 6668/Radiation Therapy Oncology Group (RTOG) 0235 that included 250 patients with NSCLC treated with concomitant radiochemotherapy, MATV was found to be an independent factor for predicting overall survival.[199]

A meta-analysis of 13 studies with 1581 patients (that did not include the results of the previously mentioned study) aimed at assessing the prognostic value of MATV and TLG found that the likelihood of worsening and death was greater for patients with higher MATV or TLG values.[200] Nevertheless, in the absence of a reproducible generalized threshold for SUV, MATV, or TLG, accurate staging remains the only prognostic indication for FDG-PET/CT.

Nodal Staging

From a practical standpoint, mediastinal nodal staging most often determines appropriateness for surgical resection. Mediastinal staging using CT scanning is based primarily on assessment of lymph node size; nodes <1 cm in their short axis are considered benign, while those >1 cm are considered potentially malignant. Unfortunately, up to 21% of nodes smaller than 1 cm are malignant, and up to 40% of nodes larger than 1 cm are benign.[201,202]

A large meta-analysis reported the median sensitivity and specificity of CT scanning for identifying malignant mediastinal nodes as 61% and 79%, respectively.[203] These results were similar to those from an earlier meta-analysis that reported an average sensitivity and specificity of 60% and 77% for CT scanning (using an axial short axis >1.0 cm), respectively.[204] In that same meta-analysis on the diagnostic performance of FDG-PET (14 studies, 514 patients) and CT (29 studies, 2226 patients), FDG-PET had a higher sensitivity and specificity for determining nodal status in patients with non–small-cell lung cancer, with a sensitivity and a specificity of 79% and 91%, respectively.[204]

The accuracy of PET in the evaluation of mediastinal lymph nodes depends on the size of the nodes. In patients with enlarged mediastinal lymph nodes, a large meta-analysis of 39 studies reported a sensitivity and a specificity of FDG-PET of 100% and 78%, respectively.[203] These numbers changed to a sensitivity and specificity of 82% and 93%, respectively, in normal-size nodes.[203] Positive PET findings in this situation should be confirmed by directed biopsy, as inflammatory and/or infectious processes can lead to false-positive results. Absence of tissue diagnosis could result in patients with surgically resectable disease being denied curative surgery.

Exact classification as N1 or N2 disease is somewhat difficult with PET alone; anatomic information provided by CT scan as part of combined PET/CT imaging is important for this purpose. In one study, the accuracy of mediastinal lymph node staging increased from 89% with PET alone to 93% with PET/CT, compared to 63% with CT, and resulted in a change in the planned treatment in up to 15% of patients.[202] In another study, PET/CT was significantly better than CT alone for nodal staging, with improved accuracy, as sensitivity rose from 70% for CT to 85% for PET/CT, specificity rose from 69% to 84%, and accuracy rose from 69% to 84%.[205]

FDG-PET is the best modality to detect tumor in normal size lymph nodes. Using an SUV_{max} of 2.5 is a reasonable threshold between benignity and malignancy, but SUV may be falsely low in lymph nodes <1 cm due to partial volume effect, and visual assessment is generally as accurate.[206] A meta-analysis following databases up to April 2013 found a sensitivity and specificity of PET-CT for evaluating mediastinal involvement of 77.4% and 90.1%, respectively, when nodal uptake was compared with mediastinal background, and 81.3% and 79.4%, respectively, when an SUV threshold of 2.5 was used.[207]

Lymph nodes containing calcification are more likely to be benign even if they accumulate FDG.[208] Interestingly, a few studies have shown that FDG-PET/CT has a lower specificity and accuracy for nodes >1 cm compared with those <1 cm, but the technique still performs better for large lymph nodes than CT alone.[209,210] False-positive nodes are generally larger in size than true-negative nodes as staged by FDG-PET and contain more macrophages.[210]

For patients with stage II or III disease, the incidence of false-negative results is higher with PET than with mediastinoscopy (11.7% and 3%, respectively).[211] These studies illustrate an important limitation of FDG-PET. The variability in false-positive examinations suggests that FDG-PET results cannot replace histologic confirmation for suspected mediastinal nodal metastases.[212] Therefore, FDG-PET-positive lymph nodes still require pathologic confirmation.[213] This is accomplished via transbronchial, transesophageal, or transthoracic nodal needle aspiration, or a more invasive surgical approach (e.g., mediastinoscopy or video-assisted thoracic surgery [VATS]). These invasive procedures can be guided by the PET findings, as mediastinoscopy is limited to the anterior mediastinum, and approximately 15% of patients may still be found to have N2 disease at thoracotomy.[214]

The use of intraoperative FDG-sensitive gamma probes to guide lymph node sampling following the injection of FDG may be helpful.[215] While studies have demonstrated that patients with metastases detected at mediastinoscopy have a worse prognosis than patients in whom N2 disease is found only at surgery,[216,217] no prospective studies have yet been performed to determine whether patients with negative mediastinal nodes on preoperative FDG-PET have a similar prognosis to patients in whom N2 disease is found at thoracotomy following a negative mediastinoscopy. Therefore, mediastinoscopy still remains part of the standard protocol for mediastinal staging.[211] On the other hand, there is low likelihood of involvement of mediastinal nodes when they are negative by both CT and FDG-PET criteria in solid tumors <1 cm or nonsolid tumors <3 cm,[191] highlighting the importance of multimodality evaluation. In fact, a cohort study that included 43,912 patients from the Surveillance, Epidemiology, and End Results–Medicare data (1998–2005) found that multimodality (CT, PET, invasive staging) mediastinal staging has increased over the years and is associated with better survival.[218]

Following the analysis of selected meta-analyses, practice guidelines, and reviews up to June 2012, the ACCP reported a sensitivity and specificity of PET scanning for identifying mediastinal metastasis of approximately 77% and 86%, respectively, in comparison to 55% and 81%, respectively, for CT scanning.[213] Current ACCP guidelines recommend the use of FDG-PET/CT to evaluate for mediastinal evidence of disease in patients with lung cancer being treated with curative intent.[213] For patients with peripheral clinical stage IA lung tumor and negative nodal involvement by CT and PET, invasive evaluation is not required,[213] whereas in patients with intermediate suspicion of N2,3 involvement with a central tumor or enlarged N1 lymph node, invasive staging of the mediastinum is recommended.[213]

Metastatic Staging

In addition to being the most accurate noninvasive imaging modality available to evaluate the mediastinum in patients with lung cancer, whole-body FDG-PET imaging evaluates extrathoracic sites for possible metastatic disease. FDG-PET is superior to conventional imaging in detecting metastases in distant lymph nodes, pleural effusions, contralateral nodules, and viscera.

In a prospective study, FDG-PET showed a high sensitivity and specificity in the detection of distant metastases alone (92% and 83%, respectively), and 11% of patients in the study had distant metastases detected by FDG-PET that other modalities had failed to detect.[212] Detection of unsuspected extrathoracic metastases can be identified in 6% to 24% of patients (mean frequency of about 13%), and the likelihood for detecting unsuspected metastases increases with the patient's stage.[211] This is particularly important in patients with locally advanced, stage III lung cancer.[219]

In one multicenter trial, addition of PET to the conventional workup prevented unnecessary surgery in one out of five patients with suspected non–small-cell lung cancer, with a 50% decrease in futile thoracotomy in comparison to conventional workup.[220] The likelihood for occult metastatic disease at presentation can be found in up to 30% of patients with adenocarcinoma or large cell carcinoma, but is less common with squamous cell carcinoma (under 15% of patients).[211] A meta-analysis that included 9 studies (780 patients) reported an overall sensitivity and specificity for PET of 93% and 96%, respectively, irrespective of the type of lung cancer metastases.[221] Based on multiple randomized clinical trials, about 20% more patients were correctly suggested as having distant or N2,3 metastases by PET compared with conventional staging.[220,222,223] However, confirmation of PET scan findings remains essential in order to prevent incorrect upstaging (which would have occurred in 5% to 42% of patients), thereby preventing a patient from a potentially curative resection.[220,222–224]

The two most common sites for NSCLC metastases are the adrenal glands and bone marrow. Studies have shown that FDG-PET has a sensitivity of 93% to 100% for the characterization of metastatic adrenal lesions in patients with bronchogenic carcinoma (specificity 80%–100% and accuracy 92%–100%).[225–227] Necrotic or hemorrhagic adrenal metastases and small lesions can lead to false-negative FDG-PET results.[227] Despite the fact that benign adrenal adenomas generally demonstrate mild FDG uptake that is less than the liver, false-positive studies may still occur.[226] FDG-PET/CT can improve characterization of adrenal masses by improving the specificity with the combination of SUV and CT attenuation.[228] A Hounsfield Unit (HU) measurement of <10 is indicative of a benign adrenal lesion, even if the SUV measurement is >3.1.[228]

In detecting bone marrow metastases, a comparison of ^{99m}Tc methylene diphosphonate (^{99m}Tc MDP) standard bone scintigraphy to FDG-PET showed a higher accuracy with FDG-PET, 96% versus 66%.[229] FDG-PET can detect bone marrow metastases before reactive bone formation takes place or prior to development of gross anatomic abnormalities. When comparing FDG-PET/CT to ^{99m}Tc MDP and ^{18}F-fluoride PET (F-PET), FDG-PET/CT had a lower sensitivity than F-PET but was superior to ^{99m}Tc MDP.[230] However, FDG-PET/CT had a higher specificity.[230] Numerous benign skeletal conditions (including trauma, infection, and physiologic variants) can cause false-positive FDG-PET results. A meta-analysis of 17 studies addressed this issue by comparing FDG-PET/CT, FDG-PET, MRI, and ^{99m}Tc MDP. The pooled sensitivity of each modality in the detection of bone marrow metastases was 92%, 87%, 77%, and 86%, respectively; the specificity was 98%, 94%, 92%, and 88%, respectively.[231] Based on these data, obtaining bone scintigraphy is not necessary when FDG-PET is performed.

Regarding the initial evaluation for brain metastases in patients with NSCLC, FDG-PET brain imaging does not provide additional clinical information,[232] which is likely due to the high background activity in the brain and small size of most brain metastases. Instead, based on current NCCN guidelines, a brain MRI or CT (if MRI is not available) is recommended in patients with stage II, III or IV disease, even if they are asymptomatic and if aggressive combined-modality therapy is being considered.[191]

Current ACCP recommendations are to obtain PET scans in patients who are considered for a curative-intent treatment with normal clinical evaluation and no suspicious extrathoracic abnormality on chest CT.[213] This should be followed by histologic confirmation in the event of a positive PET finding.

Guiding and Monitoring Radiation Therapy

During the past two decades, by adopting PET-based methodologies, radiation therapy (RT) for lung cancer has significantly improved the outcome of affected patients.[233–238] Currently, in most advanced centers, patients with lung cancer are treated based on PET/CT assessment of disease activity. This has significantly improved the efficacy of treatment for both the primary and metastatic sites. The high sensitivity of PET allows detection of metastatic lesions in the mediastinum and elsewhere and, therefore, improves the overall efficacy of PET in managing these patients.[239]

Historically, RT planning has been based on CT imaging because the excellent delineation of structures allows for precise assignment of the radiation portals. However, PET/CT has gradually replaced CT scanning since a number of studies have demonstrated the additional benefit of PET in defining and refining radiation treatment volumes. Consequently, the reduction or increase in the radiation portal allows more directed dose delivery to target tissues, thereby reducing radiation exposure of normal tissues.[240] In a study of 54 patients with locally advanced NSCLC treated with radiation therapy, PET changed the contours of lymph node stations in 51% of cases.[240]

PET/CT is particularly helpful in planning radiation therapy for patients with lung cancer associated with atelectasis. In a prospective study of 76 patients, 34% of patients eligible for radical radiation therapy after conventional staging received palliative therapies instead because PET/CT detected advanced disease.[241] FDG-PET/CT frequently changed the planning target volume, which was associated with excellent survival.[241]

In recent years, FDG-PET has been employed to assess the inflammatory complications of RT. It is well established that photon therapy using a conventional x-ray approach results in significant inflammation in the lung ipsilateral to the cancer, as well as the contralateral side (Fig. 30-21).[233,236,237] CT scanning is of limited value in detecting and quantifying such complications. By employing novel quantitative techniques, the degree of inflammation can be assessed precisely, and its course determined during and following treatment.

It has been shown that photon therapy for treating lung cancer is associated with significant inflammation compared to that of proton therapy (Fig. 30-22).[236,237] Therefore, the latter modality has gained a major position in both research and clinical settings as the most safe and effective in lung malignancies. Furthermore, PET has allowed detection of vasculitis due to RT, which is also of great importance in minimizing morbidity and mortality.[242] This serious complication is of particular importance in the aorta, as well as the coronary arteries, which may adversely impact the management of these patients.

In patients with residual parenchymal abnormalities following RT for lung cancer, FDG-PET scanning can be used to distinguish between persistent or recurrent cancer and radiation fibrosis.[243] In a study evaluating changes in FDG uptake following definitive radiation therapy, the higher the residual SUV_{max} in the primary tumor (cutoff, 3.7) or lymph nodes (cutoff, 3.1), the worse was the prognosis.[243] FDG-PET is also useful in assessing response to percutaneous radiofrequency ablation of NSCLC.[244]

FDG-PET imaging can better evaluate the response to treatment than anatomic imaging and can also provide prognostic information that correlates strongly with survival rate following initiation of therapy[199,245] (Fig. 30-23). A meta-analysis of 36 studies (5807 patients) found that high values for SUV_{max}, metabolic tumor volume (MTV), and TLG predicted a higher risk of recurrence or death in patients with surgical NSCLC.[246] Assessment of prognosis can be improved with early FDG-PET imaging, as a 50% decrease in SUV between scans performed at 1 and 3 weeks following initiation of chemotherapy has been shown to predict a favorable response.[247]

In recent years, the introduction of immune checkpoint inhibitors has made a significant impact on patients with lung cancer. The use of FDG-PET/CT to evaluate the response to immunotherapy remains a challenge in the face of issues such as pseudoprogression, hyperprogression, and immune-related side effects.[248] Only a few studies have investigated tumor response to immunotherapy outside of melanoma. FDG-PET/CT may play a future role in predicting response to immunotherapy for NSCLC.

A limited, single-institution, retrospective study of 579 patients with primary lung cancer (441 with adenocarcinoma [ADC], 103 with squamous cell carcinoma [SCC], 4 with large-cell carcinoma [LCC], 16 with small-cell carcinoma [SCLC], and 15 with large-cell neuroendocrine carcinoma [LCNEC]) who underwent complete surgical resection found that overall SUV_{max} was significantly higher in patients with PD-L1 protein expression than in those without PD-L1 expression ($p < 0.0001$) (specifically in patients with ADC, SCC, or LCC, but not in SCLC or LCNEC).[249] The link between FDG uptake and PD-L1 protein expression remains unclear, as it may depend on many factors, including cancer cells and the tumor microenvironment (e.g., glucose metabolism, hypoxia, angiogenesis, mammalian target of rapamycin [mTOR] signaling pathway), in addition to tumor-related activated immune cells, such as tumor-infiltrating lymphocytes (TILs) and tumor-associated macrophages (TAMs).[250]

A small preliminary study of 24 patients with NSCLC found that FDG-PET/CT before and 1 month after administration of the anti–programmed death 1 (PD-1) agent nivolumab could predict early therapeutic response using SUV_{max}, MTV, and TLG parameters.[251] The predictive probability of partial response (100% vs. 29%; $p = 0.021$) and progressive disease (100% vs. 22.2%; $p = 0.002$) at 1 month after nivolumab was significantly higher with FDG-PET/CT than with CT scanning. While FDG uptake was an independent prognostic

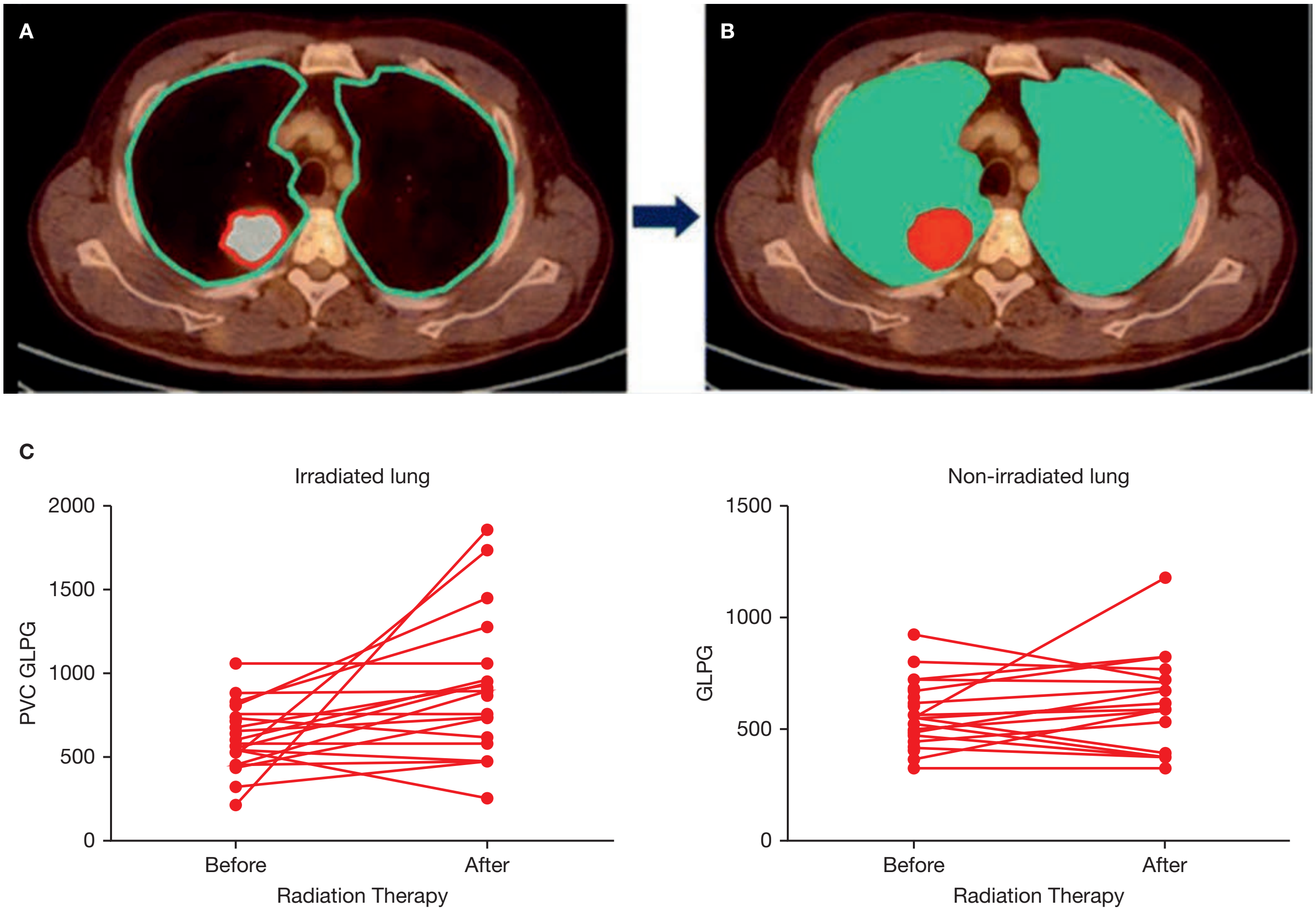


Figure 30-21 Global lung glycolysis (GLG) and global lung parenchymal glycolysis (GLPG) calculation. **A.** Manually drawn ROIs *(green)* around the irradiated right and nonirradiated left lung on a representative transverse FDG-PET/CT slice. The tumor boundary *(red)* was delineated by semiautomatic software. **B.** In the irradiated right lung, GLPG *(green area)* was calculated by subtraction of tumor total lesion glycolysis *(red area)* from the GLG. In nonirradiated left lung, GLPG *(green area)* was equal to GLG. **C.** In non-irradiated lung, GLPG is equal to GLG. In irradiated lung, PVC GLPG shows statistically significant changes between baseline and follow-up studies (PVC GLPG = GLG − PVC TLG). PVC, partial volume corrected; ROIs, regions of interest; TLG, total lesion glycolysis. *(Reproduced with permission from Abdulla S, Salavati A, Saboury B, et al. Quantitative assessment of global lung inflammation following radiation therapy using FDG PET/CT: a pilot study. Eur J Nucl Med Mol Imaging. 2014;41(2):350–356.)*

factor, PD-L1 expression and nivolumab plasma concentration could not precisely predict the early therapeutic efficacy of nivolumab.[251]

In a larger study, FDG-PET/CT scans were used to evaluate response to the anti–programmed death ligand 1 (anti-PD-L1) agent atezolizumab in 103 patients with NSCLC. Patients with an early FDG response at 6 weeks according to the European Organization for Research and Treatment of Cancer (EORTC) criteria (the first metabolic PET criteria for solid tumors)[252] achieved a higher objective response rate on subsequent CT than metabolic nonresponders (17 of 23 [73.9%] vs. 5 of 80 [6.3%]).[253]

Small-Cell Lung Carcinoma

Small-cell lung carcinoma (SCLC) accounts for about 13% of cases of lung cancer[254] and has a high proliferation rate that results in avid FDG uptake.[255] At presentation, patients are considered to have either limited disease (LD) (tumor confined to ipsilateral hemithorax and regional nodes able to be included in a single tolerable radiotherapy port) or extensive disease (ED) (tumor beyond the boundaries of limited disease, including spread to contralateral chest or distant metastases, malignant pericardial, or pleural effusion). At presentation, about 60% to 70% of patients present with ED, while about 30% to 40% of patients have LD. Except in rare cases of surgically operable, limited-stage SCLC, patients with LD receive chemotherapy and radiation vs. chemotherapy alone for ED.

The role of FDG-PET in staging of SCLC is not as widely studied as for NSCLC. Most reports are retrospective and include small number of patients.[256–260] The major impact that PET has on SCLC is that it can change management in up to 37% of patients for initial staging, and in up to 15% of patients for restaging.[255] Complete metabolic response on posttherapeutic FDG-PET/CT in patients with SCLC is an important prognostic factor, as overall survival is significantly longer than for patients who do not have complete response.[261] A recent systematic review and meta-analysis (9 articles until June 2019 with 721 patients) found a better diagnostic accuracy of FDG-PET/CT for staging SCLC compared with conventional staging.[262] A change of the binary SCLC staging (LD vs. ED) was found in 15% of patients.[262] Whether FDG-PET/CT improves survival in patients with SCLC remains uncertain and will require large prospective studies.

Mesothelioma

Benign fibrous mesothelioma is a rare, nonmalignant, localized tumor of the pleura that is unrelated to asbestos exposure. The tumor can be cured by excisional surgery. In contrast, malignant

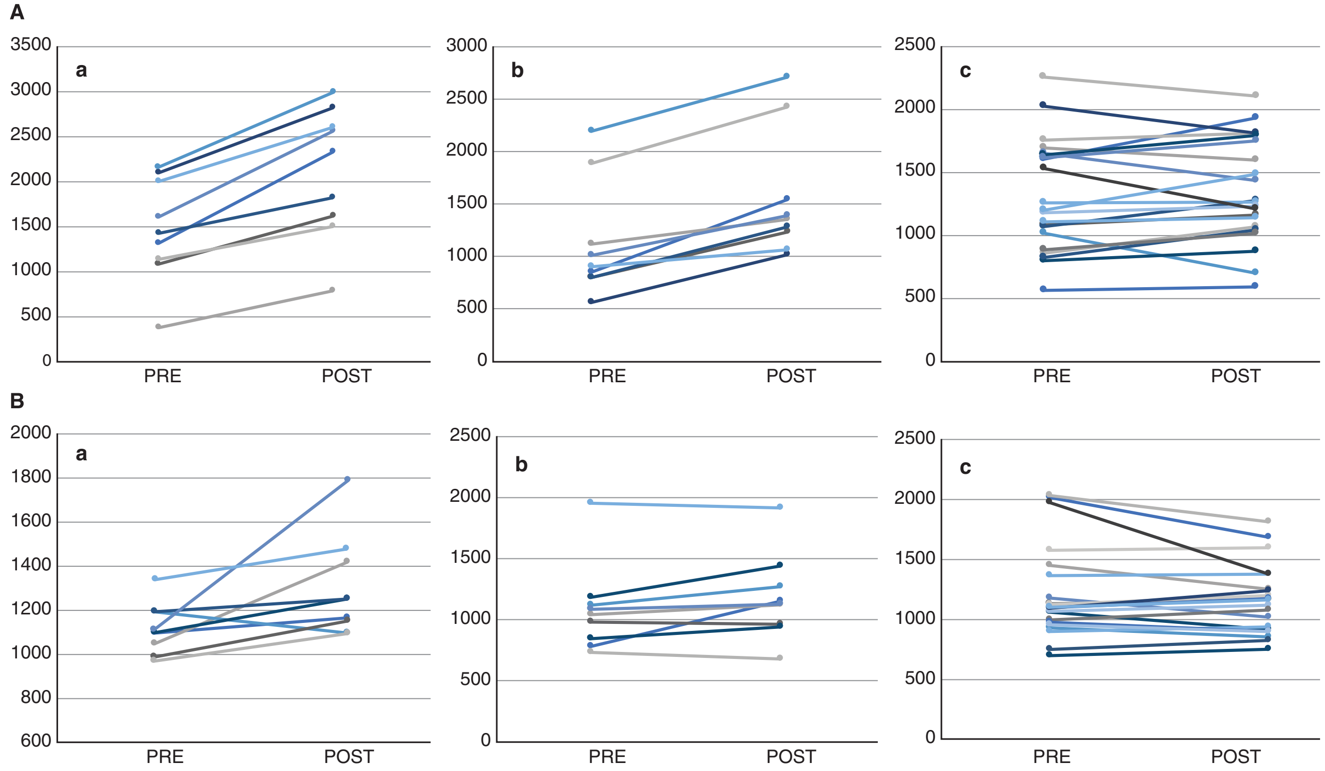


Figure 30-22 **A.** Ipsilateral lung PVC-GLPG in patients receiving (a) photon, (b) combined proton-photon, or (c) proton RT. **B.** Contralateral lung GLG in patients receiving (a) photon, (b) combined proton-photon, or (c) proton RT. GLG, global lung glycolysis; PVC-GLPG, partial volume-corrected global lung parenchymal glycolysis; RT, radiation therapy. *(Reproduced with permission from Jahangiri P, Pournazari K, Torigian DA, et al. A prospective study of the feasibility of FDG-PET/CT imaging to quantify radiation-induced lung inflammation in locally advanced non-small cell lung cancer patients receiving proton or photon radiotherapy. Eur J Nucl Med Mol Imaging. 2019;46(1):206–216.)*

pleural mesothelioma (MPM), although rare, is the most common primary pleural neoplasm. Patients affected with this disease have a median survival of 12 to 18 months. Thus, it is important to differentiate between benign pleural lesions and MPM.

The radiologic appearances of benign and malignant pleural diseases are very similar. More than 50% of patients have a pleural effusion at the time of diagnosis; however, pleural fluid cytology is positive in only approximately 25%.[263] Reverse-bevel needle biopsy and CT-guided percutaneous needle biopsy of the pleura have low diagnostic sensitivities of about 21% to 43% and 25% to 60%, respectively.[263] Distinction based on histopathologic criteria is also difficult. Currently, definitive diagnosis is based on video-assisted thoracoscopic surgery (VATS)

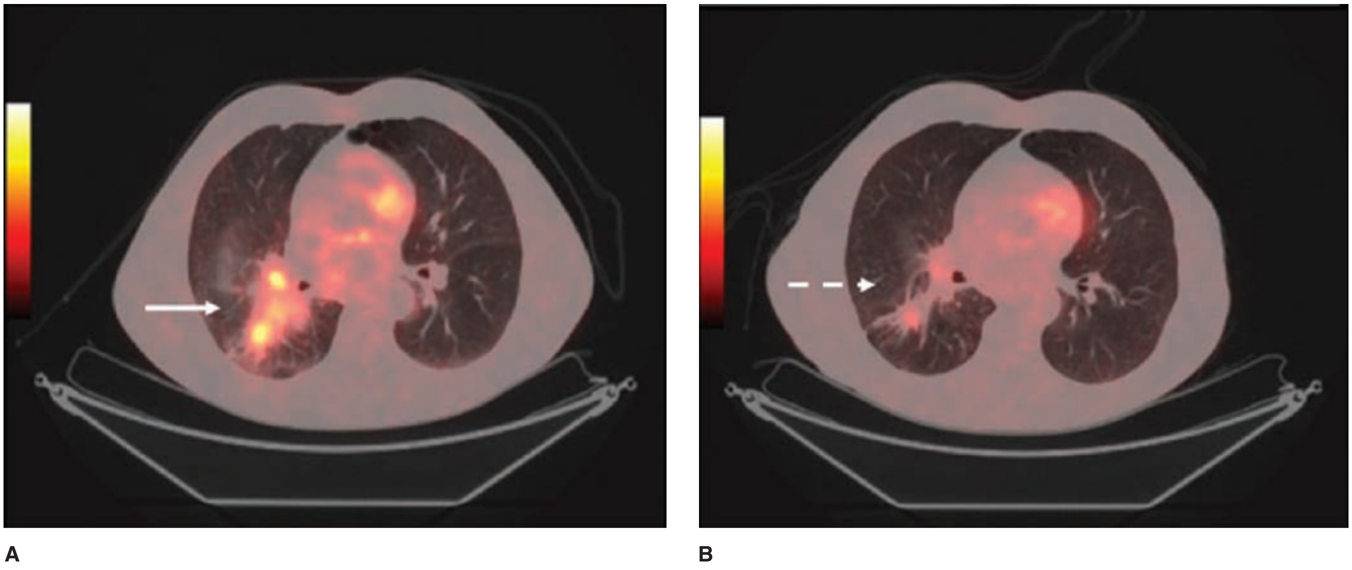


Figure 30-23 Treatment response in lung cancer. Fused transaxial PET/CT scan (**A**) at baseline shows marked FDG uptake in a tumor in the right lung hilum and mediastinal lymph nodes *(solid arrows)*. Repeat scan (**B**) after three cycles of chemotherapy reveal marked response to treatment *(interrupted arrows)*.

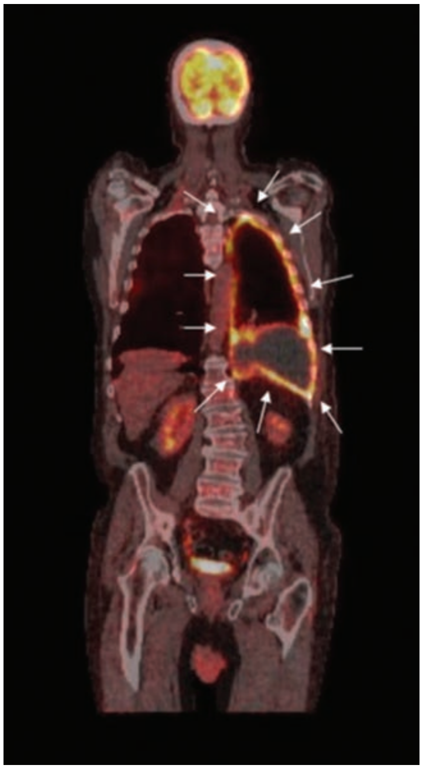


Figure 30-24 Pleural mesothelioma. Coronal view of FDG-PET/CT scan demonstrating diffusely increased FDG activity throughout the diaphragmatic, mediastinal, and left lateral pleura, consistent with malignant mesothelioma.

(sensitivity, 90%) which, for MPM, carries the risk of tumor seeding along the operative tract. Therefore, radiation therapy is performed to all entry ports following the procedure.

CT scanning and MRI cannot always differentiate between benign and malignant pleural processes and are limited in staging of MPM.[264] Findings from CT and MRI studies can be used in tandem with those from FDG-PET in managing these difficult patients (Fig. 30-24). The use of FDG-PET in mesothelioma in the mid-1990s provided a paradigm shift in the management of patients with this serious cancer.[265]

Because of the rarity of this disease, only limited studies have been performed, but FDG-PET has shown promising results in differentiating MPM from benign pleural disease. FDG uptake in MPM is significantly greater than in benign pleural disease.[266] For the first time, this approach allowed separation of a malignant etiology from that purely related to inflammatory reactions. This significantly improved the ability to determine the sites of biopsy in this population.

The degree of metabolic activity of the lesion has been shown to correlate with survival in these patients;[267] higher FDG uptake in MPM is associated with significantly shorter survival.[264] Using single SUV cutoff technique, however, may not be the optimal approach for this purpose. Dual-timepoint imaging and SUV_{max} on PET/CT in the delayed phase (120 min) have been found to be more reliable diagnostic and prognostic factors than that in the early phase (60 min).[268] By performing dual-timepoint imaging, the role of FDG-PET is further enhanced in this population.[269] This approach allows separating malignant from inflammatory lesions. While malignant lesions show increasing activity over time, inflammatory lesions show a decline. In recent years, the use of global disease assessment has become feasible with modern quantitative techniques.[270] These image segmentation methodologies permit better definition of the boundaries of malignant lesions based on PET images and provide assessments of lesional and whole-body metabolic burden.[270]

In addition to differentiating benign from malignant pleural disease and MPM prognosis, FDG-PET has shown good results in staging, planning of radiotherapy, evaluation of therapy response, and posttreatment surveillance.[270] For diagnosed cases, PET/CT currently plays an integral part in staging[271] since it has a better sensitivity than CT in the assessment of mediastinal lymph nodes.[272,273]

Several relatively small studies have shown the advantage of FDG-PET/CT over CT when determining whether a tumor is resectable. FDG-PET was found to be useful in identifying the extent of disease in the mediastinum, evaluating abnormal findings in the contralateral lung, and detecting occult extrathoracic metastases.[274–276] In a study of 29 patients, FDG-PET/CT had a major impact on increasing the accuracy of MPM TNM staging and determining appropriate therapy.[277] In one series of 42 consecutive patients with potentially resectable disease, 29% of cases (12 patients) were upstaged and made inoperable due to unexpected T4 or distant metastasis.[275]

Current consensus recommendations regarding response assessment are based on contrast-enhanced CT scanning with 1-mm sections for evaluation of local disease, or MRI with contrast and FDG-PET/CT staging. The metabolic response after neoadjuvant chemotherapy as determined by FDG-PET has been found to be an independent prognostic factor for patients with resectable MPM and may help determine which patients are good candidates for extrapleural pneumonectomy.[278]

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CHAPTER 31

Pulmonary Function Testing

Michael A. Grippi
Gregory Tino

INTRODUCTION

The assessment of human pulmonary function dates back to the seventeenth century, when the earliest measurements of tidal volume were noted. In 1800, Humphry Davy employed a hydrogen dilution technique to measure his own residual volume (RV).[1] Subsequently, John Hutchinson, in his treatise, *On the Capacity of the Lungs and on Respiratory Functions*, defined the functional subdivisions of lung volume and reported the results of vital capacity measurements performed in more than 1800 subjects. He related these measurements to the subjects' height, age, and weight, thereby establishing a basis for determining normal values.[2,3]

Progress in development of techniques for pulmonary function testing progressed slowly over the next century. However, in the 1950s, pulmonary physiologists made use of the tools provided by the evolving fields of electronics and computer science. Currently, many techniques exist for assessing both the integrated performance of the cardiovascular and respiratory systems and their individual components. This chapter focuses on commonly used tests of pulmonary function.[4–6]

Detailed assessment of integrated pulmonary and cardiovascular function is described in Chapter 32. Additional tests that have not yet been validated or are not routinely available for clinical purposes[7] are not included in the discussion.

LUNG VOLUMES AND SUBDIVISIONS

Important quantitative aspects of respiratory function are the changes in lung volume with inspiration and expiration and the absolute volume of air that the lungs hold at various times during the respiratory cycle. These volumes and changes in volume are described in subsequent sections.

Definitions and Assessment

For purposes of quantification and comparison, the total volume of gas in the lungs is conventionally subdivided into compartments (volumes) and combinations of two or more volumes (capacities). For many of these subdivisions, the end-expiratory volume—the volume of gas remaining in the lungs at the end of normal expiration—is the point of reference. Lung volumes and capacities are defined in Table 31-1 and are depicted schematically in the tracing shown in Fig. 31-1, which was obtained using a device called a spirometer. The relationships between the volumes recorded directly by the spirometer and the other lung volumes and capacities—including total lung capacity (TLC), functional residual capacity (FRC), RV, and inspiratory capacity (IC)—are highlighted in the figure.

Spirometers that measure volume or change in volume versus time have been used extensively in pulmonary function laboratories. Previously, through manual calculations, or, in modern times, through application of microprocessors, the relationships among volume, flow, and time are generated to provide a measure of the respiratory system's ability to move air. Two examples of volume-type spirometers of historic note are shown in Fig. 31-2. They are discussed briefly to highlight the ingenuity behind their use in determining clinically important physiologic measurements.

In the water-sealed spirometer (Fig. 31-2A), a mouthpiece is attached to a tube through which air passes into a lightweight bell that is inverted over a water bath. Air movement through the mouthpiece into the bell during expiration causes the bell to rise; conversely, as air is withdrawn from the system during inspiration, the bell falls. The change in volume with time can be recorded on a calibrated rotating drum or digitally noted by a computer and displayed on a screen in both graphic and numeric formats.

In the dry, rolling-seal spirometer (Fig. 31-2B), a cylinder with a rolling plastic seal is substituted for the spirometer bell and its water seal. Movement of air through the mouthpiece effects a change in the position of the piston, which is attached to a variable resistor. The resistor, in turn, generates voltage signals proportional to volume changes reflected in displacement of the piston. These signals are processed by a computer to generate graphic and numeric outputs similar to those of the water-sealed spirometer.

Currently, most pulmonary function laboratories utilize flow-type spirometers using pneumotachographs or rotating turbines to determine airflow. Two types of pneumotachographs are in general use: hot wire and flow resistive. In the hot-wire type, air flowing past a heated wire cools the wire, thereby altering its resistance

TABLE 31-1 Glossary for Static Lung Volumes and Capacities

Term	Symbol	Definition
Volumes		
Residual volume	RV	Volume of air remaining in the lungs after maximal expiration
Expiratory reserve volume	ERV	Maximal volume of air expired from the resting end-expiratory level
Tidal volume	TV[a]	Volume of air inspired or expired with each breath during quiet breathing
Inspiratory reserve volume	IRV	Maximal volume of air inspired from the resting end-inspiratory level
Capacities		
Inspiratory capacity	IC	Maximal volume of air inspired from the end-expiratory level (the sum of IRV and TV)
Vital capacity	VC	Maximal volume of air expired form the maximal inspiratory level
Inspiratory vital capacity	IVC	Maximal volume of air inspired form the maximal expiratory level
Functional residual capacity	FRC	Volume of air remaining in the lungs at the end-expiratory level (the sum of RV and ERV)
Total lung capacity	TLC	Volume of air in the lungs after maximal inspiration (the sum of all volume compartments)

[a] *The symbol TV is traditionally used for tidal volume to indicate a subdivision of static lung volumes. However, the symbol* V_T *is used for tidal volume in formulas for gas exchange.*

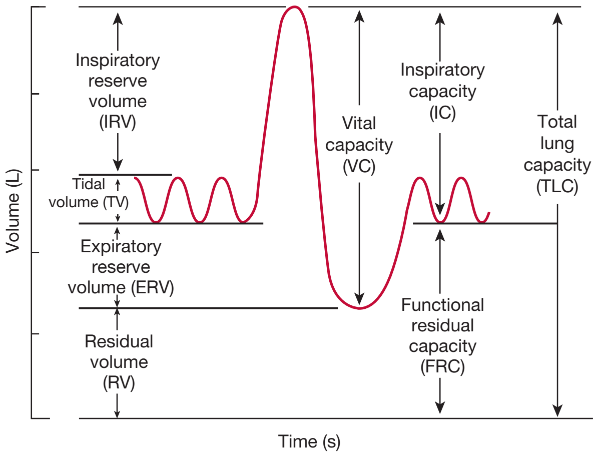

Figure 31-1 The subdivisions of lung volume as recorded by a spirometer. The record is generated on paper calibrated for volume in the vertical direction and time in the horizontal. The term *capacity* is applied to a subdivision composed of two or more *volumes*. The definitions of these subdivisions are found in Table 31-1.

in proportion to changes in airflow. Flow-resistive pneumotachographs contain a resistive element composed of parallel tubes (Fig. 31-3), a wire mesh, or a fibrous, paper-like element. Airflow through the resistive element results in a pressure gradient across the device, which can be measured by a very sensitive differential pressure gauge. In the model depicted in Fig. 31-3, the array of parallel, small-bore tubes maintains a laminar gas flow pattern through the pneumotachograph. As a result, the pressure–flow characteristics of the system can be described by Poiseuille's law:

$$\Delta P = \dot{V}\,\frac{8\eta l}{\pi r^4}$$

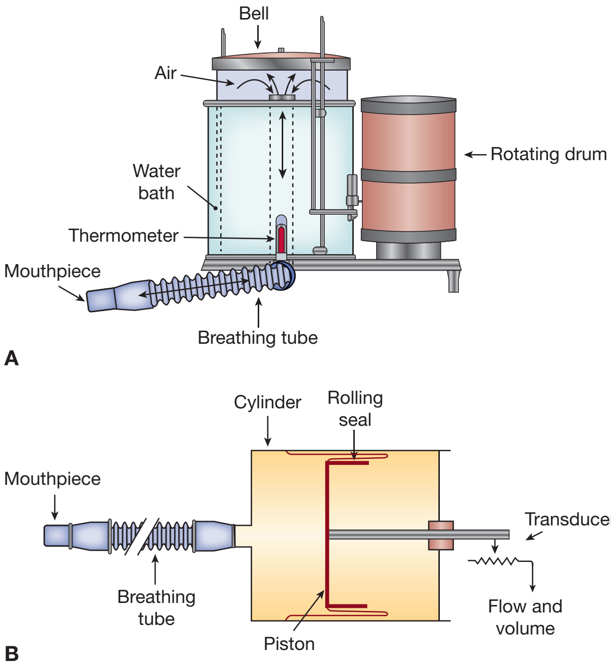

Figure 31-2 Two types of spirometers: water sealed (**A**) and dry rolling seal (**B**). Movement of air through the breathing tube results in movement of the bell (**A**) or piston (**B**). The output signal is either mechanical (pen on rotating drum) or electrical (flow and volume as voltage changes). The primary design criteria for these instruments are that inertia and resistance to airflow must be held to negligible levels, and the calibration must be accurate and stable.

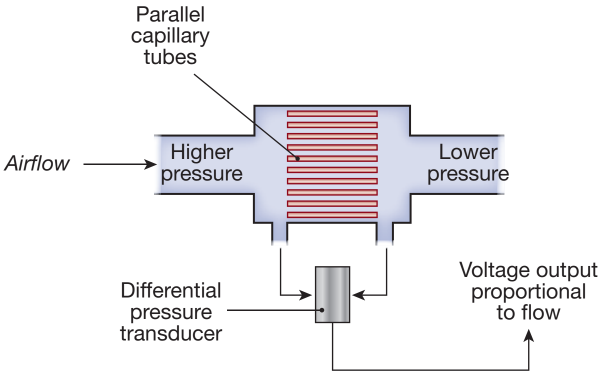
Parallel capillary tubes
Airflow
Higher pressure
Lower pressure
Differential pressure transducer
Voltage output proportional to flow

Figure 31-3 Principle of pneumotachography. During unidirectional airflow, a pressure drop is created across a resistive element made up of an array of parallel capillary tubes. The magnitude of the pressure drop is related to airflow, as described by Poiseuille's law for a laminar flow system. The pressure drop is transduced to a proportional voltage output, which can be recorded. A heating element (not shown) maintains the temperature of the expired gas near body temperature.

where

ΔP = pressure drop across the resistive element, dyn/cm^2
$\dot{V}$ = gas flow, cm^3/s
η = viscosity of gas, dyn s/cm^2
l = length of resistive element, cm
r = radius of resistive element, cm

Hence, under laminar flow conditions, the flow of gas in each tube is proportional to the pressure drop across the tube. The calculation for the overall pressure drop across the entire resistive element is based on the parallel arrangement of the array of tubes. The pressure drop across the resistive element is sensed by a pressure transducer and converted to a voltage output that is proportional to flow. The flow signal can be integrated electronically to yield volume. The output signals for flow and volume are displayed on a monitor and recorded. Minimal standards have been established by the American Thoracic Society (ATS) and the European Respiratory Society (ERS) (Table 31-2) for spirometers used either for diagnostic purposes or patient monitoring.[8–10]

In a diagnostic setting, spirometers are used to (1) evaluate symptoms, signs, or abnormal laboratory tests; (2) measure the effect of disease on pulmonary function; (3) screen persons at risk of having pulmonary disease; (4) assess preoperative risk; (5) assess prognosis; and (6) assess health status before enrollment in strenuous physical activity programs.

On the other hand, spirometers used for patient monitoring are used to (1) assess therapeutic interventions, including bronchodilator therapy, management of congestive heart failure, etc.; (2) characterize the course of diseases affecting lung function (e.g., obstructive or interstitial lung diseases, congestive heart failure, or neuromuscular diseases); (3) track pulmonary function in persons working in occupations or receiving medications known to affect the lung; (4) evaluate large numbers of people in disability assessments; and (5) provide data as part of epidemiologic surveys.[10]

In general, the diagnostic spirometer is used to assess a patient's lung function for purposes of comparison with values expected in a normal population. The monitoring spirometer, which is less expensive and more portable, is used to evaluate a patient's performance over time and to study large numbers of people for epidemiologic or other purposes.

■ The Vital Capacity and Its Subdivisions

Two methods of performing a vital capacity maneuver can be used: closed-circuit and open-circuit methods. In the closed-circuit

TABLE 31-2 Minimal Recommendations for Diagnostic Spirometry

Test	Range/Accuracy (BTPS)	Flow Range (L/s)	Time (s)	Resistance and Back Pressure	Test Signal
VC	0.5–8 L ± 3% of reading or ± 0.050 L, whichever is greater	0–14	30		3-L cal syringe
FVC	0.5–8 L ± 3% of reading or ± 0.050 L, whichever is greater	0–14	15	<1.5 cmH_2O/L/s	24 standard waveforms 3-L cal syringe
FEV_1	0.5–8 L ± 3% of reading or ± 0.050 L, whichever is greater	0–14	1	<1.5 cmH_2O/L/s	24 standard waveforms
Time zero	The time point from which all FEV_t measurements are taken			Back extrapolation	
PEF	Accuracy: ± 10% of reading or ± 0.30 L/s, whichever is greater Precision: ± 5% of reading or ± 0.15 L/s, whichever is greater	0–14		Mean resistance at 200, 400, 600 L/s must be <2.5 cmH_2O/L/s	26 flow standard waveforms
$FEF_{25–75\%}$	7.0 L/s ± 5% of reading or ± 0.200 L/s, whichever is even greater	±14	15	Same as FEV_1	24 standard waveforms
Instantaneous flows	±5% of reading or 0.200 L/s, whichever is greater	0–14		<1.5 cmH_2O/L/s	Proof from manufacturer
MVV	250 L/min at TV of 2 L within ± 10% of reading or ± 15 L/min, whichever is greater	±14 ± 3%	12–15	<1.5 cmH_2O/L/s	Sine wave pump

BTPS, body temperature and pressure, saturated with water vapor; VC, vital capacity; FVC, forced expiratory vital capacity; FEV_1, forced expiratory volume in 1 s; PEF, peak expiratory flow; $FEF_{25–75\%}$, forced expiratory flow, 25–75%; MVV, maximal voluntary ventilation; TV, tidal volume.
Reproduced with permission from Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J. 2005;26(2):319–338.

method, the seated patient, with nose clip in place, breathes quietly into the apparatus. After several breaths to establish the resting end-expiratory level, which serves as a point of reference for all subsequent measurements, the patient is urged to inspire fully and then, after reaching a plateau at maximal inspiration, to expire maximally. This expiration must be performed slowly and evenly; attempts by the patient with obstructive pulmonary disease to maximize flow often reduce expiratory volumes because of dynamic compression of the airways caused by high positive pleural pressures (see Chapter 10). Figure 31-1 illustrates schematically this relaxed or "slow" vital capacity maneuver. From the record, tidal volume, inspiratory reserve volume, expiratory reserve volume (ERV), vital capacity, and IC are calculated. A similar maneuver in which the subject breathes out as rapidly and forcefully as possible after a maximal inspiration provides a measure of the forced vital capacity (FVC). Other timed measurements of expiratory airflow (e.g., the forced expiratory volume in 1 s, or FEV_1) also are determined from this type of record (see "Dynamic Mechanical Properties of the Respiratory System," below).

In the open-circuit method of determining vital capacity, the patient inspires maximally, inserts the mouthpiece, and then exhales with a slow, constant effort to the point of maximal expiration. With this technique, the resting end-expiratory position is not recorded. Thus, only the vital capacity, not its component volumes, can be measured. The open-circuit technique offers some advantages. Since the patient inspires from room air before expiring into the apparatus, concern over acquisition of infection from contaminated inspired air is minimized. In addition, the open-circuit method is generally completed in a shorter time, providing a major advantage when epidemiologic studies are being performed on large numbers of subjects.

■ Functional Residual Capacity and Residual Volume

One compartment of the TLC that cannot be measured by spirometry is RV, the volume of air remaining in the lungs at the end of a maximal expiration. RV is determined indirectly in three steps: (1) FRC is typically measured using one of the three techniques: closed-circuit helium, open-circuit nitrogen, or total-body plethysmograph. (2) ERV is determined spirometrically. (3) RV is calculated as the difference between FRC and ERV. In principle, it is possible to determine the RV using a dilution technique or body plethysmography after maximal expiration. In practice, however, the resting end-expiratory level is a more reproducible starting point for determining FRC than is the maximal end-expiratory level for determining RV.

Closed-Circuit Helium Method

The closed-circuit helium dilution method for determining FRC is a variation of the hydrogen dilution method first used in the early 19th century. Both methods take advantage of the virtual insolubility of the test gas in body tissues and the law of conservation of mass. The development and simplification of this test were accomplished over a 20-year span in the mid-20th century. Schematic depictions of the principle upon which the technique is based and the apparatus used are shown in Fig. 31-4.

When a fully manual device is used for measuring FRC, the system is prepared by the addition of about 2 L of air and sufficient helium to achieve an initial helium concentration of approximately 10% in the apparatus. The patient, with nose clip in place, then breathes room air through the mouthpiece (Fig. 31-4A). After a preliminary period of quiet breathing to familiarize the patient with the mouthpiece, apparatus, and environment, and after the baseline resting end-expiratory level is established, the test begins.

At the end of a normal expiration, the valve at the mouthpiece is turned to connect the patient to the spirometer system (Fig. 31-4B). As the patient rebreathes from the closed circuit, the blower circulates the gas mixture. The CO_2 is absorbed by soda lime (CO_2 absorber), while O_2 is added through a valve and flowmeter at a rate corresponding to the subject's O_2 consumption. As the helium, which was at first contained entirely within the apparatus, mixes with air contained in the lungs, its concentration, as monitored by

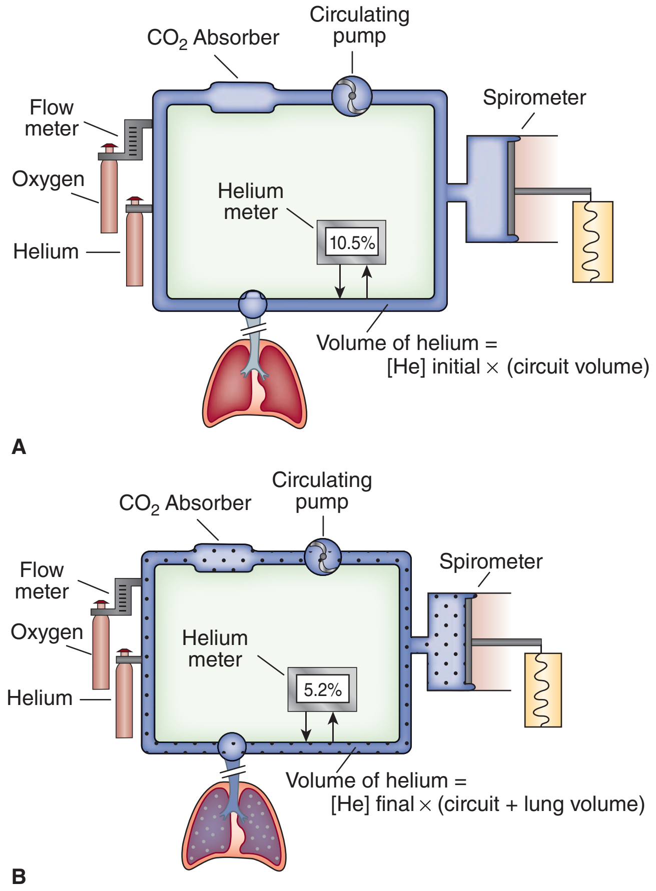

Figure 31-4 Closed-circuit helium dilution method for measurement of FRC. **A.** Spirometer and tubing system with helium before subject begins breathing through the circuit. At the end of an expiration, the mouthpiece valve is turned and the patient rebreathes through the circuit. Expired CO_2 is "scrubbed" out of the system, and O_2 is added to compensate for continued O_2 uptake in the lungs. **B.** During equilibration, the measured helium concentration falls, reflecting a dilutional effect of the additional volume (FRC) on the spirometer circuit.

the helium analyzer, falls. Stabilization of the helium concentration, indicated by a rate of change in concentration of less than 0.02% over a 30-s interval, signals the point at which the helium concentration has equilibrated throughout the lung-breathing circuit system; equilibration, the endpoint of the test, occurs within 7 min in normal persons. However, in patients in whom the distribution of ventilation is abnormal—for example, those with chronic obstructive pulmonary disease (COPD)—equilibration may take much longer. Upon equilibration, the following equation, based on the law of conservation of mass, is applied:

$$F_{0He} \times V_0 = F\mathrm{F}_{He} \times V\mathrm{F}$$

where

F_{0He} = initial concentration of helium
V_0 = initial volume of system, L
$F\mathrm{F}_{He}$ = final concentration of helium
$V\mathrm{F}$ = final volume of system, L

The initial volume of the system is the volume of the spirometer and circuit tubing, whereas the final volume consists of the initial volume plus FRC. The latter value is the only unknown in the preceding equation. Corrections are usually made for the small amount of helium dissolved in body tissues during the test and for slight volume changes caused by a respiratory exchange ratio that is not equal to 1.0.[11] Although the method described here is based on a manually operated device, the same principles hold when all the mechanical and computational steps are accomplished with a computer-controlled system.

Nitrogen Washout Method

Conceptually, the nitrogen washout method is similar to the helium dilution method described previously; however, it relies on an open circuit, rather than the closed circuit, used in the helium dilution method. The open-circuit nitrogen washout method for determining FRC[12] requires that the subject breathe 100% O_2 for 7 min; during this period, the concentration of N_2 in expired gas is monitored. When the expired N_2 concentration falls to zero, all the N_2 present in the lungs at the start of O_2 breathing has been "washed out." The total volume of gas expired and the concentration of N_2 in the expired gas are measured.

The calculation of FRC is based on the reasonable assumption that the volume of N_2 in the lungs at the start of the test (i.e., the product of lung volume and the concentration of N_2 in the lungs) is the same as the total volume of N_2 expired and collected during the period of the test—that is, the product of the total volume of gas expired and the concentration of N_2 in the expired gas:

$$F_{0_{N_2}} \times V_0 = F_{\mathrm{E}_{N_2}} \times V\mathrm{E}$$

where

$F_{0_{N_2}}$ = concentration of N_2 in the lungs
V_0 = volume of gas in the lungs, L
$F_{\mathrm{E}_{N_2}}$ = concentration of N_2 in the expired gas
$V\mathrm{E}$ = volume of expired gas, L

Since the test is started at the end of a quiet expiration, the volume of gas in the lungs is FRC. This volume is calculated by substituting into the above equation the initial concentration of N_2 in the lungs, estimated at 0.81 in fasting and 0.79 to 0.80 in nonfasting subjects, and the measured values for volume and N_2 concentration of expired gas.

Body Plethysmography

The word *plethysmography* is derived from the Greek *plethysmos*, meaning "enlargement." Although the concept of measuring FRC by recording changes in the volume of the body during "enlargement" of the chest was described in 1882, not until 1956 did DuBois and coworkers introduce a practical plethysmographic technique, based on Boyle's law, for determining thoracic gas volume (TGV).[13]

Any of three types of body plethysmographs can be used: (1) the *pressure plethysmograph*, in which pressure during breathing varies while volume remains constant; (2) the *volume plethysmograph*, in which volume varies during breathing while pressure remains constant; and (3) the *pressure-corrected flow plethysmograph*, which couples the pressure plethysmograph's fidelity of response to high-speed events with the volume plethysmograph's ability to follow large changes in volume. Since the conceptual basis for all three devices is similar, only the most popular one—the pressure plethysmograph—will be described.

The pressure plethysmograph (Fig. 31-5) contains a pneumotachograph and transducer for measuring flow and volume, and two strain-gauge transducers, one for sensing pressure at the mouth (Pm) and the other for sensing pressure in the box (Pbx). A solenoid-operated shutter mechanism is situated between the mouthpiece and the pneumotachograph. The three transducers are connected to an amplifying and monitoring system so that box pressure (or lung volume) and mouth pressure are displayed simultaneously on the X and Y axes, respectively, of an oscilloscope (Fig. 31-6).

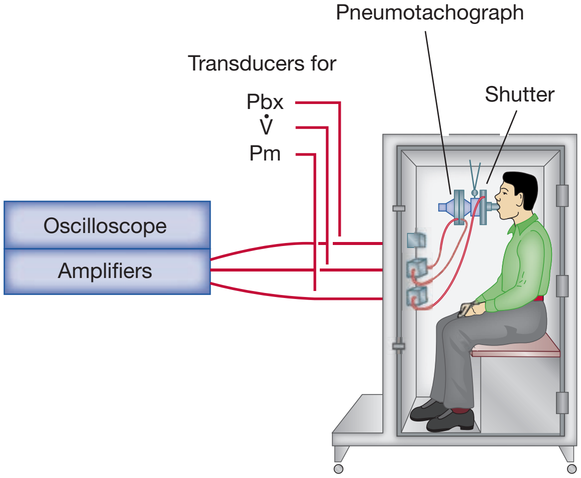

Figure 31-5 Constant-volume, variable-pressure plethysmograph used for measuring functional residual capacity and airway resistance. The device has a fixed volume. Thoracic gas volume changes associated with changes in alveolar pressure are reflected as changes in pressure within the plethysmograph.

In order to determine FRC, the patient, seated comfortably within the box with nose clip in place, is asked to breathe quietly through the mouthpiece. At the end of a quiet expiration, the shutter is closed, and the patient is instructed to pant gently against it. The panting movements cause both mouth pressure and box pressure to change. With each inspiratory effort, as mouth pressure falls and gas in the lungs is rarefied, lung volume increases. Because the plethysmograph is a closed box, the increase in lung volume produces a corresponding increase in box pressure. With each expiratory effort, as lung volume decreases, box pressure falls. Because the shutter is closed while the measurements are made, mouth pressure equals alveolar pressure (PA). These oscillations in mouth pressure and box pressure or lung volume appear on the oscilloscope as a closed loop (Fig. 31-6). Measurement of the slope of this loop is used to determine the volume of gas in the lungs at the time of shutter closure—that is, TGV or V_{TG}. When the occlusion occurs at resting, end-expiratory lung volume, the measurement yields FRC (see below).

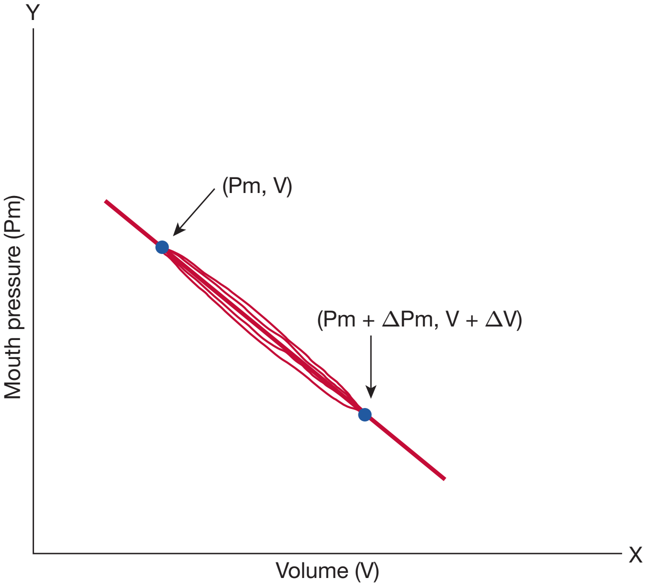

Figure 31-6 Pressure–volume loop obtained from a person seated in a body plethysmograph. Pressure at the mouth represents alveolar pressure; pressure in the box represents thoracic gas volume. After the shutter has closed at end-expiration (Pm, V), the subject attempts to inspire. Pm falls, and the pressure in the box increases. This increase in box pressure is calibrated in terms of an equivalent volume change. The new position of the trace at the end of the inspiratory effort is (Pm + ΔPm, V + ΔV). The slope of the loop depends on the volume of gas in the lungs when the shutter is closed (FRC).

Applying Boyle's law to the plethysmographic determination of lung volume,

$$PV = (P + \Delta P)(V + \Delta V)$$

where

P = pressure in the lungs at end-expiration (atmospheric pressure), cmH_2O
ΔP = change in pulmonary pressure produced by respiratory efforts, cmH_2O
V = volume of gas in the lungs at end expiration (FRC), L
ΔV = change in gas volume in the lungs produced by compression (during expiration) and rarefaction (during inspiration) secondary to respiratory efforts, L

In the pressure plethysmograph, ΔV is sensed as a change in pressure within the box, and ΔP is determined from the change in mouth pressure during breathing efforts against the closed shutter.

Rearranging the above equation and solving for V yields

$$V = \frac{\Delta V}{\Delta P}(P + \Delta P)$$

However, since ΔP is small compared to P (atmospheric pressure), it may be disregarded. The equation then becomes

$$V = P \times \frac{\Delta V}{\Delta P}$$

where

V = functional residual capacity, L
P = atmospheric pressure, cmH_2O
$\Delta V/\Delta P$ = inverse of slope of the loop on the oscilloscope

Therefore, the only unknown in this equation is V, which can be calculated by incorporating values for barometric pressure and the inverse of the slope of the plot of mouth pressure versus box pressure (ΔP/ΔV).

Two methods for measuring static lung volumes using plethysmography have been standardized by the ATS and ERS. One entails shutter closure at FRC, followed by expiration to RV, and then an IC maneuver to TLC; the other method is shutter closure at FRC, followed by an IC maneuver to TLC, and then an expiratory vital capacity maneuver to RV.[14] Application of each method may yield different calculations of lung volumes.[15]

Comparison of Methods

Compared with the dilution and washout techniques, body plethysmography is, by far, the fastest method available for determining FRC. Indeed, it enables several determinations to be made per minute. Although the equipment required for body plethysmography is more expensive than that required for the other methods, in a busy laboratory this technique generally proves to be more economical because of the time saved and the additional uses to which the equipment can be put (e.g., measurement of airway resistance; see "Airway Resistance," below). Technically, the test is only slightly more difficult than the inert gas dilution method.

Sources of error inherent in the use of body plethysmography and discrepancies between results obtained by body plethysmography and the inert gas techniques should be noted. In patients with COPD[16] or asthma,[17] values for FRC obtained by body plethysmography may be artifactually high because of pressure differences between the mouth and alveoli generated during panting across narrowed airways. Consequently, pressures recorded at the mouth during shutter occlusion of the airway underestimate changes in alveolar pressure. Overestimation of TLC using body plethysmography appears to be greatest in patients whose FEV_1 (see below) is less than 30% predicted.[18]

The inert gas dilution and washout methods are similar both in principle and in results. The values for FRC with these techniques match those from the body plethysmograph except in persons in whom considerable areas of the lungs are poorly ventilated, usually due to obstructive airway disease. In these individuals, complete mixing or washout of the indicator gas is very slow, at times requiring 45 min or longer. Because of the slow equilibration of gas concentrations in the poorly ventilated areas, the usual time allotted for the test is inadequate, resulting in a lower value for FRC by the washout methods than by body plethysmography. One strategy commonly used to deal with this problem is to prolong the washout time. The primary advantage of these techniques over body plethysmography is that they can be used in persons for whom the plethysmograph is impractical—for example, those with marked obesity, skeletal abnormalities, or claustrophobia.

Temperature Correction Factors

By convention, all lung volumes previously described and airflows (see below) are expressed in terms of body temperature and pressure, saturated with water vapor (BTPS). This practice enables direct comparison of pulmonary function data from laboratories operating at different ambient temperatures and altitudes. To convert the volume of gas collected in a volume-type spirometer under ambient conditions (i.e., ambient temperature and pressure, saturated with water vapor, or ATPS) to BTPS, a conversion factor is applied (Table 31-3). Previously, it was presupposed that air entering a spirometer was cooled *immediately* to ambient temperature and remained saturated with water vapor (ATPS). Under this assumption, only ambient temperature was considered in determining the appropriate correction factor. However, studies have addressed the assumption that expired gas is immediately cooled,[19,20] as well as the practical consequences of temperature correction errors. The ATS recommends temperature correction of results from volume-type spirometers based on *measured* gas temperature at the time of testing.

TABLE 31-3 Factors for Converting Volumes from ATPS to BTPS at Barometric Pressure of 760 mm Hg[a]

Ambient Temperature (°C)	Multiplier to Convert Volumes to BTPS[b]
20	1.101
21	1.096
22	1.091
23	1.085
24	1.080
25	1.074
26	1.069
27	1.062

[a] *Based on Boyle's, Charles's, and Dalton's laws.*
[b] *Volume at ATPS × multiplier = volume at BTPS.*
ATPS, ambient temperature and pressure, saturated with water vapor; BTPS, body temperature and pressure, saturated with water vapor.

Radiographic Assessment of Lung Volume

Although initial reports describing use of radiographic techniques to measure lung volumes date back over 40 years, these methods have not found widespread use in adult populations. More sophisticated computed tomographic (CT) applications have demonstrated good correlation with plethysmographic and gas dilution techniques in normals. However, significant differences may be observed in patients with COPD,[21] in whom TLC determinations using plethysmography may be up to 2 L greater than TLC assessed with CT scanning.[22]

STATIC MECHANICAL PROPERTIES OF THE RESPIRATORY SYSTEM

Exploration of the elastic properties of the respiratory system and their effect on lung volumes and work of breathing began in earnest during the earlier part of the 20th century. Although the groundwork had been laid centuries before (by Robert Hooke's *The Theory of Springs* in 1678), between 1923 and 1956 investigators provided a wealth of information about the elastic properties of the respiratory system and its components and the work done in overcoming these elastic forces during breathing.

Static Compliance of the Lungs

The elastic properties of the lungs are determined by relating the change in the volume of air contained in the lungs to the corresponding change in the recoil force of the lungs. Change in lung volume is most easily measured by determining the volume of gas inspired or expired at the mouth. Although expedient, this approach to determining the elastic properties of the lungs can underestimate the change in lung volume when incorporated into techniques (see below) that require the subject to expire gently against a closed shutter, a maneuver that compresses thoracic gas. However, the problem can be circumvented by placing the subject in a volume plethysmograph that uses a spirometer attached to the plethysmograph to record changes in TGV due to gas compression.

The recoil force of the lungs, measured as the transpulmonary pressure (Fig. 31-7), is the difference between the alveolar and pleural pressures (PA and Ppl, respectively). Alveolar pressure is determined as the pressure at the airway opening (Pao)—that is, the mouth—when airflow is arrested and the glottis is open. The pleural pressure is determined indirectly by measuring the pressure in the esophagus using an esophageal balloon catheter. This technique, first introduced in 1949, has been improved over the years and provides accurate reflections of changes in pleural pressure at all lung volumes except those below FRC.[23]

A thin rubber balloon, about 10 cm long, is placed over a small-diameter polyethylene catheter. Several holes in the terminal portion of the catheter allow pressure to be transmitted from the balloon, through the catheter, to a transducer. The balloon is positioned in the lower third of the esophagus, where esophageal pressure and,

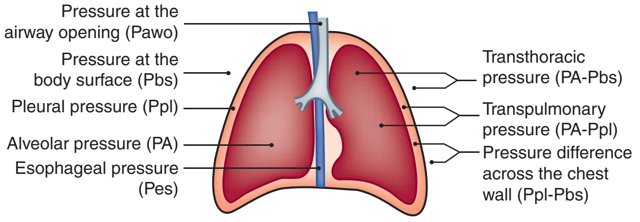
Pressure at the airway opening (Pawo)
Pressure at the body surface (Pbs)
Pleural pressure (Ppl)
Alveolar pressure (PA)
Esophageal pressure (Pes)
Transthoracic pressure (PA-Pbs)
Transpulmonary pressure (PA-Ppl)
Pressure difference across the chest wall (Ppl-Pbs)

Figure 31-7 Schematic representation of the chest depicting pressure terms and gradients used in analysis of the mechanics of breathing. The expressions for individual pressure measurements on the left are relative to atmospheric pressure. Pleural pressure (Ppl) is not routinely measured directly but is approximated by esophageal pressure (Pes) measured with a balloon catheter.

therefore, balloon pressure accurately reflect the pressure acting on the lung surface (pleural pressure). Use of an elongated balloon of low volume helps to minimize changes in pressure due to esophageal contractions. By conveying mouth pressure and esophageal pressure to opposite sides of a differential pressure transducer, an output signal is generated that is proportional to the difference between these two pressures—that is, the transpulmonary pressure (PA – Ppl).

To determine the elastic properties of the lungs, the patient, with esophageal balloon in place, is seated in a closed body plethysmograph. The patient then breathes ambient air through a tube to the outside until the volume trace, inscribed by the plethysmograph spirometer, indicates that the end-expiratory level is stable. At this juncture, the patient is instructed to first inspire slowly to TLC and then to expire slowly to the resting end-expiratory level (FRC). This maneuver is then repeated; during the second expiration, the shutter is activated to occlude the airway intermittently. Since each closure of the shutter interrupts the expiration briefly, the recorded trace of expiratory volume versus time displays a staircase pattern (Fig. 31-8A). The plateau resulting from each closure of the shutter marks a finite period of zero change in lung volume as the lungs empty during expiration. Associated with each plateau is a corresponding plateau in transpulmonary pressure.

The relationship between the change in volume and the change in pressure is a measure of the *recoil force* of the lungs at each of the lung volumes that are registered (Fig. 31-8B). The resulting curve provides several useful indices of the elastic behavior of the lungs. The slope of the curve over the range corresponding to the tidal volume is the *static lung compliance.* The transpulmonary pressure attained at TLC is the *maximal static recoil pressure.* The ratio of the maximal static recoil pressure to the corresponding maximal lung volume is the *coefficient of retraction.* However, since these values are derived from only small segments of the curve, inspection of the total static pressure–volume curve remains the most comprehensive means of assessing the elastic properties of the lungs.

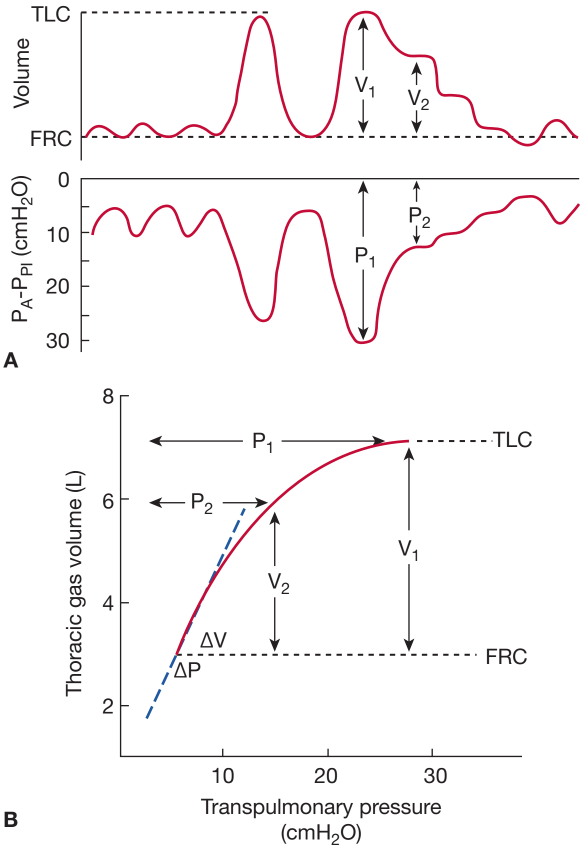

Figure 31-8 Measurement of the elastic properties of the lungs. **A.** Recordings of changes in lung volume and transpulmonary pressure (PA − Ppl) using the esophageal balloon technique described in the text. Simultaneous measurements of volume and pressure are obtained during periods of arrested airflow at lung volumes ranging from TLC to just below FRC. **B.** Thoracic gas volume is plotted on the ordinate and transpulmonary pressure on the abscissa. The curve formed by the plot using values from **A** describes the elastic properties of the lungs. The slope of the line, ΔV/ΔP, over the range of the tidal volume is the static compliance of the lungs.

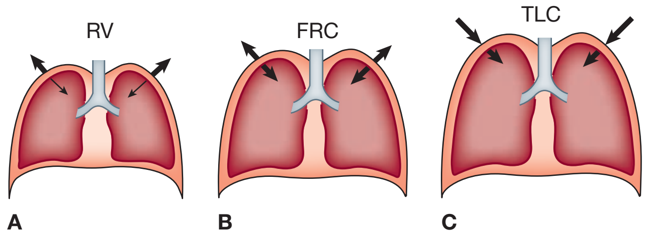

Figure 31-9 Schematic depiction of elastic recoil vectors across the lung and chest wall as determined by the level of inflation. **A.** At RV, the outwardly directed recoil pressure of the chest wall is large and the inwardly directed recoil pressure of the lung is small. **B.** At FRC, the recoil pressures of the lung and chest wall are equal and in opposite directions. **C.** At TLC, both recoil pressures are directed inward, and each contributes substantially to the overall recoil pressure of the respiratory system.

■ Static Compliance of the Chest Wall

Functionally, the chest wall includes the bony thorax, intercostal muscles, overlying soft tissue, pleura, and diaphragm. The chest wall is distensible and has its own distinctive elastic properties. In the normal, end-expiratory, resting position of the respiratory system (FRC), the inward recoil of the lung is balanced by the outward recoil of the chest wall (Fig. 31-9B). As the volume of the thoracic cavity enlarges progressively during inspiration from FRC to TLC, the outward recoil pressure of the chest wall lessens, becoming zero at approximately 70% of TLC; beyond this point, the chest wall begins to recoil inwardly (Fig. 31-9C). Conversely, as the chest wall is compressed below FRC by the action of the expiratory muscles, the natural outward recoil tendency is increased (Fig. 31-9A).

In practice, assessment of the elastic properties of the chest wall is accomplished by first determining the compliance curve of the respiratory system as a whole and then subtracting the contribution of the lungs. For a given lung volume, the pressure across the chest wall, Ppl − Pbs (Fig. 31-7), is simply the difference between the transthoracic (PA − Pbs) and transpulmonary (PA − Ppl) pressures. As indicated above, Ppl is determined using an esophageal balloon catheter.

■ Elastic Properties of the Respiratory System as a Whole

The elasticity of the respiratory system as a whole is determined by measuring the change in volume resulting from a change in pressure applied to the system—that is, the transthoracic pressure (PA − Pbs)—*while the respiratory muscles are completely relaxed.*

The first method used for this evaluation employed the relaxation technique described by Rahn and associates.[24] The subject breathes quietly into an apparatus consisting of a spirometer, a shutter, and a pressure transducer connected to the subject's side of the shutter (Fig. 31-10). After a period of quiet breathing, the subject is instructed to inspire maximally; the shutter is closed at peak inspiration, and the subject is then asked to relax the respiratory muscles completely while keeping the glottis open. Periodically, the shutter is opened, allowing a small volume of air to move from the subject into the spirometer; the shutter is then closed again. This maneuver is repeated until FRC is reached. During the periods of arrested airflow,

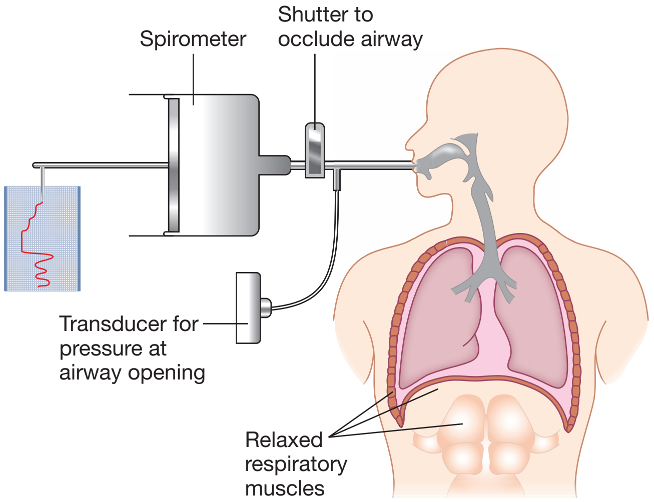

Figure 31-10 Relaxation technique for measurement of elastic recoil pressure of the respiratory system. After a period of normal tidal volume breathing, the subject inspires to TLC. A shutter in the airway is closed, and the subject relaxes his or her respiratory muscles. The shutter is periodically opened, permitting exhalation of a small volume of air measured by the spirometer. Airway pressures are recorded at times of shutter closure (i.e., during no airflow, when mouth pressure equals alveolar pressure). A pressure–volume curve is then constructed from the simultaneously recorded values for pressure and volume.

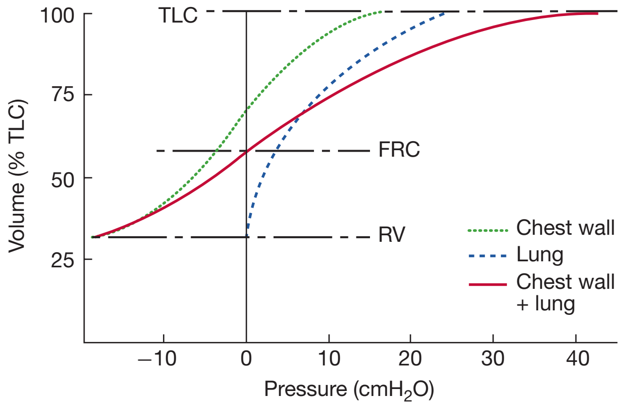

Figure 31-11 The pressure–volume curves of the respiratory system and its components. The elastic recoil pressures of the total respiratory system *(solid line)* over the vital capacity range are the sum of the recoil pressures of the lung *(dashed line)* and chest wall *(dotted line)*. At FRC, the chest wall recoil pressure is counterbalanced by the lung recoil pressure. The net result is a total system recoil pressure of 0. The total system recoil pressure is obtained by relaxation pressure or continuous positive-pressure breathing techniques. The chest wall recoil pressure is calculated as the difference between the recoil pressure of the entire respiratory system and the recoil pressure of the lungs.

pressure at the mouth (Pao) is equal to the pressure in the alveoli (PA). Provided the pressure at the body surface is atmospheric and the respiratory muscles are completely at rest, this value represents transthoracic pressure. In practice, however, full relaxation of the respiratory muscles is difficult, and a contribution by them to the pressure at the airway opening is frequently unavoidable.

A more practical technique entails the application of continuous positive pressure to the airways during spontaneous breathing. The subject breathes quietly into a water-sealed spirometer until a constant end-tidal level is achieved. A weight is then placed on the spirometer bell to increase the pressure in the respiratory system and, thereby, to raise the resting end-expiratory lung volume. This procedure is repeated using several different weights so that a pressure–volume curve of the total respiratory system can be constructed.

The individual pressure–volume curves for the lungs and chest wall and the composite curve for the intact respiratory system are shown in Fig. 31-11. As illustrated, the elastic recoil of the chest wall alone is determined by subtracting the recoil pressure of the lung from that of the total respiratory system. Chest wall elasticity is an important determinant of the subdivisions of lung volume and the overall compliance of the respiratory system; the latter is, in turn, an important determinant of the work of breathing.

Several features of the pressure–volume relationships shown in Fig. 31-11 are worth emphasizing. As lung volume approaches RV, the elastic recoil pressure of the respiratory system is largely due to the outwardly directed recoil pressure of the chest wall. At RV, the contribution of the lung to the recoil pressure of the respiratory system is minimal. At the other extreme of lung volume, TLC, elastic recoil pressure is high and directed inwardly, due to the combined elastic recoils of the lung and chest wall. At FRC, the outwardly directed recoil of the chest wall balances the inwardly directed recoil of the lung, and the transthoracic pressure is zero (i.e., PA − Pbs = 0). Indeed, the system "comes to rest" at FRC because of the counterbalancing of these forces at that volume. Since alveolar pressure at FRC is zero, no pressure gradient exists for airflow. Therefore, the system remains stationary until acted upon by the muscles of inspiration or expiration.

■ Elastic Properties of the Respiratory System in Health and Disease

The elastic properties of the respiratory system are altered by a wide variety of diseases that can affect the lung parenchyma or chest wall, either selectively or in concert. Most instances of clinically significant reductions in static compliance are due to abnormalities in the lung. The two standard clinical measures of the elastic properties of the lung are static lung compliance and maximal static recoil pressure.

Static lung compliance, Cst,L, is determined over the linear portion of the pressure–volume curve, between FRC and a lung volume corresponding to FRC plus 0.5 L. Normal values vary among laboratories, ranging from 0.147 to 0.375 L/cmH$_2$O, with a mean of 0.262 L/cmH$_2$O. Some variability is related to age and sex; Cst,L decreases with age and is higher in males than in females.

Maximal static recoil pressure is the recoil pressure at TLC. Once again, normal values vary. Data from one series of 51 normal subjects[25] are shown in Table 31-4.

TABLE 31-4 Normal Maximal Static Recoil Pressures for Adults (cmH$_2$O)

	Male Age (Years)			Female Age (Years)		
	25–35	36–64	65–75	25–35	36–64	65–75
Mean ± SD	35.9 ± 8.5	33.0 ± 8.7	33.0 ± 2.9	36.4 ± 5.8	25.7 ± 4.0	23.7 ± 3.9
Range	24.0–48.0	21.5–48.0	17.0–42.2	21.0–48.0	20.0–30.0	18.0–31.6

Data from Knudson RJ, Clark DF, Kennedy TC, et al. Effect of aging alone on mechanical properties of the normal adult human lung. J Appl Physiol. 1977;43(6):1054–1062.

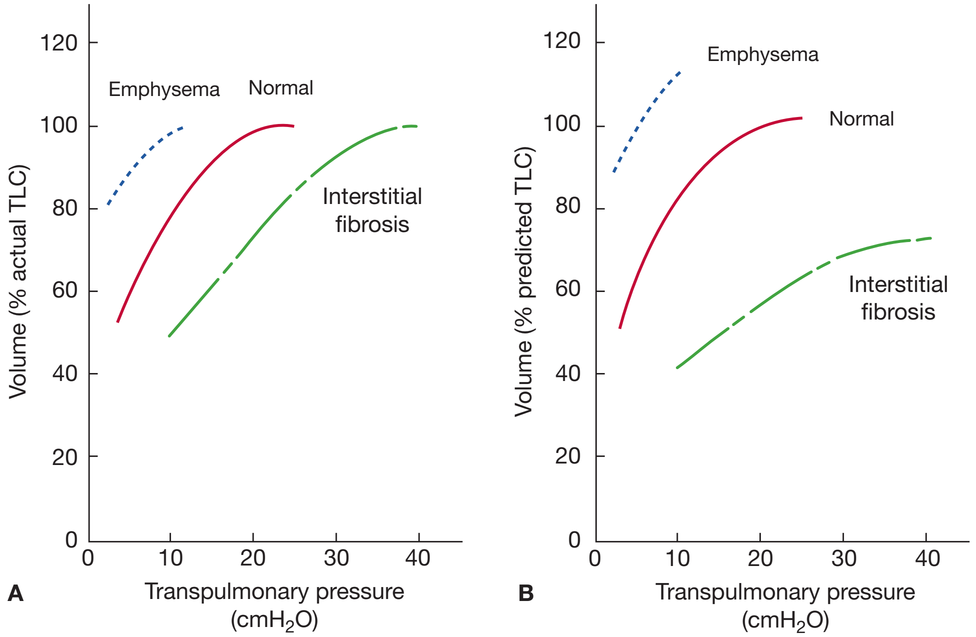

Figure 31-12 Pressure–volume curves of the lungs in health and disease. **A.** Volume expressed as percent of actual TLC. Differences in transpulmonary pressures in normal and diseases states are evident. Changes in lung volume that occur with disease are demonstrated on the plots. **B.** Volume expressed as percent of predicted TLC. In addition to the differences in transpulmonary pressures, alterations in lung volumes in the disease states are evident.

In disease states characterized by an increased elastic recoil pressure, such as diffuse interstitial fibrosis, the pressure–volume curve is shifted to the right and the static lung compliance decreases (Fig. 31-12). The increased elastic recoil pressure contributes to a decrease in FRC and TLC. By expressing the volume axis of the pressure–volume curve in terms of *percent predicted TLC* (Fig. 31-12B), instead of *absolute TLC* (Fig. 31-12A), the reduction in maximal lung volume is clearly evident; that is, maximal recoil pressure is increased, despite the reduced TLC.

In contrast to the effects of fibrosis, emphysema, which destroys alveolar walls and enlarges alveolar spaces, reduces lung elastic recoil pressure (Pel). This change increases both TLC and FRC. The shift of the pressure–volume curve upward and to the left (Fig. 31-12) indicates that lung compliance increases and that the maximal recoil pressure decreases. If the volume axis is expressed as percent predicted TLC (Fig. 31-12B), the increase in lung volume is more clearly demonstrated.

As noted previously, disorders affecting primarily the chest wall can also significantly alter the elastic properties of the respiratory system. Among these are obesity, kyphoscoliosis, and fibrothorax. These disorders limit chest wall excursion and lung expansion and reduce FRC. In addition, they produce decreases in static compliance of the lung and chest wall and maximal recoil pressure.

RESPIRATORY MUSCLE STRENGTH

Ventilatory performance depends not only on the mechanical properties of the lungs and chest wall, but also on the strength of the respiratory muscles. Evaluation of respiratory muscle strength was undertaken as early as the mid-19th century. Subsequently, using simplified methods of measurement, Black and Hyatt established normal values (Table 31-5).[26]

The maximal pressure generated by an isometric contraction varies directly with the resting length of the muscle. Consequently, values for maximal inspiratory and expiratory pressures depend on the lung volume at which the tests are performed (Fig. 31-13).[27] When TLC is less than 70% of the predicted value, the maximal expiratory pressure will be low. Similarly, when RV exceeds 40% of the predicted TLC, the maximal inspiratory pressure will be low.

The only equipment required for measurement of maximal inspiratory or expiratory pressure is an aneroid vacuum and pressure gauge. To determine maximal expiratory pressure, the patient is urged to inspire fully to TLC and then to expire as forcefully as possible into the gauge. The highest pressure attained and held for at least 1 s is the *maximal expiratory pressure* ($P_{E_{max}}$). The *maximal inspiratory pressure* ($P_{I_{max}}$) is determined by having the patient inspire maximally from the gauge after having expired completely to RV. The value recorded is the lowest pressure attained and held for at least 1 s.

TABLE 31-5 Prediction Equations and Lower Limits of Normal for Maximal Inspiratory ($P_{I_{max}}$) and Maximal Expiratory ($P_{E_{max}}$) Pressures (cmH_2O)[a]

	$P_{I_{max}}$		$P_{E_{max}}$	
	Predicted Mean (cmH_2O)	Lower Limit of Normal	Predicted Mean (cmH_2O)	Lower Limit of Normal[b]
Male	143 − (0.55 × age)	71	268 − (1.03 × age)	111
Female	104 − (0.51 × age)	39	170 − (0.53 × age)	88

[a] *Age range = 20–86 years.*

[b] *Independent of age.*

Data from Black LF, Hyatt RE. Maximal respiratory pressures: Normal values and relationship to age and sex. Am Rev Respir Dis. 1969;99(5):696–702.

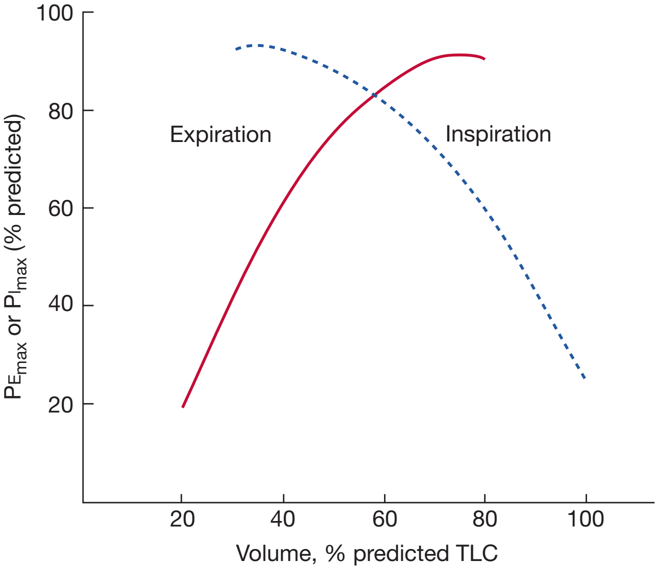

Figure 31-13 Effect of lung volume on maximal inspiratory *(dashed line)* and maximal expiratory *(solid line)* pressures. See text for discussion.

Measurement of maximal static respiratory pressures is particularly important in evaluating respiratory muscle weakness in patients with neuromuscular disease,[28] as described in Chapters 83 and 84. In such patients, spirometric tests are often normal, despite respiratory muscle weakness, because maximal pressures are not required to achieve maximal expiratory flow rates (see "Flow-Volume Relationships" below).

Another useful function of these measurements is in examining patients whose coordination in performing spirometry or whose degree of motivation is suspicious. In such patients, determination of maximal pressures is often helpful in determining whether optimal efforts are being expended during pulmonary function testing (see "Approach to Interpreting Commonly Performed Pulmonary Function Tests," below).

DYNAMIC MECHANICAL PROPERTIES OF THE RESPIRATORY SYSTEM

The static tests of pulmonary function described in the previous section are based on measurements of volume and pressure made while airflow is arrested. These static tests are particularly useful in defining the elastic properties of the respiratory system. Considerable additional information can be gained from tests done during airflow—that is, under "dynamic" conditions.

Although measurements of static lung volumes began about 300 years ago, the assessment of pulmonary function during airflow began in 1933, when the test now known as the *maximal voluntary ventilation* (MVV) was first proposed. This test did not become popular until a few years later, when Cournand and Richards developed regression equations to determine normal values. Subsequently, investigators proposed that the volume of air expired during specific time intervals be determined. In 1955, determination of the average airflow during the middle half of a forced expiratory vital capacity was described. Determination of these indices of dynamic lung function is now generally part of the battery of tests, both static and dynamic, included under the designation *spirometry.*

The more practical tests of dynamic function can, for convenience, be divided into four categories: FVC, flow–volume curves, MVV, and airway resistance. Other dynamic tests, including assessment of airway reactivity and the function of small airways, will be considered separately.

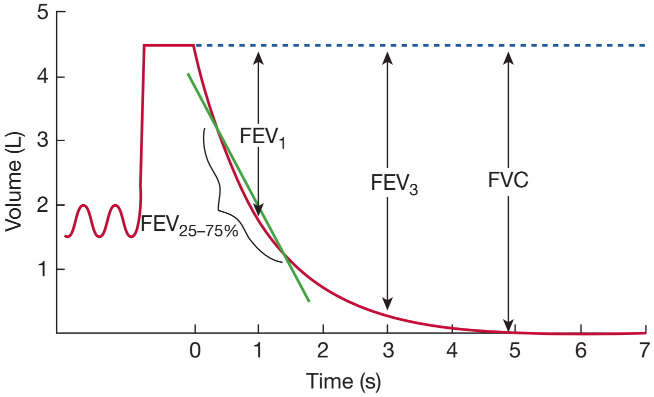

Figure 31-14 Forced expiratory vital capacity maneuver. After an initial period of tidal volume breathing, the patient inspires maximally to TLC and then exhales as rapidly and as forcefully as possible into a spirometer. Shown on the left of the tracing are a series of tidal volume breaths and the maximal inspiration to TLC. The forced expiration begins at time 0. Nearly all the volume is exhaled in the first 3 s of the maneuver. The values for FVC, FEV_1, and FEV_3 are measured from the maximal inspiratory level. The $FEF_{25-75\%}$ is the slope of the line connecting the points on the volume–time trace that correspond to 25% and 75% of the FVC.

Forced Vital Capacity

Both expiratory and inspiratory measurements of the FVC are routinely made in pulmonary function laboratories. Unless otherwise specified, FVC refers to the forced *expiratory* maneuver.

Forced Expiratory Vital Capacity

The forced expiratory vital capacity is measured during expiration. The maneuver entails two steps: a full inspiration to TLC, followed by a rapid, forceful, maximal expiration (to RV) into a spirometer. The forced expiratory vital capacity (FVC) is normally equal to the relaxed or slow vital capacity (VC). However, a discrepancy between FVC and VC appears in obstructive disease of the airways: the FVC is less than the VC.

The relationship between expired volume and time during an FVC maneuver is used to determine airflow during expiration and the volume of air expired within designated intervals; these values provide an indirect measure of the flow-resistive properties of the lung. The FVC is displayed in one of the two ways: expired volume plotted against time (Fig. 31-14) or airflow plotted against lung volume—that is, an expiratory "flow–volume curve" (see below). The normal volume–time display of the FVC consists of a smooth curve with a gradually and progressively decreasing slope. Irregularities in the curve suggest either a failure of coordination or a suboptimal effort. At times, the onset of the forced expiration is unclear (Fig. 31-15) because of hesitation on the part of the patient. When this occurs, the start of expiration ("zero time") is determined with the "back extrapolation" method (Fig. 31-15).[10] A tangent taken through the part of the curve with the steepest slope is extrapolated back to the maximal inspiratory volume; the point of intersection is considered to be the time of onset of expiration.

Several values are commonly determined from the volume–time plot of the FVC (Table 31-6, Fig. 31-14): (1) the *volume expired in the first second*, expressed either as an absolute volume (FEV_1) or as a percentage of the FVC (FEV_1/FVC%); (2) *the volume expired in the first 3 seconds*, expressed either as an absolute volume (FEV_3) or as a percentage of the FVC (FEV_3/FVC%); and (3) *the forced midexpiratory flow rate* ($FEF_{25-75\%}$). The $FEF_{25-75\%}$ is determined by locating the points on the volume–time curve corresponding to 25% and 75% of the FVC and then calculating the slope of a straight line

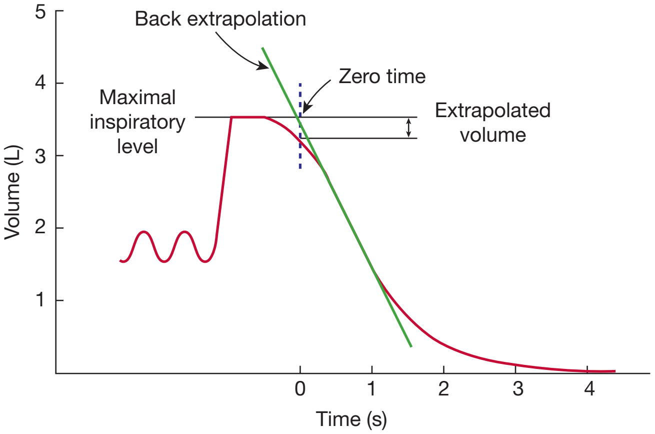

Figure 31-15 Technique of back extrapolation for determining the zero time in calculation of FEV_1. Zero time is determined as the point of intersection of a tangent drawn through the steepest portion of the spirogram and a line drawn horizontally through the maximal inspiratory level.

passing through those two points. The slope of this line represents the average airflow over the midportion of the FVC.

Although the *relaxed* or *slow vital capacity* (VC) may be normal or only modestly reduced in patients with obstructive disease of the airways, the volume–time relationship of the FVC maneuver is usually distinctly abnormal in such patients (Fig. 31-16A and B). Most obvious is a flattening of the slope of the curve at any given lung volume, reflecting the reduced airflow. In addition, the duration of the forced expiratory maneuver is prolonged. Normally, expiration is complete within 6 s; in obstructive airway disease, expiratory airflow may continue for 10 to 12 s. These changes in the expiratory airflow reduce the FEV_1 and FEV_3, the FEV_1/FVC%, the FEV_3/FVC%, and the $FEF_{25–75\%}$.

Restrictive lung disorders reduce the slow vital capacity. However, the *configuration* of the volume–time relationship may not be abnormal (Fig. 31-16C). Although the FEV_1 and FEV_3 are reduced because of the reduced vital capacity, the FEV_1/FVC% and FEV_3/FVC% remain normal or even exceed normal values. Often, because of the reduced vital capacity, the $FEF_{25–75\%}$ is also less than predicted.

Forced Inspiratory Vital Capacity

Measurement of the forced inspiratory vital capacity (FIVC) consists of two steps: (1) full expiration to RV, followed by (2) a rapid maximal inspiratory effort (Fig. 31-17). The rate of airflow over the middle half of the forced inspiratory vital capacity ($FIF_{25–75\%}$) is determined using a procedure similar to that described previously for the $FEF_{25–75\%}$.

TABLE 31-6 Values Obtained from Forced Expiratory Volume–Time Curves

FVC (BTPS) (L)	Forced vital capacity; the total volume expired
FEV_1 (BTPS) (L)	Volume of air expired in the first second
FEV_1/FVC%	Volume of air expired in the first second, expressed as percent of the FVC
FEV_3/FVC%	Volume of air expired in the first 3 s, expressed as percent of the FVC
$FEF_{25–75\%}$ (BTPS) (L/s)	Forced midexpiratory airflow

BTPS, body temperature and pressure, saturated with water vapor.

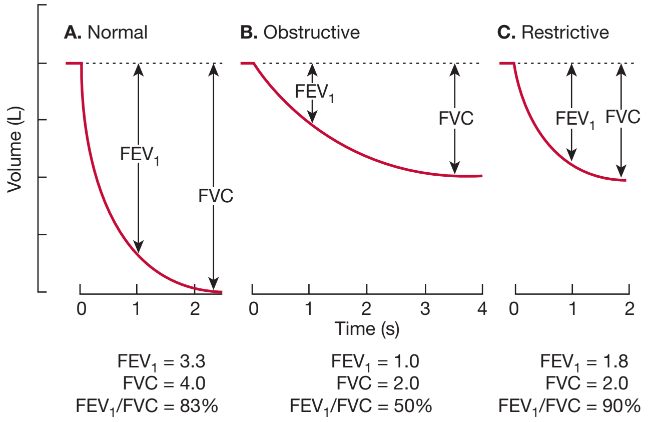

Figure 31-16 Representative spirograms from a normal subject (**A**), a patient with obstructive lung disease (**B**), and a patient with restrictive lung disease (**C**), obtained during a forced expiratory vital capacity maneuver. In the normal subject, expiration is completed within 3 s, and 83% of the volume is expired in the first second ($FEV_1/FVC\% = 83$). In the patient with obstructive disease, expiration is prolonged, and only half the volume is expired in the first second ($FEV_1/FVC\% = 50$). In the patient with restrictive disease, although the magnitude of the reduction in exhaled volume is the same as in the obstructed patient, most of the volume is exhaled within the first second ($FEV_1/FVC\% = 90$).

In normal subjects, the $FIF_{25–75\%}$ is greater than the $FEF_{25–75\%}$. Since inspiratory flow is more dependent on effort than is expiratory flow, a fall in the $FIF_{25–75\%}$ is usually a more sensitive indicator of respiratory muscle dysfunction or a suboptimal effort than is the $FEF_{25–75\%}$. When airway resistance is high, a disproportionate fall in $FIF_{25–75\%}$ relative to $FEF_{25–75\%}$ suggests an extrathoracic site of airway obstruction (see “Approach to Interpreting Commonly Performed Pulmonary Function Tests,” below).

Flow–Volume Relationships

In addition to analysis of the relationship between volume and time depicted on a spirogram, examination of the relationship between flow and volume provides useful information about lung function. A flow–volume curve, which shows the relationship between lung volume and maximal airflow as lung volume changes during a forced expiration, is shown in Fig. 31-18. The test comprises four phases of breathing into a spirometer: (1) tidal breathing for several breaths, (2) a maximal inspiratory effort to TLC, followed by (3) a maximal expiration to RV

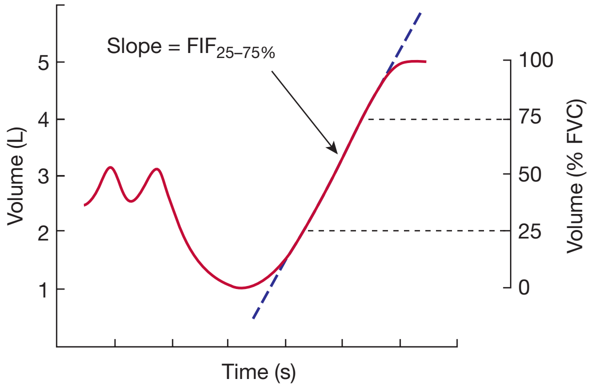

Figure 31-17 Forced inspiratory volume–time curve. The $FIF_{25–75\%}$ is the slope of a line between the points on the trace corresponding to 25% and 75% of the inspired volume.

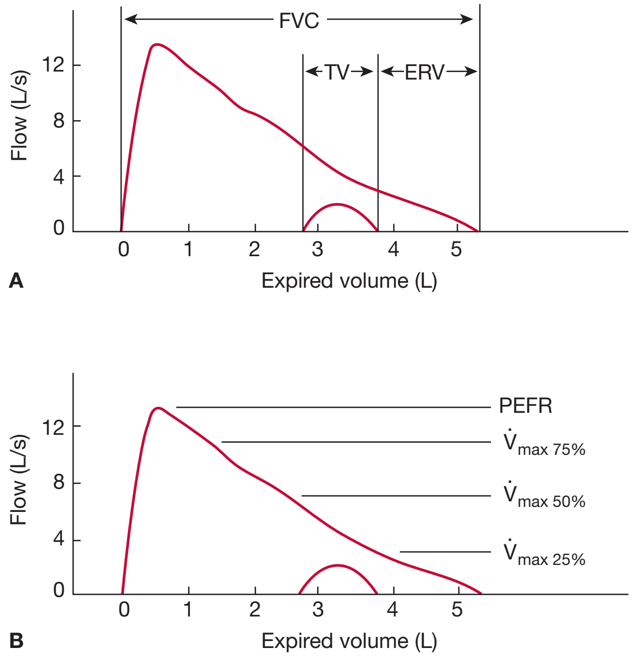

Figure 31-18 Flow–volume plots during forced expiration *(outer trace)* and quiet expiration *(inner trace)*. **A.** The subdivisions of lung volume. **B.** The common flow measurements. PEFR = peak expiratory flow rate; $\dot{V}_{max,75\%}$, $\dot{V}_{max,50\%}$, and $\dot{V}_{max,25\%}$ = flows at 75%, 50%, and 25% of the vital capacity, respectively.

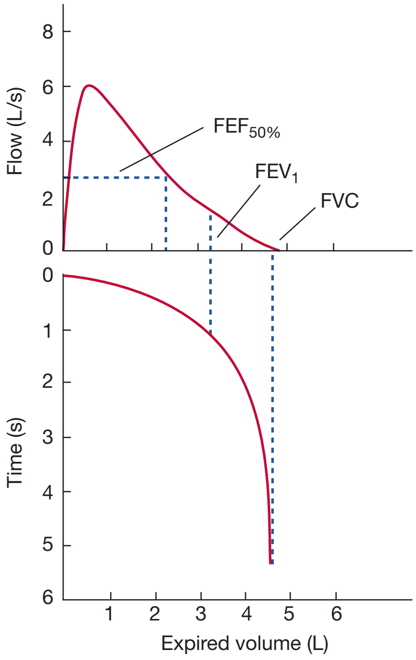

Figure 31-20 Flow–volume and volume–time curves depicting the same forced expiration aligned along a common volume axis (abscissa). Points corresponding to the FEV$_1$, FVC, and FEF$_{50\%}$ obtained from the volume–time plot are shown on the flow–volume curve.

done as forcefully and quickly as possible, and (4) another maximal inspiratory effort to TLC. Volume is displayed on the horizontal axis and airflow on the vertical axis. Airflow is measured at the mouth using a pneumotachograph; volume is measured either by integrating the pneumotachographic record during expiration or as a change in TGV, determined by a pressure-corrected flow plethysmograph. The records obtained by the two techniques for determining volume differ because the body plethysmograph senses compression of intrathoracic gas during a forced expiration, whereas measurements of volume made at the mouth do not (Fig. 31-19). Differences between curves obtained with the two techniques for measuring volume are most marked in patients with airway obstruction in whom considerable gas compression occurs during a forced expiration.

For the sake of comparison, tracings of flow versus volume and volume versus time, recorded during the same FVC maneuver and aligned by using a common volume axis as the abscissa, are shown in Fig. 31-20. Selected measurements are more evident in one tracing or the other—for example, maximal expiratory flow in the flow–volume curve and volume expired in 1 s (FEV$_1$) in the volume–time curve.

Comparison of serial curves from a single person or curves from different subjects requires that the curves be aligned on the volume (horizontal) axis so that points of maximal inspiration or maximal expiration coincide. As may be seen in Fig. 31-21A, which illustrates typical curves from a normal subject and two patients, one with pulmonary fibrosis and the other with obstructive airway disease, the

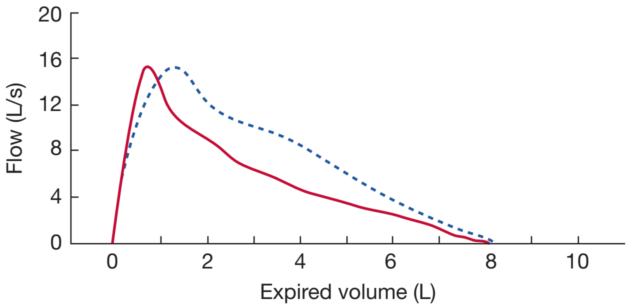

Figure 31-19 Comparison of the flow–expired-volume curve *(solid line)* with a simultaneously recorded flow–thoracic-gas-volume curve *(dashed line)*. The difference between the two curves results from the compression of gas in the lungs during a forced expiration.

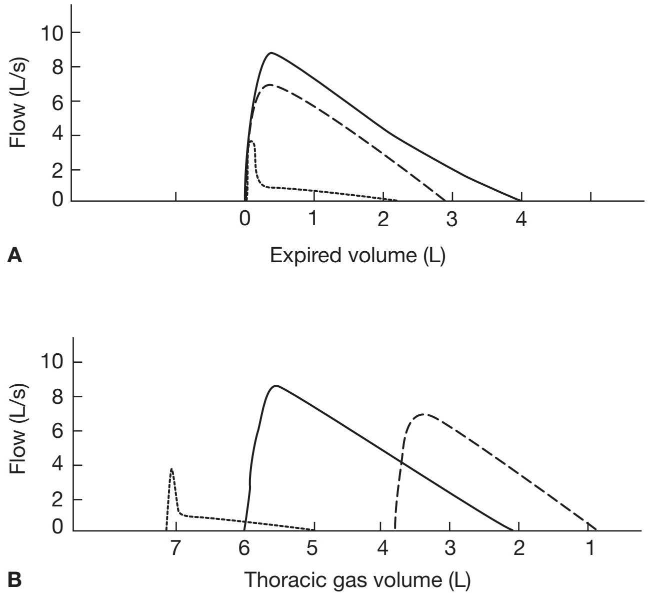

Figure 31-21 Airflow at different lung volumes. **A.** Flow–volume curves aligned at TLC. **B.** Flow–volume curves displayed relative to thoracic gas volume. Although the curves aligned at TLC (**A**) show striking differences in the pattern of airflow, they provide no insight into the relationship between lung volumes and airflow. See text for discussion.

information provided by this form of representation is limited—that is, the vital capacities and airflows from the patients are abnormally low. The limitation stems from the fact that the change in volume during expiration is shown relative to the *maximal inspiratory level* rather than to an *absolute volume* of gas in the lungs—that is, RV or TLC. When RV or TLC is known so that absolute volumes can be plotted on the horizontal axis (Fig. 31-21B), additional insight is gained into the flow–volume relationship depicted in Fig. 31-21A. The patient with obstructive disease of the airways manifests a reduction in expiratory airflow at elevated lung volumes, which should enhance airflow. In contrast, the reduced rate of airflow in the patient with pulmonary fibrosis is normal, or even supranormal, when the lung volume at which the airflow occurs is taken into account; that is, the reduced airflow is primarily a function of the reduced lung volume, rather than of airway obstruction.

Maximal Voluntary Ventilation

The previous considerations of dynamic lung function focus on a single timed maximal expiratory or inspiratory maneuver. In contrast, the MVV depends on the movement of air into and out of the lungs during continued maximal effort throughout a preset interval (Fig. 31-22). The MVV is a simple, informative test that provides an overall assessment of effort, coordination, and the elastic and flow-resistive properties of the respiratory system.[29,30]

In performing the test, the patient is urged to breathe as hard and as fast as possible. As a rule, the patient automatically adjusts frequency and tidal volume for optimal performance. However, extremes of frequency or tidal volume are to be avoided, since neither panting nor slow deep breathing leads to the highest possible values. The total volume that is expired during a 12-s interval, expressed in liters per minute (BTPS), is the MVV. In some patients the test cannot be done because of an inability to continue the necessary effort for 12 s.

A normal value for MVV indicates that the overall integrated performance of the respiratory system is intact, thereby excluding moderate to severe restrictive or obstructive disease. In addition, a normal value suggests that the elastic and flow-resistive properties of the respiratory system, respiratory muscle strength, coordination of respiratory performance, and motivation of the patient are all normal. Although this test is very useful in detecting overall disturbances in integrated performance and diffuse tracheobronchial and pulmonary parenchymal diseases, other tests are required to pinpoint specific disorders.

The difference between the MVV and the resting minute ventilation is the *breathing reserve*. At one time, a low breathing reserve was correlated with the breathlessness in lung diseases. However, this determination is now primarily of historic interest.

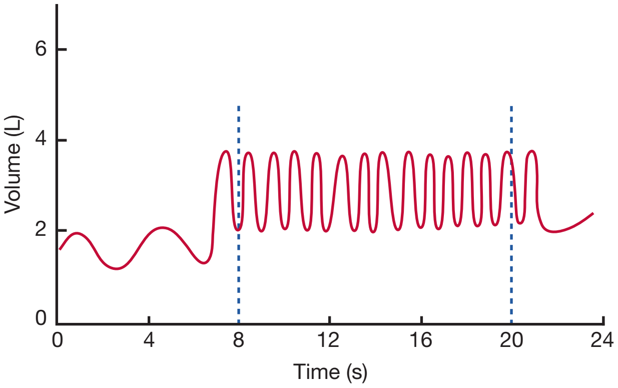

Figure 31-22 Maximal voluntary ventilation (MVV). After a period of relaxed breathing, the subject breathes rapidly and as forcefully as possible. The total volume of air inspired over 12 s and expressed in L/min is the MVV.

Respiratory Resistance

Total respiratory resistance (Rrs) is the resistance to airflow and chest expansion offered by the airways (Raw), chest wall (Rw), and lung tissue (Rti):

$$\text{Rrs} = \text{Raw} + \text{Rw} + \text{Rti}$$

The overall resistance of the respiratory system can be determined with a technique employing forced oscillation (see "Small-Airway Function," below). However, further methodologic refinements permitting determination of *pulmonary resistance*—the sum of airway and tissue resistances (Raw + Rti)—have not proved to be worthwhile clinically, particularly since measurement of transpulmonary pressure with an esophageal balloon is necessary. Other variations of the determination of resistance measurements also have been explored. However, the only clinically useful measurement of resistance is airway resistance, which is now routinely determined in pulmonary function laboratories.

Airway Resistance

Airway resistance (Raw) is defined as the ratio of the driving pressure (P) for flow to the actual rate of airflow ($\dot{V}$) along the airways—that is, the mouth, nasopharynx, larynx, and central and peripheral airways:

$$\text{Raw} = \frac{\Delta P}{\dot{V}}$$

where ΔP, the drop in pressure over the entire length of the airways, is determined as the difference between alveolar pressure (P_A) and pressure at the mouth (Pm) or airway opening (Pao).

Although airflow and pressure at the airway opening are easily measured, the difficulty in measuring alveolar pressure prevented the routine determination of airway resistance until DuBois and colleagues introduced the plethysmographic technique in 1956.[31]

With this technique, the patient, seated in the body plethysmograph, pants at a rate of about two breaths per second while airflow is measured using a pneumotachograph. During inspiration and expiration, gas in the alveoli is alternately rarefied and compressed, causing changes in pressure within the sealed plethysmograph. The relationship between plethysmograph pressure and airflow during the panting maneuver is displayed on the X and Y axes of an oscilloscope (Fig. 31-23).

While the panting continues, a shutter at the airway opening is closed so that airflow is transiently interrupted. Using the technique employed in the determination of FRC, changes in pressure in the plethysmograph (equivalent to changes in lung volume) and at the mouth are displayed on the X and Y axes, respectively, of the

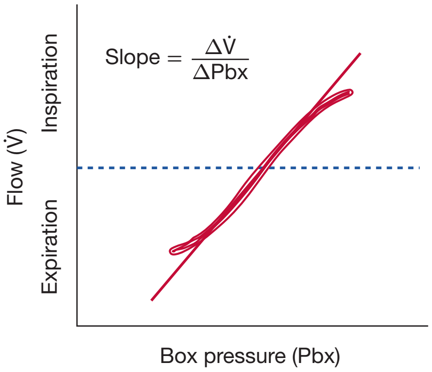

Figure 31-23 Plot of airflow ($\dot{V}$) versus body plethysmograph pressure (Pbx). The slope of this curve, in the range of 0 to 0.5 L/s of inspiratory flow, divided into the slope of the loop obtained when the shutter is closed (see Fig. 31-7) provides a measure of airway resistance (Raw).

oscilloscope (Fig. 31-6). However, since airflow is zero while the shutter is closed, the pressure at the mouth equals alveolar pressure (Pao = PA).

Panting while the shutter is open allows the determination of the relationship between airflow ($\dot{V}$) and plethysmograph pressure (Pbx)—that is, $\dot{V}$/Pbx. Similarly, panting against a closed shutter enables the determination of the relationship between alveolar pressure (PA) and plethysmograph pressure—that is, PA/Pbx. Airway resistance is calculated by dividing the slope of the loop obtained by plotting PA versus Pbx while the shutter is closed by the slope obtained by plotting $\dot{V}$ versus Pbx while the shutter is open:

$$\mathrm{Raw} = \frac{\mathrm{PA}/\mathrm{Pbx}}{\dot{V}/\mathrm{Pbx}} = \frac{\mathrm{PA}}{\dot{V}}$$

where

Raw = airway resistance, $cmH_2O/L/s$
PA = alveolar pressure, cmH_2O
$\dot{V}$ = airflow, L/s

Raw is measured during a panting maneuver for several reasons:[32] (1) The rapid respiratory frequency in panting circumvents the poor low-frequency response characteristics of many plethysmographs. (2) The small inspired and expired volumes minimize temperature fluctuations in the plethysmograph that would otherwise occur as tidal breaths of air at body temperature are exchanged with breaths of air at room temperature. (3) During panting, the glottis remains open, thereby minimizing its contribution to overall airway resistance. Use of plethysmographs linked to microprocessors that automatically correct for temperature-related volume differences has made possible the determination of airway resistance during quiet breathing instead of during panting.

Airway resistance varies inversely with lung volume; it is low at large lung volumes and increases curvilinearly as lung volume and, consequently, airway diameters are reduced (Fig. 31-24A).[33] In contrast, the inverse of airway resistance, airway *conductance,* is linearly related to lung volume (Fig. 31-24B). Interpretation of a given value for airway resistance or airway conductance requires that the lung volume at which the measurement is made be taken into account. *Specific conductance* (SGaw) is calculated by dividing airway conductance by the lung volume.

Defining the range of normal for Raw is difficult because of the lack of data obtained from populations sorted into smoking and nonsmoking groups and because of the inter- and intraindividual variations of Raw with lung volume. One classification scheme proposed for defining normal and abnormal Raw in adults in whom FRC exceeds 2 L is given in Table 31-7.

At times, an apparent discrepancy occurs between forced expiratory flow rates and values for airway resistance. For example, although the FEV_1 and $FEF_{25-75\%}$ may be abnormally low (suggesting some degree of airway obstruction), Raw may be within normal limits (arguing against appreciable airway obstruction). This apparent contradiction arises because Raw is determined during *inspiration,* when airways are enlarged because of surrounding negative pleural pressure, whereas FEV_1 and $FEF_{25-75\%}$ are determined during a forceful *expiration,* when airways are compressed by high positive pleural pressures. Therefore, the discrepancy is simply a manifestation of dynamic airway obstruction in which the narrowing is confined to expiration.

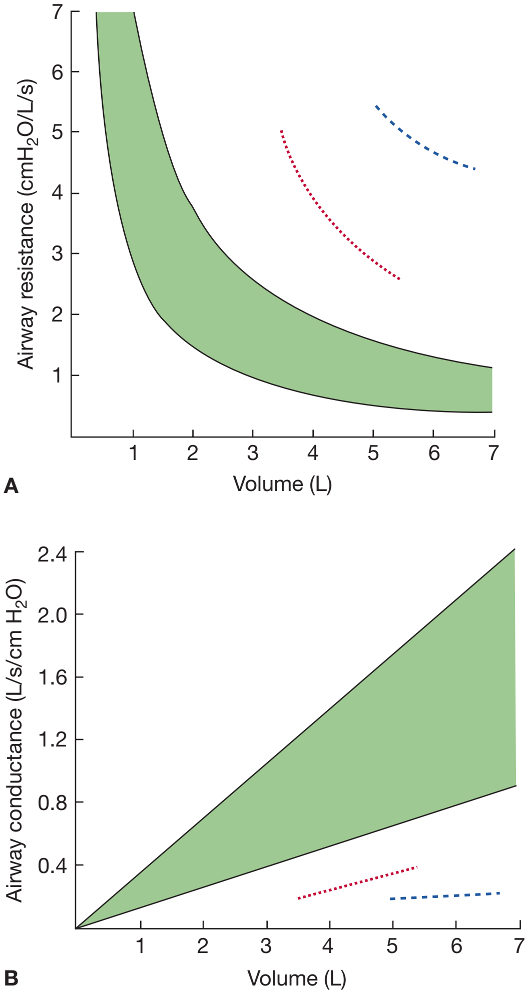

Figure 31-24 The relationship between airway resistance (**A**) and airway conductance (**B**). The shaded area represents the predicted normal range. Values are shown for an asthmatic patient before *(dashed line)* and after *(dotted line)* bronchodilator therapy. Airway resistance increases as lung volume decreases. Conversely, airway conductance, the inverse of resistance, decreases as lung volume decreases.

■ Measurement of Exhaled Nitric Oxide

Over the last two decades, the important role of nitric oxide (NO) in a variety of biologic processes has been described.[34] The concept that NO is a marker of airway inflammation, and, hence, has a potential role as a measure of airway function in the setting of inflammatory airway diseases, has been investigated.[35,36] Studies have demonstrated that, at least in asthma, levels of exhaled NO are elevated during exacerbations (when other measures of airway inflammation show activity), even in the absence of symptoms or changes in spirometry.[37,38] Exhaled levels of NO may also be helpful in classifying the severity of asthma.[39] Levels of NO decrease with inhaled corticosteroid use and rise with corticosteroid tapering. Many advocate measurement of exhaled NO as part of routine chronic asthma management.[34,40]

Standards have been developed for measuring exhaled NO levels,[34] and equipment for measuring exhaled NO is becoming

TABLE 31-7 Categorization of Increased Airway Resistance (Raw)

Category	Raw ($cmH_2O/L/s$)
Mild	2.8–4.5
Moderate	4.54–8.0
Severe	>8.0

Data from Wilson AF: Pulmonary Function Testing. Indications and Interpretations. Orlando, FL: Grune and Stratton; 1985.

common in outpatient settings in which patients with asthma are managed.

AIRWAY REACTIVITY

The dynamic tests of airway function described previously are designed to determine intrinsic properties of the airways in a subject breathing room air at rest. In many clinical situations, such as evaluation of chronic cough, assessment of airway hyperresponsiveness is desirable. This section reviews *bronchoprovocation testing* (BPT),[41–45] which assesses reactivity of the airways to selected pharmacologic or environmental agents.

Background

One test of bronchial reactivity that has been incorporated into routine pulmonary function testing is determination of the effect on airflow of administration of a nebulized bronchodilator agent. However, bronchoprovocation tests are designed to quantify the degree of bronchoconstriction following the application of a particular stimulus. A number of tests of bronchial reactivity are currently in clinical use (Table 31-8). Among the agents used for inhalation challenges are methacholine, histamine, carbacholine, and specific antigens chosen in accord with the patient's history. In addition to the inhalation challenge tests in which pharmacologic agents are used, tests of bronchial reactivity may be based on inhalation of cold or dry air, isocapnic hyperventilation, or exercise.

Indications for Bronchoprovocation Testing

The principal indication for BPT is a history suggestive of bronchospasm induced by an environmental or occupational agent, generally in the setting of normal pulmonary function tests (including determination of airflow before and after administration of an inhaled bronchodilator). For example, comparison of FEV_1 before and after administration of a pharmacologic agent such as methacholine or histamine can be useful in establishing the diagnosis of asthma. Also, inhalation of a suspected specific antigen may be useful in uncovering asthma when skin tests are equivocal, or in proving that asthma is occupation related. In some instances, exercise testing may disclose airway hyperreactivity in persons who are free of bronchoconstriction while at rest. Airway hyperresponsiveness to methacholine may presage an accelerated decline in pulmonary function.[46] However, the impact of therapy with agents like inhaled bronchodilators or corticosteroids in preventing progression is unclear.

TABLE 31-8 Tests of Bronchial Reactivity

Inhalational challenges
Pharmacologic agents
Methacholine
Histamine
Carbocholine
Specific antigens
Toluene diisocyanate
Bacillus subtilis
Pollen
Molds
House dust
Exercise-induced asthma
Cold-air challenge
Dry-air challenge
Isocapnic hyperventilation

Methods of Bronchoprovocation Testing

Several methods of BPT are in general clinical use. These include methacholine challenge, exercise challenge, and antigen challenge, each of which is described briefly in subsequent sections.

Inhalation Challenge: Methacholine

Inhalation challenge using methacholine has become popular because of standardization of the technique, ease and safety of performing the test, and high sensitivity of the test in detecting asthma.[47,48] Methacholine is a synthetic cholinergic agent that evokes airway smooth muscle constriction. Because baseline pulmonary function and breathing pattern influence the site of deposition of the inhaled methacholine particles and, thereby, the response, a standard method for aerosolizing the agent is used to ensure reproducible results.[49]

One method in common use is that of intermittent aerosol generation. Standardization entails the delivery of a 0.6-s pulse of airflow at 20 lb/in.^{2} to a nebulizer, which, in turn, discharges particles that range from 0.3 to 4 μm in diameter into the airways. Methacholine for delivery by aerosol is prepared in concentrations ranging from 0.1 to 25 mg/mL using bicarbonate-buffered isotonic saline (containing 0.4% phenol) as the diluent. The cumulative dose delivered is expressed in inhalation units. One inhalation unit is equivalent to the single inhalation of a solution containing 1 mg of methacholine per milliliter (Table 31-9).

At the outset, the patient is challenged with five inhalations containing only aerosolized diluent. The necessity of the diluent step has been recently questioned. In addition to adding time and expense, it may force a greater absolute drop in FEV_1 needed to prove bronchial hyperreactivity. A fall in FEV_1 below 90% of the baseline value (i.e., the pre-challenge control FEV_1) establishes that the airways are hyperreactive, and therefore, the test is terminated. However, if the FEV_1 does not fall below 90% of the control value, increasing concentrations of methacholine are given in stepwise increments of five-breath inhalations. The breaths are taken slowly from FRC to TLC. Then, 1 to 1.5 min after each dose, an FVC maneuver is performed. The interval between each increase in concentration is kept to a minimum because the response is judged in terms of the *cumulative* dose. However, the deep inspiration that immediately precedes the expiratory portion of the FVC maneuver may decrease bronchomotor tone in airways narrowed by methacholine. This effect lasts up to 6 min, thus limiting the shortest acceptable interval between dosage steps.[50] If the postchallenge FEV_1 falls below 80% of the control FEV_1, or if the patient experiences cough or chest tightness at any step, the

TABLE 31-9 Concentrations and Cumulative Doses of Methacholine Employed in the Methacholine Challenge Test

Methacholine Concentration (mg/mL)	Cumulative Dose (Inhalation Units)[a]
0.1	0.5
0.5	3
1.0	8
2.0	18
5.0	43
10.0	93
25.0	218

[a] *After five inhalations of a nebulized solution containing methacholine in a concentration of 1 mg/mL.*

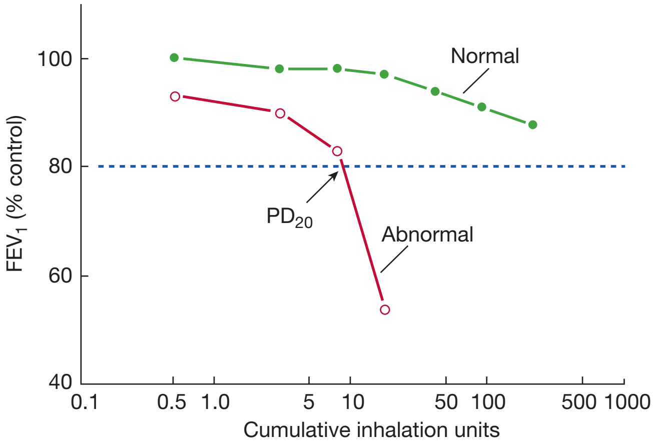

Figure 31-25 Plot of FEV$_1$,% control versus cumulative dose of methacholine administered by inhalation (logarithmic scale), to a normal subject and a subject with hyperreactive airways. The PD_{20} is the cumulative dose, which results in a 20% drop in the FEV$_1$ from the baseline measurement (after inhalation of diluent alone). In the subject with normal airway reactivity, the maximal cumulative dose of methacholine administered fails to elicit a 20% drop in FEV$_1$.

test is stopped. The magnitude of the bronchoconstrictor response to inhalational challenge is related to the control FEV$_1$. A lower baseline FEV$_1$ (even in the normal range) correlates with increased bronchial reactivity.[51–54] Additional measurements of dynamic airway function (e.g., specific conductance) may provide supplemental data but also prolong the study. Another dosing option in use is the 2-min tidal breathing protocol. This protocol typically yields results similar to the one described previously.

The results are plotted on four-cycle semi-log graph paper: the number of cumulative inhalation units, expressed logarithmically, against the FEV$_1$, as percent of control (Fig. 31-25). A curve is constructed through the points; the dose corresponding to the point at which the FEV$_1$ is 80% of the control FEV$_1$ is designated as the *provocation dose,* or PD_{20} FEV$_1$.

Exercise Challenge

Persons without a history of asthma who develop cough, wheezing, or dyspnea after exercise may have exercise-induced bronchospasm (EIB). In these individuals, an exercise test may prove useful in establishing the diagnosis. Such exercise testing in asthmatics can be useful to assess the degree of impairment during exercise, or the impact of therapies.

Several factors that may influence the outcome of the test should be kept in mind. The temperature and humidity of the laboratory should be tightly controlled. Some centers use dry air inhalation during exercise. In addition, the duration of the test needs to be monitored. The goal of testing for EIB is to produce at least 4 min of exercise at the target heart rate and ventilation. Exercise should not continue for more than 6 to 8 min, in order to avoid "run-through" of the bronchospasm—that is, reversal at the end of the test.

The type of exercise also influences the outcome. As a rule, the more intense the exercise, the more likely is bronchoconstriction to occur. Free-range running provides the most potent stimulus for bronchoconstriction, followed by treadmill running, bicycle ergometry, swimming, and walking. An asthmatic may swim comfortably at a level of exercise that is incapacitating on the treadmill. The motor-driven treadmill or electromagnetically braked cycle ergometer are the preferred modes of exercise for formal testing.

The FEV$_1$ is the most useful measurement made during testing for EIB. Measurements are made just before and immediately after the exercise and at 5-min intervals for the following 30 min. A decrease in FEV$_1$ of 10% or more below the pre-exercise value constitutes a positive test. Some have suggested that a decrement of 15% is of greater diagnostic value. False-positive responses can occur in patients with vocal cord dysfunction or abnormal posterior arytenoid motion.

Inhalation Challenge: Antigen

Compared with the relatively safe methacholine challenge test, BPT using a specific antigen is unpredictable and potentially hazardous. Since establishing the minimum dose required to induce bronchoconstriction is difficult, too much of the antigen may be given. A late response, far more severe than the initial one, often develops about 6 h after the challenge. Despite these reservations about antigen challenge, testing is warranted under certain circumstances: to uncover a particular agent in the environment that causes bronchoconstriction, to establish the diagnosis of occupational asthma, to prove that bronchoconstriction is caused by a particular antigen after routine skin tests have failed to support the clinical suspicion, and to convince a skeptical patient about the cause of his or her asthma. Recommendations for preparing concentrations of antigens and the technique of antigen challenge testing are specific to the antigen in question and may be found in the literature. These tests should be performed only in laboratories that have considerable experience in BPT.

■ Precautions and Contraindications

Although the overall risk of serious complications is low, bronchoprovocation tests may be unnecessary, invalid, or even dangerous in some circumstances (Table 31-10). For example, the patient who manifests appreciable airway obstruction by conventional testing may develop life-threatening airway narrowing during a bronchoprovocation test. In such a patient, a simple bronchodilator study would be more appropriate and informative. If bronchodilators fail to reverse the increase in airway resistance, and if it is important to prove that bronchial hyperreactivity does exist, BPT is sometimes done, with extreme caution, on another day, as antigen dosages are titrated carefully and details of the procedure monitored closely.

Absolute contraindications include severe airways obstruction (FEV$_1$ <50% predicted), myocardial infarction or stroke in the preceding 3 months, uncontrolled hypertension, or known aortic aneurysm. Moderate airflow limitation, pregnancy, lactation, and concurrent use of cholinesterase inhibitor medication represent relative contraindications.

A recent viral upper respiratory tract infection can cause airway hyperreactivity for up to 6 weeks in normal subjects. Similarly, influenza vaccination increases responsiveness to inhalation challenges in asthmatics for a few days to a week. In these conditions, BPT should not be undertaken until the sensitization effects of the infection or vaccination have worn off. Also, bronchodilators,

TABLE 31-10 Bronchoprovocation Testing: Precautions and Contraindications

- Baseline FEV$_1$/FVC% <60 (relative) or <50 (absolute)
- Recent upper respiratory tract infection
- Recent influenza vaccination
- Recent administration of bronchodilator
- Ingestion of caffeine within 6 h before testing
- Cold-air breathing, hyperventilation, exercise within 6 h before testing
- Recent acute myocardial infarction or cerebrovascular accident, uncontrolled hypertension, or known aortic aneurysm

including caffeine, should be withheld for at least 6 h before a bronchoprovocation test, if possible, in order to prevent blunting of the bronchoconstrictor response. Finally, cold air, hyperventilation, and exercise should be avoided for at least 6 h before testing in order to prevent the induction of a refractory period or late response that would overlap the test results.

SMALL-AIRWAY FUNCTION

Up to this point, discussion of tests of dynamic lung function has addressed the tracheobronchial tree as a unit. However, in a variety of common clinical settings, including asthma, COPD, cigarette smoking, lung transplantation complicated by bronchiolitis obliterans syndrome, ARDS, and cystic fibrosis,[55,60–63] structural (and functional) abnormalities of the airways may be centered primarily in the small, peripheral airways—that is, those 2 mm or smaller in diameter. Because of their small contribution to airway resistance, estimated to be about 10% to 38% (at a lung volume equivalent to 50% of VC), the small airways can undergo considerable damage before the usual tests of either static or dynamic lung function become abnormal.[64,65] Consequently, efforts have been made to utilize tests aimed at early detection of small-airway disease in the hope of early intervention to limit progression of the disease.[66]

Once obstructive disease of the peripheral airways arises, the small airways' contribution to overall resistance increases, and abnormalities in their function may be detected using specialized tests (see below), or, in some cases, analysis of selected aspects of the expiratory VC maneuver. In particular, abnormal values for $FEF_{25-75\%}$, in conjunction with normal values for FVC and FEV_1, are often useful in identifying small-airway disease. The basis for this approach is that $FEF_{25-75\%}$ measures airflow during the effort independent part of the FVC, when the small airways contribute substantially to the limitation of airflow.

A number of specialized tests of small airways' function have been developed over the last several decades, and some have found resurgent use in evaluating selected patient populations.[55] Several, along with their underlying physiologic basis, are described in subsequent sections.

Forced Oscillation Technique and Impulse Oscillometry

The forced oscillation technique (FOT) and a variation of FOT, impulse oscillometry, are based on assessment of airway impedance and a component of airway impedance, airway resistance.[56–59]

Using a loudspeaker applied to the airway opening and measuring pressure and flow over a range of oscillation frequencies, airway resistance can be measured and compartmentalized into segments reflecting resistance in medium-to-large and small airways. In normals, over an oscillatory range of 5 to 25 Hz, respiratory resistance and its major component, airways resistance, are frequency independent. With development of airways obstruction, respiratory resistance becomes frequency-dependent. Furthermore, as small airways narrow or close, a component of impedance distinct from resistance—reactance (a concept which refers to the "out-of-phase" relationship between pressure and flow during oscillation and which is ascribed to energy storage, as determined by the elastic properties of the respiratory system)—is significantly affected, particularly when measured during the expiratory phase of respiration.[55,62,63,67]

Dynamic Compliance

Dynamic compliance, defined as the change in lung volume during airflow produced by a given change in transpulmonary pressure, is normally independent of breathing frequency. However, under conditions of nonuniformity of ventilation throughout the lung, increases in breathing frequency are associated with a fall in dynamic compliance. This frequency dependence of compliance was first noted in a patient with emphysema.[68,69]

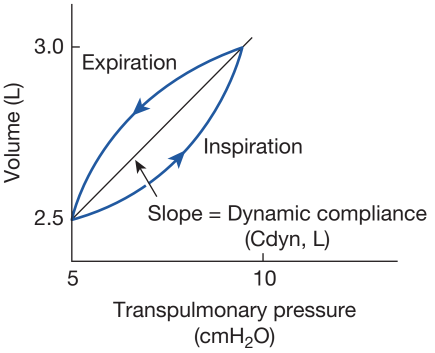

Figure 31-26 Measurement of dynamic lung compliance (Cdyn,L). During the inspiratory and expiratory phases of the respiratory cycle, a loop relating volume to transpulmonary pressure is generated. The slope of a line drawn through the points of zero airflow (at end inspiration and end expiration) is the dynamic compliance. Determination of Cdyn,L can be done at a variety of respiratory frequencies to assess the frequency dependence of compliance (Fig. 31-27).

During the test, the patient, with an esophageal balloon in place, first inspires maximally to TLC and then expires to the resting end-expiratory position (FRC); the patient then breathes at a normal tidal volume and respiratory rate (15 breaths per minute). In order to enable the patient to monitor these parameters, tidal volume and the resting end-expiratory level are displayed on an oscilloscope within sight of the patient. At the same time, changes in tidal volume and transpulmonary pressure are displayed on another oscilloscope (Fig. 31-26). The slope of the line connecting the end-inspiratory and end-expiratory points on the pressure–volume loop—that is, the points of zero airflow—is the dynamic compliance. This procedure is repeated with breathing frequencies of 30 and 60 breaths per minute. Values for dynamic compliance (Cdyn,L) at the various frequencies are expressed as a ratio of the dynamic compliance to the static inspiratory compliance (Cst,L) or as a percentage of Cst,L (Fig. 31-27) for the same range of tidal volumes.

In normal subjects, Cdyn,L/Cst,L remains above 0.8, even at frequencies greater than 60 breaths per minute. However, in the

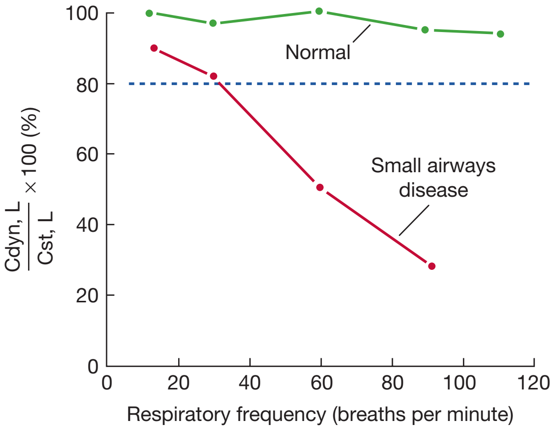

Figure 31-27 Determination of frequency dependence of dynamic compliance. Dynamic compliance is determined as shown in Fig. 36-26 and is expressed as a percentage of static lung compliance (Cdyn, L/Cst, L × 100,%) at a variety of respiratory frequencies. Normally, Cdyn,L is ≥80% of Cst,L and is independent of respiratory frequency. In patients with obstructive airway disease, including those with disease limited to the small airways, Cdyn,L falls relative to Cst,L as respiratory frequency increases.

presence of obstructive disease of the small airways, Cdyn,L/Cst,L falls progressively to values below 0.8 as breathing frequency increases. It is worth emphasizing that interpretation of frequency dependence of compliance with regard to small-airway disease is valid only if the static compliance and overall airway resistance are normal. Abnormalities in these other measurements indicate disease that is not likely to be confined to the small airways and for which frequency dependence of dynamic compliance is another manifestation. The physiologic basis for the fall in Cdyn,L/Cst,L as respiratory frequency increases is the presence of unequal time constants throughout the lung (see above).

■ Single-Breath Nitrogen Washout, Multiple Breath Nitrogen Washout, and Closing Volume

In 1949, Fowler described the single-breath nitrogen washout test for assessing the uniformity of ventilation throughout the lungs. In performing this test, the patient first expires maximally to RV before filling his or her lungs by taking a maximal breath of 100% O_2. During the subsequent expiration, the concentration of nitrogen at the mouth is continuously recorded and plotted against the volume of expired gas. Originally, interest focused on the initial part of the tracing that depicts the changing concentration in expired nitrogen as the first 750 to 1200 mL of gas is exhaled. Over this range, the change in nitrogen concentration in persons with normal lungs is less than 2.5%. In contrast, when disease of the lungs or tracheobronchial tree results in abnormal intrapulmonary distribution of inspired gas, the change in nitrogen concentration exceeds 2.5%.

Almost 20 years later, Fowler's test was modified to include a bolus of xenon at the beginning of inspiration and to record the concentration of xenon during the following expiration.[70] Abrupt changes in the concentration of expired xenon as RV was approached suggested that important information about the small airways could be obtained from the terminal portion of the curve.

These observations with xenon rekindled interest in Fowler's original technique and also directed attention to the terminal portion of expiration. The procedure is depicted in Fig. 31-28. To perform the maneuver for this measurement, the seated patient takes two deep breaths of air and then expires to RV. At the end of this maximal expiration, a valve is opened so that the patient can take a full breath of 100% O_2 to TLC. The patient then expires slowly to RV while N_2 concentration and expired volume are recorded continuously.

Four distinct phases can be identified in the continuous record relating N_2 concentration to expired volume. Phase I, the initial expirate, contains virtually no N_2, since it derives from the O_2-containing dead space. Phase II represents a mixture of gases from the dead space and the alveoli. Phase III is due to a mixture of gases from alveoli located at the apices, midlung fields, and bases. Phase IV, characterized by an upward shift in N_2 concentration, is caused by closure of alveoli in the dependent parts of the lungs at low lung volumes. This final expirate derives from alveoli in the middle and upper regions of the lungs, where N_2 concentrations are higher than at the bases.

The explanation for these phases resides in the intrapulmonary distribution of gases during the respiratory maneuvers used in performing the test. In the normal upright person, a gradient of pleural pressures exists from apex to base, so that pleural pressure is more negative at the apices than at the bases. Because the alveoli at the bases operate on a lower portion of their pressure–volume curve (Fig. 31-11), they expand more than do apical alveoli per unit change in pleural pressure. However, the less negative pleural pressures and decrease in elastic recoil pressure at the bases also cause small airways to close during expiration as lung volume approaches RV. Thus, the pleural pressure gradient from top to bottom of the chest causes nonuniform distribution of gas within the normal upright lungs.

In the single-breath nitrogen washout test, a breath of 100% O_2 is taken, starting from RV. At RV, small basal airways are closed. Therefore, at the start of the O_2 breath, the N_2-containing air remaining in the dead space is preferentially drawn into the middle and apical lung zones as 100% O_2 gradually replaces air in the dead space. As the inspiration continues, the small airways at the bases open. Since their compliances are greater than those in the middle or at the top of the upright lungs, the inspired O_2 is then preferentially distributed to the bases.

During the expiration from TLC, the four phases then represent, as indicated above, the sequential emptying of dead-space gas and a mixture of dead-space and alveolar gas, followed by mixtures of alveolar gases from different parts of the lungs, as determined by the preceding intrapulmonary distribution of inspired O_2.[71]

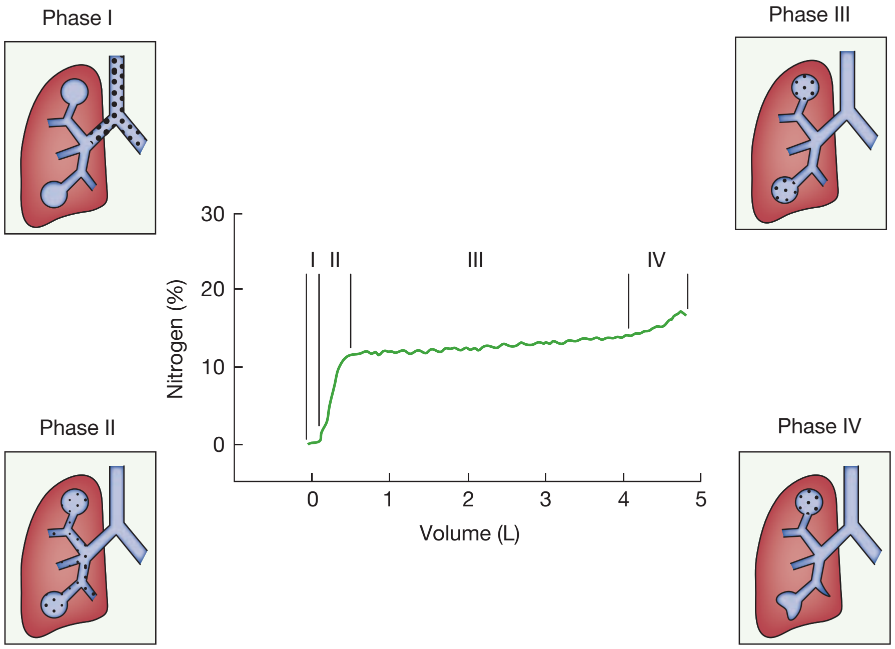

Figure 31-28 Contributions of different lung regions to the nitrogen concentration–volume curve obtained during the single-breath nitrogen washout test. See text for discussion.

The volume from the onset of phase IV to the completion of the full expiratory maneuver is termed the *closing volume* (CV). In healthy young adults, the normal closing volume averages about 10% of the VC. Narrowing or obstruction of small peripheral airways causes closing volume to enlarge. The closing volume also increases progressively as people grow older, so that by the age of 50, the closing volume sometimes reaches 25% of the VC. Cigarette smokers consistently experience an increase in closing volume. In both aging normal persons and cigarette smokers at any age, a decrease in pulmonary elasticity seems to be responsible for the increase in closing volume.

■ Helium–Oxygen Flow–Volume Curves

In 1963, the effects of changes in gas density and viscosity on maximal expiratory

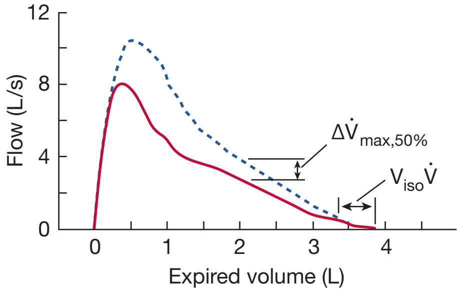

Figure 31-29 Maximal expiratory flow–volume curves generated in breathing room air *(solid line)* and breathing a helium–oxygen mixture *(dashed line)*. The airflows achieved with the less dense helium mixture are higher than those with air at all but the lowest lung volumes. The point of first intersection of these two curves demarcates the volume of isoflow ($V_{iso}\dot{V}$). The difference between the flows achieved when 50% of the vital capacity has been expired is the $\Delta\dot{V}_{max,50\%}$. The use of these measurements as indicators of small-airway disease is described in the text.

flow throughout the vital capacity range were described.[72] Almost 10 years later, gas-density-related and viscosity-related concepts were applied to determine the site of airway obstruction in asthma. These principles were then applied for the specific purpose of detecting obstruction of small airways when other tests of pulmonary function were within normal limits.[73] While application of helium–oxygen flow–volume curves in the assessment of small airways function is physiologically elegant, the test is rarely performed in clinical practice.

The use of a helium–oxygen mixture to detect small-airway disease requires comparison of two maximal expiratory flow–volume curves, one that is generated while the patient breathes air and the other while the patient breathes helium and oxygen (Fig. 31-29). At least three maximal expiratory flow curves are obtained with room air and three with helium–oxygen.[32]

In normal subjects, at lung volumes greater than 10% of the VC, the primary site of resistance to airflow is in the larger airways, where flow is turbulent and, therefore, density dependent. At these lung volumes, the flow attained with the helium–oxygen mixture will be higher than that attained with air. At lung volumes less than 10% of the VC, the primary site of resistance is in the smaller airways, where flow is laminar and, therefore, not density dependent. In this circumstance, the less dense helium mixture has no effect on flow (Fig. 31-29). In disease of the small airways, the primary site of resistance shifts at large volumes from the larger to the smaller airways. As a result, the flow-enhancing effect of the less dense gas disappears at volumes well above 10% of the VC.

In practice, two sets of maximal expiratory flow–volume curves are obtained, one while the subject is breathing air and the other after three VC breaths of the helium–oxygen mixture to replace at least 95% of the alveolar N_2. Comparisons are then made of the superimposed curves (Fig. 31-29). One comparison is made at 50% of the VC in order to compare maximal expiratory flows (i.e., the $\Delta\dot{V}_{max,50\%}$); the other is at the volume at which the flows become identical—that is, the *volume of isoflow* ($V_{iso}\dot{V}$).[74] The curves are superimposed at RV or TLC, as long as the vital capacities of each curve are within 2.5% to 5.0% of the largest VC recorded.[33]

The percentage change in expiratory flow while breathing helium–oxygen compared to air at 50% of the VC, $\Delta\dot{V}\mathrm{E}_{max,50\%}$, is calculated as

$$\Delta\dot{V}\mathrm{E}_{max,50\%} = \frac{\dot{V}\mathrm{E}_{max,50\%}\,(\text{helium–oxygen}) - \dot{V}\mathrm{E}_{max,50\%}\,(\text{air})}{\dot{V}\mathrm{E}_{max,50\%}\,(\text{air})} \times 100$$

where $\dot{V}\mathrm{E}_{max,50\%}$ (helium–oxygen) and $\dot{V}\mathrm{E}_{max,50\%}$ (air) are the expiratory flows at 50% of the VC during helium–oxygen and air breathing, respectively. As noted previously, the volume of isoflow is normally less than 10% of the VC; when it is increased, it indicates small-airway obstruction. The $\dot{V}\Delta\mathrm{E}_{max,50\%}$ is also specific for small-airway disease, and unlike the closing volume, it is considered to be unaffected by changes in the elastic properties of the lung. Questions remain, however, about the validity and sensitivity of tests of density dependence of flow in assessing small-airway disease. Although they are conceptually attractive, the practical value of helium–oxygen flow–volume curves in detecting small-airway disease is debatable.

GAS EXCHANGE FUNCTIONS

Traditional measurements of the gas exchange functions of the lung include oxygen uptake ($\dot{V}_{O_2}$), carbon dioxide elimination ($\dot{V}_{CO_2}$), respiratory dead space (VD), alveolar gas composition ($P\mathrm{A}_{O_2}$ and $P\mathrm{A}_{CO_2}$), diffusing capacity for carbon monoxide ($D\mathrm{L}_{CO}$), and arterial blood gas tensions (Pa_{O_2} and Pa_{CO_2}). These determinations require a steady state of the ventilation and circulation and constant body stores of O_2 and CO_2. A steady state with respect to O_2 implies that O_2 uptake measured at the mouth equals the rate of O_2 transport across the alveolar membrane, and that, in turn, both rates are equal to O_2 consumption by the tissues. The same type of definition applies to CO_2 exchange in the tissues, in the alveolar capillaries, and at the mouth.

Ventilation, Oxygen Uptake, and Carbon Dioxide Elimination

The total volume of air breathed per minute ($\dot{V}\mathrm{E}$) is the *minute ventilation*. It is equal to the product of the tidal volume (VT) and the breathing frequency (f). As a rule, minute ventilation is determined by measuring the volume of expired gas relative to time. When the measurement is performed manually, the necessary equipment includes gas-collecting bags, low-resistance directional valves, a stopwatch, and a device for measuring gas volume. In practice, the patient, with nose clip in place, breathes through a mouthpiece for at least 3 to 5 min while expired gas is vented to the atmosphere. This preliminary period is intended to put the patient at ease and to achieve a steady state of respiration and circulation. When a steady heart rate and breathing pattern are achieved, a valve is turned without the patient's knowledge, and expired gas is collected for 3 min.

The minute ventilation is determined by dividing the total volume of expired gas collected in the spirometer by the time of collection (3 min). The average tidal volume is obtained by dividing $\dot{V}\mathrm{E}$ by the number of breaths per minute. Values for minute ventilation and tidal volume are expressed in terms of body conditions (BTPS). In the resting adult, the minute ventilation is typically 6 to 8 L/min; the corresponding tidal volume is 0.4 to 0.6 L.

The quantity of CO_2 in inspired air is negligible. Consequently, the amount of CO_2 produced per minute ($\dot{V}_{CO_2}$) can be calculated as the product of the expired volume of ventilation ($\dot{V}\mathrm{E}$) and the concentration of CO_2 in the expired air ($F\mathrm{E}_{CO_2}$):

$$\dot{V}_{CO_2} = \dot{V}\mathrm{E} \times F\mathrm{E}_{CO_2}$$

Oxygen uptake ($\dot{V}O_2$) is calculated as the difference between the amounts of O_2 in inspired and expired air:

$$\dot{V}O_2 = (\dot{V}\mathrm{I} \times F\mathrm{I}_{O_2})\ (\dot{V}\mathrm{E} \times F\mathrm{E}_{O_2})$$

where

$\dot{V}\mathrm{I}$ = inspired volume of ventilation, L/min
$F\mathrm{I}_{O_2}$ = concentration of O_2 in the inspired air
$F\mathrm{E}_{O_2}$ = concentration of O_2 in the expired air

In the steady state, O_2 uptake by alveolar capillary blood exceeds CO_2 output from alveolar capillary blood. As a result, the expired volume of gas is less than the corresponding inspired volume. Since N_2 does not undergo exchange in the lungs, the difference between CO_2 output and O_2 uptake results in a higher concentration of N_2

in expired air than in inspired air. Based on the change in nitrogen concentration, the inspired volume of ventilation can be calculated from the expired volume of ventilation:

$$\dot{V}I = \dot{V}E\,\frac{FE_{N_2}}{FI_{N_2}}$$

where

FE_{N_2} = concentration of N_2 in expired air
FI_{N_2} = concentration of N_2 in inspired air

In the normal, resting subject who is tested after several hours of fasting, the ratio of CO_2 output to O_2 uptake, the *respiratory exchange ratio* (R), is about 0.8. The respiratory exchange ratio at any instant is calculated by simultaneously determining the P_{O_2} and P_{CO_2} in an alveolar gas sample. As indicated above, in the steady state, the R determined by sampling alveolar gas equals the R of alveolar capillary blood, which, in turn, equals the R of the tissues. The steady-state R, when alveolar gas, blood, and tissue are all in dynamic equilibrium, is the *respiratory quotient* (RQ). Hence, in the steady state, when the O_2 and CO_2 stores of the body are not changing, the RQ, reflecting cellular metabolism, can be determined by analyzing alveolar gas for O_2 and CO_2.

Unlike tidal volume and ventilation, which are expressed in terms of BTPS, $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ are given in terms of standard temperature and pressure, dry (STPD).

■ Dead Space

Not all of the air breathed participates in gas exchange. Part of each breath remains in the mouth, nose, pharynx, larynx, trachea, bronchi, and bronchioles. This volume, the *anatomic dead space,* is about equal, in milliliters, to the subject's ideal body weight, in pounds (e.g., about 150 mL in a typical adult male). Inspired air reaching alveoli that are not exposed to pulmonary capillary blood also does not participate in gas exchange. This volume plus the anatomic dead space equals the *physiologic dead space.* In a normal person, the anatomic and physiologic dead spaces are virtually identical and constitute about one-third of the tidal volume.

Determination of the physiologic dead space has proved to be of practical importance in a variety of clinical conditions. It is calculated by considering each breath (VT) to consist of dead space (VD) and an alveolar volume that participates in gas exchange (VA):

$$VT = VD + VA$$

Physiologic dead space can be calculated using a modification of the *Bohr equation*, which recognizes that all of the test gas expired derives from two sources: the physiologic dead space and the alveolar gas-exchanging volume. If we use CO_2 as the marker gas, the total amount of CO_2 eliminated per minute equals the sum of the CO_2 coming from the dead space per minute and from the alveolar compartment per minute:

$$\dot{V}E \times FE_{CO_2} = (\dot{V}D \times FI_{CO_2}) + (\dot{V}A \times FA_{CO_2})$$

where

$\dot{V}E$ = minute ventilation, L/min
FE_{CO_2} = fractional concentration of CO_2 in expired gas
$\dot{V}D$ = minute dead space ventilation, L/min
FI_{CO_2} = fractional concentration of CO_2 in inspired gas
$\dot{V}A$ = minute alveolar ventilation, L/min
FA_{CO_2} = fractional concentration of CO_2 in alveolar gas

Since, in a subject breathing room air, FI_{CO_2} is practically zero, the last equation is generally simplified as follows.

$$VE \times FE_{CO_2} = VA \times FA_{CO_2}$$

where VE and VA represent volumes of ventilation, rather than rates.

Recalling that VA = VT − VD and substituting partial pressures for the fractional concentration terms, the relationship becomes

$$VE \times PE_{CO_2} = (VT - VD)\,PA_{CO_2}$$

where PE_{CO_2} and PA_{CO_2} are the partial pressures of CO_2 in mixed expired gas and alveolar gas, respectively.

Assuming that arterial blood and alveolar gas are in equilibrium with respect to CO_2, when Pa_{CO_2} is substituted for PA_{CO_2} and the equation rearranged, it becomes

$$VD = VT\,\frac{Pa_{CO_2} - PE_{CO_2}}{Pa_{CO_2}}$$

Thus, if arterial blood is sampled during collection of expired gas, and if the partial pressures of CO_2 in expired gas and arterial blood are determined, the physiologic dead space can be calculated. In order for the physiologic dead space to be separated from the total dead space determined by the above equation, the dead space of the apparatus is subtracted from the value for total dead space.

■ Alveolar Gas Composition

In normal subjects, values for PO_2 and P_{CO_2} in an end-tidal sample approximate mean alveolar values. However, when imbalances exist in alveolar ventilation and blood flow because of lung disease, inhomogeneity in alveolar gas composition often invalidates the use of end-tidal gas tensions as a measure of mean alveolar gas composition.

In practice, mean alveolar P_{O_2} ($\bar{P}A_{O_2}$) and mean alveolar P_{CO_2} ($\bar{P}A_{CO_2}$) are often determined indirectly. Arterial P_{CO_2} is assumed to equal mean alveolar P_{CO_2} on the grounds of the narrow arteriovenous difference for P_{CO_2} across the lungs, the high solubility of CO_2, and the presumed role of pulmonary capillary blood as a tonometer. Mean alveolar P_{O_2} is calculated using the alveolar gas equation:

$$\bar{P}A_{O_2} = \bar{P}I_{O_2} - \bar{P}A_{CO_2}\left[FI_{O_2} + \frac{1 + FI_{O_2}}{R}\right]$$

The alveolar gas equation takes advantage of the fact that the total pressure of gases in the alveoli is equal to the sum of the partial pressures of the individual gases. This equation simply states that the mean alveolar P_{O_2} is the difference between inspired P_{O_2} and mean alveolar P_{CO_2}, allowing for a correction factor when the respiratory exchange ratio differs from 1.0.

■ Diffusing Capacity

The diffusing capacity of the lung for carbon monoxide (DL_{CO}) can be determined by steady-state, rebreathing, and single-breath methods. The most frequently used method is a modification of the single-breath method first described in 1915 and subsequently modified in 1957.[75] Although the single-breath test has been shown to exhibit a large interlaboratory variation, it has proved to be a valuable measure of lung function in a wide variety of disease states. In fact, with continuing refinement of the standards,[8,76,77] the variability, which may be as much as 12% or greater, is likely to decrease; however, the variability will probably not be reduced to the range for vital capacity measurements (about 4%).

The diffusing capacity is intended to provide an estimate of the rate at which test molecules—usually CO—move by diffusion from alveolar gas to pulmonary capillary blood. Factors that influence the measurement are the physicochemical properties of the test gas, the extent and thickness of the alveolar capillary barrier, the resistance to diffusion offered by the red blood cell membrane, and the reaction rates of the test gas and hemoglobin, and pulmonary capillary blood volume. As a rule, the diffusing capacity is interpreted as an index of the surface area engaged in alveolar capillary diffusion. Clinical entities that can reduce the diffusing capacity include parenchymal lung diseases, particularly interstitial lung disease, emphysema, pulmonary hypertension, and anemia. Polycythemia and alveolar hemorrhage syndromes, on the other hand, may increase the diffusing capacity.

Carbon monoxide has emerged as the most practical test gas because of its affinity for hemoglobin. The diffusing capacity for CO is defined as the amount of CO transferred per minute per mm Hg of driving pressure:

$$\mathrm{DL_{CO}} = \frac{\dot{\mathrm{V}}_{\mathrm{CO}}}{\bar{\mathrm{P}}\mathrm{A_{CO}} - \bar{\mathrm{P}}\mathrm{C_{CO}}}$$

where

$\mathrm{DL_{CO}}$ = the diffusing capacity of the lung for CO, mL/min/mm Hg (STPD)
$\dot{\mathrm{V}}_{\mathrm{CO}}$ = the amount of CO transferred, mL/min
$\bar{\mathrm{P}}\mathrm{A_{CO}}$ = the mean alveolar PCO, mm Hg
$\bar{\mathrm{P}}\mathrm{C_{CO}}$ = the mean capillary PCO, mm Hg

Since the blood Pco in nonsmokers is essentially zero, the term $\bar{\mathrm{P}}\mathrm{C_{CO}}$ is customarily neglected. In practice, $\mathrm{DL_{CO}}$ is determined by calculating $\dot{\mathrm{V}}_{\mathrm{CO}}$ as the difference between inspired and expired samples and estimating the mean alveolar Pco. Generally, one of the two techniques is used to determine $\mathrm{DL_{CO}}$: the single-breath or the steady-state technique.

The Single-Breath Method

The breathing maneuvers required for the single-breath method consist of tidal breathing for a few breaths, unforced expiration to RV, and then a single full, rapid inspiration of a gas mixture containing approximately 0.3% CO and an inert gas—traditionally, 10% helium (some newer systems use methane). The breath is held for 10 ± 2 s and then rapidly expired. An inspiratory time of less than 4 s, and a sample collection of no more than 3 s, are required. Longer expiratory times and sample collection time greater than 3 s should be noted in the test report. The initial portion of the expirate containing dead-space gas is discarded; the remainder is collected, and the concentrations of CO and helium are measured.[75] A variety of automated systems are commercially available for performing the single-breath diffusing capacity.[78] However, the essential components in all systems are a source of the special inspired gas mixture, a device for measuring the volume of gas inspired and expired, rapid response analyzers to measure the concentration of gases (see below), a timer, and appropriate valving and collection devices to trap the desired portion of the expirate.

The diffusing capacity of the lung for CO is calculated according to the following equation.

$$\mathrm{DL_{CO}} = \frac{\mathrm{VA} \times 60}{(\text{barometric pressure} - 47)} \times \text{time} \times \ln \frac{\mathrm{FA_{CO}},\ \text{initial}}{\mathrm{FA_{CO}},\ \text{final}}$$

where

VA = alveolar volume
$\mathrm{FA_{CO}}$, initial = alveolar concentration of CO at the start of breath hold
$\mathrm{FA_{CO}}$, final = alveolar concentration of CO at the end of breath hold

The concentration of CO in the alveoli at the start of the period of breath holding ($\mathrm{FA_{CO}}$, initial) is calculated from the inspired concentration of CO and, for helium-based systems, the inspired concentration of helium and the expired concentration of helium, according to the equation

$$\mathrm{FA_{CO,}}\ \text{initial} = \frac{\mathrm{FE_{He}}}{\mathrm{FI_{He}}} \times \mathrm{FI_{CO}}$$

where

$\mathrm{FE_{He}}$ = expired concentration of helium
$\mathrm{FI_{He}}$ = inspired concentration of helium
$\mathrm{FI_{CO}}$ = inspired concentration of CO

The concentration of CO in the alveoli at the end of the breath-holding period ($\mathrm{FA_{CO}}$, final) is equal to the concentration of CO in the expired gas. The alveolar volume (VA) is determined in one of two ways. Originally, VA was calculated as the sum of the RV, determined by the closed-circuit helium or body plethysmograph techniques described previously, and the volume of inspired gas, as recorded on the spirometer. Later, VA came to be calculated from the single-breath dilution of helium that occurs during the determination of $\mathrm{DL_{CO}}$. Finally, the time of breath holding is measured (in seconds) from the spirometer recording of the maneuver.

Although the single-breath method is relatively simple and has the advantage of requiring no blood samples, breath holding is clearly artificial, and the maneuver is difficult for dyspneic patients. Therefore, a steady-state method is sometimes used.

The Steady-State Method

In the steady-state method, a gas mixture containing 0.1% carbon monoxide is breathed until the rate of CO uptake from the lung is constant.[79] CO uptake ($\dot{\mathrm{V}}_{\mathrm{CO}}$) is determined from the difference between the amount of CO in the inspired and expired gas using an equation similar to that presented previously for calculation of O_2 consumption.

Comparison of Single-Breath and Steady-State Methods

Certain differences between the single-breath and steady-state techniques merit special mention.[32] The single-breath method is more popular because it is relatively easy to perform; it is well standardized, and it is less effected by nonuniformity of ventilation in comparison to the steady-state method. However, one drawback is that the patient is required to perform an inspiratory vital capacity maneuver of at least 88% of the VC and to hold his or her breath for 10 s. Another is that the test is extremely difficult to perform during exercise. The steady-state method is more attractive intrinsically than the single-breath method, since it requires no respiratory maneuvers and can be done during exercise. However, it does require an arterial blood sample (for determination of $\mathrm{P_{CO_2}}$), and it is technically more difficult to perform.

The steady-state method for determining diffusing capacity tends to give lower values for the resting subject than does the single-breath method. The discrepancy is generally attributed to the fact that the surface area for diffusion is smaller during the quiet tidal breathing employed in the steady-state method than during the full inspiration to TLC, as required in the single-breath method. Also, during quiet breathing, some areas of the lung receive considerably less ventilation than during a breath hold at TLC.

Factors Other than Diffusion That Influence Test Results

A low $\mathrm{DL_{CO}}$ need not indicate a diffusion defect. A number of additional respiratory and nonrespiratory factors may reduce or increase the $\mathrm{DL_{CO}}$. A reduction in the lung volume alone can reduce the $\mathrm{DL_{CO}}$. Therefore, some laboratories “normalize” the diffusing capacity for lung volume by dividing $\mathrm{DL_{CO}}$ by alveolar volume—a manipulation that assumes a linear relationship between $\mathrm{DL_{CO}}$ and VA, which is not the case.

Anemia artificially decreases the $\mathrm{DL_{CO}}$ as determined by either method, but the effect of low hemoglobin concentration can be adjusted by application of a correction factor.[80] Conversely, polycythemia and intrapulmonary hemorrhage tend to increase the value for $\mathrm{DL_{CO}}$. In fact, an unexpectedly high value for $\mathrm{DL_{CO}}$ may be a helpful clinical clue in detecting radiographically occult pulmonary hemorrhage.

Although the equation for $\mathrm{DL_{CO}}$ assumes that the CO back pressure in blood is negligible, the blood of a heavy smoker sometimes contains as much as 10% carboxyhemoglobin. Such levels of carboxyhemoglobin will be accompanied by appreciable concentrations of dissolved CO in the plasma. The resulting back pressure of CO will reduce the DL_{CO}. A correction equation may be applied to adjust the DL_{CO} for this effect.

Altitude also affects the DL_{CO}.[8] Pa_{O_2} falls with increasing altitude above sea level. The reduction in Pa_{O_2} allows CO to diffuse more rapidly into the blood. A specific adjustment should be made for inspired oxygen partial pressure.

Measurement of diffusing capacity is quite useful in the evaluation of patients with a number of pulmonary conditions. Decrement in DL_{CO} has been shown to predict exertional hypoxemia. In addition, DL_{CO} levels have been correlated with disease severity and prognosis in primary pulmonary hypertension, idiopathic pulmonary fibrosis, and alveolitis associated with systemic sclerosis.

■ Arterial Blood Gas Composition

The determination of arterial P_{O_2} and P_{CO_2} provides useful information about the overall efficiency of external gas exchange. Heavy reliance is placed upon them for this purpose in managing acute respiratory failure, particularly in intensive care units. Less dramatic, but important, is their use in a variety of other settings (e.g., exercise testing) and for assorted calculations (e.g., the alveolar–arterial O_2 gradient and respiratory dead space).

Technique for Sampling Arterial Blood

Arterial blood is sampled either through an indwelling arterial catheter or by percutaneous arterial puncture. Sampling through an indwelling catheter avoids the acute changes in ventilation that sometimes result from apprehension and pain associated with percutaneous puncture.

Three anatomic sites are generally used for obtaining arterial blood samples: the radial, brachial, and femoral arteries. For several reasons, the radial artery is the preferred sampling site. Because of its superficial location at the wrist, the radial artery is easy to palpate and easy to compress by direct pressure, facilitating hemostasis when sampling is complete. In addition, no large veins lie in its immediate vicinity. Furthermore, the ulnar artery usually provides an adequate collateral circulation to the hand in the rare instance of postsampling thrombosis of the radial artery.

Arterial blood samples are drawn anaerobically into plastic or glass syringes coated with heparin. Because room air at sea level has a P_{O_2} of approximately 150 mm Hg and a P_{CO_2} of approximately zero mm Hg, air bubbles in the syringe will artificially increase the arterial P_{O_2} and reduce the arterial P_{CO_2}. The sample either is immediately analyzed or is placed on ice in order to minimize the metabolism of blood cells, particularly the white cells. If the icing precaution is neglected and the analysis is delayed, the Pa_{CO_2} of the sample will increase and the Pa_{O_2} and pH will decrease; the rate of change depends on the temperature of the sample and the elapsed time before analysis (Table 31-11).[81]

Interpretations

Analysis of arterial blood gases as part of pulmonary function testing is based primarily on determination of Pa_{O_2}, Pa_{CO_2}, and pH. As a rule, these parameters are measured directly. Other values, including O_2 saturation, bicarbonate concentration, and base excess (or deficit), are usually calculated. This section deals with the interpretation of Pa_{O_2}, Pa_{CO_2}, and pH. Additional consideration of arterial blood gases, with particular reference to acid–base balance, is found in Chapter 17.

Arterial P_{O_2} (Pa_{O_2}) The physiologic determinants of normal Pa_{O_2} have been described elsewhere. For example, normal values for arterial P_{O_2} depend on altitude (Table 31-12). Therefore, normal values for arterial P_{O_2} in Denver (altitude of approximately 1500 m) are less than those at sea level by about 20 mm Hg.

TABLE 31-11 In vitro Changes in Arterial Blood Gas Values at 37°C

Measurement	Change Over 10 min
pH (units)	−0.01
P_{CO_2} (mm Hg)	+1.000
O_2 content (vol%)	−0.001

Data from Kelman GR, Nunn JF. Nomograms for correction of blood P_{O_2}, P_{CO_2}, pH, and base excess for time and temperature. J Appl Physiol. 1966;21(5):1484–1490.

Arterial P_{O_2} also decreases with age. A regression equation can be used to predict the decrease:[82]

$$Pa_{O_2} = 109 - 0.43 \text{ (age in years)}$$

The standard deviation of this relationship is ± 4.10 mm Hg.

A third physiologic influence is body position. Assumption of the supine position causes abdominal contents to displace the diaphragm cephalad, thereby closing small airways at the lung bases and creating ventilation-perfusion inhomogeneities that decrease Pa_{O_2}.

Many more pathologic conditions than physiologic states can lower Pa_{O_2}. In each instance, however, arterial hypoxemia may be attributed to one or more of the following generic mechanisms: alveolar hypoventilation, ventilation-perfusion mismatch, diffusion impairment, and venous admixture ("shunt"). Considerations of the individual disorders within these categories and the mechanisms leading to hypoxemia are found throughout this book.

Arterial P_{CO_2} (Pa_{CO_2}) and pH In a steady state, the level of Pa_{CO_2} reflects the level of alveolar ventilation. In the absence of a disorder in metabolic acid–base balance, an increase or decrease in Pa_{CO_2} beyond normal limits indicates a primary disorder in alveolar ventilation. A summary of these disorders and useful criteria for distinguishing among them, based on arterial blood gas composition, are given in Table 31-13.

Acute *respiratory alkalosis,* produced by alveolar hyperventilation, is characterized by hypocapnia (Pa_{CO_2} < 36 mm Hg) and an appropriately elevated pH (>7.44). In time (e.g., 24 h or more), renal compensation occurs, and the concentration of bicarbonate in serum decreases. If alveolar hyperventilation continues, a chronic respiratory alkalosis, partly or completely "compensated," ensues.

TABLE 31-12 Effect of Altitude on Mean Alveolar and Arterial O_2 Pressures

Altitude (Feet)	Barometric Pressure (mm Hg)	Ambient P_{O_2} (mm Hg)	Alveolar P_{CO_2} (mm Hg)
0	760	159	103
1000	733	154	98
2000	707	148	94
3000	681	143	90
4000	656	138	85
5000	632	133	81
6000	609	128	77
8000	565	118	69
10,000	523	110	61
12,000	484	101	54

Data from Wasserman K. Cardiovascular manifestations of respiratory insufficiency. Clin Notes Respir Dis. Fall; 1973;12(2):3–10.

TABLE 31-13 Classification of Primary Respiratory Disorders of Acid–Base Balance

Disorder	Definition
Acute respiratory alkalosis (acute alveolar hyperventilation)	Pa_{CO_2} below lower limit of normal (<36 mm Hg), with accompanying alkalemia (pH >7.44)
Chronic respiratory alkalosis (chronic alveolar hyperventilation)	Pa_{CO_2} below lower limit of normal, with pH normal (or near normal) due to renal compensation and lowered serum bicarbonate concentration (<19 mEq/L)
Acute respiratory acidosis (acute alveolar hypoventilation)	Pa_{CO_2} above upper limit of normal (>44 mm Hg), with accompanying acidemia (pH <7.36)
Chronic respiratory acidosis (chronic alveolar hypoventilation)	Pa_{CO_2} above upper limit of normal, with pH normal (or near normal) due to renal compensation and elevated serum bicarbonate concentration (>30 mEq/L)

A low Pa_{CO_2} is not necessarily indicative of a primary disturbance in alveolar ventilation. Instead, it may be a consequence of respiratory compensation (partial or complete) for metabolic acidosis; this possibility is signaled by the coexistence of hypocapnia and a low pH (<7.36). Since the kidney and respiratory system do not overcompensate for acid–base derangements, the coexistence of hypocapnia and acidemia suggest the presence of two primary disturbances.

Acute respiratory acidosis, caused by alveolar hypoventilation, is characterized by an abnormally high Pa_{CO_2} (>44 mm Hg) and a subnormal pH (<7.36). Again, in time (24 h or more), renal compensation for the primary respiratory disorder restores the serum bicarbonate concentration and blood pH toward normal. A high value for Pa_{CO_2} may also reflect respiratory compensation for a primary metabolic alkalosis ($[HCO_3^-] > 30$ mEq/L). In this circumstance, however, blood pH will be abnormally high (pH >7.44), rather than low. In general, the elevation in Pa_{CO_2} in compensation for metabolic alkalosis does not exceed about 55 mm Hg. A Pa_{CO_2} exceeding this value in the setting of a metabolic alkalosis suggests the likely coexistence of a primary respiratory acidosis.

This discussion has been limited primarily to alterations in arterial blood gas values in primary respiratory acidosis or alkalosis. Metabolic derangements often complicate the picture. These disorders are considered elsewhere (Chapter 17).

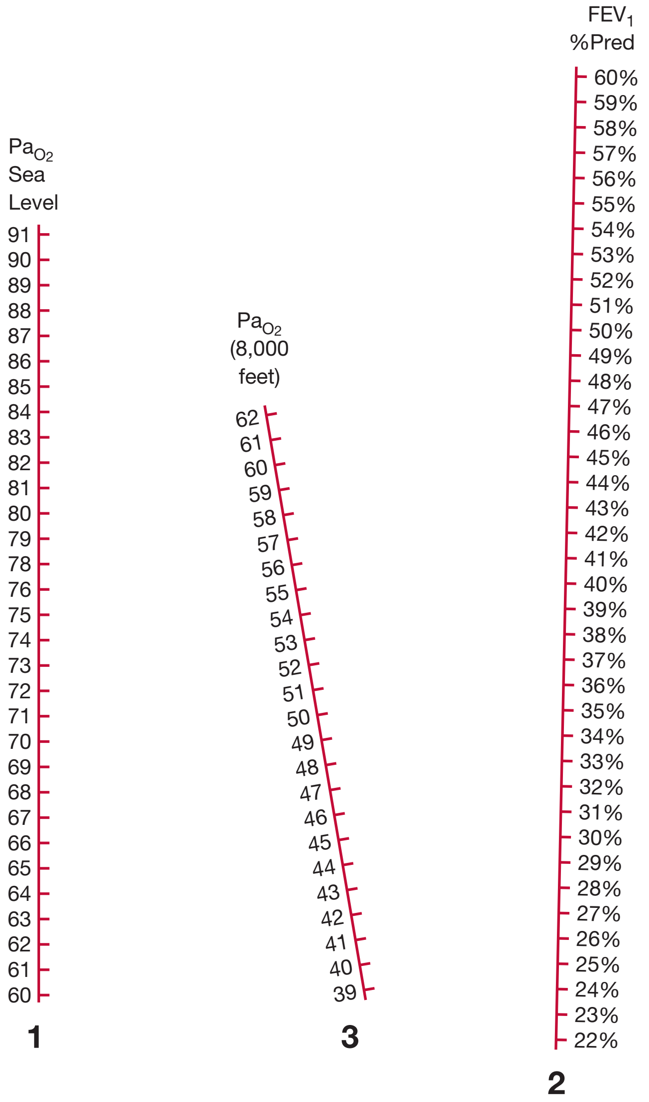

Figure 31-30 Nomogram for predicting in-flight oxygen tension. Using a straight edge, the patient's resting Pa_{O_2} at sea level (*column 1*) is aligned with his or her FEV_1 percent of predicted (*column 2*). The expected in-flight Pa_{O_2} (*column 3*) is estimated as the value where the line crosses the center scale. *(Data from Dillard TA, Berg BW, Rajagopal KR, et al. Hypoxemia during air travel in patients with chronic obstructive pulmonary disease. Ann Intern Med. 1989;111:362–367; and Knudson RJ, Slatin RC, Lebowitz MD, et al. The maximum expiratory flow-volume curve: Normal standards, variability, and effects of age. Am Rev Respir Dis. 1976;113:587–600.)*

■ Testing for Air Travel–Related Hypoxemia

Travel in commercial jet airliners typically results in exposure of passengers and crew to conditions equivalent to about 6000 to 8000 ft above sea level. For individuals with normal pulmonary gas exchange, the resulting Pa_{O_2} falls within a clinically acceptable range. However, for many patients with lung disease, the resulting Pa_{O_2} may well be problematic, even in those patients who do not require supplemental oxygen at sea level. Consequently, assessment of patients with chronic lung diseases, particularly COPD and interstitial lung diseases, has become part of the repertoire of tests offered by many pulmonary function laboratories.[83–87] One approach to estimating the resultant Pa_{O_2} during air travel is based upon use of regression equations (Fig. 31-30). Using the patient's resting Pa_{O_2} at sea level and his or her FEV_1 percent of predicted, the expected in-flight Pa_{O_2} can be estimated. Some experts advocate use of the nomogram for determining which patients ought to undergo hypoxia inhalation testing (HIT), while others advocate performance of HIT for all traveling patients at risk for in-flight hypoxemia.

HIT is based on the observation that exposure to hypoxic gas mixtures can reproducibly mimic the Pa_{O_2} arising under true hypobaric conditions. Exposure to 15.1% oxygen for 20 min reliably duplicates the resultant Pa_{O_2} at 8000 ft. During performance of the test, the patient, with nose clips in place, breathes from a reservoir though a mouthpiece. The electrocardiogram is monitored, and arterial blood gases are obtained at the conclusion of the test. Supplemental oxygen can then be titrated and prescribed according to the findings.

The British Thoracic Society (BTS) has published recommendations for use of supplemental oxygen during air travel, based on the patient's oxygen saturation at sea level and the presence or absence of risk factors.[84]

The BTS recommends no in-flight supplemental oxygen if the oxygen saturation at sea level is >95%; if the oxygen saturation is 92% to 95%, supplemental oxygen is recommended if additional risk factors are present, including hypercapnia, FEV_1 <50% predicted, lung cancer, interstitial lung disease with fibrosis, chest wall or respiratory muscle disorders, need for mechanical ventilation, cardiac or cerebrovascular disease, or travel within 6 weeks of hospital discharge following an acute exacerbation of chronic lung or heart disease. Supplemental oxygen is also recommended if oxygen saturation is <92% or if the patient uses supplemental oxygen at sea level, for whom an increase in oxygen flow during flight is advised.

The BTS also recommends supplemental oxygen for patients whose Pa_{O_2} on challenge testing (using an $F\text{I}_{O_2}$ of 15% for 20 min) is <50 mm Hg and, possibly, for those whose Pa_{O_2} is between 50 and 55 mm Hg; in the latter group, a walk test may be helpful.[84]

CONTROL OF BREATHING

The rate, depth, and pattern of breathing reflect a complex interplay of neurohumoral and chemical regulatory mechanisms that drive the respiratory apparatus. Tests used to evaluate the control of breathing, based on assessment of the ventilatory response to controlled hypercapnia or hypoxia, are uncommonly performed in the clinical setting. However, since these tests highlight important physiologic mechanisms that affect the level and pattern of ventilation, they are summarized in subsequent sections.

■ Ventilatory Response to CO_2

The ventilatory response to changes in Pa_{CO_2} is linear over a broad range (Fig. 31-31). Determination of the ventilatory response to controlled hypercapnia generally is based on one of the two methods: the steady-state method[88] or the rebreathing method.[89]

Steady-State Method

After a control period in which CO_2-free air is breathed to establish a baseline, the patient is subjected to two or more periods of breathing CO_2-enriched air. Care is taken to achieve a steady state of ventilation and circulation during each exposure. Especially at the higher concentrations of inspired CO_2, at least 10 to 20 min is required for a steady state to be reached in alveoli, arterial blood, cerebrospinal fluid, and the chemosensitive areas of the brain. The ventilatory response to CO_2 is then determined from a plot of $\dot{V}\text{E}$ versus Pa_{CO_2}. In patients without underlying lung disease, end-tidal CO_2 concentration is often substituted for Pa_{CO_2}. In addition, in order to eliminate the influence of variations in arterial PO_2 on the ventilatory response to CO_2, the inspired gas is enriched with O_2 during the control and test periods.

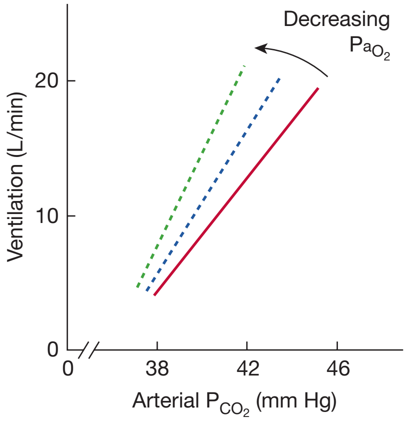

Figure 31-31 Linear relationship between minute ventilation ($\dot{V}\text{E}$) and arterial P_{CO_2}. The dashed lines show the increased slope of the relationship of $\dot{V}\text{E}$ versus P_{CO_2} as Pa_{O_2} decreases.

TABLE 31-14 Factors Associated with an Altered Ventilatory Response to CO_2

Depressed Response
Endurance training
Aging
Genetic/racial predilection
Metabolic alkalosis
Narcotics, barbiturates, and other CNS depressants
Neurologic disorders (encephalitis, brain stem disease)
Myxedema
Obesity-hypoventilation syndrome
Chronic obstructive pulmonary disease (COPD)
Accentuated Response
Metabolic acidosis
Drugs (e.g., aminophylline, salicylates, thyroxine, progesterone)

Rebreathing Method

This method entails rebreathing a CO_2-enriched gas mixture from a bag for approximately 4 min. The validity of the approach requires rapid equilibration of CO_2 among alveolar gas, arterial and mixed venous blood, and the chemosensitive areas of the brain. The bag is filled at the outset with a mixture of 7% CO_2 in O_2; O_2 is substituted for air in this mixture to avoid the ambiguity of a hypoxic stimulus to ventilatory drive.

The result of the CO_2 rebreathing test is described by the use of two terms: (1) the *slope* of the line relating change in ventilation response to change in end-tidal P_{CO_2} ($\Delta\dot{V}\text{E}/P_{CO_2}$), determined by using the method of least squares linear regression analysis, and (2) the *x-intercept* of the relationship between $\dot{V}\text{E}$ and end-tidal P_{CO_2}.

Normal Response to CO_2 and Modifying Influences

As indicated above, the normal increase in ventilatory response to increasing concentrations of inspired CO_2 is linear. Normal responses are categorized as low (<1.5 L/min/mm Hg), intermediate (1.5–5.0 L/min/mm Hg), or high (>5.0 L/min/mm Hg). Most normal persons (about 80%) have an intermediate ventilatory response. A variety of factors, both genetic and environmental, seem to influence the ventilatory response to CO_2 (Table 31-14).

■ Ventilatory Response to Hypoxia

The response to acute hypoxia in normal persons is largely determined by the peripheral arterial chemoreceptors, as long as the level of hypoxia is mild to moderate. Even at sea level, the level of arterial P_{O_2} in normal persons provides an appreciable chemoreceptor drive, accounting for about 10% of the minute ventilation. Unlike the linear response of $\dot{V}\text{E}$ to progressive hypercapnia, the response to hypoxemia is curvilinear (Fig. 31-32). The magnitude of the ventilatory response to a decrease in arterial P_{O_2} depends on the Pa_{CO_2}, increasing as the concentration of CO_2 in arterial blood is increased.

As may be seen from the hyperbolic curves in Fig. 31-32, the rate of change in ventilation is greater over the lower range of oxygenation (when Pa_{O_2} falls below 60 mm Hg). Not shown in Fig. 31-32 is the depression of ventilation brought about by severe hypoxemia, presumably because of the central depressing effect of severe hypoxia on respiratory neurons.

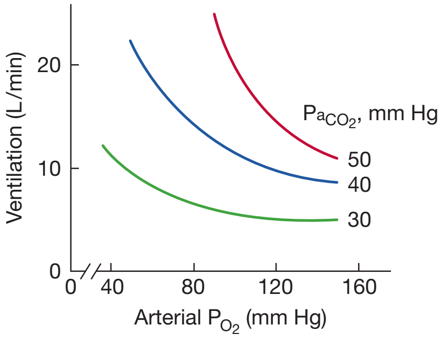

Figure 31-32 The curvilinear relationship between ventilation and arterial P_{O_2} at various levels of arterial P_{CO_2}. The rate of change of ventilation as P_{O_2} falls (slope) increases precipitously at a P_{O_2} of approximately 60 mm Hg when P_{CO_2} is 40 mm Hg. The abrupt increase in ventilation occurs at a higher P_{O_2} when the level of P_{CO_2} is elevated, and at a lower P_{O_2} when the prevailing P_{CO_2} is lower.

Although tests for assessing the ventilatory response to hypoxia are less well standardized than those for measuring the hypercapnic response, they, too, may be conveniently categorized into steady-state and non-steady-state methods. In one steady-state method,[88] successive ventilatory responses are determined to a series of increasingly severe hypoxic gas mixtures, each administered for at least 10 min; Pa_{CO_2} is kept constant by the addition of CO_2 to the inspired gas mixture as hypoxia-induced hyperventilation develops. In another, the effect of hypoxia on the slope of the plot of $\dot{V}_E$ versus P_{CO_2} as P_{O_2} is lowered from hyperoxic (at least 200 mm Hg) to hypoxic (40 mm Hg) levels is determined. The normal response to diminished inspired oxygen concentrations is characterized by an increase in sensitivity (slope) without a change in the CO_2 threshold.

Three non-steady-state techniques are currently in use. In the hypoxic rebreathing test,[90] the subject rebreathes a hypoxic gas mixture containing 7% CO_2. As arterial hypoxemia intensifies, causing an increase in ventilation and in CO_2 elimination into the closed circuit, the P_{CO_2} in the system is held constant at a predetermined level by the diversion of a fraction of the expired gas through a CO_2 absorber. The ventilatory response is determined at two or more levels of P_{CO_2}, since the hypoxic response is influenced by P_{CO_2}.

An alternative rebreathing test[91] induces progressive hypoxemia by adding N_2 to the inspired gas mixture over a 20-min period.

Finally, in a relatively simple test,[92] the patient induces a transient drop in arterial P_{O_2} by inhaling pure N_2 for a few breaths. The relationship between $\dot{V}_E$ and Pa_{O_2} is plotted; the slope of the relationship is the sensitivity to hypoxia. Because the duration of the hypoxia is brief, presumably only the peripheral chemoreceptors are stimulated. No adjustment is made for the drop in P_{CO_2} that occurs during the hypoxia-stimulated increase in ventilation.

Normal Responses to Hypoxia and Modifying Influences

The normal ventilatory response to acute hypoxia varies among individuals. Several factors may influence the relationship (Table 31-15). A high ventilatory response to CO_2 may be associated with a high sensitivity to hypoxia; in addition, higher levels of arterial P_{CO_2} are associated with a higher ventilatory response to hypoxia. Interestingly, a long duration of hypoxia before the test period, as is the case for example, in native residents at high altitude and persons with cyanotic congenital heart disease, a blunted response to acute hypoxia is observed. Finally, a variety of other clinical disorders, including myxedema and hypothyroidism, autonomic nervous system dysfunction, chronic narcotic addiction, and the chronic use of methadone, are characterized by a reduced hypoxic response.

TABLE 31-15 Factors Associated with an Altered Ventilatory Response to Hypoxia

Depressed Response
Long-standing hypoxia
High-altitude dwelling
Congenital cyanotic heart disease
Aging
Hypothyroidism
Riley–Day syndrome
Chronic use of methadone
Following carotid endarterectomy
Accentuated Response
Heightened CO_2 response
Hypercapnia

■ Nonventilatory Measures of Ventilatory Drive

Measurement of ventilation in response to acute hypoxia or hypercapnia provides a useful index of respiratory output when the ventilatory apparatus (thorax, diaphragm, abdominal muscles, lung, and airways) is normal. This situation obviously does not apply in certain neuromuscular disorders in which the thorax and diaphragm behave abnormally. In addition, it does not apply in some instances of pulmonary disease, notably obstructive airway disease, in which the respiratory apparatus may not be capable of responding normally, even though it is intact and chemosensitivity is normal. In this instance, a decrease in ventilatory response may be attributable to the excessive mechanical load placed on the muscles of respiration.

When ventilation fails to provide a reliable measure of the ventilatory drive (efferent discharge from the respiratory neurons), the diaphragmatic electromyograph (EMG) or the pressure generated by the inspiratory muscles during the first 0.1 s of an occluded inspiration (the $P_{0.1}$)[93] has been used for the clinical assessment of the control of breathing.

The electrical activity of the diaphragm is directly related to neural activity of the phrenic nerve. Therefore, it provides a measure of efferent neural traffic to the diaphragm. The diaphragmatic EMG may be recorded in patients by placing the tip of an esophageal catheter, containing bipolar electrodes, at the level of the diaphragm.

The second approach to obtaining a nonventilatory measure of ventilatory drive is the determination of $P_{0.1}$, which is the negative pressure generated by the inspiratory muscles during the first 100 ms of an inspiratory effort made against an occluded airway. During this brief period, contraction of the respiratory muscles is virtually isometric, and the force generated correlates with activity recorded by the diaphragmatic EMG.

In performing the test, airflow in the inspiratory line of the breathing circuit is randomly interrupted during the preceding expiration. The 100-ms period has proved to be so brief as to be imperceptible, thereby obviating any corrective action by the subject during the breath against the occlusion. However, the $P_{0.1}$ is far from foolproof. A major concern is that $P_{0.1}$ is affected by resting lung volume: $P_{0.1}$ is reduced when FRC is abnormally high, a common occurrence in obstructive disease of the airways.

ASSESSMENT OF INTEGRATED FUNCTIONS: 6-MINUTE WALK TEST

A complete evaluation of a patient with respiratory symptoms often requires assessment of exercise capacity, in addition to traditional pulmonary function tests and radiographic studies. A number of exercise studies can be employed, including cardiopulmonary exercise tests (Chapter 32), cardiac stress tests, and exercise-induced bronchospasm protocols. One of the most widely used, practical modalities is the 6-minute walk test (6MWT). Despite its simplicity, the 6MWT has become a powerful tool in the evaluation of functional status and prognosis of patients with a variety of functional impairments.[94]

■ Technical Aspects

The 6MWT is performed indoors. There is an initial period of rest in a chair for at least 10 min, during which baseline vital signs are taken. The patient then stands and is asked to rate baseline dyspnea and overall fatigue using the Borg scale (from 1 to 10). The patient, walking at a comfortable pace, completes 60-m laps on a walking course that is 30 m in length. Cones are used to mark the turnaround points. For patients using supplemental oxygen, the oxygen is delivered at standard rate, or as prescribed by a physician, or as determined by protocol. The patient should not carry or push the oxygen source during testing. The number of laps and a postwalk Borg scale assessment are recorded, as is the total distance walked over 6 min (6MWD).

Although pulse oximetry during the 6MWT is considered optional, it has become standard at many institutions. In some cases, pulse oximetry can be used to titrate levels of oxygen supplementation. Obtaining a high-quality oximeter signal is imperative.

A number of sources of variability are inherent in 6MWT. A modest training effect has been reported when two studies are performed within 1 week. Concomitant medication use also can impact the 6MWT. Improved test performance, for example, occurs after bronchodilator use in patients with COPD. Shorter height, female sex, and higher body weight are associated with reduced performance.[95] Despite these factors, the 6MWT has been found to have excellent reproducibility, especially when performed in evaluation of specific clinical entities, such as idiopathic pulmonary fibrosis.[96,97]

Several modifications of the 6MWT are in clinical use. During a *shuttle-walking test*, the patient walks on a 10-m course while the walking speed is increased every minute until the patient cannot reach the turnaround point within the set time. The *timed walk test (TWT),* which has been designed for patients with idiopathic pulmonary fibrosis, has three stopping criteria based on changes in oxyhemoglobin saturation.

Absolute contraindications to performing the 6MWT include unstable angina or myocardial infarction within 1 month of the study. Resting tachycardia of greater than 120 beats per minute, systolic blood pressure greater than 180 mm Hg, or diastolic blood pressure greater than 100 mm Hg are relative contraindications. The study should be terminated if the patient develops chest pain, severe dyspnea, leg cramps, diaphoresis, or profound oxyhemoglobin saturation.

■ Interpretation

Although the 6MWT is limited in its inability to provide objective measures of functional capacity, such as oxygen uptake, the test provides very useful clinical information. In addition, it realistically represents the patient's functional capacity during physical effort that more closely reflects his or her daily activity. Reliable reference equations establishing standard performance during a 6MWT in healthy patients are not currently available.

The 6MWT has several indications, including, most notably, measurement of the response to a number of medical and surgical interventions. Pulmonary rehabilitation clearly improves 6MWT performance in patients with COPD, while pharmacologic interventions for pulmonary arterial hypertension and heart failure, among other disorders, have also been shown to favorably affect test results. Lung transplantation (unilateral and bilateral) and lung volume reduction surgery for emphysema have been shown to significantly improve results of the 6MWT.

The 6MWT has also been used to assess functional status in patients with COPD, cystic fibrosis,[98] heart failure, and peripheral vascular disease, and in determining eligibility for, and timing of, lung transplantation. In the absence of well-established reference standards, the clinical value of performing a single test in these patient groups is limited. Serial studies are likely to be more useful than a single 6MWT.

Recently, a number of publications have established the value of the 6MWT in predicting morbidity and mortality from heart and lung disease. Results from the test have been shown to have an inverse relationship with mortality in severe COPD. Walk distance and velocity, as well as magnitude of oxyhemoglobin desaturation, are correlated with survival in idiopathic pulmonary fibrosis. Similar correlations have been made in heart failure and primary pulmonary hypertension.

Finally, at some institutions, results of the 6MWT are utilized to not only establish the presence of exertional hypoxemia, but also to titrate supplemental oxygen with activity.

QUALITY CONTROL IN THE PULMONARY FUNCTION LABORATORY

Meaningful interpretation of pulmonary function tests requires confidence in the accuracy and reproducibility of results provided by the pulmonary function laboratory. Previously, it was tacitly assumed that all data from all laboratories, especially when reported as "percent predicted," were equally reliable. In recent years, the fallacy of this assumption has been explicitly recognized, and steps have been taken to standardize equipment and procedures and to ensure accuracy, reproducibility, and uniformity in testing and reporting.[8,10] To accomplish this goal, both analytical and nonanalytical factors must be taken into account.

■ Nonanalytical Factors in Quality Control

A familiar example of a confounding influence that may distort test results is the anxious patient who pauses outside the laboratory door to "calm the nerves" by smoking one or more cigarettes before undergoing pulmonary function testing. Cigarette smoking before the diffusing capacity of the lungs is determined can generate enough carboxyhemoglobin to reduce a normal value to subnormal levels.

Another example of a nonanalytical factor is the failure to achieve patient understanding and comfort for tests that usually require patient cooperation. Unfortunately, a preliminary explanation before the patient arrives at the laboratory or prior exposure of the patient to the laboratory and its personnel is usually impractical. Use of explanatory sheets or descriptive brochures may prove helpful. If such materials are not available, laboratory personnel are obligated to make the patient comfortable and even perform "practice runs" before undertaking final testing.

When the patient arrives at the pulmonary function laboratory, an assessment should be made of his or her prior experiences. Did the patient undergo other tests or procedures that could alter the outcome of the pulmonary function tests in question? Is the patient fatigued or in pain? Should a period of rest precede the tests in order to ensure optimal performance? If delay is impractical, the test report should include the fact that the patient was fatigued or in pain.

Medication use before pulmonary function testing can seriously affect the results. For example, self-administration of bronchodilators before testing can artificially enhance tests of airflow. If medications have been taken before the patient arrives at the laboratory, the time of administration should be part of the record. Also, a request for pulmonary function test results for patients who regularly

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take bronchodilators should indicate whether the tests are to be done without interruption of the regular schedule of medications, whether bronchodilators are to be discontinued before the test is done, or whether regular bronchodilators are to be discontinued so that the effects of bronchodilation can be tested. Appropriate comments about bronchodilators are part of the report.

A major nonanalytical cause of misinterpreting results is the inappropriate application of predicted normal values to the patient population by the laboratory (see "Approach to Interpreting Commonly Performed Pulmonary Function Tests," below). For example, normal values based on data obtained using physically fit hospital personnel do not necessarily apply to those who have a sedentary existence. Noncomparable race, as well as lifestyle, may complicate comparisons. Anthropologic differences among control and test populations are not easily reconciled. Extraordinary height, weight, or age cannot be easily extrapolated if corresponding subjects are not represented in the control group. Using patient-reported height, rather than making measurement of patient height, may introduce an error in the selection of appropriate normal values.[99] Comparison of control and test results at different altitudes can be invalid if due regard is not paid to the influence of hypoxia on certain measurements (e.g., diffusing capacity).

Analytical Factors in Quality Control

Performance of pulmonary function tests is replete with opportunities for error. The equipment, techniques, use of control values, and calculations are potential sources of error. In an attempt to minimize errors, standardization of techniques has been advocated. For example, with respect to performing the FVC maneuver, guidelines have been established for the number of attempts required, acceptable variability between efforts, and methods for selecting test data in order to arrive at acceptable results. To avoid misuse of spirometers, criteria have been set for minimal performance with respect to capacity, accuracy, and frequency response of various spirometers; in addition, standards have been developed for determining the single-breath diffusing capacity. Potential sources of discrepancies—such as breath-holding time, concentration of hemoglobin, dead space of the equipment and the patient, $\mathrm{FIO_2}$, volume of the alveolar sample, number of tests, and acceptable variability in results—are taken into account.

Quality Control of Test Results

Guidelines for standardization play a major role in reducing discrepancies between laboratories. However, measures are also required to ensure accuracy and reproducibility within any given laboratory. Among the elements of control that merit consideration are calibration, validation of calibration, and performance of a control measurement. *Calibration* is the adjustment of an instrument's output so that it validly reflects a known input. *Verification of calibration* entails introduction of the same known input and demonstration that the correct output is reproduced. *Performance of a control measurement* refers to the testing of a substrate that has known properties, similar to those usually tested, to prove the accuracy of the instrumentation.

One example of the application of these principles is blood gas analysis. Use of control measurements derived from tonometered blood or commercially prepared buffer solutions is now widespread. Another example is assessment of diffusing capacity[100] and routine incorporation of simulator testing in its measurement.[101]

Unfortunately, similar controls do not exist for pulmonary function tests. Therefore, laboratory technologists have the responsibility for continuing to be alert, not only with respect to faithful observance of guidelines for standardization, but also to detect in-house sources of error—for example, a leak in the system, malfunction of gas analyzers, faulty analog-to-digital converters, and faulty electronics that reduce frequency response.

Responsibility and Cost in Quality Control

All who work in the laboratory must be concerned with quality control[102] and resist the frequent temptation to cut corners. Time has to be set aside for the technologist to care for and calibrate equipment, to establish proper control values for the laboratory, to search for inconsistencies in the data and interpretation, and to keep up with changing standards. Also, equipment and supplies, including calibrating syringes and calibrating gases, are expensive. However, when put into the balance, the cost and waste of producing erroneous results exceed, by far, the expense of practicing quality control.

Infection Control

Given the relatively close contact between patients and technical staff during performance of pulmonary function tests, the issue of infection control is one that must be carefully considered. To date, the role of pulmonary function equipment in transmission of disease appears to be minimal. Although the presence of potential pathogens on laboratory mouthpieces, valves, and tubing has been well documented, implication of these organisms in the transmission of disease has not been established. Nevertheless, the potential hazards should be recognized, and appropriate care exercised.

Infection control begins with practice of the basic principles of hygiene. Hand washing between patients and use of protective gloves by staff when they are handling potentially contaminated equipment are important considerations. Care must be taken in working with mouthpieces, nose clips, and any other implements that come in contact with mucosal surfaces. These devices, if reused, should be disinfected or sterilized after each use. Other equipment—manifolds, tubing, etc.—should be sterilized on a regular basis. In fact, guidelines from the ATS call for the disinfection or sterilization before reuse of any equipment surface with visible condensation from expired air.[8,103]

Because of recent growing concern over cross-contamination among patients and laboratory personnel, manufacturers now produce a variety of in-line filters and disposable pneumotachographs. Care should be taken, however, to assure that response characteristics of the test equipment are not driven to unacceptable levels by use of these devices. Current literature on this topic should be consulted regularly.

Concern over transmission of infection, to both patients and laboratory personnel, came into sharp focus in 2019 during the COVID-19 pandemic. General guidelines were established for prioritizing patients most in need of testing, use of personal protective equipment for laboratory personnel, and strict attention to laboratory air circulation times and room cleaning protocols.[104–106]

APPROACH TO INTERPRETING COMMONLY PERFORMED PULMONARY FUNCTION TESTS

A standard battery of pulmonary function tests is commonly used to identify and quantify abnormalities in the performance of the respiratory system. An organized approach to interpreting these studies is critical.[107–109]

Once a patient's baseline values are established, the tests are valuable in tracking the course of the disorder and its response to treatment.

Results of pulmonary function tests are interpreted by comparing individual patient data with reference or predicted values for normal subjects.[110,111] Ideally, predicted values should be generated from large groups of well-defined, normal or healthy subjects with proper distribution of anthropometric characteristics such as sex, age and height, and ethnic background. Despite dedicated attempts to improve prediction formulas, however, many still fail to take into account important sources of discrepancy, such as the racial and ethnic backgrounds of the patients and the control population, the effects of altitude and exposure to air pollution, and effects of inordinate body size or old age. As a result, not all sets of predicted normals are applicable in pulmonary function laboratories outside the immediate vicinity of the patient populations from whom the data were collected.[112] Extrapolation beyond the characteristics of the reference population should be avoided.

Published guidelines from a joint Task Force of the ATS and ERS recommended that in the United States, ethnically appropriate reference equations from the National Health and Nutrition Examination Survey (NHANES) III be used for individuals aged 8 to 80 years. The Task Force did not recommend any specific set of reference equations for laboratories in Europe, but it suggested the need for an investigation conducted throughout Europe to derive contemporary equations for prediction of normal lung function.

The same ATS/ERS Task Force recommended that each pulmonary function test result falling below the fifth percentile of the frequency distribution of values measured in the reference population be considered abnormal. If normal test results fall in a normal distribution, values below the fifth percentile can be estimated using Gaussian statistics. If the distribution of normal values is non-Gaussian, the lower limit of normal is estimated using a nonparametric technique, for example, the 95th percentile method. Traditionally, but without a sound statistical basis, most laboratories have used an arbitrary cutoff of 80% predicted to define normal. While this method may be reasonable in children, errors may arise if it is applied to adult test results.

Interpretation Scheme and Classification of Abnormal Patterns

A variety of schemes have been proposed for sorting out abnormalities in pulmonary function test results. Many are based on initial categorization of findings reflective of one of the four basic patterns described in the following paragraphs.

An *obstructive* pattern stems from narrowing of any portion of the airways—from upper airway to bronchioles less than 2 mm in diameter—that results in a reduction of maximal airflow in relation to maximal volume.

A *restrictive* pattern is elicited by diseases of the lung, chest wall, pleural space, or neuromuscular respiratory apparatus that reduce lung volumes, particularly TLC, and vital capacity.

A *combined obstructive–restrictive* pattern results from pathologic processes that reduce lung volumes, vital capacity, and airflow, and that also include an element of airway narrowing.

Finally, *abnormal gas transfer* may be noted as part of one of the aforementioned patterns or in isolation and reflects an abnormality in the alveolar capillary membrane, impairing oxygen uptake from alveolar gas to pulmonary capillary blood.

Overlap among categories is not uncommon. For example, widespread interstitial disease, as in idiopathic pulmonary fibrosis, often shows a pattern that indicates important components of both restrictive disease and abnormal gas transfer.

One useful sequence recommended by the ATS/ERS Task Force for analyzing a conventional battery of pulmonary function test results is illustrated in Fig. 31-33.

Analysis begins with evaluation of the ratio of FEV_1 to VC. While, historically, the ratio of FEV_1 to FVC (FEV_1/FVC%) served as the basis for distinguishing obstructive disorders from normality or restrictive disease, the ATS/ERS Task Force currently recommends using as the denominator the FVC, *or* the VC (“slow” VC or SVC), *or* the FIVC, whichever is greatest. If the ratio is less than the lower limit of normal (i.e., below the fifth percentile) and the VC (defining VC as any of the three previously noted vital capacity measurements) is at or above the lower limit of normal, the pattern is obstructive. If TLC is not at or above the lower limit of normal, a mixed obstructive–restrictive pattern is suggested. Distinction between asthma and chronic bronchitis on the one hand, and emphysema on the other, is based upon whether the DL_{CO} is normal (asthma or chronic bronchitis) or reduced (emphysema). The previous practice of using a value for FEV_1/FVC% of less than 70% to define obstruction results in misdiagnosis of airway obstruction in men over 40 years and women over 50 years of age, as well as overdiagnosis of COPD in elderly, asymptomatic nonsmokers.

If FEV_1/VC and VC are each equal to or greater than the respective lower limits of normal, spirometry is considered normal; measurement of the DL_{CO} can then help distinguish between normal pulmonary function and pulmonary vascular disorders. If VC is below the lower limit of normal, a reduced TLC supports a diagnosis of restriction, while a normal TLC indicates an obstructive pattern. Once again, in the setting of a restrictive pattern, measurement of DL_{CO} can be used to distinguish between pulmonary parenchymal disorders and disorders of the chest wall or respiratory muscles. Note that according to these guidelines, an obstructive pattern may be diagnosed in the setting of a *normal* FEV_1/VC, if VC is reduced and TLC is normal or elevated.

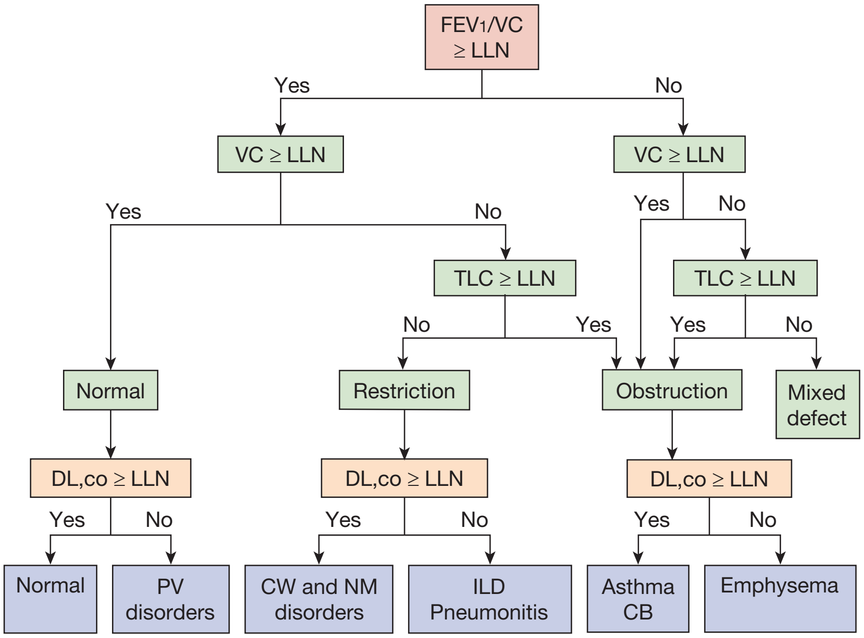

Figure 31-33 Proposed sequence of test review in the interpretation of pulmonary function tests. See text for discussion. CB, chronic bronchitis; CW, chest wall; ILD, interstitial lung disease; LLN, lower limit of normal; NM, neuromuscular; PV, pulmonary vascular. *(Reproduced with permission from Pellegrino R, Viegi G, Brusasco V, et al. Interpretive strategies for lung function tests. Eur Respir J. 2005;26(5):948–968.)*

TABLE 31-16 Grading of Severity of Abnormal Spirometry Based on FEV_1

Severity	FEV_1 Percent Predicted
Mild	>70
Moderate	60–69
Moderately severe	50–59
Severe	35–49
Very severe	<35

Modified with permission from Pellegrino R, Viegi G, Brusasco V, et al. Interpretive strategies for lung function tests. Eur Respir J. 2005;26(5):948–968.

TABLE 31-17 Conditions Associated with Reduced Peak Inspiratory (PI_{max}) and Expiratory (PE_{max}) Pressures

Condition	PI_{max}	PE_{max}
Poor effort	↓	↓
Fatigue	↓	↓
Neuromuscular disease	↓	↓
Increased lung volume	↓	N
Decreased lung volume	N	↓

↓, decreased; N, normal.

Once the predominant abnormality is defined with initial pulmonary function testing, the whole battery may not be necessary in following the course of the disease or in assessing its response to treatment. For example, particular determinations, such as spirometry, may suffice in patients with airway diseases. Notably, according to the ATS/ERS guidelines, the severity of the abnormality in each of the obstructive, restrictive, or mixed patterns is expressed on the basis of the FEV_1 (Table 31-16). Standards have been established for defining significant changes in results over time: A 15% or greater change in FVC or in FEV_1, or a greater than 10% change in DL_{CO} is considered significant.

Assessing Respiratory Muscle Strength and Effort

One additional measurement that is frequently useful in assessing results of routine spirometry is assessment of respiratory muscle strength. Respiratory muscle strength is expressed in terms of peak inspiratory (PI_{max}) and peak expiratory (PE_{max}) pressures, determined under static conditions.[26] The technique was outlined in a previous section. Any of a number of factors may be responsible for low peak inspiratory or expiratory pressures (Table 31-17): suboptimal effort, fatigue, weakness of the respiratory muscles, deformity of the chest wall, or intrinsic diseases of the lungs or chest wall. Although the first three factors characteristically reduce both peak inspiratory and expiratory pressures, disease of the lungs or chest wall often reduces, selectively, one or the other peak pressure. Thus, diseases that reduce lung volumes (e.g., widespread interstitial fibrosis) and shorten the length of the expiratory muscles at the end-inspiratory position generally reduce maximal expiratory pressure. Conversely, diseases that increase lung volume, such as obstructive airway disease, by decreasing the inspiratory muscle length at end-expiration generally reduce maximal inspiratory pressure.

If airflow during spirometry is reduced, determination of the peak inspiratory and expiratory pressures may be helpful in suggesting the mechanism. Many pulmonary function tests depend on the cooperation of the patient. Poorly reproducible peak flows that are consistently subnormal raise the question of poor effort. Conversely, consistently low values that occur despite maximal effort may signal neuromuscular disease.

Additional Details of Pulmonary Function Test Results in an Obstructive Pattern

Included in the obstructive pulmonary disorders (Table 31-18) are chronic obstructive diseases of the airways (chronic bronchitis and emphysema), bronchiectasis, asthma, small-airway disease, and upper-airway obstruction.

Except for diseases confined to the small airways, as noted previously, the hallmark of the obstructive pattern is a reduction in the $FEV_1/VC\%$. Notably, some healthy subjects have a reduced $FEV_1/FVC\%$ and an FEV_1 in the normal range. The clinical significance of these findings is unclear. Results of additional tests (e.g., lung volumes, DL_{CO}, assessment of bronchodilator responsiveness) may help distinguish those with airway obstruction from true normals.[113] Measurement of airway resistance (Raw) or specific airway conductance (SGaw) may be useful in assessing airway obstruction in subjects unable to perform a maximal forced expiratory maneuver.

Changes in lung volume commonly accompany the abnormal findings on spirometry, but, as indicated in Fig. 31-33, lung volume measurement is not mandatory in establishing the presence of obstruction. Frequently, but not invariably, lung volumes are abnormally high. Typically, all three lung volumes—RV, FRC, and TLC—are increased.

In addition to uncovering the pattern of chronic obstructive airway disease described above, certain additional tests provide insight into the sites and mechanisms of obstructive airway disease.

TABLE 31-18 Causes of an Obstructive Pattern

Disease Process	Anatomic Location of Lesion	Cause of Reduced Airflow
Chronic obstructive pulmonary disease (COPD)		
Chronic bronchitis	Large and small (<2-mm diameter) airways	Narrowing of airways by fibrosis, secretions, edema
Emphysema	Lung parenchyma	Loss of lung elastic recoil
Cystic fibrosis	Large and small airways	Narrowing of airway by fibrosis, retained secretions, edema Loss of elastic recoil
Asthma	Large and small airways	Narrowing of airways by smooth muscle contraction, edema, retained secretions
Small-airway disease	Small airways	Narrowing, stenosis of small airways
Upper-airway obstruction	Major, central airways (trachea, main bronchi)	Anatomic or functional narrowing of upper airway

Reversible versus Irreversible Obstructive Airway Disease

The response to inhaled bronchodilators traditionally has been used to help distinguish between chronic obstructive airway disease (chronic bronchitis and emphysema), in which airway resistance is virtually fixed, and asthma, in which bronchoconstriction is a prominent feature. This is an oversimplification, since a sizable minority of patients with COPD manifest a bronchodilator response. Furthermore, the absence of a bronchodilator response in a laboratory setting does not necessarily predict lack of a clinical response.

A universally agreed upon definition of reversibility is lacking. Expressing change in FEV_1 or FVC as percent of predicted values may be more advantageous than expression of changes in the values relative to baseline. In general, an increase in FEV_1 or FVC of at least 12% above baseline *and* an absolute increment of at least 200 mL is considered evidence of significant bronchodilation. If the increase in spirometric values is not significant, a decrease in lung volumes toward normal may be an indication of bronchodilator responsiveness.

Chronic Bronchitis versus Emphysema

Although chronic bronchitis and emphysema usually coexist, occasionally one or the other exists in virtually pure form. Two pulmonary function tests have proved valuable in distinguishing between the two—diffusing capacity (DL_{CO}), which is routinely measured, and static lung compliance (Cst,L), which is uncommonly measured clinically. Emphysema, characterized by a loss of alveolar units and a decrease in alveolar surface area, is associated with a low DL_{CO}, whereas the DL_{CO} in chronic bronchitis is usually normal or near normal.

The loss of alveolar units in emphysema also causes a decrease in the elastic recoil pressure of the lungs. As a result, Cst,L is increased in emphysema, whereas it is usually not appreciably altered in chronic bronchitis.

Small-Airway Disease

In obstructive disease of the small airways (i.e., those less than 2 mm in diameter), expiratory flow is usually normal, except at low lung volumes; that is, the FEV_3 and $FEF_{25-75\%}$ are abnormally low. Other, uncommonly performed tests for isolated, small-airway disease, including the helium–oxygen flow–volume loop, nitrogen washout test, and frequency dependence of dynamic compliance, would also be anticipated to be abnormal. Lung volumes and DL_{CO} are normal. Bronchodilators are virtually without effect.

The practical value of tests of small-airway function is problematic. At one time, high hopes were held that early detection of small-airway disease might reinforce measures, such as cessation of smoking, that would prevent or arrest progression to irreversible obstructive disease of the airways. However, enthusiasm for testing for small-airway disease has waned, since it is still unclear if small-airway disease is a reversible phase in the evolution of clinically significant obstructive airway disease that affects larger bronchi.

Upper-Airway Obstruction

The designation *upper-airway obstruction* is an umbrella for anatomic or functional narrowing of the large upper airways—the larynx, extra- and intrathoracic trachea, and lobar bronchi. Although upper-airway obstruction of any cause may reduce expiratory or inspiratory airflow, an alteration in the contour of the flow–volume loop has proved to be the most reliable abnormality in conventional pulmonary function testing. The observation from routine spirometry that the ratio of FEV_1 to peak expiratory flow rate (PEFR) exceeds 8 mL/L/min should prompt careful performance and review of the flow–volume loop, as described later.

Upper-airway obstruction can be divided into three major types: (1) fixed obstruction, (2) variable extrathoracic obstruction, and (3) variable intrathoracic obstruction.[114]

A *fixed obstruction,* such as tracheal narrowing by scar tissue at the site of a previous tracheotomy, is one in which the geometry and cross-sectional area of the lesion do not change during the respiratory cycle. Characteristically, both inspiratory and expiratory flows are affected about equally (Fig. 31-34A).

A *variable obstruction* is one in which the configuration of the obstructive lesion changes with the phases of respiration. Depending on its location in the tracheobronchial tree (extra- or intrathoracic), this type of lesion usually affects predominantly either inspiration or expiration.

The inspiratory arm of the flow–volume loop is primarily affected by a *variable extrathoracic* obstruction, leaving the expiratory limb relatively unaffected (Fig. 31-34B). The abnormal configuration of the flow–volume loop is attributable to the following sequence: during forced expiration, tracheal pressure exceeds atmospheric, so that the degree of obstruction decreases; conversely, during forced inspiration, intratracheal pressure becomes less than atmospheric and the trachea tends to collapse.

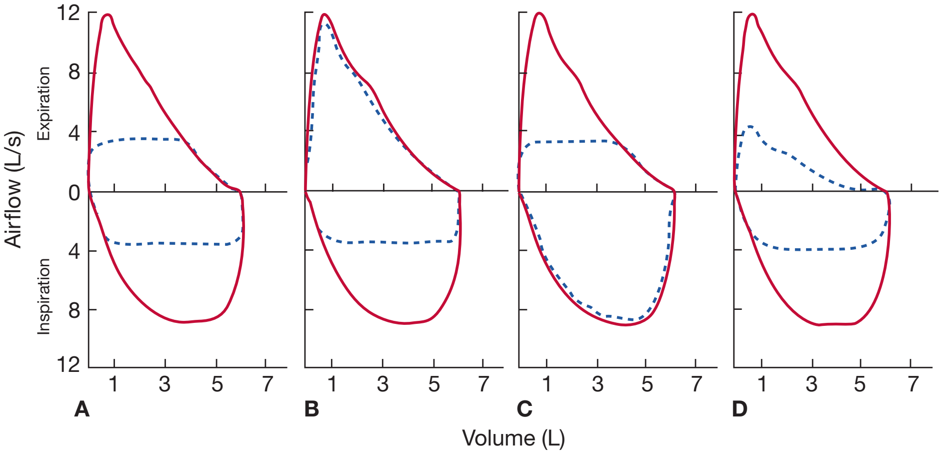

Figure 31-34 Schematic flow–volume loops in four pathologic conditions. **A.** In a fixed upper-airway obstruction, both inspiratory and expiratory limbs are truncated. **B.** In a variable extrathoracic obstruction, the inspiratory limb is flattened while the expiratory limb is not altered. **C.** In a variable intrathoracic obstruction, the expiratory limb is flattened while the inspiratory portion is unchanged. **D.** In chronic obstructive airway disease, although expiratory airflow is reduced, the tapering in airflow during expiration is generally maintained so that the configuration of the loop is different from that in variable intrathoracic obstruction.

TABLE 31-19 Distinguishing Features of Disorders Producing an Obstructive Pattern

Disorder	FEV_1	FVC	FEV_1/ VC%	Response of FEV_1 to Administration of Bronchodilator	Tests of Small-Airway Function	Lung Volumes	D_{LCO}	Flow–Volume Loop
COPD								
Chronic bronchitis	↓	↓	↓	NC	ABN	↑	NL	ABN
Emphysema	↓	↓	↓	NC	ABN	↑	↓	ABN
Asthma	↓	↓	↓	↑	ABN	↑	NL	ABN
Small-airway disease	NL	NL	NL	NC	ABN	NL	NL	NL
Upper-airway obstruction	↓	↓	↓	NC	NL or ABN	NL or ↑	NL	ABN[a]

[a] *Configuration frequently characteristic for upper-airway obstruction.*

↓, decrease; ↑, increase; NC, no significant change; NL, normal; ABN, abnormal.

The expiratory arm of the flow–volume loop is primarily affected by a *variable intrathoracic* obstruction (Fig. 31-34C). The following sequence is responsible for producing this abnormality in the flow–volume loop: during forced expiration, as pleural pressure reaches and then exceeds intratracheal pressure downstream from the lesion (i.e., toward the mouth), the obstruction tends to increase; conversely, during a forced inspiration, as intratracheal pressure exceeds pleural pressure, the intrathoracic obstruction decreases.

Variable intrathoracic lesions often coexist with obstructive airway disease. In considering a variable intrathoracic lesion, the respective roles played by obstructive disease of the airways (i.e., chronic bronchitis, emphysema, and asthma) and an obstructive upper-airway lesion (anatomic or functional) in deforming the flow–volume loop must be determined. Fortunately, this distinction is often possible. Although both upper-airway obstruction and obstructive airway disease (reversible and irreversible) do decrease maximal expiratory flow, the shapes of the flow–volume cures are frequently quite distinctive (Fig. 31-34C and D). Thus, in obstructive airway disease, despite a decrease in airflow, the expiratory limb of the loop generally retains its normal configuration (Fig. 31-34D)—that is, an early peak in flow, followed by gradual tapering. In contrast, in upper-airway obstruction (fixed and variable intrathoracic), the expiratory limb is flat and flow is decreased throughout most of expiration (Fig. 31-34C).

In addition to changes in the shape of the flow–volume loop, clues from routine pulmonary function tests often alert the clinician to the possibility of upper-airway obstruction. As noted previously, when $FEV_1/PEFR > 8$, the possibility of upper-airway obstruction should be considered. Finally, the presence of any of the following may also provide clues: $FEF_{50\%}/FIF_{50\%}$ of at least 1, where $FEF_{50\%}$ and $FIF_{50\%}$ are the forced expiratory flow at 50% of FVC and the forced inspiratory flow at 50% of FIVC, respectively; $FIF_{50\%}$ less than 100 L/min; and $FEV_1/FEV_{0.5}$ at least 1.5.

Distinguishing test features of disorders producing an obstructive pattern are summarized in Table 31-19.

■ Additional Details of Pulmonary Function Test Results in a Restrictive Pattern

The restrictive pattern (Table 31-20) characteristically occurs in several groups of disorders including (1) a primary disorder of the lung parenchyma in which functional tissue is lost through disease (e.g., an alveolar filling process, such as pneumonia, tumor, atelectasis, or fibrosis); (2) surgical removal of lung tissue (e.g., lobectomy); (3) constrictive disease of the pleura and chest wall (e.g., extensive pleural fibrosis, large pleural effusion or pleural mass, kyphoscoliosis, obesity); and (4) neuromuscular diseases, notably those in which the generation of respiratory force is reduced (e.g., disorders of the spinal cord, peripheral nerves, neuromuscular junction, and muscle).

The diagnosis of restriction is based upon the finding of a normal FEV_1/VC and reduced VC in the setting of a decreased TLC. While TLC generally is reduced in most disorders producing a restrictive pattern, FRC is usually preserved in disorders characterized by decreased respiratory force (e.g., the neuromuscular disorders) and is reduced in the others. In neuromuscular disorders, ERV is decreased because of loss of expiratory force, so that RV is often increased. In the other types of restrictive disorders, RV is usually reduced.

Whether the D_{LCO} is reduced in the restrictive disorders depends on the underlying disease process. Primary parenchymal disorders and removal of lung tissue decrease the diffusing surface area and reduce D_{LCO}. Diseases of the pleura and chest wall that limit thoracic excursion during the inspiratory vital capacity maneuver, which is part of the technique for determining D_{LCO}, also reduce this measurement.

■ Additional Details of Pulmonary Function Test Results in a Mixed Obstructive–Restrictive Pattern

Occasionally, a battery of pulmonary function tests demonstrates features of both obstructive and restrictive patterns. Most often, the mixed pattern is characterized by a low FEV_1/VC% (indicating

TABLE 31-20 Causes of a Restrictive Pattern

Disease Process	Anatomic Location of Lesion	Cause of Pulmonary Function Test Abnormality
Primary parenchymal disease	Lung parenchyma	Loss of lung tissue ⟶ reduced volumes and flows
Surgical removal of lung tissue	Lung parenchyma	Loss of lung tissue ⟶ reduced volumes and flows
Diseases of pleura and chest wall	Pleura, chest wall	Limited expansion of thoracic cavity ⟶ reduced volumes and flows
Reduced generation of expiratory force	Central nervous system, peripheral nerves, neuromuscular junction, muscles of respiration	Reduced muscle tension ⟶ reduced expiratory flow, atelectasis

TABLE 31-21 Categorization of Reduction in Efficiency of Gas Transfer: Measurement of $\mathrm{DL}_{\mathrm{CO}}$

Severity	$\mathrm{DL}_{\mathrm{CO}}$, Percent Predicted
Mild	>60, but less than lower limit of normal
Moderate	40–60
Severe	<40

Modified with permission from Pellegrino R, Viegi G, Brusasco V, et al. Interpretive strategies for lung function tests. Eur Respir J. 2005;26(5):948–968.

obstructive airway disease) and VC and reduced TLC (indicating coexisting restrictive disease).

A number of disorders can produce the mixed obstructive/restrictive pattern. Sarcoidosis and interstitial fibrosis, when severe, generally result in this pattern because the parenchymal disease causes restriction and narrowing of the airways by adjacent fibrosis, evoking signs of airway obstruction. The mixed pattern also occurs in complicated situations when there is more than one cause—for example, a lobar pneumonia or large pleural effusion occurring in a patient with underlying chronic bronchitis or emphysema.

Isolated Decrease in the Efficiency of Gas Transfer

An isolated reduction in the $\mathrm{DL}_{\mathrm{CO}}$ suggests one of the two possible abnormalities: (1) interstitial lung disease that is so mild as not to affect measurements of airflow or lung volume, or (2) widespread occlusive disease of the pulmonary microcirculation (e.g., due to an inflammatory process or multiple small emboli). In occlusive vascular disorders, tests of airflow and lung volume are usually normal. Although other disorders can also decrease $\mathrm{DL}_{\mathrm{CO}}$, almost invariably they also reduce airflow, lung volumes, or both. Quantification of the degree to which the $\mathrm{DL}_{\mathrm{CO}}$ is reduced by any of these processes is indicated in Table 31-21. Notably, interlaboratory differences are substantial for measurements of $\mathrm{DL}_{\mathrm{CO}}$.

TABLE 31-22 Characteristic Alterations in Pulmonary Function Tests According to the Major Patterns of Abnormality

Pattern	Airflow (FEV_1/VC%)	Airflow Response to Bronchodilators	Volumes	Lung $\mathrm{DL}_{\mathrm{CO}}$
Obstructive				
Irreversible	↓	↔	↑	↔ or ↓
Reversible	↓	↑	↑	↔
Small-airway disease	↓	↔	↔	↔
Upper-airway obstruction	↓	↔	↔ or ↑	↔
Restrictive				
Parenchymal disease	↔ or ↑	↔	↓	↓
Surgical resection	↔	↔	↓	↓
Pleural, chest wall disease	↔	↔	↓	↔
Reduced expiratory force generation	↔	↔	↓	↔
Mixed obstructive–restrictive	↓	↔ or ↑	↓	↓
Isolated reduction in efficiency of gas transfer	↔	↔	↔	↓

↓, decreased; ↑, increased; ↔, no change or normal.

Summary of Approach to Interpretation

Pulmonary function tests are designed to detect common disorders. Test interpretation relies heavily on recognition of major patterns of abnormality (Table 31-22). These patterns often suggest pathogenetic mechanisms and are helpful to the clinician in arriving at a diagnosis. The degree of abnormality provides a quantitative measure of the extent of involvement at a particular time. Moreover, repeated testing makes it possible to pace and quantify the course of the illness and to assess the effects of therapeutic interventions.[115]

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CHAPTER 32

Principles and Application of Cardiopulmonary Exercise Testing

Marco Guazzi
Alice Moroni

INTRODUCTION

Exercise testing using gas exchange analysis, or cardiopulmonary exercise testing (CPET), is a remarkably useful and versatile tool. CPET has evolved over time and, currently, constitutes a unique clinical approach for study of a variety of cardiopulmonary disorders that may be associated with symptoms or limit exercise performance.[1–3] Use of CPET has become more common recently, with increasing recognition that assessment of cardiac and pulmonary function at rest cannot reliably predict functional capacity, and that disease stages and severity correlate better with exercise parameters than with resting measurements. Indeed, CPET provides an overall assessment of the integrated, multiorgan response to exercise involving the oxygen-uptake cascade, including the lung, cardiovascular system, skeletal muscle, and cellular pathways for oxygen utilization.

The precision of the technology used in CPET is remarkable, and the technique provides information that facilitates an understanding of the pathophysiology underlying exercise impairment. Additionally, it enables insight into how therapeutic interventions impact effort limitation, and identifies useful markers of prognosis.[4]

A thorough evaluation of gas exchange parameters in response to various cardiopulmonary disorders was proposed in the early 1980s, including pioneering studies by Weber and Janicki.[5,6] Recently, use of CPET has been expanded considerably. Combination modalities, for example, CPET coupled with echocardiography (CPET imaging),[7] and invasive assessment of systemic and pulmonary hemodynamics have been described.

This chapter provides a conceptually balanced discussion of CPET applications based on expert recommendations, guidelines, and available data.

PRINCIPLES OF GAS EXCHANGE DURING EXERCISE

When physically challenged, for example, during exercise, the body behaves as a "machine in harmony," integrating and promoting the interaction of multiple organs and pathways. O_2 delivery from ambient air to mitochondria is essential to aerobic performance. Optimal O_2 delivery depends on a set of elegant biologic interactions among the functional components of the O_2 transport chain, including oxygenation of blood in the lung (via gas diffusion in the alveoli); O_2 transport in blood, in both hemoglobin-bound and dissolved forms; redistribution of blood flow to working muscles; adequate O_2 release and tissue O_2 extraction in metabolizing tissues; and diffusion of O_2 from capillaries into metabolizing cells (Fig. 32-1).

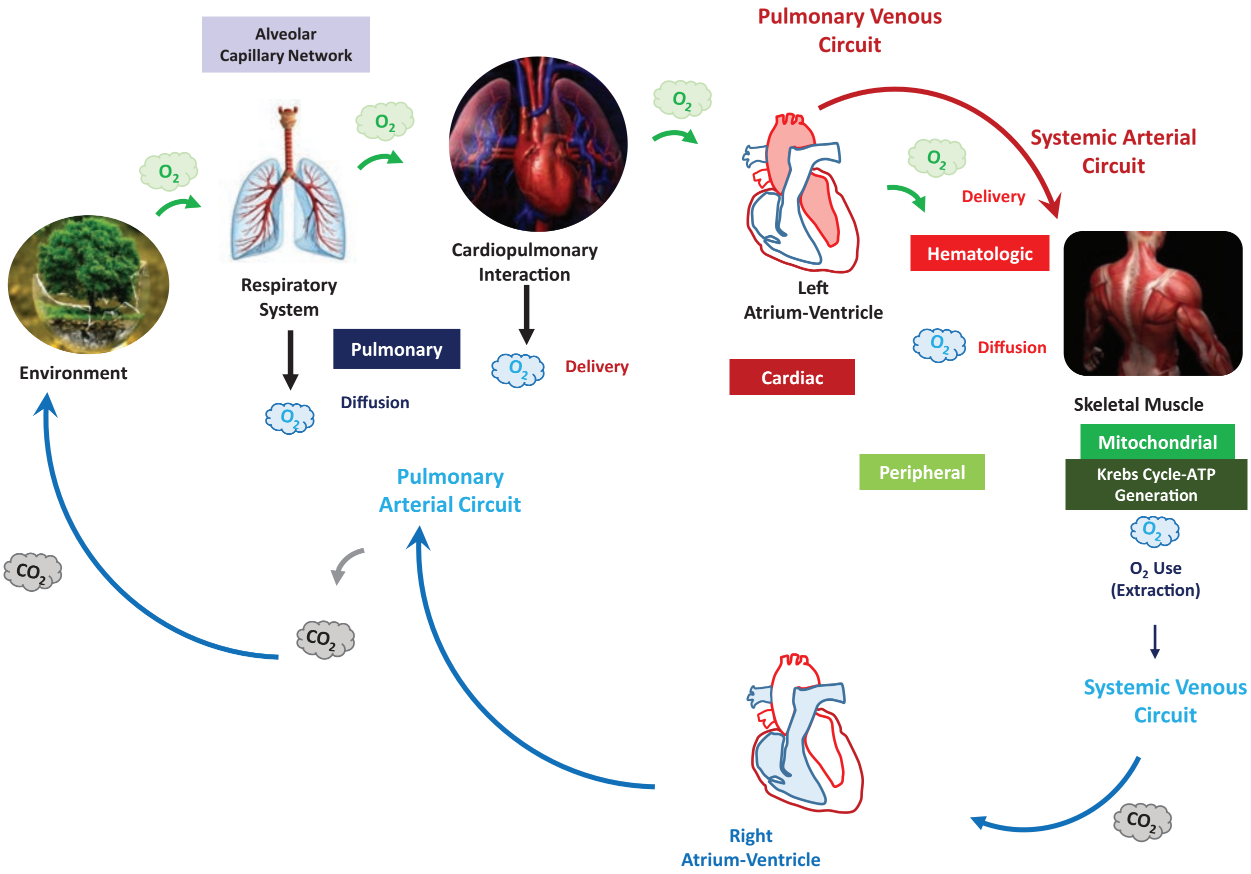

Alveolar Capillary Network
Pulmonary Venous Circuit
O_2
O_2
O_2
O_2
Systemic Arterial Circuit
Delivery
Respiratory System
Cardiopulmonary Interaction
Left Atrium-Ventricle
Hematologic
Environment
Pulmonary
O_2
Delivery
O_2
Diffusion
Cardiac
O_2
Diffusion
Skeletal Muscle
Mitochondrial
Peripheral
Krebs Cycle-ATP Generation
Pulmonary Arterial Circuit
O_2
O_2 Use (Extraction)
CO_2
CO_2
Systemic Venous Circuit
CO_2
Right Atrium-Ventricle

Figure 32-1 Organ systems involved in the O_2 utilization chain.

Direct measurement of oxygen uptake ($\dot{V}O_2$), typically expressed as $\dot{V}O_{2max}$ (in healthy subjects) or as peak $\dot{V}O_2$ (in patients), and normalized for body weight (mL/kg/min), defines maximal exercise performance and related limits of the cardiopulmonary system.[5]

One's ability to perform physical activity is critically related to the cardiopulmonary system's capacity to supply O_2 and clear carbon dioxide (CO_2) from exercising muscle. During this process, delivery of O_2 to mitochondria is essential to performing maximal exercise.[8]

According to *Fick's principle*:

$$\dot{V}O_2 = CO \times (CaO_2 - CvO_2)$$

where CO is cardiac output and (CaO_2 – CvO_2) is the O_2 content difference between arterial and venous blood.

According to *Fick's law*:

$$\dot{V}O_2 = D \times K \times PvO_2$$

where D refers to the diffusive properties of the tissue through which O_2 is diffusing, K is a constant, and PvO_2 is the partial pressure of O_2 in the venous blood draining from the tissue.

The linear increase in $\dot{V}O_2$ during exercise is achieved by matching O_2 delivery to mitochondrial O_2 utilization. In concert with alveolar gas exchange, O_2 delivery is determined by heart rate (HR) and stroke volume (SV) at a given O_2 saturation and Hb concentration. Furthermore, diffusion of O_2 from capillaries to myocytes depends on the diffusion properties of tissues and the contribution of cellular mechanisms of O_2 release to mitochondria.[9,10] Hence, O_2 delivery and extraction are two physiologic processes critical to O_2 utilization at the cellular level.

As noted above, O_2 delivery is determined not only by CO (and its distribution), but also by blood O_2 content and the mechanisms involved in O_2 dissociation from hemoglobin (Hb). Blood O_2 content is calculated as: 1.34 mL O_2/gram Hb/dL × O_2 saturation × Hb concentration (where 1.34 mL is the amount of oxygen bound to each gram of hemoglobin when fully saturated), plus O_2 dissolved in plasma, calculated as PaO_2 × 0.0031 mL O_2/dL/mm Hg (where 0.0031 is the solubility coefficient of O_2 in blood). The relationship of O_2 delivery, or "convection" (as described by the Fick principle), and diffusion (as described by Fick's law) can be represented in a diagram relating $\dot{V}O_2$ and PvO_2 (Fig. 32-2).[11]

As proposed by Wagner,[12] the diagram relates $\dot{V}O_2$ to venous PO_2 in muscle, from rest to peak exercise. The convection and diffusion lines intersect, defining the point of maximal O_2 consumption, that is, $\dot{V}O_2$ max.

O_2 extraction in tissues is the net result of O_2 delivery to peripheral tissues and O_2 utilization and is dependent on the ability of O_2 to diffuse from capillaries to cells, as well as the function of mitochondria (Fig. 32-3).

Normally, healthy adults can increase $\dot{V}O_2$ up to 6-fold during exercise. The relative contribution of the individual determinants in Fick's equation to increases in $\dot{V}O_2$ are approximately 1.2 for stroke volume, 2.5 for heart rate, and 2.5 for arteriovenous O_2 content difference. In health, multiple steps limit O_2 utilization in achieving $\dot{V}O_{2max}$. Cardiac output appears to be most important at sea level, while at higher altitudes, diffusion of O_2 in lung and muscle are more important.[13]

Heart failure (HF) represents a prototypical condition in which O_2 delivery and diffusion are impaired, as demonstrated in a study in humans with HF characterized by reduced ejection fraction (HFrEF).[14] The study addressed the relative contributions of convection versus diffusion using two different exercise modalities: incremental exercise to a maximum and, therefore, accompanied by a need for increased CO, versus isolated knee extension, with the requirement for an increase in local O_2 extraction (Fig. 32-4A). The study included analysis of muscle fiber types, mitochondrial volume, and capillary-to-muscle fiber ratios. Interestingly, in normal individuals, skeletal muscle and mitochondria contributed minimally to the limitation in O_2 utilization, supporting the concept that mitochondrial oxidative capacity largely exceeds O_2 delivery at peak $\dot{V}O_2$. However, patients with HF, when compared with controls, exhibited attenuation of both convective and diffusive components of O_2 transport during both maximal exercise and isolated knee extension (Fig. 32-4B).

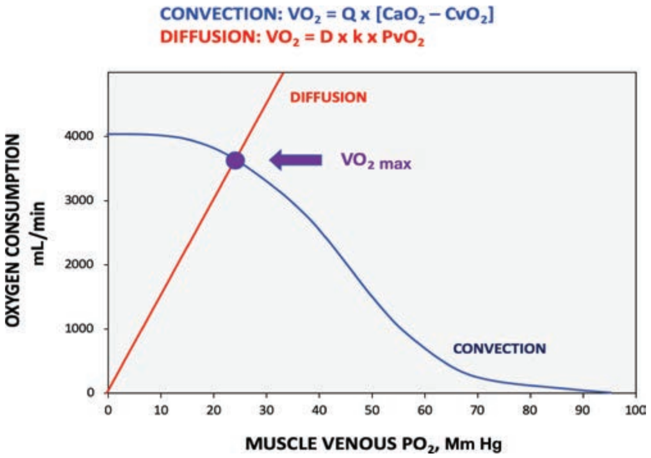


Figure 32-2 The relationship between O_2 diffusion and convection. As proposed by Wagner,[11] during exercise, $\dot{V}O_2$ relates to muscle venous PO_2 from rest to peak exercise. Shown are the line *(blue)* for $\dot{V}O_2$ convection (i.e., O_2 delivery) from rest at a high muscle venous PO_2, to a peak at a low muscle venous PO_2, and the line for O_2 diffusion *(red)*. The diffusion line goes through the origin of the plot; its slope varies according to the muscle venous PO_2; a line shifted upward and to the left represents greater diffusion. The point of intersection of the two curves is $\dot{V}O_{2max}$, the point where convection and diffusion result in maximal O_2 utilization.

More uncertainty exists regarding the limiting steps in O_2 transport and utilization in the functional response of patients with HF who have a preserved ejection fraction (HFpEF). Many of these patients are elderly and anemic and, therefore, have impaired O_2 carrying capacity.[15] In addition, they may have a defect in O_2 diffusion, as well as a lower (CaO_2 – CvO_2). To better understand the specific roles of various steps in limiting O_2 uptake pathways, phenotypic mapping may be useful and aid in delineating the high rate of interindividual variability.[16]

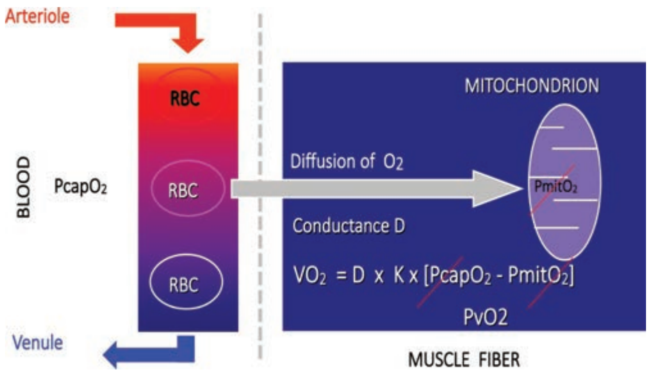


Figure 32-3 O_2 diffusion from red blood cell to mitochondria. Diffusion is an important determinant of O_2 uptake. According to Fick's law of diffusion, $\dot{V}O_2$ = D (oxygen diffusive capacity) × K (a constant, which represents the ratio of arterial to venous PO_2 [approximately 2]) × the capillary mitochondrial difference between PaO_2 and PvO_2 (assuming an intracellular partial pressure of O_2 near 0).

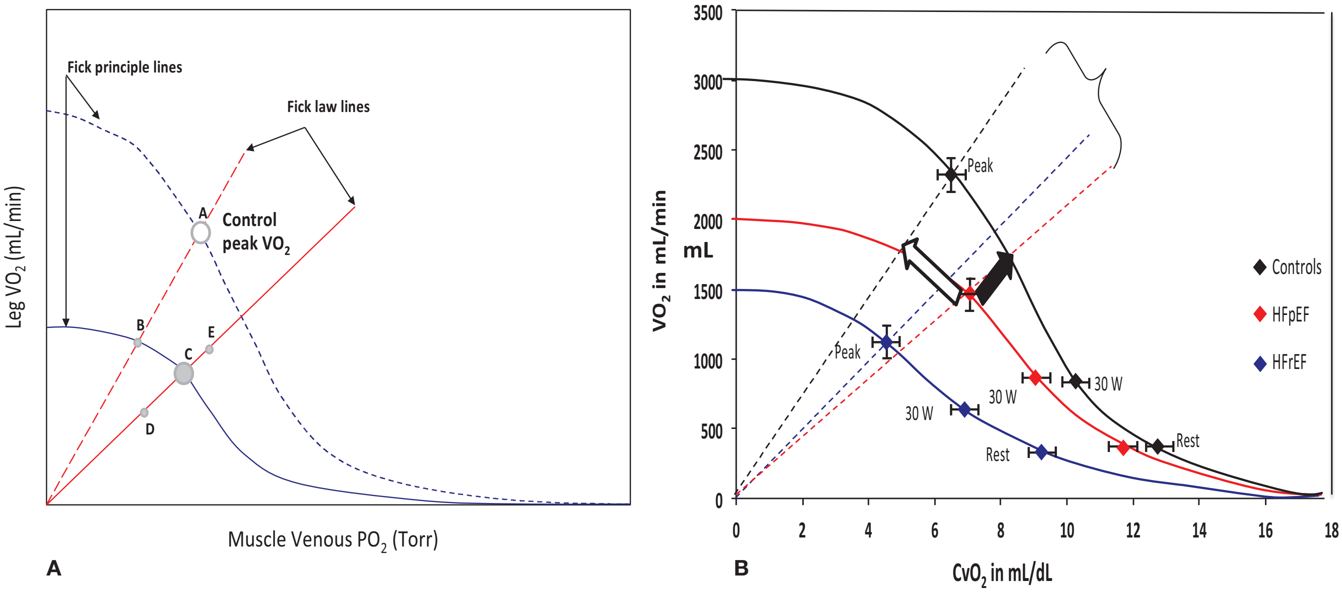


Figure 32-4 Relationships between O_2 diffusion and convection in HFrEF. **A.** Relative impairment of convection versus diffusion measured during two different exercise modalities: an incremental test to a maximum (*A, B*), and local isolated knee extension (*C,D,E*). **B.** $\dot{V}O_2$ and PvO_2 relationship in patients with HFrEF and HFpEF and controls, showing a limitation in either diffusion or convection. *(**A.** Reproduced with permission from Esposito F, Mathieu-Costello O, Shabetai R, et al. Limited maximal exercise capacity in patients with chronic heart failure: partitioning the contributors. J Am Coll Cardiol. 2010;55(18):1945–1954.)*

GAS EXCHANGE VARIABLES DEFINING ORGAN-SPECIFIC LIMITATIONS

A number of variables have been considered in the interpretation of results from CPET. Such variables are measured directly or are derived, and those used clinically have not changed to any large degree for more than two decades.[1,2] Nevertheless, appreciation of the utility of CPET measurements has evolved.[3] An overview of each, along with a highlight of its physiologic significance, is presented in Table 32-1. A basic premise in considering the aggregate measurements is that the best diagnostic potential comes from the measurements' *integrated* use and interpretation using 9-plot analysis, as originally proposed by Wasserman and coworkers.[5]

■ $\dot{V}O_2$, $\dot{V}O_{2max}$, and peak $\dot{V}O_2$

$\dot{V}O_2$ is the principal parameter examined during CPET, as it represents the patient's functional capacity and embodies all the complex interactions of organ systems involved in O_2 transport. The highest $\dot{V}O_2$ achieved during an incremental work-rate test is $\dot{V}O_{2max}$, defined as the $\dot{V}O_2$ at the plateau achieved during incremental exercise, as measured in healthy individuals, including athletes. In clinical practice, the plateau is usually preceded by occurrence of exercise-limiting symptoms. The gold standard measurement for cardiorespiratory fitness is $\dot{V}O_{2max}$.

Peak $\dot{V}O_2$ is defined as the maximal $\dot{V}O_2$ attained at maximal effort, averaged over a 20- to 30-s period. It is a useful measure of the functional capacity of deconditioned subjects and patients with cardiopulmonary disorders. Peak $\dot{V}O_2$, expressed as percent predicted and normalized for age, sex, and weight, describes the subject's overall functional capacity.

■ $\dot{V}O_2$ versus Work Rate

Under physiologic conditions, $\dot{V}O_2$ rises linearly with increases in power output. Therefore, if $\dot{V}O_2$ is plotted versus external work rate (WR), the slope of the relationship ($\Delta\dot{V}O_2/\Delta WR$) indicates the efficiency of metabolic conversion of chemical potential energy to mechanical work, as well as the efficiency of the musculoskeletal system in producing mechanical work. In healthy individuals, $\Delta\dot{V}O_2/\Delta WR$ is about 8.5–11 mL/min/watt and is independent of sex, age, height, type of work, and rate of workload increase.

$\Delta\dot{V}O_2/\Delta WR$ provides important information on the coupling of external to internal (cellular) respiration, reflecting a subject's overall ability to generate aerobically produced ATP and any pathologic derangements that affect O_2 delivery (e.g., cardiac, pulmonary, or circulatory disorders) or the metabolic efficiency of muscles (e.g., mitochondrial myopathy); each leads to a reduction in $\Delta\dot{V}O_2/\Delta WR$. The slope is altered in the presence of deconditioning and may be flattened in cardiac failure.[17]

■ Ventilatory Measures

Ventilatory measures are a key component of CPET and include: total minute ventilation ($\dot{V}_E$), tidal volume (V_T), respiratory rate (RR), and breathing reserve (BR). BR is the difference between the maximal voluntary ventilation (MVV) and the maximum ventilation achieved during exercise.

The demand for increased V_E during exercise is driven by the rate of CO_2 production; hence, the rise in V_E with increasing VCO_2 reflects the efficiency of ventilation and is reported as the slope of V_E versus VCO_2. By convention, the relationship is measured at the anaerobic threshold (see below). A value <30 for the slope of V_E versus VCO_2 is considered normal; it increases slightly with aging.[18]

During progressive exercise, three domains for $\dot{V}_E$ kinetics can be discerned: (1) a linear increase from rest to the point of so-called isocapnic buffering; (2) a steeper region as the isocapnic buffering period begins, reflecting increased ventilatory drive due to CO_2 generation via buffering of increasing lactate levels; and (3) an upward shift after the so-called respiratory compensatory point (RCP), which is further sustained by an increase in ventilatory drive due to respiratory compensation for metabolic acidosis.

Analysis of the pattern of increases in $\dot{V}_E$ during progressive increases in exercise workload enables detection of clinically relevant fluctuations in the ventilation signal, for example, "exercise oscillatory ventilation" (EOV), defined as an oscillatory ventilatory

TABLE 32-1 Commonly Measured Variables During Clinical Cardiopulmonary Exercise Testing

Variable, Unit of Measurement	Description and Technical Considerations	Physiologic Significance	Normal Value/Response	Clinical Relevance
Peak $\dot{V}O_2$, mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ or % of appropriately selected predicted value	Highest O_2 uptake during exercise	Reflection of the patient's functional capacity, derived from the integrated function and interaction of pulmonary, cardiac, and skeletal muscle systems	Wide range, depending on age, sex, exercise habits, and genetic predisposition	Expression of aerobic exercise capacity
	When derived from breath-by-breath data reported as 10- to 60-s average, depending on protocol (i.e., shorter averaging interval for protocols with shorter stages and vice-versa)	In health, response is representative of the interaction between the functional components of the O_2 transport chain (i.e., delivery and extraction)	Normal range is wide: from $\sim$80 to $\sim$15 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ in an elite athlete and healthy 80-year-old woman, respectively	Measure of cardiovascular fitness in healthy persons
				Correlates with disease severity in a great variety of patient populations, including HF, HCM, PAH, secondary PH, COPD, ILD Broad prognostic marker
$\dot{V}O_2$ at Anaerobic Threshold, mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ or % of the predicted peak $\dot{V}O_2$	$\dot{V}O_2$ above which $\dot{V}_E$ and $\dot{V}CO_2$ equally accelerate	Defines the upper limit of exercise workloads that can be sustained for a prolonged time	$\sim$50%–65% of maximal/peak $\dot{V}O_2$	Responsive to aerobic training; is a measure of fitness
	Point of exercise $\dot{V}O_2$ above which aerobic energy ATP production is supplemented by anaerobic mechanisms	Starting point of the isocapnic buffering period	Higher with advanced age and endurance training	Useful to set a tailored training intensity for exercise prescription
Peak RER	$\dot{V}CO_2/\dot{V}O_2$ ratio at maximal exercise	With exercise progression, excessive CO_2 generation due to bicarbonate buffering compared to $\dot{V}O_2$, makes RER rise	Peak RER $\geq$1.10 commonly used as indication of excellent effort	Good indicator of subject effort
	When derived from breath-by-breath data reported as 10- to 60-s average, depending on protocol (i.e., shorter averaging interval for protocols with shorter stages and vice-versa)	Depends on baseline respiratory quotient, rate of lactate accumulation, hyperventilation, and extent of exercise above AT		Best noninvasive estimate of maximal exercise test
Breathing reserve (BR), %	Difference between the maximal voluntary ventilation (MVV) and the maximum exercise ventilation	Erosion of BR is typical of COPD; low BR also occurs in athletes	Usually >20%, but variance is wide; values <15% identify ventilatory mechanical limitation	Index of mechanical ventilatory constraints
	MVV can be either directly measured or estimated as $FEV_1 \times 35–40$ with some drawbacks to be considered (see text for explanation)			
V_E/VCO_2 slope	Relationship between V_E, plotted on the y-axis, and VCO_2 plotted on the x-axis; both variables in $L \cdot min^{-1}$	Represents ventilation-perfusion matching within the pulmonary system	<30 considered normal; slightly increases with ageing	Index of ventilatory efficiency
	Nonlinear data at starting exercise and near-maximal exercise, usually excluded from measurement			Correlates with disease severity in a great variety of patient populations including HF, HCM, PAH, secondary PH, COPD, ILD Prognostic marker in certain chronic disease populations

TABLE 32-1 Commonly Measured Variables During Clinical Cardiopulmonary Exercise Testing *(Continued)*

Variable, Unit of Measurement	Description and Technical Considerations	Physiologic Significance	Normal Value/Response	Clinical Relevance
$PetCO_2$, mm Hg	Partial pressure of CO_2 at the end of a tidal breath exhalation	Represents ventilation–perfusion matching within the pulmonary system	Rest: 36–42 mm Hg	Correlates with disease severity in a great variety of patient populations including HF, HCM, PAH, secondary PH, COPD, ILD
		Low values can also reflect acute or chronic hyperventilation (consider confirmation by arterial blood gas analysis)	Increases 3–8 mm Hg by AT; decreases from AT to maximal exercise	
$\dot{V}_E/\dot{V}O_2$ at peak exercise	When derived from breath-by-breath data reported as 10- to 60-s average, depending on protocol (i.e., shorter averaging interval for protocols with shorter stages and vice-versa)	Represents ventilatory cost of O_2 uptake at peak exercise testing	$\leq$40 (50 is considered the upper limit of normal)	Has diagnostic utility in patients with suspected mitochondrial myopathy
EOV	No universal definition: most commonly defined as an oscillatory pattern at rest that persists for $\geq$60% of the exercise test at an amplitude of $\geq$15% of the average resting value Recommend using 10 s averaged V_E data for plotting	Oscillatory ventilation during exercise reflects impaired CO reserve	The presence of EOV pattern is always pathologic	Prognostic marker in advanced HF
Oxygen pulse, mL $O_2 \cdot beat^{-1}$	Ratio between $\dot{V}O_2$ (mL $O_2 \cdot min^{-1}$) and HR (bpm)	Represents the amount of O_2 extracted per heartbeat	Curvilinear increase throughout exercise, with possible plateau near maximal effort	O_2 pulse profile provides valuable information on cardiorespiratory performance
		At a near maximal work rate, it is a surrogate of stroke volume	A premature plateau or down-sloping with increasing work rate suggest low or falling stroke volume (e.g., myocardial ischemia)	Prognostic marker in certain chronic disease populations
$\Delta\dot{V}O_2/\Delta WR$, mL $\cdot$ $min^{-1} \cdot W^{-1}$	Relationship between $\dot{V}O_2$, plotted on the y-axis in mL $\cdot$ min^{-1}, and workload, plotted on the x-axis in watts	Provides important information on the coupling of external to internal (cellular) respiration	Slope is linear with a normal value between 8.5 and 11 mL $\cdot$ $min^{-1} \cdot W^{-1}$ (on average 10 mL $\cdot$ $min^{-1} \cdot W^{-1}$) Deconditioning and initial cardiac limitation make this relationship shallow Flattening or down-sloping have been described in advanced heart failure	$\Delta\dot{V}O_2/\Delta WR$ profile provides valuable information on cardiocirculatory performance
Heart rate (bpm) vs. $\dot{V}O_2$ relationship	HR increase along incremental workload	Reflects chronotropic competence and cardiac response to exercise	Increase ~10 beats per 3.5 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ increase in $\dot{V}o_2$, achieve at least 85% of age-predicted maximal HR with good effort	Index of cardiac response to exercise
				Peak HR should not be used to define effort level nor maximal exercise test
Heart rate reserve, %	Difference between the age-predicted maximal HR (calculated as 220 – age) and the maximal HR achieved during exercise	Reflects chronotropic competence and cardiac performance	>70%	Index of chronotropic incompetence (CI) CI predicts the cardiovascular risk in apparently healthy subjects CI is a prognostic marker in certain chronic pathologic conditions

(continued)

TABLE 32-1 Commonly Measured Variables During Clinical Cardiopulmonary Exercise Testing *(Continued)*

Variable, Unit of Measurement	Description and Technical Considerations	Physiologic Significance	Normal Value/Response	Clinical Relevance
Heart rate recovery, beats	Difference between maximal exercise HR and HR 1 min into recovery	Mirrors the speed of parasympathetic reactivation	$>$12 beats	Prognostic marker in subjects without cardiovascular diseases Prognostic marker in certain chronic disease populations
Exercise BP, mm Hg	BP increase along incremental workload	Reflects cardiovascular response to exercise and left ventricular afterload	SBP increase ~10 mm Hg per 3.5 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ increase in $\dot{V}O_2$ Upper range of normal maximal SBP is ~210 mm Hg for males and ~190 mm Hg for females DBP remains the same or slightly decreases	Index of cardiac response to exercise and left ventricular afterload
SpO_2, %	Noninvasive measurement of the percent of saturated hemoglobin in the capillary bed by pulse oximetry	Exercise hypoxemia is common in many lung diseases and right-to-left shunt	$\geq$95% at rest and throughout exercise	Desaturation is common in patients with COPD, ILD, PAH/secondary PH as disease severity advances
	Accuracy may vary according to device, perfusion, motion, and ambient light		Decrease by $>$5% suggests abnormal oxygenation	May have diagnostic utility in characterizing unexplained exertional dyspnea
FEV_1 ($L \cdot min^{-1}$) pre- and post-CPET	Forced expiratory volume in 1 s	Component of pulmonary function	$<$15% reduction from pre- to post-exercise test	May have diagnostic utility in characterizing unexplained exertional dyspnea (e.g., exercise-induced bronchospasm)

AT, anaerobic threshold; ATP, adenosine triphosphate; BP, blood pressure; bpm, beats per minute; BR, breathing reserve; CI, chronotropic incompetence; COPD, chronic obstructive pulmonary disease; CPET, cardiopulmonary exercise testing; DBP, diastolic blood pressure; EOV, exercise oscillatory ventilation; FEV_1, forced expiratory volume in 1 s; HCM, hypertrophic cardiomyopathy; HF, heart failure; HR, heart rate; ILD, interstitial lung disease; MVV, maximal voluntary ventilation; O_2, oxygen; PAH, pulmonary arterial hypertension; $PetCO_2$, partial pressure of end-tidal carbon dioxide; PH, pulmonary hypertension; RER, respiratory exchange ratio; SBP, systolic blood pressure; SpO_2, saturation of peripheral oxygen; VCO_2, carbon dioxide production; V_E, minute ventilation; $\dot{V}O_2$, oxygen consumption; W, watt; WR, work rate.

Data from Guazzi M, Adams V, Conraads V, et al. Clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. Circulation. 2012;126(18):2261–2274 and Arena R, Sietsema KE. Cardiopulmonary exercise testing in the clinical evaluation of patients with heart and lung disease. Circulation. 2011;123(6):668–680.

pattern at rest that persists for ≥60% of the exercise test at an amplitude of ≥15% of the average resting value.[3] Notably, EOV is seen in 20% to 30% of cases of HF (Fig. 32-5).

During low levels of exercise, an increase in V_T is the first physiologic step in augmenting V_E. Thereafter, both V_T and RR increase through 70% to 80% of peak exercise; in the last phase of achieving maximal exercise, the contribution of RR predominates. V_T usually increases 3- to 5-fold in younger subjects, while older adults demonstrate a 2- to 4-fold increase. RR typically increases up to 3-fold. In most healthy subjects, peak exercise ventilation approaches 70% of MVV (BR is typically greater than 15% of the MVV); it varies according to fitness level and age. MVV can be measured directly, or it can be estimated as $FEV_1 \times 35–40$.[19–21] In daily practice, ventilatory capacity is assessed by measuring MVV. A ventilatory mechanical limitation is identified if peak V_E is <15% of MVV. This approach is practical but likely flawed due to the lack of reproducibility of breathing rate and tidal volume when MVV curves are superimposed on flow–volume loops near peak exercise. Indeed, MVV is performed at high respiratory rates, during which end-expiratory lung volume is increased. Conversely, during exercise, end-expiratory lung volume is reduced, resulting in more advantageous positioning of the pressure-volume relationship and a lower work of breathing (Fig. 32-6).

At a moderate level of work, the partial pressure of end-tidal carbon dioxide ($PetCO_2$) increases, while the partial pressure of end-tidal oxygen ($PetO_2$) decreases; the changes occur in parallel with changes in $\dot{V}_E/\dot{V}O_2$. $PetO_2$ and $\dot{V}_E/\dot{V}O_2$ reach their nadirs near the anaerobic threshold (see below), prior to increasing as exercise effort becomes more intense. Meanwhile, $PetCO_2$ initially slightly increases, and then stabilizes, until the subsequent increase in $\dot{V}_E/\dot{V}CO_2$ (close to RCP), when $PetCO_2$ falls in tandem with a continuous increase in $PetO_2$.

CPET measurements allow an estimate of ventilation-to-perfusion ($\dot{V}/\dot{Q}$) matching during exercise, reflected in the V_D/V_T ratio, as well as ventilatory efficiency, indicated by V_E/VCO_2. When $\dot{V}/\dot{Q}$ is uniform, V_D/V_T is low. Indeed, V_D/V_T represents the fraction of

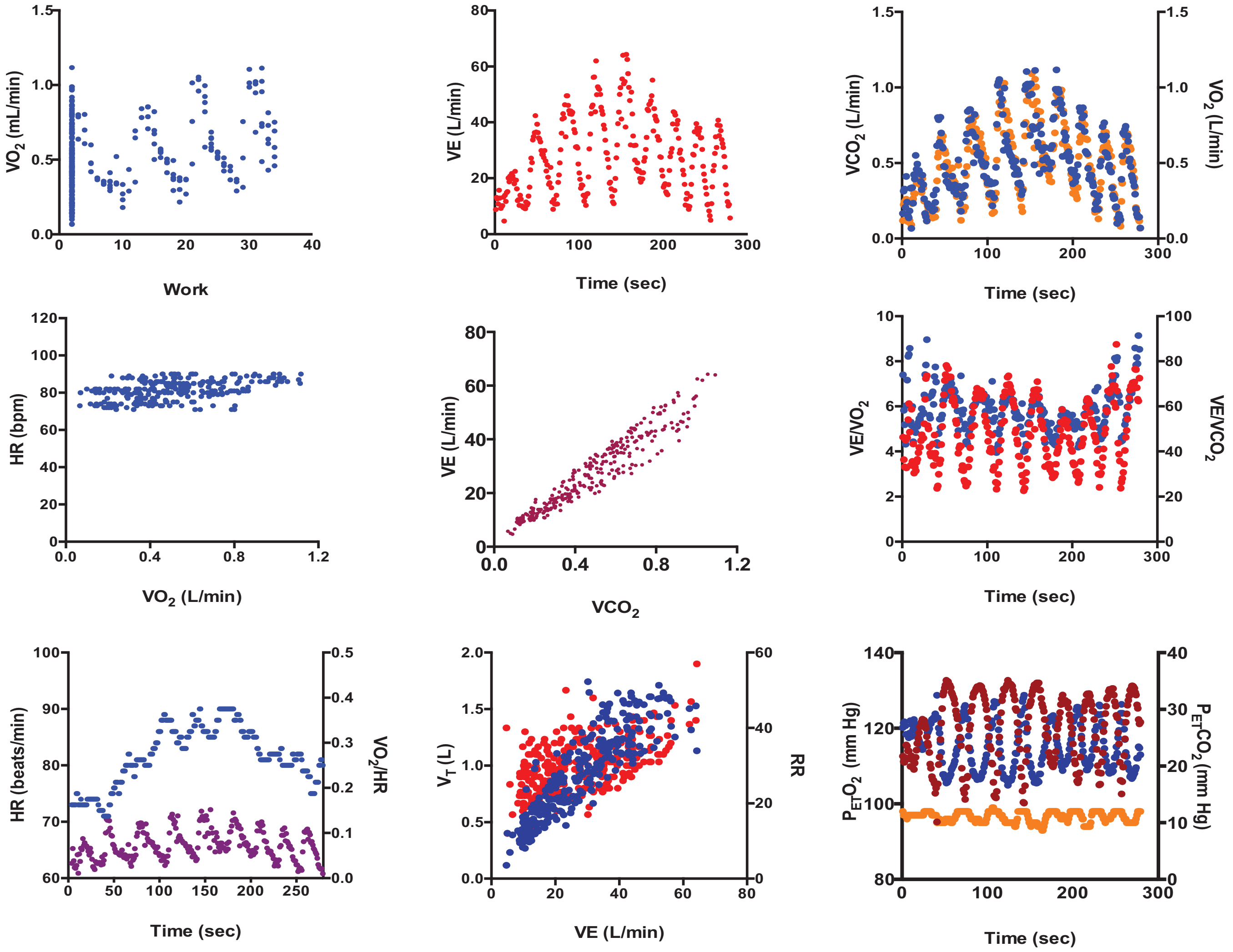


Figure 32-5 Nine-plot analysis demonstrating a typical EOV pattern. *(Reproduced with permission from Guazzi M, Bandera F, Ozemek C, et al. Cardiopulmonary Exercise Testing: What Is its Value? J Am Coll Cardiol. 2017;70(13):1618–1636.)*

each breath that is “wasted” in ventilating anatomic and physiologic dead space (i.e., nonperfused alveoli). Under physiologic conditions, V_D is approximately one-third of V_T and, during exercise, it drops to one-fifth. Accurate measurement of V_D/V_T requires arterial blood sampling. In fact, use of $PetCO_2$ to noninvasively estimate $PaCO_2$ can be misleading and may result in overestimation of V_D/V_T in normal subjects, or underestimation in patients with lung disease.

Another important parameter useful in assessing gas exchange during exercise is the alveolar–arterial oxygen gradient, $P(A–a)O_2$. Normally, $P(A–a)O_2$ is <10 mm Hg at rest; it may normally increase up to 20–30 mm Hg during exercise. However, values greater than 35 mm Hg likely indicate a gas exchange abnormality. The value for $P(A–a)O_2$ is dependent on $\dot{V}/\dot{Q}$ mismatching, right-to-left shunt, O_2 diffusion limitations, mixed venous O_2 content, and the time available for diffusion equilibrium of O_2 between alveoli and red blood cells.

■ CO_2 Output

The rate of CO_2 production ($\dot{V}CO_2$) correlates strongly with the level of ventilation (V_E). Moreover, control of CO_2 levels is important in blood pH homeostasis. When anaerobic metabolism prevails following attainment of the anaerobic threshold (see below), bicarbonate buffering of the increased lactic acid produced generates additional CO_2 that, in turn, increases ventilatory drive. Following attainment of the anaerobic threshold, the relationship between $\dot{V}CO_2$ and WR becomes steeper. $\dot{V}CO_2$ is used in calculating a number of derived variables, including the respiratory exchange ratio (RER), that is, $VCO_2/\dot{V}O_2$, and the respiratory quotient (RQ).

■ Respiratory Exchange Ratio

The respiratory exchange ratio (RER) is the ratio of $\dot{V}CO_2$ to $\dot{V}O_2$. Under steady state conditions, RER is equal to the respiratory quotient (RQ). The value for RQ depends on the fuels used for metabolism and energy production. An RQ of 1.0 indicates metabolism of primarily carbohydrates, whereas an RQ of 0.7 to 0.8 indicates metabolism of a mixture of carbohydrates and fat or protein. During CPET, a measured RER >1.0 suggests lactic acidosis or hyperventilation. RER is the best non-invasive indicator of exercise effort; when RER ≥ 1.10, exercise effort is usually considered maximal.[22]

■ Anaerobic Threshold

The anaerobic threshold (AT), or lactic acid threshold, represents the $\dot{V}O_2$ during progressive exercise above which aerobic energy used to produce ATP is supplemented by anaerobic mechanisms, resulting in increases in muscle and plasma lactate levels. Due to effective hydrogen ion buffering by the bicarbonate system, initially, blood pH remains constant. Subsequently, with progression of exercise effort, the net increase in lactic acid accumulation overcomes the buffering

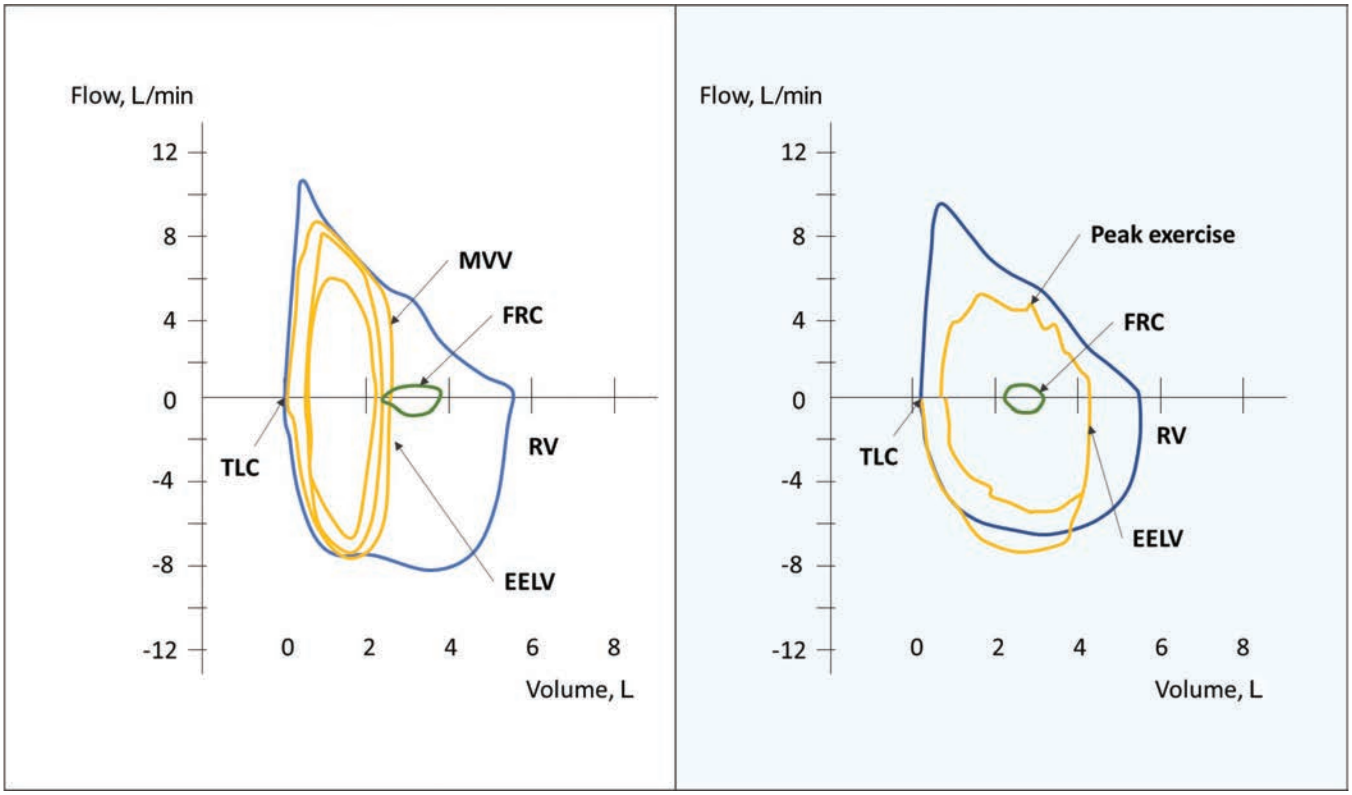


Figure 32-6 Comparison of the flow–volume loops obtained during a maximal voluntary ventilation (MVV) maneuver ***(left)*** and near maximal incremental exercise ***(right)***, in the same healthy subject. The MVV is performed at high lung volumes, as EELV is increased, thus producing a high elastic load and requiring large expiratory pleural pressures to obtain high flows in early expiration; the work of breathing is increased. In contrast, during exercise, EELV is reduced, resulting in tidal breathing at a more advantageous position of the pressure–volume relationship of the lungs and chest wall; consequently, work of breathing is reduced. Blue line, maximal flow–volume loop; yellow line, MVV maneuver (left, white panel) and incremental exercise (right, light blue panel); green line, rest tidal breathing; EELV, end-expiratory lung volume; FRC, functional residual capacity; MVV, maximal voluntary ventilation; RV, residual volume.

capacity and pH gradually decreases. This development identifies the "respiratory compensation point" (RCP). The exercise interval between the AT and RCP is called the *isocapnic buffering period*. During isocapnic buffering, the excess CO_2 generated is buffered by bicarbonate; exercise beyond the RCP triggers increased ventilation as compensation for the developing metabolic acidosis.

The main determinants of the increase in $\dot{V}O_2$ during the isocapnic buffering period are the rate of lactic acid production; the availability of bicarbonate for hydrogen ion buffering; and the partial pressure of CO_2 in arterial blood ($PaCO_2$), which is regulated by the chemoreceptors.[23] In healthy subjects, the AT occurs at 50% to 65% of peak $\dot{V}O_2$ and is influenced by age and the level of aerobic training.[3] AT can be determined invasively (through measurement of lactic acid and bicarbonate concentrations) or noninvasively (through V-slope analysis and measurement of "ventilatory equivalents") (Table 32-2). The noninvasive methods are more useful in clinical practice.

■ Heart Rate versus $\dot{V}O_2$ Relationship

During normal exercise, tissue perfusion increases as the metabolic requirements increase. The relationship of CO to increasing $\dot{V}O_2$ is nearly linear, with an approximate 6-mL/min increase in CO for every 1-mL/min increase in $\dot{V}O_2$.[24]

The increase in CO is initially achieved by increases in stroke volume (SV) and heart rate (HR). At moderate- to high-intensity exercise, a physiologic plateau to increases in SV is noted, and HR becomes the main variable contributing to further increases in CO. The increases in HR are primarily mediated by reduced vagal tone and, secondarily, by increased sympathetic activity. The difference between the age-predicted maximal HR (calculated as 220 − age, in years) and resting HR is referred to as the "HR reserve" (HRR). A useful index is calculation of HRR as a percentage of age-predicted maximal HR:

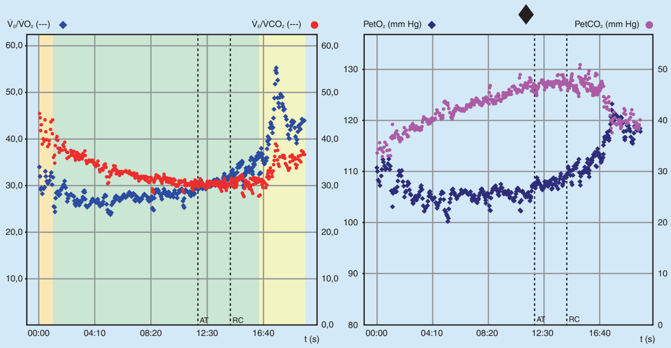
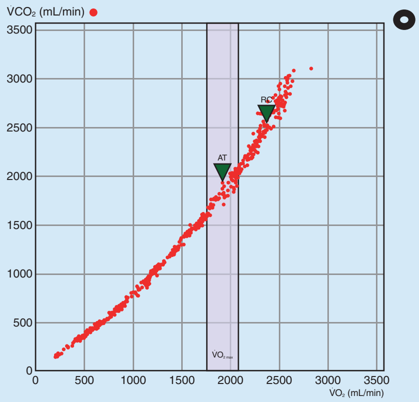
$$\frac{\text{peak exercise HR-rest HR}}{\text{peak exercise HR-age predicted maximal HR}}$$

HRR <80% of age-predicted maximal HR defines "chronotropic incompetence" and may signal that the impairment in exercise performance is due to deconditioning.[25] CI is an important contributor to exercise intolerance and an independent predictor of worse outcome in subjects with and without previous cardiovascular events.[25]

■ O_2 Pulse

O_2 pulse is defined as the ratio of $\dot{V}O_2$ to HR; it reflects the amount of O_2 consumed per heart beat. Since $\dot{V}O_2/HR = SV \times (CaO_2 - CvO_2)$, the increase in O_2 pulse during exercise depends on stroke volume and the arterial-venous O_2 content difference. At near maximal work rate, $(CaO_2 - CvO_2)$ is assumed to be maximized and constant; therefore, a change in O_2 pulse directly reflects a change in SV under these conditions. Evaluation of the O_2 pulse profile may provide valuable information on cardiopulmonary performance. Under normal conditions, O_2 pulse increases curvilinearly with progressive exercise, as there are well-known limits to increases in SV at peak exercise.

TABLE 32-2 Invasive and Noninvasive Methods for AT Determination

	Variable	AT Definition	Observations and Pitfalls	Graphical Example and Explanation
Invasive determination	Arterial lactate	$\dot{V}O_2$ at which the blood lactate level increases	• Multiple blood sampling is required • The precise definition remains controversial	*There are several mathematical models for the AT determination.*
	Arterial standard bicarbonate	$\dot{V}O_2$ at which the arterial standard bicarbonate decreases	• Multiple blood sampling is required • The precise definition remains controversial • It represents an acceptable alternative if lactate cannot be measured	
Noninvasive determination	Ventilatory equivalents method: simultaneous analysis of $\dot{V}_E$/$\dot{V}O_2$, $\dot{V}_E$/$\dot{V}CO_2$, $PetO_2$, and $PetCO_2$	$\dot{V}O_2$ at which $\dot{V}_E$/$\dot{V}O_2$ and $PetO_2$ reach a minimum and thereafter start to rise, coinciding with an unchanged $\dot{V}_E$/$\dot{V}CO_2$ and $PetCO_2$ slope	• Many factors can prevent proper identification of AT: irregular breathing, an inappropriate rate of increase in work rate, suboptimal plotting scales, or a poor patient ventilatory response; • a dual method approach (combined assessment of ventilatory equivalents and V-slope method) is recommended to minimize errors	
	V-slope method	$\dot{V}O_2$ at which the slope of $\dot{V}CO_2$ to $\dot{V}O_2$ relationship changes		

Diamonds: $\dot{V}_E$ and $\dot{V}CO_2$ initially accelerate equally above the AT. Therefore, $\dot{V}_E$/$\dot{V}O_2$ and $PetO_2$ increase, whereas $\dot{V}_E$/$\dot{V}CO_2$ and $PetCO_2$ remain constant (isocapnic buffering period). As the work rate further increases, decreasing pH acts as a strong stimulus for ventilatory drive augmentation. Consequently, V_E/VCO_2 increases, and $PaCO_2$ and $PetCO_2$ decrease, while there is a further increase in $\dot{V}_E$/$\dot{V}O_2$ and $PetO_2$. This point corresponds to the RCP.

Circles: At the beginning of exercise, $\dot{V}CO_2$ increases linearly with increases in $\dot{V}O_2$. Since the relation between O_2 consumption and CO_2 production is almost equimolar, the early slope of the relationship (S1) is slightly less than 1.0. Thereafter, the slope increases sharply (S2) due to excessive CO_2 generation from bicarbonate buffering of the increased lactic acid produced. The intercept of S1 and S2 identifies the anerobic threshold (AT).

■ Blood Pressure Response

During exercise, a reflex increase in sympathetic tone causes vasoconstriction in nonworking muscles, while release of local mediators is responsible for intense vasodilation in working muscles (a phenomenon necessary for balancing oxygen supply and demand). The net result is a fall in systemic vascular resistance. Although systolic blood pressure typically rises progressively as work rate increases, diastolic blood pressure usually remains constant or declines slightly.

■ Flow–Volume Loop Analysis

Complementary information on the source and degree of ventilatory limitation to exercise may be derived by analysis of the flow-volume loop (FVL). Indeed, examination of the FVL may explain expiratory airflow limitation and changes in lung volumes during increased physical effort.[26] "Ventilatory demand" versus "ventilatory capacity" measures can be obtained by plotting exercise tidal flow–volume loops (extFVLs) along with the maximal flow–volume loop (MFVL). Accurate alignment of the loops is crucial for reproducible, accurate analysis. Precise knowledge of any changes in end-expiratory lung volume during exercise, relative to rest, is required and may be inferred from changes in inspiratory capacity, periodically measured during the exercise test.

By plotting extFVLs and MFVL, valuable information on the ventilatory response and any ventilatory constraints can be derived. During spontaneous breathing, encroachment of V_T on the expiratory limb of the flow–volume envelope of the MFVL identifies the amount of expiratory flow limitation. In addition, an increase in end-expiratory lung volume relative to resting volume identifies development of dynamic hyperinflation. Finally, encroachment of tidal inspiratory flow rates on the inspiratory limb of the MFVL indicates that that the ability of the inspiratory muscles to generate pressure and flow is approaching a maximum.

Flow limitation and dynamic hyperinflation have been extensively studied in patients with COPD.[27] However, the significance of, and influence on, exercise performance of flow limitation and lung volume changes remain to be elucidated in other populations, including patients with heart failure, athletes, and the elderly.[1]

CLINICAL APPLICATION OF CPET IN CARDIOPULMONARY DISORDERS

CPET is used in the clinical evaluation of a wide variety of respiratory and cardiac disorders, including investigation of patients with unexplained dyspnea, possible exercise-induced bronchospasm, obstructive lung disease, a wide variety of interstitial lung diseases, and underlying pulmonary vascular disorders. CPET is also employed in assessing patients for general surgery risk; in anticipation of lung resection, volume reduction surgery, or heart or lung transplantation; and in functional evaluation of patients with heart failure.

■ Unexplained Dyspnea

Two main categories of patients with dyspnea can be distinguished: (1) those with new onset of breathing discomfort, and (2) those experiencing worsening breathlessness due to a known cardiovascular, respiratory, or neuromuscular disease. In the former group, clinical evaluation is directed toward establishing a diagnosis; in the latter, the goal is discriminating between the underlying disease and superimposition of a new, pathologic condition.[28]

Initial evaluation, including a meticulous medical history, physical examination, and basic screening tests, such as spirometry, chest radiograph, electrocardiogram, selected blood tests, and, usually, an echocardiogram, may uncover the root cause of the patient's exertional dyspnea. When this first level of evaluation is inconclusive or nondiagnostic, CPET, by providing breath-by-breath analysis of ventilation, pulmonary gas exchange, and cardiac function at rest and during incremental exercise, may help in identification of a specific diagnosis (e.g., exercise-induced arrhythmias, chronotropic incompetence, myocardial ischemia, hyperventilation syndromes, exercise-induced bronchoconstriction, or HFpEF).[29–34]

A useful alternative approach to simplification of the differential diagnosis of dyspnea is categorization of abnormalities as cardiovascular (reduced O_2 delivery), ventilatory, or peripheral/muscular (reduced O_2 utilization) in nature. The patient population undergoing CPET for evaluation of unexplained dyspnea on exertion is highly heterogeneous and includes subjects with neuromuscular, hormonal, myopathic, metabolic, and psychogenic conditions.[1] CPET may be useful in defining the degree of exercise intolerance and assessing pathophysiologic contributions to the patient's dyspnea.[1,3,5] For example, CPET may help discriminate pulmonary mechanical and pulmonary vascular limitations to exercise effort and distinguish disorders due primarily to central cardiovascular dysfunction versus those due to impaired O_2 extraction in the periphery.[35,36]

■ Evaluation of Patients with Respiratory Disease

CPET is commonly utilized in evaluating patients with a wide variety of pulmonary disorders, including obstructive airway disease, interstitial lung disease, and pulmonary vascular disorders.

Chronic Obstructive Pulmonary Disease (COPD)

Dyspnea and fatigue are hallmarks of the exercise limitation noted in patients with COPD (i.e., emphysema and chronic bronchitis).[37] The major elements contributing to the dyspnea include a decreased ventilatory capacity and an increased ventilatory requirement. The limited ventilatory capacity is caused by increased airway resistance, variably combined with reduced lung elastic recoil. The increased ventilatory requirement is principally due to ventilation-perfusion mismatching.

In emphysema, lung compliance is increased, and respiratory system relaxation volume (i.e., the point of balance between the inwardly directed elastic recoil pressure of the lung and the outwardly directed recoil pressure of chest wall) elevated. This pathophysiologic condition is known as "static lung hyperinflation." In patients with airflow limitation, the increased ventilatory demand of exercise, along with insufficient expiratory time, contribute to air trapping. As a result, end-expiratory lung volume (EELV) fails to decline to normal, leading to dynamic hyperinflation (Fig. 32-7). The magnitude of hyperinflation varies with the degree of resting lung hyperinflation, the severity of expiratory flow limitation, and the breathing pattern. Dynamic hyperinflation causes a critical reduction in inspiratory reserve volume (IRV) (i.e., the ability to augment V_T is impaired), inspiratory muscle weakness, and increased work of breathing. A substantial disparity arises between respiratory muscle effort and the resultant V_T response ("neuromechanical uncoupling"), and cardiac hemodynamics are potentially adversely affected.[38] Even in nonhyperinflated patients with moderate-to-severe COPD, progressive constraining of increases in V_T as IRV is reduced influences development of dyspnea and contributes to exercise limitation.[39]

Hence, exercise intolerance in patients with moderate or severe COPD is characterized by erosion of the ventilatory reserve ($\dot{V}_E$/MVV), which may approach or exceed 100%. Breathing adaptations consist of an increase in respiratory rate and reduction in tidal volume, resulting in a reduction in alveolar ventilation. As a result, inadequate alveolar ventilation may result in CO_2 accumulation, evident as increases in $PetCO_2$ and $PaCO_2$. Dynamic hyperinflation, resultant reduction in inspiratory capacity, and increased work of breathing further contribute to a ventilatory limitation to exercise, which may be observed prematurely, even before the AT is reached. $P(A–a)O_2$ is usually elevated, especially when P_aO_2 decreases due to underventilation of perfused alveolar units A higher nadir of the plot of V_E versus VCO_2, and a steeper plot of V_E versus VCO_2 compared to normal, reflect the increase in V_D.[40]

Another parameter related to V_E and VCO_2 appears to better depict the magnitude of the increase in V_D: the V_E intercept (V_{Eint}).[41] V_{Eint} represents the ventilatory requirement when pulmonary gas exchange is absent (i.e., $VCO_2 = 0$). Higher values of V_{Eint} characterize the ventilatory performance of patients with COPD compared to patients with heart failure who have a similar maximal exercise capacity.[42,43] Higher values of V_E*int* also directly mirror the progression of functional impairment from mild to end-stage COPD.[44]

Interestingly, exercise-related desaturation occurs more frequently in patients with predominant emphysema than in those with predominant chronic bronchitis.

Finally, a role for CPET in the prognostic evaluation of patients with COPD[45] and in monitoring treatment aimed at improving breathing strategy or reducing dynamic hyperinflation has been demonstrated.[46]

Interstitial Lung Disease (ILD)

Interstitial lung diseases are characterized by deranged lung mechanics, reduced functional pulmonary capillary bed, and reduction in the total number of functioning lung units. Dyspnea with exercise is common in patients with ILD. Multiple mechanisms contribute to the increased ventilatory demand in these patients: (1) exaggerated dead space ventilation (i.e., increased V_D/V_T), (2) ventilatory inefficiency (i.e., increased V_E/VCO_2), (3) hypoxemia, (4) early onset of metabolic acidosis, (5) possible concomitant pulmonary

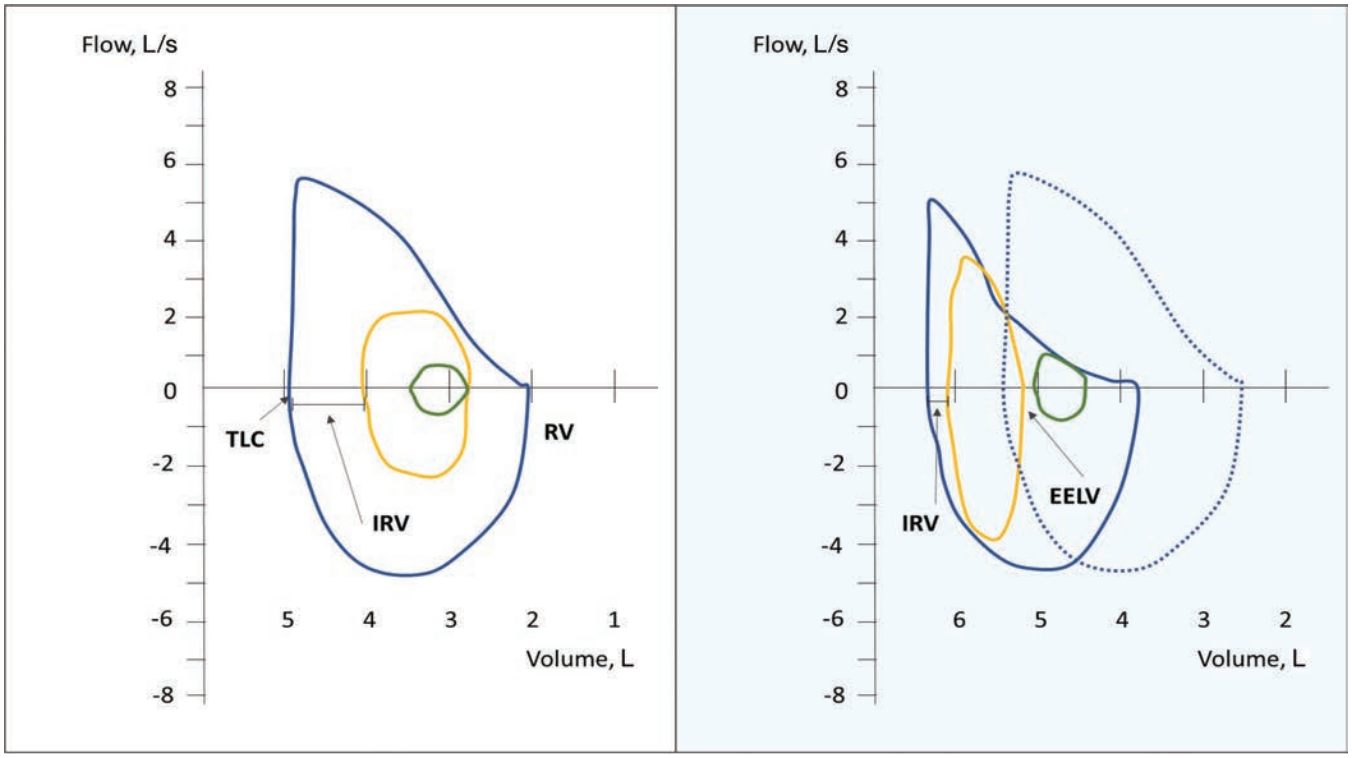


Figure 32-7 Comparison of tidal flow–volume loops at rest and during exercise in a healthy subject ***(left)*** and a typical patient with COPD ***(right)***. Shown are maximal flow–volume loops (MFVL). Notable observations regarding ventilatory demand versus ventilatory capacity in the patient with COPD include: (1) Expiratory flow limitation (encroachment of V_T during spontaneous breathing on the expiratory limb of the flow–volume envelope of the MFVL) identifies the magnitude of expiratory flow limitation at rest and during exercise. (2) Dynamic hyperinflation occurs during exercise (identified by the increase in end-expiratory lung volume relative to resting volume). (3) Progressive erosion of inspiratory reserve volume leads to critical constraints on tidal volume expansion (as reflected in the closeness of tidal inspiratory flow rates and the inspiratory limb of the MFVL). Blue line, maximal flow–volume loop; yellow line, incremental exercise; green line, rest tidal breathing; dot blue-line, predicted flow-volume loop; COPD, chronic obstructive pulmonary disease; EELV, end-expiratory lung volume; IRV, inspiratory reserve volume; RV, residual volume; TLC, total lung capacity. *(Reproduced with permission from O'Donnell DE, Banzett RB, Carrieri-Kohlman V, et al. Pathophysiology of dyspnea in chronic obstructive pulmonary disease: a roundtable. Proc Am Thorac Soc. 2007;4(2):145–168.)*

hypertension, (6) derangement of lung mechanoreceptor responses, and (7) increased central respiratory drive. Because of a mechanical limitation for increasing tidal volume, $\dot{V}_E$ increases primarily due to an augmentation in respiratory rate, except for very early exercise. A reduced ventilatory reserve also is frequently present.

During physical effort, most patients with ILD experience an abnormal widening in $P(A–a)O_2$ and arterial desaturation, likely the result of $\dot{V}/\dot{Q}$ mismatching, thickening of the alveolar capillary membrane, destruction of the pulmonary capillary bed, and hypoxic pulmonary vasoconstriction.[47,48] Cardiovascular limitations may play a concomitant role, particularly when pulmonary vascular disease and right ventricular dysfunction are present.

With some limitations, it may be possible to identify CPET responses specific for different types of ILD.[49] Patients with interstitial pulmonary fibrosis (IPF) usually experience arterial desaturation and abnormal pulmonary gas exchange with widening of the alveolar–arterial oxygen tension gradient that is greater than that seen in those with sarcoidosis or cryptogenic fibrosing alveolitis–scleroderma type. In addition, concomitant pulmonary hypertension is much more common in IPF. Patients with sarcoidosis may have a higher incidence of cardiovascular abnormalities due to myocardial involvement.

CPET is a sensitive test for unmasking subtle pulmonary gas exchange abnormalities not revealed by routine testing. Peak $\dot{V}O_2$, reduced ventilatory efficiency (i.e., increased V_E/VCO_2), and exercise-induced hypoxemia have each been reported to have prognostic value in ILD,[48] although a systematic review failed to draw definite conclusions on the utility of CPET in patients with ILD in everyday clinical practice.[50]

Pulmonary Vascular Disease

Patients with pulmonary vascular disease (e.g., pulmonary arterial hypertension [PAH], pulmonary embolism, chronic thromboembolic pulmonary hypertension [CTEPH], and pulmonary vasculitis) have abnormally high pulmonary vascular resistance (PVR). During exercise, the elevated PVR prevents physiological recruitment of the pulmonary vascular bed and an appropriate increase in pulmonary blood flow, leading to hypoperfusion of ventilated alveoli (i.e., $\dot{V}/\dot{Q}$ mismatch). Because of the increase in alveolar dead space ventilation (i.e., overventilation of the hypoperfused alveoli), minute ventilation is increased and $PetCO_2$ reduced. Exercise limitation is, therefore, characterized by an increase in the slope of the V_E/VCO_2 relationship (i.e., inefficient ventilation), an increase in V_D/V_T and in pulmonary artery pressures, and arterial hypoxemia, evident as an increase in $P(A\text{-}a)O_2$. Additionally, a reduction in AT and flattening of the O_2 pulse may be seen due to superimposed right ventricular dysfunction secondary to pressure overload and an inability to maintain adequate CO. The typical breathing pattern is reduced V_T and increased RR (presumably due to mechanical stimulation of "J-receptors," along with hyperactivation of the sympathetic nervous system, chemoreceptor hypersensitivity, and stimulation of chemoreceptors by hypoxemia). Nearly 20% of patients with significant pulmonary vascular disease experience arterial desaturation from right-to-left shunting across a patent foramen ovale.

A large body of evidence emphasizes the utility of variables measured during CPET in assessing disease severity and in predicting survival and time to clinical worsening in patients with PAH and CTEPH. In particular, peak $\dot{V}O_2$, V_E/VCO_2, and arterial oxygen saturation have been demonstrated to better predict prognosis than resting hemodynamics and lung function measurements.[51,52]

Evaluation of General Surgery Risk

CPET has a role in predicting perioperative risk in noncardiopulmonary surgical procedures. Furthermore, current literature suggests that variables measured during performance of CPET outperform alternative methods of preoperative risk stratification; they can be used as complementary tools to refine predictions of perioperative risk[53] and postoperative complications.[54] The parameters most often examined are peak $\dot{V}O_2$, AT, and V_E/VCO_2 at AT. However, the selection of variables and threshold values considered differ according to the surgical procedure planned and the patient's underlying medical conditions.[53]

In addition to its value in preoperative risk profiling, CPET measurements may guide optimization of comorbidities and preoperative exercise training, help direct the choice of procedure to be utilized, and inform aspects of postoperative care.[55] Further studies are needed to optimize use of CPET in this setting and to heighten awareness of the value of the physiologic data provided—data that have been clinically underutilized to date (e.g., chronotropic incompetence is predictive of postoperative outcome, but is still rarely reported).[56] In addition, CPET can be used in development of multiparametric risk prediction models, which include putative risk factors, biomarkers, noninvasive imaging, and objective measures of functional capacity.[57]

Evaluation for Lung Resection and Lung Volume Reduction Surgery

Lung cancer is common among patients with COPD. Although surgical resection is currently the most effective therapeutic approach for localized non–small-cell lung cancer, it carries a significant perioperative risk in patients with underlying lung disease. Along with spirometry and measurement of diffusion capacity of the lung for carbon monoxide (D_LCO), CPET has emerged as a powerful tool for risk stratification of patients with moderate or high perioperative risk.[58]

Major clinical guidelines (e.g., those of the ERS/European Society of Thoracic Surgeons, American College of Chest Physicians, and British Thoracic Society) recommend performing CPET in the preoperative evaluation of patients with lung cancer prior to lung resection. In this context, peak $\dot{V}O_2$ is the most useful prognostic parameter. A peak $\dot{V}O_2$ <15 mL/kg/min or a peak $\dot{V}O_2$% <50%–60% predicted are independent markers of increased morbidity, including postoperative complications, and mortality.[45]

Lung volume reduction surgery (LVRS) for patients with severe emphysema has been associated with improvement in survival, quality of life, and exercise capacity.[59] In patients with predominantly upper-lobe emphysema, CPET can be used to delineate the subgroup of patients who benefit more from LVRS compared with standard medical treatment alone. Indeed, a preoperative peak WR <25 W for females and <40 W for males is associated with the most favorable cost-effective outcome at 3 years.[60]

Evaluation for Heart or Lung Transplantation

A number of landmark clinical trials have addressed the role of CPET in the prognostic evaluation of patients with heart failure and in prioritization of patients for heart transplantation.[61–63] Current guidelines recommend using CPET to guide transplant listing.[64] Patients with a peak $\dot{V}O_2$ ≤14 mL/kg/min during a maximal CPET (or a peak $\dot{V}O_2$ ≤12 mL/kg/min if on beta-blocker therapy) and young females who achieve <50% predicted peak $\dot{V}O_2$ should be referred for cardiac transplant evaluation. In the case of submaximal CPET results (i.e., RER <1.05), a V_E/VCO_2 of >35 may be used as a criterion for listing. The best predictive power would likely derive from a multiparametric model incorporating $\dot{V}O_2$, V_E/VCO_2, AT, and oscillatory breathing.[65,66]

Despite the excellent prognostic power of CPET variables in assessing chronic lung diseases,[67–69] they have not been routinely used in selecting candidates for lung transplantation; nor are they currently recommended in international guidelines.[70] A consideration for the future is that CPET play a role in the setting of lung transplant evaluation, along with, or as a replacement for, the 6-minute walk test (6MWT) as a measure of exercise capacity.[71]

Exercise-Induced Bronchospasm

Exercise-induced bronchospasm (EIB) is defined as a fall in post-exercise FEV_1; it should be suspected in any patient who presents with dyspnea, wheezing, cough, or chest tightness during or shortly after exercise. A "challenge" test is useful in establishing a diagnosis of EIB and in validating use of inhaled bronchodilators in management of EIB. Comparative studies of chemical challenge, for example, using histamine or methacholine, versus exercise have demonstrated a lower sensitivity and higher specificity for exercise challenge.[29] EIB can usually be detected with incremental exercise testing, but it may be more evident using near-maximal, constant load exertion.[72] Importantly, a reduction in FEV_1 following a standardized exercise protocol may also be considered a specific index of asthma severity. Addition of cold air inhalation during the test increases the sensitivity.[73]

■ Evaluation of Patients with Cardiac Disease

Just as cardiac stress testing has a well-accepted role in evaluating patients with suspected coronary artery disease, CPET has proved very useful in clinical assessment of patients with heart failure.

Heart Failure

CPET has become the standard for functional assessment of the pathophysiologic basis of exercise intolerance in patients with heart failure, conveying impactful clinical and prognostic information.[7] Even though application of CPET has been well established in patients with advanced heart failure with reduced ejection fraction (HFrEF), in the last decade, data on patients with heart failure with preserved ejection fraction (HFpEF) have been reported. Each phenotype may demonstrate a similar extent of exercise intolerance, despite differing underlying pathophysiologic mechanisms and precipitating factors.[74]

Although results from CPET may be a strong predictor of future development of heart failure, caution is advised in its use as a primary diagnostic tool. Indeed, manifestations of heart failure are common in other chronic conditions (e.g., PAH, congenital heart defects, and interstitial lung diseases) which are characterized by a low peak$\dot{V}O_2$.[3] Accordingly, a consensus algorithm for the diagnosis of HFpEF incorporates use of CPET simply as an exclusionary initial test.[75] CPET would appear to be used most appropriately for investigating the underlying pathophysiologic consequences of heart failure, irrespective of etiology, for optimizing clinical decision-making, and for establishing a prognosis.

Pioneering studies in heart failure by Weber et al.[6] and Mancini et al.[62] introduced use of CPET into daily practice. Measurement of peak $\dot{V}O_2$ quickly became the standard for staging the severity of disease, unmasking the underlying pathophysiology, and addressing optimal timing for performing heart transplantation. The Weber classification,[62] based on four categories of peak $\dot{V}O_2$ and levels of cardiac index, facilitated establishment of many important advancements in the field.[76]

In the late 1990s, evidence for the role of abnormalities in V_E in patients with heart failure led to another useful observation: V_E/VCO_2 is a stronger predictor of adverse events than is peak $\dot{V}O_2$.[77] The advantages of V_E/VCO_2 over peak $\dot{V}O_2$ were confirmed by the effort-independent nature of the physiologic information provided,[3] as well as its prognostic utility, even in patients with a near normal peak $\dot{V}O_2$ (~18 mL/min/kg).[78]

In 2007, a ventilatory classification (VC) scheme was proposed.[4] Four classes were designated, based on V_E/VCO_2, as an integrative way of optimizing CPET-derived risk stratification in heart failure ventilatory class. VC I is defined as $V_E/VCO_2 \leq 29$; VC II as V_E/VCO_2 of 30.0–35.9; VC III as V_E/VCO_2 of 36.0–44.9; and VC IV as $V_E/VCO_2 \geq 45.0$. The higher the VC class, the greater the risk for major cardiac events (e.g., increased mortality or need for cardiac transplantation or left ventricular assist device implantation).

Currently, either VC classification or peak $\dot{V}O_2$ may be used in a multiparametric combination, along with other derived variables embedded in the score's format, for prognostic purposes[79] and as a reference endpoint in pharmacologic[80,81] or interventional trials.[82,83] These multiparametric approaches apply primarily to patients with HFrEF. However, a study combining CPET with echocardiographic evaluation (i.e., CPET imaging; see below) tested the validity of the Weber and VC classifications in a population of patients with different forms of heart failure, including those with HFrEF, HFpEF, and patients with midrange ejection fractions (mrEF). Both classifications demonstrated prognostic utility, especially when peak $\dot{V}O_2$ and V_E/VCO_2 strata were combined (Fig. 32-8).[84]

In addition to the clinical value of assessing inefficiency of V_E in heart failure, recent attention has been directed to the observation that an abnormal "exercise oscillatory ventilation" (EOV) pattern indicates an adverse prognosis. EOV is the pathophysiologic manifestation of two main processes: hemodynamic instability sustained by circulatory delay and pulmonary congestion, and impaired chemosensitivity.[85]

Assessment of exercise ventilatory patterns is particularly attractive in identifying the various phenotypes related to pulmonary hypertension secondary to left-sided heart disease. Identification of "left-sided" pulmonary hypertension is particularly important, given its prognostic role and high prevalence in both HFrEF and HFpEF.[86,87]

In a study incorporating CPET and measurement of pulmonary artery pressures, a V_E/VCO_2 cutoff of 36 was found to be the strongest predictor of a pulmonary artery pressure (PAP) ≥40 mm Hg, followed by peak exercise $PetCO_2$ of 36 mm Hg and the presence of EOV in patients with HFrEF. More compelling was the greater predictive utility when all measures were considered together.[88] Multiple trials have demonstrated that in HFpEF, a high V_E/VCO_2 is typical of patients with documented increased pulmonary vascular resistances[88,89] and right ventricle-to-pulmonary circulation uncoupling. Finally, measurements of pulmonary and systemic hemodynamics that incorporate use of echocardiography and "invasive CPET" (see below) have emerged as fundamental additions to CPET in evaluating mechanisms of exercise limitation in patients with heart failure.

CPET IMAGING

CPET imaging (CPET IM) has been recently proposed as a valuable testing modality to expand knowledge of organ system limitations to exercise performance. The technique combines physiologic data obtained from exercise testing with noninvasive measures (e.g., echocardiography) of cardiac function and geometry, valvular status, and systolic and diastolic function, including assessment of left atrial function.[7,90] Assessment of cardiac "functional reserve" using CPET IM is greatly augmented by study of the pathophysiologic response of the pulmonary circulation to exercise.

Multiple applications of CPET IM in assessing cardiopulmonary disorders have been described. For example, good discrimination between a circulatory disorder and deconditioning is signaled by a subject's inability to reach an exercise stroke volume of >50 mL/m^2.[91] Additionally, the importance of measuring CO reserve, in parallel with LV compliance and filling pressures, is well established,[90] and estimation of O_2 extraction in peripheral tissues using CPET IM and an echocardiographic-derived analysis of the determinants of the Fick equation provides useful information.[92,93]

In COPD, combined CPET and stress echocardiographic testing can be helpful in determining individual contributions to exercise intolerance. In addition to airflow limitation and hyperinflation, exercise impairment may be precipitated by hemodynamic factors. For example, in a group of patients with COPD, CPET IM reveals significant adverse effects on LV volume, right ventricular area, tricuspid regurgitation grade, heart rate, stroke volume, and $\dot{V}O_2$. The major mechanisms resulting in reduced exercise tolerance include bowing of the septum to the left, abnormal increases in the LV filling pressure, as estimated by the ratio of early mitral flow wave (E) to

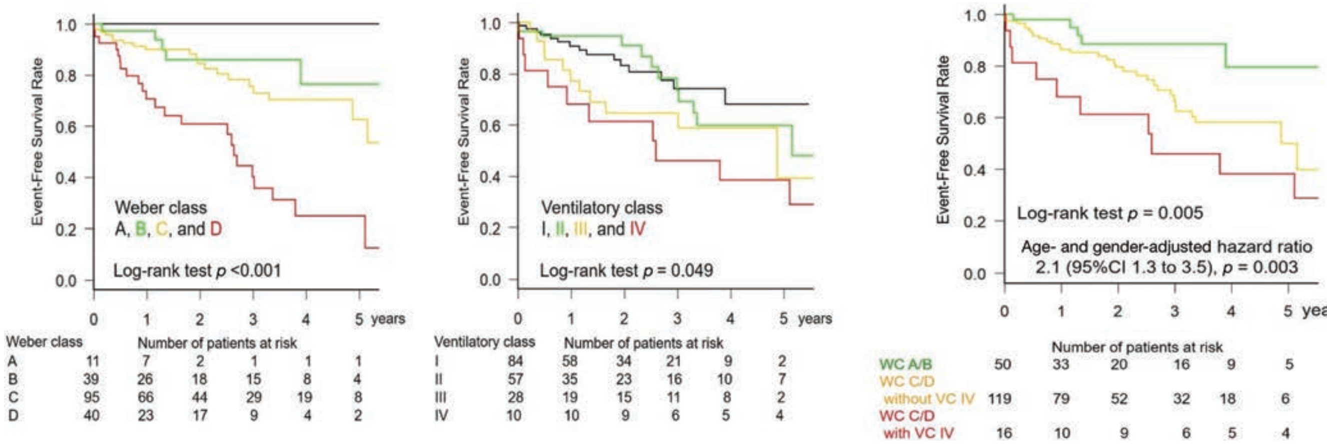


Figure 32-8 Kaplan-Meier stratification according to Weber (WC) (*A*) and ventilatory (VC) classifications (*B*) and their combined survival rates. *(Reproduced with permission from Guazzi M, Borlaug B, Metra M, et al. Revisiting and Implementing the Weber and Ventilatory Functional Classifications in Heart Failure by Cardiopulmonary Imaging Phenotyping. J Am Heart Assoc. 2021;10(5):e018822.)*

early tissue Doppler (e′), an abnormal stroke volume, and chronotropic incompetence in approximately 60% of cases.[92]

In cardiac patients, assessment of functional mitral regurgitation (MR) is relevant as a marker of disease severity and adverse outcome, that, in early stages, may be detectable only during exercise.[93] "Dynamic pulmonary hypertension" is another pathophysiologic mechanism closely related to MR and associated with specific ventilatory phenotypes of gas exchange, such as EOV.[93] In advanced HFrEF, assessment of exercise-induced RV contractile reserve may be investigated using CPET, providing important insights into potential RV functional recovery.[94]

Recently, findings suggest that an impaired left atrial (LA) dynamic during maximal exercise and during the recovery phase plays a central role in triggering RV-to-PC uncoupling and ventilatory inefficiency, especially when LV systolic function is reduced.[95,96] LA dynamic can be assessed in a feasible and reproducible way by strain analysis. Strain measures the extent of myocardial deformation and can be derived by specific echocardiographic and cardiac magnetic resonance techniques.[95,96]

The body of literature on CPET IM in patients with HFpEF is expanding, and it now elucidates how the test may be used to uncover unexplained dyspnea in patients with suspected HFpEF. CPET IM may be helpful in confirming a diagnosis of HFpEF in cases with uncertain diagnostic criteria at rest, and it may be used to predict cardiovascular risk.

The American Society of Echocardiography (ASE)/European Association of Cardiovascular Imaging (EACVI) recommendations on diastolic function evaluation advocate the use of exercise E/e′ ratio to detect diastolic dysfunction,[97] and for several years, changes in E/e′ have been taken as a reference in interpreting unexplained dyspnea in patients with suspected HFpEF.[98] In a study of 87 patients with unexplained dyspnea and hypertension during exercise, combined measurements of gas exchange and Doppler analysis led to a diagnosis of HFpEF in the minority of patients presenting with a combination of E/e′ > 15 at peak exercise and an elevated V_E/VCO_2.[99]

Additional observations have focused on how exercise E/e′ may add to the clinical follow-up of patients with established HFpEF, especially when coupled with examination of the associated changes in pulmonary pressure during effort.[100] Interestingly, CPET IM, including immediate post-exercise echocardiographic assessment, has documented that in about one of three patients with HFpEF, exercise-induced elevation of left ventricular filling pressure (i.e., E/e′EXE >13) may be absent, despite its association with reduced contractile reserve and ventricular-arterial coupling and a mild degree of functional impairment.[101] On the other hand, a similar approach has showed that peak E/e′ >15 occurred in 9% of hypertensive patients with exertional dyspnea and normal resting left ventricular function and was associated with lower peak $\dot{V}O_2$ and significantly impaired ventilatory efficiency (increased V_E/VCO_2) compared with patients with normal exercise E/e′.[99]

The rationale for using CPET IM in valvular disease is based on extensive investigation. However, systematic data are not yet available, and future investigation is desirable for assessment of surgical risk, especially in complex conditions, such as paradoxical, low-flow gradient, severe aortic stenosis.[102]

INVASIVE CPET (iCPET)

Invasive CPET (iCPET) is the gold standard for in-depth characterization of the hemodynamic basis for exercise limitation; it provides precise delineation of central and peripheral hemodynamic mechanisms. The approach has been reassessed in recent years and has been established as a routine approach in several laboratories.[103]

Measurement of pulmonary hemodynamics, left ventricular filling pressures, cardiac output (via the Fick equation), and $CaO_2 - CvO_2$ is extremely helpful in cases of unexplained exercise-induced dyspnea,[103] in the presence of severe limitation of cardiac output, and in evaluation of exercise-induced pulmonary hypertension, either idiopathic or secondary in origin.[103] A recent analysis documented that iCPET allows considerable shortening of the diagnostic interval from time of onset of exertional dyspnea to establishment of an organ-specific diagnosis. Conditions that can be diagnosed using iCPET include HFpEF, mitochondrial myopathy, preload failure, and deconditioning.[34]

Additionally, pulmonary hemodynamic measurements during exercise, especially of PAP and pulmonary arterial wedge pressure (PAWP), demonstrate increased prognostic value compared with measurements at rest.[104]

Studies have demonstrated an opportunity to diagnose HFpEF in symptomatic, euvolemic patients with normal levels of B-type natriuretic peptide, and without clear signs and symptoms of heart failure at rest.[105] In one-half of cases in whom examination of PAWP and end-diastolic LV pressure were performed, an observed increase in PAWP during exercise was diagnostic for HFpEF.

These findings have been reproduced and indicate that in patients with normal biventricular function, an increase in mean PAWP to >20 mm Hg at peak exercise, in the absence of an elevation in pulmonary vascular resistance, indicates exercise-induced HFpEF.[105] Patients with early stages of PAH and normal cardiopulmonary hemodynamics at rest demonstrate an increase in mean PAP to >30 mm Hg and in pulmonary vascular resistance to >80 to 120 $dyn \cdot s \cdot cm^5$ on iCPET with no increase in PAWP.[104]

A distinctive pulmonary hemodynamic pattern useful in defining exercise-induced dyspnea due to HFpEF is an increase in PAWP/CO.[106] A high slope for PAWP/CO (>2.0 mm Hg/L/min), combined with abnormal gas exchange measurements, for example, lower peak $\dot{V}O_2$ and V_E/VCO_2, predicts heart failure outcomes.

Exertional intolerance may be associated with preload-dependent limitations to stroke volume and CO increase. In the affected patient population, failure to augment right atrial pressure on exercise is observed with a concomitant reduction in CO.[34] Finally, impaired systemic O_2 extraction indicates left-to-right shunting or a mitochondrial myopathy. An algorithm for diagnosing these conditions has been proposed.[34]

Evaluation of the pulmonary artery pressure-flow relationship during exercise, reflected in a plot of mean PAP versus CO, provides a strong indication of any abnormality in RV-pulmonary circulation coupling.[103] A mean PAP/CO relationship >3 mm Hg/L/min is reflective of a pulmonary hypertension response, which may be seen with a typical pattern of ventilatory inefficiency during exercise, as suggested by an elevated V_E/VCO_2. Interestingly, the development of RV-pulmonary circulation uncoupling becomes the main hemodynamic substrate responsible for a delayed $\dot{V}O_2$ kinetics during early exercise.[107]

The most relevant limitations to this approach are its invasive nature and technical inaccuracies in obtaining reliable pulmonary hemodynamic tracings during high respiratory frequencies, despite the averaging of repeated measures.

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CHAPTER **33**

Diagnostic Bronchoscopy, Transthoracic Needle Biopsy, and Related Procedures

David M. DiBardino
Daniel H. Sterman
Anil Vachani

INTRODUCTION

Gustav Killian reported his experience with the first bronchoscopy in 1898. Technological advances during the next century facilitated development of bronchoscopy as a pivotal diagnostic and therapeutic tool in pulmonary medicine. Although a number of bronchoesophagologists contributed to refinement of the technique based upon use of a rigid instrument, the advent of flexible fiberoptic bronchoscopy, pioneered by Ikeda in 1967, opened new horizons to clinicians. Subsequently, transthoracic needle biopsy was added to the pulmonologist's diagnostic armamentarium, although it is now most frequently performed by radiologists under CT guidance.

This chapter comprises an overview of bronchoscopy, transthoracic needle biopsy, and related techniques. Following a general discussion of bronchoscopy and associated general instrumentation, indications for the technique and patient preparation are considered. Specific applications of diagnostic bronchoscopy are discussed. Subsequently, safety factors related to bronchoscopy and complications of the technique are reviewed. Finally, transthoracic needle biopsy is described.

GENERAL INSTRUMENTATION

The original bronchoscope, developed by Killian in Europe, and further perfected by Chevalier Jackson in the United States, was a rigid metal tube that permitted either spontaneous or assisted ventilation. With development of fiberoptic and advanced electronic technology, the flexible bronchoscope has, to a large extent, replaced the rigid bronchoscope for most diagnostic and some therapeutic indications. Therapeutic bronchoscopy is discussed in Chapter 34.

■ Flexible Fiberoptic and Videobronchoscopy

Although the optical resolution of early fiberoptic bronchoscopes was inferior to that of rigid devices, their flexibility, ease of manipulation, and simplicity of use, which permit rapid examination with local anesthesia and conscious sedation, have made flexible bronchoscopy the primary endoscopic procedure in pulmonary diseases.

Unlike the larger-bore rigid bronchoscope, the flexible bronchoscope varies from ultra-thin (allowing for greater access to the lung periphery in adults and for neonatal endoscopy) to larger, adult-size therapeutic devices. The diameter of the working channel permits aspiration of secretions or introduction of accessories required for diagnostic purposes (see below). With flexible bronchoscopy, the patient's ventilation is assured by airflow around the bronchoscope, between the external wall of the device and the tracheobronchial tree. Thus, the appropriate selection of bronchoscope size is crucial.

Fiberoptic systems have largely been replaced by videobronchoscopes, which utilize a miniaturized camera at the tip of the scope that provides electronic transmission of images to a television monitor. Flexible bronchoscopes are more fragile and more prone to damage than are rigid metal instruments. Appropriate care and adherence to safety techniques during procedures, as well as during routine cleaning and maintenance of the instruments, help assure extended instrument life and reduce repair costs.

Recently, the advent of a flexible single-use disposable fiberoptic bronchoscope attempts to address rising concerns over the efficacy of endoscope cleaning practices, the burden of repair costs, the size of a modern endoscopy tower, and the challenge of prompt bedside availability.[1] Improving image quality and improved maneuverability will undoubtedly be the focus of innovation for this device, although it has proved useful in certain scenarios such as airway emergencies, bedside bronchoscopy, and percutaneous tracheostomy.[2]

■ Ultrathin Bronchoscopes

Ultrathin bronchoscopes—flexible scopes with external diameters ≤3 mm—were initially developed for pediatric applications; however, these have now incorporated larger working channels, allowing for their use in the diagnosis of peripheral pulmonary lesions in adults.[3,4] Ultrathin bronchoscopes can be advanced to more peripheral bronchi than conventional bronchoscopes under direct observation, allowing for examination of sixth- to eighth-generation bronchi. Ultrathin scopes may be particularly useful when combined with additional diagnostic tools, such as navigational bronchoscopy and radial ultrasound probes (see below).

■ Robotic Bronchoscopy Systems

Most recently, technologic advancements in bronchoscopy involve optimizing the mechanical design of the endoscope itself with the goal of improving articulation, stability, and biopsy instrument guidance within the distal lung.[5,6] These systems integrate novel endoscopic designs with unique navigation platforms (see below). As with ultrathin bronchoscopes, the combination of these modalities may improve diagnostic yield for small, peripherally located lesions. Potentially greater accuracy in lesion access coupled with improved stability may also enable certain therapeutic applications.

■ Diagnostic Bronchoscopy Accessories

The working channel of the fiberoptic or videobronchoscope, although of relatively small diameter, allows the insertion of various diagnostic and therapeutic accessories. Often these instruments are used serially during the same procedure in the hopes that different forms of tissue acquisition will optimize sampling.

■ Biopsy Forceps

The cutting jaws of biopsy forceps may be round or elliptical and may have smooth or jagged edges. The use of nonserrated edges, however, seems to reduce tissue trauma and the concomitant risk of bleeding. The biopsy procedure is simple and generally associated with only minimal complications in the case of a visible lesion. Even peripheral lesions, which are not visible through the bronchoscope, may be biopsied. With diffuse parenchymal or interstitial lung disease, the use of fluoroscopic guidance has not resulted in higher diagnostic yield or safety. However, the use of fluoroscopy improves

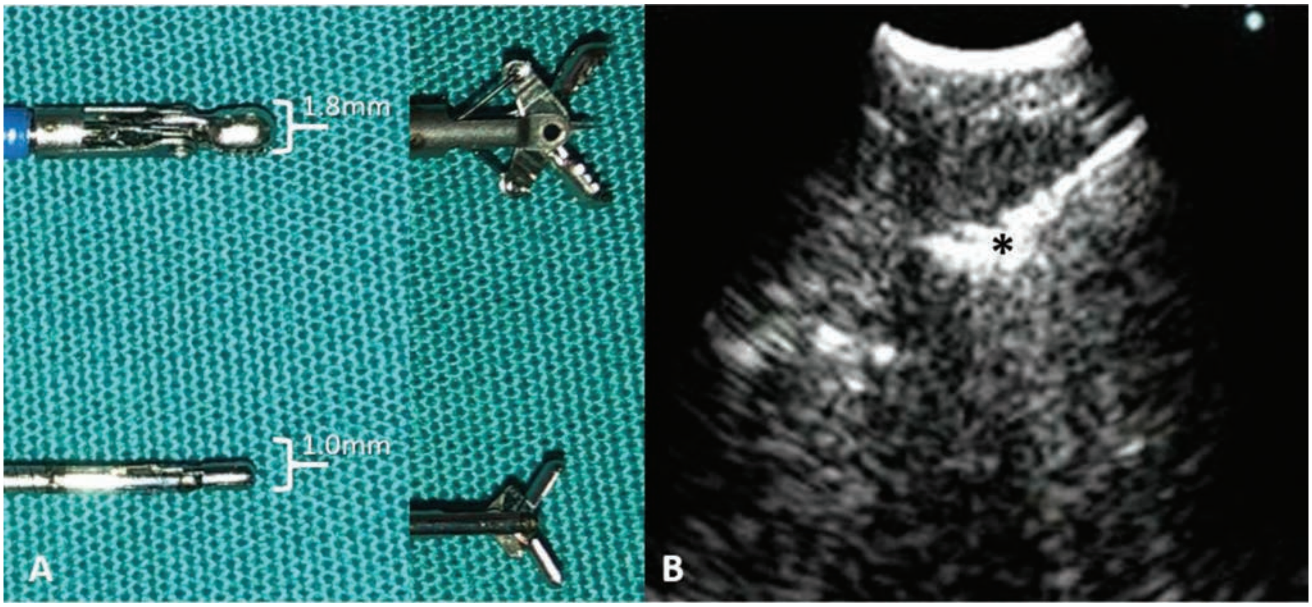

Figure 33-1 Intranodal forceps biopsy tools. **A.** Transbronchial biopsy forceps (Top, Radial Jaw 4), Intranodal biopsy forceps (Bottom, CoreDx). **B.** EBUS image of intranodal biopsy forceps open within lymph node *(asterisk)*. *(Image provided courtesy of Boston Scientific. © 2022 Boston Scientific Corporation or its affiliates. All rights reserved.)*

the diagnostic yield of biopsies for focal lesions. The development of new electromagnetic and remote guidance systems suggests that further improvement in the diagnostic yield of bronchoscopic biopsies can be expected.

More recently, miniaturized forceps have been used to obtain biopsies of mediastinal lymph nodes under real-time endobronchial ultrasound guidance (Fig. 33-1). These forceps range from 1.0 to 1.8 mm in diameter and can be passed via a previously created needle puncture or electrocautery incision.[7–9] Ideally samples obtained this way can optimize diagnostic yield for certain conditions, such as lymphoma, where fine-needle aspiration may not provide an adequate sample.

■ Bronchial Brushes

A bronchial brush consists of a rigid central wire surrounded by bristles of various sizes and shapes. To-and-fro movement of the brush against the adjacent tissue produces minor trauma but enables collection of ample specimens for cytologic or microbiologic analysis.

In some clinical circumstances, there is a need to obtain an uncontaminated specimen from the lower respiratory tract for microbiologic studies. A brush protected by an additional sheath and tip may be passed through the working channel of the bronchoscope (protected brush specimen, as discussed below). In these cases, special attention is needed not to use an excessive amount of local anesthetic or saline lavage, since these solutions contain bacteriostatic material that may inhibit microbial growth. The diagnostic yield depends on use of proper technique, appropriate choice of brush, and careful collection and preservation of the specimen.

■ Needles for Aspiration and Biopsy

The first performance of a transbronchoscopic needle aspiration (TBNA) through a rigid bronchoscope was reported by Schieppati in 1958. Wang then developed a flexible needle technique using a fiberoptic bronchoscope in 1978.[10] Initially, several models of needles were designed to obtain cytologic material; subsequently, histologic specimens from peribronchial mediastinal and hilar lymph nodes were obtained with larger-bore needles. These biopsy needles have subsequently been adapted to work under direct ultrasound guidance from within the airway (see below), although current ultrasound techniques do not yet allow for real-time guidance during biopsy of a peripheral lesion. These needles employ a sheath to protect the bronchoscope working channel and are widely available in a variety of sizes, ranging from 18 to 25 gauge. The addition of TBNA to forceps and brushes for the sampling of a peripheral lesion improves the diagnostic yield of a bronchoscopy.[11]

TBNA is generally safe, although pneumothorax and hemomediastinum may occur; rare cases of air embolism also have been reported.[12] Clinically significant bleeding is extremely rare, particularly when a 22-gauge needle is used, even if a major vessel is inadvertently punctured or if the patient suffers from superior vena cava syndrome.

■ Cryoprobe

Since 1994 flexible cryoprobes have been available for use through a bronchoscope's working channel. This instrument utilizes the Joule-Thomson effect by bringing liquefied gas from a compressed reservoir into a small orifice at the tip of the probe where it rapidly expands into gas. This conversion is associated with a rapid drop in temperature. The orifice is positioned beyond the end of the bronchoscope working channel where the cryoprobe tip freezes upon activation using a foot pedal. An endobronchial and transbronchial biopsy technique is possible through the principle of cryoadhesion, where the frozen probe tip adheres to tissue before being abruptly pulled proximally during the rapid freezing phase. Frozen tissue is removed en-bloc with the instrument and bronchoscope. The sample is then thawed in saline and collected from the probe tip before the device can be removed from the working channel, allowing for larger and better-preserved biopsy samples compared to forceps.[13]

■ Bronchoscopic Transparenchymal Nodule Access (BTPNA)

One common necessity for sampling a parenchymal lung lesion is an adequate airway to lead the biopsy tool to the abnormality. To combat this limitation, the technique of BTPNA has been developed to sample lesions with no clear connection to an airway.[14] With this method, an airway puncture site is chosen using software that maps the lesion relative to the surrounding vasculature. The airway entry point is created by expanding a needle puncture site that allows a tunneling sheath to be pushed through the lung parenchyma. Maneuvering of the tunneling sheath is guided by augmented fluoroscopy (see below). Although promising, limited data are available to adequately assess the full spectrum and frequency of potential risks or the added benefit of this approach for the sampling of peripheral lesions.

ENDOBRONCHIAL ULTRASOUND

Among the new diagnostic modalities available to chest physicians, endobronchial ultrasound (EBUS) has unquestionably had the most profound impact.[15] Two major barriers to EBUS development existed: ultrasound probe size and sound wave transmission in air-filled structures. Ultrasound engineering advances allowed the former barrier to be overcome, while the latter was surmounted by the development of an integrated, fluid-filled balloon surrounding the EBUS probe, thereby allowing for a sound wave–transducing medium interface to exist between the ultrasound probe and airway wall (i.e., ultrasonographic coupling).

Lower ultrasound frequencies provide better penetration depth with less resolution; higher frequencies provide better spatial resolution but less penetration depth. For EBUS applications, the frequencies range from 7.5 to 30 MHz. Currently, there are two EBUS probes utilized for diagnostic applications: ultra-miniature radial probes (20 and 30 MHz) and convex probe or curvilinear EBUS (CP-EBUS). Each of these is discussed in greater detail below.

■ Ultra-Miniature Radial Probes

Ultra-miniature EBUS (UM-EBUS) was developed to allow for improved assessment and sampling of peripheral pulmonary lesions (Fig. 33-2A). There are two ultra-miniature radial probes currently available, with diameters of 1.4 mm and 2.0 mm, allowing insertion into bronchoscopes with working channels of 2.0 mm and 2.6 mm, respectively (Olympus Corporation, Tokyo, Japan). When a lesion is reached with the probe, the usual normal lung "snowstorm" appearance is replaced by a focal ultrasound alteration that can be marked by fluoroscopy, a guide sheath (GS), or both fluoroscopy and GS (Fig. 33-2B and Video 33-1). Traditionally, after the lesion is localized, the GS can be left in place, allowing for guided biopsies of the lung using forceps, brush, or needle biopsy. Future developments will include more sophisticated guide sheaths and smaller radial probes that would allow real-time ultrasound guided TBNA in the peripheral lung.[16]

■ Convex-Probe EBUS

The convex-probe EBUS (CP-EBUS) bronchoscopes available have a built-in curvilinear ultrasound transducer with a larger distal diameter (6.7–6.9 mm) compared with a standard bronchoscope. White light video bronchoscopy occurs at an oblique angle with EBUS at 90° from the longitudinal axis. Dedicated biopsy needles (19-, 21-, 22-, or 25-gauge with a variety of tip styles) are inserted through the 2-mm working channel to perform aspirations of the target lesion (Fig. 33-3A). Real-time EBUS imaging displays needle penetration through the tracheobronchial wall into the target during the biopsy maneuver (Fig. 33-3B). If there is difficulty in achieving adequate EBUS images because of poor ultrasonographic coupling, a saline-filled balloon surrounding the transducer can be used to improve image quality. In addition, Doppler capabilities allow vascular structure differentiation, which minimizes the risk of unintended vascular puncture.

NAVIGATIONAL BRONCHOSCOPY

There has been continued emphasis on improving the ability to access and sample peripheral pulmonary lesions through technologic advances in electromagnetic navigational bronchoscopy (EMB), augmented fluoroscopy, and virtual bronchoscopy (VB)[17–20] (Fig. 33-4A–C). Furthermore, these guided bronchoscopy techniques can be combined with each other, UM-EBUS, guide sheaths, ultrathin bronchoscopes, and, most recently, robotic bronchoscopy platforms (Fig. 33-4D and 33-4E). The role of navigational bronchoscopy in the evaluation of peripheral pulmonary nodules is discussed below.

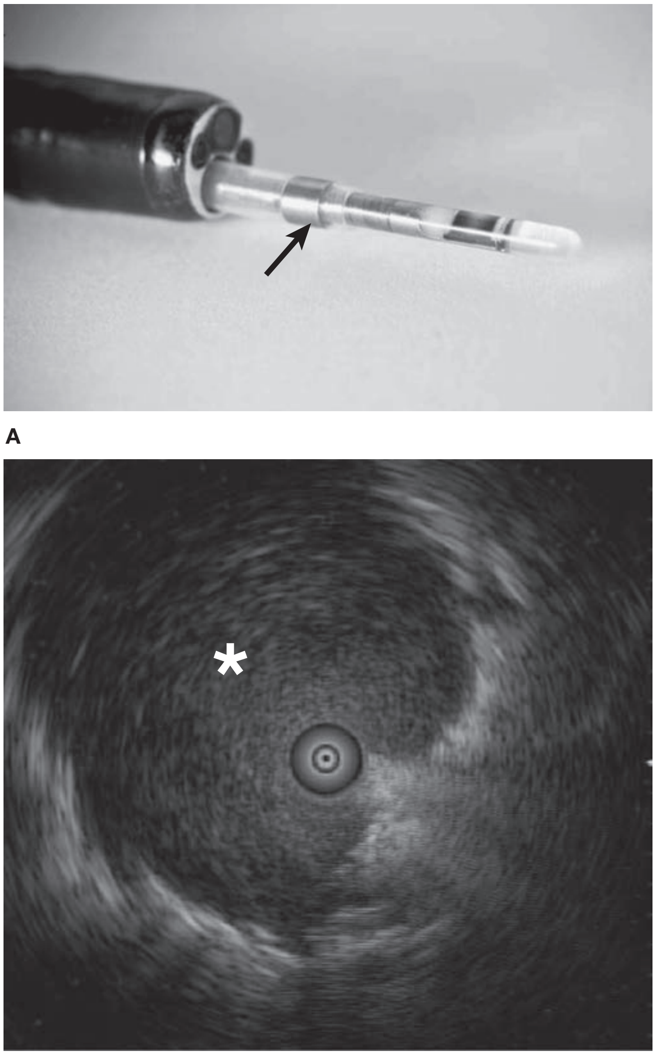

Figure 33-2 **A.** The ultra-miniature (UM)-EBUS probe contains a circulating ultrasound crystal that provides a 360° view of the surrounding structures when full airway ultrasonographic coupling occurs. The probe is inserted through a guide sheath (*arrow*; Olympus Corporation, Tokyo, Japan), which can remain in the airway upon UM-EBUS probe removal to allow for instrument guidance for biopsy. **B.** This UM-EBUS image demonstrates a focal lung lesion *(asterisk)* surrounding the probe.

Video 33-1 The ultra-miniature (UM)-EBUS probe is used via the working channel of a fiberoptic bronchoscope to identify a focal lung lesion. When the lesion is reached with the probe, there is an alteration in the ultrasound image, with replacement of the usual normal lung "snowstorm" appearance by the presence of a denser focal lesion that surrounds the centrally located probe. *Video available on AccessMedicine.com.*

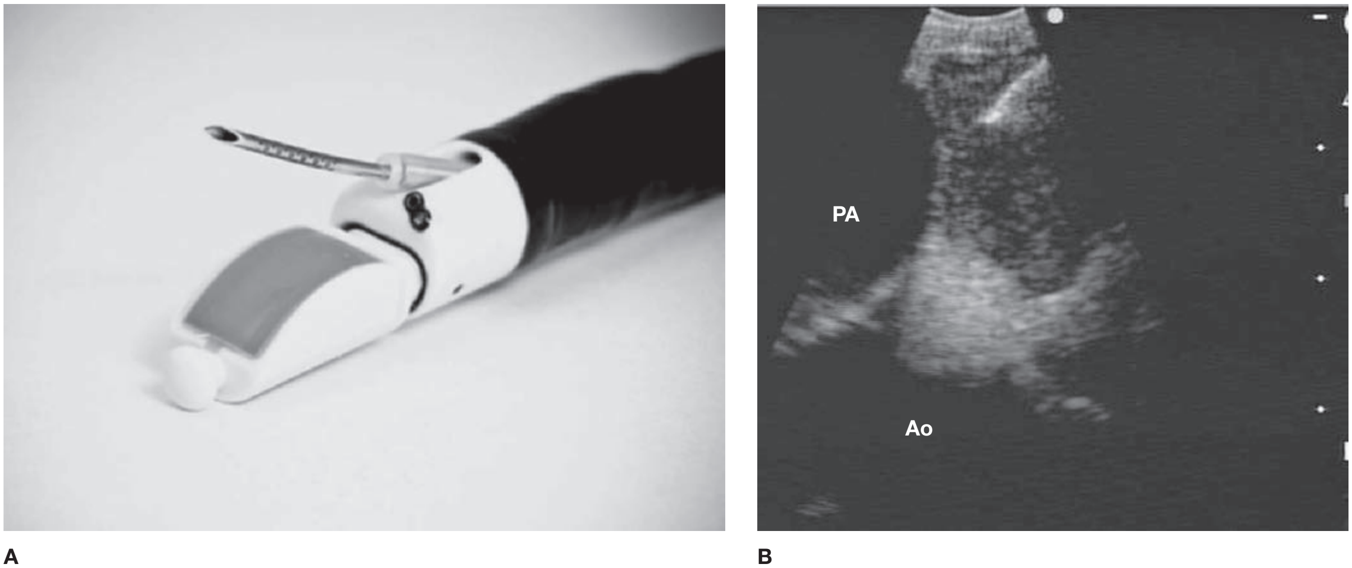

Figure 33-3 **A.** The convex probe (CP)-EBUS TBNA (Olympus Corporation, Tokyo, Japan) videobronchoscope has an integrated ultrasound probe that scans 90° perpendicular from the longitudinal axis, a 35° forward oblique video view, and a 2.0-mm working channel through which a dedicated biopsy needle can be passed. Distal tip dimples on the needle provide an echogenic surface to reflect ultrasound waves to allow needle visualization. **B.** This CP-EBUS image demonstrates a left paratracheal lymph node with the ascending aorta (Ao), the pulmonary artery (PA), and the needle present in the lymph node.

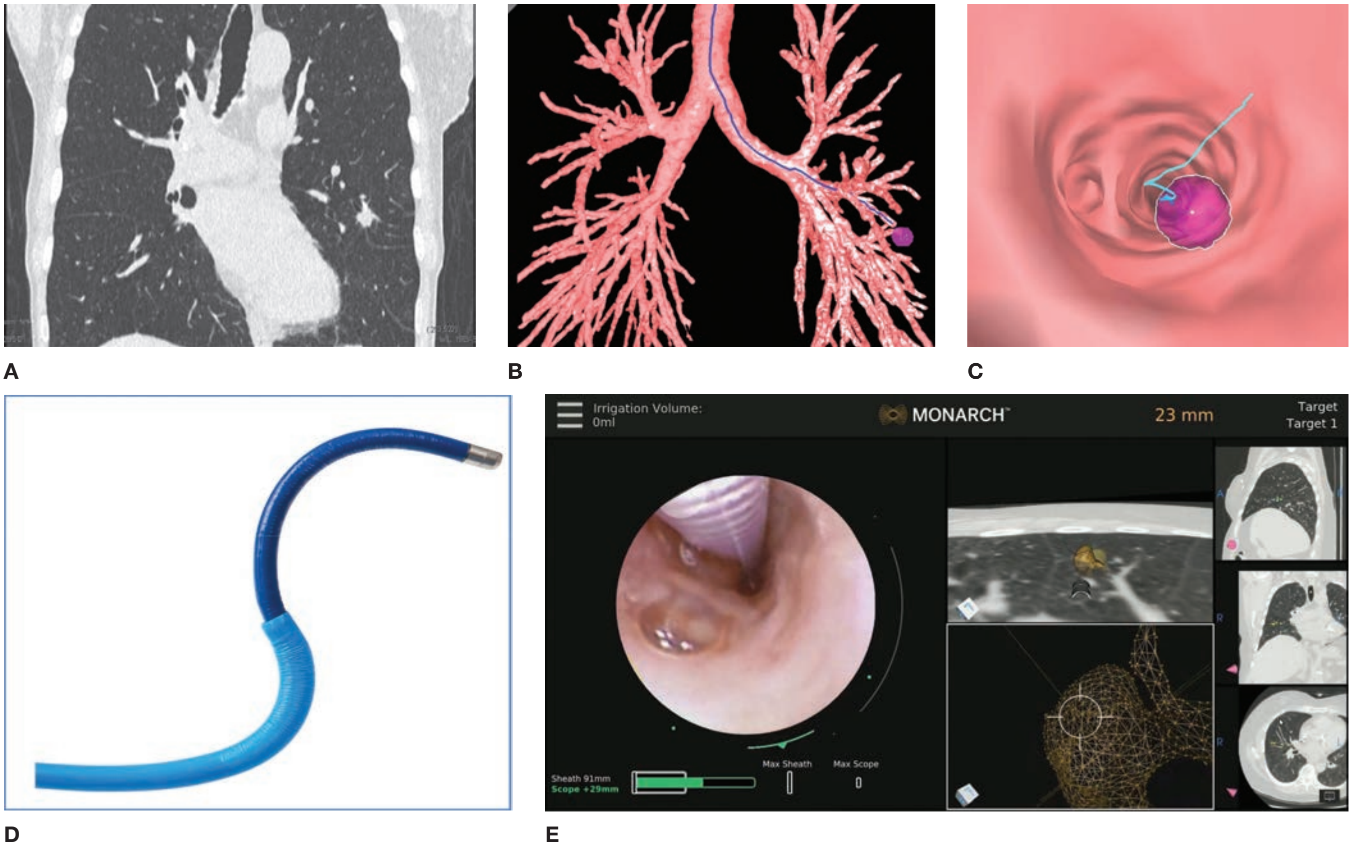

Figure 33-4 Use of a virtual bronchoscopy–based system for navigation. **A.** Chest CT image of a spiculated left upper lobe pulmonary nodule. **B.** 3-D reconstruction of the tracheobronchial tree with the nodule identified. **C.** Virtual bronchoscopic image demonstrating the pathway to the peripheral nodule. **D.** Robotic bronchoscopy arm designed with an articulating sheath and highly flexible inner endoscope. **E.** Navigation platform used simultaneously with EMN and endoscopic view. *(**D** and **E:** © Auris Health, Inc. All rights reserved.)*

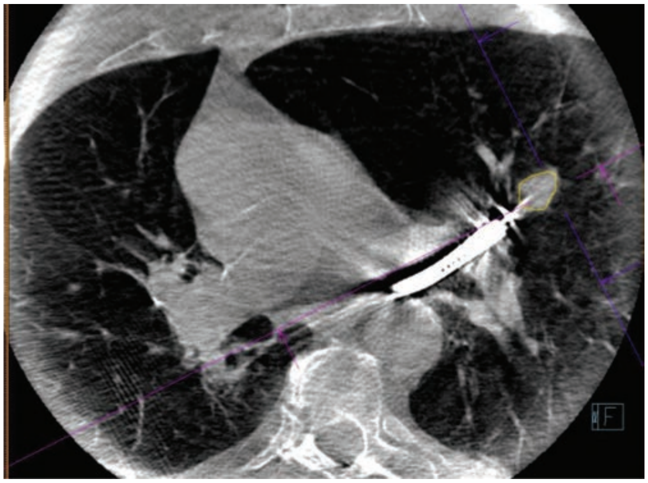

Figure 33-5 Intraprocedural cone beam–CT confirming placement of transbronchial needle within lung nodule.

EMB utilizes an electromagnetic board to generate a magnetic field around the patient, a sensor probe, an extended working channel, and three-dimensional integration of CT scan reconstruction and bronchoscopy position. In essence, this system works on the same triangulation principle as a global positioning system and allows the bronchoscopist to direct the FB through the airways to the target. There are slight variations on how the magnetic field is generated and how the sensor probe interfaces with the biopsy procedure, depending on the specific EMB equipment used. Innovation has focused on development of biopsy instruments that act as magnetic sensor probes (i.e., “tip-tracked”), approaches to account for lung movement during the respiratory cycle, and combining EMB with other technology.[21]

Augmented fluoroscopy is a technology designed to fuse previously obtained radiographic images with live fluoroscopy during a procedure (Fig. 33-5). This technique has long been utilized to aid surgical procedures involving bony structures. In the lung, this approach has evolved to the use of CT images to create a target lesion, and superimposing an artificially highlighted target to live fluoroscopy images generated during bronchoscopy.[22] Variation in patient positioning and lung volumes can be minimized between CT scan and intraprocedural fluoroscopy by using cone beam CT scan or multiple focused fluoroscopy images obtained during the procedure itself.[23] Augmented fluoroscopy can be combined with any other localization techniques such as VB and EMB.

VB based approaches utilize virtual navigation by creating a CT scan based “road map” that can be overlaid onto real-time endoscopic images. Pre-procedure CT images are assessed using a software system, a target location is selected, and a proposed airway path is suggested for an attempt at bronchoscopic sampling. Recent improvements have focused on expanding this technology to map not only the airways, but also the pulmonary vasculature. The combination of “vessel mapping” with augmented fluoroscopy allows for BTPNA.

In addition to diagnostic indications, navigational bronchoscopy can be used for fiducial placement and presents a promising tool that may be useful if future therapies for malignant nodules include focal tumor ablation or injection.[24–27]

■ Patient Preparation and Monitoring During Bronchoscopy

Success of bronchoscopy, whether diagnostic or therapeutic, depends, in large part, on proper preparation of the patient, including relief of anxiety, muscle relaxation, cough suppression, and adequate anesthesia. Time spent in achieving these goals will be well worth it in reducing the risks of complications and in increasing the ease of performance of the procedure. As with any other procedure, analysis of the risk-benefit ratio helps reduce the complication rate. During and shortly after the procedure, appropriate monitoring of hemodynamic parameters (heart rate, rhythm, and blood pressure), oxygenation, and ventilation contributes to the safety of bronchoscopy.

Most flexible bronchoscopies are performed after patient premedication with sedative agents and the use of bronchoscopically instilled lidocaine for local anesthesia of the upper airway, larynx, and tracheobronchial tree. Most frequently, moderate sedation is achieved using a combination of a short-acting benzodiazepine (e.g., midazolam) and a narcotic agent (e.g., fentanyl). Intravenous propofol also may be used to provide moderate sedation and appears to provide similar results in terms of patient satisfaction and degree of hypoxia, with the advantage of a faster recovery time.[28] Because the use of propofol can lead to deep sedation, it is important that these patients receive careful monitoring. Deep sedation (i.e., a deeper state of depressed consciousness with potential for compromised airway function and spontaneous respiration) and general anesthesia are increasingly being employed, given the shift of diagnostic and therapeutic bronchoscopy toward more complex and lengthier diagnostic procedures.

Anticholinergic medication (e.g., atropine or glycopyrrolate) has been advocated by some to reduce the risk of vasovagal reactions and to minimize airway secretions, thereby allowing for better examinations of the tracheobronchial tree. In a randomized trial comparing these two drugs with placebo, glycopyrrolate, but not atropine, led to a reduction in airway secretions.[29] There was no significant reduction in cough, patient discomfort, oxygen desaturation, or procedure time with either drug. Current recommendations discourage the use of these agents during bronchoscopy.[28]

BRONCHOSCOPY TECHNIQUE

Core elements of bronchoscopy include assessment of airway anatomy and function, evaluation of peribronchial structures, performance of biopsies, and sampling of airway and alveolar constituents. Each is discussed below.

■ Assessment of Airway Anatomy and Function

Thorough bronchoscopic evaluation begins with examination of the upper airways. Special attention should be paid to the integrity of air passages and the function of the nasopharynx and larynx. The vocal cords should be examined for the presence of polyps and tumors and for evidence of cord paralysis.

Once upper-airway inspection is completed, a systematic evaluation of the lower respiratory tract should be performed. Critically important is the distinction among normal anatomy, anatomic variations without clinical significance, and frankly pathologic conditions. These considerations have important implications regarding potential diagnostic and therapeutic approaches. For example, finding abnormal branching of a bronchus may be of no clinical significance. On the other hand, such an abnormality could explain symptoms of frequent infections due to impaired ventilation and drainage of the affected area. Special skills and observational experience are required for bronchoscopic examination after surgery, especially following bronchoplastic procedures or lung transplantation.

Assessment of airway integrity, with special attention to dynamic changes in airway caliber during either relaxed breathing or forced expiration, may be crucial in diagnosing tracheobronchomalacia (TBM) and determining appropriate therapeutic maneuvers. Airway assessment is best performed with a thin flexible bronchoscope performed with the patient spontaneously breathing.

Video 33-2 Dynamic airway examination performed to assess tracheobronchomalacia. Demonstrated is excessive dynamic airway collapse (EDAC) during exhalation, as well as anterior tracheal malacia with wide splaying of the cartilaginous rings. *Video available on AccessMedicine.com.*

Relaxation and prolapse of the membranous portion of the trachea and main bronchi secondary to destruction of elastic connective tissue may account for exacerbations of expiratory airflow obstruction. This is often referred to specifically as "excessive dynamic airway collapse" (EDAC), although distinguishing or grouping this entity with TBM becomes a matter of semantics. On the other hand, finding localized, anterior chondromalacia causing crescent-shaped TBM can have very different therapeutic implications (Video 33-2). On the basis of these bronchoscopic determinations, the choice of performing an open surgical approach or bronchoscopic therapeutic intervention may be made.

Bronchoscopic examination generally permits evaluation and localization of congenital or postsurgical pathologic changes in bronchial integrity, such as tracheoesophageal or bronchopleural fistulas. Bronchoscopic observation and early diagnosis of bronchial rupture after chest trauma also greatly influence further therapy and prognosis. The same is true for evaluation of anastomoses following reconstructive surgery or lung transplantation.

Evaluation of Tracheobronchial Mucosa

Careful examination of the mucosal surface is crucial in the formulation of differential diagnosis. Rapid development of granulation tissue is frequently associated with reaction to a foreign body. Inflammatory mucosal reactions, although not very characteristic, should raise the possibility of mycobacterial infection, nonspecific viral and nonviral infections, and other granulomatous diseases, such as sarcoidosis.

The distinction between normal, pale-pink mucosa and hypervascular areas in the tracheobronchial tree may provide important diagnostic clues. Most frequently, changes in mucosal coloration are associated with an inflammatory reaction due to bronchitis. These findings are, however, very distinct from small hemangiomas or vascular distentions due to compression by enlarged, neoplastic lymph nodes. Similarly, a network of small mucosal lymphatics may be visible, with lymphatic interruption due to surgery, radiation therapy, fibrosis, or malignancy. This is most frequently associated with local edema, which contributes to airflow obstruction. In addition, distinct and characteristic mucosal discoloration can be observed in Kaposi's sarcoma or in airway metastases from melanoma.[30–32]

Ulcerations of the mucosa are more characteristic of polyangiitis (formerly known as Wegener's granulomatosis) or malignancy. Loss of the usual mucosal luster and presence of a roughened surface may alert the expert bronchoscopist to an early infiltrative or neoplastic process. Previously sustained injuries are characterized by the formation of mucosal and submucosal fibrosis, resulting in airway retraction or distortion.

Autofluorescence bronchoscopy (AFB) permits observation and analysis of tracheobronchial mucosal surfaces using the discriminant characteristic of tissue autofluorescence (Video 33-3). With the use of a monochromatic light source, computer-controlled image analysis, and a sophisticated camera attached to a fiberoptic bronchoscope, the airways can be examined for varying degrees of autofluorescence as an indicator of early-stage malignant changes. The acquisition of images is obtained in real time and helps in the detection of minute areas of change in normal tracheobronchial mucosal fluorescence. Biopsies from areas of abnormal fluorescence increase the rate of detection of small, premalignant (dysplasia) or early malignant (carcinoma in situ) lesions in the tracheobronchial tree.

Video 33-3 White light and autofluorescence bronchoscopy (AFB) demonstrating a focal airway lesion at the carina between the lingua and superior branch of the left upper lobe superior. The lesion demonstrates abnormal autofluorescence, manifested by a brownish color on AFB. The remainder of the airway examination demonstrates normal green fluorescence. *Video available on AccessMedicine.com.*

Although AFB may provide the ability to localize these early lesions with greater sensitivity than white light bronchoscopy (WLB),[33–36] longitudinal studies demonstrate that only 0% to 9% of moderate dysplastic foci and 0% to 32% of severe dysplastic foci progress to CIS or invasive cancer;[37–39] 60% to 65% of moderate or severe dysplastic lesions regress or resolve spontaneously.[37] The uncertainty of the natural history of central airway dysplastic lesions and the increasing incidence of peripheral adenocarcinomas not accessible to bronchoscopic visualization have likely contributed to the lack of benefit observed when evaluating AFB as a screening tool, even in high-risk populations.[40]

Narrow-band imaging (NBI) uses a unique filter to select light wavelengths that preferentially are absorbed by hemoglobin, thereby permitting superior microvasculature detection. Because angiogenesis occurs preferentially in dysplastic and neoplastic lesions, NBI may identify early dysplastic lesions better than WLB or AFB. Early studies with NBI in high-risk patients demonstrated its ability to detect lesions that could not be visualized by WLB, with a similar sensitivity to AFB.[41,42] A comparison of WLB, AFB, and NBI in the same patients who presented for airway surveillance revealed similar sensitivity for AFB and NBI, but improved specificity with NBI for detecting abnormal lesions.[41] Although current clinical applications for AFB and NBI are limited, they may play a role in future risk stratification, prognostication, or chemoprevention trials in high-risk patients.

Another promising technique, optical coherence tomography (OCT), is analogous to ultrasound imaging except that infrared light waves, rather than acoustic waves, are used.[43–49] By using light instead of sound waves, OCT overcomes the major limitations of ultrasound in the lung: the inability to image through air and poor spatial resolution. At present, OCT can resolve structures as small as 3 μm, rendering this imaging technique superior to conventional CT or magnetic resonance imaging for detecting microscopic airway abnormalities (Fig. 33-6). The ability to acquire such precise views in real time may aid in the diagnosis of malignancy and interstitial lung disease in the near future.[50–52] A similar modality, confocal laser endomicroscopy (CLE), is based on confocal microscopy which allows thin section imaging via use of a fiberoptic miniprobe that can be introduced through a flexible bronchoscope. This technology does not rely on light reflectance as in OCT, but rather cellular and tissue autofluorescence upon laser excitation. This technique may offer the possibility of an "optical biopsy" of peripheral lung lesions or lymph nodes at the cellular level, with a resolution up to 3.5 μm, with a 240-μm maximum depth and 600-μm field of view (Video 33-4).[53]

Evaluation of Peribronchial Structures

The trachea and bronchi are surrounded by mediastinal and parenchymal structures. Developmental or pathologic changes in these organs may be noted during bronchoscopic evaluation. An enlarged goiter or thymus may compress upper airways, resulting in airflow obstruction. Lymphadenopathy may produce structural changes, including widening of the carina due to subcarinal involvement and compression of other bronchi—as, for example, in the right-middle-lobe syndrome. Calcification of peribronchial lymph nodes

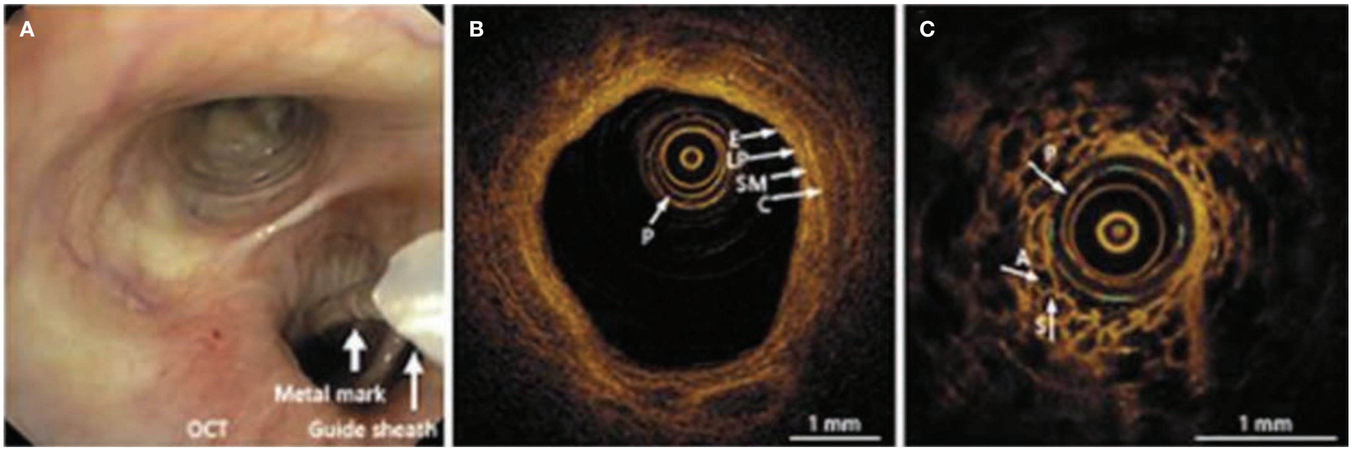

Figure 33-6 OCT imaging procedures of the airway wall and alveolar compartment. **A.** Bronchoscopic view of an OCT imaging procedure showing the guide sheath and the OCT catheter positioned in the right lower lobe. The metal mark guides the distance of 5.4 cm to the distal tip of the OCT catheter. **B.** OCT image of a normal segmental airway wall showing the airway wall layer identification. **C.** OCT image of the alveolar compartment showing normal alveoli and septae. *(Reproduced with permission from Goorsenberg A, Kalverda KA, Annema J, et al. Advances in optical coherence tomography and confocal laser endomicroscopy in pulmonary diseases. Respiration. 2020;99(3):190–205.)*

may result in erosion of the bronchial wall and formation of a broncholith. These lesions are potential sources of obstruction, infection, hemoptysis, or lithoptysis.

Development of the techniques of standard TBNA and EBUS-TBNA provide diagnostic options for the evaluation of peribronchial structures that pose much less risk and a lower complication rate than mediastinoscopy; in addition, they are less costly.[54]

Performance of Bronchial and Parenchymal Biopsies

Improvements in bronchoscopic instrumentation since the days of Chevalier Jackson have permitted performance of endobronchial biopsies, as well as biopsy of peripheral lung lesions. Knowledge of the underlying disease process has a significant influence on the choice of specific diagnostic procedures and risk of complications. In the case of diffuse lung diseases, such as sarcoidosis, use of fluoroscopy has not been demonstrated to improve the diagnostic yield of transbronchial biopsies. Fluoroscopy is useful, however, in providing information regarding the proximity of the forceps to the pleura and in more rapidly establishing the diagnosis of complications (e.g., pneumothorax).

Bronchoscopically visible lesions are generally biopsied with minimal risk; if bleeding occurs, it can usually be controlled easily (Fig. 33-6). The diagnostic yield of bronchoscopy for focal peripheral lesions depends on several factors, including lesion size, its location in the lung, and the relationship between the lesion and bronchus. The presence of a bronchus sign on chest CT predicts a much higher yield of bronchoscopy for peripheral lung lesions. In these cases, fluoroscopy is beneficial to assure proper positioning of the cytology brush, biopsy forceps, or needle. A promising approach with a number of recent innovations is the combination of radial EBUS, augmented fluoroscopy, and navigational bronchoscopy in evaluation of peripheral pulmonary nodules.

Video 33-4 This video demonstrates the findings on "alveoloscopy" using a confocal microscopy probe (Cellvizio, Mauna Kea Technologies, Paris, France). This thin probe is advanced into the distal lung parenchyma through the working channel of a flexible bronchoscope and can image auto-fluorescence of structures of the lung. In particularly, elastin in the alveolar wall is readily detected, and therefore allows for visualization of the architecture of the alveolus, including areas of breakdown in the alveolar wall as may be seen in emphysema. In addition, intra-alveolar macrophages emit significant auto-fluorescence and are therefore readily visualized with the Cellvizio probe. These are the cells seen to be mobile within the elastin-containing alveolar walls on the video. Type I and type II pneumocytes are not readily visualized with this technology. *Video available on AccessMedicine.com.*

The diagnosis of various infectious diseases can be established using a variety of transbronchoscopic sampling techniques. The role of bronchoscopic biopsy has been reaffirmed in immunocompromised hosts, in whom documentation of the precise pathogen is crucial for appropriate therapy. For example, while the presence of cytomegalovirus in bronchoalveolar lavage fluid may not be diagnostic, documentation of intracellular inclusion bodies on a transbronchoscopic biopsy specimen is practically pathognomonic.

Sampling of Airway and Alveolar Constituents

Bronchoscopy provides easy and relatively safe access to material in the tracheobronchial tree and distal alveolar spaces. A variety of studies are routinely performed on specimens obtained from the airways and alveolar spaces using several techniques. For example, aspirated secretions can be sent for microscopy and culture to determine the offending organism in cases of infection or suspected infection. Cytologic analysis of bronchoscopically obtained materials can provide proof of malignancy. Following lung transplantation bronchoscopy plays an important role in the early diagnosis of rejection or infection in these immunocompromised subjects. The most commonly employed bronchoscopic techniques for sampling the airways and alveolar spaces include bronchial wash, bronchial brush (see above), transbronchial forceps biopsy, and bronchoalveolar lavage.

Bronchoalveolar Lavage

Bronchoalveolar lavage (BAL) is commonly performed during bronchoscopy, allowing for the collection of the alveolar milieu for further analysis of its composition.[55,56] BAL is safe, even in critically ill patients, when biopsy or brushings may be contraindicated because of the risk of complications such as pneumothorax or bleeding. Normal saline solution, devoid of any bacteriostatic material, is instilled into distal airspaces through the "wedged" bronchoscope and then aspirated through the instrument's suction channel (Fig. 33-7). The fluid collected in this manner is analyzed for gross appearance to detect

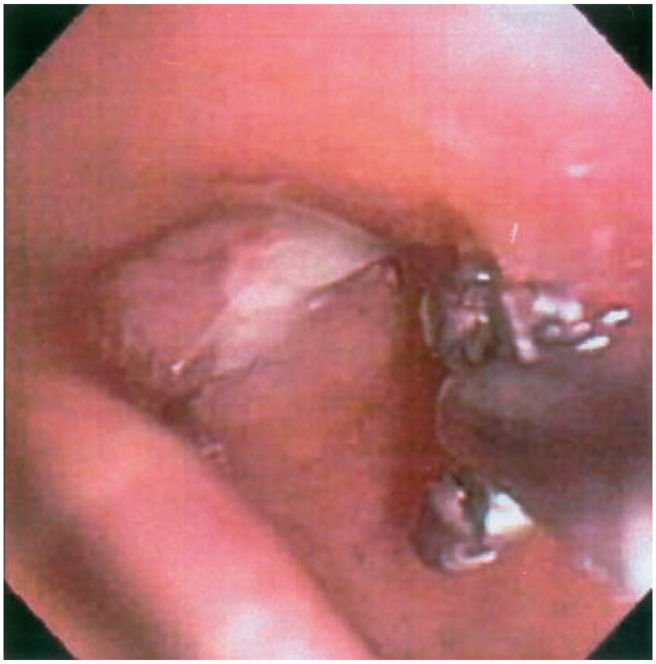

Figure 33-7 "Hot" forceps biopsy of a vascular endobronchial lesion. Use of the electrocautery forceps allows for safe, hemostatic biopsy of friable or vascularized endobronchial lesions (such as bronchial carcinoid), while obtaining pathologically interpretable tissue biopsy specimens.

possible alveolar hemorrhage. The fluid may also be subjected to a variety of tests, depending on the clinical circumstances: microbiologic testing, specific cytologic analysis and cell count, immunologic parameters, presence of various biochemical mediators related to pathologic processes, tissue markers, polymerase chain reaction, electron microscopy, flow cytometry, and DNA probes. Overall, the diagnostic yield of BAL is very much dependent on specific patient characteristics, underlying pathologic process, and many technical factors.

INDICATIONS FOR DIAGNOSTIC BRONCHOSCOPY

Although there are several indications for diagnostic bronchoscopy (Table 33-1), evaluation of a lung nodule or mass and mediastinal staging of a lung cancer are the most common. Sampling a suspected lung cancer now includes the goal of obtaining enough tissue to perform several laboratory assays aimed at immunohistochemical characterization, driver-mutation analysis, and assessment of the immune microenvironment. There are many other potential indications, some of which are discussed below.[57]

Bronchogenic Carcinoma

Bronchoscopy plays a central role in the evaluation of lung masses and nodules, including those suspicious for bronchogenic carcinoma. Centrally located lesions generally may be approached using flexible bronchoscopy with minimal risk. Bronchogenic carcinoma of the central airways may manifest as exophytic mass lesions with partial or total bronchial lumen occlusion, as peribronchial tumors with extrinsic compression of the airway, with submucosal tumor infiltration, or with some combination of these entities. The mucosal abnormalities seen with peribronchial tumors or with submucosal infiltration often are subtle—the airways should be examined closely for characteristic changes such as erythema, loss of bronchial markings, and nodularity of the mucosal surface.

TABLE 33-1 Indications for Diagnostic Flexible Bronchoscopy

Signs and symptoms
Hemoptysis
Stridor
Unilateral wheezing
Hoarseness
Unexplained chronic cough
Infections
Pneumonia in immunocompromised host
Nonresolving pneumonia
Cavitary lesion
Diffuse lung disease
Interstitial lung disease
Diffuse alveolar damage and hemorrhage
Drug-induced lung disease
Malignancy
Lung nodule or mass
Endobronchial tumor
Suspected airway invasion by adjacent malignancies (e.g., esophagus, thyroid)
Early detection (positive sputum cytology/negative CT scan)
Mediastinal or hilar lymphadenopathy or mass
Mediastinal staging or restaging
Other airway disorders
Mucus plugging
Foreign body aspiration
Benign airway stricture (e.g., idiopathic, granulomatosis with polyangiitis [formerly known as Wegener's granulomatosis], sarcoidosis, tuberculosis)
Intensive care
Bronchoscopy-guided intubation (difficult airway)
Endotracheal tube position
Miscellaneous
Lung transplant
Bronchopleural fistula
Aerodigestive fistula
Chest trauma
Chemical/thermal injury of airways
Preoperative and postoperative for lung resection surgery

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Central lesions are usually sampled using a combination of bronchial washes, bronchial brushings, and endobronchial biopsies. The yield of bronchoscopy is highest for endoscopically visible lesions, with a diagnostic yield of approximately 90%.[58] Yield can be optimized further by utilizing the cryoprobe to perform endobronchial biopsies, albeit with an increased risk of bleeding.[59] Attempts should be made to obtain biopsy specimens from areas of the lesion that seem viable. Endobronchial needle aspiration (EBNA) to obtain a "core" biopsy from centrally located tumors can be considered, particularly if the lesion appears necrotic (Video 33-5). For submucosal lesions or peribronchial disease causing extrinsic compression, EBUS-TBNA can be performed with real-time ultrasound

Video 33-5 Demonstrated in this video is the utilization of a standard 22-gauge Wang transbronchial needle aspiration needle (MW-122, ConMed, Utica, NY) for sampling of a partially necrotic endobronchial lesion in the right main stem bronchus. The advantages of bronchoscopic needle aspiration of endobronchial lesions include decreased bleeding risk compared to endobronchial biopsy or brushing; facilitation of sampling of material from the center of the lesion avoiding necrotic surface; and the ability to obtain real-time feedback through rapid on-site evaluation (ROSE) of aspirates by cytopathology. *Video available on AccessMedicine.com.*

guidance. For these indications, EBNA and EBUS-TBNA have been shown to increase the diagnostic yield over conventional sampling methods.

■ Evaluation of Peripheral Lesions and Pulmonary Nodules

The evaluation of peripheral lesions or nodules remains a common dilemma for chest physicians. A balance between pretest probability of a specific diagnosis and the complication risk associated with a biopsy method must be assessed.[60] Surgical biopsy offers a superior yield at the cost of increased morbidity. Transthoracic needle biopsy has a high yield, but it carries a 15% to 25% risk of pneumothorax.[61–63] Although bronchoscopy has the advantage of a low complication risk, it has been hampered by a significantly lower diagnostic yield than these other modalities.

The yield of flexible bronchoscopy for peripheral pulmonary lesions, defined as lesions that are not visible beyond the segmental bronchi, is significantly lower than for central lesions. Historically, in patients with high probability of malignancy, the sensitivity of standard bronchoscopy for peripheral lung malignancies has been reported to range from 35% to 88% based on studies that used a combination of transbronchial biopsy, cytology brush, BAL, and TBNA.[64–80] Recent evidence suggests that the diagnostic yield of standard bronchoscopy (without the use of navigational techniques) for peripheral lesions is under 50% overall, and only 14% in patients with screen-detected nodules.[81] Given this poor performance, conventional bronchoscopy should not be performed in the evaluation of small, peripheral pulmonary nodules.[61,76]

Much effort has been dedicated to further refining our understanding of the diagnostic performance of bronchoscopy for smaller peripheral lesions as technology has advanced. Success depends on several factors, including lesion size, location, prevalence of malignancy in the population being studied, distance from the proximal airways, and the presence of a bronchus sign. The bronchus sign on CT may reflect the relationship of a tumor with the airway and has been categorized into four patterns by Tsuboi:[82] (1) type I, in which the bronchial lumen is patent up to the tumor; (2) type II, in which the bronchus is contained in the tumor mass; (3) type III, in which the bronchus is compressed, narrowed, and displaced by the tumor, but the bronchial mucosa is intact; and (4) type IV, in which the proximal bronchus is narrowed by the submucosal and peribronchial spread of tumor or by enlarged lymph nodes (Fig. 33-8). Transbronchial biopsy has the lowest diagnostic yield for lesions with a type III or IV tumor–bronchus pattern. In these cases, the use of peripheral TBNA may improve the overall diagnostic yield of bronchoscopy.

The use of guided bronchoscopic approaches (e.g., navigational bronchoscopy, robotic bronchoscopy, UM-EBUS, or ultrathin bronchoscopy) has allowed pulmonologists to attempt sampling of much more challenging nodules and significantly improved the diagnostic yield of small, peripheral pulmonary lesions. In a randomized comparison of traditional, fluoroscopically guided transbronchial biopsies (TBB) versus UM-EBUS–guided TBB, no statistical difference was found in establishing a diagnosis for lesions greater than 3 cm; however, for lesions smaller than 3 cm, and for lesions smaller than 2 cm, the sensitivity of EBUS-guided TBB remained at 75% and 71%, whereas that of standard TBB fell dramatically to 31% and 23%, respectively.[83] Similar improvements also have been reported repeatedly with the use of EMB- or VB-based systems for peripheral pulmonary lesions in single-arm, descriptive studies. The early experience with robotic bronchoscopy and augmented fluoroscopy systems also results in similar yields.[5,84]

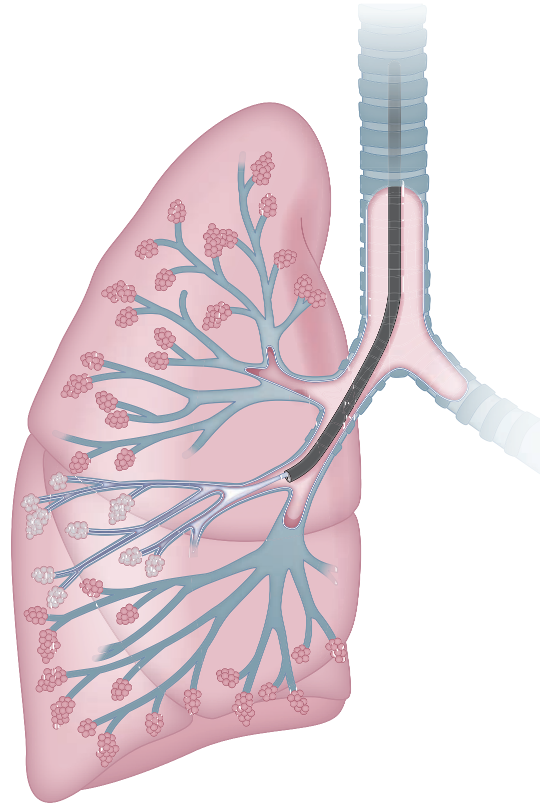

Figure 33-8 Bronchoalveolar lavage is performed by wedging the tip of bronchoscope in the segmental bronchus of interest. Normal saline is instilled into the distal airspaces, and then collected by suctioning back into a sterile container.

A recent meta-analysis of 30 studies with >3000 nodules reported a combined diagnostic yield of 70% for all available guided bronchoscopic techniques.[85] The diagnostic yield was influenced by the size of the primary lesion, with a yield of 61% for lesions <2 cm and 82% for lesions >2 cm.[85] Several other factors also impact the likelihood of obtaining diagnostic tissue using guided bronchoscopy: ability to place UM-EBUS probe completely within a lesion (as opposed to adjacent to it), presence of a bronchus sign on CT scan, location in the middle lobe or lingula, and distance from the visceral pleura.[86–89] The use of TBNA in addition to conventional diagnostic procedures (TBB and BAL) in UM-EBUS-localized lesions also significantly improves diagnostic yield.[11,90]

The evidence on guided bronchoscopy is largely composed of observational studies that provided limited guidance due to bias regarding both modality choice and determination of overall diagnostic yield. Although it is now clear that guided approaches overall are better than conventional bronchoscopy for smaller lesions, only a few comparative studies have been performed that provide evidence on the selection of a particular modality. In one randomized study of EMB alone, UM-EBUS alone, or EMB followed by confirmatory UM-EBUS, there was a significantly higher yield with the combined approach (combination, 88%; UM-EBUS, 69%; EMN, 59%),[91] suggesting that the highest yield

Video 33-6 This video demonstrates use of a 22-guage EBUS-TBNA aspiration needle (Olympus, Center Valley, PA) to sample a left hilar node. The convex probe-EBUS scope is used to identify the left hilar node, allowing visualization of the TBNA needle entering the node in real time. *Video available on AccessMedicine.com.*

may come from combining complementary diagnostic modalities. Similarly, a randomized study combining fluoroscopy, UM-EBUS, and VB with either a thin bronchoscope or ultrathin bronchoscope found benefit in using the ultrathin bronchoscope (70.1% vs. 58.7%).[92] However, a recent randomized study comparing ultrathin bronchoscopy with and without VB did not demonstrate any significant difference in the overall diagnostic yield (67% vs. 60%).[93] Furthermore, another recent randomized trial comparing standard bronchoscopy with fluoroscopy alone to the combination of a thin bronchoscope with fluoroscopy and UM-EBUS also failed to demonstrate a significant difference in diagnostic yield (37% vs. 49%).[94] Further studies are needed to define the utility and specific indications for combination approaches for the sampling of peripheral lung lesions aimed at minimizing bias and maximizing generalizability.[95]

Staging

Bronchoscopy is an important modality for establishing cancer stage. In patients with potentially resectable tumors, a thorough airway examination helps confirm the absence of a concomitant, radiographically occult lesion. For lesions that involve the central airways, it is important to document the extent of disease and the degree of involvement of the mainstem bronchi and main carina.

The use of CP-EBUS allows for real-time visualization and TBNA of hilar and mediastinal lymph nodes or tumors adjacent to the central airway (Video 33-6). Sampling of lymph nodes with EBUS-TBNA is now commonly performed for staging purposes in patients with lung cancer. This technique frequently allows the establishment of both diagnosis and nodal stage, obviating the need for, and avoiding the risks associated with, sampling of the primary parenchymal lesion. TBNA has proved particularly useful with the employment of rapid on-site evaluation (ROSE), in which a cytopathologist present in or near the bronchoscopy suite can evaluate specimens in real-time. Such precise sampling of tumor-draining lymph nodes, or a primary tumor, has led to the exploration of CP-EBUS to facilitate local delivery of cancer therapy.[96]

In general, patients with lung cancer may be separated into four categories with respect to intrathoracic radiographic characteristics, as suggested by the published guidelines on lung cancer staging (Fig. 33-9).[97] In radiographic pattern A, mediastinal infiltration is extensive, with encircling of vessels and airways. In this case, the risk of malignant involvement can be assumed, and biopsy to establish diagnosis should be performed by the safest method available for that particular case. In pattern B, there is discrete lymph node enlargement that can be measured by CT, which may also be FDG-avid. In this case, sampling is recommended, as the likelihood of mediastinal involvement is high and requires confirmation. In radiographic pattern C, the presence of a central tumor or suspected N1 disease makes the likelihood of mediastinal node involvement relatively high (20%–25%), necessitating invasive sampling. In the final group (i.e., those with a peripheral clinical stage I tumor), the chance of either distant metastases or mediastinal involvement is quite low (radiographic group D), especially if the mediastinum is also normal by PET scan.

Some patients with probable early-stage lung cancer may be poor surgical candidates due to inadequate pulmonary function or a high comorbidity burden. In this setting, local treatment approaches most commonly employ include stereotactic ablative radiotherapy (SABR) and radiofrequency ablation (RFA). For patients that will receive nonsurgical therapy, identification of occult lymph node metastases can lead to alterations in the treatment plan. The decision to pursue invasive mediastinal staging should be considered on an individual case basis. Clinical prediction tools may potentially inform the likelihood of mediastinal and hilar node involvement.[98]

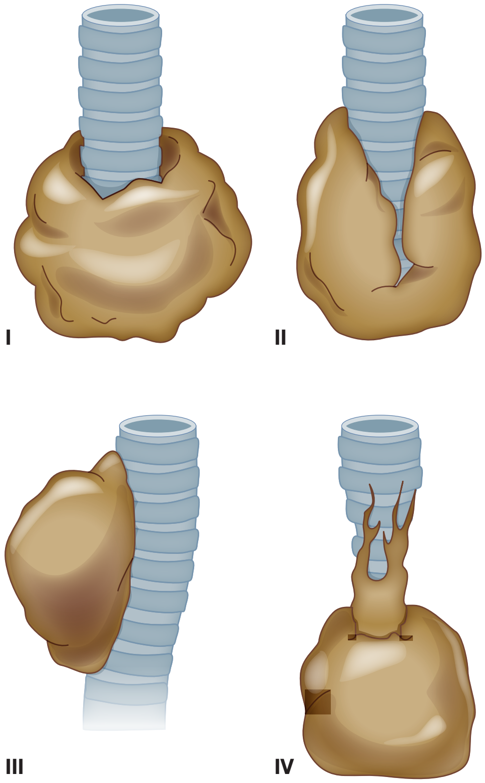

Figure 33-9 Tsuboi classification of tumor-bronchus relationship.

Several systematic reviews have confirmed that the sensitivity of EBUS-TBNA is equivalent to that of mediastinoscopy.[97,99–101] A recent randomized study of 241 patients with potentially resectable NSCLC compared mediastinoscopy alone to a combined approach of EBUS-TBNA and EUS-FNA, followed by surgical staging if the needle technique did not identify nodal metastases.[102] The needle approach followed by mediastinoscopy had significantly greater sensitivity (94%) compared with the other approaches and resulted in fewer unnecessary thoracotomies. One limitation to this approach has been the difficulty in many centers to operationalize a combined EBUS-TBNA and endoscopic (EUS)-FNA procedure. Interestingly, recent studies have shown that the EBUS-TBNA scope can be used through both the airway and the esophagus, resulting in similar results.[103,104] The aforementioned guidelines now recommend that a needle approach should be used first when performing mediastinal staging. Some authors have studied the routine use of EBUS-TBNA performed on radiographic group D patients showing the ability to detect occult metastases.[105] Interpreting a negative EBUS-TBNA should be done with caution as the negative predictive value does fluctuate tremendously based on the pre-test probability. Prediction models may aid decision-making when considering surgical staging methods.[98]

Evaluation of Hemoptysis

One of the most frequent indications for bronchoscopy is hemoptysis. Bronchoscopic evaluation may be of help in determining the precise location and source of bleeding. The choice of instrument (rigid vs. flexible scope) and timing of the procedure are dictated by clinical circumstances.[106] Studies have shown that active bleeding and its site are visualized more commonly with early bronchoscopy (within 48 hours) than with more delayed examination.[106–108] In the case of a normal chest radiograph and hemoptysis, trace signs of bleeding are commonly seen, but not the site of origin.[109] In these circumstances, examination using an ultrathin flexible instrument may be beneficial in identifying the source of bleeding in a peripheral airway once the more proximal airways have been cleared of blood by a therapeutic scope. In some instances, bronchoscopy is useful not only as a diagnostic method, but also to perform therapeutic maneuvers.

Pulmonary Infections

Bronchoscopy is a useful technique in the diagnosis of pulmonary infections, allowing for the collection of respiratory samples for evaluation with special stains and culture. Several common clinical areas in which bronchoscopy may play an important diagnostic role are described below.

Pneumonia

In general, bronchoscopy is not indicated for the diagnosis of community-acquired pneumonia, which is usually treated empirically with appropriate antibiotic therapy; however, bronchoscopy is likely to be useful and should be considered in cases of non-resolving pneumonia,[110,111] defined as a lack of improvement or worsening of symptoms despite a minimum of 10 days of antibiotic therapy or failure of radiographic abnormalities to resolve after 2 to 3 months. The causes of non-resolving pneumonia are myriad and include inadequate antibiotic therapy, resistant or highly virulent organisms, impaired host defenses, obstructing endobronchial lesions, or a noninfectious cause.

Ventilator-Associated Pneumonia

Ventilator-associated pneumonia (VAP) is defined as a pneumonia occurring more than 48 h after intubation and initiation of mechanical ventilation.[112,113] VAP is usually suspected when an intubated, mechanically ventilated patient has signs of infection and an abnormal chest radiograph (Chapter 129). Intubated patients experience colonization of their upper and lower airways with nosocomial organisms; because of an abnormal mucociliary clearance mechanism, these patients are at greater risk for developing pulmonary infections. In addition, mechanically ventilated patients are often treated empirically with broad-spectrum antibiotics and, therefore, are at greater risk for infection with resistant organisms and unusual lower respiratory tract pathogens. Guidelines support the use of either a quantitative or semiquantitative strategy in the diagnosis of VAP.[112]

Quantitative sampling can be performed using endotracheal aspirates, or BAL or protected specimen brush (PSB) collected with or without a bronchoscope.[112,114] Quantitative BAL entails the performance of a standardized BAL, with infusion of at least 120 mL of saline for adequate sampling of a pulmonary subsegment. Quantitative culture of the aspirated material is performed to determine the number of colony-forming units (CFU) recovered. PSB uses a double-catheter system in which an outer cannula and distal, biodegradable plug protect the bronchoscopic brush within the inner cannula from contamination with secretions in the upper airway and suction channel of the bronchoscope. When the bronchoscope is positioned proximal to the segmental orifice of interest, the PSB inner cannula is advanced into a subsegment and the protective distal plug ejected. The brush is then advanced peripherally, rotated gently, and retracted into the inner cannula. The inner cannula is subsequently retracted into the outer cannula and the bronchoscope removed from the airway. The distal portion of the catheter is cleaned with 70% alcohol and the brush clipped into saline solution under sterile conditions. The PSB is then submitted for quantitative bacterial culture within 15 min of performance of the procedure.

The threshold for diagnosis of VAP using PSB is 10^3 CFU per milliliter. PSB has higher specificity than sensitivity for the presence of VAP—a positive result greatly increases the likelihood that pneumonia is present. For quantitative BAL, a threshold of 10^4 or 10^3 CFU/mL is used for diagnosis of VAP.[115] The detection of VAP by quantitative BAL culture has a sensitivity of 40% to 90% and a specificity of 45% to 100%.[115] Because a larger proportion of lung parenchyma is sampled with BAL, this technique may be a better method than PSB for VAP diagnosis. However, samples contaminated by upper airway secretions (based on a high percentage of squamous epithelial cells) should be interpreted with caution. There are likely several factors that affect the diagnostic yield of the bronchoscopic methods, such as a change in antibiotics prior to sampling, inadequate technique in sampling, and lack of a gold standard for comparison.

Infections in Immunocompromised Patients

Pulmonary infections in immunocompromised patients constitute the most common complication in this population and represent an important contributor to mortality. Such infections are increasingly common, reflecting the expanding use of aggressive chemotherapeutic regimens and the ever-increasing number of solid organ and hematopoietic stem cell transplantations. The differential diagnosis of pulmonary infiltrates is broad in scope; however, most cases are caused by infectious agents, including bacterial, fungal, viral, and mycobacterial pathogens.[116] Bronchoscopy is the most commonly used diagnostic procedure in these patients and should be performed as early as possible, because a delay in diagnosis of longer than 5 days has been shown to significantly increase mortality.

The sensitivity of bronchoscopy varies, depending on the immunocompromised population studied and the specific etiologic disorder. In non–human immunodeficiency virus (HIV)-infected patients, the yield of BAL for *Pneumocystis jirovecii* pneumonia (PJP) is approximately 80%, compared with a greater than 90% yield observed in HIV-seropositive patients.[117,118] This difference is due to the much lower organism load present in HIV-negative subjects. Although empirical therapy often is initiated in patients suspected of having PJP infection, bronchoscopy should be performed in most cases to confirm the diagnosis. Bronchoscopic lung biopsy and BAL galactomannan testing may increase the diagnostic yield of BAL for diagnosis of PJP infection, particularly in the non–HIV-infected population.[117] Several PCR assays have been tested on BAL fluid, induced sputum, and oral wash specimens; these generally have been more sensitive, but less specific, than traditional microbiologic methods.

Bronchoscopy also has a high diagnostic yield for cytomegalovirus (CMV); however, because CMV cultures from BAL are not specific, the diagnosis of CMV pneumonia should be limited to patients with pathologic evidence of CMV infection demonstrated by the presence of CMV inclusion bodies on BAL or biopsy. Although bronchoscopy is also useful for the diagnosis of aspergillosis—the sensitivity is approximately 50%—the disease often is peripheral and patchy and, thus, is not easily diagnosed by BAL or bronchoscopic biopsy. Recent clinical practice guidelines now suggest the use of *Aspergillus* PCR in BAL when evaluating severely immunocompromised patients at risk for fungal pneumonia to increase the sensitivity.[119] Overall, in immunocompromised patients with infiltrates, the diagnostic yield of bronchoscopy varies from 30% to 80% and is impacted by factors such as the prevalence of an infectious etiology, timing of bronchoscopy, and use of prophylactic antibiotics.[120–127]

Mycobacterial Infections

In cases in which pulmonary tuberculosis is suspected, the initial diagnostic evaluation should consist of serial examination of sputum for the presence of acid-fast bacilli (AFB) in stained smears. Ideally, induced sputum samples should be obtained. If sputum study results are negative, or if the patient is unable to produce sputum and tuberculosis is still suspected, bronchoscopy with BAL and biopsy should be performed. The use of bronchoscopy allows for the opportunity to establish a rapid diagnosis (by positive smear or histopathology), providing the potential for earlier intervention and treatment while awaiting culture results. Bronchoscopy should be performed with appropriate infection control precautions to minimize the risk of nosocomial transmission. A bronchoscopy may cause the patient to produce sputum for several days afterwards; these specimens also should be collected and analyzed, if possible.

The utility of bronchoscopy in establishing a rapid diagnosis varies widely in the literature, with reported diagnostic yields of 30% to 70%, although the overall yield of culture is considerably higher.[128] One study has shown an improvement in diagnostic yield from 58% to 81% with use of UM-EBUS-guided biopsy and washings.[129] The yield in patients with miliary tuberculosis, in whom sputum smears frequently are negative, is approximately 70%. Bronchoscopy is also useful in tuberculosis manifesting as an endobronchial lesion or with mediastinal and hilar adenopathy, in which case diagnostic tissue may be obtained with TBNA.

Recently, nucleic acid probes have become an important component of the diagnostic armamentarium for mycobacterial disease. DNA probes can be used to rapidly speciate mycobacterium that starts to grow on culture, as is the case for *M. avium* complex and *M. kansasii*. Similarly, nucleic acid amplification and sequencing-based assays can be used on BAL samples to rapidly distinguish tuberculosis from nontuberculous mycobacterium (especially in smear-positive patients), detect drug resistance, and predict culture positivity in smear-negative samples. None of these assays replaces mycobacterial culture, as drug resistance requires confirmation on cultured organisms, and 20% to 50% of positive cultures will not be proceeded by a positive molecular test.[130]

Human Immunodeficiency Virus Syndrome

The introduction of highly active antiretroviral therapy (HAART) has resulted in a sharp decline in the incidence of opportunistic infections in HIV-infected patients. Nevertheless, infectious complications remain one of the most common indications for bronchoscopy in this population. PJP remains the most frequent serious opportunistic infection in HIV-seropositive patients. Bronchoscopy with BAL remains the preferred diagnostic procedure for this disease, although in select centers, use of sputum induction has had a relatively high diagnostic yield and may mitigate the need for bronchoscopy. As previously mentioned, bronchoscopic lung biopsy may increase the diagnostic yield of BAL.[117] Empirical therapy often is initiated in patients with suspected *Pneumocystis* infection; such therapy can impair the diagnostic yield of BAL if the procedure is not performed within 24 h. In patients receiving pentamidine prophylaxis, the diagnostic yield is decreased unless the upper lobes are sampled.[131–133]

Bronchoscopy also plays an important diagnostic role in HIV-positive patients with infections caused by mycobacteria, including tuberculosis, atypical bacterial pneumonias, and various fungal infections. Kaposi sarcoma, caused by human herpesvirus type 8 (HHV8), may be manifest as violaceous endobronchial plaques that typically occur at airway bifurcations; pulmonary parenchymal involvement is characterized by lymphangitic infiltration of tumor, leading to the development of nodules and masses.

■ Diffuse Lung Diseases

A wide range of acute and chronic pulmonary disorders can cause a diffuse interstitial lung disease pattern of injury. These processes include infection, neoplasm, pulmonary edema, alveolar hemorrhage, alveolar proteinosis, occupational lung diseases, drug-induced disease, and various types of idiopathic or collagen vascular disease–associated interstitial lung disease. The pattern of lung injury should first be evaluated using high-resolution chest CT imaging, which helps to narrow the differential diagnosis and, in some cases, is virtually diagnostic of certain disorders. In many cases, it is still necessary to obtain samples for cytologic and histologic evaluation to confirm a specific diagnosis and to help exclude other possible disorders.

The most common bronchoscopic procedures used to help establish the diagnosis in diffuse lung disease are BAL and TBB. The findings on high-resolution CT (HRCT) can be used to determine the best location for BAL or TBB. In truly diffuse disease, the right middle lobe and the lingula are the best locations for BAL; with these sites, ease of access and good fluid retrieval are typical. BAL should be performed using a total of 100 to 200 mL of saline instilled in multiple aliquots. It is important to obtain a reasonable sampling of the alveolar spaces for the necessary cellular analysis.

The value of BAL is well documented in the diagnosis of diffuse parenchymal diseases, and findings may be diagnostic in eosinophilic pneumonia, eosinophilic granuloma, and pulmonary alveolar proteinosis.[57] For example, in acute eosinophilic pneumonia the identification of more than 25% eosinophils on BAL is diagnostic in the appropriate clinical context.[134] In most other diffuse disorders, BAL findings are mostly supportive of a suspected diagnosis (Table 33-2) and help to rule out potential infectious etiologies. In disorders such as sarcoidosis (see below), hypersensitivity pneumonitis, and organizing pneumonia, the combination of BAL and bronchoscopic lung biopsy can often establish the diagnosis and avoid the need for surgical lung biopsy.

In patients with suspected pulmonary sarcoidosis without significant lymphadenopathy, the diagnosis usually is established by a combination of BAL and biopsy findings. BAL can be used to exclude the presence of tuberculosis and fungal infections and may demonstrate the characteristic high CD4+/CD8+ ratio seen in sarcoidosis, whereas bronchoscopic biopsy specimens may demonstrate the classic finding of non-caseating granulomas. In general, TBB should be performed in several affected areas, and at least five or six specimens should be taken. The sensitivity of TBB alone for diagnosis of sarcoidosis is only approximately 60% to 70%.[135–137] Yields may be improved with the additional of endobronchial biopsies, particular in patients with evidence of bronchial mucosal involvement, and with the use of nodal sampling with EBUS-TBNA, as this can provide diagnostic evidence of non-caseating granulomas in 80% to 90% of cases.[138–143] A recent randomized study showed endosonographic needle approaches to have a greater diagnostic yield when compared with bronchoscopic lung biopsy.[144] At present, the data suggest that all patients with suspected sarcoidosis should undergo EBUS-TBNA for lymph node sampling, but it is unclear if bronchoscopic biopsy should be performed in all cases, given the added risk of pneumothorax and hemorrhage. The presence of mediastinal and hilar adenopathy, with or without parenchymal lung changes, also raises the possibility of lymphoma. In cases where lymphoma is suspected, nodal sampling should include histologic samples using mini-forceps (as noted above) or core needle biopsy, and TBNA samples should be performed for evidence of clonal proliferation by flow cytometry.

Bronchoscopy has an evolving role in the diagnosis of idiopathic interstitial pneumonias (IIP), especially idiopathic pulmonary fibrosis (IPF).[145] A nonspecific increase in levels of neutrophils, eosinophils, and, less commonly, lymphocytes has been documented in BAL fluid. Histologic evidence of IPF generally requires documentation of pathologic changes consistent with usual interstitial pneumonia. This is often difficult with bronchoscopic biopsies, which are frequently limited by the small size of the specimen obtained and lack of histologic preservation because of mechanical crushing of the tissue.

TABLE 33-2 BAL Findings in Diffuse Lung Disease

Diffuse Lung Disease	Typical BAL Cellular Pattern	T Lymphocyte CD4/CD8 Ratio	Other Relevant BAL Findings
Sarcoidosis	↑ Total cell count ↑ Lymphocytes	↑	—
Hypersensitivity Pneumonitis	↑ Total cell count ↑ Lymphocytes	↓	Neutrophils can be increased with recent exposure to antigen
Chronic beryllium disease	↑ Total cell count ↑ Lymphocytes	↑	BAL lymphocyte proliferation with beryllium salts
Asbestosis	↑ Neutrophils	↑	Ferruginous bodies
Idiopathic pulmonary fibrosis	↑ Neutrophils ↓ Lymphocytes	—	—
Cryptogenic organizing pneumonia	↑ Neutrophils ↑ Lymphocytes	↓	Foamy macrophages
Pulmonary alveolar proteinosis	Variable	—	Milky fluid and foamy macrophages with PAS-positive material
Drug-induced lung disease	Variable	↓	Foamy macrophages with amiodarone exposure
Pulmonary Langerhans cell histiocytosis	↑ Total cell count Variable differential	—	CD1+ Langerhans cells
Eosinophilic pneumonia	↑↑ Eosinophils	—	Eosinophil counts greater in acute than in chronic pneumonia

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Cryobiopsy may improve the yield of bronchoscopy in IIP, including IPF, as it allows for larger biopsy specimens with increased amounts of alveolated lung parenchyma. Two recent studies reported conflicting results on the concordance between cryobiopsy and surgical lung biopsy in paired samples performed on the same patient, in the same lobe, during the same procedure, with agreement rates of 38% and 71%.[146,147] These studies had key differences in trial design and outcome measures, leaving this clinical question unanswered until further evidence becomes available. While controversy remains over the exact role of cryobiopsy in the evaluation of IIP, many experts, particularly in Europe, have adopted this technique.[148] If the diagnosis of IPF is probable or definite on the basis of clinical and HRCT criteria, bronchoscopy (and surgical lung biopsy) is not required, but in cases where the HRCT findings are not atypical for IPF, bronchoscopy can be performed to evaluate for the presence of other potential etiologic disorders. If a specific diagnosis is not established based on BAL and TBB findings, cryobiopsy or surgical lung biopsy should be considered.

COMPLICATIONS OF BRONCHOSCOPY

Bronchoscopy is a potentially hazardous procedure. Complications are generally due to inappropriate preparation of patients before bronchoscopy, effects of local or general anesthesia, and manipulation of various instruments. Appropriate training and experience of the bronchoscopist and supporting team are crucial in reducing the rate of complications.

Any diagnostic or therapeutic manipulation should be considered in relation to the underlying condition of the patient, localization of the area of investigation, and other surrounding structures in the thorax. It is essential to develop good communication between the bronchoscopist and other members of the team. While the bronchoscopist concentrates on the field of work—which, as seen through the bronchoscope, is two-dimensional—other team members are responsible for monitoring the patient (oxygen saturation, blood pressure, heart rhythm, etc.) and checking and maintaining the adequacy of ancillary equipment (suction, oxygenation, and accessories such as forceps, balloons, catheters, and laser light guides). Risks are decreased if, for example, special attention is paid to the control of accessories during their manipulation beyond the tip of the bronchoscope. Premature deployment of the needle biopsy device or inappropriate bending of the bronchoscope while an instrument is inside the flexible portion can result in perforation of the bronchoscope. Activation of the laser with a broken light guide inside the bronchoscope, or inadequate protrusion of the tip of the fiber beyond the bronchoscope, may result in airway fires or severe burns to the patient. Attention to details and proper maintenance of the equipment, including accessories, enhance safety for the patient and staff. Diagnostic yield and therapeutic results also are improved. Overall, when bronchoscopy is performed by an experienced endoscopist, backed up by a well-trained team and appropriate facilities, mortality and morbidity are very low.

■ Anesthesia and Related Blood Gas Abnormalities

Approximately half of the life-threatening complications of diagnostic bronchoscopy are associated with the risk of topical anesthesia and sedation. Risk is significantly increased in the elderly, and in those with serious concomitant illnesses. Predisposing factors include cardiovascular disease, chronic pulmonary disease, renal and hepatic dysfunction, seizures, and altered mental status. Mild sedation, anxiolysis, muscular relaxation, and anterograde amnesia increase patient cooperation and permit quicker and less traumatic procedures. Doses of benzodiazepines, opiates, propofol, and topical anesthetics must be adjusted if there is underlying organ dysfunction. In the event of severe respiratory depression from excess sedation, flumazenil and naloxone may be administered to reverse the effects of benzodiazepines and narcotics.

Inadequate topical anesthesia potentiates coughing, gagging, and patient discomfort and increases the risk of injury during bronchoscopy. However, topical anesthetics such as lidocaine, the most frequently used agent, are absorbed systemically through the respiratory mucosa, increasing the risk of cardiac or central nervous system toxicity. Although rare, these complications are more likely to occur in patients with underlying low cardiac output, hepatic dysfunction, and oropharyngeal candidiasis.

Another, less frequent complication of excessive lidocaine use is methemoglobinemia and resultant tissue hypoxia. This condition should be suspected when cyanosis occurs following the procedure, in combination with low oxygen saturation, but a higher-than-expected PaO_2 for the degree of cyanosis, and low oxygen saturation. Sampling of arterial blood reveals chocolate-brown blood. Methemoglobinemia occurs because lidocaine causes the rate of hemoglobin oxidation to exceed the reductive capacity of erythrocytes, leading to accumulation of methemoglobin. The diagnosis of this disorder may be made using co-oximetry. Methylene blue (1–2 mg/kg body weight) should be administered to symptomatic patients or when methemoglobin levels exceed 30%.

Introduction of the bronchoscope under general anesthesia or under conscious sedation with topical anesthesia frequently results in a decrease in oxygenation and in hypoventilation, with demonstrable increases in $PaCO_2$. The mechanisms responsible for hypoxemia include acute upper-airway obstruction, hypoventilation, and ventilation–perfusion mismatching. In patients with underlying chronic lung disease, severe hypoxemia may occur, triggering life-threatening cardiac arrhythmias. Skillful manipulation of rigid and flexible bronchoscopes reduces the risk of injury to the upper airways, which can result in life-threatening laryngospasm during or after completion of the procedure. Caution must be exercised in patients with underlying bronchospastic disorders, superior vena cava syndrome, or history of angioedema.

All patients undergoing bronchoscopic procedures should be monitored continuously (electrocardiogram, blood pressure, O_2 saturation, and, if indicated, expiratory CO_2 concentration). Use of supplemental oxygen during the procedure should be routine. Bronchoscopy probably should not be performed in patients who are unable to maintain adequate oxygenation on full ventilator support with high levels of supplemental oxygen.

Significant oxygen desaturation may occur during BAL. The degree of desaturation is directly related to the duration of the procedure and the volume of lavage fluid used. Return to the pre-bronchoscopy oxygen saturation may be prolonged after removal of the bronchoscope, and supplemental O_2 should be continued throughout the procedure and during the post-bronchoscopy observation period.

■ Fever and Infection

Appearance of transient fever after bronchoscopy, reported in 5% to 30% of procedures, generally does not require any therapy. The incidence of fever is increased in the elderly, in those with underlying chronic pulmonary disease or documented endobronchial obstruction, and in those with bronchoscopic interventions for malignancy. The incidence of fever and extension of pulmonary infiltrates increases with the volume of BAL fluid and the total number of pulmonary segments lavaged. In most cases, these complications resolve spontaneously within 24 h. However, persistent fever in the setting of progressive radiographic infiltrates suggests post-procedure pneumonia and necessitates antibiotic therapy. The incidence of post-bronchoscopic infections is higher in immunocompromised hosts and those with chronic suppurative lung disease (e.g., cystic fibrosis). There have also been reports of purulent pericarditis and mediastinitis following TBNA of mediastinal nodes or masses.[149,150]

In high-risk cardiac patients, including those with prosthetic valves, prior endocarditis, complicated cyanotic heart disease, or surgically constructed systemic-pulmonary shunts, American Heart Association guidelines indicate that prophylactic antibiotics are optional prior to flexible bronchoscopy.

■ Pneumothorax

Most of the serious complications related to diagnostic bronchoscopy have been reported in association with performance of transbronchial biopsies. Pneumothorax following transbronchial biopsy occurs in 4% to 5% of cases (Fig. 33-10), although a recent population-based study suggested pneumothorax rates of approximately 1%.[151–160] The impact of fluoroscopy on the incidence of pneumothorax remains controversial. Uncontrolled studies have not found a difference in the incidence of pneumothorax following transbronchial biopsy when performed with and without fluoroscopy.[161]

The risk of pneumothorax is not related to the size of the bronchoscopic biopsy forceps. The incidence of pneumothorax is increased, however, in immunocompromised hosts. This is likely due to the increased risk of pneumothorax associated with PJP. The risk is also elevated in mechanically ventilated patients, with peripheral lung biopsies, and in the presence of bullous lung disease. In rare cases, the development of pneumothorax can be delayed, with patients developing the complication after discharge. In case of a significant pneumothorax, a chest tube should be inserted immediately to avoid oxygen desaturation or tension physiology.

■ Hemorrhage

Clinically significant bleeding as a consequence of diagnostic bronchoscopy is reported to occur in 1% to 4% of cases, but it is more likely to occur after transbronchial biopsy and brushings.[159,160,162,163] This is especially important to consider before transbronchial cryobiopsy, where bleeding should be anticipated and adherence to safety guidelines is key to maximizing patient safety.[164,165] Although hemorrhage may also occur from inadvertent perforation of pulmonary vessels during TBNA, this is a very rare complication. Bleeding is more common in patients with immunosuppressed state, thrombocytopenia, uremia, liver disease, pulmonary hypertension, concurrent anticoagulation, and in those on positive pressure ventilation.

The incidence of post-bronchoscopy hemorrhage in uremic patients is reported as high as 45%. Consequently, a blood urea nitrogen (BUN) level above 30 mg/dL or a creatinine level above 3 mg/dL should be considered relative contraindications to bronchoscopy. Transbronchial biopsy or brushing should not be performed if the platelet count is below 50,000/mm^3. Thrombocytopenic patients may receive platelet transfusions if biopsy is necessary. Similarly, coagulopathic patients should receive vitamin K, fresh frozen plasma, or cryoprecipitate prior to the procedure and biopsy.

Increasingly, patients referred for bronchoscopy are receiving antiplatelet therapy for management of underlying cardiovascular disorders and post-coronary interventions. Importantly, aspirin use has not been shown to increase hemorrhage risk, and it generally does not require discontinuation prior to diagnostic bronchoscopy.[166] In contrast, the risk of bleeding from P2Y2 inhibitors (e.g., clopidogrel) is very high following transbronchial biopsy.[167] If transbronchial biopsies are necessary, P2Y2 inhibitors should be discontinued 5 to 7 days prior to the procedure. We also recommend discontinuation prior to TBNA, although the risk of major bleeding is lower, and successful TBNA may be performed without discontinuation. In cases where antiplatelet therapy cannot be discontinued (e.g., recent coronary artery stenting), careful assessment of the goals of bronchoscopy should be considered and the need for transbronchial biopsy should be clearly defined.

TRANSTHORACIC NEEDLE BIOPSY

Transthoracic needle biopsy (TTNB) has proved a valuable diagnostic procedure in patients with a range of thoracic radiographic abnormalities.

■ Indications and Contraindications

TTNB was first used for the diagnosis of pulmonary disease in 1883, when Leyden performed the procedure on three patients with

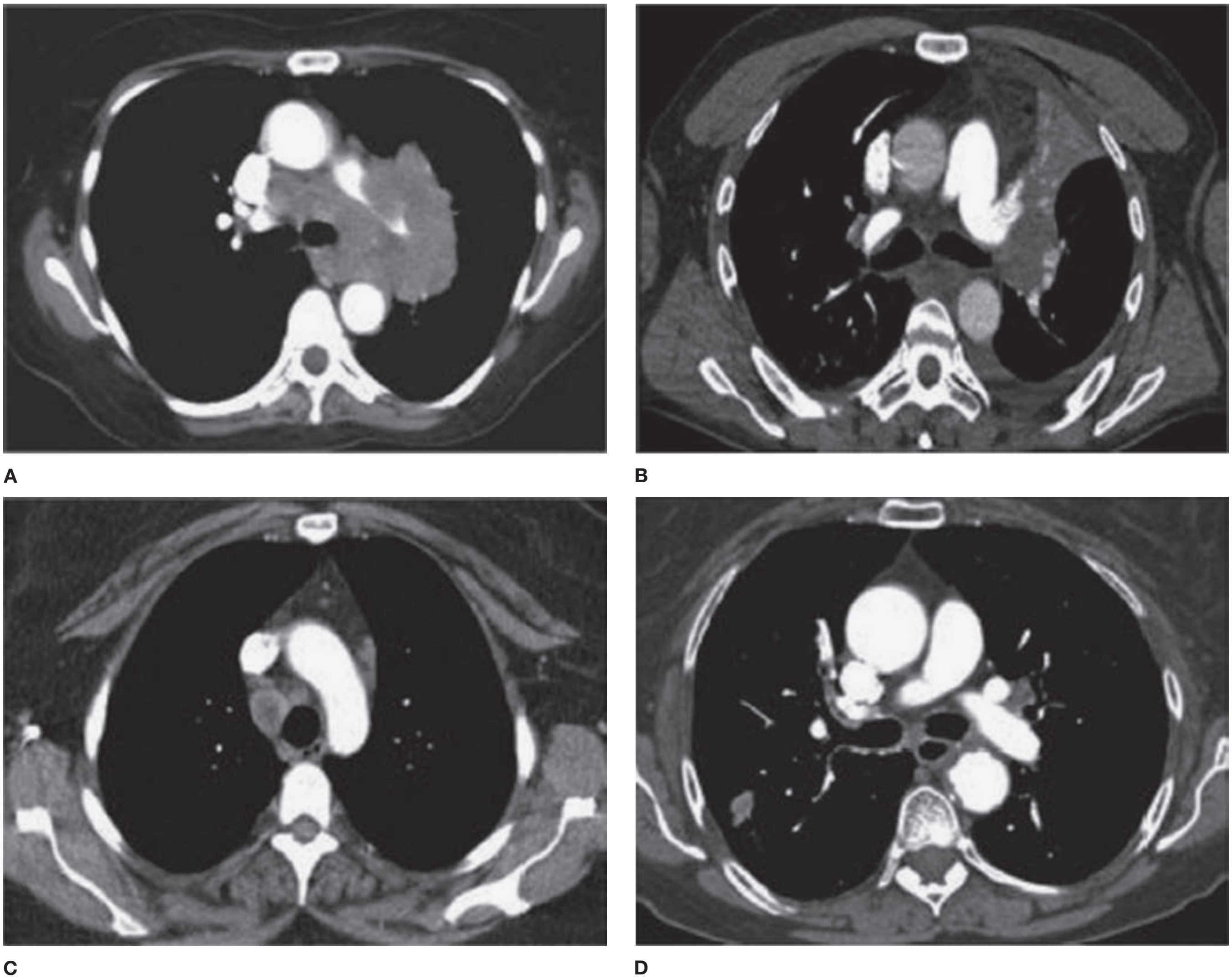

Figure 33-10 Intrathoracic radiographic (CT scan) categories of lung cancer from CHEST Guidelines. **A.** Mediastinal infiltration by tumor. **B.** Enlarged discrete N2,3 nodes. **C.** A central tumor or a tumor with enlarged N1 nodes, but a normal mediastinum. **D.** A peripheral small tumor (seen in lower left corner of image) with normal-sized lymph nodes.

pneumonia. Since that time, many published series have described the use of TTNB for the diagnosis of a variety of benign and malignant thoracic lesions.[168–177] The approach to biopsy may employ either an aspiration approach or an approach based on procuring histologic samples with use of cutting needles. The use of histologic samples provides improved diagnostic accuracy in lymphoma, both Hodgkin's and non-Hodgkin's varieties, in which anatomic structure is important in delineating the type of lymphoma and in distinguishing between clonal, neoplastic processes and inflammatory conglomerations of lymphocytes. Histologic specimens may also improve the yield in the diagnosis of pulmonary hamartomas, characterized by the presence of cartilage or adipose tissue.

The major indications for TTNB include evaluation of solitary lung nodules and masses (Fig. 33-11), mediastinal and hilar lesions, metastatic disease to the lung from a known extrathoracic malignancy, chest wall invasion by lung carcinoma, and pulmonary consolidation or infiltrates that are likely to be of infectious origin.

Few absolute contraindications to TTNB exist. These include an uncooperative patient or one with an intractable cough, as patients must be able to suspend respirations for 5 to 10 s while the needle crosses the pleura. In addition, TTNB is absolutely contraindicated in patients with a suspected pulmonary hydatid cyst because of the risk of capsule rupture and systemic dissemination. Relative contraindications include bullous emphysema, pulmonary arterial hypertension, and coagulation or platelet disorders. Patients with bullous emphysema are at increased risk of developing symptomatic or tension pneumothoraces after biopsy, although most induced pneumothoraces are small and can be treated conservatively. Those with pulmonary hypertension who undergo TTNB have a higher chance of developing pulmonary hemorrhage and significant hemoptysis.

■ Technique

Proper technique in performing TTNB is critical in obtaining adequate material for reliable interpretation. In addition to the mechanics of needle insertion and aspiration, the choice of needle type and careful specimen processing are important aspects of the procedure.

Choice of Needle

There are several different biopsy needles available for use, varying in length, gauge, and sampling mechanism. In general, needles can be divided into those used for aspiration, cutting needles for histologic evaluation, and automatic core biopsy needles. The choice of biopsy needle depends on various factors, including characteristics of the lesion, amount of tissue desired, and operator preference.[178,179]

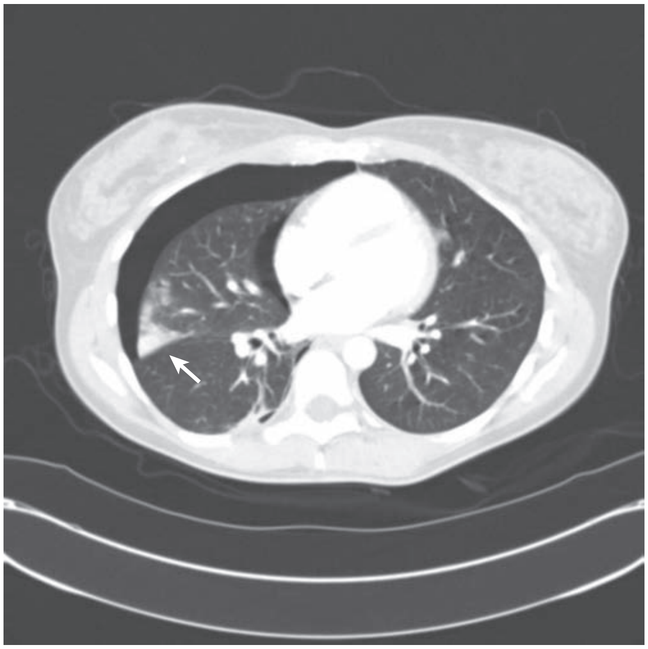

Figure 33-11 CT image demonstrating a pneumothorax of the right lung following transbronchial lung biopsy. An area of focal hemorrhage in the lateral right upper lobe *(white arrow)* as a result of biopsy can also be seen.

In the early 1960s, TTNA was performed using large-bore cutting needles; significant hemorrhagic complications were reported. More recently, thin-needle aspiration has become standard, with devices ranging in size from 18- to 22-gauge. Coaxial needle systems have been introduced for the purpose of obtaining multiple samples from a single pleural penetration. These systems are also useful for procuring specimens for histologic evaluation.

Radiographic Guidance and Biopsy Planning

Although TTNB can be performed under fluoroscopic or ultrasound guidance, CT is now the most commonly used image guidance approach for this procedure. CT can be used either intermittently during the procedure to guide needle placement, or with CT fluoroscopy (CTF) which allows for near real-time acquisition of images to guide needle adjustments. The diagnostic yield from either of these CT-based approaches appears to be similar.

Ultrasound-guided biopsies should be considered for peripheral lung lesions that extend to the pleural edge, or for the diagnosis of mediastinal masses. Ultrasound guidance also offers the advantage of real-time lesion imaging, easy portability, and absence of exposure to ionizing radiation for both the clinician and the patient.

Biopsy planning is an important step and should be performed prior the procedure. Considerations include choosing a needle path that avoids traversal of bullae, vessels, and bronchi. Crossing of interlobular fissures also should be avoided, as this increases the risk of pneumothorax.[180] In cases with more than one lesion, a more peripheral lesion is preferred to decrease the amount of lung traversed during needle insertion. In addition, upper lobe lesions are preferred over the lower lobe because of less respiratory motion in the upper lobes.

Needle Insertion

The lesion is localized using CT guidance, and the overlying skin is marked and anesthetized with 1% or 2% lidocaine. The needle is first inserted through the skin into the subcutaneous tissues. The needle is then advanced to the level of the pleura, followed by verification of the needle position and angle by CT. The needle is further advanced in one motion through the pleura to the prescribed length. The needle position can be confirmed prior to biopsy.

Ideal aspiration technique necessitates having the tip of the needle as close to the center of the lesion as possible. If an aspiration or cutting needle is used, the inner stylet should be removed. A syringe is attached to the needle hub. While suction is applied, the needle tip is advanced and withdrawn about 0.5 to 1 cm within the lesion. The needle is then removed from the chest, suction is released, and the aspirated material is flushed into a specimen container. Several samples should be obtained to increase the diagnostic yield. With a necrotic mass, aspiration should also be performed in peripheral locations of the lesion in order to obtain viable cells and to decrease the risk of false-negative results.

A coaxial technique may also be employed using a larger entry needle, which is advanced into the lesion, followed by a smaller biopsy needle that can be passed through the lumen of the larger needle into the lesion. This approach allows multiple passes into the lesion without repositioning of the needle with each pass.

■ Results

TTNB has an excellent success rate in the diagnosis of primary or metastatic pulmonary malignancies, with meta-analyses demonstrating pooled sensitivity of 90% (95% confidence interval, 88–91);[76] lower yields are seen for lesions smaller than 1.5 cm.[173,177,181] CT guidance yields better performance when compared with fluoroscopy (Fig. 33-12).[182] Aspiration biopsies have similar sensitivity to biopsies performed with cutting needles, but a poorer ability to determine a specific diagnosis from benign lesions. There is also concern that aspiration samples provide a lower likelihood of yielding sufficient tissue for molecular analysis, which is increasingly required in patients diagnosed with lung cancer.

Major causes of false-negative results in malignant disease are inadequate sampling of the lesion and aspiration in an area of necrosis or post-obstructive pneumonia. In addition, small, central malignant lesions may be difficult to diagnose accurately. Aspiration of vascular tumors, such as angiosarcoma, carcinoid, or metastatic renal cell carcinoma may yield a bloody aspirate with few, if any, malignant cells. False-positive results are extremely rare (1%–2%)

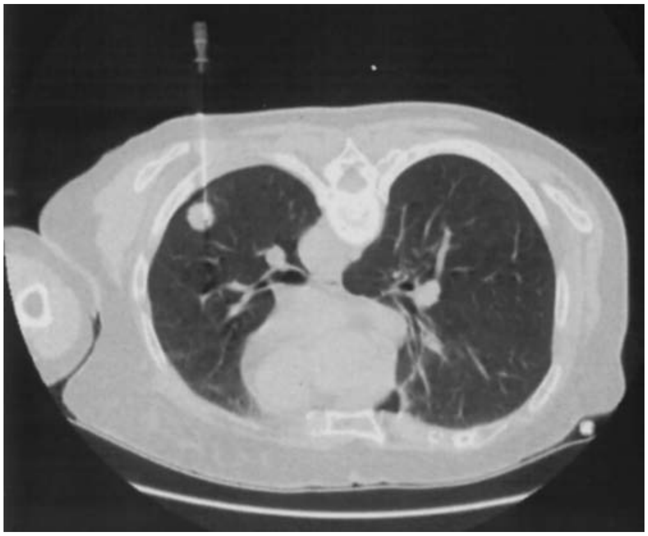

Figure 33-12 Transthoracic needle aspiration of pulmonary nodule. CT scan image of TTNA performed for a 2-cm right-lower-lobe nodule using a 22-gauge Westcott needle (Becton Dickinson & Co, Franklin Lakes, NJ). The needle can be seen entering the nodule. *(Reproduced with permission from Ana Kolansky, M.D.)*

and are typically reported in the setting of inflammatory processes, such as tuberculosis, radiation fibrosis, organizing pneumonia, and pulmonary infarction.

In the absence of a specific benign diagnosis, a lung biopsy that is negative for malignancy does not rule out the presence of neoplastic disease, especially if the biopsy was unsatisfactory. The degree of suspicion of malignancy in a particular clinical situation becomes extremely important in dictating the next step following a negative TTNB. For a smoker with a high risk of bronchogenic carcinoma, the proper course may lead to videothoracoscopic biopsy of the lesion, whereas in a young, otherwise healthy nonsmoker, close observation with serial CT scans may be the preferred option. This choice is influenced in part on the posttest probability of malignancy (after a nonmalignant result by TTNA), which depends on the pretest probability and the negative likelihood ratio (NLR). In an analysis conducted for the British Thoracic Society guidelines, the NLR was calculated at 0.10 allowing determination of posttest probability estimates.[183] As shown in Fig. 33-13, the posttest probability decreases significantly after a negative biopsy, but in patients with high pretest risk (e.g., 90%) there is still approximately a 50% chance of malignancy.

Complications

As mentioned previously, the most common complication of TTNB is pneumothorax; incidence rates reported in the literature vary from 8% to 61%. A recent population-based analysis reported a rate of pneumothorax of 15%, with 7% of all biopsies resulting in a pneumothorax requiring management with a chest tube.[62] Preexisting lung disease—in particular, bullous emphysema—is the most significant predisposing factor to development of pneumothorax after TTNB.[180,184–187] The vast majority of patients who develop clinically significant pneumothoraces after the procedure have an underlying diagnosis of chronic obstructive pulmonary disease. Other risk factors are smaller nodule size, crossing more than one pleural surface with the needle, needle size, and increased patient age.[180,184–187] Factors such as depth of lesion and increased number of transthoracic passes are controversial.[184,188]

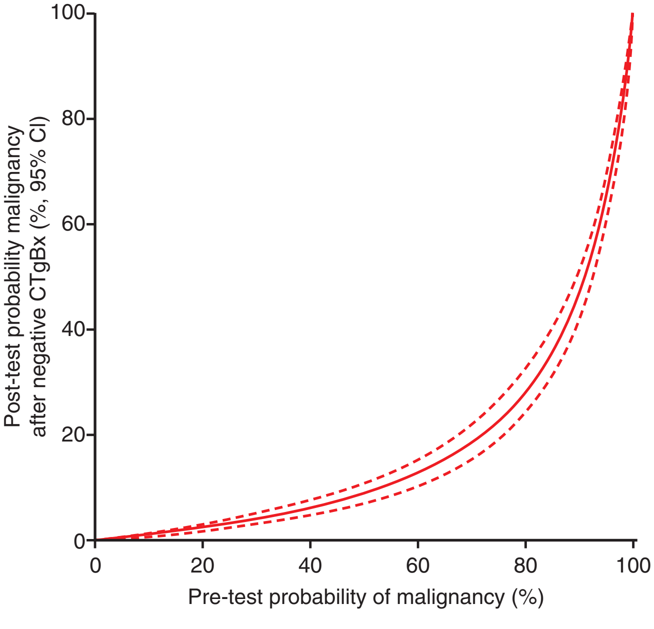

Figure 33-13 The effect of a negative CT-guided percutaneous biopsy on the post-test probability of malignancy. *(Reproduced with permission from Callister ME, Baldwin DR, Akram AR, et al. British Thoracic Society guidelines for the investigation and management of pulmonary nodules. Thorax. 2015;70:ii1–ii54.)*

Uncommon complications of TTNB include hemorrhage and hemoptysis, reported in approximately 1% of all biopsies. Although these are typically minor, one large study reported a transfusion requirement in 18% of cases with hemorrhage.[62] Cases of fatal hemorrhage from tracheobronchial obstruction from clot and subsequent asphyxia after use of large-bore (18-gauge) cutting needles have been reported.

Air embolism is a rare complication caused by creation of a communication between atmospheric air and a pulmonary vein. To minimize this risk, the needle should never be left open to air while in the chest, and the patient should be discouraged from deep breathing, straining, or coughing during the procedure. The procedure should be halted and the needle withdrawn if the patient is actively coughing. If an air embolism is suspected, 100% oxygen should be administered through a non-rebreather face mask and the patient placed in the left lateral decubitus position, with the head down; this position optimizes capture of air in the right heart. The patient should be transferred immediately to a hyperbaric chamber.

SUMMARY

Technologic advances in diagnostic bronchoscopy continue to improve our ability to perform minimally invasive, accurate evaluations of the tracheobronchial tree and to perform an ever-increasing array of diagnostic procedures. The continued development of imaging technologies and ancillary tools will certainly provide improvements in many of the modalities described above. Future improvements will include refinements in video and ultrasound imaging technology and the development of newer modalities, such as molecular imaging. This will be accompanied by further improvements in the ancillary tools, such as miniaturization of diagnostic accessories and further refinements in steerable probes that will allow improved access to peripheral regions of the lung. Improvements in image guided TTNA have also advanced the ability to safely and accurately sample lesions not accessible by bronchoscopy. These opportunities will need to be accompanied by well-designed studies to delineate the appropriate use of these techniques in clinical practice.

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CHAPTER 34

Interventional Pulmonology

Daniel G. Dunlap
Andrew R. Haas
Daniel H. Sterman

INTRODUCTION

The first known bronchoscopy was performed by Gustav Killian in 1897 when he removed a pork bone from the right mainstem bronchus of a patient. For the subsequent 70 years, bronchoscopy was predominantly a therapeutic procedure performed for foreign body extraction. Two events shifted the landscape of bronchoscopy—the lung cancer epidemic and the development of flexible bronchoscopy by Shigeto Ikeda in 1967. Following an escalation in lung cancer incidence, malignant airway obstruction requiring therapeutic intervention became much more common than foreign body extraction. As a result, new tools were developed to address malignant airway obstruction based upon a minimally-invasive bronchoscopic approach. In addition, bronchoscopy-based technology has been developed to treat asthma, as well as select chronic obstructive pulmonary disease (COPD) phenotypes. This chapter presents an overview of interventional bronchoscopy and related modalities that can be utilized for benign and malignant airway obstruction, COPD, and asthma.

TABLE 34-1 Indications for Interventional Bronchoscopy

Hemoptysis
Atelectasis from inspissated secretions
Foreign body removal
Tracheobronchial tree neoplasms (primary or metastatic)
Direct bronchoscopic debulking
Laser therapy
Electrocautery/argon plasma coagulation
Cryotherapy
Brachytherapy
Photodynamic therapy
Stent placement
Airway strictures and stenoses
Rigid bronchoscopic dilation
Stricture/stenosis incision
Balloon tracheobronchoplasty dilation
Stent replacement
Lung lavage (pulmonary alveolar proteinosis)
Bronchoscopic drainage—lung abscess
Endotracheal tube and percutaneous tracheostomy placement
Treatment of persistent air leak
Evolving therapies for emphysema
Bronchial thermoplasty in severe asthma

INDICATIONS FOR INTERVENTIONAL BRONCHOSCOPY

Many potential indications for interventional bronchoscopy have been recognized, including malignant airway obstruction, benign airway obstruction, and foreign body extraction, among others (Table 34-1). The majority of therapeutic bronchoscopies performed today are undertaken for management of malignant airway obstruction, most commonly from lung cancer. It is estimated that up to 40% of patients with lung cancer develop symptomatic airway obstruction at some point during their disease process. Although lung cancer is the most common source of malignant airway obstruction, any primary thoracic malignancy or pulmonary metastases may result in symptomatic airway obstruction. Regaining airway patency to palliate symptomatic dyspnea and other respiratory symptoms can significantly improve the quality of life for patients with advanced malignancy.

Benign airway obstruction etiologies are listed in Table 34-2 and consist of a variety of localized inflammatory and systemic conditions. Although the etiologic airway process is benign and not malignant, the interventions and management of these complex processes are far from benign to the patient. Interventional bronchoscopy techniques can often improve the presenting symptoms; however, symptomatic stenosis often recurs, and patients may require repeat procedures to maintain airway patency. Selected patients may need to proceed with airway resection of the benign stenotic airway segment.[1]

Most patients with airway obstruction present with dyspnea or cough. Depending on the rapidity of airway obstruction, dyspnea may have a rapid onset or, more commonly, an insidious evolution that gradually limits patient activities. It is not uncommon for a family member to recognize this limitation more readily than the patient. As the airway obstruction worsens, the patient may develop orthopnea, which is a harbinger of an evolving critical

TABLE 34-2 Etiologies of Benign Tracheobronchial Stenosis

Endotracheal intubation
Tracheostomy tube
Granulomatosis with polyangiitis (formerly known as Wegener granulomatosis)
Amyloidosis
Sarcoidosis
Tuberculosis
Inflammatory bowel disease
Idiopathic
Trauma
Lung transplantation
Post resection or airway repair
Trauma
Recurrent stenosis after prior stenosis resection
Sleeve resection
External beam radiotherapy or high-dose-rate brachytherapy (HDRB)
Photodynamic therapy
Thermal injury from fire exposure
Tracheobronchopathia osteochondroplastica
Postpneumonectomy syndrome
Fibrosing mediastinitis
Large vascular aneurysms

airway obstruction. Other symptoms, such as cough, inability to clear secretions, audible respirations, chest discomfort, or fever from post-obstructive pneumonia may develop. Early intervention is important to prevent worsening respiratory compromise or death.

SPECIAL CONSIDERATIONS FOR PATIENT PREPARATION, SEDATION, AND MONITORING

All patients undergoing bronchoscopy should undergo a complete pre-bronchoscopy evaluation, including a medical history, physical examination, and chest imaging. Although routine laboratory tests are not required, each evaluation should be individualized on the basis of patients' underlying conditions and the therapeutic procedures planned. CT imaging is important to assess the degree of airway involvement and to plan interventions.

Sedation and analgesia for patients undergoing interventional bronchoscopy must be considered carefully. Stable patients who can lay flat without distress can undergo bronchoscopy with moderate sedation. Should the patient have moderate or severe respiratory distress or be unable to lay flat, strong consideration should be given to additional monitoring or anesthesiology procedural assistance. Patients with high oxygen requirements may require endotracheal intubation to reduce the risk of developing hypoxemic respiratory failure during moderate sedation. Moreover, if patients are unable to lie flat, they may require an initial upright bronchoscopy with topical oropharyngeal anesthesia under minimal sedation to temporize luminal diameter before undergoing general anesthesia and more definitive interventional bronchoscopy.

Similar to diagnostic bronchoscopy, if a patient is stable for moderate sedation, topical analgesia of the oropharynx and airways should be achieved with lidocaine, followed by administration of a combination of a short-acting benzodiazepine (e.g., midazolam) and a narcotic (e.g., fentanyl).[2] Rigid bronchoscopy is most safely performed with a patient receiving general anesthesia and breathing spontaneously or paralyzed while being ventilated with a jet ventilator.[3] General anesthesia with inhaled anesthetics (e.g., sevoflurane) should be avoided in favor of total intravenous anesthesia in order to avoid exposure of the bronchoscopist to inhaled anesthetics when the ventilator circuit is open. With appropriate planning and monitoring, the vast majority of patients can undergo interventional bronchoscopy with low complication rates.

TYPES OF AIRWAY OBSTRUCTION

Figure 34-1 demonstrates the three main types of airway obstruction that may be encountered: purely intrinsic (A), purely extrinsic (B), or a combination of both intrinsic and extrinsic airway obstruction (C). Attention to preprocedural CT imaging allows fairly accurate assessment of these components and enables the therapeutic bronchoscopist to plan an approach. For lesions that are purely intrinsic, direct bronchoscopic debulking with rigid bronchoscopy, thermal ablation, cryotherapy, or snare extraction with or without stent placement is appropriate. For purely extrinsic lesions, no tumor is present to debulk, and modalities used in purely intrinsic disease cannot be employed due to the risk of airway perforation. Extrinsic lesions are most amenable to balloon bronchoplastic dilatation and endoluminal stent placement. For mixed intrinsic–extrinsic lesions, tumor debulking modalities, as well as dilatation and stent placement, are feasible.

■ Endoluminal Airway Obstruction

Endoluminal obstruction of the tracheobronchial tree may result from various benign and malignant processes. The most common cause of endobronchial obstruction is advanced lung carcinoma. In patients with inoperable central airway tumors, restoration of airway patency may provide palliation, improve quality of life, and can even prolong life, particularly in the case of impending respiratory failure or postobstructive pneumonia.

Signs and symptoms of malignant central airway obstruction vary but often include progressive dyspnea and functional limitation, wheezing, cough, stridor, hoarseness, hemoptysis, and chest pain. A careful pretreatment evaluation should be performed to distinguish symptoms attributable to focal tracheobronchial lesions from those related to underlying obstructive lung disease, parenchymal lung disease, or both. Although pulmonary function testing and thoracic imaging techniques, such as chest CT scan, may be useful in the evaluation of a patient with suspected malignant airway obstruction, bronchoscopy, either rigid or flexible, remains the diagnostic and therapeutic "gold standard." Increasingly, however, three-dimensional reconstruction CT imaging, so-called "virtual bronchoscopy," is being applied as a reliable noninvasive method of assessing the nature and extent of malignant airway obstruction, thereby allowing preprocedural intervention planning.

The bronchoscopic approach to management of malignant airway obstruction depends on the lesion location, presence or absence of associated extrinsic compression, and degree of clinical urgency. Rigid bronchoscopic debulking using adjunctive thermal ablation is recommended when airway recanalization must be performed on an emergency basis. If endobronchial obstruction is accompanied by marked extrinsic compression, stent placement may be beneficial.

The complexity of a lesion is equally important in determining the best approach to therapeutic bronchoscopy. Benign tracheal webs often are managed using laser or electrocautery-mediated resection alone, whereas complex fibrotic strictures may warrant the combination of rigid bronchoscopic or balloon dilatation, thermal incision, and stent placement. For focal tracheal stenosis in patients at low risk for complications, surgical resection with primary reanastomosis should remain the definitive treatment choice.

■ Extrinsic Airway Compression

Extrinsic airway compression usually results from malignant involvement of structures adjacent to the central airways, such as mediastinal lymph nodes or the esophagus, but it may be associated with a benign process, such as fibrosing mediastinitis, tuberculosis, aneurysmal dilatation of the aorta, or sarcoidosis. The clinical signs and symptoms of extrinsic airway compression often mimic those of endobronchial obstruction. The diagnosis is established on the basis of bronchoscopic detection of marked airway narrowing in the absence of an endoluminal mass.

Therapeutic options in the management of extrinsic airway compression are limited. Ablative endoscopic approaches, such as laser therapy, cryotherapy, PDT, and electrocautery are contraindicated because of the lack of demonstrable benefit and risk of airway perforation. Although some patients with malignant disease may benefit from endobronchial brachytherapy, tracheobronchial stent placement is the palliative treatment of choice for patients with symptomatic extrinsic airway compression.

TYPES OF THERAPEUTIC BRONCHOSCOPY INTERVENTIONS

A variety of bronchoscopic interventions are in common clinical use and are described below.

■ Rigid Bronchoscopy

The initial bronchoscope, developed by Killian, and further optimized by Chevalier Jackson, was a rigid metal tube that permitted either spontaneous or mechanical ventilation.[4] Over the decades, rigid bronchoscopes of various lengths and diameters have been developed that are adaptable for diverse applications in children and adults. Although the flexible bronchoscope has to a large extent replaced the rigid scope

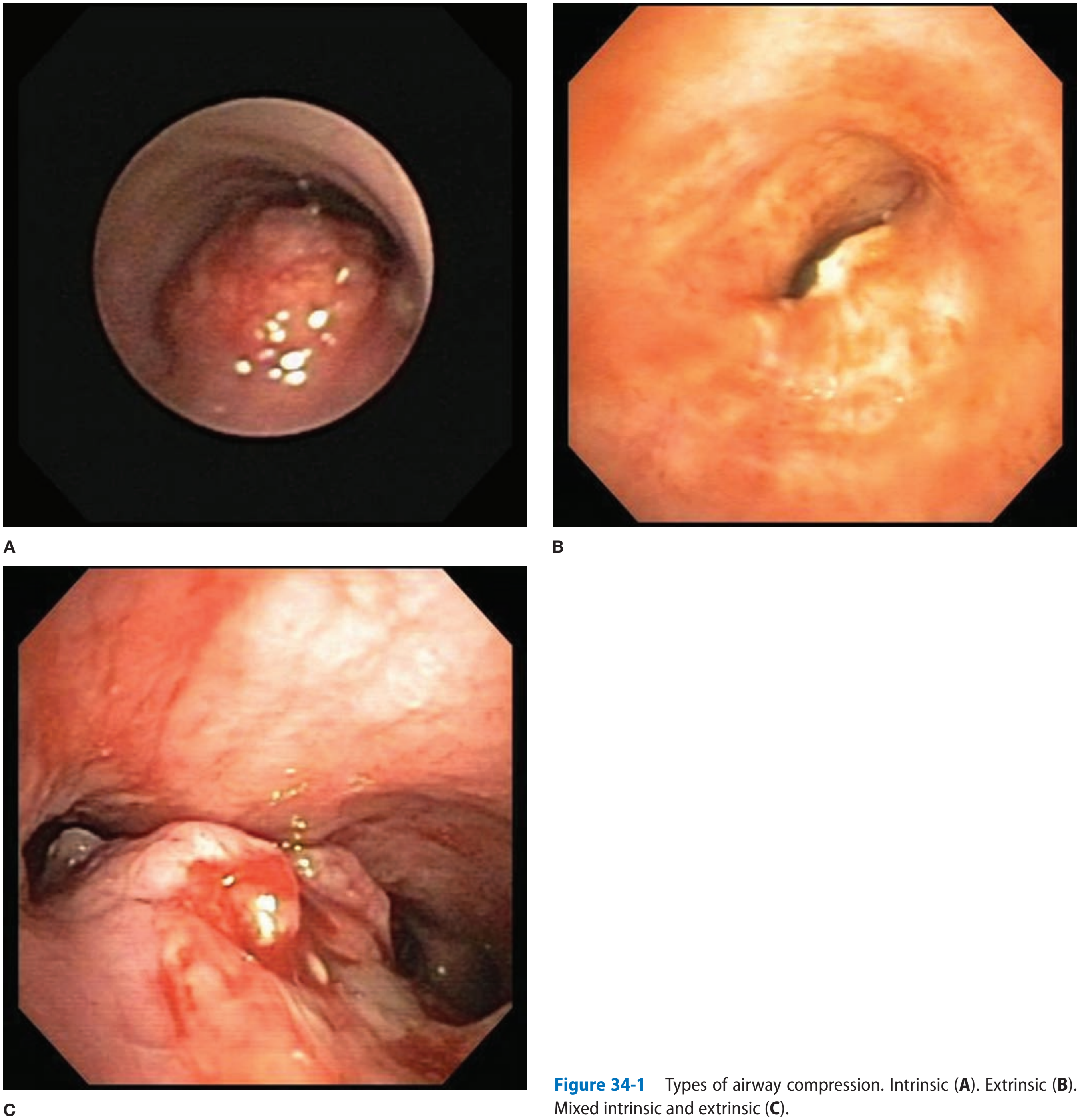

Figure 34-1 Types of airway compression. Intrinsic (**A**). Extrinsic (**B**). Mixed intrinsic and extrinsic (**C**).

for most diagnostic and some therapeutic indications, rigid bronchoscopy still has vital therapeutic applications.

Modern rigid bronchoscopy systems are equipped with optical capabilities to allow better direct, magnified, circumferential illumination and visualization. The main advantage of rigid bronchoscopy over flexible bronchoscopy is its luminal working diameter, which allows multiple therapeutic instruments to be utilized simultaneously while ventilating the patient. Rigid bronchoscopy allows a number of therapies, such as laser photocoagulation, placement of endobronchial stents, balloon dilatation, electrocautery, argon plasma coagulation, and cryotherapy to be performed safely and effectively. Perhaps most importantly, in the setting of malignant airway disease or obstruction, a rigid bronchoscope can be used to "core out" large bulky airway tumors more efficiently and effectively than any thermal modalities (Video 34-1). Initial rigid bronchoscopic debulking, followed by thermal modality ablation to cauterize remaining tumor, is common.[5] For benign, fibrotic airway stenosis, the rigid bronchoscope becomes a very effective modality to partially debulk stenotic tissue and to dilate the stenosis.[6] In experienced centers, rigid bronchoscopic airway recanalization remains the treatment of choice for serious or life-threatening tracheobronchial obstruction.

Video 34-1 A patient with a right paratracheal mass who underwent diagnostic and therapeutic bronchoscopy. Endoluminal tumor growth was present along the right lateral tracheal wall. The video demonstrates effective and efficient use of rigid bronchoscopy to mechanically debride tumor. *Video available on AccessMedicine.com.*

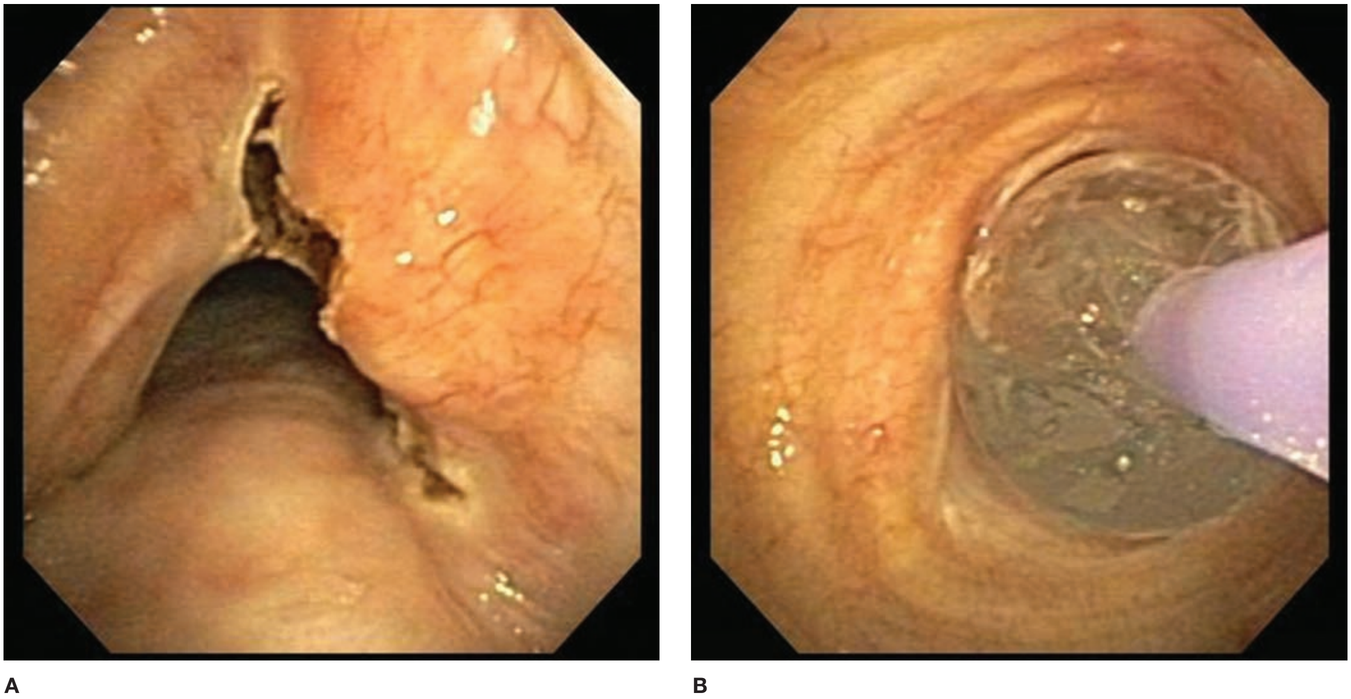

Figure 34-2 Electrocautery incisions were made into the benign stenotic lesion (**A**). Following incision, balloon bronchoplasty dilatation was performed (**B**).

The main complication from rigid bronchoscopy is dental injury from the scope fracturing teeth. Other complications, such as oropharyngeal laceration, arytenoid cartilage disarticulation, or vocal cord injury, are possible. Meticulous care upon rigid bronchoscope intubation is critical to avoid these potential complications. Intrathoracic complications, such as airway perforation, major bleeding from tumor debulking, and pneumothorax or pneumomediastinum also are possible but are infrequent in experienced hands.

■ Balloon Tracheobronchoplasty

Balloon dilatation has become an attractive alternative to rigid bronchoscopy for management of airway obstruction in benign and malignant airway obstruction, especially in anatomic locations where a rigid bronchoscope cannot enter or the luminal diameter is too narrow to allow safe rigid bronchoscope passage. High-pressure balloons of various lengths and diameters specifically designed for the tracheobronchial tree are readily available. These balloons are filled with saline or radio-opaque contrast media, advanced to the site of interest through the bronchoscope, and inflated until the desired diameter is attained.

In the setting of benign stenosis, an initial defect in the stenosis is often made with a thermal modality so as to control the stenotic release point (Fig. 34-2). This approach has been used successfully in benign stenoses from endobronchial tuberculosis, idiopathic subglottic stenosis, and posttransplant anastomotic strictures.[7] Balloon dilatation is less successful when used alone to treat airway compromise accompanied by extrinsic airway compression, as the initial bronchoscopic improvement often rapidly returns to its original position as the extrinsic process persists. Complications of balloon dilatation include bronchospasm, chest pain, mucosal laceration, airway perforation, bleeding, postprocedure airway edema, pneumothorax, and pneumomediastinum.

■ Bronchoscopic Laser Therapy

Perhaps the most widely known technique in therapeutic bronchoscopy is laser photocoagulation or photoablation. Table 34-3 compares characteristics of the laser modality compared with other modalities to be presented later. Lasers produce a beam of monochromatic, coherent light that induces tissue vaporization, coagulation, hemostasis, and necrosis. Although primarily useful in endoluminal malignant tumor ablation, bronchoscopic laser therapy also is beneficial in other tracheobronchial disorders, including inflammatory strictures, obstructive granulation tissue, amyloidosis, and benign tumors, such as hamartomas and lipomas.

Since the initial report of endobronchial laser ablation of an obstructive neoplasm by Laforet in 1976, several types of lasers have become available for management of tracheobronchial obstruction.[8] The carbon dioxide (CO_2) laser, used primarily by otolaryngologists, allows shallow tissue penetration (to a depth of 0.1–0.5 mm) with very precise cutting, but it has minimal hemostatic properties. With the development of other laser modalities, the CO_2 laser has minimal current application in endobronchial tumor ablation, and its role remains primarily in management of laryngeal lesions and subglottic stenosis.

For therapeutic bronchoscopy, neodymium:yttrium-aluminum-garnet (Nd:YAG) laser ablation is most commonly used (Video 34-2). It provides tissue penetration to a depth of 3 to 5 mm, and superior coagulation with improved hemostasis, but at the cost of less cutting precision. Nd:YAG laser procedures may be performed through a rigid or flexible bronchoscope.

Use of Nd:YAG laser photoablation therapy as a single modality is associated with a recanalization rate >90% for central airway endobronchial obstruction.[9,10] Nd:YAG laser photocoagulation may be an important treatment tool for patients with airway obstruction caused by benign endoluminal tumors. The Nd:YAP (yttrium-aluminum-perovskite) laser, with a patented wavelength of 1.34 μm,

Video 34-2 A patient who presented with a new right mainstem obstruction from lung cancer. The video shows Nd:YAG tumor coagulation and debulking. *Video available on AccessMedicine.com.*

TABLE 34-3 Therapeutic Bronchoscopy Ablation Modalities

Therapy	Type of Lesion Therapy	Type of Bronchoscope	Rapidity of Positive Result	Repeatability
Mechanical debridement	Endoluminal or submucosal	Rigid or flexible (rigid preferable)	++++	+
Laser	Endoluminal	Rigid or flexible (rigid preferable)	++++	++++
Argon plasma	Endoluminal	Rigid or flexible	++++	++++
Brachytherapy	Endoluminal or submucosal	Flexible	+	+
Cryotherapy	Endoluminal	Rigid or flexible	++	+++
Balloon dilation	Endoluminal or submucosal with extraluminal compression	Rigid or flexible (rigid preferable)	++++	++++
Photodynamic therapy	Endoluminal	Flexible	++	+++
Electrocautery	Endoluminal	Rigid or flexible	+++	++++
Stent	Endoluminal with extraluminal compression	Rigid or flexible (Dumon stent requires rigid bronchoscope; Wall stents and Gianturco stents require fluoroscopy)	++++	+++

is purported to have better water absorption at that wavelength, thereby improving the power-to-effectiveness ratio compared with traditional Nd:YAG laser and carrying a lower complication risk.

Although endobronchial laser therapy generally is safe and well tolerated, it may be complicated by cardiac arrhythmias, airway perforation, pneumothorax, hemorrhage, hypoxemia, or endobronchial fire.[11,12] Endoluminal laser utilization requires careful consideration of the lesion, anatomic location, and configuration relative to vital intrathoracic structures. If the lesion is in close proximity to the esophagus or pulmonary artery, endobronchial laser therapy carries risk for fistula formation. Laser therapy in a patient with tracheobronchial narrowing caused by extrinsic compression may result in airway perforation. In rare cases, pulmonary edema or fatal pulmonary venous gas embolism have been reported.[13] Patients with standard silicone endotracheal tubes or silicone tracheobronchial stents, and those who require high concentrations of supplemental oxygen, are at increased risk for endobronchial fire. The bronchoscopist needs to ensure the inspired oxygen level is ideally <40%, especially if the patient is receiving mechanical ventilator support during the procedure. Fortunately, the overall risk of endobronchial fire is <0.1%.

■ Endobronchial Electrocautery, Argon Plasma, and Cryotherapy

Electrocautery, argon plasma coagulation (APC), and cryotherapy are cost-effective alternatives to laser therapy for the management of tracheobronchial lesions and obstruction, as equipment expenses are substantially less compared with laser therapy. Penetration depth and per-treatment effectiveness may be less than with laser therapy.

Electrocautery effects on tissue are similar to those of Nd:YAG laser with tissue destruction induced by coagulative necrosis (Video 34-3). APC is similar to electrocautery except that it uses argon gas to conduct the electrical current, rather than a contact probe. Electrocautery and APC have a 1- to 3-mm penetration depth and are, therefore, more suitable for the treatment of superficial and spreading lesions than large central tumors (Video 34-4).

In contrast with electrocautery or APC, cryotherapy induces tissue necrosis through hypothermic intracellular crystallization and microthrombosis. Specially designed cryoprobes are inserted through the bronchoscope until they contact target tissue. Cryoprobe activation introduces liquid nitrous oxide or carbon dioxide through a small orifice in the probe under pressure, resulting in rapid cryoprobe cooling with creation of an “ice ball” (approximate temperature, −40°C) at the probe tip on target tissue. This freezing effect is maintained for approximately 30 s; the area is then allowed to thaw, and freezing is repeated two to three times to achieve necrosis by cellular rupture from repeated cycles of intracellular microcrystallization. Cryospray technology utilizes administration of liquid nitrogen at −196°C to tissue of interest in a controlled fashion, using an open airway to prevent barotrauma. This modality freezes water in cells, resulting in cell death, while preserving tissue matrix and healing.

Electrocautery, APC, and cryotherapy have been used successfully to relieve airway obstruction and treat hemoptysis caused by benign and malignant tracheobronchial tumors, polyps, and granulation tissue.[5,9,14–19] These modalities have been used effectively in radiographically occult mucosal lung cancer, carcinoma in situ, and mucosal dysplasia. Cryotherapy may be advantageous in cryoextraction of foreign bodies that can be frozen to the probe and removed.[20] This technique works very well for mucoid plugs or blood clots in large airways where other modalities may be associated with difficult removal.

Although the range of complications from electrocautery and cryotherapy are the same as those discussed for laser therapy, the most common complication of each is bleeding secondary to disruption of endobronchial tumor without full-tissue coagulation. The estimated incidence of clinically significant bleeding in patients treated with electrocautery is 2.5%. Rarely, gas embolism can occur with APC.[21,22] Importantly, unlike the heat thermal modalities, cryotherapy can be performed in patients in whom

Video 34-3 A patient with a history of renal cell carcinoma who presented with dyspnea and left lung atelectasis. CT scan demonstrated left mainstem bronchus obstruction. The video shows a rigid bronchoscopy with electrocautery snare excision and removal of a large polypoid renal carcinoma metastasis. The point of airway attachment was then cauterized using electrocautery. *Video available on AccessMedicine.com.*

Video 34-4 This patient had a prior bronchoscopy for minor hemoptysis; endobronchial biopsies demonstrated carcinoma in situ. The video demonstrates argon plasma coagulation ablation of the involved sites from prior biopsies. *Video available on AccessMedicine.com.*

high oxygen levels are required due to hypoxemia without a risk of airway fire.

Endobronchial Brachytherapy

Endobronchial high-dose-rate brachytherapy (HDRB) refers to bronchoscopic radiation delivery to a localized airway lesion. The technique aims to delivery therapeutic radiation to localized lesions while minimizing exposure to nontarget tissues. Endobronchial brachytherapy involves the bronchoscopic insertion of a thin, hollow "afterloading" catheter across an area of interest (usually malignant tissue) under direct bronchoscopic and fluoroscopic guidance. The catheter is left in place, and the patient travels to the radiation oncology department where radioactive beads are inserted into the catheter at the desired location for a predetermined period, depending on the dose rate.

Relief of airway obstruction is the primary goal of HDRB, although curative treatment may be attempted in more advanced lesions by combining HDRB with external beam irradiation in selected patients. HDRB is not effective for rapid airway recanalization due to its delay in response of 14 to 21 days. It is best used as an adjunct to rigid bronchoscopy with or without thermal tumor ablation, endobronchial stent placement, or conventional external beam irradiation to recanalize an obstructed airway. HDRB appears safest and most effective for management of central airway lesions. Among patients with malignant airway obstruction, recanalization rates range from 60% to 90%, with decreased dyspnea, cessation of hemoptysis, and relief of cough in most cases.[16,23,24] HDRB has also been shown to be effective for radiographically occult, minimally invasive cancer in central airways, carcinoma in situ (CIS), or mucosal dysplasia. Moreover, accounts of the utility of HDRB in management of benign granulation tissue in lung transplant recipients or patients with subglottic stenosis have been reported.[25–27]

Serious complications of HDRB can occur, particularly massive hemoptysis from bronchovascular fistula formation secondary to necrosis of the airway wall and adjacent vascular structures. Because of the risk of fatal hemorrhage, every effort should be made to rule out central vascular tumor involvement before HDRB application.

Photodynamic Therapy

Photodynamic therapy (PDT) is FDA-approved for palliation of malignant airway obstruction and as an alternative to surgery in selected patients with minimally-invasive central lung cancer or CIS. PDT works on the principle that certain compounds, such as hematoporphyrin derivatives or aminolevulinic acid (ALA), function as photosensitizing agents, rendering malignant cells susceptible to damage from monochromatic light. Tumor necrosis occurs as a result of oxygen free-radical formation and ischemic vasculature necrosis mediated by thromboxane A_2 release.

The selective PDT effect on malignant cells is thought to be due to greater photosensitizing agent uptake and retention in neoplastic cells compared with normal cells; the exception is reticuloendothelial cells, particularly those in the skin. The relative tumor selectivity is most pronounced within 24 to 48 h after photosensitizing agent infusion; therefore, treatment of the target lesion should be performed within that time frame. Maximal tissue necrosis occurs 24 to 48 h after laser light administration and requires repeat bronchoscopy to debride the necrotic and sloughed area treated. Due to the delayed onset of PDT action, it is not useful in patients with acute respiratory distress from airway obstruction.

Ideal candidates for PDT include patients with airway obstruction caused by malignant endobronchial masses with minimal extrinsic airway compression, and patients with minimally invasive central airway tumors. Although surgical resection remains the treatment of choice for early lung cancer, some patients refuse surgery or have tumors that are deemed inoperable because of high surgical risk. In these cases, PDT may represent an appropriate alternative. Response rates are highest in patients with small tumors and minimal airway penetration depth.[28,29] In patients with bulky tumors, endobronchial PDT may substantially reduce the obstruction with objective increases in spirometric measurements and subjective improvement in dyspnea and quality of life; however, treatment is not curative.[30]

The main PDT complication is skin photosensitivity, which occurs in up to 20% of patients; it may persist for 6 weeks or longer and can be obviated by adequate sunlight precautions.

Tracheobronchial Stenting

Anecdotal reports of attempts to implant stents in the tracheobronchial tree date back to 1915. The Montgomery T-tube, designed in the 1960s, was the first reliable, dedicated airway stent.[31] However, stent implantation in the lower trachea and bronchi did not become standard medical practice until the 1990s, when Jean Francois Dumon reported the safe and effective placement of a dedicated silicone airway stent.[32]

Two main types of endobronchial stents are in use today—silicone or self-expanding metal stents (SEMS). Silicone stents generally are placed by rigid bronchoscopy with the patient under general anesthesia. Silicone stents are relatively inexpensive (~$500 USD) compared with SEMSs (~$2000 USD). Bifurcated silicone Y-stents also are available and have been effectively used in the management of carinal compression associated with malignant tumors, tracheoesophageal fistulas, and tracheobronchomalacia.

Unlike silicone stents, SEMSs may be placed using flexible bronchoscopy and require less technical rigor than silicone stent placement. The main limitation with SEMS is that uncovered varieties may induce mucosal inflammation and granulation tissue formation, which may require repeat endoscopic intervention to maintain airway patency.[33–35] For this reason, uncovered SEMSs have an FDA black-box warning against their utilization in *benign* airway stenosis, unless all other treatment options, including silicone stenting, have been explored and failed. An exception to this warning applies in bronchial anastomotic dehiscence in lung transplantation. In this setting, insertion of a temporary uncovered SEMS across the dehiscence exploits the fact that focal granulation tissue may develop and promote dehiscence closure.[36]

Endobronchial stents have a critical role in multimodality bronchoscopic approaches to both benign and malignant airway obstruction. Airway obstruction caused by locally advanced lung carcinoma may be treated with a combination of thermal tumor ablation and stent implantation to regain and preserve airway luminal diameter by preventing tumor ingrowth (Fig. 34-3). Stent placement may be combined with balloon dilatation in the endoscopic management of benign fibrotic strictures.

Dumon and colleagues reported excellent clinical outcomes and few complications with silicone stent placement in patients with malignant airway obstruction; a lower success rate was noted among patients with tracheal stenosis caused by other disorders.[32] Success, broadly defined as symptomatic relief, in limited studies has been reported to be achieved in between 78% and 98%, although none of the early trials used objective measures to determine efficacy.[37–39] In a small study in patients who were intubated because of respiratory failure secondary to unresectable tracheobronchial and mediastinal disease, stent placement facilitated extubation in most.[40] Stent placement benefits seem to persist in patients who survive for a period of several months or years after stent implantation.

Complications from endobronchial stents include stent migration, granulation tissue formation, tumor overgrowth, stent bacterial colonization and recurring infection, stent fracture, and inspissated secretions clogging the stent. In addition, massive and

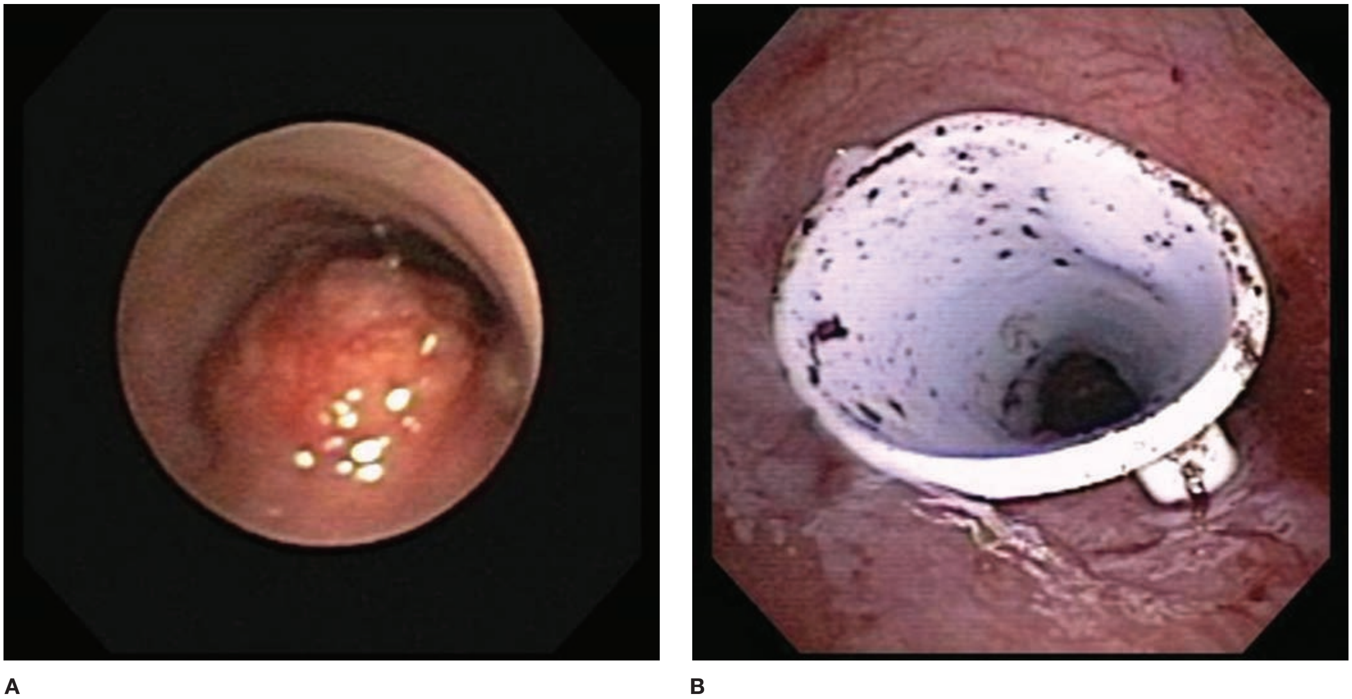

Figure 34-3 A large tumor nearly completely obstructs the tracheal lumen (**A**). Manual debulking using a rigid bronchoscope dramatically improved airway luminal diameter. An endotracheal silicone stent was placed to prevent tracheal re-occlusion (**B**).

fatal hemorrhage associated with stent erosion into central vascular structures can occur.

Stenting for Tracheobronchomalacia

Diffuse or focal tracheobronchomalacia is, perhaps, the most challenging disorder encountered by the therapeutic bronchoscopist. Cartilaginous tracheobronchomalacia refers to tracheal or main bronchi circumferential exhalational airway collapse due to loss of cartilaginous ring structural integrity. Membranous, or crescentic, tracheobronchomalacia, also known as excessive dynamic airway collapse (EDAC), is manifested by intact cartilaginous rings along with tracheal obstruction from anterior exhalational displacement of the posterior membrane from posterior membrane laxity. This condition is commonly seen with COPD, asthma, obesity, and chronic cough. Dynamic CT scanning may suggest tracheobronchomalacia or EDAC, but the gold standard remains flexible bronchoscopy performed while the patient is awake and spontaneously breathing to assess dynamic airway collapse.[41] Focal airway malacia may be a complication of long-standing intubation or an anastomotic complication following lung transplantation.[42]

The endoscopist must maintain restraint in therapeutic interventions for patients with tracheobronchomalacia or EDAC. Management of diffuse tracheobronchomalacia should focus on identifying and treating any underlying conditions that may perpetuate cartilaginous inflammation (e.g., relapsing polychondritis) and airway collapse. If the tracheobronchomalacia is symptomatic and progressive despite systemic therapy, initial consideration for tracheostomy should be entertained. If symptoms are not resolved with tracheostomy, or if they recur or progress after an initial improvement, evaluation for placement of a silicone bifurcation Y stent should be undertaken. These patients may also require nighttime ventilator support. Patients with EDAC may benefit from a trial of silicone stent placement as well, but this should not be considered definitive therapy.[43,44] For those who benefit in terms of decreased respiratory symptoms and improved pulmonary function, stent removal followed by surgical posterior membrane plication can be performed with acceptable clinical outcomes.[43,45] Recently, robotic tracheobronchoplasty with mesh has offered a minimally invasive surgical approach to treatment.[46] For many patients with focal tracheomalacia, particularly from postintubation injury, surgical resection with primary reanastomosis may be the best therapeutic option. If patients are not surgical candidates or prefer to avoid surgery, silicone stent placement often will provide the structural integrity necessary to obviate patient symptoms, at the risk of long-term stent complications.

■ Management of Hemoptysis

Bronchoscopy is valuable in hemoptysis for several reasons: to identify site of bleeding, to provide endobronchial therapy to reduce or stop bleeding, to clear blood clots that might impair gas exchange, or to place an endoluminal blocking device to prevent further airway occlusion with blood. Because of visualization difficulties during active bleeding, instruments with large and maximally effective suction channels should be used. Rigid bronchoscopy generally is preferred with massive bleeding or when the need to remove large clots is anticipated.

In attempts to cease bleeding, iced saline or an epinephrine solution can be instilled into a bleeding airway or applied topically onto a proximal bleeding site in an attempt to induce vasoconstriction. In addition, balloon catheters can be placed into the bleeding airway to tamponade bleeding to generate a hemostatic clot and prevent proximal airway soilage. Large endobronchial blockers are available to occlude the entire right or left mainstem bronchus to control bleeding. Other effective methods for control of proximal visible bleeding sources, particularly from endobronchial neoplasms, are thermal modalities such as Nd:YAG laser or APC photocoagulation.[47] In addition, flexible bronchoscopic endobronchial packing using oxidized regenerated cellulose can isolate a segmental or subsegmental bleeding site and promote endobronchial clot formation by induction of fibrin polymerization.[48,49] Frequently, these procedures are temporizing, while definitive management with surgery or bronchial artery embolization is undertaken.[50] Cryotherapy can be a valuable tool to remove a large central, organized clot from the airway by freezing the probe to the clot and removing the scope, probe, and clot en bloc.

Foreign Body Removal

Foreign body aspiration is more likely to occur in children than in adults with most foreign bodies occurring in children younger than 3 years. In children, the foreign body most often lodges in a mainstem bronchus, whereas in adults, foreign bodies usually are wedged distally, most commonly in the right lower lobe. Before bronchoscopic extraction was possible, most foreign body aspirations resulted in high morbidity and mortality, commonly from postobstructive pneumonia. Today, foreign bodies can be removed with either flexible or rigid bronchoscopy, depending on local expertise and foreign body size and composition. If available, rigid bronchoscopy remains the tool of choice for foreign body removal due to several factors: a larger access channel allowing use of larger and more adaptable retrieval tools; protection of the vocal cords from trauma upon foreign body removal; and ability to provide and maintain ventilation.

Various instruments have been developed for use with bronchoscopy for foreign body removal, including grasping forceps, balloon catheters, retrieval baskets, snares, and magnetic extractors. The instrument choice depends on the foreign body material composition, size, shape, and location in the tracheobronchial tree. Grasping forceps may be helpful in the retrieval of hard objects with an irregular surface. Smooth objects or organic material (e.g., nuts, food particles) may require use of expandable baskets or a combination of balloon catheters, suction devices, and grasping forceps. Balloon catheters frequently are used to dislodge a foreign body and bring it proximally into a larger airway before its removal with other instruments. Similar to clot extraction, cryotherapy can also be utilized by freezing the tip of the probe to the foreign body surface and subsequently withdrawing the catheter and object en bloc.

Secretion Aspiration

According to a survey of bronchoscopists in the United States, removal of retained secretions is cited as a leading indication for therapeutic bronchoscopy. Bronchoscopic secretion aspiration may be indicated in patients with respiratory muscle weakness who cannot generate adequate cough for secretion clearance. In critically ill or mechanically ventilated patients, secretion clearance may require flexible bronchoscopy. For ease of secretion removal, a flexible scope with a large working channel is ideal. Bronchoscopic secretion aspiration should not be considered “routine” in the postoperative period or in other conditions in which good chest physiotherapy and maintenance of adequate pulmonary toilet may be more effective.

Two specific disorders are worth highlighting in the context of therapeutic bronchoscopy: pulmonary alveolar proteinosis (PAP) and allergic bronchopulmonary aspergillosis (ABPA). In PAP, large-volume repeated bronchoalveolar lavage has been used for therapeutic clearance of alveolar surfactant material.[51,52] For patients with more extensive disease or impaired gas exchange, the standard approach is sequential whole-lung lavage.[53] In ABPA, lavage with saline solution may be insufficient to remove tenacious secretion impactions (described as “plastic bronchitis”), and cryoprobe extraction may prove helpful.

Closure of Bronchopleural or Alveolopleural Fistula

Persistent air leaks may be encountered following primary or secondary spontaneous pneumothorax. or following pulmonary resection. Traditional management for prolonged air leaks usually includes prolonged chest tube drainage using a Heimlich valve, attempts at surgical repair, pleural blood patch, or pleurodesis.

Therapeutic bronchoscopy may be a useful adjunct to persistent air-leak intervention in confirming suspected bronchopleural or alveolopleural fistulae and in specifying their precise location. The most common approach is to perform selective balloon catheter airway occlusion while observing the chest tube air-leak rate and volume. Depending on the fistula location and size, bronchoscopic procedures can be attempted with the goal of air leak reduction or elimination. Many different techniques for permanent closure have been reported. Several potentially useful agents have been described, including surgical gel, autologous airway blood patch, and thrombin injection to create fibrin clot, among a variety of others.[54–56] The most recent effective approach entails one-way endobronchial valve placement with complete or partial air leak resolution in the large majority of patients with persistent air leaks from diverse causes (Fig. 34-4).[57–60]

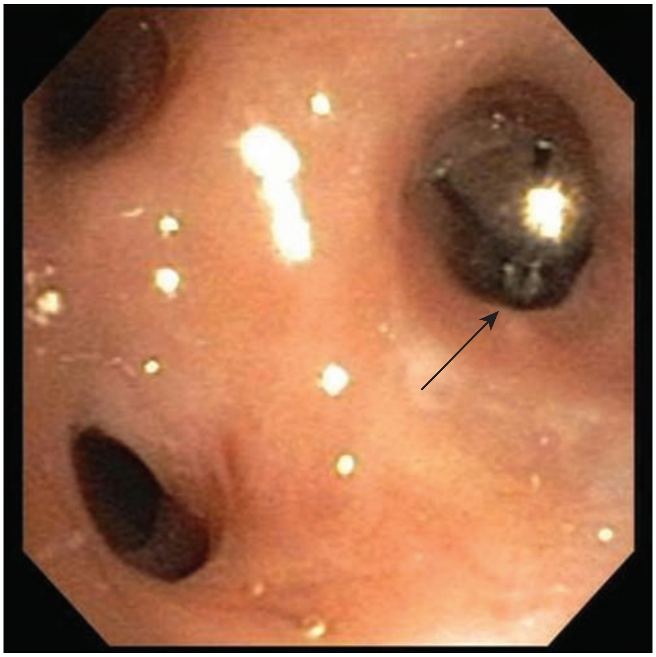

Figure 34-4 A patient presented with a spontaneous pneumothorax from severe emphysema. A chest tube was placed in the left chest and a persistent air leak was noted. Balloon occlusion localized the leak to the left upper lobe anterior segment. A one-way endobronchial valve was placed *(arrow)* with complete air leak resolution.

BRONCHOSCOPIC TREATMENTS FOR COMMON BENIGN LUNG CONDITIONS

One of the major advances in therapeutic bronchoscopy over the past decade has been the development of bronchoscopic interventions for highly prevalent lung diseases, such as asthma, chronic bronchitis, and emphysema.

Bronchoscopic Lung Volume Reduction

The National Emphysema Treatment Trial (NETT) demonstrated the role of lung volume reduction surgery (LVRS) as the first major surgical intervention for emphysema to improve patient symptoms, as well as mortality, in certain patient subsets.[61] Unfortunately, these benefits were associated with an approximate 5% procedural mortality and substantial perioperative morbidity, including persistent air leaks and cardiac arrhythmias. These factors spurred development of minimally-invasive bronchoscopic approaches to achieve similar clinical efficacy as achieved in the NETT trial, but with less morbidity and mortality.

Endobronchial valves (EBVs) have been studied most extensively and are designed to limit ventilation to the most severely involved lung regions in emphysema and to reduce total lung volume, residual volume, and dynamic hyperinflation.[62–65] When placed correctly, the valves allow one-way flow of secretions and air out of

Video 34-5 A patient with severe, heterogeneous, upper lobe-predominant emphysema who was enrolled in a clinical trial of endobronchial valves. The video demonstrates valve deployment device positioning and valve deployment. *Video available on AccessMedicine.com.*

the occluded pulmonary segment, but prevent air entry beyond the valve (Video 34-5).

The pivotal LIBERATE (Zephyr, PulmonX—Redwood City, CA, USA) and EMPROVE (Spiration, Olympus—Seattle, WA, USA) randomized controlled trials found that both EBVs were effective in improving forced expiratory volume in the first second (FEV_1) and multiple objective measures of patient symptoms and performance. The benefit was derived in patients with significant air trapping (residual volume >175%), hyperinflation, and heterogeneous, upper-lobe predominant emphysema with intact fissures and no collateral interlobar ventilation.[66,67] Benefit may also be derived in patients with homogeneously distributed emphysema, but to a lesser degree.[68] Proper patient selection is paramount; important considerations include the degree of heterogeneity of emphysema, the presence of significant air trapping and hyperinflation, and the presence of intact lobar fissures.

■ Bronchoscopic Airway Therapies in COPD and Asthma

While the available evidence is largely preliminary in nature, exciting new treatment modalities are at varying stages of development for airway-dominant COPD. In contrast to the aforementioned bronchoscopic lung volume reduction therapies that impart functional and symptomatic relief through targeted lung volume reduction, the following treatment strategies are aimed at reducing airway inflammation and peripheral airway resistance.

■ Targeted Lung Denervation

Targeted lung denervation (TLD) is another bronchoscopic adaptation of surgical vagotomy, which was commonly used to treat airway disease in the 1930s to 1950s. Using a dual-cooled radiofrequency (RF) catheter (Nuvaira—Minneapolis, MN, USA), parasympathetic nerves running along the outer surface of the bilateral mainstem bronchi are heated at a specific depth, producing ablation external to the airways, with minimal impact on the epithelium or cartilage. The AIRFLOW trial, the first randomized controlled trial studying this modality, demonstrated TLD-treated patients had significantly fewer respiratory adverse events between 3 and 6.5 months post-randomization compared with patients undergoing sham bronchoscopy.[69] An important, larger, multicenter trial is underway.

■ Cryospray

With use of a cryospray directed at treating the chronic bronchitis COPD phenotype, metered liquid nitrogen (MCS, Rejuvenair System, CSA Medical Inc—Lexington, MA, USA) is delivered bronchoscopically at −196°C in a circumferential pattern into the lobar and segmental airways. Rapid epithelial layer freezing preserves the extracellular matrix, allowing healthy cells to repopulate with fewer goblet cells without scarring or inflammation. To date, two small proof-of-concept studies have demonstrated safety and feasibility.[70] A pivotal trial in the United States is currently underway.

■ Bronchial Thermoplasty

Chronic asthma is a major cause of morbidity, increased health care utilization and cost, and death. Bronchial thermoplasty (BT) delivers controlled radiofrequency energy to the bronchial wall of conducting airways with the intent of inhibiting airway smooth muscle contractility, thereby attenuating bronchoconstriction during asthma exacerbations.

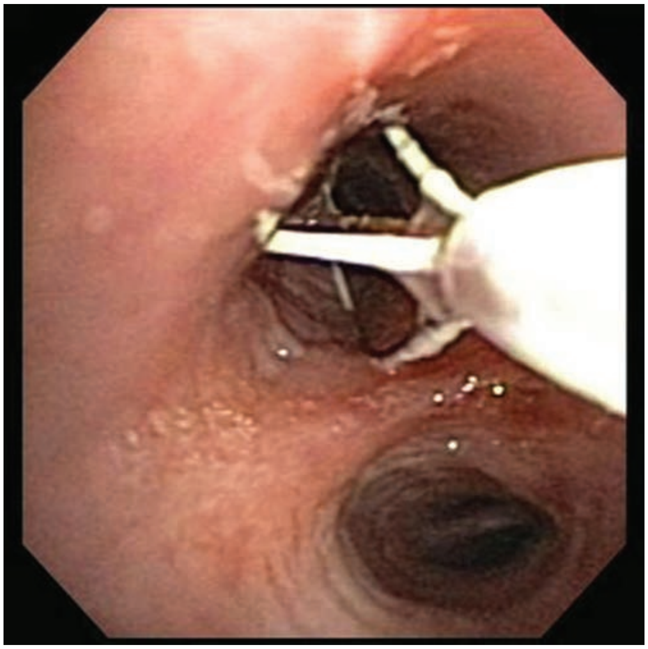

Figure 34-5 Radiofrequency array used in the airway for bronchial thermoplasty in patients with severe asthma.

BT is performed using a radiofrequency device that delivers thermal energy to the bronchial wall during an outpatient bronchoscopy. Three separate procedures are performed in order to treat all accessible upper and lower lobe airways ranging from 3 to 10 mm in diameter (Fig. 34-5). The initial randomized, multicenter Airway Intervention with Radiofrequency (AIR) trial in patients with moderate to severe disease demonstrated decreased asthma exacerbations in the group undergoing BT compared with patients on standard medical treatment alone.[71] This study was followed by a randomized, sham-controlled, multicenter trial (AIR2) that demonstrated significant improvement in the primary endpoint—asthma-related quality of life.[72] Although an increase was noted in early posttreatment asthma exacerbations requiring emergency department visits and hospitalizations, long-term follow-up data showed decreased asthma-related health care utilization for patients undergoing BT compared with those undergoing sham procedure.[73] Based on these data, BT received FDA approval for patients with severe asthma in April 2010, but procedural reimbursement remains problematic with many private insurers.

MEDICAL PLEUROSCOPY

Pleural effusions develop as a result in perturbations of the hydrostatic or oncotic pressure gradients that mediate normal pleural fluid production (transudates), or due to alterations in vascular permeability that lead to excess fluid accumulation (exudates). Congestive heart failure is the most common cause of transudates; management entails diligent diuresis and maintenance of optimal volume status. In contrast, exudates may be caused by a variety of inflammatory, infectious, or malignant etiologies. Utilizing a host of clinical, serologic, and pleural fluid–based evaluations, the etiology of an exudative effusion may be deciphered and managed accordingly. However, despite in-depth evaluation, the etiology and optimal management may remain elusive. In this setting, pleural inspection and biopsy may be necessary to identify the source of the effusion and to direct appropriate treatment.

Traditionally, pleural inspection and biopsy was performed by thoracic surgeons utilizing single-port, video-assisted thoracoscopic surgery. The procedure is performed under general anesthesia, most commonly with a double-lumen endotracheal tube used to isolate the involved hemithorax. Medical pleuroscopy was developed based on the concept that pleural inspection and biopsy can be performed without need for general anesthesia and intubation. With medical pleuroscopy, patients are given generous local anesthesia and breathe spontaneously while receiving moderate sedation for comfort. A single-entry port is created, and the semi-rigid or rigid pleuroscope is inserted into the chest. Due to the presence of the effusion and an open pleural space, adequate visualization for pleural inspection and biopsy can be acheived.[74,75] If necessary, talc poudrage may be performed following pleural biopsy, and a chest tube placed to achieve lung expansion.

SUMMARY

Technologic advances in bronchoscopy continue to improve the bronchoscopist's ability to perform minimally-invasive, accurate evaluations of the tracheobronchial tree and to implement an ever-increasing array of therapeutic and palliative airway interventions across broader disease processes. The role of therapeutic bronchoscopy will continue to evolve as further improvements are made in bronchoscopes, accessory equipment, imaging techniques, and novel technologies to treat lung diseases in which bronchoscopy was once thought to have no role. Therapeutic bronchoscopy may soon be used to provide treatment for conditions that traditionally have been treated with surgery. The major challenges in adopting many new bronchoscopic techniques into routine clinical practice include ensuring adequate procedural competence of bronchoscopists and having well-designed studies to delineate the appropriate use of the interventions.

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CHAPTER 35

Diagnostic Thoracic Surgical Procedures: Thoracoscopy, VATS, RATS, and Thoracotomy

Robert E. Merritt

INTRODUCTION

Thoracoscopy, video-assisted thoracic surgery (VATS), robotic-assisted thoracic surgery (RATS), and thoracotomy are well-established surgical techniques used by thoracic surgeons to diagnose and treat benign and malignant diseases involving the thorax.

Thoracoscopy first emerged as a diagnostic tool in the early 20th century when therapeutic pneumothorax became the surgical treatment of choice for tuberculosis. In 1910, Hans Christian Jacobaeus performed the first thoracoscopic intrapleural pneumolysis for collapse therapy in the treatment of tuberculosis.[1–3] He used a rigid cystoscope with a light source to access the pleural cavity and perform a pneumolysis. After development of effective antimicrobial therapy for tuberculosis, thoracoscopy evolved as an effective diagnostic procedure to evaluate pleural effusions and pleural disease.[4] During direct diagnostic thoracoscopy, a fiberoptic mediastinoscope or bronchoscope was placed through a small intercostal incision; pleural fluid could be aspirated and sent for analysis (Fig. 35-1). In addition, the parietal pleura, visceral pleura, fissures, hilum, and diaphragm could be inspected directly.[5]

By 1990, thoracoscopy evolved into VATS. Development of high-resolution video cameras and endoscopic linear mechanical stapling devices allowed the expansion of application of VATS into the diagnosis and treatment of pulmonary nodules and interstitial lung diseases (ILDs).[6,7] The use of diagnostic thoracotomy has declined significantly since the emergence of VATS; however, the diagnostic thoracotomy may be necessary in cases in which VATS is not feasible (Table 35-1).

TECHNICAL CONSIDERATIONS

VATS is performed in the operating room under general anesthesia. A double-lumen tube is placed to isolate the lungs to enable establishment of one-lung ventilation, which is essential for performing the procedure. The use of one-lung ventilation creates sufficient space for maneuvering within the hemithorax to perform the planned procedure. Carbon dioxide (CO_2) insufflation also can be used to provide additional working space within the chest cavity by lowering the position of the diaphragm. The more inferiorly located diaphragm provides better exposure of the costophrenic sulci and lower lobes. When CO_2 is used, the maximum insufflation pressure is maintained below 6 mm Hg to avoid decreased venous return to the right heart and associated hypotension.

The typical VATS procedure utilizes three to four incisions that range from 5 to 12 mm in size. The incisions are usually arranged in a triangular configuration, with the area of interest located in the center of the triangle (Fig. 35-2). A 5- or 10-mm fiberoptic thoracoscope is connected to a video camera and is most commonly inserted into the most inferiorly placed VATS incision (Fig. 35-3). The chest cavity is clearly visualized on a video monitor and the parietal pleura, visceral pleura, hilum, diaphragm, and mediastinum can be directly inspected. Upon completion of the procedure, a chest tube is inserted under direct visualization through one of the VATS incisions to evacuate air and pleural fluid during the early postoperative period. Simple diagnostic VATS procedures are typically well tolerated, and patients can be discharged after 1 to 2 days in the hospital. Currently, the disease processes assessed using VATS are listed in Table 35-2.

Management of Pleural Disease

Both malignant and benign diseases of the pleura may be diagnosed and managed with VATS. Although thoracentesis (including pleural fluid cytology analysis) is the initial diagnostic tool of choice for an undiagnosed pleural effusion, VATS procedures provide a higher diagnostic yield: 90% to 100% compared with 60% to 80%

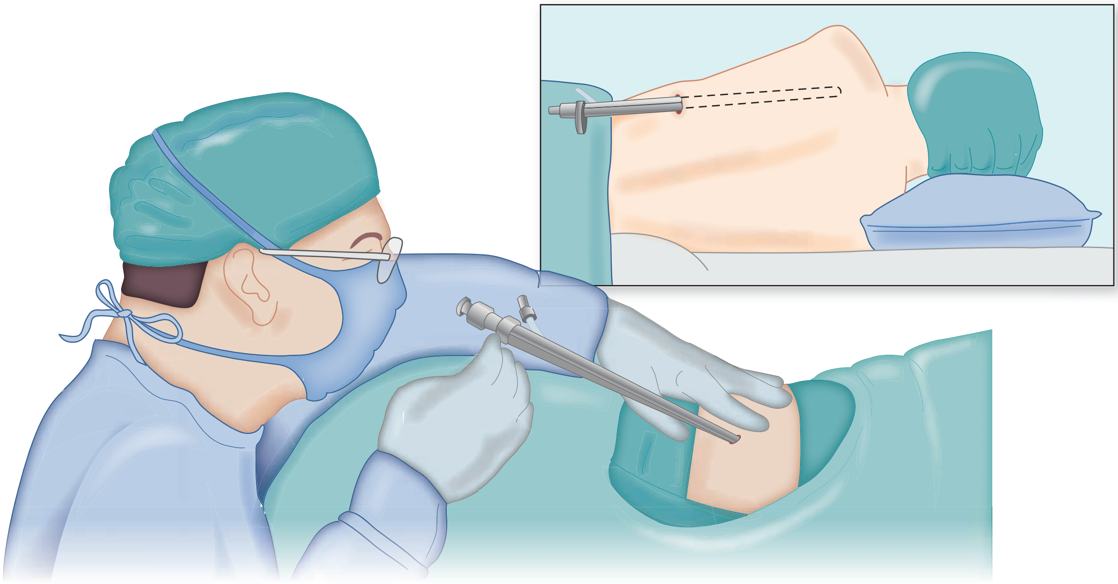

Figure 35-1 Use of a rigid bronchoscope as a thoracoscope.

TABLE 35-1 Contraindications to Video-Assisted Thoracic Surgery (VATS)

Severe hypoxia
Previous pneumonectomy or bilobectomy
Mechanical ventilator dependence
Severe chronic obstructive pulmonary disease
Pleural adhesions
Previous pleurodesis procedure
Coagulopathy
Recent acute myocardial infarction
Severe pulmonary hypertension

for thoracentesis.[8–10] When the diagnosis of a pleural effusion is not determined following thoracentesis, VATS can be utilized to obtain pleural fluid and pleural biopsies for definitive diagnosis.

Malignant pleural effusions usually present as a result of an obstruction of subpleural lymphatics and are associated with advanced primary lung cancer or metastatic epithelial carcinomas that involve the lung. VATS may provide both diagnostic and therapeutic value in the management of malignant pleural effusions. A pleurodesis can be achieved by instilling chemical agents, such as talc, doxycycline, bleomycin, or tetracycline into the pleural cavity to promote pleural adhesion formation. The process obliterates the potential space between the parietal pleura and visceral pleura, thus preventing accumulation of pleural fluid. Efficacy rates in the range of 94% to 96% for VATS pleurodesis for malignant pleural effusions have been reported,[11,12] along with a morbidity rate of 2.6%.[12] In essence, the VATS approach for diagnosis and management of malignant pleural effusions is highly effective because it provides minimally invasive access to the thoracic cavity for sampling of fluid and pleural tissue, and it enables lysis of loculated adhesions and instillation of a chemical pleurodesis agent.

The most common benign condition involving the pleura is an infection of the pleural space or empyema. Patients who present with pneumonia often have associated pleural effusions, which may be either a parapneumonic effusion or an empyema (Chapter 76). The pleural fluid should be sampled with thoracentesis to enable the distinction between parapneumonic effusion and empyema. If the pleural fluid Gram stain or culture is positive for a pathogen, or if the fluid pH is less than 7.1, an empyema is diagnosed.

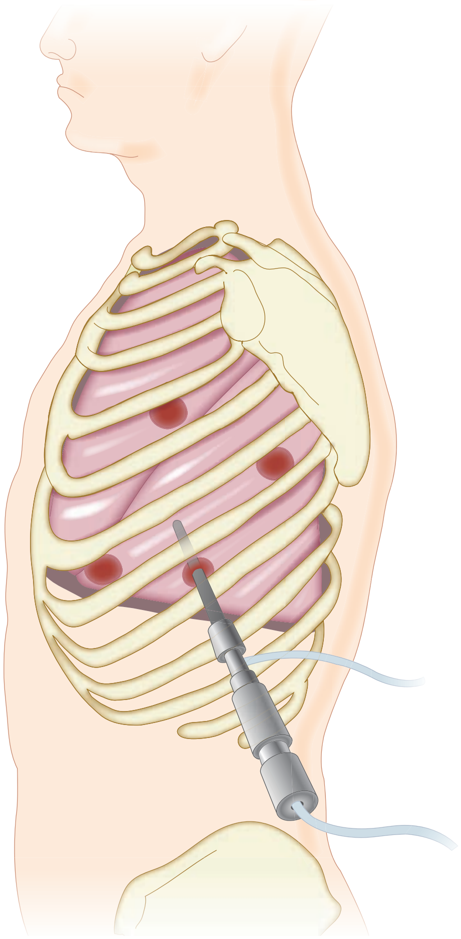

Figure 35-2 Placement of VATS incisions.

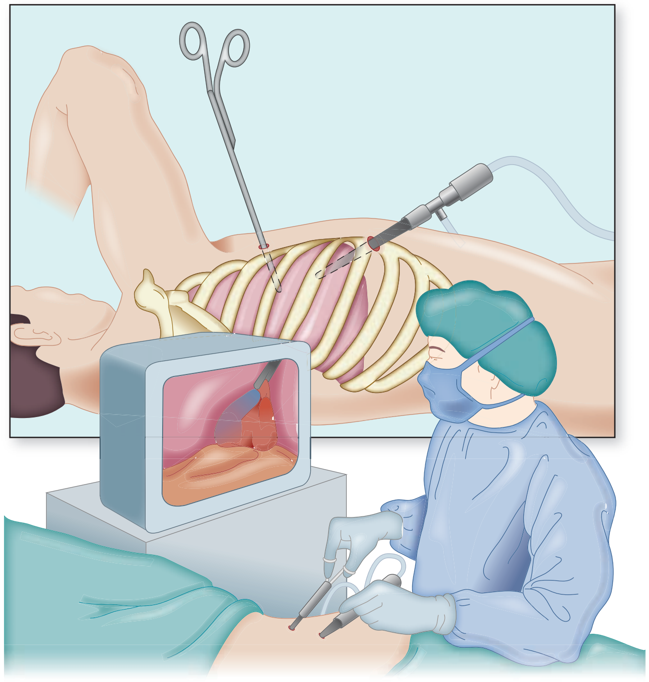

Figure 35-3 Placement of the thoracoscope through the most inferior of the VATS incisions. A video camera is connected to the thoracoscope and the image displayed on a video monitor.

TABLE 35-2 Current Indications for Video-Assisted Thoracic Surgery (VATS)

Diagnosis of pleural effusion
Drainage of empyema
Pleurodesis
Diagnosis of a suspicious pulmonary nodule
Biopsy of the pleura
Lung biopsy for diagnosis of interstitial lung disease
Resection of pulmonary metastatic nodules
Resection of primary lung carcinoma
Biopsy of mediastinal lymph nodes
Resection of blebs or bullae for treatment of spontaneous pneumothorax
Drainage of pericardial effusion

Video 35-1 Use of VATS in drainage of empyema. *Video available on AccessMedicine.com.*

The classification of empyema is based on the temporal evolution of the pleural space infection and dictates the optimal management. Three phases of empyema have been described: (1) The *exudative phase*, an initial phase characterized by free-flowing purulent fluid within the pleural space. Simple drainage with chest tube thoracostomy and intravenous antibiotics is usually sufficient to manage the pleural effusion. (2) The *fibropurulent phase*, characterized by loculated pleural fluid collections and fibrinous exudative deposits on the visceral pleural surfaces. In this phase, the empyema often requires VATS or thoracotomy to lyse adhesions, break up loculations, and promote drainage of the purulent pleural fluid (Video 35-1). (3) The *fibrous phase*, characterized by formation of a thick, fibrous rind on the visceral pleural surface of the lung. A thoracotomy is usually required to achieve a complete decortication.

Early decortication using a VATS-based approach during the fibropurulent phase is highly effective and may significantly decrease morbidity associated with empyema.[13] VATS offers a decided advantage over simple chest tube thoracostomy because of multiple factors: (1) Loculated purulent fluid may be completely drained, since adhesions are directly visualized and lysed during VATS. (2) Atelectatic lung may be re-expanded under direct vision. (3) Chest tubes can be placed in the appropriate position for optimal drainage in the postoperative period.

The definitive drainage of purulent fluid associated with empyema using VATS can significantly improve patient outcomes and prevent progression to a fibrothorax, which often requires an open thoracotomy.

Evaluation of Lung Parenchymal Disease

Diagnosis of the solitary pulmonary nodule remains one of the most common indications for VATS. A widely cited, multi-institution, randomized study demonstrating a 20% reduction in lung cancer mortality using low-dose computed tomography (CT) to screen for lung nodules in patients at risk for lung cancer[14] has certainly increased enthusiasm for screening programs and enhanced detection of indeterminate pulmonary nodules.

Currently available modalities for the diagnosis of indeterminate solitary pulmonary nodules include high-resolution CT, positron emission tomography (PET), CT-guided fine-needle aspiration (FNA), and VATS. In a randomized trial for evaluation of solitary lung nodules, CT scans performed with intravenous contrast administration have been shown to have an overall accuracy rate of 77%, sensitivity of 98%, and specificity of 58%.[15] The coupling of PET scan–based images with CT scans is often useful to determine if a lung nodule is hypermetabolic, which increases the probability of malignancy (Chapter 30). In cases of granulomatous diseases, PET scans may generate false-positive results, as inflammatory cells readily accumulate the tracer employed, 18-fluorodeoxyglucose (^{18}F-FDG). The sensitivity and specificity of PET–CT scanning in the evaluation of indeterminate solitary pulmonary nodules have been reported at 92% and 90%, respectively.[16]

Development of VATS has improved the diagnostic yield in evaluation of indeterminate solitary pulmonary nodules. This minimally invasive technique is well tolerated. Patients experience less postoperative pain and recover more quickly compared with patients who undergo conventional open thoracotomy.

Pulmonary nodules located in the outer third of the lung parenchyma are ideally suited for VATS wedge excisional biopsy. For lung lesions smaller than 10 mm, localization can be facilitated using transthoracic wire placement into the area of the lesion under CT guidance prior to the VATS procedure. In addition, the technique of navigational bronchoscopy (Chapter 34) can be employed to inject dye or place fiducial markers in close proximity to small nodules that might be difficult to locate during VATS. The diagnostic yield for VATS using wedge excision of a pulmonary nodule approaches 100%. Furthermore, since morbidity and mortality rates are exceedingly low, the VATS technique is ideal for evaluation of indeterminate pulmonary nodules (Video 35-2).

Video 35-2 Use of VATS in evaluation of indeterminate pulmonary nodule. *Video available on AccessMedicine.com.*

Although diffuse ILDs often present with characteristic patterns on CT scanning, histologic confirmation is often necessary to determine appropriate treatment. Reports indicate that in as many as 84% of cases of ILD evaluated with surgical lung biopsy, the course of therapy is altered by the biopsy findings.[17]

The VATS technique has been shown to result in less postoperative pain and lower morbidity compared with thoracotomy performed for purposes of lung biopsy.[18,19] Furthermore, in a randomized, controlled clinical trial, VATS and thoracotomy appear equivalent in postoperative outcomes when performed for diagnosis of ILD.[20] Given this diagnostic equivalency, and, in the author's experience, reduced postoperative pain, shorter hospital stay, and faster recovery associated with VATS, it remains the preferred diagnostic technique for patients with ILD who are ambulatory and have sufficient pulmonary reserve to tolerate one-lung ventilation. Thoracotomy is reserved for patients who are ventilator-dependent and too hypoxic to tolerate one-lung ventilation.

Robotic-Assisted Thoracoscopic Surgery (RATS)

The robotic surgery platform is becoming more commonly utilized for surgical management of early-stage non–small-cell lung cancer. According to data from the Society of Thoracic Surgery General Thoracic database, fewer than 50% of patients undergo thoracoscopic lobectomy for surgical management of early-stage lung carcinoma.[21] The impediments to the widespread application of VATS lobectomy may be related to the underlying limitations of the technique, which include two-dimensional optics, rigid instrumentation, and poor ergonomics. Robotic-assisted lobectomy has become more prevalent in surgical resection for lung carcinoma.[22–24] The Da Vinci Xi robotic platform (Sunnyvale, CA) has provided some improvements over conventional thoracoscopic surgery, such as a three-dimensional

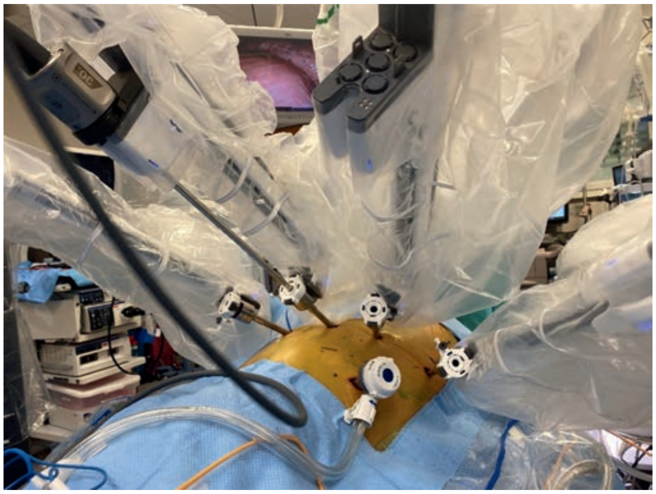

Figure 35-4 The Da Vinci robotic platform docked to the thoracic ports for a lung resection.

Video 35-3 Dissection of the pulmonary artery using the RATS technique for pulmonary lobectomy. *Video available on AccessMedicine.com.*

Video 35-4 Lymph node dissection and division of the inferior pulmonary vein using the RATS technique for pulmonary lobectomy. *Video available on AccessMedicine.com.*

Video 35-5 Division of the bronchus using the RATS technique for pulmonary lobectomy. *Video available on AccessMedicine.com.*

high-definition video-monitoring system, multijointed instruments for better dexterity, and a fully integrated linear endomechanical stapler, which make robotic surgery more intuitive and closer to conventional open surgery. Comparative studies between RATS lobectomy and VATS lobectomy have produced mixed results. A large Society of Thoracic Surgeons database study demonstrated that RATS lobectomy operative times were longer, but the complication rate, hospital length of stay, lymph node upstaging, and 30-day mortality were equivalent with VATS lobectomy.[25] However, a large hospital database study demonstrated that robotic-assisted lobectomy was costlier and had longer operative times compared with VATS lobectomy. Similarly, a small, single-institution study reporting on the initial experience of robotic-assisted lobectomy demonstrated equivalent mortality, complications, and lymph node counts compared to thoracoscopic lobectomy. The RATS approach has the potential to supplant the traditional VATS approach as robotic technology becomes more widely adopted.

The standard port placement for a RATS lobectomy includes three 8-mm ports and one 12-mm port along the 8th intercostal space (Fig. 35-4). The pulmonary artery dissection is performed with the bipolar grasper, and the division of the pulmonary artery is performed with an integrated robotic linear stapler (Video 35-3). The pulmonary vein also is dissected with the bipolar grasper and divided with the linear robotic stapler (Video 35-4). The final step of the RATS lobectomy is the division of the bronchus with the robotic stapler (Video 35-5). The removal of lymph nodes is also a very important part of the RATS lobectomy, which provides important staging information.

SUMMARY

Thoracoscopy, VATS, RATS, and thoracotomy are valuable diagnostic tools employed in the evaluation of benign and malignant diseases of the pleura and lung. VATS has emerged as a primary diagnostic method for diagnosis and treatment of malignant pleural effusions and empyema. In addition, VATS has improved the diagnostic yield in evaluation of indeterminate solitary pulmonary nodules. VATS has largely replaced diagnostic thoracotomy for ILD, since VATS results in less postoperative pain, shorter hospital stay, and faster postoperative recovery. The RATS approach had demonstrated some improved outcomes compared to VATS for pulmonary lung resections for early-stage non–small-cell lung carcinoma.

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CHAPTER 36

Evaluation of Respiratory Impairment and Disability

Lisa Ruvuna
Akshay Sood

INTRODUCTION

Management of a patient with chronic lung disease does not end with its treatment. Those with chronic pulmonary disorders need additional assistance and guidance on issues related to respiratory impairment, including causation or attribution; apportionment; eligibility for, and access to, various compensation systems; workplace modifications or removal from the workplace; and vocational and other forms of rehabilitation. Unfortunately, most physicians avoid providing these services, often with disastrous socioeconomic and medical consequences for the patient.

Multiple reasons underlie the general attitude of physician reluctance in addressing impairment. These include a fear and poor understanding of the legal system as it relates to work-related diseases, pervasive confusion about various compensation systems, a mistaken notion that those who seek impairment assistance are usually malingerers, lack of training in impairment evaluation, and a desire to avoid uncompensated, and often onerous, efforts in the context of an already burdensome clinical schedule. This chapter provides an understanding of this complex, but ignored, area in clinical pulmonary medicine.

TERMINOLOGY

This field of impairment and disability evaluation bridges medicine and law; hence, its terminology, drawn from both fields, can be confusing.

Impairment and Disability

The terms *impairment* and *disability* are often used interchangeably, but they are not synonymous. In 2001, the World Health Organization (WHO) developed the International Classification of Functioning, Disability and Health (ICF),[1] which identifies the dynamic relationship between impairment, disability, and disease. Impairments are problems in body function or structure, such as significant deviation or loss.[1,2] Disability is an umbrella term for activity limitations and participation restrictions in an individual with a health condition, disorder, or disease.[3]

For a patient with chronic lung disease, the goal of respiratory impairment evaluation is objective measurement of the extent of loss of function, primarily through application of pulmonary function or exercise testing. The physician plays a key role in impairment evaluation. On the other hand, the impact of the respiratory impairment on a person's ability to perform day-to-day activities or involvement in life situations, also termed *activity limitations* and *participation restrictions*, respectively, is called *disability*, which is typically determined through application of administrative and legal instruments by experts in these areas. The experts not only rely upon the evaluation of impairment provided by the physician, but also take into consideration other social and legal issues, as well as the energy requirements of the occupation. Impairment may occur without disability, and disability may occur without measurable impairment. Furthermore, two individuals with exactly the same respiratory impairment may suffer differing impacts on their lives and, consequently, have different levels of disability.

Respiratory impairment may be temporary or permanent. In contrast to temporary impairment, permanent impairment is not expected to improve with time or treatment. Disability may be partial or total. Total disability implies that an individual is unable to perform any work of the kind that he or she has the skills and qualifications to perform. Partial disability implies that an individual is able to perform some, but not all, of the work.

Causation

Causation or attribution refers to whether an exposure has been a "substantial" contributing factor in either causing or exacerbating lung disease. The level of certainty required in determining causation for occupational lung disease is different from the usual standard of 95% certainty used in medical research. The commonly accepted standard of certainty for occupational cases is that the illness is substantially caused, or exacerbated by, an occupational exposure on a "more probable than not" basis, or a level of certainty greater than 50%.

Apportionment

Apportionment describes the relative contribution of multiple factors to the total respiratory impairment. For instance, both chronic inhalational asbestos exposure and cigarette smoking may be contributory factors to lung cancer. From a scientific perspective, it is usually difficult, if not impossible, to "apportion" the relative roles of multiple exposures in causation of an individual's complex, multifactorial disease. Physicians are often asked to state their opinion on apportionment in the context of the body of available knowledge in that area.

AMERICANS WITH DISABILITIES ACT

Although many physicians think of impairment assessment as an evaluation that follows injury, or termination of employment, or is undertaken at an advanced stage of lung disease, in reality, important assessments also are made prior to the start of a job. The Americans with Disabilities Act (ADA), which was enacted by the United States in 1992, produced a fundamental change in the way in which physical impairments are viewed at the workplace.

Many of the regulations established by the ADA remove barriers to enable equal access to services and equal opportunities to societal needs such as employment. Prior to the ADA, it was common for employers to administer medical assessments (i.e., physical employment evaluations, comprehensive medical examinations) as part of the application process for employment.[4] During the interview stage, preemployment assessment are not allowed. Once a conditional offer is made, an employment entrance exam may be requested, with denial of employment if it is deemed that the individual is unable to perform the essential requirements of the job (with or without accommodations).[4,5]

The other major change in the determination of work-related physical fitness is that businesses are required to make "reasonable" accommodations for physical impairments, as long as the impairments do not interfere with the essential requirements of the job. Employers are not, however, required to make unreasonably extensive changes to a work area or to undertake "action requiring significant difficulty or expense" to accommodate an otherwise qualified applicant.

IMPAIRMENT SYSTEMS COMMONLY USED IN THE UNITED STATES

Patients seeking an impairment evaluation can be usually classified into three general types: (1) those with advanced lung disease who apply for disability benefits under the Social Security Impairment program; (2) those with work-related lung disease who apply under the Workers' Compensation System (but also specialized programs, such as the Black Lung Benefits Act for coal mine workers); and (3) those who develop lung disease while working for certain employers, such as the U.S. Veterans Administration. The most commonly used impairment guidelines in the United States are the Social Security Impairment program and the Workers' Compensation System. Each are discussed in greater detail in subsequent sections.

Social Security Impairment

The U.S. Social Security Administration incorporates two programs that provide financial and rehabilitative benefits to disabled individuals. Both require objective demonstration of disability using medical standards set forth in the Social Security Act.

The first program is orchestrated through Title II of the Act, known as Social Security Disability Insurance. The program is available to individuals who are insured as a result of their contributions to the Social Security Trust Fund (through federal taxes paid on employment earnings during their work careers). The second is orchestrated through Title XVI of the Act, known as Supplemental Security Income or SSI. This program is available to disabled individuals who have limited income or resources and who are not covered by contributions to the Social Security Trust Fund.

For adults, the definition of disability is the same whether the application for benefits is made under Title II or Title XVI of the Social Security Act. The Social Security Administration defines disability as "the inability to engage in any substantial gainful activity by reason of any medically determinable physical or mental impairment(s) which can be expected to result in death, or which has lasted or can be expected to last for a continuous period of not less than 12 months." The methods used for disability evaluation under Social Security are important for the physician to understand for two reasons: (1) disability designation under Social Security is a common and important source of financial support for many patients who are under the care of pulmonary physicians, and (2) the pulmonary physician often takes an active role in helping determine eligibility under this program.

Evaluation of disability under Social Security is a staged process, beginning with application to a local Social Security field office or the Office of Disability Determination Services (DDS). The Office of DDS gathers objective medical information primarily from the treating physician, who is the preferred source of medical evaluation. If the available information is insufficient to make a determination of disability, the DDS may purchase additional testing and/or request examination from a consultant, such as a pulmonary physician.

The Social Security Administration has decided that certain specific impairments of each major body system are severe enough to prevent a person from engaging in any gainful employment and, therefore, serve as prima facie evidence that disability exists. These impairments have been codified as the Listings of Impairments.[6] Listings under the respiratory system include specific categories of disease severity, including chronic respiratory disorders; asthma; cystic fibrosis; pneumoconiosis; bronchiectasis; mycobacterial, mycotic, and other chronic persistent infections of the lung; cor pulmonale due to chronic pulmonary vascular hypertension; sleep-related breathing disorders; and lung transplantation.

If a claimant cannot meet the severity criteria of the Listings, the claimant may still receive an award of benefits by presenting pertinent medical information to the DDS. An initial judgment may then be made by the DDS, but the claimant has the right to challenge an unfavorable decision and to have it reviewed by other members of the DDS staff. If the decision is still unfavorable, the claimant may appeal to the Office of Hearings and Appeals for review by an administrative law judge, who may request expert physician testimony before making a decision. Once again, the claimant may request that an unfavorable decision be reviewed by an appeals council.

The Social Security program has some unusual requirements that distinguish it from other compensation programs: (1) The program requires a "hard copy" of the volume–time curve of a recent spirogram obtained following administration of inhaled bronchodilator when obstruction is present. Similarly, the program requires legible tracings of the breath-hold maneuver for diffusing capacity. (2) The program incorporates arbitrary, height-specific cut points for men and women for spirometric parameters or diffusing capacity for deciding impairment status; these cut points are not determined by race or ethnicity. (3) The program accepts an arterial blood gas measured during steady-state *submaximal* exercise at a work rate of five metabolic equivalents (METs) for rating impairment in gas exchange. Alternatively, it accepts graphical printouts of pulse oximetry on room air at rest or after a 6-minute walk test for evaluating gas exchange impairment. (4) The program denotes the patient as either impaired or not impaired, rather than specifying a percent impairment. In this setting of binary categorization, those considered impaired under Social Security criteria are expected to have a level of impairment sufficient to prevent working for a period of 1 year or longer. (5) Unlike Workers' Compensation programs, the Social Security program does not focus on occupational causation. The sole criterion for granting benefits is whether the claimant is able to participate in gainful employment. (6) The Social Security program also takes into account impairment from coexisting nonpulmonary conditions, such as substance abuse.

Workers' Compensation System

The Workers' Compensation system is a "no-fault" system of medical care and disability insurance in which private insurers or self-insured employers pay benefits to an employee sustaining an injury or illness due to workplace exposure. Under Workers' Compensation rules, workers cannot sue their employer for injury or illness.

The rules for the Workers' Compensation system vary from one state to another, but they usually follow one of the six editions of the American Medical Association (AMA) Guides to the Evaluation of Permanent Impairment.[3] The various editions of the AMA Guides contain markedly different sets of recommendations on impairment evaluation, so one must choose the right edition for the purpose. Use of the wrong edition may result in an erroneous impairment rating. While other guidelines are available on the Internet without charge, use of web-based AMA Guides carries a fee.

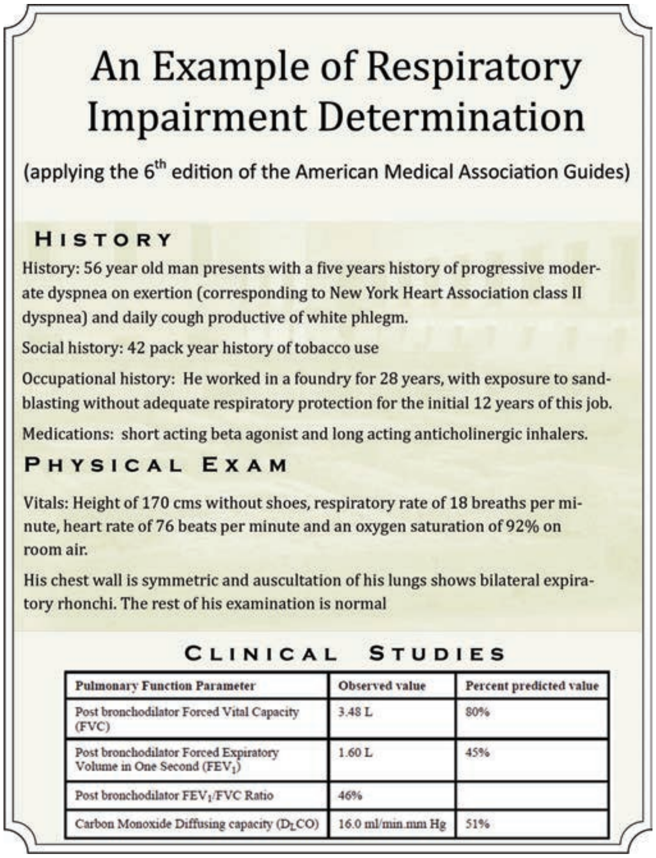
The sixth edition of the AMA Guides uses a standardized grid that incorporates five classes of impairment severity.[3] The grids incorporate objective, test-based key criteria for defining the impairment class, along with other criteria for fine-tuning the severity grade within a given class. Among the various objective tests, *the most severely affected test result is used to define the impairment class* (Fig. 36-1).

Although the American Thoracic Society (ATS) has also developed consensus guidelines for rating impairment from chronic respiratory conditions and asthma,[7,8] these guidelines may not be accepted by a specific compensation program. While the AMA Guides generally follow the ATS schema, there exist substantial differences between the two guidelines.

FIVE GENERAL STEPS FOR IMPAIRMENT RATING

Five steps constitute the process of completing a respiratory impairment evaluation (Fig. 36-2).

The first step is confirmation of the diagnosis of lung disease. Because of the medicolegal nature of the evaluation, the physician should have greater certainty of the medical diagnosis than is sometimes used in clinical practice. In other words, objective confirmation of the diagnosis is preferable.



An Example of Respiratory Impairment Determination

(applying the 6th edition of the American Medical Association Guides)

HISTORY

History: 56 year old man presents with a five years history of progressive moderate dyspnea on exertion (corresponding to New York Heart Association class II dyspnea) and daily cough productive of white phlegm.

Social history: 42 pack year history of tobacco use

Occupational history: He worked in a foundry for 28 years, with exposure to sandblasting without adequate respiratory protection for the initial 12 years of this job.

Medications: short acting beta agonist and long acting anticholinergic inhalers.

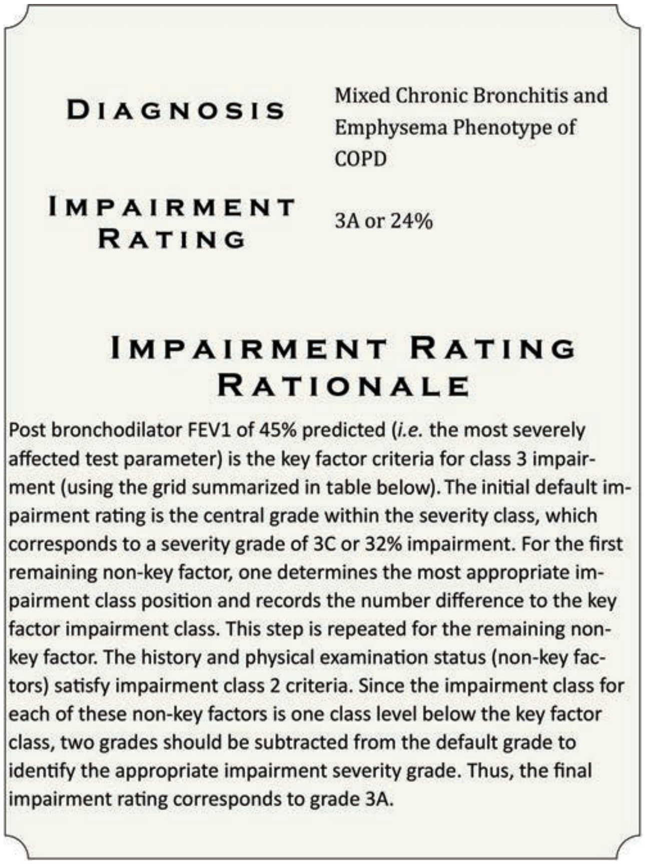
PHYSICAL EXAM

Vitals: Height of 170 cms without shoes, respiratory rate of 18 breaths per minute, heart rate of 76 beats per minute and an oxygen saturation of 92% on room air.

His chest wall is symmetric and auscultation of his lungs shows bilateral expiratory rhonchi. The rest of his examination is normal

CLINICAL STUDIES

Pulmonary Function Parameter	Observed value	Percent predicted value
Post bronchodilator Forced Vital Capacity (FVC)	3.48 L	80%
Post bronchodilator Forced Expiratory Volume in One Second (FEV_1)	1.60 L	45%
Post bronchodilator FEV_1/FVC Ratio	46%	
Carbon Monoxide Diffusing capacity (D_LCO)	16.0 ml/min.mm Hg	51%



DIAGNOSIS Mixed Chronic Bronchitis and Emphysema Phenotype of COPD

IMPAIRMENT RATING 3A or 24%

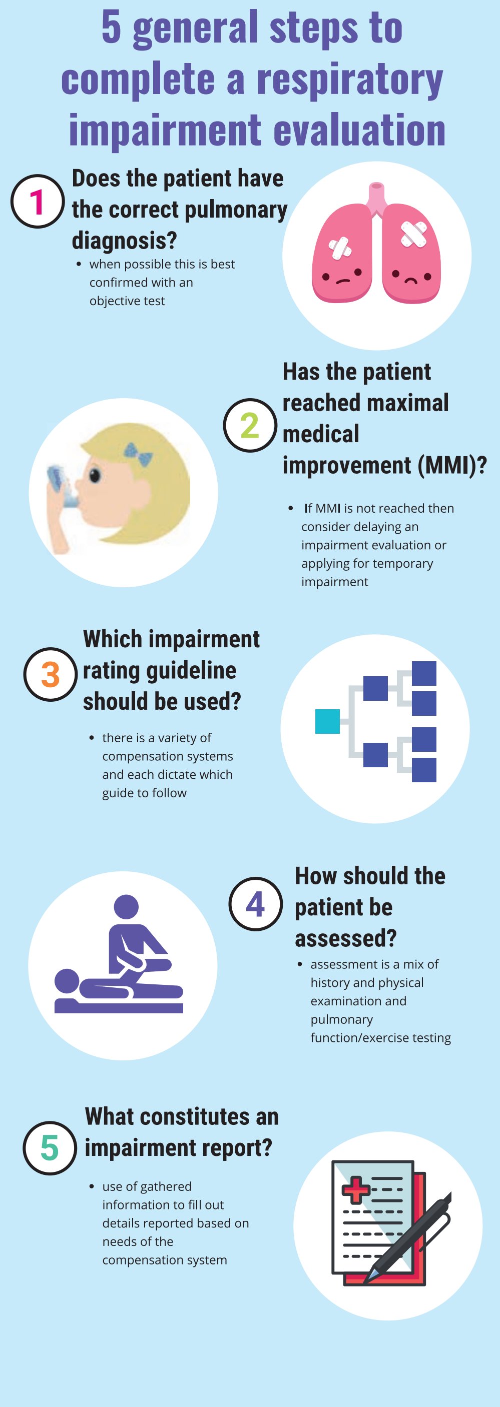
IMPAIRMENT RATING RATIONALE

Post bronchodilator FEV1 of 45% predicted (*i.e.* the most severely affected test parameter) is the key factor criteria for class 3 impairment (using the grid summarized in table below). The initial default impairment rating is the central grade within the severity class, which corresponds to a severity grade of 3C or 32% impairment. For the first remaining non-key factor, one determines the most appropriate impairment class position and records the number difference to the key factor impairment class. This step is repeated for the remaining non-key factor. The history and physical examination status (non-key factors) satisfy impairment class 2 criteria. Since the impairment class for each of these non-key factors is one class level below the key factor class, two grades should be subtracted from the default grade to identify the appropriate impairment severity grade. Thus, the final impairment rating corresponds to grade 3A.

TABLE

	Class	Class 0	Class 1	Class 2	Class 3	Class 4
	Whole Person Impairment Rating (%)	0	2–10%	11–23%	24–40%	45–65%
	Severity Grade (%)		2 4 6 8 10 (A B C D E)	11 14 17 20 23 (A B C D E)	24 28 32 36 40 (A B C D E)	45 50 55 60 65 (A B C D E)
Key Factor: FEV_1					FEV_1 between 45% and 54% of predicted	
	Class	**Class 0**	**Class 1**	**Class 2**	**Class 3**	**Class 4**
	Whole Person Impairment Rating (%)	0	2–10%	11–23%	24–40%	45–65%
	Severity Grade (%)		2 4 6 8 10 (A B C D E)	1114 17 20 23 (A B C D E)	24 28 32 36 40 (A B C D E)	45 50 55 60 65 (A B C D E)
Non-Key Factor: History				Intermittent, moderate dyspnea despite continuous treatment		
	Class	**Class 0**	**Class 1**	**Class 2**	**Class 3**	**Class 4**
	Whole Person Impairment Rating (%}	0	2–10%	11–23%	24–40%	45–65%
	Severity Grade (%)		2 4 6 8 10 (A B C D E)	11 14 17 20 23 (A B C D E)	24 28 32 36 40 (A B C D E)	45 50 55 60 65 (A B C D E)
Non-Key Factor: Physical Findings				Intermittent, moderate findings		

Figure 36-1 An evaluation of respiratory impairment using the American Medical Association (AMA) Guides' 6th edition. The FEV_1 (the most severely impacted parameter) is used as the key factor to identify the initial impairment class with the middle impairment grade of C as the default, in impairment class 3. Non-key factors in history and the physical are each rated as impairment class 2, reducing the severity grade from C to A with an overall impairment rating of 3A.



5 general steps to complete a respiratory impairment evaluation

1 Does the patient have the correct pulmonary diagnosis?
- when possible this is best confirmed with an objective test

2 Has the patient reached maximal medical improvement (MMI)?
- If MMI is not reached then consider delaying an impairment evaluation or applying for temporary impairment

3 Which impairment rating guideline should be used?
- there is a variety of compensation systems and each dictate which guide to follow

4 How should the patient be assessed?
- assessment is a mix of history and physical examination and pulmonary function/exercise testing

5 What constitutes an impairment report?
- use of gathered information to fill out details reported based on needs of the compensation system

Figure 36-2 Infographic of the five steps for a physician to complete a respiratory impairment evaluation.

The second step is defining maximal medical improvement (MMI). MMI occurs at the point when, following maximal therapy, no further clinical or physiologic improvement is expected to occur (although deterioration might). If therapy has not been maximized, the physician should either delay impairment evaluation or give a temporary rating. A permanent impairment evaluation should be performed only at, or after, MMI has been reached.

The third step is identifying the correct guideline for rating impairment. As discussed previously, several compensation systems exist, each with its own unique guideline. Therefore, identification of the compensation system for which the patient is eligible is essential, and the evaluating physician must be familiar with the specific guideline to be used. Of course, some patients may be eligible for more than one compensation program and may apply for more than one program contemporaneously.

The fourth step is to supplement the history and physical examination findings with appropriate objective tests. Performance of these tests should strictly adhere to standards of the ATS.[9–12]

The fifth and final step requires writing a comprehensive report of the patient's history, physical examination, and review of objective tests. The assessment should provide clear and accurate answers, in lay terms, to the questions asked. The evaluation should state the diagnosis and whether MMI has been reached, and it should make note of the presence and degree of respiratory impairment. The specific impairment scheme used, including the specific page and table of the guideline used, should be referenced. In work-related respiratory disorders, causation, apportionment, and work restrictions should also be addressed, as requested.

GENERAL APPROACH FOR EVALUATING RESPIRATORY IMPAIRMENT

After determining patient eligibility for a specific compensation system, as described previously, the physician gathers data relevant to rating respiratory impairment. In general, impairment criteria are based upon history, physical examination, and objective test results.

The medical history focuses on detailed past and present occupational history, tobacco use and environmental exposures, presence and severity of respiratory symptoms, such as dyspnea, cough, sputum production, and wheezing, and medication history. Relevant features in the physical examination include breathing pattern, shape of chest wall, adventitious lung sounds, cyanosis, digital clubbing, and evidence of cor pulmonale.

■ Resting Pulmonary Function Tests

Pulmonary function tests (PFTs) (Chapter 31) are the cornerstone of rating respiratory impairment and should be performed according to the most recent ATS standards.[9–12] Spirometry and diffusing capacity are the key PFTs for assessing respiratory impairment for chronic respiratory conditions. Postbronchodilator spirometry is used when airflow limitation is present. Methacholine challenge tests are used for rating impairment for asthma under the AMA Guides.[3]

Reference standards for rating severity of PFT abnormality may vary based on the impairment rating guidelines used. Adjustment of PFTs for race, ethnicity, and gender is recommended by most impairment guidelines, with the notable exception of the Social Security impairment system, which currently uses uniform height-specific cut points for all individuals, irrespective of race and ethnicity.[13,14] Furthermore, subjects 20 years or older use the same cut points under the Social Security impairment system, without accounting for the normal age-related decline in lung function. Thus, under the Social Security impairment system, older individuals are more likely to be rated as disabled than are younger individuals.

The sixth edition of the AMA Guides uses spirometric reference standards based on the National Health and Nutrition Examination Survey (NHANES) III for Caucasian Americans, Mexican Americans, and African Americans.[3,15] For the remaining population subgroups, no clear guidelines are provided. The latest ATS guidelines recommend using the Global Lung Function Initiative (GLI)-2012, multiethnic spirometry reference ranges, or NHANES III if needed for continuity.[16] For the most part, GLI-12 and NHANES III equations agree when classifying obstructive lung disease except in the elderly.[17,18] However, lack of data from many non-Caucasian populations limits the current utility of GLI-12 reference equations to Caucasians only.[19] Corrected single-breath carbon monoxide diffusing capacity (DLCO) is used under the AMA Guides, ATS guidelines, and Social Security Impairment guidelines for impairment rating, but it is not used under the Veterans

TABLE 36-1 Classification of Respiratory Impairment from Chronic Lung Diseases, Using the Sixth Edition of the American Medical Association (AMA) Guides to the Evaluation of Permanent Impairment

American Medical Association Class	Class 0	Class 1: 2%–10% Impairment of the Whole Person	Class 2: 11%–23% Impairment of the Whole Person	Class 3: 24%–40% Impairment of the Whole Person	Class 4: 45%–65% Impairment of the Whole Person
Severity grade (%)		A (2%), B (4%), C (6%), D (8%), E (10%)	A (11%), B (14%), C (17%), D (20%), E (23%)	A (24%), B (28%), C (32%), D (36%), E (40%)	A (45%), B (50%), C (55%), D (60%), E (65%)
Objective Tests					
FVC (% predicted)	≥80% predicted and	70%–79% predicted or	60%–69% predicted or	50%–59% or	<50% or
FEV_1 (% predicted)	≥80% predicted and	65%–79% predicted or	64%–55% predicted or	45%–54% or	<45% or
FEV_1/FVC%	>Lower limit of normal and/or >75% predicted) and	N/A	N/A	N/A	N/A
D_{LCO} (% predicted)	≥75% predicted	65%–74% predicted	55%–64% predicted	45%–54%	<45%
$\dot{V}_{O_2max}$					
mL/kg/min	>25 or	22–25 or	21–18 or	15–17 or	<15 or
METs	>7.1	6.1–7.1	5.1–6.0	4.3–5.0	<4.3
History	No current symptoms and/or intermittent dyspnea that does not require treatment	Dyspnea controlled with intermittent or continuous treatment or intermittent mild dyspnea despite continuous treatment	Constant mild dyspnea despite continuous treatment or intermittent moderate dyspnea despite continuous treatment	Constant moderate dyspnea despite continuous treatment or intermittent severe dyspnea despite continuous treatment	Constant severe dyspnea despite continuous treatment or intermittent extreme dyspnea despite continuous treatment
Physical Findings	No current signs of disease	Physical findings not present with continuous treatment or intermittent mild physical findings	Constant mild physical findings despite continuous treatment or intermittent moderate physical findings	Constant moderate physical findings despite continuous treatment or intermittent severe physical findings	Constant severe physical findings despite continuous treatment or intermittent extreme physical findings

FVC, forced vital capacity; FEV_1, forced expiratory volume in the first second; D_{LCO}, diffusing capacity of carbon monoxide; $\dot{V}_{O_2max}$, measured maximal exercise capacity; MET or metabolic equivalent is the multiple of basal oxygen consumption, approximately 3.5 mL/kg/min; N/A, not applicable.

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Administration guidelines. Crapo's reference standards for D_LCO are used for comparison with measured values with a correction factor used for African Americans and Asian Americans. ATS has recently updated criteria on acceptability and repeatability for D_LCO.[20]

The cut points for impairment classification, as suggested by the various impairment guidelines (Tables 36-1–36-3), are set arbitrarily and may differ from those recommended for assessing degree of lung disease severity by other professional organizations, such as the 2005 ATS statement,[10] or by the Global Initiative for Chronic Obstructive Lung Disease (GOLD).[21] Some investigators have suggested that lung function thresholds should be expressed as a z-score, which converts a raw measurement on a test to a standardized score expressed in units of standard deviations.[22,23] This strategy, although scientifically valid, is not currently used for impairment evaluation.

Methacholine bronchoprovocation tests are useful for assessing bronchial hyperresponsiveness and in rating impairment from asthma under the AMA Guide and ATS guidelines (Tables 36-1 and 36-2).[3,8] The methacholine PC_{20} (provocative concentration of methacholine, expressed as mg/mL that results in at least 20% drop in FEV_1 compared to the pretest baseline; also known as PD20, or "provocative dose," as discussed in Chapter 31, Pulmonary Function Testing) is a key parameter for rating asthma impairment under the sixth edition of the AMA Guides.[3] The performance of methacholine bronchoprovocation tests should also strictly adhere to the ATS guidelines.[24]

■ Exercise Tests

Maximal cardiopulmonary exercise tests are difficult to perform due to need for specialized equipment and trained personnel, are expensive and not readily available, and carry a risk to the patient. Test performance should strictly adhere to the ATS guidelines.[25] Clear agreement on the role of exercise tests in the evaluation of respiratory impairment is lacking. Generally, in cases in which subjective dyspnea is disproportionate to the resting PFT results, or when PFTs are difficult to interpret because of submaximal performance, cardiopulmonary exercise tests may be considered. Such tests may also help identify unanticipated coexisting conditions, such as cardiovascular or pulmonary vascular disease, as the cause of exercise limitation.

Exercise testing may also be useful in determining whether an individual can perform a specific job with a known energy requirement. Under the ATS guidelines, the estimation of impairment from oxygen consumption at peak exercise ($\dot{V}_{O_2peak}$) is based on the

TABLE 36-2 American Thoracic Society (ATS) Classification of Respiratory Impairment

Impairment Class	Normal	Mildly Impaired	Moderately Impaired	Severely Impaired
Work ability		Usually able to perform most jobs	Diminished ability to perform many jobs	Unable to meet physical demands of most jobs including travel to work
FVC (% predicted)	≥80%	60%–79%	51%–59%	≤50%
FEV_1 (% predicted)	≥80%	60%–79%	41%–59%	≤40%
FEV_1/FVC	≥75%	60%–74%	41%–59%	≤40%
D_{LCO} (% predicted)	≥80%	60%–79%	41%–59%	≤40%
$\dot{V}_{O_2max}$ (mL/kg/min)	≥25 (or 7.1 METs)			≤15 (or 4.3 METs)

FVC, forced vital capacity; FEV_1, forced expiratory volume in the first second; D_{LCO}, diffusing capacity of carbon monoxide; $\dot{V}_{O_2max}$, measured maximal exercise capacity; MET or metabolic equivalent is the multiple of basal oxygen consumption, approximately 3.5 mL/kg/min.
Data from Evaluation of impairment/disability secondary to respiratory disorders. American Thoracic Society. Am Rev Respir Dis. 1986;133(6):1205–1209.

TABLE 36-3 Impairment Rating Guidelines for Chronic Obstructive Lung Diseases Using the Social Security, Veterans Administration, American Medical Association (AMA) Guides, and American Thoracic Society (ATS) Guidelines

(A) SOCIAL SECURITY

Height Without Shoes (cm)	Height Without Shoes (in.)	FEV_1 Equal to or Less than (L, BTPS)
≤154	≤60	1.05
155–160	61–63	1.15
161–165	64–65	1.25
166–170	66–67	1.35
171–175	68–69	1.45
176–180	70–71	1.55
≥181	≥72	1.65

(B) VETERANS ADMINISTRATION

Chronic Bronchitis

Pronounced (100% rating): with copious productive cough and dyspnea at rest; PFTs showing a severe degree of chronic airway obstruction with symptoms of associated severe emphysema or cyanosis and findings of right-sided heart involvement

Severe (60% rating): with severe productive cough and dyspnea on slight exertion and PFTs indicative of severe ventilatory impairment

Moderately severe (30% rating): persistent cough at intervals throughout the day, considerable expectoration, considerable dyspnea on exercise, rales throughout chest, beginning chronic airway obstruction

Moderate (10% rating): considerable night or morning cough, slight dyspnea on exercise, scattered bilateral rales

Mild (0% rating): slight cough, no dyspnea, few rales

Emphysema

Pronounced (100% rating): intractable and totally incapacitating; with dyspnea at rest, or marked dyspnea and cyanosis on mild exertion; severity of emphysema confirmed by CXR and PFTs

Severe (60% rating): exertional dyspnea sufficient to prevent climbing one flight of steps or walking one block without stopping; ventilatory impairment of severe degree confirmed by PFTs with marked impairment of health

Moderate (30% rating): with moderate dyspnea occurring after climbing one flight of steps or walking more than one block on a level surface; PFTs consistent with findings of moderate emphysema

Mild (10% rating): with evidence of ventilatory impairment on PFTs and/or definite dyspnea on prolonged exertion

(C) AMA GUIDES AND ATS GUIDELINES

Use criteria outlined in Tables 36-1 and 36-2, respectively, in the text

FEV_1, forced expiratory volume in the first second; BTPS, body temperature and pressure saturated with water vapor.
For mixed obstructive and restrictive lung diseases with gas exchange impairment, evaluate under any of the criteria listed in Tables 36-3(A), 36-6(A), or 36-7.
Social Security impairment system has separate guidelines for patients with bronchiectasis.
Data from Social Security Administration and Veterans Administration.

widely held, but untested, assumption that a worker involved in manual labor can comfortably work at 40% of $\dot{V}_{\mathrm{O_2peak}}$ (corresponding to lower limit of generally accepted normal values for anaerobic threshold) for prolonged periods,[7] and that $\dot{V}_{\mathrm{O_2}}$ requirements can be assigned to specific occupations. Individuals whose $\dot{V}_{\mathrm{O_2peak}}$ is ≤ 15 mL/kg/min would be uncomfortable performing most jobs because they would find it difficult to travel back and forth to their place of employment (Table 36-2).[7] Unfortunately, data on $\dot{V}_{\mathrm{O_2}}$ requirements of most jobs in modern workplaces are not currently available. Furthermore, jobs with the same title may vary considerably in their $\dot{V}_{\mathrm{O_2}}$ requirements from one work site to another.

Submaximal exercise tests at a workload of approximately 17 mL O_2/kg/min (5 METs) or less of exercise can be performed at steady state to obtain arterial blood gases, which are then used to evaluate impairment of gas exchange under the Social Security impairment system when criteria for neither obstructive nor restrictive disorders are met. Oxygen saturation measured by pulse oximetry either at rest or during/after a 6-minute walk test can be alternatively used to evaluate impairment of gas exchange under the Social Security impairment system. Use of submaximal exercise tests or pulse oximetry is however not currently recommended by any other impairment guideline.

For additional information on exercise testing, the reader is referred to Chapter 32, Principles and Application of Cardiopulmonary Exercise Testing.

■ Imaging

Imaging studies are primarily useful for confirming the diagnosis of lung disease. They are less useful in rating respiratory impairment, since the correlation between radiographic abnormality and physiologic dysfunction is imperfect.

Chest radiographic evidence of pneumoconiosis is rated according to the 2011 International Labor Organization's (ILO) International Classification of Radiographs of Pneumoconiosis scheme (also called "B-reading"). The 2011 standards extended the applicability of the Classification to digital chest radiographs. The extent or profusion of small-sized parenchymal opacities is rated as 0, 1, 2, or 3. An intermediate score of 1/0 (i.e., profusion of small opacities greater than 0 but less than 1 profusion score) is often used to confirm the presence of pneumoconiosis.

Some determinations of respiratory impairment are not dependent on PFTs. They are based on environment-related diagnoses (e.g., occupational asthma or hypersensitivity pneumonitis) and warrant proscription of continuing exposure to inciting agents. In addition, impairment may be based on prognosis (e.g., unresectable lung cancer) or public health considerations (e.g., pulmonary tuberculosis).

SCIENTIFIC RATIONALE FOR CHOICE OF TESTS USED FOR IMPAIRMENT EVALUATION FOR CHRONIC RESPIRATORY DISORDERS

Impairment evaluation for chronic respiratory conditions is based on PFT values at rest and with exercise. The premise for these tests is that $\dot{V}_{\mathrm{O_2peak}}$ reasonably measures ability to work, and that resting PFTs, such as forced expiratory volume in 1 s (FEV_1) and D_LCO, reasonably predict $\dot{V}_{\mathrm{O_2peak}}$ values.

■ Oxygen Consumption at Peak Exercise as the Gold Standard for Measuring Ability to Work

Most of the available medical literature appears to support the view that $\dot{V}_{\mathrm{O_2peak}}$ value, expressed as mL/kg/min, is the gold standard for assessing impairment.[26,27] With exercise on a cycle ergometer, $\dot{V}_{\mathrm{O_2}}$ increases linearly with external work,[17] and $\dot{V}_{\mathrm{O_2peak}}$ represents the maximal work an individual can perform during a short burst of activity. Some have advocated use of percent predicted $\dot{V}_{\mathrm{O_2peak}}$ values (i.e., loss of aerobic capacity), instead of $\dot{V}_{\mathrm{O_2peak}}$ expressed in mL/kg/min (i.e., remaining aerobic ability) for evaluating impairment in patients with respiratory disease, since the latter approach overestimates impairment in older and obese subjects (Fig. 36-3).[28,29] In addition, some consider the value for $\dot{V}_{\mathrm{O_2}}$ at anaerobic threshold ($\dot{V}_{\mathrm{O_2}}$ AT) as a better index for work ability than $\dot{V}_{\mathrm{O_2peak}}$.[21] Individuals are unable to sustain work rates above anaerobic threshold values. However, no major guidelines currently use percent predicted $\dot{V}_{\mathrm{O_2peak}}$ values or $\dot{V}_{\mathrm{O_2}}$ AT to rate impairment.

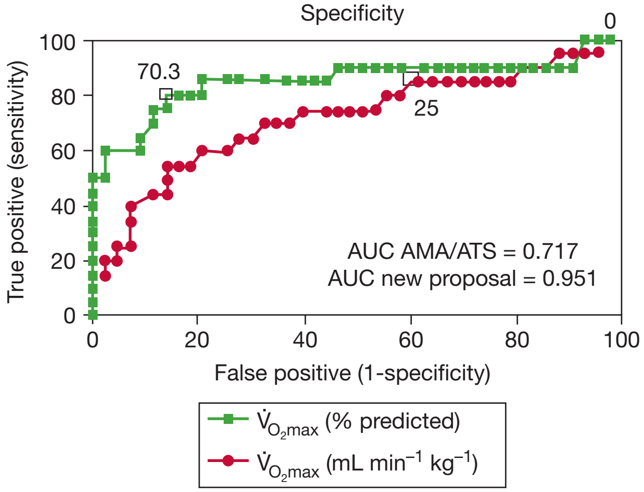

Figure 36-3 Receiver operating characteristics (ROC) curves of two classifications (AMA/ATS vs. new classification proposed by Neder et al.), using the $\dot{V}_{\mathrm{O_2}}$ at anaerobic threshold ($\dot{V}_{\mathrm{O_2}}$AT) as the "gold standard." The *open squares* represent the cutoffs for normality for $\dot{V}_{\mathrm{O_2peak}}$ using the two-classification schema. Neder et al. have advocated the use of percent predicted $\dot{V}_{\mathrm{O_2peak}}$ values (i.e., loss of aerobic capacity) instead of $\dot{V}_{\mathrm{O_2peak}}$ in mL/kg/min (i.e., remaining aerobic ability) for the evaluation of impairment in patients with respiratory disease since the latter approach overestimates impairment in older and obese subjects. AMA, American Medical Association; ATS, American Thoracic Society; AUC, area under the ROC curve; $\dot{V}_{\mathrm{O_2}}$, oxygen consumption. *(Reproduced with permission from Neder JA, Nery LE, Bagatin E, et al. Differences between remaining ability and loss of capacity in maximum aerobic impairment. Braz J Med Biol Res. 1998;31(5):639–646.)*

■ Comparison of Resting Pulmonary Function Tests with Oxygen Consumption at Peak Exercise

Low values for resting PFTs (i.e., FEV_1 or D_LCO) predict low $\dot{V}_{\mathrm{O_2peak}}$ levels; poor scores on the Short Physical Performance Battery (tests that assess lower extremity function); less distance walked during the 6-minute walk test; and a greater risk of self-reported functional limitation.[30,31]

FEV_1 is linearly correlated with $\dot{V}_{\mathrm{O_2peak}}$ levels,[31] but the reported correlations vary widely between studies, resulting in variance values ranging from 0.25 to 0.71.[31–36] Use of absolute versus percent predicted values largely yields similar correlation measures.[35] Although some studies demonstrate that FEV_1 and forced vital capacity (FVC) have similar predictive value for $\dot{V}_{\mathrm{O_2peak}}$ levels,[35] most report FEV_1 to be a stronger predictor than FVC. The 2005 ATS statement indicated that percent predicted FEV_1, rather than FVC, should be used to categorize severity of impairment for all respiratory diseases.[10] The predictive ability of FEV_1 for $\dot{V}_{\mathrm{O_2peak}}$ increases if it is used in combination with another variable, such as D_LCO, minute ventilation ($\dot{V}_E$), or dead space ventilation measure during exercise (V_D/V_T).[35] D_LCO does not predict $\dot{V}_{\mathrm{O_2peak}}$ among healthy controls,[32] but it does so among subjects with COPD and those with occupational lung diseases, where it may account for a variance of 0.25 to 0.76 in various studies.[34,35,37]

Despite the previously noted correlations in population studies, resting PFTs cannot accurately predict $\dot{V}_{\mathrm{O_2peak}}$ values among

TABLE 36-4 Degree of Impairment, as Assessed by Resting Pulmonary Function Tests and Cardiopulmonary Exercise Tests[a19]

Degree of Impairment	Resting PFT (%)	CPET (%)
None	6	28
Mild	26	36
Moderate	38	20
Severe	30	16

PFT, pulmonary function test; CPET, cardiopulmonary exercise test; FEV_1, forced expiratory volume in 1 s.

[a]Among 216 ambulatory patients with COPD with mean percent predicted FEV_1 of 54.1 ± 16.8% and mean age of 57.9 ± 6.9 years

Reproduced with permission from Fink G, Moshe S, Goshen J, et al. Functional evaluation in patients with chronic obstructive pulmonary disease: pulmonary function test versus cardiopulmonary exercise test. J Occup Environ Med. 2002;44(1):54–58.

individuals, particularly those with occupational lung diseases. In a comparison study of impairment ratings obtained using simultaneous resting PFTs and cardiopulmonary exercise tests conducted in 216 ambulatory patients with COPD, the two methods resulted in similar impairment rating in only 30.1%. Ratings were similar between the two methods in the extreme subgroups of normal or severely impaired individuals. 61.1% were found to be less impaired according to exercise testing than according to resting PFTs, and 8.8% were more impaired according to exercise testing than resting PFTs (Table 36-4). These data suggest that use of resting PFTs and exercise testing for rating impairment often yields discrepant results.

PFTs other than FEV_1 and D_LCO also may help predict $\dot{V}_{O_2peak}$ values. These include inspiratory capacity in flow-limited obstructive diseases;[38] peak inspiratory pressure in chronic obstructive diseases;[34] exercise ventilation ($\dot{V}_E$) in both obstructive and restrictive lung diseases;[27] and submaximal exercise tests, including 6-minute walk test duration.[28] Use of these tests is however not currently recommended by any impairment guideline. Performance of maximal voluntary ventilation (MVV) is not recommended except under the Black Lung Benefits Act.[39] MVV is markedly effort dependent and bears a fixed relationship with FEV_1;[40] therefore, it is of limited value.

Finally, both baseline oxygen saturation and the lowest oxygen saturation measured with a finger oximeter probe during a submaximal test correlate with $\dot{V}_{O_2peak}$ in patients with idiopathic pulmonary fibrosis,[28] but not in those with COPD.[41]

SCIENTIFIC RATIONALE FOR CHOICE OF TESTS USED FOR IMPAIRMENT EVALUATION FOR ASTHMA

Asthma is a very common disorder, the presence of which may profoundly impact an individual's ability to perform various kinds of work. Considerations of disability in asthma are discussed below.

Determinants of Work Ability in Asthma

Among subjects with methacholine-confirmed asthma, a lower self-reported work ability is associated with lower PC_{20} value (i.e., higher degree of airway hyperresponsiveness), greater clinical severity of disease (based on minimum medication need to maintain asthma control), and the presence of respiratory symptoms in the workplace.[42] However, no relationships are evident with regard to baseline FEV_1 or FVC in both unadjusted and adjusted analyses.[42] Although controversial, methacholine PC_{20} has been accepted as the key parameter for rating asthma impairment under the sixth edition of the AMA Guides.[3]

Comparison Between Respiratory Symptoms and PC_{20}

For most subjects with asthma, greater breathlessness perceived during asthma attacks is not correlated with greater decline in peak expiratory flow rate[43] or with a lower PC_{20}.[44]

Comparison Between Minimum Medication Need and PC_{20}

Almost all medications used to treat asthma improve PC_{20} values, that is, decrease bronchial hyperresponsiveness.[45–57] In one study, patients with asthma with the minimum medication needed to control symptoms were divided into four groups: (1) those who required no medication; (2) those who required short-acting β_2-agonist occasionally, but not daily; (3) those who required daily short-acting β_2-agonist; and (4) those who required additional inhaled corticosteroid dosing. The mean PC_{20} value was highest in group 1 and lowest in group 4; the differences between each group were significant.[58] Minimum medication need is, therefore, an important predictor for both work ability and airway hyperresponsiveness in asthma.

Comparison Between Percent Predicted FEV_1 and PC_{20}

In a small clinical population of smokers and nonsmokers, as well as in a population of subjects with asthma with concomitant stable bronchiectasis, baseline FEV_1 has been shown to correlate with methacholine PC_{20} values.[59]

IMPAIRMENT RATING FOR SPECIFIC LUNG CONDITIONS

Impairment evaluation for selected populations, including those with asthma or coal workers' pneumoconiosis, and in workers in nuclear weapons factories, is discussed below.

Asthma

Unlike most chronic respiratory conditions, asthma is an episodic disease, and impairment evaluation for asthma is particularly difficult. Therefore, most impairment rating schemes incorporate separate guidelines for rating asthma impairment. Further, the rating schemes differ dramatically with respect to the level of impairment (Tables 36-5A–36-5C).

The methacholine PC_{20} is the key parameter for rating asthma impairment under the sixth edition of the AMA Guides (Table 36-5B).[3] On the other hand, PC_{20} and extent of FEV_1 reversibility are given less weight than are either minimum medication need or postbronchodilator FEV_1 in the multicomponent asthma impairment scoring scheme recommended by the 1993 ATS guidelines (Table 36-5C).[8] Under Social Security impairment criteria, patients with asthma may be rated by FEV_1 or by a clinical history of frequent, severe exacerbations, despite maximal asthma therapy; a methacholine PC_{20} measurement is not required (Table 36-5A). On the contrary, AMA Guides and ATS guidelines do not incorporate frequency of acute exacerbations in the impairment rating for asthma. Given the efficacy of currently recommended asthma therapies, frequent emergency room visits or hospitalizations generally reflect inadequate treatment and failure to achieve the objectives of treatment. The AMA Guides and ATS guidelines instead use minimum medication need for asthma control as a better reflection of the severity of disease for the purpose of impairment assessment than frequency of asthma exacerbations. Hence, it is easy to see why impairment ratings for the same patient with asthma might vary widely among various compensation systems.

Impairment rating for occupational asthma is even more problematic. In these cases, both temporary and long-term impairment evaluation may be performed.[8] Temporary impairment for patients with sensitizer-induced occupational asthma should be performed after removing the worker from exposure. Early cessation of exposure improves prognosis in sensitizer-induced occupational asthma. Sometimes, physiologic tests may be normal, and symptoms and

TABLE 36-5A Impairment Rating Guidelines for Asthma Using the Social Security, Veterans Administration, American Medical Association (AMA) Guides, and American Thoracic Society (ATS) Guidelines

(A) SOCIAL SECURITY
(1) Asthma with chronic asthmatic bronchitis: evaluate under the criteria for chronic obstructive airway disease (Table 36-3A)
(2) Attacks, in spite of prescribed treatment and requiring physician intervention, occurring at least once every 2 months, or at least 6 times a year. Each in-patient hospitalization >24 h for control of asthma counts as two attacks. An evaluation period of at least 12 consecutive months must be used to determine the frequency of attacks
(B) VETERANS ADMINISTRATION[a]
Pronounced (100% rating): asthmatic attacks very frequently with severe dyspnea on slight exertion between attacks and with marked loss of weight or other evidence of severe impairment of health
Severe (60% rating): frequent attacks of asthma (one or more attacks weekly), marked dyspnea on exertion between attacks with only temporary relief by medication; more than light manual labor precluded
Moderate (30% rating): asthmatic attacks rather frequent (separated by only 10- to 14-d intervals) with moderate dyspnea on exertion between attacks
Mild (10% rating): paroxysms of asthmatic type breathing (high-pitched expiratory wheezing and dyspnea) occurring several times a year with no clinical findings between attacks
(C) AMA GUIDES AND ATS GUIDELINES
Use scoring criteria in Tables 36-5B and 36-5C, respectively

[a] In the absence of clinical findings of asthma at time of examination, a verified history of asthmatic attacks must be on record.
Data from Social Security Administration and Veterans Administration.

need for treatment may subside after early cessation of exposure, resulting in 0% measurable impairment. However, such an individual should be considered as 100% disabled on a permanent basis from working in a job that exposes him or her to the specific sensitizing agent.[8] It is not necessary to wait for long-term impairment rating to initiate vocational rehabilitation in such a case.[8] The long-term impairment evaluation is performed using the rating systems devised for nonoccupational asthma at least 2 years after cessation of exposure, when improvement has been shown to plateau.[60]

■ Pneumoconioses

According to the AMA Guides, those who develop pneumoconiosis should limit further exposure to the offending agent, “particularly if radiographic changes have occurred at a relatively young age or if there is associated physiologic impairment.”[3] It follows that an older patient who is nearing retirement, with minimal radiographic change after a long history of exposure, could elect to continue in the workplace under the assumption of a lower risk of developing future disabling disease. Such discretionary decisions should be made

TABLE 36-5B Classification of Respiratory Impairment from Asthma, Using the Sixth Edition of the American Medical Association (AMA) Guides to the Evaluation of Permanent Impairment

Class	Class 0	Class 1	Class 2	Class 3	Class 4
Whole person impairment rating (%)	0	2%–10%	11%–23%	24%–40%	45%–65%
Severity grade (%)		A (2%), B (4%), C (6%), D (8%), E (10%) (minimal)	A (11%), B (14%), C (17%), D (20%), E (23%) (mild)	A (24%), B (28%), C (32%), D (36%), E (40%) (moderate)	A (45%), B (50%), C (55%), D (60%), E (65%) (severe)
Clinical parameters (minimum medication need)	No medication required	Occasional bronchodilator, not daily	Daily low-dose inhaled steroid (<500 μg beclomethasone or equivalent)	Daily medium or high-dose inhaled steroids (500–1000 μg beclomethasone or equivalent) and/or short periods of systemic steroids and a long-acting bronchodilator. Daily use of steroids (systemic and inhaled) and daily use of maximum bronchodilators	Asthma not controlled by treatment
Maximum postbronchodilator percent predicted FEV$_1$	>80%	70%–80%	60%–69%	50%–59%	<50%
PC$_{20}$ (key factor)[a]	6–8 mg/mL	3–5 mg/mL	>0.5–3 mg/mL	0.25–0.5 mg/mL	0.125–0.24 mg/mL

FEV$_1$, forced expiratory volume in the first second; PC$_{20}$, provocative concentration of methacholine associated with 20% decrease in FEV$_1$ from baseline.
[a] The methacholine PC$_{20}$ is the key parameter for rating asthma impairment. If PC$_{20}$ cannot be obtained, postbronchodilator percent predicted FEV$_1$ is used as the key factor.
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TABLE 36-5C American Thoracic Society (ATS) Asthma Impairment Rating Statement

(A) POST-BRONCHODILATOR FEV_1

Score	FEV_1 (% Predicted)
0	>lower limit of normal
1	70–lower limit of normal
2	60–69
3	50–59
4	<50

(B) REVERSIBILITY OF FEV_1 OR DEGREE OF AIRWAY HYPERRESPONSIVENESS[a]

Score	%FEV_1 Change	PC_{20} (mg/mL)
0	<10	>8
1	10–19	8–>0.5
2	20–29	0.5–>0.125
3	≥30	≤0.125

(C) MINIMUM MEDICATION NEEDS[b]

Score	Medication
0	No medication
1	Occasional bronchodilator, not daily, and/or occasional cromolyn, not daily
2	Daily bronchodilator and/or daily cromolyn and/or daily inhaled low-dose inhaled steroid (<800 μg beclomethasone or equivalent)
3	Bronchodilator on demand and daily high-dose inhaled steroid (>800 μg beclomethasone or equivalent) or occasional course (1–3/year) of systemic steroid
4	Bronchodilator on demand and daily high-dose inhaled steroid (>1000 μg beclomethasone or equivalent) and daily systemic steroid

(D) SUMMARY OF IMPAIRMENT RATING CLASSES

Impairment Rating	Sum of Scores from Sections A, B, and C
0	0
I	1–3
II	4–6
III	7–9
IV	10–11
V	Asthma not controlled despite maximal treatment, i.e., FEV_1 remaining <50% despite use of ≥20 mg prednisone per day

FEV_1, forced expiratory volume in the first second; PC_{20}, provocative concentration of methacholine associated with 20% decrease in FEV_1 from baseline.

[a] *When the postbronchodilator FEV_1 value is above the lower limit of normal, the PC_{20} value should be determined and used for rating of impairment; when the post-bronchodilator FEV_1 value is <70% of the predicted value, the degree of reversibility is used; when the FEV_1 value is between 70% of the predicted value and the lower limit of normal, either the degree of reversibility of FEV_1 or the PC_{20} can be used.*

[b] *The need for minimum medication should be demonstrated by the treating physician, for example, previous records of exacerbations when medications have been reduced.*

Adapted with permission from Guidelines for the evaluation of impairment/disability in patients with asthma. American Thoracic Society. Medical Section of the American Lung Association. Am Rev Respir Dis. 1993;147(4):1056–1061.

based on a discussion between the patient and physician.[3] While the Veterans Administration has specific guidelines for impairment ratings for pneumoconiosis, the Social Security construct is based upon standard criteria for assessing impairment from any chronic respiratory disorder, as listed in Tables 36-3(A), 36-6(A), and 36-7.[6,61]

Coal Workers' Pneumoconiosis

In 1972, the Black Lung Benefits Act set eligibility criteria for the awarding of benefits to coal miners and their survivors in the United States. The Act defines pneumoconiosis as "a chronic dust disease of the lung and its sequelae, including respiratory and pulmonary impairments arising out of coal mine employment." This definition encompasses two classes of coal dust–related lung diseases: medical or "clinical" pneumoconiosis and statutory or legal pneumoconiosis. Medical or "clinical" pneumoconiosis includes diseases that pulmonologists usually consider as pneumoconiosis (such as coal workers' pneumoconiosis, anthracosis, anthracosilicosis, massive pulmonary fibrosis, silicosis, or silicotuberculosis). Statutory or legal pneumoconiosis includes any chronic pulmonary disease arising out of coal mine employment, including chronic bronchitis and emphysema.

A coal miner applying for Black Lung benefits must show that he or she has pneumoconiosis, that the pneumoconiosis resulted from coal mine employment, and that it has resulted in "total disability." The latter is defined by any one of the following: (1) Department of Labor thresholds of FEV_1, FVC, FEV_1/FVC ratio, MVV, or arterial blood gas values delineating criteria for "total disability;"[39] (2) presence of cor pulmonale; (3) radiographic evidence of complicated pneumoconiosis or progressive massive fibrosis; or (4) reasoned

TABLE 36-6 Impairment Rating Guidelines for Restrictive Lung Diseases Using the Social Security, Veterans Administration, American Medical Association (AMA) Guides, and American Thoracic Society (ATS) Guidelines

(A) SOCIAL SECURITY		
Height Without Shoes (cm)	**Height Without Shoes (in)**	**Vital Capacity Equal to or Less than (L, BTPS)**
≤154	≤60	1.25
155–160	61–63	1.35
161–165	64–65	1.45
166–170	66–67	1.55
171–175	68–69	1.65
176–180	70–71	1.75
≥181	≥72	1.85
(B) VETERANS ADMINISTRATION		
Leaves the rating to the judgment of the physician, according to symptoms, anatomic extent, pulmonary functions, and complications		
(C) AMA GUIDES AND ATS GUIDELINES		
Use criteria outlined in Tables 36-6A and B, respectively		

BTPS, body temperature and pressure saturated with water vapor.
In severe kyphoscoliosis, the measured span between the fingertips when the upper extremities are abducted 90 degrees should be substituted for height.
For mixed obstructive and restrictive lung diseases with gas exchange impairment, evaluate under any of the criteria listed in Tables 36-3A,36-6A, or 36-7.
Data from Social Security Administration and Veterans Administration.

medical evidence by a physician describing an inability to perform the last coal mine employment of at least 1 year duration from respiratory or pulmonary impairment.

The miner must supply medical evidence of pneumoconiosis that includes: (1) a posteroanterior chest radiograph, along with a report of the findings using the ILO classification system; (2) a physician report detailing the occupational, medical, and smoking history, as well as all manifestations of chronic respiratory disease; (3) spirometric results; (4) altitude-adjusted arterial blood gas results; and (5) biopsy or autopsy evidence, if available. Other medical evidence accepted includes diffusing capacity.

Chest radiographic findings are accepted to show pneumoconiosis if they demonstrate the presence of either small parenchymal opacities of at least category 1/0 profusion or large opacities. The

TABLE 36-7 Social Security Impairment Criteria for Evaluating Chronic Impairments of Gas Exchange Due to Clinically Documented Pulmonary Disease

(1) Arterial blood gases demonstrating values of Pa_{O_2} and simultaneously determined Pa_{CO_2} measured while at rest (breathing room air, awake and sitting, or standing), in a clinically stable condition on at least two occasions, 3 or more weeks apart within a 6-month period, equal to or less than the values specified below or arterial blood gas values during steady-state exercise breathing room air (level of exercise equivalent to or less than 17.5 mL O_2 consumption/kg/min or 5 METs), equal to or less than the values specified below.

Pa_{CO_2} (in mm Hg) and	At Test Sites <3000 ft Above Sea Level, Pa_{O_2} (in mm Hg)	At Test Sites 3000–6000 ft Above Sea Level, Pa_{O_2} (in mm Hg)	At Test Sites >6000 ft Above Sea Level, Pa_{O_2} (in mm Hg)
≤30	65	60	55
31	64	59	54
32	63	58	53
33	62	57	52
34	61	56	51
35	60	55	50
36	59	54	49
37	58	53	48
38	57	52	47
39	56	51	46
≥40	55	50	45
or			

(2) Diffusing capacity for carbon monoxide <10.5 mL/mm Hg/min (single-breath method) or <40% of predicted normal. (All methods, actual values and predicted normal values and the sources of the predicted value should be reported.)

Data from Social Security Administration and Veterans Administration.

absence of radiographic evidence of pneumoconiosis makes medical or clinical pneumoconiosis unlikely, but it may be noted in patients with statutory or legal pneumoconiosis.[39]

Pneumoconiosis in U.S. Department of Energy Employees in Nuclear Weapons Factories

The U.S. Energy Employees' Occupational Illness Compensation Program Act (EEOICPA) was enacted to provide compensation and medical benefits to workers who acquired disease in the course of their work in the nuclear defense industry. Those eligible include employees and former employees of the Department of Energy at nuclear weapons factories, as well as private contractors and subcontractors at those locations. In addition to exposure to silica, asbestos, or mixed dusts that occurred during uranium ore extraction, many workers were also exposed to beryllium (used in the manufacture of ballistic missile nose cones) and radiation. In contradistinction to Black Lung evaluation, the Part E of the EEOICPA has adopted the standards of the fifth edition of AMA Guides to the Evaluation of Permanent Impairment as the method of rating impairment.

■ Lung Cancer

According to the AMA Guides, lung cancer is a cause of severe impairment for the period extending from the time of diagnosis to 1 year thereafter. If no evidence of tumor is found at re-evaluation at 1 year, then impairment is recalculated based on the degree of physiologic impairment present at that time. On the other hand, if there is evidence of tumor, the patient remains classified as severely impaired.

Under the Social Security system, lung cancer produces impairment if it is inoperable, unresectable, recurrent, or metastatic to or beyond hilar nodes; is of small-cell histology; or involves the superior sulcus (including Pancoast tumors) with multimodal anticancer therapy. Under the Veterans Administration system, degree of impairment is not categorized clearly, but rather, is left to the judgment of the physician.

■ Sleep Apnea

Impairment ratings for sleep apnea are problematic and vary widely among compensation systems. Resting and exercise PFTs are not useful for rating impairment related to sleep apnea. Therefore, the AMA Guides recommend assessment of complications of sleep apnea, such as the presence of cor pulmonale or polycythemia, and rate the complications according to the appropriate organ systems. Any "add-on" for strictly defining respiratory impairment must be determined by a sleep specialist and should not exceed 3% of total impairment.[3] Under the Social Security system, sleep apnea is rated according to the complications related to the affected body system(s), such as chronic pulmonary hypertension; chronic heart failure; or disturbances in mood, cognition, and behavior.[6]

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PART 4

Obstructive Lung Diseases

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SECTION 7 Chronic Obstructive Pulmonary Disease

CHAPTER 37

Pathology of Chronic Obstructive Pulmonary Disease: Diagnostic Features and Differential Diagnosis

Joanne L. Wright
Andrew Churg

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a general name for the chronic airflow obstruction that develops most often as a result of chronic tobacco smoking, but also after exposure to biomass fuels and air pollution. The pathology of COPD encompasses a variety of pathologic lesions in the airways, lung parenchyma, and pulmonary vasculature, and these lesions can be correlated, to a greater or lesser degree, with changes in pulmonary function tests and clinical appearances. In general, although the mechanisms involved are complex, airflow obstruction can be attributed largely to a marked increase in airway resistance secondary to a variable mix of structural abnormalities involving all or many of the compartments of the airway. However, in individual cases, it may be difficult to prove associations between physiologic abnormalities and pathologic changes. The Global Initiative on Obstructive Lung Disease (GOLD), revised in 2017,[1] classifies patients with COPD upon a combination of indices of airflow, assessment of symptoms, and exacerbation history; thus far there is only limited integration with pathologic findings.

This chapter presents the pathologic features of COPD and how these findings can be differentiated from other lesions associated with airflow obstruction.

HISTORY OF PATHOLOGIC DESCRIPTIONS OF COPD

The word emphysema is derived from Greek and means "to blow into," hence "air-containing" or "inflated." Although "voluminous lungs" and lungs "turgid particularly from air" were described respectively by Bonet in 1679[2] and Morgagni in 1769,[3] the first description of enlarged airspaces in emphysema in the human, together with illustrations, was furnished by Ruysh in 1721,[4] followed by Matthew Baillie in 1807, who not only clearly recognized and illustrated emphysema, but also pointed out its essentially destructive character.[5,6]

Laennec,[7] writing in the early 1800s, made a number of seminal contributions to the basic descriptions of pathologic changes in COPD. He was the first to make a clear-cut distinction between interstitial emphysema and emphysema proper, and related the enlarged airspaces to the clinical syndrome of emphysema. He also recognized that air trapping and increased collateral ventilation were features of emphysematous lungs, and that the peripheral airways were the primary site of obstruction in emphysema. Furthermore, he noted that airspaces enlarged with increasing age, and he distinguished these changes from emphysema. He was the first to describe an association of emphysema with chronic bronchitis and to clearly describe the pathology of bronchiectasis.

Little of major importance was added to the gross descriptive morphology of emphysema for almost the next 150 years. The foundation of modern knowledge of the pathologic anatomy of pulmonary emphysema was laid by J. Gough in 1952[8] when he described centrilobular emphysema and distinguished it from panlobular emphysema. The paper section technique developed by Gough and Wentworth[9] was largely responsible for this advance, as it made examinations of sections of entire inflated lungs possible and simple (Fig. 37-1). A comprehensive microscopic description of emphysema was then provided by McLean,[10,11] who demonstrated the relationship of destruction to inflammatory alterations of the bronchioles and discussed the observed alterations of the vasculature.

LESIONS OF THE LUNG PARENCHYMA IN COPD: EMPHYSEMA

A major problem in describing the pathologic features of emphysema has been the lack of a generally accepted and easy to apply definition. In 1959, a Ciba Guest Symposium defined emphysema in anatomic terms as "a condition of the lung characterized by increase beyond the normal of airspaces, distal to the terminal bronchiole, either from dilatation or from destruction of their walls."[12] Subsequent definitions differed in that destruction of respiratory tissue became a requirement:[13–15] "Emphysema is a condition of the lung characterized by abnormal, permanent enlargement of the

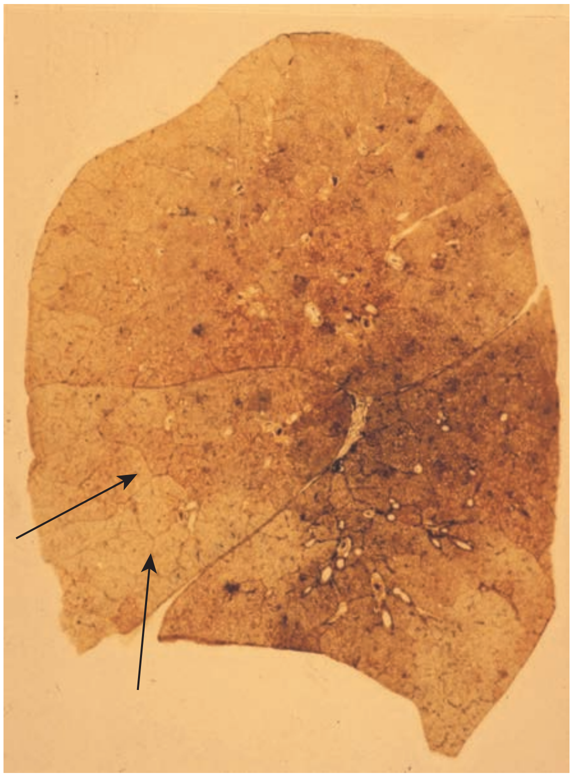

Figure 37-1 Gough sagittal section. Paper mount. Normal lung.

airspaces distal to the terminal bronchiole, accompanied by destruction of their walls." This requirement separates emphysema from enlargement of airspaces unaccompanied by destruction, the latter now being termed "overinflation."

Destruction has been similarly difficult to define in an unambiguous way. A committee of the National Institutes of Health[16] proposed that destruction was present when "there was nonuniformity in the pattern of respiratory airspace enlargement so that the orderly appearance of the acinus and its components is disturbed and may be lost." They recognized that emphysema was a subset of airspace enlargement defined as "an increase in airspace size as compared with the airspace of normal lungs. The term applies to all varieties of airspace enlargement distal to the terminal bronchioles, whether occurring with or without fibrosis or destruction." While these definitions, when strictly applied, would eliminate airspace enlargement due to overinflation or failure of septation, they would not eliminate airspace enlargement due to reorganization of the airspaces, such as is found in honeycomb lung. This may be part of the confusion when combined emphysema and fibrosis is considered (see below).

CLASSIFICATION OF EMPHYSEMA

Not only is emphysema defined in terms of lung structure, it is also classified in similar terms; therefore, several anatomic definitions are important. The part of the lung involved in emphysema is the acinus, which is defined as the unit of lung structure distal to the terminal bronchiole (final generation membranous bronchiole) and that consists of three orders of respiratory bronchioles: a single order of alveolar ducts, followed by the alveolar sacs, and finally the alveoli. Alveolar ducts are entirely alveolated and characteristically contain smooth muscle around the mouths of their alveoli. While the walls of alveolar sacs are also formed entirely by alveoli, muscle is absent. Alveolar pores of Kohn (also known as vents, stomata, or fenestrae) are normal components of adult alveoli, responsible for collateral ventilation. However, they may also be an initial site of destruction in the development of emphysema, particularly centriacinar emphysema.

The acinus is a three-dimensional anatomic structure, but it cannot be easily identified by gross examination. What can be seen instead on the surface of lung slices is the secondary lobule of Miller, defined as the tissue bounded on four sides by interlobular septa or pleura (Fig. 37-1). Lobules vary tremendously in size but are generally 2 to 4 cm on a side and contain between three to five acini. The terminal bronchiole and subtending respiratory bronchioles tend to be situated in the center of the lobule. For this reason, "centrilobular" emphysema (CLE) and "panlobular" emphysema (PLE) are reasonable and widely used approximations for the more accurate "centriacinar" and "panacinar" emphysema (see below).

The ways in which the acini are involved determine the classification of emphysema. There are four recognized patterns (Fig. 37-2). The acinus (and lobule) may be more or less uniformly involved; this is panacinar (panlobular) emphysema. The proximal portion of the acinus (center of the lobule) may be dominantly involved; the best term for this lesion is proximal acinar emphysema, although the usual term is centrilobular or centriacinar emphysema. Alternately, the proximal portion of the acinus may be normal, and the distal part (alveolar sacs and ducts) may be dominantly involved. This is distal acinar emphysema, more commonly referred to as paraseptal emphysema since the lesion is accentuated along lobular septa where the peripheral parts of the acini lie. Finally, the acinus may be irregularly involved, producing irregular emphysema or paracicatricial emphysema, so called because it is usually associated with obvious adjacent scarring.

MORPHOLOGY OF EMPHYSEMA

The morphologies of the principal types of emphysema are discussed below.

■ Centrilobular Emphysema

This destructive lesion of the respiratory bronchioles has a number of characteristic features on gross examination of the lung. In the *classic* lesion, the enlarged, destroyed respiratory bronchioles coalesce in series and in parallel to produce sharply demarcated emphysematous spaces, separated from the acinar periphery (the lobular septa) by intact alveolar ducts and sacs of normal size. The walls of the emphysematous spaces and adjacent tissue characteristically contain variable amounts of black pigment.

The lesions vary qualitatively as well as quantitatively even within the same lung. There is striking irregularity of involvement of lobules, and even within the same lobule.[17,18] The lesions are usually more common and become more severe in the upper than in the lower zones of the lung (Figs. 37-3A and 37-4A, B).[19–24] Most affected are the upper lobe, particularly the posterior and apical segments, and the superior segment of the lower lobe. In cases of severe CLE, the destruction proceeds toward the periphery of the lobule, and the distinction between CLE and PLE becomes blurred.

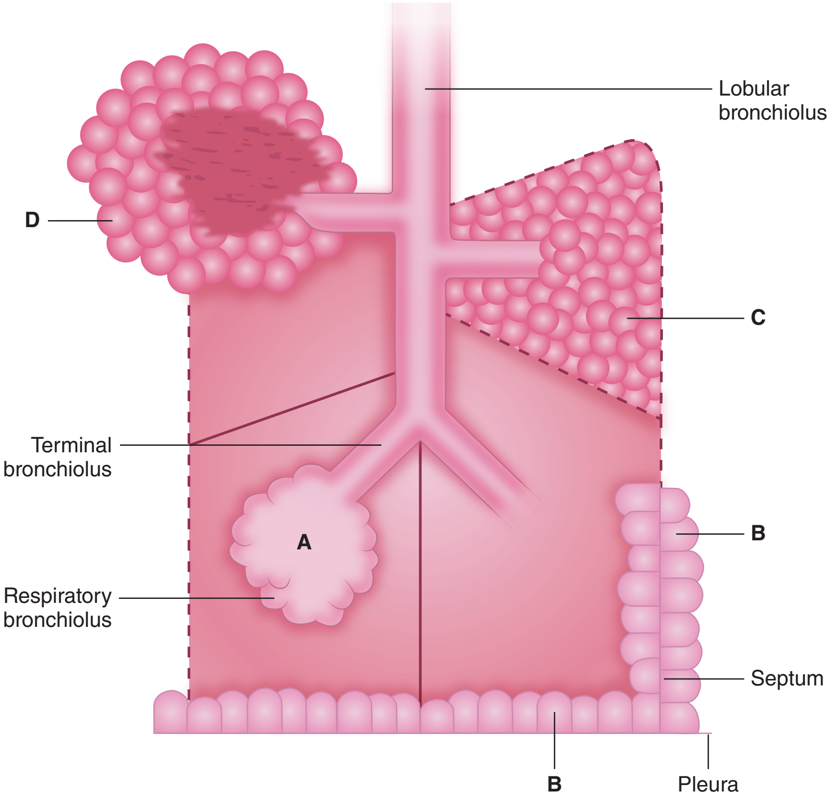

Figure 37-2 Anatomic varieties of emphysema. **A.** Centriacinar (centrilobular). **B.** Paraseptal (distal acinar). **C.** Panacinar (panlobular). **D.** Irregular (scar). The *dashed lines* mark the edge of the acinus. Only centriacinar and panacinar emphysema are commonly observed in COPD, although paraseptal emphysema often can be found in focal areas in lungs with centriacinar emphysema.

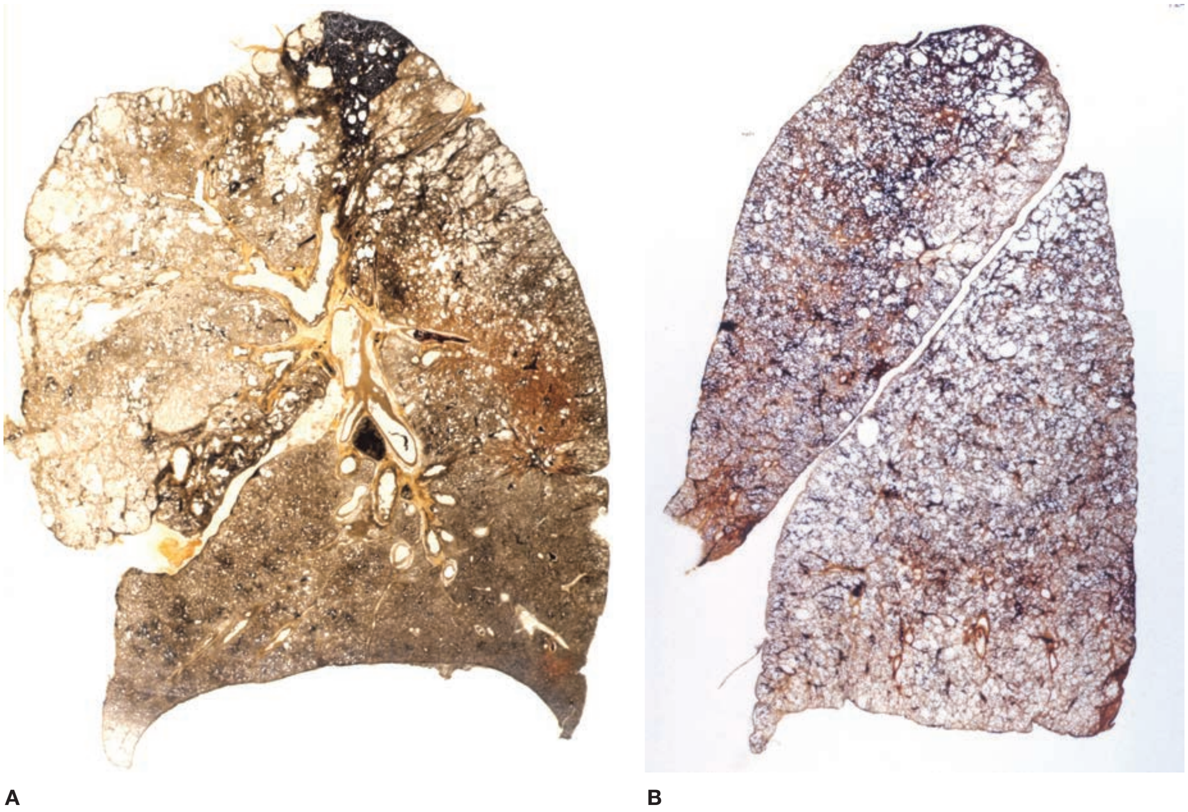

Figure 37-3 Pathologic subtypes of emphysema. **A.** Predominantly centriacinar emphysema. Emphysema is more severe in upper lobes. **B.** Predominant panacinar emphysema. Emphysema is more severe in the lower lobes.

In CLE, alveolar pores are abnormal in size and shape, and occasionally contain epithelial debris and macrophages. Although there are numerous pores of variable size in the emphysematous areas,[25] there are also increased numbers of pores in the grossly normal areas, and accentuation of these changes in the center of the lobule.[26] Thus, it appears that in CLE the pores of Kohn are possibly the initial site of destruction.

There is increased cellularity in the alveolar walls of cigarette smokers,[27] and when this has been quantified, the parenchyma in severe emphysema has increased numbers of neutrophils, macrophages, eosinophils, and both CD4 and CD8 T lymphocytes.[28] There is also a significant inflammatory cell infiltrate in the airspaces in severe emphysema, with the same cell types increased.[28] Although not readily apparent grossly or on standard histologic stains, use of histochemical stains or biochemical analysis demonstrates that collagen is increased in both centrilobular and panlobular emphysema.[29–31]

■ Panlobular Emphysema

The gross recognition of mild panlobular emphysema can be very difficult. The normal lung has a very characteristic appearance when seen through a dissecting microscope: The multifaceted alveoli form a contrast to the larger, cylindrical conducting structures that are alveolar ducts and respiratory bronchioles. In panlobular emphysema, the distinction between alveolar ducts and alveoli becomes lost as alveoli lose their sharp angles, enlarge, and then lose their contrast in size and shape with the ducts, resulting in simplification of the lung architecture, with formation of small box-like structures. As the process worsens, the architectural derangement becomes more obvious, with progressive effacement and loss of the orderly arrangement of the lung until little remains other than the supporting framework of vessels, septa, and bronchi. The best way to see panlobular emphysema grossly is to examine lung slices immersed in a water or fixative bath and then immediately after removal from the bath. The immersed specimen shows enlarged airspaces and, when the slices are lifted from the bath, panlobular emphysema can be suspected because the lung parenchyma "falls away" from the supporting structures which then protrude slightly above the parenchyma. In contrast to centrilobular emphysema, panlobular emphysema is usually worse in the lower lobes (Fig. 37-3B).

Histologic examination is a sensitive method of recognizing panlobular emphysema. The pattern is again one of simplification with diminishing contrast between alveoli and alveolar ducts (Fig. 37-4C, D). Despite the greater extent of tissue destruction, in panlobular emphysema the pores of Kohn are more uniform and inconspicuous than those found in centrilobular emphysema.[32]

Panlobular emphysema is the characteristic lung lesion seen in α1-antitrypsin deficiency,[33] but may also occur as a consequence of permanent obliteration of airways (obliterative bronchiolitis, constrictive bronchiolitis). Most often, obliteration of airways results in collapse of the distal lung parenchyma and dilatation of the bronchi proximal to the obliterated airways. This is the sequence of events in postinfective bronchiectasis. In some instances, however, the lung parenchyma does not collapse, but remains fully expanded or becomes emphysematous. The parenchymal sequel to bronchial and bronchiolar obliteration depends on the extent of the obliteration and the amount of collateral ventilation between adjacent airspaces distal to unobstructed airways. If collateral ventilation is present, then the units distal to the obliterated airways will remain expanded by virtue of the air reaching them by collateral ventilation, producing overexpansion and destruction of lung parenchyma beyond the obliterated airways. The terms *Swyer–James* or *MacLeod syndrome* are applied when this process affects most of one lung, or lobe of lung, but spares the remainder.

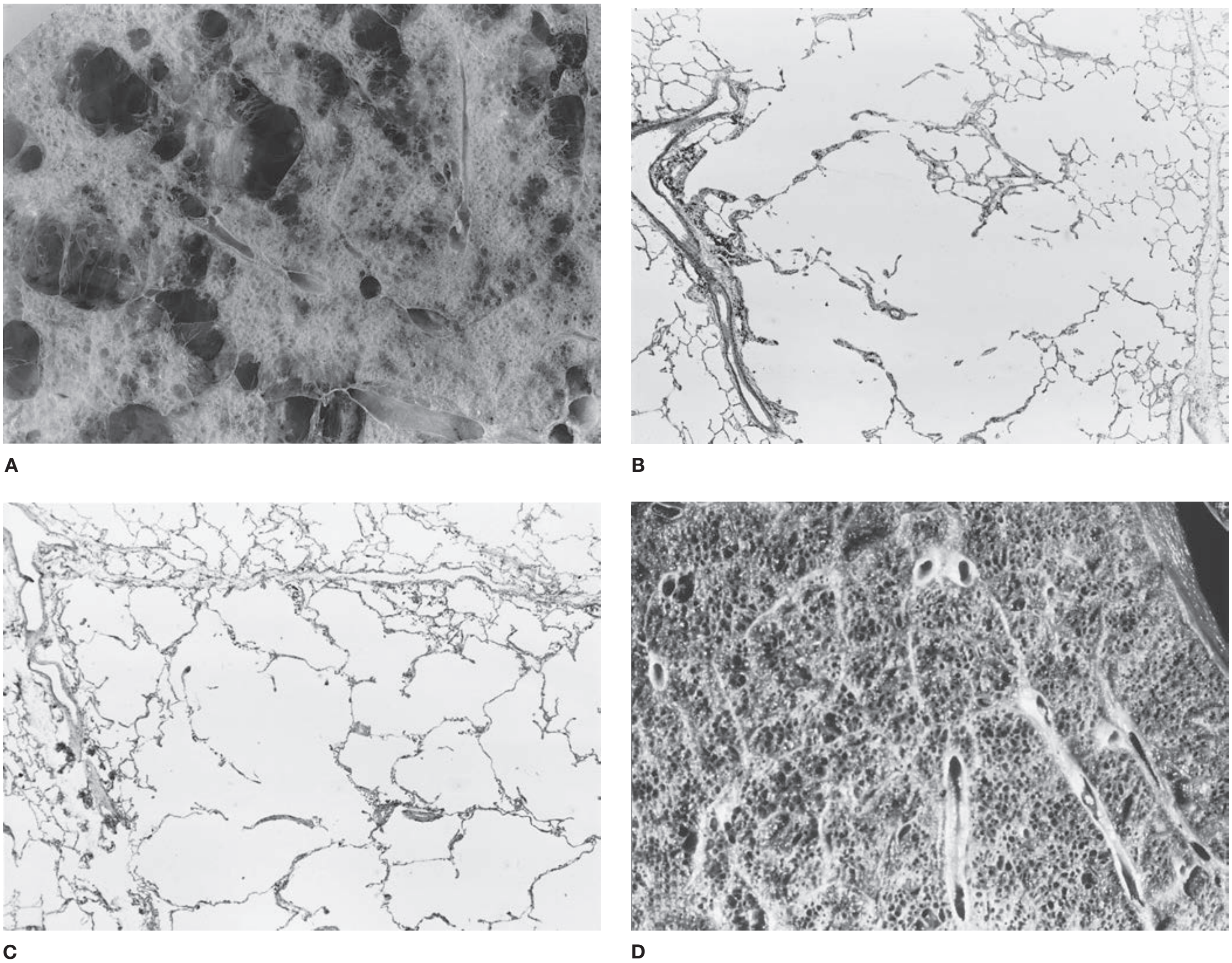

Figure 37-4 **A, B.** Gross and histologic sections illustrating centriacinar; and (**C, D**) panacinar emphysema. **A.** Cut surface from a lung with centriacinar emphysema showing holes in the center of lobules surrounded by relatively normal parenchyma. The severity varies among lobules. **B.** Microscopic section showing that the airspace enlargement in centriacinar emphysema is most marked adjacent to the abnormal respiratory bronchiole, corresponding to the center of the lobule. Also, some of the alveolar walls of the abnormal airspaces are thickened and fibrotic (H&E, ×16). **C.** Cut surface of a lung slice showing how the entire lobule is uniformly affected in panacinar emphysema. **D.** Microscopic section demonstrating that in panacinar emphysema, the airspaces adjacent to the lobular septa are enlarged to the same degree as those in the center of the lobule (H&E, ×16).

■ Distal Acinar Emphysema: Paraseptal Emphysema

The original description of distal acinar emphysema is generally credited to Loeschcke,[34] who described collections of subpleural bullae. It was Heard,[24,35] however, who first noted that the lesions could extend into the substance of the lung, where they lay along the septa, and coined the term "paraseptal" emphysema. Since the distal part of the acinus (alveolar sacs and ducts) is dominantly involved, emphysema is most striking adjacent to the pleura (superficial emphysema or mantel emphysema), along lobular septa (paraseptal emphysema), at the margins of lobules and acini (periacinar emphysema), and along vessels and airways, which, when cut longitudinally, display a linear pattern. The characteristic morphology is that of multiple contiguous, enlarged airspaces, varying from <0.5 mm to >2 cm in diameter.

Paraseptal emphysema is usually limited in extent and is found most commonly along the anterior and posterior parts of the upper lobe and along the posterior surface of the lower lobe. When extensive, it is usually more severe in the upper half of the lung. Gough has stressed that it is associated with fibrosis of the tissue between the enlarged airspaces, and this is certainly a common finding.[36] Paraseptal emphysema is frequently found in association with centriacinar emphysema,[20] but it is most known for its association with spontaneous pneumothoraces in young thin adults.[37]

■ Irregular Emphysema

Irregular emphysema is logically named, because the acinus is indeed irregularly involved in it. Irregular emphysema is almost invariably adjacent to a scar, giving name to the synonyms *scar* or *paracicatricial emphysema*. Most scars within the lung are usually small and the emphysema is limited in extent. The severity of irregular emphysema depends on the extent of damage to lung tissue, and multiple scars through the lung may lead to multiple foci of irregular emphysema.

DIFFERENTIAL DIAGNOSIS OF EMPHYSEMA

Distinctions among conditions characterized by gas trapping, nonemphysematous airspace enlargement, honeycomb lung, and combined emphysema and fibrosis are considered below.

TABLE 37-1 Differential Diagnosis of Airspace Enlargement

	Distribution	Enlarged Structure
Centrilobular emphysema	Upper lobes, center of lobule	Alveolar ducts, alveoli
Panlobular emphysema	Lower lobe, uniform in lobule	Alveoli
Paraseptal emphysema	Apical, adjacent to septum	Alveoli
Irregular emphysema	No typical site, adjacent to scars	Alveoli
Aging	Uniform in lung	Alveolar ducts
Compensatory alterations	Uniform in lung	Alveoli
Obstructive alterations	Affected area	Alveoli
Genetic alterations	Uniform in lung	Lack of septation
Asthma	During acute attack	Alveoli
Honeycomb lung	Variable—often subpleural	Total remodeling

Gas Trapping

Gas trapping may be seen in a variety of other conditions, not all of which are usually thought of as COPD. The lungs of an asthmatic who has succumbed during an attack are usually characterized by gas trapping, and thus remain inflated, with focal areas of atelectasis (Table 37-1). In a patient with long-standing asthma who has died from other causes, or has had a lung resection, there may still be areas of atelectasis. Focal bronchiectasis can be found also, particularly in the anterior segment of the upper lobe. However, parenchymal destruction is not a feature of asthma, and thus gross, microscopic, and morphometric analyses will all be normal in the chronic asthmatic. Gas trapping is also a feature of hypersensitivity pneumonitis and is a feature of connective tissue disease when it involves the small airways.

Nonemphysematous Airspace Enlargement

Although not part of the differential diagnosis of COPD, nonemphysematous airspace enlargement also occurs in infancy. In congenital lobar hyperinflation (emphysema), the lobes are overinflated rather than emphysematous, but in some instances, they may be polyalveolar.[38,39] Some other genetic abnormalities will also give enlarged airspaces, but this is due to failure of septation with a simplified rather than a destroyed alveolar framework.

At the other side of the age spectrum, the term senile emphysema was once used to describe the enlarged airspaces found in the aged. On gross examination, lungs round out with increasing age. An analysis of Gough sections showed increases in anteroposterior distance, height, perimeter, and area of the lung up to the age of 59 years. After this age, only the anteroposterior diameter continued to increase significantly, thus "rounding" the lung dimensions.[40] This change is due to an increase in the volume proportion of alveolar duct air,[41] with shallower and flatter alveoli,[42] a process termed *ductectasia*. There is no evidence of lung destruction; thus, the condition does not fulfill the criteria for emphysema.

If a part of the lung collapses or is removed, the remaining lung can expand to fill the increased amount of space available, a process known as *compensatory overinflation*. The exact way that this happens and the limits of the process are unknown. However, no tissue destruction has occurred, and, by definition, this is not emphysema. It is not clear how much larger the overinflated lung can become, or how it expands to reach the new and larger volume. It is generally thought that the possible extent of overinflation is modest and that all the parts of the acinus are equally expanded.

Obstructive overinflation can occur in adults, and two mechanisms may be involved. In one, the obstruction in the bronchus may act as a ball valve, so that air enters on inspiration but does not leave on expiration. Alternatively, the bronchus may be completely obstructed, and air may be trapped behind channels of collateral ventilation. Whatever the mechanism, the affected part of the lung can expand considerably. Obstructive overinflation differs in a number of ways from compensatory overinflation, although, in both, the lung contains too much air per unit of lung and lung tissue.

Honeycomb Lung

The airspace enlargement that occurs in cryptogenic fibrosing alveolitis (usual interstitial pneumonia [UIP]) and other fibrotic lung diseases could possibly be confused with emphysema. While honeycomb spaces are enlarged airspaces, they are the result of parenchymal remodeling with formation of new airspaces, rather than destruction of normal airspaces, and thus have thickened and irregular walls with none of the structure of an acinus. They are lined by bronchiolar epithelium, and often contain mucus; the walls have abundant and well-collagenized connective tissue, which may also contain impressive amounts of muscle and sometimes fat or even bone. There is usually interstitial inflammation in the form of varying degrees of lymphocytic and plasma cell infiltration.

Combined Emphysema and Fibrosis

Despite the definition of emphysema, which limits fibrosis, the significance of a mixture of fibrosis and emphysema has been reevaluated in relationship to its clinical, radiologic, and pathologic components.[43] The problem is that people who smoke cigarettes not only can develop respiratory bronchiolitis-interstitial lung disease (RB-ILD), but also have a higher incidence of developing UIP (idiopathic interstitial fibrosis), and mixtures of these with emphysema are not uncommon. When the combination of emphysema and UIP occurs, lung volumes can be preserved, but the diffusing capacity becomes markedly decreased, and pulmonary hypertension develops, with its associated significant negative prognosis. CT scans generally show centrilobular or mixed centrilobular and paraseptal emphysema in the upper lobes, with increased reticular markings and honeycomb remodeling in the lower lobes. Pathologically, there is both gross and microscopic emphysema and interstitial fibrosis with fibroblast foci in the areas of active fibrosis.[44] We have previously reviewed this topic with a focus on the pathologic differential diagnosis (Fig. 37-5A–D).[45] However, whether combined pulmonary fibrosis and emphysema represents a distinct entity or simply represents clustering of the two smoking conditions of emphysema and interstitial fibrosis has not yet been decided.

LESIONS OF THE LARGE AIRWAYS IN COPD

The majority of studies in this area have focused upon the lesions present when the clinical signs and symptoms of chronic bronchitis are also present.

Gross Findings

Gross lesions in the large airways are few and subtle. Bronchial pits are the dilated openings of one or more mucus glands into the epithelium. They are most often found along the margins of the cartilaginous rings and at the bifurcations of the airways. In nonbronchitis, the pits can be seen using a hand lens or a dissecting

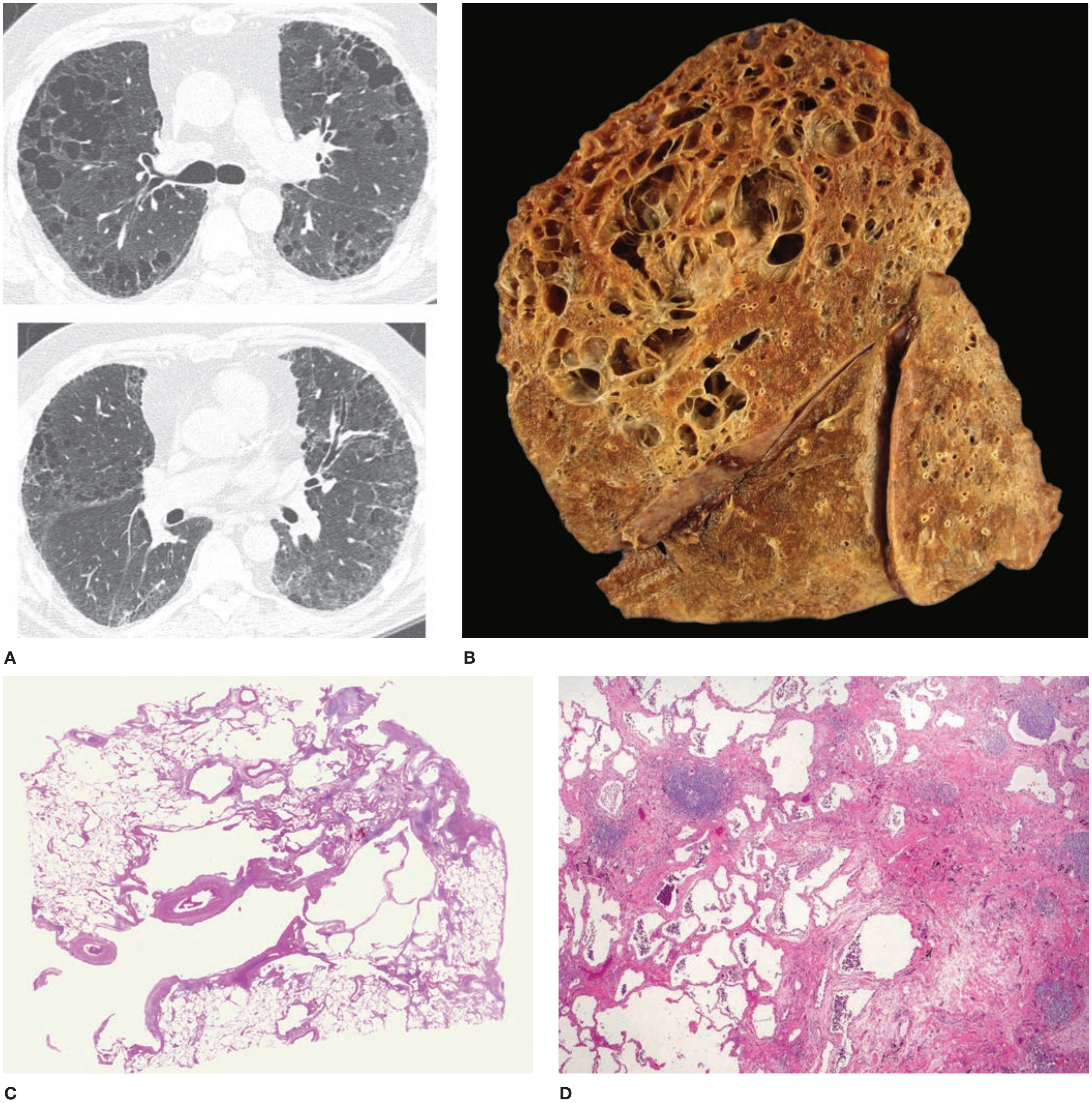

Figure 37-5 Combined fibrosis and emphysema in a case of chronic (fibrotic) hypersensitivity pneumonitis. **A.** Computed tomography scan from upper zone *(top)* shows emphysema and a suggestive of reticulation; lower image from midlung zone shows extensive reticulation indicating the presence of underlying fibrosis. **B.** Gross photo (sagittal slice) from this case showing marked upper zone emphysema, with fibrosis evident in the most posterior portion of the upper lobe, and the posterior portions of the lower lobe. **C.** Whole mount from the upper lobe. There are large emphysematous spaces, several with extensive surrounding fibrosis; at higher magnification, many of these fibrotic rims had fibroblast foci (not shown), indicating that this process is really interstitial fibrosis stretched around pre-existing emphysema. **D.** Image from lower lobe showing a UIP-like area, a common finding in chronic hypersensitivity pneumonitis. Elsewhere there were noncaseating granulomas (not shown). *(Reproduced with permission from Wright JL, Tazelaar HD, Churg A. Fibrosis with emphysema. Histopathology. 2011;58(4):517–524.)*

microscope, but in chronic bronchitis, the ducts may be distended with mucus and the mucus may protrude into the lumen of the bronchus and be visible grossly. It is not correct to refer to these as diverticula. First, these are protrusions of normal ducts; and second, they do not extend through all of the muscle coats of the bronchial wall.

While enlarged bronchial pits are the most obvious gross lesions in COPD, careful examination of lung specimens will show that the bronchi do not taper progressively as they approach the pleura,[46] and they also display prominent circular ridges, probably due to bands of hypertrophic smooth muscle.[47,48] Gross mucus may be present in the airway lumen, particularly in subjects with chronic bronchitis.[49]

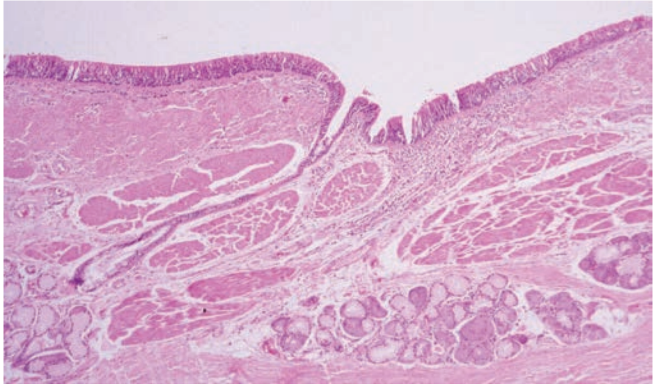

Figure 37-6 Large airway from a subject with chronic bronchitis. The overall wall is thickened with inflammation and fibrosis, and there is prominence of the smooth muscle in addition to the bronchial mucus glands.

■ Microscopic Findings

The intraluminal mucus found in the airways of subjects with COPD contains a mixed population of epithelial cells and acute and chronic inflammatory cells; large numbers of neutrophils can be found during an exacerbation.

Detailed microscopic analysis of the large airways in COPD reveals alterations in the entire airway wall (Fig. 37-6). Epithelial changes are mild in degree and are not necessarily consistent from patient to patient. Epithelial sloughing can occur, but in most instances the epithelium is generally intact and shows only mild goblet cell or squamous cell metaplasia, both of which appear to be more marked if the subject has symptoms of chronic bronchitis.[50,51] The reticular basement membrane thickness is within the normal range.

The thickness or area of mucus glands in subjects with COPD in general, or chronic bronchitis in particular, is increased over a population mean, but has a distribution that extensively overlaps that of normals and asthmatics.[52–55] Interestingly, there appears to be a decreased percentage of serous acini in these glands, a feature that apparently does not occur in asthma (discussed below).[56]

Thickening of the inner wall (area internal to the muscular layer) appears to be the most consistent component of airway wall thickening in the large airways of subjects with COPD, and appears to be generalized.[57,58] This increase in thickness can be partially attributed to edema and hyperemia of the bronchi,[59] but is also due to an increase in fibrous tissue or other matrix proteins.

In the large airways of subjects with COPD, increases in the thickness of the muscular layer have not been consistently identified. Although some studies[60] have found that the average proportion of muscle in main, lobar, and segmental bronchi was approximately doubled in patients with chronic bronchitis and airflow obstruction, others have found that a substantial number of patients fell within the normal range.[54,55,61]

Alteration in the amount of cartilage in COPD does not appear to be a consistent finding. While some studies[59,62,63] described cartilage atrophy in chronic bronchitis and/or emphysema, or circumferentially arranged cartilage that extended farther distally in nonbronchitis than bronchitis,[64] this was not supported by other reports.[54,65] However, histologic signs of cartilage damage, as judged by loss of cellular or pericellular metachromasia and vacuolated or empty lacunae, can be consistently identified.[66]

The large airways in COPD show a mild, usually mixed, inflammatory infiltrate. Bronchus-associated lymphoid tissue (BALT) is not consistently found, but its frequency appears to be considerably higher (82%) in smokers than nonsmokers (14%).[67] Bronchial biopsy analysis consistently shows an increase in CD8 T cells, with eosinophils and neutrophils found during exacerbations.[50,68] Chronic inflammation can also be found around the bronchial glands, particularly in subjects with chronic bronchitis.[69]

■ Differential Diagnosis

A number of common and uncommon disorders constitute the differential diagnosis for airways disease seen in COPD.

Asthma

In asthma the large airways are not dilated, but mucus plugs are classically identified in the large airways of subjects with fatal or near-fatal asthma,[70] and the mucus may be continuous with that present in the ducts of the mucus glands (Table 37-2). Visible bronchial pits are not a standard feature of asthma, and although the airway wall may be thickened, this is usually not apparent grossly.

In the large airways of subjects with asthma, desquamation of the epithelium is a common feature,[71,72] and this may be worse in people who have persistent rather than intermittent activity. Sloughing of cohesive epithelial clusters produces the creola bodies found in cytology specimens. Goblet cell metaplasia can be marked in both

TABLE 37-2 Pathologic Differential Diagnosis of Large Airway Lesions in COPD

	Dilatation	Structural Distortion	Pits	Glands	Submucosal Fibrosis	Basement Membrane	Epithelium	Luminal Mucus	Cartilage	Muscles
Chronic bronchitis	✓	Fibrosis and inflammation	✓	✓	✓	X	Goblet cell metaplasia	✓	✓	✓/X
Asthma	Focal	Focal	X	✓	✓	✓	Goblet cell metaplasia	✓	X	✓
Bronchiectasis	✓	Fibrosis and inflammation	✓	✓/X	✓	X	Focal goblet cell metaplasia	✓	✓	X
Tracheobronchopathia osteoplastica	✓	Bony nodules	X	X	X	X	X	X	✓	X
Tracheomegaly	✓	X	Diverticula	X	X	X	X	X	X	X
Relapsing polychondritis	✓	✓	X	X	X	X	X	X	✓	X

Check mark indicates that the feature is present; X indicates that the feature is absent.

asthma and bronchiectasis,[73] but there is a considerable degree of variability, so that this feature cannot be used in isolation to distinguish among the airways of subjects with COPD, asthma, and bronchiectasis. These epithelial cell changes result in an overall thickening of the epithelium in asthma, but not in COPD.[58] In asthma, the reticular basement membrane (lamina reticularis) is characteristically thickened. This alteration occurs early in the course of disease and remains even when the asthma is mild or well controlled.[56]

The airways of asthmatics demonstrate a greater severity of inner wall thickening, with values double those found in patients with COPD.[58] The increase in thickness is due to variable increases in fibrous tissue, inflammatory cells, edema fluid, and vascular prominence.[50,56] Analysis of the muscular wall in subjects with severe or fatal asthma compared with normal subjects or those with COPD shows a marked increase in amount of muscle, with a lesser increase in asthmatics who died with rather than from their asthma.[74] There has also been a suggestion that the increase in muscle mass may occur relatively early during childhood.[56]

Neutrophils are the predominant cells present in the mucus of patients with bronchiectasis, while eosinophils and accompanying Charcot Leyden crystals are the hallmark of asthmatic mucus. As noted, the cartilaginous destruction present in polychondritis is severe and associated with chronic inflammation, thus easily distinguishing the two processes. Depending upon the severity of the inflammation in bronchiectasis, there may be significant cartilaginous destruction.

Airways from fatal and near-fatal asthma also contain isolated aggregates of lymphoid cells, roughly in the same proportion as that present in COPD.[75] However, in asthma, by contrast to COPD, there is an inflammatory infiltrate consisting of activated eosinophils, and activated CD4 T cells in the submucosa,[76] and both mast cells and neutrophils within the glands.[70] There is little in the literature regarding the inflammatory cell infiltrates present in the airway walls in bronchiectasis. Compared with asthma, there appear to be fewer eosinophils, but a similar population of CD45 (as opposed to any specific subtype) lymphocytes, with both cell types having a greater density in the inner, as opposed to the outer aspect of the airway.[77]

Bronchiectasis

In bronchiectasis, there is, by definition, an abnormal and permanent dilatation of the bronchi; this is usually present to a much greater degree than is found in COPD and is often accompanied by airway distortion. There is exaggeration of the muscular ridges and the presence of multiple bronchial gland–based pits. The large airway walls can be thickened and/or irregularly thinned as a result of inflammation and fibrosis, and there is often inspissated mucus or actual purulent material.

Miscellaneous Conditions

Tracheobronchomegaly (Mounier-Kuhn syndrome) is characterized by a marked dilatation of the trachea and major bronchi, with diameters 5 to 10 cm above normal values.[78] In this condition there are multiple true diverticula, with outpouchings formed of membranous tracheal tissue between the cartilaginous rings,[79] with atrophy or absence of elastic fibers.[80]

Patients with tracheobronchopathia osteoplastica have an obstructive pulmonary function pattern;[81] however, unlike the trachea and large airways in COPD, cartilaginous and bony nodules are present in the subepithelial space (submucosa). Relapsing polychondritis[82,83] shows variable dynamic expiratory and/or inspiratory obstruction depending on the size and location of the airways involved. In this disease, however, the obstruction is due to impaired airway clearance of inflammatory debris, and an ineffective cough because of dynamic upper airway collapse. The airways are dilated and the walls are thickened because of the extensive fibrosis and chronic inflammation due to the immunologic nature of this condition. In particular, the cartilaginous plates show extensive destruction.

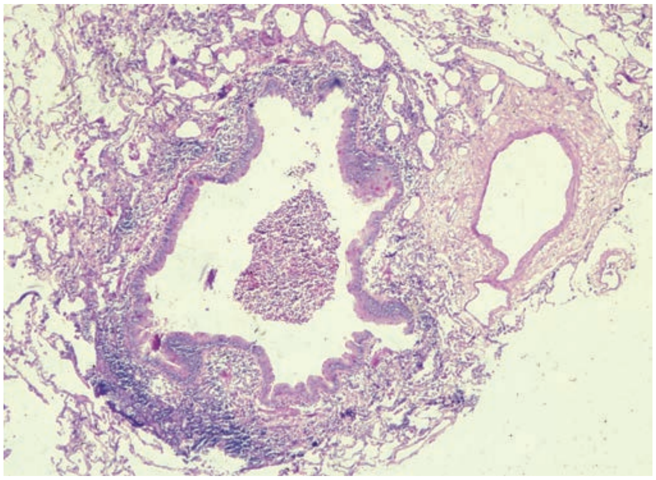

Figure 37-7 A small airway from a subject with COPD. The lumen contains mucus and inflammatory debris. There is goblet cell metaplasia of the epithelium. The subepithelial (submucosal) layer is increased in thickness due to an increase in fibrous tissue and inflammatory cells.

LESIONS OF THE SMALL AIRWAYS IN COPD

In the context of COPD, small airways refer to airways with an internal diameter of 2 mm or less. In COPD, intraluminal mucus can be found in the small airways, and there appears to be an overall relationship between the degree to which the airways are occluded by mucus and the FEV_1.[84] Goblet cells are rare in normal small airways, but goblet cell metaplasia is a frequent finding in the airways of patients with COPD.[85–87]

Similar to the large airways, there is alteration of all of the small airway wall compartments in patients with COPD (Fig. 37-7). These changes result in an overall decrease in the internal bronchiolar diameter and, as assessed by a conformity index, produce significant deformity. Similar results are obtained from three-dimensional reconstructions.[74] Detailed measurements of the airway walls show that the increased wall thickness is due to increases in the epithelium, subepithelial fibrous tissue compartment (submucosa, lamina propria), smooth muscle, and adventitia.[58,84] While there is no direct evidence, it seems appropriate that these changes would result in airway obliteration, a process that appears to happen relatively early in airflow obstruction, with the number of airways in patients with severe airflow obstruction reduced to one-tenth of the numbers calculated in the normal lung (Fig. 37-8A, B).[88] Reduction in airways of 2 to 2.5 mm can be identified using multidetector-row computed tomography (CT), and decreased numbers of terminal bronchioles can be found using a micro-CT approach. Interestingly, this latter technique has also found a decreased luminal area in these airways, again suggesting an obliterative process has occurred.[89] Although the adventitia is thickened, there is a loss of alveolar attachments to the airway wall,[90,91] an important process because it allows early airway collapse on expiration.

One of the earliest histologic abnormalities that can be detected in cigarette smokers is the presence of macrophages in the lumen of the respiratory bronchioles.[92] However, an inflammatory infiltrate can also be identified within the walls of both membranous and respiratory bronchioles in subjects with COPD. When examined in conjunction with the GOLD (Global Strategy for the Diagnosis, Management, and Prevention of COPD) stage, the proportion of airways that had measurable neutrophils appears to be increased in GOLD stages 2 to 4, and airways with measurable macrophages

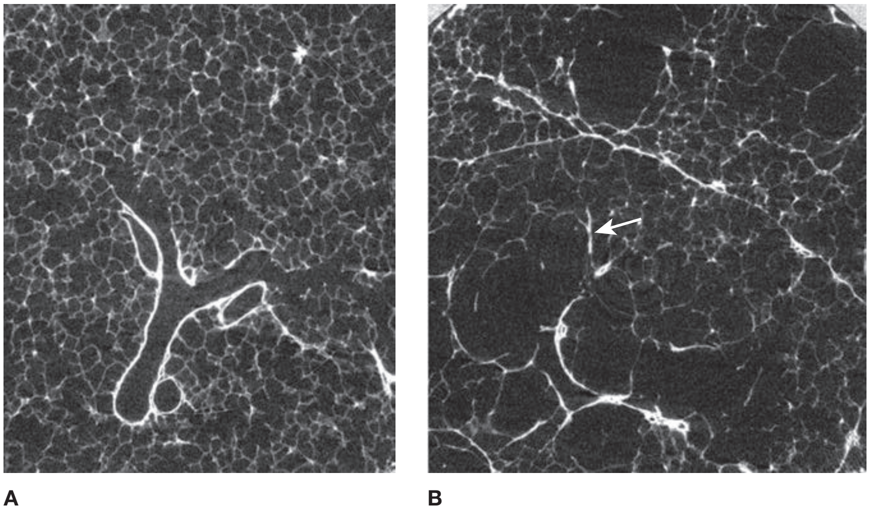

Figure 37-8 **A.** Micro-CT scan image of an airway from a normal lung. Note the regular progression from membranous bronchiole to respiratory bronchiole to alveolar duct. **B.** Micro-CT scan image of an airway from a lung with centrilobular emphysema. Note the irregular airway emptying into a centrilobular hole. Partially obliterated airway is seen at the *arrow*. *(Reproduced with permission from Dr. James C Hogg.)*

show a progressive increase from GOLD stage 0 to 4, while there does not seem to be any alteration in the percentage of airways that contain eosinophils among the GOLD stages.[93] The percentage of airways with CD4, CD8, and B cells also increase with GOLD stage, but when these data are expressed as total accumulated volume, only the B cells and CD8 cells show progressive increases. The presence of lymphoid follicles is markedly increased in GOLD stages 3 and 4. Interestingly, histone deacetylase 2 (HDAC2) appears to be downregulated in the small airways of smokers with COPD,[94] a finding that may be of considerable importance since downregulation of the HDAC system is associated with a proinflammatory cytokine profile.

■ Differential Diagnosis

A number of important clinical entities constitute the differential diagnosis of small airways disease in COPD.

Asthma

A comparison of the inflammatory and cellular mechanisms present in asthma and COPD has recently been reviewed.[95] Mucus plugs and goblet cell hyperplasia are markedly increased in the small airways of asthmatics,[73,96] and this increase is generally much greater than that seen in COPD. In addition, the basement membrane thickness is approximately 20% greater than that found in either normal subjects or patients with COPD.[73] The peripheral airways of asthmatics have an inflammatory infiltrate that features lymphocytes and eosinophils,[73,77,97] with many of the inflammatory cells in the adventitial, as opposed to the submucosal, compartment. The data regarding the vessels in the submucosa are controversial, with some studies suggesting that they are congested, but not increased in number, in asthmatics compared with COPD,[74] and others demonstrating an increased number of vessels, but a lesser total area in asthma compared with COPD.[98] Although smooth muscle is increased in asthmatics, the increase is not as great as that present in the large airways.[99] Moreover, the distribution of smooth muscle increase in the bronchial tree may be quite different, with some patients displaying a generalized increase, while in others the increase is restricted to the larger airways.[100] Overall, the small airways in asthmatic subjects who have died because of their disease have a greater area of subepithelial fibrous tissue, smooth muscle, and adventitial fibrous tissue than do subjects who died with their disease, which in turn have a greater area than do the airways of subjects with COPD.[101] Thus, although the same qualitative changes are present in both asthmatics and COPD, they are more severe in asthmatics and most severe in cases of fatal asthma. Interestingly, there appears to be a loss of alveolar attachments in cases of fatal asthma,[102] although this is less than that present in the airways of patients with COPD.

Follicular Bronchiolitis

Follicular bronchiolitis is characterized by narrowing of the bronchioles due to adventitial and subepithelial lymphoid follicles and accompanied by a lymphoplasmacytic inflammatory infiltrate.[103] The condition is classically found in patients with rheumatoid arthritis or those with IgA deficiency or common variable immune deficiency. This process can mimic severe COPD small airway disease, but the inflammatory infiltrate is generally magnified compared to COPD, while there is little goblet cell metaplasia in the airway epithelium.

Panbronchiolitis

The presence of foamy macrophages in the airway wall and lumen and extending down into the alveolar ducts and alveoli is a feature of the condition known as panbronchiolitis, originally described in Japan but now known to occur worldwide.[104,105] Follicular hyperplasia of the peribronchiolar lymphoid tissue is frequent, and bronchiolectasis is found in the more advanced lesions.

Constrictive Bronchiolitis

The term *constrictive bronchiolitis* appears to have been coined by Gosink et al.[106] In constrictive bronchiolitis, the airway lumen is occluded by a progressive thickening of the subepithelial (submucosal) space. Both the membranous and respiratory bronchioles are involved and show transmural inflammatory cell infiltrates, occasionally with epithelial necrosis. Mucus plugs also can be identified. As the process evolves, the inflammatory infiltrate wanes, and greater amounts of fibrous tissue can be demonstrated both in the peribronchial and subepithelial portions of the airway, acting to narrow or obliterate the airway lumen.[107] Lesions of constrictive bronchiolitis, particularly in the organized phase, may be difficult to demonstrate and may require elastic stains to outline the obliterated airway. Thus, the lesions in COPD differ from constrictive bronchiolitis only in degree.

Mineral dust–induced airway disease is a distinctive type of constrictive bronchiolitis, characterized by a stereotypic response of the small airways to high doses of particulate, regardless of the specific mineral dust involved. The lesions consist of fibrosis and thickening of the walls of both the membranous and respiratory bronchioles, sometimes extending down the alveolar ducts, the latter finding providing diagnostic discrimination from tobacco smoke–induced airway disease, which tends not to involve the alveolar ducts. Pigment deposition is highly variable and is not a diagnostic feature.[106] Other forms of constrictive bronchiolitis may be related to ingestion of toxic compounds such as *Sauropus androgynus* ingestion,[109–112] or related to diffuse neuroendocrine cell hyperplasia.[113–116]

Proliferative Bronchiolitis

The lesions of proliferative bronchiolitis have been elegantly described and illustrated.[115–117] Within the lumens of the membranous and respiratory bronchioles are plugs of organizing fibroblastic (granulation) tissue. Occasionally, ulceration of the epithelium can be seen, and early lesions may have fibrin. The granulation tissue is formed of a pale matrix with proliferating spindle cells, accompanied by chronic inflammatory cells. As the lesions age, the granulation tissue usually shrinks and contracts. However, in a certain proportion of cases, the bronchiolar cells proliferate over the granulation tissue and incorporate it into the subepithelial space, leaving an irregular airway lumen.

Although acute bronchiolitis, be it bacterial or viral in nature, is usually easily distinguished from the lesions of COPD by the presence of extensive epithelial damage, healed lesions may show nonspecific airway fibrosis and chronic inflammation, or the residua of proliferative bronchiolitis. Interestingly, latent adenoviral infection has been suggested as a contributor to airflow obstruction in adults by amplifying the inflammatory response in the bronchioles of cigarette smokers.[120] Airway disease complicating other diseases may also need to be distinguished from that of COPD. For example, posttransplant bronchiolitis[118,121] or airway disease in patients with inflammatory bowel disease (both Crohn disease and ulcerative colitis)[122] include both proliferative and constrictive bronchiolitis. Inflammatory bowel disease may also have large airway involvement.

LESIONS OF THE VESSELS IN COPD

There are no consistent alterations in the large elastic pulmonary arteries of subjects with COPD. Atheromata can be found,[123] but unless there is pulmonary hypertension, the incidence is probably not greater than that found in a carefully matched population.

Cigarette smokers, with or without pulmonary hypertension, have an increase in arterial muscle media thickness as well as intimal fibrosis in the muscular arteries, and progressive muscularization of the small arterioles.[122] Increases in intimal thickness with longitudinal muscle formation are a common feature in lungs of patients with COPD (Fig. 37-9).[11,125,126] There appears to be a progressive increase in the numbers of smaller muscularized arteries, percent medial thickness, and percent intimal thickness of muscularized arteries from nonsmokers, to smokers without obstruction, to smokers with airflow obstruction.[127]

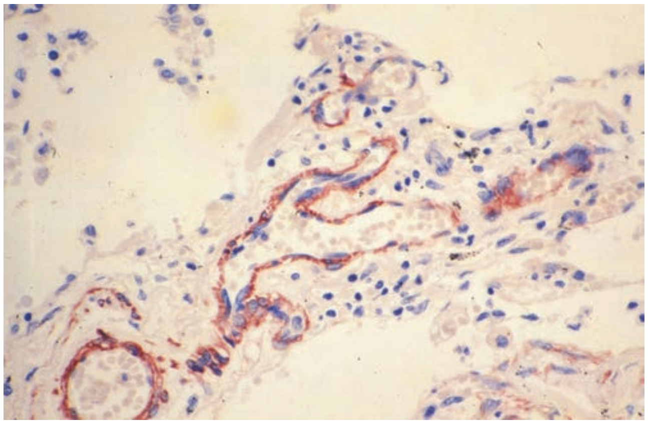

Figure 37-9 A small pulmonary artery from a subject with COPD. These vessels, situated adjacent to the alveolar ducts, are normally poorly muscularized, but in this case, the vessel has a distinct circumferential muscular layer.

The lesions of primary pulmonary hypertension and hypertension secondary to vascular shunting also include intimal fibrosis and increased muscular media thickness. Intimal fibrosis is often cellular in its early phases, but progresses to concentric laminar fibrosis, which can almost totally obliterate the vessel lumen. These changes are of much greater severity than those identified secondary to COPD. Vasculitis, fibrinoid necrosis, and plexiform lesions are never found in COPD. Lesions of chronic thromboembolic disease include eccentric intimal thickening and the occasional formation of webs due to recanalization of the thrombi.

NONPATHOLOGIC, CT SCAN–BASED, EVALUATION OF TISSUE COMPARTMENTS IN COPD

CT scanning has provided useful information on the lung parenchyma, airways, and pulmonary vasculature in patients with COPD.

■ Emphysema

The advent of high-resolution CT scanners has allowed identification of even mild emphysema and can distinguish between emphysema and senile lung airspace enlargement. When combined with general morphometric principles, emphysema can be quantified, and emphysema progression can be monitored.[128–131]

■ Airways

Evaluation of this compartment is in its developmental phase, with much of the work being performed on phantom airways or in large animals. In humans, thin-section CT scans are able to demonstrate evidence of airway wall remodeling in the more proximal airways (first- to sixth-generation airways) of subjects with COPD or asthma, and it has been suggested that changes in these airways can be extrapolated to the smaller airways.[132] Use of multidetector-row CT has extended these data.[89] Certainly, the data do suggest that these measurements correlate with lung physiology, independent from emphysema.[133]

■ Pulmonary Arteries

Measurements of the mainstem pulmonary artery are easily performed on CT scans using contrast, and these data have shown prognostic significance. Evaluation of the smaller vessels is much more difficult, but initial work has found that determination of the total cross-sectional area of the vessels that have an individual cross-sectional area of less than 5 mm^2 has a significant negative correlation with pulmonary arterial pressure, at least in patients with severe emphysema.[134,135]

SUMMARY

There are a number of pathologic alterations of the lung in COPD. These involve almost all of the lung compartments, including the parenchyma, vasculature, and large and small airways. These changes can overlap the pathologic findings present in other diseases associated with airflow obstruction, or other diseases that are manifested in the lung. It is important to be able to make the distinction among these diseases. Although the pathologic alterations roughly correlate to alterations in pulmonary function, it is important to remember that their individual contributions are not well worked out. Thus, it may be difficult on an individual patient basis to proceed from a clinical classification such as the GOLD classification to a mechanistic/pathologic explanation of the airflow obstruction. Advances in CT scanning technology have allowed evaluation and quantification of emphysema, and there is developing work suggesting that evaluation of the airways and pulmonary arterial system also may be possible.

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CHAPTER 38

Chronic Obstructive Pulmonary Disease: Epidemiology, Pathophysiology, Pathogenesis

Takudzwa Mkorombindo
Mark T. Dransfield

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a heterogeneous disease characterized by persistent respiratory symptoms and airflow limitation due to airway and alveolar abnormalities. The causative agent is usually significant exposure to noxious particles or gases and influenced by host factors, including abnormal lung development.[1] COPD includes a spectrum of pathology that involves damage to the lung parenchyma (emphysema) and abnormalities of the tracheobronchial tree (bronchitis). The manifestation of the disease varies greatly, and despite the knowledge acquired in the past 300 years, our understanding of factors that influence disease phenotypes remains incomplete. In the 16th and 17th centuries, we had the earliest descriptions of COPD, with the description of emphysematous lungs as "voluminous lungs."[2] Later, chronic bronchitis and other features were identified. While different clinical and biologic phenotypes exist, airflow obstruction characterized using spirometry is the hallmark.

Spirometry is essential in the diagnosis and is beneficial for prognostication and monitoring treatment outcomes. The most accepted criteria for airflow obstruction by spirometry is a reduction of the post-bronchodilator FEV_1/FVC ratio below 0.7. While the 0.7 cutoff value for the FEV_1/FVC ratio may underrecognize patients in the early stages and may overdiagnose disease in healthy middle-aged and older individuals, it has been the most accepted because it balances disease detection sensitivity and specificity.[3–6] Historically, further classification of severity was based strictly on airflow limitation. Over the past decade, guidelines have evolved to incorporate a multimodality assessment of symptom burden and exacerbation risk (Fig. 38-1). Additionally, there has been an interest in going beyond symptom burden (dyspnea and history of exacerbations) to incorporate the different chest imaging patterns.[7] Chapter 40 comments

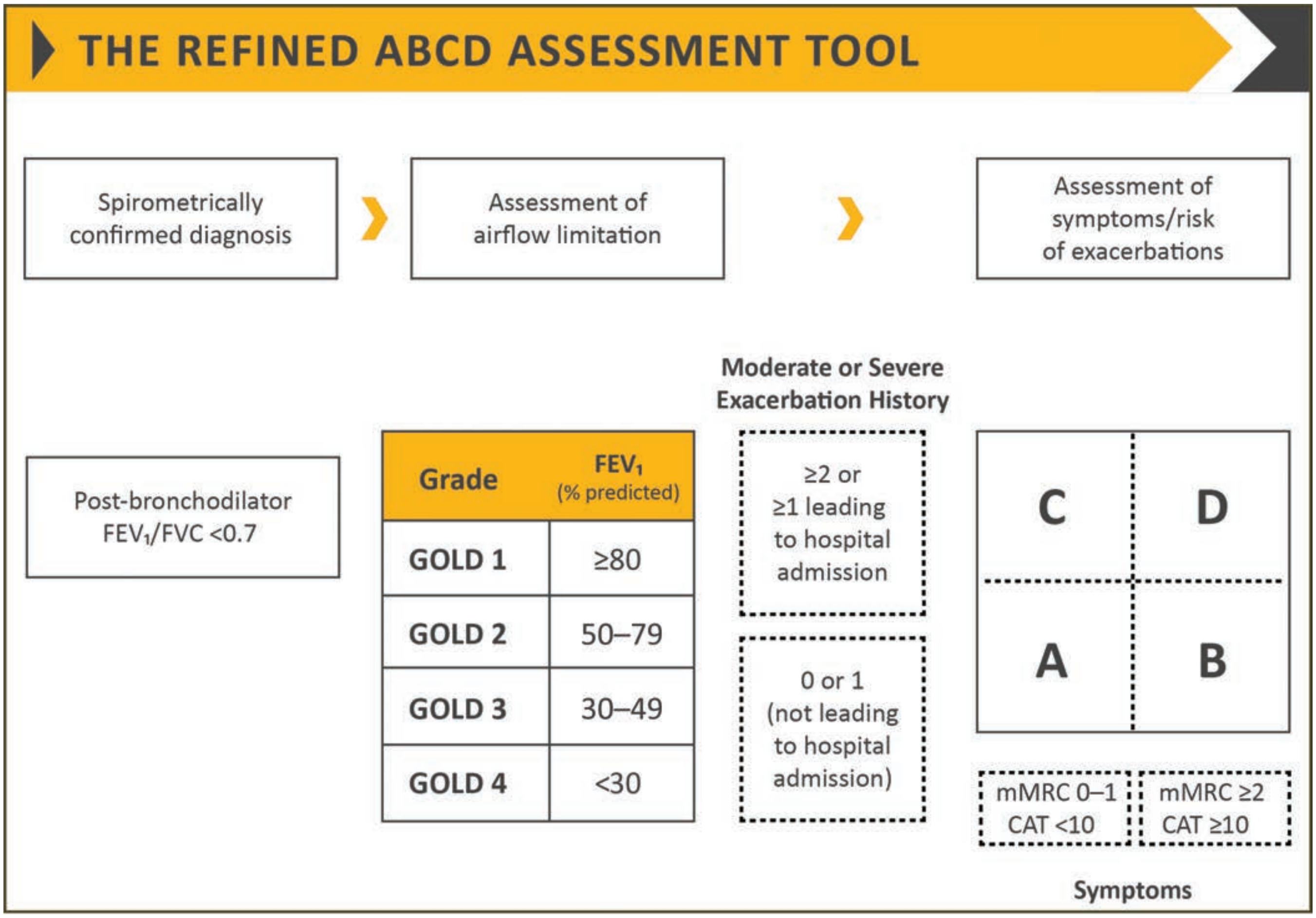
THE REFINED ABCD ASSESSMENT TOOL
Spirometrically confirmed diagnosis
Assessment of airflow limitation
Assessment of symptoms/risk of exacerbations
Post-bronchodilator FEV₁/FVC <0.7
Grade
FEV₁ (% predicted)
GOLD 1
≥80
GOLD 2
50–79
GOLD 3
30–49
GOLD 4
<30
Moderate or Severe Exacerbation History
≥2 or ≥1 leading to hospital admission
0 or 1 (not leading to hospital admission)
C
D
A
B
mMRC 0–1 CAT <10
mMRC ≥2 CAT ≥10
Symptoms

Figure 38-1 COPD Assessment tool from GOLD guidelines highlights the importance of consideration of symptoms and exacerbation frequency in assessing COPD severity. *(Reproduced with permission from Pocket Guide to COPD Diagnosis, Management, and Prevention. A Guide for Health Care Professionals. 2020 Global Initiative for Chronic Obstructive Lung Disease.)*

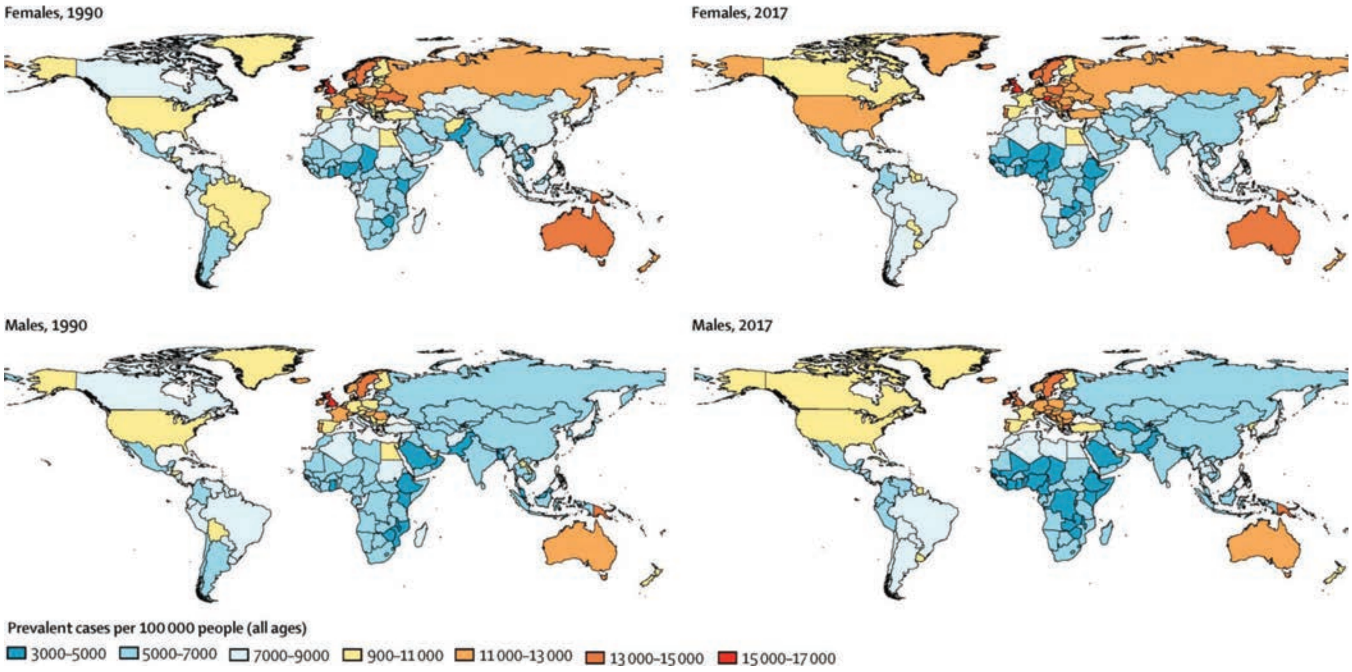

Figure 38-2 There has been a significant increase in the burden of chronic respiratory disease with 544.9 million people affected, a 39.8% increase in prevalence from 1990 to 2017. *(Reproduced with permission from Soriano JB, Kendrick PJ, Paulson KR, et al. Prevalence and attributable health burden of chronic respiratory diseases, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet Respiratory Medicine. 2020;8(6):585–596.)*

further about risk stratification. There is increasing evidence that current and former smokers can have parenchymal and airway abnormalities and can have respiratory symptoms and exacerbation-like events, even in the absence of airflow limitation. At present, these patients are not included in COPD management guidelines.[1,8,9]

EPIDEMIOLOGY

COPD is a significant health problem affecting more than 400 million people worldwide. In 1990, COPD was the sixth most common cause of disease worldwide but now ranks as the third leading cause of death, according to the Global Burden of Disease Study, after cardiovascular disease and stroke.[10] The impact of respiratory diseases, and specifically COPD, is wide-reaching as it affects countries at all levels of development (Fig. 38-2). The World Economic Forum estimates that the global costs of COPD will reach U.S. $50 trillion annually by 2030.[11]

Often viewed as a self-inflicted disease of tobacco smokers, the paradigm is shifting with an increased understanding of the disease. Fletcher and colleagues in the 1960s showed increased lung function decline in susceptible smokers and that smoking cessation would decelerate the decline of lung function.[12] Smoking remains prevalent worldwide, and while smoking is decreasing in developed nations, the global burden of disease continues to grow (Figs. 38-2 and 38-3).[13,14] Reasons for the increasing global burden of disease include an increasing burden of tobacco smoke exposure in low to middle-income countries, persistent problems with preterm birth, poor nutrition and childhood infections, toxic nontobacco exposures, and an expanding number of older adults.[15–18] Exposure to indoor and outdoor pollution from the combustion of clean fuels (gas stoves and burning petroleum) and unclean fuels (coal, charcoal, wood, or dung) plays a significant role in developing COPD in never smokers.[19–21] In areas where indoor air pollution is generated by burning biomass for heating and cooking, COPD disproportionately affects women and children.[22,23]

COPD has a high prevalence and poses a significant burden with astounding morbidity, mortality, and financial and social impact. Surveys, such as the 2017 Behavioral Risk Factor Surveillance System (BRFSS), suggest that an estimated 15 million people in the United States have COPD. The estimated worldwide prevalence ranges from 7% to 19%. Despite its wide-reaching effects, current data underestimate the burden of disease as it is underrecognized and underdiagnosed.[24–28] In the United States, the age-adjusted prevalence of COPD was 6.2%, with a higher prevalence among the less educated, lower socioeconomic status, rural communities, women, older adults, and American Indians/Alaska Natives.[26] Other statistics support these national surveys. In a study of 1575 cigarette smokers, aged 30 or older, with a 10 or more pack-year smoking history, approximately 20% met spirometric criteria for COPD.[29] The Third National Health and Nutrition Examination Survey (NHANES III) showed that life expectancy is shortened by 5.8 years for men aged 65 with GOLD stage 4 COPD, and an additional 3.5 years if smoking is continued.[30] With the growing impact of COPD, there is an urgent need for primary prevention efforts and improved recognition and management of this deadly disease.

ETIOLOGY

Risk factors for COPD development are environmental and host-based (Table 38-1, Fig. 38-4). Throughout the human lifespan, several host factors have unique and dynamic interactions with the environment that mediate one's likelihood of disease.[31] These host factors include the balance of mechanisms responsible for tissue maintenance, tissue repair, tissue regeneration, and the mechanisms associated with tissue damage and aging.[32] The interaction of host and environmental factors determines the likelihood of activating the cellular and biochemical mechanisms responsible for developing COPD. In developed countries, smoking tobacco is the predominant risk factor; however, never-smokers also develop COPD, and women predominate in this cohort.[16,33] In places where solid fuels are burned, indoor air pollution is a dominant risk factor. Other factors associated with COPD include second-hand tobacco exposure, a family history of COPD, age, socioeconomic status, education level, history of tuberculosis, prematurity, in utero

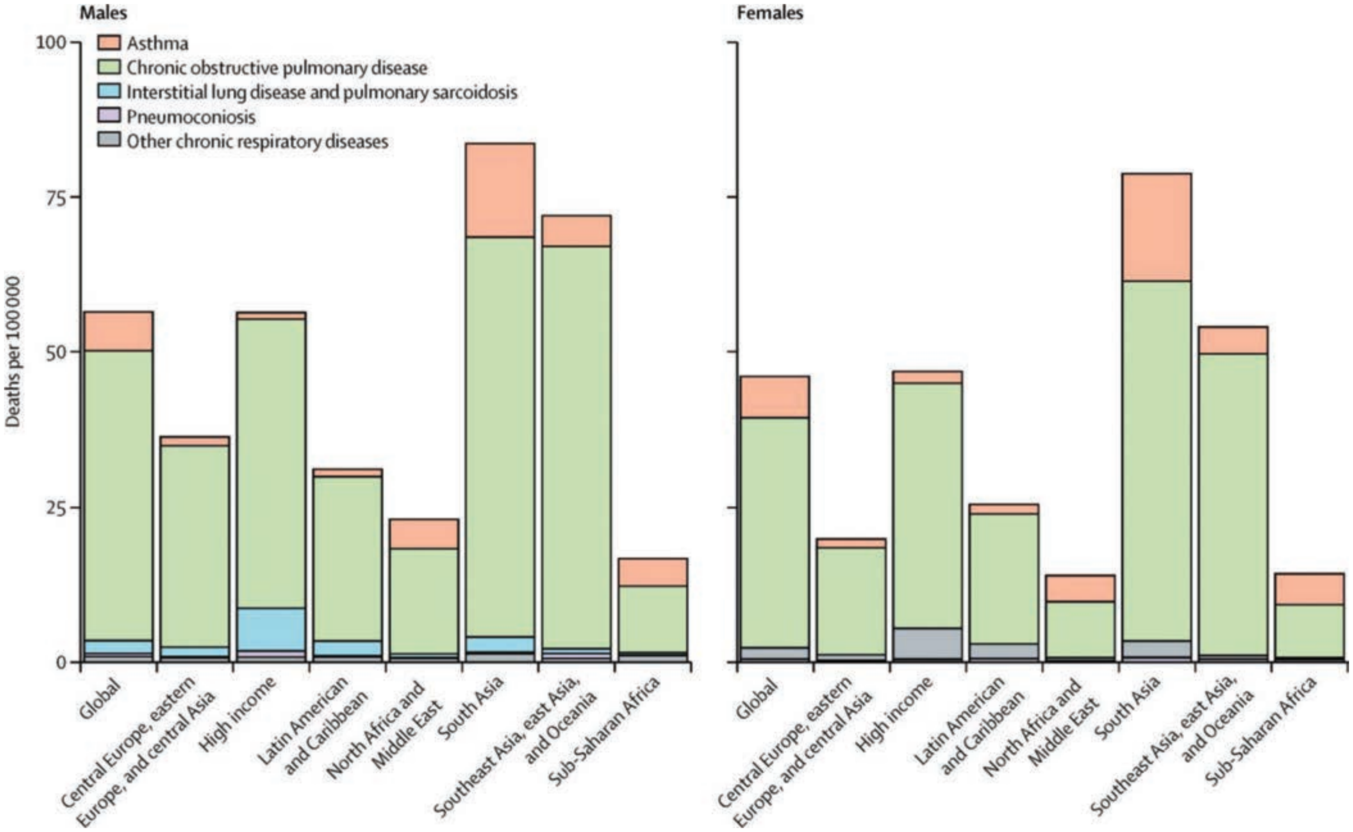

Figure 38-3 COPD accounts for the majority of respiratory disease-related mortality globally, for all ages, and in all regions of the world. *(Reproduced with permission from GBD Chronic Respiratory Disease Collaborators. Prevalence and attributable health burden of chronic respiratory diseases, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Respir Med. 2020;8(6):585–596.)*

exposures, hospitalizations for respiratory illness in early childhood, and occupational exposures.[34] Multiple risk factors may be present in a single individual.

■ Environmental

Environmental exposures include tobacco exposure, indoor pollution, occupational exposures, geography, and socioeconomic status, impacting the disease's regional burden.

Smoking

Worldwide, between 20% and 40% of all COPD patients are never-smokers.[33] This ratio is not the same in developed countries where tobacco smoke-related COPD accounts for approximately 80%.[35] In the United States, there is an overlap between smokers' geographic distribution and the geographic distribution of individuals with COPD. Although the relationship between COPD and tobacco smoke exposure is not linear, there is a correlation between overall lung health, including airflow obstruction based on FEV_1 and duration of tobacco smoke exposures. Traditionally reported as pack-years smoking, there is a growing body of evidence showing that monitoring smoking duration is more sensitive and reliable because it is more precise and not as affected by reporting and recall bias.[36–38] Tobacco smoke exposure early in childhood is even more critical as it results in stunted lung maturation. By middle age, the rate of lung function deterioration with continued tobacco smoke in children with early tobacco smoke exposure outpaces that of former smokers and never-smokers.[39–41]

TABLE 38-1 Risk Factors for COPD

Environmental	Host-based
Smoking	Genetic
Indoor air pollution	Airway hyperreactivity
Occupation	
Low socioeconomic status	

There may be other unrecognized environmental factors. For poorly understood reasons, women have more lung function reduction with early onset of COPD with lower total exposure and a higher proportion of never-smokers with COPD.[42,43] Some data indicate racial disparities in the risk of developing COPD, with African Americans showing similar severity of COPD to whites with fewer pack-years of smoking.[25,44,45] While a decline in FEV_1 is not inevitable in all smokers, those with sustained reductions in FEV_1 and continued smoking have more adverse effects on ventilatory function.[37,46–48]

Environmental Tobacco Smoke Exposure

Human exposure to environmental tobacco smoke (ETS) is associated with an increased incidence of pulmonary and cardiovascular disease and is a possible risk for carcinogenesis.[49–51] ETS is implicated in the loss of many years of the life of adults and children in the United States, with observable sociodemographic disparities.[52] Controlled experimental studies with healthy volunteers indicate that short-term exposures to ETS levels comparable to those in real-life situations affect serum cytokine levels and pulmonary function and, if recurrent or chronic, might translate into COPD.[17,53] In utero effects of maternal smoking on lung growth and subsequent risk of childhood wheezing, asthma, and lung diseases in adulthood are evident.[41,54] The association between ETS and COPD is not a direct

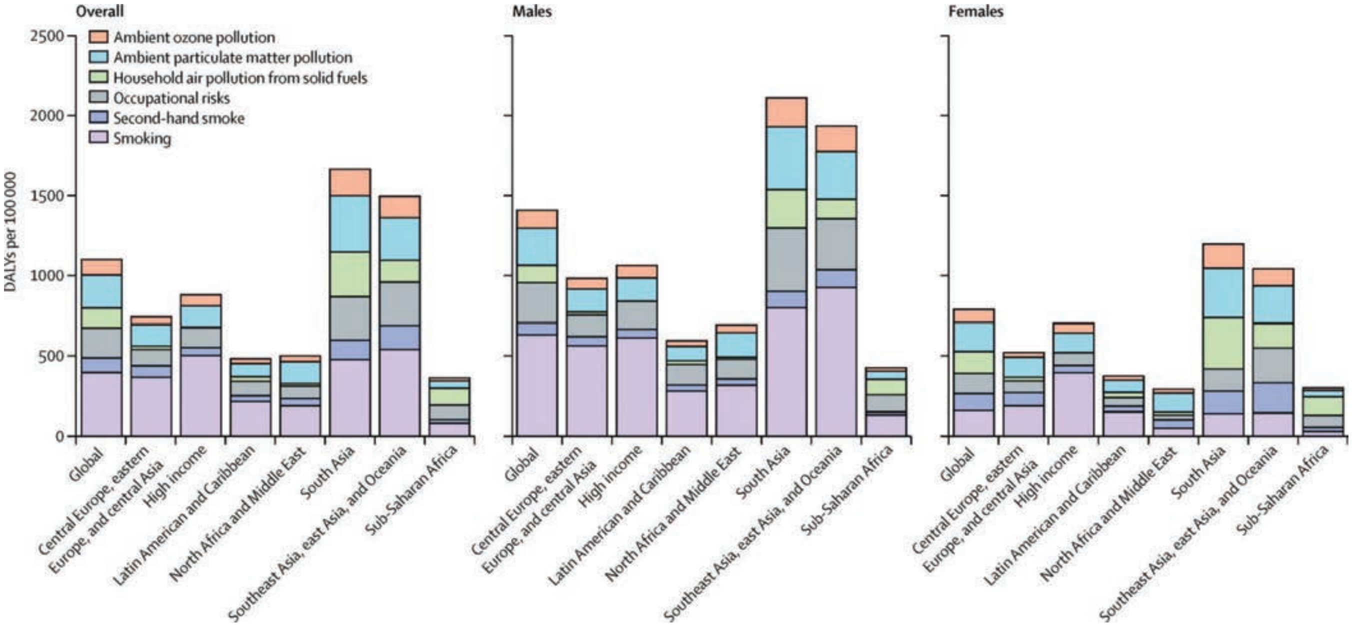

Figure 38-4 The impact of tobacco smoke exposure remains large; however, the effect of non-tobacco exposures is substantial as represented by attributable disability-adjusted life year (DALYs) rates for each risk factor across regions in 2017. *(Reproduced with permission from GBD Chronic Respiratory Disease Collaborators. Prevalence and attributable health burden of chronic respiratory diseases, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Respir Med. 2020;8(6):585–596.)*

association; however, the effect of ETS in early childhood results in alteration and limitations in the maximally attained lung function, and in some, it adversely impacts the rate of decline, thus contributing to increased COPD risk.[41,55] Like chronic smoking and occupational exposures, ETS is an independent risk factor for developing chronic lung disease, so avoidance is recommended.

Air Pollution

Long-term exposure to air pollution increases COPD risk and increases the symptom burden for those with respiratory and allergic illnesses.[56] These adverse effects on the respiratory system are observed even with very low air pollution levels, below national standards for acceptability.[20,57] The effects of outdoor air pollution are well established; however, a growing body of evidence has shown that indoor air pollution is a significant health concern. Sources include burning solid fuels such as wood and animal dung for cooking and heating. This practice is widespread in parts of the world and disproportionately exposes women and children to high smoke concentrations containing respirable particles. These complex gas mixtures are often inhaled for many hours daily. Cough and sputum often occur among those exposed to indoor air, with decreased bronchitic symptoms coincident with measures that reduce smoke levels.[19,58] The World Health Organization estimates that more than one million people a year die of COPD precipitated by indoor air pollution, so international advocacy organizations are working diligently to curb its impact.[59,60]

Occupation-Related Exposures

Many studies have assessed the relationship between COPD outcomes and occupational exposures, and about 15% of COPD cases are attributed to occupational exposures, even after accounting for tobacco smoke exposures.[61] The possibility that occupation-related inhalation of particulates and gases carries a risk for COPD was slow in gaining acceptance, but acceptance is widespread now.[62,63]

Prolonged exposure to a range of substances has the potential to cause COPD. The majority of available information on occupational exposures has focused on a few substances and industries. Most data available focuses on exposure to dust and fumes and less so on other airborne pollutants such as gas, fumes, and vapors.[64] Challenges to quantify the burden of disease related to occupational exposures include the difficulty that results from workplace heterogeneity. Most risk assessment tools do not accurately adjust for the variability in exposures based on the workplaces, country, or evolution of workplace hazards over time.[65,66] Agents that increase risk include but are not limited to dust from cadmium, grain, flour silica, minerals and other organic dusts, cadmium fumes, welding fumes, and wood ash.[67,68] In addition to the well-recognized risk of occupations involving exposure to organic and inorganic dusts, other less “risky” occupations, such as construction, plastics manufacturing, and utility work, may carry an increased risk of COPD.[69,70] The risk of adverse occupational exposure is particularly crucial in workers who smoke or have other host-based factors that raise their risk for COPD, such as genetic variants including α1-antitrypsin deficiency.[71] Occupational risks are modifiable and provide a unique opportunity for disease prevention.

■ Social Determinants of Health

Socioeconomic status plays a significant role in health outcomes. Like in many other chronic illnesses, health disparities exist in COPD-related health outcomes. Rural residence, low socioeconomic status, and potentially ancestry are identified as risk factors for COPD in the United States and other countries worldwide.[72–75] The relationship is linked to increased tobacco exposure and exposure at earlier times in life, low birth weight, respiratory infections in early childhood, limited access to medical care, rates of HIV and tuberculosis, occupational exposure to inhaled particulates, and increased exposure to household allergens.

In the United States in 2011, 45% of adults with a General Education Diploma (GED) were smokers compared to 10% of individuals with a college degree, and for adults living below the poverty level, 33% were smokers in contrast to 20% of individuals living above the poverty level.[76] Focused efforts at addressing factors that reduce health disparities have proved effective in many diseases and may impact the burden of COPD.

Infections

COPD is characterized by chronic inflammation, and while the host–pathogen interaction is not fully understood, the role of chronic and frequent infection in the pathogenesis of COPD is an area of research. Several pathogens, such as HIV and tuberculosis, have been associated with increased COPD risk. Furthermore, lower respiratory infections in childhood have been shown to affect lung health in adulthood adversely.

Tuberculosis

Tuberculosis (TB) is the most common infectious cause of death worldwide, with an estimated 1.3 million deaths in 2019. Pulmonary TB is the most common form of the disease and is associated with significant chronic pulmonary sequelae, even despite microbiologic cure.[77] Tuberculosis is a significant risk factor for COPD; however, the mechanism remains unclear and whether the airflow obstruction is from scarring and other postfibrotic changes.[78,79]

Human Immunodeficiency Virus (HIV) Infection

First identified in 1989, HIV-associated COPD has a reported prevalence of between 6% and 15%.[80,81] Individuals with HIV who smoke have an increased risk of COPD with a propensity toward emphysema development.[82–84] The risk is modulated by increased oxidative stress, systemic inflammation with chronic immune activation, and endothelial dysfunction.[81,85–87] It is unclear if these mechanisms are a direct alteration due to HIV infection or a downstream response to alteration of innate immune responses. COPD and pulmonary hypertension in smokers with HIV appear to be more common in individuals with a high viral load and lower CD4 cell counts and not an adverse consequence of antiretroviral therapy.[88,89] Despite the association of HIV disease control and adverse COPD outcomes, emphysema seen in HIV patients is not reversible in relation to viral load or recovery of CD4 cell counts.

Childhood Lower Respiratory Tract Infections

The complex interaction of host-based factors and environmental predisposition to disease is of particular significance in childhood. In utero events and exposures, early childhood infections, and other events impact peak lung function. Stunted lung maturation increases the risk of developing lung diseases such as COPD later in life.[41] Continued smokers experience further declines in FEV_1 in adulthood.[31] Since the status of lung function in very early childhood predicts ventilatory function many years later, it is essential to promote overall lung health. This can be done by efforts to minimize exposure to allergens, decreasing tobacco exposure, and optimizing access to healthcare and management of respiratory diseases.[90]

Genetic Factors

There is marked variability in COPD development among smokers, with an estimated 10% to 15% of smokers developing clinically significant disease. Genetic variation has significant effects on COPD susceptibility, and heritability estimates for COPD range from 37% to 50%.[91–93] A complex genetic disorder, COPD is caused by the interaction of multiple genes and the environment. Endotypes of COPD are when a known molecular mechanism results in observable disease such as seen in telomerase reverse transcriptase (TERT) gene polymorphisms that affect the action of telomerase and mutations that result in α1-antitrypsin deficiency. Alpha-1-antitrypsin deficiency is autosomal recessive and the most apparent genetic link to COPD.

Alpha-1 Antitrypsin Deficiency Laurell and Erikson in 1963 identified that a deficiency in the neutrophil elastase inhibitor α1-antitrypsin (α1-AT) was associated with COPD.[94] Genetic variants in *SERPINA1* (serpin peptidase inhibitor, clade A, member 1) are responsible for α1-AT. Genetic variants in *SERPINA1* result in an imbalance between α1-AT and neutrophil elastase, increasing the risk of emphysema. Most of the mutations in the 12.2-kb gene that encodes α1-AT are single nucleotide polymorphisms (SNPs) with letters specifying the allelic variants. The original letters were chosen to reflect electrophoretic mobility: F = fast, M = medium, S = slow, and Z = ultraslow (Fig. 38-5). Homozygosity for the M allele, Pi MM, is present in about 95% of adults in the United States. Homozygotes for the Z allele (ZZ), S allele (SS), and compound heterozygotes (ZS) have lower serum α1-AT levels and an increased risk for COPD and emphysema.[95–97] The relationship of heterozygosity to COPD risk had been controversial, but it is increasingly evident that Pi MZ individuals have more airflow impairment, as measured by FEV_1/FVC and more emphysema on CT scans than matched Pi MM individuals.[98,99] Even after accounting for the genetic variants in *SERPINA1* and the strong association with COPD, there remains unexplained variability in COPD risk.[100,101]

Telomerase Polymorphisms Deleterious mutations in the telomerase reverse transcriptase gene (TERT) affect the stability and processing of the enzyme.[102] TERT mutations are associated with aging effects that increase COPD susceptibility.[103] Telomeres are DNA-protein structures located at the end of the chromosome and

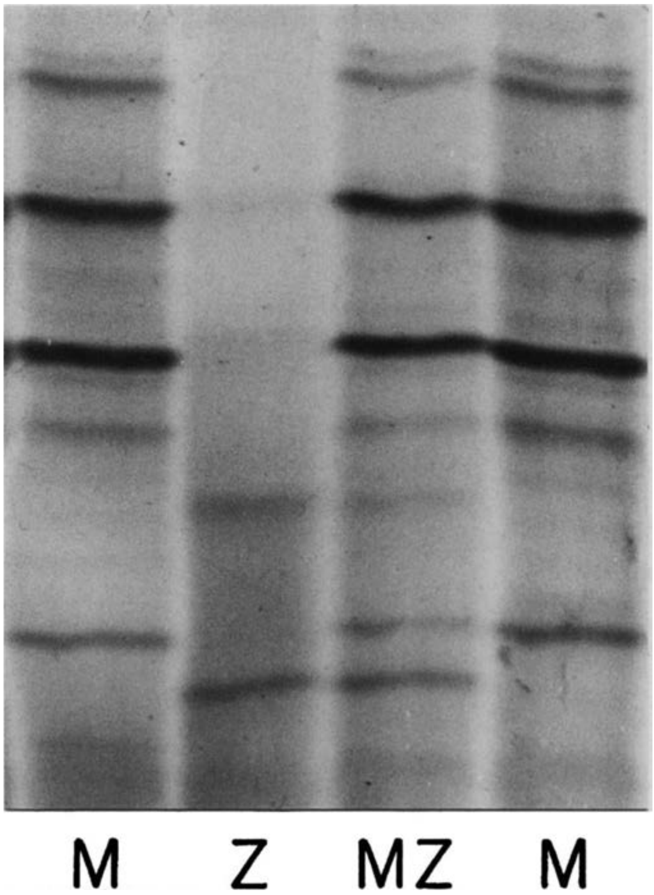

Figure 38-5 Patterns of Pi M, Pi Z, and Pi MZ α1-AT on isoelectric focus. By this analysis, α1-AT has microheterogeneity and thus appears as multiple bands. Pi M and Pi Z have distinctly different band patterns, while Pi MZ has a pattern that combines both Pi M and Pi Z. *(Reproduced with permission from John A. Pierce, M.D.)*

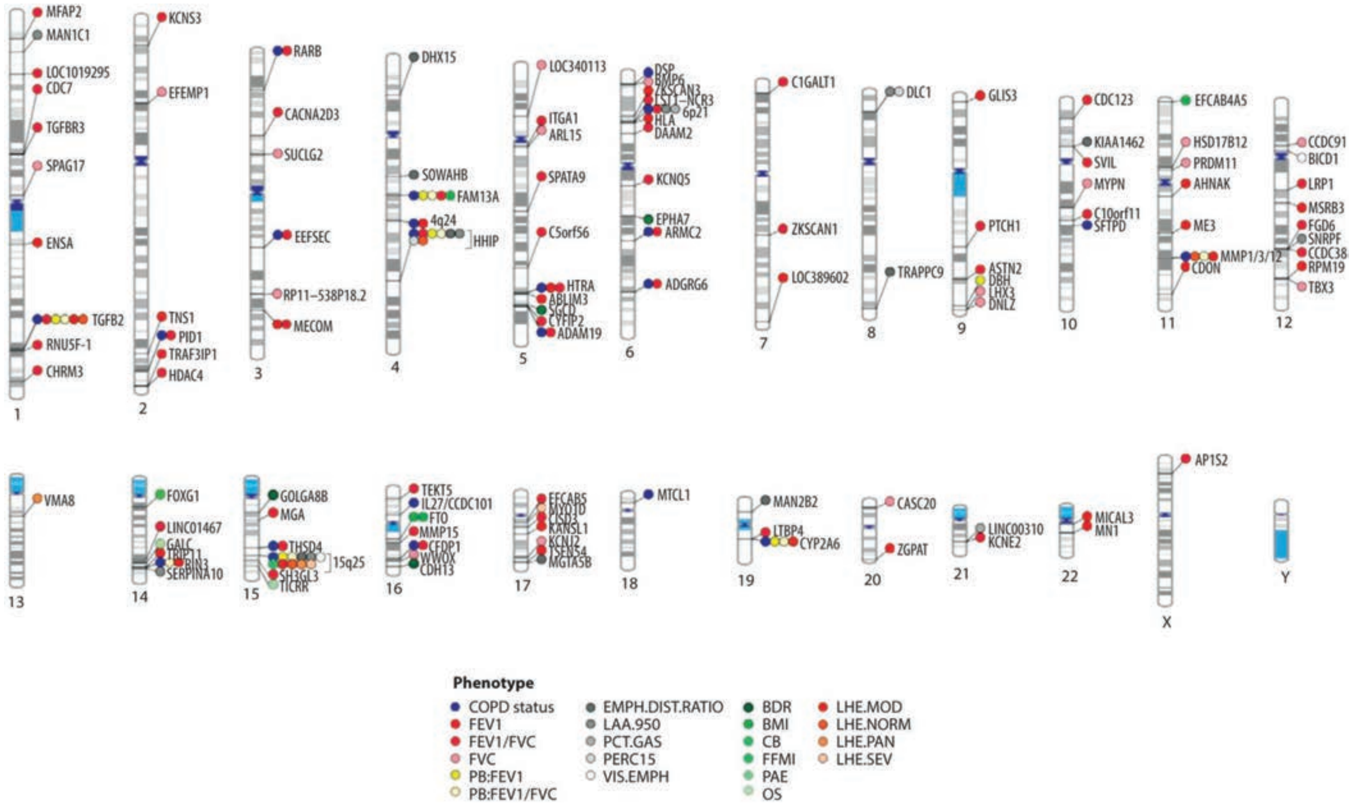

Figure 38-6 Genetic Determinants of COPD-related phenotypes. Phenogram plot of representative genetic associations of GWAS for COPD. Associations are nearest gene to the associated SNP. COPD susceptibility associations *(blue)*, lung function associations *(red)*. BDR, bronchodilator response; BMI, body mass index; CB, chronic bronchitis; EMPH.DIST.RATIO, emphysema distribution ratio of upper divided by lower lung fields; FEV1, forced expiratory volume in 1 s; FFMI, fat-free mass index; FVC, forced vital capacity; GWAS, genome-wide association study; LAA.950, percentage of lung density histogram below −950 HU; LHE, local histogram–based emphysema; MOD, moderate centrilobular emphysema on LHE; NORM, normal/nonemphysematous on LHE; OS, resting oxygen saturation; PAE, pulmonary artery enlargement; PAN, pan lobular emphysema on LHE; PB, postbronchodilator; PCT.GAS, percent gas-trapping at −856 HU on expiratory computed tomography; PERC15, fifteenth percentile point of the lung density histogram; SEV, severe centrilobular emphysema on LHE; SNP, single nucleotide polymorphism; VIS.EMPH, visual emphysema (presence/absence). *(Reproduced with permission from Ragland MF, Benway CJ, Lutz SM, et al. Genetic Advances in Chronic Obstructive Pulmonary Disease. Insights from COPDGene. Am J Respir Crit Care Med. 2019;200(6):677–690.)*

are responsible for protecting the chromosome's integrity throughout the cell cycle. Telomeres gradually shorten with cell division and maturation, and when they reach a certain threshold, they result in cell senescence and apoptosis.[104] TERT polymorphisms disproportionately affect women, increase the pneumothorax risk, and are associated with early-onset emphysema in smokers.[105] They are seen in approximately 1% of COPD patients and are described in familial idiopathic pulmonary fibrosis.[106] TERT polymorphisms highlight that small changes combined with exposures such as tobacco smoke and air pollutants contribute to increased susceptibility.[107]

Other Genetic Variants Efforts to identify other genetic loci are ongoing in multiple cohorts. The Framingham Heart Study cohort was the first genome-wide association study (GWAS) to assess lung function. In this cohort, a variant in interleukin 6 receptor (IL6R) and glutathione-S-transferase omega-2 (GSTO2) were associated with the degree of airflow obstruction.[108] COPD is heterogeneous, and mutations in several disease pathways have been associated with COPD risk and outcomes (Figs. 38-6 and 38-7). The inflammatory pathways (IL6, IL6R), protease imbalance (SERPINA1), oxidant stress (GSTO2), nicotine metabolism, and dependence (cytochrome P-450 2A6) are just a few pathways with disease-associated genetic variants.[108–112] The cholinergic nicotinic acetylcholine receptor exemplifies COPD's genetic complexity. Several mutations in this pathway, including HHIP and CHRNA3/5, have been associated with COPD risk; further, several factors, including epigenetic factors, mediate the expression and subsequent disease associations. The CHRNA3/5 locus is associated with increased smoking intensity and emphysema while the HHIP locus with COPD exacerbation frequency.[113]

Given the polygenic pathogenesis, polygenic risk scores have been shown to increase the predictive power for COPD, and this has the potential to identify susceptible individuals at an earlier age.[114–116]

PATHOPHYSIOLOGY

COPD represents the clinical expression of complex alterations in the structure and function of alveolar tissue and small airways. Many processes at the tissue and cellular levels can be implicated, including inflammation, cell proliferation, apoptosis, the altered phenotype of lung cells, and remodeling of the extracellular matrix. Numerous mediators, most notably proteinases, oxidants, and cytokines, are involved in these processes mediate the observable physiology in COPD.

Hogg and colleagues observed that airways 2 mm or less in internal diameter typically contribute only a minor part of the total airway resistance, but these airways are the principal sites of increased airway resistance in COPD.[117] The physical basis for small airway resistance in COPD has been considered a combined result of emphysema causing minor airway instability and collapse along

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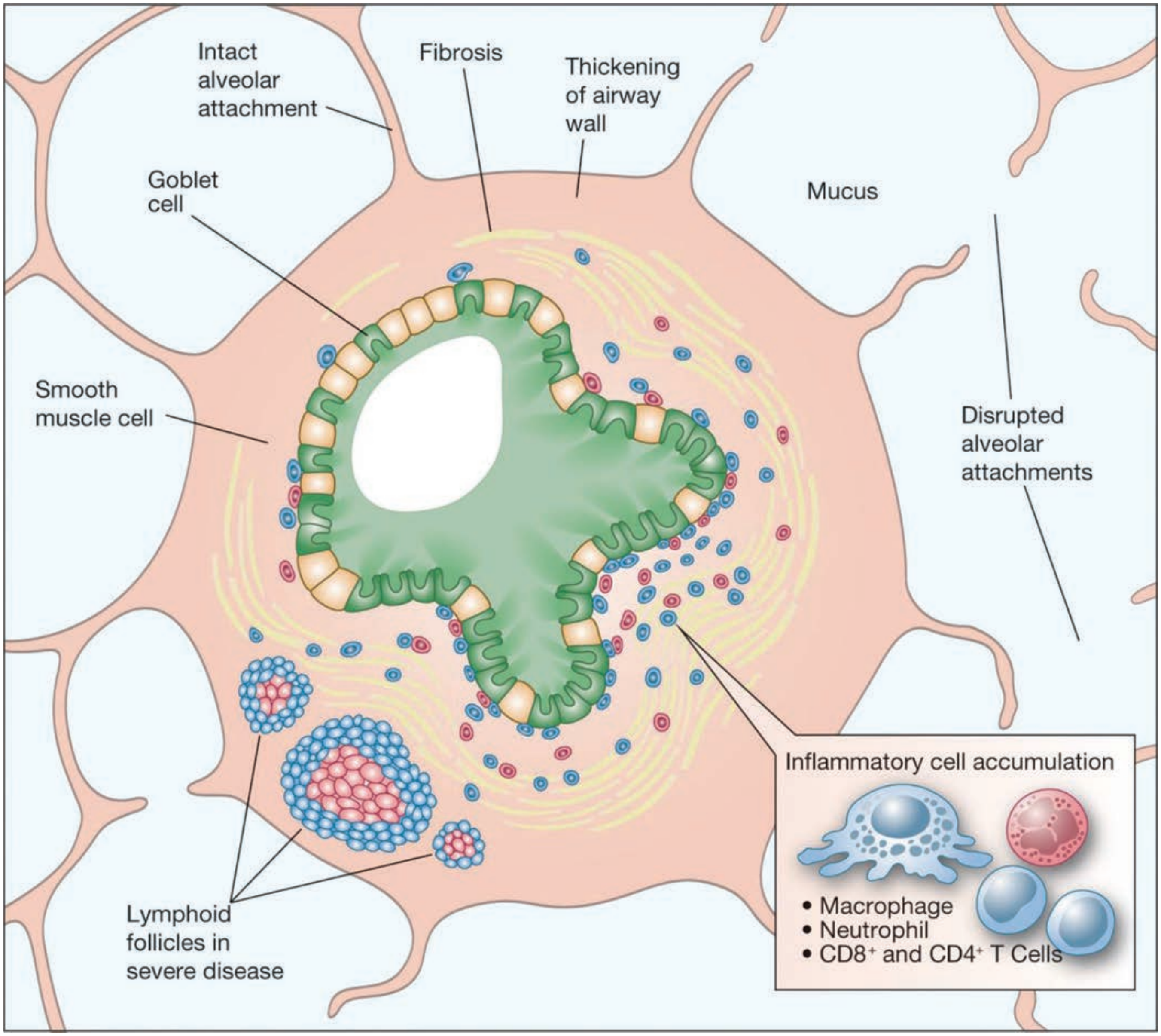

Figure 38-7 The differences in lung function decline exemplify heterogeneity of COPD outcomes. Histogram of the mean annual FEV_1 decline (L) for 751 patients with COPD followed for a median of 64 months and up to 10 years, with an average of 5.44 annual measurements (stratified by ATS/ERS and GOLD severity classification as follows: 32 [4%] mild [FEV_1% ≥80]; 256 [34%] moderate [FEV_1% 50–79]; 245 [33%] severe [FEV_1% 30–49]; and 218 [29%] very severe [FEV_1% <30]). *(Reproduced with permission from Nabel EG: ACP Medicine: Pulmonary, Hamilton, Ontario. Canada: Decker Publishing; 2011.)*

with multiple anatomic abnormalities narrowing the lumens of small airways. Because emphysema and small airway pathology are common in individuals with COPD, their relative contributions to airflow obstruction have been difficult to discern.

A fixed reduction in airflow is associated with several specific pathologic findings in the small airways of advanced COPD (Fig. 38-8). Small airways in the lungs of individuals with COPD typically show goblet cell metaplasia, replacement of Clara cells with mucus-secreting cells, and infiltration of the airway walls by inflammatory cells that, in severe disease, include an increased surface area of lymphoid follicles.[118] The cellular changes are accompanied by increased connective tissue in the subepithelial and adventitial compartments of the airway walls.[118] Alveolar tissue surrounding small airways usually provides radial traction on bronchioles at points where alveolar septa attach. Loss of these bronchiolar attachments resulting from proteolytic destruction may contribute to airway distortion, narrowing, and instability.

Advances in CT image analysis techniques, such as parametric response mapping (PRM), have identified earlier, more predictive manifestations of disease to analyze emphysema pattern and location, measures of airway caliber such as degree of expiratory central airway collapse, and distal airway dropout, among others.[119–122] The large-scale pathologic loss of terminal airways in advanced disease contributes significantly to the small airway resistance. It is unclear if the radiographic loss of small airway surface area in early disease is pathologic destruction, severe wall thickening, or mucus plugging that obscures the lumen below the radiographic resolution. However, more severe airflow obstruction is associated with increases in the thickness of all components of the airway wall.[120] The most significant relative increase in the airway wall components is in the

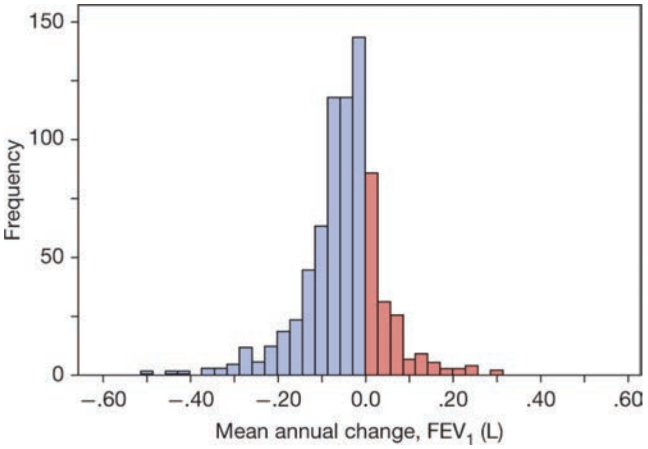

Figure 38-8 Pathologic lesions in small airways in COPD. Multiple abnormalities lead to partial obstruction of the lumen and altered shape and mechanical properties of the airways. *(Reproduced with permission from Casanova C, de Torres JP, Aguirre-Jaíme A, et al. The progression of chronic obstructive pulmonary disease is heterogeneous: the experience of the BODE cohort. Am J Respir Crit Care Med. 2011;184(9):1015–1021.)*

connective tissue–rich adventitial layer. The epithelial layer, the lamina propria, and the smooth muscle–containing layer all demonstrate significant increases in advanced disease, and small airway mucus plugs have been significantly associated with airflow limitation in severe disease.[123] The interplay of small airway pathology, radiologic loss of small airways, emphysema, and their role in causing the airflow obstruction in early COPD are ongoing research areas.

■ Airflow Obstruction

The American Thoracic Society (ATS) and GOLD recommend utilizing post-bronchodilator FEV_1/FVC less than 0.70 as the threshold for the detection of airflow obstruction. Defining and appropriately classifying persons with a reduced FEV_1 with a normal FEV_1/FVC and normal TLC has been controversial. These patients are defined as preserved ratio impaired spirometry (PRISm), an entity that some suggest should not be classified as COPD or interpreted as an obstructive ventilatory defect, while others argue that it should, given the similarity in pathogenesis and similar outcomes such as mortality when compared with COPD.[124,125]

The FEV_1 is an important marker of airflow and it reflects the balance between the elastic recoil of the lungs promoting expiratory flow and the resistance of the airways limiting flow during the performance of an FVC. In normal lungs and lungs affected by COPD, maximal expiratory flow diminishes as the lungs empty because the lung parenchyma provides progressively less elastic recoil, and the cross-sectional area of the airways falls. This leads to an increase in airway resistance. The decrease in flow coincident with the decrease in lung volume is apparent on the expiratory limb of the flow–volume curve (Fig. 38-9). In mild COPD, the abnormality in airflow is evident only at lung volumes at or below functional residual capacity, appearing as a "scooped out" lower part of the descending limb of the flow-volume curve. In many patients with advanced COPD, the entire curve demonstrates decreased expiratory flow. There is wide variability in COPD in the relationships among FEV_1, exercise tolerance, alveolar gas exchange, and quality of life.[126] The correlation between FEV_1 and small airway pathology is strong, and it likely contributes to the reduction independent of the correlation of FEV_1 with emphysema.

■ Airway Hyperresponsiveness

Airway hyperresponsiveness (AHR) is present when there is an acute, temporary decline in maximal expiratory airflow in response to inhaling potential bronchoconstricting agents such as methacholine or histamine. Historically the "Dutch hypothesis" postulated that asthma and COPD are two different manifestations of the same disease due to the similarity in features such as the presence of airway hyperresponsiveness.[127] Distinct from asthma, the type and cause of airway inflammation and consequences of the inflammatory process are different in COPD. Smokers typically do not show AHR until their FEV_1 is reduced, and experimental induction of emphysema often leads to AHR.[128] AHR is of clinical significance as it is associated with an accelerated decline of FEV_1 and is a negative prognostic marker.[129] In the Lung Health Study, AHR was second to smoking as an essential determinant of decline in FEV_1, and it was not related to the initial level of obstruction. AHR was more significant in women smokers than men smokers.[129] Although AHR decreased after smoking cessation and bronchodilator responsiveness improved, bronchodilator responsiveness did not correlate with the rate of FEV_1 decline.[130]

An important component of COPD, AHR in individuals with COPD is underestimated due to the infrequency of bronchoprovocation testing in patients with COPD. It may be a consequence of emphysema, airway wall stiffness, and parenchymal tethering by the extracellular matrix.[128] Distinctions in airway hyperresponsiveness in COPD and asthma are still a significant topic of interest.[128]

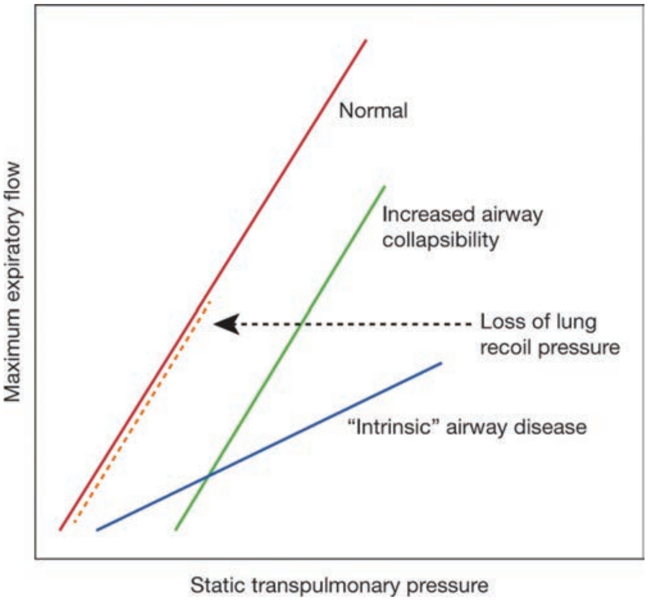

Figure 38-9 Reduced maximum expiratory flow in COPD from maximum expiratory flow versus lung recoil pressure curves. Loss of lung recoil, emphysema (heavy interrupted line)—the flow–pressure curve slope remains normal, but the curve terminates at a lower pressure than normal. Due to airway obstruction, the slope is reduced. Increased airway collapsibility, due to decreased elastic recoil, causes displace the curve to the right. In COPD, the flow–pressure curve has premature termination and a decreased slope and is shifted rightward, indicating decreased elastic recoil, increased airway resistance, and increased airway collapsibility are all involved in the reduced maximum expiratory flow. *(Reproduced with permission from Calverley PMA, Pride NB: Chronic Obstructive Pulmonary Disease. London, Chapman & Hall; 1995.)*

PATHOGENIC MECHANISMS

Numerous well-established pathogenic mechanisms result in the observable COPD phenotypes. These mechanisms include dysregulated inflammatory reactions, excess oxidant stress, mucus hypersecretion, and proteinase imbalance resulting in elastic fiber degradation and increased collagen turnover.

Inflammation

Inflammatory responses can be divided into innate and acquired types.

Innate Immune Responses

Tobacco smoking and other inhaled irritants lead to the recruitment, infiltration, and activation of innate inflammatory cells in the lungs and airways, where an excess of the products of these cells injure lung tissue and disrupt lung repair mechanisms.[118,131,132] Some inflammatory cell types important in COPD include neutrophils, macrophages, and variably eosinophils, but also dendritic cells and lymphocytes. The increased presence of airway inflammation is demonstrated by inflammatory cells in lung biopsy specimens, bronchaoalveolar lavage fluid, and sputum as well as increased volatile products of inflammation in exhaled breath.[133–137] While the presence of inflammatory change can be a normal response to oxidative stress and tissue damage due to irritants such as cigarette smoke, maladaptation of these integral functions to the innate immune dysfunction is key in COPD pathogenesis. Once COPD is established, there can be continued oxidative stress and progression from endogenous sources such as mitochondrial respiration even after the cessation of inhaled toxic exposures.[138]

Activated macrophages and neutrophils are the major participants in lung inflammation in COPD.[139] Monocytes become alveolar macrophages after migrating into the lungs by sensing and following chemoattractant gradients of cytokines and bacterial peptides produced by tissues of infection or inflammation.[140,141] Essential to establishing homeostasis of the inflammatory milieu, alveolar macrophages have both anti-inflammatory (M1) and inflammatory (M2) phenotypes. COPD patients have a dominant M2 phenotype, with several alterations that result in defective phagocytosis and changes in abnormal secretion of cytokines and chemokines.[142–144] Alveolar macrophages in COPD release proteinases that degrade the extracellular matrix of the lung and release chemotactic factors that recruit other inflammatory cells to the lungs.[145] Unlike most circulating cells such as neutrophils that decrease within weeks of limited tobacco smoke exposure, activated alveolar macrophages may be present even years after smoking cessation.[146,147]

Neutrophilic inflammation induced by byproducts of cigarette smoke, viruses, bacteria, and oxidative stress is characteristic of COPD and is the predominant mediator of mucus hypersecretion.[148,149] Neutrophilic inflammation in COPD is unfortunately not responsive to available therapies, with minimal response to steroid therapy.[148,150] Airway epithelial cell exposure to pollutants and inflammatory peptides activates the production of neutrophilic mediators and chemoattractants such as CXCL1, CXCL8, and leukotriene B4, engaging chemoreceptors CXCR2 and BLT1 receptors.[151] All of these are produced in excess in patients with COPD. Investigations into therapeutics such as CXCL8 blockade or the signaling cascade intermediaries such as TNF-α and IL-1β have not shown benefit in lung function or frequency of exacerbations.[148,150,152] Macrophages and neutrophils are commonly seen in patients with COPD; however, the role of eosinophils is now increasingly understood.

The role of eosinophilic inflammation has garnered a lot of attention. About 20% to 40% of patients with COPD have increased airway eosinophilic inflammation.[153] The presence of eosinophilic inflammation is best quantified using the direct examination of lung biopsies, bronchoalveolar lavage fluid, and induced sputum, and airway eosinophilia is associated with increased frequency of exacerbations and hospitalizations for exacerbations.[154,155] Peripheral blood eosinophilia has been advanced as a more practical surrogate marker for eosinophilic airway inflammation due to the expense and challenge and lack of availability of more directed measurements of airway inflammation. The blood eosinophil count is a promising biomarker of response to inhaled corticosteroids in COPD. The lung has tissue-resident eosinophils that are independent of those recruited by chemokine CCL5. While the origin is different, these two populations there are similarities in function.[156] Eosinophils are activated by smoke and infectious byproducts, resulting in the production of the cytokines thymic stromal lymphopoietin (TSLP) and IL-33. TSLP and IL-33 are responsible for recruiting Th2 cells and type 2 innate lymphoid cells (ILC2), which result in eosinophilic inflammation for secreted IL-5.[148] In addition to their effector functions, eosinophils contribute to the immune response through recruitment of dendritic cells (DCs), production of several Th2 chemoattractants, and by performing some functions of antigen presentation.[156–158]

While knowledge of the role of DCs is not as established, they appear to be important in the pathogenesis of COPD. DCs are antigen-presenting cells that impact the activation of adaptive immune cells. It has been shown that once they are primed, DCs in COPD play a role in increasing natural killer (NK) cell cytotoxicity toward epithelial cells.[159] Lung DCs increasing NK cell activity may be significant in COPD pathogenesis. Like alveolar macrophages, DCs are critical to the balance of inflammatory and anti-inflammatory effects.[160] The overall effect of DCs is critical to both the innate immune response and initiating adaptive immune responses.[161]

While not all people with chronic tobacco exposure develop COPD, in those who develop COPD, the inflammatory process initiated by smoking may persist long after smoking has stopped.[147,162,163] The inflammatory processes in COPD are not limited to the lungs and airways. The role of systemic inflammation is evident in stable COPD and to a higher degree in severe COPD and during acute exacerbations of COPD. Systemic inflammation is evident from increased leukocyte counts, cytokines, chemokines, acute phase reactants, or abnormalities in circulating cells.[163–166]

The various contributions from the immune system cells likely contribute to pathogenesis at separate stages and likely impact the different disease phenotypes. The innate immune response mechanisms contribute to COPD progression, and these mechanisms are interlinked with the activity of adaptive immune cells lead to increased COPD severity.

Acquired Immune Responses

Cellular and humoral immunity are also involved in COPD pathogenesis and the continued progression of COPD after smoking cessation. These COPD responses include the proliferation of B and T cells after antigen presentation by macrophages and dendritic cells. Patients with COPD have an increased presence of cytotoxic CD8+ T cells, various CD4+ subsets including Th1 and Th17, and alterations in T regulatory cells (TREGs).[140] In addition to the role of T cells, antigen exposure elicits B cell responses and antibody production. Further, in the past decade, there has been an increase in information about the function of other adaptive immune cells such as natural killer (NK) cells and natural killer T (NKT) cells in COPD. These inflammatory mediators play a different role and are impacted by smoking status and frequency of respiratory infections and exacerbations, as well as the balance of immunoregulatory cell functions.

CD4+ and CD8+ T cells and B cells accumulate in alveolar and airway tissue in COPD. Peribronchial lymphoid follicles are formed through lymphoid neogenesis and the activity of lymphoid chemokines that are important for cell migration such as CCL21, CXCL12, and CXCL13.[167,168] There is an accepted role for autoimmunity, particularly in COPD, as evidenced by an excess of

TABLE 38-2 Proteinases That May Affect the Lung Parenchyma

Proteinase	Cell of Origin
Neutrophil elastase	Neutrophil (monocyte)
Proteinase 3	Neutrophil (monocyte)
Cathepsin G	Neutrophil (monocyte, mast cell)
MMP-1[a]	Macrophage, epithelial cell
MMP-9 (Gelatinase B)	Macrophage, neutrophil, eosinophil, fibroblast, epithelial cell
MMP-12 (Macrophage elastase)	Macrophage
Cathepsin L	Macrophage
Cathepsin S	Macrophage

Parentheses denote minor cellular sources.
[a] *Lacks elastase activity.*

B cell lymphoid follicles and the presence of several autoantibodies in patients with COPD.[167,169] Antigens for immunologically mediated progression of airway disease and emphysema include microbial pathogens, peptides altered by tobacco smoke, and peptides released from damaged lung extracellular matrix.[162,170,171] Difficulties in distinguishing cellular and humoral responses to microbial colonization of advanced airway disease in COPD from pathologic self-directed immune responses will require further study.[167] Due to the complexity and multiplicative nature of the derangements in the immune response in COPD, identifying a therapeutic target, specifically in advanced disease, has been challenging. Targeting therapies in the early stages of disease progression can be a more fruitful endeavor.[172]

■ Proteinase–Antiproteinase Imbalance

The discovery of α1-AT deficiency–associated early-onset emphysema and the advent of experimental animal models producing emphysema with elastolytic enzymes promoted the imbalance of proteinases relative to their inhibitors as a critical factor for emphysema development.[94] Proteinases of several biochemical classes, and various specific inhibitors, are implicated in emphysema pathogenesis. Serine proteinases, especially neutrophil elastase and several matrix metalloproteinases, have been the proteinases for which there are the most data[173] (Table 38-2). It is notable that both neutrophils, which are the source of neutrophil elastase, and MMP-12 from alveolar macrophages are primarily related to continued smoking. Progression after smoking cessation may follow different pathways. Although neutrophil elastase and its main inhibitor α1-AT have predominated the proteinase–antiproteinase imbalance hypothesis, MMPs appear prominent in mouse models and samples from smokers and individuals with COPD. It is likely a combination of many local imbalances involving several proteinases and antiproteinases contributing to progressive lung destruction.

Several aspects of proteinases in COPD should be noted, as solely a straightforward destructive mechanism is likely an oversimplification. In addition to the destruction of lung elastin and other matrix components, proteinases process cytokines and surface receptors involved in the inflammatory and immune responses.[174] Inflammatory cells may not be the exclusive protein source, as structural cells also produce matrix-degrading proteinases.[174,175]

■ Oxidant–Antioxidant Imbalance

Reactive oxygen species in cigarette smoke or released by inflammatory cells and the lungs' structural cells in response to smoke may lead to lung injury.[176] Smoking causes both regional and systemic oxidative stress by altering the balance between oxidants and antioxidants. A puff of cigarette smoke can contain more than 1000 free radicals with more than 4000 oxidant compounds such as superoxides, epoxides, peroxides, nitric oxide (NO; 500 to 1000 ppm), nitrogen dioxide, peroxynitrite (ONOO−), and peroxyacyl nitrates.[177–180] Cigarette smoke–induced oxidative stress initiates a cascade of cellular and molecular reactions that initiate inflammation, cell injury, and apoptosis.[181] The processing of these cigarette smoking sequelae is dependent on the effect of antioxidants. Genetic mutations in antioxidant genes are linked to susceptibility and COPD severity. Genetic polymorphisms in antioxidant genes are associated with the progression of COPD, such as polymorphisms in several genes in the glutathione S-transferase (GST) gene family, including GSTM1, GSTM3, GSTP1 as well as superoxide dismutase 3 (SOD3), and microsomal epoxide hydrolase (EPHX1).[176,182–184] Mutations in transforming growth factor-β1(TGFB1) are protective.[185]

The lung tissue of smokers contains significantly higher iron content, which provides a catalyst for the production of hydroxyl radicals from H_2O_2.[186,187] This is combined with the knowledge that iron-responsive element-binding protein 2 (IREB2) polymorphism is prevalent in smokers with COPD[188,189] (Fig. 38-6). Smokers also demonstrate increased production of neutrophil myeloperoxidase, capable of yielding oxidized halogens such as hypochlorous acid (HOCl).[189,190] The harmful effects of oxidants are numerous and include modification and inactivation of protease inhibitors (α1-AT and secretory leukoprotease inhibitor) and anti-inflammatory proteins like histone deacetylase 2 (HDAC2).[191–193] Oxidants can also affect lipids and DNA, and some specific end products, such as 4-hydroxy-2-nonenal (4-HNE) and 8-hydroxy-2′-deoxyguanosine (8-OHdG), may be biomarkers of COPD.[194,195]

Oxidants can promote inflammation and proteinase expression, facilitate proteinase-mediated extracellular matrix degradation by enhancing matrix molecule susceptibility to proteolytic cleavage, and participate in nonenzymatic degradation of matrix molecules like type I collagen. In experimental animals, the combination of cigarette smoke and elastase leads to more significant emphysema than either insult alone, and antioxidant deficiency results in increased susceptibility.[196–198]

■ Apoptosis and Senescence

Cellular senescence and apoptosis occur more frequently in COPD than in healthy people due to replicative and stress-related factors. In vitro, cigarette smoke induces apoptosis of alveolar epithelial cells, endothelial cells, lung fibroblasts, and granulocytes. Bicaudal D1 (BICD1) has been identified as a susceptibility gene in COPD, with a polymorphism linked to emphysema (Fig. 38-6), and encodes for a protein essential in autophagy and critical to the apoptosis pathway.[199,200]

In addition to apoptosis, cellular senescence is important in COPD pathogenesis. Senescence is a state of stable cell cycle arrest, and usually, due to DNA damage, it makes proliferating cells resistant to growth-promoting stimuli.[201] Senescence is a driving mechanism resulting in the pathogenesis of emphysema. Senescent cells secrete copious inflammatory proteins propagating inflammatory processes and causing more senescence. Changes related to oxidative stress result in the loss of function of silent information regulator (sirtuin) 1. Sirtuin-1 and sirtuin-6 are antiaging molecules whose deacetylation regulates metabolism, increases genomic stability, and reduces cellular stress.[201,202] In animal models, several other proteins with anti-aging effects have been identified such as senescence marker protein 30 (SMP30), DNA-dependent protein kinase (DNA-PK), and Ku86.[202–204] Senescent cells (alveolar, epithelial, and endothelial cells) are prevalent in the lungs of COPD patients.[205–207] Impaired immunity, increased cancer risk, and frequent infections are seen when there is senescence of immune cells (immunosenescence). Early data suggest a potential reversal of these processes, and there are several therapeutic interventions under investigation.[201,208,209]

■ Mucus Hypersecretion

Airway mucus is a complex mixture of mucins, inflammatory cells, water, soluble mediators, and negatively charged ions. It is usually a protective barrier that is continuously replenished and cleared in healthy people. The negative charge of mucus glycoproteins results in sequestration of proteases, volatile hydrocarbons, and possibly preservation of the hydration of the ciliated layer, resulting in protection of the underlying lung and likely improved carcinogen clearance. Pathologic or excess mucus production, known as chronic mucus hypersecretion, is one of the most common respiratory symptoms in most chronic lung diseases. Obstruction of small airways and chronic inflammation are fundamental features of many chronic lung diseases such as cystic fibrosis (CF), asthma, and COPD. Exacerbations of these lung diseases are associated with increased mucus production. Sputum production and cough are associated with COPD progression and increased risk of exacerbations, and may have implications on mortality.[210–213]

Mucus production and regulation is a complex process involving cytokines, chemokines, and several inflammatory mediators as well as toxic agents that induce inflammation and reactive oxygen species (TNF-α, IL-1β, IL-6, IL-9, IL-9, IL-17, prostaglandins, neutrophil elastase, human airway trypsin, metalloproteinases, lipopolysaccharides, cigarette smoke, and airway pollutants).[214–218] In COPD, there is hyperplasia of goblet cells and hypertrophy of glands, with an increase in the ratio of glandular mucus cells to serous cells resulting in pathologic changes to mucus production. Several pathogenic mechanisms are associated with the mucus changes, including altering the mucus proteins (MUCs). Like cystic fibrosis, there is an alteration to favor a predominance of MUC5B over the typical MUC5AC form and an increase in the MUC2 form, which is uncommon in normal lung mucus.[219,220] Additionally, abnormalities in the cystic fibrosis transmembrane conductance regulator (CFTR) have been shown to alter airway mucociliary transport and contribute to COPD disease pathogenesis.[221–223] In COPD, other alterations in the mucus layer include greater acidity, less mucin glycosylation, and decreased antimicrobial peptides.[220] Mediators responsible for mucus hypersecretion include proteinases, cytokines, oxidants, and activation of several signaling pathways such as epidermal growth factor receptor (EGFR).[224–227] The small airway luminal obstruction by mucus is correlated with the degree of airflow obstruction and inversely correlated with survival after lung volume reduction surgery.[228]

■ Lung Elastic Fiber Degradation

Observations linking proteinases to emphysema led to the concept that the destruction of alveolar elastic fibers is key to emphysema development.[229] An imbalance of proteases and antiproteases result in parenchymal destruction. Macrophages, neutrophils, and other effector cells release proteases, including proteinase 3, matrix metalloproteinases (MMPs), and other cytolytic products that activate each other and inhibit other endogenous inhibitors.[230] Structurally, the extracellular matrix of the lung is organized into three interdependent cable systems: (1) an axial system that extends from the central airways through the peripheral airways to the alveolar ducts; (2) a parenchymal system that comprises the matrix of the alveolar septae; and (3) a peripheral system that arises from the visceral pleura and extends into the interlobular septae, forming a fibrous sac around the lung. Distal to the respiratory bronchioles, the axial system forms a helix encircling the alveolar ducts, extending into the interstitium of alveolar walls. Elastic fibers, of which elastin is the main component, loop around alveolar ducts, form rings at the mouths of the alveoli, and penetrate as wisps into the alveolar septae, where they are concentrated at bends and junctions (Fig. 38-10). Elastic fibers, which possess rubberlike reversible extensibility, come under tension and provide elastic recoil throughout the respiratory cycle. Unlike elastic fibers, the interstitial collagen fibers in alveolar septa are not distensible and have high tensile strength.

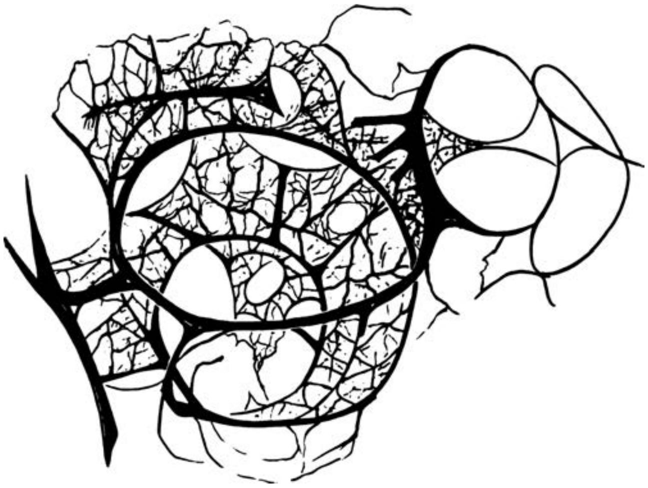

Figure 38-10 Alveolar elastic fiber network. Artist's sketch of the elastic fibers in lung parenchyma showing how elastic fibers form a helix encircling the alveolar ducts and penetrate alveolar septae. *(Reproduced with permission from Pierce JA, Ebert RV. Fibrous network of the lung and its change with age. Thorax. 1965;20(5):469–476.)*

Elastin is present in bronchi and lung parenchyma, and in alveolar regions of the lung, elastin fibers are deployed around alveolar ducts, the openings of alveoli, and extensions into alveolar septa.[231] Distraction of elastic fibers leads to tissue loss, altered alveolar structure, and emphysema. While elastin is resistant to many proteinases, some enzymes can degrade elastin (Table 38-2). Elastic fibers in the lung typically last an entire human life span.[232] Histologic studies of emphysematous lung tissue support the hypothesis that elastic fibers are perturbed in emphysema. There are fragmented elastic fibers in α1-AT deficiency and poorly formed elastic fibers, and elastin clumps in smokers with centriacinar emphysema.[232] The latter changes appear from the aberrant synthesis of new elastin and resemble the findings in emphysematous lungs induced experimentally with elastase.

Animal models employing elastase-induced emphysema have shown acute depletion of elastin following an intratracheal injection of human neutrophil elastase, followed by a burst of synthesis of extracellular matrix including elastin.[233] Over a few weeks, the elastin content of the lungs returns to normal, although the lungs still display emphysema. The elastic fibers, like the elastic fibers in human emphysema, appear disorganized. New elastin gene expression occurs even in severe emphysema in humans (Fig. 38-11). However, there are significant barriers to the effective repair of damaged elastic fibers in the mature lung. When elastic fibers are damaged enough to fail under load, there is no mechanism for cells to recreate a structure with a length many times the size of each cell. The injured adult lung lacks the mechanical and morphogen gradients that initiate alveolar formation during development and may also be unable to coordinate the expression of the many components necessary for functional elastic fiber synthesis.

■ Lung Collagen Turnover

Although elastic fiber destruction dominates the proteolytic basis for emphysema pathogenesis, the degradation of alveolar wall collagen and aberrant collagen deposition in alveolar tissue also may

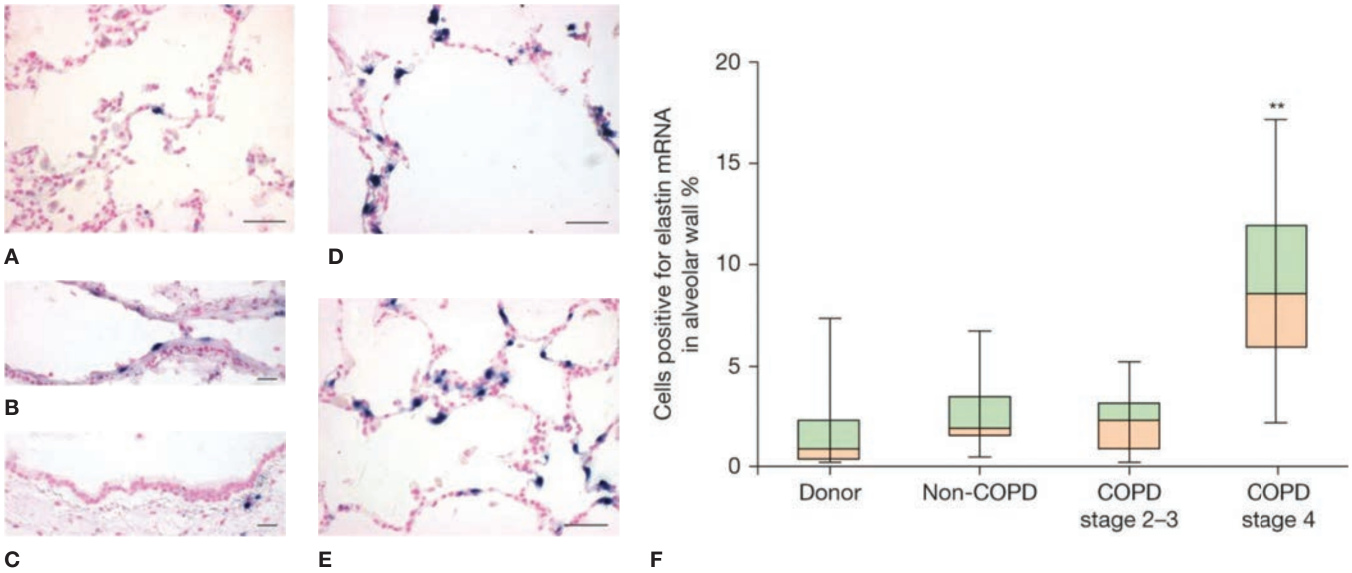

Figure 38-11 Expression of elastin production in severely emphysematous lung removed for lung transplantation. Elastin mRNA *(blue signal)* as detected by in situ hybridization is rarely detected in donor lungs in (**A**) parenchyma, (**B**) intralobal pulmonary arteries, or (**C**) airways but is prevalent in the parenchyma of patients with very severe COPD in regions with moderate (**D**) and severe (**E**) alveolar enlargement. Quantification of cells positive for elastin mRNA (**F**) reveals significantly higher elastin expression in alveolar walls of very severe COPD (GOLD stage 4) lungs compared with donor lungs or less severe COPD lungs. *(Reproduced with permission Deslee G, Woods JC, Moore CM, et al. Elastin expression in very severe human COPD. Eur Respir J. 2009;34(2):324–331.)*

be involved. There is increased collagen deposition in patients with COPD compared with smoker controls.[234] In some forms of experimental emphysema, collagen destruction appears to be a critical event. Human collagenase/matrix metalloproteinase 1 (MMP-1) is important in development of emphysema. Mice genetically engineered to harbor a transgene that leads to the expression of MMP-1 in lung tissue develop structural changes typical of emphysema. These changes occur due to the destruction of alveolar type III collagen.[235,236] In these models, emphysema occurs without obvious disruption and faulty resynthesis of elastic fibers as the elastic fibers in these lungs look normal. Expression of MMP-1 by alveolar epithelial cells in human emphysematous tissue fits with the idea that collagenolytic activity plays a role in emphysema.[175,237]

Cigarette smoke exposure leads to tripeptide proline-glycine-proline (PGP) release from the lung matrix.[238] PGP binds chemokine receptor 2 (CXCR2), a prominent chemokine receptor on neutrophils. PGP functions as a neutrophil chemoattractant, and in an animal model, PGP's repeated instillation into the lung produces emphysema by collagen breakdown.[238,239] Analogous to elastin peptides promoting emphysema in mice, PGP is generated by the sequential breakdown of collagen by MMPs 8 and 9 and prolyl endopeptidase, and blocking PGP reduces emphysema in mice exposed to cigarette smoke.[239,240]

In emphysematous lungs, the pores of Kohn are larger and more numerous than in normal lungs (Fig. 38-12). Because interstitial collagens and basement membrane collagens are prominent in alveolar walls, it is plausible that collagenous structures undergo degradation in the process of generating these interalveolar pores.

CONCLUSION

Despite advances in pathogenesis, the treatment options remain limited, with very few options that significantly impact mortality. Unlike many major causes of death, the disease burden is projected to continue to increase as cigarette smoke exposure continues to increase in low- and middle-income countries. Despite the current efforts at decreasing the burden of the disease, there remains a significant need.

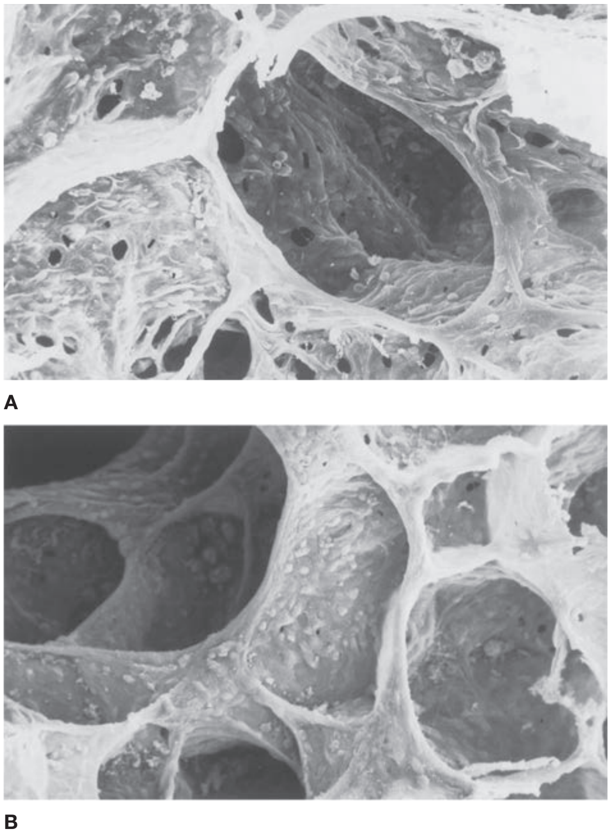

Figure 38-12 Holes in alveolar walls in early emphysema. Scanning electron micrographs of alveolar walls from surgically resected specimens: lung with mild emphysema (**A**) and nonemphysematous lung (**B**). Holes are more numerous in alveolar walls in the emphysematous lung than in the normal lung. Original magnification ×250. *(Reproduced with permission from Nagai A, Inano H, Matsuba K, et al. Scanning electron microscopic morphometry of emphysema in humans. Am J Respir Crit Care Med. 1994;150(5 Pt 1):1411–1415.)*

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CHAPTER 39

Chronic Obstructive Pulmonary Disease and α1-Antitrypsin Deficiency

Darrell N. Kotton
Andrew A. Wilson

INTRODUCTION

While predisposition to COPD is widely known to have a significant genetic basis,[1] the only known monogenic cause is the genetic mutation that results in α-1 antitrypsin deficiency (AATD). AATD was first identified in 1963 by Laurell and Eriksson, who initially described a cohort of five individuals lacking the α1 globulin fraction, as revealed with serum protein electrophoresis. Three of the five suffered from significant pulmonary disease.[2] Subsequently, AATD was shown to result from the homozygous inheritance of a single base-pair mutation in the *SERPINA1* gene, which encodes α1-antitrypsin protein.

Misfolded AAT proteins are poorly secreted and functionally abnormal—features that collectively predispose affected individuals to developing panlobular emphysema and COPD. While the prevalence in the population is not precisely known, AATD is estimated to afflict approximately 100,000 individuals in the United States and to account for approximately 1% to 4.5% of cases of COPD.[3–7] Coupled with the observation that the cysteine protease inhibitor papain induces emphysema in rats when instilled intratracheally,[8] the discovery of AATD and its association with emphysema led to the formation of the protease/antiprotease hypothesis as a basis for the pathogenesis of COPD (emphysema).

EPIDEMIOLOGY

The Z mutation is believed to have arisen from a single origin approximately 2000 years ago, potentially in the Viking population,[9,10] who then disseminated it in southern Scandinavia. Studies of gene frequency have demonstrated significant variance among European nations, in which a gradient of gene frequency has been found, including high levels in the Northwest that decrease toward the Southeast.[10] In Europe, the highest levels are found in regions of Estonia, Latvia, Sweden, France, Ireland, southern England, and northern Spain.[10] Outside of Europe, the Z mutation is found at high levels in countries where it was introduced by European migration, including the United States, Australia, and New Zealand.[9,11] Z gene frequency varies across African nations, but, on average, is approximately half of that seen in the United States; the frequency is significantly lower in other parts of the world, including China, South Korea, and Japan.[11,12]

The overall prevalence of the Pi*ZZ phenotype has been estimated from population-based studies. A screening study of 200,000 newborns in Sweden in 1972–1974 demonstrated a prevalence of 1 in 1600 newborns.[13] Studies in U.S. populations have estimated a prevalence ranging from 1 in 2857 to 1 in 5097.[14–16] Based on sampling of limited numbers of patients, the Pi*ZZ phenotype is estimated to account for 1% to 4.5% of cases of COPD in the United States.[3,4,6,7]

PATHOPHYSIOLOGY

Mechanisms responsible for the development of lung or liver disease resulting from AATD have been extensively studied (Fig. 39-1), and an understanding of these mechanisms continues to evolve as modern molecular methods and animal models of disease improve.[17–19]

Liver hepatocytes express and secrete the highest levels of α1-antitrypsin protein and, consequently, are the predominant source of circulating AAT. As the name of the protein implies, AAT functions as a serine protease inhibitor (serpin) with numerous antiprotease activities, including antitrypsin and antineutrophil elastase functions.[17,20,21] AAT is found in nearly all body fluids, including saliva, tears, breast milk, urine, and semen, with concentrations in bronchoalveolar lavage fluid reaching approximately 10% of those in the circulation.[22–26] Since AAT is found in lung tissue and is considered the major antielastase of the lower respiratory tract, these observations serve as the foundation of the hypothesis that secreted AAT from hepatocytes circulates to lung tissue, where its primary function is to protect lung matrix molecules, such as elastin, from degradation by unrestrained local leukocyte-derived proteases and elastases.[19,20,27] Deficient AAT circulating levels or incomplete antiprotease activity is postulated to result in protease–antiprotease imbalance in the lung and degradation of lung elastin over time due to overexuberant activity of elastase and other serine proteases.[27] In patients with cirrhosis due to AATD who receive liver transplantation from a normal (PiMM) donor, circulating levels of AAT are normalized,[28] consistent with hepatocytes serving as the predominant source of circulating AAT.

Multiple mechanisms in AAT-deficient individuals are responsible for both the abnormally low circulating blood levels of AAT and diminished antiprotease activity; each type of AAT mutation contributes uniquely to one or both perturbations. Mutant Z-AAT protein has been most extensively studied using patient specimens, heterologous cell lines engineered to express a cDNA encoding the human Z mutant protein, or a variety of animal models.[29–34] These studies reveal that in contrast to the normal M-AAT, which is translated and secreted as a protein monomer, Z mutant protein displays posttranslational misfolding, intracellular mistrafficking, delayed protein processing, and polymerization with other Z mutant protein polypeptides, resulting in intracellular accumulation and significantly diminished and delayed extracellular secretion.[19,34–38] The intracellular accumulation of polymerized Z protein in hepatocytes results in activation of a variety of cellular stress pathways, including ER stress, leading to hepatotoxicity and increased risk of neonatal jaundice, juvenile cirrhosis, or adult cirrhosis that is well described in individuals with PiZZ AATD.[37,39] Further exacerbating the diminished antiprotease activity that results from low levels of secreted AAT, the Z mutation also compromises the antiprotease activity of the protein itself.[19]

It is well accepted that two Z alleles result in highly polymeric AAT polypeptides, and recent reports suggest polymerization can also occur extracellularly with detectable polymers, derived from the liver, found circulating in the blood stream, or deposited in nonhepatic tissues of individuals with PiZZ AATD.[40] Less common AATD mutations (such as PiS) do not appear to be polymeric and, thus, are associated with less risk of liver disease. The presence of a single Z allele (e.g., PiMZ or PiSZ) has been shown sufficient to form polymeric AAT protein,[40] and it is well established that all genotypes with a single Z allele exhibit lower circulating serum levels due to diminished hepatic secretion.[18,19,38,41,42]

Accumulating studies in recent years have added complexity to the original and relatively simple hypothesis that COPD pathogenesis in the setting of AATD is due solely to protease–antiprotease imbalance resulting from low and ineffective levels of hepatocyte-derived

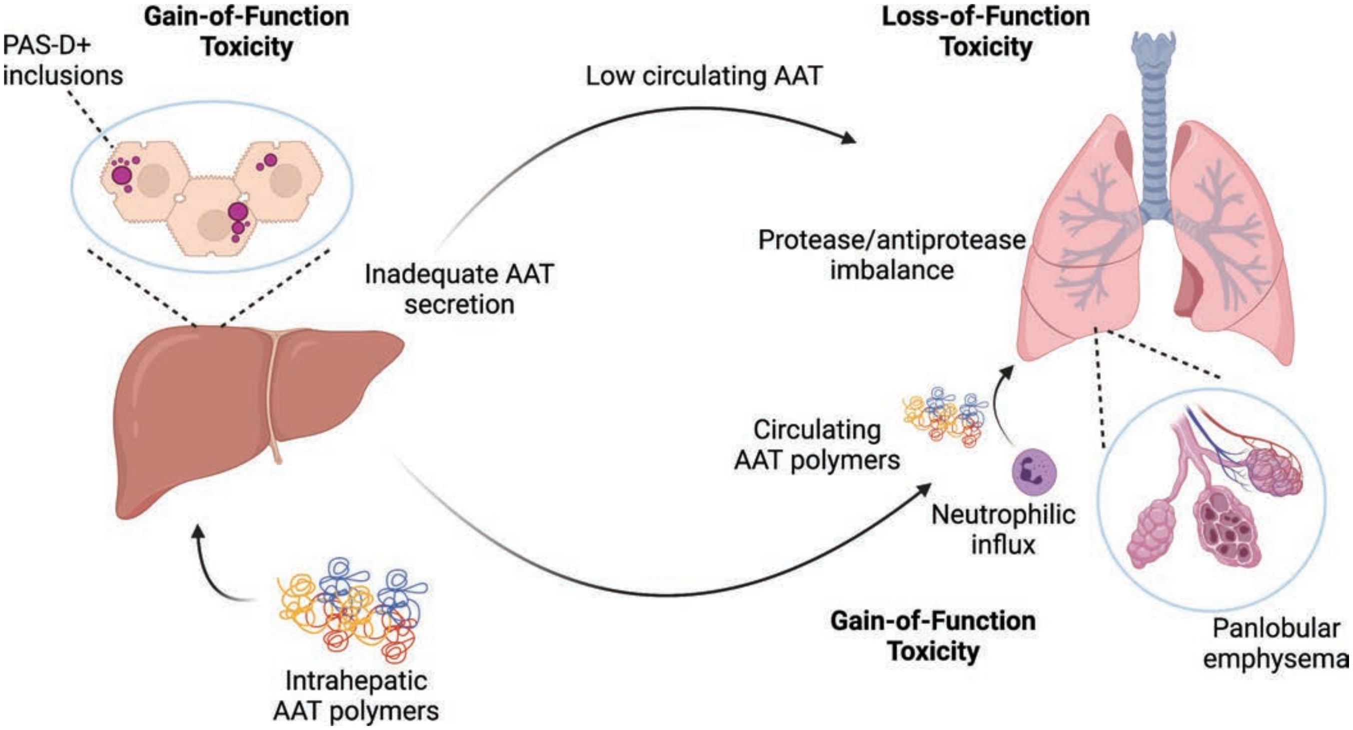
Gain-of-Function Toxicity
PAS-D+ inclusions
Low circulating AAT
Loss-of-Function Toxicity
Protease/antiprotease imbalance
Inadequate AAT secretion
Circulating AAT polymers
Neutrophilic influx
Gain-of-Function Toxicity
Panlobular emphysema
Intrahepatic AAT polymers

Figure 39-1 Pathophysiology of liver and lung disease in AATD. Misfolded Z-AAT protein forms polymers in the endoplasmic reticulum of hepatocytes, causing injury through a gain-of-toxic-function mechanism. Intrahepatic inclusions of polymerized Z-AAT protein stain positive with periodic acid–Schiff stain but are resistant to digestion with diastase (PAS-D). Poor hepatic Z-AAT secretion leads to low circulating and tissue AAT levels. Z-AAT polymers in the circulation and lung interstitium are chemoattractant for neutrophils, which are found at increased levels in the lung of PiZZ patients. Together, gain-of-function and loss-of-function mechanisms contribute to an imbalance of protease and antiprotease activity in the lung leading to tissue damage and emphysema.

circulating AAT protein. In addition to its primary role in protease inactivation, numerous investigations demonstrate that AAT exerts both anti-inflammatory and immunomodulatory effects in a variety of conditions and cell types—in some cases, independent of its antiprotease activity.[43–46] Both loss of normal M-AAT anti-inflammatory activity,[43] and gain of pro-inflammatory activities resulting from the presence of Z mutant polymeric protein deposits in tissues, combine to activate potentially destructive lung inflammation.[40,47] Effects on activation and trafficking of multiple immune cell types have been documented, including neutrophils,[48] mast cells,[49] macrophages,[50] and T cells.[51]

Additional studies further support anti-inflammatory and anti-apoptotic effects of normal M-AAT protein. Reports of organ ischemia or cigarette smoke exposure have demonstrated attenuation of neutrophilic infiltration of the kidney, liver, and lung,[52–55] as well as reduction in cell death due to simulated myocardial infarction[56] in the setting of supplementation with exogenous AAT. Collectively, these studies have demonstrated direct antiapoptotic effects of AAT, as well as inhibition of caspases[54,57,58] and anti-inflammatory effects characterized by attenuation of increases in local or systemic TNF-α. Similarly, in animal lung transplant models, treatment with AAT reduced ischemic-reperfusion injury by inhibiting neutrophilic infiltration of the lung, together with reductions in cytokines, including IL-1α, IL-4, IL-12p70, MCP-1, and TNF-α.[44,59]

In contrast to the anti-inflammatory activity of normal M-AAT, the polymeric form of Z mutant AAT is proinflammatory, resulting in cellular toxicity, leukocyte activation, and cytokine release.[60,61] Studies using animals engineered to overexpress human Z protein have found evidence of cellular toxicity or intracellular proteostatic effects in non-hepatic tissues including the lung.[43,62,63] For example, lung epithelial ER stress and dysregulation of autophagy have been found in PiZ transgenic mice.[64] These observations have raised the possibility that misfolded, polymeric AAT protein might also cause toxic gain-of-function effects in lung tissue, as has been established in hepatocytes. In the setting of true null mutations, no AAT protein is produced by the liver or any other lineage. Therefore, elevated COPD risk, without hepatotoxicity, is thought to result solely from low circulating AAT levels and diminished lung antiprotease activity.[65]

Further complicating matters, an increasing number of cell lineages are now recognized as expressing and possibly secreting AAT. While hepatocytes are the main source of circulating AAT, approximately 20% of the total is produced by other AAT-producing cell types—a list that includes monocytes and macrophages, in addition to epithelial cells of the lung, kidney, intestine, pancreas, thymus, adrenal gland, ovary, testis, and corneum.[66–73] The function of normal AAT in these lineages remains poorly understood, but a nascent literature implicates some of these alternate lineages as contributing to disease pathogenesis in AATD settings, for example, through activation of leukocytes.[74,75] Mobilization of bone marrow–derived hematopoietic populations also may be impacted as a result of AATD, since mouse models indicate that local bone marrow AAT functions to precisely regulate proteolytic release of tethered hematopoietic progenitors from their bone marrow niche.[76] It remains unclear, however, whether AAT activity in the bone marrow plays any role in AATD-related lung disease.

In summary, a broad published literature and clinical observations indicate that loss-of-function AAT mutations contribute to COPD pathogenesis in patients with AATD. For example, patients with rare null mutations are at significantly increased risk of developing COPD,[65] and mice engineered through gene editing to have deletions in AAT-encoding genes are significantly more susceptible to spontaneous (age-related) or smoke-induced emphysema.[77] More recent and still evolving literature also suggests that beyond simple loss of function, a subset of mutant AAT proteins, such as Z-AAT, likely also contributes to pathogenesis of COPD through toxic gain-of-function mutations involving protein misfolding, accumulating of polymers, and a variety of potential inflammatory and cytotoxic mechanisms.

CLINICAL MANIFESTATIONS

Patients with AATD-associated COPD present with symptoms that mirror those of the non-AATD population with COPD, including progressive dyspnea, hypoxemia, cough productive of sputum, and wheeze in the context of viral respiratory infection.[78] These similarities can make it challenging to distinguish the two populations. A typical patient with AATD experiences respiratory symptoms for years and seeks evaluation by multiple physicians prior to the diagnosis of AATD.[79,80] Early onset of symptoms in the fourth or fifth decade of life and disease out of proportion to exposure history are common historic characteristics of patients with AATD-associated COPD.[33,81] Features of the family history can be suggestive; a history revealing multiple family members with diagnoses of liver disease or COPD should increase suspicion.

Classically, patients with AATD-associated COPD manifest panlobular, lower-lobe emphysema, distinct from the upper-lobe-predominant, centrilobular emphysema typical of non-AATD COPD.[82,83] However, a variety of other clinical and radiographic presentations are common among patients with AATD-associated COPD. Case series reviewing radiographic patterns of PiZZ AATD-associated disease found that only 20% of plain chest x-rays[82] and 64% of chest CT scans[84] exhibited a basilar distribution of emphysema. Reliance on this classic radiographic presentation as the basis for testing to diagnose AATD is, therefore, insensitive and misses a large proportion of affected individuals.[85]

Aside from emphysema, bronchiectasis is the most common radiographic abnormality observed in PiZZ AATD. Reported frequency of clinically significant bronchiectasis is variable in the literature and ranges from as low as 2% of 1129 participants in the NHLBI registry to as high as 27% of 74 study participants whose lung disease was characterized by CT scan.[86] Although speculative, it seems likely that the increased clinical use of cross-sectional imaging, combined with increasing resolution capabilities of CT scanners, results in increased detection of bronchiectasis in PiZZ AATD.

Patients with PiZZ AATD commonly experience a progressive decline in FEV_1 that can occur at a rate faster than in individuals with non-AATD-associated COPD. Aggregate data from several large longitudinal cohort studies suggest a mean decline in FEV_1 of 41 to 86 mL/year among PiZZ former or never former smokers.[87–89] This decline was higher at 70 to 132 mL/year for current smokers in the same studies, consistent with exquisite sensitivity of PiZZ individuals to cigarette smoke injury. The value of smoking cessation in this population is supported by data from the Danish AAT Deficiency Registry, in which FEV_1 decline among those who quit smoking during the study period was measured at 58 mL/year compared with 132 mL/year among those who continued to smoke.[89] Predictors of accelerated FEV_1 decline among individuals with the PiZZ genotype include male sex, age range 30 to 44 years, active smoking, bronchodilator responsiveness, and mean predicted FEV_1 of 35% to 79%. Occupational or environmental exposure to pollutants also have been identified as risk factors for accelerated lung function decline.[90,91]

Aside from lung disease, the primary organ affected in AATD is the liver, where injury manifests either as jaundice among neonates, or as fibrosis in adults; a subset progress to cirrhotic liver disease. Neutrophilic panniculitis, seen in fewer than 1% of Pi*ZZ patients, can cause erythematous, tender subcutaneous nodules.[92] Other conditions associated with AATD include ANCA-associated vasculitis,[93] glomerulonephritis,[94] and chronic kidney disease.[95]

NATURAL HISTORY AND PROGNOSIS

Data from the Swedish National Registry provide insight into the longevity of individuals with PiZZ. Of 568 PiZZ never-smokers followed in this cohort, 93 had died at the time of analysis, with a median age of death of 76 years,[96] consistent with a relatively normal life expectancy. Within this never-smoking population, a higher mortality rate was observed among individuals in whom AATD was identified on the basis of respiratory symptoms than in those identified through screening, whose mortality rate was similar to that of the general population. Of these 93 participants, the underlying cause of death was identified as emphysema in 42 (45%), despite their status as never-smokers, whereas 26 (28%) died due to complications of liver disease. These findings differ to a degree from those observed in the NHLBI registry, in which 72% of deaths among 204 decedents, of whom only 16 were never-smokers, resulted from emphysema and associated respiratory failure compared to 10% from cirrhosis.[97] A third study of Swedish PiZZ adults identified respiratory failure as the primary cause of death in approximately 60% of 91 deaths, with liver disease accounting for 13%.[98] Mortality rates are not equally distributed among all those with PiZZ and are higher among smokers,[99] those with lower FEV_1,[97,100] and those identified on the basis of respiratory symptoms.[99]

Among patients with Pi*ZZ AATD, the risk of developing emphysema is quite high, although the precise risk is unknown. Of 42 NHLBI registry participants with lung tissue available for review following either autopsy or lung transplant, 100% were found to have emphysema.[101] In another study, 119 consecutive Pi*ZZ patients were evaluated in clinical practice; 17 (14%) did not have significant emphysema based on CT densitometry measurements,[84] consistent with the concept that a subset of Pi*ZZ individuals might not be afflicted. Notably, however, the mean age of these 17 individuals was only 44 years, leaving open the possibility that they eventually might develop disease.

The relative risk of Pi*Z heterozygotes, who represent a considerable percentage of the U.S. Caucasian population, has historically been uncertain. PI* SZ heterozygotes, in particular, were previously thought to be at increased risk of lung damage and were routinely offered augmentation therapy in the United States. Emerging data, however, suggest otherwise. Franciosi et al., in a prospective, observational, family-based study, reported no differences in either spirometry or symptom scores between non-index case, never-smoker individuals with Pi*SZ, and family member controls with Pi*MM or Pi*MS.[102] Zero of 19 Pi*SZ never-smokers in this study were found to have CT-based emphysema, suggesting that a single Z allele does not commonly cause disease in the absence of an environmental insult. Cigarette smoking was associated with worse spirometric outcomes in Pi*SZ ever-smokers relative to controls, although smoking cessation appeared to attenuate the accelerated decline. Intriguingly, emphysema in PI*SZ ever-smokers was noted to occur in an upper-lobe distribution, suggesting a pathophysiology distinct from Pi*ZZ AATD.

Additional data paint a similar picture for Pi*MZ heterozygotes. A family-based, prospective observational study by the investigators who authored the PI*SZ study described above found no differences between never-smoker, non-index Pi*MZs, and Pi*MM controls. Among ever-smokers matched for either high (>20 pack-years) or low (<20 pack-years) levels of smoke exposure, Pi*MZs had worse spirometric outcomes relative to controls.[103] Pi*MZ heterozygosity was associated with an adjusted odds ratio for COPD of 5.18. Additional data derived from 1693 non-Hispanic, white participants of the SPIROMICS cohort (all 40–80 years old with a ≥20-pack-year smoking history) demonstrated that white Pi*MZ heterozygotes had lower lung function, worse spirometric obstruction, and more CT-based emphysema than white Pi*MMs.[104]

In aggregate, the literature suggests that among ever-smokers, Pi*Z heterozygotes as a group are at increased risk of lung disease compared with Pi*MM individuals, consistent with a gene × environment interaction in which ongoing environmental exposure is necessary to induce disease.

DIAGNOSIS

Current clinical guidelines recommend one-time testing of all patients with persistent spirometric airflow obstruction, regardless of age or disease severity.[105–107] In addition to COPD, respiratory presentations that should prompt consideration of testing for AATD include emphysema in the absence of airflow obstruction and a family history of lung or liver disease.

Laboratory testing to diagnose AATD includes evaluation of levels of AAT protein in the serum, identification of AAT protein variants, or testing for variant gene sequences.

Serum AAT levels, most commonly measured by nephelometry, quantify the amount of AAT protein in the serum. A threshold level of 24.4 μM/L (110 mg/dL) distinguishes Pi*MM proteins from protein combinations including at least one S or Z with 73.4% sensitivity and 88.5% specificity.[108] However, because a variety of AAT allele combinations can result in serum AAT ranges with significant overlap, testing for serum AAT levels in isolation frequently does not allow one to infer the patient's phenotype/genotype. Since AAT is a known acute-phase reactant, with serum levels rising in the setting of systemic inflammation, interpretation of testing based solely on serum levels may be limited, particularly if these tests are performed in the setting of active infections or other inflammatory insults.[109,110]

Protein phenotyping to identify specific AAT variant proteins based on their migration pattern by isoelectric focusing can be a useful modality to diagnose or exclude AATD. Phenotyping can be used to identify rare variants that might be missed by PCR-based genotyping. However, the technique can be challenging to interpret in the context of null alleles or alleles that generate similar migration patterns (e.g., M-like alleles may produce a protein pattern similar to M protein).[111]

Detection of gene variants that encode deficient AAT proteins is an increasingly employed testing approach. Most commonly, targeted genotyping using PCR or RFLP analysis is performed to test for the normal M allele, together with a panel of common pathogenic variants. Rare alleles are generally not tested for and, therefore, are not detected using this approach. Gene sequencing, capable of identifying null alleles and other rare variants, can be a useful adjunct modality and is most commonly applied when the clinical presentation, reported AAT level, and genotype or phenotype are incongruent.[111]

Physician practice has lagged behind screening guidelines recommending the testing of all patients with obstructive lung disease[80,112] for AATD. This fact, together with the large size of the screenable population, suggests the need for an approach that maximizes cost effectiveness. A variety of testing algorithms have been evaluated with this goal in mind.[111] Common screening approaches outlined include testing of AAT levels, either alone or in combination with targeted genotyping. Protein phenotyping and DNA sequencing in these reports were subsequently applied if AAT levels were found to be low or if Z or S alleles were identified by genotyping.

MANAGEMENT

Medical management of AATD-related COPD is similar to management of other forms of COPD,[105] including a focus on avoidance of smoke exposure, treatment of hypoxemia, use of inhaled bronchodilators and inhaled glucocorticoids, referral for pulmonary rehabilitation, consideration of lung transplantation in those with severe COPD, and adherence to standard vaccine guidelines (Chapter 40). A significant difference from usual COPD management is consideration of genetic counseling and screening of family members for inherited AATD, as well as specific attention to the deficiency in circulating AAT in those with declining lung function.[19,105] An attempt to correct the hypothesized protease–antiprotease imbalance associated with deficient AAT levels and declining lung function forms the basis of the predominant treatment approach specific for AATD-associated COPD, so-called augmentation therapy. With augmentation therapy, levels of circulating AAT and antiprotease activities are augmented through regular intravenous infusions of normal (M) AAT protein purified from pooled human plasma specimens.[105,113]

Secreted AAT protein circulates with an average concentration of 150 to 300 mg/dL in blood plasma and a half-life of approximately 5 days.[20,37,114] In the most common deficiency state, PiZZ, circulating AAT levels are reduced to 10% to 15% of normal.[37] Several dosing approaches have been pursued in an effort to augment circulating levels in those with progressive loss of lung function due to AATD. Clinical trials have demonstrated variable results.[105,107,113,115–126]

Rather than normalizing circulating levels, the goal of augmentation therapy is to increase deficient levels to a concentration above a protective threshold. Those with treatment criteria, including severely deficient circulating AAT levels (serum levels <11 μmol/L or <57 mg/dL) and evidence of airflow obstruction, qualify for the U.S. Food and Drug Administration (FDA)-approved treatment regimen of weekly intravenous infusions of pooled human plasma-derived AAT at a dose of 60 mg/kg body weight.[105] The global initiative for COPD (GOLD) guidelines suggest patients with AATD with an FEV_1 of 35% to 65% of normal qualify for augmentation therapy,[127] whereas American Thoracic Society guidelines indicate that patients with AATD and an FEV_1 <80% are suitable candidates.[2] Some guidelines suggest evidence of emphysema on CT scan also should prompt consideration for augmentation therapy for AATD.[105]

Data in support of the clinical efficacy of augmentation therapy include randomized clinical trials, as well as longitudinal cohort follow-up studies, registry analyses, and meta-analyses focusing on outcomes such as AAT serum levels, lung function, and lung density on CT; mortality data are more limited.[105,107,113,115–126] For example, a systematic review and meta-analysis performed on data from trials performed prior to 2009 that included a cumulative total of 1509 patients concluded that augmentation therapy slowed FEV_1 decline in COPD; those with moderate airflow obstruction appeared to benefit most.[128]

In a randomized, double-blind, placebo-controlled trial of intravenous augmentation treatment in severe α1-antitrypsin deficiency (RAPID), rates of CT lung density decline were compared between 93 individuals on augmentation therapy versus 87 receiving placebo.[115] There was no statistically significant difference in the co-primary endpoint of CT density assessed at both FRC and TLC combined; however, there was significantly less annual decline in lung density in the treatment group based on CT densitometry measured at TLC, lending support to the conclusion that augmentation therapy slows the progression of emphysema in individuals with severe AATD.

In an open-label extension of the same trial (RAPID-OLE), the long-term efficacy and safety of augmentation therapy for emphysema caused by severe AATD was reported based on continued treatment of 76 participants from the original treatment group (early start group) and 64 participants from the placebo group (late start group with therapy delayed by 2 years compared with the early group).[129] The rate of lung density loss was less in the early-start treatment group. Furthermore, the rate of loss in the delayed treatment group slowed after the initiation of delayed therapy, although previously lost lung density was never recovered.

Support for the clinical efficacy of augmentation therapy is also provided by additional observational studies that suggested beneficial effects on survival and lung function. For example, a retrospective analysis of NHLBI's Alpha-1 Antitrypsin Deficiency Registry found that augmentation therapy improves survival in severely deficient patients with predicted FEV_1 between 10% and 60%.[118] Another study also found a significantly reduced rate of FEV_1 decline in a German cohort of former smokers with AATD receiving augmentation therapy compared with a Danish cohort of former smokers who did not receive therapy over a 3.2-year average follow-up period.[123] Finally, an additional study comparing rates of decline in FEV_1 in individuals followed longitudinally before and after they began augmentation therapy concluded that treatment significantly slowed the loss of FEV_1 in severe AATD.[130]

While the majority of studies finding beneficial efficacy involve the FDA-approved standard weekly intravenous dosing of 60 mg/kg pooled human plasma-derived AAT, alternative regimens, such as increased time intervals or increased dosing regimens, have been reported.[113,117,121] Based on a recent pilot study,[117] doubling the dose of augmentation therapy was found to be safe and to have potentially more anti-inflammatory effects; effects on clinical efficacy were indeterminate.

The optimal timing of initiating augmentation therapy also has been debated, with compelling arguments made for the use of CT scans to detect loss of lung function in patients with AATD earlier than would be discovered by physiologic testing or chest radiographs. Presumably, augmentation therapy would be started prior to significant and irretrievable loss of lung function.[113]

Whether augmentation therapy reduces COPD exacerbation events remains uncertain, based on mixed results from clinical trials, such as the RAPID trial,[115] which found no reduction in exacerbation rates; other studies found augmentation therapy was associated with reduced exacerbations.[131] Acute exacerbations of AATD-related COPD have been reported by some to differ from usual COPD exacerbations, as evidenced by greater frequency and duration of symptoms;[132] however, the extent and consequence of this is not known. Accordingly, conventional COPD treatments are used to treat exacerbations in patients with AATD, despite a paucity of evidence evaluating their efficacy.[132]

As with other forms of severe COPD, referral for lung transplant evaluation should be pursued in those with AATD-related severe and progressive COPD. Posttransplant survival has been studied in recipients with AATD compared to other forms of COPD[133] and was found to be similar, at least in the era since the use of lung allocation scores. In addition, a longitudinal study of patients with COPD following lung transplant[134] found that posttransplant FEV_1 over time, severity of acute rejection, and survival were similar overall in patients with AATD compared with AAT-replete patients. A notable exception were those who received double lung transplants, where FEV_1 declined faster in those with AATD, suggesting that further studies may be needed to compare outcomes in those with AATD receiving single versus double lung transplants.

Some studies have attempted to determine whether there is a beneficial role for augmentation therapy post–lung transplantation in AATD transplant recipients,[135,136] but efficacy of this approach remains uncertain. Since several decades typically elapse before loss of lung function is clinically significant in PiZZ AATD individuals, it remains speculative as to whether prolonged, transient, or episodic augmentation therapy post–lung transplantation is indicated to preserve function of the new graft in AATD transplant recipients. Thus, augmentation therapy is not currently routinely prescribed post–lung transplantation, since it is costly and lacks proven efficacy; furthermore, decisions regarding continuation versus cessation of augmentation therapy post-transplant are individualized and based on expert consultation, given the paucity of available data.

A number of emerging therapeutic options using novel technologies are being actively pursued for potential future use in patients with AATD.[137,138]

Inhaled augmentation therapy has been evaluated in several clinical trials, but clinical efficacy remains uncertain to date.[139–142]

Numerous gene therapy trials have been attempted to correct the loss of function associated with the most frequent mutations responsible for AATD.[143] In mouse models, adeno-associated virus (AAV)-based vectors for episomal overexpression of human cDNA encoding M-AAT have been successfully deployed by in vivo injection or infusion to liver hepatocytes or large muscle beds, resulting in prolonged in vivo secretion into the circulation from cells in the transfected target tissue.[144–148]

Additional proof-of-concept studies using intratracheally delivered local lentiviral overexpression in resident alveolar macrophages in mouse lungs have resulted in secretion of M-AAT into the lung epithelial lining fluid in vivo, ameliorating elastase-induced emphysema in mice.[32]

Despite the promise of gene therapy tests in animal models, in human clinical trials intramuscular injections of AAV vectors have resulted only in low circulating M-AAT levels, far below the therapeutic threshold thought to be needed for efficacy in patients.[144,149,150] Newer AAV-based vectors or RNA interfering molecules have been designed to knock down expression of mutant Z-AAT in liver hepatocytes while either overexpressing M-AAT cDNA from the same hepatocytes or replacing circulating M-AAT with intravenous augmentation therapy.[145] These emerging therapies are being studied in ongoing or planned clinical trials,[151] but to date, gene and RNAi based therapies for AATD remain experimental.

With the recent emergence of gene editing technologies, such as zinc finger nucleases, TALENs, or CRISPR, the possibility of correcting AAT gene mutations to normal in the endogenous AAT gene locus in patient-specific cells has been demonstrated.[137] Induced pluripotent stem cells have been generated from patients with AATD,[152–155] and successful gene editing of these cells from Z to M genotypes has been demonstrated, followed by in vitro differentiation of the corrected stem cells into hepatocytes for transplantation into animal models.[137] More recently, in vivo gene editing of AAT encoding loci in vivo in mouse livers has been successfully demonstrated.[156] These new and emerging proof-of-concept animal studies provide hope that innovative and potentially curative gene editing strategies to correct AATD in humans may be feasible in the future.[138]

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CHAPTER 40

Course and Treatment of Chronic Obstructive Pulmonary Disease

M. Bradley Drummond
Robert A. Wise

INTRODUCTION

In past decades, the treatment of chronic obstructive pulmonary disease (COPD) has been approached by many physicians and patients alike with a nihilistic attitude, assuming that the disease was progressive, incurable, and untreatable. More recently, as our understanding of the clinical epidemiology and value of therapy of COPD has improved, this attitude has changed. Physicians have come to approach COPD in the same way as other chronic diseases with goals of improving quality of life, functional capacity, and prolonged survival. With a comprehensive approach to treatment, COPD is compatible with prolonged survival, good quality of life, and independent functional status for many who have this illness. The purpose of this chapter is to summarize the current understanding of the course of COPD and best approaches to treatment.

OVERVIEW OF COPD

COPD is a disorder that is characterized by slow emptying of the lung during a forced expiration. In practice, this is measured as the forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) ratio, and the arbitrary definition of airflow obstruction is generally taken to be an FEV_1/FVC ratio lower than 0.70.[1] Because the rate of emptying of the lung falls with advancing age, many elderly individuals demonstrate airflow obstruction even in the absence of a clinical diagnosis of COPD. For this reason, an alternative criterion to define airflow obstruction incorporates lower limit of normal thresholds instead of the fixed ratio criteria.[2] Several disorders cause chronic airflow obstruction—long-standing asthma, cystic fibrosis, bronchiectasis, bronchiolitis obliterans, lymphangioleiomyomatosis, panbronchiolitis, silicosis, Sjögren syndrome, and diffuse interstitial processes such as eosinophilic granuloma and sarcoidosis. The diagnosis of COPD is usually limited to individuals who have chronic airflow obstruction associated with tobacco smoke or some other noxious inhalant, and it is usually not difficult to distinguish it from other causes of chronic airflow obstruction. The most common disorders associated with COPD are emphysema and chronic bronchitis. *Emphysema* is defined anatomically by airspace enlargement due to disappearance of alveolar septae (Chapter 37). This leads to the characteristic loss of elastic recoil, which, in turn, causes slowing of airflow from the lungs, hyperinflation, and air trapping. *Chronic bronchitis* is characterized by chronic cough and sputum production, which is present in about one out of three people with early COPD. Chronic cough and sputum production in cigarette smokers is often, but not always, associated with chronic airflow obstruction. When chronic mucus hypersecretion is associated with airflow obstruction, it is often called *chronic obstructive bronchitis*. Although people with nonobstructive mucus hypersecretion (nonobstructive chronic bronchitis) have a greater risk for acute respiratory illness, most such individuals will not progress to airflow limitation, and therefore, the term "pre-COPD" should be avoided.[3] It is unknown whether maintenance treatment of nonobstructive chronic bronchitis is beneficial. The anatomic correlates of chronic bronchitis are mucus gland hyperplasia and goblet cell metaplasia in large- and medium-sized airways.[4] Patients with COPD also have small- and medium-sized airway involvement with inflammation, narrowing, tortuosity, mucus plugging, and fibrosis that contributes to the airflow limitation. As the disease evolves, there is obliteration of small airways. Some patients with a long-standing history of asthma develop airflow obstruction that is not completely reversible, episodes of cough and wheeze, and chronic sputum production. These individuals are often classified as having *chronic asthmatic bronchitis* and have a better prognosis for survival than those with tobacco-related COPD.

NATURAL HISTORY OF COPD

COPD occurs in middle age and later because of the age-related decline in lung function over time. Typically, peak lung function occurs during the third or fourth decades of life. Healthy nonsmoking adults lose FEV_1 at a rate of 30 mL/year, thought to be the consequence of the aging-related loss of elastic recoil of the lung. Persons who develop COPD may start in early adulthood with low levels of lung function or with a normal rate of decline or may have normal young adult lung function and have increased rates of decline.[5,6] Studies of patients with COPD show an average annual decline in FEV_1 of 45 to 69 mL/year (Fig. 40-1A). However, there may be considerable heterogeneity between patients and over time.[7,8] This leads to the insidious loss of ventilatory reserve capacity that often is asymptomatic and unrecognized by patients and physicians alike. Chronic bronchitis may be dismissed as an innocent "smoker's cough" because patients fail to understand that it is abnormal to produce daily sputum. As ventilatory reserve decreases, people with mild COPD tend to limit strenuous activities, so breathlessness with activities of daily living is not ordinarily an early symptom of the disease. When the ventilatory reserve decreases to the extent that mild exertion such as climbing stairs, bed making, or carrying groceries is limited, patients tend to seek medical advice. In some cases, the first clinical presentation of disease is an acute episode of bronchospasm, dyspnea, or even respiratory failure in association with a respiratory infection or exposure to respiratory irritants. Thus, the onset of COPD may appear precipitous even though it is the cumulative result of decades of progression.

People who discontinue smoking with mild to moderate degrees of airflow obstruction cease the rapid decline in FEV_1 and have better survival (Fig. 40-1B).[9,10,11] The improvement in survival depends largely upon the stage of disease. Persons who quit smoking with earlier disease have better outcomes compared with those who continue to smoke or those who quit smoking later in the disease. Once the disease is advanced, the inflammatory response may persist, and the proportional loss of lung function tends to progress. Because there are many years of asymptomatic decline in lung function, it is possible to diagnose COPD with forced expiratory spirometry before the disease is apparent and implement aggressive smoking intervention programs. There is a consensus that smokers with respiratory symptoms should be tested for COPD with spirometry. However, there is debate whether it is of value to screen for COPD among all cigarette smokers.[12] Opponents of using spirometry for case-finding argue that the finding of a normal test would not alter physician behavior because all smokers should be encouraged to quit. It has also been argued that a normal spirometry test might provide a false sense of complacency for active smokers. Those who support the use of spirometry for COPD case-finding argue that early detection and aggressive smoking intervention have been

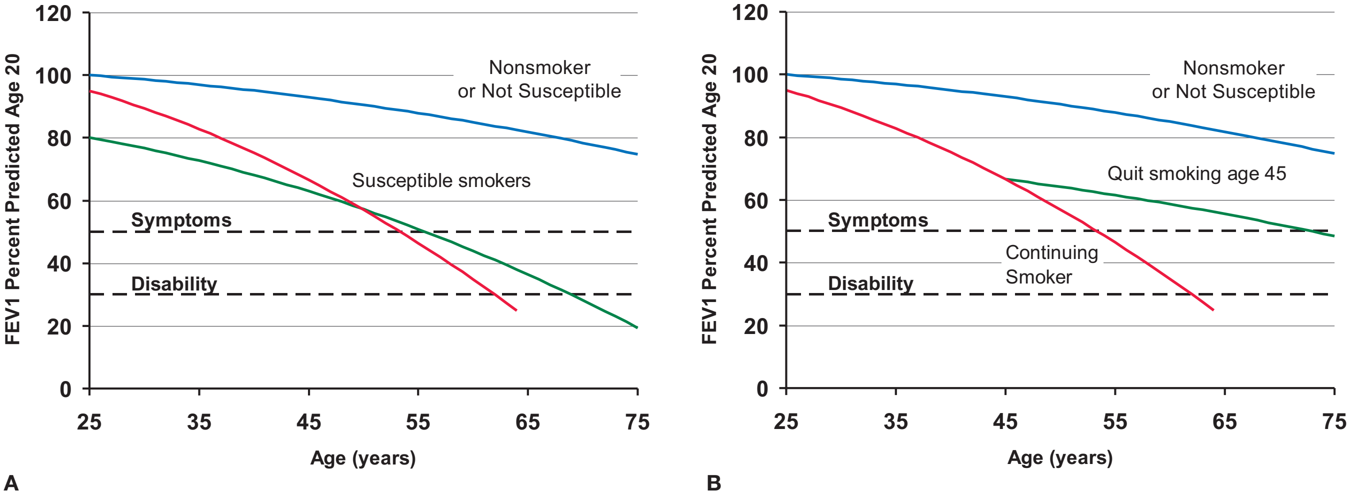

Figure 40-1 **A.** The natural history of COPD is presented for three hypothetical individuals. Pulmonary function is plotted as the percent of predicted lung function for a young adult who has attained maximal lung growth. Those who do not smoke or are not susceptible to cigarette smoke typically lose about 25% of their young adult lung function throughout life. Individuals are susceptible to the adverse effects of smoking because of increased decline of lung function, or low lung function in young adult life. Although the abnormality of lung function is detectable for many years, symptoms do not develop until there is loss of approximately 50% of lung function *(upper dashed line)*, which occurs in middle age or later. If the disease progresses, it may lead to substantial disability within a decade of the onset of symptoms *(lower dashed line)*. **B.** The natural history of COPD is displayed for a hypothetical continuing smoker, and an individual who quit smoking at age 45. The axes are identical to those in (**A**). If an individual cease smoking in the asymptomatic phase of COPD, the rate of decline of lung function reverts toward normal. In this example, the detection of abnormal lung function and cessation of smoking has a substantial effect of delaying the onset of respiratory symptoms. This plot is modified from the work of Fletcher and Peto and is commonly referred to as Fletcher-Peto curves.

proven to halt disease progression and improve survival, and the finding of abnormal spirometry may encourage patients and healthcare professionals to be more aggressive with smoking cessation. Moreover, some evidence points to the benefits of drug therapy in terms of lung function decline and survival in patients with mild to moderate airflow obstruction.[13–15]

With the progression of COPD comes progressive exercise limitation.[16] This is due to the increased work of breathing as ventilation increases with exercise. With increased respiratory rate, patients develop dynamic hyperinflation—a condition in which the end-expiratory lung volume does not return to the static end-expiratory volume of functional residual capacity (FRC). The hyperinflation that occurs causes increased work of breathing and exacerbates dyspnea. An indicator of dynamic hyperinflation is the inspiratory capacity (IC), which progressively falls with increasing ventilation. Measures that reduce dynamic hyperinflation, increasing IC, can improve exercise capacity. These include alterations in breathing pattern, oxygen supplementation, and use of inhaled bronchodilators. Similarly, episodes of anxiety can lead to tachypnea that induces dynamic hyperinflation and exacerbates the experience of dyspnea at rest. These episodes can often be minimized by explanation of the phenomenon to the patient and caregivers as well as judicious use of self-relaxation, pursed-lip breathing, and anxiolytics.

As COPD progresses, ventilation–perfusion inhomogeneity causes an increase in the alveolar–arterial oxygen difference. Eventually, alveolar hypoxemia leads to pulmonary hypertension, which manifests as cor pulmonale. The alveolar hypoxemia may be compounded by alveolar hypoventilation—manifested by arterial hypercapnia. Physical findings indicative of cor pulmonale are venous engorgement, edema, and physical findings of pulmonary hypertension and right ventricular failure including elevated venous pressure, accentuated pulmonic second heart sound, right ventricular heave, tricuspid regurgitation murmur, hepatojugular reflux, and ascites. Chest imaging shows central enlargement of the pulmonary arteries. Once cor pulmonale is clinically apparent, survival is markedly reduced in proportion to the impairment of functional capacity.

Patients with advanced COPD may restrict their activities to a bed-and-chair lifestyle because of severe exercise incapacitation. This limitation can lead to social isolation, depression, and skeletal muscle deconditioning, which, in turn, further restrict activity and impair quality of life. Protein and calorie malnutrition occur as the consequence of impaired nutritional intake caused by dyspnea.[17] Malnutrition is augmented by increased metabolic demands caused by increased basal oxygen consumption, inefficient skeletal muscle oxygen utilization, and cachexia-producing cytokines such as tumor necrosis factor α (TNF-α).[18]

DIAGNOSIS OF COPD

Physical examination and chest imaging are insensitive methods for diagnosis of COPD. Physical findings of hyperinflated lungs such as low-lying diaphragm, decreased breath sounds, and hyperresonant chest percussion are highly specific for COPD, but usually only in advanced disease.[19,20] One study has suggested that a distance between the thyroid cartilage and the sternal notch less than 4 cm in a smoker older than age 45 is highly indicative of the presence of COPD.[21] Clubbing of the fingers is rare in COPD and, if present, suggests another diagnosis such as bronchiectasis, asbestosis, or lung cancer. High-resolution computed tomography (HRCT) of the lung is useful in establishing the presence of emphysema. Quantitative analysis of HRCT is a useful technique for early detection of emphysema but is not widely available in clinical practice at this time. α_1-Antitrypsin deficiency is an uncommon, but not rare, condition associated with premature emphysema. Table 40-1 lists conditions that suggest the presence of α1-antitrypsin deficiency. Some experts advise that all patients with emphysema or fixed airflow obstruction should be tested for α_1-antitrypsin because treatments are available for those with the most severe form of deficiency.[22,23] HIV/AIDS also is associated with premature emphysema and accelerated lung

TABLE 40-1 Conditions Suggesting α1-Antitrypsin Deficiency

Early-onset emphysema (age under 45 years)
Emphysema in a nonsmoker
Emphysema predominantly in lung bases (panacinar)
Necrotizing panniculitis (Weber–Christian disease)
c-ANCA positive vasculitis (e.g., granulomatosis with polyangiitis)
Family history of early-onset emphysema or non–smoking-related emphysema
Family history of cirrhosis
Bronchiectasis without other etiology

function decline, and screening for HIV should be performed for persons with emphysema and HIV risk factors such as intravenous drug use or high-risk sexual activity.[24,25]

The diagnosis of COPD, classification of its severity, and progression of the disease can be monitored with spirometry, a simple, noninvasive, and inexpensive test. The FEV$_1$/FVC ratio, reflecting the rate of emptying of the lung, is used to define the presence of an obstructive ventilatory defect, commonly defined as a ratio less than 0.70 or below the lower limit of normal. Once airflow obstruction is established, the severity of the airflow limitation is classified by the reduction of FEV$_1$ compared with a healthy reference population. Lung volume measurements, by plethysmography, helium dilution, nitrogen washout, or single-breath methods typically show hyperinflation (elevated TLC) and air trapping (elevated residual volume [RV]), and thus are useful to exclude restrictive lung diseases. The carbon monoxide diffusing capacity (DL$_{CO}$) is an indicator of emphysema and is an independent predictor of mortality.

COPD is categorized based on the severity of airflow obstruction, presence of symptoms, propensity for exacerbations, and radiographic appearance. Airflow obstruction is based on spirometry (Table 40-2); symptoms are elicited with standard questionnaires such as the COPD Assessment Test (CAT)[26,27] and mMRC dyspnea scale (Table 40-3); exacerbation risk is determined primarily by a history of previous exacerbations requiring treatment;[28] and emphysema is quantified by CT.[29,30]

PROGNOSIS OF COPD

The prognosis in COPD may vary widely. Physicians are poor prognosticators of survival in COPD.[22] In part, this is because the disease is one of widely varying rates of progression, and in part, this is because death is often due to susceptibility to intercurrent illness and other smoking-related illness such as lung cancer rather than progressive respiratory failure. Recent studies have demonstrated heterogeneity in lung function decline, with some patients with COPD having little or no decline in FEV$_1$ over time.[7,8]

TABLE 40-3 Modified Medical Research Council Dyspnea Scale (mMRC Scale)

Grade	Description
0	Not troubled with breathlessness except with strenuous exercise
1	Troubled by shortness of breath when hurrying on the level or walking up a slight hill
2	Walks slower than people of the same age on the level because of breathlessness or has to stop for breath when walking at own pace on the level
3	Stops for breath after walking about 100 yards or after a few minutes on the level
4	Too breathless to leave the house or breathless when dressing or undressing

Data from Celli BR, MacNee W. ATS/ERS Task Force. Standards for the diagnosis and treatment of patients with COPD: A summary of the ATS/ERS position paper. Eur Respir J. 2004;23(6):932–946.

Several factors have been identified that predict poor survival in COPD. These include low FEV$_1$, low inspiratory capacity, active smoking status, hypoxemia, poor nutrition, the presence of cor pulmonale, resting tachycardia, low exercise capacity, severe dyspnea, poor health-related quality of life, anemia, frequent or severe exacerbations, comorbid illnesses, and low D$_{CO}$.[31,32] Patients with moderate to very severe airflow limitation and a history of exacerbations have about 3% annual mortality if treated with bronchodilators alone. All-cause mortality is reduced by about 40% if inhaled corticosteroids are added to the treatment regimen.[33,34] If a patient reports that they are unable to walk 100 m without stopping because of breathlessness, the 5-year survival is only 30%.[35] A multidimensional prognostic index that takes into account several indicators of COPD prognosis is the BODE index (*b*ody mass index [BMI], *o*bstructive ventilatory defect severity, *d*yspnea severity, and *e*xercise capacity).[36,37] See Table 40-4 for calculation of the BODE prognostic score. The components are derived from measures of the BMI (weight in kg/height m^2), FEV$_1$ percent predicted, and the modified Medical Research Council dyspnea score (Table 40-3). A BODE score greater than 7 is associated with a 30% 2-year mortality, whereas a score of 5 to 6 is associated with 15% 2-year mortality. If the BODE score is less than 5, the 2-year mortality is less than

TABLE 40-2 Classification of Severity of Airflow Limitation in COPD

Ventilatory Impairment	Characteristics
I Mild COPD[a]	FEV$_1$ $\geq$80% predicted
II Moderate COPD[a]	FEV$_1$ 50%–79% predicted
III Severe COPD[a]	FEV$_1$ 30%–49% predicted
IV Very severe COPD[a]	FEV$_1$ $<$30% predicted or $<$50% predicted with room air Pa$_{O_2}$ $<$60 mm Hg (8.0 kPa)

[a] *Postbronchodilator FEV$_1$/FVC $\leq$0.70.*

Data from The 2021 Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD).

TABLE 40-4 Calculation of the BODE Index[a]

	Points on the BODE Index			
Variable	0	1	2	3
FEV$_1$ (% predicted)	$\geq$65	50–64	36–49	$\leq$35
Distance walked in 6 min (m)	$\geq$350	250–349	150–249	$\leq$149
mMRC dyspnea scale	0–1	2	3	4
Body mass index (kg/m^2)	$>$21	$\leq$21		

[a] *The BODE index is calculated as the sum of points from each row.*

Reproduced with permission from Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med. 2004;350(10):1005–1012.

TABLE 40-5 Calculation of the ADO Index[a]

	Points on the ADO Index					
Variable	0	1	2	3	4	5
FEV$_1$ (% predicted)	≥ 65	36–64	≤ 35	—	—	—
mMRC dyspnea scale	0–1	2	3	4	—	—
Age (years)	40–49	50–59	60–69	70–79	80–89	≥ 90

[a] *The ADO index is calculated as the sum of points from each row.*
Adapted with permission from Puhan MA, Garcia-Aymerich J, Frey M, et al. Expansion of the prognostic assessment of patients with chronic obstructive pulmonary disease: the updated BODE index and the ADO index. Lancet. 2009;374(9691):704–711.

10%. In settings where the 6-minute walk test is not available, the ADO index (*a*ge, *d*yspnea, and *o*bstruction) also provides useful prognostic information (Table 40-5).[38] The ADO index ranges from 0 to 10 points, with each point increase in the index associated with a 42% marginal increase in odds of death at 3 years for patients with long-standing and severe COPD.

TREATMENT OF STABLE COPD

The goals of treatment of COPD are to prevent progression and complications of the disease, relieve symptoms, improve exercise capacity, improve quality of life, prevent and treat exacerbations, and improve survival.

Education

The diagnosis of COPD can be a life-changing event for people, so understanding the nature and prognosis of the disease is an important and underemphasized aspect of care. There is a wide divergence of understanding of the implications of having COPD, and many patients do not understand that COPD comprises both the diagnoses of emphysema and chronic bronchitis. Table 40-6 lists topics that should be discussed with COPD patients. It is neither possible nor effective to cover all these topics in a single session, so several sessions with repetition and expansion of the educational messages are necessary. Supplemental written materials or referral to a health educator also is necessary for many patients. Local and national volunteer health organizations provide useful educational materials and group educational sessions (e.g., www.copdfoundation.org, www.lung.org). Special counseling is needed for patients with α_1-antitrypsin deficiency and their family members to determine whether genetic testing is necessary or desired. In patients with advanced disease, discussions about end-of-life planning and advance directives regarding life support are often welcomed by patients and initiate discussions between the patient and family. Patients should be encouraged to discuss information that they obtain from newspapers or the Internet, as some may be instructive, but others are incorrect. Physicians should be prepared to deal with patients' sense of guilt, as many view COPD as a self-induced disease. Caregivers need to address the reality that COPD is often stigmatized by patients, their families, and other healthcare providers. The physician should let the patient understand that nicotine dependence is a strong physical addiction and difficulty quitting smoking is not a measure of moral weakness or lack of will. The general message provided should be realistic, but positive. Current treatments for COPD can improve quality of life, improve activity levels, maintain social interactions, and reduce the frequency of complications.

TABLE 40-6 Patient Education Topics for Management of COPD

Risk factors for COPD
Smoking cessation advice and instruction
Reduction of noxious environmental exposures
Immunization for influenza and pneumococcus
Respiratory hygiene and avoidance of infections
Nature and prognosis of COPD
Indications, dose, benefits, and adverse effects of medications
Proper inhaler and nebulizer use
Strategies to improve adherence with prescribed treatment
Pacing, arm support, pursed lip breathing, and other strategies to minimize dyspnea
Importance of regular exercise and social interaction
Options for pulmonary rehabilitation programs
Recognition and early treatment of exacerbations
Indications for and proper use of supplemental oxygen
Options for surgical management if indicated
Advance directives for end-of-life care

Prevention of COPD Progression and Complications

Presently, there are no proven treatments that prevent the progression of COPD in patients who continue to smoke cigarettes. *Smoking cessation*, however, does prevent the excessive decline in lung function and should be a primary goal for physicians caring for COPD patients. Patients with mild or moderate COPD may not know that they have underlying lung disease that can be halted by smoking cessation or may adopt a fatalistic attitude that it is too late for help. Even severely impaired patients who are dyspneic at rest or use continuous oxygen may continue to smoke cigarettes or relapse after quitting. A smoking history should be obtained at each patient encounter because many patients fail to volunteer the extent of their smoking or report a smoking relapse following cessation. In patients who do smoke, achieving cessation should be a primary and persistent goal of treatment.[39] Approaches to smoking cessation are given in detail in Chapter 41. For patients who do smoke, a direct, unambiguous, and personalized smoking cessation message should be given by the physician. The message should emphasize the harm of continued smoking, the benefits of cessation in terms of activities that are meaningful for the individual, and the understanding that smoking cessation is a realistic and achievable goal. Techniques of motivational interviewing are readily learned and are effective in changing health behaviors.[40] Assistance with pharmacologic adjuncts such as nicotine replacement therapy, varenicline, or bupropion and referral to smoking cessation groups should be offered. Follow-up of smoking status and repeated smoking cessation messages should be performed at each encounter.

Exposure to respiratory irritants should be avoided in the workplace as well as the home. Although heavy occupational dust exposure rarely is the primary cause of COPD, exposure to dusty occupational jobs in smokers can increase the lung function deterioration from smoking and increase symptoms of cough and sputum.[41] In developing countries, heavy exposure to particulates from burning of biomass fuels is associated with COPD, even in the absence of cigarette smoking.[42,43] Efforts to improve indoor air quality may be effective in reducing symptoms and disease progression. Respiratory protective equipment should be worn by patients with COPD exposed to heavy dust concentrations. There is no level of FEV$_1$ that absolutely prohibits the use of respiratory protective equipment, but patients with COPD often experience untoward breathlessness with these masks because of the increased dead space and increased inspiratory resistance. Thus, many patients with COPD need to change their work environment if they cannot tolerate protective devices. If COPD is complicated by allergy or overlaps with allergic asthma, environmental control measures should be instituted to the extent that these strategies are helpful. Smoking of marijuana and cocaine may cause airway irritation, and although there is no convincing evidence that they contribute to progression of COPD, their use ought to be discouraged. Occasionally, heavy daily marijuana smokers will develop giant bullous emphysema, which has been called "marijuana lung," but the causality remains to be established.[44,45]

Pneumococcal vaccination is recommended and has been shown to reduce community-acquired pneumonia and possibly reduce exacerbation frequency in COPD.[46] Annual inactivated *influenza immunization* can prevent subsequent exacerbations due to influenza infections.[47] High-potency influenza immunization is recommended for older patients who may have an impaired immune response to the vaccine. During influenza epidemics, the use of neuraminidase inhibitors such as oseltamivir or RNA polymerase inhibitors such as baloxovir can minimize severity of infection if taken within 48 h of onset of illness and are useful against both influenza A and B and may limit the spread of infection. Peramivir, an injectable form of neuraminidase inhibitor, is now available for treatment of individuals with respiratory failure.

Replacement therapy with α_1*-antitrypsin* should be considered for those individuals with severe deficiency. Observational studies suggest that individuals with moderate degrees of impairment (FEV_1 35%–65% predicted) appear to benefit most in terms of preservation of lung function and improved survival.[48] Studies of HRCT progression of emphysema indicate a measurable benefit across a wider range of lung function.[49,50] The human plasma–derived preparation of α_1-antitrypsin is administered intravenously in a dose of 60 mg/kg weekly. Replacement treatment is derived from pooled human plasma, so immunization for hepatitis A and B is suggested. IgA deficiency may increase the risk of allergic reactions and therefore some authorities recommend testing for IgA levels before initiating therapy.

Screening for lung cancer with low-dose CT of the chest is recommended for individuals aged 50 to 80 years with a 20-pack-year smoking history who currently smoke or have quit within the last 15 years. Many individuals with COPD meet these criteria, and these individuals should undergo shared decision-making with their clinician. The discussions should include potential benefits and harms of screening.

■ Drug Therapy

Over the past several decades, the evidence base for use of drug therapy in COPD has expanded and provides an objective and generally optimistic picture that such treatment is effective. Bronchodilators and anti-inflammatory agents are used to reverse bronchoconstriction, improve lung function, improve quality of life, increase exercise capacity, and prevent exacerbations. Recent evidence however suggests that a combination of inhaled steroids and long-acting bronchodilators may improve survival as well as reduce exacerbations.[33,34] There is a poor correlation between the effect of bronchodilating drugs on lung function and symptom relief, so monitoring of treatment requires attention to patient-reported outcomes as well as lung function. Small amounts of bronchodilation can cause considerable improvement in functional capacity through decrease in dynamic exercise hyperinflation, and reduction in days of exacerbation can lead to considerable improvement in patients' quality of life.[51]

Bronchodilators

The usual approach to drug treatment for COPD is to sequentially add agents using the minimum number of agents and the most convenient dosing schedule, starting with the agents having the greatest benefit, best tolerance, and lowest cost. One approach to step-up therapy is provided in Fig. 40-2. Inhaled bronchodilators are the foundation of treatment for COPD. They are given on a regular basis to maintain bronchodilation and on an as needed basis for relief of symptoms.[52,53] Most breathless patients benefit from regular use of a maintenance bronchodilator. Both β-agonist and anticholinergic classes are available in short-duration (4–6 h) and long-duration (12–24 h) forms (Table 40-7). The choice of bronchodilator class and duration of effect depends upon the preference of the patient, a suitable device, and the cost of the preparation. Combination of different classes of bronchodilators is often more effective than increasing the dose of a single agent, and combination inhalers with long-acting bronchodilators can simplify treatment regimens.[54] Patients with advanced COPD often use a combination of bronchodilators, including long-acting maintenance anticholinergics and β-agonists as well as symptomatic use of shorter-acting bronchodilators. Individuals with exacerbations, particularly those with eosinophilia, may benefit from a combination inhaler of corticosteroids and long-acting bronchodilator.[55,56] Chronic use of systemic corticosteroids should be reserved for individuals with very frequent or life-threatening exacerbations in those cases where discontinuation of steroids cannot be tolerated. Response to treatment is judged by symptomatic improvement, functional status, frequency of exacerbations, and spirometry. If patients are doing well for 6 to 12 months on a stable treatment regimen, then it is reasonable to see if a trial withdrawal of one of the drug components can be tolerated.

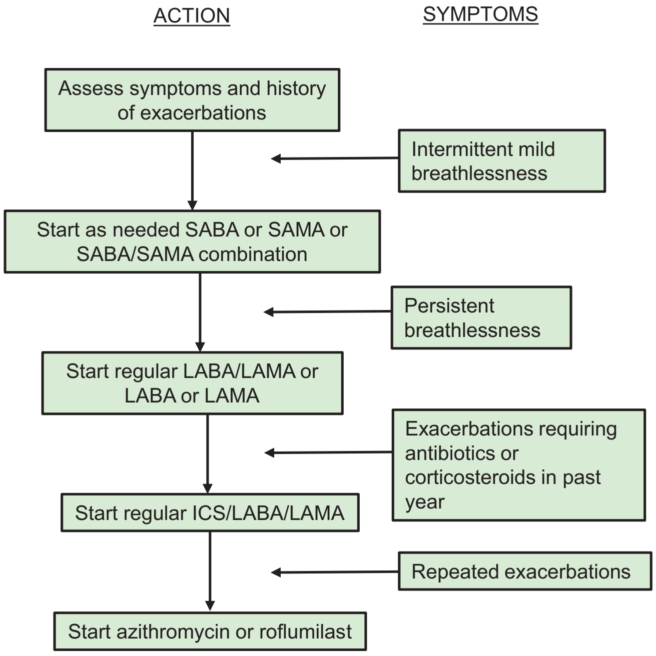
ACTION
SYMPTOMS
Assess symptoms and history of exacerbations
Intermittent mild breathlessness
Start as needed SABA or SAMA or SABA/SAMA combination
Persistent breathlessness
Start regular LABA/LAMA or LABA or LAMA
Exacerbations requiring antibiotics or corticosteroids in past year
Start regular ICS/LABA/LAMA
Repeated exacerbations
Start azithromycin or roflumilast

Figure 40-2 Flow chart for pharmacologic management for people with COPD. Treatment is based on step-up therapy depending on patient symptoms and frequency of exacerbations. Patients should be re-evaluated every 3 to 12 months for step-up or step-down of treatment. Evaluation for exacerbations should be contemporaneous with evaluation for symptoms, and ICS added to bronchodilators; however, ICS should usually not be given without bronchodilators. Patients with eosinophilia have a better response to ICS. ICS, inhaled corticosteroids; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; SABA, short-acting beta-agonist; SAMA, short-acting muscarinic antagonist.

Inhaled corticosteroids do not alter the progression of COPD in those who continue to smoke.[57,58] Inhaled corticosteroids are most useful

TABLE 40-7 Inhaled Bronchodilators

Drug Name	Dosage/Frequency	Formulation
β-Sympathomimetics		
Olodaterol		Soft mist inhaler, 5 μg
Albuterol	2 inhalations q4–6h	Metered-dose inhaler, 90 μg/puff
	3 mL nebulized q4–6h	Nebulized solution 1.25–2.5 mg/3 mL
Levalbuterol	2 inhalations q4–6h	Metered-dose inhaler, 45 μg/puff
	3 mL nebulized TID	Nebulized solution 0.63–1.25 mg/3 mL
Salmeterol	1 inhalation BID	Dry powder inhaler, 50 μg/dose
Formoterol	1 capsule inhaled BID	Dry powder inhaler, 12 μg/capsule
	2 mL nebulized BID	Nebulized solution 20 μg/2 mL
Arformoterol	2 mL nebulized BID	Nebulized solution 15 μg/2 mL
Indacaterol	1 capsule daily	Dry powder inhaler, 75 μg/capsule
Anticholinergic Bronchodilators		
Ipratropium	2 puffs q4–6h	Metered-dose inhaler, 17 μg/puff
	2.5 mL nebulized q6–8h	Nebulized solution 0.5 mg/2.5 mL
Tiotropium	1 inhalation daily	Dry powder inhaler 18 μg/dose
	2 inhalations daily	Soft Mist inhaler 2.5 μg/inhalation
Aclidinium	1 inhalation BID	Dry powder inhaler 400 μg/dose
Revefenacin	3 mL nebulized daily	Nebulized solution 175 μg/3 mL
Glycopyrrolate	1 inhalation BID	Dry powder inhaler 15.6 μg/dose
	1 mL nebulized BID	Nebulized solution 25 μg/mL
Umeclidinium	1 inhalation daily	Dry powder inhaler 62.5 μg
Combination Bronchodilator Therapies		
Ipratropium/albuterol	1 puff q6h	Soft mist inhaler, 20 μg/100 μg/inhalation
Umeclidinium/vilanterol	1 inhalation daily	Dry powder inhaler, 62.5 μg/25 μg/inhalation
Tiotropium/olodaterol	2 inhalations daily	Soft mist inhaler 2.5 μg/2.5 μg/inhalation
Glycopyrrolate/formoterol	2 inhalations BID	Metered-dose-inhaler 18 μg/9.6 μg/inhalation
Glycopyrrolate/indacaterol	1 inhalation BID	Dry powder inhaler 15.6 μg/27.5 μg/inhalation
Aclidinium/formoterol	1 inhalation BID	Dry powder inhaler 400 μg/12 μg/inhalation

in patients who have features of asthma and in COPD patients who have frequent exacerbations. Eosinophilia is a biomarker that predicts a particularly good response to inhaled corticosteroids.[59] Inhaled corticosteroids combined with bronchodilators can reduce the frequency of exacerbations and slow the decline in quality of life. In patients with exacerbations, inhaled corticosteroids improve pulmonary function, and the results are additive to those achieved with long-acting bronchodilators. Inhaled corticosteroids, although poorly absorbed, probably do contribute to steroid side effects such as cataracts, capillary fragility, and osteoporosis in susceptible individuals. High doses of inhaled corticosteroids are associated with increased risk of pneumonia.[60,61] In most cases, the risk is low compared to the benefit of treatment, but it is prudent to prescribe the lowest effective dose.

Adverse effects of inhaled therapy can occur. Inhaled anticholinergic agents are generally very safe. They may lead to an increased frequency of supraventricular arrhythmias, acute urinary retention in those with bladder outlet obstruction, or acute narrow-angle glaucoma if sprayed in the eye. β-Agonists, both short acting and long acting, may lead to side effects such as tremor, tachycardia, or hypokalemia.

Inhaled agents are administered by metered-dose inhaler (MDI), dry powder inhaler (DPI), or soft-mist inhaler (SMI), or as a nebulized solution. The selection of route of administration is made by cost and convenience of the device because all are similarly effective if used properly. There are several forms of DPI, some more intuitive to use than others, so specific instruction and demonstration is required by most patients. Because DPIs may require a high inspiratory flow, some authorities recommend screening patients with peak inspiratory flow meters before prescribing a DPI.[62] Nebulizers are easier for patients to coordinate, but each treatment takes longer to complete, and they require additional effort to maintain cleanliness. Although nebulized medications are more expensive overall, the cost of the medication is often borne by insurance, so patients may prefer nebulizers for financial considerations.

Adherence with inhaled medication, particularly when it does not provide immediate symptom relief, is poor. Typically, about half of patients do not collect or use their medication in the dose or quantity prescribed.[63] Reasons for this include a lack of understanding of the role of the medication, failure of the medication to provide meaningful benefit, complexity of the treatment program, and cost of the treatment. Many patients do not want to confide poor adherence to their physician, so it is important for the physician to ascertain this information in a way that does not interfere with the relationship with the patient. For example, a physician could inquire, “It is often difficult for patients to remember to take all of their medications. Has this been a problem for you?” or “Are you able to afford all your medication?” or “Do you think that your medicines are working for you?” If nonadherence is a problem, the treating physician can undertake actions to improve adherence, such as simplification of the medication program, education about the benefits of treatment, linking drug use to established habits such as meals or tooth brushing, or prescribing less costly drugs.

Proper use of MDIs is difficult for many patients to learn and retain. Repeated review and training of patients in MDI use is an important component of treatment of COPD and asthma. The inhaler should be held about 4 cm from the mouth to minimize deposition of larger droplets in the mouth. The patient should exhale to FRC and take a slow inhalation to TLC over about 5 seconds. The slow inhalation diminishes impaction of particles in the mouth and larynx. At the initiation of inspiration, the patient should actuate the MDI one time. After full inspiration, the patient should hold the breath for about 10 seconds to permit settling of particles in the distal airspaces. If the patient finds that hoarseness or mouth irritation occurs with inhaler use, this can often be corrected by use of a spacer, slowing the rate of inspiration, and rinsing the mouth after each inhaler use. Waiting a period of time between inhalations or between different MDIs is sometimes recommended for optimal effect, but the benefit is small compared with the inconvenience and risk of worsening adherence. Therefore, it is usually appropriate to permit the patient to take additional inhalations as soon as he or she has rested a few seconds.

If the patient has difficulty coordinating the actuation of the MDI with inspiration, a spacer device or holding chamber can be used. This device is placed directly in the mouth and the MDI is actuated prior to inspiration. DPIs usually require less coordination than MDIs, but there are many different devices, some rather complicated to use. Very frail patients may not have adequate inspiratory flow to effectively use a DPI. Therefore, each device requires individual instruction and repeated review of technique.[64] (For a compendium of patient instructions, see www.copdfoundation.org/Learn-More/Educational-Materials-Resources/Educational-Video-Series.aspx)

Roflumilast is a highly specific inhibitor of phosphodiesterase 4, which is a mild bronchodilator with anti-inflammatory properties. It is marketed in the United States for reduction of exacerbations of COPD in individuals with chronic bronchitis, $FEV_1 < 50\%$ predicted, and increased exacerbation events.[65] Gastrointestinal side effects can be minimized by starting with a low dose and increasing as tolerated. Because roflumilast causes weight loss in overweight patients and improves glycemic control in type 2 diabetics, it is particularly useful in these individuals.[66]

Oral corticosteroids are effective for treatment of COPD exacerbations. About 10% to 20% of chronic symptomatic patients show substantial short-term improvement in pulmonary function, but it is not possible to identify these patients based on clinical characteristics alone. Because of the well-defined long-term adverse effects of systemic corticosteroids, and the ill-defined long-term benefits, most patients should not be maintained on long-term oral or systemic corticosteroids. Patients with COPD who are on chronic corticosteroids can most often taper the dose at the equivalent rate of 5 mg of prednisone per week, and exclusively reserve their use for exacerbations. Long-term low doses of oral corticosteroids are occasionally needed by patients who cannot afford or tolerate inhaled agents, and who suffer frequent exacerbations. Patients on long-term systemic steroids who are at high risk for osteoporosis should be considered for prophylactic treatment with bisphosphonates and should be instructed about the need for stress-dose steroids for acute illnesses.

Long-term macrolides, which have immunomodulatory as well as antibiotic properties, have been demonstrated to reduce the frequency of exacerbations in patients susceptible to frequent exacerbations.[67] These agents can be used in patients who still have exacerbations despite maintenance treatment with bronchodilators and inhaled steroids. It remains an unsettled question whether treatment with macrolides or roflumilast is superior for preventing severe exacerbations. In secondary analyses, the benefit of azithromycin appears to be present in former smokers, with minimal exacerbation reduction in current smokers.

Mucolytic agents to control mucus hypersecretion with the use of expectorants and physical means such as high-frequency chest wall oscillation or a flutter valve is not of proven benefit in improving lung function, although symptoms are sometimes improved. N-acetylcysteine, a mucolytic with antioxidant properties, does not alter the decline in FEV_1. However, antioxidant mucolytics, such as N-acetylcysteine or carbocysteine, may have a role in reducing exacerbations.[68,69]

Opiates can be effective in the management of severe dyspnea related to COPD. Given differential response to these therapies, as well as the associated potential for respiratory depression, short-acting and low-dose preparations should be initially used. While typically associated with severe, end-stage management in the hospice setting, short-acting opiates can be considered in patients with less severe lung impairment but symptomatic dyspnea refractory to pharmacotherapy, oxygen supplementation, and rehabilitation.[70]

■ Exercise and Rehabilitation

Regular, prudent, self-directed exercise is recommended for all individuals with COPD to prevent the muscle deconditioning that often accompanies the disorder. Individuals should be encouraged to perform at least 20 to 30 min of constant low-intensity aerobic exercise such as walking at least three times per week. Even the most severely impaired patients with COPD can usually attain an exercise regimen of 30 min of walking at 1 mph (i.e., one-half mile in 30 min). It is important to instruct patients that they should exercise to a level of dyspnea that is tolerable for the entire exercise period. Patients should understand that dyspnea, by itself, is not injurious to the heart or lungs, but patients should pace themselves to avoid severe dyspnea that disrupts activity, can lead to panic reactions, and is distressing to onlookers. Patients who demonstrate desaturation with exertion may be prescribed supplemental oxygen for exercise on an individualized basis. Many patients, particularly those with marked hyperinflation, find that they can ambulate better with the use of a rolling walker that supports the arms, improving the mechanical advantage of the accessory muscles in the neck. Initiation and maintenance of an exercise program as well as educational materials are increasingly available on telehealth platforms with internet connections.

Formal in-person rehabilitation programs offer a comprehensive approach to exercise training, patient education, nutritional counseling, group support, and psychological support that cannot be efficiently provided in the physician's office. Rehabilitation programs are established as an effective component of COPD management and should be offered to patients who have substantial limitation in daily activities. After hospitalization for COPD exacerbation, enrollment in pulmonary rehabilitation is associated with reduced mortality.[71] A detailed discussion of rehabilitation is provided in Chapter 42.

■ Nutritional Support

About 25% to 40% of patients with COPD show evidence of nutritional depletion. Reasons for this include increased resting metabolic demands, inadequate caloric intake due to dyspnea and anorexia, and possibly elaboration of cachexia-associated inflammatory cytokines such as TNF-α, IL-1, and IL-6. Patients with a BMI of less than 90% of normal have increased mortality and decreased exercise capacity. Muscle wasting and loss of bone mass may be present even in patients who have normal BMI.[72] Although clinical trials of nutritional supplementation have been disappointing, it is prudent to monitor body weight in patients with COPD and encourage caloric supplementation as needed since those patients who do gain weight show improved survival.[73] High-fat diets have the theoretical advantage of offering higher caloric content with lower CO_2 production than high-carbohydrate diets, but there is no convincing evidence that this strategy is clinically superior to a well-balanced diet. For patients with less advanced disease, a balanced diet with avoidance of overweight or underweight is a rational goal. Particularly, patients with mild to moderate disease who quit smoking tend to gain excessive weight, which might adversely affect lung function.[74]

■ Sleep Disorders in COPD

Sleep disturbances, including insomnia and daytime hypersomnolence, are common symptoms in patients with COPD, and are often overlooked because of the focus on breathlessness and exercise intolerance.[75] The causes for sleep symptoms are multifactorial and include anxiety, depression, resting hypoxemia, nocturnal bronchospasm, sleep apnea, and nocturnal oxygen desaturation (NOD). Patients with COPD often relate insomnia to a fear of suffocation or death during sleep, a situation that may respond to repeated reassurance, cognitive therapy, or small doses of hypnotics, anxiolytics, or antidepressants. Patients with resting hypoxemia treated with low-flow nasal oxygen often report improved sleep quality. Nocturnal bronchospasm, more common among those with an asthmatic component to their disease, may respond to longer-acting bronchodilators, or rearrangement of the dosing schedule to provide nocturnal coverage. In some cases, treatment for gastroesophageal reflux by elevation of the head of the bed and prescription of acid suppressant drugs can help.

Sleep apnea syndrome, probably not more common in COPD patients than the general community, has particularly severe complications in COPD. Patients with COPD and sleep apnea, the so-called overlap syndrome, are prone to develop pulmonary hypertension and daytime hypercapnia.[76] Accordingly, symptoms of sleep apnea such as snoring, intermittent nocturnal breathing, and daytime hypersomnolence should be sought in patients with COPD. If present, then formal sleep studies and treatment with continuous positive airway pressure (CPAP) are indicated. NOD is common during rapid eye movement sleep in patients with COPD. The causes are not entirely understood, but contributing factors include hypoventilation, ventilation–perfusion mismatch, respiratory muscle dysfunction, and increases in upper airway resistance. NOD is thought to be associated with poorer sleep quality and pulmonary hypertension. It is controversial whether NOD is associated with poorer survival. Randomized trials have shown inconclusive results about the benefit of treating NOD with supplemental oxygen.[77] There is, however, an increasing body of evidence that patients with hypercapnia have improved survival and fewer hospitalizations if treated with noninvasive ventilation at night.[78] Although evidence is limited, it is currently recommended that patients with chronic stable hypercapnia should use nocturnal noninvasive ventilation and should undergo sleep apnea screening.[79]

Current guidelines do not recommend that all patients with COPD have nocturnal oxygen monitoring, nor do they recommend treatment with supplemental oxygen or nocturnal ventilation if NOD is found. Many physicians, though, will prescribe these diagnostic studies and treatments for selected symptomatic patients, and most insurance companies will provide reimbursement for such treatment. Patients who have resting room air daytime hypoxemia should be prescribed nocturnal oxygen at the same flow rate as used during the day, and it is usually not necessary to monitor nocturnal oxygen saturation in such patients.

■ Management of Depression

Depression is a common comorbidity in individuals with COPD and is related to the lack of social support.[80] The recognition and treatment of depression is important as this comorbidity is associated with poorer prognosis, increased risk of exacerbations, and poor health status. Although there is little evidence to suggest that depression should be treated differently in COPD patients, pulmonary rehabilitation has been shown to reduce depression with COPD.

■ Air Travel

Patients with COPD do not need to avoid air travel but must be aware of the medical and regulatory issues that are involved.[81,82] Modern airplanes are pressurized to an equivalent altitude of approximately 5000 to 8000 ft but may, on occasion, pressurize to an equivalent altitude of 10,000 ft without providing emergency oxygen. Many patients with COPD who do not use sea-level oxygen can tolerate short flights without supplemental oxygen. As flight distance becomes longer, the flying altitude becomes higher and the cabin pressure becomes lower, so transcontinental or transoceanic flights should prompt medical advice. The general rule of thumb used by the commercial airline industry is that patients who can ambulate 50 m without stopping are safe for air travel. A more conservative approach is to estimate the Pa_{O_2} during air travel by performing a high-altitude simulation test (Chapter 31).

High-altitude simulation can be performed by administering 15% oxygen via a face mask or by using 100% nitrogen in a 40% Venturi mask.[83] If the oxygen saturation falls below 86% or 50 mm Hg, then supplemental oxygen is recommended. Resting arterial oxygen saturation by itself is not a reliable indicator of oxygen desaturation at altitude. However, one study showed that a resting sea-level SpO_2 >95% with a 6-minute walk test SpO_2 >84% was highly sensitive for establishing that patients were able to fly without supplemental oxygen.[84] If resting SpO_2 is <92% or 6-minute walk test SpO_2 is <84% then oxygen should be prescribed for air travel. Patients who use oxygen supplementation at sea level should increase their resting oxygen prescription by a flow rate of 2 L/min. Patients with COPD who engage in air travel should use a pulse oximeter to monitor their saturation during the flight and adjust oxygen supplementation accordingly, particularly with pulsed-dose oxygen where equivalent constant flow rates are inconsistent.

Airlines have inconsistent policies with respect to providing supplemental oxygen for travelers, so it is important to check with the airline service desk before booking travel. The United States Federal Aviation Administration has promulgated regulations that permit approved portable oxygen concentrators to be carried on board by passengers as personal luggage with a physician's statement of need. These may be rented from oxygen supply companies or specialized websites. For battery-driven portable oxygen concentrators, extra batteries should be carried aboard to accommodate delays in the flight or extended time in the air.

The COVID-19 pandemic has focused attention on the transmission of droplet-borne viral diseases during air travel, which can be injurious to people with COPD. Therefore, it is rational to recommend use of facemasks and good hand hygiene for air travel for all individuals who may be susceptible to viral infection.[85]

■ Long-Term Oxygen Therapy

Oxygen treatment of resting severe daytime hypoxemia prolongs survival.[86–88] Guidelines recommend prescribing long-term oxygen therapy (LTOT) for at least 15 h/day for adults with COPD who have severe chronic resting room air hypoxemia (defined as $PaO_2 \leq 55$ mm Hg or $SpO_2 \leq 88\%$). Oxygen is usually administered by nasal cannula, with the flow rate adjusted to maintain a resting saturation >90%. The usual starting flow rate is 2 L/min, although some patients with severe hypercapnia require lower flows. Some patients, particularly those with concomitant interstitial pulmonary disease or cardiovascular disorders, require higher flow rates.

The most convenient and cost-effective oxygen source at home is usually a concentrator device that uses a molecular sieve to extract oxygen from room air. For ambulation, small, compressed oxygen cylinders, portable concentrators, or liquid oxygen reservoirs that can be carried provide patients with the ability to leave their homes. Conserving devices, such as reservoirs or demand valves, permit portable ambulatory oxygen tanks to last up to 10 h. Compressed oxygen cylinders or liquid oxygen reservoirs should be provided by home oxygen companies to patients who use electrically driven oxygen concentrators for emergency use in the event of a power failure. Ideally, oxygen should be used constantly 24 h per day. At least 18 h of oxygen per day, however, has been shown to have substantial benefit over 12 h per day. If continuous oxygen supplementation is prescribed following an exacerbation of COPD, it is recommended to check arterial oxygen levels in 6 weeks, as many patients will no longer require oxygen.

Nasal drying or congestion is a common symptom for those who use continuous oxygen. This may be alleviated to some extent by alternating the nasal cannula from one nostril to the other or placing it in the mouth for periods. Copious watery nasal secretions often respond well to ipratropium nasal spray, and dry, crusted nasal mucosa is treated with hourly instillations of saline nasal spray.

Smoking or exposure to any open flame is prohibited by the danger of fire and airway burns in those who use oxygen. This is a surprisingly common cause of burns in the United States, with estimates that up to 50% of patients on oxygen continue to smoke to some extent.[89] Accordingly, it is safer to counsel patients to discontinue oxygen while smoking or cooking over an open flame if they insist on doing these activities. Patients at particular risk are those who live alone, have cognitive impairment, and do not have functioning smoke detectors.

Ambulatory oxygen, although not shown to improve survival, may be provided for patients who desaturate with exertion. Some, but not all, patients show improved exercise capacity and reduced breathlessness. Patients with exercise desaturation or moderate levels of hypoxemia do not, however, benefit in terms of increased survival or decreased hospitalizations.[90] There is good evidence that oxygen supplementation during exercise training may benefit COPD patients who do not have exercise desaturation by reduction in minute ventilation and decreased dynamic hyperinflation.[91] However, in sham-controlled clinical trials where oxygen treatment does not improve exercise intensity, there is no added training benefit.[92,93] Therefore, the recommendation for oxygen during exercise training should be individualized based on patient preference and shared decision-making with the provider.

COMPLICATIONS

A variety of respiratory and cardiac complications may be seen in COPD and are discussed below.

COPD Exacerbations

Exacerbations are characterized by worsening cough, dyspnea, and sputum production beyond normal day-to-day variation. These exacerbations are associated with acute deterioration of lung function during the exacerbation and may also accelerate lung function decline. Acute exacerbations of COPD are a major cause of hospitalization, healthcare costs, morbidity, and mortality in COPD. Exacerbations have been associated with respiratory viral infections including rhinovirus, respiratory syncytial virus, influenza, adenovirus, and metapneumovirus. Bacterial infections or superinfections are also associated with COPD exacerbations. The most frequent pathogens are *Haemophilus influenzae, Moraxella catarrhalis,* and *Streptococcus pneumoniae*. In patients who have been previously treated frequently with antibiotics, gram-negative bacteria also may be present. Severe air pollution, especially particulates, sulfur dioxide, ozone, and nitrogen dioxide have been associated with elevated risk for hospitalization due to COPD. On average, patients with COPD have two to three exacerbations per year, but there is wide variation, and the frequency of exacerbations is only roughly correlated with severity of airflow obstruction. The best predictor of future exacerbations is a past history of frequent exacerbations, and these are more common in patients with chronic cough and sputum production.[94] Only half of COPD exacerbations come to the attention of treating physicians, and many of these eventually resolve without specific treatment. The management of these exacerbations depends upon the severity. Indications for hospital evaluation or hospitalization are listed in Table 40-8. Arterial blood gas studies and chest radiographs are useful for evaluating etiology and severity of acutely ill patients. Spirometry during the acute exacerbation is usually not helpful in predicting the severity or duration of the exacerbation.

TABLE 40-8 Indications for Hospitalization in COPD

Indications for Hospital Assessment or Admission for COPD Exacerbation
Sudden onset of new or severe symptoms (e.g., dyspnea)
Inability to sleep or eat because of dyspnea
Severe or very severe underlying COPD
Onset of new physical findings (e.g., edema, cyanosis, change in mental status)
Failure to respond to initial medical treatment
Associated comorbidities (e.g., cardiac, renal, hepatic failure, diabetes)
Diagnostic uncertainty (e.g., suspected pneumonia or pulmonary embolism)
Frailty or dementia
Inadequate home or social support
History of poor adherence with treatment
Indications for ICU Admission for COPD Exacerbation
Severe dyspnea unresponsive to initial treatment
Change in mental status (e.g., confusion, lethargy, coma)
Persistent or worsening hypoxemia, hypercapnia, or respiratory acidosis
Need for sedation or narcotic pain control
Need for mechanical ventilation
Need for hemodynamic monitoring

Data from The 2021 Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD).

For patients treated at home, increasing the frequency and intensity of inhaled short-acting bronchodilators for several days is effective in mild exacerbations. A hand-held inhaler and spacer are usually effective, but a nebulizer may be needed for those who cannot coordinate well or who have severe dyspnea. Increasing dyspnea accompanied by a change in the quantity or color of phlegm is usually an indication of bacterial infection and should prompt initiation of antibiotics. When readily available, C-reactive protein (CRP) levels are helpful in guiding antibiotic prescription.[95] The choice of antibiotic is determined by severity of the underlying disease, resistance patterns of likely pathogens, and likelihood of treatment failure (Table 40-9). For those not responding to treatment, the antibiotic should be tailored based on sputum cultures.

TABLE 40-9 Antimicrobial Treatment of COPD Exacerbations

First Line	
	Amoxicillin 500–875 mg PO TID
	Doxycycline 100 mg PO BID
	Azithromycin 500 mg, then 250 mg PO QD × 4 d
Alternatives	
	Amoxicillin/clavulanate 875 mg PO BID
	Clarithromycin 500 mg PO BID
	Second-generation cephalosporins
Previous antibiotics or known gram-negative pathogens	
	Levofloxacin 500–750 mg PO QD × 7 d
	Ciprofloxacin 500 mg PO QD × 7 d

A course of corticosteroids, equivalent to 30 to 60 mg of prednisone for 5 to 10 days, will shorten the duration of symptoms for patients with exacerbations managed as outpatients.[96–98] For patients admitted to the hospital, intensification of inhaled bronchodilator treatment, systemic corticosteroids, and antibiotics are administered.[99] Controlled oxygen supplementation should be provided at the lowest level needed to reverse hypoxemia and minimize the induction of hypercapnia. The selection of the oral or intravenous route for antibiotics and corticosteroids is determined by the severity of the illness and the ability of the patient to tolerate oral medication. Evaluation for the cause of the exacerbation does not have to be extensive if it responds to initial treatment and conforms to the patient's usual exacerbation pattern. Sputum culture for resistant bacterial strains, a chest radiograph for exclusion of pneumonia and pneumothorax, and an electrocardiogram for exclusion of myocardial ischemia and arrhythmia are useful tests in all hospitalized patients. Echocardiography for assessment of ventricular function, and D-dimer, Doppler venous flow studies, radionuclide, or CT lung imaging for evaluation of pulmonary thromboembolism need to be performed in selected cases. Usually, a 5- to 14-day course of steroids is sufficient for hospitalized patients.

Treatment in an intensive care setting should be undertaken for patients with severe exacerbations or those who require more constant attention (Table 40-8). For patients with respiratory failure, noninvasive mask ventilation has proved to be an effective strategy to avert endotracheal intubation, shorten duration of illness, and improve outcomes.[100] Attention needs to be paid to selecting and fitting a comfortable well-sealed mask, and providing a ventilator that minimizes the patient's work of breathing and triggering effort. When noninvasive mask ventilation is not successful in sustaining ventilation, or the patient is too ill to use the mask, endotracheal intubation and mechanical ventilation are needed to treat respiratory failure. The mechanical ventilator should be set to provide minute ventilation that does not overventilate the patient and cause alkalemia, which may ultimately impede liberation from the ventilator. The inspiratory flow rates and inspiratory to expiratory time ratios should be adjusted to provide a prolonged duration of expiration to minimize dynamic hyperinflation (auto-PEEP), which can lead to dyspnea, discoordination, and barotrauma. Weaning and liberation from mechanical ventilation can be hindered by anxiety, oversedation, mucus secretions, intravascular volume overload, myocardial ischemia, or respiratory muscle deconditioning. A hospitalization for COPD exacerbation should be considered a sentinel health event. Patients hospitalized for COPD exacerbation have a 25% 1-year mortality, with patients requiring mechanical ventilation having even poorer outcomes—with about a 40% 1-year mortality for those who survive the hospitalization.[101,102] Given the clinical impact of a hospitalized exacerbation, all COPD patients should have their maintenance COPD regimen reassessed at time of discharge for appropriate modifications and have close outpatient follow-up after discharge.

■ Pneumothorax

Smoking-related emphysema is thought to be the most common cause for secondary spontaneous pneumothorax.[103] A pneumothorax can either cause an acute symptomatic exacerbation of COPD from rupture of a bleb or may occur during the course of an exacerbation as a consequence of hyperinflation or mechanical ventilation. Because this is a life-threatening but quickly treatable cause for worsening respiratory failure in COPD, it should always be considered in the differential diagnosis for worsening dyspnea in COPD. The physical examination can be misleading because diminished breath sounds are a component of COPD. Imaging studies are usually diagnostic, but at times it can be difficult to distinguish a pneumothorax from an overdistended bulla. If the patient's clinical situation can tolerate it, imaging with inspiratory and expiratory views or chest CT can be helpful. In the intensive care unit, upright and cross-table lateral views sometimes show mobility of the pleural air.

Urgent treatment for the patient in extremis is performed by aspirating the pleural space at the second intercostal space anteriorly in the midclavicular line. Definitive emergency treatment is placement of a thoracostomy tube, which should be done with care to avoid laceration of a bulla and creation of a bronchopleural fistula. In patients with advanced COPD, recurrence of a pneumothorax is common and can be life-threatening, so definitive pleural sclerosis with surgical or medical thoracoscopy should be considered. If there is a persistent bronchopleural fistula, surgical intervention or endobronchial valve insertion may hasten recovery.[104]

■ Cor Pulmonale

Pulmonary hypertension and consequent right ventricular failure, *cor pulmonale*, are usually the consequence of chronic alveolar hypoxia, with secondary contributions from destruction of the alveolar capillary bed, lung hyperinflation, and increased blood viscosity.[105] Diagnosis of pulmonary hypertension and right ventricular failure can be difficult, as physical findings of venous engorgement and right ventricular hypertrophy and dilation are late signs. Peripheral edema is poorly correlated with resting right atrial pressure and may reflect fluid retention from activation of the renin–angiotensin–aldosterone system. Functional imaging studies including echocardiography or cardiac MRI are more probative for evaluation of right ventricular function. Doppler echocardiographic measures of pulmonary artery systolic pressure correlate poorly with severity of pulmonary hypertension by right heart catheterization.[106] In situations where cor pulmonale is not associated with chronic hypoxemia, investigations for pulmonary thromboembolism and sleep apnea overlap may be helpful. Once cor pulmonale is present, survival is diminished. If the pulmonary artery pressure exceeds 25 mm Hg, the average 5-year survival is diminished by 50%.[107,108]

The primary treatment of cor pulmonale consists of continuous oxygen to overcome hypoxemia and diuretic to optimize volume status. Calcium channel blockers and other vasodilators can dilate the pulmonary circulation, but they worsen hypoxemia and their benefit is not established. Traditionally polycythemia was thought to be common and an indication of poor prognosis in chronically hypoxemic patients with COPD, but recent cohort studies indicate that polycythemia is infrequent and has an uncertain effect on outcomes.[109]

■ Supraventricular Arrhythmias

Supraventricular tachyarrhythmias are common in patients with COPD as a consequence of right atrial enlargement, increased endogenous adrenergic tone, hypoxemia, and drug treatment—specifically bronchodilators. Treatment is similar to that in nonpulmonary patients; however, the presence of COPD should not prevent evaluation for treatable causes of arrhythmias such as pulmonary embolism, hyperthyroidism, or valvular heart disease, which may be difficult to diagnose in COPD patients.

Hypercapnia

Chronic hypercapnia secondary to alveolar hypoventilation can be considered an adaptive response to obstructive lung disease by decreasing the work of breathing, preventing respiratory muscle fatigue, and allowing a diminished sensation of dyspnea. The adverse effect of chronic hypercapnia is the development of alveolar hypoxia and consequent pulmonary hypertension. Accordingly, the approach to chronic hypercapnia is the use of supplemental oxygen in controlled concentrations. In patients who are very sensitive to oxygen, it is preferable to provide oxygen in controlled concentrations with Venturi masks rather than nasal cannula.

Nocturnal ventilation has been effective in reducing daytime hypercapnia in patients with neuromuscular disease and kyphoscoliosis. Nocturnal noninvasive ventilation may be used to normalize nocturnal hypercapnia in patients with stable chronic hypercapnia. Investigation for concomitant sleep apnea syndrome is recommended.[79,110]

ADVANCED TREATMENTS

For patients who have far-advanced disease evidenced by either severe breathlessness or short life expectancy, more aggressive treatments should be considered. Undertaking these treatments requires thoughtful consideration by patients and their families, and frank discussion of the risks and benefits by the medical caregivers.

Lung Volume Reduction Surgery

Lung volume reduction surgery (LVRS) is a surgical procedure that involves stapled resection of 20% to 30% of the lung bilaterally, usually from the apices. The procedure is equally safe and effective, done by median sternotomy or video-assisted thoracoscopy (VATS). The theory behind this procedure is that the remaining lung expands to fill the thorax, thereby increasing its elastic recoil pressure, which improves expiratory airflow. The reduction of lung volume permits the diaphragm to attain a more normal, domed configuration, which improves its mechanical efficiency. Moreover, the preferential removal of unventilated bullae reduces residual volume, permitting an increase in the vital capacity. While some patients show substantial physiologic and symptomatic improvement following LVRS, many do not.[111] Generally, LVRS should not be done on patients with an FEV_1 less than 20% predicted and either diffusing capacity less than 20% predicted or diffuse homogeneous emphysema on HRCT, because these patients have high surgical mortality.[112] The group of patients who fare best with LVRS are those who have emphysema predominantly in the upper lung zones and low exercise capacity despite pulmonary rehabilitation. These patients have improved survival after LVRS and show improved functional status and quality of life. Conversely, patients without upper lobe predominance (i.e., lower lobe emphysema or homogeneous emphysema), and who have adequate exercise capacity after rehabilitation, have worse outcomes after LVRS.

Surgical resection of a single large bulla is rarely indicated for treatment of COPD. Isolated giant bullae are usually the result of an expanding congenital cyst. The generally accepted indication for resection of a single large bulla is that it occupies more than one-third of the hemithorax and causes compression of normal lung. Some believe that a preserved D_{CO} is an indicator of those most likely to improve following a bullectomy.

Nonsurgical approaches to lung volume reduction using a variety of techniques to induce atelectasis of a target lobe have generally supplanted surgical lung volume reduction. Placement of endobronchial valves in regions of lung with severe emphysema without collateral ventilation can lead to clinically meaningful improvement in symptoms.[113,114] Because pneumothorax is common after these procedures, patients are often observed in hospital for several days after the procedure. Patients who achieve complete atelectasis of the target lobe have the best symptomatic and survival outcomes.[115]

Lung Transplantation

In younger patients with advanced disease, lung transplantation should be a treatment consideration. Criteria for lung transplantation referral in patients with COPD are an FEV_1 below 25% predicted, BODE index greater than 5, hypercapnia, resting hypoxemia, secondary pulmonary hypertension, and accelerated decline in FEV_1 in patients under the age of 65 years.[116] For additional information see Chapter 106.

Chronic Ventilator Support

Some patients remain on long-term ventilator support following an episode of acute respiratory failure. Most often these patients are treated in a long-term ventilator unit, but some can be managed at home with adequate support. In some cases, the goal of long-term ventilator support is to provide rehabilitation via respiratory care, nutrition, and exercise to eventually be liberated from the ventilator entirely or for substantial portions of the day. In other cases, the goal of care is to provide comfort and support for terminal care without attempts at rehabilitation. Whatever the goal, a coordinated team of physicians, respiratory therapists, physical therapists, nutritionists, social workers, psychologists, and nurses are needed to undertake the care of these patients.

The treatment of long-term ventilator patients differs from the treatment of acute respiratory failure in the intensive care unit. Ventilators are less sophisticated in terms of modes of ventilation and monitoring, but more portable. Ventilation is often performed with an uncuffed tracheostomy with an air leak to avoid complications at the cuff site. Sufficiency of ventilation is judged by noninvasive measures of oxygenation and patient comfort. Narcotics in small doses are administered for relief of dyspnea. Diagnostic studies and invasive testing are performed less frequently than in critical care units. Although the care in long-term ventilator units is complex and expensive, the quality of life experienced by patients in chronic ventilator units is similar to that of patients confined to a bed-and-chair existence by other chronic maladies. The survival of patients with COPD on long-term mechanical ventilation is less than 3 years on average and is less than those on such treatment for neuromuscular diseases, in part, because of their older age and comorbidities.[117]

CONCLUSIONS

COPD develops insidiously. However, the disease can be easily detected with simple spirometric testing before symptoms occur, and cessation of smoking can slow or even halt the disease progression and prolong survival. Once the disease is symptomatic, a coordinated, comprehensive, and individualized approach to treatment, both pharmacologic and nonpharmacologic, can increase functional status, prevent complications, and improve the quality of life. Exacerbations of COPD can range from those that are nuisances to those that are life-threatening, but treatment can shorten the duration of illness and improve outcomes. In advanced disease, treatments including surgical and bronchoscopic approaches are directed toward relief of symptoms. Thus, although there is certainly need for improvement in our treatment of symptomatic COPD, current treatments are effective, and a nihilistic attitude is not warranted.

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CHAPTER 41

Cigarette Smoking, Smoking Cessation, and Electronic Cigarettes

Stephen R. Baldassarri
Stephen I. Rennard

INTRODUCTION

Native Americans discovered the use of the tobacco plant, *Nicotiana tabacum*, during antiquity. By the time Columbus arrived in America, tobacco use was widespread throughout the Western Hemisphere and was well integrated into Native American cultures. Production of tobacco and its trade represented a major economic activity in the pre-Columbian Americas. Early European explorers learned of the tobacco plant from Native Americans, and by the mid-17th century tobacco was widely used in Europe.

The most important, but not the only, active psychopharmaceutical drug contained in the leaves of the tobacco plant is nicotine.[1,2] Nicotine is a major metabolic product of the tobacco plant, and it is likely that it evolved as a protection against insect predators, as nicotine is a potent insect neurotoxin.[3] Interestingly, nicotine has been exploited in this regard as a commercial insecticide. Nicotine, however, is the major addicting substance in tobacco, although the addiction to tobacco is more complex than addiction to nicotine alone. Other psychoactive compounds also are present in tobacco smoke, including monoamine oxidase inhibitors.[4] These may either have direct effects, interact with other psychoactive drugs, or both.[1,2] In addition, conditioned behavior and social interactions are important drivers of smoking.[5–8]

Nicotine is a potent euphoriant. On a molar basis, nicotine is more active than such euphoria-inducing drugs as cocaine, amphetamine, or morphine.[9] Nicotine elicits complex effects on the central nervous system (CNS), which are discussed in more detail below. Many of these effects, however, are perceived as desirable, accounting for the popularity of smoking. For example, nicotine ameliorates anxiety, reduces perception of pain,[10] mitigates symptoms of depression,[11] and induces a sense of well-being[9] while causing a state of arousal.[12] In contrast to many euphoriants that impair cognition, nicotine can improve task performance and attention time by measurable degrees in non-habituated individuals and may have beneficial effects on cognition.[12]

Despite its perceived benefits, smoking of tobacco has long been controversial. King James of England wrote in 1604 "[Smoking is] a custom loathsome to the eye, hateful to the nose, harmful to the brain, dangerous to the lungs, and in the black stinking fume thereof, nearest resembling the horrible Stygian smoke of the pit that is bottomless."[13] The Surgeon General's Report of 1964 outlined the convincing evidence for the health consequences of smoking.[14] Since that time, there has been a gradual increase in efforts to control tobacco use and the associated health consequences. Changes in social attitude, public health efforts, and both pharmacologic and nonpharmacologic approaches have been developed that have meaningful benefits. The current chapter will focus on treatment designed to help a smoker achieve abstinence. An overview of the increasingly important topic of electronic cigarettes will conclude the chapter.

NICOTINE ADDICTION

Nicotine exerts its biologic effects on "nicotinic" receptors, a subset of cholinergic receptors, whose endogenous ligand is acetylcholine.[15,16] Nicotinic receptors are homo- or heteropentamers that bind two ligand molecules and form an ion channel.[17] In humans, 17 genes code for distinct component chains, resulting in a very large number of potential pentamers, although only a relatively few are believed to have a biologic role. In the brain, nine alpha and three beta receptors are expressed. However, the major receptors are composed of complexes α4β2, α3β4, and α7. The α4β2 complex incorporates other subunits, particularly α5, α6, or β3, and these may modulate the effects of ligands, including nicotine.[17] The α4β2 receptor is believed to be particularly important in the addicting effects of nicotine. Deleting the β2 receptor in mice eliminates behavioral responses to nicotine, while mutations in the gene can result in markedly increased sensitivity to nicotine.[18] The α7 receptor, for example, is believed to mediate some of the cognitive effects of nicotine, including sensory gating and learning.[18,19] In contrast the muscarinic receptors, the other major class of cholinergic receptors, are single-chain G protein–coupled receptors. Nicotine has no effect on these receptors.

Nicotinic receptors are ion channels. Upon binding of nicotine, permeability of the channel is increased.[15–18] For example, binding of nicotine to the α4β2 allows influx of calcium. This, in turn, modulates release of neurotransmitters. It is likely that the behavioral responses to nicotine result from the actions of many neurotransmitters, but dopamine is believed to be a major mediator of nicotine effects. In this context, dopamine is a key mediator of pleasure and reward and is required for the reinforcing effects that lead to drug self-administration in animal models.[20] As such, dopaminergic signaling is believed to be key in the pathogenesis of many addictions and compulsive behaviors. Nicotine also modulates the release of other neurotransmitters, including glutamate and gamma-amino butyric acid (GABA). Interestingly, chronic administration of nicotine desensitizes neurons that release GABA, which inhibits dopamine release. In contrast, there is no desensitization of glutamate release, which augments dopamine release. Chronic nicotine exposure, therefore, can lead to further augmentation of dopamine release.[21,22] Moreover, the CNS alterations that occur following nicotine administration can be very long lasting; for example, alterations in nicotine receptor levels in rats exposed in utero persist until adult life.[23] The adolescent brain may be particularly sensitive to long-term alterations induced by nicotine.[24] This may account for the sensitivity of adolescents to addiction. Persistent changes in the brain may also account for the observation that, even after achieving abstinence, a smoker is at risk for relapse and if relapse occurs, the smoker reverts to the previous "steady-state" habit much more rapidly than that habit developed initially.

Nicotine is contained in the leaves of the tobacco plant. Nicotine is a weak base and as a result will be charged in acidic environments. Many forms of tobacco, such as cigars and chewing tobacco, are alkalinized, which results in uncharged nicotine that can be more readily absorbed through the buccal mucosa. Thus, cigar smokers do not have to inhale to achieve desired blood nicotine levels. The process of smoking a cigarette is more complex.[25] Air sucked through the burning end of a cigarette becomes heated. As the hot air passes down the bole of a cigarette, it causes the nicotine in the tobacco to vaporize. As the mixture cools, the nicotine condenses on smoke particles resulting in a nicotine aerosol. Conventional cigarettes have been designed so that the resulting particle size is ideal to reach the alveolar structures of the lung. Uncharged nicotine is lipid soluble and is rapidly absorbed from the alveolar gas into the pulmonary capillary blood and then into the arterial circulation. Inhaled nicotine, therefore, reaches the brain in about half a circulation time or about 15 to 20 s. In its neutral form, nicotine readily crosses the blood–brain barrier and exerts its psychoactive effects. A cigarette, therefore, is a very effective means of delivering nicotine to the brain. It also allows a smoker to control the dose of delivered drug with considerable precision.

After absorption, nicotine distributes into various body pools. This results in a marked difference between arterial and venous nicotine levels and a rapid drop in nicotine levels upon completion of a cigarette.[26] Nicotine is then catabolized by several enzymes. The most important of these is CYP2A6, which oxidizes nicotine to cotinine and cotinine to hydroxycotinine.[27] Nicotine can also be oxidized by alternative CYP450 enzymes and may be inactivated and excreted by glucuronidation. Genetic variants in nicotine metabolizing enzymes can influence smoking behavior. In normal metabolizers, nicotine is cleared with a half-life of about 2 h. As a result, nicotine levels increase throughout the day for individuals who smoke steadily. The increase in nicotine levels can result in levels believed to fully saturate all nicotinic receptors.[1,2] In this setting, it is likely that smoking behavior is more dependent on conditioned responses than on psychopharmacologic effects of nicotine. Conversely, nicotine levels fall at night. The drop in nicotine levels is thought to initiate the early stages of withdrawal. Importantly, the lower levels allow for nicotinic receptors to be in the unbound state. As a result, the first cigarette in the morning can have a large psychodynamic effect. This is well recognized by smokers who will often report that the "most enjoyable" cigarette is the first one smoked in the morning. In addition, the drop in nicotine levels is thought to initiate the early stages of withdrawal. How long it takes a smoker to smoke the first cigarette of the day, therefore, serves as a gauge of addiction, with short times indicating stronger addiction. Smoking within 30 minutes of awakening is a key question in the Fagerstrom test for nicotine dependence.[28]

Several lines of evidence support genetic influences on smoking behavior.[29–32] Twin studies suggest that genetics accounts for about 50% of the variance in smoking. Interestingly, there appears to be a genetic basis for withdrawal symptoms.[33] A number of genes have been suggested to play a role in both candidate gene and in genome-wide association studies. Although many of the candidate genes have been difficult to reproduce, an extremely strong signal has been consistently observed in a region of chromosome 15 that includes the genes for three nicotinic receptors.[34] Among COPD patients, this region is also associated with intensity of smoking assessed by cigarettes smoked per day, suggesting it may be related to intensity of addiction.[35] As might be expected of a gene related to smoking behavior, this region has also been strongly linked to the risk for several smoking-related diseases.[36–39] Candidate genes include not only genes in the dopamine pathway, but also other neurotransmitter pathways as well as cell adhesion molecules that are thought to contribute to long-term memory and neural adaptation.

Genetic variation in nicotine metabolizing enzymes has received particular attention.[31] Many but not all studies have demonstrated that individuals with variants in CYP2A6 who metabolize nicotine slowly smoke fewer cigarettes and maintain lower cotinine and carbon monoxide levels consistent with their requiring less total intake.[35,40,41] Consistent with a reduced level of smoking, some studies have shown reduced risk for cancer in slow metabolizers.[42,43] Similarly, better lung function has been reported among individuals with haplotypes associated with slow metabolism compared to those with genes associated with rapid metabolism who smoke the same number of cigarettes.[44]

It is plausible that the slower decline in blood nicotine levels associated with slow nicotine metabolism makes these individuals less likely to experience withdrawal. In addition, the persistence of nicotine may decrease the "reward" of smoking. Both of these effects may contribute to increased likelihood that a slow metabolizer can achieve abstinence from smoking,[40] and better quit rates have been observed among slow metabolizers in clinical trials.[31,45] On the other hand, slow metabolizers who are experimenting with smoking may have higher and more sustained nicotine levels. Consistent with this, a prospective study of adolescents observed a threefold risk of becoming a regular smoker among slow metabolizers.[46]

Smoking cigarettes is more complex than nicotine addiction. Conditioned behaviors also play a key role.[1,2] In this context, a smoker typically inhales 10 puffs per cigarette. This would be 300 puffs for a 1.5-pack-per-day smoker or more than 100,000 puffs annually. In addition, smoking frequently occurs in recurrent settings: after eating, when irritated, when bored, when sad, in specific social settings, etc. As such, smoking becomes associated with these settings that serve as operant cues to induce smoking behavior. Nicotine, moreover, has been demonstrated to increase both the intensity of operant conditioning as well as its persistence.[6,47] The development of addiction to tobacco, therefore, involves not only development of addiction to nicotine, but also acquisition of conditioned behaviors, which nicotine facilitates. Because these cue-mediated behaviors can be very persistent, they are major causes of relapse.

Tobacco addiction most commonly begins in late childhood or adolescence,[48–51] although smoking can begin in young adulthood.[52,53] Historically, in the United States, the peak incidence for developing a regular tobacco habit is in adolescence. Individuals who do not acquire a habit prior to age 20 are unlikely to do so as adults.[48] The demographics of smoking initiation have been well known to the tobacco industry. Marketing campaigns designed to promote the image of specific brands of cigarettes were carefully designed and were exceedingly effective in leading to historic logo recognition among children as young as kindergartners[51,54] and contributed to brand selection among American adolescents. The susceptibility of children to these campaigns was a major driver in leading to bans on tobacco advertising in media likely to be seen by children. Importantly, since most exploratory smoking occurs in peer-related social settings, the social context of smoking is a crucial variable in determining smoking initiation.[51,55,56]

Most children who begin to smoke do so on an occasional basis. Within a few years, however, a regular habit may develop. Most often this habit is characterized by smoking only a few cigarettes daily. As noted above, slow metabolizers may be particularly susceptible to addiction due to higher nicotine levels and longer persistence.[46] The number of cigarettes smoked, however, generally increases for the first 8 to 10 years. Important variations on this pattern exist, suggesting biologic differences among smokers. Some smokers achieve a "mature addiction" very rapidly. In contrast, as many as 15% of smokers, termed "chippers," may continue to smoke episodically and may not be fully addicted.[57,58]

Smoking is more common among those with psychiatric disorders.[59–61] This includes individuals with depression, anxiety disorders, and cognitive disorders such as schizophrenia, as well as other drug dependencies. The basis for this relationship is unclear. Nicotine has modest antidepressant and antianxiety effects, and the suggestion has been made that some individuals with mood disorders may smoke to "auto-medicate." Alternatively, it has been suggested that smoking and psychiatric disorders may share common genetic risk factors. Another possibility is that smoking early in life may lead to alterations in the CNS that may lead, in turn, to psychiatric disorders. In support of this, smoking more commonly precedes first psychotic episodes.[61] Whatever the mechanisms, the concurrent presence of psychiatric disorders can complicate efforts to achieve smoking abstinence.

Once a smoker achieves a "mature" addiction, cigarette consumption typically remains very constant. Interestingly, the smoker appears to adjust both nicotine intake and number of cigarettes smoked independently. If supplemental nicotine is administered, smokers will often reduce their cigarette-derived nicotine consumption.[62] Alternatively, if smoking is restricted, for example, by decreasing the number of cigarettes available, smokers will alter their smoking strategy, for example, by smoking each cigarette more deeply, to maintain a relatively constant nicotine intake.[63] Similarly, acidification of the urine increases while alkalinization slows nicotine clearance, and there are corresponding increases and decreases in nicotine intake that are achieved with no change in the number of cigarettes smoked.[64] Rather, smokers alter the way in which individual cigarettes are smoked, that is, the depth and duration of inhalation and the number of puffs, thus modifying the nicotine absorbed. Consistent with self-regulation of nicotine administration, low–nicotine-content cigarettes do not result in lower nicotine consumption.[65] This illustrates the complexity of smoking where both nicotine addiction and conditioned behaviors contribute.

While the pathogenetic mechanisms underlying withdrawal symptoms are incompletely understood, it is generally believed that some withdrawal symptoms are related to decreases in nicotine blood levels below certain thresholds. Variations in nicotine metabolism would be expected to affect the timing of symptom onset. Some smokers, for example, may experience nicotine withdrawal at night when sleep interferes with nicotine intake.[66] The use of nicotine replacement to help ameliorate withdrawal symptoms by maintaining nicotine blood levels is also an important concept underlying nicotine replacement as an aid to smoking cessation. In addition, susceptibility to specific symptoms may be genetically determined.[67,68]

SMOKING AS A PUBLIC HEALTH PROBLEM

Cigarette smoking is a major public health problem and is, perhaps, the most important cause of preventable disease. The number of deaths attributed to cigarette smoking in the United States has been estimated to be well in excess of 400,000 annually and has been for many years.[69,70] This exceeds deaths attributed to other specific causes with the recent exception of COVID-19.[71] The health burden attributable to smoking parallels smoking prevalence. As a result, smoking-induced disease is becoming more common in the developing world where smoking prevalence has been increasing, particularly in specific subpopulations such as young and middle-aged males.[72] In the United States, after comprehensive tobacco control programs were reduced, smoking prevalence and the burden of tobacco-related disease began to decrease.[73–75] Smoking can cause disease through a variety of mechanisms, which are reviewed in other chapters. However, some pathophysiologic effects persist after cessation. Smoking-related disease, therefore, will continue to be a major health problem for many decades.

Since Dr. Luther Terry released the first Surgeon General's report on smoking and health in 1964,[14] the prevalence of adult smokers in the United States has dropped from 40% to under 14%, although the rate has been relatively stable for the last decade.[75] Antismoking awareness has increased worldwide to the extent that smoking bans have become commonplace in public buildings, workplaces, and public transportation. In 1984, Surgeon General C. Everett Koop[76] proclaimed that the United States' number one health goal was to achieve a smoke-free society by the year 2000. Unfortunately, this goal was not achieved, but the public health initiatives that followed had long-lasting effects, evidenced by the continually decreasing overall incidence of smokers in the adult population in the United States.[73–75] A more realistic goal of adult smoking reduction to 12% in the United States was put into place through the Healthy People 2010 program.[77] Whether this goal will be obtained remains to be determined; however, it still highlights the importance of a smoke-free society. As of 2020, cigarette smoking reached an all-time low of 13.7% where it has remained.[76,77] However, this has been associated with a marked increase in vaping among youth (see below). The greatest reductions in smoking have been in states with the most comprehensive tobacco control programs, supporting the effectiveness of currently available interventions.

Public health approaches to control smoking-related disease begin with the social factors that are key in initiating and maintaining smoking.[51] The experience a child has with the initial attempts at smoking appear to be important, as is an individual's attitude toward smoking—that is, the "image" of the smoker, peer pressure, parental cigarette use, and availability.[51,78,79] Social attitudes can account for very low smoking prevalence in some groups. These observations support attempts to place restrictions on smoking in public places and other efforts to "de-normalize" smoking.[51]

As in ancient America, the use of tobacco products has become well integrated into modern cultures worldwide. Tobacco is a multibillion-dollar industry. In some regions, tobacco is a crucial cash crop in an agricultural economy. In addition, the manufacturing, distribution, marketing, and sale of tobacco products employ many individuals worldwide. Taxation on tobacco products has become an important means for the support of many governments. Thus, any changes in tobacco usage are likely to have economic impacts well beyond any health effects.

The use of tobacco has not only an economic role, but a cultural one as well. In some societies—for example, certain Native American tribes—tobacco usage has religious significance. In other groups, tobacco usage is associated with a strong cultural "image." Often this image may have been created through direct efforts of the tobacco industry to market their product. In this regard, advertising messages promoting the image of the cigarette smoker as rugged, independent, and masculine or as sophisticated, independent, and feminine have been developed.[80,81] While these images of cigarette smoking have their origins in advertising campaigns, the effectiveness of such marketing programs cannot be underestimated.[51,79] The portrayal of these images in media, such as film, may help promote smoking, which supports restrictions on advertisements as part of public health initiatives directed at tobacco control.[51,82,83] Whatever the reasons, cigarettes clearly have a cultural significance. The social and economic impact of tobacco usage, therefore, must be considered when attempting to deal with smoking as a public health problem.

In an effort to combat the public health ramifications of tobacco usage in the United States, the Master Settlement Agreement was signed into effect in 1998.[84] It served as a measure to recoup what states had lost through Medicaid expenditures due to smoking-related illnesses and as a measure to fine the tobacco industry for deceitful actions. Four major U.S. tobacco companies awarded 46 states $206 billion to be paid over 25 years and to be utilized as the states saw fit. Four states had previously settled separately. Unfortunately, since its inception, many states have failed to use the funding for tobacco control causes, instead using it to fill budget deficits or to support other state programs. Among many other actions, the agreement also prohibited advertisements targeted at youth and permitted access to tobacco industry documents. Based on current understanding of the complex factors that interact to cause tobacco addiction, these approaches are rational. The issues are also complex and controversial. It is likely that social and public health interventions will continue to evolve and be part of ongoing political debate.

SMOKING PREVENTION

As noted above, smoking initiation is generally a pediatric problem.[51] Precisely why some children begin smoking is not fully understood, although both social and genetic factors contribute as discussed above.[51] Currently, as many as 13.8% of American children experiment with cigarettes by the twelfth grade.[85] A number of factors are believed to contribute, including the child's social environment and the child's attitude toward smoking, which appears to be based, in large part, on the smoking behavior of parents, friends, and peer group role models.[51,78,79] Attitudes toward smoking appear to be important factors leading to smoking initiation, which may depend, at least in part, on advertising and marketing programs, hence the effectiveness of bans on advertising. The reasons for initiating smoking, however, are not entirely environmental, as several lines of investigation (see above) suggest a genetic basis for smoking as well. These concepts support the basis for interventions to reduce smoking initiation. Interventions aimed at altering the social milieu have benefit.[86] Participation in sporting activities is associated with lower rates of smoking initiation.[48,87]

A second approach to limiting smoking initiation is to restrict the sale of tobacco products to minors. Many states have legal restrictions on such sales. In many cases, however, these laws are not enforced. Active enforcement, however, can lead to a decrease in sales to minors[88] and a decrease in both experimental smoking and in regular cigarette use among younger smokers,[89] although the general effectiveness of these measures is unclear.[90] For such measures to be effective, they must be uniformly enforced in the community, and vending machines must be made inaccessible to minors.[91,92] Another approach to restrict tobacco usage by minors is taxation.[93] While there is controversy over how "elastic" purchase of tobacco is,[94] increasing price decreases use, and this effect may be particularly prominent among less addicted smokers.[93] Inasmuch as adolescents may have less disposable income, the effect may be even greater among adolescents. Some analyses support an association between higher price, particularly through taxation, and lower smoking initiation and prevalence.[95] However, assessment of the specific effectiveness is difficult methodologically.

Measures aimed at restricting tobacco sales to minors may lead to a deferral for smoking initiation, as young adults remain at risk for smoking initiation.[52,53] Thus, if measures are effective at delaying smoking initiation among children, parallel measures may also be required to affect smoking initiation among older adolescents and young adults. Currently available data suggest that smoking behavior among high school students decreased steadily since the initiation of efforts designed to reduce initiation. There does not appear to be a corresponding increase in smoking among older individuals, which supports the concept that smoking prevention is a legitimate and achievable public health goal. While it is difficult to determine the effectiveness of specific public health initiatives,[96] the evidence is clear that smoking rates can be decreased by population-based measures and that states with the most comprehensive programs have achieved the greatest gains.[51,73–75]

SMOKING CESSATION

Below we consider a general approach to smoking cessation, patient evaluation, and a variety of nonpharmacologic and pharmacologic approaches to management. We also address practical concerns in a smoking cessation program.

Background and General Approach

Smoking should be regarded as a primary addictive disorder.[97] This contrasts with the "classic" view of smoking as a "habit" or "life style choice." It has been estimated that 75% of American smokers wish to quit but only 3% are able to achieve prolonged abstinence in any year, which indicates the involuntary nature of the established addiction.[98] In addition, current concepts suggest smoking should be regarded as a chronic relapsing disorder.[99] In this context, a "cessation attempt" should be regarded as an attempt to induce a remission. The abstinent smoker, moreover, should always be viewed as at risk for relapse. The goal for therapy is to induce a remission that is as durable as possible. However, the clinician needs to be prepared to re-induce remission in the event that relapse occurs. Smokers who are "quit" should remain in active surveillance, and relapses should not be regarded as "failures." The health consequences of smoking should be regarded as secondary effects. Importantly, there are health benefits of cessation that are well established. These are the subject of the 2014 Surgeon General's Report.[100]

Current recommendations are to assess smoking and willingness to quit at every visit.[97,101] Interestingly, success in quitting may be related to acute problems that may have motivated a patient to be willing to consider quitting (see "Stages of Change and Smoking Cessation," below).[102] This acute motivation may be present even if the acute event is not directly related to smoking, and the clinician should be ready to utilize these windows of opportunity. In contrast, not inquiring about smoking can have adverse effects. Not asking is thought to send three messages: (1) that the physician does not care if the patient smokes; (2) that the physician does not have an effective intervention to offer; and/or (3) that the physician does not think that the patient will be able to quit. All of these "non-messages" have negative effects, particularly as smokers gradually make the decision to quit. A sense of empowerment and control over the behavior is believed to be key to making and succeeding in a quit attempt[103] and to subsequent risk of relapse.[104] Inadvertently eroding a patient's sense of mastery is an unanticipated adverse consequence of not asking about smoking. In addition, many patients are unaware of the potential available therapies; appropriate information can increase motivation to engage in quit attempts. Smokers unwilling to make a quit attempt should be encouraged as much as possible, provided with specific information if desired, and reminded that the issue will be brought up again in the future.

Approach to a Quit Attempt

A smoking quit attempt should be approached in a similar way to induction of remission from cancer. As with cancer, each patient should be given the best chance of achieving remission. In general, this will require two classes of intervention: nonpharmacologic approaches and pharmacotherapy, which should be used together to optimize success.

Evaluation

As with the management of any complex disease, smokers should undergo an initial organized assessment.[97,105] Motivation or reason to quit and the patient's confidence in their ability to stop smoking, that is, self-efficacy, should be assessed. For patients who indicate they are not currently interested in quitting, the goal is simple: to move them through the stages of change[106] so a quit attempt will be made. For some, this may be as simple as providing information about health risks. For others, it may be information about effective interventions. Motivational Interviewing is an effective technique used to guide patients toward change.[107] It allows patients to discover their own internal motivation through a nonjudgmental process of exploration. The provider provides empathy, rolls with resistance, respects patient autonomy, and empowers the patient to make changes on their own terms and at their own pace.

The intensity of addiction can be assessed with the Fagerstrom test for nicotine dependence (Table 41-1).[28] The most important question is time to first cigarette, and smokers who smoke within 30 minutes of awakening are usually heavily addicted to nicotine. These patients and those with Fagerstrom scores ≥7 constitute a group of individuals likely to benefit from nicotine replacement therapy (NRT) and varenicline and more efficacious as monotherapy as compared with bupropion. In contrast, patients with low Fagerstrom scores who are able to cope with smoke-free environments for an extended time period (>4 hours) without developing

TABLE 41-1 Items and Scoring for Fagerstrom Test for Nicotine Dependence

Questions	Answers	Points
1. How soon after you wake up do you smoke your first cigarette?	Within 5 min	3
	6–30 min	2
	31–60 min	1
	After 60 min	0
2. Do you find it difficult to refrain from smoking in places where it is forbidden, e.g., in church, at the library, in cinema, etc.?	Yes	1
	No	0
3. Which cigarette would you hate most to give up?	The first one in the morning	1
	All others	0
4. How many cigarettes/day do you smoke?	10 or less	0
	11–20	1
	21–30	2
	31 or more	3
5. Do you smoke more frequently during the first hours after waking than during the rest of the day?	Yes	1
	No	0
6. Do you smoke if you are so ill that you are in bed most of the day?	Yes	1
	No	0

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discomforting withdrawal symptoms may not require NRT. For these individuals, the benefit of pharmacologic support is unknown.

Past experience with quit attempts should be reviewed. Many patients will have a number of prior tries. Individuals who had particular difficulty with withdrawal symptoms should be prepared for this, and medications can be gauged to attempt to mitigate their intensity. Approaches that achieved abstinence, but were followed by relapse, should be considered as they are likely to succeed again. In these cases, interventions should be guided by reducing risks of relapse.

■ Nonpharmacologic Approaches

Nonpharmacologic approaches provide the smoker with guidance and support as progress is made through a quit attempt.[97,105] It is likely that effective support improves adherence with pharmacotherapy and results in therapeutic synergy. In addition, conditioned responses, that is, cue-driven behaviors, are largely dealt with thorough behavioral strategies. This generally requires individual interviews to define individual smoking patterns. These patterns can also help identify situations that increase risk of relapse. In general, success increases with the intensity of support, but most smokers will decline referral to intensive programs and will receive only the support provided in the office setting. The remainder of this section summarizes commonly used approaches.[97,105,108]

Stages of Change and Smoking Cessation

The Stages of Change model has been very useful to guide behavioral support. Prochaska and DiClemente[106] described the smoking cessation process as involving five stages: precontemplation, contemplation, preparation, action, and maintenance. These stages are viewed as a continuum with smokers progressing sequentially through each stage. In the precontemplation stage, smokers are not interested in quitting smoking and will likely be nonresponsive to direct intervention. Smokers in the contemplation stage are considering quitting smoking and may be receptive to a physician's advice about the risks and benefits of quitting. In the preparation stage, smokers are actively preparing to quit. The action stage encompasses both initial abstinence and the 6-month post-cessation period. The maintenance period commences after the 6-month abstinence period. It is rare for a smoker to progress successfully through these stages in the initial quit attempt. The cycle will likely be repeated several times before smoking a prolonged abstinence, that is remission, is achieved. Thus, the clinician must be encouraging and willing to support repeated attempts.

The National Cancer Institute's (NCI) recommended model for smoking intervention is based, in part, on five NCI-supported trials involving more than 30,000 patients and was later expanded by the Public Health Service.[97,105] This approach, popularly referred to as "the five A's," emphasizes the role of medical professionals to ask patients about their smoking status, assess their willingness to make a quit attempt, advise smokers to stop, assist them in their stop smoking efforts, and arrange for follow-up visits to support the patient's efforts. This approach utilizes brief intervention techniques and emphasizes the role of physicians as facilitators in the quitting process.

Simple advice has been assessed in a number of studies, and meta-analysis suggests a small but significant benefit of these limited interventions.[97,105] Physician advice is effective both in the outpatient and hospital setting and may also be effective when given by letter, email, or telephone.[109–111]

Group Counseling

Group counseling programs for smoking cessation are offered by several commercial and voluntary health organizations. These programs are similar in content and typically include lectures, group interactions, exercises on self-recognition of one's habit, some form of tapering method leading to a quit day, development of coping skills, and suggestions for relapse prevention. Group counseling programs sponsored by voluntary health organizations are generally the best cost value for smokers. However, these programs are generally limited to large metropolitan areas and are offered on a sporadic basis. One-year success rates associated with group counseling programs are typically in the 15% to 35% range.[97,105] The high success rates are likely affected by selection bias, that is, participants may be more motivated to quit.

Gradual Reduction Versus Abrupt Abstinence

It is unclear whether gradual reduction in cigarettes smoked per day or abrupt abstinence is the better method for achieving prolonged smoking cessation; results may depend on individual factors.

The optimal approach probably requires customization to the patient's specific needs. Gradual reduction or tapering intuitively appears to offer smokers the least abrasive way to stop smoking and may be effective for some.[112–114] However, gradually cutting down can be stressful when smokers attempt to reduce their cigarette use below their critical blood nicotine threshold. At this stage, smokers may begin to experience tobacco withdrawal symptoms. Rather than suffer prolonged discomfort, many taperers will gradually return to their customary cigarette levels and will not succeed in quitting. One of the negative consequences of tapering is that this method can strongly reinforce the smoker's belief of their underlying need for cigarettes; that is, it can undermine self-efficacy. Combining tapering with pharmacotherapy to prevent withdrawal may be useful in this setting.[113] In this context, gradual reduction with varenicline is included in package label. Abrupt abstinence is often stressful and can lead to tobacco withdrawal symptoms. However, within a few weeks of total abstinence, complete abstainers experience less frequent cigarette cravings than taperers and are less prone to relapse. Cigarette tapering is often a component of many group programs in which gradual cigarette reduction is used as a preparatory stage leading toward a target quit day.

Educational Techniques

For years, cigarette smoking was viewed as largely a social or psychological habit. As such, the ability to quit was viewed as a measure of personal motivation and psychological willpower. Motivation to stop smoking, combined with sufficient psychological resources, was seen as a driving force behind successful cigarette abstinence. Thus, if smokers could be educated about the health risks of cigarette smoking, they could theoretically become sufficiently motivated and psychologically empowered to quit. Unfortunately, anticipated benefits of the smoking cessation value of educational awareness messages were overly optimistic and simplistic. Educational programs to aid smoking cessation have produced disappointing results with high long-term failure rates.[97,105] Nevertheless, education about smoking is still regarded as a useful activity, particularly when the information can address problems of specific interest to individual patients. In this regard, as noted above, a major predictor of success is "self-efficacy," which is the patient's sense that they are likely to succeed. Education that improves self-efficacy should be a therapeutic goal.

Other Modes of Smoking Cessation

The goal of hypnosis in smoking cessation is to enable the smoker to achieve an altered state of consciousness to enhance the ability to quit. Controlled trials of hypnosis have generally been unable to document long-term smoking cessation efficacy. While one meta-analysis suggested the possibility of a treatment effect,[115] this was not supported in another meta-analysis.[116] Aversive conditioning is based on the premise that smoking is a learned response that can be extinguished by creating an association between smoking and a negative sensation. By design, aversive conditioning techniques can produce smoker discomfort and are now rarely employed. However, there are few recent studies, and a treatment benefit cannot be excluded.[115] Acupuncture has been advocated, but controlled trials with "sham" acupuncture have not clearly demonstrated an effect. Meta-analyses have not been conclusive but suggest the possibility of an effect.[115]

Available Resources

The resources available to support smoking cessation vary among communities. Some have readily available and affordable group programs, while these may be unavailable in other places. Toll-free tobacco quit lines are currently provided by many countries, including the United States and Canada. Telephone counseling is an effective smoking intervention.[111] Thus, clinicians should encourage every smoker who wishes to quit to utilize a National Quit Line (e.g., in the United States: 1-800-Quit-Now). Additional support can be found via the internet using smokefree.gov. Using this approach, a smoker can choose to talk with a telephone specialist with either internet instant messaging or telephone support. Both methods are designed to provide smokers with a personalized quit plan that would be available in most clinical settings.

■ Pharmacologic Treatment

Three classes of agents, nicotine replacement, bupropion, and varenicline, are approved to aid smoking cessation.[117] In addition, two other agents, clonidine and nortriptyline, are supported by guidelines for "off-label" use as secondary agents. In addition, several other agents are under active investigation and have shown promise.[97,105,117] As noted above, combination of nonpharmacologic support and pharmacotherapy optimizes success in achieving abstinence. The remainder of this section summarizes currently available pharmacotherapy.

Nicotine Replacement Therapies

Five nicotine replacement therapies are approved for use to aid in smoking cessation. Lozenges, polacrilex (gum), and transdermal systems are available over the counter (OTC). Nasal spray and a nicotine inhaler are available with a prescription. Initial concerns about potential hazards of concurrent smoking while using NRT led to warnings against this practice. However, the U.S. Food and Drug Administration (FDA) removed this warning from the OTC formulations, as the benefits of smoking cessation greatly exceed any potential hazards.

NRT is usually started on the scheduled quit day. The concept is to replace nicotine that would be absorbed from cigarettes and thereby reduce the intensity of withdrawal. Smokers will, however, experience withdrawal symptoms—albeit with less intensity. In clinical trials, the five approved formulations have demonstrated about twofold increases in quit rates above placebo when used alone,[97,105] and one trial comparing gum, inhaler, and nasal spray found no difference in efficacy.[118] They differ, however, in their pharmacokinetics.[119] Transdermal systems provide the slowest delivery of nicotine but maintain steady-state levels throughout the day. The other formulations allow episodic dosing. A common practice is to combine a transdermal system with another formulation, a "patch-plus" regimen.[120,121] This allows a smoker to increase nicotine delivery at times of urges. Clinical trial data support better success with combined NRT compared to monotherapy.[97,105]

Nicotine Polacrilex Gum Nicotine polacrilex gum was the first NRT to gain FDA approval. It is now commercially available OTC in 2- and 4-mg forms. In nicotine polacrilex, nicotine is bound to a resin that contains a buffering agent to improve delivery of nicotine through the buccal mucosa. The rate of chewing can influence the rate of nicotine release. In addition, acid foods or drinks convert nicotine base to its salt, which, because of its charge, does not cross the buccal mucosa. To be absorbed into the venous circulation, the nicotine-containing saliva must be retained in the mouth as long as possible. If swallowed, the nicotine can cause local irritation of the stomach. When absorbed into the portal circulation, high first-pass metabolism in the liver limits blood nicotine levels. If chewed properly, absorption takes place gradually, and blood levels peak after about 30 minutes.[119] Ad lib use of 2-mg nicotine polacrilex is associated with blood nicotine levels less than 40% of customary smoking. The 4-mg dose is recommended for individuals who are heavier smokers or who have had discomforting tobacco withdrawal symptoms on the 2-mg dose.[97,105] A fixed dosage regimen, rather than ad lib usage, may have better success,[122] perhaps because it can produce higher blood nicotine levels. A common recommendation is that a smoker use one piece of gum every 1 to 2 h for the first 6 weeks after quitting followed by gradual reduction over 6 weeks. Many smokers continue to use gum at times of craving for an extended time, and some can use sufficient gum to sustain nicotine addiction without smoking.

Although effective in clinical trials, less successful results have been observed with nicotine gum in general practice and unsupervised settings. This may be due, in part, to requirement that the gum be chewed properly. Adverse effects from the gum include exacerbation of local effects: temporomandibular joint (TMJ) disease, trauma to dental appliances, sore jaw, oral irritation or ulcers, and excess salivation; effects from swallowed nicotine: hiccups; and effects from systemic absorption of nicotine: nausea, vomiting, abdominal pain, constipation, diarrhea, palpitations, and headache. Use of the gum is not recommended in individuals with poor dentition or who have dental appliances.[117]

Nicotine Polacrilex Lozenge A nicotine polacrilex lozenge is also available "over the counter." Chewing is not required, but acid food and/or beverages will impair absorption as with gum. Dosing, absorption, and duration of therapy with the lozenge are similar to those for the gum.[123] Because it is not chewed, the lozenge does not share the problems of exacerbating TMJ disease or damaging dental appliances. Other side effects are similar to those of the gum.

Transdermal Nicotine The primary advantage of transdermal patch delivery systems are ease of use and controlled drug delivery. Several formulations are available "over the counter." In general, they achieve nicotine blood levels roughly 40% to 50% of that achieved by customary smoking of about 30 cigarettes daily.[117] Transdermal nicotine systems have been repeatedly found to reduce tobacco withdrawal symptoms and significantly enhance smoking cessation rates.[97,105] Unlike nicotine polacrilex gum, transdermal nicotine systems and the nicotine lozenge have improved quit rates in primary care settings.[102,124] This difference is likely due to the ease of patch use in this setting. The recommended use period for patches varies according to product, but a minimum of 4 weeks of therapy is probably required to help achieve long-term abstinence. Long-term patch use is safe and likely beneficial for many smokers.[125]

Patches are most commonly worn at night, providing a level of nicotine when a smoker awakes. Often this is a time when the individual is at risk to relapse, since the low nicotine levels are associated both with withdrawal and with increased effect of the smoked cigarette. On the other hand, delivery of nicotine at night may disturb sleep, particularly through vivid dreams or insomnia. Spontaneous long-term use of the patch has not been observed, suggesting that the very slow kinetics of nicotine delivery with this system is insufficient to sustain addiction effectively.[126] In addition, perhaps due to the partial replacement of nicotine, most smokers on patches will still experience some tobacco withdrawal symptoms during the first few days of quitting. While these symptoms will likely be less severe compared to quitting cold turkey, some patients will be tempted to smoke and wear patches. Early concerns about increased cardiac risk among individuals who smoked while wearing the patch have not been substantiated. In fact, reduced smoking may decrease cardiac events.[127]

Nicotine Inhaler The nicotine inhaler is a plastic nicotine-containing cartridge that fits on a mouthpiece. Nicotine is released when air is inhaled through the device, which is similar in size to a cigarette. The nicotine is not effectively delivered to the lungs as the particle size is too large. Rather, it is deposited and absorbed through the buccal mucosa, which results in pharmacokinetics that resemble nicotine polacrilex. Blood levels depend on the frequency of inhalations but can be about one-third of conventional smoking. Usual dosing is 6 to 16 cartridges per day for 6 to 12 weeks followed by gradual reduction over 6 to 12 weeks. Because the use of the inhaler recapitulates many of the actions associated with smoking such as the preparation of the device, oral stimulation, inhalation, and others, the inhalers may be particularly effective in smokers for whom these behaviors are particularly strongly conditioned. In addition to the adverse effects described for the lozenge, the inhaler may cause irritation of the throat and mouth and may precipitate bronchospasm in individuals with reactive airways.

Nicotine Nasal Spray The nasal spray delivers nicotine to the nasal mucosa through which it is absorbed. It has the most rapid pharmacokinetics of the currently available nicotine replacement formulations but does not reproduce that of a cigarette.[119] Nasal irritation is very common, particularly when initiating therapy. The recommended dose is one to two sprays per hour for 3 months with a maximum of 80 sprays per day. Because the spray can deliver large amounts of nicotine, it may be particularly effective for heavily addicted smokers. It also likely has a greater risk of nicotine overdose and may have a greater potential to sustain a long-term addiction.

Combination Therapy Various combinations of nicotine replacement may have utility for selected individuals who need higher doses. In particular, combination of a transdermal system with an ad lib modality has been demonstrated to increase quit rates.[97,105,124,128] Because of its increased success, it is recommended by some as initial therapy.[117]

Bupropion Bupropion is approved as an antidepressant, and it is also effective as an aid for smoking cessation.[97,105,129] It is believed to act by potentiating dopaminergic and noradrenergic signaling. The formulations for depression and for smoking cessation have different trade names and dosages, which has clinical relevance. First, an appropriate diagnosis is often required for reimbursement. Second, care is needed not to prescribe bupropion under one name to an individual already taking it under its other name, as overdosage can result.

In clinical trials, bupropion approximately doubles quit rates compared to placebo. Subjects with a history of depression, however, appeared to benefit from bupropion but did not with nicotine replacement, suggesting that bupropion may be a superior initial choice in such individuals. Combination of nicotine replacement with bupropion has been assessed and appears more effective than either agent alone.

The currently recommended dose is 150 mg daily for 3 days, followed by 150 mg twice daily. Because the drug is excreted slowly, steady state-levels are achieved after 6 to 7 days. For this reason, the quit date should be scheduled after a week of therapy so that blood levels are established. As the 150-mg once-daily dose was nearly as effective as the 150-mg twice-daily,[130,131] many practitioners use the lower dose routinely. The appropriate duration of therapy is not established. Clinical trials that formed the basis for approval treated for 7 weeks, although a 12-week course is commonly recommended. With prolonged therapy, there is an increase in secondary quits, and therapy for 1 year resulted in more quits than therapy for 7 weeks.

The drug is generally well tolerated. The most common adverse effects are dry mouth, insomnia, agitation, and headache. In combination with nicotine replacement, an increase in blood pressure also may occur. Bupropion reduces seizure threshold, and a seizure risk of 0.1% has been reported. Because of its reduction in seizure threshold, bupropion is contraindicated among those predisposed to seizures, or with anorexia nervosa or bulimia.

In 2008, the FDA first noted that both bupropion and varenicline (see below) had a "possible association (with) suicidal events."[132] The benefits of smoking cessation were felt to outweigh any potential risks, and the medicines were not withdrawn from the market. In 2016, the FDA removed the black box warning about possible suicidal events from the labels of both bupropion and varenicline following a subsequent large randomized controlled trial showing that the rates of major adverse psychiatric events were similar across all tobacco treatments (including varenicline, bupropion, and NRT) compared with placebo.[133] The rate of adverse psychiatric events was about 6% in patients with underlying psychiatric illness and 2% in otherwise healthy individuals. Thus, regardless of the treatment strategy chosen, it is important for all patients and their caregivers to monitor for possibility of neuropsychiatric symptoms, and patients should be monitored for changes in behavior, hostility, agitation, depressed mood, suicidal ideation, and suicide attempts. Most practitioners make a routine practice of reassessing patients 3 to 7 days after the quit day to both monitor for adverse effects and to provide additional support for the quit attempt. In this context, a second visit has been demonstrated to greatly improve success.[97,105,117]

Varenicline Varenicline is a partial agonist at the $\alpha4\beta2$ nicotinic receptor.[134] As such, it can partially activate the receptor thereby mitigating withdrawal symptoms. In addition, by occupying the receptor, it can prevent nicotine from acting, and thus can reduce the rewarding and reinforcement effects associated with nicotine. This may be particularly important in preventing a lapse from becoming a full relapse once abstinence has been achieved. Both of these effects are supported by evidence from clinical trials.[135–138] Varenicline consistently improves success in quitting compared to placebo by an effect of two- to fourfold.[138] In addition, head-to-head trials have demonstrated superiority compared to bupropion,[133,135,136] as well as to nicotine replacement.[133]

Varenicline is given orally. Usually medicine is started at 0.5 mg once daily for 3 days followed by 0.5 mg twice daily for 4 days and then 1 mg twice daily for 3 months. Individuals who have achieved abstinence at 3 months may have less relapse if therapy is continued for an additional 3 months. A quit date is usually recommended for 1 week after starting medication, but success has been reported with a broader window of quit dates from 1 to 5 weeks that was comparable to a fixed quit rate.[139,140] Gradual scheduled reduction may be helpful during this extended period. This increased flexibility may be an advantage in starting a quit attempt when patients are seen for problems other than smoking cessation.

The most common adverse reactions are nausea, insomnia, visual disturbances, syncope, and skin reactions. The incidence of nausea is reduced with the dose titration described above.[141] The most serious concerns with varenicline have been with psychiatric and cardiovascular side effects. Varenicline had the same boxed warning as bupropion, indicating that patients and their caregivers should be alerted to the possibility of neuropsychiatric symptoms, which, as noted above, has been removed.[132] Consistently, clinical trials have failed to confirm psychiatric adverse effects.[142] A meta-analysis that reported significant increase in cardiovascular events[143] was felt to be methodologically flawed, as it excluded studies with no events.[144] A subsequent meta-analysis that included all available studies found no difference between varenicline and placebo, although a small difference may be present.[144] Based on this information FDA recommended that patients taking varenicline be alert for development of new or worsening symptoms of cardiovascular disease.[145] Varenicline has also been associated with accidental injuries from falls and vehicular accidents.[146] This has resulted in an FDA advisory regarding operating heavy machinery while using varenicline.[147]

Off-Label Agents

A number of drugs have been used “off-label” in smoking cessation programs. Two are briefly considered below.

Clonidine Clonidine is an α-adrenergic agonist active in the CNS that is used to treat hypertension. A number of clinical trials have evaluated its efficacy in smoking cessation and have generally shown a trend toward benefit, although individual trials have generally not been statistically significant, and its use is supported by a meta-analysis.[148] The Department of Health and Human Services (DHHS) guidelines have suggested it can be used by experienced practitioners comfortable with the drug.[97,105] Major adverse effects of clonidine are drowsiness, fatigue, dry mouth, and postural hypotension.

Nortriptyline Nortriptyline is a tricyclic antidepressant that has been evaluated for efficacy in smoking cessation in several studies. Both individual studies and meta-analyses support its benefit as an aid to smoking cessation,[129,149] and it has also been recommended as a possible second-line agent for practitioners comfortable with its use by the DHHS guidelines.[97,105] Major adverse effects of nortriptyline include drowsiness and dry mouth. As with other tricyclics, CNS and cardiovascular effects, including arrhythmias, may occur.

■ Practical Concerns During the Quit Attempt

Smoking cessation entails consideration of a variety of practical concerns, including the general approach to be employed, patient withdrawal symptoms, including cravings and depression, and weight gain, as discussed below.

Approach

As noted above, the first step is to have a patient willing to make a quit attempt. Current practice is to optimize the chance for success with each attempt. In general, this will be achieved with nonpharmacologic support combined with pharmacotherapy. The more active the nonpharmacologic support the greater the likelihood of success. Patients vary, however, in the type of support they will accept.

It is also important to select an appropriate pharmacotherapy. The initial choice is typically customized and depends on several factors including the patient’s prior experience, comorbidities, preferences, and cost. Many practitioners initiate treatment with NRT, because of greater experience and reduced potential for adverse effects. The “patch-plus” regimen that combines a transdermal system with an ad lib formulation is often recommended.[97,105,117] Bupropion may be more appropriate for individuals with a history of depression.[136] Varenicline has the greatest efficacy.[117] The quit date should be linked to the pharmacotherapy: generally, this is 1 week after initiating bupropion or varenicline and on the same day as initiating NRT. Varenicline may offer some flexibility, with a quit date 1 to 5 weeks after starting treatment.[140] A follow-up visit should be scheduled about 10 days after initiating therapy to check for side effects, withdrawal symptoms, and general treatment effectiveness. A follow-up in the immediate post-quitting period is associated with improved success. This may be particularly important for cessation attempts that begin in hospital.[150] Longitudinal follow-up for this chronic relapsing/remitting condition is important.

Withdrawal Symptoms

The first 3 days of abstinence are usually the most difficult. Tobacco withdrawal symptoms (Table 41-2) generally peak during the first 72 hours and then gradually subside over a 3- to 4-week period. These symptoms can include restlessness, anxiety, difficulty concentrating, irritability, frustration, depression, and an almost unrelenting craving for cigarettes. Common suggestions to help smokers cope with these early withdrawal symptoms in addition to NRT can include: (1) Be active. Increased activity may curtail some of the drive to smoke. (2) Use deep breathing exercises. The simplest breathing exercise involves nothing more than extended breath holding followed by slow exhalation through pursed lips. (3) Avoid high-risk situations for smoking during the first 3 weeks of quitting. (4) Use plenty of cinnamon gum or chewable candies. (5) Combat strong urges to smoke: The urge to smoke will go away whether one smokes or not.

Cravings Of all the symptoms associated with nicotine withdrawal, cravings to smoke are the most persistent. Unlike the other symptoms, cravings can also recur long after abstinence is achieved. During the second and third weeks of abstinence, the craving waves

TABLE 41-2 **Nicotine Withdrawal Symptoms (DSM-IV)**

Dysphoric or depressed mood
Insomnia
Irritability, frustration, or anger
Anxiety
Difficulty concentrating
Restlessness
Decreased heart rate
Increased appetite or weight gain

usually occur less frequently, but can sometimes catch smokers off guard because of their unexpected intensity. The decrease in frequency is greater than the decrease in intensity, and cravings can be precipitated months and years after abstinence if precipitated by specific cues. In this context, cravings recapitulate, in some ways, the grief response. Relapse is commonly associated with concurrent alcohol consumption. It is likely that alcohol, and the associated situations in which it is consumed, serves both as a cue leading to craving and decreases the inhibitions that may prevent smoking. Ex-smokers should be aware of these moments of hazard.

Depression At some time during the first 3 months of abstinence, some smokers may experience depression. For many this depression is mild and transient. For a small minority of smokers, quitting smoking may produce a clinical depression that may require antidepressant therapy, counseling, or return to smoking. Depressive symptoms are associated with relapse.[151]

Weight Gain

One of the most disheartening components of quitting smoking is weight gain.[97,105] Rapid weight gain is common during the first 6 to 8 weeks of cigarette abstinence. This is followed by a more gradual increase in weight to roughly 4 kg at 6 months. Average weight gain at 10 years following cessation is 4.4 kg and 5.0 kg for males and females, respectively. The health risks associated with post-cessation weight gain are unknown but are likely surpassed by the health benefits of stopping smoking.

RISKS OF SMOKING CESSATION

Smoking cessation may be associated with some hazards in selected cases. Nicotine and other components of cigarette smoke may have a significant antidepressant effect, and many endogenously depressed individuals may have empirically found smoking helped alleviate their symptoms. Depression is a well-recognized manifestation of the nicotine withdrawal syndrome. At times, this depression can be of major clinical importance. Exacerbations of ulcerative colitis are more common in former smokers and may develop at times long after smoking cessation.[152] These potential adverse effects should not minimize the importance of smoking cessation, but the clinician should be prepared to address them when necessary. Anecdotal reports have suggested that asthma may worsen following cessation. However, smoking generally makes asthmatics worse[153] and induces resistance to the therapeutic effects of inhaled glucocorticoids. Thus, asthma symptoms generally improve with smoking cessation.[154] Some smokers report an increase in cough in the weeks following cessation. However, among individuals with chronic bronchitis, symptoms of cough and sputum production decrease dramatically in the months following cessation.[155,156]

SPECIAL POPULATIONS

Smoking cessation approaches for special populations (e.g., hospitalized patients, those with medical and psychiatric comorbidities, and pregnant patients) are generally the same as for the general population.[157] Smoking cessation treatment can be started in hospital at the time of acute illness.[153] Success depends on adequate follow-up and support. Interestingly, withdrawal symptoms may be particularly mild in hospital, perhaps because there are few options to smoke. Concurrent treatment of individuals hospitalized with psychiatric illness for smoking cessation can be successful and does not compromise treatment of the comorbid psychiatric problem.[157] Treatment of pregnant smokers has been extensively reviewed.[158]

Smoking is a major risk factor for COPD. All three approved forms of pharmacotherapy, NRT,[159] bupropion,[160] and varenicline,[161] have demonstrated efficacy in the COPD population.

HARM REDUCTION

A more controversial approach for smokers who are unwilling or unable to quit at all, is that the health consequences may be partially addressed by reducing the exposure to smoke-derived toxins. This approach, termed "harm reduction," has been the subject of several reviews, including an Institute of Medicine report.[162,163] Four general categories of harm reduction are theoretically possible: (1) administration of agents to counteract the effects of cigarette smoking; (2) smoking reduction; (3) development of less toxic tobacco products; and (4) alternate nicotine delivery systems. This has become particularly important with the rapid increase in prevalence of vaping (see below). It is important to recognize that clear health benefits have not been established for any of these approaches, however, and novel health risks have been clearly associated with vaping.

Since cigarette smoking is thought to cause its effects through pathogenetic mechanisms that are at least partially defined, it is appealing to use such mechanisms as targets for therapeutic intervention. In this regard, antioxidants to ameliorate the oxidant-induced injury caused by cigarette smoke, and protease inhibitors to bolster the antiprotease defenses, are both potential therapies. While conceptually appealing, no data exist to suggest that any such approach is of benefit in continuing smokers.

Pharmacologic support may facilitate reduction in smoking. The observation that most smokers maintain a relatively constant nicotine intake creates the possibility that nicotine replacement can help sustain smoking reduction. Smoking reduction has also been achieved with several formulations of nicotine replacement, and there is some evidence for physiologic benefit. Short-term smoking reduction, facilitated with the use of nicotine polacrilex gum, was associated with improvements in lower respiratory tract inflammation assessed by bronchoscopy and bronchoalveolar lavage in a group of heavy smokers.[164,165] In patients with cardiac disease who reduced smoking, there were measurable improvements in cardiac function that were associated with improved oxygen delivery to the heart due to reduced carbon monoxide.[166]

Reducing the delivery of cigarette smoke toxins while still providing the smoker with a satisfactory cigarette has been pursued by some tobacco companies. This was a major motivation in the development of filtered cigarettes and of low-tar, low-nicotine cigarettes. Unfortunately, these approaches do not reduce, and may actually increase, exposure to smoke-derived toxins. As most smokers maintain constant nicotine intake, many smokers compensate for altered smoke composition by simply smoking more or by changing the way in which they smoke each cigarette.[167,168] By causing an altered smoking strategy, filtered and low-yield cigarettes may actually deliver more toxins.

Many of the cigarette-derived toxins are generated as a result of pyrolysis.[25] As a result, tobacco products that do not burn have the promise to yield fewer toxins. Several cigarette-like devices have been developed with similar goals. Some burn small amounts of processed tobacco together with a carbon heat source to have a taste that more closely resembles a cigarette.[169] Others electrically heat the tobacco. Whether the electronic cigarette will be effective as an alternative to smoking at present remains to be determined (described in more detail below).[163] Because of the rapid and widespread uptake, electronic cigarettes ("e-cigs" or vaping) have been particularly controversial and are discussed in detail in the following section. This led to early reviews and position statements by medical groups including the pulmonary community relating to these products.[170,171] Potential harm-reduction products appear to deliver less toxins in standardized smoking regimes. However, limited data are available on physiologic effects. In one study, a reduction in lower respiratory tract inflammation and airway metaplasia was observed among heavy smokers who switched to a harm-reduction product.[172] Whether such products are associated with health benefits, however, remains to be determined.

Non-burned tobacco products may also have advantages. Moist snuff, which has low nitrosamine content due to its processing, has been widely used for several decades in Sweden. It has been associated with a measurable decrease in a number of tobacco-related diseases among Swedish men compared with cigarettes, but not compared with abstinence.[173–176]

Harm-reduction strategies may have unforeseen problems. Reduced-risk products or smoking reduction strategies may encourage smokers to continue and thus discourage quit attempts. Available data, however, suggest the opposite. Smokers who switch to harm-reduction products or who reduce with pharmacologic support appear to have an increased rate of subsequent quits. It may be that the sense of mastery that comes with the reduction effort helps make smokers “able” to quit. There are other potential hazards. Reduced-risk products, for example, might be particularly appealing for individuals beginning smoking both because they may be easier to smoke and because they are not perceived as having significant risks. Finally, if use of reduced-risk products erodes the social climate that discourages smoking, such products could increase use of conventional cigarettes.

ELECTRONIC CIGARETTES AND VAPING

Electronic cigarettes (EC, also known as “electronic nicotine delivery systems”) are battery-operated devices that heat and aerosolize a liquid solution (an “e-liquid”).[177] E-liquids typically, but not always, contain nicotine. The other main e-liquid components include alcohol-based solvents (propylene glycol and vegetable glycerin) and flavorings.[178] Upon heating, this solution becomes more complex and releases toxic constituents (aldehydes, acrolein), though in much lower quantities compared with combustible cigarettes.[179] The commercialization of ECs developed independently of big tobacco companies,[180] and the products were initially conceived as a harm reduction tool for cigarette smokers.[181] Over time, however, ECs have provoked substantial controversy among tobacco control experts.[182] On one hand, individuals switching completely from cigarettes to ECs might substantially reduce exposure to combustion products and other toxicants.[183] On the other, the products may expose youth and nonsmokers to potent nicotine products that could engender addiction and cause additional health risks.[184,185]

ECs contain three basic components: (1) a battery to provide heat; (2) a metal heating element; and (3) a liquid solution.[177] Within this basic structure, ECs are highly heterogeneous with respect to product design, emissions, toxicity, and nicotine delivery.[186,187] They vary by size, strength of battery, accessibility by the user (i.e., open or closed systems), and the e-liquid used (resulting in countless combinations of nicotine concentration and flavorings).

EC use is known as “vaping.” Vaping is the inhalation of a heated, aerosolized substance. It is distinguished from smoking by its lower temperature and the absence of combustion products in the inhaled aerosol. Although ECs were initially designed for vaping nicotine, it has become recognized more recently that some people use EC devices to consume other substances such as tetrahydrocannabinol (THC), the main psychoactive chemical in marijuana.[188] The implications of these new EC use patterns may have a significant health impact (see “E-Cigarette or Vaping Product Use–Associated Lung Injury,” below).

■ Electronic Cigarettes and Public Health

The net effect of ECs on public health remains a subject of heated debate and is currently unknown. Since its inception, EC use has skyrocketed among youth and young adults, while use of combustible cigarettes has dropped steadily to an all-time low.[189] The long-term implications of this trend raise significant questions and concerns. Does long-term use of ECs produce similar health harms compared with cigarette smoking? Will the uptake of ECs lead to more or fewer combustible cigarette smokers in the future? Will a new generation of young people develop addiction to nicotine?

A comprehensive scientific review of ECs was published in 2018 by the National Academy of Sciences.[177] The data to date provide conclusive evidence that most EC products emit toxic substances, that EC toxicity varies substantially among products and individual use patterns, that accidental high-dose exposure to e-liquids or faulty EC batteries can be highly hazardous, and that completely substituting ECs for regular cigarettes reduces user exposure to many toxicants and carcinogens.[177] Substantial evidence suggests: (1) that nicotine exposure from ECs can induce dependence and may be similar to combustible cigarettes in some users, (2) that exposure to toxic substances is significantly lower compared with combustible cigarettes, (3) that EC aerosol constituents can induce endothelial dysfunction, oxidative stress, and DNA damage, (4) that youth who use ECs may be at higher risk of subsequent combustible cigarette smoking, and (5) that completely switching to ECs from combustible cigarettes may reduce short-term adverse health outcomes in several organ systems.

Despite the existing evidence, many key questions remain unanswered. Do ECs lead to pulmonary, cardiovascular, and oncologic diseases? If so, how does disease onset, probability, and severity compare with chronic cigarette smoking? Will the presence of ECs ultimately reduce or increase combustible cigarette use at the population level? How addictive are ECs compared with combustible cigarettes? What will this mean for public health? These questions will need to be answered over the next several decades through careful investigation.

■ Electronic Cigarettes in Smoking Cessation and Tobacco Harm Reduction

The overwhelming majority of tobacco-related harm derives from cigarette smoking.[190] Although smokeless tobacco consumption carries health risk, it is substantially less harmful than smoking.[191,192] Places such as Sweden, which has a substantial number of snus (smokeless tobacco) users, has the lowest rate of lung cancer among developed countries.[193] The idea that ECs use can promote harm reduction is appealing, at least in theory. The idea is to substitute smoke inhalation with the substantially less toxic EC aerosol, which is devoid of combustion products and has lower amounts of known carcinogens compared with smoke.[179,183,194,195] The concept is similar to providing methadone, buprenorphine, or clean needles to people who inject heroin. These steps do not entirely eliminate opioid-related risk, but they reduce risk substantially.[196–198] Much of the resistance to EC use as a harm reduction strategy arises from a lack of definitive data showing effectiveness and improved outcomes in the adult smoker population, as well as concerns over effects on youth and other nonsmokers. These data, if they exist, will not be available for many years, given the relatively short duration that ECs have been in widespread use. Thus, harm reduction from EC use remains a theoretical possibility to date but remains to be proven.

There is evidence suggesting that ECs use can help some people to stop combustible cigarette smoking, both at the population and individual levels.[199–201] Although unclear whether a causal effect, smoking rates have declined more quickly in the United States since the introduction of ECs into commercial markets, possibly indicating a substitution effect (i.e., people choosing to use ECs instead of cigarettes).[202] Early clinical trials examined ECs in both motivated and unmotivated cigarette smokers. These studies found smoking quit rates similar to or non-statistically higher than the nicotine patch, as well as reductions in cigarettes smoked per day.[203,204] Study limitations included low overall smoking quit rates and the use of early-generation EC products, which likely limited the statistical power necessary to observe differences between groups.

A significant follow-up study, which is the most important to date, is a multicenter trial of 886 smokers conducted throughout the United Kingdom that directly compared second-generation ECs to traditional combination nicotine replacement (e.g., nicotine patch, gum, lozenge).[201] Both groups received behavioral counseling as part of usual care. The key study finding was that those randomized to the EC group were nearly twice as likely to achieve smoking abstinence at week 52 compared with the NRT group (18.0% vs. 9.9%; relative risk, 1.83; 95% confidence interval, 1.30–2.58), with no differences in adverse events between groups. However, 80% of subjects in the EC group were still using their EC product at the end of the study, indicating that long-term nicotine use via EC was a key factor in maintaining smoking abstinence. As noted, the long-term health effects of chronic EC use remain unclear.

■ E-Cigarette or Vaping Product Use–Associated Lung Injury (EVALI)

In mid-to-late 2019, the U.S. Centers for Disease Control and Prevention (CDC) began receiving reports of acute lung injury cases clinically resembling the acute respiratory distress syndrome (ARDS) (see Chapter 140) occurring in patients who reported a history of EC vaping and had no other clear cause for lung injury.[205] The clinical syndrome commonly affected young people and resembled a systemic illness that typically resulted in fever, dyspnea, nausea/vomiting, pulmonary infiltrates, and acute respiratory failure that sometimes required mechanical ventilation.[206–208] A wide range of pathologic patterns were reported, and the presence of lipid-laden macrophages with oil red O staining was common.[207–209] Anecdotally, corticosteroids seemed to hasten recovery.

The discovery of this syndrome led to intense scrutiny and reporting of the new disease phenotype, subsequently named “e-cigarette or vaping product use–associated lung injury” (EVALI). A variety of ECs and vaping products were reported, making it initially difficult to pinpoint a specific cause of the epidemic. Importantly, the first case series published involving patients in Illinois and Wisconsin found that 84% of EVALI cases involved vaping of tetrahydrocannabinol (THC) oils in EC devices.[206] THC is the main psychoactive chemical in marijuana[210] and had not been previously widely recognized as a substance consumed via EC vaping. A subsequent investigation by CDC and FDA revealed that bronchoalveolar lavage samples from EVALI patients contained vitamin E acetate, a cutting agent used to dilute THC-containing e-liquids.[211] Follow-up investigations into the used products from EVALI cases seized by law enforcement revealed high proportions of illicit THC e-liquids containing vitamin E acetate.[212] These discoveries provided strong support that EVALI was driven predominantly by vitamin E acetate–contaminated THC e-liquids, although other EC-related chemical causes of acute lung injury could not be definitively ruled out.

■ Practical Considerations for Clinicians Treating Patients Who Use E-Cigarettes

The clinician is very likely to encounter EC use among patients in clinical settings.[213] The optimal approach to these patients, many of whom may be current or former cigarette smokers and have other medical and psychiatric comorbidities,[214] can be challenging. On one hand, it is clearly best for patients to abstain from inhalation of all toxic substances, including combustible cigarettes and ECs; this is certainly a message that physicians want to convey strongly to patients. Yet, for former smokers, EC use may prevent relapse into combustible smoking and might reduce harm.[201] The severe health harms of continued cigarette smoking are well established.[190] Furthermore, while there have been tested approaches to smoking addiction, the optimal approach to treating vaping addiction is unknown.

Thorough social and past medical histories will help identify the patient’s level of risk, in addition to other comorbidities (i.e., mental health and other substance use disorders) that may influence the course of nicotine addiction. Routine screening for tobacco product use should include a specific question about the use of ECs and vaping. Developing an understanding of the reasons for use, the duration and frequency of use, the types of products (e.g., nicotine content, flavorings, and use of other drugs, such as THC), and where the products were obtained (e.g., authorized retailers or from informal sources such as friends) is helpful. It is important to understand whether there is dual use of combustible cigarettes and ECs and whether ECs are being used to reduce combustible use or to supplement nicotine consumption in places where smoking is forbidden. Assessing motivation to discontinue use provides an opening to encourage abstinence and trials of other treatments, such as transdermal nicotine replacement, varenicline, bupropion, and behavioral counseling.

Advice should be framed carefully, as EC use in this population may prevent relapse into cigarette smoking. It is important to note that long-term abstinence rates from cigarette smoking are low, especially for those who do not achieve abstinence for at least 3 months.[215] Thus, the population of EC users (particularly those with past or present cigarette smoking history) may represent a group with a higher level of nicotine dependence. While cessation of all inhaled substances should be encouraged, permanent and complete cessation from combustible products should be highly prioritized. If the patient is solely using ECs (and not using combustible products), it is useful to explore whether they wish to stop vaping as well. Despite a lack of evidence of effectiveness in people who vape, the combination of behavioral and pharmacologic treatments, which is the standard of care for the treatment of cigarette smoking addiction, is a reasonable starting point. It is not clear whether attempting to reduce the nicotine level in e-liquids used is a beneficial strategy to promote vaping cessation, since individuals might engage in compensatory puffing behavior (e.g., bigger or longer puffs) to maintain similar nicotine intake.[216] Longitudinal support to monitor progress and try different approaches as needed will likely be required in these patients.

■ What Is the Future of E-Cigarettes?

EC use will continue into the 21st century, alongside combustible cigarettes and other tobacco products. The economic growth of ECs since their inception has been staggering, yet the global demand for the products remains only a tiny fraction of the combustible cigarette market. Future trends in EC use may depend largely upon regulatory efforts, which, in turn, will be affected by public perception and opinion about the products’ relative harms and benefits. Scientific discovery will drive part of this discussion, but economic and political factors also will play a significant role.

A natural experiment in EC regulation may be emerging, as the United Kingdom has widely promoted EC use among its adult smokers for harm reduction, while other countries, such as the United States, have cracked down on the EC market more strongly in an effort to protect youth. It will be critical to understand how these different approaches affect tobacco use and health at the population level. Longitudinal trends in both combustible and noncombustible tobacco use, as well as health effects in both youth and adult populations, will provide needed insight into the effects of ECs.

CONCLUSION

Cigarette smoking is a complex social and medical issue. The physician has a particularly important role in curbing smoking. Not only must the physician participate in efforts to reduce smoking as a citizen, but as a protector of public health and a possessor of specific expertise in healthcare matters, the physician must take an active role in health promotion. Such a role includes discouraging smoking and vaping initiation among younger patients, encouraging and assisting smoking patients to quit, and participating in social efforts designed to reduce smoking at various levels.

For individuals who are smokers, the clinician needs to approach smoking as a chronic relapsing disorder for which a range of effective treatments are available. These include nonpharmacologic and pharmacologic therapies. Optimal results can be achieved using a combined approach.

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CHAPTER 42

Rehabilitation in Chronic Obstructive Pulmonary Disease and Other Respiratory Disorders

Andrew L. Ries
Duc M. Ha

INTRODUCTION

Rehabilitation for patients with chronic lung diseases is well established as a means of enhancing standard pharmacologic and other therapies in controlling and alleviating symptoms and optimizing functional capacity.[1–5] The primary goal of any rehabilitation program is to restore the patient to the highest possible level of independent function. This goal is accomplished by helping patients and significant others learn more about the underlying disease, treatment options, and coping strategies. Patients are encouraged to participate actively in providing their own health care, become more independent in daily activities, and be less dependent on health professionals and expensive medical resources. Rather than addressing solely reversal of the disease process, rehabilitation focuses on improving disability from disease.

Historically, pulmonary rehabilitation strategies were developed and used primarily for patients with chronic obstructive pulmonary disease (COPD). However, pulmonary rehabilitation has also been applied successfully to patients with other chronic lung conditions, including interstitial lung diseases, asthma, cystic fibrosis, bronchiectasis, pulmonary hypertension, and thoracic cage abnormalities.[3,5–7] Also, among patients with lung cancer, rehabilitation prior to resectional surgery improves exercise capacity and may reduce perioperative complications and length of hospital stay.[8] Following surgery, rehabilitation can mitigate the adverse effects of treatment and improve physical function and symptom control, especially if initiated early.[9–12] Patients with advanced lung cancer can also experience improvements in exercise capacity with training.[13]

Pulmonary rehabilitation has been used successfully in the evaluation and preparation of patients for surgery, such as lung transplantation and lung volume reduction surgery, and in maximizing recovery after surgery.[14–16] Pulmonary rehabilitation has also been used to facilitate patient recovery from acute processes such as acute lung injury, or exacerbations of chronic lung disease requiring mechanical ventilation or acute hospital care. The 2020 worldwide COVID-19 pandemic highlights the needs and potential benefits of pulmonary rehabilitation for the large number of patients recovering from lung injury.[17]

Pulmonary rehabilitation is appropriate for any patient with stable lung disease who is disabled by respiratory symptoms. Even patients with advanced disease may benefit if they are selected appropriately and realistic goals are set.

This chapter defines pulmonary rehabilitation and outlines issues related to patient selection and evaluation. There is also discussion of key components of a pulmonary rehabilitation program, results and benefits of pulmonary rehabilitation, the use of pulmonary rehabilitation in various conditions and settings, and, finally, the role of rehabilitation as an adjunct to lung surgery.

DEFINITION

In 2013, the American Thoracic Society and European Respiratory Society adopted the following definition:

> "Pulmonary rehabilitation is a comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies, which include, but are not limited to, exercise training, education, and behavior change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence of health-enhancing behaviors."[3]

This definition highlights three important features of successful rehabilitation. First, the program is *multidisciplinary.* Pulmonary rehabilitation programs utilize expertise from various healthcare disciplines that is integrated into a comprehensive, cohesive program tailored to the needs of each patient. Second, the program is tailored to the *individual.* Patients with disabling lung disease require individual assessment of needs, individual attention, and a program designed to meet realistic individual goals. Third, the program addresses *multidimensional health issues* including physical, psychological, and social function as well as healthcare utilization.

The team of healthcare professionals in pulmonary rehabilitation may include physicians, nurses, respiratory and physical therapists, mental health professionals, exercise specialists, and others with appropriate expertise. The specific team make-up depends upon the resources and expertise available, but it usually includes at least one full-time staff member. Responsibilities of team members generally cross disciplines.[18]

Within this general framework, successful pulmonary rehabilitation programs have been established in both outpatient and inpatient settings and with different formats. A key to success is a dedicated, enthusiastic staff that is familiar with respiratory problems and can relate well to pulmonary patients and motivate them.

PATIENT SELECTION

Any patient with symptomatic chronic lung disease is a candidate for pulmonary rehabilitation (Table 42-1).[19] Appropriate patients are aware of disability from their disease and motivated to participate actively in their own care to improve their health status. Patients with mild chronic disease may not perceive their symptoms to be severe enough to warrant a comprehensive care program. On the other hand, patients with severe disease who are bed bound may be too limited to benefit greatly.

Criteria based on arbitrary lung function parameters or age alone should not be used in selecting patients.[4] Pulmonary function alone is not a good predictor of symptoms, function, or improvement after rehabilitation. Chronic lung disease is commonly associated with systemic features that contribute to functional limitations and may

TABLE 42-1 Patient Selection Criteria for Pulmonary Rehabilitation

Symptomatic chronic lung disease
Stable on standard therapy
Functional limitation from disease
Relationship with primary care provider
Motivated to be actively involved in and take responsibility for own health care
No other interfering or unstable medical conditions
No arbitrary lung function or age criteria

benefit from rehabilitation.[20] In general, selection should be based upon a person's disability from their disease, potential for improvement, and motivation to participate actively in a comprehensive self-care program. Also, pulmonary rehabilitation is not a primary mode of therapy. Patients should be stabilized on standard medical therapy and should not have other disabling or unstable conditions that might limit their ability to participate fully in the program and to concentrate on the necessary tasks.

The ideal patient for pulmonary rehabilitation, then, is one with functional limitation from moderate to severe lung disease who is stable on standard therapy, not distracted or limited by other serious or unstable medical conditions, willing and able to learn about his or her disease, and motivated to devote the time and effort necessary to benefit from a comprehensive care program.

PATIENT EVALUATION

The initial step is screening patients to ensure appropriate selection and to set realistic individual and program goals. The evaluation process includes the following components: interview, medical evaluation, psychosocial assessment, diagnostic testing, and goal setting (Table 42-2).

Interview

The screening interview is an important first step. It serves to introduce the patient to the program, review the medical history, and identify psychosocial problems and needs. Family members and significant others should be included. Communication with the primary care provider is important to establish the vital link for the rehabilitation staff to clarify medical questions prior to the program and facilitate subsequent recommendations. Care and attention in this initial evaluation helps in setting goals compatible with everyone's expectations as well as appropriate programmatic objectives.

Medical Evaluation

Reviewing medical history helps to identify the patient's lung disease and assess its severity. Other medical problems that might preclude or delay participation may be identified. Available laboratory data should be reviewed, including pulmonary function and exercise tests, rest and exercise arterial blood gas measurements, chest radiographs, electrocardiogram, and pertinent blood tests. Program staff can then determine the need for any additional information or action before the program begins.

TABLE 42-2 Components of a Comprehensive Pulmonary Rehabilitation Program

- Patient evaluation
  - Interview
  - Medical evaluation
  - Psychosocial assessment
  - Diagnostic testing
    - Pulmonary function
    - Exercise
    - Arterial blood gases/oximetry
  - Goal setting
- Program content
  - Education
  - Respiratory and chest physiotherapy instruction
    - Bronchial hygiene
    - Breathing retraining techniques
    - Oxygen
  - Exercise
  - Psychosocial support

Psychosocial Assessment

Successful rehabilitation requires attention not only to the patient's physical problems but also to psychological, emotional, and social issues. Patients with chronic illnesses experience psychosocial difficulties as they struggle to deal with symptoms they may not fully understand.[21]

Neuropsychological impairment is common in patients with chronic lung diseases and cannot be accounted for solely on the basis of age, depression, or organic disease. Commonly, such patients become depressed, frightened, anxious, and more dependent on others to care for their needs. Progressive dyspnea is a frightening symptom and may lead to a vicious "fear–dyspnea" cycle: With progressive disease, less exertion results in more dyspnea, which produces more fear and anxiety, which, in turn, lead to more dyspnea. Ultimately, the patient avoids any physical activity associated with both of these unpleasant symptoms.

In addressing these problems, the initial evaluation should assess the patient's psychological state and pay attention to "psychosocial clues" that may be apparent during the screening interview (e.g., level of family and social support, the patient's living arrangement, activities of daily living, hobbies, and employment potential). Important clues in initial interviews to the patient's emotional state may be evident in nonverbal communication, such as facial expression, physical appearance, handshake, and personal space (distance between individuals when conversing). Cognitive impairment that may limit the patient's ability to participate fully in the rehabilitation program may be identified. Family members and significant others may provide valuable insight and should be included in the screening process and program whenever possible.

Diagnostic Testing

Planning an appropriate rehabilitation program requires accurate, current information. The complexity of the testing procedures performed depends upon individual patient and program goals as well as the facilities and expertise available.

Pulmonary function testing is used to characterize lung disease and quantify impairment. Spirometry and lung volume measurements are most useful. Other tests (e.g., diffusing capacity, maximal respiratory pressures to assess muscle strength) can be added as needed.

Exercise testing helps to assess the patient's exercise tolerance and to evaluate changes in arterial blood gases (e.g., hypoxemia or hypercapnia) with exercise.[22,23] This may also uncover coexisting diseases (e.g., heart disease). The exercise test is also used to establish a safe and appropriate prescription for subsequent training.

Maximal exercise of patients with chronic lung disease is limited largely by their breathing reserve, although chronic lung diseases are increasingly recognized as being associated with systemic effects that may also contribute to exertional symptoms (e.g., muscle fatigue). Simple pulmonary function tests such as spirometry can be used to estimate a patient's capacity for sustained breathing (maximal ventilation) during exercise. The forced expiratory volume in 1 second (FEV_1) is most useful in this regard. However, lung function only provides an estimate of an individual patient's maximum work capacity. Exercise tolerance depends also on the patient's perception and tolerance of the subjective symptom of breathlessness. Therefore, it is important to exercise patients to assess their physical function and symptom tolerance.

Exercise evaluation for rehabilitation is most easily performed with the type of activity planned for training (e.g., treadmill for a walking training program). Laboratory exercise testing is most commonly performed using either (1) rapid, progressive, incremental levels to a symptom-limited maximum or (2) defined steady-state levels.[22,24] The former is most useful for determining exercise tolerance and the limitations to maximum performance. The latter may be preferred for assessing training prescriptions. Simpler exercise tests, such as the 6-minute walk test, have been used increasingly in recent years to measure exercise tolerance outside of a laboratory setting.[25] These timed distance walk tests measure the maximum distance a person can walk within a defined period (e.g., 6 minutes). Such tests have the advantage of requiring less equipment and technical expertise; however, attention must be paid to the details of testing procedures because variations in factors such as the walking course, patient instructions, encouragement during tests, use of oxygen or monitoring devices, and number of tests performed will influence the results. Also, these tests do not provide the detailed physiologic data typically included in more formal laboratory exercise tests.

Measurement of arterial blood gases at rest and during exercise is important because of the frequent but unpredictable occurrence of exercise-induced hypoxemia.[26] Arterial blood gas sampling during exercise makes testing more complex. The noninvasive estimate of arterial oxygen saturation by cutaneous (e.g., pulse) oximetry is useful for continuous monitoring, but it has limited accuracy (95% confidence limits, ± 4%–5%).[27]

Goals

After a patient's medical, physiologic, and psychosocial state have been evaluated, specific goals should be set that are compatible with his or her disease, needs, and expectations. Goals should be realistic in light of the program objectives. Family members and significant others should be included so that all understand what can and cannot be achieved. Programs should evaluate individual patients to document changes before and after pulmonary rehabilitation with standardized outcome measures of exercise tolerance (e.g., 6-minute walk distance) and symptoms (e.g., dyspnea) or health status (e.g., health-related quality of life).

PROGRAM CONTENT

Comprehensive pulmonary rehabilitation programs typically include several key components: education, instruction in respiratory and chest physiotherapy, psychosocial support, and exercise training (Table 42-2). Often, the various components are provided simultaneously; for example, during an exercise session, a patient may learn and practice breathing techniques for symptom control while being encouraged and supported by staff or other patients. Although there is no consensus regarding the optimal duration of a pulmonary rehabilitation intervention, typical programs last 6 to 12 weeks with 2 to 3 sessions per week, each session including several hours of supervised exercise training and individual or group education and psychosocial interventions.

Education

Successful pulmonary rehabilitation depends upon an understanding of lung disease and active involvement by patients and important others in providing social support. Education is an integral component; even patients with severe disease can gain a better understanding of their disease and learn specific means to deal with problems. Instruction can be provided individually or in small groups, but it should be adapted to different learning abilities. Topics discussed commonly include normal lung function, chronic lung disease, medications, nutrition, travel, stress reduction and relaxation, reasons to call the physician, and planning a daily schedule. Individual instruction and coaching may be provided on the use of respiratory therapy equipment and supplemental oxygen, breathing techniques, bronchial drainage, chest percussion, energy-saving techniques, and self-care tips. The general philosophy is to encourage patients to assume responsibility for their own care and become partners with their physician in providing the care.[28]

Despite the importance of education, it is unlikely that increased patient knowledge alone will lead to improved health status. It is more difficult to change attitudes and behaviors. Patients require specific, individualized treatment strategies, instruction, and reinforcement. Thus, education is a necessary but not sufficient component of pulmonary rehabilitation.

Respiratory and Chest Physiotherapy Techniques

Patients with chronic lung disease use, abuse, and are confused about respiratory and chest physiotherapy techniques. In pulmonary rehabilitation, each patient's needs for respiratory care techniques should be assessed and instruction provided in proper use. These techniques may include chest physiotherapy to control secretions, breathing retraining techniques to relieve and control dyspnea and improve ventilatory function, and proper use and care of respiratory equipment including nebulizers, metered dose inhalers, and supplemental oxygen.

Bronchial Hygiene

Patients with chronic lung diseases frequently have abnormal lung clearance mechanisms that increase problems with retained secretions and infection. Therefore, rehabilitation programs teach a variety of chest physiotherapy techniques for secretion control (e.g., coughing, postural drainage, chest vibration, and percussion). These are important for patients who experience excess mucus production during exacerbations as well as for those with chronic sputum production. The use of mucolytic agents to reduce viscosity of secretions is of questionable benefit.[29,30]

Breathing Retraining Techniques

Pulmonary rehabilitation typically includes instruction in breathing techniques, such as diaphragmatic and pursed lips breathing—techniques aimed at helping patients relieve and control breathlessness, improve their ventilatory pattern (i.e., slowed respiratory rate and increased tidal volume), prevent dynamic airway compression, improve respiratory synchrony of the abdominal and thoracic musculature, and improve gas exchange.[31] Review of studies evaluating these techniques indicates that improvement in symptoms (e.g., dyspnea) is a more consistent finding than are measurable changes in physiologic parameters. The diaphragmatic breathing technique is a maneuver in which the patient consciously coordinates abdominal wall expansion with inspiration and slows expiration through pursed lips. The primary effect is to slow respiratory rate and increase tidal volume. Pursed-lip breathing is commonly taught to pulmonary patients, particularly those with COPD. This technique was observed by Laennec as early as 1830 and advocated as a physical exercise for pulmonary patients in the early part of the twentieth century. As a maneuver assumed naturally by many patients with respiratory disease, pursed-lip breathing is characterized by tensing the lips and narrowing the mouth opening during expiration. The aim is to slow expiration and maintain positive airway pressure to "stent the airways open" and prevent collapse.[32]

Oxygen

When chronic oxygen therapy is required, available delivery methods should be reviewed to help select the best system for the patient's needs. Supplemental oxygen is beneficial for patients with severe resting hypoxemia. Long-term continuous oxygen therapy has been clearly shown to improve survival and reduce mortality and morbidity in hypoxemic patients with COPD.[33,34] The benefits of supplemental oxygen for nonhypoxemic patients or those with intermittent hypoxemia (e.g., during exercise or sleep) are less clearly defined. Although continuous oxygen therapy is feasible and safe, maintaining patients on supplemental oxygen presents several challenges. Handling equipment is particularly difficult for physically disabled and frail patients. Therefore, it is important to assess each person's oxygen needs and provide appropriate instruction.[35,36]

Several new developments have improved the efficiency of gas delivery systems and patient compliance with continuous oxygen therapy. Liquid oxygen provides more gas with less weight than tanks of compressed gas, particularly in portable systems. Oxygen-conserving devices may increase the efficiency of delivery, reducing flow requirements and prolonging the life span of portable gas sources. Transtracheal oxygen delivery may help to improve compliance and avoid problems with nasal catheters; however, patients must be instructed carefully in caring for the catheter.[37]

■ Exercise

Exercise is important in pulmonary rehabilitation.[38] Considerable evidence supports favorable responses to exercise training in patients with chronic lung diseases.[5,36] Benefits are both physiologic and psychological. Patients may increase their maximum capacity and endurance for physical activity, even though objective measures of lung function do not usually change. Patients may also benefit from learning to perform physical tasks more efficiently. Exercise training provides an ideal opportunity for patients to learn their capacity for physical work and use and practice methods for controlling dyspnea (e.g., breathing and relaxation techniques). Of all the components in a comprehensive pulmonary rehabilitation program, exercise is probably the most costly and labor-intensive, considering the personnel, equipment, and expertise required. Principles of exercise for patients with lung disease differ from those based on normals or other patient populations because of differences in the limitations to exercise and the problems encountered in training.

Many approaches have been used to train the person with chronic lung disease. To be successful, the program should be tailored to the individual's physical abilities, interests, resources, and environment. For general application, techniques should be simple and inexpensive. As in normals and other patients, benefits are largely specific to the muscles and tasks involved in training. Patients tend to do best with activities and exercises for which they are trained. Walking programs are particularly useful. They have the added benefit of encouraging patients to expand social horizons. In inclement weather, many can walk indoors (e.g., at shopping malls). Other types of exercise (e.g., cycling, swimming) also are effective. Patients should be encouraged to incorporate regular exercise into daily activities they enjoy (e.g., golf, gardening). Since many persons with chronic lung disease have limited exercise tolerance, emphasis during training should be placed on increasing endurance. Changes in endurance with rehabilitation are often greater than changes in maximal exercise tolerance and allow patients to become more functional within their physical limits. Increase in maximum exercise is also possible as patients gain experience and confidence. Resistive training is also used commonly in rehabilitation and can lead to significant increases in muscle strength that are important for many activities of daily living.[36,39]

■ Exercise Prescription

Selecting a training target based upon a predetermined percentage of predicted maximal heart rate or ($\dot{V}O_2$) is a well-established practice for normals or patients without underlying pulmonary disease. However, in patients with chronic lung diseases, the best method of choosing an appropriate training prescription is less clearly defined. Exercise tolerance in pulmonary patients is typically limited by maximal achievable ventilation and breathlessness. Such patients frequently do not reach their limits of cardiac or peripheral muscle performance.

Much controversy exists regarding the appropriate training intensity target for patients with chronic lung disease. Use of a target heart rate has been advocated by some, although it is recognized that such a target may not be reliable for patients with more severe disease. Many patients with lung disease can be trained at a high percentage of maximal exercise tolerance, with work levels approaching or even exceeding the maximal level reached on the initial exercise test. In a study of 52 patients with moderate to severe COPD, patients were able to perform endurance exercise testing at an average workload of 95% of their baseline maximum.[40] After 8 weeks of training, these patients were training at 86% of the baseline maximum. In fact, many patients with severe COPD were exercising at levels exceeding their baseline maximum. In another study that examined 59 patients with moderate to severe COPD who trained at levels near their ventilatory limits, a mean peak exercise ventilation of 100% of measured maximal voluntary ventilation was achieved after 12 days of training and at 3 months of follow-up.[41] These findings suggest that even patients with advanced disease can be trained successfully at or near maximal exercise levels.

Based on the findings noted previously, some pulmonary rehabilitation programs define exercise targets and progression during training more by symptom tolerance than heart rate, work level, or other physiologic measurements. Ratings of perceived symptoms (e.g., breathlessness) help teach patients to exercise to "target" levels of breathing discomfort. A typical approach is to begin training at a level that the patient can sustain with reasonable comfort for several minutes and then to increase the time or exercise level according to symptom tolerance. Patients are encouraged to exercise daily and increase exercise duration up to 15 to 30 min of continuous activity. This graduated program helps patients to achieve a goal of improved tolerance for tasks of daily living, which often require a period of sustained activity.

■ Blood Gas Changes

A major problem in planning a safe exercise program for patients with lung disease is the potential for worsening of hypoxemia with exercise. Patients who are not hypoxemic at rest may develop changes in arterial oxygenation that cannot be predicted reliably from resting measurements of pulmonary function or gas exchange.[26] Normal individuals do not become hypoxemic with exercise. In patients with obstructive lung disease, Pa_{O_2} changes unpredictably during exercise. In patients with mild COPD, Pa_{O_2} typically does not change with exercise; in fact, it may even improve. However, in patients with moderate to severe COPD, Pa_{O_2} may increase, decrease, or remain the same. Patients with interstitial lung disease commonly develop worsening oxygenation with exercise.

Based on these observations, it is important to evaluate a patient's oxygenation status both at rest and during exercise. Such testing is also used to prescribe oxygen therapy at rest and with physical activity. With the availability of convenient, portable systems for ambulatory oxygen delivery, hypoxemia is not a contraindication to safe exercise training.

■ Other Types of Exercise

Exercise programs for pulmonary patients typically emphasize lower extremity training (e.g., walking or cycling). Since exercise conditioning is largely specific to the muscles and tasks involved in training, other forms of exercise may be particularly valuable for persons with chronic lung diseases.

Upper Extremity Training

Many patients with chronic lung disease report disabling dyspnea with daily activities involving the upper extremities (e.g., lifting, grooming) at much lower work levels than with the lower extremities. Upper extremity exercise is accompanied by a higher ventilatory demand for a given level of work than is lower extremity exercise. Given the aforementioned muscle specificity of training, upper extremity exercises may be important in helping pulmonary patients cope better with common daily activities.[42]

Ventilatory Muscle Training

The potential role of ventilatory muscle fatigue as a cause of respiratory failure and ventilatory limitation in patients with chronic lung disease has stimulated attempts to train the ventilatory muscles. Techniques of isocapnic hyperventilation, inspiratory resistive loading, and inspiratory threshold loading have been shown to improve function of the respiratory muscles in both normals and patients. In normals, respiratory muscle function does not limit exercise tolerance; therefore, specific respiratory muscle training is unlikely to be of clinical benefit. In patients with COPD, the patient group most extensively studied, improvement in general exercise performance from ventilatory muscle training alone has not been demonstrated consistently. Thus, the role of respiratory muscle training as a routine component of pulmonary rehabilitation has not been clearly established.

■ Psychosocial Support

An essential component of pulmonary rehabilitation is psychosocial support, the goal of which is to help patients combat progressive feelings of hopelessness and an inability to cope with chronic, progressive disease.[21] Depression is common in patients with chronic pulmonary disorders, as are anxiety (especially anxiety over dyspnea), denial, anger, and isolation. Patients become sedentary and dependent upon family members, friends, and medical services to provide for their needs. Excessive concern over other physical problems and psychosomatic complaints arise. Sexual dysfunction and fear are common and represent often unspoken consequences of chronic lung disease. Patients may also demonstrate cognitive and neuropsychological dysfunction, possibly related to or exacerbated by the effects of hypoxemia on the brain.

Psychosocial support is provided best by a warm and enthusiastic staff who can communicate effectively with patients and devote the time and effort necessary to understand and motivate them. Family members and significant others should be included in activities so that they can understand the disease and help the patient cope. Support groups also are effective. Patients with severe psychological disorders may benefit from individual counseling and therapy. Psychotropic drugs should generally be reserved for patients with more severe psychological dysfunction.

BENEFITS OF PULMONARY REHABILITATION

Pulmonary rehabilitation is an established effective management strategy for people with COPD that improves functional and maximal exercise capacity and health-related quality of life.[1–3,5] It also effectively alleviates dyspnea and fatigue, enhances the sense of disease control, and improves emotional functioning (Table 42-3). Traditionally, pulmonary rehabilitation is thought to be beneficial only for patients with stable disease. However, in more recent years, rehabilitation has been demonstrated to have an important role for those recovering from acute disease. In a landmark study, Man and coworkers recruited 42 patients within 10 days of discharge from hospitalizations for COPD exacerbations to undergo an 8-week pulmonary rehabilitation program.[43] Compared with usual care, patients who underwent pulmonary rehabilitation experienced large and clinically meaningful improvements in exercise capacity and health-related quality of life. Subsequent trials have replicated these findings, additionally demonstrate benefits towards reducing hospital readmission (Fig. 42-1) and possibly mortality risks.[44–47] The mechanisms for benefits are multifactorial and include mitigating hospital-associated disability and reversing the negative consequences of disease exacerbation on muscle and cognitive function, comorbidity control, and self-efficacy.[48] Therefore, pulmonary rehabilitation is an important therapy that spans across the life course and disease severity for people with COPD, to reduce morbidity and possibly mortality.

TABLE 42-3 Results of Pulmonary Rehabilitation

Decreases in
Medical resource utilization (e.g., hospitalizations, emergency room visits)
Respiratory symptoms (e.g., breathlessness)
Psychological symptoms (e.g., depression, fear)
Increases in
Quality of life
Physical activity
Exercise tolerance (endurance, maximal level of activities of daily living, strength)
Knowledge
Independence
Return to work possible
No change in lung function
Possible prolonged survival

Benefits and cost savings associated with pulmonary rehabilitation have been demonstrated not only in highly specialized centers, but also in community-based practice settings.[3,5,49] A collaborative study of 647 patients in 10 centers in California reported significant improvements in dyspnea and health-related quality of life along with substantial reduction in measures of healthcare utilization over 18 months of follow-up (Fig. 42-2).[50] Similar findings with a reduction in hospital and intensive care unit days in the year after compared with the year before pulmonary rehabilitation were reported by a consortium of 11 centers in Connecticut and New York in 128 patients.[51] Overall, among treatment options for patients with COPD, pulmonary rehabilitation has been shown to be very cost-effective (Fig. 42-3).[52]

PULMONARY REHABILITATION AND LUNG SURGERY

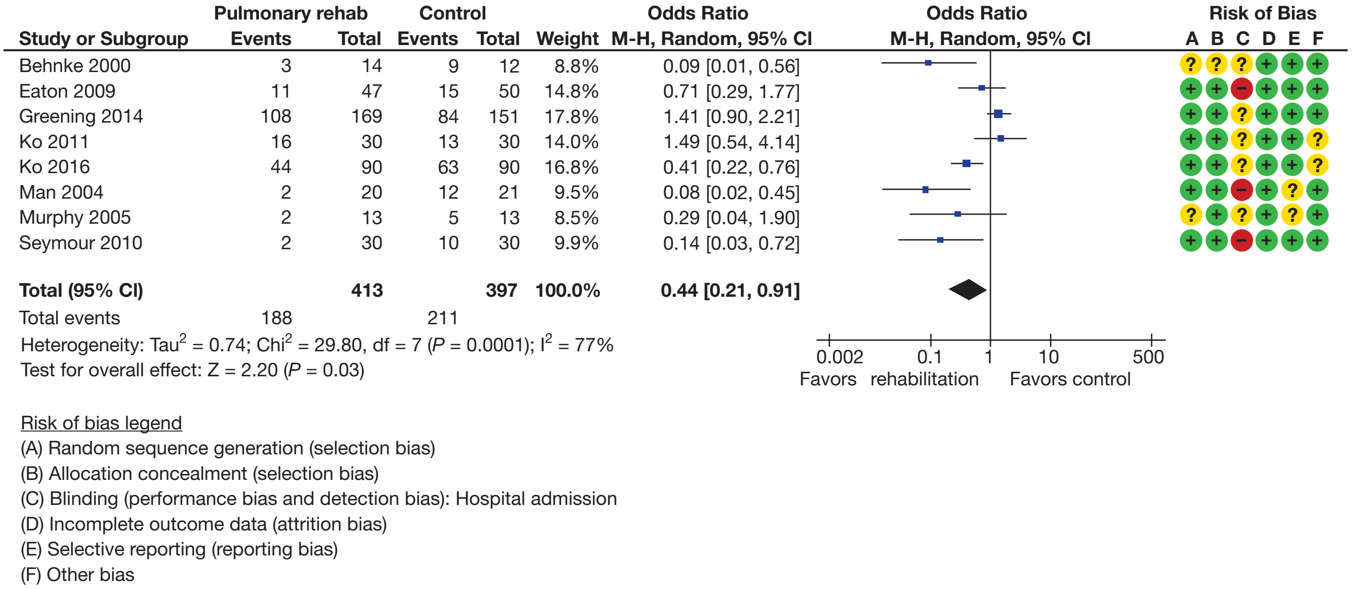
In recent years, surgical options for patients with severe, disabling lung disease have expanded. Lung surgery in these patients represents new challenges and may further compromise already reduced lung function. Pulmonary rehabilitation has been found to be a valuable adjunct in preparing the patient for surgery or in postsurgery recovery.

■ Lung Transplantation

Pulmonary rehabilitation is recommended and used commonly in both the preoperative and postoperative phases of lung transplantation programs.[14] Although the general strategies of rehabilitation may be similar, the individual and program goals and specific program components differ.

■ Pretransplant Rehabilitation

Patients with advanced lung disease who are candidates for lung transplantation are usually evaluated by the transplant team and then referred for pulmonary rehabilitation after their transplant candidacy is approved. Rehabilitation staff evaluate the patient to assess needs and plan an appropriate program that can be maintained throughout a waiting period, which may last months to



Study or Subgroup	Pulmonary rehab Events	Pulmonary rehab Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
Behnke 2000	3	14	9	12	8.8%	0.09 [0.01, 0.56]	?	?	?	+	+	+
Eaton 2009	11	47	15	50	14.8%	0.71 [0.29, 1.77]	+	+	−	+	+	+
Greening 2014	108	169	84	151	17.8%	1.41 [0.90, 2.21]	+	+	?	+	+	+
Ko 2011	16	30	13	30	14.0%	1.49 [0.54, 4.14]	+	+	?	+	+	?
Ko 2016	44	90	63	90	16.8%	0.41 [0.22, 0.76]	+	+	?	+	+	?
Man 2004	2	20	12	21	9.5%	0.08 [0.02, 0.45]	+	+	−	+	?	+
Murphy 2005	2	13	5	13	8.5%	0.29 [0.04, 1.90]	?	+	?	+	?	+
Seymour 2010	2	30	10	30	9.9%	0.14 [0.03, 0.72]	+	+	−	+	+	+
Total (95% CI)		**413**		**397**	**100.0%**	**0.44 [0.21, 0.91]**						
Total events	188		211									

Heterogeneity: $\text{Tau}^2 = 0.74$; $\text{Chi}^2 = 29.80$, df = 7 ($P = 0.0001$); $I^2 = 77\%$
Test for overall effect: Z = 2.20 ($P = 0.03$)

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias): Hospital admission
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Figure 42-1 Meta-analysis of the effects of pulmonary rehabilitation, compared with usual care, on hospital readmissions following acute exacerbations of COPD. *(Reproduced with permission from Puhan MA, Gimeno-Santos E, Cates CJ, et al. Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2016;12(12):CD005305.)*

years. Since these patients have advanced disease with limited life expectancy, the goals in the preoperative period differ from those that typically apply to rehabilitation in chronic lung disease.

The overall goals of pretransplant pulmonary rehabilitation are to maintain function, monitor disease progression, prevent complications, provide education about the underlying lung disease and lung transplantation, and offer psychosocial support for patients and families in coping with the stresses of waiting for a potentially life-saving procedure. Although patients may have some initial improvement in exercise tolerance or endurance as they begin rehabilitation, the primary goal for these patients is to maintain mobility and exercise capacity. Exercise sessions also provide an excellent means to monitor disease progression and to detect, at an earlier stage, problems that commonly occur (e.g., increased breathlessness or reduced arterial oxygenation with exercise).

The goals of education in the pretransplant period are to teach patients about their underlying lung disease, the transplant procedure itself, and expectations following transplantation. Patients can also be taught techniques for self-care and self-assessment that will be useful before and after surgery. The psychosocial stresses of waiting for transplantation are considerable. Many patients feel as though their lives are "on hold." Some may have moved away from family and social support networks to live close to the transplant center. Providing support for patients and families during this time, whether through formal group support sessions or informal contact with supportive staff and other patients, helps patients cope better with these problems.

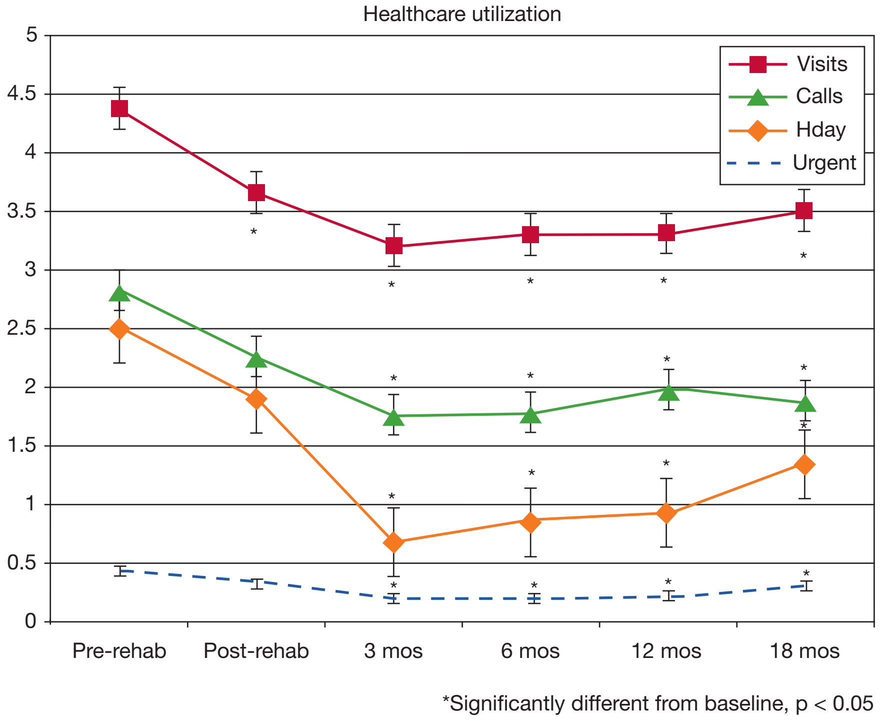


Figure 42-2 Changes in healthcare utilization over 18 months after pulmonary rehabilitation in a collaborative study of 647 patients in 10 centers in California. Results are presented as mean ± SE. *(Reproduced with permission from California Pulmonary Rehabilitation Collaborative Group. Effects of pulmonary rehabilitation on dyspnea, quality of life, and healthcare costs in California. J Cardiopulm Rehabil. 2004;24(1):52–62.)*

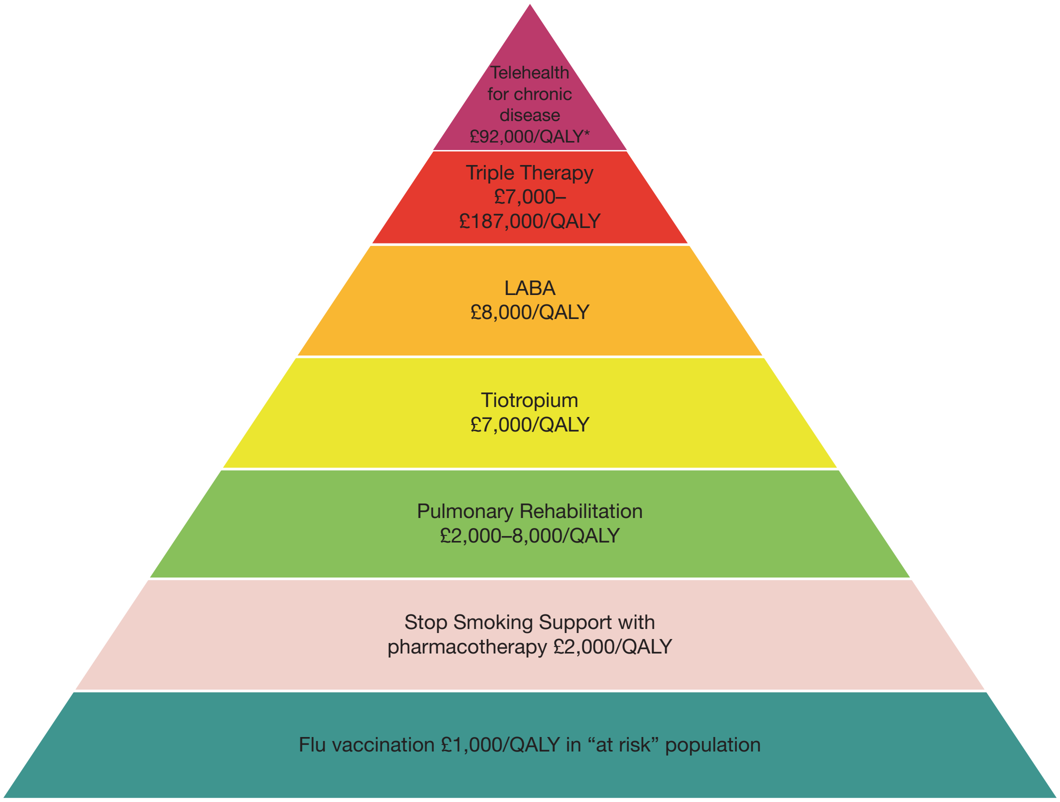

Telehealth for chronic disease £92,000/QALY*
Triple Therapy £7,000–£187,000/QALY
LABA £8,000/QALY
Tiotropium £7,000/QALY
Pulmonary Rehabilitation £2,000–8,000/QALY
Stop Smoking Support with pharmacotherapy £2,000/QALY
Flu vaccination £1,000/QALY in “at risk” population

Figure 42-3 Cost-effectiveness of various COPD interventions estimated as cost per quality-adjusted life year (QALY) by the London Respiratory Network with The London School of Economics. *(Reproduced with permission from Ashdown H, Steiner M. Delivering high value therapies in COPD: the secret is in the marketing. Eur Respir J. 2019;53(4):1900215.)*

Posttransplant Rehabilitation

After lung transplantation, patients must learn to cope with a new level of function, new expectations, and a new set of problems. Rehabilitation for patients in this phase can facilitate physical reconditioning, help implement self-care and assessment techniques, and facilitate coping with the psychosocial adaptations to a new lifestyle.

Goals of exercise training after rehabilitation are improved physical work tolerance and continued assessment of symptoms and oxygenation as early warning signs of complications, including rejection and infection. Educational goals are focused on self-care and assessment and the importance of compliance with a new medical regimen. Psychosocial support can assist with adaptation to a new set of stresses related to additional demands and expectations from both patients for themselves and significant others. Patients who are used to being sick, disabled, and cared for by others may now be expected to be well, function independently, return to work, and provide support for others.

Lung Volume Reduction Surgery

Among patients with severe emphysema, pulmonary rehabilitation is commonly part of the management plan to optimize them prior to lung volume reduction, either surgically or bronchoscopically, and to facilitate recovery following surgery.[15,16] Since these patients have severe, disabling chronic lung disease, they are typically good candidates for pulmonary rehabilitation. Enrolling patients in rehabilitation prior to surgery has the advantage of optimizing their functional status, improving physical and psychological symptoms, helping them learn more about their disease and alternative treatment options, and improving their skills for coping and actively co-managing their disease. Patients can then make an informed decision about surgical treatment based upon their optimal level of baseline function. After surgery, similar to the posttransplant period, rehabilitation helps patients to adapt to new levels of function and to reassess symptoms and oxygenation needs.

Rehabilitation After Lung Resection

Patients who undergo pulmonary resection frequently experience a significant increase in symptoms and reduced functional status. This is particularly true for patients with underlying chronic lung disease. Most commonly, surgery is used to treat patients with thoracic neoplasms who are deemed to have resectable disease and are operative candidates. Following resection, these patients with already limited lung function have to learn to adapt to a new, lower level of function. Similar changes may be observed in patients who undergo radiation therapy. Patients in a stable phase of their treatment or in remission may be appropriate candidates for pulmonary rehabilitation. Improvement in health status, physical and psychological symptoms, exercise tolerance, and quality of life—as well as reduced healthcare burdens—are potential benefits. These patients' survival may be as limited by their underlying lung disease as by their treated malignancy.[8–13]

EXPANDING ACCESS

Despite compelling evidence of benefits, pulmonary rehabilitation is delivered to <5% of eligible patients.[46,53,54] Limited program availability and geographic disparity among existing programs are significant barriers to broad and equitable delivery of pulmonary rehabilitation.[55] In addition, insufficient clinician and patient knowledge, patient fear of exercise and rehabilitation, and transportation and social barriers are factors that hinder the uptake of pulmonary rehabilitation.[54] During the 2020 global COVID-19 pandemic, center-based pulmonary rehabilitation programs were generally unavailable to these high-risk patients due to social distancing recommendations. Alternative models that enable delivery of pulmonary rehabilitation in the home setting may be important in making this important treatment available to more patients.[56] The use of telehealth technology to move pulmonary rehabilitation programs away from centers and into patients' homes shows promise.[57] For example, a randomized controlled trial of 166 patients with COPD assigned to receive 8 weeks of outpatient pulmonary rehabilitation demonstrated noninferiority for the home-based compared with center-based strategy on the 6-minute walk distance.[58] Such programs can be remotely delivered using videoconferencing, web-based platforms, mobile phones, and/or telephone with simple and portable exercise equipment.[59] In addition, these programs may also need to incorporate technology-enabled assessments to individualize exercise therapy, monitor safety, and evaluate effectiveness. While home-based strategies are associated with higher patient adherence,[60] limited in-person and group contacts may minimize some of the psychosocial benefits that are important features of center-based programs. Nevertheless, telerehabilitation may be necessary in some circumstances.

SUMMARY AND FUTURE OF PULMONARY REHABILITATION

Pulmonary rehabilitation has been well established as a means of improving functional status and reducing the disability and economic burden of the growing number of patients with chronic lung diseases. In adopting a broad rehabilitation medicine perspective, such programs provide interdisciplinary expertise directed toward the needs of the individual disabled patient.

Much of the experience in pulmonary rehabilitation has been in patients with COPD. However, it is clear that similar benefits can result for patients with other disabling chronic pulmonary conditions as well as those recovering from acute processes. Pulmonary rehabilitation may also play an important role in the preoperative evaluation, preparation, and postoperative recovery of patients undergoing surgical procedures, including lung transplantation, lung volume reduction surgery, and lung resection. In many parts of the world, a major challenge for the widespread application of pulmonary rehabilitation to the large number of patients with chronic lung diseases relates to acceptance by health policy makers and health insurers about the benefits and cost savings associated with this treatment. Given the small number of patients who currently have access to pulmonary rehabilitation programs and services, expanding access to the large number of other patients who could benefit is of particular importance. The use of new technologies, such as telemedicine, to reach more patients is particularly appealing, especially following the COVID-19 pandemic that seriously restricted access to the usual outpatient pulmonary rehabilitation centers. It is hoped that, with time and experience, the benefits of pulmonary rehabilitation as an effective, preventive health intervention that can improve patient outcomes and reduce healthcare costs will be better recognized and more widely applied.

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CHAPTER 43

The Biology of Asthma

Geoffrey L. Chupp
Matthew C. Bell
William W. Busse

INTRODUCTION

Asthma is a chronic inflammatory disease of the airways characterized by persistent variable symptoms that include shortness of breath, cough, and wheezing.[1] It is the most common chronic lung disease and one of the most prevalent diseases in the United States, affecting more than 20 million adults and 7 million children.[2] Attempts to elucidate the cellular and molecular effector pathways that contribute to asthma have led to the realization that it is a protean disease driven by many cell types and mechanisms. This degree of mechanistic variation explains the numerous clinical phenotypes that are now recognized, as well as differences in response to treatment with inhaled therapies and the targeted biologic treatments that have entered the clinic over the last decade.

Core to the pathogenesis of asthma is bronchoconstriction and variable airflow obstruction, airway hyperresponsiveness, and chronic airway inflammation.[3] It is, however, the complex interplay between these factors that eventually defines the clinical expression of disease in individual patients. Here, a close examination of the cellular and molecular mediators involved in each of these components will be presented to allow for a more comprehensive understanding of this complex disease.

ADAPTIVE AND INNATE INFLAMMATORY RESPONSES IN ASTHMA

The inflammatory response in the airways of patients with asthma is complex, heterogenous, and evolves over time, but the prototypical events seen in most patients with asthma (65%–80%) are type 2 (T2) inflammatory responses (Fig. 43-1). T2 inflammation is currently thought of as being driven by both innate and adaptive mechanisms to varying degrees in each individual with asthma, which explains much of the heterogeneity in clinical presentation, biomarkers, and treatment response. The most well-understood T2 pathway is the

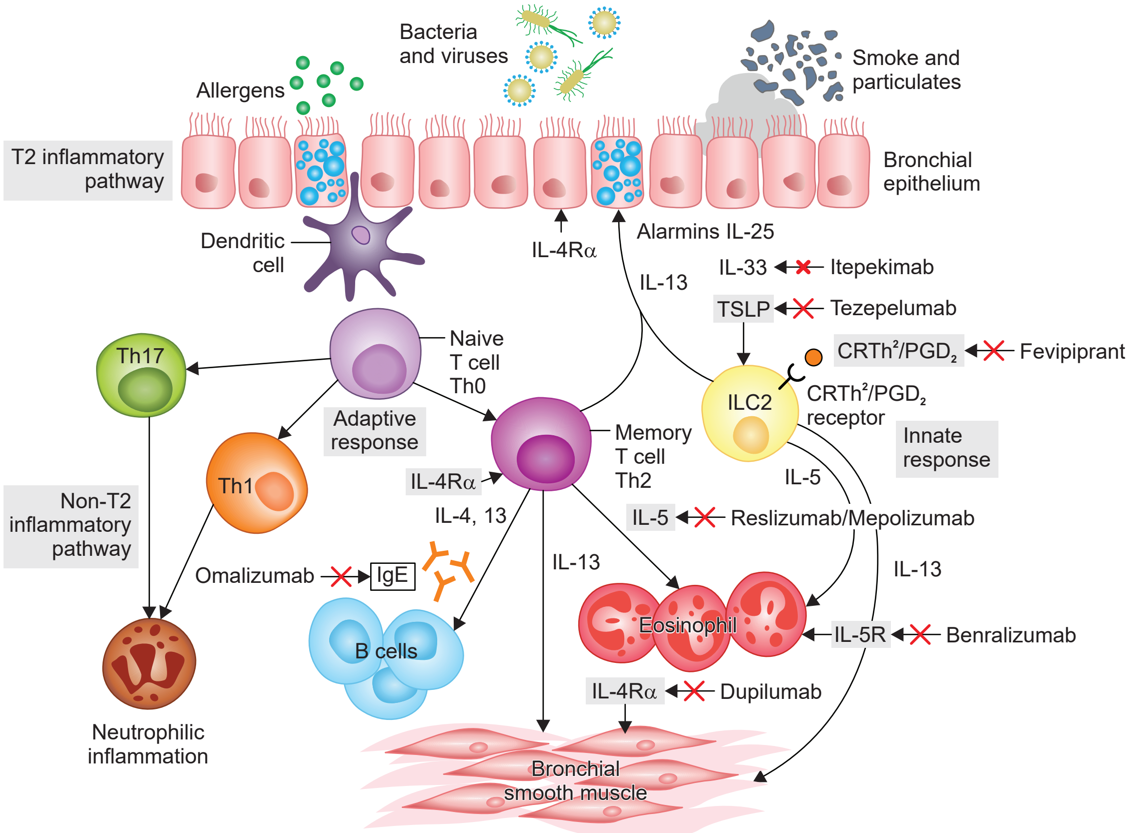

Bacteria and viruses
Smoke and particulates
Allergens
T2 inflammatory pathway
Bronchial epithelium
Dendritic cell
IL-4Rα
Alarmins IL-25
IL-13
IL-33
Itepekimab
TSLP
Tezepelumab
CRTh^2/PGD$_2$
Fevipiprant
Th17
Naive T cell Th0
ILC2
CRTh^2/PGD$_2$ receptor
Adaptive response
Memory T cell Th2
Innate response
Th1
IL-4Rα
IL-5
Non-T2 inflammatory pathway
IL-4, 13
IL-5
Reslizumab/Mepolizumab
IL-13
IL-13
Omalizumab
IgE
Eosinophil
IL-5R
Benralizumab
B cells
IL-4Rα
Dupilumab
Neutrophilic inflammation
Bronchial smooth muscle

Figure 43-1 Inflammatory pathways in asthma. The T2 inflammatory pathway with contributions from the adaptive and innate immune response leads to production of T2 cytokines IL-4, IL-5, and IL-13. The non-T2 pathway with activation of T_H1 and T_H17 cells leads to neutrophil activation. Both inflammatory pathways can lead to asthma symptoms and airway remodeling. TSLP is the target of tezepelumab; IL-5 is the target of reslizumab and mepolizumab; IgE is the target of omalizumab; CRTH2/PGD2 is the target of fevipiprant; IL-4Rα is the target of dupilumab; IL5R is the target of benralizumab. FTH, follicular T helper; ILC2, innate lymphoid cell 2; NKT, natural killer cell; TCR, T cell receptor; TSLP, thymic stromal lymphopoietin; TSLPR, TSKP receptor.

allergic inflammatory response that is, largely, an adaptive immune response to initial and subsequent exposures to inhaled allergens. While the key cellular and molecular mediators will be described in greater detail later in the chapter, we now describe the evolution of the allergic response. This is the foundation upon which other concepts have been constructed and illustrates the basis for chronic variable changes that occur in the airway in asthma and in the clinical expression of disease.

The adaptive response begins when a novel antigen (allergen) enters the airway of an individual at risk, where it becomes trapped in the mucus layer lining the airway. Here it is endocytosed by professional antigen-presenting dendritic cells. During this process it encounters tentacle-like projections or "dendrites" of the dendritic cells that are intercalated amongst bronchial epithelial cells throughout the airways.[4,5] After the uptake and processing of the antigen, the dendritic cells migrate to local lymph nodes in the lung and mediastinum, where the antigen is presented to naïve $CD4^+$ T cells via the T cell receptor (TCR).[5] Additional signals derived from the dendritic cell determine which type of $CD4^+$ memory T cell the naïve T cell will become (i.e., Th1, Th2, Th17, Treg)—which determines what repertoire of cytokines the memory T cell will produce. Prior to this event, the dendritic cell is influenced by a complex network of molecular signals that are derived from airway epithelial cells and other local cell types. For example, the production of epithelial cytokines or alarmins—such as thymic stromal lymphopoietin (TSLP), interleukins (IL)-33 and -25, and granulocyte-monocyte colony-stimulating factor (GM-CSF)—creates a milieu for dendritic cells to promote naïve $CD4^+$ T cell polarization into T_H2 that creates an environment favorable for the persistence of allergic inflammation.[5] Other cell types also are activated including B cells, which, in the presence of IL-4 and IL-13, are influenced to produce antigen-specific IgE that binds to high-affinity IgE receptors ($Fc\varepsilon RI$) on mast cells and basophils. Upon rechallenge with the sensitizing antigen, the sensitized T_H2-differentiated $CD4^+$ T cells are recruited back to the airway by other signals, such as chemokines CCL17 and CCL22 secreted by dendritic cells.[6] Upon arrival to the airway, the $CD4^+$ T_H2 cells become key sources of the T_H2 cytokines IL-4, IL-5, and IL-13, which serve as the molecular catalysts that drive the T_H2 inflammatory response.[6]

Upon subsequent exposure to the antigen, the local environment of the airways is now primed to respond to the antigen in the future, rich with T_H2 cytokines and antigen-specific IgE, which act on other cell types, either present or recruited to the airway, to amplify the allergic inflammatory response. When inhaled antigen cross-links membrane-bound IgE on mast cells and basophils, a variety of preformed and synthesized meditators are released and cause bronchoconstriction, airway wall edema, and local tissue damage.[7] Mast cells release chemoattractants such as leukotrienes and chemokines that recruit additional inflammatory cells including eosinophils, basophils, neutrophils, and lymphocytes to establish a late-phase inflammatory response.[7] The eosinophil appears to be, in most cases, the most important and abundant inflammatory cell associated with the late-phase response and the primary cell contributing to inflammation, tissue damage, and airflow obstruction through a vast number of mediators that are reviewed below.[8] Eosinophil products can cause local tissue damage, mucus hypersecretion, increased vascular permeability, and smooth muscle contraction, and they sustain the inflammatory response by recruiting other cell types that perpetuate the inflammation.[7,8] The roles of macrophages, neutrophils, and basophils in the pathogenesis of the acute- and late-phase allergic inflammatory responses are less well defined but are likely important in other subtypes of disease and clinical settings as outlined below.

While the acute allergic response to allergen illustrates the pattern of inflammation seen in asthma, it should be noted that other forms of inflammation also play important roles in asthma pathogenesis. Viral respiratory infections, especially with human rhinovirus (HRV), are important triggers of asthma exacerbations.[9] The response to HRV is a primarily T_H1-driven response with increased production of IL-8 and IL-1β and the initial appearance of airway neutrophilia, in contrast to the T_H2 response seen after allergen exposure.[9,10] With HRV infections, there is also release of epithelial cell alarmins, with IL-33 in particular activating ILC2 to generate IL-5 and recruit eosinophils to the airway and cause inflammation and airflow obstruction.[11] In asthma, there is evidence that in the milieu of the T2 response there is diminished production of type I and III interferons. Some patients with asthma may be deficient in these critical antiviral cytokines, which leads to increased risk for viral respiratory infections and a greater susceptibility to exacerbations of asthma.[9,10]

The pattern of the acute- and late-phase inflammatory responses to antigen is a central paradigm of asthma that leads to chronic variable symptoms and chronic inflammation associated with the disease. Many of the cell types and inflammatory mediators seen in asthma that were briefly touched upon in the preceding paragraphs will now be discussed in more detail.

CELL TYPES IN ASTHMA

A review of the pathogenesis of any complex disease begins at the cellular level. The importance of cells of the immune system, including mast cells, basophils, $CD4^+$ T cells, eosinophils, neutrophils, macrophages, dendritic cells, and T lymphocytes, as well as their molecular mediators, has long been recognized and appreciated in the development and regulation of inflammation. The contribution of airway smooth muscle cells, especially in relationship to the acute asthmatic response, also has been well documented. More recently, innate immune responses have been increasingly recognized as important drivers of T2 inflammation independent of the adaptive immune response in as many as 50% of patients with severe asthma.[12] In addition, bronchial epithelial cells of the airway have become the focus of intense research and are emerging as critical to both the acute and chronic inflammatory responses in asthma. Their role in airway inflammation and airway remodeling is increasingly cited as a major contributor to the severity of this disease.

■ Cells of the Immune System in Asthma

Below we consider a variety of cellular components of the immune system in asthma.

■ Mast Cells

Human mast cells are derived from the same $CD34^{+/}cKit^+$ hematopoietic stem cell population that also gives rises to eosinophils, basophils, neutrophils, and monocytes.[13] They are resident cells in most tissues of the body and are commonly found in association with blood vessels, nerves, and surfaces that have contact with the external environment.[14] Mast cells (MC) exist in two types in humans and are differentiated by their immunohistochemical staining properties.[15] MC_T mast cells contain only the neutral protease tryptase, while MC_{TC} mast cells contain chymase, carboxypeptidase A3, and cathepsin G–like protease in addition to tryptase.[15–17] In normal lung tissue, mast cells are located in the subepithelium of the bronchi, bronchioles, and alveolar walls and are almost exclusively of the MC_T type.[15] This distribution of mast cell types is also seen in mild asthma. However, in severe asthma, mast cells are primarily of the MC_{TC} type and are decreased in number in the submucosa but are increased in the airway epithelium, a finding not seen in normal airways or milder disease.[18] Mast cells also infiltrate airway smooth muscle bundles in asthma, where they likely contribute to inflammation, airway hyperresponsiveness, and bronchoconstriction through the action of their released mediators.[19]

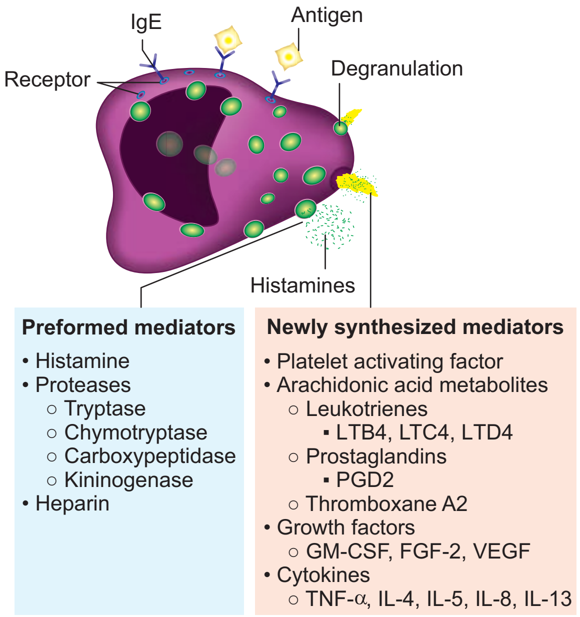


Figure 43-2 The mast cell and its mediators. FGF-2, fibroblast growth factor 2; GM-CSF, granulocyte-monocyte colony-stimulating factor; TNF-α, tumor necrosis factor alpha; VEGF, vascular endothelial growth factor.

While the role of mast cells in allergic (IgE-mediated) asthma is well established, these effector cells also appear to be important in nonallergic disease.[20] In allergic responses, antigen-specific IgE molecules bind allergen and cross-link high-affinity IgE receptors (FcεRI) present on the mast cell surface. Mast cells can also be activated by nonallergic stimuli such as heat and bronchospasm. This results in the release of preformed mediators, such as histamine, tryptase, chymase, and heparin, as well as tumor necrosis factor alpha (TNF-α) and vascular endothelial growth factor (VEGF).[21] Upon activation, mast cells generate and release newly synthesized mediators, which contribute to the ongoing inflammatory milieu. These include leukotrienes (predominantly LTC4); prostaglandins (predominantly PGD_2); thromboxane A2; platelet activating factor (PAF); growth factors including GM-CSF, fibroblast growth factor 2, and VEGF; and many other cytokines including but not limited to TNF-α, IL-4, IL-5, IL-8, and IL-13 (Fig. 43-2).[21,22]

The effect of mediators released from mast cells contributes to numerous features of the asthmatic response.[7] Histamine, leukotrienes, and proteases contribute to increased mucus production. Prostaglandins, leukotrienes, thromboxane A2, and histamine cause bronchoconstriction and increase vascular permeability. These proteases produce tissue damage and activation of many protein precursors. This, in turn, contributes to the recruitment, differentiation, and activation of other inflammatory cells, which results in the propagation of the inflammatory response.

■ Basophils

With the exception that basophils are present primarily in the peripheral circulation, basophils share many similarities with mast cells. These enigmatic cells share a common progenitor cell with mast cells, also express FcεRI on their cell surface, and release both preformed and newly synthesized mediators and cytokines upon cross-linking by IgE-antigen complexes on their surface. Like mast cells, the major preformed mediator released from basophils is histamine. Preformed heparin and tryptase also are released, albeit at lower concentrations than by mast cells.[23] Basophils synthetize and release LTC_4 upon activation, but unlike mast cells, they do not produce PGD_2.[23] Upon activation, basophils produce large quantities of IL-4 and IL-13.[23] Basophils have been shown to contribute to T_H2 differentiation by presenting antigen via major histocompatibility complex (MHC) class II and co-stimulatory molecules,[24] and basophils, along with eosinophils, are a primary target of the alarmin IL-33, a potent promoter of allergic inflammation and T_H2 polarization.[25]

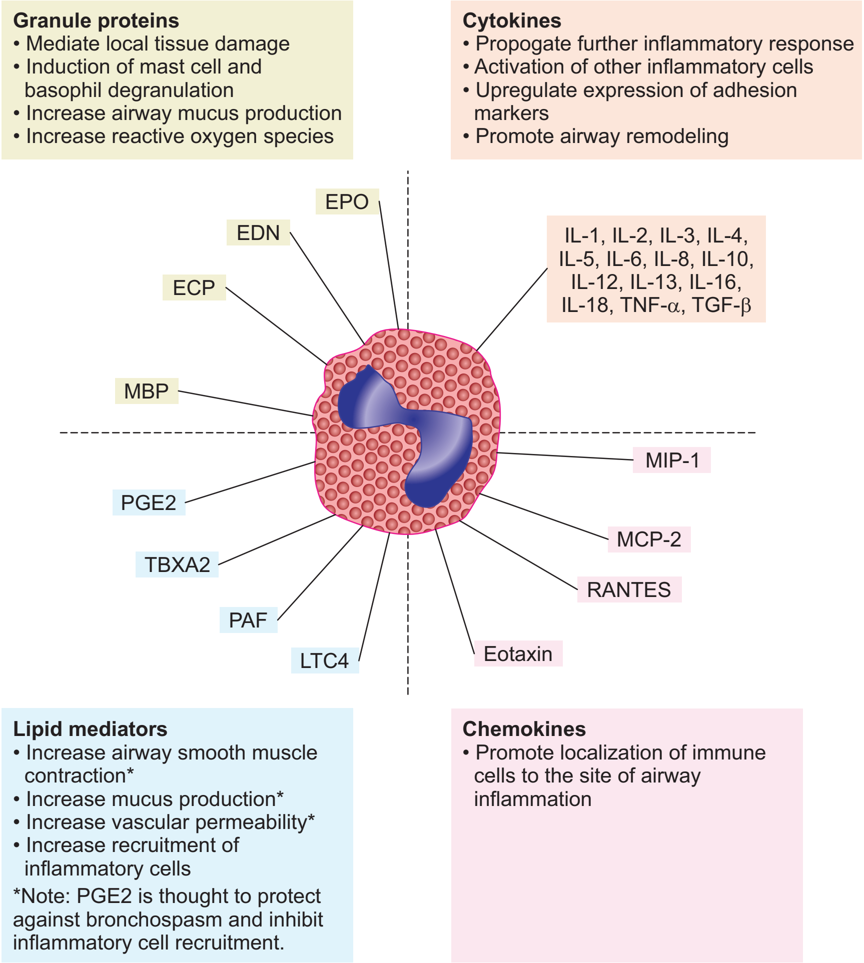
■ Eosinophils

Eosinophils, like basophils and mast cells, are granulocytes derived from $CD34^+$ hematopoietic stem cells. Early eosinophil production is highly dependent upon the presence of GM-CSF and IL-3.[26] Eosinophil precursors are recruited to the airway in asthma as the result of cytokine and chemokine signaling. This signaling involves IL-5; eotaxins; CCL5/regulated on activation, normal T cell expressed and secreted (RANTES); macrophage inflammatory protein (MIP) 1α; and macrophage chemotactic factors 2, 3, and 4 (MCP-2, -3, and -4).[27] IL-5 is critically important to the terminal differentiation of eosinophils and release from the bone marrow.[26] Blockade of the IL-5 pathway with biologic therapies in patients with asthma results in the near elimination of eosinophils from the blood, highlighting this cytokine's importance to this cell's association and contribution to asthma.[28]

Once in the airway, eosinophils are activated by mechanisms not clearly established to contribute to the inflammatory response by releasing a wide variety of mediators. These include cytokines (IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-13, IL-16, IL-18, tumor necrosis factor α [TNF-α], and transforming growth factor α and β [TGF-α and TGF-β]), chemokines (MIP-1, MCP-2, RANTES, and eotaxin), and lipid mediators (PGE_1, PGE_2, thromboxane B_2, PAF, and LTC_4) (Fig. 43-3).[29,30] Eosinophils secrete granule proteins, which are recognized as the eosinophil's essential mechanism in defense against parasites.[29,31] Eosinophils contain both primary and secondary granules. The primary granules contain Charcot-Leyden crystal protein, while the secondary granules contain the four principal cationic proteins: MBP (major basic protein), ECP (eosinophil cationic protein), EDN (eosinophil-derived neurotoxin), and EPO (eosinophil peroxidase).[29] These cationic proteins contribute to the pathogenesis of asthma through the induction of mast cell and basophil degranulation (ECP and MBP), increasing airway mucus production (ECP), and formation of reactive oxygen species (EPO).[29] The presence of Charcot-Leyden crystals has proved to be a key factor in the eosinophil's contribution to airway inflammation.[32]

Over the past 30 years, the role of the eosinophil in asthma has undergone considerable re-evaluation. Since the discovery of the eosinophil by Ehrlich in 1879 and the later discovery that Ehrlich's cells were present in the sputum of asthmatic patients, the eosinophil has been viewed as the primary effector cell in asthma.[33] Studies have noted that peripheral blood eosinophilia is a characteristic of asthma, correlated with disease severity, and that eosinophilic infiltrates were in the airways of asthma patients at autopsy, regardless of whether asthma was the primary cause of death.[34,35] Later studies detected increased eosinophils and eosinophil products in bronchoalveolar lavage (BAL) fluid after antigen challenge.[36] This concept of the eosinophil as a principal effector in asthma was largely unvalidated until the new millennium, when monoclonal antibodies against IL-5 (mepolizumab and reslizumab) and the IL-5 receptor (benralizumab) were demonstrated to be potent modulators of eosinophil levels in the blood, asthma exacerbations, and airway obstruction.[28]

Initial studies with monoclonal antibodies against IL-5 in patients with asthma (independent of their level of eosinophilic inflammation) showed a decrease in sputum and peripheral blood eosinophilia, as expected, but failed to demonstrate significant benefit in a wide variety of clinical outcome measures, including symptom score or improved airflow obstruction.[37,38] Although the



Granule proteins
- Mediate local tissue damage
- Induction of mast cell and basophil degranulation
- Increase airway mucus production
- Increase reactive oxygen species

Cytokines
- Propogate further inflammatory response
- Activation of other inflammatory cells
- Upregulate expression of adhesion markers
- Promote airway remodeling

Lipid mediators
- Increase airway smooth muscle contraction*
- Increase mucus production*
- Increase vascular permeability*
- Increase recruitment of inflammatory cells

*Note: PGE2 is thought to protect against bronchospasm and inhibit inflammatory cell recruitment.

Chemokines
- Promote localization of immune cells to the site of airway inflammation

EPO
EDN
ECP
MBP
IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-13, IL-16, IL-18, TNF-α, TGF-β
MIP-1
MCP-2
RANTES
Eotaxin
PGE2
TBXA2
PAF
LTC4

Figure 43-3 Eosinophil products in asthma. ECP, eosinophil cationic protein; EDN, eosinophil-derived neurotoxin; EPO, eosinophil peroxidase; LTC4, leukotriene C4; MBP, major basic protein; MCP-2, monocyte chemotactic protein 2; MIP-1, macrophage inhibitory protein 1; PAF, platelet activating factor; PGE2, prostaglandin E2; RANTES, regulated upon activation normal T cell expressed and secreted; TBXA2, thromboxane A2; TGF-β, transforming growth factor beta; TNF-α, tumor necrosis factor alpha.

lack of effect on these parameters of clinical asthma was a surprise, it contributed to the current understanding of asthma as a highly heterogeneous disease where inflammatory cells like eosinophils can play variable roles in different patients, thus emphasizing the importance of determining the individual phenotype of an asthma patient when judging the likely efficacy of a particular biologic agent.[28] Studies with the anti-IL-5 monoclonal antibodies mepolizumab and reslizumab, and the anti-IL-5 receptor antibody benralizumab, were conducted in patients with uncontrolled asthma. Treatment of patients with a history of multiple exacerbations and persistent eosinophilia in the blood or sputum or high exhaled nitric oxide levels despite treatment with inhaled corticosteroids (ICS) led to a substantial reduction in systemic corticosteroid-requiring exacerbations.[39,40] From these studies emerged the concept that there exists a subtype of patient with asthma in which the eosinophil plays a key role. Eosinophils are also a prime contributor to airway remodeling, mucus hypersecretion, and formation of mucus plugs, discussed later in the chapter.[41]

■ Neutrophils

Neutrophils are granulocytes also derived from CD34$^+$ hematopoietic stem cells that are normally present in the bloodstream, as well as in various tissues, including the lung. They contain primary (azurophilic) and secondary (specific) granules, which contain antimicrobial enzymes, neutral proteases, and acid hydrolases.[42] Neutrophils are attracted to the airway by numerous cytokines and chemokines including IL-8, IL-17, and granulocyte colony–stimulating factor (G-CSF).[43,44] Airway neutrophilia can be seen in many respiratory conditions, viral respiratory infections, COPD, and asthma.[10,44]

The role of neutrophils in the initial response to a viral respiratory infection is well understood. In response to inoculation with a respiratory virus, such as HRV, dendritic cells and other mononuclear cells produce proinflammatory cytokines and chemokines, which recruit neutrophils to the airway.[10] Neutrophils contribute to the inflammatory milieu by secreting cytokines such as TNF-α, IL-1, IL-8, and IL-18, to attract other inflammatory cells, upregulate cytokine production, produce airway inflammation, and enhance bronchial hyperresponsiveness.[45] Neutrophil products, such as elastase, have direct effects on the airway and contribute to mucus production.[10] Furthermore, HRV activation of neutrophils releases DNA-containing NETs that, in turn, activate $\mathrm{T_H}$2 lymphocytes to release T2 cytokines.[46] In addition, because neutrophils are found in some patients with severe asthma, they have been hypothesized to play a prominent role in this phenotype.[47] Neutrophilic inflammation has been noted in the sputum of patients with severe asthma exacerbations, in BAL fluid from patients with noninfectious status asthmaticus, and in autopsy specimens from the airway in patients with acute, fatal asthma.[48–50] Other studies have demonstrated subgroups of patients with chronic asthma in whom the primary inflammatory cell type in the sputum is neutrophils rather than eosinophils.[51,52] These patients are more often female, obese, difficult to treat, and less responsive to treatment with corticosteroids.[32]

■ Lymphocytes

Cells of lymphoid lineage are also key mediators of innate and adaptive immune responses in asthma. Among them, T lymphocytes, derived from the common lymphoid progenitor, are a household name in asthma. Numerous subsets of T cells have been identified

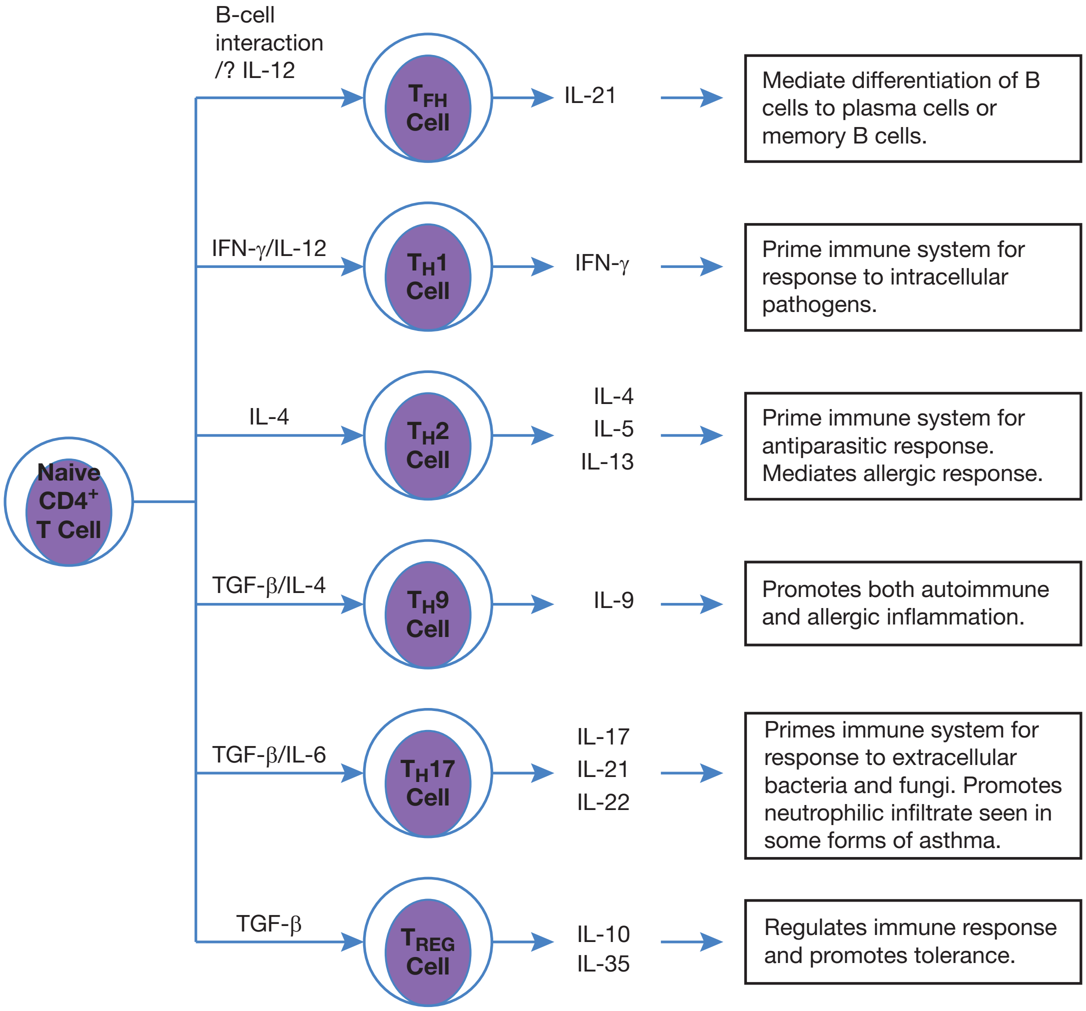

B-cell interaction /? IL-12
T_{FH} Cell
IL-21
Mediate differentiation of B cells to plasma cells or memory B cells.
IFN-γ/IL-12
T_H1 Cell
IFN-γ
Prime immune system for response to intracellular pathogens.
IL-4
T_H2 Cell
IL-4
IL-5
IL-13
Prime immune system for antiparasitic response. Mediates allergic response.
Naive $CD4^+$ T Cell
TGF-β/IL-4
T_H9 Cell
IL-9
Promotes both autoimmune and allergic inflammation.
TGF-β/IL-6
T_H17 Cell
IL-17
IL-21
IL-22
Primes immune system for response to extracellular bacteria and fungi. Promotes neutrophilic infiltrate seen in some forms of asthma.
TGF-β
T_{REG} Cell
IL-10
IL-35
Regulates immune response and promotes tolerance.

Figure 43-4 $CD4^+$ T lymphocyte subsets. IFN-γ, interferon gamma; TGF-β, transforming growth factor beta.

and are important contributors to asthma, including $CD4^+$ helper T cells and their subsets (T_H1, T_H2, T_H9, and T_H17), $CD8^+$ cytotoxic T cells, and regulatory T cells (T_{Reg}).

$CD4^+$ helper T cells recognize antigens presented to them by antigen-presenting cells (APCs) and, in turn, secrete cytokines to influence the adaptive inflammatory response. In the airway, the dendritic cell is the most important APC (discussed in detail below). A complex series of events involving cytokines and various transcription factors determines whether $CD4^+$ T cells will differentiate into T_H1, T_H2, T_H9, or T_H17 cells (Fig. 43-4).[53]

As outlined above, T_H2 cells are recognized as the primary drivers of inflammation in allergic asthma and other allergic diseases. When T_H2 cells encounter antigen presented by dendritic cells, they produce IL-4, IL-5, and IL-13, all of which play critical roles in the pathogenesis of asthma and pathophysiology in the clinical disease. This has been demonstrated by the detection of increased levels of these cytokines in the BAL fluid of patients with asthma.[54,55] IL-4 increases IgE production by plasma cells, IL-5 is critical to the terminal differentiation and homing of eosinophils to the airway, and IL-13 increases IgE production and drives airway hyperresponsiveness and tissue remodeling.[56]

The role of T_H1 cells in asthma is not as well defined as that of T_H2 cells. Although it has been presumed that T_H1 cells counteract the asthma-inducing effects of T_H2 cells, this is likely an oversimplification as T_H1-associated cytokines have been shown to be increased during asthma exacerbations.[57] Some studies have also suggested that T_H1 cells may play a more prominent role in severe asthma since levels of the canonical T_H1 cytokine, interferon γ (IFN-γ), are increased in the BAL fluid of patients with severe asthma.[58]

T_H9 cells are another adaptive cell type whose primary cytokine is IL-9. T_H9 cells function similarly to T_H2 cells in that they allow persistence of and amplify allergic inflammatory responses. Mast cells are the primary IL-9 receptor–bearing cell, and T_H9 cells are important contributors to the mast cell activation that is notable in asthma.[22] Because mast cells also produce VEGF and fibroblast growth factor (FGF)-2, T_H9 cells likely contribute to airway remodeling as well.[22] The role of targeted therapeutics against the IL-9 pathway in the treatment of asthma remains to be determined.

The last several decades of asthma research and therapeutic development have focused on T2 inflammation, bringing multiple anti-T2 therapeutics to the clinic. As a result, clinicians now have many options to treat allergic and eosinophilic asthma. In contrast, our understanding of non-T2 inflammation in asthma has been hampered by a lack of robust animal models and a consensus on the definition of low-T2 disease. In this regard, the role of T_H17 cells in asthma is an emerging area of intense research. With the identification of a subtype of asthma with primarily neutrophilic inflammation, the role of IL-17 (the primary cytokine produced by T_H17 cells) in asthma has become of an area of considerable interest. Although IL-17 is increased in patients with severe asthma,[59] it is also found in high concentrations in patients with mild asthma (forced expiratory volume in 1 s [FEV_1] >70% predicted) and correlates negatively with the provocative concentration that causes a 20% reduction in FEV_1 (PC_{20}).[60] Thus, while T_H17 cells most certainly play a role in patients with primarily neutrophilic asthma, they are also important in other forms of disease. Furthermore, treatment of severe asthma with anti-IL-17 monoclonal antibodies has not shown a consistent effect. At present, there are no biomarkers to identify the IL-17/T_H17 phenotype of asthma.[61]

The primary function of $CD8^+$ cytotoxic T cells is the destruction of human cells that are infected with viruses or other intracellular pathogens. $CD8^+$ T cells are also likely to play a role in asthma, although the extent of their contribution has yet to be fully elucidated.[56] IL-4- and IL-5-producing $CD8^+$ T cells are present in the airways of asthmatic patients.[62] IL-5 production by $CD8^+$ T cells is increased in the presence of a viral respiratory infection, and the overall cytokine production by $CD8^+$ T cells correlates with asthma severity.[63,64] Whether $CD8^+$ T cells function as direct contributors or bystanders in the worsening of asthma has yet to be determined.[56]

T_{Reg} cells also appear to play a critical role in asthma development. T_{Reg} cells serve to limit inflammatory responses and promote immune tolerance through the production of IL-10 and TGF-β.[56,65] In patients with asthma and other allergic disorders, T_{Reg} cells appear to be less effective at limiting T_H2 inflammation.[66,67] However, after allergen immunotherapy, for example, T_{Reg} cells increase in the nasal mucosa and may act to promote allergen tolerance.[68] Interestingly, farm exposure early in life is associated with a decreased incidence of allergic disease and asthma, a fact that may be related to increased numbers and function of T_{Reg} cells in infants living in this environment.[69]

Natural killer cells (NK cells) are members of the innate immune system that serve as a first line of defense against infections. Their role in the pathogenesis of asthma has yet to be fully elucidated. They proliferate in response to viral respiratory infections, and their numbers increase during asthma exacerbations.[70] NK cells are capable of producing numerous cytokines including IFN-γ, IL-4, IL-5, and IL-13.[71] NK cells from patients with atopic asthma are skewed toward the production of IL-4 as opposed to IFN-γ upon activation.[71] IFN-γ production by NK cells is also inhibited by prostaglandin D2, a T_H2-promoting lipid mediator produced by mast cells.[72] NK cells may also play a role in "dendritic cell editing" by killing immature dendritic cells, which might influence the development of the type of T_H response.[73]

Macrophages and Dendritic Cells

Macrophages and dendritic cells are descendants of the $CD34^+$ hematopoietic stem cell and arise from a common committed precursor cell.[74] Macrophages arise from circulating monocytes and function primarily to clear debris and microbes from the airway. They may also function as antigen-presenting cells, although this role is likely less important than that of the dendritic cell.[75] Alveolar macrophages may further differentiate into M1 or M2 subsets based on exposure to various cytokines and Toll-like receptor (TLR) agonists.[74] M1 macrophages are "classic" macrophages that clear microbes from the airway. They also produce cytokines, such as IL-12, IL-6, and TNF-α, as well as high levels of nitric oxide (NO).[74] M1 macrophages have traditionally been described as suppressing allergic inflammation, primarily through their secretion of T_H1 cytokines such as IL-12.[74]

Differentiation of monocytes into M2 macrophages is influenced by an environment rich in T_H2 cytokines such as IL-4 and IL-13, indicating they have a role in asthma. When compared with M1 macrophages, M2 macrophages are less effective at clearing intracellular pathogens.[74] They release cytokines such as IL-13 and thus are likely to contribute to the airway hyperresponsiveness in T2 inflammation.[74]

Dendritic cells are the lung's primary presenter of antigen to T cells and are intimately arranged among bronchial epithelial cells in the airway wall. This positions the dendritic cell at a critical junction in determining what type of adaptive T cell response will be directed by the antigen presented by the dendritic cell (e.g., T_H1, T_H2). Dendritic cells in humans exist in two broad categories: the myeloid dendritic cell (mDC) and the plasmacytoid dendritic cell (pDC). While both types of dendritic cells are present in the human lung, their relative localization within the lung is poorly understood.[5] Upon encountering antigen in the airway, dendritic cells migrate to local lymph nodes where they present antigen to T lymphocytes. Both pDC and mDC levels increase in the airway (and coincidently decrease in the blood) after exposure to inhaled allergen.[76–78] Because dendritic cells lie close to the epithelial barrier, they receive numerous signals from epithelial cells, which can influence their effect on T cells. Thymic stromal lymphopoietin (TSLP), the canonical alarmin and target of the monoclonal antibody tezepelumab, is produced by epithelial cells. This product promotes dendritic cells to drive T_H2 differentiation and recruit T_H2 cells to the airway.[5] Other epithelial cell–derived factors, such as GM-CSF, TNF-α, CCL-20, IL-1β, and TNF-related apoptosis-inducing ligand (TRAIL), have similar T_H2-promoting effects.[5] pDCs represent the lung's primary source of IFN-α, a potent antiviral cytokine. These cells are recruited to the lung during viral infections.[79] As viral infections commonly precede asthma exacerbations and may predispose infants to develop asthma, this role of the pDC should be emphasized.[80] The importance of pDC to the development of asthma was illustrated by a recent study which showed that levels of pDC in childhood were inversely correlated with number and severity of viral respiratory infections, increased episodes of wheeze, and increased asthma diagnosis.[81] The function of mDC is not as well known in human asthma, but the role of both cell types in contributing to the development and propagation of the disease will continue to be an important area of asthma research.

Structural Cells of the Airway

Other cellular components of the asthmatic response to be considered include structural cells of the airway: smooth muscle and airway epithelial cells.

Airway Smooth Muscle

Given that bronchospasm and bronchial constriction are central components of asthma, it is intuitive that the cell type responsible for this component, the airway smooth muscle cell, would be a key factor in asthma pathogenesis and pathophysiology. While this cell's importance seems obvious, the details of how airway smooth muscle function differs in the asthmatic airway compared with the normal airway have been elusive. It has been well documented that the smooth muscle layer surrounding the airway is thicker in asthmatics compared to nonasthmatic controls, likely due to remodeling via both smooth muscle hypertrophy and hyperplasia.[82] Increased inflammatory and mast cells can be found within the smooth muscle bundles of asthmatic airways, an indication of the increased communication between these cells, the airway epithelium, and the smooth muscle in asthma.[19] Numerous cytokines, chemokines, and growth factors are involved in these interactions, including those produced by the airway smooth muscle cells and by other cell types with which the airway smooth muscle cell communicates. Airway smooth muscle cells are more prolific producers of these cytokines and proliferate more rapidly in asthma compared with normal smooth muscles.[83]

Early efforts to treat asthma focused on preventing or reversing contraction of bronchial smooth muscles. β-2 agonists, both short- and long-acting, have long been key components in the treatment of asthma, by directly acting on airway smooth muscle to produce bronchodilation. More recently, attempts to alter function of airway smooth muscle with the use of bronchial thermoplasty have shown improvement in asthma control, further supporting the role that airway smooth muscle plays in asthma pathophysiology.[84,85]

■ Airway Epithelial Cells

The bronchial epithelium lining the airway is an area of intense research, and its importance, beyond being a simple anatomic barrier, is being increasingly recognized and appreciated. The airway epithelium has a vast surface area (100 m^2) that is in contact with some 10,000 L of inhaled air daily.[86] As the area of initial contact between the body and the external airborne environment, functions of the airway epithelium are a key determinant of the body's response to airborne substances.

The airway epithelium is composed of three major cell types: ciliated columnar epithelial cells, mucus-secreting goblet cells, and surfactant-secreting Clara cells.[86] Both overproduction of mucus by goblet cells and underproduction of important anti-inflammatory peptides by Clara cells have been noted in patients with asthma.[87,88] The tight junctions between epithelial cells have also been noted to be defective in patients with asthma, which decreases the ability of the airway epithelium to act as a protective barrier.[86] The airway epithelium in asthma is also less capable of defending itself against reactive oxygen species, a defect that leads to damage when the airway is inflamed.[89] Epithelial cells in asthma produce lower amounts of type I interferon in response to respiratory viruses, which can increase the risk and severity of respiratory infections and promote asthma exacerbations.[90] More recently, the importance of epithelial-derived alarmins, including IL-25 and -33, which promote both T1 and T2 inflammatory responses, has been demonstrated in asthma linking the airway epithelium with the inflammation evident in both T2-high and non-T2 inflammation.[91,92] This realization has led to the development of monoclonal antibodies directed against TSLP (tezepelumab) and IL-33 (itepekimab). In a genome-wide association study, Shrine et al. found an association between polymorphisms in MUC5AC and moderate to severe asthma raising the possibility that this gene contributes to the development of more severe asthma.[93]

MOLECULAR MEDIATORS IN ASTHMA

The aforementioned cells are able to initiate, perpetuate, coordinate, and regulate the inflammatory process with the synthesis and secretion of several different classes of molecular mediators. These mediators have a variety of functions, as discussed below.

■ Cytokines

Cytokines are small-molecular-weight glycosylated signaling molecules that are secreted by a number of different cell types with autocrine, paracrine, or endocrine directive activities.[94] The term *cytokine* includes many categories of molecular mediators including interleukins, interferons, and growth factors.[94] Cytokine secretion is usually a brief, self-limited event that requires preformed pools of intracellular cytokines and new mRNA and protein synthesis, which takes place over a matter of hours rather than seconds or minutes.[95] A variety of cytokines have been implicated in the regulation of airway inflammation and thus in the pathogenesis of asthma (Table 43-1).[96] The support for cytokine involvement in asthma was based on the detection of these mediators in the airways of patients with asthma, particularly in bronchoalveolar lavage fluid after allergen challenge and in situ hybridization of retrieved cells or biopsy materials.[97,98] In addition, effective treatment with monoclonal antibodies directed against pivotal T2 cytokines, that is, IL-5, IL-4/IL-13, have demonstrated clinical efficacy; these data indicate a likely role for these cytokines as risks for exacerbations, airflow obstruction, and symptoms (Table 43-2). The overall effect of the complex cytokine network in the airway depends on a number of factors, including the relative abundance of the cytokines, their ability to recruit and perpetuate the actions of inflammatory cells such as eosinophils and lymphocytes, and their ability to amplify or suppress inflammation by interacting with structural cells of the airway.

■ Chemokines

Chemokines are small-molecular-weight proteins, 8 to 12 kDa, that are classified into four categories based on the organization of specific cysteine residues in their protein sequence: XC, CC, CXC, and CX_3C.[99] The predominant function of chemokines is the recruitment or chemotaxis of inflammatory cells, and some chemokines have additional signaling functions.[99] There are corresponding families of chemokine receptors for each class of chemokine. Notably, there is considerable overlap and redundancy in the chemokines and their target receptors. Since the localization of inflammatory cells into the airway is dependent to a large extent on chemotaxis via chemokine signaling, chemokine receptors have become an attractive target for asthma therapy, but none has yet made it to the clinic. There are currently chemokine receptor inhibitors for CCR5 as well as others in development as potential therapy for asthma.[100,101]

■ IgE

The initial association of IgE with asthma was based on several epidemiologic studies that demonstrated increased levels of IgE in patients with asthma.[102–104] With the improved understanding of the role of mast cell mediators in the pathogenesis of asthma, the importance of IgE in triggering mast cell activation and airway inflammation was increasingly recognized. This led to the development of a humanized monoclonal antibody directed against IgE to treat patients with uncontrolled allergic asthma.[105] The antibody (omalizumab) was shown to be effective in the treatment of severe uncontrolled asthma, reducing exacerbations and allowing patients to reduce corticosteroid dosage.[106]

■ Leukotrienes

The leukotrienes (LT) are a family of lipid compounds generated by the metabolism of arachidonic acid via the lipoxygenase pathway (Fig. 43-5).[107] These compounds are typically not preformed and stored in cells for release upon activation; rather, they are rapidly synthesized following activation of the source cell. LTC_4, LTD_4, and LTE_4 are potent bronchoconstrictors that are produced by several cell types, including eosinophils and mast cells. In contrast, LTB_4 is a neutrophil attractant.[107] The leukotrienes are also able to increase mucus secretion in the airway and facilitate plasma leak and edema in the airway wall.[107,108] The leukotriene receptor antagonist montelukast is currently used in the treatment of asthma.[109] Although effective in some patients, the leukotriene modifiers are limited by their limited potency in some patients with asthma.[110]

Aspirin-exacerbated respiratory disease is associated with chronic rhinosinusitis and nasal polyps and underlying severe asthma. These patients are characterized by an underlying overproduction of cysteinyl leukotrienes, that is, urinary LTE_4, which is released in higher concentrations with nonsteroidal anti-inflammatory drugs (NSAIDs) that provoke a severe asthma attack.[111] In this syndrome, the mast cell is considered the primary source of cysteinyl leukotriene production.

■ Prostanoids

The prostanoids are a family of lipid compounds generated from the metabolism of arachidonic acid via the cyclooxygenase pathway

TABLE 43-1 Cytokines and Lipid Mediators in Asthma

Cytokines		
Cytokine	**Cell Sources**	**Proposed Cell Targets/Functions in Asthma**
Interleukins		
IL-1	DCs, monocytes, macrophages, mast cells, B and T cells, neutrophils, endothelial cells, airway epithelial cells	*Basophils:* Increased production of cytokines and histamine *DCs:* Increased cytokine production, upregulation of MHC and co-stimulatory molecules *Macrophages:* Increased cytokine production *Mast Cells:* Increased cytokine production, degranulation, and survival *Neutrophils:* Increased survival and release of proteases *B Cells:* Increased antibody production *T Cells:* Increased proliferation—especially for T_H2 and T_H17 cells
IL-2	$CD4^+$ T cells	*T Cells:* Increased survival and proliferation, increased T_H2 cytokine production
IL-3	T cells, mast cells	*Basophils:* Increased survival and release of IL-4, IL-6, and histamine *Eosinophils:* Increased degranulation *Mast Cells:* Increased survival and histamine release *Hematopoietic Stem Cells*: Increased production of mast cells, basophils, neutrophils, eosinophils, macrophages, erythrocytes, megakaryocytes, and dendritic cells
IL-4	T cells, mast cells, basophils, eosinophils	*Airway Smooth Muscle Cells:* Increased airway hyperresponsiveness *Basophils:* Increased recruitment *Eosinophils:* Increased recruitment *Goblet Cells*: Increased mucus production *Mast Cells:* Increased recruitment, upregulation of FCεRI *B Cells:* Increased class-switching to IgE, upregulation of FCεRII *T Cells:* Increased recruitment, increased T_H2 differentiation, increased production of T_H2 cytokines, decreased differentiation of T_H1 cells, decreased IFN-γ production by T_H1 cells
IL-5	T cells, mast cells	*Basophils:* Increased proliferation, maturation, and functional activation *Eosinophils:* Increased proliferation, chemoattraction, maturation, functional activation, and degranulation
IL-6	Macrophages, DCs, mast cells, neutrophils, B and T cells, endothelial cells, airway epithelial cells	*T Cells:* Increased production of T_H2 cytokines, decreased differentiation of T_H1 cells, decreased IFN-γ production by T_H1 cells, promotes differentiation of T_H17 cells, downregulation of T_{Reg} cells
IL-7	Bone marrow stromal cells	*Eosinophils:* Increased activation and survival *B Cells:* Increased proliferation and survival *T Cells:* Increased maturation and survival
IL-8	Airway epithelial cells, neutrophils, eosinophils, monocytes/macrophages	*Eosinophils:* Chemoattraction *Neutrophils:* Chemoattraction
IL-9	T cells	*Mast Cells:* Increased recruitment and maturation, increased expression of proteases, upregulation of FCεRI *T Cells:* Increased growth and proliferation
IL-10	Monocytes/macrophages, B cells, T cells (specifically T_{Reg} cells)	*DCs:* Inhibits expression of co-stimulatory molecules thus inhibiting T_H cell activation *Eosinophils:* Inhibits survival, recruitment, and maturation *Monocytes/Macrophages:* Downregulates MHC class II expression, downregulates inflammatory cytokine production *T Cells:* Downregulates IFN-γ and IL-2 production by T_H1 cells and IL-4 and IL-5 production by T_H2 cells
IL-11	Airway epithelial cells, eosinophils, airway smooth muscle cells	*Airway Epithelial Cells:* Regulates proliferation *Macrophages:* Inhibits production of TNF-α, IL-1, IL-12 *B Cells:* Increases immunoglobulin production *T Cells:* Inhibits production of TH1 cytokines, increases IL-4 and IL-10 production
IL-12	Dendritic cells, B cells, macrophages	*NK Cells:* Increased IFN-γ production *T Cells:* Increased IFN-γ production, increased TH1 differentiation, decreased T_H2 and T_H17 differentiation

(continued)

TABLE 43-1 Cytokines and Lipid Mediators in Asthma *(Continued)*

Cytokines		
Cytokine	**Cell Sources**	**Proposed Cell Targets/Functions in Asthma**
IL-13	Mast cells, T cells	*Airway Epithelial Cells:* Increased permeability, increased mucus production, production of inducible nitric oxide synthase *Airway Smooth Muscle Cells:* Increased airway hyperreactivity *Eosinophils:* Promotes migration and survival *Macrophages*: Activation and enhanced MHC class II expression *B Cells:* Increased class switching to and production of IgE
IL-14	T cells	*B Cells:* Increased proliferation, suppression of Ig secretion
IL-15	Monocytes/macrophages, DCs	*DCs:* Increased activation and survival, increased production of IFN-γ *Mast Cells:* Increased survival *Monocytes/Macrophages*: Increased phagocytic activity, increased production of IL-8, IL-12, MCP-1 *Neutrophils:* Increased survival and phagocytic activity, increased IL-8 production *NK Cells:* Increased maturation and survival, increased production of IFN-γ, TNF-α, and GM-CSF *T Cells*: Increased proliferation of memory CD8$^+$ T cells, increased proliferation of T_H17 cells
IL-16	T cells, airway epithelial cells, DCs, eosinophils, mast cells	*DCs:* Increased chemoattraction *Eosinophils:* Increased chemoattraction *Monocytes/Macrophages:* Increased chemoattraction, upregulation of MHC class II expression *T Cells:* Increased migration, maturation, and proliferation
IL-17	T cells, NK cells	*Airway Epithelial Cells:* Increased production of IL-6, IL-8, G-CSF, PGE 2 *Eosinophils:* Increased chemoattraction *Neutrophils*: Increased production from stem cells, increased chemoattraction
IL-18	DCs, monocytes, macrophages, neutrophils, airway epithelial cells	*Basophils*: Increased production of cytokines and histamine *DCs:* Increased cytokine production, upregulation of MHC and co-stimulatory molecules *Macrophages*: Increased cytokine production *Mast Cells:* Increased cytokine production, degranulation, and survival *Neutrophils*: Increased survival and release of proteases *NK Cells:* Increased IFN-γ production *T Cells:* Promotes T_H1 differentiation
IL-19	Monocytes	*T Cells:* Increased production of T_H2 cytokines and downregulation of IFN-γ production
IL-20	Monocytes	Unclear
IL-21	T cells	*B Cells:* Increased proliferation of IgA, IgG, IgM producing plasma cells and decrease in IgE-producing plasma cells *T Cells:* Increased differentiation into T_H17 cells, upregulation of T_H1 cytokine production
IL-22	T cells, NK Cells	*Respiratory Epithelial Cells:* Increased production of antimicrobial peptides
IL-23	DCs	*Macrophages:* Increased TNF-α production *T Cells:* Increased IL-17 production, promotion of T_H17 differentiation
IL-24	Monocytes, T cells	Unclear
IL-25	Airway epithelial cells, eosinophils, mast cells	*T Cells:* Increased production of T_H2 cytokines
IL-26	Monocytes, T cells	Unclear
IL-27	Macrophages, DCs	*T Cells:* Increased differentiation into IL-10-producing T_{Reg} and T_H1 cells, decreased development of T_H2 and T_H17 cells
IL-28 (IFN-λ2, -λ3)	DCs	Inhibits viral replication *DCs:* Increase ability to stimulate production of T_{Reg} cells
IL-29 (IFN-λ1)	DCs	Inhibits viral replication *DCs:* Increase ability to stimulate production of T_{Reg} cells
IL-31	T cells	*Airway Epithelial Cells:* Attenuates proliferation of epithelial cells
IL-32	NK cells, airway epithelial cells, T cells	*Macrophages:* Upregulation of proinflammatory cytokines *Airway Epithelial Cells:* Decreased production of proangiogenic factors

TABLE 43-1 Cytokines and Lipid Mediators in Asthma *(Continued)*

Cytokines		
Cytokine	**Cell Sources**	**Proposed Cell Targets/Functions in Asthma**
IL-33	Endothelial cells, airway epithelial cells, dying cells	*Basophils:* Increased production of cytokines and histamine *DCs:* Increased cytokine production, upregulation of MHC and co-stimulatory molecules *Eosinophils*: Increased proliferation, survival, and chemokine production *Macrophages*: Increased cytokine production *Mast Cells:* Increased cytokine production, degranulation, and survival *Neutrophils*: Increased survival and release of proteases *NK Cells:* Increased IFN-γ and $T_{H}2$ cytokines *T Cells:* Promotes $T_{H}2$ differentiation, enhances release of $T_{H}2$ cytokines
IL-35	T_{Reg} cells	*T Cells:* Decreased production of $T_{H}2$ cytokines, suppression of T cell proliferation
IL-36	Airway epithelial cells	*T Cells:* Increased $T_{H}1$ differentiation
IL-37	Hematopoietic cells	*Macrophages:* Decreased secretion of proinflammatory cytokines *Airway Epithelial Cells:* Decreased secretion of proinflammatory cytokines
Interferons		
IFN-α	Monocytes/macrophages	*Virus-Infected Cells:* Inhibition of viral replication
IFN-β	Monocytes/macrophages	*Virus-Infected Cells:* Inhibition of viral replication
IFN-γ	T cells, NK cells	*Macrophages:* Differentiation, activation, and expression of Fcγ receptor. Increased cytokine production *T Cells:* Increased differentiation to $T_{H}1$ cells, increased cytotoxicity of $CD8^{+}$ T cells
IFN-λ	See above	See above
Growth Factors		
bFGF	Endothelial cells	*Fibroblasts:* Proliferation and extracellular matrix formation
G-CSF	Monocytes, fibroblasts, airway epithelial cells	*Neutrophils:* Proliferation and differentiation
GM-CSF	T cells, airway epithelial cells, macrophages	*DCs:* Maturation *Eosinophils:* Increased survival, degranulation *Macrophages:* Differentiation, increased survival, increased cytokine production *Neutrophils:* Increased chemotaxis and survival
M-CSF	Fibroblasts, endothelial cells, macrophages, airway smooth muscle cells	*Hematopoietic Stem Cells:* Differentiation of monocytes
PDGF	Platelets, monocytes, macrophages	*Fibroblasts:* Proliferation and chemoattraction
SCF	Bone marrow stromal cells, fibroblasts	*Mast Cells:* Chemoattraction, induction of histamine release, differentiation, proliferation
TGF-β	Eosinophils, T cells, macrophages, airway epithelial cells, endothelial cells, airway smooth muscle cells	*Fibroblasts:* Chemoattraction and increased conversion to myofibroblasts, increased synthesis of collagen *Macrophages:* Chemoattraction *Neutrophils*: Chemoattraction *T Cells*: Increased differentiation of T_{Reg}, $T_{H}9$, and $T_{H}17$ cells, inhibition of $T_{H}1$ and $T_{H}2$ differentiation
VEGF	Macrophages, airway epithelial cells, T cells, eosinophils	*Airway Smooth Muscle Cells*: Hyperplasia and increased airway hyperresponsiveness *DCs*: Increased proliferation and activation *Endothelial Cells*: Increased angiogenesis and vascular permeability *Airway Epithelial Cells:* Increased proliferation, mucus production *Fibroblasts*: Promotion of subepithelial fibrosis
Other		
TNF-α	Monocytes/macrophages, DCs, mast cells, eosinophils, neutrophils, B and T cells, airway epithelial cells, airway smooth muscle cells, fibroblasts	*Airway Epithelial Cells:* Upregulation of adhesion molecules *Airway Smooth Muscle Cells*: Increased airway hyperresponsiveness *Endothelial cells:* Upregulation of adhesion molecules *Eosinophils*: Chemoattraction, increased activation *Fibroblasts:* Increased conversion to myofibroblasts *Macrophages:* Chemoattraction *Mast Cells:* Increased histamine release *Neutrophils:* Chemoattraction *T Cells:* Increased activation and cytokine release

(continued)

TABLE 43-1 Cytokines and Lipid Mediators in Asthma *(Continued)*

Cytokines		
Cytokine	**Cell Sources**	**Proposed Cell Targets/Functions in Asthma**
Alarmins TSLP	Airway epithelial cells	*DCs:* Increased ability to attract T_H2 cells *Eosinophils:* Induced release of proinflammatory cytokines and chemokines *Mast Cells:* Increased production of T_H2 cytokines *T Cells:* Increased differentiation to T_H2 cells
Lipid Mediators		
Mediator	**Cell Sources**	**Proposed Cell Targets/Functions in Asthma**
Leukotrienes		
Dihydroxy Acid Leukotriene (LTB4)	DCs, monocytes/ macrophages, neutrophils	*B Lymphocytes:* Increased expression of CD23, CD54, and CD105 *DCs:* Recruitment, increased skewing of T_H0 cells to T_H1 type *Eosinophils*: Recruitment *Mast Cells:* Recruitment *Monocyte/Macrophages:* Increased production of IL-6, TNF-α, MCP-1 *Neutrophils:* Recruitment and activation *Airway Smooth Muscle Cells:* Increased proliferation *T Lymphocyte:* Recruitment
Cysteinyl Leukotrienes (LTC4, LTD4, LTE4)	DCs, eosinophils, mast cells, monocytes/macrophages	*Airway Smooth Muscle Cells:* Bronchoconstriction *DCs:* Increased migration to lymph nodes *Endothelial Cells:* Increased vascular permeability and upregulation of adhesion molecules *Eosinophils:* Recruitment *Goblet Cells:* Increased mucus production *Mast Cells:* Increased production of IL-5, IL-8, TNF-α, and MIP-1β *Monocytes/Macrophages:* Increased production of MCP-1, TNF-α, and MMP-9 *T Lymphocytes:* Increased T_H2 immune response
Prostanoids		
PGD2	Mast cells	*Airway Smooth Muscle Cells:* Bronchoconstriction *Eosinophils:* Recruitment, increased degranulation *Monocytes/Macrophages:* Increased cytokine production *Neutrophils:* Inhibition of activation *T Lymphocytes:* Recruitment, increased production of T_H2 cytokines, inhibition of IFN-γ production
PGE2	Airway smooth muscle cells, airway epithelial cells, endothelial cells, macrophages	*Airway Smooth Muscle Cells:* Inhibition of allergen-induced bronchoconstriction *Eosinophils:* Inhibits recruitment *Monocytes/Macrophages:* Decreased cytokine production, downregulation of MHC class II expression *T Cells:* Decreased proliferation, decreased T_H2 cytokine production
PGI2 (Prostacyclin)	Endothelial cells, monocytes/macrophages	*Endothelial Cells:* Vasodilatation *Eosinophils:* Inhibition of recruitment *T Cells:* Increased IL-10 production
Thromboxane A2	Platelets, endothelial cells, monocytes/macrophages	*Airway Smooth Muscle Cells:* Bronchoconstriction *Eosinophils:* Recruitment

TABLE 43-2 T2-Directed Anticytokines: Effects on Asthma Exacerbations, Lung Function, and Need for Oral Corticosteroids (OCS) in Patients with Severe Disease

Agent	↓ Exacerbations	↑ Lung Function	OCS ↓	Comment
Omalizumab (IgE)	25%	±	–	Only anti-IgE drug
Mepolizumab (IL-5)	50%	+	++	Indication for EGPA
Reslizumab (IL-5)	50%	++	–	Weight-based dose (IV)
Benralizumab (IL-5R)	50%	++	++	q 8 weeks causes ADCC
Dupilumab (IL-4/IL-13)	50%	++	++	FeNO response biomarker

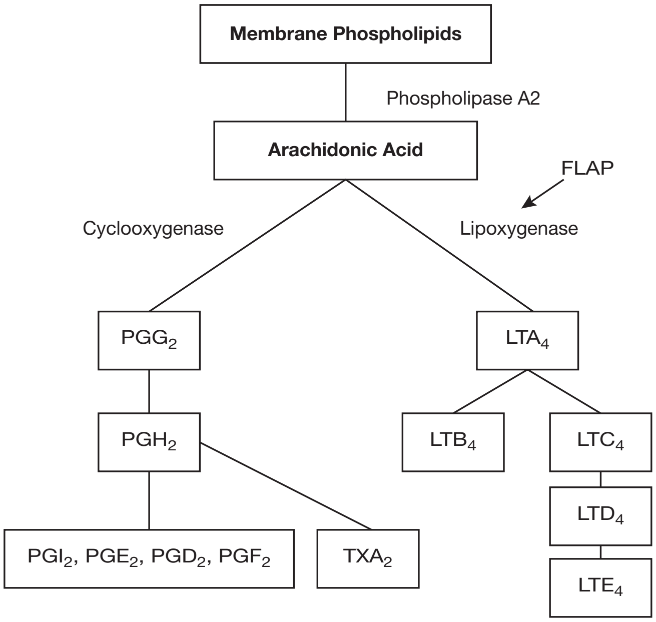


Figure 43-5 Formation of arachidonic acid metabolites. FLAP, 5-lipoxygenase activating protein; LT, leukotriene; PG, prostaglandin; TXA_2, thromboxane A2.

(Fig. 43-5).[112] Most of the prostanoids, that is, PGD_2, PGF_2, and TxA_2, are potent bronchoconstrictors and products of several cell types including eosinophils and mast cells.[112] In contrast, PGE_2 has bronchodilatory and anti-inflammatory activity.[113,114] The use of nonsteroidal anti-inflammatory medications to inhibit cyclooxygenase activity has not been shown to have an appreciable effect on airway inflammation to date. However, since PGD_2 is the predominant prostanoid involved in asthma,[115] specific PGD_2 receptor antagonists have been studied but failed to show exacerbation reduction in asthma.[116–119]

■ Nitric Oxide

The role of nitric oxide (NO) in the pathogenesis of asthma remains unclear. NO is continually synthesized at low levels in the airways of normal subjects. Sources of NO in the respiratory tract include airway epithelial cells (likely the primary source), smooth muscle cells, sensory nerves, endothelial cells, and macrophages.[120] At low levels, NO is a bronchodilator and vasodilator that antagonizes endothelin and has protective effects in the airway.[120] Higher levels of NO are found in asthma, secondary to increased inducible NO synthase (iNOS) expression that is induced by alarmins and cytokines such as TSLP and IL-13.[121] NO can react with superoxide anion in inflamed tissue to produce biologic oxidants that contribute to ongoing tissue damage and chronic asthmatic inflammation.[120] The production of NO is also thought to reflect the intensity or severity of airway inflammation. Thus, exhaled NO measurement has been utilized successfully as a tool to reflect the extent of airway inflammation as a measure of asthma control—in particular, the presence of eosinophils in the airway wall.[121]

■ Granule Proteins

Granulocytes, that is, mast cells, basophils, eosinophils, and neutrophils, all produce granular proteins that play significant roles in the pathogenesis of asthma.

Insights into the kinetics and importance of mast cell mediators were obtained from studies that measured BAL histamine and tryptase.[122] These studies demonstrated that mast cell activation is an early event: elevated BAL histamine and tryptase levels are seen 12 min after endobronchial antigen challenge. The levels of tryptase return to normal 48 h after antigen challenge while the levels of histamine remain elevated after 48 h. This suggests that other cell types that produce histamine (e.g., basophils) are recruited and activated to produce histamine at these later points or that mast cells generate and continue to release histamine over time following an initial activation.[122] Furthermore, BAL of allergic asthmatic subjects had only moderately elevated levels of tryptase at baseline but higher concentrations of tryptase following antigen challenge.[122]

Histamine is capable of inducing bronchoconstriction, increasing vascular permeability to cause edema, and increasing mucus secretion.[123] The role of tryptase is not well established, although there are data to suggest that it can activate inflammatory cells such as eosinophils, mast cells, and epithelial cells by cleaving a family of protease-activated receptors (PARs) on the cell surfaces.

The best known eosinophilic specific proteins include major basic protein (MBP), eosinophil cationic protein (ECP), eosinophil-derived neurotoxin (EDN), and eosinophil peroxidase (EPX). MPB is the principal protein constituent of eosinophil granules. It is toxic to epithelial tissues, induces airway hyperresponsiveness, and causes histamine release from basophils.[124] ECP is more cytotoxic to the epithelium than MBP and damages target cells by membrane pore formation.[125] EDN, as the name implies, damages myelinated neurons.[126] EPX has different effector functions compared with neutrophil and monocyte myeloperoxidases (MPOs); it causes LTC_4 and LTD_4 degradation and causes histamine release from mast cells.[127] Data suggest that the presence of EPX in airways indicates eosinophil activation, and that EPX may be the dominant granule-associated protein associated with tissue inflammation.[128]

The primary granules of neutrophils contain MPO and lysozyme as well as hydrolases and proteinases, which are important to tissue penetration by neutrophils.[129] The primary neutrophilic granular proteins are myeloperoxidases, best known as autoantigens associated with p–antineutrophil cytoplasmic antibody (p-ANCA)-positive vasculitis such as eosinophilic granulomatosis polyangiitis (EGPA, formerly known as Churg-Strauss syndrome). The release of MPO and neutrophil elastase enhances host defense functions but also causes tissue damage to normal tissues, including airway epithelium.[129] Secondary granules contain lysozyme and collagenases, which can also potentially damage airway tissue and contribute to airway remodeling.[129] Neutrophil granule proteins are considered toxic to airway epithelium and tissue.

REMODELING IN ASTHMA

As occurs in most chronic inflammatory disorders in which there is a chronic cycle of "injury-repair," irreversible structural changes occur in the airway in asthma that are collectively called "airway remodeling." Airway remodeling involves epithelial changes, smooth muscle hypertrophy and hyperplasia, increased angiogenesis, increased fibroblast/myofibroblast activity, and increased subepithelial fibrosis that affect the structure and function of the large and small airways of the lung.[130] Prolonged infiltration of inflammatory cells and the cytokines, chemokines, and growth factors that they generate contributes to these structural changes and leads to irreversible obstructive physiology noted in many patients with asthma. Clinically, these are patients who have persistent obstructive physiology after maximal treatment with corticosteroids and bronchodilators. A therapeutic intervention that can improve lung function in these patients remains a significant unmet need in the field of asthma.

As mentioned previously, airway epithelium serves not only as an anatomic barrier, but also as a key player in asthma pathogenesis. Defects in airway epithelium are ubiquitous in human asthma. When injury occurs, the repair process has been likened to a chronic wound, which may not heal normally as a result of repetitive and ongoing insults and may result in airway remodeling as discussed above.[131] As with other types of chronic wounds, epithelial cells attempt to heal by promoting the release of growth factors from the underlying mesenchyme. This, in turn, leads to increased extracellular matrix deposition, fibrosis, and hypertrophy and hyperplasia of airway smooth muscle cells.[132] This process has been likened to the function of the epithelial-mesangial trophic unit (EMTU), a key component of early lung morphogenesis that may become reactivated in chronic asthma.[132] The consequence of prolonged epithelial injury is a protracted release of proinflammatory alarmins, cytokines, and profibrogenic growth factors such as TGF-β. When this response is combined with the inflammatory milieu derived from immune cells recruited to the airway chronically, the result is chronic airflow obstruction that may not respond or only partially responds to pharmacologic treatment. It remains unclear if more precise treatment could reverse the chronic obstruction in these patients or if the airways are irreversibly remodeled.

PHENOTYPIC CLUSTERS IN ASTHMA

Several recent studies have begun to identify phenotypes, or subphenotypes, of asthma. These studies have confirmed that asthma is heterogenous disease and that there may be at least four different phenotypes of disease.[133,134] Specifically, studies by Haldar et al. in the United Kingdom used sputum eosinophilia, in addition to measurements of atopic status and symptoms, to identify phenotypes.[133] They identified multiple clusters of patients with concordant symptoms and inflammation but also patients who were highly symptomatic with very little eosinophilic inflammation and lacked evidence of atopic sensitization. Other subgroups fit a more "classic" pattern of asthma with evidence of eosinophilic involvement and atopic sensitization. Other clusters fell somewhere between the two. This study and others are probing the heterogeneity of the disease and discovering the reasons behind differences in disease course and response to conventional asthma therapy.[12,28]

CONCLUSION

Asthma is a complex inflammatory disease that is caused by the contributions of many different immune cells, structural cells, molecular mediators, and external factors to produce acute and chronic inflammation of the airway, airflow obstruction, and chronic symptoms. The study of these factors has led to a greater understanding and appreciation of the breadth of this disease, as well as its complexity and heterogeneity. It has also led to the realization that different phenotypes of asthma exist, and treatment of asthma based on a patient's predominant phenotype may soon be possible. Over the last decade, biologic therapeutics have been made to target specific inflammatory mediators in asthma. The fact that these treatments have not been universally successful speaks to the complexity of this disease and need for more discovery. As research delves further into the pathogenesis and pathophysiology of asthma, many more targets will emerge that reflect activation of pathways that will lead to novel therapies that will improve the lives of patients with asthma and our understanding of this chronic inflammatory airway disease.

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CHAPTER 44

The Epidemiology of Asthma

Kathleen A. Lee-Sarwar
Scott T. Weiss
Augusto A. Litonjua

INTRODUCTION

Asthma is an extremely common clinical syndrome and the most common chronic disease in children.[1] Asthma affects approximately 235 million people worldwide[2] and nearly 25 million Americans.[3] In the United States, asthma accounts for over 10 million medical visits yearly.[4] The estimated total annual cost of asthma care in the United States from 2008 to 2013 was more than 80 billion dollars.[5] These costs include $50.3 billion in medical expenses, $29 billion due to asthma-related mortality, and $3 billion due to missed work and school days.[5]

In 2018, 22% of those afflicted with asthma were children under the age of 18 years,[3] and most cases of asthma begin in preschool age.[6] This propensity to become clinically apparent early in life belies the fact that asthma originates in utero as an abnormality of fetal lung development. Asthma has important consequences in childhood and may have important consequences for adult obstructive lung disease. In addition to having clear genomic and prenatal developmental components, asthma risk and prognosis are influenced greatly by exposures including respiratory viruses, indoor allergens, maternal tobacco smoke, and other physical and social aspects of the environment. The paradox of this illness is that despite important strides in understanding etiologic environmental factors and mechanisms of airway inflammation characteristic of the syndrome, its prevalence and clinical burden remain unacceptably high. Although asthma morbidity and mortality rates have been steady for several years and have declined slightly recently,[7] the rates are dramatically higher than 30 years ago and continue to be significant, particularly for urban minority groups, low-income populations, and children.

The purpose of this chapter is to describe trends in asthma epidemiology and to examine potential reasons for these trends. We discuss the epidemiology of airway hyperresponsiveness, which is more prevalent than asthma, and review clinical heterogeneity in asthma and the concept of asthma endotypes. Environmental risk factors for asthma are discussed, with special attention to the emerging role of the human and environmental microbiomes. We conclude with a review of asthma natural history and the implications of the current trends, especially with regard to health disparities.

DEFINITION, PREVALENCE AND MORBIDITY OF ASTHMA

In 2007, the National Asthma Education and Prevention Program Expert Panel Report 3 (NAEPPR3)[8] defined asthma as a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, including mast cells, eosinophils, neutrophils, T lymphocytes, macrophages, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of coughing, wheezing, breathlessness, and chest tightness. These episodes are usually associated with widespread but variable airflow obstruction that is reversible either spontaneously or with treatment.

Because asthma is a clinical syndrome, there is no gold standard for its diagnosis. As such, physicians employ nonstandardized algorithms for making the diagnosis, such as a history of wheezing or a parental history of asthma in conjunction with evidence of obstruction on lung function testing and a favorable response to a bronchodilator to identify the asthmatic patient. Frequently, age, sex, and other patient characteristics such as smoking status or allergic sensitization may influence a physician's diagnosis.

In general, epidemiologic surveys have tended to rely on historic or questionnaire sources to identify patients with asthma. Asthma cases have been identified either by physicians or by surveys in which the definition of who is asthmatic has been left to the patients themselves, surrogates, or the report of the diagnosis having been made by the patient's physician. Clearly, each of these methods of identifying asthma patients has inherent weaknesses. One must, therefore, assume that some bias in the reporting of cases is present and that the biases in each method of gathering data are different.

Asthma Prevalence in the United States

The National Health Interview Survey (NHIS), a program of the Centers for Disease Control and Prevention (CDC), is an annual random population household interview survey that provides information on asthma prevalence in the United States. Its data demonstrate an almost doubling of asthma prevalence in the last two decades of the 20th century, from 3.2 per 100 population in 1981 to 5.5 per 100 in 1996.[9] In 1997 the NHIS questions and methodology were modified, limiting comparisons of prevalence before and after 1997. The most recent results from the CDC, which analyzed data from the NHIS through 2017, indicate a slower increase in asthma prevalence from 2001 through 2013, and a slight decrease since then from a maximum prevalence of 8.5% in 2011 to 7.9% in 2017[10] (Fig. 44-1). The prevalence in children under 18 years remains higher than in adults; in 2017, it was 8.4% in children compared with 7.7% in adults.[10]

Asthma prevalence trends over the lifespan differ between males and females. Males tend to have higher asthma prevalence during childhood, whereas sex ratios equalize in the pubertal years and females predominate throughout the rest of adult life. For example, in the United States, the prevalence for males under age 18 years in 2018 was 8.3% compared with 6.7% for females; however, in adults

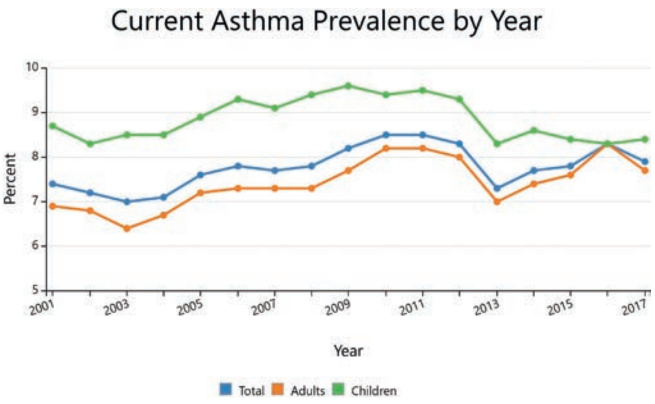

Figure 44-1 Current asthma prevalence figures from the National Health Interview Survey (NHIS), United States, by age group. *(Reproduced with permission from Centers for Disease Control and Prevention. Asthma Prevalence. www.cdc.gov/asthma/data-visualizations/prevalence.htm.)*

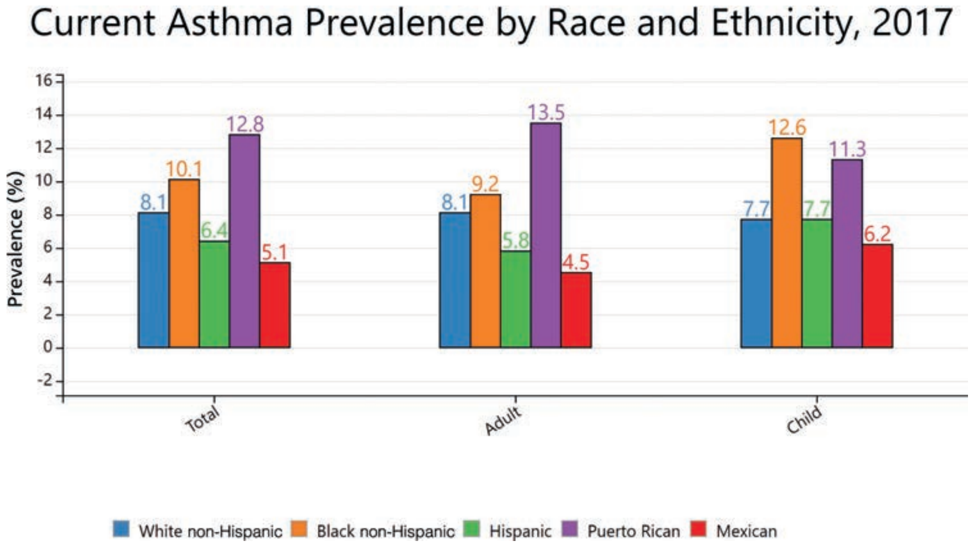

Figure 44-2 Current asthma prevalence figures from the National Health Interview Survey (NHIS), United States, by race and ethnicity and age group in 2017. *(Reproduced with permission from Centers for Disease Control and Prevention. Asthma Prevalence. www.cdc.gov/asthma/data-visualizations/prevalence.htm.)*

18 years and older, female prevalence (9.8%) is almost twice that for males (5.5%).[10] Thus, age and sex play important roles in modifying disease prevalence.

There is a striking difference in prevalence by racial/ethnic groups in the United States. The most recent data from 2016 to 2018 show that prevalence was 10.7% for black non-Hispanics, 6.5% for Hispanics, and 8.0% for white non-Hispanics.[3] It is noteworthy that the rate for Hispanics of Puerto Rican descent was very high at 14%.[3] In addition, there are marked differences in asthma prevalence by income group. Asthma prevalence was highest in 2018 among those below 100% of the poverty threshold (10.8%) and lowest among those in the highest income category, 450% of poverty threshold or higher (6.5%).[3] Figure 44-2 demonstrates these disparities using data from the United States in 2017.

Global Asthma Prevalence

Limited surveys have evaluated the global burden of asthma. The International Study of Asthma and Allergies in Children (ISAAC) used standardized surveys to determine asthma prevalence and severity in 6- to 7-year-old children in 61 countries and 13- to 14-year-old children in 97 countries between 2000 and 2003.[11] There was dramatic variation worldwide in prevalence of wheeze in the past 12 months. For example, current wheeze in 13- to 14-year-olds was reported in only 0.8% of respondents in Tibet but approximately one-third (32.6%) of respondents in Wellington, New Zealand.[11] There was a trend toward higher prevalence of current wheeze at higher-income study sites.[11] In contrast, among children with current wheeze, more severe symptoms were observed at lower-income study sites.[11]

The European Community Respiratory Health Survey (ECRHS) evaluated the prevalence, determinants, and management of asthma in 20- to 44-year-old adults from 48 centers, predominantly in Western Europe, with data reported through 1994.[12] Similar to the findings of ISAAC, ECRHS results showed marked differences in asthma prevalence between countries. Prevalence of wheeze ranged from a lower range of 4.1%–9.7% from centers in India, Algeria, and Italy to a higher range of 23.2%–32% from centers in Sweden, Denmark, Estonia, United States, United Kingdom, Australia, New Zealand, and Ireland.[12] The huge differences in asthma and wheeze prevalence between countries remains to be fully explained and likely reflects the large joint contributions of genetic and environmental factors on asthma risk.

Asthma Healthcare Utilization

The CDC in the United States collects information about physician office visits and emergency department visits from the National Center for Health Statistics and information about all-payer encounter-level hospital care data from the Healthcare Cost and Utilization Project. It also utilizes data from the National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey, which sample visits to office-based physicians, community health centers, and hospital emergency departments (EDs) and outpatient departments to evaluate medical service utilization.

Drawing from these sources, the rate of physician office visits for asthma declined among children under age 18 years from 2010 (776.8 per 10,000) to 2016 (332.9 per 10,000), while office visits for asthma remained stable among adults (372.0 per 10,000 in 2010 and 300.3 per 10,000 in 2016).[13] However, data from 2017 on ED visits and hospitalizations for asthma in the United States highlight that asthma still results in significant morbidity among the pediatric population and disproportionately affects this age group. Patients under age 18 years had more ED visits than adults: 85.3 per 10,000 compared with 38.3 per 10,000 population, and the rate was highest among those age 0 to 4 years: 139.6 per 10,000.[14] Similarly, children had more hospitalizations for asthma than adults (10.3 per 10,000 compared with 4.2 per 10,000), with the 0- to 4-year age group again having the highest asthma hospitalization rate at 17.2 per 10,000 population.[14]

The 2017 ED visit and hospitalization data for asthma in the United States also reveal staggering differences in healthcare utilization by race. There were 164.3 per 10,000 population ED visits and 13.1 per 10,000 hospitalizations for asthma among black individuals compared with 33.9 per 10,000 ED visits and 2.6 per 10,000 hospitalizations for asthma among white individuals.[14] These numbers indicate that ED visits and hospitalizations for asthma are five times more frequent in black individuals than white individuals in the United States.

Sex differences in asthma health care utilization are less striking. Males and females had similar rates of ED visits for asthma in 2017 (49.2 and 49.1 per 10,000, respectively), although hospital admissions for asthma were more frequent among females (6.5 per 10,000) than males (4.7 per 10,000).[14]

Trends in Asthma Mortality

Although asthma mortality rates are quite low, more than 3000 people die every year from asthma in the United States.[15] Recent data from 2001 to 2016 showed an encouraging decrease in the rate of death due to asthma from 15 per million to 10 per million.[15] The asthma death rate in 2016 was highest among adults age 65 years or older (29.2 per million); despite higher rates of pediatric ED visits and hospitalizations for asthma, individuals under age 18 years were nearly 5 times less likely than adults to die from asthma.[15]

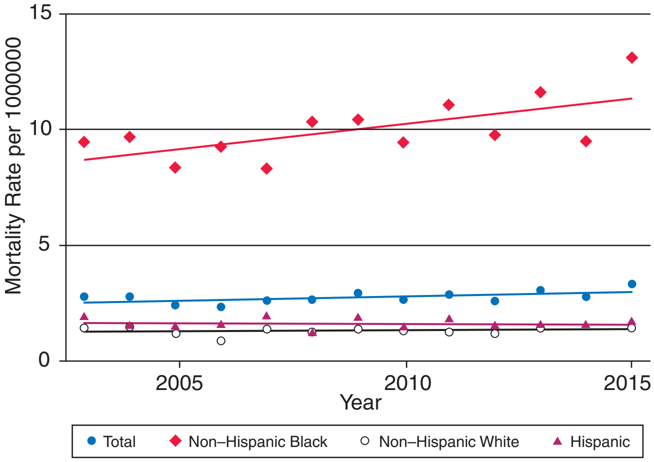

Figure 44-3 Pediatric asthma mortality rate in the United States by year among those age 3 to 19 years by race and ethnicity. *(Reproduced with permission from Arroyo A, Chee C, Camargo A, et al. Where do children die from asthma? National data from 2003–2015. J Allergy Clin Immunol Pract. 2017;6(3):1034–1036.)*

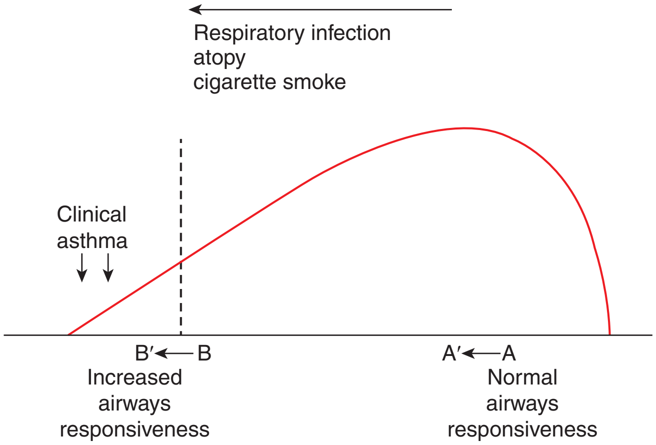

Figure 44-4 The effect of environmental exposures on the population distribution of airway responsiveness acting to move people in a more responsive direction. *(Reproduced with permission from Brown RW, Weiss ST. The influence of lower respiratory illness on childhood asthma: defining risk and susceptibility. Semin Respir Infect. 1991;6(4):225–234.)*

However, the downward trend in countrywide asthma mortality belies pockets of very high prevalence, morbidity, and mortality in certain populations. Between 2003 and 2015, there was actually an overall increase in deaths due to asthma among those under age 19 years, and non-Hispanic black children had an average annual mortality rate (10 deaths per million) 6 times higher than Hispanic children (1.62 deaths per million) and 7 times higher than non-Hispanic white children (1.33 deaths per million)[16] (Fig. 44-3). This disparity in asthma mortality between race groups in the United States has been observed since the 1980s.[17,18] While the absolute number of deaths due to asthma is very low, asthma mortality rates do represent a clear public health concern because almost all asthma deaths are preventable.

AIRWAY RESPONSIVENESS

Airway responsiveness is a defining characteristic of asthma and is both developmentally and environmentally determined. Airway responsiveness is measured by inhaling increasing doses of a bronchoconstrictor agonist, for example, methacholine or histamine, and repeatedly measuring lung function (usually FEV_1) after each dose. The dose of bronchoconstrictor that results in a 20% reduction in lung function from baseline is considered the provocative dose (or concentration), also called the PD or PD20. A low PD20 (usually less than 10 mg of methacholine) indicates significant airway responsiveness since the patient is responding to a low dose with at least a 20% drop in FEV_1.

Since flow in the airways is inversely proportional to the radius of the airway to the 4th power, small changes in airway size can have a big influence on PD20. An additional factor influencing the measurement is total lung size: the bigger the lung, the higher the PD20, and the less responsive the airway. These physiologic facts help explain some of the more relevant clinical correlates.

All individuals with active asthma have increased airway responsiveness, and it precedes and predicts asthma development,[19] but its presence in the general population exceeds the prevalence of asthma by about twofold.[20] This suggests that individuals genetically predisposed to develop increased airway responsiveness encounter relevant environmental stimuli such as viral illness, smoking, or occupational exposures and then increase their airway responsiveness and thus develop symptomatic asthma (Fig. 44-4).

Given the dependence on lung and airway size, airway responsiveness is highest at the extremes of age and in females at any given age.[21] It is known to be present at birth and correlates with gestational age, being greatest in preterm babies, which may explain why preterm birth is one of the strongest risk factors for childhood asthma.[22] In general, clinicians do not usually test for airway responsiveness in patients, preferring to infer the phenotype based on the presence of wheezing symptoms, and it is only in difficult cases where the diagnosis is in doubt that a test is required.

ASTHMA PHENOTYPES AND ENDOTYPES

Reversible airway hyperresponsiveness and inflammation are critical components of asthma pathogenesis. However, beyond these essential features, there is a wide range of clinical asthma phenotypes such that two individuals with asthma may dramatically differ in characteristics including age of asthma onset, disease severity, and comorbidities such as allergic sensitization and obesity. It is therefore now recognized that asthma is not a single disease.[23] Distinct clinical asthma phenotypes have been defined by applying analytic clustering techniques to data from large cohorts of subjects with asthma.[24–27] While methodologies and results have varied between studies, results largely converge around the existence of four phenotypes: early-onset mild allergic asthma, early-onset allergic moderate to severe remodeled asthma, late-onset nonallergic eosinophilic asthma, and late-onset noneosinophilic nonallergic asthma.[28]

While clinically intuitive, phenotypes do not map neatly onto specific disease mechanisms.[29] Just as distinct asthma phenotypes are now recognized, asthma *endotypes* have been proposed and are defined by divergent molecular and immunologic mechanisms.[30] The advent of the genomic era has enabled researchers to define asthma endotypes. The most widely recognized asthma endotyping concept categorizes individuals as having type 2 or non–type 2 asthma (Fig. 44-5). Approximately 50% of those with asthma fall into each of these categories.[31,32]

As has been recently reviewed,[22,33,34] type 2 inflammation involves activation of immune cells including T helper type 2 cells, type 2 innate lymphoid cells, eosinophils, and mast cells, as well as production of cytokines such as IL-4, IL-5, and IL-13 that together orchestrate allergic inflammation. Airway epithelial and stromal cells play a major role in the initiation of type 2 inflammation via production of IL-33, IL-25, and thymic stromal lymphopoietin (TSLP). This type of immediate hypersensitivity immune reaction is not specific to asthma and can be seen in other allergic diseases such as eczema,

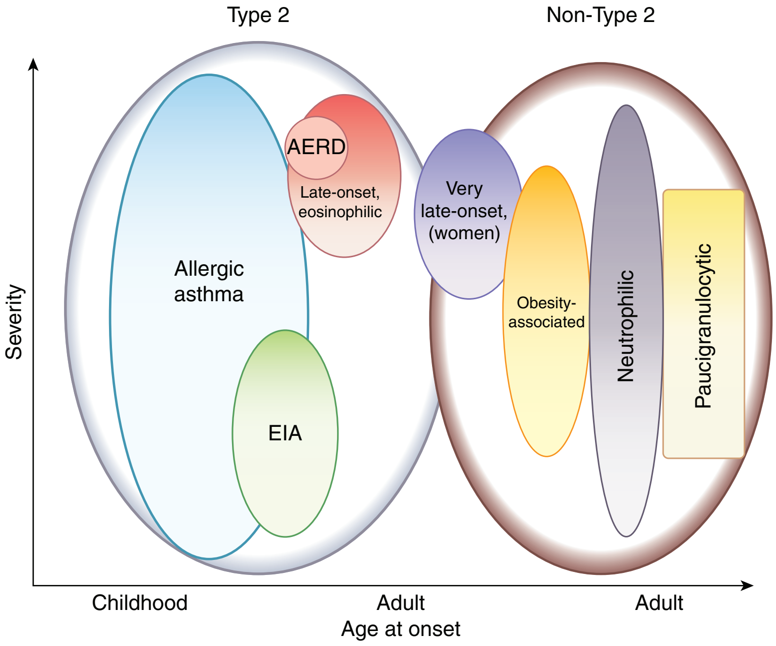

Figure 44-5 Theoretical grouping of asthma phenotypes based on the distinction between type 2 or non-type 2 asthma endotypes, age of onset and severity. Type 2 asthma consists of both early- and later-onset disease over a range of severities. Later-onset eosinophilic asthma and aspirin-exacerbated respiratory disease (AERD) are more likely to be severe, whereas exercise-induced asthma (EIA) is a milder form of type 2 asthma. Non-type 2 asthma includes very late-onset and obesity-associated asthma as well as neutrophilic asthma, and asthma in which affected individuals show little inflammation (paucigranulocytic). The intensity of the colors represents the range of severity, and the relative sizes of the subcircles suggest relative proportions of affected individuals. *(Reproduced with permission from Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches. Nat Med. 2012;18(5):716–725.)*

allergic rhinitis, and food allergy. Details on immune perturbations in asthma are provided elsewhere in this text (Chapter 43). Early-onset allergic asthma, eosinophilic asthma, and exercise-induced asthma all fall into the category of type 2 asthma, which is frequently accompanied by aeroallergen sensitization and may develop as sequelae of repeated viral infections in early life.

In contrast, non–type 2 asthma can be defined by the absence of type 2 inflammation.[35] Non–type 2 asthma encompasses heterogeneous mechanisms and may involve activation of cells such as T helper type 1 or 17 cells and neutrophils and production of cytokines such as IL-6, IL-8, IL-1β, and interferon-γ.[23,32] Neutrophilic asthma and paucigranulocytic asthma fall into the category of non–type 2 asthma, and those with non–type 2 asthma may have more severe disease.[23,35]

Obesity-related asthma also tends to fall in the category of non–type 2 asthma. This phenotype commonly begins in childhood and is associated with frequent asthma exacerbations.[36] A mechanical effect is postulated to be the result of decreased tidal volume and decreased functional residual capacity in obesity.[37] However, the critical links between obesity and asthma involve more than mechanical effects and may be related to shared genetic susceptibilities, events during fetal development, comorbidities such as gastroesophageal reflux disease, shared environmental exposures such as pollution, or common dietary and microbiome perturbations.[36,38] Immune effects may also contribute to obesity-related asthma; for example, proinflammatory cytokines can be induced or produced by adipocytes.[39] Clearly, much remains to be learned about the endotypes underlying obesity-related asthma.

Several biomarkers have been identified to differentiate asthma endotypes. Sputum cell counts are frequently used to ascertain the degree and type of asthmatic inflammation, with major categories including eosinophilic, neutrophilic, mixed granulocytic, and paucigranulocytic.[40,41] Other biomarkers of type 2 asthma include peripheral eosinophilia, elevated total IgE, and presence of allergic sensitization.[33,34] Fractional excretion of nitric oxide (FeNO) is another relevant biomarker:[42] enzymatic production of nitric oxide in the lower airway is induced by type 2 inflammation,[43] and elevated FeNO is associated with eosinophilic inflammation[44] and asthma severity.[45,46] Although less available outside of research settings, evaluation of microRNA and gene expression has been performed for endotype discovery and led to recognition of bronchial periostin expression as a type 2 asthma biomarker.[47]

Like asthma phenotypes, the asthma endotype concept has limitations. A single person with asthma may exhibit multiple contributory molecular and immunologic mechanisms or may exhibit some but not all of the characteristics of a specific endotype. For example, many individuals with asthma exhibit eosinophilia but do not have comorbid allergic sensitization or disease.[28] Additionally, different studies have used different input data types and statistical methods to define endotypes. As a result, there is no consensus endotyping schema, endotype groups necessarily overlap, and individuals with asthma are frequently not easily categorized. It is highly likely that the use of multiomic data may lead to more robust endotyping in the not-too-distant future.

Nonetheless, the endotyping concept has been critical for the development of treatments that target specific disease mechanisms, as has been reviewed.[28,34] Endotype-tailored drugs currently available for moderate and/or severe type 2 asthma include the anti-IgE omalizumab for those with evidence of allergic sensitization; the anti–IL-5 agents mepolizumab, benralizumab, and reslizumab for those with an eosinophilic phenotype; and anti-IL4ra dupilumab for those with an eosinophilic phenotype or oral corticosteroid dependence. Non–type 2 asthma is associated with poor response to glucocorticoid treatment,[35] and fewer treatments have been identified as beneficial in non–type 2 asthma, although macrolide antibiotics may be effective.[48] This topic is discussed in detail in Chapter 45.

THE ROLE OF THE MICROBIOME

The microbiome refers to the collective genomic contents in a particular environment, while the microbiota refers to the specific organisms resident in that environment.[49] The human microbiota has the capacity to profoundly influence its biochemical environment, and it has several known essential functions including nutrient harvest, vitamin synthesis, and development and maintenance of immune function.[50–53] Germ-free mice have reduced T regulatory cells, elevated IgE, and increased susceptibility to anaphylaxis and allergic inflammation, indicating a key role of the microbiome in asthma and allergic pathophysiology.[54]

Findings from germ-free mice dovetail with the concept originally framed as the “hygiene hypothesis,” which posited that reduced microbial exposure is responsible for the increased prevalence of allergic disease observed in countries like the United States. This was first proposed via an observation in 1989 that larger household size is associated with reduced hay fever[55] and has evolved into a "microbiota hypothesis" whereby a variety of early-life risk factors impact microbiome composition and thereby increase risk of allergy and asthma. Since asthma has its beginnings in early life, investigation into factors that influence the composition of the early life microbiome is intensifying. Environmental and lifestyle factors that are known to affect the microbiome and that have been linked to reduced risk of asthma and allergies include breastfeeding, living on a farm, owning a dog during infancy, birth by vaginal delivery, daycare attendance, and absence of antibiotic treatment.[56,57] Thus, environmental exposures may act through changes in the composition of the microbiome to bring about disease. The concept of "dysbiotic drift," whereby modern environmental forces drive microbial dysbiosis in a way that disproportionately impacts socioeconomically disadvantaged populations, could be a unifying hypothesis on the origins of asthma and health disparities.[58,59]

There are four major mechanisms whereby microbes could impact disease risk. First, pathogenic microbes can directly cause or worsen disease; for example, upper respiratory viral illnesses are well-known causes of wheeze and asthma exacerbations.[60] A second mechanism, discussed further below, is microbial production of bioactive metabolites. A third mechanism is elaboration of pathogen-associated molecular patterns that can directly engage with host receptors such as Toll-like receptors. For example, the amount and strength of Toll-like receptor engagement by fecal microbial lipopolysaccharides are associated with asthma and autoimmune diseases.[61] Finally, specific microbes can contribute to colonization resistance, whereby pathogenic microbes have reduced ability to establish a niche; or groups of microbes with complementary functions could form communities and together impact disease risk.[62] The role of this last mechanism is less well-established in asthma.

Both microbes present in the human host and in the surrounding environment have been associated with development of asthma and with existing asthma. These findings are discussed in this section and depicted in Fig. 44-6.

The Airway Microbiome

Although fungi and archaea are likely to play a role in asthma development, viruses and bacteria have been studied more extensively. Viruses have a well-established role in asthma development, with respiratory syncytial virus (RSV) and rhinovirus in particular implicated as causes of early-life wheeze that predispose to subsequent asthma.[60,63] RSV is the major cause of bronchiolitis in children, and RSV infection is associated with IgE production, airway inflammation, and increased airway responsiveness. Human rhinoviruses, which are more common causes of upper and lower respiratory infections than RSV, also may cause bronchiolitis;[64] rhinoviruses, especially of the rhinovirus-C serotype, have been associated with asthma onset.[65] Respiratory tract infections by parainfluenza viruses, influenza virus, and human metapneumovirus during infancy are all also associated with childhood wheezing.[63]

It is hypothesized that susceptibility to asthma associated with viral infection in early life results from the interaction of developmental, genetic, and environmental factors. In particular, the progression from wheezing with viral illness to subsequent asthma has been linked to the atopic march, as children with pre-existing atopy are at highest risk of asthma after a rhinovirus wheezing illness, perhaps in part due to the inhibitory effects of Th2 inflammation on antiviral immune responses.[65] Jackson and colleagues[65] showed that while human rhinovirus was the dominant factor in developing asthma by the age of 6 years, the risk was highest when concomitant allergic sensitization was present. This concept is supported by evidence that treatment with the anti-IgE monoclonal antibody omalizumab increases IFN-α production in rhinovirus-treated peripheral blood mononuclear cells and, in children with asthma, resulted in reduced frequency and duration of rhinovirus infection and reduced frequency of asthma exacerbations.[67,68]

In addition to their role in asthma development, viral respiratory illnesses trigger asthma exacerbations and induce nonspecific increases in airway responsiveness and airway obstruction.[69,70] A number of studies have demonstrated a close temporal relationship at the individual and population levels between viral infections and asthma exacerbations, and they have demonstrated that those with asthma may have increased susceptibility to viral lower respiratory infections.[71,72]

In contrast to viral infections, bacterial infections are not associated with asthma exacerbations,[73] and the relative importance of the bacterial versus viral airway microbiome in asthma development has not yet been determined. The lower airway was previously thought to be sterile under normal conditions, but now it is known to be colonized, most likely with microbes that originate in the upper airway and oropharynx. Studying the airway microbiome is challenging for multiple reasons. For example, it is not clear which anatomic compartment along the airway is most relevant, contamination is more of a consideration when sampling low-biomass areas such as the lower respiratory tract, and treatments such as inhaled steroids can influence airway microbiome composition.[74]

Studies in children most often utilize upper airway samples such as nasal or oropharyngeal swabs to study the airway microbiome. Longitudinal cohort studies have found that colonization early in life with *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and *Haemophilus influenzae* is associated with subsequent recurrent wheeze.[75] These taxa and other bacterial microbiome perturbations have also been associated with RSV, rhinovirus, and lower airway symptoms during respiratory infections,[76–79] raising the question of whether these bacteria have causal importance or are simply associated with pathogenic viruses.

In addition to impacting asthma development early in life, airway microbiome perturbations have been observed in children and adults with existing asthma. In particular, Proteobacteria, including the genus *Haemophilus*, is enriched in the airways of subjects with asthma.[80–83] The impact of the microbiome on asthma phenotypes, endotypes, and responses to treatment is an area of active research. Several studies have demonstrated differences in the airway microbiome between asthmatic subjects with sputum eosinophilia and those with sputum neutrophilia, or in association with blood eosinophilia.[83–87] Airway microbiome composition has been associated with other disease-related features, including airway hyperresponsiveness, lung function, and Th17-related gene expression.[83,84,88,89] Microbiome alterations may also inform response to asthma pharmacologic treatments. Of particular interest, corticosteroid resistance has been associated with airway microbiome features including enrichment of *Haemophilus parainfluenzae*.[90,91]

The Environmental Microbiome

A landmark study of the impact of the environmental microbiome on asthma compared Amish farmers from Indiana and Hutterite farmers from South Dakota.[92] These populations are genetically similar, but Amish people live in closer proximity to animal dwellings including cow stables compared to Hutterites. Interestingly, Amish children have a fourfold lower prevalence of asthma compared with Hutterites. Dust collected from Amish homes had higher perennial allergen levels, higher endotoxin levels, and different bacterial compositions compared with dust from Hutterite homes. These differences in environmental microbial exposures could contribute to differences in asthma risk. In a mouse model of OVA-induced allergic asthma, intranasal treatment of mice with

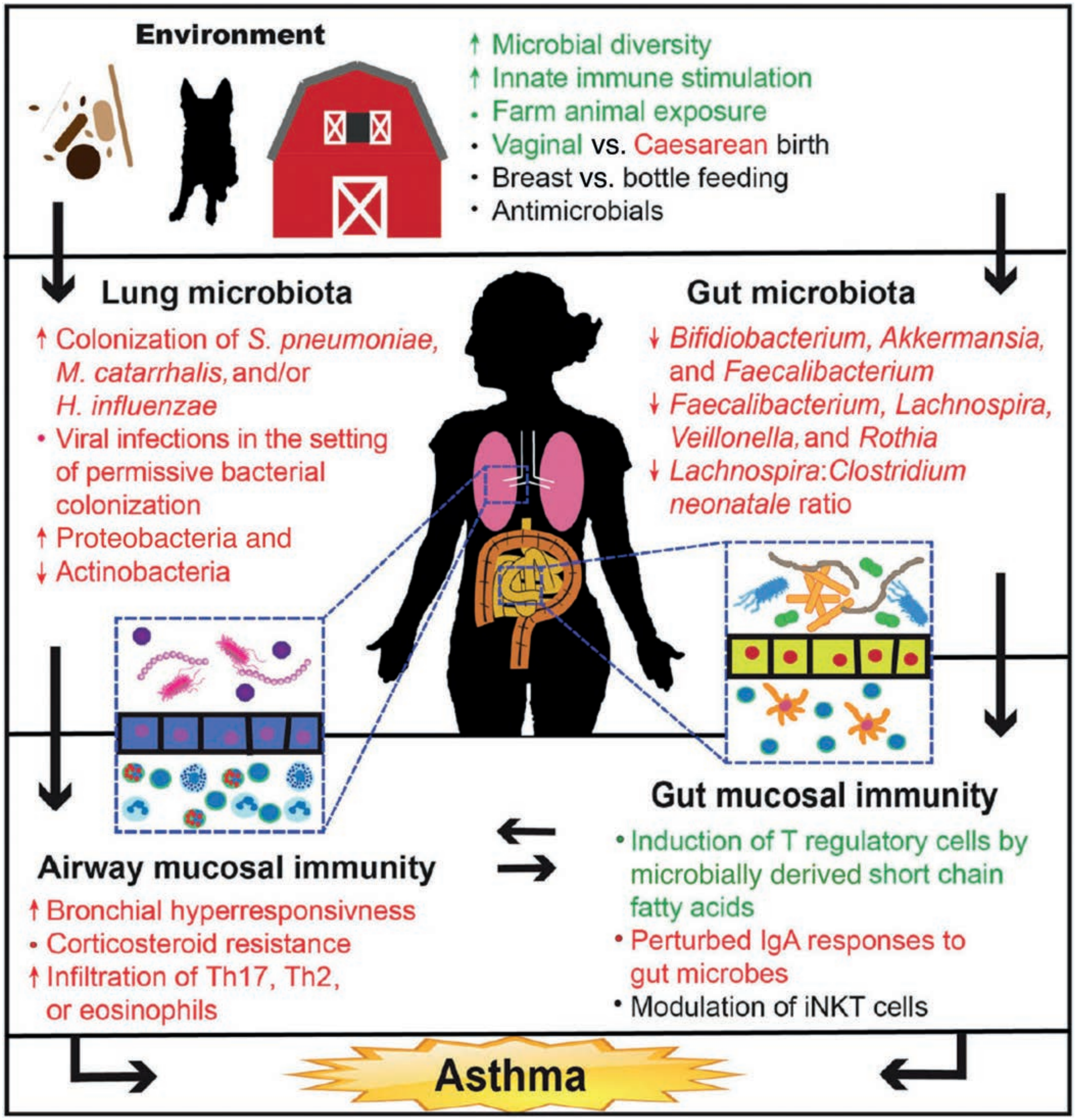
Environment
↑ Microbial diversity
↑ Innate immune stimulation
• Farm animal exposure
• Vaginal vs. Caesarean birth
• Breast vs. bottle feeding
• Antimicrobials
Lung microbiota
↑ Colonization of S. pneumoniae, M. catarrhalis, and/or H. influenzae
• Viral infections in the setting of permissive bacterial colonization
↑ Proteobacteria and
↓ Actinobacteria
Gut microbiota
↓ Bifidiobacterium, Akkermansia, and Faecalibacterium
↓ Faecalibacterium, Lachnospira, Veillonella, and Rothia
↓ Lachnospira:Clostridium neonatale ratio
Airway mucosal immunity
↑ Bronchial hyperresponsivness
• Corticosteroid resistance
↑ Infiltration of Th17, Th2, or eosinophils
Gut mucosal immunity
• Induction of T regulatory cells by microbially derived short chain fatty acids
• Perturbed IgA responses to gut microbes
• Modulation of iNKT cells
Asthma

Figure 44-6 Overview of potential microbial influences on asthma. Green type denotes protective factors, and red type denotes risk factors for asthma development. *(Reproduced with permission from Ver Heul A, Planer J, Kau AL. The human microbiota and asthma. Clin Rev Allergy Immunol. 2019;57(3):350–363.)*

Amish house dust abrogated airway resistance. The protective effect of Amish house dust was reduced in MyD88 and MyD88-Trif knockout mice, demonstrating a dependence on innate immune pathways such as Toll-like receptor activation.[92] Based on this and other studies,[93,94] there is compelling evidence for a protective effect of farm environments with a key role for innate immune activation, although the specific microbes and mechanisms at play are not fully defined. Exposure to a wider array of microbial agents via farm animals and ingestion of raw, unpasteurized milk have been postulated to mediate the effects of early life exposure to farming environments,[92,95] and it may also affect the development of the child's intestinal microbiome.[96]

Other factors are likely to impact the environmental microbiome with relevance for asthma risk. For example, although existing asthma is associated with allergic sensitization to cats and dogs,[97] living with a dog during infancy has been associated with reduced risk of subsequent asthma or wheeze.[98,99] The connection between dog ownership and asthma may be mediated by changes to the household microbiome, as pets contribute significantly to household endotoxin levels.[100,101] While a pooled analysis of 11 European birth cohorts did not find any effect of pet ownership on asthma and allergic rhinitis in school-age children,[102] it is likely that there are subsets of children for which early exposure to dogs and other pets may be helpful.[103] The protective effect of early-life dog exposure is in contrast to the effects of early exposure to other indoor allergens, such as dust mite, which is associated with increased risk of subsequent asthma as discussed in "Indoor and Outdoor Allergens," below.[104,105]

The Gut Microbiome

Although distant from the lung, the gut harbors the most numerous and diverse collection of microbes in the human body, and microbial activity in the gut can have effects in organs throughout the body.[106] Data from several birth cohort studies demonstrate that differences early in life in gut microbiome composition can be detected between children who subsequently develop asthma and those who do not.[107–110] These differences have been seen in the first months of life, but not later,[108,109] suggesting a transient "window of opportunity" for the microbiome to impact asthma risk. In contrast to the numerous published studies on the gut microbiome in early life and development of asthma, little is known about the gut microbiome in existing asthma. In one of the few studies on this topic, an increased abundance of histamine-secreting fecal microbes was found in adults with asthma compared to healthy controls.[111]

Gut microbial metabolites are felt to be major mediators of the link between gut bacterial composition and asthma risk. Short-chain fatty acids are a class of metabolites that include acetate and butyrate and have been well studied in the context of asthma. Short-chain fatty acids are derived from bacterial fermentation of dietary fiber and have several health effects including tolerogenic effects on multiple facets of immune function.[112] Both animal and human cohort studies have provided evidence of a protective effect of short-chain fatty acids on asthma development.[108,113–115]

12,13-diHOME, a metabolite of the omega-6 fatty acid linoleic acid, also plays a role in asthma development. 12,13-diHOME is enriched in stool samples from infants at risk of subsequent asthma and atopy.[109] In mouse models, peritoneal injection of 12,13-diHOME increases airway inflammation and IgE and reduces lung T regulatory cells.[116] A subset of gut microbes, but not human cells, express epoxide hydrolases that are required in the production of 12,13-diHOME; genes that encode these enzymes are present in higher abundances in stool samples from infants at risk of asthma and atopy.[116] Other classes of microbial-derived metabolites likely impact asthma risk or morbidity, including other polyunsaturated fatty acids, tryptophan metabolites, and bile acids.[117]

GENETIC SUSCEPTIBILITY AND GENE-ENVIRONMENT INTERACTIONS

Asthma is considered a complex disease that has both genetic and environmental determinants. Since the completion of the Human Genome Project in 2000, more than 100 genes have been directly linked to asthma through association studies. These studies look at single nucleotide polymorphisms (SNPs) across the genome and relate them to asthma occurrence using either a case-control or a family-based design. These genome wide association studies utilize the association of SNPs with each other, that is, their correlation, or linkage disequilibrium, to cover the whole genome by analyzing a subset of SNPs. While these studies have a variety of threats to their validity, through increasing sample size and replication, many genes for asthma have been identified.[118,119]

In 2007, in the second GWAS study ever performed, a locus on chromosome 17q21 was identified as being associated with asthma.[120] This was replicated in multiple other studies and seemed to be strongest for childhood asthma and asthma onset.[121] The locus is complex, as there are at least five genes—ORMDL3, GSDMB, GSDMA, ZPBP2, and IKZF3—that are tightly correlated with each other in the region.

Most of the initial functional work has focused on ORMDL3 and GSDMB. In 2009, a causal functional variant at this locus, rs12936231, was identified. This SNP is predicted to disrupt the binding of an insulator, CTCF, in ZPBP2 and is correlated with expression of both ORMDL3 and GSDMB.[122] In 2016, a second SNP, rs4065275, in the locus on the same haplotype was demonstrated to have a similar functional effect and was tied to IL-2 levels.[123]

Another important feature of the genetic epidemiology of the 17q21 locus is that a variety of environmental factors, including vitamin D, tobacco smoke, antibiotics, furry pets, inhaled corticosteroids, and viral respiratory illness, all interact with this locus, suggesting that it might be central to the origin of asthma.[121]

Much recent work has been done to determine the functional effect of the genes in the 17q21 locus on asthma and how they interact with the environment. Mice expressing the ORMDL3 transgene exhibited spontaneous increases in airway hyperresponsiveness, associated with airway wall remodeling and peribronchial fibrosis and airway smooth muscle hypertrophy without airway inflammation.[124] ORMDL3 is known to inhibit the enzyme serine palmitoyltransferase, the rate-limiting step in sphingolipid production.[125] In accordance with this, siRNA knockdown of ORMDL3 in human bronchial epithelial cells led to increased sphingolipid pathway metabolites,[124] and ORMDL3-overexpressing transgenic mice were found to have reduced levels of sphingolipids.[126]

Recently ORMDL3 genetics were combined with metabolomics to strengthen this association in human studies. Non-atopic childhood asthmatics were shown to have lower levels of circulating sphingolipid metabolites, and these lower levels were linked to SNPs (rs7216389 and rs8076131).[127] These SNPs are eQTLs (expression quantitative trait loci) that are correlated with ORMDL3 expression. Other recent work showed that the genetic locus was rich in vitamin D receptor binding sites and that vitamin D levels interacted with the causal rs12926321 SNP to determine childhood asthma susceptibility, that both mother and child genotypes at this locus were relevant to genetic risk, and that both vitamin D and the ORMDL3 SNP rs12926321 were linked to sphingolipid levels.[128] To summarize this portion of a complex and still developing story, higher ORMDL3 expression is associated with lower sphingolipid levels and increased airway hyperresponsiveness, and hence higher asthma risk. Vitamin D can downregulate ORMDL3 expression and also has a direct effect to increase sphingolipid levels and hence decrease asthma occurrence. This effect was observed in both white subjects and African-Americans.[128] Of note, African Americans have lower vitamin D levels than other Americans.[129]

Much work still needs to be done on this locus, including on GSDMB and how viral illness interacts with the locus to produce childhood asthma, as well as elucidating how the other approximately 100 known asthma loci contribute to disease development. However, the beginning outlines of how genes and environmental factors interact to cause asthma are now clear, and 17q21 is a central part of this story.

ENVIRONMENTAL RISK FACTORS

Below we present some of the most important environmental risk factors for the development or exacerbation of asthma not discussed earlier.

Perinatal Factors

Asthma originates in utero as an abnormality of fetal lung development. As such, several perinatal factors impact asthma risk. Prematurity is one important factor that carries an increased risk for the development of asthma. A meta-analysis showed that infants born at less than 37 weeks' gestation are at greater risk for developing asthma than term infants.[130] More recently, it was shown that the risk for asthma is likely mediated through the effects of prematurity on the development of obstructive lung function deficits.[131]

Prematurity is also associated with bronchopulmonary dysplasia,[132] a disease characterized by increased airway responsiveness and asthma symptoms. Some investigators have found that low birth weight independent of prematurity has been associated with asthma risk.[133,134] The strength of the association between prematurity and/or low birth weight on asthma or asthma symptoms appears be greatest in very young children, and the effects decrease over time.[135,136] Note that black individuals have higher rates of prematurity than white individuals; thus, prematurity may contribute to racial differences in asthma prevalence and morbidity. Despite much research, there is no conclusive evidence that breastfeeding influences atopic sensitization or the development of asthma.

Recent studies have focused on maternal diet during pregnancy and its effect on the development of asthma and allergies, with the hypothesis that nutritional deficiency or excess may lead to programming of the fetus for adult disease.[137] These studies have mostly used nutrient intake estimates derived from food frequency questionnaires that assess how often a particular standard serving of a food or drink is eaten. The responses to the questionnaire, in conjunction with a database of nutrient composition of foods, are then used to calculate the amount of a particular nutrient over a specified time period.[138] A few studies have measured the particular nutrient in either maternal or cord blood samples. A meta-analysis found that there was weak support for protective effects of higher maternal intakes of vitamin A, D, E, and zinc for the prevention of asthma in children.[139]

Vitamin D

In the strict sense of the word, vitamin D is not actually a vitamin, since humans are able to produce the compound in the skin on exposure to UVA rays from the sun. While the first report of an effect of vitamin D on asthma and allergies appeared in 1934,[140] research into the effects of vitamin D did not begin in earnest until the last decade. There are two opposing hypotheses regarding the role of vitamin D in asthma. Wjst and Dold suggested that fortification of food with vitamin D and the widespread use of multivitamins in childhood contributed to the rise in asthma and allergies.[141] On the other hand, given the documented decrease over time in the levels of the circulating form of vitamin D in population studies,[142] Litonjua and Weiss hypothesized that the increasing prevalence of vitamin D deficiency led to the increase in asthma prevalence worldwide.[143]

Many epidemiologic studies have investigated the role of vitamin D in the development and control of asthma. With regard to the development of asthma and allergies, most studies have investigated either estimated maternal intakes of vitamin D from foods and supplements or maternal levels of 25-hydroxyvitamin D (25OHD). Four observational cohort studies have reported beneficial effects of a higher maternal intake of vitamin D in pregnancy on outcomes in their children.[144–147] However, other studies have not replicated these findings.[148–151] Two clinical trials of vitamin D supplementation in pregnancy have been completed.[152,153] While neither study on its own showed a statistically significant effect, a combined analysis showed a significant protective effect of maternal vitamin D supplementation on early wheezing and asthma by age 3 years.[154] The protective effect, however, did not persist through age 6 years.[155] It is likely that there are subsets of early wheezing phenotypes that may respond to vitamin D supplementation in utero, and further studies will be needed to determine this. Additionally, both clinical trials performed vitamin D supplementation only in pregnancy. There may be additional effects of postnatal vitamin D supplementation for asthma and wheeze prevention.[156]

As for the role of vitamin D in asthma control and management, observational studies have shown that asthmatics with higher circulating vitamin D levels have greater lung function,[29,30] lower risks for exacerbations,[157,158] and generally less severe indices of disease.[159] An initial small trial of 48 children with newly diagnosed asthma showed that vitamin D supplementation led to a significant reduction in the number of exacerbations over a period of 6 months.[160] Subsequent larger studies in adults and children[161] with chronic asthma did not show an effect of vitamin D supplementation in the prevention of asthma exacerbations.

Omega-3 Fatty Acids

Omega-3 and omega-6 fatty acids are major forms of polyunsaturated fatty acids (PUFA). The essential fatty acids alpha-linolenic acid and linoleic acid are the simplest members of the omega-3 and omega-6 fatty acid families, respectively.[162] Dietary PUFAs are critical sources of bioactive metabolites and cell membrane phospholipid components: alpha-linolenic acid metabolites include eicosapentaenoic acid and docosahexaenoic acid, and linoleic acid metabolites include arachidonic acid. Diet is a major determinant of the proportions of omega-3 and omega-6 metabolites. Major food sources of omega-3 fatty acids include oily fish such as salmon, mackerel, and herring.

Omega-3 PUFAs are generally thought to be anti-inflammatory, while omega-6 PUFAs contribute to inflammation.[163] During the course of the 20th century, changes in the Western diet led to increases in consumption of omega-6 over omega-3 PUFAs, primarily due to increased consumption of linoleic acid–rich soybean oil.[164] This shift has been proposed as a potential cause of the increased occurrence of allergic disease over the past half century.[165]

With regard to asthma prevention, a trial of fish oil (omega-3 PUFAs) versus placebo (olive oil) was recently completed. The trial showed that supplementation of 2.4 g of omega-3 PUFAs beginning at 24 weeks of gestation decreased the risk for persistent wheeze or asthma at 3 years of age. This trial was notable for the high dose of PUFA used as the intervention. Prior prenatal omega-3 PUFAs supplementation trials using lower doses (400 mg[166] and 800 mg[167]) did not show an effect on childhood lung function or allergic outcomes, respectively. With regard to the role of omega-3 PUFAs in established asthma, a trial of fish oil supplementation (4 g/day) in obese asthmatics did not show any difference in asthma control when compared with placebo.[168]

■ Indoor and Outdoor Allergens

Indoor allergen sources include animals (cats, dogs, rodents); insects (mites, cockroaches); and fungi. For many decades, the prevailing hypothesis of early asthma development was that it was caused by exposure to allergens, particularly house dust mite allergens.[104,169] Allergens are well-known precipitants of asthma exacerbations and increased morbidity.[170,171] However, studies of trials of allergen reduction or avoidance have not produced definitive results. A Cochrane meta-analysis of 54 trials using varying methods of mite-allergen reduction (physical methods, chemical methods, and a combination) concluded that there was no clinical benefit of dust mite allergen reduction.[172] Factors that could explain these findings include that adherence to the demanding protocols for control of allergen exposure is difficult and may not always result in sufficient reduction in personal aeroallergen exposure, and that allergens are ubiquitous in other settings outside the home (e.g., schools and daycare[173]). Evidence that exposure to some sources of indoor allergens, such as dogs, in early life may actually be protective against asthma development is discussed in "Role of the Microbiome," above. It is likely that mechanisms are complex, and that exposure to a wide array of microbes related to dogs may override the effects of exposure to dog allergen.

Outdoor allergens include trees, grass, and weed pollen constituents. The evidence for outdoor allergen exposure relates to asthma morbidity rather than asthma development. Susceptible individuals may have increased asthma symptoms at times of pollination.[174] Assessment of sensitization to indoor and outdoor allergens is part of the management of asthma, as is monitoring of levels of outdoor allergens.[175]

■ Smoking, Second-hand Tobacco Smoke Exposure, and E-cigarettes

Maternal cigarette smoking is a major risk factor for the development of asthma in the first year of life. Both a meta-analysis[176] and a pooled analysis[177] showed that the risk of developing asthma ranges from around 40% to 85% greater among children born to mothers who smoked during pregnancy versus children born to mothers who did not smoke. This effect appears to be strongest in children who developed asthma before 2 years of age.[176]

Second-hand smoke exposure exacerbates asthma in children of all ages.[178] Wilson and coworkers evaluated a cotinine-feedback behavioral intervention administered to caregivers that successfully reduced second-hand smoke exposure and health care utilization by children with asthma at 1 year follow-up.[179] However, in a follow-up study, the effect was seen only in the children at highest risk for exacerbation.[180] In adults, cigarette smoking is associated with the development of airway hyperreactivity.[181] Whether this hyperreactivity represents asthma or COPD can be difficult to determine. Cigarette smoking and asthma produce a synergistic and accelerated decline in lung function.[182,183] Additionally, the response to corticosteroid therapy used for asthma is reduced in active smokers.[182]

In recent years, the prevalence of electronic cigarette (e-cigarette) use has increased to epidemic proportions. E-cigarettes are electronic devices that heat a liquid and produce an aerosol or a mix of small particles in the air. They are known by many different names including "e-cigs," "vapes," "vape pens," and "electronic nicotine delivery systems (ENDS)." Epidemiologic studies have shown an increased risk for asthma among e-cigarette users.[184]

■ Other Pollutants

Outdoor pollutants implicated in the development or exacerbation of asthma include ozone, sulfur dioxide, particulate matter, and components of motor vehicle exhaust.[185,186] Measuring exposure to potential pollutants is difficult, and correlating exposure with symptoms and exacerbations of disease is very expensive. Most monitoring of pollutants is from fixed external stations. Sometimes proxy measures of pollutant exposure, such as traffic counts, are used. Although potentially more accurate, monitoring of personal exposures is particularly difficult and expensive.[187] Assessing which of the many possible simultaneous outdoor inhalants affects asthma morbidity is also a formidable task. Conclusions drawn from such data may be indirect. An example is the observation that asthma morbidity is highest among low-income individuals who tend to live in less desirable areas, which are frequently those with high traffic volumes and pollution.

There has been much interest in indoor environmental pollutants, such as nitrogen dioxide, sulfur dioxide, volatile organic compounds, and particulate matter, and their possible association with asthma, particularly in inner-city homes.[188,189] As with studies of outdoor pollution, difficulties in measurement over time, controlling for other exposures such as allergens, infectious agents, and social determinants of health, and linking exposures to symptoms and physical findings make research challenging.

■ Acetaminophen

It has been postulated that acetaminophen use may increase the risk of developing asthma or asthma morbidity due to its pro-oxidant effects (by depletion of the antioxidant glutathione in lung tissue).[190] Several studies have reported on the association of acetaminophen use, in pregnancy, in early life, and in adulthood, and the development of asthma.[191–195] However, the issue with studies that investigate over-the-counter medications such as acetaminophen is the possibility of confounding by indication, meaning that these individuals have comorbidities (e.g., respiratory infections) for which they may take the acetaminophen for its antipyretic or analgesic effects. A clinical trial in young children with mild persistent asthma did not show a difference in the incidence of asthma exacerbations or loss of asthma control between the as-needed acetaminophen arm versus the as-needed ibuprofen arm.[195] While this study suggests that acetaminophen intake does not affect asthma morbidity, it does not address the potential effect of acetaminophen on asthma development, and additional studies will need to be done.

NATURAL HISTORY

The natural history of asthma in early childhood can be gleaned from data from the Tucson Children's Respiratory Study.[196,197] By following a cohort of children through the first 6 years of life, study investigators characterized four groups of children: "persistent wheezers," who wheezed both before and after the age of 3 years; "transient early wheezers," who wheezed before the age of 3 years and then stopped; "transient late wheezers," who wheezed after age 3 years but not before; and "never wheezers." Fully 40% of all children wheezed in the first year of life.

Significant predictors of persistent wheezing, and hence children at greatest risk for developing chronic asthma, were young maternal age, IgE level at 9 months, parents with asthma, maternal cigarette smoke exposure in utero, abnormal lung function at birth, and male sex. It is likely that early-life wheezing is predominantly a mechanical factor and less due to severe and chronic airway inflammation. It also seems unlikely that allergen exposure predominates as a factor in early childhood.

The characteristics of older children who wheeze are atopy, female sex, and active and passive cigarette smoking. By preadolescence, atopy and environmental allergen exposure are important risk factors for wheezing in children.

In roughly half of all childhood asthmatics, symptoms decrease or disappear by late adolescence and early adulthood. Characteristics that suggest a good prognosis include male sex, precipitation of attacks by viral respiratory illness, and children with airway parenchymal dysanapsis (i.e., small airways relative to lung size). These children are predominantly male and, although often atopic, still are likely to outgrow their asthma.

In a longitudinal study of children from East Boston, initially 5 to 9 years of age followed over a 13-year period, the effect of asthma on lung growth was different for boys than girls.[198] Boys with asthma had larger growth in vital capacity than boys without asthma and tended to have mild disease. This was associated with fewer hospitalizations for asthma, despite somewhat greater prevalence than in girls. Asthmatic girls, however, had persistent reductions in FEV_1 and were more likely to be hospitalized for asthma, despite an initially reduced prevalence relative to the boys. These data are consistent with asthma being milder in boys in that boys are more likely to "outgrow" their asthma.

In contrast, the Childhood Asthma Management Program (CAMP) followed lung function of 1041 children (420 girls and 621 boys) with mild to moderate persistent asthma, who participated in a clinical trial of asthma treatment.[199] The authors used lung function data of 5415 nonasthmatic children from the Harvard Six Cities Study for comparison. In children of both sexes aged 6 to 18 years, the FEV_1/FVC ratio was significantly lower and FVC was significantly higher for asthmatic children, compared with nonasthmatic children. In contrast to the East Boston study, boys had lower FEV_1 between the ages of 10 and 18 years, whereas there were no

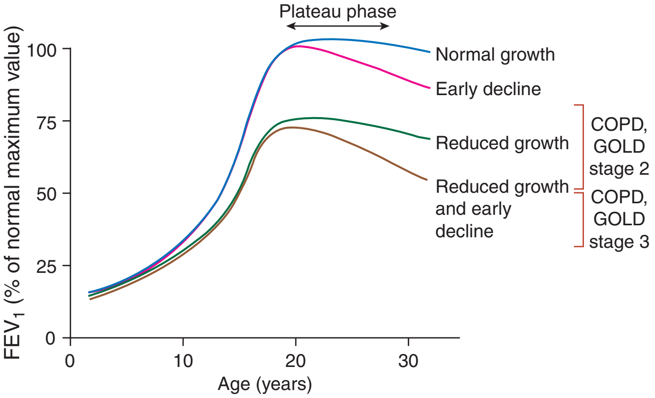

Figure 44-7 Patterns of longitudinal lung function trajectories. Normal lung growth continues after birth and reaches a peak in early adulthood. A plateau phase then ensues from the 20s to the mid-30s for most individuals. After that, gradual decline of lung function follows, mirroring physiologic aging. Perturbations of normal grown may occur, depending on environmental and other exposures over the life course of the individua. A pattern of normal growth and early decline may occur if the individual achieves normal peak lung function, but there is no plateau phase and more rapid decline starts soon after achieving peak lung function. Two other general patterns may also occur if peak lung function is not attained—that is, if reduced growth is observed. After reduced growth, a period of normal decline may ensue, or a period of early and rapid decline. These latter two patterns may increase the risk for the development of COPD later in life. *(Reproduced with permission from McGeachie MJ, Yates KP, Zhou X, et al. Patterns of growth and decline in lung function in persistent childhood asthma. N Engl J Med. 2016;374(19):1842–1852.)*

significant differences in girls. Taken together, these studies suggest that asthma that starts in early life (i.e., by age 6 years) leads to decrements in lung function that are persistent through adolescence. These patterns have been borne out in other longitudinal studies (reviewed in Grad and Morgan[200]).

In both adolescents and adults, airway responsiveness predicts the development of asthma[19,201–204] and antedates and predicts accelerated decline in lung function.[205,206] Both persistent symptoms[207] and active smoking[183] conferred more rapid rates of lung function decline in longitudinal studies. The severity of adult asthma is clearly predicted by the severity of childhood asthma, and the persistence of symptoms in childhood and early adulthood is associated with reduced lung function and more severe disease later in adult life.

The influence of childhood asthma on later adult disease continues to be elucidated by longitudinal studies. Normal patterns of lung function growth and decline have been established. In individuals with no lung disease, FEV_1 increases until early adulthood and remains stable for several years (the plateau phase). Lung function then gradually declines related to physiologic aging. Perturbations of this normal pattern give rise to increased risks for lung disease later in life (Fig. 44-7). The CAMP continuing study investigated longitudinal lung function (FEV_1) patterns among 684 children with persistent asthma.[208] About 25% of the children had a normal growth and decline pattern when compared with National Health and Nutrition Examination Survey participants who did not have asthma. The investigators categorized the rest of the children into different patterns of growth and decline: normal growth and early decline, reduced growth, and reduced growth and early decline. Each of the categories contained about 25% of the total number of children studied. At the end of the period of observation, when the mean age of participants was 26 years, 73 (11%) met spirometric criteria for chronic obstructive lung disease.

Findings from longitudinal lung function studies from CAMP and other cohorts have given rise to the idea that perturbations of lung function growth and decline can lead to increased risks for chronic obstructive pulmonary disease (COPD) or the recently recognized asthma-COPD overlap syndrome (ACO).[209] ACO is a condition that comprises clinical and biologic features of both asthma and COPD, and it applies to subgroups of patients with asthma and persistent airflow obstruction or COPD patients who have variable airflow obstruction and/or evidence of type 2 inflammation.[210,211] Because a consensus definition of ACO remains elusive, the epidemiology of ACO remains to be defined. Nevertheless, longitudinal studies of asthma in children and adults suggest that improved control might modify the risk for fixed obstructive disease later in life. For example, Sears and colleagues[212] showed that in a cohort of children followed from 9 to 26 years of age, those who had persistent wheezing consistently had lower lung function than those without persistent wheezing. Similarly, in a cohort of adult moderate to severe asthmatics with an initial mean age of 27 years and median follow-up of 11 years, participants with exacerbations had greater declines in FEV_1, such that one severe exacerbation per year was associated with a 30.2-mL greater decline per year.[213]

In summary, most asthma begins in childhood. Attention needs to be paid to the presence of risk factors that may lead to the development of asthma in childhood. Once asthma is established, it is imperative that efforts are focused on achieving good control of the disorder and preventing exacerbations, so as to limit the risk for developing more severe asthma, COPD, and ACO in adulthood.

HEALTH DISPARITIES IN ASTHMA

As discussed at the beginning of this chapter, asthma prevalence and especially morbidity and mortality are higher in some groups of individuals, notably including non-Hispanic black individuals, Hispanics of Puerto Rican descent, and those with lower household income. The extent to which these differences in asthma prevalence, hospitalization, and mortality are attributable to inadequate treatment and access to medical care remains unclear, but there is indisputable evidence of unequal treatment of minority and low-income groups by health professionals.[214]

Perceptions of a person's race influence social experiences, including those with the health system. In a study of women in the United States, black and Hispanic women were more likely to report a doctor's diagnosis of asthma, had higher total IgE levels, and were more likely to be sensitized to aeroallergens; however, they were less likely to report a diagnosis of hay fever or eczema.[215] These findings could represent underdiagnosis of hay fever and eczema by medical personnel, perhaps related to fewer referrals to an allergist or other specialist, or underreporting of symptoms by patients. Genetic differences alone are unlikely to explain differences in sensitization, which more likely relate to environmental exposures.

Socioeconomic factors tend to be inseparably linked to ethnicity and race for historic and political reasons. As a result, environmental factors that are the products of poverty, such as psychosocial stressors, poor dietary quality, and exposure to tobacco smoke or other pollutants or allergens, contribute to disparities in asthma prevalence and morbidity[216,217] (Fig. 44-8). A growing body of research on racial and socioeconomic disparities in asthma has focused on the effect of stress and violence in the pathogenesis of asthma and morbidity related to asthma.[218] Psychosocial stressors are associated not only with increased asthma occurrence, but also with reduced response to asthma medications such as inhaled beta-agonists.[219–221] Individuals in high-risk minority groups are frequently exposed to several asthma risk factors simultaneously, and this unequal exposure starts at conception and continues through childhood and into adulthood. For this reason, there is an

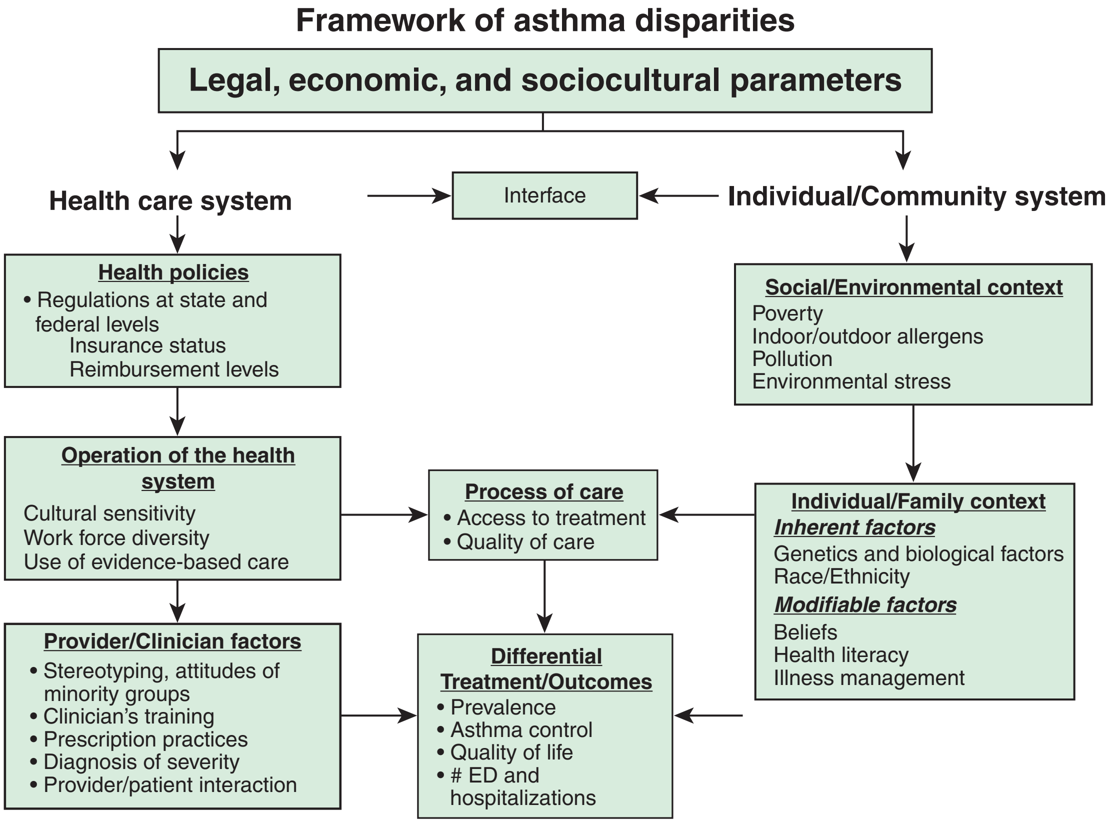
Framework of asthma disparities
Legal, economic, and sociocultural parameters
Health care system
Interface
Individual/Community system
Health policies
• Regulations at state and federal levels
Insurance status
Reimbursement levels
Social/Environmental context
Poverty
Indoor/outdoor allergens
Pollution
Environmental stress
Operation of the health system
Cultural sensitivity
Work force diversity
Use of evidence-based care
Process of care
• Access to treatment
• Quality of care
Individual/Family context
Inherent factors
Genetics and biological factors
Race/Ethnicity
Modifiable factors
Beliefs
Health literacy
Illness management
Provider/Clinician factors
• Stereotyping, attitudes of minority groups
• Clinician's training
• Prescription practices
• Diagnosis of severity
• Provider/patient interaction
Differential Treatment/Outcomes
• Prevalence
• Asthma control
• Quality of life
• # ED and hospitalizations

Figure 44-8 Multilevel model of asthma disparities. *(Reproduced with permission from Canino G, McQuaid EL, Rand CS. Addressing asthma health disparities: a multilevel challenge. J Allergy Clin Immunol. 2009;123(6):1209–1217.)*

imperative to tackle multiple environmental and social factors if the goal of reducing asthma disparities is to be achieved.

CONCLUSIONS

Although asthma prevalence, morbidity, and hospitalizations have remained stable recently, the absolute levels remain unacceptably high, particularly for certain minority groups and low-income populations. Risk factors such as obesity, prematurity, young maternal age, vitamin D deficiency, low intake of omega-3 fatty acids, and cigarette smoking are all associated with these same patient groups and speak to ongoing social and healthcare disparities. Differences in many relevant exposures are reflected by the environmental and host microbiomes, which may represent key links between exposures and asthma risk. This idea is encapsulated by the concept of "dysbiotic drift," whereby modern environmental forces drive microbial dysbiosis in a way that disproportionately impacts socioeconomically disadvantaged populations.[58] Certainly, genetic differences also exist from patient to patient. Understanding how genetic variants interact with one another and with environmental exposures to result in various asthma phenotypes will be critical to piecing together the mechanisms behind asthma prevalence and outcome disparities. With recent unprecedented computational and technologic advances in our ability to query the complex systems involved with asthma pathophysiology, we expect coming years to bring many new insights into factors that lead to distinct asthma endotypes and phenotypes and new strategies for tackling asthma disparities.

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CHAPTER 45

Asthma: Clinical Presentation and Management

Omar S. Usmani
Peter J. Barnes

ASTHMA—A HETEROGENEOUS DISEASE

Asthma is a chronic inflammatory disorder of the airways characterized by marked temporal variability in airflow obstruction that is often reversible, either spontaneously or with treatment.[1] This inflammation presents clinically in susceptible patients with recurrent symptoms of wheezing, chest tightness, cough, and, occasionally, dyspnea and contributes to heightened airway hyperresponsiveness to specific and nonspecific stimuli—a pathognomonic feature of asthma. Increased airway hyperresponsiveness manifests in patients as intolerance to smoke, dust, air pollution, and strong odors, where exposure to such agents in healthy individuals does not induce such symptoms. Asthma is not a single disease entity with a unique pathogenesis, but rather recognized to be a clinical syndrome and heterogeneous disease;[2] that is, asthma comprises multiple endotypes that manifest common symptoms but have distinct and probably different pathophysiologic and etiologic mechanisms with an interplay between genetic and environmental factors. This phenotypic heterogeneity in the expression of asthma is multidimensional and includes variability in pathologic, clinical, and physiologic parameters among different patients.[3] Recent attention has directed focus on traits that are identifiable and treatable in patients with asthma, such as persistently elevated blood eosinophils, in order to achieve precision treatment with the hope of better patient outcomes.[4]

RISK FACTORS FOR ASTHMA

Several risk factors for asthma are considered below.

Atopy and Allergens

The most important factor predisposing to asthma is atopy (Table 45-1). Asthma has been classified as *atopic* (extrinsic) *or nonatopic* (intrinsic) depending on the suspected role of allergens as etiologic factors. Atopic asthma involves an exaggerated immune response characterized by immunoglobulin E (Ig-E) activation and mast cell degradation. Atopy can be clinically elicited with a positive skin prick test or specific antibodies to IgE in serum against common aeroallergens such as house dust mite, grass and tree pollens, *Aspergillus* mold, cat and dog fur, rodents (in laboratory workers), and cockroaches (in inner-city populations). House dust mite is recognized as a significant cause of asthma throughout the developed world, although the relative importance of different indoor allergens may vary among populations. Patients with atopic asthma commonly suffer from other atopic diseases, including allergic rhinitis that may be seasonal (hay fever), and may be found in over 80% of asthmatic patients; allergic conjunctivitis; and atopic dermatitis (eczema). Nonatopic asthmatic patients (approximately 10%) have a negative skin prick test, normal serum IgE concentrations, and usually show later onset of disease (adult-onset asthma). In this group, asthma is more severe and persistent, there is more sensitivity to aspirin, and commonly patients have concomitant nasal polyps. This classification, although appropriate from a pathologic perspective, does not readily help clinicians as it does not aid in establishing an etiologic diagnosis, nor does it help in defining treatment strategies.[5] There is a high prevalence of atopy among nonasthmatics and a large percentage of skin prick–sensitive persons report no allergic symptoms. About 50% of asthma can be attributed to atopy in the developed world, and the prevalence of atopy among asthmatics is determined mainly by the general prevalence of atopy in the population.[6,7] In addition, the immunopathology in bronchial biopsies and sputum in patients with nonatopic asthma appears to be identical to that found in atopic asthmatic patients. Therefore, the finding that an asthmatic is atopic does not imply that the disease is allergic in nature or that atopy is causing asthma. Moreover, respiratory tract viruses have emerged as the most frequent triggers for exacerbations in both children and adults and may play a more prominent role than allergens as triggers of acute exacerbations in most patients.[8] House dust mites are the most common indoor allergen, where particles excreted from the digestive tract contain the principal allergen *Dermatophagoides pteronyssinus*. Other main sources of inhaled indoor allergen are cat and dog fur and cockroaches (Table 45-1). Although asthmatic symptoms often improve when the allergen is removed, rigorous allergen avoidance has not shown any evidence for a reduced risk of developing asthma.

Although allergens are often triggers of acute exacerbations of asthma, allergens themselves may induce subclinical airway inflammation that may lead to enhanced airway responsiveness

TABLE 45-1 Risk Factors and Triggers Involved in Asthma

Endogenous Factors	Environmental Factors	Triggers
Atopy	Allergens—indoor	Allergens (especially house dust mite, animal dander, cockroach, indoor fungi, perennial allergens, and seasonal pollens)
Airway hyperresponsiveness	Allergens—outdoor (fungi, pollens)	Changes in the weather (cold air, thunderstorms)
Ethnicity	Obesity	Drugs (angiotensin-converting enzyme inhibitors, aspirin, β-blockers, NSAIDs)
Gender	Occupational sensitizers	Exercise and hyperventilation
Genetic predisposition	Parasitic infections	Extreme emotional expression (laughing, stress)
	Respiratory infections (early childhood, viral)	Irritants (household sprays, paint fumes)
	Socioeconomic status	Respiratory infections
	Tobacco smoking (active and passive)	Sulfur dioxide and pollutant gases
		Tobacco smoking

and greater susceptibility to the provocative effects of other triggers such as respiratory viral infections and exercise. In this regard, it is important to understand the distinction between triggers and etiologic risk factors. A trigger is any agent capable of inducing or exacerbating asthma, and whereas triggers may lead to symptoms, they do so only in susceptible persons who already possess the underlying asthmatic diathesis.

■ Viral Infections

Acute upper respiratory tract viral infections are the commonest triggers of exacerbations of asthma and most are due to rhinovirus infections. Viral infections not only give symptoms of the common cold and cause acute inflammatory rhinitis, but may also play a role in asthma development and, potentially, airway remodeling through increasing inflammation in the lower airways.[9] Asthma is recognized to be more common in children who have had croup or lower respiratory tract infections in early life, although viral infections in the absence of atopy do not appear to be risk factors for the development of asthma.[10] Other viruses commonly implicated in acute exacerbations of asthma are respiratory syncytial virus, influenza virus, and parainfluenza virus. Bacterial infection with species of *Mycoplasma* and *Chlamydia* are also associated with exacerbations of asthma, whereas other bacterial infections are not.

■ Occupational Exposure

Occupational asthma accounts for approximately 5% of all adult cases of asthma, and the disease can often be classified according to its etiology. In these circumstances, not only is the specific agent that triggers the symptoms known, but the same agent is usually the underlying cause of asthma.

■ Exercise-Induced Asthma

Many asthma patients have worsening of symptoms on or after physical exercise; another category of asthma is exercise-induced, where exercise per se is not the cause of asthma but rather one of many nonimmunologic triggers that produce symptoms in patients who already have the disease. In this condition, the trigger is thought to be the drying of the airway mucosa as a result of hyperventilation that leads to osmotically induced mast cell mediator release and bronchospasm.[11]

■ Obesity

Obesity is a major risk factor for asthma where abdominal obesity (waist circumference) and general obesity (BMI) both show a strong correlation with the risk of new-onset asthma.[12] Obese asthmatics often have excessive symptoms and are less responsive to corticosteroid therapy.[13]

■ Drugs

Drugs that may worsen asthma control include β-blockers, occasionally angiotensin-converting enzyme (ACE) inhibitors, aspirin, and nonsteroidal anti-inflammatory drugs (NSAIDs).

■ Small Airways Disease

Although not a risk factor in the true sense, it is increasingly being recognized that untreated small airways inflammation disease may predispose patients to worsening asthma, and studies show that the prevalence of small airways disease is approximately 50% in the asthmatic population.[14,15]

CLINICAL PRESENTATION AND DIAGNOSIS

Asthma is a clinical diagnosis made on the basis of a medical history of typical symptoms, with consideration to provocative factors, and supported with objective confirmation of variable airflow obstruction. As the disease is heterogeneous in its presentation and severity, the clinical features of asthma show great variability both between individual asthmatics, and also within the same patient over time. It is also important to recognize that asthma is often associated with different comorbidities, including allergic rhinitis, atopic dermatitis, rhinosinusitis, gastroesophageal reflux disease, diabetes, depression, and obesity, all of which may affect the clinical expression and severity of the disease.[16] The following clinical features and laboratory assessments are important in the consideration of the diagnosis of asthma.

■ Medical History

The typical symptoms of asthma are paroxysmal wheezing, cough, breathlessness, and chest tightness, which may temporally be related to exposure to triggers or exercise. Cough may be productive of clear or yellow/green discolored sputum, where the latter may be tenacious and difficult to expectorate and reflect the underlying airway inflammation rather than a respiratory infection. Indeed, cough may be present in isolation to other symptoms and as the sole manifestation of an episode of asthma.[17] Breathlessness may occur as a result of the dynamic lung hyperinflation that accompanies acute asthma episodes, and patients may report the sensation of difficulty in “getting air in” their lungs. Exertional symptoms may not be apparent if the patient’s ability to exert themselves is limited by other health conditions such as rheumatologic or cardiac disease, and therefore asthma may be underdiagnosed in the elderly. No single symptom is specific or more significant for asthma, although wheezing is a useful sign, as nonasthmatics rarely report frequent wheezing. In younger patients, the symptom of chest tightness is helpful, since it occurs more often in association with asthma than with other pulmonary or cardiac disorders. The pattern of symptom occurrence, the precipitating or aggravating factors, and the profile of a typical exacerbation are important elements in the clinical evaluation.

In patients with poorly controlled asthma, symptoms may temporally evolve slowly over days or weeks, or present abruptly. The severity and frequency with which symptoms occur vary greatly within the asthmatic population. The recurrent paroxysmal nature of symptom presentation is characteristic of asthma, and symptoms improve, sometimes rather spontaneously, although usually with treatment. Nocturnal episodes are common in adult asthmatics, and typically patients awake in the early hours of the morning with symptoms. Distinguishing whether nocturnal symptoms are due to asthma, angina, or gastroesophageal reflux may be difficult, but early-morning asthma symptoms are usually relieved with administration of inhaled bronchodilators, in contrast to cardiovascular symptoms which occur at any time during the night, and gastroesophageal reflux which tends to cause symptoms soon after the patient reclines at night.

Chest symptoms that vary by season and are accompanied by symptoms of irritation of other mucus membranes, such as conjunctivitis and rhinitis, are typical of allergic asthma. Triggers such as indoor allergens (e.g., house dust mite, cockroach, animal dander proteins) are more likely to result in perennial symptoms, whereas pollens and some mold spores are likely to provoke seasonal symptoms. The presence of rhinosinusitis, nasal polyps, conjunctivitis, or eczema, coupled with a family history of asthma or atopy, may further support the diagnosis of asthma. Symptoms after heavy exertion, especially in the cold air, are highly suggestive of exercise-induced asthma, and patients typically experience symptoms at the end of exercise, rather than during its performance. Excessive coughing after exercise in the absence of wheeze may also be a sign of asthma. Premenopausal women with asthma may experience a deterioration of asthma control perimenstrually.[18] Indeed, compared to men, women have a higher incidence of asthma and experience more symptoms with more recourse to rescue medication.[19] The medical history should elicit risk factors for asthma (Table 45-1), and special consideration should address symptoms induced by aspirin or those associated with the patient's occupation.

Asthma and Aspirin Sensitivity

The association of asthma and sensitivity to aspirin or other NSAIDs is well established.[20] Aspirin-sensitive asthma affects approximately 1% to 5% of all asthmatics, although it is more common in patients with severe asthma (∼20%), in some ethnic groups (such as Eastern Europeans and Japanese), and in those frequently hospitalized for their asthma. This subtype of asthma is usually characterized by a tetrad of asthma, nasal polyps, chronic hypertrophic eosinophilic sinusitis, and aspirin intolerance.

Classically, perennial rhinitis is the first symptom in this syndrome, preceding the development of aspirin sensitivity, and then followed much later by nasal polyps that are usually bilateral and originate from the turbinates and the paranasal sinuses. Even in small doses, aspirin typically causes wheezing, facial flushing, rhinorrhea, and conjunctival irritation. Although aspirin-induced asthmatic episodes often resemble allergic reactions, there is no evidence that immunoglobulin (Ig)-E–related mechanisms are at work. Aspirin-induced asthma is due to blockade of cyclooxygenase 1 by nonsteroidal anti-inflammatory drugs and has been associated with enhanced leukotriene production and mast cell activation, but the cellular pathways responsible for these events remain unclear. The diagnosis of aspirin sensitivity is made on the basis of the clinical history and can be confirmed by a provocative aspirin challenge, although this test carries a potential health risk of anaphylaxis for the patient. Individuals with asthma, nasal inflammation, and recurring nasal polyps with sensitivity to aspirin have the condition known as "Samter's triad," characterized by dramatic worsening of respiratory symptoms as a reaction to taking aspirin or similar nonsteroidal anti-inflammatories.

Aspirin-sensitive asthma usually responds to standard therapy with inhaled corticosteroids (ICS), although the condition is associated with severe asthma, a condition comprising a group of patients often refractory to treatment with inhaled and oral CS. Hypothetically, antileukotriene therapy should be efficacious in these patients, but it has been found to be no more effective compared to their use in patients with allergic asthma. Aspirin desensitization may sometimes be needed and should only be performed in specialized centers. In all asthmatic patients with aspirin sensitivity, the nonselective cyclooxygenase (COX) inhibitors should be avoided, but when an anti-inflammatory analgesic is needed, the selective COX-2 inhibitors are usually safe to use.

Occupational Asthma

Occupational asthma is asthma arising de novo that is initiated as a consequence of exposure to a specific etiologic agent in patients without prior asthma. In contrast, work-exacerbated asthma is defined as the worsening of asthma, that is already pre-existing or concurrent, triggered by nonspecific irritants in the workplace.[21] Occupational asthma may be classified into: (1) that caused by a sensitizing agent in the workplace (sensitizer-induced asthma) where the specific sensitizing agent causes asthma through an identified underlying immunologic mechanism, and (2) asthma caused by exposure to irritant compounds (irritant-induced asthma) where the exposure agent is not considered to be sensitizing.[22] Table 45-2 highlights the causes of both sensitizer-induced occupational asthma and the common agents responsible for irritant-induced occupational asthma. The diagnosis of occupational asthma is based on a demonstrable link between asthma symptoms and workplace exposure, showing work-related variability in measurements of lung function made serially.[23] Classically, a typical history of asthma-like symptoms during the working week and improvement over the weekend or on vacation are elicited; symptoms may occur during exposure to the etiologic substance, or they may be delayed until the evening or night after the workday. Early detection and avoidance of occupational asthma is important because, if the patient is removed from exposure within the first 6 months of symptoms, there is usually complete recovery.

TABLE 45-2 Causes of Occupational Asthma

Sensitizing Agent-Induced Asthma	
Agent	**Workers at Risk**
Acrylate	Dental workers; adhesive handlers
Anhydrides	Workers using epoxy resin for plastics
Animal protein allergens	Veterinary workers; animal handlers
Cereals (grains)	Bakery workers; grain workers; farmers
Dyes	Textile workers
Enzymes	Pharmaceutical workers; bakery workers; laboratory workers
Formaldehyde, glutaraldehyde	Hospital and healthcare workers
Gums	Carpet makers
Isocyanates	Installers of insulation; manufacturers of plastics; rubbers and foam; spray painters
Latex	Healthcare workers; rubber workers
Persulfate	Hairdressers
Seafoods	Seafood handlers and processors
Wood dusts	Forestry workers; sawmill workers; carpenters
Common Agents Responsible for Irritant-Induced Asthma	
Acids (acetic, hydrochloric, sulfuric)	
Alkaline dust	
Ammonia	
Bleach	
Chlorine	
Cleaning agents	
Diesel exhaust	
Endotoxins	
Formalin	
Mustard	
Oxide (calcium)	
Paints (heated)	

Physical Examination

The most typical physical finding in asthma is wheezing on auscultation, which is usually caused by turbulent airflow through narrowed airways. Wheezing may be heard throughout the chest and is classically polyphonic, and present to a greater extent during expiration, although it may also be heard during inspiration. The quality and character of wheezing is not specific to asthma or to the severity of the underlying disease. There may be no abnormal physical findings when asthma is under control—yet conversely, in cases of very severe airway obstruction, breath sounds and wheezing may be absent. Examination of the upper respiratory tract may reveal clinical signs of rhinitis, sinusitis, or nasal polyps.

During an acute exacerbation of disease, physical signs of increased ventilation may be observed with the use of accessory

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muscles of respiration and chest signs of hyperinflation. A sign of severe airway obstruction is pulsus paradoxus, which is the exaggerated decrease in systolic blood pressure during inspiration by >10 mm Hg. As ventilatory effort can be diminished with respiratory muscle fatigue, pulsus paradoxus may be absent, but its absence does not preclude severe airway obstruction. Stridor is a high-pitched inspiratory sound and indicates airflow turbulence in the upper airways. In the acute setting, stridor should prompt a review of causes such as epiglottitis or foreign body. In chronic presentation, conditions such as upper airway tumors, tracheal–bronchial stenosis, vocal cord dysfunction/paralysis, and airway narrowing due to thyroid enlargement should be excluded.

■ Laboratory Investigation

The diagnosis of asthma is usually apparent from the medical history with symptoms of variable and intermittent airway obstruction, and objective measurements of lung function and spirometry support the diagnostic process. Similarly, the clinical history provides relevant information regarding the relationship between symptoms and allergen exposure, but skin prick testing and serology may be useful in identifying specific allergic triggers of asthma. Radiologic examination of the thorax, blood tests, and body plethysmography are not routinely indicated, unless there is some uncertainty in the diagnosis, where these tests may be used to exclude other conditions that may mimic asthma or complicate its clinical presentation.

■ Lung Function Tests

Peak flow meters are portable devices, readily available for patient use, that measure the peak expiratory flow (PEF). Serial readings of PEF that vary by more than 20% either spontaneously or in response to treatment are supportive of a diagnosis of asthma. Twice-daily PEF measurements, morning and evening, may also demonstrate diurnal variation, which is a typical feature of asthmatic patients.

Spirometry measures the expiratory volume and flow of air using forced maneuvers from full lung inflation, as a function of time. Simple spirometry is important for objectively demonstrating airflow obstruction, confirming the diagnosis of asthma, establishing the severity of the disease, and monitoring the response to therapy. Patients with asthma typically show a reduced forced expiratory flow in 1 second (FEV_1), reduced PEF, preserved forced vital capacity (FVC), and an FEV_1/FVC ratio of <0.7.[23] Home PEF monitoring may be of diagnostic use, confirming the diurnal variations in airflow obstruction, especially in patients who demonstrate normal spirometry during clinic visits. Spirometry also allows the assessment of the flow–volume loop, which shows a reduced maximum expiratory flow.

Bronchodilator reversibility is a measure of the magnitude of airway smooth muscle relaxation. A postbronchodilator increase in FEV_1 of >12% and 200 mL is often considered evidence of reversible airway obstruction, where measures are taken 15 min after an inhaled short-acting β_2-agonist (SABA). However, this level of increase is arbitrary and lacks sensitivity or specificity for detecting asthma. In addition, bronchodilator reversibility is diminished in well-controlled asthmatic patients, so it is not a good measure of asthma severity or response to therapy.

In some patients, bronchodilator reversibility may be demonstrated by a 2- to 4-week trial of oral corticosteroids (prednisone or prednisolone 30–40 mg daily). Bronchodilator reversibility may also occur in patients with chronic obstructive pulmonary disease (COPD).[24] Asthma and COPD are distinct diseases. Although an overlap "syndrome" of the two has been described, this term may be misleading due to the diversity of phenotypes arising from the variety of molecular, physiologic, and clinical features. Hence, the entity is better referred to as "asthma-COPD overlap" (ACO).[25–27] Asthmatic patients with features of COPD include smokers, patients with severe neutrophilic asthma, and chronic asthma with irreversible airway obstruction.

■ Body Plethysmography

Whole-body plethysmography is rarely required to establish a diagnosis of asthma in family practice, but it may help in patients where there is diagnostic uncertainty. In stable asthma, measurement of the lung volumes may reveal an increase in residual volume, which reflects airway closure at a lung volume that is higher than normal. Air trapping is typically seen in patients with severe asthma. Airway resistance is characteristically increased, and during acute episodes of disease exacerbation, functional residual capacity and total lung capacity also may be observed to be increased. Measurement of the diffusing capacity of the lung (DL_{CO}) may also differentiate patients with COPD from those with asthma. In stable asthma, DL_{CO} is usually normal, but there may be a small increase in some patients. In contrast, patients with COPD typically have a reduced DL_{CO}, which reflects alveolar septal destruction and loss of pulmonary capillary volume—characteristic features of emphysematous patients.

■ Bronchial Challenge Testing

Assessing bronchial hyperresponsiveness (BHR) is a sensitive tool that, although not routinely undertaken in clinical practice, may be helpful in diagnosing asthma, particularly when there is diagnostic uncertainty in the context of normal pulmonary function tests and unexplained chest symptoms (see Chapter 31).[28] Bronchial challenge tests assess the abnormally increased airway hyperresponsiveness observed in patients with asthma, by detecting the exaggerated response to inhaled bronchoprovocative agents. The provocation agents can be classified into two categories: direct and indirect. Direct stimuli such as histamine and methacholine, which are normally used in the clinic, act on airway smooth muscle receptors, whereas indirect stimuli act through intermediate pathways that include the release of mast cell mediators, and/or through local and central neurologic reflexes. Indirect stimuli include adenosine monophosphate (AMP), mannitol, exercise, hypertonic saline, and isocapnic hyperventilation.

Increased BHR is typically defined as the inhaled concentration of the bronchoprovocative agent that reduces FEV_1 by 20% (PC_{20}). This criterion for the test has maximal sensitivity but not maximal specificity and thus, when a diagnostic PC_{20} threshold of ≤8 mg/mL is used, pharmacologic challenges are sensitive tests with a high negative predictive value, that is, a PC_{20} >8 mg/mL excludes a diagnosis of asthma with a high degree of accuracy. Similarly, a positive result, although consistent with asthma, is not diagnostic. False-negative results can be obtained in patients who experience only intermittent symptoms and are tested when they are asymptomatic. The prevalence of abnormal responsiveness in nonatopic, nonasthmatic subjects who have no history of prior respiratory problems ranges between 5% and 10%. Knowledge of family history, personal atopy, and comorbidities clearly improves the prediction that abnormal airway responsiveness predisposes to the subsequent development of asthma.[29]

Technical factors related to the test procedure must be strictly controlled and follow standard operating procedures that include the aerosol generation, the method of inhalation (intermittent versus continuous), and the measurement and calculation of the response. Medications such as β_2-agonists, theophylline, long-acting muscarinic antagonists, and corticosteroids (CS) may influence the test and decrease airway responsiveness. Measuring BHR may have additional utility in the management of asthma. Patients whose disease is considered to be clinically controlled may still have BHR and underlying airway inflammation. Studies have shown that using BHR to guide treatment with inhaled corticosteroids (ICS) leads to additional improvement in symptoms, lung function, and airway biopsy findings compared with conventional assessment.[30]

Exercise testing of patients using cycle, treadmill, or free running challenges is occasionally undertaken to show post-exercise bronchoconstriction if there is a suggestive history of exercise-induced asthma.[31] In professional athletes, asthma may be both under- or overdiagnosed, and objective confirmation by appropriate lung function testing with bronchodilator or exercise challenge is often needed.[32] Allergen challenge is rarely utilized in the routine management of patients with asthma and should only be undertaken by a specialized center if a specific causative or occupational agent is to be identified, such as aspirin.

Blood Tests

Blood tests are usually not helpful in establishing the diagnosis of asthma. The eosinophil count in the peripheral blood may be raised in atopic conditions, and eosinophilia may support a diagnosis of asthma; however, a normal level does not rule out atopy or exclude asthma. In patients receiving CS, eosinophilic counts may be normal or low. Because of their poor sensitivity and specificity, blood eosinophil counts are not recommended in the routine monitoring of asthma severity or as a barometer of airway inflammation. Markedly high levels may be present in disorders such as tropical parasitic eosinophilia, allergic bronchopulmonary aspergillosis (ABPA), eosinophilic granulomatosis with polyangiitis (EGPA), and Loeffler's syndrome, as discussed elsewhere in this volume. In these hypereosinophilic conditions, clinical suspicion may warrant additional blood tests directed at ruling out vasculitis or ABPA, which are uncommon causes of asthma symptoms. Recently, blood eosinophil counts have been found to be useful in predicting which patients with severe asthma respond best to anti–IL-5 therapy.[33]

Total serum immunoglobulin E (IgE) may be measured in patients. Epidemiologic studies demonstrate an association between asthma and total serum IgE levels, standardized for sex and age. There is also a relationship between total serum IgE and asthma in patients with negative skin tests. Importantly, total IgE levels are used to calculate the dose of anti-IgE antibody therapy using anti-IgE monoclonal antibodies (e.g., omalizumab) in asthma treatment, as discussed below. Blood tests of specific IgE to inhaled allergens, radioallergosorbent testing (RAST), and ImmunoCAP may help identify or confirm allergy to specific allergens, such as house dust mite, cockroach, *Aspergillus* species, pollens, or animal dander.

In acute exacerbations of disease, arterial blood gases may reveal hypoxemia and the arterial Pa_{CO_2} may be reduced due to hyperventilation. With a severe exacerbation, the arterial Pa_{CO_2} may rise due to respiratory muscle fatigue and an inability to maintain the required alveolar ventilation.

Skin Tests

If the clinical history suggests specific aeroallergens are important triggers or when asthma symptoms in a patient are accompanied by other symptoms typical of allergic disease, such as conjunctivitis or rhinitis, skin prick tests may be helpful to determine whether the patient is allergic, and to investigate the role of specific allergens as a cause of asthma. Sensitivity to a particular allergen such as house dust mite, cockroach, *Aspergillus* species, or animal dander can be verified by skin tests or in vitro serum antibody studies (see above). Antihistamines and antidepressants should be avoided when undertaking testing, as these drugs can interfere with the response. Positive responses on skin prick testing may help encourage patients to undertake allergen avoidance measures or, in selected cases, may help develop immunotherapy regimens.

Chest Imaging

Chest radiography is usually unremarkable and normal in patients with mild to moderate asthma; however, in more severe disease, nonspecific findings such as hyperinflation, prominent hilar vessels, and bronchial wall thickening may be seen. In patients with an exacerbation of their symptoms, chest radiography may be useful to exclude a pneumothorax. Consolidation shadowing in the lung usually indicates pneumonia or eosinophilic infiltrates in patients with ABPA. High-resolution computed tomography (HRCT) of the chest may identify atelectasis, bronchial wall thickening, or areas of bronchiectasis in patients with severe asthma, but these changes are not diagnostic of asthma. Emphysema is absent. Multidetector computed tomography (MDCT) undertaken in inspiration and expiration provides additional information concerning the tracheobronchial tree during the entire respiratory cycle.

Exhaled Nitric Oxide

The measurement of fractional nitric oxide gas in the exhaled breath (FeNO) of patients is being utilized as a noninvasive test to assess intrapulmonary type 2 (T2) airway inflammation.[34] Portable, compact, handheld devices allow FeNO measurements to be undertaken at the bedside and in family practice.

Typically, asthmatic patients have elevated FeNO levels compared with healthy subjects; levels correlate with the number of eosinophils in sputum. ICS and oral leukotriene receptor antagonists have been shown to decrease FeNO levels. These observations suggest a possible role for FeNO as an index of asthma disease severity, as a test of treatment efficacy, and in the assessment of patient adherence with asthma therapy.

Measurements of FeNO have also been used successfully to titrate inhaled steroids without any loss of asthma control; thus, FeNO may be used as a tool in conjunction with other clinical measures to optimize asthma management as recommended by guidelines, that is, achieving disease control using the lowest doses of medications possible. Indeed, the combination of FeNO and blood eosinophil counts correlates with severe asthma exacerbations.[35]

In the research environment, FeNO can be partitioned into that arising from the central bronchial/conducting airways and that generated in peripheral alveolar regions, allowing an assessment of the site of intrapulmonary inflammation.[36,37] Patients with severe refractory asthma have shown greater alveolar NO concentrations compared to those with mild asthma. Increased FeNO may be a good predictor of which patients respond best to anti–IL-4/13 therapy, since IL-4Rα activation causes the release of NO from airway epithelial cells.[38]

Sputum Examination

The sputum differential count may be helpful. Induced sputum eosinophil counts have been used as an endpoint in clinical trials of therapeutic agents targeted at patients with eosinophilic lung diseases like asthma.[39] Research studies have shown that sputum eosinophilia predicts clinical outcomes, particularly asthma exacerbations, when CS are withdrawn. Induced sputum eosinophil counts have also been shown to guide anti-inflammatory treatment in patients with asthma in a management strategy that minimizes eosinophilic inflammation.[30] However, induced sputum remains a research tool, as it is a rather unpleasant procedure for the patient. Further studies are needed before measurement of sputum eosinophils can be widely used as a biomarker to monitor patients in clinical practice.

DIFFERENTIAL DIAGNOSIS

There are a number of conditions to consider in the differential diagnosis of asthma (Table 45-3). Usually, it is not difficult to

TABLE 45-3 Differential Diagnosis of Asthma

Upper Airway	Pulmonary	Cardiac	Other
Foreign body	Allergic bronchopulmonary aspergillosis (ABPA)	Angina	Anemia
Postnasal drip	Bronchiectasis	Left ventricular failure	Carcinoid
Upper airway obstruction	Eosinophilic granulomatosis with polyangiitis (EGPA)	Mitral valve disease	Functional
Vocal cord dysfunction	COPD		Gastroesophageal reflux
Tracheobronchomalacia	Cystic fibrosis Interstitial lung disease Lung cancer Pneumonia Pneumothorax Sarcoidosis		Hyperventilation Mastocytosis Obesity

differentiate asthma from other conditions causing wheeze and dyspnea. The degree of diagnostic accuracy is probably dependent on the age of the patient, where the diagnosis in young adults is usually not difficult since there are few other conditions that mimic asthma or confound its clinical presentation. With increasing age, cardiovascular disease and other forms of chronic lung disease are more common, and the differential diagnosis of episodic chest symptoms is broader.

Patients with upper airway obstruction can mimic severe asthma, and typically these patients present with localized wheeze and stridor of the large airways. Assessing the flow–volume loop in such patients will reveal a reduction in inspiratory flow as well as expiratory flow, and bronchoscopy can demonstrate the site of narrowing in the upper airways. Vocal cord dysfunction can be assessed using nasoendoscopy, which allows the observation of abnormalities in the movement of the vocal cords and is most helpful when adduction of the cords is detected in the presence of the patient's symptoms.[40] Persistent wheezing auscultated in a localized area of the chest wall may indicate endobronchial obstruction due to lung cancer or a foreign body. Eosinophilic pneumonias and systemic vasculitis, including EGPA and polyarteritis nodosa, may be associated with wheezing, and their systemic clinical manifestations may help in their identification.

COPD is usually easy to differentiate from asthma. The symptoms in patients with COPD are more persistent, show less variability, are progressive, and usually exhibit minimal reversibility to bronchodilator agents. As previously mentioned, the literature highlights an "overlap" in which patients with COPD have features of asthma with increased sputum eosinophils and a response to oral corticosteroids; these patients probably have both diseases concomitantly.[26] Important cardiologic causes to consider include left ventricular failure, where usually bibasilar lung crackles are present in contrast to the scattered polyphonic wheeze in asthma. Anemia should always be thought of as a cause of dyspnea, especially in elderly patients. The symptoms of gastroesophageal reflux disease (GERD) may be mistaken for those of asthma; however, it is important to recognize that GERD is common in patients with asthma and has been identified as a potential trigger for asthma symptoms.[41]

TABLE 45-4 Aims of Asthma Therapy

Control symptoms
Prevent (or minimize risk of) exacerbations
Eliminate emergency visits
Maintain lung function as close to as normal levels as possible
Decrease diurnal variation, especially nocturnal
Maintain normal levels of daily activities, including exercise
Eliminate or minimize adverse effects from medicine

TREATMENT OF ASTHMA

Treating asthmatic patients is generally straightforward; with effective and safe drugs, most asthmatics are now managed by family and primary care doctors. The successful management of asthma requires an appreciation of the heterogeneity of the disease with respect to etiology, clinical presentation, severity, natural history, and response to therapy. It is unlikely that a single management approach will work for all patients; hence, treatment should be tailored to the individual patient. It will also be recognized that symptom severity in patients varies over time with periods of remission that are interspersed with acute exacerbations; thus, the patient should be monitored regularly and treatment should be modified on an ongoing basis to meet the patient's current needs. There are several aims in the management of patients with asthma (Table 45-4), and although prominence has been placed on drug therapy, there are important patient-oriented approaches that focus on correct inhaler usage, emphasize self-management action plans, and address environmental control.

■ Inhaler Devices

Drug delivery to the lungs via the inhaled route remains the cornerstone of therapy for patients with asthma. Inhaled therapy targets drug directly to the lungs and allows a distinct therapeutic advantage over systemic therapy with the use of smaller drug doses, a more rapid onset of therapeutic action, and decreased adverse effects.[42]

There are several types of inhaler device and drug delivery systems used in clinical practice for the management of asthma; these include the pressurized metered-dose inhaler (pMDI), spacers, dry powder inhalers (DPIs), and nebulizers.[43] There are potentially more than 250 device drug combinations available, leading to confusion in prescribing among healthcare practitioners. Indeed, studies have shown that not just patients, but healthcare workers as well, are uncertain about the correct use of inhaler devices. Physicians' knowledge, in particular, remains poor and may be related to a lack of education and instruction about inhaler usage during their training.[44] It is confusing in the literature as there are 299 definitions of inhaler errors, but clearly it is recognized that a lack of knowledge and recognition with respect to the proper use and working of an inhaler might lead to worsening health outcomes for the patient.[45] It has been shown that training and counselling patients in their inhalation technique can increase their adherence to device usage, and patients may be assessed with respect to their suitability for a particular inhaler device by using portable handheld meters that assess inhalation flows.[46] Evidence-based guidelines from the American College of Chest Physicians[47] recommend the following points for consideration by healthcare practitioners when choosing an inhaler for their patient: (1) the clinical condition and disease severity; (2) availability of the inhaler device for the drug prescription; (3) the patient's ability to use the selected device correctly; (4) use of the same device type for all drugs; (5) the setting and convenience of outpatient and inpatient use; (6) the time required for drug

TABLE 45-5 Advantages and Disadvantages of Inhalation Devices

	Advantages	Disadvantages
Pressurized metered-dose inhaler (pMDI)	Compact and portable Multidose Quick treatment time Drug in sealed canister Inexpensive	High oropharyngeal deposition Difficulty in hand–mouth coordination Propellants may cause "cold Freon" effect and affect climate change Difficult to assess empty canister
Dry powder inhaler (DPI)	Compact and portable Quick treatment time Breath-actuated function removes need for coordination	Need adequate inhalation flow to disperse drug High oropharyngeal deposition Humidity can cause drug degradation Patients may be intolerant to additives, e.g., lactose
Nebulizers	Large doses of drug can be given Can be used with relaxed tidal breathing Suitable for young, old, and acutely ill patients Many drug solutions can be aerosolized	Bulky, cumbersome, and expensive Wasted drug in nebulizer reservoir Variation in aerosol output performance between models Time consuming Need for power source Regular cleaning and maintenance

administration; (7) cost and reimbursement; and (8) the inhaler preference of the patient as well as the prescriber. The advantages and disadvantages of the common inhaler device types are shown in Table 45-5.

Pressurized Metered-Dose Inhalers

The pMDIs contain the drug as a liquid suspension or solution with propellant in a sealed canister, and other formulation ingredients may be present such as ethanol, chemical preservatives, flavoring agents, and surfactant. Most inhaler therapies are now free of chlorofluorocarbon (CFC) propellants, which have been replaced by non–ozone-depleting propellants such as hydrofluorocarbons (HFCs). Upon actuation of the pMDI canister, there is quick vaporization of the propellant that provides the force to aerosolize and propel the liquid drug out of the canister at high velocity. Vaporization of the propellant also causes cooling of the drug aerosol, which can sometimes give rise to the "cold Freon effect"—a sensation experienced by some patients of cold aerosol hitting the back of their oropharynx, which can stop them from inhaling the drug and sometimes causes paradoxical bronchospasm. Some of the formulation ingredients added to pMDIs described above have been shown to cause bronchospasm, wheezing, and cough in asthmatic patients. pMDIs are compact, portable, and inexpensive devices. Recent advances in the technologic design of pMDIs include the addition of a dose counter.

Optimal clinical efficacy with a pMDI is obtained when the device is actuated at the start of a deep, slow inhalation lasting for 5 s, followed at the end of inspiration by a breath-hold pause of at least 5 s. Patients should be instructed to inhale "slowly, gently, naturally, deeply, and comfortably" and actuate the device in the first second following inhalation. Failure to inhale slowly and deeply with pMDIs is a more common mistake than the actual patient discoordination between inhalation and actuation.[48] However, the latter problem is more pertinent in elderly patients, and add-on spacer attachments, device-holding adaptors, and breath-actuated pMDIs have been developed to overcome the problem. Breath-actuated metered-dose inhalers utilize the patient's inspiratory force to trigger and activate the inhaler device, although it has been shown breath-actuated pMDIs offer no advantage over good conventional pMDI inhaler technique.[49] In contrast, "breath-coordinated" devices are different from "breath-actuated" metered-dose inhalers in that they do not depend upon the patient's inspiratory flow for actuation and help patients achieve coordination with aerosol inhalation. Although the current HFA propellants in pMDIs have the potential to impact climate change, the advent of new inhaler propellants will allow the complete life-cycle carbon footprint impact of pMDIs to be equivalent to other inhaler devices used in clinical practice.[50]

■ Spacers

Spacer devices are used with pMDIs and are designed to assist in the delivery of inhaled drug to the lungs by promoting ease of pMDI use, and reduce oropharyngeal deposition by slowing the high velocity of the emitted aerosol cloud.[51] The plastic walls of the spacer trap the large drug particles and this decreases oropharyngeal impaction, which may lead to a decrease in local unwanted side effects, particularly with CS, and also a reduction in systemic adverse effects by minimizing the amount of drug absorbed via the gastrointestinal tract. In addition, increasing the distance the aerosolized drug travels (by using the spacer as an extension attachment to the pMDI device) slows the emitted aerosol cloud and allows more evaporation of the propellant, leading to relatively smaller drug particles that have a greater potential to deposit within the lungs. Spacers include valve-holding reservoir chambers with a one-way inhalation valve in the mouthpiece only allowing airflow through the chamber when the patient inhales; simple extension devices that are non-valved add-on products that require a reasonably good amount of coordination; and reverse-flow devices with which the aerosol spray is actuated away from the patient into a collapsible reservoir chamber or bag through which outside air is entrained to provide the airflow stream for inhalation.

Spacer devices each differ in their design characteristics and should be prescribed only with the pMDI they are compatible with, as each spacer–inhaler combination has distinct aerosol output characteristics.[52] To reduce the electrostatic charge in spacers, which can significantly contribute to decreased drug available to be delivered to the lungs, spacers should be primed with the pMDI prior to use, and one-dose actuation at a time from a pMDI into the spacer device should be employed, as opposed to simultaneous multiple-dose administrations. Spacers should be washed with ionic detergent and air dried. Antistatic spacer devices are available.

Dry Powder Inhalers

DPIs are propellant-free devices that contain finely milled, powdered drug particles bound into loose aggregates, or drug particles associated with larger carrier molecules, such as lactose. DPI devices are breath-actuated and critically rely on the patient's inspiratory effort to de-aggregate the drug from its carrier particle to achieve optimal delivery and deposition within the lungs. Studies have shown that DPIs are highly dependent on the patient's inspiratory flow for therapeutic success. In addition, reported observations are that patients with asthma and those with COPD use suboptimal inspiratory flows from DPIs, leading to low pulmonary deposition.[53] In a large database study, insufficient inspiratory effort from DPIs was the most common inhaler error in this device class and was associated with significant worsening of asthma and increased frequency of disease exacerbations.[54]

DPIs can be classified into single-dose and multiple-dosing delivery systems. Single-dose systems may require drug to be individually loaded into the inhaler prior to use, or may be devices from which individual doses are dispensed from punctured gelatin capsules. In contrast, multiple-dosing delivery DPIs avoid the inconvenience associated with repeated drug loading and can be divided into "multi-dose" or "multi–unit-dose" systems. Multi-dose systems deliver drug that is metered from a powder reservoir, whereas multiple–unit-dose devices contain either drug sealed in individual foil blisters or drug sealed in pockets on a moving strip. Deterioration of the drug may occur in damp and humid conditions; hence, all these devices should be stored in a dry environment. A newer generation of DPIs rely less on the patient's inspiratory effort, requiring either lower inhalation flows to aerosolize the drug or, in some circumstances, deliver the drug wholly independent of the patient's breathing maneuver.

Nebulizers

The main types of nebulizer commonly used in clinical practice can be divided into two categories: ultrasonic and jet nebulizers.[55] Ultrasonic nebulizers utilize the vibration from a piezoelectric crystal at a high frequency to produce aerosol clouds for inhalation from the liquid drug. Ultrasonic nebulizers are smaller and less noisy compared to jet nebulizers, but are usually less robust, more expensive, and not as effective in nebulizing liquid suspensions of drug. Jet nebulizers use either compressed gas or an electrical compressor to generate aerosolized particles. High-velocity air streams are generated and directed through a narrow Venturi opening, across the liquid drug solution/suspension, to produce aerosolized droplets within the nebulizing chamber.

Nebulizers require tidal breathing at rest for effective use and do not require much patient coordination. However, there is great variation in the aerosol output generated from each of the different nebulizer devices, and the inhalation maneuver will affect drug delivery to the lungs that can be greatly reduced with crying, as may occur with children, or when there are shallow and rapid inhalations.[56] Consideration should be given to the nebulizer–facemask combination, as incorrect mask insertion into the nebulizer may give rise to unwanted deposition of drug onto the face and eyes, particularly in children. Generally, nebulizer devices are large, lack portability, and have a longer treatment time than conventional inhalers.

There is now a newer generation of nebulizer devices that offer a marked improvement in the efficiency and precision of pulmonary drug delivery.[57] These devices are more costly than conventional nebulizers, but they may be cost-effective by decreasing drug loss from the nebulizer chamber, particularly during exhalation, and by delivering a reduced drug dose more effectively. Nebulizer systems have also been developed to control the patient's inhalation maneuver so as to minimize the variability in dose delivery that occurs during use. Finally, there are systems that provide feedback to the patient and allow an assessment of patient compliance.

THERAPEUTIC DRUGS

A wide variety of agents are used in the management of asthma. Additional discussion can be found in Chapter 145.

Bronchodilators

Bronchodilators reverse the bronchoconstriction of asthma, principally by acting to relax airway smooth muscle, and this results in the rapid relief of symptoms. Bronchodilators are not adequate to control asthma in patients with persistent symptoms, as they have little effect on the underlying airway inflammation. The classes of bronchodilators in current clinical use include β_2-adrenergic agonists, anticholinergics, and phosphodiesterase inhibitors, with β_2-agonists being the most efficacious.

β_2-Adrenergic Agonists

Inhaled β_2-adrenergic agonists are the drugs of choice for relief of respiratory symptoms due to acute airway obstruction.

Mode of Action β_2-Agonists activate β_2-adrenergic receptors resulting in an increase in intracellular cyclic AMP, which leads to relaxation of airway smooth muscle cells. β_2-Agonists act as functional antagonists; that is, they prevent and reverse the contraction of airway smooth muscle cells by bronchoconstrictors, and it is this action that mainly accounts for their efficacy as bronchodilators in asthma. These drugs also have nonbronchodilator effects, including the inhibition of mast cell mediator release, inhibition of sensory nerve activation, and reduction in plasma exudation—all of which may be clinically useful.[58]

Clinical Use SABAs, such as albuterol and terbutaline, have a rapid onset of action and a 3- to 6-h duration of activity. This pharmacodynamic characteristic of a rapid onset of bronchodilation allows these drugs to be used as quick-relief medications or "relievers" on an as-needed basis. As a matter of caution, increasing use of SABA indicates that asthma is not controlled and patients should be reviewed. Indeed, the overuse of SABA has been linked to high levels of mortality from asthma.[59]

At recommended doses, inhaled β-agonists have few adverse effects, although when used at higher doses by nebulizer, patients may experience short-lived side effects. Long-acting β_2-agonists (LABAs) include formoterol and salmeterol. Both drugs are given twice daily by the inhaled route and have a duration of action of more than 12 h. In particular, formoterol has an onset of action as rapid as albuterol and can be used as a "reliever" component in fixed-dose combinations of LABA with ICS medication.[60] LABAs should not be used as monotherapy for the control of asthma of any severity and should not be given in the absence of ICS therapy, as they do not control the underlying inflammation. However, fixed-dose combinations of LABAs with ICS are now increasingly used in the management of asthma and have proved to be highly effective in improving control, reducing disease exacerbations and allowing use of lower doses of ICS.[61] Studies have also shown the clinical benefits of LABA/ICS fixed combinations compared with the monocomponents administered using two separate inhalers. The combinations of formoterol and budesonide, and formoterol and beclomethasone dipropionate, have been demonstrated to be effective when used as both a controller and reliever agents (single maintenance and reliever therapy [SMART]), thus providing the advantage of a single device used for both purposes.[62] Recent approaches in the management of mild asthma suggest the use of ICS with formoterol in combination as rescue medication instead of SABA, although this is as yet unlicensed.[63,64]

Adverse Effects The most common adverse effects of β_2-agonists are palpitations and muscle tremors, which are unusual with drug administration using the inhaled route; these adverse effects are seen more commonly with high-dose nebulizer therapy and in elderly patients.

The safety of β_2-agonists has been an issue of concern. An association has been demonstrated between the amount of SABA used and asthma deaths, but thorough analyses demonstrate that the increased use of rescue SABA implies poor asthma control, which itself is a risk factor for asthma death. A slight increase in deaths from asthma has been observed with the use of LABA, but this is most likely related to the lack of use of parallel ICS, as the LABA therapy on its own fails to suppress the asthmatic airway inflammation, highlighting the need to always use ICS when LABAs are given. This can be achieved by using a combination ICS/LABA inhaler.[65] Patients should also be reminded to avoid β-adrenergic receptor–blocking drugs, including those contained in topical ophthalmic preparations, as they can precipitate severe and sometimes life-threatening asthmatic episodes. Accordingly, β-blockers are contraindicated during acute asthma exacerbations; the risk–benefit ratio should be considered before β-blockers are used in stable patients with asthma. Some patients experience deterioration in their asthma control following inhaled β-agonist treatment. Possible mechanisms and contributory factors include paradoxical bronchospasm, increased BHR, and tolerance to the drug. With prolonged exposure to a drug, downregulation of the β-receptor may occur, limiting therapeutic efficacy (i.e., tachyphylaxis). Indeed, β-receptor mutations and gene polymorphisms have been implicated in influencing the response to inhaled β-agonists.[66]

Anticholinergics

Anticholinergic agents are another class of drugs to be considered in asthma management.

Mode of Action Muscarinic receptor antagonists, such as ipratropium bromide, induce airway smooth-muscle relaxation by blocking muscarinic receptors on airway smooth muscle, inhibiting vagally mediated cholinergic tone and preventing mucus secretion.[58]

Clinical Use In general, the anticholinergic drugs are not as efficacious in the acute relief of symptoms compared to the β_2-agonists. Anticholinergics prevent the cholinergic reflex component of bronchoconstriction, whereas in contrast, β_2-agonists inhibit all bronchoconstrictor mechanisms. Hence, anticholinergics tend only to be used as add-on bronchodilator treatment in asthmatics who remain uncontrolled on other inhaled therapy. In the treatment of acute severe asthma, high doses of anticholinergic therapy may be given by nebulizer, but they should only be given following β_2-agonist treatment, as anticholinergics do not have a fast onset of bronchodilation. A combination preparation of albuterol and ipratropium bromide is available for nebulization therapy. Tiotropium is a muscarinic antagonist that has been used in the management of patients with COPD and is currently the only long-acting muscarinic antagonist monotherapy that has been licensed for use in asthmatic patients with poorly controlled asthma in steps 4–5 (see below). Tiotropium has a higher selectivity for antagonism of M_3 receptors and dissociates from receptors more slowly, collectively leading to prolonged smooth muscle relaxation and long-acting bronchodilation.[67] The combination of a LAMA with ICS and LABA in one single inhaler (fixed-dose triple inhaler) has recently been licensed for uncontrolled asthma; the LAMA in the preparation is glycopyrrolate.[68]

Adverse Effects Adverse effects are usually not a concern with anticholinergics, as there is minimal absorption into the systemic circulation. The most commonly experienced side effect is dry mouth; in elderly patients, glaucoma and urinary retention can occur.

Phosphodiesterase Inhibitors

Aminophylline and theophylline are oral phosphodiesterase (PDE) inhibitors primarily used as an adjunct bronchodilator treatment. However, due to their narrow therapeutic index and adverse effect profile, coupled with availability of safer and more effective alternatives, PDE inhibitors are now infrequently used in patients with asthma.[69]

Mode of Action Theophylline and aminophylline inhibit PDEs in airway smooth muscle cells (predominantly PDE3), which increases intracellular cyclic AMP, leading to a bronchodilator effect. However, the doses required for bronchodilator activity commonly cause adverse effects, which are mainly a consequence of direct PDE inhibition. Theophylline has been shown to exhibit anti-inflammatory effects, which are likely to arise through different molecular pathways; for example, theophylline has been shown to stimulate a key nuclear enzyme, histone deacetylase 2, which is an important intracellular mechanism for switching off inflammatory genes that have been activated.[69]

Clinical Use Theophylline is normally administered as an oral slow-release formulation, either once or twice a day, a regimen that results in more steady plasma concentrations compared with standard theophylline tablets. In severe asthmatic patients, theophylline may be used as an add-on bronchodilator treatment. Plasma concentrations of 10 to 20 mg/L are typically needed—levels usually associated with adverse effects. In contrast, the anti-inflammatory effects of theophylline seem to occur at plasma levels below the traditional therapeutic range of 10 to 20 mg/L; at low doses, the drug is better tolerated. Low-dose theophylline has additive effects to ICS and is particularly helpful in severe asthmatic patients, in whom withdrawal of theophylline may result in clear worsening of asthma control. Intravenous aminophylline is now seldom used for the treatment of asthmatic patients, and only very rarely in those with acute severe asthma exacerbations.

Adverse Effects The adverse effects of theophylline are directly related to drug levels in plasma and are infrequently observed at concentrations below 10 mg/L. Measurement of plasma theophylline may be useful in determining and guiding the correct clinical dose. Headaches, nausea, and vomiting are the most common adverse effects, which arise from the inhibition of PDE4. Palpitations and diuresis may be troublesome, and with higher plasma concentrations, epileptic seizures, cardiac arrhythmias, and death may occur due to adenosine A_1-receptor antagonism. Oral theophylline is well absorbed through the gastrointestinal route and is largely inactivated in the liver by the enzyme CYP450. Consequently, drugs that inhibit CYP450 activity, such as allopurinol and erythromycin, may increase plasma levels of theophylline causing a greater potential for adverse effects.

PDE4 inhibitors increase cyclic AMP in inflammatory cells and have anti-inflammatory effects. Although the PDE4 inhibitor roflumilast is approved as an additional therapy in severe COPD patients, there have been few studies in asthma. Its use is limited by frequent side effects (diarrhea, nausea, headaches) at therapeutic doses.

■ Corticosteroids

Corticosteroids (CS) are potent anti-inflammatory agents. When administered by the inhaled route, CS are the most effective therapy available for treating and controlling asthma and have greatly contributed to a reduction in asthma mortality in the Western world.[70]

Mode of Action

CS reduce the number of inflammatory cells, as well as their activation, in the airways. The reduction in eosinophils, activated T lymphocytes, and surface mast cells contributes to the decrease in airway hyperresponsiveness that is seen with CS therapy.

Several molecular mechanisms underlie the action of CS on airway inflammation. The main pathways center on the inhibition of transcription factors NF-κB and AP-1, which switch off transcription of multiple activated genes encoding inflammatory proteins, such as cytokines, chemokines, inflammatory enzymes, and adhesion molecules.[71] Another key mechanism in the action of CS is the inhibition of the recruitment of histone deacetylase 2 to the inflammatory gene complex, which reverses the histone acetylation associated with increased gene transcription. CS increase the expression of β_2-receptors, which may contribute to the complementary clinical effects observed when CS are combined with LABA.[72] Transcriptional activation is responsible for most of the endocrine and metabolic adverse effects of CS.

Clinical Use—Inhaled Corticosteroids

CS are usually administered by the inhaled route for maintenance controller therapy in patients with asthma. ICS have been shown to prevent the symptoms of asthma, reduce severe exacerbations rates, improve lung function, and reduce airway hyperresponsiveness. Early and timely treatment with ICS appears to avert the irreversible changes in airway function that occur with chronic asthma. Patients with persistent asthma stabilized on ICS experience increased exacerbations when treatment is withdrawn, indicating that ICS suppress symptoms and inflammation but do not cure the underlying disease.

ICS are beneficial in treating asthmatic patients of any age and at any stage of disease severity. They are first-line therapy for patients with persistent asthma and are usually administered twice a day, although ICS may be effective given once a day in some patients with mild symptoms. The dose–response curve of ICS is relatively flat, meaning that higher doses are only incrementally better than low-to-medium doses. If low-to-medium doses of ICS do not control persistent asthma symptoms, it is usual practice now to add a LABA, preferably as a combination of the two drugs delivered from a single inhaler device.

Clinical Use—Systemic Corticosteroids

Oral CS are reserved to treat acute exacerbations of asthma. Typically prednisolone or prednisone, 30 to 45 mg, is given once daily for 5 to 10 days. Upon completion of the course of treatment, no tapering of the dose is required. A few asthmatic patients (approximately 1%) with severe disease may require maintenance treatment with oral CS; in these patients, it is important to determine the lowest dose necessary to maintain asthma control in light of the greater potential for adverse effects with higher doses. CS may also be administered intravenously (methylprednisolone or hydrocortisone) for the treatment of acute severe asthma, although studies have shown that oral CS are as equally efficacious and easier to take. The use of biologic therapies, such as anti-IgE and anti–IL-5, reduces the requirement for oral CS in selected patients with very severe asthma. All patients on maintenance oral CS should be considered for these therapies.

Adverse Effects

ICS may give rise to local oropharyngeal adverse effects, such as oral candidiasis, dysphonia, and hoarseness, but these may be lessened with the use of a spacer device. Concerns exist about the systemic adverse effects of ICS from swallowing of the oropharyngeal dose and lung absorption, but these effects depend upon the individual pharmacokinetic properties of the different CS. Overall, studies show that ICS have minimal systemic adverse effects.[73] At higher drug doses, ICS may suppress plasma and urinary cortisol levels, and in prepubertal children the initial decrease in attained height from use of ICS persists as a reduction in adult height; however, it is not progressive or cumulative and represents a loss in height of approximately 1 cm. Most importantly, ICS allow the effective control of asthma symptoms and disease, and maintenance therapy may decrease the need and number of prescribed courses of oral CS, thereby reducing the total systemic exposure to CS.

Oral CS give rise to greater systemic adverse effects than ICS, with a greater potential in those on chronic maintenance therapy. Adverse effects include bruising, diabetes, truncal obesity, osteoporosis, duodenal and gastric ulceration, hypertension, mood and behavioral changes, proximal myopathy, and cataracts. It is important to assess and monitor bone density if patients are administered chronic oral CS therapy so that preventive treatment for osteoporosis with bisphosphonates, or estrogen in postmenopausal women, may be initiated if levels of bone density are borderline or low. If CS adverse effects are a considerable problem, steroid-sparing agents may occasionally be considered.

■ Antileukotrienes

Leukotriene pathway inhibitors are a group of compounds that alter the pathophysiologic effects of leukotrienes derived from the 5-lipoxygenation of arachidonic acid. Two classes of agents are available: inhibitors of the 5-lipoxygenase enzyme (e.g., zileuton) and cysteinyl-leukotriene receptor type 1 antagonists (e.g., montelukast, zafirlukast, pranlukast).[74]

Mode of Action

Cysteinyl-leukotriene receptor type 1 antagonists inhibit the smooth muscle bronchoconstriction, microvascular leakage, and eosinophilic airway inflammation that occur through activation of cysLT_1 receptors. These agents act predominantly on the inflammatory mediators produced by mast cells in asthma and also, to a lesser extent, on mediators produced by eosinophils.

Clinical Use

Antileukotrienes have less effect on airway inflammation and provide modest clinical benefit compared to ICS. ICS are more effective anti-inflammatory agents and are clinically superior to antileukotrienes in controlling asthma. Antileukotriene treatments may be useful as add-on therapy in selected patients with mild asthma on low-dose ICS, although these agents are less efficacious than add-on therapy with LABA. Antileukotrienes may be helpful when CS use is poorly tolerated or not desired by the patient, or if there is concomitant rhinosinusitis. These drugs are usually given orally once or twice a day.

Adverse Effects

Antileukotrienes are usually well tolerated, but they can sometimes give rise to gastrointestinal upset, hepatotoxicity, and hypersensitivity reactions, including anaphylaxis and angioedema.

■ Cromones

Cromolyn sodium and nedocromil sodium are classified as asthma-controller drugs. Their main mechanisms of action seem to be to inhibit sensory nerve and mast cell activation; therefore, they are effective in blocking trigger-induced asthma, such as allergen- or exercise-induced symptoms. However, these drugs have a short duration of action, requiring inhalation up to four times a day, and consequently have relatively little benefit in the long-term control of asthma. They were popular in the treatment of children with asthma because they are remarkably safe, although they are inferior to ICS with respect to all relevant clinical outcomes and are no longer recommended in guidelines. Low-dose ICS are now favored in children, as they are more efficacious and have an established safety profile.

■ Corticosteroid-Sparing Treatments

Some patients experience serious adverse effects with CS therapy, especially oral CS therapy in those with severe asthma. In an attempt to minimize CS exposure and reduce patient requirement, various immunomodulatory treatments have been tried. Steroid-sparing therapies include azathioprine, colchicine, cyclosporin A, gold, methotrexate, and intravenous gamma globulin; however, none of these treatments have shown long-term efficacy and, importantly, each has been associated with a high-risk adverse effect profile. They cannot be recommended in lieu of CS.

Anti-IgE Monoclonal Antibodies

Omalizumab is a monoclonal antibody to IgE that inhibits IgE-mediated reactions by neutralizing serum IgE without binding to cell-bound IgE. It is used as an adjunctive agent for atopic asthmatic patients who are dependent on CS therapy.[75] Studies in patients with moderate to severe CS-dependent asthma show an improvement in asthma control, a reduction in the number of disease exacerbations, and a significant steroid-sparing effect. However, anti-IgE treatment is very expensive. Its use is appropriate only for specific patients who have a high circulating IgE within a precise range and whose asthma is not controlled on maximal doses of inhaled or oral CS therapy. Omalizumab is usually given as a subcutaneous injection every 2 to 4 weeks. Although relatively safe with few significant adverse effects, anaphylaxis has occasionally been reported. As there are no good predictors of clinical response, a 3- to 4-month trial of therapy should be undertaken to ascertain any objective benefit with this treatment.

Anticytokine Therapy

Despite maximal inhaled therapy and maintenance courses of OCS treatment, a small proportion of patients with asthma are extremely difficult to control and may be candidates for biologic treatment of their disease. A number of immune system modulators have recently been licensed and approved for use in patients with severe asthma. Of these, the main biological therapies are inhibitors that target key cytokines involved in the chronic airways inflammation of asthma.[76]

Inflammation in patients with asthma is usually allergic, with activation of mast cells and of eosinophils mainly orchestrated by type 2 immunity, which involves T helper 2 (Th2) cells and type 2 innate lymphoid (ILC2) cells, IL-4, IL-5, and IL-13. These key cytokines have been targeted for therapeutic purposes.[76]

Anti–IL-5 Treatments

Currently, three anti–IL-5 treatments have been approved for use in selected patients with severe type 2 asthma: mepolizumab, reslizumab, and benralizumab.[77]

Mepolizumab is a blocking antibody to IL-5 administered by subcutaneous injection every 4 weeks. Initial studies in unselected patients and those with milder disease were unconvincing in demonstrating a benefit to patients. However, recent clinical trials in severe asthma patients using specific inclusion criteria, including ongoing respiratory symptoms, frequent disease exacerbations, and increased sputum eosinophils (>3%), showed a reduction in both disease exacerbations and the maintenance dose of OCS.[78] However, there was only little improvement in respiratory symptoms, pulmonary function, and quality of life; hence, ongoing inhaled maintenance therapy with ICS/LABA may still be needed.

Reslizumab is another blocking antibody to IL-5 administered intravenously every 4 weeks (a potential drawback compared to other treatments) that has shown similar benefit to mepolizumab. Once again, the clinical effectiveness is dependent on eosinophil counts (blood eosinophils ≥400/μL).[79] Higher doses of reslizumab than mepolizumab can be administered, so it may be considered in those patients who do not show a good response to mepolizumab.

Benralizumab is an antibody to IL-5 receptor α (IL-5Rα) administered subcutaneously every 4 to 8 weeks; it has been shown to benefit not only patients with severe asthma, but also those with milder disease.[80] In a study of patients presenting with an acute asthma attack, benralizumab administered as a single dose led to decreased disease exacerbations in the following 12 weeks post-exacerbation, particularly in those patients who were hospitalized because of their acute exacerbation.[81] Benralizumab induces death (apoptosis) of eosinophils, thereby rapidly clearing eosinophils in the airways. It may have a more rapid onset of action than antibodies targeting the cytokine. Increased blood eosinophil counts predict a better response; therefore, only patients with blood eosinophil counts greater than 300/μL should be considered for this therapy.

Anti–IL-4, Anti–IL-13 Treatments

IL-4 and IL-13 signal through a common receptor, IL-4Rα, and both cytokines promote eosinophilic airways inflammation. In adult patients with asthma, IL-4 expression is low, and poor outcomes in preliminary clinical studies directed attention to blocking IL-13 directly.[76] However, lebrikizumab, an antibody specifically blocking IL-13, showed marginal benefit in two recent clinical trials and has not been pursued for clinical approval.[82] Similarly, tralokinumab, also an IL-13 blocking antibody, performed poorly in recent clinical trials and was associated with minor changes in lung function, asthma control, and exacerbation outcome measures in patients with severe uncontrolled asthma.[83] In contrast, clinical trials with dupilumab, an antibody against IL-4Rα, have shown much better clinical benefit than those using IL-13 antibodies. Dupilumab, administered subcutaneously every 4 weeks, has been shown to improve symptoms and lung function and to markedly reduce asthma exacerbations in moderate to severe asthma poorly controlled on maximal inhalation treatments. Interestingly, in these patients FeNO was a good biomarker of response, but baseline blood eosinophil counts were not.[84] The drug is also licensed for use in patients with severe eczema and is effective in the treatment of rhinosinusitis and severe nasal polyposis.

Anti-TSLP Treatment

Blocking upstream cytokines, such as thymic stromal lymphopoietin (TSLP), that orchestrate type 2 inflammation may be more effective than targeting individual downstream cytokines. Tezepelumab, a blocking antibody to TSLP, has been shown to be effective in inhibiting responses to inhaled allergen (early and late) and in reducing blood and sputum eosinophils, FeNO, and IgE in patients with mild asthma.[85] In patients with severe asthma, clear reductions in acute disease exacerbations and decreases in FeNO and blood eosinophil counts have been observed.[86] Tezepelumab is also effective in patients with low or normal blood eosinophils, as it may also target T cells (Th1, Th17, ILC1, ILC3) that orchestrate neutrophilic inflammation.

Other Immunomodulating Treatments

Currently, many drugs are in development or in early human clinical trials in patients with subtypes of severe asthma that target various aspects of the inflammatory pathways, including those directed at cytokines (IL-25, Il-33, GM-CSF, IL-1, IL-6), transcription factors (GATA-3), neutrophils (TNF, IL-17), or chemokines (CCR3, CXCR).[76] Anti–TNF-α antibodies, although mechanistically promising, have not been shown to be effective in patients with severe asthma. New, broad-spectrum anti-inflammatory treatments include phosphodiesterase 4, NF-κB, and p38 MAP kinase inhibitors; these drugs act on signal transduction pathways that are common to many immune cells and present the risk of troublesome adverse effects, particularly when administered parenterally. Research is ongoing regarding potential delivery by the inhaled route.

Clear from clinical trials of biologics and the current interest in, and development of, drugs targeting the immune pathways in asthma, is that appropriate patient selection, identification of responders, and development of biomarkers to monitor response are critical in order to guide clinicians when considering use of these very expensive treatments. The effectiveness of anti–IL-5 treatments is highly dependent on the baseline blood eosinophil count; greater clinical response is seen in patients with severe asthma with a blood eosinophil count ≥300/μL. In contrast, FeNO, rather than blood eosinophils, is a good predictor of response to anti–IL-4/13 treatments. For anti-TSLP treatment, effectiveness does not depend on raised blood eosinophil counts or FeNO.

It has also been recognized that existing specialist clinic resources must be directed at addressing nonadherence to inhaled therapy, as biologic interventions could end up becoming a very costly and expensive alternative to rectify nonadherence.[87] Most studies have been short-term (12 months). The long-term safety profile of these agents, particularly on the body's immune defense system against infections, is largely unknown. However, as licensed treatments are now being used, these data will be gathered during postmarketing surveillance.

■ Immunotherapy

Allergen-specific immunotherapy (ASIT) involves the repeated administration of allergen products to induce immunologic and clinical tolerance to the specific allergen. ASIT may be given subcutaneously.

Allergen immunotherapy is of benefit in highly selected patients with defined allergic triggers.[88] Asthmatic patients with a single specific allergic trigger and concomitant nasal symptoms derive the greatest benefit compared with patients with multiple allergic triggers. Allergen-specific studies have supported efficacy of this route of administration. There is a risk of adverse effects, including anaphylaxis. In contrast, sublingual ASIT has recently been shown to be an effective and safe alternative in patients with seasonal allergy. Clinical studies with house dust mite allergic asthma are underway.

NONPHARMACOLOGIC MANAGEMENT

Alternative therapies, which may be popular and more acceptable with some patients, include acupuncture, breathing control, chiropractic, homeopathy, hypnotherapy, and yoga. Placebo-controlled studies show these treatments lack efficacy; they should not be clinically recommended.[89] The concern with these therapies is that they may lead to discontinuation of effective drug therapy and destabilize asthma control. However, as these therapies are considered not to be harmful, patients may utilize them as an adjunct to their conventional pharmacotherapy.

■ Bronchial Thermoplasty

Bronchial thermoplasty (BT) is an endobronchial intervention for the treatment of adult patients with severe persistent asthma who remain uncontrolled with ICS and LABA. BT delivers controlled radiofrequency energy to heat the airway walls and reduces airway smooth muscle mass.

Three randomized controlled clinical trials of BT versus usual care or sham intervention in patients with severe asthma have supported its effectiveness and safety: the Asthma Intervention Research (AIR) trial[90] and the Research in Severe Asthma (RISA) trial,[91] both of which both compared BT to usual care, and the AIR2 trial,[92] which compared BT with sham intervention. The AIR2 trial observed a significant reduction in severe exacerbations of asthma, decreased emergency room visits, improved asthma quality of life questionnaire (AQLQ) scores, and fewer hospitalizations. These improvements persisted through 5 years of follow-up.[93]

Patients in the trials undergoing BT did report a transient increase in symptoms related to their asthma and, during the treatment phase, an increase in hospital admissions. An interim analysis of the 3-year follow-up results of BT in a postmarketing surveillance study mandated by the FDA (PAS2, Post-FDA Approval Clinical Trial Evaluating Bronchial Thermoplasty in Severe Persistent Asthma), confirmed findings observed from the AIR2 follow-up, with significant decreases in the percentage of patients with severe exacerbations (45%), emergency department visits (55%), and hospitalizations (40%).[94]

FUTURE TREATMENTS

Although current asthma therapy with CS and β_2-agonists is effective in controlling disease symptoms in the majority of patients, poorly controlled asthma still remains a problem in a considerable proportion of patients.[95] Poor adherence to prescribed controller therapy contributes to poor asthma control, and the use of combination LABA/ICS therapy delivered by a single inhaler device, or the use of combination LABA/ICS therapy as both a controller and reliever agent, may partly address this problem. LAMA have been used as add-on therapy in worsening asthma.[67] Recently, the combination of a LAMA (glycopyrronium) with ICS and LABA in one single inhaler (triple inhaler) has been licensed for uncontrolled asthma.[68]

In everyday practice, the vast majority of inhaler devices target treatment at the large airways. However, it is becoming increasingly recognized that it is important to target inhaled therapy to the peripheral lung regions in order to treat ongoing inflammation that may additionally be contributing to the patient's unstable clinical state.[96] Asthma continues to remain an unmet need, as the lifelong treatments currently used only address the clinical symptoms and have little effect on the underlying structural alterations associated with asthma. A pressing need exists for development of novel therapies for patients who have side effects from systemic CS.[97]

CS resistance is a particular problem in patients with severe asthma. Several molecular mechanisms have been elucidated that may lead to novel therapeutic approaches, including the reversal of this resistance by drugs such as theophylline and nortriptyline. Studies of the steroid-sparing effects of macrolide antibiotics in asthma management have yielded discordant results. Macrolides might benefit some patients with infection by atypical bacteria, but recent results are not encouraging; there may be an effect in patients with predominant neutrophilic asthma.

MANAGEMENT OF CHRONIC ASTHMA

Global directives in asthma now focus on the control of asthma symptoms using a stepwise approach to drug therapy.[1] There has been a shift away from treatment based on disease severity with the realization that asthma does not necessarily remain in the same clinical category indefinitely; it may change over months or years, and patients may move up or down in their asthma severity based on a variety of factors, such as the presence of allergens, correct or incorrect use of medications and treatments, and lack of adherence to the prescribed treatment regimen. If control at a particular step is not adequate, then treatment should be increased to the next level. Principles of therapy embody the fact that effective treatment should lead to better asthma control and allow the patient to move to a less severe category; therefore for ongoing management of asthma, classification by level of control may be more relevant and useful than disease severity. The aims of chronic therapy in asthma are highlighted in Table 45-4.

The Global Initiative for Asthma (GINA) stratifies patients into four categories of asthma control level: (1) controlled (therapy is maintained or stepped down), (2) partly controlled (consideration is given to stepping up therapy), (3) uncontrolled (treatment is stepped up until symptom control is achieved), and (4) exacerbation (patients are treated according to the exacerbation algorithms).[1]

Factors determining the level of control involve an assessment of the following: daytime symptoms experienced in the last week, limitations in activities of daily living, nocturnal symptoms or awakenings, need for rescue reliever medication during the week, lung function, and number of exacerbations (if any) in the last week and last year.

■ Stepwise Treatment

The stepwise approach to asthma management incorporates a description of the levels of treatment required to achieve good asthma control.[1] Some patients may experience acute worsening of asthma control, such as those with a concomitant upper respiratory tract infection, and may need to step up more than one step at a time.

Step 1

For all asthma patients, a SABA delivered by a metered-dose inhaler gives relief of acute symptoms. Updates to global strategy documents for the management of asthma and some national country guidelines now incorporate ICS treatment at step 1, recognizing the nature of asthma as chronic inflammatory disease and the need to control (and treat worsening) symptoms with ICS maintenance therapy.[98] The increasing use of a short-acting reliever medication more than three times a week, or triggering of symptoms from exercise, provide indications that controller therapy is needed. Recent studies in the management of mild asthma suggest the use of an ICS with formoterol in combination as a rescue medication, instead of a SABA; however, this approach is as yet unlicensed.[63,64]

An important, but often overlooked, part of asthma management relates to measures to control environmental triggers. Recognized triggers that worsen asthma control, such as aeroallergens or occupational agents, should be avoided, although this is not always possible. Patients with asthma may also have several triggers; therefore, the impact of avoiding a single trigger will vary considerably between patients. However, complete removal from exposure to house dust mite has been shown to reduce asthma severity and airway hyperresponsiveness.

Guidelines recommend that influenza vaccination should be administered in adult asthmatics. However, while studies suggest it is unlikely to induce asthma exacerbations, there is no conclusive evidence regarding the efficacy of vaccination on influenza-related asthma complications or on frequency of exacerbations. Asthmatic patients, especially the elderly or those with comorbid conditions that increase the risk of death from influenza infection, should receive inactivated influenza vaccine if there are no other contraindications. The CDC recommends a single dose of Pneumovax for adults from 19 to 64 who have chronic illnesses, including asthma.

Steps 2–3

When patient symptoms are no longer intermittent, addition of a daily long-term controller medication on a scheduled daily basis is recommended. The treatment of choice for all patients is an ICS to alleviate the underlying airway inflammation. It is usual to start with a low-to-intermediate dose of ICS twice daily (e.g., 200 μg beclomethasone dipropionate [BDP] or equivalent BID), and if symptoms are controlled after 3 months the dose should be stepped down. An alternative option is to prescribe as-needed low-dose ICS/formoterol. However, if symptoms persist and are not controlled, a LABA should be added as a fixed combination drug, with an ICS delivered from a single inhaler device, as studies show a clinical advantage compared with the monocomponents administered using two separate inhalers. Indeed, low-dose ICS in combination with LABA therapy shows complementary molecular action and has been shown to be as efficacious at high-dose ICS treatment.[99] The dose of the ICS should be adjusted up or down based on the need for rescue inhaler use and patient symptoms. Alternative add-on therapies to ICS that can be considered include an antileukotriene or low-dose ICS whenever a SABA is taken; however, these are less effective than the ICS/LABA combination.

Steps 4–5

In patients with worsening symptoms, addition of a long-acting muscarinic antagonist or a leukotriene antagonist to medium-dose LABA/ICS may be helpful. The addition of the inhaled long-acting anticholinergic tiotropium bromide to LABA/ICS treatment in patients with poorly controlled asthma significantly decreases asthma exacerbations and improves lung function.[100,101] For those whose disease remains uncontrolled, stepping up with high-dose ICS/LABA is a follow-on option.

In patients with severe asthma who fail to achieve symptom control, maintenance therapy with a systemic oral CS may be indicated; however, in view of the side-effect profile of oral CS, the clinician should always aim to titrate to the lowest possible daily (or every other day) dose that maintains asthma control.

Anti-IgE therapy with omalizumab may be tried in patients with severe allergic asthma, especially those who are CS-dependent and continue to remain uncontrolled. However, this treatment is only suitable for highly selected patients.

Anti-eosinophil biologic therapies may be considered for patients with uncontrolled severe asthma with increased blood eosinophils; benralizumab is given every 8 weeks, whereas mepolizumab and reslizumab are given by monthly injection. For asthmatics who have severe asthma with increased FeNO, dupilumab is preferred, especially in patients with concomitant nasal polyposis, rhinosinusitis, and atopic dermatitis. Allergen-specific immunotherapy may be considered in this group; however, the risk of severe events, including death, is highest in patients with severe asthma. Biologic therapy is also now indicated in a small proportion of patients.

■ Step-Down Treatment

Once symptoms of asthma are stable and the patient demonstrates stable peak flow readings, the clinician should slowly decrease therapy to find the optimal dose to control symptoms. Indeed, asthma severity may fluctuate and improve with time, owing to improved disease management, changes in environmental exposure, or the natural history of the disease. Most asthma guidelines recommend a step-down approach once patients are controlled.[1]

Overtreatment of patients, particularly with ICS, can cause significant morbidity and adverse effects, especially in moderate to severe asthmatics. Such treatment may also be unnecessarily costly. Unfortunately, in such patients there is a tendency to maintain a static treatment regimen, even after symptoms are controlled and clinical stability achieved. Studies have now supported the notion that stable asthmatic patients on high-dose ICS may be overtreated, and that reductions in the inhaled dose can be achieved without significant increases in asthma exacerbations, physician visits, or recourse to oral CS use.[102] Indeed, recent studies show that an efficient inhaler device may achieve a successful step-down without worsening symptoms, disease exacerbations, or hospitalizations.[103]

A gradual reduction in medications, starting with the treatment with the greatest toxicity, should be attempted once stability is achieved and sustained for several months. Symptoms should be monitored on a long-term basis using both objective lung function and subjective symptom measures. Most patients should be maintained on an ICS, and this treatment should not be stopped since it provides anti-inflammatory protection. For asthmatic patients who needed admission to hospital or ventilatory support, a longer period of stability on maintenance therapy may be justified before consideration of a step-down treatment approach.

MANAGEMENT OF REFRACTORY ASTHMA

Most asthmatic patients are controlled with appropriate stepwise therapy, but approximately 5% are difficult to control, do not remain symptom-free despite maximal inhaled therapy, and may require maintenance treatment with oral CS. In this group of patients, a thorough investigation of factors aggravating or contributing to poor asthma control should be undertaken. It is important to check adherence with medication and inhaler technique, particularly if the patient's disease is unstable, despite the maximal recommended dose of therapy. Nonadherence with medication remains an important factor for the poor control of asthma and may be particularly manifest with ICS, as patients may be concerned about adverse effects or describe lack of immediate clinical benefit from this treatment.[87]

Monitoring adherence to ICS therapy in the clinic is difficult, as there are no useful plasma measurements that can be made. However, in contrast, measurement of plasma cortisol suppression and absolute plasma drug concentrations may be useful in monitoring adherence to oral CS. Evidence suggests nonadherence may be more common in those with psychosocial problems or depression; these conditions should be actively sought and addressed during the clinical assessment.

A detailed review of factors, such as exposure to environmental allergens, unidentified occupational agents, or drugs that worsen asthma control, including aspirin or β-blockers, also should be undertaken.

Asthma may coexist with a number of disorders that can affect lung function, and the successful management of asthma often requires treatment of these associated conditions that are thought to aggravate asthmatic symptoms. Rhinosinusitis and gastroesophageal reflux disease are the most common of the disorders associated with poorly controlled asthma. The relationship between rhinosinusitis and asthma is well established as described in the "united airway disease hypothesis," according to which treating the inflammation of allergic rhinitis in the upper airways translates into improved asthma control.[104,105]

It has also been postulated that poor asthma control may arise as a result of the inability of current inhaler devices to target drug therapy to ongoing inflammation in peripheral lung regions. Conceivably, treatment of this lung compartment with targeted anti-inflammatory therapy may result in improved symptoms.[96] In spite of the lack of data from meta-analyses that fail to show a consistent effect of antireflux therapy on asthma symptoms and lung function, many clinicians assess and treat the possibility that gastroesophageal reflux disease may be aggravating asthma.[106]

As discussed earlier, patients with vocal cord dysfunction may present with wheeze and stridor and the need for an escalation in asthma therapy. Vocal cord dysfunction can be assessed using nasoendoscopy to observe abnormalities in the movement of the vocal cords; if the diagnosis is confirmed, patients should be weaned off CS. Speech therapy intervention may be helpful. Bronchoscopy or MDCT to exclude tracheobronchomalacia may be considered. A reconsideration of the potential differential diagnoses should be explored in the refractory asthmatic patient (Table 45-3).

Patients who require high doses of oral CS to maintain asthma control are referred to as "CS-dependent" asthmatics. In contrast, patients with complete "CS-resistant" asthma show a failure to respond to high-dose oral CS therapy. However, this is very uncommon, affecting less than 1 in 1000 patients. Several molecular mechanisms have been implicated in CS resistance and the impaired anti-inflammatory action, leading to the identification of new drug targets for future therapies.[107]

Evidence has shown that in asthmatic patients who smoke (approximately 20% of the population), smoking itself hinders the anti-inflammatory action of CS, leading to relative CS resistance and the need for higher drug doses to achieve asthma control. It is recognized that compared with nonsmoking asthmatics, smoking asthmatics have a faster decline in lung function, more severe asthma, more frequent hospital admissions, and a higher risk of death. Smoking cessation should be strongly pursued in this group, as this intervention has been shown to reduce CS resistance and improve lung function.

Some asthmatic patients have unstable disease, characterized by rapid variations in lung function that may lead to recurrent and severe attacks of asthma, despite appropriate treatment.[108] These patients may be divided into two categories: (1) type I brittle asthma, characterized by a sustained pattern of chaotic peak flow variability on a daily basis; and (2) type II brittle asthma, in which asthma symptoms and lung function are well controlled, but where abrupt and unpredictable falls in peak flow may be catastrophic and result in sudden death. These patients are difficult to treat, as they do not usually respond to maximal high-dose CS therapy and may rely on subcutaneous epinephrine injections. Assessment of treatment adherence and education on allergen avoidance are particularly important in these patients, who should wear an identification bracelet noting their condition. The importance of carrying a portable epinephrine autoinjector at all times and being taught to self-administer this treatment should be a central part of their management.

ASTHMA EDUCATION AND MONITORING

Asthma education and training are important, as patients need to understand the disease, its management, proper use of inhalers, adverse effects of treatment, and, importantly, timing of use of reliever and controller treatments. Education may improve adherence to treatment recommendations and engage the patient in self-management strategies, particularly in terms of symptom recognition, identification and avoidance of asthma triggers, objective measurement of deterioration in asthma control, and treatment of exacerbations of asthma in their earliest stages by stepping up therapy. Educating the patient in the self-administration of oral CS and access to healthcare advice are also important elements in a management program, which are designed to reduce emergency hospitalizations and patient morbidity.

Studies have shown that written personal patient action plans result in better asthma control, reduced emergency department visits and hospitalizations, and decreased morbidity, in both adults and children. Written plans are particularly useful and recommended in patients with unstable disease who have frequent exacerbations. The additional provision of a program of educational sessions (one-to-one or in small groups) with a knowledgeable healthcare professional has been shown to be more effective than provision of written materials alone. Like drug therapy, the educational program and the method and frequency of reinforcement should be tailored to the patient's individual needs. Patients should be reassured that with proper treatment, symptoms and occasional exacerbations can be minimized and, in most cases, a normal lifestyle and life expectancy can be anticipated.

Home monitoring of asthma symptoms and control is an important aspect of self-management programs. PEF measurements allow patients to be monitored on a long-term basis using simple, handheld, compact portable devices. Asthma treatment guidelines recommend patients use PEF measurements not only to monitor the course of the disease, but also to dictate self-administered treatment regimens.[1] Indeed, studies show improvements in measures of asthma control when peak flow measurements are used by patients (in relation to their personal best peak flow) to adjust medication usage.

However, despite the advantages of written plans, as discussed above, a study by the U.S. Centers for Disease Control and Prevention (CDC) analyzing data from adults and children between 2001 and 2009 in a national health interview survey showed that only one-third of patients with asthma reported being given a written asthma action plan. Furthermore, just over two-thirds of patients had been taught the appropriate response to symptoms of an asthma attack.[109]

It should be recognized that not all patients are capable of comprehending and executing complicated treatment plans. In addition, peak flow–guided self-management may lead to overtreatment with medication and the potential for increased morbidity due to adverse effects. Similarly, patients with severe asthma for whom self-management plans are more readily recommended may tend to use more oral CS, even when it may be unclear whether increased use is appropriate or medically warranted (although the increase in medication may be initially viewed as a potential benefit of peak flow monitoring). Action plans should be written using clear, simple language and should be individualized based on patients' understanding of their asthma, its severity, and their demonstrated ability to comply with instructions. The use of digital technology to help monitor inhaler use, test lung physiology remotely, and link with home and work environmental data may help predict exacerbations and alert patients to worsening asthma control.[110,111] Preliminary studies show that digital systems improve asthma control and quality of life, including a reduction in severe disease exacerbations. However, longer-term studies are needed to show a health economic impact.[112]

MANAGEMENT OF ACUTE SEVERE ASTHMA

Asthma is characterized by exacerbations of disease, which can lead to substantial morbidity, occasional mortality, and considerable medical and economic costs. Patients with asthma fear disease exacerbations, as they can be life-threatening; exacerbation-prone patients seem to be at increased risk for attacks of near-fatal asthma. Analysis of asthma mortality data has showed that patients experience worsening symptoms and deterioration in asthma control over a period of several hours to several days before the event.[113] Indeed, life-threatening episodes may develop in any asthmatic patient, particularly those patients with severe and poorly controlled disease, who frequently access the emergency room, or who are hospitalized; all are recognized to be at high risk of life-threatening events. The importance of educating all patients with asthma should not be underestimated, and healthcare professionals should identify and closely monitor such at-risk patients.

Clinical Features

Patients with a moderate exacerbation of their disease notice a deterioration in their asthma control by an increase in daytime and nocturnal symptoms of cough, chest tightness, wheezing, and dyspnea; these symptoms do not respond to the patient's usual maintenance therapy and require more reliever drug. A history of prodromal symptoms may be elicited that precedes an asthma attack, such as itching under the chin, discomfort between the scapulae, or inexplicable fear (impending doom). A fall in home peak flow recordings also signifies a worsening of asthma. The GINA guidelines classify exacerbations based on the peak flow into mild (PEF >80% predicted), moderate (PEF between 60% and 80% predicted), and acute severe (PEF <60% predicted).[1]

Patients may become so breathless in acute severe exacerbations that they become exhausted, unable to talk freely in complete sentences, and show life-threatening features of confusion, agitation, and cyanosis. Clinical examination usually shows an increased respiratory rate, chest hyperinflation, and tachycardia. In acute severe asthma, pulsus paradoxus (accentuated decrease in systolic blood pressure of >10 mm Hg during inspiration), may be present. Life-threatening signs include a silent chest, bradycardia, and hypotension. Evaluation shows a marked fall in PEF and spirometric values; oxygen saturation on room air may be reduced, and arterial blood gases may reveal a low Pa_{O_2}. Initially, Pa_{CO_2} is low due to hyperventilation. In life-threatening situations, PEF is <30% predicted; oxygen saturation (Sa_{O_2}) measured by pulse oximetry is <92%; and arterial blood gases on room air reveal a Pa_{O_2} <60 mm Hg (8 kPa). A rising Pa_{CO_2} indicates impending respiratory failure and requires immediate monitoring and therapy. A chest radiograph is not routinely recommended in the absence of a suspected pneumothorax, pulmonary consolidation, failure to respond to treatment satisfactorily, or a requirement for mechanical ventilation.

Pharmacologic Treatment

The cornerstone of therapy for worsening asthma control requires the escalation of both ICS and quick-relief inhaled β_2-agonists.[1] Exacerbations of asthma should never be treated by escalating bronchodilators alone. Asthma fatalities usually result when patients fail to promptly seek medical attention. Studies have shown patients dying from asthma commonly self-medicate with escalating doses of reliever bronchodilator medication in the days preceding an asthma attack. A short course of oral CS therapy for at least several days may be needed to control and prevent a mild to moderate exacerbation; tapering of the dose should be undertaken with close outpatient follow-up. Very mild or subacute exacerbations with mild persistent disease may be managed in some cases by escalating the dose of ICS in cases in which patients are taking low-dose CS. In less severe exacerbations, patients who promptly respond to treatment in the emergency department may be discharged, but close outpatient follow-up is essential.

In patients with an acute severe exacerbation presenting to the emergency department, oxygen at high concentrations and high flows should be given continuously by face mask to achieve oxygen saturations (Sp_{O_2}) between 94% and 98%. Hypoxemia is to be avoided at all costs, as patients die from hypoxemia in acute asthma. Oxygen therapy is critical to prevent death in severe acute asthma, so continuous monitoring of oxygen saturation is needed until there is a meaningful response to treatment.

High doses of inhaled SABA, given either by nebulizer (oxygen-driven) or via a pMDI with a spacer, should be the first-line agents in acute asthma and should be administered as early as possible. While generally well tolerated, nebulized bronchodilators occasionally cause arrhythmias; continuous electrocardiogram monitoring is required. In those patients in whom inhaled therapy cannot be used reliably, or in severely ill patients with impending respiratory failure, intravenous β_2-agonists may be given. In patients not responding to treatment, a nebulized anticholinergic (e.g., ipratropium bromide) may be added to provide additional bronchodilation. Systemic CS should be given in adequate doses in all cases of acute severe asthma for at least 5 days or until recovery; the CS should be tapered after this response over a 2-week period, particularly in cases of severe asthma exacerbations. In patients unable to take oral CS, intravenous therapy (e.g., hydrocortisone) should be administered in the emergency department.

A single dose of intravenous magnesium sulfate for patients has been shown to be effective when added to inhaled β_2-agonists. It is relatively well tolerated and can be considered in patients with acute severe asthma who have not had an initial good response to inhaled bronchodilator therapy or in those with life-threatening features.

Patients should be referred to the intensive care unit for intubation and mechanical ventilation if they have acute severe or life-threatening asthma that fails to respond to therapy, as indicated by a deteriorating PEF, worsening hypoxemia, a normal or rising Pa_{CO_2}, poor respiratory effort, or exhaustion or confusion. Intravenous aminophylline may be used, but the risks of toxicity are much greater than for inhaled β_2-adrenergic agonists. Sedatives should never be given, as they may depress ventilation. Antibiotics should not be routinely administered in the absence of clinical or radiologic signs of pneumonia.

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CHAPTER 46

Allergic Bronchopulmonary Aspergillosis (Mycosis) and Severe Asthma with Fungal Sensitivity

Geoffrey L. Chupp

INTRODUCTION

Allergic bronchopulmonary aspergillosis (ABPA) is an idiopathic inflammatory disease of the lung, characterized by an allergic inflammatory response to colonization of the airways by *Aspergillus fumigatus* or other fungi. The entity was first described in 1952 by Hinson et al., and then again in 1967, when Scadding recognized an association between the disease and proximal bronchiectasis in areas previously affected by infiltrates (predominantly in the upper lobes).[1,2] The first adult case of ABPA was reported in the United States in 1968.[3] Although most cases entail hypersensitivity to *Aspergillus* spp. (i.e., *A. fumigatus* or *niger*), the finding of a virtually identical clinical syndrome associated with immune sensitivity to *Candida albicans* (most commonly), *Helminthosporium*, *Alternaria*, *Curvularia lunata*, *Drechslera hawaiiensis*, *Stemphylium languinosum*, *Saccharomyces cerevisiae*, or *Pseudallescheria boydii* has led some to use the term *allergic bronchopulmonary mycosis* to describe the syndrome.[4] However, since the predominant causative organism is *A. fumigatus* (and the commercially available laboratory testing is for this organism and *A. niger*), ABPA is primarily designated as the diagnosis. In addition, a recently recognized entity appears to be on the continuum between fungal allergy, at one end, and ABPA at the other: severe asthma with fungal sensitivity (SAFS).[5]

The precise prevalence of ABPA is unknown, in part due to variability in diagnostic criteria used in various studies, the lack of distinction between ABPA and mold-sensitive asthma, and delays in the diagnosis of patients with long-standing disease; however, it is clear that ABPA is a relatively common entity. Estimates are that true ABPA complicates approximately 7% to 14% of cases of chronic steroid-dependent asthma and approximately 7% to 15% of cases of cystic fibrosis (CF). Therefore, it is commonly encountered by pulmonologists and allergists.[6,7]

Most cases of ABPA are recognized in the third to fifth decade of life, but the disease can also present during childhood. In some patients, it is likely that ABPA starts early in life and continues, unrecognized, until adulthood. Interestingly, familial cases have been reported, suggesting that genetic factors may underlie the development of ABPA.[8,9] The spectrum of disease is broad, which can complicate the diagnosis and initiation of corticosteroid-sparing therapy. Patients may be asymptomatic, have mild to moderate asthma, or have severe and debilitating disease that leads to severe bronchiectasis, mucoid *Pseudomonas* colonization, and the need for lung transplantation. However, if recognized early and managed aggressively, ABPA is treatable, it may enter into remission, and progressive lung damage can be avoided.

For the purposes of this discussion, the focus will be on ABPA. However, clinicians should be cognizant that diagnostic testing for other fungi should be pursued when organisms other than *Aspergillus* spp. are suspected. In addition, in patients that don't quite meet criteria of ABPA, a diagnosis of SAFS should be considered as it will affect clinical management.

PATHOGENESIS

Although the pathogenesis of ABPA is poorly understood, it is believed to be the result of an exaggerated immunologic reaction to chronic airway colonization by *Aspergillus* (or other relevant fungal) species.[10] *Aspergillus* spp. are globally ubiquitous, thermotolerant fungi that reside in decaying organic matter and colonize most domestic environments, including carpets and air duct systems.

In humans, airborne *Aspergillus* spores or conidia that are inhaled are immunologically inert. In normal individuals they are cleared by innate immune system mechanisms that maintain airway homeostasis managed by neutrophils, macrophages, and dendritic cells. The result is immunologic tolerance to the presence of the spores. However, in susceptible individuals, conidia colonize airways and germinate into somatic hyphae, stimulating a chronic allergic inflammatory response that drives IgE production and eosinophilic inflammation. This results in tissue injury and the clinical features of ABPA.[7] In contrast to a true infection in which fungal hyphae invade the lung parenchyma, colonization of the airways with germinating fungal spores represents an abnormal state that remains within the airway and promotes an exaggerated Th2 inflammatory response. While details of the mechanisms that drive this process remain poorly understood, it appears that susceptibility to *Aspergillus* colonization and development of clinical disease depend on host factors that include genetic risk, T-cell responsiveness to *Aspergillus* antigens, the magnitude of tissue response to *Aspergillus*, and the level of environmental exposure to this ubiquitous fungus.

Investigations into the genetic risk factors that are associated with ABPA have identified several candidate genes. This suggests that the pathogenesis of ABPA is dependent on both host and environmental factors.[11] Best characterized is the association between gene mutations in the CF transmembrane conductance regulator (CFTR) and the pathogenesis of ABPA.[12,13] CFTR mutations are more common among patients with ABPA compared with the general population or with individuals with severe asthma without sensitivity to *A. fumigatus*. Another genetic link to ABPA is that Th2-type T-cell reactivity to selected *Aspergillus* antigens is determined by the presence of MHC class II DR2 or DR5 alleles, which may predispose patients to the disease, whereas the MHC DQ2 allele may be protective.[14,15] In addition, investigators have determined that there is an increased prevalence of polymorphisms in the promoter region of the pathogen-associated molecular pattern receptor Toll-like receptor 9 (TLR9) in individuals with ABPA compared with controls or patients with SAFS.[16] We recently determined that children with severe asthma and ABPA are more likely to carry the chitotriosidase 1 (CHIT1) exon 10 mutation.[17,18] Individuals with the exon 10 mutation have lower levels of, or lack, chitinase activity and are unable to degrade chitin, a structural polysaccharide in the cell wall of lower life forms such as *A. fumigatus*.[19–21]

At the microscopic level, ABPA is characterized by an intense eosinophilic and mononuclear cell inflammatory response, leading to areas of parenchymal scarring, airway remodeling, and bronchiectasis.[22,23] Immunologic studies demonstrate the presence of a type I hypersensitivity reaction, with elevated serum levels of total IgE and *A. fumigatus*–specific IgE in individuals with ABPA (Fig. 46-1). In addition, patients have evidence of an exaggerated type III hypersensitivity reaction, indicated by the presence of *A. fumigatus*–specific IgG antibodies (classically called "precipitins" or precipitating antibodies) and circulating immune complexes during

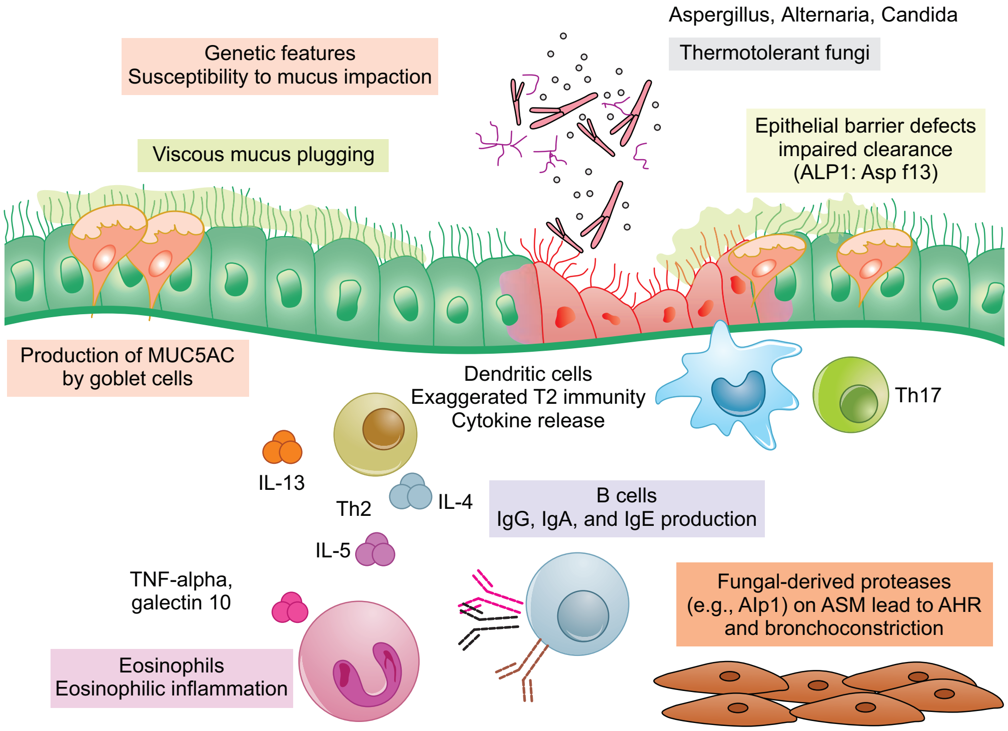

Figure 46-1 Inflammatory response ABPA. In susceptible individuals, conidia germinate into somatic hyphae. These hyphae then stimulate a chronic allergic inflammatory response that drives Th2 and Th17 with subsequent IgE production and neutrophilic and eosinophilic inflammation. This sequence of events eventually leads to tissue injury and bronchiectasis. *(Reproduced with permission from Wardlaw AJ, Rick EM, Pur Ozyigit L, et al. New Perspectives in the Diagnosis and Management of Allergic Fungal Airway Disease. J Asthma Allergy. 2021;14:557–573.)*

disease exacerbations. A type IV cell-mediated immune reaction also may be at work, based on the finding of dual (immediate and delayed) cutaneous reactions and in vitro lymphocyte transformation to *A. fumigatus* antigen stimulation in some patients.[24,25]

A substantial amount of research has been done on the immune response in ABPA, demonstrating that several cell types and pathways are involved in the pathogenesis of this destructive variant of asthma.[19,20] A pathogenetic role for helper T lymphocytes is suggested by a number of findings, including the presence of increased numbers of airway Th2 cells and elevated levels of soluble interleukin 2 (Il-2) receptors (suggesting T-cell activation) in the circulation of persons with active ABPA;[26] the derivation of *A. fumigatus*–specific T-cell clones with T helper 2 (Th2) patterns of cytokine production from the blood of patients with ABPA;[27,28] positive correlations between activated T-cell number, levels of the T cell–derived cytokines IL-4 and IL-5, and the elevated numbers of airway eosinophils in the disease; the critical role IL-5 plays in murine models of ABPA;[29–36] and increased reactivity of Th2 cells to *A. fumigatus* antigens among patients with ABPA as compared with patients with asthma and skin reactivity to *Aspergillus*.

In addition to lymphocytes, eosinophils and basophils may contribute to local airway injury; neutrophils also likely play a role in airway inflammation and tissue damage in ABPA. This is evidenced by the fact that sputum IL-8 levels correlate with sputum neutrophilia, matrix metalloproteinase levels, and FEV_1 among patients with ABPA.[37,38]

It is also clear that the fungus itself contributes substantially to the pathogenesis of disease. *A. fumigatus*–derived proteases contribute to epithelial cell injury and protective barrier disruption, triggering inflammation by allowing increased penetration of fungal antigens into the airway wall, which leads to immune hypersensitivity.[39] *Aspergillus*-derived proteases may also stimulate proinflammatory cytokines, such as IL-8, and release of growth factors; proteases also cause tissue damage that leads to bronchiectasis.[38]

A variety of other *Aspergillus*-derived antigens, including cytotoxins and heat shock proteins (demonstrated by their ability to bind IgE and IgG derived from the blood of patients with ABPA), also have been shown to drive both the IgE (hypersensitivity) and IgG immune responses. *A. fumigatus*–derived proteases with antibody-binding capacity also may amplify the inflammatory response. Other *A. fumigatus* antigens, such as Aspf1 (a cytotoxic protein), Aspf2 (a fibrinogen–binding protein), Aspf5 (a metalloprotease), Aspf6 (manganese superoxide dismutase), Aspf8 (a ribosomal protein), Aspf13 and Aspf18 (serine proteases), and Aspf3 and Aspf4, also have been implicated in the pathobiology of ABPA. Finally, host response to *Aspergillus fumigatus* antigens includes surfactant proteins (SP) A and D, which may play a protective role against ABPA by interfering with binding between *A. fumigatus* antigens and IgE. Notably, however, SPD levels do not correlate with acute exacerbations of ABPA in humans.[40–42]

CLINICAL FEATURES

Although ABPA typically presents in patients with a history of difficult-to-control asthma, the spectrum of presentation is highly variable and should be considered in any patient with difficult-to-control asthma and hypersensitivity to *A. fumigatus*.[42] Typical presenting complaints are often nonspecific and include dyspnea, wheezing, poor asthma control, cough (sometimes productive of thick, brown mucus plugs), malaise, low-grade fever, and occasionally, hemoptysis. There may be an antecedent history of recurrent asthma exacerbations in conjunction with pneumonias without a culture-identified bacterial source. In addition, atopy with rhinitis, drug allergy, and/or allergic conjunctivitis are common. It is often not until a patient has been repeatedly ill over weeks to months and unresponsive to standard treatments that the diagnosis is considered.[43] As patients with SAFS have the same clinical presentation, differentiation from ABPA is based on interpretation of laboratory testing and radiographic studies.[42]

TABLE 46-1 Criteria for the Diagnosis of ABPA

Seropositive ABPA (ABPA-S)
- History of asthma (usually difficult to control)
- Elevated total serum IgE (usually >1000 IU/mL)
- Immediate skin test reactivity to *Aspergillus fumigatus or* elevated specific serum IgE to *A. fumigatus*
- Presence of serum precipitins (by gel diffusion) or elevated specific serum IgG to *A. fumigatus*

ABPA central bronchiectasis (ABPA-CB)
- Above criteria are positive
- Central bronchiectasis by high-resolution CT scan or chest radiograph

Other supportive clinical findings
- Peripheral blood eosinophilia (may be absent if patient is on oral or inhaled corticosteroids)
- Patchy, fleeting infiltrates (may be absent if patient is on oral corticosteroids)
- Expectoration of mucus plugs or bronchial casts
- Mucoid-impacted bronchi evident on radiographic studies
- Sputum culture positive for *A. fumigatus*

Diagnostic Guidelines

In general, the diagnosis of ABPA is based on appropriate clinical features in combination with supporting radiologic and serologic findings. While there are no specific diagnostic criteria, similar guidelines have been proposed by multiple expert panels to aid clinicians in the diagnosis of ABPA (Table 46-1).[22,44] These guidelines have evolved over time and have been updated by several societies. There is no agreement on clinical criteria that should trigger screening for ABPA, but in most asthma centers, all asthmatics with difficult-to-control asthma are screened by checking for an elevated eosinophil count, total IgE, and specific IgE *A. fumigatus*, *A. Niger*, and *Alternaria* spp.

Using the Patterson criteria, ABPA is classified into two different subtypes: ABPA-seropositive (S) and ABPA-central bronchiectasis (CB). Patients with ABPA-S usually display all of the following diagnostic criteria proposed by Greenberger and Patterson: (1) history of asthma; (2) total IgE >1000 IU/mL; (3) elevated serum anti-*AF* IgE and IgG (twofold higher than *A. fumigatus* allergic asthma controls); (4) positive immediate hypersensitivity skin test to *A. fumigatus*; and/or (5) serum IgG precipitating antibodies against *A. fumigatus*. The last criterion is considered positive when the double gel diffusion, the enzyme-linked immunoassay (ELISA), or the fluorescent enzyme immunoassay (FEIA) is positive for anti-*AF* IgG antibodies.[45] Patients with ABPA-S have normal chest radiographic studies, with no evidence of bronchiectasis. Patients with ABPA-S tend to have fewer symptoms, lower IgE levels, less severe airflow obstruction, and fewer exacerbations than patients with ABPA-CB.[46] In contrast, patients with ABPA-CB are positive for all of the criteria of ABPA-S and have features of advanced disease including bronchiectasis on high-resolution CT scanning or chest x-ray.[47,48] These patients may also expectorate mucus plugs or bronchial casts and are sputum culture positive for *A. fumigatus*. Although IgE levels fluctuate with disease activity, a normal IgE level in a symptomatic, untreated patient with asthma virtually excludes the diagnosis.[49] It remains unclear whether ABPA-S is a milder form of the disease (e.g., representing a different host response) or an earlier stage of illness. Identification of *Aspergillus* (or other relevant fungus) in the sputum and dual (immediate and delayed) cutaneous reactions to challenge with *Aspergillus* (by prick test or intradermal) also are common clinical features of ABPA. Rare cases lacking a history of asthma, but meeting the other major diagnostic criteria, have been reported.[43]

Severe Asthma with Fungal Sensitivity

The broad spectrum of clinical, laboratory, and radiographic abnormalities evident in patients with asthma and fungal allergy has led to the description of additional diagnostic categories of allergic fungal disease. The most clinically relevant of these diagnoses is based on studies that demonstrate that antifungal therapies are effective in patients with poorly controlled asthma who have some of the criteria for ABPA-S but do not reach the threshold for diagnosis. These patients have been designated as having SAFS. Whether SAFS is a unique disease or is on the continuum from asthma to ABPA is not known. However, the primary distinction between SAFS and ABPA is that patients with SAFS have a milder allergic reaction and lack the exaggerated IgG response that is typical of patients with ABPA. Patients with SAFS can be difficult to distinguish from patients with ABPA-S, as their clinical features are identical and both lack radiographic evidence of bronchiectasis.

The diagnosis of SAFS is based on the interpretation of *Aspergillus*-specific immunologic studies. The diagnostic criteria for SAFS (Table 46-2) overlap substantially with ABPA-S and include: (1) severe uncontrolled asthma (treatment requirement of >500 μg/d of fluticasone or the equivalent, need for near continuous oral corticosteroids for 6 months or ≥2 oral steroid tapers per year); (2) positive skin prick test or RAST for *A. fumigatus* or other fungi; (3) elevated total serum IgE, but <417 IU/mL or <1000 ng/mL; and (4) absence of IgG against *A. fumigatus* (by ELISA, gel diffusion, or FEIA).

Typically, patients with SAFS have normal radiographic studies and a milder immunologic response similar to patients with milder asthma. Although it remains unclear whether these patients are on the continuum from asthma to ABPA or are at risk of progressing to ABPA, the clinical importance of identifying patients with SAFS is based on several studies showing that antifungal therapies can improve asthma control and reduce oral corticosteroid exposure.[50–52]

The differential diagnosis of ABPA is broad and includes corticosteroid-dependent asthma without ABPA, SAFS, chronic obstructive pulmonary disease (COPD), chronic necrotizing aspergillosis, tuberculosis, parasitic infections, hypersensitivity pneumonitis, Churg–Strauss syndrome, acute eosinophilic pneumonia (including drug-induced pneumonitis), chronic eosinophilic pneumonia, lymphoma, idiopathic hypereosinophilic syndrome, autoimmune disease, crack cocaine use, CF, and other causes of bronchiectasis. The diagnosis of ABPA in patients with mold-sensitive asthma and

TABLE 46-2 Criteria for the Diagnosis of Severe Asthma with Fungal Sensitivity (SAFS)

1. History of poorly controlled asthma despite >500 μg/d of fluticasone or the equivalent, near continuous oral corticosteroids (>50% of the time), or ≥2 oral steroid tapers per year
2. Total serum IgE <1000 IU/mL
3. Positive immediate skin test reactivity to *Aspergillus fumigatus or* elevated specific serum IgE to *A. fumigatus*
4. Absence of serum precipitins (by gel diffusion) and elevated specific serum IgG to *A. fumigatus*
5. No radiographic evidence of bronchiectasis or infiltrates

CF poses a particular diagnostic challenge. In asthmatics, by definition, bronchiectasis is absent and serum precipitating antibodies to *Aspergillus* spp. may be present in up to 25% of patients, making the distinction from ABPA-S difficult.

Persons with mold-sensitive asthma or ABPA may have peripheral blood eosinophilia and/or elevated serum total IgE levels. However, most persons with ABPA have 2- to 20-fold higher serum levels of *Aspergillus*-specific IgE and total IgE than do mold-sensitive asthmatics without ABPA.

A diagnostic conundrum occurs when considering the diagnosis of ABPA in patients with CF, because patients with CF alone may manifest chronic airflow obstruction, recurrent exacerbations with infections and/or bronchoconstriction, underlying bronchiectasis, pulmonary infiltrates, chronic sputum production, *Aspergillus* colonization of the airways, and positive serum precipitins. Distinguishing ABPA in patients with CF is critical because infectious CF exacerbations and ABPA require different treatments. The steroid treatment required for ABPA may be detrimental in the setting of infection, yet antibiotics alone given for infection may be inadequate to control the inflammation associated with ABPA. Among patients with CF, factors associated with the risk of ABPA include adolescent age, atopy, severe lung disease, and colonization with *Pseudomonas aeruginosa*. ABPA should be suspected in patients with CF who develop clinical deterioration, exhibit a greater than fourfold increase in total serum IgE (especially >1000 IU/mL), have immediate cutaneous reactivity to *Aspergillus* or increased *Aspergillus*-specific IgE or IgG, and show a change in baseline chest radiograph. Annual screening of total serum IgE is recommended; if the level rises >500 IU/mL, immediate cutaneous hypersensitivity testing for reactivity to *A. fumigatus* or testing for serum anti–*A. fumigatus* IgE is recommended.[13,53] The titer of IgE reactive against the purified *Aspergillus* allergens Aspf3 and Aspf4 may be useful in distinguishing patients with ABPA and CF or *Aspergillus*-sensitive asthma from patients without ABPA, with rising or high titers being more indicative of ABPA than a bacterial-driven flare of CF.[12]

TABLE 46-3 Clinical Stages of ABPA

Stage I: Acute
- Acute asthma symptoms
- Elevated serum IgE (>1000 IU/mL)
- Peripheral blood eosinophilia (may be absent in patients treated with oral corticosteroids)
- Fleeting infiltrates on chest radiograph (may be absent in patients treated with oral corticosteroids)
- Positive specific IgE, IgG, skin test reactivity, or precipitins to *Aspergillus fumigatus*
- Responds to steroids/antifungal therapy

Stage II: Remission
- Resolution of symptoms
- Resolution of pulmonary infiltrates
- Improvement in eosinophilia and *A. fumigatus* specific blood abnormalities

Stage III: Exacerbation/Recurrence
- Recurrence/worsening of clinical symptoms
- Recurrent pulmonary infiltrates
- Rising IgE levels

Stage IV: Steroid-Dependent Asthma
- Refractory steroid-dependent asthma
- Persistently elevated serum IgE levels
- Persistently elevated *A. fumigatus*–specific blood abnormalities

Stage V: Fibrotic Lung Disease
- Refractory, steroid-dependent asthma
- Fibrotic lung disease (irreversible obstructive and restrictive defects with impaired diffusing capacity)
- Chronic bronchiectasis symptoms (sputum production, frequent infections)

Clinical Staging of ABPA

Five clinical stages of ABPA have been recognized based on clinical, serologic, and radiographic characteristics (Table 46-3). A modified version proposed by the International Society for Human and Animal Mycology (ISHAM) has been developed but has not been widely adopted.[22,54]

Using the classic staging system, stage I, the *acute* stage, is characterized by symptoms of moderate to severe asthma, elevated total IgE (typically >1000 IU/mL), elevated anti–*A. fumigatus* IgE or hypersensitivity skin test to *A. fumigatus*, infiltrates on chest radiograph (with or without proximal bronchiectasis), peripheral blood eosinophilia (frequently >2000/mm^3), and positive precipitating or anti-IgG antibodies to *A. fumigatus* (up to fivefold concentration of serum may be required for detection of the precipitating antibodies).

Patients with stage II ABPA have disease that is in *remission*. This stage is characterized by the resolution of symptoms, radiographic clearing, and decreased of total IgE levels. Remissions are of varying length, may last several months to years, or may be permanent, allowing corticosteroid treatment to be tapered or discontinued.

Patients with stage III ABPA have *recurrent* disease or disease *exacerbations*. This stage of ABPA is common and is characterized by development of new pulmonary infiltrates and, usually, a substantial increase in total IgE. Elevation of IgE may precede clinical or radiologic worsening during this stage; an isolated increase in the severity of bronchospasm does not constitute an exacerbation in the absence of a change in biomarkers. Although a majority of disease exacerbations are associated with a concomitant increase in symptoms, exacerbations may occur in the absence of any increase in symptoms. Indeed, since up to one-third of patients with radiographic infiltrates may be asymptomatic, evolving progressive lung damage may remain unrecognized. Total serum IgE levels, pulmonary function testing, and chest imaging should be monitored intermittently. *Aspergillus*-specific IgA levels may also be elevated in an exacerbation of ABPA. Exacerbations are more likely to occur seasonally or in environments where mold counts are high.

Stage IV ABPA is defined as *steroid-dependent asthma*. In stage IV disease, total IgE, *Aspergillus* precipitins, and *Aspergillus*-specific IgE and IgG typically remain elevated, despite chronic steroid therapy. During this phase, the frequency of exacerbations may increase, become chronic, and be difficult to control.

Stage V is defined as *pulmonary fibrosis*. Stage V patients have chronic symptoms consistent with bronchiectasis that include cough and dyspnea. These patients are often steroid dependent because of persistent bronchospasm and have chronic sputum production, recurrent respiratory infections, and irreversible pulmonary function abnormalities (obstruction, restriction, and/or gas exchange abnormalities), and may have cyanosis or clubbing. The serologic profile of patients with stage IV disease is also evident in stage V. Stage V disease is generally thought to be the consequence of longstanding, often unrecognized disease, but it may occur occasionally among patients with little prior clinical evidence to suggest the diagnosis.

DIAGNOSTIC STUDIES

In addition to the blood abnormalities described earlier in this chapter, analysis of BAL fluid from patients with ABPA often reveals moderate eosinophilia (especially in steroid-naive patients) and increased levels of *Aspergillus*-specific IgE and IgA, but not IgG.[55] On bronchoscopy, mucoid impaction may be evident, and bronchial brushings may reveal mucus that contains aggregates of eosinophils, fungal hyphae, and eosinophil-derived Charcot–Leyden crystals. The finding of hyphae-filled mucus plugs is considered pathognomonic for ABPA. Pulmonary function tests typically reveal an obstructive ventilatory defect (due to bronchospasm or mucus impaction of the bronchi) during stages I, III, IV, and often V, and may not correlate with the duration of ABPA or asthma. Patients with stage V disease typically also have a restrictive ventilatory defect and a reduced DL_{CO}.

The typical radiographic manifestations of ABPA include parenchymal infiltrates and bronchiectasis (Figs. 46-2C and 46-3). The infiltrates are often irregular and transient (1–6 weeks) and have a predilection for the upper lobes, although all lobes may be affected. The bronchiectasis is classically cylindric and proximal (central), occurring within the proximal two-thirds of the lung (Fig. 46-2B). Mucoid impaction in dilated bronchi leads to a characteristic (but nonspecific) radiographic appearance of ABPA termed the "finger in glove" opacity on chest radiograph. "Tramline shadows" (parallel linear shadows extending from the hilum in bronchial distribution and reflecting longitudinal views of inflamed, edematous bronchi), "toothpaste shadows" (representing mucoid impaction of the bronchi), "ring shadows" (dilated bronchi with inflamed bronchial walls seen on end), local consolidation, or lobar collapse also are common features. Involvement of the small airways may lead to centrilobular nodules and branching tree-in-bud opacities (Fig. 46-2C). Less

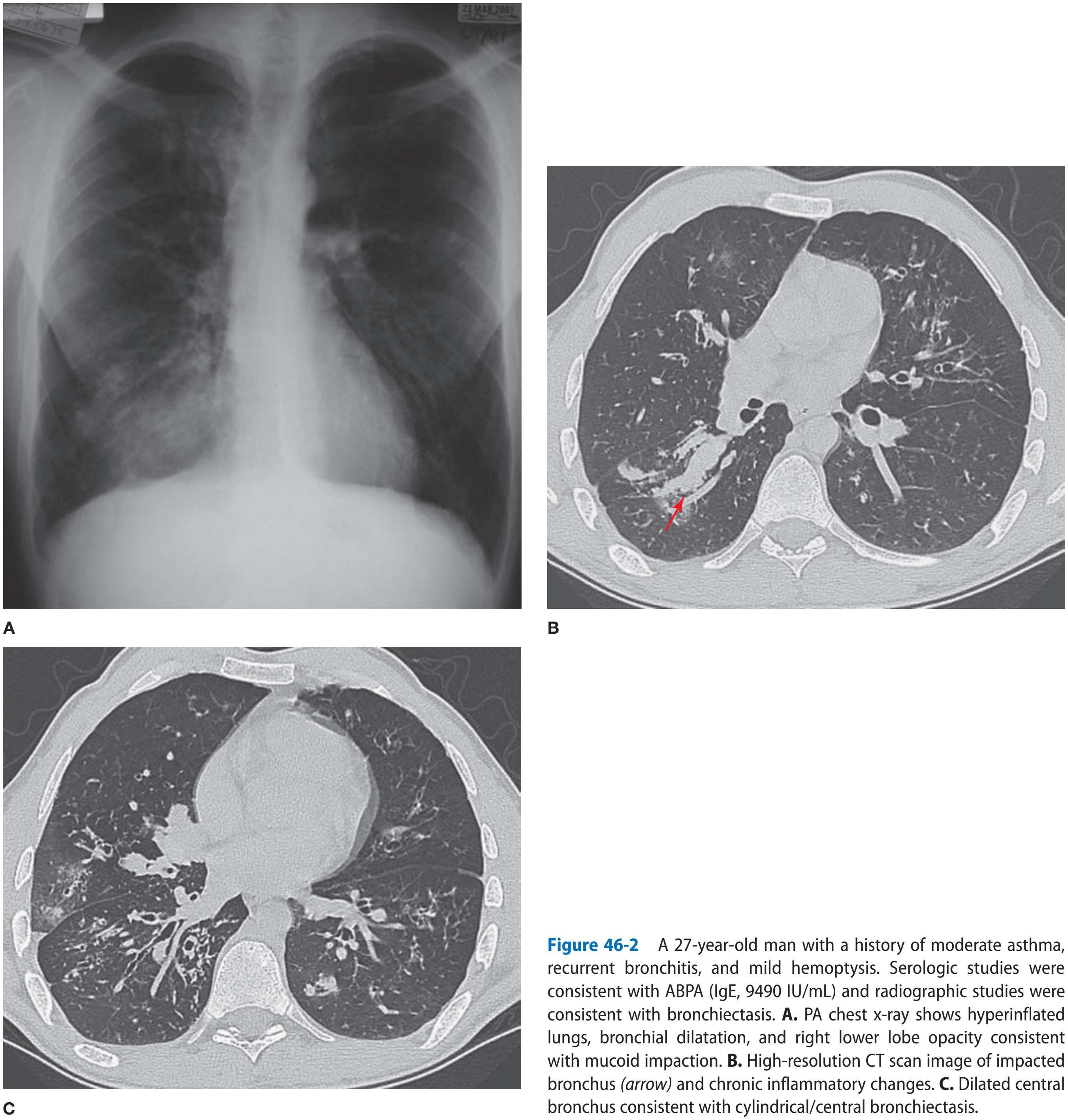

Figure 46-2 A 27-year-old man with a history of moderate asthma, recurrent bronchitis, and mild hemoptysis. Serologic studies were consistent with ABPA (IgE, 9490 IU/mL) and radiographic studies were consistent with bronchiectasis. **A.** PA chest x-ray shows hyperinflated lungs, bronchial dilatation, and right lower lobe opacity consistent with mucoid impaction. **B.** High-resolution CT scan image of impacted bronchus *(arrow)* and chronic inflammatory changes. **C.** Dilated central bronchus consistent with cylindrical/central bronchiectasis.

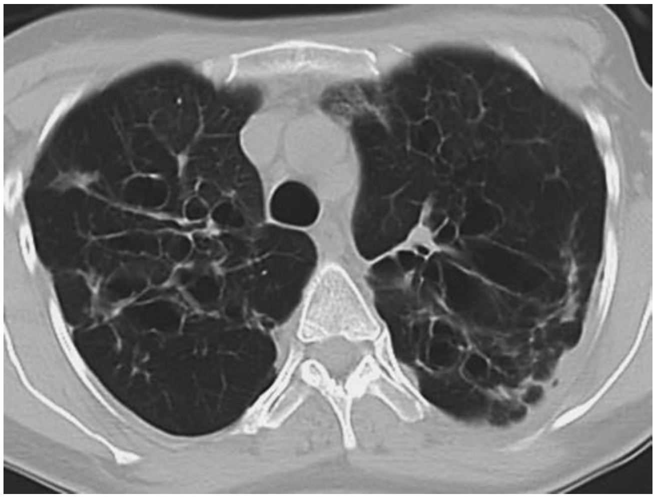

Figure 46-3 Representative CT image of the lungs of a 41-year-old woman who presented with stage V ABPA after a long history of mild asthma (IgE, 1500 IU/mL). Pulmonary function studies demonstrated severe combined obstructive and restrictive defects. CT shows bilateral upper lobe scarring and emphysematous changes.

common radiographic findings include bullous changes, pneumothorax, pleural effusion, cavitating nodular lesions, aspergilloma (Fig. 46-4), and migratory parenchymal opacities, with a ground-glass appearance. High-resolution CT scanning is the most reliable noninvasive means of detecting proximal bronchiectasis. It has largely supplanted chest radiographs to monitor ABPA patients over time and generally correlates with IgE and eosinophil levels.[56]

Surgical lung biopsy is usually not required to establish the diagnosis of ABPA and may not show specific findings, so it is generally not recommended. Histopathologic findings include intense bronchocentric inflammation with prominent eosinophilia, as well as lymphocytes, plasma cells, and monocytes. Bronchi may be filled and/or impacted with copious mucus plugs containing fibrin, Charcot–Leyden crystals, Curschmann spirals, and fungal hyphae. Bronchiectasis of segmental and subsegmental bronchi may be evident. Regions of bronchocentric granulomatosis, eosinophilic pneumonia, eosinophilic microabscesses, lymphocytic or desquamative interstitial pneumonitis, proliferative or obliterative bronchiolitis, lipoid pneumonia, or interstitial fibrosis also may be seen.

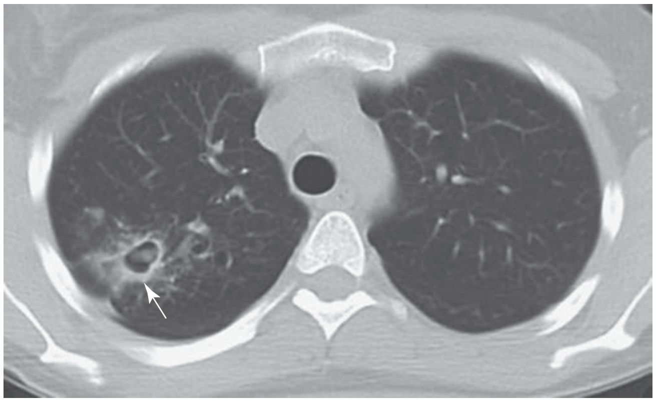

Figure 46-4 A 21-year-old woman with ABPA, who responded to treatment with oral corticosteroids and chronic antifungal therapy and then developed an aspergilloma *(arrow)* and hemoptysis. Amphotericin paste injection failed, and the patient ultimately underwent a right upper lobe lobectomy for chronic hemoptysis.

TREATMENT

The goals of treatment for individuals with ABPA consist of controlling symptoms, preventing exacerbations, and preserving normal lung function.

Systemic corticosteroids are the mainstay of therapy for ABPA. Without treatment, ABPA may cause significant irreversible lung damage due to bronchiectasis and pulmonary fibrosis. Therefore, initiation of appropriate treatment early in the course of disease is essential. Although most data are derived from small uncontrolled trials and definitive proof that corticosteroid therapy prevents the development of central bronchiectasis is lacking, retrospective studies suggest that early therapeutic intervention using corticosteroids reduces progression or irreversible lung damage.

Therapy for stage I or III disease (acute presentation and exacerbations of disease) should include prednisone, 0.5 to 1 mg/kg a day for 2 weeks, followed by 0.5 mg/kg every other day for 6 to 8 weeks with a taper (by 5–10 mg every 2 weeks) over weeks to months. The duration of treatment and pace of taper must be guided by activity and severity of disease with an aim of minimizing cumulative exposure to systemic corticosteroids. A low maintenance dose (e.g., 5.0–7.5 mg/d) may be required to control the disease and prevent recurrence in some patients.

Corticosteroid therapy leads to relief of symptoms, decreases in airflow obstruction, greater than 35% reduction in serum IgE, reductions in peripheral blood eosinophils, and resolution of pulmonary infiltrates. IgE levels should be monitored within a few months of an acute episode or exacerbation and should be followed periodically thereafter since levels may rise, reflecting increasing disease activity prior to an exacerbation in the absence of clinical symptoms. Escalation of steroid therapy should be considered if IgE levels rise more than 100%. Pulmonary function testing should be followed closely as well and imaging should be conducted intermittently if the disease is quiescent.

Although treatment of acute exacerbations is believed to be helpful in preventing fibrotic complications of ABPA, it is not known if early detection and treatment of disease flares has any effect on disease progression. Therefore, high-dose systemic corticosteroid treatment of asymptomatic individuals is not recommended. Patients with CF and ABPA flares may derive symptomatic or functional improvement from steroid treatment. However, patients with CF who are on steroids should be followed closely for the development of invasive or semi-invasive aspergillosis. It is unclear whether development of ABPA alters the course of CF disease progression.

Although not advocated as primary treatment, inhaled corticosteroids are useful for control of bronchospasm and may help minimize the dose of systemic steroid necessary to control symptoms. They can spare the need for systemic steroids during the treatment of ABPA exacerbations and the chronic management of symptoms. Adjuvant treatment with bronchodilators and antibiotics also helps control bronchospasm and secondary respiratory infections.

The development of oral antifungal agents has brought new hope to patients with ABPA.[57,58] Even though the current concept of ABPA is not that of a classic "infection," evidence is mounting to support use of the antifungal agent, itraconazole, in patients with ABPA. The presumed mechanism of action is that these agents minimize the degree of fungal colonization.

In one randomized controlled study, itraconazole (200 mg twice daily for 16 weeks) led to significant reductions in corticosteroid dose, decreased IgE levels, greater resolution of pulmonary infiltrates, and gains in exercise tolerance or pulmonary function.[59] Several clinical studies have demonstrated that treatment with itraconazole also reduces *Aspergillus* antibody titers and eosinophilia compared with placebo.[57]

Itraconazole treatment (200 mg/d or every other day) is generally recommended for patients with ABPA who are steroid dependent, who have frequent relapses, and in whom the cost and risks are thought not to outweigh the potential benefits. Itraconazole has also demonstrated utility in ABPA associated with CF. If itraconazole is used, steady-state blood levels can be checked after 1 to 2 weeks, 4 h after the dose is given, to assess drug absorption.[60]

Since itraconazole interferes with the hepatic metabolism of several medications, including cyclosporine, oral hypoglycemics, tacrolimus, terfenadine, cisapride, and midazolam, particular caution should be exercised with its use among patients taking any of these medications. Physicians must also be mindful of adrenal insufficiency associated with itraconazole treatment among patients with ABPA using inhaled corticosteroids, as itraconazole may cause reduced steroid clearance and/or possible direct suppression of adrenal steroid production. Interval screening for adrenal insufficiency should be considered among such persons. In contrast, the efficacy of itraconazole in ABPA may be less among persons taking agents that raise gastric pH, as this can reduce drug absorption.

Other antifungal agents, including nystatin, amphotericin B, miconazole, clotrimazole, and natamycin, are generally ineffective in controlling ABPA. Ketoconazole may be effective, but its utility is limited by hepatotoxicity. Efficacy of voriconazole has not yet been studied in ABPA, but anecdotal reports from our center and others suggest similar results to itraconazole.[61–64]

More recently, the new biologically engineered antibodies against T2 inflammatory mediators may help to control symptoms and reduce the need for systemic corticosteroids in patients with difficult-to-control ABPA. The first of these biologics directed against IgE, omalizumab, has been used successfully in ABPA but has not been studied in large randomized trials. Given that the recommended dosing of this biologic is based on patient weight and serum IgE level, many patients with ABPA are outside of the dosing range used in asthma. However, multiple case reports and small series indicate that at conventional doses (up to 375 mg subcutaneously every 2 weeks), administration may improve disease activity and spare oral corticosteroid dosing.[65–74] In addition, the biologics developed more recently against IL-4/13 (dupilumab), IL-5 (mepolizumab and reslizumab), and IL-5R (benralizumab) are being used with some anecdotal success in ABPA.[75,76]

In addition to medical therapy, all patients with ABPA-related bronchiectasis should be prescribed standard airway clearance treatments, including hypertonic saline and mucus clearance device (positive expiratory pressure device) and/or percussion vest, depending on the severity of disease. In addition, patients with ABPA should avoid areas and environmental conditions associated with high mold counts, such as decomposing organic materials and moldy indoor environments. HEPA filters may be useful if such exposures are unavoidable, but data are limited.

PROGNOSIS

With appropriate treatment, long-term control of ABPA is feasible, and durable remissions are common. Treatment of stage I disease using corticosteroids typically results in decreased sputum production, improved control of bronchospasm, >35% reduction in total IgE within 8 weeks, clearing of precipitating antibodies, and resolution of radiographic infiltrates. IgE levels typically do not completely normalize, but they generally decrease by approximately one-half of peak levels seen in the acute stage. Progression of stage IV disease to pulmonary fibrosis may be prevented if patients are maintained on low-dose steroids; most patients with stage V disease have a stable course over several years. Persons with an FEV_1 persistently <0.8 L have a worse prognosis.

In addition to severe airflow obstruction and pulmonary fibrosis, long-term complications of ABPA occasionally include the development of aspergilloma (Fig. 46-4), chronic or recurrent lobar atelectasis, allergic *Aspergillus* sinusitis, or *Aspergillus* tissue invasion and semi-invasive *Aspergillosis*. Transplantation has been undertaken successfully among patients with ABPA but should not be considered a cure, as post-transplant recurrence of ABPA has been reported.

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SECTION 9 Other Obstructive Disorders

CHAPTER 47

Upper Airway Obstruction in Adults

Erin DeBiasi
Christine Won
Meir Kryger

INTRODUCTION

The upper airway is conventionally described as being made up of all the structures that conduct air between the carina and the nares and includes the trachea, larynx, pharynx, nasal airway, and oral airway. Upper airway structures may change their physiologic function in response to pressures around them and anatomic structures near them. Thus, physiologically, the segments of the upper airway behave differently when they are subject to pleural pressures (anatomically intrathoracic) or ambient pressures (anatomically extrathoracic). Furthermore, extrathoracic airway function may change with posture, sleep/wake state, and the function and anatomy of tissues surrounding the airway.

The upper airway evolved anatomically in humans to subserve several important functions including swallowing, breathing, and vocalization.[1] The multifunctionality of the upper airway increases the risk of certain diseases (e.g., aspiration and sleep apnea).[2] These functions require that different segments of the airway have differing properties. The trachea receives some support by the tracheal rings, the nasal airway is surrounded by rigid structures, and the oral airway has a rigid bony roof, the hard palate. On the other hand, the pharyngeal airway does not have rigid structures supporting it. It is a collapsible tube whose patency is maintained by muscles whose function is affected by arousal state (sleep/wake, and more specifically during sleep, the stage of sleep), the structures around it, and posture. Thus, the pharyngeal airway is divided anatomically and physiologically into the nasopharynx, retropalatal oropharynx, retroglossal oropharynx, and hypopharynx.

Clinically significant obstruction in adults may occur anywhere within the upper airway. Common etiologies of upper airway obstruction (UAO) include neoplasia, scar formation, skeletal facial malformations, infection, inflammatory disorders, trauma, extrinsic compression related to pathology of adjacent structures, and functional changes related to posture and sleep/wake state. Airway obstruction may be classified as extrinsic, intrinsic, or mixed (Fig. 47-1).

UAO can be acute and life-threatening, or chronic and resulting in significant symptoms, some of which may not even relate to the respiratory system. Initial management of acute UAO focuses on securing the airway and stabilizing the patient. Often the intervention is surgical. Some diseases require bypassing the obstruction using translaryngeal intubation or tracheostomy. Definitive long-term management depends on the underlying etiology and physiology and may include both medical and surgical interventions. The still-evolving fields of imaging and interventional pulmonology offer new diagnostic and management modalities. This chapter provides an overview of acute and chronic UAO in adults and focuses on clinical presentation, assessment, etiology, and management. Obstructive sleep apnea is covered in Chapter 98 of this volume.

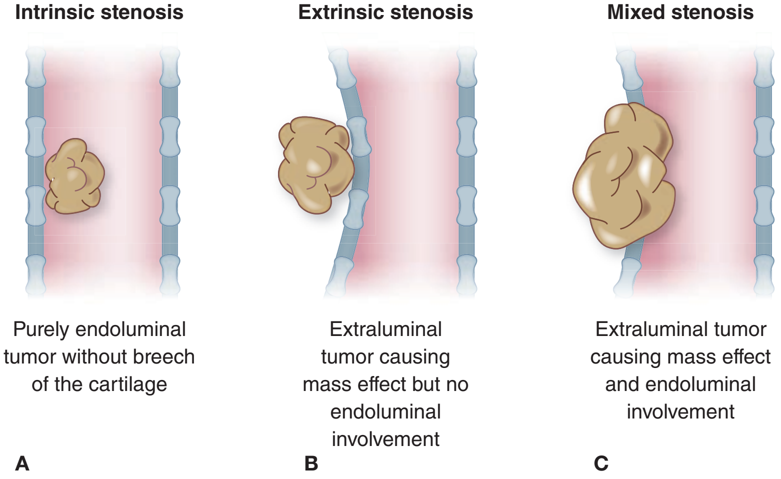
Intrinsic stenosis
Extrinsic stenosis
Mixed stenosis
Purely endoluminal tumor without breech of the cartilage
Extraluminal tumor causing mass effect but no endoluminal involvement
Extraluminal tumor causing mass effect and endoluminal involvement
A
B
C

Figure 47-1 Classification of airway tumor involvement. **A.** Intrinsic stenosis. Purely endoluminal tumor without breech of the cartilage. **B.** Extrinsic stenosis. Extraluminal tumor causing mass effect but no endoluminal involvement. **C.** Mixed stenosis. Extraluminal tumor causing mass effect and endoluminal involvement.

CLINICAL FEATURES

Upper and lower airway obstruction may present with similar symptoms (e.g., shortness of breath, noisy breathing) and physical findings (e.g., wheezing, diminished breath sounds). Asthma and chronic obstructive pulmonary disease, common causes of lower airway obstruction, are often incorrectly assumed to be causing the patient's symptoms.

Significant UAO may be asymptomatic for a prolonged period of time, resulting in delayed presentation and diagnosis, and possibly a catastrophic outcome. When UAO develops or worsens acutely, asphyxia and death may result within minutes to hours. When UAO develops slowly, diagnoses may be delayed or incorrect and, in the case of malignancy in the upper airway, may lead to incurable disease.

Dyspnea and noisy breathing, the most common symptoms of UAO, are often prominent during exercise and may also be intensified or relieved by a change in body position. The patient may indicate that breathing is labored while supine and may experience sleep disordered breathing in the forms of obstructive sleep apnea or upper airway resistance syndrome (Chapter 98). Therefore, daytime somnolence may be a prominent feature of UAO. In severely affected patients, peripheral edema as a result of cor pulmonale may be present as a consequence of chronic hypoxemia and hypercarbia during sleep and wakefulness.

In most cases, significant anatomic obstruction precedes the development of symptoms. By the time dyspnea on exertion occurs, the airway diameter at the site of obstruction is likely to be reduced to about 8 mm. Shortness of breath at rest often develops when the airway diameter is about 5 mm, and stridor is now often present. Although airway radius does play a significant role in symptom development, it is important to note that other factors such as length of stenosis and pressure differential across the stenosis also influence perceived symptoms. Stridor is a loud, musical sound of constant pitch that usually indicates the presence of extrathoracic airway obstruction most often affecting the larynx or upper trachea.

Unlike wheezing, which is a feature of diffuse peripheral airway obstruction and occurs primarily during expiration, stridor usually occurs during inspiration and is loudest in the neck. The sound can usually be appreciated without using a stethoscope. Although one would expect to be able to distinguish stridor from wheezing coming from lower airways, sound recordings from the neck and chest have shown that the sounds from the asthmatic wheeze and stridor have similar frequencies.

Breathing maneuvers that increase inspiratory airflow, such as forced inspiration or voluntary hyperventilation, accentuate the intensity of stridor. Neck flexion may change the loudness of stridor. When the obstructing lesion is fixed, both inspiratory and expiratory stridorous sounds may be heard. At times, the character of a patient's voice may be a clue to the presence of UAO. Hoarseness may be a sign of a laryngeal abnormality. Muffling of the voice may be present when vocal cords are paralyzed.

LABORATORY ASSESSMENT

Just as UAO must be quite advanced before development of symptoms, physiologic abnormalities do not become apparent on lung function testing until severe obstruction (<8 mm or 80% of normal medial tracheal diameter) occurs. The forced expiratory volume in 1 s (FEV$_1$) remains above 90% of control until a 6-mm orifice is created. Therefore, spirometry may not be an effective way to detect upper airway abnormalities. The peak expiratory flow rate (PEFR) and maximal voluntary ventilation (MVV) are more sensitive than the FEV$_1$ in detecting UAO. Of note, a noncritical airway may become so with a lesser degree of obstruction in the context of airway secretions, edema, or bleeding.[9]

The flow–volume loop, which is a recording of maximal inspiratory and expiratory flows at various lung volumes, is an important tool for the diagnosis of UAO. The configuration of the normal flow–volume loop is shown in Fig. 47-2. During a forced expiratory maneuver from total lung capacity (TLC), the maximal flow achieved during the first 25% of the forced vital capacity is dependent on effort—that is, an increase in driving pressure (effort) may result in increased flow. During the remaining 75% of the forced vital capacity maneuver, flow is determined by the mechanical properties of the lungs and is not effort dependent. During this portion of forced exhalation, a linear deceleration of flow is caused by dynamic compression of the intrathoracic airways (Fig. 47-3A). An increase in effort and therefore pleural pressure causes further compression of the intrathoracic airways and a further limitation of airflow. At higher lung volumes, flow may be limited by a UAO. At low lung volumes, flow may not be affected by a UAO, since measurement of flow in this effort-independent portion of the curve represents the function of the peripheral airways. Since the FEV$_1$ reflects a large portion of flow at these lower lung volumes, it is not a sensitive test for UAO. Because the PEFR reflects flow at higher lung volumes, it may be abnormal when the FEV$_1$ is not.

In generating the flow–volume loop, forced inspiratory flow is limited by effort during the entire inspiratory maneuver. Flow increases from residual volume to near the midportion of the curve, where it becomes maximal at the peak inspiratory flow rate. Flow then declines until TLC is reached. The pressure surrounding the extrathoracic portion of the upper airway is atmospheric. The turbulent nonlaminar airflow, which occurs during forced inspiration and causes airway pressure to fall in this portion of the airway, favors slight narrowing of the extrathoracic airway (Fig. 47-3A, B). Peak inspiratory flow, therefore, is less than peak expiratory flow in normal subjects. Because of the dynamic compression of the intrathoracic airways that occurs during exhalation, flow during the middle of inspiration, that is, the forced inspiratory flow at 50% of the forced vital capacity (FIF$_{50\%}$), is usually greater than flow during the middle of forced expiration, that is, the forced expiratory flow at 50% of the forced vital capacity (FEF$_{50\%}$). Typical patterns of the flow–volume loop may be seen, depending on whether the obstruction to flow is "fixed" or "variable," and whether the site of the obstruction is above or below the thoracic outlet or suprasternal notch.

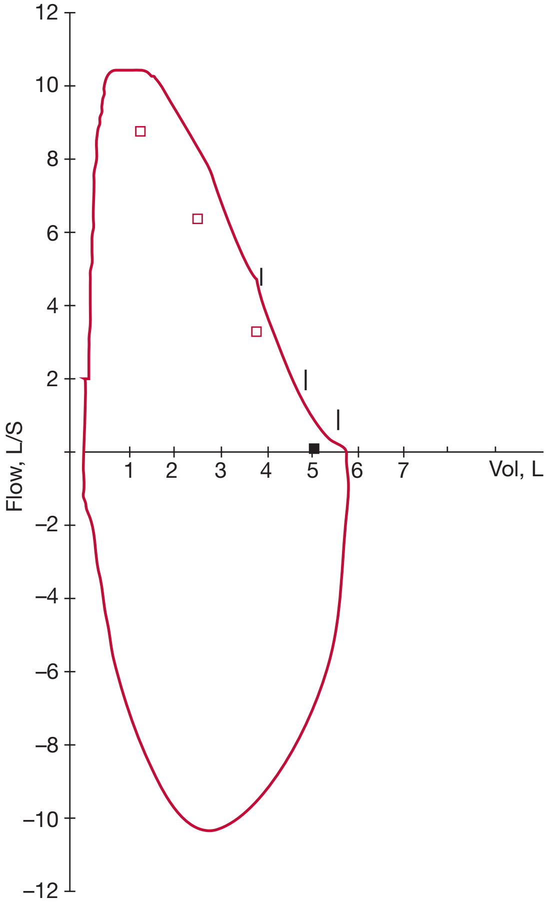

Figure 47-2 Normal flow–volume loop following maximal expiratory *(above)* and inspiratory *(below)* effort. Small vertical lines denote seconds.

Fixed obstructions of the upper airway are those in which the cross-sectional area does not change in response to transmural pressure differences during inspiration or expiration. A fixed obstruction may occur in either the intrathoracic or extrathoracic airways. Irrespective of the site of the obstruction, a fixed lesion results in the flattening of the inspiratory and expiratory phases of the flow–volume loop. A *variable obstruction* is one that responds to transmural pressure changes, eliciting varying degrees of obstruction during the respiratory cycle. Since the stresses on the intrathoracic and extrathoracic airways are different, changes seen in the flow–volume loop vary according to the site of the obstruction.

A number of conditions have been associated with nondistensible narrowing of the upper airway and fixed airway obstruction. Benign strictures and malignancy are common examples. Maximal inspiratory and expiratory flow–volume loops with fixed obstruction show constant flow, represented by a plateau during both inspiration and

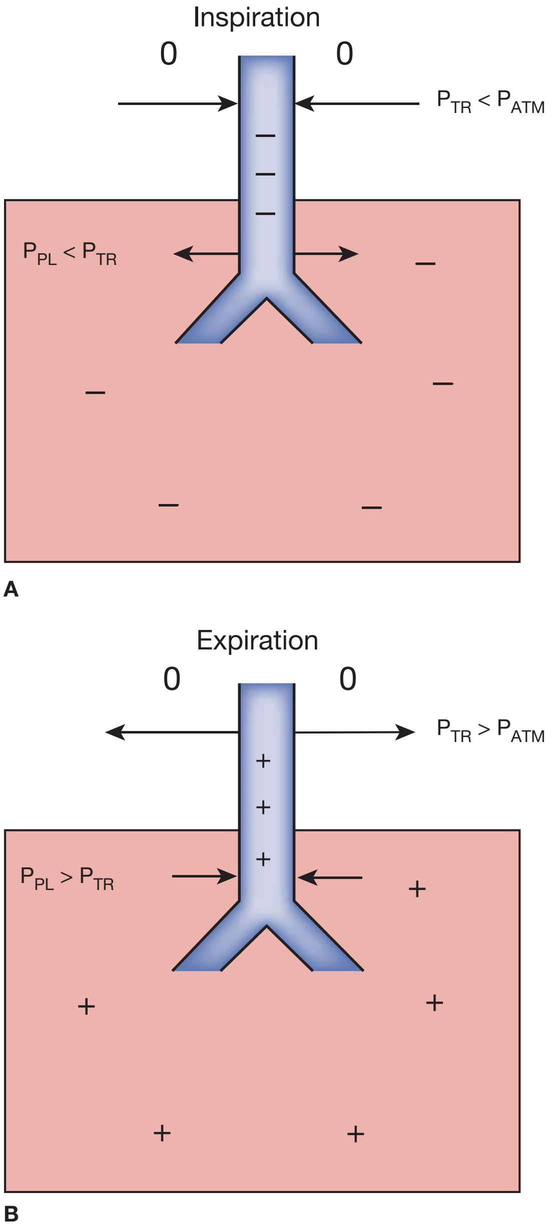

Figure 47-3 Forces acting on intra- and extrathoracic airway walls during inspiration and expiration. 0, atmospheric pressure; +, positive pressure; −, negative pressure. **A.** During inspiration, extrathoracic tracheal pressure (P_{TR}) falls below atmospheric pressure (P_{ATM}), favoring narrowing of the lumen *(arrows)*. Intrapleural pressure (P_{PL}) becomes negative, favoring airway enlargement *(arrows)*. **B.** During expiration, the extrathoracic tracheal pressure (P_{TR}) becomes positive and, therefore, greater than P_{ATM}, favoring enlargement of the lumen *(arrows)*. Intrapleural pressure (P_{PL}) is positive, causing dynamic compression of the intrathoracic trachea *(arrows)*.

expiration (Fig. 47-4A, B). On the expiratory curve, the plateau effect is seen in the effort-dependent portion of the curve near TLC; very little change is noted in the effort-dependent portion near residual volume. Since the inspiratory curve is similar in appearance, the ratio of $FEF_{50\%}$ to $FIF_{50\%}$ is normal (close to 1). The forced inspiratory volume in 1 second (FIV_1) and FEV_1 are nearly the same in fixed UAO.

Unilateral vocal cord paralysis is a common cause of variable extrathoracic obstruction. A variable extrathoracic airway obstruction increases the turbulence of inspiratory flow, and intraluminal pressure falls markedly below atmospheric pressure. This leads to partial collapse of an already narrowed airway and a plateau in the inspiratory flow loop (Fig. 47-5A, B). Expiratory flow is not significantly affected, since the markedly positive pressure in the airway tends to decrease the obstruction. The ratio of $FEF_{50\%}$ to $FIF_{50\%}$ is high (usually >2). Similarly, the FEV_1 is greater than the FIV_1.

A variable obstruction in the intrathoracic airways reverses the situation. A predominant reduction in maximal expiratory flow is associated with a relative preservation of maximal inspiratory flow. This association occurs because intrapleural pressure becomes decidedly positive during forced expiration and causes dynamic compression of the intrathoracic airways. The obstruction caused by an intrathoracic lesion is accentuated, and a plateau in expiratory flow occurs on the flow–volume loop (Fig. 47-6A, B). A plateau of flow suggests that the lesion has caused the airway lumen to reach its minimal size. A flow peak may precede the plateau, suggesting that the obstruction may not affect flow until a certain lung volume is reached. During inspiration, intrapleural pressure is markedly negative; therefore, the obstruction is decreased. The ratio of $FEF_{50\%}$ to $FIF_{50\%}$ is very low and may approach 0.3. Similarly, the FEV_1 is considerably lower than the FIV_1. Although the flow ratios are similar to those seen in patients with COPD and chronic asthma, these disorders are distinguished from UAO by the appearance of the flow–volume loop. Thus, the expiratory curve in patients with COPD and asthma is primarily altered in the effort-independent portion of the curve, leading to a characteristic shape unlike the plateau configuration of a UAO (Fig. 47-7).

When a hospital laboratory or physician's office is not equipped to perform flow–volume loops, results of other tests, such as routine spirometry, may be helpful. If the forced spirogram shows that the PEFR is reduced disproportionately to the reduction in FEV_1, a UAO should be suspected. Other findings that suggest the diagnosis include a ratio of less than 1.0 for the inspiratory flow between 25% and 75% of the inspired vital capacity ($FIF_{25–75\%}$) and a value of less than 1.0 for the expiratory flow between 25% and 75% of the expired vital capacity ($FEF_{25–75\%}$). Another indication is an FEV_1 that is decreased to the same degree as the $FEF_{25–75\%}$. The MVV also may be a useful test, since it measures both inspiratory and expiratory flows. A ratio of MVV to FEV_1 of less than 25% is often found with UAO. Whenever the MVV is reduced in association with a normal FEV_1, a diagnosis of UAO should be considered.

In contrast to the situation in patients with diffuse obstructive disease of the lower airways (e.g., COPD, asthma), the distribution of ventilation in the lungs is normal, and ventilation–perfusion mismatch does not occur. Hypercarbia is not seen unless the degree of obstruction is very severe, although nocturnal hypercarbia may occur while daytime levels of P_{CO_2} are normal. Hypoxemia is also not present except during exercise and with severe airflow limitation, when it may accompany increases in the level of P_{CO_2}. In contrast to asthma and many instances of COPD, the airflow obstruction caused by an upper airway lesion does not resolve following the inhalation of a bronchodilator unless there is also a component of small airway disease that is often the case.

IMAGING

When acute airflow obstruction occurs as a result of an abnormality of the extrathoracic airway, roentgenographic studies of the soft tissues of the upper chest and neck in the emergency setting may be helpful (Fig. 47-8). However, computed tomography (CT) has afforded the most important approach to imaging of the extrathoracic airways (Fig. 47-9). The standard chest roentgenogram is often not helpful in detecting UAO. The trachea is usually well visualized on the posteroanterior (PA) and lateral views in chest

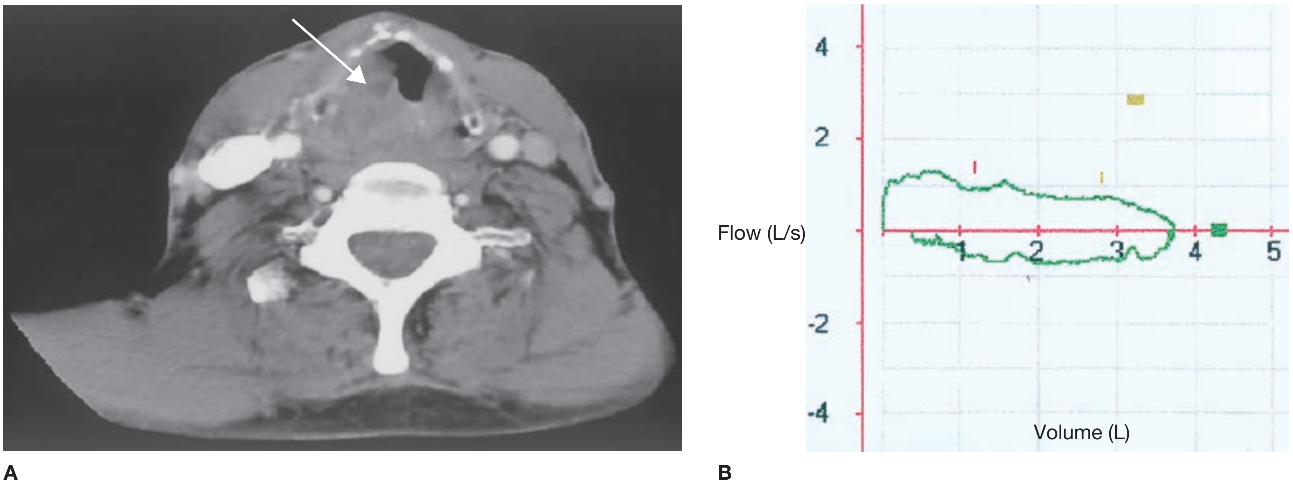

Figure 47-4 **A, B.** Flow–volume loop in fixed upper airway obstruction due to laryngeal abscess in a 56-year-old man who developed persistent wheezing, hoarseness of voice, and intermittent stridor for 3 months after a brief intubation for asthma exacerbation. Computed tomography scan of the neck (**A**) shows a laryngeal abscess with significant impingement on the laryngeal inlet. The flow–volume loop (**B**) demonstrates a plateau of flow during inspiration and expiration; the $FEF_{50\%}/FIF_{50\%}$ ratio is near 1.

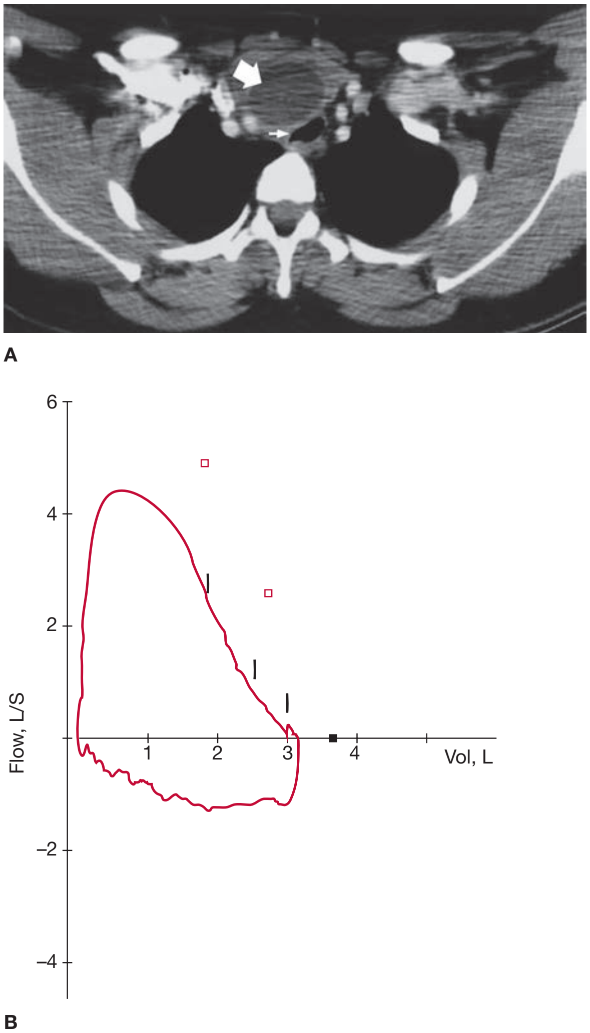

Figure 47-5 Variable extrathoracic obstruction due to thyroid cyst in a 32-year-old woman with dyspnea on exertion. **A.** Computed tomography of the neck shows a 10- × 4-cm cystic mass *(large arrow)* in the thyroid gland compressing the trachea *(small arrow)*. **B.** Flow–volume loop shows inspiratory obstruction. $FEF_{50\%}/FIF_{50\%}$ is very high, and the inspiratory curve is flattened.

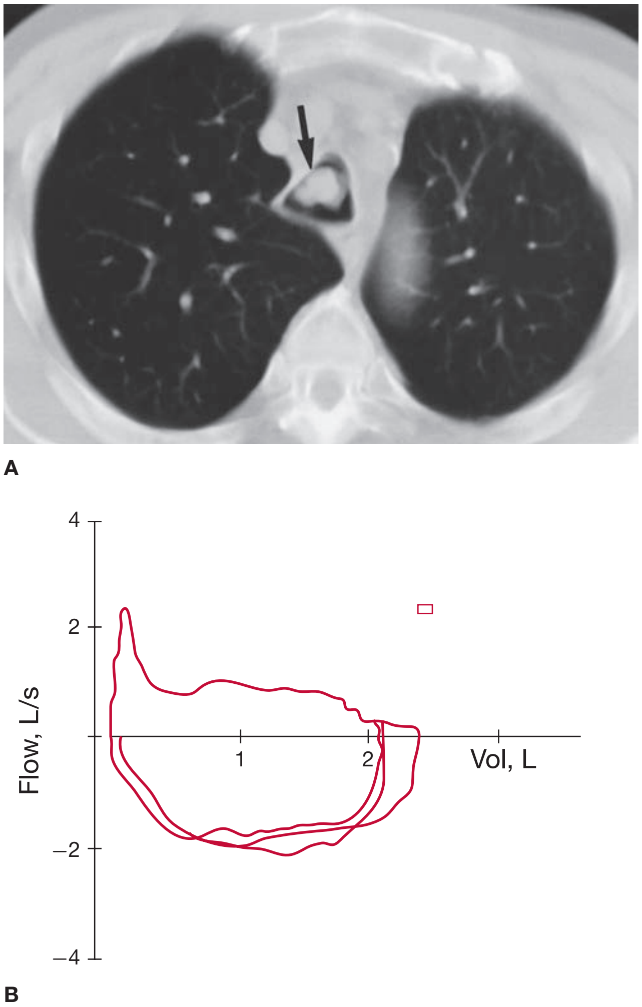

Figure 47-6 Variable intrathoracic obstruction due to squamous cell carcinoma of the trachea. **A.** Computed tomography of the chest shows a tracheal lesion *(arrow)*, which was not readily apparent on plain chest radiograph. **B.** Superimposed flow–volume loops show a plateau of expiratory flow preceded by a peak of flow at higher lung volumes. The forced inspiratory flow is preserved in comparison to expiratory flow, but it is also reduced. $FEF_{50\%}/FIF_{50\%}$ is 0.4.

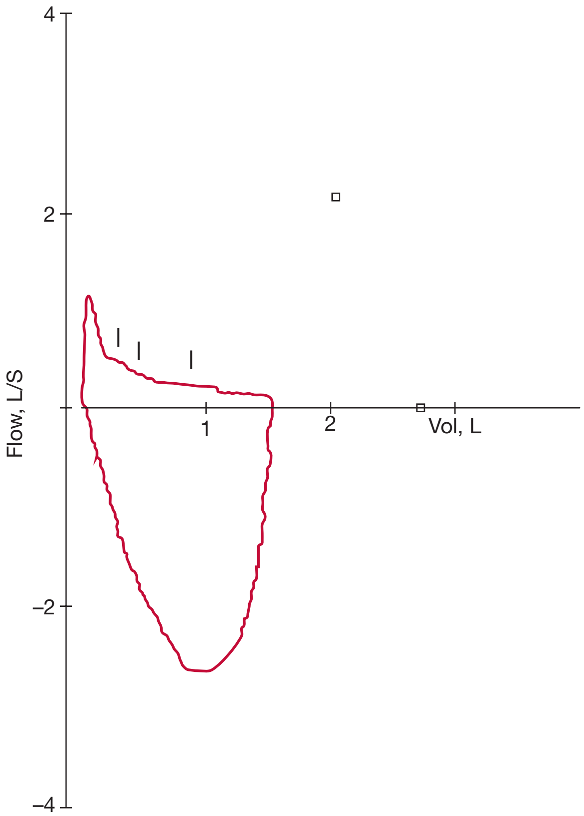

Figure 47-7 Flow–volume loop typical of chronic obstructive lung disease. Very low $FEF_{50\%}/FIF_{50\%}$ and typical curvilinear shape are noted.

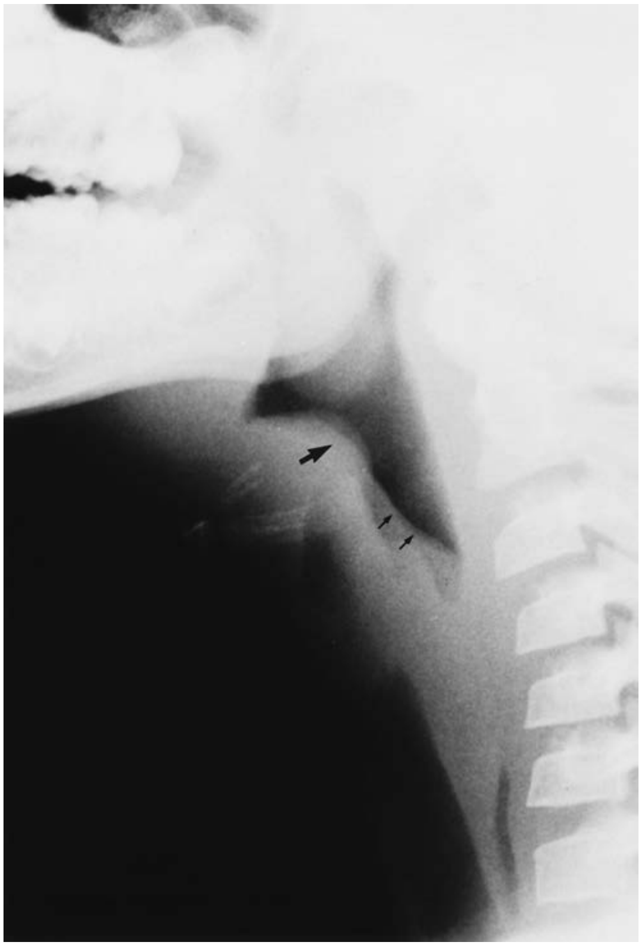

Figure 47-8 Acute epiglottitis. Lateral soft tissue radiograph of the neck of a patient with stridor shows swelling of the epiglottis *(large arrow)* and loss of normal convexity of the edematous aryepiglottic folds *(small arrows)*.

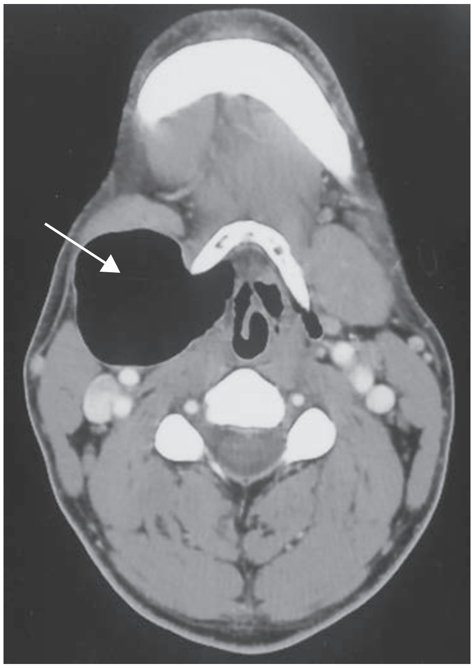

Figure 47-9 Computed tomography scan of the neck demonstrating a large laryngocele compressing the lateral wall of the larynx *(arrow)* causing positional air flow obstruction.

roentgenograms of good quality. It is located in the midline and is moderately deviated at the level of the aortic arch. However, many standard roentgenograms are underpenetrated so that the trachea may become a "blind spot." In one study, only 13 of 53 tracheal tumors were evident to the radiologist on the standard PA roentgenogram. A lateral roentgenogram can provide a less obscured image of a tracheal abnormality, especially when the posterior wall is involved. Thoracic CT studies have become the procedure of choice for imaging the upper airway.

Helical CT (HCT) scanning minimizes artifacts due to respiratory motion and provides imaging of the whole thoracic volume during a single breathhold.[10] The technique represents an improvement over conventional CT scanning in that it allows detection of intraluminal, submucosal, and extraluminal lesions (Figs. 47-10A, B and 47-11). Since the early 1990s, HCT has become the preferred noninvasive modality for evaluation of the central airways. The use of HCT using multidetector technology and thin collimation provides high-resolution images of the entire thorax, improved special resolution, greater speed of image acquisition, and excellent contrast enhancement. HCT techniques using multiplanar and three-dimensional reconstruction can provide virtual images of the thorax that enhance the perception of local and diffuse anatomic lesions of the upper airways (Fig. 47-12). The images may demonstrate the degree of tracheal widening or narrowing, show the location and longitudinal extent of abnormalities, assess tracheal wall thickness, and demonstrate associated extratracheal diseases.

The use of paired inspiratory dynamic and expiratory multislice HCT has proved helpful for the diagnosis of tracheomalacia. Because the maximal degree of collapse in tracheomalacia usually occurs during exhalation rather than at end expiration, dynamic expiratory imaging is preferable to end-expiratory imaging. If complete collapse is not demonstrated during expiration, then

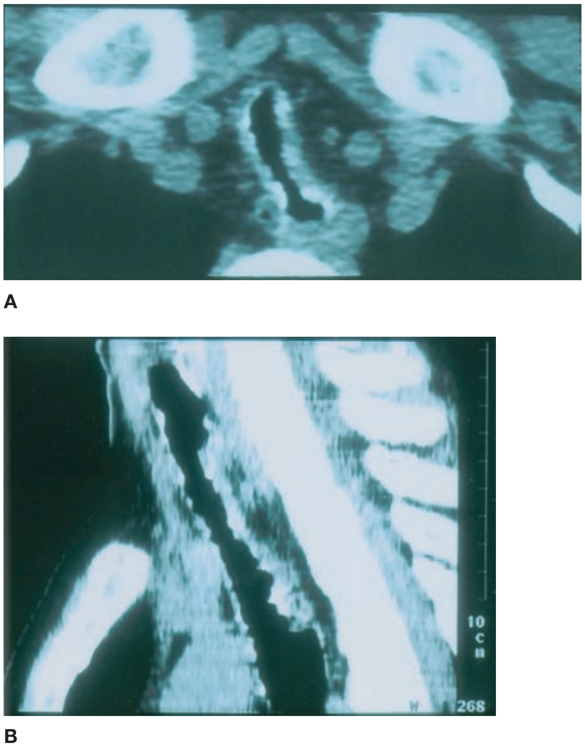

Figure 47-10 **A.** Computed tomography scan of the chest demonstrating marked narrowing of the trachea with intraluminal calcified nodular projections in a patient with tracheopathia osteoplastica. **B.** Computed tomography scan of the chest demonstrating multiplanar reformation of the trachea in the sagittal plane of the same patient.

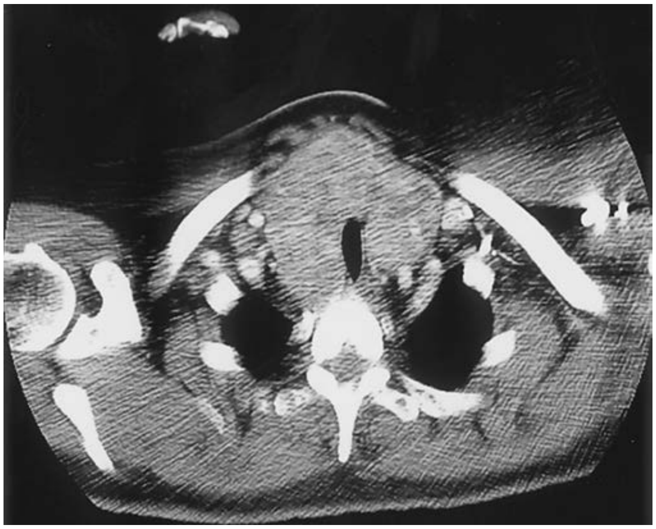

Figure 47-11 Computed tomography scan of the chest demonstrating marked extraluminal compression of the trachea caused by intrathoracic goiter.

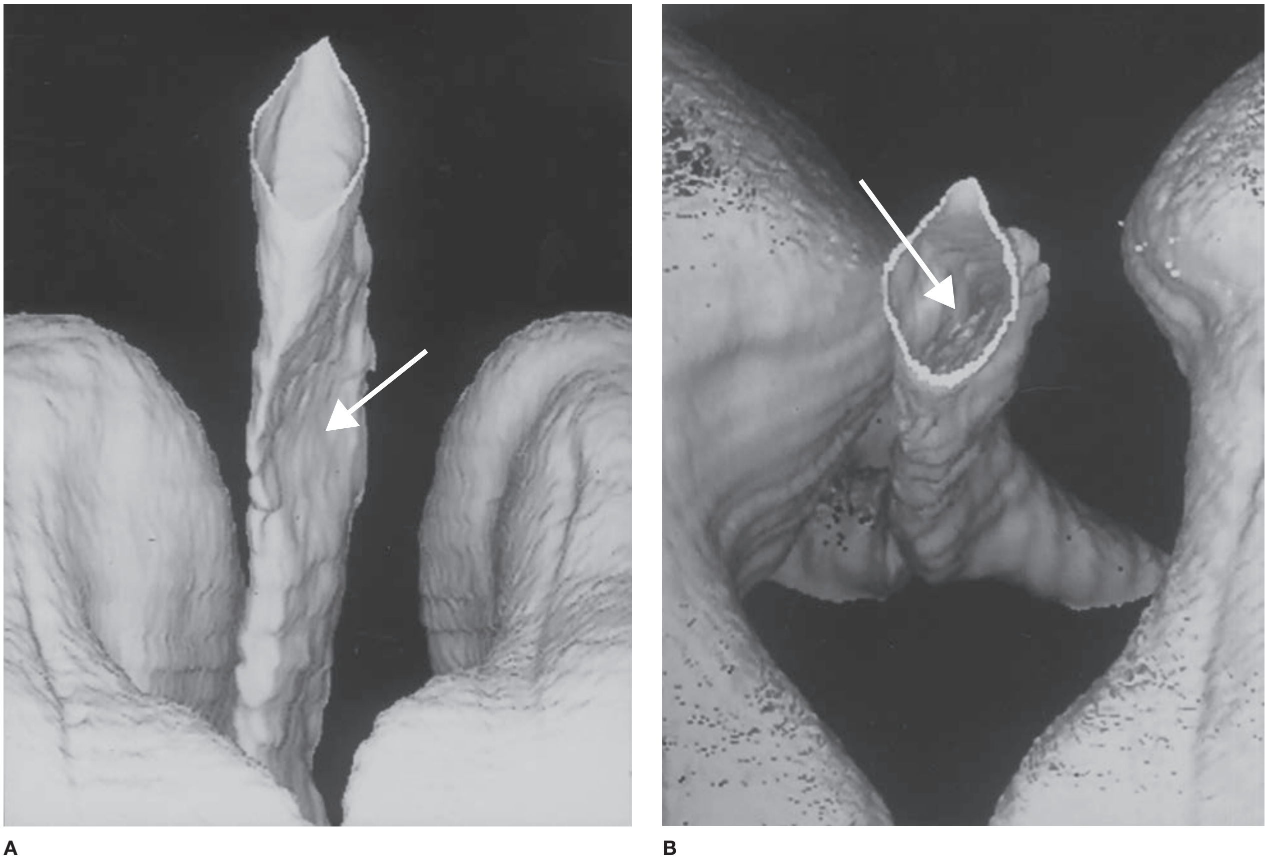

Figure 47-12 Helical computed tomography scan of the chest with three-dimensional reconstruction of the upper airway showing focal tracheal compression *(arrows)* (**A, B**).

one should confirm the diagnosis by quantitatively measuring the degree of airway luminal narrowing during expiration.

Another novel CT-based imaging technique is virtual bronchoscopy. The use of volumetric imaging allows for an intraluminal three-dimensional reconstruction of the airways and surrounding tissues. The technique has been used with a high degree of accuracy in assessing the width, length, and contour of fixed airway lesions.

Magnetic resonance imaging (MRI) provides a multiplane image of the chest without the need for contrast material. It is best used to investigate vascular structures surrounding central airways rather than the airways themselves, which are better visualized using CT scanning.

ENDOSCOPY

Bronchoscopy and direct laryngoscopy provide a real-time morphologic and functional evaluation of the upper airway. Imaging techniques are often limited by their inability to document the dynamic nature of many airway lesions and may underestimate the extent of an obstruction. With respect to laryngeal disease, endoscopy allows the operator to determine whether the vocal cords are mobile or fixed in abduction or adduction or alternatively moving paradoxically. This valuable information can help guide management. In cases of traumatic or thermal injury to the airways, edema, laryngeal fracture, or carbonaceous materials can be readily identified.

CLASSIFICATION

Stenosis classification systems are an objective tool that can be used between clinicians to provide an accurate characterization of the stenosis. While several classification systems exist for upper airway obstruction and none is universally accepted, broadly they include severity of airway narrowing, vertical length, location in the airway, cause, morphology/shape of stenosis, voice characteristics, swallowing, and functional impairment.[11]

Severity of the airway narrowing refers to the degree of reduction of cross-sectional area, with mild obstruction being less than 50% reduction in area and severe greater than 71%. Vertical length is important when considering treatment plans, as lesions >4 cm are generally considered inoperable. Location in the airway is described as relative to both the vocal cords and main carina (glottis, subglottic, tracheal, tracheobronchial). Morphology describes the shape of the airway lumen and can help determine etiology. Terms used to describe morphology include simple (short segment, concentric, <1 cm in length, and without malacia), complex (long segments >1 cm, with tracheal wall injury and/or malacia), pseudoglottic (triangular), eccentric, and circumferential. Classification of voice characteristics is on a spectrum ranging from no problems, to slight to significant impairments in audibility, to no voice. Finally, functional class is a subjective measurement of symptomatology with activities of daily living.

CAUSES OF UPPER AIRWAY OBSTRUCTION

UAO may be observed in a wide variety of settings, including infections, trauma (including iatrogenic), vascular disorders, and a wide variety of benign and malignant tumors. Each is discussed below.

■ Infection

A broad variety of infections may eventuate in UAO.

Deep Cervical Space Infections

Deep cervical space infections occur in potential spaces bounded by the deep cervical fascia. Patients with deep cervical space infections may present with sore throat, odynophagia, neck swelling, pain, fever, and dyspnea. Stridor and profound respiratory difficulty are signs of significant UAO. Parapharyngeal, peritonsillar, submandibular, and retropharyngeal abscesses appear to be common locations in adults. The bacteriology and initiating event of deep cervical infections appear to have changed over time.

Mixed infections caused by aerobic and anaerobic infections are common and have been reported in up to two-thirds of cases.[12] *Streptococcus viridans* and *Klebsiella pneumonia* are common pathogens. *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus pneumoniae*, *Escherichia coli*, and *Haemophilus influenzae* are other agents that are commonly reported. Alpha- and beta-hemolytic *streptococci* appear to have significantly declined in frequency. Overall, an odontogenic origin is probably most common. Intravenous drug abuse, mandibular fractures, iatrogenic and noniatrogenic traumatic injury to the upper airway, underlying malignancy, and poor underlying immune status are associated conditions. Ludwig's angina—an infection of the submandibular space and the floor of the mouth—is potentially lethal and is commonly associated with significant UAO. This entity is usually a cellulitic process and can affect the submandibular spaces bilaterally. Conservative management with antibiotics leads to significantly higher incidence of airway compromise compared with surgical drainage.[13] Many cases with true Ludwig's angina require tracheostomy.

Treatment of deep cervical infections involves maintenance of oxygenation and ventilation by securing an adequate airway, administration of appropriate antibiotics, and when indicated, use of surgical drainage. Complications of deep cervical infections include UAO, Lemierre's syndrome (see next paragraph), distant infection, septic embolization, carotid artery rupture, pulmonary embolism, direct extension of infection resulting in mediastinitis and empyema, and rupture of the abscess during intubation or other interventions.[14]

One particularly virulent cervical infection, known as Lemierre's syndrome, arises from a nasopharyngitis or peritonsillar abscess commonly due to *Fusobacterium necrophorum.* This lateral pharyngeal space infection results in suppurative thrombophlebitis of the internal jugular vein, septicemia, and metastatic abscess formation, particularly in the lungs and joints. Symptoms begin with a sore throat, fever, and painful swelling in the neck, followed by tender lymphadenopathy and tenderness along the sternocleidomastoid muscle due to thrombophlebitis of the internal jugular vein. Dysphagia, trismus, and UAO may occur as a result of swelling of the lateral pharyngeal space. Contrast-enhanced CT scan of the neck demonstrates thrombosis of the internal jugular vein, soft tissue abscesses, fasciitis, and myositis. Treatment with prompt antibiotics, such as high-dose penicillin with metronidazole, or monotherapy with clindamycin is key has led to the recent mortality rate of 5%.[15]

Epiglottitis

Epiglottitis is an infectious process that causes variable degrees of inflammation and edema of the epiglottis and supraglottic structures. Supraglottic structures usually are involved with variable involvement of the epiglottis in adults. Clinical presentation includes odynophagia, with inability to swallow secretions, sore throat, dyspnea, hoarseness, fever, tachycardia, and stridor. In one review, 44% of the patients had a normal routine oropharyngeal examination.[16]

Fiberoptic laryngoscopy is necessary to make the diagnosis and should be done without delay. Radiographic studies can be helpful in ruling out other etiologies with similar presentations and in evaluating potential complications but should not delay diagnosis or management.

Supraglottitis may involve the base of the tongue, uvula, pharynx, and false vocal cords. The disease may be increasing in prevalence among adults and declining in children, perhaps reflecting introduction of *Haemophilus b* conjugate vaccines. Young adult males are commonly affected. The disorder appears to be more prevalent in colder winter months and in smokers. Blood cultures are positive in less than one-third of cases. Adult supraglottitis may be caused by a variety of organisms, including *Haemophilus influenzae*, pneumococci, group A streptococci, *S. aureus*, *Streptococcus viridans*, a variety of anaerobic organisms, mycobacteria, fungi, and viruses. Throat cultures can be helpful in diagnosis and management; however, treatment should not be delayed while awaiting culture results.

Illicit drug use may be associated with epiglottitis, with inhalation of heated objects (e.g., metal pieces from a crack cocaine pipe or the tip of a marijuana cigarette) causing thermal injury to supraglottic structures. Signs, symptoms, and roentgenographic and laryngoscopic findings are similar to those of infectious epiglottitis.

Initial antibiotic therapy using a third-generation cephalosporin or extended-spectrum penicillin is reasonable. The prevalence of resistant organisms should be considered when choosing empiric antibiotic coverage. Corticosteroids often are used in management of acute epiglottitis despite lack of evidence to support their use. Based on anecdotal case reports, epinephrine also is used.

Patients should be observed closely, and experienced staff should be available immediately to secure the airway by intubation or surgical approach, if needed. In a recent study, up to 10% of patients required ICU admission, and 4.4% required airway intervention.[17] Elevated blood glucose levels and CRP as well as a relative neutropenia predicted the need for higher level of care. Males were more likely to have recurrent disease, which was associated with an increased need for airway intervention. Securing the airway is extremely important in patients who develop stridor and other signs of significant airway obstruction. Mortality is around 2% to 3% but can be significantly higher, up to 17.6%, in those who require airway intervention.[18]

Laryngotracheobronchitis and Bacterial Tracheitis

Laryngotracheobronchitis, often called croup, is commonly seen in children who present with hoarseness, barking cough, shortness of breath, and stridor. This is an acute viral illness characterized by narrowing of the subglottic area. Adult croup is a rare condition. Rare instances of diphtheritic croup have been described in adults. Noninfectious membranous tracheitis related to trauma also has been reported.

Acute bacterial tracheitis refers to involvement of the subglottic trachea by bacterial infection and usually follows an episode of viral laryngotracheobronchitis. Thick, purulent exudates and mucosal edema may cause symptoms of UAO. *S. aureus* appears to be the predominant organism. Prompt antibiotic therapy, close observation with attention to airway compromise, and frequent suctioning are important. Data to suggest effectiveness of steroids or epinephrine in adults are lacking.

Rhinoscleroma is a chronic, progressive granulomatous infection of the upper airway that may cause airflow obstruction. This disorder affects primarily the nose and paranasal sinuses, but also may involve the nasopharynx, larynx, trachea, and bronchi. The causative organism is *Klebsiella rhinoscleromatis*. Rhinoscleroma is endemic in Africa, Asia, and South America and is rare in North America. About 5% of patients have diffuse narrowing of the trachea.[19] Prolonged antibiotic therapy with trimethoprim/sulfamethoxazole is effective.

Tuberculosis

Involvement of the upper airway can be observed both with and without pulmonary disease. Primary disease can develop due to direct inoculation of the airway with acid-fast bacilli, whereas secondary disease is due to either direct spread from advanced pulmonary disease or hematogenous or lymphatic seeding. Laryngeal tuberculosis is relatively uncommon, accounting for less than 1% of tuberculosis cases. The true vocal cords and epiglottis are the areas most affected. Laryngeal tuberculosis may present as progressive hoarseness and ulceration or a laryngeal mass. Endobronchial tuberculosis can be seen throughout the tracheobronchial tree and may result in significant airflow limitation that is related to the initial lesion or subsequent stricture formation. A barking cough and sputum production are common findings. In the appropriate clinical context, a positive purified protein derivative (PPD) skin test and acid-fast bacilli in sputum may suggest the diagnosis. However, a biopsy from the laryngeal or endobronchial abnormality usually is required. Biopsy features include caseating granulomas and acid-fast bacilli. Treatment with antituberculous medications is usually adequate and should be instituted promptly, since the disease is highly contagious. Additionally, prompt treatment with antituberculous medications should decrease the development of endobronchial fibrostenosis and resultant airflow limitation. Surgical interventions, including tracheostomy, are reserved for airway obstruction and long-term complications and, in one report, were required in 12% of patients with laryngeal involevement.[20]

■ Upper Airway Tumors

Both head and neck cancers and tracheal tumors may cause UAO.

Head and Neck Cancer

The great majority of cancers that impact the upper airway are squamous cell carcinomas, and the incidence of oropharyngeal cancer appears to be increasing in some countries (Fig. 47-13).[21] Other less common cancers occurring in the oropharynx include salivary gland carcinomas, lymphomas, and lymphoepitheliomas. Tobacco, alcohol abuse, and infection with human papillomavirus (HPV), especially HPV type 16, are the most common risk factors for the development of head and neck cancers.[22–24] The incidence of head and neck cancer is declining in the Unites States, concurrent with a reduction in tobacco use, accounting for about 3% of all malignancies.[25]

The clinical manifestations of head and neck cancer depend on the location and stage. Cancers at the base of the tongue and pharyngeal walls are insidious. These cancers grow in an infiltrative or exophytic pattern. Because of the lack of pain fibers at the base of the tongue, these tumors are often asymptomatic until they are far advanced. The most common location of a primary tumor of the

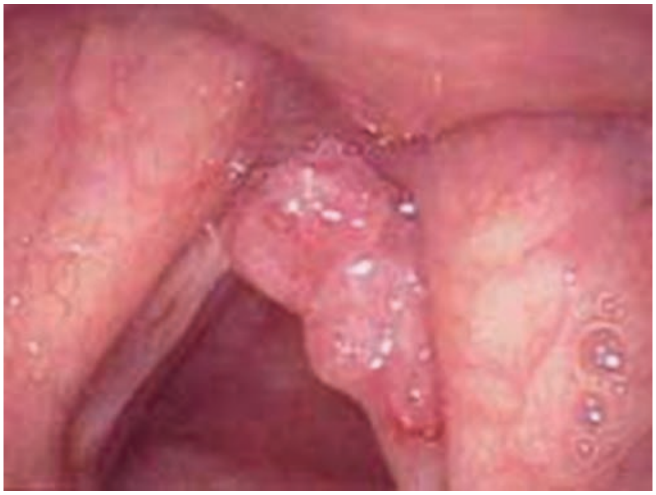

Figure 47-13 Laryngeal squamous cell carcinoma.

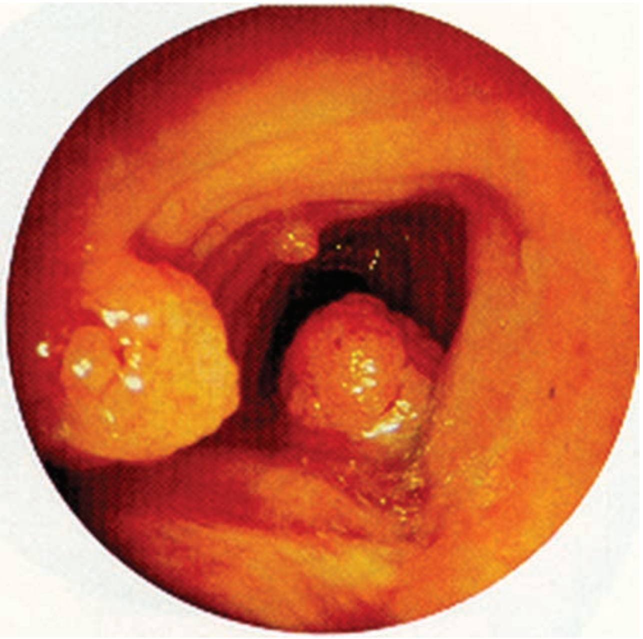

Figure 47-14 Squamous cell carcinoma of the lung.

oropharynx is the anterior tonsillar pillar or tonsil. Symptoms of these cancers include hoarseness, hemoptysis, sore throat, dysphagia, referred otalgia due to cranial nerve involvement, and trismus due to pterygoid muscle involvement. Life-threatening UAO may be seen. Patients who have had head and neck surgery for cancer have a very high prevalence of obstructive sleep apnea.

Tracheal Cancer

Tumors that originate in the trachea are uncommon and make up only about 2% of all tumors that form in the upper airway. Although rare, when they do occur, approximately 80% of tracheal tumors are malignant. Primary tracheal cancers are rare, with a reported incidence of 0.1 per 100,000 per year.[26] Dyspnea, cough, wheeze, and stridor are frequent presenting symptoms. Squamous cell carcinoma (SCC) is the predominant histology (45%), followed by adenoid cystic carcinoma (ACC) (16%).[27] SCC is almost always associated with cigarette smoking. These tumors grow quickly, and in nearly half of cases they are too large to be removed by the time they are discovered. Hemoptysis is often another presenting symptom. ACC grows much more slowly and has not been found to be related to smoking. Men and women have the same risk for this type of cancer, and it is commonly diagnosed around the age of 40 years. Hemoptysis is an uncommon presentation for ACC. Surgery remains the most effective management. Emergency treatment with procedures to recanalize the airway, including airway stenting, may be necessary pending definitive surgery. Postoperative radiation therapy appears useful for primary tracheal malignancies, particularly when surgical margins are positive. Palliative radiation is used for local control when surgery is contraindicated. Five-year survival is highly dependent on resectability. For resectable adenoid cystic and squamous cell carcinomas, survival rates are reported at 52% and 39%, respectively, whereas in unresectable disease these rates are 39% and 7%, respectively.[28] Late recurrence of ACC is possible due to early perineural infiltration. Favorable prognostic factors include negative airway margins at the time of resection and adenoid cystic histology.

More commonly, malignancies found in the trachea result from direct extension of primary lung cancer or regional extension to the lymph nodes (Fig. 47-14). Metastases to central airways from nonpulmonary malignancies are uncommon, although endobronchial metastases from breast, colorectal, renal, ovarian, thyroid, uterine, testicular, nasopharyngeal, and adrenal carcinomas, as well as sarcomas, melanomas, and plasmacytomas have been described. In an autopsy series of more than 1300 patients with solid tumors, metastatic disease to central airways occurred in 2%.[29] The mediastinal lymph nodes are also a common site for disease involvement from hematologic malignancies such as lymphoma.

Nonmalignant tracheal tumors include papillomas, chondromas, and hemangiomas (Fig. 47-15). Chondromas are the most common

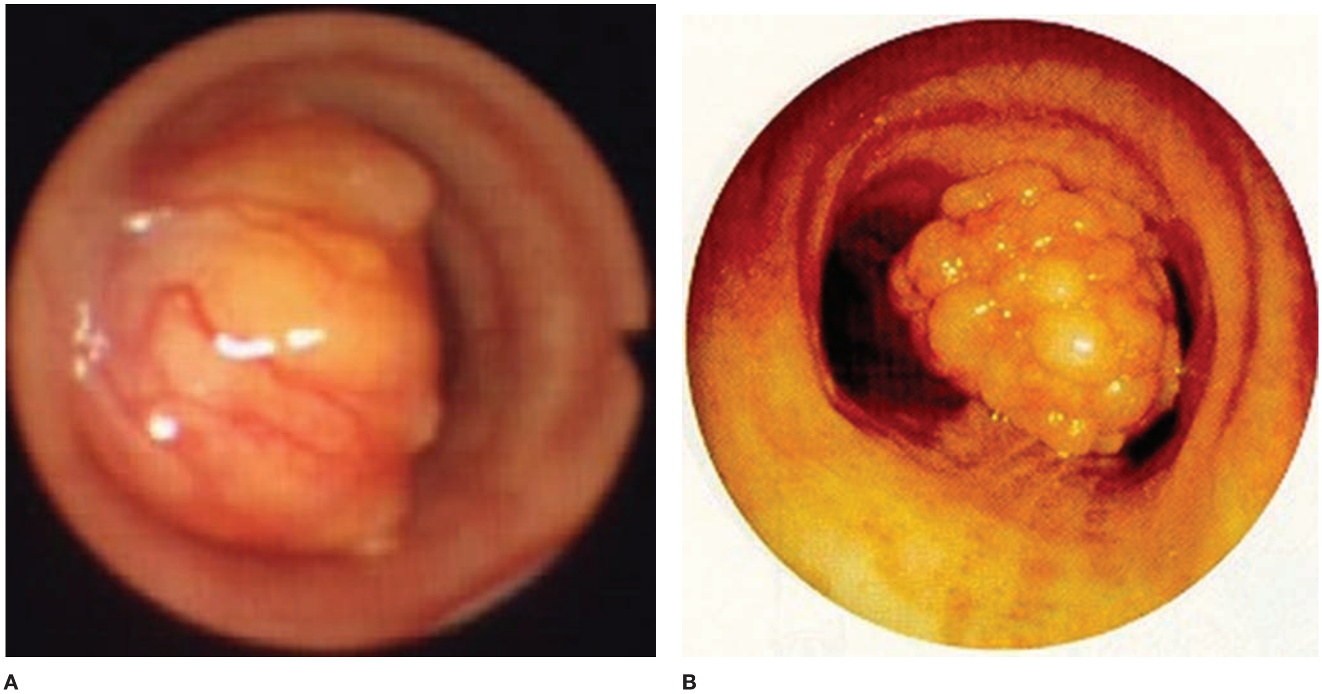

Figure 47-15 Nonmalignant tracheal tumors. **A.** Hamartoma. **B.** Papillomatosis.

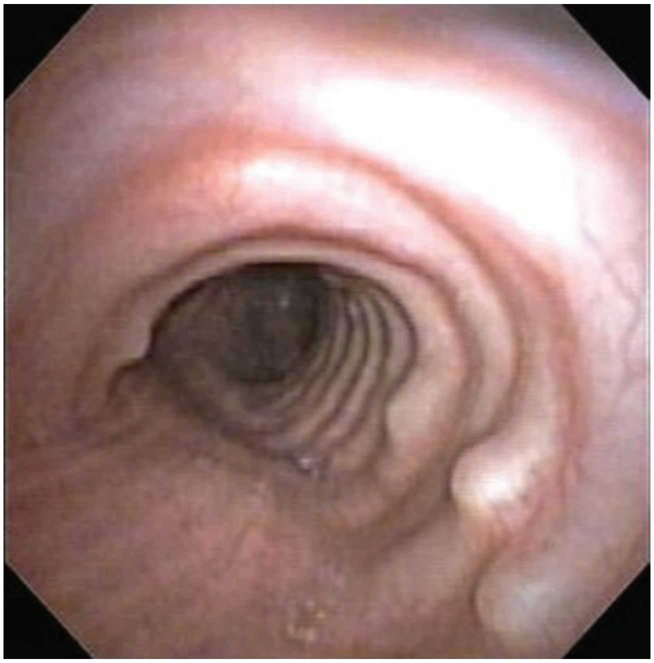

Figure 47-15 *(Continued)* **C.** Chondromas.

type of benign tracheal tumor. They are formed from the cartilage rings of the trachea and have the potential to become malignant over time. Recurrent respiratory papillomatosis in adults, caused by human papillomavirus types 6 or 11 (or, much less commonly, types 16 or 18) may result in UAO and death. Although the larynx is most commonly affected (Fig. 47-16), the tracheobronchial tree may be involved, with a predilection toward areas with prior mucosal injury, including tracheostomy sites and tracheal injuries. Lesions tend to progress down through the tracheobronchial tree. Pulmonary parenchymal involvement is rare, but it may be severe, and bronchiectasis, pulmonary nodules, and abscess formation may occur. Malignant transformation also is possible. The course of the disease is difficult to predict. Recurrent endoscopic interventions (debulking), with attendant risk of airway stenosis, are often required. It is important to minimize intervention unless clinically relevant obstruction exists due to concerns regarding extension secondary to airway injury. No controlled trials on the role of antiviral therapy have been conducted. Available data suggest beneficial effects of intralesional cidofovir, and it is recommended to treat with cidofovir when debulking is required at least every 2 to 3 months.[30] Bevacizumab also has been shown to have benefit when used in combination with debulking.[31] Favorable effects also have been reported with the use of interferon alpha, although the agent is not often used due to systemic side effects. Chemotherapy, radiation therapy, and targeted surgical resection are utilized for confirmed malignant transformation. The HPV vaccine Gardasil has shown promising results for secondary prevention of RPP as well as disease control.[32]

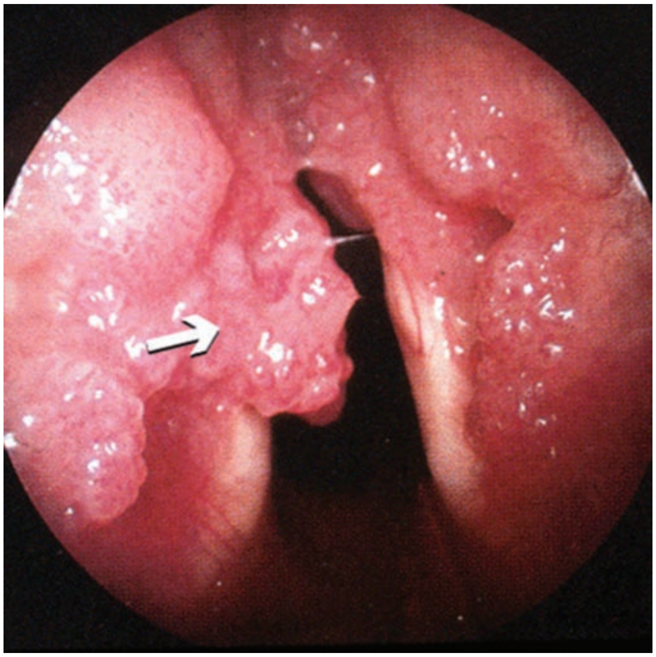

Figure 47-16 Recurrent laryngeal papillomatosis *(arrow)*.

■ Laryngeal and Tracheal Stenosis

Common causes of laryngeal and tracheal stenosis include prior intubation and tracheotomy. However, many other causes have been reported.

Postintubation and Posttracheotomy Stenosis (PITS and PTTS)

Endotracheal intubation, tracheostomy, and prior laryngotracheal instrumentation account for most cases of laryngotracheal stenosis. The reported frequencies of tracheal stenosis following tracheostomy or laryngotracheal intubation vary widely, but recent large retrospective studies suggest that the incidence of clinically significant stenosis is low (0%–1.8%) (Figs. 47-17 and 47-18).[33,34] Patient demographics associated with an increased incidence of PITS/PTTS include female sex (75%), obesity (66%), diabetes mellitus (35.4%), hypertension (51.6%), cardiovascular disease (45.1%), and current smoker status (38.7%).[35] The incidence of symptomatic tracheal stenosis following percutaneous tracheostomy is comparable to the incidence that occurs after open techniques.[36]

Tracheal stenosis in the region of the tube cuff is related to pressure-induced ischemic injury of the mucosa and cartilage, and its risk can be minimized by use of large-volume, low-pressure cuffs. The duration of translaryngeal intubation also affects the frequency and severity of laryngotracheal stenosis.[37]

Stenosis following tracheostomy may be above the stoma, at the level of the stoma, at the cuff site, or at the tip of the cannula. Damage to the cartilage above the stoma is a common cause of tracheal stenosis after tracheostomy. In addition to ischemic mucosal injury and ischemic chondritis, anterior and lateral tracheal wall damage, with "buckling in" fractures of the cartilage, is an important factor. The fractures can be minimized by avoiding excessive pressure on the cartilage during the procedure, selecting the appropriate size and length of the tracheostomy tube, avoiding infection, and using the lowest possible cuff pressure. Obesity (BMI >30) is a significant independent risk factor for development of posttracheostomy stenosis.[38]

Treatment of PITS/PTTS consists of bronchoscopic dilation, stent placement, and/or surgery for appropriate candidates. Electrocautery needle knife incisions coupled with balloon dilation has been shown to be effective.[39] Silicone stent placement is preferred over metallic stent. Stent placement is most effective when done within 6 months of stenosis and can be successfully removed without restenosis in 40% of patients.[40]

Other Causes of Tracheal Stenosis

Granulomatosis with polyangiitis may present with significant subglottic stenosis, a complication reported in 16% to 23% of patients.[41] Subglottic stenosis may be the only manifestation of granulomatosis

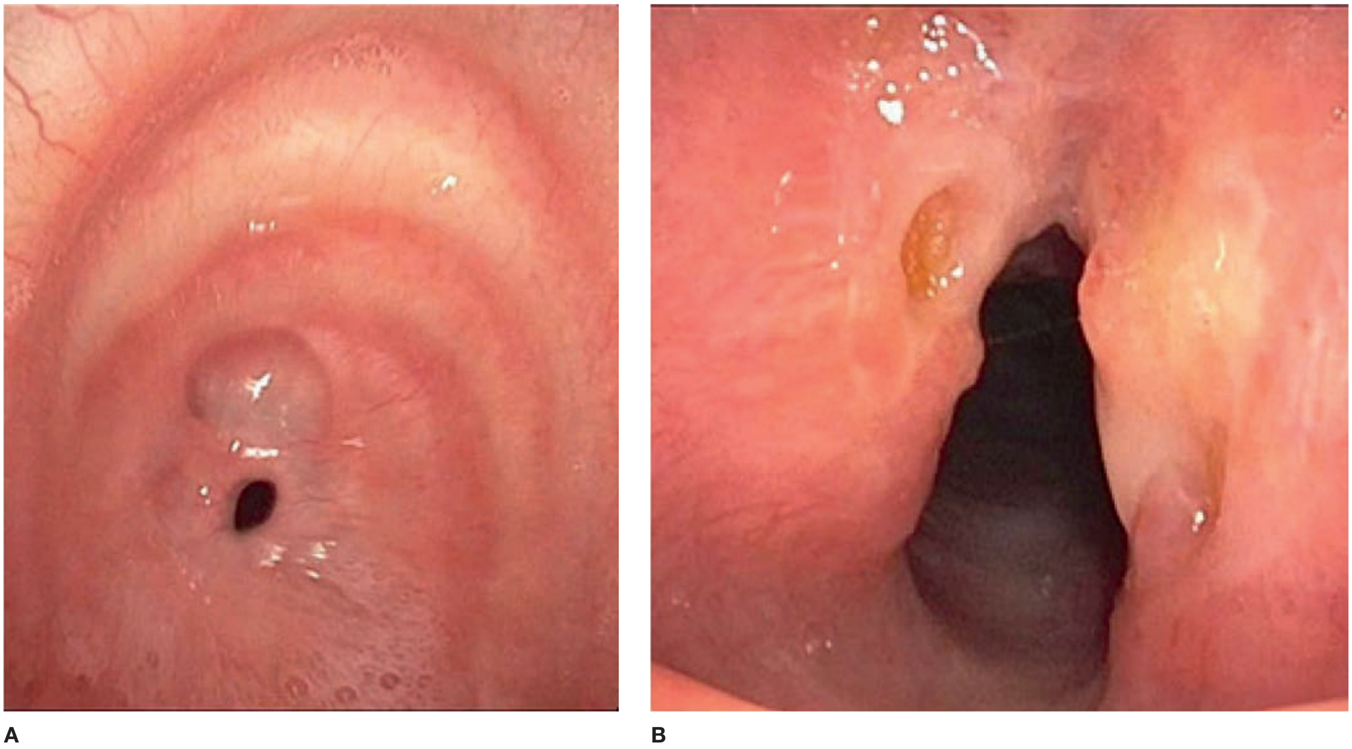
A
B

Figure 47-17 Posttracheostomy stenosis. **A.** Weblike simple stenosis. **B.** A-framed stenosis.

with polyangiitis and may have a clinical course distinct from other manifestations of the disease. Endoscopic biopsy of suspected sites of involvement is positive in only 5% to 15% of cases.

Sarcoidosis may be associated with granulomatous infiltration and obstruction of the upper airways (Fig. 47-19). Laryngeal involvement is more common, but tracheal stenosis has been described. Radiographs may show diffuse tracheal stenosis, which progresses despite corticosteroid therapy. Bronchoscopy may reveal extensive tracheal narrowing.

Pulmonary amyloidosis includes tracheobronchial manifestations. The chest roentgenogram may show diffuse narrowing and wall thickening involving a long tracheal segment. Involvement is diffuse and circumferential, often with ossification of the amyloid deposits (Fig. 47-20). Bronchoscopy demonstrates multiple plaques on tracheal walls or localized tumor-like masses.

Relapsing polychondritis is a rare systemic disease characterized by recurrent episodes of inflammation of cartilaginous structures. Respiratory manifestations are often severe and may be life-threatening. Inflammation occurs in all cartilage types, including the elastic cartilage of the ears and nose, hyaline cartilage of all peripheral joints, and axial fibrocartilage. The most common presenting symptom is pain in the external ear due to auricular chondritis. Respiratory tract involvement may develop years after the first occurrence of auricular chondritis. Symptoms include hoarseness,

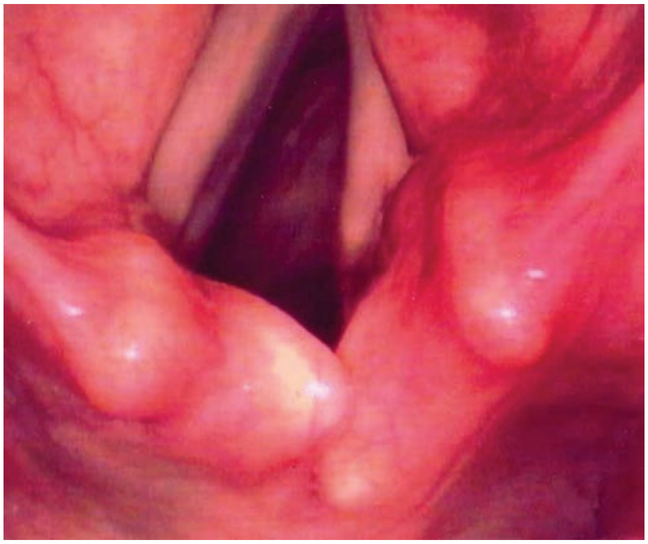

Figure 47-18 Postintubation trauma.

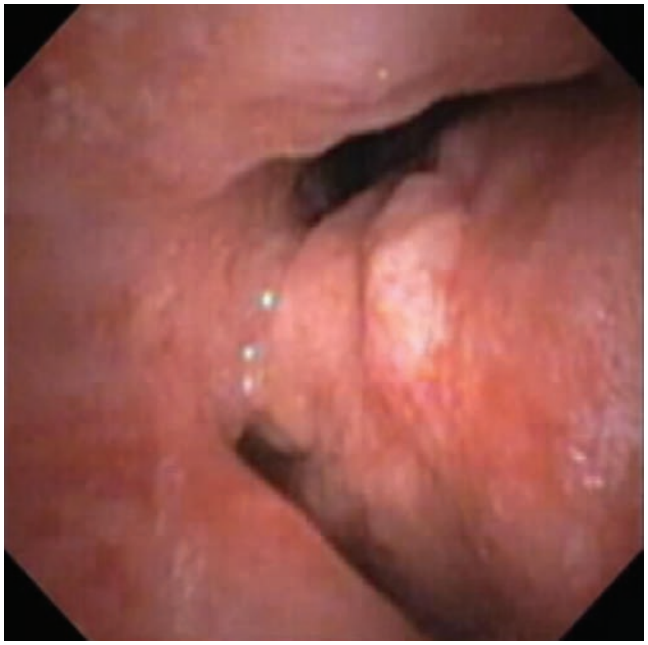

Figure 47-19 Airway sarcoid.

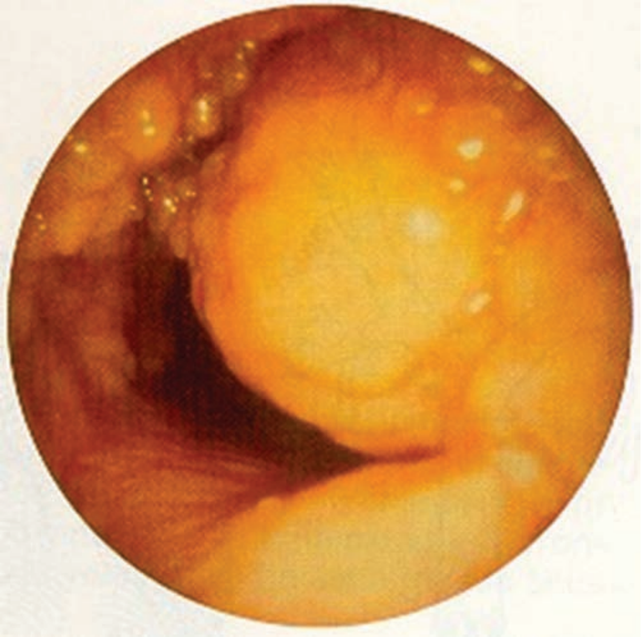

Figure 47-20 Amyloid pseudotumor.

aphonia, and choking. Tenderness over the thyroid and laryngeal cartilages may be present. When the trachea is involved, endoscopic examination shows inflammation and stenosis. CT demonstrates major airway collapse caused by destruction of cartilaginous rings or airway narrowing due to inflammatory edema and fibrosis. CT findings also include diffuse, smooth thickening of the trachea and proximal bronchi; thickened, densely calcified cartilaginous rings; tracheal wall nodularity; and diffuse narrowing of the tracheobronchial lumen. The posterior tracheal membrane is spared.[42]

Tracheopathia osteoplastica is a rare, benign disease of the trachea and major bronchi in which cartilaginous or osseous nodules project into the airway lumen, often causing considerable airway deformity. The posterior membranous portion of the tracheal wall is spared. The disorder may begin just below the larynx, but most often it affects the lower two-thirds of the trachea. Extension into the proximal portions of the major bronchi may be noted. The condition usually occurs over the age of 50 years and may cause severe airflow obstruction. Its etiology is unknown.

On rare occasions, inflammatory bowel disease produces tracheobronchial stenosis and severe airflow obstruction. The associated airway mucosal inflammation may be steroid responsive early in the course of illness. If fibrosis ensues, medical management has limited success.

Idiopathic laryngotracheal stenosis is a diagnosis of exclusion in the absence of a clear, underlying etiology. It predominantly affects women in the fifth decade of life.[43] GERD is commonly concurrently diagnosed. Since most affected patients are females, a hormonal etiology has been proposed. An imbalance in estrogen and progesterone receptor expression has been demonstrated in surgical specimens of resected stenosis.[44] Treatment includes bronchoscopic dilation. Steroid injection and aggressive medical management with proton pump inhibitors and inhaled corticosteroids may prolong the interval between required procedures.[45,46]

In addition to medical management, repeated rigid and flexible bronchoscopy-based interventions aimed at reestablishing airway patency may be necessary, particularly in those who are not considered to be surgical candidates or in those with simple weblike stenosis. In cases of weblike stenosis, radial incisions sparing the posterior membrane are made and then the airway is dilated, using either a balloon or the rigid bronchoscope barrel. With respect to more complex stenosis, endoscopic intervention is generally considered a bridge in patients considered good operative candidates with potentially resectable disease. Unfortunately resection and re-anastomosis is limited by the length of trachea to be resected.[47,48] A multidisciplinary approach incorporating medical and surgical specialists as described by Brichet is utilized in many centers.[49]

■ Tracheomalacia

Tracheomalacia refers to loss of tracheal rigidity and resulting susceptibility to collapse. Tracheomalacia may be diffuse or localized to a tracheal segment. The affected portion may be intrathoracic, in which airway obstruction is accentuated during expiration. Less common is extrathoracic obstruction resulting from cervical malacia, in which airway obstruction is most marked during inspiration. Tracheobronchomalacia is the term used to describe the condition when the mainstem bronchi are involved.

Tracheomalacia in adults may be classified as congenital or acquired. The congenital form, described more extensively in children, is related to a variety of congenital disorders and associated syndromes. The disorder may persist into adult life and is referred to as "idiopathic giant trachea," "tracheomegaly," or the "Mounier-Kuhn syndrome" (Fig. 47-21). Bronchiectasis and recurrent respiratory infections are common. Tracheal diverticuli have been reported in more advanced disease. Although atrophy of the longitudinal elastic fibers and muscularis layer has been described, the etiology of these changes is unclear. The diagnosis is made when the diameters of the trachea or right or left mainstem bronchi exceed the upper limits of normal by 3 or more standard deviations. Patients with Mounier-Kuhn syndrome may benefit symptomatically from airway stenting and tracheobronchoplasty.[50]

Acquired or secondary tracheomalacia in adults may be related to a variety of conditions.[51] Tracheostomy and endotracheal intubation are probably the most common etiologies. Usually, limited, focal weakness of the trachea and excessive dynamic airway collapse are present. Tracheomalacia may be caused by conditions that are associated with chronic pressure on the tracheal wall, inflammation of the cartilaginous support or mucosa, interference with tracheal

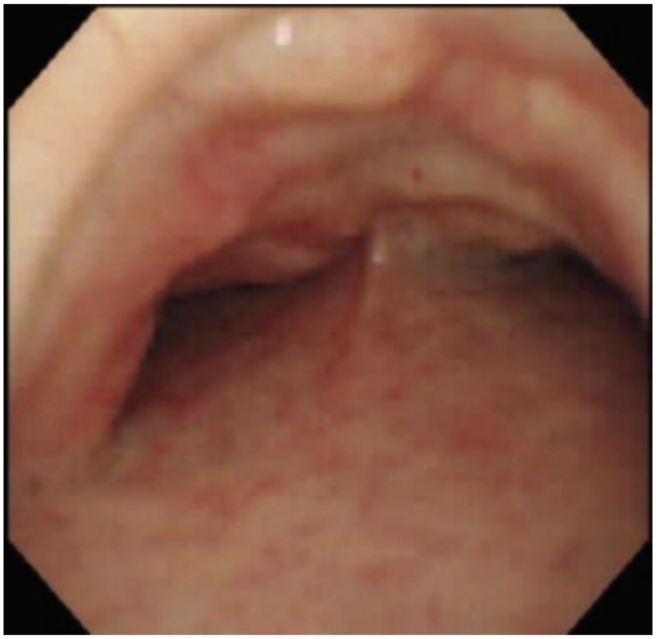

Figure 47-21 Bronchoscopic view of tracheomegaly or Mounier-Kuhn syndrome.

blood flow, or chronic infection. Traumatic injury to the central airways or surgical interventions also may lead to tracheomalacia.

Symptoms of tracheomalacia include dyspnea, a seal-barking paroxysmal cough, recurrent pulmonary infections, and respiratory failure in a small subset.[52] Many of these patients will also have decreased exercise tolerance and, in severe cases, impaired quality of life.

Tracheomalacia is defined as a reduction in cross-sectional area of greater than 50% during expiration on CT imaging. However, this cut point may not be discriminatory enough to detect clinically significant tracheomalacia.[53] Bronchoscopic visualization can confirm significant narrowing of the tracheal lumen during regular, forced expiration.

Application of continuous positive airway pressure (CPAP) has been reported to be as beneficial as pneumatic splint for the airways. Tracheobronchoplasty may be useful in selected patients and has been shown to improve quality of life and exercise tolerance.[52] Airway stents can be used to identify patients that may benefit from surgical airway stabilization.[54,55] In select patients who are not surgical candidates, but who derive both symptomatic and objective benefit from airway stents, silicone stents may be used for long-term management with appropriate monitoring for complications. Optimal medical management includes treatment of associated infections and of distal airway disease.

■ Extrinsic Compression of the Central Airway

The upper airway is subject to extrinsic compression by a variety of pathologies that involve adjacent structures. The compression may affect the intrathoracic trachea or extrathoracic trachea and upper airway.

Mediastinal Masses and Lymphadenopathy

Rarely, mediastinal masses present with serious limitation to airflow that develop either acutely or indolently. Common symptoms include chest pain, fever, dyspnea, and cough. The anterosuperior compartment is the most common site of mediastinal malignancies. Thymic neoplasms and lymphoma are the most common malignancies, followed by neurogenic tumors and teratomas. Both Hodgkin and non-Hodgkin lymphomas may be manifested by severe respiratory compromise due to airway compression. A similar syndrome may be due to a metastatic tumor in the mediastinal lymph nodes arising from bronchogenic or other carcinomas.

Patients with large mediastinal masses present a challenge during the perioperative period because of the potential for development of acute UAO and other respiratory complications. In adults, complete airway obstruction during induction of anesthesia is rare. Serious pulmonary complications develop intra- and postoperatively in about 4% and 7% of patients, respectively. Complications may occur while the patient is placed in the supine position, during induction, or following extubation. Patients with severe symptoms, including stridor, and those with greater than 50% airway obstruction, appear to be at high risk for respiratory complications; asymptomatic patients are at significantly less risk. Patients with reduced peak expiratory flow and mixed obstructive–restrictive patterns on pulmonary function testing also appear to be at increased risk for postoperative complications.

Middle mediastinal masses include benign cysts that are bronchogenic, enterogenous (duplication), pericardial, pleural, and thymic in origin. Most bronchogenic cysts are asymptomatic. However, some evoke cough, chest pain, and dyspnea. Severe respiratory distress and compressive symptoms can occur. Usually, cyst contents appear to have the density of water on CT or MRI. Mucoid contents may give the impression of solid appearance on CT. Surgical resection and transthoracic or transbronchial drainage are options for management. Surgical intervention appears to be the preferred treatment in patients who are symptomatic. The role of interventions, including surgery, in asymptomatic patients is controversial. Enterogenous cysts are usually removed surgically.

Enlarged mediastinal lymph nodes that compress the airway may arise from infectious and noninfectious benign etiologies. One notable example is fibrosing mediastinitis, defined as the presence of excessive mediastinal fibrous tissue that tends to invade and destroy normal structures. The entity is thought to represent a reaction to an infectious granulomatous disease, especially histoplasmosis. The incidence in populations exposed to histoplasmosis remains low. Constriction of the central airways and vessels and the resulting cardiopulmonary limitations may develop several years after the initial infection. Hemoptysis is common, as are cough, dyspnea, and chest pain. CT imaging shows mediastinal fibrosis, calcification, and compression of mediastinal structures. Bronchoscopic findings include concentric airway narrowing and mucosal edema with hyperemia. Unfortunately, hemoptysis tends to be recurrent, and the disease does not respond to corticosteroids or antifungal agents. Surgical intervention is generally ineffective and may be hazardous.

Neck- and Thyroid-Related Causes

Retrosternal extension of a diffuse goiter may cause extrathoracic or intrathoracic airway obstruction. Patients with substernal goiter may have obstructive respiratory and gastrointestinal symptoms.[56] Orthopnea is prevalent when the goiter is intrathoracic and may be enhanced by obesity. Flow–volume loops show evidence of UAO in one-third of patients. Lack of correlation has been reported between symptomatic obstruction and CT findings.[57]

Laryngoceles and saccular cysts, which are abnormal dilatations of the laryngeal saccule (ventricle), are uncommon. Saccular cysts usually are filled with mucus. Laryngoceles communicate with the laryngeal lumen, resulting in air-filled structures noted on radiographic studies. Laryngoceles may be internal (i.e., confined to the larynx), external (i.e., extending into the thyrohyoid membrane superiorly), or combined. Most are asymptomatic. Hoarseness, dysphagia, pain, or signs of airway obstruction or infection may occur. A neck mass during the Valsalva maneuver may be detectable. Pyocele formation (i.e., infection in the laryngocele) may result in airway obstruction, aspiration pneumonia, or infection of the lateral pharyngeal space. The incidence of laryngeal carcinoma in association with laryngoceles makes close evaluation necessary. Endoscopic and surgical approaches may be employed in management.

Parathyroid cysts may be located in the neck or mediastinum. Fifty percent are accompanied by clinical hyperparathyroidism. Paroxysmal symptoms of airway obstruction can develop. Surgical excision is the treatment of choice; results are generally good.

Cervical osteophytes, common in the elderly, are related to either degenerative spinal arthritis or more generalized idiopathic skeletal hyperostosis; the osteophytes may be associated with dysphagia. In addition, airway narrowing and ulcerations due to osteophytes have been reported. The airway compression may make even elective endotracheal intubation difficult, despite adequate preoperative evaluation.

Finally, significant upper airway compression may arise from cervical lymph node involvement with infectious or malignant disorders, hematomas or pseudoaneurysms (related to trauma, surgical interventions, central line placement, or coagulation abnormalities), abscess formation, or other expanding lesions in the soft tissue of the neck.

Diseases of the Esophagus

Involvement of the trachea, glottis, or vocal cords by advanced esophageal cancer is common and associated with a poor prognosis; estimated 1-year survival is less than 10%. Airway obstruction

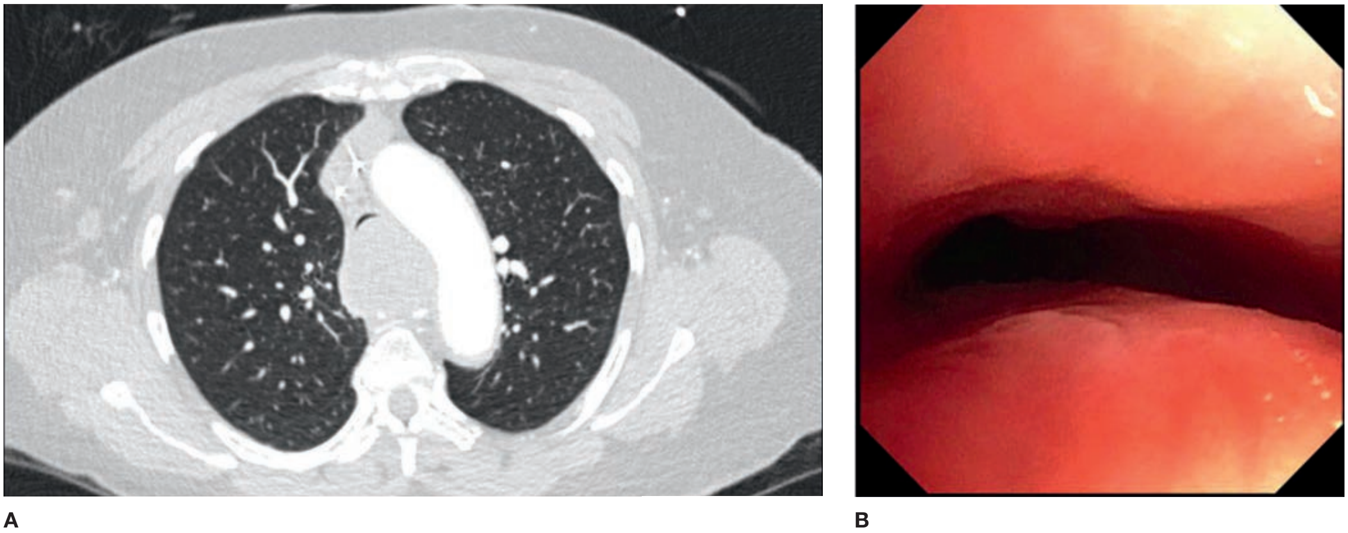

Figure 47-22 Distal tracheal compression due to esophageal tumor. **A.** CT view. **B.** Bronchoscopic view.

requiring stent placement is associated with a median survival of 1 to 4 months after the placement (Fig. 47-22A, B).[58] Tracheal obstruction may develop if an esophageal stent is placed in the setting of significant tracheal compromise. Development of tracheoesophageal fistula represents a devastating complication.

Placement of stents simultaneously in the trachea and esophagus is effective palliation for a tracheoesophageal fistula.[59] If such double stenting is anticipated for a fistula or for simultaneous esophageal and tracheal obstructions, the tracheal stent is placed first to ensure patency of the airway, followed by the esophageal stent. Palliative external or local radiation therapy, chemotherapy, or other treatment modalities (e.g., PDT) may be effective with or without accompanying airway interventions. The risk of esophageal disruption and rupture should be considered if stenting is performed after these local measures are employed.

Achalasia may cause a variety of pulmonary complications, including cough, aspiration with pneumonia or abscess formation, and rarely UAO. Tracheal compression by a dilated megaesophagus is the usual etiology. Ensuring patency of the airway and decompressing the esophagus are necessary in urgent management.

Vascular Abnormalities

Vascular rings, defined as anomalies of the aortic arch or its branches that compress the trachea or esophagus, are rare in adults (incidence <0.2%). Respiratory symptoms are common. Right-sided aortic arch occurs in less than 0.1% in adults and may be associated with complete vascular rings, while double aortic arch and right-sided aortic arch with aberrant left subclavian artery appear to be the most common etiologies of vascular rings in adults.

The right-sided aortic arch usually crosses over the right main-stem bronchus and descends on either the right or the left side. The vascular ring is usually completed by the ligamentum arteriosum arising from the descending aorta, an aberrant left subclavian artery, or an aortic diverticulum. With a double aortic arch, the left arch crosses over the left main-stem bronchus and joins the descending aorta to complete the ring; the ligamentum arteriosum does not contribute to the vascular ring. Symptoms, resulting from malacia of the compressed airway and resultant dynamic airway obstruction, may be misdiagnosed as exercise-induced asthma. An increase in aortic diameter due to rising blood pressure during exercise, intravenous fluid administration, or anatomic changes with aging may contribute to symptoms. Surgical intervention is indicated in symptomatic patients.

Pulmonary artery sling with anomalous origin of the left pulmonary artery from the right pulmonary artery is very rare in adults. In neonates, the condition is symptomatic and can be fatal without surgical intervention. However, in adults the condition is usually diagnosed incidentally on imaging a patient who has no significant symptoms. This disorder may be associated with a complete tracheal ring, forming the "sling-ring" complex. This condition may present with a right paratracheal mass noted on the chest radiograph.

Compression of the trachea by large aortic or innominate artery aneurysms or pseudoaneurysms may occur and complicate management in the perioperative period. Surgical repair is indicated to relieve symptoms.

■ Foreign Body Aspiration

Foreign body aspiration, more common in children than adults (in whom the peak incidence is in the sixth decade), is usually recognized from the patient's history. Foreign bodies commonly lodge in the bronchi after migrating through the trachea. In adults, food products are the most commonly aspirated material. The penetration syndrome, defined as the sudden onset of choking and intractable cough after aspirating a foreign body, with or without vomiting, is often followed by persistent cough, fever, chest pain, dyspnea, and wheezing. Impairment of the normal protective airway mechanisms is common; among the frequent associations are neurologic disorders, trauma with loss of consciousness, sedative or alcohol use, poor dentition, and advanced age. Emergency measures, entailing a food extractor or the Heimlich maneuver, can be life-saving. Flexible bronchoscopy is usually successful in removing foreign bodies, although backup rigid bronchoscopy should be available and is preferred as the primary procedure at some centers. A complicating chemical bronchitis from aspiration of vegetables or nuts may affect visualization and management of the foreign body. Certain nut oils also cause a significant foreign body mucosal reaction, resulting in the development of granulation tissue that may be misdiagnosed as endobronchial tumor.

■ Trauma

A variety of traumatic injuries may eventuate in UAO.

Facial Trauma

Emergency access to the airway is necessary in up to 6% of cases of facial trauma complicating motor vehicle accidents and other causes of crush injuries. If intubation is difficult or impossible due to the injury or related airway obstruction, emergency cricothyroidotomy or tracheostomy must be considered.

Laryngotracheal Injuries

Blunt and penetrating injuries to the laryngotracheal airway are rare. Without a high index of suspicion, clinicians may miss the diagnosis. The incidence of penetrating injuries appears to be increasing.

Stridor, wheezing, dysphonia, hemoptysis, and general neurologic deficits are common. Cervical crepitus and subcutaneous emphysema also may be present. Cervical ecchymoses and hematomas, pneumomediastinum, and pneumothorax should prompt consideration of a laryngotracheal injury.

Management includes prompt securing of the airway, but blind endotracheal intubation should be avoided, since it carries the risk of complete airway obstruction. Some experts recommend tracheostomy as the primary airway management strategy. Awake fiberoptic intubation can be useful. Flexible fiberoptic laryngoscopy, rigid or flexible bronchoscopy, and CT imaging may be helpful in assessing the degree of injury. Unfortunately, the mortality of laryngotracheal injuries remains high.[60] Thoracic injuries and closed head injuries are commonly associated pathologies that can influence management and prognosis.

Inhalation Injuries

Thermal and chemical injuries to the upper respiratory tract may lead to serious consequences, including airway obstruction. The mortality rate increases significantly when burns are accompanied by inhalational injury.[61] Symptoms can be delayed in becoming manifest, making early recognition and intervention vital in the management of patients with inhalational injuries. The presence of cough, dyspnea, hoarseness, or loss of consciousness, or the findings of singed nasal hairs, carbonaceous sputum, or burns involving the face indicate a high likelihood of inhalation injury.

Early flexible bronchoscopy remains important in evaluation and management of patients with inhalation injuries, enabling the assessment of the extent and severity of the injury, procurement of samples for bacteriologic studies, and bronchoscopic intubation, as necessary.[62] Translaryngeal intubation is the standard method of securing the airway in inhalation injury; early tracheostomy is used in some centers. A role for prophylactic corticosteroids or antibiotics is currently not supported by published reports. Significant tracheal stenosis may develop in patients who survive the initial insult especially in those with larger total body surface area involved, higher grade of inhalational injury, and longer duration of intubation.[63]

■ Endotracheal Tube–Related Trauma

Postextubation stridor due to glottic edema, laryngospasm, or laryngotracheal stenosis is a serious event. Risk factors include duration of intubation, emergency intubation, and height/endotracheal tube size ratio.[37] Reintubation rates for UAO due to endotracheal tube–related trauma in critically ill patients have been reported to range from 4% to 33%. An "acceptable" rate is considered to be 5% to 15%. Clinical practice guidelines support the use of pre-extubation glucocorticoids in patients deemed high risk for post extubation stridor who have failed a cuff leak test.[64]

Translaryngeal intubation may also produce either unilateral or bilateral vocal cord paralysis. Affected patients may present with hoarseness or airway obstruction. Findings may occur immediately after extubation or be delayed. Prolonged intubation, use of a large endotracheal tube, placement of the tube cuff close to the vocal cords, or use of excessive cuff pressure are risk factors. The condition usually resolves spontaneously within 10 weeks.

Vocal cord (contact) granuloma may develop 4 to 6 weeks after intubation. Symptoms include prolonged hoarseness, exertional dyspnea, and stridor. Management, using antireflux medications, inhaled and systemic corticosteroids, antibiotics, botulinum toxin injection, speech therapy, smoking cessation, and rest of the voice are usually successful. Surgical intervention is reserved for cases that fail conservative management.

On occasion, dislocation of the arytenoid cartilages occurs during intubation. Rheumatoid arthritis that affects the cricoarytenoid cartilage is a risk factor for this condition. Rigid bronchoscopy or surgical interventions may be needed to reduce the dislocation. Other disorders that may cause complications during intubation include hyperostosis of the cervical spine due to ankylosing spondylitis and cricoarytenoid joint disease due to systemic lupus erythematosus.

■ Neuromuscular Disorders

Neuromuscular disorders may affect the bulbar muscles, many of which surround the upper airway (Fig. 47-23). When this occurs, resistance to airflow is increased, and the flow–volume loop often shows an inspiratory flow plateau typical of variable extrathoracic UAO. In addition, a pattern of flow oscillations during inspiration ("sawtooth pattern") may be seen.[65] The abnormal flow pattern, first noted in patients with sleep apnea,[66] is commonly seen in extrapyramidal disorders, myasthenia gravis, and motor neuron disease; it may also be seen in patients who have functional stridor and wheezing (see "Vocal Cord Dysfunction," below). In extrapyramidal disorders, the flow oscillations correspond to vocal cord tremor. In motor neuron diseases, muscle denervation causes irregular muscle fasciculation, resulting in tremor of upper airway muscles.

Upper airway symptoms may be seen in Shy–Drager syndrome with extrapyramidal involvement and in Parkinson disease.[67,68] Patients may present with symptoms of chronic dyspnea or with stridor and respiratory failure relieved by endotracheal intubation or tracheostomy. Bilateral vocal cord paralysis may also occur with familial bulbar spinal muscle atrophy, postpoliomyelitis syndrome, Parkinson disease, multiple sclerosis, acute poliomyelitis, amyotrophic lateral sclerosis, Guillain–Barré syndrome, brain stem stroke, and large cerebral hemisphere stroke. Dystonic extrapyramidal reactions due to neuroleptic medications (e.g., haloperidol) may

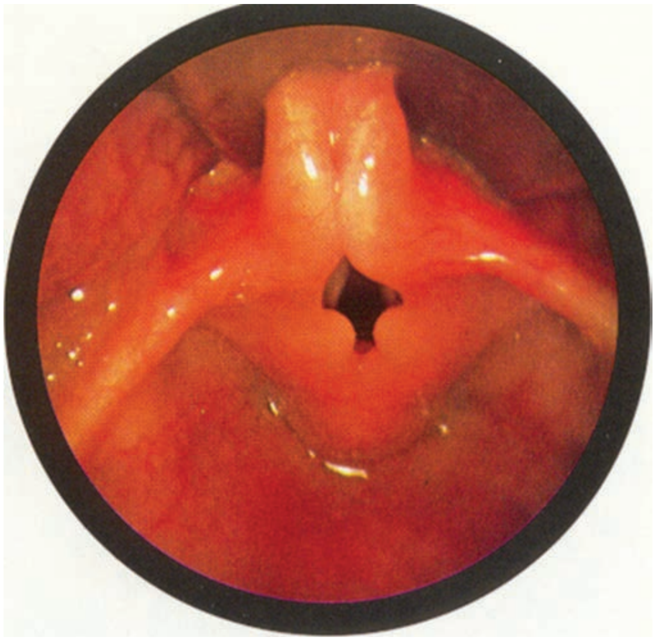

Figure 47-23 Laryngomalacia.

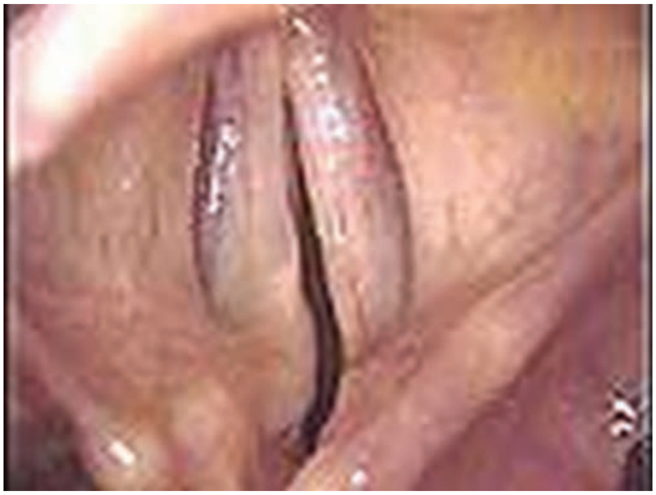

Figure 47-24 Bilateral vocal cord paralysis.

cause significant UAO. The usual reactions to these medications are akathisia, dyskinesia, dysarthria, and dystonic reactions such as torticollis. Laryngeal–pharyngeal dystonia may cause severe upper airway dysfunction, and if not reversed, symptoms can last for days or lead to respiratory arrest.

■ Bilateral Vocal Cord Paralysis

Bilateral vocal cord paralysis is a serious condition resulting in nocturnal stridor, oxygen desaturation, sleep disruption, or, in extreme cases, acute respiratory failure (Fig. 47-24). Thyroidectomy is the most common cause of bilateral recurrent laryngeal nerve injury, with its consequent bilateral vocal cord paralysis.[69] As mentioned earlier, bilateral vocal cord paralysis may occur with numerous neurologic conditions. Nonneurologic causes include endotracheal intubation injury, laryngeal trauma, infection, and thoracic aortic aneurysm. Bilateral vocal cord paralysis results in abnormalities of inspiratory flow and a distinctive flow–volume loop.

Spontaneous recovery of vocal cord motility is rare after surgical injury of the recurrent laryngeal nerve. For those patients showing no spontaneous functional recovery, several surgical techniques to achieve a glottic space enlargement are available. CO_2 laser endoscopic surgery has led to shorter hospitalization and higher patient compliance.[70,71] Endoscopic surgeries include arytenoidectomy with or without posterior true and false cord cordectomy.[72] Surgeries aim to improve breathing with minimal deglutition impairment and improve quality of voice. Restenosis of the glottis space is the main problem that leads patients to reoperations.

■ Vocal Cord Dysfunction

The glottis plays an active role in adjusting airflow, both voluntarily and through reflex control from laryngeal and lung receptors. During a normal respiratory cycle, the vocal folds widely abduct during inspiration and slightly adduct during expiration. Occasionally, the glottis can become dysfunctional in the absence of organic disease. The disorder, most commonly called vocal cord dysfunction or paradoxical vocal fold motion, is characterized by paradoxical closure of the vocal cords intermittently during inspiration. The glottis angle formed by the true vocal folds can become acute and cause airflow obstruction during inspiration and/or expiration. The mechanism is unknown but likely multifactorial. Laryngeal hypersensitivity has been associated with reflux, upper respiratory tract infections, postnasal drip, irritants, and exercise, as well as psychogenic factors.[73]

Signs and symptoms of vocal cord dysfunction resemble those of laryngeal edema, laryngospasm, vocal cord paralysis, or asthma.[74] Wheezing or stridor and shortness of breath are typical and are often so dramatic that they suggest acute asphyxia and respiratory failure. Intubation and other emergency measures are used frequently. However, symptoms are often brief and may remit without intervention. Distinguishing physical examination findings include tracheal localization of wheezing or stridor with absent peripheral airway expiratory wheezing; however, it should be understood that this might also occur during severe asthma attacks.

On pulmonary function testing, patients with vocal cord dysfunction typically have normal spirometry without evidence of obstructive ventilatory defect.[75] Some may demonstrate a pattern of variable extrathoracic airway obstruction, resulting in an increase in the ratio of $FEF_{50\%}$ to $FIF_{50\%}$. Some patients show a pattern of "sawtoothing," or fluttering of the inspiratory limb of the flow–volume loop, representing fluctuations in the abnormal cord motion (Fig. 47-25). Often, attempts to perform the flow–volume loop maneuver generate variable results from test to test. A normal alveolar–arterial oxygen gradient and absence of bronchial hyperresponsiveness are other clues to the diagnosis.

The diagnosis of vocal cord dysfunction is confirmed during direct visualization of the vocal cords during an attack. The anterior two-thirds of the vocal folds adduct and give the presence of a posterior diamond-shaped chink in the folds during inspiration.[76]

The true prevalence of the disorder is unknown because it is often mistakenly diagnosed as asthma, and many patients in fact have both vocal cord dysfunction and asthma.[77] Patients without asthma are predominantly women who have been misdiagnosed as having asthma for an average of 5 years. Typically, patients have been treated with large doses of oral corticosteroids and have experienced frequent emergency room visits, hospitalizations, and endotracheal intubations.

Psychiatric disorders are common in these patients.[78,79] Major psychiatric disorders, personality disorders, and sexual and physical

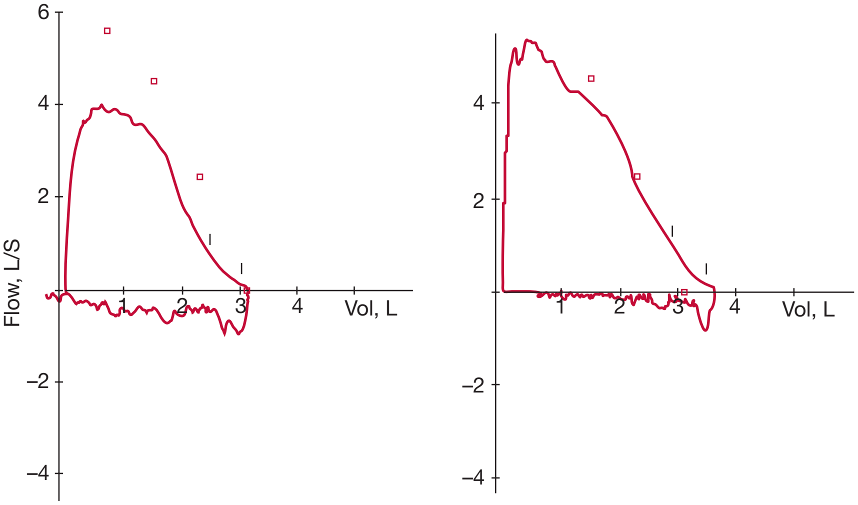

Figure 47-25 Variable extrathoracic obstruction due to vocal cord dysfunction. Two consecutive flow–volume loops from a young woman with inspiratory stridor. Variable effort accounts for the differences in configuration. $FEF_{50\%}/FIF_{50\%}$ in each is very high. The inspiratory loop is flat and demonstrates a sawtooth pattern. This pattern has also been associated with sleep apnea syndrome and various neuromuscular disorders.

abuse are commonly uncovered. Whereas many patients are unaware of their self-induced wheeze or stridor, others appear to derive secondary gain from their symptoms and manifest factitious illness. A high index of suspicion is warranted when the adventitious sounds are loudest over the neck in a patient who presents with wheezing, stridor, or both. Despite their respiratory distress, patients often have little difficulty completing full sentences and can hold their breath; the laryngeal-induced sounds disappear during a panting maneuver.

Treatment includes discussion of the diagnosis with the patient, discontinuation of unnecessary medications, and referral to a speech therapist or psychotherapist. The response to bronchodilator therapy is usually poor. Use of continuous positive airway pressure or administration of an inhaled helium–oxygen mixture may alleviate symptoms during an acute attack.[80] Botulinum toxin injection may be used in refractory cases.[81]

Angioedema

Angioedema is characterized by well-demarcated swelling of the face, lips, tongue, and mucus membranes of the nose, mouth, and throat. When the larynx is involved, UAO may occur and can be fatal. In most instances, the cause of angioedema is unclear; prior exposure to common allergens, such as drugs, chemical additives, and insect bites, should be suspected.

Counterintuitively, the most common causes of angioedema are not IgE initiated. They include reactions to histamine-releasing drugs, such as narcotics and radiocontrast materials, aspirin, other nonsteroidal anti-inflammatory drugs, and angiotensin-converting enzyme inhibitors. Hereditary angioedema, a rare cause of UAO, is an autosomal-dominant trait that causes a deficiency in production or function of C1 esterase inhibitor, a serum protease inhibitor that regulates the complement, fibrinolytic, and kinin pathways. Hereditary angioedema (HAE) is characterized by painless nonpitting edema of the face and upper airway. The disorder usually begins in childhood and becomes more prominent in adolescence. Swelling progresses over many hours and then resolves spontaneously over 1 to 3 days. Despite the slow progression, death may occur from laryngeal obstruction. Physical stimuli (cold, heat, stress) and circulating immune complex diseases (e.g., due to serum sickness or systemic lupus erythematosus) are also known to cause angioedema.

Emergency management includes foremost securing the airway. Epinephrine is used for angioedema with anaphylaxis. Administration of corticosteroids and antihistamines are often used, although current evidence suggests that such a therapy is rather ineffective in kinin-induced angioedema.[82] Thus, symptom-related medical care should be provided until the swelling has disappeared. Treatment of HAE includes C1-inhibitor concentrate, recombinant C1 inhibitor, kallikrein inhibitors (ecallantide) and bradykinin type 2 receptor antagonists (icatibant).[83–86]

MANAGEMENT OF UPPER AIRWAY OBSTRUCTION

Key elements in the management of UAO include general principles, securing the airway, and specific interventions.

General Management

The primary goals in management of any patient with UAO are assurance of adequate oxygenation and ventilation and management of the underlying condition. If airway obstruction is partial, and the patient's condition is stable, close monitoring and diagnostic studies are appropriate. Depending upon the underlying etiology, temporary measures may include close observation in an intensive care unit, elevation of the head of the bed, administration of humidified oxygen, use of a helium–oxygen inhalation mixture (heliox), systemic corticosteroids, and inhaled racemic epinephrine, pending definitive medical or surgical management.

Heliox may be useful in management of UAO when the obstruction is temporary and reversible. The physiologic rationale for heliox is based upon a reduction in work of breathing achieved through administration of a low-density gas. In particular, heliox has a lower density than does oxygen, room air, or a mixture of the two, resulting in conversion of the predominantly turbulent flow at the site of obstruction to a more laminar pattern. Furthermore, since laminar flow requires a smaller pressure gradient than turbulent flow to achieve the same flow rate, the accompanying work of breathing is less (see Chapter 10). The major limitation of the modality is an inability to deliver gas with an inspiratory fraction of oxygen ($F\text{I}_{O_2}$) of more than 40%. Despite physiologic evidence and clinical reports of efficacy, prospective, randomized studies demonstrating improved outcome in patients receiving heliox are lacking, as are data supporting use of corticosteroids or inhaled epinephrine in airway obstruction from a variety of causes.

Securing the Airway

Although under controlled circumstances, a significant portion of the so-called difficult airways and intubations may be identified in the course of a thorough preoperative assessment, the patient with impending airway obstruction presents a challenge. Under such circumstances, a critical first concern is deciding whether an artificial airway is needed emergently.[87] Regardless of the airway utilized, emphasis is placed on ensuring adequate oxygenation and ventilation.

Airways judged unsafe for routine management may be addressed according to the "difficult airway algorithm" recommended by the American Society of Anesthesiologists (see Chapter 146).[88] A difficult airway is defined as a clinical circumstance in which a conventionally trained anesthesiologist experiences difficulty using face mask ventilation, endotracheal intubation, or both.

Airway access in emergency situations may be challenging because the patient frequently is critically ill and can deteriorate quickly. The likelihood of a difficult intubation can be estimated by using the Mallampati score or a modification of the score to assess potential laryngeal exposure and prospects for adequate airway visualization.

A number of parameters, such as mouth opening distance, jaw size, thyromental distance, and cervical range of motion, have been incorporated into airway assessment scoring systems; each parameter has limited sensitivity and specificity. Combining scoring systems provides better accuracy of prediction. The "rule of threes," which is a useful, simple bedside tool, predicts successful direct laryngoscopy if the examiner can place three finger breadths (~6 to 7 cm) between the upper and lower teeth, the mandible and hyoid bones, and the thyroid cartilage and sternal notch. In the emergency setting of UAO, the most experienced physician available should secure the airway. Appropriate equipment and monitoring, along with backup resources for alternative and invasive airway management, should be available.

A variety of invasive and noninvasive techniques are available as alternatives to standard, laryngoscopy-guided orotracheal intubation. Invasive methods include surgical and/or percutaneous tracheostomy, surgical and percutaneous transtracheal (needle) cricothyrotomy, translaryngeal-guided or "retrograde" intubation, fiberoptic endotracheal intubation, and use of a rigid ventilating bronchoscope. Noninvasive techniques include use of specialized laryngoscope blades, Glidescope, guiding and lighted stylets, directional tip control tubes, and esophageal–tracheal (Combitube) or laryngeal mask airways. In selected circumstances, tactile intubation, nasotracheal intubation, or blind orotracheal intubation may be employed.

Cricothyroidotomy

Cricothyroidotomy (either surgical or based on Seldinger technique) has a long history of use in emergency access to the airway when more conservative approaches fail or are contraindicated. In early reports, a high incidence of laryngeal stenosis during long-term follow-up was noted, perhaps related to the presence of infectious laryngeal disease, the use of large-bore tubes, and prolonged intubation.[89] More contemporary reviews indicate a much lower (1.1%) incidence of airway stenosis following cricothyroidotomy.[90] The procedure is useful for short-term airway control; tracheostomy should be considered if prolonged airway access is required.

Tracheostomy

Most tracheostomies are performed on intubated patients in the intensive care unit. Percutaneous tracheostomy is rapidly becoming the method of choice in the intensive care unit and is associated with acceptable intraoperative and postoperative complication rates.[91,92] Advantages of the technique over the traditional procedure include low cost, short procedure time, and elimination of the need to transport critically ill patients to the operating room. Adaptation of percutaneous techniques for emergency situations also has been described.

In a review of more than 1100 patients who underwent tracheostomy, 76% were performed in patients who required prolonged ventilation, 6% for UAO, 7% for extensive maxillofacial trauma, and 11% as an adjunct for head and neck or chest surgeries; only 0.26% were performed as emergency procedures. Overall mortality was 0.7%.[93]

■ Interventional Bronchoscopic Techniques

Interventional bronchoscopy is discussed in Chapter 34. Use of these techniques for managing UAO is well established and is briefly summarized in the following paragraphs.

Rigid bronchoscopy allows oxygenation, ventilation, and application of various diagnostic and therapeutic interventions, including debridement of obstructing lesions, control of bleeding, and removal of foreign bodies. Complications include anesthetic risks; barotrauma; damage to teeth, lips, or gums; airway perforation; bleeding; and mucosal injury.

Thermal modalities may be used to devitalize tissue prior to mechanical debridement or to cauterize the base of lesions following debulking. Electrocautery, laser (Nd-YAG, CO_2), and argon plasma coagulation (APC) can be applied through rigid or flexible bronchoscopy. Side effects include bleeding, perforation, airway fire, and damage to cartilage. All thermal modalities are about equally as effective at achieving airway patency, and often the method of choice is clinician preference. APC has the best hemostatic properties.

Photodynamic therapy (PDT) is based on the principle of targeted tissue apoptosis after local activation of a systemically injected photosensitive chemotherapeutic agent. In essence, PDT creates a phototoxic cell reaction when nonthermal laser light is applied by bronchoscopy and activates a drug trapped in these target cells. The major disadvantage of this technique is that the tissue necrosis occurs within 48 to 72 h and as such the ability to debride the airway is delayed for several days. Bleeding and obstruction from necrotic tumor and edema are potential immediate complications. PDT may also result in airway perforation.

Standard cryotherapy, based on repeated freeze–thaw cycles to achieve cell necrosis and tissue damage, is used in benign and malignant disorders of the upper airway. A flexible cryoprobe can be inserted via flexible or rigid bronchoscopy and uses extremely cold gas at the tip cooled to −40°C to −80°C to freeze tissue. Cryotherapy has excellent hemostatic effects; the incidence of perforation or bleeding is low. Due to the delayed beneficial effect, cryotherapy is not usually used under emergent conditions. A method of debulking obstruction uses a cryobiopsy technique in which the tissue is simply frozen to the probe and then sheared from the surface, obviating the thaw cycle. Applied in this fashion, cryotherapy can be used for the immediate treatment of airway obstruction, although when used in this fashion it has less of a hemostatic effect than the thermal modalities. In addition, cryotherapy has the advantage over other thermal modalities in that cartilage is cryoresistant whereas malignant tissue is generally cryosensitive. An endoluminal cryospray catheter has been developed and has been used effectively to treat tracheal stenosis due to both benign and malignant causes.[94]

Finally, external beam radiation and brachytherapy are useful modalities for palliative management of airway obstruction and hemoptysis. For external beam radiation, unwanted exposure of adjacent structures is a limiting factor, while hemorrhage, radiation bronchitis, and fistulae with surrounding structures are known complications of radiotherapy. The maximal effect of all radiation techniques is delayed days to weeks, and there is a risk of worsening of obstruction during therapy due to airway edema.

■ Airway Stents

Airway stents are used in the palliative management of both benign and malignant airway obstruction.[95] Available tracheal stents include expandable metal, silicone, and hybrid prostheses. Major complications include stent migration, granulation tissue formation, and stent interference with mucociliary clearance. In a series of more than 1500 patients who had stents placed for UAO due to benign or malignant disorders, stent migration was reported in 9.5%, granulation tissue formation in 7.9%, and obstruction in 3.6%. Due to concerns regarding stent fracture and the likelihood that stents will remain in place longer in benign disease, the FDA posed a warning on the use of metallic airway stents for this indication. Currently, metallic stents are only recommended in benign disease for patients who are not candidates for or have failed a trial of silicone stent placement. Recent advances in 3D airway modeling and printing have allowed for the development of customized patient-specific silicone stents that have had promising results in patients with complex stenosis.[96]

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CHAPTER 48

Cystic Fibrosis

Judith A. Voynow
Andrea Kelly
Flora K. Szabo
Thomas F. Scanlin

INTRODUCTION

Cystic fibrosis (CF) is an inherited disease that has a high frequency in Caucasians. The disorder affects all exocrine glands, with symptoms involving the lungs and pancreas usually dominating the clinical picture. CF is challenging to diagnose and manage because of tremendous variability in the degree and pattern of involvement of organs in different persons and the burden of therapy to maintain health. This chapter focuses on the pathophysiology and management of CF. Our current understanding of the genetics and underlying molecular biology are highlighted. Recently, FDA-approved, highly effective oral CFTR modulators have become available to most patients. These new drugs have markedly improved CFTR function and clinical outcomes in most patients with severe mutations. The prognosis is improving. The majority of patients now live past the age of 18 years, and the median predicted age of survival is now in the late 40s. However, complications of the disorder due to established multiorgan disease persist and are addressed in this chapter. Finally, the approaches to develop therapies to correct mutant CFTR in those patients not responsive to the current CFTR modulators will be described.

GENETICS

CF demonstrates an autosomal-recessive pattern of inheritance. In the United States, the incidence of the disease is approximately 1 in 3000 in Caucasians, 1 in 10,000 in Hispanics, and 1 in 15,000 in African Americans,[1] and the incidence is being established in patients of Asian ancestry.[2] The frequency of unaffected heterozygote carriers of a CF mutation is estimated to be 1 in 26 in persons of Northern European ancestry.

CF is caused by mutations in a single gene named the *cystic fibrosis transmembrane conductance regulator* (CFTR). This gene was identified with an approach known as positional cloning, which permitted mapping of the gene without prior knowledge of the biochemical defect through use of polymorphic DNA markers. Following a series of molecular cloning experiments, which included “chromosome walking” and “jumping,” a candidate gene was identified. This “candidate gene” was proved to be the CF gene in 1989, largely through the discovery of a frequent mutation.[3,4]

The CF gene spans approximately 230 kb of DNA and contains 27 exons. The mRNA is 6.5 kb and is detected in a variety of tissues, including lungs, pancreas, and sweat glands, which are predominantly affected in pathogenesis of the disease. The deduced polypeptide was predicted to be an integral membrane glycoprotein containing 1480 amino acids (Fig. 48-1; see “Pathogenesis”). Several major and minor splicing variants in the transcripts have been described in individuals with and without CF. In most cases, however, the significance of the alternative splicing variants is not clear.

The most common CF mutation, and the first to be described, is a three-base deletion in exon 10 that causes a deletion of phenylalanine from position 508 (ΔF508 or F508del) of the CFTR glycoprotein. This mutation accounts for 66% of CF mutations.[5] However, more than 2100 CF mutations have now been reported (*www.genet.sickkids.on.ca*), and the list continues to grow. In addition, many benign sequence variations have been described. A listing of the most common mutations and their relative frequency is included in Table 48-1. The large number of mutations makes accurate detection of a satisfactory percentage of carriers extremely difficult, and carrier screening for the general population has not been recommended or implemented. Testing for 32 of the most common mutations is widely available; such testing detects approximately 90% of the carriers in Caucasians of Northern European descent. Newborn screening for CF is now established in all 50 states in the United States, but the methods employed vary from state to state.[6] In families with an affected individual and known mutations, prenatal diagnosis and carrier testing using direct detection of mutations is accurate and available. In families with a member diagnosed as having CF, but with undetected mutations, sequencing of the complete CFTR coding region and critical intronic regions also is now available to detect rare mutations.

PATHOGENESIS

Discovery of the gene responsible for CF and description of its product, CFTR, have provided the necessary foundation for understanding the pathogenesis of the disorder at the molecular and cellular levels. CFTR is an integral membrane glycoprotein of approximately 170 kDa that is expressed in epithelial cells of affected organs. CFTR contains 1480 amino acids, which are arranged in 12 transmembrane domains, 2 nucleotide-binding domains, and a putative regulatory domain (Fig. 48-1). The most common mutation, F508del, is a three-base deletion that causes deletion

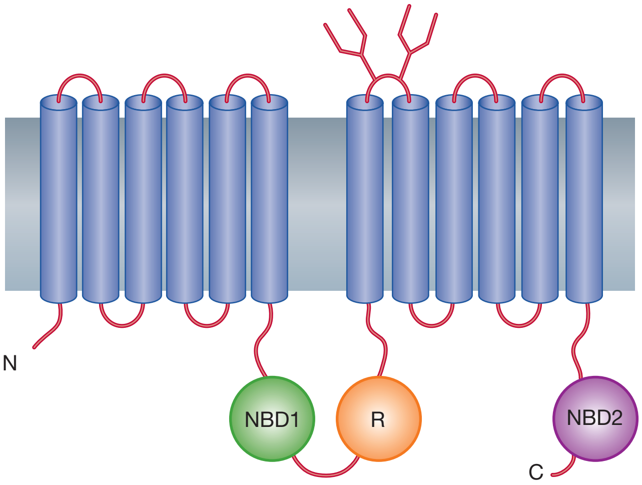

Figure 48-1 Domain model of the cystic fibrosis transmembrane conductance regulator (CFTR). Based on hydrophobicity plots, CFTR has 12 transmembrane-spanning domains, two nucleotide (N)-binding domains (NBD 1 and NBD 2), and a regulatory (R) domain. The 12 transmembrane domains form the ion channel “pore.” In the closed state, the “R” domain is believed to obstruct the channel. Channel opening requires binding of two adenosine triphosphates (ATPs) to the nucleotide binding domains. This model is similar to other ATP-binding cassette transporter proteins that bind ATP and transport ions or micronutrients. *(Reproduced with permission from Riordan J, Rommens JM, Kerem B, et al. Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA. Science. 1989;245:1066–1073.)*

TABLE 48-1 Most Common CFTR Mutations in the United States

Name of Mutation	Frequency (%)	Population with High Prevalence
ΔF508	66	
G542X	2.4	Spanish
G551D	2.1	English
3120+1G→A	1.5	African American, Arabian
W1282X	1.4	Ashkenazi Jewish
N1303K	1.3	Italian
R553X	0.9	Hispanic
621+1G→T	0.9	Multiethnic
1717–1G→A	0.7	Italian
3849+10kbC→T	0.7	Hispanic
R117H	0.7	
1898+1G→T	0.4	East Asian
ΔI507	0.3	Hispanic
2789+5G→A	0.3	
G85E	0.3	
R347P	0.2	
R334W	0.2	Multiethnic
R1162X	0.2	Multiethnic
R560T	0.2	
3659delC	0.2	
A455E	0.2	
2184delA	0.1	
S549N	0.1	Multiethnic
711+1G→T	0.1	
R75X	0.2	Hispanic[a]
406–1G→A	0.2	Hispanic[a]
I148T	0.2	Hispanic/French[a]
2307insA	0.2	African American[b]
A559T	0.2	African American[b]
ΔF311	0.2	African American[b]
G480C	0.2	African American[b]
405+3A→C	0.2	African American[b]
S1255X	0.2	African American[b]

Data based on the most frequent mutations found overall in the United States. Mutations that are expressed at higher frequency in Hispanic (a) or African-American (b) populations are indicated.

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of phenylalanine from position 508, located in the proposed first nucleotide-binding domain. The original structural model, which was based on hydrophobicity plots, has proved to be essentially correct in its main features. CFTR shares many structural features with the "adenosine triphosphate (ATP)-binding cassette" transporter family, which includes P glycoproteins, as well as several bacterial transporters. CFTR has been clearly shown to function as an apical chloride channel in airway epithelial cells.[7]

The localization of CFTR to the apical aspect of airway epithelial cells and the role of CFTR as an apical chloride channel fits nicely with the simplest hypothesis to account for the pathogenesis of pulmonary disease in CF: Decreased secretion of chloride and water by airway epithelial cells results in dehydrated mucus. However, CFTR has other functions. CFTR transports bicarbonate;[8] loss of CFTR function results in acidification of the small intestinal lumen and in the airway lining fluid, causing mucus stasis.[9] CFTR regulates other ion channels, including the epithelial sodium channel. Loss of CFTR causes increased reabsorption of sodium; increased epithelium sodium channel activity alone alters regulation of ions and water, resulting in mucus obstruction of airways.[10] Alternatively, CFTR may also function in *intracellular* membranes (e.g., endoplasmic reticulum, endosomes, phagosomes, and clathrin-coated vesicles). Loss of CFTR localization or function in intracellular membranes may explain abnormalities of CF glycoproteins: increased sulfation of respiratory mucins, with decreased sialylation and increased fucosylation of both secreted and membrane glycoproteins.[11] Altered glycosylation of airway glycoproteins may significantly impact bacterial–epithelial interactions and innate immune functions in the lung.[12]

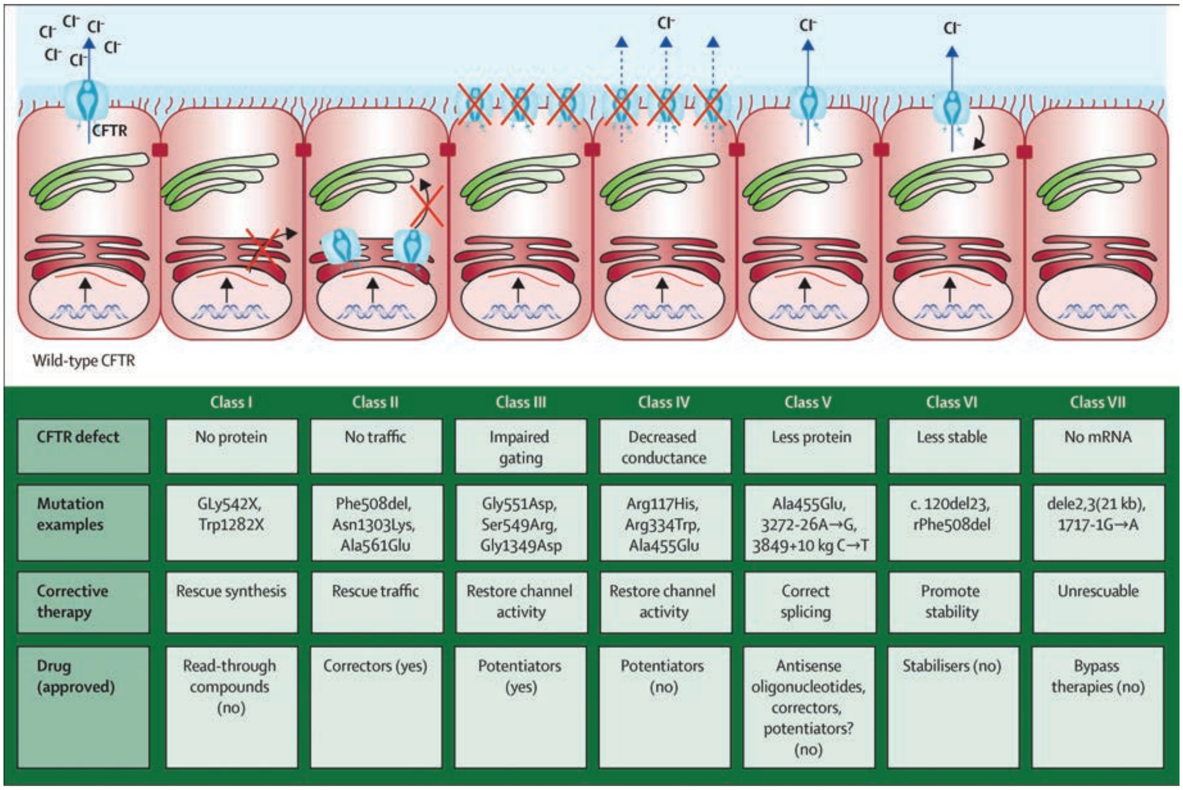
In addition to the effect of CFTR on epithelial ion channels and glycoprotein processing, loss of CFTR function negatively impacts pulmonary innate immunity.[13,14] Absence of CFTR function is associated with impaired bacterial killing both in vivo[15] and in vitro due to defective function of antimicrobials including human beta-defensin 1 and lysozyme.[16] CFTR also transports thiocyanate, a substrate required for lactoperoxidase activity; the loss of CFTR inhibits this antimicrobial.[17] Furthermore, in the CF airway milieu, macrophage function to resolve infection is impaired.[14] In addition, mucoid obstruction of airways, even in the absence of detectable infection, also activates neutrophilic inflammation.[18,19] Neutrophils have impaired phagocytosis in the CF airway, resulting in the release of neutrophil extracellular traps associated with high concentrations of neutrophil elastase in the airway.[20] In the CF airway, neutrophil elastase overwhelms the antiprotease capacity and has several proinflammatory activities.[21] Neutrophil elastase cleaves complement and immunoglobulins interfering with bacterial opsonization, upregulates respiratory tract mucins,[21] contributing to high airway mucin concentrations, and exacerbates protease injury by activating airway matrix metalloproteases.[22] CF airways have increased oxidant stress due to neutrophilic inflammation and reduced antioxidants, such as glutathione,[23] Together, these factors synergistically increase the inflammatory milieu in the airways in CF.

An impediment to progress in understanding the pathogenesis of CF lung disease was the absence of a completely suitable animal model. A number of mouse models of CF have been developed, and while these have been useful in understanding some features of the disease, such as the regulation of inflammation, a drawback has been the absence of spontaneous development of lung disease.[24] The development of CF ferret models[25,26] and CF pig models[15,27] has elucidated the mechanisms of some features of initial pathogenesis of CF.

CFTR mutations have been grouped into seven classes depending on the effect of the mutation on the expression, processing, and function of the protein (Fig. 48-2). The most common mutation, F508del, is a processing mutation (class II) in which very little of the mutant protein reaches the apical surface. In addition, if the mutant protein escapes lysosomal degradation and reaches the apical membrane, F508del protein has impaired ion channel function (a feature of class III mutations). Class III CFTR mutations localize to the cell membrane but lack ion channel function. Class I mutations are premature termination codon (PTC) mutations that decrease mRNA abundance and shorten mRNA half-life, resulting in minimal translation of CFTR protein. Classes I–III and VII constitute the most severe mutations of CFTR, while classes IV–VI are considered more mild mutations.

Class IV mutations have altered anion conductance through the channel pore; class V mutations have alternative splicing that impacts mRNA abundance; and class VI mutations have decreased channel protein half-life at the apical membrane. Class VII mutations fail to transcribe mRNA and will likely require CFTR bypass therapy.[28]

Recent insights concerning the mechanisms of these mutations have led to new highly effective CFTR modulator therapies for class



	Class I	Class II	Class III	Class IV	Class V	Class VI	Class VII
CFTR defect	No protein	No traffic	Impaired gating	Decreased conductance	Less protein	Less stable	No mRNA
Mutation examples	GLy542X, Trp1282X	Phe508del, Asn1303Lys, Ala561Glu	Gly551Asp, Ser549Arg, Gly1349Asp	Arg117His, Arg334Trp, Ala455Glu	Ala455Glu, 3272-26A→G, 3849+10 kg C→T	c. 120del23, rPhe508del	dele2,3(21 kb), 1717-1G→A
Corrective therapy	Rescue synthesis	Rescue traffic	Restore channel activity	Restore channel activity	Correct splicing	Promote stability	Unrescuable
Drug (approved)	Read-through compounds (no)	Correctors (yes)	Potentiators (yes)	Potentiators (no)	Antisense oligonucleotides, correctors, potentiators? (no)	Stabilisers (no)	Bypass therapies (no)

Figure 48-2 Classification of cystic fibrosis transmembrane conductance regulator (CFTR) mutations by molecular and biochemical abnormalities. This schematic depicts the effect of different classes of CFTR mutations on expression and function in the cell. Class I mutations block mRNA transcription. Class II mutations prevent normal CFTR protein processing and localization. Class III mutations permit CFTR localization at the apical membrane but inhibit chloride channel conductance. Class IV mutations result in partial chloride channel conductance. Class V mutations affect transcription, translation, or protein processing, resulting in reduced CFTR expression at the apical membrane. Class VI mutations cause increased turnover at the plasma membrane. Class VII mutations are due to large deletions in CFTR resulting in mRNA transcription failure. In the box below the figure, the mutant CFTR defect is described, examples of mutations in each class are provided, and the approach to corrective therapy and classes of drug therapies are listed. Class VII mutations will not be amenable to CFTR correction and potentiation because no RNA is generated; these patients will require CFTR bypass therapy.

II and III mutations (see "Treatment," below). Intensive research continues to focus on developing therapies for patients with class I and VII mutations and for rare mutations with too few patients for definitive clinical trials.

PATHOPHYSIOLOGY

In CF, all exocrine glands appear to be affected primarily, albeit to varying degrees. Because exocrine glands perform highly specialized functions in a variety of organs—for example, in the skin, respiratory tract, gastrointestinal tract, and reproductive system—the number of possible symptoms and complications in CF is large. Table 48-2 highlights the complications and symptoms of CF according to the age groups in which they most often occur. Obstruction of exocrine ducts by viscous secretions appears to play a cardinal role in the pathogenesis of almost all manifestations of the disease. In 10% to 20% of patients, the initial manifestation is often *meconium ileus*—that is, obstruction of the intestine by thick, viscous meconium stool. Chronic pulmonary disease, pancreatic insufficiency, and focal biliary cirrhosis progress gradually throughout the course of the disease, albeit at different rates in different patients. Progressive obstruction of exocrine ducts is a regular feature of the disease except in sweat glands, where obstruction of ducts has not been implicated in pathogenesis.

■ Respiratory Tract

In the lungs, hypersecretion of viscid mucus and chronic bacterial infection combine to produce a progressive and distinctive type of chronic obstructive airway disease that eventually leads to diffuse, severe bronchiectasis. The earliest pathologic lesions are found in the distal bronchioles. The viscid secretions are a primary defect due to mutant CFTR. This is supported by the demonstration in CF pig models of mucus tethered to submucosal ducts,[29] as well as failure of mucociliary clearance due to respiratory mucin adherence to airway epithelia.[30,31] Furthermore, the primary role of abnormal CF mucus in lung pathophysiology is also supported by evidence of muco-obstruction of airways in infants with CF, who have not yet developed any evidence of bacterial infection or structural injury of the airways.[19]

With the use of sophisticated culture methods, bacterial pathogens can almost invariably be isolated from the respiratory tract of patients with CF. The most common pathogens isolated from sputum cultures are *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Less commonly found are *Escherichia coli*, *Klebsiella*, and *Hemophilus influenzae*. In later stages of the disease, *Pseudomonas* usually predominates. By adulthood, more than 70% of patients are colonized with *P. aeruginosa*. Chronic infection with *P. aeruginosa* elicits an anaerobic milieu within mucus plugs in the CF airway.[32] Using anaerobic culture conditions, large numbers of anaerobes, particularly *Prevotella*, *Veillonella*, and *Propionibacterium*, were detected in CF sputum but not in induced sputum from healthy volunteers.[33] There is a correlation between *Pseudomonas aeruginosa*–positive cultures and presence of the anaerobes.

Multidrug-resistant organisms (MDRO) are detected in CF sputum cultures with higher prevalence and chronicity. They are apparently

TABLE 48-2 Presenting Signs and Symptoms of CF

Infancy	Childhood	Adolescence/ Adult
Positive prenatal test for CF mutations or hyperechoic bowel on ultrasound	Pulmonary infection with *Staphylococcus* and *Pseudomonas*	Chronic bronchitis with bronchiectasis
Positive CF newborn screen	Malnutrition with steatorrhea and pancreatic insufficiency	Pansinusitis
Meconium ileus	Heat prostration with hypoelectrolytemia and metabolic alkalosis	Hemoptysis
Obstructive jaundice	Atypical asthma with clubbing and/or bronchiectasis	Recurrent pancreatitis
Edema with hypoproteinemia and hypothrombinemia	Esophageal varices and/or hypersplenism	Cholelithiasis
Failure to thrive	Nasal polyps	Chronic abdominal pain and constipation
Salty taste and/or salt loss syndrome		Obstructive apnea
Rectal prolapse		CF-related diabetes
Intestinal obstruction with or without intussusceptions/volvulus		Osteopenia
Recurrent pneumonia/ bronchiolitis		Chronic respiratory failure

associated with acute and chronic administration of antibiotics to suppress *P. aeruginosa*. These pathogens include *S. maltophilia*, *A. xylosoxidans*, and *B. cepacia complex*. Other opportunistic pathogens, including *Aspergillus* and nontuberculous mycobacteria, also have been detected more commonly in CF sputum cultures. It is challenging to determine whether these MDRO are actively contributing to CF lung disease or are commensal pathogens present in bronchiectatic airways.

Neutrophil-dominated lower-airway inflammation also plays a primary role in the pathogenesis of the characteristic central bronchiectasis of CF.[34] Bronchoalveolar lavage fluid (BALF) demonstrates increased neutrophils, neutrophil elastase, and various cytokines, especially IL-8, in infants with CF and detectable BALF infection compared with control subjects.[35,36] Importantly, in a prospective study of serial bronchoscopies and chest CT scans in infants diagnosed with CF by newborn screening, the presence of neutrophil elastase in BALF in infants with CF at 3 months of age is associated with risk for development of persistent bronchiectasis between 1 and 3 years of age.[37,38] Viral infections in infants with CF are associated with an increased risk for acquisition of *P. aeruginosa* infection and increased BALF neutrophils and cytokines.[39]

Typically, respiratory secretions increase when a patient with CF, already chronically colonized with *Pseudomonas*, develops a viral respiratory tract infection.[39] In turn, the increase in secretions leads to a gradual increase in cough and sputum production and then to an exacerbation of the pulmonary disease, usually manifested by increase in respiratory rate; retraction of the chest during inspiration; and diffuse, coarse inspiratory crackles. Leukocytosis is common. The chest radiograph demonstrates worsening hyperinflation. Both peribronchial thickening and nodular or cystic densities are more marked than usual. Pulmonary function tests show a worsening over baseline. Usually, residual volume (RV) increases; forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1) decrease; the forced expiratory flow between 25% and 75% of the exhaled vital capacity ($FEF_{25\%–75\%}$) also decreases. Treatment using antibiotics and chest physiotherapy generally succeeds in restoring most indices of pulmonary function to, or almost to, baseline. However, *Pseudomonas* and *Staphylococcus* often persist in sputum cultures.

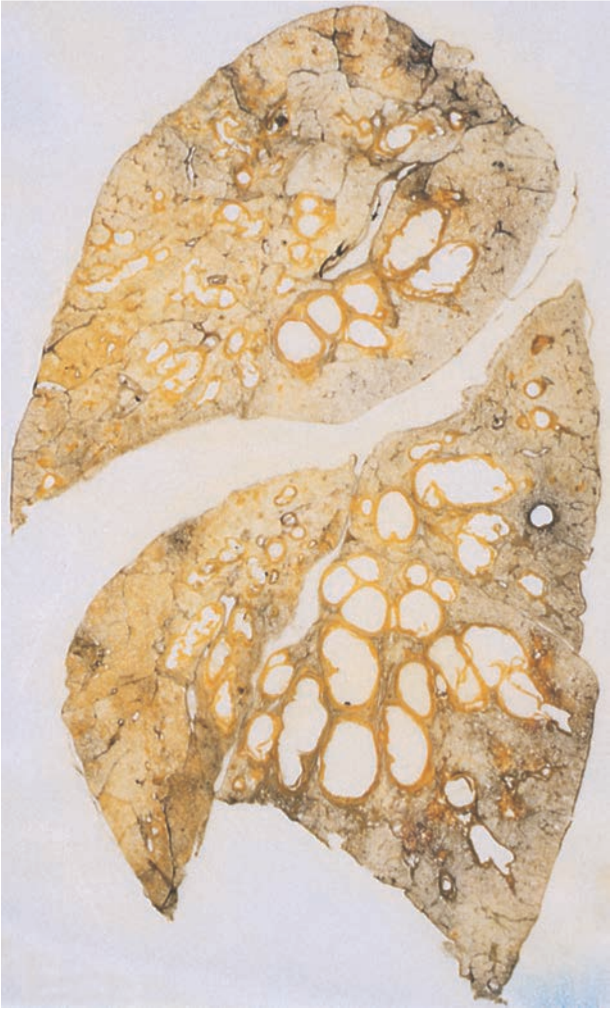


Figure 48-3 Section of lung from autopsy of a patient with CF, demonstrating remarkable dilation of large airways and preservation of intervening pulmonary parenchyma. *(Reproduced with permission from Dr. S. Moolten.)*

The most attractive hypothesis to account for the pattern of response to treatment is that therapy reduces the number and, probably, virulence of organisms. Despite the return to baseline after an exacerbation, however, the cumulative effect of repeated episodes is progressive bronchiectasis or atelectasis, or a combination of the two, accompanied by a gradual and irreversible decrease in pulmonary function. The striking degree of airway destruction and relative sparing of the pulmonary parenchyma at autopsy are shown in Fig. 48-3. A simplified scheme illustrating the evolution of the process is shown in Fig. 48-4.

■ Gastrointestinal Tract

As the average life expectancy of cystic fibrosis patients with CF has increased over the decades, gastrointestinal manifestations also have come to the forefront. Pancreatic insufficiency is one of the

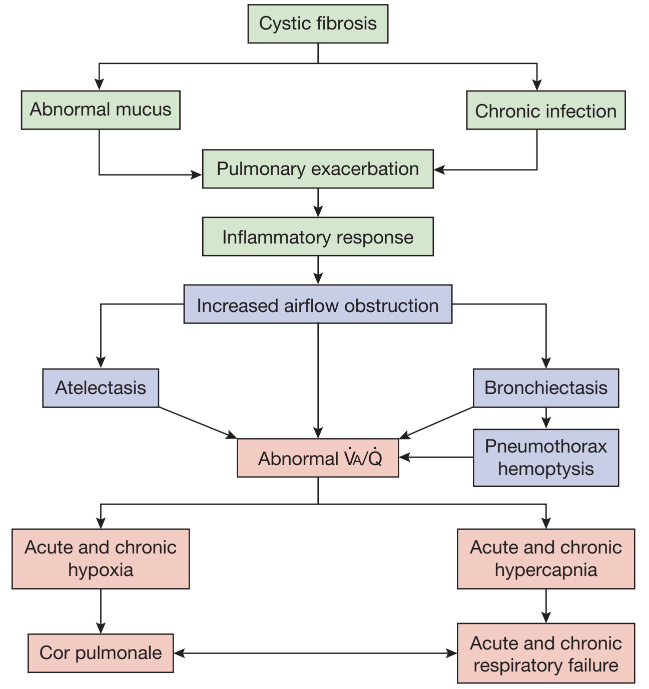


Figure 48-4 Simplified scheme for pathogenesis and progression of pulmonary disease in CF.

most recognized gastrointestinal manifestations of CF, though there are several genetic mutations that are characterized by pancreatic sufficiency.[40] Although pancreatic function may be either normal or abnormal at birth, it gradually becomes increasingly abnormal in most patients with CF, and about 85% of patients become pancreatic insufficient by 2 years of age.[41–43] As the pancreatic ducts become progressively obstructed by thick, viscous secretions from the exocrine portion of the organ, pancreatic enzymes that are trapped within the ducts lead to autodestruction of the pancreas. A cycle of destruction and obliteration of the ducts is set into motion, leading to cystic dilation of ducts proximal to sites of obstruction and fibrosis of the body of the pancreas. The term *cystic fibrosis* comes from the appearance of the diseased pancreas, characterized by cysts and fibrosis.[44] Pancreatic disease begins in utero,[45] and the degree of pancreatic insufficiency correlates with the class of CFTR mutations. Individuals with two severe mutations in classes I, II, III, and VI are at risk for earlier onset of pancreatic insufficiency. In advanced stages of the disease, pancreatic fibrosis sometimes causes obliteration of the islets of Langerhans and, consequently, diabetes. While typically described as the primary mechanism in diabetes development, this concept has been challenged by the notion that CFTR may have a direct effect on β-cell dysfunction as discussed in the next section.

The liver and biliary tract also are affected in CF. Hepatobiliary disease is thought to have a prevalence of about 30% and is now known to start in childhood. Gallbladder anomalies may be seen in about 24% to 50% of patients and include microgallbladder, gallstones, and gallbladder dysfunction.[46] Here also, the primary mechanism appears to be obstruction of small intrahepatic bile ducts by abnormally viscid secretions, leading to accumulation of toxic bile acids, depletion of hepatic antioxidants, and subsequent liver injury. CFTR is localized to the apical surface of the bile duct and gallbladder epithelium and not in the hepatocytes. Some newborn infants with CF develop the inspissated bile syndrome, characterized by prolonged obstructive jaundice starting at 2 to 8 weeks of age. The jaundice often clears without therapy. Gallstones and cholecystitis are, in part, secondary to hypokinesis of the gallbladder and affect a significant percentage of CF patients.[47,48] Interestingly, the stones are not cholesterol stones as they are in the general population, but rather pigment stones. This is thought to result from abnormal acidification of bile.

Cystic fibrosis–associated liver disease (CFLD) is now considered the third leading cause of death in CF patients following death from lung disease and from complications of lung transplantation. CFLD is more likely to occur in patients with class I to III mutations.[49] Other risk factors for liver disease appear to be male sex, meconium ileus, PiZ heterozygous state, and TGF-β1 polymorphisms. Over time, impaired secretion and deposition of viscous bile and its stagnation may damage hepatocytes directly. Asymptomatic elevations of liver enzymes (AST, ALT, and GGT) can be seen intermittently in 40% to 50% of patients with CF.[50] Hepatic steatosis is frequently seen[51] and may be related to malnutrition or deficiency of essential fatty acids, choline, and carnitine. Hepatic stellate cell activation stimulates the development of fibrosis, resulting in focal biliary cirrhosis. Multilobular cirrhosis and portal hypertension also are seen. More interest has been given to noncirrhotic portal hypertension characterized by nodular regenerative hyperplasia and obliterative venopathy secondary to luminal narrowing of the portal vein from smooth muscle hyperplasia.

There has been increasing interest in understanding the role of intestinal microbiota in the development of CF liver disease. The gut in cystic fibrosis patients is greatly affected not just by CFTR dysfunction, but also by chronic antibiotic exposures, CF-specific bacterial colonization, and increased luminal acidity and permeability.[52] The gut–liver axis via the portal vein likely plays a role in the link between altered gut microbiome and mucosal lesions and increased risk for cirrhosis.

The gut has a very high concentration of CFTR protein, so it is not surprising that this organ is greatly affected in CF. Within the gut, the duodenum has the highest CFTR mRNA levels.[53] Normally, the highest production of bicarbonate is found in the proximal intestines, quickly alkalinizing secretions from the stomach, allowing appropriate activation of pancreatic enzymes and micelle formation. The CF gut is characterized by decreased bicarbonate formation resulting in increased intraluminal acidity and increased viscosity of mucus, leading to malabsorption and bacterial overgrowth.[53–55] The CF gut is also known to have impaired motility. This may be secondary to high levels of prostaglandins and bacterial overgrowth rather than a direct effect of defective CFTR on smooth muscles.[56,57] As a result of abnormal mucus and motility, the most striking pathologic change in the intestines is hyperplasia of the mucous glands and goblet cells. Biochemical abnormalities in intestinal mucins may contribute to malabsorption of specific nutrients and bile acids. Much of the malabsorption in CF can be corrected by administration of pancreatic enzyme replacement therapy (PERT). However, the abnormal mucins may lead to slowing of intestinal transit time; the slowing, combined with maldigestion of food substances, sometimes causes fecal impaction in the terminal ileum and ileocecal area. This occurs in meconium ileus at birth and also in a condition referred to as *meconium ileus equivalent* or *distal intestinal obstruction syndrome (DIOS)* later in life. The fecal impaction, in turn, can cause volvulus or intussusception of the bowel (Fig. 48-5).

Rectal prolapse is a known, although not frequently noted, problem in CF.[58] Treatment of constipation and measures to reduce straining are usually sufficient to prevent continued prolapse.

Gastrointestinal malignancy is a growing problem, now that patients have increasing life expectancy; lifetime risk is increased 23-fold.[59,60] There are no formal recommendations regarding the timing of screening for colorectal cancers.

■ Endocrine Insufficiencies

A variety of endocrine disorders are well recognized in CF and are described below.

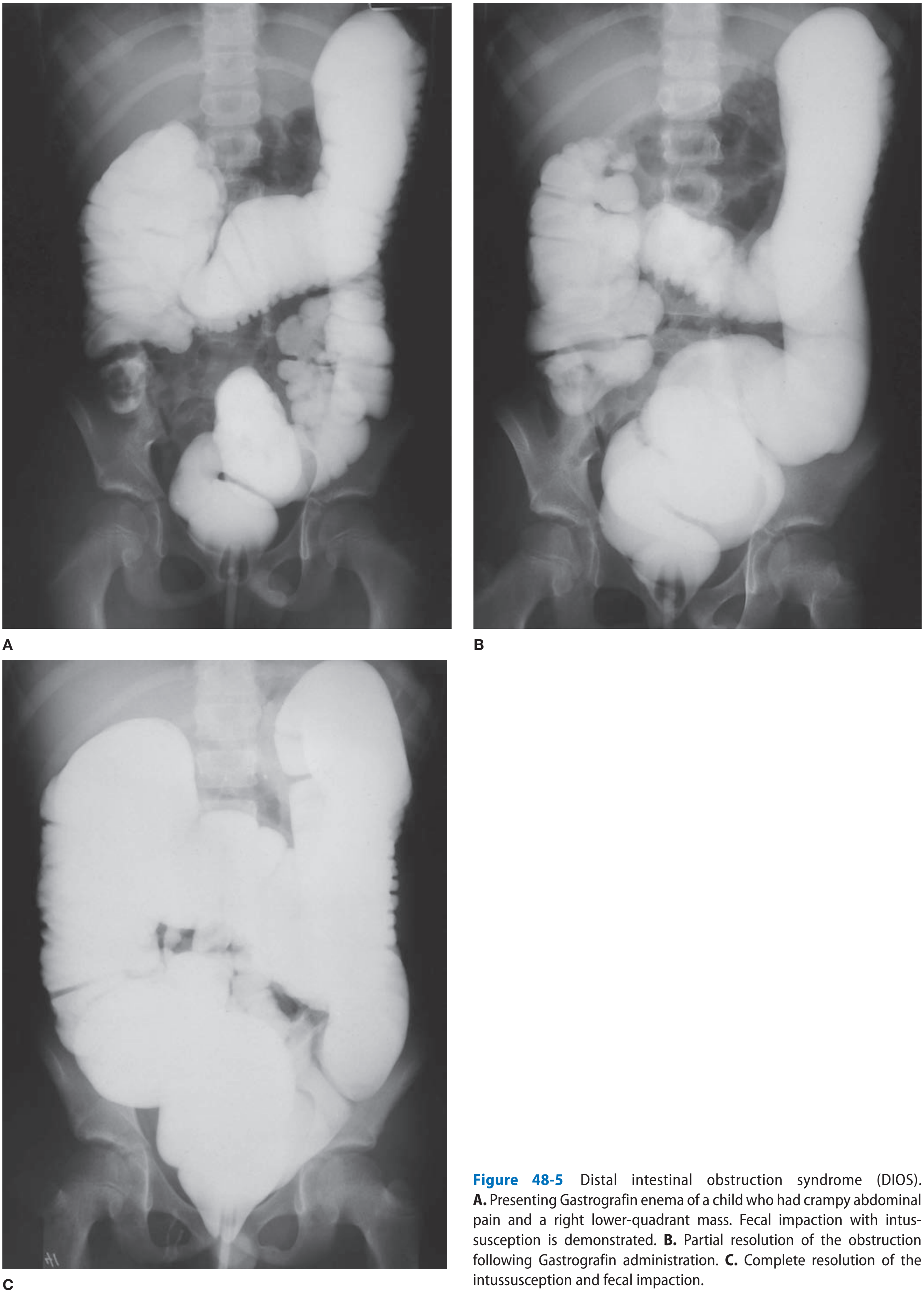


Figure 48-5 Distal intestinal obstruction syndrome (DIOS). **A.** Presenting Gastrografin enema of a child who had crampy abdominal pain and a right lower-quadrant mass. Fecal impaction with intussusception is demonstrated. **B.** Partial resolution of the obstruction following Gastrografin administration. **C.** Complete resolution of the intussusception and fecal impaction.

Cystic Fibrosis–Related Diabetes (CFRD)

Diabetes mellitus is a common comorbidity in CF, and it increases in frequency with increasing age. According to data from the University of Minnesota, where annual CFRD screening is recommended for all patients ≥6 years, CFRD affects 2% of children, 19% of adolescents, and 40% to 50% of adults with CF.[61] Similarly, CFRD was found in over a third of 775 patients age ≥6 years undergoing CFRD screening over a 15-year period.[62]

Underscoring its relevance, CFRD has been associated with decreased survival,[63–69] worse pulmonary function, and lower BMI.[68] Declines in pulmonary function and nutritional status have been observed even prior to CFRD onset.[67,70] Moreover, less significant glucose impairments are associated with greater declines in nutritional status over the previous year in children;[70] these findings suggest that more subtle glucose abnormalities may be clinically relevant in CF. One particularly relevant manifestation of impaired insulin secretion after the first 30 min of eating is compensatory late insulin secretion at 60 to 90 min that subsequently translates into postprandial hypoglycemia.[71,72] Microvascular complications such as retinopathy, nephropathy, and neuropathy also occur in CFRD but may be limited to those individuals with fasting hyperglycemia.[62]

Fortunately, early identification and treatment of CFRD appear to curb the impact of CFRD upon survival.[61] Insulin treatment of adults with CFRD without fasting hyperglycemia improves BMI,[73] and small studies have found that insulin treatment improves weight in children, even prior to development of CFRD.[74–76]

As described above, CFRD is considered an insulin-deficient state. In fact, delayed and blunted insulin secretion in response to a glucose load or meal prevail even in the setting of "normal" glucose tolerance in CF;[77–80] with oral glucose tolerance testing (OGTT), early insulin secretion defects are present for 1 h with glucoses as low as 155 mg/dL.[80,81] These abnormalities progress with worsening glucose intolerance.[77,79,82] This progressive decline in insulin secretion has traditionally been considered a product of "collateral damage" extending from obstructive damage to the exocrine pancreas.

This "bystander" model has been challenged in more recent years. Animal models suggest CFTR may play a more direct role in β-cell dysfunction.[83,84] For instance, CFTR knockout ferrets demonstrate glucose abnormalities and insulin secretion defects as newborns.[84] Islet inflammation also appears to directly impair insulin secretion in CF.[85] Additionally, disturbances in secretion/function of incretins, gut-secreted hormones that potentiate insulin secretion, have been described in CF[86] and in T2DM.[44–47,87–90] Moreover, the T2DM GWAS-implicated gene, *TCF7L2*, confers an even stronger risk of CFRD than T2DM while a genetic variant in *SLC26A9* appears to confer protection.[91–93] Initiation of therapy with the CFTR potentiator ivacaftor[94] for CFTR class III mutations is associated with improvements in insulin secretion during OGTT and acute glucose infusion, and resolution of[95] or less frequent progression to CFRD.[96] However, studies of the impact of lumacaftor/ivacaftor, a modulator therapy for patients homozygous for F508del, on glucose tolerance and insulin secretion are mixed.[97,98] The Cystic Fibrosis Foundation (CFF)-funded multicenter, longitudinal, observational Promise study will provide additional insight into the impact of highly effective modulator therapy on glucose excursion/tolerance and insulin secretion.

Cystic Fibrosis Bone Disease and Vitamin D Deficiency

Low bone mineral density occurs in as many as 40% of adults with CF, and with increasing life expectancy this comorbidity may become even more prevalent. The term *CF-related low bone mineral density* (BMD) is used to describe youth and adults with low bone densitometry or dual-energy x-ray absorptiometry (DXA)-derived measures of BMD, defined as BMD-Z score less than −2. The diagnosis of osteoporosis in youth and adults age <50 years requires low BMD-Z score and significant fracture, although the diagnosis can be made with just a vertebral compression fracture.[99,100]

The origin of osteoporosis in CF is multifactorial and is attributed to pancreatic insufficiency; malnutrition; poor growth; CFRD; deficiencies in vitamin D, vitamin K, and calcium; systemic inflammation; pubertal delay; exposure to glucocorticoids; skeletal muscle mass deficits; and decreased physical activity.[101] Bone histology in clinically stable CF adults is significant for decreased cancellous bone volume and decreased connectivity.[102] Importantly, the sequelae of low bone density in CF patients include increased risk of vertebral and rib fractures that is approximately twice as great as in the general population, and increased risk of kyphosis. With the aging CF population, additional data on risk of hip fracture, a typical osteoporotic fracture that occurs with aging in the non-CF population, is expected to emerge.

Individuals with CF are at increased risk for vitamin D deficiency, defined as 25-hydroxy vitamin D (25OHD) 20 to 30 ng/mL, and frank deficiency, defined as 25OHD <20 ng/mL. Vitamin D deficiency is due to malabsorption, as well as risk factors in the general population: low vitamin D–enriched diet, limited sun exposure, and use of sunscreen. Optimal vitamin D status has yet to be defined in either the CF or general population; CFF recommends 25OHD >30 ng/mL,[103] while the European CF guidelines recommend 25OHD >20 ng/mL.[100]

Reproductive Organs

Except for an increase in viscosity and an abnormal midcycle ferning pattern in cervical mucus, no consistent pathologic changes occur in the female reproductive tract in patients with CF. In the male reproductive tract, however, the vas deferens is either atretic or absent at birth. Although the pathogenesis of this lesion is not certain, viscous secretions may contribute to obstruction in utero, followed by failure of development of the vas deferens. Spermatogenesis and testicular development are otherwise normal. Because of either partial or complete obstruction of the vas deferens, approximately 98% of males with CF are aspermic.

Sweat Glands

The sweat glands of patients with CF manifest no distinctive histologic changes. Nonetheless, their function is abnormal. Micropuncture experiments have shown that the precursor solution secreted by the sweat glands is isotonic to plasma, both in CF patients and in normal subjects. In normal persons, as the sweat flows along the duct of the gland, sodium and chloride are reabsorbed, so that by the time that the opening at the skin surface is reached, sweat is hypotonic to plasma with respect to both sodium and chloride concentrations. In CF, the relative impermeability to chloride ions is thought to be responsible for the elevated chloride and sodium concentrations, which are the basis for the diagnostic test (the quantitative pilocarpine iontophoresis sweat test) and are also responsible for the characteristic increase in potential differences across isolated, perfused sweat glands from CF patients.

DIAGNOSIS

The diagnosis of CF requires the demonstration of abnormally high concentrations of sodium and chloride in the sweat of a person who has the characteristic history and symptoms of CF. The most prominent clinical features are chronic pulmonary disease and pancreatic insufficiency. The most compelling family history for the diagnosis of CF is a sibling with CF. If the clinical picture and/or the family history support the diagnosis, and if two sweat tests using the quantitative pilocarpine iontophoresis method are clearly positive, the diagnosis of CF can be made with assurance. Identification of two pathologic mutations, in addition to the characteristic clinical picture, is accepted as a criterion for the diagnosis. However, CF is a complex syndrome (Table 48-2), the clinical manifestations of which are sometimes subtle. In addition, the family history is not always straightforward. Therefore, a high index of suspicion, coupled with a battery of clinical tests, is sometimes required to establish the diagnosis, especially in adolescents or young adults.

Since CF occurs with a high frequency in the general population, the diagnosis should be considered routinely in a broad array of differential diagnoses. Although Table 48-2 categorizes symptoms according to the age at which they most often occur, these symptoms at any age should prompt consideration of the diagnosis of CF.

The most consistent feature of CF is an abnormally high concentration of sodium and chloride in sweat. Measurement of the chloride concentration is recommended for clinical testing. The only reliable sweat test is based on iontophoresis of pilocarpine, followed by quantitative determination of the concentration of chloride in an adequate, measured volume of sweat. Guidelines for the proper performance of a sweat test have been published.[104] In children, concentrations of chloride of <30 mEq/L are usually regarded as normal. However, the average of values for sodium and chloride concentrations are about 20 mEq/L for normal subjects and 95 mEq/L for those with CF. In children, values between 30 and 60 mEq/L are considered borderline elevated; such values call for further evaluation. As a result of recent experience with CF newborn screening, it has been suggested that sweat chloride values >30 mEq/L may be diagnostic in the first few months of life.[105]

The concentration of sodium and chloride in sweat increases gradually with age. Conditions other than CF in which the concentrations of sodium and chloride in sweat are abnormally high include malnutrition, adrenal insufficiency, hereditary nephrogenic diabetes insipidus, ectodermal dysplasia, and fucosidosis. Except in some instances of malnutrition, these conditions are readily distinguished from CF.[106] The finding of abnormal concentrations of sodium and chloride in sweat should automatically prompt evaluation of the patient to determine if, and to what extent, other organs are affected.

Genetic analysis can be used to confirm the diagnosis of CF. In patients with minimal symptoms, the diagnosis of CF can be made with certainty if two CF-associated alleles are present. As mentioned previously, screening for 32 of the most common alleles yields an overall sensitivity of 90% due to undetected alleles. Therefore, a negative mutation analysis does not rule out a diagnosis of CF, and atypical patients should be followed carefully.

Newborn screening is now established practice in the United States.[107] The initial stage of screening often uses the neonatal blood spot to determine the concentration of immunoreactive trypsinogen (IRT). If this is elevated, secondary screens vary in individual states from repeat immunoreactive trypsinogen determination to F508del or multimutation analysis. Next-generation sequencing is being introduced in addition to the IRT in a number of states.[108] The screening programs have a sensitivity that varies with the number of mutations included in the assay.[109] Risks versus benefits and the relative costs of the screening programs are being evaluated to determine the best approach.[110] Infants with positive newborn screens for CF are referred to CF centers for sweat test confirmation. It has been proposed that infants who have a positive newborn screen, but who do not otherwise fulfill the criteria for a diagnosis of CF,[107] should be termed as having "CFTR metabolic syndrome,"[53,111] or, in Europe, CFSPID (screen positive inconclusive diagnosis);[112] at a minimum they should be followed in a CF center until their status can be clarified. Another category for individuals with some, but not sufficient, features of CF is CFTR-related diseases.[113] These individuals were previously labeled as atypical or nonclassic CF. However, the comprehensive study of Miller et al. provides compelling evidence that we will need to reconsider the implications of being a carrier of a single CFTR mutation.[114]

CLINICAL EVALUATION

The evaluation of patients with CF includes chest radiography, tests of pulmonary performance, sputum culture, and assessment of pancreatic, endocrine, hepatic, and reproductive functions. Each is described below.

Chest Radiography

Rarely is the chest radiograph completely normal in CF. In the person with minor pulmonary symptoms, the manifestations may be questionable (e.g., mild hyperinflation and minimal peribronchial thickening). However, the radiographic findings become more distinctly abnormal as the disease increases in severity. Peribronchial thickening, which is often most prominent in the upper lobes of the lungs early in the course of the disease, usually progresses to affect all lobes. In the advanced stage of pulmonary involvement, ring shadows, cystic lesions, and nodular densities are increasingly apparent, as are areas of bronchiectasis and atelectasis. The central pulmonary artery often enlarges in the middle stages of the disease, but the cardiac silhouette remains within normal limits until the disease is far advanced. The variability in the chest radiograph is illustrated in Fig. 48-6 for three siblings with CF when each was 17 years old.

High-resolution computed tomography (HRCT) scans are more sensitive than plain radiographs. The most common abnormalities described are bronchiectasis, peribronchial thickening, mosaic perfusion, air trapping, and mucus plugging.[115] Early bronchiectasis is easily detected on the CT scan, even when routine chest radiographs are normal, as seen in Fig. 48-7. CT scan abnormalities may be detected prior to a change in pulmonary function tests. Chest CT scan abnormalities have been detected in asymptomatic newborn infants diagnosed by newborn screening.[116] Currently, there are no standard recommendations for CT use due to the radiation exposure incurred by these studies.

Pulmonary Performance

The lungs of patients with CF are usually morphologically and functionally normal at birth. Over time, accumulation of tracheobronchial secretions and recurrent infections progressively impair pulmonary function in almost all patients. In the fully developed clinical syndrome, all the pulmonary function abnormalities seen in chronic bronchitis, emphysema, and asthma may occur. However, one complicating regular feature of CF—bronchiectasis—modifies pulmonary performance. Chronic, local infection and airway damage increase the compliance of bronchiectatic airways, resulting in airway collapse during rapid expirations or cough. The usefulness of pulmonary function testing in CF is twofold: tracing the natural history of the disease and assessing the value of therapeutic interventions.

The earliest stages of the pulmonary disorder are the most difficult to quantify. In infants, tests are limited almost entirely to those that do not depend on the patient's understanding and cooperation. A variety of methods to measure infant pulmonary function have been devised; one method, the raised volume rapid thoracoabdominal compression technique, requires sedation of infants but provides values most similar to standard spirometry values, and has detected reduced pulmonary function in infants with CF.[117] The nitrogen multiple breath washout or lung clearance index can be performed in preschool-age children, detects early ventilation inhomogeneity that correlates with airflow obstruction by spirometry,[118] and has good positive correlation with CT scan changes.[38] After age 6 years, pulmonary function tests originally designed for adults may

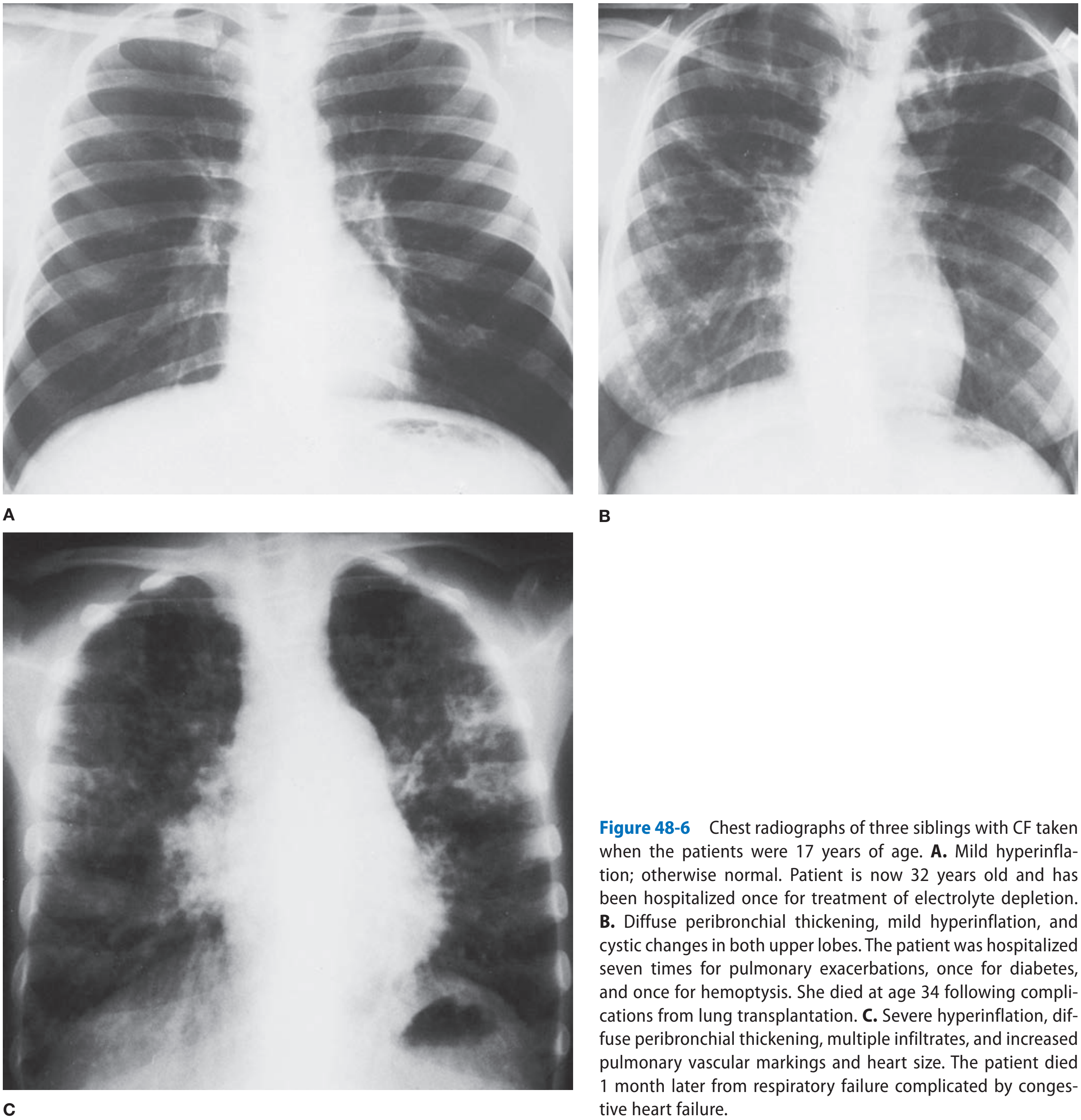


Figure 48-6 Chest radiographs of three siblings with CF taken when the patients were 17 years of age. **A.** Mild hyperinflation; otherwise normal. Patient is now 32 years old and has been hospitalized once for treatment of electrolyte depletion. **B.** Diffuse peribronchial thickening, mild hyperinflation, and cystic changes in both upper lobes. The patient was hospitalized seven times for pulmonary exacerbations, once for diabetes, and once for hemoptysis. She died at age 34 following complications from lung transplantation. **C.** Severe hyperinflation, diffuse peribronchial thickening, multiple infiltrates, and increased pulmonary vascular markings and heart size. The patient died 1 month later from respiratory failure complicated by congestive heart failure.

be performed quite readily on children. Changes in pulmonary performance throughout the natural history of CF can be described with confidence.

Obstruction in Small Airways

The small airways—that is, the bronchioles—are vulnerable to obstruction early in the course of CF. At this stage, as in cigarette smokers, results of tests for small-airway disease are apt to be abnormal, while those of tests for obstruction of large airways are still normal. Three factors interact in causing the obstruction: (1) intrinsic disease of the smaller airways, often in association with bronchiectasis in the proximal, larger airways; (2) viscid secretions, impaired ciliary action, and impaired cough; and (3) progressive decrease in lung elastic recoil.

The progressive reduction in lung elastic recoil in CF is predominantly a function of overinflation due to intrinsic airway disease, rather than loss of pulmonary parenchyma. This mechanism differs from that in chronic bronchitis and emphysema, in which the combined effects of parenchymal destruction and overinflation are responsible for the decrease in elastic recoil. Emphysema is not a regular feature of CF. In some patients, emphysema occurs only late in the course of the disease (Fig. 48-3).

Airway smooth-muscle tone increases only slightly in CF. Exercise elicits bronchodilation, followed shortly thereafter by bronchoconstriction. Both the bronchodilation and bronchoconstriction are far less impressive in CF than in asthma. Indeed, exaggerated bronchodilator responses in CF raise the possibility of superimposed asthma. In distinguishing between contributions to airway obstruction by intrinsic airway disease caused by CF and asthma, maximal expiratory flow-volume curves are sometimes helpful.

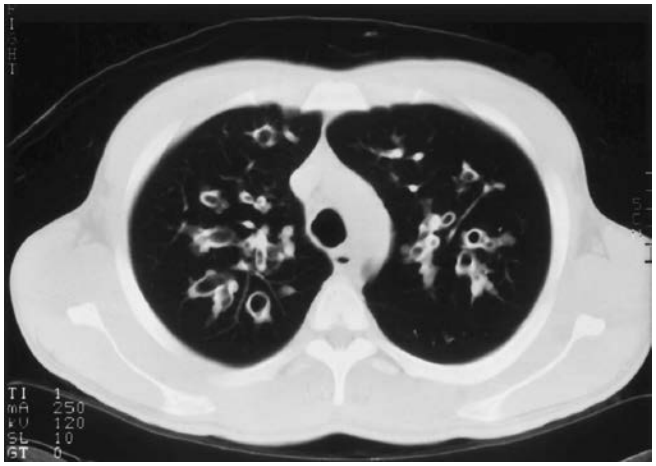


Figure 48-7 High-resolution chest computed tomography scan from a patient with CF. Marked bronchiectasis with peribronchial thickening is shown in the upper lobes.

Because of the bronchiolar locus of the early lesions in CF, abnormalities in breathing frequency–dependent tests (e.g., dynamic lung compliance), in volume-dependent tests (e.g., closing volume), and in maximal expiratory flow ($\dot{V}E_{max}$) at low lung volumes are demonstrable, even though results of tests of large-airway function (e.g., FEV$_1$ and airway resistance) are still normal.

Change in Lung Volumes

As with chronic bronchitis, emphysema, and asthma, RV in CF increases. Thereafter, an increase in functional residual capacity and, sometimes, in total lung capacity (TLC) is seen. Later in the course of the disease, air-trapping occurs, manifest as an elevated ratio of RV to TLC. This change decreases the compliance of the lung and increases the work of breathing.

Abnormalities in Gas Exchange

Early in the evolution of the pulmonary abnormalities in CF—that is, when tests of small-airway function alone are abnormal—ventilation-perfusion abnormalities usually result in widening of the alveolar-arterial oxygen gradient and an increase in the ratio of dead space to tidal volume (V_D/V_T). These abnormalities portend increasing inhomogeneities in alveolar ventilation and blood flow as the affected child grows to adulthood. The diffusing capacity for carbon monoxide (DL_{CO}) is low at rest and does not increase normally during exercise. This observation is difficult to reconcile with the preservation of the gas-exchanging surface of the lungs (in the absence of emphysema) until late in the course of the disease (Fig. 48-3).

As obstructive disease of the airways progresses and exaggerates the imbalances between alveolar ventilation and blood flow, arterial hypoxemia develops; pulmonary hypertension, cor pulmonale, and right ventricular failure follow, in turn. Late in the course of the disease, hypercapnia and respiratory acidosis contribute to the final picture of respiratory failure. At this juncture, the ventilatory response to inhaled CO_2 is depressed. Bouts of infection punctuate the course of the illness; during each episode, pulmonary function deteriorates, but it usually returns toward baseline, except in the preterminal stages of the disorder.

■ Sputum Culture

The unique respiratory flora isolated from sputum or oropharyngeal cultures from patients with CF is helpful in establishing the diagnosis and in guiding the antimicrobial therapy for acute exacerbations. In many patients with CF, *P. aeruginosa* and *S. aureus* are found alone, or in combination with other organisms, in the sputum. There is growing evidence of correlations between different organisms and CF lung disease progression. The presence of mucoid *Pseudomonas* is important because its acquisition predicts more rapid progression of CF lung disease.[119] Similarly, acquisition of methicillin-resistant *Staphylococcus aureus* is associated with a decline in pulmonary function[120] and worse survival.[121] Infection with the *Burkholderia cepacia* complex organisms may be aggressive with rapid deterioration of clinical status or may have an indolent course; the presence of mucoid-positive organisms appears to be protective.[122] Chronic antibiotic therapy to suppress *Pseudomonas* has improved clinical outcomes but has also led to a greater number of multidrug-resistant organisms identified in sputum, including *Stenotrophomonas maltophilia* and *Achromobacter xylosoxidans*. Chronic colonization with *Stenotrophomonas maltophilia* induces a serologic response and independently correlates with progression in airflow obstruction.[123]

In addition to bacteria, sputum cultures for detection of molds and nontuberculous mycobacteria are helpful to guide therapy for patients with acute exacerbations unresponsive to antibiotic therapy, or for patients with unexplained progression of lung disease. Allergic bronchopulmonary aspergillosis (ABPA) complicates CF lung disease,[124] and recent evidence suggests that *Aspergillus fumigatus* may also be associated with airway infection or allergy-triggered asthma in the absence of ABPA.[125] The prevalence of nontuberculous mycobacteria ranges from 7% to 24%, with the most frequent species identified as *M. avium* complex and *M. abscessus*.[126]

■ Pancreatic Function

The evaluation of pancreatic function is an important part of establishing the diagnosis of CF, since almost 90% of patients have pancreatic insufficiency. Infants with pancreatic insufficiency due to CF may present with failure to thrive and loose or frequent stools. However, visual appearance does not always correlate with the degree or presence of fat malabsorption. Most infants with CF are now identified early as a result of newborn screening. Currently, the diagnosis of pancreatic insufficiency can be made by measurement of fecal elastase 1 levels with the human enzyme-linked immunosorbent monoclonal assay (ELISA) for fecal elastase (FE). The fecal elastase 1 test is easier to perform than other studies for pancreatic exocrine function and requires a random single stool sample. It is easy to obtain in patients with CF and is not affected by the use of pancreatic enzyme replacement therapy (PERT). Of note, fecal elastase level can be falsely low if performed on loose stool; the sample must be at least semi-formed. The sensitivity and specificity of this test depends on what cutoff values are used. For example, a cutoff value of <84 μg/g stool has a sensitivity of 87.5%, specificity of 81.6%, PPV of 66.7%, and NPV of 93.9%.[127]

Also available is a polyclonal assay that detects human as well as porcine elastase, but it should not be used to diagnosis pancreatic insufficiency in patients already on pancreatic enzyme supplementation.

The gold standard for diagnosing steatorrhea is the 72-h fat collection; however, this test is cumbersome, requiring a 3-day period of high fat consumption with complete diary of food intake, and stool collection during the same time period for total stool fat analysis. Assessment of the degree of malabsorption is determined by the coefficient of fat malabsorption. There is some debate as to the value used for the diagnosis of pancreatic insufficiency. A malabsorption coefficient of greater than 7% is usually considered abnormal. Patients with CF usually have a malabsorption coefficient around 20% to 30%. The test is not popular with families who find the stool collections unappealing. Pancreatic stimulation tests are the most accurate measurement of pancreatic function but are invasive.

The Dreiling tube method, which required an oroduodenal tube placement for direct aspiration of pancreatic fluid following secretin or CCK administration, has been replaced by endoscopic fluid collection.[128] This method takes less time but does require anesthesia. The North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) recently published a position statement on the proposed protocol for this procedure.[129] Secretin-stimulated magnetic resonance cholangiopancreatography (MRCP)[130] and secretin-stimulated ultrasound, while measuring the degree of intraluminal duodenal filling, also are being used. Disadvantages of these methods are high cost and interobserver variability. They are also cumbersome and at this time are not clinically readily available.

Cystic Fibrosis–Related Diabetes

Because the onset of CFRD is generally insidious, and fasting hyperglycemia tends to be a late manifestation, annual CFRD screening with OGTT starting by age 10 years is recommended.[131,132] Based upon the fasting, 1-h, and 2-h plasma glucose (PG0, PG1, and PG2) during the OGTT, the following glucose tolerance categories are defined:

- Normal glucose tolerance (NGT) = PG1 <200 mg/dL and PG2 <140 mg/dL
- Indeterminate = PG1 ≥200 mg/dL but PG2 <140 mg/dL
- Impaired glucose tolerance (IGT) = PG2 ≥140 and <200 mg/dL
- CFRD = PG2 ≥200 mg/dL
  w/o fasting hyperglycemia (FH) = PG0 <126 mg/dL
  with FH = PG0 ≥126 mg/dL

Contrary to what one might expect, isolated impaired fasting glucose (PG0 100–125 mg/dL) is not associated with worse survival, nutritional status, or pulmonary function.[133] However, fasting glucose 110–125 mg/dL has been associated with progression to CFRD.[134] Over 10 years, fasting hyperglycemia occurs in 60% of patients with CFRD without FH at baseline.[62] At least in children, increased plasma glucose at 1 h during the OGTT predicts increased risk of progression to CFRD.[135]

Additional CFRD screening measures include fasting and postprandial glucose measurements during hospitalizations for acute illness.[131,132] Home glucose monitoring also should occur periodically during and after continuous overnight enteral feeds, as well as during intercurrent illnesses, intravenous antibiotic therapy, and glucocorticoid treatment.[136] While an elevated hemoglobin A1C (>6 >= .5%) is consistent with CFRD, the HbA1C tends to underestimate overall glucose intolerance in CF patients and is not generally recommended for CFRD screening.

Osteoporosis/Vitamin D Deficiency

Patients with CF are at risk for vitamin D deficiency and osteoporosis. Annual serum 25-hydroxyvitamin D levels should be monitored. In addition, the 2005 CFF guidelines recommend DXA scan to monitor bone mineral density in all adults and children greater than age 8 years with risk factors for osteopenia, including malnutrition, chronic glucocorticoid use, moderate to severe airway obstruction (FEV_1 <50% predicted), or history of fracture or delayed puberty.[101] Timing of additional DXA scans is informed by prior DXA and clinical course.[101] The more recent European CF Society guidelines recommend height adjustment of DXA-derived bone outcomes in youth with CF with growth or maturational delay;[137] robust reference data are now available to make these adjustments.[138,139]

Cystic Fibrosis–Related Liver Disease

Evaluation of liver function (transaminases, bilirubin, GGT) is an important part of the evaluation of CF. Transient elevations of serum transaminases can be often seen and may be related to intercurrent illnesses and medications. If levels of AST, ALT, GGT, and ALP are elevated, they should be repeated. The APRI (aspartate aminotransferase to platelet ratio index) has been found to be a marker of liver fibrosis.[140–142] The prothrombin time is sometimes prolonged, owing to a combination of malabsorption and decreased synthesis of clotting factors by the liver. Obtaining a PIVKA-II (protein induced by vitamin K absence II) level to assess vitamin K status can be helpful in these instances. However, these tests can often be relatively normal, even in patients with mild or moderate focal biliary cirrhosis. Liver ultrasound (US) is a useful screening tool that can identify steatosis, liver nodularity, cirrhosis, splenomegaly, and varices; however, it has low sensitivity. A liver US with Doppler may show reversal of portal blood flow in advanced disease with portal hypertension. According to a recent meta-analysis, US elastography can identify changes in liver stiffness[143] and is useful in identifying patients with precirrhotic liver disease. Once it has been established that the patient has advanced liver disease, screening endoscopy is necessary to assess for the presence of esophageal varices. Larger varices that are more likely to bleed can be banded. The mortality rate from an esophageal variceal bleed is about 30%.

Semen Analysis

Occasionally, a man who is found to have aspermia during an evaluation for infertility is found to have CF. In men with CF, a complete semen analysis is part of the evaluation. Azoospermia is found in more than 98% of men with the disorder.

Mutation Analysis

There are currently more than 2100 mutations associated with CF (*www.genet.sickkids.on.ca/cftr/*). A new initiative, The Clinical and Functional Translation of CFTR (CFTR2) (*www.cftr2.org*), funded by NIH, the US CFF, and Sequenom, is a website dedicated to publishing the functional implications of CFTR mutations. Patients homozygous for the most common mutation, F508del, have pancreatic insufficiency; patients with CF who have pancreatic insufficiency tend to have a worse prognosis. F508del is one of the major mutations classified as disease-causing; certain other mutations are associated with CF-related disorders, while some other mutations have no known clinical importance or are of unknown significance. Several mutations, including R117H, are associated with pancreatic sufficiency and a mild phenotype. Interestingly, the phenotype of R117H is linked to the expression of the polyT and polyTG intronic domains found 5′ to exon 9. A T5 polymorphism expressed with R117H results in congenital bilateral absence of the vas deferens (CBAVD) or idiopathic pancreatitis and may be complicated by mild lung disease. In contrast, R117H associated with T7 or T9 may have no manifestations of CF or CF-related disease.[144]

Certain alleles associated with CF (e.g., 3849 + 10kbC → T) are associated with nasal polyposis and bronchiectasis but normal sweat test results. The diagnosis of CF can be made with confidence in these patients. More problematic are persons with atypical presentations, normal sweat test results, and at least one CF-associated mutation. More extensive genotyping should be attempted for all patients with a high clinical suspicion for CF (see "Genetics," above), because mutation analyses will be used to determine eligibility for mutation-specific protein-correcting therapies. For example, therapy for CF patients with the G551D mutation using the CFTR potentiator ivacaftor results in astonishing improvements in respiratory tract symptoms, weight gain, and a shift from positive to borderline sweat chloride values[145] (see sections on Therapy, Genetics, and Future Directions).

Patients with the same genotype may have dramatically different phenotypes, supporting the concept that modifier genes play an important role in determining the CF phenotype. Three large GWAS consortia defined modifier genes associated with lung disease severity[146] and with specific disease manifestations, such as CFRD,[92] liver disease,[147] and meconium ileus.[148] Investigations using these large well-characterized cohorts recruited by the consortia have identified chromosomal regions of interest but have not yet confirmed gene targets or polymorphisms that confer increased risk of severe lung disease. Using a hypothesis-driven approach, several potential candidate modifier genes for severity of lung disease were identified, including α_1-antitrypsin, HLA antigens, nitric oxide synthase, mannose-binding lectin, transforming growth factor β (TGF-β), tumor necrosis factor α (TNF-α), and β_2-adrenergic receptor. However, none of these genetic polymorphisms was validated as a gene modifier by GWAS analysis in the combined consortia.

ATYPICAL CLINICAL PRESENTATIONS

Atypical clinical presentations confound the diagnosis of CF in adults; a high index of suspicion is required to establish the diagnosis. Approximately 6% of all CF is diagnosed after age 18 years. Late presentations of CF tend to occur in persons with pancreatic sufficiency; indeed, overweight or well-nourished persons may have CF. Recovery of unusual gram-negative organisms, mucoid *Pseudomonas* species, or *S. aureus* from sputum of asthmatics with persistent sputum production, chest radiographic abnormalities, or clubbing should prompt referral for sweat testing. Recurrent sinusitis and nasal polyposis may be the only manifestations of CF in a mildly affected person. Isolation of *P. aeruginosa* from deep nasal cultures should raise the suspicion of CF. Frequently, the sinus findings on CT mimic fungal sinusitis, demonstrating concentric, inhomogeneous material. Occasionally, persistent inflammation produces bony destruction that is mistaken for previous surgical intervention. Sweat testing and referral to a CF center should be considered for men with azoospermia or congenital bilateral absence of the vas deferens (CBAVD). The clinical entity "CFTR-related disease" has recently been defined by an international working group.[149] CFTR-related disease encompasses patients with evidence of CFTR dysfunction who do not meet the criteria for CF disease (for example, only one CFTR mutation, a normal sweat test, and single organ involvement). CFTR-related diseases include CBAVD, idiopathic pancreatitis, and diffuse bronchiectasis.[149]

TREATMENT

Intensive, comprehensive CF treatment programs designed to deal with specific symptoms, correct deficiencies, and prevent progression and complications of the disease have led to a dramatic increase in the median age of survival. Although the value of comprehensive treatment is beyond question, far less certain are the utility of each component of the treatment plan and the level of each component necessary for each patient. At present, the best approach appears to be determination of the type and degree of abnormality in individual patients and design of a treatment program that will improve or maintain function of the organ systems affected. Two recent reviews highlight the evidence supporting each component of CF therapy.[150,151] To ensure that the treatment regimen meets the needs of the individual patient, that necessary treatment is not omitted, or that side effects of prescribed treatments do not go unnoticed, it is often desirable to hospitalize the patient for diagnosis and evaluation. Hospitalization also provides an excellent opportunity for counseling the patient, parents, and family about the diverse aspects of the diagnosis, treatment, prognosis, and inheritance pattern of CF. Hospitalization provides the opportunity to monitor the response of individual patients to each component of the therapeutic program. Currently, the insurance requirement to demonstrate "medical necessity" often makes this option unfeasible.

An important aspect of the care of patients with CF is the network of more than 100 CF centers that exist throughout the United States and the larger network throughout the world. CF centers use a team approach to the care of patients. A CF care team ideally includes physicians, nurses, respiratory therapists, physical therapists, nutritionists, social workers, pharmacists, and genetic counselors. The current recommendation is that the patient meet with the CF team for an outpatient visit at least every 3 months for an evaluation of clinical status and for counseling to identify subtle changes in disease progression and to encourage adherence to therapy.

■ Management of Pulmonary Disease

Management of CF-related pulmonary disease can be divided into two broad categories: chronic maintenance therapy and management of acute exacerbations.

Chronic Maintenance Therapy

More than 90% of patients with CF die from respiratory failure or pulmonary complications. The goals of treating the pulmonary disorder in CF are to prevent and treat the complications of airway obstruction and infection. Although management of the pulmonary disorder consists of many components applied in combination,[152] the individual components of therapy are discussed separately below.

Chest Physiotherapy Almost all treatment programs for CF include a strategy intended to clear pulmonary secretions to prevent complications arising from airway plugging by viscous secretions. Chest physiotherapy—that is, "percussion and postural drainage"—performed regularly is the most widely prescribed method. In infants and young children, chest physiotherapy is generally performed routinely, twice daily. Percussion and postural drainage technique has been modified to exclude head-down positioning, which increased the risk of GE reflux and increased the duration of acute exacerbations of cough in infants.[153]

In addition to manual chest percussion and postural drainage, there are several other effective modalities for chest physiotherapy. These alternative measures include the high-frequency chest-wall oscillatory vest (HFCWO); the flutter device, a small pipelike device that produces an oscillating resistance during a forced expiratory maneuver; the Acapella and Aerobika devices that produce both positive expiratory pressure and an oscillating resistance during forced expiratory maneuver; positive expiratory pressure (PEP) mask; intrapulmonary percussive ventilation; autogenic drainage and active cycle of breathing; and exercise.[154]

Overall, due to the difficulty in designing unbiased, well-controlled trials with sufficient power to unequivocally distinguish efficacy between treatments, evidence does not exist to demonstrate superiority of one airway clearance mechanism over another. Therefore, the recommendations based on expert opinion are that airway clearance should be initiated in asymptomatic infants because they develop signs of lung disease within the first few months of life; and that patients should be offered and instructed in a variety of methods so that they can select the methods that they deem provide the most subjective benefit.[155] Some form of physiotherapy that is effective in mucus clearance is required daily because without chest physiotherapy, pulmonary function deteriorates.[156]

At present, most CF centers recommend that all patients with CF attempt to maintain clearance of pulmonary secretions with a method that is applied regularly (e.g., twice daily). An additional recommendation is that chest physiotherapy be applied more often during an exacerbation of the chronic pulmonary infection. Unfortunately, the recommendation of chest physiotherapy on a regular basis—a time-consuming and often arduous form of treatment—is difficult to implement without considerable support and encouragement from family and health professionals.

Mucolytics and Inhaled Hypertonic Saline Several different mucolytic agents have been tried over the years. One that has endured is N-acetylcysteine. In the test tube, this agent is quite effective in dissolving mucin components and in decreasing the viscosity of sputum from patients with CF.[157–159] Although some centers that have outstanding pulmonary outcomes have used this agent as a standard part of the chronic regimen as an adjunct to airway clearance therapy in CF, others have been reluctant to use it because of a lack of randomized controlled trials.[160] One CF center that has a track record of outstanding CF outcomes recommends using N-acetylcysteine in combination with sodium cromolyn and albuterol (W. Warwick, personal communication). We continue to recommend its use to our CF patients. Interestingly, N-acetylcysteine was found to activate CFTR Cl^- conductance in cultured epithelial cells.[161]

In 1994, Pulmozyme, a DNA-cleaving enzyme, was approved for use in patients with CF following a large, phase 3, multicenter trial.[162] Once-daily treatment maintains pulmonary function and decreases the relative risk of respiratory tract exacerbations in young CF patients with normal FEV_1 (≥85%).[163] Currently, this drug is in widespread use for CF. However, questions are currently being raised concerning duration of Pulmozyme use in the setting of administration of highly effective CFTR modifiers (see “CFTR Potentiators and Correctors,” below).

Abnormal homeostasis of airway surface fluid results in dehydrated secretions and impaired mucociliary clearance. As a strategy to improve airway surface hydration and airway clearance, inhaled hypertonic therapy was evaluated. In a large, randomized, placebo-controlled trial, patients with CF, age 6 years and older, inhaled 7% hypertonic saline twice daily following a bronchodilator for 48 weeks and had a significant reduction in the number of pulmonary exacerbations and days lost from school or work.[164] Although inhaled 7% hypertonic saline did not affect the frequency of pulmonary exacerbations in infants and children less than 6 years of age compared to control treated children,[165] in a subset of infants tested, infant pulmonary function testing revealed an improvement in $FEV_{0.5}$ in the hypertonic saline group—suggesting that this therapy may be useful and considered on an individual basis.[165]

Bronchodilators and Anti-inflammatory Agents Bronchodilators are often used in treating the pulmonary manifestations of CF. Their use should be individualized.[166] For example, in many patients, bronchospasm that is reversible with bronchodilators at one point in the course of the illness may prove refractory a short time later. In infants who are audibly wheezing, a bronchodilator can be tried. In older patients, pulmonary function testing provides a more objective and quantitative measure of bronchodilator effectiveness.

Corticosteroids have been used with good results in infants with severe obstructive airway disease that does not respond to antibiotics and bronchodilators and in patients with CF in whom the pulmonary disease is complicated by severe asthma or ABPA. Preliminary observations initially suggested that patients with CF would benefit from long-term administration of alternate-day corticosteroids, based on the presumption that corticosteroids would decrease the airway inflammatory response. However, in a large, placebo-controlled, multicenter trial of alternate-day corticosteroids administered in two dosage regimens (1 mg/kg and 2 mg/kg), the development of many side effects precluded a general recommendation for long-term corticosteroid treatment in CF.[167] Subgroup analysis led to the suggestion that patients with moderately severe obstructive airway disease and those with chronic *Pseudomonas* infection might benefit from treatment for periods of less than 1 year. Beneficial effects were sufficient to prompt further studies of anti-inflammatory agents in CF. A controlled 4-year trial of high doses of ibuprofen in 40 patients with CF showed improvement in the rate of decline of pulmonary function in children.[168] Questions remain whether side effects that might accrue with continued therapy will justify the gains. In concert, these two studies suggest that future development of a lung-specific anti-inflammatory agent with fewer systemic side effects may offer a promising approach.

Antibiotics Two major innovations using antibiotics have been implemented as part of the regimen of maintenance therapy for CF. First, inhaled therapies have been demonstrated to successfully eradicate initial *Pseudomonas* infection and postpone chronic colonization in three large prospective trials of patients with CF in North America and in Europe.[169–171] Second, chronic inhaled and/or oral antibiotic therapies successfully decrease the progression of lung disease related to chronic *Pseudomonas* infection. In addition to these therapies, it is important to emphasize that person-to-person transmission of *P. aeruginosa* and other opportunistic microbes is another source for chronic colonization. In health care facilities for CF patients, contact isolation precautions are recommended.[172]

Chronic airway colonization/infection with *P. aeruginosa* promotes progression of lung disease. Hoiby et al. championed early treatment of *P. aeruginosa*–positive sputum cultures with inhaled colistin and oral ciprofloxacin, even in the absence of symptoms, as a modality to prevent chronic colonization.[173]

The EPIC trial[169] tested four randomized regimens: cycled therapy vs. culture-driven therapy; and 28 days of inhaled tobramycin inhalation solution (TIS) in the presence or absence of 14 days of oral ciprofloxacin. Approximately 80% of patients remained free of *P. aeruginosa* for the duration of the study (18 months), with no difference concerning time to first pulmonary exacerbation attributed to regularly cycled therapy or the addition of ciprofloxacin.

The ELITE study[170] was an open-label, randomized study comparing 28 to 56 days of inhaled TIS; it revealed approximately 90% eradication at the end of therapy with 66% to 69% of patients having *Pseudomonas*-free cultures at the end of the 27-month study. Another trial comparing inhaled colistin and oral ciprofloxacin to inhaled TIS and oral ciprofloxacin showed no difference between regimens in eradication, with approximately 62% to 65% of patients having *Pseudomonas*-free cultures at 6 months.[171] Therefore, although the evidence from these three studies supports antibiotic eradication of new *Pseudomonas* infection, there is no consensus yet for a specific therapeutic regimen.[174]

Another approach that has been advocated is suppression of chronic *Pseudomonas* colonization by alternating monthly cycles of inhaled antibiotics. Inhaled, preservative-free TIS, 300 mg twice daily for 28 days on and 28 days off, improved pulmonary function (FEV_1 increased by 10%) at the end of the third treatment cycle (20 weeks) compared with placebo.[175] Recently, inhaled aztreonam, 75 mg three times per day, was tested in an open-label study of every other month regimen for patients with chronic *P. aeruginosa* infection.[176] Patients reported improved symptoms and pulmonary function during on-therapy months with sustained weight gain over the 18-month duration of the study.

Another antibiotic that has been studied as a chronic therapy in CF is oral azithromycin. Azithromycin, 250 mg or 500 mg thrice weekly, was evaluated in CF patients colonized with *P. aeruginosa*. After 6 months of therapy, patients on azithromycin had a modest improvement in FEV_1 (6.2%), increased weight gain, and decreased rates of pulmonary exacerbations.[177] Although macrolide antibiotics have been reported to have anti-inflammatory properties,[178] there is no direct evidence of azithromycin-induced anti-inflammatory activity in CF. One concern about inhaled tobramycin, inhaled aztreonam, and oral azithromycin as chronic therapies is the risk of bacterial resistance and selection for growth of MDRO. In addition, questions regarding selection of patients and timing and duration of treatment remain unanswered.

CFTR Potentiators and Correctors The most exciting breakthrough in CF therapies was announced in 2011 with the demonstration that an oral drug, ivacaftor, corrected the physiologic impact of a CFTR mutation, G551D. The G551D-mutant CFTR protein is expressed at the cell surface but does not conduct chloride or regulate other ion channels (class III mutation). Ivacaftor, a potentiator, increases the open probability of the CFTR channel to increase chloride conductance; this drug was discovered using a high-throughput screening approach.[179] In a phase 3, randomized, placebo-controlled, double-blind trial for CF patients with at least one copy of G551D mutation, ivacaftor, administered orally, 150 mg twice per day for 48 weeks, increased FEV_1 percent predicted by 10.6%, decreased risk of pulmonary exacerbations by 55%, improved CF quality of life (CFQL) respiratory symptom scores by 8.6 points, decreased sweat chloride values by 48 mmol per liter, and was associated with an average 2.7-kg weight gain.[145] Currently, other gating mutations similar to G551D and residual function mutations have been approved for ivacaftor therapy. Ivacaftor is approved for patients with CF at age 6 months and older.

Corrector and potentiator combination CFTR modulator therapies for F508del homozygous and heterozygous[180] include lumacaftor/ivacaftor (Orkambi),[181] tezacaftor/ivacaftor (Symdeko),[182,183] and triple therapy with two correctors and one potentiator: elexacaftor (ELX), tezacaftor (TEZ), and ivacaftor (IVA) (Trikafta). The corrector drugs function as chaperones to enhance intracellular processing of F508del, resulting in increased plasma cell membrane expression. These drugs were combined with the potentiator drug, ivacaftor, to increase open channel probability and improve chloride conductance.

Orkambi is FDA-approved for patients with two copies of the F508del mutation age 2 years and older. Symdeko is FDA-approved for patients age 6 years and older with two copies of the F508del mutation or one copy of F508del and one copy of one of 26 specified CFTR residual function or splice mutations. Trikafta is approved for patients with CF age 6 and older[184] who have at least one copy of F508del and a minimal function mutation.

Trikafta was compared with Symdeko in a phase 3, randomized, double-blind study of patients with CF homozygous for F508del.[185] After a run-in period of all patients on TEZ/IVA for 4 weeks, the ELX/TEZ/IVA group was compared with the TEZ/IVA group over an additional 4 weeks, and the ELX/TEZ/IVA group had a significantly greater increase in FEV_1 by 10 % predicted, greater decrease in sweat chloride concentrations of 45.1 mmol per liter, and improved CFQ-R respiratory domain questionnaire score of 17.4 points compared with TEZ/IVA alone.

Trikafta was investigated in a phase 3, double-blind, randomized, placebo-controlled trial for patients heterozygous for F508del and another minimal function CFTR mutation. In this trial, 403 subjects were randomized to drug vs. placebo over 24 weeks.[186] Patients treated with Trikafta compared with placebo had FEV_1 percent predicted 14.3% higher, rate of pulmonary exacerbations 63% lower, sweat chloride 41.8 mmol per liter lower, and better CFQ-R respiratory domain questionnaire score by 20.2 points.

The efficacy of these drugs to improve clinical status is so dramatic that studies are ongoing to determine whether standard therapies of airway clearance or nutritional therapies can be stopped when patients are on highly effective modulator therapies.

Management of Acute Exacerbations of CF Pulmonary Disease

During the past few decades of treatment of CF, antibiotics have proved to be the key element responsible for increased survival. A reasonable approach balances the dangers of overzealous administration of antibiotics against progressive airway damage and bronchiectasis resulting from untreated infection. The approach is based on sputum culture at the time of diagnosis and at regular intervals thereafter.

When signs and symptoms herald an exacerbation of pulmonary infection (i.e., increased cough or sputum production, dyspnea, decreased exercise tolerance, decreased appetite) or new abnormalities on the physical examination (i.e., increased respiratory rate, use of accessory muscles, changes on auscultation of the chest including decreased breath sounds, new crackles or wheezes, weight loss), new abnormalities on the chest radiograph, or a decline in pulmonary function tests, chest physiotherapy is increased and appropriate antibiotics are given orally—or for severe exacerbations, intravenously.

Currently useful agents for treating staphylococcal infections include dicloxacillin, cephalexin, the third-generation penicillin-clavulanic acid combinations, and macrolides. Ciprofloxacin, a quinolone derivative that can be given orally, is initially effective against many strains of *Pseudomonas* and has gained widespread use in the outpatient management of CF. A major disadvantage in its use is that resistance often develops after a few courses of treatment. A newer quinolone, levofloxacin, is often effective against both *Staphylococcus aureus* and *Pseudomonas aeruginosa*.

For treatment of a severe pulmonary exacerbation of CF caused by methicillin-resistant *Staphylococcus aureus*, vancomycin or linezolid are indicated. For *Pseudomonas,* a combination of an aminoglycoside given intravenously and a semisynthetic penicillin is generally used. This combination is presumed to act synergistically on *Pseudomonas*, and the *Pseudomonas* is less likely to become resistant to either antibiotic.

The antibiotic combination currently in wide use is tobramycin and piperacillin-tazobactam. In order to achieve high levels of antibiotics in the airways and in secretions, the aminoglycoside is generally administered in higher doses, 10 mg/kg/d instead of 7.5 mg/kg/d. A randomized trial comparing once-daily versus thrice-daily regimens of tobramycin revealed that once-daily IV therapy provides equivalent efficacy with less nephrotoxicity in children.[187] Dosing should be titrated for serum peak levels of 25 to 35 μg/L and trough levels of less than 1 μg/L.

The third-generation penicillins and cephalosporins piperacillin and ceftazidime, carbapenems such as imipenem and meropenem, and the latest beta-lactam, aztreonam, also are quite effective against *Pseudomonas.* When given alone, resistance often develops quickly. Usually, these agents are used in combination with an aminoglycoside. Because the sensitivity and resistance patterns of *Pseudomonas* often change, various combinations are tried at different times, with clinicians relying on sensitivities from recent isolates to determine which is most effective agent. For other resistant gram-negative organisms, such as *Burkholderia cepacia*, *Stenotrophomonas maltophilia*, *Acinetobacter baumannii*, and *Achromobacter xylosoxidans,* other antibiotic combinations are indicated, including ceftazidime, meropenem, ciprofloxacin, minocycline, aztreonam, chloramphenicol, or trimethoprim/sulfamethoxazole.

Staphylococcus, *Pseudomonas*, and other gram-negative organisms, such as *B. cepacia*, *A. xylosoxidans*,[188] *Acinetobacter baumannii*,[189] and *S. maltophilia*, once present on sequential sputum cultures, are difficult to eradicate. However, most other manifestations of an exacerbation of pulmonary disease abate during a 2-week course of antibiotics administered intravenously; for example, the densities seen on the chest radiograph decrease, the white blood cell count decreases, fever and respiratory rate decrease, and pulmonary function test results, which often deteriorate at the start of an exacerbation, return to their previous baseline. Although many patients begin to show improvement after 5 to 7 days, most CF centers continue antibiotics intravenously for at least 2 weeks to decrease the relapse rate and to prolong the interval between exacerbations. Indeed, some centers routinely recommend a 3- to 4-week course of intravenous antibiotics to treat an exacerbation of a pulmonary infection. Although most clinicians and the existing guidelines[190] are in agreement that increasing airway clearance and giving systemic antibiotics to cover the patient’s known pathogens are the most important elements to treat a pulmonary exacerbation in CF, there are no evidence-based guidelines on the use of steroids. However, if the patient is known to have a component of asthma to their lung disease, it is our practice as well as that of others to give a 5-day course of steroids 1 to 2 mg /kg in pediatric patients or 60 mg/day in adults. In the occasional hospitalized patient who experiences a relapse or manifests an increase in symptoms shortly after administration of intravenous antibiotics is stopped, long-term intravenous administration of an aminoglycoside can be continued with use of a heparin lock. This technique may be helpful in allowing the patient to return home while still receiving effective doses of aminoglycosides. While the 14-day course of IV antibiotics is referred to as the "gold standard," it is unclear whether a 10-day course is sufficient and if a 21-day course is either necessary or superior. The STOP 2 trial is underway to provide data to answer these questions (*clinicaltrials.gov/ct2/show/NCT02781610*).

When patients are either not improving or are deteriorating with standard treatment, other possibilities such as a new pathogen, APBA, and CFRD have been ruled out, and the sole pathogen is MDR *Pseudomonas aeruginosa*, treatment options are limited. There are anecdotal reports of patients responding to phage therapy[191] as an alternative to antibiotic therapy. A clinical trial is underway to evaluate this approach in CF patients. *Pseudomonas aeruginosa* possesses a remarkable capacity and a plethora of mechanisms to develop resistance to antibiotics.[192] Many of these pathways present novel targets to develop alternative therapies such as lectin and glycopeptide blockade,[11,12] but they remain to be fully explored. It was hoped that synergy testing would provide a solution to treat MDR *Pseudomonas aeruginosa*, but a large clinical trial did not find an advantage to synergy testing.[193] It has been suggested that employing alternative methods of synergy testing may yet prove useful.[194]

■ Nutritional Support

Patients with CF should have detailed nutrition assessment at diagnosis and annually per the CFF guidelines.[195] Nutritional status should be screened at every visit. Patients are prescribed a high-calorie balanced diet. The CFF recommends that for infants and young children (0–2 years) weight for length be maintained at the 50th percentile and that children and adolescents (2–20 years of age) have their BMI percentile at the 50th percentile.

Although it is true that pulmonary function is the predominant factor in determining morbidity and mortality in CF, it is becoming increasingly clear that overall patient status is closely tied to nutritional status. Importantly, achieving and maintaining normal nutritional status is associated with maintenance of lung function in young children and adults. Calorie goals are often 110% to 120% of usual calorie requirements. At these caloric intakes, protein intake is often adequate to meet needs. Patients are encouraged to achieve calorie goals by the ingestion of calorically dense foods. If this is hard to achieve, calorie boosters (vegetable oils, butter, cheese) are recommended followed by the use of high-calorie supplements (shakes). Calorie needs may be increased in patients with chronic lung disease, malabsorption, and chronic liver disease. Nocturnal nasogastric feeds maybe used in the short term for aggressive nutritional rehabilitation, and patients who need long-term support have placement of a gastrostomy tube for ease of care. Usually, standard formulas are used but some patients with feeding intolerance and poor weight gain benefit from hydrolyzed formulas. Intravenous or parenteral nutrition is rarely used but may be required in patients who have had GI surgery.

Pancreatic status (insufficiency or sufficiency) should be determined and monitored as needed. The mainstay in managing the pancreatic insufficiency of CF is pancreatic enzyme replacement therapy (PERT), which consists of enteric-coated capsules containing amylases, proteases, and lipases. PERT should be ingested before meals that contain protein, fat, or complex carbohydrates. Dosing guidelines have been developed by the CFF. Fibrosing colonopathy or the development of colonic strictures is a complication that appears to be related to high PERT doses exceeding 10,000 lipase units/kg/day and was first noted following the introduction of high-potency pancreatic enzymes.[196] Most patients can be managed with pancreatic enzyme doses within the published guidelines. Patients who require higher pancreatic enzyme doses should be evaluated by a dietitian and a pediatric gastroenterologist.

Patients with pancreatic insufficiency are at risk for fat soluble vitamin deficiency. Guidelines also exist for vitamin supplementation, and CF-specific vitamin products are available.[195] It is recommended that fat-soluble vitamin status be monitored yearly, and additional supplements (D) may be required if levels are still low. It is very unusual for patients with CF to be vitamin A deficient if they are on a CF-specific vitamin preparation. Supplemental salt is needed by patients to prevent salt depletion. Salt is added to infant formula, and children and adults are encouraged to salt their foods liberally and to take salt-containing liquids and snacks during hot weather and periods of increased physical activity.

■ Management of Cystic Fibrosis–Related Diabetes

Insulin is the treatment of choice for CFRD, and ideally the regimen is customized to fit the needs of the individual patient. Combinations of basal (long-acting) and bolus (rapid-acting) insulins are used in the treatment of CFRD with fasting hyperglycemia. In the absence of fasting hyperglycemia, pre-meal rapid-acting insulin is the main treatment approach. Frequent meals, snacking, and "grazing" are not uncommon in CF, and the requirement of multiple daily injections can be prohibitive for some individuals. The insulin pump offers flexibility and can negate the need for frequent injections.[197] Moreover, calories are not restricted in CFRD although either avoidance of foods of low nutritional value (sugared soda or confections) or their consumption in combination with complex carbohydrates, protein, and fats is useful in avoiding excessive hyperglycemia. Pancreatic enzyme replacement also appears to improve meal-related glucose excursion.[86]

The role of treatment of pre-diabetes and early insulin deficiency in preserving pancreatic β-cell function, pulmonary function, and nutritional status has yet to be defined. However, while not formally assessed during a clinical trial, avoiding rapid-acting sugar consumption can mitigate the postprandial hypoglycemia that occurs in the setting of early/indeterminate glucose tolerance. Occasionally, prandial rapid-acting insulin is required to minimize the hyperglycemia that frequently occurs in the first 60 min after meal consumption, the subsequent robust insulin secretion, and the ensuing hypoglycemia 3 h after a meal.

■ Management of Cystic Fibrosis–Related Bone Disease and Hypovitaminosis D

Identification of CF bone disease (CFBD), in the absence of nontraumatic vertebral fracture, relies on the measurement of bone mineral density (BMD) by DXA. The 2005 CFF guidelines, developed before robust pediatric data were available,[138,139,198,199] recommend that baseline hip and lumbar spine DXA be obtained at 18 years and whole-body and lumbar spine DXA as early as age 8 years in the setting of risk factors including poor nutritional status or pulmonary function (FEV_1 percent predicted <50), excessive systemic glucocorticoid exposure, history of fractures, or delayed puberty.[101] In contrast, the 2011 European guidelines recommend baseline DXA by age 8 to 10 years.[100] DXA is then repeated at varying intervals depending upon the previous DXA and illness course: BMD-Z >-1 (every 5 years), <-1 but ≥-2 (every 2–4 years), and <-2 (yearly). Shorter stature and delayed puberty make interpretation of DXA in youth challenging. As a result, height-age-Z adjustment or use of bone mineral apparent density[138,139] is recommended, but how these perform in CF and their relationship to fracture risk remain unknown.

Healthy lifestyle, optimizing pulmonary function, nutritional status and vitamin D, vitamin K, and calcium supplementation, as well physical activity are all mainstays of preventing and treating CFBD. More aggressive treatment with bisphosphonates is recommended in youth for vertebral compression fractures or BMD-Z ≤−2 and significant fracture, prolonged systemic glucocorticoid use, or transplant. Criteria for pharmacologic intervention in young adults is less stringent: low trauma fracture, or BMD-Z ≤−1.5 and prolonged systemic glucocorticoid use or transplant, or BMD-Z ≤−2 and increased bone loss (≥4%). The pharmacologic arsenal for osteoporosis treatment is expanding, but medications like denosumab, a monoclonal antibody that inhibits bone resorption, and anabolic parathyroid hormone (PTH)-related therapies have received limited attention in CF and are not without potential side effects.[200,201] Thus, they are generally reserved for cases in which bisphosphonates are ineffective or contraindicated.[200]

The CFF recommends monitoring 25-hydroxyvitamin D annually and more frequently (every 12 weeks) to monitor response to more aggressive supplementation initiated for suboptimal status.[202] Limited data are available to inform guidelines for cholecalciferol (vitamin D_3) supplementation: in infants, initial dose 400 to 500 IU daily and, if subtherapeutic, up to 800 to 1000 IU daily; children aged 1 to 10 years, initial dose 800 to 1000 IU daily, if subtherapeutic, up to 1600 to 3000 IU daily, and if again subtherapeutic, up to 4000 IU daily; and children age >10 years and adults, initial dose 800 to 2000 IU daily, if subtherapeutic, up to 1600 to 6000 IU daily, and if again subtherapeutic, up to 10,000 IU daily. Consultation with a specialist is recommended if adequate 25-hydroxyvitamin D cannot be achieved with these maximum doses. Cholecalciferol 50,000 IU weekly is an alternative strategy used by specialists for individuals in the general population and may be leveraged for people with CF with appropriate monitoring.

NATURAL HISTORY AND PROGNOSIS

A comprehensive treatment program for CF has unequivocally improved overall survival of patients. Fifty years ago, the median survival was only a few years of age. For the 5-year period from 2015 to 2019, the median predicted survival was 46 years of age (CFF Patient Registry, 2019 Annual Data Report, Bethesda, MD). However, because CF is a complex disorder that affects different organs to different degrees, it is difficult to describe a "typical course" for a patient with CF. Some patients die in childhood or adolescence, while others survive well beyond age 50 years.

An important determinant of the natural history of CF is the severity of the pulmonary disease and the rate at which it progresses. Although most patients' conditions improve in response to therapy, skillful management does less to influence the course of the severely affected than that of the mildly affected patient.

A variety of scoring systems have been devised for CF. The clinical scoring system devised by Shwachman and Kulczycki, and the chest radiograph scoring system devised by Brasfield and associates, were widely used. However, although these and more elaborate scoring systems are useful in categorizing patients according to the severity of illness, none has proved useful in prognosticating the course of an individual patient.

Because CF is a genetic disease, the question of a familial pattern of severity is often raised. Figure 48-6 shows chest radiographs of three siblings with CF; the radiographs demonstrate mild, moderate, and severe disease in individuals in the same family. The capsule histories, which are included in the figure legend, also illustrate the variability in courses experienced.

Patients with CF can be categorized not only with respect to severity of illness, but also by survival. For example, more than half of patients with CF who underwent surgery for meconium ileus before 1965 died in the first 2 months of life. Although this situation had improved markedly by 1976, the survival rate for patients with meconium ileus was still not as good as for all other patients with CF. In addition, the survival rate was much lower for females than for males, especially in adolescents. In recent years, differences between the patients in these groups have declined or disappeared. Because of improvements in the collection of mortality statistics, comparison of current data with those from previous years may be somewhat misleading, Median predicted age of survival is now reported annually for the USA by the CFF. However, there is a difference in outcomes among individual CF centers, and since 2005, the CFF makes selected clinical outcome data for each US CF Center publicly available on their website (www.cff.org). It is hoped and anticipated that survival statistics will improve at a more rapid rate following the introduction of highly effective CFTR modulators in the six years since 2013.

COMPLICATIONS

The course of CF is often characterized by a gradual decrease in pulmonary function, punctuated by further abrupt declines during exacerbations. Malnutrition, when present despite therapy, often correlates best with the severity of the pulmonary disease. However, the course of CF may be suddenly altered by certain complications of the disease.

■ Hypoelectrolytemia and Metabolic Alkalosis

Hypoelectrolytemia and metabolic alkalosis are serious complications that are especially apt to occur during periods of hot weather, when losses of sodium and chloride increase. Electrolyte depletion may be life-threatening, especially in infants and young children (Table 48-3). Prompt fluid replacement with isotonic saline is critical.

■ Intestinal Obstruction

Intestinal obstruction in patients with CF may be related to DIOS, volvulus, intussusception, and adhesions from prior surgery. Acute or chronic crampy abdominal pain can be seen in patients with CF with pancreatic insufficiency and pancreatic sufficiency. This is most often due to DIOS, which is related to intestinal dysmotility, poor hydration of intestinal contents, and malabsorption. Typically, the pain is in the right lower quadrant of the abdomen and is related to a build-up of stool in the terminal ileum, cecum, and ascending colon. Treatment consists of adequate fluid and electrolyte intake, use of polyethylene glycol solutions, and treatment of malabsorption. If the obstruction is incomplete and manifested solely by a tender right lower-quadrant mass, then the previously described measures are used. Nasogastric infusion of polyethylene glycol solutions is also used successfully in the hospitalized patient. If these measures are unsuccessful or the patient has an obstruction, then

TABLE 48-3 Hypoelectrolytemia and Metabolic Alkalosis in Two Cystic Fibrosis Patients

	Serum Electrolytes, mEq/L				
Patient	Na	K	Cl	CO_2	Serum pH
No. 1	123	2.2	49	48	7.60
No. 2	125	2.4	55	41	7.63

Modified with permission from Fleisher G, Ludwig S: Textbook of Emergency Pediatrics. Baltimore, MD: Williams & Wilkins; 1983.

hyperosmolar contrast enemas are administered by a radiologist after hospitalization is required. It is important that patients are well hydrated, that the terminal ileum is cleared of stool, and that an abdominal radiograph is performed to document clearance of stool prior to the patient being discharged from the hospital. Adherent stool/mucus may serve as the leading edge for a volvulus or intussusception (Fig. 48-5), and surgical consultation may be required. Careful pre- and postoperative management is essential to avoid the deterioration in pulmonary function that may follow the use of anesthesia.

Liver Disease

Liver disease is often asymptomatic and requires a high index of suspicion to detect. It can be diagnosed by evaluation of liver function tests on routine yearly studies given lack of evident laboratory markers. AST and ALT level should be monitored annually, as they can be elevated. Other important parameters to assess are a drop in platelet count over time (even if it is within normal laboratory range), elevated GGT, palpable hepatosplenomegaly, and abnormal echotexture of the liver on a liver US.[50] Other laboratory values that indicate compromised liver function are low albumin level, elevated bilirubin, and elevated INR, but these usually indicate advanced liver disease.

Assessment of liver status (synthetic function) and anatomy (abdominal US with Doppler) are important in the diagnosis of cirrhosis and portal hypertension. Only a small percentage of patients with significant liver disease will need liver transplantations, unlike in other chronic liver diseases seen in children. Liver biopsy is recommended in patients in whom an etiology other than CF-related liver disease needs to be established.[48] It is recommended that other causes of liver disease be ruled out and that patients receive hepatitis A and B immunizations.

There is a paucity of data and no strong evidence to support the routine use of ursodeoxycholic acid in patients with CF-related liver disease.[203–205] However, this medication is often used in doses of 10 to 20 mg/kg/day[206] as a choleretic agent to improve bile flow. Ursodeoxycholic acid does not help with gallstone prevention, since the main component of gallstones in CF patients is not cholesterol.

Persistent hepatomegaly or splenomegaly, or complications of portal hypertension, establish significant liver involvement. Patients may develop esophageal varices as a result of portal hypertension and present with upper gastrointestinal bleeding. Once bleeding has been identified as due to varices and hemoptysis has been excluded, therapeutic endoscopy (sclerotherapy or band ligation) must be performed. These procedures as primary prophylaxis are still controversial in pediatrics,[207] although it seems to be favored and is practiced frequently.

For adult CF patients, primary endoscopic prophylaxis is standard of care.[208] For patients with complications of portal hypertension, transjugular intrahepatic portosystemic shunting (TIPS) or surgical portosystemic shunts (splenorenal) can effectively decompress esophageal varices by decreasing portal pressure as a bridge to liver transplantation.

Of interest is how CTFR modulators affect liver function and influence CF-related liver disease. There are increasing number of reports that suggests that modulators such as ivacaftor improve liver disease.[209,210]

Liver transplantation is an option when deemed necessary for patients with CF who have end-stage liver disease. Indications include significant synthetic dysfunction, unresponsive or recurrent esophageal varices with recurrent upper GI bleeding, ascites, and encephalopathy. Patients need to be evaluated by a hepatologist. Ideal candidates are those with an FEV_1 of at least 50% of predicted. Colonization with a multidrug-resistant or panresistant strain of *Pseudomonas* is a relative contraindication to transplantation.

In patients in whom poor pulmonary function or drug-resistant pulmonary infection is an issue, double organ (liver and lung) transplantation may be considered. Despite concerns about worsening airway infection during transplant-associated immunosuppression, liver transplantation in patients with CF does not worsen their pulmonary status.[211]

Atelectasis

Atelectasis of a lung segment or lobe sometimes occurs in CF. Acute atelectasis is generally associated with few symptoms (Fig. 48-8A). If it is untreated, however, the end result of atelectasis is a severely bronchiectatic segment or lobe (Fig. 48-8B). Vigorous chest physiotherapy, in conjunction with antibiotics, is often successful in re-expanding the affected lung region. Bronchoscopy is occasionally helpful. As a rule, however, bronchoscopy is no more effective than chest physiotherapy and pulmonary pharmacotherapy. Resection of a persistently atelectatic or bronchiectatic lobe is undertaken only when the remaining areas of the lung are in relatively good condition, overall pulmonary function is good, and the evidence is convincing that the affected segment is responsible for intolerable symptoms (fever, cough, or sputum production).

Pneumothorax

Recurrent pneumothorax is common in CF, particularly in older patients (Fig. 48-8C). Tension pneumothorax occurs in up to 30% of patients with CF who develop pneumothorax. Tube thoracostomy is indicated when the pneumothorax occupies more than 10% of the area of the hemithorax seen on the posteroanterior chest radiograph. Because the frequency of recurrence of pneumothorax is high, attempts are often made at the time of the initial event to achieve chemical or surgical pleurodesis, although this is not recommended in existing guidelines.[212] Surgical pleurodesis is more effective at preventing recurrence of a pneumothorax and is no longer considered a contraindication to lung transplantation.

Hemoptysis

Expectoration of a small amount of blood-streaked sputum is a common occurrence in CF and is generally managed by intensifying home therapy for pulmonary infection. In contrast, hemoptysis (the expectoration of at least 30 to 60 mL of fresh blood) requires hospitalization, even with a chest radiograph that is virtually unchanged (Fig. 48-8D). The probable mechanism underlying most instances of hemoptysis in CF is the erosion of an area of localized infection into a bronchial vessel. Massive hemoptysis (blood loss of 240 mL) is uncommon in CF. However, it represents a potentially life-threatening situation. Bronchoscopy, and sometimes thoracic surgery, may be required to control the hemorrhage. Bronchial artery embolization has been used successfully in patients with CF and is now the treatment of choice when a physician experienced in the procedure is available.[213]

Infection with Unusual Organisms

CF produces central bronchiectasis, even though the disease initially is in the small bronchioles. Bronchiectatic airways are frequently colonized with unusual organisms, including *Aspergillus* and atypical mycobacteria. As is the case with pathogenic bacteria, eradication of these organisms from the airways is often not possible. The focus of therapy is directed toward verifying that the organisms are resulting in worsening of the disease and controlling the infection, rather than effecting a microbiologic cure.

Mycobacteria

The prevalence of infection with atypical mycobacteria in CF mandates surveillance for these organisms in sputum cultures at least

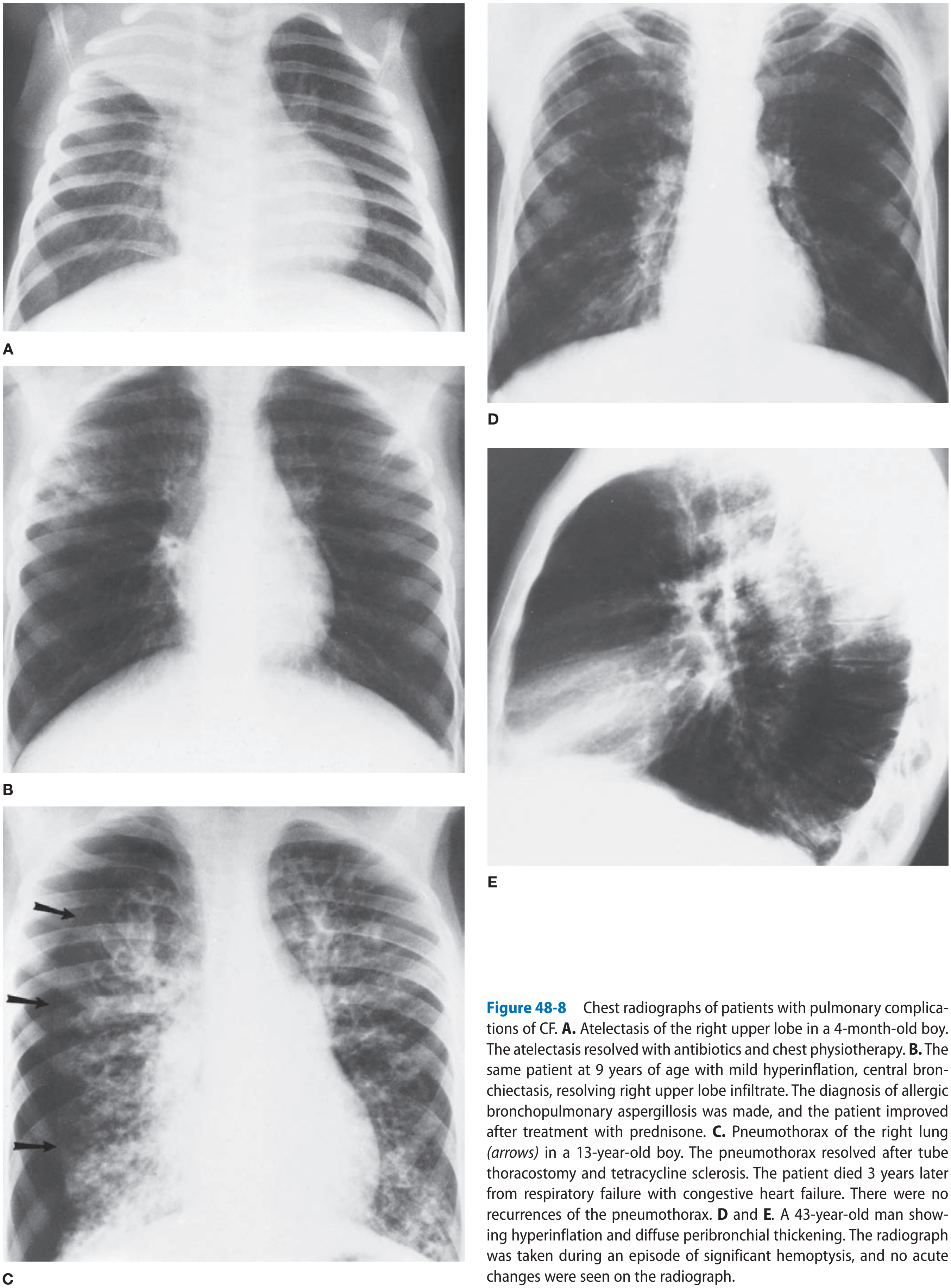


Figure 48-8 Chest radiographs of patients with pulmonary complications of CF. **A.** Atelectasis of the right upper lobe in a 4-month-old boy. The atelectasis resolved with antibiotics and chest physiotherapy. **B.** The same patient at 9 years of age with mild hyperinflation, central bronchiectasis, resolving right upper lobe infiltrate. The diagnosis of allergic bronchopulmonary aspergillosis was made, and the patient improved after treatment with prednisone. **C.** Pneumothorax of the right lung *(arrows)* in a 13-year-old boy. The pneumothorax resolved after tube thoracostomy and tetracycline sclerosis. The patient died 3 years later from respiratory failure with congestive heart failure. There were no recurrences of the pneumothorax. **D** and **E**. A 43-year-old man showing hyperinflation and diffuse peribronchial thickening. The radiograph was taken during an episode of significant hemoptysis, and no acute changes were seen on the radiograph.

annually.[214] When atypical mycobacteria are cultured, antimicrobial sensitivities should be obtained. A decision about therapy for isolation of atypical mycobacteria is based on the likelihood that the organism is contributing to airway infection and a decline in pulmonary function. Isolation of the same organism on several occasions, positive smears, presence of progressive chest radiographic changes, further decline in pulmonary status despite vigorous antipseudomonal (or antistaphylococcal) therapy, persistent night sweats, and fever are clinical clues that the atypical mycobacteria are contributing to disease. Demonstration of tissue infection with transbronchial lung biopsy is rarely recommended. A clinical database has been established by the CFF to track results of treatment for atypical mycobacterial infections in patients with CF. The current standard for therapy is treatment with several antimicrobials for synergy and to prevent development of resistance, and consensus guidelines have been published.[215]

Aspergillus

In an analogous fashion, molds, especially *Aspergillus*, are occasionally isolated from patients with CF. Approximately 5% to 15% of patients have allergic bronchopulmonary aspergillosis (ABPA) (see Chapter 46). The diagnosis of ABPA in CF is difficult because of overlapping symptoms between the two disorders. Diagnostic criteria for ABPA include (1) reversible airway obstruction, (2) proximal bronchiectasis, (3) history of pulmonary infiltrates, (4) skin test positivity to aspergillus antigens, (5) precipitating serum antibodies to *A. fumigatus*, (6) elevated total serum immunoglobulin E (IgE), (7) elevated specific serum IgE and serum immunoglobin G (IgG) to *Aspergillus*, and (8) peripheral eosinophilia. A negative skin test for *Aspergillus* effectively rules out the diagnosis of ABPA. During the active phase of ABPA, elevations in total IgE and eosinophil count are seen. Rises in *Aspergillus*-specific titers (IgE and IgG) are more specific for ABPA than are serum precipitins. ABPA in patients with CF is usually treated with corticosteroids and itraconazole; however, for patients who do not tolerate treatment with prednisone, omalizumab has been used.[216] The level of total IgE is used to follow the activity of the disease.

Gram-Negative Bacteria

In the late 1970s and early 1980s, the importance of *Burkholderia cepacia* (formerly *Pseudomonas cepacia*) was recognized. *B. cepacia* is a gram-negative, oxidase-positive rod that is uniformly resistant to polymyxin and, frequently, panresistant. Isolation of *B. cepacia* requires plating on special OFPBL (oxidative fermentative polymyxin B bacitracin lactose) or PC (*P. cepacia*) agar plates to retard growth of other gram-negative rods and enhance growth of *B. cepacia*. The plates must be maintained for a minimum of 4 days. *B. cepacia* colonization has been associated with septicemia, which is very rarely seen with *P. aeruginosa*.

The clinical course after acquisition of *B. cepacia* may be fulminant, with death occurring in a matter of months. However, most patients' disease follows a more benign course. Carefully controlled epidemiologic studies are needed to better define risk factors and to establish the true virulence of *B. cepacia*. Experimental evidence exists that at least one strain of *B. cepacia* may be transmitted in an epidemic fashion. The combination of a poor clinical course after acquisition of *B. cepacia* and the evidence supporting epidemic transmission has led to cohorting or isolation of patients with CF infected with *B. cepacia*, as recommended by the CFF and the Centers for Disease Control and Prevention (CDC).

In addition to being colonized with *Pseudomonas* and *Burkholderia* species, patients with CF may be colonized with other gram-negative, oxidase-positive organisms, such as *Stenotrophomonas maltophilia*, *Pseudomonas oryzihabitans*, and *Achromobacter xylosoxidans*. These are pathogenic organisms, similar in importance to *P. aeruginosa*. Antibiotic therapy should be directed toward these bacteria when they are isolated from the patient with CF who is experiencing an acute exacerbation.

The prolonged, suppressive use of antibiotics in CF has led to emergence of resistant organisms. A multiply resistant *Pseudomonas* is an organism that is resistant to all agents in at least two different classes of antibiotics. Resistance to oral fluoroquinolones occurs after about 3 weeks of therapy; if the agent is withheld, the organism occasionally becomes sensitive again. The existence of more refractory MDR strains has prompted investigation into the possibility of isolating and engineering a bacteriophage for use in treating these MDR strains of *Pseudomonas*.[217]

■ Respiratory Failure

As the pulmonary disease of CF progresses and the degree of hypoxemia increases, patients are at risk to develop pulmonary hypertension and cor pulmonale. An increase in hypoxemia often occurs during exacerbations of the pulmonary disease. During the acute episode, antibiotic treatment for the underlying pulmonary disorder is intensified and supplemental oxygen is added. Expectant monitoring and aggressive treatment of nocturnal hypoxemia (maintaining Sa_{O_2} ≥95%) prevent the onset of cor pulmonale. When respiratory failure develops in CF, that is, hypercarbia (Pa_{CO_2} at least 55 mm Hg) in addition to hypoxemia, management becomes extremely difficult.

Noninvasive mechanical ventilation using bilevel positive airway pressure has been used successfully in patients with end-stage CF awaiting lung transplant; it can improve oxygenation, reduce respiratory rate, and successfully transition to home nocturnal use.

Mechanical ventilation is generally instituted when an acute episode, such as viral pneumonia or status asthmaticus, leads to acute respiratory failure. This approach is indicated in the patient who has had good pulmonary function before the acute episode. Mechanical ventilation is less apt to be successful if the patient has previously experienced a bout of respiratory failure.

When respiratory failure marks the end of a chronic course of progressive pulmonary insufficiency despite adequate medical therapy, mechanical ventilation is usually unhelpful. None of the indications or contraindications for mechanical ventilation is absolute, however, and the clinical outcome depends, to a large extent, on the availability of a dedicated and skilled intensive care team experienced in caring for patients with CF.

■ Complications Related to Lung Transplantation

Lung transplantation has emerged as an option for patients with end-stage CF (see Chapter 106).[218–220] Despite initial concerns about immunosuppression in patients with suppurative lung disease, the outcome for those with CF who undergo lung transplantation is among the best reported for this procedure. Timing for lung transplantation has changed with the adoption of a lung allocation score (LAS), which takes into consideration parameters to predict 1-year survival, with a transplant versus without a transplant, and medical urgency. The impact of this organ allocation system is a dramatic decrease in the number of patients on the waiting list for transplantation and a significant shortening of wait times for transplantation.

One major complication post–lung transplantation for CF patients is the risk of infection due to resistant organisms. Colonization with *B. cepacia* complex, or rapidly growing mycobacteria such as *M. abscessus*, has been reported to negatively impact survival.[221] *Aspergillus* may cause invasive infections in the parenchyma or the anastomosis site. Other complications, not specific to CF patients, include acute and chronic graft rejection.

Acute graft rejection is associated with a humoral immune response to donor HLA antigens and complement activation.[222]

Importantly, acute graft rejection is a negative prognostic factor for chronic graft rejection.

Chronic allograft rejection is characterized by obliterative bronchiolitis following transplantation. Obliterative bronchiolitis is a progressive occlusion of the bronchiolar lumina by inflammatory cells and submucosal fibrosis. Transient improvement in airflow is seen following augmentation of immunosuppression. About 50% of transplant patients develop obliterative bronchiolitis after the second year following the procedure. The disease pursues a relentless downhill course, with a median survival of about 2 years following the initial diagnosis.

The poor prognosis associated with obliterative bronchiolitis has several important implications for patient selection and timing of referral for transplantation. First, the main reason for seeking lung transplant is to improve the quality of life, rather than to improve survival. Second, the timing of referral for lung transplantation needs to be calculated to optimize the candidate's fitness for transplant yet delay transplant until absolutely necessary considering the risk of developing obliterative bronchiolitis.

Results from clinical studies may aid with proper timing of referral for lung transplantation in CF. CF patients with severe airflow obstruction, as indicated by FEV_1 less than 30% of predicted, had a 50% 2-year mortality. Other important clinical parameters useful in determining the timing of transplantation are the presence of hypoxemia (PaO_2 under 55) and hypercarbia (Pa_{CO_2} above 50). Of interest, in both single and multivariate analyses, female sex is associated with an increased relative risk, suggesting that for female patients, referral for lung transplantation should be considered at an even earlier stage.

Because CF is a multisystem disorder, both management and proper selection of patients are more complicated than for other diseases managed with lung transplantation. Among the most difficult challenges presented by patients with CF before transplantation is the microbiology of their lower airways. As discussed previously, colonization with multidrug-resistant *B. cepacia*, specifically the genotype genomovar III, has been associated with a poor clinical outcome.

For poorly understood reasons, patients with CF metabolize drugs differently from those without CF, complicating the dosing of medications, including cyclosporine. The difficulties in achieving an optimal drug dose may be related to malabsorption or enhanced excretion of the drug.

Nutritional issues also complicate the posttransplantation management of patients with CF. About 50% of all patients with CF over 30 years of age are overtly diabetic, and administration of corticosteroids induces diabetes in another 10%. Maintenance of proper nutrition is important in CF, especially for rapid postoperative recovery. Finally, gastroesophageal reflux may negatively impact pulmonary outcomes following transplantation. Despite all the special challenges to successful lung transplantation posed by patients with CF, their actuarial survival is quite good. The 1-, 5-, and 10-year survival for adult transplant recipients in one large transplant center are 93%, 75%, and 57%, respectively.[223]

PSYCHOSOCIAL ISSUES

Psychosocial issues are important in the management of patients with CF. Special circumstances should be recognized for adults with the disorder. There is a high prevalence of depression and anxiety among patients with CF and their parents.[224] Anxiety and depression in parents adversely impact the ability to adhere to treatment for the child. In adults with CF, these issues impact their abilities in self-care.

General

Careful attention to the emotional, social, and financial well-being of the patient with CF and his or her family has considerable value in favorably influencing the course of the disease. At the time of diagnosis, it is important to strike an optimistic note while educating the patient about the illness and its management. As part of the early encounter with the patient, the importance of identifying and reinforcing the emotional and financial strengths of the family, as well as weaknesses that will need buttressing, should be recognized. Medical care for CF patients is costly, especially if hospital admissions are required. Many states have programs for children with disabilities that provide support for patients and families. Several states have also established special programs for adults with CF.

As the disease runs its course, counseling and feedback about disease progression are essential. As the patient and family go about setting educational, career, and family goals, they need guidance in realistic planning. It is vital that the physician develop and maintain a positive attitude. The patient who gives up hope is liable to undergo rapid deterioration. Conversely, even patients with severe pulmonary disease can continue to function well and be productive. At the stage when medical therapy is of no further avail, however, the patient and family require considerable emotional support to accept the inevitable. In recent years, many CF centers have allowed patients to die at home, rather than in the hospital. The family requires specific instructions about how to provide physical and emotional comfort for the patient in the home. Usually, home visits by some members of the CF team are required. Not all families have the strength or resources to care for the patient dying at home.

Special Considerations in Adult Patients

In 2020, the median life expectancy for patients with CF was about 46 years (CFF Patient Registry, 2019 Annual Data Report, Bethesda, MD). Managing a chronic illness becomes more complicated when patients must also begin to manage their independence and make life decisions regarding education, marriage, children, careers, insurance, and self-care.[225] Intense support for both patients and their families is required. Patients with a relatively mild clinical course of disease form healthy and satisfying relationships in a manner similar to their healthy, age-matched peers. With advanced disease, patients with CF have more difficulty in forming intimate relationships. Disturbances in body image, decreased mobility, and lack of opportunity to meet suitable partners are cited as reasons for the decreased ability to form intimate relationships in the severely affected young adult with CF.

The adult patient with CF faces unique problems with self-care. Families of patients with CF provide a tremendous amount of care that is expensive and time-consuming to replace for the independently living adult. When the disease flares, patients must "step up" their level of care at precisely the time when they are least able to do so. Judicious use of hospitalization and home care must be provided if the patient is to recover. The trend toward home management of a pulmonary exacerbation using intravenous antibiotics alone ignores the obvious contributions of nutrition, airway clearance, and rest toward resolution of the problem.

REPRODUCTIVE ISSUES

More than 98% of male patients with CF are sterile, secondary to bilateral absence of the vas deferens. Microsurgical epididymal sperm aspiration (MESA), coupled with in vitro fertilization, has been successful in producing pregnancies in a few carefully selected patients. Not all males with CF are sterile, however. In addition to counseling, these men should be offered semen analysis.

Pregnancy for women with CF is increasingly common, and several important issues remain unsolved. In 2004, 191 women with CF were pregnant (CFF Patient Registry, 2004 Annual Data Report, Bethesda, MD). This stands in marked contrast to the total of 13 pregnancies in 10 patients recorded from 1960 to 1966 (data from the 1994 CFF Data Registry).

Maternal clinical status before pregnancy is the most important prognostic factor of maternal outcome. In a study of 25 women with 38 pregnancies, no significant difference was seen between pre- and post-gravid gas exchange or nutritional status. A small but statistically significant decline in spirometry was noted. However, the decline was not outside the range of expected decline for the natural progression of the disease. More severely affected women suffered an irreversible decline in clinical status during pregnancy. Without an appropriately matched control group of nongravid women with CF, it was not possible to determine whether pregnancy per se was responsible for the decline or whether the decline is a reflection of the natural history of the disease. Comparison of matched groups of pregnant and non-pregnant CF women from a registry suggested that there was not a difference in the rate of decline between these groups. However the pregnant women received a greater number of therapies and more intense monitoring of their health.[226]

Recommendations about pregnancy for women who are either mildly affected or severely affected is straightforward. For the woman with moderately compromised pulmonary status (i.e., FVC_1 under 50%–60% of predicted), an overall assessment of the clinical situation is recommended, although no firm guidelines can be given. Increased incidence of fetal prematurity is noted in women with a pregravid FVC below 50% of predicted, lending additional weight against recommending pregnancy to women with moderate to severe airflow obstruction.

In any woman with CF who is contemplating pregnancy, thorough evaluation and treatment of nutritional deficiencies and pulmonary exacerbations are required. Frequent use of antibiotics is unavoidable, and the teratogenic risk of many antibiotics is unknown. Despite this theoretical risk, good maternal and fetal health depend on aggressive management of pulmonary exacerbations, including use of antibiotics. Management of the gravid patient with CF is best accomplished in a CF center that has a program in high-risk obstetrics.

A European consensus panel has published detailed guidelines for the management of pregnancy in women with CF.[227] Importantly, in the era of highly effective CFTR modulators, there are outstanding issues concerning pregnancy, lactation, and motherhood, including the impact of the modulators on fertility, exposure via lactation, and effect on offspring.[228]

For men with CF who opt for microepididymal sperm aspiration (MESA) and for women with CF who are contemplating pregnancy, all offspring are obligate heterozygotes for CF. These offspring need to be counseled that their risk of having a child with CF is about 1 in 50 if the genotype of the spouse is not known. Although genetic testing of children from affected parents is not recommended, they should receive genetic counseling on reaching adolescence.

Parents with CF also need to consider the ethical issues of a premature parental death and its effect on the family. If the spouse of a CF individual is a known carrier of a CF mutation, the availability of in vitro fertilization with preimplantation genetic testing provides a method to avoid having a child who is affected with CF. Discovery of the CF gene in 1989 led to the hope that prenatal diagnosis might eventually decrease the incidence of the disease. There is a suggestion that this may, in fact, be occurring.[229]

FUTURE DIRECTIONS

The timeline of progress in CF research and care from its initial description in the 1930s through 2017 was summarized by Ramsey and Welsh.[230] The most dramatic improvement in the care of CF patients occurred with the approval of Trikafta in the waning months of 2019. Patients who have received this triple therapy often describe it as a “game changer.” As of June 2021, the drug is available to CF patients 6 years of age and older who have either at least one copy of delF508 or one copy of other approved mutations.

To further enhance survival and quality of life in CF beyond the initial robust improvements that many CF patients have experienced from Trikafta, and to include all CF patients in treatment with highly effective CFTR modulators, physicians must look to insights gained from basic research. A tremendous amount has already been accomplished, warranting a realistic expectation that additional breakthroughs will soon occur in the treatment of the disorder. Some additional areas for investigation include harnessing new information about the CF microbiome to better treat resistant infections, and new modes of therapy to tackle unopposed protease in the airway and the associated, unrelenting inflammation to prevent progression of CF lung disease.

Progress toward the CFF’s goal of leaving no CF patient behind will require a multidisciplinary approach. Management of the lung disease in CF will probably be based on combined methods. However, the momentum gained from improved understanding of the molecular details of CFTR structure and the ability to improve its function makes it more likely that specific therapy will eventually result in better outcomes for all patients with CF.

New approaches to correct premature termination codon mutations or promote mRNA read-through and prolong mRNA half-life are being developed. Genetic engineering is also being applied to new therapies to correct any CFTR.[231–233] The envelope was pushed even further by the demonstration that administration of a CFTR modulator to pregnant CF ferrets resulted in male pups with normally developed vas deferens.[26] This suggests that early or in utero treatment of individuals who have a CF genotype may prevent or inhibit the development of some, or possibly all, of the clinical hallmarks of CF. While this is certainly speculative now, recent progress in research provides a solid foundation for optimism.

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CHAPTER 49

Bronchiolitis

Gary R. Epler

INTRODUCTION

Diseases of the bronchioles occur throughout the bronchiolar structures, from bronchiolar airways to alveolar ducts and alveoli (Table 49-1). Acute and chronic bronchiolitis are seen from near the bronchi, all the way to the respiratory bronchioles; constrictive bronchiolitis is seen in the mid-bronchioles, while diffuse panbronchiolitis occurs from the distal bronchioles to the respiratory bronchioles, and smoker's bronchiolitis involves the respiratory bronchioles. Bronchiolitis obliterans organizing pneumonia (BOOP) includes both the terminal bronchioles and alveoli and is discussed more fully in Chapter 55.

This chapter includes a discussion of the pathologic, clinical, and radiographic findings, as well as treatment of the bronchiolar airway disorders.

BRONCHIOLAR ANATOMY

Bronchioles are noncartilagenous small airways that are usually 1 mm or less in diameter; they have been called the bridge between the bronchi and alveoli.[1] The bronchioles have cartilage and mucus glands that are commonly found in the bronchi, but bronchioles also contain ciliated epithelium, smooth muscle, and bronchiolar exocrine cells.[2] Neuroendocrine cells are common in the proximal bronchioles.

More distal in the airways are approximately 30,000 terminal bronchioles that have an average diameter of about 0.6 mm. These bronchioles have circular smooth muscles in their walls; the surface cilia gradually disappear distally. Terminal bronchioles branch into 224,000 respiratory bronchioles that differ from the bronchioles: respiratory bronchioles have two to three alveolar structures in the walls containing columnar cells with cuboidal type II cells and squamous type I cells. These structures terminate in 13.8 million alveolar ducts and 300 million alveoli.

THE CLINICAL SPECTRUM OF THE BRONCHIOLAR DISEASES

The wide variety of bronchiolar diseases that may be seen in clinical practice are discussed below.

TABLE 49-1 Clinical Classification of the Bronchiolar Diseases

Airway diseases
• Acute and chronic bronchiolitis
• Respiratory bronchiolitis
• Follicular bronchiolitis
• Diffuse panbronchiolitis
• Bronchiolitis obliterans
Interstitial diseases
• Respiratory bronchiolitis–interstitial lung disease (RB-ILD)
• Bronchiolitis obliterans organizing pneumonia (BOOP)

■ Acute and Chronic Cellular Bronchiolitis

Acute and chronic cellular bronchiolitis is characterized pathologically as acute or chronic inflammation of the bronchioles without a fibrotic component.[3,4] The inflammation may be submucosal, mural, or peribronchiolar. Although common in infants and children, in the adult, bronchiolitis is rare and may be caused by respiratory syncytial virus, adenovirus, influenza, *Mycoplasma pneumoniae*, *Streptococcus pneumoniae*, and *Haemophilus influenzae* as well as acute toxic inhalational injury. Symptoms include a flu-like illness with fever and persistent nonproductive cough of several weeks' duration. There is generally no wheezing and no airflow obstruction. The chest x-ray is often normal, although the chest CT scan may show tree-in-bud opacities, ill-defined nodules, and ground-glass opacities.[4] The illness usually subsides over time. Cough suppressants may be utilized. Sometimes, a brief course of corticosteroid therapy is given for a severe, relentless cough. If symptoms are not responsive to corticosteroid therapy or if symptoms worsen, the illness may be fibrotic constrictive bronchiolitis—a disorder with a different clinical course and prognosis.

■ Respiratory Bronchiolitis

Respiratory bronchiolitis is sometimes called smoker's bronchiolitis, as cigarette smoking is almost always the cause of this disorder.[3,5] The characteristic histologic feature is the accumulation of tan-brown macrophages in the lumens of respiratory bronchioles and adjacent alveoli, often seen as an incidental finding in cigarette smokers. There are usually no clinical symptoms associated with this type of respiratory bronchiolitis. Treatment is smoking cessation.

In some situations, respiratory bronchiolitis may extend into the interstitium and is referred to as respiratory bronchiolitis–interstitial lung disease (RB-ILD).[4–6] Affected individuals have shortness of breath, bilateral crackles, reticulonodular opacities on chest radiography, decreased vital capacity, and decreased diffusing capacity. Treatment is smoking cessation, but often a course of corticosteroid therapy is needed for resolution.

■ Follicular Bronchiolitis

Follicular bronchiolitis is characterized by hyperplastic lymphoid aggregates forming 1- to 2-mm peribronchiolar nodules.[3,4,7] Follicular bronchiolitis is often limited to a pathologic description with no clinical counterpart. There may be an underlying systemic disease such as immunodeficiency syndromes or infections such as *Legionella* or *Pneumocystis*. In some patients, there may be cough and small linear radiographic opacities or hyperinflated lungs, and very rarely, advanced disease.[7]

■ Diffuse Panbronchiolitis

Diffuse panbronchiolitis is a chronic diffuse bronchiolar inflammatory disease that is strongly associated with human leukocyte antigen (HLA) alleles, especially HLA-A and HLA-B.[8] It is characterized by chronic inflammation and lymphofollicles of the respiratory bronchioles and adjacent centrilobular regions, with infiltration of histiocytosis, plasma cells, and lymphocytes.[9] There is an interstitial accumulation of foam cells in the walls of respiratory bronchioles and adjacent alveolar ducts and alveoli (Fig. 49-1). The disorder is largely restricted to the Asian countries but has been reported throughout the world.

Symptoms include chronic cough, sputum production, and shortness of breath, and almost all individuals have chronic paranasal sinusitis. Rhonchi and crackles are common. Radiographic findings show hyperinflation and diffuse small nodular opacities bilaterally. Pulmonary function testing shows airflow obstruction with decreased

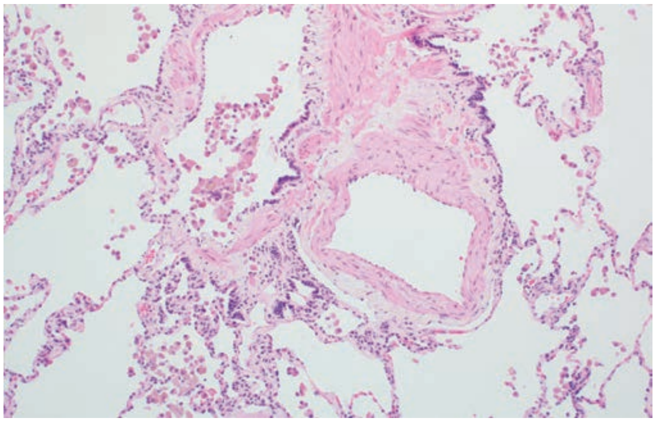

Figure 49-1 Respiratory bronchiolitis is appreciated as clusters of lightly pigmented macrophages within the lumen of a terminal airway and peribronchiolar airspaces (hematoxylin-eosin, original magnification ×100). *(Reproduced with permission from Konopka KE, Myers JL. A Review of Smoking-Related Interstitial Fibrosis, Respiratory Bronchiolitis, and Desquamative Interstitial Pneumonia: Overlapping Histology and Confusing Terminology. Arch Pathol Lab Med. 2018;142(10):1177–1181.)*

forced expired volume in 1 s (FEV_1) and FEV_1 to forced vital capacity (FEV_1/FVC) ratio. Hypercapnia and cor pulmonale occur late. There is often an associated increase in the cold-hemagglutinin titer.

The disorder is progressive. In the past, diffuse panbronchiolitis was a fatal disease with a 10-year survival of less than 20% in patients with *Pseudomonas aeruginosa* infection. However, the use of macrolides has resulted in a dramatic improvement in survival.[10]

Bronchiolitis Obliterans

Bronchiolitis obliterans can be severely disabling and deadly. Traditionally, bronchiolitis obliterans has been used as a clinical term to describe irreversible fibrosis of the bronchiolar airway that is idiopathic or occurs after accidental toxic fume inhalation or a viral pneumonia. However, pathologists may see two distinctive lesions that, in turn, have a different clinical course and response to treatment.

Histologically, the two lesions are *proliferative bronchiolitis* and *constrictive bronchiolitis* (Table 49-2). Depending on severity, obliteration of the bronchioles (the *obliterans* term) may or may not occur with these lesions. The histologic distinction between these two lesions is that constrictive bronchiolitis arises in a concentric fashion outside the bronchiole walls as a fibrotic lesion, while proliferative bronchiolitis arises from within the bronchiole walls as an inflammatory lesion.

The term *bronchiolitis obliterans* is used in this chapter, as it has been used by clinicians for more than 100 years and almost always reflects the fibrosing, constrictive, pathologic lesion.[11] The proliferative lesion is often self-limiting and less severe, or responds to corticosteroid therapy with complete resolution; it usually does not result in the clinical label of bronchiolitis obliterans.

Proliferative bronchiolitis is an inflammatory bronchiolitis characterized by intraluminal polypoid connective tissue masses of myxoid fibroblastic tissue, which resembles granulation tissue that arises from within the bronchioles.[1] Central clusters of mononuclear inflammatory cells may be found in these polypoid masses. This type of bronchiolitis includes organized polypoid granulation inflammatory tissue in the distal bronchiole airways, respiratory bronchioles, alveolar ducts, and alveoli in the form of BOOP.[12] Additional, distinctive histologic findings with proliferative bronchiolitis associated with BOOP include no disruption in the lung architecture, interstitial fibrosis, absence of traction bronchiectasis, or histologic honeycombing (Fig. 49-2).

Constrictive bronchiolitis is a fibrotic, concentric bronchiolitis lesion with or without complete obliteration (Fig. 49-3). This lesion is usually seen in the middle to distal portions of bronchioles and does not extend into the respiratory bronchioles or alveoli. The lesion is characterized by a peribronchiolar fibrotic process that surrounds, rather than fills, the lumen, resulting in extrinsic compression and obliteration of the airway.[3,4] There is mural thickening by submucosal collagenous fibrosis, with progressive concentric narrowing associated with luminal distortion, mucus stasis, and chronic inflammation.

Constrictive bronchiolitis was called “fibrosing bronchiolitis” in the German pathology literature.[13] The lesion preferentially involves membranous bronchioles and is characterized by fibrosis of the stroma and narrowing the lumen in a concentric fashion. The muscle layer may be hypertrophic in early lesions, atrophic in late stages, and replaced by fibrotic tissue at the end stage. Visscher and Myers noted that constrictive bronchiolitis is often patchy and focal, making the diagnosis difficult from a transbronchial biopsy; advanced cases may be especially inconspicuous because of lack of active inflammation and disappearance of bronchioles.[14]

There are several causes of bronchiolitis obliterans and associated systemic disorders (Table 49-3).

TABLE 49-2 Pathologic Findings of Bronchiolitis Obliterans

Constrictive bronchiolitis

- Concentric fibrotic lesion of the mid to distal bronchioles
- Surrounds the lumen causing extrinsic narrowing and obliteration
- Distortion of the lumen and mucostasis
- Muscle layer hypertrophic early, atrophic late, and replaced by fibrotic tissue in end stage
- May be patchy and focal
- Late stage includes traction bronchiectasis and bronchiolectasis

Proliferative bronchiolitis

- Intraluminal polypoid myxoid fibroblastic tissue arising with the bronchiole wall
- May be organized polypoid granulation tissue from the bronchioles to the respiratory bronchioles and including the alveoli
- No disruption of the lung architecture
- No traction bronchiectasis

Idiopathic Bronchiolitis Obliterans

Idiopathic bronchiolitis obliterans occurs among individuals who have no obvious inciting agent or associated systemic disorder, and who have airflow obstruction and constrictive bronchiolitis histologically. This disorder continues to be exceedingly rare. Symptoms begin with a nonproductive cough, and shortness of breath develops later. Physical examination shows no wheezing but may demonstrate an unusual finding of early inspiratory crackles. The crackles occur early because of the scarring around the mid-bronchiole airways, causing snapping closure of the airways and resultant crackling sound.

Pulmonary function studies show irreversible decrease in the FEV_1 and FEV_1/FVC, with no improvement after bronchodilator inhalation. The diffusing capacity is highly variable, from increased, to normal, to markedly decreased.

The chest roentgenogram is often normal or shows hyperinflation. High-resolution chest CT scans during inspiration and expiration can be helpful for establishing a diagnosis. For example, a normal

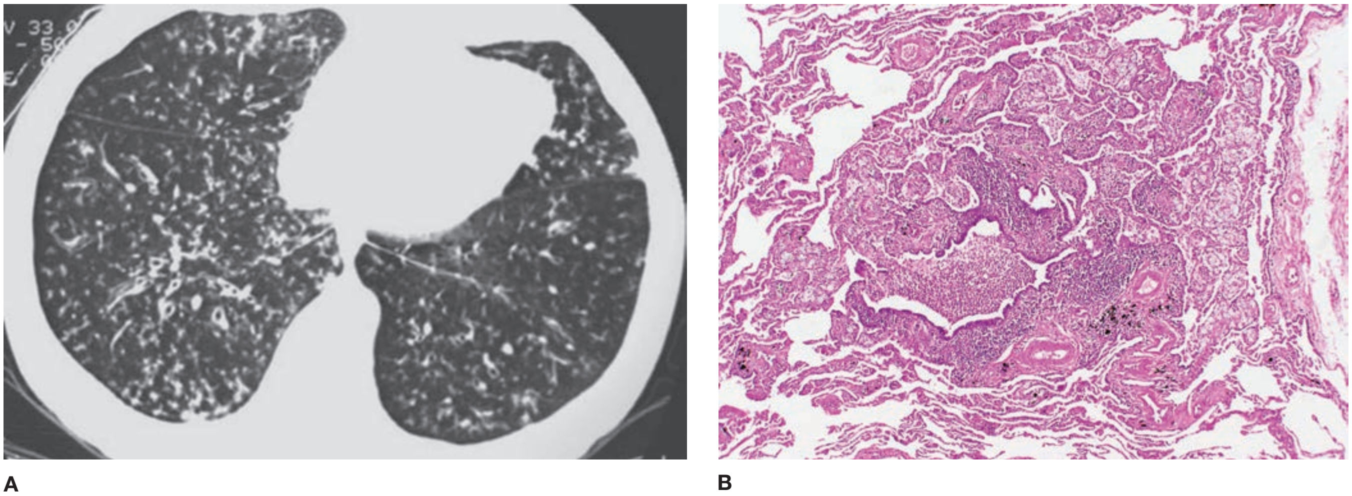

Figure 49-2 Diffuse panbronchiolitis. **A.** The chest CT scan shows bilateral centrilobular nodules with branching showing "tree-in-bud" pattern. **B.** The pathology micrograph shows chronic inflammation of the respiratory bronchioles, with interstitial accumulation of foam cells in the walls of the respiratory bronchioles, adjacent alveolar ducts, and alveoli. *(Reproduced with permission from Dr. Kenneth W. Tsang, Queen Mary Hospital, Hong Kong, China and Dr. Thomas V. Colby, Lung Pathology, Mayo Clinic Scottsdale.)*

chest CT scan may be seen in the inspiratory phase of the study, but the expiratory study will show lobular air trapping. These expiratory images show low-attenuation areas in the secondary pulmonary lobules, resulting in a typical mosaic pattern with scattered areas of low attenuation. Additional CT findings include constriction of the pulmonary vessels within the low-attenuation areas, expiratory air trapping, bronchial dilation, and, sometimes, tree-in-bud configuration with centrilobular nodules and branching linear densities.[4]

Treatment consists of corticosteroids at a high initial dose followed by lower-dose therapy for up to 1 year in patients who respond. For those who do not respond by 3 months, corticosteroids are discontinued and employed for life-threatening exacerbations. Immunosuppression treatment and lung transplantation are considered for individuals with life-threatening and severe disease.

Patients who survive the initial episode may stabilize for several years or progress to end-stage airflow disease and cor pulmonale. Myong et al.[15] described three women, aged 41 to 54, who developed cough and progressive shortness of breath over the course of 6 months to 10 years; lung pathology showed constrictive bronchiolitis with bronchiolar airway obliteration. The thin-section CT scans showed low-attenuation changes of the mosaic pattern. None responded to corticosteroid treatment.

Toxic Fume Bronchiolitis Obliterans

Toxic fume bronchiolitis obliterans is a three-phase response disease. The exposure usually occurs from an accidental explosion resulting in nose, throat, and eye irritation with no major respiratory symptoms. Phase one is an asymptomatic latency period of 6 to 12 h after exposure. Phase two begins suddenly with acute-onset respiratory failure with a white-out of the lung. If there is recovery from this acute phase, there is another asymptomatic latency period of 7 to 10 days. Phase three then occurs as constrictive bronchiolitis with irreversible airflow obstruction, progressive shortness of breath, and chronic respiratory failure.

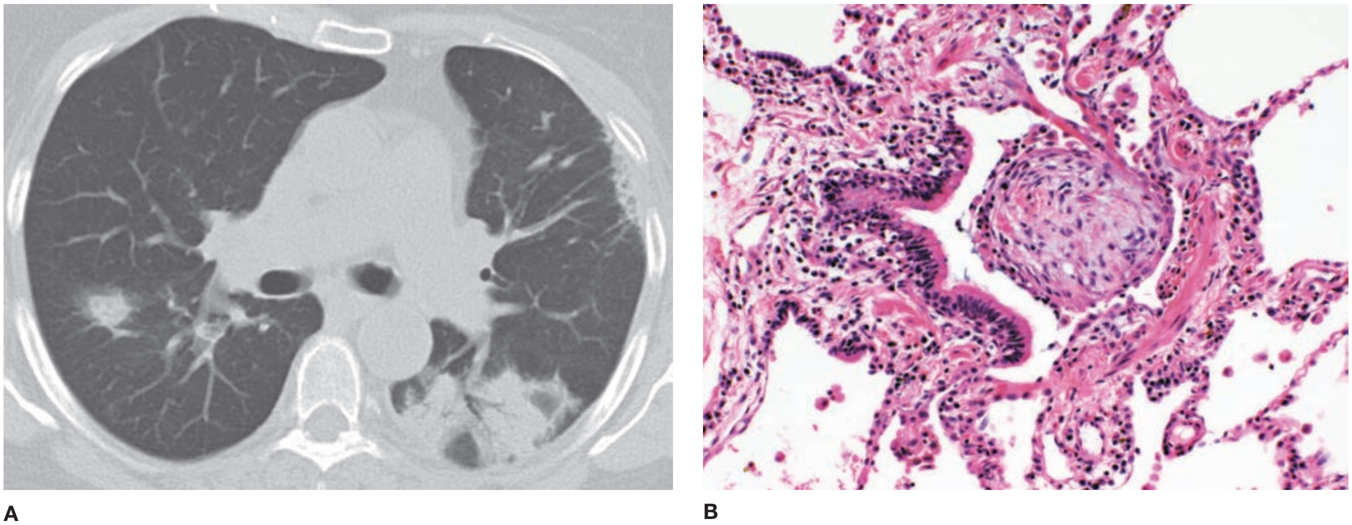

Figure 49-3 Bronchiolitis obliterans organizing pneumonia. **A.** The chest CT scan shows bilateral patchy ground-glass opacities, air bronchograms, and peripheral-based triangular infiltrates. **B.** The pathology micrograph shows organized polypoid granulation tissue filling the distal bronchiole and extending into the alveoli. *(Reproduced with permission from Dr. Ritu R. Gill, Chest Radiology, Brigham and Women's Hospital, Boston and Dr. Thomas V. Colby, Lung Pathology, Mayo Clinic Scottsdale.)*

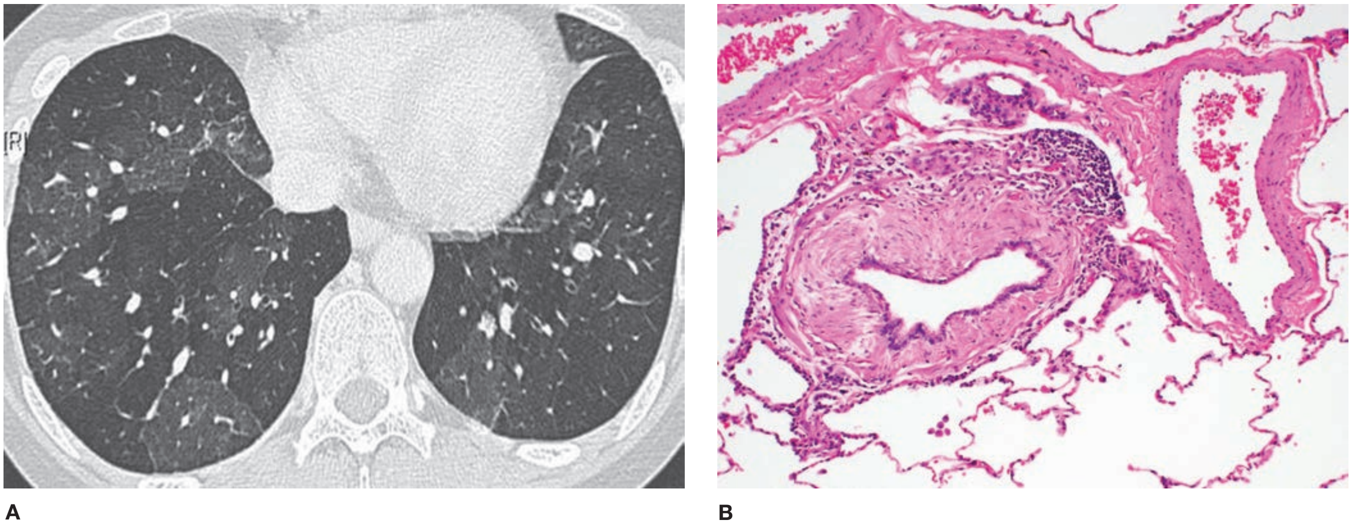

Figure 49-4 Constrictive bronchiolitis. **A.** The expiratory chest CT scan shows the mosaic pattern of air trapping seen from obliterated bronchioles. **B.** The pathology micrograph shows extrinsic fibrosis of the bronchiolar wall in a concentric manner constricting and obliterating the bronchiolar lumen. *(Reproduced with permission from Dr. Ritu R. Gill, Chest Radiology, Brigham and Women's Hospital, Boston and Dr. Thomas V. Colby, Lung Pathology, Mayo Clinic Scottsdale.)*

This disorder occurs after exposures to sulfur dioxide fumes,[16] nitric acid fumes, and nitrogen dioxide in freshly filled corn silos. Unusual accidental exposures to toxic fumes may cause the syndrome such as in a metal-cutting worker.[17] For example, two workers in a lithium battery factory were accidentally exposed to thionyl chloride, and one of them developed findings consistent with bronchiolitis obliterans.[18] This acidic compound is used in the manufacturing process and produces sulfur dioxide and hydrochloric acid fumes when in contact with water.

Smoke inhalation bronchiolitis obliterans was described in a 23-year-old man who was in a fire while sleeping in his newly constructed house.[19] He was unconscious when rescued. There was cough and mild dyspnea after recovery. He returned 3 years later because of persistent dyspnea. He had finger clubbing, an FEV_1 of 0.90 L, and an FEV_1/FVC of 34%. The burning synthetic structural materials used to build his house produced gases containing acrolein, formaldehyde, acetaldehyde, nitrogen dioxide, and sulfur dioxide.

Diacetyl appears to be a common exposure among artificial butter flavoring workers who developed constrictive bronchiolitis.[20] The use of e-cigarettes may cause severe bronchiolitis.[21]

TABLE 49-3 Clinical Classification of Bronchiolitis Obliterans

Idiopathic
Toxic fumes
Post–respiratory infections
Connective tissue disorders
Drug-related
Organ transplantation • Bone marrow and stem cell • Lung
Aspiration
Neuroendocrine hyperplasia with carcinoid
Sauropus androgynous
Miscellaneous system diseases • Stevens–Johnson syndrome • Paraneoplastic pemphigus • Primary biliary cirrhosis • Swyer–James syndrome • Ataxia telangiectasia • Inflammatory bowel disease

Post–Respiratory Infection Bronchiolitis Obliterans

Post–respiratory infection bronchiolitis obliterans may occur after adenovirus pneumonia, influenza or parainfluenza pneumonia, or *Mycoplasma* pneumonia.[22] Cough develops several days after the initial infection. Chest radiographs may show diffuse reticulonodular opacities early in the course, but they are normal or show hyperinflation later in the course of the illness. Expiratory, high-resolution chest CT scans show a low-attenuation mosaic pattern. Histology shows constrictive bronchiolitis with extensive scarring that obliterates many of the bronchioles, corresponding clinically with severe airflow obstruction. At this stage, the lesion is not responsive to corticosteroids, and lung transplantation is a treatment option. Covid-19 infection may cause BOOP but has not yet been found to be a cause of constrictive bronchiolitis obliterans.[12,23]

Connective Tissue Disease–Associated Bronchiolitis Obliterans

Connective tissue disease–associated bronchiolitis obliterans occurs most commonly in rheumatoid arthritis and has been reported in scleroderma, lupus erythematosus, and Sjögren syndrome.[24–26] Shortness of breath is the most common presenting symptom. Pulmonary function shows irreversible airflow obstruction, and chest imaging shows mosaic attenuation pattern with air trapping on expiratory views.

Rheumatoid arthritis–related constrictive bronchiolitis often has a poor prognosis, tends not to respond to therapy, and may require lung transplantation.[25] Among 11 patients with Sjögren syndrome, all had shortness of breath, chest imaging was normal in two-thirds, and hyperinflation was seen in the remaining one-third. Most patients did not respond to immunosuppressive therapy.[26] There has been a report of constrictive bronchiolitis occurring in ankylosing spondylitis in a patient who had a poor response to therapy.[27]

Paraneoplastic pemphigus has been reported as a cause of bronchiolitis obliterans that may have a fatal outcome.[28,29]

Drug-Related Bronchiolitis Obliterans

Drug-related bronchiolitis obliterans is rare and has been reported with use of penicillamine and gold in the treatment of rheumatoid arthritis. Afatinib may be a cause, with one case report describing severe shortness of breath, severe airways obstruction, mosaic pattern on chest CT, and at autopsy, lung findings of concentric fibrotic bronchiolitis with bronchiolitis obliterans.[30] There has been a report of a 54-year-old woman who developed constrictive bronchiolitis from imatinib.[31] Pembrolizumab has been reported as a cause of new-onset, severe, nonreversible airflow obstruction, chest imaging with mosaic attenuation, and minimal response to therapy.[32]

Bone Marrow Transplantation Bronchiolitis Obliterans

Bronchiolitis obliterans occurs between 6 and 12 months after transplantation and occurs in up to 10% of allogeneic bone marrow recipients. It occurs in patients with chronic graft-versus-host disease and therefore is rarely seen after autologous bone marrow transplantation. The chest CT scans show mosaic pattern with air trapping. Because this air trapping is better seen on expiratory images, for some younger patients, inspiratory studies can be eliminated resulting in less ionizing radiation.[33] The pathologic lesion is concentric bronchiolar fibrosis typical of constrictive bronchiolitis. There is generally a poor response to corticosteroid therapy with a mortality rate of more than 50%.

Stem Cell Transplant Bronchiolitis Obliterans

Stem cell transplant bronchiolitis obliterans has replaced bone marrow transplantation–associated bronchiolitis obliterans, as allogeneic hematopoietic stem cell transplantation is widespread (see Chapter 94). The diagnosis of bronchiolitis obliterans is based on the National Institutes of Health (NIH) diagnostic criteria where all four must be met, including an FEV_1/FVC ratio of less than 70% or the 5th percentile of predicted; FEV_1 less than 75% of predicted with 10% or more decline over less than 2 years; absence of respiratory infection; and expiratory chest CT showing air trapping or residual volume more than 120% of predicted.[34]

The prevalence of bronchiolitis obliterans ranges from 2% to 7% with a poor 5-year survival rate of 10%. Among 27 patients with stem cell bronchiolitis obliterans, all but 1 developed graft-versus-host disease, time to diagnosis was 18 months, and the mean FEV_1 was 44%.[35] Respiratory infections were a risk factor. The chest CT findings showed air trapping in 15 and bronchiectasis in 10.

Biopsies performed early show bronchiolitis, fibrous obliteration of the respiratory bronchioles, and inflammatory cell infiltrates; later lesions include constrictive bronchiolitis with circumferential fibrosis, and the mechanism is based on chronic rejection. Treatment includes high-dose systemic corticosteroids and immunosuppression.[36] Extracorporeal photodynamic therapy may be used successfully if used early.[37] Ruxolitinib[38] and nintedanib[39] have been used for treatment.

Lung Transplant Bronchiolitis Obliterans

Lung transplant bronchiolitis obliterans has continued to plague thoracic surgeons and patients, with minimal improvements over time in frequency or mortality (see Chapter 106).

The short-term survival within 1 year is more than 80%, while chronic lung allograft dysfunction (CLAD) continues to be the most common cause of poor long-term survival, as half of recipients develop CLAD within 5 years, and the survival at 5 years remains 50% to 70%.[40] Initially, CLAD was recognized as bronchiolitis obliterans syndrome (BOS) that was constrictive bronchiolitis with obliteration pathologically. Later, the concept of restrictive allograft syndrome (RAS) was designated, occurring in 25% to 33% of CLAD. RAS is characterized by an irreversible decline in FEV_1 and total lung capacity, upper lobe predominance radiographically, diffuse alveolar damage and fibrosis as well as pleuroparenchymal fibrosis, and a poor prognosis.[41]

Risk factors for bronchiolitis obliterans include acute cellular rejection and lymphocytic bronchiolitis as well as primary graft dysfunction, gastroesophageal reflux disease, and respiratory infections.[41] Treatment consists of fluticasone inhaler, azithromycin and montelukast (FAM), extracorporeal photopheresis, and pulmonary rehabilitation. Loading imatinib inside targeted nanoparticles is being studied.[42]

Aspiration Bronchiolitis Obliterans

Aspiration bronchiolitis obliterans was first reported in 1908 in a 2.5-year-old child who aspirated a prune pit that eventually caused respiratory failure and death.[43] Obliterative bronchiolitis has been reported in a 61-year-old man who aspirated an iron pill.[44] Gastroesophageal reflux can be a cause of bronchiolitis obliterans.[45,46]

Neuroendocrine Hyperplasia–Related Bronchiolitis Obliterans

Neuroendocrine hyperplasia–related bronchiolitis obliterans was described in a series of 44 patients.[47] Most of these patients were females with a median age of 65 years. Cough and shortness of breath were common symptoms. Pulmonary function showed airflow obstruction in 51% and restrictive pattern in 11%. The chest CT showed diffuse nodules in 95% and mosaic attenuation in 77%. Among these patients, 34 had carcinoid tumorlets and 16 had carcinoid tumors. For treatment, 25% were observed without therapy, 41% received inhaled corticosteroid, and 32% received systemic steroid or immunosuppressive agents. Follow-up showed 50% remained stable, 33% worsened, and 17% improved.

Sauropus androgynus Bronchiolitis Obliterans

Sauropus androgynus bronchiolitis obliterans has been reported among women who consume this leafy vegetable.[48] It is cultivated in India, Malaysia, Indonesia, China, and Vietnam. The leaves are boiled and blended with pineapples or guavas to make a mixed vegetable-fruit juice, which is consumed for its alleged effects of body weight reduction and blood pressure control. The leaves contain the alkaloid papaverine. Among 178 patients in Taiwan, the obstructive ventilatory defect was irreversible and resulted in progressive deterioration in some patients, resulting in lung transplantation.[49]

Miscellaneous Systemic Disorders Associated with Bronchiolitis Obliterans

Stevens–Johnson–related bronchiolitis obliterans continues to be reported from various types of antibiotics including phenytoin[50] and cefuroxime,[51] resulting in severe airflow obstruction. Paraneoplastic pemphigus has been reported as a cause of bronchiolitis obliterans.[52,53] Other disorders as a cause of bronchiolitis obliterans include primary biliary cirrhosis, Swyer–James syndrome, ataxia-telangiectasia, and inflammatory bowel disease.

SUMMARY

In summary, the bronchiolar airway diseases include acute and chronic bronchiolitis, follicular bronchiolitis, diffuse panbronchiolitis, and bronchiolitis obliterans. Acute bronchiolitis is usually transient, whereas diffuse panbronchiolitis responds to macrolide therapy. Post–lung transplantation bronchiolitis obliterans continues to be a major problem, with minimal change in frequency or response to treatment.

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CHAPTER 50

Bullous Lung Disease

Fernando J. Martinez

DEFINITIONS

A *bulla* is an air-containing space within the lung parenchyma that arises from destruction, dilation, and confluence of airspaces distal to terminal bronchioles and is larger than 1 cm in diameter (Fig. 50-1).[1] Its walls are composed of attenuated and compressed parenchyma. Bullae occur in various clinical contexts: (1) with emphysema ("bullous emphysema"); (2) with pulmonary fibrosis, as in the late stages of sarcoidosis, complicated pneumoconiosis, or COVID-19;[2] (3) in "vanishing lung," in which the parenchyma is rapidly replaced by multiple bullae; and (4) in lungs that are otherwise normal ("bullous lung disease") and, therefore, likely secondary to a mechanism different from that of bullae occurring in conjunction with emphysema (Table 50-1).[3,4] Distinctions are drawn between bullae, blebs, and cysts (Table 50-2).[3] A *bleb* is an accumulation of air between the two layers of the visceral pleura that arises when the thin covering of the bleb ruptures and permits entry of air (Fig. 50-1). *Cysts* are epithelial-lined cavities that may resemble bullae on radiographs.[4] Many fall into the category of developmental anomalies and include mixtures of mesenchymal and epithelial components that are normally present in the lung. The pathologic nature of these cystic lesions is reflected in their names: "cystic adenomatoid malformations," "peripheral bronchogenic cysts," "congenital polycystic disease," and "atypical bronchopulmonary sequestration."[1]

The term *bullous disease* is reserved for multiple bullae in lungs that are otherwise normal.[3] This entity is different in etiology and pathogenesis from that in which bullae occur in conjunction with underlying chronic obstructive pulmonary disease (COPD). Confusion occasionally arises between the two entities because some pathologists regard bullous disease as a subset of panacinar emphysema.[1] However, this view is not useful as (1) panacinar emphysema tends to occur in the lower lobes, whereas bullous disease favors the upper lobes; (2) the natural history of the two disorders is quite different; and (3) panacinar emphysema has certain distinctive features not shared by bullous disease. Bullae may occur not only as part of obstructive lung disease, but also as a complication of fibrotic lung disease (Table 50-1).

ETIOLOGY

Bullae may originate in a variety of clinical and pathogenetic settings: (1) with emphysema of distal acini; (2) in the setting of cigarette and marijuana smoking; (3) in conjunction with scar tissue formation, which "traps" areas of normal lung, enlarges airspaces by traction on surrounding intact alveoli, or produces retraction or shrinkage of intact walls of adherent alveoli; (4) in the setting of intravenous drug abuse; (5) as a result of chronic inflammation and destructive changes in terminal and first-order respiratory bronchioles, resulting in airspace distention from delayed emptying; and (6) with α_1-antitrypsin deficiency.[3,5–7]

CLASSIFICATION

Bullae are classified anatomically into three main types (Fig. 50-1B).[1,3] Type I bullae are characterized by a narrow neck that connects the bullae with the pulmonary parenchyma. This type of bulla may be caused by overinflation of a volume of flawed lung tissue. The walls of type I bullae are thin, and their interiors are empty. Type I bullae are usually found at the lung apices and along the edges of the lingula and middle lobes. They often occur in association with paraseptal emphysema. Scanning electron microscopy has demonstrated that the thin neck is a consistent feature and that

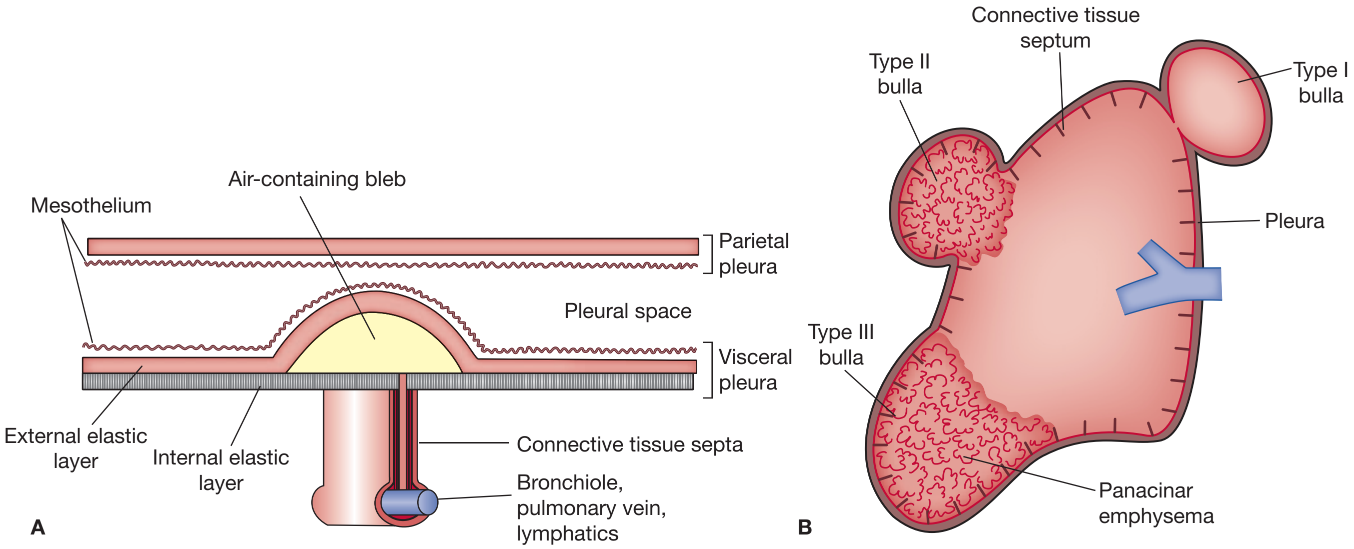

Figure 50-1 Blebs and bullae. **A.** Development of a bleb. A bleb is an accumulation of air within the pleura that is not confined by connective tissue septa within the lung. Air that escapes within the substance of the lungs makes its way to the surface, separating the internal from the external elastic layers on the visceral pleura. **B.** Different types of bullae. In contrast to a bleb, a bulla is confined by connective tissue septa of the lung and is deep to the internal elastic layer of the visceral pleura. Three different types of bullae are shown arising from a lung that has been removed from within the chest wall. A type I bulla is shown at the apex, a type II is in the middle zone, and a type III is arising at the base. The short *dark lines* denote connective tissue septa. Panacinar emphysematous parenchyma is present within the types II and III bullae. *(Adapted with permission from Reid L. The Pathology of Emphysema. Chicago, IL: Year Book; 1967.)*

TABLE 50-1 Characteristics of Bullae

- ***Primary***
  - Vanishing lung syndrome
  - Single giant bulla
  - Bullous lung disease
- ***Secondary***
  - Emphysema
    - Paraseptal
    - Panacinar
    - Centriacinar
- ***Pulmonary fibrosis***
  - COVID-19
  - Sarcoidosis
  - Idiopathic pulmonary fibrosis
  - Progressive massive fibrosis
  - Conglomerate silicosis
  - Fibrotic tuberculosis
  - Other fibrotic lung disorders
- ***Familial disorders***
  - α_1-Antitrypsin deficiency
  - Ehlers–Danlos syndrome
  - Salla disease
  - Marfan syndrome
  - Fabry disease
  - Cutis laxa

pleural mesothelial cells on the external surface are either reduced in number or completely absent; bundles of collagen fibers lie naked and separated from one other by small pores or crevices.

Type II bullae arise from the subpleural parenchyma and are characterized by a neck of panacinar emphysematous lung tissue. The interior of these airspaces consists of emphysematous lung in which blood vessels are still present. In contrast to type I bullae, the outer wall is formed by pleura covered with intact mesothelial cells. Although connective tissue septae are present within the bullae, they are not found in the wall. Type II bullae may occur anywhere in the lung, but they are most frequent in the upper lobe, at the anterior surface of the middle lobe, and over the diaphragm. Type III bullae consist of slightly hyperinflated lung connected to the rest of the lung by a broad base extending deep into the parenchyma. This type is believed to represent an atrophic form of emphysema.

TABLE 50-2 Characteristics of Blebs, Bullae, and Cysts

	Bleb	Bulla	Cyst
Site	Within visceral pleura	Arises within secondary lobule	Lung parenchyma or mediastinum
Size	1–2 cm	1 cm to 75% of a lung	2–10 cm
Lining	Elastic laminae of the pleura	Connective tissue septa	Epithelium
Associated condition	Spontaneous pneumothorax	Bronchogenic carcinoma	Respiratory infection

PATHOGENESIS

Several hypotheses have been proposed over the years for how bullae develop, although none has been proven.[1,3,4,8] These include the following: (1) Weakness of the alveolar walls predisposes to the formation of bullae, particularly at the apices of the lungs, where pleural pressures are most negative. This theory underscores the proclivity of bullae for the upper lobes and stresses the influence of mechanical forces acting upon flawed tissue. (2) Inflammatory disease of a bronchiole leads to progressive air trapping and "tension airspaces." (3) Disordered collateral ventilation produces the findings. (4) The same mechanisms responsible for generalized emphysema are operative in the formation of bullae. (5) Underlying paraseptal emphysema produces bullous disease.

Of all the hypotheses, that of underlying paraseptal emphysema is the most popular.[1,3] The hypothesis envisages destruction of alveoli adjacent to connective septae or the pleura. The pattern relates to the fact that capillaries in alveolar walls that abut connective tissue septa are less numerous than elsewhere because of a sparse network of arterioles and arteries in peripheral alveoli. Consequently, these regions of the acinus have less vascularity and greater compliance.

Dynamic computerized tomography and intrabulla pressure measurements have raised questions about the theory that bullae are formed by positive pressure within the airspace.[1,9] The lung surrounding a bulla is less compliant than the bullae itself; accordingly, the pressure necessary to inflate the surrounding lung is greater than that necessary to inflate the bulla. The pressure within a giant bulla has been found to be the same as pleural pressure. Therefore, when a bulla and its surrounding lung are exposed to the same negative pleural pressure, the bulla fills preferentially and completely like an inflated paper bag, prior to the surrounding lung inflating. Further inspiration increases the elastic recoil pressure, thereby exerting a greater retractive force on the lung parenchyma and enlarging the airspace. Nevertheless, bullae can be removed from within the lung while still maintaining their volume, indicating a positive intra-bulla pressure.

Bullae within the intact chest are molded and compressed to fit adjacent anatomic configurations. However, if the lung is released from these constraints (e.g., when removed from the chest cavity), bullae project as shiny bubbles at the lung surface (Fig. 50-2). Within the thoracic cavity, large bullae cause crowding of adjacent lung parenchyma, and structures such as bronchi are displaced, stretched, and narrowed over the bullae surfaces. Very large airspaces can expand across the midline or even extend into the neck. Bullae represent more than just overexpanded alveoli because the remnants of bronchioles and their accompanying vessels sometimes persist as trabeculae within the bullae. Interlobular septae can be incorporated into the wall as the airspace expands from within the secondary lobule.

Two important risk factors for bullous emphysema are cigarette smoking and α_1-antitrypsin deficiency. Many patients with bullous emphysema are cigarette smokers, and most bullous lesions are associated with paraseptal or centriacinar emphysema. Although bullous emphysema is typically found in young males, elderly patients with α_1-antitrypsin deficiency who are lifelong nonsmokers may develop bullous changes in later life. A hereditary predisposition to bullous emphysema is also suggested by its association with a variety of rare familial disorders, including Fabry disease, Salla disease, cutis laxa, Ehlers–Danlos syndrome, and Marfan syndrome.[1] Giant bullous emphysema has also been reported with histologic changes of placental transmogrification—a rare, benign lung disease of unknown etiology in which the lung shows bullous changes or, rarely, cysts or nodules.[10,11] Lung pathology demonstrates papillary structures similar to placental villi surrounding the pulmonary epithelium. The tight skin mouse, which has a dominant mutation for

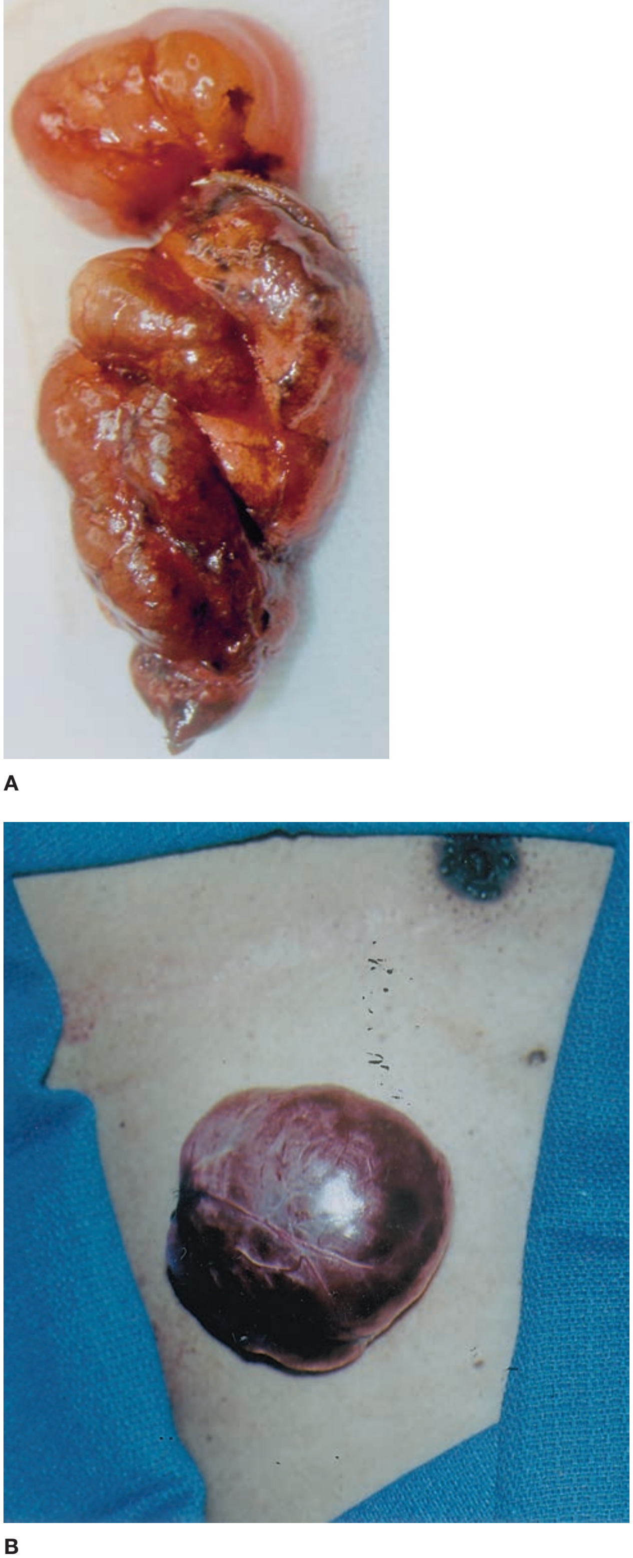

Figure 50-2 **A.** Surgically resected specimen with a bulla projecting from the lung surface. **B.** A bulla is shown projecting through a previous chest tube insertion site onto the surface of the skin.

the elastase gene and is characterized by multiple connective tissue abnormalities, serves as a unique model for bullous emphysema.[12]

DISTRIBUTION OF BULLAE

As noted previously, the tendency for bullae to occur in the upper lobes is usually attributed to the greater mechanical stresses imposed on the lung apices than bases. Because intrapleural pressure near the lung apices is more negative than at the bases, apical alveoli are subjected to greater expanding stresses than are basal alveoli. Radioactive gas studies and in situ freezing techniques have demonstrated that alveoli in the upper lung zones are considerably larger than those in the lower zones. Gravity also plays a role, as the upright lung behaves like a coiled spring, which, when allowed to dangle in the upright position, shows larger gaps between coils at the top than the bottom.

Engineering techniques used to study the distribution of stresses in aircraft have been applied to the analysis of stresses on the lung.[1] These have shown that the larger expanding stresses at the apices are directed primarily in a vertical direction, and to a lesser extent, laterally. The stresses tend to increase with expansion of the lung, but they are present also when the lung volume decreases below functional residual capacity (FRC). The increase in apical stress at low lung volumes has been attributed to an increase in the rigidity of the lungs as residual volume is approached.

EVALUATION AND DIAGNOSIS

In asymptomatic individuals, bullae may be detected during routine chest radiography. Small bullae rarely become visible on the chest radiograph but are usually easily visible by computed tomography (CT). As a rule, small bullae usually produce no symptoms, signs, or discernible alterations in pulmonary function.[13] However, rupture of one or more bullae may lead to spontaneous pneumothorax (see below). In some patients bullae give rise to progressive dyspnea or chest pain (Fig. 50-3A,B).[14] On occasion, a patient with bullous lung disease develops sudden, severe breathlessness secondary to development of a spontaneous pneumothorax[15,16] or sudden increase in bulla size due to air trapping. In patients with known bullous disease, infection in a bulla can occur (see below). Radiographically, infection is usually identified by the appearance of an air–fluid level (Fig. 50-4A–C).[5,6,8,9] The physical findings in a patient with one or more bullae usually reflect the overall state of the lungs. Only infrequently do giant bullae reach a size sufficient to cause a localized decrease in regional air entry, with absent breath sounds and increased resonance to percussion; this process can be associated with the "vanishing lung syndrome."[17]

Laboratory

Routine laboratory testing in the evaluation of bullae includes the measurement of hemoglobin and hematocrit to identify if anemia is contributing to respiratory symptoms and to assess for possible secondary polycythemia due to chronic hypoxemia.[1,14] Measuring an α_1-antitrypsin level should be obtained to diagnose α_1-antitrypsin deficiency.[18] Finally evaluation of arterial blood gases, performed while the patient is breathing room air if possible, is generally indicated in patients with severe respiratory insufficiency and those being evaluated for possible bullectomy.[14] As noted in Table 50-3, a Pa_{CO_2} greater than 45 mm Hg is considered a relative contraindication for bullectomy.[19]

Imaging

Imaging techniques employed in the evaluation of bullous lung disease include routine chest radiography, computed tomography, and nuclear medicine modalities.

Chest Radiography

Although routine chest radiography is the most practical method for identifying the presence of bullae, the technique generally discloses less than 50% of bullae identified on CT.[20] In a given patient, serial radiographs taken over years are invaluable in tracing evolution of the disease.[13] The presence of the condition is suggested by

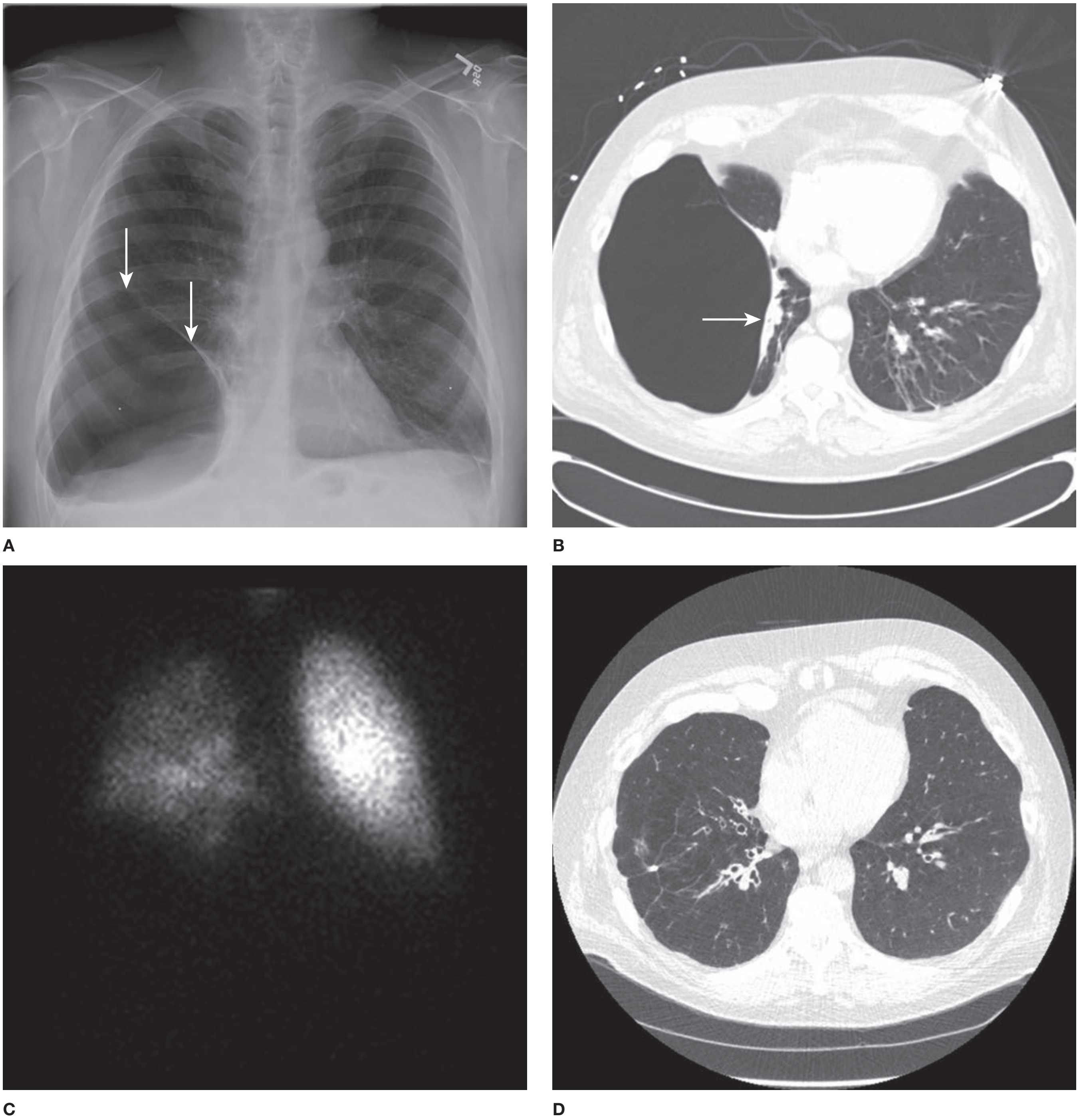

Figure 50-3 **A.** Chest radiograph demonstrating a right lower lobe bulla. Note the demarcating lines, or "hairline shadows" *(arrows)*. **B.** CT image of the lungs demonstrating the right lower lobe bulla with compressed lung *(arrow)*. **C.** Perfusion scintigraphy demonstrating decreased perfusion to the right lower lung zone. **D.** CT image of the lung following surgical resection of the right lower lobe bulla.

areas of increased radiolucency that are sharply delineated by fine radiopaque lines representing the walls of the bullae. These lines, or "hairline shadows," are composed of compressed and fused interlobular septae or pleura.[16] Because the hairline shadows appear incomplete on the chest radiograph, they delineate only segments of the bulla wall (Fig. 50-3A). Distinction between hairline shadows produced by a bulla, and thicker, sometimes irregular, walls of a cavity is usually not difficult. More difficult is distinguishing bullae from cysts. The presence of other radiologic signs of emphysema or fibrotic lung disorders suggests that the cystic structure is a bulla.[15] Similarly, distinguishing between a large bulla and pneumothorax may be challenging.[14,21,22] In general, the pleural line associated with a large bulla is usually concave relative to the lateral chest wall, whereas the pleural line associated with a pneumothorax is convex relative to the lateral chest wall.[14] Similarly, observation of the "double-wall sign" (i.e., the presence of air on both sides of the bulla wall) may be helpful in identifying the findings as due to a bulla.[16]

A chest radiograph obtained after forced expiration is sometimes helpful in demonstrating the presence of bullae: air trapping during the expiratory maneuver accentuates their outline by preventing a decrease in their size as the surrounding lung empties.[4] Large bullae

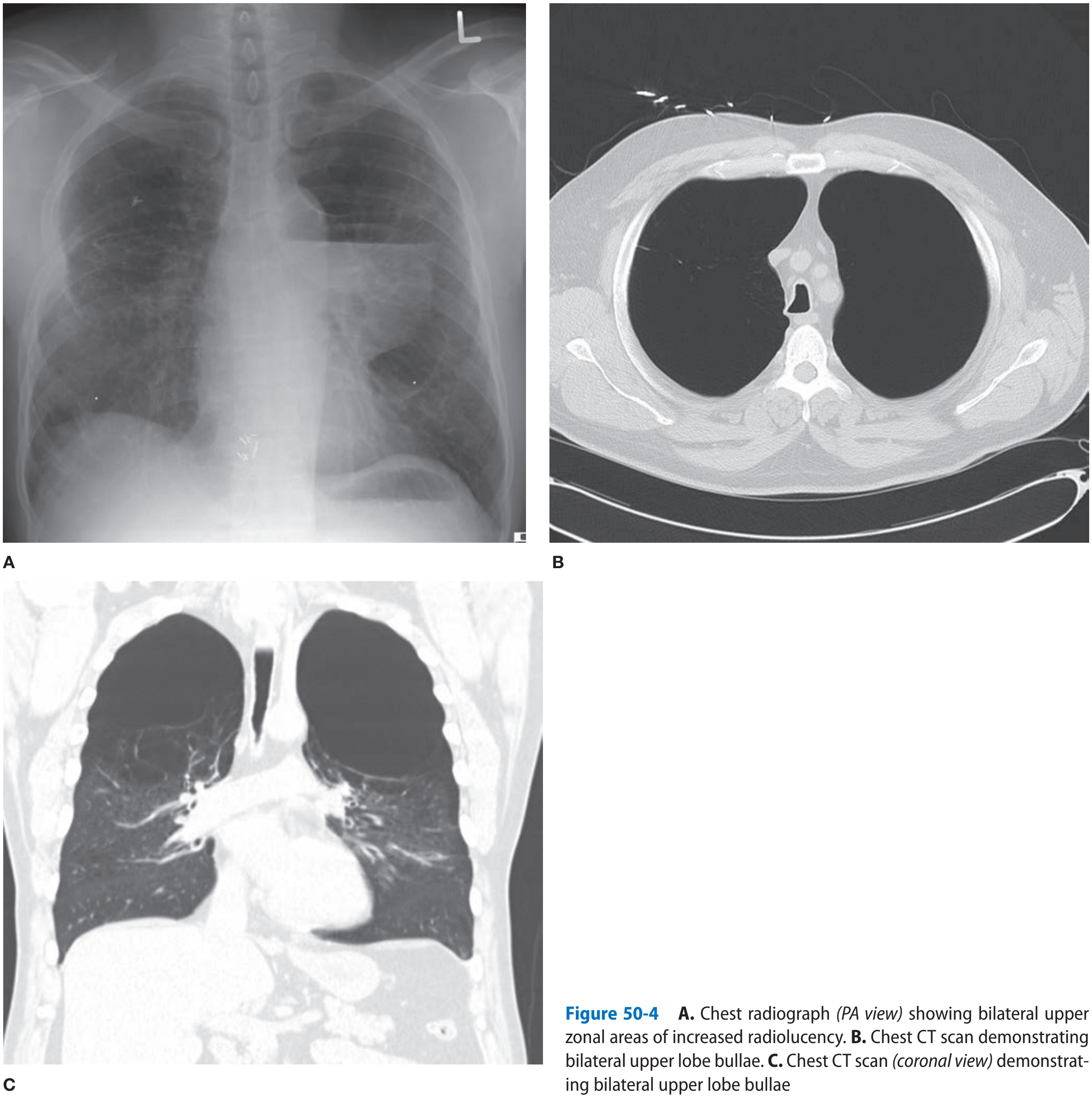

Figure 50-4 **A.** Chest radiograph *(PA view)* showing bilateral upper zonal areas of increased radiolucency. **B.** Chest CT scan demonstrating bilateral upper lobe bullae. **C.** Chest CT scan *(coronal view)* demonstrating bilateral upper lobe bullae

sometimes displace the mediastinum contralaterally and may even compress the opposite lung.

Computed Tomography

CT provides valuable anatomic information about the size, number, and relationships of bullae, as well as crowding of adjacent lung and disposition of the pulmonary vasculature (Fig. 50-3B).[17,23,24] Bullae are identified as areas of radiolucency that usually do not contain blood vessels and that are confined by visible walls. High-resolution computed tomography (HRCT) shows that large bullae are frequently associated not only with distal acinar (paraseptal) emphysema, but also with centriacinar emphysema—the type of emphysema usually associated with cigarette smoking.[17] These observations are consistent with the hypothesis that peripheral airspaces in paraseptal emphysema may coalesce to form larger bullae that may crowd normal adjacent lung. In addition, CT has shown that when bullae occur in the context of generalized emphysema, the extent of bullous emphysema correlates poorly with measurements of pulmonary function, and that the main determinant of respiratory function is the severity of emphysema in the bullous-free parts of the lung.[25] On chest CT, giant bullae are predominantly located in the upper lobes and are generally subpleural.[14] However, in patients with α_1-antitrypsin deficiency, bullae are most commonly located at the lung bases. Approximately half of the patients have bilateral bullae (Fig. 50-4), and, occasionally, deviation of the mediastinal structures to the contralateral side may be noted.[14] CT has been used to create three-dimensional reconstructions of bullae, which can then be used to calculate bullae volumes (Fig. 50-5).

Nuclear Imaging

Lung scanning using radionuclide-based techniques may provide useful preoperative information in evaluating patients with bullous

TABLE 50-3 Potential Indications and Contraindications for Classical Bullectomy

Parameter	Indications	Contraindications
Clinical	Young age (<50 years) Rapid progressive dyspnea despite maximal medical therapy Ex-smoker	Age >50 years Comorbid illness Cardiac disease Pulmonary hypertension >10% weight loss Frequent respiratory infections—chronic bronchitis Ongoing tobacco use
Physiologic	Normal or slightly ↓ FVC FEV$_1$ >40% predicted Little bronchoreversibility "High" trapped lung volume Normal or near-normal D$_{LCO}$ Normal Pa$_{O_2}$ and Pa$_{CO_2}$	FEV$_1$ <35% predicted "Low" trapped gas volume Decreased D$_{LCO}$
Imaging	*CXR*—bulla >1/3 hemithorax *CT*—large and localized bulla with vascular crowding and normal, compressed pulmonary parenchyma around bulla *Angiography*—vascular crowding with preserved distal vascular branching *Isotope scan*—well-localized matching defect with normal uptake and washout for underlying lung	*CXR*—vanishing lung syndrome Poorly defined bullae *CT*—multiple ill-defined bullae in underlying lung *Angiography*—vague bullae; disrupted vasculature elsewhere *Isotope scan*—absence of target zones, poor washout in remaining lung

Data from www.thoracic.org.

lung disease.[26] A lung perfusion scan provides a semiquantitative assessment of regional blood flow (Fig. 50-3); results of ventilation scans vary with the technique. A single-breath scan using ^{133}xenon often fails to demonstrate ventilation of a bulla, whereas a continuous ventilation scan often shows slow filling and emptying of the structure.[26,27] Complete lack of communication between the airways and bulla is reflected in the absence of filling during all phases of the continuous ventilation scan.

■ Pulmonary Physiology

Clinical evaluation of bullous lung disease is aided by assessment of pulmonary function, pulmonary mechanics, exercise performance, and the pulmonary circulation.

Pulmonary Function Tests

Pulmonary function tests have considerable practical value in distinguishing between individuals with localized bullae in whom intervening lung is normal (bullous disease), and those in whom localized bullae are part of obstructive airways disease (bullous emphysema) (Table 50-4).[14] The distinction is important, since those with obstructive airways disease are generally poor surgical candidates because of impaired pulmonary function. In individuals with bullous disease, the volume of air in the lungs can be estimated using plain radiography, CT, body plethysmography, or other pulmonary function test methods for determining lung volume, including closed circuit (helium dilution) and open circuit (nitrogen washout) techniques.[14,19] The volume of air trapped in a bulla can be determined as the difference between the functional residual capacities determined plethysmographically and by open or closed circuit methods (Table 50-4). This difference is due to the relative inability of the inert gas used in the circuit methods to enter the bulla.

Pulmonary Mechanics

Distinction between widespread obstructive airways disease with concomitant bullae and bullous lung disease has practical significance, since surgical lung resection in generalized emphysema offers a less certain therapeutic response than does resection of giant bullae in the absence of widespread obstructive lung disease (Table 50-3).[14] As large bullae expand, they initially cause relaxation of adjacent elastic lung tissue; with continued expansion, adjacent lung is compressed. Relaxation of the surrounding pulmonary parenchyma results in a decrease in radial traction on airways, thereby increasing air flow resistance. The effects of bullectomy on respiratory mechanics are inconsistent. Generally, resection of a large bulla increases lung static elastic recoil (by allowing for decompression of elastic lung parenchyma) and decreases airways resistance.

TABLE 50-4 Pulmonary Function Tests

Test	Bullous Disease	Obstructive Airways Disease and Bullae
TLC, L	N	N ↑
RV, L	N	↑
FRC, L	N	↑
FRC,[a] L	↑	↑
RV/TLC%	N	↑
FEV$_1$, L	N ↓	↓
FVC, L	N ↓	↓
FEV$_1$/FVC%	N	↓
MVV, L/min	N	↓
D$_{CO}$/Va, (mL/min/mm Hg)/L	N	↓
Raw, cm H$_2$O/L/s	N ↑	↑
Cst, exp, L/cm H$_2$O	N ↑	↑
Pst, TLC, cm H$_2$O	N ↓	↓

Note: N, normal; ↑, increased; ↓, decreased.
[a]FRC determined by body plethysmography.

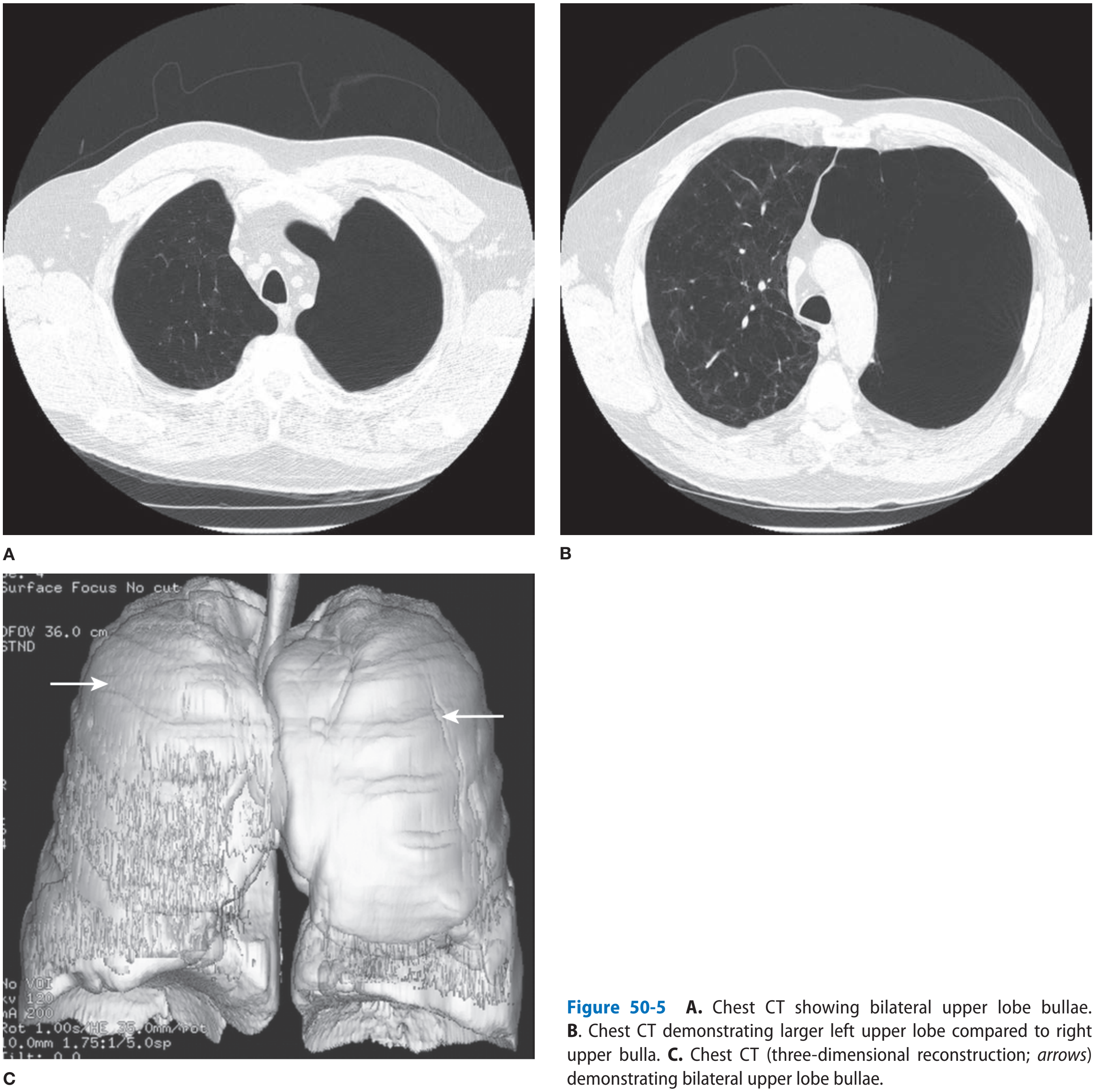

Figure 50-5 **A.** Chest CT showing bilateral upper lobe bullae. **B**. Chest CT demonstrating larger left upper lobe compared to right upper bulla. **C.** Chest CT (three-dimensional reconstruction; *arrows*) demonstrating bilateral upper lobe bullae.

The diffusing capacity, rather than lung elastic recoil, is usually determined to aid in distinguishing between widespread emphysema and localized bullae, as more widespread loss of alveolar surface area in emphysema reduces the DL_{CO}; indeed, the diffusing capacity correlates better with morphologic estimates of emphysema than do most other tests.[14,19] Although the combination of a decreased DL_{CO} and reduced static elastic recoil pressure favors the diagnosis of widespread emphysema rather than localized bullae, both measurements may also be decreased by bullae that compress adjacent normal lung (Table 50-3).[4] Respiratory muscle strength, assessed by measurements of maximal inspiratory and transdiaphragmatic pressures, improves after bullectomy in some patients with bullous emphysema.[28]

Exercise Testing

In patients with a few circumscribed bullae and otherwise normal lungs, exercise testing reveals that the alveolar–arterial difference in Pa_{CO_2}, ratio of dead space to tidal volume, diffusing capacity, and arterial oxygenation remain normal or near normal with exercise.[14] On the other hand, in patients in whom bullae are associated with panacinar emphysema, the alveolar–arterial difference in Pa_{CO_2} is widened at rest and during exercise.[29] The latter group of patients also may develop arterial hypoxemia during exercise. The Pa_{CO_2} tends to hover around the upper limit of normal at rest and during exercise, and the ratio of dead space to tidal volume is higher than in patients with normal intervening lung. The steady-state diffusing capacity is also reduced and fails to increase normally during exercise. Patients in whom bullae are associated with chronic bronchitis also show a widened alveolar–arterial difference in Pa_{CO_2} and an increase in the ratio of dead space to tidal volume at rest. However, in these patients the decrease in Pa_{CO_2} during exercise is modest, even though the Pa_{CO_2} at rest is abnormally high and increases further during exercise (indicating progressive alveolar hypoventilation).[3]

Pulmonary Circulation

In general, resting pulmonary arterial pressure and blood flow are within normal limits in patients with bullous lung disease (i.e., the bullae act like "amputated" segments of lung); the volume of the vascular bed available for recruitment as cardiac output increases is limited.[1,3] However, in patients in whom bullous disease has severely reduced the extent of the pulmonary vascular bed, pulmonary arterial pressure may be elevated at rest and during exercise; in a few instances, pulmonary hypertension and cor pulmonale may be observed.[1,3] Exercise in bullous lung disease is generally associated with an excessive increase in pulmonary arterial pressure, as increases in pulmonary blood flow are not effectively accommodated by the restricted vascular bed.[3] Underlying pulmonary disease further exaggerates the increase in pulmonary artery pressure during exercise.

COMPLICATIONS

The major complications of bullous lung disease are fluid accumulation (including infection) in the bulla, spontaneous pneumothorax, bronchogenic cancer, chest pain, and hemoptysis.

■ Fluid Accumulation

The determination that an air–fluid level is within a bulla and not in a newly formed cyst or cavity is generally based on the new appearance of fluid in a previously known bulla or the presence of other bullae.[14] CT of the chest is indicated to assure that the air–fluid level is within a bulla and to identify any surrounding pneumonia, adjacent pulmonary nodule, or an increase in wall thickness of the bulla. The latter aids in differentiating an air–fluid level within a bulla from other disorders such as tuberculosis, fungal disease, lung abscess, or cavitary bronchogenic lung cancer (Fig. 50-6). These processes typically have substantially thicker cavity walls. The presence of a fluid level within a bulla, especially if the bulla is located subpleurally, occasionally prompts the mistaken diagnosis of a loculated hydropneumothorax. CT is helpful in separating these two conditions.

Benign, Sterile Bullous Fluid

Benign, sterile fluid accumulations in a bulla can result from adjacent pneumonia or from poorly functioning bronchial communications with inadequate drainage of normally accumulating fluid.[30] In asymptomatic patients who have a thin-walled bulla without chest CT evidence of an adjacent pneumonitis or nodule, continued observation without specific therapy is appropriate.[5] Close radiologic evaluation is typically performed at 6- to 12-week intervals to ensure that an infection or bronchogenic carcinoma is not present. In patients with clinical and radiographic evidence of adjacent pneumonia antibiotic therapy is indicated.[31] The air–fluid level may persist for weeks to months after resolution of active infection.

■ Infected Bulla

A superinfection within a bulla can occur with clinical manifestations including fever, cough, purulent sputum production, dyspnea, and pleuritic chest pain. Laboratory findings may include leukocytosis and positive sputum cultures. When clinical and radiographic findings suggest an infected bulla, empiric antibiotics should be initiated based on a regimen similar to that used for community-acquired pneumonia in a patient with COPD.[5,14] Bacterial species that have been identified from infected bullae include methicillin-resistant *Staphylococcus aureus* (MRSA), *Bacteroides*, *Pseudomonas aeruginosa*, and mycobacteria.[32–34] Treatment is sometimes prolonged and may require parenteral or intrabulla administration, since poor drainage of the bulla inevitably slows resolution of the disease process.[35] The course of the infection should be followed by interval chest radiographs, in part as bulla infection has been associated with bronchogenic cancer.[36] If a patient does not improve with empiric antibiotics, percutaneous aspiration of bullous fluid can be performed under CT guidance to confirm the presence of infection and to identify the antibiotic sensitivities of the infecting organism.[5,32] It should be recognized that percutaneous aspiration carries an increased risk of pneumothorax and empyema.[14] Tube thoracostomy[37] and endoscopic drainage also have been utilized.[38]

■ Pneumothorax

Spontaneous pneumothorax may be a complication of paraseptal emphysema, particularly in patients who continue to smoke. The typical presentation is a sudden onset or worsening of dyspnea with or without pleuritic chest pain. Ultrastructural assessments suggest the possibility of air leaking through the wall of the bullae with sloughing of mesothelial cells,[39] while lung density measures suggest a valve-like effect with air trapping.[40] A few case reports have described a pneumothorax occurring when a bronchogenic carcinoma eroded through the wall of a bulla.[41] Tube thoracostomy drainage of pleural air is often required; this depends on the size of the pneumothorax and the degree of respiratory impairment.[14,42,43] Patients with ruptured bullae also tend to have prolonged air leaks, along with pleural and parenchymal infections. Subsequent management is directed at preventing recurrence. For patients with a bulla and a secondary spontaneous pneumothorax, pleurodesis using mechanical abrasion of the pleura via video-assisted thoracoscopic surgery (VATS) can be considered.[41,43,44] For patients with minimal surrounding diffuse emphysema, a bullectomy can be performed at the time of pleurodesis; for those with diffuse bullous emphysema, pleurodesis is often performed without bullectomy.[14]

■ Bronchogenic Cancer

Primary lung cancer has been reported to be associated with bullous lung disease.[45–48] Presenting manifestations include pneumothorax and hemoptysis.[48] The increased incidence of lung cancer may be due to the fact that lung cancer occurs more frequently in fibrotic lungs which are, themselves, predisposed to development of bullae.[1] Other explanations for the increased incidence of malignancy include dystrophic changes in lung parenchyma caused by bullous disease or persistence of carcinogens in poorly ventilated bullae.[1] The CT appearances for bronchogenic cancer complicating bullae include a nodule or mass extruding from the wall of the bulla, a nodule or mass confined within the lumen, a soft tissue density thickening the wall of the bulla, a pneumothorax, and an air–fluid level.[39,49–52] A proposed classification system for these malignancies includes four types, including a nodule abutting a cyst wall, a nodule arising from the cyst wall and protruding into the cyst lumen, a soft tissue density extending or thickening the cyst wall, and a multicystic aspect.[53] A case series with longitudinal CT findings noted that cystic airspaces developed wall thickening and/or a mural nodule after a median of 35 months.[45] A separate report noted that some cystic airspaces can develop in the location of a previous lung nodule.[54] The importance of all these features is reflected by recent reports that lung cancer detection error has been associated with failing to appreciate the importance of a linking cystic lung disease with bronchogenic carcinoma.[55,56]

■ Chest Pain and Hemoptysis

Chest pain may occur with a bulla and is attributed to overdistention of the structure.[14] The pain is angina-like and located retrosternally. The symptom is sometimes so severe as to constitute an indication for surgical intervention. Hemoptysis, which is occasionally massive, can result from rupture of blood vessels within the walls of bullae.[57]

TREATMENT

Many patients with bullous lung disease can be managed medically.[58] Because the natural history of a bulla is unpredictable, patients with

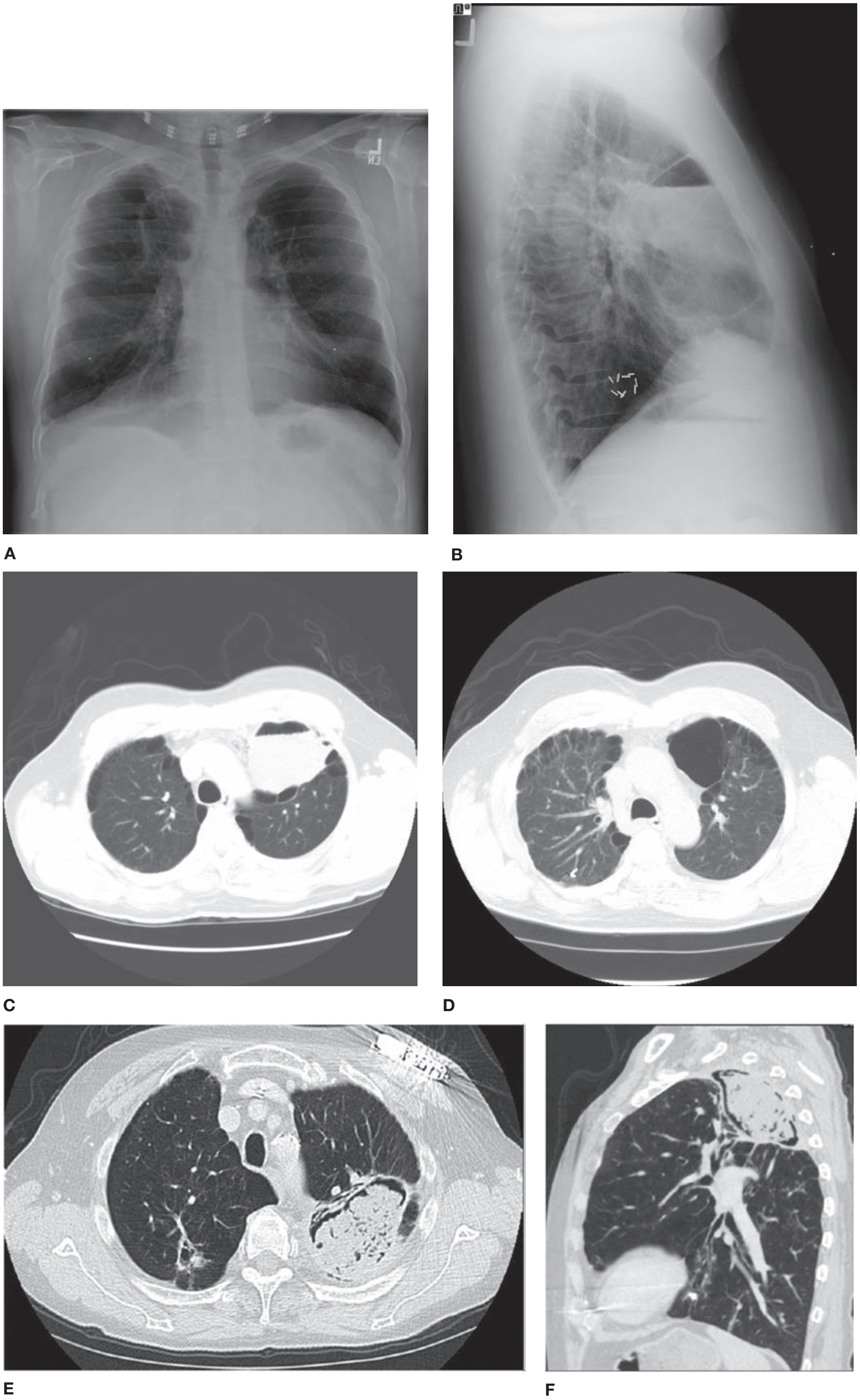

Figure 50-6 **A.** AP chest radiograph demonstrating an air–fluid level in a left upper lung bulla. **B**. Lateral chest radiograph demonstrating air–fluid level in a left upper lung bulla. **C**. CT image of the infected left upper lobe bulla. **D.** CT image of the same bulla after a prolonged course of antibiotics. **E.** CT axial view in patient with pre-existing bulla developing a fungus ball. **F.** CT sagittal view of the same patient with pre-existing bulla developing a fungus ball.

bullous disease should be monitored by chest radiography at regular intervals to ensure that the disease is stable. Occasionally, bullae enlarge suddenly and rapidly for no apparent reason; alternatively, they may shrink or disappear.[52,59,60]

■ Medical Management

The finding of a bulla in an asymptomatic patient calls for reassurance, a recommendation for annual chest radiography, advice to stop smoking, and an alert to the need for a prompt visit to a physician should symptoms develop. Activities that promote rupture of bullae (e.g., contact sports, altitude, and scuba diving) should be carefully considered.[1,61,62] Chronic bronchitis, asthma, or emphysema associated with bullae require treatment in their own right. For patients with α_1-antitrypsin deficiency augmentation therapy with antiproteases may be appropriate.[63] Endobronchial therapy with endobronchial valves (see Chapter 34) has been recently reported.[64–66]

■ Bronchoscopic Management

Over the last years bronchoscopic approaches to lung volume reduction have proved beneficial in patients with emphysema.[67] The available systems block inspired air entry into the treated lobe while air and secretions escape during exhalation. As such, valve treatment is generally reserved in patients without significant collateral ventilation to allow therapeutic lung collapse.[67] For some practitioners the presence of a large bulla has been considered problematic in this setting.[67] An increasing number of reports or small series have suggested that endobronchial therapy can be used to treat bullous disease.[64–66,68–71] One of the larger published series provides additional physiological and clinical insights.[72] In 27 consecutive patients with giant emphysematous bullae undergoing endobronchial valve therapy, 6 did not experience therapeutic collapse while 21 did; in those who experienced collapse there was little difference between lung volume measured with gas dilution technique compared with whole body plethysmography.[72] These data support that an open bulla, where endobronchial therapy would allow emptying of the treated lung, is required for optimal benefit in addition to established criteria for anatomic distribution and lack of collateral ventilation.[72] Additional, prospective comparative data are required to better define this less invasive therapeutic technique.

■ Surgical Management

Although randomized trials of giant bullectomy have not been performed, the potential benefits of elective bullectomy have been described in a number of case series.[19,73] In general, significant symptomatic and functional improvements have been reported for 5 or more years in 60% to 90% of patients.[19,73] Patients with diffuse emphysema tend to deteriorate faster than patients without diffuse emphysema.[73] A systematic review of bullectomy reported that hypoxemia was more likely to improve compared with spirometric parameters or diffusing capacity (DL_{CO}).[73] Patients with radiographic evidence of compressed lung were the most to likely experience improved oxygenation.[73] Perioperative mortality ranges from 0% to 7% for bullectomy via open thoracotomy; patients with diffuse emphysema seem to experience a higher mortality rate.[73] Causes of death include pneumonia, respiratory failure, pulmonary embolism, and cardiovascular complications.

Indications

The most common indication for bullectomy is severe dyspnea due to a bulla occupying 30% of more of the hemithorax or spontaneous secondary pneumothorax.[24,74,75] A key challenge for the clinician is selecting the optimal patient for bullectomy. A key factor suggesting that bullectomy may be beneficial is a bulla that occupies greater than 50% of the hemithorax with radiographic evidence that the bulla is compressing adjacent normal pulmonary parenchyma (Table 50-3; Fig. 50-3A,B).[19,76] An overall enumeration of criteria reported to define patients who are most likely to benefit from bullectomy is presented in Table 50-3.

As noted in Table 50-3, physiologic data have been reported to provide valuable information in guiding the decision to perform bullectomy. The majority of patients who undergo bullectomy have an FEV_1 less than 80% predicted but greater than or equal to 40% predicted; these thresholds have been supported by case series.[74] Similarly, patients likely to benefit have physiologic evidence of air trapping (e.g., total lung capacity [TLC] >100% predicted, residual volume [RV] >150% predicted).[77] Some have suggested that the difference in lung volume measured by body plethysmography versus helium dilution techniques can be compared to estimate the volume of nonventilated lung. A larger nonventilated volume suggests a more favorable response to bullectomy.[19,76]

Contraindications

As noted in Table 50-3, features associated with a less favorable result following bullectomy include older age, ongoing cigarette smoking, significant comorbid disease, lower pulmonary function (FEV_1 and DL_{CO}), hypercapnia, poorly defined bullae on chest imaging, and pulmonary hypertension.[73,74,77–83] Similarly, patients with chronic sputum production or frequent lung infections have been suggested to be less likely to improve.[73]

Preoperative Evaluation and Management

The preoperative evaluation for bullectomy includes pulmonary function testing and imaging as noted earlier. Underlying COPD should be treated aggressively with an appropriate combination of inhaled medications and pulmonary rehabilitation. Preoperative cardiac evaluation is appropriate given the increased risk of cardiovascular comorbidity among patients with COPD.[84]

Anesthetic Management

Standard monitoring during the procedure includes blood pressure, pulse oximetry, capnography, core temperature, and continuous electrocardiography.[85] Arterial and central venous pressure monitoring are not mandatory but frequently utilized. Bullectomy is typically performed under general anesthesia.[85] Short-acting anesthetic agents are preferred over longer-acting agents to facilitate early extubation.[85] Intravenous agents are typically used for induction of anesthesia, as severe bullous disease may make the uptake and distribution of inhalational agents erratic.[85] A thoracic epidural catheter is usually placed for administration of epidural anesthetic agents during and/or after surgery.[85]

After anesthetic induction, appropriate positioning, and sterile draping, an endotracheal tube that allows isolation of ventilation to one lung is placed to administer single lung ventilation to the nonoperative lung and to enable deflation of the operative lung.[85] Immediately postoperatively patients are assessed for anemia, cardiac ischemia, electrolyte abnormalities, hypercapnia, hypoxemia, and inadequate lung reexpansion.[85] If these factors are acceptable, the patient may be extubated; in the majority of cases this occurs in the operating room.[86]

Operative Approach and Techniques

Although many surgeons prefer an open approach for bullectomy, there is increasing application of VATS techniques.[77,87–90] When an open thoracotomy is performed, the posterolateral approach is generally used for unilateral bullous disease, while median sternotomy is often utilized for resection of bilateral bullae.[77] The amount of lung resected in addition to the main bulla is dependent on a balance between removing diseased tissue to optimize re-expansion of compressed tissue while avoiding resecting healthy lung tissue and minimizing prolonged air leak around the suture line.[24,73] For a single bulla that is well demarcated and has a clear, narrow pedicle, a simple stapled excision is adequate. When the bulla is broad based or when numerous bullae merge indistinctly, a broad stapled wedge resection is usually necessary.[86] Lobectomy and segmentectomy may be utilized in unusual settings.[75,77,91] Thoracoscopically treated patients who are smokers and suffer from concomitant emphysema suffer greater postoperative complications.[90]

Ablation or excision of bullae can be achieved by a variety of surgical methods, including plication, laser ablation, and excision with a stapler.[24] The latter is the most frequently utilized. Numerous approaches are utilized to minimize postoperative air leaks, including applying exogenous materials to buttress staple sutures (e.g., bovine pericardial or polytetrafluoroethylene strips), fibrin sealant to areas of air leak intraoperatively, and creating a "pleural tent."[92–95] The Brompton technique, or modified Monaldi procedure, utilizes a limited thoracotomy to visualize the bulla, insufflation of the bulla with iodized talc, and drainage of the bulla for several days with a Foley catheter under water seal.[81,96,97] Talc is subsequently instilled into the pleural cavity to achieve pleurodesis.

The postoperative approach includes careful attention to respiratory status, pain control, minimizing bronchoconstriction and hyperinflation, monitoring for development or worsening of a pneumothorax, and prevention of thromboembolic disease. Attention to the proper function of chest tubes is key to minimize the negative implications of pneumothorax. Thoracostomy tubes are generally left in place until the lung is fully expanded and there is no evidence of air leak. In those patients with persistent slow air leaks a minichest tube with a unidirectional flutter valve (e.g., Heimlich valve) can be used to facilitate discharge of the patient. The management of postoperative pain to ensure early mobilization of the patient and effective cough is crucial to minimize complications.[86]

SUMMARY

Recognition of bullous lung disease and its causes, classification, and underlying pathophysiology have important clinical implications. Careful clinical, radiographic, and physiologic assessment allows identification of patients whose dyspnea may be substantially improved through a variety of medical, surgical, and bronchoscopic interventions.

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CHAPTER 51

Bronchiectasis

Gregory Tino

INTRODUCTION

Bronchiectasis is an entity characterized pathologically by airway inflammation, and permanent bronchial dilatation, and clinically by cough, sputum production, and exacerbations with recurrent respiratory tract infections. Bronchiectasis has a long history, having been first described formally by Laennec in the early 19th century.

Bronchiectasis is a heterogeneous syndrome with many different contributing etiologies. No animal model exists for bronchiectasis, and its pathogenesis remains poorly understood. It is a disease characterized by airway inflammation arising from infection in genetically susceptible individuals. Permanent damage to ciliated airway epithelium usually results from direct impact of bacterial pathogens (neutrophil recruitment via glycoproteins and IL-8, biofilm formation), as well as neutrophil-mediated host response to these pathogens. This results in direct damage to bronchial walls, epithelial cell damage, and goblet cell hyperplasia. Human neutrophil elastase (HNE), a proteolytic enzyme mainly involved in the response against bacteria, is thought to play a key role in producing tissue damage. Peter Cole described a "vicious circle" hypothesis that provides a useful conceptual framework: According to the hypothesis, neutrophilic inflammation caused by an initial insult results in airway destruction in susceptible individuals. The anatomic disruption leads to abnormal mucus clearance, setting the stage for chronic bacterial infection that then propagates the cycle of airway inflammation and bronchiectasis.[1]

Although it has been described as an orphan disease, bronchiectasis unrelated to cystic fibrosis (CF) is commonly recognized in clinical practice. Based on a large, geographically diverse health insurance claims database, the prevalence of non-CF bronchiectasis has been estimated at 52 cases/100,000, with an estimated total number of total cases greater than 110,000 in the United States.[2] A more recent study suggested a higher prevalence of 139 cases per 100,000 persons.[3]

The prevalence of bronchiectasis increases with age and appears to be more common in women (1.3- to 1.6-fold higher prevalence) and Asians (2.5- and 3.9-fold higher prevalence in Caucasians and African Americans, respectively). The prevalence has increased by 8.7% per year.[4] Similar epidemiologic findings have been reported in Europe; the incidence and point prevalence of bronchiectasis increased yearly during the period between 2004 and 2013.[5]

Bronchiectasis is also associated with significant economic cost, including that associated with an increased number of hospitalizations compared with age-matched controls. Finally, bronchiectasis is associated with a notable impairment of quality of life and mortality, likely influenced by sputum volume, severity of airflow obstruction, and the presence of chronic gram-negative infection, particularly with *Pseudomonas aeruginosa*.

DIAGNOSIS

Establishing a diagnosis of bronchiectasis requires an organized and systematic approach, with consideration of the elements of the history and physical examination, chest imaging, and laboratory data, as well as additional studies. Identifying specific underlying causes of bronchiectasis is equally important, as doing so may directly impact treatment in as many as 40% of patients.[6]

Clinical Presentation

Bronchiectasis should be suspected in individuals who report a history of persistent productive cough and sputum production, recurrent respiratory tract infections requiring antimicrobial therapy, or *Pseudomonas aeruginosa* lung infection, especially in the absence of previously identified risk factors. The diagnosis should also be suspected in never-smokers diagnosed with COPD and thought to have recurrent COPD exacerbations. Recurrent, unexplained hemoptysis may be a presenting scenario on rare occasions.[7]

Other factors to consider include (1) patient age, as genetic causes such as CF and primary ciliary dyskinesia (PCD) are more common in younger individuals; (2) extrapulmonary signs or symptoms; and (3) comorbidities that may predispose to bronchiectasis, including allergic bronchopulmonary aspergillosis (ABPA) and connective tissue disorders such as rheumatoid arthritis (RA) and Sjögren syndrome.

The clinical course of bronchiectasis is classically punctuated by exacerbations, which generally include episodes of worsening respiratory and/or systemic symptoms that require an intervention, such as antibiotics.

A proposed consensus definition for pulmonary exacerbations[8] is a person with bronchiectasis and deterioration in at least 3 of the following key symptoms for at least 48 h: (1) cough; (2) sputum volume and/or consistency; (3) sputum purulence; (4) breathlessness and/or exercise tolerance; (5) fatigue and/or malaise; (6) hemoptysis *and* clinician determination that a change in bronchiectasis treatment is required.

Chest Imaging

High-resolution computed tomography (HRCT) of the lung, which incorporates thin sections with high spatial frequency, is an indispensable diagnostic study for bronchiectasis (Figs. 51-1 to 51-5). Characteristic radiologic findings[9] include airway dilation, denoted by a luminal diameter greater than 1 to 1.5 times the adjacent vessel (*tram lines* and *signet-ring sign*, as well as absence of tapering from the central to peripheral areas of the lung) (Fig. 51-1), bronchial wall thickening, mucoid impaction, and/or cysts arising from the bronchial wall.

Other features that may be present include a "tree in bud" pattern and areas of consolidation. Although several grading systems have been proposed to correlate clinical disease severity with the extent of bronchiectasis on imaging, none has been validated in large prospective trials. The radiologic distribution of bronchiectasis can also be useful in evaluating underlying causes. The differential diagnosis of localized or focal disease is limited and includes postinfectious causes; processes causing larger airway obstruction, including bronchial strictures; endobronchial mass lesions, such as carcinoid tumors; and foreign body impaction (Fig. 51-2).

In those with multifocal or diffuse disease, the differential diagnosis is much broader and requires casting a much wider diagnostic net. Important causes include nontuberculous mycobacterial infection; congenital syndromes, such as CF (Fig. 51-3) and PCD; immunodeficiency states (e.g., common variable immunodeficiency, HIV); immune-mediated disorders (ABPA); and RA and Sjögren syndrome, among others. Table 51-1 illustrates differential diagnosis of bronchiectasis based on radiologic distribution of findings.

In addition, specific imaging findings can be highly correlated with clinical entities. For example, the presence of right middle lobe and lingular bronchiectasis with nodular changes is highly suggestive of nontuberculous mycobacterial infection (Fig. 51-4). Central bronchiectasis with mucoid impaction is characteristic of ABPA (Fig. 51-5). The diagnosis of Mounier-Kuhn syndrome can be confidently established by the finding of tracheobronchomegaly.

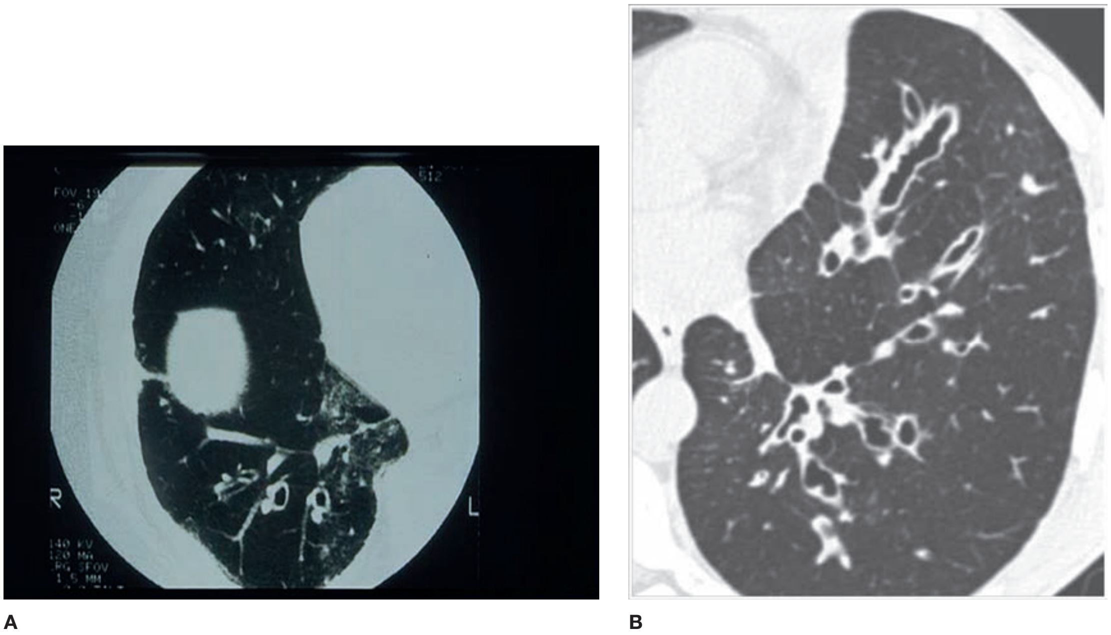

Figure 51-1 Characteristic radiologic findings of bronchiectasis: airway dilation and bronchial wall thickening. **A.** Signet-ring sign. **B.** Tram-track sign.

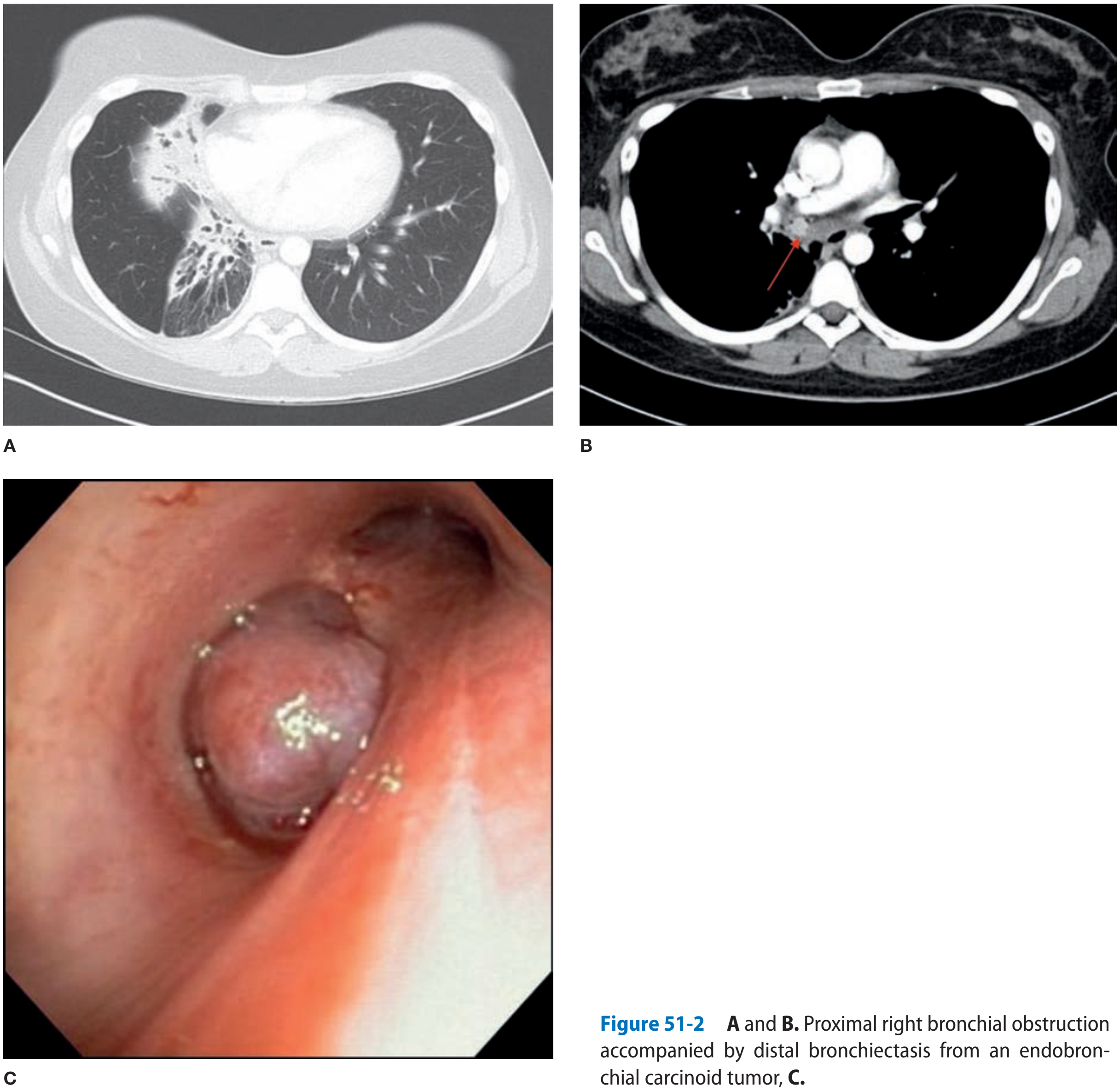

Figure 51-2 **A** and **B.** Proximal right bronchial obstruction accompanied by distal bronchiectasis from an endobronchial carcinoid tumor, **C.**

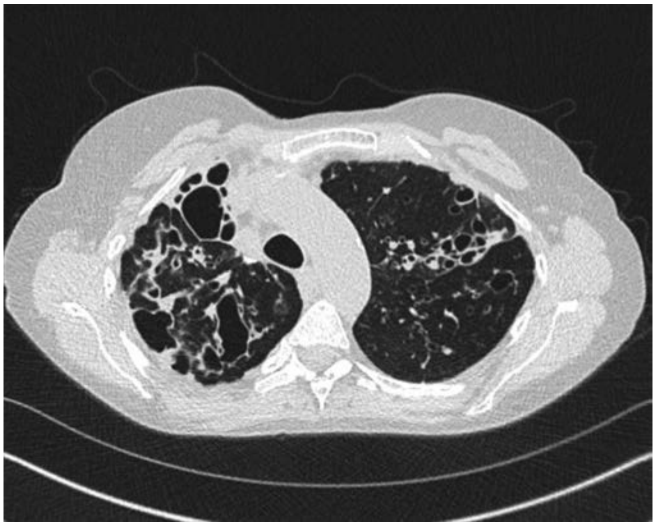

Figure 51-3 Severe upper lobe cystic bronchiectasis, consistent with cystic fibrosis.

Bilateral lower lobe bronchiectasis typically suggests possible aspiration (Fig. 51-6).

■ Laboratory Studies

Several guidelines have been published to help clinicians direct the diagnostic workup, although the recommendations are typically conditional and based on weak data. The British Thoracic Society (BTS) and European Respiratory Society (ERS) recommend a "minimum bundle" of tests that should be obtained in all patients.[10,11] These include complete blood count with differential (assessing for leukopenia, eosinophilia); serum immunoglobulins; testing for ABPA, including a serum IgE level, *Aspergillus*-specific IgE and IgG, and *Aspergillus* skin test; and routine sputum culture.

TABLE 51-1 Clinical Approach to the Patient with Suspected Bronchiectasis

History	Recurrent lower and/or upper respiratory tract infections, pneumonia Daily mucopurulent sputum production
Initial studies	CBC with differential Testing for ABPA Immunoglobulins IgG, IgM, IgA Sputum for bacterial culture
Confirms diagnosis	High-resolution chest CT scan
Other studies	Pulmonary function (spirometry pre- and postbronchodilator) Sweat chloride and/or genetic panel for CFTR alleles Connective tissue disease serologies HIV testing Sputum for AFB culture Nasal nitric oxide α_1-Antitrypsin level; phenotype Serum antibody response to bacterial antigen challenge, e.g., pneumococcal vaccine

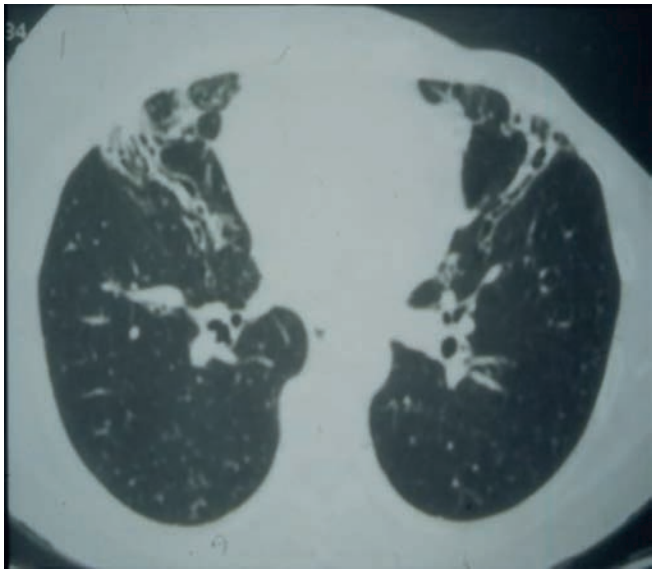

Figure 51-4 Right middle lobe and lingula bronchiectasis associated with nodular densities, highly suggestive of nontuberculous mycobacterial infection.

Additional testing should be pursued as dictated by other clinical information. Testing for CF, including both sweat chloride test and cystic fibrosis transmembrane conductance regulator (CFTR) gene mutation analysis, has been recommended for all children and all adults up to age 40 years. In those older than 40 years, CF testing should be considered in those with upper lobe bronchiectasis, persistent isolation of *Staphylococcus aureus* from the sputum, features of malabsorption, male primary infertility, history of childhood steatorrhea, and recurrent unexplained pancreatitis. The presence of dextrocardia, history of neonatal respiratory distress, chronic rhinosinusitis or otitis media, or infertility should prompt an evaluation for PCD. Table 51-1 summarizes the clinical approaches for patients with suspected bronchiectasis.

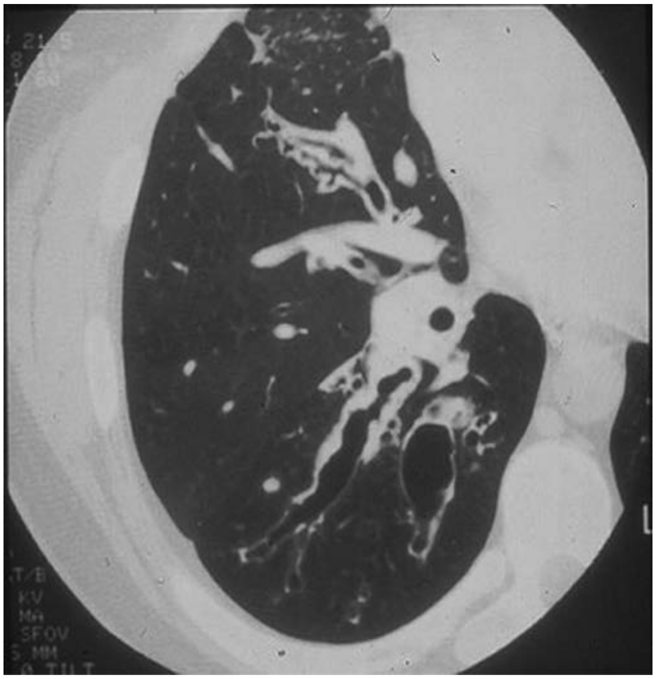

Figure 51-5 Central bronchiectasis and mucoid impaction (finger-in-glove sign), characteristic of ABPA.

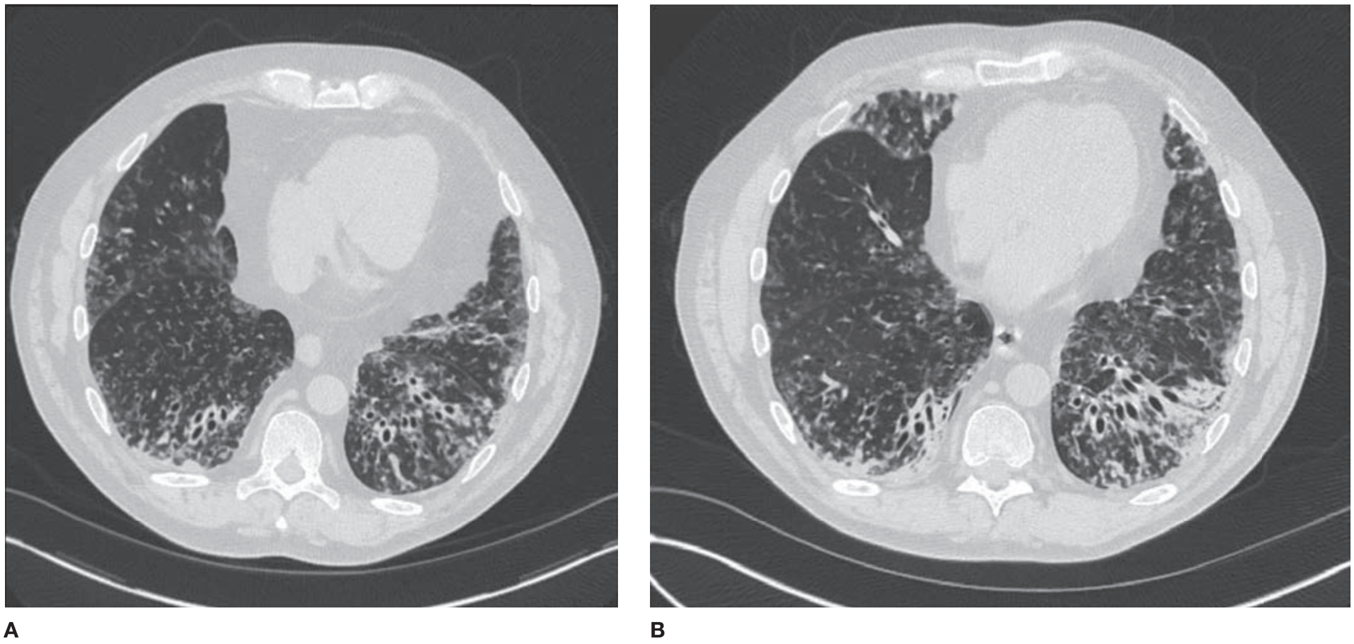

Figure 51-6 Bilateral lower lobe bronchiectasis with bronchiolitis/tree-in-bud infiltrates and consolidation, typical of GERD and acid aspiration.

PHENOTYPING

The use of clinical phenotyping has been applied to a number of lung diseases, including asthma and chronic obstructive pulmonary disease (COPD) and, more recently, to bronchiectasis. A phenotype is a physical trait that is determined by the results from a genotype. A clinical phenotype refers to the presentation of a disease in the given individual that is influenced by a number of factors. Grouping individuals on the basis of common clinical characteristics that relate to clinically meaningful outcomes, such as response to therapy and mortality, can be quite powerful and may influence endpoints for research and treatment decisions, especially in heterogeneous syndromes like bronchiectasis.

Phenotyping of bronchiectasis can be based on underlying etiology, comorbidities, or disease severity, among other considerations. However, one phenotype that has emerged is the "frequent exacerbator."[12] This phenotype was established using a database of more than 2700 subjects who were categorized by baseline exacerbation frequency. A history of frequent exacerbations, particularly 3 or more per year, was a strong predictor of future exacerbations. There was a strong relationship between a number of baseline exacerbations and the frequency in the first year of the study. Other independent predictors for frequent exacerbations include those with *Pseudomonas aeruginosa* or *Haemophilus influenzae* infection, impaired lung function (FEV_1 <50% predicted), and coexisting COPD. Importantly, frequent exacerbators exhibited worse quality of life, higher rates of hospitalization, and increased mortality.

TREATMENT

It must be stated that there are presently no approved specific therapies for bronchiectasis. In addition, available guidelines regarding management are based on low-quality evidence, and clinical trials for most of the pillars of treatment are lacking. In addition, there is significant variability in the use of treatment modalities in the United States, even at expert centers,[13] underscoring the critical need for research in this area.

Several treatment options should be considered in patients with bronchiectasis. Therapies can be grouped in several categories: (1) antimicrobials, both systemic and inhaled; (2) airway clearance measures; (3) anti-inflammatory agents; (4) surgery; and (5) treatment of underlying conditions.

Antimicrobial Therapy: Treatment of Acute Exacerbations

Antimicrobial therapy is the mainstay of treatment for exacerbations of bronchiectasis and, when possible, should be directed at identifying dominant pathogens.

The bacteriology of bronchiectasis is quite complex, but a number of studies have identified *Pseudomonas aeruginosa* and *Haemophilus influenzae* as the most common pathogens cultured. These can be isolated in as many as 35% of patients with bronchiectasis. Other important pathogens include *Staphylococcus aureus*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae*. However, an empiric antibiotic choice is often necessary as no dominant pathogen can be identified in as many as 20% to 25% of patients.

A number of factors influence the decision to start antibiotic therapy. Paramount among them is the presence of symptoms consistent with a pulmonary exacerbation, as previously described. These include cough, increased sputum volume, purulence and consistency, dyspnea, and hemoptysis, as well as systemic symptoms of fever and malaise.

Sputum analysis is critical to help guide antibiotic choice and ideally should be obtained at the time of an exacerbation. Previous microbiology and antibiotic susceptibility pattern are particularly helpful in guiding therapy, as recurrent infections often occur with the same organism. In a small trial, oral levofloxacin was reported to be as effective as ceftazidime as empiric therapy.[14] Amoxicillin is commonly recommended in those without known infection with gram-negative rods (GNR). It is important to adjust and, when possible, narrow antibiotic coverage when a specific pathogen and its susceptibility profile are available. Oral antibiotics are favored for those with mild to moderate exacerbations that do not require hospitalization. In patients with severe exacerbations, infection with resistant organisms, or poor response to oral antibiotics, intravenous antibiotics may be required.

The optimal duration of antibiotic therapy remains uncertain. A minimum of 14 days is currently recommended,[11] although longer courses may be necessary as dictated by clinical response.

In a Delphi study of clinical experts,[15] consensus was achieved for the following issues regarding antibiotic treatment of bronchiectasis: (1) 10- to 14-day duration of antibiotics for acute exacerbations; (2)

sputum volume, sputum color, and exacerbation frequency as treatment endpoints; (3) combination antibiotics should not be given for acute exacerbations treated with oral antibiotics, regardless of *Pseudomonas* colonization; (4) combination antibiotics should be used in patients with severe exacerbations with *Pseudomonas aeruginosa* or MRSA; and (5) in those individuals with a decline in FEV_1 but no changes in respiratory symptoms, antibiotics should be deferred.

Antimicrobial Therapy: Aerosolized Antibiotics

There has been great interest in the use of aerosolized antibiotics for treatment of bronchiectasis, an approach that has long been the standard care for those with CF. The goal is to reduce bacterial load, since high bacterial load (as assessed by number of colony-forming units or CFUs) is a marker of lung inflammation and has been linked to high risk of future exacerbation and hospitalization.[16] Inhaled delivery methods offer several advantages, including high concentration of drug in the airway, reduced systemic absorption, and reduced systemic toxicity. Concerns with aerosolized antibiotics include adverse airway side effects and the possible emergence of antibiotic-resistant pathogens.

Aerosolized antibiotics have been specifically directed at GNR infection, particularly *Pseudomonas aeruginosa,* which has been linked to higher mortality, high risk of hospitalization, and worse quality of life, among others.[17,18] Several agents have been studied in prospective, randomized, placebo-controlled clinical trials, including tobramycin, gentamicin, and aztreonam for inhalation solution, and colistin and ciprofloxacin in both liposomal and dry powder formulations.

Tobramycin has been the focus of several published clinical trials in treatment of acute exacerbations and as chronic maintenance therapy.[19–21] Aerosolized tobramycin has been found to have a profound microbiologic impact on *Pseudomonas aeruginosa*, without promoting emergence of resistant organisms. Improvement in symptoms, quality of life, and exacerbation frequency have been suggested, but efficacy as either maintenance therapy or in treatment of acute infectious exacerbations has not been conclusively established. Associated adverse effects, including cough dyspnea and chest tightness, are well described.

Aerosolized gentamicin was studied in a randomized, year-long, placebo-controlled trial of 65 patients, 57 of whom completed the study. Findings included a 31% eradication of *Pseudomonas* and 92.8% of other pathogens in the treatment group. No *Pseudomonas* isolates developed gentamicin resistance. Treated patients were noted to have statistically significant less purulent sputum, increased time to first exacerbation, fewer exacerbations, and improved Leicester Cough Questionnaire (LCQ) and St. George Respiratory Questionnaire (SGRQ). There were no differences in 24-h sputum volume or spirometry.[22]

Two randomized, double-blind, placebo-controlled, phase 3 clinical trials of aerosolized aztreonam did not demonstrate clinical benefit; treatment-emergent adverse events, including dyspnea, cough, and increased sputum were common.[23]

More recently, inhaled colistin was evaluated in the UK in 144 patients with bronchiectasis and *Pseudomonas* infection.[24] Participants were enrolled within 21 days of acute exacerbation and received inhaled colistin or placebo daily for up to 6 months. Fewer than 10% of patients were on macrolides. The primary endpoint, time to exacerbation, was not met in the intention-to-treat (ITT) group. However, for patients adherent to more than 80% of doses, the median time to exacerbation was statistically significantly increased to 168 days in the colistin group from 103 days in the placebo group. The reported exacerbation rate was 50% in the colistin group and 72% in the placebo group. An international clinical trial is currently underway.

Trials of liposomal ciprofloxacin (ORBIT 3,4) and dry powder ciprofloxacin (RESPIRE 1,2) have been completed. Exacerbation reduction was significantly reduced in RESPIRE 1 and ORBIT 4 but not duplicated in their parallel trials.[25–27]

In summary, use of aerosolized antibiotics in treatment of acute exacerbations of non-CF-related bronchiectasis remains controversial. Aerosolized antibiotics appear to have a clear microbiologic impact, but their clinical efficacy has not yet been conclusively proven, and none is currently approved by regulatory agencies. Importantly, the emergence of clinically relevant resistant pathogens has not been yet observed. Meta-analyses have reported that aerosolized antibiotics are generally safe and better than placebo in reducing bacterial load.[28] A number of professional societies, including the European Respiratory Society, the British Thoracic Society, and the Thoracic Society of Australia and New Zealand have suggested that long-term nebulized antibiotics should be considered for those individuals with chronic *Pseudomonas aeruginosa* infection, those experiencing frequent exacerbations (>3/year), and when other therapies have been optimized.

Unanswered questions on the use of aerosolized antibiotics include administration schedule (daily versus cycling, e.g., 28 days off/on) and their role in comparison with chronic macrolide therapy.

Airway Clearance Techniques

Airway clearance techniques (ACT) are those designed to enhance mucociliary clearance. The goals of ACT are to improve symptoms, reduce exacerbation frequency, and improve quality of life. There are a number of modalities, both mechanical and pharmacologic, used in clinical practice. ACT are safe, but there is little strong evidence to establish their efficacy. However, published guidelines have recommended the use of ACT, particularly for individuals with chronic productive cough or those who have difficulty expectorating sputum.[7,11]

Mechanical Modalities

Mechanical modalities to facilitate airway clearance include positive expiratory pressure devices and high-frequency oscillation modalities.

Use of *positive expiratory pressure (PEP)* devices is based on generation of positive expiratory pressure when an individual exhales against fixed resistance, thereby preventing airway closure and promoting mobilization of airway secretions. Several PEP devices are available, including Acapella, Aerobika, and Flutter. These devices are the most commonly utilized ACTs in the United States, as reported by the U.S. Bronchiectasis Registry.[29] A small, randomized, 3-month crossover trial of the Acapella device reported an improvement in total LCQ, increased 24-h sputum volume, and improved exercise capacity. No change in spirometry or sputum microbiology were reported.[30] Additional studies are necessary to establish the benefit of PEP devices.[31]

With high-frequency chest wall oscillation, external chest oscillations are applied to the chest using a fitted vest. Once again, convincing data on efficacy, both short- and long-term, are lacking; however, enhanced sputum expectoration and quality of life, and a decrease in hospitalization for exacerbations have been suggested.[32,33]

Pharmacologic Agents

A variety of pharmacologic approaches have been employed in facilitating airway clearance. The most common are considered below.

Hyperosmolar agents, including inhaled mannitol and hypertonic saline, are commonly used agents. A phase 3, multicenter, randomized, controlled, double-blind clinical trial of inhaled mannitol in 485 patients did not reveal a statistically significant reduction in the rate of acute exacerbations. There were statistically significant improvements in time-to-first exacerbation and QOL. Therapy was well tolerated.[34]

Use of hypertonic saline is part of standard care for CF and has been demonstrated to reduce the frequency of pulmonary exacerbations and, perhaps, improve quality of life. It is available in 3% and 7% formulations. Small clinical studies in bronchiectasis suggest a decrease in sputum viscosity and a decrement in disease exacerbations, but more definitive data are lacking. Reported associated adverse effects include throat irritation, salty taste, and dyspnea.

Use of bronchodilator agents, such as albuterol, have generally not been found to enhance bronchopulmonary hygiene.

Although use of recombinant human deoxyribonuclease (rhDNase) has been shown to be efficacious in individuals with cystic fibrosis, in a large clinical trial, pulmonary exacerbations were found to be more frequent and decline in FEV_1 greater in patients with non-CF bronchiectasis who received rhDNase.[35] Therefore, the agent should not be used routinely in bronchiectasis. This underscores the principle that extrapolation of data on treatment for patients with cystic fibrosis to those without cystic fibrosis be done cautiously.

In summary, ACT should be considered in symptomatic patients, in those who have chest congestion and difficulty expectorating sputum, and, perhaps, in those with frequent exacerbations. In the absence of data, the modality chosen should be one that maximizes patient adherence and minimizes expense.

■ Anti-inflammatory Therapy

Anti-inflammatory therapy for bronchiectasis includes macrolides and other pharmacologic agents.

Macrolide Antibiotics

Macrolide antibiotics have been a focus of study because of their myriad anti-inflammatory and immunomodulatory properties. Among other effects, macrolides inhibit mucus hypersecretion, reduce IL-8 and neutrophil elastase, inhibit neutrophil adhesion to epithelial cells, reduce biofilm formation, and inhibit production of reactive oxygen species from neutrophils. Macrolides have been used successfully in other airways diseases, including cystic fibrosis, diffuse panbronchiolitis, posttransplant obliterative bronchiolitis, and COPD. Older small studies in bronchiectasis suggested a reduction in sputum volume and exacerbation frequency with use of macrolides. The reduction of exacerbations is a particularly desirable clinical endpoint, given their adverse impact on quality of life. In addition, reducing exacerbations may also decrease hospitalizations and overall cost of care.

To date, three published clinical trials have evaluated the efficacy of macrolides in bronchiectasis. Although there were differences in methodology and agents used, all three reported significant decrements in exacerbation frequency.

The EMBRACE trial[35] was carried out at three centers in New Zealand. A total of 141 patients who had at least one exacerbation in the prior year were treated with thrice-weekly azithromycin versus placebo for 6 months. Those receiving azithromycin were found to have a 62% reduction in the rate of acute exacerbations at both 6 and 12 months, as well as increased time to first exacerbation. There were no significant differences in FEV_1, SGRQ, or 6-min walk test distance.

The BAT trial[36] from the Netherlands included patients who had experienced at least three exacerbations in the previous year. A total of 83 patients were treated with azithromycin 250 mg daily or placebo for 12 months. An absolute risk reduction of 33.5% was demonstrated in those taking azithromycin. A 1.03% increase in FEV_1 per 3 months versus a decrement of 0.1% in the placebo group also was noted.

The BLESS trial,[37] the largest of the three trials, was conducted in Australia. Of 679 screened patients, 107 completed a double-blind, placebo-controlled, single-center trial. Enrolled individuals had at least 2 exacerbations in the preceding 12 months and were treated with erythromycin, 40 mg twice daily, for 48 weeks (with a 4-week washout) versus placebo. A significant reduction in the rate of protocol-defined pulmonary exacerbations from 1.97 in the placebo group to 1.29 in the treatment group was reported. In addition, a reduction in 24-h sputum production and a 2.2% attenuation in the rate of FEV_1 decline were noted.

At present, macrolide therapy may be targeted specifically to those patients with frequent exacerbations (>3/year), normal ECG, and no significant underlying cardiac disease. Macrolides should be avoided in patients with known or strongly suspected nontuberculous mycobacterial infection in whom macrolide monotherapy is the main risk factor for development of macrolide resistance, which is associated with a poorer prognosis, including increased mortality. The optimal duration of treatment has not yet been established.

Little published data are available to guide a decision on when to use inhaled antibiotics versus long-term macrolide treatment. The 2017 ERS guidelines suggest that inhaled antibiotics be used in patients with chronic *Pseudomonas* infection and ≥3 exacerbations per year. Macrolides can be used in those with frequent exacerbations with non-*Pseudomonas* pathogens or those who exhibit intolerance or lack of efficacy with inhaled antibiotics. Combined therapy with a macrolide and inhaled antibiotics may be considered when there is a suboptimal response to either agent alone.[11]

Use of macrolide antibiotics in bronchiectasis is certainly not without other concerns. These include commonly reported adverse gastrointestinal symptoms, ototoxicity, and possible development of bacterial antibiotic resistance. In addition, a small risk of a sudden cardiac event, particularly in those at highest risk for cardiovascular disease.[38]

Other Pharmacologic Therapies

Brensocatib, an oral, reversible inhibitor of dipeptidyl peptidase 1 (DPP1), an enzyme responsible for activating neutrophil serine proteases (NSPs, such as neutrophil elastase), was recently reported to be well tolerated and associated with a significant reduction in the rate of exacerbation and significantly prolonged time to first exacerbation over 24 weeks versus placebo.[39] An international phase 3 trial is currently underway.

A rotating antibiotic strategy was commonly employed by clinicians in the past. In general, there is no evidence to support the use of systemic, nonmacrolide, suppressive, or maintenance therapy.

Inhaled or chronic systemic corticosteroids should not be used routinely in bronchiectasis unless indicated for other comorbidities, such as asthma or COPD.[11] There have been reports of an increased risk of nontuberculous mycobacterial infection associated with inhaled corticosteroid therapy.[40]

Specific therapy should obviously be used in patients with significant underlying disorders. Examples include immunoglobulin replacement for CVID, systemic corticosteroids and antifungal agents for ABPA, α_1-antitrypsin augmentation therapy in α_1-antitrypsin deficiency, and guideline-based antibiotics for nontuberculous mycobacterial infection.

■ Surgery

No robust prospective data are available comparing surgical resection to medical therapy for individuals with bronchiectasis. A number of retrospective case series have, however, demonstrated that surgery for selected patients can be accomplished with acceptable morbidity and mortality.[41,42] Surgery is an option to be considered for those with massive hemoptysis refractory to other measures, such as bronchial artery embolization; those with localized bronchiectasis who have frequent exacerbations despite medical therapy; and as an adjunct to antibiotics for patients with nontuberculous mycobacterial infection.[11,43]

Supportive Measures

Important supportive measures for bronchiectasis include appropriate vaccination, supplemental oxygen for associated hypoxemia, and pulmonary rehabilitation therapy for those with functional impairment. Short courses of systemic corticosteroids for bronchospasm associated with some exacerbations may be warranted. Finally, lung transplantation can be successfully utilized in patients with advanced disease.

NATURAL HISTORY AND PROGNOSIS

The natural history and prognosis of bronchiectasis are not well described. A study of 91 patients in the United Kingdom followed consecutively over 13 years starting in the mid-1990s demonstrated a mortality rate of 29.7%.[44] This was higher than the expected death rate for males and females of 14.7% and 8.9%, respectively, in an age-matched cohort. Of note, respiratory causes accounted for about 70% of all deaths. Predictors of mortality in this study included older age, history of *Pseudomonas aeruginosa* infection, impaired lung function, and poor quality of life.

A number of clinical prediction tools for bronchiectasis have been developed. The Bronchiectasis Severity Index (BSI) has recently been derived and validated in large cohorts as a tool for disease severity.[45] The BSI is comprised of nine parameters including age, BMI, FEV_1, hospital admissions, exacerbations, MRC dyspnea scores, *Pseudomonas aeruginosa* colonization, colonization with other organisms, and radiologic severity. Higher BSI scores are associated with higher mortality, more frequent hospital admissions, and poor quality of life as assessed by SGRQ.

Independent predictors of mortality in bronchiectasis include older age, FEV_1 <30% predicted, lower BMI, prior hospitalizations, and ≥3 exacerbations in the previous year. Independent predictors of hospitalization include prior admissions, MRC dyspnea score >4, FEV_1 <30% predicted, *Pseudomonas aeruginosa* colonization, and multifocal bronchiectasis with ≥3 lobes involved on HRCT.

The FACED Score, derived from an observational study in Spain, classifies severity according to prognosis.[46] It focuses on five variables, including chronic *Pseudomonas aeruginosa* infection, mMRC score, FEV_1, age, and number of affected lobes. The score has been validated to predict all-cause mortality.

SUMMARY AND FUTURE DIRECTIONS

In summary, bronchiectasis is a heterogeneous clinical entity that is more common and clinically impactful than previously thought. Recurrent respiratory infections and impairment of quality of life are its clinical hallmarks. Prompt and accurate diagnosis requires vigilance for suggestive clinical signs and symptoms and initiation of objective studies. Treatment is multifaceted and includes both specific and supportive measures, many of which have limited evidence-based support. Despite progress, much work lies ahead to expand basic knowledge of the pathophysiology of bronchiectasis and potential novel treatment options.

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PART 5

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CHAPTER 52

Interstitial Lung Disease: A Clinical Overview and General Approach

Aditi Mathur
Danielle E. Antin-Ozerkis

INTRODUCTION

Interstitial lung disease (ILD) refers to a heterogenous collection of lung disorders that are grouped together because they share clinical, radiographic, and pathologic features. ILD is also referred to as *diffuse parenchymal lung disease (DPLD)* to clarify that the interstitium is not the only compartment of the lung affected. For example, organizing pneumonia and pulmonary alveolar proteinosis are alveolar filling processes, whereas respiratory bronchiolitis and chronic hypersensitivity pneumonitis may center on the airway. Occasionally, purely airway-centered disease like bronchiolitis obliterans may be initially identified as an ILD because of overlapping radiographic features. A structured approach is necessary since prognosis and therapy vary considerably depending on the diagnosis. While many ILDs are extremely rare, there are some, such as idiopathic pulmonary fibrosis (IPF) and sarcoidosis, that are seen commonly in general pulmonary practice.

ILD frequently presents with dyspnea on exertion, diffuse bilateral infiltrates on chest imaging, and restriction with diffusion impairment on physiologic testing. When tissue is obtained, the lung parenchyma may contain any combination of inflammation and fibrosis. Masqueraders of ILD, such as infection, pulmonary edema, and malignancy, will be encountered in the assessment of abnormal chest imaging. Distinguishing these from true ILD is essential.

Specific diagnosis is based upon a comprehensive history and careful physical examination, as well as review of laboratory data, physiologic studies, radiography, and, in some cases, pathologic tissue obtained from lung biopsy. Multidisciplinary review is an important part of the process and can have a significant impact on diagnostic and management decisions. For each patient, decisions regarding diagnostic approach and therapy must be individualized based upon the patient's own personal approach to medical care, in combination with their respiratory status and comorbid medical conditions.

GENERAL APPROACH TO ILD

Several proposed classification schemes for ILD include radiographic, histopathologic, and clinical characteristics.[1] The American Thoracic Society (ATS)/European Respiratory Society (ERS) consensus panel classification system on the idiopathic interstitial pneumonias was published in 2002 and was updated in 2013 and 2018 with a focus on the diagnosis of IPF.[2–4] Additional guidelines on the diagnosis of hypersensitivity pneumonitis and sarcoidosis have further added to the diagnostic armamentarium.[5,6]

Despite the availability of such guidelines, in the care of any individual patient, it is useful for the clinician to have a methodical diagnostic approach. This process should incorporate a combination of historic, clinical, radiographic, and, when indicated, pathologic features. Distinguishing those patients who have a known cause for their ILD (e.g., connective tissue disease, occupational or environmental exposure, or drug toxicity) from those who do not (e.g., IPF, sarcoidosis) is one helpful diagnostic categorization (Fig. 52-1). Clinical features, such as acuity of onset and specific patient characteristics, may also help to classify disease (Table 52-1). For example, the subacute time course of symptom development in a patient with organizing pneumonia will be quite different than the insidious onset of dyspnea in IPF. Radiographic patterns often guide the clinician toward a specific diagnosis. For example, patients with IPF will have CT findings of basilar traction bronchiectasis and honeycombing, while those with sarcoidosis may demonstrate upper lobe–predominant nodular opacities with retraction and volume loss. Histopathologic characterization may range from acute inflammation to granulomatous involvement, to fixed fibrosis and collagen deposition. Pathologic pattern may be the specific feature that clarifies the ILD diagnosis.

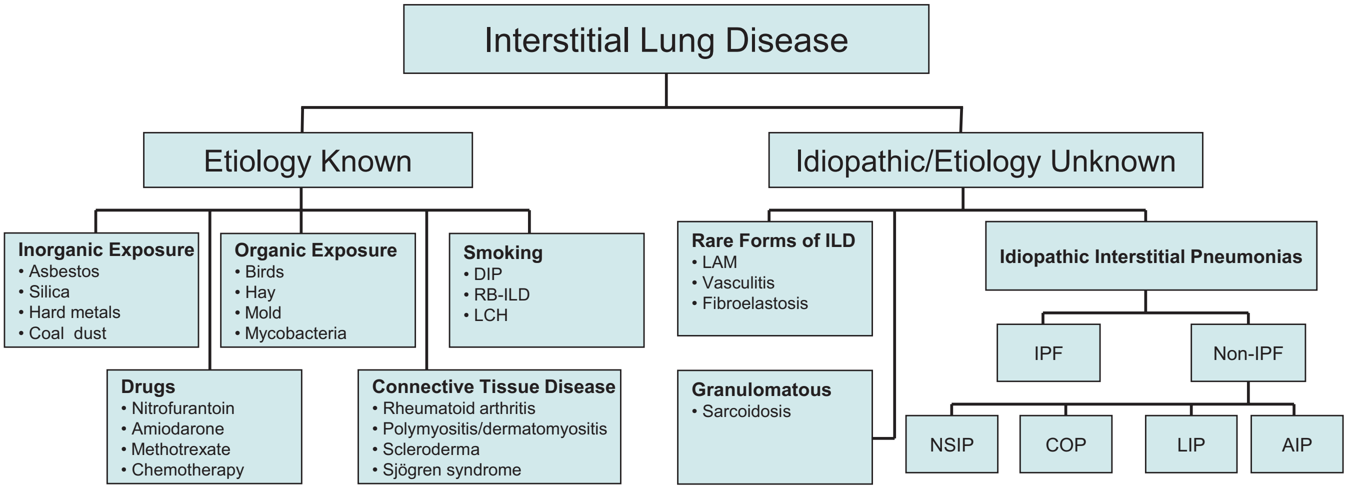
Interstitial Lung Disease
Etiology Known
Idiopathic/Etiology Unknown
Inorganic Exposure
• Asbestos
• Silica
• Hard metals
• Coal dust
Organic Exposure
• Birds
• Hay
• Mold
• Mycobacteria
Smoking
• DIP
• RB-ILD
• LCH
Drugs
• Nitrofurantoin
• Amiodarone
• Methotrexate
• Chemotherapy
Connective Tissue Disease
• Rheumatoid arthritis
• Polymyositis/dermatomyositis
• Scleroderma
• Sjögren syndrome
Rare Forms of ILD
• LAM
• Vasculitis
• Fibroelastosis
Granulomatous
• Sarcoidosis
Idiopathic Interstitial Pneumonias
IPF
Non-IPF
NSIP
COP
LIP
AIP

Figure 52-1 An overview of ILD classification. AIP, acute interstitial pneumonia; COP, cryptogenic organizing pneumonia; DIP, desquamative interstitial pneumonia; IPF, idiopathic pulmonary fibrosis; LAM, lymphangioleiomyomatosis; LCH, Langerhans cell histiocytosis; LIP, lymphocytic interstitial pneumonia; NSIP, nonspecific interstitial pneumonia; PPFE, pleuroparenchymal fibroelastosis; RB-ILD, respiratory bronchiolitis interstitial lung disease. *(Data from ATS/ERS classification, 2018.)*

TABLE 52-1 Time Course of Disease Onset

Acute
Cryptogenic organizing pneumonia
Acute eosinophilic pneumonia
Acute hypersensitivity pneumonitis
Diffuse alveolar hemorrhage
Acute interstitial pneumonia
Acute exacerbation of idiopathic pulmonary fibrosis
Subacute to Chronic
Connective tissue disease–associated ILD
Idiopathic pulmonary fibrosis
Sarcoidosis
Chronic hypersensitivity pneumonitis
Occupational lung disease
Nonspecific interstitial pneumonia
Desquamative interstitial pneumonia
Respiratory bronchiolitis interstitial lung disease
Lymphocytic interstitial pneumonia
Chronic eosinophilic pneumonia
Pleuroparenchymal fibroelastosis
Combined pulmonary fibrosis and emphysema

It is important to note that the names used to describe the clinical entities themselves must be distinguished from the radiographic and pathologic terms used to describe the findings. For example, IPF is the clinical entity associated with a usual interstitial pneumonia (UIP) pattern on chest CT and histopathology. However, the finding of a UIP pattern alone does not ensure a diagnosis of IPF, as this pattern may also be seen in other entities, including connective tissue disease and hypersensitivity pneumonitis.

CLINICAL HISTORY

Below we consider important patient characteristics, as well as respiratory and nonrespiratory presentations of ILD.

Patient Characteristics

Age and gender are key characteristics to consider. Certain forms of ILD are more common in particular age groups. IPF is a disease more common in the older population, whereas connective tissue disease–associated ILD, sarcoidosis, lymphangioleiomyomatosis (LAM), and hereditary forms of ILD are typically diagnosed at a younger age. CTD-ILD is more common in women, and LAM is almost exclusively diagnosed in women during childbearing years. A diagnosis of IPF in a 30-year-old woman, for example, should be strongly reconsidered.

Respiratory Presentation

The typical presentation of ILD is nonspecific and may include vague pulmonary complaints, such as dyspnea on exertion or cough. In some cases, the time course of the disease may suggest certain forms of ILD (Table 52-1). The acute forms of ILD must be distinguished from respiratory infections and pulmonary edema due to congestive heart failure.

Other clinical features may affect the presentation as well. In elderly or disabled patients, musculoskeletal issues may limit mobility and dyspnea may be a late symptom. In a patient with significant cardiac disease, relatively mild ILD may cause an earlier onset of disabling dyspnea and the discovery of ILD for this reason. It is helpful to attempt an objective quantification of the degree of dyspnea, such as the distance the patient walks before becoming breathless or the number of steps climbed before a rest must be taken.

Often a persistent cough after a respiratory infection leads to the initial chest radiograph. While other respiratory symptoms are less common, they may help focus the differential diagnosis. For example, a history of wheezing may suggest an airway-centered process such as hypersensitivity pneumonitis, eosinophilic pneumonia, or sarcoidosis. Substernal chest pain is commonly described by patients with sarcoidosis. Pleuritic chest pain may herald serositis in a patient with connective tissue disease, or pneumothorax in cystic lung diseases, such as lymphangioleiomyomatosis (LAM) (Chapter 60) and Langerhans cell histiocytosis (LCH) (Chapter 59).[7–9] Hemoptysis may suggest diffuse alveolar hemorrhage, although it is not present in most cases.[10]

Systemic Symptoms

Connective tissue disease is a frequent cause of ILD, and some patients may come for pulmonary evaluation with a pre-existing diagnosis. However, most will not, and it is incumbent on the clinician to search carefully for suggestive symptoms and signs of underlying autoimmune disease; the pulmonologist may be the first to make such a diagnosis, prompted by the presence of ILD. In some cases, nonspecific symptoms such as night sweats, fever, fatigue, or weight loss suggest an underlying inflammatory condition. In others, the clinician can arrive at a specific diagnosis by performing a thorough review of systems. Careful questioning regarding skin rash and other dermatologic symptoms may lead to the discovery of dermatomyositis as demonstrated by a heliotrope rash, Gottron's papules, or "mechanic's hands," all of which are relatively specific features of this disease. Patients with underlying systemic sclerosis (scleroderma) may give a history of skin tightness and thickening, telangiectasias, Raynaud's phenomenon, or digital pitting. Papular eruptions, lupus pernio, and erythema nodosum are sometimes seen in sarcoidosis.[11] Patients with systemic lupus erythematosus (SLE) may describe malar rash, photosensitivity skin reaction, or hair loss.

Gastrointestinal symptoms may be indicative of underlying esophageal dysmotility related to connective tissue diseases, such as systemic sclerosis, mixed connective tissue disease, and polymyositis, or may be the root cause of the ILD itself. In particular, symptoms suggestive of acid reflux (chest burning or pressure, cough after meals, regurgitation of food) should be sought. Chronic, intermittent aspiration can lead to progressive fibrotic lung disease from recurrent lung injury. Patient descriptions of coughing or choking while eating or noting food "going down the wrong pipe" are suggestive of frank aspiration and could lead to a discovery of progressive neuromuscular diseases, such as amyotrophic lateral sclerosis (ALS), prior cerebrovascular accident, or other causes of oropharyngeal and laryngeal dysfunction.[12] Lower gastrointestinal complaints, such as bloating and diarrhea, may suggest inflammatory bowel disease, which is associated with ILD,[13] or bacterial overgrowth due to bowel dysmotility in systemic sclerosis.

Musculoskeletal complaints also can be helpful in identifying underlying connective tissue disease. In particular, arthralgias, morning stiffness, joint swelling and erythema, and digital deformities may be evidence of rheumatoid arthritis, Sjögren syndrome, or mixed connective tissue disease. Swollen fingers ("sausage digits") may be observed in systemic sclerosis and polymyositis. Raynaud's phenomenon manifests as either blue/purple discoloration or whiteness of the digits (fingers or toes) in the cold.[14] In some cases, this may be quite profound and can be associated with digital ulceration and, rarely, digital gangrene. Raynaud's phenomenon is most commonly seen in scleroderma, mixed connective tissue disease, SLE, and antisynthetase syndrome.[15]

Ophthalmologic symptoms may direct the clinician toward particular clinical entities. Inquiries regarding dry eyes or the use of eye drops may uncover sicca syndrome, as seen in Sjögren syndrome, and overlap connective tissue diseases. Patients with a history of uveitis may have underlying SLE, vasculitis, or sarcoidosis.[16] Neurologic symptoms may suggest vasculitis or sarcoidosis.

The cardiac history may uncover sequelae of longstanding ILD. Increasing edema, syncopal events, or exertional chest discomfort may indicate severe pulmonary hypertension and cor pulmonale in the patient with advanced fibrotic lung disease and hypoxemia. Alternatively, in a patient with systemic sclerosis, these findings might indicate a second related but independent problem such as pulmonary arterial hypertension. The presence of palpitations or syncope in a patient with sarcoidosis can lead to a diagnosis of cardiac sarcoidosis.

The review of systems will sometimes lead to other important diagnoses. For example, more typical causes of chest discomfort with activity, such as cardiac ischemia, may be exacerbated by exertional hypoxemia. This is particularly important to remember, as patients with underlying immune-related diseases appear to be at increased risk for coronary artery disease.[17] In addition, pleuritic chest pain, leg swelling, and increasing dyspnea should prompt consideration of acute pulmonary embolism, as patients with ILD are at increased risk for this complication.[18–20]

PAST MEDICAL HISTORY

In addition to underlying connective tissue disease (systemic sclerosis, rheumatoid arthritis, dermatomyositis/polymyositis, SLE) and inflammatory bowel disease, other systemic disorders may lead to ILD or its mimics and will affect the approach to diagnosis. For example, the differential diagnosis for dyspnea and diffuse infiltrates on chest radiograph will vary markedly between immunocompetent patients and those who have undergone organ or bone marrow transplantation, are neutropenic from recent chemotherapy, or who have advanced HIV disease. In HIV disease, lymphocytic interstitial pneumonia (LIP) may be evident and may be associated with viral replication or immune dysregulation.[21] A history of acute or chronic kidney disease might suggest underlying vasculitis, pulmonary–renal syndromes, or connective tissue disease. Lysosomal storage disorders such as Niemann Pick[13] and Gaucher disease are a rare cause of ILD.[22] A history of liver disease could suggest sarcoidosis, primary biliary cirrhosis, or underlying genetic abnormalities resulting in short telomere length.[23–25] A history of facial nerve palsy (Bell's palsy) might represent unrecognized sarcoidosis.[26] As the clinician considers a patient's medical history, specific diagnoses may lead to a focused review of drugs used to treat these disorders since many are common culprits in the development of ILD (see "Medication History," below). For example, when a patient with inflammatory bowel disease presents with ILD, a history of recent sulfasalazine, mesalamine, methotrexate, or anti-TNF therapy should be sought.[13]

OCCUPATIONAL HISTORY

The occupational history should be thorough, including a review of all jobs held in the past. In particular, attention should be paid to any occupation in which a history of exposure to organic or inorganic products was present (Table 52-2).[27,28] Specific inquiries may be made regarding a history of construction work, including demolition, plumbing, and electrical work. The patient should be questioned about employment in factories and manufacturing plants, the electronics industry, metal working, stone cutting, and mining. The clinician should specifically inquire about exposure to asbestos, silica, hard metals, and beryllium, as workers often know when these have been present in their work environment.[29,30] Inquiries may additionally be made regarding the jobs held by household contacts of patients. For example, spouses may have been subjected to significant levels of dust inhalation via clothing worn by the worker.[31] In cases where a relevant exposure has occurred, details should be obtained regarding the worker's specific duties, the typical proximity to the exposure of interest, and any use of respiratory protection. In some cases, related respiratory illnesses in coworkers can raise suspicion.

TABLE 52-2 Occupational Interstitial Lung Disease

Occupation	Type of ILD	Exposure
Electrician Plumber Pipe fitter Construction worker Ship builder Insulation installer	Asbestosis	Asbestos
Stone cutter Miner Sand blaster Engineered stone countertop production worker	Silicosis	Crystalline silica dust
Metal grinder	Giant cell interstitial pneumonia Hard metal lung disease	Hard metals Cobalt Tungsten carbide
Metal worker Factory workers Nuclear weapons Aircrafts Electronics Ceramics Golf clubs Bicycle frames	Berylliosis	Beryllium
Coal worker	Coal worker's pneumoconiosis	Coal dust
Paint sprayer Plastic worker	Chemical worker's lung	Isocyanates
Bird breeder	Bird breeder's lung	Bird droppings Bird feathers
Farm worker Haying Mushroom compost	Farmer's lung Mushroom worker's lung	Thermophilic bacteria
Office worker	Humidifier lung Ventilation pneumonitis	Fungi/molds
Lifeguard	"Hot tub" hypersensitivity pneumonitis	Mycobacteria

There may be a long latency period between the exposure and the onset of symptoms and radiographic changes, so the occupational history must explore jobs held many years in the past.

A history of farm work or other agricultural employment should raise suspicion for an environmental cause of ILD. Exposure to moldy hay, bird feathers and droppings, and a variety of organic products can lead to chronic hypersensitivity pneumonitis.[32,33] There are several available questionnaires to screen for such exposures, but none have been validated. In recent ATS guidelines on hypersensitivity pneumonitis, it was recommended that the clinician might utilize their own questionnaire but that a future universal approach should be addressed in the ILD community.[5]

ENVIRONMENTAL HISTORY

Organic exposures are also frequently encountered in household and office settings.[27] For example, humidification systems may be contaminated with mold.[34] Hot tubs and other aerosolized water sources have led to lung disease related to growth of *Mycobacterium avium*.[35] The exposure history should include a thorough inquiry regarding the home heating and humidification system, a history of water damage, or visible evidence of significant mold growth. An assessment of the timing of any water damage relative to the onset of the lung disease can be helpful. Domestic birds are a common source of feathers and dropping antigen. Bird owners often have multiple birds and have owned birds for many years. Frequently, these pets are considered cherished members of the family, residing in bedrooms and main living spaces. A history of hobbies and materials used should also be obtained. No occupation or recreational activity should be ignored. For example, even wind instruments have been linked with contamination by fungi and bacteria leading to lung disease.[36]

Cigarette smoke is one of the most common environmental exposures and is strongly linked with several forms of ILD, including desquamative interstitial pneumonia (DIP), respiratory bronchiolitis-ILD, and LCH. Cigarette smoking has been identified as a risk factor for IPF. In recent years, the use of electronic cigarettes has led to significant respiratory illness, also known as vaping product use–associated lung injury (EVALI),[37] discussed in detail in Chapter 41. It is thought that microparticles and volatile chemicals, as well as cutting agents such as vitamin E acetate, are responsible for the lung injury.[38]

MEDICATION HISTORY

Numerous drugs have been implicated in the development of ILD, ranging from acute pneumonitis to chronic fibrotic lung disease (Table 52-3), as further discussed in Chapters 64 and 65. It is important to specifically review the medication list and to particularly seek out a history of prolonged use of commonly prescribed drugs. Nitrofurantoin, used for suppression of recurrent urinary tract infections, may lead to severe ILD.[39] Amiodarone, used for management of atrial and ventricular arrhythmias, is known to lead to lung toxicity.[40] Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used and may lead to eosinophilic and other inflammatory lung disease.[41,42] While less frequently used in the general population, a history of recent chemotherapy should trigger suspicion for drug-related lung disease.[43] Similarly, a history of immune-modulating drug use, such as in the treatment of rheumatoid arthritis or Crohn's disease, may be of concern.[39,40,44,45] Immunotherapy has become standard of care in oncology, which has produced an awareness of immune-mediated adverse events, including lung toxicity (Chapter 64).

Since numerous drugs are associated with ILD, a thorough past and present medication history should be obtained for all patients with newly diagnosed ILD. A helpful online source of information is *www.pneumotox.com*. This independent resource is compiled and regularly updated by members of the University Hospital in Dijon, France, and the GEPPI (Groupe d'Etudes de la Pathologie Pulmonaire Iatrogene). It lists all reports of suspected drug-induced lung disease, categorizes the radiographic patterns observed, and gives an assessment of the quality of the compiled information.

TABLE 52-3 Drugs Commonly Implicated in Interstitial Lung Disease

Antibiotics
- Nitrofurantoin
- Minocycline
- Cephalosporins

Antiarrhythmic
- Amiodarone
- Tocainide

Anti-inflammatory
- Azathioprine
- Etanercept
- Gold salts
- Infliximab
- Methotrexate
- NSAIDs
- Penicillamine
- Sulfasalazine

Neurologic/Psychiatric
- Carbamazepine
- Phenytoin

Drugs of Abuse
- Cocaine
- Heroin
- Talc

Chemotherapeutic
- All-trans retinoic acid (ATRA)
- Interferon α
- Antithymocyte globulin
- Bleomycin
- Carmustine (BCNU)
- Chlorambucil
- Colony-stimulating factors (GM-CSF)
- Cyclophosphamide
- Cytosine arabinoside
- Docetaxel
- Gefitinib
- Gemcitabine
- Interleukin 2
- Irinotecan
- Melphalan
- Mitomycin C
- Paclitaxel

Immunotherapy
- Nivolumab
- Ipilimumab

FAMILY HISTORY

Most forms of ILD are not heritable, although several do have a genetic component. When heritable disease is suspected, it is important to consider both systemic disorders as well as those that primarily affect the lung. In particular, by considering a patient's concomitant medical history or the history of family members, specific diagnoses may be uncovered. Several inborn errors of metabolism (Gaucher disease and Niemann Pick, for example) are inherited in an autosomal recessive fashion. Other rare diseases, such as Hermansky-Pudlak syndrome, Burt-Hogg-Dube syndrome, and neurofibromatosis type I are autosomal dominant disorders.[46] The cystic lung disease LAM may be associated with mutations in the tuberous sclerosis complex (TSC) genes, in which systemic hamartomas are present, including a high incidence of renal angiomyolipomas.[46]

Careful review of family history may reveal first- or second-degree relatives diagnosed with ILD. It is estimated that 2% to 20% of idiopathic interstitial pneumonias are familial, and of these, a large minority are due to mutations in telomerase reverse transcriptase (TERT) and telomerase RNA component (TERC).[47,48] Genome-wide linkage studies have also revealed a common variant in the promoter of the MUC5B gene to be associated with the development of familial and sporadic IPF.[49] The telomere shortening syndromes that lead to dyskeratosis congenita may lead to a phenomenon known as *genetic anticipation*, in which telomere lengths are progressively shortened in subsequent generations. This leads to the earlier onset of more severe disease in each subsequent generation.[50] The recognition of familial ILD related to short telomeres and/or telomere gene mutations is important prognostically since disease progression tends to be more rapid, independent of phenotype.[51] Several other genes have been linked with the onset of IPF, including those involved in the regulation of surfactant protein C.[52] There may be familial predisposition to sarcoidosis, but inheritance is more complex, involving an interaction of genetic and environmental factors.[53]

PHYSICAL EXAMINATION

Most patients with pulmonary fibrosis have lung findings characterized by fine, inspiratory, basilar "Velcro" crackles and many will have digital clubbing. In contrast, patients with nonfibrotic lung disease may have clear lung fields on auscultation. The location of the abnormal breath sounds may be suggestive of the underlying diagnosis, such as upper lobe findings in silicosis, chronic hypersensitivity pneumonitis, and sarcoidosis in contrast to the lower lobe abnormalities in IPF. Additional breath sounds, such as wheezing and inspiratory squeaks, can indicate airway disease, which may focus the examiner's differential diagnosis on airway centered diseases such as bronchiolitis, sarcoidosis, and hypersensitivity pneumonitis. These additional sounds should not be present in a patient with IPF.

Other cardiopulmonary manifestations of disease also should be sought. Signs of pulmonary hypertension and right heart failure include an increased P2 component, right ventricular heave, elevated jugular venous pressure, and lower extremity edema.

Dermatologic and musculoskeletal signs of connective tissue disease, including skin rashes, sclerodactyly, skin thickening, digital ulceration, "mechanic's hands," synovial joint deformities, Raynaud's phenomenon, and telangiectasias, may be extremely helpful in narrowing the differential diagnosis. More specialized examination may include nailfold capillaroscopy which can reveal dilated capillary loops, often seen in systemic sclerosis.[14] Less common findings, such as cutaneous neurofibromas or café au lait spots in neurofibromatosis, albinism and nystagmus in Hermansky-Pudlak syndrome, and facial angiofibromas, periungual fibromas, and Shagreen patch in TSC may all be key features only recognized through a careful and focused search.

CHEST IMAGING

Chest imaging in the patient with suspected ILD includes plain chest radiographs and high-resolution chest computed tomography.

Chest Radiograph

An abnormal chest radiograph is often the first indication of underlying ILD. The pattern and distribution of abnormalities often help in formulating a differential diagnosis (Table 52-4). For example, sarcoidosis, silicosis, and LCH are among the diseases with an upper lobe predominance, while IPF, connective tissue disease–associated ILD, and asbestosis are all lower lobe predominant. Peripheral alveolar opacities are typical findings in organizing pneumonia and chronic eosinophilic pneumonia. The chest radiograph is also helpful for assessing lung volumes. In particular, fibrotic lung disease such as IPF leads to small lung fields, whereas lung volumes are maintained and may even demonstrate hyperinflation in diseases such as LAM and LCH. Hilar fullness observed on chest radiograph may indicate mediastinal and hilar lymphadenopathy, a frequent feature of sarcoidosis and berylliosis.

High-Resolution Chest Computed Tomography

High-resolution computed tomography (HRCT) of the chest is significantly more sensitive than chest radiograph for abnormalities in ILD. The recommended scanning protocol for HRCT includes contiguous or overlapping noncontrast thin-section CT images (<1.5 mm). Initial scans may include supine inspiratory and expiratory imaging to look for evidence of air trapping, as well as prone imaging if position-induced changes in the dependent portions of the lungs are suspected.[54]

TABLE 52-4 Distribution and Pattern of ILD and Mimickers of ILD

Distribution of ILD	
Upper lung zone	**Lower lung zone**
Sarcoidosis	Usual interstitial pneumonia (UIP)
Silicosis	Nonspecific interstitial pneumonia (NSIP)
Coal worker's pneumoconiosis	Connective tissue disease–associated ILD
Hypersensitivity pneumonitis	Asbestosis
Langerhans cell histiocytosis	Desquamative interstitial pneumonia (DIP)
Berylliosis	
Chronic eosinophilic pneumonia	
Pleuroparenchymal fibroelastosis	
Pattern of ILD	
Peripheral reticular	**Ground glass**
Usual interstitial pneumonia	NSIP
Nonspecific interstitial pneumonia	Cryptogenic organizing pneumonia
	Eosinophilic pneumonia (chronic or acute)
	Pulmonary edema
Nodular	Infection (opportunistic or viral)
Sarcoidosis	Alveolar hemorrhage
Berylliosis	Hypersensitivity pneumonitis
Hypersensitivity pneumonitis	Desquamative interstitial pneumonia
Langerhans cell histiocytosis	Sarcoidosis
Silicosis	Pulmonary alveolar proteinosis
Metastatic disease	Mucinous adenocarcinoma
Talcosis	**Cystic**
Granulomatous polyangiitis	Lymphangioleiomyomatosis
Respiratory bronchiolitis–interstitial lung disease	Langerhans cell histiocytosis
	Lymphocytic interstitial pneumonia
	Pneumocystis jiroveci pneumonia

Several radiographic patterns have been identified to help focus the differential diagnosis. In particular, a peripheral reticular pattern that is basilar predominant may be seen in UIP (Fig. 52-2), NSIP (Fig. 52-3), and chronic hypersensitivity pneumonitis. Nodular infiltrates may suggest sarcoidosis (Fig. 52-4), hypersensitivity pneumonitis (Fig. 52-5), and LCH, although the nature of the nodules and their location may make one or another diagnosis more likely. The findings of diffuse cystic abnormalities lead to a specific differential diagnosis, including LAM, LCH, and LIP (Fig. 52-6).[55] The term "ground glass" refers to areas of lung tissues with increased attenuation, but not enough to obscure or distort lung architecture, blood vessels, and lymphatics. Alveolar opacities are a related finding and reflect more dense attenuation of lung tissue, sometimes containing air bronchograms. Many forms of ILD are characterized by ground glass and alveolar opacities. When observed in characteristic distributions, such as the peripheral, patchy, and peribronchovascular alveolar opacities in cryptogenic organizing pneumonia (COP)[56] and chronic eosinophilic pneumonia,[57] they are quite suggestive of an underlying pathologic pattern (Fig. 52-7). However,

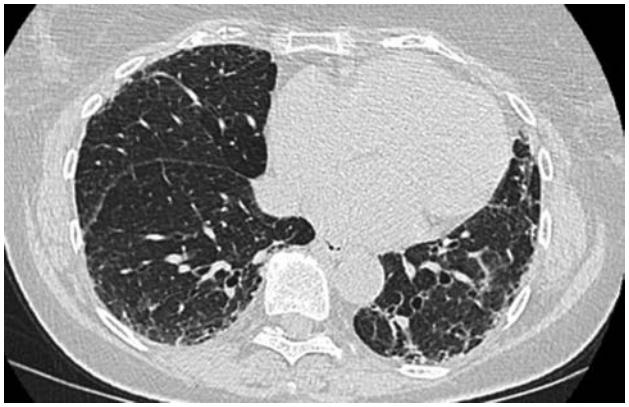

Figure 52-2 High-resolution CT image at the level of the lower thorax of a 67-year-old woman with a 40-pack-year tobacco history. There are bibasilar reticular opacities with traction bronchiolectasis suggesting a radiographic pattern of probable UIP.

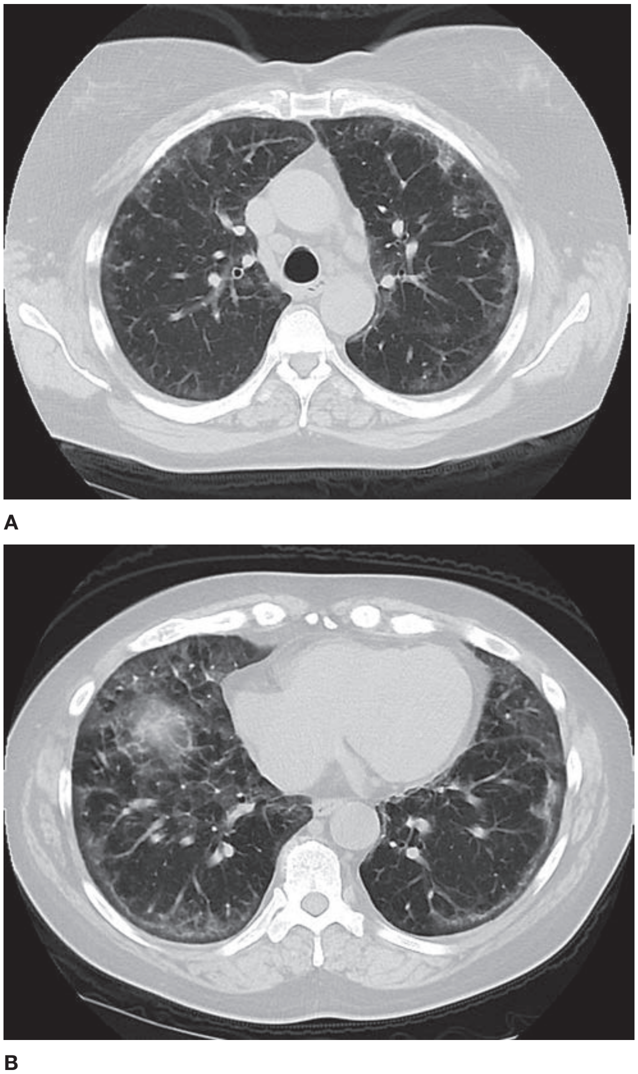

Figure 52-3 A 55-year-old woman with progressive dyspnea on exertion. She had finger swelling and Raynaud's phenomenon, with an antinuclear antibody titer of 1:2560 (nucleolar). Axial CT imaging through the mid (**A**) and lower (**B**) thorax shows ground glass opacities in a peripheral distribution, reticular markings, and mild architectural distortion. Subpleural sparing is evident. These findings are all compatible with a nonspecific interstitial pneumonia (NSIP) pattern. The final diagnosis was scleroderma lung disease.

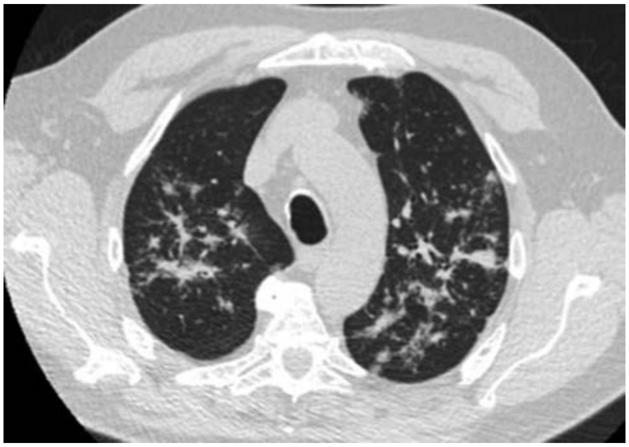

Figure 52-4 A 42-year-old man with sarcoidosis. CT images demonstrate perilymphatic irregular nodular thickening in an upper/mid lung distribution with some areas of mass-like coalescing nodules, more concentrated in the center than at the periphery—the "galaxy sign."

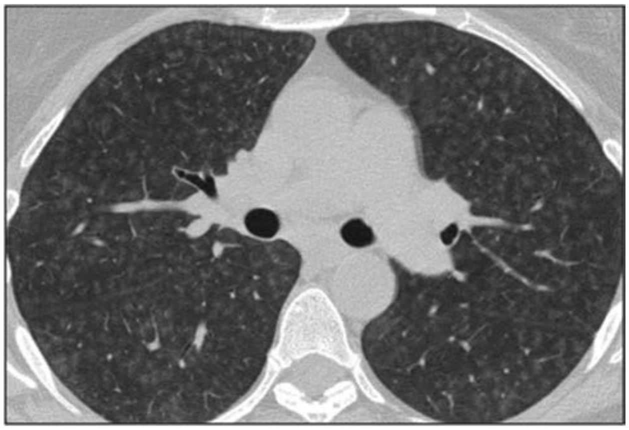

Figure 52-5 High-resolution CT images at the mid thorax level show diffuse ground glass and micronodular changes in a 66-year-old woman with dyspnea and low grade fevers for 3 months. Her hobbies included pottery making; evaluation of her potting shed revealed wet clay contaminated with mold. The patient had resolution of her imaging findings and symptoms once she stopped working with clay.

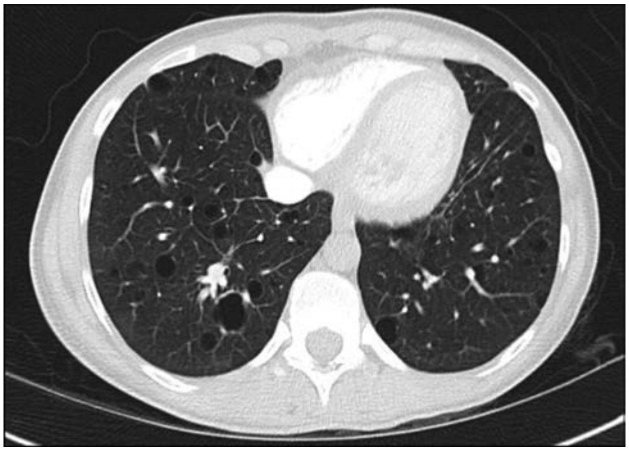

Figure 52-6 A 33-year-old woman with Sjögren syndrome underwent a chest CT with contrast to evaluate for pulmonary embolism. Images at the level of the mid thorax show multiple scattered cysts of variable sizes throughout the lungs suggestive of lymphocytic interstitial pneumonia (LIP).

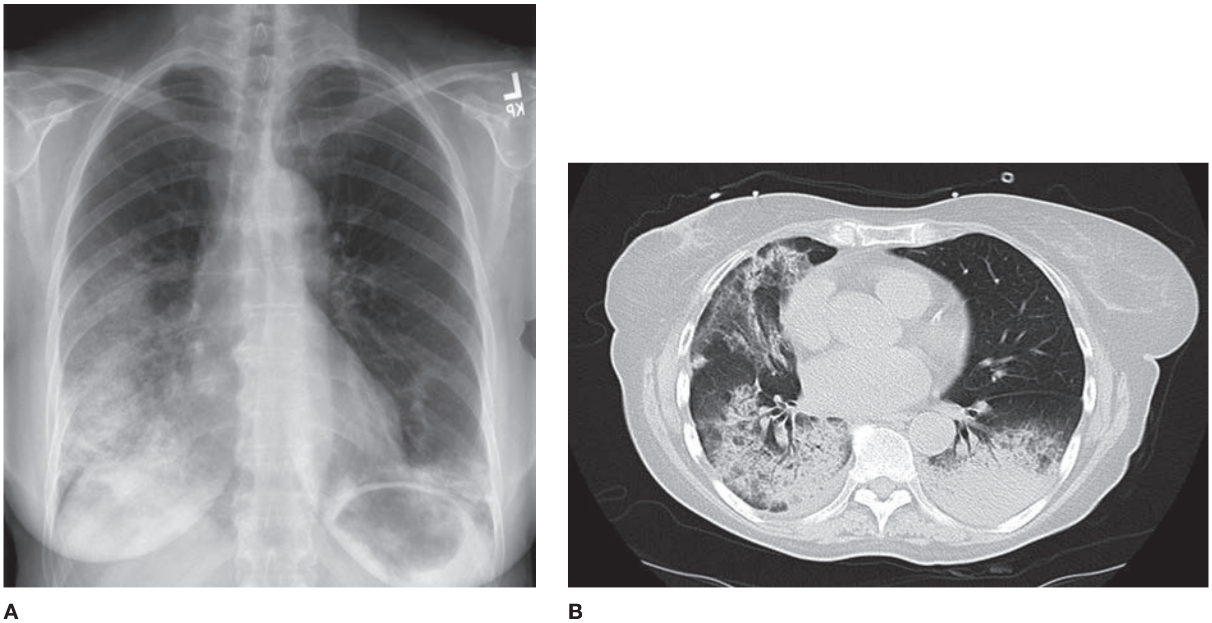

Figure 52-7 A 58-year-old woman with organizing pneumonia (OP) secondary to radiation for breast cancer. Frontal chest radiograph (**A**) demonstrates ground glass and alveolar opacities. High-resolution CT images at the level of the mid (**B**) thorax demonstrate both ground glass opacities and areas of consolidation. She had complete response to corticosteroid therapy.

the radiographic appearance in such cases is nonspecific, and other testing, including lung biopsy, may be required for diagnosis.

Characteristic patterns observed on HRCT can be quite specific in some cases. For example, the characteristic radiographic features of IPF are collectively known as the "UIP pattern" (Fig. 52-8), since these features have been demonstrated to confidently predict the presence of pathologic UIP when surgical biopsy is obtained (Table 52-5).[58,59] This pattern consists of peripheral, subpleural, basilar-predominant reticular opacities in combination with basilar honeycombing and without features, such as ground-glass opacities, cysts or nodules, to suggest another form of ILD.[60] When these features are accurately recognized, patients can be spared a surgical biopsy for diagnosis.

Connective tissue disease–associated ILD can present with a multitude of HRCT patterns including UIP, NSIP, OP, and cystic lung disease. Certain CT signs have been found to be associated with CTD-ILD.[61] Extrapulmonary manifestations of CTD noted on chest imaging include a dilated fluid- or air-filled esophagus (Fig. 52-9). Fibrosis in the anterior upper lobes of the lung, a significant degree of honeycombing, so-called "exuberant honeycombing" (Fig. 52-10), and isolation of fibrosis in the lung bases with a sharp demarcation of normal and abnormal lung parenchyma or the "straight-edge sign"

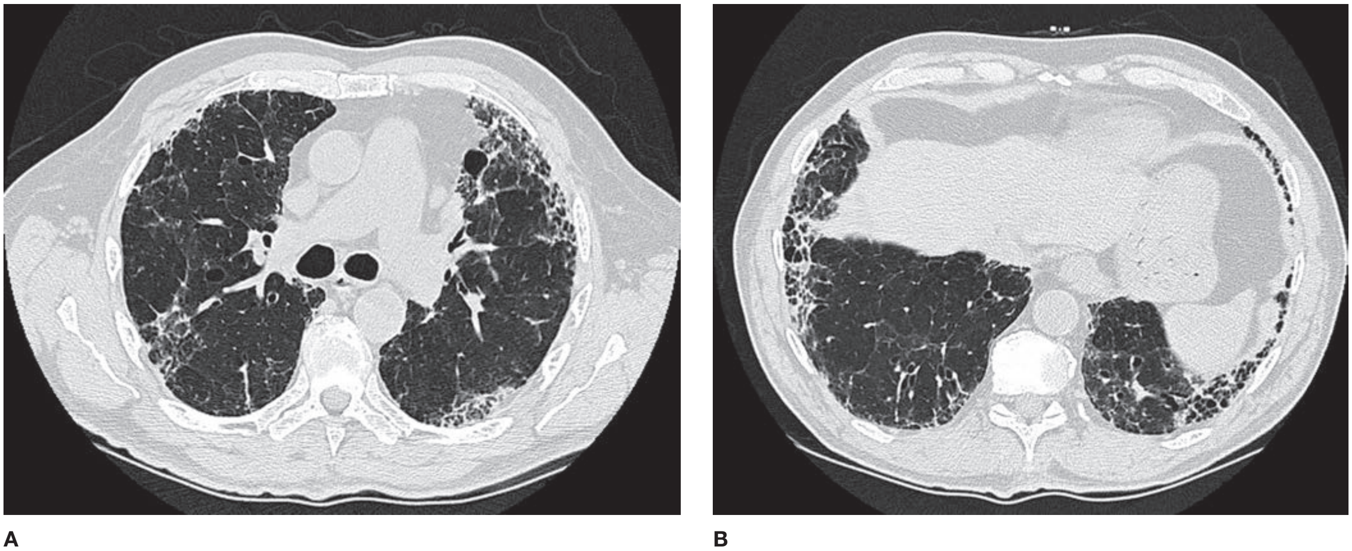

Figure 52-8 An 82-year-old man with progressive dyspnea and a usual interstitial pneumonia (UIP) radiographic pattern. High-resolution (1.25-mm-thick sections) CT images at the level of the mid (**A**) and lower (**B**) thorax show peripheral reticular markings with architectural distortion and small subpleural cysts/honeycombing. Ground glass opacities and other features atypical for IPF are absent. The patient had no exposures and no clinical evidence of connective tissue disease. The final diagnosis was idiopathic pulmonary fibrosis (IPF). No lung biopsy was performed, as a diagnosis was made based upon CT criteria alone.

TABLE 52-5 High-Resolution Computed Tomography Scanning Patterns

UIP	Probable UIP	Indeterminate for UIP	Alternative Diagnosis

Subpleural and basal predominant; distribution is often heterogeneous[a]
Honeycombing with or without peripheral traction bronchiectasis or bronchiolectasis[b]
	Subpleural and basal predominant; distribution is often heterogeneous
	Reticular pattern with peripheral traction bronchiectasis or bronchiolectasis
	May have mild GGO
		Subpleural and basal predominant
		Subtle reticulation; may have mild GGO or distortion ("early UIP pattern")
		CT features and/or distribution of lung fibrosis that do not suggest any specific etiology ("truly indeterminate for UIP")
			Findings suggestive of another diagnosis, including:
			• CT features:
			  • Cysts
			  • Marked mosaic attenuation
			  • Predominant GGO
			  • Profuse micronodules
			  • Centrilobular nodules
			  • Nodules
			  • Consolidation
			• Predominant distribution:
			  • Peribronchovascular
			  • Perilymphatic
			  • Upper or mid-lung
			• Other:
			  • Pleural plaques (consider asbestosis)
			  • Dilated esophagus (consider CTD)
			  • Distal clavicular erosions (consider RA)
			  • Extensive lymph node enlargement (consider other etiologies)
			  • Pleural effusions, pleural thickening (consider CTD/drugs)

Definition of abbreviations: CT, computed tomography; CTD, connective tissue disease; GGO, ground-glass opacities; RA, rheumatoid arthritis; UIP, usual interstitial pneumonia.

[a] *Variants of distribution: occasionally diffuse, may be asymmetrical.*

[b] *Superimposed CT features: mild GGO, reticular pattern, pulmonary ossification.*

Reproduced with permission from Raghu G, Remy-Jardin M, Myers JL, et al. Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med. 2018;198(5):e44–e68.

(Fig. 52-11) are often noted in connective tissue disease associated UIP (Table 52-6). In addition, HRCT features consistent with NSIP and OP overlap are suggestive of an underlying connective tissue disease such as the idiopathic inflammatory myopathies.[62]

Radiologic features of hypersensitivity pneumonitis vary based on the histopathologic stage of disease. Recent guidelines have focused on two patterns: fibrotic and non-fibrotic HP. Features highly suggestive of fibrotic HP can include a combination of fibrotic changes (reticulations, traction bronchiectasis, or honeycombing) in combination with airway-centered disease (Fig. 52-12). It is important to note that the distribution of radiologic findings in fibrotic HP is highly varied and can present as central, peripheral, apical, or basal-predominant disease. In contrast, nonfibrotic HP often presents with diffuse ground glass opacities, centrilobular nodules, and mosaic attenuation (Fig. 52-5).[5]

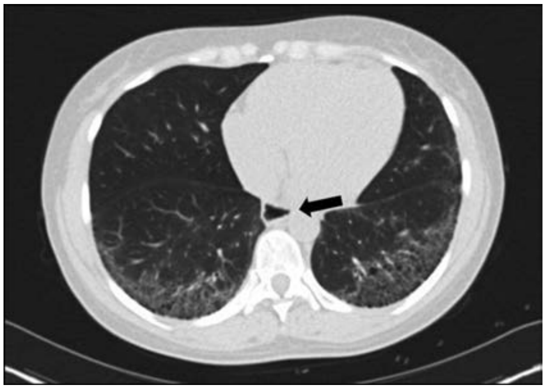

Figure 52-9 High-resolution CT image shows a dilated, air-filled esophagus *(arrow)* and bibasilar ground glass opacities suggesting fibrotic NSIP in a 47-year-old woman with systemic sclerosis.

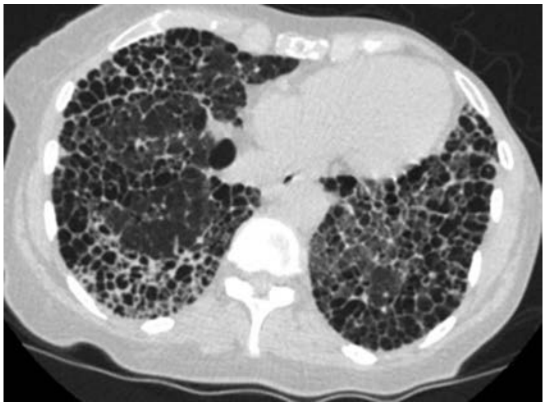

Figure 52-10 High-resolution CT images with bibasilar "exuberant honeycombing" in a 67-year-old woman with long-standing rheumatoid arthritis. Notice that honeycomb cysts constitute nearly all of the fibrotic regions of the lungs on this cross section.

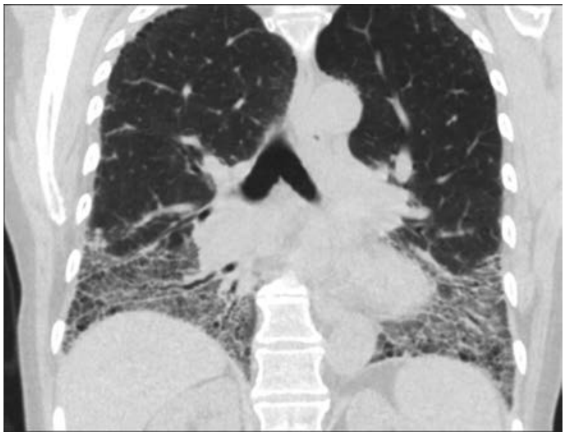

Figure 52-11 Coronal CT image from a 49-year-old woman with systemic sclerosis showing lower lobe–predominant reticular and ground glass changes with a sharp demarcation in the craniocaudal plane indicative of the "straight-edge sign."

TABLE 52-6 Radiographic Signs in ILD

Anterior upper lobe sign	Concentration of fibrosis within the anterior aspect of the upper lobes and concomitant lower lobe involvement	Suggests collagen vascular disease
Exuberant honeycombing	Honeycomb cyst formation within the lungs constituting >70% of fibrotic portions of lung	
Straight edge sign	Isolation of fibrosis to the lung bases with sharp demarcation in the craniocaudal plane without substantial extension along the lateral margins	
Three-density sign/ headcheese	Juxtaposition of lobular regions of low, normal, and high attenuation indicative of a mixed infiltrative and obstructive process	Suggests subacute hypersensitivity pneumonitis
Atoll sign/reverse halo	Central ground glass opacity surrounded by denser consolidation in the shape of a crescent or ring	Suggests cryptogenic organizing pneumonia
Galaxy sign	Mass-like lesion composed of coalescing granulomatous nodules more concentrated in the center than at the periphery	Suggests sarcoidosis

Data from Chung JH, Cox CW, Montner SM, et al. CT Features of the usual interstitial pneumonia pattern: differentiating connective tissue disease-associated interstitial lung disease from idiopathic pulmonary fibrosis. AJR Am J Roentgenol. 2018;210(2):307–313.

In patients with a smoking history, HRCT has led to clinical recognition of the simultaneous occurrence of emphysema and pulmonary fibrosis or combined pulmonary fibrosis and emphysema (CPFE) (Fig. 52-13). These patients are often noted to have an increased incidence of pulmonary hypertension. Chest imaging has also revealed an increased incidence of non–small-cell lung cancer in patients with fibrotic lung disease. Malignancy is often noted to arise in a peripheral distribution, developing in areas of honeycomb change or the border between fibrotic and nonfibrotic areas.[63]

LABORATORY TESTING

Routine laboratory testing, while often normal, may lead to the diagnosis of a previously unrecognized systemic disease, or may be suggestive of the underlying lung disease, particularly in the case of connective tissue disease.[64] More advanced testing is often necessary, including serologic testing for underlying connective tissue disease (Table 52-7). Many of the tests listed here are employed by ILD centers in the evaluation of patients newly presenting with diffuse lung disease, although no clear standard exists. Importantly, ILD can be the sole manifestation or the presenting feature of a connective tissue disease, making a careful evaluation for previously unrecognized autoimmune disease essential.

Most pulmonologists have encountered patients with idiopathic interstitial pneumonia as well as clinical features or serologic abnormalities that suggest, but are not diagnostic of, a connective tissue disease. In 2015, the ERS/ATS task force on undifferentiated forms of connective tissue disease–associated ILD suggested the nomenclature of interstitial pneumonia with autoimmune features (IPAF),

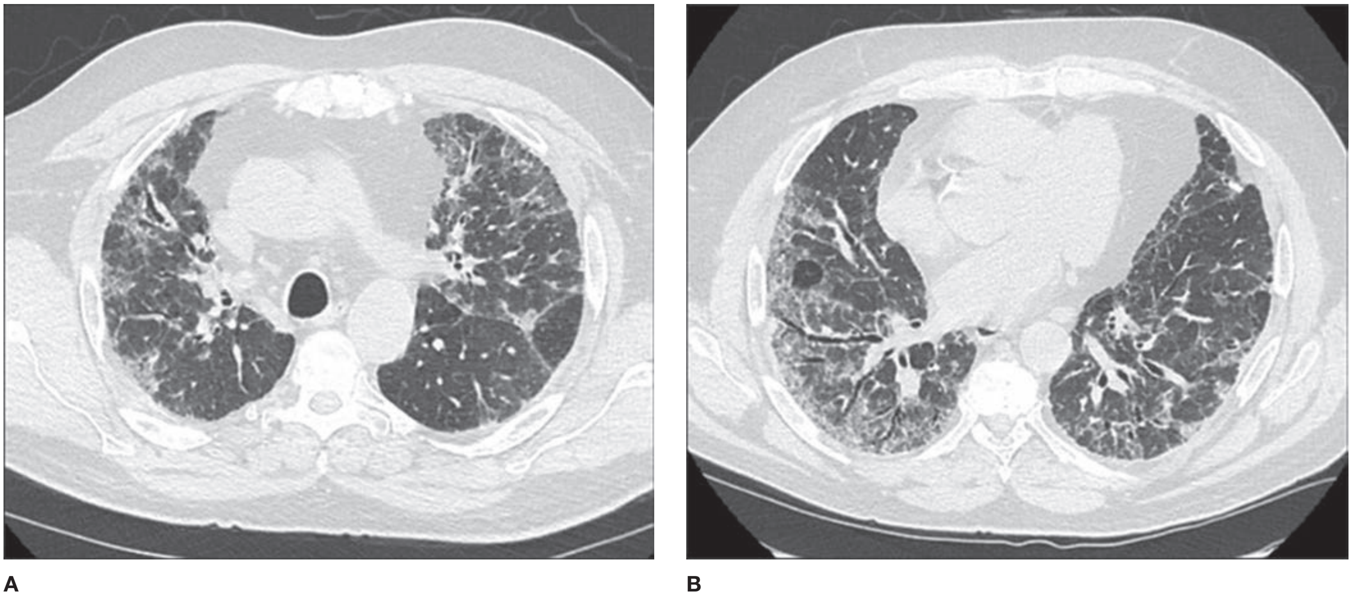

Figure 52-12 A 56-year-old woman presented with chronic cough and dyspnea on exertion. She suspected chronic mold exposure due to recurrent water damage in her basement. CT images through the mid-thorax (**A**) and lower thorax (**B**) reveal upper and lower lobe reticular changes with mild ground glass opacities. Traction bronchiectasis with both peripheral and peribronchovascular distribution is noted in the upper and lower lobes. Mosaicism is seen in the lower lobes. Pathologic findings of loosely formed granulomas along with clinical history and imaging findings are strongly suggestive of fibrotic hypersensitivity pneumonitis.

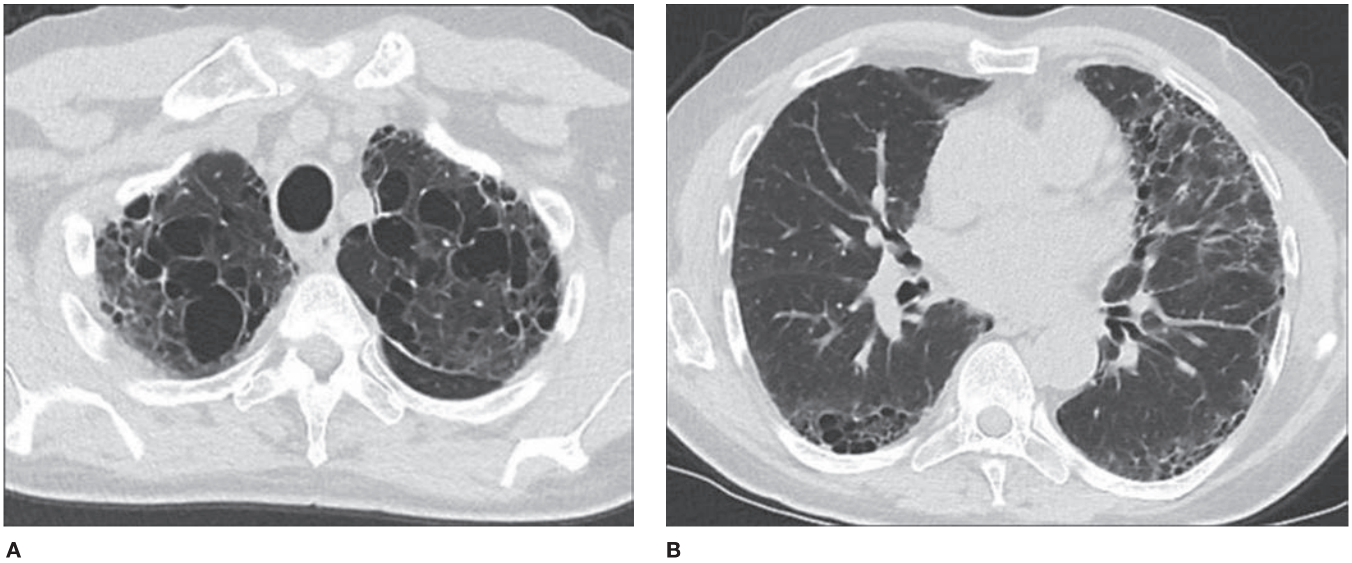

Figure 52-13 A 69-year-old former smoker with progressive dyspnea and a pattern of combined pulmonary fibrosis and emphysema (CPFE). High-resolution CT images at the level of the upper thorax (**A**) and lower thorax (**B**) show centrilobular emphysema in the upper lobes and bibasilar reticular changes with honeycombing. Pulmonary function testing revealed normal expiratory flow rates and lung volumes, but with a marked reduction in $D_{L_{CO}}$.

as well as a classification system. Patients with IPAF have ILD with no other etiology, do not meet criteria for a specific CTD, and have certain features of autoimmunity. Examples include physical examination findings of skin and joint abnormalities (inflammatory arthritis, mechanic's hands, Raynaud's phenomenon), positive autoimmune serologies, and HRCT or lung biopsy findings suggesting patterns frequently associated with CTD-ILD. It is important to note that this classification scheme is a research statement and specifically does not include guidelines on clinical care, diagnostic testing, or management of patients who meet criteria for IPAF.[65]

TABLE 52-7 Serologic Testing in ILD

Test	Disease
ANA	SLE, Scleroderma, MCTD
SSA/Anti-Ro	Sjögren syndrome, inflammatory myopathies
SSB/Anti-La	Sjögren syndrome
Myositis specific antibodies:	Inflammatory myopathies:
Jo-1, PL-7, PL-12, EJ, OJ, KS, MDA-5	Polymyositis
Myositis-associated antibodies:	Dermatomyositis
PM-Scl, Ro-52, Ku	Antisynthetase syndrome
Scl-70	Scleroderma
Anticentromere antibody	
RNA polymerase III	
Th/To	
PM/Scl 75	Myositis and scleroderma overlap
PM/Scl 100	
RF	Rheumatoid arthritis
CCP	
RNP	Mixed connective tissue disease
Antihistone antibody	
p-ANCA, c-ANCA	ANCA-associated vasculitis
Myeloperoxidase antibody	
Proteinase 3 antibody	

The importance of laboratory evaluation may also lie in the discovery of associated conditions, such as transaminitis or hypercalcemia in sarcoidosis,[66] or renal insufficiency in pulmonary renal syndromes and other connective tissue disease with renal involvement. Other examples include the presence of peripheral eosinophilia in chronic eosinophilic pneumonia, eosinophilic granulomatosis with polyangiitis, drug reaction, and other forms of vasculitis. Serum IgG testing against potential antigens associated with HP may result in further exploration of a causative agent in the patient's environment and strengthen a diagnosis of HP, but their role in routine ILD evaluation is still controversial and warrants further study.[5,67]

Anemia may worsen symptoms of dyspnea in the setting of ILD and may reflect an underlying hemolytic condition, or chronic gastrointestinal blood loss in inflammatory bowel disease. Elevated creatinine kinase and aldolase may indicate ongoing muscle damage from an idiopathic inflammatory myopathy. In addition to eliciting causes for the ILD, recognition of underlying chronic organ dysfunction will also help determine the ability of the patient to tolerate treatment.

PULMONARY FUNCTION TESTING

Pulmonary function tests (PFTs) are a mainstay in the pulmonologist's armamentarium in the evaluation and management of ILD. Importantly, they assist in assessing the severity of disease and help determine prognosis in many forms of disease.[68–70] PFTs are a relatively noninvasive method to gauge disease progression and measure response to therapy.[71] The testing typically includes spirometry, measurement of lung volumes, and diffusing capacity (Chapter 31). In certain cases, maximal inspiratory and expiratory pressures (MIPS and MEPS) are useful in the assessment of respiratory muscle strength, which may be compromised in myositis-associated ILD. Exercise testing, such as a 6-min walk test, is particularly important for patients with ILD as resting oxygenation does not reflect exertional oxygen requirements.

Typically, spirometry in most forms of ILD demonstrates a restrictive ventilatory defect due to decreased compliance and increased recoil of the lung parenchyma.[72] Forced vital capacity

(FVC) is a commonly used marker of lung function decline. It is the most commonly utilized outcome measure in clinical trials for IPF and other forms of fibrotic ILD.[73] The presence of obstruction suggests either concomitant obstructive lung disease, often from prior smoking exposure, or the presence of an airway-centered ILD such as LCH, LAM, or sarcoidosis. Decreased static lung volumes confirm the presence of restriction. In the case of airway centered diseases, the lung volume measurements may indicate unrecognized air trapping and hyperinflation. In cases of combined pulmonary fibrosis and emphysema, lung volumes may appear within normal range due to combined hyperinflation and restriction, but a markedly impaired diffusing capacity can be a clue to the true severity of the disease process.

Diffusion impairment, demonstrated by a decrement in the diffusion capacity (DL$_{CO}$), is frequently observed in ILD and is often the earliest physiologic abnormality.[74] The decreased DL$_{CO}$ reflects the presence of either fibrotic tissue or inflammatory cells (or both) in the interstitium, leading to a defect at the level of the alveolar-capillary membrane. The diffusion impairment is typically lower than predicted by alveolar volume.[72] An impairment in diffusion can also be seen with anemia and pulmonary hypertension, the latter of which should be suspected when there is a decline that cannot be explained by worsening ILD.

Both FVC and DL$_{CO}$ have been utilized in creating a staging system for IPF known as the GAP index. This score estimates mortality in years, based on patient gender, age and degree of physiologic impairment using FVC and DL$_{CO}$. The simplicity of this calculation allows for real time estimation of individual risk and change in clinical decision-making.[75] The addition of resting or exertional hypoxemia to this calculation improves 1-year mortality/transplantation prediction.[76]

Formal 6-min walk testing is quite useful, demonstrating oxygen requirements with exercise and additionally offering an assessment of exercise capacity in terms of distance walked, heart rate response, and causes for exercise discontinuation (including leg discomfort or chest pain). In addition to prognostication in IPF, it may predict prognosis in other forms of ILD as well.[77–79] If this is not available, measurement of pulse oximetry with ambulation in the clinic or with stair climbing can offer important information, including an understanding of reasons for the patient's dyspnea as well as a marker of disease severity.

BRONCHOSCOPY

Core elements in the bronchoscopic evaluation of ILD include bronchoalveolar lavage and transbronchial biopsy. More recently, transbronchial cryobiopsy has been added to the diagnostic armamentarium.

Bronchoalveolar Lavage

The simplest and least invasive assessment during bronchoscopy is the sampling of protein and cellular components of lung fluid via bronchoalveolar lavage (BAL). Tests typically performed on this fluid include cell count and differential, cytology, and a variety of viral assays and microbiologic cultures depending on the clinical scenario. In certain cases, gross inspection of fluid collected may lead to a diagnosis. For example, return of progressively bloody lavage specimens may suggest diffuse alveolar hemorrhage (DAH).[80] The presence of milky white BAL fluid with debris that settles out within 15 to 20 min would suggest a diagnosis of pulmonary alveolar proteinosis in the right clinical settings, confirmed by periodic acid-Schiff (PAS) staining.[81] BAL cellular analysis may be useful in narrowing the differential diagnosis of certain ILDs. Notably, an eosinophil differential count >25% is virtually diagnostic of acute or chronic eosinophilic pneumonia. A lymphocyte differential count >25% suggests granulomatous diseases (sarcoidosis, hypersensitivity pneumonitis, or chronic beryllium disease), NSIP, drug reaction, LIP, COP, or lymphoma.[80,82] Further investigation with flow cytometry can lead to diagnoses such as LCH and lymphoid malignancies, as well as allow characterization of T helper (CD4$^+$) and T suppressor (CD8$^+$) subsets. In the case of sarcoidosis, BAL lymphocytosis and a CD4$^+$/CD8$^+$ ratio greater than 4 may increase confidence in the diagnosis. Lymphocyte analysis may also play a role in distinguishing fibrotic HP from IPF and sarcoidosis, although specific lymphocyte count thresholds have not been established.[5]

Transbronchial Lung Biopsy

Bronchoscopy with transbronchial biopsy is a generally well-tolerated procedure than can be useful in the diagnosis of certain ILDs. The risk of pneumothorax is approximately 1% and significant bleeding less than 2%.[83,84] Biopsy forceps are introduced via the flexible bronchoscope, and tissue samples are obtained with fluoroscopic guidance. Multiple passes are made, with yield improving when more than four specimens are obtained.[85] Despite the relatively small size of these specimens as compared with cryobiopsy and surgical lung biopsy (see below), diagnostic information in certain forms of ILD are particularly amenable to diagnosis by bronchoscopy. This is especially true for granulomatous diseases such as sarcoidosis, hypersensitivity pneumonitis, and drug toxicity as well as in situations where non-ILD diagnoses are likely such as infection and malignancy.[86] The diagnosis of sarcoidosis is enhanced by the addition of endobronchial ultrasound (EBUS)-guided aspiration of mediastinal and hilar lymph nodes.[6] Newer technology such as genomic testing on transbronchial tissue specimens has been used to differentiate usual interstitial pneumonia from non-UIP when a surgical lung biopsy is not possible. The role of this biomarker in the diagnosis of fibrotic ILD is still in evolution but may play a role, particularly when the CT pattern is "indeterminate for UIP."[87,88]

Transbronchial Cryobiopsy

Transbronchial cryobiopsy is a bronchoscopic biopsy technique (Chapter 34) that can provide larger and better-preserved tissue samples compared with those obtained using traditional biopsy forceps. A cryoprobe, consisting of a long flexible insulated catheter with blunt metal tip, is advanced through the working channel of the bronchoscope into the peripheral lung. A compressed gas, such as CO_2, is released at a high flow rate into the tip of the probe, causing surrounding tissue to rapidly freeze and adhere to the cryoprobe tip. The bronchoscope and cryoprobe with attached frozen tissue are then removed en-bloc from the airway. Resulting biopsies tend to be 7 to 10 mm and notably lack crush artifact.[89]

Cryobiopsy appears to have a lower rate of mortality and acute exacerbation compared with surgical lung biopsy.[90] Several experts suggest biopsy of at least two different sites, which can be in the same lobe or different lobes. While this increases diagnostic yield, it is associated with a substantially higher risk of pneumothorax compared with cryobiopsy of one site. Comparison of transbronchial cryobiopsy and surgical lung biopsy tissue from ipsilateral lobes obtained from the same patient has shown good histopathologic agreement between the two biopsy modes, although the risk of mild to moderate airway bleeding from cryobiopsy is about 20%.[91] While some studies suggest an increase in diagnostic confidence with cryobiopsy, its role in the diagnosis of ILD is also in evolution and it is not yet a recommended part of society guidelines.[92,93]

SURGICAL LUNG BIOPSY

Despite a high yield in certain forms of lung disease, the utility of transbronchial biopsy for most of the idiopathic interstitial pneumonias (such as IPF, NSIP, and LIP) is low, and cryobiopsy may not be the preferred technique due to lack of expertise or unfavorable patient characteristics. In this case, a surgical biopsy is often

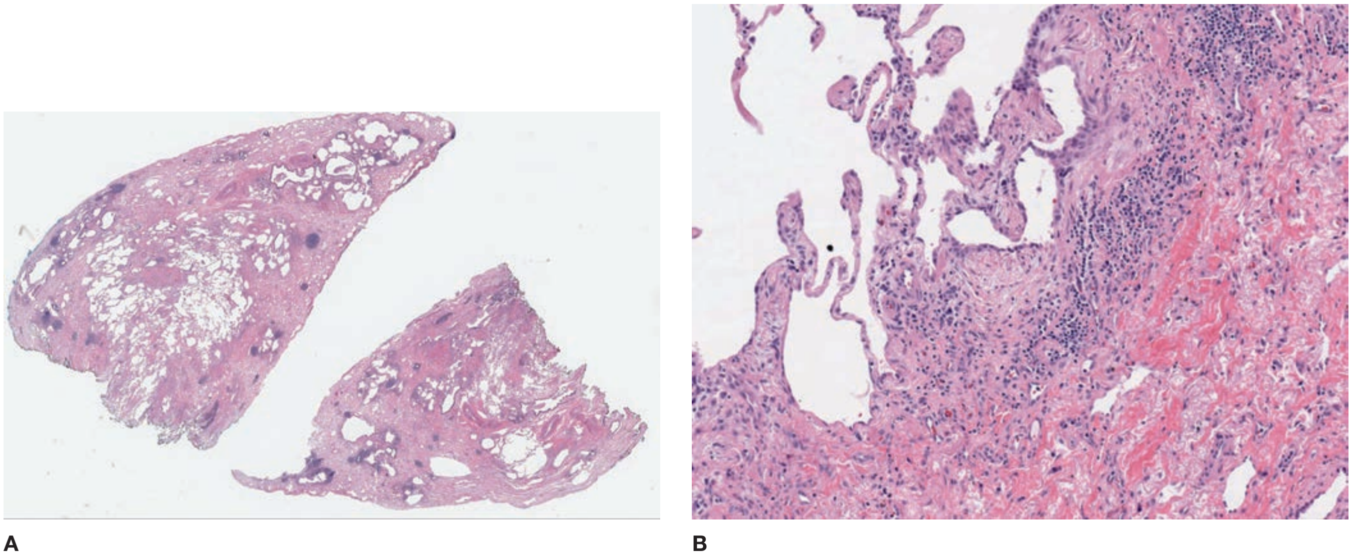

Figure 52-14 Usual interstitial pneumonia (UIP). There is heterogeneous fibrosis, which affects the periphery of the lung (**A**) when seen on low-power view. The fibroblastic foci (**B**) are the hallmark of the UIP pattern. *(Reproduced with permission from Robert Homer, MD, PhD, Yale School of Medicine.)*

required for accurate diagnosis, performed as video-assisted thoracoscopic surgery (VATS).[94]

VATS has a low morbidity and mortality in selected populations but should be performed by surgeons familiar with the techniques needed for ILD diagnosis.[95,96] Wedge biopsies are taken from three separate lobes and should include areas of normal-appearing lung; when only the most fibrotic appearing areas are sampled, specimens may not capture the active histologic pattern and show only nonspecific fibrosis. Risks of VATS include prolonged air leak, bleeding, infection, and incisional site pain.[97] Generally, the length of hospital stay after a VATS procedure is 2 to 3 days though some centers have reported even shorter stays in selected patients.[96]

For most patients, there is no significant loss of lung function; however, cases of acute exacerbation of ILD following biopsy have been reported.[97,98] Patients must be able to tolerate general anesthesia with single lung ventilation.[97] Risk factors for complications and mortality include advanced respiratory failure as indicated by high P_{CO_2} and/or severe hypoxemia, significant pulmonary hypertension, problems with clotting, and immunosuppression.[99–101] Patients older than 65 years of age have morbidity and mortality rates no different from younger patients, although those over 75 may have higher rates of air leak.[102,103] Preoperative cardiac evaluation should be considered since many patients undergoing biopsy for ILD are older or have a significant smoking history.[103]

PATHOLOGY

Several major pathologic patterns are described in the idiopathic interstitial pneumonias, including granulomatous ILD, UIP, NSIP, and organizing pneumonia. However, these same patterns may be observed in patients with systemic diseases and other causes for ILD, and therefore the pathology must be interpreted within the context of the clinical scenario and radiographic studies.

The UIP pattern is the histologic correlate of IPF and has specific features, including a heterogenous appearance in which areas of fibrosis and honeycombing are interspersed with areas of normal lung (Fig. 52-14). The changes are most pronounced in the periphery of the lung and should not predominantly involve the airways. Fibroblastic foci should be present and atypical features should be absent. The most recent guidelines offer categories in which the pathologist may interpret the pattern as "UIP," "probable UIP," "indeterminate for UIP," and "alternative diagnosis."[54] These, in combination with the HRCT and clinical features, will lead to a clinical diagnosis of IPF, "likely" IPF, non-IPF, and indeterminate for IPF. However, the clinical context must always be considered as a UIP pattern is not completely specific for IPF. For example, a patient with a prolonged history of bird exposure, whose HRCT demonstrates upper lobe predominance with lobular areas of air trapping, may have UIP on biopsy, but the final diagnosis will be chronic hypersensitivity pneumonitis. A patient with morning stiffness, deforming arthritis, high-titer anti-CCP antibodies, and UIP will be given a diagnosis of rheumatoid arthritis–associated ILD.

Nonspecific interstitial pneumonia (NSIP) is characterized by interstitial inflammation and fibrosis in a homogenous pattern, as opposed to the heterogeneity of UIP (Fig. 52-15). It may range

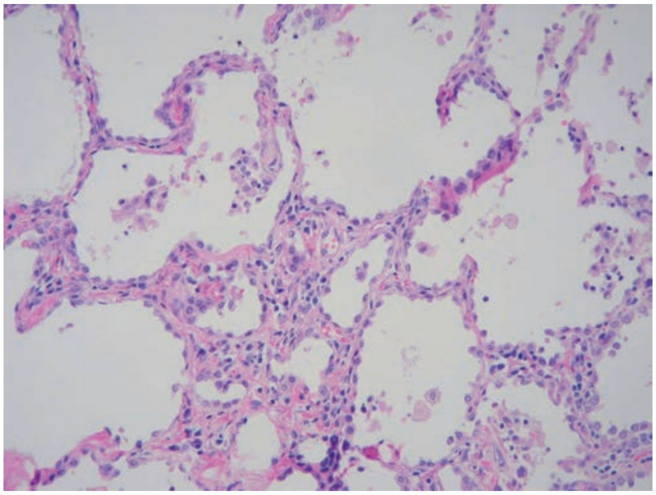

Figure 52-15 Nonspecific interstitial pneumonia (NSIP). There is diffuse, homogeneous septal fibrosis with a mild mononuclear infiltrate, as well as mild diffuse type II cell hypertrophy. No organizing pneumonitis, fibroblast foci, granulomas, or eosinophilic infiltrate are seen. Honeycombing is absent. There is a very mild accumulation of alveolar macrophages in the alveoli. *(Reproduced with permission from Robert Homer, MD, PhD, Yale School of Medicine.)*

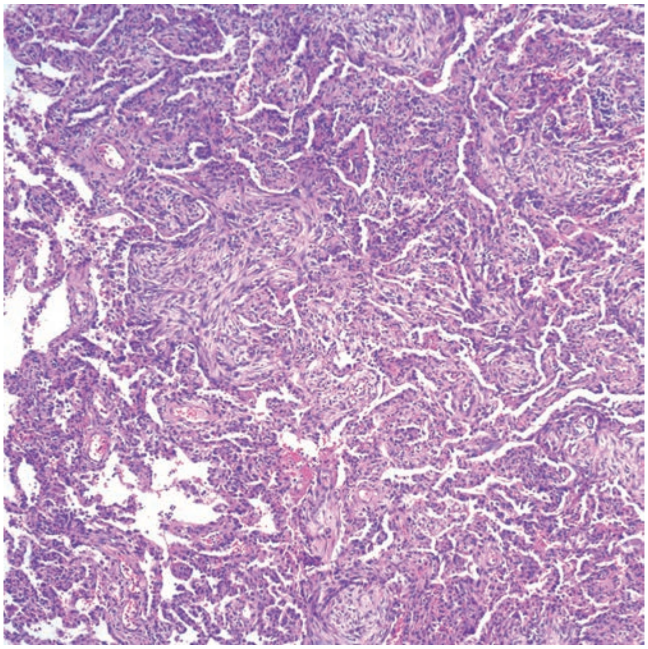

Figure 52-16 Organizing pneumonia (OP). There is fibromyxoid granulation tissue within alveolar ducts accompanied by a lymphoplasmacytic infiltrate. Notable is the absence of hyaline membranes, necrosis, neutrophilic or eosinophilic infiltrate, granulomas, and established fibrosis. *(Reproduced with permission from Robert Homer, MD, PhD, Yale School of Medicine.)*

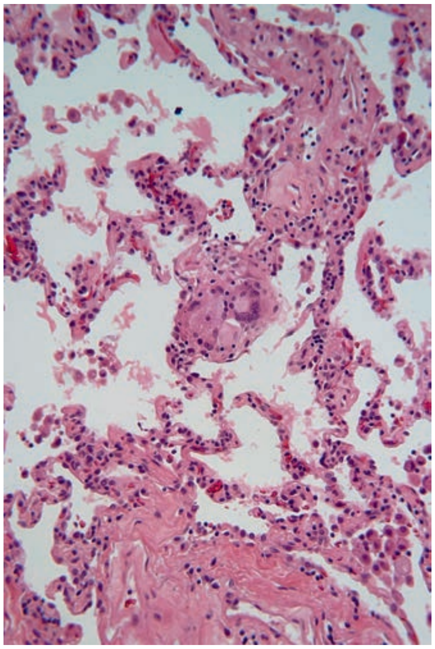

Figure 52-17 Hypersensitivity pneumonitis. There are loosely formed granulomas with background pneumonitis, including patchy lymphoplasmacytic infiltrate in the interstitium and organizing pneumonitis. *(Reproduced with permission from Robert Homer, MD, PhD, Yale School of Medicine.)*

from predominantly cellular to fibrotic in nature, with interstitial thickening but without significant honeycomb change.[104] While this pattern may be idiopathic, it is much more commonly associated with connective tissue disease; in this setting, the prognosis is better than that of idiopathic NSIP.[105] For example, a patient with a history of Raynaud's syndrome, skin thickening, esophageal dysmotility, SCL-70 antibody, and diffuse ground glass opacities on HRCT, and pathologic NSIP will be given a diagnosis of systemic sclerosis–related ILD, although biopsy would be unlikely to be indicated in this clinical scenario.

Organizing pneumonia is characterized histopathologically by intra-alveolar granulation tissue containing myofibroblasts and connective tissue (Fig. 52-16). The finding of organizing pneumonia on histopathology should prompt an exhaustive search for a cause before being called cryptogenic organizing pneumonia (COP), which is truly idiopathic. For example, a patient with peripheral alveolar opacities on chest imaging and features of OP on biopsy who is found to have taken chronic nitrofurantoin as suppressive therapy for urinary tract infections may be suffering from drug toxicity. Likewise, a patient with OP who has muscle weakness, papular lesions on the hands, and heliotrope rash likely carries a diagnosis of dermatomyositis.

Granulomatous histology may be observed in idiopathic disease, such as sarcoidosis, but it may be present in many other forms of ILD, including drug toxicity and hypersensitivity pneumonitis[106] (Fig. 52-17). In addition to ILD, the possibility of diffuse infections, including mycobacterial disease, must always be kept in mind. The morphology and location of the granulomas, as well as the appearance of the surrounding tissue, must be considered in combination with clinical features.[107] For example, a history of beryllium exposure in combination with sarcoidal granulomas on pathology will change the diagnosis from sarcoidosis to chronic beryllium disease. A patient with diffuse centrilobular ground glass nodules, a history of humidifier use, and loosely formed granulomas on histology most likely carries a diagnosis of subacute hypersensitivity pneumonitis.

THE ROLE OF MULTIDISCIPLINARY DISCUSSION

The diagnosis of interstitial lung disease is often an iterative process. A comprehensive approach including the clinical history, laboratory testing, and radiographic appearance can help assess if pathologic information is needed for accurate diagnosis. In cases of underlying connective tissue disease or a temporally correlated drug or environmental exposure, pathologic tissue may not change management and may not be worth the operative risk. Similarly, specific features on HRCT are highly predictive of the histopathologic finding of UIP by experienced observers and can spare many patients a surgical biopsy in the correct clinical setting.[54]

It has been demonstrated that the final diagnosis will often change after a group discussion involving clinicians, radiologists, and pathologists better known as multidisciplinary discussion (MDD).[108] The diagnosis also frequently differs between academic and community-based physicians, with academic physicians being less likely to arrive at a diagnosis of IPF.[109] In addition to providing a new diagnosis in a significant proportion of cases, MDD may be particularly valuable in management decisions for non-IPF ILD.[110] Remote MDD may be an option in some cases.[111]

TREATMENT

Approach to treatment includes general and specific measures, as discussed below.

■ Removal from Exposures

The treatment of ILD varies with the specific diagnosis. Importantly, if any causative exposure can be identified, this should be eliminated. For example, if a drug reaction is suspected, that drug should be discontinued. For environmental exposures, the situation may require more extensive remediation.[112] For example, in addition to removal of birds from the home, extensive cleaning of upholstery, window coverings, and ventilation systems may be required. The cleaning should not be performed by the patient. Even these measures may not remove all residual antigen, and removal of the patient from the location may be necessary.[113] In the case of extensive water damage and mold growth, significant demolition and reconstruction may be necessary. In the case of occupational exposures, some situations may be addressed by altering the particular job being done by the patient, changing the substances used, or using protective respiratory equipment, but others may require complete removal from the suspected exposure.[114] In many cases, patients' livelihoods may be at stake, involving severe financial consequences, disability, and workers' compensation. Identification of a workplace hazard for a patient may lead to the discovery of a public health issue or one that affects the health of coworkers.[115] Referral to and coordination with an occupational medicine specialist may be necessary to appropriately assess and remediate home and workplace exposures.[27]

■ Immunosuppressive Therapy

Some forms of ILD, including COP, connective tissue disease–associated ILD, and sarcoidosis, may demonstrate a favorable response to corticosteroids and other immunosuppressive agents.[116] However, in diseases such as IPF, immunosuppression has been demonstrated to carry harm without potential benefit.[117] When considering the use of these drugs, an assessment should be made regarding the likelihood of response as well as the relative risks and benefits of the therapy.

The many side effects of corticosteroids include glucose intolerance, bone loss, cataract development, and mood instability.[118] Increased risk of infection may be substantial.[119] Some inflammatory diseases such as COP, CEP, and subacute hypersensitivity pneumonitis can be quite sensitive to corticosteroids; relatively quick weaning to low dosages may be feasible and effective. In disorders such as connective tissue disease–associated ILD, when a more prolonged course of therapy is anticipated, the early addition of steroid-sparing medications, such as azathioprine or mycophenolate mofetil, can permit lower doses of corticosteroids to be used.[120] High doses of steroids have been implicated in renal crisis and should be avoided in patients with scleroderma.[121] Certain forms of ILD, including scleroderma lung disease, vasculitis with alveolar hemorrhage, and severe cases of connective tissue disease–associated ILD, may require drugs such as rituximab and cyclophosphamide, the latter of which carries increased risk for severe side effects and infertility. Such medications should only be prescribed by practitioners familiar with use and toxicities of these agents.

When actively treating ILD, objective measures of improvement, including PFTs, exercise oximetry, and chest radiography should be employed to avoid the unnecessary continuation of therapy. In particular, when corticosteroids are used, there is often an initial boost in mood and energy level that may not correspond to actual improvements in lung function. If no clinical improvement is seen after 3 to 6 months of therapy, change or discontinuation of immunosuppressive therapy should be strongly considered.

■ Antifibrotic Drugs

Clinical trials have resulted in FDA approval of two antifibrotic drugs, aimed at slowing decline in lung function from progressive fibrotic lung diseases. Pirfenidone, a small molecule drug with antifibrotic properties, is approved for the treatment of IPF in the United States as well as around the world.[122] Nintedanib, which is a tyrosine kinase inhibitor against fibroblast growth factor receptor (FGF-R), vascular endothelial growth factor receptor (VEGF-R), and platelet-derived growth factor receptor (PDGF-R), has been shown to slow the decline in lung function in IPF, scleroderma-associated ILD, and progressive fibrotic lung disease and is approved in the United States for the treatment of all.[123–125] In some situations, for example in scleroderma, patients may be treated with both immunosuppressive and antifibrotic medications.[120]

■ Future Therapeutics

There are multiple phase 3 clinical trials underway to assess the efficacy of novel agents for the treatment of IPF. PRM-151, a recombinant form of human pentraxin 2 protein, inhibits the differentiation of monocyte-derived fibrocytes, promotes the formation of immunoregulatory macrophages, and inhibits neutrophil adhesion to extracellular matrix proteins. Phase 2 clinical trial data have suggested a slowing of decline in lung function in combination with standard of care therapies when compared with standard of care alone.[126] Pamrevlumab (FG-3019) is an antibody that binds to connective tissue growth factor and inactivates it. Phase 2 trial data suggest that infusion therapy with this treatment attenuates the progression of IPF, and advanced clinical trials are currently underway.[127] Many other promising agents are being studied. Future therapeutic strategies may seek to inhibit multiple pathways simultaneously via combination therapy.

■ Supportive Therapy

Supportive therapy directed at improving quality of life and decreasing respiratory symptoms should be a part of the approach to care of all patients with ILD. Formal exercise testing in the PFT laboratory offers a standardized approach to the assessment of oxygen needs. However, a check of oximetry with simple ambulation in the hallway or with stair climbing can uncover the need for oxygen supplementation. Hypoxemia with oxygen saturation less than or equal to 88% at rest is an indication for long-term oxygen therapy for at least 15 hours a day.[128] Portable oxygen tanks and battery-powered portable oxygen concentrators are often prescribed for ILD patients with exertional hypoxemia to encourage mobility. Collaboration among physicians, patients, and oxygen providers can help identify the ideal system for each patient. Future randomized controlled trials assessing the impact of oxygen therapy in fibrotic ILD patients are underway.[129]

The role of pulmonary rehabilitation has been studied in chronic obstructive lung disease and leads to increased muscle strength and improved endurance.[130] Similar improvements may be evident in the fibrotic lung diseases.[131,132] In addition to the potential benefits of improved muscle strength and stamina, patients with ILD may also benefit from the ongoing education regarding oxygen use, breathing and pacing techniques, and social support.[133] As patients with chronic lung disease frequently suffer from anxiety and depression, pulmonary rehabilitation may benefit patients by identifying these issues, leading to appropriate specialist referrals.[134] Questionnaires that specifically assess health-related quality of life in ILD patients include the Living with IPF (L-IPF) questionnaire and the King's Brief Interstitial Lung Disease (KBILD) questionnaire.[135,136]

■ Treatment of Comorbidities

Several common comorbidities should be sought among patients with ILD. In particular, an assessment for underlying coronary artery disease should be undertaken when dyspnea on exertion is present, as the risk for ischemic heart disease is increased among patients with IPF.[137,138] Due in part to prior tobacco exposure, patients with progressive fibrotic lung disease have an increased risk of developing lung cancer.[139] Nodules should be individually assessed based on size, appearance, and growth. No specific screening recommendations for this patient population exist apart from those based on smoking history. The prevalence of obstructive sleep apnea appears to be quite high among patients with ILD, even in the absence of excessive sleepiness or large body habitus, although these features are important to assess.[140–142] There is a high prevalence of gastroesophageal reflux (GERD) among patients with IPF, although only a minority have symptoms.[143,144] Studies have suggested that GERD may be intimately involved in the pathogenesis of IPF and may be linked with progression of disease.[145] The evaluation and treatment of GERD in patients with ILD is an evolving field. Based on existing data, it is not clear how aggressive therapy should be. If symptoms such as heartburn, regurgitation, or severe cough exist, therapy is typically utilized. However, whether to seek evidence of asymptomatic GERD through more invasive testing and whether to treat such patients is not clear.[139]

In addition to native comorbidities, side effects from therapy should be assessed. In particular, the use of corticosteroids can lead to weight gain, fluid retention, diabetes, and osteoporosis. Glucocorticoid-induced osteoporosis may be prevented by the use of calcium and vitamin D supplementation early in the course of steroid use.[146] Fracture risk assessment can identify patients in whom bisphosphonate therapy is indicated.

Pulmonary hypertension develops in a significant number of patients with ILD and may be due to the effects of chronic hypoxia and the focal destruction of capillaries in the fibrotic lung tissue.[147] This is classified by the World Health Organization as group 3 pulmonary hypertension. Pulmonary hypertension contributes to progressive diffusion impairment and may contribute to progressive respiratory failure. It is important to ensure that no other cause for the pulmonary hypertension can be identified. For example, a concomitant pulmonary arterial vasculopathy, such as seen in scleroderma or MCTD, should be sought, as specific therapy for the pulmonary arterial hypertension may be indicated in those circumstances.[148] In addition, common causes of pulmonary hypertension such as left-sided systolic or diastolic cardiac dysfunction may be present.[149] Right heart catheterization can distinguish between the various etiologies of pulmonary hypertension and is often required, as echocardiogram has limited sensitivity and specificity in this population.[147] Treatment with systemic pulmonary vasodilators has been controversial, as there is concern that such agents could worsen ventilation–perfusion matching in patients with group 3 pulmonary hypertension. However, a study assessing the inhaled vasodilator treprostinil found improvement in exercise capacity and no clinical worsening in the group that received inhaled treprostinil.[150]

■ Palliative Care

Symptom control is particularly important for patients with all stages of ILD. Pulmonary rehabilitation is encouraged to improve dyspnea in all symptomatic patients. The breathlessness due to advanced ILD may be treated with oxygen supplementation, low-dose opiates, and anxiolytics.[151] Chronic cough can be a debilitating symptom leading to social isolation, difficulty sleeping, and musculoskeletal pain. Low-dose opiates, oral corticosteroids, and more recently, neuromodulators such as pregabalin and gabapentin have been used with promising results.[152] Thalidomide also has been studied for the treatment of chronic cough in IPF with positive results, but widespread use is limited by side effect profile.[153] Evaluation for acid and nonacid reflux should be considered whenever intractable cough persists. In patients with advanced restrictive lung disease leading to hypercapnia, home noninvasive ventilation may be considered.

Palliative care services and hospice referral are appropriate for patients with advanced ILD to maintain a focus on the physical, psychological, and spiritual needs of both patients and their families.[154] Prognosis in ILD may be uncertain, depending upon the specific diagnosis, severity of disease, and trajectory of disease already demonstrated. Particularly in IPF, the likelihood of either progressive respiratory failure or acute decline due to exacerbation should be discussed. End-of-life discussions and advanced directives regarding mechanical ventilation should be broached.[154]

■ Lung Transplantation

Although lung transplantation (Chapter 106) has significant morbidity and mortality, it is an important and potentially life-extending alternative for patients with progressive fibrotic lung disease. Most patients with ILD referred for lung transplantation have IPF, and for those with advanced disease, survival after lung transplantation is superior to the natural history of their disease. Patients must have a strong social support system as well as the emotional and physical ability to tolerate a complex medical regimen of immunosuppressive therapy.[155]

The timing of listing is complicated in ILD, since the rate of progression is difficult to predict, and abrupt exacerbation of disease may occur. Patients who have undergone a complex workup at a lung transplantation center are assigned a lung allocation score, which is a numerical score that can be used to estimate each subjects' medical urgency and expected posttransplant survival rate relative to other patients on the waiting list for a lung transplant.[156,157] In general, a severely impaired $\mathrm{DL_{CO}}$ (<39%), continuous supplemental oxygen use, and advanced fibrosis on HRCT predict poor survival and are considered to be triggers for active listing.[76] Early referral to a lung transplant center is useful, as it allows full evaluation and education earlier in the disease course, as well as optimization of comorbidities.[158]

Advances in procedures such as ex vivo lung perfusion (EVLP), in which a pair of lungs is maintained outside the body so that a transplant team may thoroughly determine their viability, has allowed more subjects on the transplant wait list to receive organs.[159] Similarly, the use of extracorporeal membrane oxygenation (ECMO) for cardiopulmonary support has served as a bridge to transplantation in select patients with respiratory failure awaiting lung transplantation.[160,161]

CONCLUSION

The approach to ILD includes a careful history and physical examination, with a focus on identifying an etiology for the ILD. Important considerations include a complete investigation of environmental, occupational, and drug exposures as well as a thorough search for underlying connective tissue disease. Laboratory tests, pulmonary physiologic studies, radiography, and biopsy of lung tissue may be necessary. Multidisciplinary review is an essential part of the diagnostic evaluation. Decisions regarding diagnostic and therapeutic approach must be individualized.

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CHAPTER 53

Systemic Sarcoidosis

Edward S. Chen

INTRODUCTION

Sarcoidosis is a systemic disorder characterized by noncaseating granulomatous inflammation at sites of disease.[1] Although any organ can be involved, the disease most commonly affects the lungs and intrathoracic lymph nodes. A diagnosis of sarcoidosis is most securely established by a compatible clinical presentation and laboratory and radiographic abnormalities, and is confirmed by a biopsy showing noncaseating epithelioid granulomas in more than one organ plus the exclusion of granulomatous disorders of known cause.[2] The disease results from the combined effects of genetic susceptibility and environmental exposures.[3] Disease-specific immune responses contribute to the nonnecrotizing granulomatous inflammation identified as sarcoidosis. The clinical course is highly variable according to clinical presentation and demographic features.[4] Corticosteroids remain the mainstay of treatment for patients with threatened organ failure or progressive disease. Long-term management must include a careful review of systems to identify symptoms that are not due to direct damage to tissues and organs and require alternative treatment strategies.

HISTORICAL PERSPECTIVE

The first descriptions of sarcoidosis originated in the late 1800s (Table 53-1). A series of letters and reports from Drs. Jonathan Hutchinson and Carl W. Boeck described patients who had characteristic skin lesions on their face and extremities, often referred to as Mortimer's malady, named after one of Hutchinson's patients. Several years later, Caesar Boeck (nephew of C.W. Boeck) recognized that these patients often had evidence of disease in multiple organs, such as regional lymph nodes in the neck and axilla, nasal and sinus passages, lung, and bones. The routine practice of biopsies and histopathology in the late 1800s confirmed the heterogeneity of sarcoidosis, causing granulomatous inflammation in different organs in different patients. The advent of radiography established that sarcoidosis most commonly affects the lungs.

The etiology of sarcoidosis has been ascribed to other diseases of contemporary historic interest due to overlapping clinical and histologic features. Cutaneous sarcoidosis was initially hypothesized to be a variant of lupus erythematosus, but later it was considered to be a variant of tuberculosis. Ansgar Kveim confirmed previous results reported by Williams and Nickerson, that an extract from sarcoidosis biopsy tissues caused granulomas to form 4 to 6 weeks following an intradermal injection in sarcoidosis patients.[5,6] The specificity of the Kveim reaction was evaluated by a large international case series summarized by Louis Siltzbach, in which >80% of sarcoidosis demonstrated a positive Kveim skin test, compared with <5% of patients with tuberculosis.[7] The challenges related to maintaining batch-to-batch consistency of Kveim reagent, and biosafety concerns related to the use of an extract from diseased tissues, abrogated the widespread operationalization of the Kveim skin test as a diagnostic tool.[8] More recently, the tools of cell and molecular biology have advanced our understanding of the immunologic, genetic, and etiologic basis of sarcoidosis but have not yet led to breakthroughs in the development of safe, effective therapies or cure.[3]

TABLE 53-1 Historic Sarcoidosis Discoveries and Eponyms

Descriptions of sarcoidosis by Jonathan Hutcherson (England) and Carl W. Beck (Norway) (late 1800s)	A series of letters described patients with a disease that caused characteristic skin lesions, often referred to as Mortimer's malady
Cutaneous sarcoidosis frequently presents with characteristic skin lesions on the face and scalp (1888)	Ernest Besnier (France) popularized "lupus pernio" as violaceous skin lesions of the nose, ear lobes, face, and scalp (initially hypothesized to be a variant of lupus erythematosus)
Sarcoidosis is a systemic disease—Caesar Boeck (Norway) and Jorgen Schaumann (Sweden) (early 1900s)	Advances in medical science usher the routine practice of obtaining biopsies and histopathology, characterize sarcoidosis as a systemic disease: granulomatous inflammation in the skin, lungs, eyes, bone, lymph nodes and spleen (hypothesized to be a variant of tuberculosis)
A causative agent for sarcoidosis is identified in diseased tissues	An extract prepared from sarcoidosis tissues results in granulomatous inflammation when injected into the skin of patients with sarcoidosis—Drs. Williams and Nickerson (United States, 1935) and Ansgar Kveim (Norway, 1941).
The Kveim reaction (positive skin test response) is specific to sarcoidosis	A large international case series using a standardized preparation of sarcoidosis spleen extracts demonstrates that a positive Kveim skin test is highly specific for sarcoidosis (>80% in sarcoidosis; <5% in tuberculosis); (Louis Siltzbach, 1960s)
Sarcoidosis frequently can present as an acute febrile illness, often with a good prognosis	First described in the early 1900s by Christian Heerfordt (Denmark) as a constellation of parotitis, fever, facial nerve palsy, and uveitis and later associated with sarcoidosis in the 1930's by Jan Waldenström (Sweden), now referred to as Heerfordt-Waldenström syndrome. Patients who initially present with bilateral hilar adenopathy, fever, polyarthritis, and erythema nodosum often can experience disease remission, later referred to as Löfgren syndrome (Sven Löfgren; 1940s).
Radiographic staging of pulmonary sarcoidosis	A system to categorize sarcoidosis chest x-ray findings proposed by Karl Wurm (Germany) and James Scadding (England) (1950s)
Pulmonary sarcoidosis results in granulomatous inflammation associated with a CD4+ lymphocytic alveolitis and expression of proinflammatory cytokines interferon γ (IFN-γ) and tumor necrosis factor (TNF)	Advances in medical science helped define the basic immunologic characteristics of sarcoidosis: granulomatous inflammation compartmentalized to the lung with heightened presence of CD4+ helper T lymphocytes (Th), increased expression of the Th1 cytokines IFN-γ and TNF

TABLE 53-2 Sarcoidosis Epidemiology and Genetic Associations

Sarcoidosis is found worldwide.
Worldwide, highest prevalence reported in Scandinavia; in the United States, highest prevalence in southeast coastal areas.
The peak age of onset is in middle-aged adults (40–55 years old), possibly bimodal (younger males vs. older females).
In the United States, the increased frequency and higher mortality are observed in Black Americans.
Higher prevalence among first-degree relatives of sarcoidosis probands and twin siblings.
The frequency of lupus pernio, Löfgren syndrome, cardiac involvement, and other clinical sarcoidosis manifestations is associated with race, ethnicity, and gender, supporting a genetic basis for this disease.
Genetic polymorphisms have been linked to disease risk and clinical phenotype, with the strongest associations identified within the HLA genes of the major histocompatibility complex (MHC) locus.

EPIDEMIOLOGY

Sarcoidosis is found worldwide, although accurate measurements of disease frequency are unknown because many people with sarcoidosis are asymptomatic, and there are neither sensitive nor specific diagnostic tests (Table 53-2). Traditionally, sarcoidosis was thought to have a peak onset during young adulthood. However, recent studies support that the peak age of onset ranges from 40 to 55 years old.[9] A longitudinal study from Japan found that the age at time of diagnosis steadily rose over their 40-year study period.[10] Although sarcoidosis was regarded a rare disease by some authorities,[11] the lifetime risk for developing sarcoidosis reported by developed countries is estimated to range from 1% to 3%. Based on autopsy studies, the prevalence of sarcoidosis is likely underestimated.

Recently, an actuarial study of a U.S. health insurance medial claims database reported the annual age-adjusted incidence was higher in Black Americans (17.8 cases per 100,000 per year) compared with white Americans (8.1 per 100,000),[12] and similar incidence rates have been reported by other countries in Europe, Asia, and Africa. A recent study using data from the Swedish National Patient Registry reported a prevalence of 160 sarcoidosis cases per 100,000 population.[13] Ireland and Italy are among several countries that have reported higher prevalence and geographic clustering of cases, implicating a contribution by environmental factors.[14,15] In the United States, the prevalence of sarcoidosis is highest in coastal areas of the southeastern states.[16]

The frequency of different clinical manifestations and outcomes of sarcoidosis also varies among geographic regions and ethnic groups and is influenced by gender. The prevalence of sarcoidosis in Sweden was reported to be higher in males than in females (179 vs. 141 cases per 100,000 population), and the incidence was higher in males with a lower median age at time of diagnosis (males 44.9 years vs. females 54 years).[13] Several studies report that women are diagnosed with sarcoidosis at an older age than men and the age distribution may be bimodal in some populations.[10,17,18] The results from two U.S. actuarial studies found that the risk for developing sarcoidosis is highest in Black American women compared with white American women or Black American men.[12,19] Additional studies of sarcoidosis in Black American women found that average annual incidence rate increased with age.[20,21]

Outcomes in sarcoidosis ascribed to race and gender may be influenced by other factors, including socioeconomic status, negatively affecting health care security due to disparities in health care access, trust in the medical care system, and adherence to therapy.[22,23] Future studies are needed to dissect the relative impact on these disparities on outcomes in sarcoidosis.

Whether a diagnosis of sarcoidosis is associated with increased mortality remains uncertain and may depend on the presence of comorbidities.[24] The presence of lung fibrosis, pulmonary hypertension, and older age have been associated with risk of mortality in patients with pulmonary sarcoidosis.[25,26] A recent study of a U.S. death certificate registry found that deaths attributed to sarcoidosis were significantly higher among Black Americans compared to white Americans.[27] A study of the Swedish National Patient Registry found that patients requiring treatment for sarcoidosis at the time of diagnosis had a twofold increased risk of death.[28] A recent U.S. cohort study found that sarcoidosis patients had higher rates of hospitalization compared with matched controls,[29] and a Swiss evaluation of a national healthcare database found that hospitalized sarcoidosis patients had significantly worse outcomes compared with matched controls, with longer length of stay and higher rates of in-hospital mortality and rehospitalization.[30] Taken together, sarcoidosis case rates and mortality appear to be rising, but prospective studies will be needed to determine if this is due to improved data collection or changes in risk factors or patient comorbidities.

GENETICS

Family and case-control studies provide strong evidence for a genetic influence on the risk of developing sarcoidosis and in determining clinical expression of the disease. Familial clustering of sarcoidosis has been estimated to involve 10% of cases, with a greater frequency among Black compared with white populations. The U.S. ACCESS (A Case Control Etiologic Study of Sarcoidosis) study found a higher relative risk of identifying sarcoidosis among siblings (odds ratio [OR], 5.8) or parents (OR, 3.8) of a sarcoidosis proband compared with that of the general population,[31] an observation supported by studies of twins.[32] The adjusted familial relative risk was estimated to be higher among whites in both the U.S. ACCESS study (relative risk [RR], ∼18) and in a U.K. study with mostly whites (RR, ∼36–73) and Blacks (RR, ∼2.8). Erythema nodosum is common in Scandinavian countries and Ireland but found in less than 5% of Black or Japanese patients. In contrast, lupus pernio appears more frequently among Black populations. In Japan, more than 50% of patients may have cardiac sarcoidosis.[17]

Genomic studies over the last two decades have provided insights into sarcoidosis disease presentation and prognosis.[33] Early studies using serologic and candidate gene techniques identified linkage disequilibrium with human leukocyte antigen (HLA) alleles. However, analyses using more advanced techniques have identified other genetic associations, most commonly with HLA class II and non-HLA genes within the major histocompatibility complex (MHC). The most notable example is the close association between HLA-DRB1*0301 (HLA-DR3), Löfgren syndrome, and disease resolution in northern European patients.[34] However, the results from analyses of non-Löfgren clinical presentations have been more variegated, identifying associations with both HLA class II and non-HLA genes within the major histocompatibility complex (MHC), as well as genes without known immunologic function.

More recently, multidisciplinary approaches to combine genomic and epidemiologic analyses have begun to shed light on how genetic factors modify risk for developing sarcoidosis associated with exposures such as cigarette smoke and insecticides.[35,36] The application of newer analytic techniques such as epigenetics, whole genome sequencing, and high-throughput computational methods for comparison of multimodal data (clinical, epidemiologic, proteomic, metabolomic) may help resolve the complex impact of genetic sarcoidosis risk factors.[37] The U.S. multicenter GRADS

TABLE 53-3 Sarcoidosis Immunopathology and Etiology

Sarcoidosis is identified by the presence of discrete, noncaseating, epithelioid granuloma.
Active sarcoidosis inflammation requires the presence of activated CD4+ T lymphocytes and is associated with local expression of the cytokines IFN-γ and TNF. • Potential contribution of Th17 immune responses • Reduced regulatory T-cell function
The oligoclonal expansion of αβ+ T cells compartmentalized to sites of disease is consistent with antigen-driven inflammation.
The utility of antifibrotic therapies for fibrotic sarcoidosis remains undefined.
Epidemiologic studies support positive (e.g., insecticides) and negative (e.g., cigarette smoke) environmental risk factors for developing sarcoidosis.
Certain classes of microbes (mycobacterial or propionibacterial organisms most implicated) are hypothesized to trigger sarcoidosis in genetically susceptible individuals, supporting a role for gene–environment interactions for the development of this disease. • Potential interactions with host microbiome
Serum amyloid A disaggregation within granulomas provides a mechanism for chronic disease.

study (Genomic Research in Alpha-1 Antitrypsin Deficiency and Sarcoidosis) represents the first large-scale integrative analysis of molecular, clinical, and environmental data in sarcoidosis patients.[38] A recent genome-wide transcriptome analysis of sarcoidosis BAL cells revealed genetic profiles that underscored associations between identified pathways known to be involved in sarcoidosis with pertinent sarcoidosis clinical features (Th1 and Th17 pathways with hilar lymphadenopathy, TGF-β and mTOR with parenchymal involvement, and IL7 + IL2 with airway involvement).[39]

PATHOGENESIS

Below we review key elements in the pathology and pathogenesis of sarcoidosis.

Histopathology

The pathologic hallmark of sarcoidosis is the presence of discrete, noncaseating, epithelioid cell granulomas (Table 53-3). The dominant cell in the central core is the epithelioid cell, thought to be a differentiated form of a mononuclear phagocyte (Fig. 53-1). CD4 lymphocytes and mature macrophages are typically interspersed throughout the epithelioid core, whereas both CD4+ and CD8+ T cells and B lymphocytes may be seen in the periphery of the granuloma. Occasionally, focal fibrinoid necrosis may be seen; necrosis should not be a dominant feature, and the presence of caseating necrosis must prompt an evaluation to exclude alternative

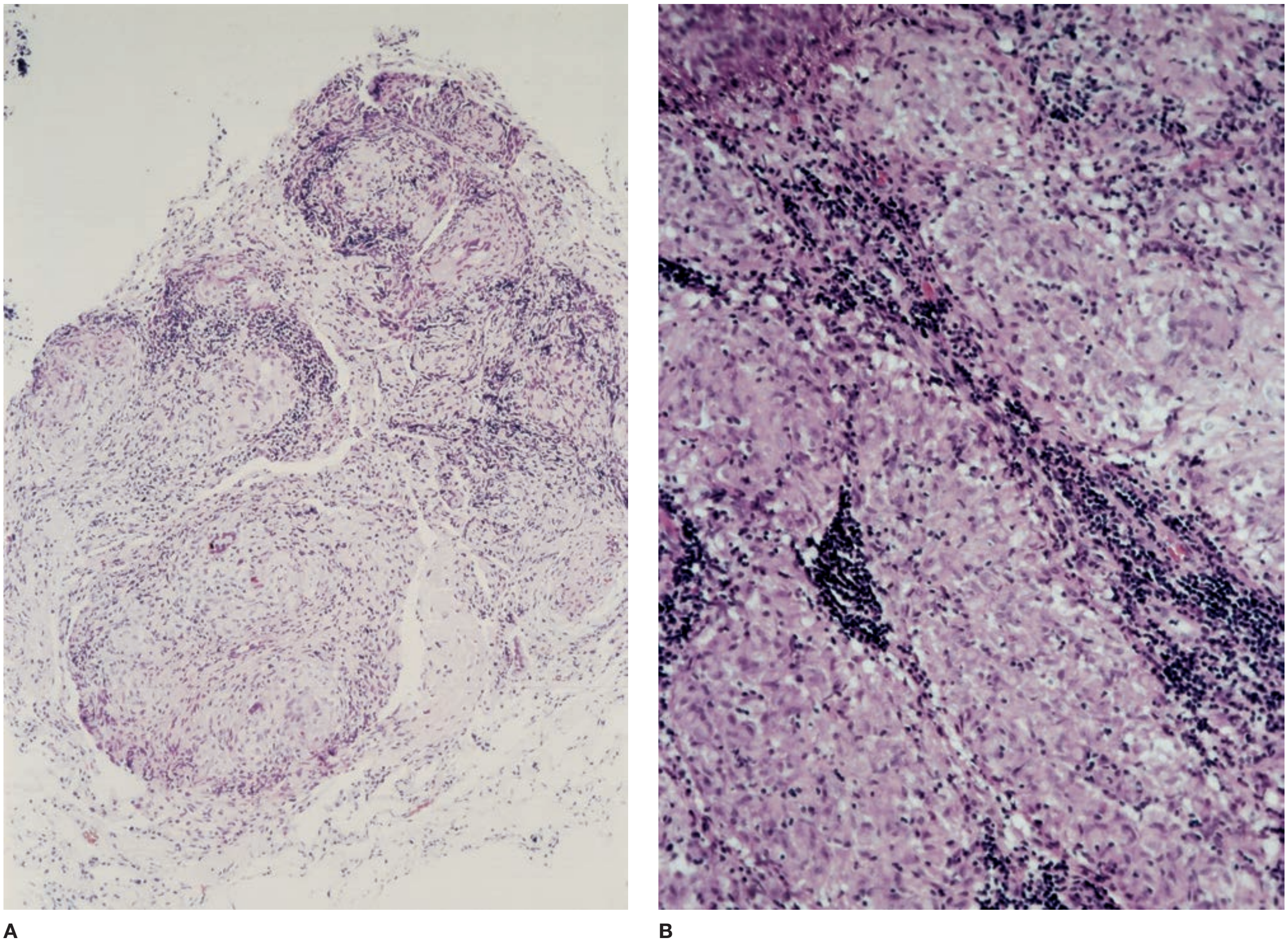

Figure 53-1 Photomicrographs of noncaseating granulomatous inflammation in sarcoidosis. **A.** Thoracoscopic lung biopsy showing extensive parenchymal involvement with granulomas, multinucleated giant cells, and mononuclear cell inflammation (×80). **B.** Mediastinal lymph node biopsy showing typical discrete epithelioid granulomas (×200).

diagnoses.[40] Additionally, the presence of organizing pneumonia and fibroblastic foci should prompt further investigation for other causes of lung injury and repair, including superimposed infection.[41,42] Giant cells, often containing cytoplasmic inclusions such as calcium- and iron-laden Schaumann bodies and Hamazaki–Wesenberg bodies, are scattered throughout the inflammatory locus. These features are not specific for sarcoidosis, as similar histopathologic findings can be seen in infections, berylliosis, Crohn disease, and local "sarcoid reactions" that occur near neoplastic, foreign body, or chronic inflammatory areas.[43]

In the lung, granulomas tend to form along perivascular, peribronchial, and septal regions, areas rich in lymphatic vessels. A mononuclear cell infiltration composed predominantly of lymphocytes is often present in the adjacent interstitium. Granulomas in sarcoidosis may resolve or undergo fibrosis, the earliest signs of which include circumferential collagen deposition, resulting in a stellate scar or hyalinized ghost of a former granuloma.

■ Immunopathology

Experimental models indicate that the first step in granuloma formation involves the tissue deposition of poorly soluble antigenic material. An initial innate immune response involves the recruitment and activation of antigen-presenting cells such as macrophages or dendritic cells expressing pattern recognition receptors and Toll-like receptors (TLRs). This results in the phagocytosis and degradation of antigenic proteins, generating peptide:MHC complexes that are displayed on the cell surface for analysis by CD4+ T cells (Fig. 53-2). The resulting adaptive immune response is characterized by the expression of effector cytokines dominated by a type 1 T helper cell (Th1; IFN-γ), Th2 (IL4/IL13), or Th17 (IL17/IL21/IL22) response, depending on the nature of the antigen and host genetic/epigenetic factors.[44] Active inflammation in sarcoidosis is strongly associated with the expression of Th1-promoting cytokines such as IL-12 and IL-18, and granuloma formation is supported by the subsequent effects of cytokines such as IFN-γ and TNF,[45] Th1-associated chemokines, and other mediators produced by activated innate and adaptive immune cells. Granulomatous inflammation is downregulated with clearance of antigen along with release of anti-inflammatory mediators such as transforming growth factor β (TGF-β) and IL-10 by local immune cells.[46,47]

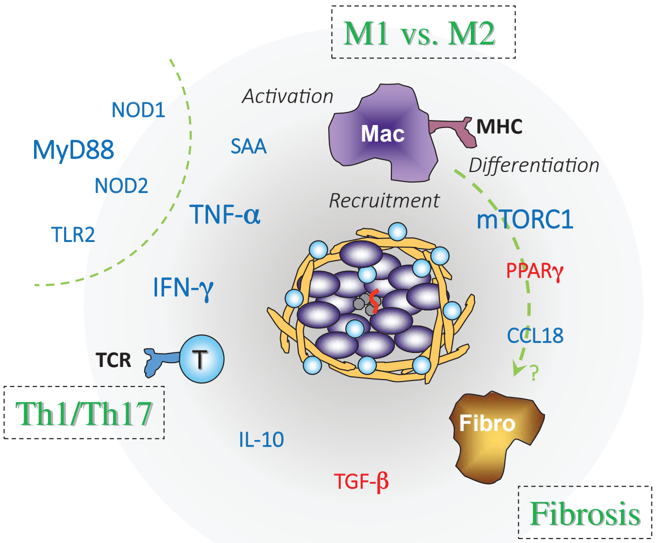

Figure 53-2 Concise model of sarcoidosis pathobiology. Granulomatous inflammation forms around an inflammatory nidus of poorly soluble antigen. Key receptors and mediators identified to be upregulated *(blue)* or downregulated *(red)* in sarcoidosis contribute to (1) localized synergistic induction of adaptive immune responses from a Th1-permissive cytokine environment; (2) initiation and maintenance of granulomatous inflammation through the activation, recruitment, and differentiation of macrophages; and (3) development of fibrosis through collagen deposition and recruitment and differentiation of fibroblasts and fibrocytes. *(Reproduced with permission from Chen ES. Innate immunity in sarcoidosis pathobiology. Curr Opin Pulm Med. 2016;22(5):469-475.)*

Sarcoidosis alveolar macrophages (AMs) express increased density of co-stimulatory molecules CD80, CD86, and CD40 consistent with their enhanced antigen-presenting capability; spontaneously produce TNF, IL-6, and IL1; and show increased activation of the transcription factor NF-κB and downregulation of the inflammation-suppressive transcription factor, peroxisome proliferator-activated receptor γ, consistent with classically activated M1 macrophages.[48,49] Other cytokines, IL-15, osteopontin, and the Th1-promoting cytokines IL-12 and IL-18 also are upregulated in sarcoidosis. Dendritic cells likely play a critical role in regulating local immune responses in sarcoidosis but have been the focus of few studies.[50,51] TNF is a key effector cytokine (therefore a therapeutic target) driving granuloma formation in sarcoidosis, as enhanced release of TNF by BAL cells is associated with persistent disease.[52] A recent study demonstrated that activation of the metabolic checkpoint kinase mTORC1 results in macrophage aggregation, hypertrophy, and proliferation resembling granulomatous inflammation in experimental models, suggesting a role in sarcoidosis.[53,54] The formation of granulomas in sarcoidosis is driven by the activation, recruitment, and differentiation of macrophages, a focus of ongoing active research (Fig. 53-2).[55]

Lymphocytes play a pivotal role in directing the inflammation in sarcoidosis. Studies of patients with immunodeficiency syndromes including untreated HIV infection demonstrate that sarcoidosis does not occur in the absence of functional CD4+ T cells, and that HIV+ patients who have a prior history of sarcoidosis can experience recrudescence of sarcoidosis upon effective treatment of HIV as part of an immune reconstitution syndrome.[56,57] Early studies identified that T lymphocytes recruited to the lung, skin (Kveim biopsy sites), and other sites of active sarcoidosis display a limited number of αβ+ T-cell receptor sequences, suggesting that sarcoidosis involves an antigen-specific response.[58–60] The best-studied example involves the remarkable expansion of Vα2.3 (AV2S3)+ BAL T cells from HLA-DRB1*0301-positive Scandinavian patients with sarcoidosis.[61] The specific antigens driving these clonally expanded T-cell populations remain uncertain but may include autoantigens such as vimentin and microbial antigens such as mKatG.[62,63]

■ Th1 and Th17 Immunity

Multiple studies confirm that pulmonary sarcoidosis is associated with enhanced expression of IFN-γ, IL-12, and IL-18 but low or undetectable levels of IL-4 or IL-5, indicating a dominant type 1 (Th1) immune response compartmentalized to the lung and other sites of inflammation.[64] Enhanced expression of IFN-γ by CD4+ T cells is one of the oldest and enduring observations in sarcoidosis. Perhaps most intriguing is the recent identification that the majority of IFN-γ-expressing CD4+ T cells in the sarcoidosis lung bear a Th17 surface phenotype,[65] supporting a hypothesis that proinflammatory Th17 cells contribute to sarcoidosis through their ability to migrate to sites of disease and functionally transform into nonclassic Th1 cells induced by the local cytokine environment enriched in Th1-promoting IL-12 and TNF.[66] Despite an established role for Th17 effector T cells in granulomatosis with polyangiitis (GPA, formerly known as Wegener granulomatosis) and tuberculosis,[67,68] it is unknown whether Th17 responses play a critical role in disease outcome or can substitute for the polarized Th1 responses documented in sarcoidosis.[69]

Reduced Treg Functional Capacity

Regulatory T cells (Tregs) maintain immune homeostasis by suppressing the function of antigen-presenting cells and effector T cells. Several groups have reported that FoxP3-positive natural Tregs (nTreg) accumulate at sites of granulomatous inflammation in sarcoidosis but may have reduced function in suppressing proinflammatory cytokine expression and granuloma formation.[70–72] Reduced Treg survival and enhanced apoptosis of Tregs may contribute to insufficient immunoregulatory function in sarcoidosis.[73] Diminished numbers of immunoregulatory natural killer T (NKT) cells have also been reported and may contribute to chronic active sarcoidosis.[74] Whether the functional impairment of nTreg or NKT cells in sarcoidosis is a primary defect or secondary to the hyperimmune Th1/Th17 responses in sarcoidosis remains uncertain.[75] One group studied the effects of nebulized vasoactive intestinal peptide (VIP) in sarcoidosis and found it significantly increased number and inhibitory function of lung CD4+CD127-CD25+ Tregs and reduced TNF production by BAL cells,[76] suggesting a potential treatment for immune-mediated lung diseases including sarcoidosis.

Role of Innate Immunity

The immunopathology of sarcoidosis can be modeled in this experimental context. Sites of granulomatous inflammation such as the lung contain activated T cells and mononuclear phagocytes that express the same proinflammatory cytokines and chemokines that have been shown experimentally to be critical in granuloma formation.[18] Active pulmonary sarcoidosis is associated with a lymphocytic alveolitis associated with CD4+CD45RO+CCR7- effector memory T cells. CD4+ T cells in sarcoidosis spontaneously produce IFN-γ and other cytokines, including TNF, and the coexpression of IFN-γ and TNF by "multifunctional" T cells has been linked to clinical outcomes, such as in patients with Löfgren syndrome who have higher rates of disease remission.[63]

Given the lack of evidence for an active mycobacterial or other viable microbial infection in sarcoidosis tissues at any point in the disease and often in the context of long-term treatment with immunosuppressive medications, another major challenge is to understand what drives chronic granulomatous inflammation in sarcoidosis. Since mycobacterial antigens (mKatG, ESAT-6) represent candidate pathogenic antigens that provoke adaptive responses in subsets of patients with sarcoidosis,[77,78] examining the events following exposure to mycobacteria may identify innate host defense pathways that contribute to the pathology of sarcoidosis.

Studies have demonstrated increased expression of genes related to the TLR2 innate signaling pathway in peripheral blood mononuclear cells (PBMCs) 24 h after incubation with *M. tuberculosis*,[79] complementing other studies that have associated polymorphisms in TLR2 with susceptibility to mycobacterial infection. Enhanced responsiveness to TLR2 stimulation, including enhanced induction of TNF, has been observed in blood and lung cells from sarcoidosis patients.[80–82] In this context, serum amyloid A (SAA) has been identified as an innate ligand expressed in sarcoidosis tissues that can induce the expression of proinflammatory cytokines including TNF, in part, through TLR2[80] (Fig. 53-3). Interestingly, TLR2 expression on respiratory epithelial cells is induced by TNF and IFN-γ, potentially resulting in a positive feedback loop in the

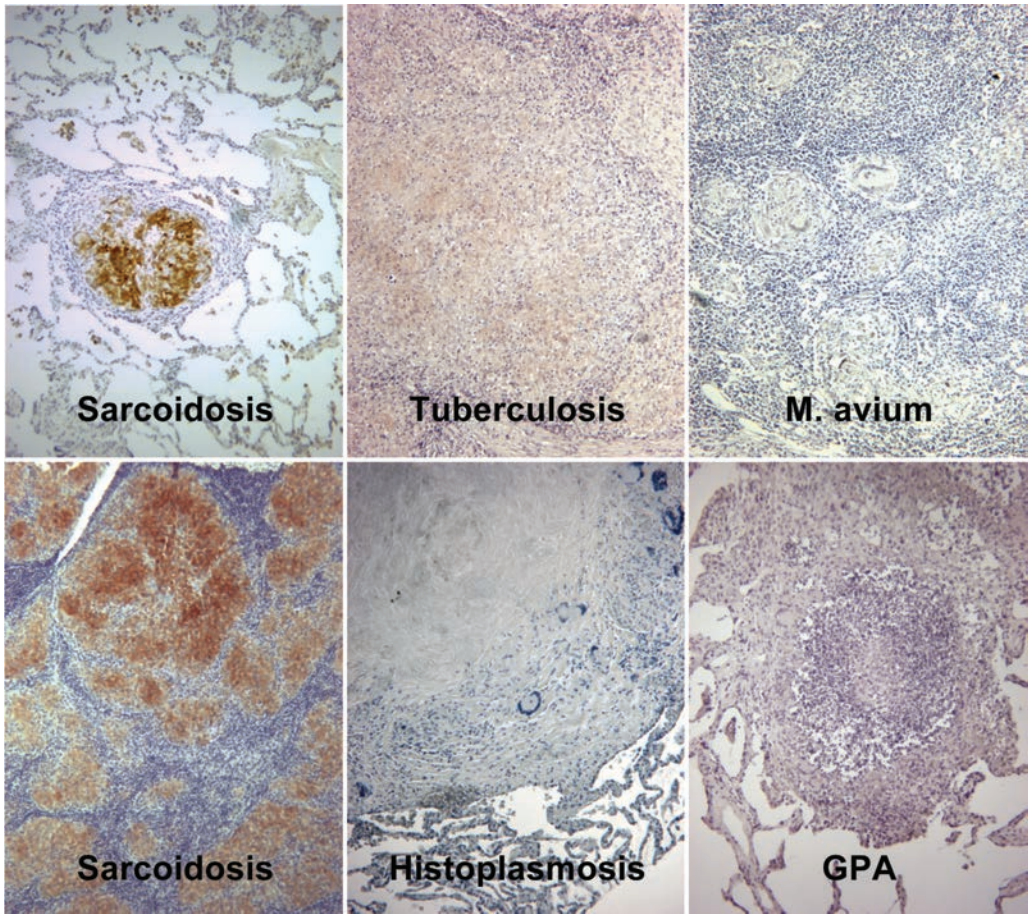

Figure 53-3 Immunohistochemistry showing focal deposition of serum amyloid A (SAA) *(brownish stain)* in tissues from patients with sarcoidosis but little or no staining for SAA in tuberculosis, *Mycobacterium avium* infection, histoplasmosis, or granulomatosis with polyangiitis (GPA).

setting of granulomatous inflammation, an effect that is enhanced by corticosteroids.[83] Aberrant TLR2 function may also play a role in anergy in sarcoidosis, an effect that can be modified by nicotine,[84] a potential clue regarding the interaction between smoking and sarcoidosis.

Mutations in the nucleotide-binding oligomerization domain 2 (NOD2) pathway have been linked with Blau syndrome, an autosomal dominant disorder causing granulomatous inflammation of the skin, eyes, and joints. NOD2 mutations have also been identified as risk factors for Crohn disease, a granulomatous inflammatory bowel disease. More recently, NOD2 has also been linked to early onset sarcoidosis in children, but this linkage has not been established in adult sarcoidosis.[85] A related study identified NOD1 stimulation as another innate pathway that contributes to heightened immune responsiveness in sarcoidosis via enhanced production of TNF and IL-12 by BAL cells.[86] A denominator for these observations is the myeloid differentiation primary response gene (MyD88), which serves as an innate immune signal transduction adaptor downstream of all NOD-like receptors, and all TLRs (except TLR 3). Of interest, polymorphisms of the MyD88 gene have been associated with risk for developing sarcoidosis.[87] While sarcoidosis is not a manifestation of an active infection, microbial proteins are a rich source of ligands to innate receptors, offering a link between exposure to microbes (e.g., previously contained, and eradicated infection) and sarcoidosis.[88]

■ Lung Fibrosis in Sarcoidosis

The mechanisms that promote pulmonary fibrosis in sarcoidosis remain uncertain. IFN-γ has direct antifibrotic effects,[89] but this pleotropic cytokine may mediate fibrosis by enhancing lung injury.[90] There is evidence that sarcoidosis AMs can transition to an alternative profibrotic M2-like phenotype,[91] which can promote lung fibrosis in pulmonary sarcoidosis through the expression of chemokines such as CCL18.[92] The lack of evidence for IL4 upregulation in sarcoidosis suggests that IL-10 or IL-13 may foster this profibrotic macrophage phenotype.[93] Sarcoidosis is associated with diminished expression of PPARγ,[49] and whether this contributes to macrophage differentiation in sarcoidosis requires further study.[94]

Increased expression of TGF-β, fibronectin, insulin-like growth factorb1 (IGF-1), laminin, and matrix metalloproteases by sarcoidosis AMs may promote a fibrosis-permissive environment in chronic active sarcoidosis through the recruitment and activation of fibroblasts (Fig. 53-2).[64] While increased TGF-β is associated with the presence of structural lung disease among sarcoidosis patients,[95] the exact role of TGF-β in sarcoidosis remains unclear since it has not only profibrotic but immunoregulatory effects.

Irreversible lung scarring can result in sarcoidosis, most commonly observed in patients with chronic active pulmonary sarcoidosis.[96] Using an animal model, repeated administration of SAA maintained experimental granulomatous inflammation, providing a possible mechanism for sustaining ongoing inflammation in sarcoidosis.[80] SAA deposition in sarcoidosis tissues correlates with local collagen deposition,[80] and a recent study of blood SAA levels found that patients with fibrotic sarcoidosis had higher SAA levels compared to sarcoidosis without lung fibrosis, suggesting this may be a marker of more severe disease.[97]

Presumably, untreated (or insufficiently treated) sarcoidosis causes lung injury with resultant scarring as part of a local healing response. Patients with fibrotic sarcoidosis are at risk for complications from bronchiectasis, mycetoma, and hemoptysis. Whether lung fibrosis associated with sarcoidosis involves abnormal fibroblast activity akin to idiopathic pulmonary fibrosis remains uncertain, and studies are needed to demonstrate whether antifibrotic therapies have a role in sarcoidosis.[98]

■ ETIOLOGY

The cause of sarcoidosis remains uncertain. While genetic factors may permit a disease such as sarcoidosis to occur, the challenge is to understand what stimulates the immune system to cause granulomatous inflammation identified as sarcoidosis. Seasonal variation in case rates and time-space clustering of cases support a hypothesis that environmental exposures are linked to sarcoidosis.[99,100] Occupation-linked risks have been described in healthcare professionals, firefighters, workers involved in the lumber industry, and military personnel,[101] and these associations are supported by a recent study using advanced high-throughput technologies.[102] Chronic beryllium disease causes a granulomatous pneumonitis histologically identical to pulmonary sarcoidosis in less than 5% of exposed workers following immunologic sensitization to beryllium.[103] Exposures to silicates and immune-sensitizing metals also can cause granulomatous inflammation.[104] The high incidence of respiratory illnesses following the 9/11 World Trade Center disaster among first-response rescue workers identified a time-space clustering of a “sarcoidosis-like” pulmonary disease.[105] However, two studies of surgical lung biopsies obtained from WTC-exposed responders and residents suggest that in most instances the pulmonary disease from WTC exposure is consistent with complex dust exposure rather than sarcoidosis.[106,107] A minority of WTC-exposed responders developed multisystem disease, supporting a likely diagnosis of multisystem sarcoidosis.[108] Collectively, these observations support the hypothesis that environmental exposures are an important source of stimuli that can trigger sarcoidosis and other inflammatory responses in susceptible hosts.

The U.S.–based multicenter study of sarcoidosis etiology, ACCESS, compared 706 newly diagnosed, biopsy-proven sarcoidosis cases with age-, sex-, and race-matched controls.[109] Results from the study did not identify any environmental or occupational associations with risk for developing sarcoidosis that met the study’s design goals of odds ratio (OR) greater than 2.0 and an exposure prevalence of greater than 5%.[110] Weak positive associations (OR, ~1.5) were found for insecticide use at work, mold/mildew exposures at work, and musty odors, suggesting possible links to microbial-rich environments. Sarcoidosis was not associated with exposure to heavy metals including beryllium, wood dusts, or rural residence as previously hypothesized. The ACCESS study found a robust negative association of smoking and sarcoidosis risk, confirming earlier studies. The lack of a single, dominant exposure associated with sarcoidosis risk supports the concept that gene–environment interactions are important in causing this disease.

Since sarcoidosis was first described, investigators have postulated an infectious cause of the disease based on the clinical and histologic similarities to tuberculosis.[111] A meta-analysis of studies published between 1980 and 2006 identified a 10- to 20-fold greater likelihood of detecting mycobacterial nucleic acids (DNA, RNA) in sarcoidosis tissues than control tissues.[112] Several groups have demonstrated that as many as 70% of sarcoidosis patients have lung and blood T-cell responses to mycobacterial antigens including mKatG, *Mycobacterium tuberculosis* ESAT-6, Ag85, and superoxide dismutase.[113–115] Along these lines, other studies identified extensive overlap in peripheral blood gene expression between individuals with sarcoidosis and tuberculosis infection.[116–118]

Japanese investigators found *Propionibacterium acnes* DNA in 80% to 98% of sarcoidosis tissues from Japan and Europe but also in 0% to 60% of control tissues.[119] However, a role for *Propionibacterium* (now reclassified as *Cutibacterium*) in sarcoidosis remains unclear because of the frequent detection of these organisms from non-sarcoidosis tissues and frequent observation of immune responses to these organisms in non-sarcoidosis control individuals.[120]

Despite the evidence linking some microbes to sarcoidosis etiology, a recent phase 2 study found that 8 weeks of antimycobacterial therapy did not result in any clinical improvement in patients with pulmonary sarcoidosis.[121] This confirms that active sarcoidosis is not caused by the presence of viable mycobacterial organisms (or other infectious microbes) in affected tissues; rather investigators favor the hypothesis that antigens originating from certain classes of microbial organisms (exposures to microbes that were eradicated by an effective host immune response) can trigger sarcoidosis in those with genetic susceptibility. However, there is growing concern that host–microbiome interactions modulate inflammation in systemic illnesses,[122] including sarcoidosis,[88,123] potentially modified by antimicrobial agents, and future studies are needed to reassess the effects of antimicrobial agents in this context.

Other microbial agents such as *Borrelia burgdorferi*, *Chlamydia pneumoniae*, or *Rickettsia helvetica* have been implicated in sarcoidosis from tissue or serologic studies, but these latter studies all lack wider confirmation. High titers of antibodies against lymphotropic DNA viruses (Epstein-Barr virus, cytomegalovirus, and human herpesvirus type 6) and HTLV1 have been described in patients with sarcoidosis but may reflect generalized B-cell activation in sarcoidosis, since a viral origin has not been substantiated by viral cultures or tissue analysis.

Some investigators hypothesize an etiologic association with autoimmunity, perhaps triggered by an infectious agent through molecular mimicry. In support of this concept, sarcoidosis is associated with features of autoimmunity, such as antinuclear antibodies, rheumatoid factor, hypergammaglobulinemia, and immune complexes. Sarcoidosis patients often express low-titer autoantibodies of unclear significance, although no disease-specific autoantibody profile has been identified. One recent study identified several potential autoantigens such as vimentin, ATP synthase, and lysyl-tRNA whose derived peptides stimulated Th1 lymphocytes in the blood or lung of sarcoidosis patients, suggesting these responses may help sustain chronic inflammation.[124]

CLINICAL FEATURES

The clinical features of sarcoidosis are discussed in detail below.

■ Classification

The clinical manifestations and course of sarcoidosis vary greatly (Table 53-4). Although any organ of the body can be affected, the lungs or intrathoracic lymph nodes are involved in more than 90% of patients with sarcoidosis. Patients may present with no symptoms or develop acute, subacute, or indolent manifestations. Systemic constitutional symptoms such as fever, fatigue, malaise, and weight loss are seen in more than 50% of patients and may be disabling. One classification scheme with prognostic information categorizes patients based on their initial manifestations as follows:

TABLE 53-4 Clinical Manifestations of Sarcoidosis

Organ System (Percent Clinical Disease)	Major/Common Manifestations
Pulmonary (>90%)	Restrictive, obstructive impairment, reduced diffusing capacity, fibrocystic disease, pulmonary hypertension, bronchiectasis, cavitating nodules, mycetomas, lobar atelectasis, tracheal or bronchial stenosis, superior vena cava syndrome, pleural disease, pneumothorax
Constitutional symptoms (>50%)	Fevers, night sweats, malaise, excessive fatigue, unintentional weight loss
Upper respiratory tract and oral cavity (5%–10%)	Hoarseness, laryngeal or tracheal obstruction, nasal congestion, sinusitis, saddle nose deformity, upper airway obstruction, sleep apnea, dacryoadenitis
Skin (20%–30%)	Chronic nodules and plaques, lupus pernio, alopecia, subcutaneous sarcoidosis, ichthyosis, alopecia, scar granulomas, tattoo granulomas, erythema nodosum (a nonspecific, nongranulomatous panniculitis)
Ocular (20%–30%)	Anterior and posterior uveitis, chorioretinitis, conjunctivitis, optic neuritis, granulomatous orbital inflammation
Cardiac (5%–20%)	Arrhythmias, heart block, cardiomyopathy, sudden death, pericardial disease, valvular disease, ventricular or atrial mass
Neurologic (5%–10%)	Facial and other cranial neuropathies (e.g., Bell's palsy), basilar leptomeningitis, encephalitis, aseptic meningitis, brain mass, seizures, hydrocephalus, pseudotumor cerebri, hypothalamic hypopituitarism, optic chiasmal involvement, Horner's syndrome, Argyll Robertson or Adie's pupil, cerebritis (white matter involvement), corpus callosum involvement, brain stem involvement, cerebellar involvement, cerebral vascular occlusion, myelopathy, transverse myelitis, intraspinal mass, cauda equina or spinal root involvement, peripheral neuropathy, mononeuritis multiplex, polyneuropathy, small fiber neuropathy
Hepatic/abdominal (10%–20%)	Hepatomegaly, jaundice, cirrhosis, abdominal/retroperitoneal lymphadenopathy, jaundice with pruritus, cirrhosis with portal hypertension, splenomegaly, pancreatic mass, dysmotility involving esophagus/small or large intestine, peritoneal implants, appendicitis
Hematologic (20%–30%)	Peripheral or retroperitoneal lymphadenopathy, splenomegaly, hypersplenism, anemia, lymphopenia, hypergammaglobulinemia, lymphedema, idiopathic thrombocytopenic purpura (ITP)
Joints and musculoskeletal (10%–20%)	Arthralgia, polyarthritis, Achilles tendinitis, heel pain, dactylitis, bone cysts, myopathy
Exocrine gland (10%–20%)	Salivary, lacrimal, and parotid gland enlargement, sicca syndrome/Heerfordt syndrome, parotid mass
Endocrine (10%–20%)	Hypercalciuria, hypercalcemia, hypopituitarism, diabetes insipidus, thyroid mass, thyroiditis
Renal (<10%)	Renal calculi, nephrocalcinosis, renal failure, interstitial nephritis, leukocyturia, microhematuria
Genitourinary (<5%)	Ovarian or uterine mass, dysmenorrhea, testicular mass, epididymitis/uterine mass, ovarian involvement, menometrorrhagia, testicular mass, epididymitis, intermittent azoospermia
Psychosocial manifestations (30%–60%)	Depression, anxiety, fatigue

(1) asymptomatic; (2) acute sarcoidosis with or without erythema nodosum; (3) sarcoidosis with symptoms or signs of pulmonary disease for less than 2 years; (4) chronic pulmonary sarcoidosis of more than 2 years; and (5) dominant extrapulmonary sarcoidosis. Two years represents an arbitrary but useful reference point for distinguishing patients who usually, but not always, have long-term disease.

Rare manifestations of sarcoidosis include unusual patterns of organ involvement, the result of granulomatous inflammation developing in unusual locations for sarcoidosis, or when sarcoidosis is associated with a second disorder. In general, rarer manifestations reflect the known pathophysiology and clinical behavior of more common organ involvement.

Asymptomatic Sarcoidosis

Up to two-thirds of patients are asymptomatic but have sarcoidosis diagnosed after an incidental radiographic finding of bilateral hilar adenopathy. Occasionally, interstitial infiltrates are seen in association with intrathoracic adenopathy in asymptomatic patients, most commonly in whites.

Acute Sarcoidosis with or without Erythema Nodosum

Sarcoidosis may manifest with the acute onset of erythema nodosum associated with bilateral hilar adenopathy, fevers, polyarthritis, and often uveitis, known as Löfgren syndrome. Erythema nodosum is characterized by tender reddish nodules several centimeters in diameter, usually located on the lower extremities; histologic examination shows panniculitis, not granulomas. The polyarthritis is often severe and incapacitating, typically involving the ankles, feet, knees, and, occasionally, wrists and elbows. Approximately 10% of patients with this syndrome have a normal chest radiograph. Löfgren syndrome is more common in European and white populations but found in less than 5% of Blacks with sarcoidosis. Some patients manifest acute arthritis, bilateral hilar lymphadenopathy, and constitutional symptoms without erythema nodosum. In either case, the prognosis is excellent for remission in 70% to 80% of patients, typically within several months.

Pulmonary Sarcoidosis

Respiratory symptoms occur in 40% to 60% of patients.[125] The most common symptoms are cough and shortness of breath, usually of a progressive, insidious nature. The cough is usually nonproductive and may be severe. Dyspnea is typically worse with exertion. Sputum production and hemoptysis are frequent in patients with fibrocystic sarcoidosis that is often associated with bronchiectasis. Ill-defined chest pain is a frequent complaint, possibly caused by nerve irritation from inflammation, scarring, or lymph node enlargement in the chest. Chest tightness and wheezing are common with endobronchial disease or fibrocystic changes. These symptoms are usually poorly responsive to bronchodilators, except in those with reversible airway hyperreactivity. Physical findings are infrequent, with lung crackles heard in less than 20% of patients; clubbing is rare.

Chest Imaging

The chest radiograph is abnormal in more than 90% of known cases and carries prognostic information.[126] Chest radiographs are categorized by international convention: stage 0 (<15%) denotes a normal chest x-ray; stage I (30% to 50%) shows symmetric bilateral hilar adenopathy often with right paratracheal adenopathy; stage II (40% to 60%) and stage III (10% to 20%) indicate the presence of pulmonary infiltrates with (stage II) or without (stage III) bilateral hilar adenopathy; stage IV (<15%) shows obvious scarring with fibrocystic changes with cephalad hilar retraction (Fig. 53-4). The hilar adenopathy often has a symmetric "potato node" appearance and calcifications are uncommon. Infiltrates most commonly appear as linear or reticulonodular markings in the middle and upper lung fields, but occasionally can present with patchy, focal alveolar consolidations mimicking infectious pneumonia, granulomatosis with polyangiitis (GPA), eosinophilic pneumonia, or malignancy. Less frequently, a miliary pattern is observed but would warrant exclusion of tuberculosis, hypersensitivity pneumonitis, chronic beryllium disease, or lymphangitic carcinomatosis. While stage IV sarcoidosis is associated with a poor prognosis,[127] the recent ACCESS study affirms the weak correlation between stages I, II, or III chest radiographs and clinical status.[128] Mycetomas often represent a complication of fibrocystic stage IV sarcoidosis.[129] Unusual radiographic signs of sarcoidosis include pneumothorax, isolated nodule or mass, lobar atelectasis, or pleural effusions.

Chest computed tomography (CT) typically demonstrates that infiltrates tend to be central, following bronchovascular structures.[130] Ground-glass infiltrates or honeycombing also can be seen. The adenopathy of sarcoidosis typically appears as multiple discrete enlarged lymph nodes rather than amorphous, mass-like growths more suggestive of malignancy. CT of the chest is often useful in the evaluation of patients with suspected sarcoidosis and to help plan bronchoscopic biopsy of enlarged lymph nodes, define unusual radiographic features, fibrocystic disease, or bronchiectasis.

Pulmonary Function Tests

Pulmonary function may be normal even when the chest radiograph demonstrates pulmonary infiltrates. However, restrictive impairment with reduction in lung volumes, forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1), is common, particularly when pulmonary infiltrates are present on chest radiograph. Reduction in diffusing capacity can be seen in association with restrictive impairment or as an isolated deficit, the latter raising concern for concomitant pulmonary hypertension.[131] Obstructive impairment is as common as restrictive impairment, particularly in advanced fibrocystic disease or endobronchial disease.[132] A subgroup of patients has bronchial hyperresponsiveness and airway obstruction that may respond to bronchodilators. Resting hypoxemia and exercise O_2 desaturation are typical when there is severe obstructive or restrictive impairment. CO_2 retention is unusual except in advanced pulmonary disease.

Pulmonary Hypertension

Pulmonary hypertension represents an important complicating factor of pulmonary sarcoidosis because it is associated with increased mortality. The prevalence of pulmonary hypertension is estimated to be 6% to 20% among patients with sarcoidosis, with highest rates (~75%) observed in patients with advanced lung disease awaiting lung transplant.[133] In patients with dyspnea disproportionate to pulmonary function impairment, pulmonary hypertension may be seen in 50% of cases.[134] The causes of pulmonary hypertension include extensive interstitial lung disease with loss of pulmonary capillary bed, granulomatous pulmonary vasculitis, pulmonary arterial impingement by lymphadenopathy or traction lung scarring of bronchovascular bundles, left heart dysfunction, or rarely, pulmonary venous occlusion.[135] Patients typically present with progressive dyspnea. Echocardiography is a useful screening technique, but right heart catheterization is needed to confirm clinically significant pulmonary hypertension.

A single-center longitudinal study of patients with severe sarcoidosis-associated pulmonary hypertension (SAPH) (mean pulmonary artery pressure [mPAP] >35 mm Hg *or* mPAP 25–35 with cardiac index <2.5 L/min/m^2) over a median follow-up period of 28 months reported that 40% either died or underwent lung transplantation.[136] Treatment with medications to treat pulmonary hypertension did not result in significant differences in outcomes, despite improvement in hemodynamic profiles. Treatment with immunosuppression medications improved hemodynamic profiles in select cases.

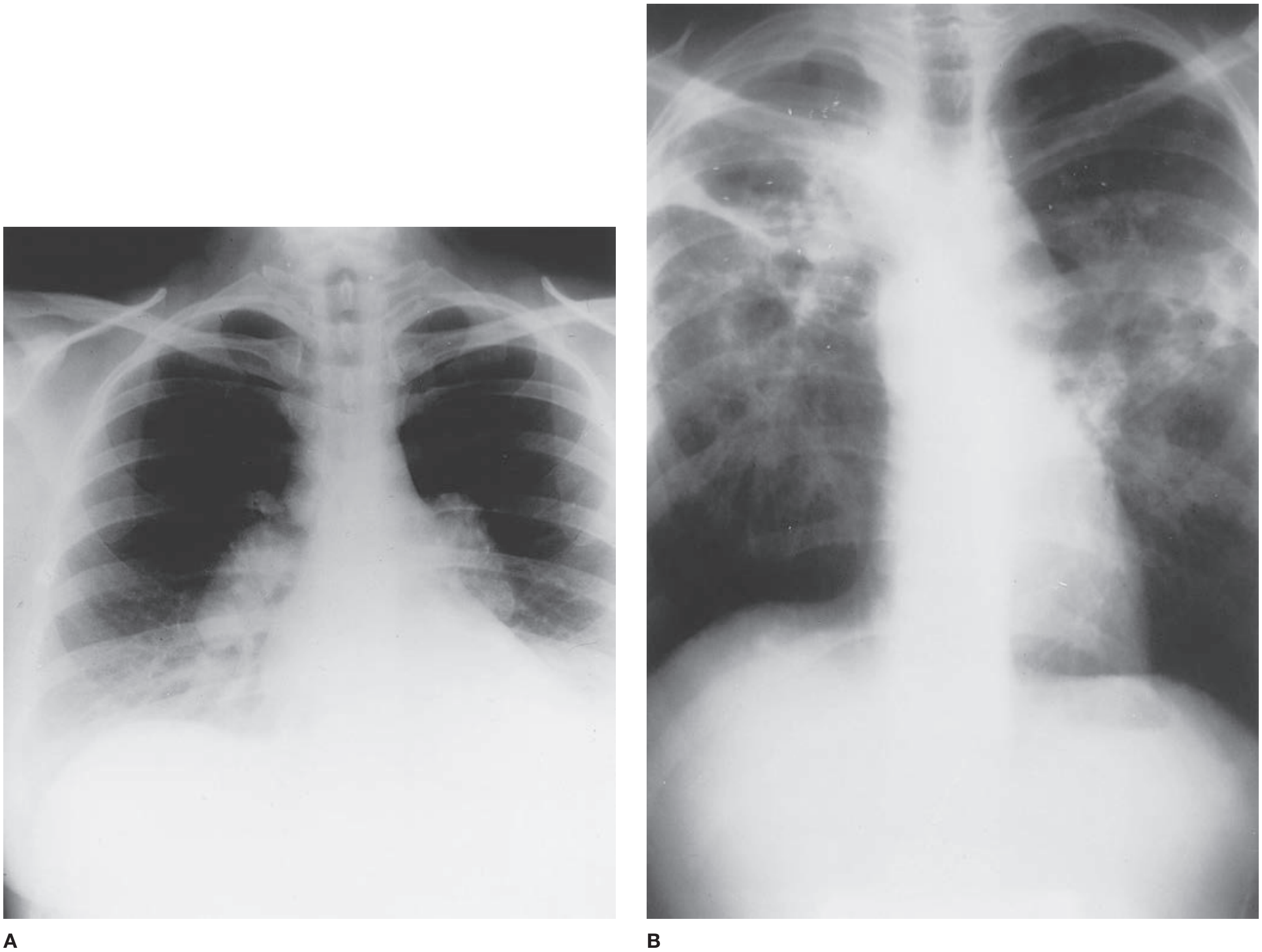

Figure 53-4 Chest radiographs of pulmonary sarcoidosis. **A.** Stage II sarcoidosis pattern with prominent, discrete "stand-away" hilar nodes, right paratracheal adenopathy, and fine reticulonodular infiltrates. **B.** Fibrocystic sarcoidosis with extensive mid and upper lung scarring, bullous and cystic changes, hilar retraction, and parenchymal infiltrates.

The results from an international Registry for SAPH (ReSAPH) reported a 5-year transplant-free survival of 62% among patients with precapillary pulmonary hypertension (mPAP ≥25 mm Hg), with reduced diffusing capacity (<35% predicted) and low 6-min walk distance (<300 m) identified as risk factors for reduced transplant-free survival.[137] Recent revisions to the definition of pulmonary hypertension warrant reassessment of the long-term effects of less severe pulmonary hypertension associated with sarcoidosis.[138]

Necrotizing Sarcoid Granulomatosis

This disorder is characterized by large, confluent, noncaseating granulomas involving both pulmonary arteries and veins but without systemic vasculitis and is often considered a variant of pulmonary sarcoidosis.[139,140] Patients may be asymptomatic or have cough, dyspnea, fever, chest pain, or constitutional symptoms. Chest radiographs typically demonstrate multiple, usually noncavitating nodules. Pleural disease with pleurisy or pleural effusions occurs in the majority of patients with this variant and may be a clue to the diagnosis. Most patients have spontaneous improvement or a rapid response to corticosteroid therapy.

■ Extrapulmonary Sarcoidosis

Many patients have manifestations of granulomatous inflammation in one or more organ systems either in addition to pulmonary involvement or without evidence of pulmonary disease (Table 53-4). The presence of these characteristic extrapulmonary manifestations may help distinguish sarcoidosis from other systemic diseases. Defining clinically significant organ involvement remains a challenge despite improved imaging techniques.

Sarcoidosis of the Upper Respiratory Tract and Oral Cavity

Sarcoidosis of the upper respiratory tract (SURT) occurs in 5% to 10% of patients, usually involving the nasal sinuses or laryngeal structures. Symptoms of nasal congestion, sinusitis, and intermittent epistaxis are often chronic and unresponsive to decongestants or topical corticosteroids. Chronic disease or surgical intervention may result in destruction of the nasal septum and a "saddle nose" deformity. Laryngeal sarcoidosis may manifest with severe hoarseness, stridor, or acute respiratory failure secondary to upper airway obstruction. Frequently, laryngeal sarcoidosis is associated with chronic skin lesions, lupus pernio, or sinus disease. Oral and pharyngeal sarcoidosis is rare but may manifest with macroglossia, tongue mass, or palatal mass with cartilaginous or bone destruction.

Cutaneous Sarcoidosis

Chronic skin sarcoidosis is seen in 20% to 30% of patients, usually manifesting as plaques or subcutaneous nodules, and is more common and severe in Blacks.[141] Typically, the plaques are located around the hairline, eyelids, ears, nose, and extensor surfaces of the arms and legs. Lupus pernio is a disfiguring form of cutaneous sarcoidosis of the face, with violaceous plaques and nodules covering the nose, nasal alae, malar areas, and areas around the eyes. Erythema nodosum is a non-granulomatous panniculitis seen in acute sarcoidosis.

Ocular Sarcoidosis

Ocular involvement is detected in approximately 20% to 30% of patients.[142] In the ACCESS study, 12% of patients had ocular manifestations as a presenting symptom.[109] Age, ethnicity, and gender may influence risk of ocular sarcoidosis; compared to white Americans, Black Americans present more frequently with this manifestation at a younger age.[143]

Uveitis is the most common ocular manifestation and is often associated with bilateral hilar adenopathy. The uveitis is more commonly anterior, and may be unilateral or bilateral, with either granulomatous or nongranulomatous features. Granulomatous conjunctivitis is less common. Optic neuritis, or severe chorioretinitis, may present dramatically with blindness. The International Workshop on Ocular Sarcoidosis (2006; revised in 2017) proposed seven clinical signs of ocular inflammation consistent with sarcoidosis including mutton-fat keratic precipitates, trabecular meshwork nodules, snowballs/string of pearls vitreous opacities, multiple chorioretinal peripheral lesions, nodular and/or segmental periphlebitis, optic disc or solitary choroidal nodules, and presence of bilateral disease.[144]

Cardiac Sarcoidosis

Although myocardial sarcoidosis is clinically apparent in less than 10% of cases in the United States at initial diagnosis, autopsy studies suggest the prevalence may be greater than 20% in the United States and greater than 50% in Japan.[145,146] Ventricular and supraventricular arrhythmias, heart block, or sudden death may be the initial manifestation due to involvement of the conduction system.[147] Myocardial inflammation can lead to dilated cardiomyopathy and congestive heart failure, wall motion abnormalities, or aneurysms. Myocardial mass, valvular dysfunction from papillary muscle dysfunction, pericarditis, and myocardial ischemia are rarer manifestations. Cases of isolated cardiac sarcoidosis have been reported, sometimes discovered at time of cardiac transplant surgery or left ventricular assist device implantation.[148] Prior to the availability of advanced cardiac imaging, radiographic scanning using thallium or technetium sestamibi myocardial perfusion scans and gallium uptake scans were used to detect cardiac sarcoidosis. More recently available modalities, such as cardiac FDG PET/CT with paired perfusion SPECT or cardiac MRI with gadolinium contrast, can reveal myocardial inflammation and scarring in a distribution not defined by normal coronary vascular anatomy (Fig. 53-5).[149] The severity of pulmonary involvement does not appear to predict the presence or severity of cardiac sarcoidosis.

Neurosarcoidosis

Neurologic manifestations of sarcoidosis are varied and are estimated to occur in 5% to 10% of patients with sarcoidosis.[150] Cranial neuropathies, with unilateral or bilateral seventh nerve (Bell) palsy being the most common, often resolve spontaneously or with corticosteroids but may recur years later. Optic neuropathy may result in sudden blindness (Fig. 53-6). Impingement of the recurrent laryngeal nerve may cause vocal cord dysfunction. The more typical presentations of sarcoidosis in the brain include a basilar meningitis or aseptic encephalitis, sometimes associated with hypothalamic pituitary dysfunction leading to diabetes insipidus, hypogonadism, or hyperprolactinemia. Meningeal granulomatous masses may mimic meningioma. Sarcoidosis-associated myelopathy (i.e., spinal cord involvement) presents a diagnostic challenge and can present with features that overlap with other inflammatory conditions (e.g. multiple sclerosis) or as a mass-like lesion resulting in paraparesis, hemiparesis, and back and leg pains mimicking radiculopathy.[151] Peripheral neuropathies account for about 20% of cases of neurosarcoidosis, typically presenting as mononeuritis multiplex or a predominant sensory deficit. The presence of a small fiber neuropathy has been demonstrated in a subset of patients with sarcoidosis and can contribute to chronic pain, excessive fatigue, and autonomic dysfunction.[152]

Hepatic Sarcoidosis

Liver biopsies show granulomatous inflammation in over 50% of patients, but clinical manifestations are much less frequent.[153] Active hepatic inflammation may be associated with fever, tender hepatomegaly, or pruritus that may mimic primary biliary cirrhosis except that autoimmune serologies are negative. Characteristically, the serum alkaline phosphatase and γ-glutamyltransferase are elevated proportionately higher than the transaminases or bilirubin, although the latter may be observed with advancing liver dysfunction. Many patients may have asymptomatic involvement of the liver; however, a minority progress to cirrhosis if not treated.

Gastrointestinal Sarcoidosis

Sarcoidosis involvement of the gastrointestinal tract is rare, and symptoms localize to the site(s) of involvement.[154] Occasionally, direct esophageal involvement may cause dysphagia, but more commonly this symptom may be caused by extensive mediastinal lymphadenopathy that impinges esophageal motility. Involvement of the pancreas and peritoneum is rare and challenging to confirm.[155] Gastric sarcoidosis may manifest as dyspepsia, abdominal pain, or gastric nodule. Although autopsy studies show scattered granulomas in the gut, clinically symptomatic intestinal sarcoidosis is rare.

Abdominal Sarcoidosis

A variant of sarcoidosis, often called abdominal sarcoidosis, manifests with liver, spleen, and often bone marrow involvement with hypercalcemia or abdominal lymphadenopathy. Constitutional symptoms are frequent with fevers and fatigue. This “triad” pattern may be seen with or without pulmonary involvement; in the latter instance, intra-abdominal malignancy or infection (e.g., tuberculosis) must be excluded.

Hematologic Sarcoidosis

Persistent, bulky, painful, or disfiguring adenopathy is seen in $<10\%$ of patients, most commonly involving the cervical, supraclavicular, axillary, or epitrochlear lymph nodes. Splenomegaly occurs in $<10\%$ of patients and may be massive and associated with hypersplenism. Because many of the clinical features of sarcoidosis and lymphoma are similar, clinicians should employ heightened awareness to exclude malignancy in patients with a known diagnosis of sarcoidosis who experience new onset of adenopathy and splenomegaly.[156]

Peripheral blood lymphopenia is common in sarcoidosis.[157] Granulomas in the bone marrow are found in about 20% of patients who come to autopsy but usually do not cause symptoms. A known feature of sarcoidosis is the impaired cutaneous response to common antigens that elicit delayed-type hypersensitivity reactions, seen in $>30\%$ of patients. The mechanism is unknown but may be related to alterations in regulatory T-cell function.

Joint and Musculoskeletal Sarcoidosis

Arthralgia is a frequent complaint in sarcoidosis. A short-lived polyarthritis is typical of acute sarcoidosis, usually associated with

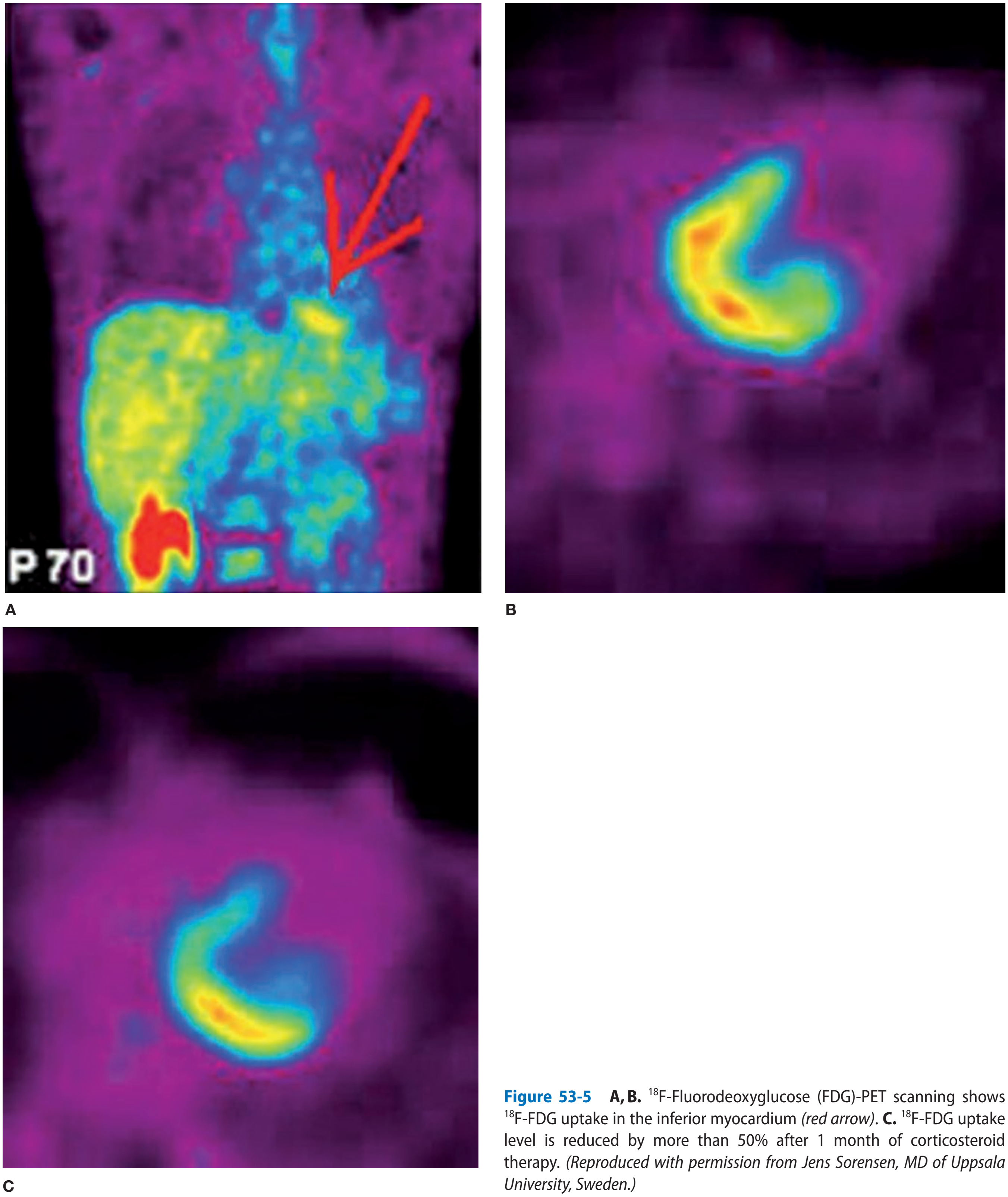

Figure 53-5 **A, B.** ^{18}F-Fluorodeoxyglucose (FDG)-PET scanning shows ^{18}F-FDG uptake in the inferior myocardium *(red arrow)*. **C.** ^{18}F-FDG uptake level is reduced by more than 50% after 1 month of corticosteroid therapy. *(Reproduced with permission from Jens Sorensen, MD of Uppsala University, Sweden.)*

erythema nodosum. Chronic joint disease is found in less than 5% of patients.[158] Joint cartilaginous erosion is rare, but "punched out" bony lesions with cystic changes and loss of bony trabeculae may be seen in subchondral locations. Sarcoidosis is a rare cause of dactylitis, often associated with concomitant cutaneous sarcoidosis. Cystic lesions of the long bones, pelvis, sternum, skull, and vertebrae are uncommon. Sarcoidosis can present as multiple bony lesions on FDG-PET and MRI scans, sometimes as incidental findings without accompanying abnormalities by x-ray or CT imaging suggesting nondestructive infiltration of the bone marrow.[159] Symptomatic myopathy with marked elevation of serum creatinine phosphokinase, aldolase, aspartate aminotransferase, weakness, and tenderness is uncommon. Typically, the myositis from sarcoidosis is responsive to systemic immunosuppression, and recalcitrant cases prompt consideration of alternative diagnosis such as inclusion body myositis.[160]

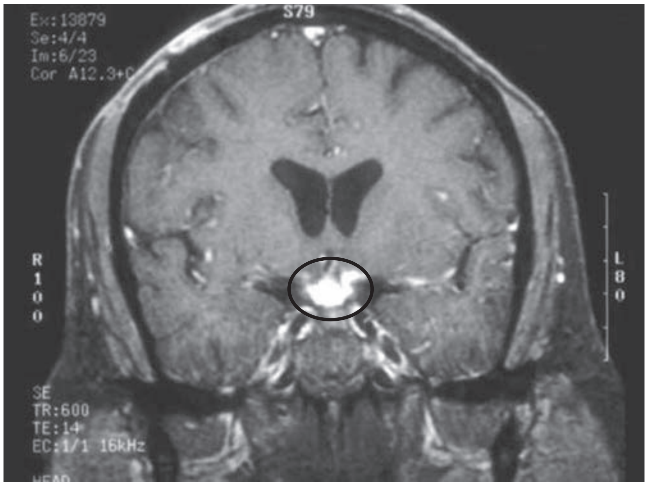

Figure 53-6 Sarcoidosis involving the optic chiasm *(circle)* resulting in blindness.

Exocrine Gland Sarcoidosis

Granulomatous inflammation of salivary, parotid, and lacrimal glands results in enlarged, tender glands and/or sicca syndrome with dry mouth and dry eyes in less than 5% of patients with sarcoidosis. The association of fever, parotid enlargement, facial palsy, and uveitis is known as uveoparotid fever, or Heerfordt syndrome, and is usually accompanied by bilateral hilar adenopathy.

Endocrine Sarcoidosis

Abnormal calcium metabolism is found in sarcoidosis; hypercalciuria is more frequent than hypercalcemia. These abnormalities are due primarily to increased conversion of 25(OH) vitamin D metabolites to active 1,25$(OH)_2$ vitamin D by tissue macrophages and epithelioid cells at sites of granulomatous inflammation.[161] Hypothalamic/pituitary insufficiency may be a manifestation of neurosarcoidosis.

Renal Sarcoidosis

Renal sarcoidosis is considered to be a rare manifestation, but its true frequency is likely underestimated due to a lack of studies judiciously evaluating early signs of renal dysfunction, such as microhematuria and leukocyturia.[162] Kidney stones are the most frequent manifestation of renal sarcoidosis, usually related to abnormal calcium metabolism. Renal failure due to nephrocalcinosis may result from chronic, often asymptomatic hypercalcemia or hypercalciuria. Granulomatous interstitial nephritis is the most typical histologic finding.

Genitourinary Sarcoidosis

Sarcoidosis of the reproductive system has been estimated to occur in less than 1% of clinically diagnosed cases and in 5% of autopsy cases. Genitourinary manifestations of sarcoidosis in men include testicular masses and acute epididymitis-orchiditis. In women, sarcoidosis may manifest with uterine or ovarian involvement that may cause dysmenorrhea or mimic malignancy or fibroids.

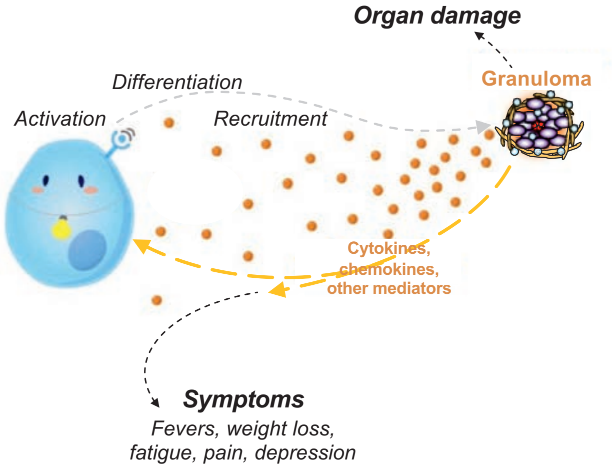

Figure 53-7 Cytokines and other circulating mediators contribute to organ damage by activating cells and directing granuloma formation. Importantly, circulating mediators contribute to patient symptoms through mechanisms other than through direct organ damage, resulting in negative effects on mobility and wellness, adherence, and quality of life.

Psychosocial and Humoral Manifestations

The biological processes involved in sarcoidosis are caused by cytokines and other circulating mediators produced during inflammation. These chemical signals contribute to activation of the immune system, resulting in the initiation and maintenance of granulomatous inflammation that directly causes damage to tissues and organs (Fig. 53-7). However, these chemical signals also contribute to patient symptoms through mechanisms other than direct damage to tissues and organs, and the term *parasarcoidosis syndromes* has been coined to raise awareness of the prevalence of these problems reported by patients. For example, active sarcoidosis can increase the conversion of inactive vitamin D-25OH (sourced from diet and sunlight exposure) into its active form, vitamin D-1,25OH, resulting in hypercalcemia and its secondary effects (osmotic diuresis, fatigue, constipation, altered mental status).[163] Tumor necrosis factor contributes to constitutional symptoms including fatigue and pain, frequently reported among sarcoidosis patients.[164] Depression is also frequently reported among patients with sarcoidosis and can represent a side effect of glucocorticoid treatment but also is hypothesized to be an effect of proinflammatory cytokines.[165–167]

A Dutch study found the prevalence of depression was 4% in asymptomatic patients and 30% in symptomatic patients with sarcoidosis, while the prevalence of depression was found to be 60% in a U.S. study of both white and Black patients with sarcoidosis.[168,169] In this latter study, depression was associated with the female sex, lower socioeconomic status, poor access to care, and increased disease severity, but not race. Using the Hospital Anxiety and Depression Scale (HADS), a German study found that objective scores for anxiety and depression were significantly higher among sarcoidosis patients compared with a control population matched by age and gender, and that dyspnea was an important symptom predicting the presence of anxiety and depression.[170] A recent study found that self-reported depression in sarcoidosis patients was associated with higher health care utilization (emergency department visits) and worse clinical outcomes (lower diffusion capacity) compared to patients without psychological symptoms,[171] supporting the impression that mental illness begets medical noncompliance.[172]

The prevalence of pain in sarcoidosis is unclear, but clinical experience suggests it is common with frequent reports of arthralgias, myalgias, headache, and chest pain, and a subset of patients meets diagnostic criteria for fibromyalgia. However, the cause of pain is often multifactorial with causes including direct granulomatous inflammation of bones, joints, muscles, or peripheral nerves. Additionally, sarcoidosis has been recognized as an inflammatory cause of small fiber neuropathy (SFN).[152,173] Although SFN can result as a complication from chronic inflammation, treatment with immunosuppression medications is often ineffective once SFN is manifest. In addition to its association with pain, SFN may cause autonomic dysfunction with gastrointestinal dysmotility, incontinence or retention, sicca syndrome, flushing, sweats, orthostatic hypotension, and sexual dysfunction.[174]

■ Associated Conditions

Important selected conditions associated with sarcoidosis are discussed briefly below.

Sarcoidosis and Pregnancy

There is usually little long-term effect on the course of sarcoidosis from pregnancy. In contrast to diseases such as asthma and systemic lupus that may progress during pregnancy, spontaneous improvement in chronic sarcoidosis has been reported in some patients during pregnancy, although exacerbations often follow several months after delivery. The reasons for the temporary clinical improvement are not known but might be related to suppressed Th1 immunity during pregnancy associated with enhanced Treg function. A population-based retrospective cohort study found that sarcoidosis was associated with higher rates of obstetrical complications but not maternal death.[175]

Altered Th1 Immunity

Sarcoidosis is associated with several clinically disparate situations associated with altered, enhanced Th1 immunity. The clearest example involves the administration of Th1-promoting therapeutics such as IFN-α, IFN-γ, IL-2, and IFN-β that may be associated with initiation or recrudescence of sarcoidosis.

Common Variable Immunodeficiency Granulomatous inflammation has been identified in several immunodeficiency states, particularly in patients with hypogammaglobulinemia secondary to common variable immunodeficiency (CVID). Within subsets of patients with CVID, case series reports suggest that a diagnosis of concurrent sarcoidosis can be inferred by a compatible history of systemic illness and confirmed by biopsy.[176] In other CVID patients who present with dominant pulmonary manifestations, CVID-associated granulomatous-lymphocytic interstitial lung disease may be present and is often resistant to treatment.[177] Since CVID occurs at any age, a high index of suspicion must be maintained, particularly in sarcoidosis patients who have recurrent infections or in any child with sarcoidosis given the low frequency of sarcoidosis in this age group.

Human Immunodeficiency Virus Sarcoidosis may develop in HIV-infected patients with immune reconstitution following initiation of highly active antiretroviral therapy, perhaps from reconstituted Th1 immunity.[57] Granulomatous inflammation of the lungs or skin is most often reported.

Autoimmune Disorders Sarcoidosis is associated with a variety of disorders of the immune system, such as Crohn's disease, ulcerative colitis, primary biliary cirrhosis, scleroderma, Sjögren syndrome, autoimmune hemolytic anemia, and autoimmune endocrinopathies.[178] Given the rarity of some of these disorders, it is reasonable to postulate that these associations are the result of a common immune disturbance, with altered Th1/Th17 immunity that may predispose to both disorders.

Recently, a syndrome of immune-mediated disorders in patients with elevated serum IgG4 levels has been described, commonly presenting as adenopathy, constitutional symptoms, and mass-like tumors.[179] Granulomatous inflammation is observed in a subset of patients mimicking sarcoidosis, and an evaluation for IgG4-related disease should be considered in patients who have clinical features atypical for sarcoidosis, such as recalcitrant eosinophilia, pancreatitis, or multiple endocrinopathies.

Cancer Noncaseating granulomas may be seen within or near 3% to 10% of tumors and in approximately 4% of regional draining lymph nodes.[180] Less commonly, multisystem granulomas consistent with systemic sarcoidosis develop in patients with a recent or past diagnosis of cancer or following chemotherapy treatment. Often the diagnosis is established by biopsy of enlarged lymph nodes or lung where the presurgical diagnosis is recurrent malignancy.[181] There is usually little functional lung impairment from pulmonary sarcoidosis in these instances, and treatment is often unnecessary with eventual remission. A possible link involves dysregulated Th1/Th2 immunity, a premise supported by several cases of sarcoidosis developing in patients with changes that result in deletion of several Th2 genes (IL4, IL13, CSF2).[182] Along this vein, induction of a sarcoidosis-like granulomatous inflammation may complicate the administration of immunotherapy for cancer.[183]

Pediatric Sarcoidosis

Sarcoidosis is significantly less prevalent among children compared with adults, and sarcoidosis is rare in the preteen ages.[184] Early-onset disease in children under 5 years of age typically involves skin, eye, and joint involvement that has considerable clinical overlap with juvenile rheumatoid arthritis or Blau syndrome, an autosomal dominant granulomatous disease caused by a NOD2 mutation.[185] This form of sarcoidosis carries a much worse prognosis than disease presenting in older children. In the teenage years, clinical manifestations and prognosis in children is similar to that of adults. Pediatric sarcoidosis may also be associated with CVID.

Sarcoidosis in the Elderly

Recurrent sarcoidosis after many years, even decades of apparent remission, is also seen, often manifesting with recrudescence of original manifestations, or with new-onset neurologic or cardiac involvement.

DIAGNOSTIC APPROACH

There is no reliable, noninvasive screening test to help confirm a diagnosis of sarcoidosis. A diagnosis of sarcoidosis is based on compatible clinical and radiologic manifestations together with a tissue biopsy demonstrating noncaseating granulomatous inflammation and exclusion of other granulomatous disorders (Fig. 53-8). Exceptions to this approach include patients who manifest with Löfgren syndrome in areas with a low prevalence of histoplasmosis, which may mimic Löfgren syndrome, in which case most experts believe a biopsy is not necessary.[186] Many experts suggest that patients with asymptomatic bilateral hilar adenopathy with presumptive stage I sarcoidosis do not need biopsy unless atypical features are present, given a low pretest probability for alternative diagnoses and the risks for potential complications of a diagnostic biopsy.[187,188] Clinical involvement of more than one organ system helps exclude local granulomatous reactions to foreign bodies, infection, or malignancy. The decision to obtain a confirmational biopsy in patients with presumed stage I sarcoidosis presenting as asymptomatic bilateral hilar adenopathy relies on an individualized assessment of a patient's cancer and/or occupational risk factors, risks associated with biopsy approach, local prevalence of infectious diseases (e.g., tuberculosis, endemic fungus), and the availability and feasibility of close medical follow-up.[2]

In general, the easiest accessible biopsy site can be approached to confirm a diagnosis of sarcoidosis. Biopsy of a skin or conjunctival nodule, enlarged superficial lymph node, or lacrimal gland may help to establish a diagnosis. Noncaseating granulomas on a liver or bone marrow biopsy are nonspecific and support a diagnosis only when competing diagnoses such as infection, drug reaction, or malignancy are excluded.

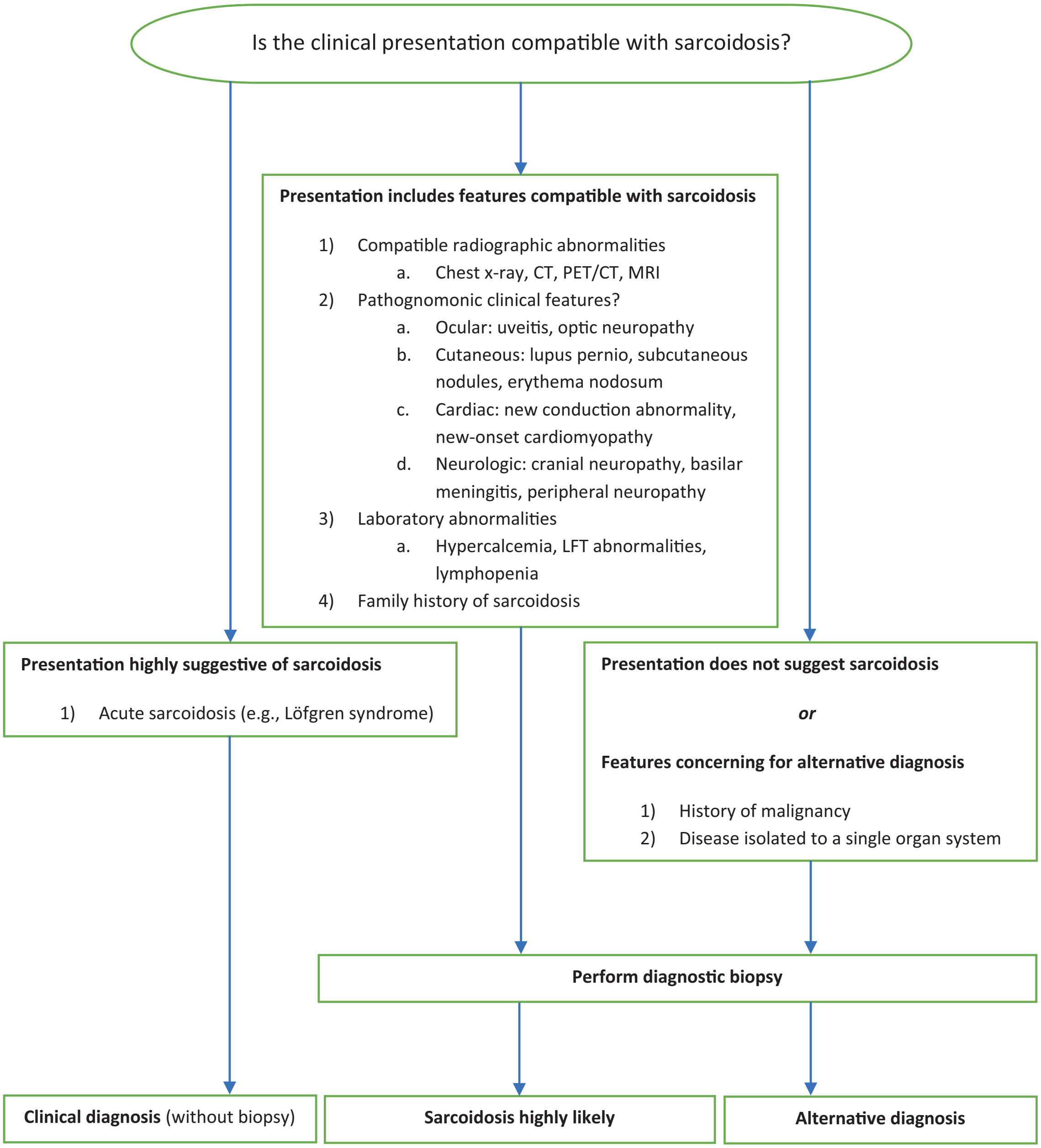
Is the clinical presentation compatible with sarcoidosis?
Presentation includes features compatible with sarcoidosis
1) Compatible radiographic abnormalities
a. Chest x-ray, CT, PET/CT, MRI
2) Pathognomonic clinical features?
a. Ocular: uveitis, optic neuropathy
b. Cutaneous: lupus pernio, subcutaneous nodules, erythema nodosum
c. Cardiac: new conduction abnormality, new-onset cardiomyopathy
d. Neurologic: cranial neuropathy, basilar meningitis, peripheral neuropathy
3) Laboratory abnormalities
a. Hypercalcemia, LFT abnormalities, lymphopenia
4) Family history of sarcoidosis
Presentation highly suggestive of sarcoidosis
1) Acute sarcoidosis (e.g., Löfgren syndrome)
Presentation does not suggest sarcoidosis
or
Features concerning for alternative diagnosis
1) History of malignancy
2) Disease isolated to a single organ system
Perform diagnostic biopsy
Clinical diagnosis (without biopsy)
Sarcoidosis highly likely
Alternative diagnosis

Figure 53-8 Diagnostic approach for evaluation of possible new case of sarcoidosis.

When a more easily accessible site is not available, biopsy by fiberoptic bronchoscopy remains the most common approach because of its high yield and relative safety. The diagnostic yield of transbronchial biopsy (TBB) is estimated to be >40% even in patients with a stage I chest radiograph and approaches 80% in the presence of lung infiltrates.[189] Transbronchial lung biopsy in advanced fibrocystic sarcoidosis has a low yield, owing to extensive fibrotic changes. Sampling by endobronchial mucosal biopsy (EMB) and transbronchial needle aspiration (TBNA) of thoracic lymph nodes provides additional sensitivity when combined with TBB.[190] The sensitivity of endoscopic bronchial ultrasound (EBUS)-guided TBNA has been found to be superior to standard TBNA in diagnosis of sarcoidosis.[191] Transbronchial lung cryobiopsy may improve diagnostic yield in challenging diagnostic situations but may be associated with higher rates of complications compared with other bronchoscopic techniques.[192] In cases of suspected malignancy, mediastinoscopy or surgical lung biopsy may be needed for histologic diagnosis.

Bronchoalveolar lavage obtained as part of a diagnostic bronchoscopy remains an important method for excluding infectious causes of granulomatous inflammation. Some studies suggest that a BAL T cell CD4:CD8 ratio >3.5 supports a diagnosis of sarcoidosis but may not differentiate some infectious or noninfectious inflammatory lung diseases.[193]

A diagnosis of cardiac sarcoidosis is usually established by a noncardiac biopsy confirming systemic sarcoidosis along with consistent myocardial imaging studies or rhythm disturbances (Fig. 53-5). Endomyocardial biopsy is positive in <20% of cardiac sarcoidosis owing to sampling inefficiencies and the infrequency of right ventricular involvement; thus a negative biopsy never excludes cardiac sarcoidosis.[194]

A diagnosis of neurosarcoidosis is usually confirmed by biopsy of a non-CNS site.[195] Rarely, brain biopsy is needed to exclude infectious or malignant disease.

For organs that are rarely involved in sarcoidosis, directed biopsy of the involved tissue is often recommended to exclude alternative causes, even when there is documentation of a prior biopsy that confirmed an original diagnosis of sarcoidosis.[196] For organs that are difficult to biopsy, ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) scanning, or contrast-enhanced MRI scanning have replaced ^{67}gallium scans in helping define sites of clinically occult inflammation that could provide an alternative biopsy approach.[197]

Laboratory tests are generally not helpful in confirming a diagnosis of sarcoidosis but may assist in establishing an alternative diagnosis, such as autoimmune disease. A diagnostic biomarker has not been identified for sarcoidosis. Serum angiotensin-converting enzyme (sACE) levels are elevated in 30% to 80% of patients with clinically active disease from activated epithelioid cells and macrophages at sites of inflammation, but can be also seen in infectious granulomatous diseases, pneumoconiosis, cirrhosis, diabetes, thyroid disease, and autosomal dominant familial clustering; thus sACE lacks specificity as a diagnostic tool.[198]

CLINICAL ASSESSMENT

Once a diagnosis is established or suspected, an initial evaluation should consist of tests to evaluate the presence and extent of pulmonary involvement and assess the presence and severity of extrathoracic disease (Table 53-5).

Specialized testing is indicated when symptoms or signs suggest extrapulmonary sarcoidosis. Guidelines for when and how to screen for potential cardiac involvement remain uncertain.[2,147,199,200] Due to its low cost and wide availability, all patients should have a yearly ECG.[2] Screening for cardiac sarcoidosis is recommended whenever symptoms such palpitations, near-syncope/syncope, orthopnea, or leg edema are present.[201] A second-level screening may include a Holter monitor, signal-averaged ECG, and echocardiogram to detect conduction abnormalities impaired, heart rate variability, or myocardial dysfunction. Advanced cardiac imaging with cardiac MRI with gadolinium enhancement or cardiac FDG-PET scanning is recommended for those patients with continued uncertainty of possible cardiac sarcoidosis. Unexplained dyspnea or chest pain may also be suggestive for sarcoidosis but may also prompt investigations for other etiologies such as pulmonary hypertension or esophageal dysmotility, respectively.[152] Thallium or technetium sestamibi myocardial scanning, in conjunction with cardiac FDG-PET or MRI, is useful to exclude coronary artery disease and may detect patchy fixed or reverse ischemia–perfusion defects consistent with myocardial inflammation or fibrosis.[202] Electrophysiologic testing may be indicated to exclude arrhythmias not detected by routine studies and assess indications for cardiac pacemaker or implantable defibrillator to reduce the risk of sudden death.[203] The presence of myocardial scar is associated with increased risk for arrhythmogenic events and all-cause mortality.[204]

TABLE 53-5 Suggested Tests for Initial Sarcoidosis Clinical Evaluation

All Patients	Organ-Specific Testing for Suspected Involvement
Chest radiograph or chest CT	Cardiac: echocardiogram, Holter monitoring, cardiac MRI, cardiac PET
Pulmonary function tests: spirometry, diffusing capacity, lung volumes	Neurologic: brain or spine MRI with gadolinium enhancement, cerebrospinal fluid examination, nerve conduction studies, small fiber nerve analysis
Ophthalmologic examination	Upper respiratory tract: flow-volume loop, ENT evaluation
Complete metabolic panel	Endocrine: pituitary function tests; thyroid function tests
Complete blood count with differential count	Kidney stones: vitamin D-1,25OH, parathyroid hormone level, 24-h urine calcium
Electrocardiogram	Renal: Urinalysis, renal biopsy
IFN-γ release assay	Cutaneous: skin biopsy

Evaluation for possible CNS and spinal sarcoidosis should include MRI with gadolinium enhancement, now considered the optimal test to detect characteristic inflammatory lesions.[195] The distribution of inflammatory loci has a propensity for periventricular and leptomeningeal areas, although the images are nonspecific and can be produced by infectious, malignant, or occasionally demyelinating disease.[151] A normal scan does not exclude neurosarcoidosis, particularly for cranial neuropathies or in the presence of corticosteroid therapy. Examination of the cerebrospinal fluid may be useful for demonstrating characteristic lymphocytic pleocytosis and/or elevated protein levels, and to exclude infection and hydrocephalus in select cases. For suspected peripheral neuropathy or myopathy, EMG or nerve conduction studies or, rarely, tissue biopsy may help to establish a link to sarcoidosis. Specialized evaluation including skin biopsy analysis of intraepidermal nerve fiber density and neurophysiologic testing may be indicated to confirm cases of small fiber neuropathy.[152]

CLINICAL COURSE AND PROGNOSIS

A clinical framework can be constructed to assist in decisions regarding monitoring and planning treatment strategies. First, organ involvement usually defines itself early in the disease. For example, only 23% of patients in the ACCESS study were found to have one or more new organ systems involved with sarcoidosis during a 2-year follow-up evaluation; the presence of extrapulmonary involvement at presentation was a risk factor for new organ development.[128] Second, patients who undergo remission usually do so within the first 2 to 3 years. Clinical experience suggests sarcoidosis rarely recurs after a prolonged period of remission, with exceptions most often involving neurologic or ocular manifestations. Third, patients with chronic sarcoidosis generally have progressive, unremitting organ impairment. High rates of relapse (>50%) are observed in patients requiring systemic immunosuppressive medications compared with those who experience spontaneous disease remission (<10%).[205–207] In these patients, the rate of progression varies from individual to individual, as does their response to treatment. A waxing–waning clinical course is uncommon except for a subset of patients with neurologic or ocular manifestations or occasionally recurrent erythema nodosum. Fourth, prognosis in sarcoidosis is strongly influenced by the initial manifestations of disease. Patients with Löfgren syndrome have remission rates of 70% to 80%. An initial stage I chest radiograph is associated with a 60% to 90% remission rate. Patients manifesting with type II chest radiographs have a poorer outcome, with spontaneous remission occurring 40% to 70% of the time. A stage III chest radiograph is associated with remission in only 10% to 20% of patients. Patients with extensive pulmonary fibrosis (stage IV) rarely undergo remission.

Currently, a consensus recommendation is that treatment decisions are best based on repeated clinical examinations and direct measurement of organ function and not on laboratory markers of disease "activity."[1,18,208] SACE levels tend to correlate with the extent of granulomatous inflammation throughout the body, particularly when interpreted in the context of known polymorphisms of ACE alleles, and usually decrease in response to corticosteroids or with disease remission—but the test is highly variable, correlates poorly with functional assessments of disease activity, and has no prognostic value. Similarly, BAL parameters such as the proportion of CD4 lymphocytosis or the CD4:CD8 ratio of BAL T cells have been inconsistent in predicting outcomes. Many inflammatory molecules have been proposed as helpful biomarkers for disease activity including sIL2R, TNF, and neopterin but are not reliable prognostic indicators.[209] PET/CT scans can be considered to detect and monitor evidence of inflammation in select cases (such as cardiac and neurologic involvement), but given the cost and risk associated with radiation exposure, further evaluation is needed to confirm its prognostic value and appropriate role for long term management.[210] More recently, studies suggest transcriptomic signatures may be useful for prognosis, but there are no currently validated markers useful for clinical purposes.[211] Monitoring for at least 3 years following presumed "disease remission" is recommended; longer periods of observation are indicated for patients with serious pulmonary or extrapulmonary manifestations.

TREATMENT

A variety of approaches have been utilized in the treatment of sarcoidosis and are outlined in this section. There are no FDA-approved systemic therapies for sarcoidosis.

Indications for Treatment

There have been attempts to provide evidence-based recommendations for treatment of sarcoidosis, but the lack of placebo-controlled clinical trials in this highly heterogeneous disease have made firm conclusions problematic. Most physicians agree that corticosteroid or other systemic therapy is indicated for the manifestations listed in Table 53-6.

Indications for treatment must account for the overall excellent prognosis for most patients with sarcoidosis, particularly for patients with stage I disease, for whom systemic therapy is usually not required. Symptomatic or local therapy is recommended whenever possible. Löfgren syndrome is usually managed with bed rest and nonsteroidal anti-inflammatory drugs; corticosteroids are recommended when symptoms, particularly arthritis, are disabling and persistent.

Corticosteroid Therapy

Corticosteroids remain the cornerstone of therapy for sarcoidosis. Although controversy exists regarding the overall effectiveness of corticosteroids in altering the long-term course of the disease, there is no disagreement that corticosteroids provide prompt symptomatic relief and reverse organ dysfunction in most patients with the degree of reversibility dependent on the extent of pre-existing fibrosis. Case series and several but not all clinical trials support the view that corticosteroids favorably affect disease outcome in chronic pulmonary sarcoidosis. One large study by the British Thoracic Society found long-term improved lung function in patients with stage II or III pulmonary disease treated with daily corticosteroid therapy compared with a group treated intermittently with corticosteroids based on symptoms.[205]

TABLE 53-6 Indications for Treatment of Sarcoidosis

Threatened organ failure • Severe ocular, cardiac, or neurologic disease
Uveitis unresponsive to topical corticosteroids
Progressive, persistent, or symptomatic pulmonary disease
Disfiguring cutaneous disease, especially lupus pernio on the face
Persistent hypercalcemia, renal or hepatic dysfunction
Symptomatic hepatic or splenic enlargement, hypersplenism (sequestration)
Symptomatic myopathy
Painful lymphadenopathy
Severe fatigue and weight loss

Optimal dosing of corticosteroid therapy has not been established by clinical trials. Most authorities suggest that initial treatment of pulmonary sarcoidosis usually does not require more than 20 to 40 mg per day of prednisone followed by a slow taper to a maintenance dose of 5 to 15 mg per day of prednisone.[212] Every-other-day dosing of prednisone may be effective in some but not all patients. Treatment is usually continued for a minimum of 6 to 24 months, since premature attempts to taper off steroids are likely to result in relapse of disease. Inhaled steroids appear to have limited effectiveness in chronic pulmonary sarcoidosis and are not recommended as sole therapy. Overall, chronic progressive pulmonary disease occurs in more than 20% of patients as oral corticosteroids are tapered or discontinued. Treatment of extrapulmonary sarcoidosis is modeled after the general approach to pulmonary sarcoidosis (Table 53-7), with special considerations for specialized testing and concerns based on specific organ involvement. Extrapulmonary sarcoidosis may require higher doses of corticosteroids, especially for cardiac, neurologic, and severe ophthalmologic cases and warrant collaboration with a specialist.

Alternative Agents

Several classes of drugs have been reported to be beneficial in subgroups of patients with sarcoidosis, but none of these drugs has been proven effective by rigorous clinical trials.

Nonimmunosuppressive Drugs

Case series suggest hydroxychloroquine is effective in many patients with mucocutaneous sarcoidosis, in those with hypercalcemia, and, occasionally, as a steroid-sparing agent in systemic sarcoidosis. Ocular toxicity is rare, and its overall safety profile provides a rationale for an early trial of this drug. Chloroquine may be

TABLE 53-7 Suggested Initial Management for Sarcoidosis

	Initial Prednisone Dose (mg/d)	Testing *Special Management Concerns*
Pulmonary	20–40	Biopsy, PFTs, chest x-ray, chest CT *Airway reactivity, pulmonary hypertension, sleep apnea*
Cutaneous[T]	20	Biopsy *Intralesional corticosteroid injections, hydroxychloroquine*
Sinonasal[T]	20–40	Biopsy, CT scan, laryngoscopy *Nasal irrigation, topical corticosteroids*
Hepatic	20	Biopsy, MRI *Cirrhosis*
Cardiac	40	ECG, echo, Holter, PET/CT, MRI *CHF management, electrophysiology study, cardiac device*
Neurologic[IV]	40–80	MRI with gadolinium, lumbar puncture *Small fiber neuropathy, hydrocephalus, neurorehabilitation*
Ocular[T, IV]	40–80	Urgent ophthalmology evaluation *Dry eye syndrome, occluded tear ducts*

[T] *Topical corticosteroids are often a first-line consideration.*

[IV] *Intravenous pulse-dosed corticosteroid are often considered for severe cases.*

efficacious in treating lupus pernio, SURT, or sinus disease, which is often recalcitrant to other therapies, although ocular toxicity has limited its use.

The tetracyclines minocycline and doxycycline may be effective in a subgroup of patients with mild cutaneous sarcoidosis but rarely as a steroid-sparing drug in systemic disease. These antibiotics have mild anti-inflammatory effects (possibly through effects on the host microbiome), which probably account for their mechanism of action given that other antibiotics with similar antimicrobial activity have not been found effective in sarcoidosis.

Case series supported the use of adrenocorticotropic hormone (ACTH) for treating sarcoidosis prior to the wide availability of oral corticosteroid medications.[213] In addition to supporting the natural production of cortisol, ACTH can interact through melanocortin receptors, which demonstrate possible anti-inflammatory effects in experimental models.[214] Therefore, ACTH has reemerged as a treatment consideration for sarcoidosis, but whether the primary systemic effect of ACTH administration is through augmenting cortisol production is unknown. Prospective studies are needed to confirm the role of ACTH for treating sarcoidosis, particularly whether ACTH (typically administered as repeated injections) has any safety (and cost) benefits compared to oral corticosteroids.

Pentoxifylline is a phosphodiesterase inhibitor with anti-inflammatory effects that was found to be effective in early pulmonary sarcoidosis in one study.[215] Other experiences have not been as favorable with responses in less than 10% of patients, generally those with mild pulmonary or systemic sarcoidosis.

Melatonin was found to be beneficial in a small case series of patients with generally mild disease, but wider experience has not confirmed its efficacy.

Thalidomide was found in one study to be beneficial in more than 80% of patients with severe skin sarcoidosis (lupus pernio unresponsive to other therapies) but was not effective in pulmonary sarcoidosis.[216] Given the drug's well-known teratogenicity and potential to cause peripheral neuropathy and sedation, the drug is recommended only in patients refractory to other treatments.

Immunosuppressive Drugs

Clinical experience in sarcoidosis suggests that all noncorticosteroid immunosuppressive therapies share the following characteristics: beneficial responses are seen in no more than 50% to 70% of patients; responses may take 3 to 6 months or longer; low-dose corticosteroid therapy is often needed for synergistic effect to obtain adequate suppression of granulomatous inflammation. Dosing and monitoring for these therapies should follow the recommendations of the American College of Rheumatology.[217]

Methotrexate is often the first immunosuppressive therapy used as an alternative therapy for refractory pulmonary or systemic sarcoidosis when corticosteroid and antimalarial therapies are ineffective or poorly tolerated. Hepatic, pulmonary, and renal toxicities limit the use of the drug. Azathioprine has shown benefit in small clinical trials and is used by some authorities as an initial potent steroid-sparing therapy. Clear advantages of methotrexate or azathioprine over low-dose corticosteroids in the routine management of sarcoidosis have not been established. Other immunosuppressive agents, such as mycophenolate mofetil, leflunomide, or cyclophosphamide, have been found beneficial in a small series of patients with manifestations of sarcoidosis refractory to corticosteroids.

Small studies have shown that cyclosporine and FK506, drugs known to inhibit T-cell activation, are not effective in pulmonary or ocular sarcoidosis or in suppressing recurrent sarcoidosis in transplants. Given their toxicities, consensus is to avoid these medications until new studies demonstrate potential benefits.

Anti-TNF Therapies and Other Biologic Agents

The scientific basis for the use of TNF inhibitors in sarcoidosis is firmly established based on the role of TNF in experimental models of granuloma formation. One multicenter study found infliximab to be effective in one of several primary endpoints (improved FVC after 24 weeks of therapy), although the effect was modest.[218] Etanercept was not shown to be effective in a smaller clinical trial of pulmonary sarcoidosis.[219] Successful treatment with rituximab has been reported in individual cases, particularly for the treatment of ocular or CNS manifestations, but the results from case series has been inconsistent.[220] Other biologic agents targeting other mechanisms involved in sarcoidosis (anti-IL12, anti-IL6, anti-CTLA4) also may be useful for treating patients who have not benefited from other treatments, but given the risk profiles of these agents, additional clinical trials are warranted to evaluate their appropriate therapeutic role.[221–223]

■ Special Circumstances

Several special considerations in the management of systemic sarcoidosis deserve particular mention.

Fibrocystic Sarcoidosis

Advanced pulmonary sarcoidosis may be complicated by mycetomas, usually from *Aspergillus fumigatus*, that colonize pre-existing cystic spaces. The fungi rarely cause invasive disease. Spontaneous resolution may be seen. The benefit of antifungal agents has not been established, but they may be used for serious hemoptysis. Massive hemoptysis associated with mycetomas or bronchiectasis may be life-threatening, requiring therapeutic embolization of the appropriate bronchial or collateral artery for control. Surgery is usually not feasible because of the severe restrictive lung disease.

Pulmonary Hypertension

Moderate or severe pulmonary hypertension is an independent predictor of reduced survival in patients with advanced lung disease awaiting lung transplantation.[133] Outcomes are associated with the severity of pulmonary hypertension, warranting the evaluation of strategies for early screening.[137] Management options include immunosuppression to control active sarcoidosis inflammation and agents targeting pulmonary hypertension, but longitudinal studies are needed to determine the roles of these therapies.[136]

Cardiac Sarcoidosis

Several large case series find prognosis in cardiac sarcoidosis, and response to treatment is related to the degree of cardiac dysfunction. Treatment of cardiac sarcoidosis consists of antiarrhythmic therapy, diuretics, and afterload-reducing agents for specific cardiac abnormalities. Although randomized trials are lacking, studies from Asia, Europe, and the United States consistently report that corticosteroids in moderate doses are associated with improved cardiac function and outcomes.[224,225] Maintenance doses of prednisone often range between 10 to 25 mg a day, although higher doses may be needed for intractable arrhythmias. Immunosuppressive drugs, including anti-TNF agents, are frequently used as steroid-sparing agents since treatment often must be maintained for years.[226] Automatic implantable cardioverter-defibrillators (ICDs) may prevent sudden death in patients with serious arrhythmias.[147,203,204]

Neurosarcoidosis and Ocular Sarcoidosis

High doses of oral corticosteroids or high-dose pulse intravenous therapy are often indicated for serious ocular or CNS disease, such as optic neuritis or encephalitis followed by maintenance corticosteroid or immunosuppressive therapy. Anterior uveitis can usually be treated with topical ophthalmologic steroid drops; intraocular corticosteroid injections can be used in more aggressive cases in patients who do not have extraocular sarcoidosis. Systemic immunosuppression may be necessary in cases of severe disease, and the use of steroid-sparing agents including TNF inhibitors should be considered to limit the risk of corticosteroid-related complications. Neuro-ophthalmologic sarcoidosis is often associated with chronic disease activity, and relapses frequently occur in some patients on de-escalation or withdrawal of therapy.[227] Small fiber neuropathy typically does not reliably respond to corticosteroid therapy, prompting trials of neuropathic drugs, TNF inhibitors, or other novel agents.[152,228]

Pregnancy

Corticosteroids are the only drugs recommended for use during pregnancy because of the potential for other steroid-sparing drugs to cause fetal toxicity or teratogenicity. Sometimes, spontaneous abatement of chronic sarcoidosis occurs in pregnant patients, allowing a temporary reduction in steroid dosage. After pregnancy, however, an exacerbation often occurs, requiring a return to the original maintenance dose.

■ Quality of Life

There is increasing recognition of the need to treat depression and pain to improve quality of life in patients with these manifestations.[229] The utility of nonpharmacologic treatments, such as exercise training or pulmonary rehabilitation, merits investigation because of the impact of these problems in sarcoidosis patients.[230]

■ Lung and Heart Transplantation

Although advanced lung disease from sarcoidosis can be successfully controlled with long-term use of immunosuppression medications, sarcoidosis patients referred for lung transplantation experience high rates of mortality.[231] Successful lung, heart–lung, and heart transplantations have been performed in patients with advanced pulmonary sarcoidosis or cardiomyopathy. Although noncaseating granulomas have been found in some transplanted lungs or hearts, these findings do not appear to significantly affect outcome.[232,233] Outcomes for lung transplant in sarcoidosis are similar to other interstitial lung diseases.

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CHAPTER 54

Idiopathic Pulmonary Fibrosis

Tanzira Zaman
Giuliana Cerro Chiang
Paul W. Noble

INTRODUCTION

Interstitial lung disease (ILD) is a heterogenous group of inflammatory and scarring conditions of the lung. Idiopathic pulmonary fibrosis (IPF) is a distinct form of ILD and represents a specific clinical entity defined by a constellation of clinical, radiographic, and pathophysiologic features. Other forms of cryptogenic ILD that do not fit into the diagnostic criteria for IPF are referred to as "unclassifiable" ILD, although some may, in fact, show a clinical trajectory that matches IPF.

IPF is the most common ILD with heterogenous and complex pathophysiology without a clear causative etiology (except in the case of familial disease). A diagnosis of IPF is made most confidently when a high-resolution computed tomography (HRCT) or histopathologic pattern of usual interstitial pneumonia (UIP) is observed in the absence of an identifiable trigger. Such etiologies include connective tissue disease, environmental exposures leading to hypersensitivity reactions, and drug-induced fibrosis. In other words, UIP is not synonymous with IPF; other etiologies of UIP must be excluded for the diagnosis of IPF.

Considered a disease of aging, IPF usually presents in the seventh decade of life. The symptoms and physical examination findings of IPF are nonspecific and can thus lead to substantial delays in diagnosis, especially as there are far more common pulmonary and cardiac abnormalities that present similarly. As will be discussed further, the scope of current therapies for IPF render them of greatest benefit earlier in the course of disease, so timely diagnosis is of importance from a therapeutic standpoint. Diagnostic delays also contribute to patient distress, and as depression and anxiety are common comorbidities in IPF, earlier establishment of a definitive diagnosis can contribute to a patient's peace of mind and ability to cope with chronic illness.

The clinical course of IPF is one of certain, yet unpredictable, progression. Long-term observational studies of patients with IPF reveal that while decline in lung function is inevitable, there is a paucity of reliable predictors to identify which patients are at risk for progression. Similarly, there are no reliable means to identify which patients are at risk for acute exacerbations of disease or when such exacerbations are likely to occur, which provides a challenge in counseling patients on prognosis and determining the ideal timing for what remains the only definitive "cure" for IPF: lung transplantation.

Biomedical research in recent years has yielded new insights into the genetic predisposition to IPF, the pathogenic pathways that are potentially targetable with experimental therapies, and molecular markers to discriminate IPF from non-IPF ILD. However, there remains an unmet need to develop medications that not only slow disease progression, but halt progression of disease entirely.

HISTORIC PERSPECTIVE

A brief review of the evolution in our understanding of IPF illustrates the contributions made by earlier investigators but also reveals the reasons for the confusion that many clinicians have regarding IPF. One of the challenges in defining IPF has been the variety of antiquated terms formerly used to describe pulmonary fibrosis. While there are many causes of ILD in general, and pulmonary fibrosis in particular, it is important to note that IPF is a unique disease rather than a catch-all term for any and all idiopathic interstitial pneumonias (IIP). A review of the history of IPF will both clarify the present terminology and distinguish contemporary nomenclature from the outmoded terms encountered in earlier literature.

Fibrosis of the lung was long recognized in association with infection or dust inhalation. In the 19th century, pulmonary fibrosis was known as "cirrhosis of the lung"; little attention was paid to this form of respiratory illness.[1] Interest in pulmonary fibrosis was ignited in 1944 when Louis Hamman and Arnold Rich published a seminal paper describing "acute diffuse interstitial fibrosis of the lungs."[2] Hamman and Rich reported a series of unusual cases that shared a unique clinical presentation featuring idiopathic subacute respiratory failure followed by death. Their report was complete with pathologic findings from autopsy. They described thickening of the alveolar interstitium and areas of dense fibrotic scar tissue within the lung, the first pathologic depiction of pulmonary fibrosis. In retrospect, the cases of Hamman and Rich best fit a diagnosis of the fibrosing interstitial pneumonia now known as acute interstitial pneumonitis (AIP).[3] However, in the 1940s, the "Hamman–Rich syndrome" became synonymous with IPF, and so it remained for the next three decades.

Over the years, clinical reports of pulmonary fibrosis suggested a number of alternate presentations that were referred to as "variants" of the Hamman–Rich syndrome.[4] This included cases that exhibited a rather protracted duration of illness compared with the "classic" Hamman and Rich cases. It was also noted that pulmonary fibrosis occurred in patients who suffered from the "rheumatoid group of collagen diseases." An assortment of abnormal patterns was noted under the microscope. Eventually, the breadth of the Hamman–Rich syndrome encompassed a heterogeneous mixture of clinical manifestations and a variety of histologic forms of pulmonary fibrosis—with no distinction made between systemic and lung-limited illness nor any acknowledgement of the prognostic implications of an acute versus chronic presentation.

In the 1960s authors began to regularly substitute the term *IPF* for *acute diffuse interstitial fibrosis*.[5,6] A debate began concerning the chronicity of this disease, with some authors suggesting a slow course punctuated by "terminal complications,"[5] while others reported an average illness of no more than 2 years.[6]

The term *fibrosing alveolitis* was introduced in England in 1964.[7] *Cryptogenic fibrosing alveolitis (CFA)* became the preferred term for pulmonary fibrosis in the European literature and is essentially synonymous with modern-day IPF. This term was originally meant to improve upon its predecessor by capturing pathologic features in a manner that was more precise and descriptive. CFA refers to the interalveolar location of the inflammation in pulmonary fibrosis as compared with the intra-alveolar inflammation of infectious pneumonia. This interalveolar septal inflammation was dubbed "alveolitis." It was maintained that alveolitis was responsible for the subsequent development of fibrosis, and it was suggested that corticosteroids be used to treat alveolitis to prevent this progression.

The most important advance came in 1964 with the publication of an improved and safe technique for performing open lung biopsy.[8] With this procedure, it became possible to carry out a widespread analysis of lung tissue from patients with suspected pulmonary fibrosis. Before long, there were new insights into the pathology associated with fibrotic lung disease.

In 1969 Liebow and Carrington heralded the modern era of ILD histopathology with the notion that IIP could be further categorized into separate pathologic subtypes. They described distinct patterns of IIP that were identified by examination of lung biopsy specimens with light microscopy. Moreover, these subtypes were found to predict prognosis and response to treatment. Based on their research findings, Liebow and Carrington produced the first detailed histopathologic classification of IIP. They created five categories that were termed *UIP*, *desquamative interstitial pneumonia (DIP)*, *bronchiolitis obliterans interstitial pneumonia (BIP)*, *lymphocytic interstitial pneumonitis (LIP)*, and *giant cell interstitial pneumonia (GIP)*. More recent observations have led to a modification of this classification of IIP subtypes. New categories have been added, such as *respiratory bronchiolitis–associated interstitial lung disease (RB-ILD)* and *nonspecific interstitial pneumonia (NSIP)*.[9,10]

Simultaneously, a revolution in thinking about the pathogenesis of IPF affected the way in which experts talked about the disease. Researchers at the National Heart, Lung, and Blood Institute (NHLBI) were major proponents of an "inflammatory theory" of pathogenesis as originally proposed by European investigators. This theory was based on studies at the NHLBI throughout the 1970s during which excessive amounts of inflammatory cells were identified in bronchoalveolar lavage (BAL) fluid obtained from IPF patients.[11] The NHLBI agreed with European researchers who had coined the term *alveolitis* and the NHLBI also endorsed corticosteroid treatment.

The inflammatory theory has since fallen from favor, mostly as a consequence of corticosteroid inefficacy, and the term *alveolitis* also has fallen out of vogue. A new hypothesis proposes that IPF is the result of heterogeneous alveolar epithelial injury, which is then followed by aberrant repair. This theory emerged from landmark ultrastructural studies performed in the mid-1980s.[12,13] Using electron microscopy, it was discovered that the alveolar epithelial cells were injured in IPF. In addition, foci of subepithelial fibrosis were first described. This concept of injury and repair was modified and expanded upon by subsequent investigators.[14]

In 1997 a modified version of Liebow's pathologic classifications was proposed.[15] The new classification scheme reinforced acceptance of certain categories within the context of an updated understanding of ILD pathogenesis. DIP and UIP were retained but some original categories were discarded and newer entities were recognized, including RB-ILD in the spectrum of smoking-related lung diseases and NSIP as a provisional category.[15,16] This modern pathologic classification became the basis for a consensus statement that finally standardized the nomenclature of ILD and IPF for the first time.

In 2002 a panel of experts convened, sponsored jointly by the American Thoracic Society (ATS) and the European Respiratory Society (ERS). This panel released an official statement for the purpose of providing a new and comprehensive classification of IIP that considered all clinical, radiographic, and pathologic features. The diseases recognized by the 2002 ATS/ERS classification of IIP are IPF, NSIP, cryptogenic organizing pneumonia (COP), AIP, RB-ILD, DIP, and LIP. Further classification of IPF has been undertaken by joint consensus statements of the American Thoracic Society and European Respiratory Society, most recently updated in 2018.[17] These statements attempt to offer strict definitions for each subtype of IIP with practical guidelines for diagnostic purposes. The benefit of attempting to utilize precise definitions is to provide a structure for consistent diagnostic decisions in both clinical practice and research.

Despite the utility of rigorously defining IIP (and IPF), there are several potential pitfalls. For instance, the current classification system relies upon an assumption that each specific IIP is a discrete clinical entity. There has never been validation of this assumption by careful phenotyping and prospective trials. In addition, these definitions are heavily reliant on surgical pathology, suggesting that pathology be considered the "gold standard"; however, evidence shows even expert pathologists can have difficulty agreeing on pathologic classification.[18] This continues to create confusion and difficulty in the diagnosis of IIPs and IPF. Continued refinement of consensus guidelines, greater expertise of clinicians with this condition, and discovery of clinically applicable molecular signatures and biomarkers will lead in the future to further differentiation of the IIPs and a less heterogeneous collection of similar syndromes that are described as IPF.

EPIDEMIOLOGY

Below we discuss the incidence, prevalence, mortality, and risk factors for IPF.

■ Incidence, Prevalence, and Mortality

The incidence and prevalence of IPF have been difficult to ascertain due to variations in case definitions, data source, and collection methods. Frequently, diagnostic medical codes are used, but these do not take into account whether the diagnosis was made according to consensus guidelines nor the level of confidence in the diagnosis. The consensus guidelines regarding diagnosis have evolved in the last decade, further complicating the analysis of trends in incidence and prevalence over time. Heightened awareness of the condition as well as the increasing frequency with which computed tomography scans (of both the chest and abdomen) are acquired and incidentally detect subclinical disease may contribute to reports of rising incidence of IPF.

Estimates of incidence and prevalence of IPF from around the world are derived from large databases of national health or insurance claims, which most often use diagnostic codes to define cases. In several studies, both narrow and broad case definitions have been utilized, leading to wide variations in estimates. In the United States and Europe, the most recent crude estimates of incidence range from 2.7 to 14.6 per 100,00 person-years.[19–21] The estimates of incidence are somewhat lower in South America and Asia, with reported crude estimates of incidence ranging from 1.2 to 4.2 per 100,000 person-years.[22,23] The prevalence of IPF in the United States ranges from 10 to 60 cases per 100,00. As IPF is a disease of aging, the prevalence is higher for each decade of life.[24,25] Mortality is reported from similar sources as incidence and prevalence data. Mortality estimates vary across regions, perhaps due to methods of reporting, and range from as low as 1.2 to 13 per 100,000.[23]

■ Risk Factors

With increasing evidence of various intrinsic and extrinsic risk factors for the development of IPF, whether this disease remains truly "idiopathic" has been debated,[26] but that IPF represents a complex and multifaceted disorder that is a consequence of multiple risk factors is widely accepted. Risk factors can be classified as those intrinsic to the individual—such as biologic sex, senescence, genetic predisposition, and a variety of comorbidities—and extrinsic factors, such as inhaled exposure to tobacco, environmental toxins, and air pollution.

Biologic Sex

IPF is a male-predominant disease across international cohorts. Men account for 65% to 80% of patients in well-phenotyped disease registries from various specialized care centers, national registries, and randomized clinical trials.[27,28] Mouse models of pulmonary fibrosis also show sexual dimorphism, with male mice developing more severe fibrosis than females.[29] Although the basis of the male predisposition has not been definitively established, differential exposure to inhaled toxins due to stereotypically male-predominant occupations or behaviors (e.g., cigarette smoking) have been hypothesized. However, sex-stratified case-control studies of some such exposures suggest that men with exposures are more likely to develop IPF than women. For example, a national case-control study from Finland found that men who smoked and had occupational exposures had twofold higher odds for IPF compared to women with similar exposures.[30] The role of sex hormones and sex-linked genes have not been thoroughly studied in IPF, but they are a plausible means of exploring the sex bias.

Senescence

Epidemiologic studies consistently demonstrate that IPF is a disease of aging. The majority of IPF cases present in the sixth through eighth decades of life, with the average age at time of diagnosis of 66 years. The prevalence of the disease increases nearly twofold with every decade above age 50 years.[24]

While aging on an organismal level is most apparent clinically, aging on a cellular level—cellular senescence—is permissive of progression of pulmonary fibrosis. Whatever the initial insults to the lung may be, senescence reprogramming renders the bronchoalveolar epithelium unable to regenerate, thus allowing a dysregulated response to injury that promotes fibrosis.[26] These changes include a senescent phenotype among lung fibroblasts that favors proliferation and collagen deposition to apoptosis.[31] Additionally, senescent bone-derived mesenchymal stem cells lose the capacity to differentiate and thus participate in lung repair.[32]

Telomeres, the repeating nucleotide sequences found at the end of chromosomes, shorten with each cell cycle division. Once telomeres reach a limit of length, a DNA damage response is activated and leads to cell cycle arrest. In the lung, this translates to an inability of the type II pneumocyte to contribute to repair. As such, shortened telomeres are a marker of cellular senescence. Shortened telomere length in peripheral blood leukocytes and lung tissue of IPF patients—well in excess of that expected for age—have been observed IPF.[33,34] Although some familial forms of IPF are associated with mutations in telomere and telomerase-related genes, shortened telomeres are found even in absence of detectable mutations.

Genetic Factors and Familial Pulmonary Fibrosis Case series of familial pulmonary fibrosis, referred to as *familial interstitial pneumonia (FIP)*, account for <2% of all cases of IPF. FIP is defined by at least two relatives within three degrees of relation presenting with IPF.[35] The largest case series report to date of FIP identified 111 families with 309 total affected members. Transmission was most consistent with an autosomal dominant pattern of inheritance with variable penetrance. This study revealed a mean age at diagnosis of 68.3 years, with a slight male predominance (55%) and an increased association with cigarette smoking, even after controlling for age and gender differences. Phenotypically, there was variation even within families on the pathologic pattern of disease, although the majority of cases (80%) still met the then-contemporary 2011 ATS/ERS joint society diagnostic criteria for probable or definite IPF.[36] More recently, radiographic screening in 105 asymptomatic first-degree relatives of patients with any form of pulmonary fibrosis observed interstitial lung abnormalities in approximately 30%.[37] The risk was similar irrespective of whether the index patient's disease was classified as sporadic or idiopathic.

The identification of familial clusters has led to the search for and discovery of multiple genes associated with risk for IPF. Genome-wide association studies (GWAS) of IPF have identified a number of loci associated with risk for IPF. These include genes that are associated with alveolar instability, activation of the unfolded protein response and apoptosis, early cellular senescence by defects in telomere maintenance, altered host defense, and cell-cell adhesion (Table 54-1).[38] Most of these genetic variants are rare, save for two: the mucin gene *MUC5B* and *TOLLIP*, a regulator of the innate immune response, which are reported to be "common" as defined by minor allele frequency in excess of 5%.[39,40] These data confirm a generally understood concept that there is a combination of genetic factors and environmental exposures that contribute to risk for IPF. That IPF represents a convergence of multiple risk factors, of which genetic predisposition is one part rather than a direct cause, accounts for the significant heterogeneity observed in this disease.

TABLE 54-1 Genes Associated with Risk for IPF

Proposed Mechanism	Consequence of Mutation	Genes
Alveolar instability	Increased endoplasmic reticulum stress	*SFTPC, SFTPA1, SFTPA2*
	Activation of the unfolded protein response	*ABCA3*
	Apoptotic signaling	
Early cell senescence	Telomere shortening	*TERT, TERC*
	Impaired telomere stabilization	*DKC1, TINF2, PARN*
		RTEL1
Altered host defense	Increased mucous accumulation	*MUC5B, MUC2*
	Proinflammatory milieu	*TOLLIP, TLR3, HLA-DRB1,*
	Reduced pathogen recognition	*IL1RN, IL8*
Cell–cell adhesion	Loss of epithelial integrity	*DSP, DPP9*

Inhaled Exposures

Approximately two-thirds of IPF patients report a history of ever smoking cigarettes, but only a small percentage of patients are active smokers by the time of diagnosis.[28,41] A meta-analysis of five case-control studies demonstrated that IPF patients were significantly more likely to report a history of smoking than controls with an odds ratio (OR) of 1.58 (95% confidence interval [CI], 1.27–1.97).[42] Risk may be dose dependent, as Baumgartner et al. reported that IPF patients with a greater than 21-pack-year smoking history had an OR of 2.26 (95% CI, 1.3–2.8) compared to individuals with less than a 20-pack-year history.[43]

Although a causal relationship has not been established, multiple deleterious effects of cigarette smoke that can promote fibrogenesis have been described: in vitro, exposure to cigarette smoke is associated with epithelial-to-mesenchymal transition and transformation to a fibroblast-like phenotype among alveolar type II cells.[44] Various in vivo models of fibrosis have reported that nicotine stimulates epithelial cell release of transforming growth factor beta (TGF-β),[45] a critical protein for fibrosis. Cigarette smoking is also associated with accelerated shortening of telomeres[46] and endoplasmic reticulum stress,[47] both of which favor fibrosis to wound repair in response to injury.

Epidemiologic studies that have linked environmental and occupational exposures to IPF predate the most current classification schema, and a significant portion of these may represent alternate ILD diagnoses, such as hypersensitivity pneumonitis or various pneumoconioses.

Comorbidities

Given the potential for lung injury with recurrent microaspiration of gastric fluids, gastroesophageal reflux (GER) has been implicated in the pathogenesis of IPF, especially given reports of high prevalence in patients with IPF. Hiatal hernias were more common on CT scans of patients IPF compared to those with COPD or asthma in a single center retrospective study.[48] Cross-sectional studies have failed to establish whether IPF is a cause or a consequence of GER. The effect of antiacid therapy on the progression of IPF has been evaluated by causal association studies, but when accounting for the biases of retrospective analysis, proton pump inhibitor therapy does not appear to attenuate the progression of IPF.[49]

Obstructive sleep apnea (OSA) is common in patients with IPF. Estimates of prevalence range from 59% to 88%.[41] The ongoing and increased respiratory efforts made by respiratory muscles in the setting of proximal airway obstruction during apneas and hypopneas occur predominantly at the most peripheral aspects of the lung. The subpleural spaces, especially at the basal aspects of the lungs, are the areas that experience the greatest degree of pleural pressure changes, which can be a stimulus for repetitive alveolar microinjury. Notably, these are the same areas of the lung that are characteristically involved in UIP. Furthermore, serum levels of the glycoprotein KL-6, a marker of lung injury and mortality in IPF, are elevated in OSA. Whether treatment for OSA can alter disease progression or survival in IPF remains unknown.

Microbial Factors

Whether microbes play a role in the predisposition to or pathogenesis of IPF has long been an area of interest. Initially, attention was focused on chronic viral infections, particularly herpesviruses. In one study, 97% of IPF patients tested positive for a herpesvirus (Epstein-Barr, cytomegalovirus, human herpesvirus 7, or human herpesvirus 8) compared with only 37% of controls. Latent infections may be one route for initiation of alveolar epithelial injury early in the pathogenesis of IPF.[50]

More recently, attention on microbial factors has shifted away from latent infections to the role of constituent organisms: the lung microbiome. As with latent infections, different phenotypes of the lung microbiome may be associated with either greater predisposition to lung injury or direct injury from the organisms themselves. While the exact role of microbiome has not yet been well defined, the greater bacterial burden has been reported in the BAL fluid of patients with IPF relative to those with COPD, and different phenotypes of the lung microbiome are associated with progression and survival in IPF.[51] Different genera of bacteria were found to be more prevalent in IPF relative to COPD and chronic hypersensitivity pneumonitis.[51,52]

CLINICAL CHARACTERISTICS

Details of the clinical presentation of IPF and associated laboratory and radiographic findings are considered below.

Clinical Presentation

Patients with IPF typically present with gradual onset of dyspnea on exertion and dry cough. Patients usually have symptoms for more than 6 months before they seek specialized medical care. A multicenter cohort from Germany revealed that participants had a mean symptom duration of 3.7 years prior to diagnosis.[53] The cough is typically nonproductive, although patients may experience phlegm production related to traction bronchiectasis.[54] Other associated symptoms are rare and include weight loss, fatigue, fever, arthralgias, or myalgias. Given the increasing use of computed tomography for other conditions (e.g., lung cancer screening, routine abdominal complaints), asymptomatic patients may also present after incidental radiographic findings that ultimately lead to the diagnosis of IPF.

Physical examination usually reveals fine, bibasilar inspiratory crackles that can extend to the upper lung zones as the disease progresses. Clubbing, a deformation of the nail base resulting in a swollen and convex distal phalanx with loss of the nail fold angle, can be found in up to 50% of patients and is associated with poor prognosis.[55] Physical examination may also aid in identifying an alternate diagnoses to IPF, such as with signs suggestive of connective tissue diseases, including sclerodactyly, Raynaud's phenomenon, synovitis, dermatomyositis, and proximal muscle weakness.

Laboratory Studies

Laboratory studies from blood tests are most useful for identifying alternate diagnoses to IPF. These include autoantibodies for conditions that can present with similar radiographic findings, such as connective tissue diseases; however, low-titer autoantibodies should not necessarily rule out a clinical diagnosis of IPF in absence of other clinical signs and symptoms, especially as autoantibodies are more prevalent in the aging population. Antineutrophil cytoplasmic antibodies, typically associated with pulmonary vasculitis syndromes, can be elevated in IPF. The clinical and radiographic findings of vasculitides vary substantially from IPF, so the two diagnoses are not often in contention in the same differential diagnosis. In patients with a history of environmental exposures suspicious for hypersensitivity pneumonitis, the presence of antigen-specific IgG can support a chronic hypersensitivity pneumonitis over IPF.

Radiology

The conventional chest radiograph is of limited utility in patients with IPF. The most common findings are lower lung zone predominant reticular changes, and occasionally, traction bronchiectasis may be appreciated as well. While the chest radiograph is abnormal in nearly all patients with IPF, up to 10% of patients may have normal appearing films, especially in early stages of the disease. As such, high-resolution computed tomography (HRCT) of the chest is the most sensitive mode for radiographic evaluation of IPF and other ILD.

HRCT differs from conventional non-contrast CT scans of the chest. HRCT allows a detailed examination of the lung parenchyma by creating ≤1.5-mm thin slices of the chest. Typically, ILD protocols include additional expiratory and prone sequences to assess for air trapping and atelectasis, respectively. HRCT uses a computerized reconstruction algorithm to maximize spatial resolution. This generates much improved image clarity such that the specificity of interpretations is increased, interobserver variability is reduced, and the overall accuracy of diagnosis is enhanced. HRCT scanning allows for the earlier diagnosis of IPF and permits the identification of alternate patterns of disease.

The primary role of HRCT in the diagnostic evaluation of ILD is the discrimination of a UIP pattern. The Fleischner Society updated diagnostic HRCT criteria of UIP in 2018 to converge with international joint pulmonary society characterization of UIP[17] into four groups (Table 54-2): the *typical UIP* (UIP in the joint society classification) pattern is defined by subpleural and basal predominant reticulation, traction bronchiectasis, honeycombing, and an absence of alternate features (Fig. 54-1). When all these features are present except honeycombing, the pattern is characterized as *probable UIP*. If the distribution of reticular changes is variable or diffuse or if there is evidence of fibrosis but with inconspicuous features suggestive of a non-UIP pattern, the pattern is described as *indeterminate for UIP*. The final group, classified as *consistent with non-IPF diagnosis* (*alternative diagnosis* in the joint society classification), is based on the presence of radiographic findings that suggest an alternate diagnosis to IPF, such as: upper lung or mid lung predominant distribution of reticulation or bronchiectasis; predominant consolidation; extensive pure ground glass opacities; extensive mosaic attenuation with lobular air trapping; and diffuse nodules or cysts.[56]

The main advantage of an HRCT is in its concordance with surgical lung biopsy findings of UIP: a *typical UIP* pattern on HRCT

TABLE 54-2 Radiographic Classification of UIP

	UIP Typical UIP[a]	Probable UIP	Indeterminate for UIP	Alternative Diagnosis CT Features Most Consistent with Non-UIP Diagnosis[a]
Distribution	Subpleural and basal predominant reticulation; distribution is often heterogeneous	Subpleural and basal predominant; distribution is often heterogeneous	Subpleural and basal predominant *or* Variable *or* Diffuse	• Peribronchovascular • Perilymphatic • Upper or midlung Subpleural sparing
Features	Reticulations and honeycombing with or without peripheral traction bronchiectasis or bronchiolectasis	Reticular pattern with peripheral traction bronchiectasis or bronchiolectasis May have mild GGO in areas of reticulation or honeycombing	Subtle reticulation May have mild GGO or distortion ("early UIP pattern")	Features of another diagnosis including: • Diffuse cysts • Extensive mosaic attenuation • Predominant GGO • Diffuse nodules • Consolidations • Pleural effusions, nodules, or thickening

[a]Fleischner Society terminology for UIP.

UIP, usual interstitial pneumonia; GGO, ground glass opacities.

Adapted with permission from Fidler L, Shapera S. Diagnostic criteria for idiopathic pulmonary fibrosis. Lancet Respir Med. 2018;6(2):e6.

corresponds to a 90% to 97% agreement with surgical lung biopsy reading of UIP; similarly, a *probable UIP* pattern corresponds to 82% to 94% agreement with a histologic reading of definite or probable UIP from a surgical lung biopsy.[57,58] The concordance between radiographic pattern and histopathologic pattern is poor with *indeterminate for UIP* and *consistent with non-IPF diagnosis (alternative diagnosis for UIP)* patterns. The caveat, however, is that patterns other than *typical UIP* and *probable UIP* do not rule out the possibility of a diagnosis of IPF, as histopathology may still show a well-defined UIP pattern in those cases. In absence of data to suggest an alternate diagnosis, a confident diagnosis of IPF could still be made in the setting of *indeterminate* or *non-IPF* radiographic patterns if typical histopathologic features are present on histopathologic evaluation.

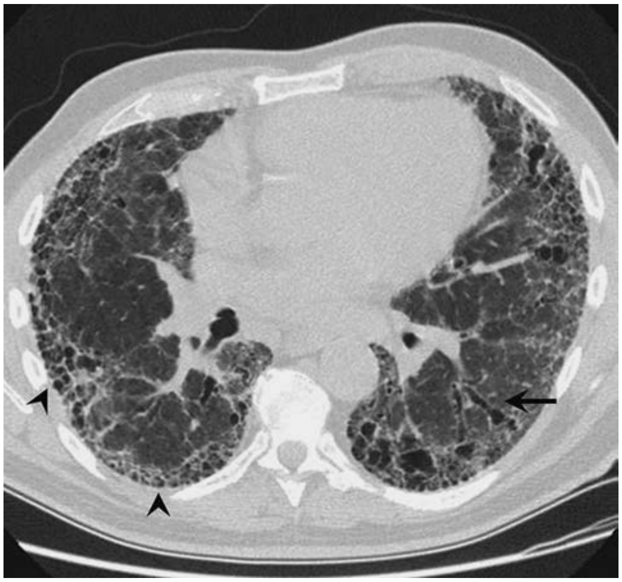

Figure 54-1 Computed tomography scan illustrates the "classic" features of idiopathic pulmonary fibrosis (IPF), the usual interstitial pneumonia (UIP) pattern. Bilateral, peripheral, and subpleural reticular infiltrates are evident. The presence of advanced fibrosis is indicated by honeycomb changes *(arrowheads)* and traction bronchiectasis *(arrow)*. These features permit experienced clinicians to make a confident radiographic diagnosis of IPF.

Pathology

Evaluation of pathologic specimens obtained from surgical lung biopsy and studies procured through bronchoscopy may be helpful in the evaluation of suspected IPF.

Surgical Lung Biopsy

Surgical lung biopsy, most commonly performed as video-assisted thoracoscopic surgery (VATS), is the gold-standard means of sampling lung tissue in the assessment of ILD. A histopathologic pattern of UIP in the absence of alternate history, exam, and laboratory findings (in essence, UIP) can lead to a confident diagnosis of IPF. The histopathologic hallmark of UIP is temporal heterogeneity: areas of dense interstitial collagen deposition, fibroblastic foci, and honeycomb changes alternating with normal lung (Figs. 54-2 and 54-3). Areas of honeycomb cysts are composed of fibrotic air spaces with cystic defects, which are often filled with mucins. The most recent clinical practice guidelines on IPF also classify histopathologic patterns of UIP into the following categories: *UIP*, *probable UIP*, *indeterminate for UIP*, and *alternative diagnosis* (Table 54-3).[17]

While a histologic pattern of UIP is necessary for the diagnosis of IPF, it is not sufficient. As with radiographs, alternate features such as granulomata and lymphoid follicles may be present along with UIP and suggest alternate diagnoses, such as hypersensitivity pneumonitis or connective tissue disease–associated ILD. As with radiographs, histopathologic findings should be correlated with HRCT pattern, history, physical examination, and other data in the context of a multidisciplinary discussion to establish a diagnosis of IPF.

Bronchoscopy

Bronchoscopic evaluation plays a limited role in the diagnosis of IPF. Bronchoalveolar lavage (BAL) fluid is typically unhelpful in

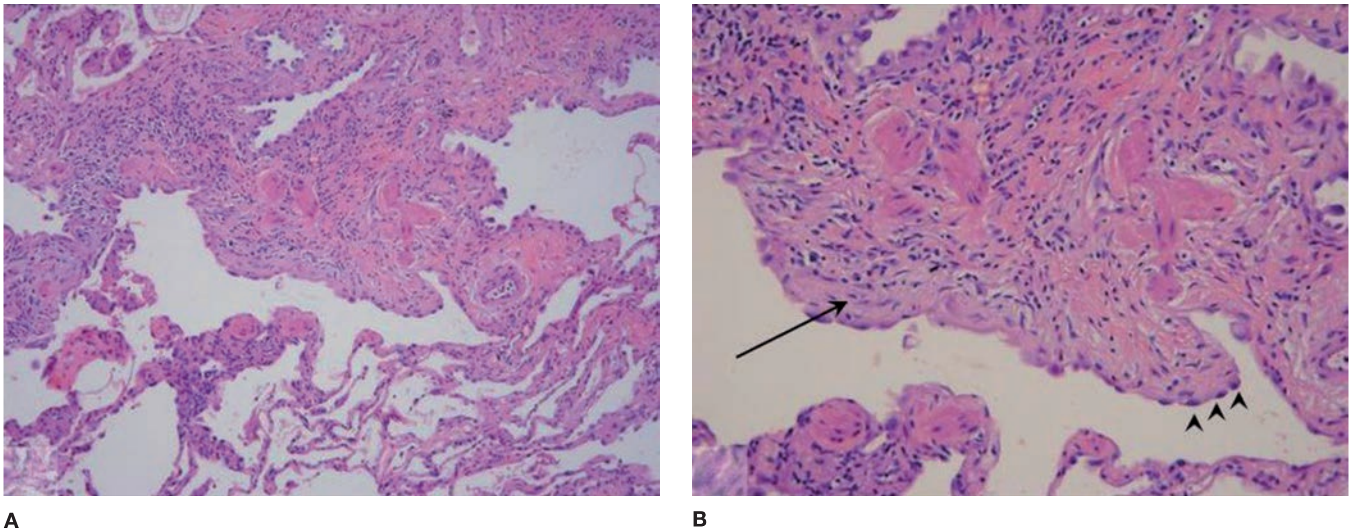

Figure 54-2 **A.** Low-magnification photomicrograph of usual interstitial pneumonia (UIP) showing the characteristic heterogeneous involvement of the parenchyma. Zones of interstitial fibrosis are seen alternating with areas of normal lung. **B.** Higher magnification demonstrates enlarged cystic air spaces lined with hyperplastic alveolar epithelium *(arrowheads)*. Beneath the mucosal layer is an advancing region of young fibrosis containing loose extracellular matrix *(pale pink staining)* and fibroblasts *(arrow)*.

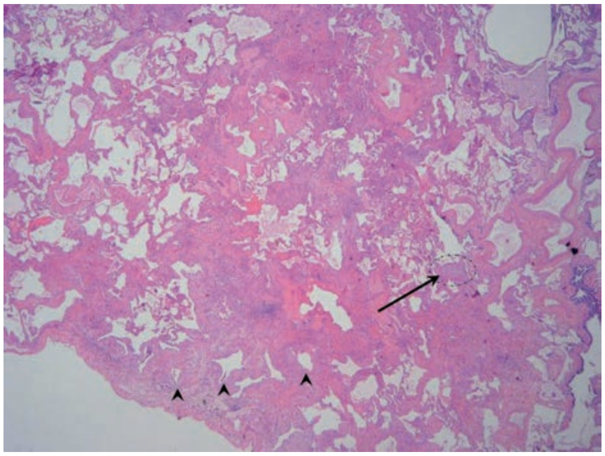

Figure 54-3 Scanning view of usual interstitial pneumonia (UIP) demonstrates the characteristic variegated appearance of UIP. Note the honeycomb change *(arrowheads)* present in the region of dense fibrosis adjacent to the pleural surface. A fibroblast focus *(arrow)* is seen at the leading edge of advancing fibrosis.

the diagnosis of IPF, but in cases of UIP in which the major differential diagnosis is that of chronic hypersensitivity pneumonitis, a lymphocytic predominance can suggest the latter diagnosis over the former. Conventional transbronchial biopsies are of insufficient size to determine the temporal heterogeneity that defines UIP. The role of transbronchial lung cryobiopsy in diagnosing UIP has not been evaluated with a large sample size. A wide range has been reported regarding agreement between surgical lung biopsy and lung cryobiopsy (20% to 70%).[59,60] There is clinical equipoise regarding its use in the diagnostic algorithm of IPF.

Given the insufficient tissue biopsy size to assess for UIP with transbronchial biopsies, and concern for perioperative complications with surgical lung biopsy in a generally older patient population with more comorbidities, a molecular signature for UIP has long been sought. Recently, a machine learning algorithm derived and validated a molecular classifier for UIP from transbronchial biopsy samples, using histopathologic diagnosis of UIP from surgical lung biopsy and lung cryobiopsy samples as the references.[61] A subsequent validation study in 96 patients reported a sensitivity of approximately 60% and specificity of approximately 92%.[62] Although the use of this molecular classifier has not yet been

TABLE 54-3 Histopathologic Classification of UIP (from Surgical Lung Biopsy)

UIP	Probable UIP	Indeterminate for UIP	Alternative Diagnosis
Dense fibrosis with architectural distortion (i.e., destructive scarring and/or honeycombing) Predominant subpleural and/or paraseptal distribution of fibrosis Patchy involvement of lung parenchyma by fibrosis Fibroblast foci Absence of features to suggest an alternate diagnosis	Some histologic features from column 1 are present but to an extent that precludes a definite diagnosis of UIP/IPF *And* Absence of features to suggest an alternative diagnosis *Or* Honeycombing only	Fibrosis with or without architectural distortion, with features favoring either a pattern other than UIP or features favoring UIP secondary to another cause Some histologic features from column 1, but with other features suggesting an alternative diagnosis	Features of other histologic patterns of IIPs (e.g., absence of fibroblast foci or loose fibrosis) in all biopsies Histologic findings indicative of other diseases (e.g., hypersensitivity pneumonitis, Langerhans cell histiocytosis, sarcoidosis, LAM)

Data from Raghu G, Remy-Jardin M, Myers JL, et al. Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med. 2018;198(5):e44–e68 formally incorporated into the diagnostic algorithm of UIP across professional societies or working groups for the diagnosis of IPF, its development has been the first to deliver on the promise of less invasive means of ascertaining a histopathologic pattern of UIP.

■ Diagnostic Algorithm

Given that the natural course and treatment of IPF varies from other ILD in its prognosis and treatment, it is imperative to ascertain a confident diagnosis. Similarly, in the clinical research setting, minimizing heterogeneity is important to establish efficacy of investigational drugs in a disease that is more driven by fibrosis rather than inflammation. Given significant interobserver variability between pulmonologists, radiologists, and pathologists when assessing a clinical scenario independently, a multidisciplinary approach has improved agreement. Although society practice guidelines advocate for a multidisciplinary approach to diagnosis, the necessary specialty expertise and format of the approach has not been specifically described.

The diagnostic algorithm (Fig. 54-4) relies on history to exclude non-IPF etiologies, such as those associated with underlying connective tissue disease, culprit drug exposure, or environmental exposures. Laboratory studies are usually pursued to evaluate for otherwise occult autoimmune disease. If there are no clear triggers for the ILD, then HRCT features are examined next. If there is a *typical UIP* pattern, then that is sufficient to make a diagnosis of IPF. However, if the radiographic pattern is not that of *typical UIP*, then a multidisciplinary discussion is recommended to evaluate for candidacy for lung biopsy. If the histopathologic pattern does not show UIP, or if a biopsy cannot be safely performed for whatever reason, then the multidisciplinary discussion itself would yield a clinical diagnosis, albeit of lesser confidence.

■ Pulmonary Physiology

Complete pulmonary function tests including spirometry, lung volumes, and diffusing capacity of the lung for carbon monoxide

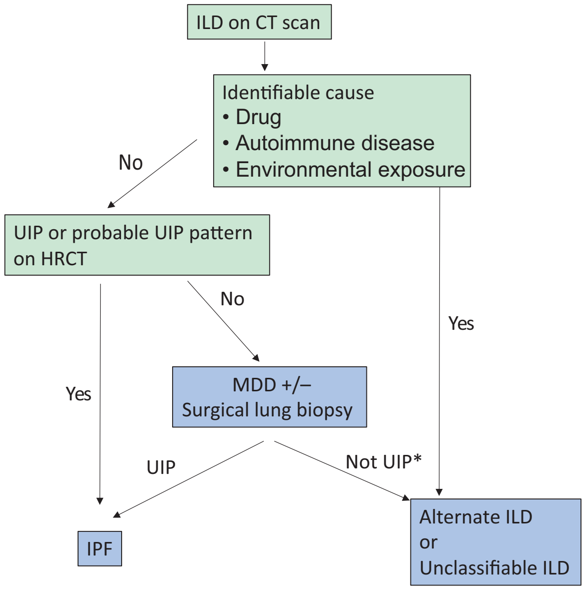

Figure 54-4 The diagnostic algorithm for IPF per joint professional society guidelines depends on the presence of an HRCT UIP pattern—in the absence of history, physical examination, or laboratory findings to suggest an alternate diagnosis—to establish a diagnosis of IPF. In cases of non-UIP patterns on HRCT, multidisciplinary discussion should take place to determine whether surgical lung biopsy is an option after accounting for the individual patient's risk for perioperative complications. IPF, idiopathic pulmonary fibrosis; MDD, multidisciplinary discussion; UIP, usual interstitial pneumonia. *Not UIP or no surgical lung biopsy performed.

(DL_{CO}) should be obtained in all patients being evaluated for IPF to gauge severity of disease. In IPF, pulmonary function tests usually identify a restrictive ventilatory defect as evidenced by a symmetrically reduced forced vital capacity (FVC) and forced expiratory volume during the first second of exhalation (FEV_1). Lung volumes are proportionally reduced. The reduced total lung capacity (TLC) and residual volume (RV) are indicative of reduced compliance. As such, the RV/TLC ratio is often normal unless there is a coexisting obstructive pathology, which occurs more frequently in smokers. The presence of a reduced DL_{CO} demonstrates an impairment in gas exchange. A reduction in diffusing capacity may precede the abnormal FVC and lung volumes. IPF can lead to pulmonary hypertension, which is also associated with a reduced DL_{CO}.

Depending on the severity of gas exchange abnormality, arterial blood gases may show a decreased Pa_{O_2} and chronic respiratory alkalosis. Patients with IPF have tachypnea and often develop a pattern of rapid-shallow breathing. The work of breathing is increased in IPF, especially in later stages. While no chemical changes can explain the observed hyperventilation, the leading theory is that rapid respiratory rates are secondary to altered mechanical reflexes resulting from an increase in elastic recoil and elastic load.

■ Natural History and Prognosis

Across the world, national registries and clinical trials of IPF describe a median survival of 3 to 5 years from time of diagnosis, which may already be several years after the onset of symptoms given known delays in IPF diagnosis. How long the disease is present in its subclinical phase, however, remains unknown. Community-based cohorts report that interstitial lung abnormalities (ILA), a subclinical radiographic phenotype of ILD, are present in 7% to 10% of such cohorts, and a subset of these do exhibit a radiographic pattern of UIP.[63–65]

Although a progressive decline in lung function is the rule in IPF, the time course of the decline is highly variable. In general, patients can exhibit a slow progression, rapid progression, as well as periods of stability punctuated by sharp declines, termed *acute exacerbations*. Any individual patient's trajectory may evolve over time from one progressive phenotype to another.

Acute Exacerbations

Acute exacerbations of IPF (AE-IPF) are episodes of sharp decline in lung function. AE-IPF are defined by an acute worsening in symptoms and/or physiology usually occurring over about a month or less that is matched by radiographic findings of new bilateral ground glass infiltrates on the background UIP pattern. Decompensation solely due to cardiogenic pulmonary edema needs to be excluded. AE-IPF may occur in the context of a clear trigger, often viral infections, but may be idiopathic events as well. Regardless of the cause, AE-IPF are associated with high morbidity and mortality. AE-IPF tend to occur in patients with more advanced disease and worse physiology, and can lead to dramatic increase in supplemental oxygen requirement, decrease in functional status, and even death. The estimated median survival after AE-IPF is approximately 3 months.[66]

Histopathologic examination of AE-IPF commonly reveals a UIP pattern with superimposed diffuse alveolar damage (DAD) characterized by diffuse alveolar septal thickening within a pale matrix that includes hyaline membranes and fibrin. UIP with superimposed organizing pneumonia has also been reported in AE-IPF. AE-IPF typically occurs in patients with established IPF; however, it has been recognized that AE-IPF can be the initial presentation of IPF as well, mimicking AIP.

There are no consensus guidelines on the management of AE-IPF. However, a recent international survey of expert pulmonologists revealed that the vast majority of practitioners administer steroids, and that a majority also initiate antifibrotic medications.[67] The response to either of these medication classes has not been prospectively evaluated, and retrospective studies in this disease state have fundamental biases that limit evaluation of efficacy.

Prognostic Factors

Across all IIP, a radiographic or histopathologic pattern of UIP is associated with worse survival. Since UIP is an integral part of the diagnosis of IPF, it is no surprise that IPF has the worst prognosis of the various IIP.

To counsel patients and to inform clinical decision-making, such as appropriate timing for lung transplantation, an ability to prognosticate survival is helpful in the management of IPF. Increasing age, male sex, and lower physiology are known risk factors for mortality in IPF. The GAP (Genders, Age, Phsyiology) index is a prognositcation tool that classifies patients into one of three stages, each of which corresponds to a different estimated 1-year mortality.[68]

Rather than static measures, changes in pulmonary function over time have been more clearly correlated with measures of long-term survival. For instance, a 10% decline in FVC over 6 months, or a 15% decline in $\mathrm{DL_{CO}}$ over 6 months, predicts shortened survival.[69,70] In clinical practice, at the present time, the use of decrements in pulmonary function remains an important objective means of assessing clinical disease progression.

PATHOGENESIS

IPF is a complex disorder with myriad pathways that contribute to its pathogenesis. Rather than a single common pathway that results in the IPF phenotype, a combination of multiple factors leads to epithelial cell injury and dysfunction, aberrant wound healing, and progressive fibrosis. There have been sufficient discoveries since the term *idiopathic pulmonary fibrosis* was first used in 1948 to challenge the veracity of the *idiopathic* moniker.[26] The modern understanding of IPF pathogenesis includes an understanding of (1) the risk factors that predispose individuals to disease; (2) the primary role of the lung epithelium as the site of disease activation and perpetuation, with endoplasmic reticulum stress promoting increased cell turnover faced with the challenge of senescence reprograming to limit the capacity for repair and regeneration; (3) the dominance of fibroblast activation and myofibroblastic differentiation to promote the progression of fibrosis that is the hallmark of IPF.[26] The IPF alveolar epithelium is likely vulnerable due to a combination of age-related and genetic factors. An accumulation of growth factors in IPF may originate from the persistent proliferative response of epithelial cells. A downstream consequence of “frustrated” epithelial cell regeneration is recruitment of fibroblasts and myofibroblasts through the release of such growth factors. In essence, the signal to recruit and maintain a pool of mesenchymal cells (fibroblasts) might originate from an inability to successfully re-epithelialize the alveolar lining surface.

Great strides are constantly being made to elucidate the mechanisms of IPF pathogenesis.[71,72] Some recent advances to highlight include increasingly larger GWAS that confirm previously identified genetic associations and identify new risk loci[73] and the leveraging of single cell technologies to better understand the unique cellular makeup of the IPF lung, to identify novel cell types (the ionocyte),[74] and to better understand the diversity and function of known cell types in IPF to widen the field for possible therapeutic targets in this disease.

■ Alveolar Epithelium

Examination of tissue from patients with IPF has confirmed an irregular pattern of alveolar epithelial cell proliferation, concurrent with dysregulation of proteins that control the cell cycle.[75,76] Multiple lines of investigation suggest that epithelial cells are critically involved in the pathogenesis of IPF.[77,78] The prevailing hypothesis is that repetitive low-level injury to a vulnerable or susceptible alveolar epithelium drives the pathologic features of IPF.[72] The source of epithelial injury, and whether it is endogenous or exogenous, remains a mystery.

Epithelial Apoptosis and Injury

An emerging body of literature supports alveolar epithelial cell injury and apoptosis as important features of IPF and in the development of experimental pulmonary fibrosis. Electron microscopic studies of human IPF tissue demonstrate injury and apoptosis of alveolar epithelial cells.[13] BAL from patients with IPF has established the presence of proapoptotic proteins.[79] In the bleomycin model of lung injury and fibrosis in animals, fibrosis can be abrogated by various approaches to inhibit epithelial cell apoptosis.[80–82] These include a reduction in experimental fibrosis by inhibiting the Fas–Fas ligand pathway, angiotensin production, or caspase activation.

In addition to direct inhibition of apoptotic pathways, factors that cause epithelial cell apoptosis are critical to the development of fibrosis. Evidence suggests that fibroblasts produce angiotensin peptides that lead to epithelial apoptosis. Other researchers have demonstrated that TGF-β is involved with promoting epithelial cell apoptosis.[83] Oxidant injury also may promote epithelial cell death, and several studies of IPF patients have confirmed excessive oxidant production as well as glutathione deficiency.[84–86] Tumor necrosis factor alpha (TNF-α) has been shown to promote alveolar epithelial cell apoptosis in vitro.[87] In a mouse model, knockout of the TNF-α receptor confers resistance to bleomycin-induced lung fibrosis, while overexpression of TNF-α in the mouse has been associated with an increase in experimental fibrosis.[88] Patients with IPF are known to exhibit an exaggerated expression of TNF-α, which may contribute to epithelial injury.[89]

Evidence of direct injury to the alveolar epithelium suggests that this may be an important model of pulmonary fibrosis. Utilizing a transgenic mouse directing expression of human diphtheria toxin receptor in surfactant protein C (SPC)-expressing cells, it was shown that targeted injury of alveolar type II (AT2) epithelial cells resulted in the development of experimental lung fibrosis.[90] The development of fibrosis in this targeted epithelial cell injury is dependent on plasminogen activating factor 1 and the recruitment of monocytes and macrophages into the lung.[91,92]

Alveolar Type II Cell Dysfunction

In addition to epithelial cell depletion, alveolar injury also drives epithelial cell dysfunction, particularly in the AT2 cell. While AT2 cells are plastic, they do not directly transform into mesenchymal cells. However, they are able to and do acquire a profibrotic phenotype that promotes the expansion of fibroblasts, the activation of myofibroblasts, and extracellular matrix deposition.[93]

Alveolar Type II Progenitor Cell Function in IPF

A subset of AT2 cells serve as progenitors to replete alveolar type I (AT1) cells.[94] State-of-the-art lineage labeling in the adult mouse demonstrated that AT2 cells can regenerate over time.[95] Thus, AT2 cells are stem cells in the alveolar space. A significant development in exploring the regenerative capacity of AT2 cell has been the employment of “alveolospheres” as in vitro organoid assays where AT2 cells can be cultured with fibroblasts in Matrigel and form alveolar-like structures.[95] Single cell analysis from several groups has clearly demonstrated that there is a loss of AT2 cells in IPF.[96–98] Interestingly, there is an expansion of basal cells. Recently it has been demonstrated that IPF AT2 cells have reduced regenerative capacity in organoid assays.[99] Mechanisms that can restore the regenerative capacity of IPF AT2 cells are being actively pursued and offer important new therapeutic approaches in IPF.[99,100]

Progenitor-capable AT2 cells reside next to fibroblasts and represent niches wherein juxtacrine Wnt signaling by fibroblasts maintains this pool of AT2 stem cells.[101] However, autocrine activation of Wnt signaling *within* AT2 cells prevents their reprograming into AT1 cells, whereas in vitro blockade of Wnt signaling in AT2 cells permits their transdifferentiation into AT1 cells.[101] These data fill the gap in knowledge of the mechanism by which long-observed upregulated Wnt signaling in AT2 cells promotes pulmonary fibrosis.[102]

Basal Cell Aberrations

In the pseudostratified respiratory epithelium, basal cells reside adjacent to the basement membrane and serve as progenitor cells. In IPF and other chronic lung diseases, expansion of basal cell populations has been observed.[103] In the normal lung, basal cells are functionally heterogenous and include subtypes that are multipotent and secretory-primed. Recently, however, single cell RNA sequencing has identified that secretory-primed basal cells dominate in IPF, and that they are found in abundance in mucin-rich areas.[104] The derivation and validation of a BAL signature that predicts mortality in IPF found that the genes associated with mortality were expressed in airway basal cells,[103] highlighting that basal cells and their derangements may be an important target for future treatments.

Endoplasmic Reticulum Stress

Mutations of surfactant proteins A2 and C have been associated with familial types of pulmonary fibrosis and suggest a potential genetic mechanism for alveolar epithelial injury.[105–110] In alveolar epithelium, during both homeostatic and inflammatory conditions, surfactant proteins are regularly produced. This production requires appropriate and coordinated folding and packaging of the proteins in the endoplasmic reticulum (ER) prior to their release.[111] When this folding does not occur correctly, the cell experiences ER stress, which results in activation of the unfolded protein response (UPR)—a cellular pathway designed to limit the deleterious consequences of misfolded proteins.[112] The fact that mutations in these proteins were associated with pulmonary fibrosis suggested that misfolding of these proteins could result in cellular stress and thereby enhance the vulnerability of the epithelium.[113] Using a mouse model that expressed a mutant form of SPC, Lawson et al.[114] demonstrated that misfolded SPC caused ER stress and thereby activating the UPR. Despite this activation the mice did not spontaneously develop pulmonary fibrosis but rather required a secondary challenge with bleomycin or viral infection.[114,115] With secondary challenge, the mice exhibiting enhanced ER stress were more susceptible to fibrosis. A growing body of literature suggests that the UPR response is defective with advancing age, which may provide a direct link to IPF as it is a disease of advanced age. ER stress and secondary insults provide an attractive model for IPF, as this model system has the potential to link both genetic- and age-related disease factors to microinjuries and a vulnerable epithelium.

■ Fibroblast Biology

The hallmark of pulmonary fibrosis is the development and expansion of scar tissue in the lung. In this context, patients develop progressive respiratory failure associated with unrelenting accumulation of extracellular matrix in the gas-exchanging regions. It is generally accepted that the predominant sources of matrix are fibroblasts. In IPF, fibroblasts accumulate in areas of advancing fibrosis and are associated with regions of alveolar epithelial hyperplasia, called fibroblast foci. Greater numbers of fibroblast foci within lung biopsies correlate with a worse prognosis in IPF.[116,117]

Myofibroblasts

One of the hallmarks of IPF pathology is the development of a subset of cells called myofibroblasts.[118] Much attention has been focused recently on the role of the myofibroblast in the pathogenesis of IPF. The defining characteristics of myofibroblasts are positive staining for α-smooth muscle actin (α-SMA) and production of new collagen. Myofibroblasts have contractile properties critical to normal wound healing, although they appear only transiently in the normal repair process.[119] By contrast, the constitutive presence of myofibroblasts and ongoing deposition of extracellular matrix is characteristic of IPF. In IPF lung biopsies, myofibroblasts have been described in abundance especially in the fibroblastic foci.[120] Myofibroblasts have also been shown to accumulate in bleomycin-induced lung fibrosis. Immunohistochemical studies have suggested that they are important in the production of newly synthesized collagen.[121]

The source of fibroblasts has been a subject of intense research and debate. Several possibilities include resident lung fibroblasts, bone marrow progenitors called fibrocytes, and epithelial cell transition in a process called epithelial to mesenchymal transition (EMT). Evidence has accumulated over the past several years to suggest that bone marrow–derived cells may contribute to the pool of lung fibroblasts in IPF. In an animal model of experimental lung fibrosis it was shown that fluorescently tagged bone marrow–derived cells trafficked to the lung where they became a source of collagen expression.[122] Interestingly these bone marrow–derived cells did not express α-SMA, nor did they express α-SMA when stimulated in vitro with TGF-β, suggesting that they are not capable of acquiring the myofibroblast phenotype. Another group of researchers observed that a newly defined cell type called fibrocytes migrated into the lungs of animals following bleomycin injury.[123] Fibrocytes are a recently recognized cell type of hematopoietic origin that circulate in the peripheral blood and have been suggested to play a role in wound repair.[124] They also have been implicated in the pathogenesis of hypertrophic scars, scleroderma, and asthma-related airway fibrosis.[125] Fibrocytes are present in the blood of patients with IPF and appear to be a marker of disease progression.[145] Still, the exact role of these cells (and their relationship to the fibroblast) remains unclear due to the lack of specificity in lineage-tracing markers.

Another possibility is that the fibroblasts in IPF are derived from the alveolar epithelium. A transformation of cell type from epithelium to mesenchyme is a well-documented phenomenon that takes place during embryogenesis and in cancer. In culture, it has been shown that isolated AT2 cells exhibit a loss of AT2 markers and express fibroblast markers when stimulated with TGF-β, a critical fibrogenic factor. Whether this occurs in IPF remains a point of controversy, with some studies demonstrating colocalization of AT2 and fibroblast markers[126] and others that do not observe evidence of this phenomenon.[127] To address this question in vivo, lineage-tracing experiments were performed. Initial studies utilized a fragment of the human SPC promoter to drive the expression of a lineage label to track AT2 cells.[128,129] Tracking AT2 cells after TGF-β or bleomycin exposure suggested that these cells were a significant source of mesenchymal cells in experimental lung fibrosis. In contrast to these observations, alternative in vivo lineage tracing using a knock-in allele of the SPC gene directing inducible expression of a fluorescent lineage tag in mature AT2 cells did not demonstrate evidence of EMT after bleomycin.[130] This work suggested a complex and heterogeneous proliferation of mesenchymal cells in experimental lung fibrosis. None of the cells that they explored appeared to be the origin of myofibroblasts.[130] Determining the origin of these cells remains an area of active investigation.

Fibroblast Phenotypes and Functions in IPF

Various growth factors that influence fibroblast function have been shown to be produced in the lung tissue of patients with IPF and also shown to mediate the pathogenesis of experimental fibrosis.[131,132] Examples include keratinocyte growth factor, TGF-β, insulin-like growth factor 1 (IGF-1), platelet-derived growth factors (PDGF-A and PDGF-B), fibroblast growth factor 2, and hepatocyte growth factor. Many of these growth factors activate tyrosine kinase signaling pathways that promote fibroblast proliferation and matrix production.

TGF-β is a critical mediator of lung fibrosis in animal models.[133] Several studies have shown that antagonizing TGF-β prevents the development of lung fibrosis.[134] Alternatively, targeted overexpression of TGF-β has been shown to produce progressive pulmonary fibrosis.[135] Evidence suggests that TGF-β has the capacity to promote epithelial cell transformation into a mesenchymal phenotype.[126] Studies have suggested that fibrosis is attenuated in the setting of targeted loss of TGF-β signaling in epithelial cells[136,137] and that epithelial expression of the integrin $\alpha\nu\beta6$ responsible for the activation of latent TGF-β is also critical to the development of fibrosis.[138] TGF-β also induces the differentiation of fibroblasts to myofibroblasts.[139,140] This effect appears to be dependent on NADPH oxidase 4.[141]

Secreted factors that influence fibroblast migration may also be important to fibrogenesis. The production of CXCL10 by innate immune cells may be critical to fibroblast migration and fibrogenesis.[142–144] Recent work highlighted lysophosphatidic acid (LPA) as an additional chemotactic factor for fibroblasts.[144] LPA interacting with its cognate receptor LPAR1 is critical for recruitment of fibroblasts. LPA was increased in the BAL fluid from IPF patients, and inhibition of LPAR1 markedly attenuated the migration of fibroblasts to IPF BAL fluid.

It appears that IPF fibroblasts have an enhanced proliferative capacity compared with non-IPF fibroblasts.[145,146] The mechanism of enhanced proliferation is not fully elucidated, but data suggest that several pathways may be involved. These include defective fibroblast/extracellular matrix interactions, aberrant activation of PI3 K/Akt/S6K1 signaling pathways, and genome-wide derangements in translation control.[147–150] The derangements in transcriptional control have the potential to allow IPF fibroblasts to circumvent normal negative feedback signals that would inhibit fibroblast proliferation and therefore limit fibrogenesis.

While cancer and pulmonary fibrosis are distinct pathologic processes, there is no doubt on the overlap in the phenotype and behavior of fibrotic lung mesenchymal cells and cancer cells, including evasion of cell death and growth suppressors, disease-promoting inflammation, and local invasion.[151] The importance of fibroblast capacity to invade matrix was also demonstrated in mice where there was deletion in regulators of G protein–coupled receptor functioning called β-arrestins. β-Arrestin null mice were protected from experimental fibrosis, and both mouse and IPF fibroblasts had suppression of fibroblast invasion when β-arrestins were inhibited.[152] Such an invasive capacity might lead to the destruction of the basement membrane and collapse of alveolar tissue, both hallmarks of IPF pathology. In an in vitro model, IPF fibroblasts were observed to spontaneously invade an artificial matrix.[153] It was also shown that targeted overexpression of hyaluronan synthase 2, an enzyme that produces the extracellular matrix glycosaminoglycan hyaluronan in myofibroblasts, resulted in enhanced invasive capacity and progressive fibrosis.[154] A subset of IPF fibroblasts have been shown to be invasive and, when instilled into immune-deficient mice in a humanized model of IPF, migrated to the lung and caused fibrosis. Unexpectedly, single cell RNA sequencing of invasive IPF fibroblasts identified an upregulation of the immune checkpoint ligand CD274, also known as the programmed death ligand 1 (PD-L1). PD-L1 was shown to be necessary for the invasive phenotype of IPF fibroblasts in the humanized model.[155] In these studies, the invasive capacity of human IPF fibroblasts could be abrogated by blockade of CD44 (the receptor for hyaluronan), inhibition of hyaluronan synthase 2 (the enzyme responsible for hyaluronic acid production), or inhibition of PD-L1, suggesting that targeting invasive fibroblasts could be a novel therapeutic approach for IPF. As PD-L1 drugs already exist in the clinical space and are widely used for the treatment of various cancers, there is rationale for their study in a clinical trial for IPF.

TREATMENT

The management of patients presents several challenges, namely whom to treat, when to treat, and how to select treatment. In the past decade, new targets for treatment have been identified and agents that inhibit cytokines, proteases, oxidants, and mesenchymal growth factors have been developed. The current treatment axis has two objectives: slow progression of fibrosis and manage symptoms. To achieve this there are pharmacologic and nonpharmacologic strategies, which we describe below.

■ Disease-Focused Therapy

Disease-focused therapies include antifibrotic medications, pulmonary vasodilators, and corticosteroids, as discussed below.

Antifibrotic Medications

Two antifibrotic therapies have been approved for the treatment of IPF: nintedanib and pirfenidone. The efficacy of these medications in slowing the progression of fibrosis is similar and modest. Both medications are associated with significant side effects that may limit tolerance and prolonged use.

In vitro studies demonstrated that nintedanib inhibits signals mediated by multiple receptor and nonreceptor tyrosine kinases, which ultimately leads to the inhibition of fibroblast growth factors that are involved in recruitment, proliferation, and differentiation of fibroblasts, as well as deposition of extracellular matrix.[156] The efficacy and safety of nintedanib was compared against placebo in three large, randomized, controlled, phase 2 and 3 trials (TOMORROW, INPULSIS-1, INPULSIS-2). The studies demonstrated a significant reduction of the rate of decline in FVC after 52 weeks of follow-up when compared with placebo. The most frequent side effect was diarrhea, occurring in more than 60% of the participants who received nintedanib.[157] On the basis of these trials, nintedanib was approved for use in IPF in the United States.

Pirfenidone reduces fibroblast proliferation and collagen production stimulated by TGF-β, but the exact mechanism is unknown.[158] Two large international clinical trials have evaluated the safety and efficacy of pirfenidone. In the first phase 3 multinational CAPACITY 004 trial, pirfenidone was associated with a significant reduction in the rate of decline of FVC; however, the validation study CAPACITY 006 failed to reach significance.[159] A subsequent clinical trial, ASCEND, demonstrated that pirfenidone was associated with a significant reduction in the proportion of patients who had a decline of 10% or greater in their predicted FVC and improved progression-free survival when compared with placebo.[160] In a combined analysis of the ASCEND and CAPACITY trials, pirfenidone was associated with a decrease in both all-cause and IPF-related mortality, which led to the approval of pirfenidone in patients with IPF in the United States.[161]

Pulmonary Vasodilators

The parenchymal architectural distortion in patients with idiopathic pulmonary fibrosis can lead to abnormalities of the pulmonary vasculature and physiology. These changes can lead to precapillary pulmonary hypertension. Sildenafil is a phosphodiesterase inhibitor that leads to pulmonary vasodilation when administered systemically. A double-blind clinical trial in patients with IPF and pulmonary hypertension did not show a statistically significant benefit in walk distance, dyspnea, or patient-reported quality of life.[162] Another trial aimed to study riociguat, a soluble guanylate cyclase stimulator, and was stopped prematurely due to serious adverse events and increased mortality.[163]

The findings in these studies suggested that therapies for pulmonary hypertension in patients with idiopathic pulmonary fibrosis should aim to induce vasodilation in well-ventilated lung areas to avoid exacerbating ventilation–perfusion mismatch, which may worsen outcomes. A more recent clinical trial studied the effect of inhaled treprostinil, an analog of prostacyclin. The investigators reported an increase in 6-min walk distance by a median of 31 m in the study arm relative to controls.[164]

Corticosteroids

Over the past two decades, the role of corticosteroids in patients with idiopathic pulmonary fibrosis has dramatically changed. Current guidelines recommend against the use of corticosteroids as maintenance therapy based on the results of the PANTHER-IPF trial, which observed increased mortality and hospitalization rate in patients who were treated with prednisone, azathioprine, and N-acetylcysteine.[165]

The role of steroids in acute exacerbations of IPF remains unclear. No randomized controlled trials have been reported in this area, and the evidence is anecdotal and based on expert opinion. The rationale behind using steroids in acute exacerbation is suppression of cellular and humoral immunity and reduction of acute inflammation.[166] Based on the limited available data, current guidelines recommend the use of corticosteroids in acute exacerbation, but the recommendation is weak, and the appropriate dose, route, and duration of therapy remain unknown.[167]

Other Pharmacotherapies

As mentioned previously, the treatment of IPF has recently changed. First-line treatment is now antifibrotic medications that are effective at slowing down the rate of FVC decline. In addition to this, large multicenter clinical trials (described below) proved the lack of benefit of other treatment options previously used.

High-dose N-acetylcysteine (NAC), a precursor of glutathione, was studied against placebo in the IFIGENIA trial in addition to prednisone and azathioprine. The study showed a preservation of FVC and $D_{L_{CO}}$, but the study was underpowered due to a high drop-out rate.[168] Subsequently, a study within the PANTHER-IPF cohort compared NAC to placebo and revealed no significant benefit in the preservation of FVC.[169]

The effect of interferon γ-1b was studied in the INSPIRE trial. At the second interim analysis, the study showed no improvement in survival in the treatment arm. As such, the study was stopped earlier than planned.[170]

The PANTHER-IPF trial aimed to determine the safety and efficacy of azathioprine, prednisone, and NAC, a combination frequently used to treat IPF in the past. The study was stopped prematurely after an interim analysis showed that the patients receiving prednisone, azathioprine, and NAC had a higher rate of death when compared with placebo.[165]

GER is commonly found in patients with IPF. GER is associated with cough, and it is believed that chronic micro-aspiration could be a contributor to the progression of IPF. Current IPF treatment guidelines provide a weak recommendation to treat GER regardless of the presence of symptoms.[167] Antiacid therapies such as second-generation antihistamines and proton pump inhibitors (PPI) have been used as a potential therapy. The data on the effect of antiacid medication is mixed. Previous studies have showed an association between antiacid medication and survival[171,172] as well as decreased rate of FVC decline; however, subsequent reanalyses have suggested that the immortal time bias accounted for these differences. Most recently, a large cohort study did not find any difference in all-cause mortality, respiratory related mortality, or respiratory-related hospitalizations in patients who received PPIs compared with those who did not. To date, there have not been any randomized controlled trials that have studied the use of antiacid medications in patients with IPF.[49]

Lung Transplantation

Lung transplantation is a life-saving and life-prolonging therapy for idiopathic pulmonary fibrosis. Patients with significant lung function decline, those with oxygen dependency, and those whose posttransplant life expectancy exceeds their current life expectancy without transplant stand to benefit from transplantation.[173] To aid providers, the International Society of Heart and Lung Transplantation (ISHLT) has established criteria for referral and listing of patients with interstitial lung disease. These criteria include histopathologic or radiographic evidence of UIP or NSIP, FVC less than 80% predicted or $D_{L_{CO}}$ of less than 40% predicted, any oxygen requirement, and any dyspnea or functional limitation attributable to lung disease.[174] Absolute contraindications for lung transplant are malignancy in the last 2 years, advanced dysfunction of another organ, nonadherence, lack of social support, and substance addiction. Age older than 65 years old is a relative contraindication.

Supplemental Oxygen

The use of supplemental oxygen for resting hypoxemia in ILD is extrapolated from studies in patients with chronic obstructive pulmonary disease (COPD).[175] The clinical practice guidelines for IPF make a strong recommendation for the use of supplemental oxygen with resting saturation below 88%, severe resting hypoxemia ($Pa_{O_2} \leq 55$ mm Hg) or moderately severe resting hypoxemia ($Pa_{O_2} \leq 60$ mm Hg), as well as with complications of chronic hypoxemia (cor pulmonale, polycythemia).[167] A recent study showed that in patients with IPF with exercise-induced hypoxemia, supplemental oxygen during exercise improved the endurance time, desaturation, and subjective symptoms compared with placebo.[176]

■ Symptom-Directed Therapy

Symptom-directed therapies include pulmonary rehabilitation and the use of antitussives and opioids.

Pulmonary Rehabilitation

Patients with IPF should be encouraged to enroll in pulmonary rehabilitation programs. Several small cohorts have shown that a combination of aerobic and strengthening exercises improve 6-min walk test distance and perception of dyspnea.[177–179] Furthermore, a randomized controlled study showed that a supervised exercise training program improved exercise tolerance, functional capacity, leg strength, pulmonary function, perception of dyspnea, and quality of life in patients with IPF.[180] In addition to these benefits, pulmonary rehabilitation programs provide education and psychosocial support system that also improve quality of life.

Antitussives

Therapies for cough aimed to suppress the central cough reflex (dextromethorphan), to target sensory neurons (lidocaine, benzonatate), or to act as mucolytics (beta agonists, macrolides) have limited efficacy with transient effect. However, agents such as gabapentin and amitriptyline, which target the central cough reflex, have shown to be beneficial in idiopathic chronic cough and could be useful for idiopathic pulmonary fibrosis.[181] Thalidomide, an immunomodulatory, anti-inflammatory, and antiangiogenic drug has been of interest. Thalidomide was initially used as an antiemetic during the first trimester of pregnancy, causing serious birth defects. It was later repurposed as an effective treatment of cancer-related emesis. Due to its mechanism of action, it was also studied as a potential therapy for IPF. An open-label, single-center clinical trial showed no effect in the course of IPF but significant reduction in cough.[182] A subsequent small, double-blind, placebo-controlled trial carried out in the same medical center showed that low-dose thalidomide improved cough and respiratory symptoms.[183]

Opioids

In advanced stages of the disease, many patients have severe breathlessness and anxiety. Although limited, randomized, placebo-controlled studies have investigated the effect of systemic opioids on the perception of dyspnea in patients with IPF. These studies have shown a significant difference in modified Borg score for dyspnea, exercise tolerance, anxiety, and agitation with no reduction of respiratory drive nor increase in the hospitalization rate.[184,185] Constipation and nausea are the most common side effects. Unlike systemic steroids, the use of nebulized opioids, aiming to target the opioid receptor in the respiratory tract, did not show any effect of symptom improvement. This suggests that the central mechanism for dyspnea plays a greater role in respiratory symptoms in IPF relative to local intrabronchial mechanisms.[186]

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CHAPTER 55

Idiopathic Interstitial Pneumonias Other Than Idiopathic Pulmonary Fibrosis

Kelly M. Hager
Ami Rubinowitz
Mridu Gulati

INTRODUCTION

The idiopathic interstitial pneumonias (IIPs) encompass a subcategory of interstitial lung diseases (ILDs) that pose significant diagnostic and management challenges. The general diagnostic approach to these disorders is discussed elsewhere in this textbook (Chapter 52), as is the diagnosis and management of idiopathic pulmonary fibrosis (IPF) (Chapter 54). This chapter details the classification, diagnosis, and management of non-IPF forms of IIPs.

In a 2013 update, the American Thoracic Society and European Respiratory Society delineated three categories of idiopathic interstitial pneumonias: the major idiopathic interstitial pneumonias, rare idiopathic interstitial pneumonias, and a separate category for unclassifiable interstitial pneumonias. The major idiopathic interstitial pneumonias include chronic fibrosing interstitial pneumonias (idiopathic pulmonary fibrosis, idiopathic nonspecific interstitial pneumonia), smoking-related interstitial pneumonias (respiratory bronchiolitis–interstitial lung disease, desquamative interstitial pneumonia), and acute/subacute interstitial pneumonias (cryptogenic organizing pneumonia and acute interstitial pneumonia). Rare idiopathic IPs include idiopathic lymphocytic interstitial pneumonia and the newly recognized entity of idiopathic pleuroparenchymal fibroelastosis. The guidelines further demarcated a diagnostic category for unclassifiable IIP, acknowledging the clinical reality that a subset of patients may not fully meet criteria for a specific diagnosis.[1] In this chapter, after a description of the specific entities, each section ends with a discussion of current therapeutic options. This information is summarized in Table 55-1.

NONSPECIFIC INTERSTITIAL PNEUMONIA

The chronic fibrosing interstitial pneumonias include idiopathic pulmonary fibrosis, discussed in Chapter 54, and nonspecific interstitial pneumonia, which is discussed below.

Definition and Historic Perspectives

In 1994, the term *nonspecific interstitial pneumonia (NSIP)* was developed by Katzenstein and Fiorelli[2] to describe a histologic pattern that demonstrates a temporally uniform appearance of interstitial inflammation and fibrosis. This definition was further refined in 1998 when Katzenstein went on to formally designate NSIP as a distinct category within the IIPs.[3] In 2008, an American Thoracic Society report recommended that clinicians recognize idiopathic nonspecific interstitial pneumonia (iNSIP) as a distinct, rather than a provisional, clinical entity.[4] In updating the previous 2002 statement, the 2013 official classification incorporated iNSIP as a chronic fibrosing ILD within the major idiopathic IIPs.[1] The NSIP histopathologic pattern may also be seen in association with other clinical disorders, such as connective tissue diseases and hypersensitivity pneumonitis.

Underlying Disease Associations

Nonidiopathic NSIP is associated with a number of underlying causes.[5,6] NSIP is the most prevalent form of ILD to complicate connective tissue diseases (CTD) and is frequently the histologic pattern seen when ILD complicates polymyositis and dermatomyositis,[7,8] Sjögren syndrome,[9] systemic sclerosis (SSc), and interstitial pneumonia with autoimmune features (IPAF).[10,11] NSIP is seen in rheumatoid arthritis (RA), though far less commonly than usual interstitial pneumonia (UIP).[12] NSIP is also encountered in the setting of hypersensitivity pneumonitis,[13] drug reactions,[2] and some forms of familial ILD.[14] Some cases of apparently idiopathic NSIP may later develop CTD, indicating that NSIP is a forme fruste of CTD.[15]

Clinical Presentation

Idiopathic NSIP most commonly affects nonsmoking middle-aged adults between 40 and 60 years of age, with a female predilection.[2,4,16] Idiopathic NSIP is a rare disease; one retrospective series reported a prevalence of 1 to 9 per 100,000[6] while a Danish cohort study estimated an incidence of 3 per million per year.[17] Like most other IIPs, NSIP tends to present with the subacute onset of dyspnea and cough. Lung examination frequently but not universally reveals bilateral crackles. Extrapulmonary examination may provide clues to an underlying CTD (Chapter 58). For example, the presence of a heliotrope rash, shawl-like rash, and digital edema/desquamation ("mechanic's hands") suggests underlying dermatomyositis. The presence of telangiectasias, calcinosis, and sclerodactyly suggests a diagnosis of scleroderma. The presence of joint effusions and radial deviation of the MCP joints suggests an underlying diagnosis of RA. Clubbing may be seen.

Underlying causes or associated conditions may not be initially evident. A complete history regarding occupational, environmental, and medication exposures must be obtained. In addition, because NSIP is frequently associated with CTD, an exhaustive rheumatologic history should be obtained, including questions regarding the presence of arthralgias, swallowing difficulties, myopathic symptoms, rash, and mechanic's hands commonly encountered in antisynthetase syndrome, ocular and/or salivary gland dryness associated with Sjögren syndrome, and Raynaud phenomenon and swallowing difficulties characteristic of SSc.

Laboratory Testing

While most sources recommend serologic testing in the diagnosis of NSIP, there exists no standardized practice guideline in this area. The 2011 ATS/ERS/Japanese Respiratory Society/Latin American Thoracic Association guidelines recommended ANA, anticyclic citrullinated peptide, and rheumatoid factor for all patients, with more specific extractable nuclear antigen antibody and myositis antibody testing recommended depending on the clinical scenario. A small, retrospective study demonstrated the potential utility of extended autoantibody panel with 6 of 17 patients reclassified as myositis-associated ILD or IPAF after testing.[18] Repeat serologic testing should be considered, as seroconversion has been documented.[19] Hypersensitivity pneumonitis may also present as an NSIP pattern. The 2020 ATS/JRS/ALAT hypersensitivity pneumonitis practice guidelines suggested performing serum IgG testing for possible antigens.[20–23] Nonetheless, the sensitivity and specificity of such tests are highly variable and do not supplant a comprehensive exposure history.

TABLE 55-1 Key Features of Major and Rare Idiopathic Interstitial Pneumonias

	Major Idiopathic Interstitial Pneumonias					Rare Idiopathic Interstitial Pneumonias	
	Chronic Fibrosing		*Smoking Related*	*Acute/Subacute*			
	IPF	**NSIP**	**DIP/RB-ILD**	**COP**	**AIP**	**LIP**	**PPFE**
Mean age of onset	60s	50s	40s	50s	50s	50s	40s
Duration of illness	Chronic	Subacute to chronic	Subacute to chronic	Subacute	Acute	Chronic	Subacute
Frequency	47%–64%	14%–36%	10%–17%	4%–12%	Rare	Rare	Rare
Smoking	Up to 2/3	Uncommon	Most	Up to 1/2	Unknown	Unknown	Unknown
HRCT	Peripheral, subpleural; basilar predominant; reticular opacities; traction bronchiectasis architectural distortion and honeycombing	Peripheral, peribronchovascular; basal, symmetric; ground-glass opacities, reticular markings, traction bronchiectasis	DIP: peripheral or diffuse ground-glass opacities, reticular markings, ± small cysts RB-ILD: bronchial wall thickening; centrilobular ground glass nodules; patchy ground-glass opacity	Patchy, bilateral, subpleural and peribronchovascular consolidation	Diffuse consolidation and ground-glass opacities often with lobular sparing	Diffuse; ground-glass opacities; septal thickening; thin-walled cysts	Upper lobe dense subpleural consolidation with traction bronchiectasis and volume loss
Key pathologic features	Variegated temporal appearance; scant inflammation; patchy fibrosis; fibroblastic foci; honeycomb change	Uniform temporal appearance; prominent inflammation; variable, diffuse fibrosis; rare honeycomb	Uniform temporal appearance DIP: diffuse variable moderate fibrosis with diffuse intra-alveolar macrophage accumulation RB-ILD: peribronchiolar intra-alveolar macrophage accumulation with only focal, mild fibrosis	Uniform temporal appearance; moderate inflammation; intra-alveolar (Masson bodies) fibroblast proliferation; foamy macrophages	Structural cell death responses; acute inflammation; hyaline membranes may be present	Diffuse interstitial infiltration, infiltrates comprised of T and/or B cell lymphocytes, plasma cells, macrophages, lymphoid hyperplasia	Upper lobe predominant, subpleural homogenous intra-alveolar fibrosis and elastosis with marked elastin deposition around alveolar walls with preserved alveolar structure, sparse/nonspecific inflammation
Prognosis	50%–70% mortality in 5 years	<10% mortality in 5 years	DIP: 30% mortality at 10 years RBILD: Limited data but favorable prognosis compared to DIP	Rare deaths	5%0–60% mortality at 1 month	Not well defined	70% mortality in 5 years
Response to steroids	Nonresponsive	Variably responsive (particularly cellular)	Responsive	Very Responsive	Standardly given; inconsistently responsive	May be responsive	Not well defined; low dose may be effective, high dose avoided due to increased risk of infection

Pulmonary Function Testing

Pulmonary function testing demonstrates a restrictive ventilatory defect characterized by a preserved forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio and a depressed FVC, total lung capacity (TLC), and diffusing capacity of the lung for carbon dioxide (DL_{CO}). The presence of obstructive physiology should raise suspicion of an alternate or superimposed diagnosis such as chronic obstructive pulmonary disease (COPD).

Chest Imaging

The imaging appearance of NSIP may vary depending on whether a cellular, fibrotic, or mixed form is present. Chest radiograph may be normal in patients with early disease or show nonspecific interstitial markings and ground-glass opacities mostly in the lower lobes with more advanced disease. Distribution of disease on chest computed tomography (CT) is typically peripheral and lower lobe predominant, but may also involve the upper lobes without an obvious apicobasal gradient. The disease may be patchy or peribronchovascular in distribution as well.[20–23] Subpleural sparing is often seen. The most common CT features include ground-glass density and reticular markings with or without traction bronchiectasis (Figs. 55-1 and 55-2). Honeycombing is sometimes seen in fibrotic NSIP but is usually not the dominant feature.[21,22] While the presence of classic findings on high-resolution CT (HRCT) can definitively make diagnosis of IPF in the appropriate clinical context,[24] HRCT is less accurate in establishing a diagnosis of NSIP and a surgical lung biopsy may be required.[25] NSIP may overlap with other patterns such as an organizing pneumonia pattern, although its presence modifies prognosis.[26]

Pathology

When a tissue biopsy is required for diagnosis of NSIP, video-assisted thoracoscopic surgery (VATS) is the procedure of choice because this approach yields sufficient tissue to accurately diagnose the IIPs. Bronchoscopic evaluation has limited utility. Lymphocytosis on bronchoalveolar lavage (BAL) has been reported[27] but not consistently.[28] Transbronchial biopsies and even transbronchial lung cryobiopsies typically yielding larger specimens fail to consistently establish an NSIP diagnosis when compared with surgical lung biopsy.[29]

The original description of NSIP categorizes its temporally uniform appearance of fibrosis and inflammation into three groups: those dominated by active inflammation (later called "cellular" NSIP) (Fig. 55-1), those dominated by established fibrosis (later called "fibrotic" NSIP) (Fig. 55-2), and those demonstrating a combination of inflammation and fibrosis (later called "mixed" NSIP).[1] NSIP infiltrates usually include a mixture of lymphocytes and plasma cells within the alveolar septum prominently found in the peribronchiolar interstitium. Histopathologic overlaps also may be found. Up to 79% of cases may demonstrate organizing pneumonia (OP), although OP features generally do not predominate; the finding of prominent OP suggests the presence of CTD-associated ILD.[30] Overlapping histopathologic features of hypersensitivity pneumonitis—the presence

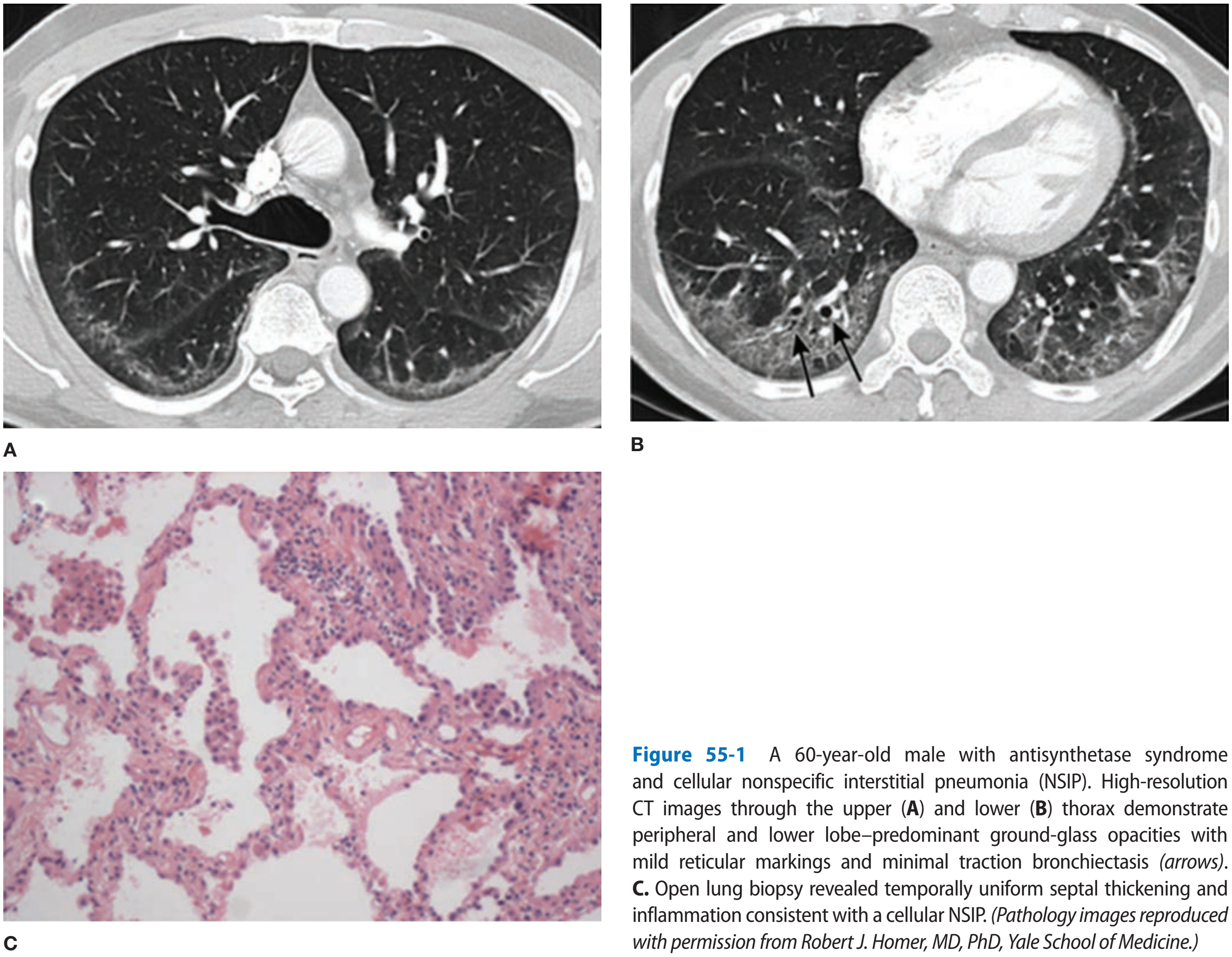

Figure 55-1 A 60-year-old male with antisynthetase syndrome and cellular nonspecific interstitial pneumonia (NSIP). High-resolution CT images through the upper (**A**) and lower (**B**) thorax demonstrate peripheral and lower lobe–predominant ground-glass opacities with mild reticular markings and minimal traction bronchiectasis *(arrows)*. **C.** Open lung biopsy revealed temporally uniform septal thickening and inflammation consistent with a cellular NSIP. *(Pathology images reproduced with permission from Robert J. Homer, MD, PhD, Yale School of Medicine.)*

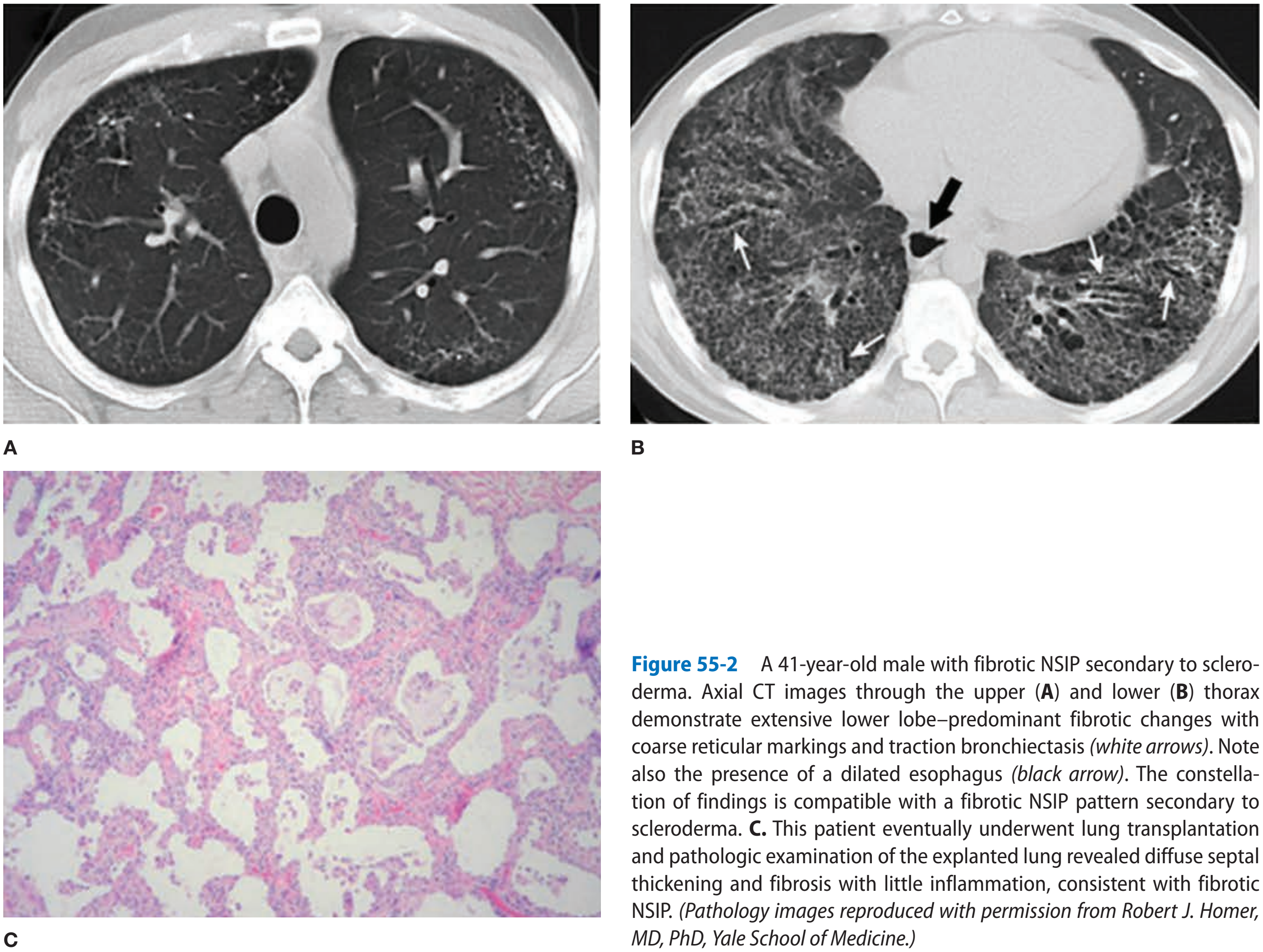

Figure 55-2 A 41-year-old male with fibrotic NSIP secondary to scleroderma. Axial CT images through the upper (**A**) and lower (**B**) thorax demonstrate extensive lower lobe–predominant fibrotic changes with coarse reticular markings and traction bronchiectasis *(white arrows)*. Note also the presence of a dilated esophagus *(black arrow)*. The constellation of findings is compatible with a fibrotic NSIP pattern secondary to scleroderma. **C.** This patient eventually underwent lung transplantation and pathologic examination of the explanted lung revealed diffuse septal thickening and fibrosis with little inflammation, consistent with fibrotic NSIP. *(Pathology images reproduced with permission from Robert J. Homer, MD, PhD, Yale School of Medicine.)*

of loosely formed granulomas—may be detected and should prompt investigation for an antigen.[31] The fibroblastic foci prominently seen in UIP are not characteristic of patients with NSIP; nonetheless a small proportion of patients may demonstrate UIP and NSIP histopathologic features in different biopsy specimens, a finding that correlates with worsened prognosis.[32]

■ Clinical Course and Outcome

Early reports suggested a favorable prognosis of NSIP compared with UIP. An ATS report described 5- and 10-year survival of 80% and 73%, respectively, in iNSIP[33] while better outcomes may be associated with CTD-associated NSIP.[34] Cellular NSIP is associated with favorable event-free survival compared to the fibrotic forms.[35] Similarly, radiographic changes that would be expected to accompany fibrotic NSIP, such as honeycombing, have been associated with reduced survival, as have progressive dyspnea and desaturation during 6-minute walk tests.[33] Serial pulmonary function testing, specifically declines in FVC and $\mathrm{DL_{CO}}$, may ultimately serve as a better predictor of survival.[36] Initially reported in IPF, acute exacerbations have been reported in other fibrotic ILDs, including NSIP, and may cause rapid deterioration in previously stable patients.[37]

■ Treatment Overview

Approach and response to treatment depends on cause, severity of disease, the presence and/or the degree of fibrosis, and rate of disease progression. In very mild situations, careful observation may be initially indicated as some patients will remain stable or progress very slowly. For cases of exposure-related NSIP related to drugs or inhalation, cessation of the offending agent, particularly in the setting of mild disease, may be the sole initial treatment strategy. In patients with CTD-associated NSIP, immunosuppression may be indicated for both lung and systemic manifestations.

Regardless of treatment plan, nonpharmacologic supportive therapy should be considered. Patients with arterial hypoxemia at rest or during exercise may benefit from the administration of supplemental oxygen.[38] Patients with exercise impairment may benefit from pulmonary rehabilitation.[39] Finally, due to the rapid deterioration that is sometimes encountered in patients with NSIP, referral for orthotopic lung transplantation (OLT) should be considered for any eligible patient. The use of immunosuppression is based on the rationale that the inflammation seen on pathology contributes to disease. More recently, antifibrotics have emerged as a treatment option. Immunosuppressive and antifibrotic therapies are reviewed below.

■ Immunosuppression

The decision to embark upon a course of immunosuppression should be considered in light of the risk–benefit ratio. Similarly, when treating a patient with NSIP in the setting of CTD, the management of these medications is best performed in collaboration with the patient's rheumatologist. The data on the use of immunosuppression in NSIP have been predominantly studied in populations with concomitant CTD. Since the pulmonary and systemic involvement may demonstrate independent responses, systemic effects must also be monitored. Patients should be seen frequently so serious and potentially fatal side effects are recognized in a timely fashion. Clinicians should advise patients to remain up to date with vaccinations and avoid live vaccinations while on immunosuppression. While the risk of *Pneumocystis* pneumonia appears to be low, mortality may be quite high, with the highest risk being among patients on high-dose steroids in combination with other immunosuppressant drugs. Prophylaxis with trimethoprim/sulfamethoxazole is recommended and highly effective in preventing disease.[40]

Corticosteroids

Despite a lack of clinical trials in this area, expert opinion recommends a trial of corticosteroid therapy in patients with NSIP. Patients are typically treated with 1 mg/kg per ideal body weight of oral prednisone for several months and then assessed for evidence of objective response on PFTs or HRCT.[23] For rapidly progressive fulminant disease, pulse intravenous steroids with doses of 750 to 1000 mg per day for 3 days may be required, followed by a tapering doses. Higher response rates may be seen in patients with cellular forms of NSIP.[41] Steroid monotherapy may be insufficient to control disease, and the side effects of steroid therapy are well known and include diabetes, bone complications, cataracts, hypertension, weight gain, and opportunistic infections.[42] Hence, every attempt should be made to add a steroid-sparing agent to transition the patient completely off steroids or at least to the lowest dose possible. Bone mineral density testing should be performed to calculate fracture risk assessment for patients who are maintained on or are ready to embark upon chronic corticosteroid therapy. In addition to ensuring adequate Vitamin D and calcium supplementation, pharmacologic therapy, most often with bisphosphonates, may be indicated in patients with established osteoporosis and should be considered in patients with osteopenia.

Azathioprine

Azathioprine, an immunosuppressive agent that inhibits purine synthesis (particularly in lymphocytes), is a common alternate therapy for patients with NSIP. Azathioprine has been associated with disease stabilization in patients with NSIP and has been studied primarily in CTD-associated NSIP.[43] No large-scale clinical trials have been performed in this area. Most case series investigated azathioprine in combination with other immunosuppression including corticosteroids or as maintenance therapy after cyclophosphamide induction.[44] Because azathioprine carries several risks including bone-marrow suppression and hepatotoxicity, many centers perform genotyping for thiopurine methyltransferase prior to initiation of therapy and reduce dosing when a mutation is uncovered, although evidence for this approach is currently lacking. Of note, a randomized control trial involving azathioprine in IPF patients noted increased mortality risk,[45] and studies have indicated that a significant proportion of patients may not tolerate the drug due to non-respiratory-related side effects.[46] The total dosage is 1.5 to 2 mg/kg per day, with a maximum dosage of 200 mg/day.

Mycophenolate Mofetil

Mycophenolate mofetil (MMF) is an immunosuppressive drug that inhibits B and T cell function through inhibition of purine synthesis. It has been particularly studied in CTD-associated interstitial lung disease. In the Scleroderma Lung Study II, patients were randomized to oral MMF for 24 months versus 12 months of cyclophosphamide followed by 12 months of placebo. Improvements in FVC were noted at 24 months with fewer side effects in the MMF arm. Other studies demonstrated a role for MMF in patients with other forms of CTD-ILD[47] and IPAF.[48] In addition to increasing risk of infection, common side effects of MMF include diarrhea and nausea. Prolonged usage has been associated with some cancers and lymphoma.

Cyclophosphamide

Cyclophosphamide is used in patients with significant or rapidly progressive lung involvement. In a prospective study comparing patients with confirmed fibrotic NSIP versus those with UIP/IPF receiving pulse therapy with methylprednisolone followed by low-dose prednisone and cyclophosphamide, 33% of subjects with NSIP, compared with 15% of UIP subjects, improved with steroids alone and 66% improved with combined therapy.[49] Perhaps the best evidence for a therapeutic benefit of cyclophosphamide was seen in patients with SSc-ILD (most of whom have NSIP) randomized to placebo or cyclophosphamide. A small but significant improvement in lung function was noted in subjects assigned to the treatment arm,[23] though subsequent analysis found this effect to dissipate after 2 years.[50] Because cyclophosphamide is associated with many side effects including bone-marrow suppression, hemorrhagic cystitis, and the long-term risk of bladder cancer and hematologic malignancies, it is reserved for severe and progressive cases of NSIP and should only be used by experienced practitioners with appropriate monitoring. As previously mentioned, the Scleroderma Lung Study II noted that patients on MMF had an equivalent response compared with those on cyclophosphamide but experienced fewer adverse effects; as such, clinicians have increasingly steered patients towards MMF. The target dose of MMF is 1500 mg orally twice daily; however, many are unable tolerate the full dose. Enteric-coated mycophenolate sodium may be substituted for those with intolerable gastrointestinal side effects.

Rituximab

Rituximab, an anti-CD20 B cell–depleting monoclonal antibody, has demonstrated potential utility in a number of studies involving connective tissue diseases including dermatomyositis-polymyositis, scleroderma, and RA.[51–53] A recent systematic review and meta-analysis of two randomized control trials and several prospective and retrospective studies in scleroderma patients demonstrated improvement in FVC of 7% at 12 months.[52] Several additional case series and retrospective studies have demonstrated responses in polymyositis patients; one study of 24 patients reported of improvements in FVC and D_{LCO} of 24% and 17% respectively, and a reduction of 34% in radiographic ILD extent, with greater improvements reported amongst those with disease duration less than 12 months or those with acute exacerbations.[54] Rituximab dosing remains variable, but 1 g given intravenously spaced 2 weeks apart with repeat dosing at 6 months has been reported. Rituximab has been associated with prolonged immunosuppression. Infusion reactions including drops in blood pressure, mild throat tightening, sweating, numbness, and nausea can occur; premedication with antihistamines and acetaminophen may reduce reactions. Panhypogammaglobulinemia resulting in infections can occur, and intravenous immunoglobulin should be considered in such patients.

Other Immunosuppressive Agents

A role for tacrolimus in the treatment of NSIP is supported by a case series of patients with polymyositis and dermatomyositis-related ILD. In one case series of 49 previously untreated patients, the addition of tacrolimus to conventional therapy with corticosteroids and intravenous cyclophosphamide or cyclosporine led to improved disease-free survival in myositis-associated ILD.[55] However, because no large-scale studies have been performed, consideration of this agent for the treatment of NSIP should be on a case-by-case basis by physicians who are experienced in the interpretation of serum levels. The most feared side effect is renal toxicity, which can be permanent and lead to kidney failure. Other adverse effects, including neurotoxicity and metabolic derangements, have been reported.

Tocilizumab is a humanized, anti–interleukin 6 receptor antibody approved by the FDA for slowing lung function decline and may be considered as an alternative to MMF. A phase 3 clinical trial (fassCinate)[56] demonstrated that fewer subjects experienced lung function decline in the open-label extension. Another study showed a reduction in FVC decline at 48 weeks in patients treated with tocilizumab compared with placebo.[57] A multicenter retrospective study of RA-ILD patients, including 13 patients with NSIP patterns, suggested potential disease stability and even in improvement in 1 case.[58] Of note, 6 cases of acute exacerbations of underlying ILD have also been reported in RA-ILD patients on tocilizumab therapy.[57,59]

■ Antifibrotics

The antifibrotic therapies nintedanib[60] and pirfenidone[61] were first approved in the United States in 2014 for IPF after the results of large, multicenter, international, randomized, controlled trials demonstrated slowing of disease progression. Subsequent studies investigated the role of antifibrotic therapies in other fibrotic interstitial lung diseases including NSIP. Pirfenidone is a pyridine compound whose mechanism remains to be fully elucidated but has antifibrotic as well as antioxidant and anti-inflammatory properties. A multicenter, double-blind, randomized, placebo-controlled international study of pirfenidone patients with progressive fibrotic ILD (presumably including NSIP patients) failed to meet the prespecified primary endpoint of mean predicted change in FVC from baseline by home-based spirometry, but did demonstrate disease slowing in secondary endpoints including FVC and $\mathrm{DL_{CO}}$ decline in pulmonary function testing at the clinical site and a reduced decline in 6-minute walk distance.[62]

Two recent multicenter studies confirmed the efficacy of nintedanib, a multiple-receptor tyrosine kinase inhibitor with antifibrotic properties, in fibrotic interstitial lung diseases beyond IPF. Common side effects include diarrhea, while other side effects include hepatotoxicity, increased risk of cardiovascular disease, GI perforation, and potential increased risk of bleeding. In the INBUILD trial,[63] reduced declines in FVC were seen across all subgroups of non-UIP patients including those with iNSIP.[64] The SENSCIS trial[65] established a role for nintedanib in patients with scleroderma-associated lung disease, demonstrating reduced declines in FVC at 52 weeks; the radiographic description of these patients included findings of ground-glass opacities suggesting the presence of NSIP. In light of these recent trials, nintedanib has been FDA approved for use in fibrotic ILDs outside of IPF.

SMOKING-RELATED INTERSTITIAL PNEUMONIAS: RESPIRATORY BRONCHIOLITIS–ASSOCIATED INTERSTITIAL LUNG DISEASE AND DESQUAMATIVE INTERSTITIAL PNEUMONIA

The entities of respiratory bronchiolitis–associated interstitial lung disease (RB-ILD) and desquamative interstitial pneumonia (DIP) are part of a spectrum of disorders affecting smokers. Important clinical and pathologic considerations in these two entities are described below.

■ Definition and Historic Perspectives

While clinically regarded as two discrete forms of IIPs, RB-ILD and DIP are generally thought of as representing ends of a continuous spectrum of disease primarily affecting tobacco smokers. The diagnostic distinction persists due to evidence indicating that RB-ILD and DIP have divergent natural histories and prognoses. The pathologic hallmark of both diseases feature cytoplasmic accumulation of golden-brown pigment in macrophages. RB-ILD pathology appears to reflect inhalational exposure, as findings center around the bronchioles with peribronchiolar inflammation and fibrosis. In contrast, DIP involves the airways but also extends into the alveolar space and may even include mild to moderate associated interstitial fibrosis. Because RB-ILD and DIP reactions are frequent and often incidental findings in the lung tissue of smokers, formal clinical diagnosis of RB-ILD or DIP hinges upon the presence of symptomatic, radiographic, and functional impairment. Taken together, RB-ILD and DIP account for up to 15% to 20% of patients with biopsied IIPs.[66–69]

■ Clinical Presentation

Patients diagnosed with RB-ILD and DIP are typically males in the fourth or fifth decade of life with an average 30-pack-year smoking history. Affected patients report nonspecific complaints of progressive dyspnea and nonproductive cough. Physical examination may be normal but might reveal dry inspiratory crackles and clubbing as seen in other forms of ILDs. Extrapulmonary findings are usually absent.

■ Underlying Associations

Tobacco smoke exposure accounts for most cases of RB-ILD and DIP, despite their categorization as “IIPs.” In fact, it has been reported that up to 90% of RB-ILD and DIP cases are causatively linked to tobacco smoke.[66] However, in one review of 49 cases, only 60% of DIP patients versus 93% of RB-ILD patients had a prior smoking history.[70] Although the lower prevalence of smoking in this study compared to prior studies may reflect referral bias, investigators should remain cognizant that such pathologies can occur independently of smoking. When viewed in this light, it is relevant that a number of additional exposures have been reported in association with DIP such as marijuana smoking, diesel fumes, beryllium, copper, fire extinguisher powder, asbestos, and certain chemicals used to process textiles.[70–73] DIP has also been reported as a complication of autoimmune disorders including RA and scleroderma[71,74–76] and has occurred in association with infections such as hepatitis C, cytomegalovirus, and *Aspergillus*.[77–79] Idiopathic DIP also has been reported.[70] RB-ILD established by surgical lung biopsy has been reported in association with an electronic nicotine delivery system.[80]

Genetic factors seem unlikely to play a dominant role; however, a few studies, particularly among children and siblings, have implicated genetic abnormalities of surfactant function, such as mutations in SP-B, SP-C, and ABCA-3 genes.[81–83] The applicability of these studies to the adult IIPs described herein remain uncertain. The difficulty in determining the contribution of other possible exposures may occur because when evaluating individuals with a smoking history, clinical providers dismiss the possible contribution of alternate etiologies.

DIP is often radiographically indistinguishable from NSIP.[84,85] Since many individuals with conditions such as rheumatologic disease do not proceed to lung biopsy, the specific underlying pathology of the associated IIP may remain unconfirmed and individuals may be assumed to have NSIP. DIP may co-exist with other pathologies including NSIP or other smoking-associated interstitial lung disease entities such as emphysema or pulmonary Langerhans cell histiocytosis.[86,87] The clinical significance of the radiographic and pathologic changes related to RB-ILD or DIP will vary particularly by extent of such findings.

■ Pulmonary Function Testing

Patients with RB-ILD often manifest a restrictive physiologic pattern with concomitant reduction in $\mathrm{DL_{CO}}$. However, given the bronchiolocentric nature of the pathology, a mixed pattern with some elements of obstruction also may be seen. DIP patients generally demonstrate restrictive ventilatory defects along with reduction in diffusion capacity. Hypoxemia may be seen in more severely affected patients. On occasion, spirometry and lung volume impairments seem less severe compared with the patient's clinical status. This phenomenon may be due to the mixed or obstructive patterns caused by the airway-centered nature of RB-ILD or concomitant smoking-related lung pathologies such as COPD.

■ Chest Imaging

The imaging findings of RB-ILD are usually subtle and not visualized on chest radiograph. CT findings include subtle, mild, diffuse or upper lobe-predominant centrilobular ground-glass nodules, and patchy ground-glass densities (Fig. 55-3).[20,23,88,89] Ancillary findings associated with cigarette smoking, including bronchial wall thickening from chronic bronchitis and tissue rarefaction and bullae reflecting emphysema, also may be present. Radiographic features of respiratory bronchiolitis with fibrosis (RBF) should not be confused with the specific ILD entity of RB-ILD. RBF is a localized area of interstitial fibrosis typically characterized by a circumscribed area of upper- and mid-zone subpleural foci of emphysema and reticulation.[90] These lesions may regress with smoking cessation.[91] The main alternative diagnosis in a patient with centrilobular ground-glass nodules on CT is subacute hypersensitivity pneumonitis. However, the ground-glass nodules with hypersensitivity pneumonitis are usually not as subtle as those seen with RB-ILD.

Similar to RB-ILD, the chest radiograph features in DIP are usually quite faint, although sometimes hazy, nonspecific, ground-glass opacities may be present. Peripherally located ground-glass opacities (Fig. 55-4) are the most common finding on CT, but they can also be diffuse.[75,79,81,92] Other CT findings including reticular markings and small cysts (which may indicate a component of fibrosis)[75,79,81,92] can be seen, but more extensive fibrotic changes such as traction bronchiectasis and honeycombing are rare. Bronchial wall thickening and emphysema may be seen as well.[75,79,81] When peripheral ground-glass opacities exist in this disease, the differential diagnosis includes NSIP, OP, and chronic eosinophilic pneumonia.

■ Pathology

The diagnosis of RB-ILD and DIP hinges upon a comprehensive clinical assessment integrating history, physical examination, PFTs, and HRCT. RB-ILD and DIP should be distinguished from respiratory bronchiolitis (RB) and respiratory bronchiolitis with fibrosis (RBF). Respiratory bronchiolitis, also referred to as smoker's bronchiolitis, was first described by Niewoher in 1974 and describes an inflammatory reaction of the small airways associated with an increase in pigmented macrophages occurring in response to tobacco smoke. Respiratory bronchiolitis with fibrosis (RBF), also referred to as airspace enlargement with fibrosis or smoking-related interstitial fibrosis in the literature, is a localized interstitial fibrosis

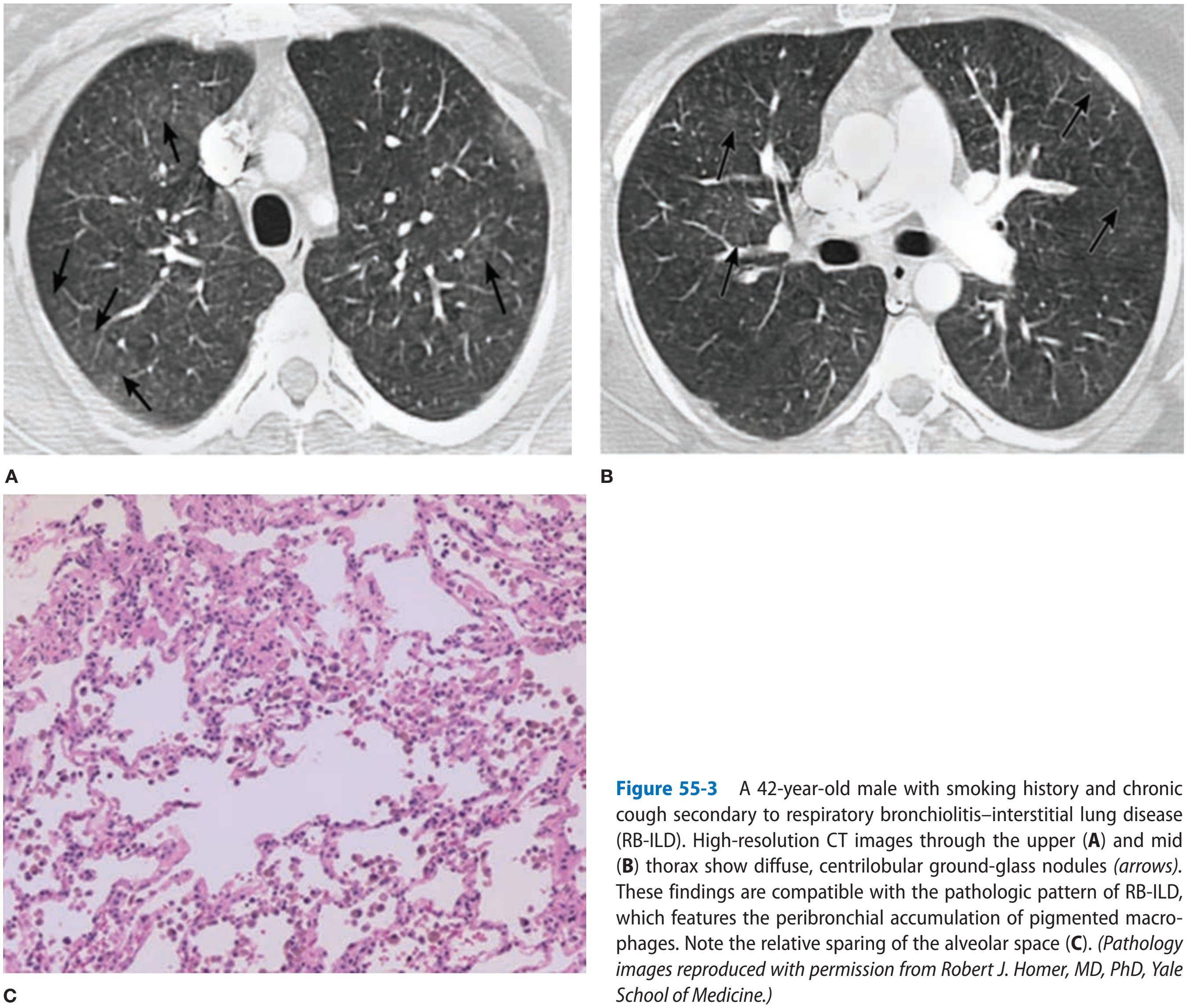

Figure 55-3 A 42-year-old male with smoking history and chronic cough secondary to respiratory bronchiolitis–interstitial lung disease (RB-ILD). High-resolution CT images through the upper (**A**) and mid (**B**) thorax show diffuse, centrilobular ground-glass nodules *(arrows)*. These findings are compatible with the pathologic pattern of RB-ILD, which features the peribronchial accumulation of pigmented macrophages. Note the relative sparing of the alveolar space (**C**). *(Pathology images reproduced with permission from Robert J. Homer, MD, PhD, Yale School of Medicine.)*

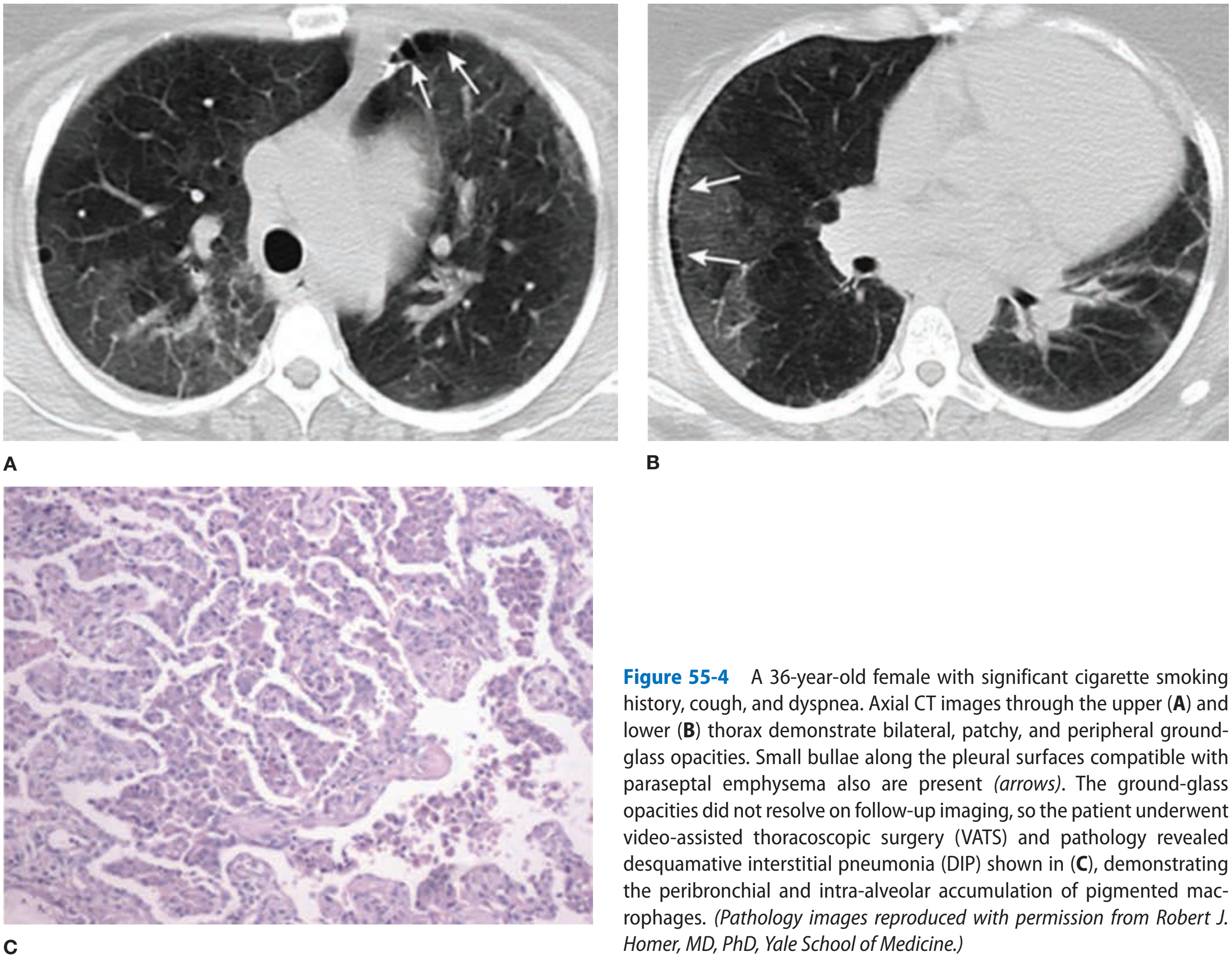

Figure 55-4 A 36-year-old female with significant cigarette smoking history, cough, and dyspnea. Axial CT images through the upper (**A**) and lower (**B**) thorax demonstrate bilateral, patchy, and peripheral ground-glass opacities. Small bullae along the pleural surfaces compatible with paraseptal emphysema also are present *(arrows)*. The ground-glass opacities did not resolve on follow-up imaging, so the patient underwent video-assisted thoracoscopic surgery (VATS) and pathology revealed desquamative interstitial pneumonia (DIP) shown in (**C**), demonstrating the peribronchial and intra-alveolar accumulation of pigmented macrophages. *(Pathology images reproduced with permission from Robert J. Homer, MD, PhD, Yale School of Medicine.)*

associated with cigarette smoking. Pathologically, the lesion is characterized by a circumscribed area of hyaline paucicellular interstitial fibrosis and emphysema, emanating from the respiratory bronchiole and reaching the pleura.[90] In contrast to the above entities, RB-ILD and DIP are clinically significant forms of ILD.

Because the histopathology of DIP and RB-ILD may exist in the lung tissue of asymptomatic smokers, pathology alone is not diagnostic. Bronchoscopy may have a role in ruling out other processes resembling RB-ILD or DIP. BAL reveals characteristic pigmented macrophages. A pronounced eosinophilia has also been reported in BAL specimens of some DIP patients. Investigators have suggested that in the appropriate clinical setting and BAL profile, transbronchial biopsy showing RB may be sufficient to support the diagnosis of RB-ILD. The role of transbronchial lung cryobiopsies yielding larger specimen sizes than traditional transbronchial biopsies will likely continue to expand.[93]

Nonetheless, for both RB-ILD and DIP, surgical lung biopsy may be necessary to formally establish the diagnosis as well as to exclude alternative causes. The pathologic hallmark of RB-ILD and DIP centers around the accumulation of pigmented macrophages, commonly referred to as smoker's macrophages. These macrophages contain iron and display glassy eosinophilic cytoplasm with a finely granular, yellowish-brown pigment that likely contains components of tobacco smoke. In heavy smokers, the pigmentation may become coarser, making the distinction from hemosiderin deposition seen in chronic alveolar hemorrhage more challenging.[70,94] In the 1980s, Myers described the phenomena of RB-ILD characterized by the intensified RB response.[95] Lung tissue from RB-ILD may demonstrate a chronic inflammatory cell infiltrate as well as a peribronchiolar fibrotic pattern more pronounced than that of uncomplicated RB (Figs. 55-3 and 55-4).

First described by Liebow in 1965,[96] DIP was highlighted as a diagnostic entity in a 1978 study by Carrington.[97] Comparison of DIP and RB-ILD reveals that in DIP the macrophages extend more diffusely into the lobule in contrast to the more limited peribronchiolar involvement found in RB-ILD, and that interstitial fibrosis, giant cells, and eosinophils are more commonly found in DIP (Fig. 55-4). Pathologists must exclude the presence of alternative ILDs on biopsy. A clinical diagnosis of RB-ILD or DIP necessitates overall assessment of the patient incorporating pathologic and radiographic findings, functional impairment, and exclusion of other diagnostic considerations pathologically and radiographically.

■ Clinical Course, Outcomes, and Treatment

Patients with RB-ILD or DIP generally have less fibrosis and experience a more favorable prognosis compared with IPF, perhaps in part due to the finding that smoking cessation and corticosteroids are often effective therapies in RB-ILD and DIP patients.[68,69,98] Progressive disease is uncommon in RB-ILD and is more often seen in patients with DIP, as one study found that 33% of DIP patients versus 64% of RB-ILD patients experienced objective radiographic or physiologic improvement.[66] Similarly, another study found that 26% of patients with DIP died compared to no patients with

RB-ILD, a finding that confirmed prior work by Carrington and Yousem.[94,97,99]

■ Smoking Cessation

The cornerstone of treatment for these diseases is tobacco smoking cessation. In patients with mild to moderate symptoms and impairment, a period of observation after smoking cessation is reasonable. Many patients stabilize and improve. Concomitant corticosteroid therapy often confounds interpretation of the efficacy of smoking cessation alone,[68] and earlier studies failed to comprehensively characterize the effect of smoking cessation. Additional confounders that complicate the assessment of improvement include the presence of other smoking-related lung pathologies such as emphysema, whose contribution to impairment will not generally respond to any intervention.

■ Corticosteroids and Immunosuppression

When symptoms and impairment are severe, treatment with systemic corticosteroids may be of benefit. A 6- to 9-month course of therapy with prednisone starting at a dose of 40 to 60 mg per day for 6 weeks is reasonable. The role of alternative immunosuppressants used in other ILDs is less defined in RB-ILD and DIP, but their use has been reported.[100] Macrolide antibiotic therapy has been reported to be an effective steroid-sparing treatment in DIP.[101] Lung transplantation may be necessary for patients with severe progressive disease. Recurrence of disease after transplant has been reported.[90]

ACUTE/SUBACUTE INTERSTITIAL PNEUMONIA: CRYPTOGENIC ORGANIZING PNEUMONIA

The entity of cryptogenic organizing pneumonia was described more than 30 years ago. Important clinical aspects and associations are described below.

■ Definition and Historic Perspectives

First described by Davison[102] and Epler[103] in the early 1980s, cryptogenic organizing pneumonia (COP) was categorized as an IIP in the 2002 working group sponsored by the ATS and the European Respiratory Society (ERS).[23] The pathologic hallmark of COP consists of whorls of myofibroblasts and inflammatory cells in a connective tissue matrix within the distal airspaces. This nonspecific pathologic pattern is termed *organizing pneumonia (OP)* and is found in a variety of settings including infection, drug toxicity, posttransplant, radiation exposure, and rheumatologic conditions; it is only in the absence of an associated condition or inciting factor that clinicians may establish a diagnosis of COP. Therefore, the diagnosis of COP rests on an integrated assessment of clinical symptoms, radiographic patterns, compatible histopathologic features (when available), and the exclusion of other associated causes and conditions.

The pathology was initially called *bronchiolitis obliterans organizing pneumonia (BOOP)*, a term that initially dominated the North American literature and was included in the seminal paper by Katzenstein and Myers in 1998.[104] Given clinical confusion between the term BOOP and the distinct airway-centered disease of bronchiolitis obliterans syndrome ("BOS"), the terminology was changed in 2002. However, because many cases of COP are associated with an underlying etiology, the inclusion of COP as an "idiopathic" interstitial pneumonia has led to confusion for some. Perhaps most perplexing to clinicians is the fact that the disease in COP dominates the airspaces and not the interstitium. However, the working group justified the inclusion of COP within the IIPs because in clinical practice COP is part of the differential diagnosis of other IIPs, and because interstitial inflammation and fibrosis may be present in COP. A unique variant of COP, known as the cicatricial form (CCOP) in which the loose fibromyxoid connective tissue progresses to dense collagenized scar tissue with preservation of underlying lung architecture, also has been described in the literature.[105]

■ Clinical Presentation

Similar to other IIPs, the epidemiology of COP is not well characterized, although it seems to affect both genders equally with a mean age of onset of 58 years. Nonsmokers or former smokers may be affected more frequently than current smokers.[106] The classic presentation of COP includes an initial prodromal flu-like illness with symptoms of fever, cough, and dyspnea. Hemoptysis, chest pain, arthralgias, or myalgias are uncommon. Chest auscultation may be clear or may reveal crackles. Patients are frequently treated with multiple courses of antibiotics before being diagnosed. The presence of systemic symptoms and/or findings consistent with CTD should lead to careful investigation for an associated underlying disease.[107]

Differential diagnostic considerations include hypersensitivity pneumonitis, chronic eosinophilic pneumonia, pulmonary lymphoma, and diffuse alveolar damage more commonly seen in acute respiratory distress syndrome. Acute fibrinous organizing pneumonia (AFOP) is included in the clinical spectrum of organizing pneumonia and is characterized by intra-alveolar fibrin depositions, referred to as fibrin "balls," associated with organizing pneumonia but without hyaline membranes. Like OP, AFOP can be idiopathic or can occur in association with CTD, hypersensitivity pneumonitis, infection, and/or drug toxicity.[108] Granulomatous organizing pneumonia (GOP) also has been described as a possible variant of OP; histopathologic features of GOP include OP in association with small poorly formed nonnecrotizing granulomas.[108,109]

■ Underlying Associations

A diagnosis of *COP* requires exclusion of associated causes. Many viral, bacterial, fungal, and parasitic infections have been implicated,[106,110] as has influenza A H1N1.[111] OP is a frequently encountered manifestation of drug-induced lung disease caused by antibiotics such as nitrofurantoin; medications such as phenytoin, amiodarone, sulfasalazine;[112] and illicit drugs such as cocaine.[113] Occupational exposures are also associated with an OP pattern of lung injury including but not limited to the aerosolized textile dye Acramin FWN, titanium nanoparticles in paint, and certain chemicals used in spice processing.[114–116] OP has been reported in patients with dermatomyositis-polymyositis,[8,117–121] RA,[122–124] scleroderma,[74,75,125] and systemic lupus erythematosus.[126–128] Because this form of lung injury may present as the initial manifestation of systemic disease, rheumatologic serologies can be helpful in identifying the presence of coexisting CTD. OP may be present in other inflammatory diseases such as Crohn disease and ulcerative colitis.[129] Radiotherapy treatment is also associated with the development of OP, particularly 3 to 6 months following treatment for breast cancer. Compared to radiation pneumonitis, which is fairly well circumscribed and characterized by retracted lung and traction bronchiectasis, postradiotherapy OP occurs diffusely, is migratory, and is highly steroid responsive.[130]

While BOS is the most commonly reported lung injury pattern in patients experiencing lung transplant rejection, OP patterns also have been described.[131,132] Similarly, bone-marrow transplant recipients may develop OP as a manifestation of transplant rejection, graft-versus-host disease, or idiopathic pneumonia syndrome.[133–135] OP can also complicate malignant or hematologic conditions such as various forms of acute and chronic leukemias and lymphomas.[136] It has also been suggested that gastroesophageal reflux with silent aspiration may play a role in the development of OP; however, this association has not been firmly established.[137] A recent study did find an association between more frequent relapse and severe disease in patients with co-existing GERD, warranting further investigation.[138]

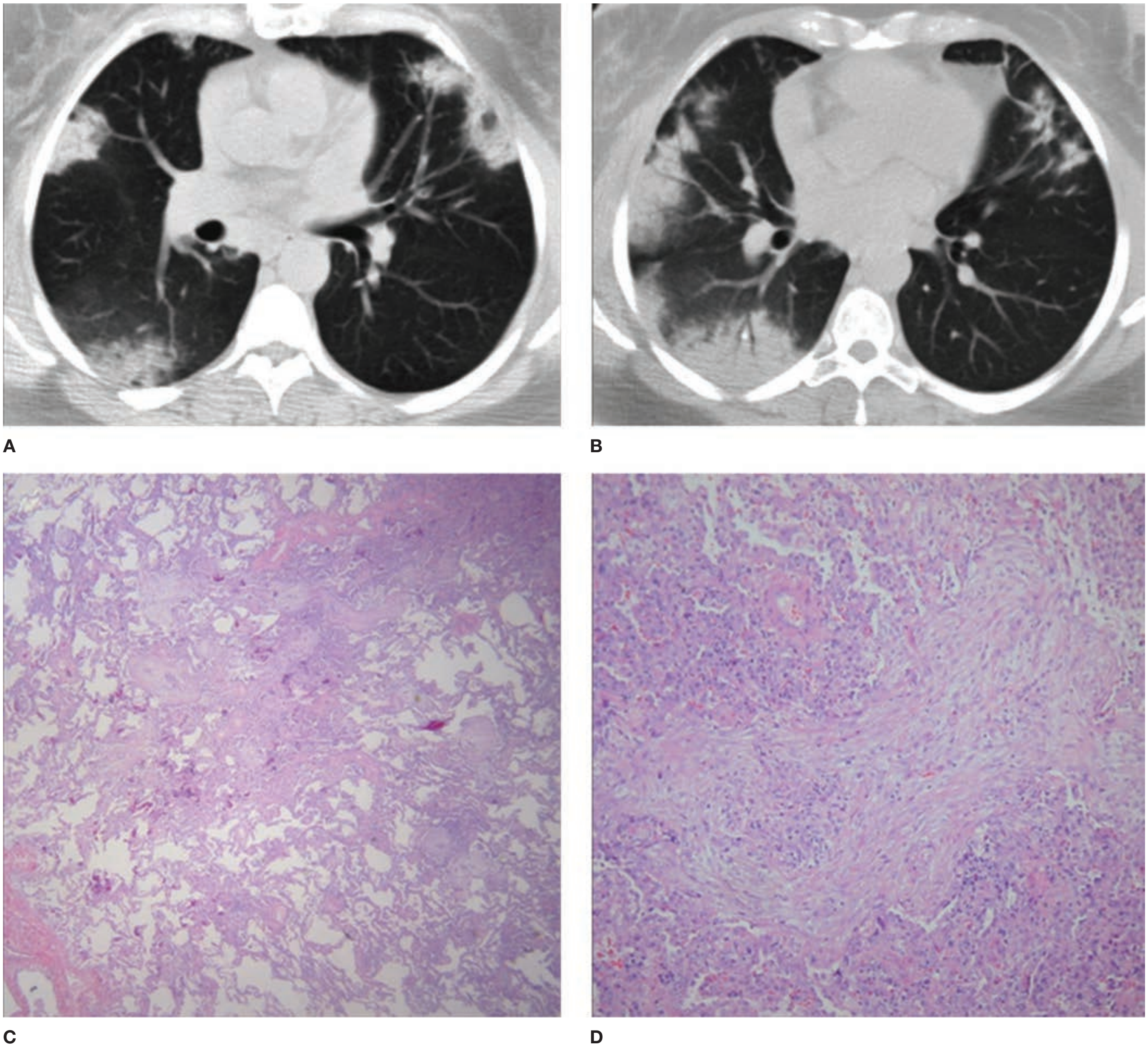

Figure 55-5 A 50-year-old female with cough and dyspnea secondary to organizing pneumonia (OP). Axial CT images through the mid (**A**) and mid to lower (**B**) thorax demonstrate multifocal, peripheral areas of consolidation with a distribution compatible with OP. Low- and high-power views (**C, D**) of lung tissue from this patient reveal a patchy organizing pneumonia pattern of exudates, fibroblasts, and inflammatory cells. *(Pathology images reproduced with permission from Robert J. Homer, MD, PhD, Yale School of Medicine.)*

■ Pulmonary Function Testing

As in other IIPs, a restrictive ventilatory defect characterized by a reduction in TLC is generally present. In a subset of patients, an obstructive ventilatory defect can be found. Hypoxemia is typically mild, although in a subgroup of patients with infiltrative opacities, severe hypoxemia may be seen.[139,140]

■ Chest Imaging

OP displays a variable imaging appearance. The chest radiograph usually shows nonspecific patchy areas of consolidation. Sometimes the imaging appearance mimics infectious pneumonia with lobar consolidation that is unresponsive to antibiotics. Peripheral, patchy, and peribronchovascular areas of ground-glass opacity and consolidation are the most classic CT findings (Fig. 55-5).[20,23,141,142,143] Nodular areas of ground glass and consolidation as well as fleeting or migratory areas of consolidation also can be seen with OP.[20,23,141,142,143] Findings suggestive of fibrosis, such as reticulation, architectural distortion, traction bronchiectasis, and honeycombing, are not typically present with this entity. An area of ground-glass opacity surrounded by a rim of increased density, also known as the atoll (or reverse-halo) sign, when present, is strongly suggestive of OP[141,142] but can also be present with other entities such as vasculitis, certain infections, or pulmonary infarction. Presentation as a solitary mass has been reported, although this is rare.[144,145]

■ Pathology

When the clinical presentation and chest imaging is insufficient for a confident diagnosis of COP, bronchoscopy with transbronchial biopsy or surgical lung biopsy can be employed. BAL typically reveals significant accumulation of lymphocytes, neutrophils, and eosinophils. Transbronchial biopsies may be performed to make a diagnosis; however, the quantity of lung tissue obtained during these procedures is quite small and may be insufficient to fully evaluate the spectrum of pathology that may exist within the lung parenchyma.[146–148] Thus, larger lung tissue specimens obtained by VATS are frequently used to provide the opportunity for more thorough analyses. The pathology of OP is characterized by intraluminal plugs of inflammatory debris within the alveolar ducts and surrounding alveoli. The plugs consist of buds of granulation tissue, along with whorls of fibroblasts and myofibroblasts in a connective tissue matrix referred to as Masson bodies (Fig. 55-5). OP patterns can be seen concomitantly in patients with NSIP or UIP, and may in certain patients represent an exacerbation of underlying ILD. In this setting, interpretation of the pathology in the context of the radiographic and clinical features can greatly aid in accurate diagnosis.

■ Clinical Course and Outcome

Patients with mild or asymptomatic disease may not require treatment.[149] When compared with other fibrotic lung diseases, COP is impressively steroid responsive—although a significant proportion of patients, ranging from 13% to 58%, experience relapse. Radiographic evidence of disease in all three lung zones, pathologic evidence of high levels of intra-alveolar fibrin on lung biopsy, and high neutrophil percentage on BAL[150] are associated with increased risk of relapse.[151] Studies investigating predictors of relapse have identified associations between radiographic findings of traction bronchiectasis and bilateral shadow patterns, FVC and Pa_{O_2}/Fi_{O_2} at presentation, and protein level at presentation, but larger-scale studies are still needed.[152,153] Fortunately, relapses are not associated with poorer long-term outcomes and death is very infrequent.

■ Pharmacologic Therapy

Historically, a 6-month course of treatment has been advised. More recently, shorter 3-month durations of corticosteroids have been recommended to avoid unnecessarily prolonged courses of steroids in patients who do not relapse.[107] Macrolide antibiotics[154–156] and steroid-sparing agents such as cyclophosphamide, azathioprine, or rituximab[157–159] have been used as alternative immunosuppressants for individuals with COP or secondary OP. However, the clinical utility of these approaches has not been completely validated. It is not known whether individuals with secondary causes of OP experience different long-term outcomes from individuals with COP. While most COP patients have favorable prognosis, a subset of patients present with a rapidly progressive and fatal form of OP. Some investigators suggest such cases represent an overlap group with acute interstitial pneumonia or acute respiratory distress syndrome (ARDS). Nonetheless, the literature does suggest that a small subgroup of COP patients suffer a progressive fibrotic course. Alternative forms of immunosuppression such as cyclophosphamide have been used in such rapidly deteriorating patients, although experience with this approach is at best limited and the clinical utility is not entirely clear.[157]

ACUTE/SUBACUTE INTERSTITIAL PNEUMONIA: ACUTE INTERSTITIAL PNEUMONIA

The original description of acute interstitial pneumonia dates back more than 75 years. Clinical hallmarks of this entity are described below.

■ Definition and Historic Perspective

Acute interstitial pneumonia, also called "AIP" or "Hamman–Rich syndrome," was first described by Hamman and Rich in 1935 and is a rare and fulminant IIP.[160] Current ATS/ERS diagnostic criteria for AIP include the following:[23] (1) rapidly progressive clinical course (≤2 months) leading to respiratory failure; (2) exclusion of infectious, toxic, autoimmune, or any other known cause of ARDS; (3) diffuse alveolar damage (DAD) on biopsy specimens (see below); (4) radiologic findings consistent with ILD; and (5) absence of chronic lung disease.

■ Clinical Presentation

AIP is quite rare and most frequently presents in previously healthy individuals with no prior lung disease. The disease has no sex predominance and most commonly affects patients more than 40 years old with a mean age of 50 to 55 years.[161–163] Unlike most other IIPs,[161] AIP typically presents with an acute onset of fever (75%), cough (70%), and rapidly progressive dyspnea (90%)[105] with many patients reporting the sensation of an infectious prodrome. Most patients are hypoxemic upon presentation and rapidly progress to respiratory failure requiring mechanical ventilation. Physical examination frequently reveals tachypnea and bilateral crackles in all lung fields. Signs of chronic lung disease such as clubbing are uncommon and argue against a diagnosis of AIP, while the presence of skin or joint abnormalities might suggest an underlying autoimmune process. While initial management focuses on stabilizing respiratory status, diagnostic evaluation should be undertaken. Once cardiogenic pulmonary edema has been ruled out by electrocardiogram, cardiac enzymes, and echocardiogram, causes of noncardiogenic pulmonary edema and ARDS should be investigated. Given the broad array of diseases and exposures associated with the development of ARDS, this assessment should include careful exposure history including medications and occupational hazards, as well as a complete rheumatologic history. The serologic and muscle enzyme testing described earlier for NSIP may also be valuable in this setting.

■ Underlying Associations

The differential diagnosis of AIP is broad and includes left heart failure, diffuse alveolar hemorrhage, OP, hypersensitivity pneumonitis, acute exacerbation of UIP/IPF, and DIP. AIP can generally be distinguished from these entities by careful history, examination of chest radiography, and ancillary tests described earlier. Once the AIP diagnosis has been established, it is imperative to seek underlying causes including collagen vascular disease such as antisynthetase syndrome[164] or lupus;[165] therapeutic exposures such as certain chemotherapies, biologic therapies, radiation, and hyperoxia;[166,167] illicit drugs such as heroin or cocaine;[168] toxic exposures such as smoke inhalation and other gases;[166] massive transfusion;[169] fat embolism; aspiration;[170] and infections such as atypical pneumonias (*Mycoplasma*[171] or *Legionella*[172]) and viral infections (influenza).[173] AIP should also be differentiated from acute exacerbations of underlying IIPs or other pre-existing forms of underlying lung disease.

■ Pulmonary Function Testing

Most patients are too ill to undergo pulmonary function testing, but a restrictive ventilatory defect and impaired diffusion capacity would be expected.

■ Chest Imaging

AIP is radiographically and pathologically indistinguishable from ARDS. Imaging findings depend upon whether the early, exudative phase or chronic, fibrotic phase is present. Diffuse consolidation and ground-glass opacities are typically seen in the early exudative phase, with the dependent areas of lung being more affected.[20,23,174,175] The early, exudative phase is difficult to distinguish radiographically from other entities such as cardiogenic or noncardiogenic edema, diffuse infection, or hemorrhage. In patients who survive the acute phase (sometime after the first week), in addition to the lung consolidation, findings of underlying fibrosis such as

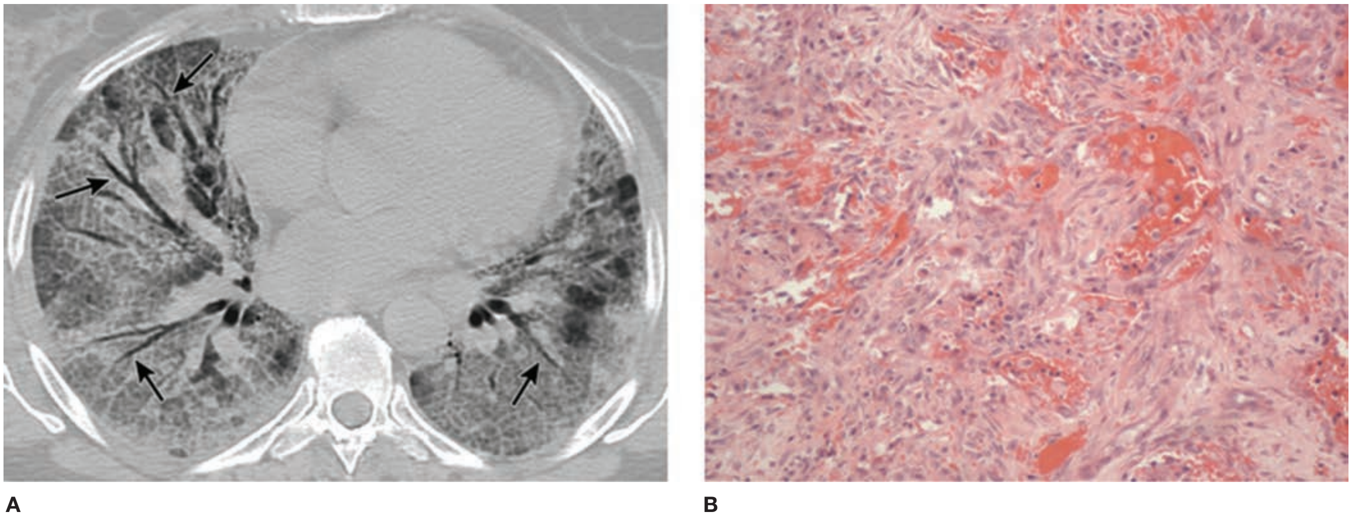

Figure 55-6 A 45-year-old female with acute shortness of breath. High-resolution CT image through the thorax (**A**) demonstrates diffuse ground-glass opacities involving every lobe. Within areas of ground-glass opacity are reticular markings and traction bronchiectasis *(arrows)* suggestive of organization and underlying fibrosis. Lung tissue obtained at autopsy revealed findings of diffuse alveolar damage, which included obliteration of the alveolar space with structural cell death responses, acute inflammation, and hyaline membrane formation (**B**). *(Pathology images reproduced with permission from Robert J. Homer, MD, PhD, Yale School of Medicine.)*

architectural distortion and traction bronchiectasis with or without honeycombing become apparent on imaging, and are usually more severe in the nondependent portions of the lung (Fig. 55-6).[20,23,175]

■ Pathology

If microbiologic testing yields negative sputum culture and viral studies, bronchoscopy with BAL should be performed to rule out undiagnosed infection or alternate diagnosis. There is generally no role for transbronchial biopsy in the diagnosis of AIP; surgical lung biopsy is the preferred approach if tissue diagnosis is required. A pathologic diagnosis of DAD demonstrates diffuse and extensive cell death accompanied hyaline membranes, which are histologically apparent layers of fibrin mixed with necrotic epithelium. This material lines the alveolus and reflects the severity and acuity of the injury (Fig. 55-6). As the injury progresses, it evolves into its organizing phase, which can either resolve into relatively normal lung or result in lung fibrosis.

■ Clinical Course and Outcomes

The fulminant and often untreatable nature of AIP endows this disease with a particularly high mortality. More than 50% of patients die during hospitalization and most patients die within 6 months of diagnosis. Those who survive are at risk for disease recurrence or the development of other forms of ILD. However, a small fraction of survivors may experience complete recovery of lung function.[162,176] Treatment is detailed below and is aimed at supporting the patient and attempting to limit the acute injury and inflammation.

■ Therapy: Nonpharmacologic

The mainstay of therapy for AIP is supportive care.[162] This includes supplemental oxygen or mechanical ventilation, adequate sedation, nutritional support, and prevention of ICU-related complications such as stress-induced ulcers, venous thromboembolism, catheter-related bloodstream infections, and ventilator-associated pneumonias.

■ Therapy: Pharmacologic

High/pulse-dose glucocorticoid therapy is frequently administered to patients suffering from AIP, but, due to the rarity and often grave nature of AIP, there have been no clinical trials assessing efficacy of this treatment.[162] Therefore, the evidence supporting this approach is anecdotal and is, in fact, based on case reports that showed a conflicting survival benefit.[161,162,177] For example, in the largest case series published in 1990, of 29 patients treated with glucocorticoids, survival was 45% in the treated group versus 33% in the untreated group.[161] Similarly, in a smaller series of only 8 patients treated with pulse-dose steroids, 7 patients survived.[177] Conversely, a different study of 9 patients treated with 8 mg/kg of methylprednisolone found a mortality of 100% with this regimen.[162] Despite this lack of clear benefit, expert opinion recommends continuation of high-dose steroids for several days followed by a maintenance dose of the equivalent of prednisone 60 mg/day that can be tapered over the ensuing weeks if the patient survives.[162]

The side effects of high-dose steroids cannot be overstated. In addition to the long-term side effects described earlier, short-term risks in the ICU include hyperglycemia, immunosuppression, neuromuscular complications, and delirium. Thus, in some settings when steroids are contraindicated or a steroid-sparing agent is required, practitioners might employ a trial of non-steroid-based therapy. Use of other agents such as azathioprine, cyclosporine,[178] cyclophosphamide, and vincristine have been reported in AIP, but these agents are not recommended for routine use.[170] OLT has been successful in several patients with respiratory failure attributed to AIP. However, because these patients are frequently too unstable for transfer to a transplant center, the utility of OLT in AIP is at best limited.

LYMPHOID INTERSTITIAL PNEUMONIA

Rare idiopathic interstitial pneumonias include lymphocytic interstitial pneumonia, discussed below, and pleuroparenchymal fibroelastosis, discussed subsequently.

■ Definition and Historic Perspectives

In 1969, Liebow and Carrington developed the term *lymphoid interstitial pneumonia (LIP)* to describe a benign polyclonal infiltration of the alveolar space and interstitium with mature B or T cells. LIP exists within a spectrum of lymphoproliferative disorders affecting the lung and, as such, its classification as an IIP has been debated. Furthermore, the malignant potential of LIP is not well defined[179,180] but all sources agree that identification of monoclonal features effectively rules out LIP and points to a malignant etiology.[181,182] However, because the clinical and radiographic features overlap with the other IIPs in terms of differential diagnosis[183] and treatment approach, the most recent ATS and ERS statement on IIPs retained LIP within this classification.[20,23] LIP is also sometimes seen in children; however, because this chapter addresses adult IIPs, pediatric LIP will not be discussed.

■ Clinical Presentation

Given its rarity, the demographics of LIP are difficult to define but available data indicate that mean age of onset is during the fifth decade of life, and the diagnosis is more common in women.[23,184] LIP typically presents as slowly progressive cough and dyspnea over several years.[184] Systemic symptoms are rare, but fever, weight loss, chest pain and joint aches have been reported.[23,184] Chest auscultation may be normal or may reveal crackles as the disease progresses.[185] Extrapulmonary findings may include lymphadenopathy or joint findings consistent with underlying Sjögren syndrome or RA. Findings consistent with severe lung disease, such as clubbing, are rarely detected.[23] Laboratory examination may reveal mild anemia. Quantification of serum immunoglobulins reveals either a polyclonal gammaglobulinemia or a monoclonal increase in either IgG or IgM in up to 75% of patients.[182,186] Immune complexes are sometimes seen, but only infrequently.[187]

■ Underlying Disease Associations

Most cases of LIP are associated with an underlying cause, such as Sjögren syndrome,[188] or immunodeficiency, such as severe combined immunodeficiency and HIV.[8,118,153,189] LIP has also been reported with RA,[190] Hashimoto disease,[191] pernicious anemia,[192] chronic active hepatitis,[193] systemic lupus erythematosus,[194] autoimmune hemolytic anemia,[186] primary biliary cirrhosis,[182] and hypogammaglobulinemia.[192,195] LIP is also seen in certain viral infections including Epstein–Barr[196,197] and human T cell lymphotropic virus type I (HTLV-I).[198,199] Truly idiopathic LIP accounts for less than 20% of cases.[184] Thus, as with NISP, a diagnosis of LIP should prompt a dedicated search for an underlying cause.

■ Pulmonary Function Testing

When present, abnormalities include a restrictive defect characterized by reduced FVC and TLC, an impaired $D_{L_{CO}}$, and, potentially, hypoxemia.[200]

■ Chest Imaging

The imaging findings of LIP are variable and depend upon the underlying disease process. The chest radiograph reveals nonspecific findings such as bilateral reticular markings and hazy, ground-glass opacities. As with the other IIPs, LIP is much better characterized by HRCT. Diffuse, patchy, or lower lobe predominant ground-glass opacities with reticular markings and small cysts is the pattern most commonly seen on CT in patients with HIV, and can be difficult to distinguish from viral or opportunistic infections such as pneumocystis or CMV pneumonia.[20,201] Thickened bronchovascular bundles, septal thickening, and centrilobular nodules are less commonly present. LIP in patients with Sjögren syndrome typically manifests as bilateral, thin-walled cysts of varying sizes (but usually larger than the cysts seen in HIV-associated LIP) scattered throughout the lungs with intervening normal lung parenchyma (Fig. 55-7).[23] Often, a vessel appears to be associated with (or adjacent to) the wall of a cyst, thus the term "perivascular cyst." Ground-glass opacities may exist as well.[23,183,202] The main differential diagnosis for this appearance would include other causes of cystic lung disease, such as lymphangioleiomyomatosis (in a female patient), Langerhans cell histiocytosis (in a cigarette smoker), and *Pneumocystis* pneumonia (in immunocompromised patient), although the latter two entities usually manifest with upper lobe–predominant cysts.

■ Pathology

LIP pathology demonstrates a dense interstitial lymphoid infiltrate containing lymphocytes, plasma cells, and histiocytes, in combination with type II cell hyperplasia (Fig. 55-7). The alveolar septa are extensively infiltrated. Lymphoid follicles with germinal centers are often seen.[23,182] Honeycombing and nonnecrotizing granulomas are sometimes detected[23,182] along with intra-alveolar organization and macrophages, but when these latter aspects are the dominant pathologic feature, the diagnosis of LIP should be reconsidered.[23]

■ Natural History, Clinical Course, and Treatment

Little is known about the clinical course and prognosis of LIP. The results of several case series suggest that approximately 50% of patients improve, 10% remain stable, and 40% will die of disease within 2 years, even when treated with immunosuppression.[23,182,184,203] Those patients who survive are subject to a small but significant chance of progression to pulmonary lymphoma[182] in addition to an increased risk of serious and potentially fatal infections related either to the underlying cause of LIP (inherited or acquired immunodeficiency) or to the immunosuppressive therapies used to treat this disease.

Idiopathic LIP

Treatment for LIP depends in part upon the patient's symptoms and the underlying cause. Asymptomatic patients with mild, idiopathic disease are typically subject to careful longitudinal follow-up with serial PFTs and chest imaging because a small percentage of these patients will spontaneously improve.[23] Patients who deteriorate over time, or those who are highly symptomatic or significantly impaired upon initial diagnosis, are offered treatment with immunosuppression. While no data exist regarding the safety or efficacy of glucocorticoids in patients with idiopathic LIP,[23] extrapolation of case series of patients with CTD-associated LIP (in which approximately 50% of patients show some evidence of response) suggests potential benefit.[203] Patients are typically started on the equivalent of 1 mg/kg (ideal body weight) oral prednisone for 8 to 12 weeks, after which chest imaging and PFTs are repeated. Those patients who demonstrate an objective response may continue their prednisone at a tapered dose for several months longer; those who do not respond generally discontinue therapy or are offered an alternate disease-modifying agent such as cyclosporine or azathioprine. Again, it should be noted that the evidence for this approach is scarce and the risk of side effects, and possible lack of efficacy, must be weighed against the potential benefit inherent in this class of drugs. In addition, patients on long-term steroid therapy should be offered prophylaxis against *Pneumocystis* pneumonia and should be monitored for bone health.

Nonidiopathic LIP

Management of LIP in the setting of CTD is similar to that of idiopathic LIP, but the use of immunosuppression in this population is based on stronger evidence.[184,203] Treatment of LIP in the setting of HIV usually involves initiation of highly active antiretroviral therapy (HAART), as in many patients this intervention will reduce symptoms and improve both radiographic disease burden and lung physiology.[204–206] For patients whose disease persists despite use of HAART, glucocorticoids are commonly used, although evidence for this regimen precedes the HAART era.[200,207] As with idiopathic and CTD-related LIP, *Pneumocystis* prophylaxis should be strongly considered for patients with HIV-related LIP who are treated with immunosuppression.

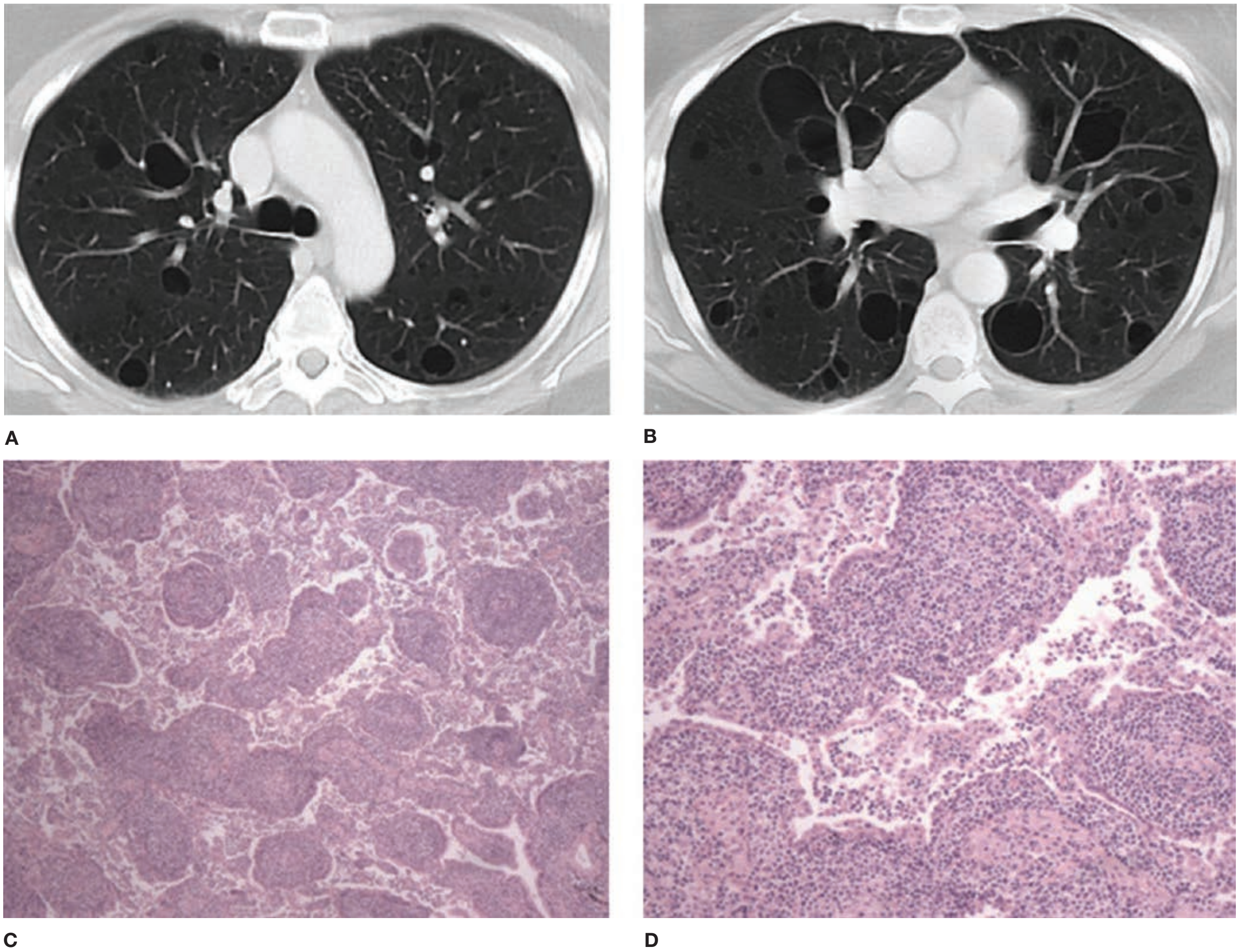

Figure 55-7 A 51-year-old female with Sjögren syndrome and lymphocytic interstitial pneumonia (LIP). Axial CT images through the upper (**A**) and mid (**B**) thorax show multiple thin-walled cysts of varying sizes bilaterally involving the upper and lower lobes. Note the presence of normal lung parenchyma between the cysts. Low- and high-power views (**C, D**) of LIP lung tissue reveal a dense interstitial infiltrate containing lymphocytes, plasma cells, and histiocytes, combined with type II cell hyperplasia and increased alveolar macrophages. *(Pathology images reproduced with permission from Robert J. Homer, MD, PhD, Yale School of Medicine.)*

IDIOPATHIC PLEUROPARENCHYMAL FIBROELASTOSIS

More than 20 years prior to its formal designation as an independent form of rare idiopathic interstitial pneumonia, a unique pattern of upper lobe–predominant lung disease characterized by pleural and parenchymal fibroelastosis was described in the literature. In 2004, Frankel first used the term *pleuroparenchymal fibroelastosis (PPFE)* to describe five cases who shared this previously uncategorized pattern of fibrosis, which also closely resembled the pulmonary upper lobe fibrosis (PULF) proposed by Amitani et al. in 1992.[1] Now, years later, it is accepted that PULF and PPFE represent the same entity, and PPFE was formally recognized as a specific independent form of rare idiopathic interstitial pneumonia by the ATS/ERS in 2013.[1] Idiopathic PPFE is reported to account for approximately 6% to 8% of all ILD,[208] but due to a lack of formal established diagnostic criteria and subsequent misdiagnosis, the true incidence and prevalence for PPFE is unknown. It usually is idiopathic, but has been linked to other diseases, as described below.

■ Clinical Presentation

PPFE is a rare disease. However, as imaging modalities improve and awareness increases, it is being diagnosed more frequently. Age of presentation is highly variable, ranging from age 8 to 87 in the literature,[209,210] distributed bimodally, with a smaller peak occurring in the third decade of life and a larger peak occurring around the sixth decade.[211] The idiopathic form generally presents during middle age, without sex difference.[1] Some reports identified a female predominance (especially among the young),[212] but other studies have not demonstrated a difference between the sexes.[213–215] Mean time from development of symptoms and diagnosis is usually 2 to 3 years.[216,217] Presenting symptoms for PPFE commonly include dyspnea with cough, similar to other ILDs, accompanied by weight loss that worsens with disease progression. Chest auscultation may be normal initially, with crackles once PPFE has extended beyond the upper zones, or if there is coexisting UIP, NSIP, or hypersensitivity pneumonitis (HP). Notably, due to volume loss in upper lobes, a large number of patients with PPFE develop platythorax, flattening of the chest associated with a reduced anteroposterior diameter, which can be noticed as the deepening of the suprasternal notch on physical examination.[218] Pneumothorax, which can be asymptomatic and recurrent, is a complication in both idiopathic and secondary disease.[219] Clubbed fingers occur in less than 25% of patients with PPFE.[212]

There are no diagnostic laboratory tests for PPFE. Some patients have elevated biomarkers for Krebs von den Lungen 6 (KL-6) antigen[220–222] and surfactant protein D (SP-D).[221] A recent study found elevated levels of urinary desmosine in individuals with biopsy-proven PPFE, but this has not yet been validated for clinical application.[223]

■ Underlying Associations

Little is known about the etiology of PPFE, and most cases are considered idiopathic without associated underlying conditions. Common secondary causes of PPFE include history of prior hematopoietic stem cell[224,225] or lung transplantation.[226] PPFE has also been described to resemble a form of chronic graft-versus-host disease in bone-marrow transplant recipients.[227–230] A few cases have occurred amongst siblings, suggesting a possible underlying genetic predisposition.[231] Specific mutations in telomere regulating genes (telomere reverse transcriptase and telomerase RNA) have been identified among those diagnosed with PPFE and are associated with more progressive disease.[210,232] A causal relationship between the development of PPFE and prior treatment with amiodarone[233] or chemotherapy (alkylating agents carmustine and cyclophosphamide) has been explored in the literature.[234] PPFE is also associated with autoimmune diseases (RA, ankylosing spondylitis, ulcerative colitis)[235,236] as well as infection (*Aspergillus*, *Mycobacterium avium intracellulare*).[237,238] Environmental exposures, including aluminosilicate dust and asbestos, have been implicated, but no association with cigarette smoking has been established.[213,239] PPFE can occur independently or coexist with other patterns of fibrosis, including UIP and HP.

■ Pulmonary Function Testing

A restrictive ventilatory defect, characterized by a reduction in TLC, decreased FVC, and increased FEV_1/FVC ratio, is generally present in PPFE, accompanied by decreased DL_{CO}. However, mixed ventilatory defects also can be found.[227] In a subset of patients, residual volumes also may be reduced; the cause for this remains uncertain, but is hypothesized to occur due to increased end-expiratory air trapping or inhomogeneous lung emptying. FVC may decline rapidly following diagnosis; this decrease is especially marked in those with telomere gene abnormalities.[210] Platythorax may also contribute to ventilation perfusion mismatch as the disease progresses.[213]

■ Chest Imaging

In early stages, bilateral irregular thickening of apices may be the only abnormality on an otherwise normal chest radiograph. As the disease progresses, reticular and nodular opacities appear in the upper lung fields accompanied by bilateral hilar opacities; lateral views may demonstrate narrowed anterior-posterior dimensions.[213] On HRCT, early stages of the disease presents with apical subpleural and reticular opacities, with characteristic sparing of other lung fields. As the disease progresses, elevated hilar shadows with parenchymal thickening with fibrosis become more pronounced, with the development of traction bronchiectasis, bullae, and large cysts, with or without air bronchograms, and volume loss (Fig. 55-8). Specific radiologic criteria for the definitive diagnosis of PPFE on CT were proposed by Reddy et al. in 2012,[216] requiring the presence of upper lobe pleural thickening with subpleural fibrosis, and limited lower lobe involvement. Other patterns of fibrosis, including HP, UIP, and NSIP, can also coexist with PPFE, with their respective findings on imaging.[217,240,241]

■ Pathology

A multidisciplinary approach is critical to the diagnosis of PPFE, with consideration of radiologic and clinical data, and confirmation by pathologic data if necessary. When the clinical presentation and imaging are insufficient for a confident diagnosis of PPFE, nonsurgical sampling with transbronchial and transthoracic biopsies can be obtained. Surgical lung biopsy also can be employed, but it is often avoided if possible due to concerns for complications, or contraindications in secondary PPFE. Characteristic histology of PPFE includes upper lobe–predominant fibrotic and elastotic changes in lung parenchyma, subpleural intra-alveolar fibrosis and elastosis (IAFE), and visceral pleural fibrosis. IAFE pathology is not exclusive to PPFE and can be found in injuries following toxicity (paraquats), radiation, and ARDS, as well as "apical cap." Both UIP and HP have been shown to coexist with PPFE.[242] UIP is most common, occurring most frequently in the lower lobes. IAFE shares similar features with UIP, including its subpleural nature and foci of fibroelastic proliferation at the interface between areas of fibrosis and normal lung parenchyma, with sparse or nonspecific inflammation. However, in addition to lacking honeycomb change, fibrosis in PPFE is accompanied by preserved alveolar structure with elastin fiber deposition leading to homogenous intra-alveolar fibrosis (Fig. 55-8). Utilization of elastic Van Gieson stain to highlight elastic fibers will show marked elastin deposition around the alveolar walls, versus a more disorganized and sparse pattern in fibrotic areas in UIP.[243] PPFE can be distinguished immunohistochemically from UIP through the positive staining of myofibroblasts for podoplanin.[244] PPPE has also been reported in patients diagnosed with chronic HP. The presence of granulomas on biopsy histology (found in approximately 15% of cases)[209,216,242,245] is associated with better prognosis, but possibly due to coexistence of an additional inflammatory process (such as HP, or infection) that is more responsive to treatment. Thus far, a factor to distinguish between primary and secondary PPFE has not been found.

■ Clinical Course and Outcomes

The prognosis for PPFE is poor. Once regarded as slowly progressing with an insidious course, a second phenotype of disease with rapid progression also has been described. Most patients experience disease progression following diagnosis, with mean survival ranging from 4 months to 11 years.[213,220,246,247] Survival rates at 1, 3, and 5 years are 88.5%, 45.5%, and 28.9%, respectively.[217,248] Patients with iPPFE, genetic mutations affecting telomere lengths, and coexisting UIP or HP may be more susceptible to rapidly progressive disease. Studies evaluating the effects of coexisting UIP on outcomes have had mixed results,[247,249] while PPFE is associated with higher mortality in patients with coexisting chronic HP.[240] As the clinical course is often progressive, bilateral lung transplantation may be the only definitive treatment.[250–254]

■ Pharmacologic Therapy

There are no effective pharmacologic treatments for PPFE. Prednisone in low doses may be helpful; higher doses of corticosteroids and other immunosuppressive agents (azathioprine, methotrexate) may increase infection risk.[212] In PPFE occurring in restrictive allograft syndrome (RAS), the antifibrotic agent pirfenidone has been used with varied results.[255,256] Data from the INBUILD trial suggest that nintedanib may have a role for patients with non-IPF progressive fibrotic ILD[63] and so could be considered in patients with PPFE. A retrospective case series demonstrates that pirfenidone may be effective in slowing disease progression as measured by FVC in PPFE patients with evidence of coexisting UIP pattern.[257] Antibiotic therapy or antifungal therapy for those prone to infection should be considered when indicated.

UNCLASSIFIABLE INTERSTITIAL PNEUMONIA

Despite advances in radiographic investigation and thorough multidisciplinary evaluation, some ILD cases cannot confidently be diagnosed, prompting the proposal of an "unclassifiable" subgroup of IIP

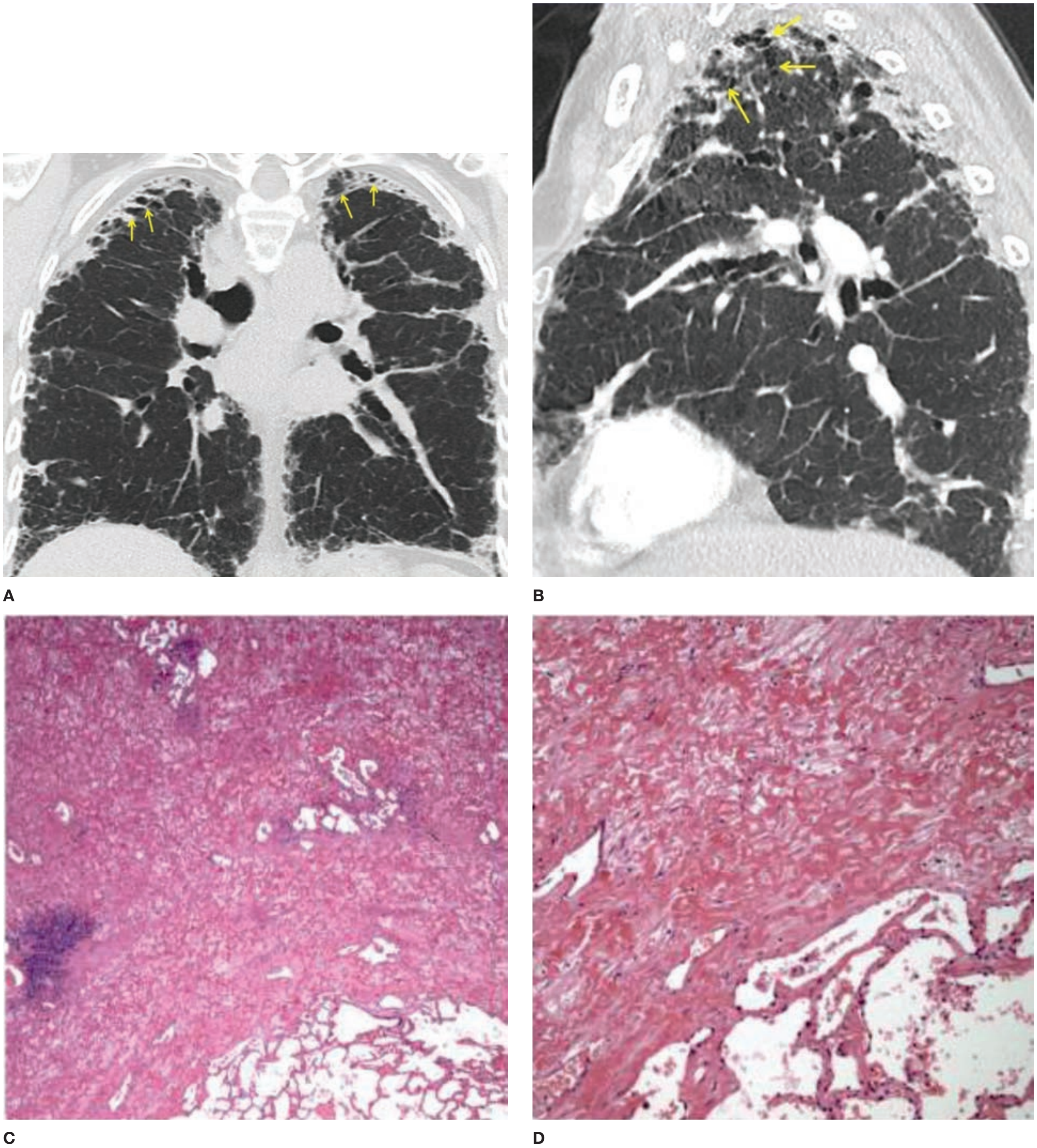

Figure 55-8 73 year old female with progressive dyspnea and pleuroparenchymal fibroelastosis (PPFE). Coronal (**A**) and sagittal (**B**) reformatted CT images demonstrate bilateral, peripheral, upper lobe predominant pleural thickening with subjacent consolidation containing fibrotic changes including traction bronchiectasis *(arrows)*. The lung parenchyma is diffusely effaced by fibroelastosis with no recognizable lung parenchyma (low-power view) (**C**). Note that conventional honeycombing (mucus filled terminal airways) is not seen. (**D**) Fibroelastosis consists of unusual extracellular matrix with both fibrosis (pink fibers) and elastic fibers (bluish-gray) (high-power view). No inflammation is present. *(Pathology images reproduced with permission from Robert J. Homer, MD, PhD, Yale School of Medicine.)*

in 2002[23] and later inclusion of "unclassifiable IIP" as a distinct entity in the ATS/ERS consensus statement on classification of IIPs in 2013.[1] As outlined by the consensus statement, circumstances that warrant labelling a condition as unclassifiable include situations in which there are discrepancies between investigative findings, there are inadequate data (most commonly due to lack of biopsy), there is a discordance between findings (either in the presence of coexisting disease or where different biopsy sites show different pathologic findings), when prior treatment makes interpreting diagnostic information impossible (for instance, biopsy results showing NIP following the use of glucocorticoid treatment for DIP),[258] or when conflicting pathologic patterns are present on HRCT.[1] Other causes for "unclassifiable IIP" designation include the discovery of a new entity or atypical presentation of a previously recognized entity. In the literature, the reported prevalence of unclassifiable disease is 12% of all ILD, but many of the studies used to compute this data point were published prior to the use of HRCT.[259] Similarly, it is difficult to determine if these cases are truly unclassifiable, versus not yet classified, as many patients are unable to undergo surgical lung biopsy due to contraindications or increased risk for complications.

Clinically, patients report dyspnea and fatigue on presentation, with physical exam findings notable for Velcro rales.[260] While there are no tests available to distinguish between IIPs, advances in biomarker and genetic testing may one day allow for a definitive diagnosis in the future. Different approaches, including cryobiopsy, are being evaluated, which may enable histology sampling in those who would otherwise have contradictions to undergoing diagnostic surgical biopsy.[261–263] There is no standardized pharmacologic treatment for unclassifiable ILD, and therapeutic regimens are individualized based on the degree of inflammation or whether fibrosis is deemed present.

CONCLUSION

The non-IPF IIPs are characterized by diverse presentations, underlying associations, natural history, and response to therapy. Given the complexity of diagnosis and management, these diseases are best managed by highly experienced practitioners using a multidisciplinary approach.

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CHAPTER 56

Hypersensitivity Pneumonitis

Prerna Mota
Richard I. Enelow

DEFINITION

Hypersensitivity pneumonitis (HP) is an interstitial lung disease believed to be mediated by aberrant cellular and humoral immune responses to various inhaled antigens in susceptible individuals, resulting in inflammatory and/or fibrotic disease of the lung parenchyma and small airways. Its clinical presentation and natural course can be quite variable, and despite the efforts of numerous expert groups and panels, clear consensus on diagnostic criteria and common nomenclature has proven elusive. Previous classification schemes described "acute HP" and "chronic HP" as two forms of the disease, the latter temporally related to the former, despite limited evidence to support this approach. The recognition that prognosis is minimally related to disease duration, and is more dependent upon extent of fibrosis, has led to the recent move to reclassify HP subtypes as "nonfibrotic HP" and "fibrotic HP." The latter represents a uniquely challenging entity, for multiple reasons discussed below.

EPIDEMIOLOGY AND ETIOLOGIES

The prevalence of HP is quite variable in different populations, presumably because of differing intensity, frequency, and duration of inhalation exposure, probable variations in environmental and occupational patterns, and heterogeneity in host susceptibility (genetic or otherwise). A large number of antigenic exposures are associated with HP, as shown in Table 56-1. At the same time, prevalence data are colored by the variability of diagnostic criteria and the absence of a clear gold standard.[1] Once thought to be a relatively rare disease, HP (by any definition) is becoming more frequently recognized, as awareness of the limitations of classic diagnostic criteria has grown. Available studies suggest an overall incidence of HP of 0.3 to 0.9 per 100,000 individuals,[2–5] with striking differences in specific populations studied. These data on incidence and prevalence largely pertain to acute (or nonfibrotic) HP, as an entity more easily recognized particularly in association with identifiable antigen exposure. The nuances of this designation, and those of the less recognizable chronic (or fibrotic) entities, will be discussed below.

The most commonly reported form of HP is bird-related, with reports suggesting that 5% to 15% of pigeon breeders (members of pigeon-breeding clubs who participated in surveys) exhibit evidence of HP, so-called pigeon breeder's disease.[6,7] Bacterial and fungal antigens (associated with "farmer's lung," "humidifier lung," and "summer-type HP") are relatively common in selected populations, although they vary widely in frequency in different regions of the world.[8–12] The frequency of disease in Finnish farmers, for example, has been reported as high as 5% to 10%.[12]

Recognition of new examples of HP often requires a cluster of new cases with a unifying exposure history. For instance, occupational exposure to nontuberculous mycobacteria (NTM) in metalworking fluids was discovered in a cluster of machinists with HP.[13] Since complete occupational and avocational histories are frequently not obtained from patients presenting with interstitial pneumonia, it is likely that there are more exposures that cause HP that have not yet been recognized and described.

CLINICAL FEATURES

HP has long been categorized as acute, subacute, or chronic, although the distinctions have not always been well defined (particularly the vague notion of "subacute" disease), and heterogenous clinical presentations are frequent in all forms of HP. As such, a two-cluster solution has been proposed by several groups to better characterize the subtypes of disease:[14,15] acute (usually associated with more recurrent systemic symptoms, often with a normal chest radiograph) and chronic (usually associated with greater restriction, hypoxemia, and radiographic evidence of fibrosis). The most readily recognizable form is an acute presentation of HP, in which patients often present with a flulike illness 4 to 12 h after exposure to an offending antigen. The physical examination may be notable for crackles, mid-inspiratory squeaks (chirping rales or squawks), and occasional hypoxemia. A more indolent presentation is the rule for "chronic HP," which is usually characterized by features similar to any chronic interstitial lung disease, including gradual onset, progressive dyspnea, and crackles on examination, often with digital clubbing.[16] However, there is considerable overlap in the acute and chronic presentations of HP, and it remains controversial whether a temporal relationship exists between acute and chronic forms of disease, or if serial evolution occurs between the two.[17] Furthermore, chronic/fibrotic HP can be easily mistaken for other forms of idiopathic interstitial pneumonia, especially since the inciting exposure may remain unknown in about 50% of patients despite a careful history.[18]

In the evaluation of a patient with suspected HP, a thorough history of occupational, avocational, and environmental exposures should be taken, high-resolution chest CT scanning should be obtained, analysis of IgG precipitins is often performed, and if an actionable working diagnosis is not established, biopsy of lung tissue may be required. Even after histopathology is obtained, diagnostic challenges often remain, as in circumstances when the clinical picture, the radiographic evidence, the laboratory data, and the pathology may be *compatible* with the diagnosis but not *typical*. The potential added value of multidisciplinary discussion has been emphasized by numerous expert panels.[15,18–20]

DIAGNOSIS

An attempt at greater rigor and consistency in the diagnostic criteria of HP was made by several joint society committees, with an aim toward more definitive diagnosis.[18,19] The classification of HP into acute, subacute, and chronic has been proposed to be replaced by two categories, nonfibrotic and fibrotic HP. (Subacute had been generally dismissed already as a subtype.) The practical value of this distinction is evident in the clear association of fibrosis (radiographic and/or histologic) with worse prognosis. The designation of radiographic and histopathologic criteria into "typical, probable, and indeterminate" serves to codify the degree of certainty (or more generally uncertainty) of the diagnosis, although there is no consensus level of certainty necessary to proceed with treatment based upon a provisional diagnosis. The utility of seemingly refined diagnostic criteria (when the quality of evidence and confidence in estimated effects of each recommendation are individually very low) is not clear in clinical settings, but despite their arbitrary nature, the criteria are likely to be useful in the design of future clinical trials. Nevertheless, it is important to consider that while the duration of symptoms in HP is not associated with survival time, the extent of fibrosis is an important predictor.[21]

In clinical practice, the three most important realms for diagnosis include (1) attempted identification of antigen exposure; (2)

TABLE 56-1 Etiologies of Hypersensitivity Pneumonitis

Disease	Antigen Source	Probable Antigen
Farmer's lung	Moldy hay	Thermophilic actinomycetes (*M. faeni* [*S. rectivirgula*], *T. vulgaris*) *Aspergillus* spp.
Bagassosis	Moldy pressed sugarcane (bagasse)	Thermophilic actinomycetes (*T. sacchari*, *T. vulgaris*)
Mushroom worker's disease	Moldy compost and mushrooms	Thermophilic actinomycetes (*M. faeni*, *T. vulgaris*) *Aspergillus* spp. Mushroom spores
Suberosis	Moldy cork	*Penicillium* spp.
Malt worker's lung	Contaminated barley	*Aspergillus clavatus*
Maple bark disease	Contaminated maple logs	*Cryptostroma corticale*
Sequoisis	Contaminated redwood sawdust	*Graphium* spp. *Pullularia* spp.
Soybean lung	Soybeans in animal feed	Soybean hull antigens
Wood pulp worker's disease	Contaminated wood pulp	*Alternaria* spp.
Wood dust HP	Contaminated wood dust	*Bacillus subtilis* *Alternaria* spp.
Compost lung	Compost	*Aspergillus* spp. *T. vulgaris*
Cheeseworker's disease	Cheese or cheese casings	*Penicillium* spp.
Wood trimmer's disease	Contaminated wood trimmings, at times in sawmills	*Rhizopus* spp. *Mucor* spp.
Thatched roof disease	Dried grasses and leaves	*Saccharomonospora viridis*
Greenhouse lung	Greenhouse soil	*Aspergillus* spp. *Penicillium* spp. *Cryptostroma corticale*
Coffee worker's lung	Green coffee dust	Unknown
Potato riddler's lung	Moldy hay around potatoes	Thermophilic actinomycetes (*M. faeni*, *T. vulgaris*) *Aspergillus* spp.
Tobacco worker's disease	Mold on tobacco	*Aspergillus* spp.
Wine grower's lung	Mold on grapes	*Botrytis cinerea*
Woodman's disease	Mold on bark and fuel chips	*Penicillium* spp.
Soy sauce brewer's lung	Fermentation starter for soy sauce	*Aspergillus oryzae*
Domestic allergic alveolitis	Decayed wood	Fungi (*Serpula lacrymans*, *Leucogyrophana pinastri*, *Paecilomyces variotii*, *Aspergillus fumigatus*)
Riding school lung	Hay in horse stall	Thermophilic actinomycetes (*M. faeni* [*S. rectivirgula*], *T. vulgaris*)
Stipatosis	Esparto grass (*Stipa tenacissima*), used to make plaster	Esparto grass antigens
Pigeon breeder's disease	Avian droppings, feathers, serum	Altered serum/feather proteins
Turkey handler's disease	Turkey products	Turkey proteins
Chicken breeder's lung	Chicken feathers	Chicken feather proteins
Bird fancier's lung	Domestic and wild bird products	Bird proteins
Duvet lung	Duvet and pillow	Goose proteins
Laboratory worker's HP	Rat fur	Rat urine protein
Pituitary snuff taker's disease	Pituitary powder	Vasopressin
Shell lung	Oyster or mollusk shell	Shell proteins
Miller's lung	Grain weevils in wheat flour	*Sitophilus granarius* proteins
Sericulturist's lung	Silkworm larvae	Silkworm larvae proteins
TDI HP	Toluene diisocyanate	Altered proteins (albumin + others)
MDI HP	Diphenylmethane diisocyanate	
HDI HP	Hexamethylene diisocyanate	
TMA HP	Trimetallic anhydride	Altered proteins

(continued)

TABLE 56-1 Etiologies of Hypersensitivity Pneumonitis *(Continued)*

Disease	Antigen Source	Probable Antigen
Ventilator lung	Contaminated humidifiers, dehumidifiers, air conditioners, heating systems	Thermophilic actinomycetes (*T. candidus*, *T. vulgaris*) *Penicillium* spp. *Cephalosporium* spp. Amoebae *Klebsiella* spp. *Candida* spp.
Basement lung	Contaminated basement (sewage or mold)	*Cephalosporium* spp. *Penicillium* spp.
Sauna taker's disease	Sauna water	*Aureobasidium* spp.
Detergent worker's disease	Detergent enzymes	*Bacillus subtilis*
Japanese summer house HP	House dust, bird droppings (?)	*Trichosporon cutaneum*
Hot-tub lung	Mold on ceiling	*Cladosporium* spp.
Tractor lung	Contaminated tractor, cab air conditioner	*Rhizopus* spp.
Machine operator's lung	Contaminated metal working fluid	*Pseudomonas* spp.
Fertilizer lung	Contaminated fertilizer	*Streptomyces albus*
Sax lung	Saxophone mouthpiece	*Candida albicans*

radiologic findings suggestive of HP; and (3) BAL lymphocytosis. Clinical history remains a key factor in diagnosis. Patients with nonfibrotic disease may present with a history of recent exposure to an inciting agent followed by symptom onset within 4 to 12 h. In contrast, patients with fibrotic HP may not have a clearly defined culprit agent and symptoms are likely more insidious. Thus it may be clinically useful to consider acute and nonfibrotic HP as overlapping in nature (as well as chronic and fibrotic), as long as the prognostic implications of the extent of fibrosis are considered. The identification of the inciting antigen is generally associated with a better prognosis,[18] but the more advanced the fibrosis, the less robust this association becomes.

Identification of antigen exposure can be derived from the clinical history itself. The history should seek to establish a link between a particular exposure (at work, at home, or elsewhere) and previous episodes of "pneumonia." Knowledge of other exposed persons with similar symptoms should be sought. Evidence of repetitive typical symptoms and laboratory and radiologic abnormalities associated with exposure to a particular environment is also highly suggestive of HP. In some instances, a "natural exposure" (i.e., documentation of appropriate symptoms and laboratory abnormalities after intentional exposure to a suspect environmental agent) has been suggested to diagnose HP. A "natural exposure" challenge should not be considered positive unless there is objective evidence of a change in temperature, total peripheral white blood cell count, chest radiograph (or high-resolution CT scan), or a decrease in diffusing capacity of the lungs for carbon monoxide ($\mathrm{DL_{CO}}$) (or arterial $\mathrm{Po_2}$). If the history suggests a relationship between exposure and pulmonary symptoms, evidence of sensitization and the nature of the pulmonary inflammatory response should be interrogated. Sensitization may be indicated by the presence of serum antibody (IgG) to an agent known to be associated with HP, although the sensitivity is generally low. An antigen questionnaire can be used, although no such validated tool has been developed to date. BAL cell counts and differentials lack diagnostic specificity but may helpful in increasing the level of concern for suspected HP; this may be most useful in patients with suspected nonfibrotic HP (in addition to exclusion of infection). Confidence in the diagnosis of HP is enhanced by radiographic imaging suggestive of a "typical HP" pattern (discussed below), a known (presumptive) antigen exposure, and BAL lymphocytosis (although the cutoff levels are uncertain), usually without obtaining histopathologic "confirmation" (which is not always achievable, even with surgical biopsy).

RADIOGRAPHIC FEATURES

The plain chest radiograph may be useful in the initial evaluation of patients with possible nonfibrotic or fibrotic HP (Figs. 56-1 and 56-2), although high-resolution CT chest (HRCT) is the preferred modality for radiographic characterization of presumptive HP (Fig. 56-3). Image acquisition should occur upon deep inspiration, in which all features of lung infiltration may be identified. However, expiratory images are useful in identifying air trapping, an expiratory finding that serves to enhance confidence in diagnosis of nonfibrotic HP, as well as confirmation of heterogeneity of lung attenuation in both forms of the disease. HRCT findings for either fibrotic or nonfibrotic HP are categorized as typical, compatible with, or indeterminate for HP.[19]

The "typical" appearance of nonfibrotic disease is exemplified by a combination of features indicative of parenchymal infiltration (such as ground glass opacification [GGO] and mosaic attenuation), as well as features of small airways disease (ill-defined centrilobular nodules and air trapping on expiration) diffusely distributed, with or without basal sparing. Mosaic attenuation on inspiratory imaging reflects the coexistence of hyperattenuated (from inflammatory infiltration) and mildly hypoattenuated regions (hypoperfusion due to bronchiolar obstruction). Features considered "compatible" with nonfibrotic HP include uniform GGO, airspace consolidation, the presence of cysts, and variant distribution (basal or peribronchovascular predominance).

The "typical" appearance of fibrotic HP is a combination of interstitial fibrosis (coarse reticulation with minimal architectural distortion/honeycombing) along with clear evidence of small airways disease (ill-defined nodules, mosaic attenuation, air trapping), notably exemplified by the "three-density sign" (Fig. 56-4). Patterns "compatible" with fibrotic HP include a UIP pattern of fibrosis, along with subtle features of small airways disease, or extensive GGO with

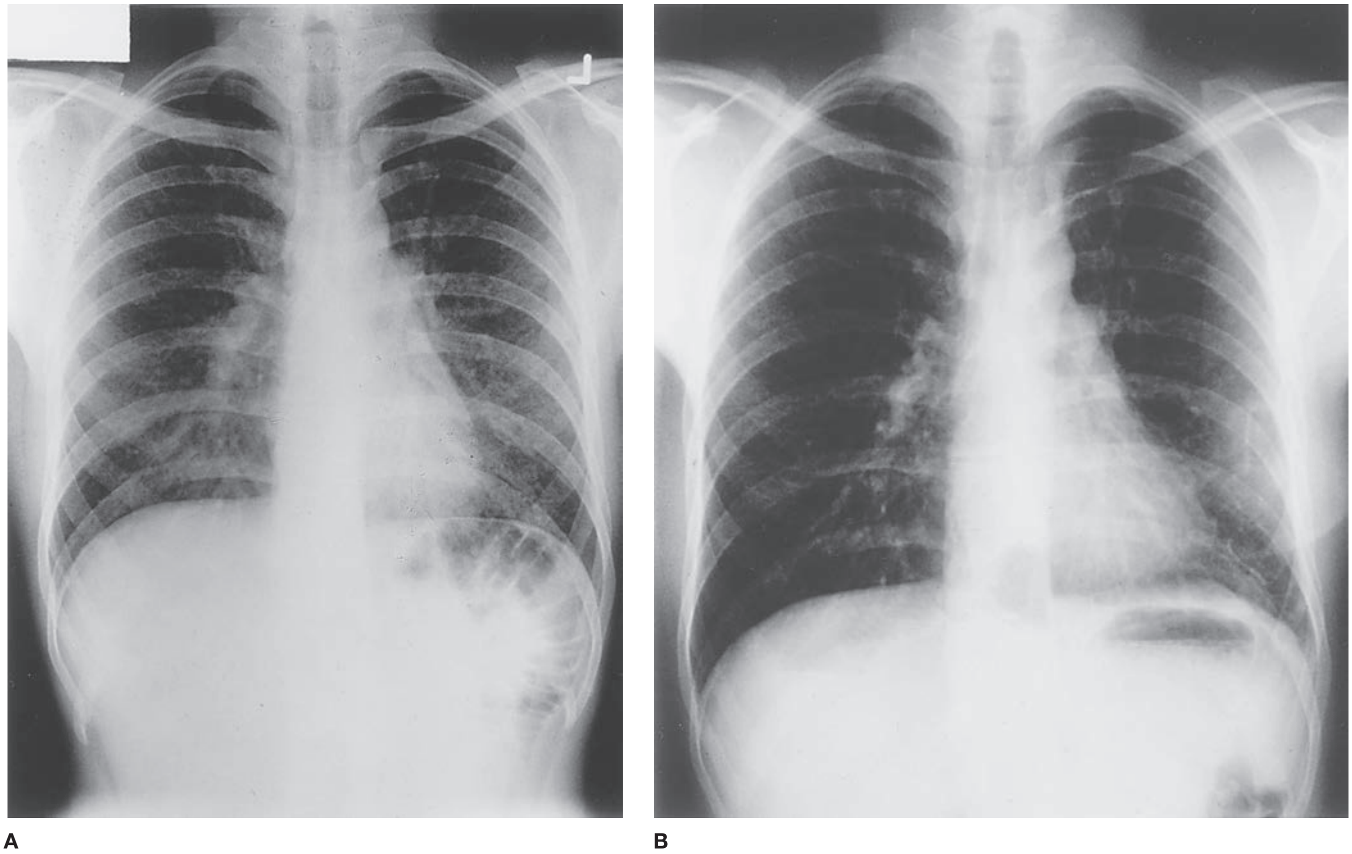

Figure 56-1 **A.** Chest radiograph of a patient with pigeon breeder's disease with fever, dyspnea, and bibasilar rales. The patient had kept pigeons for 5 years and presented with fever, dyspnea, and myalgias approximately 8 h after cleaning the pigeon coop. He had serum antibody to pigeon dropping extract. Note bilateral lower lobe 2- to 3-mm nodules. **B.** Chest radiograph of the same patient 2 weeks later without specific treatment. Note clearing of the lower-lobe nodules (and the staples in the left chest from a surgical lung biopsy).

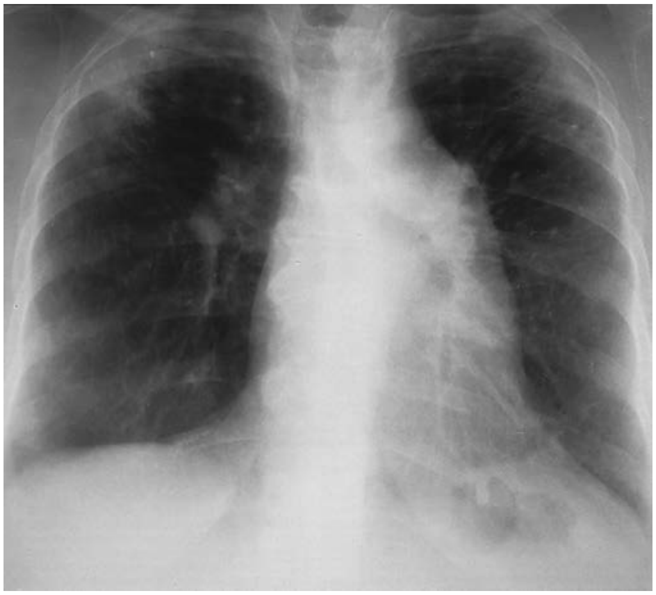

Figure 56-2 Chest radiograph of a patient with bird fancier's disease who presented with progressive dyspnea and weight loss. She had kept 2 to 3 parakeets in her home for 15 years and did not notice episodic fever or acute dyspnea. She had positive serum precipitins to parakeet serum, restrictive physiology, and exertional hypoxemia. Note the diffuse radiodensities, loss of volume of the upper lobes, and signs of pulmonary hypertension.

subtle features of fibrosis or small airways disease. "Indeterminate" patterns include a UIP or fibrotic nonspecific interstitial pneumonia (NSIP) pattern, organizing pneumonia–like pattern, and absence of features of small airways disease.[19] Highly suggestive of fibrotic HP, the three-density pattern indicates a mixed infiltrative and obstructive disease, involving sharply separated regions of three attenuations: areas of normal lung, infiltrative GGO, and patches of hyperlucent lung, or preserved lobules and low-density lobules within the same lobe.[15] Although highly specific for fibrotic HP, the three-density sign is present in a minority of cases.[22] At the same time, any pattern of interstitial lung disease that does not include evidence of small airways involvement is indeterminate for fibrotic HP,[17] although in the appropriate clinical context it may be adequate for a provisional diagnosis.

LABORATORY FINDINGS

Patients with HP often have a peripheral blood leukocytosis with neutrophilia and without eosinophilia. As mentioned above, prominent cellular abnormalities may also be seen in the BAL fluid, which may provide support for the diagnosis. At time points greater than 5 days after the last exposure, BAL fluid lymphocytosis (typically 30% to 70% of total cells) may be noted, in both nonfibrotic and fibrotic HP. This may also be helpful in distinguishing HP from idiopathic pulmonary fibrosis (IPF) and sarcoidosis, although it has been challenging to determine a threshold of BAL lymphocytosis that can distinguish HP from other ILDs with high sensitivity and specificity. However, a consensus threshold of 30% is thought to be reasonable in the absence of high-quality experimental data.[23]

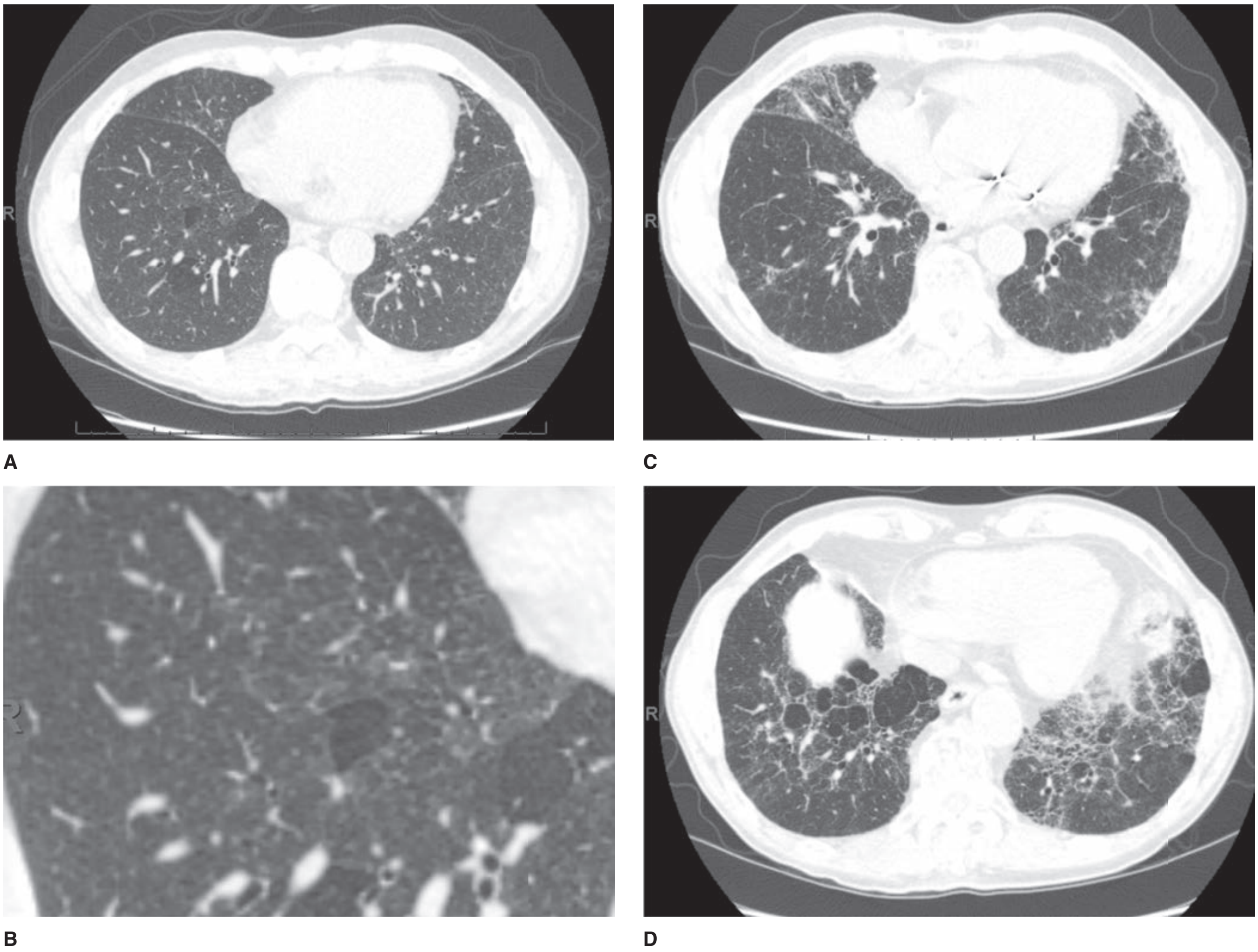

Figure 56-3 High-resolution CT scan of a nonsmoking patient without a clear exposure history who presented initially with dyspnea on exertion and a mild restrictive ventilatory defect. Bronchoalveolar lavage revealed significant lymphocytosis, and he was started on corticosteroid therapy with considerable improvement. As shown in the top left panel, there is diffuse abnormality of the lung parenchyma with patchy centrilobular nodularity and mosaic attenuation, which are quite diffuse in the craniocaudal and axial planes *(magnified image of right anterior region shown in bottom left panel)*. He was lost to follow-up, then returned 5 years later with worsening dyspnea and exertional hypoxemia. Repeat CT *(right panels)* showed continued evidence of centrilobular nodularity and mosaic attenuation, with moderately extensive reticular abnormalities, patchy ground glass, and traction bronchiectasis. The fibrotic abnormalities show a lower lung predominance. These imaging findings are highly suggestive of fibrotic hypersensitivity pneumonitis, with evolution from a nonfibrotic pattern initially, with moderate progression of fibrosis over the 5-year interval.

In most instances of HP, BAL fluid lymphocytes are virtually all $CD3^+$ (T lymphocytes), with a relative increase of $CD8^+$ cells, such that the CD4:CD8 ratio is usually less than 1 (normally 2–2.5, as in peripheral blood). The utility of BAL lymphocytosis in fibrotic HP is highly variable, although in the "proper clinical context" high BAL lymphocyte counts may increase the probability of HP.[24]

Many patients with HP have easily demonstrable serum antibodies (typically IgG, IgM, and IgA) to the offending material detectable by a variety of methods. Since antigen preparations are not standardized, it is difficult to be confident of the meaning of a negative result. Furthermore, since serum antibody is also present in many exposed, but not ill, subjects at similar levels as patients with HP, the presence of antibody should be considered supporting data in the proper clinical context. In asymptomatic pigeon breeders, the prevalence of antibody to pigeon antigens may be as high as 87%.[25] In a study of more than 3000 Finnish farmers, the prevalence of anti–*Micropolyspora faeni* serum antibody may be up to 8.6%.[26] The occurrence of serum antibody is not consistently related to apparent exposure (i.e., hours of exposure or intensity of exposure) in most instances of HP. In addition, serum antibody has been reported to wane after cessation of exposure, so patients with chronic presentations of HP who have not been exposed for some time may not have demonstrable antibody. In farmer's lung disease, approximately 50% of patients with initially positive serum antibody to *M. faeni* (*Saccharopolyspora rectivirgula*) lose demonstrable antibody 6 years after cessation of exposure, although a significant proportion of those who continue to farm may also lose detectable antibody in more than 5 years.[27] Therefore, it is possible that patients with HP will have no detectable serum antibody owing to the assays themselves or the waning of antibody over time.

Nonspecific markers of inflammation, such as increased erythrocyte sedimentation rate and C-reactive protein, are often elevated during an acute episode of HP, but they are quite nonspecific. In contrast to sarcoidosis, the serum angiotensin-converting enzyme levels are not elevated. Skin tests (either immediate or delayed type) to detect sensitization to the suspected antigens are not useful.

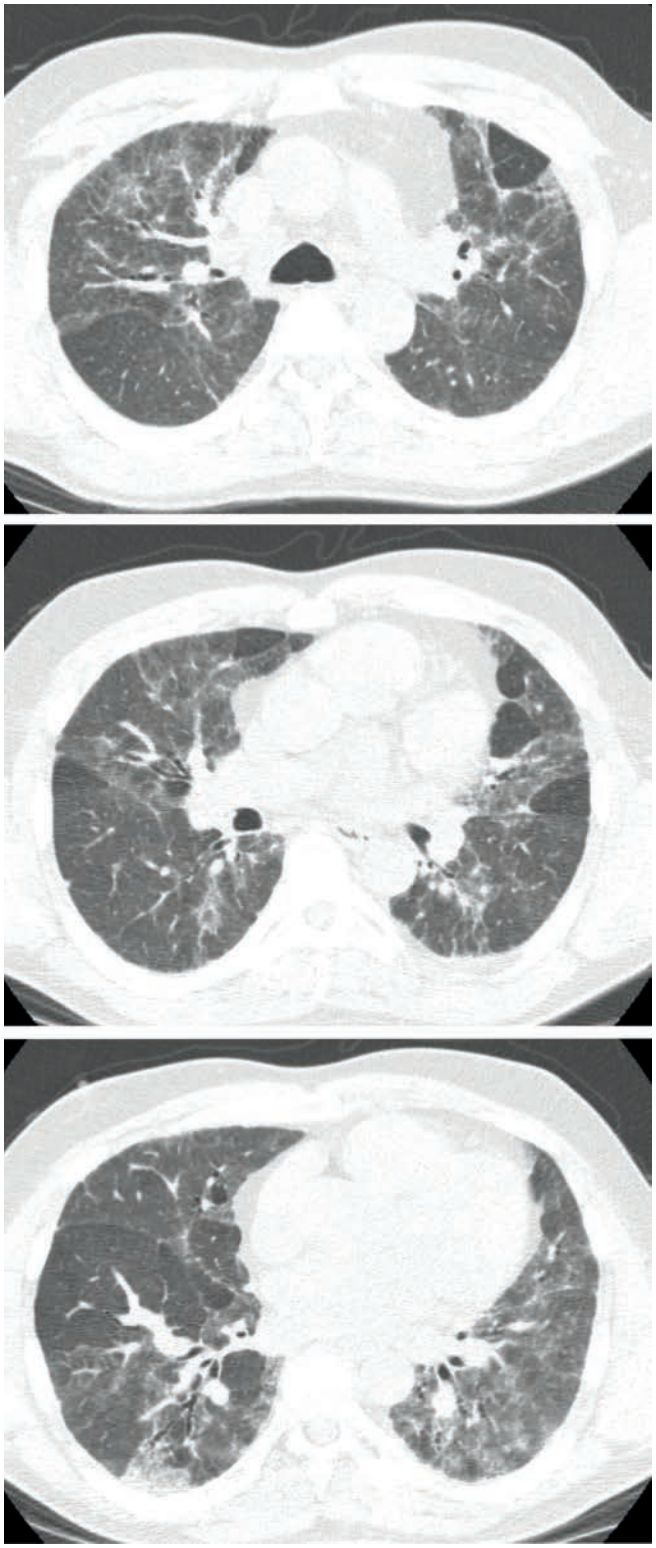

Figure 56-4 "Three-density pattern" on high-resolution CT scan strongly suggestive of fibrotic HP, in a patient (whose avocation was woodworking) with progressive dyspnea, hypoxemia, and restriction, despite empiric avoidance of wood/wood dust, and treatment with corticosteroids and mycophenolate. In each of these inspiratory images there is evidence of ground glass opacification, mosaic attenuation with zones of diminished attenuation/hypoperfusion, and areas of normal-appearing parenchyma. There is also evidence of modest reticular/fibrotic abnormalities and traction bronchiectasis.

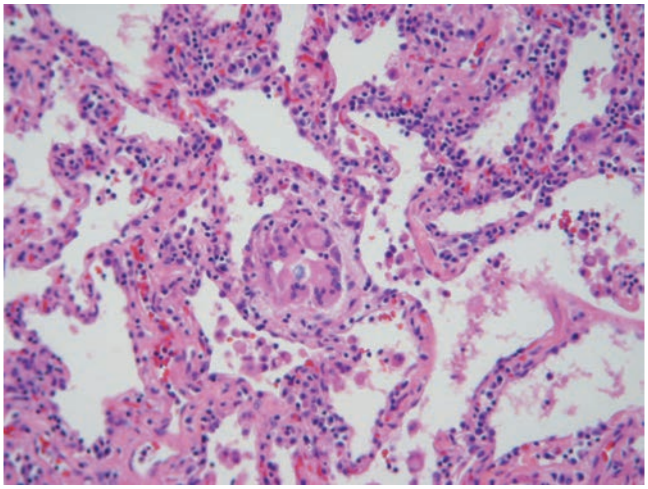

Figure 56-5 Low-power view (20×) of H&E-stained section of surgical lung biopsy from a patient with bird fancier's disease. There is nonspecific interstitial mononuclear inflammation and loosely formed granulomatous lesions.

Pulmonary function tests may be restrictive, obstructive, or mixed. There is increased lung elastic recoil, and usually decreased $\mathrm{DL_{CO}}$. Arterial hypoxemia with hypocapnia, reflecting an increased A–a oxygen gradient, either at rest or after exercise is common. However, 39 of 177 patients (22%) with $\mathrm{DL_{CO}}$ data available to the HP Study Group[14] displayed normal diffusion, defined as a $\mathrm{DL_{CO}} \geq 80\%$ predicted at the time of diagnosis. Many patients with HP (20% to 40%) also exhibit increased nonspecific airway reactivity, and 5% to 10% may develop clinical asthma.[28]

HISTOPATHOLOGY

A lung biopsy specimen may be required when there is significant doubt about the diagnosis, or when the risk of treatment based upon a provisional diagnosis outweighs the risk of the biopsy. Transbronchial lung biopsies usually do not provide sufficient material to fully establish the presence and interrelationships of granulomas, bronchiolitis, and interstitial inflammation, so surgical lung biopsies may be necessary. These often reveal chronic interstitial and alveolar inflammation with infiltration of plasma cells, mast cells, macrophages, and lymphocytes, usually with poorly formed nonnecrotizing granulomas (Figs. 56-5 and 56-6).

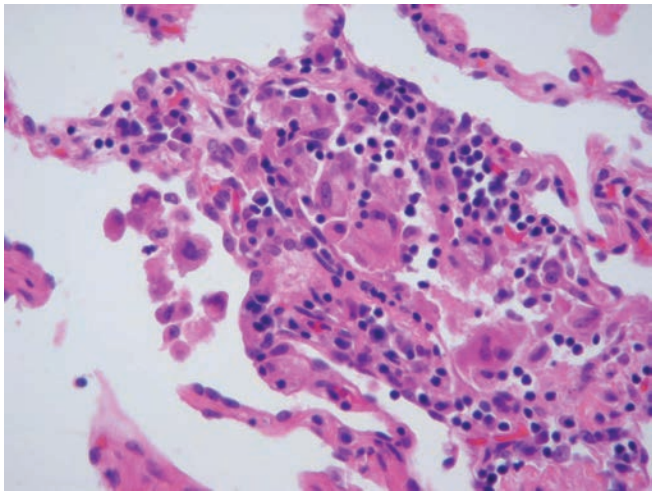

Figure 56-6 Higher-power view (40×) of the section shown in Fig. 56-5.

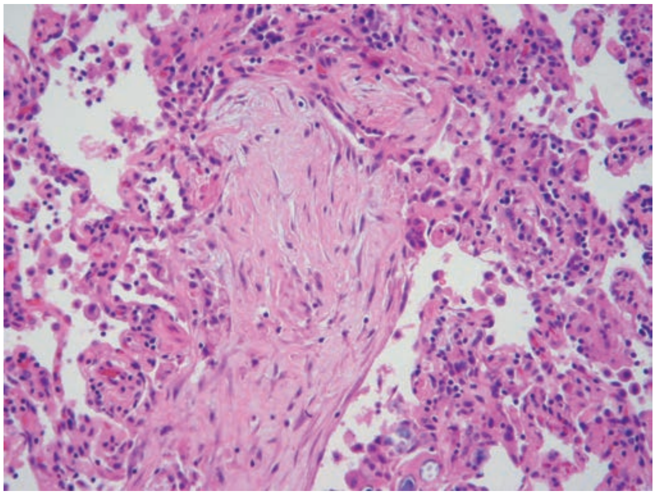

Figure 56-7 Organizing pneumonia in a patient in a patient with bird fancier's disease.

The inflammation usually extends from the terminal bronchioles into the parenchyma. Foamy macrophages are usually evident in the alveoli. There is often bronchiolitis, as well as occasional bronchiolitis obliterans. Organizing pneumonia may be present in up to half of patients with HP (Fig. 56-7). Conversely, patients with recognized cryptogenic organizing pneumonia (COP) may have underlying HP, whether or not other histologic manifestations are evident. Varying degrees of interstitial fibrosis also are often present. The granulomatous interstitial inflammatory responses of HP and sarcoidosis can be difficult to differentiate, but in HP granulomas are usually smaller, poorly differentiated, and loosely arranged and contain more lymphocytes and fewer multinucleated giant cells. The granulomas of HP also tend to occur adjacent to bronchioles, and not in subpleural regions. In the absence of granulomas, the pattern may resemble that of nonspecific interstitial pneumonitis, although the bronchiolocentric nature of the lesions and the presence of giant cells, organizing pneumonia, or bronchiolar metaplasia may be clues suggesting underlying HP.

The histopathologic findings that provide high confidence in the diagnosis of "typical" nonfibrotic (cellular) HP are bronchiolocentric cellular (lymphocytic) interstitial pneumonia, cellular bronchiolitis (particularly with organizing pneumonia and foamy alveolar macrophages), and poorly formed nonnecrotizing granulomas (particularly in peribronchial interstitial regions). Furthermore, there should be no evidence of signs of an alternative diagnosis, such as extensive lymphoid hyperplasia or well-formed and/or necrotizing granulomas. A diagnosis of "probable" nonfibrotic HP can be based upon the same features of "typical" nonfibrotic HP described previously, in the absence of nonnecrotizing granulomas. Histologic evidence of cellular NSIP, organizing pneumonia, or peribronchiolar metaplasia is "indeterminate" for nonfibrotic HP.[19]

Histopathologic findings for a high-confidence diagnosis of "typical" fibrotic HP include chronic fibrosing interstitial pneumonia with a fibrosing NSIP pattern, airway-centered fibrosis, and peribronchiolar metaplasia, with evidence of poorly formed nonnecrotizing granulomas, with or without cellular bronchiolitis or organizing pneumonia (and no evidence of an alternative diagnosis; Fig. 56-8). A diagnosis of "probable" fibrotic HP may be made with similar findings, in the absence of poorly formed granulomas. A biopsy that is "indeterminate" for HP may have chronic fibrosing interstitial pneumonia or a fibrotic NSIP pattern, with or without organizing pneumonia or cellular bronchiolitis.[19]

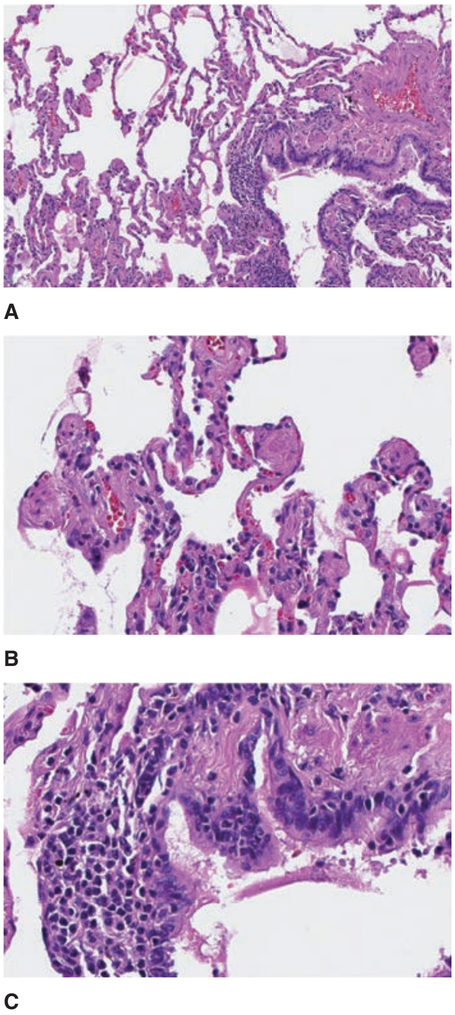

Figure 56-8 Histopathologic evidence of fibrotic HP, exemplified by a patchy, predominantly airway-centered inflammatory and fibrosing process. **A.** Low-power view of mild cellular bronchiolitis and peribronchial interstitial inflammation, with focal lymphoid aggregates and fibrosis. **B.** Higher-power view of interstitial pneumonitis with fibrosis and occasional fibroblastic foci. **C.** Peribronchial metaplasia, focal lymphoid aggregates, and fibrosis.

IMMUNOPATHOGENESIS

An important feature of HP is the great variability of susceptibility among exposed populations and the apparent resistance to illness of most exposed persons. Possible reasons include differences in the nature of the exposure, or differences in the host response to exposure, which may be inborn and/or acquired. There have been numerous reported correlations between HP and specific HLA class I and class II haplotypes.[29–32] Similar correlations have been reported between polymorphisms in the coding region of tumor necrosis factor alpha (TNF-α)[31] as well as its promoter.[33] Similarly, polymorphisms in the promoter of TIMP-3,[34,35] responsible for regulation of TNF-α processing, appear to correlate with HP disease susceptibility. Notably, a MUC5B promoter variant, described as an important risk factor for IPF, also has been associated with an increased risk of fibrotic HP.[36,37] Interestingly, a variety of polymorphisms in the telomerase complex, initially linked to familial forms of IPF, also are associated with increasing susceptibility to fibrotic HP.[37,38] These findings may suggest a genetic predisposition to progressive fibrosis, irrespective of the underlying disease, and the frequency of family history of IPF in patients with fibrotic HP suggests possible host susceptibility to progressive fibrosing manifestations of multiple types of insult to the lung.[39]

HP is seen worldwide, and the most commonly implicated antigens are thermophilic actinomycete species, fungi, and bird proteins. Thermophilic actinomycetes (e.g., *Saccharopolyspora rectivirgula*) and a variety of fungi (e.g., *Aspergillus* species and *Penicillium* species) are implicated in HP in a variety of occupations, such as farming, but may also be responsible for the disease acquired in home and work environments. A complex mixture of high- and low-molecular-weight proteins from avian serum, feces, and feathers produce the "bird fancier's lung," and it is the complexity of such antigenic mixtures that may underlie the unique immunopathologic manifestations dominated by T cell–mediated effector activites.[36,40,41] It is reasonable to assume that the normal immune responses to infectious diseases are subverted in a disease state such as HP—and thus the panoply of host responses, including innate and adaptive mechanisms, are likely activated simultaneously by inciting exposures.

There is ample evidence that the complex mixtures of antigens contain ligands for innate Toll-like receptors (TLRs), which are a family of cellular receptors that respond to pathogen-associated molecular patterns (PAMPs) common to a multitude of infectious microorganisms. This results in rapid inflammatory activation necessary for initiating a robust immune response.[42] The role of TLRs in the generation of HP is incompletely defined, but it is known, for example, that fungal cell wall components (such as beta-glucans) activate TLR2 and may be aerosolized from moldy materials, such as in mold-damaged buildings.[43] Similarly, TLR9 may be of particular importance, as it may be triggered by fungal DNA,[44] and like all the TLRs, it activates interferon α/β (IFN-α/β) responses critical in dendritic cell antigen uptake, migration to regional lymph nodes, and sensitization of CD8$^+$ T cells through cross-presentation of phagosomal antigens via class I MHC. IFN-α/β–induced cross-presentation of particulate antigens by alveolar and bronchiolar epithelial cells may also make them targets of CD8$^+$ T cell recognition.[45]

By the time the disease is clinically evident, lung tissue gene expression profiles indicate ongoing T cell–driven inflammation (in contrast to the profiles of IPF and NSIP[46]). The T cell responses evident in HP are notable for the predominance of CD8$^+$ cells and the expression of IFN-γ, the prototypic cytokine of type 1 (Th1/Tc1) inflammatory processes. Expression of IFN-γ–dependent chemokines, such as CXCL9 and CXCL10, is also observed in HP lungs, which likely serves to amplify the type 1 (Th1/Tc1) inflammation. Not unexpectedly, CD8$^+$ T cells in BAL of HP patients strongly express CXCR3, the receptor for both of these chemokines.[40] CD8$^+$ T cells isolated from patients with presumptive nonfibrotic/acute HP demonstrate oligoclonality, the characteristic result of (competitive) antigen-driven proliferation.[41] Secondary recruitment of inflammatory macrophages, and the cytokines produced by them, likely augment the inflammatory milieu.[47] TNF-α, produced by activated macrophages (as well as by CD8$^+$ T cells), likely participates both in the amplification of the inflammation and the activation/degranulation of neutrophils that may be recruited to the alveolar space.[47,48]

There is a curious predominance of nonsmokers in patients with nonfibrotic HP,[49] possibly due to the anti-inflammatory effects of nicotine.[50] Activation of nicotinic acetylcholine receptor alpha-7 has been shown to suppress not only proinflammatory cytokine production by innate immune cells such as macrophages but also reactivity of CD4$^+$ T helper cells.[50–52] However, consistent with observations in other fibrosing ILDs, long-term smoking is associated with increasing fibrosis.[53,54]

PROGNOSIS AND TREATMENT

Prognosis varies considerably with the type of HP and even the geographic location. For example, farmer's lung disease has a good prognosis in Quebec, even in farmers who continue to farm. However, farmer's lung disease in Finland often results in significant physiologic impairment and even death. Pigeon breeder's disease has a good prognosis in the United States and Europe, whereas the same disease in Mexico has a 30% 5-year mortality.[55] The reasons for these differences are not clear but may include differences in the nature of the antigen and the exposure.

Identification of the offending antigen is critical to effective avoidance, which is the primary intervention in all forms of HP. This is often not possible nor practical when the exposure is occupational, such as in farmer's lung disease. In addition, most farmers who continue to be exposed may fare no worse than those who leave their farms.[56] Nevertheless, removal from exposure to the offending antigen(s) is often sufficient to resolve symptoms and physiologic abnormalities in nonfibrotic HP. Measures to reduce antigenic burden may include protective equipment and reducing microbial contamination of the home or work environment. Elimination of excess moisture, reduction in humidity, repair of water-damaged materials, and regular cleaning of humidifiers, ventilation, and air conditioning equipment all contribute to reduction in mold and other microbial colonization that may predispose to sensitization. Removal of birds from the home of patients with bird-fancier's disease is a critical aspect of treatment, but antigens may persist for extended periods despite thorough cleaning of the home environment.[57]

Systemic glucocorticosteroids are usually required to treat severely symptomatic patients, although there is no formal evidence that such treatment is associated with long-term abatement of symptoms or radiologic or pulmonary function test abnormalities.[27,58] The usual treatment is with corticosteroids, such as prednisolone 40 to 60 mg per day for several weeks, followed by a gradually tapering dose over 1 to 2 months. Patients with farmer's lung disease treated with prednisolone, compared with those not treated, demonstrated slightly more rapid resolution of some radiologic abnormalities (GGO) and physiologic impairment (slight improvement of $D\textsc{l}_{CO}$, no difference in lung volumes or arterial $P\textsc{o}_2$). However, there were no differences between the groups 6 months after the diagnosis of HP. The management of chronic fibrotic HP is more challenging, as longer-term therapy may be necessary and steroid toxicity is limiting. Steroid-sparing agents (mycophenolate mofetil or azathioprine), which may be administered for more extended time periods with considerably less toxicity, have shown promise in several retrospective studies with improvements in $D\textsc{l}_{CO}$, although their utility has not been examined prospectively.[59] Antifibrotic agents have proved effective in slowing functional decline and disease progression in IPF, and a recent trial showed similar benefit for the use of nintedanib in progressive, non-IPF fibrosing ILD, including chronic fibrotic HP.[60,61] Finally, lung transplantation is an option for some patients with end-stage fibrotic HP; survival at 1, 3, and 5 years is better than after transplant for IPF.[62] Of note, in one study, 2 of 31 transplanted HP patients had recurrence of their disease despite immunosuppression, both of whom had moved back into their prior residence.[16]

Among patients with chronic/fibrotic HP, the inability to identify an inciting agent was independently associated with shortened survival.[63] Even when an inciting agent is identified, many patients with chronic HP present with advanced fibrosis and physiologic abnormalities that are only partly reversible after cessation of exposure. At the same time, progression of disease has been observed even after complete exposure avoidance,[64] suggesting the possibility of self-perpetuation in some cases. The specific nature of the radiographic and histopathologic findings in these patients at the time of diagnosis, particularly the extent of the fibrosis, may help predict subsequent clinical course of the disease.[65,66] In addition, patients with advanced fibrotic HP may be prone to acute exacerbations, not unlike those observed in IPF patients.[67,68]

In conclusion, HP is an immunologically mediated lung disease likely mediated primarily by T cell responses to inhaled antigens. The diagnosis requires careful history, appropriate laboratory tests, and lung biopsy in selected cases. In nonfibrotic HP, avoidance of exposure is usually associated with a good prognosis; corticosteroids are indicated in severely symptomatic patients. Steroid-sparing agents as well as antifibrotic drugs may be indicated in chronic fibrotic HP. Because of constantly changing environmental exposures, new examples of HP are continually being described, representing an ongoing challenge in patients presenting with undefined chronic interstitial lung disease.

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CHAPTER 57

Radiation Pneumonitis

James H. Laird
Kenneth B. Roberts
Roy H. Decker
Henry S. Park

INTRODUCTION

The discovery of x-rays by Roentgen in 1895 and of radium by the Curies in 1898 revolutionized medicine at the turn of the 20th century.[1–3] Roentgen's first paper on x-rays illustrated the power of diagnostic imaging with a remarkably detailed radiographic image of Frau Roentgen's hand. As researchers around the world built vacuum tubes and acquired radioactive sources for their studies, it rapidly became apparent that these invisible radiations could produce dangerous, and even lethal, injuries.[1–3] Erythema, chronic dermatitis, ulceration, loss of hair, and eye injuries were soon reported in patients who received large doses of radiation during prolonged fluoroscopy procedures, and further toxicities were observed in physicians, technicians, and scientists exposed to unshielded radiation sources. The development of these radiation injuries suggested that radiation might be useful in the treatment of cancer; indeed, patients with cancer were treated with radiation therapy as early as 1896.[1–3] Radiation was found to inhibit the growth of tumors, but this benefit came with the cost of injury to normal tissues within the irradiated areas. The relative sensitivity of the lung to injury from radiation became apparent early in the development of radiation oncology. The clinical syndromes of dyspnea, cough, fever, and radiographic infiltrates occurring weeks to months after irradiation of the thorax were dramatic enough to be described as early as 1922.[4]

For clinicians interested in pulmonary medicine, understanding radiation pneumonitis is important. Because the chemical mediators of radiation effects, both beneficial and harmful, are free radicals, understanding the pathway leading to radiation injury in the lung can be useful in elucidating mechanisms of other lung injuries.[5,6] In addition, understanding radiation pneumonitis has practical value to physicians in many areas of medicine. Nearly 40% of men and women in the United States will be diagnosed with cancer at some point in their lifetimes, and the majority of these patients will be permanently cured of their malignancies.[7] Approximately 60% of all patients with cancer receive radiotherapy at some point in the treatment of their malignancies, and radiotherapy will remain an important component of cancer treatment for the foreseeable future. Because of this, every physician can expect to care for many patients who are receiving radiotherapy or have received radiotherapy at some point in the past.

In addition to an association with acute or subacute pulmonary disease, radiation can lead to chronic toxicities. For instance, respiratory diseases are known to be a cause of increased late morbidity and mortality in the survivors of the atomic bombs in Hiroshima and Nagasaki.[8] Additionally, studies of plutonium workers have shown an excess incidence of pulmonary fibrosis, demonstrating lung injury may be produced by inhalation of insoluble particulate radionuclides that are deposited in lung tissue and produce long-term irradiation of the tissue.[9] Radiation injury to lung can occur not only through radiotherapy but also through exposure from occupations, accidents, or acts of war or terrorism.[6] An understanding of the potential toxicities of radiotherapy and other exposures to radiation, including radiation pneumonitis, can be critical to patient care.

Many neoplasms involving the thorax are treated with regimens that include the use of radiotherapy to produce either cure or palliation. Radiotherapy is principally a localized, anatomically based modality. The success of radiotherapy hinges on delivering radiation selectively to the sites of malignant disease while sparing, to the maximal extent possible, the uninvolved normal tissues.[1,10] To plan radiotherapy treatments effectively, the radiation oncologist must have a sophisticated appreciation of the malignancy being treated and understand its biologic behavior, patterns of local and metastatic spread, radiosensitivity, and factors that influence the responses of individual patients to therapy. The radiation oncologist must also consider the effects of radiation on normal tissues within the treatment volumes.

Multiple factors, including radiation dose, fractionation pattern, volume of the tumor and involved margins, prior or planned use of other therapies such as surgery or systemic chemotherapy, and presence of other diseases influence the probability of both controlling the neoplasm and producing toxic reactions. For cancers of the lung, esophagus, pleura, mediastinum, breast, and chest wall, as well as for lymphomas involving the thorax, optimal treatment frequently involves use of multiple overlapping x-ray beams (or possibly proton or electron beams) planned to encompass the tissue at risk of containing cancer. Although treatments are carefully planned to minimize exposure to healthy normal tissue, some normal tissue will necessarily be included in the radiation fields. The radiation sensitivity of the specific tissues in the irradiated fields and the acceptable level of risk for complications combine to limit the dose of radiation that can be administered. The planning of radiotherapy always involves a balance of benefit and risk; the probability of controlling the malignancy increases with increasing radiation dose, but so does the probability and severity of the potential complications.

To illustrate the mechanisms involved in planning radiotherapy treatments, a treatment plan is depicted in Fig. 57-1A. The two images displayed represent axial slices of the dose distribution for treatment of a patient with stage IIA non–small-cell lung cancer who was not a surgical candidate. Treatment was to 60 Gy in 30 fractions, and a color-wash display in which the highest radiation dose is shown in red and lower doses in shades of blue is shown for doses above 20 Gy. This represents the sum of multiple rotating arcs of radiation using intensity-modulated radiation therapy (IMRT), in which computer-based planning is used to deliver a high dose to the tumor target with specific dose limits to normal tissue structures.

In Fig. 57-1B, CT scans obtained 6 weeks post-radiotherapy demonstrate radiation-induced inflammatory changes. The changes roughly correspond to the high dose region of radiotherapy, though not precisely; the approximate correlation with the high-dose radiotherapy region is typical for IMRT plans. In this case, the patient also reported mild exertional shortness of breath and nonproductive cough, not significantly limiting her functionality. The radiation dose delivered to the lung tissue is shown in a cumulative dose–volume histogram, in Fig. 57-1C, which integrates the percentage of the volume of the organ at risk (on the vertical axis) receiving the specified cumulative radiation dose (on the horizontal axis). While this is a simplified representation of a complex dose–volume relationship, this concept has become important in analyzing radiation dose delivery and correlating dosimetry with treatment outcome. In the illustration, the volume of lung receiving greater than or equal to 20 Gy (V_{20}) is 27%, which corresponds with an under 20% risk of symptomatic radiation pneumonitis.

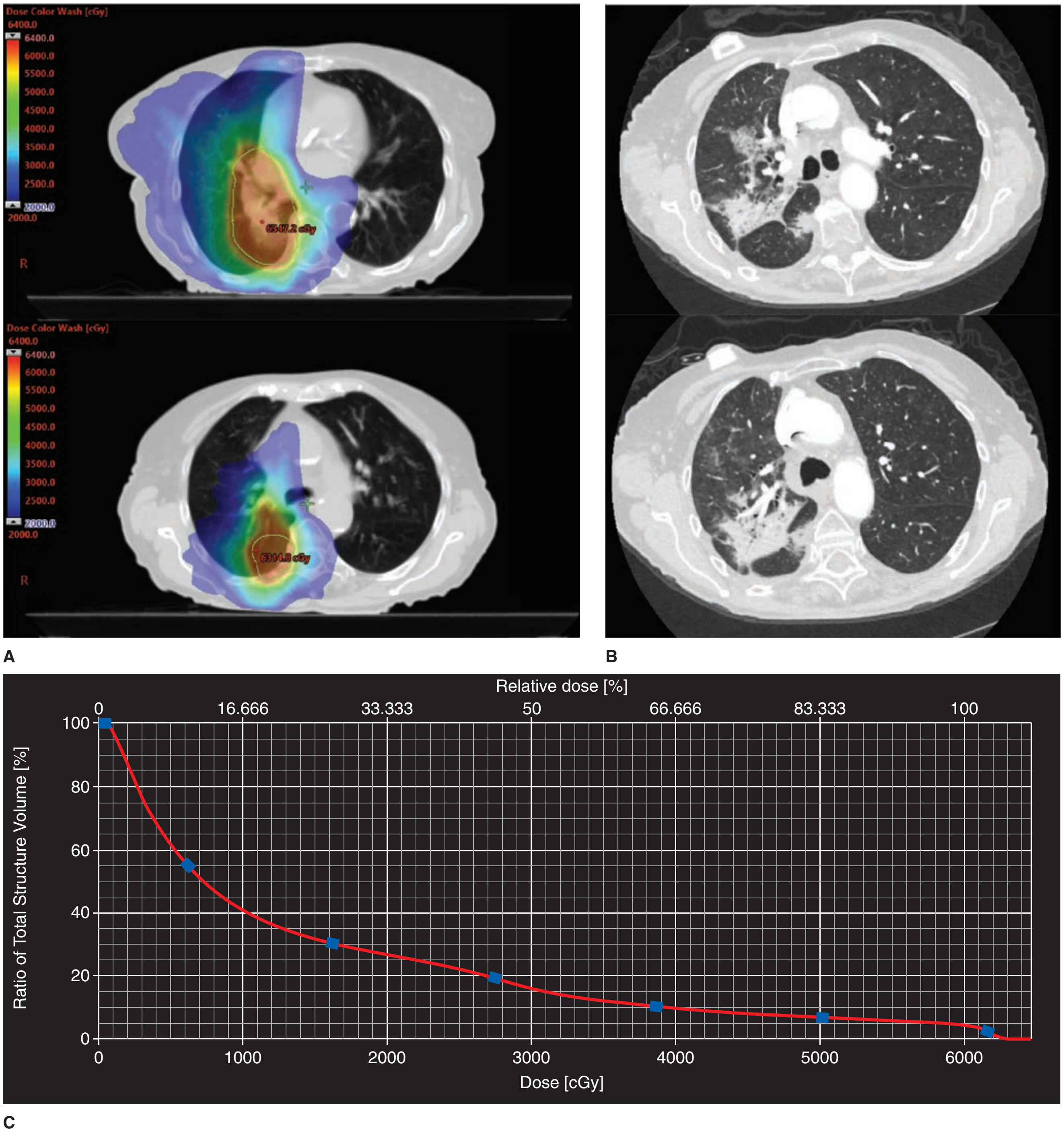
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Figure 57-1 An 89-year-old woman with stage IIA non–small-cell lung cancer was treated with radiotherapy and concurrent carboplatin and paclitaxel. **A.** Two representative axial slices of the dose distribution from a volumetric arc therapy (VMAT) plan are overlaid on a treatment-planning CT scan. Using a color-wash format, radiation dose is demonstrated from 20 Gy *(green)* to 64 Gy *(red)*. The volume intended to be treated with full dose radiotherapy (planning treatment volume) is outlined in green. **B.** Six weeks after completion of treatment, the patient developed a mild dyspnea and nonproductive cough. On CT chest, she was found to have a new multifocal consolidation near the area of treatment and within the lower-dose region (20 Gy) of radiation therapy. **C.** Cumulative dose–volume histogram of the entire treatment course for bilateral lung tissue. The volume of normal lung receiving 20 Gy or more (V_{20}) is 27%.

Radiation changes also frequently are present after high-dose focal radiation treatments such as stereotactic body radiation therapy (SBRT). Figure 57-2A displays in color-wash a radiation treatment plan for a patient with metastatic colorectal cancer and isolated progression in a left upper lobe lung metastasis. She was treated to a prescribed dose of 54 Gy in 3 fractions. Figure 57-2B demonstrates radiation changes in the left lung 6 months after treatment, which similarly correlate with the areas receiving a higher dose of radiotherapy.

In the cases presented, if the malignancy is cured, or the patient experiences the desired improvement in symptoms with tolerable toxicity from the radiotherapy, the treatment would be considered a success even if accompanied by radiographic changes or by other subclinical damage to the lung or other organs. Symptomatic

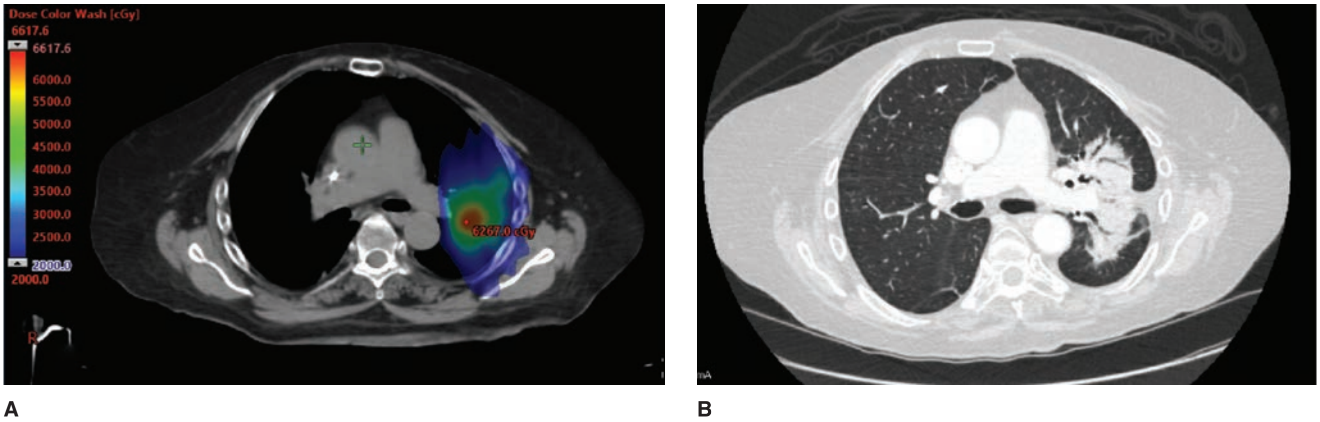

Figure 57-2 A 76-year-old woman with stage IV colon adenocarcinoma initially diagnosed 10 years earlier presented with a progressive left upper lobe lung metastasis, which was her only active site of disease after prior chemotherapy. She underwent SBRT to 54 Gy in 3 fractions. **A.** A dose color-wash overlay of her treatment plan is shown, with doses from 20 Gy to a maximum of 66 Gy. **B.** Six months after completing radiotherapy, she was noted to have a consolidation in the area of prior treatment with adjacent pleural thickening but no new respiratory symptoms, consistent with grade 1 pneumonitis.

pulmonary toxicity is, however, a potential consequence of thoracic radiotherapy that sometimes overshadows the benefits of treatment.

BRIEF OVERVIEW OF RADIOLOGIC PHYSICS

External beam radiotherapy is most commonly delivered using x-rays or gamma rays. Both of these radiations are high-energy electromagnetic waves or photons that are able to cause ionizations when interacting with matter.[11] The only difference between them lies in the manner in which they are produced: gamma-ray photons are emitted from atomic nuclei during the decay of radioactive atoms, and x-rays are produced when high-energy electrons strike a target material and interact with the electron shells of atoms in that target, causing them to emit x-ray photons (the *bremsstrahlung effect*). After its emission, an individual x-ray photon is indistinguishable from a gamma-ray photon. Thus, although the discussion below uses x-rays as examples, the principles are equally applicable to radiotherapy using high-energy gamma rays (e.g., from cobalt-60 teletherapy units or brachytherapy using implanted radioactive sources).

The x-rays used for diagnostic imaging are in a relatively low-energy range, in which the dominant interaction of photons with matter is through the "*photoelectric effect*." In this process, absorption of a photon causes an electron to be ejected from the inner shell of an atom. The probability of photoelectric interactions increases as a function of the cube of the atomic number, that is, as Z3. Consequently, large, heavy atoms absorb low-energy diagnostic x-rays much more efficiently than smaller, lighter atoms.

Diagnostic radiology capitalizes on the large differences between the absorption of low-energy x-rays in materials with different compositions, for example, air, soft tissue (which is 70% water and, therefore, composed primarily of the small atoms hydrogen and oxygen), bone (with its high calcium content), and administered contrast agents containing barium, iodine, or other heavy atoms. The differences in absorption are used to image anatomic structures. In contrast, high-energy x-rays used in radiotherapy interact with matter primarily by a phenomenon called the "*Compton effect*," in which x-rays cause ionization of atoms via interactions with their outer electron shells. The Compton effect is not dependent on the atomic number, but is, instead, a function of the electron density. Because the electron densities of most biologic tissues are relatively uniform, for the purposes of most radiotherapy dosimetry, it is reasonable to assume that a patient is of uniform density, equivalent to water.

An important caveat to radiation dosimetry involves the standard specification of doses in tissues that include a large proportion of air, such as the lung. As a single x-ray beam penetrates through water or tissue, the dose received by the tissue falls progressively, generally as an exponential function of distance. Because of its markedly lower density, air absorbs less radiation energy and, therefore, attenuates the x-rays less than does tissue or water. With the quantitative knowledge of lung density derived from CT scanning, algorithms that estimate the inhomogeneity in the absorbed dose resulting from differences in the density of lung and other soft tissues are now regularly used.[11,12] These heterogeneity corrections show that routine dosimetric calculations, which assume uniform density, underestimate the radiation doses to lung and tissues beyond the lung by 5% to 25%.

Although the effect of tissue heterogeneity is now regularly accounted for when quantifying the radiation dose delivered to the lungs, one must remember that doses delivered to the thorax and the lungs historically have been reported in the medical literature *without* heterogeneity corrections. Moreover, because the preponderance of clinical data concerning lung tolerance have been determined and reported using older dosimetric algorithms, which assume that lung has water-equivalent density, the impetus to change dose reporting is tempered by the desire to avoid confusion between the newer and older literature. The reader should assume, unless explicitly stated otherwise, that the historic radiation doses given in this chapter, or for that matter any publication, are not necessarily corrected for lung density. Without such corrections, actual dose delivery to the chest region is modestly higher than the nominal doses reported, but with potentially wide variability prior to computerized treatment planning.

Charged particle therapies, including proton therapy, exploit the unique physical characteristics of charged particles to allow for more precise dose deposition and are rapidly increasing in utilization throughout the world. Protons primarily interact through the Coulomb force with electrons in an organic target material, leading to electron excitation and ionization. These ionized electrons, which have relatively low kinetic energy, then deposit energy close to the site of the original particle interaction. The proton slows as it deposits its energy, increasing the amount of time for electron interaction, which further slows the proton until it stops. This results in most of the dose being deposited near the end of the proton's path, leading to the characteristic depth–dose distribution known as the "Bragg peak." In order to deliver dose to the entire depth of a target, beams with different depths (different beam energies) are summated to create a "spread-out Bragg peak," which also results in a higher entrance dose. The abrupt deposition of radiation dose allows for sparing of normal tissue beyond the target, such as heart or uninvolved lung. However, there are additional dosimetric challenges brought by the stopping power of protons, as accurate depth calculation requires precise knowledge of tissues and may be impacted by daily variation in anatomy.

Radiation dose is currently reported using the unit of the Système International (SI), the gray (Gy). The Gy is a measure of the energy absorbed by 1 kg of tissue; 1 Gy = 1 J/kg. The former unit of absorbed dose, called the "rad" (an acronym for "radiation absorbed dose") was measured with the CGS system: by definition, 1 rad = 100 ergs per gram. To compare old and recent literature, one must remember that 1 Gy = 100 rad. Even though the rad is not an approved SI unit, some radiotherapy literature avoids this conversion by giving the dose in centiGray (cGy), where 1 cGy = 0.01 Gy = 1 rad. Other measures of radiation dose seen in the literature include the roentgen, the Sievert, and the rem.

The roentgen measures radiation *exposure,* rather than energy *absorption,* and refers specifically to the amount of ionization produced in air under standard conditions (1 R = 1 electrostatic unit/cc = 2.58×10^{-4} coulombs/kg of "standard air" at a density of 1.29×10^{-4} g/cm^3 at 0°C and 760 torr). This unit is frequently encountered in the radiation dosimetry literature, not only because it was historically used as a measure of dose, but also because many widely used radiation monitors (e.g., ionization chambers) directly measure radiation exposure at the surface of the body. The dose absorbed by tissue is then calculated from this exposure.

The radiation protection literature uses the unit of "equivalent dose," the Sievert (Sv), which is calculated as the absorbed dose (in Gy) multiplied by a "weighting factor" that considers the differing biologic effects of different radiations. Although the weighting factors for some radiations, such as neutrons and alpha particles, can be as high as 20, the weighting factors for x-rays, gamma rays, and electrons are all defined as 1. For most purposes in diagnostic and therapeutic radiology, therefore, 1 Sv = 1 Gy. The Sv replaces the older unit of equivalent dose, the rem (1 Sv = 100 rem). Unfortunately, the literature on radiation-induced lung injury includes papers using all these different units, creating great confusion for readers. For simplicity, all doses in this chapter have been converted to Gy.

RADIOBIOLOGY OF RADIOTHERAPY

When x-rays pass through tissue, a complex series of physical and chemical reactions occurs.[1,13] As the x-rays interact with atoms along their path, energy is absorbed, and energetic fast electrons are ejected. These fast electrons travel through tissue, producing secondary ionizations, which lead within milliseconds to the generation of a variety of highly reactive free radical species. Because biologic materials are about 70% water, ions and free radicals derived from water (e.g., H, OH, H_2O^+, H_3O^+) are the main reactive species produced. These ions and radicals react with each other and with other nearby molecules, creating a wide variety of chemically reactive species and producing many kinds of damage in biologic macromolecules. Because DNA contains information that is critical to the cell, while most other molecules can be replaced readily, damage to DNA is the most important biologic effect of irradiation. Radiation produces a wide variety of lesions in DNA, including single- and double-strand breaks, damaged bases, and loss of bases, as well as chromosomal breaks and rearrangements. If these lesions are not repaired, the result can be permanent mutations or changes in chromosomal structure that lead to the death of the cell or changes in its behavior.

The cytotoxic effects of radiation are the basis for both the antineoplastic effects and the toxicities of radiotherapy. A theoretical concern is that radiotherapy may produce a mutation in a previously normal cell that leads to the development of a new malignancy. Although radiation-induced malignancies do occur and are a primary concern in considerations of environmental and occupational exposures,[8] malignant transformation is a rare enough event at the doses used in radiotherapy that the risk of inducing a second cancer in an individual patient is typically very small relative to the great benefit of curing the existing malignancy.[10] The greater risk to the patient lies in the fact that radiation is not selectively toxic to the tumor cells, but instead, damages both normal and malignant cells within the treatment field.

Although the radiochemical reactions that lead to cytotoxic damage are complete within milliseconds after the end of irradiation, cells dying from radiation injury do not die immediately. In fact, soon after irradiation, radiation-sterilized cells are indistinguishable from cells that ultimately survive irradiation in their appearance, metabolic activities, and even rates and patterns of proliferation. Most radiation-sterilized cells ultimately die during mitosis, but they may first undergo one or even several divisions, producing an abortive clone of sterile cells, which may later undergo postmitotic cell death. This delayed cytotoxicity underlies many of the effects seen in radiotherapy. Rapidly growing tumors, for example, generally begin shrinking sooner than slowly growing tumors, and many tumors continue to shrink progressively for months after radiotherapy. Analogously, radiation reactions in normal tissues reflect the normal patterns of cell turnover in the tissue.[14,15]

After irradiation, nonproliferating, terminally differentiated cells continue to perform their differentiated functions throughout their normal life spans. Other cells that are not proliferating at the time of irradiation likewise continue to function normally until they are recruited into proliferation, perhaps months or even years after irradiation; when they begin to proliferate, their progeny die. Some cell types, especially hematopoietic cells, may be induced by radiation-induced damage to enter a pathway of programmed cell death that leads to apoptosis. Other mechanisms of cell death that may be activated after radiation include necroptosis and pyroptosis; alternatively, cells may enter a state of senescence, which is characterized by the inability to replicate while remaining metabolically active.[16,17]

A typical survival curve for mammalian cells, obtained using mouse lung cells, is shown in Fig. 57-3. As a first approximation, cell survival falls exponentially as the radiation dose increases. Statistically, this implies that each incremental dose of radiation has the same cytotoxic effect; that is, each incremental dose kills the same proportion of the viable cells that were present in the population at the beginning of that irradiation. Very low doses of radiation have somewhat lesser effects; the shoulder on the cell survival curve reflects the ability of the cells to accumulate and tolerate or repair some of the damage produced by radiation.

The effect of the repair of radiation damage can be seen when the radiation dose is divided into two or more treatments separated by hours or days, rather than being delivered in a large single dose. Dividing, or "fractionating," the radiation dose allows cells to repair damage to their DNA and to proliferate between treatments.[1,10] As a result, there is less cytotoxicity from a fractionated treatment regimen than from the same total radiation dose delivered as a large single fraction (Fig. 57-4). Smaller fractions produce less cytotoxicity than larger fractions. Similarly, the cytotoxic effects of radiation are diminished when the radiation is delivered continuously at a low-dose rate, over hours or days, allowing repair and proliferation to occur during irradiation (Fig. 57-4).

Fractionating therapeutic irradiations or delivering the radiation at low-dose rates generally appears to increase the therapeutic ratio by protecting normal tissues against radiation injury, while producing a smaller increase in the relative radioresistance of the tumor; treatment outcomes are thereby improved. This increase in the therapeutic ratio is thought to reflect qualitative and quantitative

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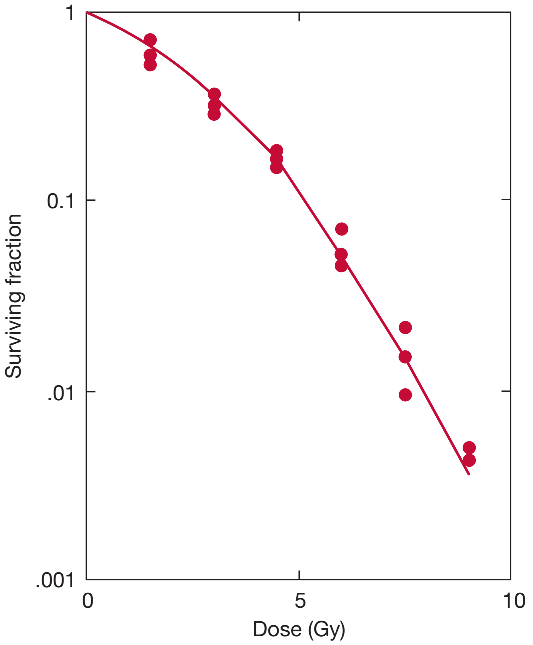


Figure 57-3 Survival of lung cells treated with different doses of radiation. Cells were explanted from mouse lungs, irradiated in vitro, and assayed for viability using a colony formation assay. *(Reproduced with permission from Guichard M, Deschavanne PJ, Malaise EP. Radiosensitivity of mouse lung cells measured using an in vitro colony method. Int J Radiat Oncol Biol Phys. 1980;6(4):441–447.)*

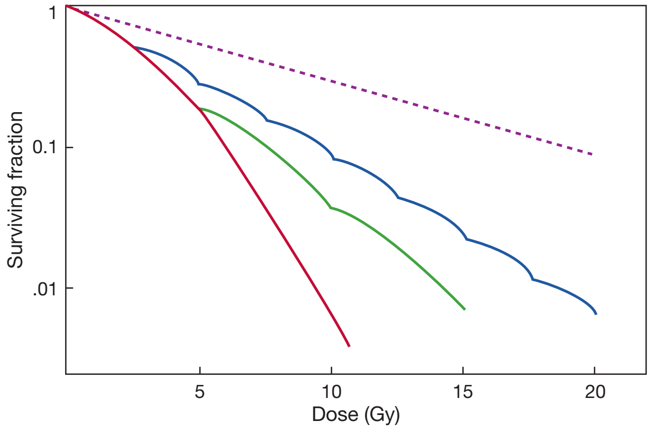
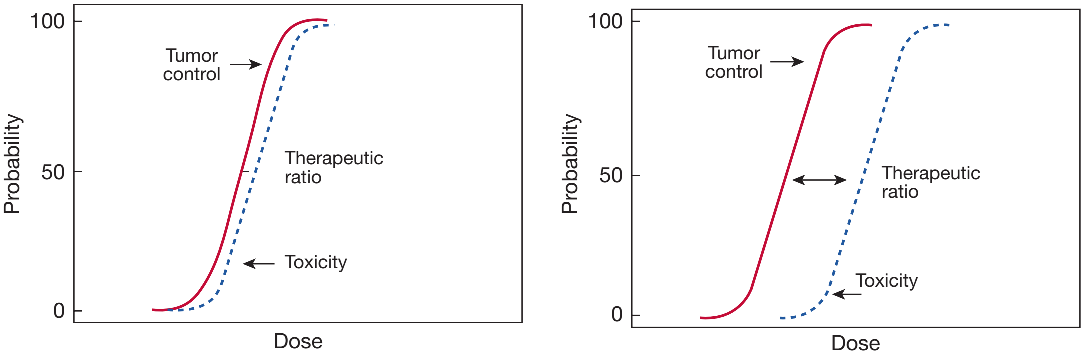


Figure 57-4 Effect of fractionated irradiation and low-dose rate irradiation on cell survival. The survival curve for lung cells treated with a single dose of radiation is redrawn from Fig. 57-3. The calculated effect of dividing the radiation dose into several daily treatments with 5 Gy/fraction or 2.5 Gy/fraction is illustrated. The *dashed line* illustrates the survival curve that would be expected for irradiation delivered continuously at a low-dose rate over several hours, allowing repair and proliferation to occur during treatment. Changes in the cytotoxicity of radiation with fractionation and at low-dose rates lead to decreased injury in lungs irradiated with analogous regimens.

differences between normal and malignant cell populations, including differences in the intrinsic radiosensitivity of the critical cells and in the patterns of cell proliferation and cell loss, as well as differences in the ability of the normal and malignant cells to repair radiation damage. Empiric observations of patients treated with radiotherapy, laboratory experiments with tumors and normal tissues in rodents, and studies with cells in culture have all been used to guide the development of the clinical fractionation schedules now in use. The development of new technologies and techniques that deliver radiation more precisely, such as SBRT, have also allowed for a departure from standard fractionation schedules by reducing the amount of normal tissue exposed to high doses of radiation. Ultimately, any improvement in the delivery of radiation therapy must improve the therapeutic ratio by producing an increased effect on the tumor without an equivalent increase in toxicity to critical normal tissues (Fig. 57-5). The art of radiotherapy lies in the design of treatment fields that minimize radiation doses to normal tissues and in the development of treatment regimens that use all available information on the biology of the tumor and of the critical normal tissues.

PATHOPHYSIOLOGY OF RADIATION PNEUMONITIS

Data on radiation pneumopathy in humans is fragmentary and complicated by the heterogeneity of the patients treated with thoracic irradiation. Most studies of radiation pneumonitis include patients with a variety of malignancies who have been treated with different irradiation regimens, often in combination with chemotherapy and surgery. Moreover, patients vary widely in age and the presence of other diseases and risk factors. Therefore, our current understanding of radiation injury to the lung remains incomplete. What is known suggests a complex, multifactorial mechanism of injury and disease progression that reflects cytotoxic effects on both epithelial and endothelial tissues. Inflammatory responses involved in this injury cascade include transient increases in reactive oxygen and nitrogen species, macrophage infiltration and activation, oxidative



Increasing the therapeutic ratio, either by selectively increasing the effect on tumor or by selectively protecting normal tissues from injury, produces therapeutic gain.

Figure 57-5 The therapeutic ratio is the critical factor determining the success of cancer therapy.

stress, induction of interstitial fibrosis with regional tissue hypoxia, and disordered cytokine and cellular signaling—including profibrogenic transforming growth factor beta (TGF-β), proangiogenic hypoxia-inducible factor 1 alpha (HIF-1α), and vascular endothelial growth factor (VEGF).[5,6,13,18–24] Similarities to lung injuries resulting from cancer chemotherapy, other drugs, inhaled chemicals, oxygen toxicity, immune reactions, and idiopathic pulmonary fibrosis are intriguing, especially when one considers that many of these diseases include pathologic responses to free radical chemical species and are likely to reflect similar underlying initial lesions.

Partial-lung resection and localized irradiation have certain similarities: Their effects are largely localized to the treated areas and, consequently, depend on the number of pulmonary lobules or alveolar–capillary units functionally destroyed. Thus, the volume of lung irradiated is an important determinant of toxicity. Just as the thoracic surgeon plans lung resection with due consideration to anticipated residual lung function, the radiation oncologist plans treatment to minimize the volume of lung and other critical tissues receiving significant radiation doses. Of course, this simple analogy has its limitations. For example, inactivation of enough lobules by radiation increases the ventilatory dead space and could lead to shunting and ventilation–perfusion mismatching. However, in clinical practice, extensive shunting generally is not observed.[25] In fact, post-radiation radionuclide ventilation–perfusion scans tend to show both underperfusion and underventilation that is dose dependent in irradiated areas of partially irradiated lungs.[26] In most cases, radiation injury in lung conforms to the radiation treatment fields, but in some, effects outside the treated areas are observed, with localized radiation inducing a more generalized or diffuse hypersensitivity pneumonitis.[27]

The effects of radiotherapy on the lung reflect the proliferation patterns of the different cellular components of the terminal capillary–alveolar units.[28] Type I pneumocytes are the dominant epithelial cells of the lung, covering about 83% of the alveolar surface. Type I pneumocytes are normally nonproliferating and do not proliferate in response to injury. Consequently, they are thought to be relatively resistant to the cytotoxic effects of radiation.

Type II pneumocytes, which constitute about 16% of the cells in the human lung, are the principal source of surfactant that modifies alveolar surface tension to prevent atelectasis. Type II pneumocytes have turnover times of about 1 month. In response to certain injuries, these granular pneumocytes can be induced both to undergo rapid mitosis and differentiate into type I pneumocytes.

Endothelial cells constitute about 30% of the cells in human lungs and form a continuous layer between the blood and the lung tissue. Although endothelial cells are classified in most tissues as stromal cells, endothelial cells in lung are actually parenchyma, because they are critical to the function of this organ. Capillary endothelial cells are a constantly renewing population, with an estimated turnover time on the order of 2 months. Endothelial cells can be induced into rapid compensatory proliferation after injury; therefore, radiation may result in depletion of both type II pneumocytes and endothelial cells.

Several lines of evidence suggest that radiation injury is related primarily to cytotoxic damage, especially to the surfactant-producing type II pneumocytes and vascular endothelial cells. Although clinical signs of pneumonitis require weeks to develop, laboratory studies reveal evidence of lung injury beginning just hours after large single doses of radiation.[23,29–32] Shortly after irradiation, electron microscopy may detect abnormalities in surfactant-containing lamellar bodies. There is an increase in surfactant in bronchoalveolar lavage specimens within hours of irradiation that persists for several weeks. Ultrastructural evidence of endothelial cell damage is also seen soon after lung irradiation, and a rapid increase in capillary permeability occurs, reflecting loss of integrity of cell junctions, intracellular vacuolization, cellular pleomorphism, and sloughing of the basement membrane. Capillary occlusion by cellular debris and microthrombi may occur at high doses.

The clinical course of lung injury occurs later and includes a pneumonitic phase, developing weeks to months after radiation, followed by a fibrotic phase, developing months to years later. To explain the two clinical phases, Rubin's and Casarett's original model of radiation lung toxicity suggested that the pneumocytes and endothelium represented two separate and distinct cellular targets, and that damage to pneumocytes led to pneumonitis, while vascular damage led to fibrosis. This older model is now thought to be incorrect; more recent data[21–23,28,33–38] suggest that the pneumonitic and fibrotic processes both are manifestations of a common pathway of injury and response.

There is a typical sequence of events that develops in the lung after large doses of radiation.[19,29,30] Within hours to days, vascular congestion and intra-alveolar edema and exudation occur, followed by infiltration of inflammatory cells and epithelial desquamation. Weeks later, collagen fibrils are deposited within areas of injury and interstitial edema, leading to a thickening of alveolar septa similar to that in hyaline membrane disease. The probability and severity of these changes are quite variable and depend on such factors as the radiation dose and treatment volume. The severity of the damage and volume of tissue affected determine whether a pneumonitic picture becomes clinically evident. Resolution of inflammatory infiltrates and alveolar exudates, which can be improved by anti-inflammatory agents such as glucocorticoids, correlates with symptomatic improvement and resolution of radiographic opacities in the affected lung.

Inflammatory cells, particularly alveolar macrophages, migrate into areas of radiation injury. This induces an ensuing cytokine cascade and mediates the host response,[6,20,22,23] similar to that which occurs in other inflammatory conditions, which can lead to pulmonary fibrosis. Rubin et al. detected a biphasic increase in mRNA expression for the proinflammatory cytokines IL-1α, IL-1β, and TNF-α at 2 and 8 weeks after radiation.[23] Beginning 24 h following radiation, TGF-β, a cytokine that mediates fibrotic responses, increases.[19] Elevated levels of VEGF may be detected 2 weeks later. Early clinical trials also suggest that elevated serum levels of IL-6 before, during, and after radiotherapy predict an elevated risk of radiation pneumonitis.[39,40] While TGF-β has been extensively studied and is thought to be a culprit for radiation-induced fibrosis in multiple organs-at-risk, clinical data have been mixed. One initial trial showed increased serum TGF-β levels at the end of radiation in patients who developed pneumonitis, but an additional prospective trial did not show a correlation with pneumonitis.[41,42] Collagen gene expression is also appreciably increased corresponding to the fibrotic changes seen histologically. These studies suggest that early and persistent elevations of cytokine production and alterations of intercellular signaling are critical to the development of radiation reactions in the lung. Similarly, ICAM-1, which promotes neutrophil transmigration into the damaged lung, is found in increased levels in blood of patients with pneumonitis at the end of radiation therapy and at the onset of pneumonitis.[43] ICAM-1 knockout mice that undergo radiation therapy have less inflammatory cell infiltration into the lung and decreased pulmonary fibrosis.[44,45]

Murine models demonstrate that genetic differences, age, and past health and treatment history can modulate the development and severity of fibrosis and hyaline membrane formation, thus determining the nature of the late toxic lesion and the time of development of radiation pneumotoxicity.[6,33,34] Single nucleotide polymorphisms in genes for methylene tetrahydrofolate reductase (MTHFR) and ataxia telangiectasia mutated (ATM) have been associated with development of symptomatic pneumonitis and severe pneumonitis.[46–48]

The processes described earlier lead to pathologic changes that conform spatially to the areas to which localized radiation was administered. Interestingly, it has been discovered that radiation can also induce an allergic alveolitis. This is observed infrequently as a diffuse pneumonitis, or occasionally as a patchy, transient cryptogenic organizing pneumonia (COP, previously known as bronchiolitis obliterans organizing pneumonia [BOOP]) occurring outside the treated fields. In its most severe form, the result is the acute respiratory distress syndrome (ARDS). Morgan and Breit[27] have suggested that this form of radiation-induced pneumonitis be termed "sporadic." The occurrence of the syndrome actually may be more common than appreciated. One series showed a 2.3% incidence of COP in women undergoing whole breast radiotherapy, occurring outside the radiotherapy fields four or more months after exposure.[49] Bronchoalveolar lavage in humans and in experimental animals frequently shows a significant increase in activated T-helper ($CD4^+$) lymphocytes, temporally related to irradiation and occurring equally in the irradiated lung and the contralateral, nonirradiated lung.[50] Gallium scanning may also show bilateral uptake not corresponding to the treated regions. Frequent reports of autoantibodies, including antibodies to collagen, in the sera of patients with cancer even before treatment suggest the possibility that malignancy-associated autoimmune reactions may be involved in the syndrome.

CONFOUNDING EFFECTS OF SYSTEMIC THERAPIES

Special consideration needs to be given to patients receiving additional systemic therapies along with radiation treatment, including chemotherapy and immunotherapy.

Chemotherapy

Many cytotoxic drugs employed as antineoplastic agents can produce pulmonary toxicity.[51–53] Bleomycin, which has been extensively studied, kills cells by generating reactive free radical species similar to radiotherapy and may give rise to both pneumonitis and fibrosis.[51] Doxorubicin, mitomycin C, irinotecan, etoposide, and gefitinib have been associated with lung toxicity, as have the antimetabolites (methotrexate, cytosine arabinoside, gemcitabine, fludarabine, and the nitrosamines) and the taxanes (paclitaxel and docetaxel).

As high-dose alkylating agent chemotherapy is used more frequently in the setting of stem cell transplantation, agents such as cyclophosphamide, BCNU, and busulfan have been associated increasingly with clinically significant pneumonitis. The direct toxicity of many widely used anticancer drugs to the lungs sounds a note of caution for those considering development of treatment protocols combining systemic chemotherapy with lung irradiation. Moreover, the concurrent administration of antineoplastic agents and radiotherapy may make it difficult to discern to what degree pulmonary injury in an individual patient is related to radiotherapy alone.

Animal studies addressing changes in respiratory rates and/or death resulting from lung injury show that the severity of the lung injury can be increased when doxorubicin, bleomycin, cyclophosphamide, mitomycin C, dactinomycin, or vincristine is administered along with radiation.[54,55] No enhancement has been documented in studies with 5-fluorouracil, cisplatin, carboplatin, hydroxyurea, vinblastine, or methotrexate, despite reports of lung toxicity from methotrexate alone.

Some radiation–drug interactions in the lung have been shown to be schedule dependent, with the effect of the combination varying with the sequence and the time between treatments with the two agents.[54] Additive, sub-additive, and even supra-additive toxicities may be observed in rodents when single treatments with the same dose of radiation and drug are given over a 24-h period, but in different sequences and different times between treatments. Such findings highlight the complexities of combined-modality therapy and the difficulty of using animal data to plan clinical treatment regimens.

Data from several specific clinical situations show that regimens combining radiation with particular chemotherapy agents can produce significant risks of pneumonitis. Docetaxel, mitomycin C, gemcitabine, and irinotecan given concurrently with radiotherapy seem to elevate the risk of pneumonitis or lung toxicity, while concurrent treatment with cisplatin and etoposide has a lower risk.[56,57] Concurrent weekly paclitaxel is associated with increased risk of radiation pneumonitis in patients with breast cancer.[58] Older clinical data from pediatric trials strongly suggest that administration of concurrent doxorubicin or actinomycin D with thoracic radiotherapy generally should be avoided or, alternatively, that the radiation doses should be reduced significantly where these drugs are used. These data are also supported by studies of anthracycline use in breast cancer patients.[59]

Sequential treatment with radiation and chemotherapeutic agents such as gemcitabine, actinomycin D, or doxorubicin is less likely to produce lung injury compared with concurrent treatment. However, a phenomenon termed "radiation recall" has been well described, in which chemotherapy administration even several months after radiotherapy will produce an inflammatory reaction in the region corresponding to the radiation treatment fields.[60] Although this reaction is best known in skin, it also has been well documented in the lungs in several case reports and has been produced in experimental animals. This has been reported with multiple chemotherapies including gemcitabine, doxorubicin, paclitaxel, etoposide, and pemetrexed. Radiation recall probably reflects the fact that the irradiated areas of the lung still retain residual, subclinical injury, which is exacerbated into clinical pneumonitis as a result of the additional injury from the drug. Therefore, the biologic basis of the recall phenomenon is analogous to that of the residual radiation injury, which decreases the ability of heavily irradiated lung tissue to tolerate a second course of radiotherapy delivered months or years later.[29,37]

Immunotherapy

Treatment with immune checkpoint inhibitors (ICIs) has become a staple of oncologic care in multiple settings. It is now part of first-line treatment for locally advanced and metastatic non–small-cell lung cancer (NSCLC) as well as extensive-stage small-cell lung cancer. As the indications for immunotherapy continue to expand, an understanding of its interaction with radiation therapy will be critical for physicians who treat cancer patients. The combination of radiation therapy and immunotherapy is particularly intriguing due to theoretically synergistic effects, with some hypothesizing that increased antigen presentation caused by damage from radiation may increase the efficacy of immunotherapy.[61,62] Multiple ongoing trials are assessing the safety and efficacy of the combination of thoracic radiotherapy and immunotherapy, either concurrently or sequentially.

Checkpoint inhibitors are immunomodulatory antibodies that enhance the immune system by interfering with inhibitory interactions between T cells and antigen-presenting cells. Antibodies to programmed death 1 (PD-1), programmed death ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) constitute most of the current checkpoint inhibitor armamentarium, and other potential targets are in development. While increased recognition of tumor by the immune system is desired, checkpoint inhibitors carry risk of adverse events related to general immunologic enhancement (immune-related adverse events), including pneumonitis. The risk of pneumonitis from PD-1 inhibition alone is typically less than 5% in clinical trials, with one meta-analysis demonstrating a 4.1% risk of any-grade pneumonitis in NSCLC patients and 1.6% in melanoma patients.[63] However, real-world populations may have additional risk factors and carry a higher risk of pneumonitis, with retrospective studies showing estimates of checkpoint inhibitor pneumonitis as high as 19%.[64] When given sequentially, immunotherapy and thoracic radiation appear to be safe with a mild increased risk of pneumonitis compared with radiation alone. In the PACIFIC trial, patients were randomized 2:1 to consolidation durvalumab or placebo after chemoradiation, with 92% of patients treated to doses between 54 and 66 Gy. Any-grade pneumonitis was observed in 33.9% of the durvalumab group versus 24.8% in the placebo group; grade 3 or 4 pneumonitis rates were 3.4% and 2.6%, respectively.[65] Retrospective data also have showed a mildly increased risk of pneumonitis after sequential chemoradiation and immunotherapy, with one study showing an 18% risk of grade ≥2 pneumonitis compared with 9% in a historic cohort of patients treated with chemoradiation alone.[66] The combination of SBRT and adjuvant immunotherapy has acceptable toxicity in early phase 1 and 2 trial data, with grade 3 pneumonitis rates typically under 5%.[67,68] However, the presence of pneumonitis in a patient treated with radiation and immunotherapy may portend improved disease response to immunotherapy, with some data suggesting that patients with immune-related adverse events after SBRT and immunotherapy have improved progression-free survival.[69]

An approach utilizing immunotherapy concurrent with radiotherapy is also under active investigation, with early reported data showing this appears to be safe. In an analysis of three clinical trials combining immunotherapy before and after radiotherapy at MD Anderson Cancer Center, grade 3 pneumonitis was reported in 2 of 60 patients treated with SBRT (up to 50 Gy in 4 fractions), 1 of 53 patients treated with 45 Gy in 15 daily fractions, and 1 of 25 patients treated with 45 Gy in 30 twice-daily fractions.[70] In a separate, retrospective, single-institution analysis of concurrent (within 30 days) immunotherapy with radiation therapy, grade 3 pneumonitis was 10.7% with SBRT and immunotherapy compared with 0% with SBRT alone.[71] Early-phase clinical trials have also demonstrated reasonable safety when adding immunotherapy to concurrent chemoradiation, with a 6.9% to 8% risk of pneumonitis for 214 patients treated with pembrolizumab, radiation, and cisplatin/pemetrexed or carboplatin/paclitaxel.[72,73] Final results of larger randomized trials will be needed better establish the safety and efficacy of concurrent radiation and immunotherapy.

In a patient who is treated with both immunotherapy and radiation therapy and develops pneumonitis, it may be difficult to differentiate whether pneumonitis was caused by radiation, immunotherapy, or both. However, there are several potential differences in the spatial and temporal presentation of radiation pneumonitis and immunotherapy-induced pneumonitis that may allow for this distinction. Radiation pneumonitis most commonly occurs weeks to months after radiation therapy, while immunotherapy typically causes pneumonitis while on treatment. Further, radiation pneumonitis may be more likely to correlate with the geographic distribution of the high-to-intermediate dose field. Treatment for both entities is similar (high-dose glucocorticoids), but differentiating the etiology may influence the decision whether to continue or discontinue the immunotherapy. The clinical presentation and treatment of radiation pneumonitis are further detailed below.

■ CLINICAL SYNDROMES

Radiation oncologists conventionally divide clinical toxicities into acute and late effects,[5,6] with both radiation pneumonitis and fibrosis considered late toxicities. Several grading systems for pneumonitis have been developed, with the most commonly used system being the Common Terminology Criteria for Adverse Events (CTCAE) (Table 57-1).

■ Clinical Manifestations During Treatment

It is relatively uncommon to observe acute pulmonary toxicity during the administration of fractionated radiotherapy. However, at relatively high therapeutic doses (50–60 Gy), acute radiation changes in the tracheobronchial tree can be expected. Bronchoscopic examination is likely to reveal erythematous mucosa, with thickened secretions that can accumulate in and obstruct the airways. Although a majority of patients remain asymptomatic, occasional patients experience an irritative, dry cough. Antitussive agents, such as codeine, adequate hydration, and reassurance are usually all that are required to manage this problem. After radiotherapy completion, the bronchial epithelium regenerates and heals over several weeks, accompanied by resolution of symptoms.

■ Subacute to Late Manifestations

The clinical course of late radiation injury to the lungs is biphasic, with both inflammatory and fibrotic components.[21,30,32]

Radiation Pneumonitis

A pneumonitic process frequently becomes evident 6 weeks to 6 months following radiotherapy. At this time, radiographs show alveolar opacities that generally conform to the treatment portals or the areas of high-to-intermediate dose radiation. The severity of radiation pneumonitis varies dramatically from patient to patient, even in those receiving identical therapeutic regimens. In most cases, the pneumonitis is asymptomatic, even though radiologic abnormalities are quite common, as noted in some prospective studies, in which as many as 50% of patients who have completed a course of thoracic radiotherapy were asymptomatic.

TABLE 57-1 CTCAE Version 5.0 for Radiation-Induced Lung Injuries

	Grade				
Term	**1**	**2**	**3**	**4**	**5**
Pneumonitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Pulmonary fibrosis	Radiologic pulmonary fibrosis <25% of lung volume associated with hypoxia	Evidence of pulmonary hypertension; radiographic pulmonary fibrosis 25%–50% associated with hypoxia	Severe hypoxia; evidence of right-sided heart failure; radiographic pulmonary fibrosis >50%–75%	Life-threatening consequences (e.g., hemodynamic/pulmonary complications); intubation with ventilatory support indicated; radiographic pulmonary fibrosis >75% with severe honeycombing	Death

CTCAE, common terminology criteria for adverse events; ADL, activities of daily living.

When symptomatic, this syndrome is often characterized by the abrupt onset of fever, cough, and dyspnea. The severity of symptoms depends on the extent of radiotherapy, increasing with the treated volume and with the radiation dose. Symptoms in patients irradiated to limited lung volumes or to relatively low doses may consist of low-grade fever, cough, congestion, and chest fullness or discomfort. Any hemoptysis tends to be minimal. In more severe situations, dyspnea, high fever, and cough occur. Malaise, weight loss, and chest pain from pleuritis or other etiologies also can be present. When large volumes of normal lung receive radiation dose, acute radiation pneumonitis is more likely and can be extremely severe, producing respiratory distress. The radiation oncologist is probably most likely to see clinically significant radiation pneumonitis that can be life-threatening when it occurs as an unanticipated consequence of standard treatment, despite appropriate treatment planning designed to minimize the volume of lung treated with high doses of radiation. However, the risk for serious toxicities may be higher in patients with pre-existing pulmonary comorbidities, and those with a large burden of locoregional disease for whom it is necessary to radiate a larger volume of lung to achieve potentially curative doses to the tumor. Mild pneumonitis is not uncommon but is readily manageable.

It is important to distinguish radiation pneumonitis from infection, recurrent tumor (particularly with lymphangitic spread), drug reactions, congestive heart failure, and other respiratory disorders. These distinctions may not be easy; one series from Duke suggested 28% of patients with radiation-associated lung toxicity have complex comorbidities that make it difficult to assign a definitive diagnosis.[74] Bacterial, fungal, viral, and pneumocystis pneumonias can be quite difficult to differentiate from pneumopathy induced by chemotherapy or radiation.

Aids in the differential diagnosis include the clinical course and temporal relationship between the irradiation and respiratory illness. Definition of the radiographic pattern of the infiltrate is also very useful, because radiation pneumonitis often conforms to area of higher dose radiation. While classically radiation pneumonitis conforms to radiation ports, a clear delineation may not be as apparent with modern radiation techniques such as IMRT **(Fig. 57-1)**. Bronchoscopy and lung biopsy also can be helpful diagnostic tools to direct therapeutic decisions, especially if other differential diagnoses can be ruled out with bronchoalveolar lavage or tissue pathology. Ruling out infection is particularly important, because treatment of symptomatic radiation pneumonitis relies on supportive care in conjunction with corticosteroids. Procalcitonin may be a useful marker to help differentiate bacterial pneumonia and pneumonitis; one study demonstrated patients with bacterial pneumonia have higher procalcitonin levels compared with radiation pneumonitis, with an area under the receiver operating characteristic (ROC) curve of 0.745 and a suggested cutoff value of 0.47 μg/L.[75]

Most studies show at least a transient decline in pulmonary function in patients who receive radiation to a significant lung volume (i.e., patients with lung cancer receiving a potentially curative course of fractionated radiotherapy). There may be a transient reduction in lung volumes such as total lung capacity (TLC) and forced vital capacity (FVC) 3 to 6 months post-radiation. Carbon monoxide diffusing capacity (DL_{CO}) may be reduced over a similar time course, but typically to a greater degree relative to baseline.[76,77] Absent the development of radiation fibrosis, these parameters tend to recover toward the patient's baseline, reaching maximal recovery at approximately 12 months.

Doses of glucocorticoids generally can be tailored to the severity of the symptoms. Asymptomatic pneumonitis may be managed with close observation. Severe cases generally warrant treatment with prednisone (or its equivalent) at a dose of 0.5 to 1 mg/kg per day in divided doses. Patients who are appropriately diagnosed and treated with high-dose steroids typically respond well, and dramatic clinical and radiographic responses are possible. Steroids should be tapered slowly after the patient is stabilized, because it is common to see a recrudescence of symptomatology when steroids are discontinued too rapidly. In these cases, reinitiation of higher doses and a slower steroid taper, such as 8 to 12 weeks, is recommended. Prophylaxis against *Pneumocystis* pneumonia should be considered due to a potentially prolonged steroid course. Failure to respond to steroid therapy is an adverse prognostic factor that suggests the prospect of rapid disease progression. Other immunosuppressive agents such as azathioprine and cyclosporine can also be considered in patients who cannot tolerate steroids or who have refractory disease, but evidence supporting these therapies is limited.[78,79]

Radiation Fibrosis

A more indolent fibrotic process may follow either subclinical or symptomatic radiation pneumonitis.[21,30,32] This begins several months after radiotherapy and peaks in radiographic severity several years later. Fibrosis tends to occur in, or adjacent to, areas of prior pneumonitis,[33] but it can also occur in the absence of clinically overt radiation pneumonitis. Fibrotic changes and the retraction of the lung parenchyma from scarring occur in the irradiated regions. When the volume of lung irradiated is relatively small and the remaining lung parenchyma contains sufficient respiratory surface area, the changes tend to be asymptomatic.

With increasing relative volumes of pulmonary fibrosis, a spectrum of symptomatology is possible, ranging from mild dyspnea on exertion to severe fibrosis with respiratory compromise, chronic cor pulmonale, cyanosis, and finger clubbing. At the severe end of the spectrum, the syndrome can be life-threatening. In general, in the absence of other underlying lung disease, symptoms are mild when less than 25% to 30% of total lung parenchyma is involved.

While most radiation fibrosis in most patients is asymptomatic, especially with more focal treatments such as SBRT, a small change in pulmonary function testing is expected. One prospective study of patients treated with lung SBRT demonstrated 3.5% to 5.7% decreases in forced expiratory volume in 1 second (FEV_1), DL_{CO}, FVC, and TLC at 1 year, and persistent declines in FEV_1 (7.6%) and FVC (8.9%) at 2 years.[80] Although statistically significant, these changes were rarely clinically significant.

Treatment options for radiation fibrosis are supportive, including oxygen supplementation and pulmonary rehabilitation. Anti-inflammatory treatments like glucocorticoids are not expected to be beneficial and should be avoided due to unnecessary toxicity.

Radiation-induced Pleural Reactions

Pleuritis may also be seen 2 to 6 months following radiation. It can be associated with pleuritic chest pain, a pleural friction rub, and an exudative pleural effusion. Large effusions are, however, distinctly unusual in the absence of other pathology. Like radiation pneumonitis, radiation-induced pleuritis may heal without significant residue, or it may proceed through a fibrotic phase that generates pleural thickening.

Radiation-induced Bronchial Stenosis

With improvements in the technical delivery of radiotherapy, recent clinical trials for lung cancer have emphasized escalation of the administered radiation dose. Because SBRT delivers significantly higher biologically effective doses than are feasible with conventional fractionated radiotherapy, there is an increased risk of bronchial stenosis when delivering SBRT to central tumors. For tumors close to the hilum, radiation-induced fibrosis may result in bronchial stenosis or necrosis, causing post-obstructive atelectasis, volume loss, and functional impairment.[81–83] Severe bronchial injury is rare with fractionated chest radiotherapy using conventional doses. However, with doses beyond those typically prescribed with fractionated radiation, bronchial stenosis becomes more likely; one retrospective series in which radiation doses ranged from 70.8 Gy to 86.4 Gy demonstrated that radiation-induced bronchial stenosis may occur in up to 25% of patients, and incidence directly correlates with radiation dose.[84]

In general, the risk of serious complications after SBRT is elevated for central lung tumors, and particularly for "ultracentral" tumors, which border or nearly border the mainstem bronchi. One study reported a 15% risk of fatal pulmonary hemorrhage in patients treated with 60 Gy in 12 fractions for ultracentral NSCLC, half of which had endobronchial tumor present.[85] Another prospective trial testing a regimen of 56 Gy in 8 fractions reported high rates of severe toxicity, including grade 5 events in 10 of 65 patients with tumors within 1 cm of the main bronchi and trachea.[86] Endobronchial tumor invasion may also contribute to the risk of fatal hemorrhage, and risk of tumor recurrence must be weighed against that of severe radiation toxicity. SBRT regimens for central tumors typically employ lower doses or greater fractionation than for more peripheral tumors.[87,88]

DEFINING THE RADIATION TOLERANCE OF THE LUNGS

Radiation tolerance is typically defined as the dose that yields a 5% risk of severe late radiation injury. When discussing the tolerance of the lungs, one must consider several different therapeutic situations. The tolerance of the lung varies with the volume of lung tissue irradiated.[89] In addition, single-dose irradiations, fractionated irradiations, and irradiations given at low-dose rates each pose different risks of injury, and therefore they must be considered separately. Additional injury from surgery, chemotherapy, or a prior course of radiotherapy also must be considered, as must the confounding effects of injury to lung tissue from coexisting cardiopulmonary disease and from the underlying malignancy. The clinical endpoints used to define a case of radiation pneumonitis vary as well, because the severity of the lung injury spans a wide spectrum of diagnostic signs and clinical symptoms.

With three-dimensional imaging and dose calculation, the dose-volume determinants of pulmonary toxicity have been explored in depth. In 2010, the available data on three dimensional dose-volume determinants of normal tissue injury were compiled in an effort known as QUANTEC (Quantitative Analysis of Normal Tissue Effects in the Clinic).[89] More recently, with the wide adoption and use of hypofractionated radiation, a similar project for SBRT regimens has been published, named HyTEC (Hypofractionated Treatment Effects in the Clinic).[90] Despite these efforts, the medical literature that defines the risks for radiation pneumonitis and fibrosis is extremely complex and often difficult to interpret due to the great heterogeneity of clinical circumstances and biologic data.

■ Whole-lung Irradiation

A good starting point for considering lung tolerance is analysis of the effects of irradiating the entire lung. This construct has direct clinical relevance because there are several circumstances in which the entire lung is irradiated. These include total-body irradiation (TBI) for bone marrow or hematologic stem cell transplantation, and whole-lung irradiation given electively or therapeutically for relatively radiosensitive tumors, such as Wilms tumor or Ewing sarcoma. These are often circumstances in which chemotherapy is administered as well.

TABLE 57-2 Actuarial Incidence of Radiation Pneumonitis After Single-fraction Whole-lung Irradiation

Uncorrected Dose	Patients	Pneumonitis (%)
<6 Gy	49	2.7
6 Gy	24	17.5
8 Gy	149	35.6
10 Gy	23	83.9

Note: Doses are not corrected for heterogeneity in tissue density.
Data from Fryer CJ, Fitzpatrick PJ, Rider WD, et al. Radiation pneumonitis: experience following a large single dose of radiation. Int J Radiat Oncol Biol Phys. 1978;4(11–12):931–936.

Published experience from the Princess Margaret Hospital in Toronto[12,91–93] provides some of the best data regarding whole-lung tolerance. Investigators from that institution have an extensive experience with delivering upper hemibody irradiation in different doses and varying fractionation patterns. They reported in 1978 on a cohort of 245 patients, most with metastatic solid tumors, who received single-fraction, upper hemibody irradiation at dose rates of 0.3 to 0.8 Gy/min to doses of up to 10 Gy.[91] The actuarial incidence of acute radiation pneumonitis, defined as the sudden onset of cough, dyspnea, and opacities visible on chest radiographs at about 16 weeks following treatment, was strikingly dose dependent (Table 57-2). The doses shown in Table 57-2 were not corrected for heterogeneity in density.[12] When doses are corrected, resulting in an upward estimation of the doses actually received by the lungs, analysis yielded the sigmoid-shaped curve shown in Fig. 57-6.[94–96]

Using heterogeneity-corrected data, the incidence of pneumonitis is estimated to be negligible for single doses less than about 7.5 Gy. Other published data regarding upper hemibody single-fraction irradiation are in general agreement with these findings.

Careful analysis suggests that the single-fraction data might predict an unacceptable risk for pneumonitis when single-fraction TBI is utilized in the setting of bone marrow transplantation (BMT). The most important treatment factor making single-fraction TBI in the range of 8 to 10 Gy (uncorrected for heterogeneity) tolerable is that treatments generally are given at a low dose rate ($\leq$0.1 Gy/min) over 1 to 2 h.[38,97] In Seattle, where hundreds of patients with leukemia have undergone BMT after TBI, using single fractions of 10 Gy (uncorrected) delivered at dose rates on the order of 0.08 Gy/min,

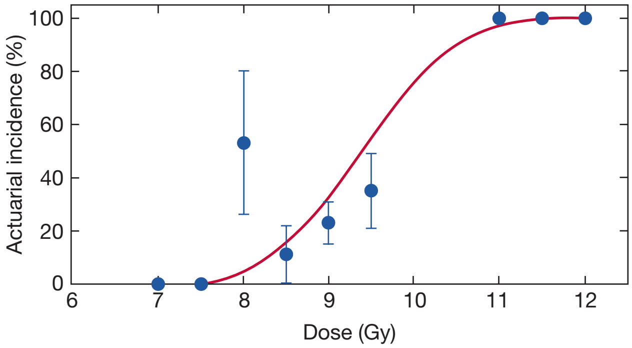


Figure 57-6 Incidence of radiation pneumonitis in patients receiving single-dose, whole-lung irradiation at dose rates of 0.3 to 0.8 Gy/min. Unlike most doses given in the text, doses on this figure *are* corrected for heterogeneity in density. The effect of this correction can be seen by comparing these data with those in Table 57-1, which were derived from an earlier analysis by the same group and are presented using uncorrected doses. *(Reproduced with permission from Van Dyk J, Keane TJ, Kan S, et al. Radiation pneumonitis following large single dose irradiation: a re-evaluation based on absolute dose to lung. Int J Radiat Oncol Biol Phys. 1981;7(4):461–467.)*

the incidence of pneumonitis is roughly 25%. Review of transplant-related single-fraction TBI with variable dose rates shows incidences of clinical lung injury varying from 25% to 70%.[92,98,99]

Toxicities of TBI can be improved further by fractionating the irradiation, as well as by delivering radiation at a low dose rate. In a randomized clinical trial comparing low-dose-rate, single-fraction TBI (10 Gy) with low-dose-rate, fractionated TBI (12 Gy in 6 fractions over 3 days) for patients with acute myelogenous leukemia in first remission, a significant improvement in event-free survival was noted with fractionation, mainly because of an improvement in early mortality.[97] Interstitial pneumonitis was decreased from 26% to 15% with fractionation. Other studies have corroborated a reduced incidence of pneumonitis to less than 20% without increasing the rate of tumor recurrence using fractionated TBI.[96,100,101] Within a range of 1.5 to 2 Gy per fraction given once or twice daily, there is no significant increase in pneumonitis risk using doses up to 15 Gy. Nevertheless, total dose delivered to the lung is a key determinant of pneumonitis risk.[92,102] In addition, at many transplant centers it has become common practice to utilize lung transmission blocks to attenuate the lung dose and thereby reduce the risk of pneumonitis, in part by compensating for the heterogeneity in tissue density due to the air within the lungs.

Lowering the dose rate of radiation delivery is typically also employed for fractionated TBI. Within the context of fractionated TBI schemes, instantaneous dose rates of 0.05 to 0.18 Gy/min generally have been employed due to practical considerations; while efficacious,[103,104] treatment times of 2 to 3 hours are impractical and poorly tolerated by patients. Whether or not higher instantaneous dose rates are detrimental in the context of fractionated TBI and lung transmission blocks remains unclear. One small study comparing dose rates of 0.075 versus 0.15 Gy/min for TBI prescribed to 12 Gy in 6 fractions reported pneumonitis risks of 13% and 43%, respectively, for these dose rates, although there were many confounding covariates.[105] Retrospective analysis of pediatric ALL patients receiving TBI as part of a myeloablative allogeneic transplant preparative regimen from both Emory and University of Minnesota show a lower risk of pneumonitis with lower instantaneous dose rates.[106,107] Another analysis of pediatric patients receiving TBI within the Children's Oncology Group experience showed that total dose to the lungs (factoring in lung blocking) rather than dose rate was a dominant risk factor for pneumonitis, suggesting that mean lung doses above 8 Gy had higher risk.[108] Contributing to pneumonitis risk was the use of lateral whole-lung fields compared with anteroposterior-oriented beams. This was loosely corroborated by investigators at Duke.[109]

Pneumonitis in the BMT setting has a multifactorial etiology, reflecting not only the effects of radiation, but also the effects of chemotherapy, graft-versus-host disease (GVHD), lung injury from tumor, opportunistic infections, and other risk factors.[98,100] Cyclophosphamide is almost universally given with TBI. The addition of other drugs is based on institutional treatment policies; many of these anticancer drugs are known to injure the lung.[51,53] In fact, BMT conditioning regimens that do not use TBI (which often use high-dose busulfan in place of radiation) have rates of interstitial pneumonitis comparable to regimens that include TBI. The presence of GVHD also is important, not only because GVHD causes lung injury directly, but also because the drugs used to control GVHD injure the lung. Perhaps, for this reason, T cell–depleted transplants, which produce less GVHD, tend to have lower risk for pneumonitis.[110]

Whole-lung irradiation has been used in the treatment of widespread lung metastases. In two published series, a combined total of 70 patients with osteosarcoma who received elective whole-lung irradiation to prevent pulmonary metastases received 15 to 17.5 Gy in 10 fractions. None of these patients developed pneumonitis.[21] Similarly, in a series of 40 patients who received 20 to 25 Gy of thoracic irradiation in 1.5-Gy fractions to treat pulmonary metastasis, no cases of pneumonitis were reported.[21] This and other clinical experience with fractionated whole-lung irradiation in the nontransplant setting and in the absence of chemotherapy indicate that 25 Gy in 20 daily fractions over 4 weeks or 20 Gy in 10 daily fractions over 2 weeks should have a relatively low risk (<5%) for radiation pneumonitis.

Historically, radiotherapy for Hodgkin disease had included whole-lung treatment in situations in which there is massive mediastinal adenopathy, hilar adenopathy, or overt pulmonary disease treated with chemotherapy. Risks of symptomatic pneumonitis ranging from 7% to 35% have been reported, with the risk highly dependent on the total radiation dose and the fractionation pattern.[21,111] When the whole lung is to be irradiated, available data suggest that the lungs should be treated through transmission blocks, rather than using open fields. This reduces both the total dose and the dose per fraction to the lungs, thereby reducing the risk of symptomatic pneumonitis to 4% to 7% over a broad range of total lung doses of 10 to 20 Gy.

Lung radiotherapy using 12 to 14 Gy for pulmonary metastases in pediatric patients with Wilms tumor (who also receive sequential doxorubicin and actinomycin D) is associated with a 10% incidence of pneumonitis.[112] Long-term follow-up in such children also shows restrictive lung disease, with total lung and vital capacities approximately 70% of the predicted values. In children receiving thoracic irradiation, inhibition of normal growth and development of the lung parenchyma and bones as a result of radiotherapy also produces significant morbidity. The effects of radiation on growth and development and the radiosensitivity of growing tissues raise special concerns in the treatment of pediatric patients.[10]

■ Partial-lung Irradiation

Estimating the risks of radiation pneumopathy for individual patients receiving radiotherapy is a daunting task, because so many confounding factors must be considered. With lung cancer, the tumor size and location influence the volume of adjacent normal lung that must be irradiated. The volume irradiated should determine the number of capillary–alveolar units destroyed and, therefore, should influence the risk of symptomatic radiation pneumonitis and fibrosis.[28] This qualitative prediction is borne out by clinical experience, but quantifying the risks is not straightforward. The lung region irradiated also is important, because the upper lung regions contribute less to gas exchange than do the lower regions. Treatment-related factors such as total dose, dose per fraction, and overall treatment time also are important, as are the other confounding factors described in the preceding sections.[32] Baseline pulmonary function also is highly variable among patients undergoing radiotherapy, reflecting age, smoking history, and the presence or absence of underlying cardiopulmonary disease. Because regional pulmonary fibrosis may be partially compensated by functional lung parenchyma, pretreatment lung status influences the severity of symptoms. For instance, it is well established that patients with interstitial lung disease (ILD) have a higher risk of treatment-related toxicity, in part because chemoradiotherapy can exacerbate ILD.[113,114]

These concepts, including the inherent difficulty in predicting pneumonitis, have borne out in preclinical studies despite increased homogeneity of experimental conditions. Mouse data from MD Anderson showed a clear shift in dose–response curves for changes in respiratory rate and pulmonary death as a function of the volume of lung irradiated.[35] As expected, the region of the lung irradiated was important: effects were more pronounced when the well-perfused base of the lung was irradiated, rather than the less well-perfused apex. The response to lung irradiation was quite heterogeneous, even within mice of the same age and sex, from a single highly inbred mouse strain, maintained in microbiologic isolation under rigorously controlled environmental conditions. The morbidity and symptomatology observed in individual mice was not always reflected in the histology findings found after necropsy.

Several clinical studies have attempted to predict radiotherapy-induced changes in FEV_1 by superimposing radiation treatment portals on quantitative ventilation and perfusion scans.[115–118] Unfortunately, the simple notion that the proportion of lung irradiated should match the drop in FEV_1, akin to the highly useful preoperative assessment of predicted postresection lung function, has not been verified. In fact, a report from the Massachusetts General Hospital examining global and regional pulmonary function in patients with lung cancer showed improvement in pulmonary function in 52% of patients and a mild decline in 37%; the decline was predicted from changes in radionuclide scans in only 11%.[116] Similar observations have been made in nonoperative lung cancer patients.[117] The technique of superimposing radiation treatment portals over quantitative lung perfusion scans is, therefore, of limited utility in predicting pneumonitis in individual patients. It has been suggested that the diffusing capacity is a more sensitive indicator of tolerance to radiotherapy.[115]

Unfortunately, there are no firm tests or data to guide the development of tolerable regimens of radiotherapy for patients with borderline lung function, except that we know the treatment volumes should be minimized. If the initial FEV_1 is below 1.0 L or $\mathrm{DL}_{\mathrm{CO}}$ is less than 50% of predicted, large-volume radiotherapy (e.g., elective nodal irradiation for lung cancer) may well be too hazardous. Despite its limitations, quantitative perfusion scanning in selected patients may give a worst-case scenario and help the radiation oncologist decide on dose and treatment volume. In clinical practice, radiation oncologists primarily analyze dose-volume parameters from a CT simulation scan to evaluate the risk of lung toxicity.

■ Dose-Volume Lung Effects with Fractionated Treatment

Radiation dose–volume histogram analyses derived from detailed three-dimensional treatment evaluations and applied to an empirical normal tissue complication model show only a fair correlation between volume and risk of complications.[89,119] Quantitative analysis of dose-volume parameters are further complicated by differences among studies in defining lung volumes; studies variably have included one or both lungs, have subtracted tumor volume or target volume from lung tissue, and have used different breathing techniques (i.e., breath hold versus gating in a certain phase of the breathing cycle versus average over the entire breathing cycle). Nevertheless, it is common practice to evaluate dosimetric parameters, such as V_{dose} or mean lung dose (MLD), to predict the risk of pneumonitis prospectively. The V_{dose} (i.e., $V_{20\,Gy}$ or $V_{30\,Gy}$) parameter is defined as the percentage of total volume receiving greater than the threshold dose (i.e., 20 Gy or 30 Gy, respectively). The MLD is defined as the average dose delivered to the whole lungs.

More complex dosimetric models fit observed normal tissue complication probabilities (NTCPs) to functions that include more comprehensive evaluations of low- and high-dose partial-volume organ exposures using standard radiobiologic models. Investigators at Duke[120] and the Netherlands Cancer Institute[121,122] have attempted to refine the correlation of dose–volume histograms with toxicity by factoring out nonfunctioning lung using lung perfusion scans. In patients with lung cancer, particularly those with chronic obstructive pulmonary disease (COPD), areas of hypoperfusion separate from tumor are seen frequently; irradiation of such irreversibly hypoperfused lung may not contribute additional toxicity. The existing data show a direct correlation between regional changes in ventilation, perfusion, or CT density with increasing radiation dose to that region (Fig. 57-7).[123]

These approaches may have broader applicability across various radiation treatment techniques, but they are infrequently used because of their complexity. In clinical practice, single radiation dose point metrics such as V_{20}, V_5, and MLD are used to optimize radiation treatment plans and assess the risk of a plan causing lung toxicity. From collected data in the QUANTEC effort, the risk of radiation pneumonitis is less than 20% when the MLD is less than approximately 20 Gy, when <30 to 35 Gy, or when V_5 <60%.[89] Similar estimates have been reported in a statewide prospective cohort study from Michigan, where a greater than 22% risk of pneumonitis was predicted independently by MLD >20 Gy, V20 ≥35%, and V5 ≥75%.[124] However, there is no clear dose threshold that defines safe versus unsafe doses of radiation, as dose correlates with risk of symptomatic pneumonitis in the range of lung doses that are clinically relevant. However, increasing the volume of lung of low-to-medium doses of radiation appears to have a greater impact than high doses of radiation (Table 57-3). Figure 57-8 shows the risk of

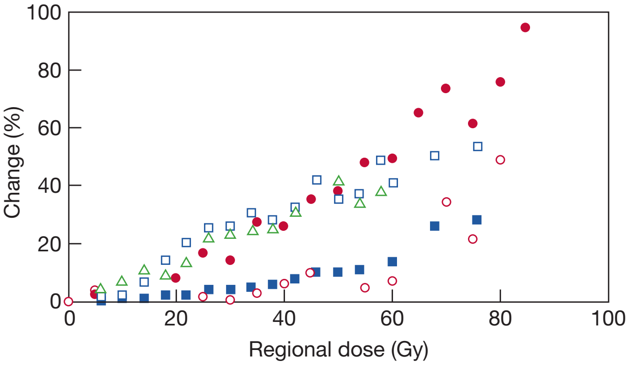


Figure 57-7 Regional changes in ventilation, perfusion, and computed tomography (CT) density from partial lung radiotherapy as a function of regional radiation dose: data from Duke University (Duke) and Netherlands Cancer Institute (NKI). Symbols in graph represent: (●) reduction in perfusion—Duke; (○) increase in CT density—Duke; (■) change in air-filled fraction—NKI; (□) reduction in perfusion—NKI; and (Δ) reduction in ventilation—NKI. *(Reproduced with permission from Marks LB, Yu X, Vujaskovic Z, et al. Radiation-induced lung injury. Semin Radiat Oncol. 2003;13(3):333–345.)*

TABLE 57-3 Univariate Models of Dosimetric Factors on Grade 2+ Radiation Pneumonitis Risk

Predictor	Odds Ratio (vs. Grade 0 or 1)	*p*
MLD (Gy)	1.11	<0.001
V5 (per 10%)	1.34	<0.001
V10 (per 10%)	1.34	<0.001
V15 (per 10%)	1.63	<0.001
V20 (per 10%)	1.79	<0.001
V25 (per 10%)	1.63	0.001
V30 (per 10%)	1.48	0.01
V35 (per 10%)	1.34	0.048
V40 (per 10%)	1.21	0.20
V45 (per 10%)	1.10	0.48
V50 (per 10%)	1.10	0.65
V55 (per 10%)	1.00	0.87
V60 (per 10%)	1.00	0.98

MLD, mean lung dose.

Data from McFarlane MR, Hochstedler KA, Laucis AM, et al: Predictors of Pneumonitis After Conventionally Fractionated Radiotherapy for Locally Advanced Lung Cancer. Int J Radiat Oncol Biol Phys. 2021;111(5):1176–1185.

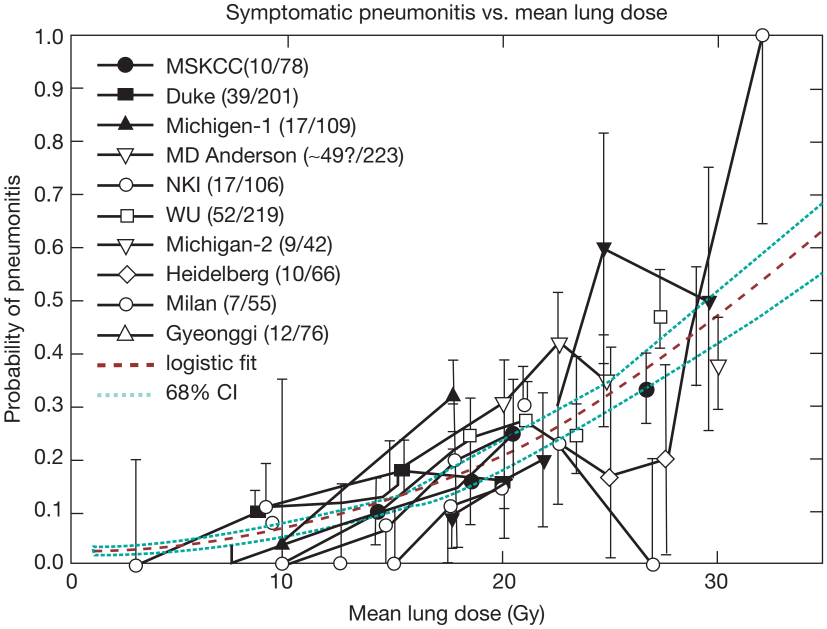


Figure 57-8 Probability of symptomatic pneumonitis versus mean lung dose; data from 10 clinical studies with *dashed line in red* fit by logistic Lyman–Kutcher–Burman dose–volume histogram model with one standard deviation shown in *light blue curves*. *(Reproduced with permission from Marks LB, Bentzen SM, Deasy JO, et al. Radiation dose-volume effects in the lung. Int J Radiat Oncol Biol Phys. 2010;76(3 Suppl):S70–S76.)*

symptomatic pulmonary complications as a function of MLD from 10 studies. These predicted risks apply to patients receiving conventional fractionation of 1.8 to 2 Gy per day and are less relevant when the dose per day is greater than 2 Gy.

In patients undergoing pneumonectomy for mesothelioma who require adjuvant radiotherapy, dosimetric parameters to avoid pneumonitis of the remaining lung are even more stringent: V_{20} should be below 4% to 10% and MLD should be below 8 Gy.[125] Hemithoracic radiation using IMRT techniques to better spare both ipsilateral and contralateral lung after pleurectomy and decortication may reduce the risk of lung toxicity. In one study of 220 patients with pleural mesothelioma after nonradical lung-sparing surgery, the incidence of grade 2+ pneumonitis was 16% when the contralateral lung was constrained to a $V_5 < 17\%$ and mean total lung dose was recommended to be under 24 Gy.[126]

■ Dose-Volume Lung Effects with SBRT

Hypofractionated treatments such as SBRT, with a high dose per fraction delivered over a reduced number of fractions, have become standard of care for inoperable early-stage lung cancer and are increasingly used in treatment of oligometastatic disease and recurrent lung cancer. Given the higher biologic effect of hypofractionated radiation, dose-volume considerations must be separated from fractionated treatments.

The authors of the normal lung-specific HyTEC effort reviewed the correlation of dosimetric factors on lung toxicity for lung SBRT.[90] In meta-analyses, mean lung dose and the V_{20} did not did not have a significant relationship with grade 2+ radiation induced lung toxicity.[127] However, multiple studies individually reported correlations between lung toxicity and mean lung dose or V_{20}. This discrepancy may be caused by differences in the definition of lung volumes, calculation of mean dose (adjusting for fraction size or not), fraction sizes, and inconsistencies in toxicity grading. Therefore, the authors advised MLD <8 Gy and $V_{20} < 10\%$ to 15% were likely to keep the risk of symptomatic lung toxicity under 10% to 15%, although there is no clear threshold tolerance level beyond which toxicity is unacceptable.

While baseline lung function has not been shown to be associated with lung toxicity after SBRT, likely due to the small volume of lung receiving high radiation dose, interstitial lung disease has been associated with an elevated risk of toxicity after SBRT.[90] For instance, in one study of 504 patients treated with SBRT to biologically effective doses between 112 and 164 Gy using an α/β ratio of 10, grade 3+ pneumonitis was noted to be 2% in patients without ILD and 32% with ILD, including 18% with grade 4+ toxicity.[128] Because of this, some radiation oncologists view ILD as a contraindication to SBRT, and at minimum physicians should strongly consider what alternative treatment options may be available for patients with ILD.

Because of the high conformality of the SBRT with small volumes of lung typically irradiated, it is feasible to treat multiple lung lesions concurrently, treat metachronous separate lung lesions, and even treat within a previously radiated area. One study of 72 patients treated with SBRT to 48 Gy in 4 fractions to an area previously overlapping a prior radiation field reported a 20.8% risk of grade 3 lung toxicity, with increased risks in patients who had poor performance status (ECOG performance score 2–3), lung function ($FEV_1 < 65\%$), and composite plan $V_{20} > 30\%$.[129] Another study demonstrated high rates of toxicity when central tumors were treated with a second course of SBRT, with grade 2+ toxicity in 8 of 11 patients, including 3 treatment-related deaths.[130]

DISEASE-SPECIFIC CONSIDERATIONS AND RISK

The risk of radiation pneumonitis is affected by the underlying malignancy being treated, as discussed below for several common disorders.

■ Lung Cancer

As most cases of pneumonitis are seen in patients treated with definitive doses of radiation therapy for lung cancer, most of the data presented above are derived from trials of lung cancer patients. Prescription doses for conventionally fractionated radiation therapy in the definitive treatment of locally advanced lung cancers typically ranges from 60 to 70 Gy in 30 to 35 fractions, preferably with concurrent chemotherapy and consolidative immunotherapy for those who are candidates. For SBRT, treatment regimens generally deliver higher doses per fraction over 1 to 5 fractions for peripheral tumors. More moderately hypofractionated courses should be considered for central lung tumors, where the risk of severe toxicities limits the safety of shorter regimens. In most series of patients receiving definitive conventionally fractionated thoracic radiotherapy, the risk of symptomatic radiation pneumonitis is usually about 10% to 20%, and some degree of radiographic fibrosis is almost universal. For SBRT, the volume of lung irradiated is typically reduced, and similarly symptomatic pneumonitis rates are lower, in the range of 5% to 15%.[89]

In clinical trials that have escalated radiation doses to the tumor (and small amount of surrounding lung) there has not been a significant increase in lung toxicity, likely because the number of nonfunctional alveoli is not greatly increased by this increase in dose.[131] In the RTOG 0617 trial, dose escalation from 60 to 74 Gy did not lead to greater grade 3+ pneumonitis rates (4% and 7%, respectively).[132] The cohorts treated with 74 Gy had decreased overall survival compared with those treated with 60 Gy, which some have hypothesized is due to increased radiation dose to the heart and esophagus.[133] Importantly, on secondary analysis patients treated with IMRT (47%) had a reduced risk of grade 3 pneumonitis compared to 3D-conformal radiotherapy (3.5% vs. 7.9%), and higher lung V20 was associated with increased pneumonitis risk.[134]

■ Esophageal Cancer

Radiation therapy plays a role in treatment for most patients who have locoregional esophageal cancers, outside of those with select T1 tumors. Radiation doses delivered are typically in the range of 41.4 to 50.4 Gy, often combined with concurrent chemotherapy for those who are medically fit to tolerate treatment. With the central location of the esophagus in the thorax, a significant amount of lung is frequently exposed to low doses of radiation, especially with IMRT. Rates of grade 3 or greater pneumonitis are typically under 5% for chemoradiation alone.[135] In patients treated with a trimodality approach, the timing of chemoradiation prior to surgery may lead to pulmonary toxicity post-operatively.[136] Proton beam therapy can be used to reduce radiation doses to the heart and lung, and to potentially reduce cardiopulmonary toxicities in turn. In a randomized phase 2 trial comparing 50.4 Gy of preoperative chemoradiation delivered with IMRT versus proton beam therapy, the novel endpoint called “total toxicity burden” was reduced with proton treatment.[137] Symptomatic radiation pneumonitis made up only a small portion of toxicities, with 3 of 72 patients treated with IMRT having grade 2 pneumonitis compared with 1 of 73 patients with proton beam therapy. However, the reduction in radiation dose to the heart and lung with protons also correlated with reduction in other pulmonary toxicities, including ARDS, pleural effusion, pneumonia, and need for re-intubation.

■ Breast Cancer

Breast cancer radiotherapy, whether after lumpectomy or after mastectomy, typically uses opposed tangential beams that irradiate a volume of lung anterolateral to a plane demarcating the midchest to the lateral axillary line. Standard fractionation to a dose of approximately 50 Gy in 25 fractions is recommended in some scenarios, and hypofractionation with approximately 40 to 42.5 Gy in 15 to 16 fractions or even shorter regimens in 5 fractions may be used in other scenarios. The volume of the ipsilateral lung irradiated can be estimated for individual patients from the simulator films and is typically about 20% of the ipsilateral lung volume. If the supraclavicular and axillary nodes are irradiated as well, the anterior treatment portals are matched to the tangential chest wall fields. As a result, the apex of the lung (roughly another 10%–15% of ipsilateral lung volume) also is irradiated. The incidence of symptomatic pneumonitis from tangential fields alone is roughly 0.5%, with some series documenting an increased risk with increasing lung volume.[59,138] It is desirable to keep the irradiated volume below approximately 25%, if possible. Nodal irradiation increases the risk for pneumonitis to 0.5% to 1.5%. Risk further increases to as high as 9% when chemotherapy is given concurrently. The risk of pneumonitis is much lower when chemotherapy and radiation are given sequentially.[59,138]

Techniques such as deep inspiration breath holding (DIBH) are frequently used to reduce the radiation dose to the heart and lungs in patients treated for breast cancer. The utility of this technique is demonstrated in Fig. 57-9. Figure 57-9A demonstrates the radiation treatment plan of a patient treated with 40 Gy in 15 fractions using DIBH technique. Figure 57-9B shows the same patient’s scan at the same axial level when the patient was breathing freely, with contours of the body, lungs, and heart in DIBH overlayed. In comparison with the DIBH technique, greater proportions of the heart and lung would be exposed to radiation.

■ Early-stage Hodgkin Disease

Radiotherapy for early-stage Hodgkin lymphoma, using moderate doses (40–45 Gy in 1.5- to 2-Gy fractions) and large volumes to treat lymph node-bearing regions, represented a remarkable success story in oncology. Because it produced very high cure rates in a young patient population, allowing for extended follow-up over several decades, this experience has also produced considerable data regarding late radiation toxicities.[139] In part due to these toxicities, the treatment paradigm has shifted toward combination chemotherapy and lower-dose/smaller-field radiation.

With the protocols that were historically employed, the chest is irradiated with treatment portals, generically called “mantle fields,”

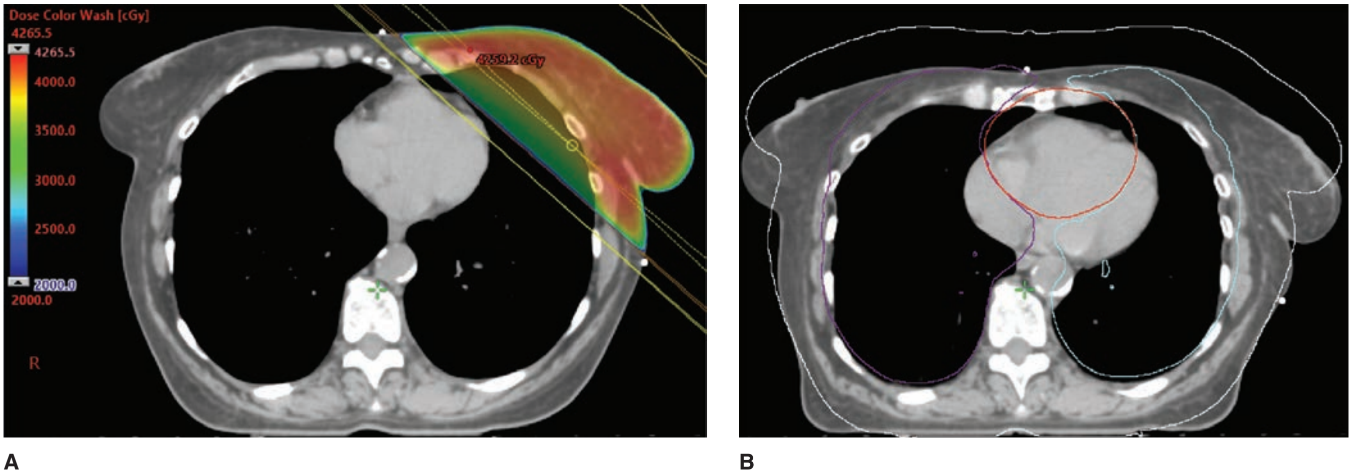


Figure 57-9 A 61-year-old woman with stage IA left sided breast cancer was treated with adjuvant radiation therapy to 40.05 Gy in 15 fractions to reduce the risk of recurrence. **A.** The radiation plan, which utilizes two opposed tangent beams matched posteriorly, is overlayed on her CT simulation scan, with doses above 20 Gy shown in color wash. The orange line next to the color wash represents the beam edge. Deep-inspiration-breath-hold (DIBH) technique was used to reduce heart dose. DIBH technique also reduces lung doses, but of note in this patient radiation dose to the lung is acceptable even without DIBH. **B.** The same patient also underwent CT simulation scan in free-breathing, which is displayed for comparison. Contours of the body (white), left lung (blue), right lung (purple), and heart (red) in the DIBH scan are drawn and demonstrate the increase in lung volumes seen with DIBH.

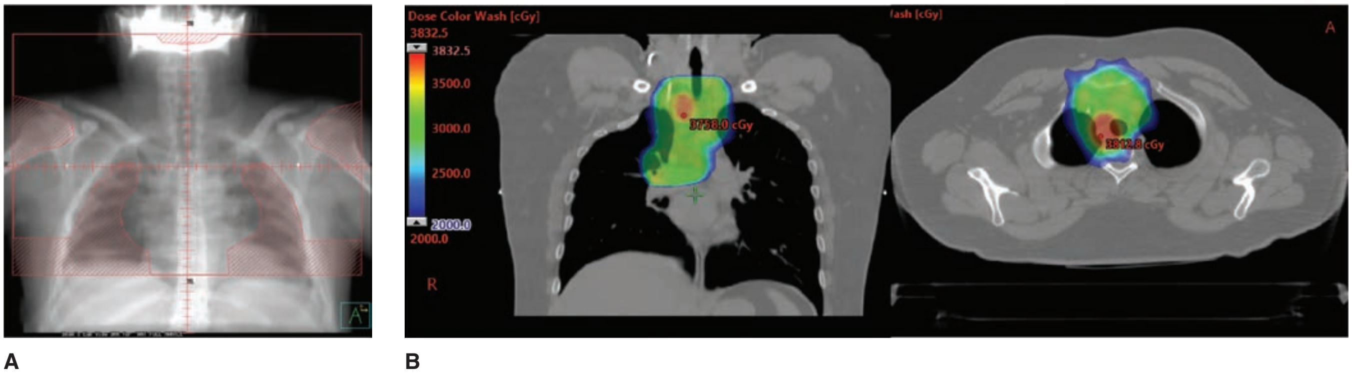


Figure 57-10 **A.** An example of a mantle radiation field shows broad inclusion of the lymph node regions above the diaphragm, with blocking of the lung and humeral head. **B.** In comparison, involved site radiation therapy only targets the specific location of disease. In this example, coronal and axial images are depicted of a treatment plan for a patient with Hodgkin's lymphoma involving the mediastinum, including a right paratracheal lymph node that did not have a complete response to chemotherapy. Involved site radiation depends on systemic therapy to treat subclinical disease in areas adjacent to the gross disease given the reduction in treatment volumes.

as depicted in Fig. 57-10A. With updated radiation techniques that used sequential shrinking fields, such as involved site radiotherapy (Fig. 57-10B), the incidence of symptomatic radiation pneumonitis was reduced to 3% to 4%.[140] The risk of pneumonitis was roughly 10% when full doses of both chemotherapy and radiation to a mantle field are given sequentially, even when bleomycin is not part of the regimen.

Studies on pulmonary function in patients with Hodgkin disease suggest that a transient reduction in FEV_1 and vital capacity, on the order of 5% to 20%, occurs 3 to 9 months after radiotherapy, corresponding to the period of pneumonitis.[141] There tends to be some recovery by about 1 year. Late follow-up of pulmonary function in patients with Hodgkin disease further suggests that mantle field radiotherapy is associated with small, and, for the most part, clinically insignificant, reductions in vital capacity and DL_{CO}.[139] These decreases in pulmonary function tests were associated with minor, if any, symptomatology, even for treatment regimens that included sequential chemotherapy with doxorubicin or bleomycin.

Primary radiotherapy for Hodgkin disease is now rarely practiced. Decades of follow-up in patients cured of their lymphomas show a steady increase in secondary cancers as well as cardiac complications. As a consequence, clinical trials have shown improved disease-free survival over 5 to 10 years with primary chemotherapy. Furthermore, rather than the larger volumes previously irradiated with mantle-field or involved-field radiation, improvements in imaging and treatment planning have allowed reduction of the treatment target volume to only the initially involved site of disease. In this setting, in which lower-dose (20–30 Gy) radiotherapy after chemotherapy is often delivered, the incidence of clinical pneumonitis is quite low. Longer-term follow-up of toxicities from combined-modality therapy in Hodgkin disease is in progress.

FUTURE DIRECTIONS

With improvements in technology, our understanding of the prediction and mitigation of radiation pneumonitis has improved significantly in the last several decades, and multiple new innovations are currently being pursued. Broadly speaking, reducing the risk of pneumonitis can be done by limiting radiation fields, improving patient selection and individual dose tolerance, or widening the therapeutic ratio through biologic innovations.

■ Improvements in the Accuracy and Precision of RT

Evolving radiation technologies have transformed the field over the last several decades. There should continue to be improvement in technologies that allow delivery of more conformal treatments, which may further reduce radiation toxicities for normal tissue. IMRT and volumetric arc therapy, which deliver radiation beams of varying intensity across multiple beams (or an infinite number of beam angles in the case of arc therapies) are now standard techniques in the radiotherapy clinic. Furthermore, daily image-guided radiation therapy is now standard of care, using CT or x-ray images obtained at the time of treatment to ensure that the patient has been set up properly.

Proton therapy is an evolving radiation treatment modality with expanding indications and improving accessibility. As discussed above, proton therapy offers a dosimetric advantage over photon radiotherapy due to the deposition of the majority of a proton's energy at the end of its path (resulting in the "Bragg peak"), and the sparing of dose to tissue beyond this point. Proton therapy has clear benefits in reducing radiation dose to organs-at-risk including the lungs, and in particular has generated excitement for thoracic targets outside of the lung, such as the esophagus or the mediastinum (e.g., mediastinal Hodgkin lymphoma). However, risks of pneumonitis for these patients are lower than when treating lung cancer, and the primary benefit of radiation is in reducing other treatment-related morbidities. In lung cancer, the role of proton therapy is not yet established but continues to be explored. A randomized trial at MD Anderson Cancer Center comparing IMRT to proton therapy (using the older technique of passive scatter rather than pencil beam scanning) for locally advanced NSCLC showed no difference in grade 3 radiation pneumonitis (protons 10.5% vs. IMRT 6.5%).[142] However, the authors noted that a large learning curve for proton treatment planning and delivery led to a decrease in symptomatic pneumonitis risk from 31% to 13% between the first and second halves of the study, demonstrating the promise of continued development of and experience with proton therapy.

Because lung tumors move significantly with respiratory motion, large margins were needed to ensure that a tumor was being appropriately treated. However, improvements in respiratory motion management have allowed for reduction in the margins needed from a lung tumor, and therefore reduction in normal lung dose targeted. Four-dimensional computed tomography (4D-CT) is now routinely used when performing CT simulation near the thorax and allows for visualization and accounting of a tumor's movement throughout a normal respiratory cycle. Reduction of treatment volumes can also be achieved by only treating during a certain part of the respiratory cycle. Known as respiratory gating, this can be performed by only delivering radiation when the tumor passes through a certain location or by using breath-hold techniques, in which a patient holds their breath at a particular point of the respiratory cycle during treatment. This requires real-time monitoring of the chest wall for respiratory motion, or the tumor itself. Real-time adaptive radiotherapy using MRI has been performed and shown to be feasible, although it is not widely available across radiation oncology centers.[143,144] Similarly, technologies that utilize real-time positron emission tomography to deliver radiation only to the current location of a tumor have been developed and are currently being clinically tested.[145]

Improvements in Patient Selection and Dose Reduction

With years of data from clinical trials, retrospective analyses, and animal studies, radiation oncologists today utilize the dose–volume parameters derived from an individual patient's anatomy, as well as the clinical risk factors in the patient's history, to estimate the risk of adverse events and weigh this against the probability of tumor control. However, a great amount of data is potentially available and unutilized in the prediction of radiation-induced lung injury, and ultimate optimization of an individual patient's treatment plan. For instance, studies of genetic predictors of radiation therapy have yielded multiple genetic risk factors including single-nucleotide polymorphisms in MTHFR,[46] ATM,[47] TGB-β1,[146] and HSPB1.[147] These associations are not strong enough on their own to guide dose modification. Future advances in computation and genetic sequencing may yield models accurate enough for the oncologist to utilize.

Additionally, advances in machine learning may allow for improved radiation pneumonitis modeling. Multiple different machine learning classification algorithms including random forest, support vector machines, and neural networks have been employed to analyze large amounts of clinical variables and model the risk of pneumonitis after treatment of lung cancer.[149] Radiomic prediction models on pretreatment CT scans have demonstrated some ability to predict outcomes in lung cancer patients including radiation pneumonitis.[150] Newer machine learning techniques such as deep learning, which utilizes layers of artificial neural networks to analyze data, have shown great potential in their ability to predict patient outcomes, and could potentially be utilized in the clinic to aid treatment decisions.

Ideally, machine learning and big data would form the basis of decision support tools that could be integrated into the clinic to aid personalized treatment decisions. While there is an enormous amount of data stored in electronic medical systems across the world, a lack of standardization in how data is collected and encoded complicates its full utilization. The ability to combine data across multiple health centers while also maintaining patient privacy will be critical in this endeavor.

Targeted Drugs and Biologic Innovations

Widening the therapeutic ratio by preferentially radiosensitizing tumor or protecting normal tissue from radiation with small molecules is an ongoing area of investigation, but attempts to reduce the risk of radiation pulmonary toxicity with systemic agents have thus far proved mostly unsuccessful. For instance, amifostine has been examined extensively because of its limited distribution into tumors and activity as a free radical scavenger, which results in a decrease in radiation cytotoxicity. Several small phase 3 trials in lung cancer suggested a benefit to amifostine during thoracic radiotherapy, with a decrease not only in pneumonitis, but also in radiation esophagitis as well.[150] However, a larger multi-institutional trial, RTOG 98-01, failed to document a difference in pneumonitis rates with amifostine,[151] and guidelines do not recommend its use for prevention of radiation toxicities. In a small trial of 40 patients randomized to pentoxifylline or placebo during radiotherapy for breast or lung cancer, there were significantly fewer patients in the pentoxifylline group that had grade 2 or 3 pulmonary toxicity (20% vs. 50%) and improvements in D_{LCO} with pentoxifylline, but this has yet to be reproduced in a larger cohort.[152] The angiotensin-converting enzyme (ACE) inhibitor captopril was shown to decrease radiation-induced pulmonary fibrosis in animal studies,[153,154] and retrospective series have shown a decrease in radiation pneumonitis associated with the incidental use of ACE inhibitors.[155,156] However, a randomized trial designed to test whether captopril mitigates radiation-induced pulmonary toxicity was unable to adequately accrue.[157]

Therapies that preferentially radiosensitize tumors have the potential to reduce the pneumonitis if the radiosensitizer allows radiation dose to be reduced. Several targeted agents like PARP inhibitors can sensitize thoracic tumors to radiation therapy, and clinical trials evaluating the use of these are ongoing. Caution should be exercised, however, as radiosensitizers may also sensitize normal tissue and increase risk of radiation pneumonitis, as has been seen with bevacizumab.[158]

FLASH radiotherapy has also generated recent excitement due to a potential to spare normal tissues from toxicity. This technique delivers radiation using extremely high dose rates, exceeding 40 Gy/s, and has been shown to preferentially spare normal tissue in animal studies, potentially due to rapid depletion of oxygen.[159] In mice treated with doses up to 30 Gy using FLASH or conventional dose rates, pulmonary fibrosis was found in 100% of animals irradiated with conventional dose rates and none with FLASH below 20 Gy.[160] Meanwhile, treatment efficacy against orthotopic lung tumors was similar between the two dose rates. A better understanding of the biological effects of FLASH and the technical challenges for its delivery will be required prior to human studies. Ultimately, well-designed, thoughtful clinical trials are necessary to establish the benefit of these potential innovations.

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CHAPTER 58

Pulmonary Manifestations of the Collagen Vascular Diseases

Kevin P. Toole
Gregory P. Cosgrove

INTRODUCTION

Pleuropulmonary involvement associated with the collagen vascular diseases occurs frequently. All the structures within the respiratory tract may be affected, either separately or in combination. This includes the respiratory muscles, the pleura, the conducting airways, and the lung parenchyma—the small airways, the interstitium, or the pulmonary vessels. Patients with underlying collagen vascular disease experience an increased incidence of community-acquired pneumonia, as well as pneumonia associated with the immunosuppressive drugs employed for treatment. Anti–tumor necrosis factor α (anti–TNF-α) agents increase the risk for infections, particularly typical and atypical mycobacterial pathogens (e.g., tuberculous and nontuberculous), *Pneumocystis jirovecii*, and *Nocardia* species. Cytotoxic drugs, particularly methotrexate and gold, also can induce various noninfectious interstitial reactions, which are often difficult to distinguish from a primary interstitial complication of a collagen vascular disease.[1]

Although most pulmonary complications appear in an established case of a collagen vascular disease, lung disease may precede the more typical systemic manifestations.[2] For example, in both rheumatoid arthritis and polymyositis–dermatomyositis, the interstitial lung disease may precede the joint and muscle disease by several months to several years. This is also the case, but to a lesser extent, for scleroderma. In one study, 19% of patients initially diagnosed with idiopathic pulmonary fibrosis developed a collagen vascular disease over a period of 1 to 11 years, primarily rheumatoid arthritis or polymyositis–dermatomyositis. These individuals were younger and more likely to be women. Pleuritis with or without effusion sometimes heralds the onset of rheumatoid arthritis or systemic lupus erythematosus (SLE). An acute immunologic pneumonitis or diffuse alveolar hemorrhage has been reported to be the initial disease manifestation in SLE, polymyositis–dermatomyositis, and mixed connective-tissue disease.

The incidence of the pleuropulmonary complications (Table 58-1) is variable. Interstitial lung disease is reported to be as high as 60% in premortem and 100% in postmortem studies in systemic sclerosis. In contrast, interstitial lung disease in ankylosing spondylitis is an uncommon event. In general, the incidence of interstitial lung disease is increasing for most of the collagen vascular diseases, primarily due to increased recognition and more sensitive screening techniques such as high-resolution computed tomography (HRCT) and bronchoalveolar lavage (BAL), which will detect abnormalities in both asymptomatic as well as symptomatic patients with normal chest radiographs. Prior studies assessing the incidence of disease relied on physiologic testing, which included spirometry, lung volumes, and diffusing capacity but did not measure rest and exercise gas exchange, which is the most sensitive physiologic marker of interstitial lung disease and pulmonary vascular disease.

TABLE 58-1 Pulmonary Complications of the Collagen Vascular Diseases

	Relative Frequency (0–4)						
Manifestation	SLE	RA	SS	PM-DM	MCTD	AS	Sjögren
Respiratory muscle dysfunction	2	1	0	2	1	0	0
Aspiration pneumonia	0	0	3	3	2	0	2
Primary pulmonary hypertension	2	1	4	1	2	0	0
Vasculitis	2	2	0	1	1	0	0
Interstitial lung disease	2	3	4	3	2	1	3
Capillaritis + DAH	2	1	1	1	1	0	0
Bland DAH	2	0	0	0	1	0	0
Diffuse alveolar damage	2	0	0	2	1	0	0
Nonspecific interstitial pneumonitis	2	3	3	3	3	0	1
Lymphocytic interstitial pneumonitis	1	2	1	0	0	0	3
Usual interstitial pneumonitis	2	3	2	2	2	1	1
Honeycomb lung	1	2	4	3	2	1	1
Bronchiolitis obliterans organizing pneumonia	1	3	1	3	2	0	1
Bronchiolitis	1	2	1	0	1	0	1
Obliterative bronchiolitis	0	2	0	0	0	0	1
Pleural effusion	2	3	1	0	2	0	1
Parenchymal nodules	0	2	0	0	0	0	1

SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; SS, systemic sclerosis (scleroderma); PM-DM, polymyositis-dermatomyositis; MCTD, mixed connective-tissue disease; AS, ankylosing spondylitis; Sjögren, Sjögren syndrome; DAH, diffuse alveolar hemorrhage.

PULMONARY PARENCHYMAL, VASCULAR, AND AIRWAY PATHOLOGY IN THE COLLAGEN VASCULAR DISEASES

The spectrum of pathologic changes in the lung parenchyma, pulmonary vasculature, and airways are considered below, prior to a discussion of clinical findings in individual collagen vascular diseases.

■ Interstitial Lung Disease

Interstitial involvement is a common manifestation of the collagen vascular disorders, presenting with a number of different inflammatory responses within the lung. Each response may represent a different form of lung injury or response to injury. Defining which response is underlying a patient's interstitial lung disease has important prognostic and therapeutic significance.

Diffuse alveolar damage (DAD) is the underlying histologic lesion that is also seen in the acute respiratory distress syndrome, idiopathic acute interstitial pneumonitis (Hamman–Rich syndrome), severe viral pneumonias, and cytotoxicity from some drugs. This damage consists of a mixed interstitial inflammatory infiltrate, interstitial edema and fibrin deposition, and characteristic intra-alveolar hyaline membrane formation. Intra-alveolar red blood cells (diffuse alveolar hemorrhage) may be present in severe cases. With progression, there is intra-alveolar organization, intra-alveolar and interstitial fibrosis, alveolar collapse, and the development of an end-stage fibrotic or "honeycomb" lung. An acute immunologic pneumonia, seen in SLE (acute lupus pneumonitis) and in polymyositis–dermatomyositis, may also demonstrate this underlying histologic appearance.

Nonspecific interstitial pneumonitis (NSIP) refers to a spectrum of histologic features with varying degrees of lymphoplasmacytic infiltration of the interstitium and collagen deposition (Fig. 58-1). In the cellular form, lymphoplasmacytic interstitial inflammation exists with associated type II alveolar epithelial cell hyperplasia. In the fibrosing form, the inflammation is accompanied by a temporally and spatially homogeneous deposition of collagen (fibrosis). Architectural distortion or honeycombing may occur in advanced cases, and the presence of fibrosis dramatically changes the clinical course and prognosis to one resembling that seen in usual interstitial pneumonitis (UIP) (see below). NSIP is most frequently seen in patients with rheumatoid arthritis, polymyositis–dermatomyositis, mixed connective-tissue disease, and scleroderma.

Lymphocytic interstitial pneumonitis refers to a monotonous infiltration of the interstitium by mature lymphocytes (Fig. 58-2). These lymphocytes tend to form germinal centers within the interstitium and to display an angiocentric distribution. Other features of lymphocytic interstitial pneumonia include macrophagic giant cells, granuloma formation, and amyloid deposition. Lymphocytic interstitial pneumonitis can progress to UIP and end-stage honeycomb lung. Among the collagen vascular diseases, this pneumonitis most commonly accompanies the primary form of Sjögren syndrome and, to a lesser extent, the secondary form of Sjögren syndrome appearing with other collagen vascular diseases, particularly rheumatoid arthritis.

Usual interstitial pneumonitis (UIP) is the pathologic lesion of idiopathic pulmonary fibrosis and can also appear in all the collagen vascular diseases. It consists of varying degrees of mononuclear cell infiltration and fibroblastic proliferation leading to collagen deposition within the alveolar interstitium (Fig. 58-3). With progression, this fibrotic reaction results in marked distortion of the lung architecture; what remains are 2- to 3-mm cystic spaces lined by metaplastic epithelium, the so-called honeycomb lung (Fig. 58-4). Other features of UIP include type II epithelial cell hyperplasia producing a "hob-nailed" appearance on the alveolar surface, collections of intra-alveolar macrophages, and smooth-muscle proliferation within the interstitium. Additional abnormalities seen in collagen vascular disease–associated UIP, but not in patients with idiopathic pulmonary fibrosis, may include focal chronic pleuritis, lymphoid follicles with germinal center formation, perivascular collagen deposition, and an increase in CD4+ T lymphocytes, especially in rheumatoid arthritis.

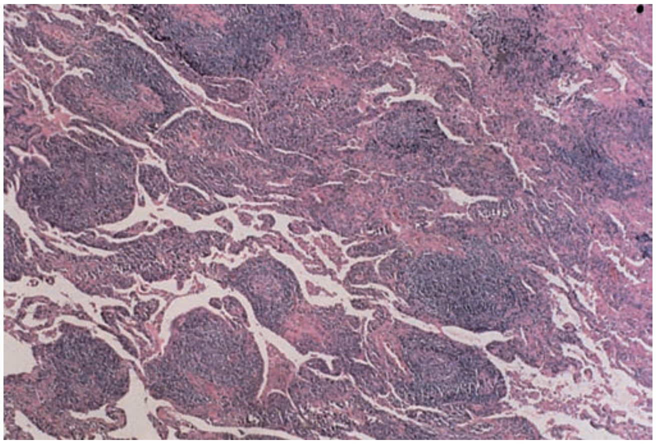


Figure 58-2 Lymphocytic interstitial pneumonitis in a patient with primary Sjögren syndrome. There is a dense lymphocytic infiltrate, broadening the interstitium and lymphoid follicles.

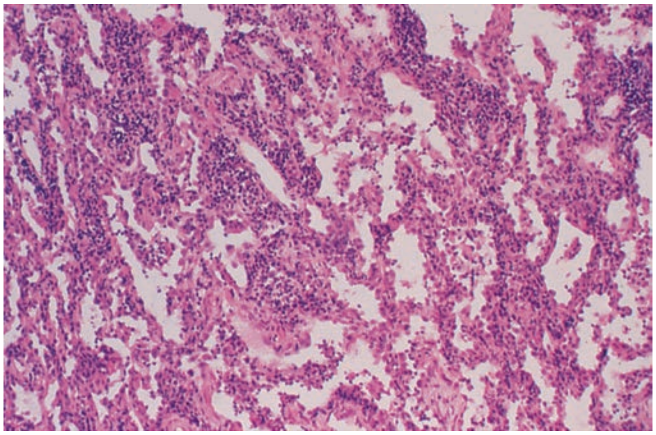


Figure 58-1 Nonspecific interstitial pneumonitis (NSIP) in rheumatoid arthritis. There is a lymphoplasmacytic infiltration of the interstitial compartment with minimal collagen deposition.

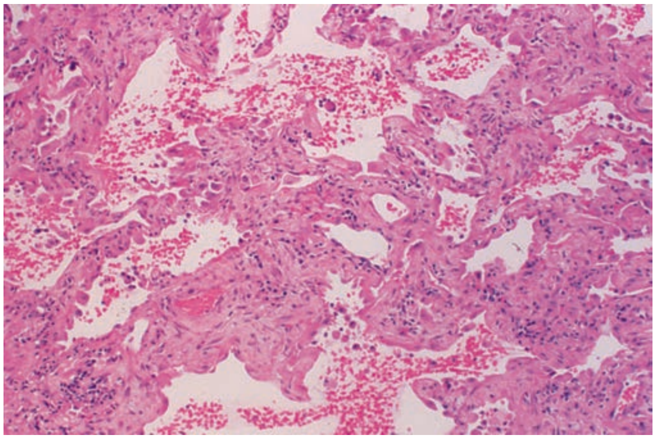


Figure 58-3 Usual interstitial pneumonia (UIP) in a patient with rheumatoid arthritis. There is broadening of the interstitium by varying degrees of mononuclear cell infiltration and collagen deposition.

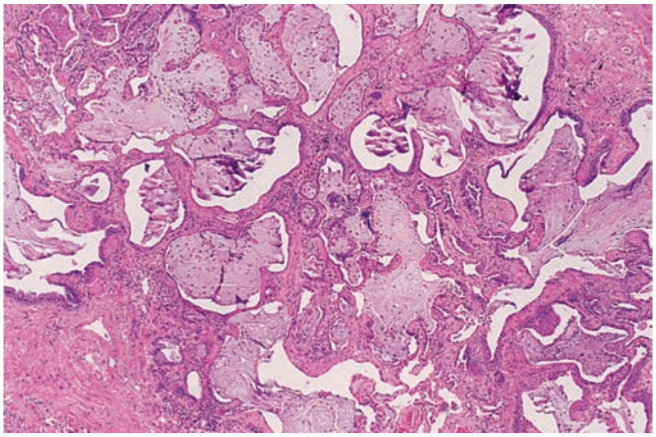


Figure 58-4 Advanced UIP in a patient with scleroderma (honeycomb lung). Normal alveolar tissue is replaced with broad bands of fibrous tissue lined by metaplastic epithelium and filled with inspissated mucus, producing a cyst-like network. *(Reproduced with permission from the Armed Forces Institute of Pathology [AFIP].)*

Organizing pneumonia, previously termed *bronchiolitis obliterans organizing pneumonia*, is a distinctive histologic lesion that follows a variety of insults to the alveolar structures including drugs, infection, radiation, and an idiopathic variety. Organizing pneumonia can also complicate the collagen vascular diseases, particularly rheumatoid arthritis and polymyositis–dermatomyositis. Three features constitute the histologic picture: (1) intra-alveolar space and intra-alveolar ductal fibroblastic proliferation with early collagen deposition (Masson bodies), (2) inflammatory polyps consisting of fibroblasts and mononuclear cells protruding into the lumens of respiratory and terminal bronchioles, and (3) alveolar septal lymphoplasmacytic infiltrate with type II pneumocyte hyperplasia within affected areas (Fig. 58-5). Organizing pneumonia has the potential for being a completely reversible lesion; however, with continuing injury it may progress to end-stage fibrosis and honeycomb lung.

■ Pulmonary Vascular Disease

A form of pulmonary artery hypertension, which most commonly appears in patients with scleroderma and is now being increasingly recognized in SLE, rheumatoid arthritis, and mixed connective-tissue disease, is histologically identical to the syndrome of idiopathic pulmonary artery hypertension (IPAH) seen in young women without collagen vascular disease, formerly known as primary pulmonary hypertension. Idiopathic and PAH associated with an underlying connective tissue disease are classified and grouped in Pulmonary Hypertension (PH) World Health Organization (WHO) Group 1 due to their similarities in pathophysiology, clinical presentation, and therapeutic options.[3] In patients with SLE and the antiphospholipid syndrome, pulmonary artery hypertension may also develop (WHO PH Group 4) due to chronic thromboembolic events and pulmonary artery obstruction.[4]

Vasculitis refers to an acute inflammatory angiodestructive process resulting in fibrinoid necrosis of the vascular wall. In the collagen vascular diseases, this is most often a small-vessel vasculitis involving arterioles and small muscular pulmonary arteries. Although uncommon, this is seen with greatest regularity in SLE and less frequently in rheumatoid arthritis, polymyositis–dermatomyositis, and mixed connective-tissue disease. Often accompanying the arteriolitis is the lesion of pulmonary capillaritis (see below).

■ Diffuse Alveolar Hemorrhage

Diffuse alveolar hemorrhage is recognized by the accumulation of red blood cells within the alveolar spaces, and with recurrent episodes, intra-alveolar and interstitial hemosiderin is deposited, and fibrosis may result. There are two different histologic subtypes seen in diffuse alveolar hemorrhage. One is devoid of inflammation and is referred to as *bland hemorrhage* (Fig. 58-6). It is therefore similar in histologic appearance to idiopathic pulmonary hemosiderosis. The other, pulmonary capillaritis, is a unique neutrophilic infiltration of the alveolar interstitium, which results in necrosis and loss of integrity of the alveolar–capillary basement membrane, capillary destruction and thrombosis, and a leakage of red blood cells into the alveolar space (Fig. 58-7). A unique feature in pulmonary capillaritis is that many of the infiltrating neutrophils are undergoing fragmentation (leukocytoclasis), and others appear as densely staining apoptotic cells. Nuclear debris ("dust") subsequently accumulates within the necrotic, edematous interstitium, and intra-alveolar compartments while red blood cells freely leak into the interstitial matrix due to capillary destruction. Capillary and arteriolar thrombosis, organizing pneumonia, and type II epithelial cell hyperplasia also may be seen.

Capillaritis is most commonly seen in the systemic vasculitides, particularly granulomatosis with polyangiitis (GPA, formerly known as Wegener granulomatosis) and microscopic polyangiitis (MPA),

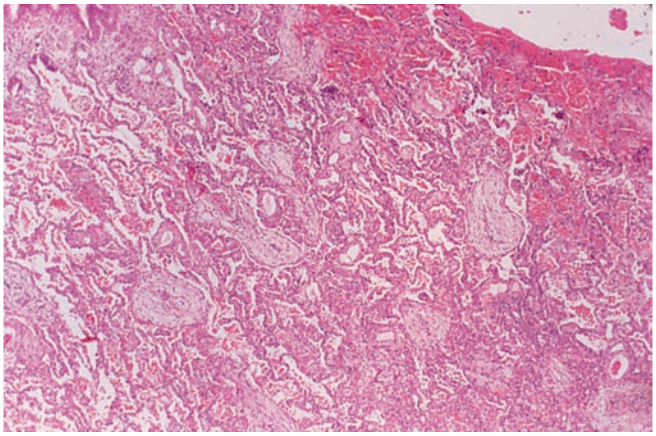


Figure 58-5 Bronchiolitis obliterans organizing pneumonia in a patient with rheumatoid arthritis. There is a mononuclear cellular infiltration of the interstitium without collagen deposition as well as alveolar duct and intra-alveolar fibroblastic proliferation and early collagen production.

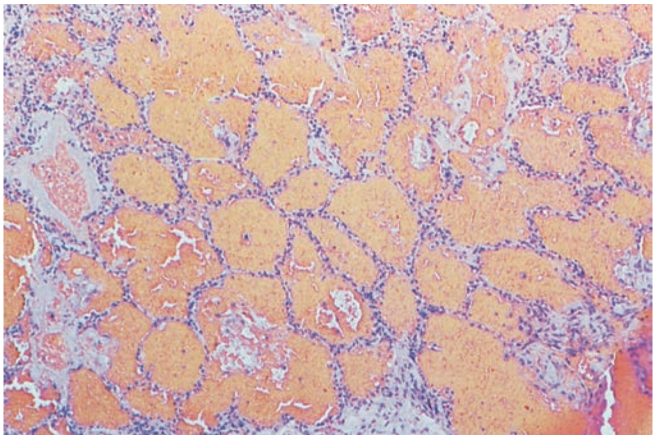


Figure 58-6 Bland diffuse alveolar hemorrhage in SLE. There is little if any interstitial reaction except for type II pneumocyte epithelial cell hyperplasia. The alveolar spaces are filled with red blood cells.

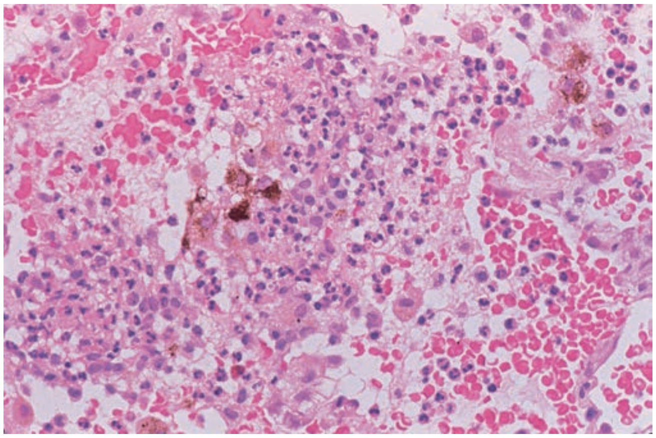


Figure 58-7 Low-power view of pulmonary capillaritis in a patient with SLE. There is marked thickening of the interstitial compartment and infiltration by acute and chronic inflammatory cells. The alveolar spaces are filled with red blood cells and neutrophils.

the small-vessel variant of polyarteritis nodosa. Of the collagen vascular diseases, both bland pulmonary hemorrhage and diffuse alveolar hemorrhage secondary to pulmonary capillaritis appear most commonly in SLE. Cases of pulmonary capillaritis have also been reported to occur in rheumatoid arthritis, Sjögren syndrome, polymyositis–dermatomyositis, and mixed connective-tissue disease.

■ Bronchiolitis

Bronchiolitis refers to an inflammatory-fibrotic process involving the terminal and respiratory bronchioles and possibly the surrounding alveolar structures. Respiratory bronchiolitis is primarily seen in smokers with or without an associated collagen vascular disease. There is also a primary form of cellular bronchiolitis that complicates the collagen vascular diseases, most often appearing in rheumatoid arthritis and Sjögren syndrome. Histologically, there is a mononuclear cell infiltration of the wall of the bronchiole without impingement of the bronchiolar lumen. In contrast, in bronchiolitis obliterans, or obliterative bronchiolitis, there is a concentric fibrous obliteration of the bronchiolar lumen leading to a severe obstructive lung disease (Fig. 58-8). Bronchiolitis obliterans is most often reported as a complication of rheumatoid arthritis.

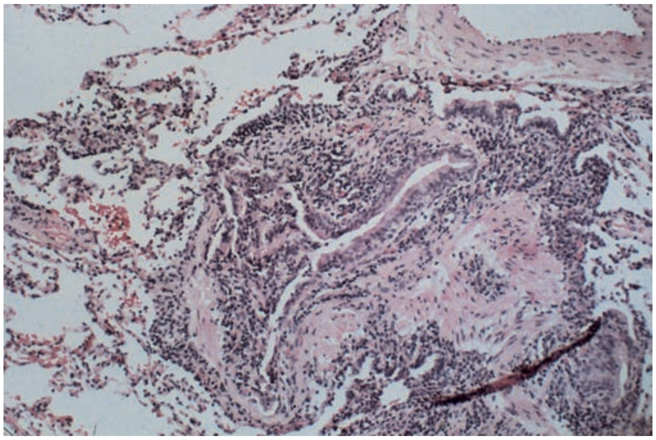


Figure 58-8 Obliterative bronchiolitis in rheumatoid arthritis. There is a marked reduction of the luminal diameter due to concentric fibrous obliteration and dense chronic inflammation. *(Reproduced with permission from Schwarz MI, Lynch DA, Tuder R. Bronchiolitis obliterans: The lone manifestation of rheumatoid arthritis. Eur Respir J. 1994;7(4):817–820.)*

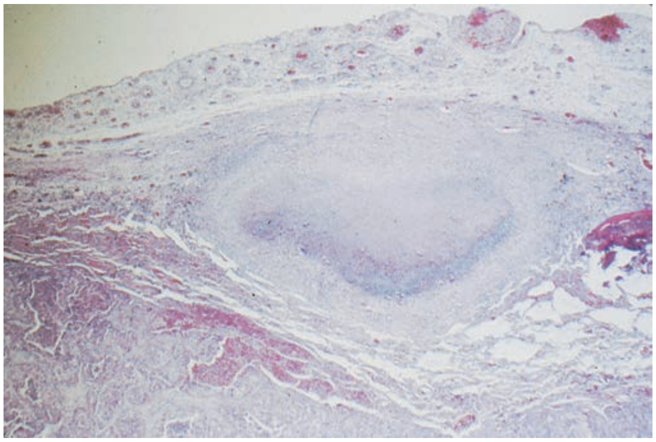


Figure 58-9 Typical subpleural location of a necrobiotic rheumatoid nodule. There is a central area of fibrinoid debris surrounded by palisading histiocytes.

■ Parenchymal Nodules

Noninfectious inflammatory parenchymal nodules occur in both rheumatoid arthritis and Sjögren's syndrome. In rheumatoid arthritis the nodules are referred to as the *necrobiotic* or *rheumatoid nodules*. These lesions are found both in the pleura and lung parenchyma and are identical in appearance to a subcutaneous rheumatoid nodule. In the lung parenchyma, these nodules are located in the interlobular septa and in the subpleural parenchyma. The necrobiotic nodule is comprised of palisading histiocytes, giant cells, and other mononuclear cells surrounding an area of fibrinoid debris (Fig. 58-9). In Sjögren syndrome, a rounded lesion known as pseudolymphoma can occasionally be detected on the chest radiograph. Pseudolymphoma is considered a localized form of lymphocytic interstitial pneumonia and is made up of a dense infiltrate of lymphocytes and histiocytes with occasional granuloma formation. There is a potential risk for malignant transformation in pseudolymphoma as well as in the other forms of lymphocytic interstitial pneumonia.

SYSTEMIC LUPUS ERYTHEMATOSUS: CLINICAL FEATURES

SLE is characterized by the production of antibodies against various cellular antigens derived from the nucleus, cytoplasm, or cell membrane. Tissue injury appears to be associated with the development of immune complexes, the presence of low serum complement levels, and the production of antibodies to native DNA. Pleuropulmonary involvement in SLE occurs in the vast majority of patients (97.8%), with pleuritis (77%), bacterial infections (58%), and diffuse alveolar hemorrhage (26%) being the most common.[5,6] Lung injury is thought to be the result of an immune complex–mediated injury and appears to increase in incidence depending on the age of the patient, duration of illness, pleuritis, and the presence of specific autoantibodies. Pulmonary vascular and shrinking lung syndrome appear to be associated with the development of the anti-RNP autoantibody.[7] A number of syndromes (Table 58-2) are associated with acute respiratory-type illness in SLE. Patients with SLE who present with a febrile illness, cough with or without productive sputum, and new pulmonary infiltrates must be considered to have an infectious pneumonia, although acute lupus pneumonitis and diffuse alveolar hemorrhage may have a similar presentation.[8] Infection can be community-acquired or a complication of immunosuppressive therapy. Infectious pneumonia represents the most common cause of pulmonary disease in SLE, and infections in

TABLE 58-2 Acute Lung Syndromes in Systemic Lupus Erythematosus

Community-acquired or immunocompromised pneumonia
Pleurisy
Pulmonary embolization
Uremic pneumonitis
Cardiogenic pulmonary edema
Acute reversible hypoxemia syndrome
Acute lupus pneumonitis
Diffuse alveolar hemorrhage

general represent the most common reason for death (33%–77%).[9] Bronchoalveolar lavage is often helpful in excluding an infectious pneumonia in the immunocompromised SLE patient.

Another important consideration in an acutely dyspneic patient with SLE is pulmonary embolism, a complication reportedly occurring in up to 25% of patients and a significant cause of mortality.[10] The occurrence of thromboembolic disease correlates with the presence in the serum of acquired antiphospholipid antibodies (lupus anticoagulant or anticardiolipin).[11] The most common epitope(s) to which antibodies exist in these patients is β_2-glycoprotein I. A more appropriate term may therefore be anti–β_2-glycoprotein syndrome. Up to a third of patients with SLE have the antiphospholipid syndrome. Thrombocytopenia, recurrent venous or arterial thrombosis, hemolytic anemia, leg ulcers, and recurrent fetal loss are also manifestations of antiphospholipid syndrome.

Other causes for acute respiratory failure in patients with SLE include a volume overload state, due either to renal failure or to congestive heart failure secondary to myocarditis. Uremic pneumonitis with underlying DAD is also a possible cause of an acutely dyspneic SLE patient with renal failure. A syndrome, *acute reversible hypoxemia*, occurring in acutely ill SLE patients who are experiencing systemic exacerbations has been described.[12] These patients have hypoxemia and a widened alveolar–arterial oxygen gradient, but both the chest radiograph and ventilation–perfusion lung scans are normal. It is postulated that there is complement-activated neutrophil aggregation in the pulmonary vasculature. The hypoxemia improves with immunosuppressive therapy. Given the high incidence of antiphospholipid syndrome in SLE, acute reversible hypoxemia should be considered only after excluding thromboembolic disease.

■ Acute Lupus Pneumonitis

Acute lupus pneumonitis is a clinical syndrome with an underlying histology of DAD, bronchiolitis obliterans organizing pneumonia, NSIP, or a combination of these different forms of lung injury.[13] Acute lupus pneumonitis mimics an acute infectious pneumonia and may be the presenting manifestation of SLE in up to 50% of patients. In those with an established diagnosis, it also appears during a flare-up of the other systemic manifestations of SLE, particularly pleuritis, pericarditis, arthritis, and nephritis. Acute lupus pneumonitis is reportedly more common in the postpartum period. It frequently recurs and cases have been documented that have progressed to a more chronic interstitial lung disease (UIP). Fortunately, acute lupus pneumonitis is a relatively uncommon complication, occurring in less than 5% of patients.

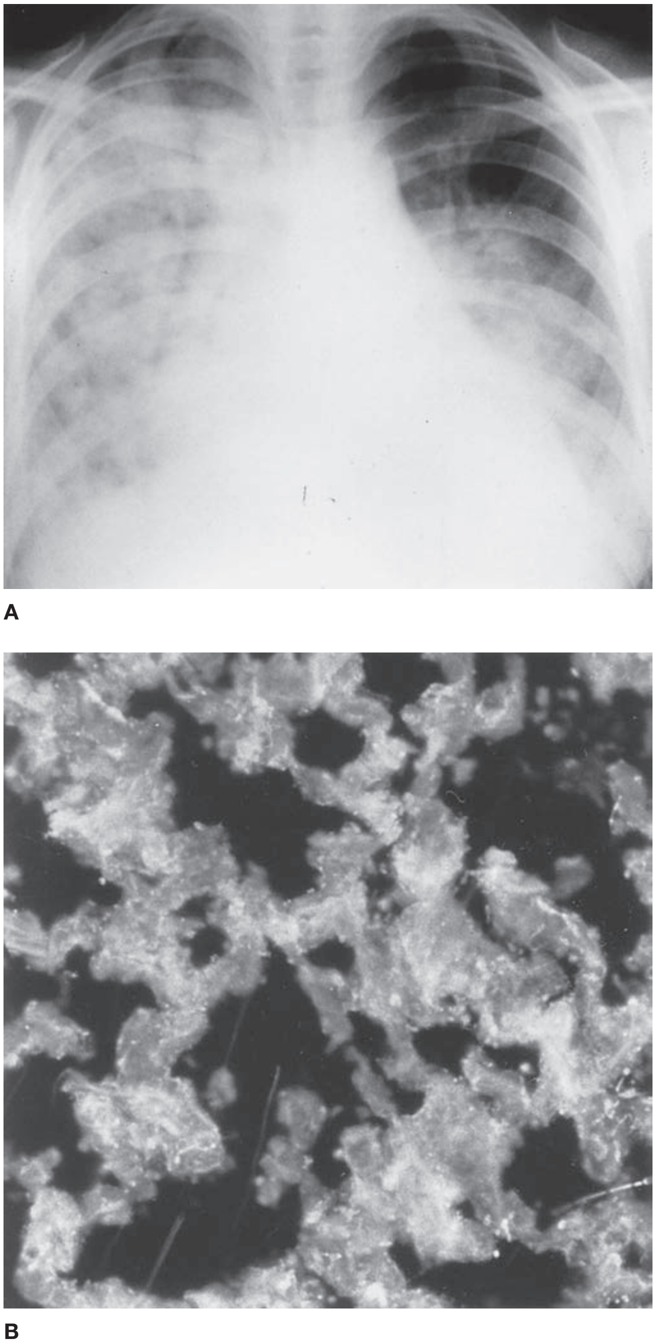


Figure 58-10 Acute lupus pneumonitis. **A.** The chest radiograph demonstrates diffuse alveolar filling with cardiomegaly (pericardial effusion vs. myocarditis). There is also a left pleural effusion. **B.** The immunofluorescent study demonstrates granular immune complex deposition in the alveolar interstitium.

Bilateral alveolar infiltrates, which can be patchy or densely consolidated and often accompanied by pleural effusions and cardiomegaly due to underlying pericardial effusion or myocarditis (Fig. 58-10A), are present on chest radiographs at presentation. White blood cell counts and sedimentation rates are elevated and serum complement is often low. Immunopathologic studies reveal the presence of complement as well as antibodies to IgG and DNA in some patients, supporting the concept of an immune complex pathogenesis (Fig. 58-10B). Because of the difficulty in distinguishing acute lupus pneumonitis from an infectious pneumonia, a bronchoalveolar lavage and sometimes an open (thoracoscopic) lung biopsy are indicated prior to instituting anti-inflammatory and immunosuppressive therapy. Acute respiratory failure in acute lupus pneumonitis often requires assisted mechanical ventilation. The mortality rate has been reported to be as high as 50%, with the causes of death in patients with acute lupus pneumonitis being respiratory failure, another complication of SLE (nephritis, cerebritis), or a superimposed infection.

■ Diffuse Alveolar Hemorrhage

Diffuse alveolar hemorrhage, although rare, may be a presenting manifestation of SLE. In several cases, recurrent diffuse alveolar hemorrhage was present for years prior to the diagnosis of SLE.[14] The majority of cases, in contrast to acute lupus pneumonitis, first appear in a well-documented case of SLE. Diffuse alveolar hemorrhage accounts for 1% to 4% of SLE-related hospitalizations.

Diffuse alveolar hemorrhage can also present with symptoms reminiscent of an infectious pneumonia or acute lupus pneumonitis, and the additional symptom of hemoptysis raises the possibility of this diagnosis. Hemoptysis is present in 30% to 50% of patients during their initial presentation, but up to 90% will have hemoptysis during their subsequent course. Routine laboratory work demonstrates a falling hematocrit, and in 60% to 90% of patients an active glomerulonephritis is present. A progressive serosanguineous bronchoalveolar lavage may be the first clue to this diagnosis. Diffuse alveolar infiltrates are present on chest radiography (Fig. 58-11), but in contrast to acute lupus pneumonitis, pleuritis and pericarditis are not prominent features. Pathologic changes that are reminiscent of both acute lupus pneumonitis (DAD and NSIP) and diffuse alveolar hemorrhage with or without pulmonary capillaritis are not unusual in a single biopsy specimen.[15] The mortality rate is approximately 50% and is independent of the underlying histopathology (bland hemorrhage vs. pulmonary capillaritis). Recurrent DAH is common and should be expected in the absence of therapeutic intervention.

There are no controlled clinical trials for the treatment of either acute lupus pneumonitis or diffuse alveolar hemorrhage. Once infection has been excluded, corticosteroids are the mainstay of therapy. Intravenous methylprednisolone, 1 to 2 g daily in divided doses for 3 to 4 days before tapering, should be considered. Concomitant oral or parenteral cyclophosphamide or azathioprine is commonly administered, given the associated incidence of lupus nephritis. Plasmapheresis, immunoglobulin therapy, and rituximab have been used successfully, consistent with the proposed immune complex pathogenesis.[16–19]

■ Lupus Pleuritis

Pleurisy and pleural effusion are the most common primary pulmonary complications of SLE, occurring in 50% to 80% of patients. Pleurisy and/or a pleural effusion may also be the presenting and sole manifestation of the disease. They are usually recurrent and may accompany more severe complications such as acute lupus pneumonitis or nephritis. Patients complain of pleuritic pain, fever, and dyspnea. The chest radiograph may be normal (dry pleurisy) or demonstrate small to moderate pleural effusions (massive effusions are rare), which are bilateral in 50% of patients. When unilateral, there is no predilection for either side.

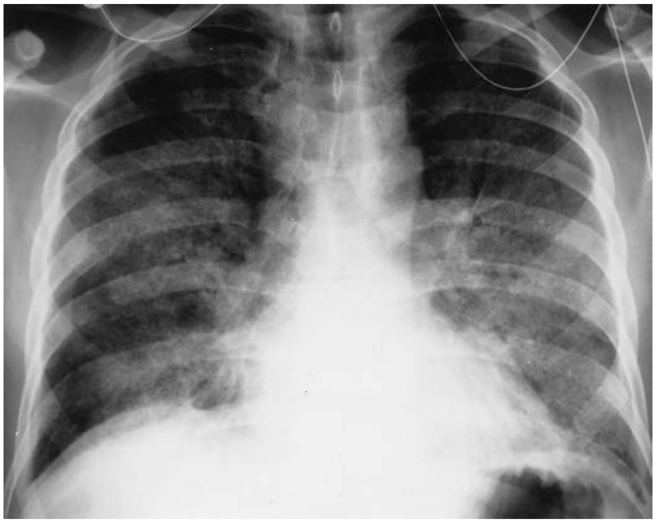


Figure 58-11 Diffuse alveolar hemorrhage in SLE. There are diffuse alveolar infiltrates without cardiomegaly or pleural effusions.

Effusions are serous or serosanguineous and exudative in nature. The white cell counts range from 5 to 10,000 cells/mm^3. Early on, neutrophils predominate, but with time mononuclear cells appear. These characteristics are nonspecific and are often seen with infectious parapneumonic effusions. In contrast to rheumatoid arthritis, the pleural fluid glucose concentration in lupus pleuritis is not reduced. Rheumatoid factor may be positive in lupus pleuritis. Pleural fluid complement levels are abnormally decreased in lupus, with both total complement activity and C3 and C4 reduced. A positive double-stranded pleural fluid DNA titer is nonspecific as opposed to the serum test since it has been found in pleural effusions due to malignancy and tuberculosis. The most helpful measurement is the pleural fluid antinuclear antibody titer. Levels greater than 1:160 are very suggestive of lupus pleuritis. Examination of the pleural tissue reveals infiltration with plasma cells and lymphocytes, and, with repeated episodes, pleural fibrosis supervenes. Occasionally, a vasculitis of the pleural vessels is detected, and immune complex deposition has been reported. Corticosteroid treatment is effective for relief of pleural pain, but time to resolution of the pleural effusion is quite variable and probably unaffected by this treatment. In the unusual case, recurrent lupus pleuritis may result in massive pleural fibrosis and lung entrapment, necessitating a pleural stripping procedure.

While pleural effusions and pleurisy are common in patients with SLE, a broad differential diagnosis should be considered. The increased incidence of infectious complications, thromboembolic disease, and pulmonary hypertension in SLE predisposes patients to parapneumonic effusions and empyema, congestive heart failure, and effusions secondary to thromboembolic disease.

■ Interstitial Lung Disease

Clinically significant interstitial lung disease is an uncommon pulmonary manifestation in SLE but UIP, lymphocytic interstitial pneumonitis, NSIP, and organizing pneumonia have all been reported. UIP is known to appear following acute lupus pneumonitis and in some cases has been documented to appear as an independent insidious disease. Using HRCT, 38% of patients with SLE patients with normal chest radiographs demonstrate pulmonary abnormalities consistent with some form of interstitial lung disease. In those who develop interstitial lung disease, a prior episode of acute lupus pneumonitis and an insidious onset of dyspnea are often noted. The prevalence of interstitial lung disease is increased in the subset of SLE patients with features suggestive of a mixed connective-tissue disease.

In patients who develop the insidious form of interstitial lung disease, the diagnosis of SLE is present for several years, and no other pattern of organ involvement predicts its appearance. These patients have progressive dyspnea and cough with interstitial infiltration on the chest radiograph. HRCT indicates combinations of ground-glass attenuation, inter- and intralobular septal thickening, and honeycomb change. Pulmonary function tests reveal a restrictive pattern with reduction in the diffusing capacity and hypoxemia accentuated by exercise. Response to therapy, either corticosteroids alone or in combination with cyclophosphamide or azathioprine, depends upon the underlying histology. Those cases with underlying NSIP or organizing pneumonia are more likely to respond to treatment than those who demonstrate excess collagen deposition and cystic honeycomb formation.

Pulmonary Vascular Disease

Pulmonary arterial hypertension, WHO Group 1, was previously thought to be an uncommon complication of SLE. It is now estimated to occur in 1% to 9% of patients.[20,21] This form of pulmonary hypertension is associated with Raynaud phenomenon, digital vasculitis, serositis, antibodies to ribonucleoprotein, rheumatoid factor, antiphospholipid antibodies, and most recently anti–endothelial cell antibodies. Patients complain of dyspnea and fatigue but have normal chest radiographs. In advanced cases, pulmonary arterial enlargement appears. Spirometry and lung volumes are normal, but there is often an isolated reduction of the diffusing capacity for carbon monoxide as well as gas exchange abnormalities. Ventilation–perfusion lung scanning and, occasionally, pulmonary arteriography are indicated, particularly in those patients with the antiphospholipid syndrome who have a potential for recurrent small pulmonary emboli. Therapeutic options include vasodilator therapy, anticoagulation, immunosuppression with cyclophosphamide, and transplantation.

Vasculitis in SLE is more likely to be discovered in lung biopsy specimens, demonstrating either diffuse alveolar hemorrhage or acute lupus pneumonitis as opposed to being an isolated finding. Autopsy series indicate small-vessel vasculitis in 20% of cases.

Airway Disease

Five percent of SLE patients are reported also to have obstructive physiology. Obliterative bronchiolitis has been documented in SLE but is rare in contrast to rheumatoid arthritis. Organizing pneumonia, with inflammatory polyps protruding into bronchiolar lumens, is one of the interstitial patterns that occurs in acute lupus pneumonitis and in chronic interstitial lung disease in SLE, but this entity causes restriction rather than obstructive lung disease. Bronchiectasis may occur in up 20% of patients but is often asymptomatic. Large airway involvement including tracheal and subglottic stenosis, vocal fold paralysis, epiglottitis, and necrotizing tracheitis have all been reported, but are rare.

Respiratory Muscle Dysfunction

It is estimated that weakness of the diaphragm and other respiratory muscles is found in 25% of patients with SLE. This accounts for the previously unexplained findings of dyspnea without evidence of interstitial or pulmonary vascular disease. These patients have subsegmental atelectasis, an elevated diaphragm on chest radiograph (Fig. 58-12), and restrictive physiology. This has been referred to as *unexplained dyspnea and shrinking lung syndrome.* Although there is a reduction in static lung volumes, the diffusing capacity, when corrected for alveolar volume, remains normal, thereby distinguishing respiratory muscle dysfunction from interstitial lung disease. The likely explanation for this is a reduction in the transdiaphragmatic pressure generated during maximal inspiration, which in turn reduces static lung compliance, producing the linear atelectasis seen on the chest radiograph. Moreover, in the patients with respiratory muscle weakness, no evidence for a generalized neuromuscular disease can be found. The pathogenesis of respiratory muscle dysfunction remains unexplained, although phrenic nerve conduction abnormalities have been excluded.[22] Abnormal diaphragmatic activation, due in part to voluntary inhibition due to pleuritic pain, may contribute to diaphragmatic dysfunction in this disorder. Clinical variables associated with the development of shrinking lung syndrome include pleuritis, double-stranded DNA antibody and RNP antibody seropositivity, serositis, and a prolonged course of SLE.[7] Corticosteroids are not a frequently effective treatment modality. Rituximab has been used successfully in the treatment of shrinking lung syndrome, albeit anecdotally in nature.[23] Progression is uncommon and most patients stabilize. Positive-pressure ventilation, particularly at night, may improve these patients' daytime symptoms, although there is limited evidence available. Rituximab has been used successfully in patients with respiratory muscle dysfunction with significant physiologic improvement.[23]

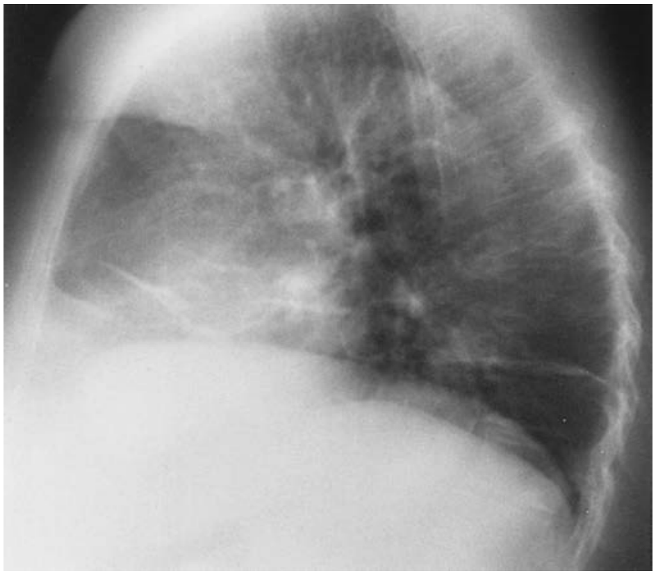


Figure 58-12 Diaphragmatic dysfunction in SLE. There is diaphragmatic elevation resulting in plate-like atelectasis.

RHEUMATOID ARTHRITIS: CLINICAL FEATURES

Rheumatoid arthritis classically affects the articular surfaces, but pleuropulmonary complications are responsible for significantly increased morbidity and mortality.[24] Most often cited is a 50% incidence for these complications, but it is likely that this underestimates their frequency.[25] Rheumatoid arthritis–associated interstitial lung disease abnormalities may be present in more than 60% of patients with RA and are clinically asymptomatic during the initial assessment.[26] In those that manifest symptoms—dry cough, chest pain, dyspnea, and others—the presence of RA-ILD, which approximates 10%, is associated with increased mortality.[27–29] Pleuropulmonary complications, including interstitial lung disease, are more apt to occur in patients with more severe chronic articular disease, with high titers of rheumatoid factor, and in patients who have subcutaneous nodules, as well as other systemic complications such as cutaneous vasculitis, myocarditis, pericarditis, ocular inflammation, and Felty syndrome.

An association between smoking and an increased risk for the development of pleuropulmonary disease, radiographic progression, and nodule formation in rheumatoid factor–seropositive patients has been reported. Several series suggest that in those patients with anti–citrullinated protein (CCP) antibodies there is an increase in parenchymal lung abnormalities, independent of current or prior tobacco exposure, supportive of the hypotheses that anti-CCPs are associated with ILD in RA and that high titers may correlate with the development of ILD.[30–32] Specific genetic factors, such as the MUC5B promoter variant rs35705950, also serve as increased risk factors for the development of RA-ILD.[33] Furthermore, elevated serum KL-6 levels have been identified as another possible risk factor, as studies performed on small groups of RA patients found elevated KL-6 levels in more than 88% of patients with active RA-ILD.[34] Additional biomarker signatures are being investigated and validated to identify patients with RA who are at risk of developing ILD and identify them earlier in their course.[35]

Pleuropulmonary disease may occur in seronegative patients, and both cytolytic and biologic therapies, commonly employed for treatment, can induce an interstitial lung disease that is often difficult to distinguish from the primary forms complicating rheumatoid arthritis.[36] Moreover, interstitial lung disease, pleuritis, and occasionally obliterative bronchiolitis may be the first and only manifestation of the rheumatoid state in up to 20% of patients, preceding the articular manifestations by months to years.

Several therapeutic agents have been suggested in literature, but the optimal treatment has yet to be recorded. These agents include immunosuppressive drugs, disease-modifying antirheumatic drugs (DMARDs), and biologic drugs. Corticosteroids are often the first line of therapy with secondary treatments soon to follow. Often cited secondary agents are methotrexate, rituximab, and TNF-α among others. Treatment is highly controversial and personalized due to the varied clinical, radiologic, and histologic spectra of RA-ILD and the risk of worsening symptoms. It is thought that early diagnosis and treatment of the disease greatly contributes to reduced morbidity and mortality.

■ Pleurisy and Pleural Effusion

In a postmortem series, pleural disease was found in 40% of patients with rheumatoid arthritis. The incidence of clinically apparent pleural disease is closer to 5%, and most patients experience mild symptoms. In approximately 20% of the patients who develop pleural complications, they do so prior to the onset of articular disease. In patients with rheumatoid arthritis, pleural complications are more common in men and occur most frequently during episodes of active articular disease and in patients with subcutaneous rheumatoid nodules.

Pleural disease is often first discovered on routine chest radiograph, and both pleural fibrosis and effusions have been reported to occur in otherwise asymptomatic patients. In one series using multidetector CT imaging, pleural thickening was noted in 49% of patients and did not correlate to the presence of symptoms.[37] Pleural effusions can be unilateral or bilateral and coexist with interstitial lung disease or necrobiotic nodules. Symptomatic patients present with pleuritic pain, dyspnea, and occasionally fever. The effusion is an exudate by protein and lactic dehydrogenase criteria, and, if chronic, cholesterol concentrations are increased. Other characteristics include a low pleural fluid pH (<7.2), thought to be due to enhanced glucose metabolism within the inflamed pleural space with resultant lactate and carbon dioxide production. The leukocyte counts can be as high as 15,000 cells/mm^3 and consist of a mixture of neutrophils and mononuclear leukocytes. As in SLE, the total and individual complement components are low, and the rheumatoid factor level is increased. The presence of rheumatoid factor in pleural fluid has also been reported with tuberculosis, malignancy, and other infectious diseases. A low pleural fluid glucose concentration, thought to be due to a defect in glucose transport, is characteristic of rheumatoid effusions. Up to 40% of patients have pleural fluid glucose levels less than 10 mg/dL, and 75% have levels under 50 mg/dL. It has been stated that cytologic examination of the pleural fluid, which demonstrates a background of necrotic debris, spindle-shaped macrophages, and multinucleated histiocytes, is characteristic of a rheumatoid effusion. Necrobiotic nodules are thought to be involved in the pathogenesis of the pleural effusions, but transthoracic pleural biopsy only occasionally will demonstrate this finding.

Treatment is not indicated for asymptomatic cases; however, corticosteroids, when used for active articular disease, are also effective in hastening the resolution of the pleural effusion. Rarely is any other form of intervention such as intrapleural corticosteroids necessary for these patients. In the unusual case, pleural fibrosis with resultant lung entrapment occurs, requiring surgical intervention. Spontaneous pneumothorax due to rupture of a necrobiotic nodule, another uncommon complication, necessitates tube thoracostomy, and with persistence of the bronchopleural fistula, surgical intervention is indicated.

■ Pulmonary Vascular Disease

In general, pulmonary vascular disease is the least common pleuropulmonary complication in rheumatoid arthritis. When it does occur, Raynaud phenomenon is commonly present. The chest radiograph reveals normal lung fields and enlarged pulmonary arteries, and there is an isolated reduction of the diffusing capacity for carbon monoxide as well as hypoxemia.

Small-vessel vasculitis in rheumatoid arthritis occurs in the setting of diffuse alveolar hemorrhage due to pulmonary capillaritis and is a very rare event in rheumatoid arthritis. Several cases have been well documented; in one, antineutrophilic cytoplasmic antibody to myeloperoxidase (p-ANCA) was present in the serum. Treatment with intravenous methylprednisolone, followed by oral corticosteroid preparations in addition to cyclophosphamide, is indicated for this complication. As noted with other systemic vasculitides, rituximab induces remission and reduces prednisone exposure in a significant proportion of patients with systemic rheumatoid vasculitis.[38]

■ Necrobiotic (Rheumatoid) Nodule

Radiographically visible parenchymal rheumatoid nodules are infrequently seen in a rheumatoid population (1%). If present, necrobiotic nodules are more common in men, particularly those who smoke, with active articular disease and high rheumatoid factors, and in those who have subcutaneous nodules. The nodules are primarily a radiographic finding, subpleural in distribution, and asymptomatic in most. Cavitation and rupture may occur rarely and are associated with pneumothorax, pleural effusions, and hemoptysis. Radiographically, the nodules can be single or multiple with upper- and midzone predilection, and approximately 50% will undergo cavitation due to the large amounts of proteolytic enzymes in these lesions. The size is variable, and nodules up to 7 cm have been reported. Spontaneous resolution and recurrence are to be expected. Continuous growth should prompt a more aggressive diagnostic approach. In most cases, no treatment is required. The major problem is differentiating the necrobiotic nodule from either malignant or infectious granulomatous disease, particularly given the increased risk of lung cancer in patients with RA.[39]

Caplan syndrome refers to a radiographic abnormality that developed in Welsh coal miners with rheumatoid arthritis and a pneumoconiosis.[40] It consists of the sudden appearance of discrete nodules primarily in the upper lobes that are histologically identical to the necrobiotic nodule (Fig. 58-13). The incidence of necrobiotic nodules is higher in rheumatoid patients with underlying pneumoconiosis, including coal workers' pneumoconiosis, silicosis, and asbestosis, than it is in a general rheumatoid population.

■ Airway Disease

Upper airway involvement by the rheumatoid process most commonly involves the cricoarytenoid joint, causing difficulty with inspiration and occasionally resulting in stridor. A sore throat, hoarseness, and globus sensation are other common complaints. The prevalence of this complication, although asymptomatic in most cases, approaches 50% when CT screening is employed. Clinically significant disease can be detected by performing flow–volume loops, which indicate a variable extrathoracic obstruction of the inspiratory loop. Cricoarytenoid arthritis may further complicate endotracheal intubation and should be considered in all patients with rheumatoid arthritis requiring general anesthesia.

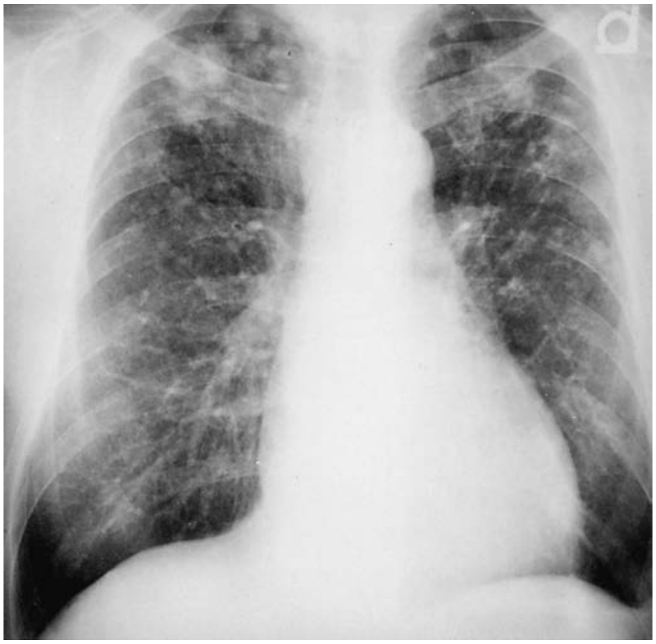


Figure 58-13 Caplan syndrome in a patient with rheumatoid arthritis and silicosis (hard-rock miner). There are multiple small nodules in the middle and upper lung representing the silicosis. In addition, multiple upper-zone rheumatoid nodules are present.

Bronchiolitis obliterans or obliterative bronchiolitis is a well-recognized cause of progressive and often severe obstructive lung disease in patients with rheumatoid arthritis.[41] The majority of patients develop bronchiolitis subsequent to the diagnosis of RA. Of note, bronchiolitis obliterans may be the initial manifestation of RA in a small group of patients.[42] This complication was first thought to be a consequence of either penicillamine or gold therapy, but many cases have appeared in the absence of either treatment. The onset of obliterative bronchiolitis is insidious, with patients complaining of progressive dyspnea and cough while having a normal or hyperinflated chest radiograph (Fig. 58-14A). It was thought that this complication was limited to women, but this is not the case. Physical examination reveals a generalized reduction of breath sounds and occasionally an inspiratory squeak. Physiologic testing reveals varying degrees of airflow limitation and hyperinflation, and the diffusing capacity may be normal or reduced. HRCT demonstrates adjacent areas of decreased and increased attenuation (geographic pattern), suggesting air trapping, which may be further identified by expiratory imaging (Fig. 58-14B). The response to therapy is generally poor. Some patients have responded to treatment with a combination of corticosteroids and cyclophosphamide, but most cases progress to hypercapnic respiratory failure.

Another form of bronchiolitis seen in RA is a respiratory or follicular bronchiolitis, consisting of a dense infiltration of lymphocytes and plasma cells surrounding the terminal and respiratory bronchioles. Cough and dyspnea are common symptoms. Chest radiographs may be normal or demonstrate a fine nodular pattern more predominant in the middle and lower lung zones. HRCT reveals a pattern of follicular bronchiolitis in up to 33% of patients with RA, demonstrating centrilobular nodules and bronchiectasis (Fig. 58-15).[37] There is usually no physiologic evidence for airflow limitation or reduced lung volumes, but rather gas exchange abnormalities dominate the physiologic picture. Treatment with corticosteroids yields variable results.

Diffuse panbronchiolitis has been reported in Japanese patients with RA. In both diffuse panbronchiolitis and rheumatoid arthritis, an association with HLADR4 and B54 haplotypes has been reported, suggesting a common genetic predisposition.[43,44]

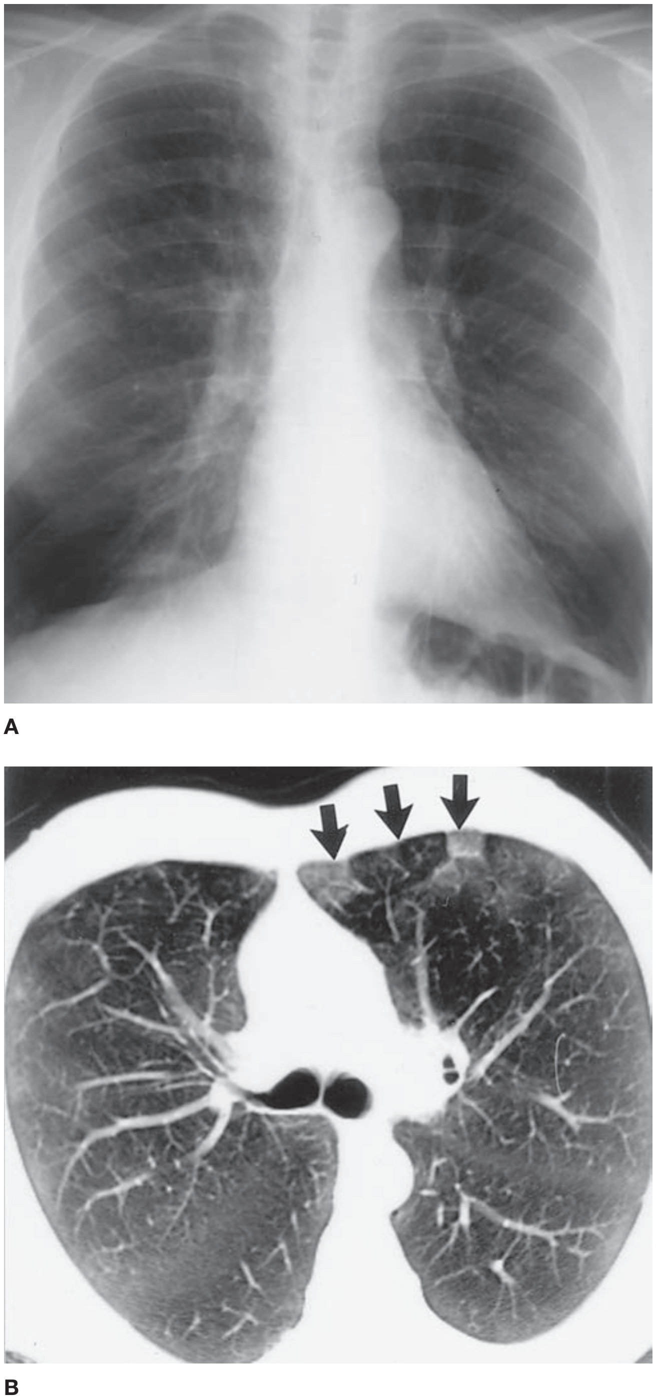


Figure 58-14 Obliterative bronchiolitis in a patient with rheumatoid arthritis. **A.** The chest radiograph is normal except for hyperinflation. **B.** HRCT demonstrating areas of increased and decreased attenuation *(arrows)*.

■ Interstitial Lung Disease

Interstitial lung disease is a relatively common complication in patients with rheumatoid arthritis. In contrast to most connective-tissue diseases, interstitial lung disease is more common in males than females (3:1), in individuals who have late-onset disease and high-titer rheumatoid factors, and in those who smoke. More recent series suggest that the presence and titer of anti–citrullinated protein antibodies are associated with ILD on HRCT imaging of

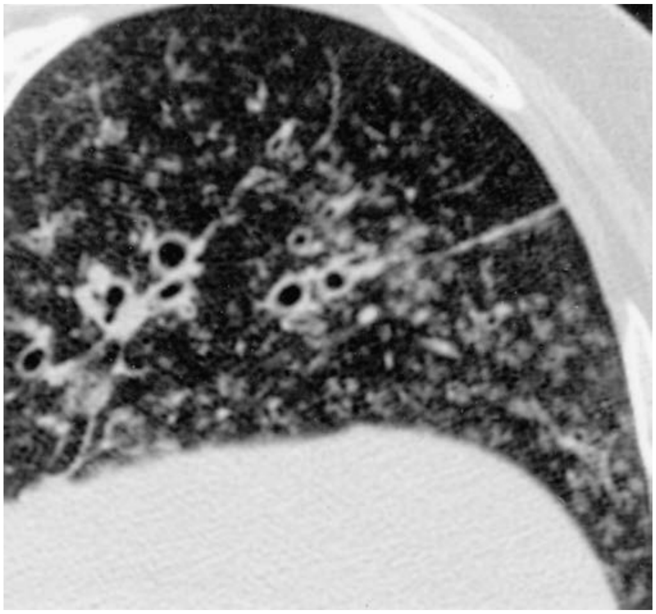
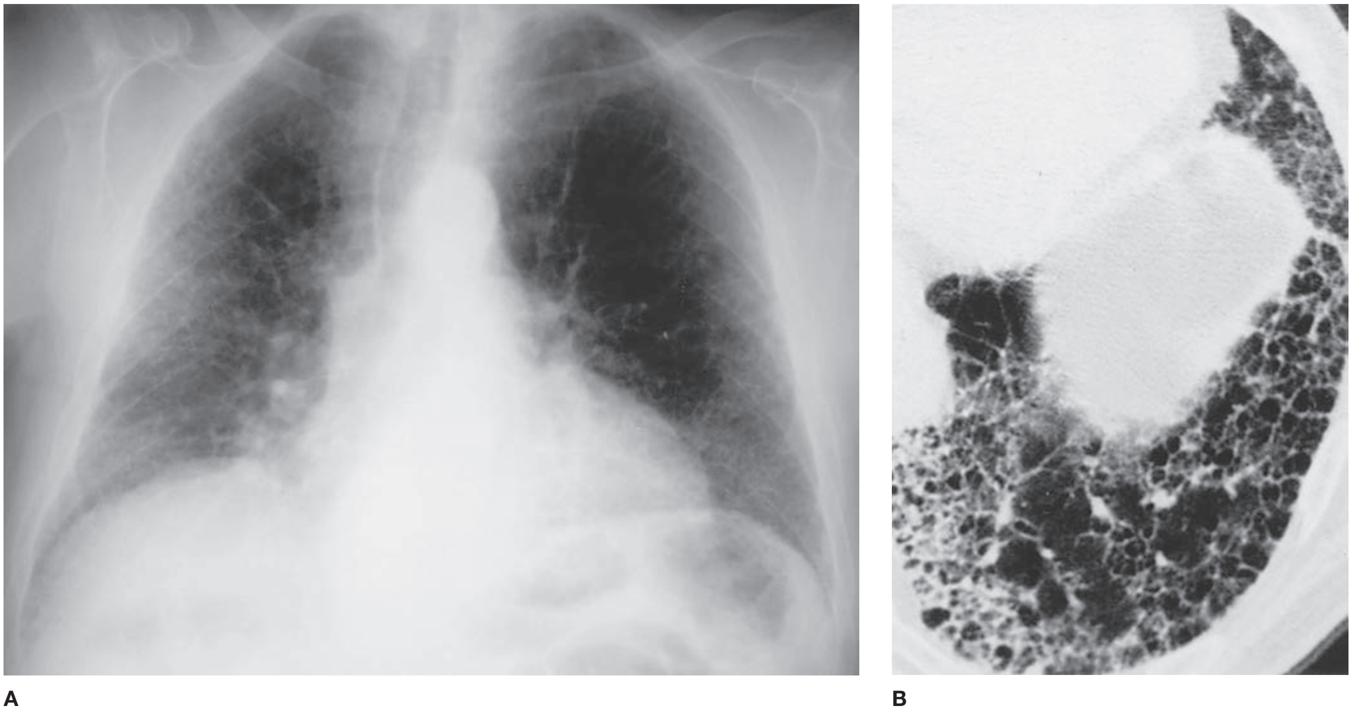


Figure 58-15 Follicular bronchiolitis in rheumatoid arthritis. HRCT demonstrating multiple centrilobular nodules.

the chest in patients with RA.[45] It is not unusual for interstitial lung disease to precede the articular manifestations for a period of months to years. The incidence of this complication in a rheumatoid population is difficult to determine, being reported in 5% to 40% of patients depending upon the methods of detection. The use of bronchoalveolar lavage indicating alveolar inflammation and HRCT scans indicating various interstitial changes, often in the face of a negative chest radiograph, are difficult to interpret. This is because follow-up studies determining whether these patients developed clinically apparent interstitial lung disease are lacking. Furthermore, some parenchymal changes described on CT such as bronchiectasis have very little, if any, clinical significance. It is likely that clinically important interstitial lung disease occurs in 5% to 10% of patients with rheumatoid arthritis, the most common forms being UIP followed by NSIP.[45,46] These patients are dyspneic and complain of cough. Physical examination reveals bibasilar crackles, clubbing of the digits, and evidence of cor pulmonale when pulmonary hypertension appears secondary to hypoxic vasoconstriction. The chest radiograph and CT scan demonstrate varying degrees of interstitial infiltrates with predilection for the lung bases and lung periphery (Fig. 58-16A). Other features include ground-glass attenuation on CT with mixed alveolar–interstitial infiltrates on chest radiograph indicating a component of NSIP. Both imaging studies in advanced disease reveal the presence of honeycomb lung (Fig. 58-16B).

Several other interstitial reactions, which produce subacute or chronic symptoms, complicate RA. The first is organizing pneumonia, which can present with symptoms identical to UIP and preempt the onset of the articular disease as well. The chest radiograph (Fig. 58-17) and CT scan differ from that seen in UIP because the infiltrates are primarily alveolar and localized, patchy, or diffuse. The second interstitial reaction is lymphocytic interstitial pneumonia, which occurs when RA is complicated by Sjögren syndrome. In addition to dyspnea and cough, these patients complain of dry mouth and eyes (xerophthalmia and xerostomia). The chest radiograph indicates patchy alveolar infiltrates primarily seen at the lung bases. In contrast to patients with primary Sjögren syndrome in which large cystic structures may develop within the lung, parenchymal cysts are uncommon in patients with RA-ILD. Eosinophilic pneumonia has been reported as a pleuroparenchymal complication of RA and may be the primary presentation of the disease. Acute interstitial pneumonitis is a rare, acute form of interstitial lung disease in RA. While it may occur as a result of an immunologic injury to the lung, medication-related pulmonary toxicity and opportunistic infections should be considered. Finally, fibrobullous disease, similar to that seen in ankylosing spondylitis, has been reported in RA and may precede the articular manifestations of the disease.



A

B

Figure 58-16 UIP in rheumatoid arthritis. **A.** Chest radiograph demonstrating lower zone and peripheral reticulonodular infiltrates. **B.** HRCT demonstrating a cystic network (honeycomb lung) at the lung base in a patient with advanced disease.

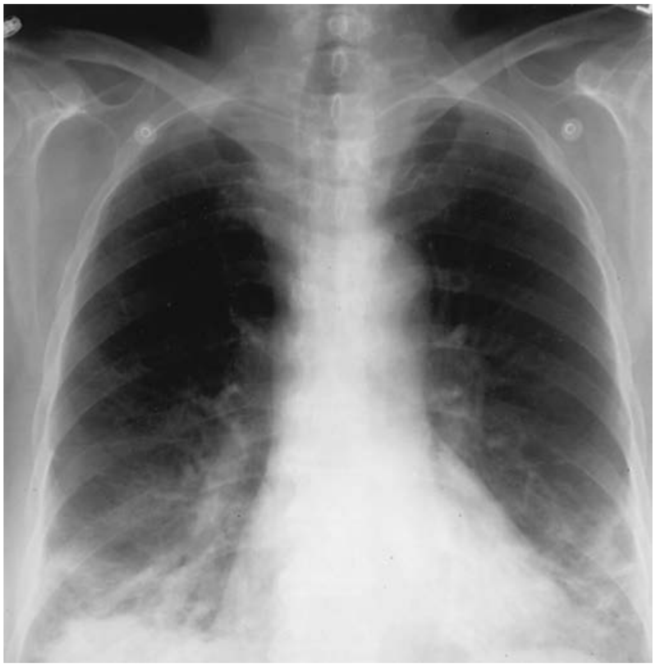


Figure 58-17 Organizing pneumonia in rheumatoid arthritis. Chest radiograph demonstrating lower-zone mixed alveolar-interstitial infiltrates.

It is important to establish the underlying histology since response to therapy and prognosis differs. Unless the imaging studies indicate end-stage honeycomb lung, which can also result from unresponsive or recurrent organizing pneumonia, lymphocytic interstitial pneumonia, or UIP, further evaluation is indicated. Bronchoalveolar lavage will not necessarily help differentiate between these three histologic pictures, but the finding of increased lymphocytic percentages as opposed to neutrophils and eosinophils indicates the potential for therapeutic responsiveness. Alveolar infiltrates and increased lymphocyte percentages are seen in lymphocytic interstitial pneumonitis. Organizing pneumonia is associated with increases in neutrophil, eosinophil, and lymphocyte percentages as well as radiographic alveolar infiltrates. The finding of increased neutrophil and eosinophil percentages in suspected underlying UIP is an indicator of poor prognosis. Therefore, patients with lymphocytic interstitial pneumonitis and organizing pneumonia are more treatment responsive when compared to those with UIP. If imaging studies and bronchoalveolar lavage cellular analysis are not definitive, thoracoscopic open lung biopsy should be considered. Treatment consists of a corticosteroid preparation and often the addition of cytotoxic drugs in the nonresponsive cases. As opposed to the idiopathic variety of organizing pneumonia, in which 66% of cases have favorable responses to corticosteroid medications, those associated with collagen vascular diseases are less responsive to treatment, often recur with tapering of the treatment regimen, and can progress to honeycomb lung. While the histopathology may be similar between RA and idiopathic pulmonary fibrosis, improved survival exists for those with rheumatoid arthritis–associated UIP but the long-term prognosis remains poor.[27,28,30,47]

Gold-induced pneumonitis must be differentiated from the primary forms of interstitial lung disease in patients with RA, particularly since the underlying histology can be similar, indicating varying degrees of NSIP and organizing pneumonia.[48] Dyspnea and cough usually begin 4 to 6 weeks following initiation of therapy, and peripheral eosinophilia occurs in a minority of cases. Occasionally, the chest radiograph will demonstrate upper- as opposed to lower-zone mixed alveolar interstitial infiltration. Bronchoalveolar lavage indicates a predominance of lymphocytes, and differentiation from rheumatoid interstitial lung disease can only be made after withdrawal of the drug results in remission. In severe cases with marked gas exchange abnormalities, corticosteroid therapy will occasion prompt reversal.

Methotrexate given in relatively low weekly doses (10–20 mg) is associated with the development of an interstitial disease in rheumatoid patients. No correlation with age, sex, duration of disease, or weekly or cumulative dose could be found. Conflicting data suggest that rheumatoid patients with underlying primary rheumatoid lung disease are predisposed to develop methotrexate pneumonitis. In rheumatoid patients treated with methotrexate, the incidence of methotrexate pneumonitis is 1% to 11%. The clinical onset is relatively acute with cough, fever, dyspnea, and new mixed alveolar and interstitial pulmonary infiltrates on chest radiograph. Increased white blood cell counts with mild eosinophilia, elevated sedimentation rates, and increased serum lactic dehydrogenase are nonspecific findings. Bronchoalveolar lavage indicates lymphocytosis and should be performed to rule out an infectious etiology. Lung tissue reveals an NSIP, organizing pneumonia, and granuloma formation reminiscent of a hypersensitivity pneumonitis. In patients who develop this clinical syndrome while on methotrexate, the drug should be discontinued since progression to end-stage fibrosis may occur. With life-threatening respiratory failure, corticosteroids given intravenously are an effective therapy.

The advent of TNF-α antagonists has revolutionized therapy for patients with RA. Their efficacy in the treatment of pleuroparenchymal complications remains unknown, with conflicting data having been reported. Of concern in those patients being treated with these agents should be the increased risk of infections, particularly both typical and atypical mycobacteria and fungi, as well as common bacterial pathogens. Several series suggest a temporal association between the use of TNF-α antagonists and the development of ILD. It remains unclear if the association is temporal or causative.[36,49–52] The compendium of therapies that have been evaluated for the treatment of RA has not been thoroughly evaluated to assess efficacy in the treatment of ILD. In those with a progressive fibrosing ILD (including RA-ILD) in the preceding 24 months, particularly with an underlying UIP radiographic pattern, nintedanib has been demonstrated to reduce the annual rate of decline of FVC compared to placebo.[53]

SYSTEMIC SCLEROSIS: CLINICAL FEATURES

Systemic sclerosis (scleroderma) is an inflammatory-fibrotic disease that results in deposition of excessive extracellular matrix in the skin and several visceral organs including the lungs, heart, kidneys, and gastrointestinal tract. Two subtypes of systemic sclerosis exist: diffuse cutaneous and limited cutaneous forms. In diffuse systemic sclerosis, extensive skin involvement of the extremities, face, and torso exists with accompanying marked visceral involvement that is progressive in nature. The limited cutaneous form, previously termed CREST variant (*c*alcinosis, *R*aynaud phenomenon, *e*sophageal dysmotility, *s*clerodactyly, and *t*elangiectasias), has a more protracted course in most patients and usually affects an older subset of patients. Pulmonary disease contributes significantly to both the morbidity and mortality of patients. The pathogenesis, although not well understood, involves a complex interaction among immune cells, endothelial cells, and fibroblasts. In addition to the excessive extracellular matrix, which in the lung results in interstitial fibrosis, endothelial cell damage with intimal thickening of pulmonary and systemic arteries occurs, leading to luminal obliteration. This may result in a form of pulmonary arterial hypertension (WHO Group 1).

The lung is involved in the great majority of cases of systemic sclerosis, with postmortem series indicating a 70% to 100% incidence.[54] Most patients with systemic sclerosis develop dyspnea during the course of their illness due to either interstitial lung disease or pulmonary hypertension. Both bronchoalveolar lavage and HRCT

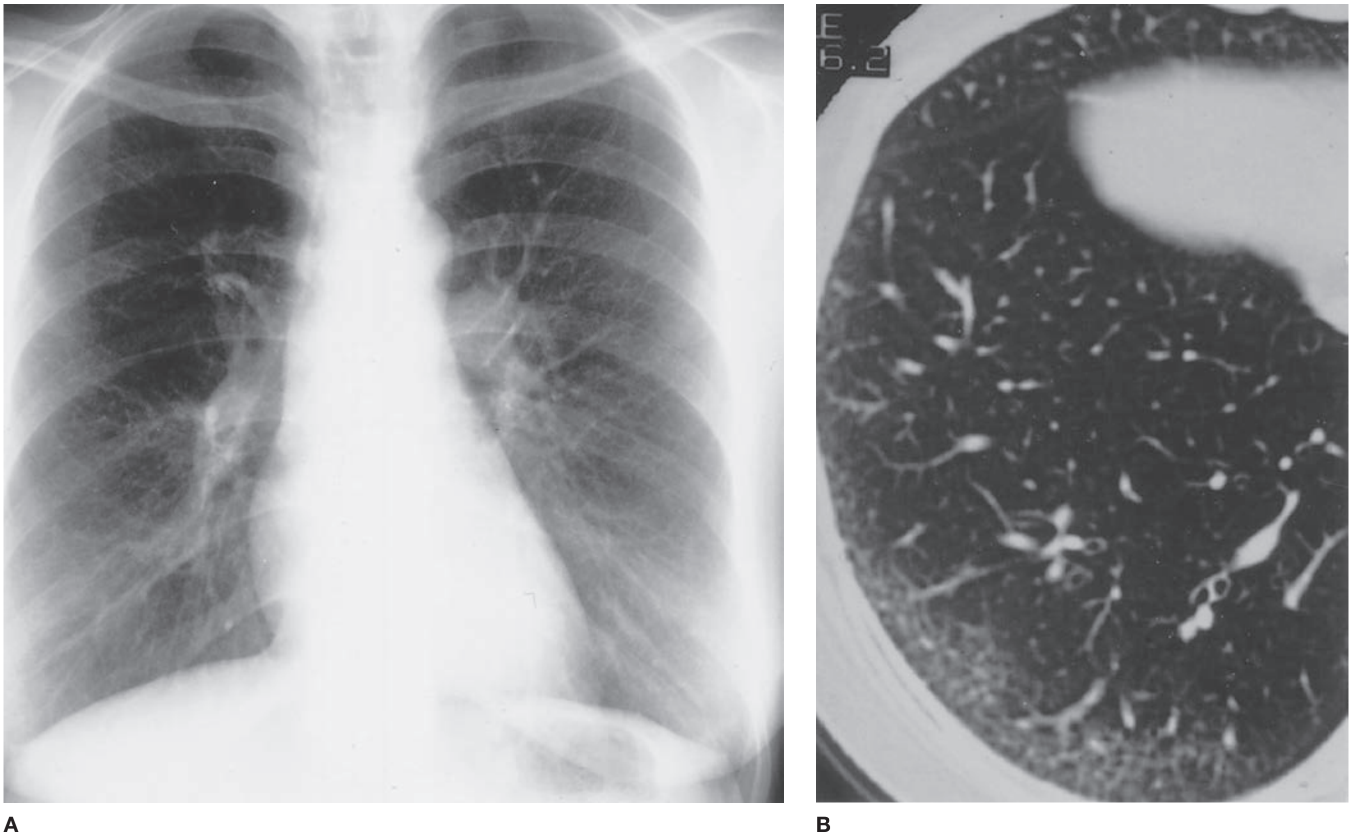


Figure 58-18 **A.** Normal chest radiograph in a dyspneic patient with scleroderma. **B.** HRCT of the same patient demonstrating reticular interstitial infiltrates.

scans, in the face of normal chest radiographs, have indicated interstitial lung disease in both symptomatic and asymptomatic patients (Fig. 58-18). Although unusual, interstitial lung disease and pulmonary hypertension have preceded the dermatologic manifestations, defined as systemic sclerosis sine scleroderma.[55] Despite the lack of skin involvement, the course in systemic sclerosis sine scleroderma does not significantly differ from the more common forms, with the exception of a greater tendency toward the development of pulmonary hypertension.

■ Pleural Disease

Although pleural fibrosis and adhesions are reported to be present in 40% of patients with scleroderma in postmortem studies, clinically apparent pleural thickening or pleural effusions on chest radiographs are considerably less frequent. The exception to this is pleural effusions secondary to congestive heart failure due to a systemic sclerosis–associated cardiomyopathy or cor pulmonale associated with pulmonary arterial hypertension.

■ Interstitial Lung Disease

Interstitial lung disease is the most common pulmonary complication of scleroderma, occurring in 30% to 100% of cases. An HRCT study indicated a greater than 90% incidence of this abnormality with up to two-thirds of patients having normal chest radiographs. As many as 60% of patients who undergo BAL will demonstrate an abnormal inflammatory cell distribution. Chest radiographic and physiologic screenings indicate somewhat lower prevalence. The significance of the BAL and CT findings remains unclear, since no longitudinal follow-up is available. Following the histologic reclassification of idiopathic interstitial pneumonias, the most common underlying histology in systemic sclerosis is NSIP with honeycomb lung. UIP, unclassifiable fibrosing interstitial lung disease, and rarely, organizing pneumonia and granulomatous lung disease resembling sarcoidosis also have been reported.[56] It was previously thought that interstitial lung disease in scleroderma was primarily a fibrotic disorder. However, recent information derived from HRCT demonstrating ground-glass attenuation, which indicates more cellular disease, BAL revealing increased inflammatory cell populations, and biopsy material demonstrating cellular infiltration of the interstitium indicates the presence of a cellular inflammatory response.[57] This predates the development of fibrosis, consistent with the cellular subtype of NSIP. It is likely that the inflammatory phase in most cases is clinically silent.

Interstitial lung disease is more likely to occur in diffuse systemic sclerosis, although it may also complicate limited systemic sclerosis, formerly referred to as the CREST syndrome. Dyspnea on exertion progressing to dyspnea at rest and cough are the predominant symptoms. Bibasilar crackles are heard, but clubbing is unusual due to the capillary destruction in the nail beds. Physical findings of cor pulmonale eventually appear. Bibasilar interstitial infiltrates followed by more diffuse changes, loss of lung volume, honeycomb cysts, and pulmonary hypertension are the typical radiographic features. Scleroderma was the first interstitial lung disease in which scar carcinoma (adenocarcinoma or alveolar cell carcinoma) was reported. Several reports suggest an increased incidence of lung neoplasms in patients with scleroderma.[58,59] Physiologic testing eventually reveals restrictive lung disease, preserved flow rates, and reduced diffusing capacity. Early on, the aforementioned measurements may be normal, and hypoxemia and a widened alveolar–arterial oxygen gradient at rest and heightened by exercise may be the only physiologic abnormality. A disproportionally greater reduction[60] of the diffusing capacity, when compared with lung volumes, most likely indicates the presence of pulmonary arterial hypertension, particularly in the limited cutaneous form of systemic sclerosis.

Other forms of interstitial lung disease seen in scleroderma include lymphocytic interstitial pneumonitis in those cases associated with Sjögren syndrome; rare cases of diffuse alveolar hemorrhage, and DAD in association with exacerbations of fibrotic lung disease in scleroderma have been reported.

Immunosuppression has been the mainstay of treatment, with corticosteroids and cyclophosphamide previously being the agents of choice. The NHLBI-sponsored Scleroderma Lung Study I confirmed prior retrospective studies suggesting improved lung function in those patients treated with cyclophosphamide. Although the improvement in lung function is of questionable clinical significance, a therapeutic effect is expected in those with ground-glass attenuation on HRCT imaging, a lymphocytic- or eosinophilic-predominant BAL, and a cellular interstitial pneumonia on lung biopsy.[61,62] Unfortunately, the durability of response to cyclophosphamide was limited, as the majority of physiologic benefit waned after 12 months of discontinuation of treatment.[63] In Scleroderma Lung Study II, treatment with mycophenolate mofetil for 24 months was associated with significant improvement in FVC percent predicted, quantitative lung fibrosis score, and patient-related outcomes (PROs). While there were no significant differences between cyclophosphamide and mycophenolate mofetil in terms of efficacy in SLS II, the tolerability and safety profile of mycophenolate mofetil is superior.[64] In a small, randomized, controlled trial, rituximab was reported to benefit patients with progressive disease in scleroderma with physiologic and radiographic improvement.[65] In an international, multicenter, randomized, placebo-controlled trial, nintedanib, which was originally approved for the treatment of idiopathic pulmonary fibrosis, reduced the annual rate of decline in FVC. No additional benefit for the nonpulmonary manifestations of systemic sclerosis was noted.[66] In a randomized, placebo-controlled trial of patients with systemic sclerosis with progressive skin disease and ILD, tocilizumab, a monoclonal antibody against the interleukin 6 (IL-6) receptor, preserved FVC at 48 weeks.[67]

Pulmonary Vascular Disease

Pulmonary arterial hypertension (WHO Group 1) occurs in approximately 10% of cases of systemic sclerosis and is primarily seen in the limited cutaneous form (CREST syndrome). In this form of systemic sclerosis, pulmonary arterial hypertension may coexist with interstitial lung disease. Patients present with a gradual onset of dyspnea and increasing fatigue. Physical examination and chest radiograph may initially be normal, and, with disease progression, physical and radiographic signs of pulmonary hypertension appear. Lung volumes and airflow parameters are maintained, unless there is concomitant interstitial lung disease. Typically, there is an isolated reduction in the diffusing capacity as well as progressive hypoxemia. Prior to the use of vasodilator therapy, the mean survival following a diagnosis of pulmonary arterial hypertension was approximately 2 years. Treatment with continuous intravenous prostacyclin, phosphodiesterase type 5 inhibitors, and endothelin antagonists have improved quality of life and exercise performance. Improved survival has been suggested with the use of these agents, specifically in those patients with isolated pulmonary arterial hypertension, in contrast to those with ILD-associated pulmonary hypertension.[68]

Aspiration Pneumonia

There is a high incidence of esophageal dilatation and decreased peristalsis (dysmotility) in patients with scleroderma, particularly in the limited variety (Fig. 58-19). This leads to dysphagia, heartburn, gastroesophageal reflux, and possibly aspiration with subsequent pneumonia.[69] It has long been held that reflux and aspiration contribute to the development of interstitial lung disease, albeit with a paucity of direct evidence.[70] In scleroderma, several different abnormalities contribute to the risk of reflux and aspiration: altered peristalsis, reduced lower esophageal pressure, presence of a hiatal hernia, gastroparesis, and autonomic nerve dysfunction.[71] Aggressive treatment to reduce the risk of reflux and aspiration is recommended despite inconclusive evidence to suggest an association. Behavioral modification and pharmacologic acid suppression are the initial interventions. In refractory situations, fundoplication may be considered in the appropriate patient, particularly in those with advanced lung fibrosis awaiting transplantation in an attempt to decrease the incidence of posttransplantation bronchiolitis obliterans and chronic rejection.[72–74]

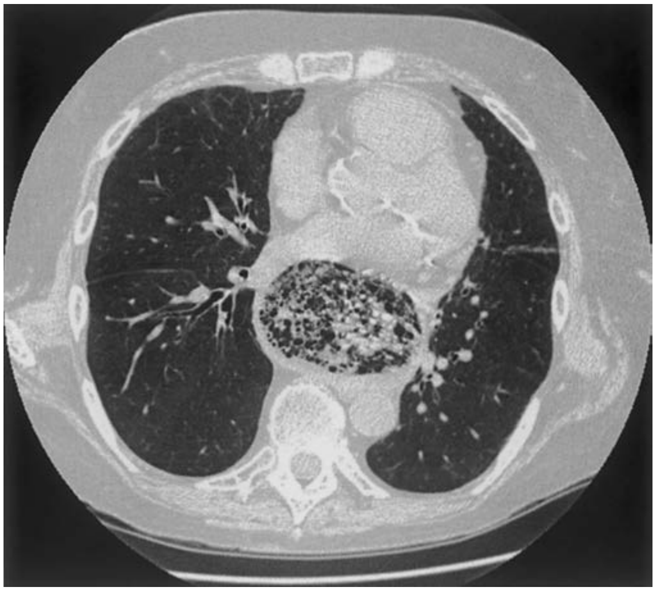


Figure 58-19 Mild peripheral, linear, ground-glass opacities in both lungs with marked thickening of the esophageal wall and severe dilatation of esophageal lumen with extensive debris filling the lumen in a patient with limited systemic sclerosis.

POLYMYOSITIS-DERMATOMYOSITIS: CLINICAL FEATURES

Polymyositis is a systemic autoimmune disorder characterized by an inflammatory myopathy. Dermatomyositis differs from polymyositis in that prominent skin involvement, characterized by a heliotropic rash and/or erythematosus scaling over the proximal interphalangeal joints, termed *Gottron papules* or *rash*, occurs with less severe myositis. In polymyositis–dermatomyositis, pulmonary complications are common and important causes of morbidity and mortality. As seen in other connective-tissue diseases, these complications often predate or overshadow the muscle or skin manifestations. Pulmonary involvement has been reported in up to 40% of cases.[75] In contrast to the other collagen vascular diseases, in polymyositis–dermatomyositis primary involvement of the airways and pleura do not routinely occur. Pulmonary arterial hypertension (WHO Group 1) has been reported on several occasions, most often in cases in which a crossover with scleroderma was suspected.

Aspiration Pneumonia

Aspiration pneumonia is a common pulmonary complication, occurring in 10% to 20% of patients with polymyositis–dermatomyositis; almost half of the patients complain of dysphagia as well. This complication results from an inflammatory myositis affecting the striated muscle of the hypopharynx and upper third of the esophagus. As a result, there is loss of normal swallowing function and failure to protect the airway. Aspiration is more likely in those patients with extensive skin or muscle involvement given the associated myositis.

Respiratory Muscle Dysfunction

Hypercapnic respiratory failure requiring assisted ventilation, due to extensive myositis involving the respiratory muscles and diaphragm, is an uncommon event (5% prevalence). In those patients presenting with unexplained hypercapnic respiratory failure, polymyositis–dermatomyositis as well as demyelinating neuromuscular disorders should be considered. With less extensive involvement of these muscles, however, there is a reduction in cough generation and the potential for the development of hypostatic pneumonia and atelectasis due to mucus plugging. Weakness can also cause a restricted physiologic defect with resulting tachypnea and dyspnea in the face of a normal diffusing capacity, normoxia, and hyperventilation. Respiratory muscle dysfunction as the cause of restrictive lung disease can best be demonstrated by measurement of the maximal pressure generated during both phases of the respiratory cycle. Sequential measurements are useful for monitoring the disease course and response to treatment.

Interstitial Lung Disease

The prevalence of interstitial lung disease in polymyositis–dermatomyositis ranges from 5% to 30%.[76,77] The incidence is significantly higher in certain populations. In Japan, it approached 40% to 80% in one series. As in the other collagen vascular diseases, the use of bronchoalveolar lavage and HRCT for screening increases the documented incidence. In those screened with HRCT imaging, the incidence approaches 78% within 3 years of diagnosis.[78]

Although UIP was previously reported to be the predominant histologic type of interstitial lung disease seen in polymyositis–dermatomyositis, NSIP with organizing pneumonia now appears to be most common, based on the revised classification system for idiopathic interstitial pneumonias. DAD, organizing pneumonia, and diffuse alveolar hemorrhage secondary to pulmonary capillaritis also may occur.[79] All forms of interstitial lung disease may precede, appear simultaneously with, or follow the muscle or skin manifestations. There is no relationship between interstitial lung disease and the extent of muscle or skin disease, the level of creatinine phosphokinase elevation, or the presence of serum rheumatoid factor or antinuclear antibodies. There is, however, a relationship between interstitial lung disease and a serum antibody directed against tRNA-synthetases, the most common of which is known as anti–Jo-1.[80] This antibody appears in 25% of patients with polymyositis–dermatomyositis in total, but in 50% of patients with interstitial lung disease and in 13% of patients without lung disease. Depending on which tRNA-synthetase antibody is present, different clinical phenotypes may occur with varying degrees of myositis and lung involvement.[81,82] Antinuclear antibodies are detected in up to 80% of patients. Different categories of autoantibodies may provide guidance into prognosis, potential organ involvement, or perhaps comorbid rheumatologic conditions. In several retrospective analyses, the presence of a (+) antimelanoma differentiation-associated gene 5 (anti-MDA5) was associated with a poorer prognosis compared with the anti–aminoacyl-tRNA synthetase (ARS) antibody-positive subjects (anti–Jo-1, anti–PL-12, OJ, EJ, PL-7, PL-12, KS, Zo, and Ha) or those without myositis-associated antibodies and ILD. Anti-MDA5 constitutes 30% of patients with dermatomyositis and is associated with a higher percentage of rapidly progressive patients and poorer 5-year survival (50%) despite treatment with immunosuppressive therapy. Myositis-specific autoantibodies, namely ARS, are associated with a more favorable response to immunosuppressive therapy (60%) and a 5-year survival of 97%. Patients with myositis-associated ILD without seropositivity were similar in their clinical course to the ARS group, with a 5-year survival of 91%.[83,84]

All forms of interstitial lung disease in polymyositis–dermatomyositis are more common in women. Several clinical syndromes occur and are associated with the underlying interstitial lung disease. The most common presentation is chronic cough and progressive dyspnea due to NSIP with varying degrees of fibrosis.[85] Digital clubbing is rarely seen. Chest radiographs demonstrate reticulonodular infiltrates, and with disease progression there is a reduction of the lung volume and the development of radiographic honeycomb lung and pulmonary hypertension. Physiologic testing indicates a restrictive pattern with a low diffusing capacity. Response to treatment depends upon the underlying histology, the more cellular disease being more responsive. In corticosteroid-resistant patients, cyclophosphamide, cyclosporine, tacrolimus, mycophenolate mofetil, intravenous immunoglobulins, and rituximab have been used with efficacy.[86]

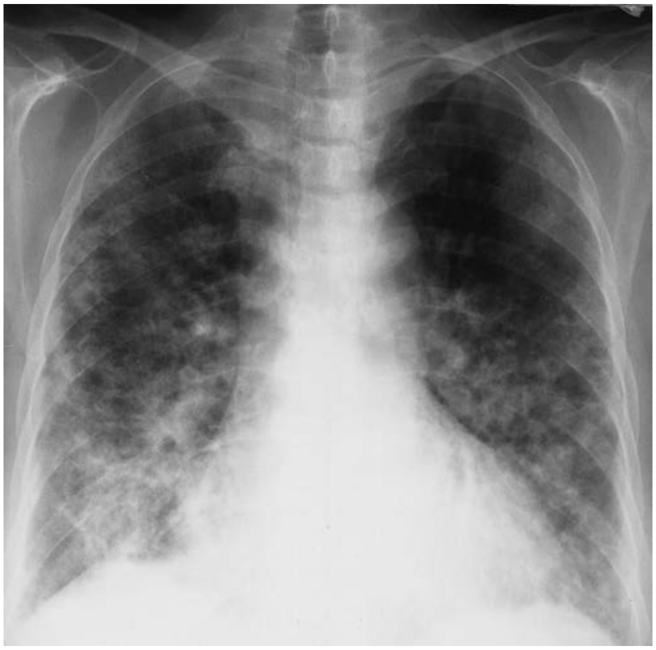


Figure 58-20 Organizing pneumonia in a patient with polymyositis–dermatomyositis and acute symptoms. Chest radiograph demonstrating diffuse patchy alveolar infiltrates.

In polymyositis–dermatomyositis, an acute pulmonary presentation with a clinical and radiographic picture reminiscent of a diffuse infectious pneumonia may occur and is associated with a poorer prognosis. The underlying lesion is DAD. Severe respiratory failure occurs, and recovery is unusual despite aggressive anti-inflammatory and immunosuppressive therapy. Organizing pneumonia may have either an acute or subacute presentation (Fig. 58-20). The differentiation from DAD becomes important because of the marked disparity in treatment outcome and survival. In organizing pneumonia, corticosteroid responsiveness with or without an additional agent is the rule rather than the exception. Diffuse alveolar hemorrhage due to pulmonary capillaritis also may occur.[87] This complication appears simultaneously with the onset of the muscle disease. Hemoptysis may or may not be present. As with other forms of pulmonary capillaritis, immunosuppression with corticosteroids and cyclophosphamide is utilized and been efficacious.

MIXED CONNECTIVE-TISSUE DISEASE: CLINICAL FEATURES

Patients with mixed connective-tissue disease have features of SLE, polymyositis–dermatomyositis, and scleroderma. Mixed connective-tissue disease is characterized by elevated titers of a specific antinuclear antibody directed against nuclear ribonucleoprotein (anti-RNP). Because of the similarity of mixed connective-tissue disease to the aforementioned collagen vascular diseases, pleuropulmonary complications are frequent, occurring in 20% to 80% of cases.[88,89]

Pleural Disease

Although pleurisy has been reported to occur in 40% of cases, pleural effusions are uncommon, appearing in approximately 5% of cases.[90] Effusions have been characterized as exudative in nature, but limited information is available in the literature.

Pulmonary Vascular Disease

Pulmonary hypertension may be caused by recurrent pulmonary emboli, hypoxic vasoconstriction secondary to interstitial lung disease, or plexogenic arteriopathy, as occurs in SLE and scleroderma. This is a significant problem for these patients; however, the incidence is unknown but may be less common than previously believed.[91] These patients, primarily women, present with dyspnea and fatigue. They have normal chest radiographs except for pulmonary arterial enlargement and an isolated reduction in the diffusing capacity for carbon monoxide. The prognosis in pulmonary hypertension secondary to mixed connective-tissue disease is similar to that noted in pulmonary hypertension seen in scleroderma and SLE. In contrast to patients without pulmonary arterial hypertension, 5-year survival is decreased from 96% to 73%.[92,93]

Medium-sized pulmonary artery vasculitis has been reported in mixed connective-tissue disease, with evidence suggesting immunologic-mediated injury with deposition (IgG, C_3) in the vascular walls. Circulating lupus anticoagulant (antiphospholipid syndrome) may also complicate the course of patients with mixed connective-tissue disease, predisposing them to thromboembolic disease.[94] It is in these patients that recurrent small pulmonary emboli may mimic the clinical picture of idiopathic pulmonary hypertension.

Aspiration Pneumonia

Patients with mixed connective-tissue disease, presenting with predominant features of scleroderma or polymyositis–dermatomyositis, are predisposed to esophageal dysmotility and dilatation, which can be a significant problem leading to reflux esophagitis and recurrent aspiration pneumonia. The presence of radiographic evidence of ILD closely associates with esophageal dilation and motor dysfunction, suggesting a common pathobiology.[95]

Respiratory Muscle Dysfunction

In those patients with features of polymyositis–dermatomyositis, an inflammatory myositis with respiratory muscle involvement may lead to hypercapnic respiratory failure or a restrictive lung disease with the development of hypostatic pneumonia.

Interstitial Lung Disease

The incidence of interstitial lung disease in mixed connective-tissue disease is increased in comparison to other collagen vascular diseases, with greater than 50% of patients having abnormal high-resolution CT imaging abnormalities.[96] The histologic pattern of NSIP and/or UIP are noted, both of which may progress to honeycomb lung, particularly in those patients with the features of scleroderma. As with the other connective-tissue diseases, this interstitial lung disease manifests as progressive dyspnea, bibasilar reticulonodular infiltrates on chest radiograph, and physiologic parameters with low lung volumes and a reduction in the diffusing capacity for carbon monoxide.

Diffuse alveolar hemorrhage has been reported in a few cases of mixed connective-tissue disease and is similar in presentation to that in SLE. It is assumed that the histology is one of either bland pulmonary hemorrhage or pulmonary capillaritis but remains unknown.[97]

SJÖGREN SYNDROME

Sjögren syndrome refers to a triad of xerophthalmia, xerostomia, and polyarthritis. This autoimmune exocrinopathy is characterized by lymphocytic infiltration of the lacrimal and salivary glands.[98] A primary form, occurring in the absence of another collagen vascular disease, and a secondary form, associated with one of the other collagen vascular diseases, most frequently RA, exist.[99] A strong female predominance exists in Sjögren syndrome (90%). A positive rheumatoid factor (95%) and antinuclear antibodies in a speckled pattern (80%) are to be expected, as well as positive tests for antibodies to extractable nuclear antigens (anti-SSA, anti-SSB), which are specific for the primary form of the syndrome.

Airway Disease

Lymphocytic infiltration and destruction of airway mucus glands result in desiccation of the tracheobronchial tree in Sjögren syndrome.[100] Patients may develop hoarseness, cough, inspissation of secretions resulting in luminal obstruction and atelectasis, recurrent pneumonias, and bronchiectasis. There is a high incidence of obstructive ventilatory dysfunction in these patients, secondary to follicular bronchiolitis. Obliterative bronchiolitis, constrictive bronchiolitis, and bronchiolectasis also have been reported.

Interstitial Lung Disease

In primary Sjögren syndrome, patients present with a nonproductive cough, dyspnea on exertion, or asymptomatic radiographic abnormalities. As occurs in the lacrimal and salivary glands, interstitial lung disease in these patients is the result of lymphocytic infiltration of the lung parenchyma. This occurs in two forms, lymphocytic interstitial pneumonitis and, less commonly, pseudolymphoma. Both lesions have the potential for lymphomatous conversion. Lymphocytic interstitial pneumonitis is an interstitial lung disease in which cough, dyspnea, and restrictive physiology manifest. Because lymphocytes may also infiltrate the alveolar spaces as well as the interstitium, the radiologic studies indicate mixed alveolar and interstitial infiltrates. In a subset of patients, variably sized cystic lesions with associated ground glass may be the only radiographic abnormality (Fig. 58-21). The development of pleural effusions or the appearance of hilar or mediastinal adenopathy should be investigated further, as it may suggest a malignant transformation to a lymphoma. Lymphocytic interstitial

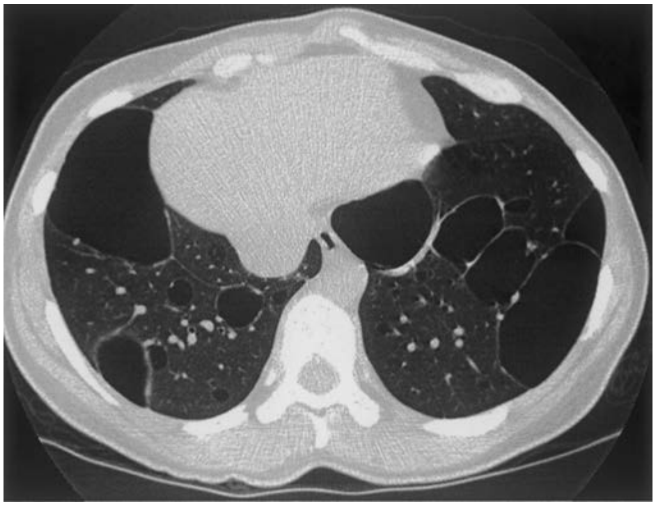


Figure 58-21 Multiple cysts of varying sizes scattered throughout both lungs in a patient with Sjögren syndrome and lymphocytic interstitial pneumonia.

pneumonia is responsive to anti-inflammatory agents such as corticosteroids. Occasionally, cytolytic therapy, such as azathioprine or cyclophosphamide, is required but remains of unproven benefit. Cyclosporine has also been recommended as an additional agent in corticosteroid-resistant cases. Rituximab, an anti-CD20 monoclonal antibody, may be beneficial in selected patients but further controlled studies are required to better assess its efficacy in primary Sjögren syndrome.[101] While the majority of patients will respond to immunosuppressive therapy, a subset of patients progress to fibrotic lung disease with honeycomb change.

Pseudolymphoma is a tumor-like proliferation appearing as single or multiple masses on the chest radiograph. It is often difficult to distinguish from a malignant lymphoma, and it has been suggested that pseudolymphoma, which is considered to be a localized form of lymphocytic interstitial pneumonitis, is a premalignant lesion.[102] When associated with a monoclonal gammopathy, malignant transformation to lymphoma is suggested.[103]

Interstitial lung disease occurs more commonly in the secondary forms of Sjögren syndrome and most likely represents a complication of the associated collagen vascular disease.[2] The histologic pattern in secondary Sjögren syndrome mimics that seen in rheumatoid arthritis, with NSIP, UIP, and organizing pneumonia reported. UIP is uncommon in the primary form of Sjögren syndrome.

ANKYLOSING SPONDYLITIS

Ankylosing spondylitis is one of the seronegative spondyloarthropathies that may eventually result in fixation of the chest wall and a mild to moderate restrictive lung disease. Muscular involvement, in contrast to polymyositis–dermatomyositis, does not occur and diaphragmatic function is preserved, limiting ventilatory failure given the preserved respiratory muscle function.

The incidence of interstitial lung disease complication is reportedly less than 2%.[104] In contrast to the other collagen vascular diseases that primarily affect the basilar portion of the lung, ankylosing spondylitis has a predilection for the upper lung zones, only appears late in the course of the chronic spondylitis, and never precedes it.[105] Interstitial lung disease often appears as fibrocystic disease on the chest radiograph (Fig. 58-22) and is difficult to distinguish from apical lung infections such as tuberculosis. Histologically, it is a fibrosing process with cystic formation. Progressive dyspnea and cough are the predominant symptoms, and treatment with corticosteroids is ineffective and therefore not suggested. Etanercept may afford patient a short-term benefit with improvements in spinal mobility and pulmonary physiology.[106] The most serious complication of this apical fibrocystic disease is infection with invasive *Aspergillus* species as well as atypical mycobacteria. Further, saprophytic colonization of the cysts by *Aspergillus* species (aspergilloma) may induce life-threatening hemoptysis.

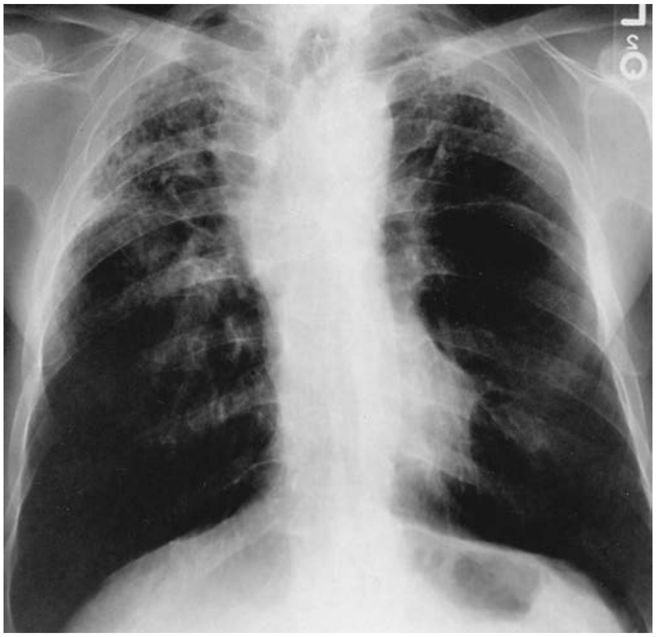


Figure 58-22 Ankylosing spondylitis. Chest radiograph demonstrating bilateral upper-zone fibronodular infiltrates.

INTERSTITIAL PNEUMONIA WITH AUTOIMMUNE FEATURES

Autoimmune signs or symptoms occur in a significant proportion of patients diagnosed with an idiopathic interstitial pneumonia but fail to meet established diagnostic criteria for a specific connective tissue disease. Interstitial lung disease may be the forme fruste of an underlying connective tissue disease by months or even years. A European Respiratory Society/American Thoracic Society Task Force established research criteria to better define this challenging clinical situation, termed *interstitial pneumonia with autoimmune features (IPAF)*.[107] Three distinct clinical domains were delineated: (1) specific extrathoracic features (signs or symptoms), (2) serologic abnormalities with specific autoantibodies, and (3) morphologic domain with radiographic, pathologic, and physiologic features. The classification established a framework to define a unique group of individuals with idiopathic interstitial pneumonia and enable prospective studies to determine the natural history and clinical implications of IPAF. In most connective tissue diseases other than rheumatoid arthritis, an NSIP radiographic and pathologic pattern is most common. Data from one retrospective series suggest a UIP radiographic pattern is more common in IPAF (65%) in contrast to NSIP.[108] Acute exacerbations may be less frequent in IPAF and more responsive to anti-inflammatory therapy.[109,110] These observations raise several important questions that need to be explored rigorously: Do individuals with IPAF develop a classifiable connective tissue disease? Is the natural history of disease different from other idiopathic interstitial pneumonias? In contrast to patients with idiopathic pulmonary fibrosis, should anti-inflammatory or immunologic therapies be considered in patients with IPAF? Suggestions from retrospective and small, single-center series have been delineated but more robust, multicenter, prospective investigations are necessary to continue define IPAF, its natural history, and appropriate treatments.

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CHAPTER 59

Pulmonary Langerhans Cell Histiocytosis

Sergio Harari
Davide Elia
Joel Moss
Abdellatif Tazi

INTRODUCTION

Histiocytosis or histiocytic disorders are characterized by abnormal function and accumulation or differentiation of specific cells, thought to be derived from dendritic cells (DCs) or the monocyte–macrophage lineage.[1] Among this group of diseases, Langerhans cell histiocytosis (LCH) is the most common and is characterized by an activation of the MAPK-ERK pathway, driven by various molecular abnormalities in this pathway, particularly the canonical *BRAF*^{V600E} mutation in about half of LCH lesions.[2,3] Importantly, the cell-specific gene expression signature in Langerin (CD207)-positive cells within specific lesions has shown that LCH cells are more consistent with immature myeloid dendritic cell precursors than with Langerhans cells.[4]

LCH clinical manifestations range from mild, with a single organ involvement, to disseminated life-threatening presentations. Depending on the sites involved and severity, the entity now referred to as LCH has been previously defined as eosinophilic granuloma, Hand-Schüller-Christian disease, and Letterer-Siwe disease. A more recent and simplified classification categorizes LCH based on single-organ or multisystem involvement.[2] The systemic presentations of the disease are usually associated with a worse prognosis, particularly when the so-called risk organs (i.e., liver, spleen, and hematopoietic system) are involved. This severe form of LCH is encountered mainly in young children and more rarely in older patients.[2,5]

Lung involvement in LCH may occur less commonly as a part of a multisystemic disease, or most frequently as a single, primary involved organ. In this latter instance, the disease is usually called *pulmonary LCH (PLCH)*.[6] PLCH belongs to the spectrum of diffuse cystic lung diseases.[7] It is characterized by the infiltration and destruction of bronchiolar walls by specialized dendritic cells organized into granulomas.[6] However, lung interstitium and pulmonary vasculature may also be involved by the pathologic process to varying extents, resulting in diverse phenotypes. Although PLCH is classically considered as a distinct entity in which smoking habit plays a role, the discovery of MAPK-ERK mutations in this group of patients suggests a biologic similarity with other subtypes of LCH.[8]

EPIDEMIOLOGY

LCH occurs sporadically, although rare familial cases and pairs of homozygous twins have been reported. The exact incidence and prevalence of PLCH are unknown. Early studies with a confirmed histologic diagnosis highlighted the rarity of the disease, which accounted for 3% to 5% of adult patients with diffuse infiltrative lung diseases.[6] However, these reports most probably underestimated the true prevalence of PLCH. Indeed, with the wide use of chest high-resolution computed tomography (HRCT) in the routine evaluation of patients, increased numbers of PLCH cases were identified; lung biopsy is not systematically performed, and some patients exhibited no symptoms or experienced spontaneous remission.[6] Occupational or geographic predisposition has not been reported. The most striking epidemiologic feature of PLCH is that it occurs almost exclusively in smokers or ex-smokers (>90% of cases).[6] The role of smoking in triggering PLCH is highlighted by the finding that most children with systemic LCH who developed PLCH in adolescence or adulthood started to smoke before onset of the disease.[6] In addition to cigarette smoking, about 20% inpatients of the French national registry are also cannabis users (Tazi, personal observation).

A peak of incidence has been observed in the second to fourth decade of life, with no gender predominance, although females may develop PLCH at slightly older ages.[6] Isolated LCH lung involvement has been rarely reported in children. PLCH seems to occur mostly among the Caucasian population, with very few cases reported in Blacks or African-Americans for unknown reasons. The disease has also been described in patients of Asian descent.[9,10]

LCH, including PLCH, is associated with increased risk of various malignancies, such as hematologic and solid tumors, including lung cancer. The type and incidence of these malignancies widely vary according to the LCH presentation (single vs. multisystem), the selected population, and the treatment (chemotherapy or radiation) the patients had eventually received for their LCH.[2,6,11–14] Cigarette smoke and tobacco compounds may play a role in the development of some of these tumors, particularly lung carcinomas. However, given the complexity of factors involved in the pathogenesis of both cancers and PLCH, shared host-related predisposing factors have been hypothesized.[14,15]

CLINICAL PRESENTATION

Clinical manifestation of PLCH may be silent or associated with nonspecific respiratory symptoms.[6] Patients come to medical evaluation after incidental findings on screening chest imaging (5%–35%), following spontaneous pneumothorax (10%–20%), or because of respiratory or constitutional symptoms. Cough, mostly not productive (50%–70%), dyspnea (40%–60%), and chest pain (10%–20%) are the most common respiratory symptoms described by patients, sometimes associated with systemic manifestations such as fatigue, weight loss, and fever in 10% to 20% of cases. Hemoptysis has been occasionally reported but should prompt a search for superimposed infection (rarely, *Aspergillus* in a lung cyst) or tumor.

In some cases, symptoms may be related to the presence of extrathoracic involvement. Localized pain and/or pathologic bone fractures may be related to the infiltration of the bone with osteolytic lesions (15%–20%), generally solitary and affecting the flat bones.[6,9,16] Skeletal involvement may precede pulmonary manifestations. Polyuria–polydipsia syndrome may occur due to pituitary stalk involvement with diabetes insipidus (5%–15% of patients) and more rarely skin involvement, usually as erythematous, maculopapular, or nodular lesions. The scalp is often involved by characteristic seborrheic and crusted lesions.[17]

In the absence of pneumothorax or extrathoracic findings as described, physical examination is usually unremarkable. At chest examination, crackles are uncommon as is digital clubbing. Manifestations of pulmonary hypertension are seen in advanced stages. Routine laboratory studies are usually unrevealing. A mild increase in peripheral neutrophil counts and blood inflammatory markers may be observed, but the peripheral eosinophil count is normal.[18]

PATHOGENESIS

The molecular basis, histopathologic findings, and role of tobacco smoking in PLCH are discussed below.

MAPK Pathway Activation

Although the pathogenesis of PLCH is still not fully understood, important progress has been made.

A critical breakthrough in the understanding of LCH pathogenesis was the identification a decade ago of recurrent somatic *BRAF*$^{\text{V600E}}$ mutations in approximately half of LCH lesions originating from different tissues, including the lung, supporting the hypothesis of a clonal/neoplastic origin of the disease.[19] *BRAF*$^{\text{V600E}}$ is a proto-oncogene mutation localized in the canonical mitogen-activated kinase (MAPK) pathway. Physiologically, MAPK activation results from the binding of an extracellular ligand to the tyrosine kinase receptor (TKR), inducing the activation of RAS thorough its transformation from Ras-GDP to Ras-GTP, leading downstream to RAF, resulting in the phosphorylation of MAPK kinase (MEK1/2) and ERK (extracellular signal-regulated kinase), which are responsible for the phosphorylation of a number of substrates involved in different cellular processes.[3,20] Somatic *BRAF*$^{\text{V600E}}$ mutation results in a modified kinase domain that is associated with constitutive activation of the MAPK pathway, thus deregulating the control of cell differentiation and survival (Fig. 59-1). *BRAF*$^{\text{V600E}}$ mutation has been detected in 30% to 75% of LCH cells in systemic LCH lesions[2,3] and in 30% to 50% of patients with PLCH.[8,21–24] This mutation is also observed in other tumors, such as malignant melanomas, and in almost all cases of hairy cell leukemia,[25] as well as in benign nevi.[26]

In several patients affected by multisystem LCH, particularly with risk organ involvement, and in a small group of cases with a single-system disease, circulating cell-free DNA *BRAF*$^{\text{V600E}}$ has been detected, allowing for diagnosis without the need to obtain a tissue sample.[27–29] Less frequently, this mutation has been observed in circulating CD11c+ precursors, CD1c+ myeloid dendritic cells, and CD14+ monocytes, as well as in bone marrow progenitors in patients affected by multisystem LCH.[30–32]

The key role played by MAPK pathway activation in the pathogenesis of the disease has been further supported by the finding of an independent activation of this pathway even in absence of the *BRAF*$^{\text{V600E}}$ mutation.[19]

MAP2K1 gene mutations have been identified in *BRAF*-wild-type LCH lesions and in 8.6% to 40% of biopsies from different tissues obtained from pediatric and adult LCH patients.[3] In LCH lesions, the presence of *MAP2K1* mutations is mutually exclusive of the presence of the *BRAF*$^{\text{V600E}}$ mutation. These mutations are able to promote the activation of ERK and are considered to be driver mutations in the disease.[8,22,33–40] Other MAPK alterations have been described in several cases and small case series, such as non-V600E *BRAF* mutations, *BRAF* deletions, *BRAF* duplications, and *ARAF-CRAF* mutations.[8,34,41–46] Additionally, in adult PLCH, *NRAS* mutations occur at a low frequency concurrently with the *BRAF*$^{\text{V600E}}$ mutation in a significant subset of cases and are carried by different clones within the lesion.[47] Overall, MAPK alterations are present in 75% to 93% of LCH lesions.[3,8,42,45] Based on these findings, LCH is considered an inflammatory myeloid neoplastic disorder, driven by mutations activating the MAPK pathway.[2] Furthermore, molecular alterations of the MAPK pathway have also been identified in most lesions of Erdheim-Chester disease (ECD), a non–Langerhans cell histiocytosis, and have led to a revision of the classification of histiocytic disorders[42,46] in which LCH and ECD are now grouped together.[1]

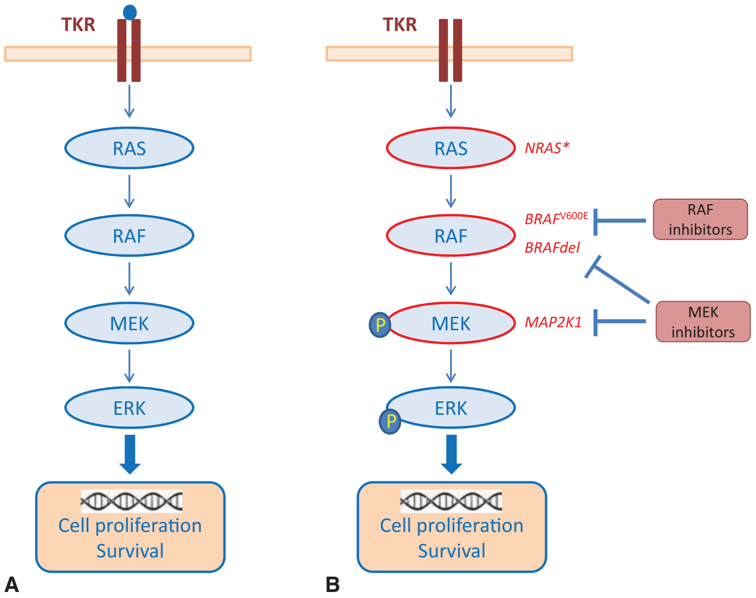

Figure 59-1 Schematic representation of the MAPK pathway and the principal molecular alterations identified in LCH lesions. **A.** In physiologic state, the RAS-RAF cascade is activated following the binding of an extracellular ligand (growth factors, cytokines) to the tyrosine kinase receptor (TKR) leading to phosphorylation (P) of MEK and ERK proteins. Ultimately, various processes are regulated by this pathway, including cellular proliferation and survival. **B.** The presence of mutations at different steps of the MAPK pathway induces its constitutive activation, without ligand binding on the TKR. The main genomic alterations identified in LCH lesions, including PLCH, are indicated. These alterations can be targeted by BRAF and MEK inhibitors. *Isolated *NRAS* mutations are rarely identified in PLCH, and they are more frequently observed at a low allele frequency concurrently with the *BRAF*$^{\text{V600E}}$ mutation in the same specimen. *BRAF*del, *BRAF* deletion; ERK, extracellular signal-regulated kinase; LCH, Langerhans cell histiocytosis; MAPK, mitogen-activated protein kinase; MEK, MAPK kinase; PLCH, pulmonary Langerhans cell histiocytosis; TKR, tyrosine kinase receptor.

PLCH Lesions

Accumulation of a large number of CD1a+/CD207+ cells in loosely formed bronchiolocentric granulomas, resulting in airspace invasion, cavitation, and consequent destruction of lung parenchyma, is a peculiar feature of PLCH.[6,23] Very few LCH cells proliferate in the lesions in PLCH granulomas, and these cells appear to be less sensitive to apoptosis.[6] The presence within and around PLCH lesions of local growth factors, granulocyte-macrophage colony-stimulating factor (GM-CSF), and chemokines (CCL20 and CCL2) suggests their role in the differentiation of myeloid hematopoietic precursors, recruited from circulating peripheral blood, in LCH lesions.[6,48] Differentiation of precursor cells residing locally in the involved tissues also is possible. It is possible that MAPK pathway activation can lead to activation of senescence pathways in CD1a+ myeloid cells that then proceed to infiltrate the lung.[24] This oncogene-induced senescence is a mechanism by which cell cycle arrest and inflammation may be perpetuated in PLCH. It is also possible that such cellular senescence may be driven by cigarette smoke exposure. The various cytokines locally produced, local neoangiogenesis, and the action for cell adhesion molecules help in the accumulation of LCH cells, T lymphocytes, and inflammatory cells.[6,48]

The ability of PLCH granulomas to destroy the bronchiolar wall and remodel the surrounding lung parenchyma may be related to a peculiar characteristic of CD1a+ cells found in the granulomas. These cells show different types of markers of membrane maturation, similar to those usually found on the surface of dendritic cells after exposure to various pathogens. However, a significant proportion of lymphocytes infiltrating the lesions are regulatory T cells,[49] and the

CD1a+ cell-mediated cytotoxic action of T lymphocytes seems to be impaired.[6] For this reason, other mechanisms involved in the tissue destruction have been hypothesized, such as locally secreted metalloproteinases.[6] In addition, activation of the Notch1 signaling pathway has been shown to be at least partly responsible for the specific phenotypic and functional profile of LCH cells.[4]

■ Role of Smoking

The role played by tobacco smoking in the pathogenesis of the disease is supported by a number of findings. For example, it has been observed that smoking induces changes in the epithelium of distal bronchioles and an accumulation of CD1a+ cells in healthy smokers, as well as in the lungs of patients with different pulmonary diseases and in murine models.[6] In addition, tobacco smoke leads to the production of local cytokines, promoting the differentiation and activation of dendritic cells in PLCH lesions.[6] Tobacco smoke also promotes the survival of dendritic cells via antiapoptotic mechanisms. Levels of glycoprotein osteopontin, secretion of which is increased by nicotine, are higher in the bronchoalveolar lavage (BAL) fluid of smoking patients with PLCH compared with healthy smokers.[6] A chemotactic effect on monocytes/macrophages and dendritic cells is induced by osteopontin, and the development of PLCH-like lesions has been induced by its overexpression in murine models.[6] Recently, a *BRAF*^{V600E} transgenic murine model elegantly showed that exposure of mice to cigarette smoke was necessary to induce lung lesions similar to those observed in PLCH.[50]

HISTOPATHOLOGY

The accumulation LCH cells (sharing features of LCs) into loosely aggregated granulomas, preferentially located in and destroying the wall of distal bronchioles, is the main histologic feature of PLCH[6,23] (Fig. 59-2). The granulomas may also extend into adjacent alveolar structures. A pale-staining cytoplasm and large convoluted nucleus is characteristic of these cells, and the classic pentalaminar cytoplasmic inclusion known as Birbeck granules can be observed by electron microscopy. The LCH cell surface is characterized by the presence of CD1a antigen and Langerin (CD207), a type II mannose lectin that is constitutively associated with Birbeck granules—both markers not observed in other histiocytic cells (Fig. 59-2). Although LCH cells react with anti-S-100 antibody, this feature is not specific, as it has been observed in other cell types (e.g., neuroendocrine cells, some macrophages) and should not be used for LCH diagnosis.

A mixture of LCH cells, eosinophils, lymphocytes, and some giant cells are localized around the smaller bronchioles in the early stages of the disease. These cells seem to invade the bronchiole, destroying the bronchial wall. Furthermore, the lesions affect pulmonary arterioles and venules. For this reason, the disease is described as showing a bronchovascular distribution.[6,23]

Pseudo-desquamative interstitial pneumonia (characterized by the accumulation of alveolar macrophages in the alveolar parenchyma between PLCH lesions) and respiratory (smoker's) bronchiolitis (with pigmented macrophages filling the lumen of bronchioles and the surrounding alveolar spaces) also have often been found on

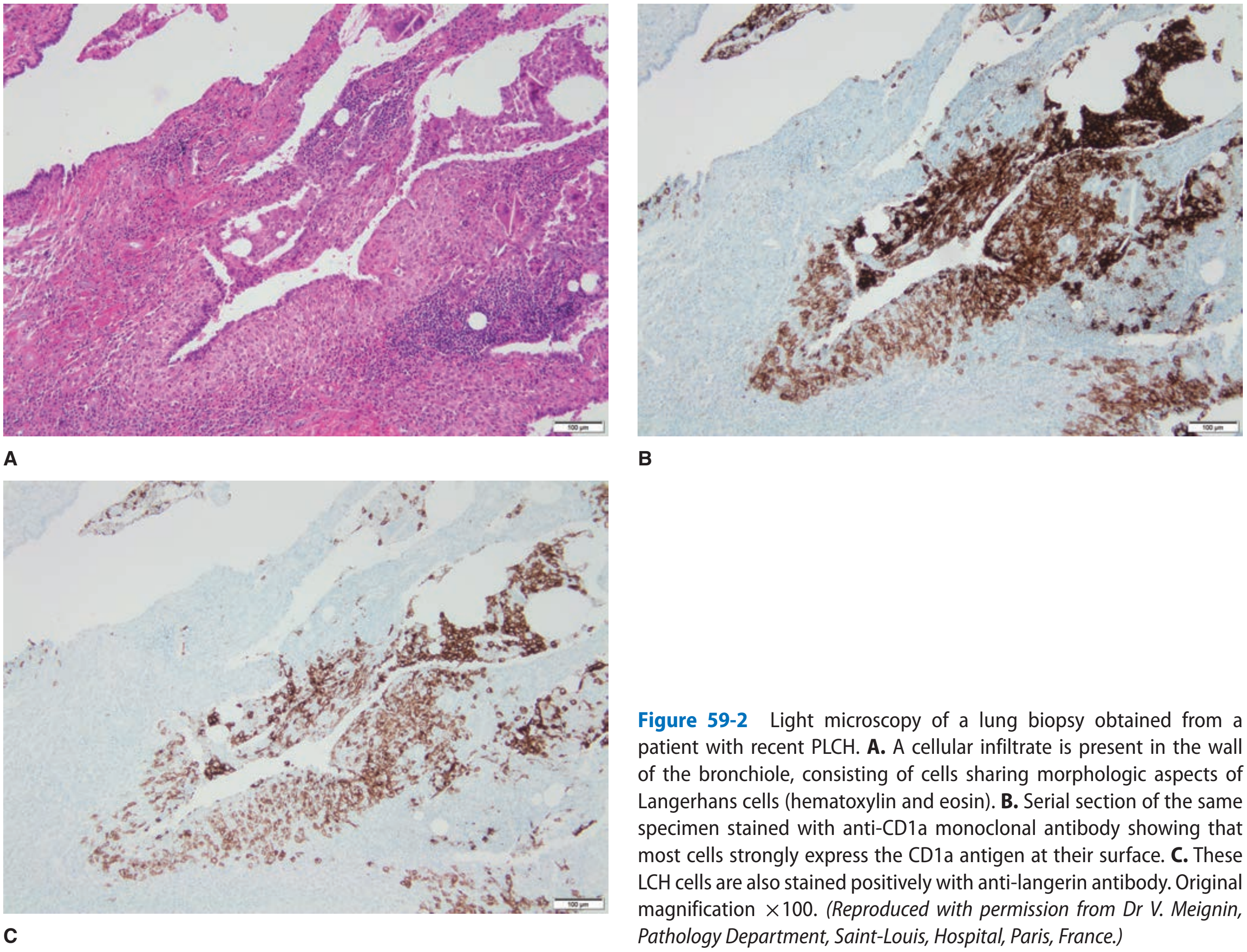

Figure 59-2 Light microscopy of a lung biopsy obtained from a patient with recent PLCH. **A.** A cellular infiltrate is present in the wall of the bronchiole, consisting of cells sharing morphologic aspects of Langerhans cells (hematoxylin and eosin). **B.** Serial section of the same specimen stained with anti-CD1a monoclonal antibody showing that most cells strongly express the CD1a antigen at their surface. **C.** These LCH cells are also stained positively with anti-langerin antibody. Original magnification ×100. *(Reproduced with permission from Dr V. Meignin, Pathology Department, Saint-Louis, Hospital, Paris, France.)*

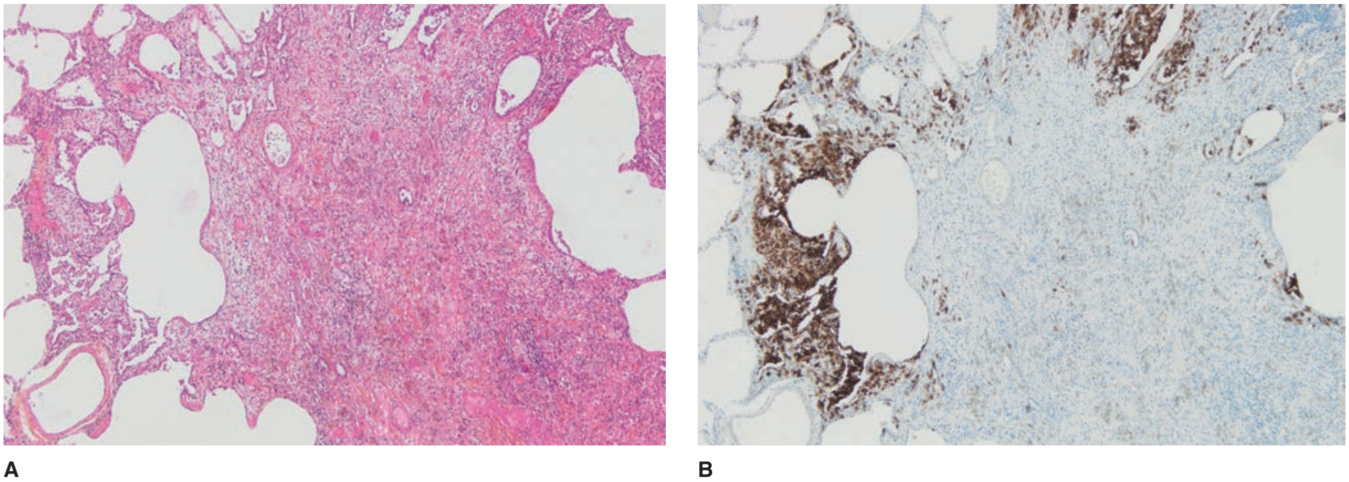

Figure 59-3 Light microscopy of a PLCH lung biopsy. **A.** The lesion is centrally cavitated and surrounded by an inflammatory infiltrate (hematoxylin and eosin). **B.** This cellular infiltrate is positively stained with anti-CD1a monoclonal antibody on a serial section. Original magnification ×40. *(Reproduced with permission from Dr V. Meignin, Pathology Department, Saint-Louis, Hospital, Paris, France.)*

lung biopsy.[6,23,51] In addition, intraluminal fibrosis is often present. Three-dimensional reconstruction of the lesions from serial sections shows that PLCH lesions are elongated, sheath-like structures of variable diameter that extend proximally and distally along bronchioles, without necessarily having spherical morphology.[6,23]

The pathologic features of PLCH change over time, and lesions of various ages are often found in the same lung biopsy specimen. Destruction of the bronchiolar epithelium occurs early in the disease process, such that the bronchiole-centered development of the lesions may be difficult to confirm on a single section. Although early lesions often seem cavitated, the cavity is the residual lumen of the bronchiole destroyed by the granulomatous reaction and does not result from tissue necrosis (Fig. 59-3). With progression of the lesions, the numbers of CD1a+ cells decrease, while inflammatory cells associated with lymphoid aggregates persist; they are subsequently replaced by either fibrosis in the form of a characteristic stellate scar, or contiguous and confluent cystic cavities surrounded by a fibrous ring. Traction emphysema contributes to the cystic appearance of advanced lesions.

IMAGING

The appearance of PLCH on routine chest radiographs, chest CT scans, and PET imaging is described below.

Chest Radiograph

In most cases, chest radiograph in PLCH is suggestive, although rarely it is normal at the time of clinical presentation. A typical PLCH radiographic pattern is characterized by the combination of ill-defined or stellate nodules (2–10 mm in size) associated with reticular opacities. Cysts are generally located in the middle to upper lobes, with sparing of the costophrenic angle.[6] Even though hyperinflation or reduced volume may be observed, total lung volume is generally normal. In advanced disease, chest radiograph may show an emphysema-like appearance. Hilar or mediastinal lymph node enlargement is rare in PLCH, and this finding should encourage further investigation for malignancy as a secondary diagnosis. Pleural effusion is not a feature of PLCH; occasionally pneumothorax can be detected at the time of the first chest radiograph, as can the presence of rib lesions.

Computed Tomography

Computer tomography (CT) images in PLCH are very characteristic, and their findings in a young smoker may be diagnostic. The CT is characterized by the combined presence of nodules, well or ill-defined, and cysts, varying in shape, size, and wall thickness[6,52] (Fig. 59-4). The distribution of the nodules is centrilobular, reflecting the bronchiole-centered development of PLCH lesions. The lesions

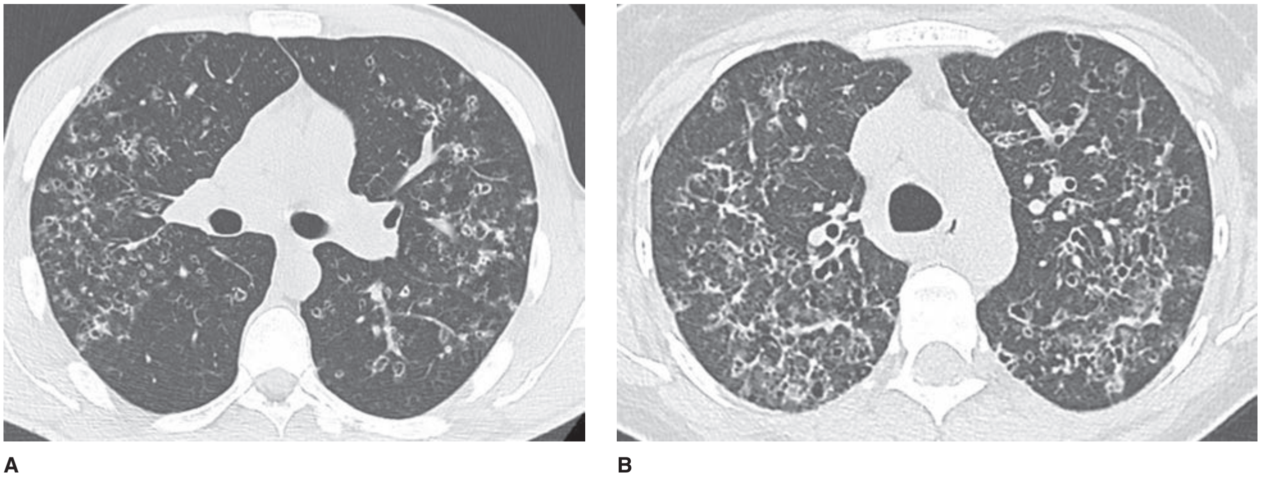

Figure 59-4 Representative HRCT images obtained from two patients with PLCH at an early stage. **A.** Characteristic association of nodules, cavitated nodules, and thick- and thin- wall cysts. **B.** More extensive similar HRCT pattern.

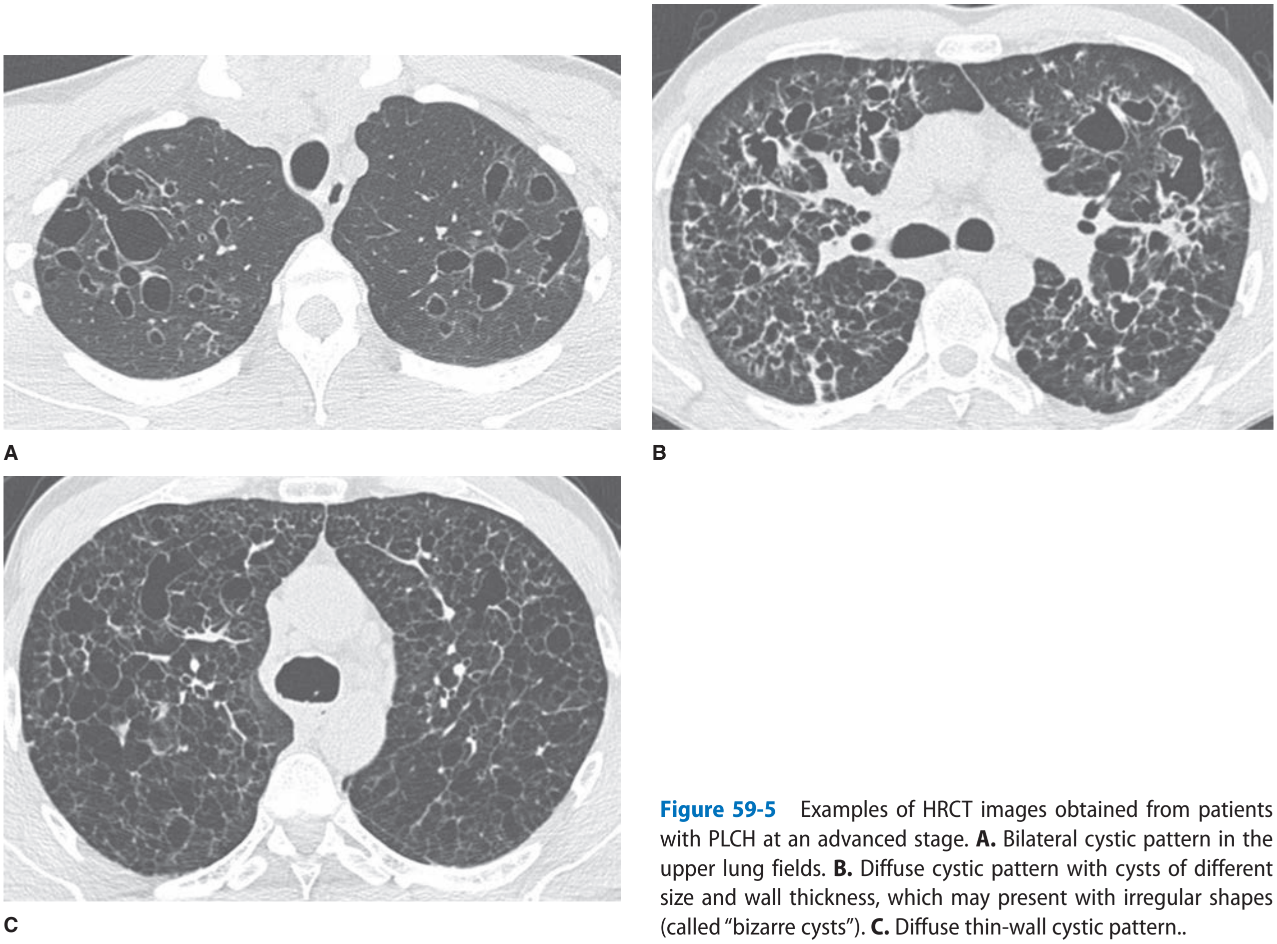

Figure 59-5 Examples of HRCT images obtained from patients with PLCH at an advanced stage. **A.** Bilateral cystic pattern in the upper lung fields. **B.** Diffuse cystic pattern with cysts of different size and wall thickness, which may present with irregular shapes (called "bizarre cysts"). **C.** Diffuse thin-wall cystic pattern..

are focal, being separated by parenchyma that appears normal. They usually predominate in the upper and middle lung fields, and tend to spare the basal portions of the lungs. As the disease evolves, cystic lesions become a predominant finding. Cysts vary in size and may coalesce to form irregular shapes ("bizarre cysts") (Fig. 59-5).

CT images reflect the histologic evolution of the disease, with serial chest CT demonstrating progression over time from nodular to cavitating to cystic lesions. Chest radiographs are not able to detect the degree of cyst formation. This may explain reports of "spontaneous remissions" before the routine use of thin-section CT.

Patients with a predominantly nodular HRCT pattern usually have minimal impairment in lung function, while worsening pulmonary function parameters correlates with the extent of cystic lesions. The utility of serial CT scanning in the monitoring and management of the disease is not clear.[52]

In rare cases, extensive ground-glass opacities on lung HRCT have been reported. This ground-glass pattern seems to reflect the extent of the histologic respiratory bronchiolitis-associated interstitial lung disease (RB-ILD)-like changes related to smoking that are observed in the lungs of these patients.[6]

■ PET Imaging

The role of 18-F-Fluorodeoxyglucose (FDG)-PET imaging in isolated PLCH needs to be better defined. It may be useful in quantifying disease activity, with positive scan results seen in patients with nodular, inflammatory lung disease, as well as those with thick-walled cysts.[53] Hypermetabolic PLCH nodules cannot be distinguished from malignant diseases. In patients with systemic manifestations, (FDG)-PET may provide valuable information regarding extrapulmonary involvement. It is still debated if PET-CT might be useful in predicting the natural course of the disease or the response of the disease to treatment.[53]

PHYSIOLOGIC TESTS

Physiologic evaluation in PLCH includes pulmonary function testing, exercise testing, and assessment for pulmonary hypertension.

■ Pulmonary Function Tests

Pulmonary function abnormalities are variable and depend on both the predominant anatomic lesions and the extent of cystic lesions on HRCT. Pulmonary function may vary from normal in the early stages (10%–15%) to an obstructive or restrictive or mixed pattern, according to the extension and the duration of the disease. The most common abnormality is represented by a reduction in the diffusing capacity for carbon monoxide ($\mathrm{DL}_{\mathrm{CO}}$), present in 80% to 90% of cases.[6,54] Disproportionately reduced $\mathrm{DL}_{\mathrm{CO}}$ is suggestive of a pulmonary vascular involvement.[6,52] Patients with a predominantly nodular HRCT pattern usually have minimal lung function alterations with an isolated reduction in $\mathrm{DL}_{\mathrm{CO}}$. The pulmonary function pattern frequently shows a reduction in vital capacity (VC), normal or increased residual volume (RV) with air trapping and preserved total lung capacity (TLC). A restrictive pattern (TLC <80% of predicted) is observed in approximately 10% of cases, with an obstructive pattern in 15% to 20%, typically in more advanced cases.[6,54] Reactive airway disease may be observed (noted in 10% of patients in a prospective study that included early-stage PLCH).[52] The extent of cystic changes in HRCT is correlated with lung function abnormalities, including airflow obstruction.[52] Blood gas levels at rest are normal in most cases, except in advanced stages.

Exercise Limitation

Patients affected by PLCH may complain of an impairment in activities of daily life and a worsening quality of life. This condition is associated with a decrease in maximum oxygen consumption ($\dot{V}O_{2peak}$) and a reduction of the 6-min walk distance. Pathophysiologic mechanisms underlying exercise limitation in these patients have been poorly investigated. Correlations between $\dot{V}O_{2peak}$ and the resting dead space/tidal volume ratio ($\dot{V}D/\dot{V}T$), residual volume, resting alveolar-to-arterial oxygen tension difference ($AaDO_2$), and DL_{CO} have been reported. Rolland-Debord et al. used cardiopulmonary exercise testing (CPET) to study a group of 62 subjects with PLCH; they found a reduction in $\dot{V}O_{2peak}$ in the majority (72%).[55] Patients with impaired aerobic capacity showed reduction in pulmonary function test values and increased $AaDO_2$. Furthermore, they presented with increased ventilatory equivalents at ventilatory threshold, $\dot{V}D/\dot{V}T$ peak, $AaDO_2$ peak, and $PaCO_{2peak}$, as well as decreased ventilatory reserve and PaO_{2peak}. No difference was observed in the dyspnea score between the two groups, suggesting the mechanism by which exercise capacity impairment might be related to pulmonary changes, independent of the perception of respiratory fatigue.[55]

Exercise capacity was reduced in 71% of 35 patients with PLCH evaluated by means of an incremental treadmill CPET. In the majority, exercise limitation was multifactorial, and the most prevalent mechanisms included ventilatory, cardiocirculatory, and signs of limitation due to pulmonary hypertension, which was detected in 40% of subjects.[56]

Pulmonary Hypertension

In advanced PLCH, pulmonary hypertension (PH) is a complication that leads to an increase in mortality. In a high percentage of patients referred for lung transplantation, severe precapillary pulmonary hypertension has been detected.[57,58] However, in a large prospective cohort, only a small minority developed PH early in the course of PLCH.[11]

PH related to PLCH is included in group 5 of the PH clinical classification. Chronic hypoxemia, abnormal pulmonary mechanics, and vascular remodeling are the likely underlying pathophysiologic mechanisms. Proliferative vasculopathy involving muscular arteries and frequent venular involvement, with aspects of veno-occlusive disease, has been observed in biopsies of subjects with end-stage disease.[59] The severity of PH is not related to pulmonary function values; in a subgroup of patients, it progressed without obvious change in the lung parenchyma, consistent with an intrinsic pulmonary vascular disease.[59]

ROLE OF BRONCHOSCOPY

Bronchoscopy is grossly normal or shows smoking-related inflammation. Bronchial mucosa biopsy specimens are not useful for the diagnosis of PLCH but are helpful to exclude alternative diagnoses in atypical cases. Bronchoalveolar lavage (BAL) is rarely diagnostic of PLCH but provides additional information; a marked predominance of alveolar macrophages reflects tobacco use.[6] Alveolar cell counts may be normal in patients who ceased smoking for more than 6 months. A moderate increase of BAL eosinophils (usually <10%) may be present. An increased percentage of CD1a+ cells (>5%) is highly suggestive of PLCH, but the finding has a low sensitivity.[6,54] An increase in the proportion of alveolar lymphocytes should make one consider an alternative diagnosis. In patients with constitutional symptoms, BAL can exclude lung infection.

Transbronchial lung biopsies may be diagnostic for PLCH in expert centers, but they have variable diagnostic yields (15%–40%) due to the focal nature of histologic lesions.[6] Multiple specimens should be obtained and examined extensively using immunohistochemical techniques.

DIAGNOSIS

Definitive diagnosis of PLCH is made with histologic confirmation. It may be obtained through transbronchial lung biopsies or, most commonly, by surgical lung biopsy that, ideally, should be taken from nodular areas on lung HRCT. Since the lesions are focal, the specimens should be sufficiently large to ensure the availability of adequate material, and an extensive search for specific lesions should be performed using CD1a/CD207 immunostaining. In some cases, the predominant features may be suggestive of RB-ILD or desquamative interstitial pneumonia, but underlying specific LCH granulomas should be sought by comprehensive examination of biopsy samples, including immunohistochemistry. Correlations between CT features and pulmonary histopathology have shown that LCH granulomas may still be observed in patients with diffuse cystic disease, and that inflammatory cells (including LCH cells) may persist even inside thin-walled cysts.[6] In difficult cases, the presence of the *BRAF*^{V600E} mutation (and other MAPK alterations) helps confirm the diagnosis.

Lung HRCT has reduced the need for surgical lung biopsy. In a young adult smoker, the presence of a typical nodulocystic HRCT pattern allows for a presumptive diagnosis, along with close follow-up.[60] In case of surgical management of a pneumothorax, a lung biopsy may be performed during the same procedure. The biopsy of an associated bone or skin lesion allows for confirmation of the diagnosis in a patient with consistent pulmonary features. The indication for lung biopsy is determined in each patient, according to the evaluation of risks and potential benefits of the procedure. The differential diagnosis of other cystic diffuse lung diseases is guided by the clinical context and lung HRCT findings.[7,61]

INITIAL EVALUATION

At the time of diagnosis of PLCH, a thorough history and a comprehensive physical examination are essential to search for extrapulmonary LCH involvement. It is recommended that a skeletal radiograph survey be performed. However, if patients are meticulously and clinically evaluated for the absence of extra-thoracic LCH manifestations, the systematic search for bone involvement is less essential.[18]

A complete blood count and blood chemistry analysis (including total protein, electrolyte, creatinine, and liver and inflammation tests) should be systematically performed. They can rarely reveal LCH-related abnormalities (e.g., cholestasis in liver LCH involvement) and are useful for distinguishing alternative diagnoses or for patient therapeutic management. Morning urine osmolality is a screening test for suspected diabetes insipidus.[60]

Pulmonary function evaluation (including spirometry, plethysmography, and DL_{CO} determination) is essential to determine the degree of functional impairment and search for complications (e.g., COPD or pulmonary hypertension).

NATURAL HISTORY

The natural history of PLCH is unpredictable. In some patients, disease may resolve or stabilize after smoking cessation.[6,54] Other patients may develop progressive lung disease, often associated with evidence of airflow limitation and pulmonary vascular dysfunction.[60] Due to the inability to accurately predict the natural history, it is important that all patients undergo longitudinal follow-up. In a recent, large prospective study, most severe respiratory complications (chronic respiratory failure and/or pulmonary hypertension) occurred within the first 5 years after diagnosis.[11]

About 50% of patients experience a decrease of pulmonary function at 5 years of follow-up, and some will develop airflow obstruction.[62] In a 2-year prospective study, up to 20% of patients experienced a significant decline in their FEV_1.[52] A minority developed respiratory failure, with or without pulmonary hypertension, that was associated with decreased survival.[6,59] Besides the known association of LCH with various solid and hematologic tumors, PLCH patients are particularly at risk of lung carcinomas.[6,11] In contrast to what was reported two decades ago in two retrospective studies, the long-term survival of PLCH appears currently more favorable (>90% at 10 years).[11] Older age and decreased FEV_1 at the time of diagnosis are associated with increased mortality.[11] Conversely, BRAF status does not influence the risk of PLCH progression.[8] In some patients, despite regression of the disease, pulmonary function continues to deteriorate as a result of smoking-related COPD.[60] In addition, these patients are at risk for cardiovascular complications.[11]

Pregnancy does not appear to modify the course of PLCH, but certain precautions are required in women with diffuse cystic lesions and impaired pulmonary function due to the risk of pneumothorax during labor. Cases of exacerbation of diabetes insipidus have been reported during pregnancy, and de novo diabetes insipidus may also be observed after delivery.

Patient follow-up is based on physical examination, standard chest radiography, and lung function tests, typically performed every 3–6 months for the first 2 years, and then annually for at least 5 years in the absence of clinical progression of the disease.[6,11] Long-term follow-up may detect respiratory dysfunction or a rare relapse with recurrent nodule formation. Serial lung HRCT is recommended in patients who exhibit changes in their clinical, functional, or chest radiographic findings during follow-up.[52] In case of unexplained dyspnea or significant decrease in $D_{L_{CO}}$, Doppler echocardiography is indicated to search for pulmonary hypertension, which needs to be confirmed by cardiac catheterization.

MANAGEMENT

Management of patients with PLCH is tailored to the intensity of respiratory symptoms, the degree of impairment of lung function, and the progression of the disease. In all cases, smoking cessation is essential.[60] Smoking cessation for at least 6 months is associated with reduced longitudinal lung function decline.[52] It is the only intervention necessary in a substantial proportion of patients,[54] and individualized smoking cessation strategies should be used to address this powerful addictive behavior. Partial or complete resolution of lung HRCT abnormalities may occur without treatment, particularly after smoking cessation[60,63,64] (Fig. 59-6).

Combined inhaled corticosteroid and long-acting β_2-agonist therapy may provide benefit to patients with wheezing and moderate (reactive) obstructive lung disease.[60] Pneumothorax management may be particularly difficult. It recurs in half of the patients and often requires surgical pleurodesis.[65] Pleurectomy should ideally be avoided in these young patients who may be candidates for lung transplantation in the future. Lower respiratory tract infection is a common cause of deterioration for PLCH and should be promptly treated. An annual vaccination against influenza and a pneumococcal vaccine are recommended for patients with impaired lung function.

There is no general consensus regarding the role of immunosuppression or chemotherapy in management. Selected patients may experience improvement in lung function with therapy. Systemic corticosteroids have been used empirically without any evidence of efficacy.[6] Vinblastine, the cornerstone treatment of pediatric LCH,[5] has limited efficacy in adult PLCH.[66] Cladribine (2-chlorodeoxyadenosine), a purine nucleoside analogue directly toxic for lymphocyte, monocyte, and dendritic cells, is used as a second-line treatment in multisystem LCH.[67,68] It has been reported to induce remission or improve lung disease in selected PLCH cases.[60,69] This treatment is highly immunosuppressive (inducing prolonged lymphopenia), so prophylaxis for *Pneumocystis jirovecii* and herpes viruses should also be given. The efficacy and tolerance of cladribine for symptomatic forms of PLCH with impaired pulmonary function is being evaluated in a phase 2 clinical trial (Clinicaltrials.gov identifier NCT01473797).

Determination of *BRAF*^{V600E} or other mutations may assist with the development of an individualized therapeutic approach in patients with refractory disease,[3] but the role of MAPK targeted therapy in PLCH needs to be further assessed. A patient with progressive PLCH unresponsive to cladribine, whose lesion harbored a *MAP2K1* deletion, was reported to respond to the MEK inhibitor trametinib.[70]

Symptomatic treatments are useful for patients with respiratory failure and or pulmonary hypertension. Patients with PLCH who develop pulmonary hypertension have a particularly poor prognosis, and early referral for lung transplantation assessment is recommended. The role of vasodilator therapy in severe PLCH/pulmonary hypertension is not well established and should be reserved for expert centers because of the risk of worsening blood gas exchange.[59] Patients with advanced PLCH benefit from lung transplantation, with similar outcomes to patients with other diffuse infiltrative lung diseases, although PLCH may relapse in the transplanted lungs.[57,58,71]

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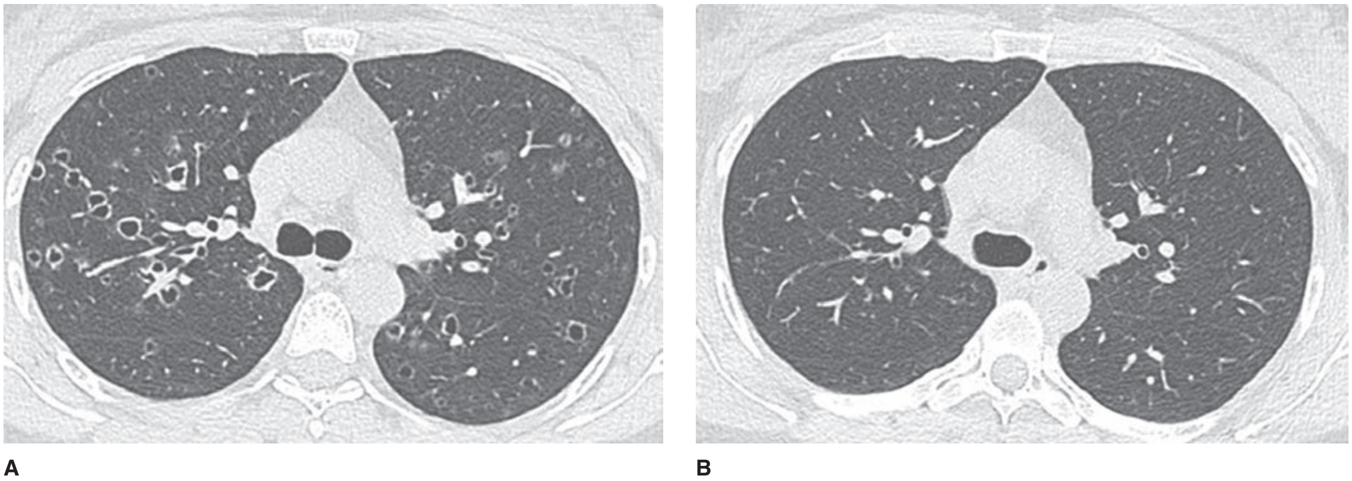

Figure 59-6 **A.** Chest HRCT at the time of PLCH diagnosis showing a typical nodulocystic pattern. **B.** Subsequent HRCT image showing spontaneous resolution of pulmonary lesions.

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CHAPTER 60

Pulmonary Lymphangioleiomyomatosis

Arnold S. Kristof
Joel Moss

Lymphangioleiomyomatosis (LAM) is a multisystem disorder, predominantly affecting women, that is characterized by cystic lung lesions, abdominal angiomyolipomas (AMLs), and lymphatic abnormalities. These pathologic features are caused by the proliferation of a neoplastic smooth muscle–like LAM cell that also has characteristics of immature melanocytes.[1] Inherited and sporadic forms of LAM have been described. Sporadic LAM is caused by somatic mutations primarily of the *tuberous sclerosis complex* (TSC) 2 (*TSC2*) gene, presumably occurring in a “cell of origin.”[2–4] Single cell sequencing of LAM lung lesions suggest that LAM cells may arise in the uterus.[5] LAM can also occur in about one-third of patients with TSC, an autosomal-dominant disorder that occurs in 1 of 6000 live births, and results from germline mutations in the *TSC1* or *TSC2* genes leading to widespread hamartomatous tumors in several organs including the brain, heart, skin, kidney, eyes, lung, and liver.[6–8]

EPIDEMIOLOGY

Until the establishment of LAM registries and the subsequent introduction of treatment with inhibitors of mechanistic target of rapamycin (mTOR),[9,10] LAM was considered to be a fatal disease of women of child-bearing age for which oophorectomy, antiestrogen therapy, and lung transplantation were the only available therapeutic options.[11] LAM is now best characterized as a chronic disease of post- and premenopausal women with an average life expectancy spanning 29 years from diagnosis.[10] Sporadic LAM is a rare disease with an estimated prevalence of 4.9 in 1,000,000 women.[12] LAM can also be detected in 30% to 40% of females patients with TSC, with the frequency increasing with age. Next-generation sequencing studies commonly indicate mosaic mutations in the *TSC1* or *TSC2* gene in patients with TSC who have no mutation identified (NMI) on analysis of a blood sample,[13,14] but mosaic *TSC2* mutations are only rarely found in patients diagnosed with the sporadic form of LAM.[15] Case series have identified LAM-like cystic lung disease in male patients with TSC, but clinically significant disease appears much less frequently in men than in women.[16,17]

CLINICAL PRESENTATION

Patients with LAM often present with a history of progressive dyspnea (Table 60-1).[9,18] Pneumothorax may cause acute onset pleuritic chest pain, is often recurrent, and occurs in up to 56% of patients on initial presentation.[19] The size of the lung cysts, as seen on high-resolution computed tomography (HRCT) scans (Fig. 60-1A) appears to be proportional to the incidence of pneumothorax.[20] Patients may also report cough, wheezing, or hemoptysis (Table 60-1). Other modes of presentation can include symptoms related to lymphatic involvement, such as lymphangioleiomyomas, which when present occur in the posterior mediastinum, retroperitoneum, or pelvis. The lymphatic involvement may also manifest as lymphadenopathy, chylothorax, chylous ascites, chyluria, or chyloptysis (Table 60-1).[9,21,22] Abdominal lymphangioleiomyomas were observed in 29% of patients with sporadic LAM, and in 9% of patients with TSC-LAM.[23] Angiomyolipomas (AML) are benign tumors usually localized in the kidneys and found in approximately 90% of patients with TSC-LAM (usually bilateral in patients with TSC) and in 30% of those with sporadic LAM (Table 60-1). AML may be identified on presentation and can spontaneously rupture and cause life-threatening hemorrhage.

The physical examination of LAM patients may disclose wheezing in 30% of patients, with a bronchodilator-responsive asthma-like presentation. In patients with TSC, typical skin lesions (e.g., angiofibroma, Fig. 60-2), or signs of neurologic impairment from brain involvement (e.g., cortical tubers, subependymal giant astrocytoma [SEGA]), may be evident.[24]

PATHOLOGY

Gross examination of lung sections shows cysts ranging in size from 0.2 to 2 cm.[1,25] Microscopically, proliferating LAM cells are found in the walls of cysts and can be found in association with narrowed or obstructed blood vessels, lymphatics, and bronchioles (Fig. 60-1B1, B2).[1,25] Focal hemosiderosis may be present. LAM cells are organized in microscopic nodules (LAM nodules) and appear to grow in a haphazard, disorderly fashion.[1,25] Two types of LAM cells have been described. Small, spindle-shaped cells predominate in the center of the lung nodules; epithelioid cells with large cytoplasm predominate at the periphery.[1,25] Both cell types react with antibodies against smooth muscle–cell antigens

TABLE 60-1 Clinical and Physiologic Features of Patients with Sporadic LAM and TSC-LAM

Demographics	TSC-LAM	Sporadic LAM
Number of patients	34	196
Age of LAM diagnosis	39.0 ± 1.6	41.4 ± 0.7
Signs and symptoms		
Dyspnea	70.6%	73.5%
Pneumothorax	47.1%	56.9%
Wheezing	58.8%	44.4%
Cough	26.5%	31.6%
Hemoptysis	20.6%	32.1%
Pleural effusions	5.9%	23.5%
Lung function		
Airflow obstruction	37.5%	60.8%
Low diffusion capacity	38.2%	60.3%
Normal spirometry	53.1%	30.7%
Extrapulmonary LAM		
Number of patients	67	256
Renal angiomyolipoma	93%	32%
Hepatic angiomyolipomas	33%	2%
Lymphangioleiomyomas	9%	29%
Ascites	6%	10%

TSC-LAM, Lymphangioleiomyomatosis associated with Tuberous Sclerosis Complex.
Data from Ryu JH, Moss J, Beck GJ, et al. The NHLBI Lymphangioleiomyomatosis Registry, Characteristics of 230 Patients at Enrollment. Am J Respir Crit Care Med. 2006;173:105; Avila NA, Dwyer AJ, Rabel A, et al. Sporadic lymphangioleiomyomatosis and tuberous sclerosis complex with lymphangioleiomyomatosis, comparison of CT features. Radiology. 2007;242:277.

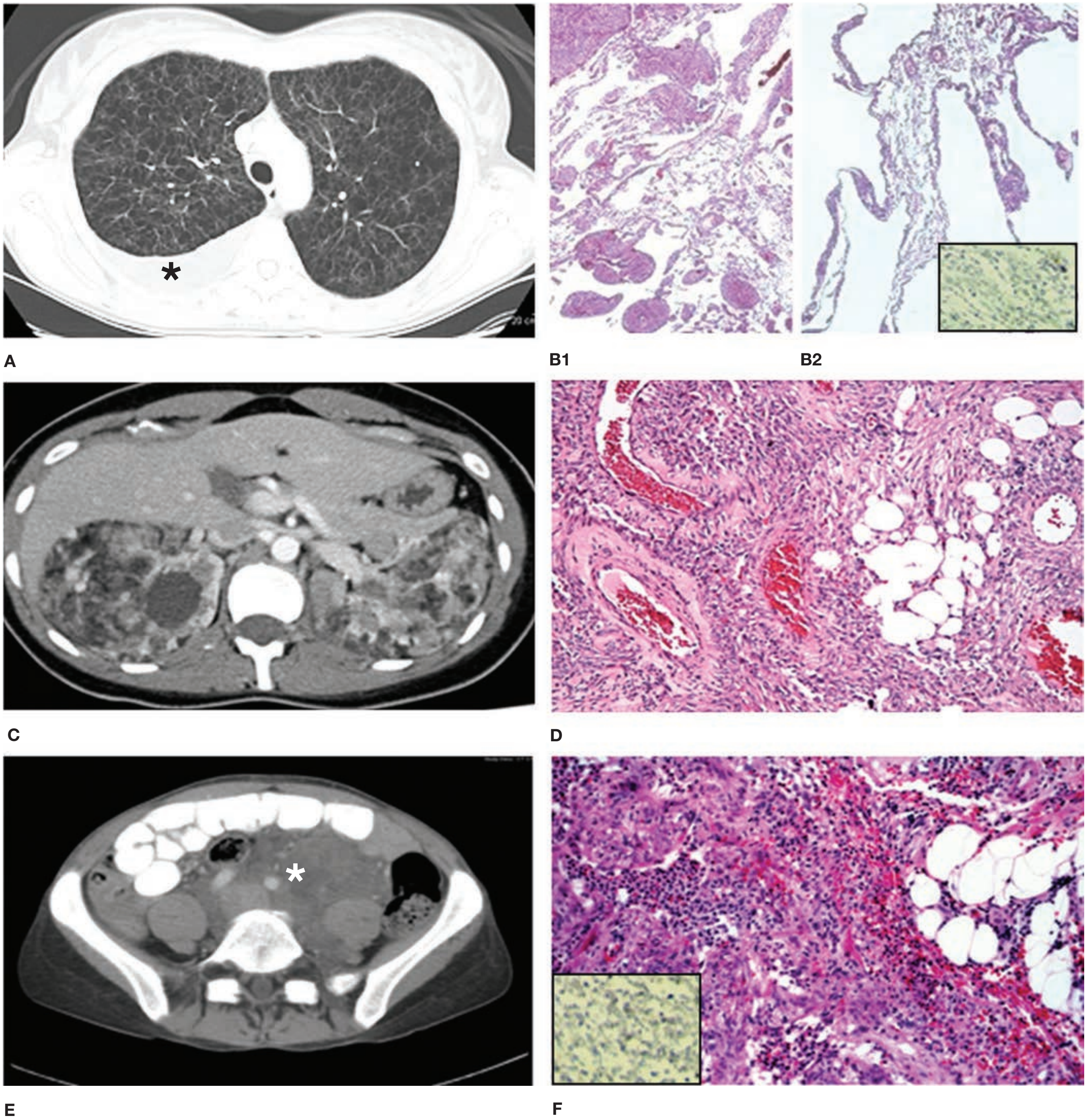

Figure 60-1 Computed tomography scans showing pulmonary and extrapulmonary images of patients with LAM, and the corresponding histopathologic findings. **A.** Multiple thin-walled cysts scattered throughout the lungs that have completely replaced the normal lung parenchyma. The *black asterisk* indicates the presence of a right pleural effusion. **B1** and **B2.** Histopathology of the lung showing characteristic nodular smooth muscle cell–like infiltrates and cystic lesions. Inset image on **B2** shows immunocytochemistry of lung tissue, showing reactivity with monoclonal antibody HMB45. **C.** Bilateral angiomyolipomas in a patient with TSC-LAM. The fatty, low-density component is clearly visualized. **D.** Histopathology of AML showing smooth muscle cell–like infiltrates, fatty tissue, and poorly differentiated vascular structures. **E.** Large, fluid-filled lymphangioleiomyoma *(white asterisk)* surrounding vascular structures. **F.** Histologic appearance of a lymphangioleiomyoma showing smooth muscle–like cells arranged in fascicular, trabecular or papillary patterns. Inset image on **F** shows immunocytochemistry of lymphangioleiomyoma tissue showing reactivity with monoclonal antibody HMB45.

(e.g., smooth muscle α-actin, vimentin). The epithelioid cells also react with human melanoma black 45 antibody (HMB-45), a monoclonal antibody that recognizes gp100, a premelanosomal protein encoded by the *Pmel17* gene (Fig. 60-1B2, inset).[1,25] Another antibody, αPEP13h, recognized the same protein, but identified a higher number (up to 85%) of cells in the LAM nodules.[26] Spindle-shaped LAM cells react with proliferating cell nuclear antigen (PCNA), indicating their high proliferative capacity.[1] Estrogen, progesterone, insulin-like growth factor, hyaluronic acid (CD44), and G protein–coupled receptors (e.g., chemokines, erythropoietin, prostaglandin, urotensin, angiotensin II) were demonstrated in LAM cells.[27–34]

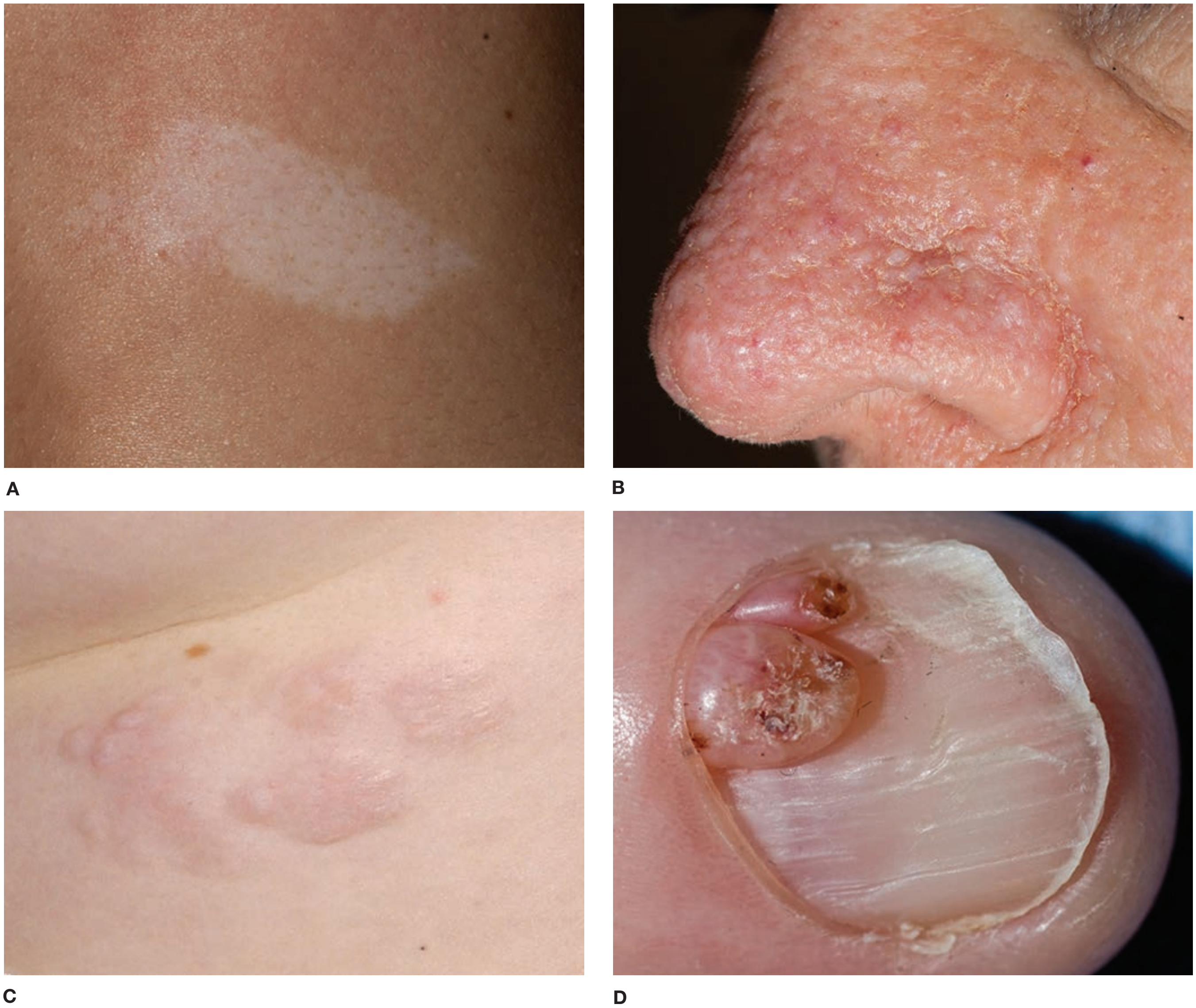

Figure 60-2 Skin manifestations of TSC in an adult woman. **A.** Large hypomelanotic macule on the back. **B.** Multiple facial angiofibromas involving the nose and adjacent cheek. **C.** Shagreen patch on the lower back. **D.** Periungual fibroma near the toenail.

AMLs are highly vascular tumors (Fig. 60-1C) comprising smooth muscle–like cells, immature, poorly differentiated blood vessels, and adipose tissue (Fig. 60-1D).[1,25] Tumors vary in size from 1 mm to more than 15 cm in diameter.[21,25] Smooth muscle–like cells found in AMLs have the same immunocytochemical properties as lung LAM cells (Fig. 60-1D).[1,25] Each of the major cell types in AML (vascular [angio], smooth muscle [myo], fat [lipoma]) may have mutations in the *TSC* genes.[2,3,35] The blood supply of AMLs originates from the renal arteries or aberrant vessels, which may completely disrupt normal kidney architecture.[21,25]

Other extrapulmonary abnormalities may include infiltration of intra-abdominal or retroperitoneal lymph nodes with smooth muscle cells, which correlate with the abdominal lymphadenopathy, as well as thoracic duct thickening and dilatation observed on imaging.[21,22,25] Lymphangioleiomyomas (Fig. 60-1E) are encapsulated lymphatic masses or chyle-filled cysts of varying sizes, composed of LAM cells arranged in fascicular, trabecular, or papillary patterns and associated with slit-like vascular channels (Fig. 60-1F).[1,22] Lymphatic vessels may be obstructed by LAM cells infiltrating their walls, resulting in the formation of tumor-like structures.

PATHOGENESIS

LAM is caused by proliferation of neoplastic LAM cells that have somatic mutations or deletions in the *TSC2* (16p13) gene, with less frequent involvement of the *TSC1* gene.[2,3,36] Consistent with Knudson's "two-hit" hypothesis of tumor development,[37] loss of heterozygosity of *TSC2* has been reported in LAM cells isolated from lung, blood, chyle, urine, and AML from both sporadic LAM and TSC-LAM patients. The presence of LAM cells in the blood, as well as the detection of identical mutations in AMLs and lung lesions from the same patients, suggested metastasis from an unknown source.[2,10,38,39] Further supporting this, LAM cells from patients receiving lung transplantation have been detected in the donor lung.[40,41] LAM cell clusters, consisting of LAM cell aggregates covered by lymphatic endothelial cells, have also been identified in chylous fluid.[42] Potential sources of lung LAM cells include AML, the lymphatic system, and the uterus.[5,43] The latter is supported by single cell sequencing analysis of pulmonary LAM nodules showing markers of uterine lineage.[5] Although the variable distribution and severity of LAM tumors suggest that LAM might be a genetic mosaic form of TSC, the detection of *TSC* genomic mutations in sporadic LAM by next-generation sequencing of blood DNA is rare.[44] It remains possible, however, that the somatic *TSC2* genomic mutations detected in LAM cells arose late in embryonic development or during postnatal development, thereby explaining the spectrum of disease.[44] Finally, a recent genome-wide association study identified a genomic variant in patients with LAM related to increased expression of an orphan nuclear receptor: *NR2F2*.[45] Its expression was also detected in LAM cells interrogated in a single cell sequencing study of LAM tumors from patient biopsies.[5]

A role for estrogens in the pathogenesis of LAM has been suggested, given the high prevalence in premenopausal women, and worsening of lung disease during pregnancy or following the administration of estrogens.[46–48] Single cell gene analysis and immunohistochemistry indicate elevated expression of female sex hormone receptors in lung and AML LAM cells.[5,27–29] Estrogens promote the proliferation of *TSC2*-null rat ELT3 leiomyosarcoma–derived cells in vitro, as well as the growth of subcutaneous tumors in a nude mouse xenograft system.[49] Estrogens also stimulate the growth of human AML-derived *TSC2*$^{-/-}$ cells, and increase matrix metalloproteinase (MMP-2) activity in LAM lung-derived cells, indicating an enhancing effect on cell invasiveness.[50–52]

The mechanism by which interstitial LAM cell proliferation causes lung cyst formation is unknown.[53] It has been proposed that compression of the airways by LAM cells leads to distention of the terminal airspaces and cyst formation.[1,25] It has also been proposed that degradation of lung elastic fibers is a major cause of the cystic lesions.[53,54] Matrix metalloproteinases (MMPs), which play a role in lung remodeling and lymphangiogenesis, are associated with LAM lesions.[55] LAM nodules contain MMP2, MMP9, MMP1, and MMP activators (MT1-MMP), as well as their inhibitors (TIMPs).[56,57] Levels of TIMP-3, which inhibits some MMP, were reportedly reduced in LAM lesions.[58,59] Compared with normal subjects, serum levels of MMP-9 were higher in patients with LAM,[60] suggesting that an imbalance between MMP and their inhibitors may contribute to lung destruction. Growth of *TSC2*-null lesions in mice was associated with an increase in MMP activity and vascular endothelial growth factor D (VEGF-D).[61] Degraded elastic fibers were demonstrated in the lung interstitium of mice with *TSC2*-null lesions,[61] and human lung LAM nodules show disrupted elastic fibers.[54] The presence of lymphatic spaces in the LAM nodules and strong immunoreactivity toward markers of lymphatic endothelial cells, including vascular endothelium growth factor C (VEGF-C), VEGF-D, vascular endothelium growth factor receptor (VEGFR) 3, and podoplanin, led to the hypothesis that disorganized lymphangiogenesis enhances metalloproteinase expression and lung remodeling.[61] Some combination of these mechanisms may be the best explanation for the pathogenesis of cystic lung destruction.

PULMONARY PHYSIOLOGY

Airflow obstruction is present in approximately 61% of patients with sporadic LAM,[9,62] with normal spirometry in about 31% and restrictive disease in the remainder. Lung disease appears to be milder in patients with TSC-LAM, with reduced frequency of obstructive or restrictive abnormality, and reduced decline in lung function over time (Table 60-1).[9,10,63,64] The cause of airflow limitation in LAM has been attributed to alveolar destruction,[65] but a study of pulmonary mechanics showed that lung elastic recoil was not significantly reduced.[66] Instead, increased upstream airway resistance was implicated as the major cause of airflow obstruction.[66,67] Reduced diffusing capacity (D_{LCO}) is present in approximately 60% of sporadic LAM patients.[9] Most patients have both decreased FEV_1 and D_{LCO}, but some patients have only a reduced D_{LCO}.[62] Ventilation-perfusion scintigraphy demonstrates reduced ventilation and perfusion, as well as a speckling pattern, correlating with the extent of cystic destruction and severity of lung function abnormalities.[68] Gas exchange, especially during exercise, is often abnormal with excessive minute ventilation and reduced breathing reserve (Table 60-2).[67,69] The appropriate reduction in dead space to tidal volume ratio during exercise is often not observed, and alveolar–arterial oxygen difference (A-a/O_2) is often increased.[67] The primary determinants of exercise limitation in LAM, therefore, are airflow limitation, decreased breathing reserve, dynamic hyperinflation, and limitations in oxygen transfer and carbon dioxide clearance due to loss of alveolar capillary surface area.[67,69,70] Pulmonary hypertension during exercise may also contribute to increased dead space and reduced gas transfer.[71]

TABLE 60-2 Cardiopulmonary Exercise Abnormalities in LAM

Decreased $\dot{V}_{O_{2max}}$ (% predicted)	57 ± 5
Decreased maximum work rate (% predicted)	68 ± 6
Decreased maximum oxygen pulse (% predicted)	67 ± 5
Decreased breathing reserve at end exercise (%)	8.5 ± 4
Decreased Pa_{O_2} (mm Hg resting vs. end exercise)	70 ± 2 vs. 60 ± 4
Increased maximum $\dot{V}_D/\dot{V}_T$ (% predicted resting vs. end exercise)	34 ± 3 vs. 38 ± 3
Increased A-a O_2 gradient (mm Hg resting vs. end exercise)	26 ± 5 vs. 42 ± 6

$\dot{V}_{O_{2max}}$, peak oxygen uptake; Pa_{O_2}, arterial oxygen tension; $\dot{V}_E/\dot{V}_{CO_2}$, ventilatory equivalent for CO_2; AT, anaerobic threshold; $\dot{V}_D/\dot{V}_T$, dead space ventilation ratio; A-a O_2 gradient, alveolar arterial oxygen tension difference.
Data from Crausman RS, Jennings CA, Mortensen RL, et al. Lymphangioleiomyomatosis: the pathophysiology of diminished exercise capacity. Am J Respir Crit Care Med. 1996;153:1368; Taveira-DaSilva AM, Stylianou MP, Hedin CJ, al. Maximal oxygen uptake and severity of disease in lymphangioleiomyomatosis. Am J Respir Crit Care Med. 2003;168:1427.

RADIOLOGY

Chest radiographs in LAM range from normal to showing a reticular or nodular irregular shadowing or, in advanced stages, severe cystic changes. CT demonstrates diffuse, well-defined, round, thin-walled cysts scattered throughout the lungs. More recent studies suggest that LAM cysts are more likely to be located in the middle regions of the lung.[72] Cysts vary in size from a few millimeters to up to 2 cm (Fig. 60-1A).[68,73] Additional findings are pleural effusions and parenchymal opacities caused by chylous congestion (Fig. 60-1A).

Correlation between the extent of the cystic parenchymal replacement, as measured by HRCT, and the severity of the disease, as determined by spirometry, D_{LCO}, or exercise performance, has been reported.[69,73–77] Computer analysis of HRCT can quantify the extent of cystic changes, represented as the "cyst score," which is the percentage of lung volume occupied by cysts, and which can be used as a biomarker of disease severity and response to therapy.[77–81] An ongoing concern regarding the use of HRCT is the cumulative radiation exposure to the patient from repeated examinations. LAM cysts can also be evaluated by ultra low-dose CTs that generate cyst scores and can visualize other changes in the lung parenchyma at radiation exposures equivalent to those of a chest x-ray, thus reducing risk to patients.[82] Small cysts may not be visualized by this procedure. However, newer Zoom technology magnifies the small cysts and may thereby increase the apparent cyst score. The small cysts seen by Zoom correlate better with the decline in D_{LCO} than with changes in FEV_1.[83] The Zoom technology also demonstrates that cysts seen in different lung diseases may differ in structure, and it detects abnormalities in areas adjacent to the cysts that may appear to be radiographically normal by conventional CT[76,77]; these emphysematous changes were also seen by histopathology.[76] ^{129}Xe MRI is a promising methodology to assess heterogeneity in cyst ventilation, which may be a marker of early disease or disease progression.[84] Low-field MRI uses oxygen as the contrast agent and is being developed as a method for following ventilation and perfusion.[85] The fact that MRI magnets are now smaller, and that oxygen is the contrast agent, increases the availability of this technique and reduces the cost of the equipment.

Abdominal CT, ultrasonography, and MRI studies may show renal AML, abdominal lymphadenopathy, lymphangioleiomyoma, ascites, and dilation of the thoracic duct.[21,86] AMLs occur primarily in the kidney; far less commonly they can be found in the liver.[87] They are recognized by their characteristic appearance, consisting of areas of fatty density intermixed with more dense areas and normal-appearing renal parenchyma (Fig. 60-1C).[21] Atypical AMLs lacking adipose have been described; they exhibit a predominance of epithelioid LAM cells and, radiologically, may mimic renal cell carcinoma. Lymphangioleiomyomas appear as well-circumscribed masses of variable dimensions, comprising a wall and a central fluid-rich region (Fig. 60-1E).[21] Diurnal variation in size of lymphangioleiomyomas due to the effect of fasting, meals, or postural changes on chyle formation, has been demonstrated by CT and ultrasound. This feature may help differentiate them from malignant tumors and may explain worsening of symptoms during daytime.[88,89]

DIAGNOSIS

The diagnosis of LAM should be strongly suspected in any woman who presents with progressive dyspnea, recurrent pneumothorax, or extrapulmonary manifestations of LAM, in the presence of diffuse cystic lung disease.[9,22,90] The differential diagnosis includes pulmonary emphysema, Langerhans cell histiocytosis, Birt–Hogg–Dubé syndrome, and lymphocytic interstitial pneumonia. Guidelines for the diagnosis and management of LAM have been produced by the American Thoracic, Japanese Respiratory, and European Respiratory Societies.[91–93] In a patient with a compatible clinical history and a characteristic CT of the chest, definite LAM may be diagnosed in the presence of any of the following: (1) a sample of the lung, extrapulmonary lesions, or body fluid showing the histo- or cytopathologic features of LAM, (2) renal angiomyolipoma, (3) chylous effusion, (4) lymphangioleiomyoma, (5) elevated VEGF-D (levels >800 pg/mL), or (6) TSC.[92] Levels of serum VEGF-D, a lymphangiogenic factor, are increased in the serum of patients with LAM compared with normal individuals, and this is associated with lymphatic involvement.[94–97] A VEGF-D serum level greater than or equal to 800 pg/mL is unlikely to be found in other cystic lung diseases and appears to be diagnostic of LAM.[96,97] Transbronchial lung biopsy may yield adequate sample size for pathologic diagnosis and may obviate the need for surgical lung biopsy in patients for whom a noninvasive evaluation did not yield a definitive diagnosis.[98,99] In patients with probable LAM who can undergo close surveillance for progression of disease, pathologic confirmation may not be required unless the initiation of mTOR inhibitor therapy is being considered.[92]

PROGNOSIS

The clinical course of LAM is highly variable but more favorable than initially reported. The estimated median transplant-free survival time for LAM patients in the United States is 29 years from symptom onset and 23 years from diagnosis.[100] A recent study utilizing the National Institutes of Health LAM Registry estimated 10-year and 20-year transplant-free survival to be 85% and 64%, respectively. Lower FEV_1 or DL_{CO} at diagnosis was associated with reduced survival.[10] Hormonal status also affects survival, as decline in lung function slows after menopause.[10,62,101] Patients whose lung tissue shows predominance of cystic lesions tend to have worse lung function and prognosis than those with predominant LAM cell infiltrates.[102]

In patients who have had a lung biopsy, the severity of lung involvement in LAM may be assessed using the LAM Histology Score (LHS), which grades the extent of replacement of normal lung tissue by cystic lesions and LAM cell infiltrates.[103] The amount of tissue involvement is graded semiquantitatively based on percentage of lung tissue involved: LHS-1, <25%; LHS-2, 25% to 50%; and LHS-3, >50% lung tissue. LHS-2 and LHS-3 scores and the presence of hemosiderin-laden macrophages are associated with decreased survival.[103] Patients with predominant cystic disease are likely to have lower FEV_1 and DL_{CO}, lower peak oxygen uptake $\dot{V}_{O_2max}$, and more exercise-induced hypoxemia.[69,104]

As noted above, the severity of lung disease in LAM can also be graded by HRCT. HRCT findings correlate with pulmonary function tests, gas exchange, and exercise performance.[68,69,73–75] HRCT digital image analysis can quantify the percentage of lung volume affected by cysts (cyst score) and can evaluate the texture of areas not involved with cysts.[76,77] Using these methods, percentage of lung volume occupied by cysts was found to correlate with FEV_1, residual volume, and DL_{CO}.[76,77] A predominance of small cysts was associated with reduced DL_{CO} and less favorable clinical outcome.[83]

The simplest method of assessing the severity of lung disease in LAM is pulmonary function testing.[9,62] Most patients have airflow obstruction and impaired gas exchange. Early in the disease, a significant number of patients may have normal spirometry or only mild airflow obstruction, along with a marked decrease in diffusion capacity. In these patients, the severity of disease is best graded by tests of gas exchange such as $DL_{CO,}$ cardiopulmonary exercise testing, or 6-min walk test.[67,69,75] Exercise-induced hypoxemia can reduce exercise tolerance and may occur in the presence of near-normal DL_{CO} and FEV_1.[69] Correlation between $\dot{V}_{O_2max}$ and LHS scores, and between CT severity grade and A-a/O_2 gradient, dead space/tidal volume ratio, and $\dot{V}_{O_2max}$ have been demonstrated.[67,69,75–77] Rates of functional decline over time may help in defining the course of disease—that is, whether it is rapidly or slowly progressive. Sequential lung function testing every 3 to 6 months is warranted to assess the progression of disease.[62,101] A positive response to bronchodilators occurs in 25% to 30% of LAM patients.[104,105] Patients who respond to bronchodilators tend to have a predominantly cellular pattern of LAM lung lesions and greater rates of decline in FEV_1.[104] A low initial DL_{CO} was also reported to be a predictor of accelerated loss of FEV_1.[106]

Patients who present with exertional dyspnea and hemoptysis tend to have more severe disease, greater rates of disease progression, and lower survival than those who present with pneumothorax.[107] This may be due to either a delay in diagnosis or an insidious course in those who present with dyspnea. Lymphatic involvement (e.g., chylous effusions, lymphadenopathy, lymphangioleiomyomas) may be associated with a more severe form of LAM.[95,108,109] Correlation between LHS and the expression of VEGF-C has been reported.[109] Serum levels of VEGF-D are especially elevated in patients with lymphatic abnormalities, and they correlate inversely with DL_{CO} and directly with HRCT scan grading of severity of lung disease.[94,95,109] Measurement of serum VEGF-D may be of value in establishing a diagnosis, predicting rate of progression, and indicating response to therapy with sirolimus.[110,111]

GENERAL MANAGEMENT

LAM patients should be told about the chronic nature of LAM, and, if feasible, they should be referred to a specialized multidisciplinary LAM clinic and national patient support organization. In keeping with contemporary rehabilitation approaches for chronic lung disease,[112] patients should be encouraged to optimize their diet to achieve optimal body mass index and exercise regularly. The limits of exercise should be dictated only by their exercise capacity, as determined by their underlying lung function and any comorbidities. Sports involving extreme physical contact (e.g., martial arts) should be avoided if there is a risk of hemorrhage from AML. Patients should be advised to continue with normal activities, and that supplemental oxygen should be used during air travel if there is evidence of resting hypoxemia. The risk of life-threatening pneumothorax associated with air travel appears to be low.[113,114] However, if patients experience sudden onset of breathlessness or chest pain prior to air travel, pneumothorax should be excluded before departure. Finally, because of the risk, most clinicians would advise patients with severely compromised lung function to avoid flying, as a pneumothorax during flight could have serious consequences.

A 6-min walk test or a cardiopulmonary exercise test to uncover exercise-induced hypoxemia, and to determine the need for supplemental oxygen, is recommended. Patients who desaturate during exercise should be given supplemental oxygen at flow rates adjusted to sustain oxygen saturation above 88% to 90%. Patients should be advised against using estrogen-containing contraceptives and avoid phytoestrogen-rich food. For menopausal symptoms, compounds for the topical delivery of estrogens can improve quality of life and do not appear to cause a significant increase in serum levels.[115] Guidelines for patients with other estrogen-responsive tumors suggest that topical hormonal administration is likely safe, but a tailored discussion regarding the potential risk and benefits should be undertaken.[116]

TARGETED THERAPY

Currently the only recommended pharmacologic agents for treatment of LAM are the mTOR inhibitor sirolimus (rapamycin) and its analogues ("rapalogues").[91,117] Efforts to develop other therapeutics have adopted a drug-repurposing approach based on putative molecular targets that are dysregulated in LAM cells or nodules. Those that have undergone early clinical development are indicated in Table 60-3 and include antineoplastic and hormonal agents. Results from preclinical models suggest that statins, inhibitors of autophagy, tyrosine kinase inhibitors, and immune checkpoint inhibitors might be effective therapies. Established and putative therapeutic targets and drugs are discussed in the following section.

Mechanistic Target of Rapamycin (mTOR) Inhibitors

The discovery that the TSC genes *TSC1* and *TSC2* are involved in the pathogenesis of LAM led to major advances in its treatment. *TSC1* and *TSC2* are tumor suppressor genes that encode the proteins hamartin and tuberin, respectively. These proteins form a cytoplasmic complex in association with a third protein, TBC1D7, that regulates the intracellular serine/threonine kinase mTOR, which integrates growth factor, energy, and stress signaling, thereby regulating cell growth, proliferation, migration, and survival.[118–120] Two different complexes involving mTOR, mTORC1, and mTORC2, have been identified.[85–87] Tuberin is a GTPase-activating protein for the guanine nucleotide–binding protein RHEB (Ras homolog enriched in brain), promoting the formation of inactive RHEB-GDP from active RHEB-GTP.[85] Inhibition or absence of tuberin, as occurs with *TSC2* gene mutations, results in excessive mTORC1 activity, which results in inappropriate anabolic and tumorigenic effects.[121] Of note, mTOR (and its protein complexes) is a highly conserved eukaryotic protein that controls diverse cellular processes, including cellular growth, proliferation, differentiation, senescence, autophagy, and metabolism. Despite its pleiotropic effects, however, the striking effect of somatic *TSC2* loss on mTORC1 activity in LAM tumors[121] indicates its potential as a therapeutic target.

Rapamycin (Sirolimus) forms a complex with FK506-binding protein 12 and inhibits mTORC1.[120] Sirolimus provides only partial inhibition of mTORC1 and has some inhibitory effect on mTORC2 signaling.[122–124] In experimental models, sirolimus was shown to decrease tumor size in animals with a germline mutation of *TSC2*.[125] Treatment with a sirolimus analogue decreased the severity of renal cystadenomas and liver hemangiomas that spontaneously develop in *TSC2*$^{+/-}$ mice, and it decreased the growth of *TSC2*$^{-/-}$ tumors xenografted in nude mice.[126] In a rat model of spontaneous renal cell carcinoma associated with germline *TSC2* mutations, tumors exhibited excessive mTORC1 activation and proliferation, and these were reduced by administration of sirolimus.[125] In human subjects with TSC or LAM who had renal AMLs, treatment with sirolimus

TABLE 60-3 Targeted Therapies for LAM

Mechanism	Target	Drug	CT.gov Accession	Phase
Antineoplastic	mTORC1/2	Sirolimus	NCT00414648	3
		Everolimus	NCT01059318, NCT00792766	1/2
	mTORC2/RhoA	Simvastatin ± sirolimus	NCT02061397, NCT00001465	1, Observational[a]
	mTORC2/proteases	Doxycycline	NCT00989742	2
	GPCR signaling	Celecoxib	NCT02484664	1
	Tyrosine kinases			
	PDGFR	Nintedanib	NCT03062943	2
		Imatinib	NCT03131999	2
	Src	Saracatinib	NCT02116712	1
	Unknown	Resveratrol + sirolimus	NCT03253913	2
Autophagy	Autophagy initiation	Hydroxychloroquine + sirolimus	NCT01687179	1
Sex hormones	Aromatase	Letrazole	NCT01353209	2
	Progesterone receptor	Progesterone	NCT00001465	Observational[a]

[a] *Observational data suggesting lack of efficacy of simvastatin or progesterone in LAM are derived from the NIH LAM Natural History Study. These studies are discussed and cited in the text.*

decreased tumor size, but the tumors tended to increase in size after cessation of therapy.[127–130]

The effect of sirolimus on pulmonary function was examined in 89 patients with LAM in the MILES trial.[131] A total of 46 patients with significantly reduced lung function were treated with sirolimus and 43 with placebo for 12 months; both groups were followed for an additional year off of therapy. Compared with the placebo group, the sirolimus group experienced improvements in FVC, FEV_1, quality of life, and functional performance. Importantly, some subjects experienced decline in lung function despite therapy with sirolimus, and, in responders, decline in lung function tended to resume after cessation of therapy and paralleled that of the placebo group. In a post-hoc analysis, reduction in serum VEGF-D levels after administration of sirolimus appeared to correlate with improvement in lung function, suggesting that VEGF-D might be a useful biomarker of treatment response.[110,111] In another study, 19 patients with either rapidly progressive lung disease or lymphangioleiomyomas and chylous effusions were treated with sirolimus for approximately 2.5 years. Instead of the expected decline in lung function, an increase in FEV_1 and DL_{CO} was observed.[132] Nine patients experienced complete resolution of their chylous effusions and abdominal lymphangioleiomyomas.

Based on the findings in the MILES trial, it is recommended that sirolimus be given to patients whose FEV_1 has fallen below 70% or those above this threshold who are exhibiting an accelerated decline in lung function.[91] Sirolimus therapy is also recommended for LAM patients with symptomatic lymphangioleiomyomas and chylous pleural effusions or ascites. The accepted starting dose of sirolimus is 2 mg/d, and sirolimus serum levels should be monitored. Although the dose in the MILES trial was adjusted to attain trough levels between 5 and 15 ng/mL, retrospective analyses suggest that lower levels may suffice.[91] The role of low-dose (1 mg/d) sirolimus in preventing progression of disease in patients with mild disease is currently being investigated (MILED; NCT03150914). Adverse events associated with sirolimus therapy include oral mucosal ulcers, hypertension, hyperlipidemia, proteinuria, increased serum creatinine, infections, acne, amenorrhea, and sirolimus-related interstitial pneumonitis. Close patient monitoring is recommended. The durability and adverse effects of long-term sirolimus therapy are the subject of an ongoing registry-based study in patients with LAM (MIDAS; NCT02432560). In one long-term follow-up study, however, prolonged administration was associated with stabilization of lung function, as well as reduction in VEGF-D levels; in this case, there was no correlation between the magnitude of reduction in VEGF-D levels and the rate of decline in FEV_1.[133]

Antiestrogen Therapy

Oophorectomy, progesterone, and gonadotrophin-releasing hormone (GnRH) analogues have been employed in the treatment of LAM but are no longer routinely recommended.[91,93] Although antiestrogen therapies for LAM have not been studied in clinical trials, case reports and uncontrolled studies claimed a beneficial effect.[134] Subsequent studies challenged this assertion, however. An early study from Stanford and Mayo Clinic found little benefit in 19 patients after oophorectomy or treatment with progesterone.[135] In a retrospective analysis, a reduced rate of decline in FEV_1 and DL_{CO} was reported in premenopausal patients treated with progesterone.[101] However, when patients with short-term follow-up were excluded from the analysis, the effect of progesterone was not significant.[101] In another retrospective study, no difference was observed in disease progression between patients treated with or not treated with progesterone.[62] Data from studies that assessed the effect of GnRH analogues also have been inconclusive.[136,137] Current guidelines recommend against the use of hormonal therapy.[91] However, experimental data from preclinical models continue to indicate female hormone activity as a therapeutic target in LAM.[49–52,138,139] Further studies aimed at suppressing estrogen secretion (e.g., aromatase inhibitors) or activity are needed.

Matrix Metalloproteinase Inhibitors

Doxycycline is an MMP inhibitor that affects MMP production in *TSC2*-null ELT3 cells[140] and inhibits MMP2 secretion by *TSC2*-null mouse embryonic and human LAM cells.[141] A potential role of doxycycline in the treatment of LAM was suggested by a report of one patient with LAM in whom treatment with doxycycline decreased urinary MMP levels and improved lung function.[142] A decrease in serum and urine levels of MMP-9 and MMP-2 in 34 patients treated with doxycycline has been reported.[143] A controlled study showed that it is unlikely that doxycycline has a useful effect in LAM,[144] and current guidelines recommend against its use.[91]

Statins

There is evidence that both mTORC1 and mTORC2 are necessary for cell proliferation and survival in *TSC2*-deficient cells.[145] In the absence of tuberin, RhoA activity is increased, resulting in increased cell survival.[145] Since sirolimus primarily suppresses mTORC1 signaling, there is a rational for new therapies targeting mTORC2 signaling. Statins inhibit both sirolimus-sensitive and sirolimus-insensitive mechanisms of *TSC2*-null cell growth by inhibiting RhoA GTPase activity.[146] In one study, atorvastatin was shown to inhibit the growth of $TSC2^{-/-}$ rat ELT-3 cells and mouse embryonic fibroblasts while decreasing RHEB-GTPase activity and function.[146] A synergistic effect of simvastatin and sirolimus in inhibiting proliferation of *TSC2*-null cells and *TSC2*-null tumor growth has been described.[145] This effect appears to be specific for simvastatin; in a mouse model of TSC, atorvastatin failed to reduce the size of liver and renal tumors.[147] In a mouse model of LAM, simvastatin prevented alveolar space enlargement and, combined with sirolimus, blocked MMP upregulation, reducing *TSC2*-null lesions and alveolar destruction.[61] However, in a retrospective study of LAM patients, the rate of decline in lung diffusion capacity for patients who were treated with statins for hypercholesterolemia was greater than that of their matched off-statin controls.[148] In agreement, a phase 1 trial performed in 10 patients with LAM who were taking sirolimus indicated that the addition of simvastatin was well tolerated and lowered cholesterol but failed to improve lung function.[149]

Inhibitors of Autophagy

As a central regulator of energy, protein, and organellar homeostasis, autophagy is thought to play a major role in the molecular pathophysiology of neoplastic processes, including LAM.[150–152] mTORC1 is an endogenous suppressor of autophagy initiation; under conditions of cellular stress, mTORC1 activity is reduced, thereby triggering autophagy. mTOR inhibitors such as sirolimus therefore facilitate or increase autophagic activity, which, in LAM, may result in a paradoxical increase in cell survival.[151–154] Therefore, the autophagy inhibitor hydroxychloroquine may reverse this pro-survival effect of sirolimus, or as observed in other cancer cells, induce cell death and reduce proliferation.[152,154,155] The combination of mTORC1 inhibition with sirolimus and inhibition of autophagy with hydroxychloroquine was found to be more effective than either treatment alone in inhibiting the survival of *TSC2*-null cells and the growth of *TSC2*-null xenograft tumors, as well as the spontaneous development of renal tumors in $TSC2^{+/-}$ mice.[154] Inhibition of autophagy with hydroxychloroquine could potentially complement the effect of sirolimus in the treatment of LAM. In a phase 1 clinical trial, there was no toxicity associated with hydroxychloroquine when given in combination with sirolimus, and serum biomarkers of dose and change in lung function were identified.[156] These observations provide a rationale and potential tools for testing the effect of chloroquine and sirolimus in LAM patients.[157]

Checkpoint Inhibitors

As is the case for many neoplastic diseases, mechanisms in the tumor microenvironment that promote tumor growth and survival are emerging therapeutic targets.[158] In pulmonary LAM, these include angio- and lymphangiogenesis, cancer-associated fibroblasts, and the myeloid and lymphoid cells observed in LAM nodules.[159–162] Recent studies indicated increased infiltration of LAM nodules with T cells expressing programmed cell death 1 (PD1), a target for tumor-induced suppression of T-cell immunosurveillance; exogenously administered inhibitors of PD1 (i.e., "checkpoint inhibitors") reduced the growth of *TSC2*-deficient tumors in murine models.[163,164] In addition to checkpoint inhibitors, adoptively transferred T cells engineered to recognize LAM cell-specific antigens were effective in reducing the burden of *TSC2*-deficient tumors in mice.[165] Proof of efficacy of these approaches awaits further testing in clinical trials.

TREATMENT OF COMPLICATIONS

Several well-recognized complications of LAM are considered below.

Pneumothorax

Small pneumothoraces may be treated conservatively by chest tube drainage. Because of the high rate of pneumothorax recurrence, chemical or surgical pleurodesis by video-assisted thoracoscopy should be considered at the time of the initial event.[92,166] Chemical sclerosis, pleurectomy, mechanical abrasion, and talc poudrage are most effective, although high recurrence rates have been reported in some studies.[166] A recent report suggested that total pleural covering with surgical mesh might reduce recurrence rates.[167] In choosing the modality of pleurodesis, potential complications during future lung transplantation related to the degree of fibrothorax produced should be considered.[168,169] However, prior pleurodesis is not a contraindication to lung transplantation at experienced centers.

Chylous Effusions and Lymphangioleiomyomas

Chylous effusions may cause dyspnea and compromise respiratory function. Frequent drainage of chylous effusions may result in protein loss, lymphopenia, and weight loss.[132,170] Several treatments such as low-fat diet, pleuro-peritoneal or peritoneal-venous shunts, and thoracic duct embolization have been employed, but there is little experience with these therapeutic modalities in LAM.[171,172] The same is true of treatment with somatostatin and octreotide.[173] Lymphangioleiomyomas may cause abdominal pain, urinary frequency, obstipation, tenesmus, and peripheral edema. Abdominal symptoms and imaging associated with lymphangioleiomyomas may mimic malignancy and create diagnostic uncertainty.[89,174–176] Sirolimus is effective in facilitating resolution of chylous effusions and in decreasing the size of lymphangioleiomyomas and is therefore considered to be first line therapy for these complications. Invasive procedures should be reserved for symptomatic patients who fail medical therapy.[132,169]

Angiomyolipomas

AMLs less than 4 cm in diameter are usually well tolerated and are associated with preserved renal function.[87] The principal complication of larger AMLs is bleeding. Embolization, rather than resection, is recommended in the setting of acute hemorrhage to preserve kidney function.[177–180] Although rare, severe pain may also be an indication for selective embolization of the tumor. Prophylactic embolization may be undertaken in patients with large AMLs and no known episodes of bleeding, but strong evidence favoring this approach is lacking. In one case series with imaging follow-up, embolization led to a durable reduction in AML volume in patients with sporadic LAM; in contrast, initial response was observed in patients with TSC, but recurrence was often observed.[180] Since treatment with mTOR inhibitors (e.g., sirolimus, everolimus) reduces tumor size in about 44% to 50% of the patients, it may also prevent bleeding and the need for embolization or surgical intervention.[131,132,181] Of note, a therapeutic response to mTOR inhibitors may require dose escalation or the use of an alternative rapalog.[130,181,182] mTOR inhibitors may be effective in the treatment of large AMLs, although most prefer arterial embolization as a definitive initial approach.[127–129] Discontinuation of sirolimus therapy may result in enlargement of the AML, although they tend to be less than their original size.

Complications Associated with Pregnancy

Of the 353 pregnancies recorded in the LAM registry, 66.9% resulted in live birth, 16.7% had spontaneous abortion, and 15% had therapeutic abortion;[9] 22% of those who had been pregnant experienced worsening of respiratory symptoms during pregnancy. Patients who were diagnosed with LAM during pregnancy had more premature births and higher frequency of dyspnea, pneumothorax, and chylothorax than those diagnosed either before or after pregnancy.[183] A recent analysis of the UK and NHLBI LAM cohorts identified 16 patients with LAM who experienced pregnancy.[48] There was a higher than expected acceleration in lung function decline and rate of pneumothorax, but little in the way of obstetric complications. These data, along with anecdotal reports of worsening symptoms during pregnancy,[184] indicate that LAM patients should be counselled accordingly prior to conception. In patients with moderate to severe disease or those in whom lung function is declining rapidly, pregnancy should be discouraged. Patients with mild disease can be advised that although disease-related complications may occur, they will likely not impact significantly on the pregnancy or delivery with close medical and obstetrics monitoring. Sirolimus is a class C teratogen and inhibits wound healing. Although teratogenicity has not been observed in transplant patients on sirolimus therapy for immunosuppression who experience pregnancy and delivery, the long-term effects of fetal exposure are unknown.[169] Should a patient with moderate to severe LAM choose to continue sirolimus therapy during pregnancy, its short-term discontinuation during the peripartum period might prevent obstetric or surgical complications.

LUNG TRANSPLANTATION

We suggest that lung transplantation be considered when FEV_1 and D_{LCO} are less than 30% predicted, and/or the patient is on continuous supplemental oxygen and unable to carry out activities of daily living. Importantly, the patient should rate her quality of life as being poor, and should be certain that she wishes to undergo lung transplantation. In all, 138 LAM patients underwent lung transplantation in the United States between 2003 and 2017. This cohort was characterized by median FEV_1 of 23% predicted, median 6-min walk distance of 787 ft (240 m), and median oxygen requirement of 5 L. Median survival was estimated at 12 years and surpassed that of other chronic lung diseases.[185] There was no apparent effect of single vs. bilateral lung transplantation on outcome. The European experience is similar to that in the United States.[186] mTOR inhibitors impair wound healing, and their use in the immediate posttransplant period was associated with fatal dehiscence of the bronchial anastomosis. As a result, some have suggested that they be discontinued while patients are on the waiting list for transplantation. However, transplantation has been safely performed on patients who continued therapy until the immediate preoperative period, and an increasing number of centers now allow patients to remain on sirolimus while on the wait list. Reinitiation of sirolimus after healing of the bronchial anastomoses may be advised for the treatment of pre-existing extrapulmonary manifestations of LAM (AML, lymphangioleiomyoma) or for control of chylous pleural effusions.[40,41] Rarely, LAM can recur in the lung allograft, but since, to a large extent, this has not been associated with significant allograft dysfunction, routine inclusion of sirolimus in the post-transplant immunosuppressive regimen is not advised.

LAM IN TUBEROUS SCLEROSIS COMPLEX

TSC is a multisystem autosomal-dominant disorder that affects men and women equally. Its frequency is 1 in 12,000 to 14,000 children under the age of 10, or 1 in 6000 births.[187–189] It is characterized by neurodevelopmental syndromes (e.g., mental retardation, autism, seizures, cortical tubers) and tumors in multiple organs (e.g., facial angiofibroma, periungual fibromas, Shagreen patches, giant-cell astrocytomas, cardiac rhabdomyomas) (Fig. 60-2).[187] In addition to inherited heterozygous germline mutations, generalized and segmental mosaic forms of TSC have been documented.[188,189] The severity of disease appears to correlate with the location and extent of tissue affected by the mosaic mutation. It is therefore possible that sporadic LAM can be an extreme mosaic form of TSC. In fact, the association of TSC and cystic lung disease has long been reported in the literature.[190] Initially the prevalence of clinically significant LAM in TSC (TSC-LAM) was thought to be relatively low, ranging from 0.6% to 2.3% of TSC patients.[190–193] However, subsequent studies showed that the prevalence of lung cysts in women with LAM ranges from 26% to 38%.[6,194,195] Lung cysts were demonstrated in 13% of men with TSC, but only 3% of male patients had >10 cysts, indicating that the disease is generally mild if present.[16] In another case series, the prevalence of LAM in males with TSC, as determined by >4 cysts on CT, was as high as 38%, but the lung disease was mild.[17] The NHLBI LAM registry reported data from 34 TSC patients who were known to have LAM or were later confirmed to have LAM (Table 60-1).[9] Renal AML occurred in 93% of TSC-LAM patients and in only 32% of sporadic LAM subjects. Lymphangioleiomyomas and chylous effusions were more common in sporadic LAM. In a study comparing CT features of 67 patients with TSC-LAM and 256 patients with sporadic LAM, severe disease was present in 25% of TSC-LAM patients versus 40% of sporadic LAM patients.[23] Multifocal micronodular pneumocyte hyperplasia (MMPH) is another pulmonary manifestation of TSC that occurs in males and females; it is thought to be benign.[8] Sclerotic bone lesions were very common in patients with TSC-LAM.[196]

Perhaps because LAM is often diagnosed incidentally or by screening in young patients with TSC, its burden and progression are thought to be milder than in its sporadic form, which, in contrast, is most often diagnosed when patients are symptomatic. Nonetheless, LAM is the leading cause of death in women with TSC,[197] and TSC patients who initially present with symptoms tend to experience more severe lung disease; clinically significant LAM in men with TSC appears to be exceedingly rare. It is therefore recommended that women with TSC be screened for LAM at least once at the age of 18 with HRCT and pulmonary function testing.[198]

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CHAPTER 61

Diffuse Cystic Lung Diseases

Nishant Gupta
Tami J. Bang
Kathryn A. Wikenheiser-Brokamp

INTRODUCTION

The diffuse cystic lung diseases (DCLDs) are a diverse set of disorders that share a common radiologic phenotype of thin-walled parenchymal lucencies.[1] Although often grouped together with other interstitial lung diseases (ILDs), the underlying pathobiology, differential diagnosis, mode of presentation, and natural history of disease progression in DCLDs are sufficiently distinct to warrant classification of DCLDs as a separate independent entity.[2] The subsequent sections of this chapter will provide an overview of the classification and differential diagnosis of DCLDs; detail the clinical, radiologic, and histopathologic features of various DCLDs; and culminate with an integrated approach toward the appropriate diagnosis and management of patients presenting with DCLD.

DEFINITION OF PULMONARY CYST

A pulmonary cyst is defined radiologically as a thin-walled (<2 mm wall thickness) parenchymal lucency interfaced with normal pulmonary parenchyma.[3] Table 61-1 lists the other parenchymal lesions that can mimic cysts and need to be carefully distinguished from cysts. Pathologically, cysts are defined as dilated spaces within the lung tissue that have an epithelial lining. Lung cysts may contain fluid or gas. Dilated spaces without an epithelial lining are referred to as pseudocysts and must be distinguished from true epithelial-lined lung cysts. Some lesions designated as cysts clinically and radiologically may not represent true cysts pathologically; the most common cyst mimics are bronchiectasis, honeycomb remodeling, pulmonary interstitial emphysema, centrilobular emphysema, α1-antitrypsin deficiency, and cavitary lesions.

CLASSIFICATION OF DIFFUSE CYSTIC LUNG DISEASES

DCLDs can be classified into subcategories depending upon the underlying pathogenesis (Table 61-2). However, as highlighted in Fig. 61-1, there can be substantial overlap among the pathogenesis of these entities, and thus some DCLDs could be classified under more than one category.[2]

GENETIC/DEVELOPMENTAL/CONGENITAL DIFFUSE CYSTIC LUNG DISEASES

Below we consider Birt-Hogg-Dubé syndrome, as well as other genetic and developmental diffuse cystic lung diseases.

■ Birt-Hogg-Dubé Syndrome

Birt-Hogg-Dubé syndrome (BHD) is a rare, autosomal dominant disorder characterized by the formation of hair follicle tumors (fibrofolliculomas), kidney tumors, and pulmonary cysts.[4] The initial description of this syndrome was provided by Hornstein and Knickenberg in 1975,[5] followed by the depiction of characteristic skin fibrofolliculomas and autosomal dominant inheritance pattern by Birt, Hogg, and Dubé two years later.[6]

Pathogenesis

BHD is caused by loss of function mutations in the *folliculin (FLCN)* gene, located on the short arm of chromosome 17.[7–9] *FLCN* functions as a tumor suppressor gene, and loss of heterozygosity following a somatic second hit in patients carrying a germline mutation in *FLCN* predisposes them to the formation of BHD renal tumors.[10] Similar findings have been reported in multiple animal models of BHD,[11–14] and the restoration of wild-type *FLCN* expression has been reported to halt oncogenesis in an in vitro cell line–based model.[15]

Multiple different mechanisms have been postulated to drive the tumor suppressor properties of *FLCN*,[16] chief among them being the modulation of the mechanistic target of rapamycin (mTOR) signaling pathway. mTOR is a central regulator that controls the cellular response to multiple environmental stimuli. Dysregulated mTOR signaling is responsible for the development of a related DCLD, lymphangioleiomyomatosis (LAM, covered in detail in Chapter 60). FLCN has been shown to modulate mTOR activity via its interaction with two proteins,

TABLE 61-1 Radiologic Definition of Pulmonary Cysts and Other Parenchymal Lucencies That Can Mimic Cysts

Cyst	Thin walled (<2 mm), spherical parenchymal lucency interfaced with normal lung
Cavity	Gas-filled space within pulmonary consolidation, mass, or nodule, typically thick walled (>2 mm) and more irregularly shaped than cysts
Bulla	Spherical focal lucency, ≥1 cm in diameter, bounded by a thin wall (<1 mm); usually accompanied by emphysematous changes in the adjacent lung
Bleb	Cystic air space bounded by a thin wall adjacent to the visceral pleura, typically <1 cm in size.
Emphysema	Permanently enlarged airspaces distal to the terminal bronchiole with destruction of alveolar walls; usually without visible walls
Pneumatocele	Approximately round, thin-walled, air-filled space in the lung; most frequently caused by infections, trauma, or aspiration of hydrocarbon fluid and usually transient
Honeycombing	Clustered cystic air spaces, typically 3–10 mm in diameter, with 1- to 3-mm wall thickness, that are often stacked on top of each other in layers; usually subpleural and associated with other features of pulmonary fibrosis such as traction bronchiectasis and reticulations
Bronchiectasis	Localized or diffuse bronchial dilatation, usually resulting from chronic infection, proximal airway obstruction, or congenital bronchial abnormality

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TABLE 61-2 Classification of Diffuse Cystic Lung Diseases

Genetic/developmental/congenital
- Birt-Hogg-Dubé syndrome
- Phakomatoses—Cowden syndrome, neurofibromatosis, proteus syndrome
- Connective tissues diseases—Marfan syndrome, Ehlers-Danlos syndrome (type IV)
- COPA syndrome
- Down syndrome/trisomy 21
- Congenital pulmonary airway malformation, bronchopulmonary dysplasia

Associated with lymphoproliferative disorders
- Lymphoid interstitial pneumonia
- Follicular bronchiolitis
- Castleman disease
- Lymphoid granulomatosis
- Amyloidosis
- Light chain deposition disease

Neoplastic
Low-grade malignancies
- Lymphangioleiomyomatosis—sporadic as well as associated with tuberous sclerosis complex
- Histiocytosis
    - Pulmonary Langerhans cell histiocytosis
    - Non–Langerhans cell histiocytoses such as Erdheim-Chester disease, Rosai-Dorfman disease

High-grade malignancies
- Primary pulmonary neoplasms
    - Non–small-cell carcinomas
    - Mesenchymal cystic hamartoma
    - Pleuropulmonary blastoma
    - Lymphoma

- Sarcomas
    - Angiosarcomas
    - Osteosarcomas
    - Synovial sarcoma
    - Ewing sarcoma
    - Leiomyosarcoma
    - Rhabdomyosarcoma
    - Endometrial stromal sarcoma
    - Wilms tumor
    - Pineal teratoma
    - Other sarcomas

- Metastatic epithelial tumors
    - Adenocarcinomas of the gastrointestinal and genitourinary tract
- Systemic malignancies
    - Lymphoma

Infectious
- *Pneumocystis jiroveci* pneumonia
- Staphylococcal pneumonia
- Recurrent respiratory papillomatosis
- Endemic fungal diseases, especially coccidioidomycosis
- Paragonimiasis
- Hydatid cysts (*Echinococcus*)
- COVID-19 pneumonia

Associated with interstitial lung diseases
- Hypersensitivity pneumonitis
- Desquamative interstitial pneumonia

Smoking related
- Pulmonary Langerhans cell histiocytosis
- Desquamative interstitial pneumonia
- Respiratory bronchiolitis/smoking-related cystic lung disease

Other/miscellaneous
- Posttraumatic pseudocysts
- Fire-eaters lung
- Hyper-IgE syndrome
- Acute respiratory distress syndrome

Cyst mimics
- Emphysema/bullae
- α1-Antitrypsin deficiency
- Bronchiectasis
- Honeycombing seen in late stage scarring interstitial lung diseases

COPA, coatomer protein subunit alpha; IgE, immunoglobulin E.

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folliculin interacting protein 1 (FNIP1) and FNIP2, and the 5’ AMP-activated protein kinase (AMPK).[17,18] However, the relationship between *FLCN* downregulation and mTOR dysregulation is complex, with studies showing evidence of activation as well as suppression, suggesting the possibility of cell context–dependent interactions between *FLCN* and mTOR.[11,14,17,19–21] *FLCN* has also been reported to regulate mTOR activity via other mechanisms such as by activating the RagC and RagD GTPases, leading to the phosphorylation of transcription factor EB (TFEB)[22] and amino acid–dependent lysosomal mTOR activation through regulation of the heterodimers Rag A/B and Rag C/D.[23–25] Other pathways that have been implicated in the tumor suppressor action of *FLCN* include modulation of canonical Wingless-related integration site (WNT) signaling,[26] vesicle membrane trafficking via structural similarities to the differentially expressed in normal cells and neoplasia (DENN) domain proteins,[27] transforming growth factor β (TGF-β) signaling,[15] regulation of mitochondrial gene expression,[28,29] modulation of autophagy,[30,31] and activation of the transcription factor E3 (TFE3).[32]

The mechanisms driving the formation of pulmonary cysts in BHD are not well established. Postulated mechanisms to date include alterations in cell–cell adhesion,[33,34] modulation of the mTOR

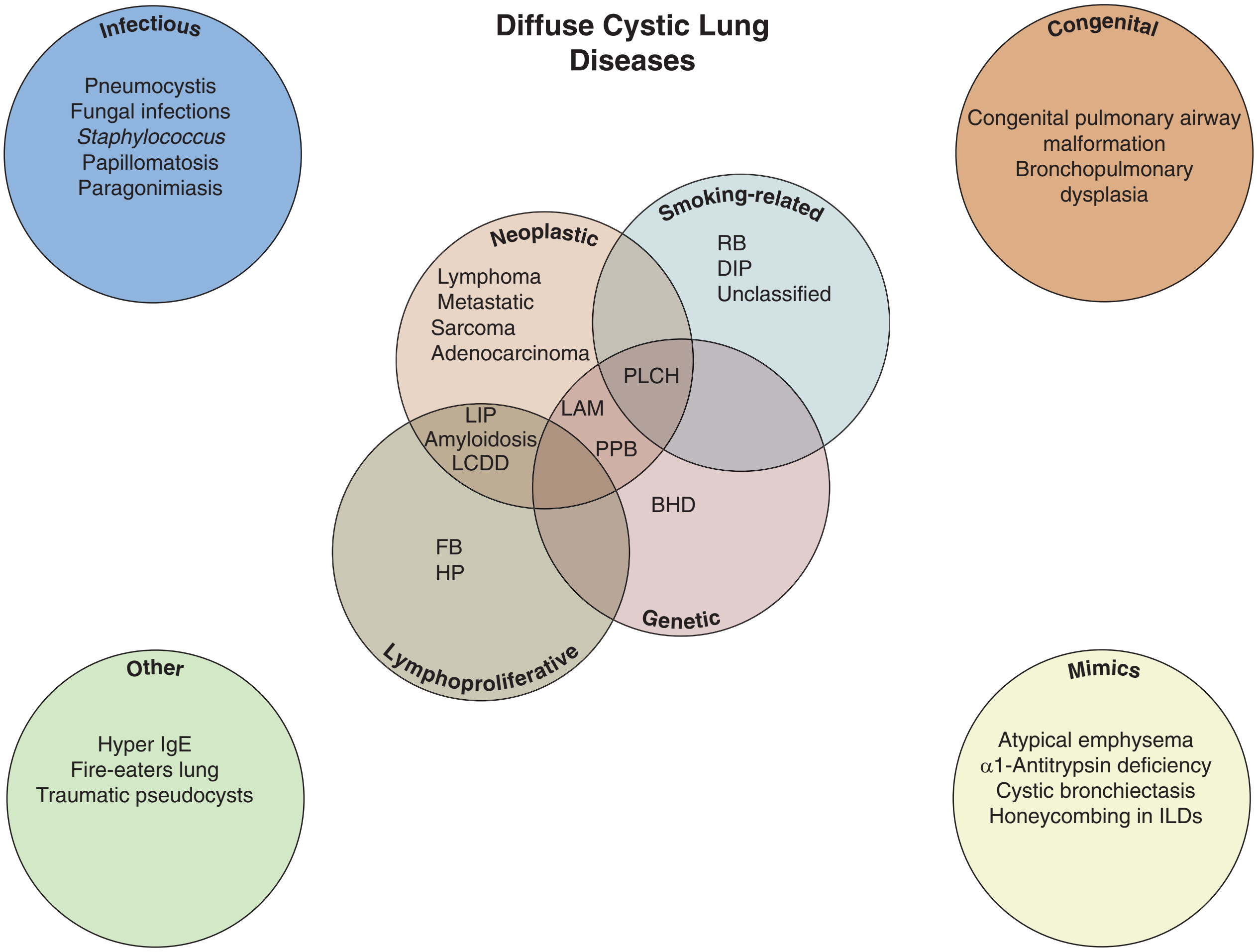
Diffuse Cystic Lung Diseases
Infectious
Pneumocystis
Fungal infections
Staphylococcus
Papillomatosis
Paragonimiasis
Congenital
Congenital pulmonary airway malformation
Bronchopulmonary dysplasia
Smoking-related
RB
DIP
Unclassified
Neoplastic
Lymphoma
Metastatic
Sarcoma
Adenocarcinoma
PLCH
LAM
LIP
Amyloidosis
LCDD
PPB
BHD
FB
HP
Genetic
Lymphoproliferative
Other
Hyper IgE
Fire-eaters lung
Traumatic pseudocysts
Mimics
Atypical emphysema
α1-Antitrypsin deficiency
Cystic bronchiectasis
Honeycombing in ILDs

Figure 61-1 Classification of diffuse cystic lung diseases (DCLDs). Subcategories of DCLDs based upon the underlying pathogenesis are depicted in this Venn diagram. The substantial overlap among the pathogenesis of different DCLDs is shown. BHD, Birt-Hogg-Dubé syndrome; DIP, desquamative interstitial pneumonia; FB, follicular bronchiolitis; HP, hypersensitivity pneumonitis; LAM, lymphangioleiomyomatosis; LCDD, light chain deposition disease; LIP, lymphoid interstitial pneumonia; PLCH, pulmonary Langerhans cell histiocytosis; PPB, pleuropulmonary blastoma. *(Reproduced with permission from Gupta N, Wikenheiser-Brokamp KA, McCormack FX: Diffuse Cystic Lung Diseases. Respiratory Medicine. Cham: Humana Press; 2021.)*

pathway,[33] increased vulnerability of the alveolar septal regions to the mechanical stress of respiration,[35] and *FLCN*-dependent effects on WNT signaling.[26] Two independent laboratories have described a relationship between *FLCN* and the adherens junction protein p0071,[34,36] suggesting the possibility that impaired cell–cell adhesion drives abnormal elastance and pulmonary cyst formation in BHD. In a murine model of BHD, Goncharova et al.[37] demonstrated that loss of *Flcn* leads to alterations in the E-cadherin–dependent epithelial cell–cell junctions, impairment of liver kinase B1 and AMP-activated protein kinase (LKB1-AMPK) signaling, caspase-dependent apoptosis of lung alveolar epithelial cells, and alveolar airspace enlargement, thus supporting a role for *Flcn* in the maintenance of epithelial cell–cell junctions and alveolar epithelial cell survival. More recently, it has been shown that loss of *FLCN* inhibits canonical WNT signaling, suggesting that the formation of pulmonary cysts reflects a defect in normal lung development.[26] Further work is needed to fully elucidate the molecular mechanisms that cause the formation of lung cysts in BHD.

Clinical Manifestations

Extensive phenotypic variability exists in the clinical presentation of patients with BHD. Patients can present with any combination of pulmonary, renal, or skin manifestations.

Cutaneous Although fibrofolliculomas, trichodiscomas, and acrochordons were described in the initial depiction of BHD,[6] the characteristic skin lesion in BHD is a fibrofolliculoma. Fibrofolliculomas are benign hair follicle tumors that present as multiple dome-shaped whitish papules most commonly seen on the face, neck, and upper torso (Fig. 61-2A). Fibrofolliculomas are seen in more than 85% of individuals affected with BHD and usually appear in the third decade of life.[4,38,39] Although other skin lesions such as angiofibromas, lipomas, and others have been described in patients with BHD, these skin lesions are not specific to BHD.[38–40]

Pulmonary The major pulmonary manifestation of BHD is the formation of thin-walled cysts. Pulmonary cysts are seen in greater than 80% of patients with BHD.[38,41–44] Although reported in all age groups, including children,[45,46] pulmonary cysts in BHD are most commonly discovered in the fourth decade of life.[4] The cysts in BHD typically involve less than 10% of the pulmonary parenchyma and do not tend to produce symptoms such as dyspnea on exertion or cough that are typical of other chronic lung diseases. Pulmonary function tests (PFTs) in patients with BHD are generally well preserved and do not tend to deteriorate over time.[43,47]

The major clinical presentation resulting from pulmonary cysts in BHD is the occurrence of a spontaneous pneumothorax, that usually manifests with sudden onset dyspnea and sharp pleuritic

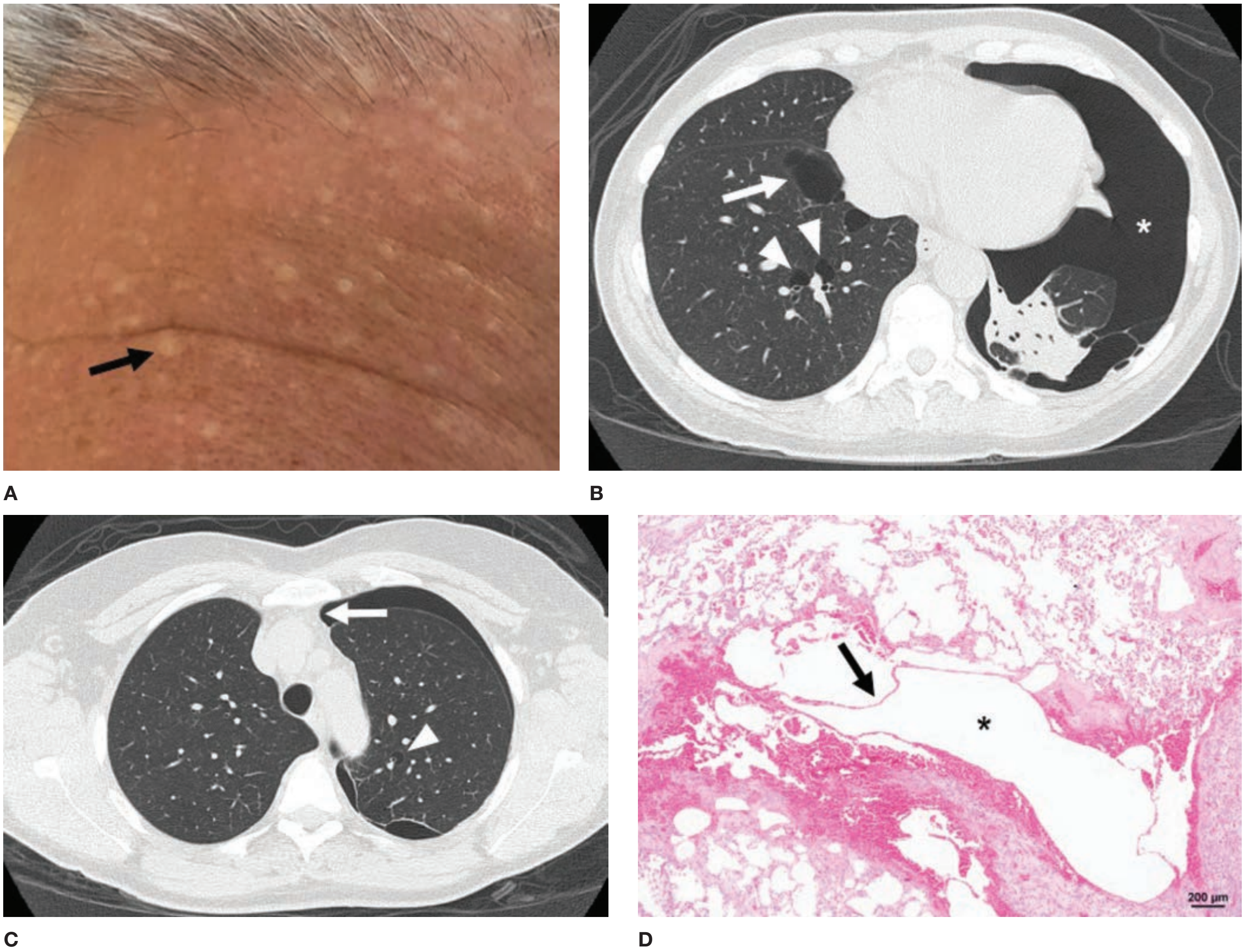

Figure 61-2 Clinical, radiologic, and histopathologic manifestations in Birt-Hogg-Dubé syndrome (BHD). **A.** Multiple, dome-shaped, whitish papules consistent with fibrofolliculomas on the forehead of a patient with BHD. **B.** Axial CT image of the lung bases in a patient with BHD demonstrating a lentiform, subpleural cyst with an internal septation *(arrow)* and perivascular cysts *(arrowheads)* in the right lower lobe. A left pneumothorax *(*)* also is present. **C.** Axial CT image from another patient showing a cyst encircling a bronchovascular bundle referred to as the air-cuff sign *(arrowhead)*. Also present is a left pneumothorax *(arrow)*. **D.** Histologically, the pulmonary cysts *(*)* in BHD have a thin wall lined by normal-appearing alveolar type I and type II epithelial cells with some cysts containing internal septations *(arrow)*. The surrounding lung parenchyma has procedure-related acute hemorrhage but is otherwise unremarkable and without significant inflammation or fibrosis as is characteristic of BHD associated lung cysts.

chest pain. Although most commonly unilateral, bilateral spontaneous pneumothorax has been reported in a minority (~5%) of cases of BHD.[42] Pneumothorax has been reported to occur in 25% to 75% of patients with BHD.[41,42] This wide range in pneumothorax occurrence can largely be explained by ascertainment bias; the 25% estimate is derived from BHD patients presenting to a dermatology/urology center,[41] and the 75% estimate is derived from a pulmonary network report.[42] The average age at the time of development of spontaneous pneumothorax in BHD is in the mid to late 30s.[41,42] There is no known gender predilection. It has been estimated that patients with BHD have a 50-fold higher risk of developing a spontaneous pneumothorax compared with age-matched healthy controls.[48] In two small studies, BHD has been estimated to be the underlying etiology for 5% to 10% of apparent primary spontaneous pneumothoraces.[49,50] Spontaneous pneumothoraces have also been reported in patients with BHD without radiologically apparent cysts on chest imaging.[51] There is an extremely high risk of recurrence (~75%) in BHD patients with a spontaneous pneumothorax.[41,42]

Renal Patients with BHD are at an increased risk of developing renal tumors that can frequently be bilateral and multifocal.[48] Approximately one-third of patients with BHD develop at least one renal tumor, with the average age at diagnosis being around 50 years.[38,44]

Other A variety of other manifestations such as thyroid nodules,[44] parathyroid adenomas,[52] and parotid gland tumors[44,53] have been reported in patients with BHD, although it is unclear if these manifestations are truly related to BHD or represent incidental findings. There is debate regarding the association between BHD and colon neoplasms, with some studies suggesting no increased risk[48] while others suggest an increased risk in patients with certain genotypes.[54]

Radiology

Plain chest radiographs in BHD are generally unremarkable, and high-resolution computed tomography (HRCT) is needed to characterize the cystic change in detail. The pulmonary cysts in BHD have distinct features: the cysts tend to be lower lobe predominant, vary in size from a few millimeters to a few centimeters, are elliptical/lentiform in shape as opposed to the round/spherical cysts in other DCLDs, can have internal structures and septations, and generally occupy less than 10% of the pulmonary parenchyma (Fig. 61-2B).[47,55,56] Cysts in BHD have a predilection to abut the pleural surfaces and indent the mediastinal fat as well as encircle the bronchovascular structures in the so called air-cuff sign (Fig. 61-2C). The intervening pulmonary parenchyma appears grossly normal on HRCT. An expert radiologist can confidently distinguish BHD from other DCLDs in >90% of the cases based on HRCT features alone.[57] Renal tumors in BHD tend to be bilateral and multifocal and are often detected on CT or magnetic resonance imaging (MRI) of the abdomen.

Pathology

Fibrofolliculomas are characterized by cords and strands of epithelial cells that are two to four cells thick, radiating from a central aberrant hair follicle and surrounded by a well-circumscribed proliferation of loose connective tissue.[40] The histopathologic features of pulmonary cysts in BHD mimic the radiologic findings consisting of lower lobe–predominant cystic change that is typically subpleural or abutting the interlobular septa. The cysts can have internal septations, and the cyst walls are characteristically composed of a thin lining of pneumocytes with the surrounding normal lung parenchyma having no significant inflammation or fibrosis (Fig. 61-2D).[35] The cysts in BHD can be easily missed without integration of the clinical and radiographic history and lack specific histopathologic features to make a diagnosis based upon histopathology alone. Renal tumors in BHD can have varying histopathologic patterns, with the most common being hybrid oncocytic and chromophobe tumors (50%), followed by chromophobe (34%), clear cell (9%), oncocytoma (5%), papillary (2%), and other subtypes.[58]

Diagnosis

The diagnosis of BHD should be considered in all patients presenting with a spontaneous pneumothorax or incidentally detected cystic lung disease, but especially in young, nonsmoking patients. Careful attention must be given to personal or family history of skin lesions, pneumothoraces, or renal tumors. It is important to note, however, that there is wide phenotypic variability in BHD and the absence of family history or other organ involvement does not exclude the possibility of BHD. Another scenario that should warrant consideration of BHD is patients presenting with multiple/bilateral renal tumors—especially patients younger than 50 years.

More than one set of diagnostic criteria for BHD has been previously proposed.[16,39,59] In a patient with characteristic cystic change of BHD on chest CT scan and skin lesions on physical examination, confirmation of the presence of fibrofolliculomas by skin biopsy can be sufficient to confirm the diagnosis of BHD.[59] Genetic testing and the detection of pathogenic *FLCN* mutation is the most definitive way to establish the diagnosis of BHD. The sensitivity of genetic testing for BHD with the currently available detection methods is approximately 90%.[16]

Management

Management of the cutaneous and pulmonary manifestations of the disorder are briefly discussed below.

Cutaneous The skin lesions in BHD are benign, do not produce symptoms such as pain or pruritis, and as such do not warrant specific treatment. However, fibrofolliculomas can be cosmetically troubling to some patients with more prominent or disfiguring lesions, thus prompting patients to seek options for treatment. Hyfrecation, followed by curettage if necessary, has been successfully employed to treat BHD-associated fibrofollicuolmas.[60] Laser ablation is another option; however, this approach is somewhat limited by the risk of relapse.[40]

Pulmonary Performance of a baseline chest CT scan in all patients with BHD is suggested to determine the extent of cystic change. Patients should be reassured that the cysts in BHD generally occupy a small portion of the lung parenchyma, do not cause physiologic limitations, and tend not to progress over time.[43,47]

The management of BHD from a pulmonary perspective is largely focused on the treatment and prevention of spontaneous pneumothoraces. Patients should be educated about the presenting signs and symptoms of a spontaneous pneumothorax and advised to seek immediate medical attention in the event of these symptoms. There is an extremely high risk of recurrence (>70%) following conservative management of a spontaneous pneumothorax in patients with BHD.[41,42] Pleurodesis can reduce the risk of recurrence by one-half and is thus recommended following the initial episode of spontaneous pneumothorax rather than waiting for a recurrent episode, as typically occurs after a primary spontaneous pneumothorax.[42,61]

The risk of a spontaneous pneumothorax associated with atmospheric pressure changes as might be experienced with air travel has been estimated to be less than 1 event per 100 flights.[42,62] As such, air travel is considered safe for the majority of patients with BHD. Although a small survey-based study has demonstrated similar risk of development of spontaneous pneumothorax with deep sea diving,[62] we counsel patients to avoid underwater diving in accordance with the British Thoracic Society recommendations.[63]

Renal Renal cancer is the most serious complication of BHD. Serial screening for renal tumors should be performed in all BHD patients starting at the age of 20 years. Gadolinium-enhanced MRI may be the best long-term modality for renal tumor screening, as it provides superior sensitivity to renal ultrasound in its ability to detect small lesions and offers an ionizing radiation–free way to scan as opposed to CT scan. In patients without a detectable lesion, repeat imaging every 3 years or so is adequate. The risk of metastasis increases after a lesion has reached a size of 3 cm, and nephron-sparing surgery is recommended for renal tumors greater than or equal to 3 cm in size.[16,64]

Genetic Testing of Relatives Family members of affected individuals with BHD, especially first-degree relatives, are at an increased risk of inheriting the disease-causing mutation. Genetic counseling and consideration of screening for mutation detection should be offered to all at-risk adult relatives of patients with BHD.[59] Individuals with identified pathogenic *FLCN* mutation should be periodically screened for renal tumors similar to other patients with BHD.

■ Other Genetic DCLDs

A variety of genetic disorders such as Marfan syndrome,[65] Ehlers Danlos syndrome (type IV),[66] neurofibromatosis,[67,68] Cowden syndrome,[69] Proteus syndrome,[70] Coatomer subunit alpha (COPA) syndrome,[71] and Down syndrome[72] (Fig. 61-3A) can be associated with pulmonary cysts in a small proportion of patients (Table 61-3).

COPA syndrome is a recently described autosomal dominant disease that is caused by mutations in the *COPA* gene located on chromosome 1 resulting in impaired cellular vesicular transport function.[73] The hallmark of COPA syndrome is marked immune dysregulation, with a variety of autoantibodies having been detected in these patients. Clinically, the most commonly affected organs are lungs, kidneys, and joints. The manifestations begin early in childhood, and a majority of the patients are symptomatic prior to the age of 5 years.[73] Pulmonary involvement is almost universal in COPA syndrome, and cystic lung disease has been described in greater than 80% of the patients. Other pulmonary manifestations of COPA syndrome include hemoptysis, diffuse alveolar hemorrhage,

TABLE 61-3 Genetic Syndromes Associated with Pulmonary Cysts

Disease	Associated Genes	Category	Pulmonary Features	Other Clinical Features
Syndromes associated with tumors				
Tuberous sclerosis complex[75]	*TSC1*, *TSC2*	AD	Pulmonary cysts (LAM) in 30%–40% in females and 10%–15% in males, MMPH, pleural effusions	Skin lesions, seizures, developmental delays, tumors in various organs
Birt-Hogg-Dubé syndrome[47,55]	*FLCN*	AD	Pulmonary cysts in >80%	Cutaneous fibrofolliculomas, renal cysts, and renal cancers
Neurofibromatosis[67,68]	*NF1*, *NF2*	AD	Emphysema (25%), cysts (25%), ground-glass abnormality (37%), bullae (50%), and reticular abnormalities (50%)	Skin lesions, hamartomas, optic gliomas, and neurofibromas
Cowden syndrome[69]	*PTEN*	AD	Cysts in 80%, nodules	Mucocutaneous and visceral hamartomas and an increased lifetime risk of thyroid, breast, endometrial, renal, and colon cancers
DICER1 syndrome[77,81]	*DICER1*	AD	Pleuropulmonary blastoma (PPB), pulmonary cysts	Thyroid gland neoplasia, ovarian tumors, cystic nephroma, and tumors at various sites
Syndromes of disordered connective tissue				
Marfan syndrome[65]	*FBN1*	AD	10% have apical blebs and bullae	Tall stature, joint laxity, aortic dilation, arachnodactyly, pectus excavatum, and ocular findings
Vascular Ehlers-Danlos syndrome (type IV)[66]	*COL3A1*	AD	Pulmonary blebs, cystic lesions, and hemorrhagic or fibrous nodules	Easy bruising, thin and translucent skin, and tissue fragility
Cutis laxa[73]	*FBLN5*, *FBLN4*, *EFEMP2*, *LTBP4*, *ELN*	AD/AR	Emphysema, bronchiectasis	Loose, saggy, inelastic skin, hernias, visceral diverticula, joint hypermobility
FLNA mutation[74]	*FLNA*	XL	Cysts, emphysema	Intellectual disability, seizures, and cardiac valvular anomalies
Others				
Down syndrome[73]	—	Chromosomal, trisomy 21	Cysts in 20%–36%; usually subpleural, sleep apnea	Dysmorphic features, developmental delay, congenital malformations
Proteus syndrome[70]	*AKT1*	Somatic mosaic mutation	Cysts in ~10%	Asymmetric growth, nevi, vascular malformations
COPA syndrome[71]	*COPA*	AD	Pulmonary cysts (80%), diffuse alveolar hemorrhage, and follicular bronchiolitis	Arthritis, proteinuria, nephropathy, autoantibodies
"Brain-thyroid-lung" syndrome[77,78]	*NKX2-1*	AD	Cysts, alveolar proteinosis, interstitial pneumonitis	Chorea, other neurologic symptoms, hypothyroidism

AD, autosomal dominant; AR, autosomal recessive; LAM, lymphangioleiomyomatosis; MMPH, multifocal micronodular pneumocyte hyperplasia; XL, X linked.
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and ILD, most commonly in the form of follicular bronchiolitis/lymphoid interstitial pneumonia.[71]

Other genetic syndromes such as cystic fibrosis, α1-antitrypsin deficiency, cutis laxa,[74] and filamin A *(FLNA)* mutation[75] (Fig. 61-3B) also cause lung destruction but manifest mainly as emphysema, bronchiectasis, and alveolar growth abnormalities rather than true pulmonary cysts. More common DCLDs such as LAM and PLCH also have a genetic basis but are better classified under the neoplastic subcategory.[1,76]

■ Developmental DCLDs

Bronchopulmonary dysplasia (BPD) and congenital pulmonary airway malformation (CPAM) are the most common developmental abnormalities that can present as DCLD. These disorders are typically identified in the pediatric age groups, although rarely the presentation may be delayed until adulthood.[77] CPAM is the most common lower respiratory tract malformation and is believed to arise due to in utero obstruction during lung development (Fig. 61-3C). CPAM is further classified based on the cyst size, which can vary from a few millimeters to more than 2 cm.[78] BPD is a chronic lung disease caused by disruption in normal alveolar growth due to premature birth and is believed to result from an aberrant reparative response to both antenatal injury and repetitive postnatal injury to the developing lungs (Fig. 61-3D).[79] Radiologically, BPD manifests as alveolar simplification that can mimic DCLDs.[80] Other congenital disorders that can produce pulmonary cystic change include congenital lobar emphysema, pleuropulmonary blastoma (PPB) due to *DICER1* mutations (discussed under neoplastic etiologies),[81] and brain-thyroid-lung syndrome caused by *NKX2-1* mutations.[78,82]

DIFFUSE CYSTIC LUNG DISEASES CAUSED BY LYMPHOPROLIFERATIVE DISORDERS

Diffuse cystic lung disease may be associated with lymphoproliferative disorders. Below we consider cystic lung disease seen with

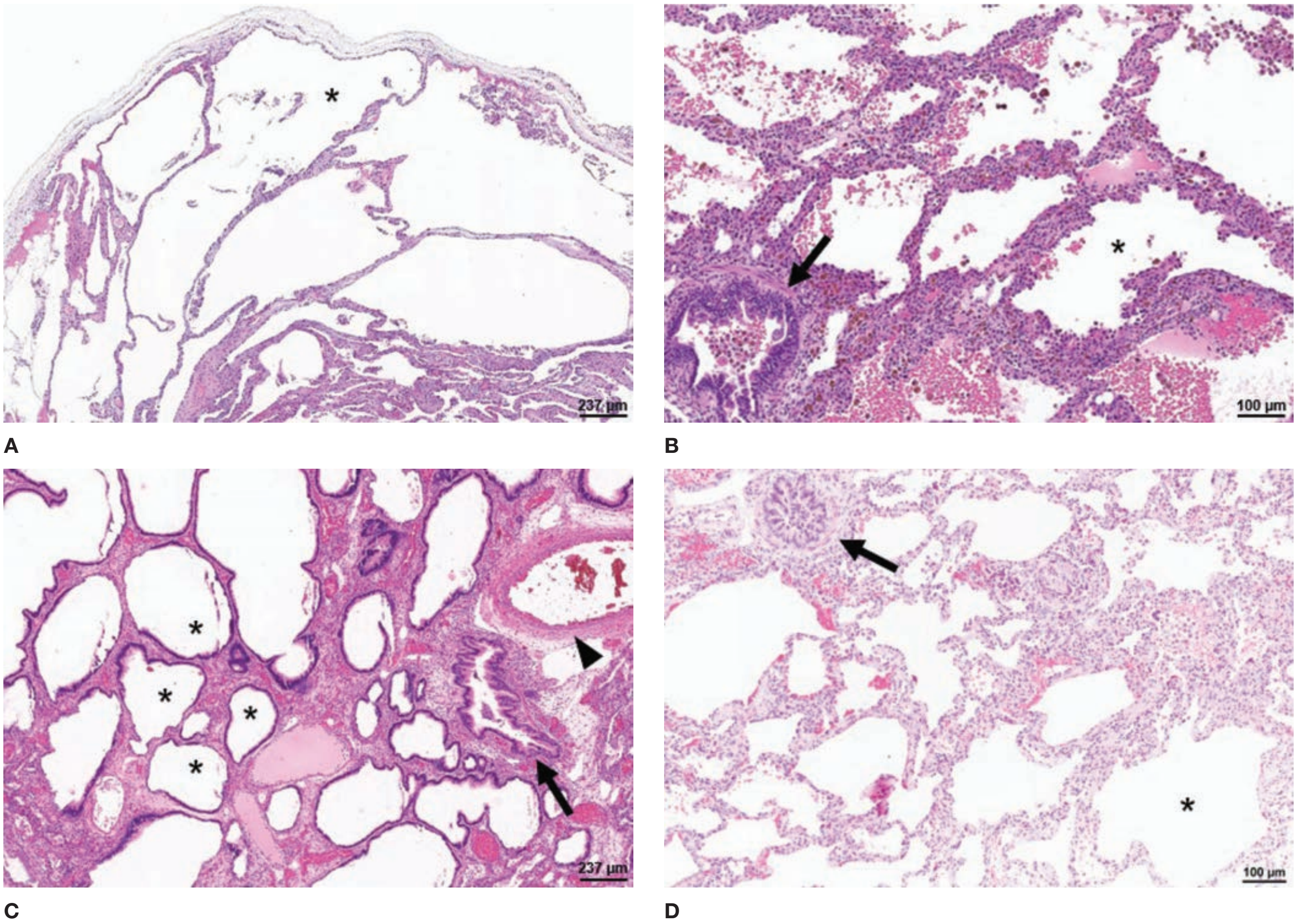

Figure 61-3 Histopathology of pulmonary abnormalities in multiple genetic and developmental diffuse lung diseases that can present as pulmonary cysts. **A.** Lung growth abnormality in a patient with trisomy 21 with cystic enlargement of subpleural alveoli *(*)* as a result of deficient alveolarization. **B.** Lung explant from a patient with a pathogenic filamin A mutation showing marked alveolar enlargement and simplification *(*)* reflective of a lung growth abnormality. The marked alveolar enlargement can be appreciated by comparing the alveoli to the bronchiole *(arrow)*, which is normally larger in size. **C.** Congenital pulmonary airway malformation (CPAM) characterized by abnormally opposed bronchiole-like structures *(*)* that unlike the normal bronchiole *(arrow)* are not accompanied by arteries *(arrowhead)*. **D.** Bronchopulmonary dysplasia manifested as chronic neonatal lung disease with prominent distension and simplification of alveoli *(*)*, which are larger than the bronchiole *(arrow)*.

follicular bronchiolitis and lymphoid interstitial pneumonia, amyloidosis, and light chain deposition disease.

■ Follicular Bronchiolitis/Lymphoid Interstitial Pneumonia

Follicular bronchiolitis (FB) and lymphoid interstitial pneumonia (LIP) are clinicopathologic terms describing two entities along a continuum. These entities are characterized by polyclonal proliferations and infiltration of lymphocytes, varying from involvement of the conducting airways to more diffuse lung involvement with cellular expansion of the pulmonary interstitium including the alveolar septa.[77] The lymphoid follicular hyperplasia is centered around the airways in FB, whereas LIP represents diffuse involvement of the pulmonary parenchyma by the reactive lymphoid cells.[83]

Pathogenesis

Although FB/LIP can occasionally occur in isolation in an idiopathic fashion, these entities are typically seen in association with underlying immune dysregulatory disorders. The most common conditions that predispose to the development of FB/LIP include autoimmune conditions such as Sjögren syndrome, systemic lupus erythematosus, and rheumatoid arthritis, as well as other immune-dysregulatory states such as common variable immune deficiency (CVID) and, principally in the pediatric population, human immunodeficiency virus (HIV) infection. These associations suggest that FB/LIP develops as a result of aberrant inflammatory responses to chronic antigenic stimulation in hosts with underlying immune-dysregulatory conditions. The exact mechanism that drives the formation of pulmonary cysts in FB/LIP is not fully understood. Proposed hypotheses include a check-valve mechanism allowing air entry but not egress due to bronchiolar compression by the reactive lymphoid tissue or ischemic parenchymal destruction due to vascular obstruction.[77]

Clinical Manifestations

The pulmonary symptoms related to FB/LIP are relatively nonspecific and most commonly consist of dyspnea on exertion and chronic cough.[84] Spontaneous pneumothorax can occur in patients with cystic FB/LIP and may be the presenting manifestation that leads to the diagnosis. However, for reasons that are not entirely clear, the incidence of spontaneous pneumothorax appears to be lower in patients with FB/LIP compared to patients with other DCLDs such as BHD and LAM.[61]

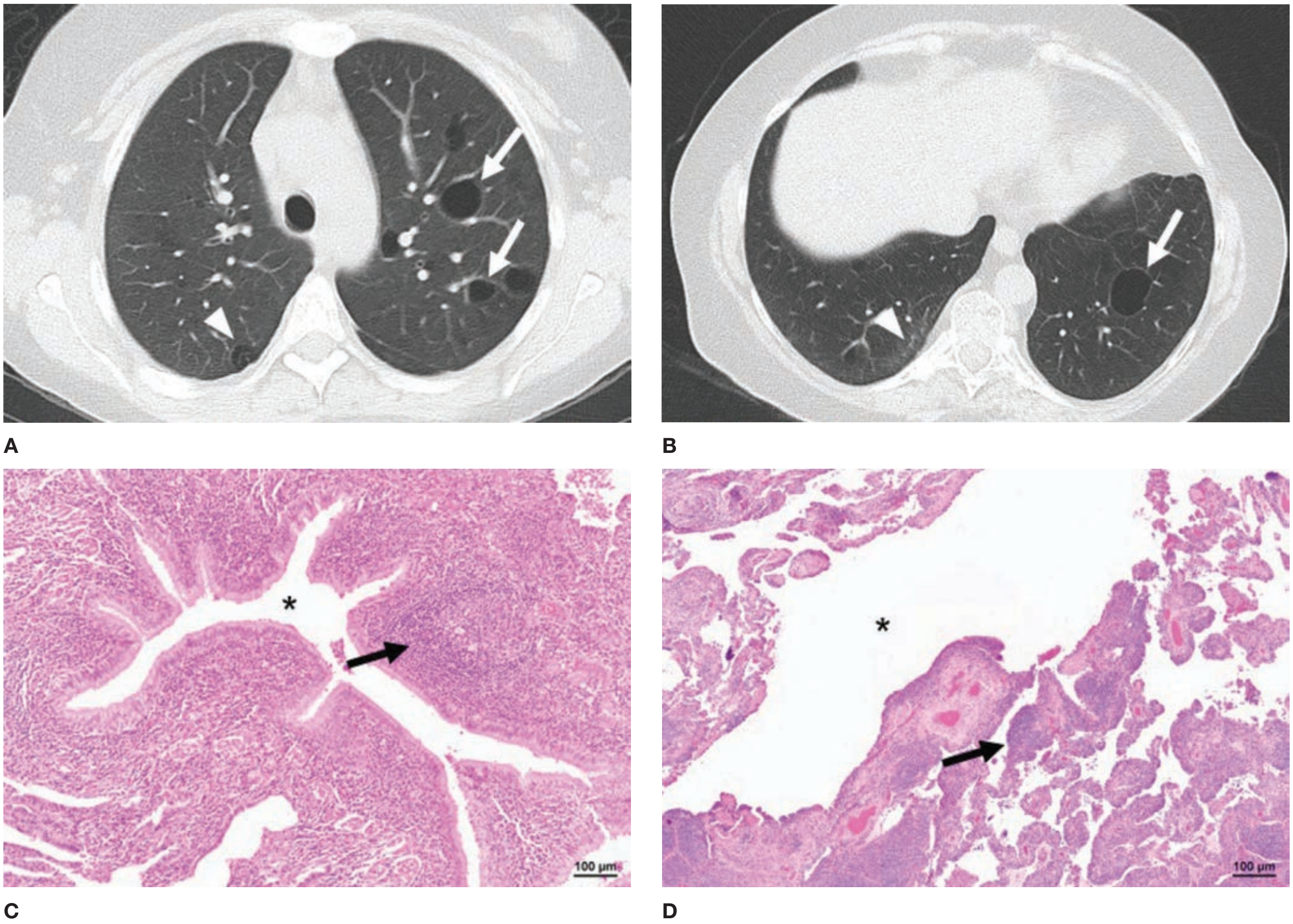

Figure 61-4 Radiologic and histopathologic manifestations in follicular bronchiolitis (FB) and lymphoid interstitial pneumonia (LIP). **A.** Multiple thin-walled cysts, some of which are bordered by eccentric vessels *(arrows)* and some with internal septations *(arrowhead)* are present in an axial CT image of a patient diagnosed with overlapping FB/LIP. **B.** Cysts *(arrow)* and areas of peripheral ground glass opacification and reticulations *(arrowhead)* are present in an axial CT image from a separate patient diagnosed with Sjögren syndrome. **C.** Histologic image of a bronchiole with features of FB with marked compression of the bronchiolar lumen *(*)* by a dense peribronchiolar chronic inflammatory infiltrate including a lymphoid follicle with a prominent germinal center *(arrow)*. **D.** The lung parenchyma in this same lung biopsy also had cystic spaces *(*)* and diffuse alveolar septal widening by a dense cellular infiltrate *(arrow)* leading to the diagnosis of LIP.

Radiology

Cystic change is frequently associated with other findings on HRCT in FB/LIP. For instance, bronchiolocentric micronodules are commonly seen in patients with FB. In addition to nodules, patients with LIP can have ground glass opacities and reticular changes on HRCT. Pulmonary cysts can be seen in greater than two-thirds of patients with FB/LIP[85,86] and often have distinct radiologic features that can help distinguish them from cysts seen in other DCLDs.[57] The cysts in FB/LIP tend to be lower lobe predominant, vary in size from a few millimeters to up to 5 to 7 centimeters, are often bordered by eccentric vessels, and frequently have internal septations and structures (Fig. 61-4A and B).[87]

Pathology

FB is characterized by a dense peribronchiolar chronic inflammatory infiltrate with prominent lymphoid follicles with reactive germinal centers sparing the intervening lung parenchyma (Fig. 61-4C). In contrast, LIP is characterized by diffuse interstitial involvement by a similar dense chronic inflammatory infiltrate leading to marked widening of the alveolar septa with compression and distortion of the alveolar spaces (Fig. 61-4D). Proteinaceous material is also often present within alveolar spaces in LIP but is not seen in FB. Fibrosis, if present, is minimal. Cases with overlapping features of FB and LIP exist, thus leading to the notion that these two entities represent a disease continuum with FB considered to be an earlier stage of disease. The inflammatory infiltrate in both FB and LIP consists mainly of small lymphocytes admixed with variable numbers of plasma cells. The lymphocytic infiltrate is composed of a mixture of B and T cells, with the B cells often localized to nodular lymphoid follicles and the prominent interstitial infiltrate in LIP composed predominantly of T cells with only scattered B cells.[77,83,88] Histiocytes and loose granulomas can be present in LIP and may be more prominent in patients with immunodeficiency, particularly CVID. Nodular lymphoid aggregates with reactive germinal centers are present in up to half of the patients with idiopathic and connective tissue disease–associated forms of LIP but are less common in patients with HIV.

Diagnosis

Confirmation of FB/LIP requires histopathologic evaluation of a lung biopsy. The yield of transbronchial biopsy is low; therefore surgical lung biopsy is the procedure of choice.[84] However, the presence of common coexisting conditions such as autoimmune or other immune-dysregulatory states in patients with characteristic cystic change of FB/LIP is often sufficient to establish a clinical diagnosis of FB/LIP and obviates the need for invasive biopsy procedures.[87]

Management

While corticosteroids and other immunosuppressive drugs have been successfully used to treat the infiltrative parenchymal manifestations of FB/LIP, the role of treatment in preventing progression of DCLD remains unknown.[84,89] In our experience, for the vast majority of patients with cystic FB/LIP, conservative management with serial physiologic and radiologic monitoring seems sufficient. FB/LIP associated with HIV can improve with antiretroviral treatment.[90] Patients with CVID and hypogammaglobulinemia may need intravenous immune globulin replacement to prevent recurrent infections.[91]

Although low, there is a risk of transformation to mucosa-associated lymphoid tissue (MALT) lymphoma in patients with FB/LIP.[84,88] Close follow-up with periodic chest imaging every 2 to 3 years may be helpful to monitor this risk. Clinicians should consider biopsy of suspicious ground glass or consolidative nodules to rule out lymphoma if there is evidence of growth on serial imaging.[77]

■ Amyloidosis

Amyloidosis consists of a heterogenous group of diseases characterized by the extracellular deposition of insoluble peptides and precursor proteins in an abnormal fibrillary fashion. These abnormal proteins are arranged in β-pleated structures instead of the normal α-helical forms.[77,92]

Multiple subtypes of amyloidosis are now recognized based upon the underlying precursor protein and the affected organs. Pulmonary involvement from amyloidosis can occur as part of systemic disease or as a localized disease. Localized pulmonary amyloidosis can manifest as multiple pulmonary nodules, pulmonary cysts, and tracheobronchial lesions with the nodular form being the most common subtype. Pulmonary nodules in amyloidosis tend to be multiple and bilateral with varying nodule size.[93]

Cystic change is an uncommon presentation of pulmonary amyloidosis and can be seen either in isolation or in the presence of a coexisting connective tissue disease, most commonly Sjögren syndrome.[93,94] The cysts in amyloidosis are thin walled and present bilaterally, either as diffuse cysts or in a lower lobe–predominant distribution (Fig. 61-5A and B). The size of the cysts tends to be variable with small (<1 cm) as well as large cysts (>4 cm) described in these patients. Some cysts are lobulated with internal structures and septations. Peribronchovascular and subpleural cyst distributions are common in amyloidosis. Most patients with amyloid-associated cystic change also have coexisting pulmonary nodules. In approximately one-third of cases, amyloidosis may be associated with underlying MALT lymphoma.[93,94]

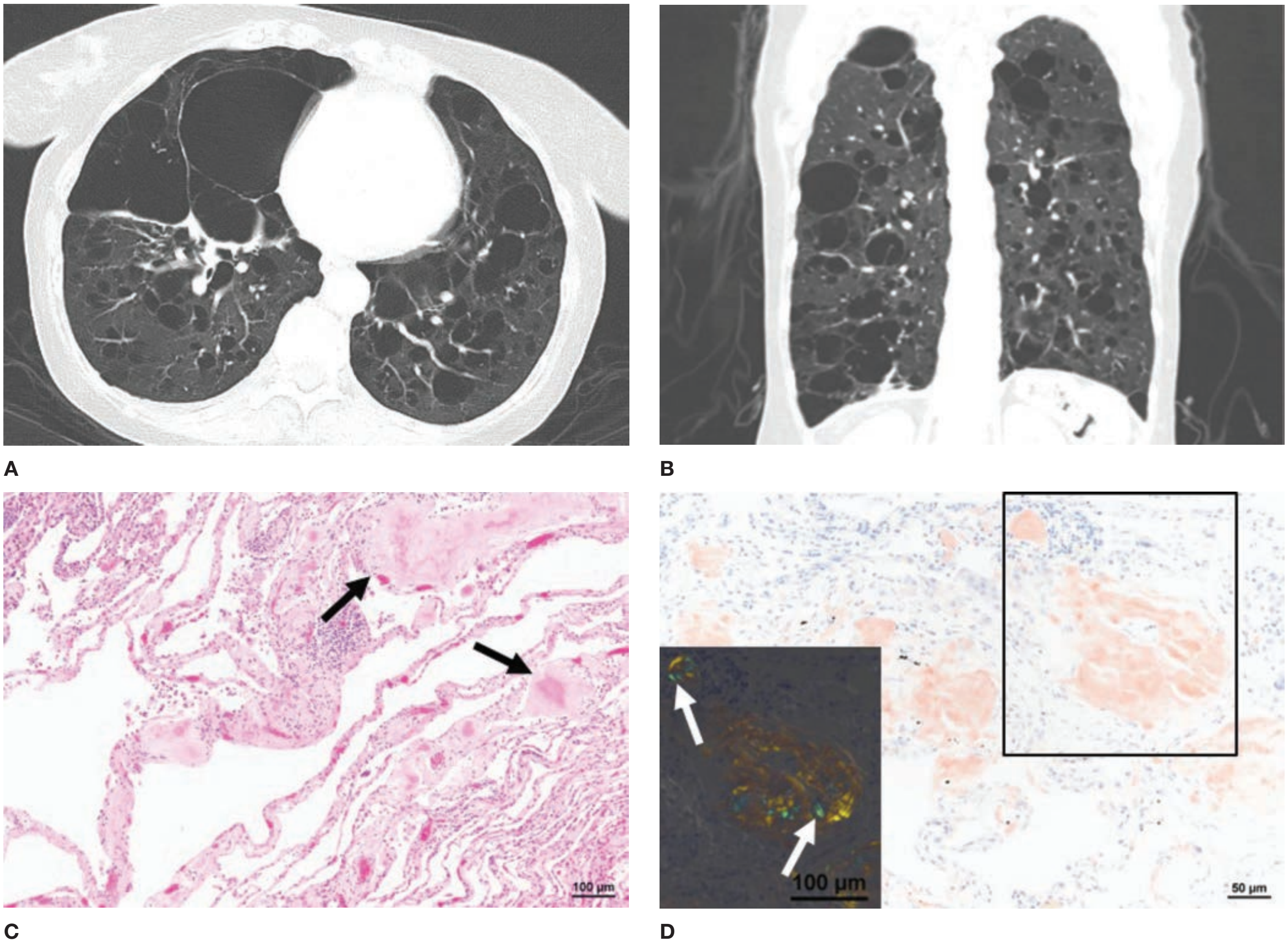

Figure 61-5 Radiologic and histopathologic manifestations in amyloidosis. **A,B.** Chest CT images of a patient with amyloid showing innumerable cysts of variable size in a diffuse craniocaudal distribution. **C.** Histologic image from a man undergoing lung biopsy for diagnosis of a suspected interstitial lung disease showing deposition of amorphous, eosinophilic material within the alveolar septa *(arrows)*. **D.** Congo red stain of the same biopsy showing the typical orange-red staining of amyloid under routine brightfield light microscopy with examination under polarized light demonstrating the characteristic birefringence reflected in the apple-green color *(arrows in inset that represents boxed area)*.

Proposed mechanisms for the formation of pulmonary cysts in amyloidosis include a ball-valve effect due to amyloid deposition around the bronchiolar walls leading to overexpansion of distal air spaces,[95] and destruction of alveolar walls either due to the action of matrix degrading enzymes or due to ischemia resulting from amyloid deposition around the alveolar capillaries.[96]

Establishing a diagnosis of amyloidosis as the cause for DCLD requires histopathologic confirmation. Diagnostic histopathologic findings in amyloidosis include demonstration of amorphous, eosinophilic amyloid deposits that exhibit apple-green birefringence in Congo red–stained sections viewed by polarizing microscopy **(Fig. 61-5C and D)**. Electron microscopy shows a typical mesh of nonbranching fibrils that are 7.5 to 12.0 nm in diameter and arrayed in a disorderly fashion. Immunoglobulin light-chain protein deposition can also be identified by immunohistochemistry.[77]

The natural history of cystic lung disease due to amyloidosis is not well understood, with single-center data suggesting progressive worsening over time in greater than two-thirds of patients.[93] Treatment of amyloidosis is based upon identification of the pathogenic protein subtype and the extent of disease involvement (localized versus systemic). While isolated pulmonary amyloidosis generally tends to have a good prognosis and may be amenable to conservative management, systemic amyloidosis almost always requires consultation with an expert hematologist and consideration of chemotherapeutic regimens or stem cell transplantation.[92]

■ Light Chain Deposition Disease

Light chain deposition disease (LCDD), first described in 1976, belongs in the family of monoclonal immunoglobulin deposition diseases and is most commonly characterized by the abnormal tissue accumulation of monotypic kappa light chains.[77,97] LCDD is often seen in association with other lymphoproliferative disorders such as multiple myeloma and monoclonal gammopathy of unknown significance (MGUS).[98] It generally represents a multisystemic disorder, with progressive renal involvement being a consistent feature.[99]

In contrast to systemic LCDD, pulmonary LCDD may be limited to the lungs and can have nodular and/or cystic forms. Pulmonary involvement by LCDD more commonly manifests as multiple, bilateral nodules; however, cystic forms mimicking other more common DCLDs such as LAM and PLCH also have been described.[100–102] Sjögren syndrome can predispose to the development of amyloidosis as well as LCDD.[87,102–104] The cysts in LCDD are multiple, thin-walled, variable in size from less than 2 cm to more than 4 cm, and present bilaterally in a lower lung zone or diffuse distribution.[100–102] Although not completely understood, elastolysis secondary to increased matrix metalloproteinase activity has been proposed as a causative mechanism for cyst formation in LCDD.[105]

Serum or urine protein electrophoresis lack the sensitivity to properly screen for the presence of underlying LCDD. An abnormal serum free light chain ratio is seen in more than two-thirds of patients with LCDD and may be more helpful as a screening test.[106] Definitive diagnosis of LCDD requires histopathologic confirmation. The characteristic histopathologic findings in LCDD include the irregular deposition of nonfibrillary acellular eosinophilic material, most commonly monotypic kappa light chains, in the walls of alveoli, small airways, and vessels. Surrounding foreign-body giant cell reaction is common. The amorphous depositions in LCDD lack the ß-pleated configuration typically seen in amyloidosis and as such do not bind to Congo red or exhibit apple-green birefringence under polarized microscopy.[77,101] Immunoglobulin light chains can also be isolated by mass spectrometry,[107] especially in those unusual cases where the diagnosis remains uncertain following expert histopathologic review.

The natural history of disease progression in LCDD is not well established, although some cases of progressive decline in lung function resulting in respiratory failure have been described.[108] No specific disease-modifying treatments exist for pulmonary LCDD. Hematopoietic stem cell transplantation was reported to stabilize lung function in a patient with pulmonary cystic LCDD associated with an extrapulmonary lymphoma.[109] Lung transplantation is an option for patients with severe pulmonary involvement.[108]

NEOPLASTIC DIFFUSE CYSTIC LUNG DISEASES

A variety of neoplastic disorders can present as DCLD **(Table 61-2)**. In fact, two of the most common DCLDs encountered in clinical practice, LAM and PLCH, represent low-grade neoplasms driven by abnormal signaling of the mechanistic target of rapamycin (mTOR) and the mitogen-activated protein kinase (MAPK) pathway, respectively.[110,111] Please refer to Chapters 59 and 60 for further in-depth review of PLCH and LAM, respectively.

Among high-grade neoplasms, cystic lung disease can be seen in both primary lung cancers as well as metastatic disease. Typically, these lesions begin as nodular opacities that subsequently cavitate to form cysts. Non–small-cell lung carcinoma (NSCLC) rarely can produce pulmonary cysts, with adenocarcinomas being the most common cause of cystic NSCLC followed by squamous cell carcinomas **(Fig. 61-6A)**.[112] The cystic change from primary lung cancers consists of thick-walled cysts/cavities, is limited to only a few cysts, and is generally not confused with the prototypic DCLDs. On the other hand, metastatic malignancies, especially from abdominopelvic sources, can produce pulmonary cysts that are more numerous and can be mistaken for other more common DCLDs.[2] As a group, sarcomas represent the most common malignancy that can produce pulmonary cysts **(Fig. 61-6B)**. Cystic and/or cavitary changes have been described in ~25% of patients with metastatic sarcomas and are frequently complicated by spontaneous pneumothoraces and portend a poor prognosis.[113] Metastatic endometrial synovial sarcoma and synovial sarcomas can produce cysts that can look quite similar to more common DCLDs such as LAM **(Fig. 61-6C and D)**.[1,114]

Pleuropulmonary blastoma (PPB) is the most common primary pediatric pulmonary malignancy, typically identified early in childhood.[81] Heterozygous mutations in *DICER1* have been identified in >70% of the cases of PPB and have significantly enhanced our understanding of the development of PPB.[115] The current pathogenic model suggests *DICER1* mutations alter early lung development to drive PPB formation, with subsequent additional somatic mutations driving progression to sarcoma.[116] PPB is classified into three subtypes based on the morphologic and radiographic appearance: type I (purely cystic), type II (mixed cystic and solid), and type III (purely solid). These subtypes represent stages in tumor progression and can help predict overall outcomes, with estimated 5-year survival rates of 91%, 71%, and 53% in type I, II, and III PPBs, respectively.[81] Radiologically, cystic PPB can manifest as multilobulated cysts with grossly normal intervening pulmonary parenchyma. The major differential diagnosis for cystic PPB is CPAM, which can be clinically and radiographically indistinguishable. Genetic testing and serial imaging are needed to identify high-risk lesions at the earliest opportunity to ensure PPB is detected and treated at the early cystic type I stage, before progressing to high-grade sarcoma that is associated with a worse prognosis. Definitive PPB diagnosis requires histopathologic confirmation with demonstration of primitive mesenchymal cells in the cyst walls.[117]

INFECTIOUS DIFFUSE CYSTIC LUNG DISEASES

Pulmonary infections can occasionally present with cystic change on chest radiographs, most commonly in the form of pneumatoceles. The prototypic infection producing cystic lung disease

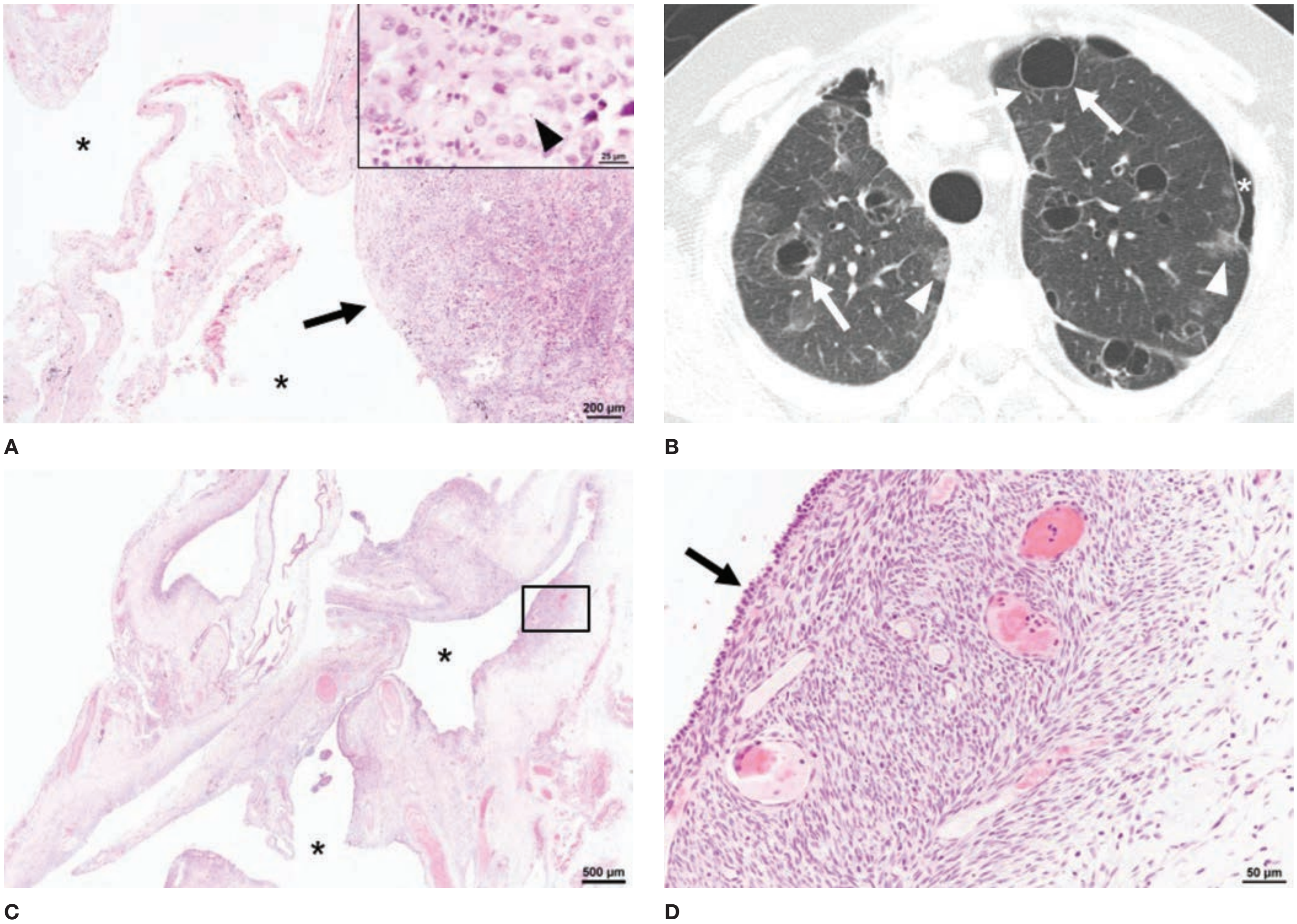

Figure 61-6 Radiologic and histopathologic manifestations in neoplastic diffuse cystic lung disease. **A.** Histologic image of a solid mass *(arrow)* adjacent to cystically dilated airspaces (*) representing bullous emphysema. Higher-magnification image *(inset)* confirmed the diagnosis of poorly differentiated non–small-cell lung carcinoma with glandular formation *(arrowhead)* indicating features of adenocarcinoma. **B.** Axial CT image of a patient with metastatic angiosarcoma showing multiple cysts *(arrows)*, areas of ground glass opacification *(arrowheads)*, and a small left pneumothorax *(*)*. **C.** Histologic image of a resected multicystic *(*)* lesion from an 18-year-old female with scattered more cellular areas noted in the cyst wall *(boxed area)*. **D.** Higher-magnification image of the boxed area in **C** showing a focus of relatively bland-appearing spindle cells immediately beneath the cuboidal epithelium lining the cystic space *(arrow)*. The suspected morphologic diagnosis of synovial sarcoma was further confirmed by molecular studies on the lung biopsy being positive for a t(X;18) translocation present in most synovial sarcomas with detection of a SS18 (*SYT*) gene rearrangement by fluorescence in situ hybridization (FISH).

is *Pneumocystis jirovecii* pneumonia (PJP). *Pneumocystis jirovecii* is a human-specific fungal pathogen that typically causes opportunistic infections in immunocompromised hosts, particularly patients with impaired cell-mediated immunity such as underlying HIV infection. The typical clinical presentation of PJP in patients with HIV is characterized by subacute onset of dyspnea, fever, and nonproductive cough; presentation is often more acute in non-HIV immunocompromised patients.[118] PJP usually manifests as bilateral, diffuse, perihilar ground glass attenuation and reticulation; however, a minority of cases (10%–34%) can present with a predominant DCLD pattern.[1,118,119] Cysts associated with PJP are usually numerous, bilateral, diffusely distributed or upper lobe predominant, and of variable size and wall thickness (Fig. 61-7A and B).[118,119] Formation of pulmonary cysts is more commonly seen in PJP associated with HIV (~56%) compared with other immune-suppressed states (~3%).[120] Spontaneous pneumothorax can occur due to rupture of subpleural cysts and portends a poor prognosis.[118] Elevated serum β-D-glucan levels can be a useful screening test; however, elevated levels can be seen in other fungal infections and as such lack specificity.[121] Diagnostic confirmation requires identification of microorganisms with appropriate staining (Fig. 61-7C and D). The cysts can shrink or completely resolve with treatment of PJP.[119,122]

Recurrent respiratory papillomatosis (RRP), caused by human papillomavirus (HPV) infections, can rarely present with a DCLD pattern. RRP is primarily seen in childhood and, in most cases, is limited to larynx and upper tracheal involvement. Distal bronchopulmonary spread of RRP is uncommon and occurs in approximately 1% to 5% of cases.[123–126] The radiologic findings of pulmonary RRP are variable and include multiple nodules in varying stages of evolution, including some with cavitation and others with cyst formation.[1]

DIFFUSE CYSTIC LUNG DISEASES ASSOCIATED WITH INTERSTITIAL LUNG DISEASES

Cystic changes, although not a dominant feature, can often accompany other fibrotic interstitial lung diseases (ILDs) such as hypersensitivity pneumonitis (HP), desquamative interstitial pneumonia (DIP), and sarcoidosis.[1] DIP is an ILD strongly associated with exposure to cigarette smoke.[127] The most common radiologic

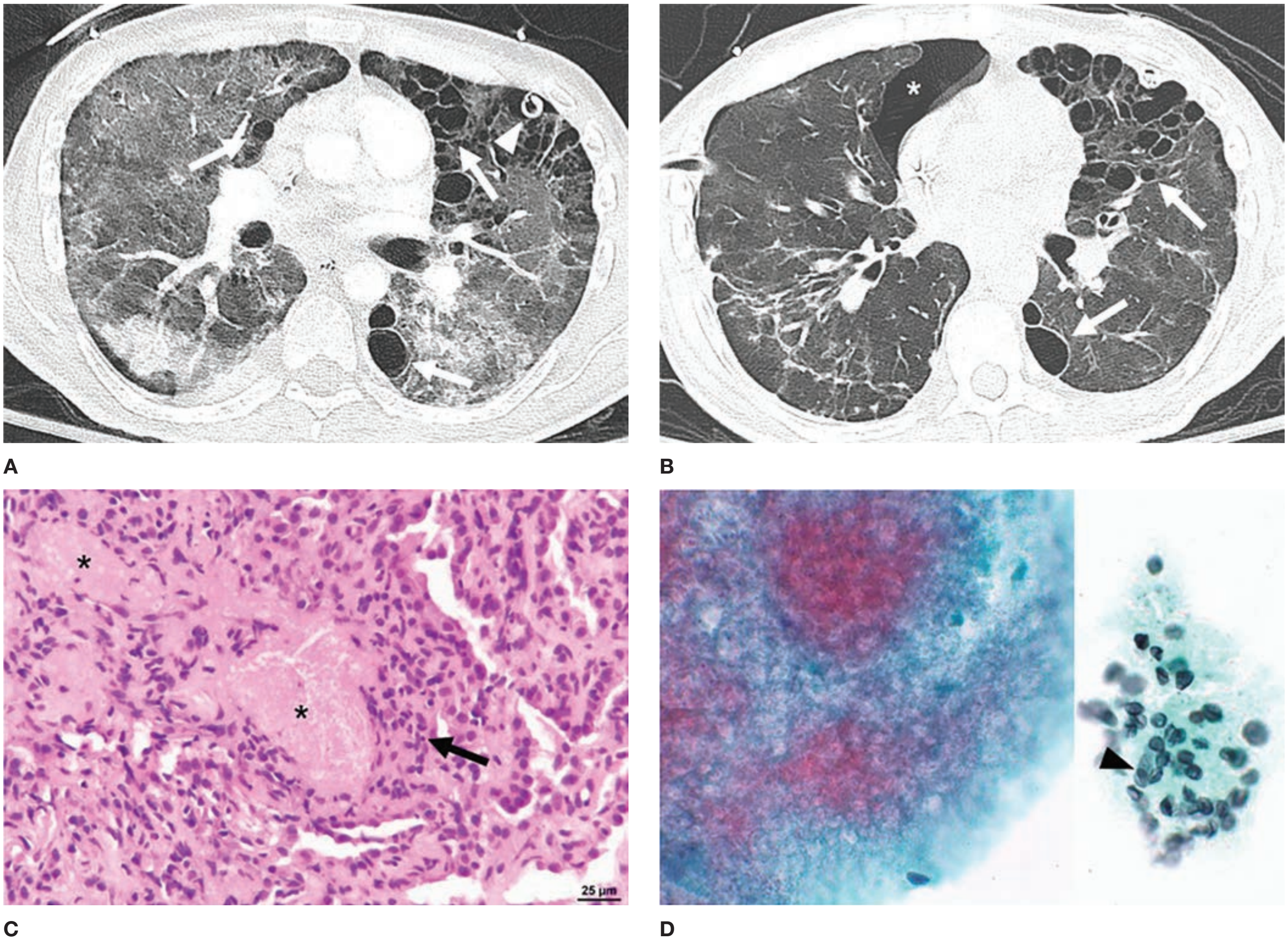

Figure 61-7 Radiologic and histopathologic manifestations in *Pneumocystis jirovecii* pneumonia (PJP). **A.** Axial chest CT image from an immunocompromised patient with acute PJP showing widespread areas of ground glass opacification with multiple cysts *(arrows)* and a left pneumothorax with a chest tube in place *(arrowhead)*. **B.** Images from a follow-up study as the patient was recovering shows better-defined cysts *(arrows)* with resolution of the ground glass opacifications and a right pneumothorax *(*)*. **C.** Histologic image of a biopsy from a patient with PJP pneumonia showing the classic frothy exudates within the alveolar spaces *(*)* with variable interstitial inflammation in the surrounding lung parenchyma *(arrow)*. **D.** The frothy exudates can also be seen in cytologic bronchoalveolar lavage preparations with diagnosis confirmed by identifying the microorganisms that appear as round, often indented or helmet-shaped, cyst forms *(arrowhead)* best highlighted with Gomori methenamine silver (GMS) stain.

abnormality in DIP is diffuse ground glass attenuation with cystic change variably reported in 30% to 75% of patients with DIP.[128,129] The cysts in DIP overlap with areas of ground glass attenuation, often involve a small percentage of the pulmonary parenchyma, and are more common in the lower lung zones (Fig. 61-8A and B).[129] The histologic hallmark of DIP is diffuse filling of the distal airspaces with abundant pigmented macrophages (Fig. 61-8C and D).

Cystic change in HP is primarily limited to areas of ground glass attenuation. It is almost always accompanied by other radiologic features of HP such as centrilobular nodules and mosaic attenuation indicative of air trapping (Fig. 61-9A and B).[130] The centrilobular nodules and ground glass attenuation seen in HP radiographically corresponds to patchy bronchiolocentric cellular chronic interstitial inflammatory infiltrates that extent into the surrounding alveolar septa (Fig. 61-9C). Loose non-necrotizing granulomas and organizing pneumonia also are frequently present (Fig. 61-9D). The cysts in sarcoidosis tend to be perihilar compared with the subpleural cysts in other fibrotic ILDs (Fig. 61-10A).[131,132] Sarcoidosis is classically manifested histologically as well-formed, non-necrotizing interstitial granulomas distributed in a lymphangitic pattern around the bronchovascular bundles and along the pleura and interlobular septa (Fig. 61-10B and C). Although associated with cystic change, the presence of other more typical radiologic findings generally makes it straightforward to distinguish these ILDs from the pure DCLDs.

SMOKING-RELATED DIFFUSE CYSTIC LUNG DISEASES

PLCH is the prototypic smoking-related DCLD (Chapter 59). DIP, discussed in the preceding section, can also produce pulmonary cysts. While PLCH and DIP are the most common smoking-related disorders that produce lung cysts, DCLD resulting from cigarette smoke exposure has been reported in the absence of these disorders and can resemble the more common DCLDs such as LAM. The mechanism of cyst formation in these cases is not well understood but is postulated to involve a ball-valve mechanism and distal hyperinflation due to small airway inflammation and mucostasis as a result of cigarette smoke exposure.[133] It is worth noting that small airway narrowing resulting in distal hyperinflation and cyst formation has also been described in other forms of bronchiolitis.[134–136]

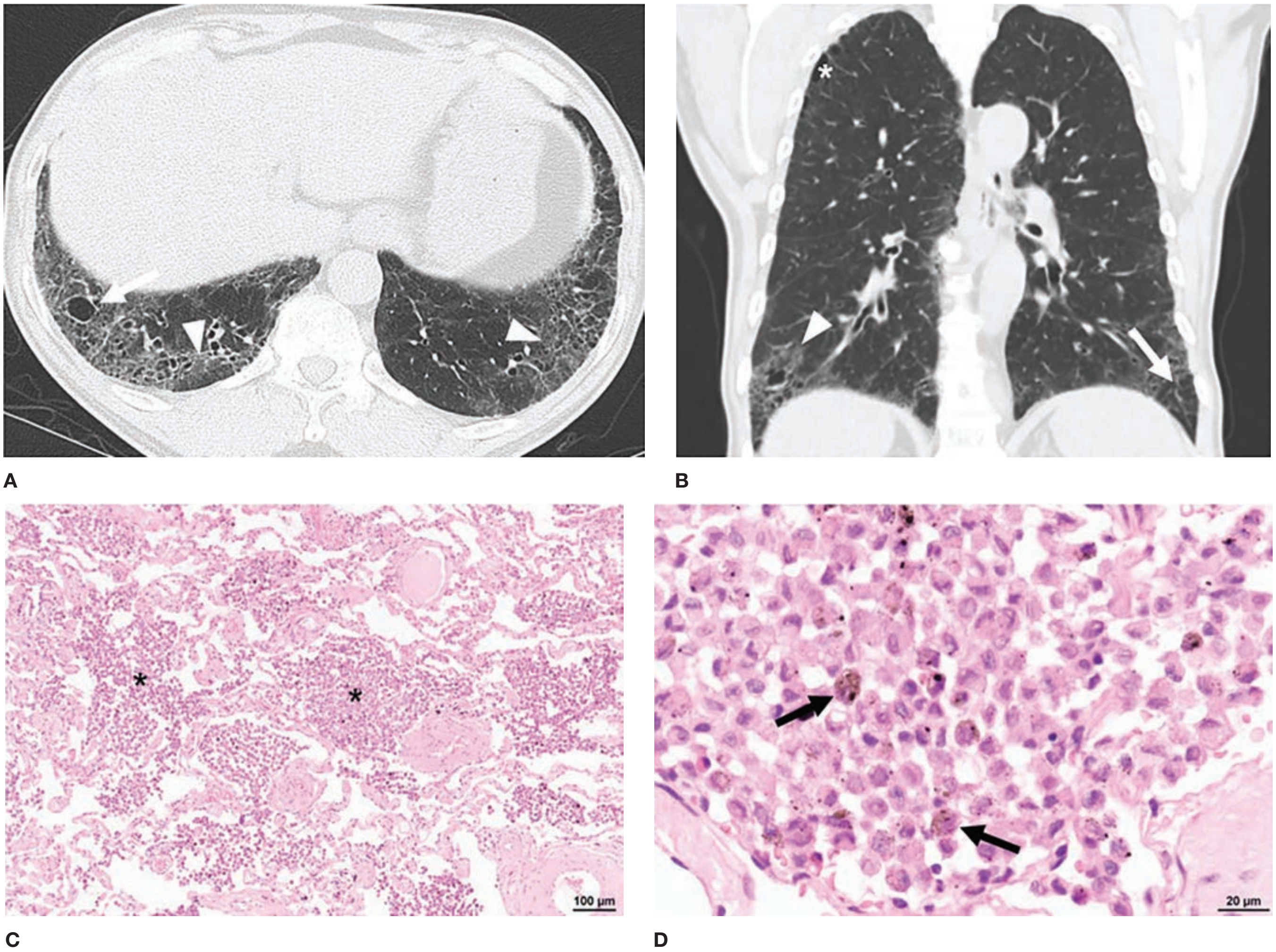

Figure 61-8 Radiologic and histopathologic manifestations in desquamative interstitial pneumonia (DIP). **A,B.** Axial (**A**) and coronal (**B**) images of a patient with DIP showing basal predominant cystic change *(arrows)* and ground glass opacification *(arrowheads)* with emphysema related to smoking in the upper lung zones *(*)*. **C.** Histologic image showing the hallmark of DIP, which is filling of distal airspaces with large numbers of pigmented macrophages *(*)*. Significant interstitial fibrosis is not a feature of DIP, and interstitial inflammation is usually absent. **D.** The cytoplasmic pigment in the macrophages is yellow-brown and variably sized with blurry borders *(arrows)*. This smoking-related pigment needs to be distinguished from hemosiderin pigment, which is typically larger and golden to dark brown with well-demarcated borders.

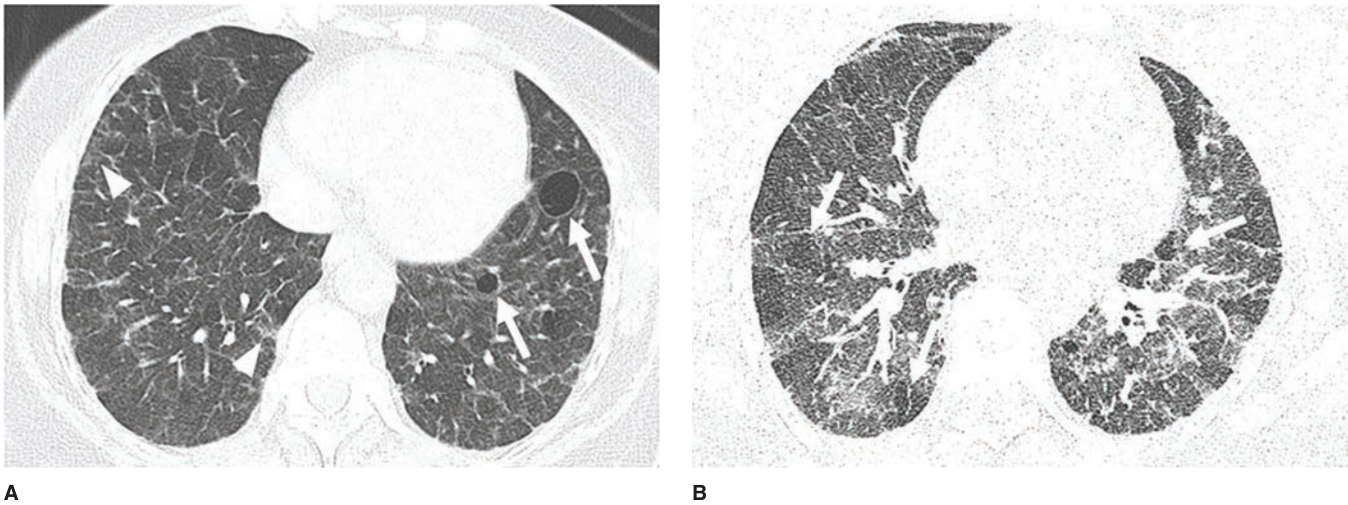

Figure 61-9 Radiologic and histopathologic manifestations in hypersensitivity pneumonitis (HP). **A.** Axial CT chest image in a patient with HP showing scattered cysts *(arrows)* and areas of ground glass attenuation *(arrowheads)*. **B.** Expiratory images from the same patient demonstrate areas of lobular air trapping *(arrows)*. *(continued)*

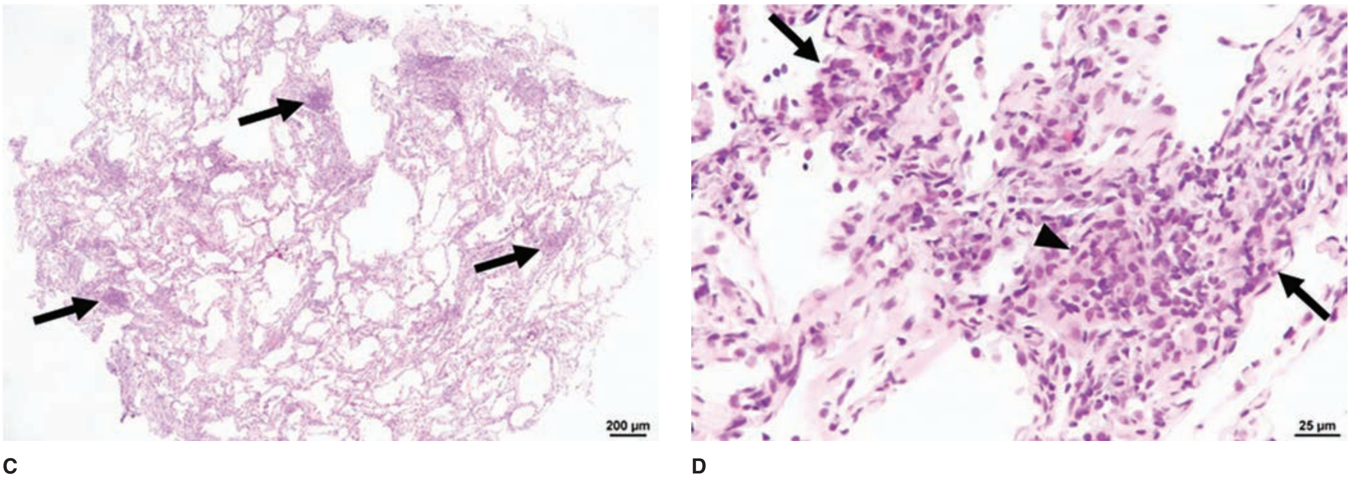

Figure 61-9 *(Continued)* **C.** A patchy cellular chronic inflammatory cell infiltrate *(arrows)* shown to be centered on small airways at higher magnification is present in a histologic image of a transbronchial cryobiopsy obtained from a patient diagnosed with HP. **D.** Higher magnification image shows extension of the lymphoplasmacytic infiltrate with scattered eosinophils into the surrounding alveolar septa *(arrows)* and a focal aggregate of histiocytes forming a loose granuloma *(arrowhead)* that can often be seen in HP.

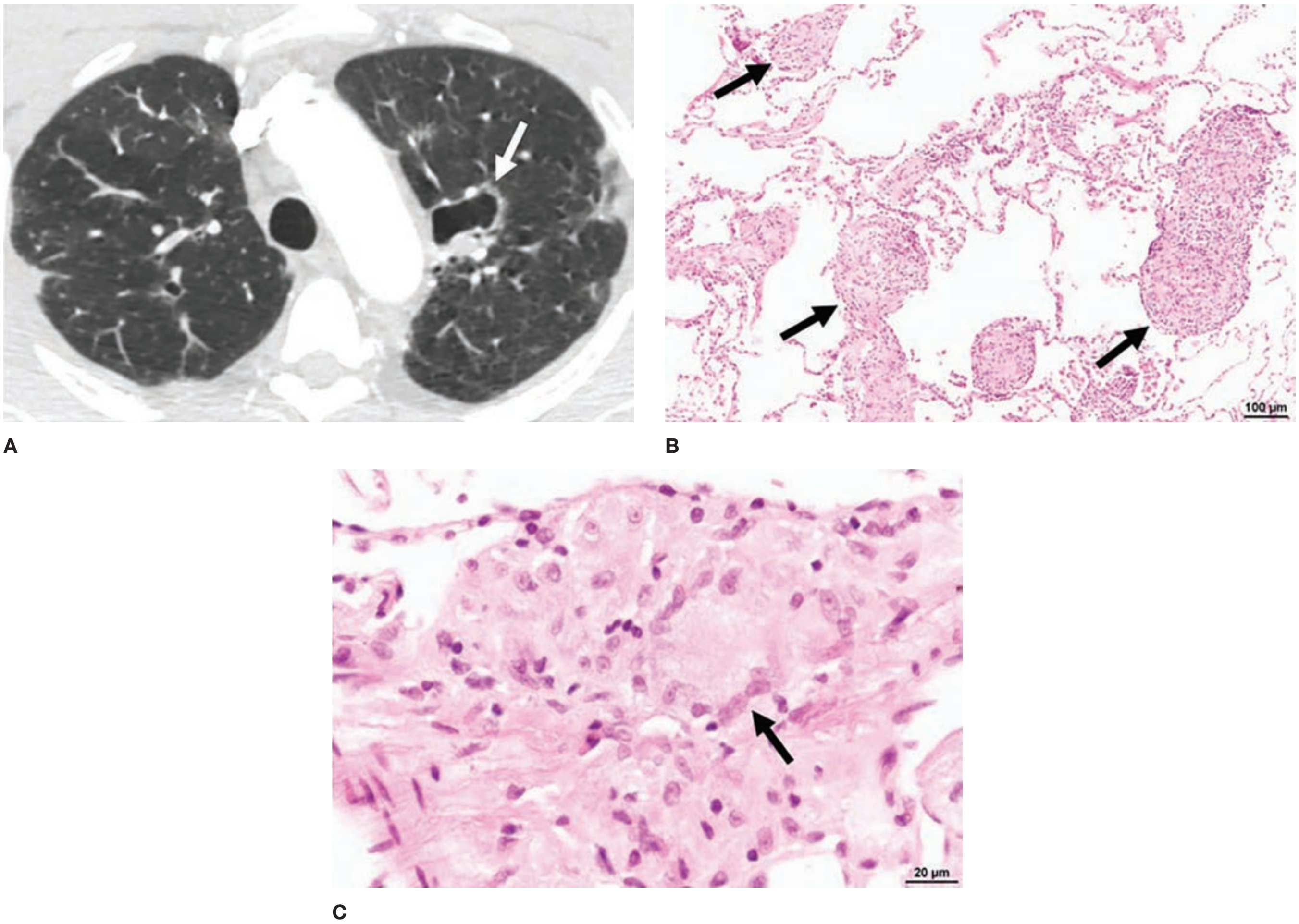

Figure 61-10 Radiologic and histopathologic manifestations in sarcoidosis. **A.** A left perihilar cyst *(arrow)* is seen in this axial CT image obtained from a patient with sarcoidosis. **B.** Tightly formed, well circumscribed, non-necrotizing granulomas confined to the interstitium *(arrows)* and distributed in a lymphangitic pattern is the classic histologic manifestation of sarcoidosis. **C.** A higher-magnification image shows the epithelioid histiocytes and multinucleated giant cells *(arrow)* constituting the granulomas.

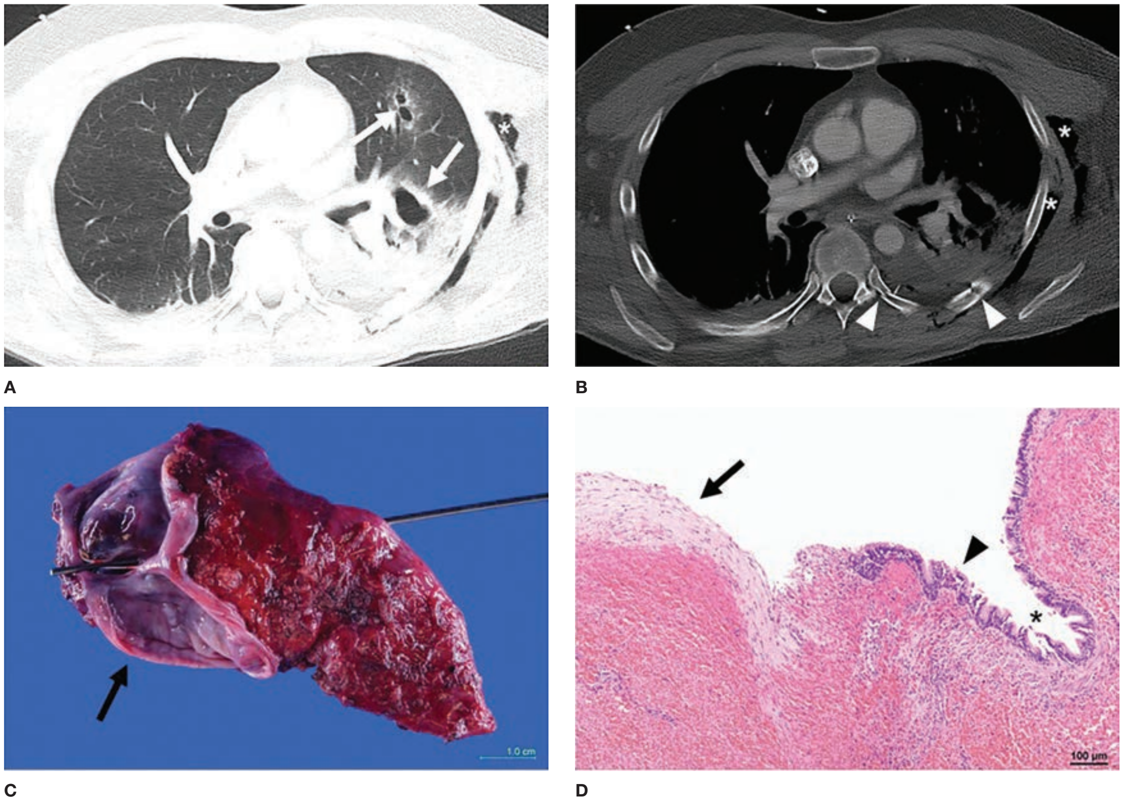

Figure 61-11 Radiologic and histopathologic manifestations of pneumatoceles. **A,B.** Axial CT lung (**A**) and bone (**B**) window images obtained from a patient with thoracic trauma showing traumatic pneumatoceles in the left lung *(arrows)* with surrounding pulmonary contusion along with displaced left rib fractures *(arrowheads)* and subcutaneous gas *(*)*. **C.** Gross anatomic image of a 4-cm, opened, air-filled cystic lesion *(arrow)* resected from an infant that was discovered during an evaluation for infection. A probe extending from the hilar bronchus to the cyst lumen demonstrates a communication between the cyst and the conducting airways. **D.** Histologic image showing the communication between the cyst with a fibrous wall lacking an epithelial lining *(arrow)* and a bronchiolar lumen *(*)* lined by ciliated bronchiolar epithelium *(arrowhead)*. The histopathologic features together with the clinical and radiographic findings were consistent with a postinfectious pneumatocele.

MISCELLANEOUS DIFFUSE CYSTIC LUNG DISEASES

Formation of pneumatoceles, whether due to infectious etiologies (discussed previously), blunt trauma,[137] or accidental aspiration of petroleum products during fire-eating/fire-blowing demonstrations,[138] can result in the formation of multiple pulmonary cysts (Fig. 61-11A and C). Pneumatoceles are acquired air-filled cysts that are thought to develop from leakage of air from a conducting airway into a region of parenchymal injury. Thus, pneumatoceles can expand rapidly to compress the surrounding lung and may rupture into the pleural cavity forming a pneumothorax. The walls of a pneumatocele are typically composed of organizing fibrous tissue without an epithelial lining that differentiates them from true cysts (Fig. 61-11D). Pneumatoceles generally tend to follow a benign course and resolve over time either spontaneously (in the case of trauma and fire-eater's lung) or with appropriate antimicrobial treatment (in the case of infectious pneumatoceles).[77] Hyper-IgE syndrome is a rare primary immunodeficiency syndrome caused by mutations in the signal transducer and activator of transcription 3 (*STAT3*) gene that is characterized by recurrent skin and sinopulmonary infections.[139] Cystic pulmonary changes can be seen in patients with hyper-IgE syndrome and likely represent infectious pneumatoceles due to staphylococcal infections.[77]

DIAGNOSTIC AND MANAGEMENT APPROACH

DCLDs are typically discovered in one of the following scenarios: (1) patients presenting with chronic dyspnea on exertion, (2) acute presentation due to a complication such as spontaneous pneumothorax, (3) detected via targeted screening, for example by a screening chest CT in adult women with tuberous sclerosis complex (TSC), or (4) incidentally discovered on imaging performed for unrelated reasons. An integrated diagnostic approach that includes thorough history-taking and physical examination, critical review of the chest imaging, and detailed histopathologic evaluation and/or genetic analysis in some cases is essential to achieve the correct diagnosis and avoid delays in patient management.

■ History

Comprehensive history-taking provides invaluable information that can assist in rendering the correct diagnosis when evaluating a patient with DCLD. Acute onset of symptoms, especially when associated with other constitutional symptoms such as fever, weight loss, etc., can point towards an infectious etiology. Exposure to cigarette smoke can suggest underlying smoking-related DCLDs. The presence of sicca symptoms can help diagnose underlying connective tissue disorders such as Sjögren syndrome. Patient demographics may make certain diseases more likely than others. For instance, developmental disorders such as CPAM and bronchopulmonary dysplasia are more commonly identified in childhood. LAM is almost exclusively restricted to adult women.[140] Detailed family history may also provide important clues. For instance, a family history of skin lesions, kidney tumors, or spontaneous pneumothoraces can suggest a diagnosis of BHD or TSC-LAM in a patient with DCLD.[59]

■ Physical Examination

While findings on pulmonary examination are typically not specific enough to help establish a firm diagnosis, extrapulmonary physical exam findings may provide important information. Careful skin examination may reveal characteristic dome-shaped papules on the face, neck, and upper torso in patients with BHD.[4] Patients with TSC often have facial angiofibromas, hypomelanotic macules, Shagreen patches, and subungual fibromas.[141] Distinct facial features or joint abnormalities such as hyperextension can be seen in connective tissue disorders such as Marfan and Ehlers-Danlos syndrome.

■ Laboratory Evaluation

Certain laboratory tests can help establish the diagnosis of DCLDs and obviate the need for invasive procedures such as lung biopsies. Elevated serum vascular endothelial growth factor D (VEGF-D) levels can be seen in 60% to 70% of patients with sporadic LAM, and levels ≥800 pg/mL are almost 100% specific in distinguishing sporadic LAM from other DCLDs.[110,142,143] Autoimmune serologies such as antinuclear antibody (ANA), anti-Ro/SSA, and anti-La/SSB antibodies, can help diagnose underlying connective tissue disorders such as Sjögren syndrome. Quantitative serum immunoglobulin levels can help suggest underlying immunodeficiency disorders such as CVID, and abnormal serum free light chain ratio can point toward LCDD. Lastly, peripheral blood and/or buccal swab genetic testing can be helpful in establishing the diagnosis in diseases harboring germline mutations, such as *FLCN* testing for evaluation of BHD.[77]

■ Radiologic Assessment

Critical review of the morphology, profusion, and distribution of cysts, along with careful attention to other noncystic findings on HRCT, is the most important noninvasive means to ascertain the underlying diagnosis in a patient with DCLD. Expert radiologists and pulmonologists familiar with DCLDs can accurately identify the common DCLDs such as LAM, BHD, and FB/LIP in approximately 80% of the cases, based on a critical review of the HRCT features alone.[57] Although DCLDs have a broad differential diagnosis (Table 61-2), it is often easy to exclude certain disorders where cystic change is associated with other radiologic

TABLE 61-4 Summary of Clinical, Radiologic, and Pathologic Features of Major Diffuse Cystic Lung Diseases

	LAM	PLCH	BHD	LIP/FB	Amyloidosis/LCDD
			Clinical Features		
Features	Dyspnea Pneumothorax Chylothorax	Dyspnea Cough Pneumothorax Constitutional symptoms such as fatigue, weight loss and fever	Pneumothorax	Dyspnea Symptoms suggestive of underlying etiologies such as sicca symptoms associated with Sjögren syndrome	Dyspnea Cough
Typical age at diagnosis (years)	20–40	20–40	30–40	Variable	Variable
Gender	F>>>M	F = M	F = M	F>>M	Unknown
Smoking	—	+++	—	—	—
Family history	± Absent in sporadic LAM Autosomal dominant in TSC	—	++ (Autosomal dominant)	—	—
Pneumothorax risk	+++	++	+++	Unknown, almost certainly less than LAM, BHD, and PLCH	Unknown, almost certainly less than LAM, BHD, and PLCH
Extrapulmonary manifestations	AMLs, lymphadenopathy, lymphangioleiomyomas, chylous effusions, TSC and its associated systemic manifestations such as seizures, cognitive impairment, skin lesions, etc.	Diabetes insipidus Bone lesions Skin rash	Skin fibrofolliculomas Renal tumors	Sicca symptoms Other varying manifestations according to underlying disease such as arthralgia, synovitis, skin rash, Raynaud, frequent infections, etc.	Lymphoproliferative disorders, renal failure, systemic amyloidosis, hematologic malignancies, Sjögren syndrome
			HRCT Features		
Cysts					
Distribution	Diffuse, random	Upper and middle lung zones; spares costophrenic angles	Basilar, subpleural, especially the paramediastinal regions, also tend to abut vessels	Diffuse, random, often with eccentric vessels	Diffuse, random
Shape	Round, uniform	Bizarre, irregular, variable wall thickness	Elliptical, lentiform	Round, variable; may contain internal structure/septations	Round, variable
Size	2 mm to 2 cm	Variable, 2 mm to 2 cm	Variable, 2 mm to >3 cm	Variable, 3 mm to >3 cm	Variable, 4 mm to >5 cm

(continued)

TABLE 61-4 Summary of Clinical, Radiologic, and Pathologic Features of Major Diffuse Cystic Lung Diseases *(Continued)*

	LAM	PLCH	BHD	LIP/FB	Amyloidosis/LCDD
HRCT Features					
Nodules	± Absent in sporadic LAM Common in patients with TSC-LAM where they represent a benign condition known as multifocal micronodular pneumocyte hyperplasia (MMPH)	++ Micro and macro nodules with or without cavitation	—	± Centrilobular, usually micronodules Larger nodules may be suggestive of underlying MALT lymphoma	+++ Nodules—can be large
Ground glass opacities	— Except in rare circumstances where they may represent chylous congestion of the pulmonary parenchyma	— Except in patients with concomitant smoking related pathologies such as DIP	—	+++	—
Other HRCT findings	Pleural effusions in ≤20% of patients Effusions more common in sporadic LAM than TSC-LAM	Reticulations	—	Interlobular septal thickening, air-trapping	Lymphadenopathy
Diagnostic Testing					
Laboratory	Serum VEGF-D	Serum and urine studies for diabetes insipidus	*FLCN* mutation analysis	Polyclonal dysproteinemia ANA, anti-SSA, anti SSB (Sjögren syndrome), HIV, quantitative immunoglobulins	Monoclonal dysproteinemia, light chain immunoglobulins
Genetic testing	Typically not needed for the diagnosis of sporadic LAM Germline *TSC* mutations in TSC-LAM	*BRAF* and other *MAPK* pathway mutations such as NRAS, MAP2K1, etc.	Germline *FLCN* gene mutation	—	—
Diagnostic yield of transbronchial lung biopsy	>50%	30%–40%	0	Unknown, likely <30%	Unknown, likely not helpful
Typical histopathologic findings on lung biopsy	Cysts and LAM cells positive for melanocytic markers, including HMB-45 in cells with a smooth muscle phenotype, that are typically most prominent around cysts	S100- and CD1a-positive Langerhans cells with intracellular Birbeck granules by electron microscopy; stellate fibrotic scars in late stages	Intraparenchymal, subpleural, and paraseptal cysts that lack abnormal cell proliferations or a significant fibroinflammatory component	LIP: diffuse dense interstitial polyclonal lymphoplasmacytic infiltrate FB: peribronchiolar dense lymphoplasmacytic polyclonal infiltrate with prominent lymphoid follicles containing germinal centers	Amyloid: amorphous protein deposits with fibrillar ultrastructure and apple-green birefringence by Congo red stain viewed under polarized light LCDD: typically monotypic kappa light chain deposition with finely granular ultrastructure lacking apple-green birefringence by Congo red stain and polarized light
Other histopathologic features	Hemosiderin-laden macrophages	Smoking-related changes in the surrounding parenchyma	Skin biopsy showing fibrofolliculomas	Lip biopsy showing focal lymphocytic sialadenitis in Sjögren syndrome	Abdominal fat pad or bone marrow biopsy showing amyloid or light chain deposition

ANA, antinuclear antibody; AML, angiomyolipoma; BHD, Birt-Hogg-Dubé syndrome; BRAF, v-Raf murine sarcoma viral oncogene homolog B; DIP, desquamative interstitial pneumonia; F, female; FB, follicular bronchiolitis; HMB, human melanoma black; HIV, human immunodeficiency viruses; LAM, lymphangioleiomyomatosis; LCDD, light chain deposition disease; LIP, lymphoid interstitial pneumonia; M, male; MALT, mucosa-associated lymphoid tissue; MAPK, mitogen-activated protein kinase; PLCH, pulmonary Langerhans cell histiocytosis; TSC, tuberous sclerosis complex; VEGF-D, vascular endothelial growth factor D.

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features such as fibrotic changes seen in other ILDs. It is important to note that solitary or few (1–5) cysts can arise as an aging phenomenon and may not necessarily reflect a pathologic abnormality.[144] The most common DCLDs that present with either pure or primarily cystic change on chest imaging include LAM, BHD, PLCH, and FB/LIP, and in some cases amyloidosis/LCDD (Table 61-4).

■ Pathologic Assessment

Histopathologic evaluation may be required for diagnostic confirmation in cases where the diagnosis remains unclear following detailed clinical, laboratory, and radiologic assessment. It is important to carefully consider the differential diagnosis prior to undertaking invasive diagnostic procedures, as the choice as well as sequence of procedures may vary depending upon the diagnoses under consideration. For instance, in a patient with lower lobe–predominant cysts where BHD may be a likely etiology, one should opt to pursue genetic testing for *FLCN* mutations prior to pursuing lung biopsy. In patients where LAM and/or PLCH is a possibility, transbronchial lung biopsy may provide a reasonable diagnostic yield and obviate the need for surgical lung biopsy.[140,145–147] Although isolated reports have suggested promise, the role of transbronchial cryobiopsy in the evaluation of patients with DCLD needs further investigation.[148] Video-assisted thoracoscopic surgery (VATS)-guided lung biopsy remains the gold standard. Histopathologic features of the most common DCLDs that are encountered in clinical practice are summarized in Table 61-4. Multidisciplinary integration of histopathologic findings with the clinical and radiologic features, as well as a review of histopathologic findings by an expert pathologist familiar with the nuances of DCLDs, is critical to ascertain the correct diagnosis.

■ Diagnostic Approach

We recommend a stepwise approach progressing from the least invasive to most invasive diagnostic modalities when evaluating patients with DCLD. For instance, in patients with mild disease, who have no or minimal symptoms with preserved PFTs and are comfortable with some degree of uncertainty, it may be reasonable to serially monitor the trajectory of disease progression and not pursue invasive diagnostic procedures. It is also important to distinguish true cysts from cyst mimics such as emphysema and cystic bronchiectasis. Once established as true cysts, we separate patients into paucicystic versus multicystic disease based on the number of cysts (≤10 vs. >10). Proposed stepwise diagnostic algorithms for evaluation of DCLDs are presented in Figs. 61-12, 61-13, and 61-14.[149]

■ Management

While management of specific DCLDs is tailored to the underlying diagnosis (e.g., mTOR inhibitors for LAM [see Chapter 60], smoking cessation for PLCH [see Chapter 59], renal cancer screening

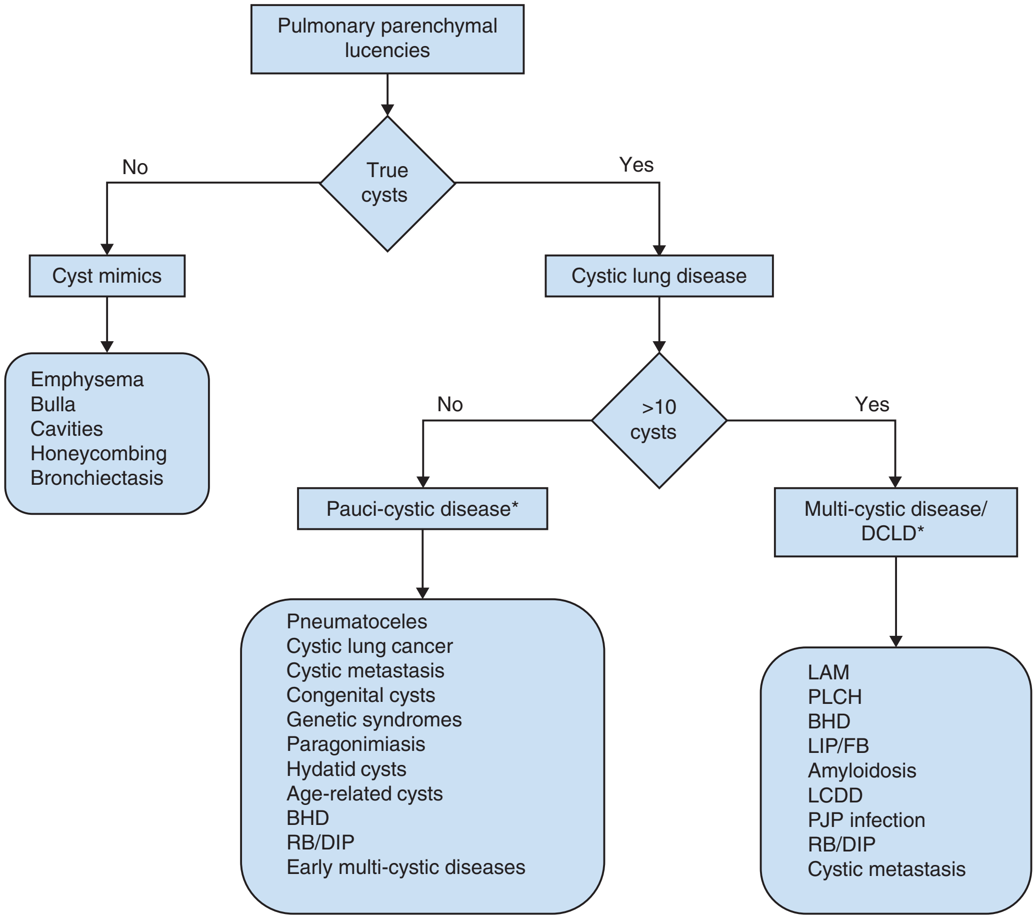
Pulmonary parenchymal lucencies
True cysts
No
Yes
Cyst mimics
Cystic lung disease
Emphysema
Bulla
Cavities
Honeycombing
Bronchiectasis
>10 cysts
No
Yes
Pauci-cystic disease*
Multi-cystic disease/ DCLD*
Pneumatoceles
Cystic lung cancer
Cystic metastasis
Congenital cysts
Genetic syndromes
Paragonimiasis
Hydatid cysts
Age-related cysts
BHD
RB/DIP
Early multi-cystic diseases
LAM
PLCH
BHD
LIP/FB
Amyloidosis
LCDD
PJP infection
RB/DIP
Cystic metastasis

Figure 61-12 Algorithm to classify diffuse cystic lung diseases based on chest computed tomography. *There can be some overlap between the etiologies of paucicystic and multicystic diseases. For instance, some disorders such as BHD, RB/DIP, and cystic metastasis can have pauci- as well as multicystic presentations. In addition, if diagnosed relatively early in their course, multicystic diseases may be identified at a paucicystic stage. BHD, Birt-Hogg-Dubé syndrome; DIP, desquamative interstitial pneumonia; FB, follicular bronchiolitis; LAM, lymphangioleiomyomatosis; LCDD, light chain deposition disease; LIP, lymphoid interstitial pneumonia; PJP, *Pneumocystis jiroveci* pneumonia; PLCH, pulmonary Langerhans cell histiocytosis; RB, respiratory bronchiolitis. *(Reproduced with permission from Gupta N, Wikenheiser-Brokamp KA, McCormack FX: Diffuse Cystic Lung Diseases. Respiratory Medicine. Cham: Humana Press; 2021.)*

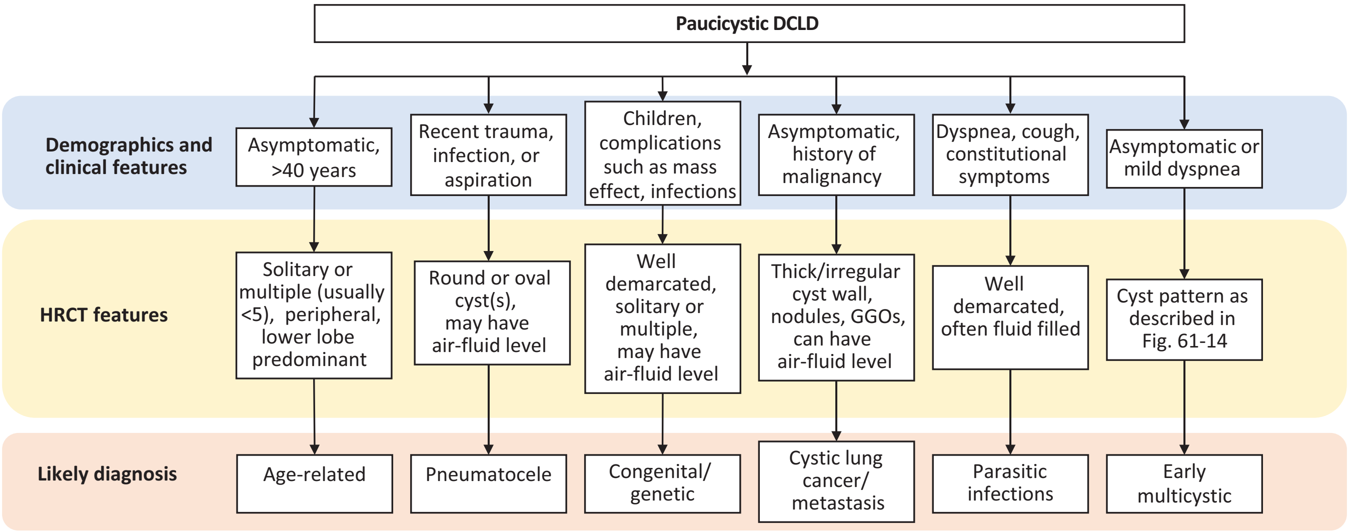
Paucicystic DCLD
Demographics and clinical features
Asymptomatic, >40 years
Recent trauma, infection, or aspiration
Children, complications such as mass effect, infections
Asymptomatic, history of malignancy
Dyspnea, cough, constitutional symptoms
Asymptomatic or mild dyspnea
HRCT features
Solitary or multiple (usually <5), peripheral, lower lobe predominant
Round or oval cyst(s), may have air-fluid level
Well demarcated, solitary or multiple, may have air-fluid level
Thick/irregular cyst wall, nodules, GGOs, can have air-fluid level
Well demarcated, often fluid filled
Cyst pattern as described in Fig. 61-14
Likely diagnosis
Age-related
Pneumatocele
Congenital/ genetic
Cystic lung cancer/ metastasis
Parasitic infections
Early multicystic

Figure 61-13 Algorithm to guide approach to the diagnosis of paucicystic lung diseases. GGOs, ground glass opacities. *(Reproduced with permission from Gupta N, Wikenheiser-Brokamp KA, McCormack FX: Diffuse Cystic Lung Diseases. Respiratory Medicine. Cham: Humana Press; 2021.)*

for BHD [discussed above]), there are certain aspects of management that are common to all DCLDs. Cigarette smoking as well as exposure to other inhaled drugs such as marijuana should be strongly discouraged. Patients should be advised to stay up to date on vaccinations such as influenza and pneumococcal vaccinations. Trial of inhaled bronchodilators is appropriate in patients with an obstructive defect on spirometry, with continued use in patients who derive symptomatic benefit.

The presence of DCLDs predisposes patients to an increased risk of developing spontaneous pneumothorax. Patients should be educated about the signs and symptoms of spontaneous pneumothorax and advised to seek immediate medical attention if they experience

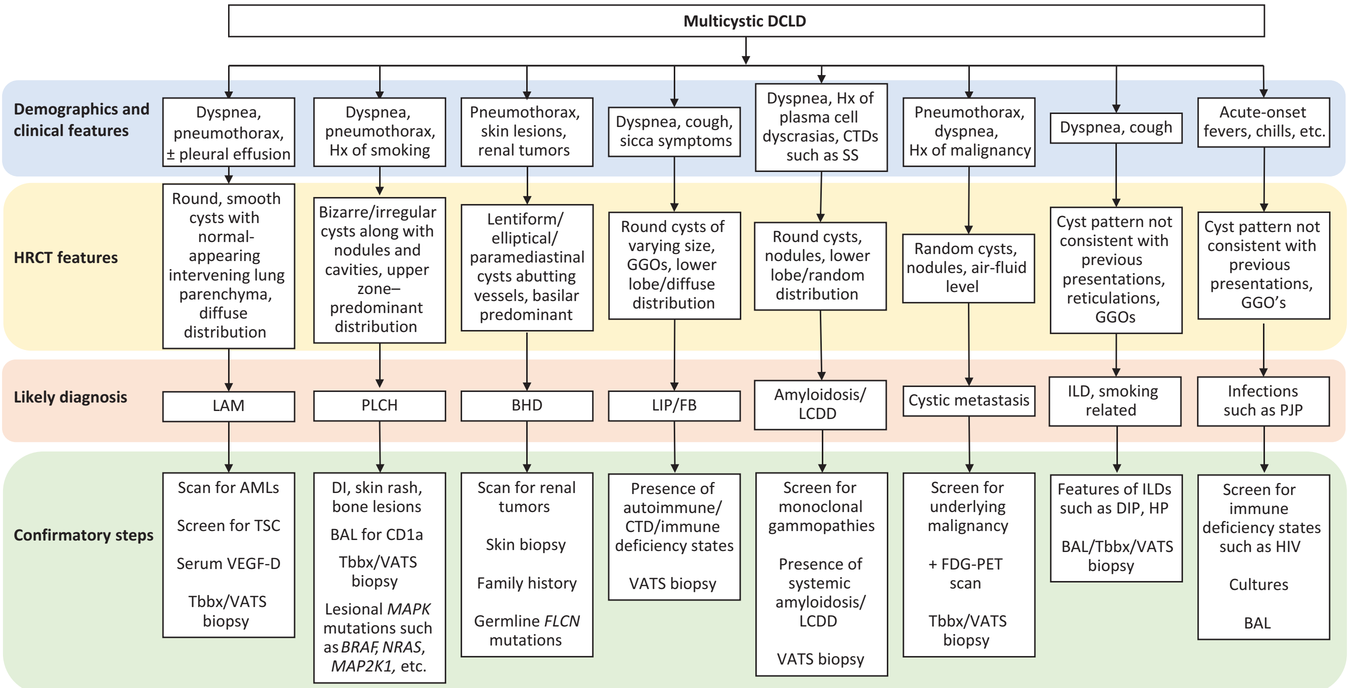
Multicystic DCLD
Demographics and clinical features
Dyspnea, pneumothorax, ± pleural effusion
Dyspnea, pneumothorax, Hx of smoking
Pneumothorax, skin lesions, renal tumors
Dyspnea, cough, sicca symptoms
Dyspnea, Hx of plasma cell dyscrasias, CTDs such as SS
Pneumothorax, dyspnea, Hx of malignancy
Dyspnea, cough
Acute-onset fevers, chills, etc.
HRCT features
Round, smooth cysts with normal-appearing intervening lung parenchyma, diffuse distribution
Bizarre/irregular cysts along with nodules and cavities, upper zone–predominant distribution
Lentiform/ elliptical/ paramediastinal cysts abutting vessels, basilar predominant
Round cysts of varying size, GGOs, lower lobe/diffuse distribution
Round cysts, nodules, lower lobe/random distribution
Random cysts, nodules, air-fluid level
Cyst pattern not consistent with previous presentations, reticulations, GGOs
Cyst pattern not consistent with previous presentations, GGO's
Likely diagnosis
LAM
PLCH
BHD
LIP/FB
Amyloidosis/ LCDD
Cystic metastasis
ILD, smoking related
Infections such as PJP
Confirmatory steps
Scan for AMLs
Screen for TSC
Serum VEGF-D
Tbbx/VATS biopsy
DI, skin rash, bone lesions
BAL for CD1a
Tbbx/VATS biopsy
Lesional *MAPK* mutations such as *BRAF, NRAS, MAP2K1,* etc.
Scan for renal tumors
Skin biopsy
Family history
Germline *FLCN* mutations
Presence of autoimmune/ CTD/immune deficiency states
VATS biopsy
Screen for monoclonal gammopathies
Presence of systemic amyloidosis/ LCDD
VATS biopsy
Screen for underlying malignancy
+ FDG-PET scan
Tbbx/VATS biopsy
Features of ILDs such as DIP, HP
BAL/Tbbx/VATS biopsy
Screen for immune deficiency states such as HIV
Cultures
BAL

Figure 61-14 Algorithm to guide approach to the diagnosis of multicystic lung diseases. AML, angiomyolipoma; BAL, bronchoalveolar lavage; BHD, Birt-Hogg-Dubé syndrome; BRAF, v-Raf murine sarcoma viral oncogene homolog B; CT, computed tomography; CTD, connective tissue diseases; DCLD, diffuse cystic lung disease; DI, diabetes insipidus; DIP, desquamative interstitial pneumonia; FB, follicular bronchiolitis; FDG-PET, 18-Fluoro deoxy positron emission tomography; FLCN, folliculin; GGOs, ground glass opacities; HP, hypersensitivity pneumonitis; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; LAM, lymphangioleiomyomatosis; LCDD, light chain deposition disease; LIP, lymphoid interstitial pneumonia; MAPK, mitogen-activated protein kinase; PJP, *Pneumocystis jirovecii* pneumonia; PLCH, pulmonary Langerhans cell histiocytosis; SS, Sjögren syndrome; Tbbx, transbronchial biopsy; TSC, tuberous sclerosis complex; VATS, video-assisted thoracoscopic surgery; VEGF-D, vascular endothelial growth factor D. *(Reproduced with permission from Gupta N, Wikenheiser-Brokamp KA, McCormack FX: Diffuse Cystic Lung Diseases. Respiratory Medicine. Cham: Humana Press; 2021.)*

these symptoms. Consideration should be given to early pleurodesis following the first episode of spontaneous pneumothorax rather than waiting for a recurrent episode due to the extremely high risk of recurrence following conservative management.[42,61,140,150–152] It is worth noting that spontaneous pneumothorax is commonly a presenting manifestation of DCLDs, and performing a screening chest CT when evaluating patients with a pneumothorax has been shown to be cost effective.[153–155] The risk of air travel–related spontaneous pneumothorax in patients with DCLDs is approximately 1 episode per 100 flights. Thus, it is generally safe for the majority of patients with DCLDs to undertake air travel.[42,152,156–158] Although there is a paucity of direct evidence, patients should be advised against scuba diving.[63,149]

CONCLUSIONS

DCLDs comprise multiple heterogenous disorders that by virtue of their unique etiopathogenic mechanisms, clinical presentation, radiologic features, and natural history are worthy of an independent classification of their own, distinct from the typical infiltrative/fibrotic ILDs. Although multiple diseases can produce pulmonary cysts, only a few disorders present with DCLD as the primary pulmonary manifestation. Ascertaining the correct diagnosis is of paramount importance, as disease-modifying treatments are increasingly becoming available for specific DCLDs. Transformative progress in DCLDs has been driven by synergy between scientists, clinicians, and patients. This model can be used as a blueprint to meaningfully advance the field in other rare as well as common pulmonary disorders.

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CHAPTER 62

Benign Metastasizing Leiomyoma

Gustavo Pacheco-Rodriguez
Olga I. Astapova
Stephen R. Hammes
Joel Moss

INTRODUCTION

Benign metastasizing leiomyoma (BML) is a rare disease of women. It is characterized by noninvasive, nonaggressive, well-circumscribed, single or multiple tumors composed of differentiated smooth muscle cells, localized to sites other than the uterus in patients with uterine leiomyomas[1–7] and, in some cases, adnexal tumors.[8] BML has been identified in lungs[3] and lymph nodes[9] which, in addition to uterine leiomyomas, are the most common sites involved. BMLs have also been identified in the mediastinum,[10,11] retroperitoneum,[12] vascular channels,[13] bone,[14,15] heart,[16] skeletal muscle,[17] spine,[18] and pancreas.[19] Pulmonary BML is usually asymptomatic and presents with either single or multiple lung nodules of varying sizes[20] found incidentally on chest x-ray or computed tomography (CT) imaging. Occasionally, patients present with mild or severe pulmonary symptoms due to BML. Most patients with BML have undergone uterine myomectomy or hysterectomy due to leiomyomas.[3,6,21,22]

The first report of BML in 1939 described a 36-year-old woman who presented with dyspnea and wheezing. Chest radiograph showed multiple lung nodules. At autopsy, lymph nodes, uterus, and lungs showed nodules composed of smooth muscle cells with identical morphology,[23] and the term *metastasizing fibroleiomyoma of the uterus* was adopted. This term was later abandoned, and the name BML was proposed because of the metastatic behavior of this disease.[3]

BML represents a diagnostic and therapeutic challenge because of its pathogenesis and metastatic potential.[3] The diagnosis should be considered in a premenopausal woman with a history of uterine leiomyoma. Patients with BML are treated by managing estrogens, either surgically or pharmacologically.[24]

EPIDEMIOLOGY

Pulmonary BML is a rare disease of unclear prevalence. More than 100 cases of BML have been reported, but the number of reports has been rising steadily over the past decade as BML is increasingly recognized; only a few studies have reported more than one case.[3,25,26] BMLs have been identified worldwide. There is no apparent ethnic or racial predominance, in contrast to uterine leiomyoma, which is more frequent in African-American women.[27,28] Countries with reports of BML are geographically diverse[6,26] and include the United States,[21] Portugal,[29] Brazil,[30] China,[31] India,[18] South Korea,[17] Japan,[32] and Turkey.[9] BML is found primarily in premenopausal women who have undergone surgical procedures for treatment of uterine leiomyomas;[3,6,33] however, there are cases of lung BML in women with no history of these surgeries.[21] The majority of BML cases were reported in premenopausal women. Reports of BML in men and children[34] have been exceedingly rare.

CLINICAL PRESENTATION

BML lung nodules have been detected in women from a few months to greater than 30 years after they have undergone uterine myomectomy or hysterectomy.[35] Although most of the reports describe BMLs in patients following these procedures, several cases have been reported in women with no such history.[3] Furthermore, there are reports of BMLs diagnosed in women prior to myomectomy or hysterectomy.[5,21,36]

Most cases of lung BML have been identified as an incidental finding on imaging procedures performed for other purposes (Fig. 62-1).[3] Occasionally, BML in younger women presents with respiratory symptoms,[37,38] including cough, wheezing, dyspnea, and pleuritic chest pain.[20,21,23,39,40] The symptoms typically follow an indolent course, but some aggressive cases have been reported.[41] Lungs and lymph nodes are the most common sites of BML, but BML can also be present in the mediastinum, retroperitoneum, vascular channels, bone, heart, skeletal muscle, spine, and soft tissues.[14,17,42] The symptoms of BML depend on the site of the metastasis.[25,43,44] Patients with BML and spine involvement can present with leg pain and paresthesia.[42] BMLs in other sites, such as uterus, heart, and lymph nodes have been described, for

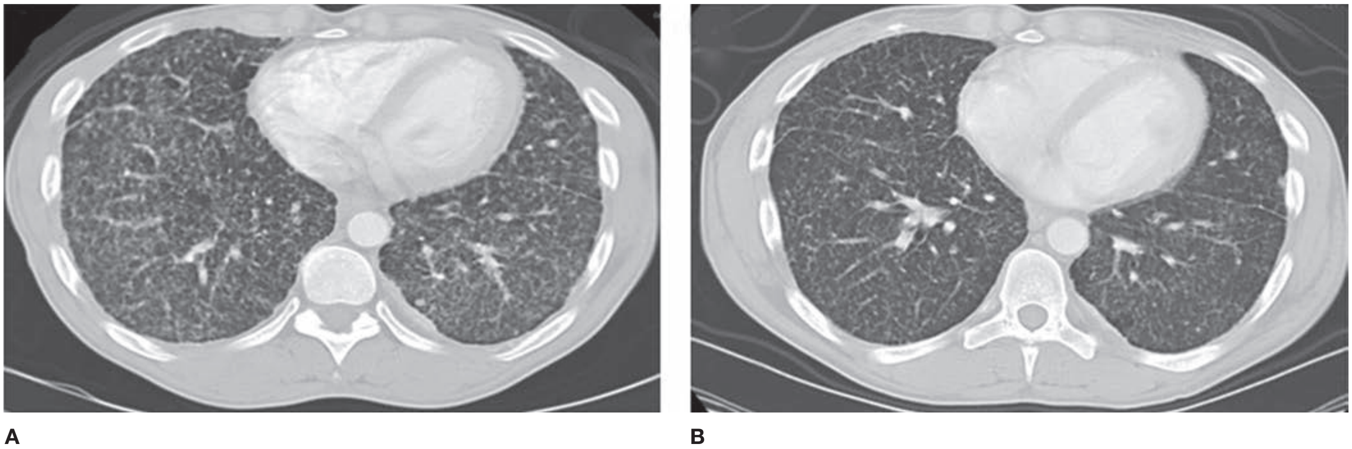

Figure 62-1 Nodular structures in BML. High-resolution computed tomography (HRCT) shows multiple diffuse, small, bilateral nodules before (**A**) and after leuprolide acetate treatment (**B**). *(Reproduced with permission from Taveira-DaSilva AM, Alford CE, Levens ED, et al. Favorable response to antigonadal therapy for a benign metastasizing leiomyoma. Obstet Gynecol. 2012;119(2 Pt 2):438–442.)*

the most part, as asymptomatic.[3] Symptoms of uterine fibroids, which are highly associated with pulmonary BML, may include abnormal uterine bleeding, pelvic pressure/pain, and reproductive dysfunction.[23,40] Recent reports highlight a potential association of melanoma and other cutaneous tumors with smooth muscle cell tumors and BML in a tumor-to-tumor metastasis model;[45] therefore, BML should be considered in a patient with melanoma and lung nodules.[46]

Clinical findings of BML may include pneumothorax,[21,47–49] hemothorax,[50] and pleural effusion;[51] in one case, BML co-presented with pulmonary arteriovenous malformation (PAVM).[52] However, in most cases, the sole findings are single or multiple unilateral or bilateral tumors with no specific lobar distribution (Fig. 62-2);[20,53,54] occasionally, BMLs have been shown to present in a miliary pattern.[55] The nodules can be solid, cystic, or complex.[21,56] The presence of pneumothoraces and cysts in patients with BML can lead to misdiagnosis as lymphangioleiomyomatosis (LAM), a multisystem disease characterized by the presence of lung cysts surrounded by proliferative smooth muscle–like cells.[57] In fact, the World Health Organization classification of lung tumors currently does not include BMLs but does include LAM lesions.[58] BML can also be misclassified as a low-grade leiomyosarcoma.[59] A number of different types of uterine tumors (e.g., leiomyoma, smooth muscle tumors of uncertain malignant potential, leiomyosarcomas, other smooth muscle tumors, endometrial stromal tumors) may be mistakenly given a diagnosis of BML. A final diagnosis, therefore, may be challenging, and requires medical history and pathologic analysis of biopsies or surgically removed tumors.

PATHOLOGY

Pathologically, BML lung nodules resemble hamartomas (the most common benign lung tumor), low-grade leiomyosarcomas, and nodules of proliferating smooth muscle cells.[60] Leiomyomas can be classified as benign or malignant, based on the number of mitotic figures. Leiomyosarcomas have more than 5 mitotic figures per 10 high-power field (HPF), whereas benign lesions have less than 5 mitotic figures per 10 HPF.[61] BML lesions contain less than 5 mitotic figures per 10 HPF, consistent with their benign nature.[25,61] BML lesions consist of well-differentiated, proliferative, benign smooth muscle cells that form intersecting fascicles and are characterized by low cellularity, low mitotic index, and no nuclear atypia (Fig. 62-3). The lesions form well-circumscribed nodules, ranging in size from a few millimeters to several centimeters in diameter.[3,6] The growth of the BML tumors is slow and, in many cases, there is no apparent size change, over long periods of time, of the multiple nodules detected by radiographic techniques. The BML nodules do not invade the surrounding tissue and may be necrotic.[33] BML tumors express smooth muscle proteins such as smooth muscle actin, desmin, and caldesmon[6,62] and most also express receptors for estrogen and progesterone, similar to uterine leiomyomas.[3,5,26] Lungs are common organs for metastasis of cells from different organs,[63,64] but as mentioned above, these tumors, including BML, can present in multiple sites (e.g., lung, lymph nodes, heart, skeletal muscle).

BML lung nodules have distinct pathologic characteristics that differentiate them from other benign lung tumors. BML nodules contain vascular structures as determined by reactivity to anti-CD34 antibody.[3,62,65] They also show reactivity with antibodies against proliferating cell nuclear antigen (PCNA), which appears in a different pattern from that seen in leiomyomatous hamartoma.[66] They express variable levels of p53, although the role of this tumor suppressor in BML cells has not been reported.[62] Most of the histopathologic sections of lung BML are not reactive with the monoclonal antibody human melanoma black 45 (HMB-45),[21,67,68] which recognizes Pmel17,[62] a melanosomal protein expressed in cells from lung hamartomas, PEComas (perivascular epithelioid cell tumors of the uterus that can metastasize to the lung[69]), and lymphangioleiomyomatosis (LAM).[70] There have been many attempts to immunologically characterize BML nodules, but these have been nonproductive since BML smooth muscle cells are not reactive with antibodies to common antigens (e.g., EMA, CD10, CD117, TTF-1, BCL-2 GPAP, S-100, calretinin, cytokeratin, chromogranin) examined in histologic clinical laboratories.

It is possible to identify cancer cells based on their molecular phenotype;[71,72] however, knowledge of the molecular characteristics of BML cells is incomplete. Expression of the micro-RNA 221 (miR-221), which has been correlated with malignancies,[73] can differentiate leiomyosarcoma from BML.[73] On the other hand, BMLs proliferate without telomeric changes, suggesting that their proliferative behavior is independent of telomeric attrition, a feature of malignant diseases.[74,75] Cytogenetic studies of BML lung tumors have shown that the cells have abnormalities in several chromosomes. The proliferative behavior of BML cells correlates with chromosomal translocations present in other noninvasive tumors.[76–78] For example, BML tumors from five cases showed 19q and 22q terminal deletions.[76] In addition, loss of chromosomes 3q and 11q has been reported.[79] These chromosomal changes differ from those reported more frequently in uterine leiomyomas, which involve translocations of chromosomes 12q14-15 and deletion of chromosome 7.[80] Interestingly, a single case showed multiple chromosomal deletions from cells isolated from several metastatic sites (e.g., thigh, lung pleura, uterus).[77,81] Rearrangement of the 6p21 region was correlated with changes in the *high-mobility group A1* gene (*HMGA1*).[77] Chromosomal translocation and mutations have been associated with high-mobility group protein isoform C (HMGIC) in leiomyomas,[82–84] but they have not been identified in the leiomyomas present in BML patients.

PATHOGENESIS

Benign lung nodular or mass lesions may be of either epithelial or mesenchymal origin.[85] BMLs have been classified as benign tumors of mesenchymal origin, but the specific cell type from which the tumors originate is unknown. Hamartomas, the most common lung tumor, are seen in both genders and, as mentioned above, may have a different histopathology from BML. Since most of the BML cases are discovered after hysterectomy or myomectomy and are strongly associated with uterine leiomyomas,[3] it is thought that BMLs mostly likely originated from a uterine cell type. There are few BML cases reported where the cells showed lack of estrogen or progesterone receptors, suggesting a nonuterine origin;[26] however, it is also possible that the proteins were downregulated due to high levels of ligands. Although there are different types of leiomyomas (e.g., mitotically active, cellular, hemorrhagic cellular, atypical, epithelioid, myxoid, vascular, lipoleiomyoma),[86] the type of leiomyoma associated with BML has not been determined. For example, PEComas of the uterus with pulmonary metastases may have a similar presentation to BML, but these tumors express Pmel7, which is recognized by the monoclonal antibody HMB-45 that reacts with LAM lung nodules.[87–89]

Genetic studies have supported a close relationship between BML nodules and leiomyomas. Whole-exome sequencing of BML nodules and patient-matched uterine leiomyomas has shown identical point mutations and copy number aberrations in all tumors, which were absent in the peripheral blood of each patient.[90,91] Clonality assays of X-chromosome inactivation and balanced karyotype studies confirm that BML lesions are probably of clonal origin and are closely related to uterine cells.[92,93] In addition, case studies identified somatic mutations in pulmonary BML that were absent in blood and leiomyomas, suggesting potential genetic drivers of metastasis in BML, such as PTEN.[90]

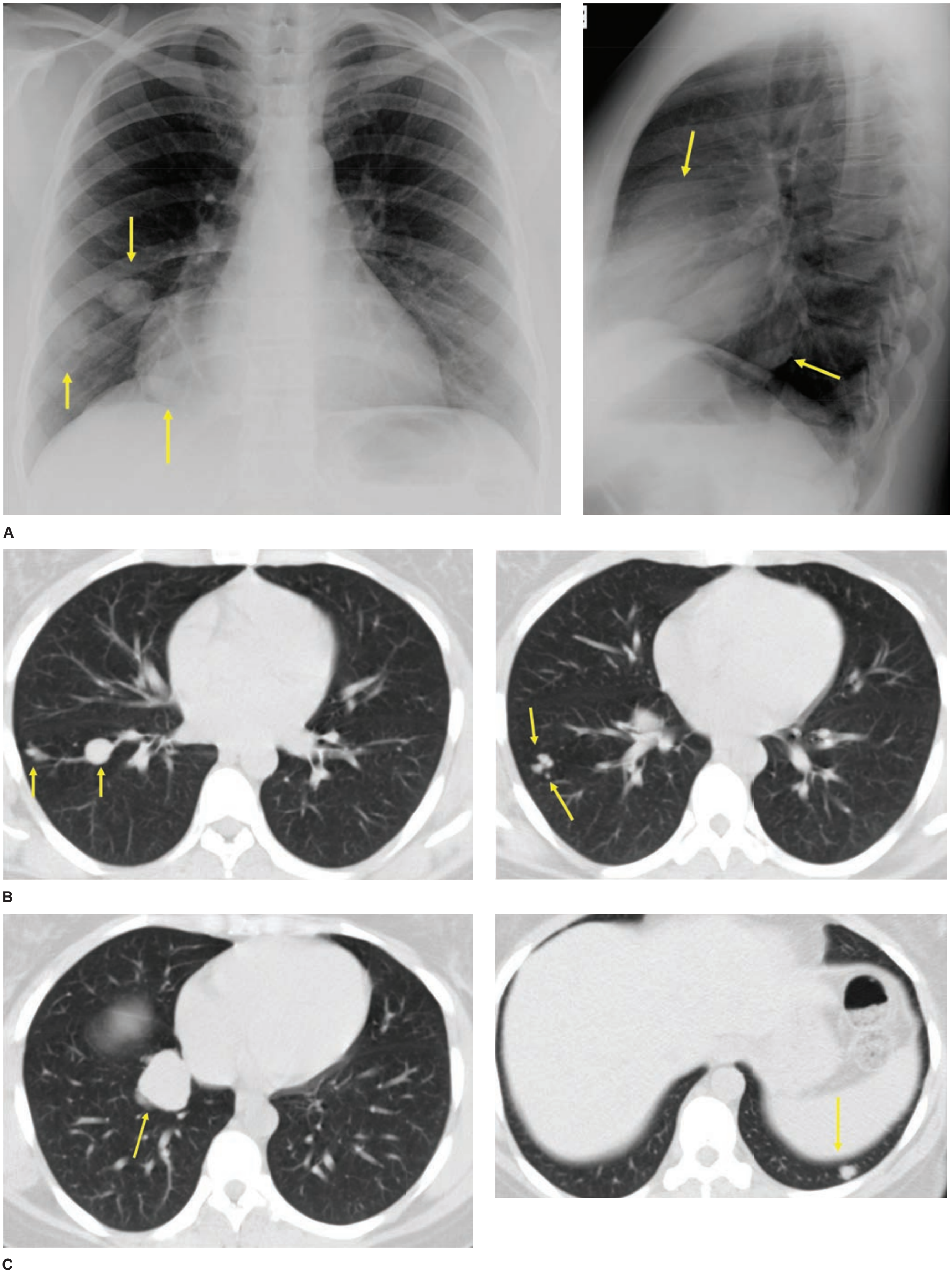

Figure 62-2 A 37-year-old woman with biopsy proven BML. Chest radiograph (**A**) and CT images (**B** and **C**) demonstrate well-circumscribed lung nodules of varying size. Arrows indicate nodules. *(Reproduced with permission from Dr. Ami Rubinowitz, Yale University School of Medicine, Radiology and Biomedical Imaging.)*

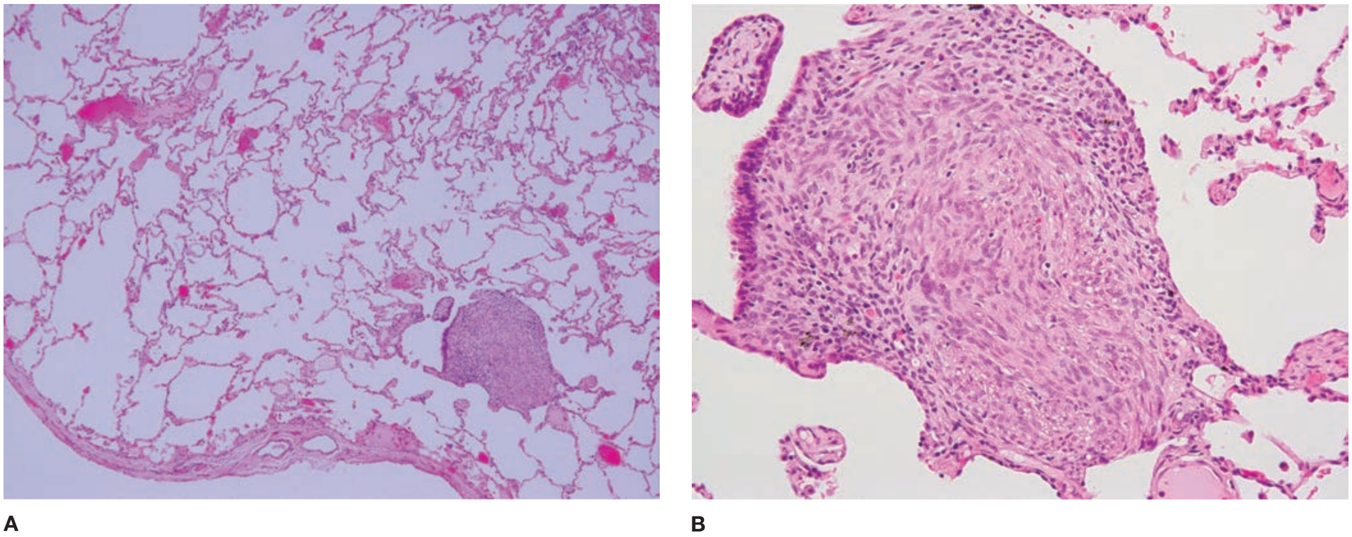

Figure 62-3 Histologic section of proliferative areas of lung BML. Tissue section shows proliferative smooth muscle cells forming fascicles characteristic of leiomyomas and BML. Panels **A** and **B** show low- and high-resolution pictures of proliferative nodules of lung BML. *(Reproduced with permission from Taveira-DaSilva AM, Alford CE, Levens ED, et al. Favorable response to antigonadal therapy for a benign metastasizing leiomyoma. Obstet Gynecol. 2012;119(2 Pt 2): 438–442.)*

Despite the growing body of evidence supporting a uterine origin of BML, its precise etiology is still debated. It has been proposed that cells responsible for the formation of pulmonary BML are derived from (1) low-grade tumors; (2) cells dislodged from uterus at the time of myomectomy and hysterectomy; (3) metastasis from uterus or an unknown site; (4) proliferation of lung smooth-muscle cells; and/or (5) simultaneous, independent development of multiple leiomyomas.

Low-grade tumors: Although other tumors may occur in patients with BML including leiomyosarcoma, adenocarcinoma, breast carcinoma, and skeletal muscle tumors,[3] their association with BML is not clear. Leiomyomas of the esophagus, lung, and uterus are found in association with multiple endocrine neoplasia type I (MEN1), but loss of heterozygosity for MEN1 has not been investigated in BML.[94] Tumors characterized as low-grade leiomyosarcomas and high-grade leiomyosarcomas do not appear to metastasize to the lung; these tumors occur mainly in the abdominal cavity.[95] It has also been proposed that BML could be an intermediate tumor stage, leading to a malignant leiomyosarcoma,[10] but high-grade leiomyosarcomas involving the lung reappear in a short period of time following surgery.[95] Low-grade leiomyosarcomas do not express progesterone and estrogen receptors, as is the case in BML.[96] Thus, it is unlikely that BMLs arise from low-grade malignancies.

Cells dislodged from uterus at the time of myomectomy and hysterectomy:

Since pulmonary BML has been associated with hysterectomy and myomectomies, it has been postulated that some of the uterine cells move into the blood circulation at the time of surgery and migrate to the lung where they remain and grow at a slow rate.[33] Lung BML has been associated with tumors in the retroperitoneal cavity,[12] pelvis, and para-aortic lymph nodes, arguing against the passive passage of cells from uterus to lung.[33] The presence of BML tumors in the pelvic region is not in agreement with the concept that uterine cells become dislodged and seed the lung. Although most cases of BML report multiple pulmonary tumors after hysterectomy, a few cases describe the occurrence of nodules before hysterectomy.[97] BML has been correlated with endometriosis, as BMLs and endometriosis have a similar course and may develop after hysterectomy or myomectomy.[5,6] Estrogen and progesterone receptors are found in lung BML cells and uterine leiomyomas, which are the most likely source of the cells. However, it is not clear if lymphatics or blood vessels are involved in the metastatic process, leading to pulmonary BML.

Metastasis from uterus or unknown site: Due to the fact that BMLs are present in multiple sites, it is possible that either uterine smooth muscle cells or cells from other nonuterine sites metastasize to the lung. About 40% of leiomyomas or myomas possess specific chromosomal abnormalities.[92] Uterine leiomyomas comprise smooth muscle cells with the extracellular matrix containing a high collagen content.[98] Lung BML nodules, however, do not have a high content of extracellular matrix. Leiomyomas contain high concentrations of estrogen[99] and progesterone[100] receptors, which drive the proliferation of cells in response to these ligands. In addition, leiomyomas contain large amounts of aromatase,[101] an enzyme involved in estrogen synthesis.[102] The presence of BML leiomyomas in lung, lymph nodes, muscular tissue, heart, vascular structures, retroperitoneal cavity, and parietal pleura[103] suggests a metastatic process.[12,16] Leiomyomas of the uterus do not tend to metastasize to the lung,[104] but BML can present with uterine vascular invasion,[31] supporting a metastatic model. Similar patterns of X-chromosome (human androgen receptor) inactivation[105] suggest that there is primarily a single BML cell source, which is the uterus.

Proliferation of lung smooth muscle cells: BML nodules could originate from proliferative lung smooth muscle cells, as is the case in primary leiomyoma.[106] However, pathologic sections of a primary pulmonary leiomyoma lack immunoreactivity for estrogen and progesterone receptors, as is found in BML.[107]

Simultaneous independent development of leiomyomas at multiple sites: Multiple BML tumors have been identified in some cases, and it is possible that they occur independently or via a metastatic process.[17] Since initial mutations have not been identified, it is possible that the mutations occurred independently in the different sites. Experimental models to study BML are not available, but human uterine cells may help us to understand the disease better.[108] Interestingly, N-nitroso compounds promoted formation of tumors in lung, reproductive and mammary organs.[109] Chronic treatment of mice with N6-(methylnitroso) adenosine (m6(NO)Ado) caused tumors in lungs and reproductive tract.[109] These findings support the hypothesis that BML could be promoted by carcinogenic processes.

Thus, although the origin of the lung BML cells is not completely understood, compilation of all the cases favors a uterine origin.

Metastatic dissemination of BML cells appears to be the most accepted mechanism for localization of BML to the lungs.[3] BML cells could metastasize via the lymphatics, hematologic spread, coelomic metaplasia, and intraperitoneal seeding.[5] Since estrogen appears to play an important role in BML development, estrogens may play a role in mutagenesis, giving origin to BML cells.[110] Extrapolating from knowledge of other metastatic diseases and animal models (e.g., LAM), estrogen may favor BML cells anchoring, seeding, and growing in the lung.[111] Galectins, formerly known as S-type lectins, are soluble and membrane-bound proteins that possess high affinity for β-galactose–containing glycoconjugates, are expressed in almost all organisms, and have been shown to play a role in cell–cell interactions and involved in tumor progression.[112,113] Galectins have been identified in pathologic sections of BML lesions, suggesting that these proteins could play a role in cell transformation, regulation of apoptosis and cell growth, cell adhesion during metastasis, and regulation of tumor invasiveness.[112] Molecular studies support the notion that BML metastasis to the lung is promoted by the inherent properties of BML cells and is not a mere byproduct of the surgical procedures.[114] A genetic and pathologic study showed that BML is clearly distinct from leiomyosarcomas, and common uterine leiomyomas[96] and intravenous leiomyomas are different from BML.

The molecular mechanisms and genetic factors that could contribute to this disease have not been elucidated. Some of the factors potentially involved in the development of uterine leiomyoma are basic fibroblast growth factor (bFGF), transforming growth factor beta (TGF-β), and granulocyte-macrophage colony-stimulating factor (GM-CSF),[115] although a role for these factors in the pathogenesis of BMLs has not been defined. A large number of uterine leiomyomas and some patients with intravenous leiomyoma possess different mutations in the mediator complex subunit 12, MED12,[116,117] which regulates transcription.[118] Due to these and other, yet unknown genetic changes, the behavior of BML, although most commonly benign, is diverse. It has been shown that intravenous leiomyoma may not appear as benign.[119] A case of aggressive BML has been reported with presentation of mutations in lung and uterus.[41] BML cells without a clearly distinct smooth-muscle phenotype may also exhibit unusual growth patterns.[120]

PULMONARY PHYSIOLOGY

Few studies have evaluated lung function in patients with BML.[21,40,95,121,122] In one study, a patient was followed for more than 10 years and serial pulmonary function tests were obtained.[21] Initially, the patient presented with diminished vital capacity and total lung capacity without any evidence of airflow obstruction or impairment in diffusion capacity (Fig. 62-4). As the disease progressed, the patient experienced a decline in diffusion capacity that could have resulted from the decline in lung volumes. In response to antiestrogen therapy, increases in vital capacity and total lung capacity were observed. In this case, the pathophysiologic profile was consistent with that of an interstitial lung disease.

RADIOLOGY

BML nodules may be identified by chest x-rays, CT, positron emission tomography (PET), and magnetic resonance imaging (MRI). The nodular structures observed in BML are well circumscribed. Bilateral pulmonary BML nodules are more common than unilateral nodules. The lung nodules can rarely be cavitating[123] or cause lung cysts.[21] Fluorodeoxyglucose-PET is negative in BML[124] and may be used to differentiate BML from some other tumors. However, many lung malignancies, such as adenomas, bronchoalveolar carcinomas, carcinoid tumors, and low-grade lymphomas also have low glycolytic activity.[125] ^{18}F-FDP-PET can, however, can distinguish BML from leiomyosarcoma, which is a more glycolytically active tumor and may be found in association with BML.[9] Computed tomography and magnetic resonance imaging have also been used to identify BML lesions in the retroperitoneal space and pelvic cavity.[126] Leiomyomas are often large enough to be recognized on pelvic examination; however, the imaging technique of choice to determine the dimensions and locations of the fibroids is a pelvic ultrasound.[127] Since, in most instances, the lung nodules are an incidental finding, a chest x-ray may be warranted after a patient is diagnosed with uterine leiomyomas.

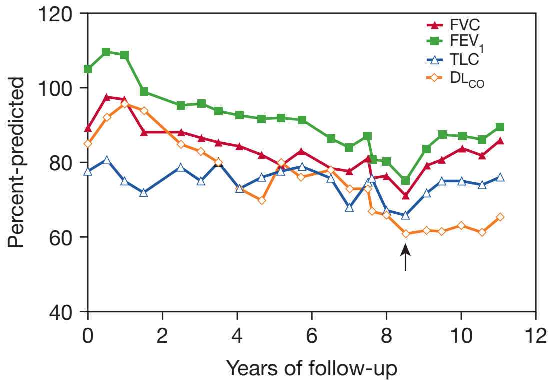

Figure 62-4 Changes in lung function before and after leuprolide acetate therapy. The patient was followed for 8.5 years before therapy and for more than 2 years after therapy. Respiratory parameters—e.g., forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1), total lung capacity (TLC), diffusion capacity for carbon monoxide (DLCO)—declined prior to therapy but improved following treatment with leuprolide. *(Reproduced with permission from Taveira-DaSilva AM, Alford CE, Levens ED, et al. Favorable response to antigonadal therapy for a benign metastasizing leiomyoma. Obstet Gynecol. 2012;119(2 Pt 2): 438–442.)*

DIAGNOSIS

The incidental finding of pulmonary nodules is a common and challenging issue. The primary objectives are to distinguish benign nodules from cancerous ones, as well as to establish a diagnosis. One criterion used to distinguish a benign nodule from a malignant one is the presence of calcification;[128] however, in many cases, this is inconclusive. The size, morphology, and growth rate of the nodules, as well as the risk factors of the patient, need to be considered.[128] A full description of the approach to lung nodules may be found in Chapter 110.

The differential diagnoses of BML nodules include infectious or metastatic lesions[129,130] (Table 62-1). Diagnosis requires a compatible medical history and pathologic analysis of biopsies and/or surgically removed tumor. CT-guided, transbronchial, or open lung biopsy may be used to establish the diagnosis.[61] Pathologic findings of BML are described above. BML patients do not present with dysregulated levels of tumor biomarkers—e.g., carcinoembryonic antigen (CEA); carbohydrate antigen 19-9, also called cancer antigen 19-9 or sialylated Lewis (a) antigen (CA19-9); carcinoma antigen 15-3 (CA 15-3); cancer antigen 125 (CA-125); cytokeratin 19 fragment (CyFRA21-1); neuron-specific enolase (NSE); alpha-fetoprotein (AFP); hyperglycosylated hCG (HCG-β); or beta-2-microglobulin (β2-MG).[130]

Since the lung is one of the main organs involved in metastasis from different types of cancers including colon, breast, pancreas, ovary, and stomach, the presence of either single or multiple lung nodules should always raise suspicion of primary or metastatic malignancy. Thus, differential diagnosis of BML should include primary pulmonary leiomyoma, primary pulmonary leiomyosarcoma, metastatic leiomyomatosis of an extrauterine source, pulmonary

TABLE 62-1 Disease Processes That Involve Pulmonary Nodules

Infectious[149]
Bacterial (tuberculosis,[153] nontuberculous mycobacteria, *Nocardia*, *Actinomyces*)
Fungal (histoplasmosis, *Cryptococcus*, coccidiomycosis)[150,151]
Parasitic[152]
Neoplastic[154]
Benign neoplasms[155]
Chondroharmartomas[156]
Hamartomas[157]
BML[3]
Malignant neoplasms
Primary lung cancer
Pulmonary sarcoma
Metastasis
Pulmonary lymphoma
Infiltrative
Amyloid[158]
Sarcoidosis[159]
Silicosis[160]
Other
Mucoid impaction syndromes[161]
Pulmonary arteriovenous malformation[162]
Plasma cell granuloma[163]
Rheumatoid nodule[164]
Granulomatosis with polyangiitis

hamartomas, and lymphangioleiomyomatosis (LAM).[3] Lung hamartomas are associated with other cancers and express the melanogenic protein Pmel17,[131] as do LAM lesions.[88,89,132] Low-grade leiomyosarcomas may mimic BML, but they can be distinguished based on lack of expression of progesterone and estrogen receptors.[106] Other diseases presenting with similar lung nodules (Table 62-1) include infectious processes (fungal, parasitic, and bacterial [e.g., tuberculosis]), amyloidosis, mucoid impaction syndromes, multiple arteriovenous malformation, paraffinoma, plasma cell granuloma, rheumatoid nodules, sarcoidosis, and silicosis.[129] The diagnosis of BML should include a complete radiologic and histologic assessment, with focus on the status of estrogen and progesterone receptors.[133]

BML, depending on location, has been classified as intravenous leiomyomatosis and disseminated BML,[12] but there are no reports of lymphatic involvement, as is the case with LAM.[57] Intravenous leiomyomatosis may involve the heart, causing severe symptoms[134] that may be fatal.[135] BML should therefore be considered in cases of tumors of the heart with uterine leiomyoma.[135] It is also important to determine the presence of intravenous leiomyomatosis in the uterine, pelvic, and cardiac veins in the presence of BML, as this has been observed.[136] Leiomyomatosis peritonealis disseminata is one of the diagnoses to consider when a BML patient presents with peritoneal lesions.[12]

PROGNOSIS

The prognosis of patient with BML is generally favorable and may be improved with treatment. The lung lesions are often identified many years after hysterectomy or myomectomy, suggesting that the growth rate of these tumors is slow. However, there have been cases of recurrence and, rarely, of BML progression to leiomyosarcoma.[137] Some experts suggest that women undergoing surgical procedures of the reproductive tract be followed with chest radiographs, although formal guidelines from major clinical consensus statements do not address this. Factors that may influence the prognosis of BML patients include involvement of other sites including heart, veins, or spine, as well as the presence of other cancers. There are only scattered reports of BML as a cause of death.

TREATMENT

Close follow-up of lung BML after treatment is important since lung BML may be difficult to distinguish from other, more aggressive diseases (e.g., leiomyosarcoma, LAM). Treatment involves tumor resection and manipulation of hormonal status.[26] Surgical treatments have been adapted from those used for uterine leiomyoma and include hysterectomy, myomectomy, dilation of the cervix, uterine artery embolization and endometrial ablation, and curettage.[21,26,130] BML tumors also respond to hormone therapy, with resolution of symptoms such as dyspnea.[25] Lung tumors may regress at menopause and during/after pregnancy, supporting a role for estrogen in the pathogenesis of BML.[138]

Oophorectomy has been reported to improve lung function and cause regression of lung tumors.[36,40,121,122,139–142] Although bilateral oophorectomy has been the most commonly used treatment, unilateral oophorectomy has been effective in treating some BML tumors.[36] Another line of treatment has involved antiestrogenic therapy. Gonadotropin-releasing hormone (GnRH) analogues (e.g., leuprolide acetate) have been used to reduce estrogen levels.[13,21,143] Other drugs shown to be effective include the selective estrogen receptor modulators (SERMs) such as raloxifene,[30,121,144] selective progesterone receptor modulators (SPRMs), and aromatase inhibitors such as anastrozole.[121] Progesterone therapy also has proved to be effective.[59,145,146] There have been some cases of BML refractory to progesterone and aromatase inhibitors.[26,38] Treatments of uterine leiomyoma have also included combinations of GnRH analogues with aromatase inhibitors[26,121,147] and antiprogestin (CDB-2914).[26,147] In some cases, total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH/BSO) has been combined with drugs.[26] It is important to consider loss of bone mineral density due to antiestrogenic therapies. The slow-growing behavior of BML suggests that these tumors can be left untreated unless the patient becomes symptomatic.

CONCLUSIONS

BML is characterized by the presence of single or multiple nodules in the lung. Pulmonary BML has been mainly associated with uterine leiomyomas. Pathologically, BML may resemble lung hamartoma (the most common benign lung tumor), low-grade leiomyosarcoma, or smooth muscle cell proliferation. Pulmonary BML is usually asymptomatic but in some cases presents with minor respiratory symptoms. Most BML cases present with multiple pulmonary tumors after myomectomy and hysterectomy. BML lesions are found predominantly in premenopausal women and express estrogen and progesterone receptors, suggesting a role of these hormones in disease pathogenesis[111] and distinguishing these lesions from other similar-appearing lung nodules. Other diseases that may be confused with BML include pulmonary nodules (e.g., primary leiomyoma, primary leiomyosarcoma, metastatic leiomyosarcoma, pulmonary hamartoma, leiomyomatous hyperplasia, lymphangioleiomyomatosis). Transbronchial and open lung biopsies have been used to diagnose and confirm BML. Pharmacologic or surgical methods that decrease estrogen in patients with BML can result in total regression, but recurrence has been reported; therefore, continued monitoring of patients is advised.

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CHAPTER 63

Depositional Lung Disorders: Amyloidosis, Pulmonary Calcification, and Pulmonary Ossification

Robert J. Homer
Christopher Gange
Natalia Neparidze

INTRODUCTION

Deposits of endogenous body constituents or exogenous materials in amounts sufficient to deform structure and impair function can occur virtually anywhere in the body. Deposits of endogenous materials in the lungs or airways cause a variety of diseases (Table 63-1). These may have different clinical manifestations depending on location (i.e., pulmonary parenchyma or conducting airways). This chapter deals with two of these manifestations: amyloidosis and diffuse pulmonary calcification and its variants. Others depositional diseases are discussed elsewhere in this text.

AMYLOIDOSIS

Amyloidosis refers to the extracellular deposition of amyloid, a fibrillar, proteinaceous, insoluble material that has characteristic light, ultrastructural, and histochemical features[1,2] (Fig. 63-1). Electron microscopic examination of amyloid reveals a dominant (95%) fibrillar component with distinctive periodicity, associated with a lesser (5%) pentagonal doughnut-shaped glycoprotein component, physically and chemically identical in all forms of amyloid, which is derived from a soluble plasma protein, soluble amyloid P protein (SAP). Amyloid also includes various glycosaminoglycans, for example, heparan sulfate and certain apolipoproteins (E and J).[3] Radiographic diffraction studies of amyloid show the fibrils to be arrayed in a β-pleated sheet configuration. This accounts for the ordered binding of the histochemical stain Congo red such that Congo red–stained amyloid appears apple-green under polarized light. When amyloid is deposited in tissues it may produce a wide variety of clinical manifestations mediated by atrophy of parenchymal cells (e.g., glomeruli), interference with mechanical function (e.g., heart and lungs), or impaired vasoconstriction of blood vessels, leading to hemorrhage (e.g., lungs and gastrointestinal tract). Mechanisms of tissue injury include direct tissue toxicity and activation of the unfolded protein response.[4] Deposition may occur in multiple organs as a systemic disease or may be limited to a single organ. As a result, classification includes both the specific moiety involved and the clinical syndrome.

TABLE 63-1 Depositional Diseases of the Lungs

Biologic Material	Disease
Interstitial deposition	
Amyloid	Amyloidosis
Water	Interstitial edema
Calcium	Calcification and ossification
Alveolar deposition	
Surfactant	Alveolar proteinosis
Water	Alveolar edema
Calcium	Alveolar microlithiasis
Blood and hemosiderin	Alveolar hemorrhage syndromes

While the main fibrillar component of amyloid can be derived from any one of many potential precursor proteins, only a few are common in disease involving the lung, including immunoglobulin light-chain, serum amyloid–associated (SAA) protein (an acute phase reactant), transthyretin (TTR, a prealbumin molecule made in the liver that binds and transports thyroxine and retinol), and β_2-microglobulin, a component of the major histocompatibility complex (MHC) class I molecule.[5,6] The established amyloid fibril nomenclature is based on the chemical nature of the fibril protein, where an A, for amyloid, is followed by a suffix that is an abbreviated form of the parent or precursor protein. These forms of amyloidosis are therefore known as AL, AA, ATTR, and Aβ_2M, respectively. Generation and deposition of these proteins into amyloid depends on increased production or reduced clearance of the precursor protein, as well as factors enhancing abnormal folding, such as inherited mutations within the precursor protein.[1] An entity related to amyloidosis is light-chain deposition disease (LCDD), in which tissue deposits are also derived from immunoglobulin light chains and are similar to amyloid by routine light microscopy but show granular deposition by electron microscopy rather than fibrils, do not include amyloid cofactors, and do not stain with Congo red.[7] It seems likely that the biochemical properties of the light chain determine the nature of the deposit produced. Finally, there is a third form of immunoglobulin depositional disease, crystal storing histiocytosis (CSH), in which the immunoglobulin forms crystals with an associated histiocytic response. CHS is associated with a range of lymphoproliferative diseases and can also form mass lesions in the lung.[8]

Systemic AL amyloidosis occurs in association with a neoplastic clonal proliferation of B cells or plasma cells that produce a monoclonal immunoglobulin or immunoglobulin fragment (monoclonal gammopathy). In most cases, the neoplastic clone may clinically manifest as multiple myeloma or lymphoma (generally lymphoplasmacytic lymphoma or other low-grade non-Hodgkin's lymphoma) or may be subclinical (formerly known as primary amyloidosis), causing bone-marrow plasmacytosis. Most often the protein source is a λ-light chain, either intact or the amino terminal fragment. Systemic AL amyloidosis can present with a variety of symptoms or signs including fatigue and weight loss, heavy proteinuria and/or nephrotic syndrome, hepatosplenomegaly, otherwise unexplained heart failure, muscle (including tongue) enlargement, waxy skin, bleeding, and neuropathy (including carpal tunnel syndrome).

AA amyloidosis can occur as a complication of any long-term inflammatory disorder.[9] It was formerly seen predominantly in patients with chronic infections (e.g., tuberculosis, leprosy, and chronic osteomyelitis) but is now seen more commonly with noninfectious chronic inflammatory diseases (e.g., rheumatoid arthritis, familial Mediterranean fever, or Crohn's disease). Rarely, it may be due to neoplasms or is idiopathic.[9] The precursor in most cases is encoded by the SAA1 gene, with rare cases of SAA2 also described. Allelic variants of SAA1 that are associated with propensity to self-aggregate increase the risk of AA. SAA is made predominantly

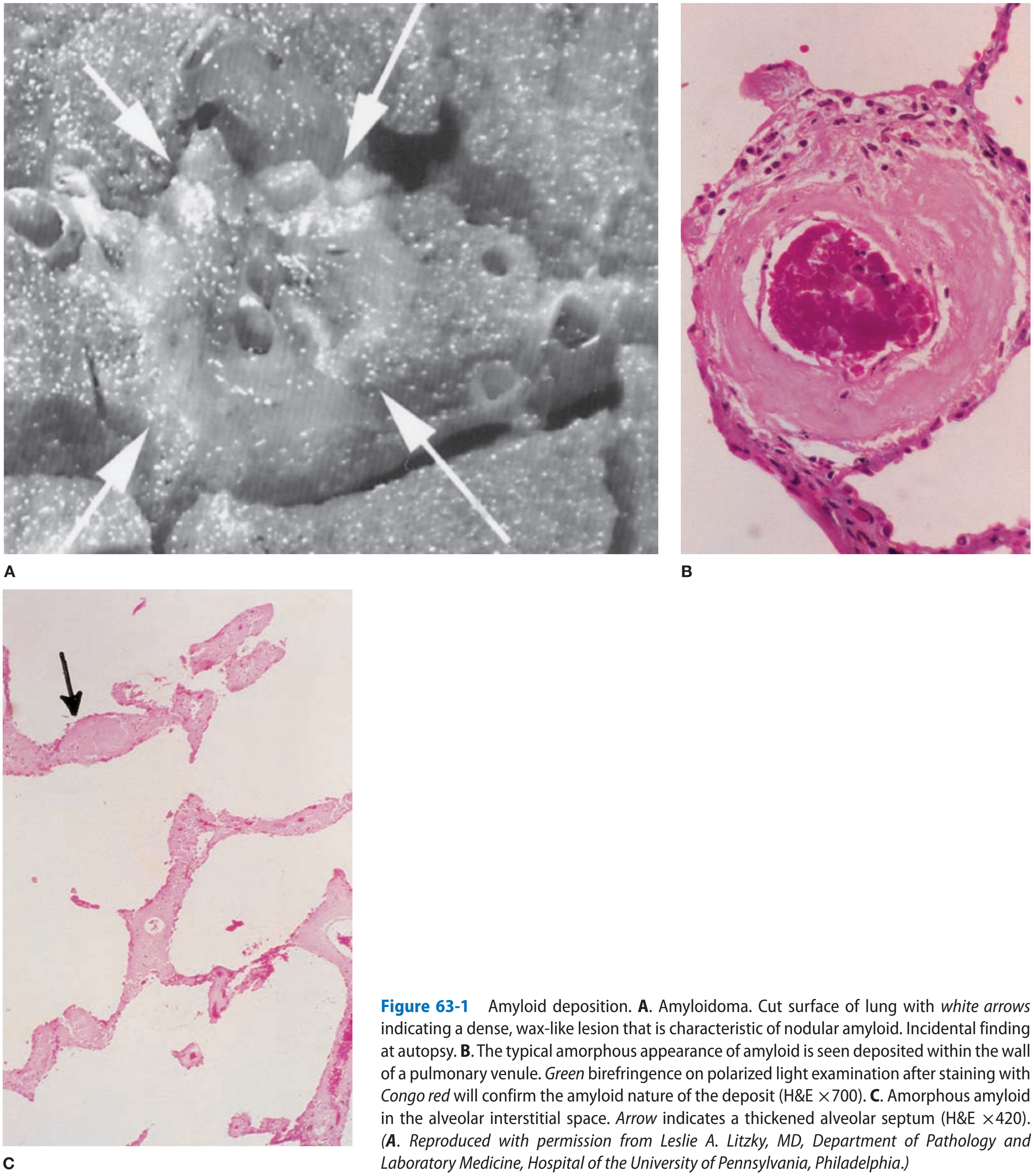

Figure 63-1 Amyloid deposition. **A**. Amyloidoma. Cut surface of lung with *white arrows* indicating a dense, wax-like lesion that is characteristic of nodular amyloid. Incidental finding at autopsy. **B**. The typical amorphous appearance of amyloid is seen deposited within the wall of a pulmonary venule. *Green* birefringence on polarized light examination after staining with *Congo red* will confirm the amyloid nature of the deposit (H&E ×700). **C**. Amorphous amyloid in the alveolar interstitial space. *Arrow* indicates a thickened alveolar septum (H&E ×420). *(**A**. Reproduced with permission from Leslie A. Litzky, MD, Department of Pathology and Laboratory Medicine, Hospital of the University of Pennsylvania, Philadelphia.)*

by the liver but is also made by other cells such as macrophages, endothelial cells, and smooth muscle under control of proinflammatory cytokines such as tumor necrosis factor, interleukin 1 beta, and interleukin 6. Systemic AA almost always presents with renal disease as proteinuria and/or nephrotic syndrome.

TTR is deposited in familial amyloid polyneuropathies in which there is a germline TTR mutation that encourages amyloid formation (referred to either as *ATTRv* for variant or *ATTRm* for mutant) and systemic wild-type ATTR (sometimes called *ATTRwt*) amyloidosis. The latter is also referred to as *systemic senile amyloidosis* as it is relatively common in an elderly population, although there is clinical overlap with the mutant form. Patients commonly show cardiomegaly and heart failure. Carpal tunnel syndrome also is common, as is spinal stenosis. Untreated patients with ATTRwt survive longer than patients with AL with equivalent amounts of cardiac involvement.[10] TTR-related amyloid can also be observed as an incidental finding in the heart at autopsy.

β_2-microglobulin deposition (Aβ_2M amyloidosis) is seen in patients with chronic renal failure on dialysis.[11] Patients with dialysis-related amyloidosis most commonly complain of shoulder pain, related to scapulohumeral periarthritis and rotator cuff infiltration by amyloid, and of symptoms of carpal tunnel syndrome.

Pulmonary Involvement in Amyloidosis

Amyloidosis involving the lung is usually a manifestation of multiorgan disease, while disease localized to the lung in absence of systemic disease is much less common.[6,12] Pulmonary-specific manifestations include dyspnea and dry cough with an interstitial radiographic pattern, nodules (amyloidomas), and rarely pulmonary hypertension. Several radiotracers have proved useful in detecting amyloidosis. The radiotracer used in routine bone scintigraphy, Tc-99m hydroxymethylene diphosphonate (HDP), is taken up specifically by transthyretin amyloid deposits and can be used in cardiac imaging to identify this type of amyloid deposit.[13,14] PET radiotracers initially developed for use in brain imaging for Alzheimer's disease are also taken up by light chain and transthyretin amyloid and are being investigated for cardiac and systemic uses.[15,16]

Tracheobronchial infiltration can cause hoarseness, stridor, airway obstruction, and dysphagia. In addition to pulmonary involvement per se, amyloidosis may also cause respiratory symptoms due to deposition in any portion of the respiratory tract or in other organs. For example, deposits in the tongue may be extensive enough to cause obstructive sleep apnea. Persistent pleural effusions may be due to both pleural and cardiac disease. Diaphragmatic deposition may lead to respiratory failure. Pulmonary involvement is most commonly due to AL (about 80%) followed by ATTR (both hereditary and wild type), AA, and Aβ2M.[6,17] Most patients can be characterized as having tracheobronchial amyloidosis, nodular parenchymal amyloidosis, or diffuse septal amyloidosis.[12] Tracheobronchial amyloid deposition and nodular parenchymal amyloid deposition (amyloidoma) **(Fig. 63-1A)** most often occur as isolated local phenomena, whereas diffuse interstitial deposition is most often seen in systemic amyloidosis.

Nodular Parenchymal Amyloidosis

Solitary amyloid nodules (amyloidomas) are commonly incidental radiographic findings in asymptomatic individuals although there is an increase in patients with Sjögren syndrome **(Fig. 63-1A)**.[5,12,18] These nodules have no distinctive imaging features on radiograph or CT and may be soft tissue attenuation, partially calcified, or rarely cavitary. Noncalcified amyloidomas are reported to have low signal intensity on T2 and are isointense to skeletal muscle on T1-weighted imaging, but due to the limitations of MR for evaluating lung nodules this is rarely performed clinically.[19] While the diagnosis of an amyloid nodule is typically made after surgical resection, it is possible to make the diagnosis on transbronchial biopsy or core needle biopsy.[20] However, surgical excision of one or more nodules may sometimes be prudent, since, on rare occasion, amyloid deposition occurs within a pulmonary neoplasm (e.g., a primary pulmonary neoplasm such as a typical carcinoid or a metastatic neoplasm such as medullary carcinoma from the thyroid). It is possible that advances in biochemical analysis of the amyloid (see below) may influence this decision, but this is not yet commonly discussed in the literature.

Nodular parenchymal amyloidosis is most often said to represent AL. However, one study showed that the deposits are a mixture of light and heavy chains, which is rare in most cases of systemic AL.[12] Histologically, the amyloid deposit is often associated with an intense inflammatory reaction consisting of plasma cells, macrophages, and multinucleated giant cells. While a clonal population of plasma cells and/or B cells can be identified in many cases—and in a few instances, nodular amyloidosis has been associated with a histologically apparent low-grade pulmonary lymphoma—clinical follow-up of nodular parenchymal amyloidosis unassociated with systemic disease is generally benign. It has been suggested therefore that in cases of AL limited to the lung, as shown by appropriate investigations such as liver function tests, renal function tests, and echocardiography, only a limited search for an occult lymphoproliferative disorder need be undertaken.[12,21] Rare cases of systemic AL, localized AA, localized ATTRwt, and localized Ab$_2$M/AL also have been reported to present as nodular amyloidosis.[6,22]

Tracheobronchial Amyloidosis

Amyloid deposition in the tracheobronchial tree can produce either plaques or tumoral masses.[23–25] Like nodular amyloid, this usually represents AL, but a clonal source is rarely found, and the material commonly has a polytypic mix of immunoglobulin light and heavy chains.[12] The more common presentation as plaques is diffuse and multifocal and represents submucosal deposition of amyloid. Diffuse or proximal involvement of the airways is apt to be symptomatic, producing cough, stridor, or hemoptysis. Less commonly, deposition of amyloid in the tracheobronchial tree produces a solitary mass, which mimics an endobronchial neoplasm with signs of bronchial obstruction or hemorrhage. Both types of airways lesions can be readily identified by bronchoscopic examination. However, as is the case with amyloid deposition at all sites, with biopsy there is a risk of hemorrhage. Although localized tumoral masses may be treated by excision or observation, more diffuse involvement may be treated by laser ablation, stents, or radiation. Involvement of proximal airway leads to significant mortality, while involvement of distal or mid airway has generally good prognosis.

Diffuse Interstitial Amyloidosis

Widespread, diffuse interstitial amyloidosis of the pulmonary parenchyma may produce either a reticulonodular or miliary pattern on the chest radiograph and CT and may result in confluent consolidations with a basilar and peripheral distribution.[5,26] The deposition of amyloid may involve the alveolar septal interstitium, the walls of small blood vessels, or both **(Fig. 63-1B, C)**. Such pulmonary involvement occurs most often in patients with systemic amyloidosis, derived from either immunoglobulin light-chain or AA protein and is only rarely localized.[5,6,27] Pulmonary interstitial amyloid deposition in secondary involvement is rarely sufficiently severe to produce clinical manifestations and is most commonly diagnosed at autopsy. Uncommonly, it may produce progressive dyspnea, hemoptysis, or restrictive pulmonary function tests. It is thought that the morbidity and mortality of diffuse septal amyloidosis in patients with systemic disease is related to concurrent cardiac amyloidosis with which tissue burden closely correlates, possibly explaining why septal amyloidosis by itself in this setting is not of more significance. On the other hand, primary diffuse interstitial pulmonary amyloidosis has been considered to have a relatively poor prognosis.

Diagnosis and Treatment of Amyloidosis

Pathologic diagnosis of amyloidosis requires tissue examination with concurrent Congo-red or equivalent amyloid-specific staining and/or electron microscopy. In cases of systemic amyloidosis, clinically uninvolved sites allow less invasive sites to be biopsied with reasonable expectation of a positive result. The classic fat pad biopsy has a sensitivity of between 60% and 85% in experienced hands.[28,29] It is important that both the aspiration and the sample processing be done by those with experience in the technique. However, this procedure has low sensitivity in patients with single organ involvement.

It is essential that the biochemical nature of the amyloid protein be established since this cannot be predicted from clinical manifestations alone. Even in patients with a known plasma cell dyscrasia, if amyloid is detected, it should not be assumed that this represents AL amyloid, since a significant number of patients with familial or senile type amyloid also have plasma cell dyscrasias. Historically, a variety of immunohistochemical and immunofluorescence tests were used, combined with genetic testing; but these commonly required frozen tissue, which were technically challenging and did not always provide an answer. More recently, improved immunohistochemistry and biochemical techniques have become available and are applicable in formalin-fixed paraffin-embedded tissue.[30] These techniques, especially mass spectroscopy, allow specific identification of the associated amyloid precursor protein including any possible genetic variants. Published data show these approaches are highly robust and generalizable to multiple clinical scenarios, although they have not yet been reported in patients with isolated pulmonary disease.

While it is beyond the scope of this chapter to discuss therapy in depth, it is important to note that therapy for systemic disease is highly dependent on the specific peptide responsible. For systemic light chain–associated amyloidosis, complete evaluation for nature of an underlying B cell or plasma cell malignancy should be conducted. Staging, including assessment for cardiac involvement, is a critical determinant of overall survival.[31] Hence, thorough cardiac assessment with combination of cardiac markers (N-terminal pro B-type natriuretic peptide [NT-proBNP], troponin levels), as well as imaging with echocardiogram and cardiac magnetic resonance, provide crucial prognostic information.

In cases of systemic AL amyloidosis, there has been considerable progress in treatment with introduction of myeloma-type therapy. For eligible patients, high-dose prednisone and melphalan therapy combined with use of hematopoietic stem-cell transplantation is effective.[31] Newer agents, such as thalidomide, lenalidomide, and related compounds—especially bortezomib, which targets plasma cells—have revolutionized the field. Bortezomib has been the backbone treatment, in combination with cyclophosphamide and dexamethasone (CyBorD); remarkable overall hematologic response rates have been noted. Novel biologic agents targeting plasma cells, such as daratumumab, which targets CD38, also represent a significant breakthrough in therapy. The combination of daratumumab plus bortezomib is emerging as a novel standard of care in systemic AL amyloidosis.[31] Finally, efforts are ongoing to target and eradicate amyloid deposits through monoclonal antibodies directed at specific epitopes of light chain amyloid fibrils, although results have not been positive to date.[31]

In contrast, treatment for AA amyloidosis focuses on the underlying inflammatory disease but may also include small molecule inhibitors.[9] Treatment for systemic ATTR (both ATTRv and ATTRwt) has been approached with small interfering RNAs and selective binders to ATTR to prevent amyloidogenesis.[32,33] In some cases, organ (liver, heart) transplantation has been explored. The significance of these therapies for lung-limited disease is unclear, since localized disease is typically treated with ablative therapy such as stents, radiation, laser treatment, resection, and other localized methods. The more recent systemic therapies have only rarely been reported in patients with initial, lung-limited disease.[5]

PULMONARY CALCIFICATION AND OSSIFICATION

Calcification of the pulmonary parenchyma may occur by deposition on normal tissues as metastatic calcification, on abnormal tissues as dystrophic calcification, or, as a special subtype, within alveoli as alveolar microlithiasis.[34–36] *Pulmonary ossification* refers to actual bone tissue formation with or without marrow elements, which is usually but not always secondary to other injury. While other organs can be affected by ectopic calcification and ossification, the lungs are particularly susceptible. Multiple factors contribute to the development of metastatic and dystrophic calcification, including increased serum levels of calcium and phosphate, alkaline phosphatase activity, and local tissue pH.

■ Metastatic and Dystrophic Calcification

Metastatic calcification (Fig. 63-2) typically but not always occurs in association with some derangement of calcium metabolism, such as primary hyperparathyroidism, secondary hyperparathyroidism of chronic renal failure, hypervitaminosis D, the milk-alkali syndrome, sarcoidosis, or increased bone turnover due to multiple myeloma or metastatic carcinoma.[37]

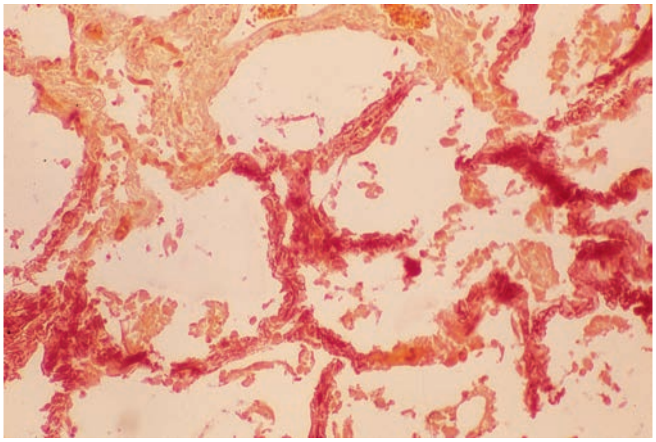

Figure 63-2 Metastatic calcification of alveolar septa in a renal dialysis patient. Photomicrograph shows calcium forming a *dark red* precipitate within the alveolar septa (Alizarin red ×280).

Although metastatic calcification can occur in almost any tissue of the body, it occurs most often in the lungs, kidneys, and the stomach (tissues with more alkaline pH), as well as the walls of blood vessels. Metastatic calcification in the lungs usually affects the interstitium of the alveolar septa and the walls of bronchioles and pulmonary vessels, sometimes localizing on elastic fibers.

On chest radiograph, metastatic calcification often appears as a patchy opacity, and calcifications in the lungs may be visible; however, mild cases may also result in a normal study.[38] These opacities may be confluent and mimic pneumonia but will persist on subsequent studies after antibiotic treatment, warranting a chest CT. Although the calcific nature of the opacity may be apparent on routine chest radiograph, a chest CT is more sensitive both in detecting interstitial deposits and in demonstrating calcification. Moreover, a CT scan may also demonstrate calcification of chest wall blood vessels, circumstantially implicating calcification as the cause of pulmonary parenchymal abnormalities.[39] Nuclear medicine studies can also be used to evaluate calcified opacities, as these deposits will show increased uptake of bone scan agents such as ^{99m}Tc-MDP and ^{18}F-NaF.[40,41]

Clinical manifestations of diffuse pulmonary metastatic calcification are unusual, occurring most often in patients who are in chronic renal failure, particularly in those on chronic hemodialysis. Only rarely do patients manifest dyspnea or arterial hypoxemia, and pulmonary function tests tend not to show signs of restrictive pulmonary disease. Unexplained dyspnea in a patient with chronic renal failure or hypercalcemia in the presence of a normal chest radiograph should lead to consideration of high-resolution computed tomography (HRCT). Rarely, respiratory failure may develop, although death from metastatic calcification is typically due to cardiac disease.

The mechanism responsible for metastatic pulmonary calcification is unknown. Although high levels of parathyroid hormone or a marked increase in the calcium-phosphate solubility product occur in some patients, diffuse calcification can occur in the absence of either. The presence and severity of metastatic calcification correlates poorly with serum calcium and phosphorus levels, degree of parathyroid hyperplasia or activity, type of primary disease, or length of dialysis. Ultrastructural observations of minimal, presumably early, lesions show selective deposition of calcium on elastic fibers, suggesting that they may serve as the initial nidus.

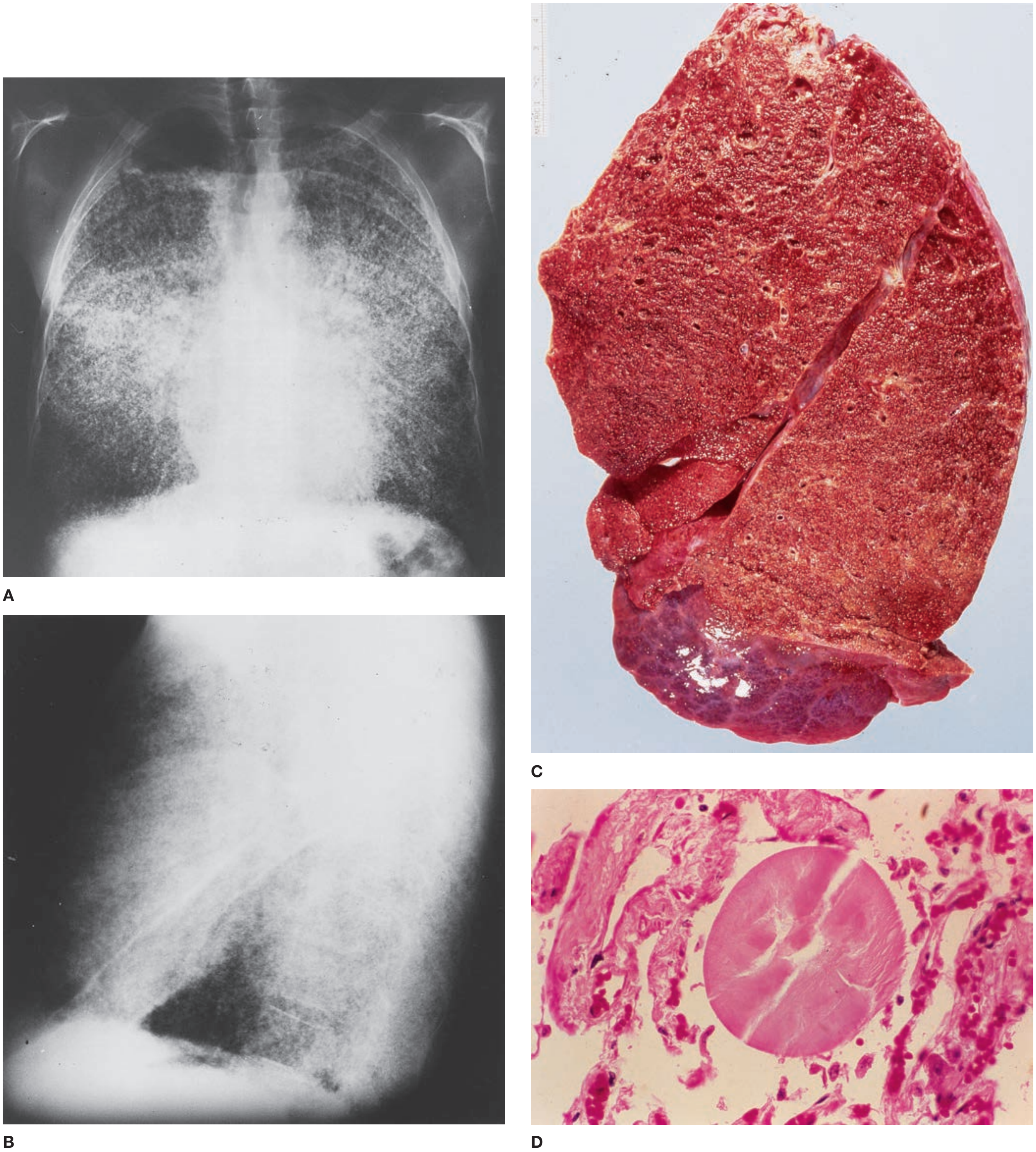

Figure 63-3 Alveolar microlithiasis in a 46-year-old man admitted for nonpulmonary problems. History included slight dyspnea on exertion and previous episodes of "pneumonia" in 1947, 1950, and 1952. Clinical examination revealed severe restrictive lung disease, pulmonary hypertension, and cor pulmonale. Diagnosis confirmed by lung biopsy. **A** and **B**. Posterior–anterior and lateral chest radiographs demonstrate innumerable, tiny calcified nodules throughout both lung fields. Thin, lucent lines on each side represent normal pleura visualized between the calcified pulmonary parenchyma and the chest wall. Emphysematous blebs in the apices displace the calcifications. **C**. Cut surface of explanted lung from a patient undergoing lung transplantation for primary alveolar microlithiasis. Note the fine nodularity that correlated with the chest radiographs. **D**. Photomicrograph demonstrating a typical calcospherite in an alveolar space (H&E ×1120). *(**C**. Reproduced with permission from Leslie A. Litzky, MD, Department of Pathology and Laboratory Medicine, Hospital of the University of Pennsylvania, Philadelphia.)*

In metastatic calcification, specific conditions that elevate the calcium-phosphate product should be corrected to prevent further calcification. Renal transplantation for patients with end-stage kidney disease often mitigates this process. In some cases, however, the calcification persists and progresses even with a functioning transplanted organ; some of these cases may be due to tertiary hyperparathyroidism. In such severe cases, parathyroidectomy may be indicated. Spontaneous resolution of MPC also has been described, although it is rare.

In contrast to metastatic calcification, dystrophic calcification, typically consisting of hydroxyapatite, occurs in injured tissue (such as within the granulomas of tuberculosis or sarcoidosis), pulmonary hypertension, other postinfectious conditions, amyloidosis, malignancies, or pneumoconiosis. This type of calcification is usually localized; its distinctive radiographic features are sometimes diagnostically helpful. It is rarely of any clinical significance beyond that of the underlying condition. Histologic variants of other calcium-containing endogenous mineral deposits, including blue bodies and myelin lamellar type bodies, also have been described.[35] These are of no known clinical significance.

■ Pulmonary Ossification

Pulmonary ossification, in contrast to calcification, refers to the formation of mature bone tissue, often with marrow elements, within the lungs. It may occur on the background of dystrophic calcification. This may be observed in chronic necrosis or in slowly growing tumor masses, particularly metastatic colonic adenocarcinoma or tumors such as metastatic osteosarcoma that produce bone.[35,42]

Pulmonary ossification can be subdivided into two histologic forms, both of which may be found in the same patient: nodular and branching (also known as dendriform) ossification. Nodular ossification is characterized by lobulated bone nodules within alveolar spaces, usually devoid of fat or marrow elements. The nodular circumscribed form of pulmonary ossification consists of small nodules, 2 to 8 mm in maximum dimension. Nodular ossification usually develops in the setting of passive congestion and pulmonary edema, as from chronic heart failure or cardiac valvular abnormalities.

Dendriform ossification in the lungs is characterized by formation of branching bone tissue that often contains marrow elements. It preferentially affects the alveolar interstitium and extends through alveolar septae. Dendriform ossification is often associated with underlying fibrotic lung disease, chronic inflammation, or sequelae of acute respiratory distress syndrome but can also be idiopathic.[42,43] Chest radiograph demonstrates coarse reticular opacities in the lower lung zones. HRCT demonstrates linear 1- to 5-mm calcific densities with high-density nodules associated with reticulations in a subpleural and basilar distribution.[44,45]

■ Pulmonary Alveolar Microlithiasis

Pulmonary alveolar microlithiasis (PAM) is a rare autosomal recessive disorder characterized by intra-alveolar accumulation of calcified concretions, commonly referred to as microliths, in the absence of any known calcium metabolism disorder.[36] It can be considered a specialized form of calcification involving alveolar spaces. This disorder usually is found incidentally with an abnormal chest radiograph in an asymptomatic patient (Fig. 63-3). Presentation may occur at any age, although symptoms usually occur in the third or fourth decade of life. Diagnosis is made on the basis of the chest radiograph or HRCT showing diffuse opacities with calcifications throughout the lungs plus genetic testing.[46] HRCT findings include linear subpleural calcifications that progress to large confluent calcifications with a lower lobe predominance. Although not usually required, bronchoalveolar lavage or biopsy also may confirm the diagnosis. Biopsy shows calcified spherules filling alveolar spaces (Fig. 63-3).

There are radiographic stages of severity ranging from few microliths and minimal calcification to extensive calcification, including of pleura, resembling a "white-out." Although usually asymptomatic at the time of presentation, alveolar microlithiasis typically progresses to end-stage lung disease; the rate of progression is highly variable. When end-stage lung disease occurs, the findings are those of restrictive pulmonary disease or exercise-induced pulmonary hypertension. No therapy has proved effective, but lung transplantation has been performed successfully in a few patients.[47]

The disease is due to a mutation in a type IIb sodium-phosphate cotransporter (SLC34A2) gene. As surfactant phospholipids are metabolized, phosphate is liberated, and the transporter is needed to eliminate the excess phosphate from the alveolar space. In the absence of this transporter, increased phosphate levels lead to microlith formation. While this is most dramatic in the lungs, many other organs, for example, kidney, stomach, prostate, also can be affected. The accumulation of microliths ultimately leads to loss of vital capacity by mass effect as well as by inducing underlying parenchymal fibrosis.

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PART 6

Drug-Induced Lung Diseases

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CHAPTER 64

Pulmonary Toxicity Related to Systemic Treatments for Cancer

Jennifer D. Possick
Erin DeBiasi
Lynn T. Tanoue

INTRODUCTION

Toxicities related to medications constitute a major category of iatrogenic illness. All agents used for cancer treatment have the potential to cause toxicity. As with every medical intervention, the risks of treatment may be acceptable if they are outweighed by the potential benefit of longer survival or cure of disease. It is essential that the patient be engaged in a discussion of this balance before embarking on treatment.

Over the past decade, the landscape of oncologic therapeutics has witnessed enormous advances, with scientific discovery driving substantial and innovative change. The emergence of molecularly targeted treatments and immunotherapy has fundamentally changed both front-line and secondary approaches for a multitude of cancers, enhancing precision and personalization of therapy. The success of new treatments inevitably will be tempered by a new array of associated pulmonary complications, the extent and severity of which may not be completely elucidated in clinical trials. We are very much still in the learning curve of recognizing and addressing related toxicities of novel therapeutics. Moreover, cancer treatments often carry the additional complexity of combination approaches with other drugs or radiation, concomitant hematopoietic support, or bone marrow or stem cell transplantation. Further, as advances in therapeutics result in improved long-term survival, cancer is becoming a chronic disease for a growing number of patients. The potential for delayed complications adds additional challenge to the evaluation of pulmonary complaints in cancer survivors.

As knowledge of biologic mechanisms fundamental to neoplasia burgeons, the horizon for treatment approaches will continue to expand, and inevitably so will the spectrum of associated pulmonary complications. Consequently, the pulmonologist must maintain a sharp awareness of the potential for treatment-related toxicities in both short- and long-term oncologic settings. This chapter reviews the evaluation of patients with suspected therapy-induced pulmonary toxicity and the potential toxicities associated with specific classes of systemic treatment.

APPROACH TO THE PATIENT WITH SUSPECTED PULMONARY TOXICITY RELATED TO SYSTEMIC TREATMENT FOR CANCER

General clinical principles related to, and pulmonary function testing and diagnostic evaluation of, patients with suspected pulmonary toxicity due to systemic therapy for cancer are discussed below.

General Principles

The evaluation of patients with cancer who develop pulmonary complications while receiving treatment is often challenging, as the diagnosis of drug-induced pulmonary toxicity is typically one of exclusion. The possibility of adverse effects of therapy must be considered within the complex medical context inherent to an individual patient undergoing physically challenging and often immunosuppressing treatment. Patients most often present with nonspecific constitutional or respiratory complaints. In many cases, symptoms and physical signs may be minimal or even absent. In these situations, the only evidence of an ongoing pulmonary process may be an abnormal chest radiograph or computed tomography (CT) scan. Even when clinical symptoms and imaging abnormalities are present and severe, they are usually nonspecific. Reasonable certainty that the patient's clinical complaints and radiographic changes represent treatment toxicity is critical, as changing a therapeutic regimen may affect the chance for prolongation of survival or cure. It is important to recognize several complicating features inherent to the oncology patient population.

- First, treatment may be given in multidrug regimens or in combination with other modalities such as radiation therapy, bone marrow transplantation, or stem cell transplantation. Assigning pulmonary toxicity to a single drug or modality within such a regimen is often impossible, as experience and published literature relevant to complications of combination therapies may be scant. Moreover, the combined toxicity of two or more drugs or a single drug with radiation therapy may exceed the individual toxicities of those drugs.
- Second, patients undergoing chemotherapy are often immunosuppressed, either from the malignancy itself or from myelosuppressive or immunologic effects of their treatment. These patients are, therefore, susceptible to both usual and opportunistic infection, which may be indistinguishable radiographically from treatment toxicity. Recognizing that the lung is the most common site of serious infection in immunocompromised patients, it is important to remember that infection is still the most likely culprit when pulmonary symptoms and radiographic abnormalities occur.
- Third, cancers themselves may mimic lung disease. This is particularly true in cases of lymphangitic tumor spread or metastases to the lung parenchyma or pleura.
- Fourth, toxicity from some drugs appears to be related to cumulative dosage levels. However, adverse reactions may occur even with a low total dose, when clinical suspicion for toxicity is low.
- Finally, pulmonary toxicity due to a single therapeutic agent may present with several different syndromes that vary clinically, radiographically, and temporally. While a severe pulmonary reaction acutely following treatment administration usually raises suspicion of drug toxicity, toxicity due to some agents may be delayed by months to even years after treatment.

Pulmonary Physiologic Testing

Pulmonary physiologic testing is commonly utilized in surveillance of patients receiving treatments with potential for pulmonary toxicity. A multitude of investigations studying the utility of pulmonary function testing (PFT) in monitoring pulmonary effects related to administration of cancer therapeutic agents, particularly chemotherapy and immunotherapy, have been reported, but the reliability of application of these findings to clinical management has not been rigorously studied.

Various physiologic abnormalities in the context of cancer treatments have been described, the most common of which are decreases in lung volumes and diffusing capacity for carbon monoxide (DL_{CO}). Patients receiving chemotherapy who are monitored serially by PFT frequently demonstrate physiologic abnormalities in the absence of clinical signs of toxicity, with abnormalities in DL_{CO} in particular thought by some to be indicative of early-onset, drug-related pulmonary injury.[1–3] Discontinuation of drug in this setting, with or without initiation of treatment such as corticosteroids, typically results in improvement. Whether early intervention based on DL_{CO} abnormalities in the absence of clinical symptoms decreases the likelihood of long-term pulmonary impairment is unclear. In situations of clinically evident drug toxicity accompanied by PFT abnormalities, withdrawal of culprit therapy may not be accompanied by improvement in physiologic measurements. For example, in a study examining pulmonary function in 116 long-term (5–13 years after treatment) survivors of Hodgkin disease in Norway, nearly 30% of patients had exertional dyspnea with associated pulmonary function abnormalities.[4] Multivariate analysis of these patients identified chemotherapy with a combination of bleomycin and anthracyclines as the sole significant predictor of lung function impairment.

A number of factors further complicate the practice and interpretation of PFT in the oncology population. Many PFT physiologic parameters are effort dependent. The ability of a patient to consistently perform test maneuvers may be affected by weakness, pain, or the use of analgesic medications. Reproducibility of results, therefore, may be a significant barrier in patients whose functional status and strength are impaired by the effects of their cancer or its treatment. Many patients have anemia induced by malignancy, medication, or chronic illness. Since DL_{CO} is affected by hemoglobin concentration, it is necessary that appropriate corrections for anemia be made. Oncology patients may also be subject to processes other than drug toxicity that will affect PFT results. Primary pulmonary malignancy, metastatic lung disease, infection, thoracic or abdominal surgical procedures, and a host of other clinical situations may all independently cause variation in physiologic measurements. Therefore, identifying pulmonary physiologic abnormalities specific to treatment may prove very difficult. Moreover, in all patients in whom therapy-related toxicity is a concern, consideration must be given to the possibility that discontinuation of a specific treatment might result in substitution of less effective therapy.

Ultimately, even though the predictive value of baseline or serial PFT remains unclear, most clinicians will continue to rely on such testing as a screening and monitoring tool. Although there are no definitive data that toxicity can be averted by such monitoring, we are limited by the absence of other means of identifying toxicity early enough to prevent severe pulmonary disease. Although the presence of subclinical abnormalities does not imply that patients will develop irreversible lung disease, such abnormalities may dictate closer monitoring, or even withdrawal of drug. Conversely, normal physiologic testing cannot predict abrupt toxicity that may produce profound pulmonary injury. As always, medical decisions based on pulmonary physiologic findings must be made in the context of the patient's overall clinical situation.

■ Diagnostic Evaluation

Given the potential impact of treatment-related pulmonary toxicity on a patient's present and future cancer treatment, it is important to establish this diagnosis as firmly as possible. Thoughtful and judicious use of invasive procedures plays an important role in that evaluation.

The approach to the cancer patient in whom pulmonary injury related to treatment is suspected should parallel the approach to any immunocompromised patient with diffuse or localized lung disease. Because clinical features are usually not specific, sampling of respiratory tract secretions and/or lung tissue may be critical to this evaluation. Direct sputum examination or culture may suggest specific pathogens or may be diagnostic of infections such as *Pneumocystis jiroveci* pneumonia, nocardiosis, or tuberculosis. In the absence of diagnostic sputum findings, invasive procedures may be necessary. Transthoracic needle aspiration of the lung may be useful with focal lesions, although the utility of this type of biopsy in diffuse lung disease is relatively low. This is particularly problematic for patients with drug-induced pulmonary toxicity, which often presents with a diffuse interstitial pattern on chest imaging. Fiberoptic bronchoscopy with bronchoalveolar lavage and transbronchial biopsy has become central to the evaluation of both diffuse and localized lung disease in the immunocompromised host. Bronchoscopy is associated with a low rate of major complications. Diagnostic yield varies widely, reflecting the broad range of disease processes that can involve the lung in the immunocompromised patient. Highest diagnostic yields are obtained in patients with infections or when the causative issue is the malignancy itself; lower yields are seen in interstitial inflammatory processes, which may include toxicity from treatment. However, even in situations in which a specific etiology is not identified, exclusion of infection or malignancy by bronchoscopy often provides clinically useful information. If other interventions and procedures are nondiagnostic, surgical biopsy may be indicated. Thoracoscopic or open lung biopsy is associated with the highest diagnostic yield and can be performed with low complication rates even in critically ill patients.

PULMONARY TOXICITIES ASSOCIATED WITH CHEMOTHERAPEUTIC AGENTS

Older studies suggest that 5% to 10% of patients undergoing chemotherapy ultimately develop therapy-related pulmonary complications.[5–7] It would be impossible to list every chemotherapeutic agent and its associated possible pulmonary toxicities. Moreover, any drug can cause an idiosyncratic reaction in an individual patient. Nonetheless, recognition of the typical patterns of pulmonary adverse reactions that can occur with such agents is an important body of knowledge for pulmonologists. This section will review the major classes of chemotherapeutic drugs used for cancer treatment and their most common pulmonary toxicities.

■ Cytotoxic Antibiotics

A variety of cytotoxic antibiotics have been associated with pulmonary toxicity; the most common of these are bleomycin, mitomycin C, and actinomycin D (Table 64-1).

Bleomycin

Bleomycin, a cytotoxic antibiotic produced by *Streptomyces verticillus*, is used in the treatment of various malignancies, including lymphomas, germ cell tumors, and squamous cell cancers of the head and neck. Lung tissue appears to be particularly susceptible to bleomycin-induced injury because of a relative lack of the inactivating enzyme bleomycin hydrolase.[8] The most severe pulmonary complication is interstitial pneumonitis progressing to fibrosis and respiratory failure; less severe syndromes include organizing pneumonia and hypersensitivity pneumonitis.[9]

Bleomycin-induced pulmonary injury is well described in animal models used for the study of pulmonary fibrosis. Endothelial injury via oxidative stress is the sentinel event, followed by the influx of inflammatory cells (predominantly macrophages, neutrophils, and lymphocytes), development of perivascular edema, elaboration of inflammatory cytokines, and, ultimately, fibroblast activation and fibrosis (Fig. 64-1).[10] A variety of mediators have been implicated in bleomycin-induced lung injury, including tumor necrosis factor α (TNF-α), transforming growth factor β (TGF-β), interleukin 6 (IL-6), and IL-1.[9] Human studies have demonstrated activation of in vitro alveolar macrophages in response to bleomycin, and patients treated with bleomycin for testicular cancer demonstrate a rise in serum TNF-α 3 to 24 h after drug administration.[11,12] The continued expression of TNF-α and IL-1 may predispose to the production of TGF-β and promotion of dysregulated collagen production

TABLE 64-1 Cytotoxic Antibiotics

Drug	Pulmonary Syndromes	Treatment	Comments
Bleomycin	• Chronic pneumonitis • Pulmonary fibrosis • Rare fulminant variant with acute respiratory failure	• Discontinue drug • Corticosteroids	• Risk Factors: Cumulative dose >400 U; supplemental oxygen; therapeutic radiation; renal insufficiency; age >70 years; additional cytotoxic drugs
	• Hypersensitivity-type lung disease	• Discontinue drug • Corticosteroids	• Dyspnea, cough, skin rash, and peripheral eosinophilia
	• Chest pain syndrome	• Discontinue drug	• Associated with drug infusion
Mitomycin-C	• Chronic pneumonitis • Pulmonary fibrosis • Rare fulminant variant after single dose	• Discontinue drug • Corticosteroids	• Risk factors: oxygen therapy; therapeutic radiation, additional cytotoxic drugs
	• Acute dyspnea and/or bronchospasm	• Discontinue drug • Bronchodilators • Supportive care • Consider corticosteroids	• Risk factors: vinca alkaloid use • May develop noncardiogenic pulmonary edema and/or chronic interstitial disease • Can recur with rechallenge with vinca alkaloids alone
	• Hemolytic uremic syndrome	• Discontinue drug • Supportive care • Poor response to plasmapheresis or corticosteroids	• Microangiopathic hemolytic anemia, thrombocytopenia, renal insufficiency, noncardiogenic pulmonary edema • Rare alveolar hemorrhage
Actinomycin-D	• "Radiation recall" pneumonitis	• Discontinue drug	• Radiation recall effect may persist

and fibrosis. Animal studies have shown that bleomycin-induced pulmonary toxicity can be ameliorated or prevented by antibodies to TNF-α and TGF-β, or receptor antagonists to IL-1; knockout of the TNF-α receptor also has demonstrated protective effects.[13–15] Bleomycin also induces direct free-radical damage after oxidation of the bleomycin-Fe (II) complex; this effect has been mitigated by iron depletion with chelators both in vitro and in vivo.[9]

The incidence of bleomycin-induced pneumonitis is reported from 6% to 18%, with overall mortality estimated at 3% or less.[9,16] Several risk factors for severe bleomycin-induced pneumonitis have been identified: (1) Toxicity appears to correlate with higher cumulative dose. While fatal injury has been observed after administration of <100 units, there is a significant escalation in toxicity with total doses >400 units, and severe toxicity develops in 20% of patients receiving >500 units.[17] (2) Exposure to high concentrations of supplemental oxygen, particularly in the setting of general anesthesia, may create synergistic toxicity. This is primarily based on animal data, including a study that demonstrated a 75% increase in mortality in hamsters treated with bleomycin and 70% oxygen for 72 h versus bleomycin alone.[18] Similar observations in humans have been largely anecdotal, but in general high fractions of supplemental oxygen are generally avoided whenever

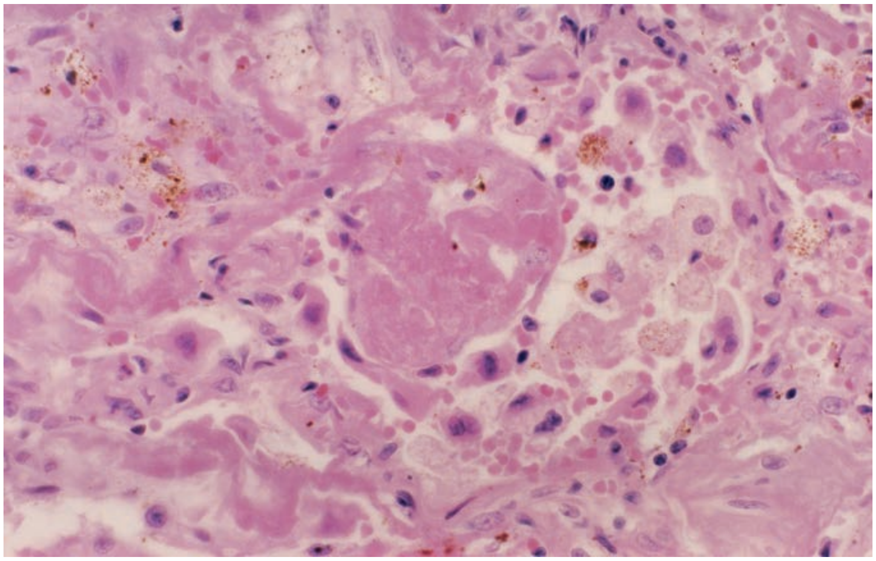

Figure 64-1 Lung biopsy specimen from a patient with clinical and radiographic evidence of bleomycin-induced pulmonary toxicity shows drug effect with acute and chronic changes. The alveolus contains an exudate of fibrin, which is undergoing organization and is surrounded by alveolar macrophages. The large and atypical cells are markedly reactive alveolar type II pneumocytes. The alveolar wall itself is scarred with collagen deposition by the spindle-shaped fibroblasts. *(Reproduced used with permission from Dr. Darryl Carter, Professor of Pathology, Yale School of Medicine.)*

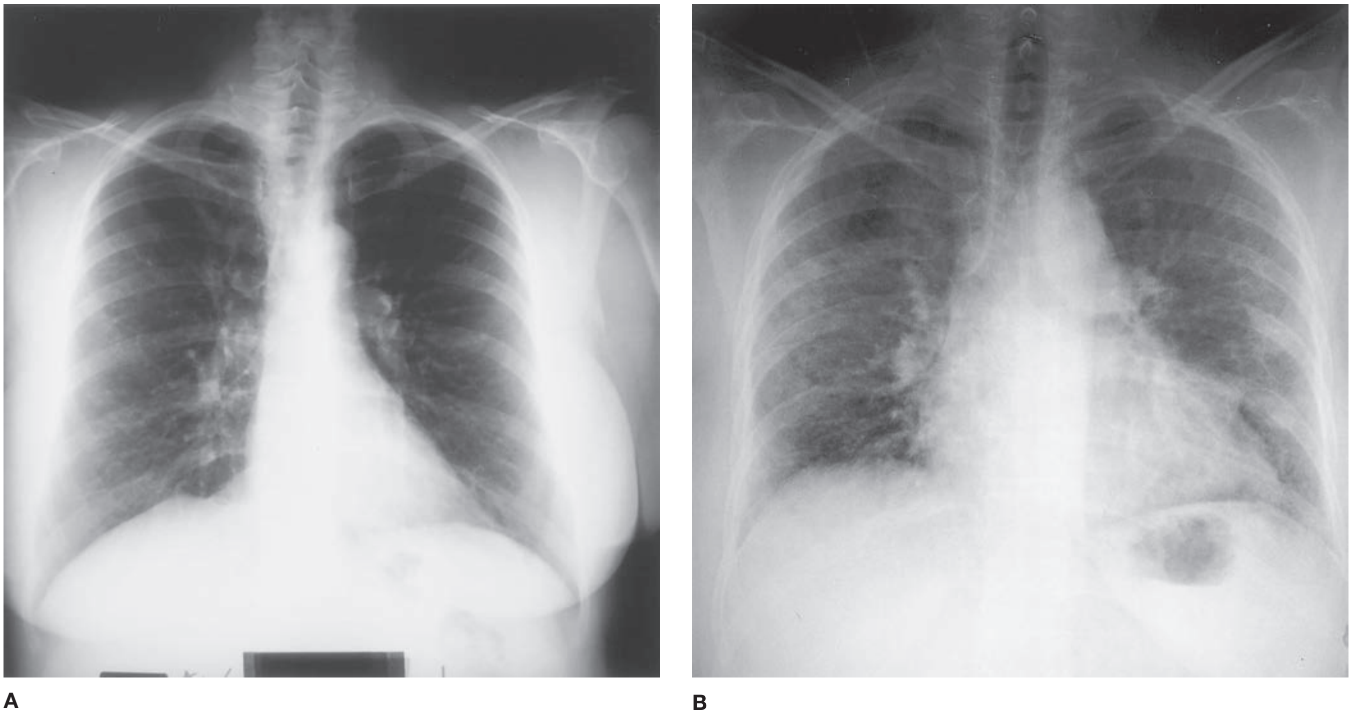

Figure 64-2 Postero-anterior chest radiographs of a 56-year-old woman with cervical carcinoma (**A**) before and (**B**) after chemotherapy with a bleomycin-containing regimen. Note the decrease in lung volume and diffusely increased interstitial lung markings in the post-chemotherapy radiograph.

possible in clinical practice. Cases have been reported of recrudescent pulmonary injury in patients exposed to even modest levels of supplemental oxygen several months after bleomycin exposure, so caution in limiting oxygen exposure for at least 6 months after treatment appears warranted.[19] (3) Thoracic irradiation prior to, concomitant with, or subsequent to bleomycin administration may be associated with an increase in toxicity. This "radiation recall" effect may extend outside the original port of irradiation and may last for years after bleomycin therapy. Delaying radiation for at least 28 days after chemotherapy may mitigate this risk.[20] (4) Bleomycin is excreted by the kidneys, and decreased creatinine clearance below 35 mL/min is associated with increased risk of toxicity.[21] (5) The risk for pulmonary toxicity increases with age; patients over 70 years of age are at particular risk.[22] (6) Concurrent use of bleomycin with other chemotherapeutic agents, including gemcitabine or cisplatin, or in combination with adriamycin/vinblastine/dacarbazine as the ABVD regimen for Hodgkin lymphoma, may result in synergistic toxicity.[20,23] (7) Some studies have suggested that external factors such as smoking or treatment with granulocyte colony–stimulating factor (G-CSF) may increase the risk of bleomycin toxicity, although these reports have not been consistently reproduced.[24,25]

The clinical presentation of bleomycin-induced pneumonitis is usually subacute and insidious, occurring within a few weeks to 6 months after treatment.[9] A more fulminant presentation with acute respiratory failure has been reported but is far less common. Patients may be asymptomatic but generally present with dyspnea, nonproductive cough, low-grade fever, or substernal or pleuritic chest pain. Common physical findings include hypoxemia and fine bibasilar crackles; rhonchi and a pleural rub also may develop.[26] Chest radiograph usually shows low lung volumes with bilateral reticular or fine nodular infiltrates with a basilar predominance, often beginning at the costophrenic angles (Fig. 64-2). However, various radiographic patterns have been described, including alveolar infiltrates, lobar consolidation, organizing pneumonia, asymmetric lung involvement, pneumothorax, pneumomediastinum, and even lung nodules. CT scanning, particularly high-resolution CT (HRCT), is more sensitive in the evaluation of radiographic abnormalities and may be useful in patients who have spirometric or clinical evidence of toxicity but negative chest radiographs (Fig. 64-3).[27] PFT monitoring demonstrates that many patients receiving bleomycin demonstrate a decrease

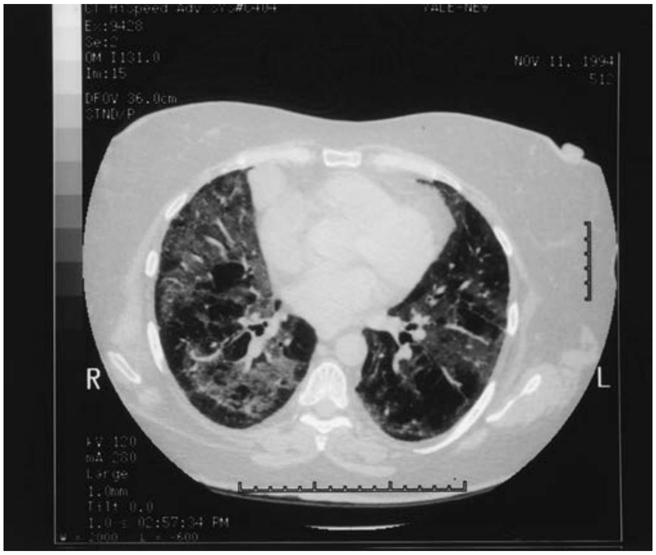

Figure 64-3 Chest computed tomography (CT) scan of same patient as in Fig. 64-2, taken at the time of radiographs in Fig. 64-2. Note the patchy distribution of bilateral infiltrates, the extent of which is clearly delineated by CT.

in $D_{L_{CO}}$ without symptoms over the course of therapy, with only a small percentage manifesting clinical signs of pulmonary toxicity and a decrease in lung volumes.[28]

Bleomycin may also cause an acute hypersensitivity syndrome of dyspnea, cough, and rash immediately following administration of drug. Lung biopsy in these cases shows eosinophilic infiltration and changes consistent with hypersensitivity pneumonitis; peripheral eosinophilia also may be observed. These cases show a particularly favorable response to steroid therapy.[29] An acute chest pain syndrome has also been reported in 1% of patients receiving bleomycin; it occurs during infusion, resolves with termination of drug, and does not appear to predict other pulmonary toxicity from bleomycin.[30]

Discontinuation of drug is recommended for patients with clinically significant bleomycin-induced toxicity and may be sufficient intervention for individuals with mild presentations. For more significant disease, corticosteroids are usually given as prednisone at 1 mg/kg/d for 4 to 8 weeks, with tapering over the next several months guided by clinical stability of the patient and recognizing that the rapidity of the taper will be up to the individual clinician. Response of bleomycin-induced pulmonary toxicity to corticosteroids is highly variable, with more responsive cases likely representing hypersensitivity pneumonitis or organizing pneumonia.[9] When improvement does occur, it is usually seen within weeks of drug cessation, but complete resolution to a stable new baseline may take up to 2 years. Patients may be left with residual radiographic and/or physiologic abnormalities, particularly if fibrosis has developed.

Mitomycin C

Mitomycin C is an alkylating agent derived from *Streptomyces caespitosus*. It is used in multidrug regimens for multiple solid organ malignancies, most commonly for bladder, gastric, pancreatic, cervical, head and neck, and breast cancers. The incidence of pulmonary toxicity due to mitomycin is variably reported between 2% and 38% (with clinically relevant toxicity likely $<10\%$) and appears to be potentiated by concurrent administration of other agents, particularly vinca alkaloids.[31] Although typically associated with intravenous therapy, cases of significant pulmonary toxicity have been reported in patients receiving both intravesicular and intraperitoneal mitomycin C.[32,33] Mitomycin C lung injury presents with multiple distinct pulmonary syndromes, including interstitial pneumonitis and fibrosis, bronchospasm, acute lung injury, thrombotic microangiopathy, veno-occlusive disease with pulmonary hypertension, and pleural disease.

The most common form of mitomycin-induced lung toxicity is a chronic pneumonitis with pulmonary fibrosis similar to that seen with bleomycin; it similarly appears potentiated by exposure to supplemental oxygen or radiation.[34] Some studies have suggested a dose–response effect, with increased risk of toxicity after higher cumulative dose, although this finding has not been consistently reproducible.[34] The exact mechanism of injury is unknown, but several have been proposed, including lipid peroxidant injury, hypersensitivity reactions, or immune complex–mediated disease. Pulmonary toxicity usually occurs after 2 to 12 months of therapy, although a more fulminant form of acute lung injury has been reported after a single dose.[35]

Clinically, patients most often present with a subacute syndrome of cough and progressive dyspnea, often with fatigue and sometimes with pleuritic chest pain.[36] Fever is less common. Chest radiographs usually show bilateral interstitial infiltrates, occasionally with alveolar or fine nodular patterns. PFTs most often demonstrate a restrictive pattern with impairment in $D_{L_{CO}}$.[3] Histologically, biopsy specimens show mononuclear cell infiltration, alveolar-lining cell hypertrophy, collagen deposition, and alveolar septal thickening; type II pneumocyte enlargement and lymphocytic or eosinophilic infiltration also have been described. This syndrome may respond to discontinuation of drug and institution of corticosteroids at an initial dose of 60 mg/d tapered over a 4- to 6-week period.[36]

The second syndrome of mitomycin-induced pulmonary toxicity is seen primarily in patients who have also received vinca alkaloids. While drugs of this latter category (vinblastine, vinorelbine, and vindesine) confer little in the way of risk of pulmonary toxicity when used alone, they may precipitate a syndrome of acute pulmonary toxicity when given concurrently with or subsequent to administration of mitomycin C.[37] Patients present with rapid onset of dyspnea or bronchospasm hours to weeks after exposure; symptoms generally abate in 12 to 24 h with cessation of drug, supportive care, and bronchodilators. In some cases, however, bilateral interstitial infiltrates or noncardiogenic pulmonary edema can develop, and patients may go on to develop chronic interstitial lung disease with permanent physiologic impairment. Rechallenge with vinca alkaloids alone, independent of mitomycin C, can also result in recrudescence of symptoms.[37]

The third syndrome of mitomycin C toxicity is a microangiopathy, with a presentation similar to thrombotic thrombocytopenic purpura and hemolytic uremic syndrome (TTP–HUS). Mitomycin C–associated TTP–HUS is associated with acute lung injury and respiratory failure in 50% of cases.[38] Pulmonary alveolar hemorrhage in this setting also has been described.[39] The mechanism of toxicity appears related to endothelial injury in the pulmonary vasculature. Prognosis is poor as patients with chemotherapy-induced TTP–HUS tend to be refractory to plasmapheresis and corticosteroids that are the typical mainstay of therapy. Cases have been reported of successful treatment with rituximab, but it should be noted that these patients did not have respiratory failure.[40,41]

In addition, mitomycin C has been implicated in two cases of fatal pulmonary hypertension caused by pulmonary veno-occlusive disease in patients with non–small-cell lung cancer (NSCLC).[42] There have also been reports of pleural toxicity, with exudative effusions and pleural fibrosis.[3]

Actinomycin D

Actinomycin D is an older antitumor antibiotic derived from *Streptomyces*, which is still used in treatment of some cancers, including for example Ewing sarcoma, rhabdomyosarcoma, and Wilms tumor. While this drug is not often associated with primary lung toxicity, it may potentiate "radiation recall" pneumonitis in patients who have received prior thoracic irradiation.[43]

■ Alkylating Agents

The chemotherapeutic property of alkylating agents results from their addition of an alkyl group to the guanine base of DNA, which ultimately results in DNA damage. Rapidly dividing cells, including neoplastic cells as well as normal cells of organs such as the skin and gastrointestinal tract, are susceptible to disruption of proliferation with such agents, which may result in both therapeutic effect as well as toxicity.[44] Nitrogen mustards are the prototypic alkylating agents, but many other drugs also exert antineoplastic effects by alkylation. Alkylating agents that have been associated with pulmonary toxicity include nitrogen mustard compounds (cyclophosphamide, melphalan, chlorambucil, ifosfamide, bendamustine), alkyl sulfonates (busulfan), platinum-based therapies (oxaliplatin, cisplatin, carboplatin), and the nitrosoureas (carmustine/BCNU,

TABLE 64-2 Alkylating Agents

Drug	Pulmonary Syndrome	Treatment	Comments
Cyclophosphamide	• Chronic pneumonitis • Pulmonary fibrosis	• Discontinue drug • Corticosteroids	• Risk factors: High cumulative dose, additional cytotoxic drugs, supplemental oxygen; therapeutic radiation • Toxicity may occur years after treatment • Pleural fibrosis may occur in late-stage disease
Busulfan	• Chronic pneumonitis • Pulmonary fibrosis	• Discontinue drug • Consider corticosteroids	• Risk factors: Cumulative dose >500 mg • Often occurs after cessation of drug • Prognosis poor
Oxaliplatin	• Eosinophilic pneumonitis • Organizing pneumonia • Diffuse alveolar damage	• Discontinue drug • Corticosteroids	• Risk factors: Preexisting interstitial lung disease
Chlorambucil Melphalan Ifosfamide	• Chronic pneumonitis • Pulmonary fibrosis	• Discontinue drug • Consider corticosteroids for patients with hypersensitivity features	• Clinical pulmonary toxicity is rare with exception of high dose melphalan (>200 mg/m^2)
Procarbazine	• Hypersensitivity-type pneumonitis	• Discontinue drug • Consider corticosteroids	• Rechallenge associated with recurrence in most patients

lomustine/CCNU). The nitrosoureas are considered in a separate section below.

Nitrogen Mustards: Cyclophosphamide and Other Nitrogen Mustard Compounds

Nitrogen mustards notoriously were initially developed as agents of chemical warfare. Their notable toxic effects on lymphocytes and white blood cells triggered interest in their potential beneficial use in lymphoid neoplasia. The treatment of a patient with lymphosarcoma in 1942 with a nitrogen mustard compound heralded a new era of chemotherapeutic approaches to patients with cancer.[45] Many such compounds continue to be widely used in oncologic practice, including cyclophosphamide, bendamustine, melphalan, chlorambucil, and ifosfamide. Important examples are listed in Table 64-2.

Cyclophosphamide is the most widely used of the nitrogen mustards. It is included as a chemotherapeutic agent in the treatment of many malignancies, including lymphomas, breast and ovarian cancers, and a variety of other solid tumors. It may be given as part of myeloablative conditioning regimens prior to bone marrow or peripheral blood stem cell transplantation. It is also used alone or in combination with corticosteroids in the treatment of nonneoplastic conditions including autoimmune diseases and systemic vasculitides.[7] The overall incidence of cyclophosphamide-induced lung injury is low, generally felt to be $<1\%$, although as with other agents, increased pulmonary toxicity may occur in the setting of radiation therapy, oxygen supplementation, or combination treatment with other cytotoxic agents.[46,47] There is less experience with pulmonary toxicities related to newer nitrogen mustards, but as they are mechanistically related, toxicities are assumed to be similar.[48]

Cyclophosphamide is administered as an inactive prodrug that is metabolized by the liver and to a lesser extent in the lung, to 4-hydroxycyclophosphamide, phosphoramide mustard (responsible for alkylation and DNA cross-linking), and acrolein (responsible for the hemorrhagic cystitis that can complicate therapy).[49] Though the exact mechanism of cyclophosphamide-induced injury to the lung is unknown, in vitro models suggest contributions from oxidative stress and upregulation of TGF-β, increase in collagen synthesis and, ultimately, fibrosis.[50] Cyclophosphamide toxicity lacks a clear dose–response relationship in humans, possibly due to genetic variations in drug metabolism.[51] In addition, the pharmacokinetics of both the inactive parent compound and the active alkylating derivative can be affected by variations in the cytochrome P450 superfamily of enzymes, as well as by interactions with other drugs. Functionally higher exposure to active drug may occur in the setting of substances that induce hepatic enzyme activity, such as rifampin, phenytoin, and alcohol, or with decreased renal clearance.

As with a number of other chemotherapeutic agents, cyclophosphamide-induced pulmonary toxicity may present either early in the course of treatment or in a delayed, progressive fashion that may begin years after treatment is completed. In cases where pulmonary symptoms occur long after exposure, an association with the drug may be difficult to identify. Clinical features are nonspecific, including nonproductive cough, dyspnea, fatigue, and fever. Occasionally, patients are asymptomatic but are discovered to have radiographic abnormalities compatible with drug toxicity. Chest radiographs and CT scans usually show evidence of bilateral interstitial lung disease (either bilateral reticular or nodular markings with ground-glass opacities or, later, fibrosis) and may also show pleural fibrosis in late-stage disease.[52] This latter radiographic finding may be helpful in distinguishing cyclophosphamide-associated interstitial lung disease from the idiopathic interstitial pneumonias.

Histologic findings in the lung are not specific. Lung biopsy in these patients is useful primarily for exclusion of other identifiable causes of interstitial infiltrates in immunocompromised patients, including infection and malignancy. When used to treat nonneoplastic lung disease, the distinction between underlying lung disease from a systemic syndrome and lung disease exacerbated by drug toxicity is often very difficult to delineate. When cyclophosphamide is used as a chemotherapeutic agent, it is rarely used alone, and thus pinpointing specific toxicity to a single agent may be impossible.

Cyclophosphamide-induced lung injury may cause significant morbidity, and a high clinical suspicion for pulmonary toxicity should result in prompt discontinuation of the drug. Early-onset pneumonitis can occasionally be fatal, but when recognized quickly, prognosis is generally favorable and recovery, while slow, is expected for most individuals. Discontinuation of the drug alone may be sufficient, although the clinical threshold to add glucocorticoid therapy is often low. The optimal regimen and magnitude of benefit in these cases remain unclear.[53] Late-onset toxicity is uncommon but can follow an irreversible and progressive, steroid-unresponsive course; mortality due to progressive respiratory failure exceeds 60%.[52]

Chlorambucil and melphalan are both slow-acting nitrogen mustards. Chlorambucil has an important role in the treatment of lymphoreticular malignancies including chronic lymphocytic leukemia (CLL) and has, in the past, also been used in the treatment of nonneoplastic diseases, such as rheumatoid arthritis and sarcoidosis. Pulmonary toxicity is less common than with other alkylating agents, occurring in <1% of patients; pulmonary fibrosis is uncommon, but when it occurs is associated with mortality in excess of 50%.[54] Chlorambucil may be administered over a prolonged time in the treatment of CLL, but there does not appear to be a clear relationship between toxicity and either cumulative dose or duration of therapy. The number of cases of reported chlorambucil pulmonary toxicity is relatively small; thus no distinct clinical pattern has emerged. In cases of chlorambucil-related interstitial pneumonitis, BAL has demonstrated a CD8+ T cell alveolitis suggestive of hypersensitivity reaction.[55] Given the possibility of hypersensitivity pneumonitis, clinical suspicion should prompt immediate discontinuation of the drug, and administration of corticosteroids can be considered in patients with progressive pulmonary disease.

Melphalan has traditionally been used in the treatment of multiple myeloma, but, like other alkylating agents, it is now used to treat a variety of malignancies. High-dose melphalan (200 mg/m^2 or more) is used in conditioning regimens prior to stem cell transplantation and has been associated with fatal pneumonitis and fibrosis.[56] Since large series of such patients are not available, the incidence of pulmonary toxicity associated with high-dose melphalan given in these situations is not known.

Ifosfamide is a nitrogen mustard that is structurally related to cyclophosphamide. It is used in the treatment of lymphoma and acute and chronic leukemias, as well as in solid tumors including sarcomas, ovarian cancer, and breast cancer. Dose limitation is usually related to bladder toxicity. Clinically evident ifosfamide-induced pulmonary toxicity appears to be rare and typically presents as interstitial pneumonitis.[57] It has also been described as a cause of acquired methemoglobinemia presenting as shortness of breath and confusion; this should be considered in the differential for patients on ifosfamide presenting with dyspnea, cyanosis, or altered mental status.[58]

Procarbazine is an alkylating agent used primarily in the treatment of lymphoma; it is associated with hypersensitivity pneumonitis and eosinophilia in a small number of patients.[59] This syndrome typically is seen after the second or third cycle of chemotherapy, although earlier as well as later occurrences have been described. Cough, dyspnea, and fever are typical symptoms, with the development of radiographic interstitial and/or alveolar infiltrates. A variable response to corticosteroids is reported, and rechallenge with procarbazine is associated with recurrence of the syndrome in the majority of patients.

Bendamustine is a newer nitrogen mustard compound used predominantly in combination regimens for lymphoid malignancies. A large study examining bendamustine-based conditioning regimens prior to autologous stem cell transplantation for treatment of lymphoma in 474 patients was triggered by a shortage of carmustine, for which bendamustine was substituted in combination with etoposide, cytarabine, and melphalan (BeEAM).[60] Notably, no severe pulmonary toxicities were noted with this regimen, although other toxicities including a higher incidence of acute kidney injury were observed.

Alkyl Sulfonates: Busulfan

Busulfan is now primarily used as a component of conditioning regimens for bone marrow and stem cell transplantation. Since these ablative regimens may not always be recognized as part of the active treatment protocol, clinicians need to recognize the specific drugs that were used solely for pretransplant conditioning. Toxicity may develop within weeks of exposure but is more typically insidious; one of the characteristic features of busulfan toxicity is this delay, with the average onset of symptoms being more than 3 years after treatment.[7] Estimates of frequency vary widely, with an average of approximately 6%.[61] As with chlorambucil for CLL, patients receiving busulfan for CML were often treated for months to years with the drug. Although it was generally well tolerated in this setting, patients receiving a cumulative dose above 500 mg appeared to be at higher risk for pulmonary complications.[62]

As noted, busulfan is currently used in conditioning regimens prior to bone marrow and stem cell transplantation. Pulmonary complications in this situation are not uncommon, and it may be difficult to clearly attribute toxicity to busulfan rather than other, more likely causes including infection, radiation-induced pneumonitis, and effects of other drugs.[63,64] In long-term comparisons of patients receiving busulfan and cyclophosphamide versus total body irradiation prior to allogeneic transplantation, bronchiolitis obliterans was far more frequent in the former group (26% vs. 5%), while rates of pneumonitis were similar; this raises the concern that the main source of pulmonary toxicity in busulfan-based conditioning regimens may be an increase in chronic pulmonary graft-versus-host disease.[65]

Symptoms of busulfan lung injury usually present insidiously, weeks to years after exposure, with cough, progressive dyspnea, fever, fatigue, and weight loss. Chest radiographs typically show bilateral interstitial infiltrates with a basilar predominance. Pathologic findings are consistent with other cytotoxic drug–induced pulmonary injuries, with type II pneumocyte hyperplasia, dysplasia, and desquamation into alveolar spaces. Fibroblast proliferation, collagen deposition, and fibrosis are usually evident. Desquamation and accumulation of alveolar debris can be severe in some cases, yielding a pattern similar to pulmonary alveolar proteinosis; unfortunately, total lung lavage is usually ineffective in such cases.[7,66]

There is no specific treatment for busulfan-induced pulmonary injury, except withdrawal of drug. However, due to the delayed nature of presentation, patients are often no longer on therapy by the time toxicity is detected; treatment is thus largely supportive. Although some spontaneous improvement may occur, when there is clinically evident busulfan-induced pulmonary toxicity the prognosis for recovery is generally poor. Corticosteroids have anecdotally been reported to be of benefit, but, as with most chemotherapeutic agents, no prospective studies are available. Given the possibility of late-onset pulmonary toxicity, it seems prudent that long-term follow-up of recipients of bone marrow or peripheral blood stem cell transplants with busulfan-based conditioning regimens should include pulmonary evaluation. However, evidence-based direction for identification or treatment of pulmonary toxicity in this situation is lacking.

■ Platinum-Based Chemotherapeutic Agents

In general, pulmonary toxicity related to the older platinum-based chemotherapeutic agents, cisplatin and carboplatin, is uncommon. These drugs have been the backbone of doublet therapy for advanced-stage non–small-cell lung cancer (NSCLC) for several decades. There has been substantial experience using platinum-based regimens in large numbers of NSCLC patients, many of whom have underlying nonneoplastic lung disease, with relatively little pulmonary toxicity attributed to the platinum half of the doublet.

Oxaliplatin is a newer platinum derivative, primarily used as part of multidrug regimens with 5-fluorouracil and leucovorin (FOLFOX) for treatment of colorectal cancer, as well as for treatment of pancreatic, breast, and ovarian cancers. As with the other platinum agents, pulmonary complications are uncommon, although several patterns of lung toxicity have been reported with FOLFOX regimens including eosinophilic pneumonia, organizing pneumonia, and diffuse alveolar damage.[67–70] The timing, severity, progression, and prognosis of individual cases have been heterogeneous, probably owing to the diversity in pathologic mechanisms. Some cases have demonstrated complete resolution with withdrawal of drug, with or without administration of corticosteroids, but others have progressed rapidly to respiratory failure and death.[68,70] In some cases, patients were successfully rechallenged with 5-fluorouracil and leucovorin, implicating oxaliplatin as the likely culprit in the original adverse reaction.[67,69] Mechanisms of toxicity are poorly understood and likely multifactorial; glutathione depletion has been suggested based on the mechanistic role in oxaliplatin-induced hepatic injury, and based on an anecdotal case report of an individual who improved when treated with a combination of corticosteroids and N-acetylcysteine.[71,72] Patients with pre-existing interstitial lung disease, even when subclinical, may be at increased risk for oxaliplatin toxicity, progression of underlying interstitial disease, or both.[72] Individuals with baseline physiologic and radiographic abnormalities, even in absence of symptoms, should be monitored carefully, and the threshold for withdrawal of drug and trial of corticosteroids should be low.

Nitrosoureas: BCNU, CCNU, Semustine, Chlorozotocin

The nitrosoureas (Table 64-3) include carmustine (BCNU, 1,3-bis-(2-chloroethyl)-1-nitrosourea), lomustine (CCNU, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea), semustine (methyl-CCNU), and chlorozotocin. These cytotoxic drugs are active against a variety of neoplasms. BCNU and CCNU are highly lipophilic and can cross the blood–brain barrier, which makes them particularly useful in the treatment of central nervous system malignancies. BCNU is also used in high-dose conditioning regimens prior to bone marrow or stem cell transplantation for a variety of malignancies, including breast cancer, Hodgkin and non-Hodgkin lymphomas, multiple myeloma, and gliomas.

Of the nitrosoureas, BCNU has been most extensively studied. Like bleomycin, this drug has been used in animal models of lung injury. BCNU exposure in rodents has been observed to result in type II pneumocyte cellular toxicity and granulomatous inflammation, eventually leading to interstitial fibrosis that progresses even after withdrawal of drug.[73] Oxidant lung injury may play a role in the pathogenesis of toxicity, as BCNU is known to inhibit glutathione reductase in pulmonary macrophages and reduces lung glutathione stores; however, the exact mechanisms by which pulmonary fibrosis occur are not well defined.[74]

Like bleomycin, BCNU toxicity appears to be dose related. In a study of 94 patients with Hodgkin lymphoma who received chemotherapeutic regimens including BCNU, doses less than 475 mg/m^2 were associated with a 15% incidence of pulmonary toxicity; doses ranging between 475 and 525 mg/m^2 with a 32% incidence; and doses in excess of 525 mg/m^2 with a 47% incidence of pulmonary toxicity.[75] Treatment of intracranial gliomas may result in substantially higher cumulative BCNU doses. Very high doses (>1200–1500 mg/m^2) result in pulmonary toxicity in as many as 20% to 50% of patients.[75–77] Of note, BCNU may be used in single high doses pre–bone marrow or stem cell transplantation or may be given sequentially over longer periods of time. Whether the pattern of administration of a given total dosage has an impact on the potential for lung injury is unknown. Reported risk factors contributing to the development of pulmonary toxicity with BCNU include underlying lung disease, a history of smoking, previous or simultaneous treatment with other chemotherapy agents (including cyclophosphamide or bleomycin), chest radiotherapy, and female sex; of these, higher dose and female sex are most consistently associated with development of pulmonary fibrosis.[76,78–81]

Pulmonary fibrosis related to BCNU falls into two patterns: an early-onset group that typically occurs within days to weeks of treatment or up to 3 years, and a late-onset group that may present years later. Early-onset pulmonary injury appears to be an underappreciated event. In a study of 152 patients treated for breast cancer with a regimen of BCNU (600 mg/m^2), cyclophosphamide, and cisplatin followed by stem cell transplantation, 59% developed a significant decrease in DL$_{CO}$ at a median time after treatment of 45 days.[76] The vast majority of patients had subclinical disease and appeared to have improvement in their pulmonary status with initiation of corticosteroid therapy. Early-onset toxicity can also present as fulminant lung injury with progression in some cases to fatal pulmonary fibrosis.[81,82]

Late-onset pulmonary toxicity, typically presenting as pulmonary fibrosis, may occur years after BCNU treatment. In 1990, O'Driscoll et al. first reported their observations on this phenomenon in survivors of childhood brain tumors.[79] Of 31 original patients, 14 died of their tumors. In a 25-year follow-up report of the 17 survivors, 9 (53%) had died of complications related to pulmonary fibrosis.[83,84] Two patients died within the first 3 years after chemotherapy, 4 died between 6 and 13 years after chemotherapy, and 3 died between 13 and 25 years after chemotherapy. Furthermore, of the remaining 8 patients still surviving, 7 had radiographic and physiologic evidence of pulmonary fibrosis. Thus, in this population of children treated with high-dose BCNU, late toxicity in the lung was extremely common and of severe clinical consequence years after treatment.

The clinical presentation of BCNU-induced lung toxicity is variable. As noted, it may present as fulminant acute respiratory failure but more commonly presents insidiously with asymptomatic physiologic abnormalities or radiographic evidence of pulmonary fibrosis. Symptoms of the latter subacute course include cough, fatigue, and progressive dyspnea. Chest radiograph is rarely normal in symptomatic patients, usually showing bilateral interstitial infiltrates with a basilar predominance. However, in O'Driscoll's series of patients with childhood brain tumors treated with high-dose BCNU who developed late-onset pulmonary fibrosis, patients demonstrated an upper lobe predominance to the distribution of fibrotic changes.[79,83,84] Patients with an acute presentation may present with confluent

TABLE 64-3 Nitrosoureas

Drug	Pulmonary Syndrome	Treatment	Comments
Carmustine (BCNU)	• Early-onset interstitial lung disease	• Discontinue drug • Corticosteroids	• Risk factors: total dose, female sex, underlying lung disease, cigarette smoking, combination treatment with other cytotoxic drugs
	• Late-onset pulmonary fibrosis	• May appear years after treatment	
Lomustine Semustine Chlorozotocin	• Interstitial lung disease	• Discontinue drug	• By extrapolation, toxicities and risk factors probably similar to BCNU

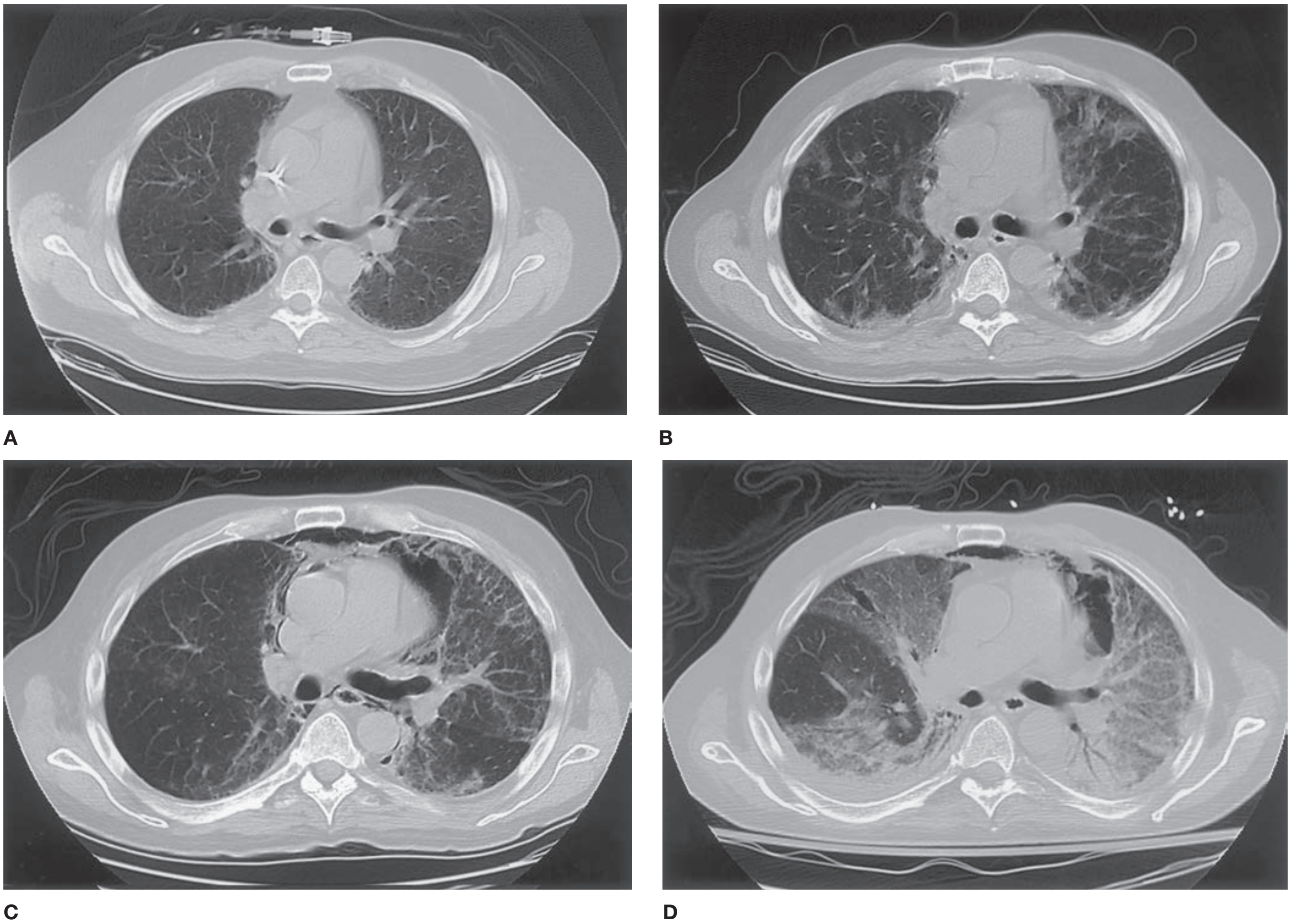

Figure 64-4 Serial chest computed tomography (CT) images of a 54-year-old man with a history of Hodgkin lymphoma, treated with a BCNU-containing regimen. The dates of the examinations span 6 months from **A** to **D**. Note the progression of diffuse interstitial patchy infiltrates, starting with the baseline normal study in **A**. Pneumomediastinum and left pneumothorax are seen in **C** and **D**. Bronchoscopy performed between examinations **B** and **C** demonstrated no evidence of infection. The patient had progressive dyspnea and respiratory insufficiency and eventually died of respiratory failure.

alveolar infiltrates. Pneumothorax has been described in a number of cases and may be bilateral (Fig. 64-4). Pulmonary physiology generally shows a restrictive ventilatory defect, with diffusion abnormalities and eventually hypoxia. As with bleomycin-related lung injury, $\mathrm{DL_{CO}}$ may decrease without radiographic or clinical evidence of disease. While it has been suggested that a decrease in $\mathrm{DL_{CO}}$ may be the earliest sign of pulmonary toxicity, prospective evaluation of screening pulmonary function studies in the diagnosis of BCNU-induced lung toxicity has not been adequately studied. However, in light of the frequency and severity with which BCNU-associated pulmonary injury appears to occur, PFT may be helpful in identifying patients at risk and in whom administration of corticosteroids might be considered. Since BCNU toxicity is common, and the likelihood of progression of BCNU-related lung injury to significant pulmonary fibrosis appears high, it could be argued that surveillance with PFT should be considered, particularly if high doses of drug are to be given.

Pathologic changes in the lung from BCNU parallel those seen with other cytotoxic agents. Type II pneumocyte hyperplasia and dysplasia, fibroblast proliferation, and deposition of proteinaceous material in alveoli have been described. However, inflammation tends not to be a prominent histologic feature, and the cardinal feature of BCNU-induced lung toxicity appears to be interstitial fibrosis. In some cases, angiocentric necrotizing granulomatous inflammation or, more rarely, pulmonary veno-occlusive disease may be seen.

The prognosis for patients with BCNU-induced lung injury is poor. For patients with early-onset lung toxicity, treatment with corticosteroids may be effective. One study of patients with breast cancer for whom BCNU was administered as part of treatment with high-dose chemotherapy followed by stem cell transplantation suggested that inhaled corticosteroids might be helpful in preventing pulmonary toxicity.[85] Late-onset pulmonary fibrosis related to BCNU does not appear to respond to corticosteroid therapy. The primary approach to BCNU toxicity should be prevention, that is, administer the lowest possible effective dose and monitor closely for signs of toxicity. Long-term treatment remains supportive. With the known long potential delay in the onset of signs of toxicity, long-term pulmonary follow-up also is warranted.

The other nitrosoureas used as chemotherapeutic agents, lomustine (CCNU), semustine (methyl CCNU), and chlorozotocin, also have been described to cause pulmonary toxicity. In general, these drugs have been used less widely than BCNU and in smaller cumulative doses. Their described lower incidence of pulmonary toxicity is likely due to these factors. As with BCNU, toxicity tends to present insidiously with interstitial pneumonitis and pulmonary fibrosis. However, given their close chemical relation, the potential for severe lung toxicity as seen with BCNU must be taken into consideration when using other drugs of this class.

TABLE 64-4 Antimetabolites

Drug	Pulmonary Syndrome	Treatment	Comments
Methotrexate	• Chronic pneumonitis • Pulmonary fibrosis	• Corticosteroids • Discontinue drug	• Most common syndrome of methotrexate-induced lung toxicity • Risk factors: older age, pre-existing lung disease, diabetes, previous use of disease-modifying drugs, hypoalbuminemia
	• Hypersensitivity-type lung disease	• Corticosteroids • Discontinue drug	• May resolve even if drug is continued, but can progress to fibrosis
	• Acute chest pain syndrome	• Discontinue drug	• Often accompanied by pleural effusions
	• Noncardiogenic pulmonary edema	• Supportive care • Discontinue drug	• Associated with intrathecal administration
Cytosine arabinoside	• Noncardiogenic pulmonary edema	• Supportive care • Discontinue drug	• Onset of symptoms usually occurs within days of initiation of treatment • Risk factor: higher cumulative dose
	• Cryptogenic organizing pneumonia	• Discontinue drug • Corticosteroids	• Risk factors: combined therapy with anthracyclines or interferon α
Fludarabine	• Hypersensitivity-type lung disease • Interstitial pneumonitis	• Discontinue drug	• Toxicity is uncommon • Treatment associated with increased incidence of delayed opportunistic infections
Gemcitabine	• Dyspnea	• Occurs within hours of dose	• Usually self-limited
	• Interstitial lung disease • Noncardiogenic pulmonary edema	• Discontinue drug • Corticosteroids • Diuretics	• Risk factors: combination treatment with taxanes or bleomycin

■ Antimetabolites

Antimetabolites as chemotherapeutic agents include an array of different compounds, all of which can be associated with lung injury (Table 64-4). Representative examples are discussed below.

Methotrexate

Methotrexate is an analogue of folic acid. It has several antimetabolic pathways, but the predominant mechanism of its ability to decrease cellular proliferation relates to decreased activation of folic acid through competitive inhibition of dihydrofolate reductase. The downstream effect of this is inhibition of thymidine, purine, and pyrimidine synthesis, with consequent inhibition of DNA, thymidylates, and protein synthesis.[86] Methotrexate is used to treat malignancies as well as connective tissue diseases and other inflammatory conditions, particularly rheumatoid arthritis. Its initial use for treatment of acute lymphoblastic leukemia in children also resulted in identification of pulmonary toxicity. In the original report by the Acute Leukemia Group B, "pneumonitis" was observed in 38 of 93 children treated with methotrexate maintenance therapy, including 3 fatal cases.[87] This report should be tempered by the recognition that "pneumonitis" does not appear to have been definitively exclusive of infection, and that these children were also treated with other drugs, including vincristine and prednisone. Subsequent estimates of the incidence of pulmonary toxicity are substantially lower, typically in the 1%–8% range, but have largely been reported in non-oncologic populations, where methotrexate is typically given in low doses for long periods of time (months to years), as opposed to high doses over short time frames that would be more typical when the drug is used chemotherapeutically.[88–90] Further, when methotrexate is used for cancer treatment, it is rarely used alone, making interpretation of its role in any pulmonary syndrome challenging. Additionally, in patients with rheumatoid arthritis or other connective tissue or inflammatory diseases, the potential for a variety of pulmonary manifestations related to the underlying disease can make the diagnosis of methotrexate-induced pneumonitis challenging.

Diagnostic criteria for methotrexate-associated pulmonary toxicity have been proposed by Kremer and colleagues, based on the initial criteria suggested by Searles and McKendry in 1987 (Table 64-5).[90,91] These criteria have never been validated in a

TABLE 64-5 Recommended Diagnostic Criteria for Adverse Pulmonary Events Associated with Methotrexate Treatment for Rheumatoid Arthritis[91]

Major criteria

1. Hypersensitivity pneumonitis by histopathologic examination (without evidence of pathogenic organisms)
2. Radiologic evidence of pulmonary interstitial or alveolar infiltrates
3. Blood and sputum cultures negative for pathogenic organisms

Minor criteria

- Shortness of breath of <8 weeks' duration
- Nonproductive cough
- O_2 saturation ≤90% on room air
- D_{LCO} ≤70% predicted
- WBC ≤15,000/mm^3

Presence of methotrexate toxicity:

- Definite: presence of major criterion 1, or major criteria 2 and 3, and at least 3 minor criteria.
- Probable: presence of major criteria 2 and 3, and 2 minor criteria

prospective cohort, and were intended for situations where methotrexate was used for treatment of rheumatoid arthritis, not cancer. Nonetheless, they provide a framework for a structured approach to methotrexate-related pulmonary toxicity, and may be useful in approaching a patient for whom methotrexate has been used chemotherapeutically for malignancy.

In a multicenter case-control study of methotrexate-induced lung toxicity in patients with rheumatoid arthritis, Alarcon et al. identified risk factors associated with the development of pneumonitis, including age greater than 60 years (associated with a sixfold increase in risk of pneumonitis compared with those <50 years of age), prior history of rheumatoid pleuropulmonary disease, diabetes, previous use of disease-modifying antirheumatic drugs, and hypoalbuminemia.[92] Toxicity does not have consistent dose dependency, but daily versus weekly administration and higher weekly doses of methotrexate have been suggested as associated with increased risk, as well as pre-existing lung disease, prior PFT abnormalities, and the presence of renal insufficiency.[5,93–95] Synergistic toxicity has been reported with combination therapy using cyclophosphamide. Tapering of corticosteroid therapy or adrenalectomy may also increase the risk of methotrexate-induced toxicity.[5,96]

The mechanism(s) of methotrexate-induced lung injury is unknown. Clinically, toxicity presents with several syndromes. The most common of these is development of a symptom complex characterized by fever, dyspnea, cough, malaise, and myalgias, usually within weeks after initiation of therapy. Chest radiography usually shows diffuse interstitial infiltrates but may demonstrate unilateral or bilateral effusions, a nodular appearance, hilar and/or mediastinal adenopathy, or may be normal. Rash is present in up to 17% of patients and peripheral blood eosinophilia in up to 40% of patients.[97] BAL in this setting may show a lymphocytic alveolitis, suggestive of a hypersensitivity reaction.[88] However, illness may resolve even with continuation of the drug, and rechallenge does not necessarily result in relapse, suggesting that hypersensitivity may not be the true mechanism of injury. This presentation of methotrexate-induced pulmonary toxicity mirrors the hypersensitivity-type syndrome that is sometimes observed with bleomycin. As some patients may go on to develop chronic pneumonitis and pulmonary fibrosis, the drug is generally withdrawn when toxicity occurs.

Pulmonary toxicity from methotrexate may also present as a more insidious subacute syndrome of interstitial lung disease. Symptoms including cough, fever, dyspnea, headache, and malaise typically occur within 4 months after the initiation of treatment. Radiographically and clinically this syndrome more closely resembles the type of chronic pneumonitis seen with other cytotoxic drugs and has been reported with all routes of methotrexate administration (oral, intravenous, intrathecal). In contrast to the lung injury associated with many other chemotherapeutic agents, the pneumonitis caused by methotrexate appears, in general, to be responsive to corticosteroids. Pathologic findings in the lung parallel those seen with lung injury due to other cytotoxic drugs, with interstitial and alveolar inflammation and fibrosis.[7,88] In addition, eosinophilic infiltration of the interstitium as well as granulomatous inflammation may be observed. These latter findings are again suggestive of a potential hypersensitivity-type mechanism of inflammation.

In addition to the above, methotrexate-induced lung injury may also appear as an acute syndrome with pleuritis and pleural effusion. Respiratory distress progressing to noncardiogenic pulmonary edema has been described after intrathecal administration of the drug and may be neurogenic in origin.

The prognosis with methotrexate-associated lung toxicity is generally thought to be favorable. As noted, symptoms and radiographic abnormalities may resolve even with continuation of treatment, although rechallenge should be avoided if possible. The use of corticosteroids is generally recommended, but prospective trials of this intervention are not available.

Cytosine Arabinoside

Cytosine arabinoside (Ara-C) is a pyrimidine nucleoside analogue that rapidly inhibits DNA synthesis. It is important in the treatment of acute leukemias and non-Hodgkin lymphoma. Pulmonary toxicity parallels intensity of treatment; high-dose regimens are associated with a 5% to 44% incidence of acute or subacute respiratory insufficiency.[5,98,99] Symptoms include fever, cough, dyspnea, and tachypnea; their onset may coincide with chemotherapeutic treatment or may be delayed for up to several weeks after treatment is initiated. Hypoxemia may be present. Chest radiograph generally shows a diffuse interstitial or alveolar pattern.

The pathogenesis of pulmonary toxicity due to Ara-C is unknown, but it appears to result in noncardiogenic pulmonary edema. In an autopsy series of 181 patients who died of acute leukemia, Haupt et al. described a group of 42 patients who had received Ara-C within 30 days of death and who had moderate to severe pulmonary edema.[100] Lung pathology showed protein-rich infiltrates in both alveoli and interstitium. Of these 42 patients, 28 had no other identifiable cause of their pulmonary edema. In these cases, Ara-C was thought to be the most likely culprit. Treatment for Ara-C lung toxicity is standard supportive care for noncardiogenic pulmonary edema. Administration of corticosteroids has been recommended by some authors but is of unclear benefit.

Ara-C has also been associated with cryptogenic organizing pneumonia when administered with anthracyclines or IFN-α.[101,102] The pulmonary manifestations typically occur within a few weeks to 2 months after drug exposure and are characterized by fever, shortness of breath, and radiographic infiltrates that may be either lobar or nodular. All patients reported to date have achieved resolution of their pulmonary disease, either spontaneously or with the use of corticosteroids. Overall mortality associated with Ara-C–induced pulmonary toxicity ranges from 6% to 13%.[7,98,100–102]

Gemcitabine

Gemcitabine is a pyrimidine analogue used in the treatment of cancers of the lung, pancreas, ovary, and uroepithelium. It is structurally similar to cytosine arabinoside. Gemcitabine is generally well tolerated when used as a single agent, which may make it appealing for use in older patients. Myelosuppression is its major toxicity. The most common respiratory complaint is dyspnea, which occurs in less than 1% of patients.[103] Dyspnea may occur within hours to days of treatment and is generally self-limited. More serious pulmonary side effects, including interstitial lung disease, pulmonary fibrosis, and acute respiratory distress syndrome, are reported much more frequently when gemcitabine is used in combination with other chemotherapeutic agents. Gemcitabine appears to have a reasonable safety profile when given with carboplatin, a treatment regimen often used for NSCLC.[2] However, severe pulmonary toxicity appears to be much more common when gemcitabine is given in combination with taxanes or bleomycin.[104–107] Acute respiratory distress has been reported with these regimens, with development of noncardiogenic pulmonary edema characterized radiographically by mixed interstitial and alveolar infiltrates. Although responses to diuretics and corticosteroids have been noted, severe pulmonary complications in this setting can be fatal. Histologic evaluation most commonly reveals type II pneumocyte hyperplasia, interstitial inflammation, and hyaline membrane formation, consistent with acute lung injury. Some patients with ultimately fatal outcome have demonstrated early symptomatology, including dyspnea, hypoxemia, and radiographic infiltrates to a milder degree with prior doses of gemcitabine. Such findings should raise consideration for discontinuation of gemcitabine.

Fludarabine

Fludarabine monophosphate is a purine nucleotide analogue used in the treatment of CLL, low-grade non-Hodgkin lymphoma, and a variety of other lymphoproliferative disorders. A major clinical issue related to pulmonary complications with fludarabine therapy is the profound immunosuppression that may persist for months after treatment. The persistent nature of this immunosuppression is unusual when compared to other chemotherapeutic agents. The risk of opportunistic infections, including *P. jirovecii* pneumonia is increased by the use of corticosteroids in this setting. Therefore, symptomatic pulmonary disease in patients treated with fludarabine within this time frame is most likely to be related to infection.

Pulmonary toxicity from fludarabine, including interstitial pneumonitis and acute eosinophilic pneumonitis, is uncommon but has been described.[108–110] Helman et al. reported the largest series to date, which included 9 patients with fludarabine-related pulmonary toxicity out of a total of 105 patients (8.6%) treated with fludarabine over an 11-year period at a single institution.[108] Toxicity did not correlate with age, prior treatment regimens, or history of prior lung disease, but it occurred more frequently in patients with CLL compared to those with other lymphoproliferative disorders. The onset of symptoms ranged from 3 to 6 days after therapy, with radiographs notable for new interstitial or mixed interstitial and alveolar infiltrates. BAL fluid revealed increased cellularity without a consistently predominant cell type. Multifocal nodular pulmonary infiltrates also have been described.[110] Biopsy specimens most commonly reveal diffuse, chronic interstitial inflammation, and fibrosis, although in some cases granulomas have been observed, suggesting the possibility of a hypersensitivity reaction. In the report by Helman et al., patients with fludarabine-associated pulmonary toxicity generally demonstrated subjective and objective improvement with corticosteroid therapy.[108] Most patients responded within days, although more delayed responses also were seen. Recrudescence of noninfectious pulmonary infiltrates has been described with fludarabine retreatment; thus, fludarabine should be avoided in future regimens in patients who have developed drug-related pulmonary toxicity.

■ Miscellaneous Chemotherapeutic Agents

A number of other agents used in treating malignant disease have been reported to be associated with pulmonary toxicity (Table 64-6). Representative examples are discussed below.

Taxanes

The taxane family includes paclitaxel, docetaxel, nab-paclitaxel, and cabazitaxel. Their therapeutic effect derives from inhibition of microtubule disassembly, with disruption of the G2 and M phases of the cell cycle. Paclitaxel, docetaxel, and nab-paclitaxel have activity against a variety of carcinomas, including breast and ovarian cancers and NSCLC, while cabazitaxel is used primarily for advanced prostate cancer. Several pulmonary toxicity syndromes have been described with taxanes.

- Interstitial pneumonitis is the most commonly seen toxicity and is associated more with paclitaxel and docetaxel than the other taxanes. Up to 5% of patients in clinical trials developed pneumonitis sufficient to require intervention or cessation of drug.[107,111–118] Factors that may be associated with an increased risk of pneumonitis include weekly versus every-3-week administration, the presence of pre-existing lung disease (particularly interstitial lung disease), combination treatment with gemcitabine, and concurrent chest irradiation. Symptoms (predominantly progressive dyspnea) may occur within a few weeks of drug initiation or may occur months into treatment. Signs and chest imaging are consistent with interstitial lung disease, with diagnosis based on exclusion of infection, pneumonitis from other causes, and other syndromes including alveolar hemorrhage (Fig. 64-5). BAL is often performed to exclude infection and may demonstrate a lymphocytic or eosinophilic predominance. The approach to a patient with presumed taxane-induced pneumonitis should include cessation of drug. Glucocorticoids should be considered for patients with evidence of more severe toxicity, including hypoxemia and progressive interstitial radiographic changes or physiologic impairment. Clinical vigilance for this group is warranted, as progression to respiratory failure and death can occur.
- Docetaxel can result in a syndrome of fluid retention related to capillary leakage.[118–120] This syndrome is characterized by the development of peripheral edema, pleural effusions, or ascites, and lack of fever or other systemic symptoms. Monitoring of weight gain with early initiation of diuretics may be helpful in limiting more severe consequences of volume overload. Recognition that this syndrome can be mitigated by pretreatment with corticosteroids has led to inclusion of pretreatment with dexamethasone in many protocols.
- Paclitaxel infusion is associated with a high incidence (up to 30%) of acute hypersensitivity reactions with symptoms including dyspnea, bronchospasm, urticaria, and hypotension. Docetaxel has a

TABLE 64-6 Miscellaneous Chemotherapeutic Agents

Drug	Pulmonary Syndrome	Treatment	Comments
Paclitaxel	• Dyspnea, bronchospasm	• Decrease infusion rate • Corticosteroids and/or histamine antagonists	• Pretreatment with histamine antagonists and/or corticosteroids reduces incidence
	• Interstitial pneumonitis	• Discontinue drug	• Tends to occur within days to weeks after administration of drug
Docetaxel	• Pleural effusions • Noncardiogenic pulmonary edema	• Discontinue drug; diuretics • Supportive care	• Pretreatment with corticosteroids may decrease incidence
	• Interstitial pneumonitis	• Discontinue drug	
Vinca alkaloids	• Noncardiogenic pulmonary edema • Interstitial pneumonitis • Bronchospasm	• Discontinue drug • Corticosteroids	• Risk factor: concurrent treatment with mitomycin-C
All-*trans* retinoic acid	• “Differentiation syndrome”	• Corticosteroids • Discontinue drug	• Treatment regimens for acute promyelocytic leukemia using all-*trans* retinoic acid should include corticosteroids

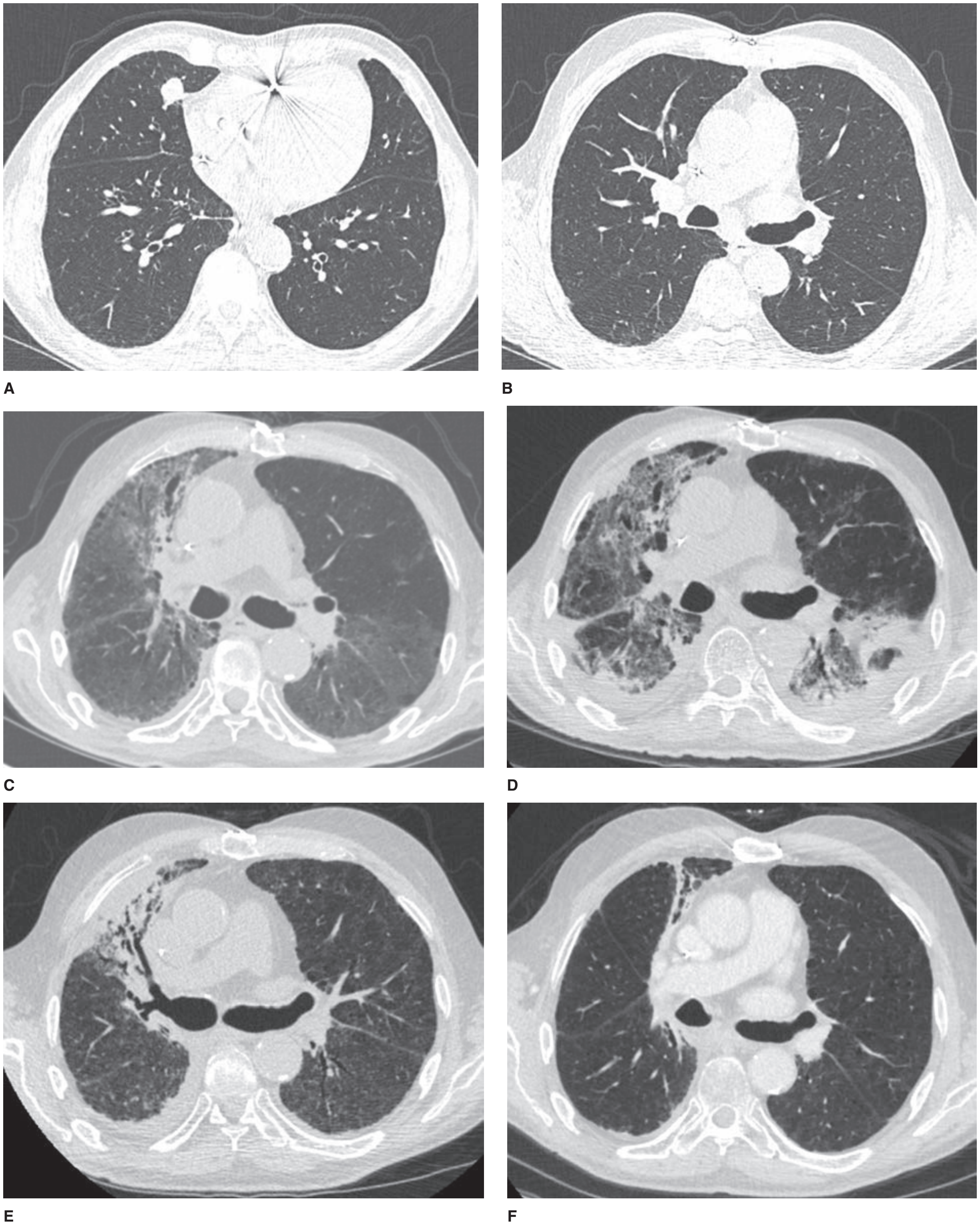

Figure 64-5 Serial chest computed tomography (CT) images of a 74-year-old man with T1N2M0, stage IIIA adenocarcinoma of the lung treated with four cycles of chemotherapy (carboplatin/paclitaxel) and concurrent radiation therapy. **A.** Representative image prior to treatment. The primary tumor was a 2.5-cm, solid, spiculated nodule in the right middle lobe. **B.** Representative image prior to treatment, approximately 1 cm inferior to the main carina. Tumor involved multiple mediastinal lymph node stations, including the subcarinal nodes. **C.** Representative image at the same level as **B**, at completion of concurrent chemoradiation. There are postradiation changes in the right middle lobe, as well as interstitial infiltrates in the right middle, right lower, and left lower lobes. **D.** Representative image at the same level as B, 6 weeks after completion of chemoradiation, demonstrating worsening of infiltrates in the affected lobes. The patient had developed cough and exertional dyspnea and a requirement for supplemental oxygen. Bronchoscopy showed no evidence of tumor or infection. The patient was felt to have paclitaxel-related pulmonary toxicity; corticosteroids were initiated. **E.** Representative image at the same level as **B**, 8 months after completion of chemoradiation and on a slowly tapering course of corticosteroids, demonstrating improvement but with residual right middle lobe infiltrate and bronchiectasis, and areas of pleural thickening. **F.** Representative image at the same level as B, 2 years after completion of chemoradiation, demonstrating residual postradiation changes in the right middle lobe and mild posterior pleural scarring.

much lower incidence of this type of acute complication.[107,117,118,121] Decreasing the infusion rate and/or administration of corticosteroids and histamine antagonists greatly reduces the frequency of this reaction to 1% to 2%.

Vinca Alkaloids

Vinca alkaloids given as sole agents are rarely associated with pulmonary toxicity. However, the combination of vinblastine, vindesine, or vinorelbine with mitomycin C has been reported to be associated with noncardiogenic pulmonary edema, interstitial pneumonitis, and bronchospasm, often in conjunction with more diffuse endothelial dysfunction (see earlier section on mitomycin C).[35] Vinorelbine as a sole agent has been associated with dyspnea in less than 5% of cases; it occurs within hours of dosing and generally responds to bronchodilators and corticosteroids.[122] Respiratory distress with pulmonary edema and interstitial pneumonitis also has been rarely described.

All-*trans* Retinoic Acid

All-*trans* retinoic acid (ATRA) is a vitamin A derivative used to treat acute promyelocytic leukemia (APL). Activity of ATRA occurs through its induction of maturation of malignant cells into mature neutrophils. A constellation of symptoms and signs known as “differentiation (retinoic acid) syndrome,” characterized by fever, weight gain from volume overload, respiratory distress with interstitial or alveolar infiltrates, pleural or pericardial effusions, hemodynamic instability, and renal insufficiency may occur from 2 to 21 days after drug initiation.[123,124] Pulmonary alveolar hemorrhage has been described as a rare complication.[125] The syndrome is frequently, although not universally, seen coincident with the development of a pronounced leukocytosis.[126] Radiographic features of differentiation syndrome include pleural effusions, cardiomegaly, interstitial edema, and widened vascular pedicle. Less frequently seen are prominent septal lines, nodules, ground-glass opacities, or parenchymal consolidation with air bronchograms. In the setting of diffuse alveolar hemorrhage, high-resolution chest CT demonstrates poorly defined centrilobular nodules and diffuse ground-glass opacification. Histologic examination most commonly reveals infiltration of the lung parenchyma with maturing myeloid cells, with or without pulmonary hemorrhage. Fibrinoid necrosis and pulmonary capillaritis also have been described. The syndrome is thought to result from endothelial damage resulting in edema, hemorrhage, fibrinous exudates, and infiltration of neutrophils.

The mechanism of ATRA-mediated pulmonary toxicity is poorly understood but is thought to reflect systemic release of inflammatory cytokines.[127] Increased expression of cell adhesion molecules on leukemic cells has been demonstrated after ATRA administration, as has increased endothelial expression of intracellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1). In addition, elevated levels of interleukin 1β (IL-1β), IL-6, and TNF-α have been observed and may promote leukocyte activation, contributing to tissue injury.

The incidence of differentiation syndrome is reported variably between 5% and 27%, with mortality among affected patients between 5% and 29%.[123,126,128,129,132,134] Prompt initiation of corticosteroids may be associated with improved outcome. Continuation of ATRA does not appear to be absolutely contraindicated, as long as corticosteroids are administered in a timely fashion. In cases with severe toxicity, discontinuation of ATRA is reasonable but does not necessarily preclude rechallenge with drug, given its known effectiveness in APL.

MOLECULARLY TARGETED AGENTS

There has been tremendous development of molecularly targeted chemotherapeutic agents over the past decade. Several classes of molecularly targeted chemotherapeutic agents exist including small molecule kinase inhibitors, monoclonal antibodies, and checkpoint inhibitors. Examples of molecularly targeted agents include epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors, BCR-Abl tyrosine kinase inhibitors, anaplastic lymphoma kinase (ALK) inhibitors, vascular endothelial growth factor (VEGF) inhibitors, MEK inhibitors, MET inhibitors, RET inhibitors, cyclin-dependent kinase inhibitors, and PI3K inhibitors (Tables 64-7 and 64-8).

■ EGFR Tyrosine Kinase Inhibitors

Small molecule inhibitors of the EGFR tyrosine kinase (EGFR TKI) were the first successful molecularly targeted agents effective for patients with NSCLC and virtually revolutionized the

TABLE 64-7 **Molecularly Targeted Agents: Tyrosine Kinase Inhibitors**

Drug	Pulmonary Syndrome	Treatment	Comments
EGFR TKI			
Gefitinib	• Interstitial lung disease • Pulmonary fibrosis	• Discontinue drug	• Develops within 3 months • Risk factors: elderly, cigarette smoking, pre-existing lung disease, Asian ethnicity
Erlotinib	• Interstitial lung disease	• Discontinue drug	• Risk factors: pre-existing lung disease
Afatinib	• Interstitial lung disease	• Discontinue drug	• Also inhibits HER2 • Risk factors: elderly
Osimertinib	• Interstitial lung disease	• Discontinue drug	• T90M mutation specific • Risk augmented with anti–PDL-1 therapy
BCR-Abl TKI			
Imatinib	• Pleural effusions	• Diuretics	
	• Interstitial lung disease	• Discontinue drug • Corticosteroids	• Risk factors: pre-existing interstitial lung disease
Dasatinib	• Pleural effusions	• Diuretics • Drug interruption	• Incidence much higher than imatinib
	• Pulmonary arterial hypertension	• Discontinue drug • Consider PAH therapy	

(continued)

TABLE 64-7 Molecularly Targeted Agents: Tyrosine Kinase Inhibitors *(Continued)*

Drug	Pulmonary Syndrome	Treatment	Comments
ALK TKI			
Crizotinib Ceritinib Alectinib	• Interstitial lung disease	• Discontinue drug	• Develops within 3 months
Brigatinib	• Interstitial lung disease	• Drug interruption • Consider rechallenge	• Develops acutely within 1 week
MET inhibitor			
Capmatinib	• Interstitial lung disease	• Discontinue drug	• Develops within 1–2 months
RET inhibitor			
Pralsetinib	• Interstitial lung disease	• Discontinue drug	
Selpercatinib	• Interstitial lung disease	• Disrupt drug • Discontinue drug if severe	• Less frequent than pralsetinib
VEGF TKI			
Sunitinib	• Dyspnea • Cough	• Supportive care	
Sorafenib	• Dyspnea • Cough • Interstitial lung disease	• Drug discontinuation	• ILD very rare but extremely fatal • Drug should be stopped with any pulmonary side effects
Pazopanib	• Pneumothorax	• Supportive care	• Risk factors: subpleural disease

approach to treatment of this group of patients (Fig. 64-6). There are now six EGFR tyrosine kinase inhibitors, including gefitinib, erlotinib, afatinib, osimertinib, lapatinib, and dacomitinib. Lung toxicity associated with lapatinib and dacomitinib is very rare. A study of the remaining EGFR TKIs indicated a 1.12% incidence of all grades of pneumonitis in more than 15,000 patients treated.[129] However, the most common cause of drug associated fatality is pneumonitis.[130]

Gefitinib was the first EGFR tyrosine kinase inhibitor available for clinical use. In a prospective study involving more than 3000 patients treated with gefitinib for NSCLC in Japan, 4% of patients developed interstitial lung disease by 12 weeks of treatment with

TABLE 64-8 Molecularly Targeted Agents: Other Kinase Inhibitors

Drug	Pulmonary Syndrome	Treatment	Comments
MEK inhibitor			
Trametinib	• Interstitial lung disease	• Discontinue drug	
Encorafenib + binimetinib	• Interstitial lung disease	• Drug disruption • Consider dose reduction or discontinuation	• Rechallenge based on severity of pneumonitis
	• Venous thromboembolism	• Drug disruption • Consider dose reduction or discontinuation	• Rechallenge based on severity
Cyclin dependent kinase inhibitors			
Palbociclib Ribociclib Abemaciclib	• Interstitial lung disease	• Drug disruption • Discontinue drug if severe	• Very low incidence in clinical trials, but with reports of severe pneumonitis emerging
PI3K inhibitors			
Idelalisib	• Interstitial lung disease	• Drug disruption • Corticosteroids	• Rechallenge based on severity of pneumonitis
	• Pulmonary infection	• Targeted to infection	
Copanlisib Duvelisib	• Interstitial lung disease	• Drug disruption • Corticosteroids	• Rechallenge based on severity of pneumonitis
	• Pulmonary infection	• Targeted to infection	• *Pneumocystis jirovecii* infection common, prophylaxis recommended
Alpelisib	• Interstitial lung disease	• Discontinue drug	

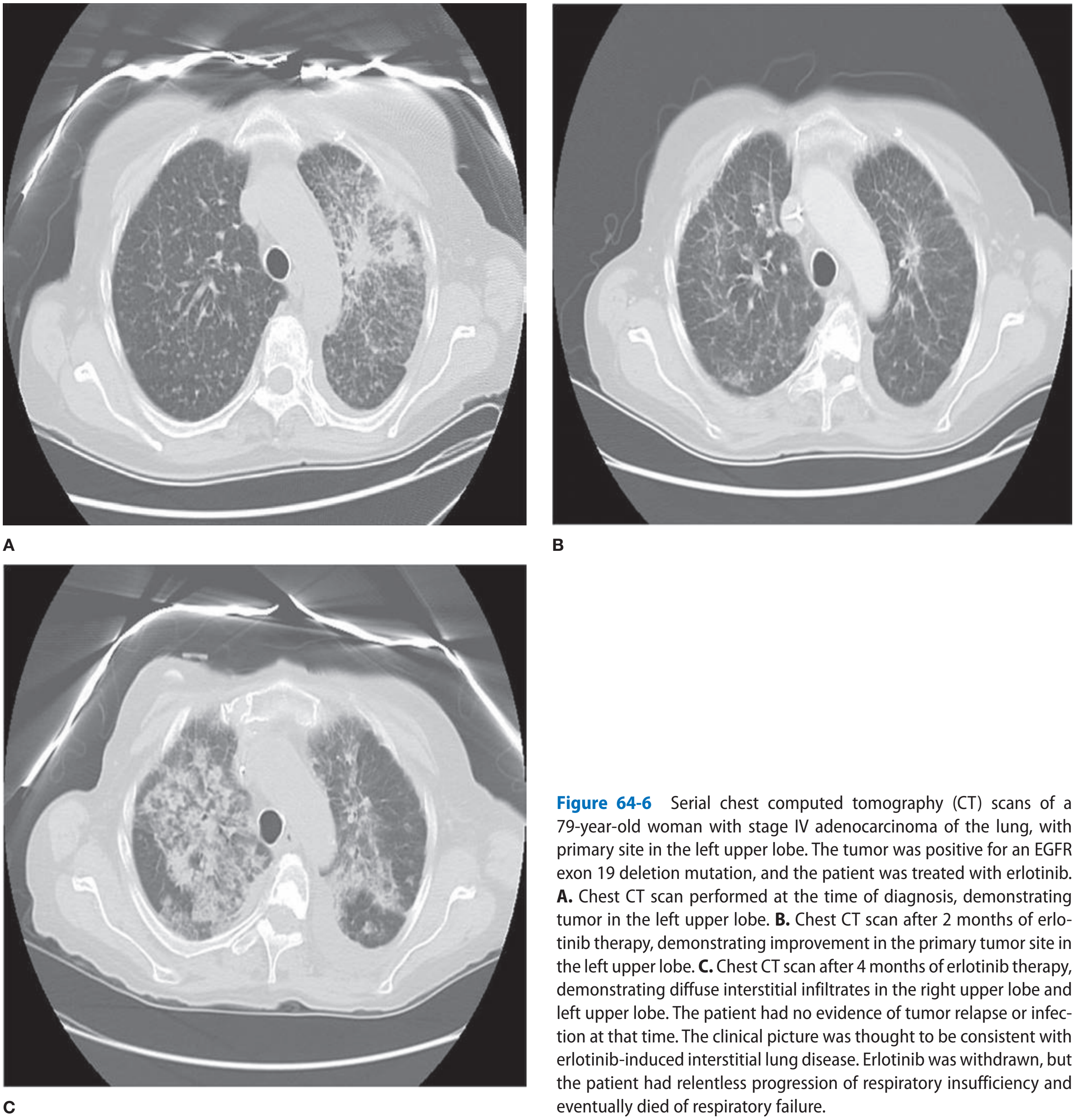

Figure 64-6 Serial chest computed tomography (CT) scans of a 79-year-old woman with stage IV adenocarcinoma of the lung, with primary site in the left upper lobe. The tumor was positive for an EGFR exon 19 deletion mutation, and the patient was treated with erlotinib. **A.** Chest CT scan performed at the time of diagnosis, demonstrating tumor in the left upper lobe. **B.** Chest CT scan after 2 months of erlotinib therapy, demonstrating improvement in the primary tumor site in the left upper lobe. **C.** Chest CT scan after 4 months of erlotinib therapy, demonstrating diffuse interstitial infiltrates in the right upper lobe and left upper lobe. The patient had no evidence of tumor relapse or infection at that time. The clinical picture was thought to be consistent with erlotinib-induced interstitial lung disease. Erlotinib was withdrawn, but the patient had relentless progression of respiratory insufficiency and eventually died of respiratory failure.

gefitinib, compared with 2.1% of patients treated with cytotoxic chemotherapy.[131] Studies done around the world have noted that pulmonary toxicity appears to vary geographically and is seen more commonly in Asian, as opposed to Caucasian or African, populations.[132–134] Toxicity typically occurs early in the course of treatment, with median exposure from 24 to 42 days. Withdrawal of drug appears in most cases to be helpful, but inexorable progression to end-stage respiratory failure and death occurs in approximately 31% of patients with gefitinib-induced pulmonary toxicity. Histologic evaluation of fatal pneumonitis demonstrated diffuse alveolar damage. Risk factors associated with a higher likelihood of developing toxicity include male sex, older age, cigarette smoking, pre-existing interstitial lung disease, and poor performance status.[131,134,135]

The mechanism of gefitinib-induced lung injury remains a subject of investigation. EGFR is known to be upregulated in response to lung injury and may be important in promoting type II pneumocyte hyperplasia in response to injury. In murine models gefitinib leads to more severe lung fibrosis in animals exposed to bleomycin. The increased frequency of this toxicity in patients with pre-existing pulmonary fibrosis lends credence to the hypothesis that gefitinib impairs the regeneration of alveolar epithelial cells in response to injury.

Erlotinib is the EGFR tyrosine kinase inhibitor used most commonly in the United States, as gefitinib is not available for clinical treatment purposes.[77,136,137] The overall incidence of pneumonitis associated with erlotinib is likely lower compared to gefitinib, which may reflect geography, as erlotinib has predominantly been used outside of Asia. In an elderly Japanese cohort of more than 9000 patients treated with erlotinib, the incidence of all grades of pneumonitis was 4.2% with a mortality rate of 1.7%, which is similar to a predominantly Japanese cohort treated with gefitinib (3.5% incidence and

1.6% mortality).[135,138] In a U.S. study predominantly of Caucasians on erlotinib plus standard chemotherapy versus chemotherapy alone, the incidence of interstitial lung disease in the erlotinib group was 1% versus 0.2% in the placebo group.[139] Three cases in the erlotinib arm were fatal and were directly attributed to the drug.[140] The time course of lung injury appears to be similar to gefitinib, with appearance of pulmonary injury occurring within weeks of initiation of treatment. The presence of underlying interstitial lung disease appears to be a risk factor for development of drug toxicity.[141]

Afatinib is a small molecule that inhibits both EGFR and human epidermal growth factor 2 (HER2) receptors. Similar to erlotinib, initial studies of safety indicated low incidence of grade 3 or higher pneumonitis ranging from 0.4% to 1%.[142,143] However, this risk may be significantly increased in the elderly population, as a study of 40 patients with a mean age of 77 demonstrated a risk of grade 3 or higher pneumonitis 7.5% with 2 deaths due to pneumonitis-associated respiratory failure.[144]

Osimertinib is a newer-generation EGFR TKI used in the treatment of patients with EGFR T790M mutation NSCLC who have progressed after treatment with conventional EGFR TKI therapy. It confers a 3% risk of pulmonary toxicity, although mortality rates are lower compared to gefitinib.[145,146] As with similar agents, toxicity generally presents within the first 3 months of therapy, manifests as nonspecific pulmonary symptoms, and typically resolves with discontinuation of drug.

Recently there has been interest in combining EGFR targeted therapy with immune checkpoint therapy, specifically anti–PDL-1 treatments (discussed below). However, this approach has been shown to have a significantly higher incidence of significant pneumonitis (25.7% vs. 4.59%).[147] This risk is predominantly when anti–PDL-1 therapy is swiftly followed by EGFR TKI therapy and possibly only limited to osimertinib rather than early-generation EGFR TKIs.[148–150]

■ BCR-Abl Tyrosine Kinase Inhibitors

Imatinib was the first clinically available and prototypic molecularly targeted therapy. Developed in the 1990s, it is a small molecule tyrosine kinase inhibitor that suppresses proliferation of cells expressing the BCR-Abl fusion protein. The fusion gene created by translocation of the Abl-1 ("Abelson") gene on chromosome 9 to a part of the "breakpoint cluster region" (BCR) gene on chromosome 22 is the "Philadelphia chromosome," a hallmark for CML. Imatinib is used for treatment of patients with CML as well as gastrointestinal stromal tumors.

The most common pulmonary complication related to administration of imatinib is the development of pleural effusions. This reflects the propensity of patients receiving imatinib to retain fluid in various anatomic compartments. The incidence of pleural effusions is rather low, affecting only 0.8% over the course of 5 years of treatment.[151] Less commonly, imatinib has been associated with the development of interstitial lung disease; underlying fibrotic lung disease may be a predisposing factor.[152] In small series, corticosteroids have been reported as potentially beneficial; rechallenge is generally not recommended but has been reported without recurrent lung disease.

Almost inevitably, tumor resistance to the small molecule tyrosine kinase inhibitors occurs, due to development of new point mutations in the tumor kinase, resulting in resistant clones of cells and relapse of disease. Second-generation BCR-Abl tyrosine kinase inhibitors include dasatinib, nilotinib, bosutinib, and ponatinib. Unlike imatinib, dasatinib-associated pleural effusions are very frequently reported. Over 5 years of treatment, the frequency of pleural effusions is up to 28%, with the highest incidence in the first year of use.[151] A dose-dependent frequency has been described.[153] Drug interruption and therapeutic thoracentesis are sometimes necessary for dyspnea. Like imatinib, dasatinib has been reported in case series to be associated with development of interstitial lung disease.[154,155]

Perhaps more concerning, there is increasing evidence of an association between the development of pulmonary arterial hypertension and dasatinib use.[156–158] Up to 5% of patients on dasatinib have elevated pulmonary pressures on transthoracic echocardiogram. In the largest cohort of 21 patients with PAH confirmed by right heart catheterization, 71% were female with a median age of 52.[159] All patients had the drug withheld, and half were treated with PAH-directed therapies. While the majority of patients had improvement in their symptoms and exercise capacity with these measures, 37% had persistent PAH despite drug discontinuation and/or PAH therapy indicating irreversible pulmonary arterial remodeling. Pulmonary hypertension has not been reported as a complication of imatinib.

Nilotinib, bosutinib, and ponatinib are newer and less widely used BCR-ABL inhibitors. The incidence of pleural effusion appears to be less frequent, and there are only case reports of other pulmonary toxicity including pneumonitis and PAH.

■ ALK Inhibitors

Crizotinib, ceritinib, alectinib, and brigatinib inhibit the ALK and have been useful in patients with NSCLC demonstrating the EML4-ALK fusion oncogene. Interstitial lung disease has been reported with crizotinib, ceritinib, and alectinib treatment.[160] Toxicity with these agents generally develops within 3 months of therapy; most cases resolve with discontinuation of drug and supportive care, although rare fatalities have been reported. In contrast, pneumonitis related to brigatinib presents acutely, typically within the first week of treatment. Some patients may be able to undergo successful rechallenge with brigatinib once pneumonitis completely resolves.[161] As these drugs are used only in a relatively small population of lung cancer patients with the specific targetable mutation, clinical information relating to potential lung injury is limited.

■ Other Small Molecule Inhibitors

Two classes of drugs are used to treat metastatic melanoma with BRAF mutations. These include inhibitors of the mitogen activated protein kinase (MEK) and direct BRAF inhibitors. The MEK inhibitor trametinib is associated with a 2% risk of interstitial lung disease.[162] Vemurafenib is a BRAF inhibitor with only case reports of pulmonary injury. Encorafenib plus binimetinib is a BRAF plus MEK inhibitor. While it has a very low incidence of pneumonitis, venous thromboembolism and pulmonary embolism can be seen in 6% and 3%, respectively.[163]

A minority of patients with NSCLC have mutations in the mesenchymal-epithelial transition (MET) gene, rearranged during transfection (RET) gene, or c-Ros oncogene 1 (ROS1). Capmatinib, a MET inhibitor, causes pneumonitis in up to 4.5% of patients (1.8% grade 3 or above).[164] Additionally, 4% of patients had grade 3 pleural effusions. In initial trials, pralsetinib, a RET inhibitor, had a high incidence of interstitial lung disease (10% total, 2.7% grade 3–4, 0.5% fatal).[165] Selpercatinib, a second RET inhibitor, has a much lower incidence of interstitial lung disease (<2%), with no reports of grade 3 or higher pneumonitis.[166] Entrectinib, a ROS1 inhibitor used in NSCLC and other solid tumors, causes pleural effusions in 10% of patients and respiratory failure in 2%.[167]

Inhibitors of the cyclin-dependent kinases (CD4/6) include palbociclib, ribociclib, and abemaciclib and are used to treat hormone receptor–negative, HER-2 negative breast cancer. A very low incidence of pulmonary toxicity was noted in initial trials involving these drugs, but with increasing use, case reports of severe pneumonitis have emerged. A postmarketing FDA warning has since been issued.[168]

There are four available phosphoinositide 3-kinase (PI3K) inhibitors available for use with varying risk profiles. Idelalisib, which is approved for chronic lymphocytic leukemia, follicular lymphoma, and small lymphocytic leukemia, is associated with an 11% risk of both infectious and noninfectious pneumonia, with 7% being grade

TABLE 64-9 Monoclonal Antibodies

Drug	Pulmonary Syndrome	Treatment	Comments
Bevacizumab	• Pulmonary hemorrhage	• Supportive care • Discontinue drug	• Risk factors: cavitary tumor, squamous cell histology
	• Tracheoesophageal fistula	• Supportive care	• Risk factors: mediastinal radiation
Cetuximab Panitumumab	• Bronchospasm, stridor	• Supportive care • Corticosteroids • Discontinue drug	• May occur during infusion • Risk factors: asthma, atopy, history of allergic reactions

3 or higher.[169] In a pooled study of 168 patients receiving copanlisib, the incidence of grade 3 to 4 lower respiratory tract infections was 13% (including *Pneumocystis jirovecii*) and pneumonitis 5%.[170] A similar rate of both infectious and noninfectious pneumonitis has been observed with duvelisib use. Alpelisib, used to treat hormone receptor–positive, HER2-negative breast cancer with a PI3K mutation has a <2% incidence of pneumonitis.[171]

■ VEGF Inhibitors

There are three main classes of inhibitors of VEGF, which include monoclonal antibodies, small molecule TKIs, and a fusion molecule inhibitor. The latter has no known pulmonary adverse events.

Bevacizumab is a monoclonal antibody directed against VEGF with activity against breast, colon, renal, and NSCL cancers (Table 64-9). Improved response rates for locally advanced and metastatic NSCLC are observed when bevacizumab is added to traditional chemotherapy.[172] In a series including 99 patients with newly diagnosed stage IIIB or IV or recurrent NSCLC, six patients developed serious bleeding complications including hemoptysis or hematemesis.[173] Four of the six patients died as a result of the hemorrhage. All six cases of hemorrhage appeared to be tumor related, with four of the six patients having squamous cell histology. Radiographically visible cavitation or necrosis was seen in five of the six cases of hemorrhage. As a result, current clinical investigations of regimens including bevacizumab generally exclude patients with cavitary pulmonary disease or squamous cell histology. Additionally, when combined with mediastinal radiation, there is a significant incidence of tracheoesophageal fistula formation.[174]

Sunitinib, sorafenib, and pazopanib are the three approved VEGF TKIs. Sunitinib has been reported to cause grade 3 to 4 cough and dyspnea in 13% and 19% of patients, respectively.[175] Sorafenib has a very low incidence of pneumonitis (0.44%); however, when present, the case fatality rate is high (41%).[176] Pazopanib is used primarily in the treatment of soft tissue sarcomas and renal cell carcinomas. In the phase 3 trial of pazopanib in soft tissue sarcomas, the incidence of pneumothorax was 3%, which was similar to the previously reported rate of spontaneous pneumothorax in this patient population.[177,178] Reports of incidence of up to 14% was reported at a single center, exclusively in patients with subpleural or pleural metastases.[179]

■ Other Monoclonal Antibodies

Monoclonal antibodies have been increasingly employed to treat a variety of malignancies (Table 64-9). Pulmonary toxicity has been reported with their use.

EGFR Antibodies

Cetuximab and panitumumab are chimeric monoclonal antibodies directed against EGFR. Infusion of cetuximab may be associated with symptoms suggestive of anaphylaxis, including bronchospasm or stridor. In severe cases, respiratory compromise may be life-threatening. Risk factors for the development of these complications include a history of asthma, atopy, or allergic reactions.[180,181] Similar reactions have been observed less frequently during infusion of panitumumab.[182] The incidence of pneumonitis is low in patients treated with either cetuximab or panitumumab.[183,184]

Rituhximab

Rituximab is a chimeric monoclonal antibody directed against the CD-20 antigen on B lymphocytes; it has demonstrated activity against non-Hodgkin lymphoma. It is increasingly used in inflammatory processes, including connective tissue diseases, autoimmune disorders, and solid organ transplantation. Like cetuximab, rituximab can be associated with infusion reactions, which, in severe form, may include bronchospasm and angioedema. Pulmonary parenchymal toxicity, while rare, is well described.[185–187] In one series of 107 patients with NHL receiving a regimen including rituximab, 9 of 107 patients developed interstitial pneumonitis associated with fever, dyspnea, and cough.[187] Treatment with glucocorticoids resulted in improvement. Re-treatment was attempted in four patients, two of whom developed recurrence of interstitial disease; therefore, rechallenge is usually not recommended.

The clinical syndrome of rituximab-induced pulmonary toxicity typically begins insidiously with cough and dyspnea, which may progress with subsequent re-exposure to rituximab. Development of hypoxemia in association with parenchymal ground-glass opacification on CT scan has been noted. Histologic examinations have revealed reactions typical of cryptogenic organizing pneumonia/bronchiolitis obliterans organizing pneumonia, as well as interstitial inflammation with T lymphocytes and extensive arterial thrombosis. While fatal outcomes have been reported, generally this entity has responded well to withdrawal of rituximab and administration of corticosteroids.

Trastuzumab

Trastuzumab is a humanized monoclonal antibody directed against the HER2 protein expressed by some breast and gastroesophageal tumors. Infusion reactions with trastuzumab are common; in severe cases, symptoms may include bronchospasm and hemodynamic instability. Rarely, patients with breast cancer receiving trastuzumab may develop acute pulmonary toxicity, with interstitial pneumonitis, organizing pneumonia, or acute respiratory distress syndrome; in some cases, glucocorticoids have been used successfully.[188,189]

Trastuzumab can be given combined with other cytotoxic drugs as conjugates in patients with breast cancer previously treated with trastuzumab and taxanes. Ado-trastuzumab emtansine (combined with cytotoxic microtubule inhibitor DM1) rarely causes acute pneumonitis (1.2%).[190] Fam-trastuzumab deruxtecan (combined with cytotoxic topoisomerase 1 inhibitor), conversely, has a high incidence of pneumonitis (14%), with fatality reported as 2.2%.[191]

IMMUNOTHERAPIES

A variety of immunotherapies for cancer have been associated with lung toxicity and are described below.

AL GRAWANY

Checkpoint Inhibitor Immunotherapies

Immunomodulatory antibodies directed against the programmed cell death 1 (PD-1) receptor (pembrolizumab and nivolumab), the PD-1 ligand (PD-L1, e.g., atezolizumab, durvalumab, and avelumab), and the cytotoxic T lymphocyte–associated antigen 4 (CTLA-4, e.g., ipilimumab) have altered the landscape of oncologic therapy. These agents are used to treat an increasing variety of advanced stage malignancies including NSCLC, melanoma, renal cell carcinoma, head and neck cancer, urothelial cancer, Hodgkin lymphoma, cutaneous squamous cell carcinoma, and Merkel cell carcinoma.

Checkpoint immunotherapies function by restoring or augmenting intrinsic antitumor immune responses that cancer cells adapt to evade. As a result of their unique mechanisms, these agents are associated with a spectrum of adverse events, including pulmonary toxicity, that reflect unintended dysregulation of immune responses throughout the body. Although pneumonitis is a relatively infrequent event compared with other immune-related complications, it is among the most serious and may be fatal if unrecognized and untreated.

The incidence of pneumonitis appears to be higher with anti–PD-1 monotherapy compared with anti–CTLA-4 monotherapy. In a meta-analysis of nearly 4500 clinical trial patients with melanoma, NSCLC, and renal cell carcinoma, the incidence of all-grade pneumonitis was 3% for anti–PD-1 monotherapy, with severe toxicity observed in <1% of patients. However, rates of toxicity more than doubled when anti–PD-1 therapy was given in combination with anti–CTLA-4 therapy.[192] Moreover, outside the clinical trial setting, rates of pulmonary complications observed in clinical practice have been significantly higher. A single-center retrospective study of 205 patients with NSCLC treated with anti–PD-1/PD-L1 therapy either as part of a clinical trial or as standard of care reported pneumonitis in 19%.[193] In a multicenter series of 915 patients, the overall rate of pneumonitis was 5% for those receiving monotherapy, and it rose to 10% for those receiving anti–PD-1/PD-L1 therapy in combination with anti–CTLA-4 therapy.[194] This same series described considerable variability in the presentation of pulmonary toxicity associated with checkpoint inhibitors. Though most cases present after 2 to 3 months of therapy, time to onset ranged from 9 days to 19.2 months. Indeed, cases of immunotherapy-related pneumonitis have been reported after drug discontinuation.

As with conventional chemotherapy-related pulmonary toxicity, clinical presentation is typically nonspecific, with cough and dyspnea as the most common features. Fever and chest pain are rarely reported. Immunotherapy-related toxicities may affect any organ system, with some patients experiencing multiple toxicities over the course of therapy or even simultaneously. In a multicenter retrospective study of 623 patients on anti–PD-1/PD-L1 therapy, pneumonitis was most commonly observed in coincidence with thyroiditis and dermatitis.[195] However, history of any prior nonpulmonary immunotherapy-related adverse event, including rash, endocrinopathy, arthralgia, or colitis, should raise the index of suspicion for immunotherapy-related pneumonitis.

There are no pathognomonic radiographic or pathologic findings. In fact, radiographic presentation varies greatly and may include interstitial changes, ground-glass opacities, focal infiltrate/cryptogenic pneumonia-like, or hypersensitivity pneumonitis-like patterns (Fig. 64-7).[196] Sarcoid-like presentations with hilar

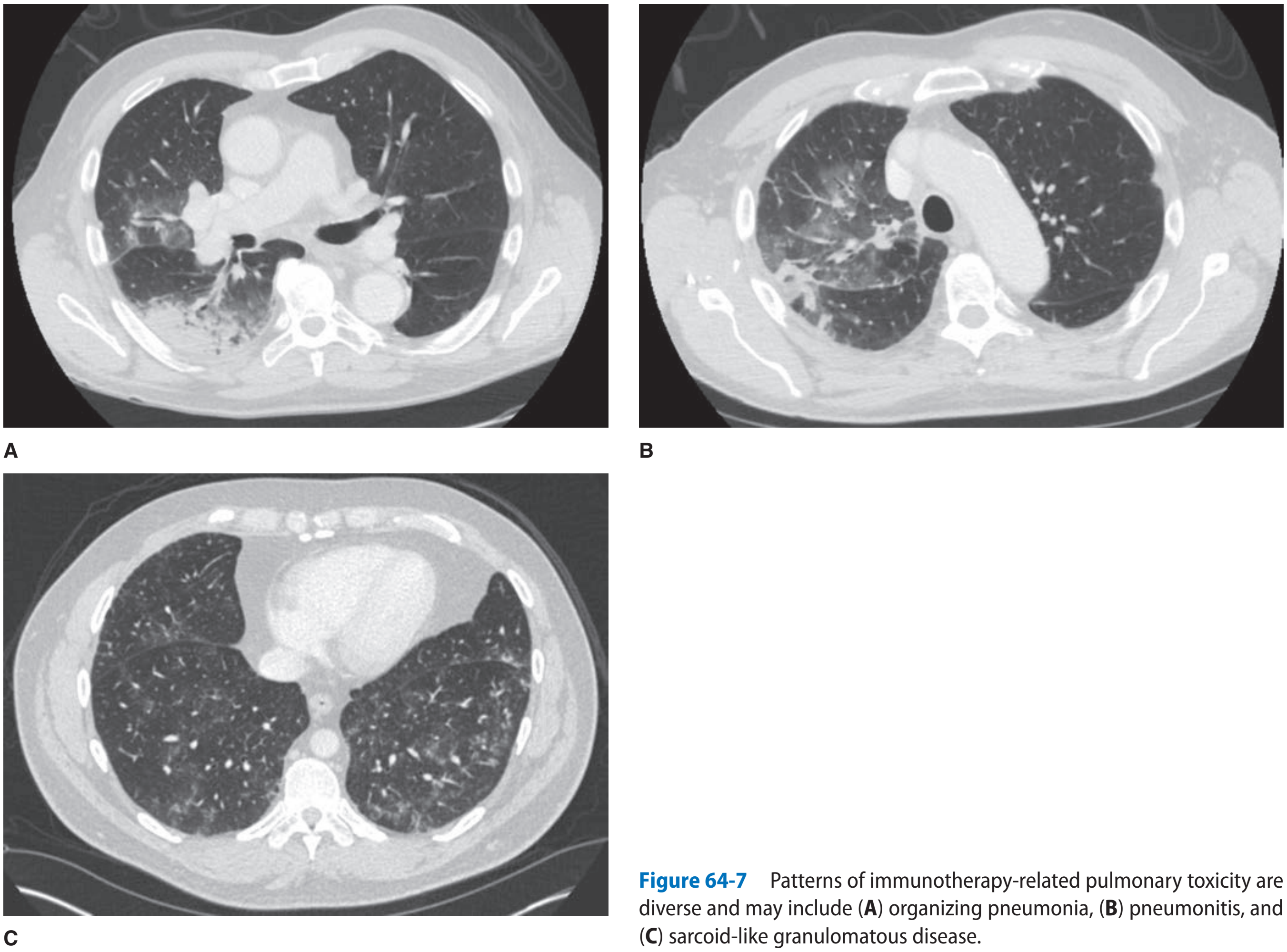

Figure 64-7 Patterns of immunotherapy-related pulmonary toxicity are diverse and may include (**A**) organizing pneumonia, (**B**) pneumonitis, and (**C**) sarcoid-like granulomatous disease.

adenopathy and nodules also have been described. Pathologic findings are similarly variable and reflective of the typical patterns associated with the radiographic presentations described above. Thus far, there are no reliable serologic biomarkers to assist in the diagnosis of suspected immunotherapy-related pulmonary toxicity; similarly, PD-L1 expression in the tumor milieu does not appear to correlate with rates of observed toxicity.

There are no prospective clinical trials describing optimal treatment; therefore aggregate anecdotal experience presently guides management and is based on clinical severity.[197,198] Asymptomatic patients with new radiographic abnormalities may be closely observed for 2 to 4 weeks while immunotherapy is held; if symptoms develop or radiographic findings progress, systemic corticosteroid therapy should be considered. The risk/benefit balance of re-challenge with further immunotherapy after mild toxicity can be approached on a case-by-case basis. In the case of symptomatic individuals, consensus experience favors the use of oral or IV systemic corticosteroids (1–2 mg/kg/d of prednisone or equivalent) tapered over several weeks. In refractory cases, additional immunosuppression with infliximab, azathioprine, mycophenolate mofetil, or cyclophosphamide has been utilized, but the impact on survival remains uncertain.[194,199,200] The majority of patients will improve with either drug cessation or the use of systemic corticosteroids, but clinical relapses after cessation of corticosteroids have been reported and may require protracted immunosuppressive therapy. Fulminant and refractory cases of pulmonary toxicity have led to rare fatalities, although attribution may be confounded by opportunistic infections in immunosuppressed individuals or progression of underlying malignancy. While concerns have been raised about the impact of immunosuppression on antitumor response, as of yet there is no evidence that treating immunotherapy-related pulmonary toxicity negatively impacts survival or the durability of the treatment response.[201]

■ Chimeric Antigen Receptor (CAR)–T Cell Therapy

Chimeric antigen receptor (CAR)–T cell therapy has recently been used to treat acute lymphoblastic leukemia (ALL) and refractory lymphomas. The treatment uses the patient's own T lymphocytes transduced with a gene encoding a CAR to direct the patient's T cells against the malignant cells. The most common pulmonary toxicity is associated with cytokine release syndrome (CRS) and is characterized by hypoxemia, tachypnea, pleural effusions, and pulmonary edema (Table 64-10). CRS is more common with bulky disease (especially seen in ALL), high infusion dose, and certain lymphodepletion regimens. Commonly, CRS beings 1 to 14 days after therapy. Grade 3 to 4 CRS is treated with a combination of tocilizumab (IL-6 receptor antagonist) and steroids.

Pulmonary infectious complications are not uncommon following CAR–T cell therapy. Infectious complications can be related to prior cytopenias or due to immunosuppressive mediations used to treat CRS. In one case series, 42% of patients with B-cell leukemia developed pulmonary infection with an associated mortality rate of 6%. Grade 3 or greater CRS was independently associated with pulmonary infection.[202]

■ Interleukin 2

Interleukin 2 (IL-2) is a glycoprotein secreted by activated lymphocytes. IL-2 therapy alone, or in conjunction with lymphokine-activated killer (LAK) cells, has proved beneficial in patients with metastatic renal cell carcinoma or melanoma. In the current era of checkpoint inhibitor immunotherapy approaches, it is generally not the first treatment of choice, but it is an option for patients with disease progressing through immunotherapy-focused regimens.

Pulmonary complications related to IL-2 largely relate to cardiovascular instability with a vascular leak syndrome. This can result in cardiogenic, as well as noncardiogenic, pulmonary edema and may be associated with hypotension, renal insufficiency, and pleural effusions.[203] Several mechanisms have been identified that may explain the increase in capillary permeability.[204,205] IL-2–activated lymphocytes produce a variety of cytokines, including tumor necrosis factor (TNF) and IL-1. These may alter endothelial permeability and are thought to be important in the pathogenesis of other capillary leak syndromes, for example, in septic shock. IL-2 also may promote the adhesion of natural killer cells to the capillary endothelium, resulting in alteration of vascular integrity. IL-2 is also associated with toxicity in multiple other organs, including the heart. Therefore, IL-2–induced cardiac dysfunction may contribute to the development of pulmonary interstitial edema.

Inhalational IL-2 has also been studied in clinical trials to treat pulmonary metastases in patients, primarily with renal cell carcinoma and melanoma.[206–208] Bronchospasm has been reported, which can be mitigated by pretreatment with inhaled bronchodilator. The inhalational route of IL-2 appears to abrogate the risk of pulmonary toxicity, while demonstrating efficacy against intrapulmonary metastatic disease.

IL-2 appears to have a cumulative dose-dependent lung toxicity that seems to be compounded by LAK cell administration.[209,210] Lung toxicity does appear to be reversible. In most cases, clinical and radiographic abnormalities resolve within several days after cessation of therapy.

TABLE 64-10 Immunotherapies

Drug	Pulmonary Syndrome	Treatment	Comments
Checkpoint inhibitors	• Pneumonitis • Organizing pneumonia • Sarcoid-like toxicity	• Discontinue drug • Corticosteroids • Secondary immunosuppression for steroid-refractory toxicity	• Rechallenge based on severity • May persist or recur despite drug discontinuation • Risk factors: combination anti–PD-(L)1/anti–CTLA-4 therapy, preexisting ILD, prior thoracic radiotherapy, combination with EGFR TKI therapy, squamous NSCLC histology
Chimeric antigen receptor (CAR)–T cell therapy	• Cytokine release syndrome (CRS)	• Tocilizumab • Corticosteroids	• Begins 1–14 days post therapy
	• Pulmonary infection	• Targeted to infection	• Related to prior cytopenias and/or immunosuppressive regimen to treat CRS
Interleukin-2	• Cardiogenic edema • Pleural effusions	• Diuretics • Supportive care	• Vascular leak syndrome • Risk factors: cumulative dose, administration of LAK cells

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CHAPTER 65

Drug-induced Pulmonary Disease Due to Nonchemotherapeutic Agents

Hilary C. Cain

INTRODUCTION

Medications have long been recognized as having the potential to cause pulmonary injury even when given at therapeutic doses. The precise incidence of drug-induced respiratory disease is difficult to ascertain and potentially is confounded by reporting bias for positive events; the signs and symptoms of lung toxicity are shared by many other pulmonary conditions and diseases. Data on adverse events are supplied to national databases such as the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) and the Japanese Adverse Event Report (JADER), and these databases can be utilized to determine patterns and incidence of events. However, these databases are limited by data input, and concerns inevitably are raised about the completeness and accuracy of direct submissions from providers and healthcare facilities compared with those from drug manufacturers.[1,2] As the categories and varieties of therapeutic drugs continue to increase, clinicians will encounter disease from new culprit drugs in addition to well-established drug reactions. A web-based data repository, Pneumotox V2.2 (*www.pneumotox.com*), is a useful tool for the clinician, as it provides frequent updates based on the emerging literature on drug-induced respiratory toxicities.

When the clinician-scientist explores the literature on drug-induced lung injury, it is critical to recognize that not all reported associations between medications, over-the-counter supplements or illegal drugs, and respiratory disease imply a definitive causal link between a specific drug and the injury pattern described. The literature needs to be cautiously interpreted before concluding that the reported associations are due to the implicated drug rather than a confluence of clinical conditions. This chapter addresses the principles that characterize drug-induced lung disease and examines some of the more common medications and drug classes that are implicated in pulmonary toxicity. Chemotherapeutic agents are discussed in a separate chapter 64.

GENERAL PRINCIPLES OF DRUG-INDUCED LUNG DISEASE

Drug-related pulmonary injury is a rare event. Reactions typically occur in a small minority of individuals exposed to a given agent. The incidence of drug- and radiation-induced interstitial disease was examined over a 12-year period (1997–2008) in a database of approximately 9 million patients from the United Kingdom, and an incidence of 0.8 per 1,000,000 patients per annum for drug-related interstitial disease was reported. Notably, this cohort was assembled before the utilization of many immunomodulatory and biologic therapies, and more recent data suggest a rate of drug-induced interstitial disease as high as 12.4 cases per million per year.[3] These data, however, reflect only a portion of the impact of drug-induced respiratory disease, because not only the interstitium is affected; the alveoli, upper and lower airways, pleura, pulmonary vasculature, muscles of respiration, and the central nervous system governing respiratory control are all susceptible to injury from ingested, inhaled, and parenterally administered agents.

In many cases, lung injury appears to be an idiosyncratic event and is not easily predicted by dose, time from drug initiation, duration of exposure, or pharmacologic characteristics of the drug. Often, there is no characteristic clinical presentation or pathognomonic histologic pattern of injury associated with a given drug, although certain histologic patterns of lung injury may occur more frequently than others. Thus, establishment of a diagnosis of lung toxicity is frequently a diagnosis of exclusion (Table 65-1). The idiosyncratic nature of pulmonary toxicity suggests that there are host-specific risk factors that influence the development of injury. The risk factors influencing individual susceptibility may be (1) genetically determined, (2) due to concurrent exposures to other medications or environmental agents, (3) related to the individual's comorbid disease, or likely (4) a function of a combination of these factors.

Genetic predisposition to drug-induced injury is not fully characterized but likely is related to individual variability of drug metabolism and biotransformation.[4] While drug metabolism occurs primarily in the liver, through the action of the cytochrome p450 family of enzymes, the lung has an enormous surface area on which blood-borne substances (therapeutic medications, nutritional supplements, illicit drugs, and/or toxins) actively interact with lung tissue and is an active site of metabolism and biotransformation. Cytochrome p450 enzyme levels in lung tissue are estimated to be 10% to 15% of those in the liver, but the existence of lung-specific cytochrome p450 isoenzymes implies lung-specific metabolism of drugs.[5] Host-specific nucleotide polymorphisms affecting drug metabolism appear to be key mediators of variable drug responses in general, and they may confer increased risk of toxicity in certain individuals.[6,7]

MECHANISMS OF PULMONARY INJURY

Mechanisms of lung injury are broadly categorized as direct cytotoxicity and immune-mediated injury, and may include (1) oxidant injury, (2) immunologic and inflammatory cell-mediated injury (including immune complex–mediated injury), (3) interference

TABLE 65-1 General Principles of Drug-induced Lung Injury

- Clinical presentation is nonspecific
- Injury occurs with variable latency from drug initiation
- Lung injury is often dose-independent
- Pulmonary toxicity may be unrelated to the drug's pharmacologic properties
- Acute, subacute, and chronic reactions may be caused by a drug
- A variety of histopathologic patterns may be induced by a drug
- Diagnosis of drug-induced injury is often made by exclusion
- Resolution of injury may occur with drug discontinuation alone
- Rechallenge with the suspected culprit drug is not recommended

with matrix formation or alveolar repair, (4) abnormal protease/antiprotease balance, and (5) interference with lipid metabolism.[7]

The role of drug-induced oxidant injury is well established for nitrofurantoin, mitomycin C, and bleomycin, and it may be the mechanism of injury of other drugs as well.[7] Biotransformation of these drugs results in generation of reactive oxygen species, including hydrogen peroxide (H_2O_2), the hydroxyl radical (•HO), and the superoxide anion (O_2^{-}•), which promote lipid peroxidation, glutathione depletion, and, consequently, cellular dysfunction or cell death.

Immunologically mediated injury is implicated in lung injury events.[7] Lymphocytic or neutrophilic alveolitis and inflammatory cell interstitial infiltrates are present in many cases of drug-induced lung injury, and the elaboration of chemokines and proteases by these cells may lead to cellular injury. The observation that drug metabolite–protein adducts can act as immunogens, resulting in hypersensitivity reactions or other immunologically mediated tissue injury, likely applies to the lung as well as other organs.[8] Complement-mediated injury has been implicated for drugs causing noncardiogenic pulmonary edema (ARDS), particularly opiates and β-agonists.

The role of disruption of phospholipid metabolism due to cellular sequestration has been well established for amiodarone-mediated lung injury, as discussed below.

■ Impact of Concurrent Exposures

The harmful effect of oxygen administration concurrent with the chemotherapeutic agent bleomycin has been well established. However, high oxygen tension does not substantially increase the risk of toxicity for most nonchemotherapeutic agents. It is plausible that the additive effect of supplemental oxygen in promoting oxidant injury may be more relevant for some individuals than others. Other exogenous factors, such as cigarette smoke, may influence lung injury through induction of cytochrome P450 enzymes.

DIAGNOSTIC APPROACH TO THE PATIENT WITH SUSPECTED DRUG-INDUCED RESPIRATORY DISEASE

Confirmation of drug-induced pulmonary toxicity is a diagnostic challenge because pathognomonic criteria for diagnosis seldom exist. The diagnosis of drug-induced disease can be reasonably established, however, if the following criteria are met: (1) history of drug exposure; (2) clinical signs and symptoms, radiologic findings, and histopathology are consistent with previously reported toxicity; (3) alternate diagnoses are excluded (e.g., infection, systemic disease, malignancy); and (4) findings regress with drug discontinuation and/or treatment. Recrudescence of the lung injury following rechallenge with the culprit drug is further confirmation of drug-induced disease, but rechallenge is generally *not* recommended due to the substantial risk of morbidity or mortality.

Recognition of a patient's risk of drug-induced injury is the first step in the diagnostic process. Drug-induced lung disease occurs with prescribed drugs, over-the-counter drugs, herbal or alternative medicine preparations (many of which contain a mixture of substances, any of which might be implicated as the culprit agent), and recreational drugs. Patients may be reluctant to offer accurate information about their use of alternative medicines or supplements and recreational drug use, and the clinician must skillfully elicit the history.

The challenge of diagnosis is compounded by the fact that the latency from the onset of drug use to development of a toxic reaction can be highly variable. The temporal relationship between the respiratory symptoms and/or pulmonary findings and the use of the culprit drug may not be readily apparent when a history is taken. Certain medications (e.g., amiodarone, nitrofurantoin) can cause acute, subacute, or chronic pulmonary toxicity, further complicating the diagnosis. Additionally, new drugs will continue to come on the market, some of which will inevitably cause lung disorders that have not yet been identified. The potential for medications to cause toxic reactions will be recognized only once the drug has been in use for a sufficient length of time to allow low-frequency events, such as drug-induced toxicity, to occur and be recognized.

In many cases, drug reactions are idiopathic, rather than dose-dependent reactions, and are unrelated to the drug's intended pharmacologic properties. Exceptions to these observations include (1) amiodarone, for which there is an increased risk of toxicity with higher daily maintenance dosages, and (2) heroin, methadone, aspirin, propoxyphene, ethchlorvynol, and colchicine, which cause pulmonary toxicity only in the setting of overdose.

The diagnosis of drug-induced lung toxicity is often difficult to establish because patients with this condition typically come to medical attention with symptoms, radiologic findings, and laboratory data that are nonspecific. The clinical presentation of drug-induced lung disease may be similar to other disorders, including infections, hypersensitivity pneumonitis due to environmental antigens, eosinophilic lung disease, systemic rheumatologic or collagen vascular disease, and idiopathic interstitial pneumonias. High-resolution computed tomography (HRCT) has utility in characterizing lung injury but is rarely specific to a drug and may not confidently predict the histologic pattern of drug-induced injury. Even in cases in which lung tissue is obtained by biopsy, the histopathologic features may not fully distinguish drug-induced disease from the alternative disorders or conditions.

An additional consideration is that the underlying disease for which a drug is given may produce pulmonary findings similar to drug-induced lung disease. For example, rheumatoid arthritis may cause pulmonary infiltrates with similar radiographic appearance and histology to toxic reactions induced by the methotrexate, gold, or penicillamine used to treat the rheumatoid arthritis.

Once the clinician has established that a patient has (1) a recognized, identifiable risk of drug-induced lung toxicity, and (2) history, physical examination, laboratory data, and radiographic findings compatible with known patterns of lung injury, then further cytopathologic or histologic evidence may be warranted to further establish the diagnosis. A multidisciplinary approach to diagnosis is recommended with pulmonologists, radiologists, rheumatologists, cardiologists, and pathologists all playing roles.

The technique of bronchoalveolar lavage (BAL) is particularly useful in the diagnostic evaluation of patients with new-onset interstitial lung disease (ILD) in whom evaluation for infection is essential. Analysis of BAL fluid is most useful when it is used in conjunction with a comprehensive clinical history and HRCT.[9] BAL cytologic analysis and culture can be particularly useful to exclude typical or atypical bacterial, fungal, viral, or parasitic infections in patients with suspected drug-induced lung injury. BAL may be helpful in diagnosing diffuse lung malignancies, such as lymphangitic spread of tumor or diffuse pulmonary lymphoma. Lung injury patterns that can be associated with drug-induced injury such as alveolar hemorrhage, whether bland or vasculitic in origin, may be diagnosed by BAL. A grossly cloudy BAL fluid that settles with gravity is consistent with pulmonary alveolar proteinosis.

The cellular differential of the BAL fluid may help narrow the diagnosis in suspected drug-induced pulmonary disease. The most common BAL cellular profile in drug-induced disease is lymphocytosis; a cell differential of ≥25% lymphocytes should earn drug-induced ILD a place in the differential diagnosis of any presentation of ILD. Recent guidelines for the use of BAL do not recommend routine measurement of lymphocyte subsets on all patients with ILD. However, if a lymphocyte alveolitis is suspected or confirmed, the subset measurement may be justified.[9] The T suppressor (CD8+) lymphocyte subset is commonly reported in drug-induced lung hypersensitivity pneumonitis. T helper (CD4+) predominance in the BAL has been associated with immunomodulatory drug injury, including methotrexate, and sirolimus. Other cellular profiles occur in drug-induced disease, and eosinophils and neutrophils are variably present. A percentage of eosinophils ≥25% is consistent with acute or chronic eosinophilic pneumonia, which may be a result of drug-induced injury.

Lung tissue obtained bronchoscopically or surgically may help characterize the injury pattern and may support the diagnosis of drug-induced injury. Lung biopsy, however, is not essential to establish the diagnosis. It is important to recognize that the histologic patterns seen in drug-induced injury, such as nonspecific interstitial pneumonia (NSIP), organizing pneumonia with or without bronchiolitis obliterans, eosinophilic pneumonia, or granulomatous inflammation, are histologically indistinguishable from other etiologies of these lung injury patterns.

Serum markers, including surfactant proteins (SP-A, SP-D), KL-6, and ADAM8, have been associated with drug-induced injury but have not entered into the diagnostic armamentarium for most routine clinical evaluations.[7] Similarly, drug-specific lymphocyte stimulation testing and lymphocyte migration inhibition testing have been shown to be useful in the diagnosis of drug-induced lung disease by some investigators, but these are not available to most clinical practices.

CLINICAL AND HISTOPATHOLOGIC PATTERNS OF INJURY

The entire respiratory system is susceptible to the adverse effects of drugs, including the upper and lower airway, pleura, lung parenchyma, pulmonary vasculature, muscles of respiration, and the central nervous system governing the control of respiration. Among these compartments, parenchymal injury in the form of ILD is the most frequent cause of morbidity and mortality.

Respiratory disease may occur as the sole consequence of drug toxicity, or it may be one manifestation of a systemic drug-induced syndrome. For example, 5% to 25% of patients with drug rash with eosinophilia and systemic symptoms (DRESS) may have lung involvement, most commonly induced by minocycline but also by aromatic anticonvulsants.[10] Drug-induced systemic lupus erythematosus (SLE), with or without pulmonary involvement, may occur from exposure to β-blockers, amiodarone, angiotensin-converting enzyme (ACE) inhibitors, hydralazine, procainamide, isoniazid, methyldopa, minocycline, and tetracycline, among others. In addition, drugs (phenytoin, hydralazine, propylthiouracil, D-penicillamine, and cocaine, among others) can cause the clinical picture of a pulmonary–renal syndrome, with evidence for pulmonary and renal vasculitis.

Parenchymal injury may manifest in the interstitial, alveolar, and/or vascular compartments. Of the processes affecting the lung parenchyma, interstitial involvement is the most common. The major histopathologic forms of ILD—cellular and fibrotic NSIP, usual interstitial pneumonia (UIP), hypersensitivity pneumonitis, organizing pneumonia (with and without obliterative bronchiolitis), eosinophilic pneumonia, desquamative interstitial pneumonitis, and diffuse alveolar damage—have been reported to occur as adverse effects of drugs. Unfortunately for diagnostic clarity, among the many case reports citing the presence of ILD, many have no tissue confirmation of the precise lung histology, and older case reports were published before the current guidelines for classification of ILDs were established. [11] It is important to recognize that few drugs have been reported to cause a single histopathologic pattern of parenchymal injury, and in the cases of many drugs, several patterns of injury may occur[12] (Table 65-2).

The radiographic and histologic characteristics of NSIP and UIP have been defined in the American Thoracic Society/European Respiratory Society (ATS/ERS) international multidisciplinary consensus statements[11,13] in 2002 and 2013.[27,28] These features are

TABLE 65-2 Histopathologic Findings and Nonchemotherapeutic Drug Associations

Histopathologic Diagnosis	Drug	Histopathologic Diagnosis	Drug
Interstitial infiltrates/ fibrosis (acute, subacute, or chronic)	Amiodarone	Eosinophilic lung disease	ACE inhibitors
	β-adrenergic blockers		Amiodarone
	Carbamazepine		Amphotericin B
	Gold salts		Carbamazepine
	Hydralazine		Cephalosporins
	Interferon-α		Erythromycin
	Methotrexate		Ethambutol
	Nitrofurantoin		Gold salts
	Penicillins		Isoniazid
	Phenytoin		Methotrexate
Organizing pneumonia	Amiodarone		Minocycline
	Amphotericin B		Nitrofurantoin
	Carbamazepine		NSAIDs
	Cephalosporins		PAS
	Cocaine		D-Penicillamine
	Gold salts		Sulfonamides
	Interferon-α		Tetracycline
	Minocycline		Trazodone
	Nitrofurantoin		
	D-penicillamine		
	Phenytoin		
	Rituximab		
	Sotalol		
	Sulfasalazine/mesalamine		

TABLE 65-2 Histopathologic Findings and Nonchemotherapeutic Drug Associations *(Continued)*

Histopathologic Diagnosis	Drug
Hypersensitivity pneumonitis	Atorvastatin
	Bupropion
	Carbamazepine
	Cephalosporins
	Ciprofloxacin
	Interferon-α
	Methotrexate
	Nitrofurantoin
	NSAIDs
	Penicillin
	Phenytoin
	Rituximab
	Sertraline
	Sirolimus
	Sulfonamides
Granulomatous inflammation	BCG
	Etanercept
	Infliximab
	Interferon-α
	Methotrexate
	Nitrofurantoin
	Sulfasalazine
Systemic lupus erythematosus	ACE inhibitors
	Amiodarone
	β-adrenergic blockers
	Etanercept
	Isoniazid
	Methyldopa
	Minocycline
	Procainamide
	Tetracycline
Airways disease	Aspirin
	ACE inhibitors
	Adenosine
	β-adrenergic blockers
	NSAIDs
ARDS	Amiodarone
	Gold salts
	HCTZ
	Infliximab
	Methotrexate
	Nitrofurantoin
	Prostacyclins
	Talc
Pulmonary edema	Acetylsalicylic acid
	Cocaine
	HCTZ
	Methadone
	Methotrexate
	NSAIDs
	Opiates
	Phenothiazines
	Tocolytic agents (e.g., terbutaline, ritodrine)
	Tricyclic antidepressants
DAH/vasculitis	Amiodarone
	Cocaine
	LTRAs
	Methotrexate
	Minocycline
	Nitrofurantoin
	Penicillamine
	Propylthiouracil
	Sulfonamides
Pulmonary hypertension	Anorexigens
	Cocaine
	Opiates
Alveolar hypoventilation	Aminoglycosides
	Corticosteroids
	Opiates
	Sedative/hypnotics

ACE, angiotensin-converting enzyme; ARDS, acute respiratory distress syndrome; BCG, Bacillus Calmette-Guérin; DAU, diffuse alveolar hemorrhage; HCTZ, hydrochlorothiazide; LTRA, leukotriene receptor antagonist; NSAID, nonsteroidal anti-inflammatory drug; PAS, para-aminosalicylic acid.

effectively indistinguishable whether due to drug-induced, systemic, or idiopathic disease, and thus it is the clinical scenario that is critical to establishing the diagnosis of drug-induced injury. Older literature on drug-induced lung disease does not necessarily conform to recent consensus definitions of NSIP, UIP, or unclassified interstitial pneumonias, making older case series more difficult to interpret. Culprit drugs leading to these interstitial pneumonias include antimicrobials, antirheumatics, tumor necrosis factor (TNF) antagonists, β-adrenergic antagonists, antiarrhythmics, anti-inflammatory drugs, antipyretics, and immunosuppressants.

■ Organizing Pneumonia

Organizing pneumonia (OP) with or without histopathologic evidence of obliterative bronchiolitis is a frequently reported pulmonary injury pattern.[12] The histologic pattern seen in drug-induced parenchymal injury is indistinguishable from cryptogenic organizing pneumonia (COP) and consists of plugs of proliferating fibroblasts, or granulation tissue that fills distal respiratory bronchioles, alveolar ducts, and alveolar spaces. This may be accompanied by mild interstitial inflammation with preserved architecture. Radiographic findings of OP are typically bilateral, patchy areas of consolidation that are often subpleural, with a tendency to lower lobe predominance or distribution along the bronchovascular bundle.

Many of the drugs that have been reported to cause OP are commonly used medications, but the frequency of lung injury among users is low. Among the implicated antimicrobials are cephalosporins, minocycline, nitrofurantoin, amphotericin B, and interferons.[12]

One of the most utilized antiarrhythmic agents, amiodarone, is known to cause OP, as are the anticonvulsants carbamazepine and phenytoin, and the anti-inflammatory agents gold, penicillamine, and sulfasalazine. In patients treated for rheumatoid arthritis (RA) with gold or penicillamine, it is important to distinguish between drug-induced OP and infiltrates reflecting OP due to the underlying RA itself.

The clinical presentation of drug-associated OP is similar to that of idiopathic or cryptogenic OP. Symptoms are nonspecific and may include shortness of breath, nonproductive cough, and, in some cases, low-grade fever and/or pleuritic chest pain. The chest radiograph typically shows bilateral patchy infiltrates that may be migratory over serial radiographs, with interval normal chest radiographs despite continuous drug exposure. As with other interstitial lung disease, the utility of BAL is primarily to exclude an infectious etiology of the infiltrates. There is no specific BAL cellular profile characteristic of OP. Lung biopsy reveals characteristic histopathology, identical to that of COP. Patients with drug-induced OP may have spontaneous resolution of disease when the offending drug is discontinued, but oral corticosteroids may be used to accelerate disease resolution if the patient is symptomatic.

■ Eosinophilic Pneumonitis

Drug-induced eosinophilic lung disease may mimic other eosinophilic pulmonary syndromes, including simple eosinophilic pneumonitis (Loeffler syndrome), chronic eosinophilic pneumonia, acute eosinophilic pneumonia, pulmonary infiltrates with peripheral eosinophilia (PIE), and eosinophilic granulomatosis with polyangiitis (previously known as Churg–Strauss Syndrome). The differential diagnosis of eosinophilic lung disease includes drug-induced injury, and a search for the culprit drug is an integral part of the diagnostic evaluation. Although the clinical presentation of drug-induced eosinophilic pneumonia may be identical to idiopathic conditions, several distinctions can be made. In idiopathic eosinophilic pneumonia, symptoms affect the lung exclusively, while in drug-induced eosinophilic pneumonia, respiratory symptoms may be accompanied by systemic symptoms such as rash and fever. Marked peripheral blood eosinophilia (>1000 cells/mL) suggests drug-induced pneumonitis, rather than acute idiopathic eosinophilic pneumonia, in which the eosinophil count tends to be more modestly elevated or normal.

The diagnosis of drug-induced eosinophilic pneumonia is supported by peripheral blood and/or pulmonary eosinophilia in a setting of exposure to a suspect drug. The diagnosis may be established when other eosinophilic lung diseases are excluded. When evaluating a patient with pulmonary eosinophilia, it is particularly important to exclude infectious causes of eosinophilia to avoid promoting progressive infection and/or death by use of corticosteroid treatment for presumptive drug-induced eosinophilic pneumonia. Tropical pulmonary eosinophilia caused by filarial infection should be suspected if the patient has a consistent travel history. *Schistosoma* and *Paragonimus westermani* are other potential pathogens to be excluded. *Strongyloides*, *Ascaris*, and *Toxocara* are indigenous to the United States and are known to cause pulmonary infiltrates and peripheral blood eosinophilia. Missing the diagnosis of a fungal infection also can be lethal. *Aspergillus* is a ubiquitous fungus that can be difficult to diagnose as a pulmonary pathogen. BAL eosinophilia may be present without definitive evidence of invasive fungal infection, which may require a tissue biopsy for diagnosis. *Coccidioides immitis* is endemic in the southwestern United States, and infection can result in peripheral blood eosinophilia and pulmonary infiltrates. Serologic testing for antibodies to *Coccidioides* and sputum or BAL cultures are useful studies to exclude coccidioidomycosis.

In a review of 196 cases of eosinophilic pneumonia, the most frequently reported drugs associated with eosinophilic pneumonias were daptomycin (n = 32), mesalamine (n = 32), minocycline (n = 17), sulfasalazine (n = 14), nitrofurantoin (n = 12), amitriptyline (n = 4), and amiodarone (n = 4). There were twice as many cases of acute eosinophilic pneumonia (n = 132) as there were cases of chronic eosinophilic pneumonia (n = 61).[14]

Successful management of drug-induced eosinophilic lung disease is achieved by identification and discontinuation of the inciting drug. Typically, resolution of symptoms in drug-induced eosinophilic lung disease occurs with discontinuation of the culprit drug, frequently without the need for corticosteroids. In contrast, idiopathic chronic eosinophilic pneumonia may require months of treatment with corticosteroids, and relapse may occur as steroids are tapered. Relapse of the disease as steroids are tapered is rare in drug-induced eosinophilic disease; recrudescence of the lung infiltrates suggests an alternate diagnosis.

■ Hypersensitivity Pneumonitis

Most cases of pulmonary hypersensitivity occur without accompanying systemic symptoms. The clinical presentation of drug-related pulmonary hypersensitivity typically consists of acute onset of dyspnea, cough, and fever. The radiographic pattern is one of diffuse reticular or peripheral alveolar infiltrates, sometimes accompanied by pleural effusion. The histopathology may include nonnecrotizing granulomas, chronic bronchiolitis, and chronic interstitial inflammation with or without fibrosis. In most cases, drug discontinuation results in disease resolution. A minority of individuals (10%) have persistent radiographic abnormalities after several months, and rarely, progressive disease may occur despite drug withdrawal. In these cases, a trial of corticosteroids is reasonable if the diagnosis has been well established.

Systemic hypersensitivity syndromes with granulomatous inflammation of the lung may be caused by various drugs, most commonly minocycline and the aromatic anticonvulsants phenytoin and carbamazepine, as well as nonsteroidal anti-inflammatory drugs (NSAIDs), and sulfonamides. DRESS can be accompanied by pulmonary histopathology consistent with OP, ILD, or granulomatous inflammation.

■ Noncardiogenic Pulmonary Edema and Acute Respiratory Distress Syndrome

Alveolar disease occurs in the form of noncardiogenic pulmonary edema, diffuse alveolar damage (DAD), and/or acute respiratory distress syndrome (ARDS). It is estimated that approximately 10% of cases of ARDS can be ascribed to drug injury.[12]

Noncardiogenic pulmonary edema may be precipitated by numerous drugs, including aspirin, opiates, calcium channel blockers, some diuretics (e.g., hydrochlorothiazide, acetazolamide), intravenous and inhaled pulmonary vasodilators (e.g., epoprostenol, nitric oxide), methotrexate, TNF-α, radiographic contrast media, tocolytics, and oxytocin, among others.[15] The onset of drug-induced pulmonary edema typically occurs in close temporal proximity to ingestion of the culprit drug and does not have a variable latency of onset.

A variety of mechanisms are implicated in the development of pulmonary edema. Increased pulmonary capillary permeability is the likely cause of aspirin-induced, interleukin-2–induced, and ethchlorvynol-induced edema. Volume expansion and sodium retention likely cause the pulmonary edema associated with the use of β2-sympathomimetic tocolytic agents. Opioid-induced edema is mediated by neurogenic reflex and deposition of immunoglobulin and complement in the lung.[30] Although the mechanisms of pulmonary edema may vary, frequently the resolution of symptoms is prompt within days of drug discontinuation.

Pulmonary edema is common in salicylate intoxication, and the risk is correlated with the degree of intoxication. A prevalence of alveolar edema as high as 20% to 30% has been reported for aspirin-intoxicated adults. An increased risk of edema is associated with chronic aspirin ingestion, older age, positive smoking history, neurologic disease, and proteinuria.[31,32]

In cases of drug-induced ARDS, this condition is considered as a clinical syndrome of lung injury, rather than a specific histopathologic pattern of disease. If we examine the more specific histopathology of DAD, many cases of drug-induced injury have been reported to have these histologic characteristics and diffuse ground-glass attenuation on CT imaging of the lung. The more commonly implicated drugs associated with DAD are amiodarone, methotrexate, infliximab, nitrofurantoin, and many chemotherapeutic agents.[12]

■ Diffuse Alveolar Hemorrhage, Vasculitis, and Pulmonary–Renal Syndromes

Drug-induced diffuse alveolar hemorrhage (DAH) is infrequently reported in the literature on drug-induced pulmonary disease. DAH should be suspected in patients with unexplained ground-glass infiltrates or consolidation, accompanied by anemia. Hemoptysis is not required for the diagnosis and may be absent in as many as one-third of patients with DAH. The classification of drug-induced DAH is based on histopathologic findings and includes (1) capillaritis, (2) bland hemorrhage due to drug-induced coagulopathies, and (3) DAD, the histopathologic finding in ARDS. Drug-induced DAD may lead to bland DAH and has been reported for amiodarone, nitrofurantoin, minocycline, methotrexate, gold, cocaine, and chemotherapeutic agents. Pulmonary capillaritis has been described as an adverse effect of many drugs, but strong associations with its development are reported for relatively few drugs. One of the best-characterized toxicities presenting as DAH is that from propylthiouracil.[16,17] The DAH is a manifestation of a systemic vasculitic syndrome characterized by leukocytoclastic vasculitis, glomerulonephritis, and pulmonary capillaritis. Use of propylthiouracil induces antineutrophil cytoplasmic antibodies (ANCAs) in as many as 46% of patients, although only a minority of these develop pulmonary toxicity; pathogenesis may be mediated by antimyeloperoxidase antibodies.[18] Cases of pulmonary or systemic vasculitis also have been reported for diphenylhydantoin, hydralazine, nitrofurantoin, and leukotriene receptor antagonists. In the case of the last group of drugs noted, there has been considerable discussion as to whether the vasculitis is a toxic effect of the leukotriene antagonists or whether withdrawal of oral corticosteroids leads to identification of pre-existing eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome). At least some reported cases of Churg–Strauss syndrome are unrelated to steroid withdrawal and appear to represent a rare complication of leukotriene antagonists.

Bland hemorrhage without capillaritis can occur (1) in the setting of therapeutic and supratherapeutic anticoagulation, (2) with the use of inhibitors of platelet aggregation (e.g., clopidogrel) and platelet glycoprotein IIa/IIIb inhibitor therapy, and (3) as a complication of thrombolysis. Bland DAH related to D-penicillamine, amiodarone, and cocaine is discussed in the sections on individual drugs in later sections.

■ Cough and Angioedema

Cough induced by angiotensin-converting enzyme (ACE) inhibitors is well characterized in several case series, and guidelines exist to guide management.[19,20] The overall reported incidence of cough associated with ACE inhibitors ranges from 1.5% to 20% and may be increased with concomitant use of ranolazine.[21,22] The latency from initiation of use to the onset of cough is variable, ranging from 1 week to 15 months. While some series have reported increased nonspecific bronchial hyperresponsiveness among subjects with cough, others have not. Symptoms typically resolve promptly 1 to 4 weeks after discontinuation of the drug, but occasionally resolution may take as long as 3 months. Less frequent side effects of ACE inhibitors include PIE, SLE, and subacute ILD, but these do not typically appear in conjunction with ACE inhibitor–induced cough. Angiotensin receptor blockers induce cough much less frequently than do ACE inhibitors and can be considered as alternative therapy.[23]

Angioedema due to ACE inhibitors is a potentially life-threatening complication of these medications. Edema more commonly affects the face (57%) and less commonly the floor or roof of mouth and tongue (26%). In 17%, the oropharynx and glottis are involved.[24] Presenting symptoms may range from simple edema of the lips and/or face to respiratory failure requiring ventilatory support. The latency for onset is even wider than that for cough, ranging from 4 weeks to 4 years after onset of ACE inhibitor use. In one series, 70% presented within the first month of treatment.

Numerous case series have reported a higher incidence of angioedema among African Americans, as well as a higher risk of intubation among those affected in this racial group.[25] Angioedema formation is likely due to elevation of circulating bradykinin as a result of ACE inhibitor–induced inhibition of its degradation, leading to vasodilatation and capillary leak. The effect of impaired bradykinin degradation may be compounded in individuals with genetically based deficiency of other bradykinin metabolizing enzymes. Most experts recommend treatment for angioedema with corticosteroids, H1- and H2-blockers, and, in some cases, epinephrine.

■ Bronchospasm and Anaphylaxis

Drug-induced bronchospasm is a relatively common side effect of many categories of medications, most commonly NSAIDs, antibiotics, and beta blockers.

Bronchospasm triggered by drugs is more common in subjects with underlying asthma, atopy, or bronchial hyperreactivity. These reactions are more common in women than in men, and there appears to be familial predisposition to reactions to some drugs.[26] Symptoms range from mild chest tightness and dyspnea on exertion to respiratory failure in susceptible individuals. Aspirin and NSAIDs are commonly implicated in bronchospasm, in one series accounting for as many as 24% of bronchoconstrictive reactions, ranging from mild to severe.[27] Other agents more commonly implicated in bronchospasm and anaphylaxis include sulfonamides, omalizumab, halothane, heparins, protamine, insulin, and neuromuscular blocking agents.

Anaphylaxis is mediated by a variety of mechanistic pathways including (1) IgE-mediated anaphylaxis, (2) non–IgE-mediated anaphylactoid reactions, (3) alteration in the cyclooxygenase (COX) and lipoxygenase pathways, and (4) mast cell activating disorders.[28,29] The effects of some drugs can be mediated by multiple mechanisms—for example, antibiotics, biologics, NSAIDs, and vaccines can lead to anaphylaxis via IgE mediated allergic reactions, but aspirin and NSAIDs will also exert their effects through non-IgE leukotriene-mediated mechanisms. In the United States, antimicrobials have been implicated as the cause of 0.7% to 10% of cases of severe bronchospasm, and penicillin remains the most important cause of anaphylaxis, accounting for up to 75% of cases annually.[30]

■ Constrictive Bronchiolitis

Constrictive bronchiolitis causes adverse lung reaction relatively infrequently. Agents that have been reported to cause small airway inflammation (bronchiolitis) include medications used in the treatment of RA, such as D-penicillamine and gold salts.[12] Interpretation of earlier literature on D-penicillamine and gold-induced bronchiolitis is complicated by the fact that RA itself can cause bronchiolitis.[31] Use of these agents has been largely supplanted by disease-modifying antirheumatic drugs, immunosuppressants, and biologics, but these implicated agents may still be used in certain cases. Drug-induced bronchiolitis typically causes shortness of breath, with or without wheezing, and cough. Spirometry may not detect small airway disease until obstruction is severe, but high-resolution CT imaging protocols may show centrilobular nodules and/or tree-in-bud opacities, as well as mosaic attenuation of the lung parenchyma, reflective of air trapping.[32]

■ Pulmonary Hypertension

Pulmonary hypertension is a relatively infrequent complication of drug therapy, but because of the subtlety of the onset of disease, paucity of symptoms until significant vascular compromise has occurred, and potential for eventual vascular collapse and death, it is critical to recognize drug-induced pulmonary hypertension early in its course. Among the drugs known to cause pulmonary hypertension are dasatinib, amphetamines, methamphetamines, cocaine, anorexigens, and toxic contaminants of food and nutritional supplements (e.g., rapeseed oil and tryptophan).[33]

The association of appetite suppressants with pulmonary hypertension dates to the late 1970s when reports of unexplained "primary" pulmonary hypertension were first published. The "epidemic" of pulmonary hypertension was linked to the use of aminorex fumarate, an amphetamine-derived appetite suppressant that came into use because its potential for addiction and abuse was lower than that of amphetamine. The use of aminorex was associated with a significant rise in the incidence of pulmonary hypertension, primarily among women in Germany, Austria, and Switzerland. Development of disease occurred as early as weeks to months from the onset of use of the drug, with a dose-dependent risk as high as 2 in 100. The mechanism of action on the pulmonary vasculature is through the release of catecholamines, including dopamine. The epidemic subsided as use of the drug declined.

Another amphetamine derivative, fenfluramine, was introduced as an appetite suppressant in the European market in the 1960s and the U.S Market in the 1970s. It was withdrawn from the U.S market in 1997 due to the association with excess rates of pulmonary hypertension and valvular heart disease, but remains relevant today because these adverse effects can be long lasting. The mechanism by which anorexigen drugs cause pulmonary hypertension is likely by acting as indirect serotonin (5-HT) receptor antagonists, inhibiting 5-HT reuptake and causing release of 5-HT from platelets. 5-HT in turn mediates vasoconstrictive responses in the pulmonary vasculature, and stimulation of 5-HT transporter expression leads to hyperplasia of pulmonary artery smooth muscle cells.[33]

Two landmark reports supported a causal relationship between pulmonary hypertension and the use of fenfluramine and dexfenfluramine. The first was published in 1993, describing a cohort of young to middle-aged users of the anorexigens who developed pulmonary hypertension indistinguishable from idiopathic primary arterial pulmonary hypertension.[34] This was followed in 1996 by the findings of the International Primary Pulmonary Hypertension Study Group, which published a case-control series of 95 patients with pulmonary arterial hypertension.[35] An odds ratio (OR) of 23.1 for development of disease was found among those who had used an anorexigen for more than 3 months, with an estimated incidence of 1 to 2 cases per million users per year. Fenfluramine was withdrawn from the market in 1995 due to its association with increased risk for pulmonary hypertension, as well as its role in the development of valvular heart disease in users of the fenfluramine–phentermine combination anorexigen known as "fen-phen."[36]

Epidemics of pulmonary hypertension also have been reported due to contaminants in a specific manufacturer's rapeseed oil in Spain, and from use of an over-the-counter L-tryptophan preparation that resulted in the eosinophilic myalgia syndrome, characterized by a systemic syndrome that included acute lung injury and pulmonary hypertension.

The use interferon-α and interferon-β in the treatment of hepatitis C and multiple sclerosis has been associated with the development of pulmonary hypertension likely through the release of endothelin 1.[37,38]

TOXICITY ASSOCIATED WITH SELECTED DRUGS

The following drugs have been selected for discussion because (1) they are very commonly used, (2) have important forms of toxicity associated with their use, or (3) have more recently entered into our pharmacologic armamentarium and, therefore, are likely associated a lower level of awareness of their potential toxicity to the respiratory system.

■ Cardiovascular Drugs

Below we consider cardiovascular drugs that are well recognized to be associated with pulmonary toxicity.

Amiodarone

Adverse reactions to amiodarone have been reported in a variety of tissues, including the lung, liver (liver function abnormalities and increased tissue attenuation on radiographic imaging), thyroid (thyrotoxicosis), skin (discoloration), and cornea.

Amiodarone is an iodinated, benzofuran-derivative antiarrhythmic used for management of life-threatening supraventricular and ventricular arrhythmias. Both amiodarone and its major metabolite, N-desethylamiodarone, are cationic, amphiphilic compounds with high lipid solubility, causing the drug to accumulate in tissues with high lipid content including adipose tissue, thyroid, liver, and lungs. The elimination half-life of amiodarone is 30 to 100 days, and the drug has been found in lung tissue as long as 1 year after discontinuation of therapy. These pharmacokinetic characteristics contribute to the drug's potential toxicity and impact treatment strategies since the toxic effects of the drug can persist even after discontinuation.

One of amiodarone's biochemical effects is to impair normal phospholipid catabolism by phospholipases, thereby leading to cellular phospholipidosis. The accumulation of phospholipids in the cell may cause direct cellular injury, and evidence supports cellular injury through production of the unstable aryl radical as amiodarone is deiodinated, leading to reactive oxygen species formation and cell death. Direct cellular injury affects type 2 pneumocytes, endothelial cells, and fibroblasts, and immune-mediated hypersensitivity further contributes to the lung tissue injury.[39] The impairment of phospholipid metabolism results in the lamellar inclusions and lipid-laden foamy macrophages that characterize the histology seen on lung biopsy and BAL. These findings are characteristic of amiodarone exposure and are not indicative of toxicity unless accompanied by the lung injury patterns discussed below.

The first reports of amiodarone pulmonary toxicity were published in 1980 and were followed by larger series of patients as amiodarone was tested in the United States in the early-to-middle 1980s. Based on two studies published in 1987, the clinical picture of amiodarone pulmonary toxicity emerged as a syndrome of pulmonary infiltrates and respiratory symptoms, most often cough and dyspnea of subacute or chronic onset, accompanied by fever, malaise, and chest discomfort in 50% of those affected. In one series, 11 of 171 patients (6.4%) treated with 400 to 1200 mg of amiodarone developed pulmonary disease; in another series, 15 of 154 subjects (9.7%) developed disease.[40–42] The time from initiation of therapy to development of symptoms was 61 to 465 days in one series and 30 to 720 days in the other. Subsequent reports have supported these initial observations.

Disease Prevalence and Risk Factors for Amiodarone Toxicity Amiodarone toxicity is estimated to occur in 10% of patients who have used the medication for 1 year, and the cumulative prevalence may be as high as 5% to 10% over years of drug use.[12] Predisposing risk factors for the identification of amiodarone pulmonary toxicity include older age, duration of therapy for >6 months, higher daily dosages, male gender, renal disease, and pre-existing lung disease.[43] The risk of pulmonary toxicity roughly correlates with daily dose, and most reports of amiodarone toxicity have been of patients receiving doses greater than 400 mg daily. In one series, 0.1% to 0.5% of patients on 200 mg per day developed amiodarone pulmonary toxicity, while as many as 50% of those using the highest dosages (e.g., 1200 mg per day) were affected.[44] The lower doses of amiodarone that are more commonly used are considered to be safer than higher doses; however, toxicity has been reported at doses as low as 200 mg per day.

Pre-existing lung disease may enhance the risk of toxicity. It is not entirely clear whether there is higher incidence of toxicity in those with pre-existing lung disease, or if prior disease results in earlier perception of symptoms and scrutiny for pulmonary causes of dyspnea. The AFFIRM (Atrial Fibrillation Follow-up of Rhythm Management) trial reported a higher risk of diagnosis of amiodarone lung toxicity if the patient had pre-existing pulmonary disease; however, there was no higher risk of either pulmonary death or all-cause mortality.[45] Patients with atrial fibrillation treated with amiodarone in the setting of chronic obstructive pulmonary disease (COPD) had a hazard ratio of 2.53 (2.2–2.89) compared to those without COPD.[43] It is considered acceptable to use amiodarone in the setting of pre-existing lung disease if vigilance is maintained for the development of symptoms suggestive of amiodarone toxicity.

The North American Society of Pacing and Electrophysiology has offered general guidelines for management and monitoring of patients on amiodarone, acknowledging that the long half-life (~100 days) makes organ toxicity potentially more severe and difficult to reverse. The Society recommends follow-up every 3 months for the first year of use, and subsequently every 6 months. Baseline pulmonary function testing is recommended for those with underlying lung disease along with careful follow-up, but baseline testing may be omitted if the patient has no known lung disease and no chronic respiratory complaints.[46]

Amiodarone is frequently used in the setting of thoracotomy perioperatively to prevent and treat atrial fibrillation. Earlier literature reported a retrospective analysis of 552 patients undergoing lung resection or pneumonectomy in which there appeared to be an 11% rate of acute lung injury ARDS among patients treated with amiodarone compared with 1.8% among those who were not treated with the drug.[47] Several authors have suggested that amiodarone pulmonary toxicity may be triggered by administration of high concentrations of supplemental oxygen, or that oxygen may act in synergy with amiodarone to enhance cellular injury. However, confounding variables have not always been well characterized in the reported cases of possible acute lung toxicity, and a more recent large meta-analysis (1075 patients, 5 randomized controlled studies) did not find a significant incidence of acute amiodarone pulmonary toxicity in the perioperative thoracic surgery setting.[48] The Society of Thoracic Surgeons practice guidelines for management of atrial fibrillation in the setting of thoracic surgery recommend caution in using amiodarone in patients undergoing pneumonectomy, but grade the evidence for this recommendation only as level C.[49]

Clinical means of decreasing the risk of amiodarone toxicity have not been well characterized. Dronedarone hydrochloride, an amiodarone-like antiarrhythmic, was developed to decrease the risk of pulmonary toxicity by the addition of a methyl sulfonyl group. However, several cases of dronedarone pulmonary toxicity are reported, with the earliest onset 2 weeks after initiation of dronedarone with ground-glass opacities and consolidation suggestive of OP, and other cases occurred at 1 month after drug initiation with ground-glass opacities on imaging and DAD on biopsy, and diffuse interstitial infiltrates with a subpleural predominance and fibroblastic foci histologically.[50,51] In some case reports the subjects had been on amiodarone immediately prior to initiation of dronedarone, and implication of the latter drug is less confident. A protective effect of ACE inhibitors against amiodarone pulmonary toxicity is supported in several publications.[52,53]

Clinical Presentation of Amiodarone Toxicity The typical clinical presentation of amiodarone pulmonary toxicity is a nonproductive cough and dyspnea, sometimes accompanied by pleuritic chest pain, fever, malaise, and/or weight loss. Symptom onset is most often 6 to 24 months into treatment (100 to 150 g cumulative dose) but can range from a few days to 10 years into therapy. Most subjects have an insidious onset of symptoms over several months, but fatal amiodarone-induced pulmonary toxicity occurring 2 weeks into therapy has been reported.[39]

The earliest abnormality identifiable on pulmonary function testing of affected individuals is impairment in diffusing capacity for carbon monoxide (DL_{CO}). There may be an accelerated decline in the DL_{CO} as the disease progresses, accompanied by mild restrictive physiology. Since a low DL_{CO} is not specific for amiodarone toxicity, a decline should not necessarily prompt discontinuation of the drug but should trigger evaluation for other cause(s) of the impairment.

Radiographic and Histologic Findings of Amiodarone Toxicity The radiographic and histologic findings associated with amiodarone pulmonary toxicity are not stereotypic and may include acute, subacute, and chronic interstitial pneumonia, OP, DAD, pulmonary fibrosis, single or multiple nodules, eosinophilic pneumonia, or diffuse alveolar hemorrhage.[12] Typical radiographic findings in patients with subacute or chronic onset of disease are diffuse or patchy, interstitial or mixed alveolar–interstitial infiltrates, which are either bilateral or unilateral (Fig. 65-1). Mild cases of toxicity may be characterized by a diffuse ground-glass pattern on HRCT, often in a peripheral, subpleural distribution. Focal and patchy areas of higher attenuation may be superimposed on the ground-glass opacification. Alveolar opacities may correspond to areas of OP that are indistinguishable from idiopathic OP. Amiodarone toxicity should be considered in cases of migratory infiltrates that are consistent with OP but that are poorly responsive to steroids. Amiodarone-induced fibrosis occurs in 5% to 7% of patients diagnosed with amiodarone pneumonitis and may be present at disease presentation. Honeycombing is rare. The most common histology observed is subacute or chronic ILD, often consistent with nonspecific interstitial pneumonia. There are also many reports of OP, pulmonary fibrosis, and DAD/ARDS, and

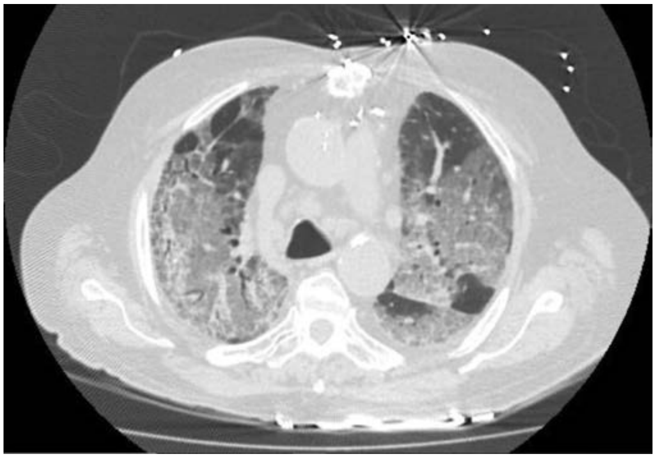

Figure 65-1 Amiodarone lung toxicity. ARDS superimposed on mild underlying fibrosis at 3 months after initiation of amiodarone in an 80-year-old man with progressive dyspnea. Dyspnea began insidiously approximately 1 month after amiodarone load.

fewer reports of solitary or multiple nodules (which can be fluorodeoxyglucose [FDG]-avid on PET imaging). Eosinophilic pneumonia and diffuse alveolar hemorrhage are more rare.[12]

Laboratory Analysis in Amiodarone Toxicity Laboratory analyses have little utility in the diagnosis of amiodarone-associated lung toxicity. Common laboratory abnormalities are nonspecific and include mild leukocytosis and elevation in serum lactate dehydrogenase (LDH). Earlier trials of amiodarone identified elevated sedimentation rates (range of 39–150 mm/h) in 9 of 11 patients with pulmonary toxicity, but nonspecificity of the ESR makes this test less useful in the clinical setting.[40] Identification of brain natriuretic peptide (BNP) that is normal, or at a patient's baseline, may be useful in distinguishing pulmonary causes of dyspnea from congestive heart failure.

Diagnostic Evaluation and Management of Amiodarone Toxicity The challenge to the practitioner considering the diagnosis of amiodarone pulmonary toxicity is that the differential diagnosis is broad for dyspnea with pulmonary infiltrates in patients with known cardiac disease. Cardiogenic and noncardiogenic etiologies must be excluded. Consideration must be given to cardiac conditions, including ischemic and nonischemic cardiomyopathies, diastolic dysfunction, mitral valve disease, aortic stenosis, and atrial fibrillation. Noncardiogenic causes may include infections; the broad range of idiopathic interstitial pneumonias; malignant causes of infiltrates (e.g., lymphangitic spread of tumor or lymphoma); systemic diseases such as sarcoidosis, amyloidosis, or autoimmune disease; exposures to inhaled agents (e.g., occupational inorganic dust exposures, or organic inhalations, with subsequent development of hypersensitivity pneumonitis); and exposures to drugs apart from amiodarone.

The risks of invasive workup must be weighed against those of empiric therapy, which includes drug discontinuation and, possibly, corticosteroids. BAL may reveal a lymphocytosis, often with a predominance of CD8+ lymphocytes, reflective of a lymphocytic alveolitis. This finding, however, is not consistently reported, and some affected individuals may have elevated BAL neutrophils as well. Significant BAL eosinophilia is rare. Abundant alveolar macrophages with a "foamy" cytoplasm, indicative of undigested phospholipids, are found in all subjects chronically exposed to amiodarone and are not indicative of pulmonary toxicity per se. Hemosiderin-laden macrophages are infrequently found, since alveolar hemorrhage is rare. As the BAL findings are neither sensitive nor specific for amiodarone pulmonary toxicity, the role of BAL in the diagnosis is to exclude other causes of the clinical picture, especially infection.

Lung biopsy findings, however, may support the diagnosis of amiodarone toxicity. Earlier reports of amiodarone pulmonary toxicity describe DAD of variable severity in all affected subjects. Those more severely affected had evidence of acute DAD, with abundant hyaline membranes and reactive type II pneumonocytes lining the alveoli, while others showed organizing DAD with interstitial and intra-alveolar proliferation of fibroblasts and prominent type II pneumocytes. All cases had abundant "foamy" macrophages in the alveolar spaces. The foamy appearance of the cytoplasm is due to the presence of lamellar bodies (~1 μm in diameter) containing lipid particles, reflecting the disrupted lipid metabolism caused by amiodarone.

The diagnosis of amiodarone pulmonary toxicity is supported by the presence of lamellar bodies in macrophages, pneumocytes, bronchiolar epithelium, and/or endothelial cells, but the diagnosis is more confidently made if there are interstitial lymphocytic infiltrates and diffuse lymphoid hyperplasia, and in some cases follicular bronchiolitis, eosinophilic infiltrate or poorly formed granulomas.[54] Despite the early reports, few patients with amiodarone pulmonary toxicity have DAD pathologically unless they fit the clinical picture of ARDS. Alveolar hemorrhage may be present, but it is not a common feature of amiodarone toxicity.

In contrast to other types of drug-induced pulmonary toxicity, resolution of amiodarone-induced toxicity often does not occur with discontinuation of the drug alone. Amiodarone becomes sequestered in tissues, and the clearance of drug is typically prolonged. Depending on the severity of respiratory symptoms, practitioners often may need to treat affected patients with corticosteroids. Specific dosages of prednisone have not been studied for efficacy, but 0.5 to 1 mg/kg is a reasonable starting point in most cases. Due to the pharmacokinetic characteristics of amiodarone, the required duration of therapy may be several months, and recrudescent disease after tapering of corticosteroids is not uncommon.

β-Adrenergic Receptor Blockers

The most common adverse effect of β-adrenergic blockers on the respiratory system is precipitation of bronchospasm in asthmatics and patients with reactive airway disease. The high frequency of clinically significant bronchospasm in hypertensive asthmatics treated with nonselective β-adrenergic blockers, such as propranolol, requires that these agents be avoided in asthmatics. β1-Receptor–selective agents and the α- and β-receptor blocker labetalol are better tolerated but should be used with considerable caution in asthmatics. The use of β-adrenergic blockers is not contraindicated in patients with COPD. Many individuals with COPD tolerate β-adrenergic blockers without significant decrement in their lung function. Patients with COPD who have clinical or spirometric evidence of airflow obstruction responsive to bronchodilators should be observed carefully for bronchospasm upon initiation of these agents. Overall, the cardiac benefit of β-blockade in these subjects likely outweighs any risk.

Pulmonary parenchymal injury associated with the use of β-adrenergic blockers is not common, but it warrants mention because of the ubiquitous use of these agents. Subacute interstitial infiltrates, PIE, and pulmonary edema have been reported in conjunction with the use of acebutolol, propranolol, labetalol, nadolol, and pindolol. Thus, the clinician should be vigilant for these reactions from using β-adrenergic blockers as a class. SLE has been reported with the use of acebutolol, propranolol, labetalol, and pindolol.

Hydralazine

Hydralazine-induced pulmonary disease is not common, but it can be associated with systemic autoimmune disease that is potentially fatal even when recognized.[55,56] Half of the patients on daily doses of greater than 200 mg have a positive ANA, but only 10% of these patients develop clinical symptoms. The most important reported complication of long-term use of hydralazine is drug-induced SLE, which occurs more frequently if daily dosing is greater than 200 mg or the cumulative dose exceeds 100 g. In addition, there have been cases of pulmonary–renal syndrome associated with the use of hydralazine.[55,57,58] Pleuropulmonary manifestations occur in 30% of affected subjects, and isolated pulmonary parenchymal disease is rare. Subacute ILD/NSIP, OP, and DAH also have been documented.

Hydrochlorothiazide

The most commonly reported pulmonary side effect of the diuretic hydrochlorothiazide (HCTZ) is noncardiogenic pulmonary edema or ARDS.[59] Pulmonary edema was first reported in 1968 as a potentially life-threatening complication of HCTZ use. The onset of symptoms is typically acute and less often occurs later in the course of HCTZ use. Typical symptoms and signs include acute dyspnea and hypoxemia; fever, tachycardia, hypotension, and shock may accompany the dyspnea. Immunologically mediated capillary leak has been suggested as a possible mechanism of action. IgG deposition in the alveolar membrane and elevated serum IgM have been reported.

Management is supportive, and symptom resolution typically occurs in a few days. Rechallenge with HCTZ can cause recrudescent pulmonary edema and is not recommended. Since HCTZ is a widely used diuretic, frequently used in patients with cardiovascular disease who are prone to pulmonary edema, the true incidence of drug-induced noncardiogenic pulmonary edema may be underreported.

Statins

In light of the wide use of statins (3-hydroxy-3-methylglutaryl coenzyme A [HMG-CoA] reductase inhibitors), there have been a number of investigations into their potential to cause lung injury. Clinicians are more familiar with the well-reported myositis and hepatotoxicity associated with statins than they are with pulmonary side effects. Lung injury has been reported in conjunction with the use of various statin compounds and may be a class effect, but the data are conflicting. A study published in 2008 pulled events from the U.S. Food and Drug Administration adverse event reporting database (FDA-AER) through 2007 and reviewed case reports in the literature. In all, 162 events were reported as statin-induced ILD, and the authors estimated that for every 10,000 adverse events associated with statins between 1 and 40 events could be ILD.[60] The prevalence of interstitial lung abnormalities (ILA) was examined in 2207 subjects in the COPDGene cohort, and it was noted that statin use was associated with the presence of interstitial abnormalities of CT imaging: of the patients with ILA, 38% were on statins and 27% of patients without ILA were using statins.[61] While these studies generated interest, neither proved causality.

The case reports in the literature suggest that the latency and radiographic and histopathologic pleuropulmonary manifestations associated with statins are variable. The reported latency of onset ranged from 1 week to 120 months (mean, 34 months; SD, ± 35 months), and the most common presenting complaints were nonspecific: dyspnea, cough, and fever. The radiographic findings may include ground glass and alveolar opacities that are diffuse in distribution, sometimes with patchy consolidation, interstitial infiltrates or fibrosis; pleural effusion is reported, but is rare.[62–64] Analysis of BAL fluid shows no characteristic predominant cellular profile. Foamy macrophages suggesting pulmonary phospholipidosis have been observed in some but not all cases. When obtained, biopsies demonstrate histopathology consistent with NSIP or hypersensitivity pneumonitis. Resolution of presumed statin-induced lung disease has been achieved with drug discontinuation, with or without corticosteroid therapy.

A subsequent study has lessened the concern for statin-induced lung injury. A nested case-control analysis of a cohort of 1.4 million patients in the Quebec health administrative database (1990–2005) identified 6665 possible cases of statin-induced ILD and compared them with matched controls.[65] After adjusting for comorbidities and confounders, there was no association found between statin use and incidence of ILD.

■ Anticonvulsants

Various types of pulmonary injury may result from exposure to phenytoin. Among the reported patterns of injury are pulmonary hypersensitivity reactions, which may be a component of systemic hypersensitivity (see the prior discussion of DRESS), or hypersensitivity pneumonitis without systemic manifestations.[66] In some cases, parenchymal infiltrates are accompanied by peripheral blood eosinophilia, suggesting chronic eosinophilic pneumonia.[67] Lymphocytic interstitial pneumonitis and OP have been described as well.[12]

■ Anti-inflammatory and Immunomodulatory Agents

A variety of anti-inflammatory and immunomodulatory agents have been associated with pulmonary toxicity.

Aspirin and Nonsteroidal Anti-inflammatory Drugs

The most common pulmonary adverse reaction associated with aspirin use is bronchospasm, which may occur with therapeutic dosing in aspirin-sensitive individuals. Aspirin and NSAIDs induce bronchoconstriction by diverting arachidonic acid metabolites toward the lipoxygenase metabolic pathway, thereby leading to enhanced leukotriene-mediated airway inflammation and bronchoconstriction. Less commonly reported pulmonary complications of aspirin use include PIE syndrome, DAH, pulmonary hypersensitivity, vasculitis, and ARDS.

Acute salicylate poisoning produces symptoms of central nervous system toxicity (tinnitus, vertigo, nausea, vomiting, and hyperventilation) in mild to moderate overdose, and it may result in coma, severe metabolic acidosis, and noncardiogenic pulmonary edema with critical overdoses. Pulmonary edema occurs in as many as 20% to 30% of patients with severe salicylate poisoning and may result in respiratory failure, often exacerbated by severe metabolic acidosis. Risk factors for salicylate toxicity include increased age and chronic aspirin ingestion. Management of severe toxicity includes supportive intensive care and sodium bicarbonate infusion to promote drug excretion.

NSAIDs are widely used and generally well tolerated. However, NSAIDs may cross-react with aspirin, producing a variety of allergic and pseudoallergic reactions affecting upper and lower airways. NSAIDs cause bronchospasm in susceptible individuals with symptoms ranging from mild to severe. NSAIDs also cause anaphylactic reactions through the same mechanism as that for aspirin. Eosinophilic pneumonia is also reported as an NSAID class effect with most cases in the literature associated with naproxen, but also with fenbufen, ibuprofen, and diclofenac.[14,68] The onset of symptoms is typically acute with in the first days of therapy, and resolution may require corticosteroids if the reaction is severe.[68]

The bleeding tendency induced by NSAIDs is well known, and reports exist of pulmonary hemorrhage associate with their use.

■ Nonbiologic Disease-Modifying Antirheumatic Drugs

The task of determining whether the presence of ILD in the setting of rheumatoid arthritis (RA) is due to new-onset RA-ILD, exacerbation of pre-existing ILD, or induction of ILD due to exposure to nonbiologic or biologic disease-modifying antirheumatic drugs (DMARDs) has made clinical management of pulmonary disease in these patients extremely challenging. A systematic review of a case series between 1975 and 2013 makes note that due to the absence of pathognomonic findings to prove drug-induced ILD, causality often is difficult to ascertain despite a time of symptom onset and clinical features that suggest drug induced-ILD.[69] Case reports and series are useful to characterize the drug-associated lung disease but give us few clues to the actual incidence of disease among users of specific medications. Overall, the incidence of pulmonary toxicity due to nonbiologic and biologic DMARDs is low even among patients with pre-existing lung disease, but the incidence of infections among treated patients is considerable. A recent case series describes a cohort of 1129 patients with RA, 87 (7.7%) of whom had lung involvement. The subjects with lung involvement were followed over a period of 6.7 ± 4.1 years. Only 2 cases of MTX lung toxicity were reported (3.1% of the treated RA-lung disease cohort), and there were no cases of rituximab-associated lung injury among the 26 RA-ILD patients using this medication.[70] Importantly, over the follow-up period, 22 patients (25.3%) developed respiratory infections requiring hospitalization, illustrating the importance of vigilance for infection among patients with RA-associated lung disease.

Methotrexate

Methotrexate (MTX) is the nonbiologic DMARD most frequently appearing in reports, with fewer reports of leflunomide, sulfasalazine, gold, and azathioprine lung toxicity.[69] MTX is a dihydrofolate reductase inhibitor used as an anti-inflammatory and immunosuppressant, as well as a chemotherapeutic agent when used in higher doses. Despite the availability of newer antirheumatic drugs, MTX has retained its position as a first-line DMARD for the management of RA. MTX affects cell replication through inhibition of dihydrofolate reductase, the enzyme that converts folic acid to its active coenzyme, tetrahydrofolate, allowing it to serve as a one-carbon carrier in the synthesis and repair of DNA. The major nonpulmonary side effects of MTX correlate with the degree of folate deficiency and can be mitigated through folate replacement. In contrast, pulmonary toxicity does not correlate with folate deficiency and may be seen at doses as low as 7.5 mg/week, a conventional starting dose for treatment of RA. Conditions that have been identified as risk factors for MTX lung toxicity include diabetes mellitus (OR, 35.6), hypoalbuminemia (OR, 19.5), rheumatoid pleuropulmonary disease (OR, 7.1), chronic kidney disease, previous use of other disease-modifying agents (e.g., gold, sulfasalazine, penicillamine), genetic predisposition (HLA-A31:01), male sex, and older age (OR, 5.1).[71,72]

MTX-induced pulmonary toxicity typically occurs within the first 2 years of treatment, but it can occur as early as 1 month into therapy. Pulmonary symptoms are most often subacute in onset, presenting over days to weeks, and include dyspnea, cough, fever, and less frequently, chest pain (<10%).[73] Symptoms may also develop acutely.[74] Radiographic changes are interstitial and bilateral in the majority of cases with features consistent with NSIP, or a mixed alveolar–interstitial pattern that may appear with ground-glass opacities on CT imaging.[73] Radiographic features less commonly appear as nodular consolidation, suggesting OP or a bronchiole-centric (tree-in-bud) pattern.[72] Fibrotic changes are less common. Laboratory testing is nonspecific, but a mild peripheral blood eosinophilia may occur in 20% to 40% of patients with subacute pulmonary toxicity.[72]

Diagnosis is challenging in with RA and suspected MTX-induced pulmonary toxicity, because similar clinical presentations may occur as a manifestation of RA itself. The most important diagnosis to exclude is infectious pneumonia, including that from opportunistic organisms. A diagnosis of MTX-induced lung disease is suggested by a predominance of lymphocytes, rather than neutrophils, on BAL.[75,76] The lymphocytic BAL fluid of MTX-induced hypersensitivity pneumonitis often has a CD8-predominant profile (low CD4:CD8 ratio), but not exclusively so. It appears that the type of inflammatory cells may predict disease severity and acuity. In one study of 56 cases of MTX pulmonary toxicity, a lymphocyte-predominant BAL fluid was associated with late onset of symptoms (>6 months from drug initiation) and lower mortality than in those with neutrophil-predominant BAL.[77] Histopathology is varied and may demonstrate ill-formed granulomas suggestive of hypersensitivity pneumonitis, NSIP, OP, or DAD in cases of acute toxicity.[72] PIE syndrome also has been reported.[99]

As with other pulmonary toxicities, prompt drug withdrawal is critical; resolution of lung injury follows in most patients. Overall fatalities have been reported in earlier series to be as high as 17%, and it appears that acute and subacute onset is associated with higher mortality.[77] Corticosteroids may accelerate recovery in those with severe disease or symptoms refractory to drug withdrawal alone. Rechallenge with methotrexate is generally not recommended, but rechallenge has been tolerated in some, arguing against hypersensitivity as the mechanism of injury in certain subjects.

Leflunomide

Use of leflunomide as a DMARD began in the late 1990s. The incidence of leflunomide lung toxicity is not as high as that associated with MTX, but concerns for leflunomide-induced lung injury have been present since its earliest use. If interstitial lung injury occurs in the setting of leflunomide use, it typically occurs within 20 weeks of initiation of the medication, and in those with underlying ILD, pneumonitis developed earlier, within 12 weeks of use.[78] Radiographic findings are variable and most commonly include bilateral ground-glass opacities and/or interstitial infiltrates.

Data from a postmarketing analysis were published by Japanese investigators from a large cohort of 5054 patients with RA treated with leflunomide.[79] Based on clinicians' diagnosis, 61 patients (1.2%) developed ILD or had exacerbation of pre-existing ILD, and there were deaths reported within the cohort. The cohort spans a time period before and after the manufacturer imposed a safety notice in leflunomide labeling, suggesting that there was an increased risk of adverse pulmonary effects among patients with pre-existing ILD. The rate of lung adverse events dropped after the warning was issued and fewer patients with pre-existing ILD were treated with leflunomide. The rate of progressive ILD among those without pre-existing ILD was only 0.7% overall compared with an incidence rate of 6% among those with pre-existing ILD (OR, 8.17) before warnings were issued. Additional risk factors for leflunomide lung toxicity identified in this cohort included male sex, age ≥60 years, low body weight (<40 kg), smoking history, and initial use of a loading dose of leflunomide.[79] Similarly a cohort of 1010 patients with RA treated with leflunomide had 10 cases of ILD occurring overall, with a significantly higher incidence among those with pre-existing ILD, emphysema, or tuberculosis.[80] It has been noted with interest that the reported incidence of leflunomide-associated ILD appears to have been higher in Japan and Korean cohorts compared with Western subjects, but the reasons for the disparity are not clear. The prevalence of pre-existing ILD was high in the Japanese cohort (14.7%), and this alone may account for the reported differences.[79] The possibility of genetic predisposition to RA-ILD or leflunomide-induced ILD has been hypothesized but by no means proven. Subsequent analyses have suggested that the apparent risk of leflunomide toxicity is more likely due to channeling bias; the use of the drug is channeled to high risk patients, many of whom had pre-existing RA-ILD or history of MTX use.[81] A recent meta-analysis of double-blind, randomized, controlled studies of adult RA patients treated with leflunomide compared with other DMARDs (predominantly MTX) found no excess risk of lung toxicity associated with the use of leflunomide, nor was there increased risk of infections.[82]

The use of leflunomide is warranted in appropriate patients with vigilance for pulmonary adverse effects, especially among those with pre-existing lung disease.

Sulfasalazine and Mesalamine

Sulfasalazine is used as a DMARD and also is commonly employed in the treatment of inflammatory bowel disease, as is mesalamine (also known as mesalazine). Both agents are 5-aminosalicylates and have similar pulmonary adverse effect profiles. Sulfasalazine and mesalamine are among the drugs that most commonly induce eosinophilic pneumonia.[14,83] Mesalamine has been associated with eosinophilic pneumonia when taken orally and when used as a suppository.[84] In addition to causing eosinophilic pneumonia, sulfasalazine has been reported to cause OP and NSIP.[12,85,86] There is one report of the development of sarcoid-like granulomatous hilar adenopathy in a patient with inflammatory bowel disease treated with sulfasalazine.[87] OP has been associated with mesalamine, as has hypersensitivity pneumonitis.[88,89]

D-Penicillamine

D-Penicillamine is used as an anti-inflammatory agent traditionally used in the management of RA, systemic sclerosis, primary biliary cirrhosis, lead poisoning, and Wilson's disease. D-penicillamine is a heavy metal chelating agent that has inhibitory effects on T lymphocytes, impairs fibroblast proliferation, and decreases levels of rheumatoid factor and immune complexes. Although currently used less frequently than first-line DMARDs, one still sees it used in the treatment of Wilson's disease and its pulmonary manifestations are important to recognize, as mortality from D-penicillamine pulmonary toxicity can be high.

Pulmonary toxicity ascribed to D-penicillamine is primarily reported in the older literature and includes pulmonary–renal syndrome with diffuse alveolar hemorrhage (DAH), obliterative bronchiolitis, acute interstitial pneumonitis, and hypersensitivity pneumonits.[90–92]

D-penicillamine is widely recognized as a cause of a number of autoimmune conditions, as well as nephrotic syndrome and rapidly progressive glomerulonephritis. It is less frequently a cause of a pulmonary–renal syndrome, with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis and in some reports a clinical presentation similar to Goodpasture syndrome.[92–94] The pulmonary–renal syndrome occurs infrequently among patients on penicillamine therapy for rheumatic disease and is reported more often for those on D-penicillamine for Wilson's disease. Symptoms at presentation include cough, dyspnea, hemoptysis, and hematuria; onset has been reported from 10 months to many years after drug initiation. No definitive dose–response relationship has been defined, but there are reports of toxicity at doses as low as 300 mg per day and as high as 3.5 g per day. Coalescing, bilateral alveolar infiltrates characterize the radiographic findings, resulting in severe hypoxemia. BAL reveals an increase in the concentration of red blood cells on serial lavage and the presence of hemosiderin-laden macrophages, both of which characterize DAH. The diagnosis of D-penicillamine–induced ANCA-associated vasculitis with pulmonary renal syndrome is supported by high serum titers of antimyeloperoxidase (anti-MPO) antibodies; the presence of antinuclear antibody (ANA) is reported in 75% of cases. Although descriptions of "Goodpasture-like" syndromes due to D-penicillamine are reported, few actually had anti-GBM antibodies detected.[95]

The syndrome may progress to include respiratory and/or renal failure. Mortality from penicillamine-induced pulmonary–renal disease has been reported to be as high as 50%.

Drug withdrawal, accompanied by high-dose corticosteroids, is the cornerstone of therapy. Adjunctive treatment with plasma exchange, cyclophosphamide, and/or mycophenolate mofetil is often offered, although studies definitively supporting their use do not exist.

No specific risk factors have been identified for D-penicillamine–induced pulmonary–renal syndrome. Monitoring for subtle onset of respiratory symptoms is warranted with long-term use of D-penicillamine. It should be noted that ANCA seroconversion can occur without full manifestation of pulmonary–renal disease, and only a small proportion of those with drug-induced ANCA positivity will have clinically significant disease.[96]

■ Biologic Immunomodulatory Drugs

Immunomodulatory biologics are being used with increasing frequently for treatment of many illnesses including dermatologic conditions, inflammatory bowel disease, systemic rheumatic diseases, asthma, and malignancies. The increased use of biologics has resulted in a wide range of sequelae due to their use. Infections are common adverse events and are most frequently reported among patients on anti-TNF therapies. Clinicians are encountering a variety of autoimmune conditions that appear to be associated with the use of biologics.

The Study Group on Autoimmune Diseases of the Spanish Society of Internal Medicine has created the BIOGEAS registry of cases (*www.biogeas.org*), a compilation of the literature on cases of autoimmune diseases ascribed to the use of all categories of biologics.[97] In this registry of 12,731 cases of biologic-related toxicity reported in 2017, interstitial lung disease was less common (n = 518) than psoriasis (n = 6375), inflammatory bowel disease (n = 845), and demyelinating central nervous system disease (n = 803). The drugs implicated reflect the practice patterns at the time the registry was compiled, and we can expect the relative proportion of cases ascribed to various classes of biologics to shift based on the prevalence of their use.

Respiratory infections are the most common complications of DMARD treatment for RA-associated lung disease, most prominently seen among those on biologics. The clinician must carefully exclude infection before a diagnosis of drug-induced ILD can be considered, especially since biologics raise the risk of both acute bacterial and viral infections, as well as indolent pulmonary infections (e.g., tuberculous and nontuberculous mycobacterial and fungal). There are no specific recommended imaging or pulmonary function testing intervals, so a high index of suspicion for pulmonary sequelae of medication should be maintained, and clinical judgment should drive serial testing and invasive evaluations.

Among noninfectious pulmonary disorders associated with the use of anti-TNF therapies, interstitial pneumonitis is the most common manifestation of drug-induced disease. Interstitial pneumonitis was reported in 0.5% of 5000 Japanese subjects treated with infliximab and in 0.6% of over 7000 subjects who received etanercept.[98,99]

An analysis of 122 cases collected between January 1990 and March 2010 characterized the scope of these pulmonary adverse events associated with biologics.[100] The vast majority of cases were in patients with RA and were associated with anti-TNF medications (58 cases with use of etanercept, 56 cases in the setting of infliximab, 5 with rituximab, and 3 with adalimumab). Of these subjects, 10% had previously been prescribed other biologics and the majority had a history of use of nonbiologic DMARDS: 63% had a history of MTX use, and fewer had been treated with azathioprine (n = 5) or leflunomide (n = 3). Dyspnea was the predominant symptom of drug-induced ILD; 44% had fever and 39% had cough. Confirmatory biopsies were performed in a minority of cases with a fairly equal distribution of UIP, NSIP, and OP as the more common histopathologic patterns. In a systematic review of drug-induced or drug-exacerbated ILD among patients on biologics for RA between 1975 to 2013, there were 31 cases of TNF inhibitor–induced or –exacerbated ILD (14 with infliximab, 9 with etanercept, 5 with adalimumab, and 3 with certolizumab).[69] The same systematic review identified 5 cases of rituximab-associated lung toxicity (3 cases with concomitant methotrexate use) and 8 reports of tocilizumab associated lung toxicity, but since the precise prevalence of use of use of each drug is not known the risk associated with each agent is not determined.

Etanercept

Of the noninfectious adverse effects of etanercept therapy, sarcoid-like reactions and new-onset ILD or progression of underlying ILD feature prominently in the pulmonary literature. ILDs related to use of anti–TNF-α agents have been reported more frequently in women (3:1 female:male) often in the sixth decade. Various patterns of ILD are reported including NSIP, UIP, OP, DAD, and sarcoid-like reactions, and most have lymphocytosis on BAL (Fig. 65-2).

In a large case series of autoimmune disease induced by TNF antagonists, 24 cases of interstitial pneumonitis were noted among 233 subjects studied.[101] In a review summarizing case series and reports published between 1990 and 2010, the mean time of onset of respiratory symptoms for subjects receiving biologic was 26 weeks, with 50% of cases occurring within the first 2 months.[102]

Sarcoid-like granulomatosis has been frequently reported with the use of anti-TNF agents. Etanercept (9 cases), infliximab (5 cases), and adalimumab (1 case) have been reported to trigger sarcoid-like reactions with symptoms of cough, chest pain, and

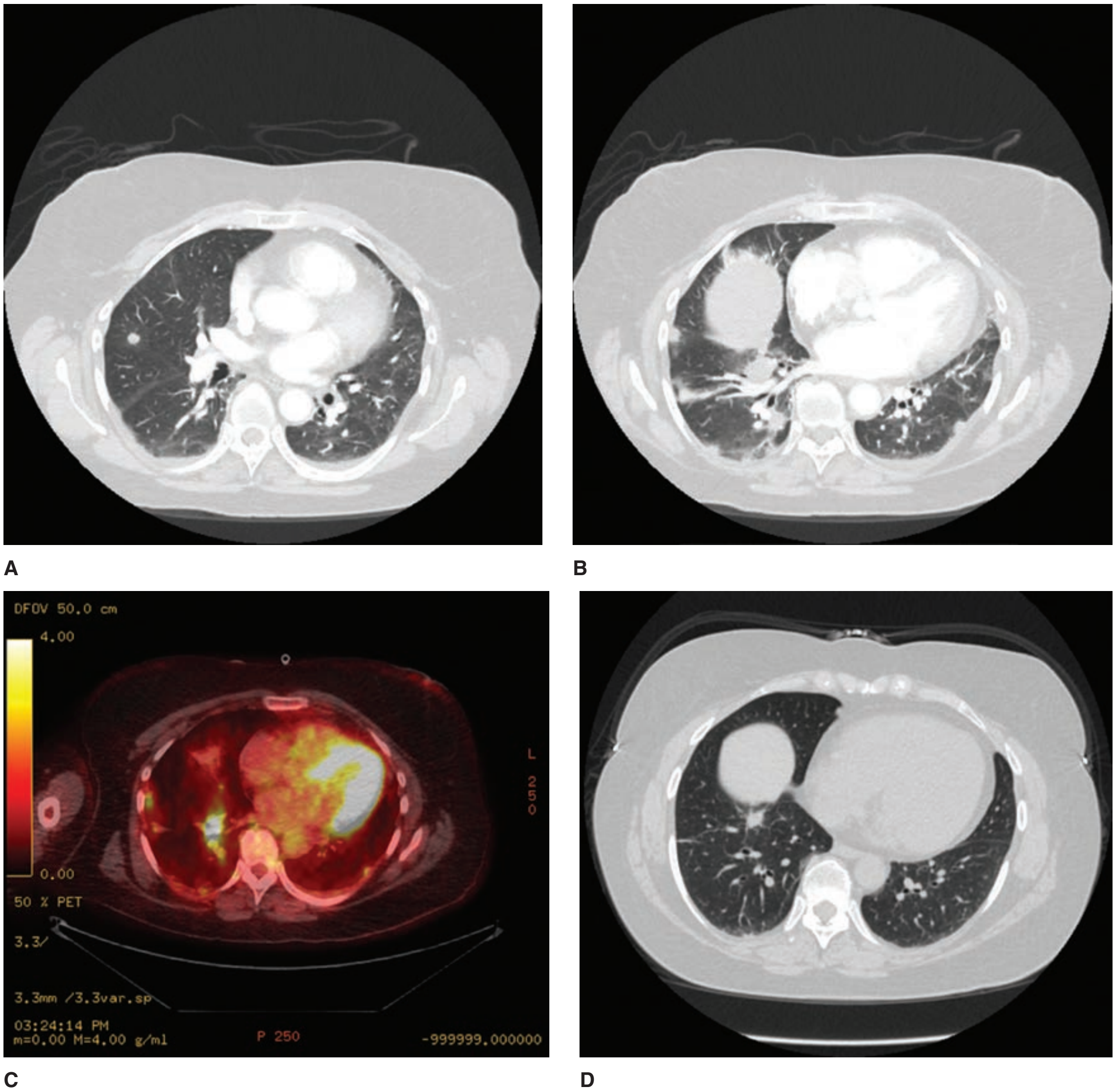

Figure 65-2 Etanercept toxicity in a 55-year-old woman with onset of pustular skin lesions 3 weeks after initiation of etanercept for psoriasis followed by dry cough, fatigue, and progressive dyspnea. **A, B.** Nodular opacities bilaterally. **C.** PET/CT showing FDG-avid nodules at same level as image **B. D.** Near-complete resolution of nodules 5 weeks after discontinuation of etanercept, and a course of prednisone.

dyspnea and lung findings most commonly including hilar and/or mediastinal adenopathy and less frequently pulmonary nodules or infiltrates.[103] Noncaseating granulomas are documented on biopsies. The subjects in whom these reactions were seen were under treatment for RA, ankylosing spondylitis, psoriatic arthritis, or juvenile idiopathic arthritis. Nonthoracic sites of sarcoid involvement were also seen as parotid enlargement, skin manifestations, and neuro-ocular disease. The sarcoidosis resolved with cessation of the drug in the majority, and in some cases corticosteroids were used. This suggests an apparently paradoxical class effect of TNF-α blockade, as these agents have been used in the treatment of refractory sarcoidosis. The mechanism of granuloma formation in the context of anti-TNF therapy is not understood but appears to derive from complex dysregulatory effects of TNF-α blockade. Among cases of sarcoid-like disease, 50% were compatible with stage 2 sarcoidosis, and two-thirds of all cases resolved with discontinuation of biologic therapy.[102]

TNF-α inhibitors, especially infliximab, have been implicated as a cause of mild lupus-like syndromes with positive ANA and anti-dsDNA, with some patients exhibiting rash, serositis, or oral ulcers, but none of the 14 patients in one series had significant respiratory system manifestations of lupus.[104] More recently the British Society for Rheumatology Biologics Register–Rheumatoid Arthritis reviewed a cohort of 12,937 of subjects started on TNF therapy compared with a biologic-naïve cohort treated with nonbiologic DMARDs (nbDMARD, n = 3673). This study found that the addition of a TNF-α inhibitor did not increase the risk of lupus-like or vasculitis-like events over the risk from nbDMARD therapy. The risk for both cohorts was calculated at 10/10,000 patient-years.[105] In one case report there was histologic demonstration of OP in small nodular opacities that appeared 16 months after etanercept as sole therapy for RA that had previously been poorly controlled with nbDMARDs.[106] The patient presented with shortness of breath and joint swelling and tenderness of her hands and wrists with a positive ANA at 1:2560, in a speckled pattern, and 1:640 in a homogenous pattern. Thus, manifestations of a lupus-like condition can be concurrent with lung toxicity, but overall, lupus-like or vasculitis-like events due to TNF-α blockade are not a major concern for the pulmonologist.

Adalimumab

Adalimumab, a TNF-α antagonist used in management of RA, also has been reported to cause pulmonary toxicity. Reports indicate lung injury occurring months to years into therapy. Patients usually present with dyspnea, cough, and radiographic and histologic findings consistent with interstitial pneumonitis and OP.[107] Acute onset of lung injury has reported within 1 h of dosing of this agent.[108] Symptoms may begin subtly as mild cough following a treatment cycle and progress with each subsequent injection. Imaging shows patchy ground-glass opacities, with or without consolidation and patchy fibrosis.[109] Patients usually require corticosteroids to achieve clinical resolution.

Rituximab

Rituximab is a CD20-directed, B cell–depleting monoclonal antibody used in the treatment of a variety of conditions including RA and RA-ILD, granulomatosis with polyangiitis, microscopic polyangiitis, systemic sclerosis, and lymphoma. A number of case reports regarding its pulmonary toxicity appear in the literature, with clinical presentations ranging from dyspnea and mild hypoxemia to fatal respiratory failure.[110] Clinical disease occurs in three different time courses, most commonly as a subacute onset of dyspnea 2 weeks following rituximab infusion, often several cycles into therapy. Radiographic imaging shows bilateral diffuse interstitial infiltrates or ground-glass opacities. Less common presentations include acute onset of ARDS within hours of first infusion of the drug and chronic, insidious onset of disease.[111] In a prospective series of 33 patients with RA treated with rituximab over 26 weeks, 22% of subjects developed subtle decline in $\mathrm{DL_{CO}}$ without respiratory symptoms, and none developed overt lung toxicity. Importantly, however, despite these reports of adverse events, rituximab has been found to stabilize or improve lung disease in patients with RA-ILD, and the safety profile is deemed to be acceptable.[70,112]

Patients who are being considered for initiation of new medications should have baseline radiologic imaging and pulmonary function testing to ascertain whether pre-existing lung disease is present. While pre-existing lung conditions are not a contraindication to therapy, patients need to be monitored for changes in symptoms that might reflect either medication-induced disease or progression of the condition for which medication is being prescribed. This is particularly relevant for RA where new or progressive RA-ILD must be distinguished from drug-induced ILD.

■ Immunosuppressants

Sirolimus and everolimus are immunosuppressive agents used in the management of patients with solid organ transplants and are used in the treatment of malignancies including breast cancer. They function as inhibitors of mammalian target of rapamycin (mTOR) and suppress organ rejection through inhibition of growth factor–induced smooth muscle cell proliferation and migration; they also inhibit T- and B-cell activation.

Sirolimus was introduced into clinical use in the late 1990s. Sirolimus-induced pneumonitis in solid organ transplant recipients is an important consideration in the differential diagnosis of dyspnea with interstitial infiltrates after exclusion of infection. Case reports of sirolimus-induced pulmonary toxicity began to appear in the literature in 2000, when the drug was first implicated as the cause of biopsy-proven bronchiolitis obliterans organizing pneumonia in a renal transplant recipient. Other case series have appeared since, with a variety of radiographic patterns including patchy peripheral consolidations consistent with OP as well as reticular and ground-glass opacities, and histology showing lymphocytic alveolitis and interstitial pneumonitis, granulomatous inflammation, alveolar hemorrhage, and/or focal fibrosis.[113,114]

A dose–response relationship is suggested for mTOR inhibitor–induced pulmonary toxicity, because dose reduction appears to ameliorate the pneumonitis. Toxicity may occur despite therapeutic serum sirolimus levels and can occur as early as 2 weeks into therapy, but it occurs more often after at least 6 weeks of therapy. The overall incidence of sirolimus-induced lung injury is 5% to 15% in solid organ transplant recipients.[115] Discontinuation of sirolimus is necessary for syndrome resolution. Complete recovery is typically achieved in all patients by 6 months.

Everolimus has been shown to cause mild, reversible pulmonary toxicity. In a large case-cohort study of renal transplant recipients on everolimus, mild lung toxicity was observed in 13 of 102 patients (12.7%).[115] The typical presentation was cough and dyspnea, and diagnosis was established at a median time of 162 (38–407) days since onset of treatment. Radiologic findings were most consistent with OP, and fewer with NSIP or a combination of patterns. All cases resolved with discontinuation of everolimus, and only 3 patients required steroids for resolution.

■ Antimicrobials

The most commonly reported respiratory syndrome for all classes of antimicrobials is pulmonary infiltrates with PIE. Among the reports of antibiotic-associated PIE syndrome are many cases of minocycline- and erythromycin-induced PIE, and fewer cases associated with penicillins, tetracyclines, sulfonamides, and cephalosporins. Cases of PIE have also been reported with the use of antituberculous drugs, including isoniazid, rifampin, and ethambutol.

Nitrofurantoin

Nitrofurantoin is one of the most commonly implicated antimicrobial agents that causes pulmonary toxicity. Although its peak usage worldwide was probably in the 1980s, it remains a widely used antibiotic for management of chronic urinary tract infections, and case reports continue to appear in the literature. Since the drug is used primary in the elderly population in whom cardiopulmonary disease is common, the differential diagnosis of respiratory compromise in this population is broad. The incidence of nitrofurantoin lung toxicity with short-term use (≤14 days) is very low; in one meta-analysis of 27 studies of 4807 patients there were no cases of pulmonary toxicity.[116] Long-term use of nitrofurantoin for prophylaxis against recurrent urinary tract infections is associated with high risk of nonsevere adverse events, and the risk of severe pulmonary toxicity appears to increase with longer duration of therapy; one meta-analysis reported only 1 case of significant interstitial pneumonitis among 511 patients, which occurred at 37 months of therapy.[117]

There is a wide clinical spectrum of respiratory disease caused by nitrofurantoin. As is the case with many types of drug-induced lung toxicity, the onset of symptoms is highly unpredictable and of variable latency. The severity of disease varies, and the histopathology is diverse. Most of the earliest reported cases of nitrofurantoin pulmonary toxicity were acute in onset, occurring within days to weeks of treatment initiation. These patients presented with fever (80%), cough (43%), dyspnea (60%), rash (20%), fatigue (12%), and arthralgias (9%). Peripheral blood eosinophilia is present in 80%.[118] As reports of toxicity have continued to populate the literature, it has become clear that subacute and chronic presentations also are common (Fig. 65-3).

Unfortunately, many cases of nitrofurantoin lung toxicity may be missed due to the long latency between the initial dose and the onset of clinical symptoms. The median time to diagnosis in one series was 4 months; however, some diagnoses were made as long as 5 years after drug initiation. Among those with chronic symptoms, the most common histopathologic pattern is that of chronic interstitial pneumonitis, with fewer reported cases of bronchiolitis obliterans organizing pneumonia and granulomatous interstitial disease. High-resolution CT findings in 18 patients with chronic nitrofurantoin lung injury showed bilateral ground-glass opacities in all subjects (diffuse in 30%, and with a middle to upper lung zone predominance in 40%). Irregular linear opacities were present

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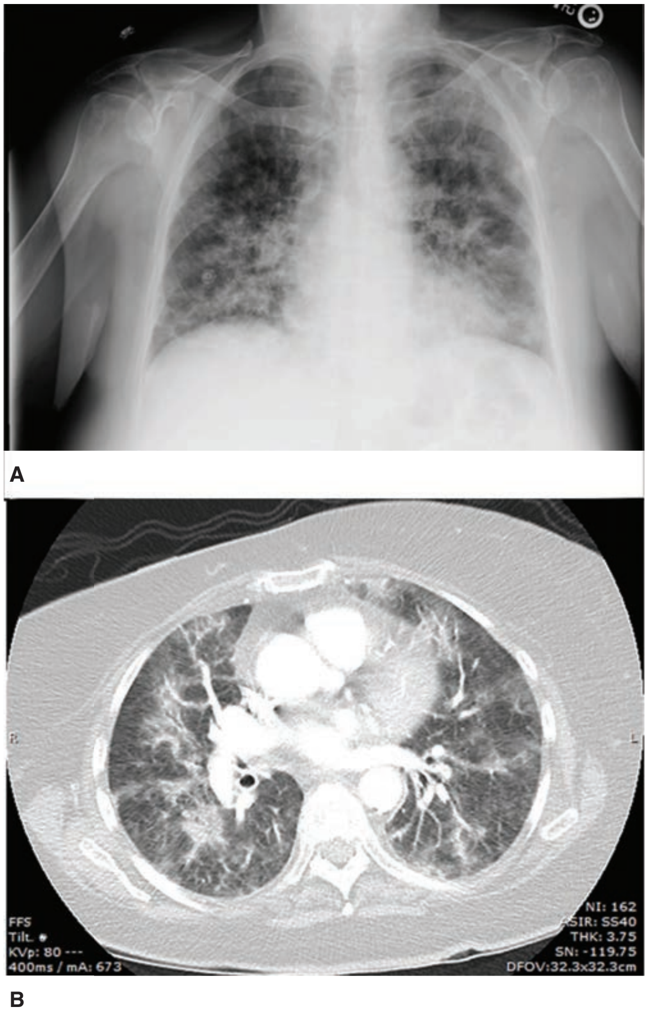

Figure 65-3 Nitrofurantoin-induced organizing pneumonia. **A.** Chest radiograph of an 80-year-old woman 1 year after initiation of nitrofurantoin for recurrent urinary tract infection. **B.** CT scan showing patchy ground-glass opacities and consolidation consistent with nitrofurantoin-induced organizing pneumonia.

in 30%, consolidation in 30%, and traction bronchiectasis in 10% (one subject).[119] Many other histopathologic patterns and clinical syndromes have been reported as associated with nitrofurantoin use, including pulmonary edema, ARDS, vasculitis, DAH, SLE, PIE, and nodules.

Interferons

The high prevalence of chronic hepatitis C worldwide and its treatment with pegylated interferon-alfa-2a has brought with it reports of systemic and pulmonary toxicity. The significant systemic side effect profile associated with interferon therapies has increased the enthusiasm for regimens of direct-acting antivirals (DAA), but their prohibitive cost limits the use of DAA in under-resourced settings. Systemic side effects are common among patients treated with interferons, typically including flu-like symptoms of fatigue, headache, anorexia, and myalgias, but pulmonary symptoms occur relatively infrequently. Ribavirin, a synthetic nucleoside analogue, is often used in conjunction with interferons to enhance their antiviral activity. Ribavirin is associated with dyspnea and cough, but it has not been reported to cause pulmonary toxicity when used alone.

Interferon-induced lung toxicity is usually in the form of interstitial infiltrates, pulmonary sarcoidosis, OP, and/or pleural effusion. The mean time from treatment onset to lung disease presentation is 11.8 weeks (range, 2–48 weeks).[120] The reported rate of pulmonary interstitial disease and/or OP is as high as 6% among patients receiving high-dose daily interferon for hepatitis C, and <1% among patients on conventional three-times-weekly dosing schedules of interferon and ribavirin.[121] Most cases of interferon pulmonary toxicity resolve fully with discontinuation of the medications.[120]

Several case reports or small series of cases characterize the association of de novo sarcoidosis or recrudescent sarcoidosis with interferon-α and interferon-α_2 a used in chronic hepatitis C.[122] The incidence of sarcoidosis among patients receiving interferon is not well established but has been reported to be as high as 5% among patients receiving treatment with interferon-α_2 a for hepatitis C.[123] Interferon-associated pulmonary sarcoidosis occurs along with involvement of other sites, including cutaneous, parotid, liver, ocular, and cardiac involvement. Prompt withdrawal of the drug is advised, and corticosteroids may be necessary for disease resolution.

■ Opiates and Illicit Drugs

Complications of illicit drug use are numerous and encompass toxic injury to the lung related to use of the drug itself, and the associated infectious sequelae of venous cannulation, including endocarditis and septic embolization. The prevalence of tuberculosis among drug users puts these individuals at high risk of active tuberculosis as well. Opiates or other sedatives may cause altered mental status and impairment of the gag reflex, substantially increasing the risk of aspiration pneumonia. Pulmonary parenchymal disease may also be caused by talc or other inert substances used to “cut” the drugs. Recognition of these conditions, unrelated to direct toxicity of the drug, broadens the differential diagnosis of respiratory symptoms in users of illicit drugs.

Heroin

Overdoses of heroin and other narcotics cause respiratory depression through stimulation of the μ-opioid receptor in the brainstem and can also result in pulmonary edema as a contributor to respiratory failure. One of the earliest reports of drug-induced lung disease was by Osler in 1880, in which he described pulmonary edema in an opiate addict and ascribed the edema to the opiate use. The frequency of heroin-induced pulmonary edema (HIPE) has been reported to be as high as 50% of subjects with heroin overdose and as low as 2.1% of cases.[124] In the latter series, one-third of the patients required intubation and mechanical ventilation, but the hypoxemia of HIPE resolved within 48 h of presentation. In fatal opioid overdoses, autopsies show pulmonary edema in the large majority of cases. It is likely that the edema occurs due to increased vascular permeability as evidenced by the higher protein content in the pulmonary edema fluid of opioid overdose compared with cardiogenic edema.[125] Shifts in vascular hydrostatic pressure in the setting of myocardial depression also may contribute, as would negative pressure pulmonary edema from respiratory efforts against an obstructed upper airway from opioid-provoked upper airway collapse in subjects with sleep apnea.

Heroin use can also cause acute bronchospasm.

Pulmonary disease associated with illicit injection drug use may be unrelated to the drug itself. Talc used to cut heroin or methadone, or other inert substances used in narcotic pills that are crushed and injected, can produce foreign-body granulomatous reactions in the pulmonary vasculature and interstitium. Characteristic radiographic findings consist of a diffuse, micronodular pulmonary infiltrate that evolves into coalescent conglomerates, often in the upper lobes, similar in appearance to that of progressive massive fibrosis. These alterations may be accompanied by emphysematous changes in the lower lobes, which may result in pneumothoraces.

Other pulmonary complications of injection drug use include septic emboli, abscess formation, bronchiectasis, and bullae independent of apical fibrotic reactions.

Cocaine

Cocaine is typically smoked as "crack" cocaine, an alkaloid derivative of cocaine hydrochloride that is mixed with ether or alcohol. Respiratory symptoms typically develop acutely, within hours of use, and include cough, hemoptysis, chest pain, and shortness of breath. Bronchospasm, which may be severe enough to precipitate respiratory failure, has been reported with and without a prior history of asthma. The radiographic appearance may be consistent with ARDS, and the histopathology is that of DAD, with or without alveolar hemorrhage that may be diffuse or focal.[126,127] Talcosis can occur as a result of cocaine inhalation and can be associated with spontaneous pneumothorax.[128]

PRINCIPLES OF TREATMENT AND DISEASE RESOLUTION

Prompt recognition of drug-induced lung disease will allow patients the greatest chance of clinical and radiographic recovery before irreversible lung injury occurs. In most cases of drug-induced pulmonary injury, discontinuation of the culprit drug is sufficient for regression of clinical symptoms and most of the radiographic findings. The decision to treat with corticosteroids must be individualized, based on the severity of the clinical picture and the expected rapidity of symptom resolution. For example, amiodarone pulmonary toxicity frequently requires oral corticosteroid administration unless the symptoms are very mild, because of the long serum half-life of the drug. Recrudescence of lung injury is rare among implicated drugs in the absence of re-exposure to the culprit drug. Overall, corticosteroids are used with apparent success, but controlled studies to determine therapeutic efficacy are lacking, and the infrequent occurrence of most drug toxicities will not allow this treatment to be convincingly studied in clinical trials.

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CHAPTER 66

Lung Injury Associated with Recreational Drug Use

Timothy E. Albertson
Patrick Mangialardi
James A. Chenoweth
Susan Murin

INTRODUCTION

Recreational drugs (RDs), sometimes called drugs of abuse or illicit drugs, are commonly used in many societies worldwide. Not all recreational drugs are illegal, but all are capable of being abused. The Australian Government estimates that in 2019, 43% of its citizens had illicitly used a drug in their lifetime, while 16.4% had used one during the prior 12 months.[1] According to the European Monitoring Center for Drugs and Drug Addiction, the estimated prevalence of illicit drug use in 2017 to 2018 in the general population of England and Wales, as assessed by survey, is similar to a decade ago, with 1 out of 10 adults aged 16 to 59 years confirming use within the last year.[2] As of 2016, almost 119 million people in the United States had used marijuana in their lifetime.[3] The same report noted that about 39 million Americans had used cocaine, 9 million had used crack cocaine, 5 million had used heroin, 18 million had used Ecstasy, and 15 million had used methamphetamine. The Global Drug Survey estimates that 64% of the global population has used an illicit drug at least once.[3]

Recreational and illicit drugs of abuse are associated with health complications that affect many different organs. It is not surprising that admissions to emergency departments and hospitals and health-care utilization in general are several times higher for adults who use illicit drugs.[4] Table 66-1 outlines potential respiratory systems adverse effects or complications associated with the use and misuse of recreational drugs. The potential respiratory system anatomic areas of insult by recreational drugs can be divided into oral/airways, pleural space/extrapulmonary, pulmonary vasculature, and lung parenchyma/alveolar space.

These pulmonary complications can result from an overdose of RDs, as a result of the dosing approach or route used, or as an effect of the drug itself.[5] The pulmonary complications of drug use/abuse can also be classified as either infectious or noninfectious.[6] Infectious complications are common, and include typical respiratory pathogens as well as tuberculosis,[7] skin abscesses, endocarditis, and septic emboli to the lung. Mechanical noninfective and foreign body complications of RD use can be significant, as can the effects of inhalation or intravenous use of RD that have been diluted or "cut" with talc (hydrated magnesium silicate) or other foreign materials.

Recreational drug use in some vulnerable populations is thought to provide a "double hit" that may worsen underlying pathology, such as in patients with human immunodeficiency virus (HIV) who use intravenous heroin or methamphetamine. They appear to be at greater risk of developing pulmonary hypertension and have a higher associated mortality than do non-drug-using HIV patients.[8]

This chapter primarily focuses on the pulmonary toxicity and injury associated with the RDs and drugs of abuse, including marijuana, cocaine, methamphetamine and derivatives, and heroin/opioids. It will also review the pulmonary complications associated with volatile substance misuse.

METHAMPHETAMINE AND AMPHETAMINE DERIVATIVES

Methamphetamine, its metabolite amphetamine, 3-4-methylenedioxy-methamphetamine (MDMA, "Ecstasy"), and cathinone derivatives ("Bath Salts") all share related chemical structures and some toxicities (Fig. 66-1). These drugs are often used as RDs, and most are considered illicit drugs of abuse. A number of toxic manifestations affecting the respiratory system have been described as a result of their use, illicit manufacturing or processing, and overdose.

Methamphetamine use was associated with more acute hospital admissions in California between 1990 and 2005 for RDs than all

TABLE 66-1 Potential Recreational Drug Adverse Effects on the Lung

- Upper respiratory tract and airways
    - Bronchospasm
    - Thermal injury
    - Bronchitis/bronchiectasis
    - Foreign body aspiration
    - Gastric aspiration
    - Emphysema/chronic obstructive pulmonary disease
- Pleural space/extrapulmonary/barotrauma
    - Pneumothorax
    - Pneumomediastinum
    - Pneumopericardium
    - Subcutaneous emphysema
- Pulmonary vasculature
    - Pulmonary hypertension
    - Pulmonary embolism
    - Foreign body embolism
    - Septic emboli
    - Vasculitis
- Lung parenchyma/alveolar space
    - Cardiogenic pulmonary edema
    - Noncardiogenic pulmonary edema/acute respiratory distress syndrome (ARDS)
    - Pulmonary infection/pneumonia/bronchitis
    - Atelectasis
    - Granulomatous disease
    - Pneumonitis including aspiration
    - Pulmonary fibrosis
    - Eosinophilic pneumonia
    - Cancer
    - Alveolar hemorrhage
    - E-cigarette or vaping product use–associated lung injury (EVALI)
    - Giant bullae
    - Lung cancer
    - Alveolar proteinosis

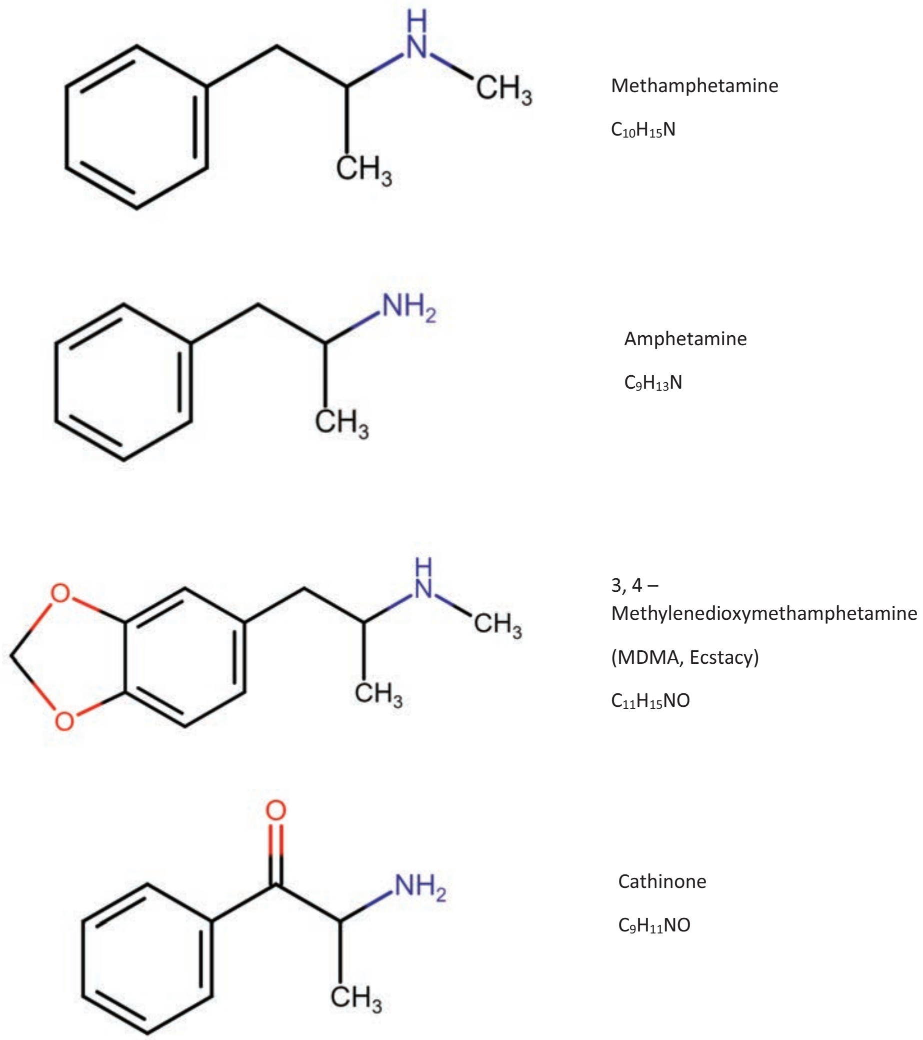

Figure 66-1 Methamphetamine and amphetamine related structures.

other RDs except alcohol.[9] Higher adjusted mortality rates were also seen with methamphetamine-related admissions. Table 66-2 provides a summary of the pulmonary toxicity reported with the use of these drugs. Methamphetamine use is common worldwide with some regional variation. Both MDMA and the cathinone derivatives have lower prevalence but are also used worldwide. The various reported respiratory system effects are discussed below, according to the anatomic area affected.

■ Upper Respiratory Tract/Airway

"Meth-mouth" can occur both as a result of illicit manufacturing and the repeated use of methamphetamine.[10] "Meth-mouth" consists of poor dental hygiene, xerostomia, dental caries, and excessive tooth wear. In IV methamphetamine users compared with matched non-users, tooth decay rates were significantly ($p= 0.04$) higher in the user group. Methamphetamine users have a distinctive pattern of tooth surface wear with carious surface involvement highest on the maxillary central incisors, followed by maxillary posterior premolars and molars.[11] In addition to grinding of teeth and oral exposure to solvents during manufacturing, methamphetamine users had higher levels of sugary beverage consumption compared to controls.[12] These changes were not dependent on dose or route of methamphetamine use. The oral findings of poor dentition not only act as indicators of methamphetamine use but also likely increase the risk of lung infections, given known associations between poor dentition and respiratory infections.

■ Pleural Space/Extrapulmonary/Barotrauma

Spontaneous or nontraumatic pneumomediastinum, pneumothorax, pneumopericardium, and diffuse subcutaneous emphysema have been reported after IV, snorted, and inhaled methamphetamine use[13,14] and after inhaled, snorted, and oral use of Ecstasy or MDMA.[15–23] The use of the cathinone derivative mephedrone was associated with a pneumomediastinum after inhalation.[24,25] This barotrauma results from sudden increases in intrathoracic pressures and intra-alveolar pressures generated during snorting, exaggerated inhalations (including inhalation of heated drugs) and "Valsalva-like" maneuvers performed by users. Some users do almost ritualistic forced Valsalva maneuvers after snorting or smoking methamphetamine or amphetamine derivatives. The mechanism by which methamphetamine, Ecstasy, or cathinone derivatives cause barotrauma when the agents are taken intravenously or orally may be due to coughing or retching. Based on the numbers of case reports of barotrauma, it does appear to be a real complication of the use of recreational methamphetamine and amphetamine-like compounds via these routes of administration. The actual incidence and risk of barotrauma are not known.

■ Pulmonary Vasculature

The recreational or illicit use of methamphetamine has been associated with the development of pulmonary hypertension. In studies in mice, methamphetamine/amphetamine inappropriately enhances mitochondrial oxidative phosphorylation and pulmonary artery DNA damage associated with hypoxia and pulmonary artery vascular remodeling thought to be a contributor to the development of pulmonary hypertension associated with the use of methamphetamine and its derivatives.[26] Using rats, Liu et al.[27] found that the serotonin uptake inhibitor fluoxetine given with methamphetamine attenuated pulmonary artery remodeling that is associated with pulmonary hypertension. Fluoxetine also downregulated the protein expression of the serotonin transporter protein and serotonin (5-HT_{IB}) receptor both of which are normally increased with methamphetamine exposures.

The incidence of methamphetamine and its derivatives inducing pulmonary hypertension in recreational users is unknown, but it does appear to be common and associated with an aggressive form of pulmonary hypertension. Pulmonary hypertension associated with recreational methamphetamine use and the therapeutic use of amphetamine-like anorectic drugs has been reported with or without foreign body granuloma formation.[28–35] In a case series of 90 patients with pulmonary hypertension associated with methamphetamine use compared to 97 patients with idiopathic pulmonary hypertension, the methamphetamine patients had worse outcomes and more severe pulmonary hypertension.[35] Zhao et al. similarly found that both methamphetamine-associated pulmonary hypertension and cardiomyopathy were associated with an increased mortality risk.[29]

TABLE 66-2 Pulmonary Toxicity Associated with Methamphetamine and Amphetamine Derivative Use

Toxic Effect
Upper respiratory tract and airways
• Dental disease (meth mouth)
• Emphysema
Barotrauma/pleural space/extrapulmonary
• Barotrauma
Pneumothorax
Pneumomediastinum
Pneumopericardium
Pulmonary vasculature
• Pulmonary hypertension
• Foreign body granulomas
Foreign body embolism
Lung parenchyma/alveolar space
• Pulmonary edema
Noncardiogenic
ARDS
Cardiogenic
• Pulmonary infection
Pneumonia
Bronchitis
• Alveolar hemorrhage

■ Lung Parenchyma/Alveolar Space

Noncardiogenic pulmonary edema including acute respiratory disease syndrome (ARDS) has been reported rarely after the recreational or illicit use of methamphetamine.[36–38] Considering the frequency of the use of methamphetamine and its derivatives, only a relatively few cases have been noted, suggesting this is an infrequent complication. The mechanisms of noncardiogenic pulmonary edema are not known but could include direct toxic effect of the drug or its metabolites, or the thermal products or toxic gas byproducts of the manufacturing process. An example of the latter can be seen in the deaths with severe pulmonary edema of three people manufacturing methamphetamine in a hotel room where they were exposed to phosphine gas that was accidentally generated through the heating of red phosphorous in the presence of acids.[36] Other than direct toxic effects on the lung, other proposed mechanisms include neurogenic pulmonary edema (from sympathetic vasoactive effects of methamphetamine or from methamphetamine-generated seizures), attempted inspiration against a closed glottis (negative-pressure pulmonary edema), or aspiration of gastric contents.[5]

Cardiogenic pulmonary edema is seen in acute but more commonly in chronic users of methamphetamine who develop decompensated heart failure from methamphetamine-associated acute or chronic cardiomyopathy.[29,39–41] Catecholamine excess is thought to be a major cause of this cardiomyopathy.[41] Additionally, amphetamines can stimulate heart rate, expired carbon dioxide (CO_2), and inspiratory drive in rats in a dose-dependent manner.[42] Standard treatments for noncardiogenic and cardiogenic pulmonary edema including noninvasive or invasive ventilation with positive end-expiratory pressures, avoidance of toxins, diuretics, and afterload reducers are used. The careful use of beta blockers also can be considered.

A case report of diffuse alveolar hemorrhage following inhalation of a synthetic cathinone has been reported.[43] Cathinone and methcathinone have been used and abused as RDs since the early 1990s.[44] More recently, a variety of synthetic cathinones have been reported and are responsible for episodic outbreaks of toxicity in western Europe and the United States.[45]

In the study of hospitalizations between 2005 and 2011 in California, methamphetamine use was found also to be associated with increased risk of hospitalization for pneumonia, acute respiratory failure, and exacerbations of COPD.[46] A wide range of other reports have noted pulmonary toxicities including foreign body pulmonary granulomas associated with nasal inhalation[47] and intravenous use of methamphetamine.[28] Nasal inhalers of amphetamine and amphetamine derivatives have been broken apart, dissolved, and used intravenously, generating pulmonary granulomas.[48] Severe emphysema has also been reported with the IV use of crushed methylphenidate pills in several young patients.[49,50] A case of "speed-balling" or taking simultaneously a stimulant (methamphetamine) and heroin intravenously reported needle embolization into the right ventricle with numerous foreign body granulomas in the lung.[51] The frequency of these complications of amphetamine RD use has not been determined but seems rare.

OPIOID-ASSOCIATED LUNG TOXICITY

Opioids are a common RD. Figure 66-2 gives the chemical structures of some common opioids. There are multiple routes for the recreational use of opioids including snorting, skin popping, IV administration, oral ingestion, and inhalation. Acute opioid use reduces respiratory drive and the sensation of dyspnea in a dose-dependent manner subject to tolerance.[52] Respiratory drive is generated from the respiratory center located in the pons and medulla of the brain and is stimulated by increases in blood CO_2, and decreases in oxygen and pH. With reduction of respiratory drive by opioids, changes in arterial CO_2 content and pH that would normally stimulate increases in minute ventilation fail to generate a response. In general, the opioid antagonist naloxone reverses this opioid-induced blunted response to arterial CO_2 and reduced pH. Patients with pre-existing elevated arterial partial pressures of CO_2 (Pa_{CO_2}) such as those with obesity-hypoventilation or severe chronic obstructive pulmonary disease (COPD) may be more sensitive to opioid-induced respiratory depression. Table 66-3 summarizes major reported respiratory system toxicities with opioid use, which are further discussed below.

■ Upper Respiratory Tract/Airway

Opioid use has been associated with a variety of airway-related disorders. One case series describes nasal perforations with nasal insufflation of acetaminophen/hydrocodone. Another describes a case of septal, soft palate, and sinus necrosis with insufflation of oxycodone.[53] Cough and bronchospasm associated with opioid use are thought to be due to allergic reactions and/or histamine-releasing processes.[52,54,55] Both the smoking of heroin and opium and the intravenous use of heroin have been associated with acute bronchospasm in both asthmatics and nonasthmatics.[53,56] Inhalation of heroin was shown to be associated with an increase in asthma exacerbations in case series, case-control trials, and retrospective cohort analysis.[57] Heroin users also were found to require intubation more frequently during asthma exacerbations than non-users (17.0% vs. 2.3%, respectively; $p = 0.0036$).[58] Among 512 heroin users on methadone maintenance therapy, with a mean age of 26.8 ± 1.0 years, 6% were found to have obstructive changes attributed to asthma or chronic bronchitis and 7% had restrictive changes due to interstitial lung disease.[59] A total of 190 subjects (38%) had low diffusing capacity of the lungs for carbon monoxide (DL_{CO}), with most having normal lung volumes and spirometry. Foreign

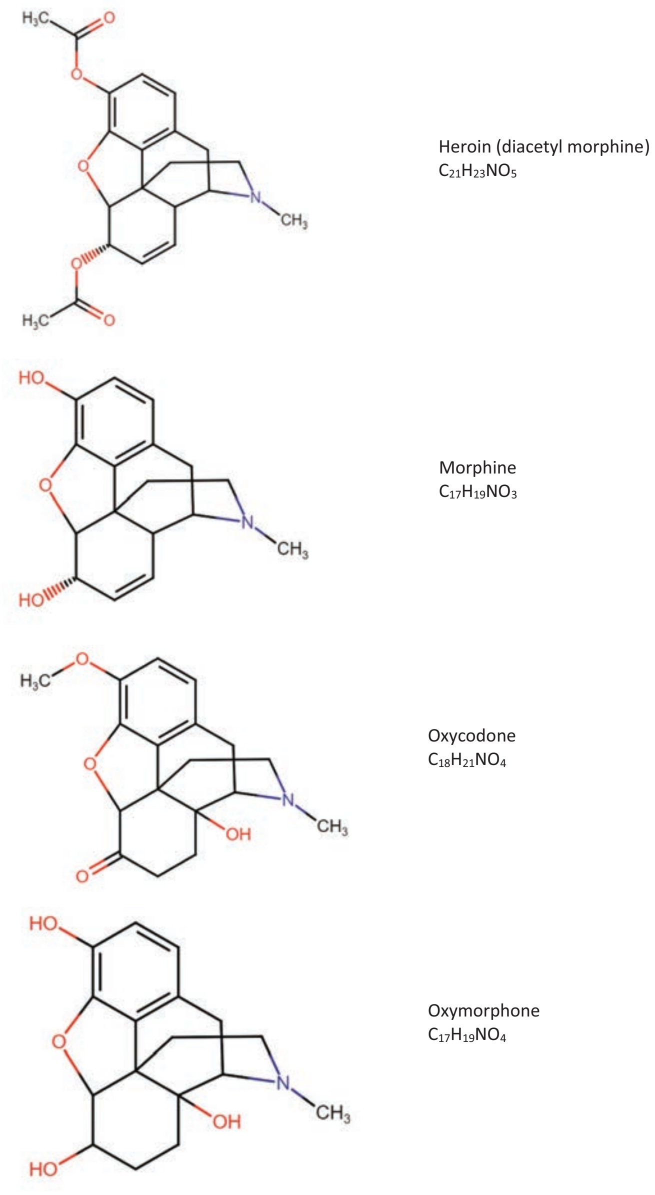

Figure 66-2 Heroin, morphine and oxycodone chemical structures.

TABLE 66-3 Recreational Opioid Use Pulmonary Toxicity

Toxic Effect
Upper respiratory tract/airway
• Cough/histamine release/bronchospasm
• Worsening obstructive sleep apnea
• Asthma exacerbations
• Nasal septum perforation
• Vocal cord paralysis
• Bronchiolitis and airway obstruction
Barotrauma/pleural space/extrapulmonary
• Wooden chest syndrome—rigid thorax
• Pneumothorax
Pulmonary vasculature
• Foreign particle embolization
• Septic pulmonary emboli
Lung parenchyma/alveolar space
• Acute respiratory distress syndrome/noncardiogenic pulmonary edema
• Lung cancer
• Pneumonia (aspiration and non-aspiration)/immune modulation
• Pulmonary hemorrhage
• Atelectasis
• Granulomatous change
• Tuberculosis
• Eosinophilic pneumonia
• Pulmonary bullae
• Alveolar proteinosis

particle emboli were thought to be the cause of the reduced DL_{CO}.[59] A 2002 study that described pulmonary function tests in methadone maintenance patients found reduced forced expiratory volume in 1 second (FEV_1) compared with non-users, but these patients were more often tobacco smokers. A 2011 trial of heroin drug users maintained on inhaled heroin showed no change in spirometry over 10 months.[53] Another study of 161 current or former heroin smokers (122 [75.8%] had also smoked "crack" cocaine) found that they experienced an increased burden of respiratory symptoms and a greater decline in FEV_1 over 18 to 24 months than tobacco smokers with COPD and healthy non-smokers.[60]

Upper lobe large bullae were reported in 24% of a case series of opium smokers in one study from Singapore.[61] Bronchiolitis and airway obstruction also were seen in these patients, which may be the mechanism for development of such bullae.

■ Pleural Space/Extrapulmonary/Barotrauma

Pneumothorax and pneumomediastinum have been reported with recreational opioid use.[53,56,62] The causes range from mechanical consequences of using the supraclavicular fossa IV approach ("pocket shot") to other causes independent of the IV approach. This includes a case of bilateral pneumothoraces associated with septic emboli from right-sided endocarditis.[56] Another complication of the "pocket shot" reported in IV heroin users is vocal cord paralysis which can be unilateral or bilateral. It can present immediately or later as the consequence of neck abscess.[53]

Rapid death from opioid use can involve more than just respiratory drive suppression. Fentanyl-induced chest wall muscle rigidity (wooden chest syndrome) is well described in the anesthesia literature.[63,64] It is concerning due to the fact that wooden chest syndrome is not readily reversible by naloxone.[65] With the increased use of fentanyl as a drug of abuse on the streets and a marked increase in reported deaths despite increased availability of naloxone in the community, it has been postulated that wooden chest syndrome is a contributing factor.

■ Pulmonary Vasculature

Foreign body talc granuloma formulation in the pulmonary vasculature has been noted with resulting pulmonary hypertension in IV heroin users.[66] Similarly, talcosis occurs with inhalation of heroin cut with talc. In a study comparing talc granuloma formation in inhaled or IV heroin users, 11 cases demonstrated the mean lung talc particle size to be 3.7 ± 2.9 μm for those who inhaled heroin and 14.2 ± 9 μm ($p < 0.01$) for those who injected heroin.[66] As noted earlier, septic emboli from right-sided endocarditis is a major problem associated with IV heroin use. Septic pulmonary emboli can generate multiple endovascular and parenchymal abscesses in the lung.

Lung Parenchyma/Alveolar Space

The lung parenchyma and alveolar space are frequent sites of toxicity among opioid users. Opioid-induced noncardiogenic pulmonary edema was first described by Osler in a patient with morphine overdose and has since been observed with morphine, heroin, codeine, methadone, and fentanyl overdose.[52] Evidence of pulmonary edema is reported in 95% of autopsy cases and in 94% (opioids excluding fentanyl) and 96% (fentanyl) of opioid overdose post-mortem CT scans.[67,68] Aspiration was thought to have occurred in 68% of patients in the CT series and may have contributed to the development of pulmonary edema.[68] The sudden rise in fentanyl and fentanyl analogue use has led to many related deaths in opioid-tolerant heroin users and in non-heroin users.[69,70] Cases of opioid-induced noncardiogenic pulmonary edema including ARDS have been severe enough to require extracorporeal membrane oxygenation therapy.[71]

There are multiple other pulmonary parenchymal complications among opiate users. Poor respiratory effort associated with opioid-induced toxicity can lead to pulmonary atelectasis.[62] Patients with opioid overdoses with and without aspiration of gastric contents can develop pneumonia. A case of heroin inhalation with a Valsalva maneuver is thought to have resulted in acute pneumonitis.[72] Two cases of pulmonary hemorrhage were reported following acute heroin overdoses.[73] Additional, even more rare, lung complications have been reported such as the case of a person who smoked fentanyl patches for 3 months developing chest pain, fevers, night sweats, shortness of breath, weight loss, and malaise with bilateral crackles. Chest CT showed bilateral, extensive central lobular nodularity with focal septal thickening. A video-assisted thoracoscopic lung biopsy demonstrated granular eosinophilic material typical of pulmonary alveolar proteinosis.[74] It is unclear if this condition was from the material in the patch or from the fentanyl itself, but it improved after the patient ceased smoking the patches. Multiple case reports of eosinophilic pneumonia have also been reported with the inhalational use of heroin.[53]

The risk of lung cancer among those who smoke or inhale opium or heroin remains unclear.[75] An Iranian study of chronic opium smokers found it to be a significant independent risk factor for developing lung cancer with an odds ratio (OR) of 3.1 (95% confidence interval [CI], 1.2–8.1).[76] When concomitant heavy smoking was combined with chronic opium smoking, the OR increased dramatically to 35.0 (95% CI, 11.4–107.9). A dose-dependent increase in cancer mortality was also seen in opium smokers in Iran.[77] A total of 50,045 adults were enrolled in this study between 2004 and 2008 and followed until 2015 with follow-up rate of 99%. Opium use was determined by questionnaire. The adjusted hazard ratio (HR) for death from a respiratory disease was 3.84 (95% CI, 2.61–5.67). Malignant causes of respiratory deaths were a significant component of these deaths.

Opioid use is associated with some immunosuppression, but the clinical importance has been questioned.[78] Whether due to immunosuppression by the opioids, lifestyle risk, or IV drug use, the rates of tuberculosis among opium users was 5.3% (95% CI, 1.3–10.3), and this rate was higher than among asthma patients or nonsmokers who visited an emergency department for nonrespiratory complaints.[75] Even the use of therapeutic doses of opioids in elderly patients results in an increased risk of pneumonia (OR, 1.38; 95% CI, 1.08–1.76).[79] HIV patients who are also IV drug users are at increased risk for tuberculosis.[80] Separating the roles of lifestyle, IV drug use, and opioids as contributors to this risk is difficult.

MARIJUANA AND SYNTHETIC CANNABINOIDS

Several countries and many states within the United States have relaxed their laws to allow more access to "medicinal" and recreational marijuana.[81] Several comprehensive reviews have been written about the pulmonary effects of marijuana use.[81–84] Although there are some excellent reviews on the chemistry and epidemiology of the more than 50 different synthetic cannabinoids or "spice agents,"[85,86] little is known about the pulmonary complications of their use.[87] Both marijuana/tetrahydrocannabinol (THC) and the synthetic cannabinoids have common psychotropic and acute cognitive effects, but the synthetic cannabinoids demonstrate more agitation and psychosis.[87] Figure 66-3 provides the chemical structure of THC and other cannabinoids. Table 66-4 outlines and summarizes major pulmonary toxicity associated with the use of marijuana and the limited knowledge about the effect of synthetic cannabinoids.

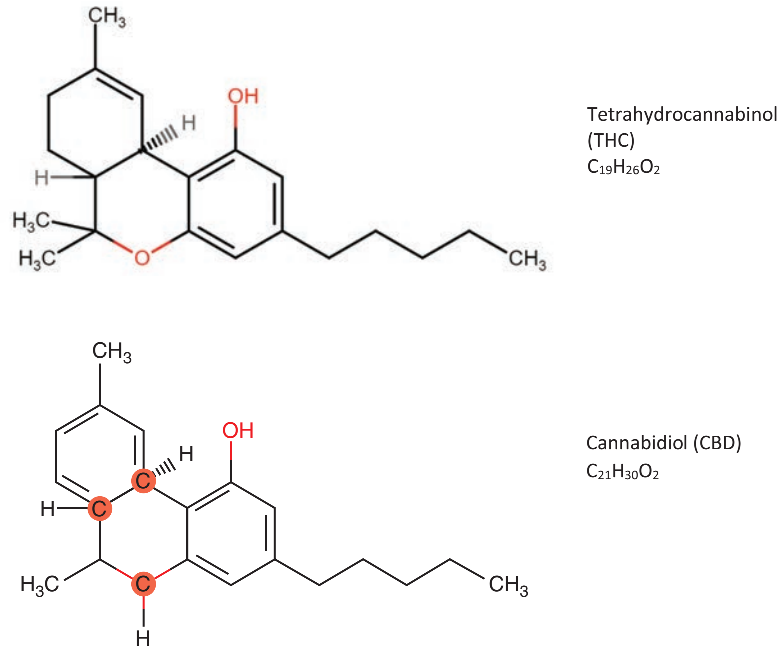

Figure 66-3 Structure of tetrahydrocannabinol (THC) and cannabidiol (CBD).

The combustion of marijuana and the various plant leaves on which synthetic cannabinoids/spice are sprayed gives off both a volatile or gas phase and particulate phase of smoke that are similar to those of tobacco.[81] In contrast to tobacco, which contains nicotine, marijuana contains THC and more than 60 different cannabinoid products. Carbon monoxide, ammonia, hydrocyanic acid, acetaldehyde, isoprene, formaldehyde, acrolein, dimethyl- and methylethyl-nitrosamine, and other polycyclic aromatic hydrocarbons are found in the gas phase of both tobacco and marijuana smoke.[81] The particulate contains phenols and a number of toxic polycyclic aromatic hydrocarbons.

Upper Respiratory Tract/Airway

Unlike tobacco, acute smoking of marijuana can cause bronchodilation probably from the stimulation of cannabinoid airway receptors like CB-1.[82,84,88] The determination of chronic effects of smoking marijuana and synthetic cannabinoids is complicated by the confounder of frequent tobacco smoking in these patients. Both marijuana and synthetic cannabinoids can cause cannabinoid hyperemesis syndrome (CHS) with long-term heavy use.[89–91] This debilitating complication puts patients at risk for aspiration

TABLE 66-4 Recreational Marijuana and Synthetic Cannabinoid Use Pulmonary Toxicity

Toxic Effect
Upper respiratory tract/airway
• Thermal epiglottis
• Asthma exacerbations
• Chronic bronchitis/cough/sputum production
• Possible impaired lung function/chronic obstructive pulmonary disease
Barotrauma/pleural space/extrapulmonary
• Pneumothorax
Pulmonary vasculature
• Pulmonary embolization
Lung parenchyma/alveolar space
• Cannabinoid oil vaping/e-cigarette vaping product use–associated lung injury (EVALI)
• Talcosis with interstitial lung changes
• Noncardiogenic pulmonary edema/acute respiratory distress syndrome (ARDS)
• Pulmonary infections/pneumonia/bronchitis
• Organizing pneumonia
• Pulmonary upper lobe bullae—“pons lung”
• Eosinophilic pneumonia
• Pulmonary hemorrhage
• Possible increased risk for *Aspergillus fumigatus* and *Mycobacterium tuberculosis* in immunocompromised patients including HIV/AIDS
• Possible lung cancer/aerodigestive malignancies

pneumonia. Use of synthetic cannabinoids is also associated with respiratory depression that is rarely seen with the use of marijuana.[92]

Thermal injury resulting in acute epiglottitis has been reported after inhaling or swallowing a lighted marijuana cigarette. In a series of cases of thermal epiglottis from illicit drug use, the majority (3/4) were associated with crack cocaine inhalation and the remaining case with marijuana.[93]

A recent comprehensive review of marijuana smoke exposure concluded that asthmatics should avoid its use in addition to avoiding tobacco smoke.[94] Despite the finding of acute bronchodilation with marijuana smoke inhalation[95] and even after controlling for the use of tobacco, marijuana smokers had more wheezing, cough, sputum production, asthma exacerbations, and emergency department visits for respiratory problems (including asthma exacerbations) than nonsmokers of marijuana.[94] For asthmatics that use marijuana, the overall exacerbation rate is higher, the use of the emergency department is greater, and the asthma treatment adherence and outpatient clinic care use is less than nonusers.[94] Marijuana-related allergies including allergic rhinitis, new-onset asthma, allergic conjunctivitis, eczema, drug eruptions, food allergy, contact urticaria, and anaphylaxis have all been reported with both marijuana inhalation and the ingestion of marijuana in food, teas, and candies.[94] In a systematic review and meta-analysis, increased risk of cough, sputum production, wheezing, and dyspnea was repeatedly seen in adolescents and adult marijuana users compared with nonusers.[96] Heavy use of marijuana by smoking rolled leaves (“joints”) or from a water pipe (“bong”) results in the bronchitis symptoms noted above, and bronchitis pathology has been confirmed by direct airway visualization with airway biopsies showing inflammatory changes.[97,98]

The effects of marijuana smoking on lung function remain controversial in part because of the difficulty of separating out the effects of concurrent tobacco smoking. A cross-sectional study of 2304 current and former tobacco smoking subjects who were also classified as never marijuana smokers, former marijuana smokers, and current marijuana smokers found that marijuana use had little to no association with negative spirometry changes. In fact, increased FEV_1 and forced vital capacity (FVC) numbers were seen in current marijuana smokers. However, higher joint-years (one joint-year equals smoking one joint per day for one year) had more chronic bronchitis symptoms.[99]

A large cross-sectional study of adults in the United States failed to show adverse spirometric lung changes with up to 20 joint-years of marijuana exposure.[100] However, the same study found that patients with greater than 20 joint-years exposure had a twofold increase in odds of having a FEV_1/FVC ratio less than 70%.[100] Interestingly, that was attributed to an increase in FVC rather than the typical decrease in FEV_1 seen among tobacco smokers.[101]

The cross-sectional and longitudinal Canadian Cohort Obstructive Lung Disease (Can COLD) study evaluated older (40–85 years) male and female smokers of tobacco, marijuana, both tobacco and marijuana, and never smokers ($n = 5291$ in the cross-sectional study and 1285 in longitudinal study).[102] When never-smokers were compared with heavy marijuana (>20 joint-years) and heavy tobacco smokers (>20 pack-years), the heavy marijuana or heavy tobacco smokers had a faster decline in FEV_1 by about 29.5 mL/year ($p < 0.0007$) and 21.1 mL/year ($p < 0.0001$), respectively, compared with never-users of either.[102] The greatest decline in FEV_1 of 32.3 mL/year was seen in those who smoked both marijuana and tobacco ($p < 0.0001$). The OR for heavy marijuana users developing COPD was 2.45 (95% CI, 1.55–3.88). These results are limited by the small sample size of the marijuana-only smokers ($n = 181$ in the cross-sectional study and 33 in the longitudinal study).[103] Minimal evidence of obstructive airway disease exists for up to moderate marijuana users, but the effects of heavy use of marijuana are poorly quantitated—in part again because of the frequent confounding by the simultaneous heavy use of tobacco.[81,88,96]

■ Pleural Space/Extrapulmonary Barotrauma

A systematic literature review on pneumothorax and lung emphysema in marijuana/cannabis users included 18 case reports of patients with upper lobe bullae and 8 cases of spontaneous pneumothorax, all in combined tobacco and marijuana smokers.[104] Two additional cases of bullae in the upper lobes were reported in smokers of just marijuana. Further, it was suggested that in patients under age 35 presenting with spontaneous pneumothorax, the incidence of upper lobe bullae was higher in the combined tobacco and marijuana smokers than in the tobacco-only smokers.[104] The mechanism of spontaneous pneumothorax/pneumopericardium and large upper lobe bullae with marijuana smoking is thought to be in part from the mechanical effects of deep breathing and breath holding, Valsalva maneuver during breath hold, and the forcible exhaling of marijuana smoke into another individual’s mouth (“shotgunning”).[81]

■ Pulmonary Vasculature

Limited data exist on whether the use of marijuana or synthetic cannabinoid use can alter the pulmonary vasculature. Two case reports have been published in which the smokers of synthetic cannabinoids developed pulmonary emboli. One case occurred in a 29-year-old and the second in a 32-year-old without any other thromboembolic risk factors noted.[105,106]

■ Lung Parenchyma/Alveolar Space

Inhalation of marijuana and other cannabinoids has been associated with a broad variety of parenchymal abnormalities of the lung. Talcosis with biopsy-proven granulomatous inflammation of the lung and interstitial lung changes on chest CT was reported in a patient who smoked adulterated marijuana.[107] Acute lung injury associated with vaping of THC or cannabidiol (usually with noncommercial products) using an e-cigarette device is called e-cigarette or vaping product use–associated lung injury (EVALI) and is covered in Chapters 41 and 140. Briefly, EVALI appears to be caused by inhalation of oil-based ingredients such as vitamin E acetate in the THC products. It is characterized by bilateral, patchy, mid to upper lobe, ground-glass opacities with subpleural sparing sometimes evolving to diffuse bilateral infiltrates and ARDS requiring mechanical ventilation.[108,109]

Diffuse miliary-micronodular pattern on chest radiography and patchy foci of lower lobe atelectasis and consolidation, with diffuse centrilobular nodules and tree-in-bud pattern on chest CT, has been reported in several patients after inhalation of synthetic cannabinoids.[110] Three out of four patients had lung biopsies that demonstrated organizing pneumonia, with one of the three also showing patchy alveolar damage with eosinophilia. Acute eosinophilic pneumonia associated with respiratory failure was reported in a 21-year-old who smoked synthetic cannabinoids.[111] Acute respiratory failure with diffuse bilateral nodular densities was also seen in two male chronic smokers of synthetic cannabinoids, both of whom ultimately recovered.[112,113]

The concept of "smoking wet" is the process of dipping marijuana in various fluids or lacing it with additional substances.[114] Two cases in which marijuana was tainted by phencyclidine and formaldehyde resulted in acute respiratory failure with ARDS-like infiltrates requiring intubation and extracorporeal membrane oxygenation. Diffuse alveolar hemorrhage (DAH) has been reported after inhalation of both marijuana and synthetic cannabinoids.[115–117] All four DAH patients had acute respiratory failure requiring mechanical ventilation, and negative evaluation for classic causes of DAH. Three of four of the patients were treated with bolus systemic steroids with recovery in all four.

Case reports and case series have reported "bong lung" or large peripheral bullae often associated with pneumothoraces.[118,119] A review of the literature found 57 published cases of bullous lung disease associated with smoking marijuana.[120] It has been postulated that like other forms of barotrauma, these are the results of repeated frequent breath holds and Valsalva maneuvers. A cross-sectional study of 339 subjects divided into nonsmokers, tobacco only, cannabis only, and combined tobacco and cannabis smoking showed reduced lung density on high-resolution lung CT scans in the subjects who smoked cannabis.[121] Microscopic emphysema was seen in 1.3% of cannabis-only smokers, 16.3% of combined cannabis/tobacco smokers, 18.9% of tobacco-alone smokers, and 0% of nonsmokers.

Bronchial biopsies of habitual heavy marijuana users have demonstrated some precancerous histologic changes.[84] A pooled analysis of six case-control studies failed to show an association with smoking marijuana and lung cancer.[84] Two additional studies include a case-control study of 2252 in the Los Angeles area[122] and a smaller case-control trial of 403 subjects in New Zealand.[123] The Los Angeles trial failed to find any correlation with marijuana smoking and lung cancer or oral cancer, while the New Zealand trial found a substantial increased risk for those in the higher marijuana usage group. The Los Angeles study also failed to show an increased risk for oral or pharyngeal cancers with marijuana when adjusting for confounders such as smoking tobacco.[122] A recent systematic review and meta-analysis of 19 case-control, 5 cohort, and 1 cross-sectional studies failed to demonstrate a correlation of marijuana use as measured by joint-years to lung and oral cancers, but the studies had high risk of bias and were not able to be effectively combined.[124]

Marijuana smoking may predispose the user to an increased risk of bronchitis and pneumonia from the loss of ciliated epithelium in the large central airways and hyperplasia of mucous-secreting cells.[84] Several reports of immunocompromised marijuana smokers developing *Aspergillus fumigatus* or *Mycobacterium tuberculosis* infections have been reported.[81] A recent report evaluating the longitudinal Multicenter AIDS Cohort Study found that long-term marijuana smoking was associated with both an increased risk of pulmonary infection and noninfectious pulmonary diseases in patients with HIV.[125] The increased risk of infectious pulmonary diagnoses and of chronic bronchitis with marijuana smoking was independent of tobacco smoking and other known risk factors, with hazard ratios of 1.43 (95% CI, 1.09–1.86) and 1.54 (95% CI, 1.11–2.13), respectively. Shotgunning of marijuana smoke is a potential method of transfer of respiratory pathogens such as tuberculosis.[7] Further prospective and epidemiologic studies are needed to understand infectious disease risks, if any, with extended marijuana use in patients without HIV.

COCAINE-INDUCED PULMONARY TOXICITY

Cocaine has been a common RD over the last 60 to 80 years in the United States, with prevalence of use varying over time and by region. Persons in the United States over age 18 reporting use of cocaine in the past year increased from 2.11% in 2008 to 2009 to 2.26% in 2017, with some states (e.g., California) reporting an increase from 2.2% to 3.04% of the population ($p = 0.002$).[126] Cocaine use appears to be a reemerging public health issue in the United States, with the National Survey of Drug Use and Health (NSDUH) indicating that in 2015, about 968,000 people (0.4% of the population) older than 12 years used cocaine within the last year.[127] In the young adult population between 18 and 25 years old, the U.S. National Survey estimates showed a significant increase ($p \leq 0.05$) in prior-year use from 4.5% (95% CI, 4.22–4.83) in 2013–2014 to 4.98% (95% CI, 4.65–5.34) in 2014–2015.[127] Cocaine overdose deaths also have steadily increased from 4400 in 2012 to 6800 in 2015.[127]

Cocaine hydrochloride or benzoylmethylecgonine (Fig. 66-4) is a naturally occurring alkaloid extracted from the leaf of the plant/shrub *Erythroxylon coca*. When water-soluble cocaine salt is processed via solvent and alkaline extraction, the "freebase" of cocaine is formed. This form has higher volatility and stability and can be smoked. As the crystals or "rocks" of freebase cocaine are heated, it makes a cracking sound leading to the name "crack" cocaine. Cocaine blocks the reuptake of catecholamine in the brain and vasculature, resulting in vasoconstriction. It also has a sodium channel–blocking effect and can act as a local anesthetic. A wide range of respiratory system toxicities are reported with cocaine use (Table 66-5).

A number of contaminants have been found in cocaine sold on the street including phenytoin, local anesthetics, sugars, stimulants, inert compounds, and toxins like strychnine.[128,129] These contaminants have their own toxicities, which will not be discussed here. The combination of cocaine and ethanol generates a unique metabolic product called cocaethylene, which is more potent and likely more toxic than cocaine or its normal metabolites.[130–132] Starting around 2005, the synthetic imidazothiazole derivative levamisole, which has immunomodulatory properties and is a veterinary anthelminthic agent, has been regularly reported as an adulterant in cocaine.[133–136] As a cocaine adulterant, it has been associated with vasculitis, neutropenia, agranulocytosis, skin necrosis, arthralgias, and retiform purpura with or without bullae. Pulmonary complications reported in association with levamisole include pulmonary hemorrhage[133] and the formation of aminorex-like compound

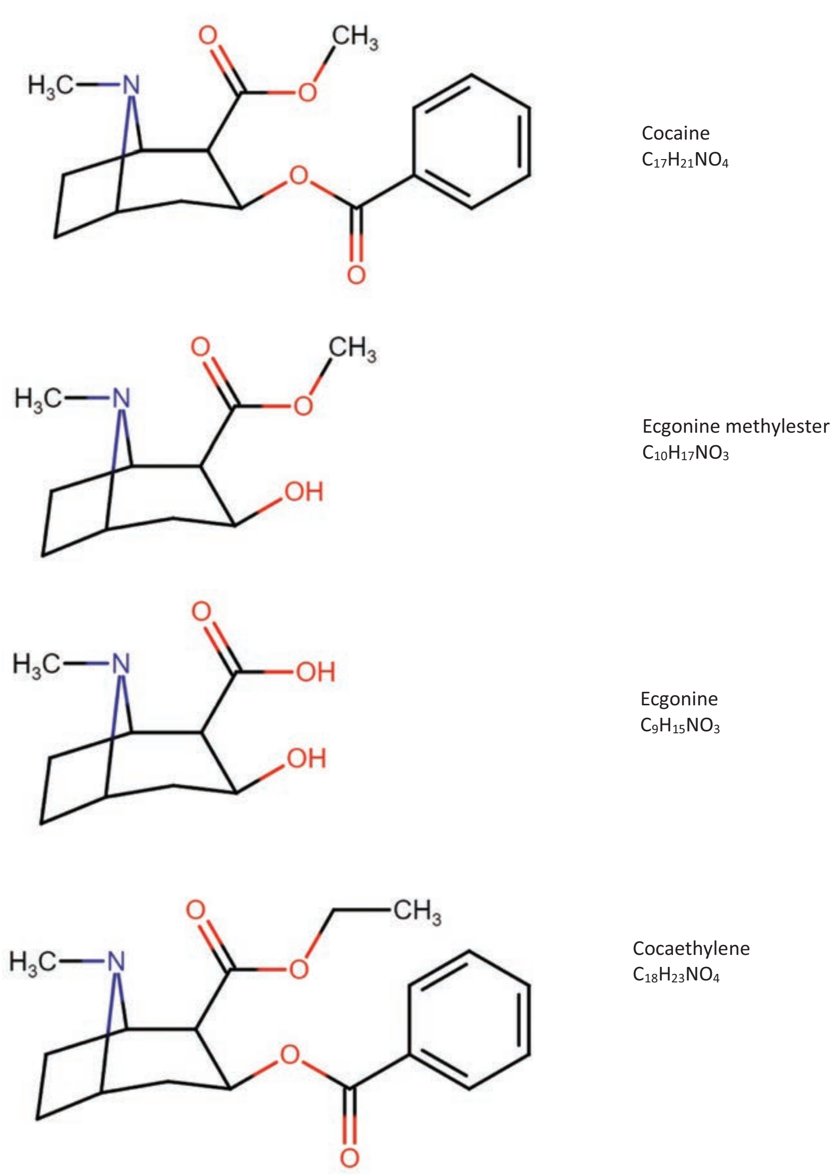

Figure 66-4 Structure of cocaine and metabolites.

metabolites known to cause pulmonary hypertension.[136] Cocaine-induced cardiac affects including myocardial ischemia, cardiogenic pulmonary edema, cardiomyopathy, myocarditis, aortic dissections, endocarditis, and cardiac arrhythmias with sudden death have direct and indirect respiratory system manifestations.[137] Even in animal models with sedation that suppressed most seizure activity, cocaine led to respiratory depression in high doses.[138] Respiratory arrest in human users of cocaine commonly follows seizures, stroke, or cardiac arrest but can also be related to direct central nervous system depression.[139]

■ Upper Respiratory Tract/Airway

The upper respiratory tract is a common site for cocaine toxicity. Snorting or sniffing cocaine deposits large amounts of the drug in the sinuses and cartilaginous areas including the nasal septum. Upper airway necrosis leading to saddle nose deformity and osteolytic sinusitis have been reported.[140–142] Cocaine-induced midline destructive lesions (CIMDL) that mimic granulomatosis with polyangiitis (Wegener granulomatosis) involving the ears, nose, and throat are reported, often in association with positive antineutrophil cytoplasmic antibodies (ANCA).[142–144] Presenting symptoms of CIMDL include nasal/facial pain, nasal obstruction, epistaxis, nasal reflux, and dysphagia. Nasal septal and soft and hard palate perforations can occur with CIMDL.

Upper airway distress from upper airway and tracheal burns is a frequent complication of smoking "crack" cocaine utilizing "crack" pipes or other superheated vaporizing paraphernalia.[145] Stridor, paradoxical vocal cord motion, uvular edema, and necrotic and/or acutely inflamed mucosal tissue are commonly seen. Glass pipes with wire mesh are sometimes used to smoke "crack" cocaine. In one case report, a red-hot wire mesh was aspirated into the pharynx and then swallowed.[146] This caused thermal injury and second-degree burns to the pyriform fossae and the aryepiglottic folds but no injury to the esophagus. There have been several additional cases of inhaled wire-mesh thermal injury to the upper airway from a crack cocaine pipe.[147,148] Severe tracheal thermal damage has also been reported either from an intratracheal ignition of the freebase cocaine ether vehicle or from the resulting housefire.[149]

Both thermal and nonthermal supraglottitis and epiglottitis from cocaine smoking are reported.[93,148,150] Laryngeal aperture narrowing and edema with vocal cord and laryngeal polyps are seen with cocaine smoking[151] and can lead to upper airway obstruction requiring emergent tracheostomy.[151,152] Foreign body aspiration associated with cocaine use is not limited to the previously mentioned pipe components. A freebase cocaine smoker used a 25-gauge hypodermic needle to punch holes in aluminum foil to create a screen for his "crack" pipe, forgot about it, and aspirated the needle into his left upper lobe.[153] Another patient with a long history of nasal cocaine insufflation aspirated a portion of his nasal septum.[154]

Freebase cocaine smoking is associated with exacerbations of asthma and bronchospasm in small case series.[155–157] The largest was a case series of six patients who presented with severe and life-threatening asthma exacerbations after smoking "crack" cocaine.[157] A study of 14 healthy subjects demonstrated that smoking cocaine, but not IV cocaine use, resulted in acute bronchoconstriction thought to be mediated by local airway irritation.[158] Several case reports of freebase cocaine smokers developing obliterative bronchiolitis and bronchiolitis obliterans with organizing pneumonia have been published.[159–163]

Taskin et al. found that compared with age-, sex-, race-, and tobacco/marijuana use–matched non-users, non–freebase cocaine smokers had a mild reduction in DL$_{CO}$, obstructive abnormalities on pulmonary function tests, and respiratory symptoms of cough, black sputum, and chest pain.[162] Although the majority of studies report reduced DL$_{CO}$ among "crack" cocaine smokers, several other studies evaluating DL$_{CO}$ as a measure of the integrity of the alveolar-capillary membrane or interface have failed to show a reduction.[82] Confounders, such as hemoglobin levels, baseline carboxyhemoglobin levels, tobacco and marijuana smoking history, specifics of the cocaine smoking history, and small sample size may explain the variable DL$_{CO}$ results. Smoking "crack" cocaine can produce carbon monoxide, which may confound DL$_{CO}$ determinations. A small study of "crack" cocaine smokers presenting to the ED found that

TABLE 66-5 Recreational Cocaine Use Pulmonary Toxicity

Toxicity
Upper respiratory tract/airway
• Thermal injury
• Foreign body aspiration
• Supraglottitis
• Airway obstruction
• Bronchospasm
• Nasal septum destruction
• Palatal necrosis
• Osteolytic sinusitis
• Asthma exacerbation
• Reduced pulmonary diffusion capacity
Barotrauma/pleural space/extrapulmonary
• Pleural effusions
• Pneumomediastinum
• Pneumothorax
• Pneumopericardium
Pulmonary vasculature
• Pulmonary embolism
• Vasculitis
• Pulmonary hypertension
• Pulmonary infarction
• Foreign body embolism
Lung parenchyma/alveolar space
• Foreign body/cellulose/talc granulomatosis
• Interstitial lung disease
• Alveolar hemorrhage/hemoptysis
• Pulmonary infiltrates
• Increased pulmonary iron concentrations
• Lipoid pneumonia
• "Crack lung"—acute respiratory failure/alveolar hemorrhage/ eosinophilic inflammation
• Pulmonary edema
• Bronchiolitis obliterans organizing pneumonia
• Eosinophilic pneumonia/Loeffler syndrome
• Infections

57% had carboxyhemoglobin levels greater than 4.5%, highlighting the need to measure and control for this variable.[164]

Pleural Space/Extrapulmonary/Barotrauma

Barotrauma leading to subcutaneous emphysema, pneumopericardium, pneumomediastinum, and pneumothorax have been reported among users of cocaine.[82,142,165,166] Forced inspiration with a partner blowing back on a person (back pressure), Valsalva maneuvers, and vigorous inhalation while smoking "crack" cocaine are reported mechanisms for this barotrauma.[167–170] Thermal injuries and adverse vascular effects are reported to be associated with barotrauma.[140,171]

Cocaine-induced pleural and pericardial effusions have been reported in association with negative serologic tests, skin biopsy consistent with leukocytoclastic vasculitis, and renal biopsy revealing proliferative glomerulonephritis.[172] An additional case of pericardial and pleural effusion, without evidence of heart failure or pulmonary emboli, was reported in a "crack" cocaine user.[173]

Pulmonary Vasculature

Evidence of clinically inapparent alveolar hemorrhage has been demonstrated in habitual "crack" cocaine smokers, suggesting chronic damage to the pulmonary microcirculation.[174] The acute use of IV cocaine in chronic habitual "crack" cocaine smokers did not cause short-term increases in pulmonary artery pressures or stroke volume index but did increase the cardiac index.[175]

International classification systems have included cocaine as a possible cause of World Health Organization (WHO) classification 1.3 drug- and toxin-induced pulmonary hypertension.[176] This pulmonary hypertension is thought to result from a direct effect of cocaine on the pulmonary vasculature but also may be related to IV use of cocaine resulting in embolism of talc and cellulose particulate matter in the pulmonary vasculature.[177] A recent study of 88 patients and documented cocaine use with most being "crack" cocaine smokers found systolic pulmonary artery pressures were higher (30.1 ± 13.1 vs. 22.0 ± 9.8 mm Hg; $p < 0.001$) by echocardiogram than those of partially matched controls.[178] The likelihood of having pulmonary hypertension was also increased in the cocaine users (25% vs. 10%; $p = 0.012$). The metabolism of the cocaine adulterant levamisole to aminorex, a known cause of pulmonary hypertension, has been suggested as another potential mechanism for the development of pulmonary hypertension among cocaine users.[179]

Needle and needle fragment embolization into the lungs and heart have been reported in IV cocaine users.[180] A cocaine user "speedballing" (IV injecting the combination of heroin and cocaine) died suddenly and on autopsy was found to have a small-caliber needle protruding into the distal right ventricle with hyperemic myocardium surrounding the needle.[51] Lung sections showed numerous foreign-body type giant cells with polarizable foreign material contributing to presumed pulmonary hypertension from the patient's IV drug use. Media hypertrophy of small- and medium-sized pulmonary arteries without evidence of foreign body microembolization has also been reported in cocaine users.[82] Septic embolism from right-sided endocarditis can be seen in IV cocaine users.[5] Pulmonary infarctions have also been linked to cocaine use.[181]

Lung Parenchyma/Alveolar Space

Cocaine is one of many drugs that can cause lung parenchymal changes.[182] The term "crack lung" defines a syndrome that is seen between 1 and 48 h after heavy smoking of cocaine and manifests as fever, hypoxemia, hemoptysis, diffuse alveolar infiltrates without pleural effusions, pulmonary and peripheral eosinophils, and IgE deposition within the lung.[142,183,184] Removing the cause by stopping the use of "crack" cocaine is clearly indicated, but it is unclear whether supportive care alone or supportive care plus immunosuppressive agents like corticosteroids is the optimal treatment. A series of three patients in the United Kingdom developed "crack lung" after smoking cocaine prepared with ammonia.[185] One unconscious patient had the diagnosis of "crack lung" aided by the presence of bilateral thermal burns and later confirmed by history.[186]

Diffuse pulmonary hemorrhage outside of the complete "crack lung" syndrome also has been reported.[159,187–189] Diffuse pulmonary hemorrhage has been observed after the use of cocaine hydrochloride by the nasal route.[190] The pulmonary hemorrhage associated with cocaine smoking can result in massive hemoptysis.[191] Subclinical hemorrhage appears to be relatively common, as suggested by a study of volunteers including nonsmokers, "crack" cocaine smokers, "crack" cocaine and tobacco smokers, and smokers of tobacco alone who underwent bronchoalveolar lavage.[192]

Macrophages from cocaine or cocaine and tobacco smokers had elevated iron and ferritin levels compared with nonsmokers or tobacco-only smokers.

As noted previously, chronic damage to the pulmonary microcirculation occurs in "crack" cocaine smokers;[174] pulmonary hemorrhage associated with anti–glomerular basement membrane antibody-mediated glomerulonephritis also has been noted.[193] A spectrum of cocaine-induced vasculitis has been described, some with positive ANCA and some without.[194] The cocaine additive levamisole has been associated with the development of a positive ANCA and Wegener-like granulomatosis with chronic sinus disease, hemoptysis, skin abnormalities, and glomerulonephritis.[195–197] A case of cocaine-induced eosinophilic granulomatosis with polyangiitis (Churg-Strauss vasculitis) with pulmonary infiltrates and skin/muscle biopsies demonstrating eosinophilic angiitis has been reported.[198] Another cocaine smoker was reported to develop rhabdomyolysis and hemoptysis that mimicked a pulmonary embolism.[199] Other cocaine-associated reports of parenchymal lung abnormalities include a "crack" cocaine–induced syndrome that mimicked sarcoidosis, as well as talc foreign body and cellulose granulomas in cocaine sniffers,[200–202] and cocaine-induced eosinophilic lung diseases/Loeffler syndrome.[203–205] In a case of progressive chronic interstitial pneumonitis associated with "crack" cocaine abuse, a lung biopsy revealed histiocytes with extensive accumulation of silica.[206]

Although cocaine-associated pulmonary edema is noted on autopsy of patients who have died of cocaine overdoses,[207] an early report of a series of five acutely ill patients demonstrated what was thought to be noncardiogenic pulmonary edema.[208] Several other case reports have reported presumed noncardiogenic pulmonary edema after smoking or using cocaine IV.[209,210] Pulmonary edema in an infant following passive freebase "crack" cocaine smoke exposure also has been reported.[211] Postoperative pulmonary edema occurred in a cocaine addict despite reportedly not having used cocaine for 2 weeks.[212] Reactive oxygen species as the result of norcocaine and subsequent redox cycling between the N-hydroxy metabolite and a nitroxide radical of cocaine are postulated as one cause of pulmonary edema and interstitial lung disease with cocaine.[213] Two cocaine users who developed a "flu-like" syndrome after using cocaine and presented with interstitial lung damage had allelic variants for a vitamin K epoxide reductase complex and CYP2C9/CYP2C19.[214]

In addition to noncardiogenic pulmonary edema and other interstitial lung changes with cocaine, alveolar accumulation of carbonaceous material on bronchoalveolar lavage in a cocaine smoker with pulmonary infiltrates was reported.[215] A retrospective study of bronchoalveolar fluid or sputum in 14 hospitalized patients with a history of heavy cocaine smoking found carbonaceous sediment similar to heavy tobacco smokers but, unlike in tobacco use, in the cytoplasm of alveolar macrophages.[216] One of the hallmarks of "crack" cocaine smokers is the production of carbonaceous sputum.

Other parenchymal injuries include the case of patient with bronchiolitis obliterans organizing pneumonia thought to be associated with heavy freebase cocaine smoking.[217] Pulmonary embolism with infarction was also reported in a healthy young cocaine smoker without pre-existing disease or distal source.[218] A case of exogenous lipoid pneumonia was reported from a smoker of cocaine who mixed his freebase cocaine with petroleum jelly to make the drug last longer.[219] The obvious limitation of these case reports and few case series is that the association of these pathologic processes with cocaine use does not establish causality.

Little evidence exists, though, of an increased risk for chronic bronchitis, and only a slight increased risk of pneumonia was seen in cocaine users between 35 and 49 years of age in the United States between 2005 and 2007 in the National Surveys on Drug Use and Health.[220] In contrast, data from London using a case-control study approach found a relative risk of 2.4 (95% CI, 2.0–2.9; $p < 0.001$) for smear-positive tuberculosis compared with non-drug users.[221] A case of botulism from a *Clostridium botulinum* sinusitis was reported in a 25-year-old male who had used intranasal cocaine.[222] His initial bulbar paralysis became complete flaccid quadriplegia that required 6 months of mechanical ventilator support before a gradual recovery.

HUFFING/VOLATILE SUBSTANCE MISUSE

The use of volatile substances to induce intoxication ("huffing") is inexpensive and popular among teens but used by all ages.[223] Aerosol paints, adhesives, glues, air fresheners (butane or isobutene), gas fuels, and computer dusters containing 1,1-difluorothane are the volatile substances (VS) most abused.[223] The U.S. National Electronic Injury Surveillance System has reported a fivefold increase in duster spray inhalation–related injuries between 2008 and 2016.[224] VS toxicity is mainly neurologic, cardiac, and dermatologic, but the respiratory tract also may be affected. Rapid airway compromise from upper airway frostbite following recreational use of "huffed" air duster has been reported.[225] Orofacial and digital frostbite from VS abuse using aerosolized computer cleaner containing the fluorocarbon HFC-134a resulted in a loss of consciousness but no requirement for intubation.[226]

Volatile substance misuse (VSM) involves a variety of compounds that can cause a variety of pulmonary injuries. An outbreak of pulmonary toxicity occurred following a change in formulation of a commercial leather conditioner, with complaints of cough, chest pain, and shortness of breath.[224] A case of pneumomediastinum and pneumopericardium along with subcutaneous emphysema was reported after a 32-year-old man inhaled 6 to 10 cans of a computer cleaning product containing 1-1-difluoroethane.[227] An 18-year-old male who sniffed keyboard cleaner developed pneumonia, diffuse alveolar hemorrhage, and hemoptysis culminating in death.[228] Using technetium-99m DTPA aerosol to study alveolar-capillary permeability has shown that glue-sniffers and other VS abusers have abnormalities in pulmonary alveolar-capillary membrane function.[229] A case-control study compared 31 males with an average age of 14.6 years (9–18) at the onset of VSM to 19 control subjects.[230] The VS abusers had complaints of nasal congestion (45.2%), sputum production (38.7%), exercise intolerance (32.3%), and cough (22.6%). A reduction in FVC consistent with a restrictive pattern was noted on spirometry, and these changes seemed to correlate with abnormalities on HRCT.[230] Sudden death with pulmonary edema has been reported as a result of VSM using glue and gasoline.[231,232] Anti–glomerular basement membrane (GBM) disease (Goodpasture syndrome), an autoimmune disease that is characterized by glomerulonephritis, diffuse alveolar hemorrhage, and anti-GBM antibodies has been linked in part to hydrocarbon exposure.[233] A review of all reported cases of anti-GBM disease and hydrocarbon exposure determined that such cases accounted for 6% of all reported cases and found no disease features or predictors of outcome associated with type or duration of hydrocarbon exposure.[233] The 2005–2007 National Surveys on Drug Use and Health for bronchitis with relationship to inhalant exposures of ≤1 year, 2 to 10 years, and ≥11 years in duration found that compared with "never-users," the OR for development of bronchitis was 1.54 (95% CI, 1.30–1.82), 1.51 (95% CI, 1.21–1.89), and 1.46 (95% CI, 0.92–2.26), respectively. The same exposure categories for pneumonia found an OR of 1.52 (95% CI, 1.22–1.90), 1.68 (95% CI, 1.26–2.24), and 1.57 (95% CI, 0.98–2.50), respectively.[220] Although the literature is not as deep for pulmonary toxicity with VSM as with the other RDs reviewed, it still suggests a significant respiratory risk.

CONCLUSION

Use and abuse of RDs are associated with a variety of abnormalities of the respiratory system, ranging from upper airway injury to infectious and noninfectious disorders of the pulmonary vasculature and lung parenchyma. Patterns of involvement vary by drug and route of administration. Some respiratory manifestations are related to mechanisms of administration (embolization of needle fragments or pneumothorax due to supraclavicular drug injection) and adulterants, rather than due to the RDs themselves. RD use that includes sniffing, inhaling, IV injecting, or burning and smoking agents appear to be associated with significant pulmonary risks. Familiarity with the various direct and indirect respiratory system manifestations of RD use and abuse is crucial for the practicing pulmonary physician.

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CHAPTER 67

The Lungs in Patients with Inborn Errors of Metabolism

Timothy Craig Allen

INTRODUCTION

A variety of inherited systemic conditions cause different types of disease-producing chemical imbalances affecting essentially all organs to some degree; these conditions are called *inborn errors of metabolism* and also are termed *inherited metabolic disorders.*[1–16] Each is characterized by a specific genetic defect resulting in an abnormality of an enzyme necessary for the degradation of a chemical substance.[2,6] The disruption of the chemical constituent's degradation results in disease by causing either a deficiency of a substance or a pathologic accumulation of a substance.[1,2,6,9] The first of these disorders was identified by Sir Archibald Garrod, who coined the term *inborn errors of metabolism* in 1902.[14] There are currently more than 600 inborn errors of metabolism that have been discovered.[2,15]

Each specific inborn error of metabolism is rare, but overall, approximately 1 in 1000 people are affected.[1,2,6] Most show autosomal recessive inheritance; however, X-linked recessive inheritance occurs, and, less commonly, autosomal dominant inheritance.[9] Most of these diseases arise in children; however, with the identification of attenuated variants, and with continuing improved survival, some of the conditions must be considered in any-age patients.[1,2,6]

Inborn errors of metabolism often present with unexpected findings and lead to a high clinical suspicion. Fast and accurate radiologic diagnosis and clinical–radiologic correlation are critical for successful therapy because newer and more effective approaches are being designed and require early diagnosis.[2,6] While specialists with expertise in various inborn errors of metabolism are found in academic institutions, primary care physicians and pediatricians are frequently the first physicians to encounter these patients.[9]

Some conditions fall into a few broad groups, including disorders of amino acid metabolism, organic acidurias, urea cycle defects, disorders of ketogenesis and ketolysis, disorders of fatty acid oxidation, lysosomal storage disorders, and mitochondrial disease.[2,6] The lung is rarely a primary site of clinical disease in these patients; however, pulmonary involvement occurs in many of the disorders, resulting in clinically significant lung disease in some.[2,5,16] Pulmonary infections are not an uncommon secondary feature in many inborn errors of metabolism. This chapter highlights some specific inborn errors of metabolism in which lung disease may be a clinically significant feature.

ACID SPHINGOMYELINASE DEFICIENCY (NIEMANN-PICK DISEASE TYPES A AND B)

An autosomal recessive condition, acid sphingomyelinase (ASM) deficiency, has a phenotype that occurs in a continuum. Niemann-Pick disease type A (NPA) shows severe, neuropathic disease with early symptoms, resulting in death in infancy or early childhood. Niemann-Pick disease type B (NPB) shows nonneuropathic disease with generally later onset and milder symptoms.[1–4,17–25] Patients with NPA typically develop hepatosplenomegaly by approximately 3 months of age. Hepatosplenomegaly may become massive and is often fatal within 3 years. Psychomotor development usually takes place within 2 months, after which patients deteriorate. NPB patients typically exhibit milder hepatosplenomegaly, and patients may survive to adulthood. These patients often have progressive, clinically significant pulmonary alterations.[22,26,27] Diagnosis is confirmed by demonstration of <10% normal residual acid sphingomyelinase activity in peripheral blood lymphocytes or cultured skin fibroblasts.

NPA causes radiographic changes of interstitial lung disease due to sphingomyelin storage[30] within pulmonary macrophages. Patients with NPA often have low arterial blood oxygen levels. They experience frequent respiratory infections that may culminate in respiratory failure and death.[17,20,21,29,30] Patients with NPB may develop pulmonary complications at any age.[29,30] Radiographic changes of interstitial lung disease occur even though each individual patient's symptoms may vary dramatically. Further, the radiographic changes usually do not correlate with the severity of their pulmonary function alterations.[20,22,26] Cystic lung disease may be seen in patients with NPB.[31] Whole lung lavage has been attempted for symptomatic treatment.[32] Pulmonary fibrosis occurs over time.

Radiographically, patients with MPB exhibit nodular infiltrates and linear strands, with predominantly basilar honeycombing.[27,33] Histologically, there is predominantly normal interstitial architecture, with airspaces filled with Niemann-Pick cells, which are enlarged histiocytes with finely vacuolated cytoplasm[34] (Figs. 67-1 and 67-2). CD68 immunostain highlights these cells and may assist in establishing their presence. Pathologists have termed these collections of cells *sea blue histiocytosis* because of their vivid blue staining with May-Grunwald Giemsa stain. Pulmonary fibrosis may occur over time (Fig. 67-3).

NIEMANN-PICK DISEASE TYPE C

A rare, autosomal recessive inborn error of metabolism, Niemann-Pick disease type C (NPC) is characterized by impaired intracellular lipid trafficking and accumulation of cholesterol and glycosphingolipids in the brain and other organs.[35–42] Diagnosis is rendered via biochemical testing showing impaired cholesterol esterification and positive filipin staining in cultured fibroblasts.

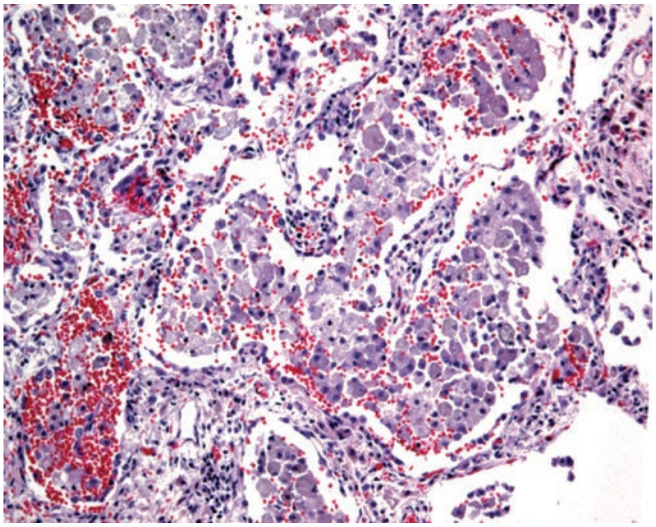

Figure 67-1 Low-power image of lung in Niemann-Pick disease showing collections of foam cells within alveoli.

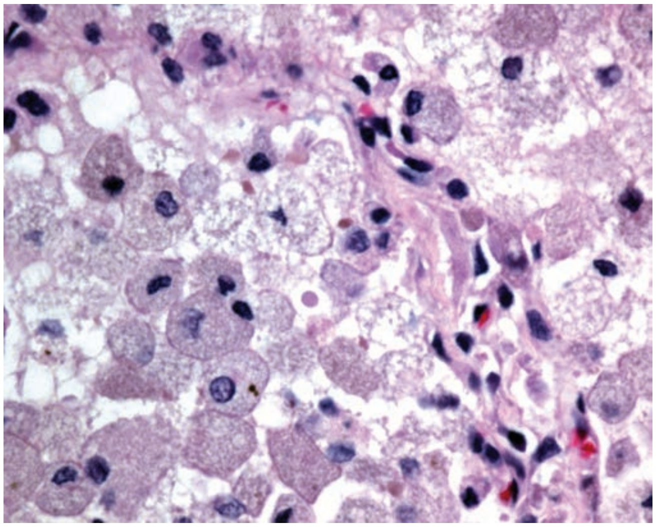

Figure 67-2 High-power image of lung in Niemann-Pick disease showing enlarged histiocytes with finely vacuolated cytoplasm within the alveolar spaces.

Patients exhibit saccadic eye movement abnormalities or vertical supranuclear gaze palsy; cerebellar signs include ataxia, dystonia/dysmetria, dysarthria and dysphagia, gelastic cataplexy, and epileptic seizures.[35,41] Cataplexy, dystonia, and seizures are treated symptomatically, and physical therapy is used to maintain independent mobility. Approximately 95% of cases of NPC are due to mutations of the *NPC1* gene, and the remainder are due to mutations of the *NPC2* gene.[35]

NPC may produce symptoms in patients of any age, and the initial presentation may occur from neonate to adult. Infants usually display nonspecific symptoms, making a definitive diagnosis difficult. In addition to liver disease, infants may present with often-fatal pulmonary failure caused by impaired gas exchange secondary to infiltration of the lungs with foam cells. Patients presenting in childhood, adolescence, or adulthood usually do not have pronounced pulmonary involvement.[38–40,45] These patients may develop pulmonary alveolar proteinosis, perhaps secondary to the loss of normal NPC2 protein expression in alveolar macrophages and accumulation of functionally inactive cholesterol-rich surfactant.[41,42,44]

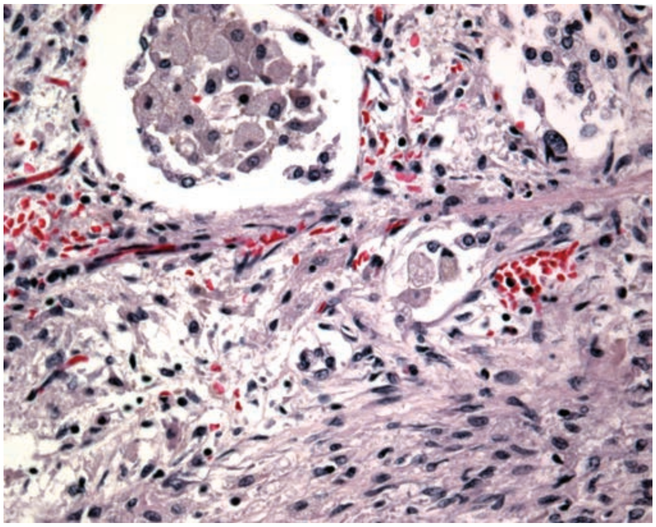

Figure 67-3 High-power image of lung in long-standing Niemann-Pick disease showing developing pulmonary fibrosis.

Bronchoalveolar lavage reportedly improves pulmonary symptoms in children with foam cell infiltrates. Pathologic features on biopsy are similar to those seen with patients with NPA and NPB.

GAUCHER DISEASE

An autosomal recessive disease, Gaucher disease (GD) is due to inadequate lysosomal enzyme glucosylceramidase activity, resulting in the accumulation of glucosylceramide, the enzyme's undegraded substrate, and other glycolipids.[1–4,16,46–49] The undegraded substrate arises primarily from the breakdown of red blood cells and other tissue cells and is then engulfed by monocytes and macrophages. Central nervous system involvement with GD may be due to membrane ganglioside turnover; however, neuron death also may be causative.[50]

GD consists of three main clinical subtypes and two additional subtypes, each with its own characteristic features. Types 1, 2, and 3 GD often exhibit lung involvement. Type 1 GD is clinically characterized by bone disease, particularly osteonecrosis, lytic and sclerotic, lesions, and osteopenia. Anemia, thrombocytopenia, and hepatosplenomegaly also occur. These patients usually do not exhibit central nervous system involvement.

Type 2 and type 3 GD are both characterized by central nervous system involvement with disease. Patients with type 2 GD usually present with disease before age 2 years and exhibit poor psychomotor development. They rapidly deteriorate and usually die between ages 2 and 4 years. In contrast, patients with Type 3 GD usually present before age 2 years; however, these patients slowly progress, and some survive to adulthood. There are also 2 additional subtypes of GD, in which pulmonary involvement is not characteristic. Cardiovascular GD exhibits mitral value and aortic valve calcification, corneal opacities, and supranuclear ophthalmoplegia. Perinatal lethal GD shows nonimmune hydrops fetalis or skin abnormalities.

GD may be caused by mutations in saposin C and acid-β-glucosidase.[51] Diagnosis requires the demonstration of inadequate glucosylceramidase activity in peripheral blood leukocytes or other cells. Treatments for these patients include enzyme replacement therapy and substrate reduction therapy.[52–55]

Pulmonary involvement in patients with GD involves pulmonary hypertension, lobar consolidation, and interstitial lung disease.[1,2,5,16,47,56,57] Pulmonary hypertension is a frequent finding in patients who have hepatic disease, possibly due to patients' inability to detoxify gut-derived factors that affect the pulmonary endothelium, with resultant pulmonary hypertension. However, it may also arise in patients without liver diseases.[56] Some patients with type 1 GD without pulmonary disease may, nonetheless, exhibit rapid fatigability, probably due to GD-induced circulatory impairment.[4,16,57,58]

Histologically, GD cells infiltrate the liver, spleen, and bone marrow. Lung involvement with GC cells is common in pediatric patients but not in adults.[59] Lung involvement with GC cells may cause clinical sequelae in up to one-third of patients.[60] GD cells usually involve septal capillaries, constituting the likely the cause of GD-associated pulmonary hypertension.[60] Intra-alveolar involvement with GD cells may be seen in infants and children and has been found to cause substantial septal thickening and patchy involvement in a lymphatic distribution.[60] The Gaucher cell has a characteristic "wrinkled paper" appearance (Fig. 67-4), and these cells are highlighted with periodic acid–Schiff (PAS) staining. Gaucher cells are CD68 negative, in contrast to alveolar macrophages, which display CD68 positivity.[61]

FABRY DISEASE

Fabry disease (FD) is an X-linked lysosomal storage disease caused by a deficiency of α-galactosidase A enzyme activity. The deficiency causes globotriaosylceramide accumulation in several tissues, including cardiomyocytes, smooth muscle cells, and endothelial

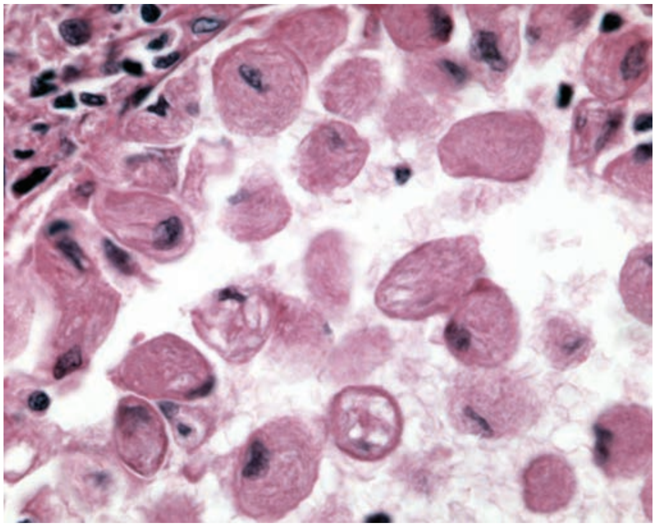

Figure 67-4 High-power image of Gaucher cells within an alveolar space showing the characteristic "wrinkled paper" appearance.

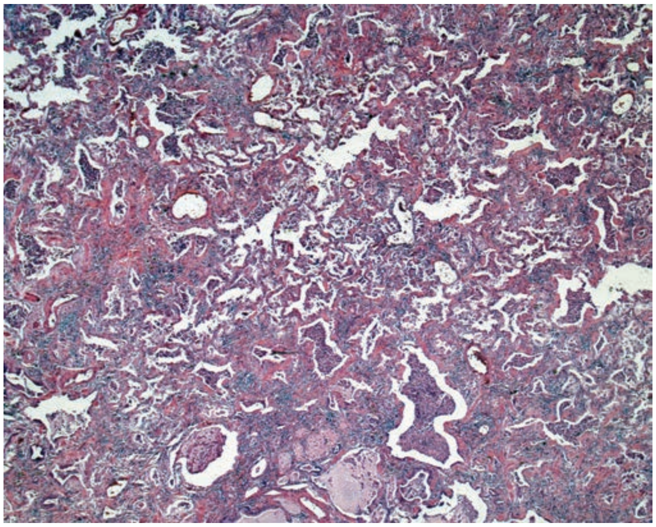

Figure 67-5 Medium-power image of lung in Hermansky-Pudlak syndrome showing a nonspecific interstitial pneumonia–like pattern.

cells.[1,2,4,62–65] Males with less than 1% enzyme activity develop the classic form of FD, which usually arises in childhood or adolescence and is characterized by proteinuria, corneal and lenticular opacities, angiokeratomas, hypohidrosis, and periodic episodes of markedly painful extremities. Gradually worsening renal disease leads to end-stage renal disease by the third to fifth decade of life. If these patients do not succumb to renal disease, they usually die of their cerebrovascular or cardiovascular disease.

Men with greater than 1% enzyme activity usually either exhibit a renal variant resulting in end-stage renal disease, but without extremity pain or skin lesions, or they exhibit a cardiac variant, often in their sixth to eighth decade, with proteinuria, mitral value insufficiency, cardiomyopathy, and left ventricular hypertrophy, but without end-stage renal disease. Women with FD, heterozygous for the disease, typically show later disease onset and milder symptoms than men. They may be asymptomatic throughout life or have mild symptoms mimicking men with classic FD. The diagnosis in men is made by displaying α-galactosidase A enzyme deficiency in leukocytes, cultured cells, or plasma. Enzyme measurement is not a reliable test for women, as some carriers have decreased enzyme activity, while others show normal activity. Enzyme testing for a mutation in *GLA*, the gene associated with FD, is necessary for diagnosis in women carriers. Men essentially always show a *GLA* mutation. Male patients with FD and symptomatic women carriers can be treated with enzyme replacement therapy.[58,62–64]

Both women and men may have pulmonary involvement with FD.[2,4,16,66–68] Patients with FD often exhibit dyspnea, wheezing, and chronic bronchitis; pulmonary function tests may show obstruction. Radiologic changes may be minimal and are not associated with the severity of pulmonary function. Histologic diagnosis of FD is made by identification of laminated inclusions in type II pneumocytes and capillary endothelium.[68] Lamellar inclusions reportedly have been identified in alveolar macrophages, ciliated epithelial cells, and goblet cells cytologically in induced sputum samples, brushings, and bronchoalveolar lavage specimens.[68–71]

HERMANSKY-PUDLAK SYNDROME

A rare, autosomal recessive, multisystem disease, Hermansky-Pudlak syndrome (HPS), also termed *oculocutaneous albinism syndrome*, involves intercellular trafficking and is characterized by tyrosinase-positive oculocutaneous albinism, a platelet storage pool deficiency that causes bleeding diatheses, and sometimes, pulmonary fibrosis.[4,72–84] Patients with HPS display congenital nystagmus, decreased visual acuity, iris transillumination, and variable skin and hair hypopigmentation. Approximately 15% may also develop granulomatous colitis.[76–78,85,86]

HPS is diagnosed clinically, and the ultrastructural absence of platelet dense bodies may be used as a confirmatory test. Patients with HPS usually exhibit easy bruising and prolonged bleeding. HPS is caused by mutations in several genes and causes several HPS subtypes, including *HPS1*, causing HPS-1; *AP3B1*, causing HPS-2, *HPS3*, causing HPS-3; *HPS4*, causing HPS-4; *HPS5*, causing HPS-5; *HPS6*, causing HPS-6; *DTNBP1*, causing HPS-7; *BLOC1S3*, causing HPS-8; and *BLOC1S*, causing HPS-9.[78,79,88]

Pulmonary involvement in patients with HPS often presents clinically and radiologically as pulmonary fibrosis. It is usually symptomatic by the fourth decade. The disease is progressive and causes restrictive lung changes, and it may cause death within a few years of pulmonary symptom onset. Pulmonary fibrosis is often identified in patients with HPS-1, HPS-2, and HPS-4; it is particularly prevalent in patients with HPS-1 from Puerto Rico.[77,85,89–96] Pulmonary fibrosis is not characteristically present in patients with HPS-3, HPS-5, or HPS-6 disease. Lung transplantation may be appropriate for some patients.[97] The cause of the pulmonary fibrosis is unknown; however, it has been hypothesized that a postinflammatory response is the causative factor.[98] Treatment with pirfenidone has been attempted in patients with pulmonary function greater than 50% of normal, with some reported benefit.[90]

Histologically, the pulmonary fibrosis may show a pattern of usual interstitial pneumonia or nonspecific interstitial pneumonia.[85,98] Ceroid-filled macrophages fill airspaces and the lung interstitium (Figs. 67-5, 67-6, and 67-7) and may be identified with bronchoalveolar lavage.[99]

CHOLESTERYL ESTER STORAGE DISEASE

Cholesteryl ester storage disease (CESD) is a rare autosomal recessive disease characterized by lysosomal acid lipase/cholesteryl ester hydrolase deficiency. Patients with CESD have some enzyme activity, and patients with complete enzyme deficiency are properly diagnosed as having Wolman disease.[101–103] In patients with CESD, there is deposition of cholesteryl ester in the liver, as well as in the bone marrow, gastrointestinal tract, and spleen. Gastrointestinal bleeding, often occult, and hepatomegaly are frequently identified.[103] Patients usually survive into adulthood, ultimately succumbing to chronic hepatic failure or premature atherosclerosis.[101]

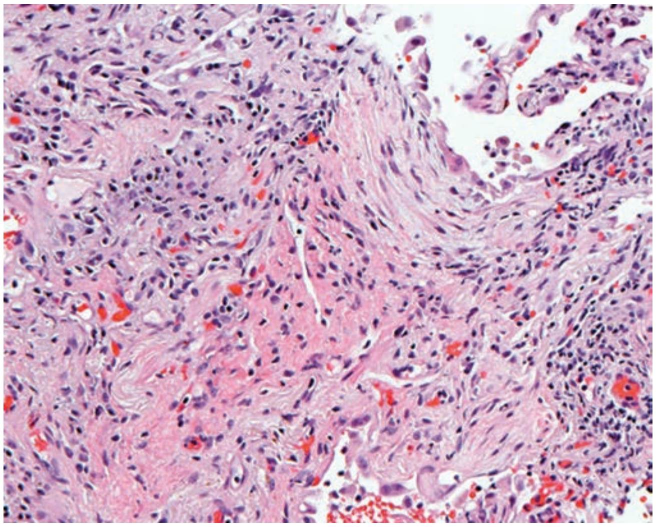

Figure 67-6 Higher-power image of lung in Hermansky-Pudlak syndrome showing a usual interstitial pneumonia–like pattern.

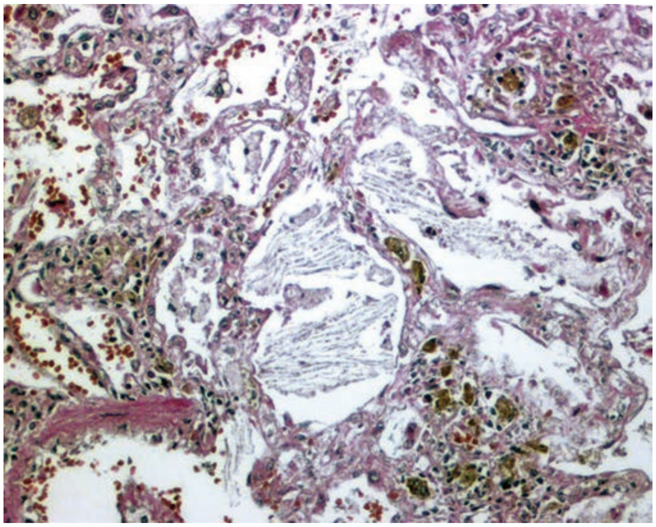

Figure 67-8 Medium-power image of lung in cholesteryl ester storage disease showing cholesteryl ester accumulation within alveolar macrophages, and interstitial fibroblasts.

Pulmonary involvement with CESD is uncommon but may occur secondary to the accumulation of cholesteryl esters in alveolar macrophages and interstitial fibroblasts **(Figs. 67-8 and 67-9)**. The pulmonary arteries can also develop intimal foam cell deposits, often complicated by associated reactive fibrosis.[104,105] Treatment of pulmonary disease is supportive; however, for most patients, pulmonary involvement is not life-threatening.[104]

MUCOPOLYSACCHARIDOSIS TYPE I

Mucopolysaccharidosis type I (MPS1), an autosomal recessive disease, is a progressive multisystem lysosomal storage disorder caused by deficiency of the enzyme α-L-iduronidase.[106,107] Patients with MPS1 vary in disease severity. Patients with Hurler syndrome, Hurler-Scheie syndrome, and Scheie syndrome show overlapping clinical features and no biochemical differences and currently are diagnosed clinically with either severe MPS1 (formerly, Hurler syndrome) or attenuated MPS1 (formerly, Hurler-Scheie Syndrome and Scheie Syndrome). MPS1 is diagnosed by demonstration of insufficient α-L-iduronidase activity in plasma, cultured fibroblasts, or peripheral blood leukocytes. Treatments include enzyme replacement therapy and bone marrow transplantation.[106–109] Attenuated patients with MPS1 may have pulmonary disease and demonstrate changes in forced vital capacity. In patients with pulmonary disease, respiratory complications are usually the cause of death.[110]

MUCOPOLYSACCHARIDOSIS TYPE II

Mucopolysaccharidosis type II (MPSII), also termed *Hunter syndrome*, is inherited as an X-linked recessive multisystem disease and is characterized by the pathologic lysosomal storage of glycosaminoglycans.[111–113] Most patients are men; carrier women rarely display clinical features.

Patients with MPSII usually have central nervous system involvement, with progressive deterioration of cognitive function. These patients usually have macrocephaly, with or without communicating hydrocephalus, hoarseness, hearing loss, macroglossia, splenomegaly, hepatomegaly, short stature, dysostosis multiplex, and joint contractures.[112,113] Severe cases have had cardiac disease and progressive airway disease and often died before or within their second

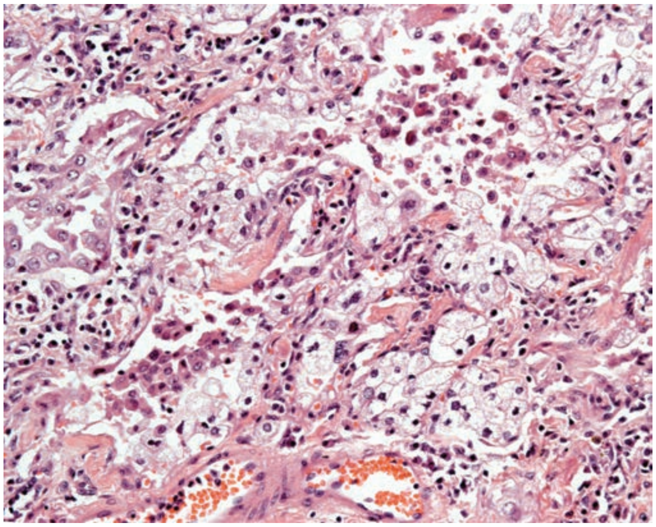

Figure 67-7 High-power image of lung in Hermansky-Pudlak syndrome showing ceroid-filled histiocytes within alveolar spaces.

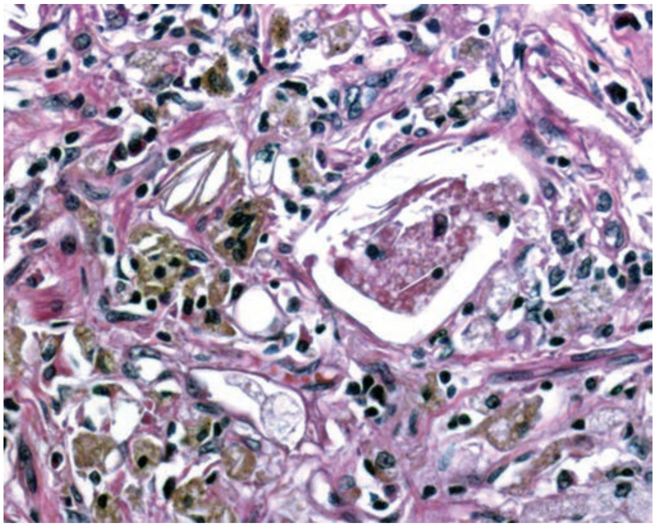

Figure 67-9 High-power image of lung in cholesteryl ester storage disease showing alveolar macrophages containing cholesteryl esters.

decade of life. Disease severity is on a continuum, and clinical manifestations and progression can vary significantly. Some patients with milder forms of disease display normal intelligence into early adulthood and survival into the sixth decade.[112,113]

Testing for deficient iduronate sulfatase enzyme activity in plasma, fibroblasts, or white blood cells may be performed, and diagnosis may be confirmed by molecular testing of *IDS*, the gene associated with MPSII. Treatment has traditionally been supportive.[111] Bone marrow transplantation has been unsuccessfully attempted.[114] Enzyme replacement therapy is being studied.[112,115–118]

Patients with MPSII frequently develop frequent upper respiratory infections early, with progressive airway narrowing due to severe airway obstruction caused by the accumulation of glycosaminoglycans in the tongue, upper airway, and trachea.[111,113] Progressive airway obstruction with associated sleep apnea may require tracheostomy. Airway obstruction, along with hepatomegaly and splenomegaly, thick pulmonary secretions, and chest wall stiffness may reduce lung volumes.[112]

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CHAPTER 68

Alveolar Hemorrhage Syndromes

Joseph P. Lynch, III
Michael C. Fishbein
Tisha S. Wang

INTRODUCTION

Diffuse alveolar hemorrhage (DAH) is a potentially catastrophic complication of myriad immune and nonimmune disorders.[1–3] Clinical features are broad, but hemoptysis, infiltrates on chest imaging, hypoxemia, and progressive respiratory insufficiency are commonly seen in many other diverse etiologies.[3] Other causes of diffuse parenchymal infiltrates (e.g., cryptogenic organizing pneumonia, hypersensitivity pneumonia, pulmonary alveolar proteinosis, other interstitial or alveolar lung disorders) must be excluded. Additionally, *nonimmune causes* of pulmonary alveolar hemorrhage include endobronchial tumors, arteriovenous malformations or aneurysms, ulcerative tracheobronchitis, hemorrhagic pneumonia, bronchiectasis, congestive heart failure, uremia, thrombocytopenia or coagulopathy, pulmonary veno-occlusive disease, massive pulmonary embolism, and infections.[4,5] Depending upon the clinical scenario, coagulation profiles and ancillary tests (e.g., echocardiogram, chest computed tomographic [CT] pulmonary angiography, bronchoscopy) may be required to establish a specific diagnosis. A discussion of these disorders is beyond the scope of this chapter, which focuses primarily on *immune-mediated* causes of DAH. We begin with an overview of the many syndromes causing alveolar hemorrhage before discussing each individually.

AUTOIMMUNE CAUSES OF ALVEOLAR HEMORRHAGE: DIFFERENTIAL DIAGNOSIS

Autoimmune DAH results from diffuse injury to the pulmonary microvasculature (termed *capillaritis* or *endotheliitis*) (Table 68-1).[2,6] Systemic necrotizing vasculitides[1,7–10] (principally, microscopic polyangiitis [MPA][11–15] and granulomatosis with polyangiitis [GPA, formerly Wegener granulomatosis])[6,16] account for most cases of autoimmune DAH. Both GPA and MPA are often linked to antineutrophil cytoplasmic antibodies (ANCA)[13,16] and are encompassed in the term *ANCA-associated vasculitis (AAV)*.[17] Eosinophilic granulomatosis with polyangiitis (EGPA) (formerly Churg-Strauss Syndrome) is included as an AAV, even though EGPA is only rarely associated with DAH.[17–20] Other causes of autoimmune DAH include anti–glomerular basement membrane (anti-GBM) antibody disease,[21–25] connective tissue disease (CTD, principally systemic lupus erythematosus [SLE]),[26–30] and exogenous agents or drugs.[31–34] In many of these disorders, rapidly progressive glomerulonephritis (RPGN) is concomitantly present.[35,36] In most patients with autoimmune DAH and glomerulonephritis (GN), anti-GBM antibody and immune complexes are lacking.[36] The term *pauci-immune glomerulonephritis* has been used to refer to this group of patients, who encompass a heterogenous group of disorders.[36–38] Interestingly, rare patients with “pauci-immune capillaritis” have DAH but no extrapulmonary involvement.[39] Idiopathic pulmonary hemosiderosis, a rare cause of recurrent DAH with no renal or extrapulmonary component, occurs primarily in children[40–42] and remains a diagnosis of exclusion.

TABLE 68-1 Etiology of Autoimmune Diffuse Alveolar Hemorrhage

Anti–glomerular basement membrane antibody disease (Goodpasture syndrome)
Antineutrophil cytoplasmic antibody (ANCA)-mediated vasculitis (e.g., granulomatosis and polyangiitis [formerly Wegener granulomatosis], microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis [formerly Churg-Strauss syndrome], pauci-immune glomerulonephritis)
Idiopathic rapidly progressive glomerulonephritis
Collagen vascular disease (e.g., systemic lupus erythematosus)
Immunocompromised status (e.g., bone marrow transplant, AIDS)
Exogenous agents or drugs (e.g., trimellitic anhydride, isocyanates, D-penicillamine, cocaine)
Idiopathic pulmonary hemosiderosis (pathogenesis unknown)

Differentiating these diverse syndromes can usually be accomplished by serologic studies and by kidney biopsy. In such cases, lung biopsy is not required. GN can be demonstrated in the great majority of patients with DAH complicating MPA,[1,12,13] GPA,[1,16] or anti-GBM disease.[24] By contrast, the kidneys may be spared in DAH associated with CTD,[26,28,29] stem cell transplant recipients,[43–46] or immunocompromised patients.[47,48] Urinalysis (to look for microscopic hematuria, red cell casts, and proteinuria) and measurement of renal function should always be done in the diagnostic evaluation of DAH. Findings consistent with GN warrant a prompt and aggressive evaluation that should include percutaneous needle biopsy of the kidney.

CLINICAL FEATURES OF AUTOIMMUNE ALVEOLAR HEMORRHAGE

Irrespective of etiology, the clinical, radiographic, and histopathologic features of DAH may be similar.[1–3] Classic findings are hemoptysis, diffuse alveolar infiltrates, hypoxemia, renal failure, and iron-deficiency anemia.[3] However, the clinical spectrum is wide, and many of these features may be subtle or absent. In this context, the diagnosis of DAH may be difficult, as signs and symptoms overlap with diverse etiologies of diffuse alveolar infiltrates. Prompt diagnosis and institution of therapy is vital to avert early mortality from DAH and late sequelae from end-stage renal disease (ESRD). Chest radiographs typically reveal bilateral alveolar infiltrates, often with a batwing appearance. However, focal, and even unilateral, patterns indistinguishable from pneumonia may occur.[49] Following cessation of bleeding, infiltrates markedly improve or normalize within 24 to 72 h (Fig. 68-1). A presumptive diagnosis of DAH can often be made by a combination of clinical and serologic findings and bronchoalveolar lavage (BAL) fluid. Grossly bloody BAL fluid (with progressively more blood with serial aliquots),[2,3,49] large numbers of hemosiderin-laden macrophages,[2,47] and the absence of purulent secretions or ancillary evidence for infection strongly support DAH as the cause of pulmonary infiltrates. Ancillary studies including serologies, renal function tests, and urinalysis may support the diagnosis.

DIAGNOSIS

Diagnosis of an alveolar hemorrhage syndrome may entail lung or kidney biopsy, as discussed below.

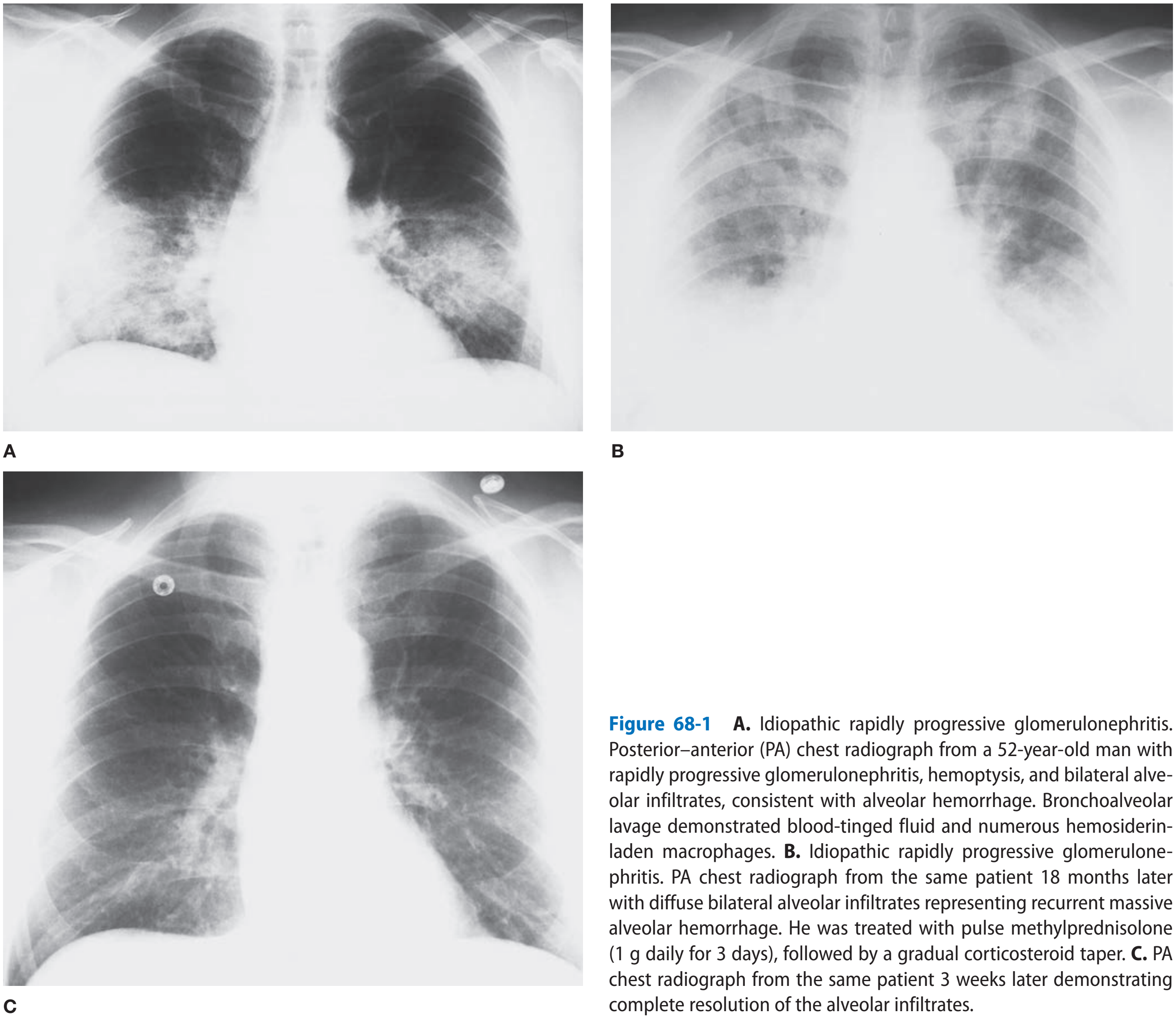

Figure 68-1 **A.** Idiopathic rapidly progressive glomerulonephritis. Posterior–anterior (PA) chest radiograph from a 52-year-old man with rapidly progressive glomerulonephritis, hemoptysis, and bilateral alveolar infiltrates, consistent with alveolar hemorrhage. Bronchoalveolar lavage demonstrated blood-tinged fluid and numerous hemosiderin-laden macrophages. **B.** Idiopathic rapidly progressive glomerulonephritis. PA chest radiograph from the same patient 18 months later with diffuse bilateral alveolar infiltrates representing recurrent massive alveolar hemorrhage. He was treated with pulse methylprednisolone (1 g daily for 3 days), followed by a gradual corticosteroid taper. **C.** PA chest radiograph from the same patient 3 weeks later demonstrating complete resolution of the alveolar infiltrates.

■ The Role of Lung Biopsy

The role of lung biopsy in the diagnosis of DAH and the determination of its etiology is controversial. We believe the risks of open or thoracoscopic lung biopsy are excessive in patients with severe DAH and respiratory failure. Postoperative complications, such as infection and air leaks, may be exacerbated by corticosteroids (CS) or immunosuppressive agents (IA) used to treat many of these immune-mediated DAH syndromes. Furthermore, histologic features are usually nonspecific. Predominant findings are extensive intra-alveolar hemorrhage and necrotizing pulmonary capillaritis (endotheliitis) (Fig. 68-2).[2] Capillaritis is characterized by neutrophilic infiltration of capillaries, fragmented neutrophils (leukocytoclasis), and necrosis of the capillary walls[2] (Fig. 68-3). Loss of the integrity of the alveolar-capillary basement membrane results in leakage of red blood cells and neutrophils into the alveolar space.[3] Hemosiderin-laden macrophages (siderophages) accumulate within the alveolar spaces and interstitium; their presence is a clue to prior episodes of alveolar hemorrhage[2] (Figs. 68-2B, 68-2C, and 68-4).

Capillaritis was initially described as a marker of systemic vasculitis, but it may also be observed in myriad disorders associated with DAH (e.g., SLE,[26] CTD,[3] anti-GBM disease,[21,24] stem cell/bone marrow[43,44] or lung transplantation,[50] and drug-induced DAH).[31,49,51] An associated venulitis and arteriolitis may sometimes be present, but larger vessels are spared.[2] Capillaritis is subtle and often overshadowed by DAH filling the alveolar spaces.

Pulmonary capillaritis can be diagnosed by transbronchial biopsy, but this diagnosis is made with greater confidence when larger biopsy specimens are obtained by video-assisted thoracoscopy or limited thoracotomy.[2] Additional pathologic features may be seen in patients with underlying granulomatous vasculitis (e.g., granulomas, necrosis, eosinophils).[2] Nongranulomatous inflammation in airways and lung interstitium, interstitial fibrosis, diffuse alveolar damage (DAD), fibrinous pleuritis, and organizing pneumonia have also been described in DAH associated with AAV.[2] It should be emphasized that histologic findings of alveolar hemorrhage and capillaritis, although distinctive, are nonspecific.[2] Immunofluorescent (IF) stains (of lung or kidney) or serologic markers (e.g., anti-GBM antibody, ANCA) are required to differentiate the various causes of autoimmune DAH[1,2] (Table 68-2). Linear deposits of immunoglobulin G (IgG) along alveolar septa are pathognomonic for anti-GBM disease.[21,24] A granular or "lumpy-bumpy" pattern of immune complex deposits may be seen in SLE, systemic necrotizing vasculitis, or immune complex–mediated idiopathic RPGN.[2] In ANCA-associated capillaritis, immune complexes are usually lacking (hence

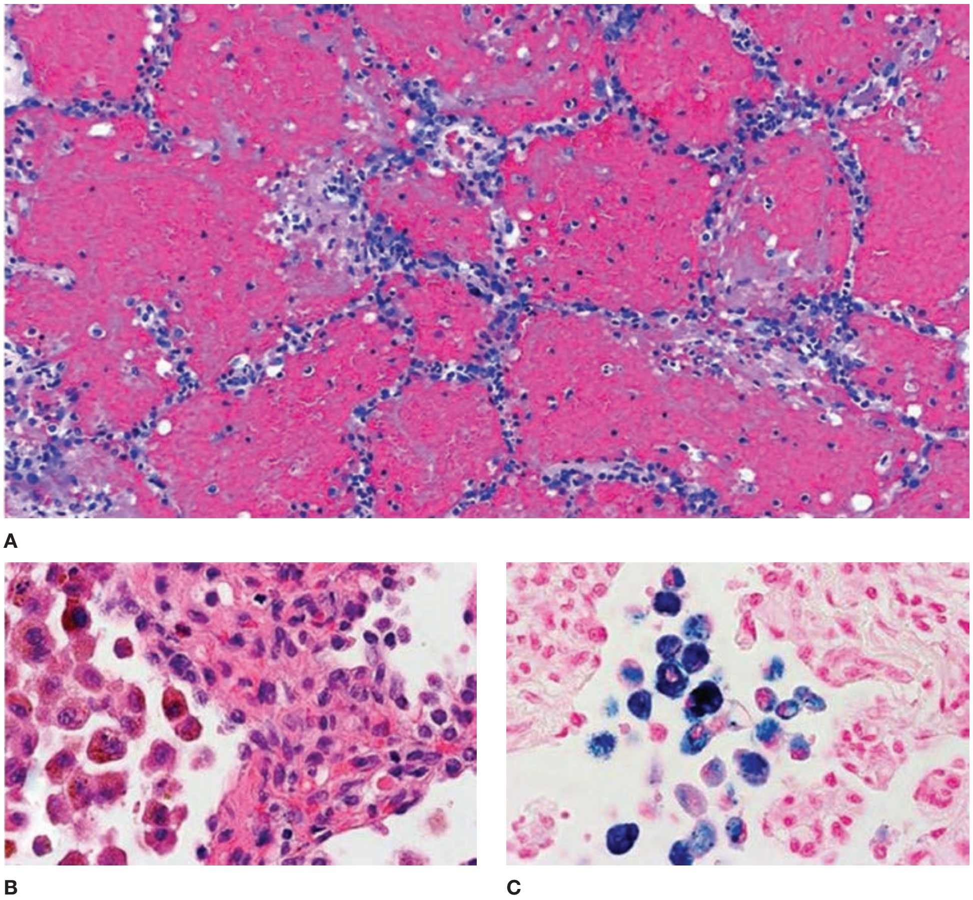

Figure 68-2 Alveolar hemorrhage. **A.** Acute hemorrhage with blood filling alveolar spaces (H&E stain, ×40). **B.** Pigment-laden macrophages (H&E stain, ×200) shown in **C** to be full of iron (blue cytoplasm) indicative of prior hemorrhage (Prussian blue stain, ×200).

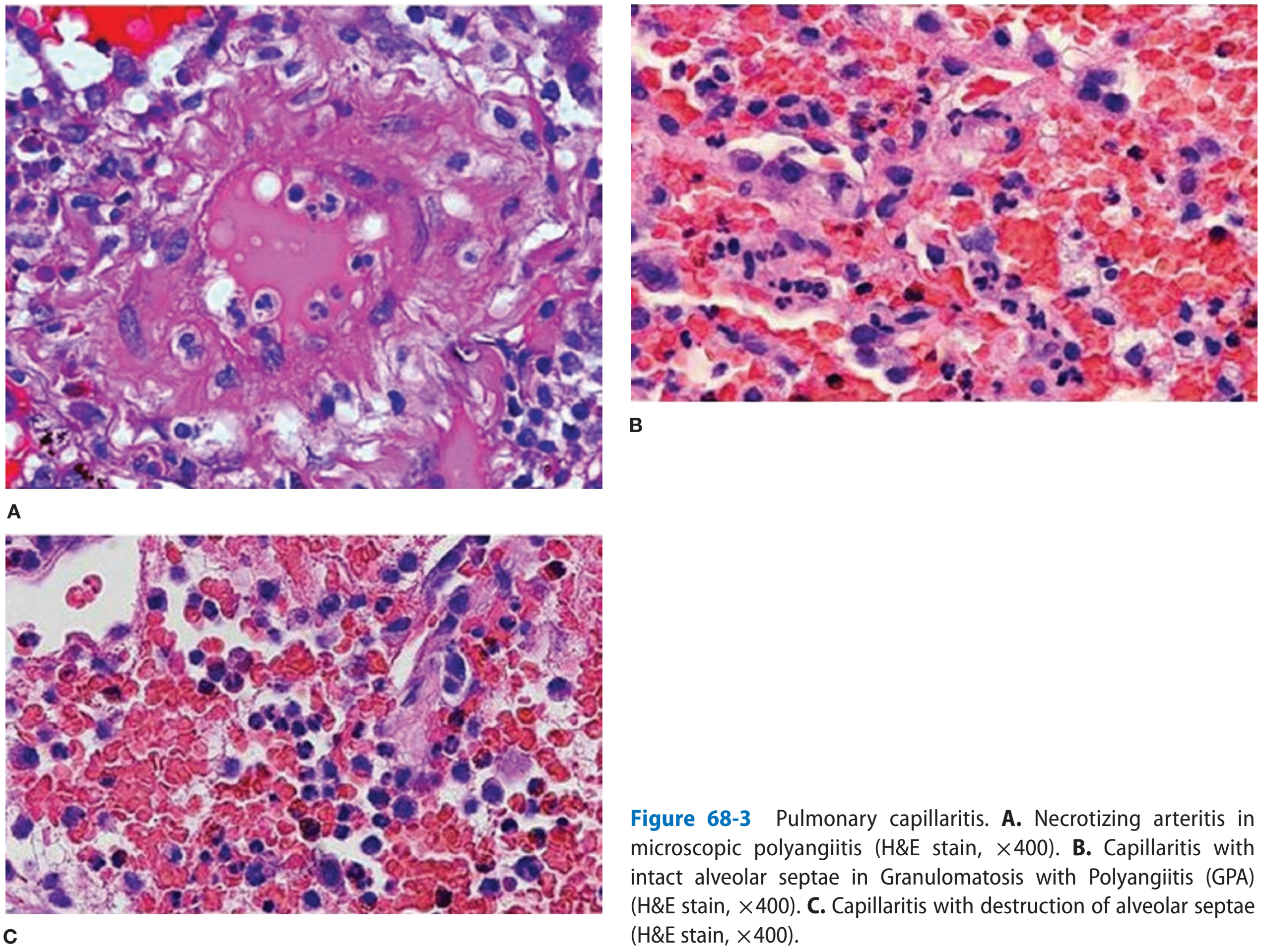

Figure 68-3 Pulmonary capillaritis. **A.** Necrotizing arteritis in microscopic polyangiitis (H&E stain, ×400). **B.** Capillaritis with intact alveolar septae in Granulomatosis with Polyangiitis (GPA) (H&E stain, ×400). **C.** Capillaritis with destruction of alveolar septae (H&E stain, ×400).

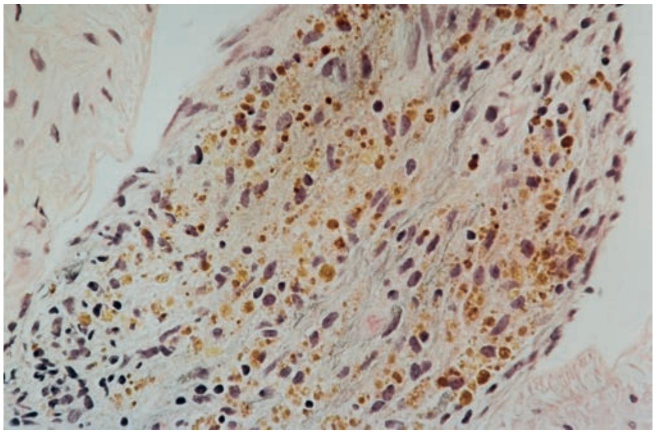

Figure 68-4 Hemosiderin-laden macrophages (siderophages) are prominent in the alveolar interstitium in a patient with recurrent alveolar hemorrhage (H&E). *(Reproduced with permission from Joseph Fantone, MD.)*

the term *pauci-immune*).[12,13] When immune DAH is suspected, a portion of the lung biopsy can be frozen for IF stains, but IF stains of lung tissue are logistically difficult, and nonspecific background staining may lead to misinterpretation. When GN is present concomitantly, kidney IF stains are more sensitive and reliable.

Despite the greater accuracy of surgical lung biopsy in evaluating DAH, flexible bronchoscopy with BAL is usually adequate to exclude infectious etiologies and support the diagnosis of DAH with a much better safety profile.[2,49] Bloody or serosanguinous BAL fluid (consistent with active or recent bleeding)[3,49] or hemosiderin-laden macrophages[2] (a clue to prior episodes of alveolar hemorrhage) may be sufficient to justify initiation of therapy provided clinical and serologic features are consistent. Thoracoscopic lung biopsy may be useful in *non-critically ill* patients with suspected DAH when ancillary studies, kidney biopsy, and BAL are nondiagnostic.[2]

■ The Role of Percutaneous Kidney Biopsy

Necrotizing GN is a cardinal (albeit nonspecific) feature of most immune-mediated DAH syndromes.[8,38] The histologic spectrum is varied, ranging from mild mesangial thickening to severe crescentic GN.[38] Vasculitis of renal arterioles is rarely found, even in granulomatous vasculitides. Because of the strong association of autoimmune DAH and GN, percutaneous kidney biopsy should be performed in any patient with suspected DAH who has abnormalities on urinalysis or renal function tests. Conventional hematoxylin and eosin (H&E) stains are nonspecific, but the demonstration of glomerular inflammation with necrosis and crescents supports the diagnosis of an immune-mediated etiology[52] (Fig. 68-5). IF stains may clarify the nature of the underlying disorder. Bright, linear IF staining along GBMs is pathognomonic for anti-GBM disease[22,24] (Fig. 68-6). A lumpy-bumpy IF pattern, consistent with deposits of immune complexes, is found in some cases of CTD[26] and in idiopathic immune complex–mediated GN.[53] Negative IF stains are characteristic of pauci-immune GN of necrotizing vasculitis.[37,38] Serologies are critically important in defining the underlying disorder responsible for DAH (particularly ANCA, anti-GBM antibody, and antinuclear antibodies). Recognizing the different pathogenetic mechanisms of these DAH syndromes is important, as the prognosis and treatment strategies may differ.

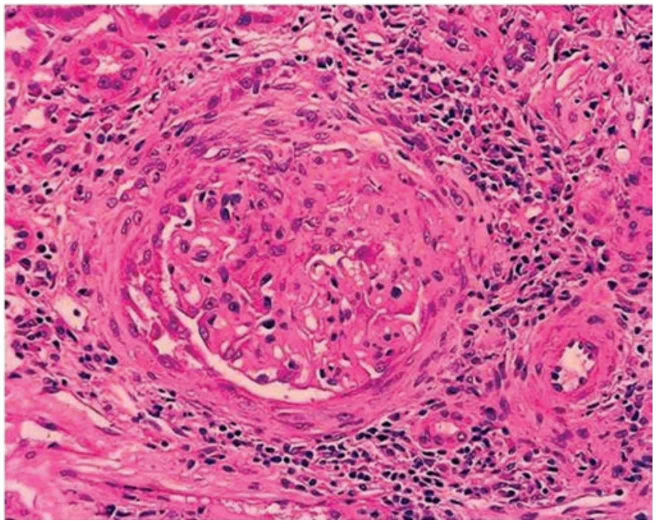

Figure 68-5 Segmental and necrotizing crescentic glomerulonephritis due to vasculitis (H&E).

THERAPY OF IMMUNE-MEDIATED ALVEOLAR HEMORRHAGE

Irrespective of etiology, the most immediate concern in patients with severe DAH is to control intrapulmonary bleeding, which may be fatal.[8] Measures to ensure adequate oxygenation are essential. Mechanical ventilation (MV) may be necessary in fulminant cases of DAH, to prevent death due to refractory hypoxemia. Priorities

TABLE 68-2 Autoimmune Diffuse Alveolar Hemorrhage: Pathology and Serology

	Lung Pathology		Renal Pathology		
	Histopathology	Immunofluorescence	Histopathology	Immunofluorescence	Serology
ABMA disease (Goodpasture syndrome)	± Capillaritis	Linear	Variable	Linear	ABMA (± p-ANCA)
Granulomatosis with polyangiitis	Capillaritis (± granulomatous)	Negative	Segmental necrosis, crescents	Pauci-immune	ANCA (c-ANCA ⋙ p-ANCA)
Microscopic polyangiitis	Capillaritis	Negative	Segmental necrosis, crescents	Pauci-immune	ANCA (p-ANCA or c-ANCA)
Systemic lupus erythematosus	Capillaritis	Granular	Variable	Granular	ANA
Idiopathic pulmonary hemosiderosis	± Capillaritis	Negative	Normal	—	Negative

ABMA, anti–basement membrane antibody; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; p-ANCA, perinuclear antineutrophil cytoplasmic antibody; c-ANCA, cytoplasmic antineutrophil cytoplasmic antibody.

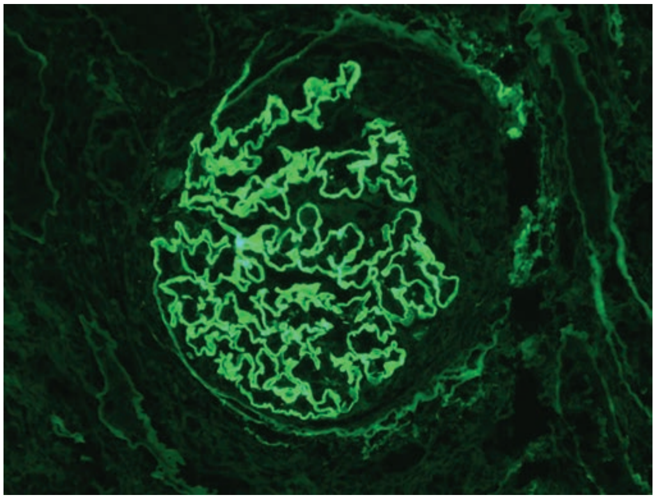

Figure 68-6 Linear immunofluorescent staining along glomeruli due to deposition of anti–glomerular basement membrane (anti-GBM) antibody.

should be airway protection, rapid hemodynamic stabilization, and intubation with a large (≥8 mm) endotracheal tube for severe cases requiring MV.[54] This allows for effective ventilation and facilitates the passage of a bronchoscope for suctioning as well as tamponade. Transfusion of red blood cells may be required to maintain an acceptable hematocrit and adequate blood pressure. In patients with severe hypoxemia despite MV, extracorporeal membrane oxygenation (ECMO) may be life-saving.[55–58]

Immune-mediated DAH (regardless of etiology) is a medical emergency and requires prompt administration of IV "pulse" methylprednisone (MP) 500 to 1000 mg daily for 3 days, even while pursuing a diagnostic workup.[49,59] Delaying pulse therapy in a critically ill patient for even a few hours may be catastrophic. Following initiation of therapy, bleeding may resolve quickly (often within 24 to 72 h) (Fig. 68-7). Following the 3-day pulse, the dose of MP should be reduced to approximately 60 mg per day (or equivalent) until control of the bleeding and extrapulmonary manifestations has been achieved. The subsequent dose and rate of corticosteroid (CS) taper need to be individualized, based upon clinical, radiographic, and serologic response. Optimally, the dose of CS should be reduced to 5 mg daily within 6 months, as data from the PEXIVAS Trial (including patients with AAV [GPA or MPA] with renal involvement or DAH) demonstrated that reduced dose of CS was noninferior to "standard" dose of CS and resulted in fewer infections.[60] For GPA, MPA, and anti-GBM disease, a second IA (typically, cyclophosphamide [CYC])[35,49,61] is added. For GPA and MPA, rituximab (RTX) may be given in lieu of CYC, as RTX is at least as effective, and possibly more effective than CYC,[62,63] with potentially less toxicity. Treatment of anti-GBM disease includes CS plus oral CYC (2 mg/kg/d), in addition to therapeutic plasma exchange (TPE; see below).[24] The role of IA or RTX for other causes of DAH or pulmonary renal syndromes has not been elucidated, as data are limited. Prophylaxis against *Pneumocystis jirovecii* is mandatory in patients receiving dual-agent immunosuppression. TPE is a central component of therapy for anti-GBM disease,[21,23,64] but its role for other disorders associated with DAH remains controversial[65] (see "ANCA-Associated Vasculitis," below).

Although data are limited to small series and case reports, anecdotal successes have been cited with recombinant activated factor VIIa (rFVIIa) in fulminant DAH secondary to vasculitis, anti-GBM disease, and SLE.[1,66,67] However, this agent does not have a primary role in DAH.

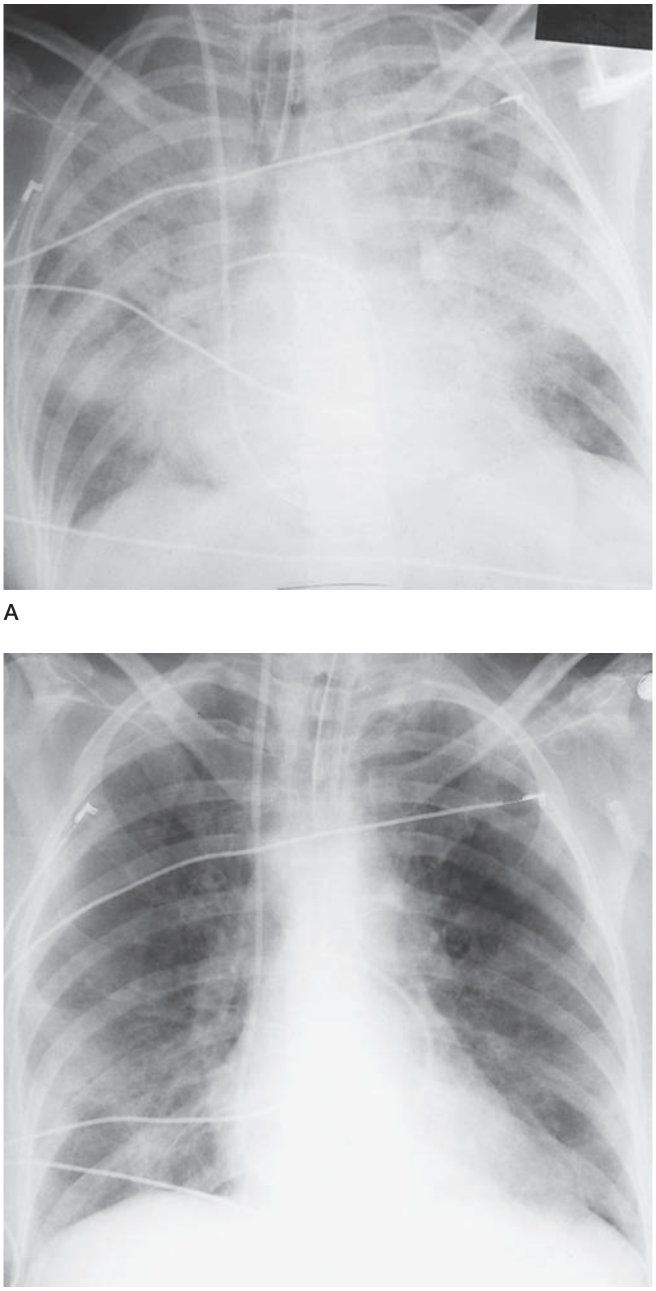

Figure 68-7 **A.** Alveolar hemorrhage due to microscopic polyarteritis (MPA). Posterior–anterior (PA) chest radiograph demonstrating massive alveolar infiltrates involving all lobes. Because of the severity of respiratory failure (requiring 16 cm H_2O of positive end-expiratory pressure to achieve acceptable oxygenation), no lung biopsy was performed. Urinalysis demonstrated numerous red cells and occasional red cell casts. Serum creatinine was 1.4 mg%. Pulse methylprednisolone (1 g daily × 3 days) was initiated, and renal biopsy was scheduled for the following morning. **B.** Alveolar hemorrhage due to MPA. PA chest radiograph from the same patient 12 h following initiation of pulse methylprednisolone. Marked improvement in alveolar infiltrates is evident. Renal biopsy demonstrated glomerulonephritis and a necrotizing vasculitis involving renal arterioles; no granulomas were present. Cyclophosphamide (2 mg/kg/d) was instituted, and corticosteroids were continued. Within 5 days, the infiltrates had cleared completely, and serum creatinine was 0.6 mg%.

SPECIFIC SYNDROMES

In the sections that follow, we discuss each of the autoimmune DAH syndromes.

Anti-GBM Disease (Goodpasture Syndrome)

Anti–glomerular basement membrane (anti-GBM) disease (Goodpasture syndrome), the prototype of pulmonary–renal syndromes, accounts for 18% to 32% of immune-mediated DAH.[22,24,68] This was the first disorder in which a primary role of antibodies was recognized as a cause of renal and/or pulmonary injury.[64] The demonstration of anti-GBM antibodies in tissue (typically kidney)[24,69] or in serum[21,24] is the cornerstone of the diagnosis. Classically, anti-GBM disease manifests as DAH and RPGN.[21,22,24,69] In 30% to 50% of patients with anti-GBM disease, GN occurs *without* DAH; DAH alone is rare (<5%).[21,24,68]

Epidemiology

Anti-GBM disease typically affects individuals between 20 and 45 years of age with a distinct male predominance.[21,24] The incidence has been estimated as 1 to 3 cases per million population per year.[70–72] Data from hospitalized patients in the United States identified 964 cases of anti-GBM disease from 2003 to 2014, for an overall prevalence of 10.3 cases per million admissions.[72]

Pathogenesis

The pathogenesis of anti-GBM disease is unknown, but both genetic[24] and environmental factors[73] may play roles. Patients with anti-GBM disease preferentially express certain immunoglobulin Gm allotypes, and links between anti-GBM disease and the HLA-DR2 histocompatibility antigen have been noted.[24,74] Exposure to hydrocarbon-containing solvents, hard-metal dust, chlorine gas, D-penicillamine,[15,21,24,68] cigarette smoke,[24] cocaine and amphetamine,[24] antecedent viral illnesses (particularly influenza),[24] and use of alemtuzumab[75] have been cited as possible risk factors.

Clinical Features

The clinical expression of anti-GBM disease is highly variable. Most patients present with progressive dyspnea, diffuse alveolar infiltrates, and hypoxemia; hemoptysis occurs in 45% to 94%.[21,24,68] Glomerulonephritis is a cardinal feature.[24,64,76] Microscopic hematuria, red cell casts, or proteinuria are almost always present. Gross hematuria occurs in up to 41% of patients.[21,24] Azotemia is noted in 55% to 71% of patients at presentation.[15,24] Fatigue and weakness are common.[21] In the absence of therapy, progressive renal insufficiency ensues, often resulting in ESRD within days to weeks of the onset of symptoms.[15,24] Oliguria, severe renal failure, or greater than 50% crescents on renal biopsy are associated with a poor prognosis and low rate of recovery of renal function.[15,21,24,69] The course may be fulminant, with severe renal failure and explosive, life-threatening DAH.[15,21,24] Chest radiographs typically reveal dense bilateral alveolar infiltrates, often with air-bronchograms.[24] With cessation of bleeding, infiltrates may resolve within 24 to 36 h. Pleural effusions are rare and suggest an alternative diagnosis. Pulmonary function tests are rarely helpful in the acute setting of DAH.[21,24] Bloody or serosanguineous BAL fluid (that worsens with serial aliquots) suggests DAH but is nonspecific.[2] Anemia is present in more than 90% of cases and may be profound. Serum iron and ferritin levels are usually decreased, reflecting diminished iron stores. Factors associated with a higher incidence of DAH include exposure to high concentrations of oxygen, upper respiratory tract infections, and increased hydrostatic (pulmonary capillary) pressures.[15,21]

Establishing the Diagnosis

Serologic assays for anti-GBM antibody are invaluable to confirm the diagnosis and monitor the adequacy of therapy.[21,24] Radioimmunoassays or enzyme-linked immunosorbent assays (ELISA) for anti-GBM antibody are highly sensitive (>95%) and specific (>97%)[15,21,24] but are performed in only a few laboratories. Results are usually not available for 2 to 4 days. Since delay in the institution of therapy may preclude a favorable outcome, percutaneous renal biopsy is usually performed while awaiting the results of serum assays.[24]

Histopathology

Percutaneous kidney biopsy is the preferred invasive procedure to substantiate the diagnosis of anti-GBM disease.[24] Light microscopy demonstrates a proliferative or necrotizing GN, often with cellular crescents.[21,24] Over time, the crescents may fibrose, and frank glomerulosclerosis, interstitial fibrosis, and tubular atrophy may be observed.[24,69] Although these microscopic features are nonspecific, IF stains are the cornerstone of the diagnosis. Bright linear deposits of IgG and complement (C3) along the glomeruli are pathognomonic of anti-GBM disease[21,24] (Fig. 68-6). All four subclasses of IgG are represented, but IgG_1 and IgG_3 predominate.[24] Rare cases of linear deposits of IgM or IgA have been described.[68] Lung biopsies are rarely necessary,[2,21,24] as the histologic features on renal biopsy are usually adequate to establish the diagnosis. When lung biopsy has been done, extensive hemorrhage predominates[2] with accumulation of hemosiderin-laden macrophages within the alveolar spaces.[2] Foci of DAD and capillaritis also may be found.[2] Interstitial or intra-alveolar inflammation is minimal or absent. Extensive necrosis or large-vessel vasculitis is not found. Similar histopathologic features may be seen with a wide gamut of immune-mediated DAH syndromes.[2] IF stains of lung tissue may be diagnostic, provided a clear linear pattern of immunofluorescence is present. However, IF stains are technically difficult in lung tissue, and autofluorescence may obscure the linear IgG deposits.

Pathogenesis

Antibodies are directed against the α3 chain of type IV collagen, an antigen highly expressed in both alveolar and glomerular basement membranes.[24,74] Anti-GBM antibodies bind the GBM and activate complement, initiating an inflammatory pathway that elicits injury.[24] Injury to kidney (and/or lung) basement membranes results in increased capillary permeability, exposing the Goodpasture antigen (α3 chain), which is then recognized as foreign, eliciting a T-helper cell response.[68,73] In addition to circulating antibodies, autoreactive T lymphocytes directed against the α3 antigen are key mediators for development of RPGN.[24,68] Up to one-third of patients with circulating anti-GBM antibodies have concomitant ANCA (usually MPO).[24,52] Other serologic studies are negative or nondiagnostic.

Treatment

Before the availability of current therapy and renal dialysis, mortality exceeded 90%.[15] Therapeutic plasma exchange (TPE) was introduced as a therapeutic option for anti-GBM disease in the 1970s[64] and was quickly adopted worldwide and incorporated in all clinical trials. Currently, with the combination of TPE, CS, and CYC, 5-year survival exceeds 80%.[15,21,24,69,72] Because of the rarity of anti-GBM syndrome, only one small randomized trial compared immunosuppressive therapy (CS + CYC) with the *combination* of CS + CYC *plus* TPE.[64] In that study, TPE plus CS + CYC was associated with more rapid disappearance of anti-GBM antibody and improved renal function compared to treatment with CS + CYC *alone.*[64] The optimal extent and duration of TPE have not been defined. Most investigators advocate TPE daily or every other day for 2 to 3 weeks, until the clinical course has improved and serum anti-GBM antibodies are nondetectable.[24,77] Immunosuppressive therapy is required to inhibit antibody production and rebound hypersynthesis that may occur following discontinuation of TPE.[24]

Treatment of acute, life-threatening DAH in anti-GBM disease is similar to that of other autoimmune disorders. Pulse MP (typically 1 g daily for 3 days) is given, followed by a gradual taper of CS.[21] CYC is initiated once the diagnosis of anti-GBM disease is substantiated. Most investigators favor CYC over other IA,[15,21,24] but studies comparing other IAs in anti-GMB disease have not been done. RTX has been used as an adjunct to conventional therapy, with anecdotal successes in some cases,[78] but data are insufficient to recommend RTX in lieu of CYC.[24] CYC is maintained for the duration of therapy, unless complications such as leukopenia necessitate dose reduction. CS are gradually tapered over several months. With treatment, circulating anti-GBM antibodies usually clear within 8 to 12 weeks and self-tolerance is restored.[24,68] This tolerance may be achieved by regulatory CD4+ and CD25+ T cells[24,68] or anti-idiotypic (blocking) antibodies,[73] but this remains speculative.

Immunosuppressive therapy may be discontinued within 3 to 6 months provided a sustained remission has been achieved and anti-GBM antibodies have disappeared.[15,24] Early relapse (within the first 2 months) may occur when circulating antibodies are still present. This typically manifests as DAH. Risk factors for relapse include infection, volume overload, and cigarette smoking.[24] Late recurrence, associated with renewed antibody synthesis following a remission, is rare.[21,24]

In summary, aggressive therapy with TPE, CS, and CYC has dramatically improved prognosis in anti-GBM disease.[21,24,72] With this approach, 5-year survival exceeds 80%, although >50% of patients remain dialysis-dependent at 1+ years.[21,24,72,74] Factors associated with increased inpatient mortality include age older than 70 years, sepsis, or the development of respiratory, circulatory, renal, or liver failure, whereas factors associated with reduced inpatient mortality include more recent year of hospitalization and TPE.[72]

Early recognition and treatment of anti-GBM disease are critical, as the prognosis for recovery of renal function depends upon the initial extent of injury.[24,52,69,76,79] Recovery of renal function can be expected in patients with minor functional impairment.[79] By contrast, patients manifesting initial serum creatinine greater than 4 mg/dL, oliguria, or greater than 50% crescents on renal biopsy rarely recover and usually progress to ESRD requiring chronic dialysis.[24,52,69,76] In one study of 71 patients with anti-GBM disease (all of whom were treated with CS, CYC, and TPE), renal survival was linked to extent of renal failure at presentation.[25] Renal survival rates at 1 year were as follows: 8% among 39 patients requiring dialysis at presentation; 82% among 13 patients with creatinine >5.7 mg/dL but not requiring dialysis; and 95% among 19 patients with initial serum creatinine <5.7 mg/dL.[25] In a study of 123 cases of anti-GBM disease from 6 centers worldwide from 1986 to 2015, the extent of normal glomeruli and extent of interstitial infiltrate on renal biopsy and need for dialysis at presentation predicted the incidence of ESRD at follow-up.[79] Histologic class on renal biopsy predicted long-term renal survival ($p < 0.001$). Among 15 patients with ≥50% normal glomeruli on renal biopsy, only 1 developed ESRD. In sharp contrast, cases with >50% sclerosis of glomeruli or 100% crescents on renal biopsy did not recover from dialysis dependence.[79] Renal transplantation has been successful in patients with ESRD, provided serum anti-GBM antibodies have been undetectable for a minimum of 6 months.[24,80]

■ Systemic Vasculitis

DAH is a common complication of microscopic polyangiitis (MPA)[1,12,13,49] and GPA[16] and rarely complicates eosinophilic granulomatosis with polyangiitis (EGPA) (formerly Churg-Strauss syndrome),[17,19] Behçet's disease,[81] mixed cryoglobulinemia,[82] Henoch-Schoenlein purpura,[1,83] and other systemic necrotizing vasculitides.[49,84] Classic polyarteritis nodosa (PAN) rarely involves the lung.[2] Necrotizing small-vessel vasculitis accounts for the majority of autoimmune DAH syndromes.[49,85] RPGN is usually present in each of these DAH syndromes, but the disease is sometimes limited to the kidneys or lungs. Circulating antibodies directed against cytoplasmic components of neutrophils and monocytes (ANCA) have been detected in most patients with these "pulmonary renal syndromes,"[8,53,84,86] suggesting a common pathogenesis and mechanism of lung injury in these diverse vasculitic disorders.

ANCA-Associated Vasculitis

More than two-thirds of patients with pulmonary–renal syndromes are mediated by ANCA antibodies without anti-GBM or immune complexes (i.e., pauci-immune).[1,8,10,49,53,61,84] Depending upon clinicopathologic features, some cases with pauci-immune GN and DAH may meet criteria for GPA or EGPA, while others exhibit a multisystemic small-vessel vasculitis but lack granulomatous inflammation of the respiratory tract. In this context, the term microscopic polyangiitis (MPA) is used.[12,13] The availability of serum assays for ANCA has profoundly influenced the classification of immune DAH and GN. ANCA-positive patients with pauci-immune DAH and GN are now considered to have MPA.[13] The spectrum of AAV is not limited to patients with pulmonary–renal syndromes but includes individuals with MPA limited to the lung (i.e., manifesting as DAH) or kidney (i.e., necrotizing GN).[13] Brief definitions of AAV are outlined below.

■ Granulomatosis with Polyangiitis (GPA)

Formerly called Wegener granulomatosis, GPA is the most common of the pulmonary vasculitides. Typically, GPA involves the upper respiratory tract (e.g., sinuses, ears, nasopharynx, oropharynx, trachea), lower respiratory tract (bronchi and lung), and kidney, with varying degrees of disseminated vasculitis.[16,87] The annual incidence of GPA has been estimated as 4 to 12 cases per million.[16,87] Severe DAH is an uncommon (<20%) complication of GPA, reflecting diffuse injury to the lung microvasculature (i.e., capillaritis)[49,62] (Fig. 68-8). In this context, RPGN is present in more than 90% of patients.[16,87]

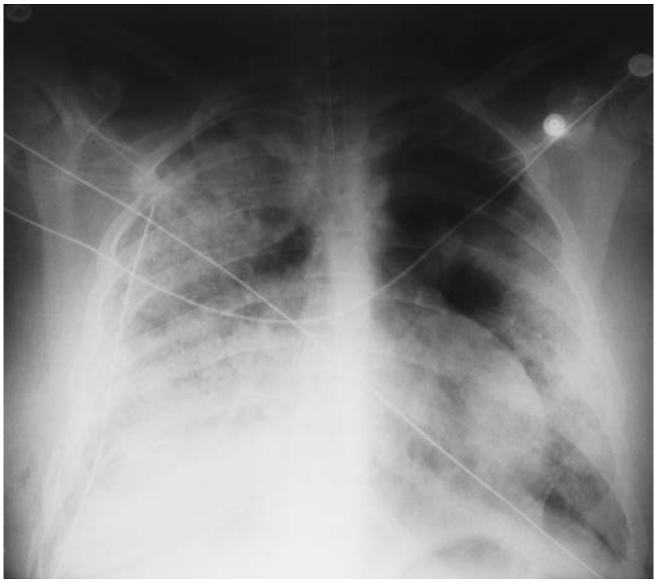

Figure 68-8 Granulomatosis with polyangiitis (GPA) (formerly called Wegener granulomatosis). Posterior–anterior chest radiograph demonstrated bilateral alveolar infiltrates in a 13-year-old girl with hemoptysis and respiratory failure. A right chest tube is in place from an open lung biopsy performed 2 days earlier. Open lung biopsy demonstrated capillaritis and massive alveolar hemorrhage. Pulse methylprednisolone, followed by oral cyclophosphamide and prednisone, was associated with a complete remission.

The salient histopathologic features of GPA include small-vessel vasculitis (involving capillaries, arterioles, venules), geographic necrosis, hemorrhagic infarcts, a mixed inflammatory cellular infiltrate, and a granulomatous component.[16,87] Circulating c-ANCAs (PR-3 epitope) have been detected in more than 90% of patients with active generalized GPA and in 40% to 70% with active regional GPA.[16,86–88]

Beginning in the early 1970s, oral CYC (2 mg/kg/d) plus prednisone was the treatment of choice for GPA for more than 4 decades.[16,87,89] With this regimen, remissions were achieved in 70% to 93% of patients, with early mortality rates of less than 15%.[16,87,89–92] After sentinel studies in 2003,[90] less toxic IA, such as azathioprine (AZA)[90,91] or methotrexate (MTX),[91] were substituted for CYC after 3 to 6 months, assuming complete remissions were achieved. Treatment was continued for a minimum of 12 to 18 months (total duration).[16,87] MTX was also used in patients with limited disease or those experiencing significant toxicity from CYC.[92,93] In 2010, two sentinel studies showed that RTX was as effective as, and possibly more effective than, CYC for GPA and AAV.[62,63] Since then, most clinicians favor RTX over CYC, owing to outstanding efficacy and less morbidity.[94–97]

RTX is used as induction therapy, usually with CS, although CS can be discontinued within 3 to 6 months if remissions are complete. Further, RTX can be used as *maintenance* therapy for GPA. In a retrospective study, the French Vasculitis Study Group reported 66 cases of CPA who received RTX as induction therapy from 2002 to 2013.[98] At 6 months, 79% had responded (complete [38%] or partial [41%]). These responders received 500 mg RTX at 6, 12, and 18 months and were followed for a mean of 34.2 months.[98] Relapses occurred in 11.2/100 patient-years at a mean of 13.5 months after the last dose of RTX.[98] In a subsequent study, these investigators randomized 115 patients with AAV (GPA [n = 87]; MPA [n = 23]; renal limited AAV [n = 5]) who had achieved complete remissions (CR) with CS and CYC to receive *maintenance* therapy with RTX (500 mg at 0 and 14 days, and thereafter at months 6, 12, and 18) or AZA (dose 2 mg/kg × 12 months, then 1.5 mg/kg × 6 months, then 1.0 mg/kg × 4 months).[97] At 28 months, major relapses occurred in 3 of 57 (5%) cases receiving RTX compared with 17 of 58 (29%) receiving AZA ($p = 0.002$). Serious adverse effects were similar between the study groups ($p = 0.92$). Two patients died (both in the AZA group). Other studies support the use of RTX for both *induction and maintenance* therapy for GPA and MPA.[94–96] Data are sparse and insufficient to assess the role of RTX as therapy (induction or maintenance) for EGPA. TPE has no proven role in GPA, although benefit with TPE and IA was suggested in a single case report with massive DAH.[99]

■ Microscopic Polyangiitis (MPA)

MPA typically presents with GN and pulmonary capillaritis manifesting as DAH.[8,12,13] Clinical and serologic features of MPA overlap with GPA and EGPA.[13,100] MPA is rare, with an annual incidence of 2.1 to 17.5 cases per million.[20,70,101] As its name implies, MPA involves small vessels (arterioles, venules, or capillaries); extension to larger vessels occurs in a minority of cases.[13,85] Small vessels are always spared in classic PAN.[85,102] In contrast to GPA or EGPA, neither granulomas nor eosinophils are prominent in MPA.[13,85]

Circulating ANCA (typically p-ANCA; myeloperoxidase [MPO] epitope) are present in 50% to 90% of patients with MPA,[13,85,100] suggesting a relationship with other AAV. A necrotizing, crescentic, pauci-immune GN is nearly invariably present in MPA[8,13,85] but is rare in classic PAN.[85] DAH occurs in 30% to 50% of patients with MPA and is often the dominant and most life-threatening manifestation.[12,13,100] In a retrospective study from Peking, China, severe DAH developed in 12 of 131 (9.2%) cases of AAV.[8] Associated involved sites included GN (100%); fever and arthralgias/myalgias (91.7%); GI tract (42%); ENT (25%); cardiovascular (16.7%); and nervous system (16.7%). All were treated with CS + CYC; 7 received IV pulse MP. Additional therapies included TPE (41.7%); MV (41.7%); and dialysis (25%). Despite aggressive therapy, 3 died of fulminant DAH during the first week of treatment, and another 4 died of septic shock (n = 2), severe heart failure (n = 1), or systemic fungal infection (n = 1) 10 to 32 days after the onset of DAH.

Treatment for MPA has been similar to GPA, typically employing CS with an IA (typically oral CYC [2 mg/kg/d]).[13,90,100] With this approach, favorable responses have been achieved in more than 80% of patients; 10-year survival exceeds 70%.[13,90,100] By 3 to 6 months, once CR has been achieved, AZA, MTX, or another IA may be substituted for CYC.[13,90] As was discussed in the section on GPA, RTX appears to be as efficacious as CYC-containing regimens for AAV (MPA or GPA)[62,63,94–96] and is considered by many experts to be first-line therapy (in lieu of CYC).

■ ANCA-Associated Pulmonary-Renal Syndromes

The ANCA-associated pulmonary–renal syndromes constitute an important collection of disorders and are discussed below.

Clinical Features

The clinical and radiologic manifestations of ANCA-associated DAH are similar to other immune causes. Acute necrotizing GN is nearly always present, but the renal lesion is nonspecific.[13,37,53,103] Distinguishing the specific underlying disorder may be difficult. The pathologic lesions in AAV share characteristic features, regardless of the organ affected. The three key histopathologic findings are a segmental (focal) distribution of vascular injury, infiltration with neutrophils, and fibrinoid necrosis.[85,100] The latter results from lysis of the vascular wall, allowing plasma coagulation factors to enter the interstitium and come into contact with thrombogenic substances, generating fibrin. Neutrophils that infiltrate vessel walls undergo disruption and karyorrhexis, leading to the typical leukocytoclastic pattern of injury in capillaries and venules.[85] ANCA-associated vascular injury is accompanied by few, if any, immune deposits (pauci-immune).[1,36] However, the presence of immune deposits may be associated with more severe renal injury.[53] The salient lesion of renal vasculitis is a segmental necrotizing GN, usually accompanied by extracapillary proliferation of Bowman's capsule (crescents)[53] (Fig. 68-5). Depending on the duration and extent of renal injury, varying degrees of glomerular fibrosis and sclerosis may be seen.[36] Vasculitis affecting the kidney often involves only the glomerular capillaries; macroscopic arteritis is seldom apparent.[85] When the lung is involved, the histopathology is nonspecific, demonstrating only capillaritis and intra-alveolar hemorrhage.[1,13,51] Immune deposits are absent.

Clinical features of ANCA-associated DAH syndromes overlap. Striking elevations in ESR and CRP may be observed in all the syndromes, particularly when disseminated vasculitis is present.[1] Anemia and leukocytosis are common. Marked eosinophilia is characteristic of EGPA[17,104] but is not a feature of MPA[1,13] or GPA.[87] Extrapulmonary and extrarenal manifestations suggesting small-vessel vasculitis (e.g., palpable purpura, leukocytoclastic vasculitis, mononeuritis multiplex, arthralgias or arthritis, ocular disease, sinusitis) may direct biopsies at these sites. Histologic features of granulomatous vasculitis are consistent with GPA[16] or EGPA,[17] whereas granulomas are lacking in MPA.[9,13,85] Chest radiographic features may discriminate granulomatous vasculitides from MPA. In GPA (and, less commonly, in EGPA), focal nodular or cavitary mass lesions may be seen.[16,87] These are not found in MPA.[9,13] The diagnosis of EGPA can usually be readily established by a pronounced eosinophilic component in the blood or in extravascular sites.[17,104] However, discriminating GPA from MPA may be difficult or impossible as small-vessel vasculitis is common to both disorders.

By definition, GPA is associated with concomitant granulomatous inflammation typically, but not invariably involving the upper and lower respiratory tracts.[16,87] The latter may lead to the highly distinctive features attributed to GPA including sinusitis, otitis media, nasal or laryngotracheal ulcerations, subglottic stenosis, and cavitary pulmonary nodules.[87]

Characteristics of ANCA

The identification of circulating antibodies directed against cytoplasmic components of neutrophils and monocytes (i.e., ANCA) represented a major advance in the classification and understanding of vasculitis.[84,86] Using ethanol-fixed granulocytes incubated with patient serum, two distinct patterns of ANCA are identified by IF techniques: cytoplasmic (c-ANCA) and perinuclear (p-ANCA) (Fig. 68-9).

The p-ANCA pattern is an artifact of fixation causing movement of the target antigens to a perinuclear location. These IF patterns reflect distinct antigenic specificities. The antibody responsible for c-ANCA is directed against proteinase 3 (PR-3),[84] whereas the p-ANCA pattern is usually due to an antibody to myeloperoxidase (MPO).[84] MPO-ANCA is usually associated with small-vessel vasculitis, but multiple p-ANCA antibodies directed against a variety of antigens (e.g., cathepsin G, lactoferrin, elastin) may be seen in nonvasculitic inflammatory disorders, including CTD and inflammatory bowel or liver disease.[86] Therefore, while c-ANCA is more than 90% specific for small-vessel vasculitis, p-ANCA is nonspecific. In untreated GPA, circulating c-ANCA (PR3-ANCA) is detected in more than 70% of patients; the incidence is lower (40%–65%) in patients with limited disease (e.g., involvement confined to the upper respiratory tract).[16] By contrast, p-ANCA (MPO-ANCA) is rarely found in GPA. Circulating ANCAs are present in more than 70% of patients with MPA[13,51,100] and 30% to 70% of patients with EGPA.[17,19] In MPA, either c-ANCA or MPO-ANCA may be present, but MPO is more common.[13,84,100] Individual patients almost never have both c-ANCA and p-ANCA.

The antigenic specificities of ANCA (i.e., PR3 or MPO) may provide clues to the nature of the underlying disorder and may assist in categorizing the type of disease, but overlap exists.[84,86] Biopsies are important to differentiate the nature of the underlying vasculitic disorder. For example, patients with c-ANCA and small-vessel vasculitis may be misclassified as MPA if clinically inapparent areas of granulomatous inflammation are overlooked. For clinical purposes, distinguishing GPA from MPA is not critical, because therapy and management are similar.[16,90] Circulating p-ANCA (MPO) or c-ANCA (PR3) are present in more than 70% of patients with pauci-immune necrotizing GN (renal vasculitis).[38,84,86,105] ANCA-negative patients usually have disease limited to the kidney. Nearly all patients with concomitant DAH have circulating ANCA.[1] Indeed, a negative ANCA provides strong evidence against vasculitis as the cause of DAH and GN. When applied to patients with RPGN, a positive ANCA almost invariably predicts pauci-immune necrotizing GN.[38] In the setting of clinical, laboratory, and radiologic features that are highly suggestive of DAH and RPGN, a positive c-ANCA or MPO-ANCA, together with a negative anti-GBM and ANA assay, is virtually diagnostic of systemic vasculitis (e.g., GPA or MPA). Similarly, a positive ANCA (usually MPO-ANCA) is sufficient to diagnose lung-limited MPA, provided the clinical presentation is typical of DAH and nonimmune causes of DAH have been excluded. Most patients previously diagnosed as having idiopathic pulmonary hemosiderosis (IPH) likely had lung-limited MPA or ANCA-associated pulmonary capillaritis.

Problems with using serum ANCA to diagnose vasculitis arise when the clinical presentation is ambiguous. The low incidence of vasculitis in the general population dictates that the positive predictive value of ANCA will be low when applied indiscriminately. Routine assay of serum ANCA in patients with nonspecific respiratory complaints yields a high rate of false-positive results. Given the risks of immunosuppressive therapy, misinterpretation of ANCA may lead to devastating consequences. Accordingly, results of serum ANCA assays must be interpreted in light of the entire clinical picture.

Anti-GBM disease and vasculitis have traditionally been viewed as distinct clinicopathologic entities. However, up to 30% of patients with anti-GBM disease (as evidenced by anti-GBM antibody in serum and linear deposits of IgG in kidney biopsy) also have serum MPO-ANCA.[21,24,51,52,68] The coexistence of ANCA and anti-GBM

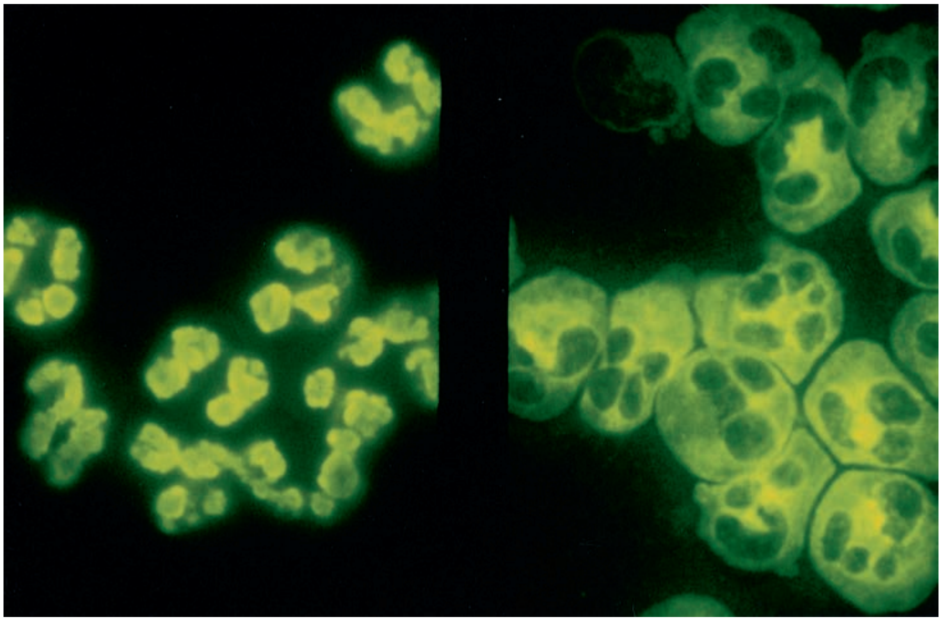

Figure 68-9 Indirect immunofluorescent stains demonstrating two distinct types of antineutrophil antibodies. On the left panel, note the perinuclear pattern of immunofluorescence characteristic of p-ANCA (myeloperoxidase epitope). On the right panel, a coarse granular pattern of immunofluorescence within the cytoplasm is evident, characteristic of c-ANCA (proteinase-3 epitope).

antibodies is almost certainly not a chance occurrence, given the rarity of both antibodies in the general population.[68] It is possible that ANCA initiates vascular injury, and anti-GBM antibody then forms in response to the damaged basement membrane. ANCA antibodies almost certainly mediate vascular damage.[84,86,88,105] Sera from patients with either C-ANCA or P-ANCA induce neutrophils to undergo a respiratory burst with release of reactive oxygen species and proteolytic enzymes.[84] Cytokine-primed neutrophils are stimulated by ANCA to damage human endothelial cells in vitro.[84] These observations, together with correlations of ANCA titer with clinical disease in humans (although imperfect), suggest that ANCAs are not innocent markers of vasculitis but play a crucial role in mediating vessel injury.[84,86,105]

Therapy

Therapy of DAH due to AAV depends on the underlying disorder and the extent and severity of symptoms. Irrespective of etiology, the most immediate concern in patients with severe immune DAH is to control intrapulmonary bleeding, which may be fatal. Besides general supportive measures, high-dose, IV "pulse" MP (followed by a tapering regimen of CS) should be given. For GPA or MPA, CYC or RTX should be initiated. As will be discussed later, the role of RTX to treat EGPA has not been clarified.

Therapeutic Plasma Exchange (TPE) TPE has been used, with anecdotal successes, for AAV with severe renal insufficiency[106–111] or DAH[8,99,106] but is not considered standard therapy. Because ANCAs likely play a pivotal role in mediating tissue injury, TPE may be beneficial in *selected* patients (particularly those with DAH[106] or severe renal failure, i.e., serum creatinine >4 mg/dL[77,112] or dialysis dependency[107,109,111,113]). In 2007, Jayne et al. reported 137 patients with AAV and severe renal failure (serum creatinine >5.8 mg/dL).[112] Overall, 95 (69.3%) had MPA and 42 (30.7%) had GPA. A total of 70 patients were randomized to receive 7 plasma exchanges; 67 patients were randomized to receive IV pulse MP (3000 mg). Both groups received oral CYC and oral prednisolone. The primary endpoint was dialysis independence at 3 months. Secondary endpoints included renal and patient survival at 1 year and severe adverse event rates. At 3 months, 48 of 70 (69%) receiving TPE were alive and independent of dialysis compared with 33 of 67 (49%) treated with IV MP ($p = 0.02$). Furthermore, only 19% of patients receiving TPE progressed to ESRD by 12 months compared to 43% among those receiving IV MP. Patient survival and severe adverse event rates at 1 year were similar (73% and 50%, respectively) in the TPE group compared with 76% and 48%, respectively, in the IV MP group. Thus, TPE was associated with a higher rate of renal recovery in patients with AAV when compared with IV MP while patient survival and severe adverse event rates were similar in both groups.[112]

Despite the apparent benefit of TPE in that 2007 publication,[112] a subsequent multicenter, global clinical trial randomized 682 AAV patients with renal insufficiency (creatinine clearance <50 mL/min/m^2) *and/or* DAH to TPE (7 exchanges within 14 days) or no TPE.[60] All patients received induction therapy with either CYC or RTX. Additionally, cases were randomized to reduced dose oral CS or "standard"-dose CS. Cases were followed for up to 7 years, and composite outcome (death from any cause or ESRD) was assessed. Rates of death or ESRD were 100/352 (28.4%) in the TPE group and 109/352 (31.0%) among controls ($p = 0.27$). Additionally, death or ESRD developed in 92/330 (27.9%) in the reduced-dose CS group compared with 83/325 (25.5%) receiving standard-dose CS, which met criteria for noninferiority. Serious infections at 1 year were less frequent in the low-dose CS group compared with controls (incidence ratio, 0.69). These data cast doubt on the role of TPE for patients with *autoimmune* DAH (other than anti-GBM disease) and renal insufficiency. However, limitations of that important study should be emphasized. Severe DAH (defined as O_2 saturation $\leq 85\%$ on room air or requiring MV) was present in fewer than 9% of cases, and only 20% required dialysis on study entry.[60] At 1-year follow-up, there was a nonsignificant advantage with TPE (hazard ratio [HR], 0.77).[60] Importantly, TPE was not associated with increased adverse events at 1 year. While this study[60] suggests that *routine* use of TPE is not appropriate in most cases of AAV with renal insufficiency, TPE may have a role in *selected* cases (e.g., those with markedly elevated ANCA titers, renal insufficiency *approaching* need for dialysis, or severe DAH).[65] When TPE is used to treat ANCA-associated DAH, it may be preferable to use an apparatus that efficiently removes both IgM and IgG, because of the reported association of IgM-ANCA and DAH.[113]

Recent therapeutic options for AAV include (1) combining RTX and CS with short-course low-dose oral CYC; (2) combining RTX and CS with short-course low-dose IV pulse CYC, followed by maintenance AZA; (3) combining CYC or RTX plus either avacopan (an oral C5a receptor inhibitor) and low-dose CS versus standard-dose CS. Additional strategies for patients failing or intolerant of conventional therapies include high-dose intermittent IV IgG.[114] The mechanism of action is uncertain but may involve binding of ANCA idiotype by anti-idiotype antibodies in the IV IgG preparation.[114]

Patient Follow-up and Assessing Response to Therapy

The role of serial ANCA determinations in following patients with vasculitis is controversial. We do not base therapeutic decisions on the ANCA titer alone. However, a rising titer should alert the clinician to the possibility of disease exacerbation, and clinical follow-up should be intensified. Serial ANCA titers may help differentiate disease relapse from nonimmune causes of pulmonary infiltrates. However, ANCA titers do not obviate the need to aggressively evaluate patients with vasculitis presenting with a new pulmonary process while receiving immunosuppressive therapy.

■ Eosinophilic Granulomatosis with Polyangiitis (EGPA)

Formerly known as Churg-Strauss Syndrome, or allergic angiitis and granulomatosis, EGPA is a rare, small-vessel vasculitis associated with a prominent allergic component, asthma, and eosinophils in blood or involved tissues.[17] EGPA involves capillaries, venules, and arterioles.[17] Granulomas, eosinophils, and palisading histiocytes in extravascular tissues are hallmarks of the disorder[17,104] and distinguish EGPA from other vasculitides.[17,115,116] The annual incidence of EGPA has been estimated at 0.6 to 6.8 cases per million.[17,20,70,117]

In the classic form of EGPA, vasculitis develops after a several-year history of atopy or asthma.[104] Pulmonary involvement is nearly invariably present.[17,104] Asthma is present in 96% to 100%, and focal infiltrates on chest radiographs are present in 30% to 70% of cases.[17,104] DAH is a rare complication of EGPA. In a French series of 112 patients with EGPA, moderate DAH was observed in 3 of 43 ANCA-positive patients and in 5 of 69 ANCA-negative patients.[118] DAH was cited in only 1 of 32 patients in a Spanish series[119] and 1 of 19 in an Italian series[120] of EGPA. Severe DAH has thus only rarely been reported in EGPA.[17,121] Extrapulmonary manifestations of EGPA include mononeuritis multiplex (63%–93%); skin (50%–78%); cardiac (16%–56%); kidney (16%–49%); and gastrointestinal (GI) tract (17%–58%) involvement.[17,115] Factors associated with a worse prognosis include cardiac or GI tract involvement, renal insufficiency, and age >65 years.[17,122]

ESR, CRP, and blood eosinophil count are elevated in more than 80% of patients during the acute phase of vasculitis or exacerbations.[17,19,104,122] Circulating ANCAs (primarily p-ANCA) have been detected in 40% of patients with EGPA.[17,118,123,124] Interestingly, the presence of ANCA was associated with a higher incidence of renal involvement and DAH, but a lower frequency of cardiac involvement.[123]

CS (alone or combined with IA) have been the mainstay of therapy for EGPA.[17,19] CS achieve remissions in more than 80% of patients with EGPA and are first-line therapy for mild to moderate cases.[17,125] Oral or pulse CYC (or other IA such as AZA, MTX, or mycophenolate mofetil) have been added for severe or multisystemic disease or CS-recalcitrant cases or when unfavorable prognostic factors are present.[17,19,122,125,126] Data regarding RTX to treat EGPA are scant and insufficient to recommend RTX for this disorder. TPE is rarely used to treat GPA, but theoretically it may be useful in ANCA-positive CSS patients with severe pulmonary–renal syndrome failing CS and CYC.[17,106,112]

■ Connective Tissue Disorders

Alveolar hemorrhage may complicate connective tissue disorders, including systemic lupus erythematosus, among others.

Systemic Lupus Erythematosus (SLE)

DAH is a rare, but potentially catastrophic, complication of SLE, with mortality rates as high as 62%.[26–28,127–132] DAH complicating SLE is almost invariably accompanied by other manifestations of active SLE.[26,127,128,130–133] GN is present in more than 90% of cases of DAH complicating SLE.[26,127,128] Diffuse, bilateral alveolar infiltrates, dyspnea, and hypoxemia are characteristic (Fig. 68-10). Hemoptysis is noted in a minority of patients at presentation but usually develops during the course of the disease.[26,128,133] The diffuse pulmonary infiltrates must be differentiated from other pulmonary complications of SLE,[134,135] including lupus pneumonitis, opportunistic infections, congestive heart failure, uremia, or pulmonary embolism.

The risk of surgical lung biopsy is substantial in critically ill patients with fulminant DAH, and biopsy is contraindicated. In addition, as with other immune DAH syndromes, histopathologic features of DAH complicating SLE are nonspecific. The dominant feature is intra-alveolar hemorrhage and capillaritis, without macroscopic necrosis.[2,26] The small-vessel necrotizing vasculitis rarely extends to arterioles and small muscular arteries in addition to capillaries. Granular deposits of IgG or C3 (consistent with immune complexes) have been found in up to 50% of cases of DAH complicating SLE.[26,136] Provided that clinical features are consistent, the diagnosis of DAH can be established by flexible bronchoscopy with BAL. The presence of gross blood in the airways or serosanguineous BAL fluid, large numbers of hemosiderin-laden macrophages,[2] absence of purulent sputum, and lack of infectious organisms by appropriate stains strongly support the diagnosis of autoimmune DAH and justify institution of therapy. Transbronchial lung biopsies should not be done in acutely ill patients with severe DAH and respiratory failure. In this context, BAL alone is adequate, primarily to exclude local or infectious causes of bleeding.

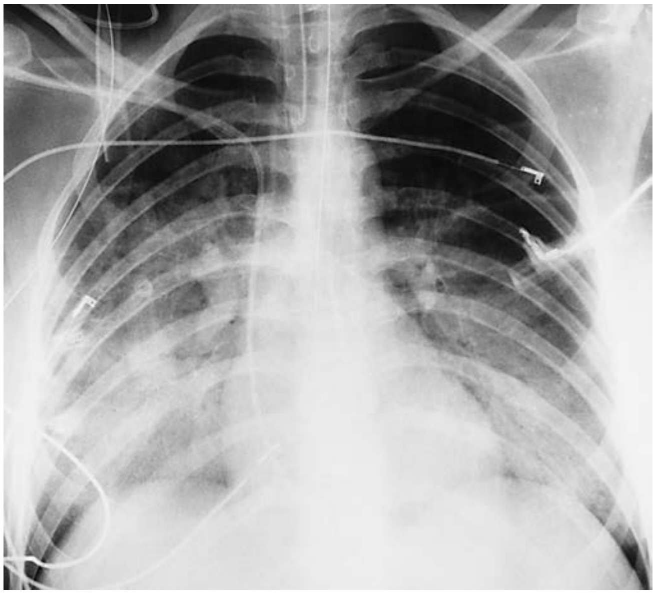

Figure 68-10 Systemic lupus erythematosus (SLE). Posterior–anterior chest radiograph reveals extensive bilateral alveolar infiltrates in a 22-year-old woman with SLE, hemoptysis, and anemia.

Mortality rates of SLE-associated DAH are high, even with aggressive therapy with CS and CYC. In one large, tertiary care center, 19 episodes of DAH were observed among 15 patients with SLE over a 10-year period, accounting for 3.7% of hospitalizations for complications of SLE.[26] The majority (66%) were women, with a median age of 27 years. The onset was often abrupt (<3 days in 12 episodes) and was the presenting feature of SLE in 3 cases. Lupus nephritis was present in 14 of 15 cases. Hemoptysis was present in only 42% at presentation but developed in all during the hospitalization. Lung tissue (available in 10 cases) showed capillaritis in 8, and overall mortality was 53%. Factors associated with heightened mortality included need for MV (62% vs. 0%); infection (78% vs. 20%); and treatment with CYC during that hospitalization (70% vs. 20%), likely reflecting increased infection risk from prior outpatient treatment with CYC for lupus nephritis.

Martinez-Martinez reported 29 episodes of DAH in 22 SLE patients, with 15 deaths.[128] In 4 cases, the diagnosis was made at autopsy. Thrombocytopenia, renal failure, the need for MV, and high APACHE II scores were associated with increased mortality.

Canas et al. reported 7 cases of DAH among 122 SLE patients (5.5%).[133] Five were women with a mean age of 24.3 years. Mean duration of SLE was 15.7 months; in 2 cases, DAH was the presenting feature of SLE. All 7 had evidence for active SLE, including GN in 4. BAL revealed bloody fluid and hemosiderin-laden macrophages in 5 of 7 cases, and 6 patients required MV. All received IV pulse MP and IV pulse CYC; TPE was added in 4 failing pharmacologic therapy. Only one died, suggesting that aggressive therapy including TPE was life-saving.

Columbian investigators reported 17 cases of DAH complicating SLE who required admission to the ICU.[28] Of these, 11 (65%) were women; median age was 28 years. All received IV pulse MP and TPE; 13 (79%) also received IV pulse CYC. Five (29%) died during the hospital stay. Factors associated with increased mortality included need for MV and vasoactive/inotropic support.

Korean investigators reported 21 cases of DAH among 1521 SLE patients (1.4%) admitted to the hospital;[127] 13 died (62%). Independent risk factors for DAH included SLE disease activity score >10 ($p = 0.029$) and neuropsychiatric SLE ($p = 0.002$). Factors associated with increased mortality included need for MV and presence of infection.

The prognosis is worse in juvenile-onset (jSLE) compared with adult-onset (aSLE) SLE.[129] DAH occurred in 13/263 (4.9%) cases of jSLE and 15/1522 (1.0%) cases of aSLE. MV was required in 85% of jSLE compared with 47% in adults ($p = 0.055$); mortality rates were higher in jSLE (69% vs. 13%; $p = 0.006$). Treatment regimens were similar in both groups.

In another study of 847 cases of jSLE, DAH developed in 19 (2.2%).[132] All 19 had cough, dyspnea, hypoxemia, and diffuse infiltrates on chest x-ray or CT. MV was required in 14 (74%); 9 (47%) died. These patients with DAH were compared with 76 jSLE cases *without* DAH with the same disease duration (3 [1–151] vs. 4 [1–151] months, respectively). Compared with the jSLE controls *without* DAH, 19 cases of jSLE with DAH showed higher frequencies of constitutional involvement (74% vs. 10%; $p < 0.0001$), serositis (63% vs. 6%, $p < 0.0001$), and sepsis (53% vs. 9%, $p < 0.0001$).[132] Further, median disease activity score (SLEDAI-2 K) was significantly higher in jSLE patients with DAH compared to controls *without* DAH (18 [5–40] vs. 6 [0–44]; $p < 0.0001$). Further, jSLE patients with DAH had a higher incidence of thrombocytopenia (53% vs. 12%; $p < 0.0001$), and the use of IV MP (95% vs. 16%; $p < 0.0001$) and IV CYC (47% vs. 8%; $p < 0.0001$) was significantly higher in DAH patients.[132]

Xu et al. performed a meta-analysis of five studies assessing risk factors for DAH among patients with SLE.[131] The following factors were associated with DAH: neuropsychiatric involvement (OR, 4.32; $p = 0.002$); nephritis (OR, 3.15; $p = 0.001$); serositis (OR, 6.03; $p = 0.015$); and lower serum C3, C4, and hemoglobin.

Kim et al.[130] reported 47 SLE patients with diffuse lung infiltrates, of whom 24 (51%) had DAH. Factors associated with DAH included lower hemoglobin (OR, 3.46; $p < 0.01$); low serum C4 (OR, 1.21; $p = 0.02$); hypoxemia (OR, 23.1; $p = 0.03$); and need for MV (OR, 64.6; $p = 0.02$).

Due to the rarity of SLE-associated DAH, prospective, controlled trials evaluating therapy have not been performed. As with other causes of immune DAH, IV pulse MP (500–1000 mg daily for 3 days), followed by gradual CS taper[26,129,133] and CYC (IV pulse or oral) have been the mainstay of therapy.[128,129,133,137] RTX has been efficacious in anecdotal cases of SLE-associated DAH,[137–140] but data are sparse. The role of TPE has not been elucidated, but anecdotal successes with TPE have been cited for severe DAH complicating SLE.[26,113,129,133,141,142]

Other Connective Tissue Diseases

Anecdotal reports of DAH, with or without capillaritis, have been described in association with rheumatoid arthritis,[143] scleroderma,[144] mixed-connective tissue disease,[143] polymyositis,[145] dermatomyositis,[146] antiphospholipid antibody syndrome,[147–150] Henoch-Schönlein syndrome,[151,152] and Behçet's disease.[81,153] The clinical spectrum ranges from minimal hemoptysis to life-threatening respiratory failure. In addition to capillaritis and DAH, additional histopathologic features on lung biopsies include vasculitis of small and medium muscular pulmonary arteries, DAD, and organizing pneumonia. In view of the rarity of DAH complicating these diverse CTDs and vasculitic syndromes, data regarding therapy are limited. IV pulse MP is advised as initial treatment. In patients with fulminant or CS-recalcitrant disease, CYC, alone or combined with TPE,[113,144] should be added.

■ Alveolar Hemorrhage in Immunocompromised Hosts

DAH may occur in immunocompromised patients.[47,154] In this setting, it may reflect injury to pulmonary endothelial or epithelial cells (secondary to chemotherapy or radiation toxicity), thrombocytopenia (secondary to bone marrow toxicity), pulmonary edema, pulmonary malignancies, and diverse infectious and nonspecific interstitial pneumonias.[154] The incidence of DAH in severely immunocompromised hosts with hematologic malignancies or bone marrow transplants has varied from 11% to 64%.[43,154] The variable frequency in large part is due to differing diagnostic criteria for the diagnosis of DAH. Subclinical alveolar hemorrhage (as evidenced by increased numbers of hemosiderin-laden macrophages in BAL) occurs in up to one-third of immunocompromised hosts with pulmonary infiltrates and may reflect pulmonary endothelial or epithelial injury from diverse causes.[47] Nonimmune causes of DAH in this patient population include coagulopathy, thrombocytopenia or platelet dysfunction, renal failure, congestive heart failure, bronchopulmonary Kaposi's sarcoma, and diverse infections.[47,48]

Alveolar Hemorrhage Complicating Bone Marrow Transplantation

DAH occurs in approximately 5% (range, 2%–31%) of hematopoietic stem cell transplant (HSCT) or bone marrow transplant (BMT) recipients receiving pretransplant conditioning with high-dose chemotherapy or radiation therapy.[43,44,155–159] Opportunistic infections or thrombocytopenia account for some cases of DAH,[44,157] but a distinct syndrome of DAH in this population unrelated to infection is well accepted.[154,155] The incidence of DAH is similar among autologous and allogeneic HSCT recipients.[43,155,158]

Risk factors for DAH include age >40 years;[156,158] myeloablative conditioning;[43,156,158] thoracic[160] or total body irradiation;[43,159,161] acute severe graft-versus-host disease (GVHD);[156,161] severe oral mucositis;[162] renal failure;[43] airway inflammation or increased proportions of bronchial neutrophils and eosinophils;[163] and leukocyte recovery.[43,163] Thrombocytopenia or coagulopathy do not predict DAH.[43,160]

DAH usually develops within 10 to 40 days after BMT but may develop earlier or later.[155,159–161] DAH developed in ~5% of 1228 allogeneic HSCT recipients at the University of Minnesota from 2008 to 2015 at a median of 30 days post-transplant.[159] The incidence was increased in recipients of umbilical cord blood (UCB) transplants compared with peripheral blood (PB) or bone marrow (BM) grafts (HR, 2.08; $p = 0.01$). Multivariate analysis demonstrated that delayed neutrophil engraftment or primary graft failure was associated with increased incidence of DAH following PB or BM transplant (HR, 5.51; $p = 0.02$) and delayed platelet engraftment was associated with increased incidence of DAH among UCB recipients (HR, 6.96; $p < 0.05$). Total body radiation was a risk factor for DAH in PB, BM, and UCB transplant recipients (HR, 1.8; $p = 0.l05$). DAH was associated with increased 6-month transplant-related mortality (HR, 6.09; $p < 0.01$) and lower 2-year survival (HR, 4.2) in all graft source groups. Case reports of DAH developing immediately following autologous BMT suggest that components within the transfusion (e.g., dimethyl sulfoxide [DMSO] for cryopreservation of blood stem cells) may mediate acute lung injury in some cases.[164]

DAH typically manifests as progressive dyspnea, hypoxemia, and respiratory failure.[43,156,158] Even with extensive DAH, hemoptysis is uncommon (<20%).[155,158,163] Chest radiographs *initially* demonstrate predominantly interstitial opacities, which evolve to diffuse alveolar opacities, with a confluent alveolar pattern involving all lobes. Serosanguineous or frankly bloody BAL fluid,[155,156,158] with negative stains for infectious organisms, support the diagnosis of DAH. Lung biopsies or necropsies typically reveal histologic features of both DAD and DAH.[157,163,165] However, the risk of lung biopsy is excessive in critically ill patients, many of whom are thrombocytopenic.[158] Hence the diagnosis is made by clinical, radiographic, and BAL findings.[155,158]

The clinical course of DAH is variable, but severe respiratory failure requiring MV is common.[155,162] Mortality rates in patients with DAH are high (60-day mortality ranging from 48% to 84%).[44,155,156,162] In one study, hospital mortality was lower among autologous (28%) compared with allogeneic (70%) SCT recipients; further, mortality was lower (32%) in early-onset DAH (within 30 days of transplant) compared with 70% mortality for late-onset DAH.[155] Secondary infections are serious and potentially lethal.[44,154,156,157]

Multiple mechanisms may mediate DAH in this patient population. Diffuse injury to the pulmonary microvasculature, secondary to chemotherapy or radiation therapy, is coupled with a heightened inflammatory response in the airways.[43] Bleeding may be amplified by a precipitating factor such as coagulopathy, pulmonary edema, GVHD, or infections. DAD, a pathologic hallmark seen in toxic lung injury from chemotherapy, radiation therapy, or viral infections, is frequently observed in lung biopsies or necropsies in BMT recipients with DAH.[155] An association between microangiopathy and DAH in patients receiving BMT for hematologic malignancies has been cited.[166] Neutrophils and other inflammatory cells likely play important roles in the pathogenesis of DAH. The onset of DAH frequently coincides with marrow recovery and reappearance of neutrophils within the circulation or BAL fluid. Influx of neutrophils may promote lung injury by release of oxygen radicals, proteases, and other inflammatory mediators.[43,163] Hematopoietic growth factors (e.g., granulocyte colony–stimulating factor) may exacerbate alveolar damage and capillary leakage by increasing neutrophil influx into the lungs.[43]

High-dose pulse IV CS is considered the standard of care for DAH,[43,44,155,157] but RCTs are lacking and a survival benefit has not been established. Unfortunately, DAH or bloody BAL fluid may be seen in infectious causes of pneumonia (particularly due to cytomegalovirus [CMV] or *Aspergillus* spp),[158] and high-dose CS could be disastrous in these circumstances. Infectious etiologies must thus be rigorously excluded. Among patients who respond favorably to CS, the dose can be gradually tapered over 2 to 6 weeks.[43,155] A more prolonged course is appropriate for patients with GVHD or other complications requiring long-term CS therapy. Anecdotal response to recombinant factor VIIa was cited in one allogeneic SCT recipient with DAH.[167]

Alveolar Hemorrhage Complicating HIV Infection

DAH can complicate human immunodeficiency virus (HIV) infection. The incidence and clinical significance of DAH is not clear, as additional pulmonary processes (e.g., opportunistic infections,[168] Kaposi's sarcoma[169]) are usually present.[48] Subclinical episodes of AH are common, as studies in HIV-infected patients with pulmonary infiltrates detected more than 20% hemosiderin-laden macrophages in BAL fluid in 15% to 44% of patients.[47,48] In one study of 203 HIV-infected patients with pulmonary symptoms who underwent BAL, AH was detected in 73 (36%); however, AH was severe in only 8 patients, and AH did not affect survival.[48] Thrombocytopenia, coagulopathy, renal failure, hydrostatic pulmonary edema, CMV pneumonia, and Kaposi's sarcoma were more frequent in patients with AH compared to HIV-infected controls *without* AH.[48] Pulmonary capillaritis has been cited in occasional patients, most of whom had concomitant opportunistic infections. CMV pneumonia has been implicated as a cause of DAH in HIV-infected patients.[168] CMV exhibits tropism for endothelial cells, and CMV may induce vascular injury or thrombotic microangiopathy. Antiviral therapy (e.g., ganciclovir, valganciclovir) may be curative for CMV-associated DAH. The incidence and appropriate therapy of DAH of unknown etiology in the setting of HIV infection has not been well defined.

■ Alveolar Hemorrhage Due to Exogenous Agents

Certain exogenous agents or drugs[31,51] (e.g., trimellitic anhydride,[170] isocyanates,[171] D-penicillamine,[172] cocaine,[32] diphenylhydantoin,[173] propylthiouracil,[174] hydralazine,[175] sulfasalazine,[175] allopurinol,[49,175] all-*trans*-retinoic acid [ATRA],[176] minocycline[177]) are rare causes of DAH. An exhaustive list of drugs capable of causing DAH is available at *www.pneumotox.com*. Circulating ANCAs, GN, and DAH have been linked with some agents (particularly D-penicillamine,[172] hydralazine,[178] propylthiouracil,[174] methimazole, and carbimazole[179]). Lung biopsies have rarely been performed in these cases of DAH. However, pulmonary capillaritis (without immune deposits) is the most common finding.[31,51]

ATRA, a therapeutic agent for acute promyelocytic leukemia, may be associated with "retinoic acid syndrome," characterized by fever, thrombosis, pulmonary infiltrates, and DAH.[176] The onset is 2 to 21 days after initiation of treatment. In this circumstance, ATRA is often continued, but high-dose IV CS should be administered.

Propylthiouracil can cause a systemic small vessel vasculitis with necrotizing GN, leukocytoclastic vasculitis, ANCA, and DAH secondary to pulmonary capillaritis.[174,175] Withdrawal of the drug may be associated with resolution of the disease, but CS or IA are indicated in patients with severe DAH or renal failure. A variety of chemotherapeutic agents (e.g., bis[chloroethyl] nitrosourea [BCNU], carmustine, CYC, MTX, mitomycin C, bleomycin, busulfan) may cause lung injury and fibrosis.[31,180] In some cases, DAH may result from epithelial injury and injury to the alveolar capillary basement membranes.[31] In this context, fatality rates are high (>50%).[31,180] High-dose CS are recommended, but efficacy is uncertain.

Trimellitic anhydride (TMA), a chemical used in manufacturing plastics and epoxy resins, may elicit DAH and anemia.[170,171] Most patients with DAH secondary to TMA recover within a few days following removal from the offending environment. An immune mechanism is likely, as circulating IgG antibodies against trimellitic protein were found in some patients with DAH, suggesting that TMA acts as a hapten.[171] TMA may cause asthma, rhinitis, and hemolytic anemia mediated by IgE antibodies directed against trimellitic protein. Animal models of TMA-induced lung disease also have been developed.[170] Induction of serum antibodies against epitopes of TMA produced acute lung injury in animals, mediated by at least two types of humoral antibodies. It is also possible that TMA may exert a direct toxic effect on alveolar endothelium. This syndrome is exceptionally rare; only sporadic cases have been described. Exposure to isocyanates in spray paint has been linked to occupational asthma and (in a few cases) DAH.[181] The mechanism is likely mediated by high levels of IgE and IgG antibodies against diisocyanates.[171] Thus, exposure to TMA or isocyanates, and possibly other chemicals, can elicit hemorrhagic pneumonitis, likely mediated by circulating antibodies (IgG or IgE) and immune complexes.

Smoking, snorting, or IV "crack" cocaine has been associated with hemoptysis and varying degrees of DAH,[32,182] including rare fatalities. Histopathologic features of cocaine-induced DAH are nonspecific but include DAD, acute or chronic DAH, interstitial pneumonitis/fibrosis, and intra-alveolar edema.[183] The mechanism of DAH is not clear but may relate to direct toxic injury from cocaine or its contaminants, vasospasm, or a combination of both mechanisms. This syndrome typically reverses with cessation of exposure. The frequency of clinically significant DAH associated with inhaled or IV cocaine has not been established.

When drug- or hapten-induced DAH is suspected, immediate avoidance of the implicated agent or drug is essential. For acute or severe cases, a brief course of high-dose CS is warranted. TPE or IA may be considered for fulminant cases refractory to CS, but data supporting their use are lacking.

Finally, coagulopathies, severe thrombocytopenia, or the use of anticoagulants, thrombolytic agents, or platelet inhibitors may rarely cause DAH.[184–186] In this context, the histology is "bland," without evidence for capillaritis or acute inflammation.

■ Alveolar Hemorrhage Due to Molds

Acute, life-threatening DAH in infants identified fungal contamination as the etiology[187,188] after exposure to *Stachybotrys chartarum* and other toxigenic fungi.[187] *Stachybotrys chartarum* produces several classes of toxins including hemolysins, proteinases, macrocyclic trichothecenes, phenylspirodrimanes, and others.[187,189] Acute respiratory distress, progressing to respiratory failure requiring MV, may occur.[187] High-dose IV CS are warranted for acute DAH. Long-term management mandates removal of infants from the residential environment to avoid relapse.[187,188] This syndrome has rarely been reported in adults, but must be considered in water-damaged homes or environments where mold/fungal contamination exists.[188,189]

■ Idiopathic Pulmonary Hemosiderosis (IPH)

IPH is an exceptionally rare cause of DAH that occurs primarily in infants and children.[190–193] The estimated incidence is 0.2 to 1.2 cases per million.[40,194] Many children with IPH have a history of milk or gluten sensitivity.[195] A subset of adults with celiac sprue manifest IPH,[196] which may respond to elimination of gluten from the diet.[197] Clinical features of IPH are similar to immune causes of DAH, but extrapulmonary or renal involvement is lacking.[190] Serum or tissue antibodies (e.g., ANCA, immune complexes, anti-GBM) are absent. A diagnosis of IPH can be made *only* when other specific causes of DAH have been *reliably* excluded. Most early series of IPH, published in the 1960s and 1970s, antedated the availability of serologies and immunohistochemical assays (e.g., ANCA, anti-GBM antibody).[198] It is likely that most cases formerly diagnosed as IPH in adults had AAV or underlying CTD.

The onset of the disease is typically in infants and young children (<5 years old).[190,191] The clinical course of IPH is variable, but recurrent episodes of DAH over several years are characteristic.[190,193,199] Spontaneous remissions without long-term sequelae have been cited in up to 25% of cases.[193] Sequelae of recurrent episodes of DAH include pulmonary fibrosis, progressive respiratory failure, and cor pulmonale.[190,193,199] Early studies cited median survival rates of 3 to 6 years,[191,194] but more recent studies suggest a more favorable prognosis, with many patients surviving more than 10 to 15 years.[193,199] During acute episodes, chest radiographs demonstrate bilateral alveolar infiltrates. Following cessation of bleeding, chest radiographs may normalize within 1 to 2 weeks. Reticulonodular infiltrates may be observed as the process is resolving or with recurrent episodes (Fig. 68-11). CT reveals areas of ground-glass opacification, representing foci of AH. Thickening of interlobular septae and honeycombing may be observed in a subset of patients who progress to pulmonary fibrosis.[200] Hemoptysis may be absent, particularly in young children who may be unable to expectorate blood. Iron-deficiency anemia is characteristic and can be profound.[190,193,199,201] Iron deficiency may persist despite normal total body iron stores, because hemosiderin within alveolar macrophages is not available to developing erythrocytes. Siderophages may be found in sputum, BAL fluid, or tracheal or gastric aspirates in patients with recent DAH.[40,193,199] Lung biopsies may reveal fresh areas of AH or patchy interstitial fibrosis and aggregates of hemosiderin-laden macrophages from prior episodes of AH[190,193] (Fig. 68-12).

The pathogenesis of IPH is not known. In children, associations between IPH and cow's milk hypersensitivity, celiac disease,[201] IgA monoclonal gammopathy, autoimmune hemolytic anemia, and autoimmune thyrotoxicosis have been suggested,[193] but a pathogenetic link has not been substantiated. Resolution of pulmonary symptoms following elimination of milk products or gluten from diet[196,201] supports a role for exogenous factors in the pathogenesis in at least some cases. No genetic basis has been found, but clusters within families have been described.[202]

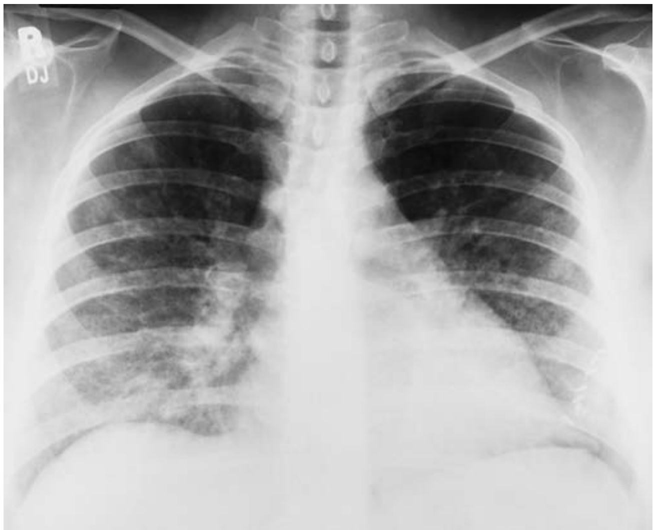

Figure 68-11 Idiopathic pulmonary hemosiderosis (IPH). Posterior–anterior chest radiograph demonstrates bilateral reticulonodular infiltrates in a 28-year-old woman with IPH confirmed 10 years earlier by open lung biopsy.

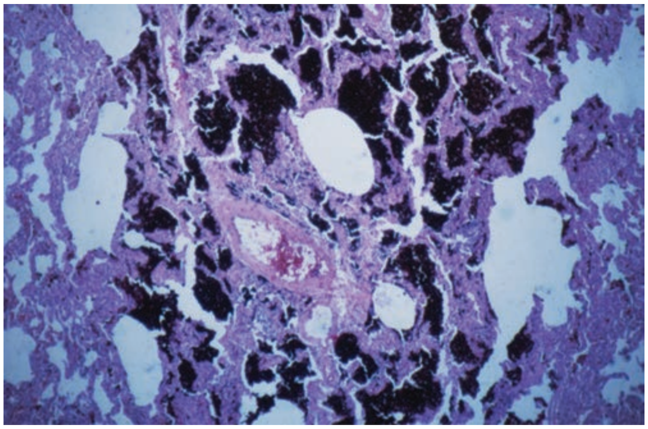

Figure 68-12 Idiopathic pulmonary hemosiderosis (IPH). Photomicrograph demonstrating extensive deposits of hemosiderin within alveolar interstitium (Prussian blue stain).

In view of the rarity of IPH, optimal therapy is not clear. CS are considered the mainstay of therapy,[40,190,192,203] but RCTs have not been done. Because IPH is life-threatening, most physicians treat acute episodes with daily CS and taper to the lowest dose that appears to control the disease. Long-term (and possibly indefinite) therapy may be required to prevent recurrences. Favorable responses have been cited with AZA,[204] CYC,[205] or other IA[199] in patients failing CS. Chronic IA may improve prognosis for patients with CS-recalcitrant disease or patients experiencing repetitive relapses of DAH.[199] In this context, we prefer AZA over CYC given the heightened risk of neoplasia and gonadal toxicities associated with the long-term use of CYC.[206]

RECOMMENDED READING

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CHAPTER 69

Aspiration-Related Pulmonary Disorders

Paul E. Marik

“Captain of the Men of Death”

—William Osler’s reference to pneumonia[1]

INTRODUCTION

Aspiration is defined as the misdirection of oropharyngeal or gastric contents into the larynx and lower respiratory tract.[2] An assortment of pulmonary syndromes may occur following aspiration depending on the quantity and nature of the aspirated material, the chronicity of aspiration, and the nature of the host’s defense mechanisms and the host’s response to the aspirated material. The most important syndromes include “*aspiration pneumonitis*” or Mendelson’s syndrome, which is a chemical pneumonitis caused by the aspiration of gastric contents, and “*aspiration pneumonia*,” an infectious process caused by the aspiration of oropharyngeal secretions colonized by pathogenic bacteria.[2] While there is some overlap between these two syndromes, they are distinct clinical entities.[2] The distinction between these two syndromes is based largely on clinical criteria (Table 69-1). Although gastric biomarkers for aspiration are increasingly available (e.g., pepsin, amylase, lipid-laden macrophages), none has been clinically validated.[3–5] Serum procalcitonin and other inflammatory markers are unable to distinguish aspiration pneumonitis from aspiration pneumonia.[6] The administration of antibiotics is central to the management of aspiration pneumonia, while the treatment of aspiration pneumonitis is largely supportive.[2] In addition to aspiration pneumonitis and aspiration pneumonia, a variety of pulmonary conditions result from chronic recurrent occult aspiration, most notably “*diffuse aspiration bronchiolitis*.”[7] Other aspiration syndromes include airway obstruction, lung abscess, exogenous lipoid pneumonia, chronic interstitial fibrosis, and *Mycobacterium fortuitum* pneumonia. This chapter focuses on the pathophysiology, clinical features, and management of aspiration pneumonitis, aspiration pneumonia, and diffuse aspiration bronchiolitis.

ASPIRATION PNEUMONITIS

Aspiration pneumonitis is best defined as acute lung injury following the aspiration of regurgitated gastric contents.[2] This syndrome occurs in patients with a marked disturbance of consciousness, such as drug overdose, seizures, coma due to acute neurologic insults, massive cerebrovascular accident, following head trauma, and during anesthesia. It is important to emphasize that aspiration pneumonitis occurs only in patients who have a depressed level of consciousness with impairment of airway protective reflexes. In clinical practice, drug overdose is the most common cause of aspiration pneumonitis, occurring in approximately 10% of patients hospitalized following a drug overdosage. Adnet and Baut demonstrated that the risk of aspiration increases with the degree of impairment in consciousness (as measured by the Glasgow Coma Scale).[8] Historically the syndrome most commonly associated with aspiration pneumonitis is Mendelson’s syndrome, reported in 1946 in obstetric patients who aspirated while receiving general anesthesia.[9] Mendelson’s original report consisted of 44,016 nonfasted obstetric patients whom he studied between 1932 and 1945, of whom more than half received an “operative intervention” with ether by mask without endotracheal intubation. He described aspiration in 66 patients (1 in 667). Although several of the patients were critically ill from their aspiration, recovery was usually complete within 24 to 36 h and only 2 patients died (1 in 22,008).

Although aspiration is a widely feared complication of general anesthesia, clinically apparent aspiration in modern anesthesia practice is exceptionally rare, and in healthy patients the overall morbidity and mortality are low (see “Anesthesia and Aspiration,” below). The risk of aspiration is greatly increased in patients intubated emergently in the field, emergency room, or ICU. In these patients, every effort should be made to reduce the risk of aspiration. These efforts include removing dentures, clearing the airway, and in certain circumstances, placing a nasogastric tube to empty

TABLE 69-1 Contrasting Features of Aspiration Pneumonitis and Aspiration Pneumonia

Feature	Aspiration Pneumonitis	Aspiration Pneumonia
Mechanism	Aspiration of sterile gastric contents	Aspiration of colonized oropharyngeal material
Pathophysiologic process	Acute lung injury from acidic and particulate matter	Acute pulmonary inflammatory response to bacteria and bacterial products
Bacteriologic findings	Initially sterile, with subsequent bacterial infection possible	Gram-negative rods, gram-positive cocci, and rarely anaerobic bacteria
Major predisposing factors	Depressed level of consciousness	Dysphagia and gastric dysmotility
Age group affected	Any age group, but usually young persons	Usually elderly persons
Aspiration event	May be witnessed	Usually not witnessed
Typical presentation	Patient with a history of depressed level of consciousness in whom a pulmonary infiltrate and respiratory symptom develop	Institutionalized patient who presents with features of a “community-acquired pneumonia” with an infiltrate in a dependent bronchopulmonary segment
Clinical features	No symptoms or symptoms ranging from a nonproductive cough to tachypnea, bronchospasm, bloody or frothy sputum, and respiratory distress 2 to 5 h after aspiration	Tachypnea, cough, fever, and signs of pneumonia

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the stomach prior to intubation. If there is an immediate risk of airway compromise, endotracheal intubation should be performed prior to placement of a nasogastric tube. However, if the patient is likely to have a full stomach (e.g., from upper GI bleed, small bowel obstruction, ileus), it may be prudent to place a nasogastric tube prior to endotracheal intubation. When intubating emergently, suction equipment must be immediately available and rapid-sequence induction using cricoid pressure should be performed.

■ Pathophysiology

Mendelson emphasized the importance of acid when he showed that unneutralized gastric contents introduced into the lungs of rabbits caused severe pneumonitis indistinguishable from that caused by an equal amount of 0.1 N hydrochloric acid.[9–11] However, if the pH of the vomitus was neutralized before aspiration, the pulmonary injury was minimal. Experimental studies have demonstrated that the severity of lung injury increases significantly with the volume of the aspirate and inversely with its pH, with a pH of less than 2.5 required to cause aspiration pneumonitis.

In experimental models, when acid is instilled into the lungs, a two-phase injury results. The initial injury phase (within 1 h of acid exposure) is primarily due to the acid's direct caustic effects on pulmonary tissue, whereas the second injury phase (beginning at 3–4 h and peaking at 4–6 h postexposure) results from recruited neutrophils.[12,13] The intensity of the alveolar neutrophil infiltration is related to the severity of the acute lung injury. Once localized to the lung, neutrophils play a key role in the development of lung injury through the release of reactive oxygen species (ROS) and proteases that are injurious to the lung.

NADPH oxidase is the major source of ROS in activated neutrophils; other sources of ROS following gastric aspiration include superoxide anion generated by xanthine oxidase.[14] ROS exacerbate acute lung injury through several mechanisms, including direct cellular injury, nuclear factor κB (NF-κB) activation, and activation of other proinflammatory mediators, such as tumor-necrosis factor α (TNF-α) and interleukin 8 (IL-8). The activation of NADPH oxidase in neutrophils is linked to the generation of neutrophil extracellular traps (NETs). NETs are extracellular strands of decondensed (unwound) DNA in complex with histones and neutrophil granule proteins. NETs contain serine proteases and other antimicrobial products that damage the lung.

The stomach contains a variety of other substances in addition to acid. Several experimental studies have demonstrated that aspiration of small, particulate food matter from the stomach may cause severe pulmonary damage, even if the pH of the aspirate is above 2.5.[15,16] These studies suggest that cell recruitment and expression of inflammatory mediators are most pronounced after injury with combined acid and small food particles. These data are supported by findings where the most severe lung injury was observed in patients following aspiration with particulate food matter.[17,18] Gastric acid prevents the growth of bacteria; therefore, the contents of the stomach are normally sterile. Hence, bacterial infection does not play a significant role in the early stages of acute lung injury following aspiration of gastric contents. However, acid aspiration pneumonitis reduces host defenses against infection, increasing the risk of superinfection.[19] The incidence of this complication has, however, not been well studied. Furthermore, experimental models suggest that acid aspiration pneumonitis "primes the lung," making secondary infection more severe.[19,20]

Colonization of the gastric contents by potentially pathogenic organisms may occur when the gastric pH is increased by the use of antacids, histamine 2 (H2) receptor blockers, or proton pump inhibitors. In addition, gastric colonization by Gram-negative bacteria occurs in patients receiving enteral feedings, as well as in patients with gastroparesis and small bowel obstruction. In these circumstances, the pulmonary inflammatory response is likely to result from both bacterial infection and the inflammatory response of the gastric particulate matter.

■ Anesthesia and Aspiration

Aspiration pneumonitis has traditionally been regarded as the major cause of serious anesthetic complications. However, with the recognition of the importance of this complication and that it is largely preventable, the risk of aspiration pneumonitis is modern anesthesia is extremely low. Nevertheless, aspiration pneumonitis is an important perioperative complication and remains the commonest cause of anesthesia-related death. The risk of aspiration with modern anesthesia is reported to be between 2.9 and 4.7 per 10,000 general anesthetics (about 1 in 3000 anesthetics) with a mortality of approximately 1:125,000, accounting for 10% to 30% of all anesthetic deaths.[21,22]

Warner et al. published data from a study of 215,488 anesthetics and observed 67 episodes of aspiration in adults (3.1 per 10,000 patients) undergoing general anesthesia.[11] In a study involving 99,441 patients undergoing nonobstetric anesthesia, perioperative pulmonary aspiration occurred in 14 patients (1 in 7103 procedures).[23] All 14 patients had 1 or more risk factors for aspiration. The Thai Anesthesia Incident Monitoring Study prospectively recorded reports on aspiration from 51 hospitals across Thailand during a 6-month period in 2007.[24] In the study, 28 reports met the definition of pulmonary aspiration (denominator not reported). Most of the incidents occurred in American Society of Anesthesiology (ASA) class 1–2 patients (85.7%), during daytime hours (64.3%), and when the anesthesiologists were in charge (67.9%). A total of 11 incidents (39.3%) occurred during induction, 7 (25%) during maintenance, and 7 (25%) during the emergence phase. All the incidents except 1 (96.4%) were considered human error, and 25 (89.2%) were considered preventable. In all, 13 patients (46.4%) had major physiologic changes, and 10 (35.7%) of them required unplanned ICU admission; 10 patients (35.7%) needed prolonged ventilator support, and 2 (7.14%) died.

The most definitive and extensive review on the risk of airway problems associated with intubation was reported by Cook et al., who summarized the findings of the fourth National Audit Project of the Royal College of Anaesthetists.[25,26] In this 1-year prospective audit, the authors examined the occurrence of serious airway complications in anesthesia, ICUs, and emergency departments of all the National Health Service hospitals in the United Kingdom. The authors found 184 cases that met the inclusion criteria: 133 from anesthesia, 36 from ICUs, and 15 from emergency departments. A concurrent national census of anesthesia activity over a 2-week period was performed to provide denominator data for anesthesia, which indicated 2.9 million anesthetic procedures annually, resulting in a nominal incidence (using the 133 anesthesia events) of 1 serious airway complication per 22,000 anesthetics. In total, 38 deaths were attributable to airway complications, and the death rate was 16 of 133 (12%) in anesthesia, 18 of 36 (50%) in the ICUs, and 4 of 16 (25%) in the emergency departments. Pulmonary aspiration of gastric contents was the commonest cause of death and brain damage. A supraglottic airway was the planned technique in more than 50% of cases associated with death or brain damage. A statistical analysis of the reports suggested that as few as 25% of relevant incidents may have been reported. The authors suggest, therefore, that this audit provides an indication of the lower limit for the incidence of such complications.

Emergency surgery (particularly, trauma and abdominal surgery with delayed gastric emptying) procedures performed at night, inadequate anesthesia, obesity, elderly immobilized patients, and obstructive sleep apnea have been associated with a higher risk of aspiration.[22,27] Obtunded adults and children with known gastroesophageal reflux are more likely to aspirate even without narcotic or sedative impairment of airway reflexes. The factors increasing the

TABLE 69-2 Factors Increasing the Risk of Perioperative Aspiration

Recent eating
Delayed gastric emptying
Diabetic neuropathy
Opioids
Paralytic ileus
Small bowel obstruction
Pregnancy
Emergency surgery
Obesity
Obstructive sleep apnea
Reflux esophagitis
Achalasia
Esophageal stricture
Previous gastric bypass surgery
Traumatic brain injury
Cerebral infarction/bleed

risk for aspiration are listed in Table 69-2. Patients who are at risk before surgery are also at increased risk during the postoperative period when immobility, residual effects of anesthetic agents, and narcotics combine to decrease protective airway reflexes.[28–30]

The incidence of aspiration appears higher in obstetric patients, as highlighted by the pioneering study of Mendelsohn.[9] A study from 1973 reported an incidence of 1 in 6000 obstetric patients receiving general anesthesia for vaginal deliveries and 1 in 430 for patients undergoing cesarean section.[31] In more recent studies, an aspiration incidence of 1 in 1547 and 1 in 1431, were described for caesarean section under general anaesthesia;[28,30] a more recent audit showed an incidence of 1 in 900 in women undergoing caesarean section.[29] The risk of pulmonary aspiration is, therefore, at least double or three times as high as in general surgical patients. Pregnant women are at increased risk of aspiration because of gastroesophageal reflux and delay in gastric emptying.[32,33]

Gastroesophageal reflux is common in pregnancy and can be demonstrated even in the absence of symptoms. There is no difference in basal and evoked gastric acid secretion in pregnancy, but there is a reduction in lower esophageal barrier pressure, which is likely to be a progesterone effect present from early pregnancy. The surgical procedure may itself increase aspiration risk through the adoption of lithotomy or Trendelenburg positions or the creation of a pneumoperitoneum.

The laryngeal mask airway (LMA) does not reliably protect the lungs from regurgitated stomach contents and should be avoided in patients at an increased risk for aspiration.[34,35] In a meta-analysis of 12,901 low-risk cases, where the standard contraindications to the use of the LMA were followed (e.g., absence of gastrointestinal pathology, obesity, history of reflux, or emergency surgery), only three cases of aspiration were identified, representing an incidence of 2.3 per 10,000.[36]

Inadequate reversal of neuromuscular blockage at the end of surgery is an important risk factor for aspiration. After the administration of nondepolarizing neuromuscular blocking agents, it is essential to ensure adequate return of normal neuromuscular function. Residual paralysis decreases upper esophageal tone, coordination of the esophageal musculature during swallowing, and the hypoxic ventilatory drive.[37] These factors significantly increase the risk for aspiration. Adequate recovery of postoperative neuromuscular function cannot be guaranteed without objective neuromuscular monitoring. Good evidence-based practice dictates that clinicians should always quantitate the extent of neuromuscular blockade by objective monitoring (train-of-four monitoring).[37] To exclude clinically significant residual neuromuscular blockade, the train-of-four ratio, when measured mechanically or by electromyography, must exceed 0.9. If sufficient recovery (i.e., train-of-four ≥0.9) has not been documented objectively at the end of the surgical procedure, the neuromuscular block should be antagonized.

Prevention of Aspiration

In recent years, more liberal preoperative fasting guidelines have been promoted. In healthy adults without an increased risk of regurgitation or aspiration, solids should be avoided after midnight; however, a light meal such as dry toast may be considered up to 6 h before anesthesia, and clear liquids, such as water, coffee without milk, or fruit juice, can be given up to 2 h before induction.[38,39] Meta-analyses of randomized controlled trials comparing fasting times of 2–4 h versus more than 4 h report smaller gastric volumes and higher gastric pH values in adult patients given clear liquids 2–4 h before a procedure; this approach is currently endorsed by the ASA.[40]

Preoperative antacids, H2 receptor blockers, proton pump inhibitors, and prokinetic agents have been used to reduce the volume or acidity of the gastric contents. There is, however, a lack of data indicating that any of these drugs reduce the risk of aspiration pneumonitis.[41] The routine use of these drugs is not recommended by the ASA guidelines.[40] However, it is not unreasonable to use these drugs in patients at an increased risk of aspiration. It is important to realize that it takes time for the clinical effects of the acid suppressive drugs to manifest, and these drugs should, therefore, be dosed at least 2 h prior to induction.[42]

Standard teaching suggests that rapid sequence induction with cricoid pressure should be performed when intubating patients at an increased risk of aspiration. Cricoid pressure, known as the Sellick maneuver, is designed to occlude the cervical esophagus by compressing it between the cricoid cartilage and the vertebral bodies.[43] Passively regurgitated gastric contents are thereby prevented from entering the pharynx. Neither rapid sequence induction nor cricoid pressure has been prospectively studied and proven to decrease the incidence of aspiration.

Rapid sequence induction shortens the time between the onset of unconsciousness and securing the airway, which may be of benefit if the aspiration risk is high. However, the use of cricoid pressure is controversial.[44] The esophagus cannot be reliably occluded between the cricoid cartilage and the vertebral bodies. Studies in volunteers (men and nonpregnant women) clearly show that the esophagus often does not lie in the midline or that cricoid pressure displaces the esophagus laterally without occluding it.[45] More recent data suggest that the hypopharynx posterior to the cricoid cartilage is in continuity with the esophageal inlet and this hypopharyngeal area is occluded with the Sellick maneuver.[46] Cricoid pressure is often applied incorrectly or without the appropriate amount of force and may reduce visualization of the vocal cords and impede intubation. Although not proven to reduce the risk of aspiration during emergent intubations, cricoid pressure is currently considered the standard of care in this situation.

Clinical Presentation

Aspiration of gastric contents can present dramatically with a full-blown picture that includes gastric contents in the oropharynx, wheezing, coughing, shortness of breath, cyanosis, pulmonary edema, hypotension, and hypoxemia; this may progress rapidly to severe ARDS and death (Fig. 69-1). However, many patients may not develop signs or symptoms associated with aspiration, while others may develop a cough or wheeze. In some patients' aspiration may be clinically silent, manifesting only as arterial desaturation

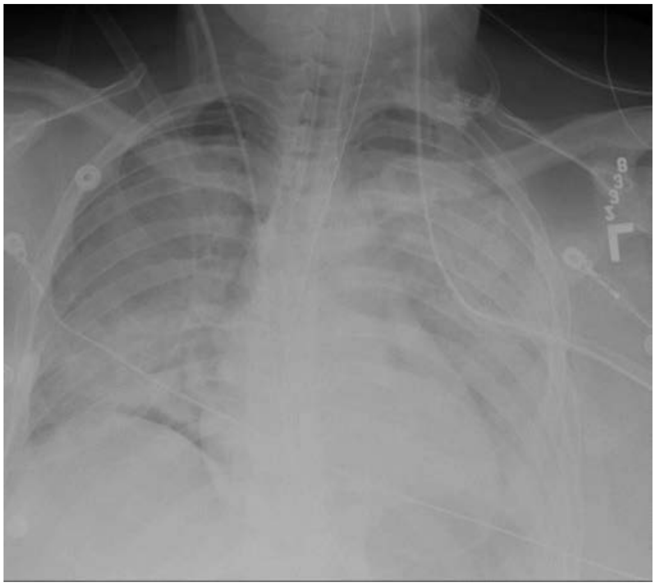

Figure 69-1 Chest radiograph demonstrating severe bilateral airspace disease (ARDS) in a patient who aspirated following anesthesia.

with radiologic evidence of aspiration. Warner et al. studied 67 patients who aspirated while undergoing anesthesia.[11] Of these patients, 42 (64%) were totally asymptomatic, 13 required mechanical ventilatory support for more than 6 hours, and 4 died.

Management of Aspiration Pneumonitis

The upper airway should be suctioned following a witnessed aspiration. Endotracheal intubation should be considered in patients who are unable to protect their airway. While common practice, the prophylactic use of antibiotics in patients with suspected or witnessed aspiration is not recommended. Similarly, the use of antibiotics shortly after an aspiration episode in a patient who develops a fever, leukocytosis, and a pulmonary infiltrate is discouraged as it may select for more resistant organisms in a patient with an uncomplicated chemical pneumonitis. However, empiric antimicrobial therapy is appropriate in patients who aspirate gastric contents in the setting of small bowel obstruction or in other circumstances associated with colonization of gastric contents (such as acid-suppressive therapy and tube feeds).

Antimicrobial therapy should be considered in patients with an aspiration pneumonitis that fails to resolve within 48 h. Empiric therapy with broad-spectrum agents is recommended. Antimicrobials with anaerobic activity are not routinely required.

Recently, serum procalcitonin has emerged as a potential biomarker that has been postulated as useful in discriminating bacterial infections from nonbacterial inflammatory disorders.[47] El-Solh et al. investigated the predictive accuracy of serum procalcitonin in distinguishing aspiration with bacterial pneumonia from "sterile" aspiration pneumonitis.[6] In this study, serum procalcitonin levels had poor diagnostic value in separating bacterial pneumonia from aspiration pneumonitis based on quantitative bronchoalveolar lavage culture. This finding is not surprising, considering that proinflammatory mediators play a central role in the pathophysiology of both syndromes and are responsible for the transcription of procalcitonin.[48]

Immunomodulating Agents and Pneumonitis

Corticosteroids are potent anti-inflammatory agents that act largely by repression of the transcriptional activity of NF-κB. Glucocorticoids have been used in the management of aspiration pneumonitis since 1955.[49–51] However, their role as monotherapy appears limited, possibly due to their limited effect on neutrophils and ROS.

Vitamin C, acting synergistically with low-dose corticosteroids, has emerged as an important strategy in treating various conditions characterized by widespread and profound inflammation.[52] Vitamin C is a potent antioxidant and inhibitor of NADPH oxidase and would likely reduce the severity of acute lung injury after acid aspiration.[53] In addition, vitamin C inhibits NETosis.[54] We have previously described two patients with "anesthesia"-related aspiration pneumonitis and severe ARDS who were treated with hydrocortisone, ascorbic acid, and thiamine (HAT therapy) and who appeared to respond dramatically to this intervention.[55] A recent prospective, randomized, controlled trial demonstrated that high-dose intravenous vitamin C reduced mortality in patients with ARDS.[56] Additional studies are required to confirm these findings to be considered for patients with acid aspiration–induced acute lung injury.

ASPIRATION PNEUMONIA

Aspiration pneumonia refers to the development of a radiographic infiltrate and clinical features of consistent with pneumonia in a patient with risk factors for increased oropharyngeal aspiration (Fig. 69-2). Approximately half of all healthy adults aspirate small amounts of oropharyngeal secretions during sleep. Presumably, the low virulent bacterial burden of normal pharyngeal secretions, together with forceful coughing, active ciliary transport, and normal humoral and cellular immune mechanisms result in clearance of the inoculum, without sequelae. However, if the mechanical, humoral, or cellular mechanisms are impaired or if the aspirated inoculum is large enough, pneumonia may follow.

Any condition that increases the volume or bacterial burden of oropharyngeal secretions in the setting of impaired host defense mechanisms may lead to aspiration pneumonia. Indeed, in stroke patients undergoing swallow evaluation there is a strong correlation between the volume of the aspirate and the development of pneumonia.[57] Factors that increase oropharyngeal colonization with potentially pathogenic organisms and that increase the bacterial load may augment the risk of aspiration pneumonia. The clinical setting in which pneumonia develops largely distinguishes

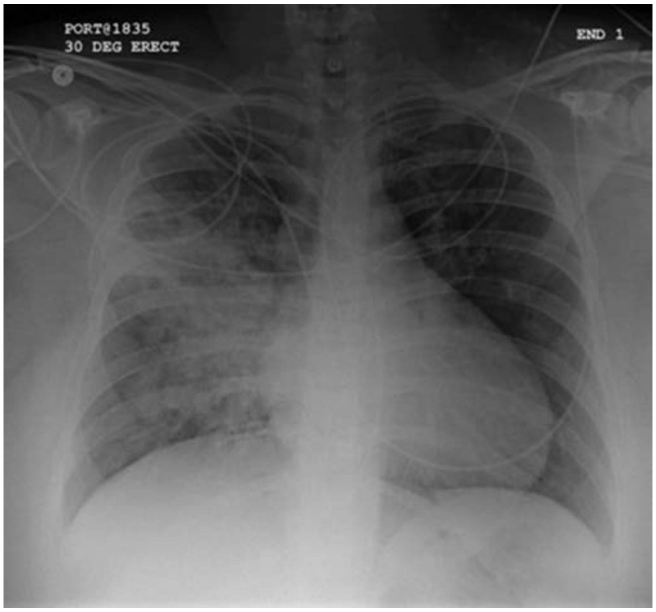

Figure 69-2 Opacification of the right perihilar region and superior segment of the right lower and upper lobes consistent with aspiration pneumonia in a 75-year-old patient who suffered a stroke.

aspiration pneumonia from other forms of pneumonia. However, there is much overlap. This is illustrated by the fact that otherwise healthy elderly patients with "community-acquired pneumonia" have been demonstrated to have a significantly higher incidence of silent aspiration when compared with age-matched controls.[58]

■ Epidemiology

The lack of specific and sensitive markers of aspiration makes the epidemiologic study of aspiration syndromes difficult. Furthermore, most studies do not make the distinction between aspiration pneumonitis and aspiration pneumonia. Nevertheless, several studies list "aspiration pneumonia" as the cause of community-acquired pneumonia (CAP) in 5% to 15% of cases.[59,60] CAP is a major cause of morbidity and mortality in the elderly, and it is likely that aspiration is the major cause of pneumonia in these patients. Epidemiologic studies have demonstrated that the incidence of pneumonia increases with aging, with the risk being almost six times higher in those over the age of 75 years, compared with those less than 60 years of age.[61,62] The attack rate for pneumonia is highest among those in nursing homes.[63]

■ Dysphagia in Aspiration Pneumonia

Swallowing is a complex function with both voluntary and reflexive components. Five cranial nerves and more than 50 muscles in the head and neck are involved in oropharyngeal swallowing. Both brainstem and cortical areas are involved in the neural processing of swallowing. The coordination of swallowing requires bilateral input from the sensorimotor cortex with descending input to the brainstem medullary swallowing center.[64] Functional and anatomic imaging studies have identified several sites that play an important role in swallowing, including the primary sensorimotor cortex, insula, anterior cingulate, internal capsule, basal ganglia, and thalamus.

The swallowing process can be divided into the oropharyngeal phase and esophageal phase.[65] The oropharyngeal phase includes biting and chewing in the oral cavity, and the transport of food into the pharynx. In simplified terms, this process is accompanied by elevation and anterior movement of the larynx to meet with the epiglottis for protection of the airway. It is followed by passage of the bolus through the upper esophageal sphincter into the esophagus (esophageal phase). During the esophageal phase, the lower esophageal sphincter relaxes, and food is advanced into the stomach by peristalsis and gravity.

Dysphagia refers to difficulty in swallowing. The severity of dysphagia varies from moderate difficulty to complete inability to swallow. Dysphagia is the major risk factor leading to aspiration pneumonia. In addition, dysphagia contributes significantly to protein-energy malnutrition and dehydration. Impairment in any component of the swallow mechanism, including anatomic abnormities of the upper airway or esophagus, can lead to dysphagia. Dysphagia has traditionally been associated with brainstem and bilateral cerebral infarction, although it has more recently been shown to occur in isolated cerebral infarctions as well. Furthermore, dysphagia is commonly associated with silent cerebral infarction.

Dysphagia is remarkably common in Westernized nations and is a major cause of morbidity and mortality. Indeed, aspiration pneumonia is probably the final common pathway by which most chronically ill patients die. It has been estimated that more than 16 million senior citizens in the United States suffer from dysphagia.[66] Furthermore, an additional 300,000 to 600,000 patients develop dysphagia each year in the United States from neurologic disorders.[67] Dysphagia affects more than 30% of patients who have had a cerebrovascular accident; 52%–82% of patients with Parkinson's disease; 84% of patients with Alzheimer's disease; up to 40% adults aged 65 years and older; and more than 60% of elderly institutionalized patients.[68]

TABLE 69-3 Risk Factors for Dysphagia and Aspiration Pneumonia

- Cerebrovascular disease
  - Ischemic stroke
  - Hemorrhagic stroke
  - Subarachnoid hemorrhage
- Degenerative neurologic disease
  - Alzheimer dementia
  - Multi-infarct dementia
  - Parkinson disease
  - Amyotrophic lateral sclerosis (motor neuron disease)
  - Multiple sclerosis
- Head and neck cancer
  - Oropharyngeal malignancy
  - Oral cavity malignancy
  - Esophageal malignancy
- Other
- Scleroderma
- Diabetic gastroparesis
- Reflux esophagitis
- Presbyesophagus
- Achalasia

The efficiency of the swallow mechanism decreases with aging, increasing the risk of aspiration and pneumonia in the elderly. Kikuchi et al. evaluated the occurrence of silent aspiration in otherwise "healthy elderly patients" with CAP and age-matched control subjects using indium^{111} chloride scanning.[58] Silent aspiration was demonstrated in 71% of patients with CAP compared to 10% in control subjects. The impaired swallow mechanism in the elderly may be attributed to diminished sensation, silent cerebral infarction, cerebral atrophy, a delay in the synapse conduction in the afferent inputs to the central nervous system, and lingual weakness (due to sarcopenia) caused by aging.[69,70]

■ Risk Factors for Dysphagia

The major risk factors for dysphagia are listed in Table 69-3. In patients with an acute stroke the incidence of dysphagia ranges from 40% to 70%.[71] Dysphagic patients who aspirate are at an increased risk of developing pneumonia.[72,73] Although dysphagia improves in most patients following a stroke, in many the swallowing difficulties follow a fluctuating course, with 10% to 30% continuing to have dysphagia with aspiration.[74,75]

■ Cough Reflex in Patients with Aspiration Pneumonia

An intact cough reflex is an important respiratory defense mechanism. Sekizawa et al. demonstrated a marked depression of the cough reflex in elderly patients with pneumonia.[76] Furthermore, the greater the derangement of the cough reflex the greater the risk of pneumonia.[77] Nakazawa et al. demonstrated impairment of the swallow and the cough reflex in elderly patients with aspiration pneumonia, but not in patients with dementia who had no prior history of aspiration pneumonia.[78]

Angiotensin-converting enzyme (ACE) modulates the cough reflex. Along with its effects that cleave angiotensin I to angiotensin II, ACE also metabolizes the protussive peptides substance *P* and bradykinin. Substance *P*, which is released from vagal sensory nerves in the pharynx and upper airways, mediates the cough reflex.

In one study, investigators found that substance *P* levels in sputum were reduced substantially in elderly patients with pneumonia.[79] Bradykinin, an inflammatory peptide that mediates cough due to ACE inhibitions, sensitizes airway sensory nerves and enhances the cough reflex. A number of reports indicate that the insertion/deletion (*I/D*) polymorphism of the ACE gene (ACE DD allele) is associated with an increased risk of pneumonia.[80,81] Furthermore, the use of ACE inhibitors is associated with a reduced risk of aspiration pneumonia (see "Pharmacologic Management," below).

Factors That Increase the Risk of Pneumonia in Patients Who Aspirate

While the presence of dysphagia and the volume of the aspirate are key factors that predispose patients to aspiration pneumonia, a number of other factors play an important role.[57] Colonization of the oropharynx is an important step in the pathogenesis of aspiration pneumonia. The elderly have increased oropharyngeal colonization with pathogens such as *Staphylococcus aureus* and aerobic gram-negative bacilli (e.g., *Klebsiella pneumoniae*, *Escherichia coli*). Although this increased colonization may be transient, it underlies the increased risk in the elderly of pneumonia with these pathogens. Furthermore, colonization of dental plaque may be an important risk factor for aspiration pneumonia.[82]

The defects in host defenses that predispose to enhanced colonization with these organisms are uncertain; however, dysphagia with a decrease in salivary clearance and poor oral hygiene may be major risk factors.[83] Residents of long-term care facilities are prone to poor oral health due to lack of oral hygiene care as well as conditions of periodontal or dental disease. Langmore et al. reported that in elderly patients the number of decayed teeth and never or only occasionally brushing teeth were independent predictors of aspiration pneumonia.[84] Similarly, Azapazhooh and Leake performed a systematic review demonstrating that the presence of cariogenic and periodontal pathogens in dental plaque and saliva and decayed teeth were independent predictors of aspiration pneumonia.[85] Others have demonstrated that persons with 10 or more periodontal pockets had an increased risk of death from pneumonia.[86]

Proton pump inhibitors increase gastric and oropharyngeal colonization with potentially pathogenic organisms. Investigators have reported that the concurrent use of proton pump inhibitors in patients over the age of 60 increased the risk for community-acquired (aspiration) pneumonia.[87]

Diagnosis and Management of Aspiration Pneumonia

There is no "gold standard" diagnostic test for aspiration pneumonia. Furthermore, in patients with aspiration pneumonia, unlike the case of aspiration pneumonitis, the episode of aspiration is generally not witnessed. Rather, the diagnosis is inferred when a patient with known risk factors for aspiration develops clinical features compatible with pneumonia (e.g., fever, shortness of breath, purulent sputum) with an infiltrate in a characteristic bronchopulmonary segment (Fig. 69-2). In patients who aspirate in the recumbent position, the commonest sites of involvement are the posterior segments of the upper lobes and the apical segments of the lower lobes. In patients who aspirate in the upright or semirecumbent position, the basal segments of the lower lobes are favored. The usual picture is an acute pneumonic process that runs a course similar to that of a typical CAP. However, when untreated, these patients appear to have a higher incidence of cavitation and lung abscess formation.[88]

Antimicrobial therapy is essential in patients with aspiration pneumonia. The choice of antibiotics depends on the setting in which the aspiration occurs, as well as the patient's premorbid condition. Factors to be considered include whether the aspiration occurred in the community or in a health care facility, and patient characteristics such as alcoholism, oral hygiene, injection drug use, and the recent use of antibiotics or acid-suppressive therapy.[89]

In otherwise "healthy" outpatients, a narrow-spectrum antibiotic that targets organisms that include *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Hemophilus influenzae* is recommended. However, most patients with aspiration pneumonia have risk factors for colonization and infection with aerobic Gram-negative organisms and require treatment with antimicrobials such as third-generation cephalosporins, fluoroquinolones, piperacillin, or carbapenems.[89–92] In addition, vancomycin or linezolid should be considered in patients at risk of infection with methicillin-resistant *Staphylococcus aureus* (MRSA).

Although commonly prescribed (and often considered the standard of care), antimicrobials with specific anaerobic activity are not routinely warranted. The anaerobic bacteria that colonize the oropharynx are intrinsically of low virulence. In an experiment dating back to 1930, Smith introduced bacteria isolated from patients with Vincent's angina into the lungs of rabbits.[93] Cultures of a single organism failed to produce pneumonia; only when multiple different organisms were instilled into the lungs did the animals develop pneumonia (synergistic anaerobic infection). In the most rigorous study to date, El-Sohl et al. performed protected quantitative bronchial sampling in 95 patients with severe aspiration pneumonia.[92] Of the 67 pathogens identified, Gram-negative enteric bacteria were the predominant organisms isolated (49%), followed by anaerobic bacteria (16%) and *Staphylococcus aureus* (12%). A single anaerobic bacterium was isolated from 11 patients, usually in association with a Gram-negative pathogen. Although 7 cases with anaerobic isolates received initially inadequate antimicrobial therapy, 6 had effective clinician response. Antimicrobials with specific anaerobic activity may only be indicated in patients with periodontal disease, patients expectorating putrid sputum, and those with a necrotizing pneumonia or lung abscess on chest radiograph.[2,89–91]

Assessment and Management of Dysphagia

All elderly patients with CAP, as well as patients with a recent cerebrovascular accident and those with degenerative neurologic diseases, should be referred to a speech and language pathologist (SLP) for a formal swallow evaluation[73,94] (Video 69-1). Those patients with dysphagia require the formulation and implementation of an individualized management strategy. A clinician's bedside assessment of the cough and gag reflex is unreliable in screening for patients at risk of aspiration. Because objective swallowing evaluation can be performed with a nasogastric tube or feeding tube in place, it is not necessary to remove the tube (and interrupt enteral feedings) to evaluate dysphagia. Similarly, there is no contraindication to leaving a nasogastric tube in place to supplement oral alimentation.[95]

Video 69-1 An 82 year-old male admitted with PNA, required multiple intubations and eventual tracheostomy. Fiberoptic endoscopic evaluation of swallowing (FEES) completed with #5XLT proximal/cuffless tracheostomy (patient capped on room air) and Dobhoff feeding tube in place. FEES revealed a severe pharyngeal dysphagia. There is pooling of secretions throughout pharynx/larynx (valleculae and pyriform sinuses) with aspiration of secretions. With pureed texture there is residue throughout the pharynx suggestive of generalized reduced pharyngeal contraction. The residue in the valleculae is a result of reduced base of tongue retraction, epiglottis dysfunction, and poor hyoid elevation. The residue in the pyriform sinuses is a result of cricopharyngeus dysfunction/inadequate upper esophageal sphincter opening. There is a delayed pharyngeal swallow response with nectar consistency with bolus spilling to the pyriform sinuses resulting in + aspiration before/during/after the swallow response due to reduced arytenoid tilt and vocal fold adduction. *(Used with permission of Randy Dubin.) Video available on AccessMedicine.com.*

The management of patients with dysphagia requires the coordinated expertise of a number of health care professionals, including the patient's primary care physician, pulmonologist, SLP, clinical dietician, occupational therapist, physiotherapist, nurse, oral hygienist, dentist, and primary caregivers. The goal is to optimize the safety, efficiency, and effectiveness of the oropharyngeal swallow, to maintain adequate nutrition and hydration, and to improve oral hygiene. Enhanced quality of life, wherever possible, should direct management, and oral intake (when possible) is preferred over tube feeding.

A fundamental principle of rehabilitation is that the best therapy for any activity is the activity itself; as swallowing may be considered the best therapy for swallowing disorders, rehabilitation should be aimed at identifying ways of ensuring safe and effective swallowing in individual patients. Current treatment for dysphagia includes prevention of aspiration in the form of diet and fluid modifications, compensatory maneuvers, position changes, and rehabilitation exercises.[96]

Diet modification is a common treatment for dysphagia. Modifications in food consistency are individually determined by means of the clinical swallow or videofluoroscopic swallow evaluation. Reduction in bolus volume and enhancement of bolus viscosity significantly improve the safety of swallowing and reduce the risk of aspiration.[69] The SI physical unit of dynamic viscosity is the pascal-second (Pa·s). The prevalence of aspiration is maximal with water and thin fluids (20 Pa·s) and decreases with nectar (270 Pa·s) and pudding (3900 Pa·s) boluses.[69] By increasing the viscosity or thickness of the food or liquid bolus in patients with oral sensory or motor deficits, the material is less likely to escape from the oral cavity, fall into the laryngeal inlet, or penetrate the incompletely sealed larynx during the delay before pharyngeal swallowing starts. Videofluoroscopic studies have demonstrated that increasing viscosity of liquids to that of pudding significantly reduces the risk of aspiration.[97,98]

In addition to changes in diet, maintenance of oral feeding often requires compensatory techniques to reduce aspiration or to improve pharyngeal clearance. A variety of behavioral techniques are used, including modifications in posture, head position and respiration, and specific swallowing maneuvers. The chin-down posture has been suggested to reduce the risk of aspiration.[98–100] Welch et al. noted that the posterior shift of anterior pharyngeal structures with the chin-down posture improved airway protection.[101] The preferred intervention in patients with dysphagia and the impact of these interventions on the risk of aspiration pneumonia is, however, unclear.[102]

Neuromuscular electrical stimulation (NMES) is a relatively new treatment for oropharyngeal dysphagia.[103–107] NMES for dysphagia entails applying electrodes to the muscles of the head and neck, and stimulating those muscles that are weakened or hemiparetic by means of electric pulses. This is generally combined with the subject swallowing food or fluids that are predetermined to represent the most appropriate consistency that the person can tolerate without aspiration. Clinical studies to date suggest that the early application of NMES appears to be a useful supplementary treatment of traditional dysphagia treatment to help rehabilitate acute/subacute dysphagic stroke patients by improving their swallowing coordination.[103–107]

Tube Feeding

Tube feeding is not essential in all patients who aspirate. Short-term tube feeding, however, may be indicated in elderly patients with severe dysphagia and aspiration in whom improvement of swallowing is likely to occur.

Nakajoh et al. demonstrated that the incidence of pneumonia was significantly higher in stroke patients with dysphagia who were fed orally compared with those who received tube feeding (54.3 vs. 13.2%; $p < 0.001$), despite the fact that the orally fed patients had a higher functional status (higher Barthel index).[77]

The FOOD trials consisted of two large randomized studies that enrolled dysphagic stroke patients.[108] In the first trial, patients enrolled within 7 days of admission were randomly allocated to early tube feeding or no tube feeding. Early tube feeding was associated with an absolute reduction in risk of death of 5.8%. The second trial allocated patients to early nasogastric feeding or early feeding via a percutaneous endoscopic gastrostomy (PEG) tube. PEG feeding was associated with an absolute increase in the risk of death of 1% and an increased risk of death or poor outcome of 7.8%. Patients with a PEG were less likely to be transitioned to oral feeding than the nasogastric group and were more likely to be living in an institution. This may in part explain the higher mortality of the PEG-fed patients. Furthermore, it is interesting to note that PEG-fed patients were more likely to develop pressure sores, suggesting that these patients may have been cared for differently from a nursing perspective. The results of the FOOD trials suggest that dysphagic stroke patients should be fed early via a nasogastric or feeding tube and transitioned to oral feeding as their dysphagia resolves. Those patients whose dysphagia does not resolve may be candidates for placement of a PEG tube.

Oral Hygiene

Dental plaque, as well as "tongue coating," serve as a reservoir of potentially pathogenic organisms.[82] Occupants of residential homes have been shown to have poor oral hygiene and rarely receive treatment from dentists and oral hygienists.[109] An aggressive protocol of oral care will reduce colonization with potentially pathogenic organisms and decrease the bacterial load, measures that have been demonstrated to reduce the risk of aspiration pneumonia.[110–113] Oral care should not be overlooked in edentulous patients, as "tongue cleaning" is associated with a decreased oropharyngeal bacterial load.[114,115]

Pharmacologic Management

The neurotransmitter substance P is believed to play a major role in both the cough and swallow sensory pathways. ACE inhibitors prevent the breakdown of substance P and may theoretically be useful in the management of patients with aspiration pneumonia. A number of studies have demonstrated a lower risk of aspiration pneumonia in stroke patients treated with an ACE inhibitor compared with other antihypertensive agents.[116,117] This observation was initially noted in Japanese patients; it has been suggested that this benefit was restricted to Asian populations.[118] Furthermore, it has been postulated that lipophilic ACE inhibitors may be more beneficial than hydrophilic ACE inhibitors.[119] However, a population-based case-control study from the United Kingdom demonstrated that the current prescription for an ACE inhibitor was associated with a reduction of the risk of pneumonia in the general population (OR, 0.75; 95% CI, 0.65–0.86).[120] Nicergoline, an ergot alkaloid derivative, has been demonstrated to upregulate substance P and improve dysphagia with an efficacy similar to that of ACE inhibitors.[121] Additional studies are required with this drug to determine its role in preventing aspiration pneumonia.

Sedative medication has been demonstrated to increase the risk of pneumonia in residents of long-term care facilities and should therefore be avoided.[122] The prescription of phenothiazines and haloperidol should be very carefully considered, as they reduce oropharyngeal swallow coordination, causing dysphagia.[123,124] Medications that dry up secretions, including antihistamines and drugs with anticholinergic activity, make it more difficult for patients to swallow and should therefore also be avoided.[123,125]

DIFFUSE ASPIRATION BRONCHIOLITIS

Occult aspiration can result in lung damage with a variety of radiographic, clinical, and histologic manifestations. Occult aspiration

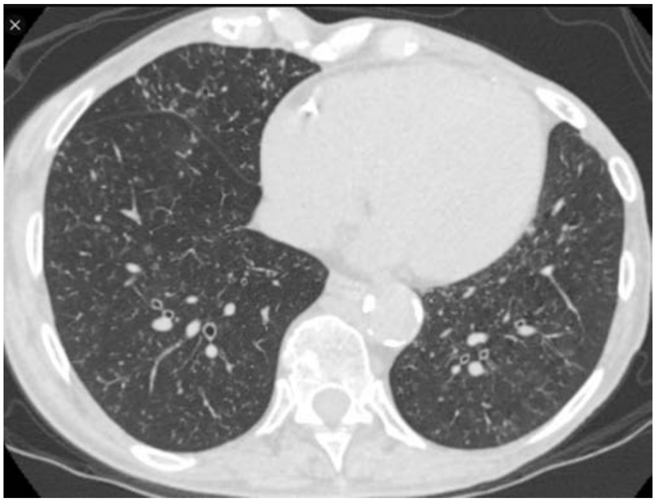

Figure 69-3 Computed tomographic scan of a patient with diffuse aspiration bronchiolitis with diffuse centrilobular nodules with a tree-in-bud pattern.

in the elderly is usually associated with esophageal dysmotility, gastroesophageal reflux disease (GERD), and neurologic impairment (dysphagia) and frequently presents with acute onset of symptoms while sleeping.[126] Diffuse aspiration bronchiolitis is a distinct clinical entity that was first defined by Matsuse et al. in 1996 as a syndrome characterized by chronic bronchiolar inflammation from recurrent aspiration of foreign matter (food).[7] Their case series was based on autopsy findings and represented an elderly, chronically debilitated population. Dysphagia was recorded in more than half of the patients, and two-thirds of patients were bedridden.

Diffuse aspiration bronchiolitis (DAB) should be suspected in elderly patients with recurrent episodes of bronchorrhea, bronchospasm, and dyspnea. However, this syndrome has been reported in middle-aged patients (mean age, 50 years) with "asymptomatic" GERD.[127] Typical findings on the chest radiograph include the presence of regional or disseminated small nodular shadows and hyperlucency. Air space consolidation is relatively rare. Chest CT scans demonstrate diffuse centrilobular nodules with a tree-in-bud pattern (Fig. 69-3).[128] It is likely that this disease is underrecognized and therefore often inappropriately managed. Macrolides appear to reduce the number of acute exacerbations of DAB.[129]

CONCLUSIONS

Aspiration pneumonitis and pneumonia are common clinical syndromes. Aspiration pneumonitis follows the aspiration of gastric contents, usually in patients with a marked decreased level of consciousness. Treatment of aspiration pneumonitis is essentially supportive; however, corticosteroids and other immunomodulating agents may have a role in these patients. Aspiration pneumonia occurs in patients with dysphagia and usually presents as a "community-acquired pneumonia," with a focal infiltrate in a dependent bronchopulmonary segment. Patients with aspiration pneumonia require treatment with broad-spectrum antibiotics and management of the underlying dysphagia. Diffuse aspiration bronchiolitis presents with radiographic evidence of widespread centrilobular and tree-in-bud opacities; clinicians must be aware of the possibility of occult aspiration in order to make the correct diagnosis.

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CHAPTER 70

Pulmonary Alveolar Proteinosis Syndrome

Bruce C. Trapnell
Cormac McCarthy
Brenna Carey

INTRODUCTION

Pulmonary alveolar proteinosis (PAP) is a rare syndrome characterized by myeloid cell dysfunction, progressive pulmonary surfactant accumulation, hypoxemia, innate immunodeficiency, and in some individuals, serious infections, pulmonary fibrosis, respiratory failure, and death.[1] While PAP-causing diseases are clinically and mechanically heterogeneous, they are usefully categorized based on pathogenesis into primary, secondary, and congenital PAP. Primary PAP is caused by impaired granulocyte-macrophage colony-stimulating factor (GM-CSF)-dependent surfactant clearance by alveolar macrophages and accounts for about 90% of cases.[2] Secondary PAP occurs as a consequence of a comorbid condition that impairs surfactant clearance by alveolar macrophages and accounts for about 5% to 10% of cases.[3] Congenital PAP—more appropriately, surfactant metabolic dysfunction disorders—constitutes a clinically distinct and heterogeneous group of genetic diseases associated with acute respiratory failure at birth from surfactant deficiency/dysfunction or progressive pulmonary fibrosis, production of abnormal surfactant, and varying degrees of surfactant accumulation (hence, their consideration as PAP); these disorders account for less than 5% of cases.[4] Importantly, research on the pathogenesis of primary PAP identified a critical role for GM-CSF in surfactant homeostasis, alveolar stability, lung function, and host defense. Because of its increased occurrence and greater research attention, primary PAP is the primary focus of this chapter; data for secondary and congenital PAP are provided when available.

PATHOGENESIS

In their 1958 report, Rosen et al.[5] established that the material accumulating in alveoli in PAP was composed primarily of lipids with lesser amounts of proteins, and minimal carbohydrate. Subsequent research identified the material to be primarily surfactant (with an increased cholesterol-to-phospholipid ratio) with smaller amounts of uncleared cell debris and cytokines.[6,7] In about 90% of patients, pathogenesis is driven by disruption of GM-CSF signaling to alveolar macrophages,[1,8–10] which blocks their terminal differentiation in the lungs, their ability to clear surfactant, and a number of other functions.[11–14]

GM-CSF is a 23-kDa cytokine produced by respiratory epithelium and other cells,[15–17] initially identified by its ability to stimulate the formation of macrophage and granulocyte colonies from hematologic progenitors and subsequently shown to stimulate functions in mature myeloid and other cells. While GM-CSF is similarly expressed in humans and mice and has remarkably similar regulatory effects on their respective target cell populations, the murine and human homologues are neither immunologically cross-reactive nor functionally interchangeable. GM-CSF binds to cell surface receptors composed of a GM-CSF–binding α-chain (CD116), an affinity-enhancing β-chain (CD131), and an associated Janus kinase 2 (JAK2). Ligand binding activates multiple intracellular signaling pathways including signal transducer and activator of transcription 5 (STAT5), regulating diverse functions of myeloid cells including survival, differentiation, proliferation, and host defense priming.[17,18] GM-CSF also has regulatory effects on lymphocytes and alveolar epithelial cells.[19–21]

In primary PAP, pathogenesis is caused by disruption of GM-CSF signaling by neutralizing GM-CSF autoantibodies (autoimmune PAP) or by recessive mutations in *CSF2RA* or *CSF2RB* (encoding GM-CSF receptor α-chain [CD116] or β-chain [CD131], respectively) (hereditary PAP).[1,2,22–28]

■ Surfactant Homeostasis

Surfactant is an oily substance vital to lung function normally present at the air–liquid–tissue interface as a thin layer or multilayer several molecules thick. It is composed of (roughly) ~80% phospholipids, ~10% neutral lipids (primarily cholesterol), ~10% proteins (surfactant protein [SP]-A, -B, -C and -D), and less than 1% carbohydrate.[29] SP-B and SP-C are hydrophobic phosphoproteins that contribute significantly to the surface active properties of surfactant.[30] SP-A and SP-D are hydrophilic collectin family members that contribute to lung host defense.[31] Surfactant lipids and proteins are synthesized, stored, and secreted into the alveoli by type II alveolar epithelial cells. In the extracellular space, surfactant "large aggregates" contribute to formation of a thin film that reduces surface tension on the alveolar wall thereby stabilizing the alveolus.[32] Surfactant is expelled from the film as "small aggregates" that are internalized by type II cells and alveolar macrophages in roughly equal amounts (Fig. 70-1). Type II cells recycle and catabolize internalized surfactant in roughly equal proportions via mechanisms that are incompletely defined but that do not appear to require regulation by GM-CSF.[32–34] In contrast, alveolar macrophages catabolize internalized surfactant phospholipids and proteins, and export cholesterol under regulation by GM-CSF, which is required for cholesterol homeostasis to stimulate the rate of excretion.[13,35]

■ Animal Models of PAP

The discovery that gene-ablated, GM-CSF-deficient (*Csf2*^{KO}) mice develop a pulmonary disease indistinguishable from primary PAP provided an important pathogenic clue (Fig. 70-2).[22,23] In *Csf2*^{KO} mice, neither production of surfactant by type II cells nor its uptake by alveolar macrophages was impaired.[36,37] Rather, surfactant clearance by alveolar macrophages was impaired.[25] Replacement of GM-CSF in the lungs by direct instillation or expression in airway epithelium corrected the lung disease.[20,38,39] Disruption of the GM-CSF receptor β (i.e., *Csf2rb*^{KO} mice) caused a similar lung phenotype[40] that could be corrected by bone marrow transplantation, which indicated the critical cell type driving pathogenesis was myeloid (i.e., alveolar macrophages) and not epithelial (i.e., type II cells) in origin.[41] PAP also occurs in mice deficient in the GM-CSF receptor α chain—*Csf2ra*^{KO} mice.[42] PAP in *Csf2ra*^{KO} and *Csf2rb*^{KO} mice can be corrected by direct instillation of wild-type congenic macrophages into the lungs without myeloablation, thus verifying the alveolar macrophage as the primary cellular site of pathogenesis in PAP caused by the disruption of GM-CSF signaling.[42,43] Surfactant clearance in *Csf2*^{KO} alveolar macrophages could be also corrected by retroviral expression of PU.1, a transcription factor normally expressed in murine alveolar macrophages in vivo under tight regulatory control of pulmonary GM-CSF.[44] PU.1 also mediates the effects of GM-CSF on surfactant clearance and other functions in human alveolar macrophages.[14] These studies established

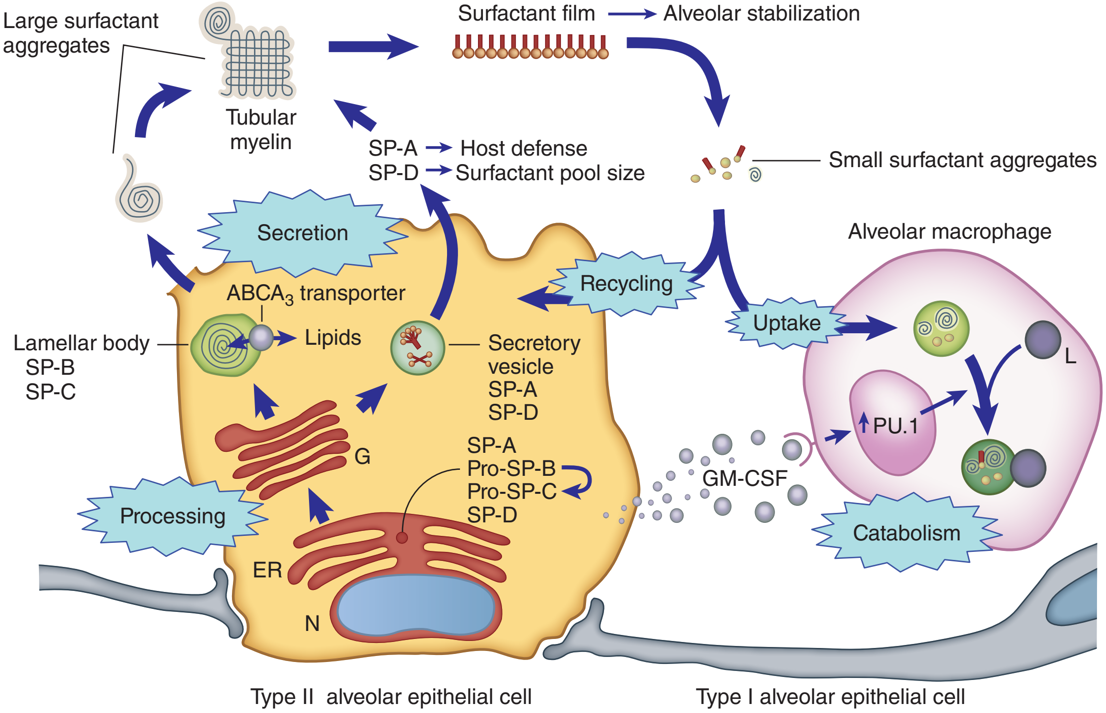
Large surfactant aggregates
Tubular myelin
Surfactant film
Alveolar stabilization
Small surfactant aggregates
SP-A → Host defense
SP-D → Surfactant pool size
Secretion
ABCA$_3$ transporter
Lamellar body
SP-B
SP-C
Lipids
Secretory vesicle
SP-A
SP-D
Recycling
Uptake
Alveolar macrophage
L
PU.1
G
SP-A
Pro-SP-B
Pro-SP-C
SP-D
GM-CSF
Processing
Catabolism
ER
N
Type II alveolar epithelial cell
Type I alveolar epithelial cell

Figure 70-1 Schematic illustration depicting mechanisms of surfactant production, recycling, and catabolism. Surfactant phospholipids and proteins are synthesized in type II alveolar epithelial cells that line pulmonary alveoli. Surfactant B and C precursor proteins are processed, transported to lamellar bodies, and then secreted into the alveolar space where they interact with surfactant protein A to form tubular myelin. Surfactant monolayers and multilayers are formed from tubular myelin and function to reduce surface tension at the air–liquid–tissue interface, thus stabilizing the alveoli. Surfactant remnants are taken up and either catabolized or reutilized by type II alveolar epithelial cells. Alveolar macrophages play a critical role in surfactant homeostasis by taking up and catabolizing surfactant remnants. GM-CSF is required to maintain surfactant homeostasis and acts by stimulating catabolism of surfactant lipids and proteins in alveolar macrophages. *(Reproduced with permission from Whitsett JA, Wert SE, Trapnell BC. Genetic disorders influencing lung formation and function at birth. Hum Mol Genet. 2004;13[Spec No 2]:R207–R215.)*

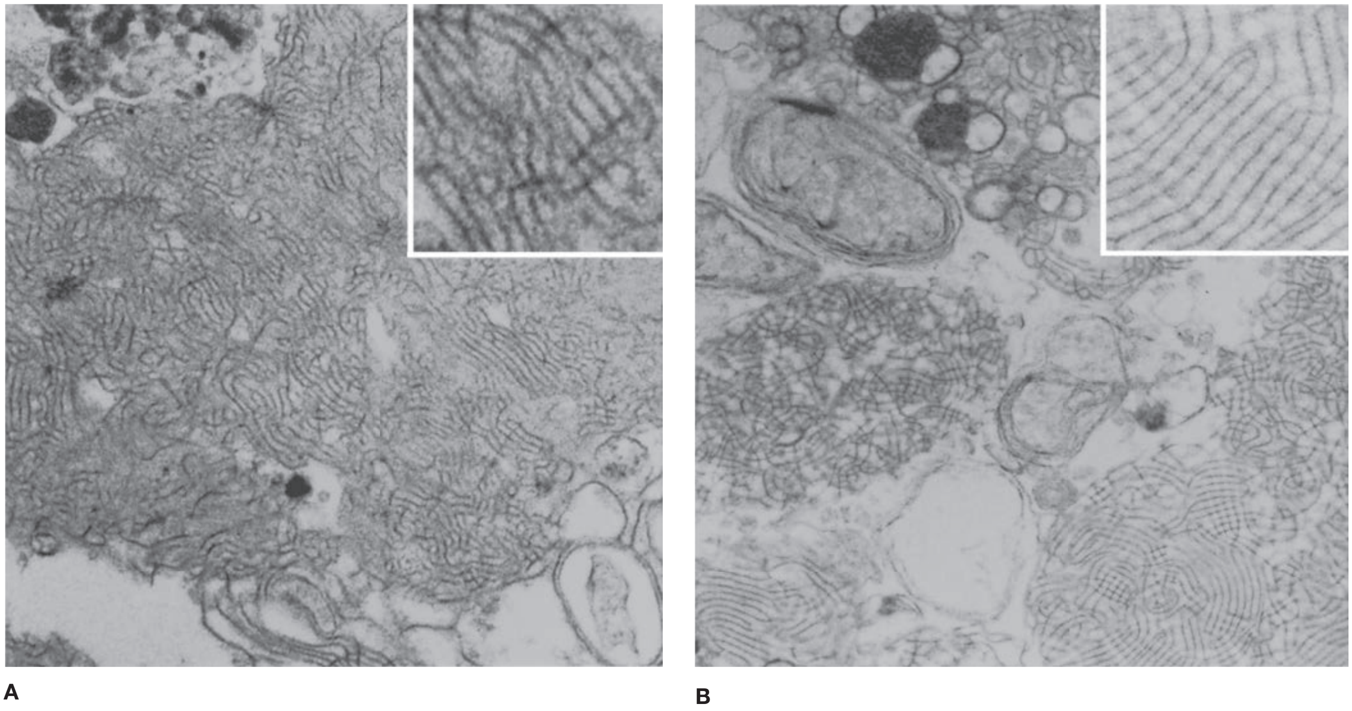

Figure 70-2 Ultrastructural appearance of the sediment from the lungs of a human patient with primary PAP (**A**) and a GM-CSF–deficient mouse (**B**). Note the presence of lamellated, fused membrane structures and amorphous debris (uranyl acetate, ×30,000).

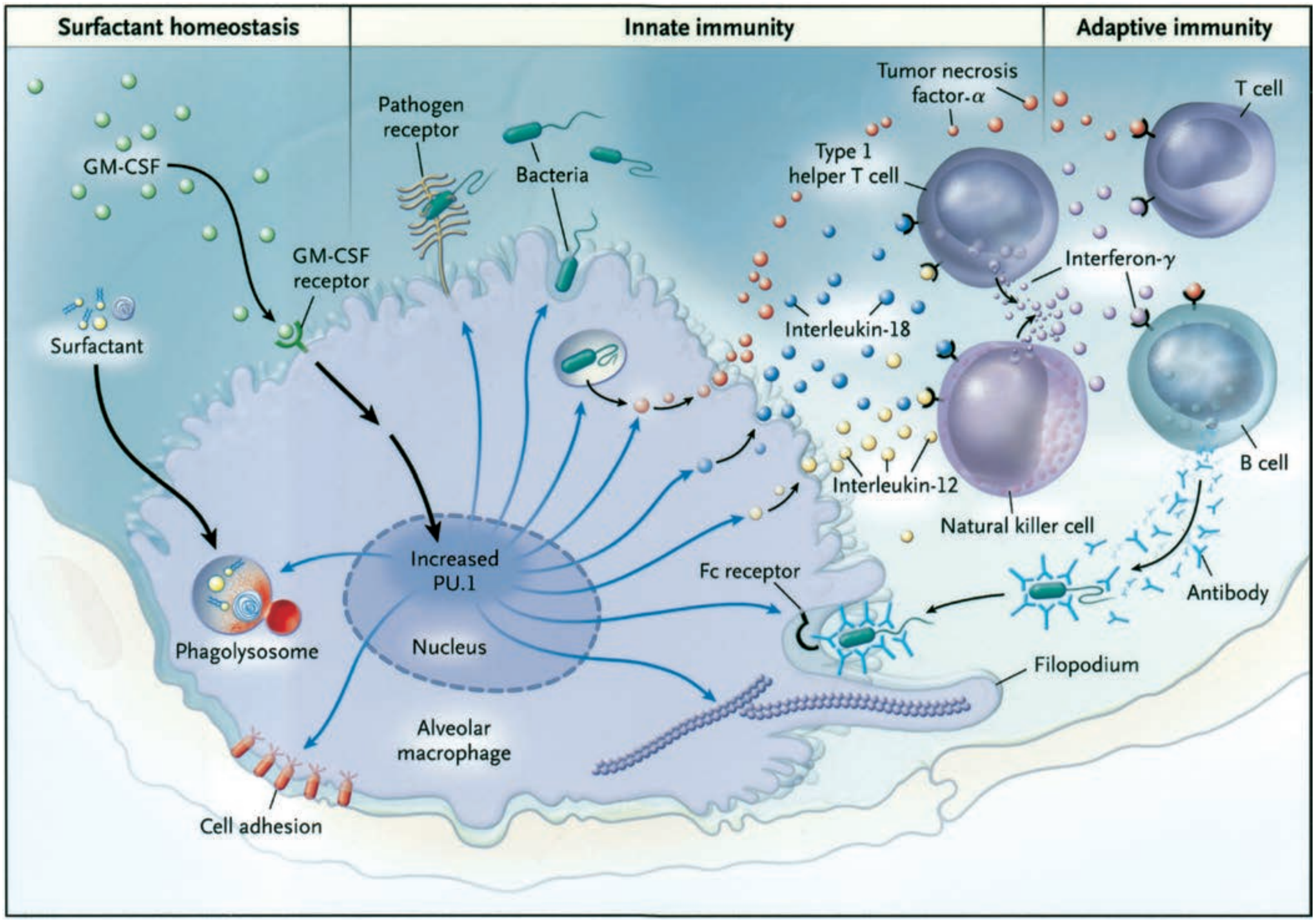

Figure 70-3 Role of GM-CSF in modulating the function of alveolar macrophages in mice. Pulmonary GM-CSF stimulates increased levels of the transcription factor PU.1 in alveolar macrophages in the lungs in vivo. Alveolar macrophages from mice deficient in GM-CSF have a number of functional defects including defects in cellular adhesion, catabolism of surfactant proteins and surfactant lipids, expression of pathogen-associated molecular pattern receptors (e.g., Toll-like receptors and the mannose receptor), Toll-like receptor signaling, phagocytosis of pathogens, intracellular killing of bacteria (independent of uptake), pathogen-stimulated secretion of cytokines (tumor necrosis factor α, interleukin [IL]-12, and IL-18), and Fc-receptor–mediated phagocytosis. Cytoskeletal organization is abnormal and may in part account for defects in phagocytosis. The ability of alveolar macrophages to release IL-12 and IL-18 severely impairs the interferon γ response to pulmonary infection, thus impairing an important molecular connection between innate and adaptive immunity in the lung. Retroviral-mediated expression of PU.1 in alveolar macrophages from GM-CSF knockout mice corrects all these defects, suggesting that GM-CSF stimulates terminal differentiation of the macrophages primarily through the master transcription factor PU.1. The *blue arrows* represent the functions regulated by PU.1 that are affected by the absence of GM-CSF. *(Reproduced with permission from Trapnell BC, Whitsett JA, Nakata K. Pulmonary alveolar proteinosis. N Engl J Med. 2003;349(26):2527–2539.)*

that GM-CSF, via PU.1, was required for surfactant clearance in alveolar macrophages in humans and mice (Fig. 70-3).

Passive immunization with human PAP patient–derived neutralizing GM-CSF autoantibodies resulted in recapitulation of the cardinal pathologic features of autoimmune PAP in nonhuman primates.[9,10] The abnormalities induced in alveolar macrophages included impaired GM-CSF signaling, GM-CSF–dependent gene expression (including PU.1), surfactant clearance, and increased cholesterol and cholesterol ester accumulation within intracytoplasmic droplets (as a cell-protective mechanism responding to increased cholesterol) resulting in foamy-appearing alveolar macrophages. Murine macrophages also require expression of the transcription factor PPARγ in order to clear surfactant normally.[45–47] Finally, a series of studies have identified GM-CSF/PU.1/PPARγ-regulated expression of the cholesterol transporter ABCG1 as critical for cholesterol export and surfactant clearance by human and mouse alveolar macrophages.[6,7,48] These animal models provide strong support for disruption of the GM-CSF signaling axis (GM-CSF>PU.1>PPARγ>ABCG1) as the critical driver of PAP pathogenesis.

As a model of secondary PAP, depletion of alveolar macrophages has been shown to increase lung surfactant pool size in rats.[49] Congenital PAP models have been created in mice by disruption of the genes required for normal surfactant production (*Sftpb*, *Sftpc*, *Abca3*).[50–52]

■ Primary PAP

Autoimmune and hereditary forms of primary PAP are considered below.

Autoimmune PAP

A second important clue about the pathogenesis of the disease previously reported as idiopathic PAP, acquired PAP, and a number of other terms was its association with neutralizing, anti–GM-CSF autoantibodies (Fig. 70-4).[22,53] Subsequently, GM-CSF autoantibodies were shown to be (1) polyclonal, (2) composed of immunoglobulin

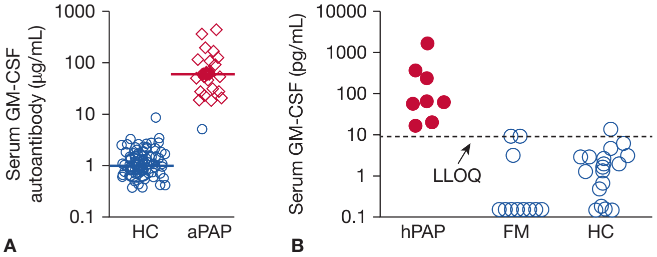

Figure 70-4 Biomarkers of use in identifying individuals with primary PAP. **A.** Serum GM-CSF autoantibody concentration. Shown are data for healthy controls (HCs) and patients with aPAP (autoimmune PAP). **B.** Serum GM-CSF concentration. Shown are data for children with hereditary PAP (hPAP) caused by recessive *CSF2RA* or *CSF2RB* mutations, members of their immediate family who were healthy (FM), or unrelated HCs. The lower limit of quantification (LLOQ) of the assay was 7.8 pg/mL *(dashed line)*. The serum levels of GM-CSF (median, interquartile range) in children with hPAP (52 pg/mL [28–101 pg/mL]) were increased compared with healthy family members (0.0 pg/mL [0.0–3 pg/mL]) and unrelated healthy controls (0.0 pg/mL [0.0–1.9 pg/mL]) ($n = 8, 11, 30$, respectively; $p < 0.001$; Kruskal–Wallis analysis of variance on ranks with comparisons using Dunn's method). *(**A.** Reproduced with permission from Uchida K, Nakata K, Suzuki T, et al: Granulocyte/macrophage-colony-stimulating factor autoantibodies and myeloid cell immune functions in healthy subjects. Blood. 2009;113(11):2547–2556; **B.** Reproduced with permission from Suzuki T, Sakagami T, Young LR, et al. Hereditary pulmonary alveolar proteinosis: pathogenesis, presentation, diagnosis, and therapy. Am J Crit Care Med. 2010;182(10):1292–1304.)*

G subclass 1 (IgG$_1$) and IgG$_2$ (in roughly equal proportions) with smaller amounts of IgG$_3$ and IgG$_4$, (3) of high affinity for binding GM-CSF—in the 3- to 20-pM range, exceeding that of the binding to the GM-CSF receptor alpha chain, and (4) capable of neutralizing GM-CSF bioactivity in vivo.[54,55] Notwithstanding, several findings were difficult to reconcile. GM-CSF autoantibodies were also present in healthy individuals albeit at lower levels,[55] and levels of GM-CSF autoantibody in PAP patients did not correlate with disease severity.[56] Reproduction of PAP in nonhuman primates by the injection of PAP patient–derived GM-CSF autoantibodies firmly established their critical role in the pathogenesis of idiopathic PAP.[9,10] The low levels of GM-CSF autoantibodies in healthy individuals[55] (and intravenous immune globulin[57,58]) and lack of correlation with disease severity in idiopathic PAP was explained by a model in which constitutive in vivo stimulation of GM-CSF–dependent myeloid cell functions (including surfactant clearance) declined in parallel with the level of GM-CSF autoantibody level until a concentration (known as the critical threshold) was reached where GM-CSF stimulated functions were reduced to zero (and could go no further).[55,59] This threshold level was similar in humans and passively immunized nonhuman primates.[9,10,55] These studies provided the evidence needed to demonstrate that GM-CSF autoantibodies were pathogenic and led to a recommendation to change the name from idiopathic PAP to autoimmune PAP.[59]

Hereditary PAP

While no humans with PAP caused by GM-CSF deficiency have been identified to date, in 2008, a child with GM-CSF autoantibody–negative PAP was found to have compound heterozygous mutations in *CSF2RA* (encoding GM-CSF receptor α) as the cause of familial PAP.[23] Additional patients were identified by exploiting use of a biomarker, increased serum GM-CSF, to screen sera from a repository including patients with PAP of unknown etiology, which identified a cohort of patients with PAP-causing *CSF2RA* mutations (Fig. 70-4).[24] Subsequently, *CSF2RB* mutations were identified as a cause of hereditary PAP.[25,60] Detailed characterization including molecular cloning and expression studies to recapitulate the receptor dysfunction established that the pathogenesis of hereditary PAP is caused by recessive or compound heterozygous mutations in the *CSF2RA* or *CSF2RB* genes. Subsequently, various mutations were identified in these genes as the cause of hereditary PAP including missense mutations, nonsense mutations, small insertions and deletions, exon deletion, and gene deletion.[23,24,26,28,60] Together, these studies defined the clinical presentation, pathogenesis, diagnosis, and therapy of hereditary PAP caused by disruption of GM-CSF signaling.

■ Secondary PAP

Results from a national registry confirmed that secondary PAP occurs in association with a heterogeneous group of underlying diseases including hematologic disorders, primarily myelodysplasia (76%–88% of cases); infectious diseases (2%–3%); other autoimmune diseases (7%); immunosuppression after organ transplantation (7%); and nonhematologic malignancies (5%).[61,62] Secondary PAP also occurs in association with (and presumably due to) heavy inhalation exposure to inorganic dusts (e.g., silica, titanium, aluminum) and other gasses and fumes, or as a consequence of systemic infections, for example, during human immunodeficiency virus (HIV) infection.[63,64] Secondary PAP appears to be caused by a reduction in the numbers or clearance capacity of alveolar macrophages, consistent with macrophage depletion studies in rats.[49]

■ Congenital PAP (Surfactant Metabolic Dysfunction Disorders)

PAP occurs in neonates, infants, and children in association with various defects in the genes encoding SP-B, SP-C, ABCA3—a lipid transporter expressed in type II alveolar epithelial cells—or TTF-1, a transcription factor essential for lung development and surfactant expression.[4,65–68] In contrast to primary and secondary PAP that are caused by reduced surfactant clearance, these disorders result from production of abnormal surfactant. While surfactant accumulation does occur to varying degrees in surfactant production disorders, these disorders are clinically, histopathologically, and pathogenically distinct from primary and secondary PAP.

■ The Emerging Role of GM-CSF in Innate Immunity

Csf2^{KO} mice have increased susceptibility to a broad range of microbial pathogens, increased mortality from spontaneous infections,[69,70] and numerous host defense defects in macrophages and neutrophils.[31,52] In macrophages, all these diverse defects could be corrected by forced expression of PU.1 (Fig. 70-3).[44] Similar defects are present in alveolar macrophages and neutrophils from humans and nonhuman primates with disruption of GM-CSF signaling.[1,2,8,71] *Csf2*^{KO} mice also have systemic immune and inflammatory abnormalities[70] including reduced severity in models of arthritis,[72] an observation that has led to conduct the human trials of GM-CSF signaling disruption as therapy of rheumatoid arthritis.[73,74] These and other studies have led to an emerging understanding of the important roles that GM-CSF plays in the regulation of alveolar macrophage terminal differentiation, the basal functional capacity of circulating neutrophils, and autoimmune and inflammatory diseases.[75]

EPIDEMIOLOGY

Our knowledge of the epidemiology of PAP has improved over the past decade. Results from a national registry study in Japan estimated the incidence and prevalence of autoimmune PAP in Japan to be approximately 0.49 and 6.2 per million in the general population, respectively.[76] A study based on the evaluation of health insurance claims data for 15 million Americans, each associated with a unique anonymizing number, resulted in an estimate of the prevalence of PAP of 7 per million in the general population in the United States.[77] Further, studies in both Japan and the United States have shown that prevalence is proportional to population density.[78,79] In recent reports from specialized clinical centers, the mean age at diagnosis of autoimmune PAP in years (number of patients, country) were 52 (248, Japan),[76] 42 (241, China),[80] 43 (70, Germany),[81] and 40 (81, Italy),[82] although the diagnosis has been made in children as young as 3 years (unpublished). In these reports, the male:female ratio varied from 1.3 to 2.2 overall but was close to 1.0 in nonsmokers. Autoimmune PAP occurs in various racial backgrounds including Asian, Black, and Caucasian, in Hispanic and non-Hispanic individuals, and in wide geographic distribution. Several studies have shown that autoimmune PAP accounts for approximately 89% to 90% of all cases of PAP.[76,78]

A subsequent report from the Japanese registry[61] described 40 cases of secondary PAP identified premortem resulting in a prevalence estimate of approximately 0.3 per million. The incidence and prevalence of congenital PAP are unknown but likely each on the order of 1 to 3 per million in the general population.

CLINICAL FEATURES

Below we consider in detail the clinical, radiographic, laboratory, and bronchoscopic features of PAP. In addition, we review its lung pathology and enumerate the secondary infections associated with the disorder.

■ Presentation

Autoimmune PAP typically presents as progressive dyspnea of insidious onset in previously healthy adults between the ages of 20 and 50 years but has been identified in children as young as 3 years old and in adults as old as 90 years old. In several series, dyspnea occurred in 67% to 94% of patients, followed by cough (23%–66%) and fatigue (49%), whereas fever (4%–11%) and sputum production (1%–4%) were less common.[76,80–82] In the Japanese registry study, one-third of patients were asymptomatic and identified only by mandatory health screening programs and were asymptomatic at presentation (although some developed symptoms subsequently).[76] A history of diffuse pneumonia poorly responsive or unresponsive to antibiotic therapy is usually elicited, and a history should raise the suspicion of PAP. The physical examination is often normal but may include faint inspiratory crackles especially in dependent areas. Cyanosis is occasionally present in more severe cases. Digital clubbing is typically absent in autoimmune PAP. Hereditary PAP presents in remarkably similar fashion but at a mean age of 4.8 ± 1.6 years.[24] Secondary PAP has been reported to present at a median age of 49 years, most frequently accompanied by exertional dyspnea (40% of cases) followed by fever (38% of cases).[61,62] In patients with lung disease associated with abnormal surfactant production, dyspnea is common, crackles may be present, and digital clubbing is not uncommon.

■ Radiographic Appearance

The chest radiograph in primary PAP usually reveals diffuse, bilateral alveolar opacities often with a perihilar predominance resembling the "bat wing" appearance of pulmonary edema but without other signs of left-sided heart failure (Fig. 70-5A, C). The peripheral lung is sometimes spared, resulting in lucency along the diaphragmatic, mediastinal, and peripheral borders. High-resolution computed tomography (HRCT) scanning reveals a characteristic geographic pattern of ground-glass opacification (reflecting the filling of secondary lobules) with superimposed interlobular septal and intralobular thickening, commonly referred to as "crazy paving" (Fig. 70-5B, D), which is characteristic but not diagnostic of PAP.

■ Laboratory Findings

In primary PAP, routine blood counts and chemistries are usually normal in primary PAP except for serum lactate dehydrogenase (LDH), which is increased two- to threefold and correlates well with the degree of functional impairment as determined by physiologic testing and arterial blood gas analysis. A number of biomarkers have been identified in autoimmune PAP including increased serum levels of GM-CSF autoantibody, SP-A, SP-B, SP-D, KL-6, CEA, Cyfra-21-1, cytokeratin 19, and others.[1,76,81–83] Many of these biomarkers are also increased in hereditary PAP.[23–26,60] Importantly, serum GM-CSF is specifically elevated in hereditary PAP but not in autoimmune PAP, which was important in identifying an initial cohort of patients for study (Fig. 70-4).[24] Biomarkers of secondary and congenital PAP have been less well studied.

■ Lung Function

In primary PAP, spirometry and lung volume testing is usually normal or near normal but may show a restrictive pattern of impairment with modest reduction in the vital capacity and total lung capacity (TLC) and a disproportionate reduction of the carbon monoxide diffusing capacity (DL_{CO}). Arterial blood gas analysis in symptomatic patients reveals hypoxia caused by ventilation–perfusion inequality and intrapulmonary shunting, resulting in a widened alveolar–arterial diffusion gradient ($A\text{-}aDO_2$).

■ Bronchoscopic Findings

The bronchoscopic appearance of the airways in primary PAP is normal but white, frothy proteinosis material is occasionally seen.[24,71,81,82] The bronchoalveolar lavage (BAL) fluid is opaque and has a milky or waxy appearance and develops a thick layer of sediment upon standing overnight (Fig. 70-6). The sediment consists of large, acellular, eosinophilic bodies in a diffuse background of granular material that stains with periodic acid–Schiff (Fig. 70-7A). The cellular fraction contains large, foamy macrophages (Fig. 70-7B), smaller monocyte-like macrophages, and lymphocytes with relatively few neutrophils unless infection is also present. Surfactant protein levels are increased, and electron microscopy reveals the presence of lamellar bodies and tubular myelin that are characteristic of surfactant (Fig. 70-2).

■ Lung Pathology

Macroscopically, the cut surface of the lung in autoimmune PAP reveals a patchwork of 2- to 3-cm grayish-yellow regions of consolidation exuding an oily substance. Microscopically, alveoli are filled with a granular eosinophilic material (Fig. 70-7C) that stains strongly for surfactant proteins (Fig. 70-7D).[1] In primary PAP, the alveolar wall and interstitial architecture are usually well preserved (at least early in the disease). Parenchymal lymphocytosis also is present and, in some patients, especially later in the disease course, pulmonary fibrosis can occur. The vasculature appears normal. Electron microscopy reveals alveolar macrophages containing characteristic, concentrically laminated surfactant bodies within the granular material and smaller, single, membrane-delimited, intracytoplasmic vesicles containing esterified cholesterol (a cellular mechanism to protect cells from against an increased cholesterol level). The gross and microscopic appearance of the lung in autoimmune and hereditary PAP are similar.[23–25,28,60] The lung pathology in secondary PAP and congenital PAP varies significantly depending on the disease but is often associated with significant parenchymal pulmonary fibrosis.

■ Secondary Infections

Individuals with autoimmune PAP have an increased risk of infections, which contribute significantly to increased morbidity and

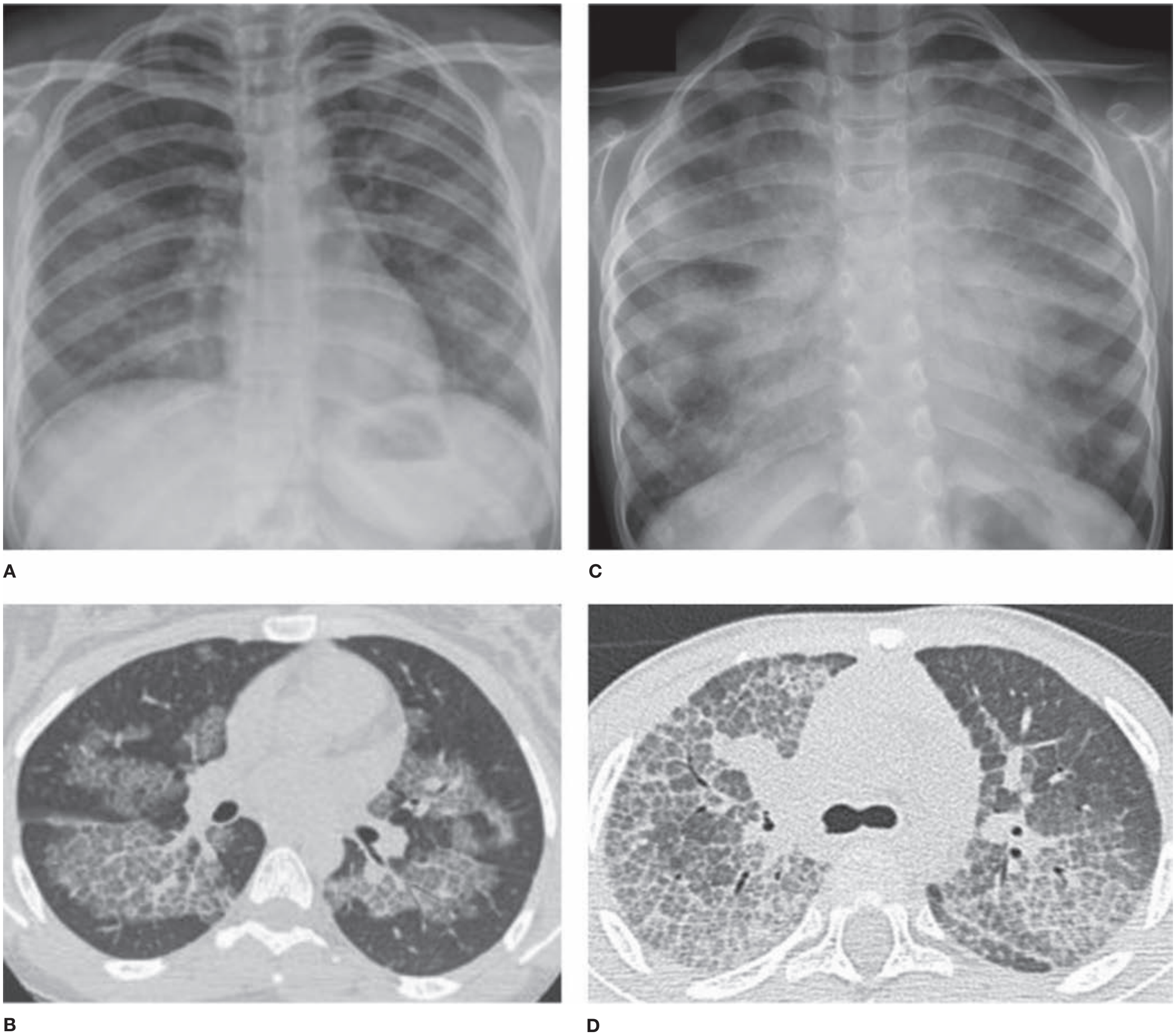

Figure 70-5 Radiographic appearance of primary PAP. **A.** Chest radiograph of a 25-year-old woman with autoimmune PAP. **B.** Corresponding chest HRCT scan. **C.** Chest radiograph of a 6-year-old girl with compound heterozygous *CSF2RA* mutations. **D.** HRCT of a 3-year-old girl with recessive null *CSF2RA* mutations.

mortality.[1,8,83] Although pathogens commonly seen in community- and hospital-acquired lung infections are sometimes identified, opportunistic organisms are often responsible and can include *Nocardia*, *Mycobacterium*, *Aspergillus*, *Cryptococcus*, and others. Infections can occur at both pulmonary and extrapulmonary sites, supporting the concept that a systemic defect in host defense is present secondary to defects in the antimicrobial functions of macrophages and neutrophils.

DIAGNOSIS

While PAP syndrome can be suspected based on historic, physical, and radiographic lung function findings, further studies are needed to exclude other conditions in the differential diagnosis such as hypersensitivity pneumonitis, pulmonary edema, pneumonia, and interstitial lung diseases. Traditionally, transbronchial or surgical lung biopsy have been considered necessary and are commonly used to identify the presence of PAP syndrome. However, none of these histology- and cytology-based approaches including an adequately sized surgical lung biopsy can identify any PAP-causing disease. In contrast, the development and testing of several disease-specific and semispecific biomarkers have been particularly useful. The serum-based GM-CSF autoantibody enzyme-linked immunosorbent assay (Fig. 70-4A) was developed,[84] optimized, and evaluated extensively[8,54,55] and found to have a sensitivity and specificity for a diagnosis of autoimmune PAP approaching 100%.[85] Measurement of GM-CSF signaling in heparinized blood (via STAT5 phosphorylation in leukocytes[23]) also is useful in the differential diagnosis of PAP.

An increase in serum GM-CSF is a sensitive method for diagnosis of hereditary PAP (Fig. 70-4A),[86] which is further supported by a negative GM-CSF autoantibody test and an abnormal STAT5-phosphorylation index test.[23,24]

Secondary PAP can usually be distinguished from primary PAP based on the clinical context and histologic or immunohistochemical evaluation of lung biopsy specimens. Further, PAP disease "mimics," like *Pneumocystis* pneumonia, can be distinguished by special histochemical stains.

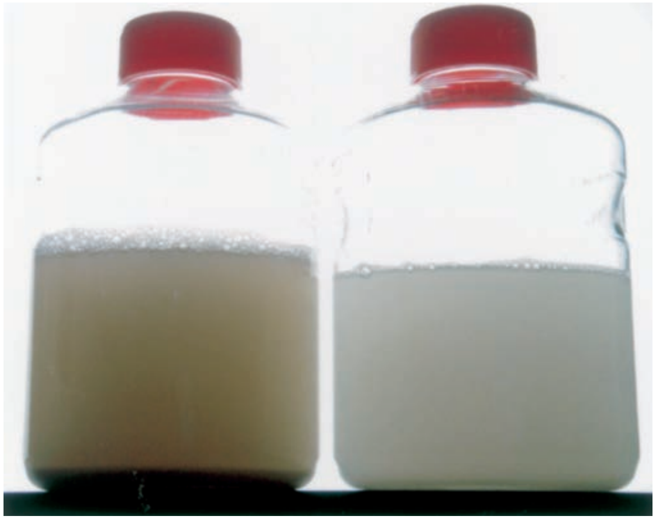

Figure 70-6 Lavage fluid obtained during the whole lung lavage procedure of a patient with autoimmune PAP has a characteristic turbid appearance and a sediment that forms upon standing. The marked opacity and sediment of the fluid observed at the beginning *(left bottle)* shows progressive clearing by the end of the procedure *(right bottle)*.

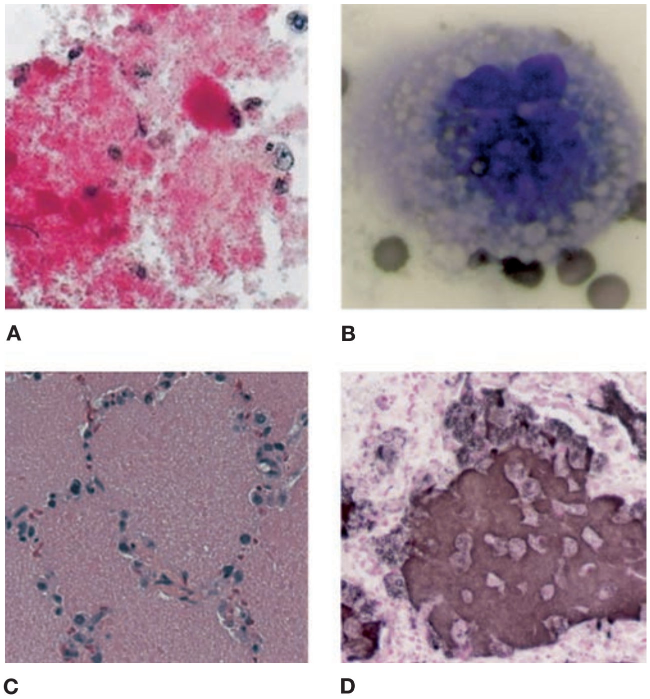

Figure 70-7 Cytologic, pathologic, and immunohistochemical appearance of the lipoproteinaceous material from patients with autoimmune alveolar proteinosis. **A.** Positive periodic acid–Schiff staining of the sediment from bronchoalveolar lavage (×100). **B.** Cytologic appearance of a typical "foamy" alveolar macrophage. **C.** Histopathologic appearance of the lung biopsy specimen from a 10-year-old child with primary PAP. Note the homogeneous staining pattern, normal alveolar wall architecture, and absence of inflammatory cells (H&E, ×200). **D.** Immunohistochemical staining reveals the presence of abundant accumulation of surfactant protein A in a lung biopsy specimen (human anti–surfactant protein A immunostain, ×200).

An important diagnostic clue is that radiographic abnormalities in PAP are often increased out of proportion to the severity suspected on clinical grounds; however, the practical application of this sign requires a high degree of clinical awareness and suspicion.

NATURAL HISTORY

Prospective, longitudinal studies of the natural history of PAP have not been conducted. However, experience from several large retrospective and cross-sectional PAP cohorts (number of patients) at tertiary referral centers in Japan (248), China (241), Germany (70), and Italy (81) have recently been reported.[76,80–82] In these reports, the "time to diagnosis" ranged from 9 to 11 months, which is similar to a report by Seymour and Presneill[83] and less than a recent report estimating this time at 18 months (range, 0.5–13.5 years).[78]

Most patients have slowly progressive disease with mild, persistent symptoms while some have rapidly progressive disease. Spontaneous remission has been reported to occur in 5% to 7% of cases (based on a sample including 399 PAP patients[76,81,82]), confirming a previous estimate of 6% by Seymour and Presneill[83] (based on 410 PAP patients). The consideration of lung disease severity in PAP must account for the degree of surfactant accumulation (which impacts the degree of gas exchange impairment) and on the time-dependent nature of the surfactant accumulation (which impacts the frequency that treatment is required). The variation in the time-dependent rate of surfactant accumulation is seen in autoimmune PAP and hereditary PAP. The latter is a particularly good example since siblings from consanguineous marriages with the same genetic defect in GM-CSF signaling sometimes have widely varying rates of surfactant accumulation and need for therapy.[24]

In the study by Seymour and Presneill, the 5-year survival was 85% without therapy and 95% with whole lung lavage (WLL) therapy.[83] Of deaths attributable to PAP among 303 PAP patients, 47 were due to respiratory failure, 12 were due to overwhelming infection, and 1 was due to cardiac arrest during WLL therapy.[83]

The prognosis of secondary PAP is worse than primary PAP due to linkage with the underlying disease, with an estimated 5-year survival of 20% to 40%.[61,62]

The prognosis of congenital PAP varies, ranging widely from death at birth for SP-B deficiency and some ABCA3 mutations to respiratory insufficiency or failure from interstitial lung disease in adolescence or adulthood for SP-C mutations and some ABCA3 mutations.[4,67]

THERAPY

Therapy of PAP varies by disease. In primary PAP, therapy is required by most but not all patients and is usually initiated when symptoms become limiting. In secondary PAP, treatment is aimed at the underlying clinical condition, although WLL can be effective. In congenital PAP, therapy is generally limited to supportive care, although SP-B deficiency has been treated successfully by lung transplantation.[87]

■ Whole Lung Lavage

WLL is the most widely used therapy of primary PAP[76,80–82] and is still the recommended standard approach. It can be helpful in secondary PAP but has little to no utility in congenital PAP, likely due to the extensive parenchymal derangement present in these patients. In independent cohorts, WLL was used in 54% to 90% of a combined total of 899 patients.[76,80–82] While the indications for initiation of WLL therapy vary widely among centers, some include a histopathologic diagnosis of PAP; PaO_2 <60 mm Hg; A-aDO_2 gradient >40 mm Hg; shunt fraction >10% to 12%; or severe dyspnea at rest or with exercise.[88,89] The technical execution of the WLL procedure itself also varies among centers. WLL requires general anesthesia, separate endotracheal intubation to isolate each lung, and simultaneous mechanical ventilation of one lung while repeatedly filling and draining the other lung with warm saline with or without chest percussion to emulsify and physically remove the alveolar surfactant. Infusion volumes of up to 50 L per lung have been used in adults but may reach diminishing returns above 20–30 L. Other variations include use of extracorporeal or hyperbaric oxygen, and whether the lungs are both treated the same day or different days. While specific therapeutic response criteria have not been defined, most patients experience clinical, physiologic, and radiographic improvement following WLL.[68] Physiologic parameters shown to improve with WLL include an increase in the forced vital capacity (FVC), TLC, $\mathrm{DL}_{\mathrm{CO}}$, and PaO_2 at rest and with exercise, and a decrease in $\mathrm{A\text{-}aDO}_2$ and shunt fraction. WLL improves the 5-year survival from 85% ± 5% to 94% ± 2%.[61] Two studies have reported a duration of response to WLL of 15 months.[60,61] Sequential lobar lavage performed during bronchoscopy as an alternative to WLL has been used for patients deemed unable to tolerate WLL. The use of extracorporeal membrane oxygen therapy is sometimes used in more severely affected PAP patients to permit the use of WLL therapy.

■ Experimental Approaches

Our improved understanding of PAP as a disease driven by reduced GM-CSF–dependent surfactant clearance in alveolar macrophages has stimulated the development of specific pharmacologic therapy. One such strategy is based on augmentation with recombinant human GM-CSF,[90] and multiple clinical trials of subcutaneous or inhaled administration have demonstrated the therapeutic efficacy and safety of GM-CSF therapy of autoimmune PAP.[91–100]

In an early, open-label, nonrandomized study of 39 patients with mild to moderate autoimmune PAP, 62% of the patients receiving inhaled GM-CSF therapy had improvement in the $\mathrm{A\text{-}aDO}_2$ gradient.[96] Several reports have documented the improvement with inhaled GM-CSF by quantitative evaluation of ground-glass opacification (GGO) on chest CT—a measure of the total surfactant burden in PAP.[7,99–102] Two large, phase 3, randomized, double-blind, placebo-controlled clinical trials reported that inhaled GM-CSF improves the clinical manifestations, pulmonary gas exchange, health-related quality of life measures (Saint George's Respiratory Questionnaire score), and GGO.[99,100] To date, none of the studies have identified any important safety concerns, and a current study (IMPALA-2) is underway to gather sufficient data to support the regulatory approval for the use of inhaled GM-CSF as therapy of autoimmune PAP.[91–100] Nevertheless, GM-CSF therapy of autoimmune PAP is still in development and several questions remain unanswered, including the optimal dosage, frequency of administration, and duration of therapy. Data from one of these studies have demonstrated that daily dosing is superior to intermittent daily dosing on alternating weeks. This is consistent with the half-life of GM-CSF–stimulated cholesterol export from alveolar macrophages of 21 h.[6]

Immunotherapy targeting GM-CSF autoantibody–producing cells (rituximab) has been tested as an approach to reduce anti–GM-CSF autoantibody levels;[103–106] however, while encouraging, the number of patients studied is very small and results should be interpreted cautiously.

Statins have been reported to have efficacy in autoimmune PAP related to effects on promoting efflux of cholesterol from alveolar macrophages;[7] however, few patients have been reported to have undergone this treatment approach. Thus, while encouraging, results for this approach should be interpreted cautiously.

A novel *Csf2ra*/*Csf2rb* gene correction approach combined with pulmonary macrophage transplantation (PMT) has shown extraordinary therapeutic efficacy, treatment durability, and improvement in survival/longevity with no safety signal in preclinical studies in validated models of hereditary PAP;[42,43] a clinical trial to test this treatment approach in human patients is planned.

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CHAPTER 71

Eosinophilic Lung Diseases

Lauren Cohn
Carolyn L. Rochester
Brian J. Clark

INTRODUCTION

Eosinophils cause lung disease when they release granule proteins, cytokines, arachidonic acid metabolites, superoxide anions, and metalloproteases and other mediators that cause tissue damage, lead to bronchial hyperresponsiveness, and further activate immunologic cascades that enhance inflammation. Pulmonary eosinophilia is a result of enhanced eosinophil development through eosinophil-lineage commitment and maturation in the bone marrow, recruitment into the lung from the circulation, and prolonged eosinophil survival.

Interleukin 5 (IL-5) is the primary cytokine responsible for eosinophilia. While not absolutely essential for eosinophil development, IL-5 enhances eosinophil development and function by stimulating eosinophil differentiation, proliferation, and maturation in the bone marrow, as well as tissue recruitment, activation, and survival. In addition to IL-5, granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-3, and IL-33 have lesser but important effects on eosinophil differentiation, maturation, and activation.[1] IL-5 acts by binding to IL-5 receptor alpha and signaling through a heterodimeric type 1 cytokine receptor composed of the alpha and beta chain. IL-5 receptors are predominantly expressed on eosinophils, but also on some basophils and B cell precursors.[2] The importance of IL-5 in eosinophilic diseases was tested in animal models using mice with deletion of the IL-5 gene. These animals had marked reductions in eosinophil development, circulation, and recruitment, and absent eosinophil damage in tissues.[1] IL-5 is elevated in the respiratory tract in eosinophilic lung diseases including eosinophilic pneumonias. In human diseases, the importance of IL-5 is highlighted by monoclonal antibody therapies directed against IL-5 and the IL-5 receptor, which have been highly effective in the treatment of pulmonary eosinophilic disorders including asthma and eosinophilic granulomatosis with polyangiitis.

Activated circulating eosinophils bind to inflamed vascular endothelium and migrate into the tissue in response to chemotactic factors including the CCR3 ligands CCL11, CCL24, and CCL26 (eotaxins 1–3), and lipid mediators such as LTB4 and IL-5.[3] High levels of eosinophil chemokines in addition to IL-5 have been demonstrated in the lung and circulation in pulmonary eosinophilic lung diseases.[1,4] Elevation in eosinophil cytokines and chemokines is a common pathway by which pulmonary eosinophilia occurs and, in general, does not differentiate among pulmonary eosinophilic disorders. In each of the pulmonary eosinophilic diseases we review here, the triggers that lead to eosinophilia and eosinophil localization in the lung may be different, but there are shared pathways by which eosinophils develop, migrate, and are activated in the lung to cause damage.

The association between pulmonary infiltrates and eosinophilia was first identified by Loeffler in 1932. It is now recognized that the eosinophilic pneumonias are a heterogeneous group of disorders characterized by varying degrees of pulmonary parenchymal and/or blood eosinophilia. The precise role that eosinophils play in the pathogenesis of the different eosinophilic disorders is not clear. Normally, <2% of the leukocytes in the bronchoalveolar lavage (BAL) are eosinophils. The presence of increased BAL and/or tissue eosinophils, and our knowledge of the biology of eosinophils, does, however, suggest that they play a variety of roles, including initiation, perpetuation, and amplification of tissue inflammation and injury. The different roles of eosinophils in these disorders can be appreciated when comparisons are made between parasitic infections and disorders such as asthma or allergic bronchopulmonary aspergillosis (ABPA). In the former, eosinophils aid in eradicating the infectious pathogen; in the latter, eosinophils accumulate in the lung as a result of immune hypersensitivity, but in both cases, they are prominent mediators of tissue injury. The spectrum of diseases that can be primarily or secondarily associated with blood or pulmonary eosinophilia is shown in Table 71-1. It is beyond the scope of this chapter to discuss each of these disease entities in detail. Instead, discussion will focus on diseases in which eosinophilic infiltration of lung tissue is a characteristic feature.

TABLE 71-1 Diseases Associated with Pulmonary Infiltrates and Eosinophilia

Pulmonary Eosinophilic Syndromes of Known Cause

- Parasitic-induced eosinophilic pneumonias (including Loeffler syndrome)
- Drug- or toxin-induced eosinophilic pneumonias
- Tropical pulmonary eosinophilia
- Allergic bronchopulmonary mycosis

Pulmonary Eosinophilic Syndromes of Unknown Cause

- Idiopathic acute eosinophilic pneumonia
- Chronic eosinophilic pneumonia
- EGPA (allergic granulomatosis and angiitis)
- Idiopathic hypereosinophilic syndrome

Other Lung Diseases Variably Associated with Eosinophilia

- Asthma/allergy
- Bronchocentric granulomatosis
- Bronchiolitis obliterans–organizing pneumonia
- Infections
  - Fungal (esp. coccidioidomycosis, *Aspergillus, Pneumocystis jirovecii*)
  - Tuberculosis
  - Viral
- Interstitial lung disease
  - Idiopathic pulmonary fibrosis
  - Collagen vascular disease associated
  - Sarcoidosis
  - Hypersensitivity pneumonitis
  - Eosinophilic granuloma (pulmonary histiocytosis X)
- Malignancy
  - Non–small-cell cancer of lung
  - Non-Hodgkin lymphoma
  - Myeloblastic leukemia
  - Metastatic disease
- Miscellaneous (e.g., lung transplantation, lung allograft rejection, ulcerative colitis)

TABLE 71-2 Parasitic Infections Associated with Eosinophilic Lung Disease

Helminths Parasites
Intestinal nematodes
Ascaris (lumbricoides and suum)
Ancylostoma duodenale
Necator americanus/Necator brasiliensis
Strongyloides stercoralis and other species
Toxocara canis/Toxocara cati
Trichinella spiralis
Filarial worms
Wuchereria bancrofti
Brugia malayi
Dirofilaria immitis

Most common parasites associated with eosinophilic lung disease. For more detailed listing of pleuropulmonary parasitic infections, see Vijayan VK. Parasitic lung infections. Curr Opin Pulm Med. 2009;15(3):274–282.

PARASITE-INDUCED EOSINOPHILIC LUNG DISEASE

Infections with parasites are commonly associated with pulmonary infiltrates and blood or pulmonary eosinophilia.[5–7] The most common parasites associated with the development of pulmonary eosinophilic syndromes are listed in Table 71-2. In the United States and other Western countries, the parasitic agents most commonly associated with eosinophilic lung diseases are *Ascaris*, *Ancylostoma*, *Toxocara*, and *Strongyloides*.[5] The prevalence of infection with all parasitic organisms varies with geographic location, socioeconomic status, and host immunity. Parasites may invade the lung via direct pulmonary invasion or hematogenous seeding. The site of transit, life cycle, and length of stay of the parasitic agent, and the persistence of the host immune response, are reflected in the human disease.

■ Loeffler Syndrome (Transpulmonary Migration of Helminth Larvae)

Passage of the larvae of helminth parasites through the lungs is the cause of Loeffler syndrome. Loeffler first described this transient, self-limited clinical syndrome characterized by mild respiratory symptoms, peripheral blood eosinophilia, and migratory pulmonary infiltrates. Subsequently, the term *Loeffler syndrome,* or *simple pulmonary eosinophilia,* has been used to define similar cases caused by other parasites, fungal infections, and drug- and toxin-induced pulmonary eosinophilia.[8] In fact, a majority of the original cases were likely caused by the immune response to the parasitic nematode *Ascaris lumbricoides or human roundworm*. *Ascaris* is now uncommon in the United States.

Ascaris lumbricoides and several other helminth parasites including *Ascaris suum*, hookworms (*Ancylostoma duodenale*, *Necator americanus*, *Necator brasiliensis*), *Strongyloides*, *Trichinella spiralis*, and *Toxocara canis* have life cycles in which infecting larvae enter the lungs from the bloodstream and cross into the alveoli.[5,6,9] *Ascaris* is the most common cause of Loeffler syndrome, yet it occurs in only a small minority of *Ascaris*-infected individuals.[10]

Following ingestion of *Ascaris* ova, the larvae hatch within the small intestine, then cross the intestinal wall to enter the splanchnic and ultimately the pulmonary circulation. The larval worms then migrate across pulmonary capillaries into alveoli. The transpulmonary migration of parasite larvae leads to acute inflammation in the lung characterized by eosinophilia that resolves after the larvae pass through. The larvae subsequently migrate into the airways, ascend the large airways, and descend into the alimentary tract into the small bowel where they complete their life cycle.

The hookworm *Ancylostoma* causes a nematodal infection endemic to the southeastern coastal regions of the United States, Mexico, and Central and South America.[5,7] The organism is present in soil contaminated by stool from infected domestic animals. It penetrates human skin most commonly through the feet. This results in the development of the "creeping eruption" lesion—a raised, erythematous, serpiginous, tunnel-like, and often itchy lesion on areas of exposed skin.[11] Loeffler syndrome occurs in up to 50% of cases of "creeping eruption."

Clinical Features

Loeffler syndrome affects people of all ages. Transpulmonary migration of parasitic larvae leads to characteristic symptoms including low-grade fever, nonproductive cough, dyspnea (mild to severe), chest discomfort with coughing or deep breathing, wheezing, and, occasionally, hemoptysis.[5–7] The respiratory manifestations of Loeffler syndrome are usually self-limited, typically resolving in 1 to 2 weeks.

Diagnostic Studies

Laboratory examination of peripheral blood from patients reveals moderate to extreme eosinophilia, which may be at peak levels as respiratory symptoms resolve, and eosinophilia may resolve over several weeks.[5] Expectorated sputum frequently contains eosinophils and/or Charcot–Leyden crystals.[5,7] Radiographic imaging shows transient or migratory, nonsegmental, bilateral, interstitial, and alveolar infiltrates (often peripheral or pleural based).[6] Infiltrates typically clear after several weeks. Pulmonary function testing typically reveals a mild to moderate restrictive ventilatory defect with a reduced diffusing capacity for carbon monoxide ($\mathrm{DL_{CO}}$).

Diagnosis of parasitic infection can be made during the pneumonic stage of the illness by recovery of parasite larvae from respiratory secretions, either sputum or bronchoalveolar lavage, or from a gastric aspirate.[5] In keeping with the life cycle of *Ascaris*, stool examination for ova and parasites is typically negative until 8 weeks after the onset of the respiratory syndrome.[12] Histologic evaluation of lung tissue is not required for confirmation of the diagnosis. When tissue has been obtained, a characteristic and striking eosinophilic infiltration of interstitial and alveolar–capillary units has been noted. Increased numbers of macrophages also have been observed. Tissue necrosis and vasculitis are not features of the disorder. *Ascaris* or hookworm larvae may be identified in the tissue specimen.[5]

Treatment and Prognosis

Bronchodilators, and rarely corticosteroids, may be used for alleviation of pulmonary symptoms, although these symptoms are usually self-limited. In adult cases due to *Ascaris*, treatment with oral mebendazole (100 mg twice a day for 3 days or a single dose of 500 mg)[13] should be given to prevent late GI manifestations of *Ascaris* infestation, which may include malnutrition, diarrhea, abdominal pain, and/or intestinal obstruction. These late GI symptoms begin typically 8 weeks or more after onset of respiratory symptoms. Pyrantel pamoate, albendazole, or ivermectin are alternate treatment options.[5] Since stool specimens are negative for ova and parasites early in the illness, clinical follow-up over a 2- to 3-month period is indicated.

■ Paragonimiasis

Paragonimiasis is caused by lung flukes of the genus *Paragonimus*. Most cases have been reported in Asia due to *P. westermani* as a result of eating raw or undercooked crustaceans or wild boar.[14]

Paragonimiasis has been reported in North America in immigrants from Asia, due to consumption of imported shellfish and, rarely, due to *Paragonimus kellicotti*, the only indigenous species of lung fluke in North America.[15] Once ingested, the *Paragonimus* metacercariae penetrate thru the duodenal wall, cross into the peritoneal cavity, migrate through the diaphragm, and move to the parietal pleura. In the pleural space or lung, the metacercariae mature into adult worms. This trophism for the lung is unique to paragonimiasis species, although in some cases it also invades extrapulmonary sites, most commonly the brain and skin.[16] Adult worms in the lung produce large, thick-shelled eggs (approximately 80 × 50 μm) that are released into the airways, then coughed up and swallowed. The cycle of infection continues when unembryonated eggs from stool or sputum are released into freshwater ecosystems and infect snails followed by crustaceans.

Clinical Features

The clinical syndrome of paragonimiasis reflects the migratory path of the parasite and its interaction with the host immune system. Fever, cough, chest pain, hemoptysis, and peripheral eosinophilia are common and typically begin 2 to 16 weeks after ingesting the infective larvae.[16] Those infected with lower parasite burdens may be asymptomatic or have intermittent cough, fevers, and/or night sweats. Pleuritis is common and caused by worms in the pleural cavity leading to unilateral or bilateral eosinophilic pleural effusion. Chest pain may occur when worms migrate through the pleura and sometimes cause pneumothorax. When worms invade the lung parenchyma, they may cause cough, sputum production, and hemoptysis, and chest imaging may reveal infiltrates. In some cases paragonimiasis may be mistaken for pulmonary tuberculosis.[15]

Diagnostic Testing

Diagnostic testing includes laboratory evaluation, examination of pathologic specimens, and radiographic imaging.

Laboratory Testing Definitive diagnosis of paragonimiasis is made by detection of *Paragonimus* eggs in sputum or stool, but the eggs are not commonly identified. In a series from Japan, eggs were detected only in sputum, BAL fluid, pleural effusion, or feces in 11.7% of cases.[14] Most often the diagnosis relies on serologic testing by ELISA. Elevation of blood eosinophils and IgE were present in 80% of infected patients.[17]

Pathology Pathologic specimens from lung biopsies may contain 1- to 3-mm cysts adjacent to or communicating with airways. Adult flukes may be found in the cystic cavities, whereas the eggs may be found in the lung parenchyma. Granulomatous inflammation with associated eosinophils, eosinophilic microabscesses, and eosinophilic vasculitis are common.[18]

Imaging Chest imaging is abnormal in most cases of pulmonary paragonimiasis. Pleural effusion is the most common radiographic finding. Parenchymal consolidations are typically seen early after lung penetration, whereas peripheral nodules or worm-containing cysts are seen in the late stage after infection. Other CT findings include serpentine worm migration tracks, pneumothorax, and lymphadenopathy.[15,19]

Treatment

All confirmed cases of paragonimiasis should be treated with praziquantel (75 mg/kg per day in 3 doses for 2 days).[13] Treatment failure is rare.

■ Tropical Pulmonary Eosinophilia

Tropical pulmonary eosinophilia (TPE) is a rare manifestation of human filarial infections, mostly from *Wuchereria bancrofti* and *Brugia malayi.* TPE represents a distinct immune response to the microfilaria in the lung that occurs in less than 1% of those infected. TPE is most prominent in India, Africa, and Southeast Asia, but it may be seen worldwide in filarial-endemic regions.[5,6,20] Disease may also be present in nonendemic regions among immigrants or travelers.[20,21] TPE is approximately four times more common in men, and most patients with TPE manifest the disease between the age of 25 and 40 years, although children and older adults also may be affected.[5,20] There is no known seasonal or genetic propensity to this disease, and it remains unclear why only such a small percentage of patients with filarial infection develop TPE.

Clinical Features

Infected larvae are typically introduced into humans by a mosquito bite and subsequently develop into adult worms that inhabit the lymphatics for many years, where they typically do not cause any symptoms. Pregnant females discharge microfilariae, some of which enter into the bloodstream and are trapped in the pulmonary vasculature. In TPE the release of antigens from degenerating microfilariae in the pulmonary vessels causes an intense pulmonary and systemic inflammatory response characterized by parasite-specific antibodies and eosinophilia in peripheral blood and within the lung.[5,7,20] The immune response to filaria is complex and involves many facets of the immune system, but it remains unknown what drives susceptibility to development of TPE and why such a small percentage of infected patients develop pulmonary disease.[22]

TPE may develop months to years after the filarial infection and is characterized by fevers, malaise, anorexia, weight loss, paroxysmal dry cough with dyspnea or wheezing, marked peripheral blood eosinophilia, and spontaneous resolution over several weeks.[5,23] The most common distinguishing symptom of TPE is spasmodic cough that usually occurs at night.[20] Dyspnea and wheezing, which can be severe, are common, and the clinical presentation may resemble status asthmaticus. Chest pain, muscle tenderness, and cardiac, pericardial, and CNS involvement also have been reported. Rarely, patients remain asymptomatic. Physical examination of patients with TPE is notable for coarse rales or rhonchi and wheezing, although no abnormalities are found in approximately 20% of patients.[20] Generalized lymphadenopathy and hepatosplenomegaly, pericarditis, and musculoskeletal or CNS manifestations may be present, but they are less common in adults than in children.[5,20]

Diagnostic Testing

Important elements in the clinical evaluation of suspected tropical pulmonary eosinophilia include laboratory testing, pulmonary function testing, examination of pathologic specimens, radiographic imaging, and application of diagnostic criteria.

Laboratory Testing Microfilariae are not detected in blood or sputum, nor are filarial ova identified in the stool or urine.[5] In contrast, microfilariae have been identified in tissue from lung and lymph nodes, especially when lymphadenopathy is present. High titers of filarial-specific IgE and IgG confirm an infection,[6,7] but in endemic regions this is not diagnostic due to the high prevalence of filarial infection. Other diagnostic tests are, therefore, essential to aid in diagnosis of TPE. Elevated eosinophils in the blood and lung are typical of TPE. Peripheral blood eosinophils may be extremely high, often more than 3000 eosinophils per cubic millimeter and up to 90% of the leukocyte differential, and may persist for several weeks, although the degree of eosinophilia generally does not correlate well with clinical disease severity or radiographic findings.[5,7,20] Blood eosinophils may show signs of activation including degranulation and increased cytoplasmic vacuoles.[20] Eosinophils are also elevated in the sputum and BAL. Eosinophils may make up to 50% of the leukocyte differential in the BAL.[5,7] Pleural fluid, when present, also is eosinophilic.[5] Total serum IgE is usually elevated (>1000 U/mL), and hypergammaglobulinemia results from polyclonal activation of B cells.[5] BAL and pleural fluid contain elevated levels of total IgE, IgM, IgG, and filarial-specific IgE.[5,7] Serum α1-antitrypsin is reduced and returns to normal with treatment.[5,24]

Lung Function Testing Pulmonary function test findings vary with the duration of disease. An obstructive ventilatory defect was observed in up to 30% of patients, particularly when symptoms were present for less than 1 month. Typical of long-standing disease is a restrictive ventilatory defect and reduced $D_{L_{CO}}$, with or without a concomitant obstructive defect.[5–7] Mild arterial hypoxemia may be present.[20]

Pathology In the first 2 weeks after symptoms begin, lung tissue is characterized by histiocytic inflammation in the alveolar, interstitial, peribronchial, and perivascular spaces, with preservation of lung architecture.[5,20] Tiny nodules may be palpable within the lung tissue. One to three months after symptom onset, eosinophilic infiltration with eosinophilic bronchopneumonia and microabscesses is present in lungs of untreated patients. Degenerating microfilariae may be present within the center of the microabscesses, and some destruction of alveolar walls may be evident. Local bronchial walls are also edematous and inflamed, with evidence of epithelial disruption. Long-standing untreated disease is associated with the presence of chronic mixed-cell inflammation (histiocytes, eosinophils, and lymphocytes) in a nodular pattern and the development of pulmonary fibrosis.[5,20] Foreign body–type granulomatous lesions are often present. Lymph node biopsies may reveal degenerating microfilariae or adult worms, surrounded by aggregates of eosinophils, their granule products, and giant cells.

Imaging The chest radiograph may be normal at the time of presentation in up to 20% of patients.[5,6,20] More commonly in TPE, there are ill-defined, diffuse reticulonodular infiltrates primarily affecting the mid to lower lung fields.[5,6,20] Bronchovascular markings may be prominent, and hilar adenopathy and pleural effusions have occasionally been reported.[5,6,20] In rare cases where *Dirofilaria* is the causative agent, the chest radiograph may reveal solitary or multiple nodules thought to represent infarcts caused by parasitic emboli. CT scans often show widespread, ill-defined bronchocentric nodules, mediastinal adenopathy, bronchiectasis, and areas of calcification.[25]

Diagnostic Criteria The diagnosis of TPE is usually established on the basis of the clinical and laboratory findings described earlier including pertinent exposure history. Lung or other tissue biopsies are not typically required. The diagnostic criteria for TPE are summarized in Table 71-3.[20] Biopsy of enlarged lymph nodes (e.g., scalene) may assist in establishing the diagnosis in some cases. A rapid treatment response may provide confirmatory evidence that the correct diagnosis has been made. The differential diagnosis includes Loeffler syndrome, CEP, ABPA, drug reactions, other parasitic infections, hypereosinophilic syndrome (HES), and lymphangitic spread of carcinoma. In nonendemic areas, the disease may also masquerade as asthma, atypical pneumonia, sarcoidosis, EGPA, granulomatosis with polyangiitis, or tuberculosis (TB). Diagnosis in nonendemic regions is often delayed, and a careful review of travel history and a high index of suspicion are necessary to prompt the diagnosis.

TABLE 71-3 Diagnostic Criteria for Tropical Pulmonary Eosinophilia

Relevant exposure in endemic area
Paroxysmal nocturnal cough, dyspnea
Infiltrate on chest radiograph
Leukocytosis with eosinophilia
Elevated serum IgE
Elevated serum antifilarial IgE, IgG (*W. bancrofti*, *B. malayi*)
Clinical improvement with diethylcarbamazine treatment

Treatment and Prognosis

Diethylcarbamazine, a piperazine derivative, is the therapy of choice for TPE, typically at a dose of 6 mg/kg/d in 3 doses for 14 or 21 days.[5] Diethylcarbamazine acts by both direct and indirect mechanisms. It is directly filaricidal to both adult worms and microfilariae. A marked clinical improvement and decrease in eosinophil count usually occurs in the first 7 to 14 days of therapy. Clinical improvement following diethylcarbamazine treatment has been correlated temporally with the resolution of eosinophilic alveolitis. In addition, improvement in pulmonary function, reduction in BAL eosinophilia, a decrease in total and filarial-specific IgE and IgG, increase in serum α1-antitrypsin levels, and radiographic clearing generally occur within 1 to 4 weeks of treatment.[5]

Patients treated with diethylcarbamazine generally have a benign course, and diethylcarbamazine therapy for 3 weeks is curative in most patients. However, acute relapses related to reinfection or release of microfilaria from persistent adult worms occur in up to 20% of patients.[5] Patients with low α1-antitrypsin levels after initial treatment may be at greater risk of relapse.[24] Patients who experience acute relapses often respond to additional treatment with diethylcarbamazine at higher doses of 2 to 4 mg/kg three times a day for 21 to 30 days. Persistent clinical symptoms have been reported over 2- to 5-year follow-up periods in up to 13% of patients with TPE treated with a standard course of therapy. If left untreated, TPE usually persists for weeks to months. Disease may remit spontaneously, but it commonly recurs within months to years. Mild, chronic inflammation may persist and lead to chronic interstitial lung disease with persistent respiratory symptoms, radiographic findings, and hematologic and serologic abnormalities.[20,21,26]

Strongyloidiasis *Strongyloides* infection is endemic in tropical and subtropical regions including rural areas in southeastern United States.[6,27] In soil contaminated by human feces, the larvae enter through bare skin. Acute strongyloidiasis may rarely cause Loeffler syndrome about 1 week after infection as larvae migrate from the skin into the bloodstream, then through the lungs.

Clinical Features It is more typical to have absent pulmonary complaints, but mild GI symptoms may occur about 3 weeks after infection when the parasite becomes established in the small intestine. In the intestines, the adult worms produce larvae that initiate repeated cycles of endogenous infection known as *autoinfection*. The larvae then re-enter the colonic wall or perianal skin and the bloodstream. This cycle can persist for many years, as the intact immune system keeps the process in check but cannot eliminate the parasite.[27,28]

Chronic strongyloidiasis is typically asymptomatic or characterized by mild pulmonary, GI, and/or skin symptoms. Repeated cycles of reinfection and migration of larvae through the lungs can lead to fever and pneumonias, often mistaken as bacterial pneumonias. Chronic strongyloidiasis is well-known for causing recurrent asthma-like symptoms, and because of the cycles of reinfection/migration, patients may be diagnosed with frequent asthma exacerbations. Strongyloidiasis is more common in patients with underlying lung disease, making diagnosis of parasitic infection more complex.[28] Immunosuppression with systemic corticosteroids to treat asthma or COPD has the potential risk of worsening of nondisseminated infection.[28]

The hyperinfection syndrome results from accelerated autoinfection leading to widespread dissemination of the parasite in immunocompromised patients with defects in cell-mediated immunity (such as with corticosteroid use; in lymphoma, HIV, or human T-lymphotropic virus type 1 [HTLV-1] infection; and in transplant recipients).[27] Respiratory manifestations include cough, dyspnea, chronic bronchitis, wheezing, hemoptysis, and patchy pulmonary infiltrates, in association with blood eosinophilia. In severe *Strongyloides* hyperinfection with dissemination, acute respiratory distress syndrome (ARDS) has been reported.[27,28] GI manifestations are common, including abdominal pain, diarrhea, paralytic ileus, nausea and vomiting, bowel perforation, and secondary sepsis from gram-negative bacteria. Central nervous system (CNS) manifestations such as meningitis are also possible. Mortality in the hyperinfection syndrome can reach 80% and is typically due to gram-negative bacterial sepsis.[29]

Diagnostic Testing Elements of the diagnostic evaluation of Strongyloides infection are discussed below.

Laboratory Testing Definitive diagnosis of chronic *Strongyloides* infection is difficult and requires direct parasite detection or culture of eggs or larvae from stool or other fluids. Parasite culture and identification is of low sensitivity due to the intermittent release of eggs by the adult female worm.[27] In contrast, in hyperinfection syndrome with dissemination, large numbers of larvae are released in stool, BAL, and other fluids, and diagnosis is feasible. Molecular detection using nucleic acid amplification methods, such as PCR, have greater sensitivity than direct identification techniques, but in asymptomatic patients with low larval levels, sensitivity is still not high.[30] Serologic assays, such as ELISA, to detect anti-*Strongyloides* IgG are commonly used to help to establish a diagnosis. These methods, though, have limitations including cross-reactivity with other parasites and cannot distinguish between early or late, acute or chronic disease.[30] Patients at risk for *Strongyloides* hyperinfection syndrome should be screened for the parasite prior to initiation of immunosuppressive therapy.[6] In general, the high negative predictive value of serologic testing is useful to exclude *Strongyloides stercoralis* infection.

During the migratory phase, when the microfilariae move from pulmonary capillaries into the alveoli, there is commonly peripheral eosinophilia and elevated serum IgE.[28] In this phase, there may be pulmonary infiltrates with eosinophilia, or asthma without pulmonary infiltrates. Peripheral blood eosinophilia may be absent in up to one-third of *Strongyloides*-infected patients, and eosinophilia is seen only in a minority of hyperinfection cases.[27,31]

Imaging Radiologic findings in strongyloidiasis include ground-glass opacities, septal thickening, consolidations, and patchy migratory infiltrates. Miliary pulmonary micronodules are less common. Secondary bacterial infections and hemorrhage may often overlap the other features. Diffuse bilateral infiltrates in ARDS also may be observed.[19]

Treatment and Prognosis Ivermectin is the treatment of choice and is used at 200 μg/kg for 2 days for the treatment of uncomplicated disease. Hyperinfection syndrome associated with *Strongyloides*, which can have severe consequences, should be treated urgently and therapy should be continued for a minimum of 2 weeks after stool samples test negative for larvae. A reduction in immunosuppressive therapy should be considered.[27]

■ Visceral Larvae Migrans

Systemic infection with the intestinal roundworm of the dog, *Toxocara canis*, is the predominant cause of visceral larva migrans (VLM). *Toxocara catis* and *Ascaris suum* are less-common causes of VLM. VLM occurs worldwide, particularly in tropical climates. Humans are accidental hosts of *Toxocara* when infective eggs are ingested in soil contaminated with dog feces or when raw animal products are consumed. Once ingested, the eggs hatch and penetrate the intestinal wall and disseminate in the circulation to various tissues including lungs, liver, eyes, heart, brain and muscle. The larvae are unable to grow or replicate in the tissues, but the host inflammatory response to the larvae can cause local damage.

Clinical Features

VLM is characterized by hepatomegaly, leukocytosis, fever, hypergammaglobulinemia, and persistent blood eosinophilia.[32] Pulmonary involvement of varying severities occurs in 20% to 80% of cases and includes mild cough, wheezing, bronchiolitis, asthma, and pneumonitis. Because the disease most commonly affects young children, a high degree of clinical suspicion is necessary to establish the diagnosis in adults. Diagnosis is suspected when there is history of geophagia or ingestion of raw animal parts along with allergic symptoms.

Diagnostic Testing

Laboratory evaluation reveals peripheral blood and BAL eosinophilia and elevated serum levels of IgE. Eosinophilia may persist for many months, even in self-limited disease.[5] ELISA testing for *Toxocara* larval antigens is diagnostic. CT imaging most frequently shows multiple, bilateral, peripheral nodules, some with a halo sign, or ground-glass opacities.[33]

Treatment and Prognosis

Most patients have mild, self-limited disease and do not require antihelminthic treatment. Symptomatic patients are typically treated with albendazole 400 mg daily for 5 days or mebendazole.[13] Antihistamines and sometimes corticosteroids may speed recovery in patients who are severely ill.

ACUTE EOSINOPHILIC PNEUMONIA

Initial reports of acute eosinophilic pneumonia (AEP) described a respiratory illness of unknown cause,[34] but over the past four decades, numerous studies have shown that a majority of cases are caused by inhaled exposures, most commonly tobacco smoke.[34–39] Although seen in patients of both genders and in any age group, AEP tends to occur in patients between the age of 20 and 40[35,40,41] and is more common in men.[34] AEP occurs commonly in previously healthy people and represents an acute inflammatory reaction to an inhaled agent.[37,39] Many cases have been reported in patients who have recently commenced smoking cigarettes,[38,39,42,43] vaping,[44,45] used flavored tobacco products,[46] or had other changes in smoking habits. The disease may recur when former smokers resume smoking.[47,48] Overall, up to 70% of patients with AEP have a history of smoking.[35,49] Similar cases have been reported in persons with a history of chronic myelogenous leukemia, hematopoietic stem cell transplantation, or HIV infection.[50–52] In addition, cases have been reported in persons treated with venlafaxine,[53] minocycline,[35] daptomycin,[54,55] and several other drugs.[35] It has also been reported among persons who have been involved in activities with unusual exposures, including exposure to dust from the World Trade Center collapse in New York City,[56] during military deployment in Iraq,[57] cave exploration, gasoline tank cleaning, plant repotting, woodpile moving, and indoor renovations.[35,58] AEP has also been seen following inhalation of cocaine or heroin,[59,60] and in association with H1N1 influenza infection.[61,62] Although none of the patients in the original reported series had atopy or asthma, cases have since been described in persons with a history of atopy. No definite seasonal variation has been identified.

■ Clinical Features

AEP presents as an acute illness with dyspnea, fever, nonproductive cough, tachypnea, pleuritic chest pain, hypoxemia (arterial Pa_{O_2} under 60 mm Hg), and sometimes with myalgias.[34,35,49] Symptom duration is typically less than 7 days, although longer courses of up to 30 days have been described.[61] Patients usually have diffuse inspiratory crackles on chest auscultation, wheezing may be present, and rapid progression from mild dyspnea to overt respiratory failure requiring mechanical ventilation is common.[35,38,57] Early clinical features may be mistaken for community-acquired pneumonia.

Diagnostic Testing

Major components of the diagnostic evaluation of suspected AEP include laboratory testing, pulmonary function testing, imaging, examination of pathologic specimens, and application of diagnostic criteria.

Laboratory Testing

Common findings in AEP include a moderate leukocytosis with left shift,[38] but blood eosinophilia is usually absent at the onset of disease.[35,57] Blood eosinophilia may develop later in the course of the disease and may provide a clue to the diagnosis.[38,63] Serum IgE levels may be moderately elevated.[35,64] The erythrocyte sedimentation rate (ESR) may be elevated as well. Serum levels of thymus and activation-regulated chemokine (TARC)/CCL17 (a ligand for CCR4 on Th2 lymphocytes) may be elevated and may help to distinguish AEP from other causes of acute lung injury (ALI), even in the early phase of disease before blood eosinophilia is present.[65] In contrast, levels of KL-6, a marker for alveolar cell damage, tend to be lower in AEP than in other forms of ALI.[65] If a bronchoscopy is performed, a BAL cell differential should be requested. Eosinophilia (25%–55%) is present in BAL fluid.[39] Increased numbers of lymphocytes (up to 20%) and neutrophils (up to 15%) are commonly also present in BAL fluid in AEP.[66] Pleural effusions are common, and fluid analysis typically reveals a high pH and marked eosinophilia.[36]

Pulmonary Function Testing

Pulmonary function testing is not usually done in AEP due to the acute nature of the disease. Limited data show a restrictive ventilatory defect with a reduced $D_{L_{CO}}$, both of which typically normalize following treatment.[66] An elevated fraction of exhaled nitric oxide (FeNO; e.g., levels >23.5 ppb) may help to distinguish AEP from non-AEP disorders and FeNO levels decreased following corticosteroid treatment.[67]

Imaging

Early in the course of illness, chest radiographs reveal subtle, patchy infiltrates with Kerley B lines.[35,39,68] As disease progresses, CT findings include bilateral patchy areas of ground glass, and areas of consolidation and interlobular septal thickening in a random distribution[39,69] (Fig. 71-1). Thickening of the bronchovascular bundles and lymphadenopathy also are common.[39] Small to moderate bilateral pleural effusions are common (affecting up to 50%–70% of patients).[38]

Pathology

Light microscopic examination of lung tissue reveals prominent eosinophil infiltration in interstitium and/or alveolar spaces, and bronchial walls.[70] The pathologic pattern of diffuse alveolar damage with hyaline membranes and eosinophilic infiltrates should suggest the possibility of AEP. Lymphocytic infiltration of interstitium, type 2 pneumocyte hyperplasia, and intra-alveolar fibrinous exudate also are common. Granulomas, alveolar hemorrhage, and nonnecrotic perivascular inflammation have been reported.[70] Basal lamina damage is unusual.[68] Extrapulmonary involvement is rare.

Diagnostic Criteria

Diagnostic criteria include (1) acute respiratory illness of less than or equal to 1 month duration; (2) pulmonary infiltrates on chest radiography or computed tomography (CT); (3) pulmonary eosinophilia as demonstrated by more than 25% eosinophils in BAL fluid (can be accompanied by variably increased percentages of lymphocytes and neutrophils) or eosinophilic pneumonia on lung biopsy (bronchoscopic or surgical); and (4) absence of known causes of pulmonary eosinophilia, including drugs, toxins, infections, and eosinophilic diseases such as EGPA, HES, and APBA.[39,71]

Using these criteria, idiopathic AEP should be considered in a patient who presents with an acute febrile illness, apparent ALI, or ARDS without a typical antecedent illness and is a diagnosis of exclusion.[36] A history of recent changes in smoking habits should be a flag for possible AEP. A careful search must be undertaken for other causes of pulmonary infiltrates, especially fungal or other infection, and drug or other exposures. Specimens of blood, sputum, stool, BAL, and often transbronchial biopsy specimens should be obtained for stain and culture as well as serologic testing to rule out viral, bacterial, mycobacterial, fungal, and parasitic infection.[35,49]

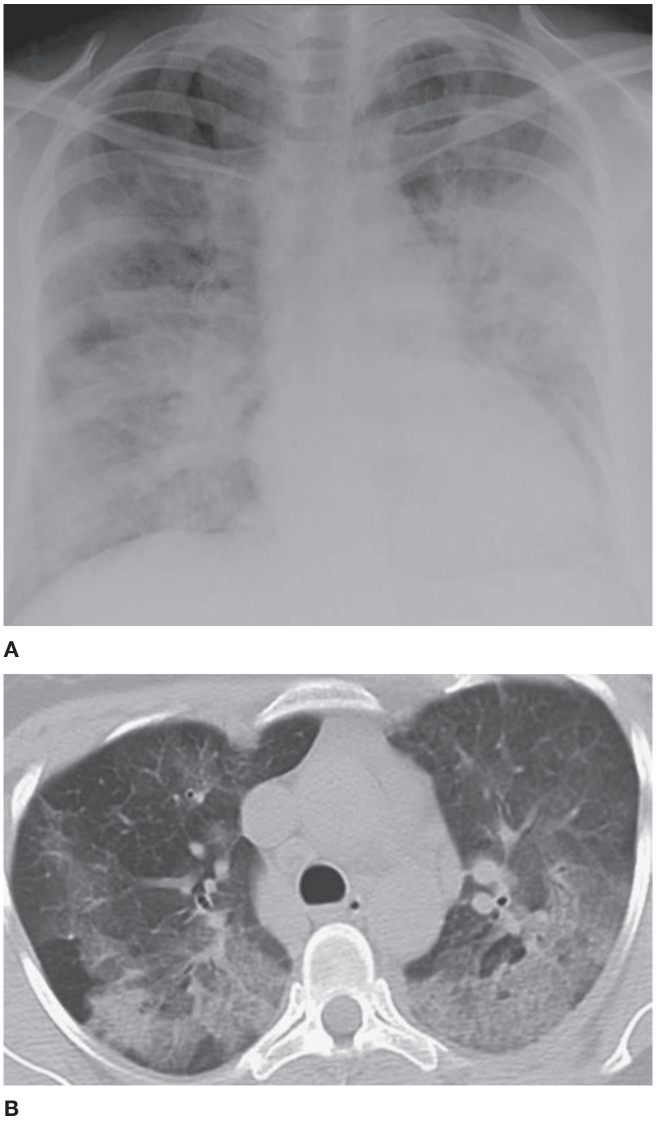

Figure 71-1 Radiographic appearance of idiopathic acute eosinophilic pneumonia (AEP). **A.** Diffuse bilateral alveolar and interstitial infiltrates apparent on chest radiograph. **B.** Diffuse parenchymal ground-glass opacity and consolidation evident on computed tomography scan.

Mechanisms of Disease

The pathogenesis of idiopathic AEP is not defined. The occurrence of cases following environmental inhalational exposures, most commonly cigarette smoke, suggests that these exposures are disease-inciting events that trigger an inflammatory response. It is unknown if the exposure activates the pulmonary innate immune response in an antigen-nonspecific manner and/or if AEP involves an immune response to an (unidentified) specific antigen. One past explanation is that AEP is initiated by a type 1 hypersensitivity reaction involving IgE-mediated mast cell degranulation, although this has not been confirmed.[37] Another hypothesis is that epithelial damage leads to activation of both innate and adaptive immune responses leading to release of type 2 cytokines and chemotactic factors that drive pulmonary eosinophilia.[39]

There is evidence of cell damage in AEP, with elevated BAL levels of damage-associated molecular patterns (DAMPs) including IL-33, uric acid, and ATP.[4] The presence of high IL-33 levels suggests there is epithelial damage,[72] although it is unclear if the release of DAMPs is part of the inciting trigger of AEP or an effect of inflammation. DAMPS can activate eosinophils, and eosinophil-derived granule proteins can cause tissue damage. IL-33 can activate innate lymphocyte type 2 (ILC2) cells and drive the adaptive immune response leading to CD4 Th2 development.[72]

Type 2 cytokines including IL-5, IL-4, and IL-13 have been identified in the BAL of patients with AEP.[4] IL-5 is essential for eosinophilia. In the respiratory tract, eosinophils are recruited to and activated by IL-5. Circulating IL-5 stimulates bone marrow eosinophil production and maturation. IL-13 stimulates production of eosinophil chemotactic factors. Type 2 cytokines are produced largely by lymphoid cells, specifically ILC2 cells and CD4+ Th2 cells. ILC2 cells can be activated rapidly, whereas CD4+ Th2 cells are part of the adaptive immune response and require a period of days to weeks to develop. Eosinophils, mast cells, basophils, gamma-delta T cells, and various other innate immune cells also can produce type 2 cytokines. One day after smoking challenge, an AEP subject had a rise in all leukocyte subsets and IL-4, IL-5, and TNF-α in the BAL, along with a rise in serum IL-5, eotaxin, and other chemokines.[73] The rapid, recall reactivation of the immune response in this patient along with type 2 cytokine release suggests CD4+ Th2 cells are involved in AEP.

Eosinophil chemotactic factors are also present in the BAL of patients with AEP, including the CCR3 ligands CCL11, CCL24, CCL26 (eotaxins 1–3), and CCL13 (MCP-4) and other chemoattractants and lipid mediators such as LTB4.[4] These mediators enhance eosinophil migration into the lung. This elevation of eosinophil chemokines and type 2 cytokines in the BAL is not unique to AEP; it is common in eosinophilic lung diseases, although the levels of all cytokines in AEP were significantly higher when compared with chronic eosinophilic pneumonia.[4]

In summary, eosinophilic lung diseases exhibit common downstream pathways of eosinophil recruitment and activation involving elevation of type 2 cytokines and eosinophil chemokines. The inciting events leading to AEP remain unknown, including the specific agents and triggering mechanisms. AEP is an uncommon disease caused often by a common exposure, cigarette smoke. This suggests that its development involves multiple factors in a predisposed individual, and the triggering factor/event may be different from one individual to another.

Treatment

Treatment of AEP should begin with cessation of exposure to the offending cause if it can be identified. Corticosteroids induce apoptosis of eosinophils and lead to resolution of all eosinophilic pneumonias. Most patients demonstrate rapid, dramatic improvement in response to corticosteroid therapy with abatement of fever and respiratory symptoms within 12 to 48 h and complete resolution of infiltrates, pleural effusion, and pulmonary function impairment usually within 1 month.[34,35,38,49,66] Initial doses of methylprednisolone typically range from 60 to 125 mg administered every 6 h. After resolution of respiratory failure, oral prednisone (in doses of 40–60 mg/d) may be continued for 2 to 4 weeks with a subsequent slow taper over the next several weeks.[35] While corticosteroids are highly effective in reducing eosinophilia, the optimal regimen has not been determined, and while believed to be appropriate therapy, spontaneous disease regression has also been reported.[39,71] In contrast to chronic eosinophilic pneumonia, AEP does not typically relapse after therapy is completed. AEP due to infection requires identification of the pathogen and appropriate antimicrobial therapy.

CHRONIC EOSINOPHILIC PNEUMONIA

Chronic eosinophilic pneumonia (CEP) was first described by Carrington as a clinical entity marked by fevers and radiographic peripheral opacities that rapidly responded to glucocorticoids.[74]

Clinical Features

CEP may develop at any age, but the peak incidence occurs between ages 30 and 45 years.[75–77] Women are affected approximately twice as often as men, and CEP has been reported during pregnancy and following radiation therapy for breast cancer.[78] In one series, asthma was diagnosed in 49% of patients prior to CEP, in 15% contemporaneously, and in 13% after CEP diagnosis.[79] CEP-related asthma is often severe and may lead to fixed airflow obstruction (approximately 10% of patients) despite medical therapy.[79] Approximately one-third to one-half of patients have antecedent atopy, allergic rhinitis, nasal polyps, or urticaria.[75] In addition, a majority of patients with CEP are nonsmokers.

CEP typically has a subacute presentation, with symptoms present for weeks to several months before diagnosis.[75,77] Common presenting complaints include dyspnea, low-grade fevers, malaise, drenching night sweats, and moderate weight loss (10–50 lb).[77,80] Cough, often dry initially and later productive of small amounts of mucoid sputum, is a virtually universal finding.[77] Rhinitis or sinusitis may be present. Two of the nine patients described in Carrington's original series had minor hemoptysis. Patients ultimately develop progressive dyspnea, which may be associated with wheezing in those with asthma. Very rarely, patients with CEP have severe, acute respiratory failure with hypoxemia requiring mechanical ventilation. Rarely, arthralgias, skin rash, diarrhea or colitis, mononeuritis, hepatitis, pericarditis, or unexplained heart failure have been described, raising suspicion that there may be a continuum between CEP and eosinophilic granulomatosis with polyangiitis (EGPA).[77] Cases have been reported in which patients initially diagnosed with CEP later developed EGPA.[81,82]

Diagnostic Testing

Findings on laboratory testing, imaging, pulmonary function testing, and examination of pathologic specimens are discussed below.

Laboratory Testing

Patients with CEP frequently have moderate peripheral blood leukocytosis. The majority (66%–95%) have elevation of blood eosinophils (typically $>1000/\text{mm}^3$) with eosinophils constituting more than 6%, and often up to 20% to 30% of the leukocyte differential.[76,77,83] However, a lack of peripheral blood eosinophilia does not rule out the diagnosis. Normochromic, normocytic anemia and thrombocytosis may be present. Elevation of C-reactive protein and erythrocyte sedimentation rate are common, and IgE levels are elevated in up to one-half of cases.[77] Blood and sputum cultures routinely fail to identify an infectious etiology. Analysis of BAL fluid reveals increased eosinophils, typically accounting for 40% or more of the leukocyte differential, with a range of 12% to 95% reported.[75,77,80,84] Eosinophil

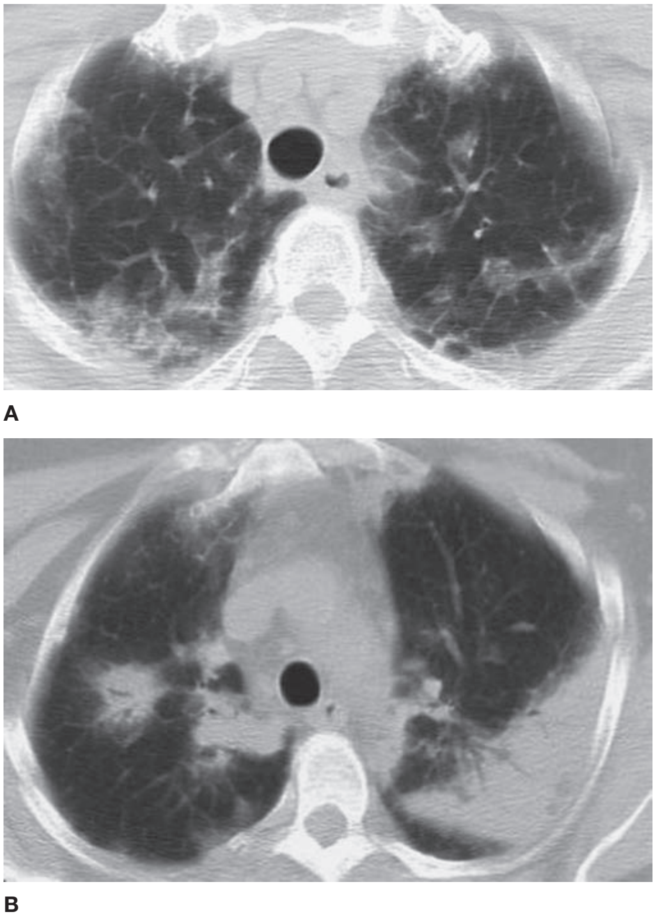

Figure 71-2 Radiographic appearance of chronic eosinophilic pneumonia (CEP). Variable computed tomography appearance of infiltrates in two patients with chronic eosinophilic pneumonia. Peripheral upper lobe–predominant infiltrates may have a ground-glass appearance (**A**) or may appear as regions of dense consolidation or nodular opacity (**B**).

chemoattractant cytokines IL-5, eotaxin, and RANTES (CCL-5) are elevated in BAL fluid of patients with CEP, suggesting that Th2 cells recruit and attract eosinophils to the lung.[77,85]

Imaging

Originally, Carrington et al. described three radiographic features that are characteristic for CEP: (1) peripherally based, progressive dense infiltrates; (2) rapid resolution of infiltrates following corticosteroid treatment, with recurrences in identical locations; and (3) the appearance of infiltrates as the "photographic negative of pulmonary edema."[74,85] The pulmonary infiltrates associated with CEP are typically dense and patchy areas of airspace consolidation with ill-defined margins usually affecting the outer two-thirds of the lung fields (Fig. 71-2). Infiltrates are most commonly bilateral, tend to be located in the mid to upper lung zones, and may mimic loculated pleural fluid. They are frequently nonsegmental, subsegmental, or lobar in distribution. The characteristic "photographic negative of pulmonary edema" occurs in <50% of cases.[86] Pleural effusions and cavitation are rare.[76,87,88] The infiltrates may be migratory in up to 25% of cases. Occasionally, the chest radiograph can be normal.

Findings on CT scan may vary depending on the timing of the CT relative to the onset of symptoms. Typical areas of dense, peripherally located airspace consolidation are found in most cases within the first several weeks of disease onset. Areas of peripheral consolidation often involve the middle and/or upper lung zones, and ground-glass opacities also are common.[76,89–92] Mediastinal adenopathy, which may be evident on conventional chest radiograph, may also be identified on CT scan.[92] Less typical radiographic findings include nodular infiltrates, linear oblique or vertical densities, bronchial wall thickening, pleural effusion, and areas of fibrosis unassociated with anatomic divisions. Streaky bandlike opacities may appear when symptoms have been present for more than 2 months.[89]

Pulmonary Function Testing

Abnormalities in pulmonary function depend on the stage and severity of disease. In the initial stage, prior to treatment with corticosteroids, testing may reveal restrictive, obstructive, or normal physiology.[77] Obstructive ventilatory defects, while more common in patients with a history of asthma, are also encountered in patients without pre-existing asthma. Restrictive physiology may result from eosinophilic infiltration of lung parenchyma. Diffusing capacity may be reduced, and the alveolar–arterial oxygen gradient may be mildly elevated.[77,80]

Pathology

Pulmonary lesions of CEP are characterized by varying degrees of leukocytic infiltration of the alveolar airspaces and alveolar septae. These infiltrates are predominantly eosinophilic, with some associated macrophages, a small to moderate number of lymphocytes, occasional plasma cells, multinucleated giant cells, and an associated fibrinous exudate.[68,74,80] Unlike AEP, the basal lamina may be disrupted, but frank alveolar necrosis is absent.[68] Eosinophilic microabscesses can be found. Focal edema of the capillary endothelium, focal type II epithelial cell hyperplasia, and proteinaceous and fibrinous alveolar exudates also can be appreciated. Histologic evidence of proliferative bronchiolitis obliterans or bronchiolitis obliterans–organizing pneumonia may occur in up to one-third of cases, and a mild, nonnecrotizing microangiitis affecting the small venules may be seen. Biopsy specimens of lymph nodes from patients with intrathoracic lymphadenopathy reveal lymphoid hyperplasia and eosinophil infiltration.[68,74,80]

■ Mechanisms of Disease

The cause of CEP is unknown. No specific genetic predisposition has been identified, although CEP was reported in identical twins, raising the question of a familial tendency toward the disease. An association has been reported between rheumatoid arthritis and CEP, but no clear causal relationship has been identified.[93,94] Although the precise immunopathogenesis of CEP is unknown, evidence suggests that type 2 helper T (Th2) cells have a role in disease pathogenesis. The levels of type 2 cytokines including IL-5, IL-4, and IL-13 and of eosinophil chemoattractants are elevated in the BAL fluid of patients with CEP, albeit at lower levels than typically observed in AEP.[4] Likely, the release of these mediators reflects a common mechanism in eosinophilic pneumonias that drives eosinophil accumulation and activation in the respiratory tract, as reviewed above. The factors that initiate and perpetuate CEP, though, are unclear. Because CEP has a protracted course and high rate of recurrence, this suggests a potential role of Th2 lymphocytes in the pathogenesis of CEP.

■ Diagnostic Criteria

The diagnosis of CEP is based on the presence of compatible clinical characteristics, radiographic findings of peripheral opacities, BAL eosinophilia, and the absence of infection or other known causes of eosinophilic lung disease. The clinical signs and symptoms of CEP are nonspecific, however, and blood eosinophilia and typical radiographic features may be absent in some cases. Transbronchial biopsy, usually performed to rule out other diagnostic entities, may reveal eosinophil and mononuclear cell infiltrates. Surgical lung biopsy is rarely required. Because of the profound responsiveness of CEP to steroid treatment, a therapeutic trial of steroids is often useful in establishing the diagnosis. Failure to document rapid clinical improvement should alert the clinician to consider other diagnoses. The differential diagnosis of CEP includes drug-induced eosinophilic pneumonia, infection (especially TB, fungal diseases such as cryptococcosis, and parasitic disease), sarcoidosis, Loeffler syndrome, desquamative interstitial pneumonitis, cryptogenic organizing pneumonia, ABPA, chronic hypersensitivity pneumonitis, acute idiopathic eosinophilic pneumonia, EGPA, and eosinophilic granuloma.

■ Treatment and Prognosis

CEP rarely resolves without therapy and, if left untreated, may result in fibrosis.[95] Corticosteroids are the mainstay of therapy for CEP. Dramatic clinical, radiographic, and physiologic improvements have been documented following steroid treatment in all series reported.[75,77,89] Even patients presenting with severe respiratory failure may respond well to steroid treatment. In most cases, treatment with steroids leads to resolution of fever within 6 h, reduced dyspnea, cough, and blood eosinophilia within 24 to 48 h, resolution of hypoxemia in 2 to 3 days, radiographic improvement within 1 to 2 weeks, complete resolution of symptoms within 2 to 3 weeks, and normalization of the chest radiograph within 2 months.[75,76,80] No comparative studies exist to determine optimum treatment doses or duration of steroids, but a recommended regimen is prednisone 0.5 mg/kg/d (40–60 mg a day) continued until 2 weeks after resolution of symptoms and radiographic abnormalities, generally for 4 to 6 weeks. The dose of prednisone can then be tapered slowly by 0.25 mg/kg/d and then continued for the subsequent 8 weeks. Treatment is usually maintained for at least 3 months and optimally for 6 to 9 months; during this phase prednisone can be decreased by 5 mg every 4 weeks. Shorter courses of prednisone also may be effective.[77]

The prognosis of CEP is generally favorable.[96] In steroid-treated patients, morbidity and mortality directly related to CEP are low. Patients may require 1 to 3 years of initial steroid treatment to control the disease, and up to 50% may require long-term maintenance treatment (2.5–10 mg prednisone a day) to remain disease-free.[75,77] The lowest possible dose of steroid that suppresses disease activity should be used. Inhaled steroids are inadequate monotherapy to treat CEP; however, may have some role in preventing relapses particularly in those with asthma.[79,97,98]

CEP relapses are common, occurring in 50% to 80% of cases when steroids are tapered or discontinued.[75–77,80] Relapses may involve radiographic infiltrates in the same or different anatomic distribution compared with the original disease. Relapsing CEP must be distinguished from the development of new or worsening asthma. No obvious factors exist to identify persons who are likely to relapse or require long-term steroids, although relapses are more common in persons treated initially with a short course (<6 months) of steroids. Relapses should be managed by increasing the prednisone dose to ≥40 mg per day until 2 weeks after symptom control has been achieved, with gradual taper thereafter. The reinstitution of steroids generally leads to improvement, and relapses do not appear to indicate a worse prognosis, increased likelihood of treatment failure, or increased morbidity.

Biologic agents with anti-eosinophilic activity are now a possible steroid-sparing treatment option for disease. The anti–IL-5 antibody mepolizumab has shown some success in treatment of relapses of CEP and has been associated with fewer relapses, improvement in imaging findings, and reduction in oral steroid dosing.[99–101] There is less experience with the anti–IL-5R antibody benralizumab, although there are reports of successful treatment in patients with relapsed disease and as initial therapy in a patient who refused prolonged glucocorticoids.[101–103] Omalizumab, an anti-IgE antibody, has been reported to be a successful steroid-sparing agent in cases of CEP with elevated IgE and allergic sensitization.[104] Dupilumab, an anti–IL-4Rα antibody, has been reported as both a treatment and a cause of CEP.[105,106] Since there can be elevation of blood eosinophils in dupilumab-treated patients, it should not be used to treat CEP until further evidence of benefit is available.[107] The direct, anti-eosinophilic effect of IL-5 pathway drugs, as well as the lack of a requirement for allergic sensation, make them a more universal choice for treatment at this time.

OTHER CHRONIC EOSINOPHILIC LUNG DISEASES

A variety of other chronic eosinophilic lung disorders are considered in detail below.

■ Allergic Bronchopulmonary Aspergillosis (Mycosis)

ABPA is a disorder caused by a hypersensitivity response to inhaled fungal antigens.[108–115] Since the disease is most commonly induced by *Aspergillus* species, it is usually known as ABPA. When induced by non-*Aspergillus* species, the syndrome is called *allergic bronchopulmonary mycosis*.

Clinical Features

ABPA occurs most commonly in immunocompetent patients and complicates 1% to 2% of cases of persistent asthma and 7% to 14% of cases of chronic steroid-dependent asthma, most often among patients in the third to fourth decade of life.[116] ABPA also complicates up to 15% of patients with cystic fibrosis (CF), most often during the teen years.[110,117] Rare cases of ABPA have been reported that lack a history of asthma, but meet the other major diagnostic criteria (summarized in Table 71-4).[118] The diagnosis of ABPA is based on appropriate clinical features in combination with supporting serologic and radiologic findings.[109] The features of ABPA are believed to result from an immunologic reaction to chronic airway colonization by *Aspergillus* (or other relevant fungal species) that includes features of type I, type III, and type IV immune responses.[109] T-helper lymphocytes, neutrophils, eosinophils, genetic susceptibility factors,

TABLE 71-4 Diagnostic Criteria for ABPA (ISHAM Working Group)[127]

Predisposing conditions
Asthma
Cystic fibrosis
Obligatory criteria *(both should be present)*
Type I *Aspergillus* skin test positive (immediate cutaneous hypersensitivity to *Aspergillus* antigen) or elevated IgE levels against *Aspergillus fumigatus*
Elevated total IgE levels (>1000 IU/mL)[a]
Other criteria *(at least two of three should be present)*
Presence of precipitating or IgG antibodies against *Aspergillus fumigatus* in serum
Radiographic pulmonary opacities consistent with ABPA[b]
Total eosinophil count >500 cells/µL in steroid-naïve patients (may be historic)

[a] *If the patient meets all other criteria, an IgE value <1000 IU/mL may be acceptable.*

[b] *The chest radiographic features consistent with ABPA may be transient (i.e., consolidation, nodules, tram-track opacities, toothpaste/finger-in-glove opacities, fleeting opacities) or permanent (i.e., parallel line and ring shadows, bronchiectasis and pleuropulmonary fibrosis).*

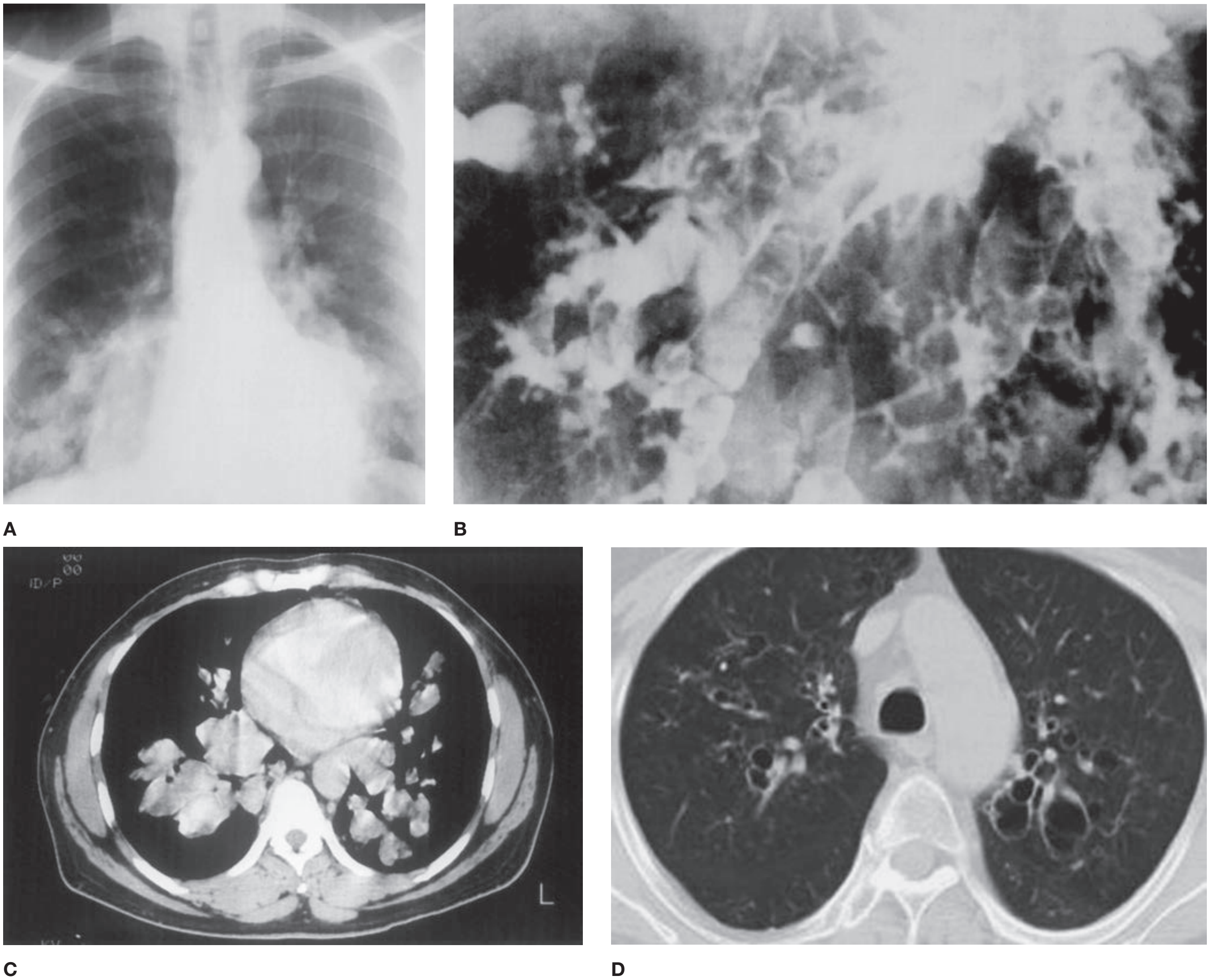

Figure 71-3 Radiographic appearance of allergic bronchopulmonary aspergillosis (ABPA). Extensive infiltrates with tubular configuration and “gloved finger” appearance are present, in this case predominantly in the lower lobes (**A**), the bronchogram (**B**), and computed tomography (CT) of the chest (**C**) reveal extensive proximal bronchiectasis. Extensive mucoid impaction of the bronchi is evident on CT scan (**C**). Central bronchiectasis and tram-track shadows in a patient with ABPA may also be present without mucoid impaction (**D**).

and the fungus itself all likely contribute to the pathogenesis of the disease.[108,119]

Typical symptoms of ABPA include wheeze, cough, dyspnea, and sputum production, with occasional expectoration of brownish/black mucus plugs. Other symptoms may include malaise, myalgias, low-grade fever, chest pain, weight loss, or hemoptysis. The diagnosis of ABPA should be considered in any patient with asthma or CF who experiences frequent exacerbations of respiratory symptoms, and/or the combination of asthma and eosinophilia. Worsening of lung function, steroid dependence, or failure to improve clinically following antibiotic therapy for a suspected bacterial infection suggests the diagnosis in patients with CF.[117,120]

Diagnostic Testing

Diagnostic evaluation includes radiographic imaging, examination of pathologic specimens, and application of diagnostic criteria.

Imaging Typical radiographic manifestations of ABPA include transient, irregular pulmonary infiltrates with a predilection for the upper lobes (Fig. 71-3).[90,121] Other common radiographic features include “finger-in-glove opacities,” “tramline shadows,” “parallel lines,” “toothpaste shadows,” “ring shadows,” and lobar consolidation (Fig. 71-3). These findings result from bronchial and bronchiolar wall inflammation, edema, and remodeling, and from mucoid impaction of the bronchi with or without parenchymal involvement. As noted, central (proximal) bronchiectasis, another characteristic radiographic manifestation of ABPA, occurs in many but not all patients. The presence of high-attenuation mucus on HRCT may be a marker for disease severity.[122]

Pathology ABPA is not typically diagnosed by tissue sampling. Nevertheless, histopathologic findings of ABPA include intense bronchocentric inflammation with eosinophils, lymphocytes, plasma cells, and monocytes, bronchocentric granulomatosis, and mucoid impaction of bronchi.[117,123] Fungal hyphae are typically present in mucus plugs without bronchial tissue invasion. The histologic findings may vary in differing parts of the lung and in different stages of the disease.

Diagnostic Criteria Originally, Greenberger and Patterson proposed five minimal essential criteria needed to establish the diagnosis, including (1) asthma, (2) positive immediate hypersensitivity skin test to *Aspergillus,* (3) total IgE greater than 1000 ng/mL (or >417 IU/mL), (4) elevated serum anti–*Aspergillus fumigatus* (AF) IgE and IgG (>2-fold greater than for asthmatic controls), and (5) serum precipitins to AF or other relevant fungus.[124] These features, as well as a history of current or previous pulmonary infiltrates and/or central bronchiectasis evident on high-resolution CT scan (HRCT) and peripheral blood eosinophils (∼10,000 cells/mL), constituted the initial diagnostic criteria of ABPA.[108,111,123–126] An updated criterion adopted by the International Society for Human and Animal Mycology (ISHAM) working group provides a more simplified approach (Table 71-4). These require a predisposing condition (asthma or cystic fibrosis). Obligatory criteria are skin test positivity to aspergillus or elevated IgE against *Aspergillus* and an IgE above 1000 IU/mL. Additional criteria, of which two are required, include the presence of precipitating or IgG antibodies against aspergillus, thoracic imaging findings consistent with ABPA, and peripheral blood eosinophils >500 cells/μL.[127]

Five clinical stages of ABPA have been described: acute illness (stage 1); remission (stage II); exacerbation (stage III); steroid-dependent asthma (stage IV); and fibrotic lung disease (stage V).[109,110,124] Two variants of ABPA have been recognized: seropositive ABPA (ABPA-S), wherein the preceding essential criteria are met and there is no evidence of central bronchiectasis; and ABPA with central bronchiectasis (ABPA-CB) in which CB also is present.[110,128] It is unclear whether ABPA-S is an earlier stage of disease that precedes ABPA-CB or whether it is a milder form of the disease. The differential diagnosis of ABPA is broad, and in addition to other pulmonary eosinophilic disorders, includes asthma with fungal sensitization without ABPA, refractory asthma without fungal sensitization, *Aspergillus* bronchitis, and other nonfungal infectious bronchitis or pneumonia. ABPA often goes unrecognized due to overlap of clinical features with these disorders. ABPA may also be challenging to recognize due to the varying clinical presentations at different stages of disease.

Treatment and Prognosis

The goals of treatment are to control symptoms, preserve normal lung function, and prevent exacerbations and disease progression. Early recognition and aggressive treatment are essential to prevent development of permanent airway remodeling, bronchiectasis, and pulmonary fibrosis.[110] Systemic corticosteroids, with careful patient monitoring of clinical symptoms, IgE levels, and chest radiograph, are the mainstay of therapy.[122,129,130] Corticosteroid doses that reduce IgE levels by at least half of acute stage levels within 6 to 8 weeks and induce clearing of radiographic infiltrates should be used to control the disease. These doses are typically higher than those needed to control symptoms alone. The recommended initial prednisone dose is 0.5 mg/kg/d for 2 weeks followed by every-other-day dosing for 6 to 12 weeks, followed by a gradual taper of 5 to 10 mg every 2 weeks over 3 to 6 months.[110] Children with CF may require higher doses and/or longer duration of treatment. Total serum IgE levels should be measured at the time of diagnosis, at 4 and 8 weeks, and every 2 months thereafter for 1 year.

Treatment with the antifungal agent itraconazole can also help control the symptoms and immunologic features and exacerbations of the disease and may enable reduction of the systemic corticosteroid dose.[131–134] Voriconazole may be a suitable alternate antifungal agent, and a single nonblind trial showed a high response rate.[135–137] In case series, the anti-IgE antibody omalizumab helped to control ABPA in steroid-dependent patients who failed itraconazole treatment.[138–141] The anti-IL5 antibody mepolizumab led to reduction in systemic glucocorticoid dose, number of disease exacerbations, and improved quality of life in a case series of 20 patients with ABPA and asthma, but it has not been studied in a controlled fashion.[100] In case reports, patients with ABPA have had positive responses to benralizumab (anti–IL-5 receptor), including one patient who did not respond to omalizumab.[103,142] Dupilumab (anti–IL-4 receptor alpha) was effective therapy in a case series of three patients, leading to reductions in systemic glucocorticoid doses, but with the notable side effect of hypereosinophilia in two of the patients.[143] Additional studies to evaluate the efficacy of biologic therapies in ABPA are ongoing. Bronchodilators and antibiotics help control bronchospasm and secondary respiratory infections. Inhaled corticosteroids alone are inadequate to treat acute episodes of ABPA, yet high doses of inhaled corticosteroids are standard treatment to control disease. Patients should be monitored with at least yearly spirometry and assessed for concurrent gastroesophageal reflux, rhinosinusitis, or environmental mold exposures.[110]

■ Eosinophilic Granulomatosis with Polyangiitis

In 1939, Rackemann and Greene reported a subgroup of patients with polyarteritis nodosa and concomitant allergic disease. The histopathology and clinical features associated with this disease entity were first described in 1951 by Churg and Strauss, who reported a form of necrotizing vasculitis in several organs associated with eosinophilic tissue inflammation and extravascular granulomas occurring in asthmatics with associated fever and peripheral hypereosinophilia (Churg–Strauss syndrome).[144] This disease entity, now termed *eosinophilic granulomatosis with polyangiitis (EGPA)*, is an uncommon systemic disease.[145–147] An overall prevalence of 10.7 to 13 cases per million inhabitants is estimated among the general population, and up to 64 cases per million persons per year is estimated among patients with a history of asthma.[148] The mean annual incidence has been estimated at 0.5 to 6.8 per million population across various countries.[148] The precise incidence of EGPA is unknown due to uncertainties regarding diagnosis and variable clinical presentation and may be higher than is generally recognized.

Clinical Features

EGPA may occur in patients of any age, but it develops most commonly in patients between the ages of 38 and 50.[75,149,150] It is rare in persons older than age 65, as well as children and adolescents. However, among affected children, it tends to follow a more aggressive clinical course.[151] There is no clear gender predominance.[148,150]

EGPA tends to follow a subacute course with symptoms ranging over months to years. Historically, three distinct clinical phases of the disease have been recognized: the prodromal phase, the eosinophilic phase, and the vasculitic phase.[152,153] The *prodromal phase* has been characterized by “late-onset” (in the second or third decade of life) allergic rhinitis and atopy in persons often lacking a family history of atopy. Severe allergic rhinitis, sinusitis, and drug sensitivity are usually present for 8 to 10 years, and up to 30 years before EGPA disease recognition. Asthma is a feature of EGPA in all cases. It typically precedes the onset of vasculitis by 3 to 6 years.[153] The *eosinophilic phase* is typified by the development of marked peripheral blood eosinophilia and eosinophilic tissue infiltration, most commonly of the lung, GI tract, and skin. The *vasculitic phase* is characterized by vasculitis of the small and medium vessels with vascular and extravascular granulomas. The onset of the vasculitic phase is often heralded by development of constitutional symptoms, including fever, malaise, weight loss, arthralgias, myalgias, and increased allergic or asthmatic symptoms. Although the vasculitis tends to occur several years after the onset of allergic manifestations of the disease, in some cases it develops within months of, or concomitant with, the onset of asthma. A short duration between the onset of asthma and vasculitis has been associated with increased severity of vasculitis. During the vasculitic stage, the asthma symptoms may persist and worsen, or they may diminish. When asthma dissipates, it often flares later in the course of illness and may require prolonged steroid treatment. Not all patients progress sequentially through these phases, and overlap of clinical features of the phases is often present. Although EGPA typically affects multiple organ systems, limited forms of disease also have been described.[148,154] Manifestations in the lungs, heart, skin, and nervous system are most common.

An association between asthma therapies and the development of EGPA has been noted, including leukotriene receptor antagonists (LTRA) and 5-lipoxygenase inhibitors, inhaled glucocorticoids, and omalizumab.[151,155–160] It is uncertain whether these steroid-sparing agents caused the development, or if EGPA was unmasked by the reduction in systemic corticosteroid dosing following initiation of these agents.

Lung involvement occurs in nearly all patients with EGPA.[148] Most of the respiratory manifestations of EGPA occur in the prodromal and eosinophilic phases of the disease. All patients have asthma at some point in the illness. Upper airway allergic disease, including sinusitis, rhinitis, and polyposis, is seen in 75% to 85% of patients and may be the presenting symptom.[75,148] Unlike granulomatosis with polyangiitis (GPA), necrotizing granulomas involving the upper airway are unusual in EGPA. The asthma and upper airway disease usually are long-standing, severe, and often require steroid therapy (systemic, inhaled, intranasal) to maintain control of symptoms.[148] Pulmonary symptoms include dyspnea, cough, and wheezing. Spirometry may reveal an obstructive ventilatory defect.[161]

Cardiac manifestations generally are not evident on initial presentation of EGPA. However, they typically occur during the vasculitic phase of the disease and are a major source of morbidity and the principal cause of death (in up to 50% of cases) from the disorder.[148,149,162] Patients may be asymptomatic. Progressive congestive heart failure (CHF) can occur because of endomyocardial infiltration by eosinophils or ischemic cardiomyopathy resulting from necrotizing vasculitis of the coronary arteries.[75,162,163] Acute pericarditis and cardiac tamponade have been reported.[164] Constrictive pericarditis may develop over time. Cardiac involvement is more common in patients with EGPA who lack serum ANCA.[165,166] Electrocardiogram, echocardiography, N-terminal pro–brain natriuretic peptide and troponin 1 levels, and/or cardiac MRI are recommended to evaluate patients with suspected EGPA for the presence of cardiac involvement.[148,167] ^{18}FDG/^{13}N ammonia positron emission tomography (PET) imaging also may be useful to identify cardiac involvement in EGPA.

A wide array of neurologic manifestations may develop in EGPA. Mono- or polyneuropathy (most notably mononeuritis multiplex) is common. The common peroneal, ulnar, and internal popliteal nerves are most frequently affected.[148] CNS manifestations occur more rarely and include cranial nerve impairment (especially optic neuritis), seizure, subarachnoid hemorrhage, and cerebral infarction. Magnetic resonance imaging may show T2-weighted signals in subcortical matter suggestive of CNS vasculitis.[148]

Skin, GI, renal, and other systemic alterations have been well described in EGPA. Skin findings are present in 40% to 70% of cases and may develop in localized crops. They can manifest as nonthrombocytopenic purpura (particularly on the lower extremities), urticaria, a maculopapular rash, petechiae, ecchymoses, or livedo reticularis. Skin biopsies typically demonstrate eosinophilic infiltration and leukocytoclastic vasculitis.[168] Tender cutaneous or subcutaneous nodules (which may ulcerate) containing extravascular granulomas may preferentially involve the fingers, scalp, and extensor surface of the elbow.[148] GI manifestations of EGPA are present in up to 60% of cases. They can include eosinophilic gastroenteritis or vasculitis that can lead to diarrhea, abdominal pain, intestinal obstruction, cholecystitis, pancreatitis, bleeding, liver function test abnormalities, and bowel perforation.[148] GI disease also carries a poor prognosis and is the second leading cause of death in patients with EGPA.[148] A degree of renal insufficiency occurs in 25% to 50% of patients with EGPA. Eosinophilic interstitial nephritis with necrotizing features is the most common histopathologic finding, but focal segmental glomerulosclerosis, hematuria, and proteinuria also occur.[149,169,170] Severe, difficult-to-control hypertension is also a major sequela of EGPA. In contrast to granulomatosis with polyangiitis, overt renal failure is not commonly seen in EGPA.[149] Mild lymphadenopathy (in 30%–40%), rheumatologic manifestations (migratory polyarthralgias, myalgias, temporal arteritis), urologic disease (ureteral, urethral, prostatic), and ocular manifestations (scleritis, uveitis, optic neuropathy, conjunctival nodules) also have been described.[148]

Mechanisms of Disease

The pathogenesis of EGPA remains poorly understood. A possible pathogenic role of antineutrophil cytoplasmic antibody (ANCA) is suggested by the finding of ANCA in 40% to 60% of patients with EGPA.[150] ANCA may contribute to tissue inflammation and injury by activation of inflammatory cells, release of proteolytic enzymes, and generation of oxidative stress; alternatively, its presence may be a consequence rather than a cause of the tissue injury.[148] The strong association with allergy, atopy, eosinophilia, and elevated blood levels of type 2 cytokines and IgE (especially during the vasculitic phase of the disease) has raised the likelihood of augmented Th2 immunity.[148,171–174] Eosinophils likely also contribute significantly to the tissue injury since blood, BAL, and urine specimens contain eosinophil-derived cytotoxic granule proteins.[148,175] Based on these collective findings, it has been proposed that repeated antigenic stimulation in patients with a heightened T-cell and eosinophil response may be important in the development of the disorder. Heightened humoral immunity with immune complex disease also may play a role. Genetic factors including polymorphisms in the IL-10 gene, HLA-DQ, and HLA-DRB107 showed associations with EGPA[176] and support findings of heightened autoimmunity in EGPA.

Diagnostic Testing

Diagnosis rests on radiographic imaging, laboratory testing, examination of pathology, and application of diagnostic criteria.

Imaging Chest radiographs have transient, migratory, patchy, nonlobar, nonsegmental, often peripheral pulmonary infiltrates, with no regional predilection.[177–179] Nodular lesions, reticular opacities, bronchial wall thickening, bronchiectasis, and hilar adenopathy are less common. Cavitary lesions are less frequent than in GPA. Pleural effusions are common and may be associated with pleuritic chest pain.[179] The chest radiograph may occasionally be normal. HRCT scanning has demonstrated bronchial wall thickening, pulmonary artery enlargement (in comparison to the corresponding bronchi), irregular stellate configuration of some vessels, adenopathy, areas of interlobular septal thickening, and scattered patchy parenchymal opacities with ground-glass, nodular, consolidated, or tree-in bud appearance.[75] Nodules may be present within areas of ground glass.[92,179,180] These findings have been reported to correlate with pathologic findings evident on open lung biopsy such as eosinophilic pneumonia, alveolar hemorrhage, eosinophilic infiltration of the bronchial wall, and septum.[178]

Laboratory Testing Most patients with EGPA have a striking, but fluctuating, degree of peripheral blood eosinophilia (mean values between 5 and 20,000/mm^3; 20%–90% of the WBC differential) at diagnosis.[75,148] The degree of eosinophilia tends to parallel the vasculitis activity and may be suppressed by corticosteroid treatment of asthma. Serum C-reactive protein levels and total IgE levels are elevated (range, 500–1000 U/mL) in 75% of patients.[75] Elevated blood levels of type 2 cytokines IL-4, IL-5, and IL-13, as well as serum IgG4, TARC/CCL17, CCL26 (eotaxin-3), and urinary eosinophil–derived neurotoxin, also correlate with disease activity but are not currently used clinically. BAL fluid from patients with active EGPA also contains increased levels of the type 2 cytokines IL-4, IL-5, and IL-10 compared with inactive EGPA.[171,181–187] Rheumatoid factor titers may be positive, but antinuclear antibodies are usually negative.[148] Hypergammaglobulinemia and circulating immune complexes may also be seen.

Approximately 40% to 60% of patients with EGPA have positive antinuclear cytoplasmic antibodies with a perinuclear staining pattern (pANCA).[165,166,188] The majority of these are directed against myeloperoxidase (MPO) and a minority against proteinase 3 (PR3). The absence of ANCA does not exclude the diagnosis. Indeed, recent case series suggest that EGPA patients with positive and negative ANCA have different clinical features.[189] Patients with positive ANCA (the "vasculitic phenotype") tend to have biopsy-proven vasculitis, purpura, ENT manifestations, peripheral neuropathy, and renal disease, but have less cardiac involvement.[165,166,190] In contrast, those with negative ANCA (the "eosinophilic tissue infiltration phenotype") manifest more commonly with fever, eosinophilic pneumonia, and eosinophilic myocarditis.[165,166,191]

Laboratory examination of pleural fluid, if present, reveals an eosinophil-predominant exudate with low glucose levels.[148] Pleural biopsy shows chronic pleuritis with eosinophilic infiltration. BAL reveals an increased percentage of eosinophils, the magnitude of which is generally less than that seen with CEP or idiopathic HES. However, patients have been described whose BAL fluid leukocyte differential contained 81% eosinophils.[192]

Pathology Open lung biopsy is the gold standard for tissue biopsy but is rarely necessary. Transbronchial biopsy may reveal the diagnosis if there is alveolar involvement but is often nondiagnostic. In addition, the blood vessels required to make the diagnosis of vasculitis are often absent from transbronchial biopsies. Biopsy of other sites (e.g., skin, pericardium, muscle, nerve, gut), more often include a blood vessel and may be more helpful in establishing a diagnosis.

Although lung biopsy is rarely required for diagnosis, the histopathologic hallmarks of EGPA vary depending on the stage of illness but include tissue (interstitial, blood vessel, and alveolar) infiltration by eosinophils, eosinophilic necrotizing giant cell vasculitis of small arteries, arterioles, and, to a lesser extent, small veins, venules, and capillaries and perivascular and interstitial eosinophilic granulomas (typically microscopic).[193–195] Both pulmonary and systemic vessels may be affected. The precise histopathology of vascular impairment depends on the stage of the lesion. Early lesions demonstrate eosinophilic infiltration of the vessels and perivascular region (Fig. 71-4). Later lesions are characterized by necrotizing arteritis or vessel obliteration and scarring. The extent of vascular impairment varies from mild, eosinophilic perivascular cuffing to severe transmural inflammation with necrotization. Lesions may be sparse or widespread. In the lung the granulomas may have central necrosis with eosinophilic inflammation, may involve interlobular septae, and may extend along the pleura. Diffuse capillaritis and alveolar hemorrhage have been reported. Eosinophilic lymphadenopathy also may be present. Biopsies of skin, nerve, or muscle may also confirm the diagnosis.[162]

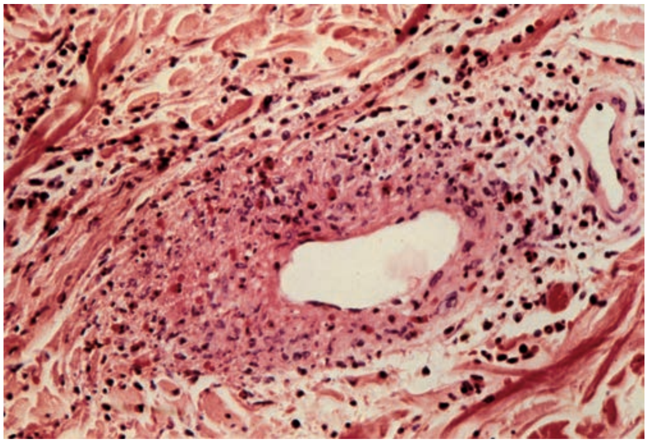

Figure 71-4 Pathologic appearance of small arteriole in eosinophilic granulomatosis and polyangiitis (EGPA). Intense perivascular inflammation with eosinophilia is present.

Diagnostic Criteria The diagnosis of EGPA is generally based on clinical features. Various diagnostic criteria have been reported.[152,195] In 1990, the American College of Rheumatology published diagnostic criteria for EGPA, based on assessments of the sensitivity and specificity of the diagnostic criteria used previously.[195] The presence of at least four of the following six criteria yielded 85% sensitivity and 99.7% specificity in establishing the diagnosis: (1) asthma, (2) peripheral eosinophilia greater than 10%, (3) mono- or polyarthropathy, (4) migratory or transient pulmonary infiltrates, (5) paranasal sinus abnormality, and (6) extravascular eosinophils in a blood vessel on a biopsy specimen. The presence of asthma or allergy as well as more than 10% eosinophilia was 95% sensitive and 99% specific in distinguishing EGPA among a subgroup of patients with well-documented systemic vasculitides. Subsequently, the Chapel Hill Consensus Conference recommended that diagnostic criteria for EGPA include (1) appropriate clinical setting and histopathology and (2) eosinophil-rich and granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small and medium vessels with associated asthma and eosinophilia.[196] However, these criteria require tissue biopsy and are less sensitive for EGPA than others that have been proposed; hence, they may be less useful to assist diagnosis in the routine clinical setting.

The differential diagnosis of EGPA includes polyarteritis nodosa, microscopic polyangiitis, granulomatosis with polyangiitis, CEP, ABPA, idiopathic HES, Loeffler syndrome, asthma, fungal or parasitic infection, drug-induced vasculitis, sarcoidosis, and Hodgkin lymphoma. EGPA can be distinguished from granulomatosis with polyangiitis since compared with the latter, patients with EGPA have nasal polyps and allergic rhinitis but lack significant necrotizing upper airway lesions and cavitation of lung nodules and are more likely to have pANCA (in contrast to the cANCA seen in granulomatosis with polyangiitis). EGPA can be distinguished from MPO-positive microscopic angiitis since patients with the latter syndrome have leukocytoclastic vasculitis without granulomas and do not have upper airway involvement, asthma, and eosinophilia. Further, unlike EGPA, cardiac involvement is rare in microscopic polyangiitis. EGPA may be difficult to distinguish from idiopathic HES among patients who lack ANCA and/or neuropathy without overt vasculitis.[197] In this setting, EGPA is the more likely diagnosis in patients with lower eosinophil counts who later develop vasculitis.

Treatment and Prognosis

Patients in whom EGPA goes untreated have a poor prognosis: up to 50% die within 3 months after the onset of vasculitis. As such, efforts at early recognition and treatment are important.

The choice of treatment depends in part on the clinical features at the time of diagnosis, since the presence of some features portends a worse prognosis and requires a more aggressive treatment approach.[198–200] The 2011 revised five-factor score can aid in assessing prognosis. A point is assigned for each of the following features: age >65 years, cardiac insufficiency, renal insufficiency (serum creatinine ≥1.7 mg/dL), gastrointestinal involvement, and absence of ENT involvement.[190,200] A score ≥2 is associated with a poor prognosis.

In patients *without* poor prognostic features, corticosteroids are the mainstay of treatment and generally lead to dramatic clinical improvement, with disease stabilization or cure. Prednisone, 1 to 1.5 mg/kg/d (or 60 mg/d in adults) is given for 3 to 12 weeks, aiming to eliminate constitutional symptoms and cardiac, renal, neurologic, or other vasculitic manifestations. Higher doses (e.g., 15 mg/kg/d methylprednisolone) are occasionally required for control of life-threatening symptoms. Severe hypertension and mononeuritis multiplex often require prolonged steroid treatment and may be difficult to eliminate. Once the vasculitic phase is controlled, corticosteroids may be tapered, with doses titrated to maintain disease control. Low-dose prednisone (e.g., 5–10 mg) is often given every day or every other day for up to 1 year. Although relapses are uncommon, patients should be followed closely for evidence of clinical deterioration and should have periodic screening of total WBC and differential, ESR, and IgE levels. Most reports suggest the pANCA is not useful to monitor disease activity or direct therapeutic intervention, but one case series demonstrated that patients with ANCA-positive EGPA had more frequent relapses and lower 5-year relapse-free survival rates than ANCA-negative patients.[190]

Patients who have poor prognostic features at the time of disease presentation, or who have severe systemic involvement should receive high-dose intravenous methylprednisolone or oral prednisone for 3 days plus induction therapy with cyclophosphamide.[148,201,202] Patients treated with cyclophosphamide should be monitored closely for hemorrhagic cystitis, renal insufficiency, bone marrow suppression, bladder fibrosis, and urologic malignancies. Patients with severe disease treated with corticosteroids and cyclophosphamide have better survival than those treated with corticosteroids alone.[203] Azathioprine maintenance therapy (2 mg/kg/d) for 18 to 24 months may be beneficial once remission of disease has been achieved.[148,149,198] Methotrexate has been used along with glucocorticoids for induction and maintenance of therapy but is associated with a high relapse rate.[204]

Anti–IL-5 pathway agents are also effective in the treatment of EGPA. Compared to corticosteroids, they have fewer side-effects and require less frequent dosing. In a multicenter randomized control trial, the anti–IL-5 monoclonal antibody mepolizumab (300 mg every 4 weeks) led to more accrued weeks of remission, reduction in glucocorticoid dosing, and a lower relapse rate.[205] As a result, mepolizumab was FDA approved for use in EGPA.[206] The anti–IL-5 antibody reslizumab (3 mg/kg every 4 weeks) was associated with glucocorticoid reduction and improved symptoms in a cohort of 9 patients with EGPA.[207] In a series of five patients with EGPA the anti–IL-5 receptor α antibody benralizumab was associated with a reduction in glucocorticoid dose and improvement in patient reported outcomes.[208]

Intravenous immunoglobulin (IVIg) may be beneficial for use in pregnant women and for reducing symptoms and organ involvement and improving long-term disease control among persons with severe organ involvement in EGPA.[209] The immunoregulatory cytokine interferon α (IFN-α) has led to improved pulmonary function tests, reduction in corticosteroid dose, and decreased WBC count and may be considered as an alternative treatment in patients with refractory disease but may be of limited efficacy and can cause cardiac toxicity.[210] Plasma exchange may also be a successful adjunct treatment in some patients, particularly those with ANCA positivity and glomerulonephritis.[148,211] Rituximab may be effective as an alternate therapeutic agent, but further studies are needed to clarify benefits of treatment in EGPA as compared with other forms of ANCA-positive vasculitis.[212] Patients on prolonged courses of higher doses of glucocorticoids and other immunosuppressive agents should receive prophylaxis for *Pneumocystis jirovecii*.

Prolonged treatment may be necessary to maintain disease control. Long-term overall remission can be achieved in approximately 81% to 92% of patients; relapses occur in 25% of cases and are most common within 1 year.[148,162] In a series of 30 patients collected over the period 1950 to 1974, a median survival of more than 9 years was reported in patients treated with steroids; 1-year survival was 90%, 3-year survival was 76%, and 62% survival was noted at 5 years. More recent studies suggest 85% to 100% survival at 5 years.[75,190,202]

■ Hypereosinophilic Syndrome

Hypereosinophilic syndrome (HES) is a rare disorder first described in 1968 by Hardy and Anderson. In 1975, Chusid et al. revised the definition of HES to include only cases in which no other underlying cause of hypereosinophilia could be found.[213] HES is now recognized as a clinically heterogeneous syndrome with a wide range of disease severity. HES likely represents several diseases of distinct etiology that share common features.[214–216] Three appear to be most common.

The *myeloproliferative variant* (primary/neoplastic HES): In this variant there is clonal expansion of eosinophils related to stem cell, myeloid, or eosinophil neoplasms. Clinical features include anemia, thrombocytopenia, hepatosplenomegaly, elevated leukocyte alkaline phosphatase, circulating immature leukocytes, and elevated B_{12} levels.[217] The most common chromosomal abnormality noted is deletion on 4q12, leading to fusion of genes for and constitutive activation of the tyrosine kinase fusion protein FIP1L1-PDGFRA.[218] Other chromosomal abnormalities also have been reported.

The *lymphocytic variant* (secondary, reactive HES, ~30% of cases): This variant is related to clonal expansion of Th2 T cells with an abnormal surface antigen phenotype (CD3−/CD4+) and increased production of IL-5.[219,220] Increased amounts of IL-4, IL-13, GMCSF, and hypergammaglobulinemia may be present.[221] Skin and soft tissue involvement are the predominant clinical features of this variant.

The *idiopathic variant* (~50% of cases): The disturbances present in the previously noted variants are lacking, but end-organ damage is present.[216]

Clinical Presentation

HES is a rare disorder. Although persons of any age may be affected, disease onset is most common between 20 and 50 years of age.[222,223] Men are more frequently affected than women (9:1).[222] When it occurs in children, it often heralds a clonal hematologic disturbance.[223] There is no known racial or ethnic predisposition. Familial cases with autosomal dominant transmission have been reported.

Clinical features and symptoms vary according to the organ system(s) affected. Presenting complaints are often nonspecific and include weakness, fatigue, low-grade fevers, myalgias, cough, angioedema, rash, retinal lesions, and dyspnea. Involvement of virtually every organ system has been described. The respiratory system is affected in an estimated 63% of patients with HES.[224] The most common symptoms include a predominantly nocturnal cough, which is either nonproductive or productive of small quantities of sputum, wheezing, and dyspnea. In general, respiratory manifestations are mild.[224] Pulmonary hypertension, ARDS, and pleural effusions (which may be due to CHF) have been reported but are rare. In patients with pulmonary manifestations, the chest radiograph or CT may reveal transient focal consolidation, ground-glass opacities, or diffuse pulmonary infiltrates (with no predilection for any particular distribution), small nodules, pleural effusion(s), adenopathy, or pulmonary emboli.[213,224]

Cardiac disease is the major cause of morbidity and mortality in patients with HES.[222,225] The most common cardiac manifestations are progressive CHF due to eosinophilic myocarditis and endocarditis, intracardiac thrombi, and endocardial fibrosis.[222] Cardiac involvement in HES, which may be clinically silent, is believed to progress from an initial acute necrosis stage, followed by endocardial thrombus formation and eventually development of fibrosis, which may lead to restrictive cardiomyopathy or valvular dysfunction such as mitral regurgitation.[222] Intracardiac thrombus formation can lead to ischemic embolic events. The cardiac damage is believed to be mediated at least in part by eosinophil-derived granular protein (EDGP). Elevation in serum troponin can provide a clue to the presence of cardiac involvement in HES.[226] Cardiac involvement correlates poorly with the peripheral blood eosinophilia; hence echocardiographic follow-up at 6-month intervals is recommended. Cardiac MRI also detects eosinophil-mediated cardiac injury or intracardiac thrombus.[227]

Involvement of the central or peripheral nervous system, which occurs in up to 60% of patients, also is a major cause of morbidity.[228] Neurologic manifestations of HES include encephalopathy with neuropsychiatric dysfunction, memory loss, gait disturbances with or without signs of upper motor neuron injury, visual changes, and sequelae of thromboembolic events, including hemiparesis. Peripheral neuropathy with sensory and/or motor axonal loss (no vasculitic or eosinophilic infiltration) is extremely common in HES.

The bone marrow is universally affected in HES, and eosinophils make up to 25%–75% of the differential. Other hematologic manifestations are venous and arterial thromboembolism, anemia, thrombocytopenia, elevated vitamin B_{12} levels, hepatosplenomegaly, and lymphadenopathy (in 12%–20%).[229]

Cutaneous manifestations may include eczema, urticaria, angioedema, nodular or papular lesions, skin thickening, erythroderma, or dermatographia.[222,230] Mucosal ulcerations may develop. As noted, cutaneous manifestations are more likely seen among patients with the lymphocyte HES variant.[220] Patients with papules are likely to have the FIP1L1-PDGFRA variant.[231] GI (20%–30% of patients), renal (10%–20%), musculoskeletal, ocular, and endocrine manifestations also are all well described.

The organ damage in HES is believed to be due to both eosinophilic infiltration of tissues and tissue injury caused by thromboembolic events.[232,233] Eosinophils probably contribute to tissue damage via antibody-mediated cytotoxicity and the release of toxic granule products such as major basic protein and eosinophil cationic protein. The precise events inciting the extreme eosinophilia in HES are unknown, but several mechanisms have been proposed, including overproduction or abnormal activity of cytokines leading to eosinophilia, and defects in cytokine signaling or signal transduction.

Diagnostic Testing

Diagnostic methods in the evaluation of suspected HES are discussed below.

Laboratory Testing Findings associated with HES include peripheral blood eosinophilia $>1.5 \times 10^9$/L,[212] elevated total serum IgE (25%–38%), hypergammaglobulinemia, circulating immune complexes (32%–50%), and ESR above 15 mm/h (68%).[213] Anemia and elevated serum B_{12} and leukocyte alkaline phosphatase are present in the myeloproliferative variant.[234] Fungal and parasitic serologies, as well as analysis of body fluids for ova and parasites, are negative. Blood and BAL eosinophilia are both prominent in patients with pulmonary involvement.

Pathology Histopathologic examination of affected lung specimens most commonly reveals intense interstitial infiltration with eosinophils. Less commonly, necrotic areas of parenchyma are found. These are believed to be due to pulmonary microemboli. In contrast to EGPA, significant vasculitis is not present.

Diagnostic Criteria Current consensus defines hypereosinophilia as blood eosinophils $>1.5 \times 10^9$/L on two examinations separated by ≥1 month and/or tissue eosinophilia (defined as >20% of cells in a bone marrow specimen, tissue infiltration defined by a pathologist, and/or marked deposition of EDGP in tissue).[235] The term *HES* is defined as the presence of hypereosinophilia together with eosinophilic tissue infiltration and organ damage. Other causes of hypereosinophilia and organ damage should be excluded. Occasionally, the disease presents with the incidental finding of blood eosinophilia before development of other complications. The total peripheral leukocyte count is typically elevated to above 10,000 (typical range, 10,000 to 30,000), with a preponderance of eosinophils (up to 70%). The leukocytosis may be progressive. Tests recommended to assess for end-organ damage also include serum chemistries, liver function tests, CPK, troponin, ECG, echocardiogram, chest x-ray and/or CT, pulmonary function tests, abdominal CT scan, and tissue biopsy as indicated. Serum tryptase, vitamin $B_{12,}$ and Ig levels also may support the diagnosis.[236] In addition, patients with suspected HES should undergo bone marrow aspirate and biopsy, FIP1L1-PDGFRA mutation analysis, and T lymphocyte phenotyping by flow cytometry or karyotype analysis to evaluate for the HES subtypes noted earlier. Proper diagnosis of the HES subtypes has implications for choosing therapy for the disease.

The differential diagnosis of HES includes parasitic infection, acute eosinophilic leukemia, drug-induced hypersensitivity, EGPA, episodic angioedema with eosinophilia, tuberculous or fungal infection, allergic or autoimmune disease, other acute or CEPs, TPE, other lymphoproliferative disorders, and paraneoplastic syndromes (Table 71-5). Patients with eosinophilic leukemia have immature eosinophils or blasts in the bone marrow and/or blood, whereas patients with HES typically do not. Patients with HES do not have asthma or vasculitis characteristically associated with EGPA, and patients with episodic angioedema typically lack the multiorgan involvement associated with HES.

Treatment and Prognosis

Before the discovery of an effective therapy, the prognosis of HES was poor. In one early series, 81% of 48 patients died within 1 year of diagnosis. Overall, without therapy, average survival was 9 months, and 3- to 4-year survival was estimated at 10% to 12%.[213] The greatest mortality occurs within the first year after diagnosis. Death may occur from refractory CHF, azotemia, hepatic failure, venous thromboembolism, a perforated abdominal viscus, or infection. Patients with the myeloproliferative variant of HES (especially those with FIP1L1-PDGFRA-positive disease) tend to have an aggressive course with high mortality without treatment. The advent of effective therapy for HES has led to a marked improvement in median survival to more than 10 years.

Favorable prognostic features include a rapid clinical response to treatment with reduction in blood eosinophilia, the presence of angioedema, elevated IgE, and absence of findings associated with myeloproliferative disorder.[222,236–238] Factors associated with a poor prognosis in HES include presence of total blood WBC greater than 100,000/mm^3, myeloblasts in the peripheral blood, refractory CHF, basophilia above 3%, identifiable chromosomal abnormalities in bone marrow cells, and elevated serum B_{12}.[222,239]

Patients with the incidental finding of peripheral eosinophilia but without evidence of end-organ dysfunction can be followed closely at 3- to 6-month intervals without specific treatment, as they tend to follow a benign course. Patients should be monitored routinely at 6-month intervals with chemistries, ECG, echocardiogram, and pulmonary function tests as well as monitored for clinical signs of thrombotic complications. Additional monitoring and testing should be done as indicated depending on symptoms and other known organ involvement.

In patients presenting with life-threatening manifestations, including eosinophilia $>100 \times 10^9$/L, signs of cardiac or neurologic involvement, or thromboembolism, glucocorticoids should be initiated while awaiting the results of the initial evaluation. Those

TABLE 71-5 Comparative Features of the Pulmonary Eosinophilic Syndromes

	Loeffler	TPE	AEP	CEP	ABPA	EGPA	HES
Clinical course	Acute	Acute, subacute, chronic	Acute	Subacute	Acute, subacute, chronic	Acute, subacute, chronic	Subacute, chronic
Respiratory symptoms	Self-limited, mild	Severe	Severe	Mod-severe	Mod-severe	Mod-severe	Mild
Hx allergic disease/ asthma	—	—	±	+ (30%–60%)	Nearly 100%	100%	—
Blood eosinophilia	Mod to very high, but transient	Very high	May be absent (delayed)	Moderate in most	Typical	Very high, fluctuates	Extremely high, persistent
Sputum/BAL eosinophilia	+	+	++	++	±	+	++
Elevated serum IgE	Normal or elevated	High	Mod in some	Mod–high in 50%	Very high, fluctuates w/disease	Mod–high	Mod–high in some
Etiologic agent	*Ascaris, Ancylostoma*, *Necator, Strongyloides*, etc.	Filarial infection	Cigarette smoke, other inhaled exposures, unknown	Unknown	*Aspergillus* (or other fungus)	Unknown	Unknown
Radiographic findings (CXR, CT)	Patchy, often peripheral unilateral or bilateral consolidation and GGO; usually transient, migratory, nonsegmental	Diffuse, reticulonodular	Diffuse, alveolar and interstitial GGO and airspace opacities, interlobular septal thickening, pleural effusion	Predominantly, peripheral consolidation and GGO; "photographic negative of pulmonary edema"	Tram-track opacities, finger-in-glove opacities, fleeting opacities, bronchiectasis, and fibrosis	Transient, migratory peripheral, rarely diffuse; patchy peribronchial and septal thickening, patchy parenchymal GGO or consolidation, pleural effusion	Transient, focal or diffuse GGO or consolidation
PFTs	± Mild RVD	OVD early, RVD late, or mixed pattern	RVD	Normal, OVD, or RVD	OVD ± RVD	OVD ± RVD	Mild RVD in some
Characteristic diagnostic findings	Parasite larvae in sputum, BAL, gastric aspirate	Filaria-specific IgE, IgG, microfilaria in LN/lung	>25% eosinophils in BAL	None	See Table 71-4	Histopathology showing eosinophilic vasculitis plus appropriate clinical setting	Extreme, persistent eosinophilia and multiorgan dysfunction (no other cause)
Vasculitis	None	None	None	Occasionally mild, nonnecrotic	None	Characteristic (see text)	None
Extrapulmonary manifestations	GI late, if untreated	Cardiac, CNS rare	None	Very rarely reported	None	Typical of vasculitic phase	Cardiac, neurologic, GI, hematologic, other
Therapy	Mebendazole, if *Ascaris* or hookworm	Diethylcarbamazine	Stop exposure, corticosteroids	Corticosteroids	Corticosteroids, bronchodilators, antifungals, others (see text)	Corticosteroids, anti–IL-5 antibodies, other immunosuppressives (see text)	Depends on disease variant (see text)
Chronic/recurrent disease	None	Relapses may occur	None	Common	Typical	May occur (∼25%)	Chronicity typical

+, yes or present;—, no or not present; BAL, bronchoalveolar lavage; CT, computed tomography; GGO, ground-glass opacity; GI, gastrointestinal; Hx, history of; LN, lymph node; mod, moderately; OVD, obstructive ventilatory defect; CXR, chest x-ray (radiograph); PFTs, pulmonary function tests; RVD, restrictive ventilatory defect.

with possible exposure to *Strongyloides* should receive concomitant ivermectin. Doses ranging from 1 mg/kg/day of prednisone to 1 g of methylprednisolone may be used depending on the severity of illness.[239]

The tyrosine kinase inhibitor imatinib mesylate (initial dose 400 mg/d) is the first-line therapy for all patients with the PDGFRA-positive variant of HES.[215,218,240,241] Patients with cardiac involvement should receive concomitant systemic corticosteroid therapy to avoid further cardiac damage that might be induced by imatinib.[242] Case reports have suggested that other tyrosine kinase inhibitors, nilotinib and sorafenib, can be effective alternate therapies in cases of resistance to imatinib therapy.[243,244]

A mainstay of therapy for patients with HES and organ involvement who lack FIP1L1-PDGFRA fusion or other imatinib-responsive mutations includes glucocorticoids such as prednisone at 1 mg/kg/d for several weeks. If the disease stabilizes or resolves (e.g., if blood eosinophilia and symptoms are controlled), steroids can be tapered gradually to alternate-day dosing and should be continued for approximately 1 year at the minimal dose that effectively controls disease activity.[215]

Mepolizumab (300 mg every 4 weeks), an anti-IL-5 monoclonal antibody was associated with reduction in the number of flares of FIP1L1-PDGFRA-negative HES in a phase 3, multicenter, randomized, controlled trial.[100] An earlier study showed reduction in glucocorticoid dosing without increase in disease activity in FIP1L1-PDGFRA-negative HES patients receiving 750 mg of mepolizumab.[245] Mepolizumab (300 mg) is now approved by the FDA for treatment of HES ≥6 months of duration without an identifiable cause.[206] In a small phase 2 trial, benralizumab (30 mg every 4 weeks), an anti–IL-5 receptor α monoclonal antibody, was associated with a reduction in absolute eosinophil count in PDGFRA-negative HES.[246]

IFN-α and hydroxyurea were used more often prior to the approval of IL-5 pathway biologics, and are less likely to be needed, at least as monotherapy, in patients who can receive those agents. IFN-α, a mediator that suppresses eosinophil function in vitro, has been beneficial in management of HES, perhaps by inhibiting eosinophil proliferation and differentiation. IFN-α can be tried as a second-line agent in patients with HES or as a steroid-sparing agent.[215] IFN-α monotherapy should be avoided among patients with lymphocyte-variant disease.[247] Pegylated interferon may be an effective alternate therapy in selected cases.[248] Hydroxyurea (0.5–1.5 g per day) may be added to the regimen if there is evidence of further disease progression or steroid toxicity, with the aim of reducing the peripheral leukocyte count to the range of 5000 to 10,000.[215]

Vincristine may be used as a chemotherapeutic inducing agent in patients with extremely high peripheral WBC counts.[216] The JAK inhibitors tofacitinib and ruxolitinib have been used successfully in a small case series of lymphoid or idiopathic HES with cutaneous involvement.[249] Case reports have also demonstrated efficacy of the anti–CD-52 antibody alemtuzumab, which targets eosinophils and T cells in the lymphocyte variant of HES.[250–252]

Allogeneic bone marrow transplantation has also been reported anecdotally to be successful in selected severe cases of HES in which end-organ damage is potentially reversible.[253] Anticoagulation with warfarin and/or antiplatelet agents may be needed for management of thromboembolic events.[225]

DRUG- AND TOXIN-INDUCED EOSINOPHILIC PNEUMONIA

A vast number of drugs and toxic exposures have been associated with the development of pulmonary eosinophilia, most commonly leading to eosinophilic pneumonia, making this a very common cause of eosinophilic pneumonia.[54,254–257] Drug- and toxin-induced eosinophilic lung disease is a heterogeneous syndrome and may be classified as acute eosinophilic pneumonia or chronic eosinophilic pneumonia. When associated with rash, fever, and other systemic symptoms it is called *drug reaction with eosinophilia and systemic symptoms (DRESS)*. A partial list of drugs that have been associated with eosinophilic pneumonia is given in Table 71-6, and information regarding pulmonary drug toxicities may also be found online at *www.pneumotox.com*. Of the medications implicated, many are commonly used antibiotics, nonsteroidal anti-inflammatory agents, anticonvulsants, cardiovascular medications, and antidepressants. In addition to medications, a number of toxic exposures also may be associated with eosinophilic pneumonia.[257] For example, eosinophilic pneumonia has been described following radiation therapy for breast and lung cancer,[257–259] after exposure to iodinated contrast agents or 1,1,1-trichloroethane (Scotchgard),[260] and after inhalation of cocaine or heroin.[59,261] Nicotine- and vaping-induced AEP have been described above.

TABLE 71-6 Drugs That Cause Eosinophilic Pneumonia

Drug Class	Specific Drug
Angiotensin-converting enzyme inhibitor	Captopril, perindopril
Antidepressant	Fluoxetine, imipramine, venlafaxine
Antiepileptic	Carbamazepine, levetiracetam, phenytoin, valproic acid
Antimicrobial	Azithromycin, chloroquine, dapsone, daptomycin, ethambutol, minocycline, nitrofurantoin, penicillins, pyrimethamine, sulfonamides
Anti-inflammatory	Acetaminophen, gold salts, infliximab, montelukast, mesalamine, methotrexate, NSAIDs (acetylsalicylic acid, ibuprofen, indomethacin, naproxen), tacrolimus, zafirlukast
Chemotherapeutic	Bleomycin, fludarabine, gemcitabine
Other	Amiodarone, cannabinoids, cocaine, heroin, iodine contrast, L-tryptophan, propylthiouracil, simvastatin, tobacco smoke

Data collected from pneumotox.com[256] and references 254, 255, and 257.

Whereas most cases of drug- or toxin-induced pulmonary eosinophilia are sporadic, outbreaks of pulmonary eosinophilia have occurred following ingestion of rapeseed oil (contaminated with aniline derivatives)[262] or L-tryptophan.[263] The precise incidence of drug- or toxin-induced pulmonary eosinophilia is difficult to assess, since most of the literature pertaining to these syndromes is published in the form of case reports, rather than large series or controlled trials. For the same reason, the precise pathogenesis and the definition of the clinical syndromes associated with individual exposures are difficult to characterize.

■ Clinical Features

A diagnosis of drug- or toxin-induced eosinophilic pneumonia is based upon a careful history and review of medications and other drugs and exposures (including nonprescription drugs, herbal preparations, street drugs, and environmental exposures). Other causes of eosinophilic lung disease must be excluded. A concurrent skin rash and pleural effusion can support the diagnosis of drug-induced eosinophilic pneumonia.

In general, drug-induced pulmonary eosinophilic syndromes have an acute or subacute onset and are not always related to either

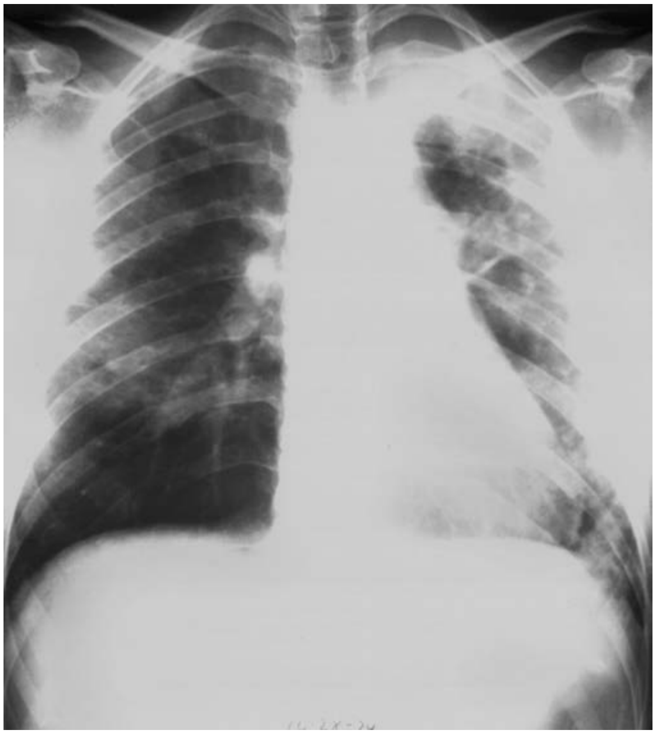

Figure 71-5 Chest radiograph of a 23-year-old woman with acute sulfasalazine-induced eosinophilic pneumonia. Bilateral interstitial and alveolar infiltrates are present.

the cumulative dose of the drug or the duration of treatment. Respiratory symptoms vary widely in severity, from a mild illness with dyspnea, cough, wheezing, and fever to severe fulminant respiratory failure. The DRESS syndrome consists of acute eosinophilic pneumonia with drug rash and systemic manifestations.[264]

■ Diagnostic Testing

In general, laboratory testing does not help to establish the diagnosis. Peripheral blood eosinophilia may be present but does not exclude the diagnosis of drug- or toxin-induced eosinophilic pneumonia.[255] The most common radiographic findings were bilateral airspace consolidations and ground-glass opacities in an asymmetric and peripheral distribution (Fig. 71-5). In half of the cases, the infiltrates involved mainly the upper lobes.[265] Multiple, small nodules in a centrilobular distribution and interlobular septal thickening also were observed.[265]

■ Diagnostic Criteria

Diagnostic criteria include the following: (1) acute or chronic eosinophilic pneumonia by diagnostic criteria (eosinophilia on lung biopsy or in BAL fluid (typically >25%) in the setting of parenchymal infiltrates; (2) a potential candidate drug or toxin in an appropriate time frame; (3) exclusion of other causes of eosinophilic pneumonia, such as infection; (4) clinical improvement after cessation of the drug or toxin; and (5) recurrence with re-challenge to the drug or toxin. (Although, in practice, clinical improvement after cessation of a suspected agent is usually sufficient to complete the diagnosis without the need for re-challenge.)

■ Treatment and Prognosis

The prognosis is favorable in most cases. Elimination of exposure to the drug or other toxin usually leads to resolution of symptoms, eosinophilia, pulmonary infiltrates, and normalization of lung function within a month. Supplemental therapy with corticosteroids is not universally required, but it may hasten recovery in patients who are severely ill.[255]

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CHAPTER 72

Pulmonary Arterial Hypertension

Nick H. Kim
Jess Mandel
Kimberly A. Smith
Jason X.-J. Yuan

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a progressive disease of the pulmonary vasculature that results in right heart failure and excess morbidity and mortality without effective treatment. Although rapid progress has resulted in the availability of therapies that can improve the outlook for many patients, true full reversal of disease remains elusive. Furthermore, long delays in disease recognition are common, exposing patients to prolonged suffering and potentially irreversible harm. PAH should not be confused with other mechanisms leading to elevation of pulmonary arterial pressure, such as hypoxemic lung disorders (e.g., chronic obstructive pulmonary disease [COPD], interstitial lung disease [ILD]), left heart disease (e.g., systolic, diastolic, or valvular dysfunctions), or chronic thromboembolism.[1,2] Prompt and accurate diagnosis of PAH followed by treatment based on the latest evidence-based guidelines are essential in successfully managing PAH.

CLASSIFICATION OF THE PULMONARY HYPERTENSIVE DISEASES

A "sclerosis of the pulmonary arteries" ("Uber Sklerose der Lungen Arterie") without identifiable cause was first described by Ernst von Romberg in 1891.[3] Exclusively descriptive reports of pathologic findings continued until the 1950s when the development of catheterization techniques allowed for hemodynamic evaluation. Using such methods, Dresdale et al. described a hypertensive vasculopathy of the pulmonary circulation involving vasoconstriction, elevation of pulmonary arterial pressure (PAP), and a measurable response to the injection of the nonselective α-adrenergic antagonist tolazoline.[4] No cause could be identified for the pulmonary arteriopathy, and the term *primary pulmonary hypertension (PPH)* was introduced.[5]

Subsequent classification schemes for diseases causing pulmonary hypertension have been adopted by international consensus panels. These have evolved from systems based primarily on histopathologic findings to a current model that emphasizes the grouping of entities according to similarities in etiology and clinical characteristics (Table 72-1).[6]

TABLE 72-1 Updated Classification of Pulmonary Hypertension[a]

1.	Pulmonary arterial hypertension	
	1.1	Idiopathic PAH
	1.2	Heritable PAH
	1.3	Drug and toxin induced
	1.4	Associated with:
	1.4.1	Connective tissue disease
	1.4.2	HIV infection
	1.4.3	Portal hypertension
	1.4.4	Congenital heart diseases
	1.4.5	Schistosomiasis
	1.5	PAH long-term responders to calcium channel blockers
	1.6	PAH with overt features of venous/capillaries (PVOD/PCH) involvement
	1.7	Persistent PH of the newborn syndrome
2.	Pulmonary hypertension due to left heart disease	
	2.1	PH due to heart failure with preserved LVEF
	2.2	PH due to heart failure with reduced LVEF
	2.3	Valvular heart disease
	2.4	Congenital/acquired cardiovascular conditions leading to postcapillary PH
3.	Pulmonary hypertension due to lung diseases and/or hypoxia	
	3.1	Obstructive pulmonary disease
	3.2	Restrictive lung disease
	3.3	Other pulmonary diseases with mixed restrictive and obstructive pattern
	3.4	Hypoxia without lung disease
	3.5	Developmental lung disorders
4.	PH due to pulmonary artery obstructions	
	4.1	Chronic thromboembolic PH
	4.2	Other pulmonary artery obstructions
	4.2.1	Sarcoma (high or intermediate grade) or angiosarcoma
	4.2.2	Other malignant tumors (e.g., renal carcinoma, uterine carcinoma, germ cell tumors of the testis)
	4.2.3	Non-malignant tumors (e.g., uterine leiomyoma)
	4.2.4	Arteritis without connective tissue disease
	4.2.5	Congenital pulmonary artery stenoses
	4.2.6	Parasites (e.g., hydatidosis)
5.	PH with unclear and/or multifactorial mechanisms	
	5.1	Hematologic disorders (e.g., chronic hemolytic anemia, myeloproliferative disorders)
	5.2	Systemic and metabolic disorders (e.g., sarcoidosis, pulmonary Langerhans cell histiocytosis, Gaucher disease, glycogen storage diseases, neurofibromatosis)
	5.3	Others (e.g., chronic renal failure with or without hemodialysis, fibrosing mediastinitis)
	5.4	Complex congenital heart disease

[a] *6th WSPH Nice 2018.*

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It is important to note the specific nomenclature purposefully adopted in the current classification scheme. The group of patients with PAH is identified as distinct from those patients with other causes of pulmonary hypertension (e.g., due to chronic left heart or respiratory disease). This grouping recognizes similarities in the histologic and many clinical features of patients with identifiable genetic causes of PAH (i.e., those with heritable PAH), those with collagen vascular or other diseases known to be associated with PAH (associated PAH), and patients in whom no known associated entity or genetic cause has been found. This last group is referred to as having *idiopathic PAH (IPAH)*. IPAH replaces the previously (and often loosely) applied term "PPH." Abandonment of the term "primary" also is important as a means of discouraging the use of the confusing and clinically inappropriate term "secondary" pulmonary hypertension. Use of such "primary" and "secondary" groupings may inappropriately suggest clinical similarities among the many very different conditions previously referred to as "secondary" pulmonary hypertension (e.g., patients with COPD and those with congenital heart disease). It may also promote a failure to recognize important similarities in clinical features (including appropriate treatment) between what was previously called "primary" pulmonary hypertension and entities inappropriately labelled "secondary" (e.g., patients with Eisenmenger syndrome or HIV infection).

DETERMINANTS OF PULMONARY ARTERY PRESSURE AND PULMONARY VASCULAR RESISTANCE

The pulmonary circulation normally is a high-flow, low-resistance, low-pressure system that carries blood into the pulmonary microcirculation where the blood takes up oxygen and unloads excess carbon dioxide. PAP is the product of cardiac output (CO) and pulmonary vascular resistance (PVR) as shown in Equation 1 (Eq. 1), where PVR is the vascular resistance of the entire lung, including the pulmonary arteries, capillaries, and veins.

$$\mathrm{PAP} = \mathrm{CO} \times [\mathrm{PVR}_{\text{arteries}} + \mathrm{PVR}_{\text{capillaries}} + \mathrm{PVR}_{\text{veins}}] \qquad \text{(Eq. 1)}$$

From this equation, it is clear that PAP can be raised by an increase in CO or an increase in arterial, capillary, or venous resistance. It would be expected then, that during periods of increased CO, such as during strenuous exercise, there would be a significant increase in PAP. However, in a normal healthy individual, the PAP is only slightly increased during periods of increased CO due to the compensatory increase in the cross-sectional area of the pulmonary vascular bed (due to recruitment of previously unperfused vessels and distension of vessels) resulting in a decreased PVR.[7] Arterial distension and optimal recruitment are dependent upon the compliance of the blood vessel walls. Loss of this compliance and recruitability due to vascular remodeling leads to pulmonary hypertension. As demonstrated in Eq. 1, an increase in PVR of any of the three components of the pulmonary vasculature can lead to an increase in PAP.[8]

Eq. 1 demonstrates the physical laws that govern blood flow in the lungs. To further understand and use this equation, it is important to understand its physical and anatomic foundations. When a liquid (e.g., blood) flows through a cylindrical tubular structure (e.g., a blood vessel), the resistance (e.g., PVR) is inversely proportional to the fourth power of the radius of the lumen of the tube. This is demonstrated by the Poiseuille equation (Eq. 2), where L is the length of the tube (or vessel), r is the inner radius of the tube, and η is the coefficient of viscosity of the liquid (blood). Therefore, even small changes in the radius of a vessel can significantly change the PVR.[8]

$$\mathrm{PVR} = (8L\eta)/(\pi r^4) \qquad \text{(Eq. 2)}$$

PULMONARY VASCULAR STRUCTURAL AND FUNCTIONAL CHANGES IN PULMONARY HYPERTENSION

Regardless of the initial genetic or pathogenic trigger, the increased PVR seen in pulmonary hypertension can be attributed to the collective effects of sustained vasoconstriction, vascular remodeling, in situ thrombosis, and increased arterial wall stiffness (Fig. 72-1).[8–13]

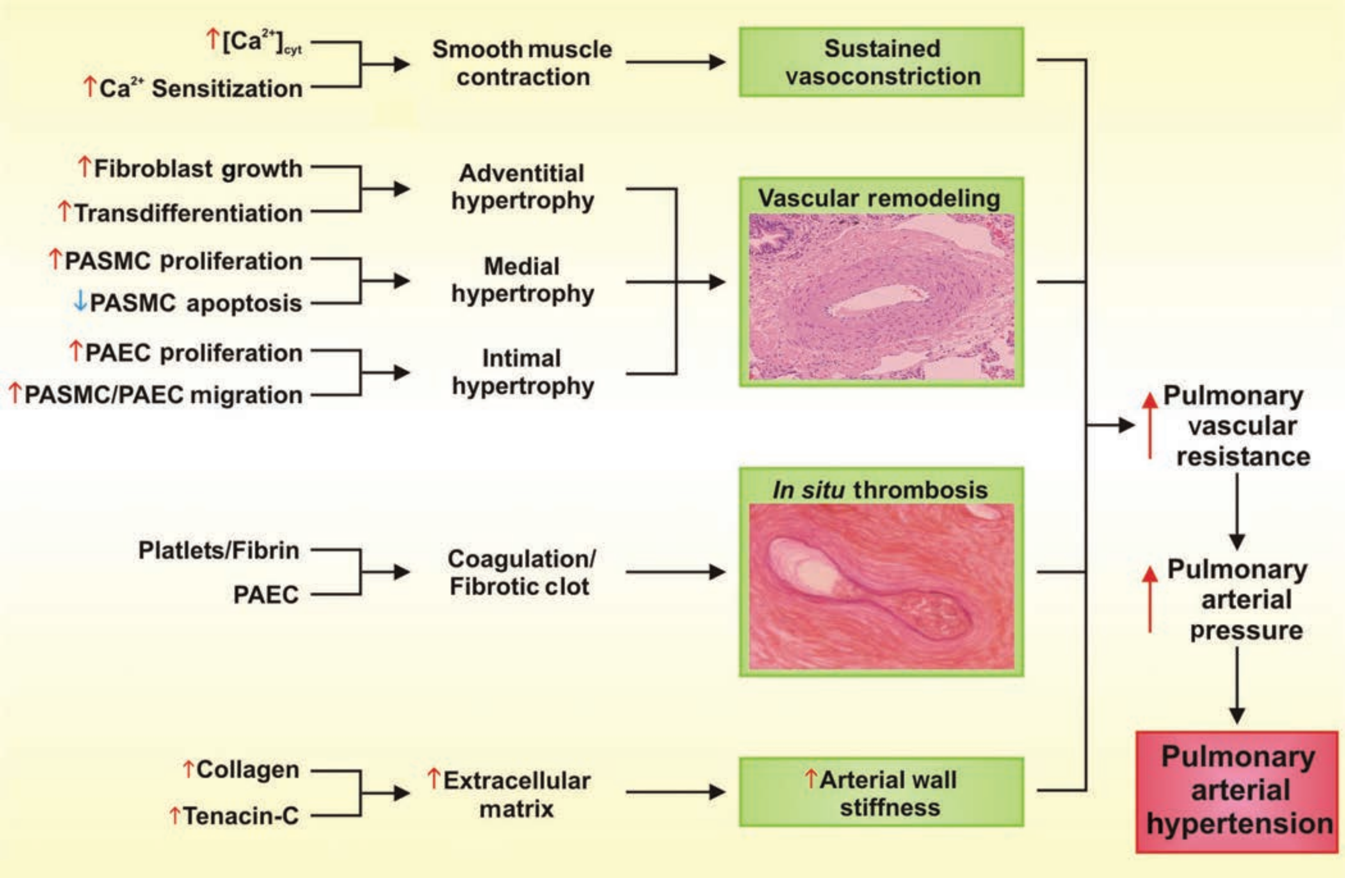

↑[Ca²⁺]cyt
↑Ca²⁺ Sensitization
Smooth muscle contraction
Sustained vasoconstriction
↑Fibroblast growth
↑Transdifferentiation
Adventitial hypertrophy
↑PASMC proliferation
↓PASMC apoptosis
Medial hypertrophy
↑PAEC proliferation
↑PASMC/PAEC migration
Intimal hypertrophy
Vascular remodeling
↑Pulmonary vascular resistance
In situ thrombosis
Platelets/Fibrin
PAEC
Coagulation/ Fibrotic clot
↑Pulmonary arterial pressure
↑Collagen
↑Tenacin-C
↑Extracellular matrix
↑Arterial wall stiffness
Pulmonary arterial hypertension

Figure 72-1 Schematic illustration of pathophysiologic components contributing to the development of increased pulmonary vascular resistance, pulmonary arterial pressure, and pulmonary arterial hypertension. *(In situ thrombosis figure reproduced with permission from Zwicke D. PAH and pregnancy: physiological changes, challenges, and outcomes. Adv Pulm Hypertens. 2011;10(3).)*

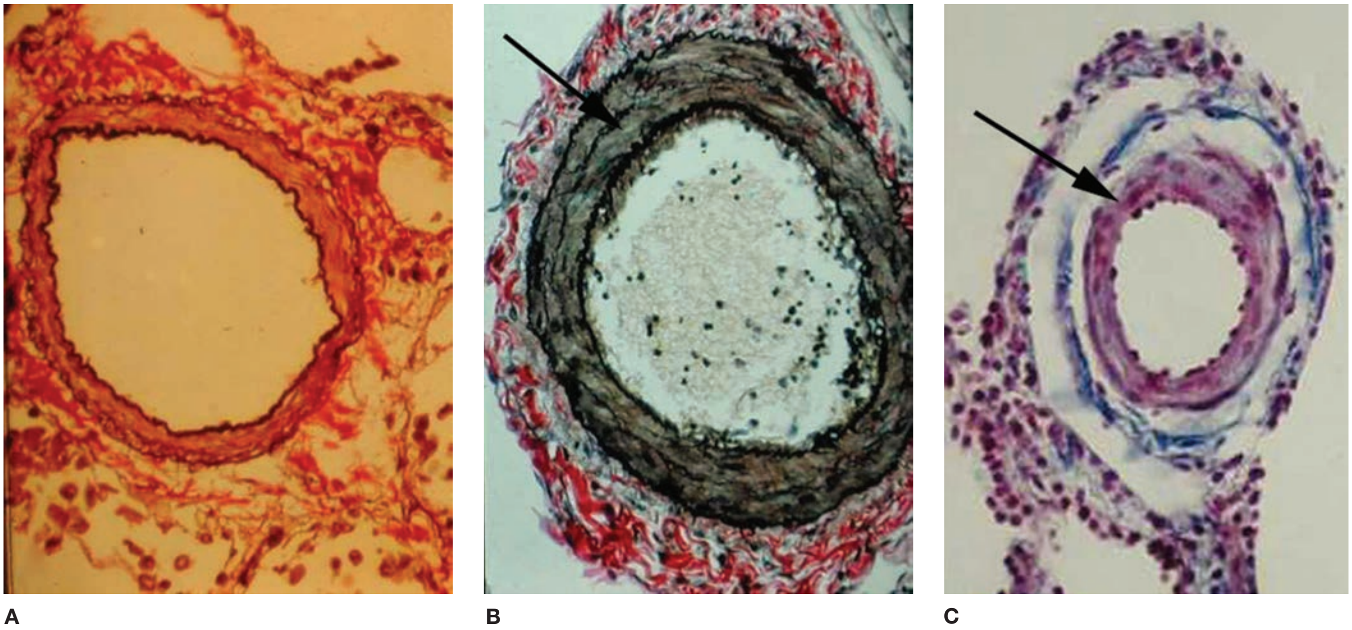


Figure 72-2 Vascular remodeling. As compared with a normal vessel (**A**), hypertrophy of smooth muscle cells *(arrow)* is seen in the pulmonary artery of a patient with pulmonary arterial hypertension (**B**). Extension of muscle *(arrow)* into normally nonmuscularized small intra-acinar pulmonary vessels is another prominent feature of pulmonary arterial hypertension (**C**). *(Reproduced with permission from Taichman DB: Pulmonary Vascular Disease. Philadelphia, PA: WB. Saunders; 2006.)*

A rise in cytosolic free Ca^{2+} concentration ($[Ca^{2+}]_{cyt}$) in pulmonary arterial smooth muscle cells is a major trigger for vasoconstriction and a key stimulus for pulmonary arterial smooth muscle cell proliferation and migration, which contributes to pathologic vascular remodeling.

Sustained Vasoconstriction

Pulmonary vasoconstriction can be a major contributor to increased PVR and hence PAP. Vasoconstrictive lesions include medial hypertrophy involving an increase in the number and size of pulmonary arterial smooth muscle cells. The elevated PAP and sustained vasoconstriction in PAH can, in turn, enhance pulmonary arterial smooth muscle cell hypertrophy and hyperplasia.[14] Marked smooth muscle hypertrophy can eventually cause medial atrophy, fibrosis, and the subsequent thinning of the media and dilation of the vessel lumen. Extension of pulmonary arterial smooth muscle cells into vessels normally only partially muscularized or nonmuscularized is a common and often prominent feature of precapillary vessels (Fig. 72-2).[15]

Hypoxic pulmonary vasoconstriction is an adaptive mechanism important for redirecting blood flow away from poorly ventilated areas of the lung and into the better ventilated areas to optimize ventilation–perfusion matching and maximize oxygenation of blood.[16–19] Hypoxia induces vasoconstriction in pulmonary arteries isolated without the endothelium and also induces contraction in a single isolated pulmonary arterial smooth muscle cell model, indicating that hypoxic pulmonary vasoconstriction is an intrinsic property of pulmonary arterial smooth muscle cells. In chronic hypoxia, two factors contribute to increased PAP: vascular remodeling due to pulmonary arterial smooth muscle cell proliferation and sustained vasoconstriction and structural changes that develop within a matter of weeks.[20,21] This remodeling is characterized by thickening of the media of the small pulmonary arteries and arterioles, and by peripheral extension of muscle into minute pulmonary vessels that are normally devoid of muscle (Fig. 72-2).[22] Although the precise mechanism by which hypoxia induces pulmonary vasoconstriction is still somewhat unclear, the signaling pathways initiated in response to acute and chronic hypoxia seem to relate, at least in part, to disrupted Ca^{2+} homeostasis.[8,23]

Vascular Remodeling

The thickness and tissue mass of the pulmonary arterial walls are maintained at an appropriate level by a fine balance between proliferation and apoptosis of fibroblasts, pulmonary arterial smooth muscle cells, and pulmonary arterial endothelial cells. Thickening of the vessel wall and luminal narrowing and eventual obliteration can occur if the balance is tipped in favor of cellular proliferation. These structural changes that lead to and include hypertrophy and/or luminal occlusion are referred to as pulmonary vascular remodeling.[24–26] The precise cellular and molecular mechanisms contributing to vascular remodeling are extremely complex. However, vasoconstriction and cellular proliferation share a common pathway. Increased proliferation and hypertrophy of pulmonary arterial smooth muscle cells have been implicated in the development of PAH, and these processes, like vasoconstriction, relate in part to disturbed Ca^{2+} homeostasis.[7] Resting $[Ca^{2+}]_{cyt}$ is increased in proliferating pulmonary artery smooth muscle cells compared with growth-arrested cells, demonstrating a role for enhanced Ca^{2+} in both proliferation and vasoconstriction.[27,28] In addition to increased proliferation, decreased apoptosis has been implicated in the development and maintenance of severe pulmonary hypertension,[29] and induction of apoptosis has been shown to promote the regression of hypertrophied pulmonary vascular walls in animal experiments.[30] Hypoxia can induce proliferation of pulmonary arterial adventitial fibroblasts, and in pulmonary hypertension patients, hypoxia induces the appearance of α-smooth muscle actin in the proliferative and matrix-producing fibroblasts, suggesting these cells have transdifferentiated into myofibroblasts.[31] Therefore, fibroblasts may play an important role in vascular remodeling due to hypoxia.

Complex lesions such as plexiform lesions also contribute to vascular remodeling. Plexiform lesions are aneurysmatic dilations of a muscular artery that can occur in very small arteries and arterioles.[8,32] These lesions are often found in patients with IPAH, but they also occur in the lungs of patients with severe PAH associated with left-to-right cardiac shunts, HIV infection, liver cirrhosis, and scleroderma. Although not pathognomonic, the plexiform lesion has been the focus of many studies of the cellular and molecular pathogenesis of PAH.[33–36] They contain collections of proliferating endothelial and smooth muscle cells, together with myofibroblasts and matrix proteins that can partially or completely occlude the vessel lumen. Narrowing or complete obliteration of the parent vessel by intimal thickening is a frequent associated finding, as is destruction of its media. Plexiform lesions often coexist with other obliterative vascular changes such as concentric laminar intimal thickening.[37]

The origin of plexiform lesions is complex and somewhat controversial. Originally, plexiform lesions were considered a congenital malformation.[38] Currently, there are investigators who believe that plexiform lesions develop due to the proliferation of pulmonary arterial smooth muscle cells that transform into myofibroblasts.[39–41] Other investigators propose that, in IPAH patients, plexiform lesions develop due to an endothelial-initiated response to cytokines, growth factors, or vascular injury.[39,41,42] Endothelial cells isolated from the plexiform lesions of IPAH patients proliferate in a monoclonal fashion. However, plexiform lesions from patients with forms of pulmonary hypertension other than IPAH develop from a polyclonal cell population, suggesting that different mechanisms contribute to plexiform lesion development in different forms of PAH.[8,43]

In Situ Thrombosis

Monoclonal proliferation of pulmonary arterial endothelial cells, pulmonary arterial smooth muscle cell migration, and accumulation of circulating inflammatory cells, platelets, and progenitor cells can result in occlusion of smaller vessels.[11,42] Thrombosis is frequently seen within the small vessels of patients with PAH. This occurs without evidence of a remote (embolic) source of the thrombus,[44–47] suggesting a local imbalance of pro- and anticoagulant forces. Activation and altered function of the endothelium leading to a shift from anti- to procoagulant activities might be due to the effects of shear stress associated with elevated pressure and/or flow. In addition to altered endothelial cell activity, platelets also promote thrombus formation by releasing vasoactive and mitogenic factors such as thromboxane metabolites and serotonin.[48] These, as well as other platelet-derived products (e.g., platelet-derived growth factor [PDGF], transforming growth factor-beta [TGFβ], and vascular endothelial growth factor [VEGF]) likely also contribute to the remodeling of vessel walls seen in PAH.

Increased Arterial Wall Stiffness

Increased arterial wall stiffness can also contribute to increased PVR.[49,50] The normal turnover of extracellular matrix proteins is accelerated with remodeling of the vasculature in PAH patients.[51,52] The expression of tenascin-C, as an example, is increased in experimental pulmonary hypertension induced by either monocrotaline in rats or increased blood flow in swine.[53–55] Indeed, inhibition of tenascin-C expression by antisense RNA ameliorates monocrotaline-induced pulmonary vascular lesions.[56] Elevated levels of this extracellular matrix protein are also seen on pulmonary arteries of patients with PAH.[57,58] Decreased vascular compliance resulting in the inability to recruit previously unperfused vessels due to increased parenchymal stiffness can also contribute to the development of PAH.[11,42] As a result, there is little capacity for distention and modest increases in pulmonary blood flow can elicit disproportionate elevations in PAPs. This situation is in marked contrast to that of the normal pulmonary circulation, in which an amputation of considerable lung parenchyma rarely suffices, per se, to raise PAPs to pulmonary hypertensive levels, as the remaining vessels retain their normal high capacitance. In some interstitial lung diseases, such as progressive systemic sclerosis, the parenchymal disease and the pulmonary vascular disease can evolve independently. In other connective tissue disorders, such as systemic lupus erythematosis, combinations of interstitial disease and intrinsic vascular abnormalities can contribute to pulmonary hypertension. While there are many structural changes in the pulmonary vasculature that lead to the development of PAH, vasoconstriction and vascular remodeling characterized by intimal, medial, and adventitial hypertrophy are the major structural changes that contribute to the increased PVR/PAP seen in PAH patients.

No single histologic feature distinguishes between the clinical PAH diagnoses. Each of the changes described can be seen in varying proportions in all clinical forms of PAH. For example, the vascular remodeling seen in chronic hypoxia-induced pulmonary hypertension is virtually indistinguishable from that seen in IPAH.[8] The predominant causes of the increased PVR in patients with PAH are sustained vasoconstriction, vascular remodeling, in situ thrombosis, and increased arterial wall stiffness. Persistent pulmonary hypertension, regardless of the cause, can ultimately lead to the development of cor pulmonale with hypertrophy of the right ventricle, its eventual dilation, and ultimately its failure (Fig. 72-3).

PATHOGENIC MECHANISMS OF PULMONARY HYPERTENSION

The pathogenic mechanisms leading to pulmonary hypertension have been conceptualized in six categories (Table 72-2): (1) *passive,* due to obstruction to pulmonary venous outflow (e.g., fibrosing mediastinitis, mitral stenosis, or left heart failure); (2) *hyperkinetic,* due to abnormally high pulmonary blood flow (e.g., left-to-right shunts); (3) *obstructive,* due to pulmonary thromboembolic disease; (4) *obliterative,* due to destruction of the pulmonary vascular bed by parenchymal proliferative disease; (5) *vasoconstrictive,* due to hypoxic vasoconstriction; and (6) *idiopathic* (i.e., without discernible cause).[59] Each mechanism leads to pulmonary vascular remodeling discussed previously, although the progression and reversibility may vary between entities. Other anatomic alterations can be seen in several categories, and, over time, distinctions between categories tend to become blurred (e.g., thrombosis may complicate obliterative vascular disease). Also, by the time pulmonary hypertension becomes manifest clinically, the pulmonary arterial tree has undergone considerable remodeling that limits its area and distensibility.

These mechanisms share commonality with the clinical classification of pulmonary hypertension, although overlap of mechanisms occurs. The most clearly linked is chronic thromboembolic pulmonary hypertension (CTEPH) with the obstructive mechanism. The most common form of pulmonary hypertension, that related to left heart disease, can also closely be tied to its passive mechanism along with fibrosing mediastinitis, which is classified in group 5 with unclear multifactorial mechanisms. Pulmonary hypertension due to lung diseases and/or hypoxia, group 3, can be understood as having two primary pathogenic mechanisms, vasoconstrictive in the chronic hypoxic subset and obliterative in the parenchymal disease/fibrosis subset, although these two often overlap. Group 5, pulmonary hypertension with unclear multifactorial mechanisms, contains multiple pathogenic mechanisms. Group 1 remains the most diverse and difficult to equate to a particular mechanism, as hyperkinetic, vasoconstrictive, obliterative, and other idiopathic mechanisms may all contribute to disease pathophysiology.

GENETIC, CELLULAR, AND MOLECULAR MECHANISMS OF PULMONARY ARTERIAL HYPERTENSION

The development of PAH involves increased PVR due to sustained vasoconstriction, vascular remodeling, in situ thrombosis, and

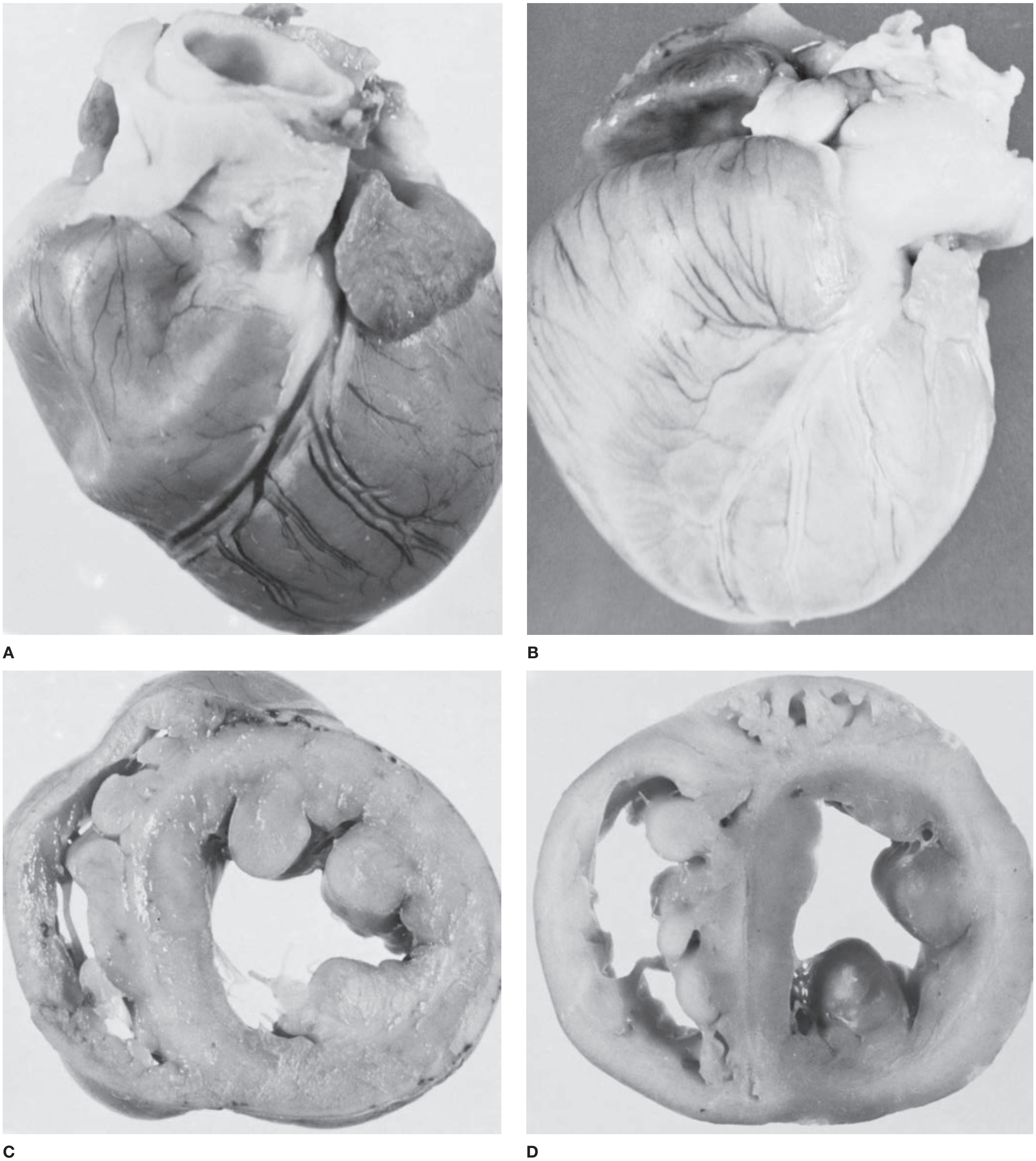


Figure 72-3 Right ventricular hypertrophy and dilatation in experimental pulmonary arterial hypertension in the dog. **A.** Normal heart. **B.** Changes from severe pulmonary hypertension. **C.** Cross section of normal heart to show thin wall of the right ventricular cavity. **D.** Cross section of heart with pulmonary hypertension show hypertrophy of the right ventricular myocardium and enlargement of the right ventricular cavity. *(Reproduced with permission from Dr. B. Atkinson.)*

increased atrial wall stiffness (Fig. 72-1). Abnormalities in the expression of numerous vasoactive mediators, vasoconstriction mediators, growth factors, and cytokines cause or result from changes in pulmonary arterial endothelial cells, pulmonary arterial smooth muscle cells, and platelet function and together result in a thickened vessel wall and markedly narrowed or even completely obliterated lumen. Some of the mechanisms for this combination of uncontrolled vasoconstriction, cell proliferation, and thrombosis are highlighted here.

■ Imbalance of Vasoactive Mediators

Relative deficiencies of factors with vasodilatory properties and a simultaneous excess in those promoting vasoconstriction have been noted in both animal models and patients with PAH. In addition

TABLE 72-2 Pathogenetic Mechanisms of Pulmonary Hypertension

	Mechanism	Examples
Passive	Pulmonary venous hypertension	Mitral stenosis, left atrial myxoma, fibrosing mediastinitis, pulmonary venoocclusive disease
Hyperkinetic	Increased pulmonary blood flow[a]	Left-to-right intracardiac shunts
Obstructive	Thromboembolic pulmonary vascular disease	High grade obstruction of large pulmonary arteries by organized thromboemboli, multiple pulmonary emboli
Obliterative	Inflammatory and/or proliferative pulmonary vascular disease	Interstitial lung disease, pulmonary arterial hypertension, schistosomiasis
Venoconstrictive	Hypoxia	High altitude, chronic bronchitis and emphysema (COPD)
Idiopathic	Unknown	Drug-associated pulmonary hypertension, portopulmonary hypertension, HIV infection

[a] *Most categories overlap to some extent. For example, increased pulmonary blood flow is usually coupled with anatomic changes in the resistance vessels to produce pulmonary hypertension.*

to vasoconstriction/dilation, these same factors influence cell proliferation and thrombosis. Deficiencies in the production of the potent vasodilators nitric oxide (NO) and prostacyclin have each been observed, and indeed both substances have been used as a basis for effective therapies for PAH. Normally produced by vascular endothelial cells, each promotes the formation of cyclic nucleotides (cGMP and cAMP) by pulmonary arterial smooth muscle cells resulting in their relaxation and vasodilation. In addition, both prostacyclin and NO inhibit pulmonary arterial smooth muscle cell proliferation and platelet aggregation. In patients with PAH, the chronic administration of prostacyclin analogues improves hemodynamics, exercise capacity, and survival. The overexpression of NO synthase (NOS) by transgenic animals protects against the development of hypoxia-induced pulmonary hypertension, whereas mice lacking the gene for this enzyme develop severe pulmonary hypertension upon exposure to mild hypoxia.[60–62] In rats, monocrotaline-induced pulmonary hypertension can be prevented, or even reversed, with the administration of endothelial progenitor cells overexpressing human endothelial NOS (eNOS).[63] Inhaled NO has been proposed for the treatment of PAH and persistent pulmonary hypertension of the newborn;[64] however, inhaled NO has limitations regarding dose and duration of the exposure.[65] The inorganic anion nitrite (NO_2^-) is an oxidative product of NO metabolism and can function as an intravascular reservoir of NO bioactivity that can be converted to NO under physiologic and pathologic conditions.[65] Studies have shown that inhaled nebulized nitrite can prevent and reverse established pulmonary hypertension in the monocrotaline-induced rat pulmonary hypertension model.[66,67]

Vasoactive intestinal peptide (VIP) also promotes vasodilation and inhibits smooth muscle proliferation and platelet aggregation. VIP levels are reduced in patients with PAH. In a preliminary study of eight patients with IPAH, treatment with inhaled VIP improved hemodynamics and exercise capacity.[68] The acute effect of inhaled VIP was confirmed in a subsequent study that included patients with multiple etiologies of pulmonary hypertension including IPAH, congenital heart disease, CTEPH, and pulmonary hypertension related to parenchymal lung disease, although the modest effect on hemodynamics had questionable clinical relevance.[69] A subcutaneous, sustained-release VIP analogue is being investigated for the treatment of PAH.

■ Increase in Vasoconstriction Mediators

In addition to deficiencies in vasodilators, excesses of other mediators capable of promoting vasoconstriction, smooth muscle proliferation, or platelet aggregation have been noted in patients with PAH. Thromboxane, an arachidonic acid metabolite produced by endothelial cells and platelets, causes vasoconstriction and platelet aggregation, and is a smooth muscle mitogen. Increased thromboxane metabolites have been documented in the urine of patients with PAH.[48] Attention was focused on the effects of serotonin (5-HT) on the pulmonary circulation by the epidemic of PAH in patients who ingested the appetite suppressants aminorex and fenfluramine.[70] These agents increase plasma 5-HT levels by inducing the release of 5-HT from platelets and interfering with its reuptake.[71] The 5-HT hypothesis was supported by the occurrence of pulmonary hypertension in fawn-hooded rats with an inherited defect in the platelet storage of 5-HT, and by an increase in circulating 5-HT in a patient with platelet storage disease and PAH.[72] 5-HT causes vasoconstriction and is a smooth muscle mitogen (Fig. 72-4). A key regulator of 5-HT action is the 5-HT transporter (5-HTT) whose expression is increased above normal in platelets and pulmonary arteries of patients with IPAH. The overexpression of the 5-HTT gene in recombinant mice results in worsened hypoxia-induced pulmonary hypertension,[73] whereas loss of the gene's function is protective against hypoxia or monocrotaline-induced disease.[74,75] A polymorphism in the 5-HTT gene that increases its activity may confer an increased susceptibility to the development of pulmonary hypertension in patients with COPD.[76] While some studies have suggested a similar role in IPAH,[77] larger data sets have not found such an association.[78] Blockade of the 5-HT receptor has successfully prevented the development and progression of experimental pulmonary hypertension in rats, yet a human trial was not able to show significant decreases in PVR.[79,80]

Endothelin 1 (ET-1) is one of the most potent endogenous vasoconstrictors yet discovered. Its expression is increased in the blood and tissues of patients with idiopathic and other forms of PAH and correlates with disease severity.[81–83] In addition to its vasoconstricting properties, ET-1 is mitogenic for both pulmonary arterial smooth muscle cells and fibroblasts (Fig. 72-4).[84,85] ET-1 administration or overexpression in animal models has been shown to result in fibrosis, inflammation, and platelet aggregation.[86,87] ET-1 binds endothelin A (ET_A) and B (ET_B) receptors on the surface of pulmonary arterial smooth muscle cells, resulting in potent vasoconstriction. In contrast, ET_B receptors on pulmonary arterial endothelial cells increase the production of nitric oxide, resulting in vasodilatation. ET_B receptors are also active in the clearance of endothelin. The net effect of endothelin's vasoconstricting or dilating actions may be both site and context dependent, as both the distribution and relative expression of the ET_A and ET_B receptors differ according to vessel location in normal lung tissue, and are altered in patients with IPAH.[88,89] Indeed, both selective ET_A and dual ET_A/ET_B inhibition improve the hemodynamic derangements and clinical outcome of patients with PAH.[90–92]

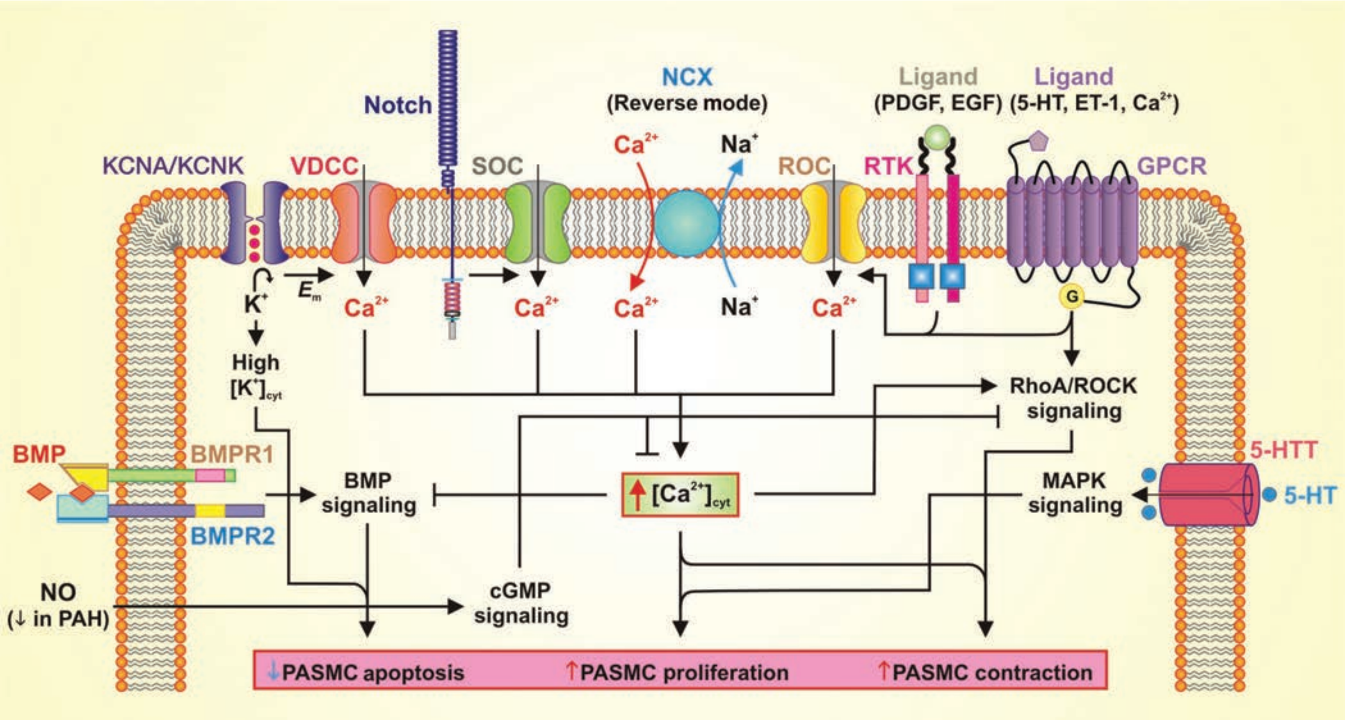


Figure 72-4 Potential mechanisms involved in the development of pulmonary arterial hypertension. Schematic diagram depicting potential mechanisms involved in the development of pulmonary arterial hypertension. BMP, bone morphogenic protein; BMPR, bone morphogenic protein receptor; cGMP, cyclic guanosine monophosphate; E_m, membrane potential; ET-1, endothelin 1; EGF, epidermal growth factor; GPCR, G protein–coupled receptor; 5-HT, hydroxytryptamine (serotonin); 5-HTT, hydroxytryptamine (serotonin) transporter; KCNA, voltage-gated K^+ channel; KCNK, two-pore domain K^+ channel; MAPK, mitogen-activated protein kinase; NO, nitric oxide; NCX, Na^+/Ca^{2+} exchanger; PAH, pulmonary arterial hypertension; PASMC, pulmonary arterial smooth muscle cell; PDGF, platelet-derived growth factor; ROC, receptor-operated Ca^{2+} channel; RTK, receptor tyrosine kinase; SOC, store-operated Ca^{2+} channel; VDCC, voltage-dependent Ca^{2+} channel.

■ Increased Expression of Growth Factors

Growth factors that promote the maturation and stabilization of the developing vasculature have also been implicated in the pathogenesis of PAH. Elevations in angiopoietin 1 and its ligand TIE2 correlate with disease severity in patients with multiple forms of PAH.[93] Angiopoietin 1 is overexpressed in most forms of nonfamilial PAH;[93,94] however, how angiopoietin becomes elevated in these patients is not clear. Several lines of evidence suggest that angiopoietin 1 regulates pulmonary arterial smooth muscle cell hyperplasia in PAH.[9] Interestingly, in an animal model of PAH induced by monocrotaline, the overexpression of angiopoietin is actually protective.[95] Whether this discrepancy represents differences in human versus animal tissues or the differing insults to the vasculature involved is not clear. Another modulator of development, VEGF and its target tyrosine kinase receptor, are increased in the pulmonary vasculature of patients with PAH. Increased VEGF expression has been reported specifically within plexiform lesions[34,96] where its proangiogenic properties are hypothesized to mediate disordered endothelial cell proliferation.[97] Whether such changes are primary, secondary, or indeed detrimental is not entirely clear. Like elevations in angiopoietin, increases in the expression of VEGF thought to be deleterious in some situations might be beneficial in others that promote the development of pulmonary hypertension. In animal models of hypoxia, the inhibition of VEGF signaling results in proliferative vascular abnormalities,[98] and promotion of VEGF signaling is protective against the development of monocrotaline-induced PH.[99]

PDGF along with its receptor, tyrosine kinase, are also found to be increased in the pulmonary vasculature of patients with PAH (Fig. 72-4).[100] PDGF has been implicated in smooth muscle cell proliferation and migration, which is thought to contribute to PAH pathogenesis. The tyrosine kinase inhibitor imatinib has a particular affinity for the PDGF receptor, and several small studies have identified a potential benefit in PAH patients.[101] The IMPRES study with imatinib therapy showed improvements in exercise capacity and hemodynamics in patients with advanced PAH, but serious adverse events including multiple cases of subdural hematoma were observed in the treatment arm.[102] As a result of safety concerns, imatinib has not been approved for the treatment of PAH.

Cellular microparticles recently have been implicated as vasoactive mediators in PAH. Microparticles represent vesicle fragments of the cell membrane containing various proteins and antigens that are involved in cellular communication.[103] These small particles are released during cell activation or apoptosis and can be derived from multiple cell lines including endothelial cells, platelets, leukocytes, red blood cells, and fibroblasts. Circulating levels of endothelial microparticles are increased in PAH, which may represent endothelial dysfunction and has also been correlated with disease survival.[104] Microparticles, when isolated from rats with hypoxia-induced pulmonary hypertension, have been shown to impair endothelium-dependent vasorelaxation in pulmonary arteries and decrease NO production.[105] Circulating microparticles have also been linked to inflammatory signaling in the lung.[106]

■ Increased Cytokines and Inflammation

The close association of systemic inflammatory disorders to IPAH has implicated inflammation as an important factor in vascular remodeling. Numerous cytokines have been implicated in the pathogenesis of PAH including tumor necrosis factor α and interleukins (ILs) 1b, 2, 4, 6, 8, 10, and 12p70. Early data showed increased levels of IL-1β and IL-6 in IPAH patients,[107] and higher IL-6 levels were later found to be associated with mortality.[108] The chemokine fractalkine (CX3CL1) is elevated in CD4 and CD8 T cells of PAH patients, and further studies have shown that CX3CL1 may promote proliferation in pulmonary arterial smooth muscle cells.[109,110] Monocyte chemotactant protein (MCP)-1 is also elevated in serum and lung samples from IPAH patients and may influence monocyte and T-cell recruitment to the diseased lung.[111] Increased expression of Regulated upon Activation, Normal T cell Expressed and Secreted (RANTES) has been found in lung samples from PAH patients.[112] As a chemoattractant for monocytes and T cells, RANTES is thought to promote inflammation but may also play a role in the synthesis of endothelin 1, a potent vasoconstrictor.

FUNCTIONAL CHANGES IN MEMBRANE RECEPTORS AND ION CHANNELS

Important functional changes in membrane receptors and ion channels in IPAH are discussed below.

■ Ca^{2+} Channels in IPAH

Sustained vasoconstriction and vascular remodeling are both directly mediated by pulmonary arterial smooth muscle cell contraction and proliferation. A rise in $[Ca^{2+}]_{cyt}$ due to Ca^{2+} influx through various Ca^{2+}-permeable channels in the plasma membrane is a major trigger for pulmonary arterial smooth muscle cell contraction and a key stimulus for pulmonary arterial smooth muscle cell proliferation.[113] Therefore, understanding how the regulation of Ca^{2+} homeostasis is disrupted in IPAH is important to understanding how IPAH develops. Pulmonary arterial smooth muscle cells isolated from IPAH patients have an elevated $[Ca^{2+}]_{cyt}$.[114–117] Ca^{2+} influx through the plasma membrane in pulmonary arterial smooth muscle cells involves multiple Ca^{2+}-permeable channels including (1) voltage-dependent Ca^{2+} channels (VDCC) regulated by changes in membrane potential,[118] (2) receptor-operated Ca^{2+} channels (ROC) activated by interaction of agonist with membrane receptors, and (3) store-operated Ca^{2+} channels (SOC) activated by depletion of Ca^{2+} from the intracellular stores (Fig. 72-4).[8] Decreased expression and/or function of K^+ channels leads to sustained membrane depolarization, activation of VDCC, and increased $[Ca^{2+}]_{cyt}$. Ca^{2+} influx through ROC, termed receptor-operated Ca^{2+} entry (ROCE), and through SOC, referred to as store-operated Ca^{2+} entry (SOCE), is enhanced in IPAH-associated pulmonary arterial smooth muscle cells compared with those from normal controls.[114–117] Several experimental studies have demonstrated increased expression of several proteins involved in ROCE/SOCE such as TRPC3, TRPC6, STIM2, and Orai2, in pulmonary arterial smooth muscle cells from IPAH patients.[114–117,119,120] In addition, a single-nucleotide polymorphism (SNP) has been identified in IPAH patients that results in enhanced expression and function of TRPC6.[115]

■ K^+ Channels in IPAH

Vascular tone might also be altered in IPAH by changes in the expression of voltage-gated K^+ (Kv) channels as well as other types of K^+ channels (Fig. 72-4). Their activation normally allows an efflux of K^+ and resultant changes in intracellular Ca^{2+} that promote vasodilation.[121] Gene expression of Kv channel family members is downregulated by hypoxia-induced pulmonary hypertension in rats,[122,123] whereas induction of their expression can reverse the hemodynamic effects of hypoxia.[122,124] The expression of specific Kv channels is also decreased in the lungs of patients with IPAH,[125–127] possibly contributing to heightened vasoconstriction resulting from a more depolarized membrane leading to increased $[Ca^{2+}]_{cyt}$ due to activation of VDCC. Kv channels may also mediate the effects of certain drugs. The anorexigens dexfenfluramine and aminorex inhibit smooth muscle Kv channel activity, thus causing pulmonary vasoconstriction.[128] In contrast, enhanced activity of Kv channels may be one mechanism by which sildenafil promotes vasodilation, in addition to its activity as an inhibitor of phosphodiesterase-5.[122] One final way in which decreased activity of Kv channels might promote the development of PAH is by inhibiting apoptosis, thus enabling unchecked pulmonary arterial smooth muscle cell proliferation. Apoptosis requires a loss in cell volume as well as the function of specific caspases, both of which require appropriate K^+ movement via Kv channels.[129,130]

■ G Protein–Coupled Receptors in IPAH

The Ca^{2+}-sensing receptor is a G protein–coupled receptor in the plasma membrane that can be activated by extracellular Ca^{2+} (and Mg^{2+}), polyamines (e.g., spermine), amino acids, and neomycin.[131–134] Activation of the Ca^{2+}-sensing receptor results in activation of intracellular Ca^{2+} signaling pathways that lead to pulmonary arterial smooth muscle cell contraction, proliferation, and migration (Fig. 72-4).[135,136] Like some G protein–coupled receptors coupled to Gq (e.g., endothelin receptors), Ca^{2+}-sensing receptor activation increases the synthesis of inositol 1,4,5 triphosphate (IP_3) and diacylglycerol via phospholipase C. IP_3 binds to the IP_3 receptor on the sarcoplasmic reticulum (SR) membrane and releases Ca^{2+} from the SR to the cytosol. Depletion of Ca^{2+} from the SR induces Ca^{2+} entry via SOCE, and diacylglycerol directly activates ROCE. In addition to increasing $[Ca^{2+}]_{cyt}$ via ROCE and SOCE, the extracellular Ca^{2+}-induced activation of CaSR also activates other signal transduction pathways (e.g., Akt/mTOR and MAPK/ERK) to induce cellular proliferation.[137–139] One study[135] indicated that the extracellular Ca^{2+}-induced increase in $[Ca^{2+}]_{cyt}$ by activation of the Ca^{2+}-sensing receptor is enhanced and the Ca^{2+}-sensing receptor protein expression is upregulated in IPAH-pulmonary arterial smooth muscle cells compared with normal pulmonary arterial smooth muscle cells. These observations suggest that upregulated expression and enhanced function of Ca^{2+}-sensing receptor in pulmonary arterial smooth muscle cells are involved in the development of sustained pulmonary vasoconstriction and pulmonary vascular remodeling in patients with IPAH and animals with experimental pulmonary hypertension. In addition to Ca^{2+}-sensing receptor, many other G protein–coupled receptors are reported to be involved in PAH such as endothelin receptor, prostacyclin receptor, and serotonin receptor.[48,140,141]

■ Na^+/Ca^{2+} Exchanger in IPAH

The Na^+/Ca^{2+} exchanger (NCX) is a ubiquitously expressed protein that transports Ca^{2+} across the plasma membrane along the electrochemical gradient of Na^+ and Ca^{2+}.[142] The NCX can operate in either forward mode, transporting 3 Na^+ ions into the cell and 1 Ca^{2+} ion out of the cell, or the reverse mode, transporting 1 Ca^{2+} ion into the cell and 3 Na^+ ions out of the cell, based on the Na^+ and Ca^{2+} concentration gradients and membrane potential. Due to the reverse mode of the NCX, a small increase in the cytosolic Na^+ concentration ($[Na^+]_{cyt}$) can greatly increase $[Ca^{2+}]_{cyt}$. The canonic transient receptor potential (TRPC) channels, such as TRPC6, which is overexpressed in IPAH patients, are permeable to both Na^+ and Ca^{2+}, and for many TRPC channels, the permeability to Na^+ is greater than the permeability to Ca^{2+}. The reverse mode of the NCX has been shown to couple to TRPC6, and localized increases in $[Na^+]_{cyt}$ result in transport of Ca^{2+} into the cell resulting in increased $[Ca^{2+}]_{cyt}$ in pulmonary arterial smooth muscle cells.[143] The NCX is overexpressed in PASMC isolated from patients with IPAH, and is found localized in caveolae along with other G protein–coupled receptors, ROC, and SOC resulting in a functional coupling of these receptors and contributing to increased $[Ca^{2+}]_{cyt}$, resulting in increased proliferation and contraction of PASCM in patients with IPAH.[116,144]

ALTERED SIGNALING PATHWAYS IN IPAH

Alterations in signaling pathways have been observed in IPAH and are discussed below.

Cyclic Guanosine Monophosphate in IPAH

IPAH is associated with abnormally low levels of the potent pulmonary arterial smooth muscle cell relaxant NO. In pulmonary arterial endothelial cells, NO produced by eNOS freely diffuses across the cell membrane to pulmonary arterial smooth muscle cells and activates intracellular soluble guanylate cyclase (sGC), which catalyzes the conversion of guanosine 5′-triphosphate (GTP) to cyclic guanosine monophosphate (cGMP). cGMP then activates cGMP-dependent kinases, which can reduce $[Ca^{2+}]_{cyt}$, inhibit Rho signaling, and inhibit phosphorylation of myosin-binding protein, all of which lead to smooth muscle relaxation.[145,146] In the lung, metabolism of cGMP is controlled by phosphodiesterase 5 (PDE-5). PDE-5 inhibitors block the breakdown of cGMP, leading to vasodilation due to an accumulation of cGMP in the tissue.[147] In 2005, following several clinical studies, sildenafil was approved for the treatment of PAH.[148] Tadalafil was approved for the treatment of PAH in 2009.[149] Both sildenafil and tadalafil share structural similarities with cGMP and inhibit PDE-5 by competitively binding to the catalytic site.[147]

PDGF and Akt/mTOR Signaling in IPAH

PDGF and its receptor PDGFR have been implicated in the pathogenesis of IPAH. Previous studies have indicated that PDGF increases SOCE in rat and human pulmonary arterial smooth muscle cells, thereby promoting cell proliferation (Fig. 72-4).[119,150] Binding of PDGF to PDGFR leads to activation of phosphatidylinositol 3-kinase (PI3K),[151] which activates Akt. Akt promotes cell growth through the downstream mediator mammalian target of rapamycin (mTOR) or by directly phosphorylating proteins involved in cell cycle regulation and apoptosis.[152] The Akt/mTOR pathway has been shown to be important for pulmonary arterial smooth muscle cell proliferation[150,153] and the development of PAH.[154] Inhibition of mTOR and Akt by rapamycin and Akt inhibitor VIII, respectively, abrogated the PDGF-induced increased SOCE and Ca^{2+} channel expression in normal and PAH-pulmonary arterial smooth muscle cells,[150,155] suggesting that the PDGF-mediated increase in SOCE occurs via the Akt/mTOR pathway.

RhoA/ROCK Signaling in IPAH

The RhoA/ROCK signaling pathway is a major mediator of Ca^{2+}-sensitization/desensitization and a key regulator of vascular tone (Fig. 72-4).[156,157] RhoA is a GTP-binding protein that is activated following activation of G protein–coupled receptors by vasodilators. In addition, RhoA can be activated by serotonin, which enters the cell through its transporter 5-HTT, and by an increase in $[Ca^{2+}]_{cyt}$.[158] Activation of RhoA leads to activation of Rho kinase (ROCK), which increases the Ca^{2+} sensitivity of contraction in pulmonary arterial smooth muscle cells by inhibiting myosin light chain phosphatase and increasing the phosphorylation of myosin light chain kinase, leading to increased contraction of pulmonary arterial smooth muscle cells.[20,21] Recent studies have indicated that the RhoA/ROCK signaling pathway is enhanced in patients with IPAH.[159,160] Small clinical studies have demonstrated that inhibition of the RhoA/ROCK signaling pathway with fasudil, a selective ROCK inhibitor, results in acutely improved pulmonary hemodynamic variables in patients with IPAH.[161,162]

Notch Signaling in IPAH

Notch signaling is involved in vascular development and has been implicated in the development of IPAH (Fig. 72-4).[163,164] Both Notch receptors (Notch1, Notch4) and their ligands, Jagged (Jag1 and Jag2) and Delta-like (Dll1, Dll3, and Dll4), are single-transmembrane–spanning proteins that restrict Notch signaling to adjacent cells. After ligand binding, Notch undergoes a series of proteolytic cleavages resulting in the release of the Notch intracellular domain, which translocates to the nucleus where it interacts with recombination signal binding protein for immunoglobulin kappa j region (RBPjκ) to function as a transcription factor, resulting in activation of transcription of Notch target genes.[163,165–167] The most commonly induced Notch target genes are the basic helix–loop–helix transcriptional repressors of the *Hes* (*Hairy/Enhancers of Split*) and *Hrt* (*Hes-related transcription factor*) gene families. In addition, Notch signaling has been shown to upregulate expression of PDGFR-β,[168] which is known to be upregulated in IPAH.[155,169] Notch3 signaling has recently been implicated in PAH. Lung tissue from IPAH patients displays increased Notch3 and Notch3 intracellular domain (N3ICD) expression when compared with normotensive patients.[164] In addition, Notch3 and N3ICD expression is increased in two animal models of pulmonary hypertension, hypoxic-induced pulmonary hypertension in mice and monocrotaline-induced pulmonary hypertension in rats.[164] This suggests that the Notch signaling pathway may be an important pathway to target for the development of new drugs for the treatment of IPAH.

GENETIC ALTERATIONS RELATED TO IDIOPATHIC AND HERITABLE PAH

Identification of bone morphogenetic protein receptor II (BMPR2) gene mutations has led to increasing interest in genetic susceptibility to pulmonary hypertension. As a receptor for the TGFβ super family, BMPR2 is involved in diverse cell growth and differentiation processes in multiple systems. Engagement of a BMP receptor with its ligand normally results in the activation of intracellular mediators (Smads) and their translocation to the cell nucleus and regulation of the transcription of target genes. The resulting activation of some genes and the inhibition of others varies according to the BMP pathway and tissue involved. BMP signaling is essential to both normal vascular development and the maintenance of the normal adult pulmonary vasculature, likely by regulating the growth and apoptosis of endothelial and smooth muscle cells (Fig. 72-4). Loss of such regulation gives rise to pulmonary hypertension.[170] Normally found primarily on endothelium and to a lesser extent smooth muscle cells, the expression of BMPR2 is reduced and its function abnormal in patients with various types of PAH, most notably those with mutations of the *BMPR2* gene.[171] The ability of BMP to inhibit smooth muscle proliferation and induce apoptosis is suppressed in cells isolated specifically from smaller pulmonary vessels in patients with IPAH (e.g., 1–2 mm, where occlusive vascular pathologic changes predominate).[29,172,173] Germline mutations in *BMPR2* have been identified in up to 70% of patients with heritable PAH, and in 20% of patients with IPAH,[174–180] as well as disease associated with anorexigens,[181] congenital heart disease,[182] and pulmonary venoocclusive disease (PVOD).[183] Nearly 300 different mutations of *BMPR2* have been identified.[177]

Further work has identified other genetic alterations in the TGF-β pathway including activin receptor kinase-like 1 (*ALK1*), endoglin (*Eng*), and Smad 8.[184] ALK1 is a receptor for TGF-β and endoglin is its coreceptor, while Smad 8 is a downstream second messenger of BMPR2. Mutations in *ALK1* and *Eng* have been shown to confer susceptibility to the development of PAH in patients with hereditary hemorrhagic telangiectasia.[185,186] In addition, concomitant thrombospondin 1 gene mutation (*THBS1*) has been detected in a small subset of heritable PAH patients with BMPR2 mutations; this mutation has been proposed to further promote pulmonary hypertension development and increase genetic penetrance.[187]

Several other genetic mutations have been more rarely described in heritable PAH. These include alterations in the genes encoding

TABLE 72-3 Presenting Symptom(s) Attributable to PAH

Symptom	Percentage of Patients at Presentation
Abdominal distention	4%
Chest pain/discomfort	2%
Cough	14%
Dizziness/lightheadedness	15%
Dyspnea at rest	11%
Dyspnea on exertion	86%
Edema	21%
Fatigue	27%
Presyncope/syncope	17%
Palpitations	13%

Data from Brown LM, Chen H, Halpern S, et al. Delay in recognition of pulmonary arterial hypertension: factors identified from the REVEAL registry. Chest 2011;140(1):19–26.

TABLE 72-4 World Health Organization Functional Classification of Patients with Pulmonary Hypertension

Class I: Patients with PH but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.

Class II: Patients with PH resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.

Class III: Patients with PH resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.

Class IV: Patients with PH with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

Adapted with permission from Rich S. Primary Pulmonary hypertension: executive summary. Evian, France. World Health Organization, 1998.

5-hydroxytryptamine (serotonin) transporter, mothers against decapentaplegic homologue 9 (SMAD9), caveolin 1, and potassium channel subfamily K member 3 (KCNK3).[77,188–190]

CLINICAL EVALUATION OF PULMONARY HYPERTENSION

The symptoms and signs of PAH are nonspecific, overlapping with many more common entities. As a result, patients experience problematic delays between the time of symptom onset and appropriate diagnosis.[191,192] The problem is often flagged by findings suggestive of pulmonary hypertension on an electrocardiogram or transthoracic echocardiogram. However, there are useful aspects of history taking and physical examination findings that may raise one's suspicion for PAH.

Patient History in Pulmonary Hypertension

Except for mild breathlessness—often attributed to being "out of shape"—PAH is generally asymptomatic until severe. Because of the nonspecific nature of the symptoms (Table 72-3), underrecognition of the disease by healthcare providers, and its confusion with other conditions, a significant delay between the onset of symptoms and the diagnosis of PAH is common. The mean time from symptom onset until PAH diagnosis was more than 2 years in a National Institutes of Health (NIH) registry assembled in the 1980s.[193] Twenty years later, registries in China, France, Germany, and the United States each found that similarly disappointing delays of more than 2 years persist.[192,194–196] As a result, diagnosis is delayed until most patients have severe functional impairment, with more than one-half reporting World Health Organization (WHO) functional class III or IV symptoms (Table 72-4).

Symptoms due to pulmonary hypertension are generally difficult to dissociate from symptoms of underlying pulmonary or cardiac disease. In IPAH, the first symptoms generally occur during exertion, usually as dyspnea and, less often, chest pain, dizziness, or syncope.[197] Dyspnea on exertion is by far the most common presenting complaint. Often, because of the lack of other signs or symptoms, it is attributed to physical deconditioning or anxiety. Other initial complaints, particularly easy fatigability and chest discomfort, are often similarly dismissed. Angina-like or nonspecific chest pain is common in patients with severe pulmonary hypertension and generally attributed to right ventricular overload and myocardial ischemia. Chest pain might also occur due to the extrinsic compression of the left main coronary artery by an enlarged pulmonary artery.[198]

In time, in the absence of amelioration of the pulmonary hypertension, right-sided heart failure evolves. Syncope, or light-headedness on exertion, is a less common but more ominous complication of pulmonary hypertension. It occurs in patients with severe pulmonary hypertension and a fixed low CO. The cause is inadequate cerebral blood flow due to a combination of failure to increase the CO, along with diversion of systemic blood flow toward the exercising muscles. Syncope may also occur at rest in association with the onset of bradycardia, presumably vagal in origin. Hoarseness, due to paralysis of the left recurrent laryngeal nerve, may result from trapping of the nerve between the aorta and the dilated left pulmonary artery (a form of Ortner syndrome). If the right ventricle should fail, lower extremity swelling is common, as are abdominal signs and symptoms including a sensation of "bloating," early satiety, tender hepatomegaly, ascites, and abdominal pain. Symptoms of right ventricular failure and the presence of syncopal events are associated with a worse prognosis. Hemoptysis in the setting of pulmonary hypertension is most often due to pulmonary venous congestion but when mitral stenosis is present, it is generally attributed to bleeding from bronchial veins. Occasionally, hemoptysis occurs in other forms of pulmonary hypertension and may originate in alveolar capillaries, precapillaries, or elsewhere in the pulmonary arterial tree.

Not infrequently, the suspicion of pulmonary hypertension is raised by the presence of a known risk for pulmonary hypertension (e.g., systemic sclerosis) or by serendipitous discovery of right ventricular enlargement by an electrocardiogram or chest radiograph taken for other reasons (Figs. 72-5 and 72-6). Initial recognition of the presence of pulmonary hypertension also frequently occurs in the absence of reported symptoms when an echocardiogram is performed for the evaluation of a murmur. Alternatively, echocardiographic evidence of pulmonary hypertension may be found unsuspectedly when the study is obtained as "routine" evaluation of a patient complaining of any of a number of chest symptoms, including dyspnea. Patients with severe pulmonary hypertension are prone to sudden death, and its occurrence may be the first indication of disease. Death has occurred unexpectedly during normal activities, cardiac catheterization, and surgical procedures, and

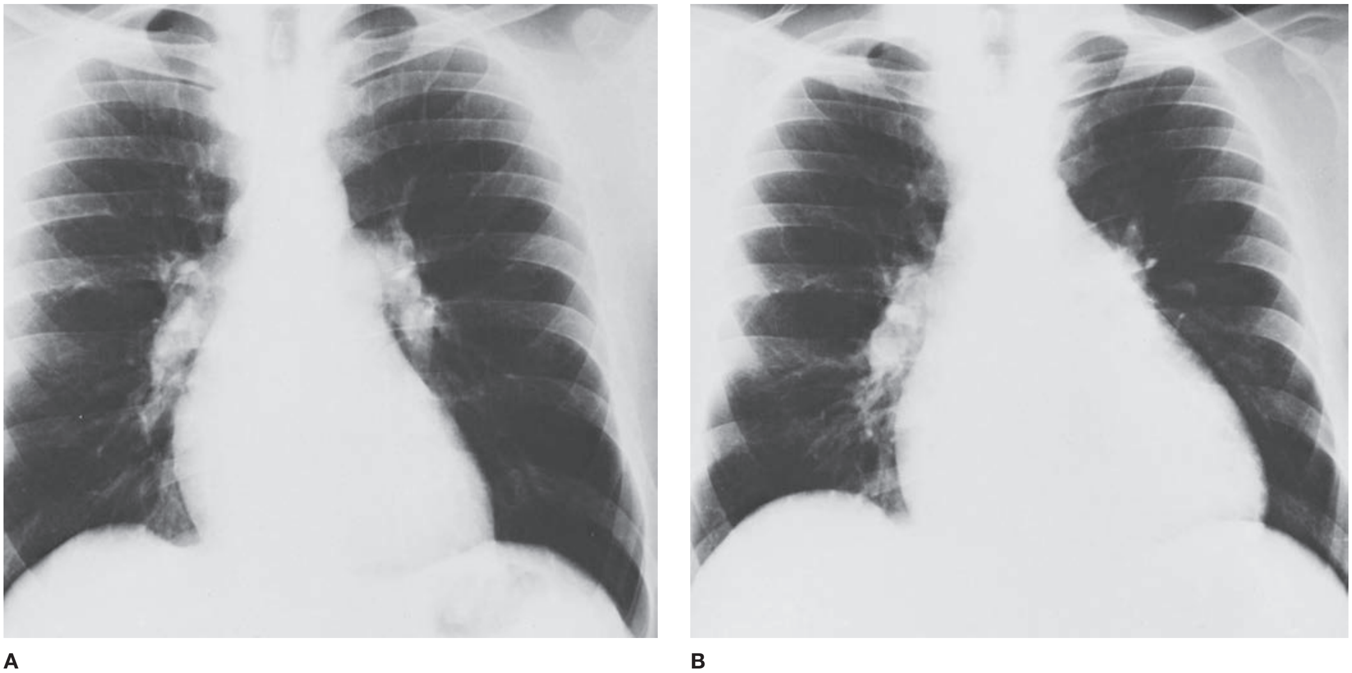


Figure 72-5 Radiographic changes in idiopathic pulmonary arterial hypertension. Compared with a chest radiograph 14 months earlier (**A**), enlargement of the cardiac silhouette has occurred in a 30-year-old man in association with increasing dyspnea (**B**).

after the administration of sedatives or anesthetic agents. In some instances, bradycardia precedes cardiac arrest and death.

An important hint to the presence of pulmonary hypertension is a history of long-standing dyspnea that has not responded to treatment for other more common disorders. Patients have often seen several clinicians before an appropriate diagnosis is made. Younger patients have frequently been told their symptoms are due to asthma, yet failed to improve significantly with aggressive anti-inflammatory and bronchodilator therapies. In older patients, dyspnea or exercise limitation may have been blamed on COPD, often despite a trivial history of tobacco use. Unfortunately, a further clue in such patients is learning that these "diagnostic" labels were never investigated with pulmonary function testing. Patients should be asked about important symptoms or risk factors that might suggest the presence and cause of pulmonary hypertension. These include symptoms of collagen vascular disease (e.g., dysphagia, skin or joint changes, Raynaud's phenomenon), sleep apnea (e.g., witnessed apneic events, daytime hypersomnolence), history of risks for thromboembolism, HIV infection, liver disease, or anorectic agent use. A history of tobacco use and chronic sputum production, or a known history of asthma with poor control, might be important clues to the presence of obstructive airway disease and hypoxia as the cause of pulmonary hypertension. A prior history of interstitial lung disease or any cause of chronic hypoxia must be noted. A careful family history should be taken including inquiring about relatives with poorly understood cardiopulmonary conditions.

■ Physical Examination

A careful physical examination is necessary to recognize the presence of pulmonary hypertension and begin elucidating its cause (Table 72-5). In mild to moderate pulmonary hypertension, the physical examination is apt to be unrevealing unless suspicion has been aroused that pulmonary hypertension may be present. Right ventricular enlargement is an important clue but notoriously difficult to detect in its early stages on physical examination. Evidence of pulmonary hypertension, such as prominent closure of the

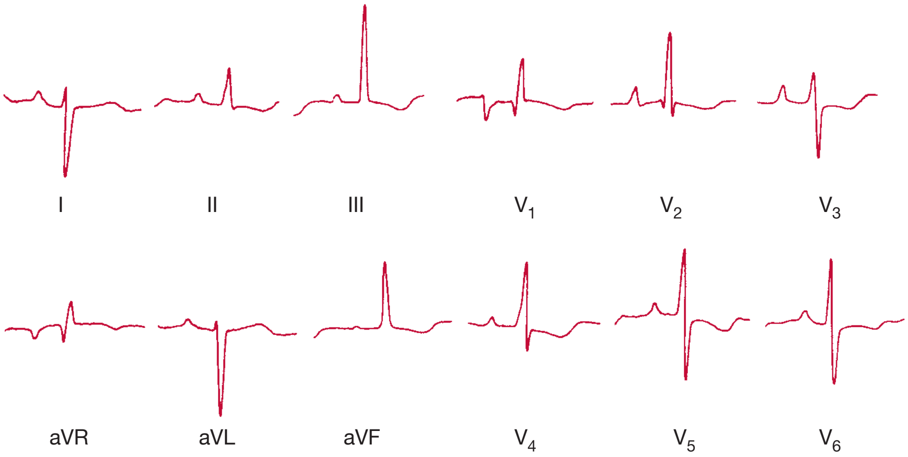


Figure 72-6 Twenty-six-year-old woman in whom the first evidence of idiopathic pulmonary arterial hypertension was by electrocardiography. The record shows marked right axis deviation and dominant R waves over the right precordium consistent with right ventricular hypertrophy.

TABLE 72-5 Physical Examination Findings in Pulmonary Hypertension

Physical Signs that Reflect Severity of PH	
Sign	**Implication**
Accentuated pulmonary component of S2 (audible at apex in over 90%)	High pulmonary pressure increases force of pulmonic valve closure
Early systolic click	Sudden interruption of opening of pulmonary valve into high-pressure artery
Midsystolic ejection murmur	Turbulent transvalvular pulmonary outflow
Left parasternal lift	High right ventricular pressure and hypertrophy present
Right ventricular S4 (in 38%)	High right ventricular pressure and hypertrophy present
Increased jugular "a" wave	Poor right ventricular compliance
Physical Signs that Suggest Moderate to Severe PH	
Sign	**Implication**
Moderate to severe PH	Tricuspid regurgitation
Holosystolic murmur that increases with inspiration tricuspid regurgitation	
Increased jugular "v" waves	
Pulsatile liver	
Diastolic murmur	Pulmonary regurgitation
Hepatojugular reflux	High central venous pressure
Advanced PH with right ventricular failure	
Right ventricular S3 (in 23%)	Right ventricular dysfunction
Distention of jugular veins	Right ventricular dysfunction or tricuspid regurgitation or both
Hepatomegaly	
Peripheral edema (in 32%)	
Ascites	
Low blood pressure, diminished pulse pressure, cool extremities	Reduced cardiac output, peripheral vasoconstriction
Physical Signs that Suggest Possible Underlying Cause or Associations of PH	
Sign	**Implication**
Central cyanosis	Abnormal V/Q, intrapulmonary shunt, hypoxemia, pulmonary-to-systemic shunt
Clubbing	Congenital heart disease, pulmonary venoocclusive disease
Cardiac systolic murmurs, diastolic murmurs, opening snap, and gallop	Congenital or acquired heart or valvular disease
Crackles, dullness, or decreased breath sounds	Pulmonary congestion or effusion or both
Crackles, accessory muscle use, wheezing, protracted expiration, productive cough	Pulmonary parenchymal disease
Obesity, kyphoscoliosis, enlarged tonsils, narrowed pharyngeal opening, macroglossia	Disordered ventilation, sleep apnea
Sclerodactyly, arthritis, telangiectasia, Raynaud phenomenon, rash	Connective tissue disorder
Peripheral venous insufficiency or obstruction	Possible venous thrombosis
Venous stasis ulcers	Possible sickle cell disease
Pulmonary vascular bruits	Chronic thromboembolic PH
Splenomegaly, spider angiomata, palmar erythema, icterus, caput medusa, ascites	Portal hypertension

PH, pulmonary hypertension.

Adapted with permission from McLaughlin VV, Archer SL, Badesch DB, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension a report of the American College of Cardiology Foundation task force on expert consensus documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. J Am Coll Cardiol. 2009;53(17):1573–1619.

pulmonary valve, is apt to be overlooked or discounted, especially in younger individuals; recognition of tricuspid insufficiency or a right ventricular gallop is often delayed until pulmonary hypertension becomes severe and has led to heart failure.

Once pulmonary hypertension is suspected, the physical examination can offer important signs. When symptoms first become manifest, a large *a* wave generally can be detected in the jugular venous pulse. Auscultation usually discloses splitting of the second heart sound with accentuation of the pulmonic component. A sharp systolic ejection click over the region of the pulmonary artery is usually heard. As pulmonary hypertension persists, enlargement of the right ventricle becomes evident as a palpable cardiac impulse near the left sternal border and in the hypogastrium. An important sign of more advanced heart failure is a right-sided (ventricular) diastolic

(S_3) gallop; it is accentuated by inspiration. Less helpful is the right atrial gallop (S_4), which occurs immediately before the first heart sound and suggests an increase in the filling pressure of the right side of the heart.

In time, tricuspid insufficiency develops. It is manifested by a holosystolic murmur, best heard in the fourth interspace to the left of the sternum; the murmur characteristically increases in intensity during inspiration (as do the third and fourth heart sounds). A prominent *v* wave appears in the jugular pulse, and distended neck veins pulsate with each heartbeat. The onset of right ventricular failure is often marked by discomfort in the right upper quadrant due to hepatic engorgement as well as edema in the lower extremities. The liver often also shows expansive pulsations that are synchronous with the heartbeat. Hydrothorax and ascites are uncommon, even after right ventricular failure has progressed to the stage of hepatomegaly and pedal edema. Systemic arterial hypoxemia is often present. Assessment of oxyhemoglobin desaturation with activity is an important component of the patient evaluation; if desaturation is noted, formal exercise testing to titrate oxygen therapy should be pursued promptly. Late in the disease, many patients develop peripheral cyanosis secondary to a reduced CO and peripheral vasoconstriction; central cyanosis also occurs preterminally in some patients because of right-to-left shunting through a patent foramen ovale.

The physical examination should be focused on the presence of additional signs to indicate a possible cause of pulmonary hypertension. Systemic hypertension, a risk factor for coronary artery disease or diastolic dysfunction, may suggest left-sided heart disease. Abnormal lung sounds might include wheezing suggesting airflow obstruction, or crackles suggesting either pulmonary edema or diffuse parenchymal lung disease. Additional findings suggestive of lung disease include hyperresonance to percussion or hyperinflation of the thorax (barrel chest) suggestive of COPD or kyphoscoliosis causing a restrictive pattern. Skin changes such as rash or telangiectasias are clues to the presence of collagen vascular disease, as are digital ulcers in patients with the CREST variant of systemic sclerosis. The presence of digital clubbing should also be noted as it may indicate congenital heart disease, certain forms of chronic hypoxic lung disease (e.g., cystic fibrosis or certain interstitial lung diseases), or PVOD.[199] Narrowing of the posterior oropharynx, macroglossia, and a large neck size may suggest obstructive sleep apnea.

■ Diagnostic Studies

Diagnostic testing is used to confirm the presence of pulmonary hypertension, identify the etiology, assess severity and prognosis, and help guide appropriate therapy. Table 72-6 lists tests that are essential in the evaluation of pulmonary hypertension.[200] Table 72-7 lists the criteria required for a diagnosis of PAH.

Following a detailed history and physical examination, an electrocardiogram, chest radiograph, and echocardiogram are indicated if there is suspicion of pulmonary hypertension, and often as logical tests to evaluate symptoms such as dyspnea even if concern for pulmonary hypertension has not been raised.

Chest Radiograph and Electrocardiogram

Early in the evolution of pulmonary hypertension, the chest radiograph appears normal. In time, the central pulmonary arteries become increasingly prominent as the peripheral vessels become

TABLE 72-6 Evaluation of Patients with Pulmonary Hypertension

Detection	Detailed history and physical examination	Suspicion of pulmonary hypertension and possible causes/associations
	Electrocardiogram	Help exclude other causes of cardiopulmonary symptoms
	Chest radiograph	
	Echocardiogram (at rest, to consider repeat with exertion)	Evaluate for presence of pulmonary hypertension, assess chamber sizes and function, valvular abnormalities, contrast (bubble) study to evaluate possible shunt
Essential testing	Pulmonary function testing	Exclude obstructive or restrictive lung disease
	Overnight oximetry	Screen for sleep-disordered breathing
	Lung (V/Q) scan	Exclude thromboembolism
	Blood serologies (e.g., CBC, liver function, renal function, HIV, ANA, antiphospholipid antibodies)	Exclude collagen vascular disease, liver disease, infection, and other possible causes of pulmonary hypertension
	Oxygen desaturation study	Assess need for supplemental oxygen (rest and exertion)
	6-Minute walk test	Establish baseline
	Right cardiac catheterization	Confirm diagnosis, assess other cardiac causes (shunt); consider left heart catheterization
Contingent testing	Transesophageal echocardiogram	Assess for patent foramen ovale, atrial septal defect, abnormal valves, and other abnormalities Characterize valvular function
	Computed tomogram of chest	Assess interstitial lung disease, adenopathy
	Polysomnogram	Diagnosis and treatment of sleep-disordered breathing
	Pulmonary angiogram	Assess presence and location of organized thromboemboli and suitability for pulmonary thromboendarterectomy
	Blood studies (BNP, clotting studies, genetic testing)	
	Lung biopsy	Exclude subtle interstitial lung disease vasculitis and other uncommon diseases (PVOD, PCH) to assist planning

Data from Barst RJ, McGoon M, Torbicki A, et al. Diagnosis and differential assessment of pulmonary arterial hypertension. J Am Coll Cardiol. 2004;43(12 Suppl S): 40S–47S.

TABLE 72-7 Requirements for the Diagnosis of Pulmonary Arterial Hypertension

Required Testing	Rationale
Cardiac catheterization:	Confirm presence of pulmonary hypertension
• A mean pulmonary artery pressure >20 mm Hg • Pulmonary artery wedge or left ventricular end diastolic pressure ≤15 mm Hg • Pulmonary vascular resistance ≥3 Wood units[a]	Exclude left heart disease as the cause of pulmonary hypertension (pulmonary venous hypertension) (group 2 PH)
PFTs, chest imaging without evidence of more than mild lung disease	Exclude chronic hypoxemic lung disease as cause of PH (group 3 PH)
Ventilation–perfusion scan without evidence of unmatched perfusion defects	Exclude chronic thromboembolic pulmonary hypertension (group 4 PH)

[a] *An elevated pulmonary vascular resistance is not included in all published criteria for the diagnosis of PAH.*

attenuated, and the cardiac silhouette enlarges (Fig. 72-7). The chest radiograph (together with pulmonary function tests) may also suggest the presence of underlying lung disease. An electrocardiogram should be obtained and may indicate signs of ischemic heart disease or conduction abnormalities. Findings suggestive of the presence of pulmonary hypertension include right axis deviation, right atrial enlargement, and right ventricular hypertrophy (Fig. 72-6). Arrhythmias are uncommon until late in the course of the disease, when they may contribute to syncopal episodes and coincide with clinical deterioration.

Echocardiogram

When there is suspicion, the echocardiogram is the appropriate first test to assess if pulmonary hypertension is present.[197,201] Indeed, as noted earlier, the unsuspected finding of pulmonary hypertension on an echocardiogram often first brings the issue to attention. A carefully performed Doppler examination is able to quantify the tricuspid regurgitant jet in the majority of cases.[202] A modified Bernoulli equation is used to estimate right ventricular systolic pressure (RVSP = $4v^2$ + right atrial pressure; v = tricuspid jet velocity in meters per second) and is assumed equal to the pulmonary artery systolic pressure when the pulmonic valve is normal. Normal RVSP has been reported as 28 ± 5 mm Hg. Echocardiographic evaluation with exercise is an additional consideration when estimates of RVSP at rest are normal and there is a high suspicion of pulmonary hypertension (e.g., dyspnea in a patient with systemic sclerosis and no other obvious cause). Echocardiographic measurements taken at peak exercise may reveal undue elevations, perhaps signaling the presence of earlier disease. However, normative echocardiographic values of RVSP with exercise have not been well established and whether patients with "exercise-induced" pulmonary hypertension require or benefit from therapies useful for patients with resting pulmonary hypertension is debated.

The echocardiogram also reveals important anatomic and functional information that may assist in identifying the cause of

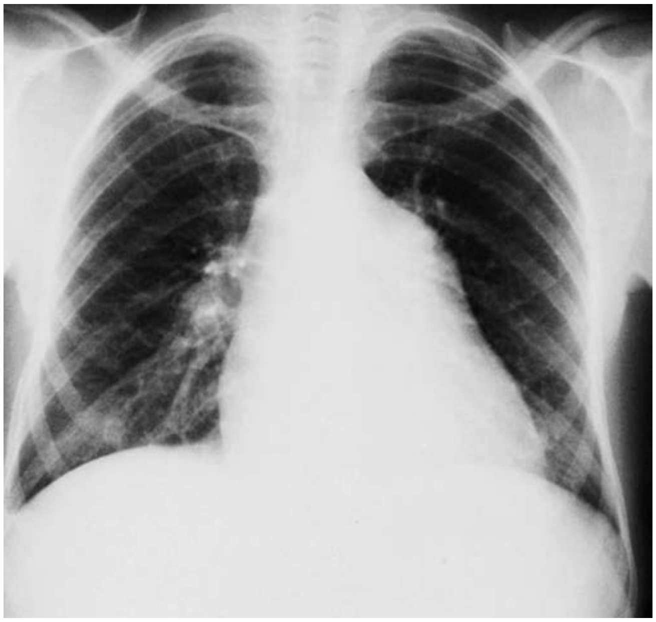


Figure 72-7 Chronic thromboembolic pulmonary hypertension. Prominent central pulmonary arteries in conjunction with the marked pruning of the peripheral tree reflect marked pulmonary hypertension in a patient with a history of multiple pulmonary thromboemboli.

TABLE 72-8 Potential Causes of Pulmonary Hypertension That May Be Identified by Echocardiography

Conditions that Predispose to Pulmonary Hypertension
Congenital or acquired valvular disease (MR, MS, AS, prosthetic valve dysfunction)
Left ventricular systolic dysfunction
Impaired left ventricular diastolic function (hypertensive heart disease, HCM, Fabry disease, infiltrative cardiomyopathies)
Other obstructive lesions (aortic coarctation, supravalvular AS, subaortic membrane, cor triatriatum)
Congenital disease with shunt (ASD, VSD, coronary fistula, patent ductus arteriosus, anomalous pulmonary venous return)
Pulmonary embolus (thrombus in IVC, right-sided cardiac chamber, or PA; tricuspid or pulmonic valve vegetation)
Pulmonary vein thrombosis/stenosis
Findings that Suggest Specific Disease Entity
Left-sided valve changes (SLE, anorexigen use)
Intrapulmonary shunts (hereditary hemorrhagic telangiectasia)
Pericardial effusion (IPAH, SLE, systemic sclerosis)

Reproduced with permission from McLaughlin VV, Archer SL, Badesch DB, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation task force on expert consensus documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc. and the Pulmonary Hypertension Association. J Am Coll Cardiol. 2009;53(17):1573–1619.

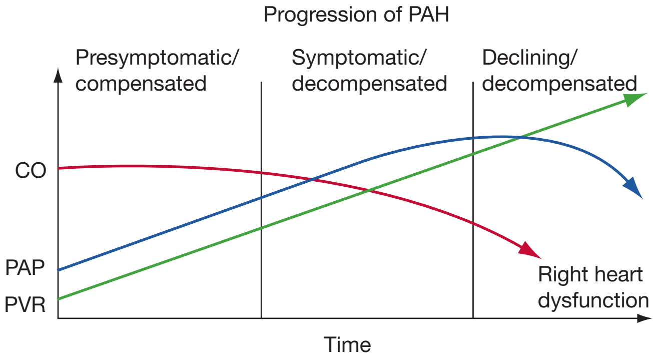


Figure 72-8 Hemodynamic changes during the progression of pulmonary arterial hypertension. With progressive increase in the pulmonary vascular resistance (PVR), the pulmonary artery pressure (PAP) initially increase until a failing right heart can no longer generate the required pressures to maintain cardiac output (CO). At this late stage both the cardiac output and pulmonary pressures may fall. *(Reproduced with permission from Taichman DB: Pulmonary Vascular Disease. Philadelphia, PA: WB. Saunders; 2006.)*

pulmonary hypertension (Table 72-8). Evaluation for a patent foramen ovale and intracardiac or intrapulmonary shunting of blood should be performed (e.g., using "bubble" contrast). Echocardiography can help to rule out related anatomic abnormalities, such as acquired or congenital mitral valve disease or left atrial myxoma. Left ventricular hypertrophy, signs of diastolic noncompliance, decreased systolic function, or focal hypokinesis as well as mitral or aortic valvular defects all are vital observations when evaluating the likely cause of pulmonary hypertension. Assessment of right ventricular size and function is essential, as the symptoms caused by pulmonary hypertension and the prognosis of patients with PAH are determined in large measure by the status of the right heart (Fig. 72-8). Indeed, unexplained echocardiographic findings of RV dilation and/or decreased function warrant further investigation regardless of whether pulmonary hypertension appears to be present by echocardiographic estimate. The degree of RV function is often evaluated subjectively, but more quantitative approaches to assessment are becoming more commonly reported, have variably been shown to predict right ventricular output and patient prognosis, and may provide better means of assessing change with disease progression or in response to therapy. Such approaches include evaluation of the tricuspid annular plane systolic excursion, tissue Doppler imaging, and myocardial performance index (Tei-Doppler index).[203] The presence and greater size of a pericardial effusion are also poor prognostic signs.[204–207] Flattening of the intraventricular septum is seen with advanced right heart dilation and failure, and the leftward movement of the septum may impair left ventricular filling (Videos 72-1 and 72-2).

While the correlation between echocardiographic estimates of pulmonary arterial systolic pressure and measurements taken at right heart catheterization is generally good, there is significant variability and confirmation by catheterization is absolutely required when the presence of pulmonary hypertension will influence the approach to treatment. For example, in the setting of some patients with severe COPD in whom an echocardiogram reveals evidence of pulmonary hypertension, confirmation by right heart catheterization might not impact medical therapy. If, on the other hand, there is consideration of surgical interventions for the COPD (e.g., transplantation or volume reduction), confirmation of the presence of pulmonary hypertension with catheterization may be important. When the diagnosis might be PAH, diagnostic catheterization is absolutely required to confirm the diagnosis and to guide appropriate therapy. Cardiac catheterization in the evaluation of pulmonary hypertension is described in the following section.

Video 72-1 Short-axis view of an echocardiogram of a patient with pulmonary hypertension demonstrating flattening of the interventricular septum with bowing toward the left ventricle during diastole. The right ventricle is hypocontractile. A small pericardial effusion is demonstrated as well. **Video 1, still shot 1**: An echocardiogram performed during diastole in the short-axis view demonstrates an enlarged right ventricle (RV), a flattened interventricular septum (IVS) with bowing toward the left ventricle (LV), and a small pericardial effusion (PE). **Video 1, still shot 2**: An echocardiogram performed during systole in the shortaxis view demonstrates an enlarged right ventricle (RV), a flattened interventricular septum (IVS), and a small pericardial effusion (PE). Impaired filling of the left ventricle (LV) during diastole compromises stroke volume. *(Reproduced with permission from Drs. Lissa Sugeng and Wassim Fares, Yale School of Medicine.) Video available on AccessMedicine.com.*

Pulmonary Function Testing, Ventilation–Perfusion Scanning, Sleep Studies

Once echocardiographic evidence of pulmonary hypertension has been established, testing for possible causes is in order. Pulmonary function tests, a radionuclide ventilation–perfusion scan, and overnight oximetry are essential to screen for possible underlying obstructive/restrictive lung disease, occult chronic thromboembolic pulmonary hypertension, and sleep-disordered breathing, respectively. Although computed tomographic (CT) angiography may reveal the presence of organized thrombus and is frequently useful for evaluation of other possible causes of the patient's symptoms, it is less useful to definitively exclude CTEPH. Since a diagnosis of CTEPH as a cause of pulmonary hypertension will markedly alter therapeutic approach, its exclusion with a ventilation–perfusion scan remains an essential test (Fig. 72-9). A history or the presence of examination findings suggestive of sleep-disordered breathing should prompt performance of overnight oximetry and/or polysomnography. Treatment of significant sleep apnea may be all that is required to treat mild pulmonary hypertension in some patients with preserved right ventricular function who are followed closely for compliance and resolution of pulmonary hypertension.

■ Laboratory Testing

Blood tests including HIV antibody, rheumatologic serologies (e.g., ANA), liver function tests, and a complete blood count are essential. Dyspnea due to PAH may be the presenting symptom leading to the initial diagnosis of systemic sclerosis or HIV infection, and the presence of either would alter required therapeutic plans. Abnormal liver function should prompt further evaluation for possible portal hypertension as an explanation for PAH.

Video 72-2 A four-chamber view of an echocardiogram in a patient with pulmonary hypertension. The right ventricle (RV) is enlarged, dilated, and hypocontractile. The right atrium (RA) is enlarged. The interventricular septum (IS) moves paradoxically toward the left ventricle (LV) during diastole, impairing LV filling. A small pericardial effusion (PE) is demonstrated. **Video 2, still shot 1**: An echocardiogram in the four-chamber view demonstrating an enlarged, dilated RV and RA, as well as a relatively underfilled left ventricle LV and a small PE. The moderator band (MB) of the right ventricle is well visualized. *(Reproduced with permission from Drs. Lissa Sugeng and Wassim Fares, Yale School of Medicine.) Video available on AccessMedicine.com.*

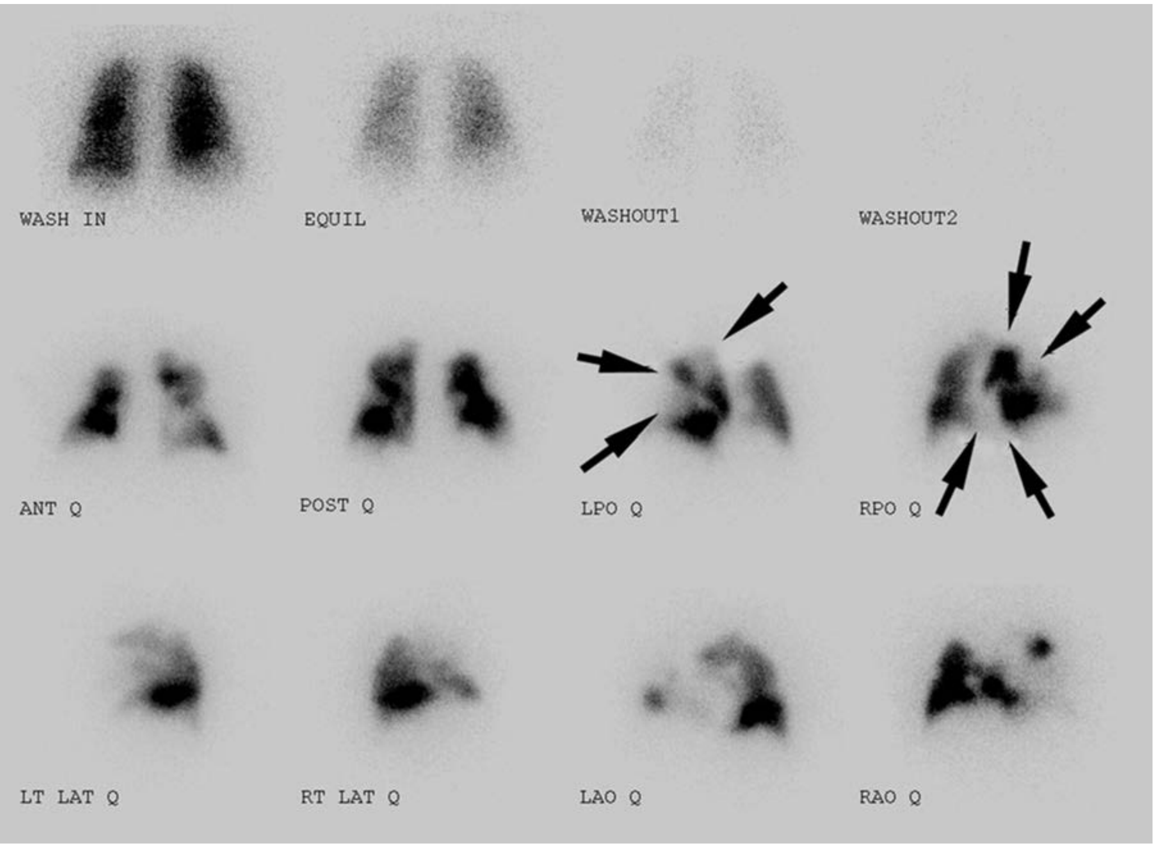


Figure 72-9 Ventilation–perfusion scan in chronic thromboembolic pulmonary hypertension. The top row of images shows normal ventilation; images in the following two rows reveal multiple unmatched perfusion defects, indicated by arrows in the posterior oblique views. *(Reproduced with permission from Kim Kerr, MD.)*

Exercise Testing and Assessment of Oxyhemoglobin Saturation

Baseline testing should also include assessments of exercise tolerance and a determination of whether supplemental oxygen is required. A 6-min walk test is a useful means of assessing exercise capacity and prognosis. It may be useful when choosing initial therapy and serial testing can be helpful in evaluating the response to therapy. Measurements of arterial oxyhemoglobin saturation both at rest and with exertion are important to ensure adequate levels are maintained, and to titrate supplemental oxygen appropriately.

Cardiac Catheterization

Right heart cardiac catheterization is required to confirm the diagnosis of pulmonary hypertension, test for important cardiac causes, and in appropriate patients perform acute vasodilator trials to determine an initial approach to therapy. Both to ensure appropriate interpretation and to avoid the need to subject the patient to repeated invasive testing when initial testing is inadequately performed, cardiac catheterization should be performed under the direction of expert operators sufficiently familiar with the evaluation of pulmonary hypertension. Except in those considered to be at very low risk of coronary artery disease, many expert centers also perform a left heart catheterization in all patients. In addition to coronary angiography, measurement of the left ventricular end-diastolic pressure (LVEDP) is important to exclude left atrial hypertension (e.g., as seen in diastolic dysfunction) as an important cause of pulmonary hypertension (pulmonary venous hypertension). Although pulmonary artery wedge pressure (PAWP) is routinely obtained during right heart catheterization, it does not always provide an accurate estimate of LVEDP. To maximize the chance of an accurate measurement, PAWP should be made at end expiration and not on the basis of digitally computed "mean" PAWP.[208,209] The PAWP should be measured with equipment levelled at the midchest position (halfway between the table surface and skin surface at the sternum). Discrepant readings between the PAWP and the LVEDP may occur frequently, and so the need for left heart catheterization to directly measure left-sided pressures should be carefully considered given the therapeutic implications of the findings.[210]

During right heart catheterization, serial measurements of blood oxygen saturation should be performed for evidence of a "step up" in oxyhemoglobin saturation suggesting the presence of left-to-right shunting of blood as an etiology of PAH. Attention should also be paid to the right atrial pressure, as significant elevation has been associated with a poorer prognosis. When suspicion of pulmonary hypertension is high and resting pressures are normal, some centers assess values with exercise (e.g., with serial leg lifts, arm raising with weights, or a stationary bicycle). As noted previously, however, normative values for pressures with exercise have not been well established and whether exercise-induced PAH represents an early stage of disease or alone warrants treatment remains debated.

A diagnosis of PAH requires a mean pulmonary artery pressure greater than 20 mm Hg and an elevated PVR greater than or equal to 3 Wood units. An adequately measured PAWP or a directly recorded LVEDP of less than or equal to 15 mm Hg is required to exclude pulmonary venous hypertension (WHO group 2 disease). The CO is obtained by either thermodilution or use of measured arterial and venous hemoglobin saturations and the Fick principle; the latter is likely more accurate when either significant tricuspid or pulmonary regurgitation is present or the CO is very low. The PVR is calculated as (mean PAP–PAWP)/CO. A normal PVR may be seen if pulmonary hypertension is due to pulmonary venous hypertension, or abnormally high CO (as may occur, for example, in patients with hyperthyroidism, thiamine deficiency, Paget disease of the bone, or arteriovenous fistulae in hereditary hemorrhagic telangiectasia). PH with an elevated CO and normal PVR may also be found in some patients with liver disease (which is to be distinguished from those with PAH associated with liver disease, termed portopulmonary hypertension [POPH] and characterized by an elevated PVR and PH and a variable CO). It must also be noted that although the hemodynamic profile of patients with PAH (an elevated mean PAP with a normal PAWP) may be seen in patients with pulmonary hypertension and pulmonary parenchymal disease (group 3) but pulmonary function testing and chest imaging distinguish these patients from those with PAH.

In patients with PAH, acute vasodilator testing is often performed at the time of right heart catheterization to identify those few patients in whom a trial of treatment with oral calcium channel antagonists is appropriate (discussed below). Agents commonly used for acute vasodilator testing include inhaled nitric oxide, intravenous adenosine, or intravenous epoprostenol.[211–216] Although the definition has varied, the currently accepted definition that requires a decrease in the mPAP of at least 10 mm Hg from baseline to a value less than 40 mm Hg, together with a CO that is unchanged or increased (but not decreased), is generally considered a "positive" acute vasodilator response.[6,197,217]

Acute vasodilator testing can have significant risk when performed incorrectly.[218] It should not be performed when PVOD is suspected, as the inability of the venous system to accommodate an acute increase in flow may precipitate pulmonary edema.[219] Acute vasodilator testing should be performed only at experienced centers and when the results will influence therapy. Patients who do not demonstrate acute vasoreactivity at the time of right heart catheterization should not receive calcium channel antagonist therapy.

EPIDEMIOLOGY OF PAH

Estimates of the incidence of PAH in studies from France, Scotland, Spain, and the United States range between 2.4 and 7.6 cases per million people. Prevalence estimates range between 15 and 26 cases per million people.[192,194,220,221] Overall, PAH appears to occur more frequently among women (around 2:1) and at a mean age of approximately 50. IPAH and PAH associated with connective tissue diseases appear to be the most commonly recognized in published studies, although limited studies suggest that the burden of schistosomiasis-related disease is likely large.

In the largest such study to date, the mean (± SD) age of patients enrolled in a multicenter U.S.-based national registry of 2525 patients with PAH was 50.1 ± 14.4 years and 79.5% were female. Nearly half of the patients were diagnosed with idiopathic disease (Fig. 72-10). It is important to note that 86% of these were prevalent patients, with a mean of almost 3 years from the time of initial PAH diagnosis until enrollment in the study, thus limiting the ability to extrapolate these data to incident disease.[194]

The prognosis of patients with PAH is worse when hemodynamic variables indicate right heart dysfunction (e.g., elevated right atrial pressure or a depressed CI), and varies according to the specific diagnosis, with PAH associated with scleroderma and portal hypertension portending a worse prognosis than other forms of PAH. Although the outlook appears to have improved with advances in disease management and the availability of multiple drug classes for therapy, many patients continue to require consideration of lung transplantation, and many continue to die. Several risk prediction tools have been recently developed, derived using data from both incident and prevalent patients managed with currently available therapies.[222] One such tool derived, validated, and updated with patients in a large U.S.-based cohort is shown in Fig. 72-11. This, as well as other risk prediction models, has been validated in populations from other countries.[222–225]

SPECIFIC PAH DISEASE SUBTYPES

In the sections to follow, the various PAH disease subtypes will be discussed in detail.

■ Idiopathic Pulmonary Arterial Hypertension

IPAH is a rare disease with an estimated incidence of 1 to 2 cases per million in industrialized countries.[226–228] The paucity of numbers of patients with IPAH and the likelihood that diverse causes and pathogenetic mechanisms can produce the same clinical syndrome have complicated descriptions of its natural history. In the past,

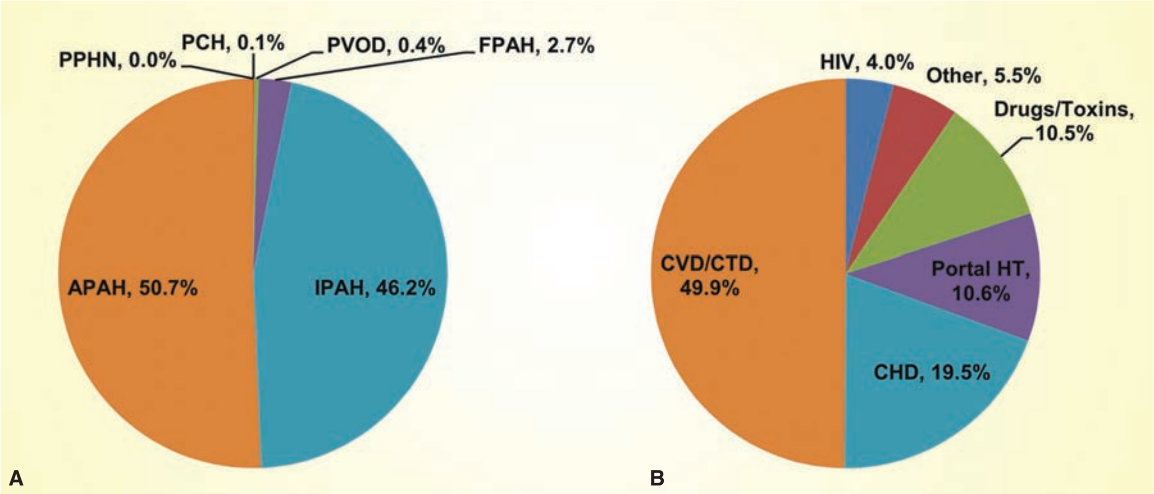
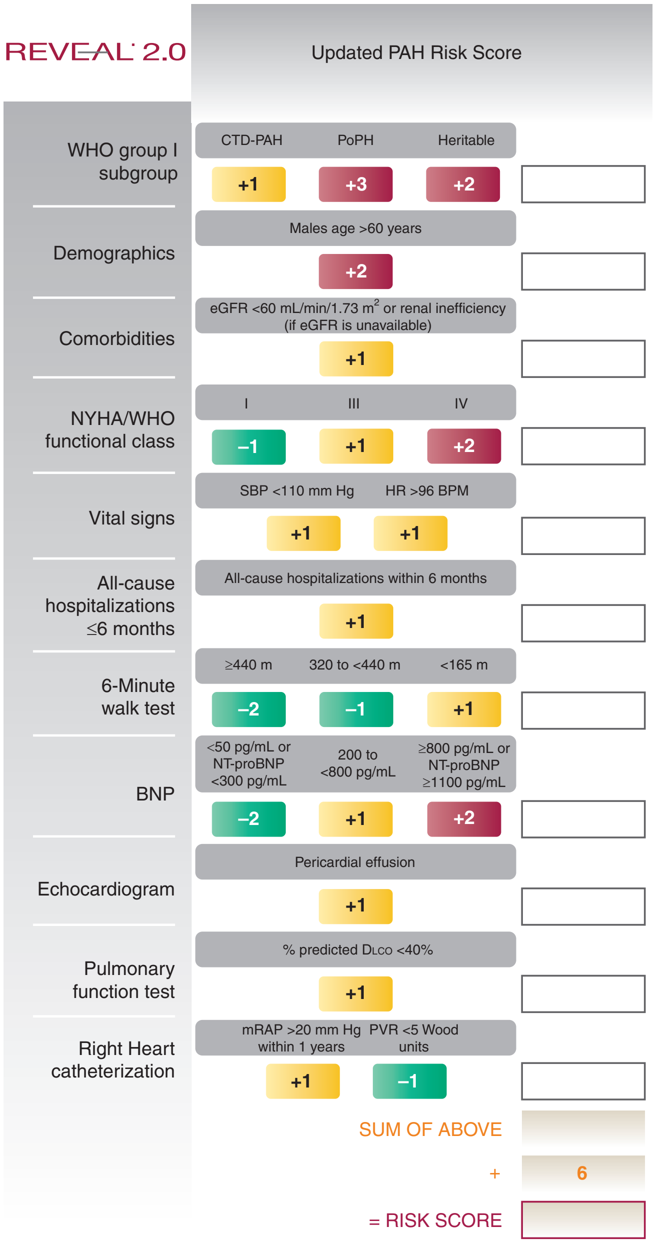


Figure 72-10 Distribution of pulmonary arterial hypertension diagnoses among 2525 prevalent patients in a United States national registry. World Health Organization (WHO) group I pulmonary arterial hypertension classification of REVEAL patients at enrollment. **A.** WHO Group I PAH classification. **B.** Breakdown of associated PAH subgroup. APAH, associated PAH; CHD, congenital heart disease; CVT/CTD, collagen vascular disease/connective tissue disease; HPAH, heritable PAH; PAH, pulmonary arterial hypertension; PCH, pulmonary capillary hemangiomatosis; PPHN, persistent pulmonary hypertension of the newborn; PVOD, pulmonary venoocclusive disease; REVEAL, Registry to Evaluate Early and Long-term PAH Disease Management.



REVEAL 2.0 Updated PAH Risk Score

WHO group I subgroup	CTD-PAH +1	PoPH +3	Heritable +2	
Demographics		Males age >60 years +2		
Comorbidities		eGFR <60 mL/min/1.73 m² or renal inefficiency (if eGFR is unavailable) +1		
NYHA/WHO functional class	I −1	III +1	IV +2	
Vital signs	SBP <110 mm Hg +1		HR >96 BPM +1	
All-cause hospitalizations ≤6 months		All-cause hospitalizations within 6 months +1		
6-Minute walk test	≥440 m −2	320 to <440 m −1	<165 m +1	
BNP	<50 pg/mL or NT-proBNP <300 pg/mL −2	200 to <800 pg/mL +1	≥800 pg/mL or NT-proBNP ≥1100 pg/mL +2	
Echocardiogram		Pericardial effusion +1		
Pulmonary function test		% predicted DLCO <40% +1		
Right Heart catheterization	mRAP >20 mm Hg within 1 years +1		PVR <5 Wood units −1	
			SUM OF ABOVE	
			+	6
			= RISK SCORE	

Figure 72-11 REVEAL Registry PAH Risk Score Calculator 2.0. *(Reproduced with permission from Benza RL, Gomberg-Maitland M, Elliott CG, et al. Predicting Survival in Patients With Pulmonary Arterial Hypertension: The REVEAL Risk Score Calculator 2.0 and Comparison With ESC/ERS-Based Risk Assessment Strategies. Chest. 2019;156(2): 323–337.)*

certain stereotypes were regarded as the norm: young women with Raynaud syndrome, with acute onset of dyspnea and fatigue, and death within 3 years. Now it is appreciated that even though there is such a subset, prolonged survival in response to medical therapy is not unusual and the disease may affect all ages, both sexes, and different ethnic groups.[229,230]

To overcome the limitations of sporadic reports, the NIH established a nationwide registry in 1981 to collect and analyze data on IPAH (then called PPH). Criteria for entry of a patient into the national registry included normal pulmonary function tests (except for a moderate reduction in diffusing capacity); a right heart catheterization to exclude congenital or left heart disease; perfusion scans and, if inconclusive, pulmonary angiography to exclude CTEPH; and serologic testing to rule out collagen vascular disease. Included in the registry were certain associated diseases, such as hepatic cirrhosis, because the reason for the association was unclear and because of the suspicion that the association might provide a clue to etiology.

By the close of the registry in 1987, data were available on 187 patients.[231] The mean age was 36.4 years and similar for women and men, although the female-to-male ratio was 1.7:1. Few patients were older than 60 years, although race and ethnicity of the cohort was similar to that of the general population. Similar demographic trends have been reported in series from France, Israel, Japan, and Mexico.[228,232,233] Dyspnea was the most common initial symptom, and the mean time to diagnosis among patients in the NIH registry was 2 years.

Prognosis of IPAH

Without effective therapy the prognosis of IPAH is very poor. The median survival of patients in the NIH registry was 2.8 years; estimated survival at 1, 3, and 5 years was 68%, 48%, and 34%, respectively.[231] Similar or even poorer figures have been reported absent effective treatment in other series from various countries.[46,234] Most patients die of right heart failure. The outlook is worse with more advanced symptoms. NIH registry patients with WHO functional classes III and IV symptoms had a median survival of only 31.5 months, compared with 58.6 months in patients with milder impairment (class I or II; Table 72-4). Although the figures have improved, functional status remains a significant indicator of prognosis even with effective advanced therapy.[228,235–237] Functional assessment with a 6-min walk test, for example, is a useful means of following response to therapy and independently predicts prognosis.[236,238–240] Maximal oxygen consumption has also been used to assess response to therapy and can correlate with survival.[240]

On echocardiogram, an enlargement of the right atrium, the presence of a pericardial effusion and its severity are each associated with an increased risk of death.[204–207] A relative increase in the isovolumetric contraction and relaxation times of the RV as compared with RV ejection time is indicative of RV dysfunction and a significantly poorer prognosis.[241]

Levels of endothelin, catecholamines, and atrial natriuretic peptide have been correlated with disease severity, whereas elevations of uric acid, von Willebrand factor, D-dimer, troponin-T, and brain natriuretic peptide have each been associated with a poorer survival in patients with IPAH.[242–248] More recently, a low serum albumin has been associated with an increased risk of death, independent other measures that would reflect passive hepatic congestion or right heart dysfunction.[207] None of these putative prognostic markers is currently incorporated into clinical decision-making.

Hemodynamic variables reflecting the development of right heart failure (an increased right atrial pressure and decreased cardiac index) are associated with a poorer prognosis.[233,249,250] Worsened survival has been seen in association with both increasing and decreasing mean pulmonary artery pressures (mPAPs). These observations are not necessarily contradictory. Rather, they reflect the natural history of right heart failure in PAH: mPAP rises initially as the vascular derangements worsen only to fall later as the right heart fails and is no longer able to generate an increased pressure (Fig. 72-8).

A regression equation based on hemodynamic data from the NIH registry has been used to predict survival.[233,251] Because of the dismal prognosis expected, long-term "control" groups without treatment in clinical trials are unethical and assessments of survival with new therapies have been compared with outcome as predicted by the NIH equation. Such comparisons have suggested improved survival with epoprostenol and endothelin receptor antagonists. These improvements are addressed in the discussion of individual therapies in the following sections. As a growing number of effective drugs are now routinely employed, the relevance of survival estimates based on data from an era lacking effective treatment is questionable. The NIH registry equation is no longer sufficient for predicting survival given current standards of care and background therapies. When applied to a more recent cohort of patients treated with current agents, the NIH equation underestimated survival.[207]

It is not surprising that the prognosis of patients with IPAH who have suffered cardiac arrest is dismal even when resuscitative efforts are initiated promptly. In a retrospective review of the records of over 3000 patients, 132 episodes of attempted cardiopulmonary resuscitation (CPR) following cardiac arrest were identified. Survival at 90 days following CPR was only 6%.[252]

■ Heritable Pulmonary Arterial Hypertension

A family of patients with what was then termed "PPH" was first described by Dresdale in 1951.[4] Thereafter additional families were reported, and Loyd and Newman identified an autosomal dominant pattern of inheritance, a greater tendency for female carriers to manifest clinical disease, and an earlier onset in successive generations (genetic anticipation).[253,254] Linkage analysis led to a marker at chromosome 2q31–32, and mutations in the gene for a member of the TGF-β family of receptors, bone morphogenetic protein receptor II (BMPRII), were identified as the cause of heritable PAH.[175,176,255,256] In addition, concomitant thrombospondin 1 gene mutation (*THBS1*) has been detected in a small subset of heritable PAH patients with BMPR2 mutations; this mutation has been proposed to further promote pulmonary hypertension development and increase genetic penetrance.[187]

Mutations in another member of the TGF-β family, ALK1, predispose patients with hereditary hemorrhagic telangiectasia to develop PAH.[185,186,257,258] Several other genetic mutations have been more rarely described in heritable PAH. These include alterations in the genes encoding 5-hydroxytryptamine (serotonin) transporter, mothers against decapentaplegic homologue 9 (SMAD9), caveolin 1, and potassium channel subfamily K member 3 (KCNK3).

TGF-β receptors control an array of cell growth and differentiation systems. BMP signaling is involved in the control of normal vascular development as well as the homeostasis of the adult pulmonary vasculature, likely by regulating the growth and apoptosis of endothelial and smooth muscle cells.[170] In an assessment of mutations from the coding sequence of *BMPRII* in 210 patients, more than 140 distinct mutations were identified, the majority predicting premature truncation of the gene transcript. Disease is believed to result from haploinsufficiency, where inadequate quantities of BMPR2 protein are produced for normal function.[177] In addition, the low penetrance observed in heritable PAH suggests that additional environmental factors likely contribute to disease development in genetically susceptible individuals.[259] Up to 70% of patients with heritable PAH have germline mutations in a *BMPRII* allele, as do some patients with idiopathic and other associated forms of PAH.[175,176,178–183] Clinically asymptomatic carriers may have evidence of mild pulmonary hypertension on echocardiogram.[260] Common ancestries have been identified that link previously assumed "sporadic" cases of IPAH. Failure to recognize heritable cases of PAH may arise due to incomplete family history taking or reporting, and low disease penetrance, particularly in smaller families.[179,261]

There are no established differences in the approach to treating patients with heritable PAH compared with IPAH. At present, the clinical evaluation of patients remains the same. Genetic testing of family members should be considered to assess the risk of developing PAH. As a rough guide, there is a one in five chance of PAH developing in a first-order relative who carries a disease-causing *BMPRII* mutation. If genetic testing has not been performed, the risk of disease developing in the first-order relative of a patient with known heritable PAH is approximately one in ten. In the absence of a disease-causing *BMPRII* mutation, the risk of disease is the same as in the general population (estimated at one in a million).[259] Because of the potential interpersonal, psychological, and economic implications of identifying an at-risk genotype, genetic testing should be performed only in conjunction with professional genetic counselling.

■ Pulmonary Arterial Hypertension Associated with Specific Conditions

Pulmonary arterial hypertension has been reported in a wide variety of disorders, as discussed below.

Connective Tissue Disease

The lungs and the pleura are commonly affected in patients with connective tissue disease. Although the incidence in each of the connective tissue diseases varies, interstitial lung disease is more common than isolated involvement of the pulmonary vasculature. When present, however, PAH is frequently a more rapidly lethal development than interstitial lung disease. It is important in this population to differentiate between pulmonary hypertension associated with interstitial lung disease and the true development of PAH that occurs in the absence of significant interstitial changes. Pulmonary hypertension may also develop due to left heart ischemia or diastolic dysfunction, or to thromboembolic complications of collagen vascular disease.[262] Unfortunately, both interstitial lung disease and true PAH coexist in many patients. Most clinical studies of PAH therapy have excluded patients with collagen vascular diseases and evidence of "significant" restriction (usually defined as an FVC of <70% of predicted values) or interstitial changes on radiographs. Drugs that are efficacious in PAH have not proved effective in the treatment of pulmonary hypertension that accompanies interstitial lung disease. Among patients with systemic sclerosis, PAH occurs most commonly in those with limited disease or the CREST syndrome. Prevalence estimates have ranged significantly, but when investigated with right heart catheterization, PAH has been found in 7% to 12% of patients.[263,264] The prognosis of patients with scleroderma is worse when their disease is complicated by PAH than by pulmonary fibrosis, even when the latter is severe. Nearly one-half of patients with PAH in the context of scleroderma die within 1 year, compared with a 3-year 50% mortality when the lung is affected by fibrosis alone.[265,266] Even with the use of equivalent therapies, the outcome of patients with PAH associated with systemic sclerosis is less favorable than for IPAH (Fig. 72-12).[90,235,265,267,268]

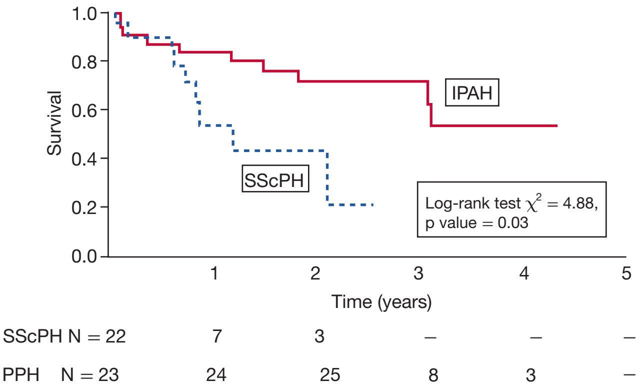


Figure 72-12 Survival of patients with systemic sclerosis–associated pulmonary arterial hypertension is worse than that of patients with idiopathic pulmonary arterial hypertension despite equivalent therapies. *(Reproduced with permission from Kawut SM, Taichman DB, Archer-Chicko CL, et al. Hemodynamics and survival in patients with pulmonary arterial hypertension related to systemic sclerosis. Chest. 2003 Feb;123(2):344–350.)*

When estimated by echocardiography, pulmonary hypertension has been identified in approximately 4% to 10% of patients with systemic lupus erythematosis, but as many as 43% when patients are followed prospectively.[269–274] Estimates of prevalence are variable and most were obtained without confirmation by catheterization in patients with mixed connective tissue disease. Regardless of frequency, however, when it is present, PAH appears to be a significant cause of death in these patients. PAH occurs in numerous other rheumatologic disorders, including Sjögren syndrome and rheumatoid arthritis, although firm data on incidence or impact on survival are lacking.

Human Immunodeficiency Virus

Patients infected with the human immunodeficiency virus (HIV) are at increased risk of developing PAH. The mechanism by which HIV predisposes to the development of PAH is not known, but it does not appear to be due to direct viral infection of pulmonary vascular endothelial cells.[275] Infection may cause elevations in local concentrations of growth factors or other mediators such as endothelin to indirectly result in the development of PAH.[276–278]

The estimated annual incidence of PAH among HIV-infected patients is approximately 0.5%, significantly higher than the estimated annual incidence of 1.7 per million in the general population.[225,279] The annual incidence of pulmonary hypertension in a large Swiss cohort of HIV-positive patients appears to be declining, having peaked at 0.24% in 1993 as compared with 0.02% in 2001; this decline was hypothesized to relate to the introduction of highly effective antiretroviral therapies.[280] However, no such change was seen in a French study population, comparing rates of HIV-associated PAH between the early 1990s and 2008.[281] It is unclear, therefore, if better control of HIV infection alters the risk of developing PAH.

Symptoms, hemodynamic findings, and survival of PAH associated with HIV appear to be similar to IPAH.[282] Like IPAH, the prognosis is worse with more advanced symptoms (e.g., WHO functional class III or IV compared with either I or II). A CD4 lymphocyte count below 212 cells/mm^3 also has been associated with a poorer prognosis.[283] Mortality is more often directly attributable to PAH and right heart failure than to infectious complications.[282,283]

Portal Hypertension

The lung may be affected by chronic liver disease in several ways, including the hepatopulmonary syndrome with the development of vascular dilatations and resultant hypoxemia, the development of pleural effusions (hepatic hydrothorax), and pulmonary hypertension. Liver disease is frequently characterized by a low systemic vascular resistance and high CO; the accompanying increased flow and blood volume result in pulmonary hypertension although the PVR is normal or even decreased. Vascular changes resulting in an elevated PVR, on the other hand, are seen with the development of PAH associated with portal hypertension, also termed POPH. Evaluation of pulmonary hypertension in these patients may be difficult, as the high CO state of liver disease may precede or accompany the developmental POPH. Thus, compared with patients with IPAH, patients with similar degrees of clinical impairment and POPH may display numerically smaller elevations in PVR or decrements in CO.[284]

The pathologic changes seen in POPH are similar to those described in other forms of PAH: vasoconstrictive, proliferative, and obliterative changes including both plexiform and thrombotic lesions.[285,286] The pathogenesis is not well understood and may involve abnormal proliferative (or other) vascular responses, but inducing triggers are not well defined. Portal hypertension might alter the vasoactive mediators to which the pulmonary circulation is exposed because of blood bypassing the liver via portosystemic shunts and returning to the systemic circulation.[287] As in other forms of PAH, altered levels of vasodilators and vasoconstrictors have been observed in patients with POPH.[288,289] Women with portal hypertension appear to be at greater risk for the development of POPH than men, as do patients with autoimmune hepatitis. The severity of portal hypertension does not appear to influence the risk of POPH.[290,291] Predisposing, likely genetic, factors are also believed to determine why only some patients with liver disease develop POPH.[292] The degree to which mutations in *BMPR2* are involved in the development of POPH remains unclear.

The prevalence of PAH in patients with liver disease has not been established. Estimates of up to 16% have been reported in studies screening patients with advanced liver disease.[288,293] In one series of patients evaluated for liver transplantation, the prevalence of POPH was 8.5%.[285] Incidence has not been evaluated. Without effective treatment the prognosis of POPH is poor, with a mean survival of only 15 months reported in one retrospective series of 78 patients.[294] Survival with current therapies is worse for patients with POPH than IPAH. In the REVEAL cohort, despite less severe hemodynamic derangements at the time of enrollment, 5-year survival of 174 patients with POPH was significantly worse than of 1478 patients with IPAH/HPAH (40% vs. 64%, respectively), although the initiation of therapy appeared to have been delayed in POPH compared with IPAH.[284]

The symptoms and findings on physical examination of POPH reflect the presence of both PAH and chronic liver disease. While shortness of breath may be overshadowed by abdominal complaints and fatigue, dyspnea becomes prominent as POPH progresses. Differentiating between the contributions of PAH-related cor pulmonale and cirrhosis as the cause of fatigue, edema, and abdominal complaints such as satiety, bloating, and ascites can be difficult.

Compared with IPAH, there are a paucity of data regarding effective treatments for POPH, due to the small number of patients with POPH and their exclusion from nearly all PAH clinical trials until the PORTICO study (discussed more below). Mild disease usually does not require specific treatment; whether early therapy will prevent progression is unknown. Treatment for more severe disease differs from that of other patients with PAH in that some experts have advised against the use of calcium channel antagonists even if acute vasoreactivity is documented during cardiac catheterization. This concern is based upon the potential worsening of intrahepatic venous gradients by calcium channel antagonists.[295–298] Diuretics are particularly important in POPH due to the frequent presence of both cor pulmonale and cirrhosis causing fluid retention, edema, and ascites. Anticoagulation is less frequently employed due to pre-existing coagulopathy related to underlying hepatic synthetic deficiencies or the presence of splenomegaly and significant thrombocytopenia.

The experience with currently available PAH targeted agents in the treatment of POPH has been reported in small case series.[299–308] The PORTICO study was the first randomized controlled trial investigating the efficacy and safety of the endothelin receptor antagonist macitentan in patients with POPH.[309] Macitentan improved the primary endpoint of PVR reduction at 12 weeks without significant hepatic safety concerns. These results should not be generalized across other endothelin receptor antagonists due to known association of liver function abnormalities with bosentan and differing mechanism of action with the selective antagonist ambrisentan.

Many patients with advanced hepatic dysfunction require liver transplantation. The perioperative mortality is significantly increased by the presence of severe PAH, however, and therefore a mean PA pressure above 50 mm Hg is considered a contraindication to transplantation at most centers.[310,311] Effective treatment to lower PAPs has been used in some patients who subsequently underwent orthotopic liver transplantation successfully.[299–302,306,312]

It is therefore essential that POPH be recognized in patients being considered for liver transplantation prior to surgery. All potential liver transplant patients should be assessed by echocardiography, and cardiac catheterization should be undertaken when the estimated right ventricular systolic pressure approaches 50 mm Hg. Serial monitoring for the development of pulmonary hypertension should be performed in patients listed for liver transplantation.[313] Unlike the hepatopulmonary syndrome, in which liver transplantation results in resolution of the pulmonary vascular abnormality, liver transplantation is not reliably curative of POPH. While some cases of reversal have been reported, POPH has progressed in other patients following transplantation.[295]

Drugs and Toxins

The term "dietary pulmonary hypertension" refers to the fact that substances taken by mouth can damage the pulmonary circulation. In animals, ingestion of *Crotalaria spectabilis*, an annual shrub, causes multiorgan injury, including damage to the lungs. In humans, certain appetite suppressant drugs exert similar effects.

Anorectic Agents—Aminorex and Fenfluramine Derivative Between 1966 and 1968, an epidemic of PAH erupted in Switzerland, Austria, and Germany where the incidence increased 20-fold.[314] The epidemic followed the introduction in these countries of an appetite-depressant agent, aminorex (2-amino-5-phenyl-2-oxazoline), in November 1965. Although only 2% of those exposed to the drug developed PAH, the relative risk compared to unexposed individuals was 52:1.[315] Aminorex resembles epinephrine and amphetamine in chemical structure; both of these agents release endogenous stores of catecholamines. Aminorex was banned in 1968, and the epidemic subsided. After stopping the drug, the level of pulmonary hypertension decreased or stabilized at a tolerable level in some patients and completely reversed in others. However, in many patients, the disease continued inexorably from pulmonary hypertension to cor pulmonale and death despite discontinuation of the drug. The pathology produced by aminorex in humans was identical to that of IPAH, including plexiform lesions and intimal fibrosis. Unfortunately, attempts to produce pulmonary hypertension by administering aminorex to experimental animals were consistently unsuccessful.

This outbreak had several important epidemiologic implications: (1) A medication taken by mouth could damage pulmonary arteries and arterioles; (2) because few of the many individuals who used the agent developed pulmonary hypertension, the possibility was raised of genetic susceptibility to injury by aminorex; (3) other anorectic medications that resemble the catecholamines and amphetamines in structure might have similar effects in predisposed individuals (this possibility was reinforced by experience with phenformin, an antidiabetic agent that resembles the amphetamines in structure); and (4) pulmonary hypertension can be reversible, particularly when detected early in its course and before pressures reach systemic levels.

After the aminorex epidemic, a variety of appetite-suppressant medications were used with little heed to the possibility that these agents might cause PAH. Then, in the early 1990s, Brenot et al.[316] called attention to possible association in Europe of PAH and the use of fenfluramine derivatives for weight reduction, prompting the establishment of an international registry in Europe to assess the incidence and risks of IPAH. Among the 95 patients enrolled in the registry, anorectic agent use was clearly associated with an increased risk of PAH, especially when taken longer than 3 months (odds ratio, 23.8). In 1996, Abenheim sounded the alarm that an epidemic might be in the making: the Food and Drug Administration in the United States had approved the use of dexfenfluramine, a fenfluramine derivative, for the long-term treatment of obesity even though experience with long-term use was extremely sparse.[226]

Approval of dexfenfluramine by the FDA was followed by a tremendous increase in sales of this and other anorectic agents. A registry of idiopathic and anorectic agent associated PAH in the United States revealed that use of fenfluramine was strongly associated with the development of PAH (odds ratio, 7.5 with >6 months use). A high prevalence of anorectic agent use in patients with other forms of PAH was also seen, suggesting these agents might also precipitate disease in the presence of other risks such as a collagen vascular disease.[317]

Several points were illustrated: (1) Although aminorex and the fenfluramines differ in their pharmacologic characteristics, the pulmonary vascular lesions in the patients who die of pulmonary hypertension after taking either drug are identical; (2) the longer the anorectic agent is used, the more likely pulmonary hypertension is to develop; and (3) the occurrence of pulmonary hypertension in users of anorectic agents likely is related to other determinants of susceptibility, perhaps genetic.

Aminorex and fenfluramine derivatives may cause PAH by altering blood levels of serotonin (5-HT). These agents cause the release of serotonin from storage in platelets and inhibit its reuptake,[71] and serotonin is a potent vasoconstrictor and induces the aggregation of platelets. An additional mechanism by which aminorex and fenfluramine derivatives might contribute to pulmonary vasoconstriction is via the inhibition of potassium channels that mediate vasodilation.[128] An inductive role of anorexigens in promoting the development of PAH in genetically susceptible individuals also has been hypothesized. Genotyping for the presence of mutations in *BMPRII* (with heritable PAH) has not revealed a significant number of abnormalities among patients with anorexigen-associated PAH.[181,318]

In one series of 62 patients with fenfluramine-associated PAH evaluated over a 10-year period at a single center in France, the interval from drug exposure to the development of dyspnea was approximately 4 years. Hemodynamic values at the time of diagnosis were similar to a control group of patients with IPAH, although the anorectic agent–exposed patients were less likely to demonstrate acute vasoreactivity and thus be treated with calcium channel antagonists.[319] The approach to therapy for PAH associated with anorectic agent use, however, is similar as for IPAH.

Relatively little is known regarding the prognosis of anorectic agent–associated disease. Data conflict regarding prognosis as compared with IPAH. In one retrospective study of 104 patients with aminorex-associated PAH and 69 with IPAH, survival was better in both groups for patients treated with warfarin, and better overall for the anorectic-agent associated disease patients.[320] With the use of advanced therapies, survival in fenfluramine-exposed patients with PAH appears similar to that of IPAH patients.[319] When matched according to treatments and disease severity, however, a separate study of IPAH and fenfluramine-exposed patients found poorer survival in the anorectic agent group.[321]

Toxic Oil Syndrome Another episode of dietary pulmonary hypertension unfolded with the occurrence of the "toxic oil syndrome." In May and June 1981, rapeseed oil adulterated with aniline was sold door to door as olive oil in Spain and caused an outbreak of noncardiogenic pulmonary edema.[322] Twenty thousand persons were affected, and approximately 375 died. About 2000 individuals experienced sequelae. As a consequence of close surveillance, the features of three stages of the disease were categorized as early (first 6 months), intermediate (6 months to 2 years), and chronic (persisting years). From the outset, it was clear that the damage was widespread (affecting lungs, liver, skin, nervous system, immune system, muscle, and fat) and that pervasive endothelial injury featured prominently in the pathogenesis of the clinical syndromes.

The early stage was characterized by noncardiogenic pulmonary edema, eosinophilia, and pulmonary hypertension in a subset of patients; these findings resolved within 6 months. The intermediate stage was marked by thromboembolic events, weight loss, and neuromuscular dystrophies; PAH developed in some but often resolved. The chronic stage (particularly 4 and 5 years after the oil was ingested) involved progressive PAH and cor pulmonale. Increasingly evident were vascular lesions of intimal fibrosis and proliferation in association with organized pulmonary thromboemboli. Plexiform lesions also were seen.

Unfortunately, the exact chemical ingredients in the toxic oil responsible for the syndrome remain enigmatic and are unlikely to be identified, since the bootleggers could provide no recipe for the adulterated cooking oil. Nonetheless, the outbreak did show that material taken by mouth—often in small quantities—could cause widespread endothelial injury in the lungs. It also underscored the spontaneous reversibility of the pulmonary hypertension (as well as the ineffectiveness of vasodilators tried at different stages in the disease).

Hemoglobinopathies

Patients with sickle cell anemia and other hemoglobinopathies are at increased risk for the development of pulmonary hypertension. Pulmonary hypertension in this setting is currently categorized within group 5 disease. Multiple factors likely contribute to the pathogenesis of pulmonary hypertension in patients with hemolytic states, including recurrent thromboembolism, recurrent infectious or hemolytic crises causing lung damage and hypoxia, asplenia, and the microvascular effects of intravascular hemolysis itself. Hemolysis contributes to the development of pulmonary hypertension by reducing the bioavailability of NO. Hemoglobin is released into the plasma from destroyed red blood cells where it can bind and sequester NO. There is also destruction of the substrate for NO production, L-arginine, by increased levels the enzyme arginase, also released into plasma by hemolysis. Further effects of hemolysis include an increase in the expression of vascular adhesion molecules, platelet activation, the production of free radicals, and elevated levels of endothelin, all of which might contribute to the vasculopathy.[323–325]

The reported prevalence of pulmonary hypertension in patients with sickle cell anemia has ranged from 0% to 40%. Factors influencing this wide range include the age of patients examined, whether the study involved asymptomatic or symptomatic patients, and whether testing involved echocardiography or cardiac catheterization. In one prospective study of 195 adult patients with sickle cell anemia, 32% of patients had echocardiographic evidence of pulmonary hypertension, of whom more than 90% had the SS phenotype.[326] Pulmonary hypertension is associated with a poorer prognosis in patients with sickle cell anemia.[323,326] Pulmonary hypertension has also been noted in patients with other chronic hemolytic disorders, including thalassemias, hereditary spherocytosis, and paroxysmal nocturnal hemoglobinuria.[327–332]

The hemodynamic findings of pulmonary hypertension associated with sickle cell anemia differ from those seen in patients with idiopathic or other forms of associated PAH. Specifically, the mean PAP tends to be lower and CO higher in patients with sickle cell anemia diagnosed with pulmonary hypertension than in patients with IPAH. In addition, many patients with hemoglobinopathy and pulmonary hypertension demonstrate a combination of intrinsic pulmonary vascular disease suggested by an elevated vascular resistance together with left heart diastolic dysfunction with an elevated PAWP.[333] As an example, in 20 patients with pulmonary hypertension associated with sickle cell anemia the mean PAP was 36 mm Hg, CO 8.6 L/min, and PAWP 16 mm Hg; one-half of the patients had PAWP values above 15 mm Hg.[334]

The optimal treatment of patients with pulmonary hypertension associated with a hemoglobinopathy has not been established. As markers of ongoing hemolysis correlate with the severity of pulmonary hypertension as well as survival in patients with sickle cell disease, maximizing treatment of the hemolytic anemia is likely an important therapeutic consideration.[323,326] Treatment includes the use of hydroxyurea or transfusions to minimize anemia and ongoing hemolysis. Supplemental oxygen to prevent hypoxia should be used as in other forms of pulmonary hypertension. While not studied in patients with hemoglobinopathy for treatment of pulmonary hypertension itself, anticoagulation to prevent thromboembolic complications of sickle cell anemia is also a consideration. Intravenous prostacyclin can acutely decrease the mean PAP and PVR in patients with PAH associated with sickle cell anemia, but its long-term benefits have not been established.[334] Improvement with oral sildenafil was initially reported in small, uncontrolled series of sickle cell anemia patients.[335,336] However, a larger randomized controlled trial in sickle cell anemia and PH (Walk-PHaSST trial) was halted due to increased rates of pain crises and hospitalizations in the sildenafil group with no appreciable difference observed in exercise capacity.[337]

■ Pulmonary Venoocclusive Disease

PVOD is a rare form of PAH in which there is even less understanding of mechanisms and less experience with therapy.[219,338] PVOD and pulmonary capillary hemagiomatosis (discussed below) are believed to represent closely related and at times overlapping conditions. Some combination of pathologic changes on both the arterial and venous sides of the pulmonary circulation is found in all forms of PAH, but arterial changes tend to predominate in most cases. There is patchy occlusion of pulmonary veins by fibrous tissue, intimal thickening, and large numbers of hemosiderin-laden macrophages. Lymphatic dilation in the lung and pleura are additional features, likely related to pulmonary capillary hypertension and consequent chronically increased hydrostatic movement of fluid from the capillaries into the interstitium.

The incidence and prevalence of PVOD are unknown, owing at least in part to frequent misdiagnosis as IPAH. Thirteen percent of cases in the NIH registry had histologic changes of PVOD.[37] In a pooling of IPAH patient series in which cases meeting criteria for a diagnosis of PVOD were reported, an incidence of 0.1 to 0.2 cases per million persons in the general population has been estimated.[219] Prospective studies have not been performed, however, and this figure likely underestimates the true incidence of PVOD, as some cases are likely misclassified as either interstitial lung disease or heart failure because of similarities in radiographic appearance.[338] There is no apparent predilection for women (as is seen in IPAH), and patients have been diagnosed from infancy to the seventh decade of life.[339]

Although risk factors for sporadic PVOD are not well known, a genetic defect in familial cases of PVOD has been identified.[340] EIF2AK4 mutations were linked to 13 of 13 families with PVOD. In addition, this defect was also seen in 5 of 20 sporadic cases of PVOD. Case reports of PVOD complicating treatment of cancer with various chemotherapeutic agents (notably mitomycin, bleomycin, carmustine, and gemcitabine) or following bone marrow transplantation suggest that toxic exposures might elicit pathologic vascular responses.[341–353] Other case reports have noted the development of PVOD in association with various thrombophilic states, autoimmune disorders, or following bacterial or viral infection, including HIV.[354–361]

Patients with PVOD usually present with dyspnea and fatigue; symptoms less typical of other forms of PAH such as cough, orthopnea, and hemoptysis also have been observed.[199,362–366] The presence of basilar inspiratory crackles on physical examination favors a diagnosis of PVOD over other forms of PAH although these are clearly nonspecific. Decreased basilar breath sounds might suggest the presence of pleural effusions, which tend to occur more commonly in PVOD.[367,368]

The diagnosis of PVOD is suggested by the triad of pulmonary hypertension, radiographic evidence of pulmonary edema, and a normal PAWP. Unfortunately, all three are not universally present in cases of PVOD and the diagnosis frequently is delayed because of confusing findings during evaluation. As an example, "high probability" findings on ventilation–perfusion scanning, a frequent finding in PVOD due to heterogeneously impaired venous runoff, may lead to an erroneous diagnosis of CTEPH.[369] Findings on plain radiographs and CT scans in PVOD include enlargement of the central pulmonary arteries, peribronchial cuffing, Kerley B lines, interstitial infiltrates, and pleural effusions that in other circumstances might suggest left heart failure.[199,370]

In the appropriately placed pulmonary artery catheter with its balloon inflated, there is a static column of blood from the catheter tip to the left atrium and the pressure transduced is reflective of left heart chamber filling pressures (which should be normal in patients with PVOD).[371,372] Obtaining an adequate tracing, however, can be difficult and may require positioning the catheter in multiple areas. Of note, there may be a marked rise in measured pressure and a subsequent slow decline back to normal when saline is flushed through the wedged catheter; this is presumed due to impaired run-off of fluid through the restricted pulmonary venous vessels.

The definitive antemortem diagnosis of PVOD often requires surgical biopsy but this frequently is avoided due to increased operative and anesthetic risk in the setting of severe pulmonary hypertension, particularly given the questionable impact on therapy that establishing the diagnosis produces. However, establishing a diagnosis does provide prognostic information to the patient, may influence the urgency of evaluation for lung transplantation, and may be helpful in avoiding needless and possibly harmful therapies.

The features atypical of other forms of PAH (e.g., radiographic abnormalities "normally" consistent with left heart failure) should prompt caution when considering acute vasodilator testing.[199,370] Acute pulmonary edema, at times life-threatening, has been precipitated by the administration of vasodilators to patients with PVOD.

There are no established therapies for PVOD. Controlled studies have not been performed and only anecdotal reports are available. These describe both positive and negative responses to various agents. Some patients have experienced benefit while others have died with the use of calcium channel antagonists, intravenous epoprostenol, or other advanced therapies.[199,373–378] Glucocorticoids and other immunosuppressive agents have been attempted but experience has been anecdotal, with mixed results, and their use is not generally recommended except in rare cases where a concomitant inflammatory condition exists.[338,379,380] As in other forms of PAH, diuretics and supplemental oxygen should be employed as indicated. Lung transplantation is the only therapeutic option for many patients. The prognosis of patients with PVOD is poor, with most dying within 2 years of diagnosis.

■ Pulmonary Capillary Hemangiomatosis

Pulmonary capillary hemangiomatosis is another rare form of PAH with predominant involvement of the pulmonary veins. In many cases, its features overlap with PVOD, leading many to consider the two entities a single process. Pathologically, the findings are those of "pulmonary microvasculopathy" marked by angioproliferative capillary lesions that appear to invade the pulmonary vessels, interstitium, and in some cases the airways.[381,382] The etiology is unknown. Descriptive studies have reported the presence of vascular growth factors as well as markers of altered endothelial cell proliferation; altered expression of nitric oxide synthase also has been noted.[383–385] Mutations in EIF2AK4 have also been observed in both familial and sporadic cases of PCH—further supporting the overlap with PVOD.[386]

Epidemiologic features of the disease are not well understood, as only scattered case reports are available for evaluation. Pulmonary capillary hemangiomatosis may present with dyspnea and episodes of hemoptysis, and cases both with and without associated pulmonary hypertension have been reported. The radiographic findings are described as diffuse bilateral reticulonodular infiltrates, often associated with enlargement of the central pulmonary arteries.[387,388] The prognosis is poor, with most cases reported as fatal, often rapidly. Attempts at treatment with intravenous epoprostenol have resulted in pulmonary edema.[389–391] Successful treatment of several patients has been described with interferon α; another patient with superimposed endotheliomatosis was stabilized with doxycycline.[392,393] Urgent evaluation for lung transplantation is recommended.

■ Schistosomiasis

Schistosomiasis, also referred to as bilharzia or snail fever, is caused by infection with any of several species of the trematode flatworm fluke *Schistosoma.* Typically, humans contract schistosomiasis by contact with shallow water that contains snails that are intermediate hosts of the *Schistosoma* pathogen. Cercariae, the life-cycle stage released from infected snails, may penetrate human skin and after a conformational change to become schistosomulae, reach the lungs.[394] Lung involvement tends to develop after extensive chronic liver involvement, and there is debate about the relative contributions of POPH, periovular granulomas in the lungs, and host immunologic changes in producing PAH-like pathologic changes in up to 9% of patients.[395] It is estimated that up to 300 million individuals worldwide have schistosomiasis, and as such it is likely to be one of the most numerically important causes of PAH. Patients generally present clinically with dyspnea on exertion and other features similar to PAH due to other causes. Diagnosis requires documentation of PAH via hemodynamic assessments along with clinical and serologic evidence of *Schistosoma* infection.

Much remains unknown regarding the prognosis and optimal approach to therapy. One series of 54 patients in Brazil suggested a more benign course than IPAH patients at the same institution.[396] Treatment with prostenoids, endothelin antagonists, and phosphodiesterase 5 inhibitors appears efficacious in improving hemodynamics and 6-min walk distance, although large randomized trials are lacking.[397] The antischistosomal agent praziquantel can reverse pulmonary hypertension and vascular remodeling in murine schistosomiasis although its efficacy in human disease is not documented.[398]

THERAPY FOR PULMONARY ARTERIAL HYPERTENSION

The many facets and challenges in treating pulmonary arterial hypertension are presented below.

■ A Cautionary Note: Non-PAH Forms of Pulmonary Hypertension

Therapy must be driven by an appropriately established diagnosis.[399] As noted previously, PAH is but one form of pulmonary hypertension and overall less common than pulmonary hypertension due to parenchymal lung or left heart disorders. Appropriate therapy for pulmonary hypertension due to left heart disease or parenchymal lung disease centers on optimal management of the underlying left heart disorder or lung disease, respectively. Far too often focus on the presence of pulmonary hypertension distracts clinicians' attention from the underlying cause. This not only leads to inappropriate use of drugs that are of established benefit only among patients with PAH, but may be accompanied by a failure to pursue appropriate therapies more likely to relieve a patient's symptoms (such as appropriate fluid management for left heart failure, interventions for coronary artery disease, correction of a mitral or aortic valvular dysfunction, bronchodilators and other inhaled medications for obstructive lung disease, or control of systemic hypertension). Other times, when underlying lung or left heart disorders have been maximally treated and symptoms remain, frustrated clinicians and patients may be driven to "blame" persistent problems on the presence of pulmonary hypertension. They may try drugs approved for treatment of PAH, reasoning that "there is nothing else to do," or that "it couldn't hurt." Unfortunately, such an approach is currently ill-informed and potentially harmful.

The use of drugs approved for treatment of PAH in patients with other forms of pulmonary hypertension has not been found to be beneficial and is associated with known harms ranging from well-established side effects to worsening survival.[400] For example, randomized trials of patients with decreased left ventricular systolic function have raised concerns for worsened heart failure with the use of endothelin receptor antagonists, and have resulted in an increased risk for death with epoprostenol infusion.[401,402] Another randomized trial of patients with COPD and echocardiographic evidence of pulmonary hypertension found use of bosentan worsened hypoxemia and quality of life, and failed to improve exercise capacity.[403] Despite suggestion of improved exercise capacity among patients with left heart dysfunction and pulmonary hypertension treated with sildenafil in a preliminary study, a larger randomized trial found no improvement, and there were more adverse events among the participants who received sildenafil.[404,405] Sildenafil was also associated with more adverse events compared with placebo in the SIOVAC study of patients with pulmonary hypertension after corrected valvular heart disease.[406] In the RISE-IIP study randomizing patients with idiopathic interstitial pneumonia to riociguat versus placebo, there were more deaths observed in the treatment arm, which prompted early termination of the study.[407] Accordingly, the misapplication of PAH targeted therapies is not just costly or ineffective, but can also be associated with serious harm including premature death.

■ General Management

A variety of pharmacologic and nonpharmacologic interventions are used in treatment of pulmonary arterial hypertension. PAH-specific pharmacotherapy is discussed in a separate section, below.

Exercise and the Avoidance of Deconditioning

Regardless of the cause, patients with pulmonary hypertension and cor pulmonale should be encouraged to maintain as active a lifestyle as possible. Recommendations that the patient minimize exertion for fear of further raising pulmonary pressures generally result only in deconditioning of the muscles and an increase in fatigue and breathlessness when an activity is attempted. Regular, steady aerobic exercise should be encouraged and is often best initiated under guidance of a pulmonary or cardiac rehabilitation program. Indeed, randomized trials of exercise rehabilitation in patients with PAH or CTEPH have demonstrated not only the safety of exercise in these patients, but improvements in exercise capacity (e.g., 6-min walk distance) greater than that observed in randomized clinical trials of currently available pharmacologic treatments for PAH. Clinically significant improvements in exercise capacity, as well as health-related quality of life, occurred in both an intensive exercise regimen beginning with inpatient therapy, as well as a 10-week outpatient program of treadmill walking similar in intensity to that commonly used in pulmonary and cardiac rehabilitation programs.[408,409] In addition to improving strength and endurance, the benefits of a supervised rehabilitation program may include a decrease in the fear many patients with dyspnea experience when initiating exercise programs. Many rehabilitation programs teach techniques to cope with dyspnea when it occurs, allowing exercise to continue. Importantly, activities that cause patients to experience lightheadedness or syncope should be avoided, including hot showers or baths and bending over to lift heavy objects.

Oxygen Therapy

Although controlled studies analogous to those performed in the treatment of COPD have not been conducted,[410] it is recommended that patients with pulmonary hypertension avoid acute hypoxia, as hypoxic pulmonary vasoconstriction will add to the burden on the right ventricle. Oxygen relieves hypoxic pulmonary vasoconstriction, thus decreasing vascular resistance and improving CO. It also lessens renal vasoconstriction, improving urinary sodium excretion, and alleviates tissue hypoxia by improving oxygen delivery. Measurements of arterial oxyhemoglobin saturation should be performed at rest, with exertion, and with sleep. Levels of arterial oxygen saturation below 90% should prompt supplemental oxygen. Maintenance of adequate oxygen saturation may be difficult in patients with severe pulmonary hypertension in whom a patent foramen ovale allows right-to-left shunting.

Air travel is a particular concern because of the threat of hypoxic pulmonary vasoconstriction. Measurements made during commercial airline flights lasting a mean of 3.6 h in a series of patients with PAH or CTEPH found that oxyhemoglobin desaturation below 85% occurred in 26% of participants, at a mean cabin pressure of 1971 ± 73 m (6467 ± 240 ft) with the lowest occurring at 1829 m (6000 ft).[411] More than one-third of patients developed symptoms during flight. Although more definitive studies have not been performed, it seems prudent to evaluate pulmonary hypertension patients who plan air travel that will last more than a few hours for in-flight oxygen use, particularly among patients with prior need of supplemental oxygen (including with sleep only). Many pulmonary function laboratories can simulate conditions of high altitude with an inspired oxygen concentration of 15% to determine whether the patient requires supplemental oxygen to maintain adequate oxyhemoglobin saturation. Patients should contact airlines in advance of travel as requirements differ, as do costs (which regrettably may not be covered by insurance). An attractive alternative to stored oxygen systems are portable concentrators, which most airlines will permit patients to carry on board without special arrangements.

Immunizations

Immunizations against influenza and pneumococcal pneumonia are important preventive measures in all patients with pulmonary hypertension and cor pulmonale. Influenza vaccination should occur annually, and the 23-valent polysaccharide pneumococcal vaccine and the 13-valent pneumococcal protein-conjugate vaccine should be administered per recommended protocols.

Fluid Management and Diuretics

Careful attention to avoid fluid overload is central to the management of right heart dysfunction of any cause. Patients must be educated regarding appropriate dietary habits and to restrict sodium intake to minimize fluid retention and the development of right heart failure. Patients should weigh themselves daily so that any trend toward fluid retention can be reversed before progressive right ventricular overload results in failure that may then be more difficult to reverse and require inpatient treatment.

Management of right heart failure relies heavily on diuretic therapy. Spironolactone is often used to manage mild fluid retention. It may also have beneficial effects in heart failure by modulating neurohormones. Loop diuretics are often required to prevent more significant fluid retention and right heart failure. Indeed, high doses and combinations of diuretics are often required to maintain appropriate fluid balance but must be used cautiously to avoid electrolyte imbalances and volume depletion.

Digitalis

It is unsettled whether cardiac glycosides should play a role in treating right heart failure. In a series of 17 patients with PAH and right ventricular failure, the intravenous administration of 1 mg of digoxin resulted in a modest increase in CO after 2 h[412] but longer-term data are lacking. Approximately 25% of patients in the REVEAL registry were using digoxin,[194] but many physicians avoid use of this agent even when right-sided heart failure is evident on account of a lack of sufficient evidence regarding its use in PAH and the potential for toxicity.

Anticoagulation

In the absence of contraindications, anticoagulation was previously recommended for patients with significant IPAH.[194,200] This is reasoned to be of benefit on the basis of autopsy studies revealing in situ thrombosis in both venous and arterial vessels without evidence of an embolic source in a significant proportion of patients with PAH.[44–46] Anticoagulation is also justified on the basis of the increased risk of venous thromboembolic disease in patients with severe heart failure and immobility, and based on their expected poor tolerance of embolic events. The efficacy of anticoagulant therapy in patients with PAH has never been studied in randomized controlled trials. Recent large registries, however, have shed more light—but also provided some conflicting results regarding the role of anticoagulation and PAH. In the European COMPERA registry of 1283 consecutive PAH patients, there was a survival benefit observed in IPAH treated with anticoagulation compared with those not on anticoagulation therapy.[413] They observed no benefit of anticoagulation with other forms of PAH in this registry. In contrast, the REVEAL registry in the United States compared PAH patients initiated on warfarin and matched those cases with similar PAH patients not on warfarin therapy.[414] They observed no survival difference among the IPAH patients treated with warfarin with matched controls. Furthermore, patients with scleroderma-associated PAH treated with warfarin had worse survival than the matched controls not on warfarin therapy. Accordingly, firm guidance regarding the use of oral anticoagulation therapy in PAH is lacking and the practice is shifting with time. The evidence remains weak but favors the use in IPAH. A role for newer, non-warfarin oral anticoagulants (e.g., rivaroxaban, dabigatran, apixaban) has not been defined in patients with PAH.

Contraception and Pregnancy

Pregnancy in women with IPAH is associated with a high maternal mortality, on the order of 30% to 50%.[415–417] Expert consensus is that pregnancy should be avoided, and early termination recommended on account of the high maternal mortality.[194,200] Effective contraception should be ensured; if hormonal contraception is chosen, anticoagulation may be advisable to reduce the risk of venous thromboembolism. Although the successful management of pregnancies in PAH has been reported,[418] single and multicenter series continue to report high rates of maternal death despite the use of aggressive treatments including intravenous prostenoids.[419–421]

Other Considerations

Patients should be queried about the concomitant use of medications and herbs. Warfarin is particularly apt to be associated with drug–drug interactions. The use of vasoconstrictor or serotonergic medications for unrelated illnesses, such as migraine, also should be undertaken cautiously. Surgical procedures may entail considerable operative and postoperative risk in patients with hemodynamic compromise from PAH. The vulnerability of patients with severe PAH to vasovagal events has to be kept in mind. An attack can be precipitated by pain, nausea, vomiting, or straining (Fig. 72-13). The induction of anesthesia and intubation may be a particularly troublesome time. The combination of bradycardia and systemic vasodilation can lead to a precipitous drop in systemic blood pressure. Atropine or a similar agent should be kept at hand during invasive procedures.

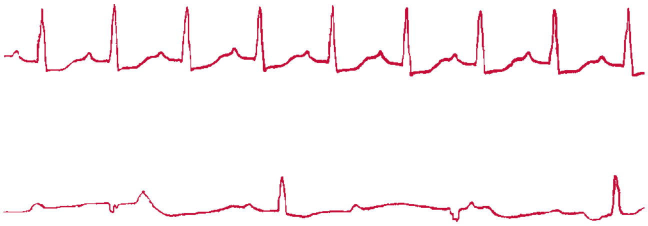


Figure 72-13 Idiopathic pulmonary arterial hypertension. Bradycardia and prolongation of atrioventricular conduction progressed to atrioventricular dissociation while patient was on bedpan. Associated with syncope.

PAH-TARGETED PHARMACOTHERAPY

Treatment of PAH aims to improve the hemodynamic derangements and right heart dysfunction caused by pulmonary hypertension. Although commonly referred to as pulmonary vasodilators, the approved PAH targeted agents also importantly have antiproliferative properties that may ameliorate some of the detrimental vascular changes seen in untreated disease.[422] Remarkable progress in the treatment of PAH has resulted in the availability of multiple therapies affording a significantly improved outlook and long-term survivors. No currently available medical treatment, however, is curative and despite durable clinical improvement in many patients, histopathologic changes of vasculopathy often remain.[423] Lung transplantation remains an option when patients continue to progress despite optimal medical management.

The majority of PAH subjects studied in controlled clinical trials have been patients with idiopathic or heritable PAH, and PAH associated with connective tissue diseases. Since most of these early studies compared a single agent to placebo, our knowledge regarding the relative efficacy of available agents is limited by the lack of head-to-head comparisons. In addition, patients treated in earlier studies were generally sicker than those treated in more recent PAH studies, which have allowed for stable background PAH therapy prior to enrollment.

In the absence of head-to-head comparison trials, care must be taken in comparing and applying the results of clinical trials of different pharmacologic agents. Most clinical trials have enrolled patients and assessed response at least in part on the basis of a WHO modification of the New York Heart Association functional assessment of patients with heart failure (Table 72-4), and there appears to be substantial variability in even expert clinicians' judgments of a given patient's functional class.[424,425] The early PAH studies most commonly used an exercise surrogate endpoint of 6-min walk test. With few exceptions, improvements in this parameter have been the basis for most of the PAH drugs approved by the FDA. The minimal clinically meaningful change in 6-min walk distance (6MWD) in patients with PAH has been estimated to be between 33 and 42 m.[426,427] These estimates, however, have been made using data from trials of predominantly treatment-naïve patients and may not be applicable when additional therapies are added.[428,429]

There has not been a new targeted pathway for PAH therapy since the FDA approval of sildenafil for this indication in 2005. The subsequent drug developments were either alternative analogues or novel mechanisms of action within the three established PAH treatment pathways. Rather than simply replicating earlier study results, these newer agents had to demonstrate safety and efficacy on top of background therapy(-ies) and/or show improvements in clinical outcomes beyond 6MWD.[430] Furthermore, rather than short 12- or 16-week clinical trials comparing walk distances as in many of the early PAH drug registration trials, more recent trials have shifted to morbidity and mortality endpoints requiring larger sample size and longer study duration. In such trials, 6MWD has been incorporated into a component of a composite endpoint, rather than serving as the primary endpoint. This evolution in PAH trial design and study conduct has also influenced our treatment expectations from short-term specific parametric gains (such as exercise tolerance based on the surrogate of 6MWD) to long-term global patient benefit (e.g., fewer clinical events such as disease progression or hospitalization related to PAH).

In general, the choice of initial therapy depends upon an assessment of disease severity and the patient's prognosis and risk for further deterioration. Multiple PAH risk assessment tools have been proposed to guide such clinical decisions and offer prognostic information.[431–433] This judgment involves an assessment of a combination of variables, including right heart assessment via hemodynamics and echocardiographic findings, exercise capacity, functional classification, and recent clinical stability or deterioration (Table 72-9).[399] The REVEAL 2.0 risk score is another powerful risk assessment tool incorporating additional patient factors such as age, vital signs, renal function, and hospitalizations within the previous 6 months (Fig. 72-11).[433]

Regardless of the choice of risk assessment tool, patients deemed to be at low or intermediate risk are generally treated with oral agents, whereas high-risk patients are treated with a regimen including parenteral prostanoid therapy.[434] No single variable determines the choice of therapy. For example, a WHO functional class III patient without rapid recent clinical change and a cardiac index above 2.5 L/min/m^2 might be appropriately treated initially with oral therapy. A WHO functional class III patient who is either rapidly declining clinically or who has more severely depressed cardiac index due to right heart dysfunction, however, might be more appropriately managed initially with intravenous prostanoid therapy. Personal preferences often influence a patient's willingness to undertake intravenous therapy. In addition, psychosocial issues, cognitive abilities, and other determinants of patient adherence may make certain therapies unsafe even if otherwise medically indicated.[435]

Although there are not well-established guidelines to follow up individual PAH patients after initiation of therapy, there are some general principles shared by expert PH centers. In addition to the clinical and functional class assessment, varying combinations of 6MWD, echocardiogram, and serum biomarkers are examined as part of a global PAH risk assessment. Right heart catheterization is also valuable depending on the clinical scenario in order to provide additional objective information and help guide further treatment. Reassessment frequency typically depends on the relative stability and risk profile of the individual PAH patient. The optimal strategy of interval testing to improve patient outcomes has not been clearly determined, nor has the relative cost-effectiveness of different approaches.

■ Calcium Channel Blockers

Calcium channel blockers (CCBs) were available prior to the three PAH targeted pathways discussed below.[436] Although not approved for PAH treatment, CCBs are still have a therapeutic role in the rare subset of PAH patients with demonstrated acute pulmonary vasoreactivity.[6] CCBs diminish vascular tone by preventing an increase in cytosolic calcium concentration through inhibition of both the influx of extracellular calcium and the release of calcium from intracellular stores. The long-term prognosis is good for some PAH patients who respond acutely to the administration of short-acting pulmonary vasodilators such as inhaled nitric oxide, intravenous adenosine, or intravenous epoprostenol, and are then treated subsequently with CCB therapy. In one study, the survival rate of acutely vasoreactive patients treated chronically with oral calcium antagonists was maintained at 94% when measured at 1, 3, and 5 years.[436] Unfortunately, relatively few patients demonstrate acute vasoreactivity (∼10% by recent estimates), and of these only about one-half experiences a sustained clinical response.[437]

Oral CCBs should not be used as vasodilator therapy in the absence of documented acute vasoreactivity. The current definition of a positive acute vasoreactive response is a decrease in mean pulmonary arterial pressure (mPAP) by ≥10 mm Hg to absolute mPAP

TABLE 72-9 PAH Risk Assessment: 2015 ESC/ERS Guidelines

Determinants of Prognosis[3] (Estimated 1-Year Mortality)	Low Risk <5%	Intermediate Risk 5%–10%	High Risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope[13]	Repeated syncope
WHO functional class	I, II	III	IV
6MWD	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing	Peak$\dot{V}O_2$ >15 mL/min/kg (>65% pred.) VE/VCO, slope <36	Peak$\dot{V}O_2$ 11–15 mL/min/kg (35%–65% pred.) VE/VCO, slope 36–44.9	Peak$\dot{V}O_2$ <11 mL/min/kg (<35% pred.) VE/VCO, slope >45
NT-proBNP plasma levels	BNP <50 ng/L NT-proBNP <300 ng/L	BNP 50–300 ng/L NT-proBNP 300–1400 ng/L	BNP >300 ng/L NT-proBNP >1400 ng/L
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 No pericardial effusion	RA area 18–26 cm^2 No or minimal pericardial effusion	RA area >26 cm^2 Pericardial effusion
Hemodynamics	RAP <8 mm Hg CI >2.5 L/min/m^2 SvO >65%	RAP 8–14 mm Hg CI 2.0–2.4 L/min/m^2 SvO 60%–65%	RAP >14 mm Hg Ci <2.0 L/min/m^2 SvO <60%

Reproduced with permission from Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 2016;37(1):67–119.

≤40 mm Hg, with an unchanged or increase in cardiac output.[6] Those failing to demonstrate acute vasoreactivity not only fail to benefit from CCB therapy, but are also prone to adverse side effects including systemic hypotension, decreased cardiac output because of negative inotropic effects, arrhythmias, salt and water retention, syncope, and death. Acute vasodilator testing as described earlier is therefore required to determine whether a clinical trial of CCB therapy is appropriate. Patients treated with CCBs must be monitored for the development of side effects including systemic hypotension, peripheral edema, and gingival hypertrophy, as well as for evidence of continued benefit.

■ Prostacyclin Pathway Therapies

The prostacyclin analogue epoprostenol was the first FDA-approved therapy for the treatment of PAH.[438] To this day, intravenous prostacyclin therapy remains invaluable for the treatment of PAH and represents the most potent of PAH therapies. Prostacyclin is a powerful vasodilator (both pulmonary and systemic) as well as an inhibitor of smooth muscle proliferation and platelet aggregation. It is a product of arachidonic acid metabolism and acts, at least in part, by stimulating the intracellular production of cAMP. Its major source is the vascular endothelial cell and deficiencies are noted in patients with PAH, although it is unclear whether these lower levels represent a cause or an effect of PAH. Several synthetic prostacyclin analogues are available for the long-term treatment of PAH, including formulations administered by continuous intravenous infusion (epoprostenol and treprostinil), subcutaneous infusion (treprostinil), inhalation (treprostinil and iloprost), or oral therapy (treprostinil). In addition, selexipag is an oral specific IP receptor agonist that selectively targets the prostacyclin receptor.

Parenteral prostanoid therapies require a capable and compliant patient for safe administration, preferably in conjunction with a strong social support system at home. Intensive patient and family education is required for safe initiation of therapy. Particularly for intravenous prostanoid initiation, the patient is typically hospitalized until appropriate understanding and proficiency in self-care is demonstrated. While appropriate expertise in the management of PAH is required for nonparenteral treatments, parenteral prostanoid therapy in particular requires the intensive support of a dedicated team of nurses and physicians at a program with sufficient expertise, typically with the additional assistance of nurses from specialty pharmacies.[439]

Intravenous Prostanoid Therapy (Epoprostenol, Iloprost, and Treprostinil)

The first prostanoid therapy shown in randomized clinical trials to be beneficial in the treatment of PAH was epoprostenol.[438] Because of its short half-life in the order of minutes, it requires continuous intravenous infusion. In an initial study, 81 patients with IPAH were randomized to receive epoprostenol infusion or treatment considered “standard” at the time (oral vasodilators, diuretics, cardiac glycosides, and anticoagulants). After 12 weeks of treatment, hemodynamic values were improved in the epoprostenol group (e.g., a 21% decrease in PVR compared with an increase in control patients), as was the 6MWD (increased by 31 m compared with a decrease of 29 m). None of the patients treated with epoprostenol died during the study; a 20% mortality by 12 weeks was observed with conventional therapy. Intravenous epoprostenol for IPAH was approved by the FDA in 1995 and remains to date one of the most potent and effective PAH therapies.

Additional reports have confirmed and extended these observations. Although originally conceived as a “bridge” to lung transplantation in patients with severe PAH, the long-term use of epoprostenol and other treatments was followed by a decrease in the demand for lung transplantation for this indication.[440] In a cohort of 162 IPAH patients treated with intravenous epoprostenol in the United States, the observed 1- and 3-year survival rates were 88% and 62%, compared with rates of 59% and 35% predicted by the NIH registry equation.[237] Remarkably similar results were observed in a cohort in France of 178 epoprostenol-treated patients with IPAH at 1 and 3 years.[236] In each case, survival was improved over that predicted by the NIH registry equation.

Epoprostenol infusion therapy has also been used in other forms of PAH. A randomized multicenter trial in patients with systemic sclerosis–associated PAH (without significant interstitial lung disease) showed improvements in both hemodynamics and exercise capacity.[441] Favorable results of epoprostenol treatment have also been reported in uncontrolled series of patients with systemic lupus erythematosis,[442] congenital left-to-right shunts,[443] anorectic agent use,[319] HIV, portopulmonary hypertension (PoPH),[299] and inoperable CTEPH.[444] Epoprostenol has been used successfully in some patients with PVOD. The use of epoprostenol in patients with PVOD must be approached with extreme caution, however, as its use in patients with impeded venous blood flow has precipitated pulmonary edema in some individuals.[219] Isolated attempts at treating patients with pulmonary capillary hemangiomatosis (also characterized by predominant involvement of the pulmonary veins) have resulted in death.[393] In one randomized trial of patients with left ventricular dysfunction (FIRST study), the use of epoprostenol was associated with a trend toward increased mortality, resulting in early termination of the study.[401] This study remains an important reminder that PAH-targeted therapy applied in other PH populations may be harmful.

Treprostinil is an alternative prostanoid analogue for intravenous therapy that has a longer half-life (4 h) and greater stability at room temperature. Treprostinil appears to have acute hemodynamic effects similar to those of epoprostenol.[445] In one uncontrolled, 12-week, open-label study of 16 PAH cases (8 with IPAH and 6 and 2 associated with connective tissue disease and congenital heart disease, respectively) intravenous treprostinil infusion resulted in an 82-m improvement in 6MWD as well as improvements in hemodynamic values.[446] In a subsequent 12-week, placebo-controlled, randomized trial of 44 PAH patients, continuously infused treprostinil resulted in an 83-m placebo-corrected increase in 6MWD and improvements in functional class.[447] Importantly, this randomized study involved the placement of central venous catheters for placebo infusions (associated with harm, including one death). This has raised ethical concerns and questions regarding optimal conduct of future investigations.[448,449]

Intravenously administered iloprost, another prostanoid, is available in some European countries, but not in the United States. In uncontrolled trials it has been used in patients with IPAH, connective tissue disease–associated PAH, and CTEPH.[450–452] The acute hemodynamic effects are similar to those of epoprostenol, but no controlled trials of its efficacy are available. In a retrospective analysis of 50 patients with PAH treated at multiple centers in Germany with intravenous iloprost following insufficient or deteriorating clinical status after the use of oral therapy with endothelin receptor antagonists or phosphodiesterase type 5 inhibitors, only ∼25% had an improved functional class at 3 months, and more than 50% of patients died or required lung transplantation within 1 year.[453]

Epoprostenol therapy is initiated at 2 ng/kg/min and gradually increased in 0.5- to 1-ng/kg/min increments at intervals dictated by patient side effects and response. Treprostinil is initiated at 1.25 ng/kg/min and similarly increased as dictated by clinical response, typically in increments of 1.25 ng/kg/min. Induced metabolism mandates a need for continuous increases in dosage to maintain improvements in symptoms. Increases are usually required at more frequent intervals initially to relieve symptoms due to PAH (e.g., dyspnea and lightheadedness), although many patients will reach a more stable dosing with less frequently required increases after several weeks to months. Such titration must be closely monitored for prostanoid side effects (nausea, tachycardia, diarrhea, masticatory jaw pain).[439] Patients lacking an acute vasodilator response (e.g., to inhaled nitric oxide or infused epoprostenol) have shown improved hemodynamics and exercise capacity after sustained treatment, suggesting that the beneficial effects are not mediated merely through acute vasodilation but rather by beneficial vascular remodelling.

Intravenous treatment with epoprostenol or treprostinil requires a tunnelled central venous catheter and thus is associated with a significant risk of bacterial infection. In an evaluation of 1146 patients who received intravenous prostanoid therapy during more than 3 years of the multicenter observational U.S.-based REVEAL cohort, an approximate threefold increase in bloodstream infections of any type and more than a sixfold increase in those due to gram-negative organisms was observed among patients receiving intravenous treprostinil compared with intravenous epoprostenol.[454] A retrospective study by the U.S. Centers for Disease Control of data from seven PAH treatment centers also concluded that rates of bloodstream infection were higher with continuous intravenous infusions of treprostinil than epoprostenol. The higher rate of infection did not appear to be due to intrinsic drug contamination[455] but may have been related to the neutral pH of the treprostinil diluent, as substitution with the basic pH epoprostenol diluent appeared to eliminate the increase in infection rates with treprostinil at one institution.[456]

Prostanoid infusion requires the use of a battery-powered portable infusion pump that must be carried at all times. A back-up medication cassette and pump must also be immediately available, as an interruption of only minutes can result in hemodynamic compromise. In theory, the risk with interrupted treprostinil infusion is somewhat lower on account of its longer half-life. The originally available formulation of epoprostenol is unstable at room temperature and must be mixed daily and kept cool with ice packs. Like treprostinil, a subsequently approved formulation of epoprostenol has greater stability at room temperature and does not require continuous cooling with ice packs.[457] Experience suggests that a higher dosage of treprostinil is required than epoprostenol to maintain an improvement in symptoms.[458] Further observation is required to establish whether survival is similarly improved with treprostinil as with epoprostenol. Experience and established duration of benefit is greatest with epoprostenol infusion, and it remains an important treatment for severe PAH and a benchmark against which other therapies are often compared.

Subcutaneous Prostanoid Therapy

Treprostinil was first approved for subcutaneous (SC) administration prior to intravenous use. In a large, randomized, double-blind, placebo-controlled trial of 470 patients with IPAH or PAH associated with congenital heart or connective tissue disease, SC treprostinil resulted in improvements in hemodynamic parameters and a modest improvement in 6MWD of 16 m at 12 weeks.[459] In an open-label extension study of participants previously enrolled in the randomized trial, together with de novo patients, survival up to 4 years was evaluated in 332 IPAH patient for whom baseline hemodynamic measurements were available. Observed survival was 91% and 72% at 1 and 4 years, respectively, compared with survival rates of 69% and 38% at 1 and 4 years predicted by the NIH registry equation.[460]

The major advantage of SC treprostinil is avoidance of an intravenous catheter and the associated risk of life-threatening bacteremia. The major drawback of SC treprostinil has been a significant incidence of troublesome infusion-site pain. This occurred in 85% of patients in the pivotal clinical trial and led to discontinuation in 8%.[459] Of 860 total patients in the previously noted open-label study, 196 (23%) discontinued SC therapy due to infusion-site pain or reactions.[460] Management strategies to reduce the occurrence and severity of pain have been reported, including initial "dry" catheter insertions with delayed infusion of medication, less frequent site rotations, and the application of topical analgesics and anti-inflammatory agents.[461] For those with severe pain refractory to these measures, narcotic analgesics may be required. Another relative disadvantage is a slower rate of dosage titration compared with intravenous therapy, making it less attractive for severely ill patients in need of a rapid response. In select patients, however, SC treprostinil has proved to be effective therapy and has allowed for avoidance of the risks and inconveniences associated with intravenous therapy.

Inhalational Prostanoid Therapy (Iloprost and Treprostinil)

Inhaled prostanoid therapies have been developed in the hopes of avoiding the need for an invasive delivery system. Iloprost is an inhaled prostacyclin analogue. A pivotal 12-week, randomized, placebo-controlled trial of 203 patients demonstrated improvement in composite primary endpoint including a placebo-corrected improvement of 36 m in 6MWD.[462] Most of the patients studied had IPAH; the remainder had PAH associated with anorectic agent or connective tissue disease, or had inoperable CTEPH. Functional class and quality-of-life measures also improved in association with treatment. Hemodynamic variables were improved at 12 weeks when measured following a dose of iloprost, although pre-inhalation values were unchanged. As in other trials of PAH therapies, hemodynamic variables were worse compared with baseline following 12 weeks of placebo. Following another 3-month placebo-controlled study, 52 patients received open-label iloprost therapy. At 2 years, 36 (69%) remained on iloprost while treatment was discontinued in 16 patients due to death, lack of efficacy, and adverse events in 2, 6, and 6 patients, respectively. The study included patients with PAH and non-PAH forms of disease. The 2-year event-free survival was 74% in the IPAH patients, compared with a predicted survival of 63% according to the NIH formula.[463]

Treprostinil is also available for inhalational therapy. A 12-week, double-blind, placebo-controlled, randomized trial of 235 patients with PAH already receiving either endothelin receptor antagonists or phosphodiesterase type 5 inhibitor therapies demonstrated an overall 20-m improvement in post-inhalation 6MWD compared with baseline (14 m in pre-inhalational distance), as well as improved measures of quality of life. There was no difference in the time until clinical worsening.[464] An open-label extension of 206 patients from this trial found a median 18-m improvement over baseline 6MWD after 24 months.[465]

In addition to the lack of need for invasive administration equipment, inhaled prostanoid therapy is easier to initiate. However, frequent dosing is required (four times daily for treprostinil and between six and nine times per day for iloprost) and compliance may be a challenge. In addition, as the hemodynamic effects wane prior to each administration, whether patients receive the same benefit as with continuously infused prostanoid therapy is unclear.[466]

Iloprost inhalational therapy is initiated at a dosage of 2.5 μg and increased to 5 μg with the subsequent dose if tolerated. Treprostinil is started at 18 μg (three breaths) four times a day, with dose escalation suggested every 1 to 2 weeks to a maximum and target dose of 54 μg (nine breaths) four times daily. Inhaled prostanoids are each administered with drug-specific portable delivery devices. Prostanoid side effects are seen with inhalational therapy, including headache, nausea, diarrhea, flushing, and jaw discomfort. Systemic hypotension and syncope also may occur, although they have not been associated with further clinical deterioration in clinical trials.

Oral Prostanoid and Prostacyclin Receptor Therapy

An orally active prostacyclin analogue, beraprost, has been studied in two randomized placebo-controlled trials of patients with various forms of PAH and appears to result in a nonsustained improvement in exercise capacity. An initial trial of 130 patients demonstrated an improvement in 6MWD after 12 weeks of therapy, but in a subsequent study of 116 patients the effect was not sustained beyond 6 months.[467,468] Neither trial demonstrated significant hemodynamic improvement compared with placebo, and beraprost is currently approved only in several Asian countries. An oral formulation of treprostinil has been studied with mixed results. In the Freedom M (monotherapy) study, 349 patients not on any approved background PAH therapy were randomized to either oral treprostinil or placebo for 12 weeks.[469] The primary endpoint of 6MWD noted a treatment effect of 23.0 m in patients receiving oral treprostinil. The most common side effects were headache (69%), nausea (39%), diarrhea (37%), and jaw pain (25%). In the parallel Freedom C (combination) study, 310 PAH patients were randomized between oral treprostinil and placebo for 16 weeks.[470] Unlike the monotherapy study, patients in this combination study were receiving background PAH therapy with either endothelin receptor antagonist or phosphodiesterase type 5 inhibitor, or both therapies at the time of enrollment. There were no significant differences in the primary endpoint of 6MWD at 16 weeks, nor in any secondary endpoints. Similar to Freedom M, the common treatment-related side effects were headache (71%), diarrhea (55%), nausea (46%), flushing (35%), and jaw pain (25%). Oral treprostinil was approved by the FDA for PAH based on these trials. The subsequently completed Freedom V study reported benefits of oral treprostinil in reducing risk of clinical worsening when added to PAH background monotherapy (26% event rate in treated group vs. 36% in the placebo group; HR, 0.74; $p = 0.028$).[471] Unlike in the prior Freedom studies, oral treprostinil was administered three times daily instead of twice daily in attempt to improve tolerability. The reported side effects, however, were similar to the prior two studies.

IP Receptor Agonist

The most recently approved therapy to target the prostacyclin pathway is the novel IP receptor agonist selexipag. Selexipag is an orally administered nonprostanoid IP receptor agonist that has been studied in the largest PAH clinical trial to date.[472] The GRIPHON study was designed as a morbidity/mortality study. This event-driven study randomized 1156 PAH patients and allowed for stable background mono- or combination PAH therapies. The first event to morbidity and mortality occurred in 41.6% of the placebo group versus 27.0% in the selexipag-treated group (HR, 0.60; $p < 0.001$). Within the composite primary endpoint, difference was driven by reduction in disease progression and hospitalizations due to PAH. Treatment discontinuation rate during the study was 14.3% in the selexipag group versus 7.1% in the placebo group. The most common adverse events associated with selexipag therapy included headache (65.2%), diarrhea (42.4%), nausea (33.6%), and jaw pain (25.7%). Following the approval of selexipag for the treatment of PAH, the safety and feasibility of switching from inhaled prostanoid to selexipag was investigated.[473] Of 34 patients on inhaled treprostinil as part of their PAH treatment, 32 patients maintained the switch from inhaled treprostinil to oral selexipag by 16 weeks and 28 of those patients met all predefined criteria for sustained transition. Treatment satisfaction questionnaire noted improvements in convenience from baseline to 16 weeks for those maintaining selexipag therapy. However, this was a small, uncontrolled study with a relatively brief follow-up. The safety of transitioning from or to other inhaled/oral prostanoid analogues is unknown. The current consensus opinion is that oral selexipag should not be initiated as replacement for parenteral prostanoid therapy or in high-risk PAH patients in need of parenteral therapy.[474]

Endothelin Receptor Antagonists

Endothelin 1 (ET-1) is a member of the endothelin family of peptides secreted by endothelial cells that promotes vasoconstriction and the proliferation of vascular smooth muscle and endothelial cells. ET-1 is overexpressed in the vasculature of patients with various forms of PAH, and antagonists of its interaction with its receptors (ET_A and ET_B) have been developed for oral use. Two dual ET_A/ET_B and one relatively ET_A-selective antagonist are currently available.

Bosentan is a dual ET_A/ET_B antagonist that improves hemodynamics, exercise capacity, WHO functional class, and the time to clinical worsening (defined as death, PAH-related hospitalization, need for altered therapy, or lung transplantation).[90,475] In a double-blind, randomized, placebo-controlled trial of patients with IPAH and PAH associated with connective tissue disease (predominantly systemic sclerosis), bosentan improved the 6MWD by 44 m compared with placebo at 16 weeks. Exercise capacity improved in IPAH patients, while stabilization or a slowing in the rate of deterioration was observed in patients with systemic sclerosis. The beneficial effects of bosentan on exercise capacity and functional class persist at 1 year with open-label use.[476] In a double-blind, randomized, placebo-controlled trial of PAH patients with less severe symptoms (WHO functional class II), bosentan treatment for 6 months improved hemodynamics and delayed clinical worsening compared with placebo.[477] However, there was no significant difference in exercise capacity as measured by 6MWD; both groups at baseline had 6MWD greater than 430 m. Survival of IPAH patients treated with bosentan in these trials and their open-label extensions was 96% at 1 year and 89% at 2 years, compared with “expected” survival of 69% and 57%, respectively, as predicted by the NIH registry equation.[92]

In a 16-week randomized controlled trial of patients with Eisenmenger syndrome that was primarily examining safety, bosentan use was associated with improved hemodynamics and exercise capacity, with persistent effects seen during a 24-week open-label extension.[478,479] Nonrandomized reports have suggested a benefit of bosentan in other specific PAH populations. A prospective open-label study of 16 patients with PAH associated with HIV infection reported improved hemodynamics, exercise capacity, and quality of life after 16 weeks.[480] Retrospective observational studies have reported the successful use of bosentan in pediatric patients with PAH.[481,482]

Ambrisentan is a relatively ET_A-selective antagonist. In concurrent double-blind, placebo-controlled studies of patients with PAH, 5 and 10 mg daily of ambrisentan for 12 weeks resulted in placebo-corrected improvements in 6MWD of 31 and 51 m, respectively, in one trial, and 32 and 59 m with 2.5 and 5 mg treatments, respectively, in the other trial.[483] A delay in the time to clinical worsening was seen in one of the trials, and health-related quality of life improved in both. In open-label extension studies, ambrisentan therapy was accompanied by improved hemodynamic values at a median duration of more than 1 year and persistent improvements in exercise capacity at 2 years.[484,485] Lower rates of elevated transaminases are observed with ambrisentan than bosentan and the FDA label requirement for monthly liver function monitoring has been removed for ambrisentan, although experts continue to recommend intermittent evaluations. Notable side effects include peripheral edema, anemia, and nasal congestion. Endothelin receptor antagonists as a class are teratogenic, and contraception and pregnancy testing are required for use in women with childbearing potential.

The third and most recently approved endothelin receptor antagonist is the dual ET_A/ET_B antagonist macitentan. The approval of macitentan was based on the first event-driven randomized controlled study in PAH (SERAPHIN).[486] This study represented the first shift from short-term surrogate endpoint trials in PAH to a long-term, larger morbidity or mortality trial. With 742 randomized patients with median double-blind treatment duration of 115 weeks, SERAPHIN was then the largest and longest PAH trial to date. For the group receiving macitentan 10 mg daily, there was 45% reduction in primary events compared with the placebo group. The treatment benefits with macitentan 10 mg daily were driven mainly by lower rates of disease progression and PAH-related hospitalizations. Unlike earlier PAH trials, SERAPHIN allowed for stable background PAH therapy at the time of enrollment. At baseline, 63.7% were receiving either phosphodiesterase type 5 inhibitor or oral/inhaled prostanoid therapies. Improvements were observed for both patients who were PAH drug naïve or already on background therapy. Like the other two endothelin receptor antagonists, female patients of childbearing potential require the use of highly effective contraception and monthly pregnancy testing. Nasopharyngitis, headache, and anemia were noted more frequently in the macitentan group compared with placebo; rates of reported edema were similar between macitentan and placebo. Treatment with macitentan does not require additional monthly laboratory monitoring.

Macitentan was also studied in portopulmonary hypertension (PoPH,) a PAH subgroup typically excluded from other PAH trials.[309] In one prospective, 12-week, multicenter, double-blind, placebo-controlled, phase 4 study, macitentan 10 mg daily in PoPH demonstrated a 35% reduction in the primary endpoint of pulmonary vascular resistance (PVR). There were no differences in 6MWD or functional class, and no significant hepatic safety concerns. Edema, bronchitis, and anemia were reported more frequently in the macitentan group compared with placebo. Macitentan was also studied in Eisenmenger syndrome, with 226 patients randomized to either macitentan or placebo for 16 weeks.[487] As with the prior study of bosentan in Eisenmenger syndrome, no new safety signal was noted with macitentan in this population. There was no significant difference observed in the primary endpoint of change in 6MWD.

Nitric Oxide Pathway Therapies

The roles of phosphodiesterase type 5 inhibitors and soluble guanylate cyclase stimulator are considered below.

Phosphodiesterase Type 5 Inhibitors

The relative deficiency of nitric oxide (NO)-mediated vasodilation and modulation of cell growth in patients with PAH has led to attempts to augment its effects therapeutically in order to promote improvements in microvascular remodelling. NO acts through the second messenger cGMP, which is metabolized in the lung predominantly by phosphodiesterase type 5. Specific inhibitors of phosphodiesterase type 5 can promote acute pulmonary vasodilation by reducing the degradation of cGMP.[488]

In a double-blind, randomized, placebo-controlled trial of 278 patients predominantly with IPAH but also some with congenital heart or connective tissue disease, sildenafil administered orally at 20, 40, or 80 mg three times daily improved exercise capacity, hemodynamics, and functional class.[148] Although the time to clinical worsening was not affected in this single trial, the improvement in 6MWD (51 m compared with baseline) was maintained over 1 year among the subset of patients continuing open-label use of sildenafil at 80 mg three times daily. The FDA-approved dosage for treatment of PAH is 20 mg by mouth three times daily, as there was no difference observed in among the doses in the primary endpoint. In open-label follow-up of a subset of patients up to 3 years following 12 weeks of randomized therapy with sildenafil, 46% demonstrated continued improvement over baseline exercise capacity, although additional therapies had been added to sildenafil during this period.[489] An initial 12-week, double-blind, placebo-controlled trial of sildenafil for treatment of PAH in children aged 1 to 18 years demonstrated efficacy in improving exercise capacity and hemodynamics at some doses, although the optimal regimen requires further study.[490]

The longer-acting phosphodiesterase type 5 inhibitor tadalafil was studied in a 16-week, double-blind, placebo-controlled trial of PAH with 53% already on stable background bosentan therapy.[149] Four different doses of tadalafil were studied, ranging from 2.5 mg up to 40 mg daily. The overall treatment effect was a 33-m improvement in 6MWD at 16 weeks (although statistically significant only for the highest dose group, 40 mg daily). The time to clinical worsening and quality of life also improved. The mean improvement in 6MWD was greater among the treatment-naïve participants (44 m) than those already receiving bosentan (23 m). During open-label extension for up to 1 year, improvements in 6MWD in patients receiving either 20 or 40 mg daily of tadalafil appeared to be maintained.[491]

Common side effects of phosphodiesterase type 5 inhibitors used to treat PAH are headache, flushing, diarrhea, epistaxis, and myalgias. Systemic hypotension also has occurred, particularly with concomitant nitrate use, and this combination should be avoided.

Soluble Guanylate Cyclase Stimulator Riociguat is an orally administered guanylate cyclase stimulator that augments cGMP differently than phosphodiesterase type 5 inhibitors. Riociguat can work either in conjunction with endogenous NO or in the absence of NO to produce cGMP. Riociguat has demonstrated safety and benefit both in patients with PAH and in those with inoperable CTEPH.[492,493] The PATENT-1 study in PAH randomized 443 patients into three groups: placebo, 1.5 mg three times per day, and an uptitrated dose to a maximum of 2.5 mg three times per day. By week 12, treatment effect of 36 m was observed between the 2.5-mg group and the placebo group. There were also significant improvements in secondary endpoints in PVR, NT-proBNP levels, WHO function class, time to clinical worsening, and Borg dyspnea score. The most commonly reported side effects were headache (27%), dyspepsia (19%), and peripheral edema (17%). In the open-label extension study PATENT-2, sustained improvements in 6MWD were observed out to 1 year.[494] No new treatment-related adverse events were noted.

■ Combination Pharmacotherapy

There is a growing body of evidence in PAH that favors treating more than one pathway with combination PAH-targeted therapies. With rare exceptions, combination therapy is now the standard of care for the treatment of PAH (Fig. 72-14).[434] The first major signal ushering in combination therapy in PAH came from the PACES study.[495] A total of 267 PAH patients receiving chronic intravenous epoprostenol infusion therapy were randomized to receive either sildenafil or placebo for 16 weeks. There was a placebo-adjusted increase of 28.8 m in the primary endpoint of 6MWD in patients receiving sildenafil therapy (titrated up to maximum 80 mg three times daily). There was also significant difference in time to clinical worsening, which was one of the secondary endpoints of the study. Notably, 7 deaths occurred in the placebo group versus none in the sildenafil group. This was the first study to suggest that combining therapies may confer a survival benefit over monotherapy.

The pivotal evidence for up-front combination therapy came from the AMBITION study with 500 newly diagnosed PAH patients in functional class II or III randomized to receive monotherapy versus combination of approved therapies in an event-driven study.[496] The patients received either ambrisentan (10 mg) or tadalafil (40 mg) alone (starting with half the dose of each and titrated to full dose over 4 weeks), whereas the combination group received both agents titrated to full doses over a period of 8 weeks following randomization. The primary endpoint was time to first occurrence of death, hospitalization for worsening PAH, disease progression, and predefined unsatisfactory long-term clinical response. The combination group saw a 50% reduction in primary endpoint compared with the pooled monotherapy group (HR, 0.50; $p < 0.001$). Additional efficacy endpoints at week 24 demonstrated that the combination group was superior to the pooled monotherapy group in reduction of NT-proBNP, satisfactory clinical response composite

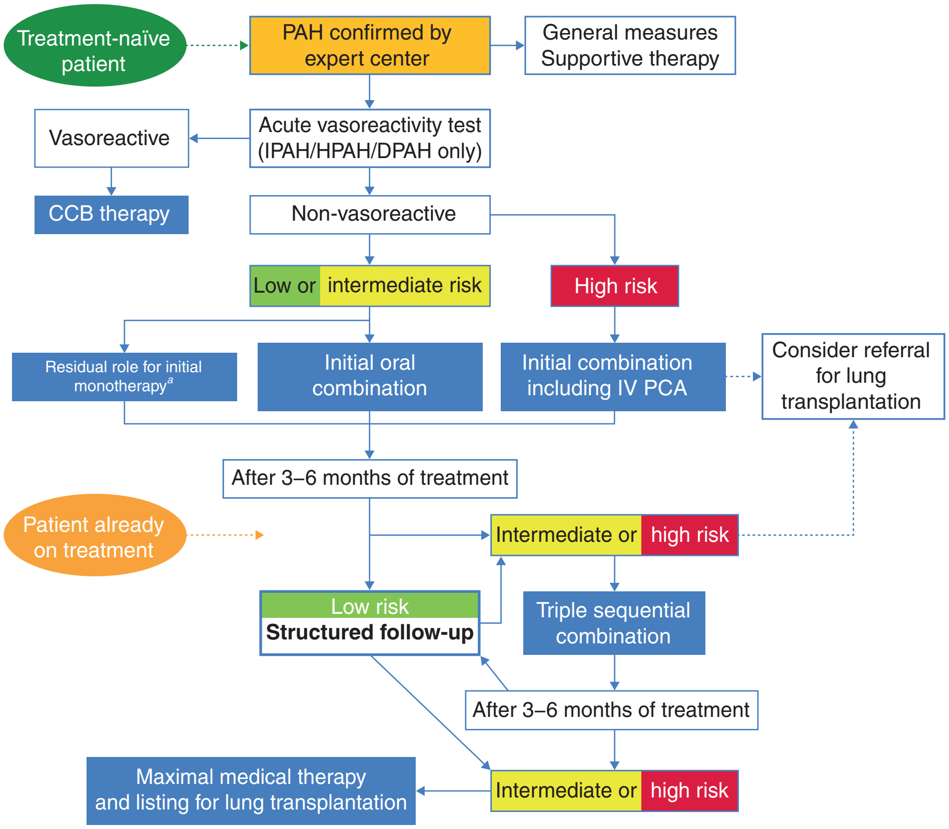

Treatment-naïve patient
PAH confirmed by expert center
General measures Supportive therapy
Vasoreactive
Acute vasoreactivity test (IPAH/HPAH/DPAH only)
CCB therapy
Non-vasoreactive
Low or intermediate risk
High risk
Residual role for initial monotherapy[a]
Initial oral combination
Initial combination including IV PCA
Consider referral for lung transplantation
After 3–6 months of treatment
Patient already on treatment
Intermediate or high risk
Low risk
Structured follow-up
Triple sequential combination
After 3–6 months of treatment
Maximal medical therapy and listing for lung transplantation
Intermediate or high risk

Figure 72-14 PAH treatment algorithm: World Symposium PH 2018. [a]See Table 19 in Ref. 399. *(Reproduced with permission from Galiè N, Channick RN, Frantz RP, et al. Risk stratification and medical therapy of pulmonary arterial hypertension. Eur Respir J. 2019;53(1):1801889.)*

at week 24, and improvement from baseline 6MWD. The combination therapy group reported more peripheral edema, headache, nasal congestion, and anemia compared with the monotherapy groups. The discontinuation rates were the same across the three treatment groups.

The results of AMBITION and observations from PACES are now reflected in current PAH treatment guidelines, which recommend combination treatment strategy. The exceptions for using monotherapy include cases of acutely vasoreactive PAH benefiting from CCB monotherapy, and existing PAH patients who are maintaining low-risk assessment status and continued benefit from monotherapy.[434] In certain newly diagnosed PAH patients with concerns for comorbidities that may either limit response to PAH therapy or cause tolerance issues (e.g., cases that may have been excluded from AMBITION study inclusion due to select comorbidities), starting with monotherapy may be justified.[434]

Two notable uncontrolled studies highlighted the hemodynamic impact of initial combination therapy in newly diagnosed PAH patients. One retrospective report looked at newly diagnosed IPAH patients (all function class III or IV at baseline) treated with up-front triple combination therapy including intravenous epoprostenol, bosentan, and sildenafil.[497] By 4 months follow-up, PVR went from a baseline of 1718 ± 627 dyn • s • cm^{-5} to 564 ± 260 dyn • s • cm^{-5}. At subsequent follow-up, all 18 patients were improved to functional class I or II with sustained improvements in hemodynamics and 6MWD. The same center also coordinated the prospective, phase 4 OPTIMA study, which investigated the safety and efficacy of combining macitentan and tadalafil up front in newly diagnosed PAH patients.[498] In this single-arm study of initially 46 subjects, the combination of macitentan and tadalafil resulted in a 47% reduction in PVR (reduction of 416 dyn • s • cm^{-5} from baseline) by week 16. Despite the limitations of a single-arm study and caution with comparing across reports, this magnitude of PVR reduction was not observed in prior hemodynamic studies with either endothelin receptor antagonist (bosentan: reduction of 223 dyn • s • cm^{-5} from baseline)[475] or phosphodiesterase type 5 inhibitor (sildenafil: reduction of 122 dyn • s • cm^{-5} from baseline)[148] as monotherapy agents.

The benefits of combination strategy appear not to be limited to newly diagnosed PAH patients. The large event-driven studies with macitentan (SERAPHIN), selexipag (GRIPHON), and oral treprostinil (FREEDOM V) predominantly were with prevalent PAH patients with study drug added on top of background therapy/therapies. In all three studies, the added combination therapy was associated with lower rates of disease progression and hospitalizations related to PAH. In a proof-of-concept hemodynamic study with selexipag, 43 PAH patients on background endothelin receptor antagonist and/or phosphodiesterase type 5 inhibitor were randomized to either selexipag or placebo for 17 weeks.[499] The selexipag-treated group saw a PVR reduction of 30.3% compared with the placebo group. The ATHENA-1 study enrolled 33 PAH patients with suboptimal response to phosphodiesterase type 5 inhibitor monotherapy and added ambrisentan.[500] This single-arm, hemodynamic, observational study noted a 32% reduction in PVR by 24 weeks after addition of ambrisentan. In the PATENT-1 study, which led to the approval of riociguat for PAH, half of the patients were already on background PAH therapy and still benefited from the addition of riociguat.[492]

Although evidence currently favors combination over monotherapy in PAH, whether an early proactive sequential add-on approach yields similar results to up-front simultaneous start is unknown. The potential benefits of a sequential add-on approach in real-world practice include challenges with drug approval and procurement, as well as pinpointing and troubleshooting drug-related side effects. Combination therapy in PAH does not refer to combining agents within the same therapeutic pathway. For instance, phosphodiesterase type 5 inhibitor and riociguat taken together is contraindicated.

Current and future PAH clinical trials investigating new treatment pathways will need to demonstrate safety and efficacy on top of standard care—which now commonly is combination therapy.[400] Accordingly, the bar has been raised for new drug target discovery and begs for more efficient and responsible trial conduct.

NONPHARMACOLOGIC INTERVENTIONS FOR PAH

Lung transplantation is addressed in Chapter 106. Here, it will suffice to note that lung transplantation remains an important consideration for some patients with PAH whose disease fails to respond adequately to medical therapy. Although changes in the method of allocating donor lungs within the United States have improved wait times, mortality on the wait list for patients with PAH remains excessive compared to patients with other indications for lung transplantation.[501] To help address this issue, PAH patients who are deteriorating despite optimal medical therapy, and who have a cardiac index <1.8 L/min/m^2 or a right atrial pressure >15 mm, may qualify for a lung allocation score exception.[502]

Balloon dilation atrial septostomy has been performed as a palliative measure, as well a "bridge" to lung transplantation in some patients with severe PAH and symptoms refractory to other therapies. At the expense of worsening systemic oxygenation, the creation of a right-to-left shunt at the atrial level can help offload the struggling right ventricle and improve cardiac output and symptoms in carefully selected cases with PAH.[503] Controlled studies have not been performed, and evidence-based selection criteria have not been established. Right atrial pressure greater than 20 mm Hg prior to balloon dilation atrial septostomy has been associated with a 10-fold increase in mortality and is considered a contraindication. The procedure should be performed only at experienced institutions.[504]

Pulmonary artery denervation (PADN) applies the concept of renal denervation as means of potentially modulating vascular tone to the pulmonary circulation.[505,506] Both radiofrequency ablation and intravascular ultrasound-based techniques have been reported.[507] PADN remains an experimental therapy in PAH, lacking controlled data and standardization and in need of validation.

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PART 8

Disorders of the Pulmonary Circulation

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CHAPTER 73

Pulmonary Thromboembolic Disease

Timothy M. Fernandes
Peter F. Fedullo

INTRODUCTION

Pulmonary thromboembolic disease refers to the condition in which blood clot(s) (thrombus or multiple thrombi) migrate from the systemic circulation to the pulmonary vasculature (Fig. 73-1). The field of pulmonary thromboembolic disease has continued to evolve, and aspects of clinical care remain shrouded in controversy. What is certain is that the incidence of pulmonary embolism (PE) appears to be increasing over the past few decades, probably reflecting an increase in the availability and sensitivity of CT scanning. Despite this increase in diagnosis, the mortality related to acute PE continues to decline.

Most of the thrombi arise from the deep veins of the lower and upper extremities (deep venous thrombosis, DVT). From a clinical perspective, DVT and PE can be considered a continuum of the same disease, and the two terms are often collectively referred to as *venous thromboembolism (VTE)*. For the purposes of this chapter, we will focus on PE.

EPIDEMIOLOGY

The exact annual incidence of PE in the United States remains uncertain but appears to be increased in incidence in recent years.[1] In a retrospective analysis of data involving 2218 Olmsted County residents over a 10-year period, community residents who were not hospitalized within a 90-day period had an incidence of PE of 3.6 (95% confidence interval [CI], 3.2–4.0) per 10,000 person-years.[2] A slightly lower incidence of 2.3 per 10,000 person-years was reported in an earlier study in Massachusetts.[3] This translates to an annual incidence of approximately 100,000 cases in the United States. However, the true incidence of PE is likely to be much higher since many cases remain undiagnosed. A systematic review revealed that silent PE was present in 32% of patients with DVT.[4] An earlier report estimated that as many as 630,000 patients develop PE every year in the United States with 200,000 related deaths, the majority in patients in whom the diagnosis was never made.[5]

Although considerable effort is directed toward the development of new diagnostic techniques and therapeutic agents, a considerable impact on PE-related mortality has resulted from the routine use of prophylactic strategies, an understanding of the often subtle clinical presentation of the disease, the appropriate application of existing diagnostic techniques, and the use of newer treatment modalities associated with better outcomes. This has translated to decreased PE-related mortality in recent years. In the RIETE Registry, the 30-day PE-related mortality decreased from 3.3% in 2001 to 1.8% in 2013 ($p < 0.01$) (Fig. 73-2).[6,7]

SOURCES OF EMBOLI

Most cases (80%–95%) of PE occur as a result of thrombus originating in the lower extremity. Thrombus often begins at a site where blood flow is turbulent, such as at a venous bifurcation or behind a venous valve (Fig. 73-2). When thrombus propagation exceeds the rate of thrombus organization and adherence to the endothelium, part or all of the thrombus may break away and migrate via the venous system to the lungs. Most thrombi originate in the deep veins of the calf (anterior tibial, posterior tibial, and peroneal veins) and propagate proximally to the popliteal and femoral veins. Calf-limited thrombi pose a minimal embolic risk, while those that extend into and above the popliteal vein represent the most common source of acute symptomatic pulmonary embolism. This is not meant to imply that calf-limited thrombosis represents a benign condition, though, as proximal propagation may occur in as many as 15% of untreated patients along with a higher risk of thrombotic recurrence and postthrombotic syndrome.[8]

Emboli may originate from other sources, most often from the pelvic veins—in which case a predisposing factor such as pregnancy, uterine fibroids, pelvic thrombophlebitis or pelvic infection, prostate disease, or recent pelvic surgery can often be identified. Emboli may also originate from upper-extremity thrombosis, which is frequently associated with central venous catheters or intravascular cardiac devices, or may be associated with thoracic outlet obstruction or effort thrombosis (Paget-Schroetter syndrome).[9] A small number of patients with PE may have evidence of right ventricular thrombus (so-called clot in transit) at presentation, and this has been associated with more hemodynamic instability and an increase in mortality.[10,11]

PREDISPOSING FACTORS

The nomenclature used to describe the predisposing factors for acute PE has changed over the last decade. Terms previously used such as *provoked* or *unprovoked VTE* no longer appear in most recent iterations of guidelines issued by the European Respiratory Society and the American College of Chest Physicians.[7,12] Newer terminology favors describing the treatment of PE as the initial phase pertaining to the first 3 months of anticoagulation and the extended phase. Patients with lower risk for recurrence can stop anticoagulation after the initial phase, while those with higher risk for recurrence should consider extended anticoagulation. Patients who have major transient risk factors (such as major surgery, estrogen therapy,

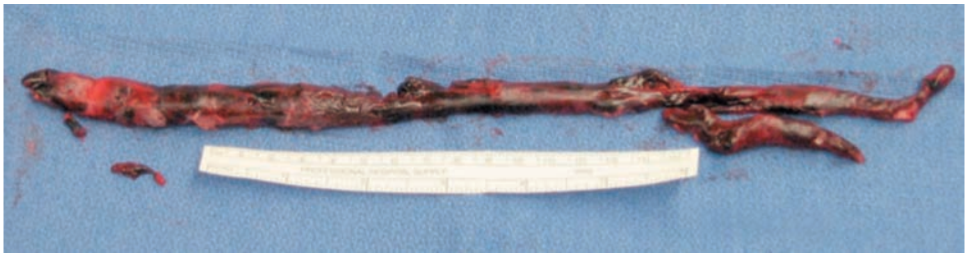


Figure 73-1 Large, well-organized embolism representing "cast" of a lower-extremity vein removed from pulmonary artery at pulmonary embolectomy.

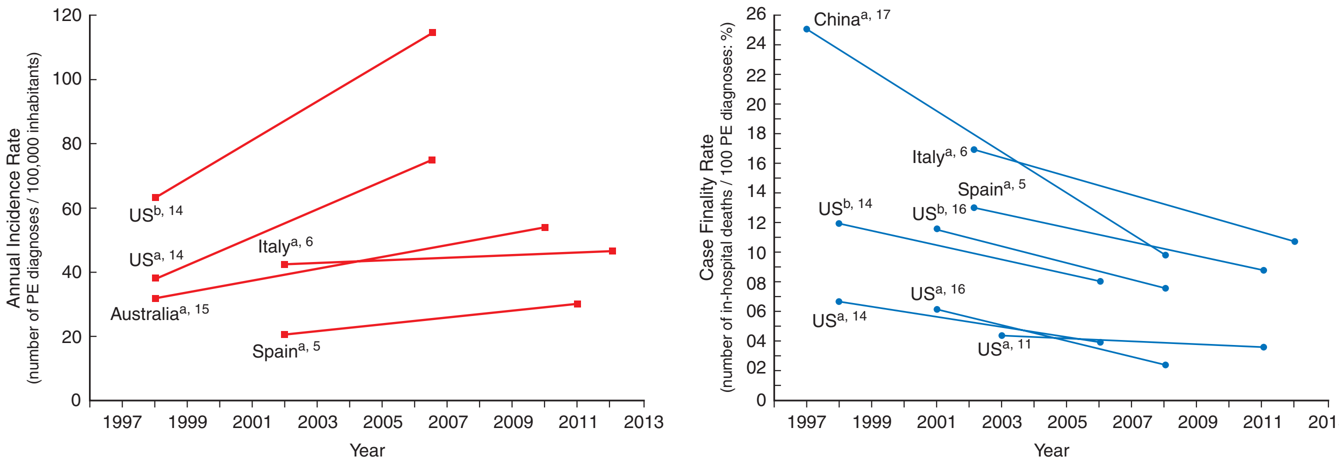


Figure 73-2 The incidence of PE has increased *(left)* while the mortality associated with PE has decreased *(right)*. *^{a}PE listed as principal diagnosis. ^{b}Any listed code for PE was considered. (Reproduced with permission from Konstantinides SV, Barco S, Lankeit M, Meyer G. Management of pulmonary embolism: an update. J Am Coll Cardiol. 2016;67(8):976–990.)*

pregnancy, leg injury, air flights >8 h, or prolonged medical hospitalization) for VTE can consider stopping anticoagulation after the first 3 months, whereas indefinite anticoagulation is favored for those with no identifiable risk factor or a persistent risk factor (malignancy, certain hypercoagulable states).

Rudolf Virchow first described the phenomena of "embolism" and "thrombosis" in the mid-nineteenth century, and three main factors contributing to the formation of venous thrombosis (Virchow's triad) are attributed to his work: venous stasis, hypercoagulability, and injury to the venous wall (endothelium).[13] One hundred fifty years later, this basic classification remains useful in helping clinicians stratify an individual patient's risk of developing VTE (Table 73-1). Inflammation, while not part of the classic Virchow triad, is common to all three components of the triad and is a shared feature of many of the medical conditions that predispose to VTE. It is important to recognize that there is an interplay between acquired (Table 73-2) and genetic risk factors leading to the development of DVT and/or PE, and that multiple factors can often be found in individual patients.

TABLE 73-1 Virchow's Triad: Clinical States Predisposing to Venous Thrombosis

Stasis	Immobility Bed rest Anesthesia Congestive heart failure/cor pulmonale Prior venous thrombosis
Hypercoagulability	Malignancy Anticardiolipin antibody Nephrotic syndrome Essential thrombocytosis Estrogen therapy Heparin-induced thrombocytopenia Inflammatory bowel disease Paroxysmal nocturnal hemoglobinuria Disseminated intravascular coagulation Protein C and S deficiencies Antithrombin III deficiency
Vessel wall injury	Trauma Surgery

■ Transient Risk Factors

The risk imposed by a major surgical procedure is well recognized. Without prophylaxis, venous thrombosis occurs after approximately 20% of all major surgical procedures with associated embolism in 1% to 2% of cases.[14] The incidence of thromboembolism without prophylaxis is even higher in orthopedic patients with over 50% of major orthopedic procedures complicated by venous thrombosis. In the absence of prophylaxis, the frequency of fatal postoperative PE ranges from 0.1% to 0.4% in patients undergoing elective general surgery and from 1% to 5% in patients undergoing elective hip or knee surgery, emergency hip surgery, major trauma, or spinal cord injury.[15] Although surgery is a major transient risk factor for development of VTE, there is a low risk of recurrent VTE after the initial 3 months of therapy, with a recurrence rate of 3% within 5 years after the event.

Major traumatic injuries, most notably those of the head, spine, lower limbs, and pelvis, are also associated with high risk of VTE. The basis for this risk is multifactorial, involving all three components of Virchow's triad. Among patients in a trauma unit, 56% those with lower limb or pelvic fractures had evidence of DVT, while 40% of patients with injuries to the face, chest, or abdomen had DVT.[16]

Although initially recognized and studied in surgical patients, it is now appreciated that hospitalized medical patients may be equally prone to developing DVT.[17] In about 80% of cases, one or more risk factors may be present when extensive investigative testing is performed. Major risk factors include New York Heart Association class III and IV congestive heart failure, chronic obstructive pulmonary disease, sepsis and other inflammatory disorders, recent myocardial infarction, advanced age, stroke, critical illness, and prolonged bed rest.

Any prolonged period of immobilization may increase thromboembolic risk and explains the occurrence of thrombosis under such circumstances as paralysis, bed rest, and prolonged air travel. Long-distance traveling (economy class syndrome) is associated with a 1.5- to 3-fold increase in thromboembolic risk, depending on the travel duration.[18] Despite the relative increase in risk, the actual incidence of PE associated with air travel is quite low.[19]

TABLE 73-2 Predisposing Factors for Venous Thromboembolism

Strong risk factors (OR >10)
Fracture of lower limb
Hospitalization for heart failure or atrial fibrillation/flutter (within previous 3 months)
Hip or knee replacement
Major trauma
Myocardial infarction (within previous 3 months)
Previous VTE
Spinal cord injury
Moderate risk factors (OR 2–9)
Arthroscopic knee surgery
Autoimmune diseases
Blood transfusion
Central venous lines
Intravenous catheters and leads
Chemotherapy
Congestive heart failure or respiratory failure
Erythropoiesis-stimulating agents
Hormone replacement therapy (depends on formulation)
In vitro fertilization
Oral contraceptive therapy
Post-partum period
Infection (specifically pneumonia, urinary tract infection, and HIV)
Inflammatory bowel disease
Cancer (highest risk in metastatic disease)
Paralytic stroke
Superficial vein thrombosis
Thrombophilia
Weak risk factors (OR <2)
Bed rest >3 days
Diabetes mellitus
Arterial hypertension
Immobility due to sitting (e.g., prolonged car or air travel)
Increasing age
Laparoscopic surgery (e.g., cholecystectomy)
Obesity
Pregnancy
Varicose veins

HIV = human immunodeficiency virus; OR = odds ratio; VTE = venous thromboembolism.

Data from Vandenbroucke JP, Rosing J, Bloemenkamp KW, et al. Oral contraceptives and the risk of venous thrombosis. N Engl J Med. 2001;344(20):1527–1535 and Vinogradova Y, Coupland C, Hippisley-Cox J. Use of hormone replacement therapy and risk of venous thromboembolism: nested case-control studies using the QResearch and CPRD databases. BMJ. 2019;364:k4810.

Pregnancy is the most common cause of VTE in women less than 40 years old, and if untreated it may account for 20% to 50% of all pregnancy-related deaths. Compared with nonpregnant women, the risk of venous thrombotic events is increased 5-fold during pregnancy and 60-fold in the first 3 months after delivery.[20,21] The increase may be a result of decreased mobility, pregnancy-related hypercoagulable state (increases in factors II, VII, VIII, and X, acquired activated protein C resistance, decreased free protein S level), and venous obstruction from uterine compression. The incidence is estimated at 0.76 to 1.72 cases per 1000 pregnancies and occurs in roughly equal distribution over all trimesters. Most cases of postpartum DVT occur within the first 6 weeks after delivery. Cesarean section, premature birth, multiple births, preeclampsia, advanced maternal age, and maternal history of cardiac disease have all been identified as contributing factors. Interestingly, 90% of all pregnancy-related DVT cases are noted in the left leg, presumably because of the anatomic relationship between the uterus and inferior vena cava.[22]

The use of oral contraceptive agents and hormonal replacement therapy has also been associated with an increased risk of VTE.[23,24] Although the risk of VTE is higher among users of oral estrogen-containing contraceptives, the absolute risk is low. In terms of oral contraceptive agents, the relative risk of developing venous thrombosis is increased four- to sixfold. There appears to be a synergistic effect of oral contraceptives with obesity.[25]

Hormone replacement therapy appears to be associated with a two- to fourfold increased risk of VTE.[26] Studies have suggested that venous thromboembolic risk is lower with transdermal hormone preparations.[24] However, none of these studies involved randomized trials. Given that the baseline risk of thrombosis increases with age, the use of hormonal replacement therapy in a postmenopausal population has a considerably higher impact on absolute rates of thrombosis.

Obesity has been associated with VTE, particularly in women. The Nurses' Health Study found that a body mass index greater than or equal to 29 kg/m^2 was an independent risk factor.[27] The metabolic syndrome, defined by abdominal obesity, elevation of blood pressure, elevated fasting blood sugar and triglycerides, and low levels of high-density lipoprotein cholesterol, appears to be associated not only with an increased risk of atherosclerotic disease but also of VTE.[28]

The risk of VTE increases with age. A recent study, using hospital discharge surveys over a 21-year period, found that patients 70 years or older have an approximately 25-fold increased risk, compared with those 20 to 29 years of age.[29] Presumably, the difference may be due to decrease in mobility and increase in comorbidities in this population. Although PE is suspected less commonly prior to death in elderly patients, they appear to have a higher mortality due to PE.

■ Persistent Risk Factors

Patients with cancer, particularly those with primary malignancies from lung, pancreas, brain, ovary, and stomach/colorectal tracts, are at a high risk for VTE.[30] Cancer is estimated to increase the risk of VTE four- to sixfold. Patients with cancer also have a higher risk of thromboembolic recurrence and have a higher overall mortality rate than cancer patients without thrombosis. Multiple factors are probably involved and include the development of abnormalities in the hemostatic system related to the malignancy itself as well as those induced by chemotherapeutic agents, immobility, infectious complications, and the presence of chronic indwelling central venous catheters. Although most instances of cancer-associated VTE occur after the diagnosis of the malignancy, approximately 5% to 10% of patients with idiopathic venous thrombosis have a malignancy diagnosed within the next 2 to 3 years. There is no evidence at this time to recommend an aggressive search for cancer (such as routine CT of the abdomen and pelvis in search of a malignancy) in patients with idiopathic thrombosis.[31] Age-appropriate cancer screening (including colonoscopy, mammogram, and PAP smears) should be recommended in all patients with VTE.

Various hematologic conditions such as polycythemia vera, essential thrombocytosis, and acute promyelocytic leukemia may result in significant overproduction of different cell lines, which in turn may increase the risk of VTE by increasing blood viscosity (hyperviscosity syndromes) and through the release of procoagulants.[32,33] This type of thrombosis seems to occur more frequently in the hepatic or portal veins and may be the presenting symptom of the underlying disorder.

Paroxysmal nocturnal hemoglobinuria is a rare condition associated with a VTE incidence of approximately 40%.[34] Many cases involve non–lower extremity sites, particularly in the intra-abdominal vessels. The reason for thrombosis is not clear but may be related to a decrease in blood complement levels in these patients.

The presence of antiphospholipid antibodies, most notably the lupus anticoagulant, appears to be an independent risk factor for VTE.[35] Among patients with venous thrombosis, a lupus anticoagulant has been reported in 5% to 15%, and this abnormality has been estimated to lead to a ninefold increased risk of thrombosis. Among patients with antiphospholipid antibody syndrome, those with triple positivity (positive dilute Russell viper venom testing, anti-aβ2GPI, and anticardiolipin antibody testing) are at high risk for recurrent VTE and benefit from use of warfarin rather than any of the direct oral anticoagulants.[36]

The frequency of VTE in patients with nephrotic syndrome may be as high as 40%.[37] There is a higher tendency for the thrombosis to present in unusual locations such as the cerebral sinus or as arterial thrombosis. Rarely, thrombosis may also be the presenting symptom of the nephrotic syndrome. The mechanism for VTE in these patients is not clear, but various factors such as functional or quantitative changes in coagulation factors like acquired deficiency in proteins C and S, diminished fibrinolytic activity, platelet hyperreactivity, and increase blood viscosity have been proposed.

Patients with inflammatory bowel disease are at substantially increased risk of both venous and arterial thrombosis.[38] The exact pathogenic mechanism remains unclear. The majority of thrombotic complications occur during an active phase of the disease, and inflammatory mechanisms have been proposed.

■ Inherited Risk Factors

Many patients who develop VTE are found to have an inherited risk factor due to either abnormal levels or functional abnormalities of coagulation factors (inherited thrombophilia). The relative risk of thrombosis varies widely depending on the hemostatic defect. In general, this group of patients tends to be younger (<50 years) and has a tendency to develop recurrent VTE.[39]

The first known inherited thrombophilic trait was antithrombin III deficiency, originally described in 1965. Subsequently, a number of other genetic mutations associated with VTE have been reported. The most common of these inherited predispositions was first described in 1993 by Dahlbeck and designated as a factor V Leiden mutation.[40] It is the consequence of a single point mutation on the factor V gene (adenine for guanine), resulting in factor Va having diminished sensitivity to the natural anticoagulant effect of activated protein C. Approximately 5% of Caucasians in Europe and North America are heterozygous for this genetic defect; lower rates of carrier frequency have been reported among Native American, African, and Asian populations. The heterozygous state carries a 5- to 10-fold increase in lifetime risk for VTE, whereas the risk among patients homozygous for this mutation may be increased 80-fold. Factor V Leiden mutation appears to be an important risk factor for VTE during pregnancy, in the postpartum period, and during oral contraceptive use.[41] Compared with women who do not use oral contraceptives and are not carriers of the factor V mutation, the risk of thrombosis among those with both risk factors is increased approximately 30-fold.[42]

Another common mutation has been identified in the 3′ untranslated region of the prothrombin gene (substitution of A for G at position 20210) and is present in 2% to 4% of the general population.[43] This mutation results in an overproduction of prothrombin, which is otherwise functionally normal. It is associated with a three- to fourfold increased risk of lower extremity venous thrombosis and appears to act in a synergistic manner with other forms of thrombophilia in increasing both the initial and recurrent thrombosis risk.

In clinical practice, factor V Leiden mutation and prothrombin gene mutation are the most common inherited conditions (5% and 3% of Caucasians, respectively, carry one copy of the gene) and account for more than half of the cases of inherited thrombophilia-related VTE. While presence of these mutations increases the risk for recurrence of VTE on a population scale, the effect of these mutations on an individual's risk for recurrence is negligible (hazard ratio [HR] for recurrence in patients with inherited thrombophilia compared to VTE patients without an inherited thrombophilia, 1.50; 95% CI, 0.82–2.77; $p = 0.187$), and therefore routine evaluation of factor V Leiden or prothrombin gene mutation after a VTE is unnecessary.[44] Three other conditions (deficiencies in antithrombin III, protein C, or protein S) account for most of the remainder of the inherited thrombophilias. Occasionally one may also encounter patients with VTE who may have other conditions, particularly related to dysfibrinogenemias. It is important to recognize that when multiple inherited risk factors coexist (such as factor V Leiden and prothrombin gene mutation), the risk of recurrent VTE may increase substantially, and lifelong anticoagulation may be necessary in these patients.

PATHOPHYSIOLOGY

Once detached from their point of origin, emboli travel via the systemic venous system, through the right chambers of the heart, and eventually reach the pulmonary arterial system. The physiologic effects and clinical consequences of pulmonary thromboembolism vary widely, ranging from asymptomatic disease to hemodynamic collapse and death. Major factors that determine the outcome include (1) size and location of emboli; (2) coexisting cardiopulmonary diseases; (3) secondary humoral mediator release and vascular hypoxic responses; and (4) the rate of resolution of emboli.

■ Hemodynamic Consequences

Obstruction of the pulmonary vascular bed by embolism acutely increases right ventricular afterload. Compensatory mechanisms exist that allow up to 70% obstruction of the pulmonary vascular bed before right ventricular failure develops.[45,46] The normal pulmonary arterial system is a low-pressure system capable of accommodating substantial increases in blood flow with only modest increases in pressure. The thin-walled right ventricle is poorly equipped to generate the pressure necessary to overcome any significant increase in pulmonary vascular resistance (Fig. 73-3).[7] Since the left and right ventricle share the same pericardial space (ventricular interdependence), the intraventricular septum begins to flatten in response to increases in right ventricular end-diastolic pressure (RVEDP); eventually, the septum bows into the left ventricle, which can impair cardiac output. The perfusion of the right coronary is determined by the difference between mean arterial pressure and

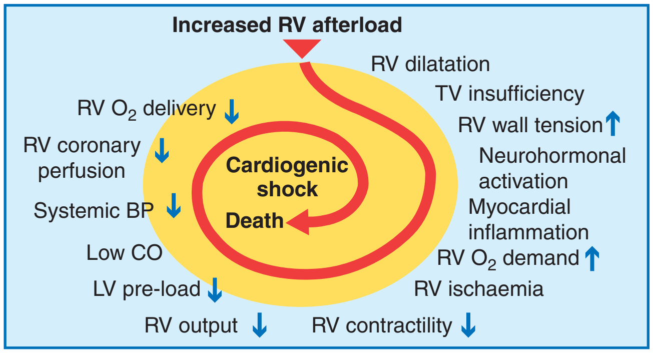


Figure 73-3 Increased right ventricular afterload leads to right ventricular ischemia and eventual cardiogenic shock. BP, blood pressure; CO, cardiac output; LV, left ventricular; RV, right ventricular; TV, tricuspid valve.

the RVEDP. As the RVEDP increases and cardiac output decreases in response to acute PE, there is a resultant decrease in perfusion to the right ventricle. This "RV death spiral" is common to all causes of right ventricular failure (i.e., pulmonary arterial hypertension, cor pulmonale, chronic thromboembolic pulmonary hypertension) but is especially severe in acute PE where the change is pressure is abrupt and the RV has not had time to hypertrophy in response to more gradual increases in afterload.

In the absence of preexisting cardiopulmonary disease, obstruction of less than 20% of the pulmonary vascular bed results in minimal hemodynamic consequences as a result of recruitment and distention of pulmonary vessels. When the degree of pulmonary vascular obstruction exceeds 30% to 40%, modest increases in right ventricular pressure occur, but cardiac output is maintained through an increase in heart rate and myocardial contractility. Compensatory mechanisms begin to fail when the degree of pulmonary artery obstruction exceeds 50% to 60%. Cardiac output begins to fall, and right atrial pressure increases dramatically. Mixed venous oxygen saturation falls, and a lactic acidosis may develop. With further acute obstruction, the right heart dilates, right ventricular wall tension increases, right ventricular ischemia may develop, the cardiac output falls, and systemic hypotension develops. In patients without prior cardiopulmonary disease, the maximal mean pulmonary artery pressure capable of being generated by the right ventricle appears to be 40 mm Hg (pulmonary artery systolic pressure of approximately 70 mm Hg).[45]

Other factors may affect the hemodynamic consequences of PE. Patients with preexisting cardiopulmonary disease often have diminished pulmonary vascular reserve, and even a relatively minor embolus may result in significant hemodynamic instability (Fig. 73-4). Alternatively, if the right ventricle has had time (months to years) to hypertrophy in response to a gradual increase in demand (left ventricular disease, idiopathic pulmonary arterial hypertension, chronic thromboembolism, etc.) a significantly higher pulmonary artery pressure may be seen.

Several observations suggest that other mechanisms are involved in hemodynamic consequences of acute PE. For example, patients develop only minimal hemodynamic instability during elective lobectomy, pneumonectomy, or even single lung transplantation despite complete and acute interruption of blood supply during cross clamping. Certain patients develop disproportionately large and fluctuating pulmonary hemodynamic changes in response to relatively small emboli, suggesting that other mechanisms such as reflex vasoconstriction and release of vasoactive compounds also may be involved.[47] There appears to be an imbalance between excessive vasoconstrictors such as serotonin, thromboxane, and endothelins and a loss of nitric oxide and prostacyclins that further exacerbates the hemodynamic consequences of the PE beyond the degree attributable to the obstruction alone.[48]

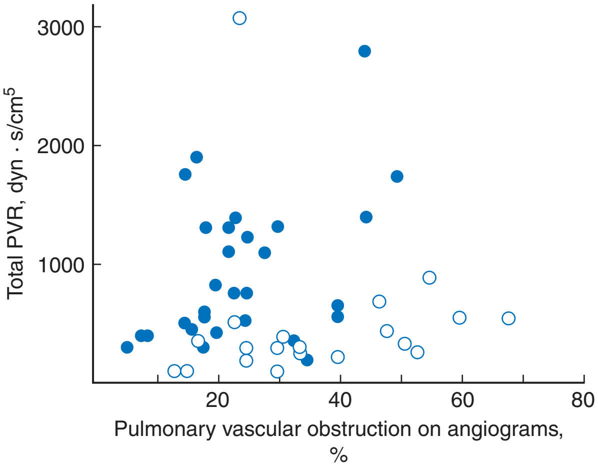


Figure 73-4 Hemodynamic consequences of pulmonary embolism and the underlying state of the pulmonary vasculature. Patients in whom the pulmonary vasculature was previously normal *(open circles)* develop little increase in pulmonary vascular resistance (PVR) until the clot burden exceeds 50%. In those with antecedent cardiopulmonary disease *(solid circles)*, the PVR increases appreciably with only modest clot burden. *(Reproduced with permission from Sharma GV, McIntyre KM, Sharma S, et al. Clinical and hemodynamic correlates in pulmonary embolism. Clin Chest Med. 1984;5(3):421–437.)*

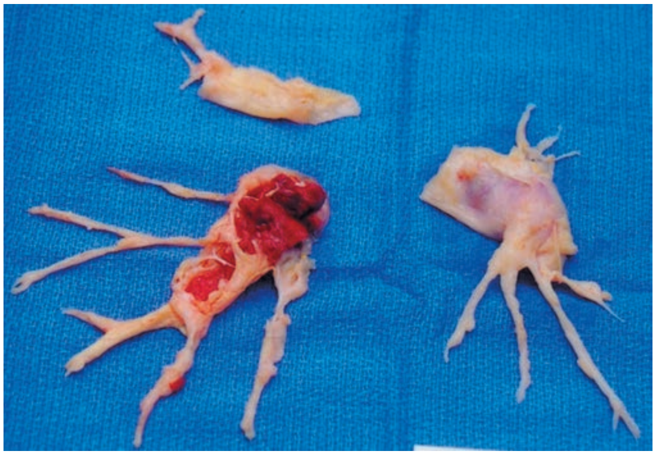


Figure 73-5 Chronic thromboembolic material dissected from pulmonary arteries at pulmonary thromboendarterectomy. Resolution of emboli is usually complete, but certain patients may be left with significant emboli residua.

As expected, large or multiple emboli tend to cause more severe symptoms and changes in oxygenation and hemodynamics. Given the large surface area of the peripheral pulmonary vascular bed compared with the central pulmonary vasculature, symptomatic improvement may occur when a large central embolus is fragmented by forces generated by cardiac contractions or even with chest compressions during cardiopulmonary resuscitation. Eventually, the emboli may either resolve by fibrinolysis, or organize and become scar-like tissue that adheres to the vascular endothelium (Fig. 73-5). Recent data suggest that complete resolution is uncommon and that as many as 50% of patients have some residual obstruction 6 months after the embolic event.[49,50]

■ Gas-Exchange Abnormalities

Hypoxemia is the most common immediate physiologic consequence of PE. Obstruction of the pulmonary vasculature prevents systemic venous blood from reaching the pulmonary capillaries of the involved vessels and redirects the blood flow to other parts of the pulmonary vascular bed. This results in an increase in ventilation–perfusion ($\dot{V}/\dot{Q}$) inequality, intrapulmonary shunting, and decreases in the mixed venous O_2 level, thereby magnifying the effect of the normal venous admixture.[51,52] Further shunting and increase in alveolar dead space can also occur as a result of alveolar hemorrhage or atelectasis related to loss of surfactant. Despite an increase in alveolar dead space, patients with pulmonary embolism often develop hypocapnia. This is thought to be due to hypoxia-induced intrapulmonary reflex vagal stimulation, with resulting hyperventilation. Finally, embolic events large enough to increase right atrial pressure may result in intracardiac right-to-left shunting through a patent foramen ovale.

TABLE 73-3 Incidence of Signs and Symptoms of Pulmonary Embolism

	Massive PE[a] (%)	Submassive PE[a] (%)	Without Pre-existing Cardiopulmonary Disease (%)[b]
Dyspnea	85	82	73
Pleuritic chest pain	64	85	66
Cough	53	52	37
Hemoptysis	23	40	13
Tachypnea	95 (>16 breaths/min)	87 (>16 breaths/min)	70 (>20 breaths/min)
Tachycardia (>100 beats/min)	48	38	30
Increased pulmonic component of second heart sound	58	45	23
Rales	57	60	51
Phlebitis	36	26	11

[a] *Data from Bell WR, Simon TL, DeMets DL. The clinical features of submassive and massive pulmonary emboli. Am J Med. 1977;62(3):355–360.*

[b] *Data from Stein PD, Terrin ML, Hales CA, et al. Clinical, laboratory, roentgenographic, and electrocardiographic findings in patients with acute pulmonary embolism and no pre-existing cardiac or pulmonary disease. Chest. 1991;100(3):598–603.*

One uncommon consequence of PE is pulmonary infarction. Infarction is uncommon because the pulmonary parenchyma has three potential sources of oxygen: the pulmonary arteries, bronchial arteries, and airways. Two of these three sources must be compromised before infarction develops. Therefore, in a patient with no coexisting cardiopulmonary disease, infarction is rare, with about 16% of acute PE patients affected.[53,54] Infarction occurs in approximately 20% of patients with significant cardiac or pulmonary disease that compromises either bronchial arterial flow or airway patency. In patients with left ventricular failure, increased pulmonary venous pressure may decrease bronchial flow and infarction may occur.

DIAGNOSIS OF PULMONARY EMBOLISM

Highly sensitive D-dimer assays, stratification according to clinical assessment, and the application of Bayesian analysis, followed by imaging such as Doppler ultrasonography and/or computed tomography in the highest-risk patients, are the cornerstones of the diagnostic approach to suspected PE. Recognition of the clinical signs and symptoms associated with embolism is valuable because clinical findings and clinical suspicion represent an essential first step in the diagnostic pathway.

Clinical Presentation

The mainstay for the diagnosis of PE is a high index of suspicion tempered by the reality that most patients with embolism have one or more factors predisposing them to the condition. These predisposing factors need not be major or readily apparent. Recent surgery, a period of bed rest, medical comorbidities, or a minor traumatic injury can result in the development of VTE. The absence of a known clinical or thrombophilic predisposition, however, should not dissuade an objective evaluation if the clinical presentation is consistent with embolism.

Although a somewhat arbitrary classification (as presenting symptoms and signs of embolism frequently overlap), the presentation of acute PE can be categorized into one of three clinical syndromes: (1) isolated dyspnea; (2) pleuritic pain or hemoptysis; and (3) circulatory collapse.[55,56] The most common presenting symptom of acute embolism is the sudden onset of dyspnea.[55] Dyspnea usually occurs over minutes to hours, but in approximately 15% it occurs over days. Although usually present at rest, dyspnea may only be noted with exertion in certain cases. It is important to recognize that dyspnea does not occur in approximately 25% of patients ultimately proven to have embolism. Other symptoms include pleuritic chest pain, cough, leg swelling or pain, and hemoptysis. Hemoptysis is rare among patients suspected of having PE (5%), but its presence significantly increases the odds ratio (OR) that PE will be found (OR, 2.86; 95% CI, 1.36–6.03).[57] Syncope is rare among all patients with acute PE, but, among patients admitted with first episode of syncope, PE is ultimately found in 17% of patients.[58] The most common physical finding is tachypnea (respiratory rate >20/min), present in approximately 70% of patients with embolism. Less frequent physical findings include rales, tachycardia, and an increased pulmonic component of the second heart sound. Fever may develop some hours after the event and often reaches, but rarely exceeds, 38.3°C.[59]

These symptoms and signs are notably nonspecific (Table 73-3). In the PIOPED study, none of the presenting symptoms or signs with the exception of signs of DVT (unilateral leg swelling), jugular venous distention, and an increased pulmonic component of the second heart sound were significantly different between those with positive and negative CT angiograms.[55]

Assessment of Pretest Probability

A major advancement in the diagnostic approach to PE has been a transition from a purely technique-oriented approach to one that uses Bayesian analysis. In doing so, the pretest probability of the disease, derived independently of a particular test result using either empiric means or a standardized prediction rule, is calculated. This pretest probability aids in the selection and interpretation of further diagnostic tests to create a posttest probability of the disease. This posttest probability can then be used as a basis for clinical decision-making. For PE a number of such scores have been developed and validated. The Wells score is a prospectively validated, rapid, seven-item bedside assessment to estimate the clinical pretest probability for PE[60] (Table 73-4). An alternative scoring system, the YEARS criteria, was developed from the variables in the Wells score in combination with a D-dimer test; the presence of hemoptysis, signs of DVT, and PE as the most likely diagnosis, when combined with D-dimer, can reduce the need for CT scanning in patients with suspected PE[57] (Fig. 73-6).

Laboratory Findings

Routine laboratory testing is not useful in confirming or excluding the diagnosis of PE but may be helpful in suggesting other diagnoses. A modest leukocytosis may accompany embolism but rarely exceeds 20,000/mm^3.[61] A higher neutrophil-to-lymphocyte ratio (NLR) among patients with PE conveys a higher risk for 30-day mortality, but increased NLR, a nonspecific finding seen in many inflammatory conditions, is not helpful in establishing the diagnosis

TABLE 73-4 The Wells' Clinical Prediction Score

Variable	Points
DVT symptoms/signs	3.0
PE likely or more likely than alternative diagnosis	3.0
Heart rate >100	1.5
Immobilization/surgery previous 4 wk	1.5
Previous DVT or PE	1.5
Hemoptysis	1.0
Malignancy	1.0
Total Score	**Pretest Probability**
<2.0	Low
2.0–6.0	Moderate
>6.0	High
Dichotomized Score	
≤4	PE unlikely
>4	PE likely

Data from Wells PS, Anderson DR, Rodger M, et al. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. Thromb Haemost. 2000;83(3): 416–420.

of PE.[62] As noted, hypoxemia is common in acute PE although the diagnosis cannot be excluded based upon a normal PO_2.[63,64] The more extensive the obstruction of the vascular bed, the more severe the hypoxemia is likely to be. However, many other conditions also cause hypoxemia, and embolism does not invariably cause hypoxemia or even a widening of the $(A\text{-}a)O_2$ gradient. In the PIOPED trial, no combinations of blood gas values were identified that reliably excluded PE. Although most patients with embolism have a low Pa_{O_2}, low Pa_{CO_2}, and/or high $P(A\text{-}a)O_2$ gradient, the absence of such abnormal values, alone or in combination, did not exclude PE. Hypercapnia resulting from increased dead space ventilation is rare and appears with embolism only in patients with marked antecedent ventilatory limitation or when such limitation has been imposed because the patient is on controlled mechanical ventilation when embolism occurs.

■ Electrocardiogram

The electrocardiogram is nonspecific in the diagnosis of PE, and its major value may be in identifying other clinical disorders (e.g., acute myocardial infarction and pericarditis) that may present in a similar fashion. Findings in acute PE include tachycardia, T-wave changes, ST-segment abnormalities, incomplete right bundle branch block, and left- or right-axis deviation (Fig. 73-7).[65] Atrial arrhythmias may occur but appear to be more common in patients with underlying cardiopulmonary disease. The S1Q3T3 pattern, commonly considered to be specific for PE, is seen in only a minority of patients. Electrocardiographic findings can offer insight into the extent and hemodynamic consequence of the embolism. The electrocardiogram is rarely normal in the setting of embolism associated with right ventricular dysfunction. The presence of an S1Q3T3 pattern, right bundle branch block, or T-wave inversion in leads V1–V3 in a patient with embolism should suggest the presence of right ventricular dysfunction, and these findings at presentation are associated with increased mortality.[66]

■ Chest Radiography

Most patients with PE have abnormal but nonspecific chest radiographic findings.[55,67] Common radiographic findings include atelectasis, pleural effusion, pulmonary infiltrates, and mild elevation of a hemidiaphragm. Classic findings of pulmonary embolism—such as Hampton's hump (a pleural-based opacity) or decreased vascularity (Westermark sign)—are suggestive but infrequent

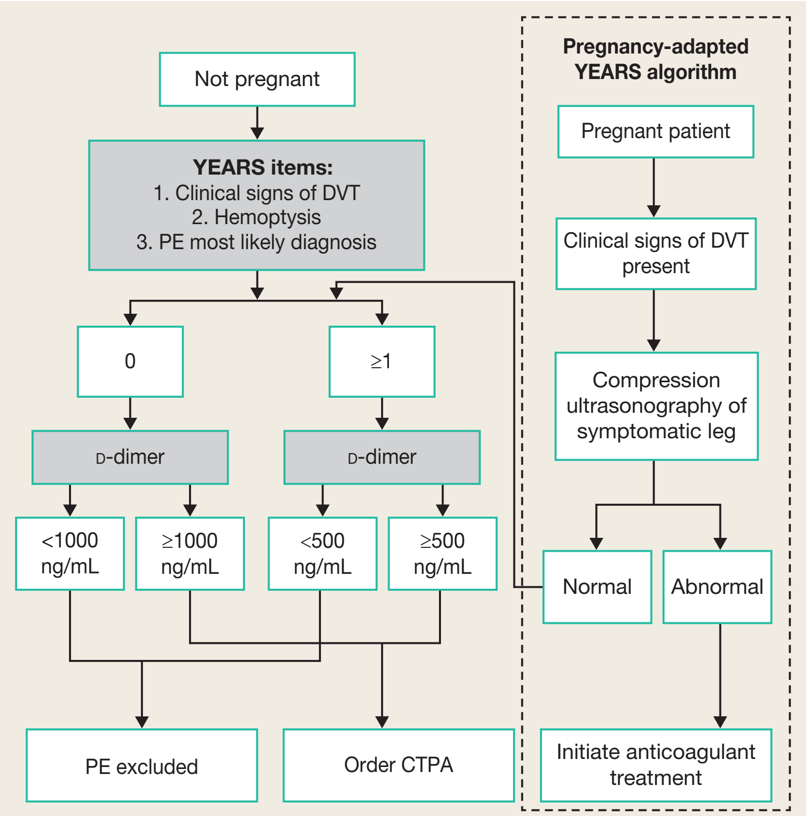


Figure 73-6 The YEARS Criteria along with D-dimer testing can be used in both pregnant and nonpregnant patients to exclude PE in the majority of patients without need for imaging. *(Reproduced with permission from MDCalc. www.mdcalc.com.)*

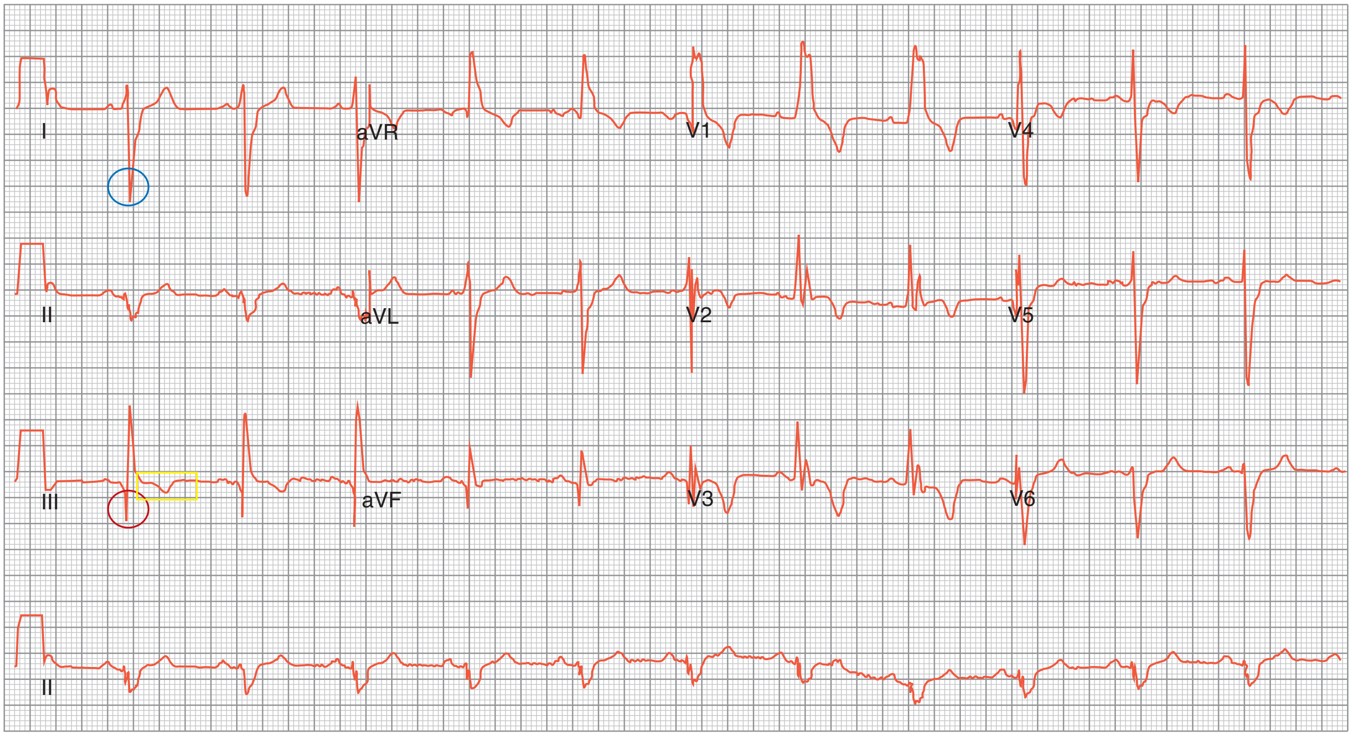


Figure 73-7 The S1Q3T3 pattern can be seen in right ventricular dysfunction such as acute PE.

(Fig. 73-8). There is some confusion about the diagnostic configuration of infiltrates due to embolism. These infiltrates, although usually abutting a pleural surface, can be of any shape, not necessarily wedge-shaped. Although pleural effusions occur in almost half of the patients, the majority of effusions are small and involve only blunting of the costophrenic angle. The main use of the chest radiograph in suspected embolism is to exclude diagnostic possibilities such as pneumothorax, which may simulate the disease. A normal chest radiograph in a patient with otherwise unexplained acute tachypnea, dyspnea, or hypoxemia should raise the possibility of embolism.

■ D-Dimer

The development of a rapid and accurate blood test capable of diagnosing VTE has been the subject of considerable investigative interest. A number of different hemostasiologic markers have been investigated. Of these, D-dimer, alone and in combination with other noninvasive studies, has been subjected to the most rigorous clinical evaluation.[68] D-Dimer testing has proved to be highly sensitive but not specific. Increased levels are present in nearly all patients with thromboembolism but also occur in a wide range of other circumstances, including advancing age, pregnancy, trauma, infections, the postoperative period, inflammatory states, and malignancy.

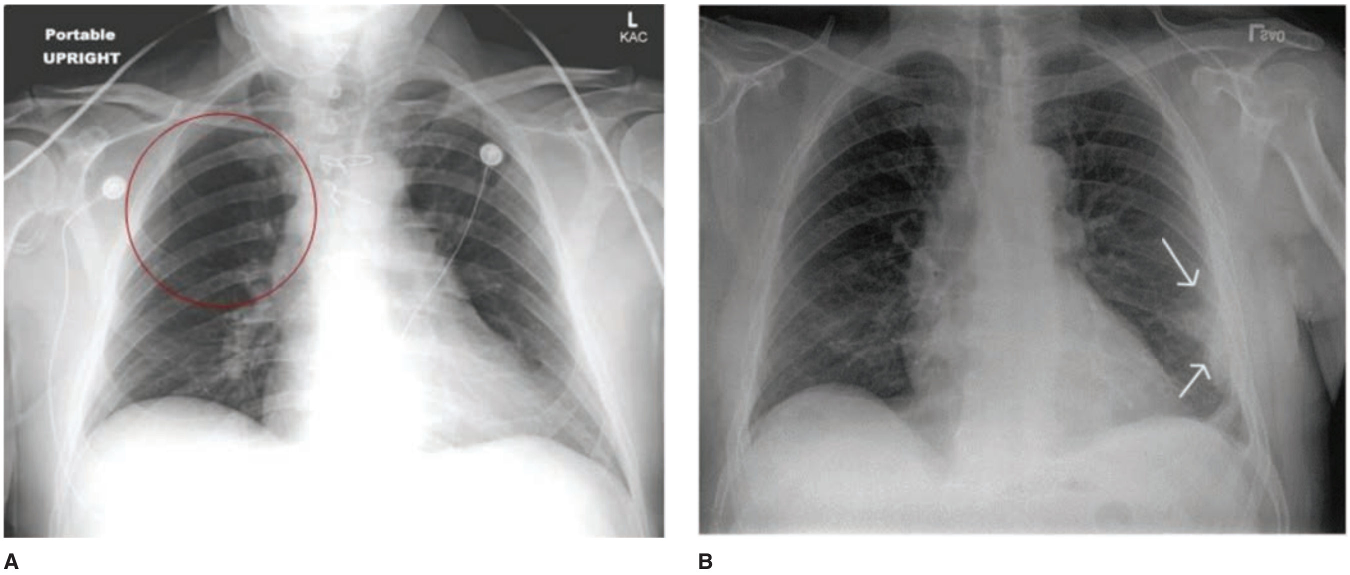


Figure 73-8 **A.** Westermark sign demonstrating oligemia in the right upper lobe due to occlusion from acute PE. **B.** Hampton's hump seen at the arrow heads due to evolving pulmonary infarction in the setting of acute PE. (*A. Reproduced with permission from Omar M, Elaini T, Natt B. Medical image of the week: Westermark sign. Southwest J Pulm Crit Care. 2015;10(3):125–126;* ***B.*** *Reproduced with permission from Tarleton GP, Manthey DE. The elusive Hampton's hump. J Emerg Med. 2003;24(3): 329–330.)*

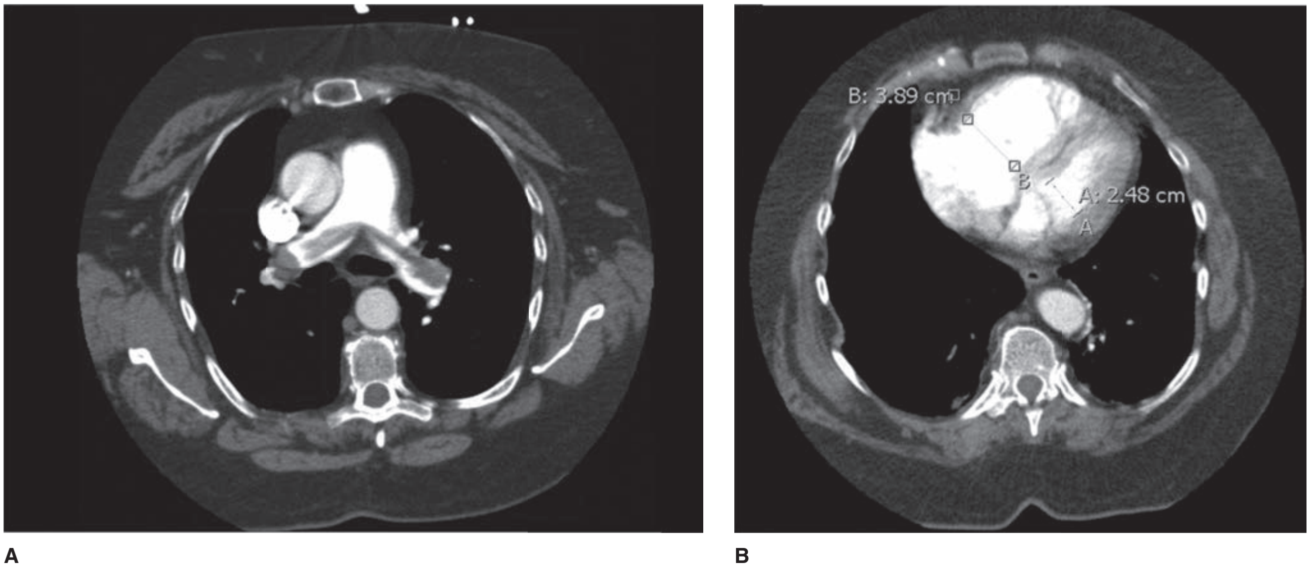


Figure 73-9 **A.** Computed tomographic angiography with classic finding of saddle pulmonary embolism. **B.** Images of the heart in the same patient demonstrate an increased RV:LV ratio and characteristic flattening of the intraventricular septum ("D-shaped septum") seen in submassive pulmonary embolism.

However, the high negative predictive value of a low D-dimer, especially in conjunction with the clinical signs and symptoms of VTE, make D-dimer testing an important tool to limit radiation exposure in outpatients presenting to the emergency departments with possible PE. The study is of limited utility in inpatients given the high frequency of positive results in this population.[69]

Multiple assays for D-dimer have been developed with a range of sensitivities and specificities.[70] Highly sensitive assays such as the enzyme-linked immunosorbent assay (ELISA) are capable of excluding thromboembolism when applied to the outpatient and emergency department patients in whom it has been well studied. Less sensitive assays (e.g., latex agglutination, red cell agglutination) lack the ability to exclude thromboembolism in isolation but have been used successfully in combination with either a clinical probability estimate or noninvasive diagnostic study. D-Dimer testing has been used successfully as part of a number of different diagnostic strategies. Negative results of standardized, highly sensitive assays (ELISA) have proved capable of safely excluding PE in outpatients presenting with a low or intermediate clinical likelihood of the disease.

■ Computed Tomography

Due to widespread availability, computed tomographic angiography (CTA) has become the first-line imaging test for PE (Fig. 73-9).[71] CT technology has evolved from single-detector scanners to 64-section multidetector row CT (MDCT) scanners. Using the latest-generation scanners, visualization of the entire chest with sub-millimeter resolution extending to the sixth-generation arteries can now be performed within a single breath hold. The PIOPED II trial, which used predominantly 4-MDCT technology and a composite reference standard, demonstrated sensitivity for the diagnosis of PE of 83%, specificity of 96%, positive predictive value of 86%, and negative predictive value of 97% (Table 73-5).[55] The predictive value of CT varied substantially when clinical assessment was taken into account, with the major variance occurring when there was discordance between the clinical assessment and CTA finding. Both the positive predictive value in patients with a low clinical probability and the negative predictive value in those with a high clinical probability were in the range of 60%. At the present time, CT can be considered confirmatory in excluding PE in patients with a low likelihood of disease and a negative CTA and confirming embolism in patients with intermediate or high probability of disease and a positive CTA. When discordance exists between the clinical assessment and CT findings, additional studies should be considered.

CTA can also provide additional information about the severity of the PE. A ratio of the right ventricle to left ventricle short-axis diameters (RV/LV) greater than 1 on the initial CT is predictive

TABLE 73-5 **Prevalence of Pulmonary Embolism in PIOPED II: Value of Correlating CT Interpretation with Clinical Assessment**

		Clinical Assessment		
		High No./Total (%)	Intermediate No./Total (%)	Low No./Total (%)
CT Scan Interpretation	**PPV of CTA**	22/23 (96%)	93/101 (92%)	22/38 (58%)
	PPV of CTA-CTV	27/28 (96%)	100/111 (90%)	24/42 (57%)
	NPV of CTA	9/15 (60%)	121/136 (89%)	158/164 (96%)
	NPV of CTA-CTV	9/11 (82%)	114/124 (92%)	146/151 (97%)

PPV of CTA, positive predictive value of computed tomographic angiography; PPV of CTA-CTV, positive predictive value of combined computed tomography angiography + venography; NPV of CTA, negative predictive value of computed tomographic angiography; NPV of CTA-CTV, negative predictive value of computed tomographic angiography + venography.
Data from Galli M, Luciani D, Bertolin G, et al. Lupus anticoagulants are stronger risk factors for thrombosis than anticardiolipin antibodies in the antiphospholipid syndrome: a systematic review of the literature. Blood. 2003;101(5):1827–1832.

TABLE 73-6 Pulmonary Embolism Rule-Out Criteria

Is the patient >49 years?
Is the pulse rate >99 beats per minute?
Is pulse oximetry <95% on room air?
Does the patient have current hemoptysis?
Is the patient taking exogenous estrogen?
Does the patient have a history of venous thromboembolism?
Has the patient had surgery or trauma requiring hospitalization in the past four weeks?
Does the patient have unilateral leg swelling?

Note: If the patient is considered to be at very low risk of pulmonary embolism (<15% risk) based on the physician's pretest suspicion, and answers "no" to all eight questions, the criteria results are considered negative.
Data from Kline JA, Courtney DM, Kabrhel C, et al. Prospective multicenter evaluation of the pulmonary embolism rule-out criteria. J Thromb Haemost. 2008;6(5):772–780.

of 3-month mortality and is important to the nomenclature of the acute PE (i.e., intermediate-low or intermediate-high risk), which is discussed in the upcoming risk stratification section.[7,72] Other findings that convey right ventricular dysfunction such as the reflux of contrast into the inferior vena cava and flattening of the intraventricular septum may be seen and have also been independently correlated with adverse outcomes in acute PE.[73]

Concerns have been raised that the widespread utilization of CTA is resulting in the overdiagnosis of embolism, defined as diagnosing clinically insignificant disease.[74] CTA has been compared to $\dot{V}/\dot{Q}$ for suspected PE, with comparable mortality and false-negative rates for the two imaging modalities but with a 35% higher rate of PE diagnosis for CT.[75] It has been suggested, based on the known natural history of subsegmental embolism, that patients with isolated subsegmental PE do not necessarily need to be treated with anticoagulants provided they have no evidence of DVT by ultrasonography of all four extremities.[12] Additionally, CTA, as a result of its easy availability, may be overutilized in outpatients without adequate patient screening through validated methods such as the Wells criteria/D-dimer model or the Pulmonary Embolism Rule-out Criteria (PERC) (Table 73-6).[76]

■ Ventilation–Perfusion Scanning

Ventilation–perfusion ($\dot{V}/\dot{Q}$) scanning had been the pivotal diagnostic test for suspected PE for many years but has been replaced by CT imaging. Despite limitations, $\dot{V}/\dot{Q}$ scanning can provide valuable information if used and interpreted appropriately. The PIOPED (Prospective Investigation of Pulmonary Embolism Diagnosis) trial provided valuable insight into the strengths and limitations of $\dot{V}/\dot{Q}$ scanning.[77] A negative study is capable of ruling out the diagnosis of PE with the same degree of certainty as a negative pulmonary angiogram and with a higher degree of certainty than can be achieved by a negative CT scan (Fig. 73-10). The positive predictive value of a "high-probability" study (one characterized by multiple, segmental-sized, mismatched defects) approximates 88%; when coupled with a high clinical probability of embolism, the positive predictive value increased to 96%. However, only 28% of patients in PIOPED had scans characterized as high probability or normal, the only categories that can be considered definitive. The majority of patients with embolism do not have a high-probability scan, while the majority of those without embolism do not have a normal scan.

There are certain situations in which $\dot{V}/\dot{Q}$ scanning may be preferred over CTA. IV contrast is not required for $\dot{V}/\dot{Q}$ scanning, making it a more desirable option in patients with renal dysfunction or a severe iodinated contrast allergy. In addition, with a portable gamma scintillation camera, the perfusion portion of the study can be performed at the bedside, which may be a major advantage in a critically ill patient for whom transportation to the CT scanner may be deemed too high risk. Preference for $\dot{V}/\dot{Q}$ scanning versus CTA in pregnancy remains controversial, although fetal risk due to radiation exposure appears to be low with both modalities.[78]

■ Echocardiography

Although transthoracic echocardiography (TTE) performs poorly in the diagnosis of acute PE with a sensitivity of only 50%,[79] certain findings of RV strain display high specificity that may be useful to "rule in" PE at the bedside in patients with a high pretest probability.[80] The classic echocardiographic finding of right ventricular free wall akinesis with sparing of the apex (McConnell's sign) has a 94% specificity for acute PE (Video 73-1).[81] Echocardiography may also disclose "clot in transit," which can be seen in about 5% of patients with acute PE.[11]

TTE has emerged as an important tool for risk assessment and treatment guidance in patients with acute PE. The presence of right

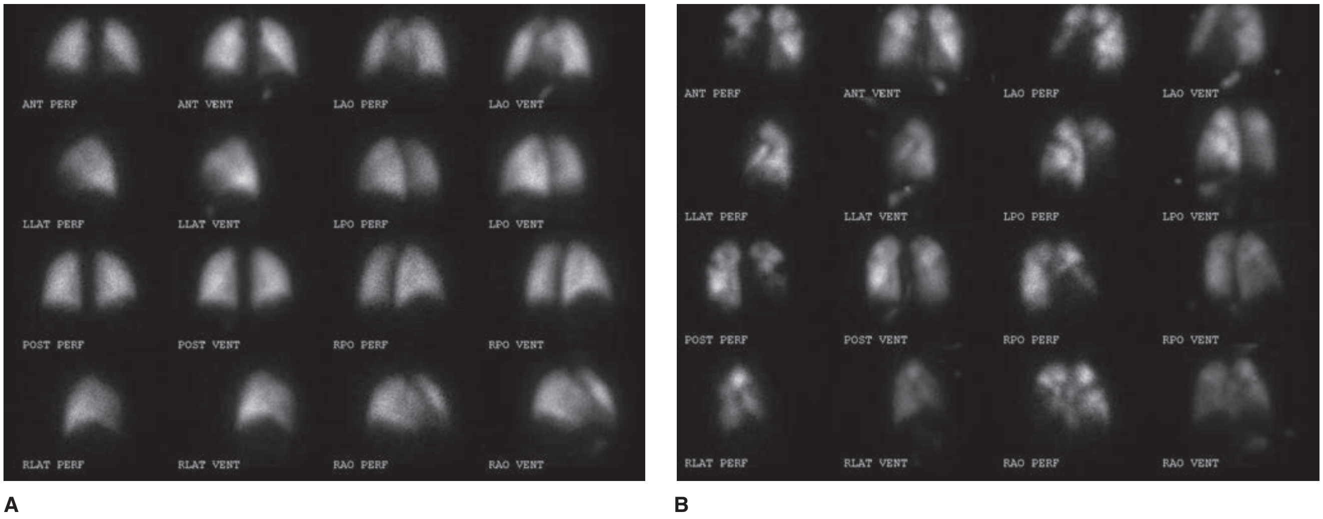


Figure 73-10 **A.** Normal ventilation images seen in the panels labeled VENT and matched normal perfusion in the panels labeled PERF. **B.** High-probability VQ scan with multiple segmental defects including the entire right lower lobe, right middle lobe, and segmental defects in the anterior left upper lobe and anteromedial basal left lower lobe.

Video 73-1 McConnell sign of acute PE with right ventricular free wall akinesis with sparing of the apex. *(Reproduced with permission from Dr. Ken Chen, M.D.) Video available on AccessMedicine.com.*

ventricular dysfunction on a baseline echocardiogram in normotensive patients appears to represent an independent predictor of an adverse outcome or early death.[82] More specifically, four TTE parameters are independently associated with mortality: ratio of RV to left ventricular end-diastolic diameter, RV systolic pressure, tricuspid annular plane systolic excursion, and inferior vena cava collapsibility.[83] Echocardiography may also prove valuable in the evaluation of competing diagnostic possibilities such as right ventricular infarction, endocarditis, pericardial tamponade, and aortic dissection in patients with unexplained shock and evidence of elevated central venous pressure.

■ Lower Extremity Evaluation

Duplex ultrasonography, which refers to the combination of Doppler venous flow detection and real-time B-mode imaging, has assumed a central role in the noninvasive diagnosis of symptomatic lower extremity DVT.[84] A number of criteria are used to diagnose venous thrombosis, the most reliable of which is noncompressibility of a venous segment. Secondary, less reliable criteria include the presence of echogenic material within the venous lumen; venous distention; and loss of phasicity, response to Valsalva, and augmentation of spontaneous flow. The absence of an echogenic luminal mass cannot be considered useful in excluding the diagnosis of venous thrombosis because acute thrombus may not demonstrate echogenicity. Multiple studies over the past two decades have demonstrated sensitivities and specificities of duplex ultrasonography exceeding 95% in *symptomatic* patients with proximal venous thrombosis.

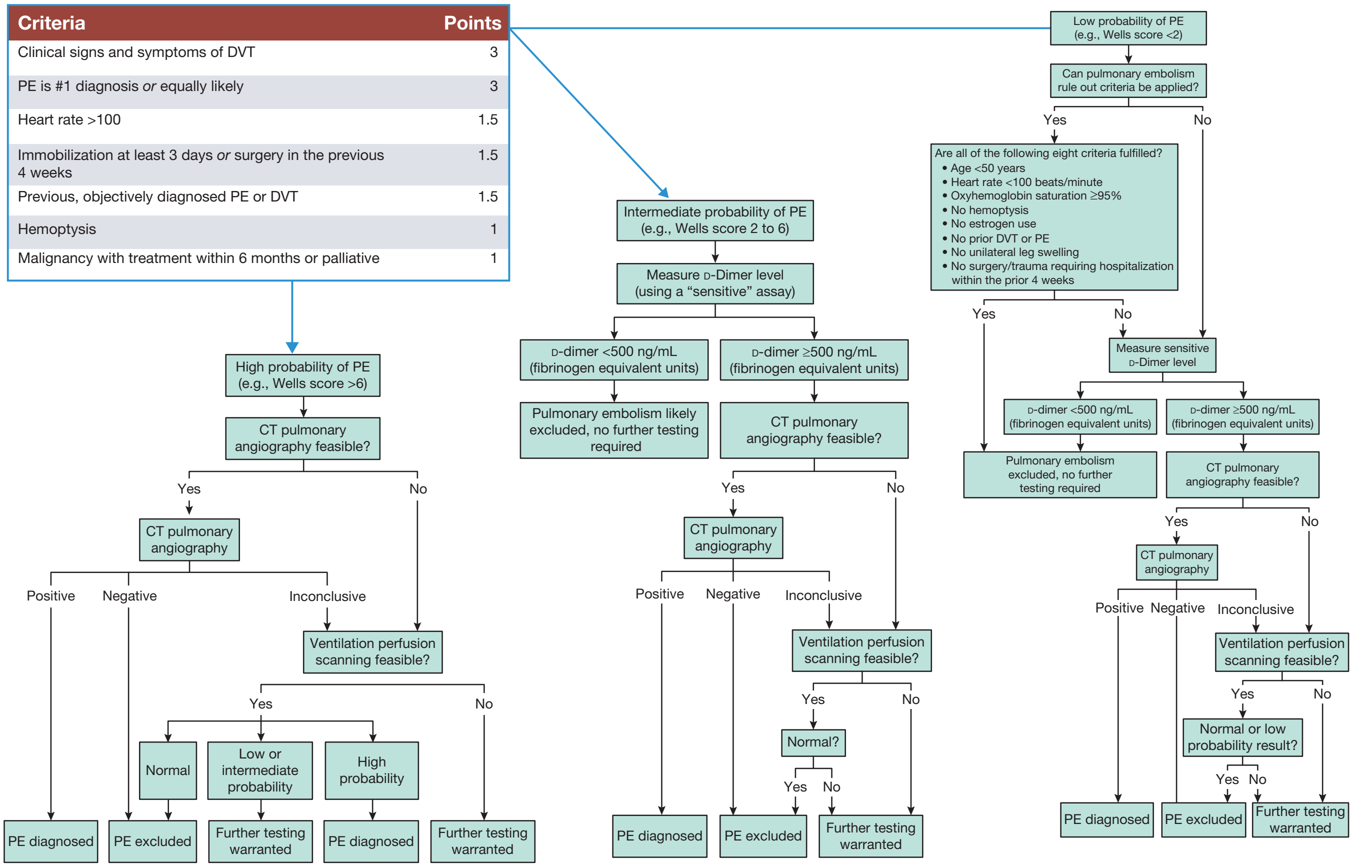
While duplex ultrasonography is highly sensitive and specific in the diagnosis of DVT in symptomatic patients, its accuracy in the diagnosis of acute PE is less clear. Approximately 40% to 50% of patients with PE will also have DVT, and the HR for all-cause mortality is 2.05 times higher for those with concomitant DVT compared to those with PE alone.[85] However, given the sensitivity of lower extremity Doppler ultrasonography of 41% with suspected PE, its use as the initial diagnostic study should be reserved for those patients with clinical evidence of DVT and for situations in which it is preferable to avoid exposure to radiation or contrast material.[86]

DIAGNOSTIC APPROACH

The diagnostic approach to PE should be targeted toward the patient population being studied (Fig. 73-11). For outpatients, the use of a clinical prediction rule coupled with D-dimer testing or the use of the PERC criteria can substantially reduce the number of imaging studies performed.[87–89]

In the outpatient setting, D-dimer results would not alter the need for an objective imaging study in patients with a high probability of PE. In patients with a low or intermediate clinical likelihood of embolism, a negative D-dimer study is sufficient to exclude the possibility of embolism, assuming a highly sensitive assay is used. An imaging study should be performed in all patients with a high probability of disease as well as those with a low or intermediate probability whose D-dimer tests are positive.

Patients with signs or symptoms of lower extremity DVT should initially undergo lower extremity duplex ultrasonography.



Criteria	Points
Clinical signs and symptoms of DVT	3
PE is #1 diagnosis *or* equally likely	3
Heart rate >100	1.5
Immobilization at least 3 days *or* surgery in the previous 4 weeks	1.5
Previous, objectively diagnosed PE or DVT	1.5
Hemoptysis	1
Malignancy with treatment within 6 months or palliative	1

High probability of PE (e.g., Wells score >6)
CT pulmonary angiography feasible?
Yes
No
CT pulmonary angiography
Positive
Negative
Inconclusive
Ventilation perfusion scanning feasible?
Yes
No
Normal
Low or intermediate probability
High probability
PE diagnosed
PE excluded
Further testing warranted
PE diagnosed
Further testing warranted
Intermediate probability of PE (e.g., Wells score 2 to 6)
Measure D-Dimer level (using a "sensitive" assay)
D-dimer <500 ng/mL (fibrinogen equivalent units)
D-dimer ≥500 ng/mL (fibrinogen equivalent units)
Pulmonary embolism likely excluded, no further testing required
CT pulmonary angiography feasible?
Yes
No
CT pulmonary angiography
Positive
Negative
Inconclusive
Ventilation perfusion scanning feasible?
Yes
No
Normal?
Yes
No
PE diagnosed
PE excluded
Further testing warranted
Low probability of PE (e.g., Wells score <2)
Can pulmonary embolism rule out criteria be applied?
Yes
No
Are all of the following eight criteria fulfilled?
• Age <50 years
• Heart rate <100 beats/minute
• Oxyhemoglobin saturation ≥95%
• No hemoptysis
• No estrogen use
• No prior DVT or PE
• No unilateral leg swelling
• No surgery/trauma requiring hospitalization within the prior 4 weeks
Yes
No
Measure sensitive D-Dimer level
D-dimer <500 ng/mL (fibrinogen equivalent units)
D-dimer ≥500 ng/mL (fibrinogen equivalent units)
Pulmonary embolism excluded, no further testing required
CT pulmonary angiography feasible?
Yes
No
CT pulmonary angiography
Positive
Negative
Inconclusive
Ventilation perfusion scanning feasible?
Yes
No
Normal or low probability result?
Yes
No
PE diagnosed
PE excluded
Further testing warranted

Figure 73-11 Diagnostic algorithm for acute PE using the Wells criteria to develop a pretest probability followed by utilization of D-dimer testing to limit imaging to the highest-risk patients. *(Copyright ©2022 UpToDate, Inc. and its affiliates and/or licensors. All rights reserved.)*

TABLE 73-7 Non-massive, Submassive and Massive Nomenclature for Acute PE Severity

	Incidence	Definition	Shock	sPESI >1	Imaging with RV Dysfunction	Cardiac Biomarkers	Mortality Risk
Non-Massive PE	75%	Absence of hypotension, RV dysfunction and myocardial necrosis	–	–	–	–	Low (<1%)
Submassive PE	20–25%	Systolic blood pressure >90 mm Hg and either: (1) RV dysfunction by imaging (echocardiogram or CT RV:LV ratio >1) (2) Positive biomarkers (elevated proBNP, positive troponins)	–	+	Either Positive +/–	+/–	Intermediate-Low (<5%)
			–	+	Both Positive +	+	Intermediate-High (10%)
Massive PE	<5%	Acute PE with hypotension (SBP <90 or drop greater than 40 mm Hg for longer than 15 minutes)/obstructive shock/cardiac arrest	+	+	+	+	High (>25%)

A positive lower extremity study, although not proving PE has occurred, has the same therapeutic implications. Although such an approach will yield a confirmatory study in only about 40% of embolic suspects, it avoids the cost and radiation exposure associated with CTA. A negative study is insufficient to exclude the possibility of embolism.[90]

Whatever approach is undertaken, the treating physician should be aware of the type of D-dimer assay, discriminant value of that particular assay, and generation of CT scanner used. "Negative" findings on a low-sensitivity D-dimer assay or a single-row CT scanner have very different implications than similar findings using a highly sensitive D-dimer assay or 64-MDCT scanner.

The role of D-dimer testing and clinical assessment in hospitalized patients is limited. A substantial proportion of hospitalized patients have a positive highly sensitive D-dimer result related to an active inflammatory process, malignancy, recent surgery, liver disease, and even advancing age.[91] Comorbid conditions affect the clinical likelihood assessment. Therefore, a far higher proportion of hospitalized embolic suspects require an imaging study to confirm or exclude the diagnosis.

RISK STRATIFICATION

An important element in determining treatment for patients with acute PE is determining the risk for adverse outcomes. When describing PE, there are several categories that have important implications for the risk of mortality, duration of therapy, and risk for recurrence. First among these is the distinction between massive, submassive, and nonmassive PE (Table 73-7).[7] A massive PE is a hemodynamically significant clot with obstructive shock, need for CPR, or hypotension present; this category conveys the highest short-term mortality risk. A submassive PE does not exhibit hypotension, but there are signs of right ventricular dysfunction by imaging (echocardiogram or CT with RV:LV ratio >1) and/or positive cardiac biomarkers (NT-proBNP, troponin). Patients with submassive PE are at risk for clinical deterioration and require close monitoring with consideration of advanced therapies in select populations. Finally, nonmassive PE represents the majority of PE diagnoses and convey a low risk for mortality; many of these patients can safely be treated as outpatients.[92]

A number of risk scores to predict mortality are available. The simplest to use and most widely validated is the Simplified Pulmonary Embolism Severity Index (sPESI) (Table 73-8). This score assigns a point for any of the following: age >80 years, history of cancer, chronic cardiopulmonary disease, tachycardia >110 beats per minute, systolic blood pressure <100 mm Hg, and arterial oxygen saturation <90%. If any one of these is present, the patient is deemed high risk. In the external validation of the sPESI score, 36.2% of patients were classified as low risk with a 30-day mortality of 1.1% (95% CI, 0.7–1.5) as opposed to the 63.8% of high-risk patients with a 30-day mortality of 8.9% (95% CI, 8.1–9.8).[93] The real value of this sPESI score lies in the high negative predictive rate of 98.9%. A sPESI score of zero portends that patients will do well and can be used to identify patients who can safely be managed at home.[94]

Aside from imaging, biomarkers, and risk scores, the presence of concomitant DVT should be considered in determining the risk from an acute PE. First, patients with PE and concomitant proximal DVT have a 2.02 times higher HR for PE-related death than patients with PE alone.[85] Patients with intermediate-risk PE and concomitant proximal DVT may benefit from other interventions such as suction embolectomy or IVC filter placement. Likewise, the presence of clot-in-transit (i.e., thrombus in inferior vena cava, right atrium, RV, or left atrium [if a patent foramen ovale is present]) merits consideration for potential interventions.

Most of the PE-related mortality occurs in the first 24 h after the diagnosis is made.[95] Over the past decade, there has been a movement to develop PE response teams (PERT) to rapidly risk-stratify

TABLE 73-8 Simplified PESI Score

Clinical Feature	Points
Age >80 years	1
History of cancer	1
Chronic cardiopulmonary disease	1
Pulse ≥110/min	1
Systolic blood pressure <100 mm Hg	1
Arterial oxygen saturation <90%	1
	Total
Low risk (30-day mortality 1.1%)	0
High risk (30-day mortality 63.8%)	≥1

patients and determine whether advanced therapies such as thrombolysis, catheter-directed therapies, surgical embolectomy, or VA ECMO are warranted. These teams are typically multidisciplinary, involving pulmonologists, intensivists, cardiothoracic surgeons, and interventionalists (cardiologists and/or interventional radiologists).[96] The team quickly assembles the data, determines the risk, and then decides on an approach to management. While organization of the team and rapid decision-making in acute PE are warranted, the impact of PERT on outcomes is uncertain. Early analysis of the PERT experience demonstrates a more invasive and costly approach to the management of submassive PE with no significant improvement in mortality.[97]

APPROACH TO PE MANAGEMENT

Management of acute PE consists of a systematic approach that involves patient risk stratification, early intervention when warranted, selection of therapy, and determination of treatment duration. Only in the high-risk groups (massive and intermediate- to high-risk submassive PE) are the advanced therapies for PE considered; the nonmassive and intermediate- to low-risk submassive patients will do well with anticoagulation alone. The goals of therapy in PE are several: to assure adequate oxygenation, provide hemodynamic support, and prevent thrombus propagation and embolic recurrence. Regardless of how the patient is risk stratified, anticoagulation remains the most important initial element of the management of these patients.

There is little controversy about the management of both nonmassive and massive PE. Nonmassive pulmonary embolism is managed with anticoagulation alone, and the options for anticoagulation are discussed later. Many nonmassive patients can safely be discharged home to continue anticoagulation. Either the HESTIA score (Table 73-9) or a sPESI score of 0 can be used to identify those patients who are safe for discharge.[92] Hospitalization should be mandatory for older patients who may have less cardiopulmonary reserve or significant coexisting illnesses, or those who may not be able to follow instructions or have adequate follow-up. Other indications for hospitalization include hypoxemia or sufficient renal disease to contraindicate the use of low-molecular-weight heparin or a factor Xa inhibitor. Options for the initial phase of anticoagulation are further discussed below.

Likewise, there is little controversy related to the management massive PE. There is consensus among the societal guidelines that patients with hypotension with obstructive shock should receive thrombolytics.[7,12] The standard dose of tissue plasminogen activator (tPA) is 100 mg administered over 2 h via peripheral IV. In patients experiencing cardiac arrest, consideration can be given to bolusing tPA 50 mg followed by a 50-mg drip. These guidelines are based on one small study of massive PE with patients randomized to either tPA or standard care; patients who received tPA all survived while those treated with standard care anticoagulation alone did not all survive.[98] In those patients deemed to be too high-risk for bleeding complications with thrombolysis, surgical embolectomy or suction embolectomy are potential therapeutic options. Finally, veno-arterial extracorporeal membrane oxygenation is an option for patients with profound obstructive shock and right ventricular failure related to massive PE.

TABLE 73-9 Hestia Criteria

If any of the below are answered "Yes," the patient should NOT be treated as an outpatient.

1. Hemodynamically unstable?
2. Thrombolysis or embolectomy necessary?
3. Active bleeding or high risk of bleeding?
4. Oxygen supply to maintain oxygen >90% >24 hours?
5. Pulmonary embolism diagnosed during anticoagulant treatment?
6. In severe pain needing IV pain medication >24 hr (or multiple doses in the ED)?
7. Medical or social reason for treatment in hospital >24 hr?
8. Creatinine clearance less than 30 mL/min?
9. Severe liver impairment or disease?
10. Pregnant?
11. Documented history of heparin-induced thrombocytopenia?

In contrast to nonmassive and massive pulmonary embolism, the management of patients with submassive PE remains an area of significant controversy. While these patients clearly have a higher mortality than patients with nonmassive PE, the majority do well with anticoagulation alone. In the PEITHO trial of tenecteplase in patients with intermediate risk PE, 94.6% of patients randomized to standard-of-care anticoagulation alone did well with no further clinical deterioration.[99] Identifying those patients at highest risk for deterioration to offer advanced therapies to prevent morbidity and mortality remains an elusive target. In the past decade, several catheter-directed therapies (including those using thrombolytics delivered locally to the thrombus and devices to mechanically dislodge or disrupt the thrombus) have emerged as potential treatment options with hypothetically less risk for bleeding complications.

While the nonmassive, submassive, and massive pulmonary embolism nomenclature is based on the risk for morbidity and mortality, these should not be thought of as silos. Patients with submassive PE are at increased risk for complications and merit close attention in the first hours to days after diagnosis. The majority of these patients will do well but, should patients develop signs of clinical deterioration (i.e., hypotension, syncope, tachycardia, shock), the need for more aggressive intervention should be addressed expeditiously by a multidisciplinary team.

OPTIONS FOR INITIAL TREATMENT

A variety of options can be considered for initial treatment.

■ Heparin

Anticoagulation with heparin remains the standard initial therapy for hospitalized patients. The major anticoagulant effect of heparin is to reduce thrombus propagation and prevent embolic recurrence. Choices include either intravenous unfractionated heparin (UFH) or subcutaneous low-molecular-weight heparin (LMWH) preparations. Given that failure to achieve rapid therapeutic levels of anticoagulation appears to be associated with an increased recurrence rate, it is important to ensure adequate anticoagulation as soon as possible.[100]

Physician practices in the administration of intravenous UFH have often resulted in substantial delays before adequate prolongation of the activated partial thromboplastin time (aPTT) is achieved. To overcome these problems, standardized protocols for heparin administration and monitoring have been recommended. One commonly employed dosing regimen using an initial IV bolus of 80 units of heparin per kilogram followed by a continuous infusion initiated at 18 units per kilogram per hour has been demonstrated to reach therapeutic thresholds more quickly than regimens using fixed dosing.[101] The heparin drip is adjusted based on monitoring of the activated partial thromboplastin time (aPTT), drawn 6 h after the initial bolus dose, then 6 h after each dose adjustment, with a target aPTT ratio of 1.5 to 2.5. Because attempts to straddle the lower therapeutic range may result in periods of inadequate anticoagulation, it is prudent to maintain the ratio in the upper range of the recommended target. Although more costly than aPTT, many centers have adopted heparin protocols targeting anti-Xa levels. The anti-Xa level is a more accurate direct measure of heparin activity against activated factor X and is unaffected by the baseline PTT (which can be prolonged in cases such as those with antiphospholipid antibodies). The anti-Xa level can be falsely low in the setting of antithrombin III deficiency.[102]

The major advantages of intravenous UFH are that it can be bolused to rapidly achieve a therapeutic window and can be shut off if there is a need for thrombolysis or bleeding complications develop. While there is disagreement between American and European guidelines on the matter, most would recommend stopping heparin infusion prior to administering thrombolytics and restarting therapeutic anticoagulation with heparin drip after the infusion is completed.

With the exception of special circumstances, LMWH preparations have displaced UFH as the anticoagulant of choice in uncomplicated VTE, as the incidence of recurrent thromboembolic events was found to be lower in those treated with LMWH than in those treated with UFH.[103] Situations in which the use of UFH is still appropriate include renal insufficiency; extremes of body weight; and circumstances in which a rapid adjustment or reversal of anticoagulation is needed, such as women in the late stage of pregnancy who may need cesarean sections, patients with recent surgery or recent history of bleeding, and hemodynamically unstable patients with VTE who may need surgical procedures such as emergency embolectomy.

Available evidence suggests that LMWH is at least as effective as UFH in treating acute PE. Advantages of LMWH compared with UFH include (1) longer half-life and ease of use; (2) ability to consistently achieve early therapeutic anticoagulation; (3) no need to monitor anticoagulant effects; and (4) reduced incidence of major bleeding complications. Even though there are differences in the FDA-approved indications for different LMWH preparations in the United States, it is not clear that their actions differ significantly.

In general, therapeutic monitoring is not needed with LMWH, but there are situations where the therapeutic effects may be less predictable and monitoring with anti-Xa levels is indicated. These include (1) patients with antiphospholipid antibodies or other circulating anticoagulants leading to elevated baseline aPTT; (2) extremes of body weight (<40 kg and >150 kg); (3) creatinine clearance <30 mL/min; (4) pregnancy; and (5) unexplained bleeding or recurrent thrombosis during therapy. A therapeutic target range for peak anti-Xa levels ranges from 0.6 to 1.0 IU/mL, measured 4 h after administration. The target range for peak anti-Xa levels with once daily enoxaparin is >1.0 IU/mL whereas it is >0.85 IU/mL with tinzaparin and 1.3 IU/mL and 1.05 IU/mL with nadroparin and dalteparin, respectively.[104]

Intravenously administered direct thrombin inhibitors (lepirudin, argatroban) represent another class of anticoagulant agents that have been approved for the management of patients with PE in the setting of heparin induced thrombocytopenia (HIT).[105] Their mechanism of action differs from that of heparin and the synthetic pentasaccharides in that they directly inhibit the active site of thrombin and do not require interaction with antithrombin to produce an anticoagulant effect. Argatroban is a synthetic agent derived from arginine. It has a half-life of approximately 45 min and is cleared by the liver. Lepirudin is a recombinant polypeptide similar to hirudin. It has a half-life of 40 to 60 min and is cleared by the kidneys. Both agents are administered by continuous IV infusion and dose adjustments made with monitoring of the aPTT. Both agents affect the international normalized ratio (INR), thereby complicating the transition to oral warfarin therapy.

■ Thrombolytic Therapy

Unlike anticoagulants, thrombolytic drugs cause direct lysis of thrombi by increasing plasmin production through plasminogen activation. The use of thrombolytics is considered in patients with cardiopulmonary compromise, as these agents rapidly lyse the emboli causing obstructive shock. However, the potential benefits are often offset by the relatively high incidence of hemorrhagic complications. Proper patient selection and dosing are key to the safe use of these agents.

Multiple thrombolytic agents are available. Those most studied for the management of acute PE include streptokinase, alteplase (rt-PA), urokinase, and tenecteplase, all of which are FDA-approved for use in the United States. The exact role of thrombolytic agents in acute PE remains controversial. While thrombolytic therapy does appear to accelerate the rate of thrombolysis, there are no high-quality data to show that thrombolysis decreases mortality in submassive PE.[106] The one issue about which there can be little controversy is that the use of thrombolytic agents is associated with a substantially increased risk of bleeding, including intracranial hemorrhage. The absolute and relative contraindications are listed in Table 73-9. Compared with anticoagulation alone, the risks for both major bleeding (9.24% vs. 3.42%) and intracranial hemorrhage (1.46% vs. 0.19%) are increased in patients receiving thrombolytics, although this risk is not elevated in those <65 years of age.[107]

Based on these data, and assuming there is no contraindication to its use, the use of thrombolytic therapy for PE appears to be appropriate when an accelerated rate of thrombolysis is considered to be potentially lifesaving—that is, in patients with PE who present with hemodynamic compromise in whom the mortality rate approaches 30%. The role of thrombolytic therapy in patients with anatomically massive embolism or echocardiographic evidence of right ventricular dysfunction in the absence of systemic hypotension has been thoroughly studied but remains poorly defined. In the PEITHO trial, 1006 patients with intermediate-risk PE (normotensive patients with both RV dysfunction by imaging and evidence of elevated cardiac biomarkers) were randomized to either tenecteplase plus heparin or placebo plus heparin.[99] While the study met its primary endpoint of reducing the combined rate of death and hemodynamic collapse (2.6% in the tenecteplase group vs. 5.6% in the placebo group; $p = 0.02$), this came at the expense of increased risk for hemorrhage (6.3% with tenecteplase vs. 1.2% with placebo; $p < 0.001$) and stroke (2.4% vs. 0.2%; $p = 0.003$). The improvement in the combined endpoint was driven not by an improvement in mortality but rather a reduction in hemodynamic decompensation (1.6% vs. 5.0%; $p = 0.002$). These data provide reassurance that the majority of these submassive, intermediate-high risk patients will do well with anticoagulation alone, but they require careful monitoring for deterioration, which occurred in about 1 in 20 patients.

Some have advocated using lower doses of thrombolytic to reduce the risk of bleeding complications. There is even less evidence to support this approach. In the MOPPET study, a lower dose of tPA, 50 mg, was compared to standard of care for patients with a nonstandard definition of moderate PE (based on radiographic size of the thrombus and clinical signs of disease burden).[108] Methodologic flaws, single-center design, and the poorly chosen endpoint of echocardiographic evidence of pulmonary hypertension at 6 months with extraordinarily high rates of pulmonary hypertension seen in both groups severely limit the interpretation and generalizability of this study. Additional data derived from multicenter, randomized controlled trials is needed before lower-dose peripheral thrombolytics can be recommended.

■ Catheter-Directed Therapy

Over the past decade, a number of intravascular catheters have been developed to treat submassive PE (Fig. 73-12).[109] These catheters are utilized for either catheter-directed thrombolysis or suction embolectomy. These catheter-based approaches may offer more rapid recovery and are associated with lower bleeding risks compared with systemic thrombolysis.[110]

The rationale for catheter-directed thrombolysis is that by delivering the thrombolytic into or in close proximity to the thrombus, higher

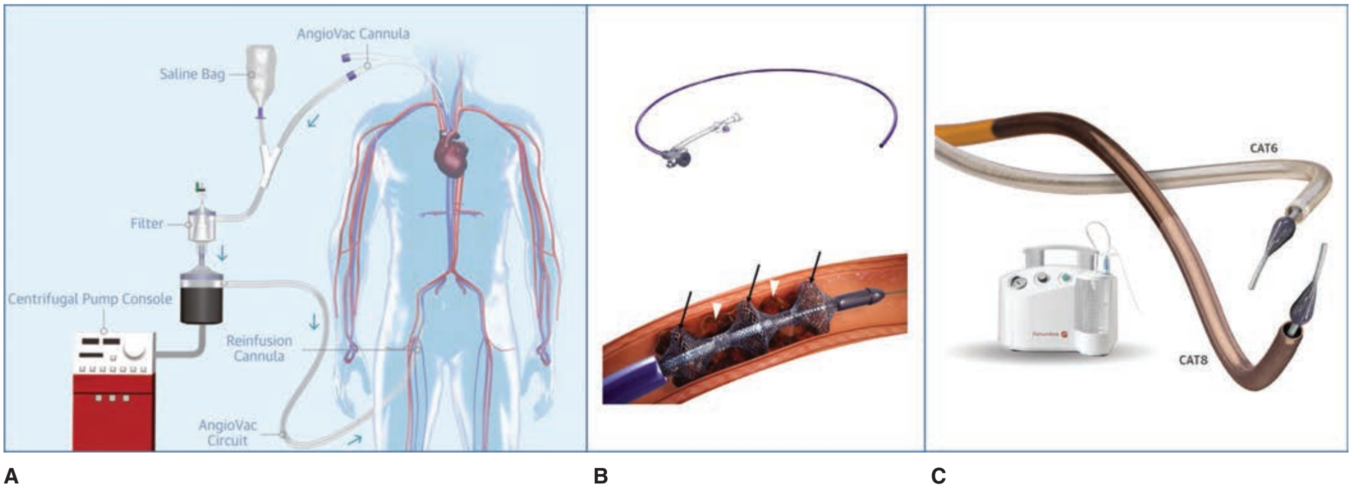


Figure 73-12 Examples of available suction embolectomy catheters. **A.** The AngioVac system is a large-bore (26-F) aspiration catheter requiring a centrifugal pump and return cannula. **B.** The FlowTriever system uses a 22-F aspiration guide catheter with syringe for suction and a catheter with nitinol discs for mechanical disruption of thrombus. **C.** The Penumbra aspiration system uses a smaller-bore catheter (6- to 8-F) with separator wires for mechanical disruption of thrombus and uses an automated aspiration system. *(Reproduced with permission from Jaber WA, Fong PP, Weisz G, et al. Acute Pulmonary Embolism: With an Emphasis on an Interventional Approach. J Am Coll Cardiol. 2016;67(8):991–1002.)*

local concentrations can be achieved with lower total doses of the lytic. Many catheters mechanically fragment the thrombus or provide ultrasonic vibration that theoretically enables the lytic to permeate into the thrombus. It is not clear that catheter-directed thrombolysis mitigates the systemic lytic effect as seen with IV administration; since the half-life of tPA is 4 min, the effect of recirculation of tPA is 5 times greater than the effect of the first pass. Indeed, the risk of bleeding with catheter-directed thrombolysis in the SEATTLE-II trial was similar to that of systemic tenecteplase in the PEITHO trial.[99,111] Additionally, there is no demonstrable benefit to the addition of ultrasound assistance in the resolution of clot. In a study of iliofemoral DVT treated with catheter-directed thrombolysis regimen, the addition of intravascular ultrasound did not accelerate thrombus resolution.[112]

The data to support the use of catheter-directed thrombolysis come mainly from three studies, only one of which was randomized and controlled. The ULTIMA study randomized patients with submassive PE to either ultrasound assisted, catheter-directed thrombolysis or standard anticoagulation to assess a change in RV:LV ratio at 24 h.[113] Patients treated with the catheters achieved significant improvement in mean RV/LV ratio, which was reduced from 1.28 ± 0.19 at baseline to 0.99 ± 0.17 at 24 h ($p < 0.001$); patients in the heparin arm had no significant difference in RV:LV size at 24 h. In the prospective, single-arm SEATTLE-II study of patients with PE treated with ultrasound-facilitated, catheter-directed, low-dose fibrinolysis, similar improvement in RV:LV ratio at 24 h was seen but this came at the expense of moderate bleeding complications in 10% of patients.[111] The PERFECT trial was a single-arm safety study with no major procedure-related complications, major bleeding, or hemorrhagic strokes.[114] No study of catheter-directed therapy to date has shown a mortality benefit or any evidence of reduction in the long-term morbidity from PE.

A more recent advance in catheter-directed therapy is the emergence of suction embolectomy and mechanical thrombectomy catheters. There are a number of FDA-approved devices that are now available, and these have the main benefit of avoiding thrombolytics and thus have less risk for bleeding complications than catheter-directed thrombolysis. In the FLARE study of the FlowTriever suction embolectomy catheter (Inari Medical), similar improvements in RV:LV ratio were seen compared to those from catheter-directed thrombolysis, but there were fewer bleeding events (0.9% with major bleeding, all at catheter insertion sites) and shorter median length of stay.[115] The EXTRACT-PE study with the aspiration system from Penumbra achieved a significant reduction in RV/LV ratio at 48 h with similar low rates of bleeding complications.[116] There are several options for mechanical thrombectomy including the Amplatz thrombectomy catheter and the AngioJet Catheter, which both use proprietary mechanisms to fragment the embolic material and then create a vacuum to aspirate it. Rheolytic embolectomy with the Angiojet catheter was associated with a higher incidence of bradycardia, hemolysis, and procedure-related deaths in a meta-analysis, which resulted in a Black Box warning for this device in acute PE.[117] The AngioVac system can be considered for clot in transit in the right atrium or ventricle. The device incorporates extracorporeal bypass to return the blood removed after the clot is filtered out; about 25% of patients will require transfusion with an average drop in hemoglobin of 1 gram/dL.[118]

The role of catheter-directed therapy remains in flux. None of the major societal guidelines support the routine use of these devices in patients with submassive PE. As experience with the devices increases, the safety of the intervention as well as improved patient selection may expand their use. However, large randomized controlled trials comparing these interventions to the standard of care of heparin anticoagulation are needed before widespread use of these devices is recommended.

■ Vena Cava Interruption and Vena Cava Filter

The concept of vena cava interruption came from the historic practice of surgical ligation (by complete vascular ligation or partial interruption using surgical suture) of the inferior vena cava (IVC) in an attempt to prevent thrombus migration. A variety of IVC filters are now available including both permanent and temporary (removable as well as biodegradable) options (Fig. 73-13).

The central indication for IVC filter placement is to prevent PE in patients with VTE who have a contraindication to anticoagulation. Recent data suggest that the utilization of IVC filters has expanded since their introduction and that IVC filters are being placed for alternative reasons, including prophylaxis.[119] Much of this expansion in utilization can be attributed to the development of retrievable IVC filters which, in many instances, are never removed.[120] Guidelines for filter placement, albeit based on limited data, have been established by the American College of Chest Physicians (ACCP) and the Society of Interventional Radiologists (SIR).[12,121] These recommendations are somewhat disparate, with the SIR recommendations being considerably more liberal than those of the ACCP.

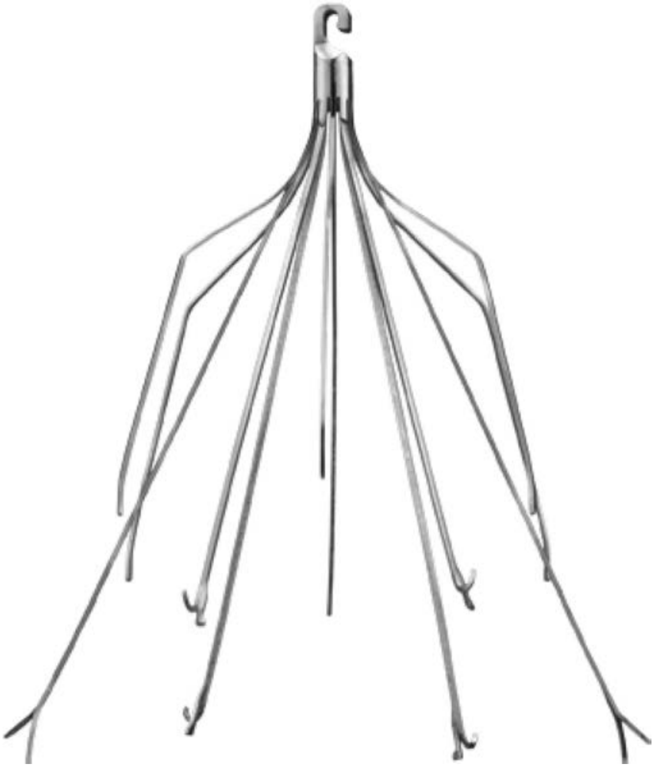


Figure 73-13 Example of retrievable inferior vena cava filter. The Denali retrievable IVC filter by BD. There are similar retrievable filters from other manufacturers.

Retrospective analysis of registry data has suggested a mortality benefit with IVC filter insertion in acute PE.[122] Randomized controlled trials have evaluated filter efficacy in several situations. In the PREPIC trial, 400 patients with proximal DVT were randomly assigned to either standard anticoagulation alone or anticoagulation plus insertion of a Vena Tech, Greenfield, Bird's Nest, or Cardial IVC filter.[123] During the first 12 days after randomization, significantly fewer patients in the IVC filter group suffered PE (1% vs. 5%). However, after a 2-year follow-up period, there were no significant differences in survival or symptomatic PE between the two groups, and a significantly higher rate of recurrent DVT was observed among patients who had received an IVC filter (21% vs. 12%).[124]

Patients with concomitant PE and DVT clearly represent a higher-risk population with HR for death about 2.05 times higher than those with PE alone.[85] The PREPIC-2 trial sought to determine the role of retrievable IVC filters in this patient population.[125] Patients with acute PE and deep or superficial vein thrombosis were included if they had one of the following risk factors: age >75 years, chronic heart failure, chronic respiratory insufficiency, active cancer, RV dysfunction or myocardial injury, recent stroke with leg paralysis, or bilateral deep vein or iliocaval thrombosis. The majority of patients were included based on age or comorbidity rather than the higher-risk groups of RV dysfunction or more proximal DVT. The deployment of a retrievable IVC filter did not reduce the risk of recurrent PE when compared with anticoagulation alone in this study. The rationale for considering use of IVC filters in those with intermediate-risk PE and concomitant DVT (especially those with more proximal DVT) remains unanswered by the PREPIC-2 study.

Placement of an IVC filter is not a benign procedure and carries several possible risks including potential DVT formation, filter migration, filter tilt, filter thrombosis, and the possibility of a higher incidence of lower extremity thrombotic events and postthrombotic syndrome.[126] Furthermore, as retrievable filters replace the permanent filters, attention should be given to the removal of the filter after 3 to 6 months of therapy. Despite the use of retrievable IVC filters, Medicare claims data demonstrate that only about 14% were removed.[127]

LONG-TERM MANAGEMENT

Long-term management centers on use of a variety of anticoagulants and antiplatelet agents, as discussed below.

Direct Oral Anticoagulants

In the past decade, the direct oral anticoagulants (DOACs) have altered the treatment paradigm for acute PE. There are four drugs that have been approved for the management of venous thromboembolism in this class: apixaban, rivaroxaban, edoxaban, and dabigatran[128] (Table 73-10). The first three are Xa inhibitors, while dabigatran is a direct thrombin inhibitor. All four were individually

TABLE 73-10 Summary of the Direct Oral Anticoagulants Approved for Management of Pulmonary Embolism

	Apixaban	Rivaroxaban	Edoxaban	Dabigatran
Mechanism of Action	Factor Xa inhibitor	Factor Xa inhibitor	Factor Xa inhibitor	Direct Thrombin Inhibitor
Acute VTE Dosing	10 mg BID × 7 days then 5 mg BID	15 mg BID × 21 days then 20 mg daily	60 mg daily	150 mg BID
Parenteral Therapy Required at Initiation	No	No	5–10 days of parenteral therapy	5–10 days of parenteral therapy
Extended Therapy Dosing (after initial 6 months of therapy)	Option to reduce to 2.5 mg BID	Option to reduce to 10 mg daily	No data on dose reduction	No data on dose reduction
Study Name	*AMPLIFY*	*EINSTIEN-PE*	*HOKUSAI-VTE*	*RECOVER*
VTE Recurrence Rate	2.3% (vs. 2.7% with warfarin)	2.1% (vs. 1.8% with warfarin)	3.2% (vs. 3.5% with warfarin)	2.4% (vs. 2.1% with warfarin)
Major Bleeding Rate	0.6% (vs. 1.8% with warfarin)	1.1% (vs. 2.2% with warfarin)	8.5% (vs. 10.3% with warfarin)	1.6% (vs. 1.9% with warfarin)
Renal Considerations	Avoid if CrCl <15 mL/min	Avoid if CrCl <30 mL/min	Avoid if CrCl <15 mL/min	Avoid if CrCl <30 mL/min
Special Consideration		Must be taken with food		Avoid if dyspepsia/GI symptoms present

compared to warfarin in efficacy for treatment of VTE and were all noninferior; in those same trials, the DOACs were all associated with less relevant bleeding than warfarin.[129–134] The DOACs do not require monitoring and all now have widely available reversal agents: andexanet alfa for the Xa inhibitors and idarucizumab for dabigatran.[135,136]

Edoxaban and dabigatran require parenteral lead-in with at least 5 to 10 days of either heparin drip or LMWH subcutaneously.[132,133] Apixaban and rivaroxaban do not require parenteral lead-in but do require dose escalation during the initial treatment period.[129,131] In patients with low sPESI scores and no contraindication to early discharge, the ease of use for both apixaban and rivaroxaban, as well as the excellent associated outcomes, have led to more patients being discharged early from the emergency department.

Apixaban and rivaroxaban have been used successfully for extended therapy after the first 6 months of treatment in patients with PE. With either drug, there is an option for reducing the dose after the first 6 months of therapy. Extended thromboprophylaxis with apixaban 2.5 mg twice daily was evaluated in the AMPLIFY-EXT trial; compared to placebo, treatment with apixaban 2.5 mg resulted in significantly fewer recurrent venous thromboemboli (1.7% vs. 8.8%, a difference of 7.2 percentage points; 95% CI, 5.0–9.3) with no significant increase in bleeding (0.5% in the placebo group; 0.2% in the apixaban group).[137] Compared to extended treatment with full-dose rivaroxaban 20 mg or aspirin 81 mg, there was less recurrent VTE among those on rivaroxaban (1.5% with 20 mg of rivaroxaban and 1.2% with 10 mg of rivaroxaban) compared with 4.4% receiving aspirin alone. The risk of major bleeding was similar among all three groups.[138]

■ Warfarin

Oral anticoagulation using warfarin, a vitamin K antagonist, has historically been used for long-term treatment of VTE because of its proven efficacy, but it has largely been replaced by the DOACs in the past decade. Still, there are many patients for whom warfarin is used including those with antiphospholipid antibodies, recurrent thrombosis, and mechanical valves and those in whom the cost of the DOACs precludes their use. Warfarin has a broader anticoagulation effect due to inhibition of gamma carboxylation activation of coagulation factors II, VII, IX, and X as well as proteins C and S. The drug is usually started soon after the initiation of heparin therapy. Use of warfarin without heparin is strongly discouraged as it generally takes 3 to 5 days of warfarin administration to achieve full therapeutic efficacy. In patients with protein C deficiency, skin necrosis or paradoxical thrombosis may occur in the absence of concurrent heparin therapy.

Warfarin has a narrow therapeutic index, and patients are generally monitored closely by measuring the prothrombin time corrected to the reagent being used (the International Normalized Ratio or INR). To maximize efficacy while minimizing side effects, an INR range between 2 and 3 is recommended for most patients. Individuals metabolize warfarin differently, and age, genetic variations in CYP2C9 alleles, nutritional factors, and concomitant medications can affect anticoagulant levels significantly. Multiple mechanisms of drug interaction are possible, including alterations of absorption (cholestyramine), induction of hepatic CYP450 (barbiturates, carbamazepine), inhibition of CYP3A4 (amiodarone), inhibition of CYP2C9 (metronidazole, clotrimazole), and displacement of protein-bound warfarin (phenytoin).[139]

To minimize the potential for subtherapeutic anticoagulation, it is generally recommended that patients should receive at least 5 days of combined heparin and warfarin therapy, including at least 2 days in which the INR is in a therapeutic range prior to stopping heparin. The safety and effectiveness of both short- and long-term anticoagulation can be optimized by a systematic, evidence-based approach to therapy, often in the context of a dedicated anticoagulation management service.[140] In carefully selected patients, self-management of warfarin therapy using INR measurement with "point of care" devices is an option.[121]

■ Heparin

LMWH and subcutaneous UFH continue to have a role in the management of select patients after PE such as those who cannot take oral medications, pregnant women, those with need for frequent procedures who benefit from the short half-life, and certain patients with cancer-associated VTE. Compared with vitamin K antagonists, LMWH has similar rates of VTE recurrence (OR, 0.83; 95% CI, 0.60–1.15; $p = 0.27$) but less risk for major bleeding (OR, 0.51; 95% CI, 0.32–0.80; $p = 0.004$).[141] Enoxaparin is the most prescribed LMWH in the United States and can be given either 1 mg/kg twice per day or 1.5 mg/kg daily. In a large, retrospective propensity analysis of the RIETE registry, patients on enoxaparin once daily had fewer major bleeds (HR, 0.16; 95% CI, 0.04–0.68) and also fewer deaths at 30 days (HR, 0.19; 95% CI, 0.07–0.54) compared with those on enoxaparin twice daily.[142] Aside from risk of bleeding, prolonged use of subcutaneous UFH or, to a lesser extent, LMWH, is associated with increased risk of osteoporosis.[143]

■ Aspirin

The role of aspirin in the long-term management of patients with VTE remains incompletely defined. In the WARFASA (Warfarin and Aspirin) trial, aspirin reduced the risk of thromboembolic recurrence by 40% when given to patients with unprovoked VTE following discontinuation of anticoagulant therapy.[144] In the ASPIRE (Aspirin to Prevent Recurrent Venous Thromboembolism) trial, however, aspirin compared with placebo did not significantly reduce the rate of recurrence of VTE but resulted in a significant reduction in the rate of major vascular events, with improved net clinical benefit.[145] The use of aspirin has further been obfuscated by recent shift away from primary prophylaxis for cardiovascular events due to excessive risk for bleeding.[146] Ultimately, we recommend that patients with unprovoked PE but low risk for major bleeding complications remain on indefinite anticoagulation; if the patient declines, we would consider using aspirin 81 mg in those patients without a contraindication.

FOLLOW-UP AFTER ACUTE PE

The most common long-term sequelae of an acute PE are recurrent embolism and incomplete resolution of clot. More than 50% of patients develop or have worsening dyspnea after PE.[50] Patient symptoms may vary in degree, ranging from mild dyspnea due to dead space ventilation, to severe functional limitation as a result of chronic thromboembolic pulmonary hypertension (CTEPH). Therefore, the follow-up visit after the initial 3 months of anticoagulation for PE provides an opportunity to assess the risks and benefits of extended anticoagulation and to evaluate the etiology of dyspnea for those patients who have not yet returned to their pre-PE baseline.

■ Duration of Therapy

Over the past decade, data have emerged that have significantly changed recommendations regarding duration of anticoagulation after VTE. Central to this change has been awareness that VTE often represents a recurrent disease and that the risk for recurrence is based on the initiating factors, persistence or resolution of those factors, and anatomic consequences of the initial event.

Patients with VTE associated with a transient risk factor appear to be at a low risk of recurrence. Patients who experience postoperative VTE are at especially low risk for recurrence. Three months of anticoagulation appears to be adequate in this group, assuming

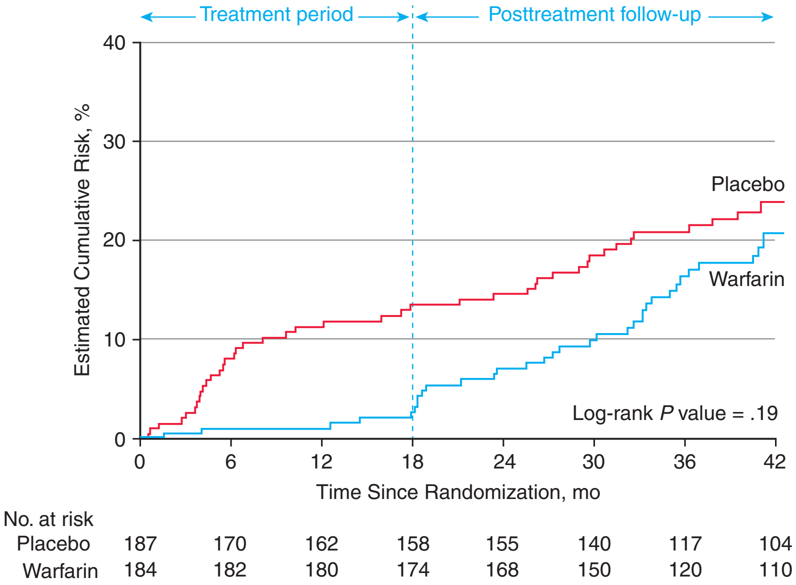


Figure 73-14 PADIS-PE Study demonstrates high long-term risk for recurrent VTE after unprovoked initial VTE if anticoagulation stopped.

The unadjusted hazard ratios for warfarin-placebo were 0.23 (95% CI, 0.09-0.55) during the treatment period and 0.74 (95% CI, 0.47-1.17) for the entire study period. The y axis that is shown in blue indicates the range of estimated cumulative risk from 0% to 10%.

the risk factor has resolved. Patients with idiopathic (unprovoked) VTE have a substantially higher rate of recurrence, corresponding to an annualized event rate of 7.9% per patient-year.[147] For these patients, anticoagulation may simply delay subsequent recurrent thromboembolic events, and ongoing risk factors may be present that have yet to be identified. In the PADIS-PE trial of extended anticoagulation with warfarin in patients with unprovoked PE, prolonged anticoagulation to 24 months was associated with a lower rate of VTE recurrence compared with 6 months of anticoagulation; this effect was lost after anticoagulation was stopped at 24 months with no difference in the rate of VTE recurrence between the two groups at 3.5 years (Fig. 73-14).[148] Therefore, it is recommended that strong consideration be given to extended therapy in those patients with unprovoked VTE and a low/moderate risk of bleeding complications.[129]

While decisions regarding extended anticoagulation can often be made based on the provoked or unprovoked nature of the VTE, there are several validated tools that are available for granular quantification of VTE recurrence risk should anticoagulation be discontinued (Table 73-11). The HERDOO2 rule identifies adult women

TABLE 73-11 Risk Assessment Tools for Unprovoked VTE Recurrence After Cessation of Anticoagulation

Risk Assessment Tool	Factors	Points	Total Score	Annual Risk of Recurrence
HERDOO2	Post-thrombotic signs	1	0–4	Men: 8.4–13.7%
	D-dimer level 250 μg/L	1		Women with score <2: 1.6–3.0%
	BMI 30 kg/m^2	1		Women with score 2: 7.4–14.1%
	Age ≥65 years	1		
DASH	D-dimer level abnormal at 1 month post-anticoagulation discontinuation	2	−2 to 4	Score 1: 0.5–5.3%
				Score 2: 6.4–6.7%
	Age 50 years	1		Score 3: 6.8–12.3%
	Male	1		
	Hormone use at VTE onset	−2		
Vienna Prediction Model	Sex	NA	0–350	2–15%, depending on nomogram-based score
	Location of VTE	NA		
	D-dimer level elevated at 3 weeks post-anticoagulation discontinuation	NA		
Ottawa	Female sex	1	−3 to 3	Score <0: 2.4–4.5%[a]
	Prior VTE	1		Score 0: 4.5–8.8%[a]
	Primary lung cancer	1		Score ≥1: 15.9–19%[a]
	Primary breast cancer	−1		
	Tumor stage (TNM 1)	−2		

[a] *Risk of recurrent VTE at 3–6 months.*

with prior unprovoked VTE who have an annual risk of VTE of less than 3% and can, therefore, safely discontinue anticoagulant therapy.[149] According to the HERDOO2 rule, women with 0 or 1 of the following risk factors can safely discontinue anticoagulation: postthrombotic signs (e.g., hyperpigmentation, edema, redness in either leg), elevated D-dimer on anticoagulation, BMI of 30 kg/m^2 or greater, or age 65 years or greater. Similarly, the DASH prediction score identifies patients at risk for recurrent VTE based on elevated D-dimer levels 1 month post-anticoagulation discontinuation, age, sex, and hormone use at VTE onset.[150] The Vienna Prediction Model evaluates VTE risk recurrence on a spectrum based on sex, location of VTE, and elevated D-dimer 3 weeks after anticoagulant discontinuation.[151] Finally, the Ottawa score assesses risk for recurrent cancer-associated VTE and considers sex, cancer type and stage, and prior VTE.[152] The HERDOO2, DASH, and Ottawa prediction models provide discrete risk categories, whereas the Vienna prediction model gives a continuum of annualized risk, which may be a more accurate portrayal of the nuances of recurrence risk. Both the DASH and Vienna models evaluate D-dimer levels after discontinuation, but discontinuation of therapy may not be wise for some patients. The HERDOO2 model is the only tool that considers D-dimer levels in anticoagulation and does not require discontinuation of therapy.

In patients with VTE associated with an irreversible risk factor, the absolute recurrence risk depends on the underlying disease or condition.[131,132] Patients with heterozygous factor V Leiden mutation and the prothrombin G20210A mutation, although at higher recurrence risk than those without the mutations, do not appear to warrant prolonged anticoagulation while those with homozygous disease or a combined thrombophilia (e.g., heterozygous factor V Leiden combined with heterozygous prothrombin mutation) do. Patients with antiphospholipid antibody syndrome, active cancer, and deficiencies of protein S, protein C, and antithrombin III (ATIII) are at considerable risk for thromboembolic recurrence and should remain on lifelong therapy. In summary, long-term anticoagulation should be individualized based on the risk for recurrent thromboembolism and bleeding. The appropriateness of ongoing therapy should be continuously reevaluated, and the prophylaxis stopped if the benefit no longer appears to exceed the risk.

Assessment of Recovery from the Initial PE

The expectation is that, with adequate anticoagulation, patients will recover fully to their pre-PE baseline. However, the reality is that approximately 50% of patients report worsening dyspnea compared with their pre-PE baseline after 6 months of anticoagulation.[153] Additionally, some 30% to 50% of patients will have an abnormal perfusion scan after 6 months of anticoagulation.[49,50] Determining whether the dyspnea experienced by these patients is due to persistent perfusion defects requires assessment with cardiopulmonary exercise testing and echocardiography. Patients with dyspnea after at least 3 months of anticoagulation should be evaluated for thrombus resolution and a ventilation–perfusion scan should be obtained (Fig. 73-15). Screening echocardiography in all patients after PE to exclude CTEPH is very low yield and not recommended,[154] but echocardiograms should be obtained in patients with dyspnea and/or persistent perfusion defects to screen for resting pulmonary hypertension. Some centers use noninvasive cardiopulmonary exercise testing to quantify dead space ventilation and assess the stroke volume response to exercise.[155] If significant perfusion defects are seen, pulmonary angiography should be obtained to confirm the diagnosis of chronic thromboembolic disease.

Early diagnosis and treatment of CTEPH is essential for optimal patient outcomes. A number of factors pertaining to the acute PE and comorbidities have been identified and increase the risk for development of CTEPH after acute PE (Table 73-12), specifically having an unprovoked PE, hypothyroidism, a delay in PE diagnosis >2 weeks, or right ventricular dysfunction on CT angiography at the time of the acute PE.[156] Patients with recurrent PE also have higher odds for development of CTEPH (OR, 3.2; 95% CI, 1.7–5.9).[157] Patients with these risk factors merit close follow-up and screening to assess resolution of dyspnea. In patients without dyspnea who have returned to their pre-PE baseline, routine screening for CTEPH is not recommended after PE. However, the 2019

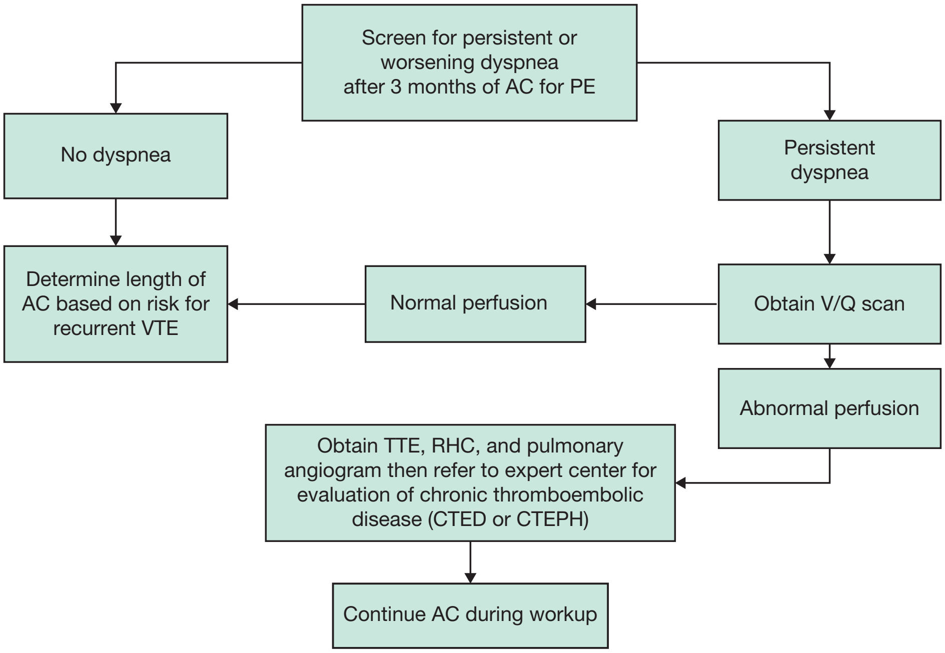

Screen for persistent or worsening dyspnea after 3 months of AC for PE
No dyspnea
Persistent dyspnea
Determine length of AC based on risk for recurrent VTE
Normal perfusion
Obtain V/Q scan
Abnormal perfusion
Obtain TTE, RHC, and pulmonary angiogram then refer to expert center for evaluation of chronic thromboembolic disease (CTED or CTEPH)
Continue AC during workup

Figure 73-15 Recommended evaluation of dyspnea post-PE. AC = anticoagulant; CTED = chronic thromboembolic disease; CTEPH = chronic thromboembolic pulmonary hypertension; PE = pulmonary embolism; RHC = right heart catheterization; TTE = transthoracic echocardiogram; V/Q = ventilation/perfusion; VTE = venous thromboembolism.

TABLE 73-12 Selected Risk Factors and Univariate Odds Ratios for CTEPH

Risk Factor	Comparator	OR (95% CI)
VA shunt	IPAH	19.49 (2.47–2520)
Splenectomy	IPAH	22.09 (2.97–2824)
Massive/submassive PE	IPAH	13.03 ($p = .004$)[a]
VTE history	IPAH	49.01 ($p < .001$)[a]
Recurrent VTE	IPAH	45.02
Thyroid replacement	IPAH	(21.00–114.73) 5.41 (2.70–12.23)
Hypothyroidism	Resolved PE	4.3 (1.4–13.0)
Prior VTE	IPAH	19.36 (11.66–33.79)
APS/lupus AC	IPAH	3.28 (1.58–7.50)
Non-blood group O	IPAH	3.12 ($p < .001$)[a]
Malignancy	IPAH	1.99 (1.01–4.26)
Unprovoked PE	Resolved PE	20.0 (2.7– >100)
RV dysfunction at diagnosis	Resolved PE	4.1 (1.4–12.0)
Symptoms >2 weeks prior to PE diagnosis	Resolved PE	7.9 (3.3–19.0)
Age >60 years	Resolved PE	2.9 (1.2–7.2)

[a] *Adjusted for age and sex.*

ESC/ERS guidelines do recommend consideration of CTEPH in PE survivors with exercise dyspnea.[7] Evaluation for CTEPH should be based on clinical suspicion due to persistent symptoms or dyspnea following at least 3 months of adequate anticoagulation therapy.

SPECIAL POPULATIONS

Several populations of patients with VTE merit special mention, including pregnant women, patients with underlying malignancy, and those with chronic thromboembolic disease.

Pregnancy

VTE is a leading cause of maternal morbidity and mortality during pregnancy but remains a diagnostic and therapeutic challenge.[158] The mechanical compression of the pelvic veins by the gravid uterus and the hormonal milieu of pregnancy and the puerperium period increase the risk for VTE above baseline. However, dyspnea and lower extremity edema are common in pregnancy, and the typical screening algorithms dependent on use of the D-dimer test are not useful in pregnancy, a condition associated with increased baseline D-dimer levels. Several tools have been developed to limit the need for imaging and therefore avoid radiation exposure to the mother and developing fetus. The "LEFt Rule" uses three variables (symptoms in the left leg [L], calf circumference difference ≥ 2 cm [E], and first-trimester presentation [Ft]), with excellent negative predictive value with none of the variables present and increasing risk with the number of variables present.[22,159] Additionally, the YEARS criteria (signs or symptoms of DVT, hemoptysis, PE as most likely diagnosis) paired with a higher D-dimer threshold have been used to limit the need for imaging to diagnose or exclude VTE in pregnancy[160] (Fig. 73-6). In pregnant women, the diagnosis of DVT by ultrasonography should be leveraged to establish the presence of PE without imaging the chest. In those with normal compression ultrasound, both (1) presence of no YEARS criteria and (2) one to three criteria with D-dimer <500 ng/mL effectively ruled out PE. Those with one to three YEARS criteria and D-dimer <500 ng/mL require imaging to exclude PE.

The optimal imaging to diagnose PE during pregnancy remains in flux.[161,162] Most would prefer $\dot{V}/\dot{Q}$ scanning if the woman has a normal chest x-ray. The radioactive albumin is excreted in the urine, and a Foley catheter should be placed to immediately drain the bladder and limit fetal radiation exposure. If the CXR is abnormal or $\dot{V}/\dot{Q}$ scanning is not immediately available, the recommendation should be to shield the gravid uterus with lead and obtain a CT pulmonary angiogram. This does still expose the fetus to internal scatter radiation but is most likely to yield a diagnostic result and not require further radiation exposure.

Due to the teratogenic potential of warfarin and the potential for DOACs to cross the placenta, as well as lack of safety data, UFH or LMWH should be used in pregnant women who develop VTE during pregnancy. Most would recommend LMWH earlier in pregnancy with consideration to switching to UFH closer to the due date due to short half-life. The ideal anti-Xa target for treatment in pregnancy has not been thoroughly investigated.[163] Since the risk of VTE may be highest in the postpartum period, anticoagulation should be continued for at least 3 to 6 months, including a minimum of 4 to 6 weeks after delivery.

Malignancy-associated VTE

Patients with cancer represent a high-risk population for both recurrent thrombosis and bleeding complications. The malignant tumors release tissue factor that, in turn, initiates the clotting cascade. The release of inflammatory cytokines in response to the malignancy, as well as the inflammatory response to chemotherapy, further promotes the hypercoagulable state.[164] Until recently, LMWH was the preferred anticoagulant due to fewer recurrent thromboembolic events and bleeding complications compared with warfarin in the CLOT trial.[165] Recent randomized clinical trial data now demonstrate similar reduction in VTE recurrence with apixaban and edoxaban compared with LMWH.[166,167] Pilot data exist supporting the safety of rivaroxaban as well.[168] The rates of bleeding in these were similar between apixaban and LMWH but slightly higher with edoxaban and rivaroxaban, driven by increased major bleeding in DOAC-treated patients with gastrointestinal malignancy.

Chronic Thromboembolism

Anatomic resolution of PE is rarely complete, and these persistent perfusion defects can lead to dyspnea by either development of pulmonary hypertension or significant dead space ventilation. In a few, the residual thromboembolic burden is sufficiently extensive to cause resting pulmonary hypertension, a condition termed *chronic thromboembolic pulmonary hypertension (CTEPH)*. Estimates of the incidence of CTEPH in patients actively surveyed after acute PE range from 0.5% to 8.8% following an initial episode of acute PE, to 13.4% following recurrent episodes.[169] Approximately 25% of patients who develop CTEPH have no documented history of acute DVT or PE, and this feature greatly impedes the diagnosis. Anticardiolipin antibodies or a lupus anticoagulant have been detected in approximately 10% to 20% of patients and elevated factor VIII levels detected in 40%.[170] No other defined thrombophilic or fibrinolytic abnormality has been encountered in this population. Age greater than 70, systolic pulmonary artery pressure (PASP) greater than 50 mm Hg at the time of diagnosis of acute embolism, systolic PASP greater than 50 mm Hg at the time of hospital discharge following acute PE, previous PE, prior splenectomy, ventriculo-atrial shunts, the presence of antiphospholipid antibodies, and a larger degree of pulmonary vascular obstruction at the time of acute PE have been identified as risk factors for CTEPH.[171]

The optimal management of CTEPH is surgery (pulmonary thromboendarterectomy or PTE), which involves the dissection of endothelialized thrombi under cardiopulmonary bypass and

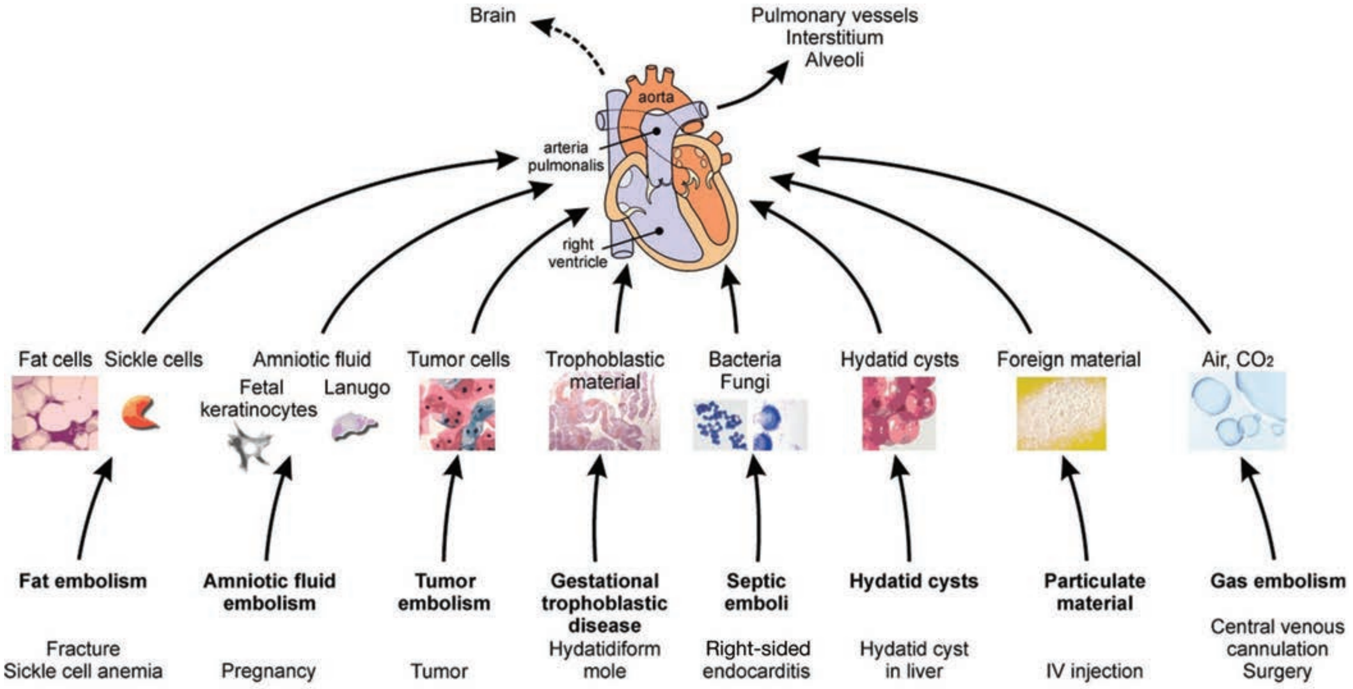

Brain
Pulmonary vessels
Interstitium
Alveoli
aorta
arteria pulmonalis
right ventricle
Fat cells
Sickle cells
Amniotic fluid
Fetal keratinocytes
Lanugo
Tumor cells
Trophoblastic material
Bacteria
Fungi
Hydatid cysts
Foreign material
Air, CO2
Fat embolism
Amniotic fluid embolism
Tumor embolism
Gestational trophoblastic disease
Septic emboli
Hydatid cysts
Particulate material
Gas embolism
Fracture
Sickle cell anemia
Pregnancy
Tumor
Hydatidiform mole
Right-sided endocarditis
Hydatid cyst in liver
IV injection
Central venous cannulation
Surgery

Figure 73-16 Nonthrombotic pulmonary embolism (NTPE) includes fat emboli, amniotic fluid, tumor emboli, septic emboli (bacteria, fungi), foreign material (such as talc or other byproducts of IV drug abuse), or gas. *(Reproduced with permission from Jorens PG, Van Marck E, Snoeckx A, et al. Nonthrombotic pulmonary embolism. Eur Respir J. 2009;34(2):452–474.)*

deep hypothermia.[172] For the majority of patients, successful PTE is considered curative. However, the hemodynamic outcome is incomplete in approximately 20% of patients. When PTE is not an option due to the distal nature of the disease or the comorbidities convey a prohibitive risk, pulmonary arterial hypertension–targeted pharmacotherapy with riogicuat[173] and balloon pulmonary angioplasty represent potential therapeutic alternatives.[174] Regardless of management, therapeutic anticoagulation should be continued indefinitely in all patients with CTEPH.

OTHER VARIETIES OF EMBOLIC DISEASE

Although the majority of cases of PE are the result of thrombus migration (hence *thrombo* embolism), other materials may occasionally obstruct the pulmonary vascular bed (Fig. 73-16).[175] Because the lung receives all of the blood flow returned from the venous system, the pulmonary vascular bed serves as a "sieve" for all particulate substances entering the venous blood and is the first vascular bed to be exposed to any toxic substance injected intravenously. As a result of its strategic position, the pulmonary vascular bed is, therefore, exposed to a wide variety of potentially obstructing and injurious agents.

■ Venous Air Embolism

An increasingly common form of nonthrombotic embolism is venous air embolism. The increasing frequency of the problem reflects the wide variety of invasive surgical and medical procedures now available, the broad use of indwelling central venous catheters, the use of positive-pressure ventilation with high levels of positive end-expiratory pressure, and the frequency of thoracic and other forms of trauma.[176] The simple inadvertent transection or loss of closure of a large-bore intravenous catheter, particularly in the jugular or subclavian vein, can result in ingress of substantial quantities of air. Air bubbles enter the pulmonary vascular bed and, from there, can enter the arterial system and be diffusely distributed throughout the body by way of either an intracardiac shunt (atrial septal defect, patent foramen ovale) or, more likely, through microvascular pulmonary shunts.

Physiologic consequences are related to the volume of air entrainment and rate of accumulation. An abrupt rise in pulmonary artery pressure and noncardiogenic pulmonary edema may develop, lung compliance falls, and hypoxemia ensues. The symptoms of venous air embolism are variable and nonspecific, and they may include alterations in sensorium, chest pain, dyspnea, or a sense of impending doom.[177] These and other consequences appear to be due to two phenomena: actual lodgment of the bubbles in capillary beds that interfere with nutrient supply to the affected organs, and the formation of platelet–fibrin aggregates, creating diffuse microthrombi. Thrombocytopenia may be seen as a consequence of this latter event. The most serious consequences result from cerebral or coronary artery air embolism, with the severity of the consequences depending upon the rate and volume of air gaining access to the circulation.

The best approaches to air embolism are prevention and early detection. Treatment consists of measures designed to restore flow and promote reabsorption of the intravascular air.[178] Measures designed to restore flow include patient positioning (Trendelenburg position, with the left side down), removal of air through central venous catheters or direct needle aspiration, and closed chest cardiac massage. Measures designed to increase absorption include the use of 100% oxygen and hyperbaric oxygen therapy. Using such aggressive measures, mortality from venous air embolism has been dramatically reduced.

■ Fat Embolism

Another reasonably frequent and dramatic form of nonthrombotic embolism is fat embolism.[179] A rather characteristic syndrome follows entry of neutral fat into the vascular system, consisting of the onset of dyspnea, hypoxemia, petechiae, and mental confusion. Seizures and focal neurologic deficits have been described. There is a variable lag time of 24 to 72 h in the onset of the syndrome following the inciting event; rarely, cases occur within 12 h or as late as 2 weeks after the event.

By far, the most common inciting event is traumatic fracture of long bones, with incidence rising with the number of fractures and with fractures involving the femur.[180] However, orthopedic procedures and trauma to other fat-laden tissues (e.g., fatty liver) occasionally can be followed by the same syndrome. Although considerably less common, fat embolism syndrome has been reported following both liposuction and lipoinjection procedures.

The basis for the variability in the incidence and severity of the syndrome after apparently comparable injuries has not been well defined; neither has the reason for the delay in clinical presentation been explained. The pathophysiologic consequences appear to derive from two events: (1) actual vascular obstruction by neutral particles of fat; and (2) the injurious effects of free fatty acids released by the action of lipases on the neutral fat. The latter effect is probably the more important, causing diffuse vasculitis with leakage from cerebral, pulmonary, and other vascular beds. The time necessary to produce toxic intermediaries may explain the delay from the inciting event to clinical presentation.

The diagnosis of fat embolism syndrome is a clinical one, suggested by the onset of dyspnea, neurologic abnormalities, petechiae, and fever in the proper clinical context. Petechiae, typically distributed over the head, neck, anterior chest, and axillae, are present in only 20% to 50% of cases and are often evanescent. Therefore, their absence should not preclude consideration of the disease. No laboratory test is diagnostic of the syndrome. Fat can be demonstrated in the serum of a majority of patients with long bone fractures, so this finding is not specific for fat embolism syndrome. Similarly, the finding of lipid-laden macrophages in bronchoalveolar lavage fluid is common in patients with traumatic injuries irrespective of the presence of fat embolism syndrome.

Although a variety of treatments have been suggested (e.g., intravenous ethanol, albumin, dextran, heparin), none has proved effective. The role of corticosteroid therapy to prevent the onset of fat embolism syndrome after an inciting event remains controversial.[181] Supportive treatment, including mechanical ventilatory support when necessary, is the primary approach, and survival is now the rule with meticulous support.

Amniotic Fluid Embolism

Amniotic fluid embolism is a rare but unpredictable and catastrophic complication of pregnancy. It represents a leading cause of maternal mortality and is reported to occur in approximately 2.0 per 100,000 deliveries.[182] This disorder occurs during or after delivery when amniotic fluid gains access to uterine venous channels and, therefore, to the pulmonary and general circulations. The diagnosis is confirmed when four criteria are present (Table 73-13): (1) sudden-onset cardiopulmonary arrest or hypotension with respiratory compromise; (2) disseminated intravascular coagulation (DIC); (3) clinical onset during labor or within 30 min of placental delivery; (4) absence of fevers.[183] Exclusion of PE as an alternative diagnosis is important. Cesarean delivery, instrumented vaginal delivery (use of forceps), placental abnormalities (previa, abruption, accreta), and preeclampsia or eclampsia have been associated with increased risk of amniotic fluid embolism.[184]

TABLE 73-13 Diagnostic Criteria for Amniotic Fluid Embolism

- Sudden onset of cardiopulmonary arrest, **or** both
  Hypotension (systolic blood pressure <90 mm Hg) **and**
  Respiratory compromise (dyspnea, cyanosis, or hypoxia [SPO_2 <90%])
- DIC following initial symptoms[a]
- Onset during labor or within 30 minutes of delivery
- No fever (>38.0°C) during labor

All four criteria must be met to confirm diagnosis.

[a] A score of greater than 3 using the following three variables is compatible with disseminated intravascular coagulopathy:
Platelet count >100,000/mL = 0; Platelet count <100,000/mL = 2
PTT increase <25% = 0, 25–50% = 1, >50% = 2
Fibrinogen level >200 mg/L = 0; <200 mg/L = 1

Amniotic fluid contains particulate materials that can cause pulmonary vascular obstruction, but the major pathogenic mechanism of the syndrome remains uncertain. Amniotic fluid has thromboplastic activity that leads to extensive fibrin deposition in the lung vasculature and, occasionally, other organs. As a consequence of fibrin deposition, severe consumptive coagulopathy develops, including marked hypofibrinogenemia and thrombocytopenia. Following the acute event, an enhanced fibrinolytic state often occurs.

Although various forms of therapy have been suggested (e.g., antifibrinolytic agents such as aminocaproic acid, cryoprecipitate), the best approach is supportive. This supportive care includes vasopressors, intubation and mechanical ventilation, and consideration for ECMO. Despite these efforts, maternal mortality in amniotic fluid embolism remains high with the best estimates of mortality at 20%.[185]

Septic Embolism

Septic embolism is increasing in frequency owing to widespread IV drug abuse and the expanding use of indwelling intravenous devices.[186] Previously, septic embolism was almost exclusively a complication of septic pelvic thrombophlebitis due to either septic abortion or postpuerperal uterine infection.[187] However, almost any venous structure can be involved, either as a focus of primary infection or from intravascular or contiguous spread: septic cavernous sinus thrombosis resulting from meningitis, sinusitis, or facial cellulitis; septic portal venous thrombosis resulting from diverticulitis or liver abscess; or septic tonsillar or internal jugular venous thrombosis (Lemierre syndrome) resulting from oropharyngeal infection with *Fusobacterium* species. Increasingly common causes are those related to IV drug use and to infected intravascular catheters.[188]

Microscopically, septic phlebitis consists of purulent material admixed with fibrin thrombus. Embolization of this material can result in obstruction of small pulmonary vessels, but the major consequence is pulmonary infection. Characteristically, the chest x-ray or chest CT demonstrates scattered wedge-shaped pulmonary infiltrates that undergo cavitation. An increasing number of such infiltrates develops over periods of hours to a few days. Symptoms and signs include fever, dyspnea, cough, pleuritic chest pain, and hemoptysis. Initial treatment consists of appropriate antimicrobial drugs. If an indwelling catheter is the source of the infection, it should be removed. If there is not a prompt response to this regimen, surgical isolation of the septic vein, if present, should be considered. The role of systemic anticoagulation remains uncertain. Endocarditis may complicate septic phlebitis or mimic it.

Tumor Embolism

Involvement of the pulmonary vascular bed by tumor cells is not unusual given the frequency with which circulating tumor cells can be identified in patients with a wide range of malignancies and the frequency with which tumor emboli are discovered as an incidental finding at autopsy.[189] Tumor embolism becomes clinically apparent, however, in only a minority of patients with malignancy.

Microvascular tumor embolism is associated with a wide range of malignancies, the most common sites of origin being the mucin-producing adenocarcinomas of the breast, lung, prostate, stomach, and liver. Renal cell carcinoma may invade the renal vein with serpiginous spread into the inferior vena cava and has been associated with tumor emboli. Tumor embolism of large fragments occurs rarely and may mimic acute thromboembolic disease. In this setting, survival following tumor embolectomy has been reported.

The clinical presentation of microvascular tumor embolism is typically subacute and involves progressive dyspnea, tachycardia, and tachypnea. Jugular venous distention, a prominent P2, tricuspid regurgitation, or a right-sided S3 may be present on physical examination if the extent of pulmonary vascular obstruction is sufficient to cause pulmonary hypertension.

The development of pulmonary hypertension is a common accompaniment of symptomatic, microvascular tumor embolism and remains a major cause of mortality. Pulmonary hypertension appears to result from both an obliteration of the pulmonary vascular bed by an admixture of tumor cells and thrombus as well as the development of medial hypertrophy, intimal fibrosis, and fibrinoid necrosis encountered in other etiologies of pulmonary hypertension.

Hypoxemia and a compensated respiratory alkalosis are commonly present. The chest radiograph is most often normal, but focal or diffuse infiltrates, which may be fleeting, have been described. $\dot{V}/\dot{Q}$ scanning most commonly demonstrates a mottled appearance or peripheral, subsegmental defects; segmental or larger defects, indistinguishable from those associated with thromboembolic embolism, may occur in those rare instances of large-vessel involvement. CT may demonstrate peripheral, wedge-shaped defects consistent with infarcts; a pattern of multifocal dilatation and beading of the peripheral pulmonary arteries has been described.[177]

Pulmonary angiographic findings may include delayed vascular filling, pruning, and tortuosity, similar to that seen in other forms of small-vessel pulmonary hypertension. The angiographic findings in large-fragment tumor embolism may be indistinguishable from those seen in acute PE. The optimal diagnostic approach has not been agreed upon. Open lung biopsy, bronchoalveolar lavage, and aspiration of blood from a wedged pulmonary artery catheter may have roles in the approach, but aggressiveness of the diagnostic approach should be individualized and based on the prognosis of the underlying malignancy as well as the patient's preferences.

The differential diagnosis of tumor embolism includes thrombotic embolism, parenchymal metastasis, lymphangitic carcinomatosis, malignant pericardial effusion, and chemotherapy-related lung toxicity. The premortem diagnosis is often one of exclusion. Parenchymal metastasis, lymphangitic carcinomatosis, and chemotherapy-related lung toxicity can be differentiated from tumor embolism by findings on high-resolution CT. Differentiation of tumor embolism from thrombotic embolism may be somewhat more problematic, especially if there is large-vessel involvement.

■ Other Emboli

Because of its sieve function, the pulmonary vasculature may also be the target of a wide variety of other materials that enter the venous system.[190] Trophoblastic tissue can escape the uterus and lodge in the pulmonary circulation during pregnancy. After head trauma, brain tissue has been found in the lungs; the same is true of liver cells following abdominal trauma and bone marrow after cardiopulmonary resuscitation. Pulmonary cement embolism is a rare but known complication of vertebroplasty.[191]

Noninfectious vasculitic-thrombotic complications occur in association with the illicit intravenous use of crushed tablets intended for oral administration. Medications associated with pulmonary complications include methylphenidate hydrochloride, oral opiates (pentazocine, meperidine, methadone), and antihistamines. Particulate and irritant drug carriers (e.g., talc, cellulose) and occasionally the drugs themselves may cause vascular inflammation and secondary thrombosis. The clinical presentation is diverse and includes diffuse micronodular opacities, lower lobe emphysema, diffuse interstitial fibrosis, and progressive massive fibrosis.[192] Repetitive insults may lead to severe and irreversible pulmonary hypertension. In many IV drug users, perfusion scans demonstrate segmental or smaller defects. The diagnosis is often suggested by the clinical history. Radiographic findings include small, diffuse, well-defined nodular densities. These nodules may progress, and massive fibrosis may ensue. Lower lobe panlobular emphysematous changes mimicking α1-antitrypsin deficiency also may be present. Diagnostic confirmation often requires lung biopsy, either open or transbronchial; many times, confirmation is not necessary if the imaging is consistent with talcosis and the patient admits to injection of crushed pills. Fundoscopic examination, revealing birefringent material in retinal vessels, is a noninvasive means of establishing the diagnosis. The prognosis is poor, with progressive pulmonary disease being the rule.[193]

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CHAPTER 74

Pulmonary Vasculitis

Rodrigo Cartin-Ceba
Ulrich Specks

INTRODUCTION

Pulmonary vasculitis is usually a manifestation of a systemic disorder leading to inflammation of vessels of different sizes by a variety of immunologic mechanisms. Vasculitis can be separated into primary and secondary vasculitis. The primary systemic vasculitides are a heterogeneous group of syndromes of unknown etiology, which share a clinical response to immunosuppressive therapy (Table 74-1). Their wide spectrum of frequently overlapping clinical manifestations is defined by the size and location of the affected vessels as well as the nature of the inflammatory infiltrate. Secondary vasculitis may pose significant management problems in the context of a well-defined underlying disorder, such as diffuse alveolar hemorrhage caused by systemic lupus erythematosus. Alternatively, secondary vasculitis may be an incidental histopathologic finding, for instance, in the context of an infection or necrotizing sarcoid granulomatosis.

TABLE 74-1 Chapel Hill Consensus Nomenclature of the Primary Systemic Vasculitides

Name	Respiratory Manifestations	Presence of ANCA
Large vessel vasculitis		
Giant-cell arteritis	Rare	No
Takayasu arteritis	Frequent	No
Medium-sized vessel vasculitis		
Polyarteritis nodosa	Rare	No
Kawasaki disease	No	No
Small vessel vasculitis		
ANCA-associated vasculitis		
Granulomatosis with polyangiitis (Wegener)	Frequent	>80%
Microscopic polyangiitis	Frequent	>80%
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) syndrome	Frequent	>50%
Immune complex small vessel vasculitis		
Anti-GBM disease	Frequent	No
IgA vasculitis	Rare	IgA-ANCA reported
Cryoglobulinemic vasculitis	Rare	No
Hypocomplementemic urticarial vasculitis	Frequent	No
Variable vessel vasculitis	Rare	No
Behçet disease		

CLASSIFICATION AND DEFINITIONS

Classification schemes and definitions of the various forms of vasculitis have evolved over the past decades. Historically, the classification of the vasculitides has been based on the size of the most prominently affected vessels. The primary purpose of classification and nomenclature is to standardize communication between clinicians and investigators and to facilitate more uniform treatment approaches. Ideally, the classification system reflects the current understanding of pathogenesis. The first international consensus conference on the nomenclature of systemic vasculitides held in 1992 in Chapel Hill aimed to reconcile definitions and classification schemes used by European and American investigators. The resulting nomenclature and definitions were based mainly on histopathologic criteria, particularly the size of the vessels involved, but allowed for radiographic and clinical surrogates to fulfill the definitions. These definitions, nomenclature, and classification found wide acceptance. The terminology was revised and updated at the second 2012 Chapel Hill international consensus conference so that it reflects novel insights into the pathogenesis of various vasculitides while avoiding the use of eponyms as much as possible.[1] In this chapter, the specific definition of each form of vasculitis is discussed in detail as part of the description of the clinical manifestations and differential diagnosis of each entity.

The 2012 Chapel Hill nomenclature is clinically very useful to pulmonologists as it reflects the clinical and histopathologic pulmonary features and facilitates the therapeutic approach to individual patients. The three small vessel vasculitides that present most often with respiratory symptoms are granulomatosis with polyangiitis (GPA; formerly Wegener granulomatosis), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA; formerly Churg-Strauss syndrome). Most patients with these syndromes have antineutrophil cytoplasmic autoantibodies (ANCA) detectable in the serum at the time of initial presentation.[2] Consequently, this group of small vessel vasculitides is referred to *in cumulo* as "ANCA-associated vasculitis."

In patients with vasculitis, two types of ANCA are of clinical significance. In more than 80% of patients with GPA (Fig. 74-1), ANCA occurs and is associated with a cytoplasmic immunofluorescence pattern (C-ANCA) on ethanol-fixed neutrophils that react with the neutrophil granule enzyme proteinase 3 (PR3-ANCA). In

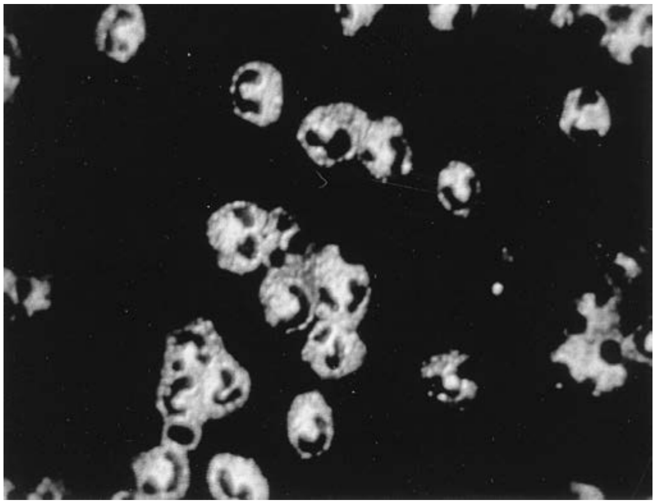

Figure 74-1 Cytoplasmic indirect immunofluorescence (C-ANCA) pattern in ethanol-fixed neutrophils caused by ANCA reacting with PR3.

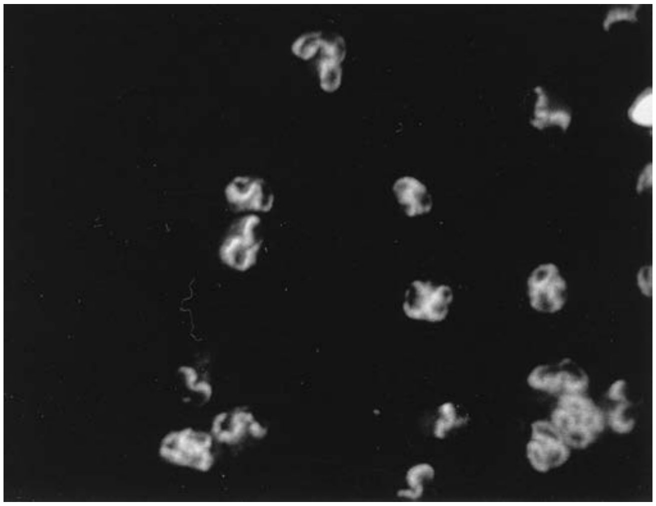

Figure 74-2 Perinuclear indirect immunofluorescence (P-ANCA) pattern in ethanol-fixed neutrophils caused by ANCA reacting with MPO.

contrast, ANCA that causes a perinuclear immunofluorescence pattern (P-ANCA) on ethanol-fixed neutrophils and reacts with myeloperoxidase (MPO-ANCA) occurs in fewer than 10% of patients with GPA but in the majority of patients with MPA (Fig. 74-2). MPO-ANCA are also the predominant type of ANCA encountered in patients with EGPA, in which PR3-ANCA is the exception. Despite these circulating autoantibodies, hardly any immunoglobulin deposits can be detected in the tissue lesions of ANCA-associated vasculitis, and they are consequently called “pauci-immune” lesions.

EPIDEMIOLOGY

The primary systemic vasculitides are rare, and few epidemiologic studies have been conducted, mostly in ethnically homogenous populations.[3] Giant-cell arteritis is the most frequent form of systemic vasculitis with an annual incidence of 13 per million adults (40 per million over the age of 60). It appears to be increasing in frequency and becoming cyclical over time. The latter observation has been interpreted as possibly suggesting a relationship with infections. Respiratory manifestations rarely represent significant management problems in these patients.

Various studies from different regions of the world report a fairly uniform annual incidence of one to two cases per million for Takayasu’s arteritis. Pulmonary vascular complications occur in about half of the afflicted patients. The estimated annual incidence of GPA has been rising over the decades from 0.5 to 0.7 per million during the 1970s and early 1980s to current estimates of about 10 to 12 per million. Similar increases in annual incidence have been observed for MPA and EGPA. The average frequency of MPA is similar to that of GPA; for EGPA it is estimated to be of the order of one to three per million. A recent population-based study of ANCA-associated vasculitis in Olmsted County, Minnesota from 1996 to 2015 identified an annual incidence of 3.3 per 100,000, with a prevalence of 42.1 per 100,000, which is substantially higher than the rates reported in other areas worldwide.[4] In this study, the incidence of GPA was similar to that of MPA.

The ANCA-associated vasculitides have different ethnic predilections: GPA affects predominantly whites, and northern Europeans appear more prone to develop GPA. In contrast, individuals of southern European and Mediterranean descent appear to be relatively more apt to develop MPA. GPA and MPA can affect individuals of any age. However, the incidence of GPA plateaus after age 50, whereas the likelihood of developing MPA continues to increase with age.

The annual incidence of the secondary vasculitides varies widely. The reported frequencies for rheumatoid vasculitis and vasculitis in systemic lupus erythematosus are 12.5 per million and 3.6 per million, respectively. Behçet disease has a peculiar geographic distribution along the old Silk Road, with the highest prevalence being reported from Turkey and central and far-eastern Asia, where the frequencies range from 100 to 380 per 100,000, compared with only 1 per 100,000 in western Europe.

The available population-based studies need to be interpreted with some caution because they do not distinguish between whether the observed increased incidence of systemic vasculitis is true or the result of more frequent recognition of the disease. Moreover, whether individual diagnoses are accurate and consistent is challenged by the changing definitions of the syndromes over time.

ANCA-ASSOCIATED VASCULITIS

Below we consider the ANCA-associated vasculitides, including granulomatosis with polyangiitis, microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis.

Granulomatosis with Polyangiitis: Clinical Presentation and Diagnosis

GPA is the most common form of vasculitis to involve the lung. The Chapel Hill Consensus Conference defined GPA as “necrotizing granulomatous inflammation usually involving the respiratory tract, and necrotizing vasculitis affecting predominantly small to medium-sized vessels.”[1] However, it is important to recognize that GPA is a systemic disease that can affect almost any organ (Table 74-2). The most frequently involved sites are the upper airways, lungs, and kidneys.[5] Symptoms and clinical disease manifestations are the result of necrotizing granulomatous inflammation and small vessel vasculitis that occur in variable degrees of combination.

In the 1960s the term *limited Wegener’s granulomatosis* was introduced to indicate patients with GPA who lacked renal disease. The use of this term and its implications have evolved over the last two decades. Even in the absence of renal involvement, patients may have life-threatening pulmonary or neurologic disease requiring aggressive immunosuppressive treatment. For instance, a patient who “only” has alveolar hemorrhage in the absence of glomerulonephritis should never be classified as having “limited” GPA. Consequently, today, the use of the term *limited GPA* implies that (1) the pathology is predominantly a necrotizing granulomatous inflammation, and the vasculitis seen on biopsy is of lesser clinical significance; and (2) there is no immediate threat either to the patient’s life or of irreversible damage to the affected organ. In this sense, “limited GPA” should now be avoided and replaced by *nonsevere GPA*, in contrast to “severe” GPA, which by definition either threatens the patient’s life (e.g., alveolar hemorrhage) or a vital organ with the risk of irreversible damage (e.g., rapidly progressive glomerulonephritis, scleritis, mononeuritis multiplex). These definitions and distinctions form the basis for stratification of current standard therapy defined in the 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of ANCA-associated vasculitis.[6]

More than 90% of patients with GPA first seek medical attention for symptoms arising from the upper and/or lower airway. Nasal and sinus disease is characterized by congestion and epistaxis due to mucosal friability, ulceration, and thickening. Patients may also have features of chronic sinusitis and recurrent or chronic serous otitis. Perforation of the nasal septum and/or saddle nose deformity may result from ischemia of the nasal cartilage (Fig. 74-3). Oral manifestations include gingival hyperplasia (Fig. 74-4) and oropharyngeal ulcerations. Subglottic stenosis occurs in approximately 20% of patients and can cause life-threatening compromise of the airway.

TABLE 74-2 Organ Systems Affected by ANCA-Associated Vasculitis

Feature	Granulomatosis with Polyangiitis (Wegener)	Microscopic Polyangiitis	Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss)
Upper airway disease	90%–95%	No	50%–60%
Pulmonary parenchymal disease	54%–85%	20%	30%
Alveolar hemorrhage	5%–15%	10%–50%	<3%
Glomerulonephritis	51%–80%	60%–90%	10%–25%
Gastrointestinal tract	<5%	30%	30%–50%
Eyes	35%–52%	<5%	<5%
Nervous system	20%–50%	60%–70%	70%–80%
Heart	8%–16%	10%–15%	10%–15%
Skin	33%–46%	62%	50%–60%
Eosinophilia	Rare	Rare	Yes
Asthma	No[a]	No[a]	Yes
Granulomatous inflammation	Yes	No	Yes

[a] *Not more than general population.*

Subglottic stenosis may occur in the absence of other features of active GPA. Symptoms include dyspnea, hoarseness, cough, or stridor; the latter is occasionally mistaken for wheezing.

GPA involving the lower airways can affect the pulmonary parenchyma, the bronchi, and rarely the pleura.[7–9] Presenting features of parenchymal involvement may include cough, dyspnea, chest pain, or hemoptysis. However, some patients may be completely asymptomatic. Patients with diffuse alveolar hemorrhage usually present with acute or progressive dyspnea and anemia (Fig. 74-5). Hemoptysis is absent in about one-third of patients. Patients with diffuse alveolar hemorrhage may deteriorate rapidly and experience respiratory failure, which has a mortality rate up to 50%.

The clinical presentation of diffuse alveolar hemorrhage is caused by pulmonary capillaritis (Fig. 74-6). The predominant inflammatory cells are neutrophils. However, eosinophils or monocytes also may be present. Capillaritis usually causes fibrinoid necrosis of alveolar and vessel walls and may culminate in the destruction of the underlying architecture of the lung. An important hallmark of capillaritis is the presence of pyknotic cells and nuclear fragments from neutrophils undergoing apoptosis, a feature called *leukocytoclasis*. This hallmark enables distinction between true capillaritis and margination of neutrophils related to surgical trauma. Depending on the

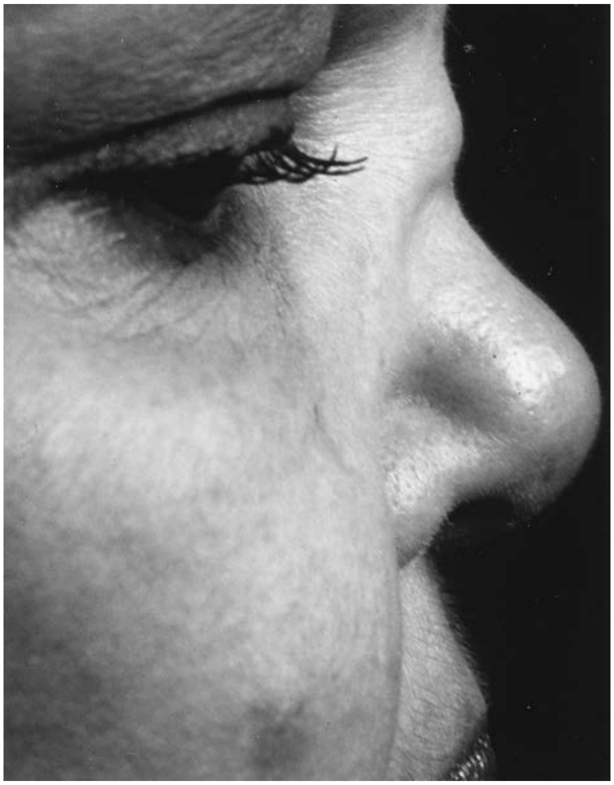

Figure 74-3 Saddle nose deformity of granulomatosis with polyangiitis.

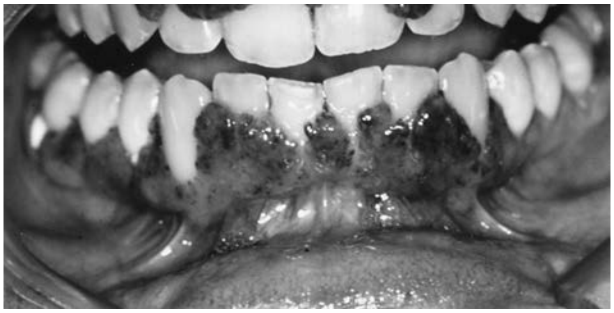

Figure 74-4 Strawberry or mulberry gums in a patient with granulomatosis with polyangiitis.

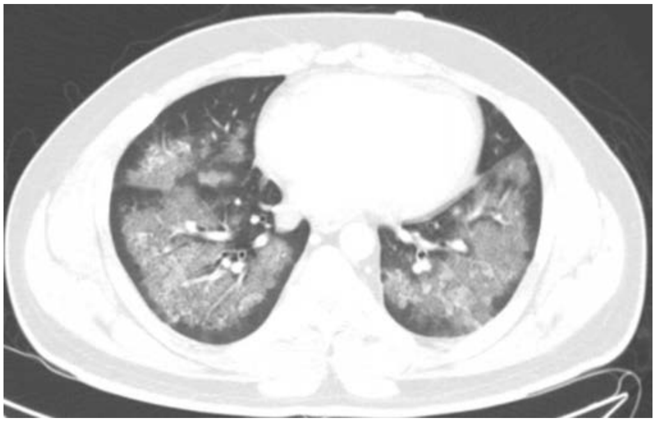

Figure 74-5 Computed tomography scan of a patient with granulomatosis with polyangiitis displaying an alveolar filling pattern indicative of diffuse alveolar hemorrhage.

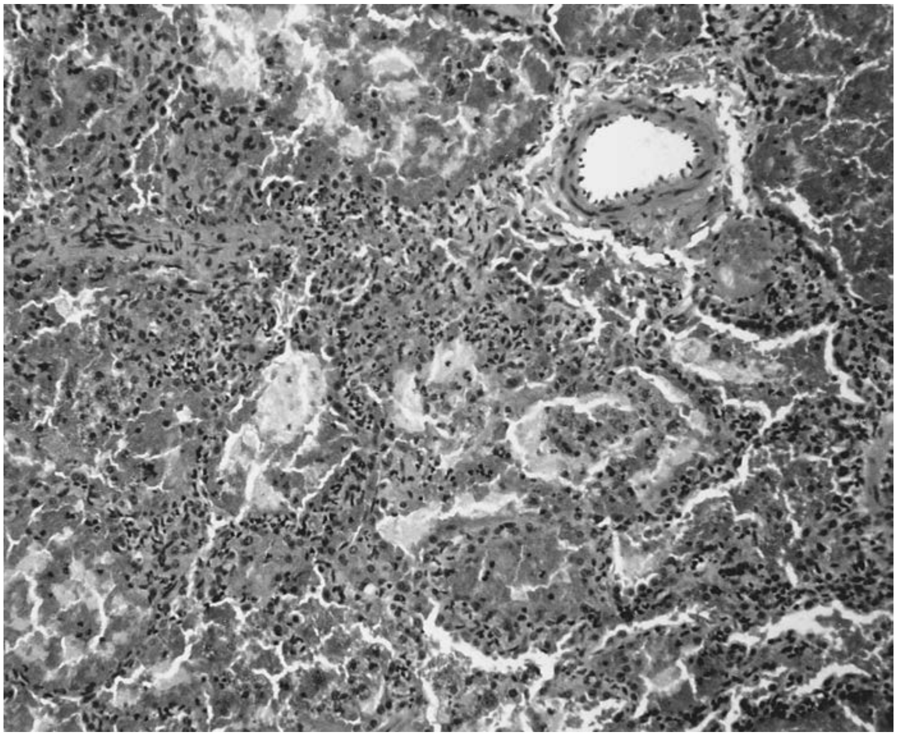

Figure 74-6 Alveolar capillaritis causing pulmonary hemorrhage in granulomatosis with polyangiitis.

acuteness and duration of alveolar hemorrhage, hemosiderin-laden macrophages and interstitial hemosiderin deposits may be present.[10]

The most common form of pulmonary involvement in GPA is caused by necrotizing granulomatous inflammation and presents radiographically as nodules or mass lesions, which may cavitate (Figs. 74-7, 74-8, and 74-9). These lesions may be incidental findings on thoracic imaging studies as they cause few symptoms and do not result in significant abnormalities of pulmonary function. Prominent air–fluid levels can be seen when the necrotic center of the inflammatory lesion becomes superinfected (Fig. 74-8). These necrotizing granulomatous lesions are a disease-defining feature of GPA.[1] Their presence easily separates GPA from MPA. In the absence of other features of small vessel vasculitis in other organs, infections, particularly with fungal organisms or *Nocardia*, organizing pneumonia, and malignancies are the main differential diagnostic considerations.[11,12] The differential diagnosis of GPA can be particularly challenging when the disease manifestations are limited to the lung and when patients are ANCA negative. Organizing pneumonia represents a noteworthy challenge because cryptogenic organizing pneumonia can be radiographically indistinguishable from GPA, organizing pneumonia can occur in GPA, and, like GPA, cryptogenic organizing pneumonia responds to glucocorticoids.[9] Multiple bilateral pulmonary nodules require histopathologic investigation to exclude metastatic disease or lymphoproliferative disorders. Lymphomatoid granulomatosis is a mimic of GPA, as this rare, angiocentric, angiodestructive, Epstein–Barr virus–related, T-cell rich B-cell lymphoma also often affects different extrapulmonary organs.[13]

To establish the histopathologic diagnosis based on pulmonary nodules or masses, video-assisted thoracoscopic surgical (VATS) lung biopsy has the highest diagnostic yield, but only patients with isolated lung involvement require this approach to establish a diagnosis. Bronchoscopy may be useful in patients with suspected GPA to obtain samples for cytology and microbiologic studies.

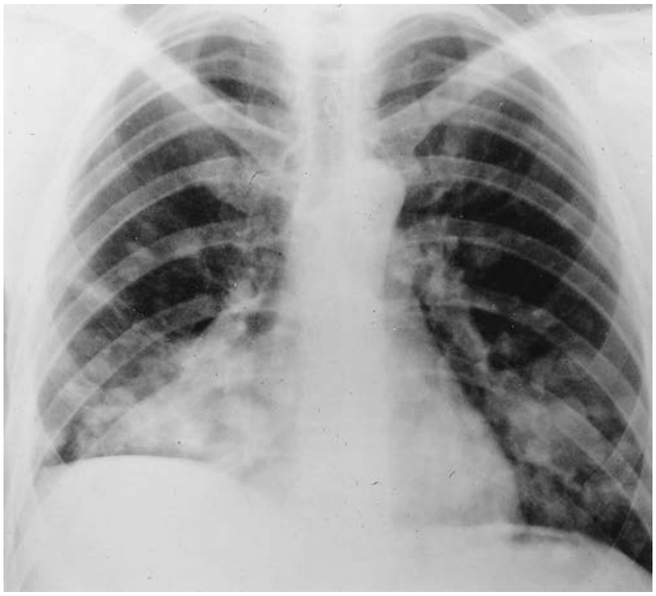

Figure 74-7 Chest radiograph of a patient with granulomatosis with polyangiitis displaying multiple nodules with and without cavitation.

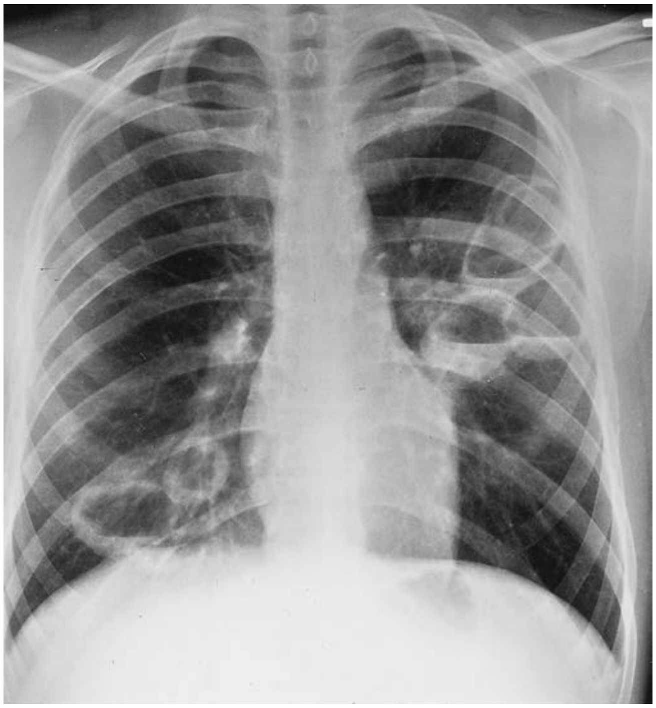

Figure 74-8 Chest radiograph of a patient with granulomatosis with polyangiitis showing multiple large cavities, some with air–fluid levels.

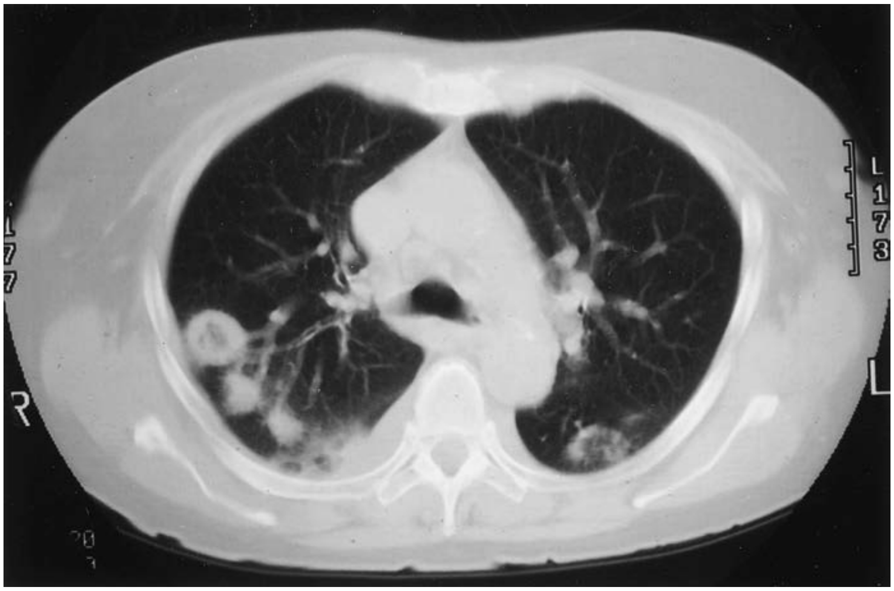

Figure 74-9 Computed tomography scan of a patient with granulomatosis with polyangiitis showing multiple nodules, some with cavitation. There are also small bilateral pleural effusions.

Transbronchial lung biopsy specimens support the diagnosis of GPA in about 50% of patients in conjunction with other supportive clinical features or positive ANCA test results but are diagnostic by themselves in only 20% of cases.[14] CT-guided core needle biopsy may be the preferred approach for peripheral lesions.

The lung nodules of GPA have very characteristic histopathologic features. Small necrotizing microabscesses appear to be the earliest lesion. They enlarge and coalesce until the typical geographic and basophilic appearance of the necrosis has developed (Fig. 74-10). The necrotic center is surrounded by palisading histiocytes and scattered giant cells. Occasionally the necrosis may be bronchocentric. When this type of necrotizing granulomatous inflammation extends into the walls of small vessels it is referred to as *granulomatous vasculitis* (Fig. 74-11). In contrast to capillaritis, this type of vasculitis seems to be a secondary phenomenon of the necrotizing granulomatous inflammation affecting the lung parenchyma. The inflammatory background of the granulomatous necrosis and vasculitis consists of a mixed cellular infiltrate containing lymphocytes, plasma cells, scattered giant cells, and eosinophils. It may cause extensive parenchymal consolidation mimicking organizing pneumonia. Well-defined sarcoid-like nonnecrotizing granulomas are not found in GPA.

Tracheobronchial involvement is common in GPA, occurring in 15% to 55% of patients, but rare in MPA, and women are more frequently affected.[8,14,15] PR3-ANCA are more common than MPO-ANCA in patients with tracheobronchial inflammation, including subglottic inflammation and subsequent stenosis.[8,15] Tracheobronchial inflammation is viewed as a surrogate of necrotizing granulomatous inflammation, even though classic histopathologic features of GPA are rarely found in endobronchial biopsies. Endobronchial disease may be an incidental finding on bronchoscopy or present with cough, hemoptysis, wheezing, dyspnea, or symptoms related to atelectasis or postobstructive pneumonia. Biopsies of tracheobronchial lesions often show nonspecific mucosal inflammation, ulcerations, and stenosing fibrosis, but rarely vasculitis. The tracheobronchial inflammation of GPA is localized or patchy in distribution throughout the airway. Affected areas and normal-appearing airways are next to each other, a feature differentiating the tracheobronchial inflammation of GPA from that of relapsing polychondritis, which is much more diffuse.[16] Any level of the airway can be affected. Transmural inflammation is detectable by CT imaging of the chest, which can reveal significant thickening of the airway walls. Tracheo- or bronchomalacia may result from inflammation affecting tracheobronchial cartilages, and significant expiratory dynamic airway collapse may ensue, which is detectable by bronchoscopy or by dynamic expiratory chest CT.[17] The differential diagnosis of tracheobronchial involvement of GPA includes relapsing polychondritis,[16] inflammatory bowel disease,[18,19] sarcoidosis,[20] and infections, particularly with fungal organisms.[21] The differential diagnosis may be challenging because a minority of patients with GPA remain ANCA negative, whereas nonspecific ANCA or P-ANCA with or without MPO-ANCA specificity can occur in patients with relapsing polychondritis, inflammatory bowel disease, or infections.[22]

Spirometry including inspiratory and expiratory flow-volume loops may show characteristic abnormalities indicative of degree and location of airway narrowing. Subglottic stenosis represents a fixed airway obstruction resulting in flattening of both the inspiratory and expiratory loops. If the intrathoracic trachea, or more commonly, one or both mainstem bronchi are affected, flattening of the expiratory curve can be found.

Pleural effusions are an uncommon manifestation of GPA and are usually small, asymptomatic, and incidental findings (Fig. 74-9). Other thoracic manifestations of GPA include inflammatory pleural pseudotumors and hilar adenopathy. The latter should raise the suspicion of infection, sarcoidosis, or lymphoma.

Glomerulonephritis is among the most concerning disease manifestations of GPA

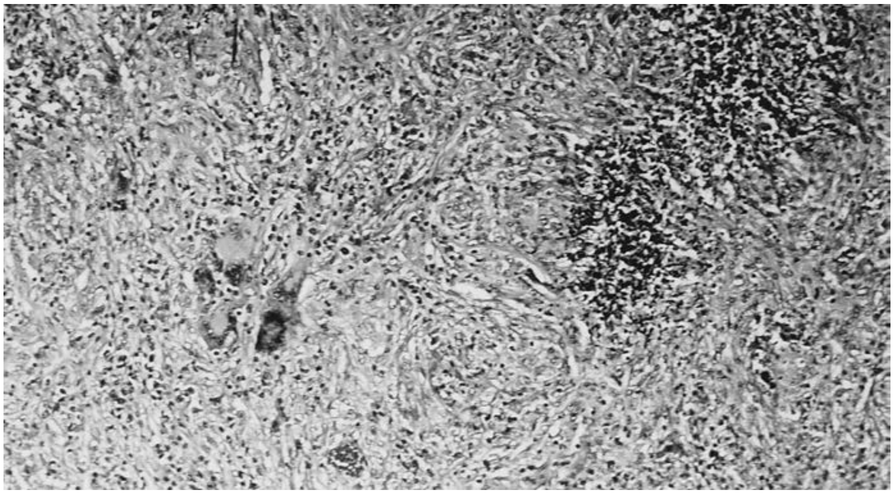

Figure 74-10 Geographic basophilic necrosis with palisading histiocytes and giant cells from a lung nodule in a patient with granulomatosis with polyangiitis.

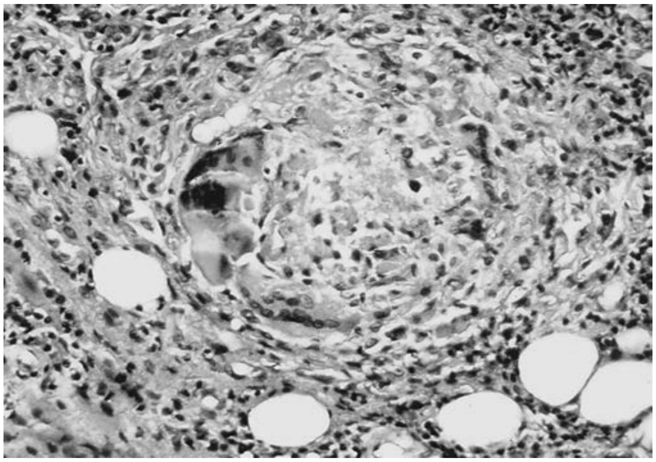

Figure 74-11 Granulomatous vasculitis with giant cells in a lung biopsy of a patient with granulomatosis with polyangiitis.

as it can progress to frank renal failure in the absence of symptoms. It is usually detected by the presence of abnormal laboratory results such as active urine sediment with microscopic hematuria and red cell casts, proteinuria, and declining renal function. Continued vigilance for glomerulonephritis is essential as it is present at diagnosis in less than half of all patients. However, over the course of their disease, the kidneys are affected in 80% of patients.

A renal biopsy is useful to establish a diagnosis of ANCA-associated vasculitis and to estimate the renal prognosis. The glomeruli are not affected uniformly (focal) by segmental, necrotizing inflammation (Fig. 74-12), and cellular crescents (Fig. 74-13) are frequently found. The number of glomeruli affected, degree of crescent formation, and destruction of individual glomeruli as well as the amount of sclerosis found determine the chance of recovery of renal function. In addition, tubular fibrosis and atrophy affect renal outcomes.[23] Direct immunofluorescence reveals no or only scant immune deposits (pauci-immune glomerulonephritis). Granulomatous inflammation affecting the renal parenchyma and tubulointerstitial nephritis rarely can be present.

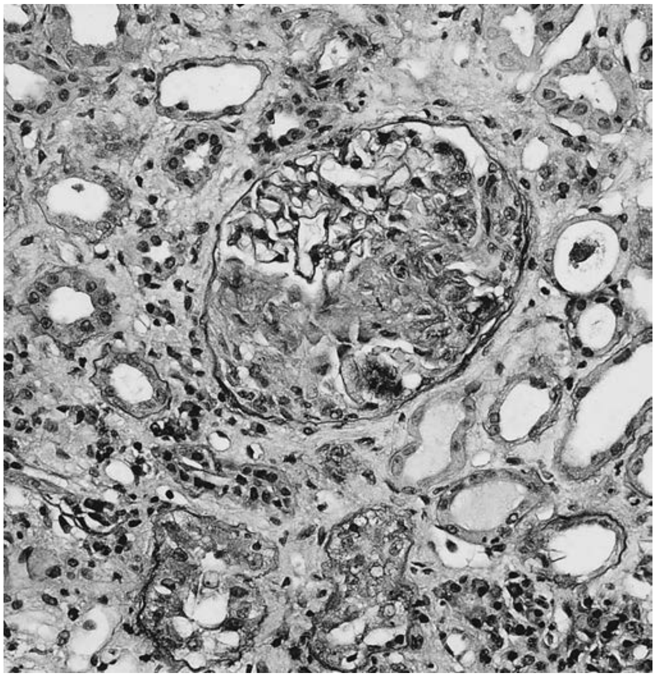

Figure 74-12 Focal necrotizing glomerulitis of granulomatosis with polyangiitis.

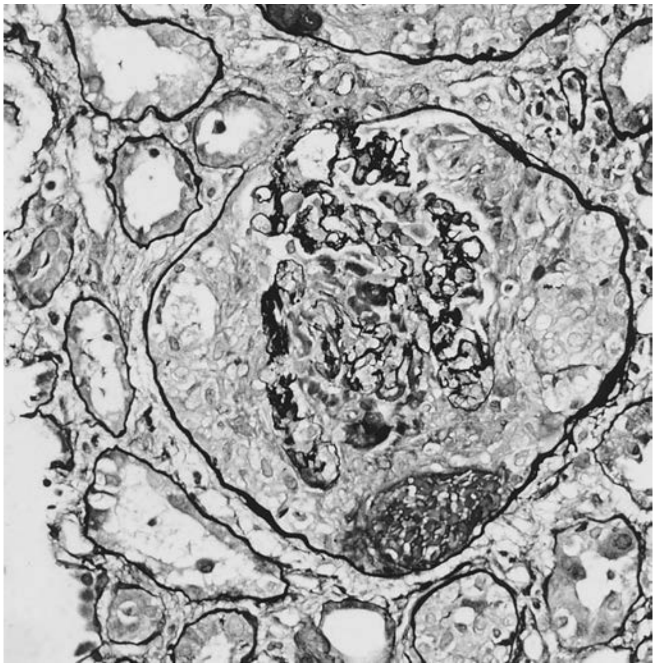

Figure 74-13 Rapidly progressive crescentic glomerulonephritis in granulomatosis with polyangiitis.

A wide spectrum of ocular manifestations has been observed in GPA, which may threaten vision by affecting the eye directly or involving its contiguous structures. Manifestations may include conjunctivitis, episcleritis, scleritis, keratitis, corneal ulceration, uveitis, and retinal vasculitis. Involvement of the lacrimal system may result in epiphora, dacryocystitis, and fistula. Retro-orbital inflammatory pseudotumors may affect one or both eyes, threaten the vision, and represent one of the most difficult challenges in the management of GPA (Figs. 74-14 and 74-15). Any patient with GPA who presents with eye pain or redness, proptosis, change in visual acuity, diplopia, or loss of visual field should be referred for emergent ophthalmologic consultation.

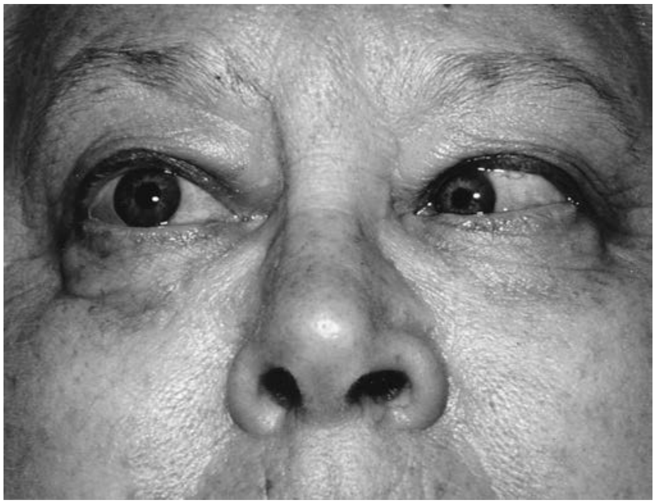

Figure 74-14 External ophthalmoplegia of the left eye due to orbital involvement with granulomatosis with polyangiitis.

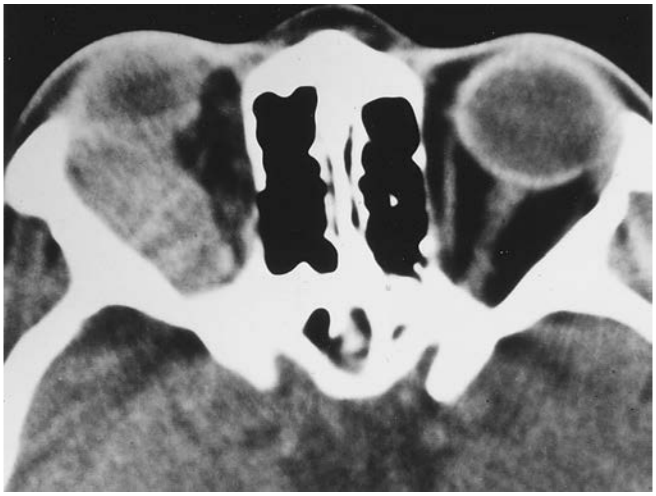

Figure 74-15 Computed tomography scan of the orbits in a patient with granulomatosis with polyangiitis showing a mass in the right orbit causing external ophthalmoplegia.

Nervous system involvement may occur in up to one-third of patients. Mononeuritis multiplex of the peripheral nervous system is caused by inflammation of the vasa nervorum. Central nervous system vasculitis and pachymeningitis represent severe disease manifestations with substantial risk of irreversible damage, persisting even after the acute inflammation is adequately controlled.

Cardiac involvement may be occult. Regional wall motion abnormalities with a noncoronary distribution pattern are frequent echocardiographic findings.[24] It is unclear whether this type of cardiomyopathy is the result of small vessel disease or inflammatory infiltration of the cardiac muscle. Pericarditis, valvulitis, and inflammatory pseudotumor also have been described.

A wide spectrum of cutaneous manifestations may be observed in GPA. Leukocytoclastic vasculitis presenting as palpable purpura is most common, followed by pyoderma gangrenosum-like lesions (Fig. 74-16) and so-called Churg-Strauss granulomas.

■ Microscopic Polyangiitis: Clinical Presentation and Diagnosis

Histopathologically, the necrotizing small vessel vasculitis of MPA causing necrotizing crescentic glomerulonephritis and pulmonary capillaritis is indistinguishable from that encountered in GPA.[25] Consequently, there is substantial overlap in organ manifestations and symptoms between the two syndromes (Table 74-2). A timely diagnosis of MPA may be delayed by a gradual onset or the nonspecific nature of symptoms such as fever, malaise, and weight loss. All organ systems may be involved. The kidneys are most commonly affected, involving up to 80% of patients. Another commonly encountered disease manifestation is diffuse alveolar hemorrhage due to pulmonary capillaritis, affecting 10% to 30% of patients. MPA is the most frequent cause of pulmonary-renal syndrome. Several cases of MPA in association with severe obstructive airways disease or bronchiectasis also have been described. More recently, several case series have highlighted an association between interstitial lung disease (ILD) and ANCA with or without MPA (see "Interstitial Lung Disease and ANCA with or without MPA," below).

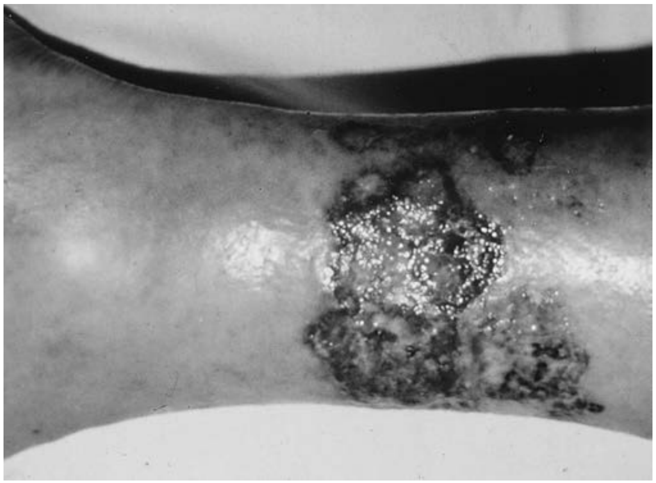

Figure 74-16 Pyoderma gangrenosum of the leg in a patient with granulomatosis with polyangiitis.

Palpable purpura caused by leukocytoclastic vasculitis of the skin, and musculoskeletal complaints, such as arthralgias and myalgias, also are common. Gastrointestinal involvement occurs in about one-third of patients. This is in contrast to GPA, in which gastrointestinal involvement is very rare. Visceral angiography is generally not helpful for the evaluation of abdominal symptoms, as the vessels involved are too small to be visualized. CT with or without contrast injection may be more helpful if gastrointestinal involvement is suspected. However, the use of contrast is relatively contraindicated in patients with active renal involvement. Sinusitis and asthma are rarely found in MPA, and their presence should lead to the consideration of an alternative diagnosis, particularly EGPA.

Most patients with MPA have ANCA, and in 40% to 80% they are of the P-ANCA variety, reacting with MPO. C-ANCA reacting with PR3 are seen less frequently. Occasionally patients with MPA later develop granulomatous inflammation and are reclassified as having GPA; this is more likely to occur in patients with C-ANCA.

As in GPA, a histopathologic diagnosis may be necessary to confirm the diagnosis before the patient is committed to prolonged immunosuppressive therapy. The biopsy specimen should be sought from the most accessible site. Renal biopsy shows pauci-immune focal segmental necrotizing glomerulonephritis, with extracapillary proliferation forming crescents. In contrast to GPA, granulomatous inflammation is not a feature of MPA. All other histopathologic features are indistinguishable from those of GPA. Treatment of MPA should follow the principles applied to the management of GPA[6]. Consequently, most cases of MPA require immunosuppressive therapy used for patients with severe GPA.

Interstitial Lung Disease and ANCA with or without MPA

A growing number of reports from all over the world have described patients with ILD who are ANCA positive, with or without signs or symptoms of MPA, as well as patients with MPA who also had ILD at the time of diagnosis.[26–30] Whether there is a pathogenic relationship between MPO-ANCA and pulmonary fibrosis, or whether lung fibrosis is a disease manifestation of ANCA-associated vasculitis rather than an independent comorbidity, remains unclear and controversial. A recent report from Japan identified an association of the MUC5B promotor polymorphism in patients with MPA who also had ILD, compared to patients with MPA without ILD and healthy controls, but similar to patients with ILD without MPA or patients with rheumatoid arthritis and ILD.[31] The ILD identified in the context of MPA usually has radiographic and histopathologic features of usual interstitial pneumonia (UIP) or of nonspecific interstitial pneumonitis (NSIP).[26,32] Atypical features including follicular bronchiolitis have also been reported.[26,33] Patients with ILD without signs of MPA may have ANCA. MPO-ANCA are the predominant ANCA type encountered, whereas PR3-ANCA occurs rarely. These patients may or may not have abnormal markers of inflammation, and signs or symptoms of MPA in other organs should be looked for. If ground-glass infiltrates are part of the ILD of a patient with MPO-ANCA, bronchoscopy with BAL is mandatory to rule out alveolar hemorrhage. Patients with ILD who are MPO-ANCA positive have a 25% chance of subsequently developing clinical features of MPA, a progression that has been documented for patients with MPO-ANCA, but not PR3-ANCA.[28,29]

In patients with MPA the presence of ILD is associated with increased mortality and determines their overall prognosis.[34] The vasculitis disease manifestations of these patients with MPA and ILD, including DAH superimposed on their ILD, respond to immunosuppressive therapy as expected for MPA, whereas the ILD may only respond if it has features of cellular NSIP or other inflammatory features. In contrast, if the lung fibrosis pattern is consistent with UIP, the lung fibrosis will not respond to immunosuppression given for the vasculitis features of the MPA. Consequently, once remission of the vasculitis has been induced with immunosuppression, patients with MPA and UIP should be offered treatment with antifibrotic agents.

■ Eosinophilic Granulomatosis with Polyangiitis: Clinical Presentation and Diagnosis

EGPA was originally described in 1951 as "allergic granulomatosis, allergic angiitis and periarteritis nodosa" by Jacob Churg and Lotte Strauss in a report based mostly on autopsy findings. The authors recognized the allergic background, blood and tissue eosinophilia with granulomatous inflammation leading to necrosis, and vasculitis; this combination reflects the final outcome of the disease before any mitigating therapy was available.[35] The syndrome subsequently known by its eponym, Churg-Strauss syndrome, for half a century was renamed at the 2012 Chapel Hill Consensus Conference on nomenclature of the vasculitides, and the new term intends to reflect the most prevalent pathology, pathogenic role of eosinophils, and similarities of the vasculitis shared with GPA and MPA.[1] It is because of the similarities of the small vessel vasculitis that EGPA is included among the ANCA-associated vasculitides even though only 40% to 70% of patients with active EGPA are ANCA positive.[36–38]

EGPA is the third type of vasculitis that commonly affects the lung. EGPA is primarily distinguished from GPA and MPA by a high prevalence of asthma and peripheral blood and tissue eosinophilia. Three distinct disease phases of the disease have been described. The first is a prodromal allergic phase with asthma. This phase may last for a number of years. The second is an eosinophilic phase with prominent peripheral and tissue eosinophilia. This phase may also last a number of years, and the manifestations may remit and recur over this time period. The differential diagnosis for patients in this phase of the disease includes parasitic infection, chronic eosinophilic pneumonia, and hypereosinophilic syndrome. The third vasculitic phase consists of systemic vasculitis and may be life threatening. The three phases are not seen in all patients and do not necessarily occur in this order; they may even coincide. However, asthma usually predates vasculitic symptoms by a mean of 7 years (range, 0–61). Formes frustes of EGPA have also been described with eosinophilic vasculitis and/or eosinophilic granulomas in isolated organs without evidence of systemic disease.

Pulmonary parenchymal involvement occurs in 38% of patients. Transient alveolar-type infiltrates are most common (Fig. 74-17). These have a predominantly peripheral distribution and are indistinguishable from infiltrates seen in chronic eosinophilic pneumonia. Occasionally, nodular lesions may be seen in EGPA. In contrast to GPA and MPA, alveolar hemorrhage is exceedingly rare. Renal involvement in EGPA is less prominent than in GPA and MPA and does not generally lead to renal failure. In contrast, peripheral nerve involvement, typically in the form of mononeuritis multiplex, is more frequent. The peripheral nerve involvement can result from both capillaritis and direct toxicity from eosinophil granule proteins. Skin, heart, central nervous system, and abdominal viscera also may be involved.

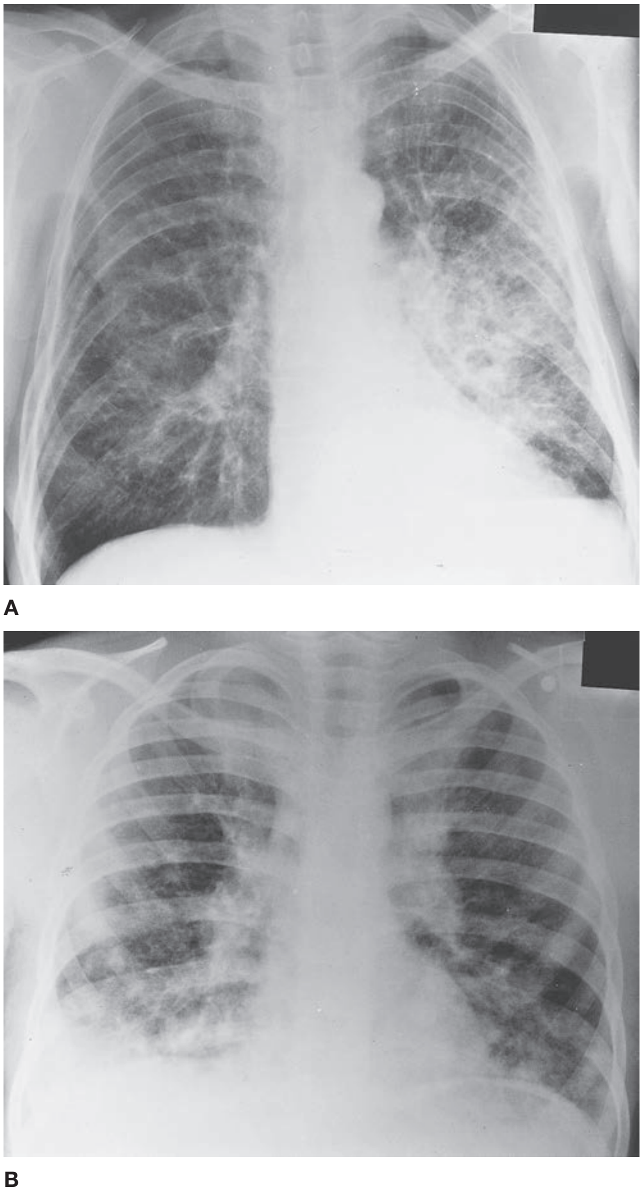

Figure 74-17 Chest radiographs of patients with eosinophilic granulomatosis with polyangiitis. **A.** Nonspecific gnomonic infiltrates. **B.** Multiple vague, patchy infiltrates. *(Reproduced with permission from Chumbley LC, Harrison EG, DeRemee RA: Allergic Granulomatosis and angiitis (Churg-Strauss syndrome): Report and analysis of 30 cases. Mayo Clin Proc. 1977;52(8):477–484.)*

The classic histopathologic picture consists of necrotizing vasculitis, eosinophilic tissue infiltration, and extravascular granulomas. However, not all features are found in every case, and they are not pathognomonic of the condition. Particularly the finding of a "Churg-Strauss granuloma" on skin biopsy should not be confused with the diagnosis of EGPA. While this type of necrotizing extravascular granuloma may be seen in EGPA, it may occur in other systemic autoimmune diseases, including GPA and rheumatoid arthritis.

If ANCA are present, they are usually P-ANCA reacting with MPO. The ANCA status appears to correlate with disease activity. Recent studies suggest a more vasculitic disease phenotype in the presence of ANCA, with ANCA being particularly frequent among patients with glomerulonephritis. Patients with heart involvement are less likely to be ANCA positive. However, not all studies have found this consistently, and there remains substantial overlap of organ manifestations between patients with EGPA who are ANCA positive and those who are ANCA negative.

Significant attention has been devoted to EGPA detected in patients using leukotriene receptor antagonists when these agents were first introduced into the management of asthma. Available case studies and limited population-based incidence estimates suggest that these agents may lead to unmasking of vasculitic symptoms in asthmatics, by allowing dose reductions or discontinuation of oral glucocorticoid therapy. There is no evidence suggesting that these agents cause EGPA.

The prognosis of EGPA is better than that of GPA and MPA. Most deaths are secondary to cardiac involvement, and patients should be carefully screened for signs and symptoms of cardiomyopathy, valvulitis, or pericarditis.[39]

Pathophysiology of ANCA-Associated Vasculitis

The etiology of ANCA-associated vasculitis remains unknown. Several different pathways and mechanisms have been proposed for the pathogenesis.[40,41] A genetic predisposition for autoimmunity, epigenetic factors, and environmental triggers seem to play a role in the development of ANCA-associated vasculitis. Currently available clinical and experimental evidence suggest that infections or other environmental exposures can lead to the loss of tolerance and an inflammatory environment that is conducive to the production of autoantibodies (ANCA) in predisposed patients. In the context of an inflammatory milieu, ANCA can cause specific tissue inflammation and injury by a variety of different mechanisms that involve direct interactions with PR3 or MPO.

Multiple studies have reported skewing in polymorphisms of a variety of immune response genes and genes encoding for ANCA target antigens and α_1-proteinase inhibitor with potential effects on disease outcome. A genome-wide association study found major histocompatibility complex (MHC) and non-MHC associations with GPA and MPA.[42] Notably, these syndromes were genetically distinct, but the strongest genetic associations were based on the antigenic specificity of the ANCA (PR3-ANCA vs. MPO-ANCA) rather than with the clinical syndrome (GPA vs. MPA). For PR3-ANCA-positive patients, strong associations were found with *HLA-DP*; the serpin A1 gene (*SERPINA1*), which codes for α1-antitrypsin, the major inhibitor of PR3; and the *PRTN3* gene, which encodes PR3. In patients with MPO-ANCA only an association with *HLA-DQ* was found.

The expression of ANCA-target antigens on the neutrophil surface, particularly PR3, is increased in patients with GPA and genetically determined. Moreover, epigenetic modifications that interfere with the normal silencing of genes coding for the ANCA-autoantigens in mature neutrophils may also contribute to the observed inappropriately increased expression of PR3 and MPO by these cells in patients with GPA or MPA.

Recent studies indicate that a separation of patients with ANCA-associated vasculitis by ANCA specificity (PR3-ANCA versus MPO-ANCA) provides a clinically more informative classification than the grouping by conventional phenotypic diagnosis (GPA versus MPA).[43] This concept is supported by results from genome-wide association studies discussed above,[42] analysis of cytokine patterns,[44] treatment response to rituximab,[45] and relapse risk.[46] Patients with limited GPA who remain ANCA negative rarely develop systemic vasculitic disease manifestations. Patients with glomerulonephritis and PR3-ANCA lose renal function much more rapidly than patients with MPO-ANCA. Patients with PR3-ANCA also have a higher relapse rate than patients with MPO-ANCA. Experimental data and animal models support a pathogenic role of ANCA in the development of vasculitis. Recent studies have also suggested a different clinical phenotype of ANCA-positive patients with EGPA compared with ANCA-negative patients.[47,48]

In GPA, the presence of PR3-ANCA appears most closely related to the development of vasculitic complications compared to patients who are ANCA-negative. Furthermore, systemic vasculitic relapses without recurrence of ANCA are extremely rare. Yet, remission may be maintained for extended periods of time in up to one-half of the patients despite the presence of ANCA. These clinical observations suggest that ANCA alone are not sufficient to cause disease activity, but ANCA seem to be required for the development of vasculitic complications of GPA and systemic relapses.

Many in vitro studies have demonstrated proinflammatory effects of PR3-ANCA and MPO-ANCA on neutrophils, monocytes, and endothelial cells, which enhance and perpetuate endothelial cell and tissue damage. ANCA may increase the adhesion of neutrophils to endothelial cells by enhancing the expression of cell adhesion molecules on endothelial cells. ANCA can activate primed neutrophils, resulting in the release of oxygen radicals and proteolytic enzymes. The latter may in turn induce endothelial cell apoptosis. ANCA-mediated neutrophil activation involves both Fc-γ-receptor engagement and recognition of expressed target antigen on the surface of primed neutrophils. ANCA may also cause endothelial cell damage by direct cytotoxicity or localized immune complex formation with target antigens bound to the endothelial cell surface. The latter may initiate localized complement activation. Finally, ANCA are thought to contribute to the recruitment of more inflammatory cells to the area of tissue injury by stimulating the release of chemotactic chemokines and agents from neutrophils, monocytes, and endothelial cells.

Rodent models of MPO-ANCA-associated vasculitis support the hypothesis of a pathogenic role of ANCA. They clearly indicate that ANCA contribute directly to the development of vasculitis and glomerulonephritis, and that the interaction of ANCA with its target antigen is required for the development of lesions. Furthermore, the localization of lesions is determined by the site of this interaction. At the same time, animal models support the significance of genetic determinants for the development of autoimmunity, vasculitis, and a specific phenotype with characteristic organ involvement and histopathologic features. Finally, animal model studies indicate that infections may be significant disease modifiers. Even though proinflammatory effects of murine PR3-ANCA could also be documented in vivo, the animals did not develop organ pathology typical of GPA or microscopic polyangiitis, and good animal models for PR3-ANCA-associated vasculitis remain elusive. This may be due to substantial differences between human and murine PR3, as the latter behaves more like human elastase than human PR3.

Many patients with ANCA-associated vasculitis relate the onset or recurrence of their disease to preceding infectious episodes, leading some to postulate the following mechanistic link. Most ANCA-mediated effects on neutrophils and monocytes require priming of the cells. This cytokine-dependent process is not unique to vasculitis. Cytokine stimulation of neutrophils and monocytes, typically by tumor necrosis factor (TNF), with resulting increased surface expression of ANCA target antigens, occurs normally in the context of infections. Patients with active vasculitis have indeed been shown to have both increased expression of ANCA target antigens on the surface of their neutrophils and elevated levels of TNF. In combination, these observations allow the hypothesis that neutrophil priming, which occurs in response to cytokine stimulation during infection, enables ANCA to interact with their target antigen on the neutrophil surface. This in turn sets the documented proinflammatory effects of ANCA in motion, aggravating and perpetuating the inflammatory reaction at the endothelial cell interphase.

To date, the causes of the production and persistence of ANCA remain poorly understood. Yet infections may be instrumental for the development of this specific type of autoimmunity. ANCA directed against a broad variety of target antigens have been documented in association with viral, fungal, bacterial, and protozoal infections. In the rare instances of C-ANCA/PR3-ANCA observed in infections, the ANCA disappeared with appropriate antimicrobial therapy. These observations suggest that ANCA can occur transiently in the setting of infection, and that the persistent ANCA response in patients with vasculitis may be the result of molecular mimicry in susceptible hosts. Subsequent diversification of T- and B-cell responses ("epitope spreading") may lead to responses against different epitopes on the same target molecule (intramolecular spreading) or extend to other molecules (intermolecular spreading). Bacterial superantigens also have been implicated in the pathogenesis of ANCA-associated vasculitis. GPA patients colonized with superantigen-producing *Staphylococcus aureus* are at high risk for relapse. GPA patients had expansion of T cell clones expressing Vβ genes specific for *S. aureus* superantigens more frequently than controls. This supports the theory that *S. aureus* contributes to the pathogenesis of vasculitis. By inducing potent T- and B-cell activity, superantigens produced during an *S. aureus* infection could initiate and maintain both ANCA production and cytokine release, thought to be required for the cascade that results in necrotizing granulomatous inflammation and vasculitis.

The crucial role of the alternative complement pathway for the development of capillaritis was first recognized in the murine model of MPO-ANCA-associated vasculitis. Specifically, the generation of activated complement factor 5 (C5a), which is a potent attractant and activator of neutrophils, via activation of the alternative complement pathway was shown to be necessary for the development of vasculitis.[41,49] Stimulation of neutrophils with C5a and ANCA not only results in the neutrophil respiratory burst and degranulation, but also activates the coagulation system and generates thrombin, thus bridging the inflammation and coagulation systems. In view of these results, targeting the C5a-mediated neutrophil activation, resulting from activation of the alternative complement pathway, appears to be an effective therapeutic option and has been utilized in recent clinical trials.

Treatment of Granulomatosis with Polyangiitis and Microscopic Polyangiitis

The first goal of therapy for patients with ANCA-associated vasculitis is to induce a remission as quickly as possible, so that irreversible organ damage is minimized. To this end, early diagnosis and prompt application of an appropriate immunosuppressive regimen are crucial. At the same time the treatment plan needs to minimize the risk of treatment-related toxicity. Once remission has been induced, the second goal of therapy is to maintain remission with as few side effects as possible. These overarching principles apply to the therapy of both GPA and MPA.[46]

Remission Induction Therapy

Remission induction therapy is best tailored to the patient's degree of disease severity, extent, and acuity.[6,41] Rarely, patients who present with indolent GPA localized to the upper and/or lower airways and who are ANCA negative can be treated with trimethoprim/sulfamethoxazole at a dose of 160/800 mg twice daily. The mechanism of action of trimethoprim-sulfamethoxazole is unclear but possibly related to antimicrobial effects on *S. aureus*, the organism most frequently cultured from the nostrils of patients with GPA. It is also possible that this agent has immune-modulatory effects not shared by other antibiotics. Trimethoprim-sulfamethoxazole monotherapy should not be used in ANCA-positive patients, in the setting of glomerulonephritis, or in any other severe disease manifestation, and patients treated with trimethoprim-sulfamethoxazole need continued long-term observation, as some will later develop more severe disease manifestations requiring immunosuppressive therapy. It should be noted that this treatment option for patients with localized indolent ANCA-negative disease is not mentioned in the most recent guideline for the management of ANCA-associated vasculitis.[6]

Standard remission induction therapy for most patients categorized as having "limited" or "nonsevere" or "early-systemic" GPA consists of oral prednisone at doses of 0.5 to 1 mg/kg per day (generally not to exceed 80 mg/day) in combination with methotrexate with a target dose of 20 to 25 mg once a week.[50,51] This dose can be administered orally or subcutaneously. To minimize toxicity and the risk of *Pneumocystis* pneumonia (PCP), this immunosuppressive regimen should be supplemented by folic acid, 1 mg/day, and standard PCP prophylaxis. Azathioprine or mycophenolate mofetil are alternative options for patients who do not tolerate methotrexate.

For several decades, standard remission induction therapy for GPA or MPA patients with severe disease (also called "generalized" or "organ-threatening" disease) had consisted of oral prednisone in combination with oral cyclophosphamide at a dose of 2 mg/kg daily for 3 to 6 months.[52] One randomized controlled trial had shown that IV pulse therapy with cyclophosphamide consisting of three pulses of 15 mg/kg given 2 weeks apart followed by 15-mg/kg pulses given every 3 weeks for 6 months, was equally effective in inducing remission in severe GPA or MPA.[53] Based on results from a large, multicenter, randomized, double-dummy controlled trial that compared four once-weekly doses (375 mg/m^2 of body surface) of rituximab to standard oral cyclophosphamide for remission induction in severe ANCA-associated vasculitis, rituximab has now been approved for this indication by most regulatory agencies across the globe and is also included in therapeutic guidelines from multiple scientific societies.[6,54,55] The long-term follow-up of this study has shown that the efficacy of a single course of four once-weekly doses of rituximab (375 mg/m^2 of body surface) remains equivalent to continued standard daily oral immunosuppressive therapy with cyclophosphamide followed by azathioprine for 18 months.[46] These three remission induction regimens (IV or oral cyclophosphamide, rituximab) have been shown to be equivalent for newly diagnosed patients with severe GPA or MPA. Remission can be achieved in up to 90% of patients with either of these regimens. For patients presenting with a severe disease relapse, rituximab has been found to be superior to cyclophosphamide.[46,54,56] Rituximab was also found to be superior to cyclophosphamide for patients with PR3-ANCA, whereas for patients with MPO-ANCA no difference in efficacy was detected.[45] Rituximab is also the preferred agent for young patients in whom fertility needs to be preserved. The most recent guideline for the management of ANCA-associated vasculitis "conditionally recommend rituximab over cyclophosphamide for remission induction in patients with active, severe GP/MPA."[6] If oral cyclophosphamide is used, patients need to be monitored carefully to minimize the risk of bone marrow toxicity. The dose of cyclophosphamide should be adjusted in patients with impaired renal function, and the patient's complete blood counts need to be monitored at least biweekly for the duration of therapy. Optimal dosing with oral cyclophosphamide is achieved when the lymphocyte count is reduced but the total white blood count is maintained above 3500. To avoid bladder toxicity of cyclophosphamide, the entire dose is applied in the morning and patients are instructed to drink at least three liters of fluid per day.

In patients with rapidly progressive, fulminant disease, such as those presenting with alveolar hemorrhage or rapidly deteriorating renal function, IV methylprednisolone, 1000 mg per day for 3 to 5 days, may be initially necessary for effective control of inflammation.

More recently, given the role that the alternative complement pathway activation plays in ANCA-associated vasculitis, avacopan, a C5a receptor–blocking molecule, was tested in two phase 2 trials and one phase 3 and was found to be safe and effective in replacing glucocorticoids during induction of remission in patients with ANCA-associated vasculitis.[57–59] However, regulatory approval of this novel agent is still pending.

Role of Plasma Exchange in Remission Induction

If standard induction therapy does not generate the desired effects of controlling disease activity promptly, plasma exchange (PLEX) has been considered as an adjunct treatment modality. PLEX has long been proposed and used for patients with severe disease manifestations (severe progressive glomerulonephritis or diffuse alveolar hemorrhage) under the assumption that its effects are swift and supported by our understanding of the pathogenic role of ANCA. For two main reasons the application of PLEX has been considered and advocated especially for cases progressing to respiratory failure. First, analogous to anti–glomerular basement membrane disease (anti-GBM disease), PLEX allows the rapid removal of ANCA, which are thought to be pathogenic.[60] Second, a single retrospective uncontrolled cohort study of 20 patients with diffuse alveolar hemorrhage caused by MPA reported resolution of diffuse alveolar hemorrhage in all patients and only 1 death, outcomes far superior compared to previous reports of patients with pulmonary renal syndromes.[61] However, more recent evidence no longer supports the use of PLEX for patients with diffuse alveolar hemorrhage caused by ANCA-associated vasculitis.

The largest single center cohort study comprising 73 consecutive patients with diffuse alveolar hemorrhage due to GPA or MPA compared 32 patients treated with PLEX to 41 patients who did not receive PLEX.[62] There was no difference in hospital mortality, hospital length of stay, ICU length of stay, or days requiring respiratory support between patients who received PLEX compared with those who did not.[62] After adjusting for factors associated with disease severity affecting the likelihood of receiving PLEX and for the treatment choice of cyclophosphamide versus rituximab, the use of PLEX was not associated with achieving complete remission by 6 months (odds ratio [OR], 0.49; 95% confidence interval [CI], 0.12–1.95). A thorough review of the available literature also did not support a therapeutic benefit of PLEX in patients with diffuse alveolar hemorrhage secondary to ANCA-associated vasculitis.[62]

Finally, a large randomized controlled trial comprising 704 patients with ANCA-associated vasculitis with active renal disease or diffuse alveolar hemorrhage evaluated the efficacy of PLEX as adjunct to standard remission induction therapy (PEXIVAS trial).[63] This trial cohort included 191 patients with diffuse alveolar hemorrhage. There was no beneficial effect of PLEX on the primary outcome of death from any cause or end-stage kidney disease or on any of the secondary outcomes; there was also no evidence of interactions according to prespecified subgroups including diffuse alveolar hemorrhage with or without respiratory failure (oxygen saturation on room air $>85\%$ or $\leq 85\%$ or ventilated).[63] The only situation in which most experts seem to agree on the use of PLEX are patients who test positive for both ANCA and anti-GBM antibodies.[6]

Remission Maintenance Therapy

Once remission has been achieved, the prednisone dose is tapered gradually over the course of 1 to 6 months with the goal of complete discontinuation. The PEXIVAS trial also evaluated the role of a reduced dose of prednisone or prednisolone compared with standard dosing. At 6 months, the cumulative dose of oral glucocorticoids in the reduced-dose group was less than 60% of that in the standard-dose group. In addition, the reduced dose was noninferior to a standard dose regimen with respect to the risk of death or development of end stage kidney disease and resulted in a lower risk of serious infections in the first year of treatment.[63]

Patients with "nonsevere" disease should be maintained on methotrexate for remission maintenance.[51] Patients treated with cyclophosphamide for remission induction should be switched to either methotrexate or azathioprine for remission maintenance after 3 to 6 months of cyclophosphamide therapy.[64] Azathioprine is preferred in patients with any degree of renal insufficiency. Mycophenolate mofetil is an alternative for patients who cannot tolerate either methotrexate or azathioprine for remission maintenance. However, mycophenolate mofetil was found to be less effective than azathioprine for remission maintenance in one randomized controlled trial.[65] Remission maintenance therapy is continued for at least 18 to 24 months beyond achievement of remission, and longer in patients who are C-ANCA/PR3-ANCA positive or have suffered relapses. Early discontinuation of immunosuppressive therapy is associated with an unduly high relapse rate.

The need for remission maintenance therapy following remission induction with rituximab in newly diagnosed patients remains unclear. Over 18 months a single remission induction course of rituximab is as effective as oral cyclophosphamide followed by azathioprine, but PR3-ANCA-positive patients with GPA are at risk for relapse once peripheral blood B lymphocytes are reconstituted (after 6 to 12 months) and may benefit from long-term remission maintenance therapy.[66] Recent studies have evaluated the use of rituximab for maintenance of remission and have demonstrated that rituximab is effective and superior to azathioprine when utilized at a fixed dose of 500 mg every 6 months or when the therapy is individualized based on peripheral blood B lymphocytes and ANCA titers.[67,68]

Long-term remission maintenance therapy with trimethoprim-sulfamethoxazole beyond immunosuppression also may be beneficial. In one study, patients who received trimethoprim-sulfamethoxazole at a dose of 160/800 mg twice daily had a lower rate of disease relapse than those who received placebo.[69]

Treatment of Patients Refractory to Standard Therapy

About 10% of patients do not respond adequately to therapy with cyclophosphamide and fail to achieve remission. Over the last decade many cohort studies have found rituximab to be very effective in such patients, and rituximab has now become the de facto standard of care for refractory GPA.[56,70] These patients are particularly challenging, and other immunosuppressive drugs have been utilized with less success. Anti–TNF-α agents have not been shown to be effective in such patients. One large, multicenter, double-blind, placebo-controlled, randomized trial conducted in GPA did not demonstrate any benefit of adding etanercept to standard therapy.[64] Moreover, a higher frequency of malignancies was observed in the treatment arm compared with the control arm of that trial. All patients with malignancies had also received cyclophosphamide. For this reason, the use of etanercept in patients who have received cyclophosphamide is now strongly discouraged. Smaller, uncontrolled open-label studies with infliximab conducted in Europe have suggested some efficacy of that agent, but many complicated infections were observed in these patients.

Current guidelines recommend that patients who experience an inadequate response (refractory disease) to the original remission induction agent (rituximab or cyclophosphamide) be switched to the alternative agent.[6] Because of the prolonged B cell–depleting effect of rituximab this "switch" de facto represents the addition of cyclophosphamide to ongoing rituximab therapy.

Supportive Therapy

PCP still carries a mortality of up to 35%. Therefore, prophylaxis with trimethoprim-sulfamethoxazole is recommended for all non-sulfa-allergic patients with ANCA-associated vasculitis receiving immunosuppressive therapy including rituximab. Patients who have a sulfa allergy can be desensitized against the drug. Those who fail this approach or have other contraindications for the use of this drug should be given other agents for PCP prophylaxis. Patients receiving methotrexate for remission induction or maintenance should also receive PCP prophylaxis. This can be safely accomplished with trimethoprim-sulfamethoxazole at recommended doses for this purpose, provided that folic acid, 1 mg daily, is also given. Patients undergoing intense immunosuppression during the remission induction phase may also benefit from prophylactic antifungal therapy. Finally, every patient treated with glucocorticoids for ANCA-associated vasculitis should receive osteoporosis prophylaxis with calcium and vitamin D supplements and possibly bisphosphonates.

Treatment of Tracheobronchial Disease in GPA

The management of tracheobronchial involvement in GPA patients requires an individualized approach and goes beyond standard immunosuppressive therapy. Tracheobronchial inflammatory lesions may be more resistant to systemic immunosuppressive therapy than other disease manifestations. High-dose inhaled glucocorticoids are an integral part of therapy for patients with airway involvement, as they may facilitate the tapering of oral glucocorticoid dosing. Airway obstruction due to scarring may progress during otherwise successful immunosuppressive therapy, causing fixed airway obstructions that will only respond to dilation procedures or placement of silastic airway stents. Tracheo- or bronchomalacia with dynamic airway collapse also may benefit from airway stent placement or from continuous positive airway pressure treatment. Tracheobronchial inflammation of GPA is often associated with persistent or recurrent airway infections with *S. aureus* or *Pseudomonas aeruginosa*. These should not be dismissed as "colonizers" but treated with antibiotics according to antimicrobial susceptibility results, as these infections may play a pathogenic role as "antigenic drivers" of the autoimmune inflammation. Finally, as silent gastroesophageal reflux may induce or aggravate airway inflammation, patients should be instructed in the use of dietary and behavioral reflux precautions in addition to acid-blocking therapy.

Treatment of Interstitial Lung Disease and ANCA with or without MPA

The current literature supports the following practical management approach to patients with ILD and MPO-ANCA with or without overt signs of MPA.[72] Patients with any ILD and active MPA should receive standard remission induction immunosuppressive therapy for severe MPA, usually consisting of glucocorticoids in combination with either cyclophosphamide or rituximab.[41] Patients with a positive MPO-ANCA and an ILD characterized by radiographic changes of NSIP or other inflammatory features such as bronchiolitis may need further diagnostic testing to rule out signs of active vasculitis, particularly diffuse alveolar hemorrhage. Once ruled out, such patients should be given a trial of glucocorticoids together with either azathioprine or mycophenolate mofetil as glucocorticoid-sparing and maintenance agent. Patients with usual interstitial pneumonia (UIP) pattern and positive MPO-ANCA but without signs of vasculitis need to be monitored carefully for the future development of vasculitis but should not receive immunosuppressive therapy, as this has been shown to increase the mortality of patients with UIP.[73] These patients should be offered antifibrotic therapy.

■ Treatment of Eosinophilic Granulomatosis with Polyangiitis

Even though mortality of EGPA is lower than that of GPA or MPA, the management of EGPA remains a challenge. The management concepts for EGPA are modeled after those for GPA and MPA. Patients should benefit from a multidisciplinary evaluation at a center of excellence and expertise with the disease. As all treatment aims to minimize tissue damage caused by disease activity or treatment toxicity, the diagnosis should be established as early as possible, the inflammation needs to be controlled as effectively as possible, and drug toxicities including those associated with cumulative glucocorticoid exposure should be prevented as best as possible. For EGPA this means to effectively target eosinophils and their activity while at the same time minimizing glucocorticoid exposure by preventing disease relapses and optimizing the management of chronic asthma and rhinosinusitis.[74,75]

Treatment choices for EGPA are stratified by disease severity. "Severe" disease is defined as life- or organ-threatening, comprising heart, gastrointestinal, kidney and CNS involvement as well as mononeuritis multiplex and diffuse alveolar hemorrhage. Other disease manifestations and organ involvement including nose or sinus disease, asthma and eosinophilic pulmonary infiltrates, or pulmonary nodules or skin vasculitis are considered "nonsevere" disease. The term *refractory disease* refers to disease activity that flares during glucocorticoid tapers or requires doses of 7.5 mg of prednisone or greater to control disease activity.

Glucocorticoids are used as primary remission induction agent for all patients. There are no clinical trials that provide clear guidance regarding glucocorticoids in EGPA. The reports from the French Vasculitis Study Group are difficult to interpret with respect to this disease, because patients with EGPA were not separated from those with polyarteritis nodosa and MPA, two diseases with distinct clinical manifestations, pathophysiology, and prognosis.[76,77] Yet, these studies suggest that it is appropriate to treat EGPA according to the principles applied to the management of GPA and MPA. In patients with "nonsevere" disease, standard disease-modifying drugs like azathioprine, methotrexate, or mycophenolate mofetil are customarily used as glucocorticoid-sparing agents if the prednisone dose cannot be reduced down to 10 mg per day without relapsing disease activity.[78] For patients with "severe" disease manifestations, additional immunosuppressive agents such as cyclophosphamide or rituximab are given in conjunction with glucocorticoids for induction of remission. Cyclophosphamide is the preferred agent for heart, gastrointestinal, peripheral, and central nervous system involvement. When cyclophosphamide is used for induction of remission, it should be replaced when remission has been achieved after 4 to 6 months by another glucocorticoid-sparing agent such as azathioprine for maintenance of remission.[78]

Rituximab has also been used for patients with EGPA, particularly if patients are MPO-ANCA positive and present with predominant small vessel vasculitis disease manifestations including kidney involvement or the rare occurrence of DAH.[79,80] Rituximab has also been shown to allow significant glucocorticoid dose reductions in patients with EGPA, even when glucocorticoids were primarily used for the control of severe chronic asthma.[80,81]

Most recently, biologic therapy targeting interleukin 5 (IL-5), which is elevated in EGPA and known to induce the proliferation and maturation of eosinophils, has shown promise as an effective glucocorticoid-sparing approach in EGPA. In a large, randomized, double-blind, placebo-controlled, phase 3 trial, mepolizumab demonstrated significant and clinically relevant glucocorticoid-sparing effects in the majority of patients with EGPA.[75,82] However, patients with severe eosinophil-driven or vasculitic disease manifestations were excluded from the trial, and consequently the effect of IL-5 targeted therapy in these circumstances remains unclear.[82]

In a recent phase 2 study, benralizumab, a monoclonal antibody that targets the IL-5 receptor α subunit, showed safety and efficacy in the treatment of EGPA.[83] A randomized, double-blind, double dummy–controlled, phase 3 trial comparing benralizumab to mepolizumab is ongoing. Refractory disease and disease dominated by difficult-to-control eosinophilic inflammation may respond to interferon α (IFN-α) therapy.[84] However, continued long-term IFN-α therapy may be necessary, and this treatment carries the risk of substantial toxicity.

OTHER DISORDERS PRESENTING WITH PULMONARY VASCULITIS

Below we consider a wide variety of entities characterized by pulmonary vasculitis, including giant-cell arteritis, Takayasu arteritis, polyarteritis nodosa, Behçet disease, idiopathic pauci-immune pulmonary capillaritis, and systemic lupus erythematosus, among others.

■ Giant-Cell Arteritis

Giant-cell arteritis (GCA) is a generalized inflammatory disorder involving large- and medium-sized arteries.[85] GCA is the most common form of vasculitis in the northern hemisphere and affects predominantly elderly patients. It is often associated with polymyalgia rheumatica and is considered a systemic inflammatory syndrome often presenting with nonspecific systemic symptoms such as low-grade fever, malaise, and weight loss. New-onset headache, scalp tenderness, facial pain, or jaw claudication are the most common symptoms of GCA. Transient or permanent vision loss affects 20% and 10% of patients, respectively. Temporal arteries are often palpably tender or nodular, and pulses are decreased. Markedly elevated markers of inflammation—erythrocyte sedimentation rate (ESR) and C-reactive protein—are found in most if not all patients. Granulomatous inflammation of the wall of affected vessels is the histopathologic finding of temporal artery biopsies.

Respiratory symptoms have been reported in up to 25% of patients. Cough, hoarseness, and throat pain usually resolve promptly with prednisone therapy.[86] Chest roentgenograms and pulmonary function tests rarely show abnormalities attributable to the disease. Occasionally respiratory symptoms are the initial manifestations of giant-cell arteritis. Therefore, this possibility should be considered in any elderly patient with new onset of cough, hoarseness, or throat pain without other identifiable cause, and it is reasonable to measure the ESR in such patients. Isolated cases with pleural effusion or multinodular pulmonary lesions have also been reported in giant cell arteritis. Such cases are difficult to interpret. Particularly in the latter situation, GPA should be considered in the differential diagnosis, because it may also present with temporal arteritis. Glucocorticoid-sparing agents such as methotrexate are recommended for selected patients with giant-cell arteritis. More recently, high-quality evidence has shown that tocilizumab (humanized monoclonal antibody against the interleukin 6 receptor) is an effective glucocorticoid-sparing agent in these patients and has been approved for this condition.[87,88]

■ Takayasu Arteritis

Takayasu arteritis (TAK) is a large vessel vasculitis predominantly affecting the aorta and its major branches, usually in young patients.[85] Gender distribution and preferentially affected vascular territories vary in different parts of the world.[89] TAK is a chronically relapsing disease that may present with nonspecific constitutional symptoms, low-grade fever, and arthralgias and myalgias. Variable pulses in affected vascular territories are typical exam findings. Claudication, renovascular hypertension, pulmonary hypertension, and ischemia in distal tissues are disabling consequences.[89]

TAK affects large- and medium-size pulmonary vessels in the form of a unique arteriopathy.[90] The inflammatory infiltrate of the vessel walls consists predominantly of lymphocytes, and giant cells are a prominent feature of the inflammation. Pulmonary artery stenosis and occlusion are the result of progressive defects in the outer media and ingrowth of granulation tissue–like capillaries, thickening of the intima, and proliferation of subendothelial smooth muscle cells; these changes can also cause pulmonary hypertension of variable severity in up to one-half of all patients. The involvement of pulmonary arteries is common but often asymptomatic. It is detectable by conventional angiography, perfusion scan, or magnetic resonance angiography. CT may show areas of mosaic attenuation as a result of regional hypoperfusion, subpleural reticulolinear changes, and pleural thickening. Chest roentgenograms are usually normal. Fistula formation between pulmonary artery branches and bronchial arteries, as well as nonspecific inflammatory interstitial lung disease, also have been reported.

Therapy for TAK consists primarily of immunosuppression with glucocorticoids. Other immunosuppressive agents, including methotrexate, are used as in conjunction with glucocorticoids for remission induction and as glucocorticoid-sparing agents for remission maintenance. Unfortunately, many patients relapse when the glucocorticoid dose is reduced below 15 mg daily. There are no controlled studies with anti–TNF-α agents such as infliximab in TAK. Observational data, mostly with infliximab, suggest that these agents improve event-free survival and decrease disease flares and organ damage. Treatment with tocilizumab targeting interleukin 6 has also been reported to be of benefit and is recommended for patients with relapsing disease.[87,88] In addition, small case series have reported beneficial effects with rituximab.[91] Vascular bypass or stenting procedures may be beneficial in severe disease, but their long-term benefits remain unclear.

■ Classic Polyarteritis Nodosa

Since its formal separation from microscopic polyangiitis, this form of vasculitis affecting predominantly medium-sized vessels is diagnosed rarely. Because it does not affect capillaries, it does not cause either glomerulonephritis or diffuse alveolar hemorrhage. However, there are rare case reports of classic polyarteritis nodosa with lung hemorrhage caused by involvement of the bronchial or bronchiolar arteries.[92] Most cases of classic polyarteritis nodosa diagnosed today are associated with viral infections, specifically hepatitis B and C. Consequently, antiviral therapy plays a prominent role in the management of such cases in addition to immunosuppression. Classic polyarteritis nodosa is far less likely to relapse than microscopic polyangiitis, and therefore can generally be treated with a shorter course of immunosuppression.

■ Behçet Disease

Behçet disease is a rare, chronically relapsing, systemic inflammatory disorder characterized by aphthous oral ulcers and at least two or more of the following: aphthous genital ulcers, uveitis, cutaneous nodules or pustules, or meningoencephalitis. Respiratory manifestations are common in Behçet disease and include cough, hemoptysis, chest pain, and dyspnea.[93] Hemoptysis is often massive and fatal. The vasculitis of Behçet disease is immune complex–mediated and may affect vessels of all sizes. If the veins are affected, secondary thrombosis with major venous occlusion can occur. This type of thrombosis may not be preventable by anticoagulation, but the use of aspirin 81 mg/day has been advocated. Massive hemoptysis is the result of destruction of the elastic lamina of pulmonary arteries leading to the characteristic aneurysm formation, secondary erosion of bronchi, and arterial–bronchial fistulae. Pulmonary artery aneurysms are detectable by CT or MR angiography, and pulmonary angiography is no longer necessary. Recurrent pneumonia as well as bronchial obstruction as a consequence of mucosal inflammation also have been described.

Therapy of the underlying disease consists of immunosuppression. Prednisone alone may not be sufficient to control the vasculitis. The addition of other drugs, such as colchicine, chlorambucil, methotrexate, cyclosporine, or azathioprine, is recommended. The addition of azathioprine or cyclophosphamide to glucocorticoids has resulted in resolution of pulmonary aneurysms. More recently, observational studies have shown that TNF-α inhibitors seem to be a highly effective option for remission induction of refractory Behçet disease with vascular involvement with acceptable safety data.[94] Once pulmonary arteritis has been identified in these patients, anticoagulation should be avoided. The prognosis of pulmonary involvement is poor. About one-third of patients die within 2 years of developing pulmonary involvement, most from fatal pulmonary hemorrhage. Embolization therapy may be used as treatment and prevention of hemorrhage from pulmonary artery aneurysms.

■ Idiopathic Pauci-immune Pulmonary Capillaritis

Idiopathic pauci-immune pulmonary capillaritis is a rare diagnosis of exclusion.[95,96] The diagnosis is based on the histopathologic confirmation of capillaritis in the absence of (1) a defined systemic disease process with extrapulmonary organ involvement, (2) specific circulating autoantibodies, and (3) detectable immune deposits on the lung biopsy specimen. This isolated pauci-immune pulmonary capillaritis is histopathologically indistinguishable from that of ANCA-associated vasculitis. Despite the lack of clear evidence of an immune etiology, the cases reported to date have responded to immunosuppressive therapy following the principles of the management of ANCA-associated vasculitis with diffuse alveolar hemorrhage—that is, remission induction therapy with the combination of glucocorticoids and cyclophosphamide or rituximab.[95–97] Since disease relapses have been described, remission maintenance therapy should be considered for individual cases.

■ Systemic Lupus Erythematosus and Other Collagen Vascular Disorders

The disease manifestations of systemic lupus erythematosus (SLE) are highly variable. Pulmonary capillaritis leading to diffuse alveolar hemorrhage is rare in patients with SLE. However, it represents one of the most serious complications of the disease. In contrast to the pauci-immune pathology of ANCA-associated vasculitis, prominent immune complex deposits can be detected by direct immunofluorescence in the affected tissue of patients with SLE (Fig. 74-18). Hence, the development of pulmonary capillaritis in SLE is thought to be immune complex mediated.

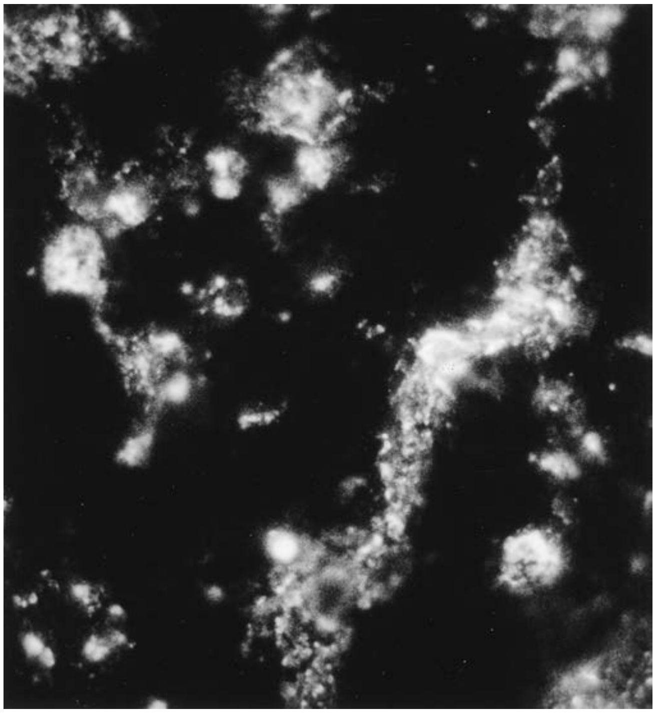

Figure 74-18 Lung biopsy of a patient with lupus erythematosus and alveolar hemorrhage showing so-called lumpy, bumpy deposition of immune complexes as demonstrated by direct immunofluorescence.

The onset of diffuse alveolar hemorrhage in patients with SLE is usually abrupt, and it is seldom the first sign of SLE. In the overwhelming majority of patients, the rapid development of pulmonary infiltrates is associated with fever. Hemoptysis may be absent in up to one-half of patients. Consequently, the differentiation of diffuse alveolar hemorrhage from infection may be difficult in patients with SLE and may require a diagnostic bronchoalveolar lavage. Mechanical ventilation, infection, and cyclophosphamide therapy were identified as negative prognostic factors in one cohort.[98] However, no multivariate analysis was performed in that cohort study, and these factors may simply identify patients with more severe disease. The reported mortality from diffuse alveolar hemorrhage in SLE varies widely, between 0% and 90%. Treatment mainly consists of glucocorticoids and cyclophosphamide.[99,100] The use of PLEX has been suggested, but its benefit remains unproved.[100]

In a recent systematic review of patients with SLE presenting with diffuse alveolar hemorrhage (174 episodes of alveolar hemorrhage in 140 patients), the overall survival was 61%, corticosteroids were nearly universally used therapeutically, cyclophosphamide was used in 55% of patients, and PLEX was used in 31% of the patients but did not appear to be associated with survival.[101] Rituximab use in these patients has been described in case reports with conflicting results.[100]

Respiratory complications are very common in all other types of collagen vascular or connective tissue disorders. However, pulmonary capillaritis presenting as diffuse alveolar hemorrhage is rare. Isolated cases have been reported with polymyositis, rheumatoid arthritis, and mixed connective tissue disease. Consequently, serologic testing performed as part of an evaluation of diffuse alveolar hemorrhage should include studies aimed at the identification of these potential underlying disease entities.

■ Antiphospholipid Syndrome

Antiphospholipid syndrome is defined by arterial and venous thromboses, and/or recurrent miscarriages occurring in patients with antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant, or both). If antiphospholipid syndrome occurs in the context of another autoimmune disease, malignancy, or drug exposure, it is labeled secondary antiphospholipid syndrome. In the absence of other coexisting disorders, it is considered primary. Hypercoagulability can cause pulmonary embolism and infarction, pulmonary microthrombosis, and pulmonary arterial thrombosis with secondary pulmonary hypertension as consequence (i.e., chronic thromboembolic pulmonary hypertension). However, primary pulmonary hypertension also has been reported in antiphospholipid syndrome. Acute respiratory distress syndrome (ARDS) is another possible complication of catastrophic antiphospholipid syndrome. Antiphospholipid syndrome can also be complicated by diffuse alveolar hemorrhage, presenting with cough, dyspnea, fever, and bilateral pulmonary infiltrates. Because of this nonspecific clinical presentation and the lack of hemoptysis in more than one-half of the reported antiphospholipid syndrome patients with alveolar hemorrhage, early performance of bronchoalveolar lavage may help to distinguish alveolar hemorrhage from ARDS. Tissue necrosis from microthrombosis as well as pulmonary capillaritis have been implicated as the cause of alveolar hemorrhage in antiphospholipid syndrome. As in SLE, the capillaritis of antiphospholipid syndrome appears to be immune complex–mediated.

Most patients respond to glucocorticoids.[102,103] Yet, the coexistence of thrombosis and capillaritis with alveolar hemorrhage represents a therapeutic dilemma, as anticoagulation may need to be interrupted to control the hemorrhage. The largest case series of primary antiphospholipid syndrome–associated diffuse alveolar hemorrhage demonstrated a very poor prognosis with limited therapeutic options that included immunosuppression. Agents such as azathioprine or mycophenolate mofetil, in combination with glucocorticoids, failed to control disease activity.[102] However, cyclophosphamide or rituximab were associated with the highest likelihood of remission induction and should be considered early. This case series also reported the use of PLEX in three patients, with no response observed in any of these patients. However, others have reported improved outcomes with the use of early PLEX in addition to immunosuppressive therapy.[104]

■ Cryoglobulinemic Vasculitis

Diffuse alveolar hemorrhage has been reported as a rare complication of cryoglobulinemic vasculitis with an associated poor prognosis. Among 125 patients hospitalized with cryoglobulinemia over a 23-year time period, 4 patients developed alveolar hemorrhage.[105] These were analyzed in conjunction with 6 additional cases from the literature reported to that date. Of these 10 patients, 9 also had glomerulonephritis, and 6 deaths were attributed to the diffuse alveolar hemorrhage.[105] Treatment consisted of aggressive immunosuppression in various combinations with or without PLEX.[105]

■ Anti–glomerular Basement Membrane Disease

Historically the syndrome of diffuse alveolar hemorrhage and glomerulonephritis has been called Goodpasture syndrome. To avoid any confusion and reflect our understanding of the pathogenesis of the disease, the 2012 Chapel Hill Consensus conference recommended avoidance of the eponym and the use of the term anti-GBM disease for alveolar hemorrhage or necrotizing glomerulonephritis caused by autoantibodies directed against the NC1-domain of the α3 chain of basement membrane collagen type IV.[6] Autoantibodies can only access this epitope in the basement membranes of kidneys and lungs. Diffuse alveolar hemorrhage is common in anti-GBM disease but is thought to require an additional inhalational injury, particularly smoking, for the development of the pulmonary manifestation of this disease. Isolated alveolar hemorrhage in the absence of renal disease is rare in anti-GBM disease. The finding of circulating anti-GBM autoantibodies in the serum may facilitate the early implementation of appropriate therapy. However, methods used for their detection are of highly variable sensitivity and specificity, and a definitive diagnosis depends on the documentation of linear anti-GBM deposits in the kidney or lung (Fig. 74-19).

In most patients, tissue from the kidney is more easily accessible for histopathologic evaluation than lung tissue. Anti-GBM disease is arguably not a vasculitis. Bland pulmonary hemorrhage is the most frequently described histopathologic pattern in diffuse alveolar hemorrhage associated with anti-GBM disease. However, capillaritis as a secondary histopathologic feature has been encountered in some patients.

Early implementation of immunosuppressive therapy with high doses of glucocorticoids in conjunction with PLEX is the key to a favorable outcome in patients with anti-GBM disease.[106] Cyclophosphamide or rituximab can be added to prevent subsequent rebound antibody formation.[106–108] The use of extracorporeal membrane oxygenation has been reported as salvage therapy for isolated cases of severe diffuse alveolar hemorrhage caused by anti-GBM disease.[109,110]

■ IgA Vasculitis (Henoch-Schönlein)

Henoch-Schönlein purpura has been renamed as *IgA vasculitis (Henoch-Schönlein)* at the 2012 Chapel Hill Consensus Conference to reflect the evolving understanding of its pathogenesis. The disease affects predominantly children and young adults and presents with fever, purpura, large joint arthralgias and arthritis, gastrointestinal symptoms, and usually self-limited and mild proliferative and necrotizing glomerulonephritis.[1] The diagnosis is based on characteristic IgA deposits detected in skin- or kidney biopsies. Pulmonary manifestations in IgA vasculitis are rare. IgA deposits along the pulmonary capillary walls, analogous to those found in vessels of the skin and glomeruli of affected kidneys, are pathognomonic features of IgA vasculitis, detectable by direct immunofluorescence. Diffuse alveolar hemorrhage has been reported as the cause of several deaths in patients with IgA vasculitis;[111] its presence in IgA vasculitis should thus warrant aggressive immunosuppressive therapy.

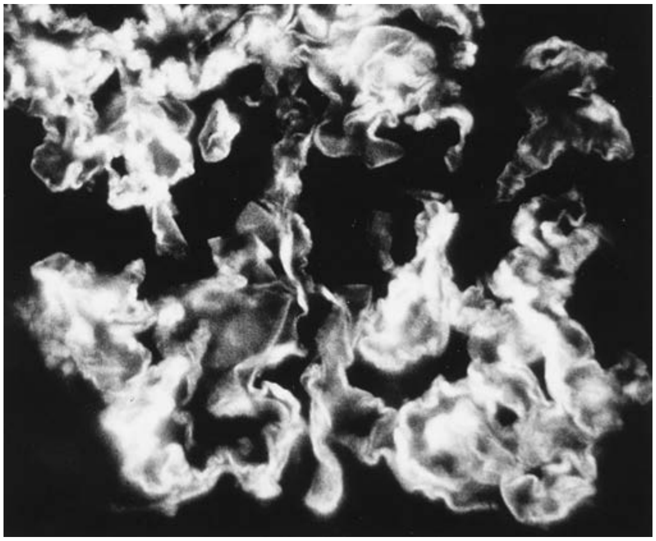

Figure 74-19 Kidney biopsy of a patient with anti–glomerular basement membrane (GBM) disease showing linear immunofluorescence of the glomerular basement membrane due to fixation of IgG anti-GBM antibodies.

■ Drug-Induced Vasculitis

The list of drugs described in association with vasculitis includes a long list of therapeutic agents as well as drugs of abuse.[112] The clinical spectrum of drug-induced vasculitis ranges from isolated and mild vasculitis of the skin to severe multiorgan system disease. Small- to medium-sized vessels are usually affected. Based on clinical manifestations, drug-induced vasculitis cannot be distinguished from the primary vasculitis syndromes.

The following drug-induced syndromes merit special attention. First, a variety of drugs including propyl-thiouracil, D-penicillamine, hydralazine, sulfasalazine, minocycline, and allopurinol can induce an ANCA-associated vasculitis. Pulmonary capillaritis as a manifestation of an ANCA-associated vasculitis induced by these agents is well documented. Drug-induced ANCA-associated vasculitis should be treated with immunosuppression according to the principles for primary ANCA-associated vasculitis. However, once the offending drug has been eliminated, the likelihood of a relapse seems low.

The use of all-*trans*-retinoic acid in acute promyelocytic leukemia can cause a syndrome of fever, leukocytosis, fluid retention, hemorrhage, thrombosis, and organ failure. Pulmonary complications of this syndrome are frequent, and pulmonary capillaritis has been reported in this context.

Some chronic nasal cocaine abusers develop severe midline destructive lesions. In its early stage, such a lesion is clinically and histopathologically difficult to differentiate from limited GPA, particularly in patients who do not volunteer the history of abuse.[113]

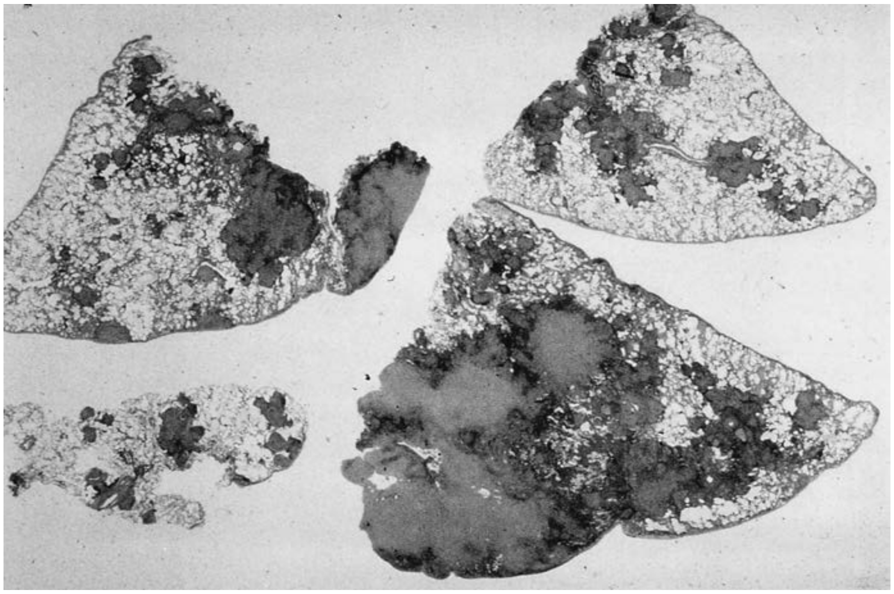

Figure 74-20 Low-power photomicrograph of lung revealing coalescing necrotizing granulomas in a patient with necrotizing sarcoid granulomatosis.

The presence of ANCA reacting with human neutrophil elastase (HNE) appears to be an immunologic marker separating patients with cocaine-induced midline destructive lesions from those with GPA.[114]

More recently, levamisole has become a common adulterant of cocaine.[115,116] Levamisole is a polyclonal B cell–stimulating agent that can induce a variety of autoantibodies including antigranulocyte antibodies, antiphospholipid antibodies, and ANCA. The ANCA reactivity is directed against multiple target antigens including MPO, PR3, and HNE.[115,116] The clinical picture of patients exposed to levamisole can mimic systemic vasculitis.

■ Pulmonary Capillaritis after Lung Transplantation

Several cases of pulmonary capillaritis after lung transplantation have been described in the literature. In the largest case series that included 40 episodes of capillaritis in 35 patients, the presentation of posttransplant capillaritis was similar to that of acute cellular rejection but with a distinct histologic pattern and a dissimilar response to corticosteroid therapy.[117] Pulmonary capillaritis is now believed to be a manifestation of antibody-mediated acute rejection and typically occurs in association with development of donor-specific alloantibodies. Early histologic diagnosis and aggressive immunosuppression, in conjunction with PLEX, is employed to control the inflammatory activity and prevent relapses.

■ Necrotizing Sarcoid Granulomatosis

Vasculitis is a prominent histopathologic feature of necrotizing sarcoid granulomatosis. The disease is usually limited to the lungs. The characteristic pulmonary nodules are bilateral and may be an incidental finding in asymptomatic patients. Alternatively, patients may complain of cough, dyspnea, and/or sputum production. Generalized constitutional symptoms occur rarely. The differential diagnosis of necrotizing sarcoid granulomatosis includes primarily infectious processes. Special sputum and tissue stains and cultures should always be obtained to exclude mycobacterial or fungal disease. Clinically, these patients are difficult to differentiate from "nonsevere" GPA. Histopathologically, there are characteristic necrotizing epithelioid granulomas that may form aggregates (Fig. 74-20). In contrast to GPA, these granulomas are well circumscribed. Vasculitis is a central histopathologic feature of necrotizing sarcoid granulomatosis. Liebow originally described three types of vasculitis: an epithelioid-granulomatous form, a form reminiscent of giant-cell arteritis with prominent histiocytes and multinucleated giant cells in the inflammatory infiltrate of the vessel wall, and a lymphocytic form lacking granuloma formation and giant cells. The separation from sarcoidosis remains controversial. Yet, the extensive vasculitis and necrosis seen in necrotizing sarcoid granulomatosis are unusual for sarcoidosis. The chest roentgenographic appearance of pulmonary nodules, or masses and pleural involvement, are also atypical for sarcoidosis. Finally, extrapulmonary involvement has only rarely been documented in necrotizing sarcoid granulomatosis.

It is debatable whether necrotizing sarcoid granulomatosis should be included with the systemic vasculitides. Most authors would argue against this inclusion because of its limitation to the lungs and good prognosis (spontaneous remission may occur). Therapeutically, necrotizing sarcoid granulomatosis is approached in similar fashion to chronic pulmonary sarcoidosis, with oral glucocorticoid therapy representing the primary treatment of choice.

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CHAPTER 75

Pulmonary Arteriovenous Malformations

Tyler J. Peck
Josanna M. Rodriguez-Lopez

INTRODUCTION

In the normal pulmonary circulation, blood leaves the right ventricle of the heart via the pulmonary artery, and the entire blood volume is routed to the pulmonary capillary bed adjacent to alveoli, allowing for gas exchange. The normal diameter of blood vessels making up the pulmonary capillary bed is approximately 6 μm.[1] After drainage from the pulmonary capillaries, the blood then returns to the heart via the pulmonary veins. Pulmonary arteriovenous malformations (PAVMs) are abnormal vascular connections between pulmonary arteries and pulmonary veins, preventing exposure of blood to normal pulmonary capillaries and many times leading to hypoxemia due to shunting of deoxygenated blood into the pulmonary venous system and into the systemic circulation. Additionally, the size of these abnormal connections is typically larger than the size of pulmonary capillaries, allowing for transmission of particles in the blood stream (e.g., venous thromboemboli) from the venous circulation into the arterial circulation, leading to complications like stroke or septic emboli. Pulmonary AVMs are commonly aneurysmal and can frequently be seen macroscopically on advanced imaging (e.g., CT angiography).

Pulmonary AVMs were first described by Churton in 1897 in an autopsy case report of a 12-year-old boy with hemoptysis, epistaxis, and edema.[2] In the early 20th century, PAVMs were found to be associated with hereditary hemorrhagic telangiectasia[3] (HHT; also known as Osler–Weber–Rendu syndrome), a genetic vascular disorder manifesting with mucocutaneous telangiectasia and AVMs of various organ systems, including the lung. It is now known that at least 60% to 70% of PAVMs are associated with HHT,[4,5] although some reports indicate rates of up to 95%.[6]

In this chapter, we discuss the epidemiology, pathobiology, and etiologies of pulmonary AVMs, clinical manifestations and diagnostic evaluation of these abnormalities, associated complications, and management options.

EPIDEMIOLOGY OF PULMONARY AVMs

PAVMs are generally uncommon, occurring in only 3 cases among 15,000 consecutive autopsies performed at Johns Hopkins Hospital[7] (translating to a disease prevalence of 0.02%). However, disease frequency has been found to be higher in populations of patients with HHT—reported in case series as ranging from 17%[8] to 48%.[9] PAVMs occur about twice as often in women compared with men,[4,10] although a majority of cases identified in newborns occur in males.[11]

Disease frequency of HHT varies between populations, estimated at 1 in 8000 in a northern Japanese population,[12] 1 in 6000 in European populations,[13] and 1 in 16,500 the U.S. state of Vermont.[5] A study of U.S. insurance claims data found a disease prevalence of 0.33 cases per 10,000 individuals.[14] However, a few geographically isolated populations show higher prevalence, likely due to founder events; for example, 1 in 1331 individuals was found to be affected in the Afro-Caribbean population of the Netherlands Antilles.[15] These statistics likely underestimate the true disease prevalence of this rare disease that may be underrecognized.

PATHOLOGY

PAVMs are structurally made up of three components: a vascular aneurysmal sac, a feeding artery (or arteries), and a draining vein (or veins). A majority of PAVMs have a single feeding artery with a single draining vein (approximately 80%[16,17]) and are thus considered "simple." However, some PAVMs are categorized as "complex" given their more complicated anatomy with two or more feeding arteries and/or draining veins.

The aneurysmal sac of PAVMs typically has paper-thin walls made up by a thin-walled vascular channel lined with endothelium and scant surrounding connective tissue stroma that does not have communication with surrounding lung tissue.[7] The vascular channel may be made up of a large single sac, a plexiform mass of dilated vascular channels, or a dilated and often tortuous communication between artery and vein.[18,19] These dilated vascular channels gradually increase in size over time[8,20] and acutely with pregnancy.

PAVMs are most commonly found in the lower lobes of the lung, attributed to increased hydrostatic pressure in the dependent portions of the lung.[16] In a case series detailing pathologic anatomy in 350 patients with PAVMs, 75% of PAVMs were unilateral, 36% had multiple lesions, and half of those with multiple lesions had bilateral disease.[18,19] PAVM sacs typically range in diameter from microscopic up to 5 cm, although there are many case reports of larger PAVMs in select cases.[19]

A small subset of patients have diffuse PAVMs, a rare subtype associated with diffuse lung involvement, increased risk of complication, and worse prognosis compared to other patients with PAVM[21,22] (Fig. 75-1).

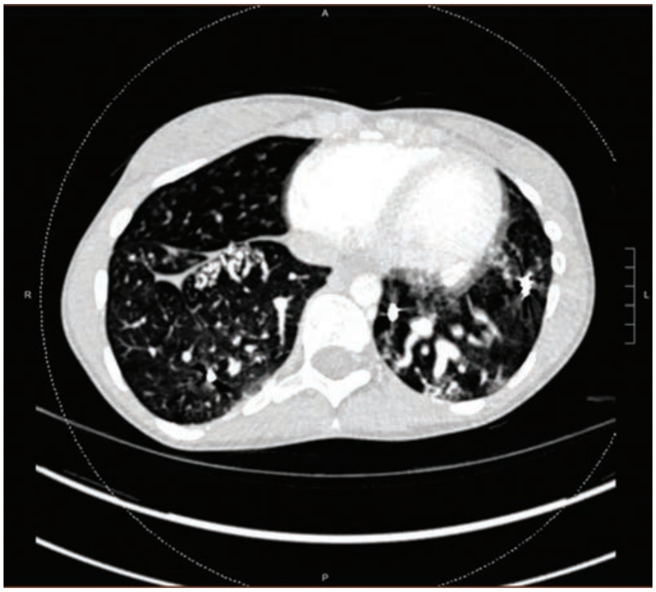

Figure 75-1 Diffuse, bilateral pulmonary AVMs in a 20-year-old woman without diagnosis of heredity hemorrhagic telangiectasia, with progression of PAVMs following prior coil embolization.

TABLE 75-1 Identified Genes Associated with Hereditary Hemorrhagic Telangiectasia and Pulmonary Arteriovenous Malformations

Gene—Protein	Chromosomal Location	Function	HHT Form	Frequency of Pulmonary AVMs
ENG—endoglin[123,124]	9q34	Transforming growth factor β (TGF-β)-binding protein found on endothelial cells	HHT1	85%[125]
ACVRL1 (also known as *ALK1*)—activin A receptor, type II–like 1[126]	12q13	Type I cell-surface receptor for the TGF-β superfamily of ligands	HHT2	35%[125]
SMAD4 (also known as *MADH4*)—SMAD family member 4[34,127,128]	18q21	Downstream mediator of TGF-β signaling, acting as a transcription factor	Juvenile polyposis/HHT syndrome (JPHT)	50%[127]

GENETICS AND PATHOGENESIS

Most PAVMs are congenital and are associated with HHT, an autosomal dominant disease that primarily affects blood vessels. HHT is associated with mutations in *ENG*, *ACVRL1*, or *SMAD4* (Table 75-1). However, approximately 15% of patients with a clinical diagnosis of HHT do not have identified mutations in these genes, suggesting the presence of additional causative mutations for HHT.[23–26] Additional HHT-associated genes have been isolated in select cases lacking mutations in the aforementioned identified genes, but these are less well understood and are under investigation.[27,28]

ENG, *ACVRL1*, and *SMAD4* gene products play various roles in the transforming growth factor β (TGF-β) signaling pathway, which has been implicated in angiogenesis and vascular remodeling.[25] TGF-β signaling regulates endothelial cell function through either stimulation or inhibition of their proliferation.[25] Animal studies have shown that *endoglin* and *ALK1* knockout mice die mid-gestation due to defective vascular development including excessive fusion of capillaries, dilated major blood vessels, abnormal differentiation and localization of vascular smooth muscle cells, and development of AVMs.[29–33] Knockout animals for *SMAD4* also have increased formation of AVMs, endothelial cell proliferation, and disruption of artery-vein identity.[34] ACVRL1 (or ALK1, as this gene product is commonly known) serves as a type 1 receptor for the TGF-β/BMP superfamily, and endoglin (ENG) is a coreceptor that promotes TGF-β signaling via the ACVRL1 receptor. This receptor complex has kinase activity that activates a SMAD signaling cascade, leading to the activation and translocation of transcription factors into the nucleus where they function to activate or repress transcription of specific target genes that modulate vascular responses.[25,35] SMAD4 is an intracellular mediator of TGF-β signaling as part of the SMAD signaling cascade, forming a heteromeric complex with other SMAD molecules activated by cell-surface receptors and translocating to the nucleus to modulate gene expression via endothelial-specific transcriptional modulators[25,34] (Fig. 75-2).

Analysis of mutations in *ENG* and *ACVRL1* in patients with HHT shows loss-of-function mutations in nearly all cases.[26] It remains less clear why vascular abnormalities occur in specific sites in the various phenotypes of HHT, likely owing to haploinsufficiency[36–38] or somatic mutations leading to biallelic loss of gene function.[39]

The pathogenesis of PAVMs is not clearly understood aside from its foundation in aberrant vascular development and remodeling associated with disruptions in the TGF-β signaling pathway as described above. Hypotheses regarding development of PAVMs include a defect in terminal arterial loops allowing dilation of thin-walled capillary sacs,[40] incomplete resorption of vascular septae separating the arterial and venous plexuses that normally anastomose during fetal development,[41] and failure of capillary development during fetal development.[41]

ETIOLOGIES OF PULMONARY AVMs

The most common disease associated with PAVMs is HHT, primarily due to mutations in *ENG*, *ACVRL1*, or *SMAD4*, as previously described. Various reports indicate that at least 60% to 70% and up to 95% of PAVMs are associated with HHT.[4–6] Additional associations reported in the literature include schistosomiasis,[42] mitral stenosis,[43] trauma,[43] actinomycosis,[43] Fanconi syndrome,[44] metastatic thyroid cancer,[45] and surgical correction of congenital heart disease.[46,47] However, many of these associations may be spurious rather than causative, as many represent single case reports.

Idiopathic PAVMs, not associated with HHT, are more commonly solitary and more evenly distributed throughout the lung. Because they are often solitary, idiopathic PAVMs are associated with fewer complications and are more easily treated with embolotherapy.[48]

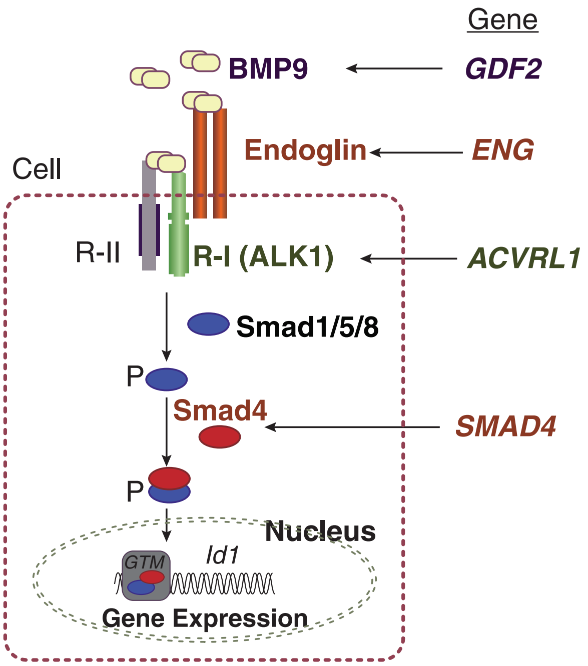

Figure 75-2 TGF-β cell signaling pathway, including the gene products of *ENG*, *ACVRL1*, and *SMAD4*, mutations in which are associated with HHT. *(Reproduced with permission from Wooderchak-Donahue WL, McDonald J, O'Fallon B, et al. BMP9 mutations cause a vascular-anomaly syndrome with phenotypic overlap with hereditary hemorrhagic telangiectasia. Am J Hum Genet. 2013;93(3):530–537.)*

Hepatic cirrhosis can cause a condition called hepatopulmonary syndrome (HPS), a pathologic dilatation of small vessels in the pulmonary circulation that leads to hypoxemia.[49] The pathology of HPS is distinctly different from that of PAVMs. HPS is caused by the release of vasoactive mediators including tumor necrosis factor α (TNF-α) and nitric oxide associated with portal hypertension and increased rate of enteric translocation of bacteria.[50] In contrast to PAVMs, HPS does not typically cause direct arteriovenous connection.

CLINICAL MANIFESTATIONS

Pulmonary AVMs are commonly asymptomatic, identified in many cases as an incidental finding on chest imaging or through screening of patients diagnosed with HHT. In general, symptoms of PAVM include dyspnea, exercise intolerance, and hemoptysis. Dyspnea on exertion is the most common respiratory symptom of PAVM but is not universally present, occurring in 14% to 59% of patients.[6,51–53] Hemoptysis is less common, occurring in 9% to 30% of cases[51,52] and ranging in severity from minor self-limited bleeding to massive hemoptysis. The severity of symptoms also depends on the disease burden of PAVMs in terms of number, size, and shunt fraction. Patients with diffuse microvascular PAVM are nearly universally symptomatic.[54] Given the significant overlap with HHT, many patients who have PAVM associated with HHT have nonpulmonary symptoms and features related to HHT rather than symptoms due to PAVM itself—for example, epistaxis is reported in up to 79% of patients with PAVM.[55]

There are several findings on physical examination that are associated with PAVM, although many cases lack physical findings. Hypoxemia, an effect of right-to-left intrapulmonary shunting in PAVM, is more common in severe cases with higher shunt fraction. A case series of patients with idiopathic PAVM (excluding patients with HHT diagnosis) found that 20% of patients had hypoxemia on presentation.[48] A much larger proportion of patients with diffuse PAVM are hypoxemic, 100% in one case series.[21] When severe, hypoxemia may be associated with cyanosis on exam.

In addition to hypoxemia, some patients may have positional variation in dyspnea and hypoxemia, referred to as platypnea and orthodeoxia, respectively. Platypnea is described as shortness of breath in the upright position that improves with reclining into a recumbent position[56] and is a rare finding in PAVM[57] despite being classically described. Orthodeoxia, defined as oxygen desaturation (by ≥2%) of arterial blood in the upright position and improved in the recumbent position, is more common, reported in 29%[57] to 65%[58] of patients with PAVM. These findings occur due to the predominance of PAVM in the lower lobes of the lungs, which leads to increased fraction of pulmonary blood flow through PAVMs (as a portion of the total pulmonary blood flow) in the upright position due to gravity's effect on the distribution of lung perfusion.[59] Although these findings are described in PAVM, they are not specific to this condition and are found also in other causes of right-to-left shunt such as hepatopulmonary syndrome[60] and intracardiac shunt (for example, via atrial septal defect or patent foramen ovale).[61]

Pulmonary bruit, a murmur-like sound auscultated over a PAVM, has been reported in pooled case series as occurring in 43% of patients.[19,62] This sound is attributed to the increased turbulent flow through a dilated AVM and is most commonly heard in the lower lobes during inspiration.

Cutaneous findings in patients with PAVM include telangiectasia and clubbing. Telangiectasias are small, dilated blood vessels found near the surface of the skin or mucous membranes. They manifest as small red partially-blanchable blemishes and most commonly present on the face, lips, tongue, oral mucosa, conjunctivae, and fingertips/nailbeds.[5]

Telangiectasias occur in about half of patients with PAVM[19] and are found almost exclusively in patients whose PAVMs are due to underlying HHT. Although reported frequently in older case series (in up to 82% of cases),[19] digital clubbing in more recent case series is found much less commonly, ranging from 0%[48] to 19%.[62] Clubbing is more common in cases with severe hypoxemia and cyanosis and has been noted to improve following embolotherapy for PAVM.

The most common laboratory abnormality attributable to PAVM is polycythemia, reported in 75% of patients with diffuse PAVM.[21] This finding, also known as secondary erythrocytosis, occurs as a compensatory mechanism for chronic hypoxemia through increased erythropoiesis in patients with adequate iron stores and serves to maintain adequate arterial oxygen content despite decreased oxyhemoglobin saturation.[63] Many patients with HHT lack this finding due to iron-deficiency anemia associated with chronic blood loss via gastrointestinal AVMs.

In the absence of concomitant lung disease, pulmonary function testing in patients with PAVM typically reveals normal spirometry and lung volumes. PAVM has been shown to have no substantial impact on the mechanical properties of the lung, even in patients with numerous and bilateral vascular lesions.[64–66] In contrast, diffusing capacity may be reduced and the alveolar-arterial oxygen gradient increased, reflective of abnormal gas exchange.[64,66] Despite resting hypoxemia, patients with PAVM in the absence of concurrent lung disease demonstrate normal peak exercise capacity, as measured by maximum oxygen consumption ($\dot{V}O_{2max}$). This is facilitated by compensatory mechanisms to maintain normal oxygen delivery to tissues despite reduced oxyhemoglobin saturation: polycythemia (assuming adequate iron stores) and increased stroke.[65] Patients with PAVM display relative hyperventilation at rest and with exercise, the magnitude of which is directly related to the magnitude of right-to-left shunt.[64,65]

COMPLICATIONS ASSOCIATED WITH PULMONARY AVMs

There are several known complications associated with PAVMs. These are related to a few different mechanisms: the associated hypoxemia and systemic adaptations, the loss of filtration by the pulmonary capillary bed allowing for arterial embolic disease, and hemorrhage due to PAVM rupture. The primary organ systems affected by PAVM-related complications are the pulmonary and neurologic systems.

■ Pulmonary Complications

Well described as a clinical feature of PAVM, hypoxemia is typically asymptomatic and well tolerated in this population, likely due to compensatory mechanisms that increase oxygen delivery to peripheral tissues like increased blood hemoglobin concentration (polycythemia), increased cardiac output, and increased ventilation.[67] However, long-term effects of chronic hypoxemia and polycythemia are not well studied in this population.

Hemorrhagic complications of PAVM are feared due to their life-threatening nature but are relatively rare. Hemorrhage occurs due to rupture of a PAVM sac and can manifest as bleeding into the airways and subsequent hemoptysis or bleeding into the pleural space surrounding the lung with development of a hemothorax. The incidence of hemorrhage due to PAVM is increased in pregnancy when an increase in cardiac output, blood volume, and vascular distensibility as well as hormonal effects contribute to an increased risk of bleeding.[68] Ference et al. documented an 8% incidence of life-threatening pulmonary hemorrhage (defined as either massive hemoptysis or hemothorax requiring hospitalization) in HHT patients with PAVM, with 27% of these cases occurring in pregnant women.[69] Pulmonary hemorrhage can also occur years after embolotherapy for PAVM due to formation of bronchial artery collateral circulation. Occasionally, patients with HHT may have hemoptysis due to endobronchial telangiectasias with or without PAVM, an alternate mechanism of bleeding.

PAVMs in patients with HHT may be associated with pulmonary hypertension, and although this may not be a direct complication of PAVMs, development of PH in this population can lead to significant morbidity including right heart failure and death. Typically, PAVMs create a low-resistance circuit through the pulmonary vasculature, lowering the pulmonary vascular resistance. However, patients with HHT may also have high cardiac output due to liver AVMs or anemia (due to enteric AVMs and chronic blood loss) that leads to an increase in pulmonary artery pressures.[70] Rarely, patients with HHT and PAVMs associated with mutation in the *ACVRL1* gene may have pulmonary arterial hypertension (PAH), caused by small vessel vasculopathy typical of idiopathic and other forms of PAH.[70,71] These changes include intimal hyperplasia, medial thickening, in situ thrombosis, and plexiform lesions. Caution should be exercised if embolotherapy is considered as treatment for patients with PAVMs and pulmonary hypertension, as occlusion of low-resistance flow through PAVMs could lead to worsened pulmonary hypertension and right heart failure.

■ Neurologic Complications

Neurologic complications are the most common type of complication in PAVM, observed in about 30% of patients.[19] These include migraine headaches, ischemic strokes, transient ischemic attacks (TIAs), and brain abscesses. Most of these complications occur because PAVMs allow small emboli (either septic or thrombotic) to bypass the pulmonary capillary bed that typically acts as a filter between the systemic venous and arterial systems.

Migraine headache is the most common neurologic complication of PAVM, occurring in 21% to 43% of patients,[58,72,73] although some series report a frequency as low as 4%.[74] Proposed mechanisms include migraine triggering by paradoxical emboli and modified metabolism of vasoactive amines.[67]

Ischemic strokes occurred in approximately 18% of PAVM patients in large case series, with TIAs occurring in 12% to 37% of cases.[58,62] In one retrospective study, 51% of patients admitted for PAVM occlusion were found on cerebral imaging to have evidence of either cortical or subcortical infarct; the frequency was highest in patients with multiple PAVMs.[75] Higher-grade right-to-left shunt on contrast echocardiography and feeding artery greater than 3 mm are associated with higher incidence of ischemic stroke,[76,77] suggesting that paradoxical embolism is the principal mechanism. Alternatively, there are reports of stroke due to impaired cerebral perfusion in the setting of polycythemia associated with PAVM.[77] Other risk factors for ischemic stroke in this population include low serum iron and fibrinogen[79] as well as low pulmonary artery pressure,[80] likely due to increased platelet aggregation and facilitated paradoxical embolism, respectively.

Brain abscess is another serious neurologic complication of PAVM, occurring due to the loss of pulmonary capillary filtration, which allows passage of septic emboli into the systemic arterial circulation and into the brain. This can occur even with transient bacteremia, such as with dental procedures. Brain abscess in PAVM occurs less frequently than ischemic stroke, with a prevalence ranging from 5% to 13% in various studies,[62,75,80] but it is associated with a high mortality rate of up to 24%.[21] Due to the increased risk of brain abscess compared with the general population, patients with known PAVM should receive prophylactic antibiotics prior to dental procedures and other nonsterile procedures with potential for bacteremia.[19]

DIAGNOSIS OF PULMONARY AVMs

Diagnostic evaluation for PAVMs should be pursued in patients in whom PAVMs are suspected due to clinical and/or radiographic features and in those with a known or suspected diagnosis of HHT. Patients with documented HHT whose initial screening for PAVMs is negative should undergo repeat screening after puberty, after pregnancy, within 5 years preceding planned pregnancy, and otherwise every 5 to 10 years.[81] Screening techniques assess for the presence of right-to-left shunting, most commonly with contrast echocardiography. Patients who have a positive screening test or who have a high pretest probability for PAVM should undergo diagnostic imaging to confirm the presence of PAVM, most commonly with chest CT.

■ Contrast Echocardiography

Contrast echocardiography (commonly referred to as a “bubble study”) is a standard screening tool for identification of PAVMs. In this test, echocardiography is performed in the apical four-chamber view while agitated saline (saline blended with a small amount of air) is administered intravenously. A right-to-left shunt is identified by the presence of microbubbles in the left atrium; delayed appearance of the microbubbles after four cardiac cycles is considered positive for an intrapulmonary right-to-left shunt (Fig. 75-3) as opposed to the immediate appearance in association with intracardiac shunts. A study of 281 patients with HHT who underwent screening contrast echocardiography for PAVMs demonstrated sensitivity and negative predictive value of 97% and 99%, respectively, using CT scans as the gold standard.[82] These excellent performance characteristics define contrast echocardiography as a highly suitable initial screening study, given that it is unlikely to miss clinically significant PAVMs.

Notably, contrast echocardiography is associated with a high false-positive rate, resulting in a positive predictive value as low as 51%.[82] This finding is primarily due to the identification of clinically insignificant “micro” PAVMs that are not detected on CT or post–treatment completion angiography[83] and would not be considered targets for treatment. This issue can be addressed by adding a grading system to contrast echocardiography, in which studies are graded by intensity of left heart opacification with microbubbles[84] (Fig. 75-4). Using a grading system to assess the severity of right-to-left shunt, patients with grade 1 shunt (<20 microbubbles) are unlikely to have visible PAVMs on follow-up CT[85] (Fig. 75-4). There are also other conditions that cause intrapulmonary right-to-left shunt (for example, hepatopulmonary syndrome) that should be considered in the absence of visible PAVM on CT scanning or other imaging modality.[86]

■ Other Assessments of Right-to-Left Shunt in Suspected PAVM

Assessment for right-to-left shunt in the initial stages of PAVM diagnosis can be performed though alternate methods other than contrast echocardiography. Degree of shunting can be calculated using the 100% inhaled oxygen method to determine the fraction of cardiac output that is shunted from right to left without oxygenation in the alveoli. In this method, an arterial blood gas is obtained after the patient breathes 100% oxygen via a tight-fitting mask or mouthpiece for 15 to 20 min; Pa_{O_2}, Sa_{O_2}, and Pa_{CO_2} are then used to calculate the shunt fraction. Various studies have shown that a measured shunt fraction greater than 5% has sensitivity of 98% for detection of clinically significant PAVMs.[19,87,88]

Radionuclide scanning can also demonstrate right-to-left shunt and can be useful as a screening tool for PAVM. In this test, ^{99m}Tc pertechnetate-labelled macroaggregated albumin or albumin microspheres are injected intravenously. The size of these

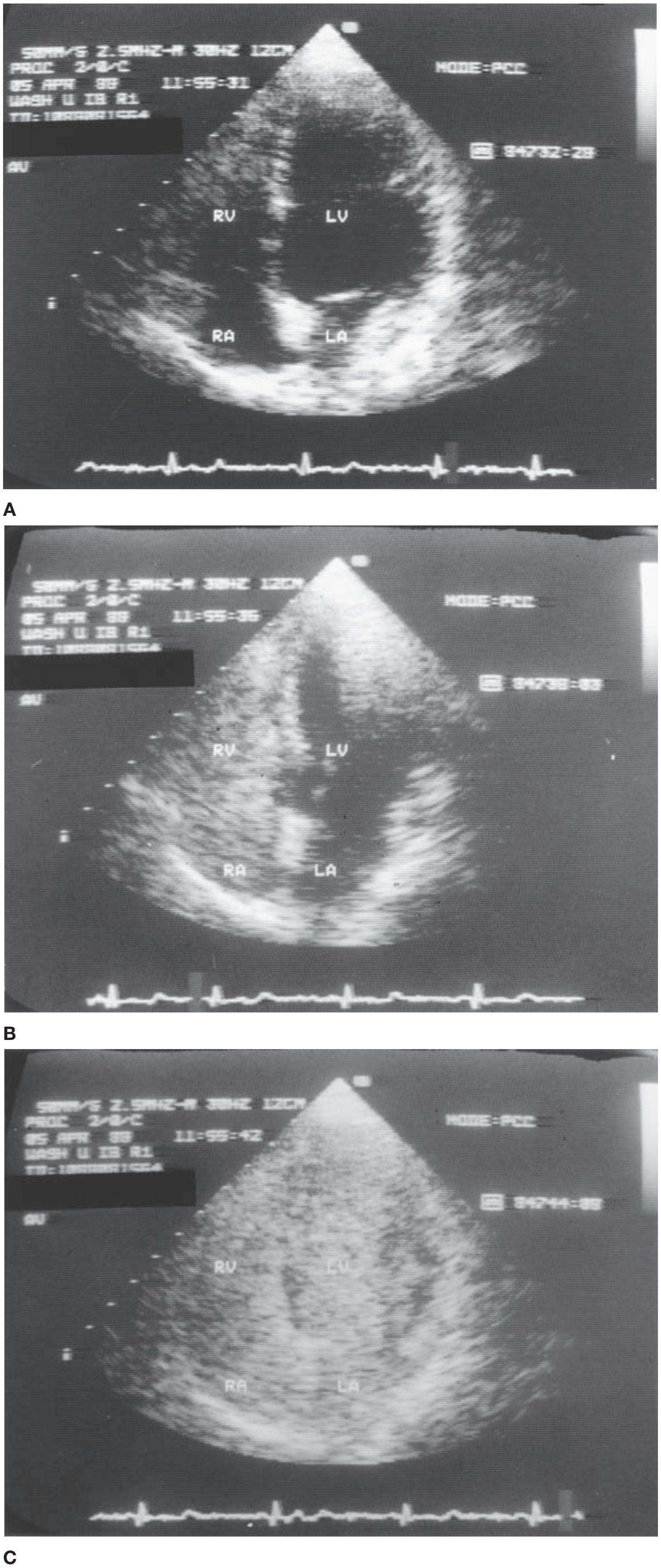

Figure 75-3 Echocardiographic images using saline contrast. **A.** Before contrast. **B.** Right-sided chamber opacification. **C.** Delayed high-degree left-sided chamber opacification indicative of large intrapulmonary shunt.

particles (ranging from 7 to 60 μm) is large enough to be filtered by the capillaries of the lung; however, anatomic right-to-left shunts such as in PAVM allow passage of these tagged particles into the arterial circulation and deposition into other tissues such as brain and kidneys. The shunt fraction can be calculated by quantifying the amount of deposition of radionuclide tracer in the systemic tissues as opposed to deposition in the pulmonary microvasculature. A small study of 19 patients with PAVMs demonstrated excellent agreement between shunt fractions determined by the radionuclide scan method and the 100% inhaled oxygen method.[89] Another study comprising 66 patients with HHT and PAVM showed that a shunt fraction greater than 3.5% on radionuclide scan performed after embolization had an 87% sensitivity and 61% specificity for detection of residual PAVMs.[90] Use of this imaging modality is limited, however, by cost and availability. It should be noted that radionuclide scanning and the 100% inhaled oxygen method identify the presence of right-to-left shunt rather than the anatomic location of the shunt (intrapulmonary vs. intracardiac). Use of contrast echocardiography provides more information about the location of the shunt based on the timing of bubbles seen in the left heart.

Other methods of PAVM screening have been investigated. One such method is transcranial Doppler (TCD) with agitated saline,[91] which has high sensitivity for right-to-left shunt (100%) but relatively low specificity (given the inability to distinguish between intrapulmonary and intracardiac shunting). However, the high negative predictive value (100% when using a cutoff of TCD grade <3) makes this a useful test for ruling out right-to-left shunt in at-risk patients in facilities where this test can be performed.

Chest Radiography

Although chest radiographs can reveal large PAVMs and have historically been included as part of the diagnostic evaluation, they will miss up to 60% of PAVMs.[88,92] As such, a normal chest radiograph does not rule out the presence of PAVM. However, presence of classic features of PAVM on chest radiograph is highly suggestive and specific. These features include a round, oval, or lobulated soft tissue mass, often situated in the lower lobes, with one or two adjacent pulmonary vessels that may extend to the mass from the hilum[19,93] (Fig. 75-5).

Computed Tomography

Computed tomography (CT) scanning is generally considered the gold standard for identification of PAVM because of its high sensitivity (98% in one study[17]) and ability to demonstrate the angioarchitecture, size, and location of individual PAVMs. It is commonly performed as a confirmatory test after contrast echocardiography demonstrates evidence of right-to-left shunting or in patients with a high clinical suspicion for PAVM. Helical CT scanning with thin (1- to 2-mm collimation) axial images and three-dimensional reconstruction provides the most detail for these lesions and can distinguish between vascular and nonvascular structures.[17,93,94] PAVM on CT classically appears as a well-defined peripheral lung nodule (with aneurysmal sac commonly 0.5–5 cm in diameter) that is rounded or multilobulated and has at least one feeding artery and one or more draining veins

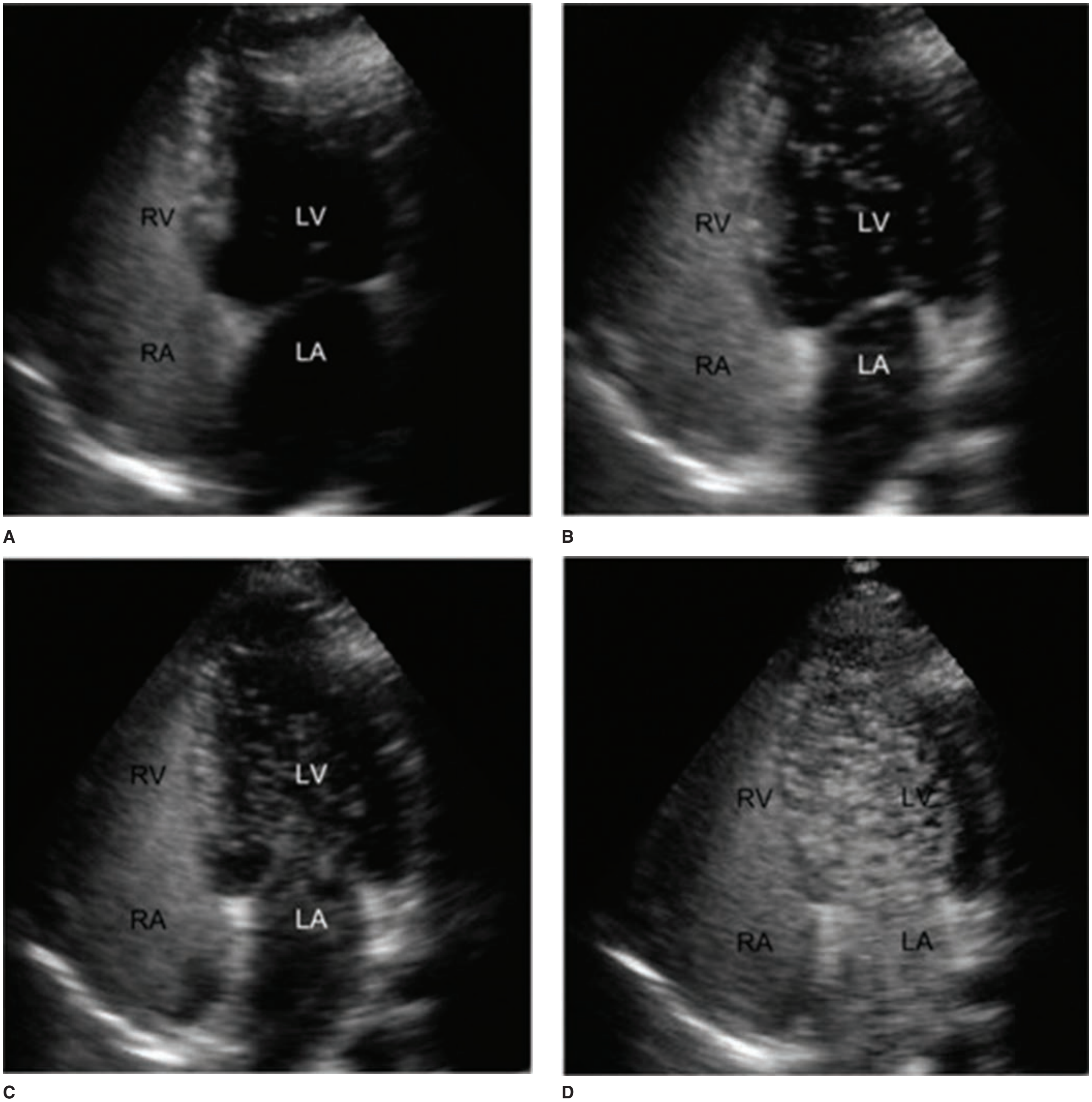

Figure 75-4 Appearance of left ventricular opacification following injection of agitated saline solution during transthoracic contrast echocardiography, demonstrating each grade of severity. **A.** Grade 1, minimal opacification. **B.** Grade 2, moderate opacification. **C.** Grade 3, extensive opacification. **D.** Grade 4, extensive opacification with endocardial definition. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. *(Reproduced with permission from Zukotynski K, Chan RP, Chow CM, et al. Contrast echocardiography grading predicts pulmonary arteriovenous malformations on CT. Chest. 2007;132(1):18–23.)*

(Fig. 75-6). Intravenous iodinated contrast administration can provide additional image detail with improved identification of feeding and draining vessels,[93] although contrast is not needed in most cases given the high spatial resolution and high contrast difference between bright pulmonary vessels and low-attenuating pulmonary parenchyma.

Magnetic Resonance Imaging

Magnetic resonance (MR) angiography is less commonly used for evaluation of PAVM, primarily due to its lower sensitivity compared with CT imaging. Initially studied using conventional spin-echo MR,[95] flowing blood within vessels results in absent or minimal MR signal intensity, giving this technique limited ability to distinguish small vessels from surrounding air-filled lung tissue.[19] More recent studies using breath-hold gadolinium-contrast-enhanced MR angiography,[96] ultrafast time-resolved 3D MR angiography,[97] and non-contrast-enhanced MR angiography with time-spatial labeling inversion pulse (time-SLIP MRA)[98] demonstrate improvements in sensitivity and imaging quality for detection of PAVMs, particularly

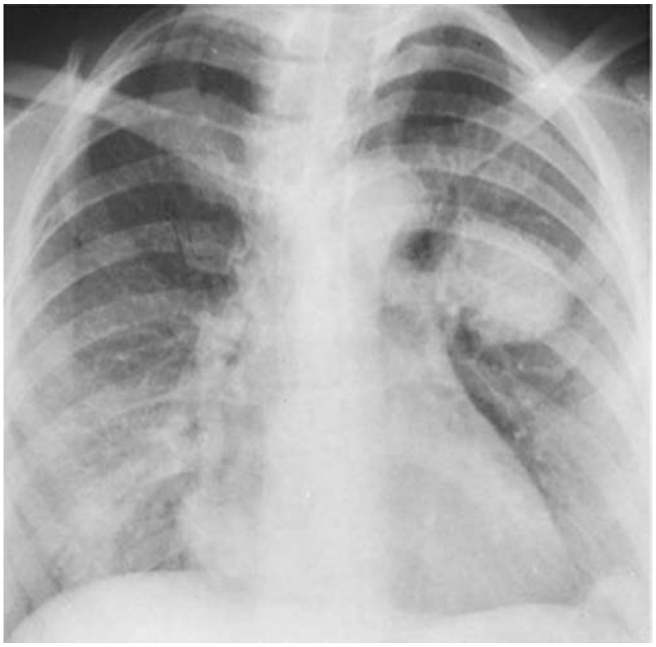

Figure 75-5 Pulmonary arteriovenous fistulas in a pregnant 24-year-old woman with hereditary hemorrhagic telangiectasia. Pre-existing pulmonary AVMs were found to be strikingly enlarged on chest radiograph at her seventh month of pregnancy. *(Reproduced with permission from Dr. M Rossman.)*

for clinically significant PAVMs with feeding artery diameter equal to or greater than 3 mm. However, use of MR angiography for diagnosis of PAVM remains limited due to longer breath-holding requirements, increased cost, and lower sensitivity and specificity compared to CT.

Pulmonary Angiography

Catheter pulmonary angiography is performed primarily for diagnostic confirmation at time of embolotherapy rather than as a standalone diagnostic test, as most PAVMs can be identified on noninvasive imaging. This technique involves introduction of an intravascular catheter into the pulmonary arterial circulation, followed by injection of radiopaque contrast through this catheter, and use of fluoroscopy to obtain dynamic images of the vessels filled with contrast including any PAVMs in the selected vascular bed. Pulmonary angiography provides detailed information about the angioarchitecture of individual PAVMs prior to embolotherapy, particularly when performed as hyperselective angiography in which the catheter is advanced to a distal pulmonary artery (at the segmental or subsegmental level) or to the feeding artery of an individual PAVM.[17] Digital subtraction angiography is commonly used to provide higher-quality images of blood vessels during angiography, with digital image processing to remove nonvascular structures from images obtained, allowing for lower radiation dose and contrast amount.

MANAGEMENT OF PULMONARY AVMs

Historically, thoracotomy with excision (ranging from wedge resection to total pneumonectomy) was the only treatment available for PAVM. This option carried risks associated with general anesthesia and thoracotomy and involved loss of lung tissue, particularly with repeat procedures. In the 1970s, endovascular mechanical occlusion was shown to be a successful option,[99] providing an alternative that soon supplanted surgery as the procedure of choice. PAVMs with feeding vessel diameter of 3 mm or larger should be embolized (even if symptoms are absent),[100] and PAVMs down to 2-mm vessel diameter are increasingly embolized if technically feasible. Patients with symptomatic PAVM should be considered for embolotherapy regardless of findings on noninvasive imaging. Diffuse PAVMs are less amenable to embolotherapy due to the presence of many small PAVMs that continue to contribute to symptoms and complication risk despite embolization of larger

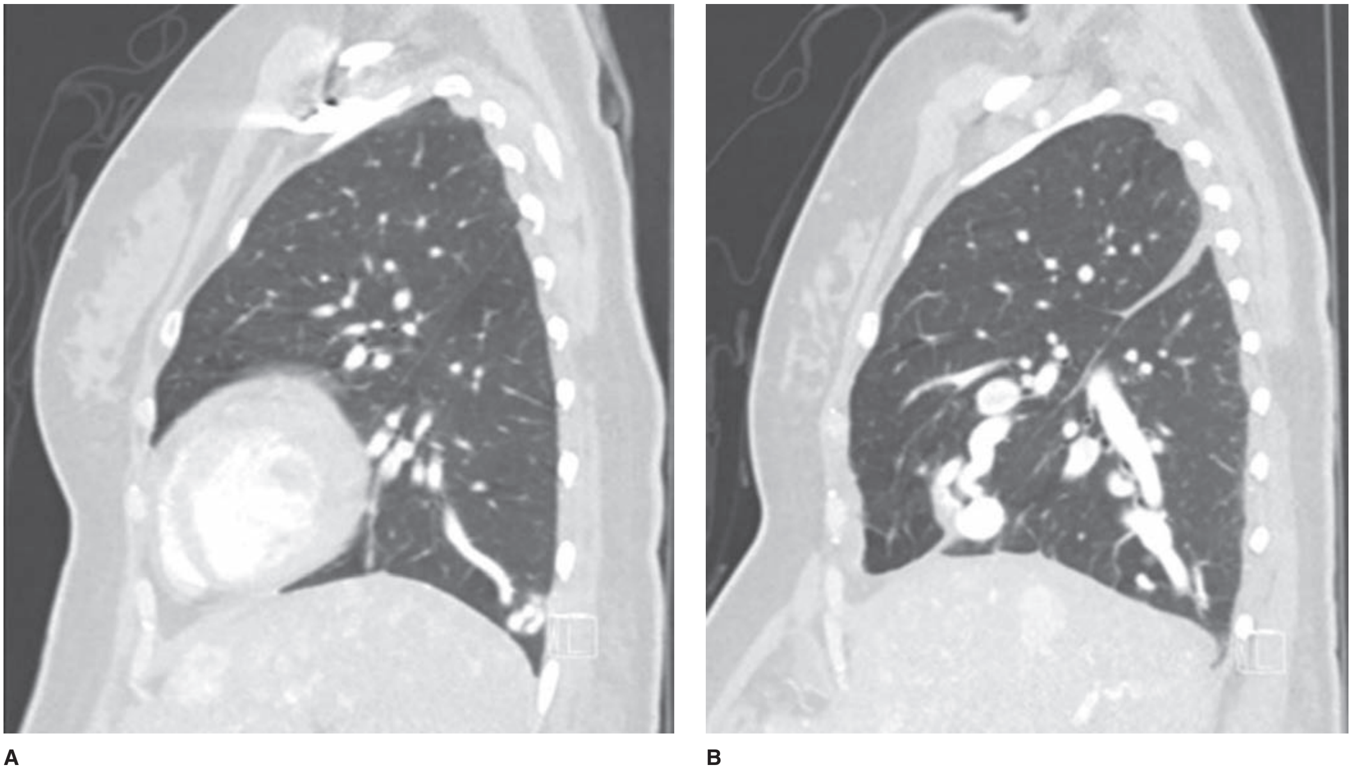

Figure 75-6 Pulmonary arteriovenous fistulas in the right middle lobe and both lower lobes, identified on sagittal (**A** and **B**) and *(continued)*

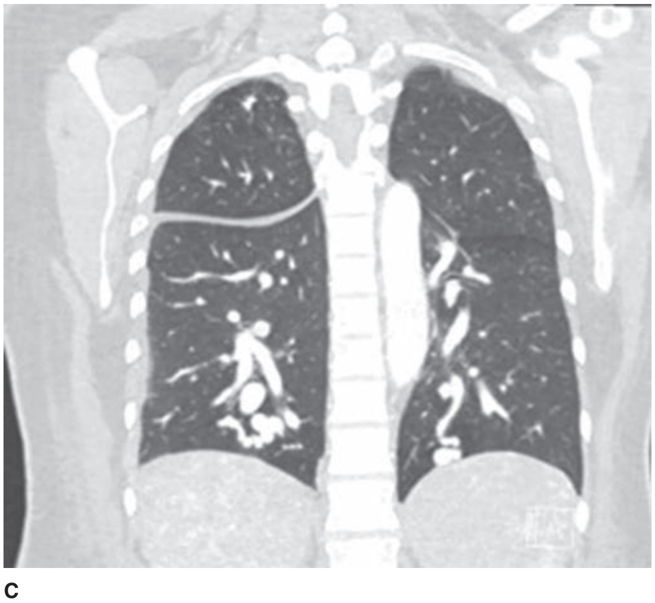

Figure 75-6 *(Continued)* coronal (**C**) CT images in a 39-year-old woman with hereditary hemorrhagic telangiectasia due to *ACVRL1* mutation.

visible PAVMs.[101] For patients whose PAVMs are smaller than the size threshold for interventional treatment and who are asymptomatic or minimally symptomatic, a strategy of observation and monitoring can be implemented instead. Management options are discussed in greater detail in the following section.

■ Endovascular Treatment

Embolization of PAVMs, also commonly referred to as embolotherapy, has become the standard first-line intervention for PAVMs that meet criteria for treatment. This minimally invasive procedure is performed endovascularly with placement of coils,[74] Amplatzer vascular plugs,[102] or microvascular plugs[103] to occlude blood flow through the embolized PAVM, reducing the shunt fraction and the risk for complications like brain abscess and embolic stroke[104] (Fig. 75-7). Detachable silicone or latex balloons also have been used but are now less commonly used due to limited availability. Embolization is considered successful if follow-up imaging shows more than 70% shrinkage of the draining vein or aneurysmal sac.[105] Embolotherapy may also be used in patients with diffuse PAVM to occlude blood flow to segments of lung with diffuse involvement, rather than targeting individual PAVMs.[22]

Risks of embolotherapy are low with essentially no reported mortality; adverse effects and complications include air embolism, pleuritic chest pain, hemoptysis, and migration or paradoxical embolism of embolization materials (potentially causing stroke or other end-organ injury). It has been shown that pulmonary artery pressure is not significantly increased by embolotherapy for PAVM in patients without baseline severe pulmonary hypertension,[106] although caution should be exercised in patients with pre-existing pulmonary hypertension, and severe pulmonary hypertension is considered a relative contraindication to PAVM embolization. Embolotherapy has been used successfully in pregnant patients as early as 16 weeks' gestation and has been found to be safe and effective.[68,107]

Coils for embolization are typically made of steel or platinum and are deployed into the feeding afferent vessel as close as possible to the aneurysmal sac. Obstruction of blood flow and prothrombotic coil materials/design (such as addition of nylon fibers) cause luminal thrombosis and PAVM occlusion.[108] However, shunt persistence after coil embolization has been observed in up to 25% of cases, with 91% of persistent PAVMs resulting from recanalization through an existing coil nest.[105] Recurrences can be effectively treated with repeat embolotherapy.

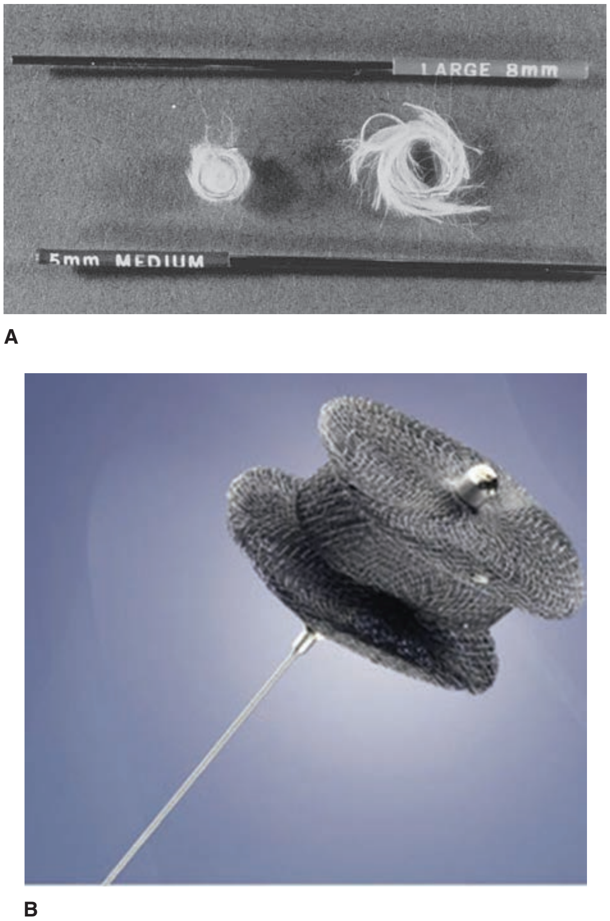

Figure 75-7 Embolotherapy devices. **A.** Embolization coils of two sizes. **B.** Amplatzer vascular occlusion plug.

Vascular occlusion devices such as Amplatzer vascular plugs and microvascular plugs are increasingly used as standard embolization devices for PAVM embolotherapy. These devices are typically composed of a self-expanding nitinol mesh and can be resheathed and redeployed if placement is not ideal after initial deployment.[102] Placement of a vascular plug into the feeding vessel of a PAVM can also be followed by coil embolization to the same vessel if perfusion of the PAVM is still seen on angiography[104] (Fig. 75-8). Successful initial occlusion of PAVMs with microvascular plugs and Amplatzer vascular plugs has been shown to occur in greater than 97% of cases,[103] and embolized PAVMs are less likely to recanalize with use of vascular occlusion devices compared to embolization with coils alone.[109]

A CT scan should be obtained within 6 to 12 months following embolotherapy and then repeated every 3 to 5 years in asymptomatic patients to evaluate for reperfused PAVMs or enlargement of previously small PAVMs now large enough for treatment.[81,110] Development of symptoms and signs of new or recurrent PAVMs should prompt more immediate imaging. Most patients have right-to-left shunting present on post-embolotherapy contrast echocardiography,[83] which limits its usefulness. A recent small study suggested that graded contrast echocardiography might have greater

Video 75-1 Saline contrast echocardiogram demonstrating characteristic delay of left-sided contrast in patient with intrapulmonary shunt. *(Reproduced with permission from Dr. Daniel Goodenberger.) Video available on AccessMedicine.com.*

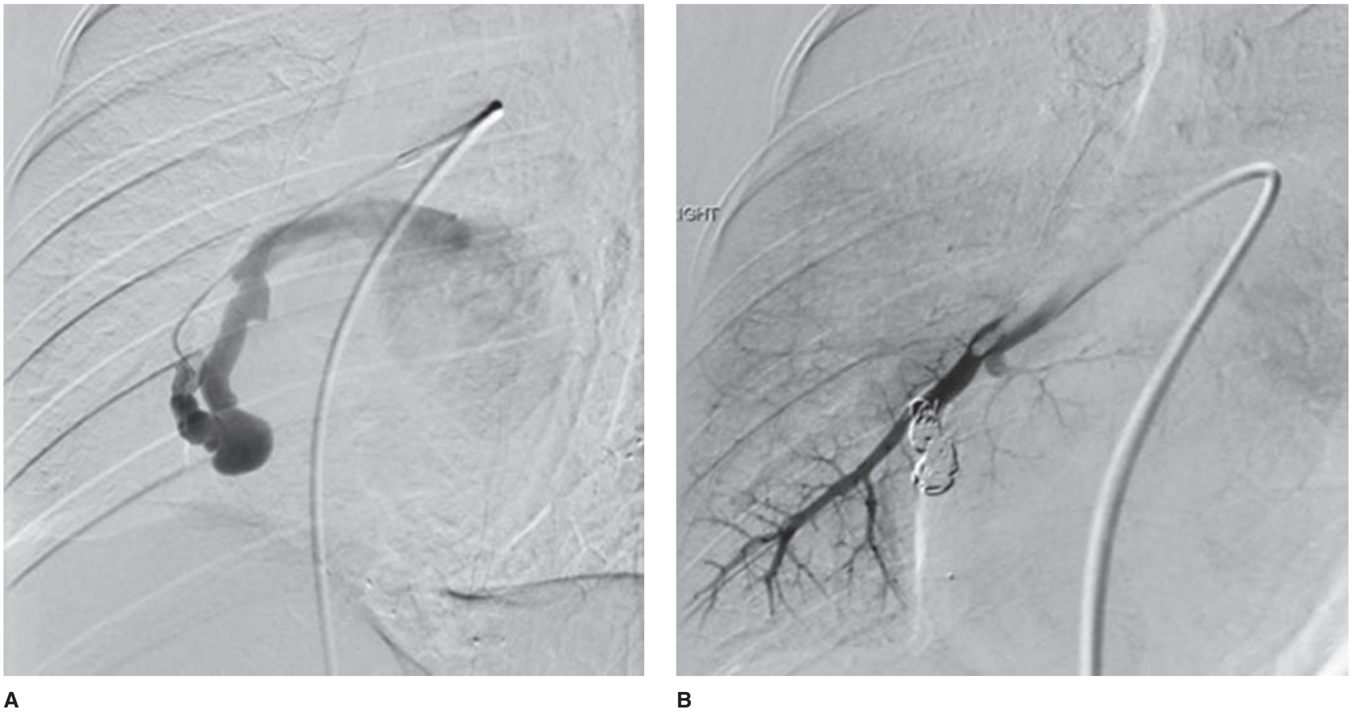

Figure 75-8 Successful embolization of a pulmonary arteriovenous malformation of the right middle lobe using a combination of a vascular plug and coil for complete embolization. **A.** Pulmonary angiography prior to embolotherapy demonstrates a simple PAVM with a single feeding artery. **B.** Pulmonary angiography following embolization shows absence of perfusion of the previously identified PAVM.

utility in predicting the need for repeat embolotherapy; no patients with grade 1 shunts had PAVMs amenable to embolotherapy by CT scan criteria. MR angiography has also been shown to be a feasible method of follow-up and may have a growing role in this area to minimize risk of radiation exposure.[111]

■ Surgical Treatment

With the advent of embolotherapy, surgical resection is now restricted to cases of PAVMs that are not amenable to embolization or select cases involving acute hemorrhage. Surgical excision can be customized in terms of extent based on necessity, ranging from local excision up to total pneumonectomy, with the goal of minimizing the loss of viable lung tissue. Lung transplantation is an option for patients with severe or diffuse disease not adequately treated with other options.[112,113] However this treatment option should be considered carefully given the significant risk of morbidity and mortality with lung transplantation and the demonstrated longevity of patients with PAVMs even with severe hypoxemia.[114]

■ Conservative Management

Asymptomatic patients with small (<2 mm feeding artery diameter) should be followed for development of symptoms, and CT imaging is recommended every 3 to 5 years given the risk of PAVM growth. Recent data demonstrating little to no growth of small and microscopic PAVMs during this time interval[115,116] have raised the possibility of safe extension of this interval to 5 to 10 years.

Certain adjunctive recommendations have been made to reduce the risk of paradoxical embolization of particles, air emboli, and septic emboli in patients with treated and untreated PAVM. Use of an inline filter during IV infusion is recommended to avoid introducing air or particles into the circulation. The size of inline filters is typically 0.22 to 0.45 μm, although blood filters ranging up to 260 μm are considered effective in avoiding large air emboli. Scuba diving should be avoided due to the increased risk of decompression sickness and paradoxical air embolism. Antibiotic prophylaxis should be used with dental procedures to reduce the risk of bacteremia and brain abscess,[117] and care should be taken to optimize dental hygiene.

Hypoxemia can be surprisingly well tolerated in patients with PAVM, primarily due to compensatory mechanisms like polycythemia, increased cardiac output, and improved aerobic conditioning to avoid tissue hypoxia. Patients who are symptomatic may benefit from use of supplemental oxygen, although hypoxemia due to PAVM does not typically improve with use due to the physiology of right-to-left shunting. Because secondary erythrocytosis is considered an adaptive response, therapeutic phlebotomy should be used only in cases of hyperviscosity with evidence of end-organ injury. Treatment of iron deficiency, particularly in cases of ongoing blood loss due to epistaxis and GI bleeding in HHT, is helpful in maintaining adequate erythrocyte production, an important component of adaptive response in PAVM.[67]

Special caution should be taken in pregnancy, as there is an increased risk of maternal death (1%), life-threatening pulmonary hemorrhage (1.4%), and stroke or myocardial infarction due to paradoxical embolism.[118] Although a majority of pregnancies in this population are ultimately uneventful, pregnancy in patients with PAVM (or HHT) is considered high risk, and patients considering pregnancy should be counseled about this risk and the need for careful monitoring during pregnancy and delivery.

PROGNOSIS

Prior to the development of embolotherapy in the 1970s, published case series reported PAVM-related mortality in patients with untreated PAVM ranging from 7.7% to 55%.[4,55,92,119–121] Untreated PAVMs are complicated by stroke and brain abscess as previously described, and these are sources of significant morbidity and mortality. Implementation of embolotherapy and recommended follow-up surveillance for PAVM has led to a significant reduction in morbidity and mortality. However, the risk of death or complication is higher in the subgroup of patients with bilateral diffuse PAVM, reported as 35% over a 27-year follow-up period in one case series, with a third of deaths due to PAVM-associated complications.[22] Risk factors for PAVM persistence on follow-up imaging include complex angioarchitecture[105] and smoking.[122]

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PART 9

Disorders of the Pleural Space

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CHAPTER 76

Nonmalignant Pleural Effusions

Christopher M. Kapp
David Feller-Kopman

INTRODUCTION

Pleural effusion occurs in more than 1.5 million patients each year in the United States.[1] The prevalence of ultrasound-detected pleural effusion in critically ill patients has been reported to be as high as 62%;[2] mortality is increased for those with an effusion.[3] Among the causes of pleural effusions, heart failure, pleural infection, and malignancy are most common.[4] Nonmalignant pleural effusions (NMPEs) arise from a vast assortment of conditions (Fig. 76-1); some etiologies have been associated with worse survival than effusions due to malignancy.[5,6]

PLEURAL ANATOMY AND PHYSIOLOGY

The pleural space is defined as the area between the visceral pleura, which lines the lung, including the fissures, and the parietal pleura, which lines the chest wall, diaphragm, and mediastinum. The visceral and parietal pleural membranes consist of a single layer of mesothelial cells, a layer of connective tissue, a superficial elastic layer, a loose connective tissue layer, and a deep fibroelastic layer.[7]

The normal pleural cavity is estimated to contain 0.26 mL of fluid per kilogram of body weight, with most of the fluid both produced and absorbed on the parietal surface.[8,9] Fluid production and resorption are dependent on the balance of hydrostatic and oncotic pressure differences between the systemic and pulmonary circulations and the pleural space. The lymphatic vessels in the parietal pleura are capable of increasing resorption by a factor of 20 in response to an increase in pleural liquid formation before being overloaded. Therefore, both a significant increase in fluid formation and a reduction in fluid resorption are required to produce a clinically significant pleural effusion.[8]

Pleural effusions typically form by one or more of the following mechanisms: (1) injury to the pleura that changes membrane permeability and leads to exudative effusions, (2) increased intravascular hydrostatic forces and/or decreased oncotic forces that lead to transudative effusions, and (3) extravasation of fluid from lymphatic or vascular structures or from translocation of fluid across the diaphragm.

EPIDEMIOLOGY

There is a paucity of large-scale epidemiologic data describing the incidence or etiology of NMPEs. When speaking broadly about pleural effusions, the two most common causes are generally accepted to be related to congestive heart failure and parapneumonic effusion.[1] The third most common cause is believed to be a malignant pleural effusion, which is discussed elsewhere in this book. Rounding out the top five causes of pleural effusion are pulmonary embolism and viral illness.[10]

Table 76-1 depicts the most common causes of pleural effusions in the United States and their estimated annual incidence. Other causes of NMPE include chronic liver disease, renal disease, asbestos exposure, rheumatoid arthritis and other autoimmune diseases, and post-cardiac surgery.[10] As up to 30% of patients may have more than one cause of their pleural effusion (e.g., malignancy *and* congestive heart failure), a complete clinical evaluation may be necessary even in the setting of a seemingly obvious diagnosis.[11]

DIAGNOSTIC CONSIDERATIONS

Initial patient workup should begin with a thorough history and physical examination. When a pleural effusion is suspected, workup should be expeditious, as delay in diagnosis and treatment may lead to increased morbidity and mortality.[12]

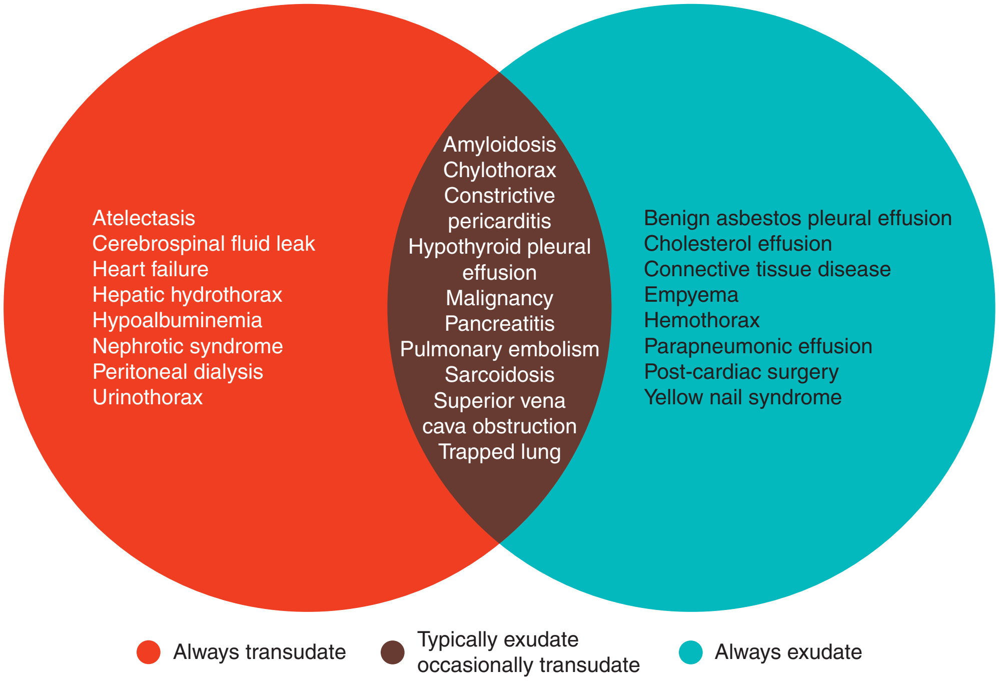
Atelectasis
Cerebrospinal fluid leak
Heart failure
Hepatic hydrothorax
Hypoalbuminemia
Nephrotic syndrome
Peritoneal dialysis
Urinothorax
Amyloidosis
Chylothorax
Constrictive pericarditis
Hypothyroid pleural effusion
Malignancy
Pancreatitis
Pulmonary embolism
Sarcoidosis
Superior vena cava obstruction
Trapped lung
Benign asbestos pleural effusion
Cholesterol effusion
Connective tissue disease
Empyema
Hemothorax
Parapneumonic effusion
Post-cardiac surgery
Yellow nail syndrome
Always transudate
Typically exudate occasionally transudate
Always exudate

Figure 76-1 A non-exhaustive list of causes of pleural effusions and their characterization by Light's criteria.

TABLE 76-1 Most Frequent Causes of Pleural Effusions in the United States

Etiology	Annual Incidence (U.S.)
Congestive heart failure	500,000
Infectious etiology	300,000
Malignancy	200,000
Pulmonary embolism	150,000
Viral illness	100,000
Cirrhosis	50,000
Post–cardiac surgery	50,000

TABLE 76-2 Rules to Classify Pleural Fluid as Exudate Versus Transudate

Rule	Criteria
Light's criteria	PF/serum protein ratio >0.5, or PF/serum LDH ratio >0.6, or PF LDH > two-thirds upper limits of the laboratory's normal serum LDH
Rule that does not require serum tests	PF protein >2.9 g/dL, or PF cholesterol >45 mg/dL, or PF LDH >0.45 times upper limit of the laboratory's normal serum LDH

LDH, lactate dehydrogenase; PF, pleural fluid.

Often, a pleural effusion is discovered when an imaging study is performed for another reason (e.g., chest x-ray for cough). A patient's history is frequently nonspecific, as patients may describe pleuritic chest pain, dyspnea, and a dry, nonproductive cough. Special attention should be paid to past occupational exposures (e.g., asbestos), exposures to infectious diseases (e.g., tuberculosis), and underlying medical conditions (e.g., congestive heart failure, cirrhosis, collagen vascular disease, malignancy). Further, medication history may be important, as some commonly used drugs have been implicated as causes to pleural effusions, including methotrexate, amiodarone, and beta blockers.[13] The physical examination may provide clues to the presence of more common causes of pleural effusion, such as collagen vascular disease or heart failure, as well as more obscure causes, such as yellow nail syndrome. Once an appropriate differential diagnosis is devised, the clinician should choose wisely the next steps in diagnostic evaluation—which frequently include the assessment of other organ systems.

When selecting the best test to evaluate the pleuropulmonary space, current guidelines recommend the use of upright chest x-ray as an initial test.[14] It should be noted that supine and semirecumbent chest x-rays frequently underestimate the size of a pleural effusion, and that the lack of a meniscus sign on chest x-ray does not preclude existence of an effusion.[15] Once an effusion is confirmed or strongly clinically suspected on x-ray, a thoracic ultrasound should be performed, even before more advanced imaging, such as computed tomography. The use of portable, point-of-care ultrasound has significantly improved our ability to quantify, predict etiology, and access pleural effusions and is often the imaging modality of choice in the intensive care unit.[16–19] The reader is referred to Chapter 29 for further details on thoracic ultrasonography.

The sonographic characteristics of a pleural effusion may be useful in helping the clinician determine the nature of the fluid and deciding on whether to perform thoracentesis or tube thoracostomy.[20] A transudative effusion is typically be anechoic, while an exudative effusion may be anechoic, complex and septated, complex and nonseptated, or homogenously echogenic.[21] While evidence of septations may suggest an exudate and a complicated effusion, septations are not specific for infection.[18,21] Additional imaging findings that can be detected on ultrasound are the thickness of the pleura and pleural nodules.[18] Sonographic evidence of pleural thickening greater than 7 mm or presence of a pleural nodule are predictive of a malignant pleural effusion.[18,22]

■ Thoracentesis

Pleural effusions with greater than 1 to 2 cm of fluid separating the visceral and parietal pleura should undergo pleural drainage, assuming that there are no safety concerns (e.g., uncorrectable coagulopathy, patient agitation) that preclude safe performance of the procedure. One notable exception is a clinical setting suggestive of congestive heart failure; a trial of diuresis is the recommended first step, reserving thoracentesis for patients who fail to respond appropriately.[23] Thoracentesis is a well-tolerated procedure, even in patients requiring positive pressure ventilation, and the safety profile improves with use of thoracic ultrasound and in the hands of an experienced proceduralist.[14,24,25]

Transudates versus Exudates

Categorization of the fluid as a transudate or an exudate simplifies the differential diagnosis and may guide management of the effusion.[26] Light's criteria for differentiating exudate from transudate have remained the standard method of initial categorization of pleural effusions since their inception in 1972.[27] Light's criteria focus on the use of pleural fluid lactate dehydrogenase (LDH) and pleural fluid total protein relative to their serum values (Table 76-2)[27] for distinguishing between transudates and exudates. Light's criteria serve as a very sensitive test, correctly classifying nearly all exudates. Approximately 25% of transudates are misclassified as exudates, particularly in the setting of heart failure patients who are receiving diuretics.[28,29] Alternative rules, listed in Table 76-2, avoid some of these limitations and perform equally as well as Light's criteria.[30–32] There are a battery of both routine and specialized tests that can be sent for pleural fluid analysis, depending on the pretest probability of the diagnosis (Table 76-3).

■ Pleural Biopsy

Pleural biopsy can be considered for patients with an exudative effusion who remain undiagnosed after initial thoracentesis. The approach to pleural biopsy ranges from minimally invasive (i.e., a closed needle biopsy with an Abrams needle), to image-guided percutaneous pleural biopsy, to biopsy by video-assisted thoracoscopic surgery (VATS) or medical thoracoscopy (also referred to as pleuroscopy).[33,34]

Medical thoracoscopy, often performed under moderate sedation and local anesthesia, is an alternative to VATS, which is commonly performed under general anesthesia. The other main difference between VATS and medical thoracoscopy is that medical thoracoscopy is typically limited to biopsy of the parietal pleura and adjunctive procedures, such as pleurodesis or placement of an indwelling pleural catheter (IPC), whereas more complex surgeries can be performed with VATS. A review of 78 medical thoracoscopy and 99 VATS procedures showed no difference in diagnostic yield, major or minor complications, or need for additional pleural procedures. However, there was a significantly longer length of stay and higher cost associated with VATS.[35]

TABLE 76-3 Pleural Fluid Test Results and Commonly Associated Conditions

Test	Result	Most Common Suggested Conditions
Erythrocytes	PF/S HCT >0.5	Hemothorax
Neutrophils	>10,000/μL	Parapneumonic effusion, lupus pleuritis, acute pancreatitis
	>50,000/μL	Empyema
Lymphocytes	>85%–95%	TB pleurisy, sarcoid, chronic rheumatoid pleurisy, yellow nail syndrome, chylothorax
Eosinophils	>10%	Hemothorax, pneumothorax, benign asbestos pleurisy, pulmonary infarction, coccidioidomycosis, paragonimiasis and other parasites, drug-induced pleurisy, duropleural fistula, Churg–Strauss syndrome, sarcoidosis, TB pleurisy
Protein	<1 g/dL	Peritoneal dialysis, CVC erosion, duropleural fistula
	>4 g/dL	TB pleurisy
LDH	>1000 IU/L	Bacterial empyema, paragonimiasis, amebic empyema, septic emboli, rheumatoid pleurisy
Glucose	PF/S <0.5	Complicated parapneumonic effusion, chronic rheumatoid pleurisy, paragonimiasis, amebic empyema, esophageal rupture, TB pleurisy, lupus pleuritis, urinothorax
	PF/S >1	Peritoneal dialysis, CVC erosion
pH	<7.30	Esophageal rupture, chronic rheumatoid pleurisy, complicated parapneumonic effusion, paragonimiasis, amebic empyema, TB pleurisy, lupus pleuritis, urinothorax, pancreaticopleural fistula
Amylase	Elevated	Esophageal rupture, acute pancreatitis, pancreaticopleural fistula
Cholesterol	>200 mg/dL	Cholesterol effusion
Creatinine	PF/S >1	Urinothorax
Beta 2 transferrin	Elevated	Duropleural fistula, ventriculoperitoneal shunt migration
Triglycerides	>110 mg/dL	Chylothorax, CVC erosion if lipids infused
Chylomicrons	Present	Chylothorax
Bilirubin	PF/S >1	Biliopleural fistula
Glycine	PF/S >1	Glycinothorax
ADA with lymphocytosis	>40 IU/dL	TB pleurisy

ADA, adenosine deaminase; CVC, central venous catheter; TB, tuberculous.

As medical thoracoscopy provides the ability to perform visualized biopsies of the pleura, this procedure has generally replaced biopsy using an Abrams needle. The one notable exception is in areas of the world that have a high prevalence of tuberculosis, since Abrams needle biopsy has a relatively high diagnostic yield in diagnosing tuberculous effusions.

TRANSUDATIVE EFFUSIONS

Selected etiologies of transudative pleural effusions are discussed in the following sections. They include common causes (e.g., congestive heart failure, liver cirrhosis, nephrotic syndrome) and rare causes (e.g., constrictive pericarditis, urinothorax, Meigs syndrome, peritoneal dialysis, cerebrospinal fluid leakage, ventriculoperitoneal shunts).

■ Congestive Heart Failure

Consistent with cardiac disease being the leading cause of death in the United States, it is also the most common cause of pleural effusion, with a prevalence of 50% to 90% in persons hospitalized with congestive heart failure (CHF).[36,37]

The mechanism of pleural fluid collection in CHF is related to an elevated left atrial pressure that generates pulmonary edema and provokes leakage of interstitial lung water down a hydrostatic pressure gradient into the pleural space.[38,39] Elevated left ventricular pressures have been implicated as an essential factor for producing CHF-related effusions; however, transudative effusions may also occur in a minority of patients with pulmonary arterial hypertension and isolated right ventricular failure.[40] Pleural effusions related to CHF are classically bilateral (60%–85%) and larger on the right side. When unilateral, they occur more commonly on the right, with a ratio of 2:1 right-sided to left-sided.[23]

Initial management of a suspected CHF pleural effusion involves a trial of diuresis. A thoracentesis may be considered if effusions fail to improve or resolve with diuretics. NT-proBNP is a sensitive marker of a CHF exacerbation, and elevated levels may be helpful in discriminating transudates associated with CHF from other etiologies.[41] Pleural fluid NT-proBNP correlates linearly with serum levels and can be used to help identify CHF-related effusions.[42] In cases where the serum NT-proBNP is very elevated and CHF is the lone suspected cause of the effusion, pleural drainage is not indicated except for providing symptomatic relief after failed diuresis.

Classically, CHF-related effusions are transudative; however, up to 30% of effusions fulfill Light's criteria for an exudate.[28,29] Pathophysiologic mechanisms for exudative pleural effusions in CHF include (1) fluid formation as a byproduct of a coexisting diagnosis (e.g., pulmonary embolism or recent cardiac surgery);[43] (2) water reabsorption that is more rapid than reabsorption of other molecules in the pleural space, resulting in a rise in the concentration of protein and LDH with diuresis;[23,28] and (3) elevated fluid erythrocyte counts (>10,000/μL), causing LDH release during autolysis of red blood cells.[44] Several strategies for determining that an exudative effusion in the setting of CHF is related to heart failure, rather than a comorbid condition, are listed in Table 76-4.

With improvement in heart function and volume status, CHF-related pleural effusions gradually resolve. Rarely, effusions in patients with refractory heart failure may require pleurodesis or placement of an IPC for palliation of symptoms, both of which may successfully palliate symptoms in up to 92% of patients.[45–48] IPCs may obviate the need for repeated thoracenteses and recurrent hospitalization and should be considered in select patients with the ability to manage them safely at home.[47]

TABLE 76-4 Rules for Evaluating Heart Failure–Related Effusions Misclassified as Exudates

Test Results	Comments
• PF-to-S albumin gradient >1.2 g/dL • PF/S albumin ratio <0.6 • PF-to-S protein gradient >3.1 g/dL (less accurate than the albumin-based tests above)	These three rules more accurately establish CHF as cause of an effusion for patients with a high pretest probability of CHF compared with Light's criteria
• Serum assay of amino terminal fragment of proBNP (NT-proBNP) >1500 pg/mL CHF-related <400 pg/mL CHF-unrelated	More accurate than protein or albumin-based testing rules
• Pleural fluid assay of NT-proBNP >1500 pg/mL CHF-related <400 pg/mL CHF-unrelated	High accuracy but no advantage over serum NT-proBNP
• Pleural fluid BNP >400 pg/mL CHF-related <100 pg/mL CHF-unrelated	Lower discriminative properties compared with NT-proBNP

BNP, brain natriuretic peptide; PF, pleural fluid; S, serum.

Hepatic Hydrothorax

Hepatic hydrothorax occurs when a pleural effusion develops in a patient with liver cirrhosis and portal hypertension in the absences of cardiopulmonary disease.[49] Hepatic hydrothorax is characterized by a transudative pleural effusion greater than 500 mL and is a relatively rare complication of cirrhosis, occurring in only 5% to 10% of cirrhotics.[50] The disorder has also been reported in 2% of liver transplant recipients with prior hepatitis C infection.[51]

The pathophysiology is believed to be related to the accumulation of ascites in the peritoneal cavity that herniates blebs of peritoneum into the chest through small diaphragmatic irregularities.[50] When these blebs rupture, ascites flows from the positive-pressure peritoneal space into the negative-pressure pleural space.[52] Small (<1 mm) diaphragmatic defects have also been visualized, and studies using air, blue dye, and iodine 131–labeled albumin have confirmed transdiaphragmatic migration through the defects.[53,54] These stomata occur more commonly in the tendinous portion of the right hemidiaphragm compared with the thicker, more muscular left, leading to 80% of hepatic hydrothoraxes occurring on the right side, 18% on the left, and 2% bilateral.[55] Up to 20% of patients will not have clinically apparent ascites due to decompression of the abdominal fluid into the pleural space,[56,57] but ultrasound or CT will demonstrate residual ascites in the large majority patients.[58]

Clinically, patients with hepatic hydrothorax may have a diverse presentation, ranging from asymptomatic to varying degrees of dyspnea, depending on effusion size and underlying cardiopulmonary disease. In rare instances, respiratory failure may occur in persons with rapid development of pleural effusion secondary to ascites and sudden rupture into the pleural space.[57] Thoracentesis yields a transudative effusion in 94% of patients.[56] Light's criteria may misclassify up to 18% of hepatic hydrothoraces as exudates; some authors suggest that a pleural fluid–to–serum albumin ratio of <0.6 is more accurate in this group of patients.[59] Diagnosis is one of exclusion, and caution must be exercised in assuming that an effusion in a cirrhotic patient is due to hepatic hydrothorax. A prospective study of 60 cirrhotic patients with pleural effusions showed that 30% were from conditions other than hepatic hydrothorax (e.g., pleural tuberculosis, malignancy, spontaneous bacterial empyema), particularly in patients with left-sided effusions.[53]

Management of hepatic hydrothorax closely resembles that of abdominal ascites, including dietary sodium restriction, diuretic therapy, and symptom management with thoracentesis. A transjugular intrahepatic portosystemic shunt (TIPS) can also be considered and has been demonstrated to achieve a good clinical response in refractory cases.[60] Hepatic hydrothorax typically resolves after liver transplantation. Outcomes in transplanted patients with hepatic hydrothorax are not inferior to those without.[61]

Chest tube placement, with or without pleurodesis, is often ineffective in treatment of hepatic hydrothorax, as more than one-quarter of patients fail due to rapid reaccumulation of fluid.[62]

Complications of pleurodesis include pain, fever, pneumothorax (due to non-expandable lung), and renal failure (likely secondary to intravascular volume depletion similar to patients undergoing large-volume paracentesis).[62]

IPCs have been used in refractory cases of hepatic hydrothorax, sometimes as a bridge to transplantation. While IPCs provide successful palliation of dyspnea, complications appear to be higher than in those with malignant pleural effusion, with empyema the most common.[63,64] If an IPC is considered, a multidisciplinary discussion involving members of the hepatology and transplant surgery teams should be conducted prior to placement.

Constrictive Pericarditis

Greater than 50% of patients with constrictive pericarditis develop a pleural effusion, which can be the initial presentation of pericardial disease.[65] The pathogenesis is not well understood but may be related to migration of coexisting ascites into the pleural space or compromised left ventricular function that causes a transudative effusion.[66] Constrictive pericarditis may occur as a result of surgery, radiation, or infectious etiologies; obtaining a diagnosis may be helpful in treatment. The effusions may resolve once the pericarditis is treated. In cases without an obvious medical cause, pericardiectomy can be considered, although this procedure is associated with significant morbidity.

Nephrotic Syndrome

Pleural effusions may be seen in up to 21% of patients with nephrotic syndrome.[67] They are typically related to severe hypoalbuminemia and are usually seen only when the serum albumin is <2 g/dL. Increased hydrostatic pressure due to salt retention and hypervolemia are contributing factors in their development. The effusions are typically bilateral; treatment focuses on decreasing protein loss in the urine, use of diuretics, and a low-sodium diet.

Urinothorax

Urinothorax is defined by the presence of urine in the pleural cavity and typically occurs secondary to obstructive uropathy. It is a rare cause of pleural effusion, which is predominantly unilateral and typically very large, occupying more than two-thirds of the hemithorax.[68,69] If suspected, the diagnosis is supported by pleural fluid that has the odor of urine and is characterized by low protein concentration but high LDH. The diagnosis is confirmed by demonstrating a pleural fluid–to–serum creatinine ratio of >1, along with imaging confirming obstructive uropathy. Relief of the obstruction successfully treats the urinothorax in the vast majority of cases.[69]

Peritoneal Dialysis

Pleural effusion is a rare complication of peritoneal dialysis (PD), affecting approximately 2% of all PD patients.[70,71] The pathophysiology is linked to passage of dialysis fluid from the positive-pressure peritoneal cavity into the negative-pressure pleural cavity via pleuroperitoneal communications resulting from diaphragmatic blebs or defects, similar to patients with hepatic hydrothorax.[70] The effusion is typically unilateral and transudative. The diagnosis rests on demonstration of an elevated pleural fluid glucose concentration exceeding that of plasma. Management centers around interruption of PD, and if an alternative method of dialysis is not a permanent option, thoracoscopic pleurodesis or repair of the diaphragmatic defects can be performed before reinitiation of PD.[70]

■ Cerebrospinal Fluid Leakage into the Pleural Space

Cerebrospinal fluid (CSF) may be the etiology of a pleural effusion when a duropleural fistula forms. Occurrence is rare, and typically results from trauma, as a complication from spinal or thoracic surgery, or due to rupture of a pre-existing intrathoracic meningocele.[72,73] The presence of headache, nausea, vomiting, meningismus, and other neurologic findings serve as clues that a duropleural fistula might be the underlying cause of pleural effusion.[74]

The pleural fluid is typically clear, is essentially acellular, and has low protein and LDH concentrtations.[73] Beta-trace protein and beta-2 transferrin are specific biomarkers that can be measured in the pleural fluid in cases where a duropleural fistula is suspected.[75] Once confirmed, these effusions rarely subside on their own and typically require surgical intervention.

■ Ventriculoperitoneal Shunts

Pleural effusion is a rare complication of an indwelling ventriculoperitoneal (VP) shunt, typically placed for hydrocephalus not responsive to medical management.[76] This can be due to catheter tip migration into the thorax or to efflux of fluid from the peritoneal cavity through diaphragmatic defects.[76,77] Pleural fluid characteristics are consistent with typical CSF, with no cells, low protein and LDH, and elevated beta-2 transferrin.[72] A radionuclide shunt-gram may confirm the diagnosis.[77,78] Treatment involves revision of the shunt.

■ Trapped Lung

Non-expandable lung serves as an "umbrella" term for trapped lung and lung entrapment.[79,80] Lung entrapment effusions are typically exudative and related to an acute or subacute underlying condition (e.g., malignancy, infection).[80,81] With pleural drainage, the lung fails to expand due to the development of visceral pleural thickening, endobronchial obstruction, or any disease process that increases pulmonary elastic recoil (e.g., lymphangitic carcinomatosis). Entrapment may resolve if the underlying inflammatory process improves (e.g., underlying pneumonia), or it may progress to trapped lung.

Trapped lung results from abnormal healing of an exudative effusion (e.g., post-CABG), development of visceral pleural thickening, and formation of a "pleural effusion ex-vacuo." Once the initial inflammatory process has resolved, the corresponding pleural effusion associated with trapped lung is typically transudative.[80,82]

Many patients with trapped lung are asymptomatic, and the diagnosis is frequently not discovered until pleural fluid drainage is attempted.[83] With drainage of the effusion, patients may develop chest discomfort, likely related to the significant decrease in pleural pressure.[84] Pleural manometry can help distinguish lung entrapment from trapped lung; however, manometry has not been shown to prevent the development of chest discomfort during thoracentesis.[84,85] As patients are often asymptomatic, treatment for trapped lung is observation and reassurance. Those with significant dyspnea can be evaluated for placement of an IPC or VATS decortication.[86,87]

EXUDATIVE EFFUSIONS

Causes of nonmalignant, exudative effusions are common, including infection, pulmonary embolism, and cardiac surgery–related; less common etiologies include chylothorax and hemothorax. The following section discusses diagnosis and management of exudative pleural effusions.

■ Parapneumonic Effusions and Empyema

The clinical significance of an infected pleural space has been known for centuries. According to Hippocrates, "Persons who become affected with empyema after pleurisy, if they get clear of it in forty days from the breaking of it, escape the disease; but if not, it passes into phthisis."[88] Parapneumonic effusion (PPE) and empyema are the most common exudative effusions and stem from infection in the lung parenchyma.[89]

Parapneumonic effusions constitute any effusion due to an underlying pneumonia, whereas empyema is defined as the presence of purulent pleural fluid or a positive pleural fluid Gram stain or culture. A parapneumonic effusion results when inflammatory cells migrate to the pleural space from an adjacent zone of lung infection and release pro- and anti-inflammatory cytokines that alter pleural membrane permeability, leading to recruitment of additional inflammatory cells.[90–92] This leads to an influx of protein-rich fluid, initially creating a sterile and free-flowing effusion. Development of a parapneumonic effusion may be followed by invasion of bacteria into the space, leading to neutrophilic pleocytosis, increased LDH, increased platelet-activating factor, and decreased fibrinolytic activity that favors fibrin deposition in the pleural space.[93]

PPEs occur in 20% to 57% of patients hospitalized for community-acquired pneumonia; the incidence has been increasing, especially in the elderly population.[12,94,95] Patients with PPE have increased mortality compared with patients with pneumonia who do not have an effusion.[94,96,97] Delayed drainage is associated with a higher mortality.[98]

Risk factors for PPEs include diabetes, immunosuppression, alcoholism, cancer, poor dental hygiene, and increased severity of the pneumonia index.[99] Parapneumonic effusions are classified as uncomplicated when effectively treated by antibiotics alone, and complicated when pleural drainage is required.[100,101] Table 76-5 delineates commonly ordered tests in evaluation of suspected infectious effusions and provides parameter values that may suggest a diagnosis.

The clinical presentation of PPE and empyema are typically those of the underlying pneumonia—cough, fever, and sputum, as well as chest pain. It should be noted, however, that in elderly patients, these symptoms are frequently absent, and anemia, fatigue, and failure to thrive often predominate, making the clinical diagnosis more difficult.[99,102] Potentially related to underdiagnosis, elderly patients often present with a more complicated pleural space, leading to higher failure rates of nonsurgical therapy.[103] Table 76-6 highlights the natural timeline of an empyema.

Treatment of patients with PPE and empyema relies upon the selection of appropriate antibiotics. Patients with community-acquired pneumonia typically require coverage for *Streptococcus* species and anaerobes (e.g., *Bacteroides*), while patients with a hospital-acquired infection will, at least initially, require therapy directed at more resistant pathogens (e.g., methicillin-resistant *Staphylococcus* and *Enterobacter*).[104]

In addition to antibiotics, drainage of the pleural space is an essential component of treatment. Drainage should initially be attempted with a tube thoracostomy. Data derived from large retrospective studies suggest that outcomes related to mortality and need for subsequent surgery are equivalent with use of small-bore tubes (≤14-French) compared to larger-bore tubes. Additionally, smaller tubes are associated with less pain during insertion and while in

TABLE 76-5 Commonly Ordered Pleural Fluid Tests

Test	Clinical Significance
Cell count and differential	Leukocyte counts vary depending on the stage of empyema formation; frank empyemas may have low leukocyte counts because cells have undergone lysis. The effusions are neutrophil predominant although a mononuclear cell predominance may exist with partially treated parapneumonic effusions.
Protein	Defines an exudate when >3.0 g/dL. Tuberculous effusions almost invariably >4.0 g/dL. Values >7.0 g/dL suggest Waldenström macroglobulinemia, multiple myeloma, or a cholesterol effusion.
LDH	Defines an exudate in Light's criteria rule; usually >1000 IU/L in empyemas.
Microbiologic staining and culture	Microbiologic staining and culture with sensitivity blood culture bottles. Cultures positive in ~60% of patients who have signs of pleural infection.
pH and glucose	Pleural fluid pH and glucose decrease because of intrapleural bacterial metabolism and inflammatory cell activity that utilize glucose and release lactic acid. A PF pH <7.20 and glucose <60 mg/dL suggest that a parapneumonic effusion is complicated and requires drainage. The studies upon which these recommendations are based, however, have extensive limitations in design.
Amylase (ordered in selected settings)	Elevated in patients with empyema secondary to esophageal rupture (elevated salivary isoenzyme of amylase); elevated in pancreaticopleural fistula (elevated pancreatic isoenzyme of amylase).

LDH, lactate dehydrogenase; PF, pleural fluid.

TABLE 76-6 Stages of an Empyema

Exudative	Increased permeability of pleural membranes with influx of inflammatory cells and protein-rich exudate. Most patients will respond to antibiotics without pleural drainage.
Fibrinopurulent	
Early fibrinopurulent	Increased procoagulant activity in the pleural space promotes deposition of fibrin with early septation of the effusion. Pleural fluid becomes more viscous with increasing LDH and decreasing glucose and pH. Some patients may respond to antibiotics alone but drainage becoming increasingly likely.
Late fibrinopurulent	Extensive fibrin deposition on pleural membranes causing loculations and pleural rind. Viable bacteria present with markedly increase PF LDH and low glucose and pH. Pleural fluid appears macroscopically purulent. Pleural fluid drainage and possibly decortication required.
Organizing	Fibroblast proliferation generates a fibrous pleural peel that requires decortication. A trapped lung may occur if the empyema space is not obliterated.

place.[105] Tubes smaller than 12-French have a higher failure rate in empyema,[105] making a 14-French tube a reasonable initial choice in most situations.

If the pleural space is not fully drained with a chest tube alone, typically due to a multiloculated space, instillation of tissue plasminogen activator (t-PA) and DNAse has been demonstrated to achieve effective drainage, a lower likelihood of being referred for surgery, and a shorter mean hospital stay.[105] Despite improvements in these clinical outcomes, a mortality benefit has not yet been demonstrated with t-PA and DNAse. Additionally, t-PA is associated with a median hospital length of stay of 12 days, which is considerably longer than the 5- to 7-day length of stay reported in series employing VATS drainage.[106–109] Pleural thickening >4 mm, a parenchymal abscess, or necrotizing pneumonia were found to be predictors of treatment failure.[110]

Saline irrigation alone via tube thoracostomy for pleural infection has been shown in a pilot study to improve pleural fluid drainage and decrease surgical referral[111] and, thus, can be used in patients who are not candidates for surgery or tPA/DNAse.[112]

Indications for, and optimal timing of, surgical drainage in PPE and empyema are less clear. VATS may be definitive treatment in 85% to 91% of patients and, as noted above, may actually shorten length of stay compared to nonsurgical management.[106,113] Earlier surgery has been associated with a lower risk of conversion to thoracotomy and fewer complications than when performed later in the disease course.[114] Based upon the assumption that earlier surgical intervention may be warranted in patients at higher risk for poor outcomes, a risk stratification model has been developed that predicts mortality at 3 months. The RAPID (Renal function, Age, Purulence, Infection source, Dietary factors) scoring system classifies patients at presentation into low-, medium-, and high-risk categories that are associated with 3-month mortality of 3%, 9%, and 31%, respectively.[104] Further validation of this model, as well as confirmation that patients identified as high risk would, indeed, benefit from earlier surgical intervention, are required before use of this model in decision-making can be considered standard of care.

Empyema management was evaluated in nearly 4100 patients in the New York State Inpatient Database from 2009 to 2014.[107] The initial modality of treatment was as follows: chest tube (68%), VATS (19%), or open surgical intervention (14%). Patients who initially received a chest tube were older and had more comorbidities and higher levels of shock. For patients initially receiving a chest tube, nonsurgical management was achieved in 56% of patients, while 85% of patients receiving an initial VATS were managed successfully. In patients receiving surgical therapy initially, the hospital mortality, 30-day readmission rate, and need for another intervention were all significantly lower. However, there were limitations of this study, including a healthier patient population undergoing VATS. Furthermore, the study did not take into account patients who received tPA and DNAse.

■ Tuberculous Pleurisy

Geography plays a pivotal role in determining the pretest probability of a tuberculous pleural effusion. In the developing world, tuberculosis (TB) accounts for 30% to 80% of all pleural effusions and may result from primary infection or reactivation of disease.[115,116] This percentage estimate drops to roughly 1% in developed countries. Interestingly, pleural effusions are seen in up to 30% of patients in the developing world who present with pulmonary TB, versus only 3% to 5% in developed countries.[117] One caveat to this rule in the developed world is a higher prevalence of disease in persons with HIV coinfection.[117]

Two mechanisms for development of a tuberculous pleural effusion have been postulated. One suggests a T helper cell–mediated delayed hypersensitivity reaction related to the entry of mycobacterial antigen into the pleural space from a ruptured subpleural caseous foci.[118] Another suggests a paucibacillary infection of the pleural space that likely spread from an adjacent parenchymal lesion.[117,119] In any event, the clinical presentation is often acute or subacute, with fever (75%), pleuritic chest pain (50%–75%), and a nonproductive cough (70%–75%). Other symptoms include night sweats (50%), dyspnea (50%), and weight loss (25%–85%).[120,121]

Tuberculous effusions are typically unilateral and encompass less than two-thirds of the hemothorax. Chest CT scans can detect parenchymal changes consistent with active pulmonary TB in up to 80% of patients.[122] Sampling of the effusion typically demonstrates a lymphocyte predominance (>60% lymphocytes), although a neutrophilic predominance exists early in the disease course. Hence, in the proper clinical setting the clinician should still consider TB. Other pleural fluid chemistry characteristics include protein concentrations greater than 3g/dL in 55% to 77% of cases, and glucose and pH levels that mirror those of serum.[123,124]

Adenosine deaminase (ADA) can be a useful tool to support a diagnosis of TB. In endemic areas, a lymphocytic predominant effusion with an ADA >40 confirms the diagnosis in more than 90% of patients after a single thoracentesis.[120,121] However, it should be noted that ADA may be elevated in other diagnoses (e.g., lymphoma).[125,126] An ADA level of <40 adequately excludes the diagnosis in high-prevalence settings.

Pleural fluid staining for acid-fast organisms has a low yield (frequently <20%) except in the presence of concomitant HIV infection.[126] Pleural fluid culture sensitivity has traditionally been reported to be less than 50%; however, with use of liquid culture the yield may approach 75%.[127,128] Although sputum culture is positive in only 4% of patients with isolated pleural TB, the yield is >50% in patients with parenchymal infiltrates; when combined with pleural fluid cultures, a diagnosis may be established in 79% of cases.[129] In cases where a diagnosis is not achieved through thoracentesis and sputum culture, closed or ultrasound-guided pleural biopsy can increase the diagnostic yield to 82%–92%.[130] At least six pleural biopsies should be obtained, with samples sent for acid-fast stain, culture, and histopathologic inspection for granulomata.[131]

Without treatment, a tuberculous effusion typically undergoes slow resolution; however, an untreated patient has a 65% chance of developing active pulmonary or extrapulmonary TB in the next 5 years.[126,132,133] Treatment of tuberculous pleurisy is the same as for pulmonary tuberculosis, with a four-drug regimen for susceptible organisms. Consultation with an infectious disease expert is recommended in managing patients who reside in, or have emigrated from, regions with high levels of drug resistance.[134] Two-thirds of patients have residual pleural thickening, which can result in trapped lung and dyspnea due to a restrictive ventilatory defect. Complex or loculated effusions, long duration of symptoms prior to therapy, and CT evidence of extrapleural fat proliferation have been identified as risk factors for pleural thickening at 1 year.[135]

■ Other Infectious Etiologies

Acute viral respiratory infections may be associated with transient pleural effusions and likely account for a higher percentage of effusions than is generally appreciated.[136] In one study of patients with signs and symptoms of a lower respiratory tract infection and a positive viral PCR, 20% of patients had pleural effusions.[137] Pleural effusions may be seen in up to 62% of patients with adenovirus pneumonia,[138] endemic influenza, and avian influenza (H1N1) influenza, as well as endemic coronavirus and SARS-CoV-2.[139–141] Effusions due to viral infections are typically exudates with a mononuclear cell predominance.[142] Bacterial superinfection should be ruled out in patients with a pleural effusion temporally related to a viral infection.

Fungal infections may lead to pleural effusions, particularly in an immunocompromised host, and are typically caused by pleural seeding from a fungal pneumonia or other site of infection. Commonly implicated pathogens include *Candida*, *Aspergillus*, *Blastomycosis*, and *Coccidioides* species.[143,144] *Coccidioides*, in particular, has the ability to spread from an acute pulmonary infection to the pleural space in up to 15% of patients hospitalized with the infection.[145,146] The pleural fluid in acute coccidiomycosis infection is classically exudative and rich in eosinophils.[145,146] *Cryptococcus* and *Histoplasma capsulatum* rarely produce pleural effusions, and effusions due to *Histoplasma* may be attributed to fibrosing mediastinitis.[147,148]

■ Pulmonary Embolism

Pulmonary embolism (PE) is estimated to be the fourth leading etiology of pleural effusion in the United States.[149] Pleural effusions occur in 35% to 47% of patients with PE, and most are unilateral, typically occupying less than half the hemithorax.[150] The pathogenesis of pleural effusion associated with PE is unknown, but it is believed to be related to a cascade of events involving occlusion of the artery leading to ischemia distal to the embolus, and cytokine release leading to increased vascular permeability.[150–152] This, in turn, leads to increased fluid formation in the pleural space and overwhelming of the capacity of the lymphatic vessels to remove the fluid.[153]

The presence of unilateral, pleuritic chest pain in a patient with a pleural effusion should raise suspicion of PE. Pleural fluid is exudative and bloody (>10,000 RBC/μL) in approximately two-thirds of patients. Pleural fluid eosinophilia is seen in up to one-third of patients and may provide a clue to etiology.[150] Reabsorption of pleural fluid after initiation of anticoagulation typically occurs within 7 to 10 days in patients without radiographic evidence of infarction, and in 14 to 21 days in those with this finding.[154] It is reasonable to forego thoracentesis in most patients with small effusions in the setting of proven PE unless there are atypical features suggesting an alternative diagnosis (e.g., fever, large effusion). In particular, an increase in the size of the effusion after initiation of anticoagulation should prompt thoracentesis to evaluate for secondary hemothorax.

■ Hemothorax

Many pleural effusions have an appearance of being “bloody,” as a pleural fluid hematocrit >5% may have a similar appearance to blood.[150,155] To meet criteria for hemothorax, however, the pleural fluid hematocrit must be >50% of the simultaneous peripheral blood hematocrit.[152] If the pleural fluid is not spun for a hematocrit, one can estimate the pleural fluid hematocrit by dividing the pleural fluid RBC count by 100,000. If the pleural fluid appears bloody and the hematocrit is <50%, it is considered a hemorrhagic effusion but not a true hemothorax.

The majority of cases of hemothorax are related to blunt or penetrating trauma, or to thoracic procedures and surgery (Table 76-7).[152,156] Rarely, spontaneous hemothorax occurs from either a torn adhesion between the parietal and visceral pleura, rupture of a vascularized bullae in the lung, deposits of endometrial tissue in the thorax (catamenial hemothorax), or congenitally aberrant vessels between the parietal pleura and bullae.[155] In instances of trauma, initial evaluation with ultrasound in the emergency department has a sensitivity of 92% and a specificity of 100% for detecting hemothorax.[157]

Tube thoracostomy is the best first step to drain a hemothorax. A large-bore (at least 28Fr) tube has traditionally been recommended to prevent obstruction of the tube from clots; however, more recent

TABLE 76-7 Causes of Hemothorax

Condition	Comments
Coagulopathy and bleeding diatheses	Hemothorax due to primary coagulopathies, thrombocytopenia, anticoagulant therapy, or systemic and intrapleural fibrinolytic therapy rarely occur
Pneumothorax and ruptured lung bullae	Hemothorax uncommon with spontaneous pneumothorax but can occur especially with ruptured lung bullae
Neurofibromatosis	Rupture of friable vasculature in patients with neurofibromatosis may occur by vascular invasion or arterial dysplasia
Arteriovenous malformations	Arteriovenous malformations rarely bleed into the pleural space with one-half of instances related to Osler–Weber–Rendu disease
Aneurysms	Dissection or rupture of a major intrathoracic artery is a common and usually clinically apparent cause of hemothorax; most commonly aortic but also pulmonary vasculature
Ehlers–Danlos disease	Associated with internal mammary artery rupture
Connective tissue diseases	Rare reports
Extramedullary hematopoiesis	Rare reports
Endometriosis	Varying degrees of hemorrhagic effusions or hemothorax
Exostoses	Formation of new bone on the surface of existing bone creates sharp bony edges that can erode adjacent vascular structures and cause hemothorax
Postpartum	Related to thoracic pressure changes during labor straining

data suggest no difference between a 28Fr and 20- to 22Fr tube with respect to successful drainage or complications.[158] Surgical exploration is indicated for persistent bleeding or shock and is typically a definitive procedure.[159–162] Clinicians must be mindful of retained and loculated collections of blood, as these can be a nidus for infection and the development of fibrothorax and resultant trapped lung.[163]

Vasculitis

Pleural effusions have been reported in multiple vasculitides, including granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA), giant cell arteritis, and Behçet disease.[164–166] In most of these disorders, pleural effusion occurs in a minority of the cases and is a late clinical manifestation. Reports of pleural fluid evaluation in vasculitides are rare, but they typically describe nonspecific exudates. EGPA has been reported as having increased eosinophils.[167,168] Treatment of the effusion includes systemic immunosuppression, although if disease is advanced, more invasive management may be required.[166]

Superior Vena Cava Syndrome

Pleural effusion complicates superior vena cava (SVC) syndrome in 6% to 70% of cases.[169] SVC syndrome occurs when there is either external compression or intrinsic blockage of the SVC. It is seen most commonly in patients with mediastinal malignancies, but it has also been described in neonates after placement of central venous catheters.[169–174] The effusion is exudative and may be chylous (18%). It is relieved with resolution of SVC syndrome.[171,172,174]

Systemic Lupus Erythematous

Pleurisy is one of the 11 diagnostic criteria for systemic lupus erythematous (SLE) and occurs in 34% to 60% of patients during their disease course.[175] Approximately 80% of patients have other organ involvement, and 16% will have concomitant pericardial effusions.[176] Pleural inflammation may manifest as pleuritic pain in the absence of pleural effusion, but more commonly presents with either unilateral or bilateral pleural effusions. The presence of pleuritic pain has been reported to be a poor prognostic indicator, with a mean survival of less than 4 years.[177] Because patients are commonly on immunosuppressive agents, an infectious etiology must also be considered.[178]

The typical pleural fluid profile is shown in Table 76-8. Pleural fluid ANA is usually positive, but it does not provide incremental diagnostic value beyond that of a positive serum ANA.[178,179] Occasionally, lupus erythematous cells can be identified on cytologic examination of the fluid.

Nonsteroidal anti-inflammatory drugs are the initial treatment of choice, with corticosteroids reserved for refractory cases. Relapses occur in approximately 13% of patients.[176] In rare instances where effusions are large and refractory to treatment, pleurodesis may be necessary.[180] Lupus pleuritis may also rarely progress to fibrothorax and trapped lung if the disease course is not altered by treatment.[181]

Rheumatoid Arthritis

The most common thoracic manifestation of rheumatoid arthritis (RA) is pleural disease, including pleural thickening and pleural effusion that may occur at any time throughout the disease course.[180,182,183] Pleural effusions occur in up to 20% of patients, with 80% occurring in men.[184] Patients are most commonly asymptomatic from the effusion but often have concurrent evidence of active arthritis, rheumatoid lung lesions, or subcutaneous nodules.[181,182,184] The pleural profile is listed in Table 76-8, but clinicians must always rule out an infectious etiology, given that pleural fluid glucose and

TABLE 76-8 Pleural Fluid Test Results in Common Autoimmune Causes of Pleuritis

Finding	Lupus Pleuritis	Rheumatoid Arthritis
Appearance	Clear	Variably serous, purulent, milky, hemorrhagic
Protein	Low in exudative range	High in exudative range
Glucose	Similar to serum	Often low <30 mg/dL
Leukocytes	3–5000/μL	Usually $<10{,}000$/μL
Complement	Low	Low
Immune complexes	High	High
PF ANA	Positive	Variable
LDH	Twice upper limits of normal for serum	High
Rheumatoid factor	Low	Elevated

PF, pleural fluid; LDH, lactate dehydrogenase; ANA, antinuclear antibody.

pH are commonly low. Low pleural fluid glucose is due to impaired glucose transport through the pleura,[185] and pleural fluid glucose levels of <30 mg/dL are seen only in patients with RA or empyema.

Most effusions related to RA resolve spontaneously or with systemic disease-modifying medication, although a recent study suggested the presence of an effusion as an independent marker for mortality.[186] Large, refractory effusions should be drained, as without intervention fibrothorax and trapped lung may result.[181] Chronic rheumatoid arthritis–related effusions are also one of the most common causes of "cholesterol" or "pseudochylothorax" effusions.[187]

Other connective tissue diseases also can manifest with pleural effusion. Patients with Sjögren syndrome commonly develop recurrent pleuritic chest pain, but only 9% of patients have pulmonary manifestations, and 1.2% have pleural effusions.[188] Up to 7% of patients with systemic sclerosis may have a pleural effusion, which is typically lymphocytic-predominant.[175] Mixed connective tissue disease commonly involves the pleural space, with 35% of patients experiencing pleurisy and 50% having a pleural effusion.[189] Ankylosing spondylitis, dermatomyositis, and polymyositis have rarely been reported as complicated by exudative effusions.[190–194]

■ Sarcoidosis

Sarcoidosis is a multisystem disease, the hallmark of which is the presence of noncaseating granulomas.[195,196] Pleural involvement is infrequent, with the majority of published clinical series suggesting a prevalence of 1% to 2%.[196] Patients with sarcoidosis-related effusions tend to have both pulmonary parenchymal and extrapulmonary disease.[196–198] Effusions are typically unilateral, and the majority are exudative, although transudative effusions also have been described.[195] The effusions tend to be lymphocytic predominant, with a high CD4/CD8 ratio.[195]

A definitive diagnosis of sarcoidosis-related pleural effusion requires demonstration of noncaseating granulomas on pleural biopsy and exclusion of infectious etiologies, such as TB and fungal disease.[199] Administration of corticosteroids leads to resolution of the fluid in as little as 2 weeks, but reports have also described spontaneous resolution without therapy.[200]

■ Pancreatitis and Pancreatic Fistulae

Pleural effusions are frequently present in patients hospitalized with acute pancreatitis, with a prevalence approaching 50% in some case series.[201–203] The mechanism of pleural fluid formation in pancreatitis is attributed to multiple etiologies, including the release of proinflammatory mediators from the pancreas into the circulation, transdiaphragmatic transit of parapancreatic inflammatory exudates, lipolysis of mediastinal fat, and early formation of pancreaticopleural fistulae.[201] The pleural fluid is exudative and often has a low pH and high amylase.[204,205] It should be remembered that elevated pleural fluid amylase can also be seen in patients with TB, esophageal rupture, and malignancy. The presence of a pleural effusion is associated with more severe pancreatitis, and patients may have a mortality of up to a 30%.[202,203] The majority of pleural effusions (68%) are left-sided; bilateral (22%) and right-sided (10%) effusions occur less commonly.[206,207] Effusions are typically small, exudative, occasionally bloody, and characterized by a high amylase (as high as 30 times the serum level).[204]

A pancreaticopleural fistula may develop when the main pancreatic duct is disrupted, leading to leakage of pancreatic enzymes through the diaphragm. Posterior disruptions of the duct can track into the retroperitoneum, then mediastinum, and, ultimately, rupture into the pleural cavity, creating a connection between the pancreatic duct and the pleural cavity.[207–210] This is more commonly seen in chronic pancreatitis, with alcohol-related pancreatitis (51%) representing the most frequent underlying cause.[209–211] Magnetic resonance cholangiopancreatography (MRCP) is the most sensitive means of demonstrating a pancreaticopleural fistula; other options include endoscopic retrograde cholangiopancreatography (ERCP) and abdominal/chest CT scanning.[207,211–213] Closure of the fistula can be achieved via medical therapy aimed at treating chronic pancreatitis or endoscopic or surgical procedures.

■ Chylothorax

The thoracic duct carries 60% to 70% of ingested fat from the intestines and contains large amounts of cholesterol, triglycerides, chylomicrons, and lymph.[214] Additionally, chyle is rich in lymphocytes and immunoglobulins.[215] The thoracic duct originates in the cysterna chyli and courses superiorly through the esophageal hiatus of the diaphragm into the thorax. It travels extrapleurally on the right side of the chest, crosses the midline at approximately the level of the fourth to sixth thoracic vertebrae, and terminates in the cervical region in the subclavian vein. This "textbook" path, however, occurs in only 65% of patients, and multiple other routes have been described.[214]

A chylothorax occurs when chyle leaks into the pleural space as a result of disruption of the thoracic duct at any point along its course. Trauma accounts for approximately 50% of cases and can be a consequence of thoracic surgery, neck surgery, blunt or penetrating chest trauma, or instrumentation, such as central venous catheter or pacemaker insertion.[214,216–221] Disruption of the duct subsequently leads to buildup of chyle in the mediastinum, with subsequent rupture of the mediastinal pleura and chylothorax.[222] Malignancy, most commonly lymphoma, is the most frequent nontraumatic etiology.[223] Other less common nontraumatic etiologies include yellow nail syndrome, amyloidosis, retrosternal goiter, lymphangioleiomyomatosis, and sarcoidosis (Table 76-9).

Chylous effusions are most commonly unilateral, but they may be bilateral in 20% of cases.[223] The laterality of the effusion is dictated by whether the site of disruption is below or above the T5 vertebral body, where the thoracic duct typically crosses over from the right to the left side. Although chylous fluid classically has a characteristic milky appearance (Fig. 76-2) in patients eating a standard diet, this characteristic is often lacking in fasting patients. A pleural fluid triglyceride level of >110 mg/dL is considered diagnostic, while a level <50 mg/dL excludes the diagnosis.[224] If the pleural fluid triglyceride level is between 50 and 110 mg/dL, chylomicron analysis is indicated, although not all centers can perform this test.[225] In one

TABLE 76-9 Causes of Chylothorax

Classification	Comments
Traumatic	Account for 50% of chylothoraxes with thoracic surgery most common cause. Also occur after neck surgery, central venous catheter and pacemaker insertion, blunt chest injury, traction injuries to the chest and neck, and sudden pressure changes with sneezing, vomiting, or labor and delivery.
Nontraumatic	Lymphoma has decreased in incidence to 11% because of earlier lymphoma diagnosis. Less common causes include congenital or acquired lymphatic disorders, constrictive pericarditis, SVC syndrome, lymphangiomatosis, lymphangiectasias, lymphangioleiomyomatosis, Noonan syndrome, yellow nail syndrome, Down syndrome, granulomatous infections, and thyroid goiter.
Idiopathic	Small number idiopathic despite a complete diagnostic evaluation.

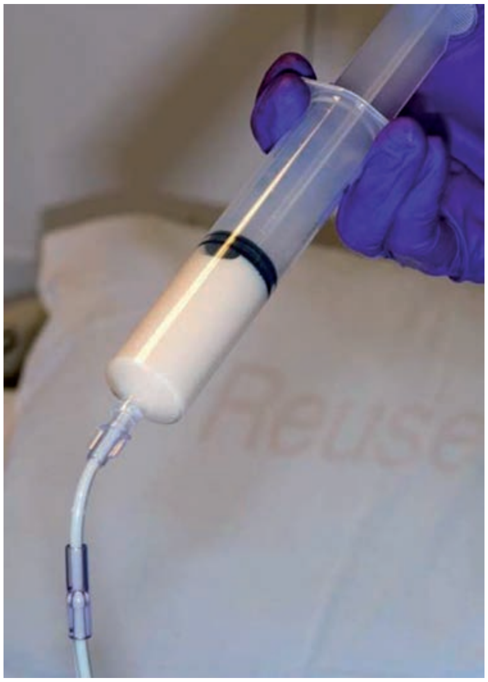

Figure 76-2 Sample of pleural fluid from a patient with chylothorax.

series, detection of chylomicrons was seen in 14% of patients with a triglyceride level less than 110.[226] If chylomicron analysis is not available, repeat pleural fluid triglyceride measurement after ingestion of a high fat meal can sometimes confirm the diagnosis.

Once the diagnosis has been established, continued drainage of the pleural space via chest tube or repeated large-volume thoracentesis should be avoided, as this can result in depletion of protein and lymphocytes, potentially leading to malnutrition and immunosuppression. Conservative measures to decrease the formation of chyle by administration of a low-fat/high medium chain triglyceride diet or total parenteral nutrition can lead to resolution of the leak in some cases of traumatic chylothorax, and it may take up to 2 weeks for chest tube output to improve.[227] Treatment of the underlying medical cause for chylothorax may be effective (e.g., administration of chemotherapy for lymphoma or sirolimus for lymphangioleiomyomatosis).

For those with refractory effusions, imaging to identify the site of thoracic duct disruption is often performed. This was previously accomplished using lymphangiography or lymphoscintigraphy, but magnetic resonance lymphangiography has supplanted these modalities at some centers.[228]

Thoracic duct embolization has emerged as a nonsurgical option for treating refractory thoracic duct leaks, with a success rate of up to 90% for traumatic chylothoraxes, and 50% for nontraumatic cases when performed by an experienced operator.[229] Surgical ligation of the thoracic duct is reserved for patients who fail more conservative measures and is best suited for postoperative chylous effusions. Finally, IPCs and pleurodesis may be an effective measure for both traumatic and nontraumatic cases; however, outcomes are typically better with traumatic chylothoraces, and surgery remains the treatment of choice as long as patients are good surgical candidates.[224,230]

■ Pseudochylous Effusions

Pseudochylothorax (also called “chyliform” or “cholesterol pleural effusion”) derives its name from the often milky appearance of the pleural fluid, similar to chylothorax. Pseudochylothorax, however, results from a markedly elevated cholesterol content and does not contain chylomicrons.[231]

Pseudochylothorax is usually the result of an exudative effusion that remains in the pleural space for an extended period of time—often 5 years or longer—with gradually increasing cholesterol concentrations (most commonly, high-density lipoprotein) due to impaired transfer out of the pleural space.[232,233] The most frequent causes are TB and rheumatoid pleuritis; rare causes include infection (e.g., echinococcosis, paragonimiasis), neoplasia, trauma, and prior pericardial injury (e.g., following cardiac surgery).[231,234–236] Most pseudochylous effusions are unilateral and accompanied by pleural thickening.

Pleural fluid analysis demonstrates a high cholesterol content (>200 mg/dL) and may have cholesterol crystals seen on microscopy. Triglyceride levels are typically below 110 mg/dL.[231] Pleural biopsy may occasionally reveal the etiology, but the yield is quite low.[237] Treatment is directed at the underlying etiology, such as TB or rheumatoid arthritis. Most patients are asymptomatic, but large effusions causing dyspnea may be addressed with thoracentesis, pleurodesis, or, in cases of trapped lung, decortication.[237,238]

■ End-Stage Renal Disease

Approximately 50% of patients receiving hemodialysis with acute respiratory complaints have pleural effusions when evaluated by CT scans.[238,239] The most common causes of pleural effusion in this patient population mirror those of the general population and are related to congestive heart failure, pneumonia, tuberculosis, malignancies, and volume overload.[240]

Pleural effusions can also develop as a consequence of uremia.[241,242] The mechanism by which uremia leads to pleural inflammation and effusion is not well understood, but it likely shares a similar pathogenesis with uremic pericarditis. Effusions may be unilateral or bilateral and can be large, occupying 50% or more of the pleural cavity.[241] Pleural fluid is exudative, lymphocytic predominant, and bloody nearly half the time. As there are no characteristic features, uremic pleuritis is a diagnosis of exclusion.[241]

Treatment involves initiation or augmentation of hemodialysis, which leads to disappearance of fluid in 52% to 75% of patients.[241,243–247] Rarely, decortication is necessary for patients who develop pleural fibrosis with trapped lung.[248]

■ Post–Cardiac Surgery

At least 40%, and up to 63%, of patients who undergo coronary artery bypass graft (CABG) surgery develop a pleural effusion in the first 28 days post-surgery as a consequence of the surgery itself, in the absence of complications.[249–251] While effusions post-CABG have been most widely reported, the incidence of effusion after valve-only surgery can approach 45%.[252]

The pathogenesis of these effusions is likely related to some combination of the effects of topical cardiac cooling, surgical interruption of the lymphatic channels, direct surgical injury of the pleura, and pericarditis.[251,253] The effusions are typically left-sided and occupy less than 25% of the hemithorax.[251,253] Most effusions resolve spontaneously. If effusions persist, enlarge, or cause dyspnea, it is reasonable to pursue a thoracentesis to exclude other etiologies or for symptomatic relief. If thoracentesis is required, the minority of patients will require more than one or two procedures. Although some clinicians routinely use nonsteroidal anti-inflammatory medications or corticosteroids, data supporting their use are lacking. Pleural fluid present within the first 30 days of surgery is typically bloody and neutrophilic and may contain >10% eosinophils. Late-developing effusions are typically nonbloody and have a lymphocytic predominance.[251,253,254]

An alternative cause for pleural effusions developing in the early post-operative period is postcardiac injury syndrome (Dressler syndrome), which is characterized by pericarditis, pulmonary infiltrates, and pleural effusions.[255–257] In contrast to the more commonly occurring asymptomatic effusions described above, patients who develop this syndrome are often febrile and experience chest pain. The presence of a pericardial or pleural friction rub is a clue to the diagnosis. Pleural effusions are usually small and left-sided, hemorrhagic, and neutrophil-predominant in the acute phase, evolving to lymphocyte-predominant over time.[258] Nonsteroidal anti-inflammatory drugs are the initial treatment of choice. Corticosteroids are used in more severe or refractory cases.

■ Meigs Syndrome

Meigs syndrome is defined by the presence of pleural effusions and ascites in association with an ovarian fibroma or fibrothecoma.[259,260] Pleural fluid accumulation in Meigs syndrome is postulated to result from efflux of ascites from the peritoneal cavity into the pleural space via diaphragmatic rents. The mechanism responsible for development of ascites is a matter of conjecture. One theory suggests that inflammatory cytokines and growth factors, possibly produced by the ovarian tumor, lead to vascular permeability within the peritoneal cavity.[261] The finding of high levels of vascular endothelial growth factor (VEGF) and interleukin 6 in serum, ascites, and pleural fluid in patients with Meigs syndrome support this hypothesis.[262] Weeping of fluid from the tumor itself also may play a role. Elevated CA-125 levels have been detected in patients with Meigs syndrome, creating diagnostic uncertainty by raising suspicion for a malignant ovarian tumor.[263]

As with most pleural effusions that result from ascites, the pleural effusion in Meigs syndrome is most commonly unilateral and right-sided, occupying more than one-third of the hemithorax in two-thirds of cases.[262] Presenting symptoms include dyspnea, abdominal distention, fatigue, and weight loss. The published literature contains scant information on pleural fluid characteristics but suggests that most effusions due to Meigs syndrome are exudative. The finding of a transudative effusion does not, however, exclude this diagnosis.[262]

Treatment of Meigs syndrome centers on surgical removal of the responsible ovarian tumor, which is considered curative, given the benign nature of the tumors associated with this syndrome. Pleural effusion and ascites typically resolve within several weeks of tumor resection.

MANAGEMENT OF RECURRENT AND PERSISTENT EFFUSIONS

Independent of etiology, many nonmalignant pleural effusions are responsive to initial drainage and treatment of the primary disorder. However, there exists a subset of patients whose effusions persist or recur despite conservative management. In these instances, additional intervention(s) may be required.

■ Repeat Thoracentesis

Repeat thoracentesis under ultrasound guidance is typically the first-line option. This can serve as a destination therapy in patients who derive symptomatic improvement with drainage and have slowly reaccumulating effusions, and also for patients with a short life expectancy. Additionally, a repeat thoracentesis affords the clinician another opportunity to make a minimally invasive diagnosis if the etiology is still in question. Repeated thoracenteses should be avoided in asymptomatic patients and those who did not experience relief with initial drainage. For those who do benefit, but who require more than two or three thoracenteses in a relatively short time, a more definitive therapy (e.g., pleurodesis or IPC) should be considered.

■ Pleurodesis

Pleurodesis is defined as obliteration or ablation of the pleural cavity through induction of pleural inflammation and fibrosis.[264,265] This can be achieved via chemical (e.g., talc) or mechanical (e.g., manual abrasion) means. Chemical pleurodesis can be performed via a chest tube (i.e., talc slurry) or thoracoscopically (i.e., poudrage/insufflation), while mechanical pleurodesis is performed only via surgical intervention. Chemical pleurodesis utilizes a variety of sclerosing agents, but the most commonly used presently is talc. Treatment failure rates for patients with malignant pleural effusion are similar for chemical pleurodesis administered via chest tube and VATS; however, comparative efficacy data are lacking in patients with nonmalignant effusion.[265,266]

Patients best suited for pleurodesis are those who experience symptomatic improvement following drainage, have expandable lung, or experience rapid reaccumulation of fluid, and for whom indwelling pleural catheter is deemed to be an inappropriate or less suitable alternative. Case series have documented successful management in patients with such diverse etiologies as peritoneal dialysis-related effusions,[267,268] yellow nail syndrome,[269] chylothorax,[270,271] nephrotic syndrome,[272] heart failure,[46,273,274] and hepatic hydrothorax.[62,275–277] The success rate of pleurodesis in NMPEs ranges from 47% to 80%, depending on the case series and etiology, with hepatic hydrothorax having a higher rate of failure and a high risk of infectious complications.[62,278–280] Importantly, the pleural space needs to be fully (or at least ~90%) drained and the parietal and visceral pleura apposed for optimal results. This may be difficult to achieve with high-volume, rapidly reaccumulating effusions that often characterize hepatic hydrothorax. Some centers advocate the use of multiple chest tubes and large-volume paracentesis (for patients with concurrent ascites that is deemed to be the source of the pleural effusion) in order to keep the pleural space as dry as possible when pleurodesis is performed.

■ Indwelling Pleural Catheter

IPCs are tunneled under the skin and provide a source of intermittent drainage of the pleural space that obviates the need for repeated thoracenteses. They remain in place for several weeks to months and ideally are removed once fluid accumulation has ceased. A systematic review of 13 studies encompassing 325 patients with benign pleural effusions found that spontaneous pleurodesis occurred following IPC placement in 51% of patients, with slightly higher rates in noncardiac causes. Complications occurred in 17% of patients, including empyema and cellulitis.[48,281]

FUTURE DIRECTIONS

The last decade has seen a tremendous increase in our understanding of nonmalignant pleural effusions, primarily resulting from large, multicenter, randomized trials. There are still many unanswered questions, however. For example, pleural infection affects a broad group of patients with a diverse spectrum of comorbidities. We need to examine if current predictive models, such as the RAPID score[104] or chest ultrasound, can be used to select patients for medical versus early surgical therapy.

In an ongoing trial (ISRCTN18192121), investigators are comparing early intrapleural TPA/DNase versus early VATS in patients with pleural infection.[282]

The optimal management for effusions due to CHF and hepatic hydrothorax also needs to be investigated, given that these disorders comprise a significant healthcare burden and are associated with extremely high mortality rates.[5,282]

As we better understand the molecular mechanisms of pleural fluid formation, it may be possible to directly inhibit formation or stimulate resorption. The formation of multicenter collaborative groups whose focus is on pleural disease will certainly contribute to high-quality research, improve our understanding of disease and treatment, and ultimately improve the care of our patients.[283,284]

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CHAPTER 77

Malignant Pleural Effusions

Jeffrey C. Thompson
Kevin C. Ma

INTRODUCTION

A malignant pleural effusion is defined by the accumulation of fluid in the presence of malignant cells or tumor tissue in the pleural space. Malignant pleural effusions are common, affecting approximately 15% of patients with malignancies, and account for more than 125,000 hospitalizations in the United States annually, with estimated healthcare costs of greater than $5 billion per year.[1,2] The incidence of malignant pleural effusions is expected to rise as a result of the increasing global cancer prevalence and development of more effective systemic therapies.[3] The presence of a malignant pleural effusion is a hallmark of advanced-stage disease and denotes a poor overall prognosis, with a median survival ranging between 3 and 12 months depending on the primary tumor type.[4] Although some patients may be asymptomatic, the majority develop dyspnea at rest with associated reduced quality of life.[5] Despite advancements in understanding the pathophysiology of malignant pleural effusions and remarkable progress in cancer treatments over the last decade, management strategies for malignant pleural effusions remain palliative, with the goal of relieving patient symptoms and minimizing the need for repeat invasive procedures.

ETIOLOGY

Although any malignancy may involve the pleura, epithelial malignancies account for approximately 80% of malignant pleural effusions, with lung and breast cancer representing the majority of cases (Table 77-1). Lung cancer is the leading cause of a malignant pleural effusion, which is present in an estimated 15% of lung cancer patients at diagnosis and develops in up to 50% of patients during the course of their disease. Effusions can occur with any lung cancer histology but are most frequent in adenocarcinomas.[6,7] Breast cancer is the second leading cause of a malignant pleural effusion. Approximately 7% to 11% of breast cancer patients will develop a malignant effusion, and these effusions are typically unilateral and ipsilateral to the primary tumor site.[8–10] Other carcinomas that commonly cause malignant pleural effusions include malignancies of gastrointestinal and ovarian origin. Lymphomas, including both Hodgkin and non-Hodgkin lymphomas, are the most common hematologic malignancies associated with malignant pleural effusions and account for approximately 7% to 16% of all cytologically confirmed malignant pleural effusions.[11,12] Patients with a malignant pleural effusion due to lymphoma typically have mediastinal lymph node involvement.[13] The primary origin of the tumor is not identified in approximately 10% of malignant effusions.[2,11] Malignant mesothelioma is the most common primary pleural tumor to cause a malignant pleural effusion; the incidence varies by geographic region and is highly correlated with exposure to asbestos.

TABLE 77-1 Most Common Primary Malignancies Among Patients with a Malignant Pleural Effusion (n = 126,825)

Cancer Type	Frequency
Lung	37.8%
Breast	15.2%
Hematologic	11.2%
Gastrointestinal	11.0%
Gynecologic	9.0%
Other	15.8%

Data from Taghizadeh N, Fortin M, Tremblay A. US Hospitalizations for Malignant Pleural Effusions: Data From the 2012 National Inpatient Sample. Chest. 2017;151(4):845–854.

Patients with malignancies may also have alternative causes for a pleural effusion. Effusions that are not the direct result of neoplastic involvement of the pleura but are still related to the primary tumor are termed *paramalignant effusions*.[14] For example, bronchial obstruction from a tumor may lead to postobstructive atelectasis resulting in a pleural effusion. These patients may also develop a postobstructive pneumonia producing a parapneumonic effusion. The hypercoagulable state of malignancy increases the incidence of pulmonary embolism in cancer patients, which is a common cause of exudative effusions. Other considerations include obstruction of the thoracic duct causing a chylothorax, cachexia leading to hypoalbuminemia and low plasma oncotic pressure, trapped lung as a result of an inflammatory pleural peel or extensive tumor involvement of the visceral pleura, and the impact of systemic treatments such as chemotherapy and radiation therapy ultimately leading to pleural effusions. Furthermore, concurrent comorbidities such as congestive heart failure may also account for pleural effusions in patients with malignant disease.

PATHOGENESIS

A pleural effusion develops when pleural fluid production exceeds reabsorption. The parietal pleura has lymphatic stomata: 2- to 12-µm openings between parietal pleura mesothelial cells that ultimately drain into lymphatic channels, with flow directed toward the mediastinal lymph nodes. This lymphatic system is the primary means by which pleural fluid and proteins are reabsorbed,[14] and the network has the ability to significantly augment lymphatic flow in response to increased pleural fluid production.[15] A pleural effusion develops as a consequence of substantial increases in pleural fluid production, impaired lymphatic drainage, or a combination of these two factors. In malignant pleural effusions, cancer cells can infiltrate this lymphatic system anywhere between the parietal pleura and mediastinal lymph nodes, resulting in the development of a pleural effusion.

Autopsy studies of lung cancer patients have shown that tumor cells metastasize through the pulmonary vasculature with subsequent embolization to the ipsilateral visceral pleura.[1,16] Dissemination to the parietal pleura occurs from direct extension from the visceral pleura through pleural adhesions or by exfoliation into the pleural cavity.[1,17] Pleural metastases may also develop through lymphangitic spread or through direct invasion of the pleura by the primary tumor. However, not all patients with pleural metastases have a malignant pleural effusion, and the presence of a malignant pleural effusion has been more closely associated with carcinomatous infiltration of the mediastinal lymph nodes than the extent of pleural involvement by metastases.[1,16] Although lymphatic obstruction secondary to tumor invasion was previously recognized as the primary pathophysiologic mechanism for the development of a malignant pleural effusion based on early autopsy studies,[16,18] blockade of pleural fluid reabsorption alone is not sufficient to explain malignant pleural effusion formation. Evidence suggests that additional factors are involved since fluid accumulation and protein content in cases of malignant pleural effusions often exceed the amount expected from lymphatic obstruction alone, and malignant pleural effusions are often bloody.[19,20] Increasingly, plasma leakage through hyperpermeable pleural vascular networks leading to increased fluid production is being recognized as a primary driver for the development of malignant pleural effusions, and significant progress has been made in recent years elucidating the molecular mechanisms involved in this process.[19]

The development of a malignant pleural effusion involves a complex interplay between tumor cells and host inflammatory, mesothelial, and endothelial cells within the pleural microenvironment to stimulate pleural inflammation, tumor angiogenesis, and vascular permeability. Both tumor and host cell production of vascular endothelial growth factor (VEGF) serves a central role in the development of malignant effusions.[21–23] VEGF is a powerful angiogenic factor and potent stimulator of vascular hyperpermeability, and a number of studies have demonstrated higher VEGF levels in the effusions of patients with malignant compared with nonmalignant effusions.[24,25] In an immunodeficient mouse model, IV injections of human lung cancer cells led to pleural metastases and produced pleural effusions with high levels of VEGF, and silencing of the VEGF gene resulted in significantly decreased malignant pleural effusion formation.[22,23] However, a more recent immunocompetent mouse model of malignant pleural effusion showed that inhibition of the transcription factor nuclear factor (NF)-κB limited pleural fluid effusion formation independent of VEGF levels, highlighting the role of alternative mediators involved in pleural effusion formation.[26]

More recent evidence suggests that tumor–host interactions, through autocrine and paracrine signaling networks, promote a cascade of inflammatory and vasoactive events that culminate in pleural effusion formation. These events are triggered by paracrine signaling to host cells, mediated through distinct transcriptional programs including NF-κB and signal transducer and activator of transcription (STAT) 3, to release inflammatory and vasoactive effector molecules including tumor necrosis factor α, interleukin (IL)-6, C-C-motif chemokine ligand (CCL) 2, secreted phosphoprotein 1 (SSP-1, also known as osteopontin [OPN]), and VEGF.[21,26–29] In addition, these mediators induce activation of resident host cells and stimulate the influx of inflammatory cells that promote a feedback loop further activating inflammation, vascular permeability, angiogenesis, and tumor progression. The recruitment of myeloid cells has been implicated in the pathogenesis of malignant effusion formation through secretion of IL-1β and subsequent activation of tumor NF-κB signaling.[30,31] The T cell population in malignant pleural effusions is dominated by central memory and regulatory T cells that support an immunosuppressive microenvironment enabling immune evasion and tumor growth; however, the role of lymphocytes in the development of malignant effusions remains uncertain.[32–34] These findings outline the contemporary view of the pathophysiologic mechanisms involved in the development of malignant pleural effusions, which involve complex host–tumor cell interactions that produce vasoactive and inflammatory signaling, host cell recruitment and activation, vascular permeability, angiogenesis, and tumor progression that culminate in fluid formation. Ultimately, these mechanistic insights may pave the way for novel therapeutic strategies for the management of malignant pleural effusions.

CLINICAL MANIFESTATIONS

Dyspnea, chest pain, and cough are the most common symptoms in patients presenting with a malignant pleural effusion, with dyspnea present in greater than half of all cases.[18] Dyspnea is often debilitating and can significantly impair quality of life. Since patients with a malignant pleural effusion have advanced-stage disease, systemic symptoms such fatigue, anorexia, and weight loss are often present. However, approximately 25% of patients may be asymptomatic at the time of initial presentation.[18] Malignant pleural effusions are often in excess of 500 mL, and the majority of patients will have an abnormal chest examination including decreased breath sounds and tactile fremitus, and dullness to percussion.

The mechanisms by which pleural effusions result in dyspnea have not fully been elucidated. Two observations argue strongly against lung atelectasis as the principal cause: (1) the magnitude of improvement in lung volumes following pleural drainage is far less than the volume of fluid removed; and (2) patients with trapped lung often derive significant symptomatic improvement after pleural drainage despite inability of the lung to re-expand. Evidence from several studies suggests that the major mechanism of breathlessness relates to outward displacement of the chest wall and downward displacement (and often inversion) of the hemidiaphragm.[35–37] Conversely, the often immediate improvement in dyspnea following a therapeutic thoracentesis is likely secondary to the restoration of chest wall and diaphragmatic mechanics.

DIAGNOSTIC APPROACH

Diagnostic evaluation includes imaging, pleural fluid analysis, and various pleural biopsy modalities.

Radiologic Evaluation

Imaging techniques employed in the evaluation of suspected malignant pleural effusions include chest radiography, thoracic ultrasonography, computed tomography, magnetic resonance imaging, and positron emission tomography.

Chest Radiography

Malignant pleural effusions are typically unilateral and ipsilateral to the primary tumor, although effusions may be bilateral in approximately 10% to 15% of cases.[18,38,39] The size of malignant pleural effusions varies from small volumes that partly obliterate the costophrenic angle on plain chest radiographs to larger volumes that result in complete opacification of the hemithorax and contralateral shifting of the mediastinum. The majority of malignant pleural effusions are in excess of 500 mL, with less than 10% of patients presenting with smaller effusions.[18] Malignant pleural effusion is the most common cause of a unilateral effusion occupying greater than two-thirds of the hemithorax (Fig. 77-1).[39] In a study evaluating 163 patients with an effusion occupying greater than two-thirds of the hemithorax, malignancy was identified in 55% of cases.[40]

In patients with large effusions, the absence of mediastinal shifting to the contralateral side suggests the possibility of obstruction of the mainstem bronchus by tumor as occurs in lung cancer, fixation of the mediastinum as a result of malignant lymph node involvement, or extensive pleural involvement as occurs in mesothelioma. Other abnormalities on chest radiography that may also be appreciated in the setting of a malignant pleural effusion include the presence of a pulmonary or mediastinal mass, thoracic lymphadenopathy, and lytic or sclerotic bony lesions. However, in patients with malignant tumors other than lung cancer or lymphoma, an effusion may be the only abnormality appreciated on chest radiography.[41]

Thoracic Ultrasonography

The use thoracic ultrasonography for the diagnosis of malignant pleural effusion has evolved significantly over the last decade as a

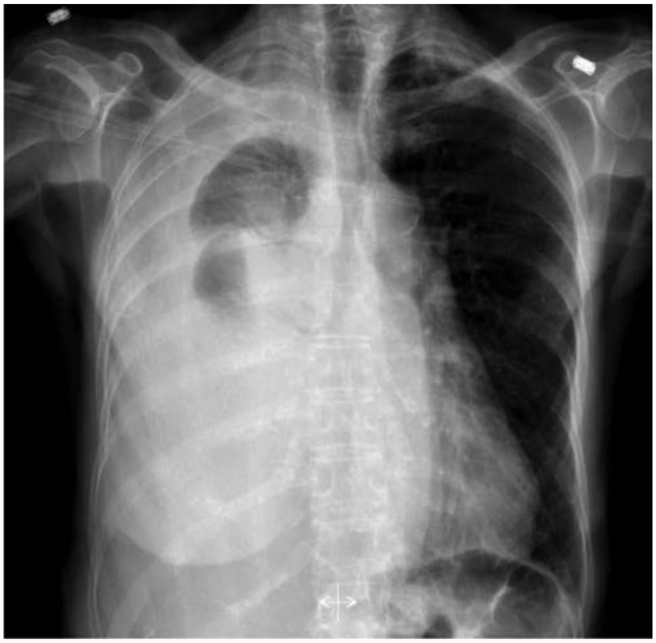

Figure 77-1 A posteroanterior chest radiograph from a patient presenting with shortness of breath showing a new, massive right pleural effusion. A thoracentesis was performed, and pleural fluid cytologic evaluation identified lung adenocarcinoma cells consistent with a malignant pleural effusion.

result of the increasing affordability, convenience, and quality of images obtained by point-of-care ultrasound devices. It enables the assessment of the size and depth of an effusion, the echogenicity of fluid, whether septations and loculations are present, and the presence of pleural thickening or nodules (Fig. 77-2).

The presence of parietal pleural thickening (>10 mm), pleural nodularity, and/or diaphragmatic nodularity or thickening (>7 mm) is highly suggestive of malignant disease, with a sensitivity and specificity of 73% and 100%, respectively.[42] Thoracic ultrasound may also be useful in the evaluation of patients with complete opacification of the hemithorax on chest radiography. In a prospective study of 50 patients with complete opacification of the hemithorax, 9 patients had no pleural effusion by ultrasonography.[43] The use of ultrasound to guide pleural procedures has been associated with improved success rates and reduced complications including lower rates of visceral organ injury and pneumothorax.[44–46] As a result, the use of ultrasound imaging to guide pleural interventions is now recommended across multiple thoracic society guidelines.[47,48] Given the low cost, safety, and efficacy profile of point-of-care thoracic ultrasound, its role in the characterization and management of malignant pleural effusions is likely to continue to expand in the coming years. The reader is referred to Chapter 29 for additional details.

Computed Tomography

Improvements in imaging technology have led to the significant expansion in the utilization of computed tomography (CT) for a variety of clinical applications.[49] The use of chest CT scans in patients with pleural effusions may unveil pathology suggestive of an underlying malignancy such as pulmonary nodules, masses, mediastinal adenopathy, or distant metastases. A contrast-enhanced chest CT scan may also provide valuable information in discriminating benign from malignant effusions. The presence of pleural nodularity, pleural thickening ≥1 cm, circumferential parietal pleural thickening, and thickening of the mediastinal pleura are strongly indicative of a malignant effusion (Fig. 77-3).[50,51]

While complete evacuation of the pleural space prior to imaging is not necessary to enhance the diagnostic accuracy of chest CT to detect pleural abnormalities,[52] it may be beneficial in detecting parenchymal or airway abnormalities in areas of atelectatic lung. A proposed CT scoring system that included the presence of any pleural lesion ≥1 cm; the presence of liver metastases, an abdominal mass, or a lung nodule/mass; and the absence of either pleural loculations, pericardial effusions, or cardiomegaly had a sensitivity of 88% and specificity of 94% for distinguishing benign from malignant effusions.[53] Although these CT features are informative when present, these imaging abnormalities do not have sufficient

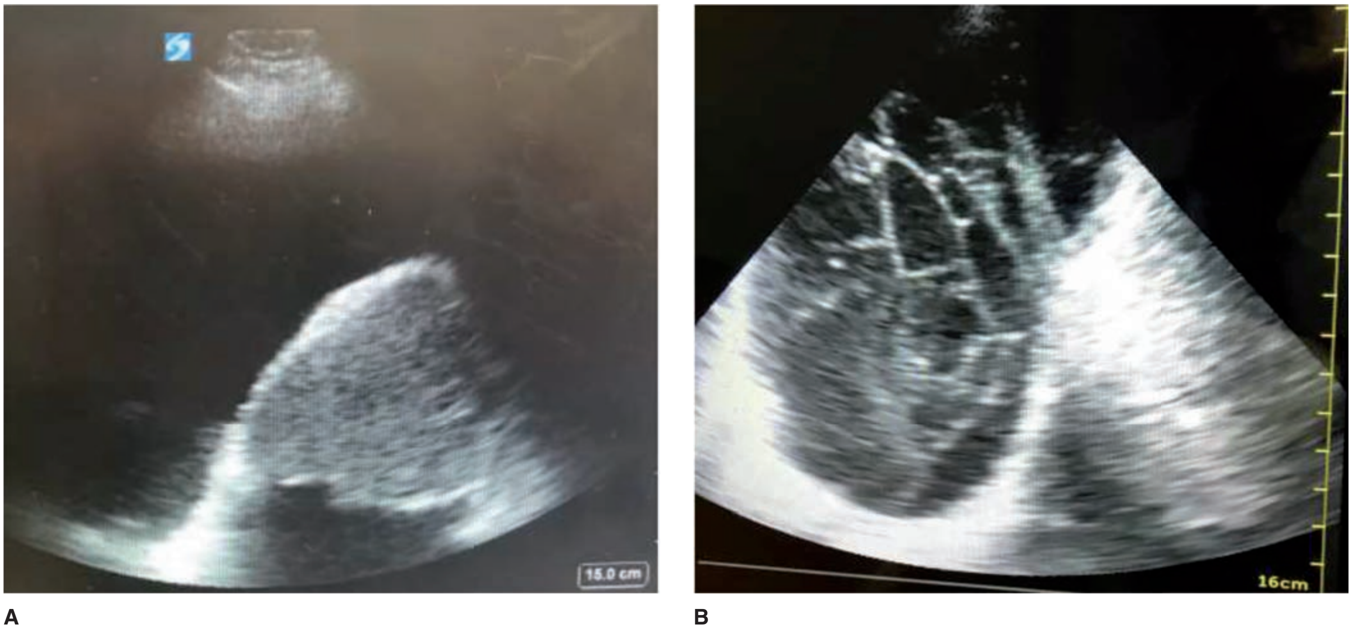

Figure 77-2 **A.** Ultrasound of the right hemithorax of a patient with a malignant pleural effusion showing a large, simple, anechoic effusion. **B.** Ultrasound of the right hemithorax demonstrating pleural fluid septations in a patient with a known right malignant pleural effusion.

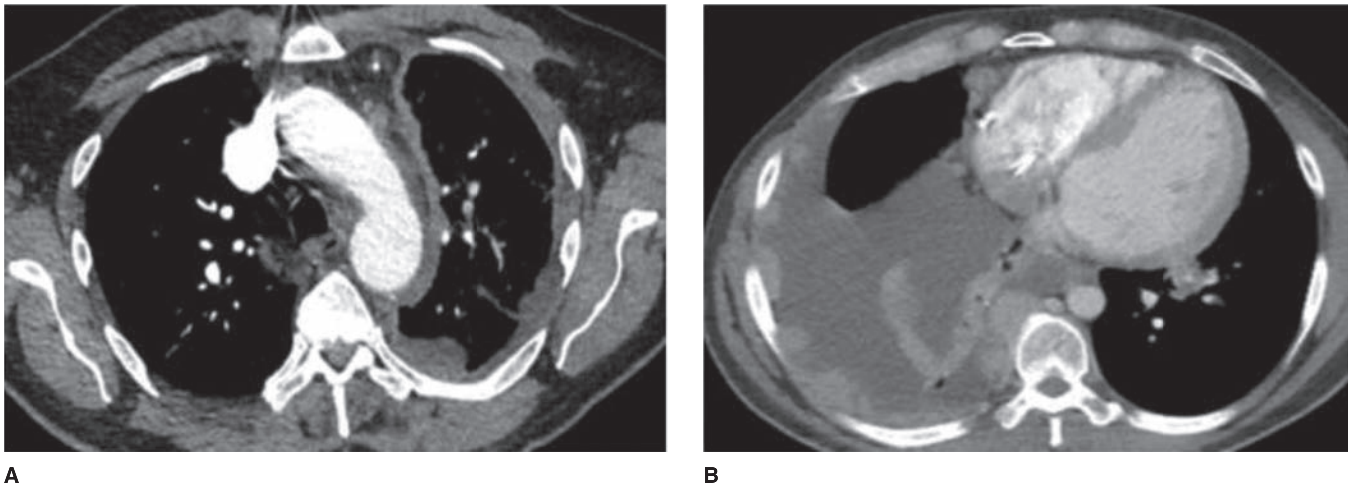

Figure 77-3 **A.** A CT scan of the chest demonstrating left mediastinal pleural thickening and pleural nodularity in a patient with a left malignant pleural effusion. **B.** A CT scan of the chest demonstrating a large right pleural effusion and multiple pleural nodules along the right pleural surface. Pleural fluid examination from a right thoracentesis revealed atypical cells suspicious for a malignant neoplasm. A subsequent CT-guided transthoracic needle aspiration of a right pleural nodule showed metastatic lung squamous cell carcinoma.

performance characteristics to obviate the need for routine cytologic examination to obtain a definitive diagnosis, and the absence of suspicious CT features should not preclude further assessment.

Magnetic Resonance Imaging

The long imaging acquisition times and susceptibility to motion artifacts have limited the use of magnetic resonance imaging (MRI) in the evaluation of pleural disease.[54,55] MRI may have a role in the diagnostic assessment and response to therapy in malignant pleural mesothelioma (MPM).[56–58] It can be particularly useful in cases of MPM when evaluating the extent of chest wall or diaphragmatic invasion by tumor, or as an alternative imaging modality in patients in whom iodinated contrast is contraindicated.[59,60] However, it currently does not have a defined role in the initial evaluation of a malignant pleural effusion.

Positron Emission Tomography

Fluorodeoxyglucose positron emission tomography (FDG-PET) scanning is a widely used imaging modality for the staging of primary malignancies; however, its role in the evaluation of malignant pleural disease remains limited. In a meta-analysis involving 14 studies and 639 patients that assessed the diagnostic usefulness of PET imaging in patients with pleural effusions, PET-CT had a sensitivity of 81% and specificity of 74% for the diagnosis of a malignant pleural effusion. False positives were frequently seen as a result of other metabolically active infectious or inflammatory lesions (e.g., prior talc pleurodesis).[61] This false positive rate severely limits the clinical utility of PET-CT in cases of suspected malignant effusion, and the moderate accuracy of PET-CT to discriminate benign from malignant effusions precludes its routine recommendation.

■ Pleural Fluid Characteristics

Ultrasound guided thoracentesis is the initial procedure of choice to sample pleural fluid in cases of suspected malignant effusion. Pleural fluid aspiration may be both diagnostic and therapeutic, often alleviating symptoms of dyspnea. It is reasonable to send pleural fluid for routine biochemical analysis (total protein, lactate dehydrogenase [LDH], and glucose), pH, cell count and differential, amylase, microbiologic studies, and cytopathology in cases of suspected malignancy. Malignant pleural effusions are almost always exudative, with transudates reported in approximately 1% to 5% of cases.[62,63] The majority of malignant effusions have a pleural fluid protein–to–serum ratio greater than 0.5. In cases where this ratio is less than 0.5, the pleural fluid LDH almost always meets exudative criteria.[64]

Malignant pleural effusions may appear serous, serosanguineous, or grossly bloody. A bloody appearance of the fluid is suggestive of malignant pleural disease.[65] Malignant pleural effusions typically have a predominance of either lymphocytes or mononuclear cells.[65] Malignancy and tuberculosis are the most common causes of an exudative effusion containing greater than 50% lymphocytes.[65,66] Although pleural fluid eosinophilia (>10%) is often seen in the setting of blood or air in the pleural space, the presence of pleural fluid eosinophilia does not exclude a malignant effusion. In a study evaluating 135 patients with an eosinophilic pleural effusion, a malignancy was identified in 35% of cases.[67]

A pleural fluid pH less than 7.3 is seen in approximately one-third of patients and is typically associated with glucose values less than 60 mg/dL. Patients with a low pH and glucose tend to have a greater burden of tumor within the pleural space, and these biochemical findings have been associated with increased diagnostic yield on cytology, decreased response to pleurodesis, and shorter overall survival.[68,69] Accurate measurement of pleural pH is dependent on sample collection and handling, with variations observed with presence of air, lidocaine, or delays in processing. Pleural fluid glucose measurements are less susceptible to variation with these factors.[70] The pleural fluid amylase level is elevated in approximately 10% of malignant pleural effusions, and the amylase is usually the salivary isoenzyme rather than the pancreatic isoenzyme. The presence of an elevated pleural fluid amylase, particularly the salivary type, in the absence of pancreatic disease or esophageal rupture is highly suggestive of malignancy.[71]

■ Cytology

The identification of malignant cells by cytologic analysis establishes the definitive diagnosis of a malignant pleural effusion in approximately 55% of cases (Table 77-2); however, there is considerable variability in diagnostic yield depending on tumor type.

For instance, exfoliative tumors such as lung adenocarcinomas and ovarian carcinomas often have diagnostic yields in excess of 70%, while lung squamous cell carcinomas and mesotheliomas are positive on cytology in less than 50% of cases.[72–74] A prospective study evaluating pleural fluid cytology in 515 patients with malignant pleural effusions demonstrated an overall sensitivity of 46%, with a sensitivity of 82% for lung adenocarcinomas, 71% for breast carcinomas, 14% for lung squamous cell carcinomas, and only 6% for malignant mesothelioma.[74]

TABLE 77-2 Sensitivity of Pleural Fluid Cytology

Primary Tumor Type	Sensitivity (%) (n = 840)[a]	 (n = 515)[b]
Overall	59%	46%
Lung	58%	56%
Adenocarcinoma	78%	82%
Squamous cell carcinoma	25%	14%
Small cell carcinoma	53%	44%
Breast	68%	71%
Hematologic	61%	40%
Gastrointestinal	48%	68%
Ovarian	70%	95%
Unknown Primary	70%	33%
Mesothelioma	27%	6%

Adapted with permission from Porcel JM. Diagnosis and characterization of malignant effusions through pleural fluid cytological examination. Curr Opin Pulm Med. 2019;25(4):362–368.

[a] *Data from Porcel JM, Esquerda A, Vives M, et al. Etiology of pleural effusions: analysis of more than 3,000 consecutive thoracenteses. Arch Bronconeumol. 2014;50(5):161–165.*

[b] *Data from Arnold DT, De Fonseka D, Perry S, et al. Investigating unilateral pleural effusions: the role of cytology. Eur Respir J. 2018;52(5):1801254.*

The yield of cytology specimens is often limited due to the scarcity of tumor cells, inherent difficulty in distinguishing cancer cells from reactive mesothelial cells, and the experience of the cytopathologist.[75] Pleural fluid samples of at least 50 to 75 mL are sufficient to ensure the diagnostic accuracy of cytologic examination,[76–78] but minimum volumes of 150 to 200 mL may be needed when downstream molecular profiling is indicated, as in cases of lung adenocarcinomas. The diagnostic yield of cytology does not increase significantly beyond two serial measurements. In a study of 214 patients with malignant pleural effusions and an initially negative cytology specimen, a repeat thoracentesis was diagnostic in 55 cases (26%).[73] However, the yield from further repeat measurements is limited.[73,74] While cytologic examination can identify the presence of malignant cells and can typically further characterize the cells into a specific histology (e.g., adenocarcinoma) based on morphologic characteristics, further testing is often required to determine the primary site of origin.

The use of immunohistochemical stains can assist in differentiating reactive mesothelial cells from an underlying malignancy, determining the origin of the primary tumor, and identifying markers of response to targeted therapies in tumor types such as lung and breast cancer. Morphologic overlap exists between reactive mesothelial cells, malignant mesothelioma, and metastatic adenocarcinomas. Markers that identify metastatic adenocarcinomas include BerEp4, MOC-31, CEA, Bg8, and B72.3, while calreticulin, cytokeratins 5/6, WT-1, and D2-40 are mesothelial markers. It is recommended to utilize at least two of the above mesothelial markers and two epithelial markers in addition to TTF-1 when attempting to differentiate cases of epithelial malignancies from malignant mesothelioma.[79] The loss of BRCA-associated protein 1 (BAP1) staining and the homozygous deletion of the *CDKN2A*/p16 gene, detected either by fluorescence in situ hybridization (FISH) or by methylthioadenosine phosphorylase (MTAP) immunohistochemistry, are highly specific markers for mesothelioma. However, the absence of these molecular abnormalities cannot exclude a diagnosis of mesothelioma.[80] Other examples of immunomarkers that may be useful in assessing the origin of the primary tumor include TTF-1 and napsin A for lung adenocarcinomas; mammaglobin, ER/PR, GCDFP-15, and GATA-3 for breast carcinomas; and CDX-2 and CK20 for gastrointestinal malignancies.[81] Flow cytometry is a useful adjunct to pleural fluid cytology in cases of suspected lymphoma. Finally, pleural fluid immunohistochemistry can serve as a minimally invasive technique to identify biomarkers of response to targeted therapies such as the detection of anaplastic lymphoma kinase (ALK) and reactive oxygen species 1 (ROS1) fusions. In lung adenocarcinomas, detection of ALK fusions by immunohistochemistry can serve as a standalone test to determine candidacy for an ALK tyrosine kinase inhibitor. Immunohistochemistry assays to detect ROS1 fusions have a high sensitivity but limited specificity; thus, detection of a ROS1 fusion requires confirmatory testing using FISH or other molecular methodologies.[82]

Pleural fluid cytology samples may also be used for comprehensive genetic profiling. Therapeutically targetable mutations occur in 20% to 30% of patients with metastatic nonsquamous non–small-cell lung cancer (NSCLC). The list of therapeutic targets is rapidly expanding beyond *EGFR*, *ALK*, *BRAF*, and *ROS1* and now includes molecular alterations in *MET*, *RET*, *ERRB2*, and *NTRK*. In cases of advanced nonsquamous NSCLC, the National Comprehensive Cancer Network guidelines strongly recommend the use of broad molecular profiling systems that assess for the presence of these molecular alterations simultaneously.[83] Any cytology sample with adequate cellularity and preservation may be utilized for molecular testing,[84] and evidence suggests that sequencing of malignant pleural effusions has comparable diagnostic performance with corresponding tissue specimens.[85,86] In a study of 30 NSCLC patients with a malignant pleural effusion, the concordance between tissue biopsy specimens and pleural effusion samples was 87%.[86] Thus, cytologic evaluation of malignant pleural effusions offers a minimally invasive means to establish diagnostic and staging information, and provides source material to detect actionable mutations in order to match patients to appropriate personalized therapies.

■ Tumor Markers

Given the limited sensitivity of pleural fluid cytology to diagnose malignant pleural effusions, a number of studies have evaluated various molecular markers in pleural fluid to better distinguish benign from malignant effusions. A study evaluating the use of a combination of tumor markers measured in pleural fluid including carcinoembryonic antigen (CEA), cancer antigen 125 (CA-125), carbohydrate antigen 15-3, and cytokeratin 19 fragments (CYFRA 21-1) in 416 patients with benign and malignant effusions demonstrated a sensitivity of 54% for the diagnosis of a malignant effusion when utilizing cutoff values with 100% specificity for the four markers. This combination of markers had improved diagnostic accuracy in exfoliative tumors such as lung and breast adenocarcinomas (sensitivity 69%), with limited sensitivity in tumors such as lung squamous cell carcinoma and mesothelioma (sensitivity ~40%).[87] In MPM, a disease for which cytologic yield is approximately 30%, elevation in pleural fluid mesothelin level has a sensitivity of 67% and specificity of 95%.[88] An additional marker, fibulin-3, was found to have a sensitivity and specificity of 84% and 92%, respectively, for discriminating MPM effusions from effusions that were not secondary to mesothelioma.[89] Novel markers, such as analyzing cell-free DNA fragmentation patterns and the phenotyping of individual cells (e.g., identification of metabolically active cells) within pleural fluid, also have demonstrated promise in distinguishing benign from malignant effusions.[90–93] However, in order to be clinically useful for the diagnosis of a malignant pleural effusion, these assays must have a specificity of 100%, and this prerequisite often limits the sensitivity of these tumor markers. The presence of a malignant pleural effusion has important diagnostic, staging, and prognostic implications, and one would not want to incorrectly establish this diagnosis in a patient with a benign effusion. As a result, these markers have limited clinical utility but could potentially be utilized to select patients for more invasive procedures to definitively diagnose a malignant effusion. Although the aforementioned biomarkers, as well as a number of emerging biomarkers, are promising, larger studies and prospective validation are needed before they can be incorporated into clinical practice.

■ Pleural Biopsy

Pleural biopsy may be performed using a "closed" biopsy technique or via medical or surgical thoracoscopy.

Closed Pleural Biopsy

Pleural biopsies are often performed to further evaluate cytologically negative exudative effusions of unknown etiology. Closed pleural biopsies can be performed in the outpatient setting and are well tolerated, with a low rate of complications such as pain, bleeding, and pneumothorax. The diagnostic yield of blind closed pleural biopsy (non-image-guided) to diagnose pleural malignancy is low (<60%), largely secondary to the often patchy distribution of malignant pleural involvement.[66,94,95]

The use of image guidance to obtain closed pleural biopsies significantly increases diagnostic yield by enabling the practitioner to target specific pleural abnormalities, such as pleural nodularity or thickening, or to sample areas more likely to contain pleural metastases, such as the basal pleura.[96] In a study evaluating 50 patients that utilized real-time ultrasound to perform closed pleural biopsies, the diagnostic yield was 94%.[97] In another study of patients with undiagnosed exudative pleural effusions, the use of ultrasound-guided thoracentesis and pleural biopsy had a combined diagnostic yield of 90% for malignancy.[98] CT is also a useful imaging modality to guide pleural procedures, with a reported sensitivity of 77% to 88% for diagnosis of malignant pleural disease.[95,96,99]

In summary, the use of image-guided closed pleural biopsy serves as an accessible, minimally invasive, and low-cost method to evaluate patients with undiagnosed exudative effusions, and may be particularly useful in patients with pleural abnormalities and in centers where medical thoracoscopy is not readily available.

Medical Thoracoscopy

Medical thoracoscopy, also known as pleuroscopy, is a minimally invasive procedure that involves accessing the pleural space with a rigid or semirigid thoracoscope that is typically performed with a local anesthetic and moderate sedation. The procedure enables the direct visualization of the parietal pleura in order to direct biopsies to visually abnormal areas. The sensitivity of medical thoracoscopy in diagnosing malignant pleural disease is approximately 90% to 95%,[99,100] and therapeutic pleurodesis or tunneled pleural catheter insertion can be performed during the same procedure. The diagnostic yield is similar to video-assisted thoracic surgery (VATS) pleural biopsy. However, medical thoracoscopy is associated with lower cost and shorter hospital length of stay, as the majority of cases can be performed in the outpatient setting.[101] Medical thoracoscopy is well tolerated and safe, with a mortality rate less than 0.5%.[100]

A recent study evaluating 1926 patients who underwent medical thoracoscopy showed that major complications, including lung laceration, major bleeding, prolonged air leak, and re-expansion pulmonary edema occurred in <1% of patients.[102] A CT scan of the chest, preferably with IV contrast, should be performed prior to the procedure to evaluate the size of the effusion, determine the presence of loculations, and assess for pleural abnormalities, such as pleural thickening, nodules, and masses. Contraindications to the procedure include lung adherent to the chest wall throughout the hemithorax, hypercarbia or severe respiratory distress, and uncontrollable cough. Optimal patient selection is best achieved through a multidisciplinary collaboration between interventional pulmonologists and thoracic surgeons.[100,103]

The field of medical thoracoscopy continues to evolve, and with advancements in thoracoscopic equipment and imaging technologies enabling smaller ports of entry and improved visualization of pleural abnormalities, the diagnostic and therapeutic indications for medical thoracoscopy are likely to continue to expand in the coming years.

Surgical Thoracoscopy

A surgical pleural biopsy is typically performed using VATS. Careful assessment of the patient's comorbidities and performance status should be performed to ensure that they can tolerate general anesthesia and single lung ventilation required for this procedure. Although VATS is still considered the gold standard for the diagnosis of malignant pleural disease, the diagnostic yield of >90% and complication rate of VATS is similar to medical thoracoscopy.[101] While evidence suggests that medical thoracoscopy is a less invasive and cost-effective alternative to VATS for the evaluation of an undiagnosed pleural effusion, approximately 12% of patients may still require a VATS or alternative surgical intervention following medical thoracoscopy for management of the pleural space.[103]

Although pleural fluid cytology, CT imaging of the chest, and thoracoscopy are diagnostic in the majority of cases, approximately 5% to 31% of patients with cytologically negative exudative effusions will remain undiagnosed following these procedures.[104] Thoracoscopic biopsies in these cases typically demonstrate nonspecific pleuritis that does not yield a specific etiology. While the majority of patients with nonspecific pleuritis are ultimately diagnosed with benign disease, approximately 14% will eventually be diagnosed with a malignancy, mostly mesothelioma.[104] As a result, these patients warrant close follow up for 1 to 2 years following thoracoscopy.

PROGNOSIS

The prognosis for patients with a malignant pleural effusion remains poor, with median survival estimates ranging from 3 to 12 months.[4] Survival is highly variable and depends on a number of factors including the primary tumor type, performance status, and pleural fluid markers. One of the most important determinants of survival is the primary tumor type. In a study evaluating prognostic estimates for malignant effusions across three international cohorts, the median overall survival for all patients was 4.5 months, with median survival estimates in lung cancer of 2.4 months, breast cancer 6.3 months, hematologic malignancies 7.2 months, and mesothelioma 11.2 months.[105]

The prognosis of the patients with a malignant pleural effusion may assist in guiding decisions regarding management options. For instance, in patients with very limited life expectancy, treatment may be focused on symptom relief and end-of-life care rather than definitive pleural intervention. As a result, a number of scoring systems have been developed to more accurately predict survival.

The LENT score is a prospectively validated scoring system to estimate survival in patients with a malignant effusion. The score includes the pleural fluid LDH, performance status, serum neutrophil-to-lymphocyte ratio, and primary tumor type, resulting in a composite score that separates patients into low-, moderate-, or high-risk groups, with median survival in these groups of 319, 130, and 44 days, respectively.[105] The accuracy and simplicity of this score makes it an attractive option for clinical use.

The more recently developed and validated PROMISE score combines well-known clinical prognostic factors with a novel pleural fluid biomarker, tissue inhibitor of metalloproteinases 1 (TIMP1), to predict 3-month mortality. By combining the prior receipt of chemotherapy, radiation therapy, performance status, primary tumor type, hemoglobin levels, white blood cell count, and C-reactive protein with measurement of TIMP1, patients are grouped into risk stratification categories ranging from category A ($<25\%$ absolute risk of death) to category D ($\geq 75\%$ absolute risk of death).[106] The majority of parameters within the PROMISE score are readily available in the clinical setting, and the score accurately estimates 3-month mortality; however, further external validation is needed before its routine use in clinical practice.

MANAGEMENT

The primary goal of treatment is palliation of symptoms related to the effusion and improvement in overall quality of life. Ideally, the therapy should minimize the need for hospitalization or medical visits while being affordable and safe. The preferred treatment option takes into consideration a patient's clinical condition and personal values to balance all competing factors.

Clinical observation may be offered for patients with small, asymptomatic, malignant pleural effusions. For patients with symptomatic effusions, management options include thoracenteses, drainage, and chemical pleurodesis via either chest tube thoracostomy or thoracoscopy/pleuroscopy, or the placement of an indwelling pleural catheter (IPC).

In patients with respiratory symptoms potentially attributable to a malignant pleural effusion, a therapeutic thoracentesis can be performed during the initial diagnostic evaluation. A thoracentesis enables the assessment of symptomatic relief following drainage, determination of whether the lung is nonexpandable following the procedure, and assessment of the rate at which fluid reaccumulates. Patients who derive symptomatic relief of dyspnea following thoracentesis should be considered for definitive pleural interventions (e.g., placement of a tunneled pleural catheter, pleurodesis), while those with persistent dyspnea despite effective fluid drainage should have further diagnostic testing to investigate alternative causes of dyspnea, such as lymphangitic carcinomatosis or a pulmonary embolism. Approximately 15% to 27% of patients may not appreciate significant improvements in dyspnea following therapeutic drainage. A thoracentesis can be performed quickly and safely both in the outpatient and inpatient settings. When performed by experienced operators, the respective risks of pneumothorax and bleeding are each less than 1%.[107] Traditional teaching recommends that drainage should be limited to 1 to 1.5 L to avoid the risk of re-expansion pulmonary edema.[48,108] However, evidence suggesting that the volume of fluid removed is not correlated with re-expansion pulmonary edema challenges this assertion.[109]

Thoracentesis is sufficient for many patients in controlling symptoms, especially amongst patients who are just beginning treatment with systemic therapies. If the rate of reaccumulation is sufficiently slow, serial thoracentesis can be performed. However, it is important to recognize that this therapeutic strategy is not appropriate for patients with rapidly recurring pleural effusions, as serial thoracenteses in this population have been associated with increased number of pleural procedures, complications, and emergency department visits.

For rapidly reaccumulating effusions, a more durable solution is recommended. One such option is pleurodesis, which involves generating inflammation within the thoracic cavity to promote adhesion of the visceral and parietal pleura. Successful pleurodesis obliterates the potential space for fluid reaccumulation, leading to sustained pleural effusion resolution. Pleurodesis is typically achieved chemically by the intrapleural instillation of a sclerosing agent. Many chemical sclerosants have been utilized to promote pleurodesis including talc, doxycycline, bleomycin, and povidone-iodine. Although there is no current consensus regarding the optimal chemical sclerosing agent, two recent studies suggest that the administration of talc is associated with fewer pleurodesis failures than other commonly used agents.[110,111] Talc has a pleurodesis success rate of approximately 70%[111] and can be delivered into the pleural space either as a slurry suspension via a chest tube or by direct aerosolized application (poudrage) via video thoracoscopy with similar efficacy.[111,112]

Small-bore intercostal catheters (10–14French) are similar in efficacy to large-bore intercostal tubes (24–32French) for pleurodesis but are associated with less pain.[113] Historically the median hospitalization time for a pleurodesis procedure is 7 days.[112] Pleurodesis is contraindicated in patients who cannot achieve apposition of the visceral and parietal pleura due to lack of lung expansion (Fig. 77-4).

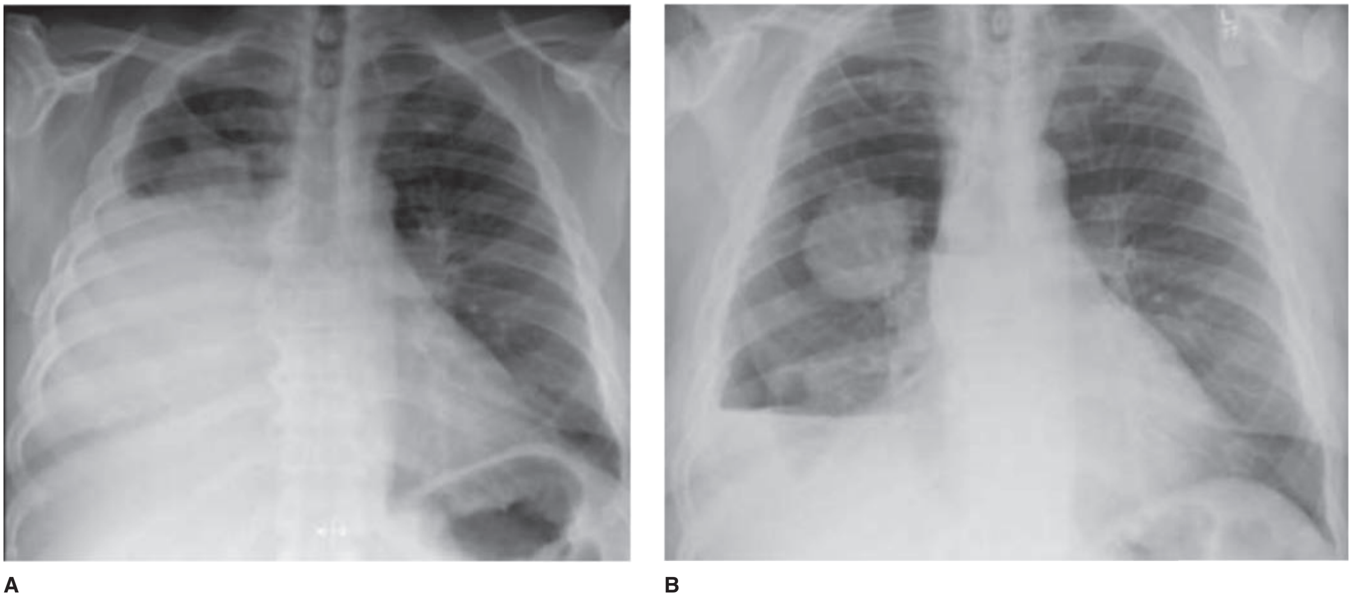

Figure 77-4 **A.** A chest radiograph of a patient presenting with shortness of breath found to have a large right pleural effusion. Cytologic evaluation of the right pleural fluid reveals metastatic lung adenocarcinoma. **B.** A chest radiograph in the same patient following a right thoracentesis showing a right upper lobe mass and lack of lung re-expansion. This patient would not be a candidate for pleurodesis due to the lack of lung re-expansion.

Fever and pain requiring oral or parenteral analgesics are the most common adverse events associated with chemical pleurodesis.[110] Postprocedural pain typically resolves within the first 24 h and can be mitigated by the intrapleural administration of a topical anesthetic prior to the instillation of the sclerosing agent. Previous reports of the development of the acute respiratory distress syndrome (ARDS) following talc pleurodesis were thought to occur as a consequence of nongraded/small-particle talc previously used in the United States; however, this risk appears minimal with modern talc preparations that include large-particle, graded talc.[114,115]

IPCs are an attractive alternative to pleurodesis. IPCs are fenestrated silicone catheters that are tunneled subcutaneously in the chest wall and subsequently inserted into the pleural space. They can be placed as an outpatient procedure, allowing immediate relief of symptoms without the need for hospitalization.[116–118] An IPC can be left in place indefinitely to allow regular drainage of the pleural space at home. Drainage can be performed by the patient, family members, or a visiting nurse. In patients with rapidly recurring malignant effusions without lung expansion, IPCs may be a more attractive solution than repeat thoracenteses. Compared to talc pleurodesis, IPC placement offers better control of dyspnea at 6 months, fewer days in the hospital, and less need for another pleural procedure such as thoracentesis or intercostal catheter placement. For these reasons, IPC placement is increasingly becoming the favored definitive approach to malignant pleural effusion management. The most common complications associated with IPCs include empyema, cellulitis, and catheter blockage.[119,120] These complications are usually minor and rarely necessitate removal of the catheter.

In 30% to 50% of patients with an IPC, sustained resolution of the effusion can be accomplished via a combination of response to

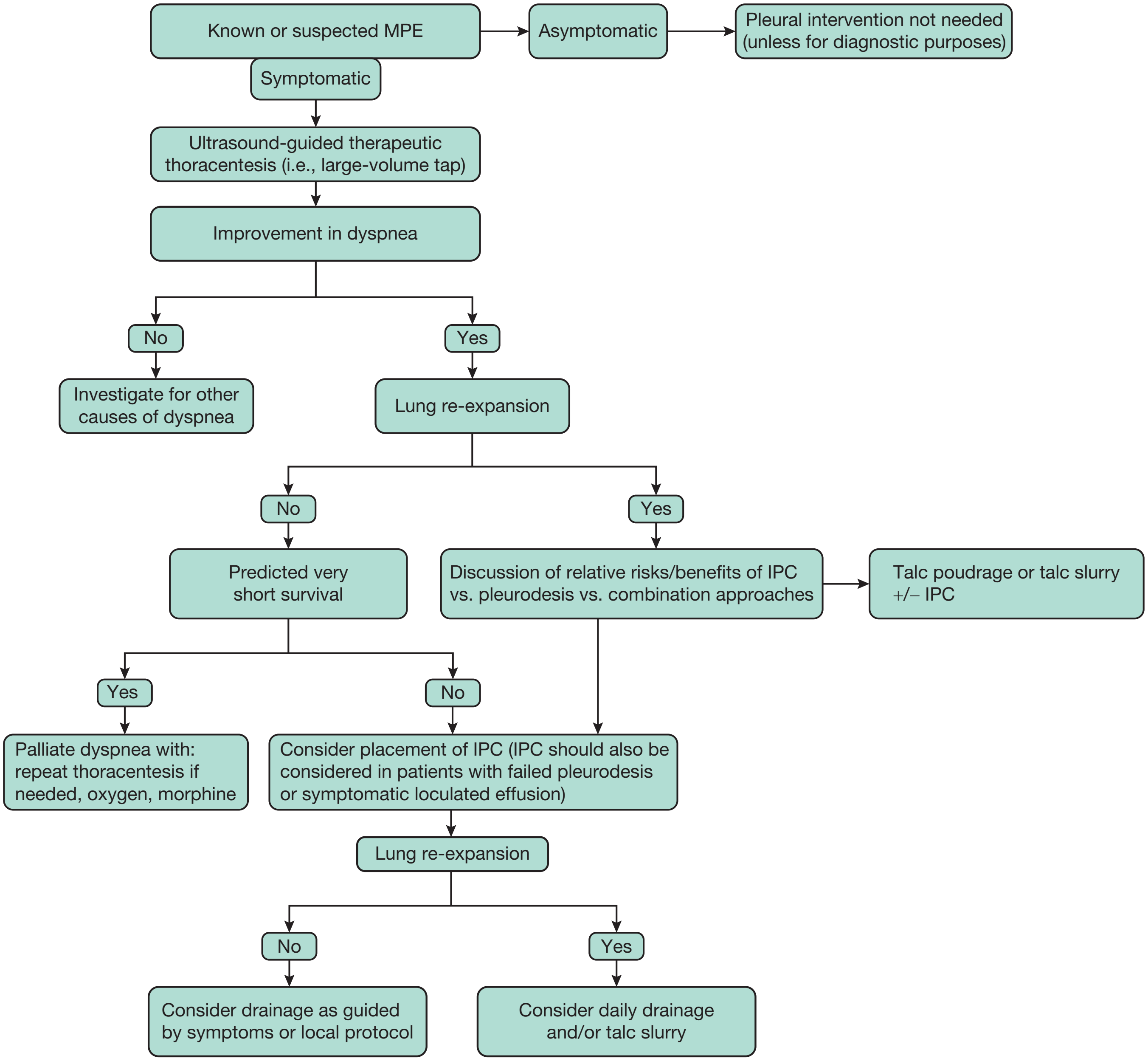
Known or suspected MPE
Asymptomatic
Pleural intervention not needed (unless for diagnostic purposes)
Symptomatic
Ultrasound-guided therapeutic thoracentesis (i.e., large-volume tap)
Improvement in dyspnea
No
Yes
Investigate for other causes of dyspnea
Lung re-expansion
No
Yes
Predicted very short survival
Discussion of relative risks/benefits of IPC vs. pleurodesis vs. combination approaches
Talc poudrage or talc slurry +/– IPC
Yes
No
Palliate dyspnea with: repeat thoracentesis if needed, oxygen, morphine
Consider placement of IPC (IPC should also be considered in patients with failed pleurodesis or symptomatic loculated effusion)
Lung re-expansion
No
Yes
Consider drainage as guided by symptoms or local protocol
Consider daily drainage and/or talc slurry

Figure 77-5 Suggested management pathway for malignant pleural effusion. *(Adapted with permission from Feller-Kopman DJ, Reddy CB, DeCamp MM, et al. Management of Malignant Pleural Effusions. An Official ATS/STS/STR Clinical Practice Guideline. Am J Respir Crit Care Med. 2018;198(7):839–849.)*

systemic treatment and the proinflammatory effects of the catheter itself. The median time to "autopleurodesis" in published series has been between 30 and 60 days.[116–118] Randomized, controlled trials comparing different drainage protocols have demonstrated higher autopleurodesis rates in association with more frequent drainage. In one study, every-other-day drainage was shown to have a pleurodesis rate of 24% at 90 days, compared with 47% in subjects who drained their catheter every day.[39] In another, similar trial, only 11% of subjects who drained their catheter on an as-needed basis achieved pleurodesis at 60 days, compared with 37% of subjects who drained their catheter daily.[121] Daily drainage demonstrated similar improvements in dyspnea compared with symptom-guided drainage and was not associated with more pain or pleural infections. Despite the improved rate of pleurodesis, a recent cost-effectiveness analysis showed that daily drainage was not a cost-effective alternative to symptom-guided drainage, as daily drainage demonstrated considerably higher costs compared with symptom-guided drainage.[122]

Recent studies have attempted to combine the benefits of chemical pleurodesis with the convenience of IPCs. In a randomized, placebo-controlled trial of patients with malignant effusions and expandable lung, chemical pleurodesis with talc slurry 10 days after IPC placement was associated with significantly higher pleurodesis rates at 35 days (43%) compared with IPC alone (23%).[123] This strategy was also associated with improved symptom and quality-of-life scores compared with IPC alone. Although the rate of successful pleurodesis was significantly lower than conventional chemical pleurodesis through a chest tube, this strategy offers the convenience of avoiding the time and cost of a hospitalization and is a promising approach for patients without nonexpandable lung. A trial studying the efficacy of this combined procedure compared with VATS pleurodesis is currently ongoing (ClinicalTrials.gov identifier NCT04322136).

Significant advancements have been made in the management of malignant pleural effusions over the last 20 years. The recent American Thoracic Society/Society of Thoracic Surgeons/Society of Thoracic Radiology Clinical Practice Guidelines on the Management of Malignant Pleural Effusions synthesize the latest body of evidence and provide a suggested management pathway for malignant pleural effusions (Fig. 77-5).[47]

Ongoing work continues to explore the optimal combination of treatment strategies that maximize quality of life while minimizing cost and risk to the patient. Improvements in understanding the underlying pathophysiology may ultimately enable the development of intrapleural targeted therapies that control pleural fluid formation to optimize patient care and minimize the need for symptomatic drainages.

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CHAPTER 78

Malignant Mesothelioma and Other Primary Pleural Tumors

Daniel H. Sterman
Edmund K. Moon
Keshav Mangalick
Leslie A. Litzky

INTRODUCTION

The pleura is a membranous structure covering the entire surface of the lung and lining the inside of the chest cavity. It is composed of a thin mesothelial layer with underlying fibroblasts and varying amounts of collagenous fibrous tissue with interdigitating capillaries and venules. The most common tumors of the pleura are metastatic neoplasms, predominantly of lung, breast, or colonic origin. Tumors arising primarily from the pleura are rare but still constitute a variety of benign and malignant lesions from several different cells of origin, some of which have yet to be identified.

MALIGNANT MESOTHELIOMA

The most common primary malignant tumor of the pleura is malignant mesothelioma, an insidious neoplasm with a generally dismal prognosis arising from the mesothelial surfaces of the pleural and peritoneal cavities, as well as from the tunica vaginalis and pericardium. Eighty percent of all cases of mesothelioma are pleural in origin.

■ Epidemiology

The incidence of mesothelioma in the United States is estimated to be 3300 cases per year.[1] The incidence within the United States peaked in the year 2000 and is now declining, secondary to control of asbestos exposure.[2] However, incidence is increasing in other parts of the world, such as Europe, Japan, and Australia. Deaths from mesothelioma in Great Britain continued to increase and peaked at an annual average of 2540 deaths per year between 2012 and 2018 before decreasing to 2369 in 2019. However, this trend was largely driven by a peak and decrease in deaths among males, and it is unclear when female deaths will peak (https://www.hse.gov.uk/statistics/causdis/mesothelioma/mesothelioma.pdf).[3] Subsequent mesothelioma rates were expected to drop in England and other developed countries because of legislation aimed at reducing asbestos exposure in the workplace and the general environment. In contrast, mesothelioma incidence rates are predicted to escalate for much longer times in developing countries because of poor regulation of asbestos mining and widespread industrial and household utilization of asbestos.[3–5]

■ Etiology

Inhalational exposure to asbestos has been clearly established as the predominant cause of malignant mesothelioma in humans. Approximately 70% of cases of pleural mesothelioma are associated with documented asbestos exposure. In ancient Greece, the philosopher Pliny first established the association between asbestos exposure and lung disease by making the observation that slaves working in asbestos mines were less healthy than other slaves. It was not until 1960, with the publication by Wagner et al.[6] of a series of 33 mesothelioma cases occurring in a crocidolite mining community in South Africa, that the etiologic connection between asbestos and mesothelioma was established. Wagner's study was soon followed by several other accounts of mesothelioma afflicting asbestos workers at locations around the world. In addition to asbestos miners and workers, other occupations at especially high risk include plumbers/pipefitters, mechanical engineers, and ship and boat building and repairing.[4]

The lifetime risk of developing mesothelioma among asbestos workers is thought to be as high as 8% to 13%.[7] There is a latency period of approximately 30 to 40 years from the time of initial asbestos exposure to the development of mesothelioma. It remains unclear whether there is a dose–response relationship between asbestos exposure and development of mesothelioma. The possibility of a dose–response relationship was demonstrated in a cohort study of more than 4500 people who resided in an Australian city that produced crocidolite asbestos but who did not directly participate in its mining or milling. In this study, the incidence of mesothelioma increased significantly with greater environmental exposure, based upon the neighborhood and duration of residence. In a cohort of textile workers with heavy exposure to asbestos, the risk of pleural mesothelioma was increased and was proportional to the latency period. In contrast, many well-documented cases of mesothelioma occur after brief, but intense, or longer-term low-level exposures to asbestos (e.g., spouses of asbestos workers exposed by washing clothes).[8]

Asbestos is not a specific compound, but the commercial name for a group of hydrated magnesium silicate fibrous minerals divided into two major types: the serpentines and the amphiboles. Serpentine chrysotile fibers, which account for more than 95% of the asbestos previously used for industrial purposes in the United States, are spiral-shaped, pliable, easily breakable, and soluble in tissues, whereas the amphiboles (crocidolite, amosite, tremolite, anthophyllite, actinolite) are rigid, long, and needle-like, with a longer biologic persistence than the serpentine fibers. The carcinogenicity of asbestos is thought to depend on dose, biodurability, surface reactivity, and the physical properties of the fibers. Fibers with a high length-to-width ratio, such as crocidolite, which are able to more readily penetrate through the lung to the pleural surface, are considered more carcinogenic. Among the remaining asbestos fibers, amosite has an intermediate carcinogenic risk, chrysotile the lowest. It is unclear whether the cases of mesothelioma attributed to chrysotile exposure are caused primarily by the chrysotile itself or by contamination with tremolite fibers. All asbestos fiber types, however, have carcinogenic potential.[3,4]

The development of malignant pleural mesothelioma has also been associated in rare cases with other etiologic factors, including therapeutic ionizing irradiation to supradiaphragmatic fields,[9–13] intrapleural thorium dioxide (Thorotrast), and inhalation of other fibrous silicates such as erionite. Epidemiologic studies of a region in central Anatolia (Turkey) with an abnormally high incidence of pleural mesothelioma (22 per 10,000 individuals >25 years old) implicated routine household use of a locally ubiquitous silicate, erionite, as a potential etiologic agent. However, it appears that only specific families (who appear to have as yet to be fully defined genetic abnormalities) are susceptible to erionite-induced mesothelioma.[14]

■ Molecular Pathogenesis

The latency period from asbestos exposure to the development of mesothelioma ranges from approximately 20 to 50 years, suggesting the necessity of multiple genetic alterations for eventual malignant transformation of the mesothelium. Despite extensive investigation, the exact mechanisms of asbestos carcinogenesis have not yet been fully elucidated. In rodent model systems, asbestos fibers act like tumor promoters in combination with a carcinogen, eliciting proliferation of mesothelial cells. Asbestos fibers can also interact with the mitotic spindle to cause missegregation of chromosomes and aneuploidy. In rat pleural mesothelial cells, asbestos fibers and erionite have been shown to induce the proto-oncogenes c-fos and c-jun in a prolonged and dose-responsive manner. Several growth factors, secreted by mesothelial/mesothelioma cells in an autocrine fashion, have been implicated in various stages of mesothelioma tumorigenesis. Platelet-derived growth factors A and B (PDGF A and B), insulin-like growth factors 1 and 2 (IGF-1 and IGF-2), basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), hepatocyte growth factor, and transforming growth factor β1, β2, and β3 (TGF-β1, -β2, and -β3) constitute a complex mixture of autocrine and paracrine stimuli for mesothelioma cell proliferation as well as initiation of tumor angiogenesis. More recently, asbestos has been shown to induce necrotic cell death with resultant release of high-mobility group protein B1 (HMGB-1) in the extracellular space, which leads to a chronic inflammatory response involving macrophage accumulation and secretion of tumor necrosis factor α (TNF-α). This in turn activates NF-κB, leading to survival of human primary mesothelial cells that have accumulated genetic damage from asbestos exposure. There is also evidence implicating aberrant activation of the Wnt signaling pathway in mesothelioma.[15,16]

It has been well established that chronic inflammation predisposes to cancer development. Asbestos fibers appear to stimulate the production of chronic oxidative stress in lung macrophages and other cells for many years. In animal models, crocidolite fibers clearly induce specific DNA adducts (8-hydroxydeoxyguanosine, 8-OHdG) associated with oxidative damage in the DNA from peritoneal cells and macrophages of asbestos-exposed animals. These same types of 8-OHdG DNA adducts have been observed in the blood lymphocytes of asbestos-exposed individuals decades after exposure, suggesting chronic exposure to oxidant stress.[17]

The pathogenesis of malignant mesothelioma involves molecular changes such as chromosomal alterations in tumor suppressor genes, allele loss, gene silencing by DNA methylation in specific chromosomal regions, epigenetic dysregulation of tumor suppressor genes by histone acetyltransferase and histone deacetylase (HDAC), chromatin condensation/decondensation balance, and gene mutations. Analysis of explanted human mesotheliomas and cultured human mesothelioma cell lines has revealed a number of cytogenetic aberrations that may predispose to the development of the malignant phenotype. Partial or total loss of chromosomes 1, 3, and 4, deletions of 9p, and monosomy of chromosome 22 are the most common abnormalities seen. For mesotheliomas, 9p deletions have been associated with the loss of function of the p16INK4 cdk inhibitor, a putative tumor suppressor gene, engendering unchecked cdk4-mediated phosphorylation of the retinoblastoma 1 (Rb1) gene product and leading to loss of regulation of cell division. Monosomy 22, the most frequent numeric cytogenetic abnormality in mesothelioma, has recently been correlated with mutations in the neurofibromatosis 2 (NF2) tumor suppressor gene mutations more commonly associated with acoustic neuromas, schwannomas, and meningiomas. The product of NF2, Merlin, appears to inhibit cell proliferation and cell cycle progression by repressing cyclin D1 expression as well as inhibiting invasiveness. The presence of the Wilms tumor suppresser gene (WT1) in human mesotheliomas raises the possibility that alterations in this gene or binding of the WT1 gene product to the p53 tumor suppressor may predispose to mesothelial cell carcinogenesis.[15,16,18]

Viral Oncogenes

Simian virus 40 (SV-40) is a polyoma virus with oncogenic potential in humans. Its actions are thought to result from inactivation of tumor suppressor genes such as the retinoblastoma gene (Rb) and wild-type p53 (wt p53) by a peptide known as the SV-40 large T antigen (Tag). SV-40 is a potent oncogenic virus in human and rodent cells; SV-40 DNA sequences have been identified in brain tumors, osteosarcomas, and lymphomas.[19] SV-40 is the only agent known to cause malignant transformation of human primary mesothelial cells in vitro.[20] When cell lines are exposed to both SV-40 and asbestos fibers, the rate of transformation increases significantly. Animal studies have also shown that crocidolite asbestos and SV-40 can act as cocarcinogens.[21] Several studies have documented the presence of SV-40 in patients with mesothelioma (some of whom did not have obvious asbestos exposure), as well as in cases of atypical mesothelial proliferation.[22–26] As an example, one report examined 35 archival mesothelioma specimens and found that SV-40–like sequences were present in 86% of cases.[23] However, the possibility that technical factors can produce false-positive results suggestive of SV-40 infection also has been raised.[27,28] Despite the fact that there was worldwide dissemination of SV-40–contaminated polio vaccines in the 1950s and 1960s, there is no convincing epidemiologic evidence linking SV-40 exposure to the development of malignant mesothelioma.

Nonetheless, it is possible that Tag interference with Rb and wt p53 may play an accessory role in the carcinogenesis of malignant mesothelioma.[29] If this hypothesis is validated, novel strategies of vaccination to prevent mesothelioma or molecular techniques to improve early diagnosis may become possible.

Genetic Predisposition

Gene polymorphism studies are in their early stages in asbestos-exposed populations. Some suggestive associations in DNA repair genes with mesothelioma development have been reported but need validation. One study reported an increased incidence of mesothelioma among asbestos-exposed individuals in Finland found to be lacking the glutathione-S-transferase M1 (GSTM1) gene and carrying the "slow-acetylator" type of the *N*-acetyltransferase 2 (NAT-2) gene.[30] The GSTM1 gene is important in the detoxification of several carcinogens, including polycyclic aromatic hydrocarbons; NAT-2 is associated with the biotransformation of aromatic amines. Some genetically predisposed families have been identified, but without identification of a specific "mesothelioma" gene. An increased frequency of polymorphisms in the NOD-like receptor pyrin domain (NLRP) inflammasome complex among a cohort of Italians with mesothelioma also has been described.[31] Inactivation of the nuclear deubiquitinase BAP1, which appears to regulate key histones and transcription factors related to the development of tumors, is associated with malignant pleural mesothelioma.[32] A so-called BAP1 "syndrome" has been described in some families bearing this gene mutation, in which there is higher frequency of mesothelioma, ocular melanoma, and melanocytic lesions of the skin, sometimes even occurring simultaneously in the same individual.[33]

Pathology

Gross and microscopic pathologic findings in malignant mesothelioma are discussed below.

Gross Pathology

The vast majority of malignant mesotheliomas involving the pleura are those tumors that diffusely involve the pleura and are properly termed *diffuse pleural mesothelioma*. A rare localized gross variant of malignant mesothelioma that forms a single mass arising in the pleura but is otherwise microscopically identical to diffuse malignant mesothelioma has been described and termed *localized pleural mesothelioma*. Diffuse malignant mesothelioma begins as multiple discrete nodules that, in earlier stages, tend to preferentially involve the parietal pleura over the visceral pleura. In time, these nodules tend to coalesce on the visceral and parietal pleural surfaces with subsequent fusion of the pleurae. Progressive tumor growth typically leads to partial or complete encasement of the lung with rinds of pleural tumor that can be several centimeters in thickness but may show only minimal penetration of the underlying lung parenchyma (Fig. 78-1). Advanced cases show more extensive spread along interlobar fissures, deeper invasion into the underlying lung parenchyma and through the diaphragm, and contiguous involvement of the chest wall, pericardium, and mediastinum. Although it is rare for patients with mesothelioma to present clinically with metastatic disease, peribronchial lymphovascular spread, regional lymph node metastases, and extrathoracic hematogenous metastases become increasingly common over the course of the disease. Seventy percent of patients have mediastinal lymph node involvement at autopsy. Hematogenous metastases follow the exact same pattern of spread as non–small-cell lung carcinomas with involvement of the contralateral lung and pleura, liver, adrenals, bone, brain, and kidney.

Histology

The 2021 revision of the WHO classification of pleural tumors recognizes three major histologic subtypes: epithelioid, sarcomatoid, and biphasic.[34] The desmoplastic variant is considered a subtype of sarcomatoid mesothelioma. The entity formerly termed *well-differentiated papillary mesothelioma* has been removed from the mesothelioma grouping and is now its own separate entity. This particular entity has been renamed *well-differentiated papillary mesothelial tumor* and is restricted to an exceptionally rare and distinctive mesothelial tumor that is composed of papillary stromal formations covered by cytologically bland mesothelial cells lacking invasion.[34] Part of the practical diagnostic utility of the WHO classification is that each mesothelioma subtype is associated with a particular differential diagnosis that guides the pathology workup. This workup requires additional time and expense because of the ancillary studies that are required for definitive diagnosis. From a prognostic perspective, studies have shown that the pure epithelioid subtype has a difference in survival in many instances and hence may affect therapy selection. It should also be recognized that the larger the tissue sample, the more frequent the histologic variation and the higher the incidence of biphasic tumors.[35]

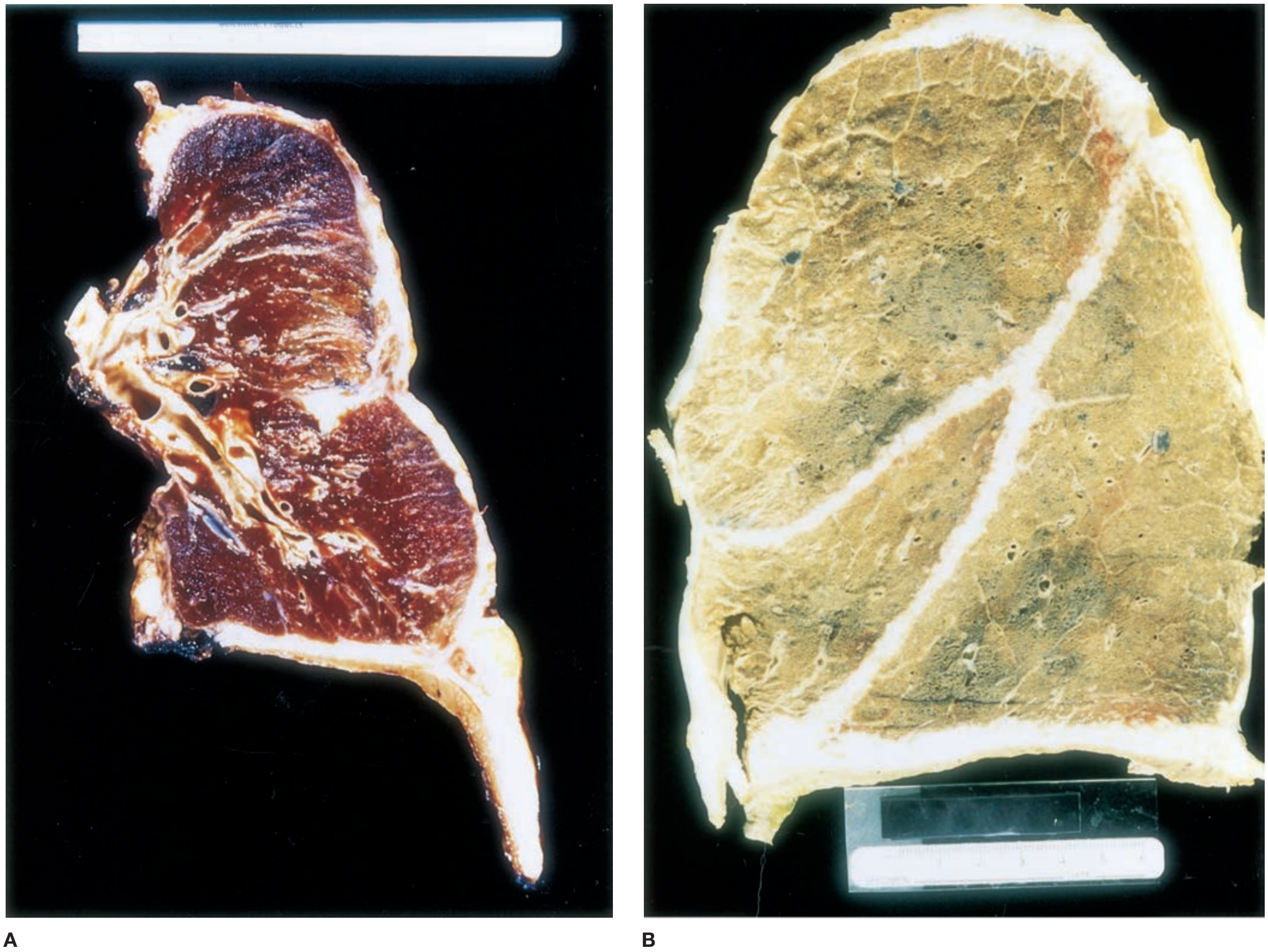

Figure 78-1 **A.** Transverse section of an extrapleural pneumonectomy surgical specimen with the entire right lung, parietal and visceral pleurae, portions of pericardium, and the majority of the right hemidiaphragm. Note the thick rind of tumor along the pleural surface encasing the lung and invading the diaphragm. **B.** Postmortem mesothelioma specimen with overnight formalin inflation and fixation. The right lung pictured is covered by a thick, whitish rind of tumor involving the entire pleural surface, which has also infiltrated and demarcated the interlobar fissures.

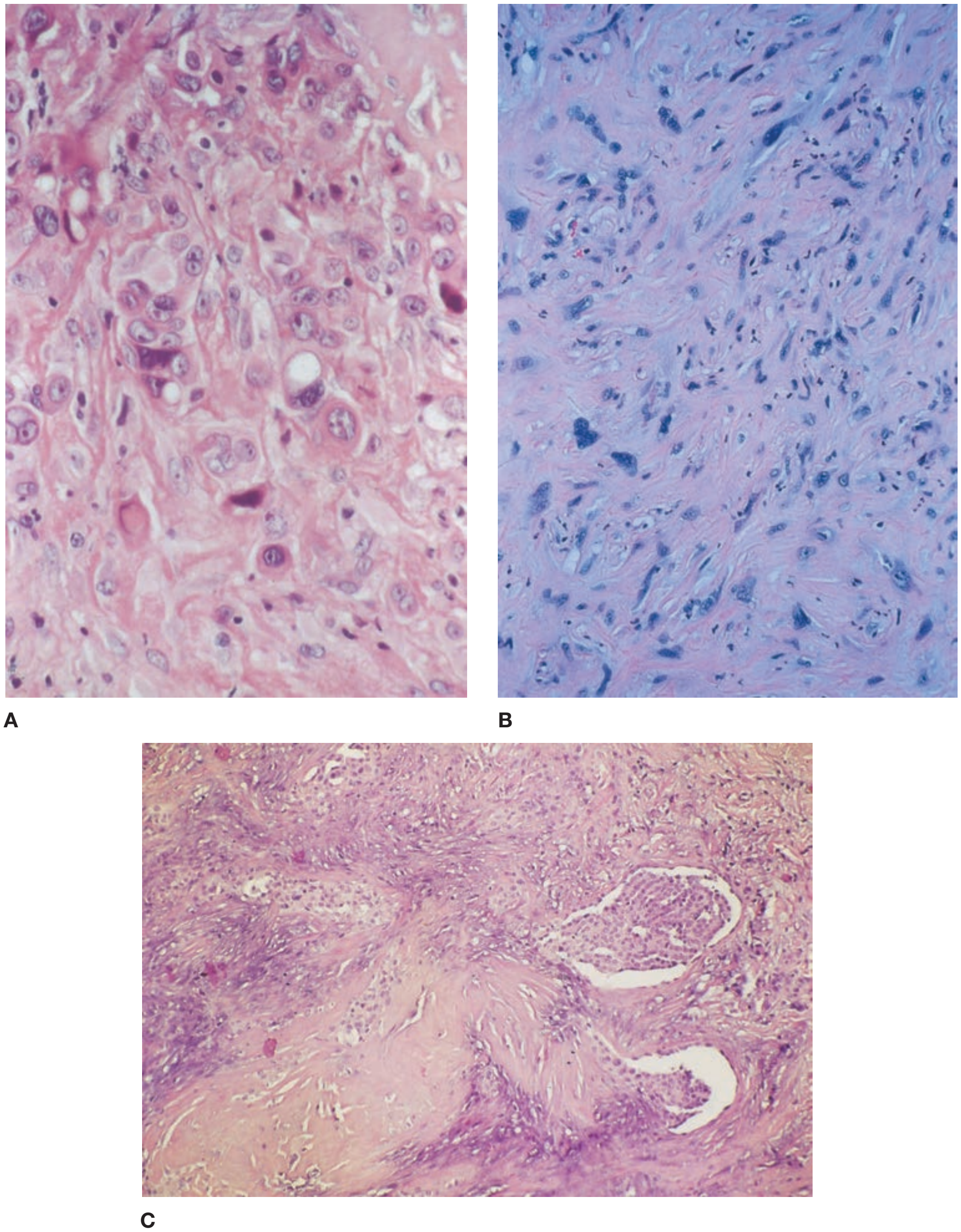

Figure 78-2 **A.** Photomicrograph of an epithelial malignant mesothelioma. These sheets of pleomorphic cells are epithelial in appearance, with eosinophilic cytoplasm and fairly well-defined cell borders. Note the cytoplasmic vacuoles, which can lead to confusion with a signet ring type of adenocarcinoma. By electron microscopy, these vacuoles can be shown to contain crystallized hyaluronic acid (H&E, ×400). **B.** Photomicrograph of a sarcomatoid malignant mesothelioma. This tumor has a malignant mesenchymal appearance with bizarre, spindled cells and a growth pattern resembling that of a sarcoma. These cells demonstrated strong cytokeratin positivity on immunohistochemical staining, distinguishing this tumor from a sarcoma (H&E, ×400). **C.** Photomicrograph of a biphasic malignant mesothelioma. This tumor demonstrates several areas of epithelioid histology with a papillary growth pattern seen against a background of spindled and more poorly differentiated epithelioid cells (H&E, ×200).

The epithelioid subtype is the most common, with a wide range and mix of histologic patterns. Common histologic variants of this subtype include tubulopapillary, trabecular, micropapillary, and solid (Fig. 78-2A). Less common variants include adenomatoid, rhabdoid, deciduoid, small cell, and signet ring patterns. A myxoid matrix may be prominent and may be mistaken for mucin, but this matrix is actually hyaluronate and shows hyaluronidase-sensitive staining with Alcian blue. There are data to support the utility of nuclear grading of pleural diffuse epithelioid mesothelioma. The proposed grading system is based on a score for nuclear atypia and mitotic count, as well as the presence or absence of necrosis.[34] Although grading of epithelioid mesothelioma had not been widely performed prior to the 2021 WHO classification, it is now recommended in both biopsy and resection specimens to help in the recognition of tumors that may behave in a more aggressive fashion. Pleomorphic features—specifically prominent anaplastic/bizarre nuclei and multinucleated giant cells—can be seen in the epithelioid type and should be reported as another indicator of aggressive behavior. Lymphohistiocytoid features—characterized by dense lymphoid infiltrates composed mainly of CD8+ T cells that obscure the malignant histiocytoid appearing tumor cells—similarly should be reported. Both pleomorphic and lymphohistiocytoid features can be seen in biphasic or sarcomatoid subtypes and should be recorded as well.

Sarcomatoid mesotheliomas can also have a wide variety of histologic patterns. The most frequently encountered pattern is that of fibroblastic-like spindle cells arranged in storiform, fascicular, or haphazard patterns that mimic a fibrosarcoma (Fig. 78-2B). Some sarcomatoid mesotheliomas have "heterologous elements" such as rhabdomyosarcoma, osteosarcoma, and chondrosarcoma. Benign osteoclast-like giant cells also may be seen, as well as the previously mentioned pleomorphic or lymphohistiocytoid features. Transitional features have been described as elongated but plump tumor cells, intermediate in morphology between the epithelioid and sarcomatoid subtypes. The transitional tumor cells are more round than sarcomatoid tumor cells but more discohesive than epithelioid tumor cells. A reticulin stain will highlight single tumor cells. The survival data to date appear to support grouping these tumors with transitional features with sarcomatoid mesothelioma.

Desmoplastic mesotheliomas, by definition, have areas of densely collagenized tissue with atypical cells arranged in a storiform or "patternless" pattern. This pattern should constitute at least 50% of the tumor in resection specimens. The deceptively bland appearance of the tumor makes its separation from fibrous pleuritis exceedingly difficult, particularly with limited sampling. Studies that have examined the criteria used for diagnosis have highlighted the importance of "interface biopsies" in which unequivocal evidence of invasion into the underlying adipose tissue, skeletal muscle, or lung may be demonstrated. Other criteria, which may require multiple tissue sections to detect, include obvious sarcomatoid areas, foci of necrosis, and distant metastases. Bone metastases similarly may be deceptively bland and confused with a primary benign fibrous tumor of bone.

Biphasic mesotheliomas have both epithelioid and sarcomatoid components (Fig. 78-2C). Each component should represent at least 10% of the tumor for the designation of biphasic mesothelioma in resected specimens. However, a tumor can be designated as biphasic regardless of the percentage of each component in a small biopsy sample. Whether in a small biopsy specimen or larger resection, the percentage of the sarcomatoid component should be noted because of the potential impact on treatment options and prognosis. Biphasic mesotheliomas represent about 30% of cases. As previously noted, the percentage of biphasic tumors increases with larger tumor samples.

Immunohistochemistry

Immunohistochemistry (IHC) has replaced electron microscopy as the gold standard for diagnosis. This is because of the comparative low cost, ease, and greater availability of IHC, as well as the expanded array of commercially available antibodies that are reliable markers of mesothelial differentiation. Because there is no single marker with sufficiently high sensitivity and specificity for malignant mesothelioma, it is standard practice for pathologists to employ a panel of markers (both positive and negative) to confirm the diagnosis of malignant mesothelioma. Guidelines for the pathologic diagnosis of malignant mesothelioma were first published in 2009 in a consensus statement from the International Mesothelioma Interest Group and are periodically updated.[36] As in any instance in which IHC is used as an adjunct in tumor diagnosis, careful consideration must be given to the tumor's histologic appearance as well as the clinical-radiographic context and the differential diagnosis that is generated from this information.

Broad-spectrum cytokeratin (CK) antibody cocktails are essential in the diagnosis of malignant mesothelioma. In epithelioid tumors, strong and diffuse CK positivity can be used to exclude the rare case of large cell lymphoma, epithelioid vascular tumors, or melanoma involving the pleura. CK reactivity usually differentiates malignant mesotheliomas from many sarcomas, although there are occasional CK-negative sarcomatoid mesotheliomas as well as focally CK-positive sarcomas. Although CK positivity does not distinguish malignant mesothelioma from reactive lesions, positive CK staining may help to highlight invasion into adjacent structures.

Common affirmative immunohistochemical markers, which, if positive, can be used to support a diagnosis of malignant mesothelioma include calretinin, CK5/6, the Wilms tumor 1 (WT1) antigen, and D2-40 (Fig. 78-3).[36] These markers are most useful in the narrow differential diagnosis of malignant epithelioid mesothelioma versus primary pulmonary adenocarcinoma. It should be noted that these markers do not invariably exclude other tumors, including metastases from nonpulmonary primary sites. A wide variety of markers can be used to support a diagnosis of adenocarcinoma, as opposed to malignant mesothelioma. Markers such as MOC31, CEA, Ber-EP4, thyroid transcription factor 1 (TTF-1), and napsin A are commonly included in such panels.[36] The sensitivity and specificity of both the affirmative mesothelioma markers as well as the adenocarcinoma markers vary greatly when the differential diagnosis is broadened to include other subtypes of primary pulmonary carcinoma such as squamous cell carcinoma or metastases from extrapulmonary sites such as the kidney and ovary. Both categories of markers are generally less reliable with focal to absent staining in the differential diagnosis of sarcomatoid lesions. The immunohistochemical panel that is recommended for the initial evaluation of a sarcomatoid tumor involving the pleura includes CKs (including AE1/3, CAM5.2, CK18, and CK7), calretinin, and D2-40.[36] If other types of sarcomas are being considered, then the marker panel should be expanded accordingly to include antibodies such as CD31, CD34, desmin, myoglobin, and S-100. The guidelines previously mentioned include a number of specifically recommended panels to assist pathologists in the selection of markers according to the differential diagnosis and the need to exclude other primary sites.

IHC has also been utilized to increase our understanding of the interface between tumors and surrounding/infiltrating immune cells, otherwise known as the tumor microenvironment (TME). Marcq et al. analyzed the TME of samples from patients with malignant mesothelioma, some of whom had been previously treated with chemotherapy, and others who were treatment-naïve. In their study population, PD-1 and CD45RO expression in the tumor stroma was associated with worse response to chemotherapy, whereas PD-1, CD4, AND TIM3 expression in lymphoid aggregates was associated with improved clinical prognosis. Interestingly, the investigators were able to confirm qualitative visual evidence of tumor-infiltrating lymphocytes in their samples, and in the previously treated samples there was no tumoral expression of PD-1 or PD-L1, possibly providing mechanistic support for the combination of chemotherapy and immunotherapy.[37] A study by Uijie et al. specifically examined markers on tumor infiltrating immune cells from 230 patients with malignant mesothelioma and compared their IHC findings with clinical data, noting that higher infiltration of CD163+ macrophages and CD8+ T cells was associated with improved survival, whereas decreased infiltration of CD163+ macrophages and higher levels of CD20+ T cells were both associated with poorer survival.[38]

■ Other Ancillary Studies

Histochemical stains for the presence of intracytoplasmic mucin are still occasionally used as a means of differentiating adenocarcinomas from epithelioid malignant mesotheliomas. Mucicarmine and periodic acid–Schiff (PAS) with diastase are the two most frequently used. These stains are technically easy to perform, inexpensive, and rapid. Care must be taken to exclude the possibility of false-positive staining that can be seen with hyaluronate. The use of histochemical

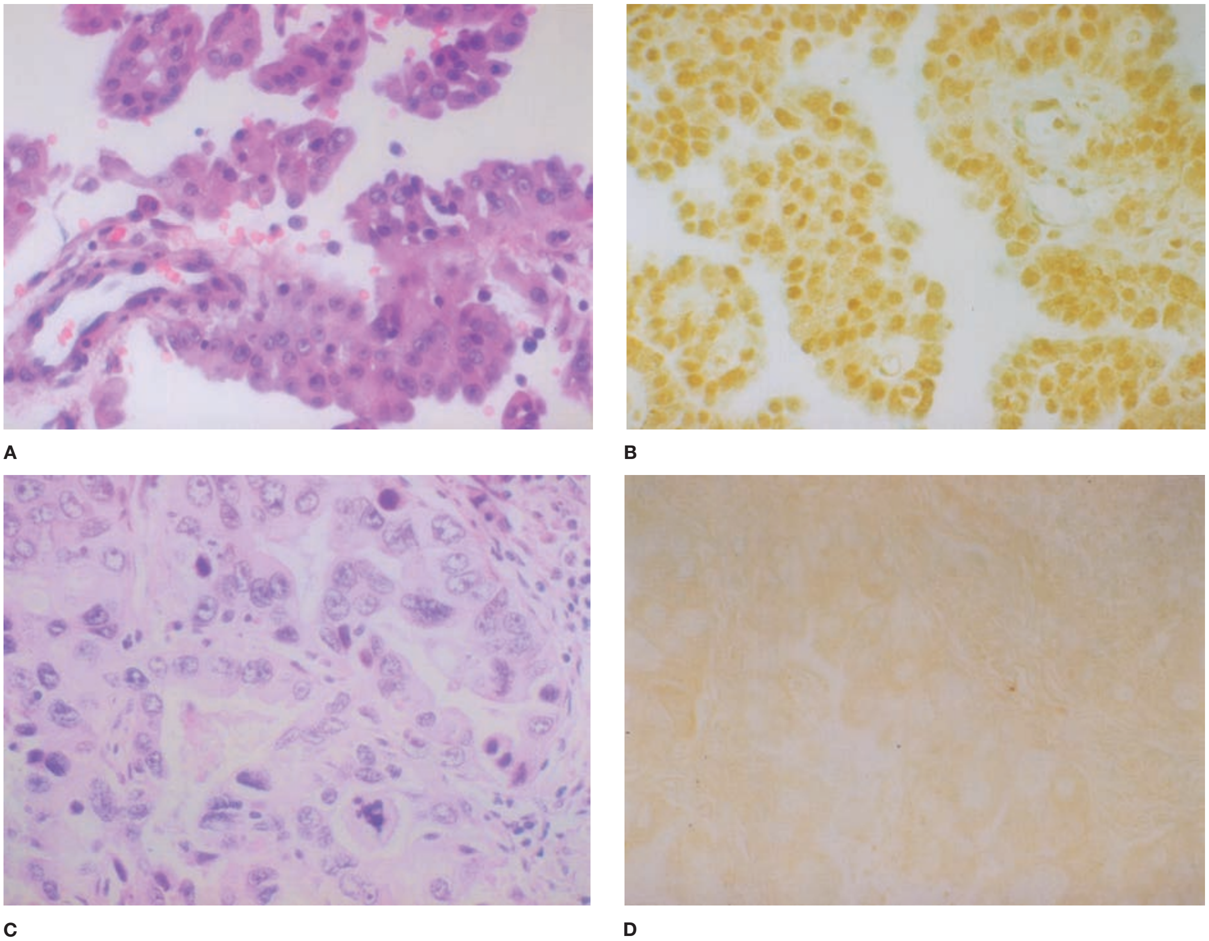

Figure 78-3 **A.** Photomicrograph of an epithelial mesothelioma (H&E, ×400). **B.** Photomicrograph of epithelial mesothelioma demonstrating positive nuclear staining with an antibody to the Wilms tumor 1 (WT1) gene product (×400). **C.** Photomicrograph of an adenocarcinoma metastatic to the pleura (H&E, ×400). **D.** Photomicrograph of pleural adenocarcinoma stained with an anti-WT1 antibody (×400). Only minimal background staining is present.

staining (Alcian blue with hyaluronidase) to detect the high levels of hyaluronic acid in mesothelioma cells was used far more frequently before the widespread use of IHC.

Electron microscopy had traditionally been considered the gold standard for the diagnosis of malignant mesothelioma and ultrastructural analysis.[39] The predominant epithelioid form is composed of polygonal cells with numerous long surface microvilli, prominent desmosomes, and abundant tonofilaments (Fig. 78-4). Electron microscopy of the sarcomatoid variant reveals the presence of elongated nuclei, CK and vimentin filaments, copious rough endoplasmic reticulum, some intracellular attachments, and rare microvilli. Electron microscopic studies may be inconclusive in poorly differentiated tumors of either subtype and have no utility in the diagnosis of desmoplastic malignant mesothelioma. Molecular analysis can be performed on formalin-fixed, paraffin-embedded tissue to demonstrate the X:18 translocation characteristic of synovial sarcoma—a biphasic or monophasic sarcomatoid tumor that can involve the pleura. As discussed at the end of the chapter, synovial sarcoma should be considered in the differential diagnosis of a pleural tumor with a biphasic or monophasic spindle cell appearance.

■ Molecular Profiling

Compared with routine histologic evaluation and classification, the examination of multiple expressed genes and/or proteins within individual tumors may be more informative for making diagnoses, estimating prognosis, and anticipating response to therapy. The development of microarray methodology, which permits the expression of thousands of genes to be assayed simultaneously, represents a powerful technique to read the "molecular signature" of an individual patient's tumor, a process termed *gene expression profiling*. Gene expression profiling studies have been used to identify genes with potential pathogenic significance, such as aurora kinases or key inhibitors of apoptosis proteins. Profiles have also been identified that help to reliably differentiate different subtypes of mesothelioma. By using gene expression ratios, it is possible to reliably distinguish between epithelioid mesothelioma and lung adenocarcinoma or ovarian carcinomas from peritoneal mesotheliomas.[40,41] An area of active investigation is the use of expression profiles as a means of predicting outcome and clustering groups of patients with pleural mesothelioma into those with good-risk disease (i.e., more likely to be cured using aggressive therapy) and poor-risk disease (i.e., with a low cure rate despite aggressive therapy). Some groups have found this approach to be highly predictive, whereas others suggest the accuracy has been overestimated.[42]

Over the past several years, as the ability to sequence genomes and characterize and quantify gene expression has improved, more has been discovered about the molecular profile of malignant mesothelioma. A large genomic analysis of tumors from patients with MPM by Bueno et al. found a heavy burden of mutations in the genes *BAP1*, *NF2*, *TP53*, *DDX3X*, *SETD2*, *SF3B1*, and *TRAF7*. However, the tumor samples had a relatively low level of mutations that caused alterations in the resultant proteins. In addition, distinct

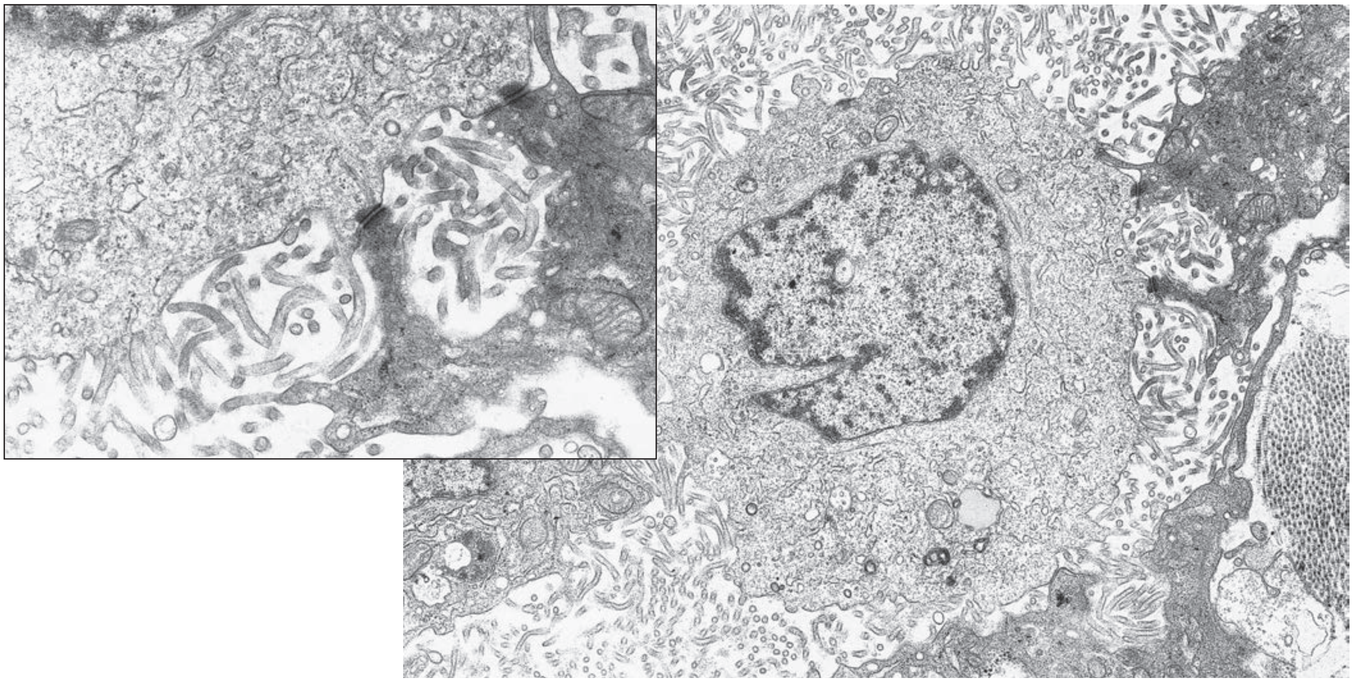

Figure 78-4 Electron micrograph of a human mesothelioma cell showing abundant microvilli arising from the cell surface and prominent desmosomes (×10,500; inset, ×30,000). *(Reproduced with permission from Dr. Giuseppe G. Pietra, Department of Pathology and Laboratory Medicine, University of Pennsylvania Medical Center, Philadelphia.)*

mutational profiles for sarcomatoid and epithelioid histologies were determined, with biphasic tumors more closely resembling a sarcomatoid profile.[43]

Clinical Presentation

Malignant mesothelioma most commonly presents in the fifth to seventh decades of life. Most patients diagnosed with mesothelioma earlier in life have a history of childhood asbestos exposure. The most frequent presenting symptoms of pleural mesothelioma, which are caused by the presence of extensive intrathoracic disease, are nonpleuritic chest pain (60%–70% of patients), dyspnea (25%), and cough (20%). Some patients are asymptomatic at diagnosis, with unilateral pleural effusions found incidentally on routine chest radiographs. Mesothelioma is typically a unilateral disease—only 10% of patients with mesothelioma have bilateral involvement at presentation. In more advanced stages of disease, physical findings may include unilateral dullness to percussion and decreased air movement throughout the hemithorax, asymmetric chest wall expansion during respiration, palpable chest wall masses, and scoliosis toward the side of the malignancy.

Radiographic Presentation

The most common initial radiographic manifestation of pleural mesothelioma is a large unilateral pleural effusion, often with contralateral mediastinal shift (Fig. 78-5A). Sixty percent of patients have right-sided lesions, putatively related to the gravitational predilection for inhaled asbestos fibers and dusts to travel directly to the right lower lobe airways. Occasionally, mesothelioma can present as unilateral, concentric, plaque-like, or nodular pleural thickening, but effusions may obscure the presence of the underlying pleural thickening. The tumor frequently extends into the fissures, which become thickened and irregular in contour. Only 20% of patients with pleural mesothelioma have radiographic signs of asbestosis (i.e., bibasilar interstitial fibrosis), although many have evidence of pleural plaques and/or calcifications. In later stages of disease, ipsilateral mediastinal shift is seen secondary to encasement of the lung by a thick rind of tumor and resultant significant unilateral loss of lung volume. Patients with advanced mesothelioma may also have other radiographic signs of volume loss—diaphragm elevation and intercostal space narrowing. They may also have mediastinal widening owing to direct tumor invasion or lymph node involvement, enlargement of the cardiac margins secondary to pericardial invasion with effusion, and evidence of rib destruction or soft tissue masses extending from the chest wall.[44] Chest computed tomography (CT) is important in detecting invasion of chest wall, ribs, and mediastinal structures, as well as extension along the pleural surfaces and diaphragm (Fig. 78-5B). Furthermore, CT scans can distinguish between pleural thickening and effusion.[45] Coronal magnetic resonance imaging (MRI) is helpful in discerning the extent of disease, particularly invasion of the chest wall, endothoracic fascial involvement, and extension of pleural mesothelioma through the diaphragm into the peritoneal cavity.[46] In one study of 95 patients with pleural mesothelioma, MRI was directly compared with CT scan. The overall diagnostic accuracy for mediastinal nodal disease was approximately 50% for both modalities, but MRI outperformed CT for detection of diaphragmatic invasion (82% vs. 55% accuracy, respectively), and for detecting invasion of endothoracic fascia or chest wall (69% vs. 46%, respectively).[47]

Positron Emission Tomography

The role of positron emission tomography (PET) imaging, particularly PET/CT, in the care of patients with mesothelioma is multifold. It can be used in diagnosis and staging by evaluating the extent of pleural disease, establishing mediastinal lymph node involvement, evaluating tumor invasion into the lung and thoracic wall, and detecting extrathoracic metastases. It is becoming particularly useful to assess the treatment response to chemotherapy and radiotherapy and also plays an important role in the planning of radiation therapy.

The role of PET scans with 18-fluorodeoxyglucose (FDG) in staging and preoperative evaluation is evolving. In a small study of

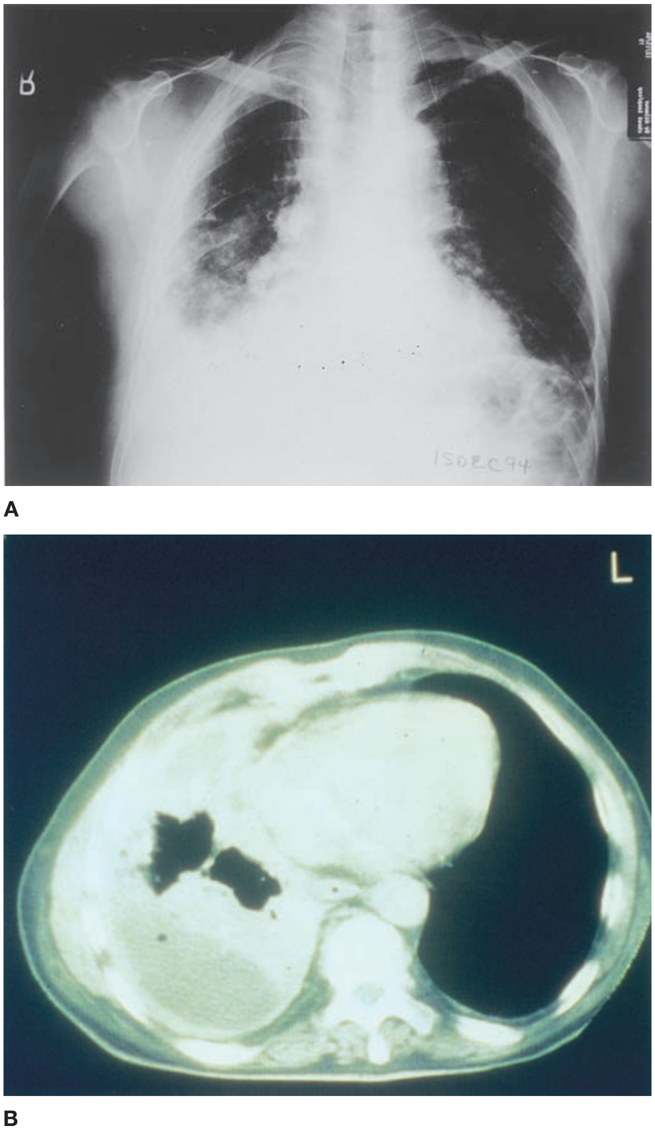

Figure 78-5 **A.** Posteroanterior chest radiograph in a patient with malignant pleural mesothelioma demonstrating significant right-sided pleural effusion and diffuse pleural thickening associated with marked volume loss of the right hemithorax. No definite calcified pleural plaques are seen. **B.** Computed axial tomographic image from a patient with pleural mesothelioma, illustrating complete encasement of the ipsilateral lung with a thick rind of tumor, neoplastic invasion of the interlobar fissures, small residual pleural effusion, and marked unilateral volume loss.

28 patients with suspected pleural mesothelioma who underwent 18-FDG PET scanning followed by thoracoscopic or open surgical biopsy, PET was shown to be better than CT for differentiating malignant from benign pleural processes. Uptake of FDG was significantly higher in malignant lesions, and an overall sensitivity and specificity of 91% and 100% could be achieved with PET scanning for the detection of malignant compared with benign disease. However, hypermetabolic lymph nodes were detected in 12 patients (of whom 9 had a normal CT scan), and only 5 had histologically proven malignant nodal disease.[48]

In another small study, PET assessment demonstrated pleural lesions in 12 of 13 patients with malignant pleural disease (malignant pleural mesothelioma in 10 patients, adenocarcinoma in 2 and liposarcoma in 1), also revealing distant metastases in 2 patients. A patient with an epithelial mesothelioma had a false-negative result. In a study of 16 patients with pleural changes, PET correctly identified all 12 malignant cases; conversely, the 4 patients who had no FDG uptake all had benign pleural disease (fibroma, tuberculous pleurisy, empyema, and pleural fibrosis).[49]

PET scan appears more sensitive than CT for finding extrathoracic disease, but it has limited sensitivity for locoregional staging (i.e., determining potential resectability). In a retrospective study, 60 patients with malignant pleural mesothelioma were identified who had undergone PET scans preoperatively and the results of clinical staging were compared with surgical and pathologic results. FDG uptake was detected in 59, and the 1 false-negative case had disease limited to the parietal pleura (stage IA). The sensitivity of PET scans for determining the presence of T4 (unresectable) disease was only 19% (7 of 21 patients). Among the 31 patients whose nodal status was assessed pathologically, only 1 of 9 patients with N2 disease was correctly identified by PET scan, and the overall sensitivity for nodal disease was only 11%.[50]

PET scanning may help differentiate between benign and malignant pathology when patients present with a chest radiograph demonstrating pleural abnormalities. One study demonstrated that dual timepoint FDG PET scanning, which measures uptake of ^{18}F-FDG over time, could distinguish between benign and malignant pleural diseases among 55 suspected cases.[51]

One of the potential future uses of PET that needs to be further evaluated is its utilization in the screening of patients with a history of significant asbestos exposure. These patients may potentially harbor microscopic disease, not apparent on CT or MRI, which may be amenable to early aggressive therapy. Because of the limits of detection of current ^{18}F-FDG PET technology, the use of PET for screening for pleural mesothelioma must await the development of novel radiopharmaceuticals.

PET scans can also be used to predict survival and response to therapy. One study involving 177 patients with mesothelioma found that patients with tumors demonstrating intense FDG avidity (standardized uptake value >5) had a far worse prognosis. Another study showed that decreased radiopharmaceutical uptake on follow-up PET scans performed early after treatment may be an excellent predictor of overall clinical response.[52] Furthermore, there is evidence supporting the use of PET scans after neoadjuvant chemotherapy to determine those who will benefit most from moving on to surgical resection.[53]

Laboratory Studies

Although there are no specific pleural fluid biomarkers for malignant mesothelioma, evaluation of pleural fluid chemistries may still be beneficial. Effusions associated with mesothelioma are strongly exudative, with elevated protein concentrations in the range of 4 to 5 g/dL and a lymphocytic predominance. Pleural fluid lactate dehydrogenase (LDH) concentrations often exceed those of patients with carcinomatous pleural effusions, with levels greater than 600 IU/L. In patients with advanced disease and extensive involvement of visceral and parietal pleura, pleural fluid pH and glucose are commonly low. In patients with mesothelioma, the presence of a low pleural fluid pH denotes both a poor overall prognosis and refractoriness to achieving successful palliative pleurodesis. In addition, the pleural effusion associated with mesothelioma is characteristically highly viscous, presumably because of elevated concentrations of hyaluronic acid.[54] An increased pleural fluid hyaluronidase level is suggestive but not diagnostic of mesothelioma.[55] The cytokine profile of pleural effusions related to mesothelioma is somewhat unique in that the tumor constitutively produces high concentrations of interleukin 6 (IL-6) and transforming growth factor-β (TGF-β), but relatively low levels of IL-1β and TNF-α. These elevated intrapleural levels of IL-6 in patients with malignant mesothelioma are postulated to induce systemic manifestations such as fever, cachexia, and thrombocytosis.[56,57]

Pulmonary function testing typically demonstrates a restrictive pattern resulting from pleural effusions, tumor encasement of the lung, or chest wall involvement.

Mesothelin and Other Novel Serum Markers

There is increasing evidence supporting the clinical utility of a monoclonal antibody–based serum assay for a soluble form of the protein mesothelin (soluble mesothelin–related peptide [SMRP]). Mesothelin is a 40-kDa glycoprotein that is found in low levels on the cell surface of normal mesothelial cells (lining the pleura, peritoneum, pericardium, and tunica vaginalis), but is highly expressed on mesothelioma, pancreatic cancer, and ovarian cancer cells.[58,59] Multiple studies have observed that SMRP can be elevated in serum and pleural fluid of patients with mesothelioma.[60] Increased levels of SMRP were found in serum samples from 37 of 44 patients with mesothelioma (87%), compared with 3 of 160 patients with other cancers or inflammatory lung or pleural diseases (2%), and none of 28 controls without a past asbestos exposure.[61] At the present time, SMRP levels play an adjunctive role in the diagnosis of patients with mesothelioma. A meta-analysis of 16 diagnostic studies found that the sensitivity ranged widely from 19% to 68%, depending on the specific criterion for positivity.[60] SMRP has also been measured in pleural fluid. In a retrospective study of 192 patients with pleural effusion (52 patients with malignant mesothelioma, 56 with nonmesotheliomatous malignancies, and 84 with nonneoplastic effusions), the assay had a sensitivity of 67% with a specificity of 98%.[62] It is intriguing to posit that SMRP may also play a role in screening of high-risk patients for incipient mesothelioma. In one report, 7 of 40 asbestos-exposed individuals had elevated levels and 4 of these 7 subsequently developed mesothelioma or lung cancer within 1 to 5 years.[61] However, measurement of SMRP is indicated currently only for monitoring patients in whom the diagnosis has already been established.

Osteopontin, a glycoprotein that mediates cell–matrix interactions and is overexpressed in several types of cancer, was higher in patients with malignant mesothelioma than in patients with asbestos-related nonmalignant pleural disease or no prior asbestos exposure in a study of 190 patients.[63]

Fibulin-3 is an extracellular glycoprotein that is encoded by the epidermal growth factor–containing fibulin-like extracellular matrix protein 1 (EFEMP1) gene. Initial studies found that elevated levels of fibulin-3 in the plasma had high sensitivity and specificity (97% and 96%, respectively) in distinguishing patients with pleural mesothelioma from those with a history of asbestos exposure but without mesothelioma and from those with other malignancies or benign causes of pleural effusion. Levels of fibulin-3 decreased in patients with mesothelioma who underwent surgical resection. Additional studies will be required to determine its role as a biomarker for early diagnosis and monitoring of patients who have undergone therapy.[64]

Diagnosis

The differential diagnosis of malignant pleural mesothelioma includes both benign and malignant processes. Inflammatory reactions such as chronic, organized empyema can mimic the dense pleural thickening and large, viscous pleural effusions characteristic of mesothelioma. As discussed, epithelial mesotheliomas can be extremely difficult to distinguish grossly and histologically from metastatic adenocarcinoma to the pleura from any number of primary sources, including lung, breast, stomach, kidney, ovary, and prostate. Sarcomas such as fibrosarcoma can present in similar fashion to sarcomatoid mesotheliomas. The mixed-cellular (biphasic) subtype of mesothelioma can bear a significant histologic resemblance to sarcomatoid carcinomas and synovial sarcoma.

Thoracentesis or closed pleural biopsy can often establish the diagnosis of pleural malignancy but may not provide enough diagnostic material to determine the specific diagnosis of mesothelioma. Immunohistochemical markers and monoclonal antibodies may aid in differentiating mesothelioma from other carcinomas on cytology specimens. In addition, certain cytopathologic features of cells obtained from pleural fluid have been found to correlate well with the presence of mesothelioma, including papillary aggregates, multinucleation with atypia, cell-to-cell apposition, nuclear pleomorphism, and macronucleoli. Gene expression ratios also may be increasingly helpful in this regard. Negative results from thoracentesis and/or pleural biopsy do not exclude the diagnosis of mesothelioma, and therefore surgical biopsy, which has a higher diagnostic yield, should be pursued in patients with high clinical suspicion.

Surgical intervention, via video-assisted thoracoscopic surgery (VATS) or open thoracotomy, is often necessary to firmly establish the diagnosis. Boutin et al. from Marseille prospectively evaluated VATS for the diagnosis of malignant pleural mesothelioma in 188 consecutive patients from 1973 to 1990 and found that thoracoscopic biopsy was diagnostic in 98% of cases, compared with only 26% for thoracentesis alone, and 39% for fluid cytology and closed pleural biopsy. These thoracoscopic procedures were performed under local anesthesia in an endoscopy suite with minimal morbidity or complications.[65] It is important to note that approximately 10% of patients who undergo a transthoracic diagnostic procedure for mesothelioma may seed the biopsy site with tumor cells, later developing chest wall recurrences. This complication can potentially be prevented by prophylactic radiation therapy to the surgical incision or thoracentesis sites (Fig. 78-6).

Concurrent bronchoscopy may be important in distinguishing between mesothelioma and metastatic adenocarcinoma of the lung, as endobronchial lesions are rarely seen in mesothelioma. In addition, both endobronchial ultrasound–guided transbronchial needle aspiration (EBUS-TBNA) and mediastinoscopy play important roles in the diagnosis and staging of mesothelioma, as several studies have documented the significant negative prognostic implications of mediastinal nodal invasion in this disease. In comparative trials, EBUS-TBNA may actually have a higher sensitivity and specificity for determining mediastinal nodal involvement than mediastinoscopy.[66,67]

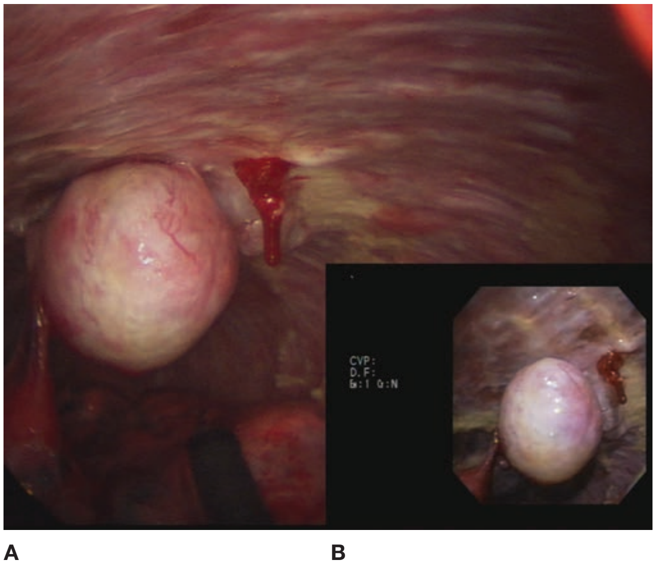

Figure 78-6 **A.** View of a mesothelioma tumor in the pleural cavity attached to the visceral pleura through surgical thoracoscope. **B.** View of the same tumor through a flexible medical pleuroscope.

TABLE 78-1 Butchart Staging System

Stage I	Tumor confined within the "capsule" of the parietal pleura
Stage II	Tumor invading chest wall or involving mediastinal structures
Stage III	Tumor penetrating diaphragm to involve peritoneum; involvement of opposite pleura; lymph node involvement outside the chest
Stage IV	Distant blood-borne metastases

Staging

The staging of malignant mesothelioma has proved to be more controversial than that of many other tumors. The most commonly used schema was devised by Butchart in 1976 (Table 78-1). Although useful, its ability to predict survival is weakened by lack of inclusion of lymph node involvement and chest wall invasion. For this reason, the Union Internationale Contre le Cancer (UICC) in 1990 first proposed a staging system based on the TNM (tumor, node, metastasis) standard used for many other tumors. In the TNM staging system, stages I and II disease have pleural involvement, potentially including diaphragmatic muscle or pulmonary parenchyma, but no evidence of lymph node involvement, distant metastases, or locally advanced, unresectable disease. Stage III mesothelioma includes those cases with regional lymph node involvement. Stage IV includes those with locally advanced and unresectable disease, contralateral lymph node involvement, supraclavicular lymph node involvement, and/or distant metastases.[68] More recently, Rusch et al. from the International Mesothelioma Interest Group (IMIG) proposed an updated staging system based upon tumor descriptors, providing precise anatomic definitions of the local extent of the primary tumor. This staging system (Table 78-2) was designed to provide the framework for proper analysis of prospective clinical trials of new treatment modalities.[69]

Clinical Course and Complications

The morbidity and mortality associated with mesothelioma are chiefly related to inexorable local invasion. Patients typically develop dyspnea and chest pain as tumor and fibrosis gradually obliterate the pleural space and replace any pleural fluid. As the tumor spreads, it covers both visceral and parietal pleural surfaces, encasing the ipsilateral lung with a thick, fibrous peel that extends into interlobar fissures and occasionally into lung parenchyma. Deoxygenated blood is shunted through the trapped lung, leading to significant dyspnea and to hypoxemia that is often refractory to supplemental oxygen. Dyspnea also results from abnormal chest wall mechanics secondary to tumor invasion into ribs as well as intercostal nerves and muscles. Local invasion of crucial thoracic structures can result in dysphagia, hoarseness, cord compression, brachial plexopathy, paralysis, Horner syndrome, and superior vena cava syndrome. Hilar and mediastinal lymph node involvement occurs at diagnosis in fewer than 50% of patients but is a harbinger of poor prognosis. Transdiaphragmatic spread into the abdominal cavity rapidly leads to intraperitoneal dissemination, with encasement of the mesentery and small and large bowel. Local invasion into the pericardial space can lead to pericardial effusion and tamponade. Distant metastatic disease by hematogenous spread is unusual early in the course of mesothelioma but may present in liver, bone, brain, adrenals, thyroid, and kidney. Widespread metastatic disease is more often a manifestation of end-stage malignant mesothelioma.[5,70–73]

TABLE 78-2 International Mesothelioma Interest Group (IMIG) Staging System

T1	T1a: Tumor limited to ipsilateral parietal pleura T1b: Tumor involving ipsilateral parietal pleura, with scattered foci of tumor on visceral pleural surface
T2	Tumor involving all ipsilateral pleural surfaces with diaphragmatic invasion or extension into underlying pulmonary parenchyma
T3	Involvement of the endothoracic fascia; mediastinal fat; solitary, resectable chest wall focus; or nontransmural pericardial invasion
T4	Diffuse extension into chest wall, peritoneum, spine, mediastinal organs, contralateral pleura, internal surface of pericardium or myocardium
NO	No regional lymph nodes metastases
N1	Metastases in the ipsilateral bronchopulmonary or hilar lymph nodes
N2	Metastases in the subcarinal or ipsilateral mediastinal lymph nodes
N3	Metastases in the contralateral mediastinal or internal mammary lymph nodes or any supraclavicular node metastasis
Staging	
Stage I	Ia: T1aN0M0 Ib: T1bN0M0
Stage II	T2N0M0
Stage III	Any T3M0, any N1M0, any N2M0
Stage IV	Any T4, any N3, any M1

Mortality

Median survival of patients with mesothelioma is between 8 and 14 months and varies depending on stage, histologic subtype, and concomitant medical problems. Patients with pleural mesothelioma most commonly die from local extension and respiratory failure, primarily related to spread to the contralateral hemithorax. As mentioned, tumor extension below the diaphragm may result in death from small bowel obstruction. Patients may also die from arrhythmias, heart failure, or stroke caused by tumor invasion of the heart or pericardium.[5,70–73]

Paraneoplastic Syndromes

Disseminated intravascular coagulation, migratory thrombophlebitis, thrombocytosis, Coombs-positive hemolytic anemia, hypoglycemia, and hypercalcemia associated with secretion of a parathyroid hormone–like peptide have all been described in the setting of mesothelioma.[73]

Prognostic Factors

Poor prognosis at the time of presentation is indicated by the presence of thrombocytosis, leukocytosis, low hemoglobin, fever of unknown origin, sarcomatoid or mixed histology, age greater than 65 to 75 years, poor performance status, and male sex. Good prognosis at presentation is associated with epithelioid histology; percentage of epithelioid histology; stage I disease; age under 65 years; Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1; absence of chest pain; and the presence of symptoms for more than 6 months prior to diagnosis.[74–78] Based on data from the most recent Surveillance, Epidemiology, and End Results (SEER) study of patients with mesothelioma, those who were female, were younger, received surgery with or without radiation, and had early-stage disease tended to have longer survival.[79] Patients with mesothelioma who are considered for surgery tend to be a highly selective group with highly localized disease and excellent performance status, corroborating these findings. However, the association of female sex with increased survival does not have a clear etiology, and it may be prudent for future clinical trials in mesothelioma to control for the percentage of female subjects enrolled when calculating mortality data.

The prognostic scoring systems derived by the Cancer and Leukemia Group B (CALGB) and the European Organization for Research and Treatment of Cancer (EORTC) are the most useful clinical prognostic scoring schemes available. They incorporate both the extent of disease and systemic factors. The CALGB evaluated the impact of clinical characteristics on the survival of 337 patients treated with chemotherapy for advanced mesothelioma in sequential phase II treatment studies over a 10-year period. In multivariate analysis, serum LDH greater than 500 IU/L, poor performance status, chest pain, platelet count greater than 400,000/μL, nonepithelial histology, and age older than 75 years jointly predicted poor survival. Six distinct prognostic subgroups were generated with median survival times ranging from 1.4 to 13.9 months. The median survival overall was 7 months. This prognostic schema was subsequently validated in an American phase II trial evaluating the investigational agent ranpirnase, and in an independent European data set.[77]

The EORTC prognostic scoring system was derived from an analysis of data from 204 adults who were entered into 5 consecutive phase 2 trials over 9 years. When 5 factors were taken into consideration (poor performance status, high WBC count, male sex, sarcomatoid cell type, and the certainty of the diagnosis), favorable and poor prognostic groups could be delineated, with 1-year survival rates of 40% and 12%, respectively. Median survival from the date of study entry was 8.4 months.[80,81] The relevance of these earlier prognostic indicators is somewhat limited given that the study was performed in the pre-pemetrexed era. However, the prognostic significance of the EORTC index has subsequently been confirmed in a multivariate analysis of a phase 3 trial assessing cisplatin plus raltitrexed.

■ Current Approaches to the Treatment of Pleural Mesothelioma

Over the past several years, advances have been made that have improved our ability to treat malignant pleural mesothelioma and, possibly, the quality and quantity of life for patients with mesothelioma. Extensive investigation has demonstrated significantly increased efficacy of combination immunotherapy as a new frontline therapeutic option for a subset of patients with mesothelioma, adding to the existing multimodality treatment programs that combine surgical cytoreduction with novel forms of radiation therapy and chemotherapy regimens. Innovative palliative approaches have proved successful in alleviation of the symptoms experienced by many mesothelioma patients. Continued investigation of immunotherapy and gene therapy present a window of hope for all mesothelioma patients to obtain significantly increased survival and quality of life.

Chemotherapy

Over the past 20 years, several phase 2 single-agent and combination chemotherapy studies have been performed in mesothelioma. These studies have demonstrated evidence of antitumor activity with anthracyclines, platinum derivatives, and antimetabolites. Combination chemotherapy has been associated with higher overall response rates but not, until recently, longer median survivals.[82]

The current standard of care for first-line chemotherapy in good performance status patients with unresectable mesothelioma is combination treatment with cisplatin and pemetrexed. Pemetrexed is an antifolate compound that targets multiple enzymes in the folate metabolism pathway. Pemetrexed is a potent inhibitor of thymidylate synthase, the rate-limiting step in the synthesis of thymidylate, which is required for DNA synthesis. Thymidylate synthase is also the enzyme inhibited by the cytotoxic agents 5-fluorouracil and raltitrexed.

In 2003, Vogelzang et al. reported the results of a phase 3 randomized clinical trial in chemotherapy-naïve mesothelioma patients comparing treatment containing pemetrexed and cisplatin with cisplatin monotherapy. A total of 456 patients were randomized: 226 received pemetrexed and cisplatin, 222 received cisplatin alone, and 8 never received therapy. Median survival time in the combination pemetrexed/cisplatin arm was 12.1 months versus 9.3 months in the cisplatin-only arm ($p = 0.\ 02$). The hazard ratio for death of patients in the combination arm versus those in the control arm was 0.77. Median time to progression was significantly longer in the pemetrexed/cisplatin arm: 5.7 months versus 3.9 months ($p = 0.\ 001$). Response rates were 41.3% in the pemetrexed/cisplatin arm versus 16.7% in the control arm ($p < 0.0001$). The addition of folic acid and vitamin B_{12} to chemotherapy resulted in reduction in the severity and frequency of hematologic and nonhematologic toxicities in the pemetrexed/cisplatin arm.[83] Another randomized phase 3 study of cisplatin with a newer-generation antifolate, raltitrexed showed similar increases in survival.[84] Pemetrexed plus carboplatin may be an alternative regimen if cisplatin toxicity is a particular concern, particularly in elderly patients or those with compromised renal function.[85]

For over a decade, the standard of care for first-line chemotherapy for unresectable mesothelioma was combination therapy with cisplatin and pemetrexed.[83] In 2016, the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS) trial was the first trial to demonstrate the efficacy of antiangiogenesis in the treatment of mesothelioma. Patients who received bevacizumab in combination with standard chemotherapy demonstrated significantly longer survival than those receiving pemetrexed and a platinum agent alone (overall survival 18.8 months vs. 16.1 months). However, the addition of bevacizumab was also associated with an increase in adverse events (71% vs. 62%), particularly vascular adverse events—a substantial consideration in a disease that primarily affects older adults.[86]

The combination of gemcitabine and cisplatin or carboplatin is also a valid first-line option in the treatment of mesothelioma owing to its acceptable toxicity profile, good response rate, and palliative effects. A Northern Italian phase 2 study of gemcitabine and carboplatin in patients with pleural mesothelioma reported a 26% partial response rate and a median response duration of 55 weeks. There were also significant palliative benefits: decreased dyspnea in 46% of patients, weight gain in 40%, and pain reduction in 26%. Median survival for patients in this study was 66 weeks.[87] The potential value of the gemcitabine plus cisplatin regimen was also demonstrated in a second multicenter phase 2 trial, in which 106 previously untreated patients were treated with gemcitabine plus cisplatin and randomly assigned to receive either bevacizumab or placebo. The median survival was approximately 15 months in both treatment arms, consistent with the results seen with cisplatin plus pemetrexed. The trial showed no benefit from the addition of bevacizumab to the regimen.[88] An ongoing randomized clinical trial in Europe is evaluating the benefit of bevacizumab in combination with standard first-line pemetrexed-based chemotherapy.

There is no current standard of care for second-line chemotherapy in mesothelioma following treatment with cisplatin and pemetrexed. The most commonly used second-line regimens include gemcitabine or other drugs with single-agent activity such as vinorelbine. A large, double-blind, randomized clinical trial of the HDAC inhibitor vorinostat in second-line therapy for mesothelioma showed no survival benefit for study drug over placebo.[89] There exists insufficient evidence to recommend second-line chemotherapy as a standard treatment. Patients with adequate performance status should be enrolled onto clinical trials of second-line experimental therapies.

Radiation Therapy

Contrary to the prevailing wisdom that malignant pleural mesothelioma is a radioresistant neoplasm, it has been demonstrated that mesothelioma cell lines are actually more responsive to ionizing radiation in vitro than non–small-cell lung cancer cell lines. External beam radiation therapy for mesothelioma is, however, somewhat limited by the large treatment volumes required and the radiation sensitivity of the surrounding organs (heart, lung, esophagus, spinal cord). Although palliative radiotherapy with an attempt to treat the entire involved pleural surface is technically challenging, and associated with a high risk of radiation pneumonitis, myelitis, hepatitis, and myocarditis, it can provide effective local palliation in up to 50% of patients.[90]

There are anecdotal reports of long-term survivors following high-dose external beam irradiation, and even after intrapleural administration of radioactive isotopes. However, most studies have shown no significant effect upon overall survival in patients with mesothelioma.[91]

Radiation therapy may play a role by preventing chest wall recurrences after invasive procedures, and in improving local control after pleurectomy or extrapleural pneumonectomy (EPP).[4,91–93] Mesothelioma frequently implants along the tracts of biopsies, chest tubes, thoracoscopy trocars, and surgical incisions, producing uncomfortable subcutaneous nodules. This can be prevented with prophylactic radiotherapy. In a small randomized trial, Boutin et al. demonstrated that 21 Gy administered in three daily fractions, 10 to 15 days after thoracoscopy, decreased local recurrence from 40% to 0%.[94] These findings have been confirmed by other investigators as well.

Multimodality approaches commonly include adjuvant radiation following surgery, although there are no randomized trials that demonstrate its efficacy. Because the lung remains in place after pleurectomy, radiotherapy doses must be lower than when EPP is performed. The Radiation Oncology group at The University of Texas MD Anderson Cancer Center reported encouraging results using intensity-modulated radiotherapy (IMRT) following extrapleural pneumonectomy.[95,96] Employing careful treatment planning and IMRT, radiation doses of up to 50 to 60 Gy were possible without severe toxicity. With the combination of EPP and IMRT, local recurrences after surgery were virtually eliminated; however, novel distant disease patterns have begun to emerge. These data suggest that the combination of EPP and IMRT requires an additional treatment modality (i.e., chemotherapy or immunotherapy) to limit distant tumor growth. Although IMRT following EPP appeared to be more effective for local disease control in this initial series, a second series from the Dana-Farber Cancer Center suggested there was a significant increase in severe toxicity. In that report, 6 of 13 patients developed fatal pneumonitis in the contralateral lung.[97] More recent studies have demonstrated safety and efficacy of IMRT, either after EPP or in the adjuvant setting post–radical pleurectomy in the presence of an intact lung.[98–100] Novel forms of radiation therapy, including proton beam therapy, are currently under investigation for treatment of mesothelioma.[101,102]

Though not a traditional form of radiation therapy, there has also been interest in utilizing tumor treating fields (TTF), a technology that uses alternating electric fields to produce an antimitotic effect. The STELLAR trial was a phase 2, multicenter, single-arm trial combining TTF with standard-of-care chemotherapy (pemetrexed and cisplatin or carboplatin) as first-line treatment for unresectable malignant pleural mesothelioma. Of note, the study population had a high proportion of patients with non-epithelioid histology, and yet an overall survival of 18.2 months was achieved. This survival outcome was superior to historic controls of standard-of-care chemotherapy alone, and prompted FDA approval for TTF in this setting under a humanitarian device exception.[103] Caveats to implementation of TTF as in the STELLAR trial include the absence of a control arm from the trial, as well as the fact that the device is worn in the form of an external vest with a battery pack worn for approximately 18 h per day, which may affect quality of life for patients receiving this therapy.

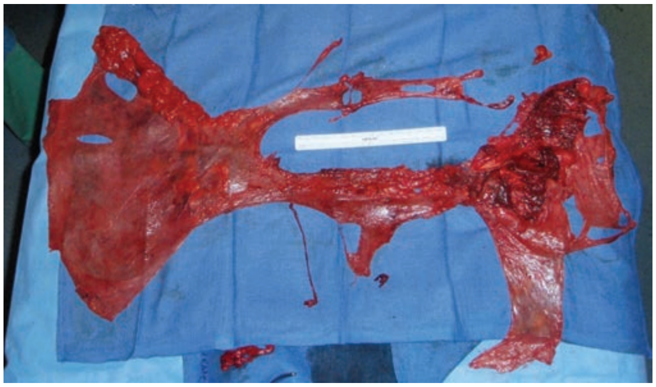

Figure 78-7 Gross photograph of a surgically resected pleurectomy/decortication specimen from a patient with malignant pleural mesothelioma. This involves the removal of the diseased pleura as an attempt to free the underlying lung to allow it to expand more freely. The steps involved are usually (1) incision and exposure of the parietal pleura, (2) dissection of parietal pleura from endothoracic fascia, diaphragm, and mediastinum, (3) incision of the parietal pleura and exposure of the visceral pleura, (4) decortication of the visceral pleura, and (5) reconstruction.

Surgical Approaches

Although associated with substantial morbidity, surgical management of mesothelioma has made significant strides in palliating the major symptoms of the disease, as well as potentially offering some improvement in survival for highly selected patients. The increased use of VATS, in conjunction with novel biomarkers, has facilitated early diagnosis of mesothelioma in more patients, at which point they may be candidates for more aggressive attempts at "definitive" surgical treatment (along with neoadjuvant/adjuvant therapies). However, definitive surgical intervention is only possible in a small percentage of patients. Furthermore, fewer than 25% of those who undergo aggressive surgical intervention will be alive at 5 years, and even fewer will be disease free at that timepoint.[104] The vast majority of pleural mesothelioma patients have locally advanced disease at the time of presentation, which, along with advanced age and/or other comorbid medical illnesses, often precludes aggressive surgical intervention.

EPP is a radical surgical procedure involving complete removal of the ipsilateral lung along with the parietal and visceral pleura, pericardium with portions of the phrenic nerve, and the majority of the hemidiaphragm (Fig. 78-7 and Video 78-1). EPP achieves

Video 78-1 Video recording from intraoperative thoracoscopic view of radical pleurectomy for malignant pleural mesothelioma performed through a thoracotomy incision. This surgical therapy for MPM is an alternative to extrapleural pneumonectomy. The procedure often takes up to several hours and involves extrapleural dissection, dissection of the diaphragm and pericardium, visceral pleurectomy, and lymph node dissection. *Video available on AccessMedicine.com.*

the greatest degree of cytoreduction and, because the lung has been removed, allows higher radiation doses to be delivered to the ipsilateral hemithorax. It is the only debulking procedure possible when a thick tumor rind obliterates the pleural space. There is a small group of long-term survivors following EPP when it is a component of a multimodality treatment program, suggesting that this procedure may alter the natural history of the disease in appropriately selected patients with early-stage disease.[105] Unfortunately, the benefits of EPP with adjuvant chemotherapy ± local radiotherapy are limited to otherwise healthy patients with early-stage disease, epithelioid histology, and no mediastinal lymph node involvement. Patients with biphasic or sarcomatoid histology and/or mediastinal or hilar node positivity have an ominous prognosis.[93,106]

EPP alone is an excellent means of palliating the profound dyspnea and orthopnea associated with the severe ventilation/perfusion mismatch resulting from lung encasement by mesothelioma. However, EPP alone has no influence on survival in the absence of adjuvant therapy.[107,108] In most EPP series, median survival from surgical debulking alone is less than 2 years, and 10% to 20% of patients are 5-year survivors. Biphasic/sarcomatoid histology and/or involvement of mediastinal lymph nodes confer a poorer prognosis and lack of demonstrable survival benefit from surgical intervention.

Several approaches for adjuvant therapy in conjunction with EPP have been studied. Investigators at Brigham and Women's Hospital have combined EPP with sequential postoperative chemotherapy and up to 55 Gy of adjuvant radiation therapy to the postoperative hemithorax.[109] More recently, the Brigham Thoracic Program has been investigating the role of hyperthermic intracavitary chemotherapy as an adjuvant to maximal cytoreductive surgery, in combination with hemithoracic irradiation and systemic chemotherapy.[110,111] In addition, several investigators have evaluated the utility of post-resectional photodynamic therapy (PDT) with or without adjuvant chemotherapy or immunotherapy.[112] One randomized trial conducted by Pass et al. at the National Cancer Institute failed to confirm any benefit for adjuvant PDT compared with surgery alone.[113,114] Novel photosensitizers are currently under study that may provide better local control, decreased photosensitivity, and perhaps improved induction of systemic antitumor immune responses. Other novel multicenter clinical trials combine maximal surgical debulking with adjuvant IMRT or alternatively assess the role of neoadjuvant chemotherapy prior to cytoreductive surgery to improve long-term outcomes. EPP in these contexts is designed as a cytoreductive, not a curative procedure.[115–117]

Parietal pleurectomy, that is, open surgical stripping of the pleura from the apex of the lung to the diaphragm, is more successful than talc pleurodesis in reducing the recurrence of pleural effusion in mesothelioma (Fig. 78-8). Thoracoscopic pleurectomy has been employed to achieve similar results as the open procedure, but with less morbidity.[92,118]

Complete parietal and visceral pleurectomy, referred to as extended pleurectomy/decortication or radical pleurectomy (EPD/RP), is designed to achieve maximal cytoreduction while leaving the ipsilateral lung intact. It involves complete resection of the entire parietal and visceral pleural including the diaphragmatic pleura and extends into the hilum to resect the pleural surfaces of the interlobar fissures. Some surgeons performing EPD/RP will also resect portions of the diaphragmatic musculature as well as the ipsilateral parietal pericardium. EPD/RP includes extensive dissection and removal of mediastinal, hilar, intercostal, and internal mammary lymph nodes. Although the procedure has not been shown by itself to prolong survival in patients with mesothelioma, it has largely become standard of care for surgical treatment of resectable malignant pleural mesothelioma.[119] A retrospective analysis of patients who underwent EPD/RP demonstrated a mean overall survival of 20.7 months, with the subgroup who achieved macroscopic complete resection surviving for 23.2 months, suggesting that durable responses may be attainable with less invasive surgical strategies.[120] There have been no prospective head-to-head trials comparing outcomes of EPD/RP with those following EPP, but several retrospective studies have demonstrated better survival for mesothelioma patients who underwent EPD/RP compared with those treated with EPP despite a higher rate of local recurrence.[121,122] There is an ongoing trial in the United Kingdom comparing radical pleurectomy plus pemetrexed/platinum agent versus chemotherapy alone, which will likely help dictate the future utility of this procedure.[123]

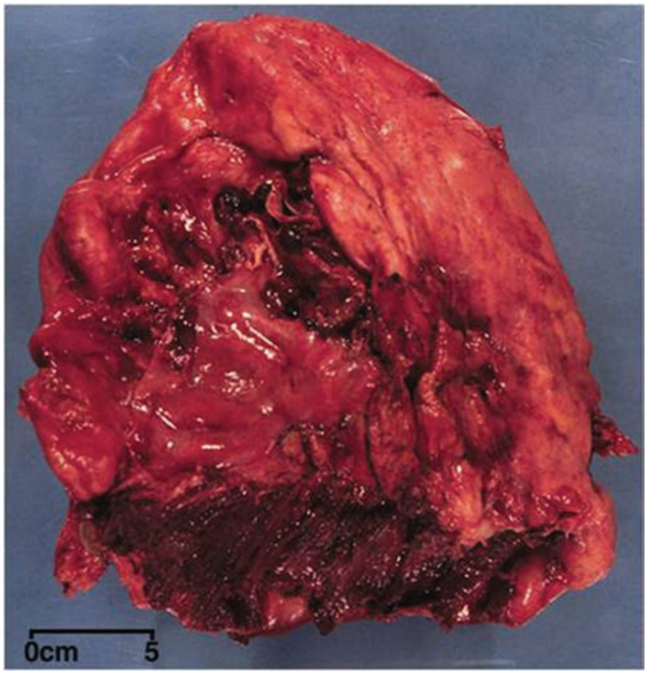

Figure 78-8 Gross photograph of a surgically resected extrapleural pneumonectomy specimen from a patient with malignant pleural mesothelioma. The specimen includes the completely removed lung along with the parietal and visceral pleura, pericardium with portions of the phrenic nerve, and the majority of the hemidiaphragm.

Investigators have evaluated the combination of EPD/RP with postoperative intrapleural radiation therapy, external beam irradiation, and/or systemic chemotherapy.[124–127] One single institution study reported a median survival of 22.5 months and a 2-year survival rate of 41% in a group of 27 patients, predominantly with the epithelioid subtype.[124,126]

There have been several recent reports describing EPD/RP as the cornerstone of multimodality treatment with various adjuvant intraoperative therapies such as intrapleural PDT,[128] intrapleural hyperthermic chemotherapy (cisplatin, gemcitabine),[129] and hyperthermic perfusion with povidone-iodine.[130] Hyperthermia is believed to disrupt intercellular bridges to allow for greater direct reach of chemotherapy to distant microscopic foci of tumor cells, as well as possibly synergizing with cytotoxic agents to facilitate tumor cell death. Many trials combining EPD/RP pleurectomy with intrapleural hyperthermic cisplatin have been published with attainment of durable responses with mean overall survival >20 months, improvement in postoperative functional status versus EPP, and the ability to concentrate cisplatin in the pleural space while allowing much lower serum levels of cisplatin to reduce systemic adverse effects.[131–133] Intrapleural hyperthermic therapeutics have also been administered in association with IMRT in the presence of intact lung with demonstration of preserved/improved pulmonary function. In all cases, adjuvant chemotherapy was administered, unless patients had received preoperative (neoadjuvant) chemotherapy.

Management of Pleural Effusions

The most common and discomforting symptom in mesothelioma is debilitating dyspnea from large, unilateral pleural effusions. A reasonable palliative approach is complete drainage of the pleural effusion by tube thoracostomy or VATS and instillation or insufflation of a sclerosing agent into the pleural space to induce pleurodesis. At present, the most widely used compound for pleurodesis is sterile, asbestos-free talc, administered either as a powder or slurry.[134,135] Thoracoscopic application (poudrage) may be more successful than other methods of pleurodesis (e.g., by tube thoracostomy). The effect of talc may be enhanced by an ability to induce apoptosis in some mesothelioma cell lines in vitro.[136] Interestingly, there have been reports of prolonged survival in mesothelioma patients after talc pleurodesis with no other active therapy for the disease.[137] Rintoul et al. performed a randomized trial (Meso-VATS) comparing talc pleurodesis with partial pleurectomy via VATS for the management of pleural effusions in patients with mesothelioma. The results demonstrated no significant difference in survival between the groups, but the VATS group experienced significantly longer hospitalization and more postoperative complications.[138]

Entrapment of the lung by a thick visceral pleural peel of tumor compromises the efficacy of pleurodesis in patients with pleural mesothelioma. In the setting of trapped lung, the use of a semipermanent tunneled intrapleural catheter for intermittent drainage of recurrent effusions provides excellent palliation of dyspnea.[139,140] Pleuroperitoneal shunting, an alternative approach for dealing with lung entrapment in pleura mesothelioma, carries the overt risk of malignant seeding of the peritoneal cavity. The primary concerns regarding the use of tunneled pleural catheters in mesothelioma are the development of tumor implants at the insertion site or along the subcutaneous tunnel, as well as the risk of chest wall and/or intrapleural infections with long-term use of the catheter. Recent reports of tunneled catheters for mesothelioma show equivalent results for the control of effusions compared with talc slurry pleurodesis.[141,142] Therefore, these catheters should be considered for management of symptomatic effusions in patients with mesothelioma, even in those whose lungs are able to expand.

Treatment of Nonpleural Forms of Mesothelioma

Patients with peritoneal mesothelioma, the second most common form of mesothelioma after the pleural form, most often present with abdominal pain, distention, and ascites. In addition, peritoneal mesothelioma can be associated with hypoalbuminemia, night sweats, inguinal and umbilical hernias, and hypercoagulability. Laboratory investigation shows an increased platelet count in about 50% of patients, and many patients also have elevation of the tumor marker CA-125. As with pleural mesothelioma, single-agent chemotherapy for the peritoneal variant has a response rate of only 10% to 15%, whereas combination chemotherapies, such as cisplatin plus pemetrexed, improve the response rate to about 25%. Immunotherapeutic agents such as interferons (IFNs) and various cytokines may have a role in treating this disease, especially when the extent of disease is minimal.[143–145]

Patients diagnosed with peritoneal mesothelioma appear to have a better overall prognosis relative to the pleural form. This may reflect the technical ease of delivery of intraperitoneal chemotherapy as well as the capacity for multiple resections/debulking of peritoneal masses. One-third of patients with peritoneal mesothelioma in a Dana-Farber phase 2 series of 25 patients remained disease free at 2 to 3 years after treatment.[144] Multimodality treatment protocols include surgical debulking followed by intraperitoneal administration of cisplatin, doxorubicin, and IFN-γ, second laparotomy with attempted resection of any residual disease, and intraoperative hyperthermic perfusion with cisplatin and mitomycin followed subsequently by whole abdominal radiotherapy. In one study, the median overall survival of the 27 patients treated was 68 months.[146]

Pericardial mesothelioma is quite rare but characteristically presents with pericardial effusion and, often, tamponade physiology. Mesotheliomas of the tunica vaginalis are even less common than the pericardial variant but typically present with a bloody hydrocele. There is no effective therapy for mesothelioma of the pericardium or tunica vaginalis other than palliation; these neoplasms share the dismal prognosis of the pleural form of the disease.

Novel and Evolving Therapeutic Approaches

Despite the small but significant improvement in survival achieved with intensive multimodality therapy for mesothelioma, it is obvious that less morbid, more effective interventions are needed. Many investigators, focusing on the hemithorax as the primary site of disease, have attempted to treat this disease primarily by direct instillation of chemotherapeutic and other compounds into the pleural space, but with minimal success. Based on anecdotal reports that mesothelioma patients with greater amounts of intratumoral lymphocytic infiltration had improved median survival rates,[147] several groups have looked at immunotherapy as an alternative means of achieving better tumor response rates.

Immunotherapy

The use of compounds to stimulate an antitumor immune response against pleural malignancy stemmed from the observation that patients who developed empyemas post-thoracotomy for primary lung carcinoma had improved survival rates.[148,149] Subsequently, intrapleural bacille Calmette-Guérin (BCG) was studied as a surgical adjuvant, but no significant benefit was seen.[150] More recently, clinical trials for multiple primary solid tumors have studied the use of a *Listeria* vaccine that expresses mesothelin, otherwise known as CRS-207. A phase 1 trial of CRS-207 in patients with advanced cancers, including mesothelioma, demonstrated a dose-dependent inflammatory response, as well as mesothelin antigen–specific T-cell activation.[151] A subsequent study with CRS-207 in combination with chemotherapy in mesothelioma has since been halted due to a similar study in pancreatic cancer obtaining negative results.[152,153] However, given the significant and specific immune activation with CRS-207, there may be potential in combining this vaccine with systemic immunotherapy.

Several systemic immunotherapies have been administered to patients with mesothelioma, including IL-2 and IFN-γ, both of which demonstrated limited efficacy and significant side effects. The major disadvantage to using these cytokines is that they can also have anti-inflammatory end-results. For example, IL-2 can support the activity of T regulatory cells. Additionally, IFN-γ can lead to downregulation of MHC molecules and upregulation of checkpoint ligands on tumor cells. Subcutaneous IFN-α-2a was found to have some efficacy; in a study of 25 patients, 1 complete response and 3 partial responses were documented, and the therapy was well tolerated.[154] One European phase 1/2 study of intrapleural IL-2 administered by continuous infusion via an intrapleural catheter revealed a 19% partial response rate with marked dose-related toxicity, primarily the development of ipsilateral empyemas. Of note were the high ratios of intrapleural/systemic IL-2 levels approaching 1000:1, particularly in the highest doses.[155]

Boutin et al. in Marseilles, France, pioneered the intrapleural administration of immunostimulants to treat mesothelioma and demonstrated significant local tumor responses with both intrapleural IL-2 and intrapleural IFN-γ. Most impressive were the results of intrapleural IFN-γ in patients with early-stage mesothelioma (Butchart stages I and II). A total of 89 patients were treated over 46 months with an overall response rate of 20%. In all, 8 patients had histologically confirmed complete responses, and 9 had partial responses with greater than 50% reduction in tumor volume. Overall, patients with stage I disease had a response rate of 45%. The effectiveness of IFN-γ against mesothelioma was thought to be mediated in part by direct inhibitory effects on mesothelioma cell growth as well as by decreased intrapleural IL-6 production, with resultant activation of tumor-directed macrophages and cytotoxic T lymphocytes.[156,157] Other groups have demonstrated only limited activity with the combination of intrapleurally administered autologous-activated macrophages and IFN-γ. The overall response rate was 11% in a trial of 19 patients, with 1 patient having a partial response that lasted for 30 months.[158]

Immunotherapy trials in Australia demonstrated tumor regression with repeated intralesional injection of granulocyte-macrophage colony-stimulating factor (GM-CSF), but with substantial complications related to the catheters used for cytokine instillation.[159–161]

Over the past decade, implementation of immune checkpoint inhibitors (CPI) has changed the treatment paradigm of mesothelioma. The landmark phase 3 trial CheckMate 743 demonstrated significantly increased survival with first-line combination PD-L1/CTLA4 CPI versus standard-of-care chemotherapy in patients with untreated unresectable mesothelioma, particularly in those with sarcomatoid and biphasic histologic subtypes and >1% PD-L1 expression. This combination regimen was approved by the FDA in 2020—the first immunotherapy regimen approved for the treatment of mesothelioma of any stage. Interestingly, there was no statistical difference in severe adverse events between both experimental groups, despite high rates of immune-related adverse events in previous trials with combination immunotherapy in other tumor types.[162]

Prior investigation of single-agent regimens as second-line therapy with CTLA-4 inhibition, such as with the CPI tremelimumab, in pretreated patients did not demonstrate significant improvement in outcomes despite initial promise in phase 2 clinical trials.[163] However, PD-1/PD-L1 inhibition has shown stronger evidence for efficacy in mesothelioma. Single-agent treatment with nivolumab in previously treated patients demonstrated improved survival and resulted in FDA approval as second-line therapy.[164] Treatment with avelumab, a PD-L1 inhibitor, in previously treated patients and first-line treatment with durvalumab, a PD-1 inhibitor, in combination with standard-of-care chemotherapy demonstrated durable responses in early-stage trials, prompting ongoing study.[165,166]

Currently a large degree of research effort is being spent to answer two questions for CPI in mesothelioma: (1) Why do the majority of mesothelioma patients receiving CPI not respond? and (2) What biomarkers can accurately identify mesothelioma patients who will respond to CPI?

"Targeted" Therapy

The presence of platelet-derived growth factor (PDGF) and epidermal growth factor (EGF) pathways in some mesothelioma cell lines in vitro suggested that novel inhibitors of these pathways might prove useful clinically, either as monotherapy or in combination with chemotherapy. Unfortunately, early-phase clinical trials in mesothelioma of imatinib mesylate and gefitinib (and erlotinib), inhibitors of the tyrosine kinases essential to PDGF and EGF signaling, respectively, failed to demonstrate any significant clinical benefits.[167–169] Clinical trials have been conducted with other novel targeted agents, such as the antiangiogenic agents bevacizumab and thalidomide, and the copper-chelating agent tetrathiomolybdate, which depletes copper, a key cofactor in tumor angiogenesis. Only the latter compound has shown any demonstrable benefit to date in human trials.[170–172] Currently, there are several clinical trials of combinations of targeted agents to see if they may have synergistic effects upon growth of mesothelioma in patients with advanced disease.

Other pathways of cellular metabolism also have been targeted in mesothelioma, one of the most promising of which is intracellular utilization of arginine. Szlosarek et al. published the first trial examining arginine deprivation in cancer, specifically treating patients with arginosuccinate synthetase 1 (AS1)-deficient tumors with pegylated arginine deiminase (ADI-PEG20). In comparison with standard supportive care, they demonstrated an increased progression-free survival, and the subgroup with at least 75% reduction in AS1 had improvements in both progression-free survival and overall survival.[173] Beddowes et al. performed a dose escalation study with pegylated arginine deiminase in combination with standard-of-care chemotherapy in patients with mesothelioma or non–small-cell lung cancer, and no dose-limiting toxicity was noted, while achieving partial responses in 7 of 9 patients.[174] These studies have increased interest in targeting this pathway to treat mesothelioma, and there is an ongoing multicenter, randomized, controlled trial studying the combination of ADI-PEG20 with standard-of-care chemotherapy in mesothelioma.[175]

There have also been several trials evaluating tyrosine kinase inhibitors that are FDA-approved for other indications. A phase 2 trial of pemetrexed/platinum agent plus/minus nintedanib in patients with epithelioid and biphasic mesothelioma demonstrated significantly increased progression-free survival. However, a phase 3 trial with nintedanib did not demonstrate a significant improvement in outcomes.[176,177]

Gene Therapy

In the absence of other effective, nontoxic therapies for malignant mesothelioma, several groups of investigators have looked to the newly evolving technologies of gene therapy for new treatment modalities.[178] Gene therapy is attractive because mesothelioma remains localized initially and pleural access to the tumor is easy and safe. A large number of approaches have been used in cell culture and in animal models. Gene therapy vectors have included liposomal/DNA complexes and modified herpes, vaccinia, and adenoviruses. Transgenes have included suicide genes, cytokines, tumor suppressor genes (e.g., p53), and proapoptotic genes. Studies have also been done using replication-restricted, tumor-selective adenoviruses and herpes viruses as well as carrier cells, such as modified ovarian carcinoma cells.[178,179] Danson et al. conducted a phase 1/2A clinical trial with intrapleural administration of HSV1716, a replication-restricted strain of herpes simplex virus without expression of RL1, allowing it to only replicate in dividing cells, in 13 patients with mesothelioma. The patients subsequently demonstrated seropositivity to the virus, viral replication, development of antitumor antibodies, and short-term stabilization of disease in half the study participants without dose-limiting toxicities.[180] While there was not significant tumor response to this oncolytic virus alone, the significant immune activation may provide avenues of investigation to develop an adjunctive intrapleural/intratumoral therapy on top of systemic checkpoint inhibition.

Additional early phase 1 clinical trials of intrapleural gene delivery have been performed in patients with advanced mesothelioma. These include a "suicide" gene therapy strategy employing the instillation of recombinant adenovirus (rAd) genetically engineered to contain the herpes simplex virus thymidine kinase "suicide gene" (HSVtk).[181,182] The rationale for the suicide gene approach for mesothelioma was that administration of rAd.HSVtk into the pleural cavity would sensitize the cells to the normally nontoxic antiviral agent ganciclovir. The vector was well tolerated, gene transfer was seen at higher doses, and a number of patients had clinical responses, including patients with minimal radiographic evidence of disease 7 years after treatment, with no other intervening antineoplastic therapy. The HSVtk gene was also introduced into patients using an irradiated allogeneic ovarian cancer cell line. A phase 1 trial with intrapleural administration of an adenoviral vector expressing the HSVtk gene in combination with valacyclovir, celecoxib, and standard-of-care chemotherapy in patients with malignant pleural effusion caused by many different primary solid malignancies demonstrated durable responses in a subset of patients, and there are ongoing trials with gene-mediated cytotoxic immunotherapy in a variety of solid malignancies.[183]

A few early-phase trials have recently completed using adenoviral-mediated immunogene therapy delivering the cytokines IFN-α and IFN-β, which have a number of antitumor immune effects. The vector was well tolerated (most common adverse events were lymphopenia, hypoalbuminemia, hypotension, anemia, hypocalcemia, and mild cytokine release syndrome), resulted in detectable intrapleural levels of the interferon proteins in most patients, and was accompanied by antitumor immune responses in multiple patients. A number of patients with low tumor burdens had disease stability or clinical responses.[184–186]

A pilot study evaluating intrapleural Ad-IFN-α in combination with celecoxib and either first-line chemotherapy or second-line chemotherapy in previously treated patients demonstrated durable responses, with the first-line chemotherapy group attaining mean overall survival of 12.5 months, and the second-line chemotherapy group achieving mean overall survival of 21.5 months.[187] These results prompted further study in the INFINITE trial, a multicenter, randomized, controlled trial that recently halted accrual due to competing enrollment with other studies (NCT03710876).

Other gene therapy approaches have been studied by various groups attempting to achieve high-level expression of other immunostimulatory cytokines such as IL-2, IL-12, TNF, and GM-CSF. In addition, there are ongoing phase 1 trials of intrapleural delivery of oncolytic viruses, including measles, herpes simplex, and vaccinia viruses, all of which have shown significant antitumor activity against mesothelioma in vitro and in preclinical models.[178]

Adoptive Cellular Therapy

Adoptive transfer of T cells and other immune cells into patients after ex vivo expansion has demonstrated very promising results in diseases like malignant melanoma and leukemias. Groups have attempted to acquire tumor-reactive tumor-infiltrating lymphocytes (TILs) from mesothelioma samples, expanding them ex vivo, then reinfusing them back into the host with minimal success. Since this method utilizes polyclonal T cells, all of which may not be reactive to a patient's mesothelioma tumor, research efforts have been made to genetically tailor otherwise nonreactive T cells to target a specific mesothelioma's tumor-associated antigen. Researchers at the University of Pennsylvania and Memorial Sloan Kettering have successfully genetically modified T cells to express a chimeric antigen receptor (CAR) that recognizes the tumor antigen mesothelin through a single-chain formulation of the variable chain (scFv) of an antimesothelin antibody that activates the T-cell through a combination of internal signaling domains from the T cell receptor.[188,189] The mesothelin CAR T cells were able to eradicate large mesothelioma tumors in mice, and this has led to subsequent early-phase clinical trials assessing the feasibility and safety of multiple doses of CAR T cells reactive to mesothelin.

There have been two mesothelin-targeted CAR T cell trials recently published demonstrating the potential of this technology in mesothelioma. Haas et al. at the Abramson Cancer Center of the University of Pennsylvania reported the results of a phase 1 study of lentiviral-transduced mesothelin-directed CAR T cells in 15 patients with advanced solid cancers including mesothelioma.[190] This came after an initial test using multiple doses of mRNA-electroporated T cells with only transient CAR expression demonstrated safety in patients.[191] Of 15 patients, 11 demonstrated stable disease by Response Evaluation Criteria In Solid Tumors (RECIST) methodology after IV infusion of CART-meso cells, and only 1 patient experienced dose-limiting toxicity. CAR T-cells expanded in the periphery and reached peak levels by ~1 to 2 weeks post-transfer but were transient in persistence. Cyclophosphamide pretreatment improved persistence but not beyond 28 days. In 7 of 10 cases where posttreatment biopsies were obtainable, CAR DNA was detectable. These initial efforts were based on a monoclonal mouse–antihuman antibody (SS1) identified by Dr. Ira Pastan. Researchers have switched to a fully humanized construct in light of the demonstration of human–antimouse antibody responses with anaphylaxis in one patient.[192]

More recently, Adusumilli et al. at Memorial Sloan-Kettering Cancer Center published the results of a phase 1 trial of regional mesothelin-targeted CAR T-cell therapy in patients with malignant pleural disease, including mesothelioma (tumor cell mesothelin expression >10%), in combination with the anti–PD-1 agent pembrolizumab. The design for this trial was based upon preclinical murine studies that demonstrated limited antitumor activity of intrapleural CAR T-cell administration in mice with large tumor burdens mediated by mitigation of T-cell exhaustion with coadministration of systemic anti–PD-1 monoclonal antibody. This study has the distinction of being the first published trial of intrapleural CAR T-cell therapy in humans. Importantly, there were no dose-limiting toxicities, although several patients experienced cytokine release syndrome requiring hospitalization and IL-6 inhibition with tocilizumab. In this single-arm noncontrolled study, median overall survival after CAR T-cell treatment in patients with malignant pleural disease who received pembrolizumab was 23.9 months, with some associated dramatic responses on imaging.[193]

Other cellular therapies that are being investigated are injection of mesothelioma tumor lysate-pulsed dendritic cells and lymphokine-activated killer cells.[194,195] A single cohort of 10 patients with previously treated mesothelioma were treated with dendritic cell vaccination and cyclophosphamide, and 8 of 10 patients achieved disease control, 2 of whom had durable responses and were still living at 55 months. These results prompted an ongoing phase 3 trial evaluating standard-of-care chemotherapy plus/minus dendritic cell vaccination (NCT02649829).

SOLITARY FIBROUS TUMOR OF THE PLEURA

Solitary fibrous tumors of the pleura had been previously referred to in the literature as "benign mesothelioma." This is an inappropriate expression, both in terms of histogenesis and because of the potential for confusion with malignant mesothelioma. Solitary fibrous tumors have also been called localized fibrous tumor because of the occasional incidence of multiple masses. Solitary fibrous tumor is a mesenchymal tumor of fibroblastic origin, and similar tumors have been described in other extrathoracic sites.[34] It is important to note that there is no significant association of solitary fibrous tumors with asbestos exposure or other environmental agents. Although the peak age range of affected patients is similar to that of mesothelioma (40–70 years), solitary fibrous tumors can affect patients of all ages, including children as young as 5 years old.

Clinical Presentation

Patients with solitary fibrous tumors of the pleura are usually asymptomatic and are diagnosed incidentally by routine chest radiography, but they can present with nonpleuritic chest pain, dyspnea, cough, or pleural effusion. A significant proportion (up to 40%) of patients present with symptomatic hypoglycemia, thought to be secondary to elaboration of insulin-like growth factors. Clubbing of fingers and toes is common, as are diffuse arthralgias, but the incidence of pulmonary hypertrophic osteoarthropathy is controversial.[196–199]

Radiography

Solitary fibrous tumors typically present radiographically as large, rounded, well-circumscribed, pleura-based masses, but occasionally they can appear to be intraparenchymal. Some of these masses can be very large (>30 cm in diameter) and can cause clinically significant compression of the lung. About 17% present with an ipsilateral pleural effusion.[197,200]

Gross Pathology

The typical solitary fibrous tumor of the pleura arises from a pedicle off the visceral pleura surface and rarely invades beyond the visceral pleura itself (Fig. 78-9A). The tumors are usually well-circumscribed, firm, often pedunculated masses that vary in size from 1 cm to more than 30 cm in diameter. When sectioned, the cut surface has a whorled appearance. Attention should be paid to areas of hemorrhage or necrosis. Malignant solitary fibrous tumors have been described, although they are less frequent.[34,201–203]

Microscopic Pathology

Histologically, solitary fibrous tumors have what has been described as a "patternless pattern" (Fig. 78-9B). Sections typically show alternating areas of hypocellularity and hypercellularity with short fascicles of interlacing spindle cells, creating a storiform pattern. These fascicles are interspersed between areas of variably collagenized tissue. A hemangiopericytoma-like branching vascular pattern is also quite typical. Histologic criteria that may predict a malignant course include increased cellularity, infiltrative growth, cytologic atypia, necrosis, and a mitotic rate with greater than 2 mitoses/mm^2.[34] Immunohistochemical stains confirm the diagnosis. These tumors are CD34 (Fig. 78-9C) and STAT6 positive but CK negative. Expression of CD34 and STAT6 may be lost in dedifferentiated solitary fibrous tumors, and therefore the diagnosis might require the exclusion of other malignant tumors such as malignant mesothelioma, monophasic synovial sarcoma, and peripheral nerve sheath tumors.

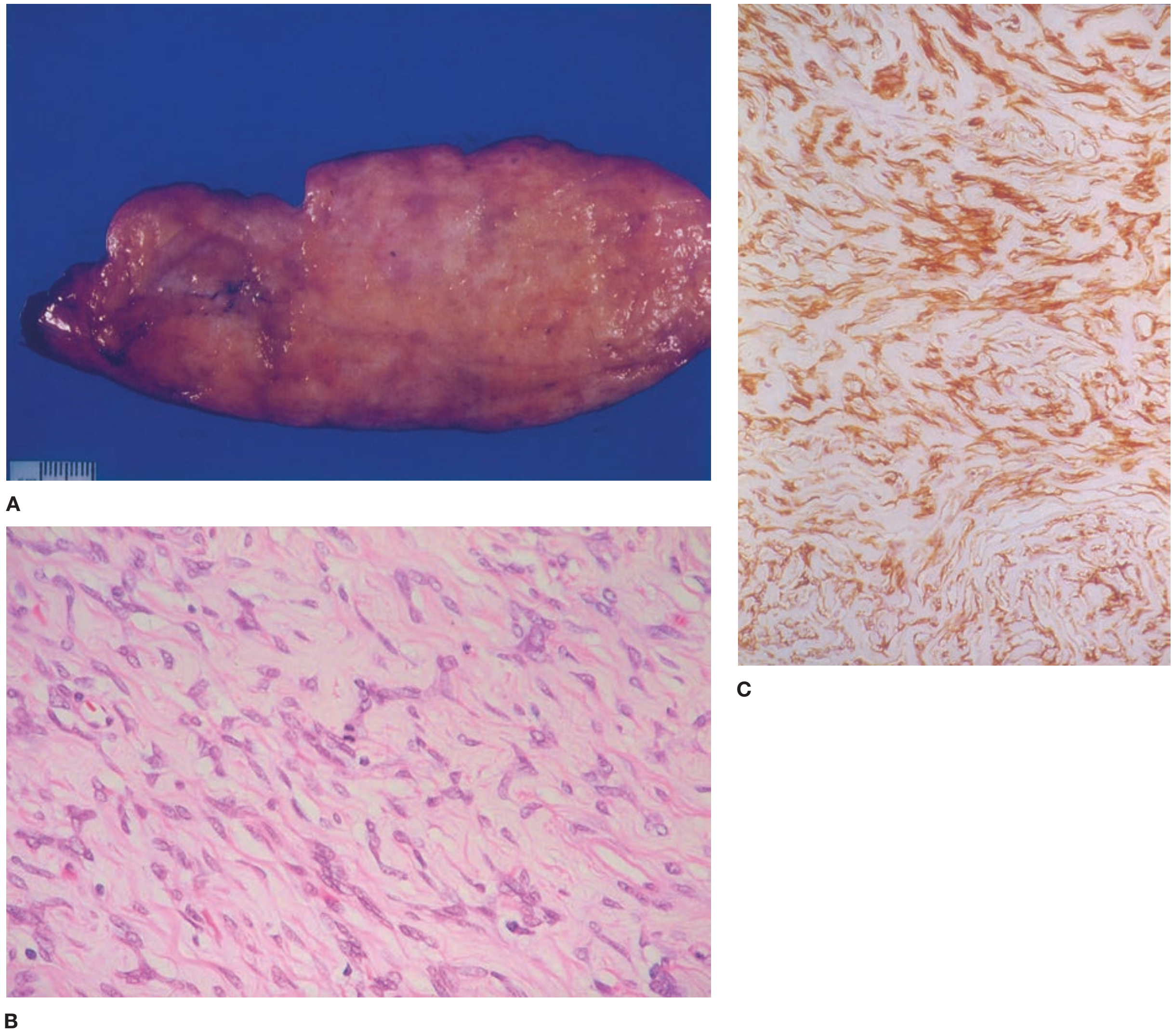

Figure 78-9 **A.** Gross photograph of a surgically resected, solitary, benign pleural fibrous tumor. Note the well-circumscribed nature of this firm, slightly lobulated mass with its smooth-cut surface and punctate areas of hemorrhage and necrosis. **B.** Photomicrograph of a typical solitary fibrous tumor demonstrating the "patternless pattern" (H&E, ×400). **C.** Photomicrograph of a section of solitary fibrous tumor stained with an antibody directed against CD34, a cell surface marker found commonly on endothelial cells and some smooth muscle and vascular tumors (×400). Positive staining for CD34 helps distinguish these lesions from mesotheliomas and other pleural neoplasms. *(Reproduced with permission from Dr. Matt van de Rijn, Department of Pathology and Laboratory Medicine, University of Pennsylvania Medical Center, Philadelphia.)*

Treatment

Surgical resection of solitary fibrous tumors of the pleura is curative with little risk of recurrence. There is typically a discrete separation between the tumor and underlying compressed lung, so extensive pulmonary resection is usually unnecessary. Some tumors may require a limited chest wall resection. A small percentage of patients develop recurrences several decades after surgical resection and may die from extensive local disease. Some of these recurrent fibrous tumors of the pleura demonstrate more aggressive histologic features but are often successfully cured by surgical excision, in particular the pedunculated lesions.[197–199]

Even with malignant solitary fibrous tumors of the pleura, complete resection portends a favorable prognosis in most patients. In one series, complete resection was achieved in more than 90% of patients, with disease-free survival rates of 72% and 61% at 5 and 10 years, respectively.[199]

OTHER PRIMARY PLEURAL TUMORS

As discussed in the differential diagnosis of sarcomatoid mesotheliomas, there are other relatively rare malignant mesenchymal tumors that can be primary within the pleura. These tumors include vascular tumors (pleural epithelioid hemangioendothelioma/angiosarcoma) and synovial sarcoma.

Pleural epithelioid hemangioendothelioma is a malignant vascular tumor composed of epithelioid endothelial cells within a distinctive myxohyaline stroma.[34] The clinical presentation of patients with these tumors, as well as the radiographic features and gross appearance, are essentially identical to malignant mesothelioma. Patients present with diffuse pleural thickening, pleural effusion, and/or chest pain. Microscopic examination with the ancillary use of IHC is required for diagnosis. These tumors usually have a biphasic pattern with nests of epithelioid cells embedded within a spindle cell stroma. The epithelioid cells characteristically have intracytoplasmic vacuoles, and the associated stroma typically has a distinctive myxohyaline or chondroid appearance. As with malignant mesotheliomas, a tubopapillary pattern may also be present.

Vascular differentiation is demonstrated by strong positive staining with one or more endothelial markers (CD31, CD34, and ERG), although there is significant variability in expression. CK positivity may also be present and can be misleading if the diagnosis of a vascular tumor is not considered. The diagnosis can be confirmed by identification of the *WWTR1-CAMTA1* or *YAP1-TFE3* fusion transcripts. These tumors behave aggressively, with most patients dying of disease within 1 year.[34] Angiosarcoma of the pleura has a similarly aggressive clinical course.

The diagnosis of pleural synovial sarcoma has improved with increased awareness and the greater availability of molecular testing for its distinctive X:18 translocation that now can be demonstrated in formalin-fixed paraffin-embedded tissue. Synovial sarcomas present as either a biphasic epithelioid and spindle-cell tumor or as a monophasic spindle-cell tumor. In either instance, synovial sarcoma can be mistaken for malignant mesothelioma or a pulmonary sarcomatoid carcinoma. On average, patients tend to be younger than those with malignant mesothelioma, but there is a wide reported age range that encompasses older patients into their eighth decade. There is a similar overlap in clinical presentation with malignant mesothelioma that includes chest pain, pleural effusions, dyspnea, and pneumothorax. Although pleural synovial sarcoma is more commonly a localized, solid tumor, diffuse pleural thickening does occur. The tumors can be quite large (mean size of 13 cm) and can have areas of necrosis and cystic degeneration. There are some histologic features that are suggestive of synovial sarcoma, in particular its long interweaving fascicles, but the immunohistochemical profile of these tumors is not distinctive. The epithelioid component may show focal positive staining for CK, EMA, CEA, or BER-EP4. The spindle-cell component may express calretinin. Confirmation of the diagnosis requires molecular testing for the X:18 translocation. Pleural synovial sarcoma is an aggressive disease with a generally poor prognosis.[204–209]

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CHAPTER 79

Pneumothorax

Rodolfo A. Estrada
Jay I. Peters
Nilam J. Soni
Philip G. Ong

DEFINITION

The abnormal presence of air in the pleural cavity, separating the visceral from the parietal pleura, is known as *pneumothorax*. Traditionally, pneumothorax has been classified as having occurred spontaneously or as a result of trauma. Spontaneous pneumothorax can occur in a background of clinically normal lungs (primary spontaneous pneumothorax [PSP]) or in the setting of underlying lung disease (secondary spontaneous pneumothorax [SSP]). Since underlying anatomic lung abnormalities (subpleural blebs) are often identified in PSP,[1–3] it is now believed that the majority of PSPs occur in the setting of occult lung disease. Nevertheless, this method of classification is still common in practice.

Traumatic pneumothorax results from a disruption of the structural integrity of the lung, chest wall, esophagus, trachea, or bronchi secondary to either blunt or penetrating trauma to the chest. It can also occur as a consequence of diagnostic or therapeutic procedures such as central-line insertions, thoracentesis, or mechanical ventilation, in which case it is referred to as *iatrogenic pneumothorax*.

PATHOPHYSIOLOGY

As noted above, air does not normally exist within the pleural space. During both inspiration and expiration, the pressure within the pleural space is negative with respect to the alveolar pressure. This pressure gradient is called *transpulmonary pressure*, which results from the tendency of the lung to collapse (elastic recoil) and of the chest wall to expand. This negative pressure is not uniform throughout the pleural space, causing a greater distention of the alveoli at the apex of the lung secondary to higher negative pressure (Fig. 79-1). A gradient of 0.25 cm of water per centimeter of vertical distance can be measured between the apex and the base of the lung. The pleural pressure is also negative compared with the atmospheric pressure (760 mm Hg at sea level during end inspiration); nevertheless, the pressure gradient still favors net movement of alveolar air into the capillaries (average pressure of all gases in capillaries is 706 mm Hg) and not into the pleural space. Under normal circumstances, most individuals do not generate a net negative inspiratory force of −54 mm Hg.[4]

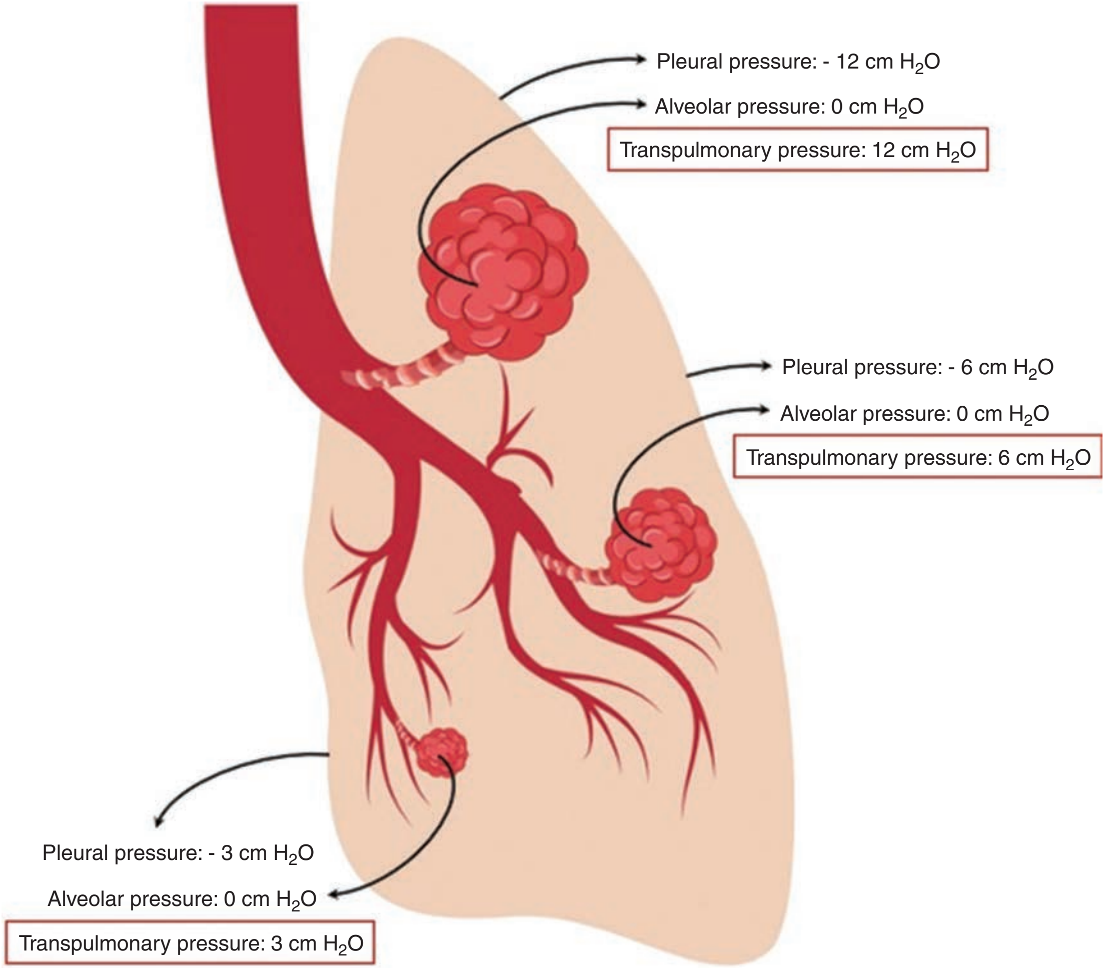
Pleural pressure: - 12 cm H_2O
Alveolar pressure: 0 cm H_2O
Transpulmonary pressure: 12 cm H_2O
Pleural pressure: - 6 cm H_2O
Alveolar pressure: 0 cm H_2O
Transpulmonary pressure: 6 cm H_2O
Pleural pressure: - 3 cm H_2O
Alveolar pressure: 0 cm H_2O
Transpulmonary pressure: 3 cm H_2O

Figure 79-1 Transpulmonary pressure changes related to lung zone.

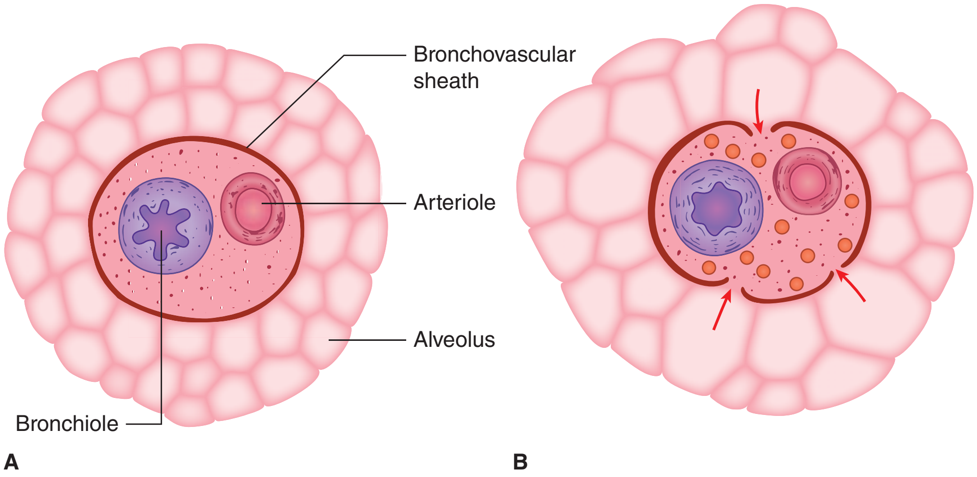

Figure 79-2 Proposed mechanism of alveolar rupture in spontaneous pneumothorax. **A.** Normal structures. **B.** Overdistention of marginal alveoli. Pressure in the adjacent bronchovascular sheath remains lower than in the overdistended alveoli. This pressure gradient may lead to rupture of the alveoli with dissection of air toward the pleura or mediastinum.

The presence of air in the pleural cavity is thought to occur by one of three events: a communication between the pleura and the alveolus, a communication between the atmosphere and the pleural space, or the presence of a gas-producing organism within the pleura.[4] When a communication develops between an alveolus and the pleural space, air will move from the alveolus into the pleural space until there is equalization of pressure or until the communication is sealed. The same happens with a communication between the chest wall and the pleural cavity. The greater the amount of air that enters the pleural cavity, the more the lung collapses. If unabated, enough air may enter the pleural space to cause a shift of the mediastinum and eventually lead to hemodynamic compromise, a condition referred to as *tension pneumothorax*.

Although the mechanism responsible for PSP is not completely understood, experimental overdistention of normal lungs results in rupture of subpleural alveoli.[5] Air can dissect along the bronchovascular sheath medially to produce pneumomediastinum, which may be accompanied by subcutaneous emphysema or pneumothorax (Fig. 79-2), or it can dissect to the peripheral portion of the lung.[6] Peripheral dissection of air may result in an air-containing space within or immediately beneath the visceral pleura. Pathologic studies of resected lungs from patients with PSP usually show one or both of these types of airspaces, a bleb or a bulla. A pneumothorax may occur when these peripheral bullae or blebs become distended and rupture into the pleural space.

The clinical impact of a pneumothorax depends on the degree of lung collapse, and the main physiologic consequences are a decrease in the vital capacity of the lung and a decrease in the Pa_{O_2}. The reduction in arterial Pa_{O_2} appears to be caused by low ventilation–perfusion ($\dot{V}/\dot{Q}$) ratios, absent ventilation (or anatomic shunts) and alveolar hypoventilation. Total lung capacity, functional residual capacity, and diffusing capacity are all also reduced, although less than vital capacity. Air in the pleural space causes a more uniform and therefore reduced regional lung ventilation by means of eliminating the gravitational gradients of pleural pressure. Lungs demonstrate airway closure at low lung volumes, which is the main cause of $\dot{V}/\dot{Q}$ imbalance in patients with pneumothorax.[7] If perfusion to the collapsed lung is preserved, there is an increase in pulmonary shunt and substantial hypoxemia. However, if perfusion to the collapsed lung is reduced by hypoxic vasoconstriction, hypoxemia may be minimal. In general, a pneumothorax occupying less than 25% of the hemithorax is not usually associated with significant shunt.[8] Hypoxemia tends to abate within 24 h under normal circumstances despite the degree of pneumothorax, presumably from redistribution of pulmonary blood flow.

In the healthy person, the decrease in vital capacity and Pa_{O_2} is typically well tolerated. In patients with compromised pulmonary function prior to pneumothorax, the decrease in vital capacity may result in respiratory failure with resultant hypoxemia and respiratory acidosis from alveolar hypoventilation. Upon evacuation of air from the pleural space, the Pa_{O_2} usually improves. In animal studies, the Pa_{O_2} returns to baseline immediately after re-expansion of the lung but in humans, normalization of the Pa_{O_2} takes longer and may occur over hours to several days; the delay in improvement may be related to the duration of the pneumothorax.[9]

REABSORPTION OF PLEURAL GASES

Between 1% and 6% of a pneumothorax is absorbed in 24 h with observation alone.[10] Gas reabsorption from the pleural space is achieved by simple diffusion from the pleural space into the venous blood and depends on four variables: (1) the pressure gradient for the gases between the pleural space in relation to the venous blood, (2) the diffusion properties for the gases present in the pleural space, (3) the area of contact between the pleural gas and the pleura, and (4) the permeability of the pleural surface (i.e., a thickened, fibrotic pleura will absorb less than normal pleura).

The solubility and diffusion properties of different gases vary considerably, and the speed of reabsorption will depend on the type of gas; nitrogen is the slowest gas to be reabsorbed, and carbon dioxide is the quickest along with water vapor. Tissue gas tensions are close to those of systemic venous blood: typically, $\text{pCO}_2 = 46$ mm Hg, $\text{pO}_2 = 40$ mm Hg, $\text{pH}_2\text{O} = 47$ mm Hg, and $\text{pN}_2 = 573$ mm Hg. Under normal circumstances, the gas pressure in the pneumothorax approximates that of the atmosphere, or 760 mm Hg, resulting in reabsorption via a positive pressure gradient toward the lung tissue with a capillary gas tension of 706 mm Hg. However, when breathing room air, this driving force is only 54 mm Hg (760–706 mm Hg) and this limits the rate of resorption. During inhalation of 100% oxygen, the partial pressure of nitrogen reduces from 573 to 0 mm Hg rendering a total gas pressure of 146 mm Hg. Although this is associated with an increase in oxygen in arterial blood, oxygen consumption in the tissues ensures that the partial pressure in the end-capillary blood rises only slightly (from 40 mm Hg to ~54 mm Hg). The results of small trials demonstrate that administration of high-flow oxygen expedites resolution of a pneumothorax.[11,12]

PRIMARY SPONTANEOUS PNEUMOTHORAX

PSP refers to development of a pneumothorax in the absence of underlying lung disease.

Epidemiology

The age-adjusted annual incidence of PSP ranges from 7.4 to 18 cases per 100,000 population in males and 1.2 to 6 cases per 100,000 in females. The male-to-female ratio ranges from 3:1 to as high as 6:1, and the peak incidence is in the third to fifth decade of life.[4,13]

Patients with PSP tend to be taller and thinner than control populations. A study of military recruits who developed spontaneous pneumothorax found subjects to be, on average, 2 inches taller and 25 lb lighter than the typical military recruit.[14] In another study, the frequency of PSP rose with increasing stature and reached an incidence of 200 per 100,000 person-years for subjects at least 76 inches tall.[13]

In addition to stature and male sex, tobacco smoking significantly increases the risk of spontaneous pneumothorax and has been associated with a ninefold or greater risk of developing a first PSP.[15] The relative risk of PSP has been shown to exhibit a dose–response relationship with the quantity of cigarettes per day and the length of exposure, increasing more than 20 times in men who smoke one-half pack per day and 100 times in men who smoke one pack per day compared to nonsmokers. The lifetime risk in healthy smoking men may be as high as 12%, as opposed to 0.1% in nonsmokers.[15] One review of 402 patients with PSP reported that 92% of the patients were smokers or ex-smokers.[8] Another study showed that patients who had stopped smoking more than 1 year before their first spontaneous pneumothorax had no recurrence during a follow-up of 5.2 years.[16]

Etiology

Although the diagnosis of PSP is restricted to patients without primary lung disease, it is likely that many of these patients do in fact have underlying lung pathology. Thus, a more accurate description of PSP is pneumothorax occurring in patients with no *obvious* lung disease.[17] While the exact mechanism by which a spontaneous communication between the alveolar space and the pleura has not been elucidated, most authors believe that rupture of a previously unidentified bleb or bulla adjacent to the pleura is to blame for the development of PSP.[18] These subpleural blebs and bullae are typically referred to as *emphysema-like changes (ELCs)* when seen on CT scan, and although it has been shown that the majority of patients with PSP have ELC, no causal relationship has clearly been established. These blebs are demonstrated by chest radiograph in only 20% of cases of PSP but can be seen in approximately 80% of affected patients by both CT imaging and by surgical evaluation.[19,20] In two studies, ELCs were found in 89% on the ipsilateral side and up to 80% bilaterally, while only 20% of those without PSP had these changes.[2,21] Another study showed that 81% of nonsmokers with healed PSP had ELCs, while those nonsmokers without PSP had none.[22] Despite this clear association, a causative relationship is still debated. In part, this is due to the observation that only a minority of blebs are observed to be ruptured at the time of surgery, and other lesions, termed *pleural porosity*, are observed.[4] Pleural porosity is believed to predispose the pleura to air leakage by disruption or replacement of the mesothelial cells of the visceral pleura with inflammatory cells that increase pleural permeability.[20]

The pathogenesis of these bullae, blebs, and pleural porosity is not definitively known but has been associated with a variety of elements, most commonly with airway inflammation.[23,24] Airway inflammation secondary to cigarette smoking may be associated with or contribute to the development of these blebs. Respiratory bronchiolitis in smokers may be an important element in the development of PSP.[25] Pathologic evidence of respiratory bronchiolitis was found in more than 88% of smokers undergoing surgery for PSP.[26]

In addition to airway inflammation, other factors have been linked to ELC and pleural porosity, including connective tissue abnormalities, hereditary influences, increased negative pressure at the apices associated with ectomorphic body habitus, anatomic bronchial abnormalities, and overdistention of alveoli with poor collateral ventilation. Pleural pressure is most negative at the apices, and the degree of negativity relates to the height of the lungs. The alveoli of taller persons are subjected to greater mean distending pressures. Over a long period, this phenomenon could lead to the formation of subpleural blebs in a taller population genetically predisposed to bleb formation.

There are multiple reports of genetic associations or patterns of PSP. Some reports suggest that PSP is inherited through an autosomal dominant gene with variable penetrance,[27] while others report an associated autosomal recessive[28] or X-linked recessive inheritance pattern.[27] Genetic risk factors that have been associated with PSP include the HLA haplotype A_2B_{40},[29] the α_1-antitrypsin phenotypes M_1M_2, and the FBN1 gene mutations.[30] Gene mutations have been found in both sporadic and familial cases of PSP. Familial spontaneous pneumothorax (FSP) occurs in family clusters and accounts for 12% of PSP cases; a significant subset of these patients have mutations in the *FLCN* gene.[27,31] Recurrence rates of FSP are difficult to compare with sporadic pneumothorax given the different study methodologies, but they are thought to be higher regardless (~70% in FSP vs. 33% in sporadic).[32] This supports a lower threshold for surgical intervention after the first pneumothorax if known family history is present.[33–38] A genetic approach to management is not addressed by current guidelines but should be routinely implemented in suspected FSP cases.[32] Further workup (i.e., detailed history/physical exam, CT chest, genetic testing, and referral to a genetic specialist) should be pursued when key features of FSP are noted, such as isolated family history of PSP, family history of bleb/cyst/bullae, and personal history of non-apical bleb/cyst/bullae. The importance of diagnosing FSP goes beyond PSP to include patient surveillance of other syndromic pathologies and family screening protocols.

The rate of recurrence after a PSP is approximately 33% (range, 23%–52%), and recurrence usually occurs within 1 to 2 years after the first episode.[39] The rate of recurrence may increase with each successive pneumothorax. In one study, the risk of recurrence increased to more than 60% after the second pneumothorax and to 83% after the third.[40] Although there is no predilection for the right or left hemithorax with the initial episode, more than 75% of recurrences occur on the same side as the first pneumothorax. Despite the documentation that pleural blebs occur bilaterally in many patients with PSP, the risk of contralateral pneumothorax is only 5% to 10%. Risk factors for recurrence that have been identified include greater height, lower weight, and smoking status.[41] Death rarely occurs after PSP.[42] In a study of spontaneous pneumothorax in which patient ages ranged from 15 to 34 years (most likely representing patients with PSP), the mortality rate was reported to be 0.09% for men and 0.06% for women.[43]

SECONDARY SPONTANEOUS PNEUMOTHORAX

SSP is a more serious event than PSP because, by definition, the patient has underlying lung disease. A pneumothorax in a patient with already diminished pulmonary reserve can be life-threatening and requires more immediate medical attention and intervention.

Epidemiology

The incidence of SSP is similar to that of PSP. An epidemiologic study in Olmsted County, Minnesota documented an incidence of

TABLE 79-1 Etiology of Secondary Spontaneous Pneumothorax

Obstructive Lung Disease
Chronic obstructive pulmonary disease (COPD)
Asthma
Interstitial Lung Disease
Idiopathic pulmonary fibrosis (usual interstitial pneumonitis [UIP])
Nonspecific interstitial pneumonitis
Langerhans cell histiocytosis
Lymphangioleiomyomatosis
Sarcoidosis
Radiation pneumonitis or fibrosis
Infection
P. jiroveci pneumonia
Tuberculosis
Coccidioidomycosis
Acute bacterial pneumonia (i.e., *Staphylococcus*)
Malignancy
Primary lung carcinoma
Pulmonary metastasis (especially sarcomas)
Complications of chemotherapy
Connective Tissue Disease
Rheumatoid arthritis
Ankylosing spondylitis
Marfan syndrome
Ehlers–Danlos syndrome
Polymyositis/dermatomyositis
Scleroderma
Other
Catamenial pneumothorax
Pulmonary infarction
Pulmonary alveolar proteinosis
von Recklinghausen disease
Granulomatosis with polyangiitis (Wegener)

SSP of 6.3/100,000 year for males and 2/100,000 year for females.[13] On average, patients with SSP are 15 to 20 years older than patients with PSP due largely to the older age of patients with emphysematous lung disease. The risk of recurrence for SSP is somewhat higher than for PSP and ranges from 40% to 80%, again likely due to the underlying lung pathology. Although airway diseases (chronic obstructive pulmonary disease [COPD], cystic fibrosis [CF], and severe asthma) are the most common underlying lung disorders, a wide spectrum of pulmonary diseases has been associated with SSP (Table 79-1).[44]

COPD

COPD is the most common cause of SSP. The Veterans Administration Cooperative Study on Pneumothorax noted that pneumothorax tended to occur in patients with moderately severe COPD, with one-quarter of the participants having an FEV_1 below 1 L and a mean FEV_1/FVC ratio of 57%.[45] Persistent bronchopleural fistula was also noted to be common in patients with obstructive lung disease, and 35% of patients had an air leak for more than 5 days. In another series of more than 500 patients with SSP, COPD was the etiology in 69%, primary or metastatic tumor in 18%, granulomatous disease (sarcoid and tuberculosis) in 7%, and other pulmonary infections in 3%.[46] In contrast to the low mortality rate associated with PSP, patients with SSP have a much higher risk of death. The VA Cooperative study reported an analysis of three papers that, combined, revealed a mortality of 16% for SSP.[45] Another study[47] showed that SSP increased the mortality of age-matched COPD patients 3.5-fold.

Cystic Fibrosis

Pneumothorax is a common and potentially serious complication of CF lung disease. It occurs more frequently in CF than in the general population and results in significant morbidity and mortality, typically occurring with more advanced disease.[48–50] Approximately 3.5% of patients with CF will suffer this complication at some point in their lives. The majority occur in adulthood, with a median age of 21 years.[51] Pneumothorax may also be a marker of poor prognosis, with one study showing the median survival after the first spontaneous pneumothorax to be only 29.9 months.[52]

The pathophysiology of spontaneous pneumothorax in CF is likely related to chronic airway inflammation that eventually leads to structural changes with severe airflow obstruction, inflammation with poor clearance of thick and inspissated secretions, air trapping in the distal airways, and eventual rupture of the pleural surface with rising alveolar pressures.[51]

The risk of developing pneumothorax increases with age and with declining pulmonary function (FEV_1). One study of pneumothorax in CF demonstrated that the risk of pneumothorax increased by 50% when FEV_1 was <30% predicted.[50] Other important risk factors for the development of pneumothorax include the presence of *Pseudomonas aeruginosa*, *Burkholderia cepacia*, or *Aspergillus* in the airways, the use of dornase alfa, and the use of noninvasive mechanical ventilation. The presence of these airway pathogens may increase inflammation and secretions leading to obstruction, and the use of inhaled dornase alfa may cause bronchospasm leading to acute decline in FEV_1 with inhalation.[53]

CF-specific recommendations exist regarding the management of pneumothorax.[49] A full discussion of these is beyond the scope of this chapter, but several points regarding airway clearance in the setting of pneumothorax are of particular importance. With small pneumothoraces it is recommended that most airway clearance modalities be continued, with the exception of those providing positive-pressure or percussive ventilation, which could further increase the size of pneumothorax. With large pneumothorax, it is recommended that airway clearance modalities be held.[49,54] Although the use of inhaled medications could provoke coughing, it is not recommended that these be held.

Recurrence of pneumothorax is more frequent in this population. An estimated failure rate of 37% with initial tube thoracostomy alone has been reported, but up to 70% of all patients have an overall failure rate with tube thoracostomy (i.e., initial failure plus ipsilateral recurrence) ultimately needing more definitive treatment.[55] Despite the recurrence rate being so high, the guidelines recommend reserving pleurodesis for large recurrent pneumothoraces.[49] However, because the recurrence rate in CF is high, many CF centers still consider pleurodesis after the first episode. In the past, there was concern that pleurodesis would preclude patients from lung transplantation. However, recent studies have shown that pleurodesis does not add appreciably to complications during lung transplantation.[56,57] Although center-dependent, pleurodesis is no longer considered a contraindication to transplantation.[56]

Catamenial Pneumothorax

Catamenial pneumothorax is an uncommon condition that occurs in women and is defined as recurrent pneumothoraces occurring

72 hours before or after the onset of menses. One study reported a mean of 3.17 episodes (range, 2–10) in a population of women prior to surgical treatment.[58] This syndrome, by definition, occurs during the reproductive years, usually in the third or fourth decade of life; however, cases associated with hormone replacement have been reported.[59] Although initially felt to be extremely rare, the condition is becoming increasingly recognized. A series from the Mayo Clinic found the condition in 5.6% of women with spontaneous pneumothorax over a 21-year period; however, more recent studies suggest the incidence of this disorder may fluctuate between 18% and 33% in women of reproductive age with recurrent spontaneous pneumothorax.[60,61]

There is no single, definitive etiology for the development of catamenial pneumothorax. One hypothesis suggests pleural and/or diaphragmatic endometriosis as the basis for this disorder, but less than one-third of women are found to have endometrial deposits at the time of surgical exploration.[61] Alternative mechanisms that have been proposed include peritoneal air entering the thoracic cavity through diaphragmatic defects during menstruation, endometrial implants in the terminal bronchioles causing obstruction, and increased circulating levels of prostaglandin $F_2\alpha$ during menstruation causing bronchospasm and vasospasm that leads to alveolar rupture.[59] It is possible that various pathogenic mechanisms are involved.

The diagnosis, as mentioned above, is based on *recurrent* pneumothorax occurring at or around the time of menstrual flow. Onset is typically heralded by chest pain and dyspnea. Over 90% of catamenial pneumothoraces affect the right hemithorax, but isolated left-side or bilateral pneumothoraces have been reported. Catamenial pneumothoraces are usually mild or moderate but can rarely be life-threatening.

Given the unacceptably high recurrence rate of 50% to 100% with medical treatment alone, management with surgery followed by medical/hormonal therapy is typically indicated.[59,62,63] Surgical treatment, which can be accomplished with video-assisted thoracoscopy, involves excision of endometrial implants, closure of any diaphragmatic defects, stapling of any blebs, and pleurodesis. Medical treatment is aimed at suppressing the ectopic endometrium and ovulation and at preventing further seeding. This is typically accomplished by using oral contraceptives, danazol, or gonadotropin-releasing hormone agonists. No controlled trials have examined the efficacy of one medication over another. If menses is not suppressed, there is a risk of recurrence, even after surgical treatment. Hysterectomy with bilateral oophorectomy will induce surgical menopause and has been employed to prevent pneumothorax.[59]

Pneumothorax in Acquired Immunodeficiency Syndrome

Patients with acquired immunodeficiency syndrome (AIDS) have a significantly increased risk of developing pneumothorax. Roughly 2% of AIDS patients experience spontaneous pneumothorax. In one study, pneumothorax complicated 1.2% of 599 HIV patient admissions over 3 years.[64] Mortality was significantly higher (30.8%) in patients with pneumothorax than in those without (5.8%).

Pneumothorax in AIDS patients is associated with multiple infectious and noninfectious etiologies. *Pneumocystis jiroveci*, bacterial infections, Kaposi sarcoma, cytomegalovirus, pulmonary *Cryptococcus*, coccidiomycosis, and mycobacterial disease have all been associated with spontaneous pneumothoraces. Other risk factors for the development of pneumothorax in HIV include tobacco use, treatment with inhaled pentamidine, and the presence of a pneumatocele on chest radiograph. With the introduction of highly active antiretroviral therapy (HAART), HIV has become a chronic disease; as HIV-infected patients age, they are at increased risk of pulmonary diseases including COPD, lung cancer, interstitial lung disease, and cancer. Each of these disorders increases HIV patients' susceptibility to SSP.[65]

Most studies have shown *Pneumocystis jiroveci* pneumonia (PCP/PJP) to be the primary etiology. However, an observational study of 105 HIV patients with spontaneous pneumothoraces found bacterial pneumonia to be the major underlying etiology (34.3%) followed by PCP (29.5%) and pulmonary tuberculosis (15.2%).[66] In addition, the authors noted that bacterial pneumonia was a more common cause among drug users and those with CD4+ count greater than 200 cells/mL, whereas PCP was a more common cause among patients with sexually transmitted HIV and CD4+ counts less than 200 cells/mL. Given the strong association with PCP, evaluation and treatment for PCP is recommended in any patient with AIDS who presents with an otherwise unexplained spontaneous pneumothorax.

The high frequency of pneumothoraces seen in patients with PCP is thought to be secondary to the presence of subpleural cysts and subpleural necrosis associated with this entity. Extensive tissue invasion within the alveolar interstitium is common in severe PCP and may result in subpleural necrosis. These cystic changes are thought to be due to repeated episodes of inflammation and cytotoxic effects of HIV on pulmonary macrophages with elastase production and necrosis of lung tissue.[56,67] These lesions occur most frequently at the apices of the lungs and consist of necrotic alveoli filled with *P. jiroveci* organisms, macrophages, eosinophilic exudate, and fibrinous material.[68] Because of the necrotizing nature of the pneumonia, spontaneous pneumothorax from PCP is notoriously difficult to treat. Persistent air leaks often require tube thoracostomy for several weeks, and up to one-quarter of patients require surgical intervention. Patients with advanced AIDS are often discharged with Heimlich valves.[69] Some authors recommend early thoracoscopic therapy in good surgical candidates to avoid prolonged hospitalization. Therefore, if surgical intervention is planned, some authors recommend preoperative CT scan of the chest and median sternotomy in patients with significant bilateral disease to facilitate bilateral pleurodesis.[70]

Pulmonary tuberculosis (TB) is still a significant problem in patients with HIV. Pneumothorax has been reported in approximately 7% of HIV patients with pulmonary TB.[71] All pneumothoraces associated with TB should be treated and often require prolonged periods of chest tube drainage. In cases of TB, it has been suggested that thoracotomy should not be considered until the patient has received antituberculosis therapy for at least 6 weeks; however, objective evidence that this affects outcome is lacking.

TRAUMATIC PNEUMOTHORAX

Trauma is the most common cause of pneumothorax, which is a potentially life-threatening injury. Traumatic pneumothoraces are present in around 20% of patients who have undergone either polytrauma or trauma to the thorax.[72] Noniatrogenic traumatic pneumothorax can result from either penetrating or nonpenetrating chest injury. Computed tomography is routine in the evaluation of both blunt trauma and penetrating trauma in the emergency department and often identifies an "occult pneumothorax" (seen on CT scan but not on initial chest radiographs). While current guidelines recommend chest tube placement for traumatic pneumothoraces, especially in patients receiving positive-pressure ventilation, this area remains controversial. Recent studies suggest the majority of occult pneumothoraces in stable patients can be managed conservatively even in the setting of positive-pressure ventilation.[72,73]

Penetrating chest trauma produces a pneumothorax by allowing air to enter the pleural cavity directly through the chest wall. In addition, if the visceral pleural is penetrated, air may leak from the tracheobronchial tree. If the continuity of the chest wall is disrupted, an open pneumothorax is produced. If the opening in the chest wall is larger than the diameter of the trachea (1.0–2.1 cm in an adult), air movement occurs through the pathway of least resistance, and air is preferentially inspired into the thoracic cavity through the open chest wound. Any open chest wound must be occluded to assure adequate ventilation of the patient.

Pneumothorax is also a frequent finding in patients with blunt trauma to the chest. The visceral pleura may be lacerated secondary to a rib fracture or dislocation; however, in almost one-half of patients with pneumothorax secondary to blunt trauma, there are no associated rib fractures. This is especially common with blunt trauma to the chest secondary to blast injuries and high-altitude falls into water. In such incidents, the abrupt increase in the pressure gradient between the alveolus and the adjacent bronchovascular sheath causes disruption of the alveolar membrane. Dissection of air through the interstitial space results in either pneumothorax or pneumomediastinum.

Occasionally, patients with traumatic pneumothorax have coexisting injuries of the tracheobronchial tree or esophagus. In a patient with a traumatic pneumothorax, fiberoptic bronchoscopy should be performed in the presence of hemoptysis or a persistent air leak. Eighty percent of injuries to the tracheobronchial tree are within 2.5 cm of the carina, most commonly on the right side at the membranous–cartilaginous interface. The main lobar bronchi and the cervical trachea are the next most common sites of injury.

Traumatic rupture of the esophagus usually produces a hydropneumothorax. Therefore, if a patient with a traumatic pneumothorax also has a pleural effusion, the possibility of esophageal rupture should be entertained. Almost all patients with perforation of the thoracic esophagus also have dysphagia and pneumomediastinum. An elevated pleural fluid amylase concentration is a reliable screening procedure for esophageal rupture. Once the diagnosis is suspected, contrast radiographic studies of the esophagus should be performed as soon as possible. Untreated, esophageal rupture results in mediastinitis and septic shock; therefore, a high index of suspicion is essential in making an early diagnosis.

IATROGENIC PNEUMOTHORAX

Increasing utilization of invasive diagnostic and therapeutic interventions has significantly increased the rate of iatrogenic pneumothorax. These cases may result in considerable morbidity, prolonged hospitalization, and even death, for the affected patient.[74] Iatrogenic pneumothorax can occur as a complication of multiple procedures, but the leading cause of iatrogenic pneumothorax is transthoracic needle aspiration followed by subclavian vein catheter insertion, thoracentesis, transbronchial biopsy, pleural biopsy, and positive-pressure ventilation.[75] The incidence ranges between 17% and 26% with transthoracic needle aspiration; risk factors include COPD, depth of lesion within the lung, and lesions smaller than 2 cm.[76–78] Pneumothorax may also occur with transbronchial needle aspiration, liver biopsy, intercostal nerve block, mediastinoscopy, and tracheostomy among others.

Central venous catheterization carries the second highest risk of iatrogenic pneumothorax. The reported risk ranges from 2% to 12% (most studies <3%) when using anatomic landmarks for guidance. Subclavian catheterization carries a higher risk than internal jugular catheterization. The increasing use of real-time sonographic guidance for central venous catheterization has significantly decreased this risk for both internal jugular and subclavian approaches.[79,80] Similarly, the routine use of real-time ultrasound guidance for localization of needle puncture site during thoracentesis may decrease the risk of pneumothorax, which develops in approximately 5% of cases[81] (Table 79-2).

Mechanical ventilation is a frequent, potentially lethal cause of iatrogenic pneumothorax. The overall incidence of pneumothorax during mechanical ventilation ranges from 4% to 15% but may be significantly higher in patients with underlying inflammatory diseases such as aspiration pneumonia.[82] The incidence of pneumothorax is also increased during mechanical ventilation if patients have chronic pulmonary disease, are on increased amounts of positive end-expiratory pressure, or have right mainstem intubation.[82] The incidence of pneumothorax has been reported to be 6.9% to 14% of patients with acute respiratory distress syndrome (ARDS).[83,84] Another study reported a 48.8% incidence of pneumothorax in patients with severe ARDS requiring extracorporeal support.[85]

TABLE 79-2 Iatrogenic Pneumothorax Rate of Common Procedures

Procedure	Pneumothorax Rate
Flexible bronchoscopy (any procedure)	0.10%–0.16%[168]
Thoracentesis	6%[169]
Transbronchial biopsy (TBB)	1%–6%[168]
Transbronchial cryobiopsy (TBCB)	4.8%–20%[170]
Transbronchial needle aspiration (TBNA)	1%–6%[171]
Endobronchial ultrasound (EBUS)-TBNA	0.2%[172]
Central line insertion	<0.2%[173]
• Internal jugular vein	<0.1%[173]
• Internal jugular vein, ultrasound guided	0.45–3.1%[173]
• Subclavian vein	
Mechanical ventilation	4–15%[174]
CT-guided percutaneous fine needle aspiration	17–26.6%[175]
Navigational bronchoscopy	4.3%[176]
Percutaneous nephrolithotomy	7%[177]
Percutaneous liver biopsy	0.8%[178]

A pneumothorax should be suspected in any patient whose clinical status acutely decompensates on the ventilator. Bedside clues include a sudden increase in respiratory rate or appearance of patient–ventilator dyssynchrony. An increase in the peak and plateau pressures on the ventilator can be a sensitive indicator if the patient is on volume-cycled ventilation. The peak inspiratory pressure often rises suddenly as the lung compliance falls. If the patient is on pressure control ventilation, decreased tidal volumes will be a sign of pneumothorax.

Radiographs of critically ill, mechanically ventilated patients are frequently obtained only in the supine or semi-supine position. In one study, supine and semierect radiographs were obtained in 88 critically ill patients with 112 cases of pneumothorax.[86] The radiologist initially failed to detect the pneumothorax in 30% of the cases. Patients with extensive infiltrates, such as in the setting of ARDS, may have no suggestion of lung collapse on chest radiograph. In these patients, the only radiologic sign that may be evident is that of a deep sulcus on the side of the pneumothorax. This finding, as well as any increased lucency on a supine film, should raise suspicion of a pneumothorax and be evaluated by either erect or decubitus views, or ultrasound. If erect or decubitus films cannot be obtained or ultrasound is unavailable, CT scans of the chest may be necessary.

It should be noted that recipients of bilateral lung transplants and patients who have had a "clamshell" thoracotomy do not have an intact mediastinum. Because of this, the normally separate pleural spaces may be in direct communication with each other. Physicians performing procedures on these patients need to be aware that the patient can develop bilateral pneumothoraces because of this anomaly.[87]

CLINICAL FEATURES

The main symptoms with the development of a pneumothorax are chest pain and dyspnea, which occur in 95% of patients. The pain is usually acute, localized to the side of the pneumothorax, and typically pleuritic. Cough, hemoptysis, orthopnea, and Horner syndrome are uncommon manifestations of a pneumothorax.[8,88] A small percentage of patients are asymptomatic or complain only of generalized malaise and fatigue.

Spontaneous pneumothorax usually occurs at rest, and fewer than 10% occur during strenuous exercise. In PSP, both the dyspnea and chest pain may subsequently abate over the first 24 h. This may explain why nearly half of patients have symptoms for 2 days before seeking medical attention and why 18% wait for more than a week.[8] Most patients with SSP have more severe symptoms than patients with PSP, and dyspnea frequently seems out of proportion to the size of the pneumothorax.[89] Patients with SSP often present in respiratory distress with significant tachycardia and tachypnea. Patients with tension pneumothorax, most commonly seen in the setting of mechanical ventilation or after cardiopulmonary resuscitation, often progress to profuse diaphoresis, marked hypoxemia, cyanosis, respiratory acidosis, and hypotension.

Small pneumothoraces (<20%) are usually not detectable on physical examination. In patients with COPD, even larger pneumothoraces may be difficult to detect since decreased breath sounds and hyperresonance may already be present.[90] On physical examination, vital signs are usually normal, with the exception of moderate tachycardia and to a lesser degree tachypnea. Examination of the chest may reveal the affected side to be larger and move less during respiration. Tactile fremitus is absent, the percussion note is hyperresonant, and breath sounds are absent or reduced on the side with the pneumothorax.

In patients with PSP, arterial blood gases often show hypoxemia and hypocarbia from hyperventilation. Hypoxemia is usually mild when less than 25% of the lung is affected. When more than 25% of the lung is involved, pulmonary shunts occur more frequently and hypoxemia may be severe. In patients with SSP, pulmonary reserve is already diminished and life-threatening hypoxemia and hypercapnia may be present. In one study, the mean pO_2 was 48 mm Hg and the mean pCO_2 was 58 mm Hg when patients with emphysema presented with a spontaneous pneumothorax.[90]

Patients with a left pneumothorax may show changes on ECG suggesting an anterolateral myocardial infarction. A rightward shift of the frontal QRS axis and clockwise rotation of the heart result in a diminution of precordial R-wave voltage, a decrease in the QRS amplitude, and precordial T-wave inversion.[91] These electrocardiographic features differ from a transmural myocardial infarction because of the absence of ST-segment elevation or significant Q waves. An anterior subendocardial infarction may present with T-wave inversion but without the rightward shift in the frontal axis. The electrocardiographic changes with a left pneumothorax may normalize when the patient is in the upright or right lateral decubitus position.

RADIOGRAPHIC APPEARANCE

Below are considered the radiographic (plain radiography and CT) and ultrasound findings in pneumothorax.

Plain Radiography

Classically, the diagnosis of pneumothorax is established by demonstrating the outer margin of the visceral pleura (and lung) separated from the parietal pleura (and chest wall) by a lucent space devoid of pulmonary vessels (Fig. 79-3) on the chest radiograph. The pleural line may be difficult to detect with a small pneumothorax unless high-quality upright films are obtained. In erect patients, pleural gas collects over the apex, and the space between the lung and chest wall is most notable there. In the supine position, gas migrates along the broad ventral surface of the lung, making detection on a frontal radiograph difficult. In the supine position, the juxtacardiac area, the lateral chest wall, and the subpulmonic region are the best areas to search for evidence of pneumothorax. Several studies have shown that expiratory films have little or no advantage over upright inspiratory films in the diagnosis of pneumothorax.[92–94] Data from the Trauma Audit and Research Network (TARN) noted that 48% of subjects presenting to the emergency department after trauma had "occult pneumothoraces" missed on plain chest radiographs.[72]

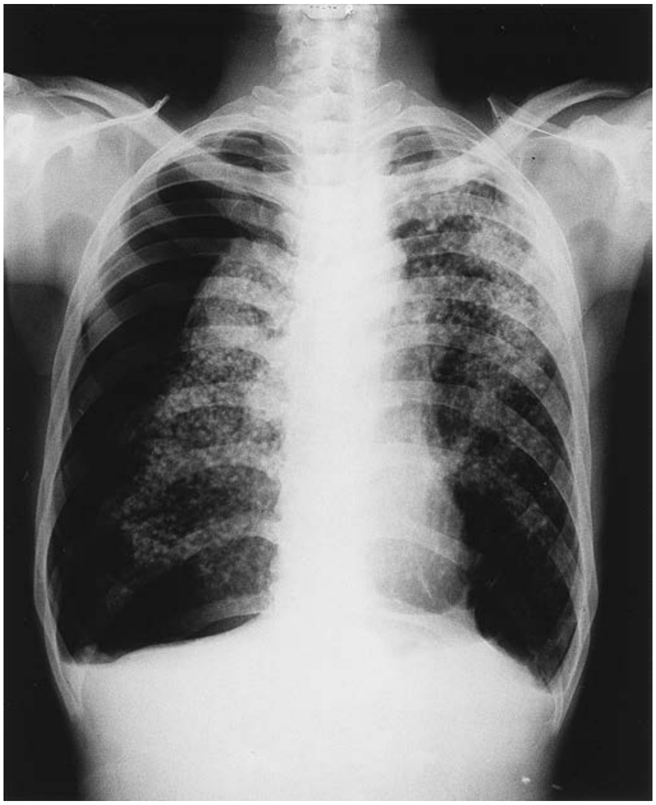

Figure 79-3 A patient with nodular silicosis and a spontaneous secondary pneumothorax. The visceral pleural line is clearly seen with the absence of vascular workings beyond the pleural line. There are cicatricial bullae in both bases.

It is very important to differentiate the pleural line of a pneumothorax on chest radiographs from that of a skinfold, clothing, tubing, or chest wall artifact. Careful inspection of the film may show that the artifact extends beyond the thorax, or that lung markings are visible beyond the apparent pleural line. In the absence of underlying lung disease, the pleural line of a pneumothorax usually parallels the shape of the chest wall. Artifactual densities generally do not parallel the course of the chest wall over their entire length. Avascular bullae or thin-walled cysts can be mistaken for a pneumothorax. The pleural line caused by a pneumothorax is usually convex at its center toward the lateral chest wall. As opposed to a pneumothorax, the inner margins of bullae or cysts are, in general, concave rather than convex towards the chest wall and do not exactly conform to the contour of the costophrenic sulcus. A pneumothorax with a pleural adhesion may also simulate bullae or lung cysts. An adhesion tends to form a straight line connecting the lung to the parietal pleura; bullae or cysts have rounded edges. Such features are not 100% specific, and if there is any doubt as to whether the patient has a bulla or cyst or a pneumothorax, a CT scan should be obtained as CT can usually differentiate the two.[95] Pleural effusions may occur coincident with pneumothorax in up to 20% to 25% of cases. Hemopneumothorax occurs in 2% to 3% of cases of spontaneous pneumothorax. Bleeding is believed to represent rupture or tearing of vascular adhesions between the visceral and parietal pleura as the lung collapses.

Quantification of the size of a pneumothorax on chest radiographs is helpful, but the methods for quantifying lack uniformity and are by no means precise. Light suggested measuring the average diameters of the collapsed lung and of the affected hemithorax, then cubing these diameters to estimate the percentage of collapsed lung by the following equation: $100 \times (1 - \text{diameter of collapsed lung}^3/\text{diameter of hemithorax}^3)$.[88] For example, if the diameter of the collapsed lung is 6 cm and the diameter of the hemithorax is 10 cm, the collapsed lung is estimated by the formula $100 \times (1 - 6^3/10^3)$. Thus, the estimated size of the pneumothorax is 78%.[88] Rhea et al.[96] proposed the use of a nomogram to calculate the size of the pneumothorax. With this method, the average intrapleural distance is calculated by measuring the interpleural distance at the apex and at the midpoints of both the upper and lower lungs. These three values are then averaged, and the number is reported on a nomogram, which gives an estimated size of the pneumothorax (Fig. 79-4).

The most common radiographic manifestations of tension pneumothorax are mediastinal shift, diaphragmatic depression, and rib cage expansion (Fig. 79-5). Any significant degree of displacement of the mediastinum from the midline position on maximum inspiration, or any depression of the diaphragm, should be taken as evidence of tension. The degree of lung collapse is an unreliable sign for or against the presence of a tension pneumothorax since underlying lung disease may prevent collapse even in the presence of tension.

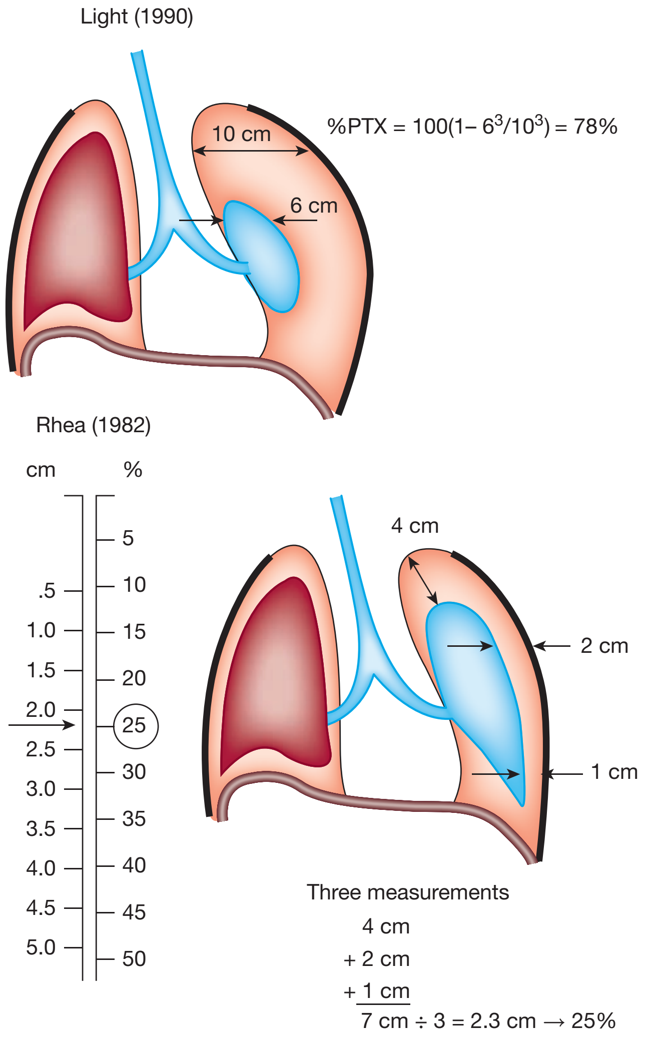

Figure 79-4 Estimation of the size of the pneumothorax according to the method described by Light[89] and Rhea et al.[97] *(Reproduced with permission from Pearson FG, Deslauriers J: Thoracic Surgery. Philadelphia, PA: Churchill Livingstone; 1995.)*

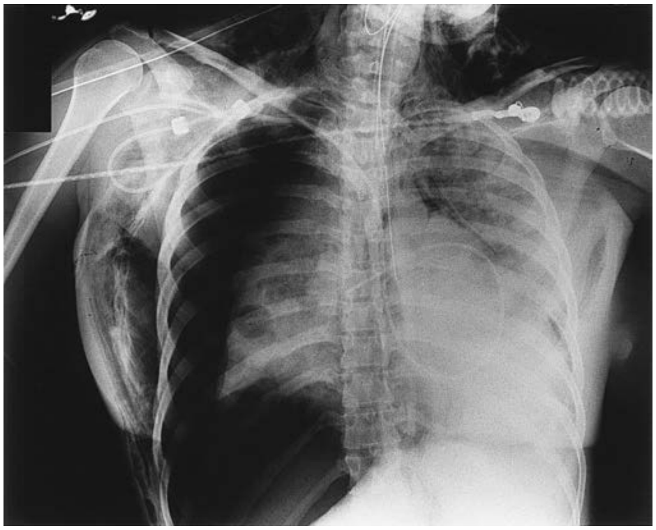

Figure 79-5 Right tension pneumothorax in a young patient with staphylococcal endocarditis and septic emboli. There is marked depression of the right hemidiaphragm, shift of the mediastinum, and subcutaneous emphysema. Note that the pulmonary artery catheter, endotracheal tube, and nasogastric tube (midchest) are all displaced to the left.

■ Computed Tomography

CT scans of the chest are being used with increasing frequency in patients with pneumothorax. CT scans may be necessary to diagnose pneumothorax in assessment of trauma patients in the emergency room and in critically ill patients when upright or decubitus chest radiographs are not possible. CT scans may also prove helpful in predicting the risk of recurrence in patients with spontaneous pneumothorax. One study demonstrated that patients who have larger or more numerous blebs on chest CT scans are more likely to have recurrence.[97] CT scans also have the ability to assess the volumetric size of a pneumothorax and can accurately assess changes over time.[98]

Traumatic pneumothoraces, if large, can be detected both clinically and with chest radiography. However, a small, posttraumatic pneumothorax may be easily missed by both physical examination and chest radiograph. One prospective series revealed that 51% of trauma patients presented with an occult pneumothorax that was not seen on initial chest radiograph, but identified on CT imaging.[99] In another large series looking at multiple trauma patients, 4.4% had a pneumothorax and 38.8% of these were detected only by CT scan.[100] Of note, recent studies suggest that traumatic pneumothoraces measuring 35 mm or less on CT scans can be managed conservatively in more than 90% of cases.[73] Early incorporation of a routine CT scan in all patients with chest trauma or multiple traumatic injuries may be required to successfully diagnose traumatic pneumothoraces.

■ Lung Ultrasound

Ultrasound has evolved to become an indispensable bedside tool for rapid diagnosis of pneumothorax.[100–103] Since the early 1990s, our understanding of lung and pleural ultrasonography has continued to mature as new research has emerged and more clinicians

Video 79-1 Normal lung sliding. This sagittal view using two-dimensional ultrasound shows normal lung sliding through an anterior chest interspace. Two ribs that cast shadows are seen on the left and right edges of the image. The pleural surface is seen below the ribs. The visceral and parietal pleura are apposed giving a shimmering, glistening appearance as the visceral pleura slides back and forth against the parietal pleura with respirations. *Video available on AccessMedicine.com.*

Video 79-2 Absence of lung sliding due to pneumothorax. Using two-dimensional ultrasound in a sagittal plane, the absence of lung sliding can be appreciated as the shimmering, glistening appearance of the pleura is not seen below the ribs. *Video available on AccessMedicine.com.*

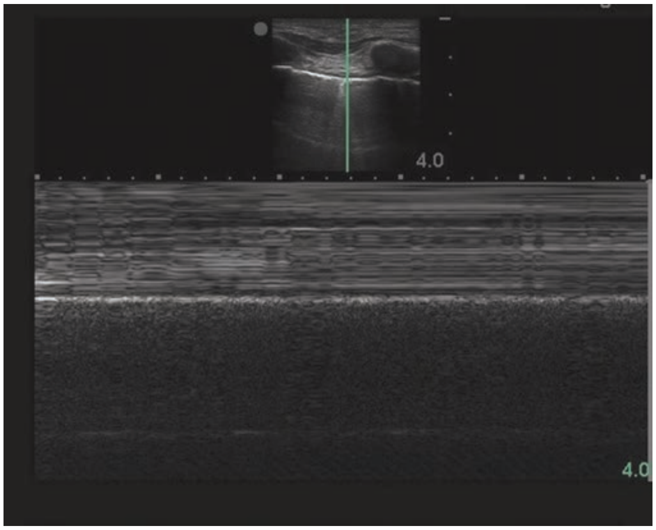

Figure 79-6 Normal lung in M-mode. A two-dimensional ultrasound image at the top shows the sample line along which the movement of all tissues is recorded and displayed below. The chest wall creates a series of horizontal lines. Also noted are the hyperechoic line of the pleura and a granular pattern created by aerated lung.

have integrated point-of-care ultrasound into clinical practice (see Chapter 29).

Lung ultrasound is more sensitive than chest x-ray for detection of pneumothorax when using chest CT as the gold standard. Early studies established superiority of lung ultrasound compared with chest x-ray to detect pneumothorax, with sensitivities and specificities ranging from 66% to 100% and 91% to 100%, respectively.[104–107] Meta-analyses report pooled sensitivities of 79% to 95% and specificities of 98% to 99% for lung ultrasound in detecting pneumothorax. In contrast, pooled sensitivity and specificity for chest radiography have been reported at 40% to 52% and 99% to 100%, respectively.[108–110]

Normal lung and pleura are characterized by two ultrasound findings: lung sliding and A-lines. By conventional two-dimensional ultrasonography, normal visceral and parietal pleura appear as a bright white (hyperechoic) line that glistens with respirations as the visceral pleura slides back and forth against the parietal pleura (Video 79-1). A principal finding to diagnose pneumothorax is absence of lung sliding (Video 79-2). The presence of air in between the visceral and parietal pleura in pneumothorax prevents propagation of ultrasound waves beyond the parietal pleura, and the sliding, shimmering appearance created by apposed pleura is not seen.[111,112] Presence of lung sliding definitively rules out pneumothorax with a negative predictive value of 100%.[104] However, absence of lung sliding is not specific to pneumothorax and can be seen with any cause of pleural symphysis (chemical pleurodesis, infectious/inflammatory adhesions, fibrosis) or lung volume loss (mainstem intubation, massive atelectasis, mucus plug, pneumonectomy, apnea).[111] If lung sliding is absent, identification of the lung point, a specific sign of pneumothorax, can confirm the diagnosis. The lung point is the edge of a pneumothorax, or boundary between collapsed and aerated lung, and a lung point is 100% specific to rule in pneumothorax.[107] The defining feature of a lung point is visualization of aerated lung sliding into the field of view next to collapsed lung (Videos 79-3 and 79-4). It is essential to avoid mistaking the edge of lung along the heart border or diaphragm for a lung point. In a supine patient, the lung point can be found anteriorly when the pneumothorax is small, and laterally when it is large.[112]

Evaluation of lung sliding can be confirmed using M-mode, or motion mode. M-mode displays movement of tissues over time. The normal M-mode pattern of lungs includes horizontal, linear lines at the top, corresponding to the chest wall; a hyperechoic line corresponding to the pleura; and a granular pattern at the bottom corresponding to aerated lung parenchyma. The normal M-mode pattern is called "seashore" sign with the aerated lung parenchyma representing the beach and the chest wall representing the ocean (Fig. 79-6). In pneumothorax, the granular pattern of aerated lung parenchyma is lost, and horizontal, linear lines are seen throughout the display. The M-mode pattern of pneumothorax is often referred to as a "stratosphere" or "barcode" sign (Fig. 79-7).[111] The lung point

Video 79-3 Lung point sign (lateral chest wall). The edge of a pneumothorax, or lung point, can be seen on the curvature of the lateral chest of a mechanically ventilated patient with a large, postprocedural pneumothorax. Aerated lung superiorly *(left)* slides into the field of view next to the collapsed, nonsliding portion of lung *(right)*. *Video available on AccessMedicine.com.*

Video 79-4 Lung point sign (anterior chest wall). The edge of a pneumothorax, or lung point, can be seen on the anterior, inferior chest wall of a patient with a small, spontaneous pneumothorax. Aerated lung slides in and out of the field of view next to the collapsed, nonsliding portion of lung. *Video available on AccessMedicine.com.*

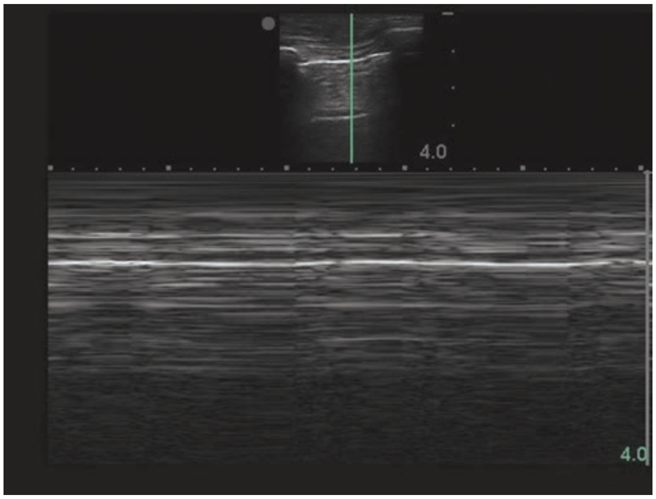

Figure 79-7 Pneumothorax in M-mode. The separation of visceral and parietal pleura by air from a pneumothorax prevents ultrasound waves from reaching the visceral pleura resulting in loss of the granular pattern of normal lung at the bottom of the M-mode image. A series of horizontal lines is seen throughout the M-mode image and is often called "stratosphere sign" or "bar code sign."

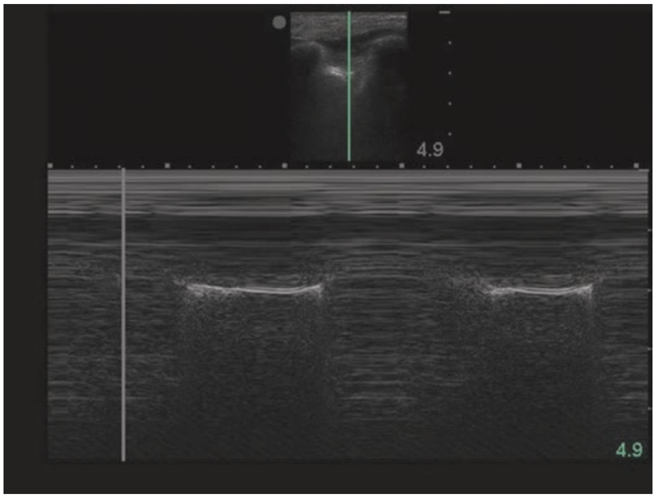

Figure 79-8 Lung point in M-mode. This M-mode image displays alternating patterns of normal lung and pneumothorax as normal, aerated lung slides over the area of collapsed lung.

will display a distinct M-mode pattern with alternating segments of "seashore" and "barcode" pattern (Fig. 79-8).

A-lines are ultrasound image artifacts due to repeated reflections, or reverberations, between the highly reflective pleura and transducer. A-lines are seen as a series of equidistant horizontal white lines deep to the pleura (Fig. 79-9). A-lines are seen in normal lungs but also in pneumothorax, pulmonary embolism, COPD, or asthma due to reverberations between the parietal pleura alone and transducer. Therefore, presence of A-lines supports a diagnosis of pneumothorax but is not specific for pneumothorax. In contrast, the presence of B-lines, an artifact arising from the pleura, rules out pneumothorax with a negative predictive value of 100% (Video 79-5).[106] In the absence of lung sliding, visualization of B-lines or other vertical artifacts called comet-tails rules out pneumothorax (Video 79-6).

A focused lung ultrasound examination to evaluate for pneumothorax can be performed rapidly—in less than 1 min in one study by experienced clinicians.[107] A phased-array, linear-array, or microconvex transducer is most often used. Specifically, for evaluation of pneumothorax, a high-frequency (5–10 MHz), linear-array transducer is preferred because of its higher resolution and sensitivity (82% vs. 76%) compared with convex-array transducers.[110] Air in the pleural space accumulates in the least dependent parts of the chest, which are anterior and inferior in supine patients. The anterior chest wall is scanned by placing the transducer in the midclavicular line at the level of the clavicle with the transducer orientation marker pointed cephalad. The transducer is then slid inferiorly to the diaphragm, evaluating each intercostal space sequentially for lung sliding. If absence of lung sliding is detected, the transducer is moved laterally in search of the lung point to confirm presence of a pneumothorax and to qualitatively assess the size of the pneumothorax. M-mode may be used to confirm the presence or absence of lung sliding.[112] The lateral and posterior chest walls should be interrogated subsequently, although most pneumothoraces will be detected on the anterior chest wall in supine patients unless the pneumothorax is loculated.

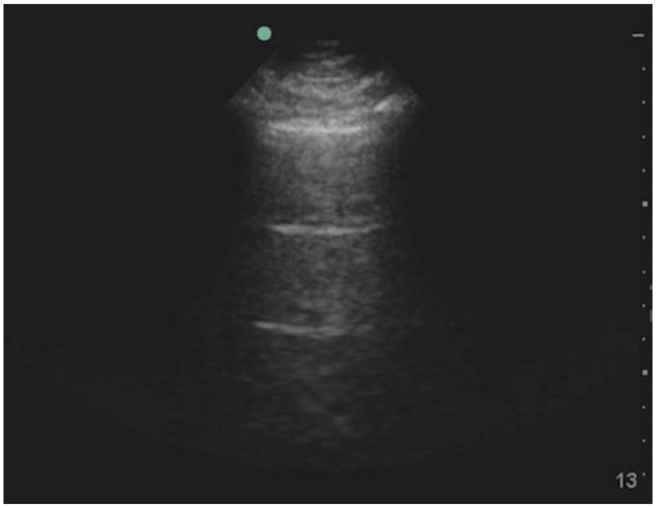

Figure 79-9 A-lines. A-lines are a type of reverberation artifact seen as equidistant horizontal lines that are generated from reflections of the pleura. A-lines are seen in normal, aerated lungs, but are also seen in pneumothorax, pulmonary embolism, chronic obstructive pulmonary disease, and asthma.

Video 79-5 B-lines. B-lines are a type of reverberation artifact, also known as comet-tail artifacts, that arise from the pleural surface and extend vertically to the bottom of the screen as discrete, hyperechoic rays that slide with pleural movement. Presence of B-lines rules out pneumothorax. *Video available on AccessMedicine.com.*

Video 79-6 B-lines and absence of lung sliding. Although lung sliding is absent in this patient with pneumonia, visualization of B-lines confirms apposition of the visceral and parietal pleura ruling out pneumothorax. *Video available on AccessMedicine.com.*

Given the difficulties associated with diagnosing small pneumothoraces by plain chest radiograph, as well as the cost and delay of CT scans, thoracic ultrasound is quickly emerging as a valuable tool for the diagnosis of occult pneumothorax. The small size and portability of newer machines, as well as the advantage of immediate bedside interpretation, make ultrasound especially helpful in the management of critically ill and hemodynamically unstable patients. Most data have come from trauma literature where ultrasound has a more well-established role. Hand-held ultrasonography was shown to have better sensitivity (48.8 vs. 20.9%) and similar specificity compared with chest radiograph for detection of traumatic pneumothorax using CT as the gold standard.[113] A review of ultrasound specifically in ICU patients concluded that ultrasound had a sensitivity of 95% and specificity of 94% compared with CT for the detection of pneumothorax.[114] Ultrasound has the additional advantage of serving as a guide to direct the site of drainage.[115]

MANAGEMENT

The American College of Chest Physicians (ACCP)[116] and the British Thoracic Society (BTS)[3] have published society guidelines for the management of spontaneous pneumothorax; unfortunately, these guidelines have not been updated since 2001 and 2010, respectively. In 2015, the European Respiratory Society (ERS) published a task force statement on PSP.[117] However, all three guidelines are somewhat outdated and fail to capture significant recent studies on the treatment options for pneumothorax. There is considerable heterogeneity and deviation from guideline-based management,[118] probably reflecting the lack of randomized trials and the disparities in the recommendations from various society guidelines.

Therapy for pneumothorax is dependent on the size of the pneumothorax, symptomatology, and etiology. The basic tenets of therapy are to evacuate the space, achieve closure of the leak, and either prevent or reduce the risk of recurrence. A variety of treatment methods and adjuncts exist. The choice of therapy depends on many factors, including the clinical status of the patient, the cause of the pneumothorax, evidence for concomitant lung disease, prior history of pneumothorax, risk of recurrence, and, finally, the experience and preferred techniques of the physicians caring for the patient as well as the availability of specific therapeutic options.[119] Major categories of treatment methods are listed below, followed by suggested guidelines for their application.

■ Observation

Simple observation of the patient with a pneumothorax requires evidence that the air leak is sealed (i.e., that there is no further progression of the pneumothorax). Conservative management of pneumothoraces is not a new concept. In 1966, Stradling and Poole[120] reported the safety and efficacy of conservative management and the low risk in patients with PSP. Recently a large, multicenter, randomized trial[121] was performed in patients with moderate to large PSP (≥32% on chest radiography using the Collins equation), where the conservative group was observed for at least 4 h in the emergency department. Chest tube drainage was performed if symptoms persisted despite analgesia or if the patient became physiologically unstable with or without enlarging pneumothorax on repeat chest radiograph. In the conservative group, 84.6% did not undergo interventions. Lung re-expansion at 8 weeks was noninferior in the conservative group compared with the intervention group (94.4% vs. 98.5%). This form of management is generally reserved for patients with PSP since pulmonary reserve is reduced in most patients with SSP.

■ Aspiration

Aspiration of pneumothorax has been advocated by some but has shown varied levels of success, and there is poor consensus between guidelines as to which patients warrant this approach.[122] Most studies on aspiration have been performed in patients with PSP. A meta-analysis of randomized controlled trials of simple aspiration versus chest tube insertion concluded that simple aspiration was advantageous because of shorter hospitalization times and no significant difference in recurrence rates at 1 year.[123] In these studies, approximately 66% of patients had resolution of their pneumothorax. A more recent meta-analysis of all hemodynamically stable adults with spontaneous pneumothorax compared needle aspiration versus small-bore chest tube (<14 French) versus larger-bore chest tube and found no statistical differences between the various forms of therapy.[124] However, patients with secondary or a recurrence of spontaneous pneumothorax generally do not have good results with simple aspiration.[122,125–127]

■ Tube Thoracostomy

This entails the placement of an indwelling catheter into the pleural space for continual removal of the intrapleural gas. For uncomplicated pneumothorax without evidence of significant amounts of fluid or blood, one may use small thoracostomy tubes (pig-tail catheters) ranging from 8 to 14 French to minimize the discomfort of a larger tube in the intercostal space. Generally, a safe site for a chest tube or pleural catheter placement is the lateral chest wall above the fourth to sixth ribs in the mid- to anterior axillary line. For small pneumothoraces, an anterior midclavicular chest tube can be placed in the second or third intercostal space. Large-bore chest tubes have essentially been replaced by the insertion of pig-tail catheters placed under ultrasound. The main indications to place a large-bore chest tube are hemothorax and selective cases of small pneumothorax in patients on mechanical ventilation where the risk of injuring the lung is deemed too high to place a catheter by needle insertion.[128]

Following insertion, the tube is then connected to a pleural drainage system. Commercial systems commonly employ variations on the three-chamber system (Fig. 79-10). The three-chamber system

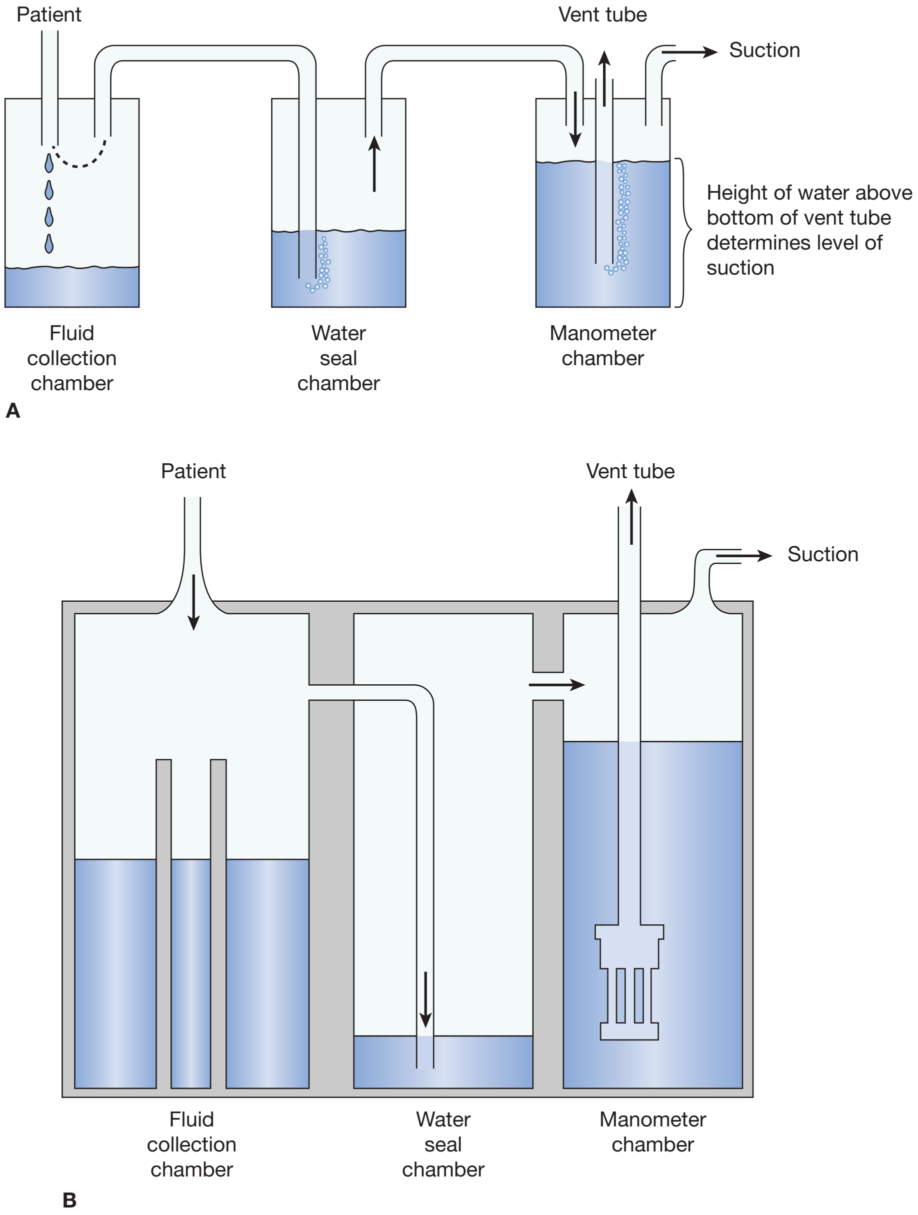

Figure 79-10 **A.** Three-bottle chest tube drainage system. The system consists of a collection bottle, a water-seal bottle, and a suction-control bottle. The collection bottle allows sterile drainage from the pleural spaces. The water-seal bottle acts as a one-way valve in the absence of suction, and the suction bottle allows for the regulation of negative pressure applied to the pleural space. **B.** Commercially available, compartmentalized plastic drainage system.

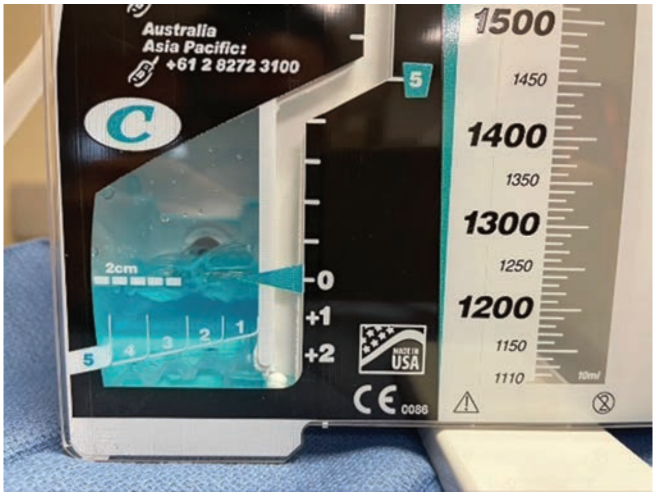

Figure 79-11 A dry suction chest tube drain system showing the appearance of air bubbles from left to right in the air leak monitor, which signifies an active air leak. The air leak monitor is graded from 1 (low) to 5 (high) to allow for monitoring the extent of the air leak.

consists of a fluid collection chamber attached to a water seal chamber to allow egress of gas from the pleural space, but in a one-way fashion. The final connection is to a manometer bottle, which regulates the degree of suction being applied to the system. (Newer "dry vac" systems use a resistor rather than water to regulate the amount of negative pressure [Figs. 79-11 and 79-12].) After placement of the tube, care should be taken with regard to immediate placement to suction because of the potential for re-expansion pulmonary edema (REPE). In many cases it may be prudent to leave the tube to water seal and allow the lung to expand gradually. Once the majority of the pneumothorax is evacuated, suction is applied for the next 24 h. If an air leak exists, as evidenced by continual or intermittent egress of gas through the water seal chamber, suction is maintained (Table 79-3). Once there is no evidence of an active air leak, the tube may be placed to water seal. After an additional period of observation of 12 to 24 h, the chest tube may be removed if the pneumothorax does not recur.[129] Tube thoracostomy alone will result in closure of an air leak in most cases by complete evacuation of the pleural space and apposition of the visceral and parietal pleura. Persistence of an air leak for more than 72 to 96 h generally presages a leak that will not close by this regimen and should prompt consideration of more aggressive therapy.[130]

TABLE 79-3 Cerfolio Classification of Air Leaks

During forced expiration only, usually asking the patient to cough	Grade 1, (FE) forced expiration
Expiratory only	Grade 2, (E) expiration
Inspiratory only	Grade 3, (I) inspiration
The air leak chamber shows continuous bubbling during both inspiration and expiration, which correspond to large leaks usually	Grade 4, (C) continuous

Data from Cerfolio RJ. Advances in thoracostomy tube management. Surg Clin North Am. 2002;82(4):833–848.

Potential problems with small catheters relate to a greater propensity for blockage of the tube. Also, the smaller size makes them more prone to kinking, clotting from blood or fluid, and sealing of the side- and end-ports of the tube by the lung. Flushing pig-tail catheters is often required to assure they remain functional and to clear blood or fluid.

A variation on the use of pleural drainage systems is the substitution of a one-way valve to permit early discharge from the emergency department or hospital with subsequent ambulatory management of the patient.[131] The most common is the Heimlich flutter valve, which is particularly useful in cases in which there is a protracted air leak but surgical therapy is declined or not possible. This valve is not widely recommended, however, owing to a potential for problems with blockage, which may not be immediately recognized on an outpatient basis. A recent, open-label, randomized study compared a self-contained device with a drainage chamber and internal Heimlich valve (Rocket Pleural Vent) and demonstrated statistically fewer days of hospitalization but a higher incidence of serious adverse events related to the procedure.[132]

Pleurodesis

Pleurodesis is an adjunct to the other forms of therapy. The goal is to achieve pleural symphysis, or adhesion of the visceral and

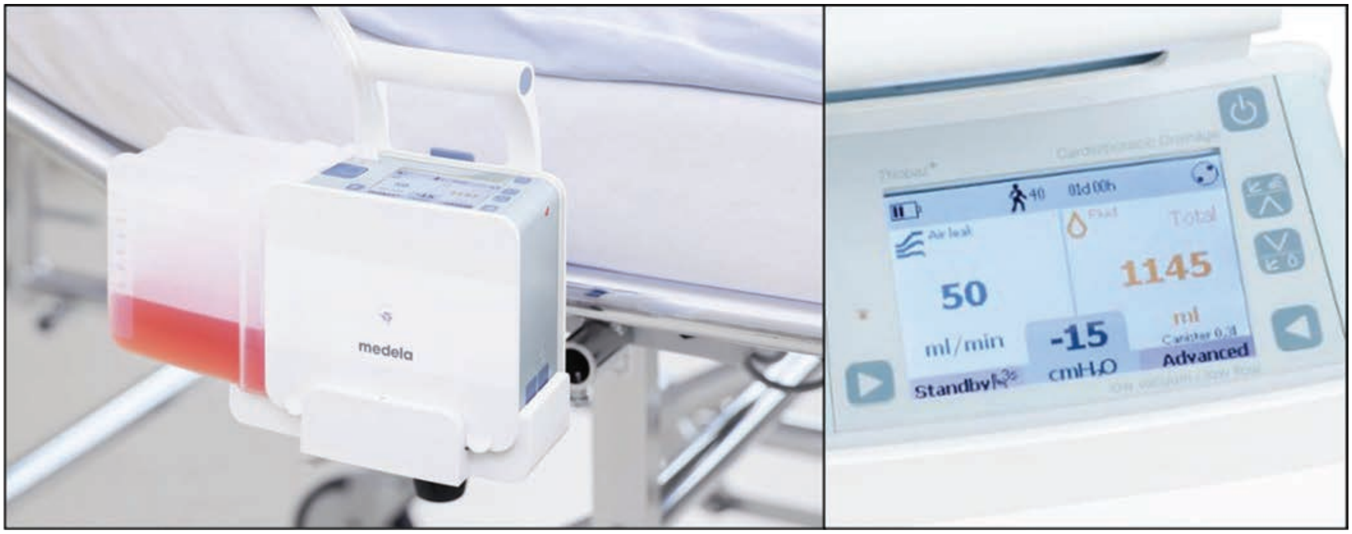

Figure 79-12 Thopaz digital chest drainage and monitoring system. (©2022 Medela.)

parietal pleura to obliterate the pleural space. Sealing the visceral and parietal pleura together will prevent future air leaks and prohibit the lung from "falling away" from the chest wall. The basic mechanism entails chemical or physical irritation of the pleural surface to promote an inflammatory response and subsequent adhesion formation.

The goal of pleurodesis is to prevent recurrence in both PSP and SSP. There is good consensus for the use of pleurodesis in both; however, the timing and approach remain somewhat controversial.

Chemical pleurodesis may be used in combination with tube thoracostomy or surgical therapy. In patients who are unable to undergo a surgical procedure (e.g., due to severe comorbidity), pleurodesis can be achieved by administering the sclerosing agent through a chest tube. The success rates of pleurodesis utilizing antibiotics (doxycycline, minocycline) or talc by slurry have been shown to be superior to chest tube drainage alone.[16]

As an adjunct to tube thoracostomy, the chemical of choice is suspended in fluid and instilled through the tube. The tube is clamped for 1 to 2 h, then placed back to either suction or water seal. Periodically changing patient position during this pleurodesis has not been shown to improve outcome with tetracycline derivatives.[133,134] Success is largely dependent on apposition of the visceral and parietal pleura during the period of inflammation while the tube is clamped. Excessive pleural fluid will dilute the sclerosing agent, and an air leak will allow the lung to separate from the chest wall. Doxycycline pleurodesis in the face of an air leak has been successful in safely closing the air leak;[135–137] however, all agents have significantly reduced success rate with a persistent air leak present.

The ideal agent should be effective, safe, easy to administer, widely available, and affordable. A number of pleural irritants have been suggested, including talc, antibiotics (minocycline and doxycycline), quinacrine, silver nitrate, bleomycin, and autologous blood. Side effects of pleurodesis with a sclerosing agent include chest pain (variable in severity), dyspnea, and fever that occasionally persists for over a week.[138]

Tetracycline was shown to be very effective in creating sufficient pleural fibrosis formation when compared with hydrochloric acid, quinacrine, nitrogen mustard, bleomycin, or sodium hydroxide.[5] A randomized study comparing the recurrence rates in PSP after drainage alone with that of drainage plus tetracycline or talc found recurrence rates of 36%, 13%, and 8%, respectively.[136] Tetracycline, however, is no longer commercially available. Minocycline and doxycycline have replaced tetracycline, with experimental and clinical data suggesting equal efficacy.[116,139–141] Typical doses of these antibiotics are 0.5 to 1 g of doxycycline in 50 to 100 mL normal saline and 600 mg of minocycline in 50 to 100 mL of normal saline.

Talc has also been shown to be a very effective sclerosing agent when applied as slurry via a chest tube or by talc poudrage during thoracoscopy.[142,143] The choice between talc slurry (via chest tube) or talc insufflation (thoracoscopic) usually depends on the medical circumstance and the ability of the patient to tolerate single lung ventilation. In an experimental study, talc was noted to be as efficacious as mechanical abrasion.[144] In a meta-analysis, talc achieved a success rate of 91%.[145] Doses of 3 to 5 grams of graded-sterile talc in 100 to 200 mL of normal saline are felt to be optimal for talc slurry. The potential drawbacks of talc slurry include prolonged pleural drainage and inhomogeneity of deposition. The distribution of talc may lead to loculation and incomplete symphysis. The advantage is that it can be performed easily at the bedside. There are data, however, that suggest an increased incidence of acute respiratory failure and systemic complications associated with the use of talc as a sclerosant. The size of the talc particles (<15 μm) and the dose (>5 g) may be associated with a higher incidence of side effects. A comprehensive literature review[146] revealed an incidence of acute respiratory failure of only 0.15% for patients treated with pharmaceutical-grade talc poudrage.

As an adjunct to surgical therapy, the most commonly employed material is talc. Sterile, asbestos-free talc is insufflated during thoracoscopy or thoracotomy to coat the visceral pleural surface. Typically, 3 to 5 g of talc are used.[145,147] A recent prospective cohort study of video-assisted thoracoscopic surgery (VATS) with talc poudrage evaluated the outcomes in more than 1400 patients with PSP undergoing surgery for recurrent pneumothorax (93%) or persistent air leak (7%).[148] The rate of recurrent pneumothorax was 0.2% in nonsmokers, 4.2% in active smokers, and 3.8% in those with a prolonged air leak.

Mechanical pleurodesis may be performed as part of a surgical procedure. It may consist of simple abrasion of the parietal pleural surface or may entail stripping of the parietal pleura (pleurectomy). The second method has a greater potential for complications, including injury to an intercostal neurovascular bundle or excessive bleeding from the large raw surface area. Also considered in this category is the use of an Nd:YAG laser or an argon beam coagulator, which essentially cauterizes the pleural surface.[149]

The performance of pleurodesis in someone who may need future thoracic surgery is somewhat debatable and relates to the degree of pleural symphysis that can be obtained and the method utilized. Currently, guidelines suggest evaluation for pleurodesis in patients with prolonged air leaks for greater than 4 to 5 days, in those with recurrent pneumothorax, and as part of the treatment of catamenial pneumothorax and pneumothorax associated with HIV.[3,116] Either chemical or mechanical pleurodesis may result in significant adhesion formation. Clearly there is a significant reduction in the incidence of recurrence. However, in some cases, there are concerns that future surgical procedures, such as pulmonary resection, open lung biopsy, and lung transplantation, may be hampered by this degree of pleural symphysis. The application of pleurodesis thus depends on an assessment of the risk of recurrent pneumothorax and the potential morbidity to the patient should a recurrence occur versus the potential for later operative procedures in the thorax. Although prior pleurodesis renders explantation of the native lung more difficult and increases the risk of intraoperative bleeding, it is not a contraindication to subsequent lung transplantation. One suggested compromise is limitation of the pleurodesis to the apical area, as this is the most common location for air leaks to occur. Later thoracic procedures may be done, albeit with more difficulty, by entrance inferior to the area of pleurodesis and subsequent adhesion lysis apically. Localized pleurodesis is not possible when it is performed as an adjunct to tube thoracostomy. A second potential compromise is the use of tetracycline analogues such as doxycycline or minocycline. Experimental studies and anecdotal reports indicate that with the use of tetracycline derivatives, the degree of pleural symphysis and density of adhesions are not as great as with talc or mechanical pleurodesis.[136,137,139,141,144]

■ Operative Therapy

Operative treatment (mechanical pleurodesis with or without stapling of blebs or pleurectomy) is generally thought to be the most effective in assuring expansion of the lung, with complete evacuation of the pleural space, and providing for the best means of reducing the risk of recurrence. In addition, it provides a means of potentially identifying an air leak and closing it. However, increased patient discomfort, risks of general anesthesia, and greater costs of the procedures, combined with moderate success of the less invasive methods, result in restricted application of surgery for pneumothorax.

Operative therapy is indicated in cases in which the abovementioned, less invasive techniques have failed, with persistence or recurrence of the pneumothorax, in cases of protracted air leak, or in some very selective cases of patients with limited pulmonary reserve. This risk of recurrence should include an assessment of the potential morbidity or mortality to the patient should another pneumothorax occur.

Longitudinal studies have indicated that the recurrence rate is approximately 30% after tube thoracostomy alone for treatment of a spontaneous pneumothorax. Among patients in whom the disease recurs once, the subsequent recurrence rate continues to increase.[150] Evidence suggests that a more definitive procedure—namely surgery—is indicated with the first recurrence. In patients with localized lung disease, such as congenital lobar emphysema or a single large bulla, surgery may be indicated for the initial episode of pneumothorax. Patients who have high-risk lifestyles, such as pilots or scuba divers, or patients who may not have ready access to medical care may possess a relative indication for surgical treatment of a first occurrence of spontaneous pneumothorax because of the risk to the patient should a pneumothorax occur. Patients who present with bilateral or tension pneumothorax may also fall in this category of morbidity assessment.

Patients with a pneumothorax from any cause who have a persistent air leak despite prolonged chest tube drainage should also be considered for operative therapy. An air leak that fails to close after 72 to 96 h of suction has a very low chance of closing spontaneously. This is the recommended time for surgical referral.[130] Finally, patients in whom the previous forms of therapy result in incomplete re-expansion of the lung should be considered for surgery. This situation may reflect loculation of the pneumothorax or trapping of the lung by a fibrotic "peel," which will require surgery to be released.

VATS has emerged as the preferred surgical approach when surgical intervention for pneumothorax is required. It is associated with less postoperative discomfort and decreased length of hospital stay compared with standard thoracotomy. The decreased morbidity is the result of the ability to examine the pleural space and manipulate the lung without significant muscle division or rib spreading.[147] In most cases, the technique requires general anesthesia with double-lumen endotracheal ventilation (single lung ventilation). Those patients who are at high risk (elderly or significant underlying lung disease) can undergo this procedure under local and epidural anesthesia.[151] Up to three separate ports are placed in the intercostal spaces to effect installation of the camera as well as manipulating devices. The entire lung can be inspected and a search for the air leak carried out. In general, the apical area is the most common location, and this area can then be closed with the use of a stapler. Stapled resection of bullae also can be performed. In patients with concomitant lung disease, particularly COPD, the staple line can be reinforced with the aid of bovine pericardium to minimize persistence of air leaks.[152] The pleural surface can then be abraded or talc insufflated, as mentioned above, to achieve some degree of pleural adhesion following re-expansion of the lung. Long-term follow-up of recurrence rates has shown results similar to those for open thoracotomy.

The less invasive nature of VATS compared to open thoracotomy has prompted earlier and more frequent surgical referral. While the risks associated with general anesthesia remain, overall costs are generally less than with thoracotomy owing to shorter hospital stay. The cost of VATS as an initial procedure for spontaneous pneumothoraces may be less in the course of the treatment of the disease compared with more conservative therapies for both PSP and SSP.[153] These conclusions, however, are not based on prospective randomized trials and should be verified in larger prospective studies.

Open Thoracotomy

Although VATS has supplanted thoracotomy as the surgical treatment of pneumothorax in many institutions, open thoracotomy remains a valuable option in the treatment of complicated cases.

Thoracotomy allows examination of the lung for the site of an air leak, enables lysis of previous adhesions that may lead to a loculated pneumothorax, and enables the release of a fibrotic peel that occasionally forms, leading to incomplete re-expansion of the lung. Recurrence rates are generally less than 2%.[154] Drawbacks include the potential risks associated with general anesthesia, increased costs, and the significant amount of patient discomfort. Discomfort is generally most severe with a standard lateral or posterolateral thoracotomy with muscle division and rib spreading.

In an effort to minimize the level of discomfort, variations have been developed, including the use of smaller incisions, the so-called muscle-sparing thoracotomies, and the axillary thoracotomy. Lung examination and air leak closure and possible pleurodesis or pleurectomy can then still be performed.[154]

SUGGESTED GUIDELINES FOR MANAGEMENT

Based on the relative efficacy of the various forms of therapy combined with relative risks for the major categories of pneumothorax, the following guidelines are suggested.

■ Primary Pneumothorax

Patients with a first-time uncomplicated PSP can be treated with observation or with interventional management. Observation should include a minimum of 4 to 6 h of observation and documentation that the patient's pneumothorax does not increase in size and the patient is able to walk comfortably, is physiologically stable, and does not require supplemental oxygen. Initial interventional management can include simple aspiration or placement of a small 8 to 10 French catheter. Subsequent small-tube thoracostomy is indicated for failure of simple aspiration or observation (enlarging pneumothorax, persistent tachypnea >30 breaths per minute, saturation $<90\%$ on room air). Patients not requiring hospitalization should be discharged with analgesia and close follow-up with repeat chest radiograph.[155]

Patients who undergo successful tube thoracostomy with complete lung re-expansion and absence of an air leak may opt for a chemical pleurodesis while the chest tube is in place. Since the risk of recurrence is low (approximately one in five), most physicians recommend patients in good general health defer this procedure until a second pneumothorax occurs. Patients with persistent air leaks for more than 72 to 96 h after insertion of a chest tube should be referred for surgical therapy. Because of the progressive increase in risk of recurrence, patients with their first recurrence of a primary pneumothorax should undergo chemical pleurodesis or be referred for surgical therapy, preferably VATS, with stapling of any air leak and pleural abrasion or chemical pleurodesis.

■ Secondary Pneumothorax

In general, therapy for secondary pneumothorax should be more aggressive because of the higher rate of recurrence due to the underlying lung pathology. Specific conditions with pneumothorax as a common occurrence are as listed below.

COPD

Most cases of pneumothorax in patients with COPD should be treated with tube thoracostomy. In patients who are not good surgical candidates, chemical pleurodesis with a tetracycline derivative (minocycline or doxycycline) or talc should be performed once there is complete re-expansion and absence of an air leak. In COPD patients who are good surgical candidates or in patients with a persistent air leak longer than 72 to 96 h, more aggressive therapy should be considered.[47] Recommended therapy includes VATS or thoracotomy with talc insufflation, mechanical pleurodesis, stapling resection, and/or pleurectomy. This approach provides a more effective way of achieving a lower risk of recurrent pneumothorax.

Cystic Fibrosis (CF)

Although there are no clinical trials to guide therapy in patients with CF and pneumothorax, retrospective reports offer suggestions for management. Clinically stable patients with small pneumothoraces may be followed with observation. Clinical instability or large pneumothorax requires chest tube placement. Pleurodesis should be considered after recurrence of a large pneumothorax. Surgical pleurodesis is associated with fewer recurrences in the CF population and is the preferred modality. Noninvasive positive-pressure ventilation, positive expiratory pressure devices, and intrapulmonary percussive ventilation should be stopped until the pneumothorax has resolved, but aerosols need not be held. Because of the future possibility of lung transplantation for patients with CF, localized pleurodesis is recommended as an adjunct to surgical closure of the air leak.[49,50]

AIDS

For most patients with AIDS who present with a pneumothorax, tube thoracostomy is the primary mode of initial treatment. Because of the high primary and secondary treatment failure rates, patients who have no air leak with complete lung re-expansion should undergo talc slurry pleurodesis. For patients with a persistent air leak who are deemed to be poor surgical risks because of severe debilitation, a Heimlich valve may be utilized. For patients who are deemed good risks for surgery, VATS with talc insufflation is recommended.[56]

Other Conditions

While there are insufficient data to make firm recommendations for all situations, some suggestions are offered. Patients with pneumothorax secondary to iatrogenic causes may be treated with observation or aspiration according to the guidelines previously listed. In patients who have a small traumatic pneumothorax (<35 mm on CT scan), simple observation can be considered. Tube thoracostomy should be considered in patients with larger pneumothorax, those with hemopneumothorax, and patients with limited physiologic reserve. Patients who experience a pneumothorax while on positive-pressure ventilation should usually have tube thoracostomy placement to avoid progression to a tension pneumothorax.[156] Patients who present with bilateral pneumothoraces or a tension pneumothorax, but who are not on positive-pressure ventilation, should have placement of tube thoracostomy. Further therapy with regard to chemical pleurodesis versus surgery is dependent on underlying lung pathology.

Persistent Air Leak

A persistent air leak is usually caused by a broncho- or alveolopleural fistula.[157] In more recent literature, it is generally accepted to be present if an air leak lasts more than 5 days,[157,158] although definitions vary among different authors. Initial conservative management is advised by most guidelines. Some persistent air leaks take as long as 14 days to resolve without surgical interventions.[3] A retrospective study showed that 97% of patients with primary spontaneous pneumothorax resolved at around this time frame.[159] Patients with underlying disease may take longer. The use of Heimlich valves has been recommended by guidelines as a conservative measure as an option in this setting prior to more invasive options (Fig. 79-13). Persistent air leaks can result in increased morbidity, prolonged hospitalization, and increased health care costs to the patient and often require surgical intervention in patients with SSP and adequate pulmonary reserve.[160] In general, guidelines recommend observation for at least 4 days before surgical evaluation to close the air leak.[116] Surgical interventions can be performed by thoracotomy or thoracoscopically. As mentioned above, these interventions include chemical or mechanical pleurodesis; oversewing or stapling the air leak; creating muscle, omental or pericardial flaps; or occasionally lobectomy.[161] The success rate of surgical closure for bronchopleural fistulas has been reported to be between 80% and 95% but carries additional operative risk.[158] Because of limited pulmonary reserve, many patients may not be operative candidates.

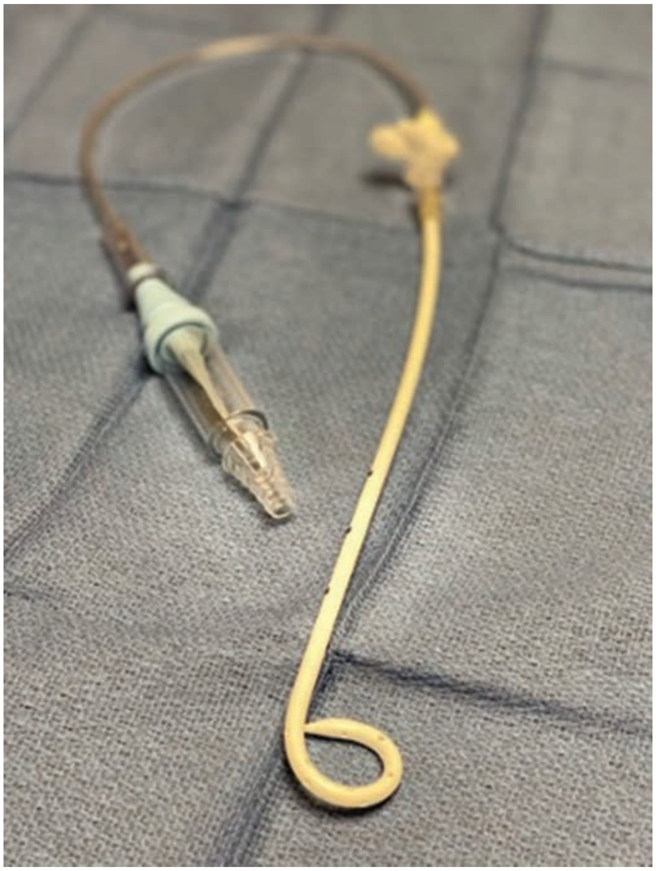

Figure 79-13 A Heimlich valve attached to a pig-tail chest tube catheter.

In patients who are not surgical candidates, several less invasive procedures can be tried. Perhaps the least invasive procedure is the use of an autologous blood patch. Usually, 50 to 100 mL of venous blood is instilled through the chest tube and flushed with 10 mL of normal saline. Elevating the chest tube about 2 feet above the chest allows the blood to remain in the pleural space. The chest tube should not be clamped since the presence of a persistent air leak could result in a tension pneumothorax. According to a review of the literature, a blood patch pleurodesis was effective in approximately 90% of patients;[162] however, in our experience, the success rate is significantly lower.

Chemical agents have also been instilled into the pleural space to seal a persistent air leak. The technique used is similar to that used for an autologous blood patch. Tetracycline derivatives have been shown to be safe in an animal model of pleural air leaks and did not induce an inflammatory reaction in the lung. A retrospective study of PSP patients and persistent air leak showed a success rate of 63%; however, long-term follow-up to determine recurrence was not reported.[163] The safety of using talc in patients with persistent air leaks has not been defined. A retrospective study in patients with air leaks after surgical lung resection used talc in most of their patient population and reported a success rate of greater than 95%.[160] Since talc has been associated with acute lung injury, we believe further studies demonstrating safety are required before it can be recommended.

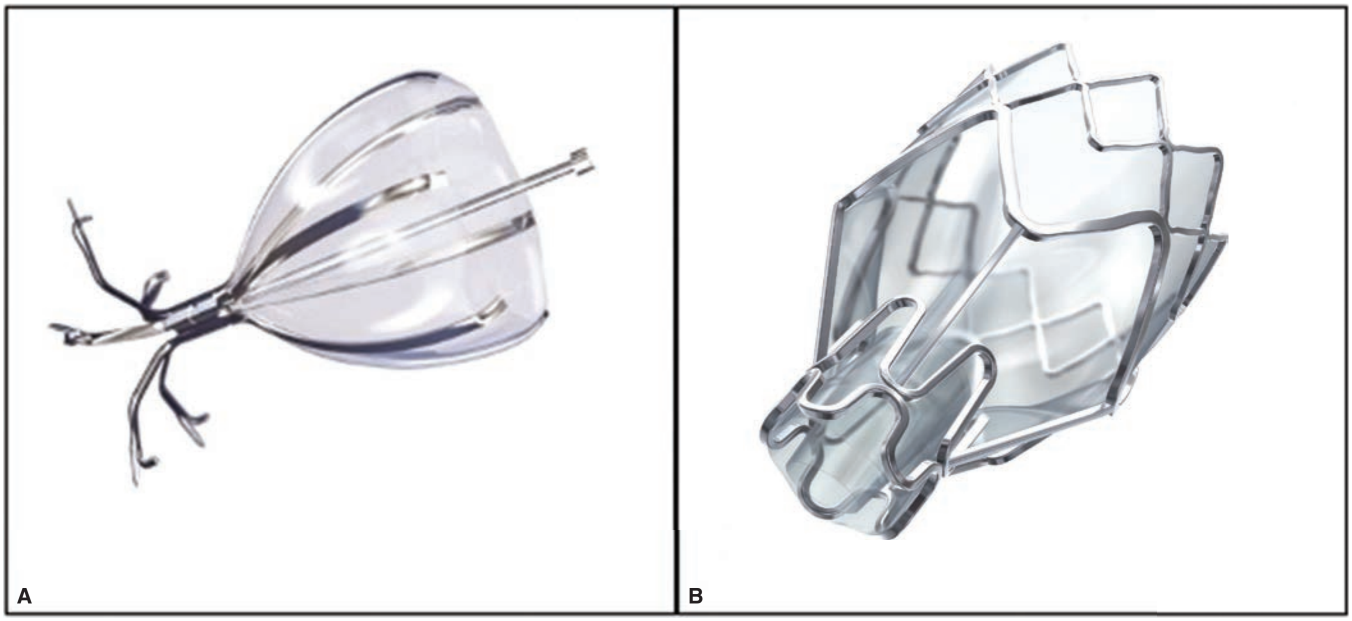

Figure 79-14 Available bronchial valve systems in the United States. **A.** Spiration Valve System (SVS). **B.** Zephyr Valve PulmonX Corporation. (***A.*** *Image courtesy of Olympus America Inc, Center Valley, PA.* ***B.*** *Reproduced with permission from PulmonX Corporation, Redwood City, CA.)*

Current guidelines do not recommend considering bronchoscopic approaches as first-line treatment in the management of persistent air leaks. However, since the publication of these guidelines, endobronchial techniques such as endobronchial one-way valves have been developed and utilized for persistent air leaks, especially in postsurgical patients (Fig. 79-14). A retrospective multicenter study[164] showed successful valve implantation in 91% of patients with complete resolution of air leak in 88%, reduction of air leak in 9%, and no benefit in 3%. A systematic review[161] with more than 200 SSP patients undergoing placement of endobronchial valve placement for persistent air leaks revealed complete resolution rates ranging from 47.5% to 100% with an observed recurrence of 9%. Unfortunately, there are no randomized clinical trials exploring the benefit of one-way endobronchial valves, and the current cost of endobronchial valves is significant.

Air Travel

The U.S. Federal Aviation Administration (FAA) guidelines require commercial airlines to be pressurized to an equivalent of 2438 m (8000 ft) at the maximum operating altitude ("cabin altitude").[165] Due to pressure–volume relationships from Boyle's law, it is estimated that the volume of residual pneumothorax can expand by as much at 38% at this altitude compared with sea level.[166] This has been postulated to occur in the air trapped in blebs or bullae as well, predisposing these patients to pneumothorax in flight.[167] Most recent guidelines recommend that patients should obtain a chest x-ray to confirm resolution of pneumothorax before flight, and wait an additional 7 days (or 14 days, in the case of traumatic pneumothorax) before flying.[166] However, these recommendations are based largely on expert opinion and available case reports. Patients found to have bullae or blebs, and those with cystic lung diseases including lymphangioleiomyomatosis and Birt-Hogg-Dubé syndrome, are considered higher risk for in-flight pneumothorax.[167] Overall, it is important for clinicians to discuss the risk of air travel in patients who are at risk for spontaneous pneumothorax and to explain the potential options to prevent recurrence in all patients with either primary or secondary spontaneous pneumothoraces.

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PART 10

Diseases of the Mediastinum

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CHAPTER 80

Nonneoplastic Disorders of the Mediastinum

Luis F. Tapias
Cameron D. Wright

INTRODUCTION

The mediastinum may be the site of a variety of neoplastic (Chapter 82) and nonneoplastic disorders. In this chapter, we first describe the anatomy of the mediastinum, including its boundaries, compartments, and distribution of lymphatics. We then consider the important clinical entities of pneumomediastinum, acute mediastinitis, and chronic mediastinitis before concluding with a discussion of spontaneous mediastinal hemorrhage.

ANATOMY OF THE MEDIASTINUM

The boundaries defining the mediastinum, as well as its subdivisions or compartments, and important anatomic considerations regarding mediastinal lymphatics are discussed below.

Boundaries

The mediastinum is defined as the potential space between the two pleural cavities bounded by the sternum anteriorly, the vertebral column posteriorly, the thoracic inlet superiorly, and the diaphragm inferiorly (Fig. 80-1).[1] The major mediastinal structures are the heart and great vessels, the trachea and main bronchi, and the esophagus, all closely related to one another and connected by loose connective tissue. Also present are the thymus, lymph nodes, nerves, and fat. Hence, air or infection can disseminate widely throughout the mediastinal space, contained laterally only by the mediastinal pleural reflections. The mediastinum communicates with both the neck and the retroperitoneum, and these portals can also serve as routes of egress from the mediastinum. Fascial planes connect the neck, mediastinum, and retroperitoneum and thus facilitate movement of air or infection from one location to another.

Compartments

Several subdivisions of the mediastinum have been emphasized in the surgical and radiologic literature, but there is no consensus. Most often, three compartments are proposed: anterior, middle (visceral), and posterior (paravertebral sulcus) (Fig. 80-2).[2] The boundaries of these divisions are not agreed upon, further emphasizing their nonanatomic origins. Shields proposed a simple three-compartment subdivision in 1972 that makes both anatomic and surgical sense. Each of these compartments extends from the thoracic inlet superiorly to the diaphragm inferiorly. The anterior compartment is bounded by the sternum and the anterior surface of the pericardium and great vessels. The middle (visceral) compartment extends from the posterior limit of the anterior compartment to the anterior surface of the vertebral columns. The posterior compartment (paravertebral sulcus) extends from the anterior surface of the vertebral column to the anterior surface of the paravertebral ribs. The structures in these compartments are listed in (Table 80-1). The pericardial sac is the only true compartment of the mediastinum, and it provides a strong barrier to infection. Subdividing the mediastinum into compartments proves most helpful when one is interpreting a plain radiograph that shows a

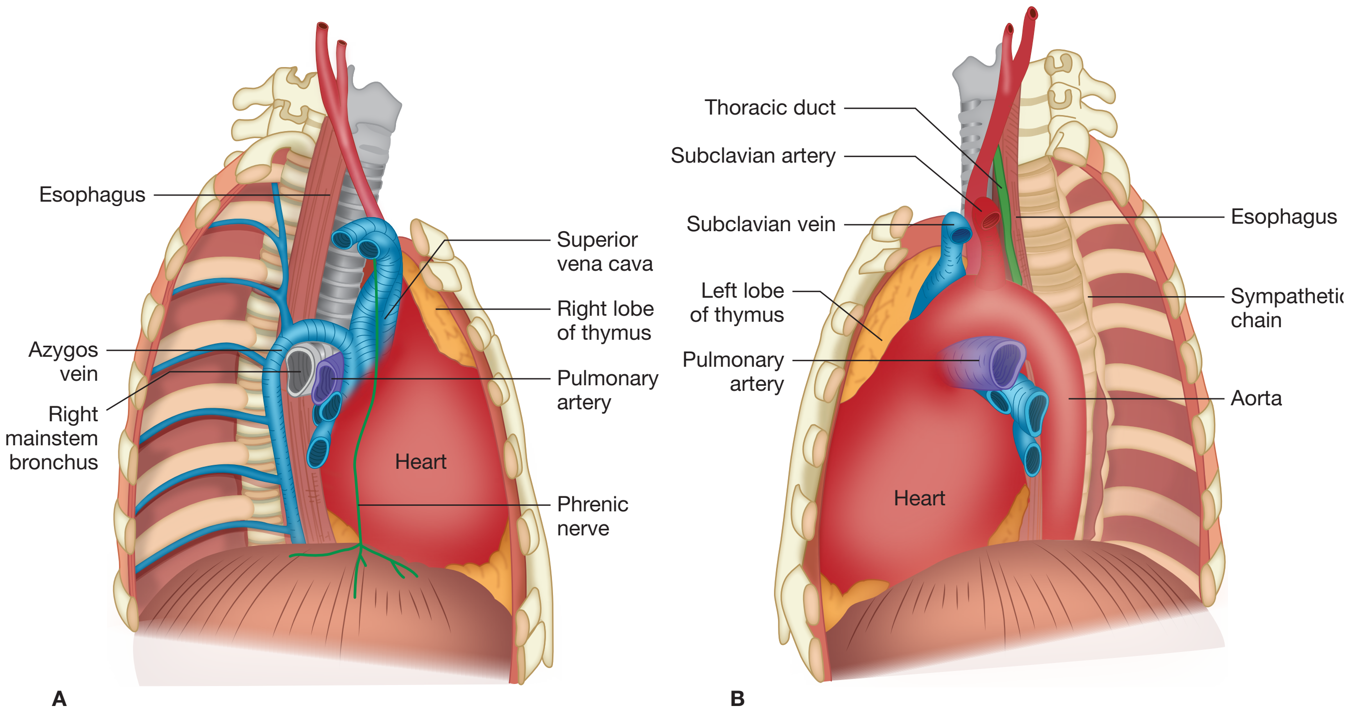

Figure 80-1 **A.** Lateral view of the mediastinum as seen through a right thoracotomy. **B.** Lateral view of the mediastinum as seen through a left thoracotomy. *(Reproduced with permission from Shields TW: Mediastinal Surgery. Philadelphia, PA. Lea & Febiger; 1991.)*

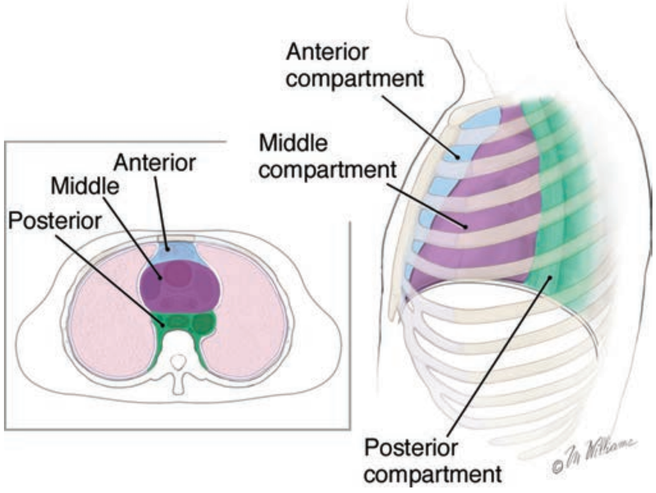

Figure 80-2 The mediastinum is divided into three compartments: anterior, middle, and posterior. This is particularly useful when dealing with mediastinal tumors for the convenience of diagnosis and surgical approach. *(Reproduced with permission from Marcia Williams.)*

mediastinal mass. Knowledge of the contents of the involved compartment facilitates arriving at a proper diagnosis. However, due to the lack of true anatomic boundaries, it should be emphasized that diseases or masses of the mediastinum often extend from one compartment to another.

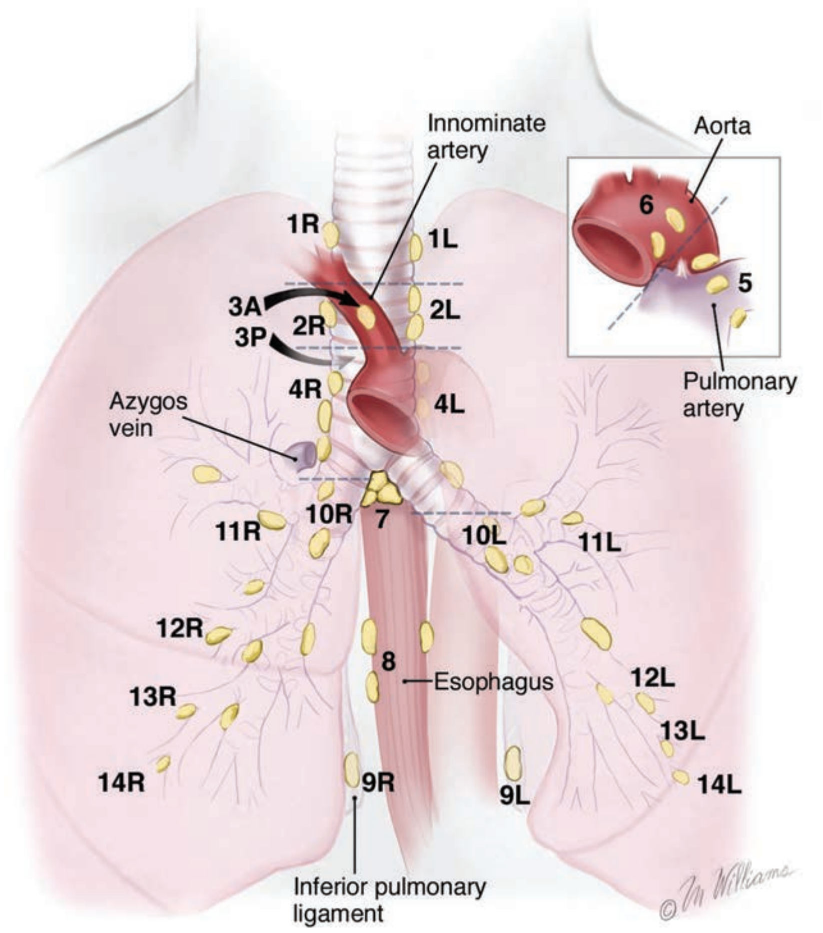

Figure 80-3 Lung cancer lymph node stations map. Note that any double-digit numeral is considered N_1 disease. A, anterior; L, left; P, posterior; R, right. *(Reproduced with permission from Marcia Williams.)*

TABLE 80-1 Contents of Mediastinal Compartments

Anterior	Middle	Posterior
Thymus gland	Pericardium	Azygos and hemiazygos veins
Pericardial fat	Heart	
Lymph nodes	Trachea and main bronchus	Thoracic duct
	Esophagus	Sympathetic trunk
	Aorta	
	Phrenic and vagus nerves	Intercostal nerves
	Lymph nodes	

■ Lymphatics

The mediastinal lymphatic system is quite complex and variable. Mediastinal lymph nodes are interconnected; thus, involvement of one group of lymph nodes in a pathologic process frequently leads to involvement of other groups. Similar to subdividing the mediastinum into compartments, naming individual nodal stations is somewhat arbitrary and leads to the mistaken notion that these nodal stations are discrete. To the contrary, the mediastinum is covered in a dense network of lymphatic vessels and lymph nodes with no predictable boundaries. Nonetheless, there are commonly accepted nodal stations that have clinical importance, especially in the staging of thoracic malignancies, particularly lung cancer. The lymph node map proposed by Naruke in 1978 has been widely accepted and serves as a standard for communication of lymph node involvement (Fig. 80-3).[3] Briefly, lymph node stations denominated by a single digit (i.e., stations 1 through 9) correspond to true mediastinal lymph nodes, whereas stations denominated by two digits (i.e., stations 10 and above) correspond to lymph nodes that are within the pleural sac and thus are extramediastinal.

PNEUMOMEDIASTINUM

Pneumomediastinum (mediastinal emphysema) is an uncommon condition characterized by the accumulation of air or gas in the mediastinum. Depending on the cause, management may be expectant or may involve specific treatment directed at the underlying abnormality.

■ Anatomic Considerations

Pneumomediastinum is frequently associated with other forms of extra-alveolar air, including pulmonary interstitial emphysema, pneumopericardium, pneumothorax, subcutaneous emphysema, pneumoretroperitoneum, and pneumoperitoneum. The key to understanding the distribution of extra-alveolar air lies in the recognition of the common fascial planes that unite these areas. In the neck, the deep layer of the deep cervical fascia ensheathes the trachea and esophagus as they descend into the mediastinum. The trachea and esophagus are thus enclosed in this visceral space; therefore, air can readily travel from the mediastinum to the neck or retroperitoneum (Fig. 80-4).[4] This fascial plane extends into the hilum of the

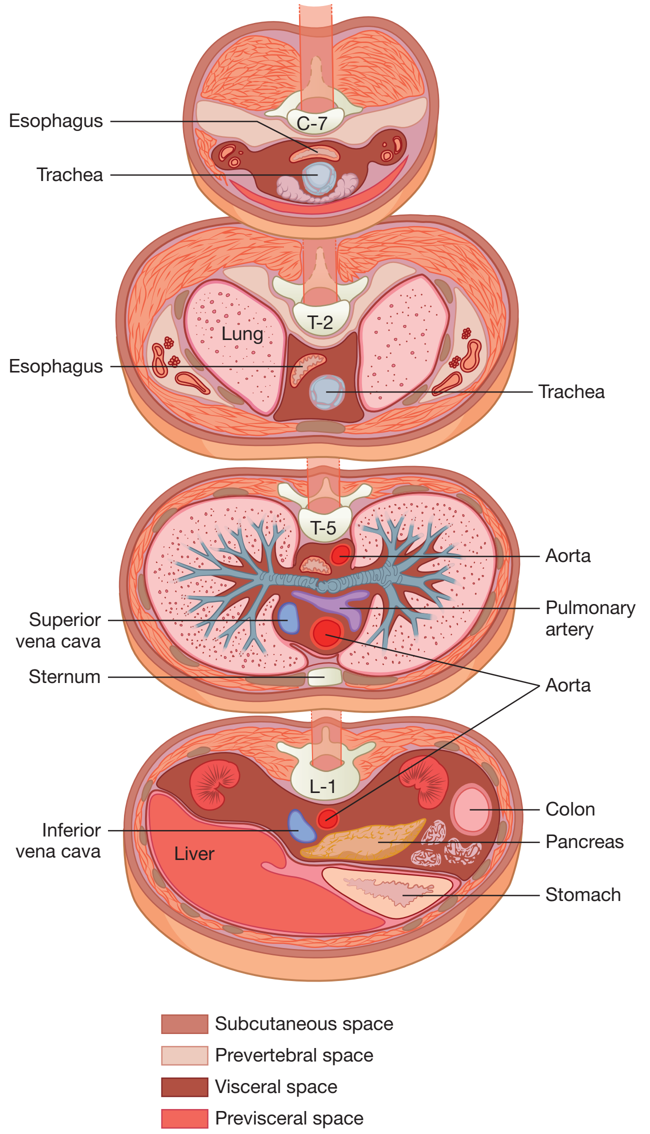

Figure 80-4 Soft tissue compartments of the neck, thorax, and abdomen demonstrating continuity of visceral space between regions.

lung and merges with the bronchovascular sheaths that surround the terminal bronchioles, arteries, and veins. The bronchovascular sheath also merges with and is continuous with the pericardium. After alveolar rupture, air enters the perivascular interstitium and dissects proximally within the bronchovascular sheath toward the mediastinum (Fig. 80-5). Air can then enter the pericardial space, resulting in pneumopericardium, or it may dissect along the adventitia of the great vessels (Fig. 80-6). More commonly, mediastinal air can decompress by extension into the cervical, subcutaneous, and retroperitoneal spaces. A pneumomediastinum that ruptures into the free pleural space results in a pneumothorax. Pneumothorax may also result from air dissecting out toward the visceral pleural surface of the lung and rupturing. Macklin, in 1944, in an elegant experimental cat model, confirmed this theory of progression of extra-alveolar air following alveolar rupture.[5] Pneumomediastinum usually results from a ruptured alveolus due to a Valsalva maneuver or mechanical ventilation. There are many other possible sources, however, that must be considered when the physician has to manage a patient with pneumomediastinum (Table 80-2). Dental procedures, especially those on the mandible with the addition of compressed air to maintain a clear field, are an occasional cause of mediastinal emphysema.

TABLE 80-2 Etiology of Pneumomediastinum

- Upper respiratory tract
  - Head and neck infection
  - Fracture of facial bones
  - Trauma to hypopharynx and larynx (especially intubation)
  - Dental procedures (especially mandibular)
- Lower respiratory tract
  - Trauma
  - Bronchoscopy, especially therapeutic bronchoscopy (i.e., YAG laser, rigid core-out, dilation, and transbronchial biopsy)
- Lung
  - Trauma
  - Surgery
  - Spontaneous alveolar rupture
    - Straining and Valsalva maneuver
    - Local airway obstruction
    - Scuba diving
    - Mechanical ventilation
- Gastrointestinal tract
  - Esophageal perforation
  - Perforated viscus
- Infection
  - Acute mediastinitis
  - Descending necrotizing mediastinitis
- Air from outside the body
  - Trauma
  - Surgery (especially mediastinoscopy, tracheostomy, and sternotomy)
  - Pneumoperitoneum (especially with laparoscopic hiatus hernia repair)

Spontaneous Pneumomediastinum

Idiopathic spontaneous pneumomediastinum is a rare self-limited condition that most commonly affects young adult men. Hamman is credited with the original description of this entity in 1939, including the characteristic crepitation synchronous with the heartbeat heard in these patients (Hamman sign).[6] The majority of patients with spontaneous pneumomediastinum have predisposing factors that cause increase in airway pressure, which leads to alveolar rupture.[7–9] Most commonly, this results from straining against a closed glottis (i.e., the Valsalva maneuver) as during vomiting, coughing, or exercising. Other mechanisms include sudden and/or severe increases in lung volume, as occur during marijuana smoking, vaping, inhaling of cocaine, or during anxiety attacks or seizures. Activities that involve environmental pressure changes, like diving, have been reported in association with pneumomediastinum. Localized airway obstruction from tumor, foreign bodies, asthma, or parenchymal lung disease also can cause alveolar rupture. An accurate history is most important to define the mechanism in a particular patient.

Macia and colleagues[8] reported an incidence of spontaneous pneumomediastinum of 22 cases per 1,000,000 emergency

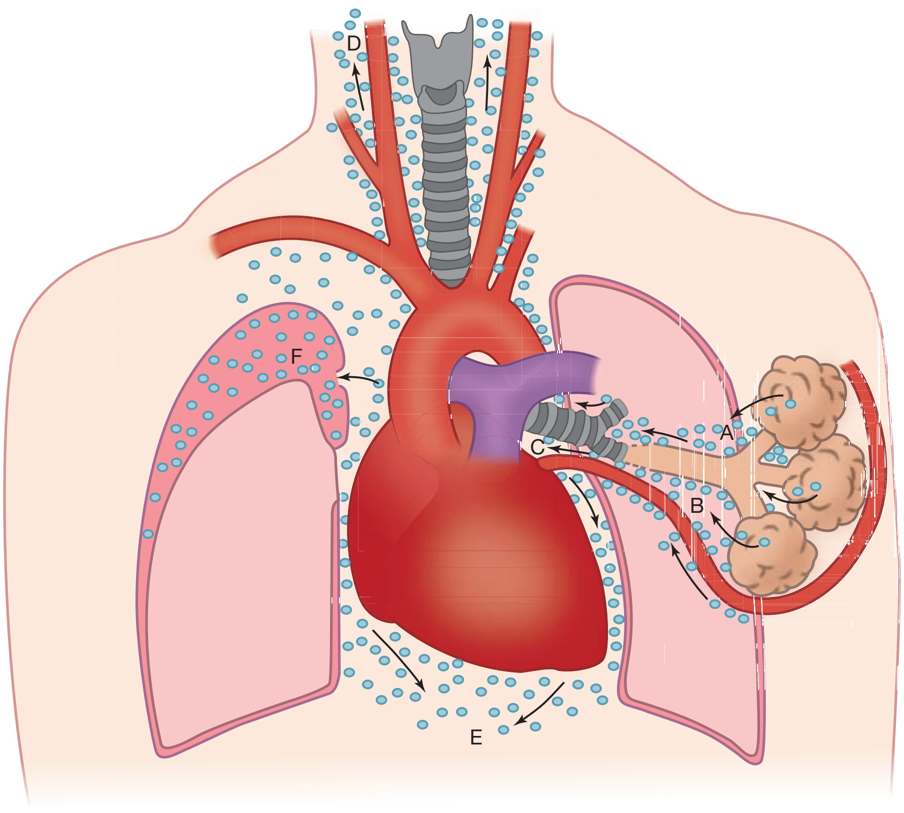

Figure 80-5 Possible routes of air following alveolar disruption. Air from the alveolus (**A**) enters the perivascular interstitium (**B**), dissecting proximally within bronchovascular sheaths toward the mediastinum (**C**). As mediastinal pressure rises, decompression occurs in cervical (**D**), subcutaneous, and retroperitoneal (**E**) soft tissue spaces. A pneumothorax is possible if the pleura (**F**) is ruptured.

department visits. Spontaneous pneumomediastinum almost always presents with substernal pain, often pleuritic, which may radiate to the neck or back. Additional symptoms that may occur, either separately or in combination, include dyspnea, dysphagia, odynophagia, and dysphonia. Air in the subcutaneous tissues of the neck produces a characteristic change in voice quality, a higher-pitched nasal tone that the experienced clinician easily recognizes. Examination often reveals palpable subcutaneous emphysema in the neck. Auscultation of the chest may reveal a crunching or clicking sound heard over the pericardium, synchronous with the heartbeat (Hamman sign). Low-grade fever is present in about one-third of cases and mild leukocytosis in about one-half. Nonspecific electrocardiographic changes, such as ST-T wave changes and ST elevation, also may be present. A chest radiograph usually demonstrates a thin radiolucent strip along a mediastinal fascial plane, most commonly along the left heart border. The aortic knob may be highlighted as well (Fig. 80-6). Computed tomography (CT) is more sensitive in detecting air than are plain radiographs (Fig. 80-7) and can provide information on alternative diagnoses. Air may be evident deep in the neck as well as in the subcutaneous tissue.

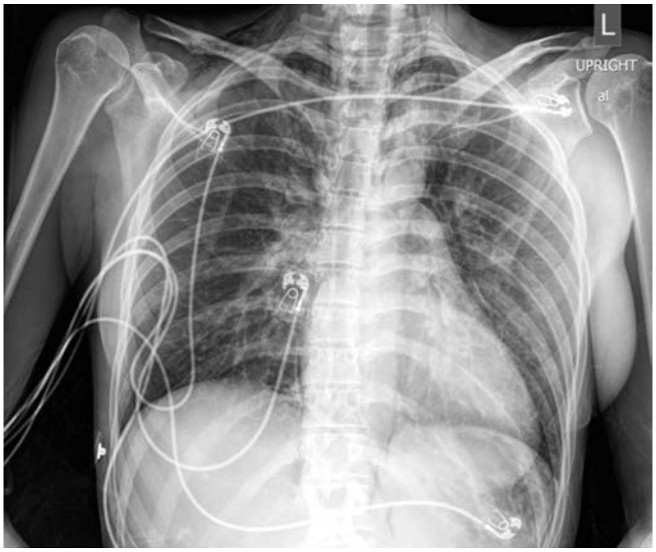

Figure 80-6 Chest radiograph of a patient with spontaneous mediastinal emphysema. Mediastinal air is seen along the right heart border and the upper mediastinum tracking into the neck.

The differential diagnosis is broad and includes musculoskeletal, pleural, pulmonary, tracheobronchial, cardiac, and esophageal causes. Although most patients who present are not acutely ill, an occasional patient may suffer an acute, catastrophic onset with hypotension and hemodynamic compromise. Esophageal perforation is the condition most likely to be confused with spontaneous pneumomediastinum. Worrisome features suggestive of esophageal perforation include recent esophageal instrumentation, a history of esophageal problems, severe retching, the presence of a pleural effusion or mediastinal fluid on CT imaging, or shock. Bakhos et al.[10] showed that patients with pneumomediastinum secondary to esophageal perforation are older (58 vs. 19 years), have a higher white blood cell count (15×10^3 vs. 12×10^3), and more frequently present with pleural effusions on imaging (54% vs. 0%) when compared with patients with spontaneous pneumomediastinum. In a review of 249 patients with pneumomediastinum on chest radiography or CT, Potz et al.[11] found that 24 patients (10%) had an esophageal perforation. Factors associated with the presence of esophageal perforation were older age (63 vs. 25 years), history of hemoptysis, presence of a pleural effusion, and leukocytosis (18.1×10^3 vs. 10.9×10^3). A contrast esophagogram should be obtained immediately if there is any question of an esophageal perforation, since a delay in making this diagnosis often proves fatal. A high index of suspicion regarding esophageal perforation should always be present whenever a patient presents with mediastinal emphysema.

Treatment of spontaneous pneumomediastinum is supportive and is primarily directed at pain relief and reassurance. Appropriate management of contributing causes such as foreign bodies, asthma, and parenchymal lung disorders should be instituted. The patient should be followed both clinically and radiographically to exclude another cause for mediastinal emphysema and to detect a possible pneumothorax. Prompt resolution is the rule. Supplemental oxygen to hasten reabsorption (similar to that proposed for pneumothorax) has been reported but is probably not necessary. Needle aspiration

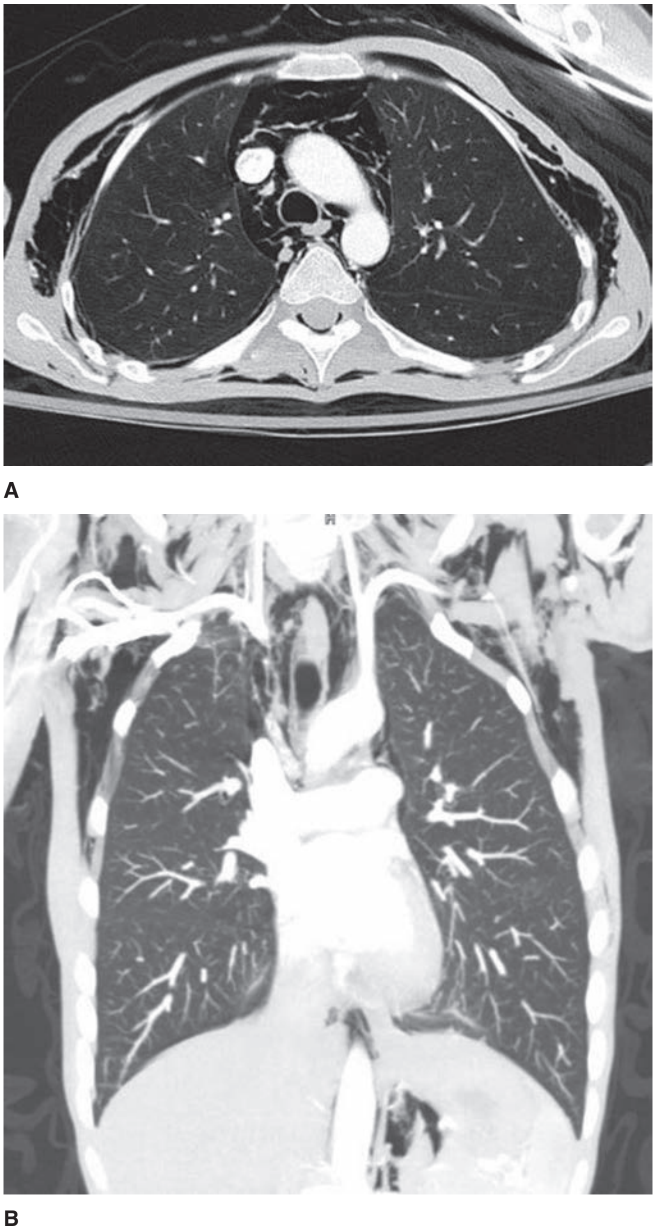

Figure 80-7 **A.** Axial CT scan image illustrating classic mediastinal emphysema from spontaneous pneumomediastinum. **B.** Coronal CT image again illustrating mediastinal emphysema.

or skin incision to relieve subcutaneous emphysema is almost never necessary and is discouraged. Prophylactic tube thoracostomy is unnecessary. However, a concomitant pneumothorax can occur and may require intervention to evacuate air and re-expand the lung. For patients who present with minimal findings and a clear inciting factor (such as coughing), only a short period of observation in the emergency department is required. Some patients require admission for a short period of pain control and observation, with an excellent prognosis. Recurrence is rare.

A recent large case series reinforces these principles. Iyer et al.[9] reported on 62 adult patients with spontaneous pneumomediastinum over an 11-year period at a large academic medical center. The median age was 30, and 66% were men. Pre-existing lung disorders were identified in 44% of patients, including interstitial lung disease (18%), asthma (15%), bronchiolitis obliterans syndrome (8%), bronchiectasis (8%), chronic obstructive pulmonary disease (8%), primary or metastatic lung malignancy (6%), and cystic lung lesions (3%). Precipitating factors were clearly identified in only one-third of cases and included inhalational drug use (10%), upper respiratory infection with coughing (8%), asthma exacerbation (6%), severe retching (6%), and athletic activities (3%). Common symptoms included chest pain (63%), cough (45%), dyspnea (44%), neck pain (18%), light-headedness (18%), dysphagia (5%), and dysphonia (5%). Common signs included subcutaneous emphysema (45%). Hamman sign was not observed in this series, although it was reported in 12% of cases in another published series.[8] Simple chest radiographs demonstrated pneumomediastinum in 90% of patients imaged. In the other 10%, the diagnosis was reached by CT of the chest; in half of these patients, the volume of pneumomediastinum was too small to be detected with chest radiography. A concomitant pneumothorax was identified in one-third of patients; however, only a minority required placement of a chest tube. Additional diagnostic procedures were performed in 44% of patients to exclude aerodigestive injuries as the cause of the pneumomediastinum. Investigations included contrast esophagography (35%), bronchoscopy (6%), and esophagogastroduodenoscopy (3%). In all cases, findings were normal. Median length of stay was 2.5 days, and all patients were treated with supportive care. After a median follow-up of 6 months, only 1 patient (2%) experienced recurrence of pneumomediastinum, which was attributed to persistent inhalational drug use.

■ Pneumomediastinum Associated with Mechanical Ventilation

Mechanical ventilation is commonly associated with pneumomediastinum and may lead to life-threatening tension pneumothorax. Alveolar rupture results from high peak inspiratory pressures, which increase alveolar pressures in patients with abnormal airways or parenchyma (decreased compliance). Classic predisposing factors include high tidal volumes, high levels of positive end-expiratory pressure (PEEP), and patient–ventilator dyssynchrony. Air trapping with occult positive end-expiratory pressure (auto-PEEP) is an underrecognized cause of barotrauma. It is not clear if a particular mode of ventilation (pressure-controlled vs. volume-limited) is associated with a decreased incidence of barotrauma. Pneumomediastinum associated with mechanical ventilation has been observed recently in approximately 10% of patients in the setting of the coronavirus disease 2019 (COVID-19) pandemic caused by infection with SARS-CoV-2,[12] which has resulted in an unprecedented number of patients requiring invasive mechanical ventilation. Similar rates of pneumomediastinum associated with mechanical ventilation were observed during the SARS-CoV-1 outbreak in 2003 (12%).[13]

Unlike spontaneous mediastinal emphysema, pneumomediastinum occurring in a patient on mechanical ventilation is potentially catastrophic because of its frequent association with tension pneumothorax. The chest radiograph should be closely examined to detect even a small pneumothorax, and if such is present, tube thoracostomy should be promptly performed. Obviously, a sudden deterioration marked by hypotension and increased pulmonary pressures should prompt immediate attention with insertion of unilateral or bilateral chest tubes, depending on the clinical examination. The issue of inserting a tube prophylactically is controversial if pneumomediastinum without pneumothorax is identified. At a minimum, a thoracostomy tray should be kept at the patient's bedside. Removing the patient from mechanical ventilation as soon as possible is an ideal way of mitigating risk of barotrauma. Since this is seldom possible, efforts should be directed at minimizing alveolar distention. These efforts include relief of bronchospasm, optimizing sedation to minimize "fighting" the ventilator, reducing tidal volume and PEEP, and manipulation of inspiratory flow and timing to reduce auto-PEEP.

Pneumopericardium

Pneumopericardium as a form of barotrauma is much more frequent in neonates, presumably due to immature fascial planes. Hemodynamically significant tamponade is also much more likely to occur in infants than adults and has resulted in collapse and death. Pericardial drainage with a subxiphoid tube should be performed promptly in the neonate. In the adult, drainage should be performed only if there is hemodynamic embarrassment.

ACUTE MEDIASTINITIS

Acute mediastinitis is a life-threatening disorder that causes severe morbidity in the afflicted patient. All three mediastinal compartments can be affected: the anterior compartment most commonly after sternotomy for cardiac surgery, the middle compartment usually from esophageal perforation, and the posterior compartment from direct extension from the neck, lung, or spine. Iatrogenic perforation of the esophagus secondary to instrumentation is the most common cause of acute mediastinitis in the United States.

Mediastinitis from Esophageal Perforation

Instrumental perforation of the esophagus now accounts for more than one-half of all esophageal perforations.[14] Perforation is more common after rigid esophagoscopy, dilation of a stricture, and pneumatic dilation for achalasia, but it also occurs after variceal sclerosis, esophageal tube placement (nasogastric, Sengstaken–Blakemore, and stents), and simple flexible esophagoscopy. Boerhaave syndrome (post-emetic rupture) was first described in 1724 but still represents a diagnostic challenge and remains a major consideration in patients with otherwise unexplained mediastinitis (Fig. 80-8). Instrumental perforation of the esophagus most frequently is localized to the cervical esophagus, whereas Boerhaave syndrome usually results in perforation of the distal thoracic and abdominal esophagus.

Patients with mediastinitis due to esophageal perforation usually present with the abrupt onset of severe substernal chest pain. In cases of Boerhaave syndrome, onset of pain is preceded by forceful vomiting or retching. Dyspnea is common even in the absence of pneumothorax. Shock may ensue quickly, and the patient usually appears gravely ill. Examination reveals tachypnea, tachycardia, fever, hypotension, splinting of the chest and abdomen, and cervical emphysema. Radiographic findings include cervical or mediastinal emphysema, pneumothorax, and pleural effusion. A contrast esophagogram (usually with water-soluble contrast) should be performed immediately when the diagnosis is suspected, but one should be aware that this study has a false-negative rate of 10%. A chest CT scan is the next best study in a patient in whom esophageal perforation is suspected but who has a negative esophagogram. Prompt diagnosis and, therefore, a high index of suspicion are essential, as the frequency of complications and the mortality rate are directly dependent on the time elapsed between perforation and treatment.[15] The differential diagnosis is broad and includes perforated ulcer, acute pancreatitis, myocardial infarction, pneumonia, aortic dissection, and pulmonary embolism.

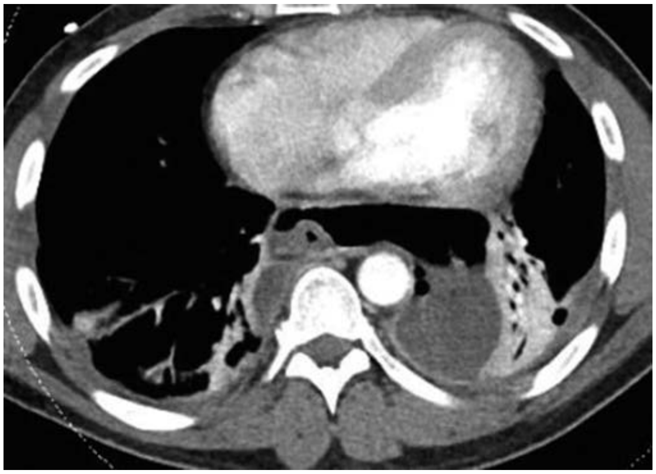

Figure 80-8 CT image of a patient with a delayed diagnosis of a post-emetic esophageal rupture. There is extensive air surrounding the lower esophagus with bilateral loculated effusions and left lower lobe atelectasis.

Treatment should be instituted urgently and involves surgical debridement of necrotic tissue, secure closure of the perforation, correction of any distal obstruction, and wide drainage, usually performed through a left thoracotomy.[16] Recently, management of esophageal perforations with covered esophageal stents and image-directed percutaneous drainage has gained traction and is a widely accepted treatment strategy.[17,18] However, esophageal stents have a higher failure rate in cases of perforations of the cervical esophagus or gastroesophageal junction and in perforations greater than 6 cm in length.[19] Appropriate broad-spectrum antibiotics with anaerobic coverage and the maintenance of proper nutrition are also integral components of the management plan. Esophagectomy is occasionally required in the presence of a perforated, non-dilatable stricture, a destroyed esophagus in which direct repair is not possible, or cancer. Nonoperative treatment is occasionally appropriate and may be instituted in highly selected cases (i.e., contained, asymptomatic instrumental perforations) in which a significant interval has passed and the patient is clinically stable. Mortality is less than 10% if the perforation is recognized and repaired within 24 h, whereas mortality, the rate of reintervention, and hospital stay increase if more than 24 h have elapsed between perforation and repair. Mortality rises even higher with advanced patient age.

Tracheobronchial Perforation

Tracheobronchial perforation is rare and is most commonly seen following trauma or instrumentation. Less common causes include anastomotic dehiscence after lung transplantation or airway surgery and necrotizing infections involving the airway. Intubation is now the most frequent cause of tracheobronchial injury, but injury can be avoidable with gentle and proper technique. The incidence of tracheobronchial injuries is estimated at 1 in every 75,000 single-lumen intubations and 1 in every 575 percutaneous dilatation tracheostomies.[20]

Blood in the airway, airway obstruction (infrequent), subcutaneous and mediastinal emphysema, and pneumothorax are the common presenting signs. Severe mediastinitis is rare after tracheobronchial disruption, presumably due to the less noxious nature of its contents and better containment. Diagnosis is suspected on clinical grounds and is confirmed with CT and/or bronchoscopy. Prompt recognition and surgical consultation for operative repair are necessary and yield excellent results, although small tears in the cervical trachea or those involving the membranous wall of the trachea only may often be managed conservatively with antibiotics alone, without operation.[21]

Descending Necrotizing Mediastinitis

Mediastinitis occasionally develops after severe deep head and neck infections that originate from the mouth, oropharynx, or hypopharynx.[22–28] Extension of the cervical infection down the layers of the deep cervical fascia into the mediastinum leads to this syndrome of descending necrotizing mediastinitis. Downward spread is aided by gravity, negative intrapleural pressure, and lytic dissolution of fascia and fat. The deep cervical fascia consists of three layers: the superficial (buccopharyngeal) layer, the middle (visceral) layer, and the deep layer that is further subdivided into the alar and prevertebral layers. All layers originate from the base of the skull. The superficial layer terminates at the superior chest. The visceral layer terminates as a continuation of the pericardium. The potential space between the superficial and middle layers, called the retropharyngeal space, allows infection to descend to the middle of the chest. The alar layer terminates at the diaphragm. The potential space between the middle and the alar layer confines infection above the diaphragm. Rare infections between the alar and prevertebral layers may allow the spread of infection below the diaphragm. Endo et al.[25] classified descending necrotizing mediastinitis according to the extent of the infection to guide the surgical management according to this classification: type 1, infection above the carina, type IIA, infection to the level of the lower anterior mediastinum, and type IIB, infection involving the lower anterior and posterior mediastinum.

The criteria for diagnosing descending necrotizing mediastinitis include (1) severe head and/or neck infection, (2) radiographic evidence of mediastinitis, (3) evidence of necrotizing infection, and (4) establishment of a relationship between the cervical infection and necrotizing mediastinitis.[24] Previously, these infections had a fulminant, often lethal course with mortality as high as 40%. Ridder et al.[23] reported a large series and performed a meta-analysis of collected series that illustrate the cardinal features of this important clinical problem. Patients present with odynophagia (66%), neck swelling (41%), neck pain (21%), dyspnea (21%), and chest pain (5%). Signs include fever (100%) and swelling and redness of the oropharynx (69%). About two-thirds of patients have comorbidities that are associated with immunosuppression or chronic illnesses, such as diabetes, malnutrition, advanced age, renal failure, alcoholism, liver cirrhosis, or underlying malignancy. Common causes include tooth abscesses, pharyngitis, peritonsillar abscess, epiglottis, and perforation of the pharynx. Pharyngeal or tonsillar origin of infections seems to be more frequent than odontogenic. Most patients present with a mixed aerobic and anaerobic infection, reflective of the oropharyngeal microflora. A period of delay of either presentation or diagnosis is common.

CT with intravenous contrast should be performed on all severe neck infections and suspected cases of descending necrotizing mediastinitis to identify radiologic signs of mediastinitis that may not be clinically apparent (Fig. 80-9). *Streptococcus* species are the most common aerobic organisms, and *Bacteroides* and *Peptostreptococcus* species are the most common anaerobic organisms isolated. The mainstay of treatment consists of antibiotic therapy, drainage of abscesses, and debridement of devitalized tissue. Broad-spectrum antibiotics should be started promptly upon clinical suspicion of this diagnosis. All patients require cervical incision, exploration, drainage, and treatment of the underlying condition. Many patients also require transthoracic drainage most commonly by thoracotomy or video-assisted thoracoscopy (VATS). Often, image-guided percutaneous drainage is appropriate to help drain mediastinal abscesses. In a review of 89 cases of descending necrotizing mediastinitis in Japan, Sumi[29] reported transcervical drainage in 28%, VATS in 24%, thoracotomy in 24%, and percutaneous drainage in 17%. Frequently, patients had a combination of approaches to achieve complete drainage of the infection. Many patients require several trips to the operating room for serial debridement and drainage procedures. The mean length of stay is 36 days reflecting the severity of this illness. Recent series report an average mortality of 10% to 15%.

Finally, airway management needs to be considered, as these infections are associated with severe oropharyngeal and supraglottic edema that can lead to prolonged intubation or extremely difficult reintubation should the endotracheal tube become dislodged. Therefore, tracheostomy is often required, as this facilitates airway control.

■ Mediastinitis from Direct Extension

Mediastinitis has been reported after endoscopic procedures used for diagnostic purposes in conditions of the mediastinum or lung cancer staging, including endoscopic ultrasound (EUS) and endobronchial ultrasound (EBUS) with needle aspiration.[30,31] A review of 7345 cases of EBUS with transbronchial needle aspiration (TBNA)[32] documented an incidence of mediastinitis of 0.1% (7 cases). Seeding of the mediastinum is attributed to the translocation of oropharyngeal or lower respiratory flora by the needle puncture, particularly, when targeting necrotic or cystic lesions or lymph nodes. It has been demonstrated that up to 7% of patients experience bacteremia after EBUS-TBNA, with cultures demonstrating typical oropharyngeal microorganisms.[33] Moreover, culture of needle washings is positive in up to one-third of cases. However, infectious complications after EBUS-TBNA are so infrequent that routine preprocedural antibiotic prophylaxis has not been recommended.[34]

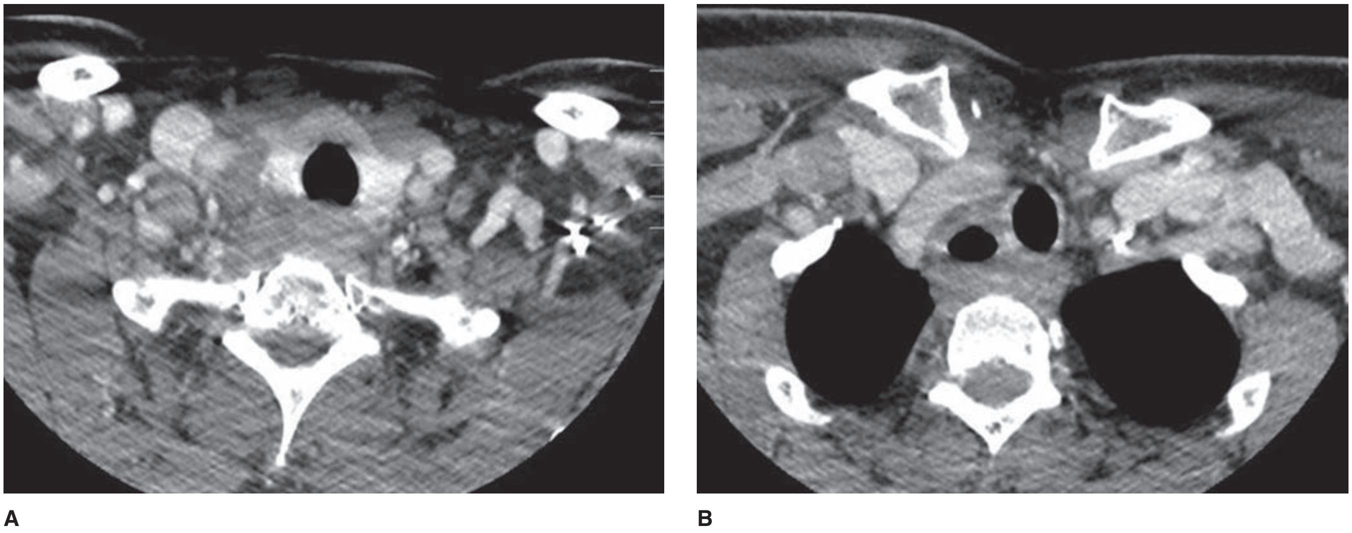

Figure 80-9 Representative CT images from a patient with descending necrotizing mediastinitis from a peritonsillar abscess. **A.** CT image at the base of the neck with soft tissue swelling along the right carotid sheath and also tracking down the retropharyngeal space to the mediastinum. **B.** CT image from the upper chest in this patient with a right superior mediastinal abscess from descending necrotizing mediastinitis.

Necrotizing pneumonias may cause mediastinitis by direct extension, most often in immunocompromised patients. Aspergillosis of the posterior mediastinum has been reported with increasing frequency and is highly lethal. Treatment involves reversal of immunosuppression (if possible), appropriate antibiotic therapy, and surgical drainage and debridement.

Pancreatitis can extend from the retroperitoneum into the mediastinum and may present as a mediastinal process with evidence of mediastinitis. Pancreatic pseudocysts can also erode into the mediastinum and cause pleural effusions with increased levels of amylase. Treatment is directed at providing adequate drainage of the pseudocyst, usually by internal drainage into the stomach. Pleural effusions may require tube thoracostomy drainage.

■ Poststernotomy Mediastinitis

Sternal wound infection with resulting mediastinitis is a condition most relevant after cardiac surgery. The incidence remains low at 0.5% to 1% of all sternotomies, but such infection is a source of major morbidity, prolonged hospital length of stay, and significant mortality (0%–30%; average, 15%). Risk factors include prolonged preoperative stay, advanced age, smoking, BMI >30 kg/m^2, chronic obstructive pulmonary disease, diabetes, renal failure, reoperation, use of internal thoracic artery grafts, blood transfusions, poor technique during sternotomy or closure of the sternotomy, and re-exploration for bleeding.[35,36] *Staphylococcus aureus* is the most common causative organism. Other organisms commonly isolated include *Staphylococcus epidermidis*, various gram-negative organisms, *Candida* species, and atypical mycobacteria. The etiology appears to be a combination of intraoperative contamination and hematogenous seeding of mediastinal clot in the early postoperative period.

Most patients with poststernotomy mediastinitis have an insidious presentation with low-grade fever and leukocytosis, wound problems (erythema, drainage, sternal instability), and eventually bacteremia. Infections caused by gram-negative organisms tend to manifest earlier than those caused by gram-positive organisms. Most infections occur within the first or second week following the operative procedure. A high index of suspicion must be maintained so that an early diagnosis can be made and appropriate treatment instituted. The diagnosis is established clinically based on symptoms and physical exam findings (e.g., unstable sternum, erythema or discharge from the surgical site). CT imaging can aid in making the diagnosis and establishing the extent of the infection. Exploration in the operating room remains the definitive diagnostic and therapeutic maneuver, and material should be obtained for culture at that time if it has not been obtained before or has been unrevealing.

If the infection is relatively early and the bony sternum appears viable, debridement, drainage, and saline (or antibiotic) irrigation with reclosure are indicated.[36] Although it may seemingly violate time-honored surgical principles (leaving contaminated wounds open, to close by secondary intention), primary closure of the early, infected sternum yields excellent results in many patients if adequate debridement is carried out. Of course, proper and prolonged antibiotic therapy is necessary. Reported mortality rates approach zero for these early infections if managed appropriately. Late sternal wound infections with mediastinitis present a more formidable challenge, due in part to the extensive sternal osteomyelitis and necrotic soft tissue that, when debrided, result in significant dead space, thereby creating a favorable environment for continued bacterial proliferation and persistent infection. The presence of prosthetic material, such as sutures, Teflon pledgets, or prosthetic grafts further complicates the problem and may lead to catastrophic hemorrhage with a fatal outcome. Mediastinitis in the presence of a prosthetic aortic graft is a particularly disastrous complication. Most surgeons favor extensive sternal debridement, usually with total sternal excision and rotation of pectoralis muscle flaps (bilateral) or transposition of gastrocolic omentum to fill the dead space with viable tissue. More recently successful outcomes have been reported with the use of negative-pressure wound therapy (vacuum-assisted closure [VAC]).[37,38] Caution is required to protect the right ventricle or coronary bypass grafts when using negative-pressure wound therapy to prevent erosion with subsequent hemorrhage.[39]

■ Anthrax Mediastinitis

Anthrax is caused by *Bacillus anthracis*, which has a nearly worldwide distribution existing in the soil in the form of spores. It causes infection in farm animals and rarely in humans in contact with infected animals or contaminated animal products. Clinically, four different presentations of anthrax exist: cutaneous, gastrointestinal, injectional, and inhalational. Anthrax, particularly its most lethal inhalational form, was prominent in the mainstream media after the bioterrorism attacks of 2001 in the United States when anthrax spores were sent through the mail. The potential use of anthrax as a biologic weapon was suspected after an outbreak in the Soviet Union in 1979 (in the current area of Yekaterinburg, Russia), when at least 66 people died to inhalational anthrax following the suspected accidental release of anthrax spores to the atmosphere from a research facility. Autopsy studies from this outbreak have established the key pathologic processes of inhalational anthrax.[40] The inhalation of anthrax spores allows entry into the lungs with subsequent transport to the mediastinal lymph nodes by alveolar macrophages. Hemorrhagic necrosis of the mediastinal lymph nodes with hemorrhagic mediastinitis quickly ensues followed by widespread dissemination, including meningitis. Death is common. Gram-positive bacilli are usually present in tissue specimens. A total of 22 cases of anthrax were documented after the 2001 attacks in the United States with 5 deaths.[41,42] Diagnosis is confirmed by culture, polymerase chain reaction assays, or histopathology.

Treatment of inhalational anthrax involves combination antimicrobial therapy including a fluoroquinolone, such as ciprofloxacin; a protein inhibitor, such as linezolid; and a drug with excellent penetration of the central nervous system, such as meropenem.[42] Adjunctive therapies include antitoxins (monoclonal antibodies, anthrax immune globulin), and drainage of pleural and pericardial effusions and ascites, as these are rich in toxins.

CHRONIC MEDIASTINITIS

Several important clinical entities within the spectrum of chronic mediastinitis, including mediastinal granuloma, fibrosing mediastinitis, and compression syndromes arising from fibrosing mediastinitis, are presented below.

■ Mediastinal Granuloma

Granulomatous mediastinitis is a disease of the mediastinal lymph nodes usually resulting from infection by *Histoplasma capsulatum* and occasionally from tuberculosis, other fungi, and sarcoidosis. In certain areas of the country (e.g., Ohio and Mississippi river valleys) where *Histoplasma* is endemic, this disease is fairly common. Coalescence of caseous necrosis in mediastinal lymph nodes with dystrophic calcification can result in a single large mass that incites a considerable fibrotic response, which can result in encapsulation and produce a mediastinal granuloma.[43] The right paratracheal area is the most common site for development of an encapsulated mass. When calcification is absent and the patient presents with what appears to be mediastinal adenopathy, a tissue diagnosis is required to exclude malignancy. With progressive increase in the size of this “benign” mass, compression of the tracheobronchial tree, superior vena cava, pulmonary vessels, or esophagus can occur. In a report from the Mayo Clinic, 35% of patients with mediastinal granuloma

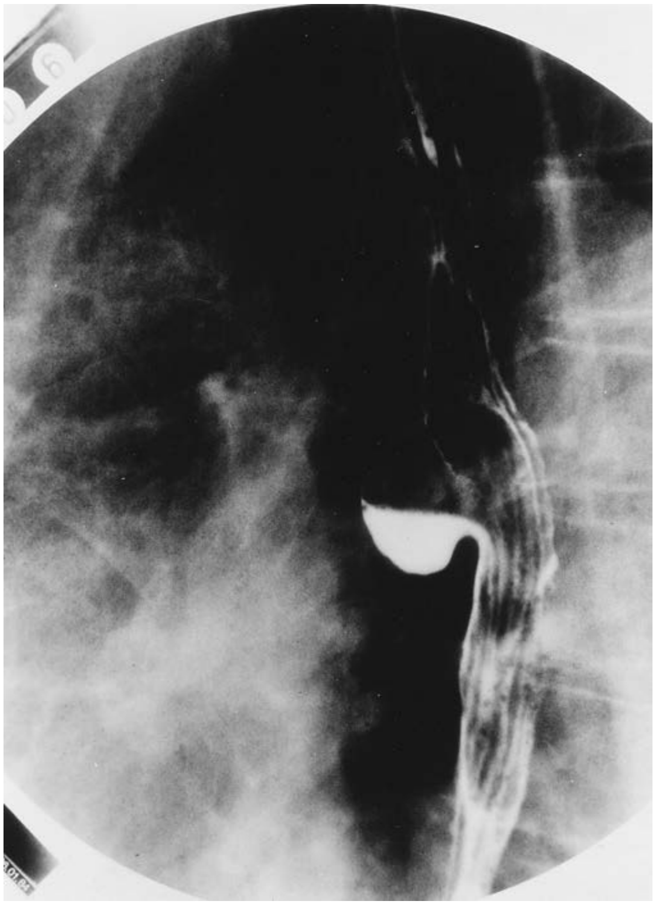

Figure 80-10 Barium swallow of an elderly woman with a history of treated tuberculosis with symptomatic midesophageal traction diverticulum adjacent to calcified subcarinal lymph nodes.

went on to develop mediastinal fibrosis over a 2-year period.[43] Based on such reports, most authors suggest that there exists a spectrum of diseases ranging from mediastinal granuloma to fibrosing mediastinitis, with varying degrees and extension of inflammation and desmoplastic reaction. Caseating lymph nodes can also erode into and rupture in the esophagus, be associated with traction esophageal diverticula (Fig. 80-10), and erode into the airway, causing obstruction or bleeding.

Mediastinal granulomas should be excised if symptomatic. Although complete excision is sometimes possible, the intense surrounding fibrosis places important structures at risk for operative injury. Evacuation of the granulomatous mass is usually a safer option. Specimens for culture and special stains should be obtained at the time of operation, but organisms can rarely be identified or grown in culture.

Mediastinal lymph nodes involved by the granulomatous process may become calcified as individual masses and—because of the proximity of lymph nodes to the tracheobronchial tree—ultimately erode into the airway. The presence of calcified lymph node masses within the bronchi is referred to as *broncholithiasis*. Erosion into the airway, if it occurs, does so over a prolonged period of time and may remain clinically silent, only to be noted if a bronchoscopy is performed for some other indication. Broncholithiasis may also present with symptoms of cough, obstruction, or bleeding. Symptomatic broncholithiasis should prompt bronchoscopy for documentation of findings. Rarely, if ever, should broncholiths be removed bronchoscopically, the exception being the occasional "stone" that is completely free within the bronchus. An effort to remove a broncholith that is not completely detached from the wall of the bronchus may be accompanied by catastrophic hemorrhage due to their close proximity and adherence to pulmonary artery branches. Most symptomatic broncholiths should be removed at thoracotomy, where the pulmonary artery may be managed. These can be extremely difficult and hazardous operations and should be carried out by thoracic surgeons experienced in the management of granulomatous disease. Usually lobectomy or segmentectomy is required, since removal of the calcified mass will almost certainly take a portion of the bronchial wall.

Fistulas occurring between the trachea and esophagus or esophagus and mediastinum as a result of granulomatous lymphadenitis should be closed and reinforced with viable tissue.[44] There is no consensus regarding management of large asymptomatic mediastinal granulomas, but some have recommended excision to forestall the development of compression syndromes or fibrosing mediastinitis.

Fibrosing Mediastinitis

Fibrosing mediastinitis results from extensive chronic inflammation with deposition of fibrous connective tissue, mainly in the visceral compartment of the mediastinum. It represents the end of the spectrum of diseases that, most commonly, are presumed to start with a mediastinal granuloma. Fibrosing mediastinitis may cause a variety of clinical syndromes due to the compression or obstruction of vital mediastinal structures by the dense fibrous tissue reaction that is present (see below).[45] In North America fibrosing mediastinitis is most commonly associated with *Histoplasma capsulatum* infection. Other rare causes include tuberculosis or other mycobacterial infections, infection with other fungi (e.g., aspergillosis, blastomycosis, cryptococcosis, mucormycosis), sarcoidosis, silicosis, exposure to the drug methysergide (an ergot derivative used in the treatment of refractory migraines), autoimmune disorders (e.g., Behçet disease, granulomatosis with polyangiitis, IgG4 disease), rheumatic fever, radiation therapy, trauma, and familial multifocal fibrosclerosis.[46–52] Fibrosing mediastinitis is labeled as idiopathic if there is no identifiable cause, which can occur in 10% to 20% of cases.

Goodwin et al.[53] proposed the most widely accepted hypothesis that fibrosing mediastinitis results from an excessive immune reaction to fungal, mycobacterial, or other antigens in a susceptible individual that results in ongoing inflammation and fibrogenesis. Strock et al.[54] found that the human leukocyte antigen HLA-DQB1*04:02 is associated with histoplasmosis-related fibrosing mediastinitis, further supporting the notion that an abnormal immune response is responsible for this phenomenon. In addition, Richmond et al.[55] explored potential genetic susceptibility to developing fibrosing mediastinitis by studying genome-wide single nucleotide polymorphisms (SNPs) in 58 patients and comparing them with 7115 controls. They found 16 SNPs in 14 genes that were differentially expressed in patients with fibrosing mediastinitis (3 SNPs involving the gene HYDIN located in chromosome 1), thus raising the possibility that the exaggerated fibrotic response seen in these patients has genetic underpinnings.

Pathologic features include the presence of dense fibrotic tissue surrounding the trachea and hila of the lungs, often extending into contiguous structures. Compression of the airway, esophagus, superior vena cava, pulmonary arteries, or pulmonary veins may occur because of this process. Histologic features include dense hyalinized collagenous tissue, aggregates of plasma cells and lymphocytes, and occasionally granulomas. Cultures are usually negative, as are special stains for organisms; however, efforts should be made to try to identify an inciting pathogen. Some cases present with radiographic features that suggest malignancy, particularly if calcification is minimal, leading to surgical biopsies for diagnosis.

McNeeley et al. recently reported a review of imaging of fibrosing mediastinitis.[56] The chest radiograph is usually abnormal in fibrosing mediastinitis, but findings are usually nonspecific. The most common findings include mediastinal widening, lymphadenopathy, and calcified nodes. Contrast-enhanced CT is the imaging modality of choice and shows fibrotic tissue with variable enhancement. Multiplanar reformatted views are especially helpful in demonstrating compression of vessels and airways and for planning an intervention. A practical differential diagnosis for granulomatous fibrosing mediastinitis includes lung cancer, mediastinal nodal metastases (especially sclerosing adenocarcinomas), sclerosing non-Hodgkin lymphoma, nodular sclerosing Hodgkin lymphoma, and tuberculosis. In a recent review, Garrana et al.[57] differentiated the imaging findings in focal (i.e., granulomatous) and diffuse fibrosing mediastinitis (i.e., idiopathic, autoimmune, drug or radiation induced). CT imaging of patients with focal disease reveals localized infiltrative mediastinal soft tissue, predominantly in the right paratracheal or subcarinal regions. Calcifications are common. Extrathoracic calcified granulomas might suggest a previous histoplasmosis infection. On the other hand, cases of diffuse fibrosing mediastinitis show a diffuse infiltrative soft tissue lesion often involving multiple mediastinal compartments. Calcifications are rare. Extrathoracic findings can include retroperitoneal fibrosis, sclerosing cholangitis, or features suggestive of autoimmune pancreatitis. In both instances, positron emission tomography (PET) measuring the uptake of ^{18}F-fluorodeoxyglucose (FDG) is variable and not reliable for diagnosis. However, some authors have reported cases with a well-documented increase in FDG uptake on PET in areas of mediastinal or retroperitoneal fibrosis, which can be used to monitor disease activity and response to anti-inflammatory treatments with good correlation.[58,59]

Fibrosing mediastinitis may be asymptomatic in up to 40% of patients, discovered incidentally on imaging studies obtained for other reasons. In the remaining patients, symptoms are primarily caused by compression of vital mediastinal structures, including major vessels, airway, and esophagus, as detailed in the following sections.

The most common mediastinal compression syndrome seen in fibrosing mediastinitis is the superior vena cava syndrome, which occurs in 20% to 50% of patients.[45] Although malignant disease account for the vast majority of cases of superior vena cava syndrome, fibrosing mediastinitis is the most common benign cause. Patients present with distention of the veins in the neck; edema and plethora of the face, neck, and arms; and central nervous system complaints such as headache and visual disturbances. Men often note as a first sign an increase in collar size, and symptoms become worse upon bending over. Because this syndrome is usually of gradual onset, venous collaterals develop over the anterior chest wall and, in many patients, provide adequate decompression (Fig. 80-11). Confirmation of the diagnosis of superior vena cava syndrome is easily made with contrast CT or venography, which demonstrate blockage of contrast at the thoracic inlet and the presence of collateral vessels. Bilateral upper extremity venograms demonstrate the precise anatomy of the involved veins and are helpful if surgical decompression is contemplated. Surgical bypass is reserved for patients with intractable symptoms and is performed

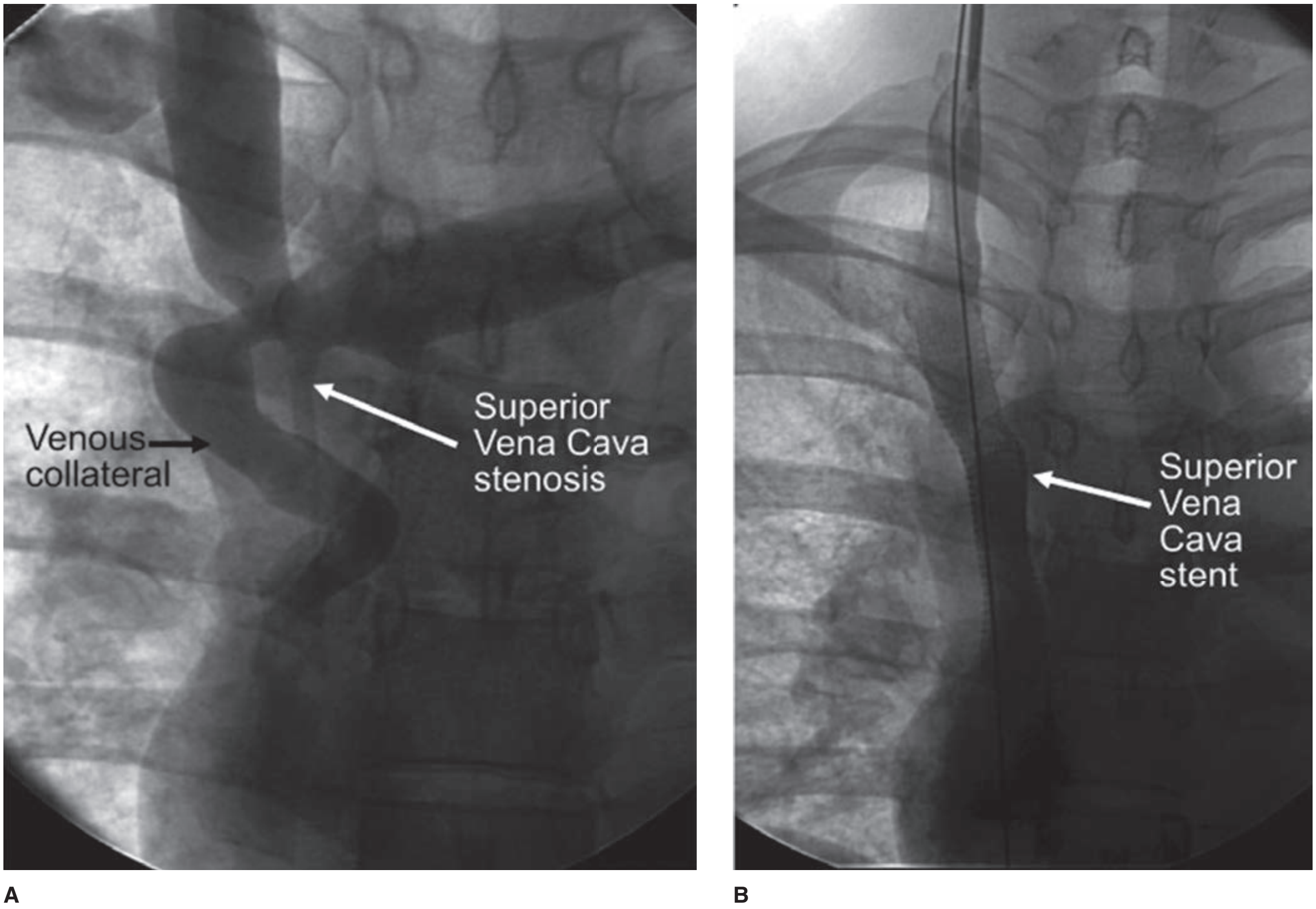

Figure 80-11 **A.** Venography demonstrates stenosis of the superior vena cava (SVC, *white arrow*) with a well-developed venous collateral *(black arrow)* due to fibrosing mediastinitis. **B.** Following stenting, there is significant improvement in the size of the SVC *(white arrow)*. *(Reproduced with permission from Fender EA, Widmer RJ, Knavel Koepsel EM, et al. Catheter based treatments for fibrosing mediastinitis. Catheter Cardiovasc Interv. 2019;94(6):878–885.)*

by connecting an unobstructed large brachiocephalic vein to the right atrial appendage with a graft of either a saphenous vein or an externally supported polytetrafluoroethylene graft. Favorable long-term results have been reported. Percutaneous angioplasty and stenting of a stenotic superior vena cava has been reported.[60] In one of the largest series of endovascular interventions in fibrosing mediastinitis,[61] 12 patients underwent endovascular stenting for superior vena cava syndrome. This resulted in increased SVC luminal caliber, decreased pressure gradients, and symptomatic improvement in all patients. However, 7 (58%) of these patients experienced restenosis and required repeated interventions. Median time to recurrence was 24 months.

Tracheobronchial compression also is common and leads to dyspnea, obstructive pneumonias, wheezing, hemoptysis, cough, atelectasis, and the middle lobe syndrome (Fig. 80-12). A localized stenotic area sometimes can be dilated, but often pulmonary resection is required. Resection is the procedure of choice if chronic infection has been present. Bronchoscopic interventions are appropriate if lung parenchyma remains normal. The bronchoscopic placement of stents into the trachea and/or mainstem bronchi may allow for

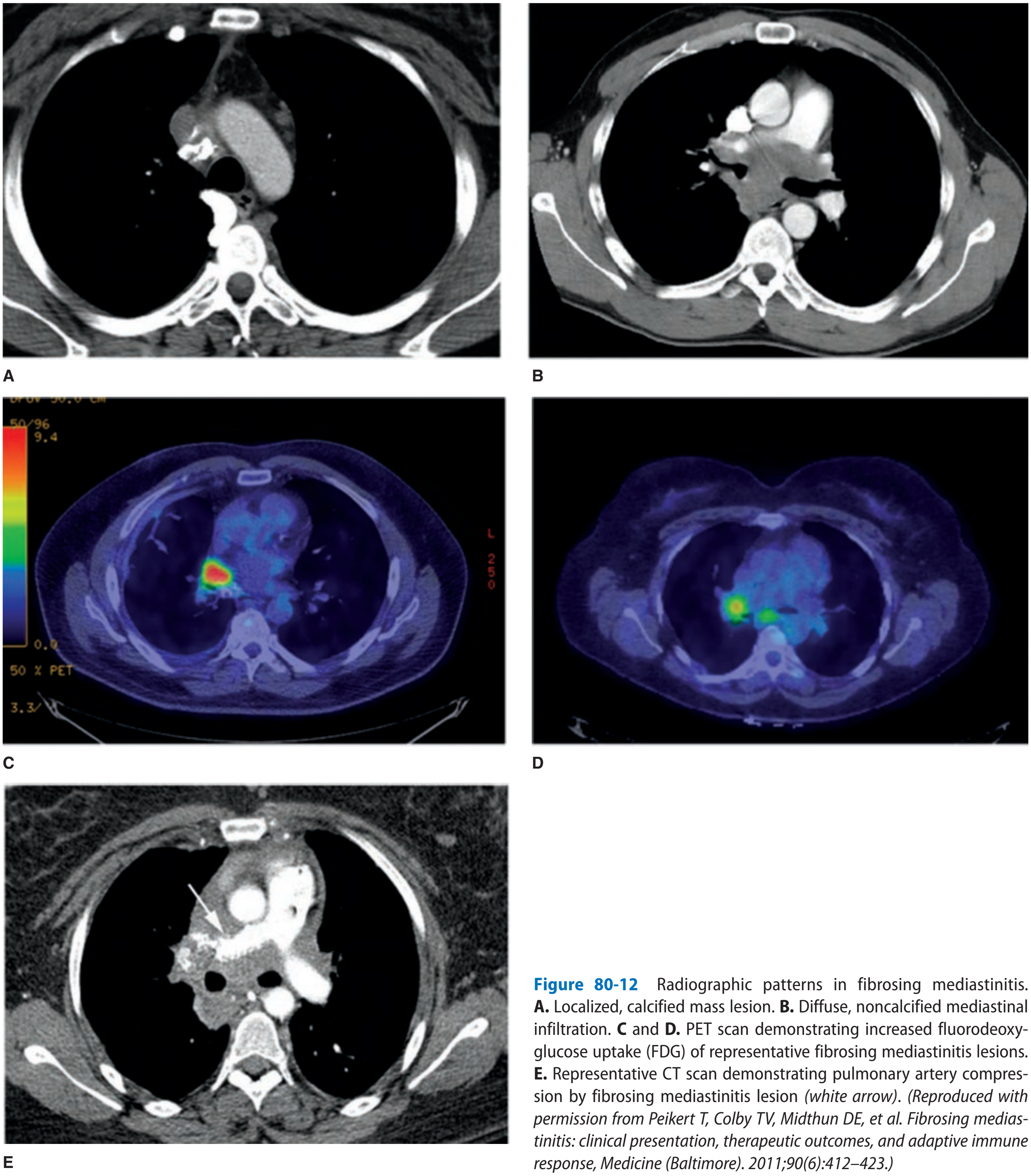

Figure 80-12 Radiographic patterns in fibrosing mediastinitis. **A.** Localized, calcified mass lesion. **B.** Diffuse, noncalcified mediastinal infiltration. **C** and **D.** PET scan demonstrating increased fluorodeoxyglucose uptake (FDG) of representative fibrosing mediastinitis lesions. **E.** Representative CT scan demonstrating pulmonary artery compression by fibrosing mediastinitis lesion *(white arrow)*. *(Reproduced with permission from Peikert T, Colby TV, Midthun DE, et al. Fibrosing mediastinitis: clinical presentation, therapeutic outcomes, and adaptive immune response, Medicine (Baltimore). 2011;90(6):412–423.)*

adequate management of a compressed airway. A Y-bifurcation stent and individual self-expanding stents placed in the trachea or bronchi are available. Kern et al.[62] described the use of silicone stents in 7 patients with extrinsic central airway compression due to fibrosing mediastinitis (representing 5% of all patients with fibrosing mediastinitis during the study period). There were 3 cases of unilateral mainstem bronchus stenting, two of bilateral mainstem bronchus stenting, and two distal tracheal Y-stents. Repeat bronchoscopies to clear impacted secretions or remove granulation tissue were frequently required. In most cases, the airway stents remained in place for months to several years, but they were eventually removed in 5 of 7 patients. Airway management must be individualized based on findings at bronchoscopy. Often the airway strictures are so fibrotic that they are not amenable to stenting.[44]

Complete or partial unilateral or bilateral pulmonary artery obstruction can result from fibrosing mediastinitis (Fig. 80-12).[44,47,48] Dyspnea and signs of right heart failure can be present and the presentation can mimic that of idiopathic pulmonary arterial hypertension or chronic pulmonary thromboembolism. The fibrosis may also extend to involve the pulmonary veins, producing a syndrome mimicking pulmonary veno-occlusive disease. Involvement of multiple pulmonary veins is frequent given their proximity. Surgical correction of these disorders is rarely possible due to the extreme fibrosis present around the vessels. Angioplasty and/or stenting of the pulmonary arteries and veins has been reported. Albers et al.[61] reported stenting of 26 pulmonary arteries in 19 patients with improved vessel diameter and concomitant decrease in PA systolic pressure gradients. Only 1 (5%) patient required reintervention due to restenosis of a PA stent. Another study of 9 patients[63] documented a 90% patency rate of pulmonary artery stents at 1 year. Complications from pulmonary artery endovascular interventions include vessel injury with complete occlusion, reperfusion pulmonary edema, and thrombosis requiring anticoagulation. Endovascular intervention is also possible in cases of pulmonary vein involvement, although restenosis rates of 25% to 50% and a 1-month mortality rate of 38% have been reported.[61,64] Complications from pulmonary vein endovascular interventions include pulmonary hemorrhage with hemoptysis, vessel dissection or rupture, and systemic embolic events. If the situation is unilateral with associated airway obstruction, a pneumonectomy may be an alternative.

Esophageal obstruction resulting from fibrosing mediastinitis most frequently involves the middle third of the esophagus because of its relationship to the subcarinal space. Dilation, enucleation of scar, and resection are therapeutic options. Fistulas may occur between the subcarinal lymph nodes and the esophagus or into the tracheobronchial tree. Operative treatment for fistula formation is directed at closing the fistula and separating the airway and esophagus using viable tissue such as muscle. An esophageal diverticulum may form from inflammatory adherence to the subcarinal lymph nodes but is usually asymptomatic (Fig. 80-10).

Beyond the palliative interventions for compression of vital mediastinal structures described above, the optimal treatment of fibrosing mediastinitis remains unknown. Case reports have suggested that antifungal, anti-inflammatory, or antifibrotic treatment may have some benefit, but large case series mostly refute these observations. Westerly et al.[65] reported on the successful use of rituximab, an anti-CD20 monoclonal antibody targeting B lymphocytes, in three patients with mediastinal fibrosis with improvement of symptoms and a reduction in size and metabolic activity of the fibrotic lesions on imaging after B cell depletion.

Peikert et al.[45] from the Mayo Clinic reviewed one of the largest series comprising 80 patients with fibrosing mediastinitis that nicely summarizes our current understanding of this disease. Their clinical definition of fibrosing mediastinitis was radiographic evidence of an infiltrative mediastinal process with associated vascular, airway, or esophageal compression. The pathologic definition was that of a predominance of extensive paucicellular fibrotic tissue infiltrating and obliterating adipose tissue with or without patchy infiltration of mononuclear cells. The median age at presentation was 42 years with an equal gender distribution. There was evidence of histoplasmosis (by culture, fungal stains, or positive serologic titer) in 83% of patients. The involved mediastinal organs that were compressed were vascular (48%), bronchial (27%), superior vena cava only (20%), and esophagus (3%). Only 5% of patients were asymptomatic at presentation. Presenting symptoms included dyspnea (47%), cough (21%), symptoms compatible with the superior vena cava syndrome (21%), chest pain (20%), and hemoptysis (20%). Focal mediastinal abnormalities on chest CT were seen in 95% of patients, while diffuse mediastinal infiltration was seen in 5%. Calcifications were seen in 73% of patients. PET scans, when obtained for the suspicion of malignancy, were uniformly positive. Medical therapy with antifungal treatment was minimally effective, with only an 18% rate of a partial response. Endovascular interventions were successful in 11 of 13 patients with vascular compression; however, the majority required repeat interventions for stent stenosis. Bronchoscopic balloon dilatation of stenotic airways was performed in 2 patients but failed to produce symptomatic relief in either case. Surgical interventions were successful in 16 of 17 patients (94%). These included bypass of the SVC with a spiral vein graft (3 patients) or polytetrafluoroethylene graft (2 patients), anatomic lung resections to control hemoptysis (4 patients), bronchoplasty or decompression of the airway (3 patients, 1 unsuccessful), pulmonary artery bypass (2 patients), decompression or enlargement of the pulmonary veins (2 patients), and decompression of the esophagus (1 patient). There were no periprocedural deaths. Long-term survival of these patients was identical to that of age-matched controls.

SPONTANEOUS MEDIASTINAL HEMORRHAGE

Mediastinal hemorrhage is usually due to aortic dissection, contained rupture of a thoracic aortic aneurysm, trauma, or iatrogenic injury. Spontaneous mediastinal hemorrhage is extremely rare. Although it can occur in otherwise healthy patients, spontaneous mediastinal hemorrhage has been reported in patients with bleeding diathesis, such as patients with end-stage renal disease on chronic dialysis or those on anticoagulation.[66–68] Symptoms are usually of sudden onset and consist of substernal pain, dyspnea, and, rarely, hemodynamic compromise. The hemorrhage is usually brief and self-limited. Treatment is supportive, and secondary causes of mediastinal hemorrhage must be excluded. Mediastinal fibrosis has rarely been reported following mediastinal hemorrhage.

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CHAPTER 81

Congenital Cysts of the Mediastinum: Bronchopulmonary Foregut Anomalies

Erik E. Lewis
Daniel P. McCarthy
Malcolm M. DeCamp

INTRODUCTION

Mediastinal masses encompass a diverse spectrum of solid tumors, vascular abnormalities, and cysts, arising from and associated with each of the structures found within the mediastinum.[1–4] Cystic lesions account for up to 25% of reported mediastinal masses.[1,3–5] These cysts may be congenital or acquired, or they may represent cystic degeneration of a previously solid tumor. In this chapter, we focus on congenital cystic lesions within the mediastinum, specifically addressing foregut cysts including bronchogenic cysts, enterogenous (esophageal duplication) cysts, and neurenteric cysts. Together, they constitute up to 9% of all primary mediastinal masses. We will also briefly consider simple cysts arising from the thymus, pericardium, and thoracic duct. Many other solid mediastinal neoplasms (dermoids, teratomas, thymomas, parathyroid adenomas, and thyroid goiters) may present with cystic components. These lesions are discussed separately in Chapter 82.

ANATOMY

Cysts may arise in each of the three anatomic compartments of the mediastinum. The boundaries of these compartments, based on cross-sectional imaging, were recently codified by the International Thymic Malignancy Interest Group, with small but significant changes to previous descriptions.[6–9]

The *prevascular compartment* is bounded superiorly by the thoracic inlet, inferiorly by the diaphragm, laterally by the parietal mediastinal pleura, anteriorly by the sternum, and posteriorly by the anterior aspect of the pericardium, as it wraps around the heart and vessels in a curvilinear fashion. Thymic cysts and endocrine lesions, such as thyroid goiters and cystic adenomas of the parathyroid gland, are found in this compartment.[6,7]

The *visceral compartment* is the site of origin of most congenital foregut cysts. The boundaries of the visceral compartment include the thoracic inlet superiorly and the diaphragm inferiorly. The anterior border is the anterior aspect of the pericardium as it wraps around the heart and vessels in curvilinear fashion. The posterior border is defined as a vertical line transecting each thoracic vertebrae 1 cm posterior to its anterior margin. Bronchogenic cysts, enterogenous cysts, pericardial cysts, and thoracic duct cysts arise in this compartment.[6,7]

The *paravertebral compartment* also extends from the thoracic inlet superiorly to the diaphragm inferiorly. The anterior border is the “visceral-paravertebral compartment boundary line” (1 cm posterior to the anterior margins of the vertebrae). The posterolateral margin is defined as the vertical line against the posterior margin of the chest wall at the lateral margin of the transverse processes of the thoracic spine. The paravertebral compartment includes both costovertebral sulci and segmental nerve roots, as well as the sympathetic chain and paravertebral soft tissues. Neurenteric cysts arise within this compartment.[6,7]

It is important to note that lesions that arise primarily within the mediastinum may also extend above the chest into the neck or below the diaphragm into the retroperitoneum, where they present as extrathoracic mass lesions. In addition, cysts within one mediastinal compartment may also extend into the adjacent compartment, since there are no strict anatomic barriers.

EPIDEMIOLOGY

In published series of mediastinal masses, the prevalence of primary cysts ranges from 10% to 25% and has remained steady for the past seven decades (Table 81-1) with relatively similar incidences in males and females. Some minor heterogeneity over this time span is accounted for by variations in the ages of patients reported in each series.[1,3–5,11–13]

Bronchogenic cysts account for approximately 40% of mediastinal cysts, while pericardial cysts account for 35%, enteric for 10%, and nonspecific cysts for 15%. The etiology and distribution of cystic mediastinal masses are different in children and adults. Cysts of foregut origin account for only half of the lesions found in adults, whereas they constitute nearly 90% of cystic lesions reported in pediatric series (Table 81-2). Conversely, pericardial cysts account for up to one-third of all cystic lesions in adults, whereas true pericardial cysts are

TABLE 81-1 Prevalence of Primary Cysts in Reported Series of Mediastinal Tumors over Six Decades

Year	*n*	Mediastinal Cysts (%)	Reference
1952	101	20	Sabiston and Scott[69]
1963	92	24	Heimberger et al.[5]
1972	209	9	Benjamin et al.[2]
1987	400	25	Davis et al.[4]
1993	257	18	Azarow et al.[1]
1999	124	4	Whooley et al.[10]
2003	806	13	Takeda et al.[11]
2017	409	14	Liu et al.[12]

TABLE 81-2 Origin of Mediastinal Cysts

Cyst Type	All Ages (*n* = 477) (%)	Pediatric Only (*n* = 85) (%)
Bronchogenic	39	53
Enteric	11	33
Pericardial	26	1
Other	24	13

Data from Azarow KS, Pearl RH, Zurcher R, et al. Primary mediastinal masses: a comparison of adult and pediatric populations. J Thorac Cardiovasc Surg. 1993;106:67–72; Benjamin SP, McCormack LJ, Effer DB, et al. Primary tumors of the mediastinum. Chest. 1972;62:297–303; Bower RJ, Kiesewetter WB. Mediastinal masses in infants and children. Arch Surg. 1977;112:1003–1009; Whooley BP, Urschel JD, Antkowiak JG, et al. Primary tumors of the mediastinum. J Surg Oncol. 1999;70(2):95–99; Takeda S, Miyoshi S, Minami M, et al. Clinical spectrum of mediastinal cysts. Chest. 2003;124(1):125–132. Liu T, Al-Kzayer LFY, Xie X, et al. Mediastinal lesions across the age spectrum: a clinicopathological comparison between pediatric and adult patients. Oncotarget. 2017;8(35):59845–59853.

exceedingly rare in children. Among congenital lesions of the foregut and tracheobronchial tree seen in children—including pulmonary sequestrations, congenital lobar emphysema, cystic adenomatoid malformations, arteriovenous malformations, and bronchial atresias—simple foregut cysts (bronchogenic, enterogenous, and neurenteric) constitute between 13% and 29% of reported cases.[4,5,11–14]

Although the relative frequencies of cystic and solid mediastinal masses have remained fairly constant, the advent of cross-sectional imaging techniques, such as computed tomography (CT) and magnetic resonance imaging (MRI), has substantially increased the detection of all mediastinal lesions.[15–19]

Multidetector computed tomography (MDCT) with volumetric acquisition provides fast acquisition of high-resolution images and multiplanar reconstructions. Both two-dimensional and three-dimensional imaging may help with improving diagnostic accuracy, surgical planning, and assessing resectability preoperatively. In most cases, CT imaging provides enough information to make accurate diagnostic and therapeutic decisions without further testing. In selected cases, MRI may offer advantages over other modalities for detecting and identifying cystic, or fluid-filled mediastinal masses, because of the intrinsic high soft tissue contrast and direct multiplanar imaging capabilities. Regardless of the modality, sagittal or coronal reformations can provide invaluable anatomic information that the transaxial images may not.

BRONCHOGENIC CYSTS

The embryology, clinical presentation, diagnosis, and management of bronchogenic cysts are discussed below.

Embryology and Terminology

The primitive respiratory and upper gastrointestinal systems have a common embryologic endodermal origin. The primitive foregut gives rise to a variety of aerodigestive organs and tissues, beginning with the pharynx and subsequently giving rise to the larynx, upper and lower respiratory tracts, esophagus, stomach, proximal duodenum, liver, pancreas, and associated ducts.[20] Cystic malformations of foregut origin may have a variety of epithelial linings that reflect the embryologic tissues from which they are derived. The lung bud develops caudally from the laryngotracheal tube, beginning in the fourth week of gestation. By the fifth week, the single bud has divided into right and left main bronchi, which grow into the surrounding splanchnic mesenchyme that is destined to become bronchial cartilage and smooth muscle as well as visceral pleura. Dichotomous branching of the primitive bronchi continues until about the 24th week, when the terminal bronchioles begin to give rise to primitive alveoli.

Throughout this period of embryogenesis, abnormal bronchi and bronchioles may form larger saccular structures, which are clinically recognized as bronchogenic cysts. Such saccular malformations may be invested by their own splanchnic mesenchyme (neopleura). Abnormal bud separation may lead to cyst formation lined with respiratory epithelium. Some investigators believe that mediastinal bronchogenic cysts arise early in the cycle of bronchial branching, whereas intrapulmonary bronchogenic cysts represent derangements occurring later in fetal development. If the separation occurs early, the cyst is associated with the large airways within the mediastinum, whereas delayed bud separation may lead to cyst formation more distally within the lung parenchyma. Approximately three-quarters of bronchogenic cysts are within the mediastinum and associated with the large airways and one-quarter are intraparenchymal.[19] Cysts abutting the trachea, carina, or hilum are termed *mediastinal bronchogenic cysts*; they rarely maintain communication with the respiratory tract (Figs. 81-1 and 81-2). Less frequently, these lesions are contained within the pulmonary parenchyma, most commonly in the lower lobes and are termed

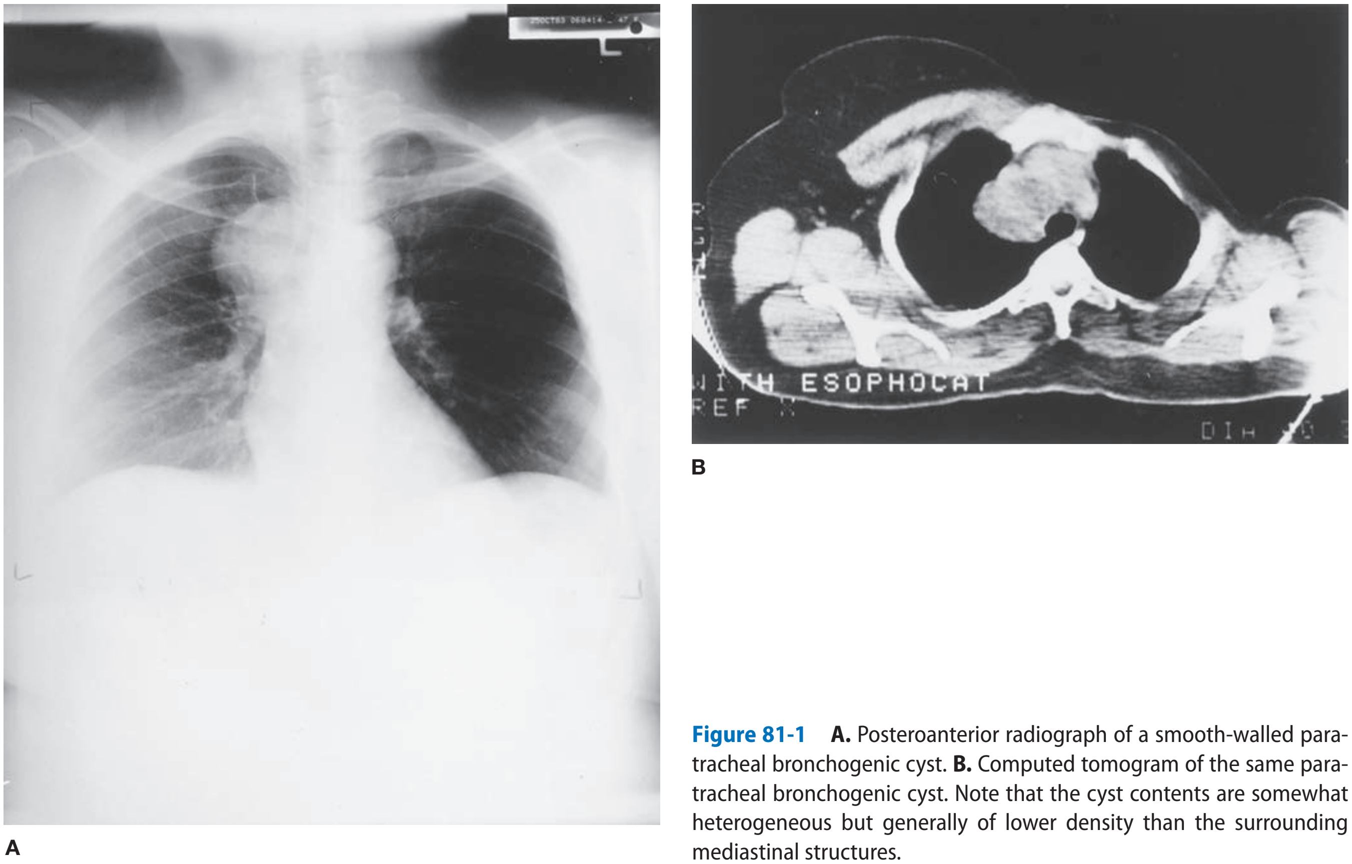

Figure 81-1 **A.** Posteroanterior radiograph of a smooth-walled paratracheal bronchogenic cyst. **B.** Computed tomogram of the same paratracheal bronchogenic cyst. Note that the cyst contents are somewhat heterogeneous but generally of lower density than the surrounding mediastinal structures.

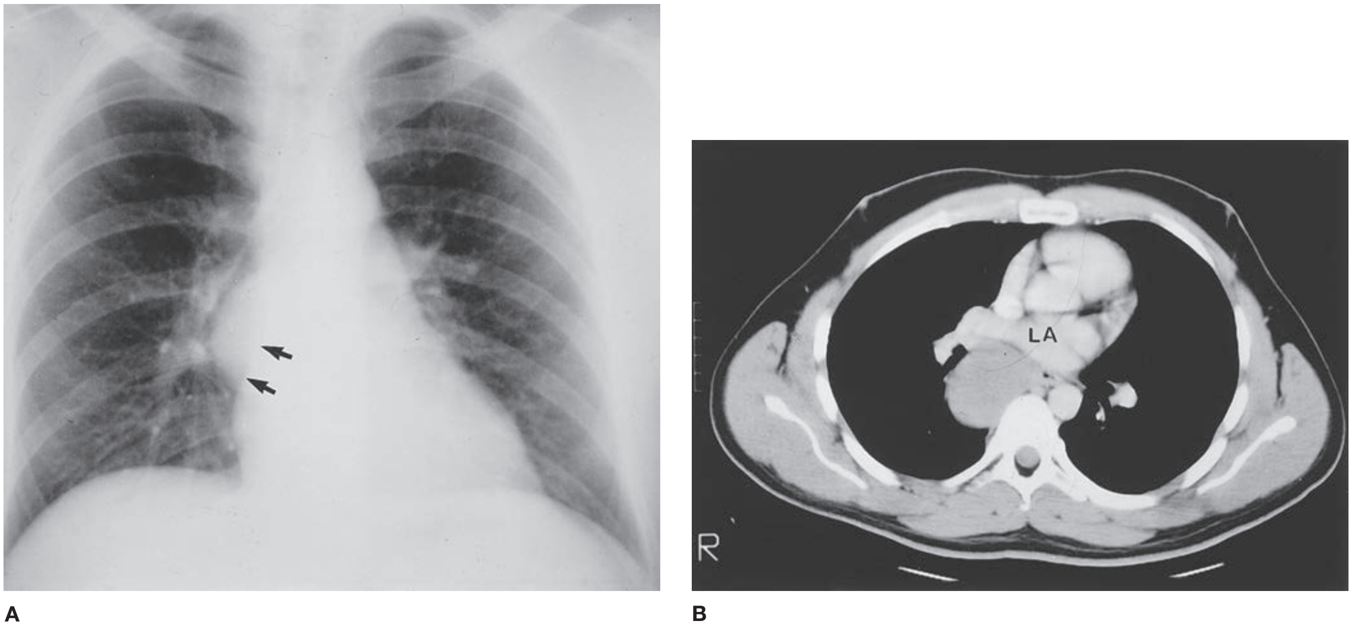

Figure 81-2 **A.** Posteroanterior radiograph of a smooth-walled subcarinal bronchogenic cyst. Note that the cyst is distinct from the right heart border *(arrows)*. **B.** Contrast-enhanced axial CT image of the homogeneous, subcarinal bronchogenic cyst. This patient presented with atrial dysrhythmia attributed to left atrial *(LA)* compression by the cyst. *(Reproduced with permission from Baue AE, Geha AS, Hammond GL, et al. Glenn's Thoracic and Cardiovascular Surgery, 6th ed. Stamford, CT: Appleton & Lange; 1996.)*

intrapulmonary bronchogenic cysts (Fig. 81-3). Other locations include the neck, esophageal wall, pleura, diaphragm, and, rarely, the skin. Bronchogenic cysts are lined by respiratory epithelium and may contain cartilage within their walls. Because they uniformly arise before alveoli form (at 28 weeks), bronchogenic cysts have no gas exchange potential even if their bronchial communications persist, an extremely rare event.

■ Presentation and Diagnosis

Bronchogenic cysts are the most frequent cystic lesions found in the mediastinum and represent up to 15% to 20% of all mediastinal masses. The majority of mediastinal bronchogenic cysts are located below the carina (77%), while the remainder occur above the carina (23%). Most young patients with bronchogenic cysts have symptoms at the time of diagnosis (Table 81-3), although in a significant minority of patients (20%–30%), the cysts may be identified incidentally on CT scans performed for other reasons. The pediatric population is particularly predisposed to symptomatic cysts due to the smaller size of their thorax and more malleable airways.[1,5,11,13] Eraklis et al. noted life-threatening respiratory compromise in 70% of infants with foregut cysts.[21] Mass effects from the cysts, which caused compression, "ball valving," or differential ventilation, were the predominant causes of respiratory distress. These neonates were often cyanotic, with wheezing or stridor, and their radiographs

TABLE 81-3 Clinical Characteristics of Cysts in the Mediastinum (Symptoms and Signs)[a]

Characteristics	Bronchogenic *n* = 47	Esophageal *n* = 4	Thymic *n* = 30	Pericardial *n* = 12	Pleural *n* = 7	Others *n* = 5	Total *n* = 105
Asymptomatic	28	3	18	10	6	2	67 (63.8)
Chest pain	6	0	6	2	0	1[b]	15 (14.3)
Dyspnea	3	1	3	0	1	0	8 (7.6)
Cough	5	0	2	0	0	0	7 (6.7)
Fever	5	0	1	0	0	0	6 (5.7)
Hoarseness	1	0	4	0	0	0	5 (4.8)
Sputum	3	0	0	0	0	0	3 (2.9)
Dysphagia	1	1	1	0	0	0	3 (2.9)
Cyanosis	0	0	0	0	1	0	1
Hemoptysis	1	0	0	0	0	0	1
Others	1	0	1	0	0	2[c]	4

[a] *Data are presented as No. or No. (%).*

[b] *Chest pain associated with thoracic duct cyst.*

[c] *Neurofibromatosis associated with meningocele.*

Reproduced with permission from Takeda S, Miyoshi S, Minami M, et al. Clinical spectrum of mediastinal cysts. Chest. 2003;124(1):125–132.

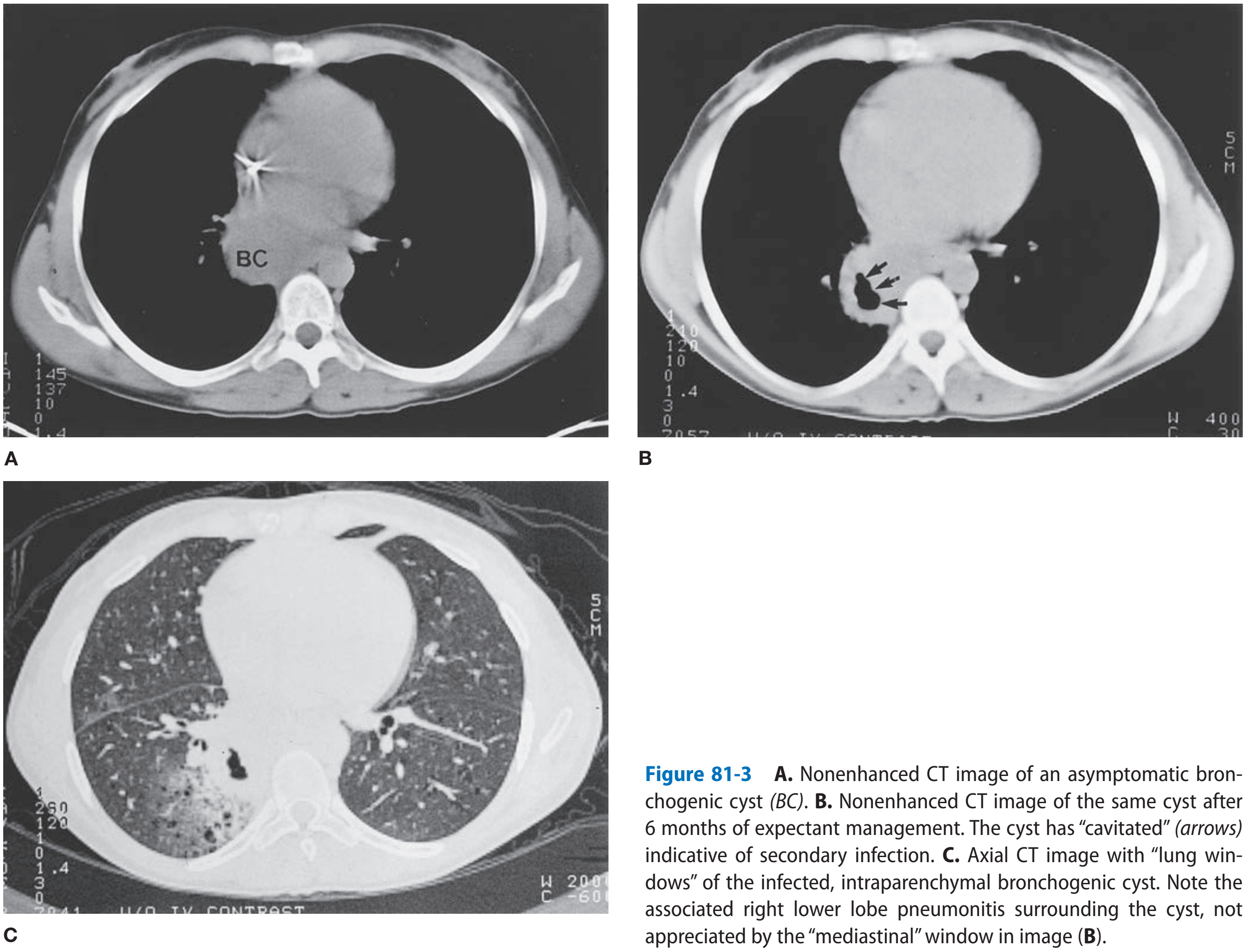

Figure 81-3 **A.** Nonenhanced CT image of an asymptomatic bronchogenic cyst *(BC)*. **B.** Nonenhanced CT image of the same cyst after 6 months of expectant management. The cyst has "cavitated" *(arrows)* indicative of secondary infection. **C.** Axial CT image with "lung windows" of the infected, intraparenchymal bronchogenic cyst. Note the associated right lower lobe pneumonitis surrounding the cyst, not appreciated by the "mediastinal" window in image (**B**).

demonstrated inhomogeneous aeration, lobar collapse, and/or mediastinal shift. In published series of non-neonatal children, up to 95% had symptoms. Signs and symptoms of infection may be present, especially in the older children.

In adults, symptomatic bronchogenic cysts are less common.[1,4,13,22,23] In a large series, symptoms were present in about one-third of patients and included chest pain, cough, wheezing, stridor, dyspnea, dysphagia, cyanotic spells, and pneumonia. Other manifestations include compression of the superior vena cava or left atrium, or evidence of infection such as pneumonia or empyema (Fig. 81-3C). In more recent series, 75% to 95% of patients were asymptomatic when the lesions were detected.[23–27] With long-term follow-up, however, two-thirds of patients who were initially asymptomatic eventually developed symptoms.

The presence of a bronchogenic cyst is suggested by plain chest radiographs in up to two-thirds of cases in any age group. The usual appearance is that of a 2- to 10-cm ovoid, smooth, homogeneous mass that abuts the mediastinum or hilum or splays out the carina.[28] An air–fluid level connotes either persistent bronchial communication or secondary infection of the cyst (Fig. 81-3). As mentioned earlier, some cysts (especially in infants) may exert a mass effect, causing airway compression, parenchymal atelectasis, or cardiovascular compression (Fig. 81-2B). In 60% to 65% of patients, posteroanterior and lateral plain chest radiographs make it possible to diagnose these lesions and to document their precise location.

Ultrasonography is helpful in confirming the cystic nature of mediastinal lesions in infants and children. Prenatal diagnosis also is feasible. Such forewarning allows for the expeditious management of these infants antenatally or at the time of delivery when most affected infants quickly develop symptoms coincident with inflation of the lungs. In the adult, surface ultrasonography has little to offer in the acoustic visualization of suspected bronchogenic cysts because air within the lungs is a poor conductor of sound. Endoscopic ultrasound can be useful in the diagnosis of mediastinal bronchogenic cysts, but needle aspiration through the esophagus should not be performed due to the possibility of infection and sepsis.[29,30]

Cross-sectional imaging techniques, using either CT or MRI, have become the diagnostic procedures of choice for investigating mediastinal masses. These methods provide helpful details of cyst structure, including the density and type of cystic fluid, amount of calcium in the cyst wall, vascularity of the cyst, and the relationships of the cyst to adjacent mediastinal structures. MRI and CT are probably equally useful in the diagnosis of mediastinal-based cysts, although in most situations a CT scan will provide all the necessary information. CT is superior for the examination of intrapulmonary cysts because of its ability to delineate more sharply the cystic lesion from the surrounding air-filled parenchyma (Figs. 81-1–81-3). On CT, bronchogenic cysts appear as a single, smooth, round, or elliptical mass with a well-defined, thin, smooth wall and nonenhancing homogeneous cyst mass. Half of these lesions have the same density as water with attenuation values in a range consistent with serous fluid (0–20 Hounsfield units [HUs]), and others have a CT density that varies depending on the cyst's protein content.[18,19,28] Higher attenuation in the range of 30 to 130 HU is the result of the presence of calcium, proteinaceous fluid, mucus, and/or blood within the cyst. The presence of especially high-attenuation fluid within the cyst on CT scan suggests a high calcium content (milk of calcium).[19] On MRI, bronchogenic cysts frequently show signal intensity higher than that of muscle on T1-weighted images. Variable signal intensity may be due to variable cystic components and presence of protein, blood, or mucoid material. On T2-weighted images, cysts show high signal intensity.

Bronchoscopy is normal in most cases, but abnormalities include extrinsic compression of the airways, secretions from infected cysts, and, rarely, direct communication with the cyst cavity. Rupture into the airway, esophagus, or pericardium also has been documented.

■ Therapy

The treatment options for bronchogenic cysts include observation, resection, and aspiration. In the absence of definitive diagnosis, surgical exploration is recommended for nearly all patients with an abnormal mediastinal mass. Bronchogenic cysts are the most commonly treated mediastinal foregut anomaly and account for 60% of all mediastinal masses. Once a bronchogenic cyst is diagnosed, surgical excision is indicated to relieve clinical symptoms, to address enlarging cysts, or to prevent possible complications including infection, malignant transformation, tracheal or vascular compression, or hemoptysis.[31–33] Complete excision of the cyst should be performed, thus minimizing the chance of recurrence and the potential for complications.

The techniques used for resection have evolved over time, but the fundamental principle of complete resection remains the same. Traditionally, a thoracotomy was necessary. Since most cysts are located in the subcarinal area, a right fifth interspace thoracotomy is usually recommended. With this technique, the right lung is mobilized anteriorly, and access is gained to the area below the azygos vein. The mediastinal pleura is incised, and the cyst is meticulously dissected free from the surrounding structures, with particular attention paid to the areas of attachment to the airway, esophagus, and pericardium. Over the last two decades, minimally invasive techniques utilizing video-assisted thoracoscopic surgery (VATS) with or without robotic assistance have been utilized with increasing frequency to resect mediastinal cysts with excellent results, low conversion rates to open procedure, and no significant increases in recurrence rates.[34–39] Multiple port configurations can be utilized for both VATS and robotic-assisted cases, with variations depending on the approach used and surgeon preference. Minimally invasive techniques allow less surgical trauma while adhering to the core principles of surgical management. The robotic platform has several theoretical strengths in addressing these lesions. Subcarinal bronchogenic cysts can extend to the mid or distal left main bronchus and may be densely adherent to the airway or esophagus, in a narrow and deep operative field. The robotic platform's three-dimensional magnified viewing system facilitates excellent visualization in hard-to-reach areas. In addition, the wristed instrumentation allows precise dissection along multiple trajectories even in a small and deep operative field.[39] As with open surgery, decompression of the cystic lesion by aspiration of its contents may sometimes facilitate handling and dissection.[36]

Additionally, there are other techniques that may be used for certain, specific circumstances. Urschel and Horan[40] described piecemeal resection of a mediastinal bronchogenic cyst using a Carlens mediastinoscope, introduced through a small suprasternal incision. This may be particularly helpful in the treatment of recurrent subcarinal cysts previously approached through a thoracotomy.

In some cases, full cyst resection is not possible. Partial resection of a bronchogenic cyst may occasionally be necessary, if the cyst is found to be densely adherent to and inseparable from the membranous airway, main pulmonary vessels, esophagus, phrenic nerve, or aorta. In these cases, most of the wall of the cyst should be excised and the mucosa lining the remaining cyst wall should be ablated with electrocautery, in an effort to prevent recurrences. When subtotal excision is necessary, symptomatic recurrences requiring re-excision have been reported.

Aspiration of a cyst to confirm a benign diagnosis and to instill a sclerosing agent (ethanol or bleomycin) has been used to manage some cysts in lieu of surgery. The advent of endobronchial ultrasonography with transbronchial intervention has resulted in an even less invasive management option. However, the fluid is almost always thick and viscous and unlikely to be drained through a long, small needle. Reports of long-term follow-up for this approach to both the diagnosis and therapy of bronchogenic cysts are scant. However, it may represent a useful form of therapy for inoperable patients.

Whatever the operative approach, the goal of surgery should be complete excision of all elements of the cyst. Occasional case reports of malignancy arising from the cyst mucosa support the general concept of complete resection for any bronchogenic cyst.[41] A variety of tumors have been associated with bronchogenic cysts including adenocarcinoma, squamous cell carcinoma, carcinoid tumors, anaplastic carcinoma, and leiomyosarcoma in both children and adults.

Treatment of asymptomatic cysts remains controversial.[42] A conservative approach can be considered for small, asymptomatic cysts that do not compress adjacent structures, do not enlarge over time, do not display atypical characteristics, and do not arouse any suspicion of malignancy.

ENTEROGENOUS (ESOPHAGEAL DUPLICATION) CYSTS

The embryology, clinical presentation, diagnosis, and management of enterogenous cysts are discussed below.

■ Embryology and Terminology

Enterogenous cysts are also termed *esophageal duplications*. They arise from the elongating esophagus, which separates from the respiratory tract at about the fifth week of gestation (see Chapter 4). As with most intestinal duplications, enterogenous cysts represent failure of normal recanalization during embryogenesis.[43] Most esophageal duplications are of the closed and cystic type. Rarely are they tubular or demonstrate preserved communication with the alimentary tract.

■ Presentation and Diagnosis

After leiomyomas and benign polyps, esophageal cysts are the third most common esophageal mass, although they remain much less common than bronchogenic cysts. Of all mediastinal cysts, only 5% to 15% are esophageal in origin. The majority of esophageal duplication cysts occur in infants or children, and nearly 75% of esophageal duplication cysts are recognized before 16 years of age.[44–46] In up to 60% of patients they are located adjacent to or within the lower one-third of the esophageal wall in the lower visceral mediastinum with a two-to-one predilection for cysts to be on the right side. Most adults are asymptomatic, with cysts incidentally identified on chest CT.[47] The natural history of esophageal cysts is variable, but if left untreated most will become symptomatic. Symptoms are usually due to compression of the airways resulting in cough, dyspnea, and occasionally stridor.[48–50] Dysphagia is surprisingly infrequent. In asymptomatic patients, the most common clue leading to this diagnosis is the coexistence of other gastrointestinal duplication(s). Associated conditions include other intestinal cysts, esophageal atresia, tracheoesophageal fistula, and spinal abnormalities. Unlike bronchogenic cysts, which are always lined with respiratory mucosa, enterogenous cysts may have a variety of epithelial linings, including the squamous epithelium native to the esophagus. From 50% to 60% of esophageal cysts contain ectopic gastric mucosa, with some containing pancreatic tissue. The presence of gastric mucosa containing parietal cells capable of acid secretion may explain events such as spontaneous hemorrhage and perforation.[49]

Esophageal duplications usually present radiographically as smooth-walled, visceral mediastinal lesions at the base of the right hemithorax (Fig. 81-4A). A barium swallow demonstrates deviation of the lumen around the cyst but rarely shows communication with it (Fig. 81-4B). Proximal esophageal dilatation is not common because the cysts usually are not obstructive. In patients with suspected duplication, a technetium pertechnetate nuclear scan may suggest the presence of ectopic gastric mucosa within the chest. Cross-sectional imaging (CT or MRI) is routinely employed to characterize the contents of a cyst and to define the relationship of the cyst to contiguous structures (Fig. 81-4C). The characteristic CT and MRI findings are identical to those of bronchogenic cysts, except that the wall may be thicker and in closer contact with the esophagus. Endoesophageal ultrasound has provided a useful, minimally invasive tool to investigate these lesions and to allow sampling of cyst contents to confirm that the lesion, in an otherwise asymptomatic patient, is benign.[29,51] There is, however, potential risk of infection and aspiration should be avoided if the echo characteristics suggest a simple cyst. Esophagoscopy, when performed, will demonstrate a smooth, soft, compressible mass without mucosal abnormality or communication with the extraluminal mass.

■ Therapy

As in the case of bronchogenic cysts, esophageal duplications are likely to become larger or infected over time. Thus, resection is recommended for all enterogenous cysts, whether for current symptoms or for the high likelihood of future complications. Esophageal

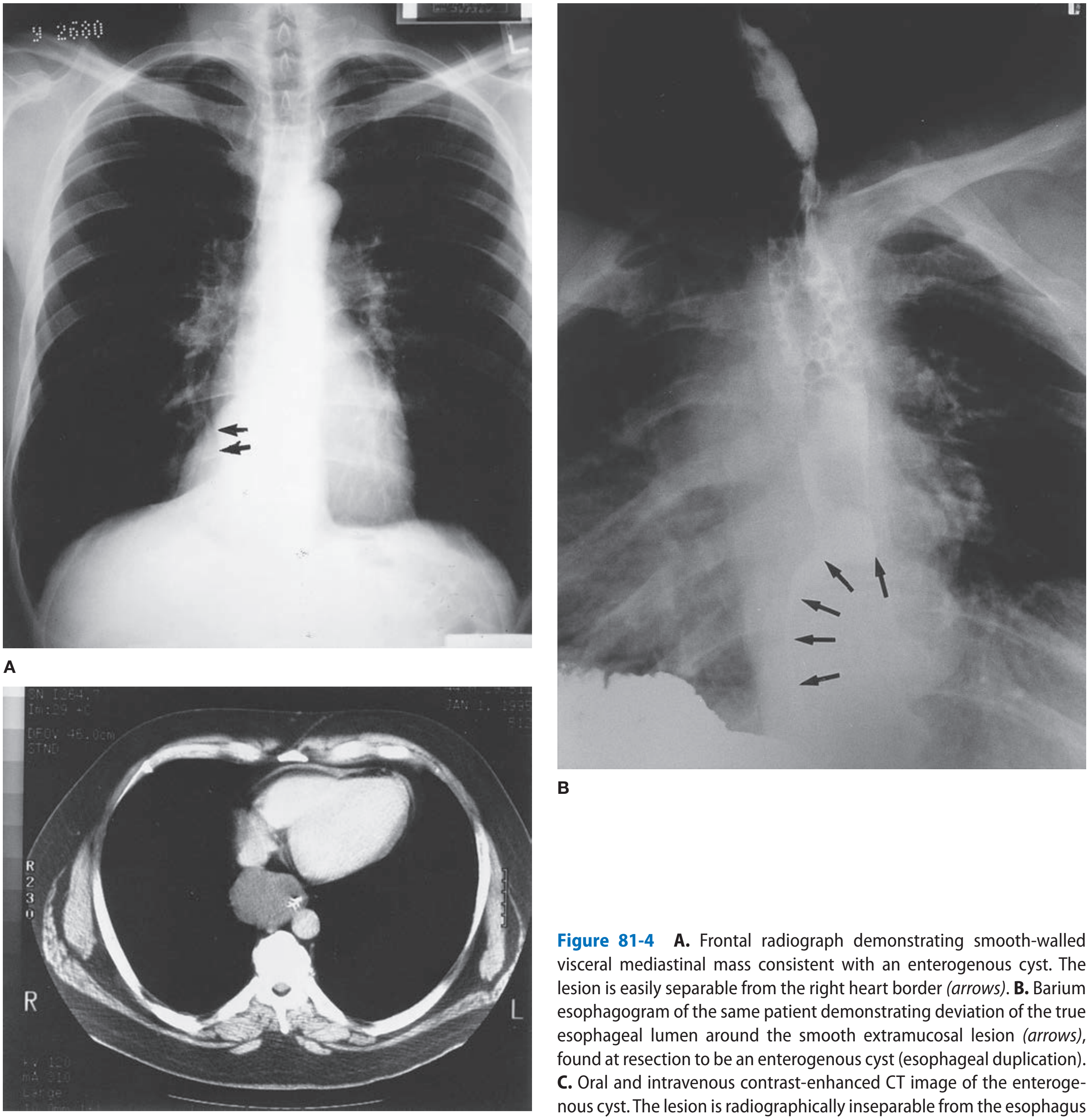

Figure 81-4 **A.** Frontal radiograph demonstrating smooth-walled visceral mediastinal mass consistent with an enterogenous cyst. The lesion is easily separable from the right heart border *(arrows)*. **B.** Barium esophagogram of the same patient demonstrating deviation of the true esophageal lumen around the smooth extramucosal lesion *(arrows)*, found at resection to be an enterogenous cyst (esophageal duplication). **C.** Oral and intravenous contrast-enhanced CT image of the enterogenous cyst. The lesion is radiographically inseparable from the esophagus but free of all cardiac structures.

duplication cysts can be approached through a standard thoracotomy, VATS, or robotic techniques.[52–58] Regardless of the approach, the following steps should be emphasized: (1) preservation of the muscular layer for repair, (2) identification and preservation of the vagus nerves, and (3) assessment of mucosal integrity via air insufflation under water. In most cases a plane of dissection in the submucosa can be achieved to complete the resection. Despite the lack of communication with the esophageal lumen, cyst resection may leave defects in the esophageal wall that must be meticulously repaired. If the mucosa is breached, the esophagus should be closed primarily in layers, and the repair should be reinforced with a locally procured flap of vascularized tissue. Options for buttressing include the pericardial fat pad, pleura, intercostal muscle, pericardium, or omentum. Case reports documenting the occurrence of an adenocarcinoma in esophageal duplication cysts underscore the need for resection at the time of diagnosis.

NEURENTERIC CYSTS

The embryology, clinical presentation, diagnosis, and management of neurenteric cysts are discussed below.

Embryology and Terminology

During the third week of normal embryogenesis, the notochord should separate from the primitive foregut (see Chapter 4). If this separation is incomplete, the mesodermal masses, which normally encircle the neural tube, cannot enclose it and vertebral anomalies arise. The attached foregut often spawns an associated mediastinal enteric cyst. This form of congenital cyst accounts for only 5% to 10% of all foregut lesions and is consistently associated with bony anomalies of the spine.[59] The spectrum of vertebral anomalies includes butterfly vertebrae, hemivertebrae, and anterior spina bifida. They occur primarily in the lower cervical and upper thoracic regions and are usually cephalad to the cystic lesion, since the esophagus descends (or the pharynx ascends) during fetal development. The fluid within the cyst may be nearly identical to cerebrospinal fluid or may be milky, cream-colored, yellowish, or xanthochromic. Neurenteric cysts may be intradural, extramedullary, and situated ventral or ventrolateral to the spinal cord.[60]

Presentation and Diagnosis

Neurenteric cysts are exceedingly rare; virtually all present within the first year of life.[61] More than half of afflicted children have neurologic complaints or findings. These include back pain, motor deficits of a lower extremity, and gait disturbance, especially if there is communication with the spinal canal. Often the triad of a mediastinal mass, airway symptoms, and a vertebral anomaly will be present. The diagnosis is frequently made after detection of vertebral anomalies on the chest radiograph. CT scans show vertebral abnormalities in 50% of affected patients and can define bony abnormalities and demonstrate extension of the cystic lesion into the spinal canal. MRI has supplanted CT myelography and provides a complete, noninvasive assessment of the bony abnormality, the intraspinal extent of the cyst, and the degree of spinal cord or nerve root compression associated with a neurenteric cyst.[62]

Therapy

Careful imaging of suspected neurenteric cysts is paramount for successful extirpation. MRI is useful to exclude extension of the cystic component into a neural foramen or the spinal canal proper and to exclude an associated meningocele. Such findings would require a staged resection employing a posterior neurosurgical approach first, to decompress the cord or its nerve roots, followed by resection of the mediastinal component by standard thoracotomy or VATS.[62–65] Complete cyst excision is the treatment of choice. When preoperative diagnostic imaging shows no intraspinal extension of the cyst, thoracoscopic excision may be possible. When there is only minimal involvement of the vertebral body, resection can be accomplished with VATS or more commonly a posterolateral thoracotomy. If the

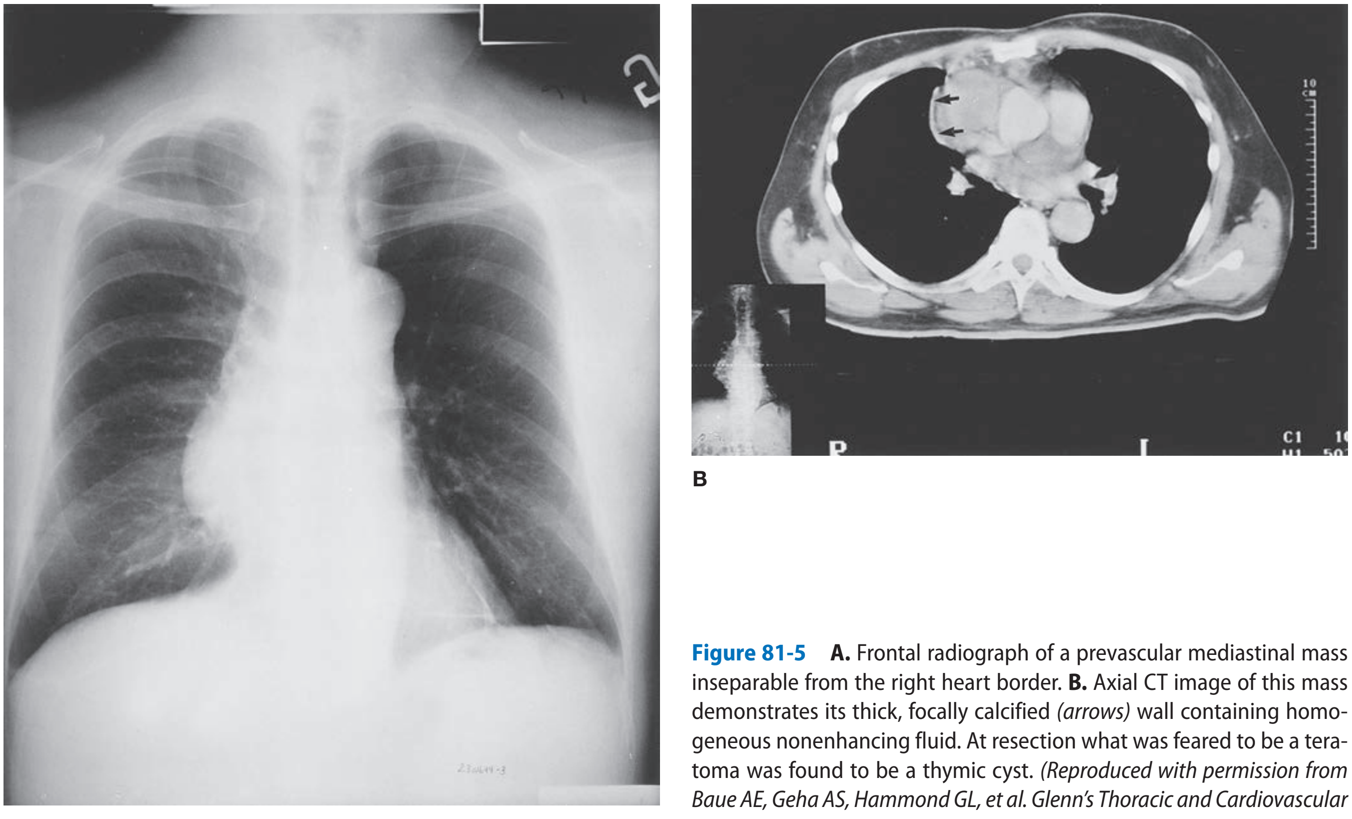

Figure 81-5 **A.** Frontal radiograph of a prevascular mediastinal mass inseparable from the right heart border. **B.** Axial CT image of this mass demonstrates its thick, focally calcified *(arrows)* wall containing homogeneous nonenhancing fluid. At resection what was feared to be a teratoma was found to be a thymic cyst. *(Reproduced with permission from Baue AE, Geha AS, Hammond GL, et al. Glenn's Thoracic and Cardiovascular Surgery, 6th ed. Stamford, CT: Appleton & Lange; 1996.)*

spinal abnormality is severe, a combined neurosurgical and thoracic approach is recommended.

THYMIC CYSTS

The thymus is derived from the third pharyngeal pouch. Its development is incomplete at birth, and the gland continues to grow throughout childhood into adolescence. Cysts within the gland are thought to occur during adulthood, when gland architecture involutes and central cells degenerate and are replaced by fat.

Thymic cysts are rare congenital or acquired lesions embryologically derived from the pharyngeal pouches. They account for only 3% to 5% of all prevascular mediastinal masses.[4–6,11,14,19] Most thymic cysts are asymptomatic and discovered incidentally on imaging studies performed for other reasons. Although thymic cysts are benign, they must be distinguished from thymomas, germ cell tumors, and lymphomas—all of which may have areas of cystic degeneration. These cysts arise in the prevascular compartment (Fig. 81-5) and may extend to the visceral compartment, especially in the aortopulmonary window (Fig. 81-6).[66] Congenital cysts are typically unilocular and contain clear fluid and an imperceptibly thin wall. Multilocular thymic cysts are usually acquired lesions. Plain radiographs do not differentiate thymic cysts from other non-lobulated thymic masses; therefore CT and MRI are employed for diagnosis. Both CT and MRI demonstrate clear tissue planes separating the cyst from other vital structures (Figs. 81-5 and 81-6). If hemorrhage or infection occurs, the cyst may show high signal intensity. In older patients, benign cysts may degenerate and present as a complex, thickened cystic mass with calcified walls that contain heterogeneous fluid (Fig. 81-5). Such lesions are easily confused with a mediastinal teratoma. Multiloculated thymic cysts can occur in association with thymic neoplasms, including thymoma and thymic carcinoma. Complete thymic excision can be accomplished through sternotomy, thoracotomy, VATS, or robotically.[36,37,56–58]

PERICARDIAL CYSTS

Pericardial diverticula and pericardial cysts represent slightly different stages of a lesion that has a common embryogenesis. When a communication exists between the pericardial sac and the extrapericardial fluid collection, the lesion is a diverticulum. Absence of communication defines a pericardial cyst.[67] Both diverticula and cysts derive from the ventral recess of the pericardial coelom, rather than from the pericardial lacunae. The discovery that a diverticulum-like structure in the ventral recess of the pericardial coelom occurred during development of the pericardium at the site

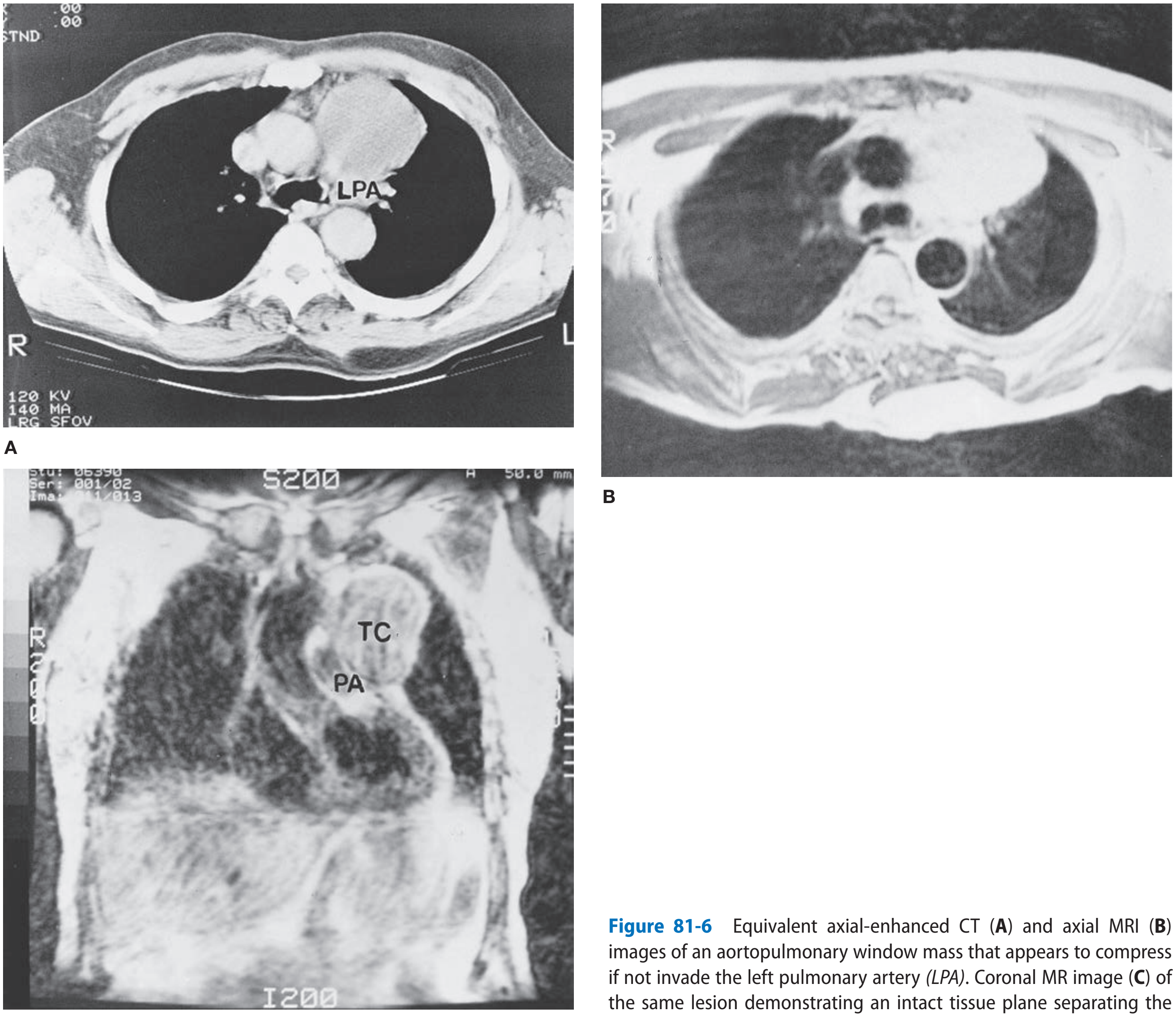

Figure 81-6 Equivalent axial-enhanced CT (**A**) and axial MRI (**B**) images of an aortopulmonary window mass that appears to compress if not invade the left pulmonary artery *(LPA)*. Coronal MR image (**C**) of the same lesion demonstrating an intact tissue plane separating the benign thymic cyst *(TC)* from the pulmonary artery *(PA)*.

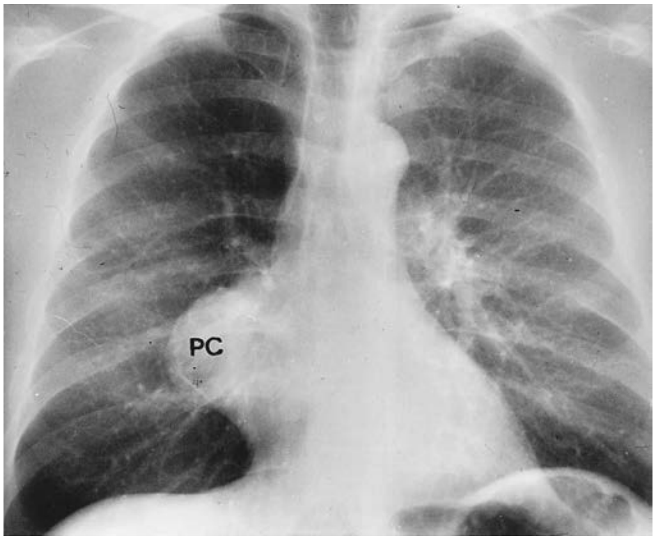

Figure 81-7 Frontal radiograph of a mediastinal mass, isodense with and inseparable from the right heart border. Thoracoscopy showed this to be a broadly based pericardial cyst *(PC)*.

where so many of these lesions were found led to speculation as to their possible relationship. Persistence of the recess results in formation of a diverticulum, while constriction of the proximal part of the persistent recess accounts for either a diverticulum with a narrow neck or a cyst in communication with the pericardial cavity. If the proximal portion of the recess is completely pinched off, an isolated pericardial cyst occurs in the cardiophrenic angle.

Pericardial cysts are simple, smooth-walled cystic lesions (Fig. 81-7) that are commonly located at the lateral basal edge of the pericardium, where it fuses with the diaphragm at the right cardiophrenic angle.[68] They can be mistaken for foramen of Morgagni hernias or prominent pericardial fat pads. They can be differentiated from more solid mediastinal tumors by CT or MRI. Pericardial cysts characteristically contain clear, low-density serous fluid. The appearance of these thin-walled, translucent cysts containing crystal-clear fluid gave rise to the term "spring water cysts."[64] They have no malignant potential and rarely get infected. Potential complications include hemorrhage or spontaneous rupture. Needle aspiration is often followed by reaccumulation of fluid and is not generally recommended. Surgery for pericardial cysts or diverticula is not indicated in the majority of cases, because these lesions are always benign, and most are asymptomatic. Resection should be reserved for cysts that cause symptoms (hemodynamic compromise, arrhythmia, chest discomfort, substernal pain, atelectasis) or for those demonstrating significant enlargement over time.[68] The operative approach, whether endoscopic or open, is dependent upon the location, size, and proximity of the cyst to vital structures. Most often, a right VATS approach is successful in excising the cyst. In most cases, standard two- or three-incision technique is utilized. Because pericardial cysts often overlie the right phrenic nerve, an unroofing procedure or subtotal resection is acceptable therapy if total excision would jeopardize diaphragmatic function.

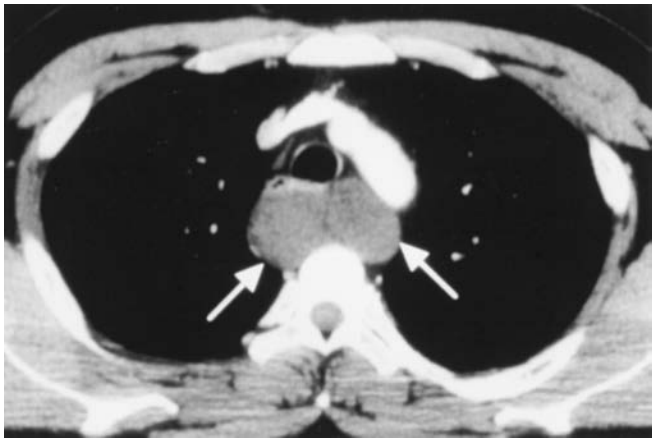

Figure 81-8 Axial contrast-enhanced CT scan of the chest revealed a large cystic mass measuring 3 × 5 × 15 cm *(arrows)*, displacing the esophagus and trachea anteriorly. *(Reproduced with permission from Chen F, Bando T, Hanaoka N, et al. Mediastinal thoracic duct cyst. Chest. 1999;115(2):584–585.)*

THORACIC DUCT CYSTS

Lymphatic channels develop from the lateral plate mesoderm, either as outgrowths of the venous system or by the fusion of mesenchymal clefts into vessels. The lymphatic sacs, which develop by the second month of gestation, are connected by these primitive lymphatic channels. It is these channels that unite the jugular lymph sacs to the cisterna chyli to form the thoracic duct. A congenital weakening of the thoracic duct wall is postulated to be responsible for some thoracic duct cysts.[69] These cysts are exceedingly rare; fewer than 40 cases have been reported in the literature. Histologically, they are similar to the thoracic duct, with the presence of occasional

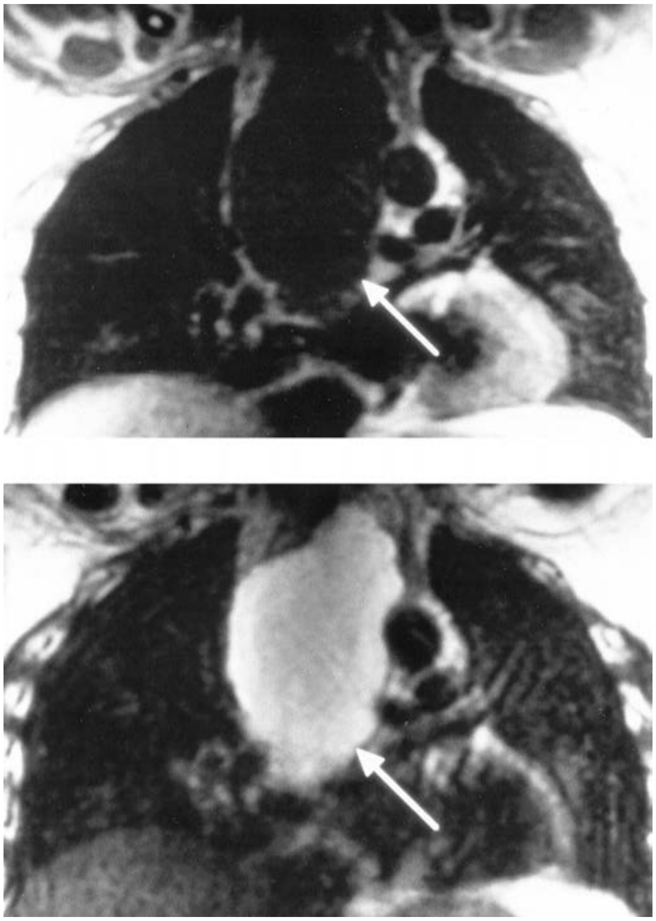

Figure 81-9 MRI scan. Top: Coronal T1-weighted imaging showing a low-intensity mass with a well-circumscribed margin *(arrow)*. Bottom: Coronal T2-weighted imaging showed a high-intensity mass *(arrow)*. *(Reproduced with permission from Chen F, Bando T, Hanaoka N, et al. Mediastinal thoracic duct cyst. Chest. 1999;115(2):584–585.)*

endothelial cells lining the cyst. They occur anywhere along the course of the duct from the cisterna chyli to the supraclavicular area.[70–72] Age at detection varies widely, and up to half of all patients are asymptomatic. Symptoms arise from compression of adjacent structures resulting in dyspnea, cough, chest pain, dysphonia, or dysphagia.[72–74] Plain films may demonstrate a visceral or sometimes paravertebral mediastinal lesion, with CT demonstrating a smooth, homogeneous cystic mass (Fig. 81-8).[15] MRI is superior to CT for evaluation, permitting superior delineation of the cyst boundaries (Fig. 81-9). As thoracic duct cysts can contain varying degrees of lipids and proteins, their MRI characteristics may vary accordingly. Contiguity with the thoracic duct and dilation of the thoracic duct aid the radiologist in making the correct diagnosis.[75] Confirmatory diagnosis may be made using lymphangiography or the presence of high triglyceride content in aspirated fluid, but these techniques are not commonly employed. Endobronchial ultrasound with transbronchial needle aspiration also can lead to the correct diagnosis.[76] Small cysts are generally observed, whereas symptomatic and larger cysts should be resected. Successful surgical management is contingent upon appropriate control of both afferent and efferent thoracic duct pedicles to avoid postoperative chylothorax. Excision can be accomplished through thoracotomy or VATS with application of clips or energy devices that fuse the vessel walls to control the afferent and efferent lymphatic channels.[70,76,77]

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CHAPTER 82

Primary Benign and Malignant Neoplasms of the Mediastinum

Natalie S. Lui
Joseph B. Shrager

INTRODUCTION

Primary lesions of the mediastinum are less common than lesions that secondarily involve the mediastinum. Overall, the majority of masses discovered in the mediastinum will be found to be metastases from a primary lung cancer. Neoplasms that arise primarily in the mediastinum, however, are often encountered in the clinic and are represented by a variety of lesions. This chapter first reviews the anatomy of the mediastinum and then focuses on the benign and malignant neoplasms that arise within each of the anatomic regions of the mediastinum. Covered elsewhere in this textbook are nonneoplastic disorders of the mediastinum that include pneumomediastinum, acute mediastinitis, chronic mediastinitis, and other miscellaneous disorders (Chapter 80); as well as congenital lesions of the mediastinum—which are nearly always benign—such as bronchogenic, enterogenous, neurogenic, thymic, pericardial, and thoracic duct cysts (Chapter 81).

ANATOMY OF THE MEDIASTINUM

The mediastinum constitutes an anatomic space located between the thoracic inlet superiorly, the diaphragm inferiorly, and the pleural cavities on the left and right sides. This central anatomic location houses or borders vital structures of almost every major organ system, including the heart and great vessels of the circulatory system, the esophagus of the digestive system, major airways of the respiratory system, the thymus of the immune system, and the phrenic and vagus nerves of the neurologic system. Further, various endocrine organs may extend into it, distant malignancies may metastasize to it, and infectious processes can manifest themselves within it.

The mediastinum is compartmentalized based upon the borders of anatomic structures as seen on a lateral chest radiograph (Fig. 82-1). We believe that the most anatomically appropriate and clinically useful model of the mediastinum is the three-compartment model, which divides the mediastinum into anterior, middle, and posterior compartments.[1] A new classification scheme developed by the International Thymic Malignancy Interest Group divides the mediastinum into similar compartments (prevascular, visceral, and paravertebral) based on computed tomography (CT) scans.[2] The anterior mediastinum extends from the thoracic inlet superiorly to the diaphragm inferiorly, and from the posterior table of the sternum anteriorly to the anterior pericardium and the great vessels posteriorly. It contains most importantly the thymus, but also fat, lymphatic tissues, and the internal mammary arteries and veins. The middle mediastinum is bounded anteriorly by the pericardium and posteriorly by the pericardium and posterior wall of the trachea, extending only as high as the pericardial reflection. It contains the heart, pericardium, superior and inferior vena cavae, ascending and transverse aorta, trachea and mainstem bronchi, and lymphatic tissues. The posterior mediastinum extends from the thoracic inlet to the diaphragm and lies posterior to the posterior pericardium and airway. It contains the descending aorta, thoracic duct, esophagus, vagus nerves, and lymph nodes, as well as structures emerging from the spinal canal such as intercostal nerves.

One of the main advantages of dividing the mediastinum into compartments is the ability to generate a differential diagnosis for a mediastinal mass based on the structures that are contained within the compartment in which it arises (Table 82-1). Such a classification scheme allows a clinician to proceed systematically to determine the appropriate diagnostic or therapeutic approach depending on the differential diagnosis.

EPIDEMIOLOGY AND INCIDENCE

The incidence and type of primary mediastinal neoplasms vary with patient age. In a combined series of 3017 adult patients, thymomas and thymic cysts (26.5%) and neurogenic tumors (20.2%) were the most common, followed by germ cell tumors (GCTs) (13.8%), lymphomas (12.7%), foregut cysts (10.3%), and pleuropericardial cysts (6.6%). In a combined series of 718 children, neurogenic tumors were most common (41.6%), followed by GCTs (13.5%), foregut cysts (13.4%), lymphomas (13.4%), angiomas and lymphangiomas (6.1%), and thymic tumors or cysts (4.9%).[3] In general, the incidence of anterior mediastinal masses is higher in adults, while posterior mediastinal masses predominate in children. Further, the incidence of malignancy differs among primary mediastinal masses arising in each of the different compartments. In one of the largest series, Davis et al. demonstrated that among 400 consecutive patients with mediastinal masses, malignancy was found in 59% of those in the anterior mediastinum, 29% of those in the middle mediastinum, and 16% of those in the posterior mediastinum.[4]

As discussed below, mediastinal masses are often incidentally detected on imaging studies obtained for other reasons. An estimate of the frequency of “incidental” mediastinal masses has been provided by a large lung cancer screening study. Of the 9263 individuals at high risk for lung cancer who underwent CT screening, 71 (0.77%) had a mediastinal mass. The majority of these incidental masses were thymic, and most were managed nonoperatively.[5]

SIGNS AND SYMPTOMS

Signs and symptoms of mediastinal tumors can vary widely at presentation and usually offer only nonspecific clues to the nature of the underlying disease process. While more than 60% of patients do present with symptoms, it is also quite common for an asymptomatic mass to be detected incidentally. Most asymptomatic patients with a mediastinal mass have benign lesions, while most symptomatic patients have an underlying malignant process. In Davis' series of 400 patients with mediastinal masses, only 17% of the lesions found on routine chest radiographs were malignant, but this increased to 57% in symptomatic patients.[4]

The presenting symptoms of a mediastinal mass are influenced by the anatomic location and the presence of malignant invasion or mass effect. Dyspnea or cough may result from airway invasion or abutment, tamponade, or the presence of a pleural effusion. Dysphagia is seen with esophageal compression, and chest pain may represent chest wall or neural invasion or abutment. Invasion of the airway may result in hemoptysis, invasion of the recurrent laryngeal nerve may present as hoarseness, and invasion of the superior vena cava can present with swelling of the face or neck due to superior vena cava syndrome. Constitutional symptoms such as fevers, night sweats, and weight loss (B symptoms) are often associated with

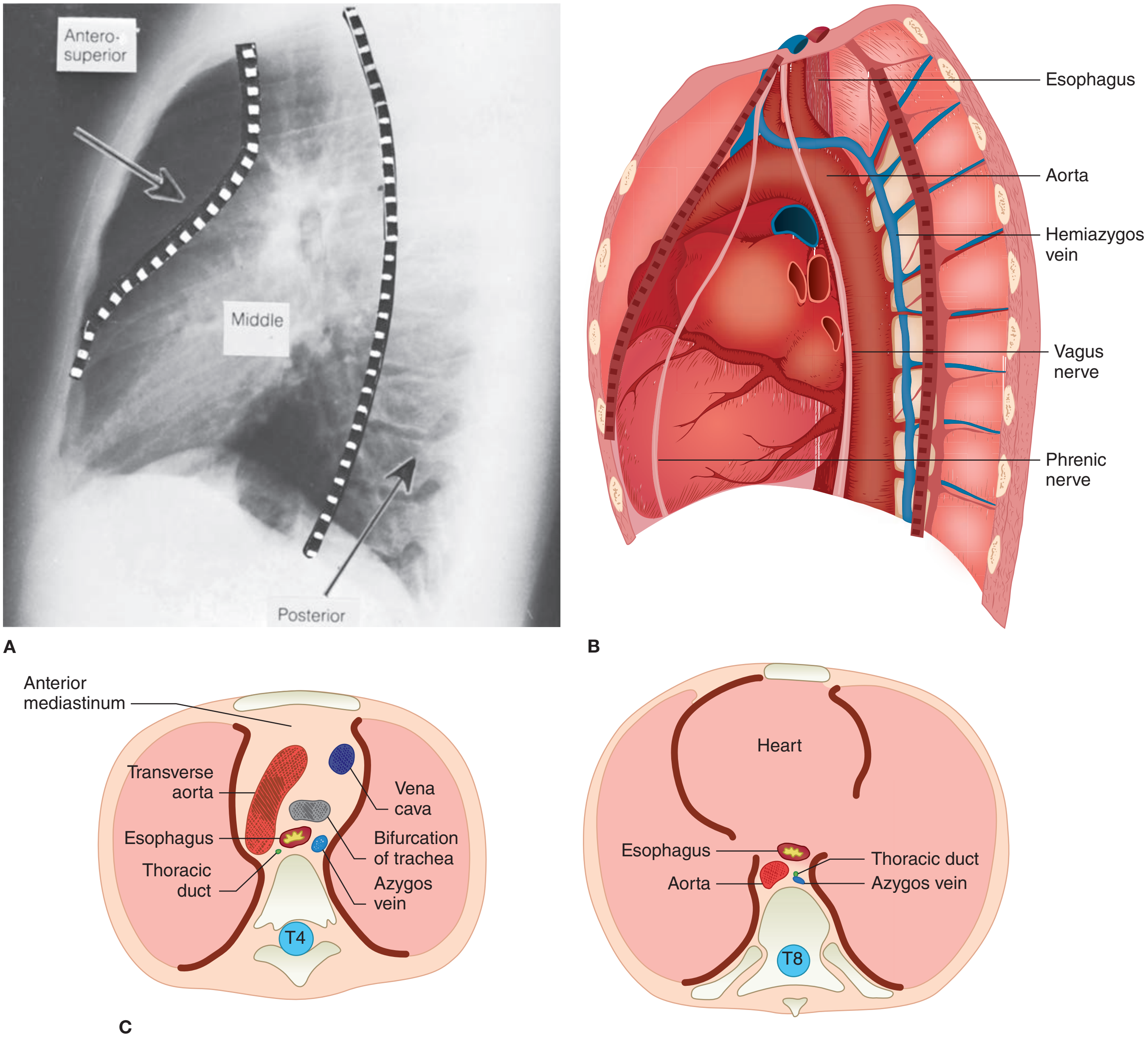
Antero-
superior
Middle
Posterior
A
Esophagus
Aorta
Hemiazygos
vein
Vagus
nerve
Phrenic
nerve
B
Anterior
mediastinum
Transverse
aorta
Esophagus
Thoracic
duct
Vena
cava
Bifurcation
of trachea
Azygos
vein
T4
Heart
Esophagus
Aorta
Thoracic duct
Azygos vein
T8
C

Figure 82-1 Three-compartment model of the mediastinum. **A.** Lateral radiograph of the chest. **B.** Schematic representation of the contents of the three compartments of the mediastinum. **C.** Cross sections of the thorax at T4 (left) and T8 (right) to show relative positions of mediastinal structures.

mediastinal lymphoma, and myasthenic symptoms are suggestive of thymoma.

ANTERIOR MEDIASTINAL NEOPLASMS

Below we discuss the clinical evaluation of the patient with an anterior mediastinal mass before individually considering a variety of etiologies.

■ Evaluation of the Anterior Mediastinal Mass

In a patient with an anterior mediastinal mass, it is often possible to make a strong provisional diagnosis based upon clinical evaluation and imaging data.[6] Whereas specific workup for common anterior mediastinal mass lesions is described in the following sections, some general principles are reviewed here.

■ History and Examination

In an individual younger than 40 years, lymphoma is the most likely diagnosis, and the presence of B symptoms (fever, weight loss, or night sweats) or lymphadenopathy elsewhere further increases the level of suspicion. In contrast to lymphoma, thymic neoplasms are very uncommon before the fourth decade of life. The presence of a paraneoplastic syndrome associated with an anterior mediastinal mass (most commonly myasthenia gravis [MG]) essentially clinches the diagnosis of thymoma. The majority of GCTs (benign or malignant) are diagnosed in the second or third decade of life. Whereas patients with a thymoma often have an indolent presentation, patients with a lymphoma or a malignant GCT often have a rapid onset of symptoms. Workup must include examination of the testes to rule out a testicular primary GCT.

■ Serum Studies

Antibodies to the acetylcholine receptor (AChR-Ab) should be measured, as their presence is virtually diagnostic of MG, even if the patient is without obvious symptoms. Tumor markers, such as beta-human chorionic gonadotropin (β-hCG) and alpha-fetoprotein (AFP), are

TABLE 82-1 Structures and Primary Neoplasms in the Three-compartment Model of the Mediastinum

Structures	Common Lesions	Rare Lesions
Anterior compartment		
Thymus	Thymomas	Thymic carcinoma; benign thymic tumors and cysts
Fat and lymphatics	Lymphomas	Vascular lesions
Internal mammary vessels	Germ cell tumors	Mesenchymal tumors
Thyroid (occasional)		Endocrine tumors (e.g., ectopic parathyroid, goiter)
		Castleman disease
Middle compartment		
Heart	Foregut cysts	Pleural and pericardial cysts
Pericardium	Lymphoma	Castleman disease
Aorta		
Superior and inferior vena cava		
Trachea and main bronchi		
Lymph nodes		
Posterior compartment		
Descending aorta	Nerve sheath tumors	Vascular tumors
Esophagus	Neurogenic tumors	Mesenchymal tumors
Vagus nerves		Lymphatic lesions
Thoracic duct		Neurenteric cysts
Sympathetic chain		
Lymph nodes		

elaborated by most malignant GCTs but not by benign GCTs.[7] Elevated serum LDH is suggestive of lymphoma. Evidence of hypo- or hyperthyroidism, as measured by thyroid-stimulating hormone (TSH) and thyroid hormones (T3 and T4), suggests mediastinal goiter, although goiter is not invariably associated with abnormal hormone production.

■ Imaging Studies

CT provides valuable data about the tumor's anatomic location, physical characteristics (fatty, solid, or cystic), and degree of invasiveness. Occasionally, magnetic resonance imaging (MRI) can distinguish cystic from solid masses when unclear on CT[8] or provide useful additional information concerning obliteration of normal tissue planes and vascular invasion. Cysts containing highly proteinaceous fluid can be difficult to separate from solid masses on CT alone. Although imaging is most often not diagnostic of the specific type of tumor, some imaging features can be pathognomonic. For example, the finding of a well-encapsulated lesion in the anterior mediastinum containing several tissue elements—calcium, fat, and fluid—is essentially diagnostic of a mature teratoma.

■ Need for Biopsy

The decision whether to perform a biopsy of an anterior mediastinal mass is not simple. Routine biopsy should not be endorsed, not only because of the unnecessary morbidity and costs associated with the procedure, but also because of the potential risk of tumor spread, particularly for thymoma. If a clinical diagnosis of thymoma is made with a high level of confidence, and the tumor is resectable, surgical resection should be performed without preliminary biopsy, as these tumors have a predilection for local recurrence once the thymic capsule has been violated. Unfortunately, however, this approach may lead to occasional unnecessary resection of lymphoma, which is ideally treated nonsurgically.

Locally invasive or unresectable anterior mediastinal masses should most often be biopsied; such lesions may represent lymphoma, aggressive thymomas that could benefit from neoadjuvant treatment, malignant GCTs that also should be treated initially with systemic therapy, or other rare diseases. These patients should undergo either a CT-guided core needle biopsy or a Chamberlain procedure (anterior mediastinotomy) for diagnosis, depending upon the pathologist's level of comfort in classifying lymphoma on the basis of cytology alone at one's institution. When palpable peripheral nodes are present, the diagnosis of lymphoma is often most easily obtained by excisional biopsy of one of these. Resection of lymphoma is not indicated and can almost always be avoided by performing a diagnostic biopsy when lymphoma is suspected.

Surgical resection is the mainstay of treatment for mature (low-grade) GCTs, and biopsy is not indicated for these lesions if they have the characteristic imaging characteristics. Malignant GCTs, on the other hand, are treated primarily with chemotherapy, radiotherapy, or both; surgery is sometimes considered after a good response to these modalities. In situations where GCT is suspected but tumor markers (AFP and β-hCG) are not markedly elevated, biopsy should be performed.

■ Thymoma

Below are considered the clinical presentation, diagnostic approach, staging, treatment, and outcomes for patients with thymoma.

Presentation

The age distribution of patients with a thymoma is represented by a broad peak between approximately 35 and 70 years with a median age of about 54 years.[9] The ratio of men to women with this disease is about equal. Approximately one-third of patients with a thymoma will not report significant symptoms, and one-third will report symptoms of cough, dyspnea, or chest pain reflective of compression or invasion of adjacent structures. Patients may also present with symptoms of an associated paraneoplastic syndrome. Some 40% to 45% of patients with a thymoma will present with MG, and, conversely, 5% to 15% of patients with MG will be found to have a thymoma.[10–12] Thymomas may also be associated with pure red cell aplasia, agammaglobulinemia, systemic lupus erythematosus, and other autoimmune disorders; these respond less consistently than MG to thymectomy.[13]

Diagnosis

A clinical diagnosis of thymoma is often sufficient to proceed to resection without biopsy (see above). The presence of a paraneoplastic syndrome associated with an anterior mediastinal mass essentially clinches the diagnosis of thymoma. Antibodies to the acetylcholine receptor (AChR-Ab) should be measured, and their presence is diagnostic of MG and also clinches the diagnosis of thymoma. Interestingly, AChR-Ab are demonstrated in approximately 60% of patients who have thymoma without neurologic symptoms.[14] In addition, MG can develop some time after diagnosis of thymoma, and occasionally even following resection, highlighting the necessity of complete resection of both the thymoma and the entire thymus gland. All patients with thymoma should have preoperative

AChR-Ab testing, even if asymptomatic, since positive levels are a risk factor for development of MG after thymectomy.[15–17]

It is not necessary to obtain a preoperative tissue biopsy for a small, resectable anterior mediastinal tumor whose radiographic features are typical of thymoma in an asymptomatic patient. Although there are no pathognomonic imaging features that differentiate thymoma from several other mediastinal tumors, in a patient without B symptoms to suggest lymphoma, the diagnosis of thymoma is strongly suggested by a CT scan demonstrating a well-circumscribed, solid anterior mediastinal mass without the low-density areas that would suggest the cystic and fatty components of a teratoma (Fig. 82-2). Most thymomas are solid tumors, but up to a third may have components that are necrotic, hemorrhagic, or cystic. Several small studies have investigated the utility of PET in evaluation of thymoma and have suggested greater FDG uptake in thymic carcinoma and lymphoma compared with thymoma.[18–20] Our institutional experience with 77 patients with an anterior mediastinal mass eventually shown to be either thymoma or lymphoma showed that 100% of discrete mediastinal tumors were thymoma and thus could be safely resected without the need for preliminary biopsy, while 100% of tumors with SUVmax above 12.85 were lymphoma.[21]

Once a diagnosis of thymoma is strongly supported, the goal is to proceed directly to resection without preliminary biopsy, as these tumors have a predilection for local recurrence once the capsule has been violated. A definitive tissue diagnosis is needed primarily when a presumed thymoma is so advanced that it would be best treated either nonoperatively or with neoadjuvant chemotherapy or chemoradiotherapy, or in instances where there is a strong possibility of lymphoma. If required, the pathologic diagnosis of thymoma can usually be achieved by image-guided core needle biopsy, or if that fails, through open surgical biopsy. The success rate of needle biopsy in establishing the diagnosis of thymoma is approximately 60%, and the success rate of surgical biopsy is approximately 90%.[22]

In our opinion, video-assisted thoracoscopic surgical (VATS) biopsy of an anterior mediastinal mass in which thymoma is in the differential should be assiduously avoided, due to the great potential of spread into the pleural space. If core needle biopsy fails and a diagnosis is required, a Chamberlain procedure (anterior mediastinotomy) is typically the better approach than VATS.

All patients with suspected thymoma should be evaluated for MG. This evaluation usually begins with a careful assessment for the presence of ocular, bulbar, and limb muscle weakness. The diagnosis of MG in a patient with a characteristic history and physical examination requires two positive confirmatory tests among pharmacologic (Tensilon test), serologic (AChR-Ab), and electrodiagnostic (EMG) studies. If there is any suggestion of MG on initial presentation, the patient should undergo preoperative evaluation by a neurologist. Medical optimization prior to surgery using some combination of cholinesterase inhibitors, intravenous immunoglobulin, plasmapheresis, and occasionally steroids, can help avoid the rare occurrence of respiratory failure or a myasthenic crisis in the perioperative period.

Staging

The most widely utilized classification scheme for thymoma was proposed by Masaoka in 1981 and is based on the local invasiveness of the tumor (Table 82-2).[23] The Masaoka classification system has prognostic value and permits stratification for adjuvant therapy.[24] One difficulty with this system is that it is based upon the findings at the time of surgical resection, thus precluding its use for triaging some patients to neoadjuvant therapy. The American Joint Committee on Cancer adopted a Tumor, Node, Metastasis (TNM) staging system in the eighth edition (Table 82-3) that was created by an international collaboration that included the International Thymic Malignancy Interest Group (ITMIG) and the International Association for the Study of Lung Cancer (IASLC).[25,26] This system frequently stages tumors lower (for example, macroscopic invasion into the mediastinal pleura is stage I in the TNM system) and will reduce recommendations for adjuvant radiation therapy.[27] In addition, it is unclear whether mediastinal lymph node staging is necessary when only 2% of thymomas have involved nodes, and these nodes are difficult to access through minimally invasive techniques.[27]

Thymomas are also classified histologically. A thymoma is composed of a mixture of thymic epithelial cells with bland features as well as lymphocytes in various stages of development. The neoplastic cell of origin is believed to be the thymic epithelial cell and not the lymphocyte,[28] and thymomas appear histologically benign even when they are invasive. In 1985, Müller-Hermelink proposed a novel histologic classification system to separate all thymomas into categories of cortical, medullary, or mixed, based on the histologic appearance of the thymic epithelial cells.[29] Cortical thymomas are composed of large, round, or polygonal epithelial cells, and medullary thymomas contain smaller, spindle cell–shaped epithelial cells with irregular nuclei. This histologic classification system was found

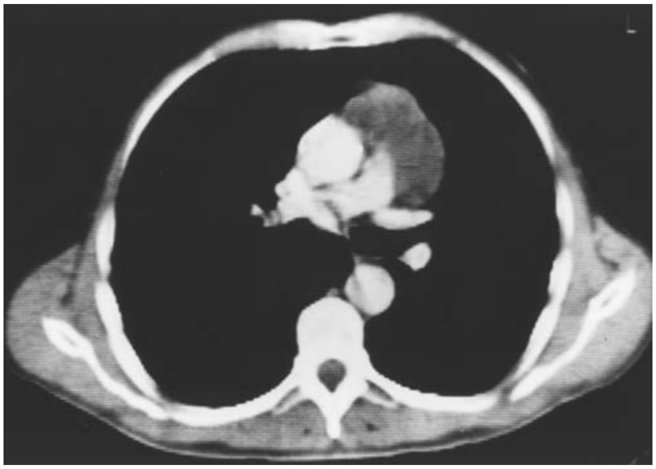

Figure 82-2 Thymoma. Axial section from a CT scan demonstrates a 4-cm mass abutting the thoracic aorta without any evidence of invasion.

TABLE 82-2 Masaoka Staging of Thymic Malignancies

Stage	Description	10-Year Survival (%)
I	Encapsulated tumors without gross or microscopic invasion	90 (75–100)
II	Transcapsular invasion	75 (42–100)
IIA	Microscopic invasion	
IIB	Macroscopic invasion	
III	Macroscopic invasion of surrounding tissues (lung, pericardium, vena cava, or aorta)	56 (26–84)
IVA	Disseminated disease within the chest	38 (22–47)
IVB	Distant metastases	Unknown

Data from Detterbeck FC. Evaluation and treatment of stage I and II thymoma. J Thorac Oncol. 2010;5(10 Suppl 4):S318–S322.

TABLE 82-3 American Joint Committee on Cancer Eighth Edition TNM Staging for Thymoma

Category	Stage	Description
T	X	Primary tumor cannot be assessed
	0	No evidence of primary tumor
	1	Tumor encapsulated or extending into the mediastinal fat; may involve the mediastinal pleura
	1a	No mediastinal pleura involvement
	1b	Direct invasion of mediastinal pleura
	2	Direct invasion of the pericardium
	3	Direct invasion into lung, brachiocephalic vein, superior vena cava, chest wall, phrenic nerve, or extrapericardial pulmonary vessels
	4	Invasion into the aorta, arch vessels, main pulmonary artery, intrapericardial pulmonary artery, myocardium, trachea, or esophagus
N	X	Regional lymph nodes cannot be assessed
	0	No regional lymph node metastasis
	1	Metastasis in anterior (perithymic) lymph nodes
	2	Metastasis in deep intrathoracic or cervical lymph nodes
M	0	No pleural, pericardial, or distant metastasis
	1a	Separate pleural or pericardial nodule(s)
	1b	Pulmonary intraparenchymal nodule or distant organ metastasis

T	N	M	Stage Group
1ab	0	0	I
2	0	0	II
3	0	0	IIIA
4	0	0	IIIB
Any	1	0	IVA
Any	0–1	1a	IVA
Any	2	0-1a	IVB
Any	Any	1b	IVB

to reliably predict tumor behavior and prognosis, with medullary thymomas behaving in an essentially benign fashion and cortical thymomas more frequently demonstrating evidence of invasive and malignant disease.[30] Later studies have demonstrated that both the Masaoka staging and Müller-Hermelink grading systems are strong and independent prognostic indicators of both overall and disease-free survival.[24,31,32]

More recently, the World Health Organization (WHO) proposed a histologic classification system (resembling the Müller-Hermelink system) that has become the histologic grading system of choice in the current era and is useful to distinguish between thymoma, thymic carcinoma, and thymic carcinoids (Table 82-4).[33] It is now accepted that the Masaoka or TNM staging criteria used in combination with the WHO grading criteria provides the most accurate prognostic information for survival and recurrence in thymoma.[34,35]

Treatment

Surgical resection is the mainstay of treatment for Masaoka stage I–III thymoma while the treatment of stage IVa thymoma is controversial. Resection of even a small stage I thymoma with MG should include removal of the entire thymus, as total thymectomy is the ideal treatment for MG even in the absence of thymoma. Total thymectomy should also be performed in all cases where AChR-Abs are present in asymptomatic patients. Asymptomatic patients with no antibodies and small tumors may do equally well with a thymomectomy without total thymectomy, as long as wide tumor-free margins can be achieved. The gold standard surgical approach to thymoma remains median sternotomy, but minimally invasive approaches including VATS and robotic techniques are likely equally effective for smaller tumors in experienced hands.[36,37] It is critically important, however, that the tumor capsule not be disrupted during surgery to avoid pleural dissemination, and thus a "no-touch" technique is always used whether via median sternotomy or minimally invasive approaches. Certainly, if there is suspicion of invasion into adjacent structures, sternotomy is the preferred approach as it is critical that the involved portions of these structures are resected en bloc with the thymus gland and tumor. This may require resection of lung, pericardium, innominate vein, superior vena cava, phrenic nerve, and even aorta.

Stage I thymomas are treated adequately with complete resection alone. Thymoma is a radiosensitive tumor, and postoperative radiotherapy is recommended for patients who have incomplete resection. It is sometimes used after complete resection for stage II and higher thymoma, although there are conflicting data about additional benefit.[38–40] For patients with stage III or IV thymoma, chemotherapy is recommended and is often administered preoperatively, followed by radiation for patients with incompletely resected disease. For thymoma that is initially considered unresectable, induction chemotherapy followed by surgical resection can result in favorable rates of overall and disease-free survival.[41,42] Further, surgical resection plays an important role in the management of recurrences, and complete resection of a recurrence may result in improved overall survival.[43] Immunotherapy is rarely used

TABLE 82-4 World Health Organization (WHO) Histologic Classification System of Thymomas

Type	Description
A	Tumor in which foci having features of type A thymoma are admixed with foci rich in lymphocytes
B1	Tumor resembles normal functional thymus; combines large expanses having an appearance practically indistinguishable from that of normal thymic cortex with areas resembling thymic medulla
B2	Tumor in which neoplastic epithelial component appears as scattered plump cells with vesicular nuclei and distinct nucleoli among a heavy population of lymphocytes; perivascular spaces are common and sometimes very prominent; a perivascular arrangement of tumor cells resulting in a palisading effect may be seen
B3	Thymoma predominantly composed of epithelial cells having a round or polygonal shape and exhibiting no or mild atypia; they are admixed with a mild component of lymphocytes, resulting in a sheet-like growth of the neoplastic epithelial cells
C	Thymic tumor exhibiting clear-cut cytologic atypia and a set of cytoarchitectural features no longer specific to the thymus, but rather analogous to those seen in carcinomas of the other organs; type C thymomas lack immature lymphocytes; whatever lymphocytes may be present are mature and usually admixed with plasma cells

for thymoma given the increased risk of immune-related adverse events.[44]

Outcome

Although thymomas (not thymic carcinomas) are generally indolent tumors, they should be considered a malignant neoplasm as they have the ability to metastasize locoregionally to the pleura, pericardium, and, rarely, to distant sites. One study reported that 4% of 207 patients evaluated for surgical resection of a thymoma had lymph node or distant metastasis at presentation, and another 16% developed nodal or distant metastases at some point in their course.[45] Other studies have shown that distant metastases can occur with any stage or histology.[46,47]

Detterbeck reviewed 15 surgical series of at least 100 patients each (2437 patients total) and demonstrated favorable 10-year survival rates of approximately 90% for stage I, 70% for stage II, 55% for stage III, and 35% for stage IVa thymoma.[22] Complete resection is the most important prognostic factor and is associated with longer survival in all large studies examining this issue.

Locoregional recurrence is far more common than distant recurrence, and about half of all local recurrences involve the pleural space or the lung. The average recurrence rate for stage I tumors is 3% but increases to 11% and 30% for stage II and III tumors, respectively.[9] The relatively indolent nature of a thymoma is reflected by an average time to recurrence of 5 years, with rare recurrences seen as far out as 20 years.

The presence of MG is no longer considered a negative prognostic factor, as it was in older studies. More than 30% of patients with MG and thymoma ultimately achieve a complete remission of the MG following thymectomy, and up to 80% have some degree of improvement in their MG.[48] Of note, a randomized trial recently showed improved MG outcomes after extended thymectomy in most patients with MG without thymoma.[49] Similarly, approximately one-third of patients with associated red cell aplasia experience improvement following thymectomy. In contrast, hypogammaglobulinemia associated with thymoma generally does not respond to thymectomy.

■ Thymic Carcinoma

A clinical approach to diagnosis and management of thymic carcinoma is considered in the sections that follow.

Presentation

Thymic carcinomas (WHO type C malignant thymic epithelial tumors) are highly aggressive neoplasms of thymic epithelial origin and are very different from thymomas (WHO types A, AB, and B). Thymic carcinomas are rare, constituting approximately 10% of all thymic neoplasms.[43] They can occur at any age but are most frequently observed in persons between 30 and 60 years of age. Most patients with thymic carcinoma present with symptoms of local invasion or compression such as cough, chest pain, or superior vena cava syndrome. Pericardial and/or pleural effusions are often seen. Thymic carcinoma is typically not associated with MG. Unlike thymomas, thymic carcinomas frequently metastasize to lymph nodes and distant sites. Eighty percent of patients have local invasion of contiguous mediastinal structures at the time of presentation, and 40% of cases have metastatic spread to bones, lung, pleura, liver, or lymph nodes.[50] More than half of the patients will present with locally advanced, although potentially resectable, disease.[51,52]

Diagnosis

Thymic carcinomas can be distinguished from thymomas based on their malignant histologic features and different immunohistochemical and genetic characteristics. Imaging studies often reveal a more invasive presentation, and for this reason, and because lymphoma and thymic carcinoma can appear similar on imaging, percutaneous needle biopsy should generally be undertaken in patients with clear invasion of surrounding structures on imaging.

Staging

The Masaoka and TNM staging systems and the WHO histologic classification system are used to stage thymic carcinoma, just as in thymoma. In the WHO system, thymic carcinomas are type C lesions. These tumors are distinct from thymoma and should not be considered in the same light as a thymoma with local invasion. Histologically, thymic carcinoma contains a number of different cell types, but they are unified by their unequivocal malignant appearance on light microscopy. Division of patients into those with low-grade histology and those with high-grade histology has prognostic significance. The median survival for patients with low-grade histology (squamous, mucoepidermoid, and basaloid thymic carcinomas) is 29 months, compared with 11 months for patients with high-grade histology (sarcomatoid and clear cell thymic carcinoma).[53]

Treatment

While there is no standard-of-care approach to patients with thymic carcinoma, a multidisciplinary strategy is recommended. The prevailing practice is that patients with stage I–III and some IVa patients believed to have resectable disease should be treated with some combination of surgical resection plus chemotherapy and/or radiotherapy.[54] For the rare thymic carcinoma patients with clearly resectable disease, surgery is considered the primary therapeutic modality. For those with disease thought to be initially unresectable or disease that appears likely to be invading one or more surrounding organs or major vascular structures, neoadjuvant chemotherapy and/or radiation may improve operability and permit subsequent resection.[53,55,56] Immunotherapy has been used for refractory or recurrent thymic carcinoma, but there is concern for immune-related adverse events.[44]

Outcome

The prognosis for patients with thymic carcinoma is much worse than for patients with thymoma, with 5-year overall survival rates in the range of 30% to 50%.[52,57,58] A more recent clinicopathologic study of 65 cases of primary thymic carcinoma, however, reported a more favorable 5-year survival rate of 66%. In this study, 63% of the patients received additional therapy in the form of chemotherapy or radiation.[51] Similar to thymoma, patients with completely resected thymic carcinomas have longer overall and progression-free survival rates than those who undergo incomplete resection or are unresectable. In a recent series of 60 patients with thymic carcinoma (40 treated surgically), complete resection and early Masaoka stages are the most important factors associated with successful disease control and long-term survival. Five-year survival of 85% was obtained after complete resection, compared with 29% in those with incomplete resection.[59] In another series of 16 patients, a multimodality approach that included surgery resulted in complete resection in 88% of the patients and a mean survival of 4.2 years for the entire group.[60]

■ Other Thymic Neoplasms

Clinical assessment and management of a variety of other thymic neoplasms are considered below.

Thymic Hyperplasia

Thymic hyperplasia is a term used to describe either a histologically normal thymus that is enlarged for the patient's age, or a thymus that histologically shows cellular hyperplasia, which is also generally associated with gross enlargement of the gland. This condition can present as a spectrum of disease ranging from respiratory compromise due to impingement on the airway (almost exclusively in the pediatric population) to the more common situation of an incidental finding on an unrelated imaging study. Many of the thymus glands removed from patients with MG demonstrate "true thymic hyperplasia" (cellular hyperplasia), and this is thought to contribute to the pathogenesis of the disease. In addition to MG, thymic hyperplasia can be seen following severe or chronic illness, the so-called "thymic rebound." Steroid use will also generally lead to substantial thymic hyperplasia. Practically speaking, when a diffusely enlarged thymus without a discrete mass is discovered in an otherwise asymptomatic patient without elevated serum AChR-Abs, this can be followed expectantly, as these glands have a negligible risk of harboring significant thymic disease.[61]

Thymolipoma

Thymolipomas are distinguished from simple mediastinal lipomas by their location within the thymic capsule. Histologically, these neoplasms are composed of mature adipocytes as well as normal thymic components.[62] Thymolipomas, like thymomas, can be associated with thymic paraneoplastic syndromes such as red cell aplasia, hypogammaglobulinemia, and aplastic anemia. These lesions can grow to significant size and result in compressive and obstructive symptoms. The treatment of thymolipomas is surgical excision.

Thymic Neuroendocrine Tumors

Thymic neuroendocrine tumors, also known as thymic carcinoid tumors, are very rare neoplasms of the thymus.[63] They have a strong association with endocrinopathies such as multiple endocrine neoplasia type I. Unlike other carcinoids, they rarely present with carcinoid syndrome, but many do secrete adrenocorticotropic hormone (ACTH) resulting in Cushing syndrome. Thymic neuroendocrine tumors tend to be very aggressive. Upon presentation, most thymic carcinoids are locally invasive and almost half of all patients will have metastatic disease.[64,65] Surgery is the therapy of choice for resectable thymic neuroendocrine tumors and should include aggressive wide margins. The prognosis is poor despite aggressive therapy, and most patients present with local recurrence or metastases within 5 years of surgery and will die within 10 years.

Germ Cell Tumors

Germ cell tumors (GCTs) constitute a group of neoplasms that arise from gonadal tissue. The anterior mediastinum is the most common location for occurrence of extragonadal GCTs. GCTs account for 15% of all anterior mediastinal masses in adults (85% of which are benign, mature GCTs) and 25% of anterior mediastinal masses in children.[66] GCTs typically occur in young adults in the second to fourth decades of life with no gender predilection.

While previously thought to be metastatic from a gonadal primary, it is now accepted that these neoplasms are primary mediastinal tumors. The precise origin of the germ cells that form these tumors in sites heterotopic to the gonads is still not completely clear, but it is postulated that mediastinal GCTs may result from aberrant migration of germ cells during embryonic development. Because primordial germ cells are undifferentiated cells from which a variety of different tumors can arise, there have been numerous overlapping and sometimes confusing classification and grading systems proposed for these tumors. Even more confusing for classifying GCTs is that it is common to see two or more GCT histologies arising from within a single mass. Based on the need for standard classification, investigators from the Armed Forces Institute of Pathology developed a reproducible histologic classification system (Table 82-5) and clinical staging system (Table 82-6) based on review of more than 300 cases.[67]

TABLE 82-5 Classification of Mediastinal Germ Cell Tumors

Mature teratoma
Immature teratoma
Teratomas with malignant component:
Type I: with an associated GCT (seminoma, etc.)
Type II: with another epithelial malignancy (squamous, adenocarcinoma, etc.)
Type III: with sarcomatous component (rhabdomyosarcoma, osteosarcoma, etc.)
Type IV: a combination of any of the above
Seminoma
Yolk sac tumor (endodermal sinus tumor)
Embryonal carcinoma
Choriocarcinoma
Combined GCT without teratomatous component

Mediastinal GCTs include benign and malignant neoplasms that for descriptive purposes can be simplified into three categories. Benign tumors are primarily benign mediastinal teratomas, which account for 60% of all mediastinal GCTs. Malignant tumors are divided into seminomatous GCTs, which account for 40% of malignant mediastinal GCTs, and nonseminomatous GCTs (NSGCTs) which account for 60% of malignant mediastinal GCTs. NSGCTs include embryonal cell carcinomas, choriocarcinomas, yolk sac tumors, and malignant teratomas.

Mediastinal Teratomas

Teratomas are defined by the presence of tissue from more than one of the three primitive germ cell layers. Mature (benign) teratomas are composed of well-differentiated elements such as fat, muscle, and cartilage (mesoderm); hair, skin, and teeth (ectoderm); and intestinal tissue (endoderm). Mature teratomas can be symptomatic or asymptomatic upon presentation. Symptoms may include chest pain, dyspnea, cough, or fever (if the tumor becomes infected). Occasionally the tumor may erode into an airway and a patient may cough up hair (trichophytosis) or oily sebum that is pathognomonic of a benign mediastinal teratoma.

CT with contrast is the diagnostic procedure of choice and usually demonstrates a thick-walled cystic mass. Calcification is often present, and when this is intermixed with areas of fat and/or fluid

TABLE 82-6 Clinical Staging of Mediastinal Germ Cell Tumors

Stage	Characteristics
I	Well-circumscribed tumor with or without focal adhesions to the pleura or pericardium but without microscopic evidence of invasion into adjacent structures
II	Tumor confined to the mediastinum with macroscopic and/or microscopic evidence of infiltration into adjacent structures (pleura, pericardium, great vessels)
III	Tumor with metastases
IIIA	With metastases to intrathoracic organs (lymph nodes, lung, etc.)
IIIB	With extrathoracic metastases

density, the diagnosis can be made radiographically with a high degree of certainty.[68] Benign teratomas can also be primarily solid, and in these cases the diagnosis is more challenging. Tumor markers such as β-hCG and AFP should be measured but will not be elevated in benign teratoma. Needle biopsy of a mass that is highly suspected to be a benign teratoma based on imaging is not necessary. Such a patient should go directly to surgical resection.

The treatment for benign GCTs is total resection before the development of complications. Even benign teratomas are frequently densely adherent to adjacent structures such as lung, blood vessels, and pericardium; en bloc resection of involved structures is sometimes required, although mature surgical judgment must be exercised in determining when a near-complete resection is satisfactory for these benign lesions. Radiation and chemotherapy play no therapeutic role unless concurrent malignant disease is present. Outcome after resection of a benign teratoma is excellent, with 10-year survival exceeding 90%.[69] Occasionally, teratomas will contain less well-differentiated tissues and behave more aggressively, resembling malignant teratomas (see below).

Malignant Seminomatous Germ Cell Tumors

Malignant GCTs, both seminomatous and nonseminomatous, are almost exclusively diseases of men. Seminoma usually presents during the third or fourth decade of life as a large anterior mediastinal mass, although it rarely occurs in the middle and posterior mediastinum. Most patients are symptomatic upon presentation; symptoms are variable and most commonly include chest pain and dyspnea.[70]

Careful bimanual examination and ultrasound of the testicles should be performed to rule out a primary testicular tumor, and a thorough staging workup should be performed including CT scan of the abdomen (looking primarily for retroperitoneal disease) along with the chest. Measurement of serum tumor markers is critical to the diagnosis and follow-up of patients with mediastinal seminomas. Patients with mediastinal seminomas will typically demonstrate mild elevation of β-hCG (<100 mIU/mL), while higher levels than this should raise the suspicion of a mixed tumor or an NSGCT.[71] An elevated AFP level excludes the diagnosis of seminomatous tumor and defines the tumor as an NSGCT or mixed GCT.

Chest CT is the most useful imaging modality for a seminoma, which typically appears as a large, bulky homogeneous mass that may obscure tissue planes or invade adjacent structures and is often surrounded by bulky lymphadenopathy (Fig. 82-3). These tumors are usually FDG-avid, and PET may be useful in monitoring response to therapy. A biopsy is usually necessary to secure the diagnosis and percutaneous core needle biopsy is the preferred initial approach, reserving open surgical biopsies for cases in which percutaneous sampling is inconclusive.

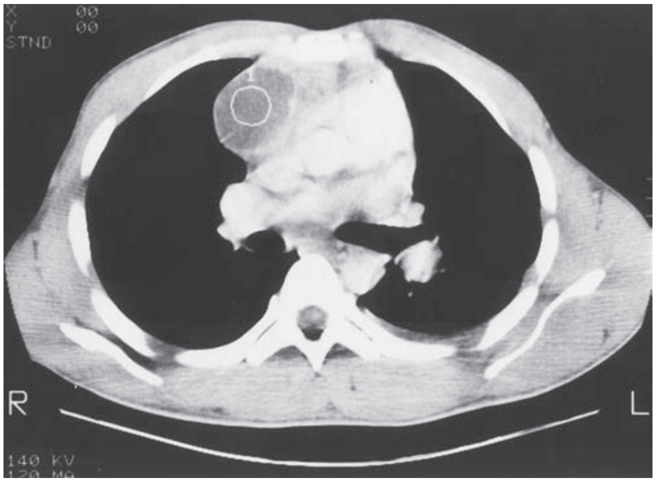

Figure 82-3 Mediastinal seminoma. Axial section from a CT reveals a homogeneous mass within the anterior mediastinum.

Some 60% to 70% of patients with mediastinal seminoma will present with metastatic disease, primarily to intrathoracic organs, although distant metastases also can be found. The treatment of primary mediastinal seminomatous tumors has evolved over the past 20 years from a primarily surgical approach to a chiefly nonsurgical approach. It has become clear that the first line of treatment in all cases of mediastinal seminoma should be chemotherapy, and 5-year survival rates exceeding 90% are achieved with cisplatin-based chemotherapy regimens.[72,73] As is the case with testicular seminomas, pure mediastinal germ cell seminomas are radiosensitive. Whereas radiotherapy alone may achieve complete remission in only about 65% of patients,[74] the addition of radiotherapy to chemotherapy appears to enhance the benefit of chemotherapy alone. The role of surgical resection in this disease remains controversial. Surgery is generally reserved for patients with residual mediastinal masses following chemotherapy and radiation when residual active disease is a concern (e.g., with persistently elevated or rising markers, or increasing FDG avidity on PET). The benefits of surgical resection in this setting would be to document if there is residual malignant seminomatous tumor (as opposed to necrotic debris) and to completely resect it; in addition, occasional patients have a previously unrecognized nonseminomatous malignant component of the tumor.[75]

Malignant Nonseminomatous Germ Cell Tumors

NSGCTs are malignant tumors that are seen almost exclusively in men. There is a particular propensity for men with Klinefelter syndrome to develop these tumors. A variety of nonseminomatous histologies have been categorized, and their incidence is best gathered from a large published series of 229 cases.[67] NSGCTs are composed of teratocarcinoma (41%), endodermal sinus (yolk sac) tumor (35%), choriocarcinoma (7%), embryonal carcinoma (6%), and mixed histologies (11%). Further, non–germ cell components including sarcoma or epithelial carcinoma were found in 58% of teratocarcinomas.

Mediastinal NSGCTs are characterized by rapid local growth and early distant metastases, and patients often present with advanced disease. Most patients will have symptoms caused by compression or invasion of adjacent structures. Constitutional symptoms, including weight loss, fever, and weakness are more common in patients with NSGCT compared with pure seminoma. Like seminoma, sites of metastases in NSGCT include the lung, pleura, lymph nodes, and liver; 85% to 95% of patients with an NSGCT will have at least one site of metastases.[76,77]

Workup should include CT of the chest and abdomen and measurement of serum tumor markers. Chest CT will typically reveal a large, irregular anterior mediastinal mass with poorly defined margins and multiple areas of necrosis and hemorrhage (Fig. 82-4). Unlike seminoma, more than 90% of patients with NSGCT will have an elevation of either β-hCG (30%–35% of patients) or AFP (80% of patients), and an AFP level greater than 500 ng/mL is essentially diagnostic of NSGCT.[71,78] NSGCTs, especially those with yolk sac histology, are associated with a variety of hematologic malignancies including leukemia, and these occur independently of the chemotherapy used to treat the tumor.[79]

As most patients present with bulky or metastatic disease, surgical resection is not the first line of treatment. Historically, patients with NSGCT had an exceedingly poor prognosis, but this has dramatically improved with the implementation of intensive cisplatin-based chemotherapy protocols. A summary of studies of patients treated with first-line cisplatin-based combination chemotherapy

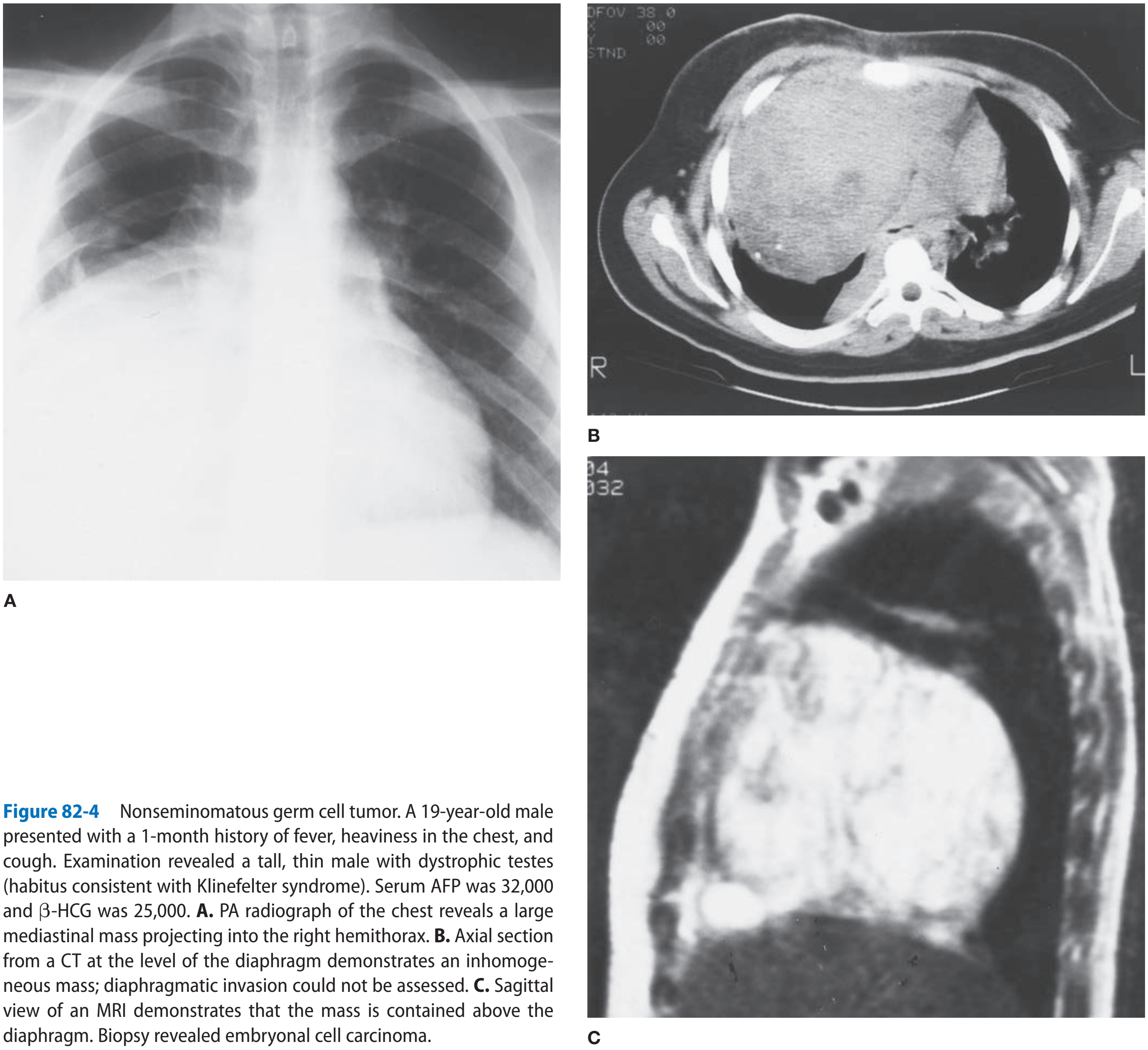

Figure 82-4 Nonseminomatous germ cell tumor. A 19-year-old male presented with a 1-month history of fever, heaviness in the chest, and cough. Examination revealed a tall, thin male with dystrophic testes (habitus consistent with Klinefelter syndrome). Serum AFP was 32,000 and β-HCG was 25,000. **A.** PA radiograph of the chest reveals a large mediastinal mass projecting into the right hemithorax. **B.** Axial section from a CT at the level of the diaphragm demonstrates an inhomogeneous mass; diaphragmatic invasion could not be assessed. **C.** Sagittal view of an MRI demonstrates that the mass is contained above the diaphragm. Biopsy revealed embryonal cell carcinoma.

regimens showed an overall long-term survival rate of 42%.[80] After completion of chemotherapy, patients should be restaged with a CT of the chest and abdomen, and serum tumor markers should be remeasured.

Most patients will be found to have residual masses or radiographic abnormalities after completing chemotherapy. Regardless of whether tumor markers are elevated, these patients should undergo surgical resection of residual masses if technically feasible because salvage chemotherapy is usually ineffective,[81] and surgical resection is curative in a substantial portion of patients.[82,83] In addition, occasional patients will be found to have a previously unrecognized mature (benign) teratoma component, which can be cured only by resection.

■ Lymphoma

Both Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) can present as anterior mediastinal masses. HL accounts for approximately 50% to 70% of mediastinal lymphomas. The three most common types of lymphoma found in the mediastinum are nodular sclerosing HL, large cell lymphoma, and lymphoblastic lymphoma.[84] In general, these are systemic diseases that also involve the mediastinum, although some patients do present with disease limited to the mediastinum alone. Due to the generally widespread nature of these diseases, treatment is centered on systemic chemotherapy and radiation is the primary modality used for local control. Surgery is not typically utilized as a therapeutic option but may be required to make a histologic diagnosis.

Hodgkin Lymphoma

HL has a bimodal age distribution with its incidence peaking in young adulthood and again after 50 years of age. HL is divided into four subtypes: nodular sclerosing (most common), lymphocyte-rich, mixed cellularity, and lymphocyte-depleted. Most patients present with asymptomatic lymphadenopathy, but up to 25% of patients will experience B symptoms consisting of fever, night sweats, and weight loss.[85] Over half of all patients with HL will have involvement of the mediastinum, almost always in the anterior mediastinum or involving paratracheal lymph nodes (Fig. 82-5). Suspicion for HL warrants a tissue biopsy, and the presence of Reed–Sternberg cells is pathognomonic. Because the tumors tend

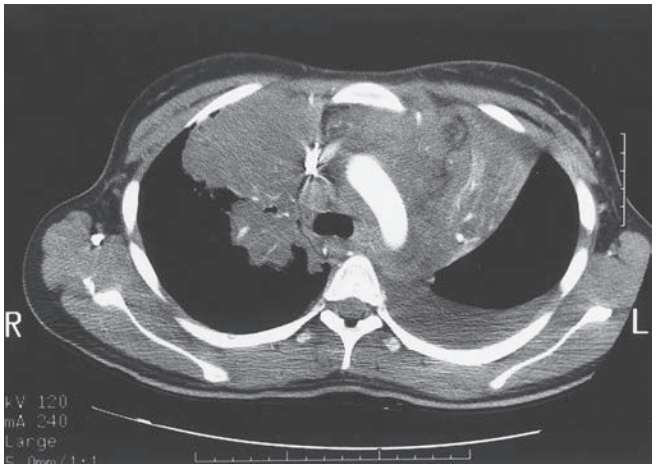

Figure 82-5 Hodgkin disease. Axial section from a CT shows a bulky mediastinal mass and pleural effusion.

to be quite fibrotic, with only scattered malignant cells, surgical biopsy is often required to establish a diagnosis, either by cervical mediastinoscopy (for paratracheal or middle mediastinal nodes) or by anterior mediastinotomy (for anterior mediastinal masses). PET generally demonstrates high FDG avidity in lymphomas, and therefore PET/CT may be useful in guiding sites for biopsy. The Lugano classification (Table 82-7) is used for staging and is based on the Ann Arbor classification with Cotswolds modification. Invasive staging (laparotomy and splenectomy) has fallen out of favor.[86]

Treatment approaches to HL are separated into those for early-stage disease (stage I and II) and advanced-stage disease (stage III and IV). Modern treatment protocols most often involve chemotherapy and radiation therapy. Patients with advanced-stage disease as well as patients with B symptoms are treated with chemotherapy regimens such as ABVD (Adriamycin, bleomycin, vinblastine, dacarbazine). Radiation is sometimes used in cases of bulky disease, and patients who relapse may benefit from a hematopoietic stem cell transplant. Cure rates are greater than 90% for stage I and II HL, 30% to 90% for stage IIIA, 60% to 70% for stage IIIB, and 50% to 60% for stage IV.[84,85]

TABLE 82-7 Lugano Classification of Hodgkin and Non-Hodgkin Lymphoma (Based on the Ann Arbor Staging System with Cotswolds Modification)

Stage	Characteristics
I	Involvement of one lymph node region (one node or a group of adjacent nodes) or single extranodal lesion (I_E)
II	Two or more lymph node regions on the same side of the diaphragm, or limited contiguous extranodal involvement (II_E)
III	Lymph node regions or lymphoid structures on both sides of the diaphragm
IV	Noncontiguous extralymphatic involvement
Modifications	
A	Absence of systemic B symptoms (only for Hodgkin lymphoma)
B	Fever, night sweats, weight loss >10% in 6 months (only for Hodgkin lymphoma)
E	Extranodal involvement
Bulky	Bulky disease (a nodal mass greater than 10 cm or greater than one-third of the transthoracic diameter) is described by the size, no longer with X

Non-Hodgkin Lymphomas

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of systemic diseases that are categorized into many classes and grades. Mediastinal tumor burden in NHL is more likely to be part of the generalized disease process than the main focus of disease, and only 20% of patients with NHL will have involvement of the mediastinum at the time of presentation. This disease is not limited to the anterior mediastinum and can occur in the middle and posterior mediastinal compartments. Of patients with primarily mediastinal disease, the majority will have either lymphoblastic lymphoma or large B-cell lymphoma. The mean age of presentation for these patients is between 28 and 35 years.

Lymphoblastic lymphomas are highly aggressive tumors, and invasive symptoms including cough, wheezing, dyspnea, and manifestations of superior vena cava syndrome, cardiac tamponade, or tracheal obstruction are common. The central nervous system, skin, and gonads may be involved and bone marrow involvement with blasts is relatively common.[84] Primary mediastinal B-cell lymphoma is composed histologically of large cells with expression of the B cell–associated antigen CD20; immunohistochemistry and/or flow cytometry are critical to the diagnosis. Presentation with symptoms related to invasion or obstruction of adjacent structures is common, but there is less involvement of extrathoracic sites and bone marrow than in lymphoblastic lymphoma. Staging of NHL is performed according to the Lugano classification, and CT scans of the chest, abdomen, and pelvis are the initial and often only necessary imaging (Fig. 82-6).

Treatment regimens for mediastinal NHL are dependent upon stage and histologic subtype. Due to its propensity to involve the bone marrow, treatment of lymphoblastic lymphoma commonly employs a regimen similar to that for acute lymphoblastic leukemia, often including intrathecal chemotherapy and bone marrow transplantation. Patients with primary mediastinal B-cell lymphoma can be treated with conventional chemotherapy regimens, but high-dose chemotherapy and "involved field" radiotherapy are sometimes employed. In general, relapses in NHL are common and the long-term prognosis is worse than for HL.

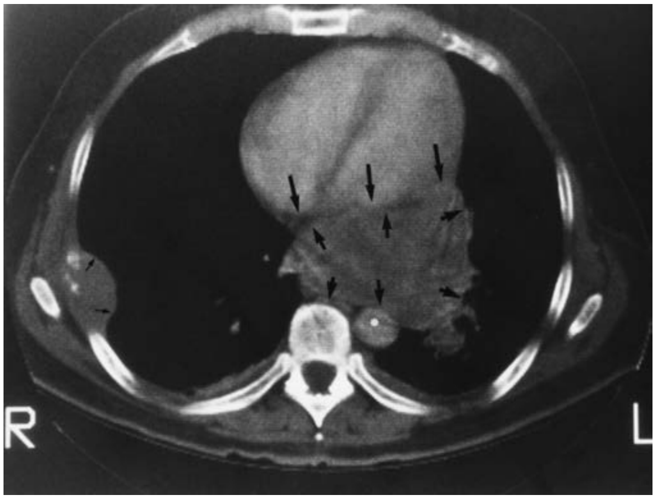

Figure 82-6 Non-Hodgkin lymphoma. Axial section from a CT demonstrates a large middle and posterior mediastinal mass with distant metastasis to a rib in the contralateral chest. This skip involvement is typical of non-Hodgkin lymphoma.

Other Anterior Mediastinal Neoplasms

Other anterior mediastinal neoplasms include substernal thyroid and parathyroid adenoma.

Substernal Thyroid

Substernal and ectopic thyroid tissue can present as an anterior mediastinal mass but may involve the middle mediastinum if the thyroid tissue descends more caudally into the paratracheal space. In most cases, the substernal thyroid is a euthyroid goiter and an enlarged thyroid gland will be palpable in the neck. We have found that a noncontrast CT is the single most useful test in differentiating substernal thyroid from other mediastinal masses. Because of its iodine content, substernal thyroid tissue shows enhancement on a noncontrast CT scan, and this along with a visible connection to the gland within the neck usually confirms the diagnosis. I-123 SPECT/CT can also be useful for characterization of mediastinal ectopic tissue that may not have a connection to the normal cervical gland.[87] Surgical resection is recommended, as needle biopsy cannot rule out malignancy in such a large lesion, and substernal goiters will often cause symptoms of airway compression as they continue to grow. Nearly all substernal goiters can be removed via a cervical incision, although some do require a partial upper sternotomy.

Parathyroid Adenoma

The anterior mediastinum is the most common location for an ectopic parathyroid tumor. Often, ectopic parathyroid glands will present as persistent primary hyperparathyroidism after an unsuccessful neck exploration. Before proceeding with mediastinal exploration, localizing studies such as technetium-99m-sestamibi scintigraphy and CT are recommended. MRI may be useful to reveal well-defined masses; however, they are usually small (<3 cm). The adenoma is typically embedded within the thymus gland. Surgical resection of the adenoma, typically requiring resection of the thymus itself, is curative. We find the surgical technique of transcervical thymectomy, performed via the neck with a retractor lifting the sternum anteriorly, is ideal for this disease process and can be performed on an outpatient basis. VATS and/or robotic approaches also are applicable in this scenario.

MIDDLE MEDIASTINAL NEOPLASMS

Metastatic bronchogenic carcinoma is the most common etiology of middle mediastinal masses, as the mediastinal lymph nodes in the middle mediastinal compartment are a frequent site of lung cancer metastases. The most common primary masses of the middle mediastinum are lymphoma (described above) and benign cysts. Cysts constitute 12% to 20% of all primary mediastinal masses and are found chiefly in the middle compartment. These cysts comprise congenital foregut cysts, bronchogenic cysts, neurenteric cysts, and pericardial cysts and are reviewed in Chapter 81.

POSTERIOR MEDIASTINAL NEOPLASMS

Neurogenic tumors are the most common neoplasms of the posterior mediastinum, collectively representing 12% to 21% of all mediastinal masses and occurring almost exclusively (95%) in the posterior compartment.[88] Neurogenic tumors are categorized into three groups based on the neurogenic tissue of origin. Neoplasms arising from the nerve sheath include schwannoma, neurofibroma, and rarer malignant nerve sheath tumors. Nerve sheath tumors are the most common neurogenic tumors found in the adult. Neoplasms arising from the sympathetic ganglia include ganglioneuroma, ganglioneuroblastoma, and neuroblastoma, and these tumors are more commonly found in children. Neoplasms arising in parasympathetic ganglia include paraganglioma and chemodectoma, both of which also occur in the posterior mediastinum and are exceedingly rare. Approximately 98% of neurogenic mediastinal tumors in adults are benign, whereas it is estimated that more than 50% of neurogenic tumors in children are malignant.

Nerve Sheath Tumors

Schwannoma (neurilemmoma) and *neurofibroma* are the most common mediastinal neurogenic tumors.[89] Both of these are benign, slow-growing tumors. Most commonly, they appear as encapsulated and well-marginated masses found in the costovertebral sulci where they arise from intercostal nerve rami. Less frequently they can be found in the middle mediastinal compartment when they occur as tumors of the vagus or phrenic nerves. CT typically reveals a solitary, smoothly rounded mass in the upper half of either paravertebral sulcus abutting the vertebra (Fig. 82-7). An MRI should be employed to rule out intraspinal extension, if there is any possibility of this on CT.[90] Upon presentation, most patients are asymptomatic, although neurologic symptoms from intercostal nerve involvement or intraforaminal extension can be present.[91] Thus, many of these are identified as incidental findings on scans performed for other reasons. Over one-third of patients with neurofibromas will have neurofibromatosis (von Recklinghausen disease), and these patients tend to present at an earlier age and may have café au lait spots suggesting the diagnosis.[91,92]

Surgical resection is the definitive treatment for these benign nerve sheath tumors, and this can commonly be performed with VATS or robotic techniques with favorable results.[93,94] Excellent long-term survival is obtained with complete surgical excision of the tumors, and recurrence is uncommon.[88,93] However, additional neurofibromas or schwannomas may develop in patients with neurofibromatosis. Ten percent of these tumors extend through the intervertebral foramen and create a "dumbbell" appearance on imaging studies. For these lesions, combined thoracic (lateral) and neurosurgical (posterior) approaches can allow en bloc resection and can be achieved with low morbidity.[95] Typically this is accomplished with a posterior laminectomy followed by an anterior thoracoscopic approach.

Malignant nerve sheath tumors are essentially spindle cell sarcomas of the mediastinum and include malignant schwannoma, neurofibrosarcoma, and malignant neurofibroma. These tumors are rare, affect men and women equally in the third to fifth decades of life, and are highly associated with neurofibromatosis. Malignant schwannomas remain one of the most poorly characterized of all soft tissue sarcomas. In general, patients with malignant schwannomas present with large invasive tumors and have a poor prognosis. Complete surgical resection is rarely possible, and even when accomplished, local recurrence is common. Neurofibrosarcoma likely evolves from the malignant degeneration of a neurofibroma. Unlike benign nerve sheath tumors, patients with neurofibrosarcoma generally have symptoms of pain and nerve impingement.[96] On CT imaging, these tumors often appear as round masses with central areas of necrosis and hemorrhage. Radical surgical excision provides the only hope of cure; however, the 5-year overall survival rates are low (16% in patients with neurofibromatosis) and no survival benefit is gained by adjuvant chemotherapy.[96,97] Chemotherapy and radiotherapy are options for unresectable tumors.

Sympathetic Ganglion Tumors

Tumors of the sympathetic ganglia likely represent malignant degeneration of the nerve cell rather than the nerve sheath. These tumors are represented by the spectrum of ganglioneuroma, ganglioneuroblastoma, and neuroblastoma. In children, mature tumors such as ganglioneuroma occur in older individuals (median age, 7 years) and tend to behave in a benign fashion, whereas immature tumors such as neuroblastoma tend to occur in younger patients (median age, <2 years) and behave aggressively.[98]

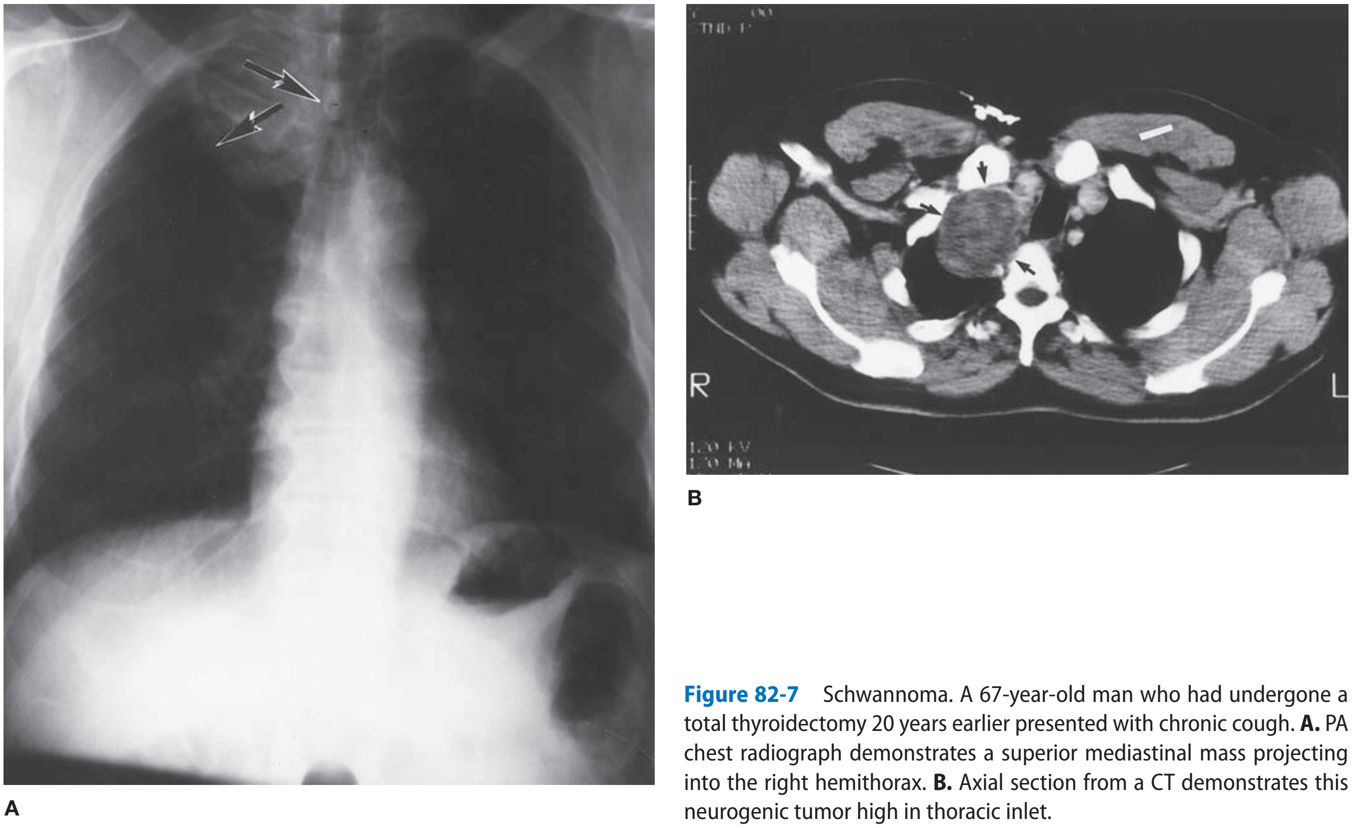

Figure 82-7 Schwannoma. A 67-year-old man who had undergone a total thyroidectomy 20 years earlier presented with chronic cough. **A.** PA chest radiograph demonstrates a superior mediastinal mass projecting into the right hemithorax. **B.** Axial section from a CT demonstrates this neurogenic tumor high in thoracic inlet.

Ganglioneuromas are the most benign type of sympathetic ganglion tumor. They are typically diagnosed in the second or third decade of life and are the most common neurogenic tumors occurring in childhood. Most patients with ganglioneuroma are asymptomatic upon presentation, although larger tumors may result in symptoms such as cough, dyspnea, dysphagia, chest pain, and Horner syndrome, and symptoms related to the secretion of catecholamines have been reported. Ganglioneuromas are generally large, well-circumscribed, and encapsulated tumors located in the paravertebral sulci. Surgical resection is a highly successful treatment for ganglioneuromas.[99]

Ganglioneuroblastoma is a tumor that demonstrates histologic elements similar to the well-differentiated ganglion cells seen in a ganglioneuroma as well as less-differentiated neuroblastoma-like features, and the degree of malignant behavior is related to the extent of the latter. Presentation is in the first decade of life, and both sexes are equally affected. Approximately half of patients will present with symptoms. Most children present with a solitary mass that is amenable to complete surgical resection. The treatment of ganglioneuroblastoma is primarily surgical, although chemotherapy is indicated in intermediate and high-risk groups. Overall these tumors are associated with relatively high 5-year survival rates, reported to be 88% in one large series.[100]

Neuroblastomas are the most malignant of the sympathetic ganglion tumors. These highly aggressive and readily metastasizing tumors are found almost exclusively in children, with 95% occurring in patients less than 5 years old.[101] Most patients present with symptoms that include chest pain, dyspnea, myelopathy from spinal canal involvement, and symptoms of excess catecholamine production. Distant metastases are common.[102] On CT, mediastinal neuroblastomas appear as elongated paraspinous masses often impinging on adjacent structures and causing bony destruction. Eighty percent of tumors demonstrate calcification.[103] MRI is useful for determining nodal, chest wall, and intraspinal involvement. The International Neuroblastoma Staging System (INSS) is the most commonly used staging system for this disease. It includes factors such as tumor size, lymph node metastases, and extent of unresectable disease and can be used to predict survival.[104] Amplification of the oncogene N-myc has additionally been shown to correlate with worse prognosis.[105] The treatment of neuroblastoma depends primarily on stage. For patients with stage I disease, resection alone is usually curative.[106,107] For patients with partially resectable stage II and III diseases, surgical resection is followed by postoperative multiagent chemotherapy. Patients with stage IV disease are generally treated with chemotherapy and radiation.

■ Neoplasms Arising in Parasympathetic Ganglia

Paragangliomas are rare tumors that arise from specialized neural crest cells associated with autonomic ganglia, called paraganglia. Paragangliomas can be categorized into two groups based upon association with either the parasympathetic system or the sympathetic system. Parasympathetic paragangliomas do not secrete catecholamines and were previously called chemodectomas. They may arise from mediastinal chemoreceptors including the aortopulmonary glomus or anywhere along the vagus nerve and are chromaffin-negative tumors. Tumors connected with the sympathetic nervous system are divided into functional paragangliomas and nonfunctional paragangliomas based on their ability to secrete catecholamines. These tumors were previously called extra-adrenal pheochromocytomas.

Both genders are equally affected by mediastinal paragangliomas, usually in the third or fourth decade of life. The clinical presentation includes symptoms of local mass effect as well as varying degrees of hypertension and hypermetabolism secondary to the production of epinephrine and norepinephrine. Excess plasma and urinary levels of catecholamines can often be detected. Preoperative localization is essential. CT, MRI, and echocardiography can be useful for anatomic imaging, and functional imaging studies such as ^{131}I-metaiodobenzylguanidine (MIBG) scintigraphy can be used to localize lesions not seen on other scans. Treatment requires surgical excision, and presurgical conditioning with alpha and then beta blockade is usually necessary for functional lesions to prevent severe hypertension intraoperatively.[108]

OTHER MEDIASTINAL TUMORS

Additional neoplasms of the mediastinum include those seen in Castleman's disease and a variety of mesenchymal tumors.

Castleman Disease

Castleman disease is a rare lymphoproliferative disorder that can involve enlargement of one (unicentric Castleman disease) or multiple (multicentric Castleman disease) lymph nodes. Most adults with unicentric disease are asymptomatic. The mediastinum is the most common location of unicentric disease, and lesions most frequently occur in the anterior and middle mediastinal compartments.[109,110] Multicentric Castleman disease is characterized by peripheral lymphadenopathy and hepatosplenomegaly; a subset of patients also demonstrates mediastinal and intra-abdominal adenopathy. Multicentric Castleman disease is classified as human herpesvirus 8 (HHV-8) associated, typically occurring in immunocompromised patients, and as HHV-8-negative or idiopathic multicentric Castleman disease.

Castleman disease is categorized into two histologic types (hyaline vascular and plasma cell), but the centricity rather than histology is more important in predicting long-term outcome. Complete surgical resection should be performed in unicentric disease and is associated with greater than 95% overall survival and greater than 80% disease-free survival at 5 years.[110] Multicentric Castleman disease can be rapidly progressive and often fatal, and the role of surgery is primarily to obtain tissue to establish a diagnosis, with the treatment being systemic therapy. Castleman disease can mimic many other mediastinal tumors and must be kept in mind as a rare possible diagnosis.

Mesenchymal Tumors

A variety of mesenchymal tumors constitute approximately 6% of all tumors that occur in the mediastinum.[3] More than half of these lesions turn out to be malignant. A large variety of categories exist for mesenchymal tumors of the mediastinum, and their spectrum runs the entire gamut of soft tissue tumors, including but not limited to adipocytic tumors (lipoma, lipomatosis, liposarcoma), vascular tumors (hemangioma, lymphangioma), fibroblastic tumors (fibrous tumors), smooth muscle tumors (leiomyoma, leiomyosarcoma), skeletal muscle tumors (rhabdomyoma, rhabdomyosarcoma), and chondro-osseous tumors (chondrosarcoma, osteosarcoma). Their management is similar to that of extrathoracic soft tissue tumors, with resection indicated if possible.

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PART 11

Disorders of the Chest Wall, Diaphragm, and Spine

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CHAPTER 83

Nonmuscular Diseases of the Chest Wall

George E. Tzelepis
F. Dennis McCool

INTRODUCTION

The chest wall is a major component of the respiratory pump and consists of the rib cage and abdomen. It is inflated by the inspiratory muscles of the rib cage and the diaphragm, and its integrity is key to sustaining ventilation. Disorders affecting the nonmuscular structures of the chest wall (the thoracic spine, ribs, costovertebral joints, abdominal wall, and sternum) may lead to respiratory dysfunction. When the integrity of these nonmuscular components is severely compromised, respiratory failure may ensue. The pathophysiology of disorders affecting these nonmuscular components is generally related to the imposition of excessive elastic loads placed on the respiratory muscles. In some disorders, such as kyphoscoliosis and obesity, the load on the respiratory muscles is chronic and progressive. By contrast, with flail chest, the load on the respiratory muscles is acute. If the respiratory muscles have not adapted or had little time to adapt to loads that increase the work of breathing, respiratory failure may quickly ensue. Other disorders, such as ankylosing spondylitis and pectus excavatum, have a minimal impact on respiratory function. The respiratory muscles are discussed in Chapters 3 and 142.

KYPHOSCOLIOSIS

Kyphoscoliosis (KS) refers to a three-dimensional spinal deformity characterized by excessive curvature of the spine in the lateral plane (scoliosis) and sagittal plane (kyphosis), as well as by vertebral axis rotation.[1] Scoliosis, defined as a lateral curvature greater than 10 degrees, is generally associated with kyphosis and spinal axis rotation.[2,3] KS is one of the most common spinal abnormalities, with estimates of prevalence in the United States ranging from 1 in 10,000 people for severe deformities to 1 in 1000 people for mild deformities.[4] It is classified as idiopathic (no known cause), secondary or paralytic (due to neuromuscular disease), or congenital (associated with vertebral malformation at birth) (Table 83-1).[5]

Etiology and Diagnosis

Idiopathic KS usually manifests in late childhood or early adolescence and involves primarily females (ratio of 4:1).[2,5] Although largely unknown, the cause of the idiopathic KS likely includes a combination of genetic and environmental factors, which through abnormal bone, muscle growth, or hormonal imbalance lead to increased spine curvature.[6] Idiopathic KS is believed to be a multigene condition of autosomal or sex-linked inheritance with variable phenotypic expression.[2] Individuals with idiopathic KS may complain of back pain or may have psychological problems.[2] When KS is severe, complaints include dyspnea with exertion and constitutional symptoms related to nocturnal hypoventilation. Respiratory failure also may develop.[7]

Paralytic or secondary KS may be due to a number of neuromuscular disorders including polio, muscular dystrophy, cerebral palsy, and spinal bifida.[5] With these diseases, KS typically occurs when the individuals become nonambulatory. Congenital KS results from developmental vertebral anomalies that are usually present at birth.[8] Although uncommon, it can lead to serious neurologic complications such as paraplegia.

The diagnosis of KS is readily made by physical examination and radiologic assessment. In severe KS, physical examination typically reveals a dorsal hump due to angulated ribs and shoulder asymmetry. In addition, there may be "hip tilt" related to spinal rotation (Fig. 83-1A). In mild KS, subtle changes in spinal curvature may be elicited by performing the *Adam's forward bend test*. With this test, the patient bends forward at the waist with feet together and knees straight, until the spine becomes parallel to the floor. The observer, then, examines for thoracic and lumbar region symmetry from behind and alongside the patient.

Radiographic studies (upright PA and lateral views of the spine) are used to confirm the diagnosis, and to assess severity by measuring the *Cobb angle* on the coronal or sagittal plane of imaging.[9] This is the angle formed by the intersection of two lines, each of which is parallel to the top and bottom vertebrae of the scoliotic or kyphotic curves (Fig. 83-1B). The greater the Cobb angle, the more severe the deformity. Cobb angles less than 60 degrees are generally not associated with ventilatory impairment; those greater than 100 degrees are invariably associated with respiratory symptoms, and those greater than 120 degrees with respiratory failure.[10,11] Among symptoms, dyspnea on exertion typically progresses with age and the degree of spinal deformity. Sequential radiographic studies are useful in evaluating progression of the spinal deformity.

Respiratory Mechanics

Severe restrictive respiratory impairment is the pathophysiologic feature of KS. Specifically, respiratory system compliance is reduced,

TABLE 83-1 Causes of Kyphoscoliosis

- **Congenital**
- **Paralytic or secondary**
  - Neuromuscular
  - Poliomyelitis
  - Muscular dystrophy
  - Cerebral palsy
  - Friedreich ataxia
  - Charcot-Marie-Tooth disease
  - Neurofibromatosis
  - Syringomyelia
  - Disorders of connective tissue
  - Marfan syndrome
  - Ehlers-Danlos syndrome
  - Morquio syndrome
  - Vertebral disease
  - Osteoporosis
  - Osteomalacia
  - Vitamin D–resistant rickets
  - Tuberculous spondylitis
  - Spina bifida
  - Postthoracoplasty
- **Idiopathic**

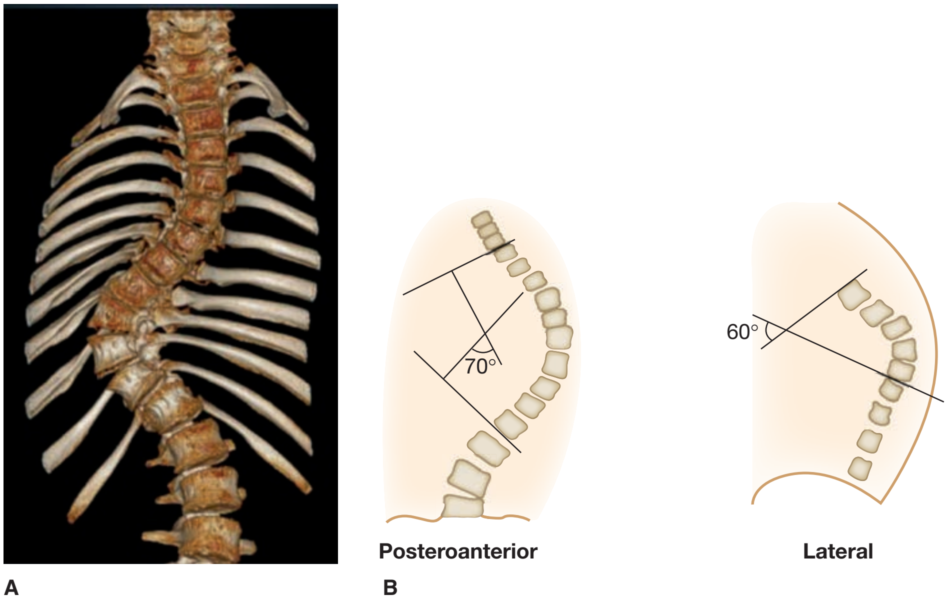

Figure 83-1 **A.** Three-dimensional CT reconstruction showing kyphoscoliosis in the lower thoracic and lumbar spine with rotation of the spine and the rib cage. **B.** Schematic of the posteroanterior radiograph depicting the lines constructed to measure the Cobb angle of scoliosis and the lines drawn on the lateral radiograph to measure the Cobb angle of kyphosis. (***A.*** *Reproduced with permission from Chen AM, Neustadt JB, Kucera JN. Rib head dislocation causing spinal canal stenosis in a child with neurofibromatosis, type 1. J Radiol Case Rep. 2017;11(8):8–15 https://www.radiologycases.com/index.php/radiologycases/article/view/3113;* ***B.*** *Data from Murray JF, Nadel JA: Textbook of Respiratory Medicine. Philadelphia, PA: WB Saunders; 1988.)*

and the pressure required to inflate the lungs at any given volume is greater than in a healthy individual. Consequently, functional residual capacity (FRC) is invariably decreased, the elastic load placed on the respiratory muscles is increased, and the work of breathing is significantly increased.[12]

In KS, reduced respiratory compliance is primarily related to a decrease in chest wall compliance and to a lesser extent to a decrease in lung compliance resulting from microatelectasis.[7,13] The respiratory pressure-volume relationship is shifted to the right, thus requiring greater than normal pressures to inflate the lungs (Fig. 83-2). In addition, the straight portion of the pressure-volume curve, where compliance is fairly constant in the normal individual, is diminished, largely due to a significantly decreased total lung capacity (TLC). The poorly distensible chest wall reduces the resting position of the respiratory system (FRC), and tidal breathing occurs on a flatter portion of the pressure-volume curve.[7] Greater inspiratory effort is needed for relatively small tidal breaths, which increases the work of breathing. The increase in the oxygen cost of breathing may reach values 3 to 5 times greater than those measured in healthy individuals and thus places patients at risk for respiratory muscle fatigue.[14,15]

In idiopathic KS, the compliance of the chest wall and respiratory system both decrease as the Cobb angle increases (Fig. 83-3), with the most pronounced reductions in chest wall compliance seen in individuals with Cobb angles greater than 100 degrees. Cobb angles up to 50 degrees do not significantly decrease respiratory system compliance.[12]

The reduction in chest wall compliance promotes breathing with shallow tidal breaths, and the reduction in FRC leads to breathing at low lung volumes. Both factors predispose to the development of atelectasis and may thus reduce lung compliance. Although lung compliance may be diminished, it is not as severely reduced as chest wall compliance.[13] Since chest wall compliance decreases with age,[16] respiratory mechanics invariably deteriorate with age even in the absence of spinal deformity progression.[17]

Respiratory muscle strength, as measured by the maximal static inspiratory (PI_{max}) and expiratory pressure (PE_{max}), is generally normal in individuals with idiopathic KS and Cobb angles of less

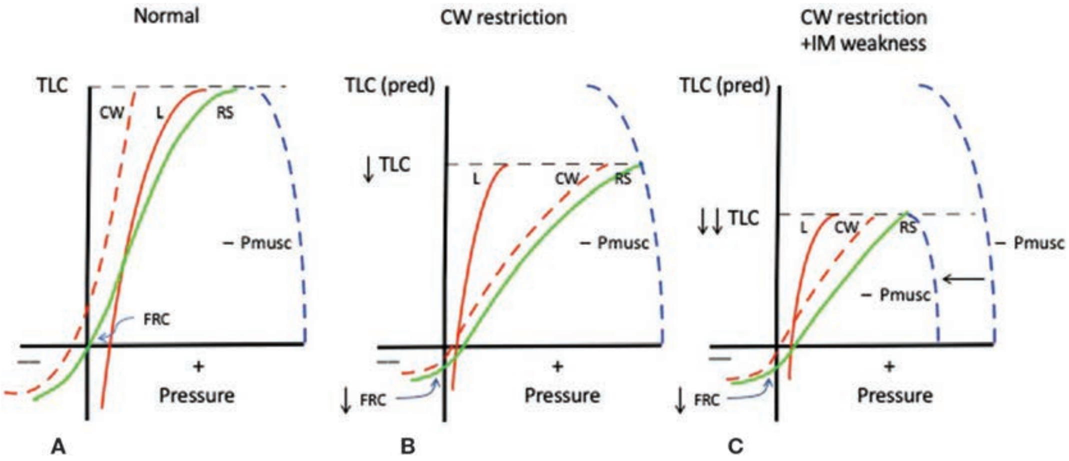

Figure 83-2 Schematic showing the volume-pressure relationships of the chest wall (CW), lung (L), and respiratory system (RS) for (**A**) healthy individuals, (**B**) individuals with chest wall restriction, and (**C**) individuals with chest wall restriction complicated by inspiratory muscle (IM) weakness. In panel **B**, the reduced chest wall compliance lowers respiratory system compliance, FRC, and TLC. In panel **C**, maximal inspiratory muscle pressures (P_{mus}) are half of predicted and the restriction is amplified by the presence of IM weakness.

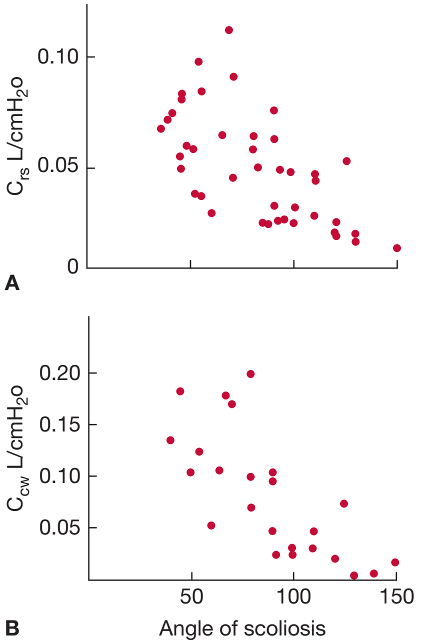

Figure 83-3 Relationship between (**A**) the angle of scoliosis and compliance of the total respiratory system and (**B**) the angle of scoliosis and compliance of the chest wall in patients with idiopathic scoliosis. *(Reproduced with permission from Kafer ER: Mechanical properties of the respiratory system and the ventilatory response to carbon dioxide. J Clin Invest. 1975;55(6):1153–1163.)*

than 50 degrees. With Cobb angles greater than 50 degrees, PI_{max} and PE_{max} may be mildly to moderately reduced and accompanied by only a mild decline in vital capacity (VC).[18] In idiopathic KS, reductions in PI_{max} may be due to mechanical disadvantage of the respiratory muscles coupled to a distorted rib cage.[19] In secondary KS, however, reductions in PI_{max} are related to intrinsic muscle weakness.[20]

The reductions in VC in idiopathic KS are typically seen in patients with severe spinal deformities (Cobb angles greater than 100 degrees). In this setting, TLC and VC may be reduced to 30% of predicted[11,17] (Fig. 83-4). Forced vital capacity (FVC) decreases in proportion to the reduction in TLC in the absence of obstructive airway disease. Residual volume (RV) may be normal or slightly increased, resulting in a relatively high RV/TLC ratio.[21] In mild and moderate KS (i.e., Cobb angles less than 60 degrees), VC and TLC may be only mildly reduced. Although uncommon, obstructive airway dysfunction in nonsmokers has been described.[22] This includes reductions in mid-expiratory flow rates or FEV_1 related to torsion or compression of major bronchi from the distorted spine[23,24] (Fig. 83-5).

Factors other than Cobb angle can contribute to the reduction in TLC and VC. These factors include the location of the spinal curve (thoracic vs. lumbar), number of vertebrae involved, patient's age, degree of spinal rotation, and, most importantly, the presence or absence of inspiratory muscle weakness. Coexistent respiratory muscle weakness significantly affects the severity of restriction. In the paralytic type of KS, the degree of lung restriction is primarily determined by the magnitude of respiratory muscle weakness rather than by the degree of spinal curvature.[20] Thus, for a similar Cobb angle, patients with paralytic KS are likely to have greater pulmonary function impairment than patients with idiopathic KS.[20] In patients with congenital KS, coexisting rib deformities or underlying lung abnormalities similarly lead to a greater loss in VC for a given degree of spinal deformity than seen in patients with idiopathic KS.[25]

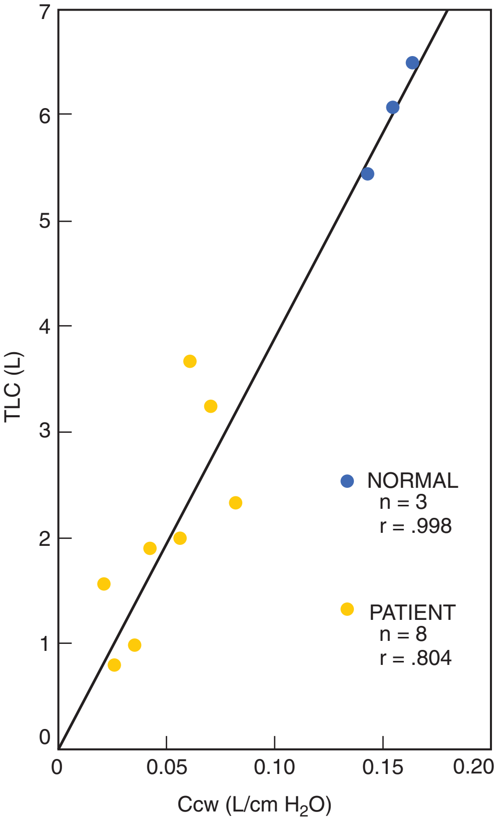

Figure 83-4 The reduction in total lung capacity (TLC) in kyphoscoliosis is related to the reduction in chest wall compliance (CCW). *(Data from Ting EY, Lyons HA. The relation of pressure and volume of the total respiratory system and its components in kyphoscoliosis. Am Rev Respir Dis. 1964;89:379–386.)*

The work of breathing is increased in KS largely due to increased elastic load related to the stiff chest wall.[12] Consequently, the oxygen cost of breathing may be three to five times that seen in healthy subjects. Concomitant inspiratory muscle weakness decreases ventilatory reserve and predisposes the respiratory muscles to fatigue and contributes to respiratory failure in these patients.[26]

■ Exercise Capacity

In KS with Cobb angles greater than 60 degrees exercise capacity may be severely limited. Typically, maximal oxygen consumption is reduced to about 60% to 80% of predicted, heart rate is higher per workload, the ratio of tidal volume to vital capacity (VT/VC) is greater than 0.5, and the ratio of maximum exercise ventilation to maximum voluntary ventilation ($\dot{V}E_{max}$/MVV) can reach 0.7. Decreased respiratory system compliance, increased work of breathing, and respiratory muscle weakness all contribute to poor exercise capacity.[27,28] Concomitant pulmonary hypertension in those with Cobb angles >100 degrees may independently contribute to exercise limitation.

In individuals with mild to moderate spinal curves (Cobb angles 20–45 degrees), poor exercise tolerance with reduction in $\dot{V}O_{2max}$ is usually due to limb muscle deconditioning rather than to ventilatory constraints.[29]

■ Control of Breathing

Individuals with severe KS compensate for the increased elastic loads on the inspiratory muscles by adopting a rapid shallow breathing pattern consisting of low tidal volumes, shortened inspiratory time (T_I), and an increased respiratory rate (i.e., reduced total breath

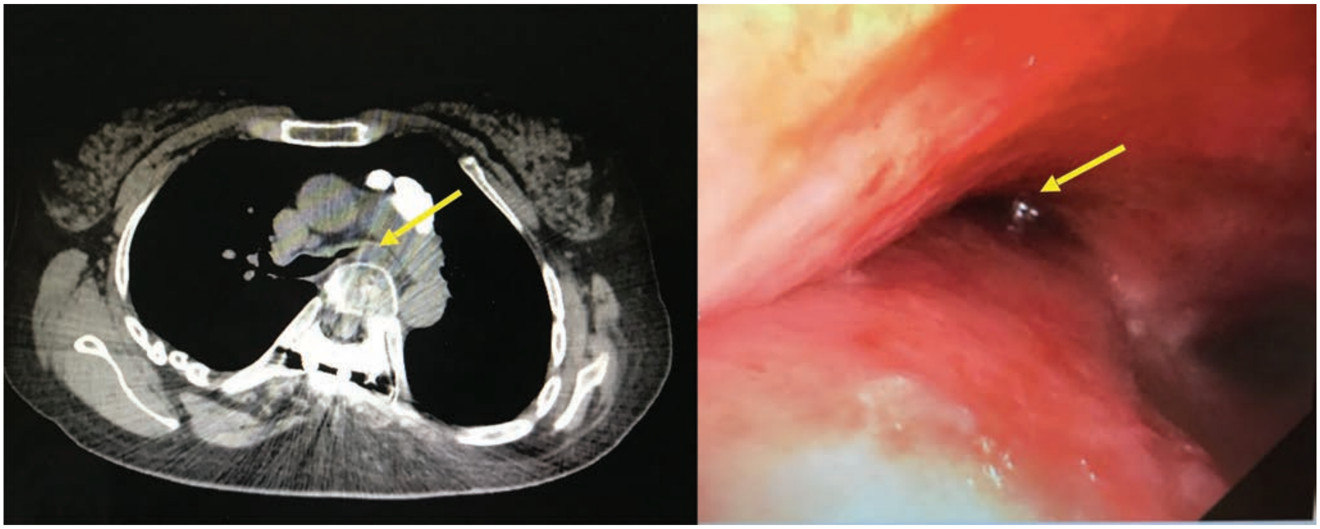

Figure 83-5 Chest CT and bronchoscopic images of extrinsic compression of the left mainstem bronchus *(arrows)* due to distorted spine in kyphoscoliosis.

time, T_{TOT}).[26,30] In young patients with KS and normal blood gases, T_I and duty cycle (T_I/T_{TOT}) correlate negatively with the angle of scoliosis.[30] In the setting of reduced respiratory system compliance, this breathing pattern minimizes the work per breath and the pressure needed to inhale, thus lessening the likelihood of developing inspiratory muscle fatigue and respiratory failure. The disadvantage of a rapid shallow breathing pattern is an increase in dead space ventilation, which reduces alveolar ventilation, causes hypoxemia, promotes atelectasis through airway closure, and further decreases lung compliance.[31]

Another strategy to compensate for the increased elastic loads is by increasing neural drive to the respiratory muscles.[30] Indirect measurements of the neural drive to the respiratory muscles, such as mouth occlusion pressure at 100 ms (P0.1) measured during quiet breathing, exercise, or breathing stimulated by hypercapnia, are usually elevated in these individuals and correlate positively with the angle of deformity.[30] The increase in neural drive is not necessarily associated with increased alveolar ventilation, as the stiff chest wall and the weak respiratory muscles will limit any augmentation in alveolar ventilation.

■ Sleep Disordered Breathing

Nocturnal hypoventilation commonly occurs in severe KS and classically precedes the development of chronic hypercapnia.[17,31] While awake, individuals with Cobb angles >100 degrees can maintain adequate alveolar ventilation by increasing neural drive to the diaphragm and recruiting accessory inspiratory muscles.[26,30] However, during sleep, neural drive to the inspiratory muscles is diminished, especially during REM sleep.[32] Since these patients are dependent exclusively on the diaphragm to maintain alveolar ventilation in REM sleep, they are at risk for becoming hypercapnic and hypoxemic. The risk of hypoventilation is amplified if there is diaphragm dysfunction.[33] Of interest, the magnitude of nocturnal hypoventilation may not correlate with the degree of thoracic deformity, pulmonary function testing, or neural drive to the respiratory muscles.[33] This observation suggests that inspiratory muscle weakness may be a more important factor for developing nocturnal hypoventilation. Persistent nocturnal desaturation and hypercapnia may further weaken the respiratory muscles, aggravate hypoxemia, and lead to pulmonary hypertension and cor pulmonale. Obstructive sleep apnea, which has a similar prevalence in KS to that of the general population, also may complicate nocturnal hypoventilation.[34] Since nocturnal hypoventilation is treatable and typically occurs before the onset of cardiorespiratory failure, the clinician must be aware of the sleep breathing abnormalities in these patients and promptly diagnose them with overnight polysomnography.[34]

■ Gas Exchange

Abnormalities in gas exchange frequently exist in patients with KS, with normocapnic hypoxemia being the most common abnormality. In nonsmokers with idiopathic KS, Pa_{O_2} correlates directly with VC and inversely with the angle of scoliosis. The age-dependent decrease in Pa_{O_2} is greater than that of normal individuals, and oxyhemoglobin desaturation can occur with minimal activity.[7,17] Hypoxemia is primarily due to ventilation/perfusion mismatch and less often to intrapulmonary shunt associated with atelectasis.[35] In severe KS with chronic hypercapnia, hypoventilation also contributes to hypoxemia. Hypercapnia initially occurs only during sleep or with exercise.[17] With aging or as the disease progresses, hypercapnia is seen at rest while awake.

■ Clinical Course

The natural history of KS largely depends on underlying etiology and degree of spinal deformity. Congenital KS with severe spinal deformities may progress rapidly, resulting in marked restrictive dysfunction, cor pulmonale, and early death.[36] Secondary KS may also progress to develop severe restrictive dysfunction and cardiorespiratory failure.[37] In general, when KS manifests early in life (age 0–8 years) there is a greater risk for rapid progression of the spinal deformity during growth, continued progression of the deformity after skeletal maturity, and development of respiratory failure.[37]

In contrast, idiopathic KS typically has an overall benign course. If the spinal deformity at skeletal maturity is mild, these individuals have an excellent prognosis with little respiratory impairment, and an overall good quality of life.[2] In individuals with idiopathic KS and moderate or severe deformity at presentation (age 12–16 years), the risk of deformity progression and development of respiratory impairment increases significantly.[2] Risk factors for deformity progression generally include large curves at presentation, skeletal immaturity, and curves with a thoracic apex.[2] By rough estimates, individuals with thoracic deformities greater than 50 degrees at skeletal maturity are at risk for a progressive increase in the spinal curve at a rate of about 1 degree annually.[10]

Most young individuals with idiopathic KS are asymptomatic. As deformity progresses with aging, many will develop back pain and dyspnea. Initially, dyspnea may occur only with activities and eventually be present at rest.[17] Consequently, older individuals with severe idiopathic KS, especially those with a Cobb angle >110 degrees and VC of <45% predicted, should be monitored for respiratory complications.[17] When cardiorespiratory failure develops, the prognosis is poor, and without supplemental oxygen or ventilatory support death may occur within 1 year. The risk of respiratory failure is even greater in patients with inspiratory muscle weakness, sleep-disordered breathing, obesity, or bronchial compression and central airway obstruction by the distorted vertebrae. Pregnancy generally does not increase the risk for respiratory failure; however, women with idiopathic KS and a VC of less than 1 L may develop respiratory problems during pregnancy.[38]

■ Treatment

General measures for adults with KS include smoking and vaping cessation, maintenance of a normal body mass index, frequent physical activity to improve exercise tolerance and minimize deconditioning, routine vaccinations, prompt treatment of respiratory infections, and psychological support for those with diminished self-image. Supportive therapy with supplemental oxygen during activity or sleep may be needed if there is evidence of oxyhemoglobin desaturation with exertion or sleep. Domiciliary oxygen therapy may be sufficient if it corrects nocturnal hypoxemia without inducing hypercapnia. However, hypercapnia needs to be closely monitored, especially in individuals with a VC less than 50% of predicted. If hypercapnia is present, nocturnal noninvasive ventilatory support should be initiated. Dyspnea, morning headaches, poor sleep quality, fatigue and the presence of cor pulmonale are symptoms and signs that should alert the clinician to the presence of nocturnal hypoventilation.[39] Long-term, nocturnal noninvasive ventilation should be offered to all patients with KS and chronic hypercapnic respiratory failure, as it reduces mortality.[39–42]

Noninvasive positive-pressure ventilation can be delivered via a nasal mask or full-face mask, with or without supplemental oxygen. When prescribing a positive pressure device, either a pressure- or volume-preset ventilator can be used.[43] Apart from the potential for greater leakage with the pressure mode, pressure or volume ventilation have equivalent beneficial effects on physiologic and clinical parameters as well as overall health status. Contraindications to noninvasive ventilation include the inability to protect the upper airway due to impaired cough, excessive airway secretions, or inability to cooperate.[39] When noninvasive ventilation has failed or is contraindicated, invasive ventilation should be considered.

The benefits of noninvasive ventilation include improvements in gas exchange, sleep efficiency, pulmonary hemodynamics, respiratory drive, quality of life, and survival (Table 83-2).[39,42] By contrast, measurements of VC, PI_{max}, twitch transdiaphragmatic pressure, and respiratory muscle endurance are not usually improved by noninvasive ventilation.[44] Accordingly, the lower incidence of respiratory failure in patients undergoing positive-pressure ventilation may be attributed to improvements in respiratory control rather than improvement of respiratory muscle contractility.[44] Long-term noninvasive ventilation substantially reduces the number of hospitalizations for respiratory failure and the length of hospital stay.[39] Survival benefit of KS patients treated with noninvasive ventilation and supplemental oxygen over those patients treated with just oxygen has been demonstrated by comparative and observational studies (Fig. 83-6).[40–42,45]

TABLE 83-2 Therapeutic Benefits of Noninvasive Mechanical Ventilation in Patients with Kyphoscoliosis

Gas Exchange Indices	
Pa_{O_2}	Increase
Pa_{CO_2}	Decrease
Bicarbonate	Decrease
Pulmonary Function Tests	
FVC	No change
FEV_1	No change
TLC	No change
FRC	No change
Respiratory Mechanics	
PI_{max}, PE_{max}	No change or slight increase
Twitch P_{di}	No change
Chest wall compliance	No change
Lung compliance	No change
Hemodynamic Parameters	
PAP	Decrease
Ventilatory Control	
Hypercapnic ventilatory response	Improved
Sleep	
Epworth sleepiness scale	Decrease
Quality of Life	Improvement
Survival	Increase

FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; TLC, total lung capacity; FRC, functional residual capacity; PI_{max}, maximum inspiratory pressure; PE_{max}, maximum expiratory pressure; P_{di}, transdiaphragmatic pressure; PAP, pulmonary artery pressure.

Operative and nonoperative (brace) approaches in skeletally immature children with idiopathic KS have been used to prevent or delay the deformity progression. A brace is generally used in growing children with angles between 25 and 45 degrees,[46] and surgery is recommended for adolescents with angles greater than 45 to

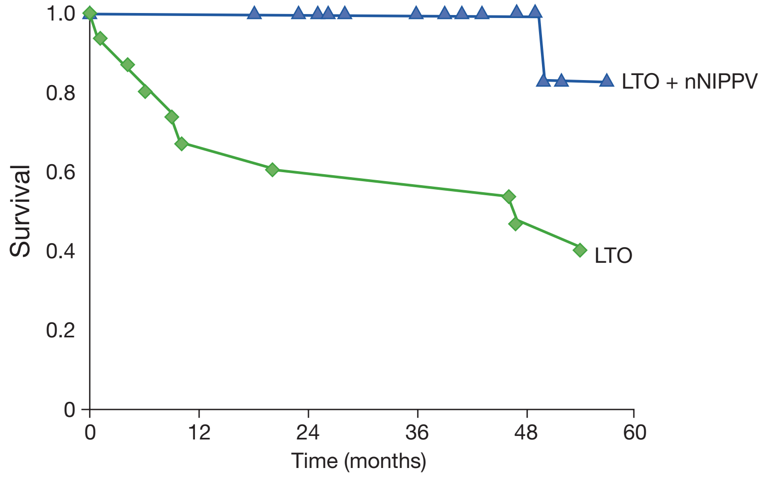

Figure 83-6 Survival curves of kyphoscoliotic patients treated with long-term oxygen therapy (LTO) or LTO and nocturnal nasal intermittent positive-pressure ventilation (nNIPPV). *(Reproduced with permission from Buyse B, Meersseman W, Demedts M: Treatment of chronic respiratory failure in kyphoscoliosis:oxygen or ventilation? Eur Respir J. 2003;22(3):525–528.)*

50 degrees.[3,47] Of the surgical techniques, fusion of the affected vertebrae with rod fixation to the spine is accomplished via the posterior or anterior approach. Spinal fusion has considerable disadvantages, as it has been associated with restrictive respiratory defects, decreased ability to carry out daily activities, and poor cosmetic results.[48] In young children (age <10 years), severe restrictive respiratory disease (VC <50% of predicted) may occur in roughly 50% of patients undergoing spinal fusion, especially in those with extensive thoracic fusions or in those with fusions of the proximal thoracic spine.[48] Surgical fusion of the spine may have a role in children with congenital spinal deformities or in children with KS secondary to neurologic defects.[49] Newer nonfusion approaches include implantation of growth-friendly rods such as expandable spinal rods, titanium rib implants, or remotely distractible magnetically controlled rods.[50] These latest techniques permit control of spinal deformity while allowing continued spinal growth and pulmonary development.[50] In the absence of randomized controlled studies, the overall efficacy of bracing or surgery in restoring pulmonary function to that of nonscoliotic individuals and minimizing the possibility of respiratory failure is not clear.[2,3,51]

THORACOPLASTY

Thoracoplasty refers to a surgical procedure aimed to reduce the volume of a hemithorax. In the pre–antituberculous chemotherapy era, thoracoplasty was the standard operative approach to control cavitary pulmonary tuberculosis. It consisted of different combinations of rib removal, rib fracture, phrenic nerve resection, or lung compression by filling the pleural space with foreign material (e.g., ping pong balls) (Fig. 83-7). Since the procedure was largely performed in the 1940s and 1950s, very few people who had undergone the procedure are still alive.[52] Historically, these individuals commonly developed dyspnea, severe restrictive dysfunction, and chronic hypercapnic respiratory failure as they aged.[52] The severity of the restrictive defect was often comparable to that seen in KS (Tables 83-3 and 83-4) and was related to the number of ribs removed, presence of fibrothorax, lung fibrosis secondary to underlying granulomatous disease, prior lung resection, or intentional phrenic nerve damage.[52] As in most restrictive chest wall diseases, these patients had impaired gas exchange, limited exercise tolerance, and an increased oxygen cost of breathing, and they eventually would develop cor pulmonale. Progressive scoliosis with aging further impaired respiratory function. Although this procedure is of historic interest, the purpose of reviewing thoracoplasty in this chapter is that the procedure is still occasionally performed. Currently, thoracoplasty is indicated for treatment of bronchopleural fistulae that have failed to close following decortication or for treatment of persistent empyema in which decortication is not feasible or has failed to eradicate the infection (Fig. 83-7).[53] Treatment of individuals who are post-thoracoplasty and have developed restrictive disease consists of supplemental oxygen, antibiotics for respiratory infections, and noninvasive ventilatory support.

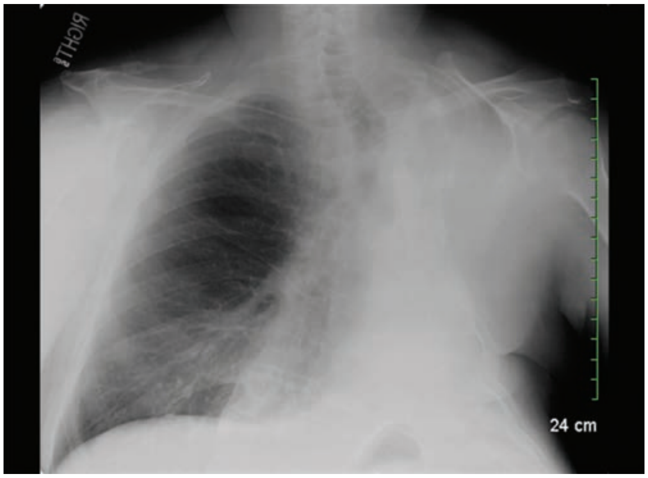

Figure 83-7 Chest radiograph of a patient who is post-thoracoplasty as part of the treatment of postpneumonectomy empyema. *(Reproduced with permission from Borges N, Saha S. Thoracoplasty for Postpneumonectomy Empyema Associated with Bronchopleural Fistula: A Case Series. Int J Angiol. 2015;24(2):151–154.)*

TABLE 83-3 Pulmonary Function in Diseases of the Chest Wall

	KS	Post-THOR	PE	AS
TLC (% predicted)	44	64	90	85
VC (% predicted)	30	49	90	79
RV (% predicted)	94	91	100	97
FEV$_1$ (% predicted)	40	41	93	81
FEV$_1$/FVC	80	57	81	74

KS, kyphoscoliosis; Post-THOR, postthoracoplasty; AS, ankylosing spondylitis; PE, pectus excavatum; TLC, total lung capacity; VC, vital capacity; RV, residual volume; FEV$_1$, forced expiratory volume in 1 s; FVC, forced vital capacity.

PECTUS EXCAVATUM

Pectus excavatum, also known as funnel chest, is a congenital chest wall deformity characterized by excessive depression of the sternum and the adjacent ribs producing a caved-in appearance to the rib cage.[54] It is the most common congenital deformity of the chest wall, with a prevalence of about 1 in 1000 live births and a male-to-female ratio of 3 to 1.[55] A family history may be present in up to 40% of cases.[56] Based on chest CT measurements, a recent large, population-based, multiethnic cohort study found a pectus excavatum prevalence of 0.4% or 1 in 250 adult individuals (median age 45 years).[57]

■ Etiology and Clinical Features

Although its pathogenesis is unknown, pectus excavatum is believed to result from an abnormal growth of cartilage around the sternum due to a defect in collagen formation.[58] In support of this mechanism is the relatively high prevalence of pectus excavatum in Marfan syndrome, Ehlers-Danlos syndrome, and Noonan syndrome.[59] Additionally, up to 40% of these individuals have scoliosis.[60]

Although occasionally present at birth, pectus excavatum typically becomes visible in early childhood and during the adolescent growth

TABLE 83-4 Respiratory Mechanics in Diseases of the Chest Wall

	KS	Post-THOR	PE	AS
CRS (% predicted)	50	50	—	70
CCW (% predicted)	30	40	—	60
CL (% predicted)	60	50	80	80
PI$_{max}$ (cm H_2O)	37	50	90	56
MVV (L/min)	37	37	107	80

KS, kyphoscoliosis; Post-THOR, postthoracoplasty; AS, ankylosing spondylitis; PE, pectus excavatum; CRS, compliance of respiratory system; CCW, compliance of chest wall; CL, compliance of lungs; PI$_{max}$, maximum inspiratory pressure; MVV, maximum voluntary ventilation.

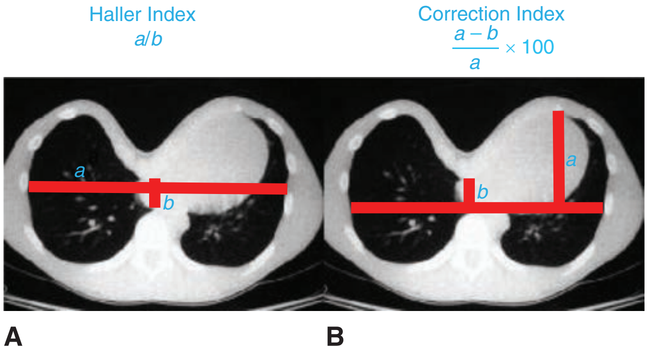

Figure 83-8 Chest computed tomography of a patient with pectus excavatum. The Haller index is the ratio of the transverse to anterior-posterior (AP) diameters of the rib cage at the level of the deepest sternal depression. (**A**) The difference between the minimum distance used to calculate the Haller index, and the distance between the anterior spine and the most anterior portion of the chest is used to calculate the correction index. (**B**) The difference of the two distances is divided by the maximum distance and expressed as a percentage.

spurt. The sternal depression may be minimal or prominent. The most frequent complaints of individuals with pectus excavatum are usually cosmetic. The psychological impact of the pectus deformity becomes more troublesome during the teenage years when body image becomes more important.[56] Exertional dyspnea and exercise intolerance may occur in 30% to 70% of patients.[61] However, these symptoms cannot be entirely explained by the mild restrictive pattern that is sometimes seen (Table 83-3) or by limitations in cardiac output. Adults with pectus excavatum also may experience daily physical and psychosocial symptoms and complain of poor sleep quality.[62,63]

The degree of sternal depression and the percentage of the chest that needs to be corrected are assessed by calculating the Haller index and the correction index, respectively, from chest CT images. The Haller index is the ratio of the transverse to anterior-posterior (AP) diameters of the rib cage at the level of the deepest sternal depression (Fig. 83-8A).[58] In normal individuals this ratio is about 2.5. A ratio greater than 3.25 is considered significant sternal depression.[58] The correction index uses the difference of two distances, a minimum and a maximum (Fig. 83-8B). The minimum distance is that used to calculate the Haller index, and the maximum distance is that between the anterior spine and the most anterior portion of the chest. The difference of the two distances is divided by the maximum distance and expressed in percentage.[64] Normal correction index is 10% or less.[54]

Pathophysiology

Severe pectus deformities may be associated with mild reduction in TLC and VC, especially with a Haller index of 5 or higher.[65] With concomitant scoliosis, the restriction may be more pronounced. Although obstructive defects are infrequent (approximately 2% of cases),[61,65] RV and the RV/TLC ratio are commonly increased. The elevated RV and RV/TLC may be due to stiffness of the rib cage resulting in reduced chest wall compliance in these young individuals rather than air trapping or expiratory muscle weakness. In most cases there is no underlying lung disease, and lung compliance is normal. Unlike ankylosing spondylitis, the mobility of the rib cage is not impaired at rest or during exercise in pectus excavatum.[66,67]

Cardiopulmonary exercise testing is usually normal in individuals with pectus excavatum. Indices such as maximal work rate, maximum oxygen consumption, and maximal oxygen pulse are not different from those of healthy individuals. In severe deformities, limited exercise capacity with reductions in maximal work rate or oxygen consumption at a given work rate may occur and often are out of proportion to the mild restrictive respiratory impairment found in these patients.[68] The explanation for the limited exercise capacity in this group of patients may be a reduction in venous return to heart associated with right ventricular compression due to sternal depression. Distortion of right ventricular geometry may be detected by echocardiographic (Fig. 83-9) or cardiac magnetic resonance imaging studies.[69] However, the role of these findings in limiting exercise capacity is not entirely known.

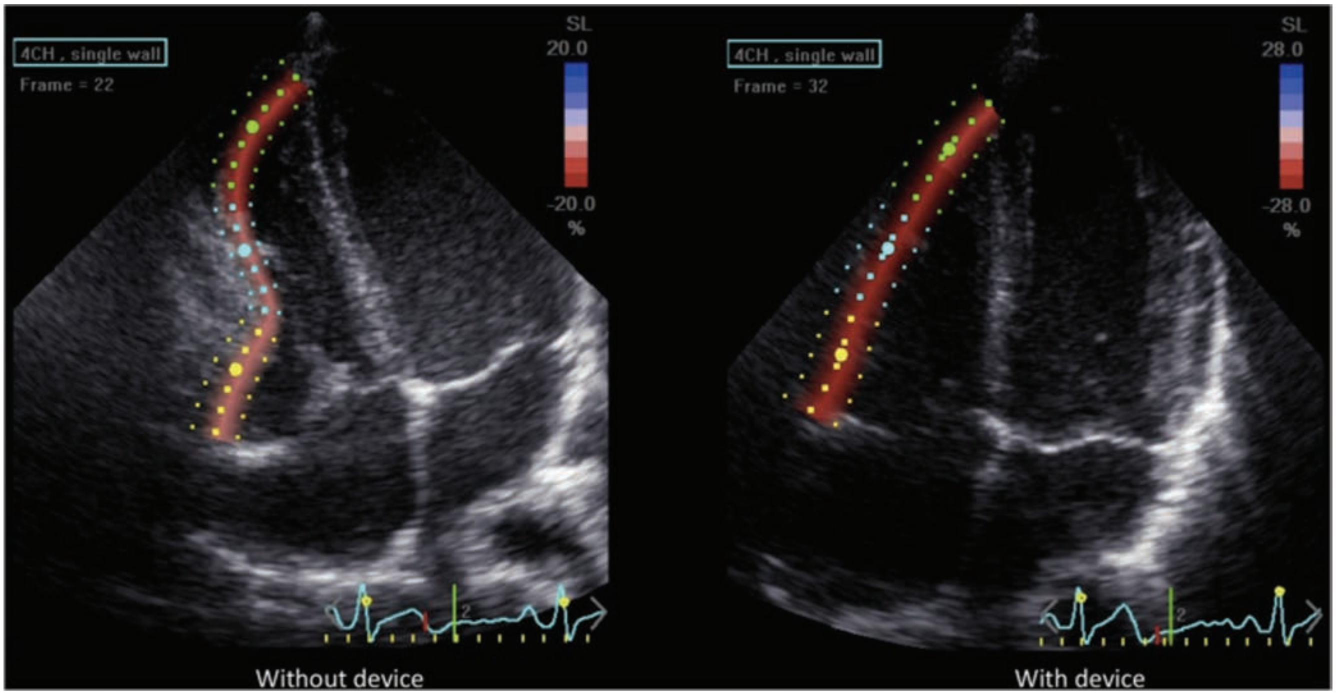

Figure 83-9 Four-chamber echocardiogram showing compression of the right ventricular free wall (red dotted line) by the pectus deformity, which is reversed by applying negative suction to the chest wall. *(Reproduced with permission from van Schuppen J, de Beer SA, van der Hulst AE, et al. Impact of vacuum bell on thoracic shape and cardiac function in pectus excavatum. J Cardiovasc Comput Tomogr. 2018;12(5):e17–e19.)*

Treatment

Conservative treatment with a vacuum bell for a minimum of one hour daily can be used in selected patients with pectus excavatum. With this device, better outcomes were noted in individuals with age less than 11 years, chest depth less than 1.5 cm, and chest wall flexibility.[70]

Although surgery is most often performed for cosmetic reasons, it is clearly indicated when the deformity has significant physiologic and psychological repercussions for the individual.[71] The optimal timing for repair is around 10 to 14 years of age or at a younger age if there is significant cardiopulmonary compromise. Individuals selected for repair typically have a Haller index greater than 3.25 or a correction index of more than 20%.[64,71]

The most common surgical approaches include modifications of the open-resection method originally described by Ravitch or the minimally invasive approach described by Nuss.[58] The first method involves resection of costal cartilage and a sternal osteotomy, with or without fixation of the sternum by external or internal supports. This procedure may be complicated by sternal necrosis, infection, or recurrence of the deformity. Recurrence may arise in younger children in whom sternal supports are not used. The invasive approach is best suited for older adults and for individuals with combined pectus excavatum and carinatum, marked asymmetry, or extensive defects involving the upper ribs.[58]

The Nuss procedure, developed in the 1990s, provides a minimally invasive alternative to reconstructing the deformity.[72] It consists of placing a curved metal bar under the sternum at the point of deepest depression through small incisions made on each side of the rib cage. The sternum is then pushed forward and stabilized by the metal bar (Fig. 83-10). With this procedure, the costal cartilage is not resected. The bar is generally left in place for 2 to 4 years, resulting in permanent chest wall remodeling. Selected adults more than 30 years old can also undergo the minimally invasive procedure.[73] Complications of this approach include bar displacement or rotation that would require reoperation, as well as pneumothorax, pericarditis, and infection. The use of thoracoscopic techniques has minimized associated complications. Overall, the rate of complications does not differ significantly between the two surgical approaches.[74] Deformity repair with either procedure impacts positively on the psychosocial well-being of the individual.[74]

Improvements in cardiopulmonary function with invasive or minimally invasive procedures remain controversial.[61] If there is improvement, it is mostly modest and clinically insignificant. Improvements in exercise tolerance, cardiac output, and VO_{2max}

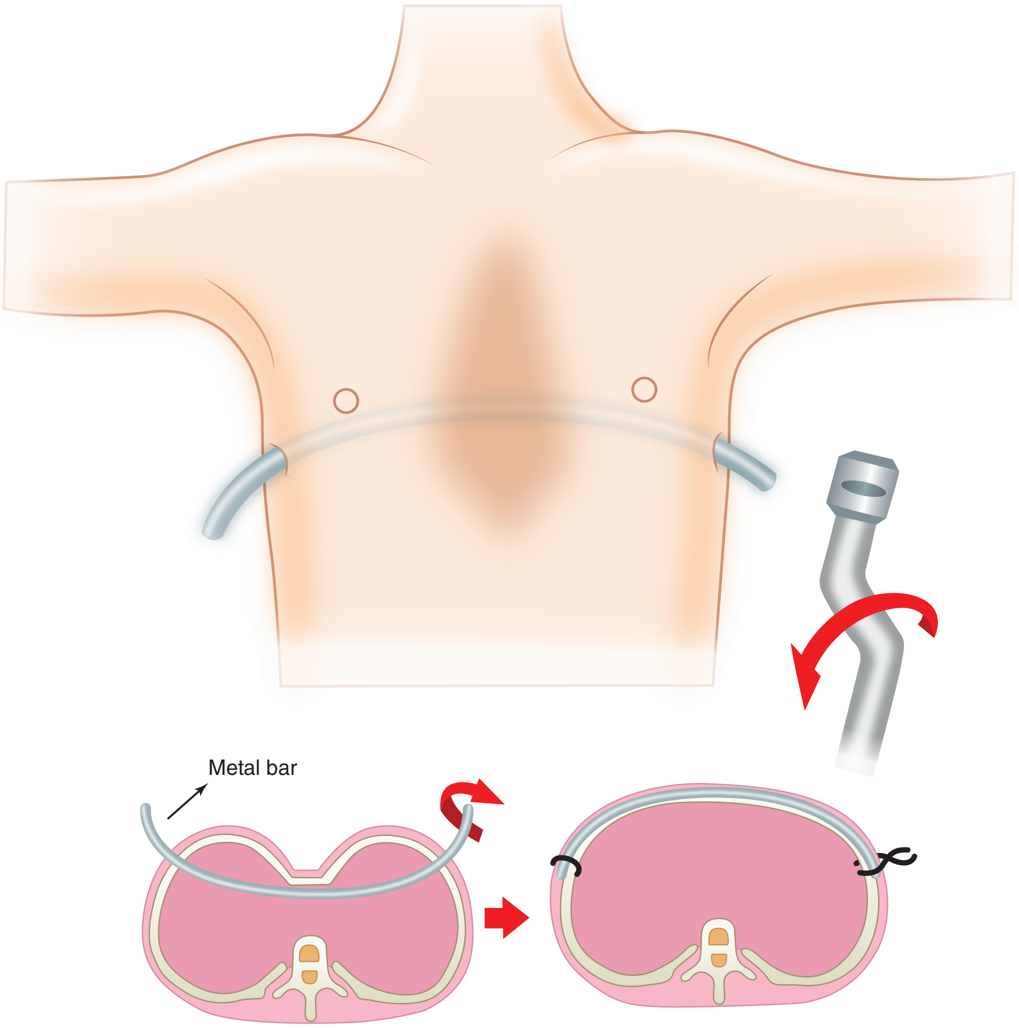

Figure 83-10 Schematic depicting the Nuss procedure in a patient with pectus excavatum. A curved bar is inserted behind the sternum and then rotated to displace the depressed sternum ventrally.

after surgical correction have been described in some but not all studies.[75,76] Discrepancies among studies may be due to differences in patient populations (younger versus older patients), surgical techniques, the interval at which tests are performed following the operation, or the effects of growth on pulmonary function. One year following surgery, any improvement in pulmonary function is independent of which surgical procedure was performed.

ANKYLOSING SPONDYLITIS

Ankylosing spondylitis (AS) is a chronic multisystem disease characterized by inflammation of the spine and sacroiliac and peripheral joints as well as involvement of extra-articular organs including the lungs and the heart.[77] The chronic inflammation of the spinal structures and costovertebral, apophyseal, and sacroiliac joints leads to fibrosis and ossification of these structures and bony ankylosis of the costovertebral and sternoclavicular joints.[78] Consequently, spinal mobility is reduced and rib cage expansion is considerably limited.[79]

■ Etiology and Clinical Features

AS affects roughly 0.1% of the general population and is more common in men than in women, with a ratio of 16:1. Its etiology is unclear. There is a genetic predisposition for AS, as 95% of whites with AS have the HLA-B27 antigen.[80,81]

Clinically, patients in late adolescence or early adulthood present with back pain, morning stiffness due to progressive spinal rigidity, or inflammation of peripheral joints. Extra-articular manifestations such as nongranulomatous uveitis, aortitis, and dilatation of the aortic root also may occur. Onset of symptoms after the age of 45 is rare. Typically, the symptoms are worse in the morning or after prolonged rest.

Chest pain due to inflammation of manubriosternal junction and/or the sternoclavicular joints with inability to fully expand the chest on inspiration can occasionally occur (Fig. 83-11).[82] On physical exam, there may be tenderness of the anterior chest wall, the costochondral region, or the manubriosternal junction. Chronic back pain may cause sleep fragmentation resulting in difficulties with daytime somnolence and fatigue.[83] Upper airway obstruction due to cricoarytenoid cartilage involvement is a rare complication.[84]

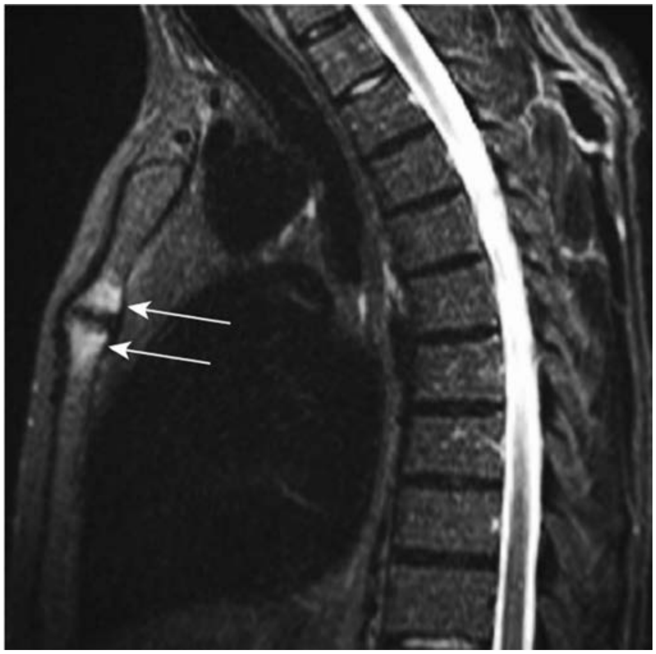

Figure 83-11 Inflammatory lesions of the anterior chest wall displayed by whole-body MRI in an ankylosing spondylitis patient complaining of anterior chest wall pain. Arrows point to bone marrow edema in both parts of the manubriosternal joint. *(Modified with permission from Weber U, Lambert RGW, Rufibach K et al. Anterior chest wall inflammation by whole-body magnetic resonance imaging in patients with spondyloarthritis: lack of association between clinical and imaging findings in a cross-sectional study. Arthritis Res Ther. 2012;14(1):R3.)*

Individuals with advanced AS have reduced rib cage motion and are more dependent on diaphragmatic breathing. Prominent abdominal excursion during inspiration may be apparent in supine or upright individuals. The degree of rib cage immobility can be assessed by measuring the change in rib cage circumference at the level of the fourth intercostal space between a full inspiration and full expiration. Rib cage expansion less than 3 cm should raise the possibility of AS in young patients with chronic low back pain.[85]

■ Respiratory Pathophysiology

Limited rib cage expansion is the pathophysiologic hallmark of AS.[78] This limitation results from fusion of the costovertebral and sternoclavicular joints and possibly leads to intercostal muscle atrophy.[78] Rib cage motion is similar to that in healthy individuals in terms of direction, but the magnitude of motion is severely limited.[31] Rib cage stiffness leads to a reduction in chest wall and total respiratory system compliance, but lung compliance remains normal except in cases of coexisting lung fibrosis (Table 83-4).[86] Since rib cage expansion is severely limited in advanced AS, chest wall inflation is primarily accomplished through diaphragmatic displacement of the abdomen, that is, the lung expands along the "path" of least resistance (Fig. 83-12). This pathway accounts for most of the tidal volume change during quiet breathing, speech, or exercise.[79,86,87] In this setting, the increased diaphragm shortening and the relatively greater transdiaphragmatic pressure required to inflate a stiff rib cage[78] may potentially provide a training stimulus to the diaphragm.

Only mild reductions in VC or TLC (75%–80% of predicted) may be present despite moderately severe reductions in rib cage mobility (Table 83-3).[85,88] The mild restrictive impairment is usually proportional to disease activity and duration, and to the degree of spinal and rib cage mobility.[88] The restrictive defect may increase in advanced disease when kyphosis supervenes.[89] Mild reductions of respiratory muscle strength (PI_{max} and PE_{max}) may be recorded in individuals with severely limited rib cage expansion.[88] However, diaphragmatic strength is typically intact in these patients.[78]

In the absence of parenchymal lung disease, Pa_{O_2} is either in the normal range or mildly reduced.[88] Exercise capacity may be mildly

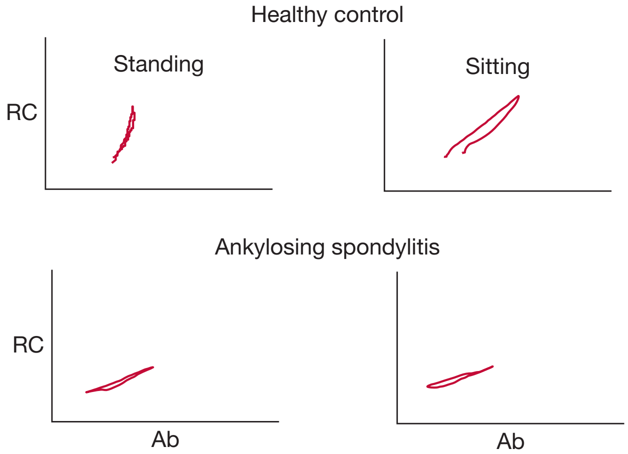

Figure 83-12 Changes in anteroposterior dimensions of the rib cage (RC) and abdomen (Ab) in a healthy individual and one with ankylosing spondylitis (AS). There is limited mobility of the rib cage in all positions resulting in greater motion of the abdomen relative to the rib cage.

decreased in patients with AS, especially in those with marked rib cage restriction.[90] The mechanism of limited exercise is most likely related to peripheral deconditioning rather than ventilatory constraints.[90]

■ Pleuropulmonary Abnormalities

Upper lobe fibrobullous disease occurs in a small percentage (up to 4%) of individuals with AS.[91] It is more common in males with long-standing disease and may manifest as interstitial infiltrates, fibrosis with honeycombing, or cavitation that may mimic tuberculosis.[91] The pathogenesis of upper lobe fibrobullous disease is unknown. Possible mechanisms include diminished upper lobe ventilation, apical mechanical stress due to rib cage rigidity, and recurrent lung infection due to impaired cough. These patients usually do not have symptoms but are at risk for spontaneous pneumothorax and infections with *Aspergillus* or atypical mycobacteria.[91] Fibrobullous disease tends to be progressive and its course is not altered by steroid treatment. Because resection of the lung segment with fibrobullous disease can be complicated by bronchopleural fistula in 50% to 60% of patients, surgery is reserved for treatment of massive hemoptysis.[91] Additional pleuropulmonary abnormalities that can be detected by chest CT in about 10% to 20% of AS patients include interstitial lung disease, pleural thickening, parenchymal bands, and bronchial wall thickening.[92] These abnormalities are subtle and do not correlate with clinical or functional impairment.

■ Sleep-Disordered Breathing

An increased prevalence of obstructive sleep apnea may occur in AS, especially in patients with long-standing disease (>5 years).[93] Because fatigue is a common complaint in AS, clinicians should have a high index of suspicion for concomitant sleep-disordered breathing contributing to excessive daytime sleepiness and screen these patients with polysomnography.[93]

■ Treatment

Treatment of individuals with AS should include pain relief, physical therapy, and measures to maintain posture and spinal flexibility and reduce complications.[80] Physical therapy exercises that promote rib cage expansion have beneficial effects on pain and spinal mobility.[94] Smoking or vaping should be avoided, and baseline chest radiographs and spirometry should be obtained.

Over the past two decades, the use of antagonists of tumor necrosis factor α (TNF-α) and most recently of monoclonal antibodies blocking IL-17A have had a dramatic effect on pain control, fatigue, spinal flexibility, and quality of life in AS patients.[80,95] Rib cage expansion is also improved following treatment with biologic agents.[94] The effectiveness of TNF-α blockade can be maintained for several years with continued treatment. Since anti–TNF-α agents do not prevent new bone formation in AS patients, their overall effects on the natural history of the disease await further assessment.[96] An adverse effect of the anti–TNF-α therapy is reactivation of tuberculosis. Therefore, AS patients who are candidates for anti–TNF-α therapy should be screened for latent tuberculosis and receive prophylactic treatment with isoniazid prior to starting treatment.[97] Additional rare adverse pulmonary complications of anti–TNF-α blockade include interstitial lung disease and development of a sarcoid-like disorder.[97,98]

OBESITY

Obesity has become a serious health problem worldwide, with its prevalence nearly tripling over the last five decades.[99] In the United States, by most recent estimates the age-adjusted prevalence of obesity in adults was 42.4%, with no significant differences between men and women, and with the prevalence of both obesity and severe obesity in adults increasing over the last two decades.[100] The trend of increasing prevalence is predicted to continue during the next decade.[101] Childhood obesity also is rising in the United States, with the latest figures showing nearly 1 in 5 children being obese.[102] The World Health Organization (WHO) has declared obesity one of the top ten risk conditions worldwide and one of the top five in developed countries. According to WHO, globally there are more people who are obese than underweight and that overweight and obesity are linked to more deaths worldwide than underweight. Obesity is associated directly or indirectly with several comorbidities, increased disability, and decreased life expectancy.[103] It is a significant contributor to escalating health care costs.[103]

TABLE 83-5 **Diagnostic Criteria for Obesity Hypoventilation Syndrome**

BMI >30 km/m^2
Daytime Pa_{CO_2} >45 mm Hg
Rise in Pa_{CO_2} of >5 mm Hg during sleep
Sleep disordered breathing
Absence of other known causes of hypoventilation

Severity of obesity is commonly assessed by calculating the body mass index (BMI), defined as body weight (BW) in kilograms divided by the square of height (Ht) in meters (BW/Ht^2). An individual with a BMI between 18.5 and 24.9 kg/m^2 is normal; a BMI between 25 and 29.9 kg/m^2 is overweight, and a BMI greater than 30 kg/m^2 is considered obese; BMI greater than 40 kg/m^2 is considered class III or severe (morbid) obesity.[104] Morbidity and premature mortality usually begin to increase at a BMI of 25 to 29.9 kg/m^2 and further increase with a BMI greater than 30 kg/m^2.

■ Clinical Features

Obesity-associated respiratory morbidity results primarily from derangements in respiratory mechanics and the control of breathing.[105] Obesity may decrease lung volumes, decrease respiratory muscle strength, increase the work of breathing, and reduce respiratory drive.[106,107] Despite these limitations, most morbidly obese patients remain eucapnic—referred to as simple obesity (SO). However, a subgroup of morbidly obese individuals develops hypercapnia.[108] These individuals have obesity hypoventilation syndrome (OHS) (Table 83-5).

■ Pulmonary Function and Chest Wall Mechanics

In SO, the most common impairments in pulmonary function include a decrease in expiratory reserve volume (ERV) and FRC.[109] In contrast, TLC is normal or only mildly reduced (Table 83-6). The lower than normal FRC is due to the increased volume of abdominal and thoracic fat that makes pleural pressure less subatmospheric.[110,111] Both factors lower resting end-expiratory relaxation volume (FRC). Residual volume (RV) may be normal or even slightly increased in SO.[109] As a result, ERV—which is the difference between FRC and RV—is reduced.[109] Expiratory flow rates and the FEV_1/FVC ratio are usually normal in SO except for modest reductions in forced vital capacity (FVC) when the BMI exceeds 45 kg/m^2.

In OHS, FRC and ERV are more severely reduced than they are in individuals with SO and a comparable BMI (Table 83-6). In OHS, TLC is reduced but to a lesser extent than FRC and ERV.[105] With BMI >60kg/m^2, up to 75% of these individuals, especially men, have diminished TLC.[106] These differences in pulmonary function between SO and OHS may be explained by differences in the distribution of adipose tissue. Individuals with OHS typically

TABLE 83-6 Pulmonary Function, Gas Exchange, and Respiratory Mechanics in Simple Obesity (SO) and Obesity Hypoventilation Syndrome (OHS)

	Normal	SO	OHS
BW (% ideal)	105	195	201
BMI (kg/m^2)	24	45	46
FVC (% predicted)	95	88	70
FEV$_1$ (% predicted)	100	85	70
FRC (% predicted)	100	83	80
ERV (% predicted)	96	52	32
TLC (% predicted)	100	95	83
MVV (% predicted)	159	129	89
PaO$_2$ (mm Hg)	90	83	58
PaCO$_2$ (mm Hg)	37	38	55
CRS (L/cm H$_2$O)	0.11	0.05	0.06
RRS (cm H$_2$O • L^{-1} • sec)	1.2	4.0	7.8
PImax (cm H$_2$O)	100	95	60
Work (J/L)	0.43	0.74	1.64

BW, body weight; BMI, body mass index; FVC, forced vital capacity; FEV$_1$, forced expiratory volume in 1 s; FRC, functional residual capacity; ERV, expiratory reserve volume; TLC, total lung capacity; MVV, maximum voluntary ventilation; CRS, compliance of respiratory system; RRS, resistance of respiratory system; PI$_{max}$, maximum inspiratory pressure.

have a central pattern of fat distribution. For a given BMI, a central pattern of fat distribution (measured as the waist:hip circumference ratio) is associated with greater impairment in lung function than a peripheral (around the hips) fat distribution.[112] This pattern is seen more commonly in men than in women.[113]

Respiratory system compliance is invariably decreased in obese individuals.[111,114,115] In morbidly obese patients, respiratory system compliance decreases exponentially as BMI increases. The reduction in respiratory system compliance can be primarily attributed to a decrease in lung compliance.[111] When FRC is reduced with obesity, lung compliance decreases due to airway closure and development of atelectasis. Whether a stiffened chest wall contributes to the reduction in respiratory system compliance remains controversial. Differences among studies reporting either normal or reduced chest wall compliance may be due to difficulties measuring chest wall compliance when the respiratory muscles are not fully relaxed.[111,116,117] To circumvent this issue, chest wall compliance has been measured in anesthetized, paralyzed obese individuals and found to be normal.[111,115] In this setting, the chest wall pressure-volume curve has the same slope as a nonobese individual but is shifted rightward. This rightward shift is consistent with mass loading of the thorax. Mechanistically, the excess chest wall adipose represents an inspiratory threshold load. Once the threshold load is overcome, the chest wall inflates similar to the normal chest wall.[111]

Morbidly obese individuals may have increased airway resistance,[118] exhibit expiratory flow limitation,[119] and develop intrinsic positive end-expiratory pressure (PEEP).[119] Since airway resistance remains elevated when correcting for lung volume (i.e., specific airway conductance is reduced to 50% to 70% of normal), additional factors must be contributing to increased airway resistance.[118,120] Expiratory flow limitation has been described in obese individuals during tidal breathing, especially in the supine position.[119] Flow limitation may be primarily related to shifting FRC to a region on the flow-volume curve where tidal breathing encroaches on the maximal flow-volume envelope. In the supine position, further reductions in FRC[118] increase the likelihood that expiration will be flow-limited. Intrinsic PEEP develops as a consequence of expiratory flow limitation especially in circumstances where expiratory time is reduced or tidal volume increased (i.e., exercise). Intrinsic PEEP may also develop in the supine position when FRC is further reduced. Consequently, obese individuals may complain of orthopnea.[119]

Respiratory muscle strength, as measured by PI$_{max}$ and PE$_{max}$, as well as respiratory muscle endurance, as measured by MVV, are generally preserved in SO.[121] In contrast, individuals with OHS often have a reduction in MVV and exhibit respiratory muscle weakness, with strength diminished to approximately 40% of predicted.[105,121] Mechanisms that potentially explain respiratory muscle weakness in OHS include respiratory acidosis and mechanical disadvantage of the diaphragm related to its rostral displacement by adipose tissue.[105,121]

■ Control of Breathing

Differences in the control of breathing may underlie the development of hypercapnia in some but not all obese individuals with similar BMI. In eucapnic obese individuals, the central respiratory drive (as measured by P0.1 or ventilatory or EMG responses to hypercapnia or hypoxia) is normal or increased due to excessive elastic or threshold loads imposed on the inspiratory muscles.[122–124] Specifically in the eucapnic morbidly obese, added elastic and threshold loads increase respiratory drive by 2 to 3 times that of the nonobese subject;[123] transitioning from the sitting to supine position increases further the respiratory drive in obese but not in nonobese individuals.[122] Overall, the augmented respiratory drive is strongly associated with BMI,[122] is decreased following weight loss,[125] and is important for maintaining normocapnia in obesity.[122]

Patients with OHS generally do not exhibit increased respiratory drive in response to loads placed on the respiratory muscles, and the P0.1 or ventilatory or EMG response to hypoxia or hypercapnia is diminished.[126] The mechanism accounting for the diminished ventilatory drive in OHS is unknown. Genetic tendency or respiratory mechanical disadvantage do not seem to explain it, as the ventilatory drive is intact in first-degree relatives[127] and most patients with hypercapnia can normalize Pa$_{CO_2}$ through voluntary increase in ventilation.[128] Factors that may attenuate chemosensitivity in OHS include the presence of sleep apnea, chronic hypoxia or hypercapnia, or reduced leptin or leptin resistance.[105] Leptin, a hormone produced by adipose tissue, acts in the hypothalamus to regulate appetite, food intake, and weight and also to stimulate breathing, through both central and peripheral receptors.[129–132] High serum levels of leptin are associated with reduced respiratory drive in severely obese individuals.[133] Therefore, the development of leptin resistance or relative leptin deficiency may contribute to reduced ventilatory drive and hypercapnia in OHS (Fig. 83-13).[133]

Basal O$_2$ consumption and CO$_2$ production are increased in morbid obesity.[116] Because of these increased demands, morbidly obese individuals require higher levels of alveolar ventilation to maintain eucapnia and thus have an increased work of breathing.[117] To attain the requisite levels of ventilation and minimize the work per breath, obese individuals adopt a rapid shallow breathing pattern with breathing frequency about 40% higher than that of nonobese individuals.[124] The increase in breathing frequency is accomplished by shortening both inspiratory and expiratory time while the ratio of inspiration to total breath time (T_I/T_{TOT}) remains normal.[124,134] A rapid shallow breathing pattern allows them to minimize the elastic and resistive work per breath. This pattern is amplified in OHS.[123,134] These individuals have a breathing frequency that is higher and a tidal volume that is about 25% lower than individuals with SO.[123,134]

Exercise capacity is near normal in SO.[135] During treadmill exercise, minute ventilation, respiratory rate, heart rate, and oxygen

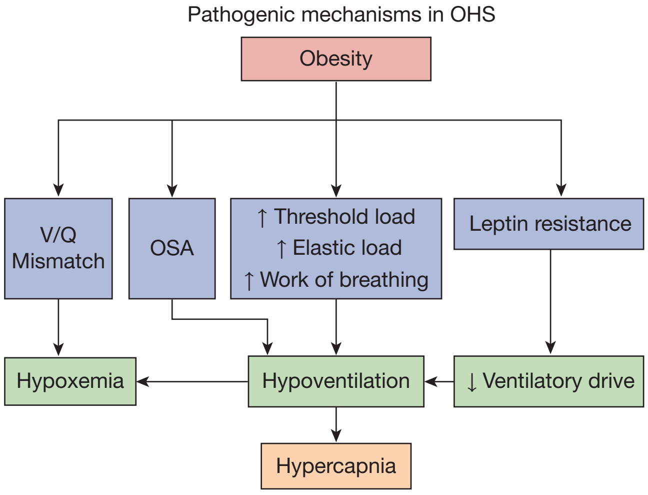

Figure 83-13 Factors involved in the pathophysiology of obesity hypoventilation syndrome. OSA, obstructive sleep apnea.

consumption are generally higher in obese individuals than in normal-weight individuals.[135] However, the anaerobic threshold is lower than in normal-weight individuals.[135] With weight loss, the metabolic demands are reduced and carbon dioxide production and alveolar ventilation are reduced by approximately 20%.[136]

Gas Exchange

Hypoxemia is either mild or absent in SO, whereas it is usually present in OHS.[137] Hypercapnia during wakefulness, the defining characteristic of OHS, rarely occurs in overweight individuals with BMI less than 30 kg/m^2.[137] In obese individuals with BMI greater than 30 kg/m^2, Pa_{O_2} is negatively and Pa_{CO_2} positively related with BMI (Fig. 83-14).[137] In OHS, gas exchange abnormalities are due primarily to hypoventilation. The presence of ventilation-perfusion mismatch at the lung bases widens the alveolar-arterial oxygen gradient and worsens hypoxemia.[138] Gas exchange abnormalities are amplified when obese individuals assume the supine position. This can be a major concern during induction of anesthesia, as these individuals may become profoundly hypoxemic.[139]

Treatment

Although difficult, dietary changes combined with exercise and behavioral modifications can lead to weight loss in some obese individuals. However, these modalities are usually not successful in maintaining long-term weight loss.[140] Bariatric surgery has evolved into a relatively common intervention that can produce not only weight loss but also long-term maintenance of weight loss.[141] In patients with OHS and acute or chronic hypercapnic respiratory failure, the use of positive airway pressure devices with sleep may improve gas exchange, daytime somnolence, and quality of life.[108,142,143]

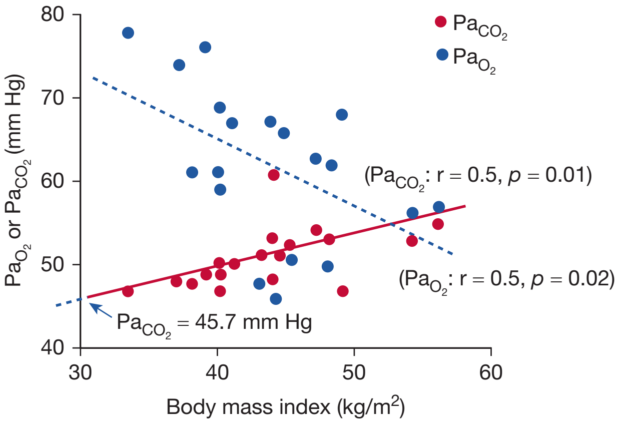

Figure 83-14 Relationship between Pa_{CO_2} and Pa_{O_2} with body mass index in patients with obesity hypoventilation syndrome. *(Reproduced with permission from Mokhlesi B. Obesity Hypoventilation Syndrome: A State-of-the-Art Review. Respir Care. 2010;55(10):1347–1362.)*

Weight loss, induced either by diet or surgical intervention, has beneficial effects on pulmonary function, gas exchange, and ventilatory control in both OS and OHS.[105,144] A weight loss of about 40 kg leads to a significant increase in ERV and, to a lesser extent, increases in FRC, VC, and TLC.[105] However, there is no correlation between the magnitude of weight loss and the degree of improvement of lung volumes. The Pa_{O_2} increases by about 4 to 8 mm Hg due to improved ventilation of the lung bases; additionally, CT may show clearing of air trapping.[145] In OHS, the effects of weight loss on ERV and FRC are more pronounced than in SO, with VC increasing as well.[146] Additional benefits of weight loss include improvements of respiratory muscle performance,[147] dyspnea scores,[144] sleep apnea,[148] 6-min walk test,[149] airway responsiveness,[150] and respiratory drive.[125] Overall, the effective and sustained weight loss that may follow bariatric surgery appears to be the best option for ameliorating the various comorbid conditions related to obesity such as hypertension, hyperlipidemia, or type 2 diabetes.[151]

FLAIL CHEST

Flail chest refers to a condition in which multiple rib fractures produce a segment of the rib cage that deforms noticeably during breathing. According to a classic definition, double fractures of three or more adjacent ribs or the combination of sternal and rib fractures are required to produce a flail segment of the rib cage and lead to respiratory failure.[31] The flail segment is displaced inwards rather that outward during inspiration. By contrast, the term "non-integrated chest wall" denotes a similarly unstable segment of the chest wall resulting from multiple single rib fractures in a single plane and causing respiratory failure.[152]

Etiology and Diagnosis

Flail chest can occur in up to 15% of adults with chest wall trauma.[153] The most common cause of flail chest is trauma related to automobile accidents or falls.[154] Other causes include rib fractures after aggressive cardiopulmonary resuscitation and rarely pathologic rib fractures (i.e., multiple myeloma, other metastases).

The diagnosis of flail chest can readily be made in spontaneously breathing individuals by observing the paradoxical motion of the flail segment of the rib cage. In fully sedated mechanically ventilated patients the diagnosis may be delayed until patients resume spontaneous breathing.[155] Chest radiographs showing multiple rib fractures confirm the diagnosis but usually miss 50% of rib fractures, especially those at the costochondral junction.[156] Chest CT with reconstruction of the rib cage is the best imaging modality to visualize rib fractures and to demonstrate the extent of injuries to the pleura and pulmonary parenchyma (Fig. 83-15).[157]

The mortality of chest wall trauma with no flail present ranges between 7% and 14%. When chest wall trauma is complicated by flail chest, the mortality rate further increases.[152,158] This can be attributed to pulmonary complications such as pulmonary contusion, hemothorax, or pneumothorax, which can occur in up to 60% of patients with flail chest.[158] In addition, trauma sufficient to cause flail chest is often accompanied by extrathoracic injuries such as head trauma, rupture of the aortic arch or other arteries, laceration of the spleen or liver, and fractures of the long bones, all of which increase morbidity and mortality.[158] Patients with multiple

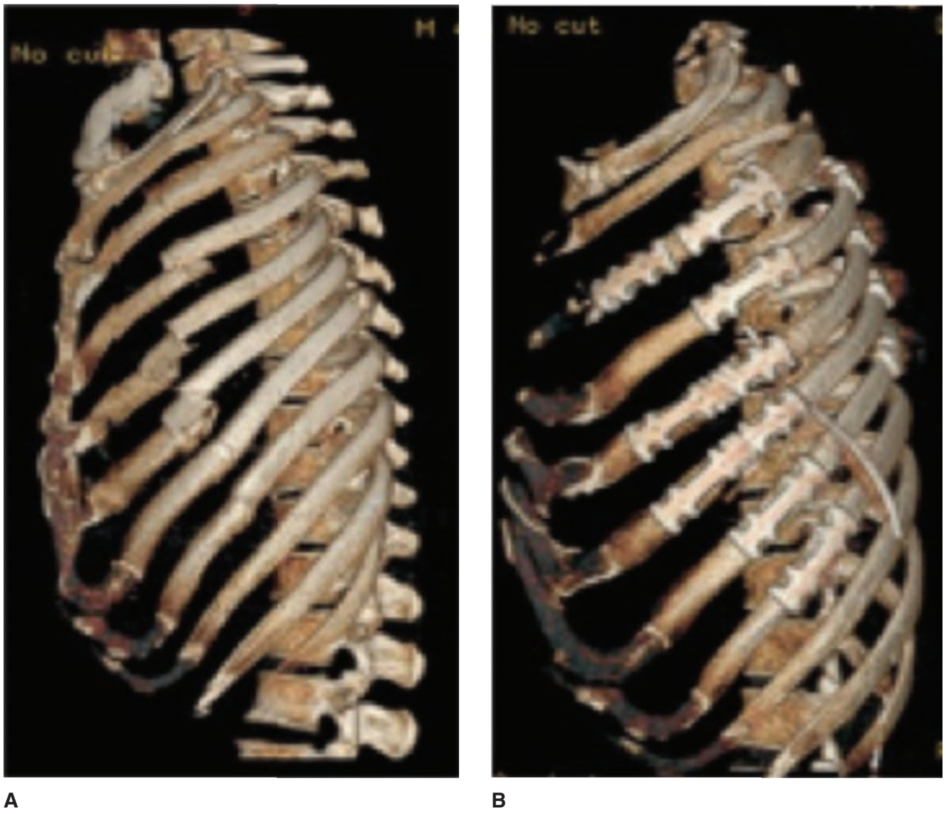

Figure 83-15 Reconstructed three-dimensional computed tomographic scan depicting a flail chest before (**A**) and after (**B**) repair with osteosynthesis plates to enable chest wall fixation. *(Reproduced with permission from Zhang X, Guo Z, Zhao C, et al. Management of patients with flail chest by surgical fixation using claw-type titanium plate. J Cardiothorac Surg. 2015;10:145.)*

trauma and lung contusion complicating flail chest have mortality as great as 56%. Age greater than 65 years is strongly associated with increased mortality in patients with flail chest.[159] In survivors of flail chest, long-term disability consisting of chest tightness, chest pain, or exertional dyspnea may occur.[160]

■ Respiratory Function and Respiratory Mechanics

Disruption of the rib cage integrity in flail chest seriously alters the function of the chest wall. Normally, rib cage expansion is accomplished primarily through the coordinated contraction of the diaphragm and the intercostal muscles and through an increase in intra-abdominal pressure in the zone of apposition of the diaphragm to the rib cage. At low lung volumes, the outward acting elastic recoil of the chest wall also assists rib cage expansion. During inspiration, pleural pressure becomes subatmospheric, which is inflationary to the lung and deflationary to the rib cage. With flail chest, a segment of the chest wall is uncoupled from the forces that promote rib cage expansion, therefore making the flail segment responsive to intrapleural pressure changes (Fig. 83-16).[161] Consequently, the flail segment moves inwards rather than outwards during inspiration. During expiration, pleural pressure becomes more positive, and the flail segment moves outward. When the normal swings in pleural pressure are augmented by reduction in lung compliance (pulmonary contusion, or atelectasis) or increase in airway resistance (bronchial secretions, or bronchospasm), there is greater paradoxical motion of the flail segment.[161]

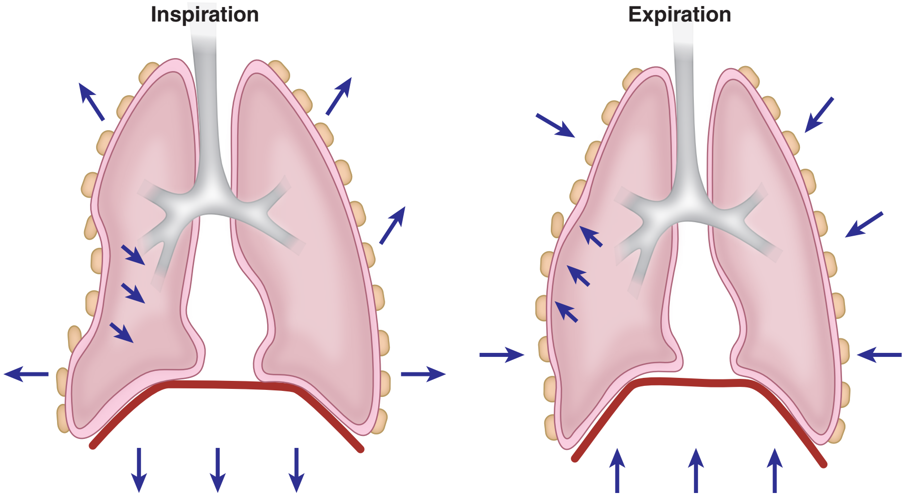

Figure 83-16 During inspiration, pleural pressure becomes more negative causing the flail segment to move paradoxically inward as the remainder of the chest wall is moving outward. During expiration, pleural pressure increases, causing the flail segment to move outward as the remainder of the chest wall becomes smaller.

The most common anatomic location for flail chest is the lateral rib cage. Anterior flail chest occurs when there are separations between the sternum and the ribs.[158] Posterior flail chest is associated with less severe clinical derangements due to splinting provided by the paravertebral muscles. The pattern of paradoxical rib cage and abdominal motion is not unique to the location of the flail segment. Paradoxical chest wall motion may occur within the rib cage itself (i.e., between the upper and lower rib cage), or between the rib cage and abdomen (i.e., lower rib cage and anterior abdominal wall).[161] These different patterns of motion of flail chest may reflect different respiratory muscle recruitment patterns.[161] Supporting evidence for alteration in the pattern of respiratory muscle action is the observation that EMG activity of the external intercostals muscles increases more than threefold in the flail region.[162]

VC and FRC can be reduced to as much as 50% of predicted in patients with flail chest.[163] Paradoxical movement of the flail segment and coexisting pulmonary contusion contribute to reductions in VC. In patients with pulmonary contusion complicating flail chest, VC and FRC may remain reduced for up to 4 years due to fibrous changes in the contused area.[155] With surgical stabilization of the flail segment, VC usually returns to normal range in about 3 months.[164]

The pathogenesis of respiratory failure in flail chest is complex. The simplified theory of a pendelluft-like movement of gas from the normal hemithorax to the flail hemithorax is not valid. Rather, flail-induced changes in lung and respiratory muscle function likely contribute to respiratory failure. Specifically, flail chest is accompanied by considerable pain, which can impair cough effectiveness, cause regional atelectasis, induce rib cage muscle spasm, and alter the pattern of respiratory muscle activation and recruitment. In addition, flail chest may increase the elastic load imposed on the respiratory muscles through development of regional (near the flail segment) or generalized atelectasis (due to splinting and pain). Associated pulmonary contusion also would increase the elastic load and work of breathing. In addition, the work of breathing is increased because the inspiratory muscles have to shorten more for a given tidal volume. The excessive muscle shortening represents extra work that is not measured using standard calculations of work per breath. (The muscles shorten but do not produce measurable flow at the mouth.)[161] Another adverse consequence of excessive inspiratory muscle shortening is a reduction in the mean operating length of the inspiratory muscles. When the inspiratory muscles are activated at a shorter than optimal length, inspiratory muscle efficiency is reduced, thereby adding to the oxygen cost of breathing.[161] The combination of added work of breathing, respiratory muscle inefficiency, hypoxemia due to atelectasis, and pulmonary contusion all combine to predispose these patients to respiratory muscle fatigue and respiratory failure (Fig. 83-17).

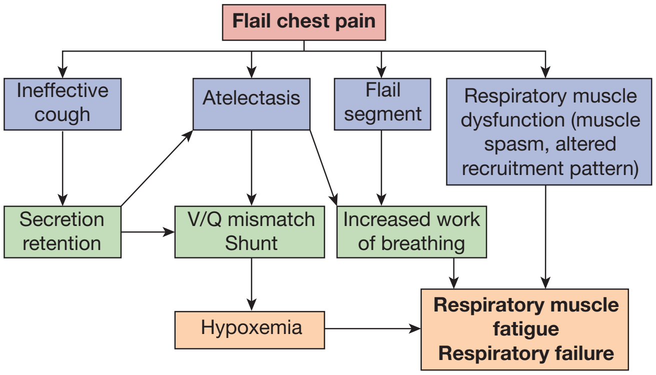
Flail chest pain
Ineffective cough
Atelectasis
Flail segment
Respiratory muscle dysfunction (muscle spasm, altered recruitment pattern)
Secretion retention
V/Q mismatch Shunt
Increased work of breathing
Hypoxemia
Respiratory muscle fatigue Respiratory failure

Figure 83-17 Factors involved in the pathophysiology of flail chest.

Treatment

Early restoration of structural and functional integrity of the chest wall is crucial to preventing flail chest–related complications. Conservative and surgical methods are used to stabilize the flail segment. The basic objective of conservative treatment is to control pain and minimize atelectasis through chest physiotherapy and clearance of bronchial secretions. Pain control can be accomplished by use of oral or intravenous narcotics, intercostal nerve blocks, or epidural anesthesia.[165] Adequate pain relief in combination with supplemental oxygen, frequent tracheal bronchial toilet, and cautious fluid replacement often prevents development of respiratory failure and leads to successful treatment of flail chest.

Mechanical ventilation with positive-pressure breathing can stabilize the flail segment by eliminating the subatmospheric changes of pleural pressure that occur during spontaneous breathing. Prolonged mechanical ventilation as a means of treating flail chest was proposed in the 1960s and was initially accomplished through tracheostomy. However, complications related to mechanical ventilation, such as pneumonia and increased morbidity and mortality, led to abandoning this modality as a primary means of stabilizing the chest wall. Currently, mechanical ventilation is indicated when there is respiratory failure, concomitant central nervous system or intra-abdominal injuries, shock, or the need to operate for other injuries. If mechanical ventilation delivered via an endotracheal tube is instituted, ventilator modes that minimize patient effort and the generation of subatmospheric pleural pressure should be employed. For example, low-impedance modes of mechanical ventilation (i.e., high-flow continuous positive airway pressure) are associated with less chest wall distortion during inspiration.[161]

Noninvasive positive-pressure ventilation may provide an alternative means of stabilizing the flail segment in selected patients who are breathing spontaneously.[166,167] This modality in conjunction with regional anesthesia can improve gas exchange and enable physiotherapy and early patient mobilization. In selected patients with flail chest, noninvasive ventilation may significantly reduce morbidity and length of hospitalization.[166,167] A randomized control trial comparing patients with mask CPAP versus assist control ventilation found that patients treated with mask CPAP had fewer complications, a shorter hospital and intensive care unit length of stay, and less ventilator time than patients with similar degrees of blunt thoracic trauma treated with assist control ventilation.[166] Although larger trials evaluating noninvasive positive-pressure ventilation in flail chest are needed for further validation, this modality may be useful when pain is controlled and hypoxemia is not severe.[168]

Surgical fixation of the flail chest has received increased attention over the last two decades, as it can potentially provide substantial benefits to mechanically ventilated patients. In selected patients with flail chest, fixation of the chest wall with wires, steel plates, and splints improves respiratory mechanics and reduces the duration of mechanical ventilation as well as hospital stay (Fig. 83-15).[169–172] Operative fixation will likely benefit patients who are ventilator dependent and able to protect their upper airways. Other potential candidates may be patients undergoing thoracotomy for intrathoracic injuries, young patients with severe chest deformation, or patients with large unstable segments and borderline pulmonary function. The indications for operative fixation remain controversial largely due to the lack of studies comparing operative and nonoperative treatment.[173]

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CHAPTER 84

Effects of Neuromuscular Diseases on Ventilation

Gerard Joseph Criner
Nathaniel Marchetti

INTRODUCTION

Neuromuscular diseases are a diverse group of disorders that vary markedly in etiology, rate of progression, pattern of respiratory involvement, prognosis, and therapy. Neuromuscular disorders impair the respiratory system as a vital pump; however, depending on the particular disease, the respiratory pump may be impaired at the level of the central nervous system (e.g., cerebral cortex or brain stem), spinal cord, peripheral nerve, neuromuscular junction, or respiratory muscle (Table 84-1).

The pattern of ventilatory impairment among these disorders is highly dependent on the specific neuromuscular disease. For example, some disorders may impair ventilation at only one level (e.g., isolated diaphragm paralysis) or simultaneously affect it at different levels (e.g., multiple sclerosis). Additionally, the severity of impairment may be minimal and totally resolve with time and proper treatment (e.g., Guillain-Barré syndrome) or is characterized by relentless progression to eventual respiratory death (e.g., amyotrophic lateral sclerosis). Moreover, some neuromuscular diseases concomitantly affect several structures (e.g., swallowing dysfunction in poliomyelitis, interstitial lung disease in polymyositis), increasing ventilatory workload in patients who already have diminished ventilatory reserve.

In this chapter we describe the etiology, pathophysiology, and treatment of ventilatory dysfunction in neuromuscular diseases.

RESPIRATORY PATHOPHYSIOLOGY

Substantial information exists concerning the ventilatory function of patients with neuromuscular disease at rest and during sleep, as well as the effects on maximum static inspiratory and expiratory efforts and responses associated with these disorders to hypoxic and hypercapnic challenges. In general, the response of the respiratory system to moderate or severe neuromuscular disease is relatively stereotyped. The typical features are a reduced forced vital capacity, reduced respiratory muscle strength, and, in some cases, malfunction of the neurons that control breathing.

Control of Breathing

The breathing pattern is often abnormal in patients with neuromuscular disease. In comparison with healthy subjects, patients with respiratory muscle weakness have a low tidal volume and a high respiratory rate that persists in response even to hypoxic or hypercapnic challenge. Moreover, this rapid, shallow breathing pattern is not due to abnormalities in gas exchange (i.e., hypoxemia or hypercapnia) but is more likely to be due to severe muscle weakness and/or disordered afferent and efferent output in motor neurons impaired by the underlying neuromuscular disease.[1]

Changes in ventilation can be used to evaluate ventilatory drive in subjects with normal lung and respiratory muscle mechanics. However, ventilation is not a good index of respiratory motor activity in subjects with significant respiratory muscle weakness because the thoracic bellows cannot perform increased work of breathing. Decreased ventilatory response to hypoxic or hypercapnic challenge in these patients could indicate abnormalities in afferent information from diseased respiratory muscles, abnormal lung or chest wall mechanics, or upper motor neuron dysfunction, rather than an abnormality in the central control of breathing. In some neuromuscular diseases, degenerative changes in the muscle spindle, impaired afferent stimulation from abnormal stretch reflexes in the muscle spindles, or decreased mechanoreceptor output from tendons may explain the altered breathing pattern.[1]

Measurement of mouth occlusion pressure generated during the first 100 ms of inspiration ($P_{0.1}$) is relatively independent of inspiratory effort and therefore is a more reliable estimate of central ventilatory drive independent of respiratory muscle mechanics.[2] $P_{0.1}$ is maintained or increased in patients with neuromuscular disease despite substantial muscle weakness. The relationship between respiratory mechanics, respiratory muscle strength, and control of ventilation has been examined in patients with neuromuscular diseases in comparison with healthy control subjects. Although

TABLE 84-1 Levels of Respiratory System Dysfunction Induced by Neuromuscular Diseases and Conditions

Level	Disease or Condition
Upper motor neuron	Parkinson disease
Cerebral	Vascular accidents Cerebellar atrophy Trauma
Spinal cord	Trauma Tumor Syringomyelia Multiple sclerosis
Lower motor neuron	
Anterior horn cells	Poliomyelitis Spinal muscle atrophy Amyotrophic lateral sclerosis
Motor nerves	Cardiac surgery Charcot–Marie–Tooth disease Diabetes Polyneuropathy Toxins Guillain–Barré syndrome
Neuromuscular junction	Neuralgia amyotrophy Critical illness polyneuropathy Myasthenia gravis Eaton–Lambert syndrome
Muscle	Botulism Organophosphate poisoning Drugs Dystrophy Acid maltase deficiency Malnutrition Corticosteroids Polymyositis

patients had 37% and 52% reductions in maximum inspiratory and expiratory mouth pressures, respectively, their $P_{0.1}$ was 66% greater than that of controls.[1]

Similar findings were encountered when normal subjects had acute muscle weakness induced by curarization. After severe muscle weakness was induced, significant increases in $P_{0.1}$ were observed during hypercapnic challenge.[3] Partial curarization of spontaneously breathing cats also produced a marked increase in phrenic nerve discharge despite a substantial decrease in minute ventilation.[4] These studies indicate that under conditions of substantial respiratory muscle weakness, ventilation is not a reliable measure of central respiratory drive, and that central respiratory drive, at least when measured by $P_{0.1}$, is usually well preserved.

■ Respiratory Muscle Function

Patients with neuromuscular disease who develop significant respiratory muscle weakness may experience fatigue, dyspnea, and impaired control of secretions, recurrent lower respiratory tract infections, acute or chronic presentations of respiratory failure, pulmonary hypertension, and cor pulmonale.

The pattern, prognosis, and degree of respiratory muscle weakness attributable to a neuromuscular disorder are varied. They depend on the level of neuromuscular system impairment, the prognosis of the underlying disorder, and whether therapy is available. Patients with neuropathy, such as in Guillain-Barré syndrome, tend to have less severe respiratory muscle weakness than patients with lower motor neuron lesions or neuromuscular junction disorders, such as myasthenia gravis. Even when respiratory muscle dysfunction is observed, not all respiratory muscles are equally impaired, and the course of the underlying neuromuscular disease and degree of respiratory and nonrespiratory muscle impairment can be very different between patients with the same disease. In some neuromuscular disorders, respiratory muscle weakness is the only presentation of an underlying disease (i.e., neuralgia amyotrophy of the diaphragm); in the case of muscular dystrophy, significant respiratory muscle weakness may occur only late in the disease course. Severe, relentless, progressive dysfunction of the respiratory muscles may occur, as in amyotrophic lateral sclerosis, or be characterized by exacerbations and relapses (e.g., multiple sclerosis). Finally, respiratory muscle weakness may completely reverse with time (phrenic nerve injury after open-heart surgery) or with therapy (plasmapheresis in myasthenia gravis).

A significant proportion of patients with severe respiratory muscle weakness were also found in 50% of 30 asymptomatic patients with stable chronic neuromuscular disease. Reductions in inspiratory and expiratory mouth pressures did not correlate with general muscle strength assessment; however, the type of neuromuscular disease and distribution of general muscle weakness both correlated with respiratory muscle impairment.[5] Patients with myopathy, rather than polyneuropathy, whose involvement produced proximal rather than distal limb muscle weakness, were more likely to have significant respiratory muscle weakness. Pulmonary symptoms correlated poorly with evidence of respiratory muscle weakness.

Explanations for the lack of pulmonary complaints in these two studies, despite significant muscle weakness, are not clear. Patients with chronic and severe neuromuscular disease are usually sedentary and incapable of exertion and, therefore, seldom stress the respiratory system—which may explain their lack of symptoms.

The rapid, shallow breathing pattern found in patients with respiratory muscle weakness may be due to decreased respiratory muscle force generation, but it may also be due to changes in lung and chest wall elastic recoil. A decrease in inspiratory muscle tone may lead to unopposed lung elastic recoil, which reduces lung volume and produces chronic changes in chest wall tone and distensibility. Once inspiratory muscle strength decreases to approximately 30% of normal, abnormalities in gas exchange (manifested primarily by hypercapnia) commonly occur.

Expiratory muscle weakness is also commonly observed in patients with neuromuscular disease. It causes ineffectual cough and impaired secretion clearance, which in some patients leads to recurrent lower respiratory tract infections. In normal persons, dynamic compression of the central intrathoracic airways by large changes in pleural pressure generated by forceful contraction of the expiratory muscles acts to propel secretions proximally, where they can be expectorated. As expiratory muscle weakness progresses, pleural pressures generated during coughing efforts are reduced and airway clearance is impaired.

■ Lung and Chest Wall Mechanics

A characteristic hallmark of chronic neuromuscular disease is a decreased vital capacity (VC). The VC is reduced because of respiratory muscle weakness, and the decrease in VC parallels the progression of the underlying disease, but the magnitude of the reduction in VC is greater than expected solely based on the reduction in respiratory muscle force. The sigmoidal shape of the pressure–volume curve would suggest that large reductions in pressure initially produce only small reductions in lung volume. In 25 patients with a variety of neuromuscular diseases, De Troyer found that reductions in VC were much greater than expected, solely based on the reductions in inspiratory muscle strength[6] **(Fig. 84-1)**.

It appears that in addition to muscle weakness, alterations in the mechanical properties of the lung and chest wall contribute to the reduced VC. Using the mean deflationary pressure–volume curve of the lung in 25 patients with moderate to severe neuromuscular disease, De Troyer et al. found, on average, a 40% decrease in lung compliance[6] **(Fig. 84-2)**. Furthermore, measurements of static lung compliance measured during inspiration in patients with neuromuscular diseases also show marked reductions, suggesting that chronic respiratory muscle weakness changes the elastic properties of the lung itself.[7]

The cause of reduced lung distensibility in patients with neuromuscular disease is unknown. Several causes—such as failed maturation

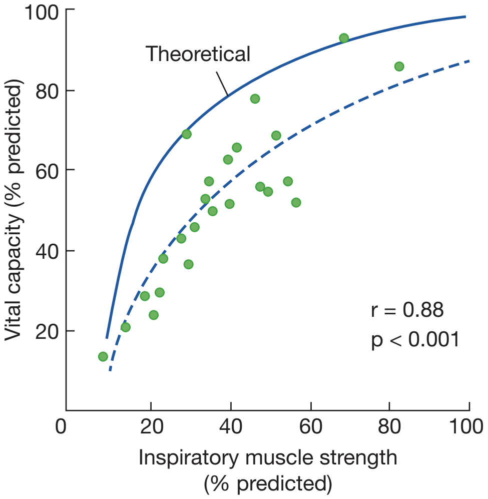

Figure 84-1 The *solid curve* represents the theoretic effect of respiratory muscle weakness on vital capacity (VC) on the assumption that the relaxation pressure–volume characteristic of the lung and chest wall are normal and that the inspiratory and expiratory muscles are uniformly involved. *Dashed curve* is the logarithmic regression calculated in 25 patients with neuromuscular disease *(closed circles)*. Data suggest that loss of lung volume is out of proportion to the degree of inspiratory muscle weakness. *(Data from De Troyer A, Borenstein S, Cordier R. Analysis of lung volume restriction in patients with respiratory muscle weakness. Thorax. 1980;35(8):603–610.)*

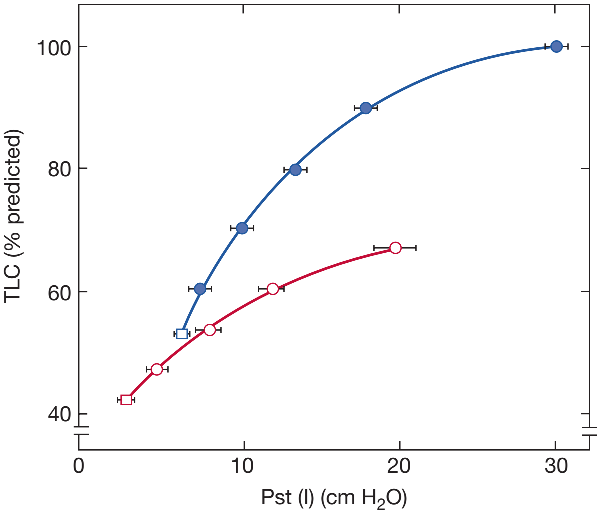

Figure 84-2 Static expiratory pressure–volume curve in patients with neuromuscular disease and respiratory muscle weakness. *Open circles* represent average data in 25 patients. Volume is displayed on the Y-axis as a percentage of predicted total lung capacity (TLC). *Closed circles* represent mean predicted values. In patients, absolute lung volume was decreased for any given transpulmonary pressure. *(Data from De Troyer A, Borenstein S, Cordier R. Analysis of lung volume restriction in patients with respiratory muscle weakness. Thorax. 1980;35(8):603–610.)*

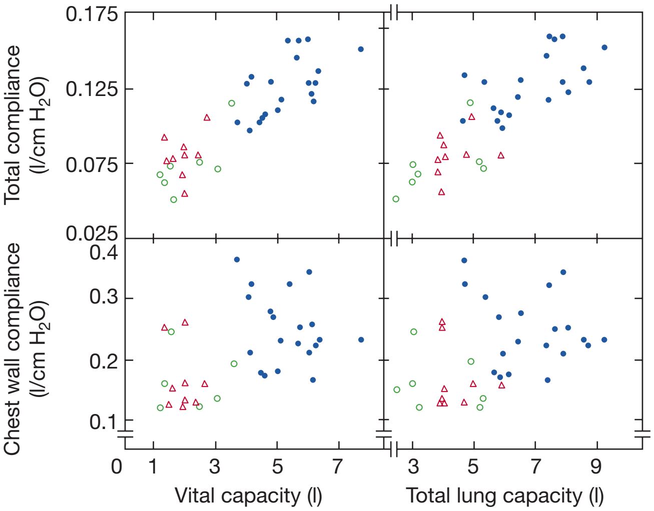

Figure 84-3 Relationships between total respiratory system compliance and VC and TLC (upper panels) and between chest wall compliance and VC and TLC (lower panels) in 16 patients with chronic neuromuscular diseases *(open symbols)* compared to 20 healthy controls *(closed circles)*. *Triangles* symbolize patients who are quadriplegic, *squares* symbolize patients who are paraplegic and four patients had generalized neuromuscular diseases *(circles)*. Compared to healthy controls *(closed circles)*, those with neuromuscular disease had significant reductions in both total respiratory system and chest wall compliance. *(Data from Estenne M, Heilporn A, Delhez L, ety al. Chest wall stiffness in patients with chronic respiratory muscle weakness. Am Rev Respir Dis. 1983;128(6):1002–1007.)*

of normal lung tissue during childhood or congenital neuromuscular diseases, the presence of micro- or macroatelectasis, increased alveolar surface tension caused by breathing chronically at low tidal volumes, and alteration in lung tissue elasticity—have been proposed.

Impaired lung maturation is unlikely, since patients who develop neuromuscular disease in adulthood also have a reduction in VC that is disproportionate to the magnitude of respiratory muscle weakness. The presence of micro- and macroatelectasis also appears untenable because most patients who have significant reductions in VC typically do not have alveolar collapse on radiographic imaging. Although rapid and shallow breathing patterns are encountered in patients with chronic severe neuromuscular disease, mechanical hyperinflation of the lung does not restore lung distensibility. Therefore, increased alveolar surface tension is not considered the principal cause of reduced lung compliance in patients with chronic neuromuscular disease.

Theoretically, a reduction in lung tissue elasticity may also contribute to a reduction in lung compliance in patients with neuromuscular disease, but there is no evidence that lung collagen, elastin, and other matrix proteins change in these diseases. Currently, the reason for the reduction in lung compliance in patients with chronic neuromuscular disease is unknown and awaits further study.

Many studies indicate that chest wall compliance is decreased by approximately 30% in patients with chronic neuromuscular disorder. In 16 patients with chronic neuromuscular diseases (e.g., spinal cord injury, Duchenne muscular dystrophy, myasthenia gravis), the weighted spirometer technique was used to examine chest wall compliance in comparison with that of 20 healthy control subjects. The weighted spirometer technique delivers an airway pressure that causes an increment in thoracic volumes so as to construct the pressure–volume relationship. In 12 of these patients, chest wall compliance was reduced[8] (Fig. 84-3). Based on the contour of the pressure–volume curve of the normal relaxed chest wall at lower lung volumes, a reduction in functional residual capacity (FRC), as seen in patients with chronic neuromuscular diseases, may, in itself, reduce static chest wall compliance. However, in other disorders in which FRC is decreased owing to parenchymal lung disease (e.g., pulmonary fibrosis), a reduction in chest wall compliance has not been demonstrated. The mechanism for the reduction in chest wall compliance in patients with chronic neuromuscular disease has not been definitely established, but limitations in respiratory excursions have been proposed to lead to increased rib cage stiffness by decreasing the viscoelasticity of chest wall structures. Regardless of the mechanism, it appears that a reduction in chest wall compliance, along with a decrease in lung compliance, contributes to the marked decrease in VC observation in patients with neuromuscular disease.

Although reductions in VC appear to be clearly established in patients with chronic neuromuscular disease, the effects of chronic neuromuscular disease on FRC and residual volume (RV) are contradictory. FRC and RV have been reported to be unchanged, decreased, or mildly increased. Discrepancies between these studies could be explained by differences in the type of severity, and stages of neuromuscular diseases studied or body positions in which testing were performed. However, in two separate studies, patients with a wide variety of chronic neuromuscular diseases, all studied in a similar seated position, were found to have approximately 20% reductions in FRC but normally predicted values of RV.[9,10] Furthermore, confirmation of these findings was demonstrated in eight patients with myasthenia gravis given pyridostigmine, which acutely decreased FRC by approximately 15% without any significant change of RV.[11] On the basis of the above data, it appears that patients with chronic neuromuscular disease have moderate reductions in VC and total lung capacity (TLC) that are associated with a moderate decrease in FRC and a normal RV. The decrease in VC not only is due to respiratory muscle weakness but also appears to result from decreased lung and chest wall compliance. Table 84-2 summarizes the effect of neuromuscular diseases on both lung volumes and central respiratory drive.

■ Sleep-Related Breathing Disturbances

Breathing during sleep is often abnormal in patients with neuromuscular disease. Impaired sleep quality and hypopnea and hypercapnia

TABLE 84-2 Characteristic Changes in Respiratory Mechanics in Patients with Neuromuscular Disease

Central drive	Rapid shallow breathing pattern
	Decreased ventilatory response to hypoxic or hypercapnic challenge
	Normal or increased $P_{0.1}$ to hypoxic or hypercapnic challenge
Lung volumes	Decreased vital capacity (VC)
	Decreased inspiratory capacity (IC)
	Decreased functional residual capacity (FRC)
	Decreased expiratory reserve volume (ERV)
	Maintained residual volume (RV)

related to rapid eye movement (REM) sleep are frequent. Patients with chronic neuromuscular disease of various causes have significant and numerous episodes of nocturnal desaturation, which are most prevalent during REM sleep and are characterized by hypoventilation rather than upper-airway obstruction[12] (Fig. 84-4). Of six patients, 16 to 22 years of age, with advanced Duchenne muscular dystrophy, randomized to breathing either air or oxygen on two consecutive nights, five demonstrated significant oxygen desaturation during REM sleep and approximately 35% reductions in minute ventilation compared with their baseline awake values. Furthermore, the severity of diaphragmatic dysfunction was related to the degree of oxygen desaturation.[13]

Several hypotheses have been proposed to explain nocturnal desaturation. Patients with chronic neuromuscular diseases develop an even more rapid and shallow breathing pattern during REM sleep. A rapid and shallow breathing pattern leads to increased dead-space ventilation, which promotes hypercapnia and worsened oxygenation. Reductions in ventilatory drive may be accentuated during sleep in patients with underlying neuromuscular disease—especially in those who have preexisting abnormalities of ventilatory control, which may further contribute to worsened nocturnal hypoventilation.

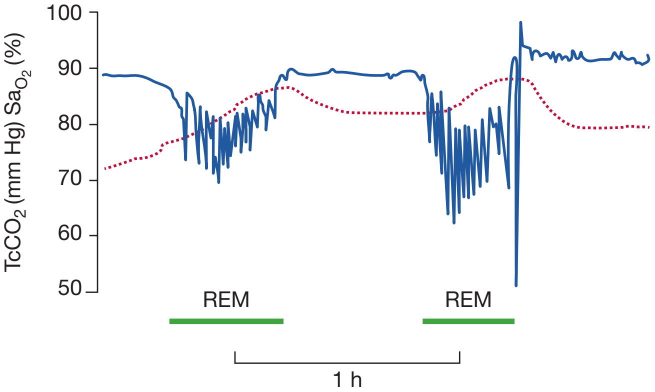

Figure 84-4 Oxygen desaturation and hypercapnia in REM sleep shown from a recording of an all-night sleep study. Transcutaneous carbon dioxide ($TcCO_2$) is shown as the *dashed line*; arterial hemoglobin oxygen saturation (Sa_{O_2}) is shown in the line with sharp deflections. Patients with neuromuscular diseases are often at risk for hypoventilation during REM sleep resulting in a decrease in Sa_{O_2} and increase in TcO_2. *(Data from Bye PT, Ellis ER, Issa FG, et al. Respiratory failure and sleep in neuromuscular disease. Thorax. 1990;45(4):241–247.)*

It has been hypothesized that patients with neuromuscular disease, especially with diaphragmatic dysfunction, may be more prone to nocturnal desaturation during REM sleep. Intercostal muscle and accessory respiratory muscle activity during REM sleep are depressed, with a greater contribution of the diaphragm required for maintenance of eucapnia and oxygenation. Support for this hypothesis comes from studies that have found diaphragm dysfunction to be highly correlated with the presence and magnitude of REM-related oxygen desaturation. A direct relation has been found between the lowest SaO_2 value measured during REM sleep and the percentage fall in VC measured between the erect and supine positions, using the latter measurements as an index of diaphragm weakness. Similarly, among patients who have paradoxical abdominal movement, signifying a decrease in diaphragmatic contribution to ventilation, a greater oxygen desaturation in both REM and non-REM sleep is observed.[14] In contrast, patients with isolated diaphragmatic dysfunction with intact accessory muscle function are not predisposed to severe nocturnal hypoventilation.[15] Accordingly, severe hypoventilation may become evident only when diaphragmatic weakness is found in the background of global accessory and intercostal muscle weakness, or when ventilatory reserve is severely reduced for other reasons, such as asthma or chronic obstructive pulmonary disease (COPD).

Abnormalities in nocturnal gas exchange are harbingers of problems in daytime gas exchange. Hypoventilation during sleep precedes the appearance of daytime hypercapnia, and patients with the most impaired gas exchange during REM sleep have the greatest degree of daytime hypercapnia. Moreover, patients with normal nocturnal gas exchange are unlikely to have abnormal daytime values. Noninvasive (e.g., nasal positive-pressure ventilation, external negative-pressure ventilation) or invasive (e.g., positive-pressure ventilation by tracheostomy) mechanical ventilation improves nocturnal gas exchange and sleep quality, with simultaneous improvement in daytime gas exchange.

Two theories have been proposed to explain the sustained improvements in gas exchange during daytime spontaneous breathing in patients with chronic neuromuscular disease who receive nocturnal ventilatory support. One theory states that nocturnal ventilation rests chronically fatigued respiratory muscles, thereby permitting improved spontaneous ventilation and gas exchange. Although several studies have demonstrated that noninvasive ventilation provides inspiratory muscle fatigue in patients with neuromuscular disease, or that mechanical ventilation consistently increases respiratory muscle strength, evidence that inspiratory muscle fatigue is commonly present in patients with neuromuscular disease or that mechanical ventilation consistently increases respiratory muscle strength is lacking. An alternative hypothesis suggests that nocturnal ventilatory support lowers the central respiratory center CO_2 set point and, thereby, sets the central controller to maintain a lower spontaneous daytime CO_2 level. This hypothesis is supported by studies showing that after several weeks of chronic nocturnal ventilation, hypoventilation was less severe in nocturnal studies without ventilation than it had been on baseline nights before chronic intermittent ventilation. Moreover, interruption of successful nocturnal noninvasive ventilation in patients with neuromuscular disease and chronic respiratory failure results in a return of nocturnal hypoventilation and symptoms of impaired gas exchange without evidence of respiratory muscle dysfunction. To date, neither of the above theories has been established conclusively, and further investigation is warranted, as one or the other, or both, may be valid in different patients.

ASSESSMENT OF RESPIRATORY FUNCTION

Patients with significant respiratory muscle impairment may range from being totally asymptomatic to having moderate dyspnea at rest

TABLE 84-3 Innervation of the Respiratory Muscles

Muscle Group	Innervation	
	Level	Nerve
Upper airway		
Palate, pharynx	IX, X, XI	Glossopharyngeal, vagus, spinal accessory
Genioglossus	XII	Hypoglossal
Inspiratory		
Diaphragm	C3–C5	Phrenic
Scalenes	C4–C8	
Parasternal intercostals	T1–T7	Intercostal
Sternocleidomastoid	X1, C1, C2	Spinal accessory
Lateral external intercostals	T1–T12	Intercostal
Expiratory		
Abdominal	T7–L1	Lumbar
Internal intercostals	T1–T12	Intercostal

or, in some cases, overt respiratory failure. Some patients with neuromuscular disease may have significant weakness of the respiratory muscles and be asymptomatic,[16] whereas others may present with ventilatory failure without an established history of a neuromuscular disease. In the latter patients, the diagnosis of neuromuscular disease may initially be entertained only after difficulty is encountered in weaning the patient from mechanical ventilation. A detailed history and physical examination, coupled with appropriate diagnostic tests, enable the physician to diagnose the presence and type of neuromuscular disease and its effect on the respiratory system. The following section reviews features of the history and physical exam and the diagnostic studies considered useful in the assessment of respiratory function in patients with neuromuscular disease.

In order to provide an organized approach to direct the clinical history-taking and physical examination of patients with neuromuscular disease, Table 84-1 characterizes the types of neuromuscular diseases that present at different levels of the neuromuscular system, and Table 84-3 describes the innervation of the different groups of respiratory muscles.

Clinical History

The signs and symptoms of respiratory muscle weakness due to a neuromuscular disease are usually nonspecific and of limited value. Moreover, the clinical manifestations of respiratory muscle dysfunction depend on the specific muscle or muscles affected and the extent of their impairment. In conditions of mild weakness, or in the early stages of neuromuscular disease, the patient may be totally asymptomatic.[16] As respiratory muscle weakness progresses, however, dyspnea on exertion, followed by dyspnea at rest, occurs. Disturbances in sleep and daytime hypersomnolence resulting from nocturnal hypoventilation may occur, and if the expiratory muscles are affected, patients may have impaired cough and repeated lower respiratory tract infections. As respiratory muscle weakness becomes more severe, hypercapnia or hypoxemia becomes evident and respiratory failure may ensue, requiring ventilatory support.

The clinical history is invaluable in that it may be the first clue that a neuromuscular disease is the cause of the patient's pulmonary dysfunction. A history is also useful in characterizing the type of neuromuscular disease that is present. Dyspnea, and impaired cough with or without recurrent lower respiratory tract infections, may be the first clinical clues that a neuromuscular disease is present. Impaired swallowing due to bulbar symptoms and the presence of peripheral limb muscle weakness are indications that one is dealing with generalized neuromuscular disease.

Physical Examination

Although the physical exam may yield normal results in patients with early or mild impairment of the respiratory system, patients with more established disease often demonstrate tachypnea at rest. Further clinical information on the nature of the underlying disease and the extent of underlying muscle impairment can be gleaned from the pattern of respiratory muscle contraction in both seated and supine positions. Respiratory rate should be recorded along with any evidence of nasal flaring, intercostal muscle retraction, or palpable evidence of contraction of the sternocleidomastoid and scalene muscles. Furthermore, inward paradoxical motion of the rib cage or abdomen should be sought, as its presence may indicate a respiratory workload that is greater than the patient's respiratory muscle strength, or evidence of severe weakness of the diaphragm as a result of the underlying neuromuscular disease. Besides gross paradoxical movement of the rib cage or abdominal compartments, asynchronous compartmental movements (e.g., one compartment moving faster than the other) may be early evidence of impaired respiratory pump performance.

The hallmark finding of severe diaphragm weakness or paralysis is paradoxical inward movement of the abdomen with inspiration. In the presence of severe diaphragm weakness, the upper abdomen moves inward when the upper rib cage moves outward—in stark contrast to the normal pattern of synchronized outward movements of the rib cage and abdominal compartments. Besides paradoxical movement of the upper abdomen, a marked increase in respiratory rate, accompanied by progressive accessory muscle use, and increased dyspnea occur when patients assume the recumbent position due to hypoxemia, hypercapnia, and placing the accessory inspiratory muscles at mechanical disadvantage. Upon reassuming the upright posture, patients may have palpable phasic contractions of the abdominal expiratory muscles. Physiologically, this inward movement of the abdomen on expiration enables passive outward movement of the upper abdomen and diaphragm descent during expiratory muscle relaxation in early inspiration.

Besides a detailed examination of the respiratory musculature and breathing pattern, the physical exam should include a complete neuromuscular examination to exclude systemic involvement. Inspection for atrophy or fasciculations of respiratory and nonrespiratory muscles may point to a lower motor neuron disease. The presence of scoliosis may contribute to the development of restrictive ventilatory pattern.

Radiographic Assessment

In patients with severe inspiratory muscle weakness or bilateral diaphragm paralysis, maximum inspiration is limited, and lung volume appears reduced on chest radiograph. Unilateral hemidiaphragm paralysis produces an elevated hemidiaphragm on the affected side.[17]

Fluoroscopy is often used in the assessment of diaphragm paralysis with the patient making a forceful sniff in the supine position.[17] In unilateral diaphragm paralysis, a positive "sniff" test may demonstrate paradoxical upward movement of the affected hemidiaphragm. However, "sniff" tests have a false-positive rate as high as 6% in normal persons. The use of the "sniff" test to diagnose bilateral diaphragm paralysis is limited by compensatory abdominal muscle contraction. With abrupt cessation of abdominal muscle contraction during early inspiration, the abdominal contents descend caudally. The abdominal wall moves outward, and the diaphragm will then appear to descend caudally, at least radiographically. Besides the fact that passive diaphragm descent due to active abdominal muscle contraction is a limitation during fluoroscopy, the fluoroscopic observational field used to examine the diaphragm is limited because of the small visual band that encompasses only the diaphragmatic dome and adjacent ribs. If rib cage rostral movement exceeds diaphragm ascent, the diaphragm will appear to descend lower than the thorax and may falsely suggest the presence of diaphragm shortening.[18]

Although the diaphragm itself is poorly echogenic, ultrasound can be used to assess its function because the parietal pleura and peritoneal membranes lining the diaphragm are brightly echogenic. The two approaches used are the visualization of the dome or measurement of the muscle thickness at the zone of apposition.[2] Craniocaudal movement of the dome of the diaphragm can be measured by placing an ultrasound probe on the upper abdomen or on the lateral chest. This technique has compared favorably with the traditional fluoroscopic procedures used to assess diaphragm movement. Because the costal portion of the diaphragm is close to the skin, the zone of apposition is an ideal area to use ultrasound for assessment of the diaphragm thickness and estimation of length. The thickness of the diaphragm increases with increasing lung volumes and is inversely proportional to its length. Measurement of the zone of apposition will permit the detection of diaphragm contraction during inspiratory efforts when trying to diagnose diaphragm paralysis. As the subject with diaphragm paralysis makes an inspiratory effort there will not be thickening of the diaphragm at the zone of apposition. Measurement of the thickness also allows for the assessment of atrophy or the effect of neuromuscular diseases.

■ Arterial Blood Gas Analysis

Arterial blood gas abnormalities usually occur only in patients with severe respiratory muscle weakness. Hypoxemia is usually mild and may occur as a result of macroatelectasis and subsequent intrapulmonary shunting or ventilation–perfusion mismatch. In addition, patients with impaired muscle strength have impaired cough and may retain secretions that further contribute to the development of hypoxemia. Measurement of arterial oxyhemoglobin saturation by pulse oximetry, which has become an extremely common laboratory test for oxygenation, is an insensitive indicator of hypoventilation. In patients with mild to moderate respiratory muscle weakness, the value of solely measuring the level of oxygenation is limited and may be misleading.

Hypercarbia is an insensitive measure of respiratory muscle strength. The Pa_{CO_2} does not increase until respiratory muscle strength (measured by maximum inspiratory and expiratory mouth pressures) is less than 50% of predicted. In patients with severe respiratory muscle weakness, however, an elevation in Pa_{CO_2} may be evident. Serum bicarbonate and arterial pH values may help determine whether an acute or chronic respiratory acidosis is present. Because daytime hypercapnia is usually followed by nocturnal hypoventilation, the presence of daytime hypercapnia should prompt investigation of the breathing pattern and gas exchange during sleep, so that appropriate therapy (e.g., nocturnal supplemental oxygen or noninvasive ventilation) can be implemented.

■ Respiratory Muscle Strength

A variety of tests can be used to assess respiratory muscle strength. Each is discussed below.

Maximum Mouth Pressures

Maximum static inspiratory and expiratory mouth pressures, measured at the airway opening during a voluntary contraction against an occluded airway, are the simplest and most commonly performed tests of respiratory muscle strength. Although several methods exist, the technique of Black and Hyatt is still the most widely used.[19] In this technique, mouth pressures are measured using a handheld manometer with the patient seated upright with a nose clip on. During these maneuvers, the patient purses the lips inside a circular wide-bore rubber mouthpiece, which prevents perioral air leakage. This small orifice (2 mm in diameter, 15 mm in length) is placed in the circuit to minimize the contribution of the facial muscles to airway pressure and to keep the glottis open. Maximum inspiratory pressures (PI_{max}) are measured near residual volume after maximal expiration, while maximal expiratory pressures (PE_{max}) are measured at or near total lung capacity. In each case, efforts are maintained for at least 1 s. Maximum inspiratory and expiratory mouth pressures in normal males and females are listed in Table 84-4. Reported values in normal subjects vary widely and may be due to differences in techniques between different studies or a learning effect in subjects who perform these maneuvers.[20–25]

TABLE 84-4 Reported Values for Maximum Static Airway Pressures in Normal Adults

Study	Sex	No. of Subjects	Age Range (Years)	PI_{max} (cm H_2O)	PE_{max} (cm H_2O)
Black and Hyatt[20]	Males	60	20–54	124 ± 22	233 ± 42
	Females	60	20–54	87 ± 16	152 ± 27
Ringqvist[25]	Males	100	18–83	130 ± 32	237 ± 46
	Females	100	18–83	98 ± 25	165 ± 30
Leech et al.[22]	Males	325	17–35	114 ± 36	154 ± 82
	Females	480	15–35	71 ± 27	94 ± 33
Rochester Arora[21]	Males	80	19–49	127 ± 28	216 ± 41
	Females	121	19–49	91 ± 25	138 ± 39
Vincken et al.[24]	Males	46	16–79	105 ± 25	140 ± 38
	Females	60	16–79	71 ± 23	89 ± 24
Wilson et al.[23]	Males	48	19–65	106 ± 31	148 ± 34
	Females	87	18–65	73 ± 22	93 ± 17

Values are mean ± standard deviation.

A major factor affecting PI_{max} is lung volume. PI_{max} is greatest at residual volume, whereby the inspiratory muscles are at greatest mechanical advantage and the outward elastic recoil of the respiratory system is maximum. On the other hand, measurement of PE_{max} is greatest at total lung capacity because expiratory muscles are at greatest mechanical advantage and inward elastic recoil of the respiratory system is greatest (Fig. 84-5). Only at functional residual capacity, where the respiratory system recoil pressures measured at the airway opening are zero, are maximum inspiratory and expiratory mouth pressures solely a function of the pressure generated by actively contracting respiratory muscles (P_{mus}).

Changes in lung volume due to chest wall or lung pathology may have important effects on the generation of maximum respiratory pressures in patients. For example, patients with COPD and significant hyperinflation have a larger FRC and residual volume than normal subjects; therefore, PI_{max} performed at FRC or RV usually results in lower values than in age- and sex-matched normal subjects. Likewise, a reduction in total lung capacity due to restrictive ventilatory diseases may result in a reduction in measured values for PE_{max}. Therefore, it is important to realize that in patients with pathologically altered lung volumes, all or part of the reduction in mouth pressures may be due to inspiratory muscle mechanical disadvantage.

Maximum inspiratory and expiratory mouth pressures in patients with neuromuscular diseases range from normal to severely reduced. Patients may have significant respiratory muscle weakness without

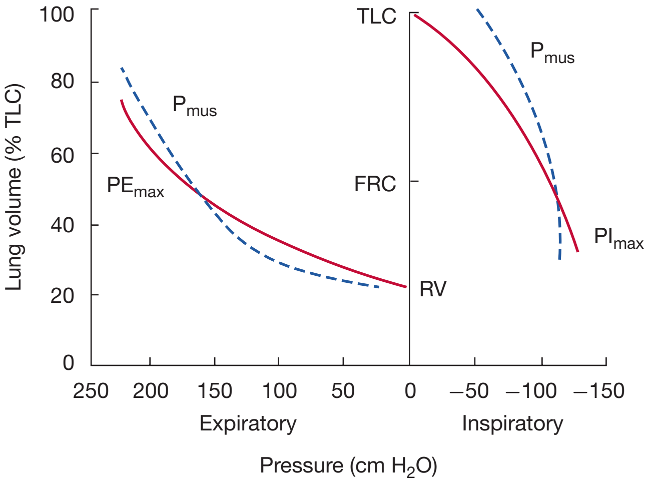

Figure 84-5 The effect of lung volume on maximum respiratory pressures (PI_{max} and PE_{max}) measured at the airway opening displayed by *solid lines*. Both PI_{max} and PE_{max} are made up of two components: the pressure generated by the respiratory muscles (P_{mus}, *dashed lines*) and the recoil pressure of the respiratory system. Only at FRC when recoil pressures are zero are PE_{max} and PI_{max} solely due to P_{mus}.

any pulmonary complaints, and no correlation exists between respiratory muscle strength and the presence of generalized nonrespiratory muscle weakness.[16] When PI_{max} falls below 30 cm H_2O, ventilatory failure commonly ensues.

The assessment of a patient's ability to generate an effective cough is extremely important when managing the pulmonary effects of neuromuscular diseases. Nearly all these disorders result in weak cough, which puts the individual at risk for aspiration and pneumonia. While a normal PE_{max} ensures that the patient has adequate cough, a low PE_{max} could result from poor effort, bulbar weakness not allowing a tight seal around the mouthpiece, or true expiratory muscle weakness. Therefore, there is interest in developing a test that will allow the assessment of cough strength in a nonvolitional manner. Measurement of positive pleural pressures with an esophageal balloon during a forceful cough ($P_{es\ cough}$) has also been proposed as a measure of expiratory muscle strength. $P_{es\ cough}$ has been shown to decrease in parallel with PE_{max} when expiratory muscle weakness is induced by progressive curarization. A study examined the use of measurement of gastric pressures during cough ($P_{ga\ cough}$) in a group of normal subjects and in those with suspected respiratory muscle weakness from pulmonary and neuromuscular disease. The measurement of $P_{ga\ cough}$ is theoretically better because it takes into account the abdominal musculature, it eliminates the problem of leak around the mouthpiece, and a cough maneuver is easier to perform than the PE_{max} maneuver. In 122 patients with a normal PE_{max}, more than 95% also had a normal $P_{ga\ cough}$, but in 171 patients with a low PE_{max} 72 had a normal $P_{ga\ cough}$ suggesting a high false positive rate of a low PE_{max}. Conversely, in 105 patients with a low $P_{ga\ cough}$ only 6 had a normal PE_{max} suggesting a low false-positive rate for a low $P_{ga\ cough}$.[26]

Transdiaphragmatic Pressure Measurement

While maximum static airway pressures are useful measures of global respiratory muscle strength, they fail to assess individual respiratory muscle function. Since the diaphragm is the primary muscle of inspiration, and may be susceptible to isolated disease (e.g., phrenic nerve paralysis after open-heart surgery or idiopathic diaphragm paralysis), specific testing of diaphragm strength is desirable in some patients. Assessment of diaphragm strength is made by measuring gastric (P_{ga}) and endoesophageal (P_{es}) pressures with balloon-tipped catheters placed in the stomach and midesophagus, respectively. Transdiaphragmatic pressure (P_{di}) is then calculated as the algebraic subtraction of P_{es} from P_{ga} ($P_{di} = P_{ga} - P_{es}$).[2]

Maneuvers to elicit maximum transdiaphragmatic pressures (Pdi_{max}) have been the subject of intensive study. Earlier studies measured Pdi during maximum static inspiratory efforts against a closed airway (e.g., the Mueller maneuver) at FRC or RV. However, this maneuver results in submaximal diaphragm activation, with the degree of activation varying widely from subject to subject. Several studies have demonstrated significant intraindividual variability, with a coefficient of variation as high as 40% in measurement of Pdi_{max} during the Mueller maneuver. When five maneuvers to measure Pdi_{max} in 35 subjects (10 normal, 13 with restrictive lung disease, and 12 with COPD) were compared, a combined maneuver of active expulsion with superimposed Mueller maneuver yielded the most reproducible and maximal transdiaphragmatic pressure.[27]

Phrenic Nerve Stimulation

A crucial factor in the measurement of diaphragm strength is the ability to consistently obtain maximal activation of the diaphragm during volitional efforts. Electrophrenic stimulation is a method that has been utilized to consistently activate the diaphragm. Besides assessing diaphragm strength, this technique has the added advantage of assessing phrenic nerve conduction and excluding the possibility of phrenic nerve injury in patients with diaphragm weakness of unknown origin.[2]

The phrenic nerve is stimulated in the neck near the posterior border of the sternocleidomastoid muscle, at the level of the cricoid cartilage, where the phrenic nerves are most superficial. Stimulation may be performed either transcutaneously with surface electrodes (electrical stimulation electrodes) or magnetic coil, or percutaneously with needle or wire electrodes. The percutaneous method is rarely used now. Stimulation of the phrenic nerves must be supramaximal with regard to voltage and current. Supramaximal conditions are ensured by increasing the stimulus intensity until maximum diaphragm muscle action potential (DMAP) or P_{di} is achieved. The DMAP is measured by surface EMG electrodes, and the P_{di} is measured by measuring the esophageal and gastric pressures via two pressure transducers as described above. The DMAP is then checked periodically throughout the study to ensure that consistent stimulation is maintained.[2,28]

The most commonly used technique of electrophrenic stimulation now employs a frequency of one pulse per second to measure P_{di} during a single unfused twitch contraction (i.e., $P_{di,tw}$). $P_{di,tw}$ has also been used to assess maximal static P_{di} indirectly by the twitch occlusion technique.[2,29] In this method, single twitches are superimposed on progressively stronger voluntary P_{di} contractions. As voluntary effort and P_{di} increase, the increment in P_{di} produced during the twitch (the twitch deflection superimposed on the P_{di}) decreases (Fig. 84-6A). When there is no discernible $P_{di,tw}$ deflection, it is assumed that the diaphragm is maximally activated. If the $P_{di,tw}$ does not go to zero then the extrapolation of the line of this relationship to the X-axis has been interpreted as representing maximum static P_{di} (Fig. 84-6B).

An alternate way to perform phrenic nerve stimulation is via magnetic stimulation.[2,30] In this technique, an electric current is run through a coil thereby producing a magnetic field. The coil is placed over the spinous process of the seventh cervical vertebral body (cervical magnetic stimulation) stimulating the C3–C5 cervical roots of the phrenic nerve and causing the diaphragm to contract. Magnetic stimulation of this area will also stimulate contraction of neck and upper rib cage muscles as well. The advantages of this technique are that it is less painful than the electrical stimulation method, and it is easier to evoke diaphragm contractions. Also, it is possible to perform magnetic stimulation of the phrenic nerve while the patient is

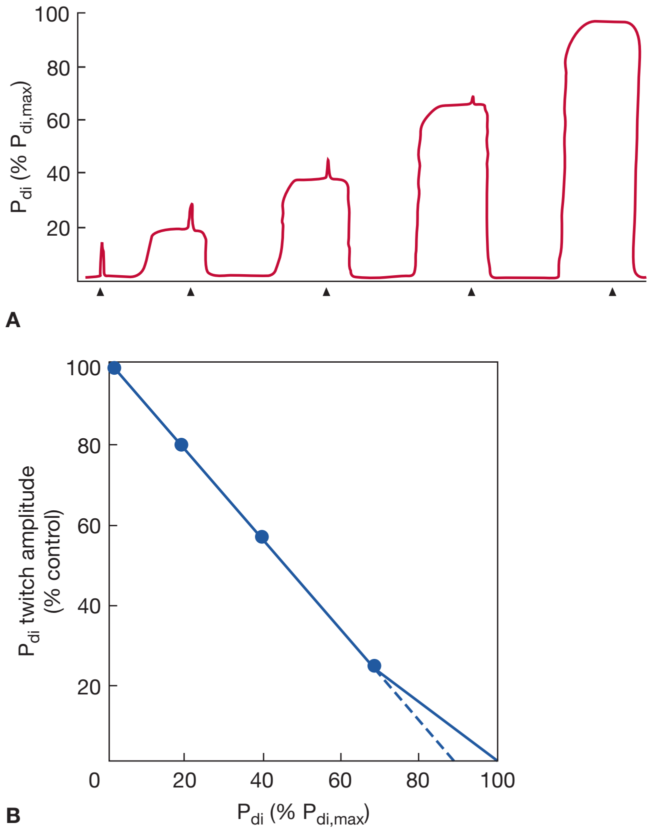

Figure 84-6 **A.** Illustration of a typical P_{di} tracing during twitch occlusion study. As the P_{di} increases during volitional efforts, the superimposed P_{di} deflection during phrenic nerve 1-Hz stimulation (twitch) decreases. At 100% of $P_{di,max}$, the diaphragm is maximally activated and no superimposed twitch is seen. *Arrows* on the horizontal axis mark indicate the phrenic nerve twitches. **B.** Data from A plotted as $P_{di,tw}$ amplitude versus voluntary P_{di}. Using linear regression, $P_{di,max}$ can be extrapolated from results obtained during submaximal efforts. It has been suggested that extrapolation performed from P_{di} values below 70% of maximum may underestimate $P_{di,max}$ by approximately 10% *(dashed line)*.

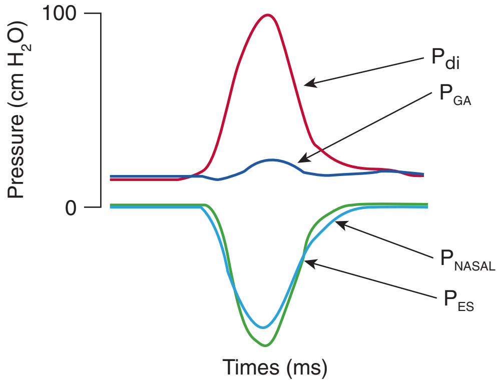

Figure 84-7 Pressure tracing produced utilizing sniff maneuver in a normal individual with gastric and esophageal balloon manometry in place. The noninvasive P_{NASAL} pressure closely mirrors that of the invasive P_{ES}. P_{GA}, gastric pressure; P_{di}, transdiaphragmatic pressure; P_{ES}, esophageal pressure; P_{NASAL}, nasal pressure during sniff maneuver.

in the supine position by placing the magnetic coil anterior to the sternum. This would allow for hospitalized bedbound patients to be evaluated for diaphragm weakness via phrenic nerve stimulation. One of the disadvantages of magnetic stimulation is that it lacks the specificity that electrophrenic stimulation has for the diaphragm, and obtaining an EMG_{di} signal can be more difficult with magnetic stimulation. When comparing magnetic stimulation $P_{di,tw}$ to electrophrenic $P_{di,tw}$, the $P_{di,tw}$ tends to be 20% to 25% higher with magnetic stimulation.

In addition to assessing diaphragm strength, phrenic nerve stimulation can be used to assess phrenic nerve function. The EMG_{di} is measured via surface or esophageal electrodes during electric or magnetic phrenic nerve stimulation, and the phrenic nerve conduction time can be measured.[2] This measurement is useful when assessing possible injury to the phrenic nerve from thoracic surgery, trauma, or neuropathies (e.g., critical illness polyneuropathy or Guillain-Barré syndrome). The normal conduction time via electrical stimulation is 7.5 to 9 ms, but the normal conduction time via magnetic stimulation has not been well defined because activation of the brachial plexus affects the phrenic nerve conduction time. However, Luo et al. demonstrated that if the magnetic coil is placed anteriorly to the cricoid cartilage, then the phrenic nerve conduction time was very similar to that obtained by electric stimulation. The authors believe that this occurred because there was more brachial plexus activation in the lower position compared with the higher position.[31]

Because of the relative invasiveness of electrophrenic stimulation of the diaphragm, and the large coefficient of variation in some studies when P_{di} was measured during maximal volitional efforts, some investigators prefer measuring maximum inspiratory pressures during a sniff maneuver (Fig. 84-7). In this technique, the subject performs a vigorous sniff against an unoccluded airway. During such an effort, the nose acts as a Starling resistor, thereby generating intrathoracic pressures against an occluded airway. Some investigators argue that this maneuver approaches a more natural respiratory effort than other types of maneuvers used to measure maximum inspiratory pressures and thus should be easily mastered by patients and more reproducibly performed by technicians.[32]

Analysis of Rib Cage and Abdominal Motion

During normal tidal breathing, the chest and abdominal compartments move synchronously in an outward direction, owing to diaphragm contraction decreasing pleural pressure and increasing abdominal pressure. In situations where the diaphragm is severely paretic or paralyzed, however, the flaccid diaphragm cannot counterbalance the negative changes in pleural pressure generated by contraction of the inspiratory muscles of the neck and rib cage. Instead of moving normally in a caudal direction the flaccid diaphragm moves paradoxically cephalad into the thorax. This change in diaphragm motion gives rise to a paradoxical inward motion of the upper abdomen indicative of severe diaphragm weakness or paralysis.

Changes in rib cage and abdominal pressure, or volume displacement during respiration, can provide important information about diaphragm strength. Partitioning of respiration can be examined from changes in abdominal and pleural pressures, as proposed by Macklem et al.[33] Changes in abdominal and pleural pressures during inspiration, expressed as the ratio of delta P_{ab}:delta P_{PL} are normally negative as pleural pressure becomes more negative and abdominal pressure becomes more positive. This ratio has a maximum value of +1 when the diaphragm does not contribute to inspiration and is valid only if the expiratory muscles do not contribute significantly to the pressures being generated. Alternatively, the partitioning of ventilation can be noninvasively measured by compartmental changes in rib cage and abdominal volume by respiratory inductance plethysmography or magnetometry. Optoelectronic plethysmography (OEP) is a technique that allows for measurement of chest wall and abdominal motion as well as lung volumes. A series of 89 retroreflective markers are placed on the thorax and abdomen that are monitored by a series of 6 to 8 cameras (Fig. 84-8). The cameras record

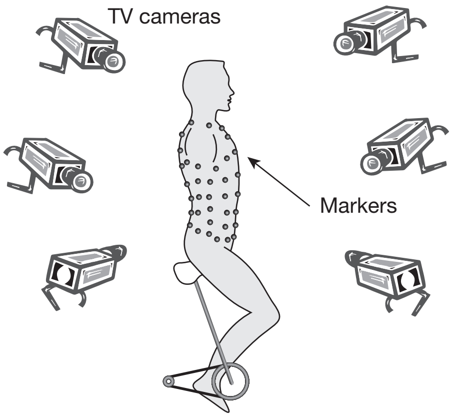

Figure 84-8 An example of optoelectronic plethysmography. A series of markers are placed on the subject's thorax and abdomen. A group of cameras record the distance the markers move in all planes thus permitting calculation of lung volumes during the breathing cycle. *(Reproduced with permission from Vogiatzis I, Aliverti A, Golemati S, et al. Respiratory kinematics by optoelectronic plethysmography during exercise in men and women. Eur J Appl Physiol. 2005;93(5-6):581–587.)*

the distance the markers move in space, and using Gauss' theorem the total thoracoabdominal lung volume can be calculated. OEP can differentiate between volume generated by the rib cage (rib cage musculature) and volume generated by the abdomen (diaphragm).[34] OEP can also be used to measure flow and is a nonvolitional test that can be done in any spontaneously breathing individual without regard to the degree of muscle weakness.[34] This technique has been used in patients with Duchenne muscular dystrophy to show that with disease progression the proportion of the tidal volume attributable to the abdomen decreases while the tidal volume attributable to the rib cage increases. Furthermore, those that had this change in breathing pattern were more likely to have nocturnal desaturation.[35]

Spirometry

Respiratory muscle weakness induced by neuromuscular disease produces a restrictive pattern on spirometric testing with a reduction in VC.[6] As previously mentioned, the reduced VC is commonly out of proportion to the reduction in maximal respiratory muscle force. Reductions in lung and chest wall compliance also probably contribute. Moreover, because of the contour of the pressure–volume curve, large reductions in the respiratory muscle forces have to occur before VC is significantly reduced. A decrease in VC greater than 25% on moving from the upright to supine postures has been used as a sign of diaphragmatic weakness and a greater likelihood of sleep-related hypoventilation.[14,36]

Forced expiratory volume in 1 s (FEV_1) and measurements of midexpiratory flow rates (FEF_{25-75} or FEF_{50}) are often greater than normal predicted values in patients with neuromuscular disease. Further increases in expiratory flow may occur in patients with neuromuscular disease due to increased lung recoil. Two independent studies have shown that partial curarization in normal subjects produces a decrease in peak expiratory flow with an increase in midexpiratory flow rates compared with baseline.[3,37] Moreover, in patients with myasthenia gravis in their baseline state of weakness before the administration of pyridostigmine, midexpiratory flow rates are increased over the range of vital capacity when referenced to absolute lung volume[6] (Fig. 84-9).

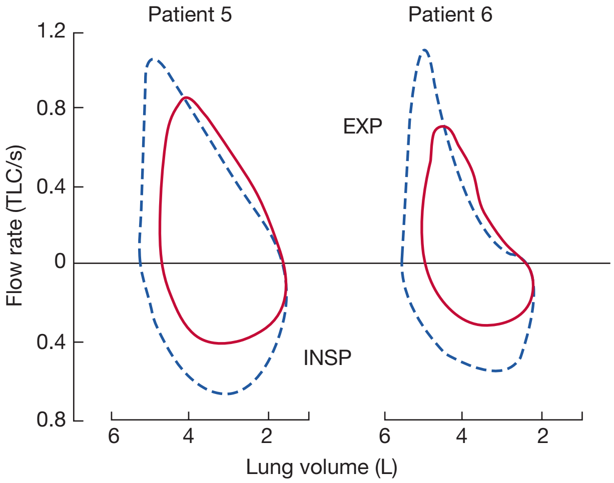

Figure 84-9 Two representative patients with myasthenia gravis and respiratory muscle weakness illustrating the effect of anticholinesterase therapy on maximum flow–volume curves. *Solid curves* represent pretreatment data; *dashed curves* were obtained following the injection of pyridostigmine. Prior to administration of pyridostigmine the midexpiratory flow rates were greater even though respiratory muscles were weaker and lung volumes were lower. *(Reproduced with permission from DeTroyer A, Borenstien S. Acute changes in respiratory mechanics after pyridostigmine injection in patients with myasthenia gravis. Am Rev Respir Dis. 1980;121(4):629–638.)*

Flow–Volume loops

Changes in the configuration of the flow–volume loop occur in various neuromuscular diseases.[2,38,39] These changes reflect respiratory muscle weakness or malfunction of upper-airway muscles. "Sawtoothing" of the flow contour is seen in extrapyramidal disorders affecting upper-airway muscles.[40] Similarly, plateauing of the inspiratory flow wave form indicative of extrathoracic airway obstruction has been described in vocal cord paralysis caused by extrapyramidal neuromuscular disorders. An abnormal flow–volume curve is significantly more common in patients with clinically apparent bulbar muscle involvement (90% vs. 15%, respectively), and the presence of an abnormal flow–volume loop predicted bulbar and upper muscle involvement by a neuromuscular disease with a high sensitivity and specificity.[41] A characteristic flow–volume contour showing involvement of the upper-airway muscles by motor neuron disease is shown in Fig. 84-10.

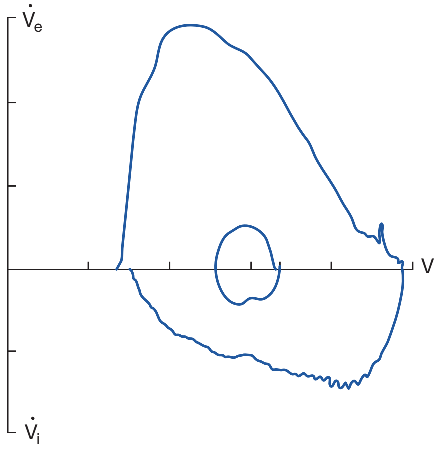

Figure 84-10 Flow–volume loop in a patient with motor neuron disease, showing inspiratory flow oscillation and inspiratory flow limitation. Subdivisions on volume and flow axis represents 1 L, flow axis 1 L/s. *(Data from Vincken W, Elleker MG, Cosio MG. Determinants of respiratory muscle weakness in stable chronic neuromuscular disorders. Am J Med. 1987;82(1):53–58.)*

Among patients with stable, chronic neuromuscular disease, the flow–volume loop is significantly more disturbed in those with respiratory muscle weakness, and these abnormalities correlate with reduced mouth pressures. Several features of flow–volume loop configuration correlate with reduced maximum static inspiratory and expiratory mouth pressures: a reduced peak expiratory flow, a decreased slope of the ascending limb of the maximum expiratory curve, a drop-off of forced expiratory flow near residual volume, and a reduction in forced inspiratory flow at 50% of vital capacity (Fig. 84-11). A flow-volume loop score composed of the above parameters has a high degree of specificity and 90% sensitivity in predicting respiratory muscle weakness.[41]

Lung Volumes

A restrictive ventilatory pattern is demonstrated in patients with neuromuscular disease. A reduced TLC and a normal or reduced FRC are common. The RV is usually elevated and is a sign of expiratory muscle weakness.

Maximum Voluntary Ventilation

Maximum voluntary ventilation (MVV) is an index of respiratory muscle endurance in the presence of normal expiratory flow rates. This appears to be appropriate in patients with neuromuscular disease, since airway resistance and FRC are usually within the normal range. Values for MVV correlate with respiratory muscle strength and may be even more sensitive than VC in detecting respiratory muscle weakness.[2]

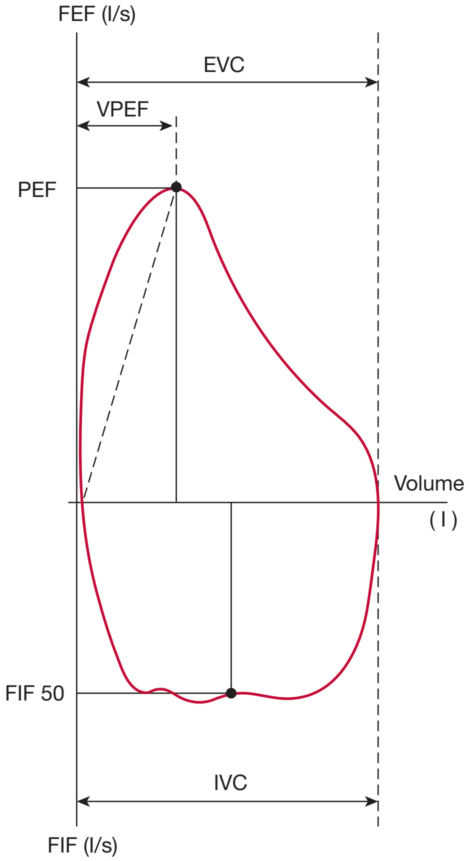

Figure 84-11 Representative flow–volume loop of a patient with chronic neuromuscular disease, showing different volume loop parameters indicative of respiratory muscle weakness. These parameters quantify the effects of respiratory muscle strength on the effort-dependent portions of the flow–volume loop. These four parameters are peak expiratory flow (PEF); ratio of PEF to the exhaled volume at which PEF was achieved, rapid vertical drop of forced expiratory flow at residual volume, and forced midinspiratory flow. *(Data from Vincken W, Elleker MG, Cosio MG. Determinants of respiratory muscle weakness in stable chronic neuromuscular disorders. Am J Med. 1987;82(1):53–58.)*

SELECTED NEUROMUSCULAR DISEASES

A helpful approach toward understanding how specific neuromuscular diseases affect the respiratory system is to localize the anatomic involvement of the respiratory system. A detailed description of the neuroanatomy of respiration is outside the scope of this chapter and is covered elsewhere in this text. In general, however, neuromuscular disorders can be broken down into disorders that involve the upper motor neuron, the lower motor neuron, or the muscle itself.

Lesions that arise in the cerebral cortex, brain stem, or spinal cord are classified as upper motor neuron lesions and are characterized by an increase in muscle tone or spasticity, the presence of an extensor plantar response, and increased reflex activity. Lesions in the lower motor neuron system demonstrate flaccidity, depressed reflexes, muscular fasciculations, and atrophy. The location and character of the patient's weakness may enable one to identify the exact site of the lesion in the lower motor neuron system (i.e., the anterior horn cell, the peripheral nerve, the neuromuscular junction, or the muscle itself).

The following describes the effect of specific neuromuscular disease on the respiratory system and makes recommendations for treatment.

■ Upper Motor Neuron Lesions

Below we consider the respiratory effects of stroke, spinal cord injury, Parkinson disease, and multiple sclerosis.

Stroke

Hemispheric ischemic strokes reduce chest wall and diaphragm movement on the side contralateral to the cerebral insult. Decreased diaphragm excursion with stroke correlates with diaphragmatic cortical representation identified by transcranial magnetic stimulation. Bilateral hemispheric strokes are also associated with Cheyne-Stokes respiration, which is progressive hyperventilation alternating with hypoventilation and ending in apnea. This breathing pattern may result from increased responsiveness to carbon dioxide as result of interruption of normal cortical inhibition. The significance of Cheyne-Stokes respiration to stroke remains unclear but it appears to be more common with bilateral than unilateral insults. Besides its effects on an alteration of breathing pattern, up to 50% of patients with strokes may have signs of pulmonary aspiration due to dysfunction of upper-airway muscles that protect the airway.

Spinal Cord Injury

The degree of respiratory impairment depends on the level and extent of the spinal cord injury. High cervical cord lesions (C1 to C3) cause paralysis of the diaphragmatic, intercostal, scalene, and abdominal muscles. Because all respiratory muscle activity is lost except for accessory and bulbar muscle function, high cervical cord injuries almost always require ventilatory assistance. In some patients, spontaneous breathing can be accomplished by glossopharyngeal breathing or diaphragmatic pacing because the phrenic nerve motor neurons (C3–C5) remain intact.

Middle cervical cord (C3–C5) lesions destroy the phrenic motor neurons and prohibit the use of phrenic nerve pacing. Patients with more caudal lesions (i.e., C4–C5 level) have an improved chance to wean from ventilator support compared to those with more cranial lesions. (Forty percent of patients with C3 lesions remain ventilator dependent.) Patients with lower cervical (C6–C8) and upper thoracic (T1–T6) cord lesions have intact diaphragm and neck accessory muscle action but have denervated intercostal and abdominal muscles. These patients usually require ventilatory support only during the period immediately after the injury and rarely require long-term ventilation. Despite this these patients still have increased mortality. In a group of spinal cord injury patients not requiring mechanical ventilation or tracheostomy followed prospectively for a median of 4.5 years, predictors of death included age, cardiac disease, diabetes, smoking history, and lower FEV_1.[42] The decline in FEV_1 and FVC in these patients is related to aging, increasing BMI, smoking, persistent wheeze, and lower MIP.[43] These data suggest that there are modifiable risk factors that can be altered to improve outcomes in those with spinal cord injuries that do not require mechanical ventilation.

In a study of C5 or lower spinal cord injured patients, inspiratory muscle strength was reduced to approximately 60% of predicted but was dependent on the level of cord injury. In this study, PI_{max} values in low cervical, midthoracic, and lower thoracic–upper lumbar lesions were 61%, 69%, and 75% of predicted, respectively, whereas PE_{max} values were 30%, 32%, and 54% of predicted, respectively. The lower PE_{max} values were explained by a paralysis of abdominal and intercostal muscles resulting in reduced cough and decreased clearance of bronchial secretions. Abdominal muscle paralysis probably accounts for an abnormally compliant abdomen in patients with lower spinal cord injury, which is in stark contrast to the 30% reduction in chest wall compliance believed due to abnormal rib cage stiffness.[8]

Patients with spinal cord injuries also have alterations in thoracoabdominal motion during tidal breathing that is further accentuated by changing from the erect to supine position. In quadriplegic patients with relatively intact diaphragm function, the distribution of respiratory muscle weakness results in paradoxical inward motion of the upper rib cage during inspiration owing to weakness of the parasternal and scalene muscles. This pattern of abnormal thoracoabdominal movement is more marked in the supine than in the upright position. Patients with high quadriplegia (above C3–C5) may be able to sustain short periods of spontaneous respiration because of inspiratory activity of the sternocleidomastoid and trapezius muscles. Phasic inspiratory electromyography (EMG) activity has been observed in the platysma, mylohyoid, and sternohyoid muscles. Analysis of ribcage motion in these patients shows increased upper rib cage diameter due to the inspiratory action of the neck accessory muscles pulling the sternum cranially and expanding the upper rib cage.

The distribution of muscle paralysis in low cervical cord spinal patients also has a profound effect on the performance of forced expiratory maneuvers. In contrast to healthy normal subjects, in whom VC is moderately decreased on assuming the supine position, in quadriplegic patients there is a paradoxical increase in VC in the supine compared to seated position without a significant increase in TLC. In 14 quadriplegic patients (C4–C7), there was a 16% increase in VC on changing from the upright to supine position and a reduction in RV (29%) and TLC (on average, 6%).[44] The mechanism believed to be responsible for the increase in VC in supine quadriplegic patients is the hydrostatic effect of abdominal contents, causing cephalad displacement and diaphragm lengthening and thereby placing the diaphragm on a more favorable portion of its length tension curve. The use of elastic binders when quadriplegics assume upright posture has been advocated to prevent the increase in abdominal compliance. Abdominal binding may have physiologic benefit by maintaining diaphragm precontraction length in a more optimum position on its length-tension curve.[45]

It was previously believed that all expiratory muscles were paralyzed in lower cervical cord injuries. However, studies of C5 to C8 quadriplegics indicate that phasic EMG activity of the clavicular portion of the pectoralis major is associated with a marked decrease in the anteroposterior diameter of the upper rib cage.[46] This portion of the pectoralis muscle receives innervation from the C5 to C6 cord level. With the arms placed at the subject's side, contraction of the caudate head of the pectoralis major causes caudal displacement of the manubrium sterni and upper rib cage. This expiratory action has been shown to decrease expiratory reserve volume (ERV) by 60% when the shoulders are held in abduction. After 6 weeks of pectoralis muscle isometric training, patients with low quadriplegia can have a marked increase in maximum pectoralis muscle isometric strength and a significant reduction in ERV.[47] Conceivably, therefore, training of this muscle could improve the effectiveness of cough in patients with low spinal cord injury.

In the months following spinal cord injury, pulmonary function typically improves. In patients with spinal injuries below the C5 level, VC is approximately 30% of predicted in the first week after injury but increases to 45% of predicted by the fifth week—and by the fifth month to approximately 60% of predicted.[48] Improvements in VC have been attributed to spasticity developing in previously flaccid intercostal and abdominal muscles thereby increasing the rigidity of the thorax and abdomen and improving diaphragm force generation.

There is a role for corticosteroid use in the acute management of spinal cord injury. Methylprednisolone given as a 30-mg/kg bolus followed by a 24-h infusion at 5.4 mg/kg/h has been shown to improve motor function at 6 weeks, 6 months, and 1 year, but only in those who received the drug within 8 h of injury.[49] A subsequent study compared methylprednisolone infusion (5.4 mg/kg/h) for 48 h to 24 h after the administration of a bolus (30 mg/kg).[50] There was no difference in functional outcome between the two infusion periods except in those where the bolus dose was given between 3 and 8 h after the injury. If the methylprednisolone was started between 3 to 8 h after the injury, then those that received the infusion for 48 h did have improved motor function at 6 weeks and 6 months. There were higher rates of pneumonia and sepsis in the 48-h infusion group, but mortality was not different.[50] No trial has shown a mortality benefit, and it should be recognized that the outcome measured was an improvement in the functional independence measure (FIM) score and not a return to normal motor function.

Parkinson Disease

Parkinson disease is due to degeneration of neurons in the substantia nigra and has a prevalence in the United States of approximately 200 cases per 100,000 people. Parkinson disease can be either primary (e.g., idiopathic) or secondary, as in postencephalitic parkinsonism associated with the influenza pandemic, or part of a more generalized disorder, such as multiple system atrophy or drug abuse with MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine).

Parkinson disease has been thought to be a purely motor disorder, but recently nonmotor findings are being associated with Parkinson disease and can predate motor symptoms.[51] These findings have led to speculation that Parkinson disease could alter respiratory control at the level of the brainstem. A study in 15 subjects with early Parkinson disease and normal respiratory flow and volumes found that 7 of 15 had an abnormal ventilatory response while 11 of 15 had an abnormal occlusion pressure response ($P_{0.1}$) to hypercapnic challenge testing, suggesting abnormal respiratory control.[52]

Respiratory abnormalities are common in Parkinson disease, with pneumonia being the most common cause of death. A substantial problem with Parkinson disease is glottic muscle dysfunction.[53] An abnormal flow–volume loop contour showing flow oscillations commonly occurs. On direct fiberoptic visualization of the upper airway, these oscillations correspond to rhythmic involuntary movements of glottic and subglottic structures. Physiologic evidence of upper-airway obstruction may be present. In addition to the presence of oscillations in flow, a rounding off of the peak of the midexpiratory flow–volume curve, a lowered peak expiratory flow rate, and a delayed appearance of peak expiratory flow have been observed in Parkinson patients. These results have been interpreted as evidence for less coordinated or less "explosive" respiratory muscle contractions.[38,40]

Patients with mild to moderate Parkinson disease are able to perform simple single respiratory efforts (e.g., measurements of lung volume and maximum static inspiratory pressures) but have difficulty performing more complex, repetitive ventilatory efforts (i.e., sustaining inspiratory resistive loads to exhaustion and performing maximum unloaded breathing efforts). Performance of repetitive respiratory tasks is associated with an increased work of breathing when compared with that of an age-matched control group. These findings are similar to derangements in task performance exhibited by peripheral skeletal muscle groups in Parkinson patients.[54]

Treatment significantly improves neurologic scores, maximum expiratory pressures, and peak inspiratory flow. A recent meta-analysis has demonstrated that levodopa improves peak expiratory flow and FVC in Parkinson disease.[55] Deep brain stimulation by stereotactically placing electrodes into the suprathalamic nucleus or the globus pallidus nucleus has been shown to be equally effective when treating medically resistant patients.[56] The electrodes produce a low-voltage high-frequency stimulation that results in inhibition of the neurons in the nucleus. Although the effect on respiratory function has not been directly studied, this procedure has been shown to improve motor function and quality of life.[57]

Multiple Sclerosis

Multiple sclerosis (MS) is a demyelinating disorder of the central nervous system, characterized clinically by remissions and relapses of clinical symptoms due to disseminating CNS lesions. MS is the most common neurologic disease afflicting young adults, with an estimated prevalence of more than 2 million affected individuals worldwide and 400,000 cases in the United States.[58] The disease is associated with fully or partially reversible episodes of neurologic disability typically lasting days to weeks (relapsing-remitting course). While 15% of patients will have a progressive course from symptom onset (primary progressive MS), most will not develop progressive symptoms for 10 to 20 years.[58] The progressive deterioration is characterized most commonly by impaired ambulation, bladder incontinence and impaired cognition. The cause of MS is unknown, although epidemiologic evidence points to genetic and environmental factors. Classic clinical symptoms include paresthesia, motor weakness, diplopia, blurred vision, dysarthria, bladder incontinence, and ataxia.

Because MS can cause focal lesions anywhere in the central nervous system, different patterns of respiratory impairment can occur. Impairment of the respiratory centers and the medulla can cause failure of automatic breathing (Ondine's curse) and apneustic or neurogenic pulmonary edema. The three most common respiratory manifestations of MS are respiratory muscle weakness, bulbar dysfunction, and abnormalities in respiratory control. Despite advances in treatment MS is associated with a decreased life expectancy. MS rarely is the sole cause of death but rather death results from complications of the disease. A recent population-based study of death certificate data on adults from British Columbia, Canada demonstrated that aspiration pneumonia (OR, 7.15; CI, 6.23–8.22) and respiratory infection (OR, 3.03; CI, 2.73–3.36) were among the most common contributors to death in patients who had MS listed on their death certificate.[59]

Acute respiratory failure rarely occurs in this disease, but it can occur because of severe demyelination of the cervical cord. Diaphragmatic paralysis resulting in respiratory insufficiency also has been reported. Even with severe disability and impaired respiratory muscle strength, patients with MS seldom complain of dyspnea. This paucity of respiratory complaints may be due to restricted motor activities and greater expiratory than inspiratory muscle dysfunction. Clinical signs that may be helpful in predicting respiratory muscle impairment are weak cough and inability to clear secretions, limited ability to count on a single exhalation, and upper extremity involvement. Advanced MS is frequently complicated by aspiration, atelectasis, and pneumonia.

In a group of 38 patients who were not bedridden or wheelchair-bound without bulbar involvement and a diagnosis of MS for 9.2 years, there was a significant decrease in the maximal inspiratory pressure (MIP) and the maximal expiratory pressure (MEP) to 77% and 60% predicted, respectively.[60] In a group of 21 ambulatory stable MS patients, the % predicted MEP was significantly reduced when compared with age-matched healthy controls (69.4% vs. 85.6%; $p = 0.03$). Furthermore, these patients had a greater change in the upright versus supine FVC compared with healthy controls (262 vs. 98 mL; $p = 0.001$).[61] Not surprisingly the MEP had an inverse correlation ($r = -0.47$; $p = 0.04$) with MS functional scores. These data suggest that even in ambulatory MS patients without respiratory symptoms, respiratory muscle weakness is present and should be monitored periodically (particularly MEP).

In 60 bedridden MS patients, pulmonary function studies revealed severely decreased MIP (47% predicted), severely decreased MEP (30% predicted), and vital capacity that was 80% of predicted. In those with a vital capacity below 80% predicted, the MIP and MEP were significantly lower than those with a normal vital capacity.[62] Another study of 73 wheelchair-bound MS patients demonstrated that 72.6% of patients had respiratory impairment (defined as FVC <80% predicted)[63] with a mean VC of 57.9% ± 33.5% predicted. The VC was <50% predicted in 46.6% of the patients. As in previous studies, the MEP was lower (26.9% ± 22.1% predicted) than the MIP (33.1% ± 22.7% predicted). Cough was impaired in 61.6% of the patients (mean peak cough flow of 3.14 L/s), and 37% had severe cough impairment defined as peak cough flow <27 L/s.[63] These studies suggest that respiratory impairment is often present in MS patients whether they remain ambulatory, are wheelchair bound, or bed bound. In all these studies the MEP was more affected than the MIP, and the respiratory muscle weakness directly correlated with the severity of the subject's overall neurologic function.

Smeltzer et al. developed a pulmonary dysfunction index for patients with MS and found that it correlated with MEP measurements. The score assesses the patient's assessment of cough and ability to handle secretions, the examiner's assessment of cough, and how high the patient can count on a single exhalation (Table 84-5). A subject with normal cough efficacy would have a score of 4 while an individual with the most impairment would have a score of 11.[64] As in other neuromuscular disorders the use of respiratory muscle training remains controversial. Gosselink et al. examined the effect of respiratory muscle training (e.g., three sets of 15 expiratory contractions at 60% of MEP twice daily) on respiratory muscle strength and the subject's pulmonary index score in a group of severe MS patients.[65] At 3 months there was a statistically significant improvement in MIP, and although the MEP improved the p value was 0.07 compared with control patients. The pulmonary index was statistically better at 3 months and 6 months following expiratory muscle training, but the FVC was not.[65]

A subsequent study in 17 ambulatory MS patients who underwent expiratory muscle training was able to statistically improve MEP, but this did not improve pulmonary function or markers of cough effectiveness.[66] Another study looked at effect of inspiratory muscle training performed as 3 sets of 15 repetitions per day for 10 weeks on respiratory muscle function in 37 non-ambulatory MS patients (age 60.5 ± 8.6 years). The MIP did improve from a baseline of

TABLE 84-5 Pulmonary Dysfunction Index for Multiple Sclerosis Patients

Clinical Signs		Score
Patient rating		
1. History of difficulty handling secretions	No	1
	Yes	2
2. Cough	Normal	1
	Weak	2
Examiner rating		
3. Strength of cough when asked to cough voluntarily as hard as possible	Normal	1
	Weak	2
	Very weak/inaudible	3
4. Value reached when patient counts aloud on a single exhalation after a maximal inspiratory effort	>30	1
	20–29	2
	10–19	3
	<9	4

Data from Smeltzer SC, Skurnick JH, Troiano R, et al. Respiratory function in multiple sclerosis. Utility of clinical assessment of respiratory muscle function. Chest. 1992;101(2):479–484.

25.9 ± 16.4 cm H_2O to 30.6 ± 17.6 cm H_2O ($p < 0.05$). The MIP remained improved up to 8 weeks following the IMT training, but there was no improvement in the MEP. The investigators did not look at lung function or overall functional status.[67] Based on these data the American Academy of Neurology gives inspiratory muscle training a grade of weak evidence in treatment of patients with MS and suggests that IMT is possibly effective.[68]

Treatment of MS has traditionally included the use of immunosuppressive agents such as high-dose corticosteroids, cyclophosphamide, intravenous immunoglobulin (IVIG), and azathioprine. However other more effective and less toxic disease-modifying treatments have emerged over the last ten years, including medications such as glatiramer, mitoxantrone, interferon beta (IFN-β-1a), natalizumab, fingolimod, alemtuzumab, teriflunomide, and ocrelizumab.[69,70] The choice of therapy depends on the clinical situation and whether relapsing remitting or secondary progressive disease is being treated. Now that many disease-modifying therapies are available, the American Academy of Neurology recommends individualization of treatment regimens, which should take into consideration patient preferences, comorbidities, and potential side effects of medications when initiating or changing disease-modifying therapies.[70] Ocrelizumab, a humanized monoclonal antibody the selectively depletes CD20+ B cells, has been shown to be superior to IFN-β-1a for relapsing MS[71] and is the only drug to date that has demonstrated the ability to slow disease progression in patients with primary progressive MS.[72]

Despite the use of disease-modifying agents, acute exacerbations or remissions will occur, and it is important to educate patients and caregivers regarding these events.[70] Treatment of these acute attacks of the relapsing remitting form of the disease centers on high-dose corticosteroids.[69] In one randomized, placebo-controlled study, treatment with 10 days of high-dose oral methylprednisolone resulted in improved neurologic function, but there was no difference in the reoccurrence of future acute exacerbations.[73] More recent evidence demonstrated that 1000 mg of oral methylprednisolone for 3 days is noninferior to 3 days of 1000 mg of intravenous methylprednisolone. The investigators randomized 100 patients to oral methylprednisolone arm and 99 to intravenous methylprednisolone. The primary outcome, the proportion of patients who had improvement in functional score by day 28, was similar between the two groups (81% oral vs. 80% intravenous; treatment difference of 0.5%; 90% CI, –9.5 to 10.4).[74]

The use of IVIG has been controversial due to a lack of randomized controlled trials, but it does appear that IVIG can both delay and prevent the occurrences of acute attacks in the relapsing and remitting form of the disease in some patients.[75] Achiron et al. have shown that in patients given IVIG within the first 6 weeks of neurologic symptoms, there was a significant reduction in disease activity as measured by MRI imaging and neurologic symptoms.[76] However, there was no significant additional benefit to adding IVIG to methylprednisolone therapy, and a recent study looking at the effect of IVIG use for 27 months in secondary progressive multiple sclerosis failed to show any difference in progression of disability.[77] Although there are only case series and single-center retrospective studies to support its use, most experts suggest that plasmapheresis be used when high-dose steroids do not result in a clinical response.[69]

■ Lower Motor Neuron Lesions

Two notable lower motor neuron disorders have a significant respiratory impact and are considered below: poliomyelitis and amyotrophic lateral sclerosis.

Poliomyelitis

In the early part of the 20th century, poliomyelitis was the most common cause of lower motor neuron disease in the United States. Paralytic poliomyelitis is the most devastating respiratory presentation of poliomyelitis infection and is preceded by a period of fever and mild illness. After several days of mild fever and myalgia, symptoms disappear; then, 5 to 10 days later, fever reoccurs with signs of meningeal irritation and asymmetric flaccid paralysis. Respiratory motor nuclei may be directly involved, resulting in diaphragmatic or other respiratory muscle dysfunction. In 6% to 25% of paralytic cases, bulbar symptoms may arise, increasing the risk of upper-airway obstruction, pooling of pharyngeal secretions, and pulmonary aspiration. Moreover, the central respiratory centers can be directly affected, resulting in irregular respirations.[78]

In contrast to Guillain-Barré syndrome, sensation is intact. Tendon reflexes are significantly diminished or absent. Cerebrospinal fluid analysis shows a pleocytosis associated with mild protein elevation, and electroneuromyography shows widespread patchy denervation.

Some 15% to 30% of adults with paralyzing infection die, and treatment overall is supportive. Many patients require aggressive ventilatory and hemodynamic support during the acute phases of their illness. As temporarily damaged nerve cells regain function, recovery begins and may continue for as long 6 months. Paralysis persisting beyond that point is permanent, however, and may be associated with complaints of severe pain, which sometimes recurs years after the illness.

Some patients develop progressive muscle weakness 20 to 30 years after the initial infection. This has been termed "post-polio syndrome."[78] Symptoms vary from mild to moderate deterioration of function, with fatigue, joint pain, or weakness that may progress to muscle atrophy. The most common symptom is muscle pain (typically after exertion), which occurs in 36% to 86% of the patients. The weakness tends to progress slowly, with an average decline in muscle strength of approximately 1% per year. The pathogenesis appears to be due to dysfunction of surviving motor neurons, with slow disintegration of axonal terminals eventually leading to muscle denervation. Although respiratory complaints are common in this disorder, significant hypoventilation with elevated Pa_{CO_2} rarely occurs.[79] Respiratory failure is more common in those who required mechanical ventilation during the acute poliomyelitis phase.

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a chronic, degenerative neurologic disorder characterized by death of motor neurons in the cerebral cortex and spinal cord. The result is a combination of upper and lower motor neuron dysfunction, manifested by spasticity and hyperreflexia muscle wasting, weakness, and fasciculations. It has an incidence of approximately 1 to 2 cases per 100,000 people. Males are more commonly affected than females—by a 2:1 ratio. Most cases are sporadic, but approximately 10% of cases are familial, and there is no difference in response to therapy in those with familial ALS (FALS) or sporadic cases.[80] ALS is now recognized as a multisystem disorder that can initially present as cognitive defects prior to the development of motor symptoms and is known as ALS with frontotemporal degeneration (FTLD). Additionally, some FTLD patients go on to develop motor symptoms consistent with ALS. The main pathologic finding is abnormal accumulation of insoluble proteins in the cytoplasm of motor neurons.[81] Recently it was discovered that two of these proteins are TAR DNA–binding protein 43 (TDP-43) and fused in sarcoma/translated in liposarcoma (FUS/TLS). Mutations in the genes encoding for these proteins have been found in FALS, SALS, and FTLD, but not in ALS associated with mutations in the superoxide dismutase 1 (SOD-1) gene on chromosome 21.[81] Even in FALS, genetic mutations have been discovered in only about 30% of the cases and most remain unexplained.[81]

The usual clinical presentation is progressive weakness of the distal extremities, although severe respiratory muscle weakness, particularly intercostal muscle and diaphragm weakness, has resulted in some ALS patients presenting with respiratory insufficiency as the initial symptom. Respiratory muscle impairment is more evident in the advanced stages of the disease. Abnormalities in pulmonary function are apparent, even in patients with mild extremity weakness. Progression of respiratory impairment is much faster in ALS than in other chronic neuromuscular disorders, and serial lung function studies in ALS patients show progressive reduction in FVC and MVV. In contrast to patients with other neurologic disorders, however, patients with ALS usually have a normal or slightly elevated transpulmonary pressures at FRC, and RV is usually increased and continues to rise as the disease progresses with maintenance of a normal TLC.[82] These changes are thought to be due to earlier involvement of the abdominal musculature, with preservation of intercostal and diaphragm function. Support for these physiologic findings comes from pathologic studies that show a more pronounced loss of motor neurons in the lumbosacral and lower thoracic spinal segments than in the upper and mid-thoracic regions.

The use of spirometry and respiratory muscle testing has been used to help determine the prognosis and help clinicians decide when to initiate ventilatory assistance. Investigators used the placebo arm of a clinical trial of topiramate in ALS to study the decline of FVC over 12 months in 97 patients with ALS.[83] They found that the FVC declined linearly over 12 months and that the rate of decline in FVC was an independent predictor of mortality. Those with an FVC% decline in 3 months that was greater than the median rate of decline had a mortality rate of 47% compared with 8% in those with a slower rate of decline. Forceful exhalation during the FVC maneuver can cause fatigue or bronchospasm in ALS patients, thus underestimating lung capacity.

The slow vital capacity (SVC), a slower gentle exhalation after maximal inhalation, is thought to be easier for patients with neuromuscular disease and particularly ALS. The rate of SVC decline was studied in 893 placebo-treated patients from 2 large clinical trials and an ALS trial database.[84] These data were used to assess the relationship of decline in SVC to respiratory-related events in ALS. The decline in SVC demonstrated weak but significant correlation to onset of dyspnea ($r = 0.23$; $p < 0.001$), orthopnea ($r = 0.23$; $p < 0.001$), and respiratory insufficiency ($r = 0.26$; $p < 0.001$). The investigators also created a Cox proportional hazards regression model of time to clinical events and found that if the slope of SVC decline decreased by 1.5 percentage points per months there was a 23% reduction in tracheostomy or death at 6 months.[84] The authors concluded that the rate of decline in SVC is associated with clinically meaningful events and can be a meaningful clinical outcome measure for use in in clinical trials. The sniff nasal inspiratory pressure (SNIP) test is theoretically easier than the FVC or the SVC maneuver for the ALS patient, because a tight seal around a mouthpiece is not required. A sniff is a short voluntary inspiratory maneuver, which has been shown to correlate with invasive nonvolitional tests of diaphragm strength. A SNIP <40 cm H_2O was associated with a hazard risk for death of 9.1, with a median 6-month survival of 50%. Surprisingly, in those with SNIF <40 cm H_2O, 66% had an FVC above 50%, and the hazard risk for death was 13.6 in this group.[85] When comparing the two techniques for the ability to predict 6-month mortality, the SNIP test had a sensitivity of 97% and specificity of 79% while the FVC was 58% sensitive and 96% specific.[85]

A separate study also has shown that in ALS patients without bulbar involvement SNIP was superior to both vital capacity and maximal inspiratory pressure in predicting the development of respiratory failure as defined by hypercapnia (Pa_{CO_2} >45 mm Hg) with a specificity of 85% and sensitivity of 81%.[86] In patients with significant bulbar involvement, there was no single test of respiratory muscle function that reliably predicted the development of respiratory failure.[86]

The shape of the flow-volume curve may also pinpoint the subgroup of ALS patients with greater weakness of the expiratory muscles. In patients with severe expiratory muscle weakness, the flow-volume curve near RV shows a sharp drop in flow such that the maximum expiratory curve has a concave appearance. This group of ALS patients usually has lower maximum expiratory pressures, smaller VC, reduced expiratory reserve volume, and a higher RV than do ALS patients with more-normal-appearing flow-volume curves.[82] A prospective study of 55 ALS patients demonstrated that the peak expiratory flow time increased over baseline at a rate of 4.7% per month while the decline in the FVC was only 1.2% per month. The authors concluded that the peak expiratory flow rate can be used as an earlier marker of pulmonary involvement from ALS.[39]

ALS is a progressive and uniformly fatal neuromuscular disease, and all patients will eventually develop respiratory failure, which will necessitate the discussion of mechanical ventilation (Chapters 148 and 149). Currently, guidelines from the American Academy of Neurology recommend treatment with noninvasive mechanical ventilation once the FVC is below 50% of predicted, MIP < −60 cm H_20, or SNIP <40 cm H_2O, or once orthopnea is seen.[87] Ventilation with noninvasive bilevel positive airway pressure has been shown to increase both survival and quality of life in patients with ALS, while those with orthopnea seemed to derive the most benefit.[88–91] A randomized controlled trial of noninvasive ventilation compared to standard of care in 41 patients with ALS who had orthopnea with PI_{max} <60% predicted or symptomatic daytime hypercapnia confirmed these findings. The investigators found that overall survival was prolonged in the noninvasive ventilation group (219 [75–1382] vs. 171 [1–878] days; $p = 0.006$), with the greatest benefit in those without severe bulbar symptoms.[90] There was also improved quality of life in the noninvasive ventilation group overall, but the effect was seen only in those without severe bulbar symptoms.[90]

Although noninvasive ventilation (NIV) is commonly used at night in ALS and other neuromuscular diseases, the effect NIV on sleep quality was not addressed in early NIV studies. One group of investigators admitted 24 ALS patients to the sleep lab for titration of NIV based on polysomnogram (PSG) parameters and nocturnal capnography.[92] The mean inspiratory pressure was 14 ± 2 cm H_2O, and the mean expiratory pressures were 4 ± 1 cm H_2O with a backup rate of 16 ± 2/min for those on ST mode. They found that NIV improved stage 3 and REM sleep even though overall sleep time was not increased. Furthermore, there was less nocturnal hypoxemia and less time with transcutaneous CO_2 >55 mm Hg at night compared with the baseline study. There were significant improvements in daytime sleepiness as measured by the Epworth Sleepiness Scale (8.0 [3.8–10.0] vs. 4.5 [3.0-7.3]; $p < 0.05$) and overall sleep quality as measured by the Pittsburgh Sleep Quality Index (8.5 [6.8–13.30] vs. 5.0 [3.0–8.3]; $p < 0.01$).[92]

There was interest in using diaphragm pacing via phrenic nerve stimulation in patients with ALS after initial uncontrolled studies demonstrated efficacy. However, two randomized controlled trials both were stopped early due to increased mortality in the diaphragm pacing groups.[93,94] Although the mechanism for increased mortality is unclear, the authors hypothesize that it could be due to acceleration of ALS following a surgical procedure, the combination of a natural and unnatural (paced) respiratory rhythm, or the stimulation of already damaged motor neurons leading to even more damage.

Due to weakness of both inspiratory and expiratory muscles, patients with ALS have diminished cough reflex. Impaired cough becomes even more important when airway secretions are increased during respiratory infections or in those with bulbar symptoms. One group of investigators prospectively followed 53 patients with ALS for 1 year and found that peak cough flow (PCF), peak cough flow/peak velocity time (PCF/PVT), and severity of bulbar symptoms were most predictive of ineffective cough during a respiratory infection.[95] A mechanical insufflation-exsufflation (MI-E) device can be used to augment cough in patients by providing positive airway pressure at 40 to 45 cm (insufflation) for a few seconds and then suddenly switching to 40 to 45 cm of negative pressure (exsufflation). This creates high-volume expiratory airflow that can be timed with coughing during exsufflation. MI-E increased PCF by 19% in ALS subjects with bulbar symptoms and 21% in those without bulbar symptoms.

Treatment of the other respiratory complications of ALS includes a high index of suspicion for impaired swallowing due to bulbar involvement. Difficulty in swallowing food or even saliva predisposes patients with ALS to a markedly high risk for pulmonary aspiration. Special swallowing precautions, earlier placement of enteral feeding tubes, or antisialogogues may be required.

Riluzole (an antiglutamate medication) and edaravone (a free radical scavenger of peroxyl radicals and peroxynitrite) are pharmacologic agents currently approved for use in ALS. Riluzole has been shown to induce a significant improvement in median survival from 11.8 to 14.8 months and to decrease the rate of deterioration in muscle strength in comparison with a placebo.[96,97] A randomized controlled clinical trial (RCT) with edaravone enrolled 137 patients with early ALS defined as disease duration of <2 years and FVC >80% predicted.[98] The primary outcome was change in an ALS Functional Rating Scale-Revised (ALSFRS-R), which is a 12-item questionnaire regarding functional status with higher scores indicating better function (range of score 0–48). There was a slight decrease in rate of decline in ALSFRS-R for the edaravone group compared with placebo (-5.01 ± 0.64 vs. -7.50 ± 0.66; $p = 0.0013$). The FVC declined by 15.61 percentage points in the edaravone group compared with a decline of 20.4 percentage points in the placebo group, but the difference was not statistically significant.

More recently, a RCT compared sodium phenylbutyrate-taurursodiol to placebo and found a slower functional decline on the ALSFRS-R in the medication arm—and as with other pharmaceuticals there was not a significant difference in SVC.[99] Subsequent analysis of this trial demonstrated that those in the phenylbutyrate-taurursodiol group had improved survival compared with the placebo arm (median survival, 25.0 vs. 18.5 months; HR, 0.56; CI, 0.34–0.92; $p = 0.023$).[100]

However, despite any pharmacologic interventions, ALS is a progressive and fatal neuromuscular disease, and all patients eventually develop respiratory failure and ventilatory assistance will therefore need to be considered. In those without bulbar involvement, noninvasive forms of ventilatory support are clearly indicated and will provide both a survival and quality-of-life benefit. Airway intubation may be required because of bulbar dysfunction further impairing cough and the inability to clear secretions. Long-term invasive ventilatory support is infrequently applied in ALS patients, but decisions must be made on an individual basis.

■ Disorders of Peripheral Nerves

Phrenic nerve dysfunction can be a significant cause of respiratory weakness in patients with neuromuscular diseases due to a variety of causes.

Diaphragm Paralysis

Unilateral or bilateral diaphragm paralysis following phrenic nerve injury can result from cardiac surgery, trauma, mediastinal tumors, infections of the pleural space, or forceful manipulation of the neck. Phrenic nerve injury during open-heart surgery is one of the most common causes of unilateral and bilateral diaphragm paralysis and is due either to cold exposure during cardioplegia or to mechanical stretching of the phrenic nerve during surgery. Diaphragm paralysis may also be seen with a variety of motor neuron diseases, myelopathies, neuropathies, and myopathies.

Bilateral diaphragm paralysis is characterized by a severe restrictive ventilatory impairment, with VC being frequently less than 50% of predicted in the upright position and a further reduction of 25% or more in VC in the supine position. TLC is also markedly decreased, as are FRC and static pulmonary compliance. In most patients with nontraumatic bilateral diaphragm paralysis, the most important clinical feature is orthopnea out of proportion to the severity of the underlying cardiopulmonary disease.[15]

In patients with nontraumatic bilateral diaphragm paralysis, the diaphragm usually goes unrecognized until they present with cor pulmonale or cardiorespiratory failure. A chest radiograph showing elevation of both hemidiaphragms with volume loss and/or atelectasis at the lung bases is common. The diagnosis of bilateral diaphragm paralysis should be considered when any of the following four abnormalities is present: (1) a 40% or greater reduction in VC in the supine compared to upright position; (2) fluoroscopically observed paradoxical movements of both hemidiaphragms during a "sniff" test; (3) absence of phrenic latency or phrenic nerve conduction velocity tests or lack of EMG evidence of spontaneous diaphragm activity; and (4) transdiaphragmatic pressure two standard deviations below the expected mean for normal subjects with paradoxical inward abdominal motion during maximum inspiratory efforts.[2,17,18,101]

Because, in most patients, bilateral diaphragm paralysis occurs in the context of global respiratory muscle impairment, measurements of PI_{max} and PE_{max} may be sufficient to arouse suspicion of diaphragm paralysis as a cause of the patient's complaints. With diaphragm paralysis, a marked reduction in PI_{max} with preservation of PE_{max} should be found, and in general, there is a correlation between maximum inspiratory pressures and Pdi_{SNIFF}. Reductions in Pdi_{SNIFF} to less than 30 cm H_2O are accompanied by orthopnea, a supine decrease in VC, and the presence of abdominal paradox. In most cases, the presence of severe bilateral diaphragm weakness can be diagnosed from physical exam, measurements of VC in the upright and supine positions, and PI_{max} and PE_{max}. In cases where the diagnosis is uncertain, or when definite documentation is desired, measurement of transdiaphragmatic pressures, phrenic nerve conduction times, EMG activity, transdiaphragmatic pressures during phrenic nerve stimulation, or ultrasound imaging of the diaphragm may be performed.[2] An elevation in Pa_{CO_2}, particularly in the supine position in patients with diaphragm paralysis has been reported but is not consistent.

Hemidiaphragm paralysis is more common than bilateral paralysis and is usually diagnosed from unilateral elevation of the hemidiaphragm on chest radiograph. Ultrasound of the diaphragm can be performed to confirm the diagnosis as well.[2] Most disorders reported as causing bilateral diaphragm paralysis have also been reported as causes of unilateral paralysis (e.g., cervical spondylosis, spine cord injury, poliomyelitis, and muscular dystrophy). Other, more specific causes of unilateral diaphragm paralysis are pneumonia, trauma from central vein cannulation, and viral infections of the cervical nerve roots.

Patient complaints and physical examination abnormalities in unilateral diaphragm paralysis are usually the same as with bilateral diaphragm paralysis but are less striking. Orthopnea is a frequent complaint, but it is less dramatic than in patients with bilateral paralysis. Moreover, physical examination findings are nonspecific but occasionally may show paradoxical inward motion of the paralyzed hemidiaphragm with a reduction in breath sounds at the affected lung base and an increase in dullness on percussion. The alveolar arterial oxygen gradient may be increased with mild hypoxemia due to the reduction in ventilation and perfusion of the lower lobe on the affected side.

Tests of diaphragm function are intermediate between those in patients with bilateral diaphragm paralysis and normal predicted values. VC in the upright posture may be reduced to 74% to 81% of predicted, with a fall in VC also present in the supine compared to erect position, but of lesser magnitude than in patients with bilateral diaphragm paralysis. In patients with right hemidiaphragm paralysis, the fall in VC may be almost twice as great (19% vs. 10%) in comparison with left-sided paralysis, owing to the weight of the liver further encroaching on lung volume. Maximum inspiratory mouth pressures are frequently reduced to approximately 50% to 62% of normal. Similar reductions are found in maximum P_{di} measured during maximum static voluntary efforts and during maximum sniff.

Treatment of patients with bilateral diaphragm paralysis is similar to that of other patients with chronic neuromuscular diseases. Eliminating nocturnal hypoventilation, especially during REM sleep, is warranted, and the implementation of noninvasive ventilation, especially positive-pressure ventilation, may be indicated. In some cases of symptomatic unilateral hemidiaphragm elevation, surgical plication of the affected hemidiaphragm may relieve symptoms and improve FVC and transdiaphragmatic pressure. A series of 22 patients who underwent diaphragmatic plication were followed for an average of 4.9 years, and the investigators found that the percent decline in FVC from seated to supine position improved from 34% (range, 10%–47%) preoperatively to 9% (range, 0%–21%) postoperatively ($p = 0.004$). There also was an improvement in the transitional dyspnea index (TDI) postoperatively, but the TDI did not correlate with the improvement in spirometry.[102] Surgical plication is achieved by placing a series of 6 to 8 U-shaped sutures in the diaphragm, which results in the diaphragm becoming fixed and immovable. This prevents excursion of the diaphragm into the thoracic cavity during inspiration and permits the accessory muscles of respiration to generate negative intrathoracic pressure.

Guillain-Barré Syndrome

Guillain-Barré syndrome (GBS) precipitates respiratory failure more often than any other peripheral neuropathy. It is an acute idiopathic polyneuritis with an annual incidence of 0.89 to 1.99 cases per 100,000 people.[103] It usually presents as paresthesia and ascending paralysis of the lower extremities with absent deep-tendon reflexes in a symmetrical distribution. Objective findings of sensory loss are variable, and the degree of motor weakness can range from mild paresis to complete paralysis. Maximum weakness of the lower extremities occurs within 2 weeks in 50% of cases, and 90% of cases reach their nadir in weakness by 4 weeks. After the nadir is reached, patients remain at that level for an additional 1 to 4 weeks before recovery begins. Facial, ocular, and oropharyngeal muscles may be impaired as well as the respiratory muscles. Respiratory muscle weakness and, specifically, severe diaphragm weakness may be found in patients with GBS.[103]

The distribution of muscle weakness between respiratory and non-respiratory muscles is not uniform in GBS, and peripheral muscle strength does not correlate with the presence or absence of respiratory muscle weakness. However, ventilatory failure correlates with diaphragmatic weakness.

The impairment on respiratory tests in GBS is similar to that for other generalized neuromuscular diseases. A decline in FVC and maximum inspiratory and expiratory mouth pressures, impairment in nocturnal gas exchange during REM sleep, and the onset of hypercapnia detected by arterial blood gas analysis have all been reported in symptomatic GBS patients. An FVC of 15 cc/kg is a sign of imminent respiratory failure in GBS.[103,104]

Hypercapnia is a late sign of respiratory failure, with the average Pa_{CO_2} at the time of intubation 43 mm Hg when FVC is less than 12 cc/kg.

Respiratory treatment of GBS patients is mainly supportive. Since bulbar involvement, leading to swallowing dysfunction, increases the propensity for pulmonary aspiration, special precautions for feeding and control of upper-airway secretions may be required. Primarily because of bulbar dysfunction in those with respiratory failure, noninvasive ventilation has not been used outside of a few case reports. Individual cases without bulbar dysfunction merit special consideration, and the use of noninvasive ventilation may be appropriate. Approximately 20% to 30% of GBS patients will require mechanical ventilation. Airway intubation and mechanical ventilation should be initiated when one major criterion or two minor criteria are present (Table 84-6).[103] Earlier intubation and assisted ventilation may be indicated to avoid complications that arise from progressive respiratory failure, overwhelming pulmonary infections, or both. When indicated, intubation and mechanical ventilation should be initiated early because emergent intubations have been associated with worse outcomes. It is well established that mechanical ventilation is indicated when the vital capacity falls below 15 cc/kg. However, it would be ideal to predict the need for mechanical ventilation at an earlier time.

A Dutch group of investigators demonstrated that the most important factors in predicting respiratory failure in the first week of hospitalization were Medical Research Council (MRC) sum score (a muscle strength score), days between onset of weakness and hospitalization, and the presence of facial and/or bulbar weakness at hospitalization.[105] Based on their model the Erasmus GBS Respiratory Insufficiency Score (EGRIS) was made and is shown

TABLE 84-6 Criteria for Airway Intubation and Mechanical Ventilation in Guillain–Barré Syndrome

Major Criteria	Minor Criteria
Hypercarbia (Pa_{CO_2} ≥48 mm Hg)	Ineffective cough
Hypoxemia (Pa_{O_2} ≤56 mm Hg)	Impaired swallowing
Vital capacity <15 cc/kg	Atelectasis

TABLE 84-7 Erasmus GBS Respiratory Insufficiency Score (EGRIS) for Predicting Respiratory Failure in the First 7 Days of Hospitalization

Measure	Categories	Score
Days between onset of weakness and hospitalization	>7 days	0
	4–7 days	1
	≤ 3 days	2
Facial and/or bulbar weakness on hospitalization	Absent	0
	Present	1
MRC sum score at hospitalization	60–51	0
	50–41	1
	40–31	2
	30–21	3
	≤ 20	4
EGRIS	**Risk of Intubation (%)**	
Low (0–2)	4	
Intermediate (3–4)	24	
High (5–7)	65	

GBS, Guillain-Barré syndrome; MRC, medical research council.

in Table 84-7. Patients at highest risk for intubation (EGRIS 5–7) should be admitted to the ICU for close observation and timely intubation if required. Evaluation for discontinuation of mechanical ventilation is not different in individuals with GBS, but if dysautonomia is present at the time of extubation then reintubation rates are exceedingly high (73% vs. 26.7%; $p = 0.008$)[106] while an improvement of >4 mL/kg in vital capacity was associated with a 90% positive predictive value for extubation.[106] Aggressive pulmonary toilet, including repeated bronchoscopy, may be needed to decrease atelectasis and the incidence of nosocomial pneumonia.

In a multicenter trial, plasmapheresis (total of four treatments), using either albumin or fresh frozen plasma as replacement fluids, produced short-term benefits in earlier motor recovery, ambulation, and reduction in number of patients who required assisted ventilation, and shortened the duration of mechanical ventilation.[107] A subsequent study from the same group showed that two plasmapheresis treatments were better than none in mild disease, but four were better than two in moderate and severe disease. Greater than four treatments were not beneficial even in severe disease. Intravenous immunoglobulin (IVIG), given within 2 weeks after the onset of GBS, may also be effective therapy.[108] IVIG has been compared to plasmapheresis; recovery was as effective as plasmapheresis and may have been slightly better. In a study of 150 patients with GBS, 53% of the group treated with IVIG had an improvement of one grade (on a seven-point scale) in muscle strength compared with 34% of those treated with plasmapheresis after 4 weeks of therapy.[109] Currently, there is no evidence from randomized controlled trials to support the use of corticosteroids in the treatment of GBS.

Critical Illness Polyneuropathy

Critical illness polyneuropathy (CIP) was initially described in five patients that had survived sepsis and multisystem organ failure, and the entity is now recognized as a serious complication of critical illness that contributes significantly to morbidity and mortality.[110,111]

The disease is common, with as many as 68% of patients with sepsis and multisystem organ failure requiring mechanical ventilation having evidence of CIP on electromyography/nerve conduction studies. Patients affected by this disorder typically exhibit varying degrees of musculoskeletal weakness, which ranges from mild weakness to near total paralysis with hyporeflexive deep-tendon reflexes. Unfortunately, physical exam is unreliable as the sole means of diagnosis, and electromyography with nerve conduction studies (EMG/NCS) are required to confirm the diagnosis. EMG studies in these patients show a reduction in the amplitude of the compound muscle action potential without significant prolongation of stimulus latency, suggesting primarily axonal nerve damage rather than a demyelinating process.

Recognition of CIP is important because the disease affects patient management and the prognosis of recovery from the critical illness. Patients who develop CIP tend to require a longer period of mechanical ventilation and longer hospital stays compared to those without CIP. Garnacho-Montero et al. found in a group of patients with sepsis and prolonged mechanical ventilation that those with CIP required 34 days of mechanical ventilation versus only 14 days for those without CIP. Additionally, the weakness associated with CIP results in an extended rehabilitation period, and there is evidence of persistent neuropathy on EMG/NCS as long as 5 years after discharge from the intensive care unit. Patients who develop CIP appear to have a higher mortality, with one study showing a 3.5-fold increase in ICU mortality, and another with significantly higher in-hospital mortality.[112]

Although the exact mechanism for axonal damage in this syndrome is unknown, several risk factors for the development of CIP have been described. Two of the most important risk factors are the presence of the systemic inflammatory response syndrome (SIRS) and the APACHE III score. One study looked at 98 patients prospectively and found that 72% of patients with SIRS and an APACHE III score above 85 will develop CIP. Multivariate analysis of associated risk factors from another study found that hyperosmolality, parenteral nutrition, the use of neuromuscular blocking agents, and neurologic failure (GCS <10) were associated with an increased risk of developing CIP.[113] Exactly how these risk factors lead to the development of CIP is not known, but possibilities include nerve toxins released during episodes of multisystem organ failure, antibiotics impairing neuromuscular transmission, protracted use of neuromuscular blocking agents, and hyperglycemia causing nerve ischemia by endovascular shunting.

Because no specific therapy for CIP exists, treatment is purely supportive and includes aggressive rehabilitation, nutrition support, and treatment of any medical complications. It should be emphasized to both patient and family that recovery may be prolonged (as long as 5 years).[114]

■ Disorders of the Neuromuscular Junction

Below we discuss important disorders of the neuromuscular junction that may have profound respiratory effects: myasthenia gravis, Eaton-Lambert syndrome, and botulism.

Myasthenia Gravis

Myasthenia gravis is an autoimmune disorder characterized by impaired transmission of neural impulses across the neuromuscular junction due to the production of antibodies directed against the acetylcholine receptor. The prevalence of myasthenia gravis is estimated to be approximately 1 in 10,000 people, with 2-to-1 female-to-male predominance. It occurs more often in younger than older adults. The typical myasthenic patient presents with fluctuating muscular weakness, with improvement after rest and the administration of anticholinesterase agents (e.g., edrophonium chloride). Ocular, facial, and neck muscles are commonly affected, but patients who have the most severe respiratory involvement have either acute fulminating or late severe classifications of myasthenia gravis.

In 17 patients with moderate, generalized myasthenia gravis, pulmonary function studies before the administration of edrophonium chloride reveal a mild reduction in VC and moderate reductions in both maximum inspiratory (approximately 54% of predicted) and expiratory (reduced to approximately 52% of predicted) mouth pressures.[115] Because of increased lung recoil pressure, normal or supranormal values of maximal expiratory flow are seen in relation to lung recoil pressure or absolute lung volume. Although upper airway obstruction due to bulbar muscle involvement is theoretically possible, it has rarely been reported. However, Putman and Wise examined flow–volume loops in myasthenia gravis patients that were adequate for interpretation. They found that in 12 patients with myasthenia gravis with reproducible flow–volume loops, 7 had either a variable extrathoracic or fixed upper airway obstruction suggesting that upper airway obstruction maybe more common than previously thought.[116]

Acute respiratory failure usually occurs in the setting of a myasthenic crisis or cholinergic crisis or as the initial presentation of the disease. A myasthenic crisis refers to worsening of the basic underlying disease, usually precipitated by decreased anticholinesterase medication, surgery, or administration of neuromuscular blocking medication. Clinical parameters useful in predicting the development of postoperative respiratory failure include the severity of the disease (e.g., acute fulminating or late severe categories of myasthenia gravis), a low preoperative VC, and bulbar symptoms.[117] The most common complications of myasthenic crisis are respiratory failure and recurrent pneumonias due to aspiration from bulbar involvement and impaired cough. The mean duration of mechanical ventilation in myasthenia gravis in a series of 22 patients was 8 days, with 6 patients (32%) requiring tracheostomy for prolonged mechanical ventilation. Of the 22 patients, 21 survived and were totally weaned from ventilatory support over 1 to 32 days.[118] Noninvasive bilevel positive-pressure (BiPAP) ventilation is a viable option to treat respiratory failure during a myasthenic crisis until effective therapy is delivered. BiPAP was used in a series of 11 myasthenic crisis events in 9 patients. The mean pressures used were 13/5 cm H_2O, and endotracheal intubation was avoided in all but 4 instances. The only predictor for failure of BiPAP was a Pa_{CO_2} above 50 mm Hg.[119]

A subsequent study in 24 patients treated with BiPAP (mean pressure 14/6 mm Hg) had similar findings in that 58% of myasthenia crisis patients avoided intubation, and the best predictor of BiPAP failure was a Pa_{CO_2} >45 mm Hg. Although there was no difference in mortality, those treated with BiPAP had a shorter ICU length of stay (7 vs. 13 days; $p = 0.002$).[120] These data suggest that the use of early noninvasive ventilation prior to the development of severe hypercapnia can reduce intubation rates and ICU length of stay.

The treatment of myasthenia gravis includes anticholinesterase agents, high-dose corticosteroids, thymectomy, and plasmapheresis in patients refractory to steroid or immunosuppressive therapy. Anticholinesterase agents are the first line of treatment. Most patients improve significantly with anticholinesterase agents, but only a few regain normal function. Remissions can be induced in up to 80% of patients with the use of corticosteroids. However, corticosteroids may cause temporary worsening of muscle weakness, usually on the sixth to tenth day of therapy, and close observation for signs of respiratory insufficiency is advisable.[117] Other immunosuppressive agents (e.g., cyclosporine and azathioprine) may be useful with or without concomitant corticosteroids.

In retrospective studies, thymectomy improves survival and relieves clinical symptoms, even in the absence of thymoma. In patients with thymoma, thymectomy is also indicated because the risk for malignant transformation is high in patients less than 55 years of age. In up to 80 percent of myasthenia gravis patients without thymoma, clinical improvement after thymectomy occurs during prolonged follow-up.

Plasmapheresis and the use of intravenous immunoglobulin (IVIG) produce a temporary reduction in acetylcholine receptor antibody level and may be helpful in patients with respiratory failure not responding to anticholinesterase and immunosuppressive agents. Plasmapheresis and IVIG have been compared and both are equally efficacious. However, IVIG was associated with less severe adverse reactions and therefore is the preferred initial agent in the treatment of myasthenic crisis.

Eaton-Lambert Syndrome

Eaton-Lambert syndrome is a rare myasthenia disorder resulting from a reduction in neurotransmitter release from presynaptic terminals that develops in association with tumors (especially small-cell lung carcinoma). Although patients may respond weakly to administration of edrophonium chloride, the disease is differentiated from myasthenia gravis by the predominant involvement of limb and girdle muscles compared to the ocular and bulbar muscle involvement in myasthenia gravis. Respiratory muscle weakness is often detected on pulmonary function tests, but respiratory failure is infrequent.

Botulism

Botulism is a rare disorder caused by the *Clostridium botulinum* toxin. It occurs as a result of eating improperly cooked food, wound contamination by the organism, or, especially in infants, the absorption of toxin from the GI tract. There are eight types of toxins, although human diseases are usually caused by type A, B, or E.

Botulinum toxin binds to the calcium channel in presynaptic terminals, impairing neuromuscular transmission of acetylcholine. GI symptoms predominate early in the disease, followed by neurologic impairment, including descending paralysis of the neck, trunk, and limb muscles. Weakness of the respiratory muscles requiring mechanical ventilation is frequent, especially with botulinum type A toxins. Spirometry usually reveals a restrictive ventilatory defect, and recovery from respiratory muscle weakness may take months, often requiring prolonged mechanical ventilation. The average duration of ventilatory support for type A poisoning is 58 days, in contrast to 26 days for type B botulism. Exertional dyspnea and poor exercise tolerance may persist, even with normal lung function.

■ Muscular Dystrophies and Myopathies

Respiratory function may be significantly affected by a variety of inherited muscle disorders and acquired myopathies (Table 84-8). The inherited muscular dystrophies refer to a heterogeneous group of progressive, degenerative, hereditary skeletal muscle diseases that cause severe muscle weakness, eventually resulting in repeated pneumonias, respiratory failure, and, in some cases, death. Respiratory failure, often accompanied by pneumonia, contributes to death in more than 75% of patients with Duchenne muscular dystrophy.

Duchenne Muscular Dystrophy

Duchenne muscular dystrophy (DMD) is the best characterized of these heredofamilial muscle diseases. This disease is transmitted by an X-linked recessive gene, although approximately one-third of cases arise from spontaneous mutation. The disease is due to the mutation of the gene for skeletal protein dystrophin, a

TABLE 84-8 Myopathies Likely to Produce Respiratory Abnormalities

Inherited Myopathies	Acquired Myopathies
Muscular Dystrophies	Inflammatory (dennatomyositis, polymyositis)
Duchenne	
Myotonic	Systemic lupus erythematosus
Fascioscapulohumeral	Endocrine myopathies
Limb—girdle	Thyroid dysfunction
Oculopharyngeal	Hyperadrenocorticism
	Acute steroid myopathy
Congenital myopathies	Electrolyte disorders
Nemaline myopathy	Rhabdomyolysis
Centronuclear myopathy	
Metabolic myopathies	
Acid maltase deficiency	
Mitochondrial myopathies	

subsarcolemmal protein believed to play a major role in providing structural integrity in the muscle cell surface membrane. The mutation of the dystrophin gene commonly occurs in one of the 79 exons in the gene, which leads to a reading frame disruption resulting in the lack of dystrophin expression.[121] Lack of dystrophin leads to a weaker cell membrane that becomes further impaired with muscle contraction. Muscle inflammation, necrosis, and fibrosis subsequently lead to severe atrophy and loss of function. Approximately 30% to 40% of the normal amount of dystrophin must be expressed in order to prevent major myopathic symptoms. The diagnosis is confirmed by demonstrating mutation of the dystrophin gene in DNA from peripheral leukocytes, or an absence or abnormality in dystrophin in muscle biopsy samples.

Symptoms usually present in early childhood. Gait disturbances and delayed motor development are common manifestations, with proximal weakness resulting in an exaggerated lumbar lordosis. Most patients are wheelchair bound by the age of 12 to 15 years, with death occurring around the age of 20 years as a result of progressive respiratory failure and pneumonia. Kyphoscoliosis commonly develops due to severe muscle weakness and further contributes to a restrictive ventilatory deficit. Pulmonary symptoms are often minimal early on, despite significant weakness of the respiratory muscles.

Maximum inspiratory pressure is reduced at all lung volumes in patients with DMD and declines with time. FVC increases with growth during the first decade and may mask early respiratory muscle dysfunction before it plateaus and progressively decreases about 5% to 6% per year after 12 years of age[122] (Fig. 84-12). Reductions in maximum inspiratory pressure, therefore, occur early in the clinical course of DMD and may precede the reduction observed in VC. In a series of 58 DMD patients, the median decline in FVC was 0.18 L (0.04–0.74) per year; and once the FVC fell below 1 L the median survival was 3.1 years with a 5-year survival of 8%.[123]

A more contemporary cohort of 60 DMD patients aged 5 to 24 years had 131 visits with spirometry. Investigators confirmed that the raw peak FVC will occur in teenage years and then precipitously drop, but when data are expressed as % predicted there is a linear decline with age (Fig. 84-13). Peak expiratory flow had a very similar pattern.[124] Inspiratory muscle weakness does not necessarily parallel the development of expiratory muscle weakness. Maximum expiratory mouth pressures are substantially lower than maximum inspiratory mouth pressures, possibly leading to a marked decrease in the effectiveness of cough.

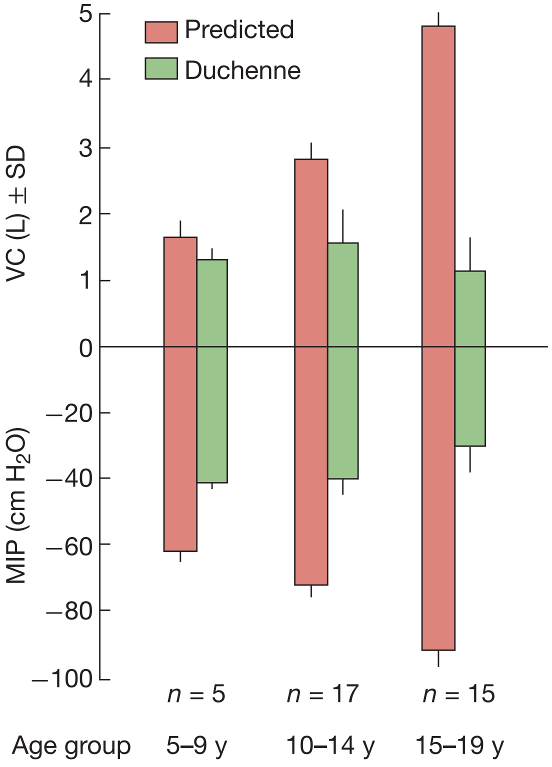

Figure 84-12 Mean vital capacity (VC) and maximum static inspiratory pressures (MIP) in 37 DMD patients in three age groups *(shaded bars)* in comparison to normal predicted values *(unshaded bars)*. MIP decreases gradually as DMD progresses, despite body growth, whereas VC increases until patients reach their early teens. *(Data from Smith PE, Calverley PM, Edwards RH, et al. Practical problems in the respiratory care of patients with muscular dystrophy. N Engl J Med. 1987;316(19):1197–1205.)*

FVC should be measured annually in patients who are able to ambulate and every 6 months in nonambulatory DMD patients. Additionally, peak cough flow, MIP, MEP, and pulse oximetry should be measured every 6 months in nonambulatory patients. Additionally, end-tidal CO_2 or transcutaneous partial pressure of carbon dioxide in blood should be measured every 6 months or any time the pulse oximetry is <95% on room air.[125]

Despite severe and progressive muscle weakness, hypercapnia is uncommon in patients with DMD in the absence of pulmonary infections. The absence of hypercapnia despite severe muscle weakness is believed to be due to relative preservation of diaphragm function until very late in the illness. Once hypercapnia occurs, however, the courses is rapidly progressive, and mean survival is approximately 10 months.

Since ventilation is heavily dependent on diaphragmatic function in DMD patients, severe nocturnal hypoventilation may occur during REM sleep, when activity of chest wall and neck muscles is markedly attenuated and has been documented in DMD patients with normal daytime gas exchange. The American Thoracic Society has recommended that an annual sleep study be performed when the patient becomes nonambulatory unless symptoms of nocturnal hypoventilation are present.[126] Sleep-related hypoxemia may contribute to respiratory insufficiency and the development of cor pulmonale.

Management of patients with DMD is mainly supportive. Ambulation should be maintained and encouraged as long as possible to retard the development of scoliosis. Surgical correction may attenuate the scoliotic contribution to the fall in VC and improve

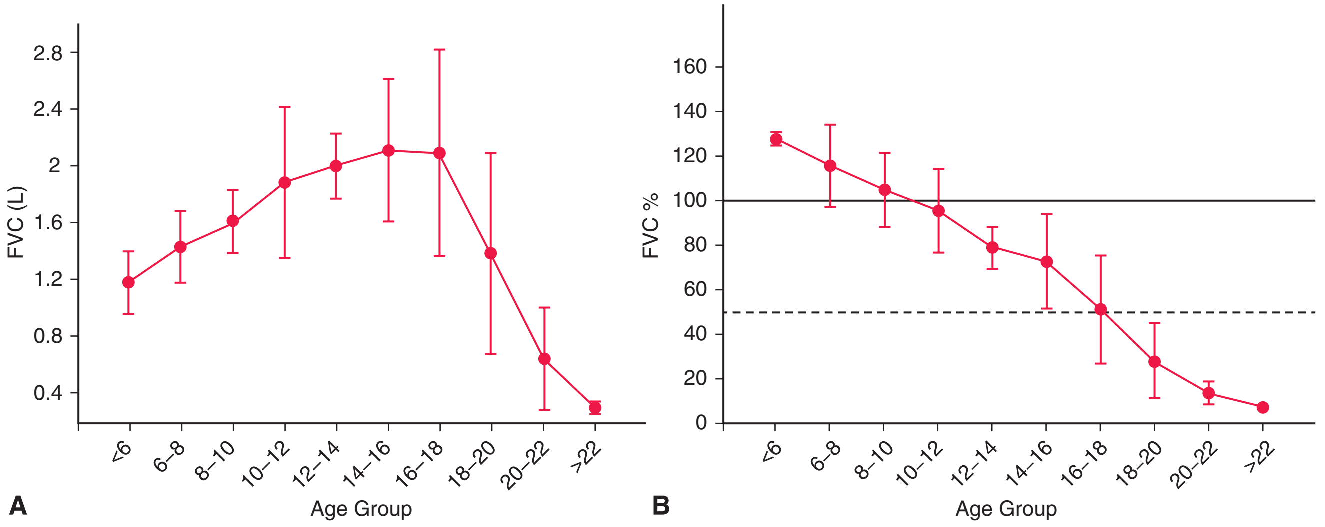

Figure 84-13 Prospectively collected FVC data in 60 children with DMD (median age, 10.3 years; range, 5–24). **A.** FVC in liters increases linearly until about age 10, then plateaus until about age 18, after which there is a precipitous decline. **B.** FVC percent predicted declined nearly linearly from the 6- to 8-year-old cohort through the 20- to 22-year-old cohort. *(Data from Mayer OH, Finkel RS, Rummey C, et al. Characterization of pulmonary function in Duchenne Muscular Dystrophy. Pediatr Pulmonol. 2015;50(5):487–494.)*

patient morale and quality of life overall. While the decline in FVC will continue postoperatively, it may be slowed somewhat. In a group of 56 DMD patients who underwent posterior spinal fusion for scoliosis, the decline in FVC decreased from 4% per year preoperatively to 1.75% per year postoperatively ($p < 0.0001$).[127]

General physiotherapy may be helpful in preventing contractures. Maintenance of proper nutrition, with an emphasis on weight control, is important. Patients with DMD have a propensity to become overweight through a combination of inactivity, reduced energy requirements, medications, and a misguided desire to improve muscle bulk by overeating. Some authors have emphasized a high-protein (more than 80 g protein daily), low-calorie diet, aiming to achieve a body weight somewhat lower than the ideal weight in patients of a similar height and normal muscle mass.

Inspiratory muscle training (IMT) has been examined as a tool to prevent further decrease in respiratory muscle function in those with DMD, but its routine use remains controversial. Because there is loss of the protective mechanism of nitric oxide release in children with DMD, IMT could potentially be detrimental. Koessler et al. studied the effect of 2 years of IMT on a group of 27 patients with neuromuscular disease (18 DMD and 9 spinal atrophy) and showed a clear increase in PI_{max} and maximum voluntary ventilation (MVV). There was a plateau reached after 10 months of training.[128] Because there is potential for harm and no long-term studies support its use, ATS guidelines do not suggest the use of routine IMT in this group of patients.[126]

Maintenance of cough and adequate airway clearance is extremely important in attempting to prevent atelectasis and pneumonia in this patient population. A PE_{max} of at least 60 cm H_2O has been shown to be adequate to generate an effective cough in patients with DMD, while a drop below 45 cm H_2O has been associated with ineffective cough.[126,129] Once an ineffective cough is recognized there are multiple treatment modalities. The most studied technique is the use of a manual insufflator-exsufflator, which stimulates cough by providing a positive-pressure breath immediately followed by a negative-pressure exsufflation. The technique can be used on patients with or without a tracheotomy and is generally well tolerated. It has been shown to be effective in generating cough and clearing airways in children with DMD, especially once scoliosis has developed.[126]

As FVC decreases in DMD, patients begin to develop chest wall noncompliance and atelectasis, and lung volumes decline. Guidelines recommend lung volume recruitment utilizing either a self-inflating manual ventilation bag or mechanical insufflation-exsufflation devices to provide deep lung inflation once or twice daily.[125]

Respiratory tract infections are a serious complication in DMD patients and must be treated aggressively with physiotherapy, postural drainage, assisted cough techniques, and appropriate antibiotics. All patients, regardless of cough status, should receive vaccination against pneumococcal pneumonia and influenza.

In some patients, assisted ventilation is required once respiratory insufficiency or symptoms of sleep-related breathing disorders are present. Other indications include FVC <50% predicted, MIP <60 cm H_2O, awake baseline saturation <95%, or Pa_{CO_2} >45 mm Hg. Intermittent noninvasive positive-pressure ventilation (NPPV) prolongs survival, improves quality of life, and may attenuate the decline in FVC and MVV. Longer-term follow-up of DMD patients treated with noninvasive ventilation demonstrates that pulmonary function continues to deteriorate 3 to 4 years after the initiation of noninvasive ventilation, with patients requiring longer periods of ventilation and/or transition to tracheostomy with positive-pressure ventilation.[130] Once patients require the use of NPPV, the pressure should be titrated in the sleep laboratory to eliminate nocturnal apneas and hypopneas. Generally, bilevel noninvasive positive airway pressure with a backup rate should be used in those with significant daytime or nocturnal hypoventilation, and CPAP should be used primarily in those with obstructive sleep apnea without evidence of hypoventilation.[125]

There is evidence to suggest that prednisone treatment is beneficial. In a randomized, double-blind, controlled 6-month trial of prednisone in 103 boys with DMD, patients were assigned to low-dose prednisone (0.75 mg/kg per day), high-dose prednisone (1.5 mg/kg per day), or placebo. Both prednisone groups showed significant improvements in muscle strength, functional scores, and FVC at 6 months compared with placebo, but there was no difference between low- or high-dose prednisone.[131] A subsequent study found that muscle strength was greater in DMD patients taking 0.75 m/kg compared to 0.3 mg/kg of prednisone for 6 months.[132] The effect of steroid therapy on respiratory muscle function has been less clear, but a prospective cohort study involving 440 patients at 20 centers found that those on steroids for >1 year had a delay in progression to milestone events such as the age at loss of ambulation, which was

13.40 ± 0.29 years versus 10.00 ± 0.29 years in those on steroids for less than 1 month ($p < 0.001$). Age at loss of ambulation was found to predict future age at progression to FVC <1 L, suggesting that a delay in the loss of ambulation can lead to better lung function. The authors also found that those on steroids for >1 year had improved survival compared to those on steroids <1 month over a 10-year time period (9% vs. 19%; $p = 0.0501$).[133] An earlier case-control study found that steroid therapy for a mean duration of 8.2 years resulted in improved FVC, MIP, MEP, peak cough flow, and FVC compared with those not treated with prednisone.[134]

Deflazacort is a heterocyclic glucocorticoid prodrug with both anti-inflammatory and immunosuppressant effects. In a multicenter, placebo-controlled, phase 3 clinical trial in 196 children with DMD, deflazacort was compared to prednisone or placebo for 12 weeks. Even as early as 12 weeks, deflazacort led to greater improvement in muscle strength compared with placebo, and at 52 weeks muscle strength was significantly improved in the deflazacort group compared with the prednisone group.[135] In addition, there was less weight gain in those treated with deflazacort compared to prednisone (5.05 vs. 8.45 kg; $p < 0.0001$). A meta-analysis of the placebo arms from two large DMD trials compared disease progression in those on deflazacort and those on prednisone. They found that those treated with deflazacort had a lower decline in their 6-min walk distance by 28.3 m (95% CI, 5.7–50.9; $p = 0.01$) at 48 weeks.[136] Based on these data expert panels have recommended that corticosteroid therapy be used in DMD patients prior to any substantial decline. Guidelines recommend either prednisone (0.75 mg/kg/day) or deflazacort (0.9 mg/kg/day) but leave the choice of therapy to the clinician.[125]

While corticosteroid therapy may improve muscle strength, functional status, and lung function, it clearly is not a cure for DMD, and most experts believe that gene therapy will be applicable to DMD in the future as a potential cure for the disease. Traditional gene therapy is limited in DMD by the large amount of skeletal muscle, the large size of the dysmorphin gene, and patient immunity against viral vectors.[137] A more recent method of gene therapy known as exon skipping is an attractive approach because some DMD mutations result in mRNA, which causes a premature stop in translation of the dystrophin protein.

Small oligonucleotides known as phosphorodiamidate morpholino oligomers (PMOs) can be developed to bind exons and block them from being incorporated into mRNA, which allows for translation of a truncated dystrophin protein resulting in some function of the native protein.[138] Eteplirsen is a PMO that binds to exon 51 of dystrophin pre-mRNA that has been demonstrated to increase the percentage of dystrophin-positive fibers in skeletal muscle biopsy and improve 6-min walk distance by 67.3 m compared with placebo ($p < 0.0001$).[139] The investigators found that the percentage of fibers positive for dystrophin in skeletal muscle increased more with time on drug rather than in a dose-dependent manner.[139] A pooled analysis compared three eteplirsen arms to a control group with the same exon 51 mutation and found that the decline in FVC percentage in the 3 different studies (−2.79, −3.66, and −3.79%) was significantly slower compared with the control (−6.00%) over a period of 2 to 4 years.[140] Since mutations in exon 51 account for only 13% of patients with DMD, other PMOs are being developed. Golodirsen is a PMO targeting exon 53 and also has been shown to increase dystrophin production in patients with DMD.[141] PMO cocktails that target multiple exons (exons 45–55) are in development and may be able to treat as many as 65% of DMD patients with in-frame and out-of-frame mutations.[142]

Despite recent pharmacologic advances, DMD remains a relentlessly progressive disease that eventually will lead to respiratory failure requiring invasive mechanical ventilation (Chapter 148). End-of-life care and plans for the use of invasive mechanical ventilation should be discussed with the family and the patient well in advance, if at all possible. While the institution of mechanical ventilation has been shown to prolong life in the appropriate setting, little is known on the effect on quality of life, and decisions must be made on an individual basis.

TABLE 84-9 Clinical Differences Between Myotonic Dystrophy 1 and 2

	Myotonic Dystrophy 1	Myotonic Dystrophy 2
Age of onset	Typically younger age	30–40
Family history	Subsequent generations worse (anticipation)	No anticipation
General appearance	Balding forehead, temporal wasting, ptosis, frequent bulbar symptoms	Rare bulbar symptoms
Muscle	Distal muscle weakness and atrophy, mytotonia of handgrip and tongue	Proximal and axial muscle weakness and atrophy, mild proximal myotonia, myalgias common
Sleep disturbances	Central and obstructive sleep apnea	Central sleep apnea
Central nervous system	Daytime sleepiness ubiquitous, concentration problems	Daytime sleepiness common, frequent hearing impairment

Myotonic Dystrophy

Myotonic dystrophy is the most common form of hereditary muscular dystrophy in adults, with an estimated incidence of 1 in 2500 people. It is now recognized that there are two forms of myotonic dystrophy (Table 84-9). Myotonic dystrophies are progressive autosomal dominant diseases caused by an abnormal expansion of an unstable nucleotide repeat located in the noncoding region of the DMPK gene for type 1 and CNBP in type 2 myotonic dystrophy.[143] Increased number of repeats present in type 1 disease correlates with increased severity of disease and earlier onset. The repeats in type 1 myotonic dystrophy increase in number with subsequent generations (called anticipation) which results in earlier onset and more severe phenotype in subsequent generations.[143] Anticipation has not been reported to occur in type 2 myotonic dystrophy. Type 1 leads to weakness in distal muscle groups, facial muscles, and ankle dorsiflexors, while type 2 myotonic dystrophy typically exhibits proximal muscle weakness with muscle pain being a common feature. Median survival has been reported to be 53.2 years, and the most common causes of death were respiratory related (43%), cardiovascular cause (especially arrhythmias) (11%), and malignancies (11%).[144] Symptoms usually present during adolescence and in early adulthood, although the syndrome may be recognized as early as infancy.[145]

Respiratory muscle weakness is common and can be severe, despite mild limb muscle weakness. Myotonia (delayed muscle relaxation) of the respiratory muscles contributes to an increased work of breathing by increasing inspiratory impedance. Studies have suggested that the presence of a chaotic breathing pattern may explain the higher prevalence of chronic hypercapnia in patients with myotonic dystrophy than in patients with other forms of muscular dystrophy. Support for these findings came from studies that showed abnormal ventilatory responses to hypercapnic challenges in patients with myotonic dystrophy. However, studies that have used mouth occlusion pressures ($P_{0.1}$) have revealed normal or supranormal responses in $P_{0.1}$ in patients with myotonic dystrophy compared with controls.[146] These data seem to suggest that prior studies showing hypercapnia in patients with myotonic dystrophy underestimated the severity of respiratory muscle weakness by itself as a limitation in the ability to mount a normal ventilatory response. The chaotic breathing pattern observed in some patients with myotonic dystrophy has been suggested to be related to disordered afferent information from diseased muscle spindles.

As in other neuromuscular diseases affecting the lung, regular testing to include measurement of FVC and MIP/MEP, and cough peak flow, is recommended at 6-month intervals.[147] The guidelines stress all patients should be screened for sleep-disordered breathing with overnight polysomnography at least once (particularly those with MIP <60 cm H_2O or FVC $<50\%$ predicted) and then have recurrent overnight pulse oximetry/transcutaneous capnometry every 6 months or repeat polysomnography as indicated. Daytime blood gas analysis is necessary, especially in the setting of respiratory muscle weakness to screen for daytime hypercapnia ($Pa_{CO_2} >45$ mm Hg).

Patients with myotonic dystrophy are particularly susceptible to development of respiratory failure with general anesthesia and sedatives, and postoperative respiratory monitoring is essential if surgery or the use of these agents is required. Extubation should be done in a recovery room or intensive care unit due to side effects of anesthesia in DM1. Pharyngeal and laryngeal dysfunction increases the risk of aspiration, and patients should be referred to specialists in dysphagia evaluation if there is suspicion as suggested by cough associated with eating, drooling, aspiration, or dysphonia.[147] Sleep-related breathing disturbances are common and may include both central and obstructive forms of sleep apnea. Nocturnal positive-pressure ventilation is indicated when FVC is $<50\%$ predicted, sleep-disordered breathing is present on polysomnography, or daytime hypercapnia occurs.[147]

Facioscapulohumeral Dystrophy

Other inherited adult muscular dystrophies are facioscapulohumeral dystrophy (FSH) and limb-girdle dystrophy. FSH is an autosomal dominant dystrophy that primarily affects muscles of the face and the proximal portion of the upper extremities. FVC is significantly reduced in patients with FSH, although facial weakness complicates spirometric assessment. In 20% of patients with FSH, the disease affects pelvic girdle and trunk muscles, sometimes impairing respiratory function.

Limb-Girdle Dystrophy

Limb-girdle dystrophy is a heterogeneous group of autosomal dominant recessive disorders. The disease usually becomes evident in the second or third decade of life. Several case reports have documented the development of chronic hypercapnia in patients with limb-girdle dystrophy who have severe diaphragm weakness or bilateral diaphragm paralysis as the basis for hypercapnia. However, not all patients with limb-girdle dystrophy develop hypercapnia. Most patients have moderate respiratory muscle weakness with normal gas exchange.

Acid Maltase Deficiency (Pompe Disease)

Two metabolic myopathies, acid maltase deficiency and mitochondrial myopathy, have received attention as potential causes of respiratory failure. Acid maltase deficiency is a type I glycogen storage disease due to the deficiency of the lysosomal enzyme responsible for hydrolysis of both the α 1–4 and α 1–6 linkages of glycogen. The disease presents in three clinical forms: infantile, childhood, and adult. In adult-onset disease, onset usually occurs after 20 years of age and presents with progressive proximal muscle weakness. The diagnosis may be difficult to establish in some patients, as respiratory failure or sleep-related complaints, secondary to respiratory deterioration during REM sleep, may be the initial presentation. Diagnostic studies include elevated serum muscle enzymes; myopathic changes on electromyography, and vacuoles filled with lysosomal breakdown products on muscle biopsy. Enzyme replacement therapy with recombinant human acid maltase, alglucosidase alfa, is now available for both early- and late-onset disease. In a study of 99 patients with late-onset Pompe disease, treated for 78 weeks with biweekly infusions of alglucosidase, the investigators found an improvement in FVC and 6-min walk distance.[148]

Mitochondrial Myopathy

Mitochondrial myopathy represents a heterogeneous group of disorders that affect mitochondrial function and may present as complex multisystem disorders with brain and striated skeletal muscle being the predominant organs affected: (1) Kearns-Sayre syndrome; (2) myoclonic epilepsy, "ragged red fibers," and mitochondrial myopathy; and (3) encephalopathy, lactic acidosis, and stroke-like episodes. The clinical manifestations may be broad and include myalgia and exercise intolerance, proximal muscle weakness, and external ophthalmoplegia with unexplained respiratory failure. All three disorders are characterized by hypoventilation and depressed responses to hypoxia and hypercapnia and, in some cases, unexplained respiratory failure. Skeletal muscle biopsy establishes the diagnosis of mitochondrial myopathy by showing "ragged red fibers," which are accumulations of mitochondria identified with modified trichrome staining. Treatment is supportive. Once identified, patients should be cautioned regarding the use of sedatives, and special attention is required when sedation or surgery is planned.

TREATMENT

Principles in management of respiratory dysfunction in patients with neuromuscular disease include (1) preventative therapies designed to minimize the impact of impaired secretion clearance, alveolar hypoventilation on gas exchange, and lower respiratory tract infections, and (2) stabilization of patients who develop acute or chronic respiratory failure. Because patients with neuromuscular disease usually have nonpulmonary symptoms and signs before the onset of respiratory problems, preventive actions can be taken to preserve their respiratory status.

In neuromuscular disorders causing bulbar dysfunction, swallowing precautions and airway control measures are required. With advanced bulbar symptoms, upper-airway control with a cuffed tracheostomy tube may be needed to protect the airway and facilitate suction of lower respiratory tract secretions, averting atelectasis and pneumonia. In patients with impaired cough, assisted coughing (e.g., ancillary hand thrust in the substernal location to increase intrathoracic pressure and expel secretions mouthward) may be helpful, along with posture drainage and the use of incentive spirometry. Treatment modalities used for treating pulmonary complications of neuromuscular disease include respiratory muscle training, mechanical ventilation (invasive and noninvasive), and glossopharyngeal breathing.

■ Diaphragmatic Pacing

To increase independence from mechanical ventilation, diaphragmatic pacing may be a treatment option in selected patients. Although phrenic nerve pacing by external stimulation has been well documented since the late 1940s, long-term phrenic nerve stimulation did not become a reality until a small implantable electrode and receiver were developed in the late 1960s.

Diaphragmatic pacing consists of a radiofrequency transmitter and an antenna that discharges stimulatory signals to a receiver that when activated by radiofrequency waves, transmits electrical impulses in an electrode placed over the phrenic nerve. Surgery is required to implant the electrodes and receiver. Electrode implantation around the phrenic nerves can be achieved by a cervical or thoracic approach; however, the thoracic approach is preferred to ensure stimulation of

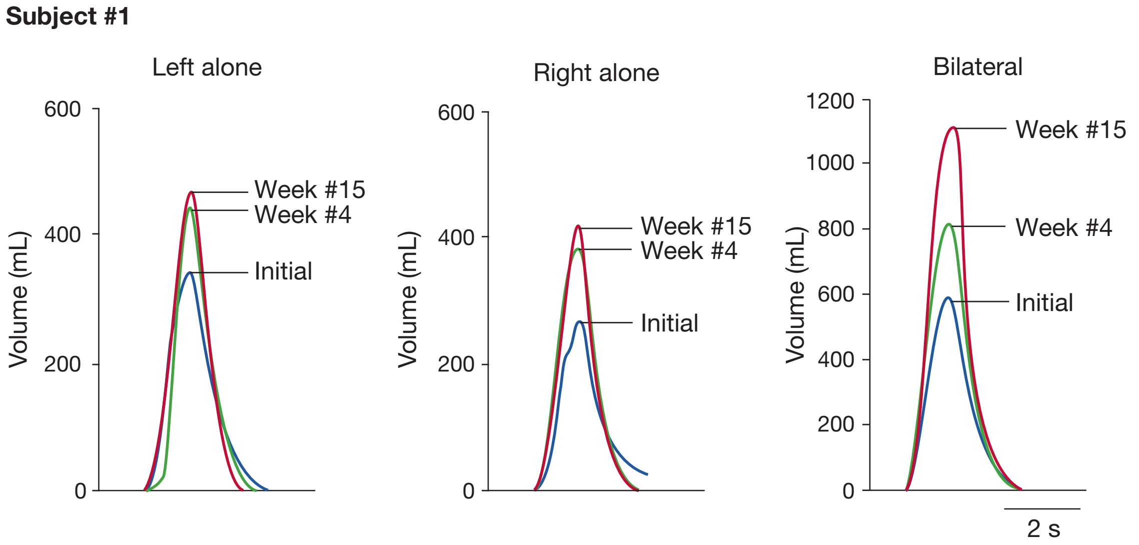

Figure 84-14 Reconditioning of the diaphragm as evidenced by increased inspired volumes initially, at 4, and 15 weeks postoperatively after left and right hemidiaphragm and bilateral diaphragm contraction via diaphragmatic electrode pacing. *(Data from DiMarco AF, Onders RP, Ignagni A, et al. Phrenic nerve pacing via intramuscular diaphragm electrodes in tetraplegic subjects. Chest. 2005;127(2):671–678.)*

all phrenic nerve roots while avoiding the brachial plexus. The subcutaneous receiver is usually placed in the lower anterolateral rib cage to allow it to be superficial, but in an area where soft-tissue movement is limited.[149–151] The subject must have intact phrenic nerves in order for the procedure to be successful, and the phrenic nerve is typically assessed by measuring conduction times along the nerve. Electric stimulation is applied transcutaneously in the neck region and surface diaphragm EMG is monitored. The nerve conduction time can then be calculated; normal is approximately 7.5 to 9 ms.

Diaphragmatic pacing has a number of potential limitations, including its high cost, the potential to fail abruptly, the development of upper-airway obstruction, and the induction of diaphragm fatigue. On the other hand, successful implantation allows patients to be independent from ventilatory support for prolonged periods, and to speak more freely.

While implantation of phrenic nerve electrodes has become an accepted procedure, there is ongoing research into placing diaphragmatic electrodes laparoscopically, and the technique has been performed successfully in a few centers.[152] This approach would be less invasive and more cost efficient, and would have less morbidity than the current approach. Two electrodes are placed on each hemidiaphragm near the motor points of the phrenic nerve. Initially, removable suction electrodes are placed until a location is found that induces maximal contraction of the diaphragm and a large intra-abdominal pressure change by both twitch and high-frequency stimulation. The wires are then brought through the skin and connected to the stimulator. Because patients on chronic mechanical ventilation develop diaphragm atrophy,[153] a reconditioning period is required before the restoration of maximal diaphragm function.

Figure 84-14 shows the tidal volume generated gradually increased with time as the muscle is reconditioned and the tidal volume is greatest with bilateral stimulation. In a case series using this technique, 3 of 5 subjects achieved independence from mechanical ventilation. One other was free of mechanical ventilation for 20 h per day, and the other did not have activation of the diaphragm. This individual most likely did not have intact phrenic nerves.[150]

Intact phrenic nerves are required for successful intramuscular diaphragm pacing as evidenced by animal studies showing no diaphragm activation with intra-muscular pacing after transection of the phrenic nerves. This probably occurs because the mechanism of intramuscular pacing is by stimulation of phrenic nerve roots in the diaphragm.

Because the intercostal muscles are capable of contributing up to 35% to 40% of the vital capacity they should be able to liberate a subject from mechanical ventilation if stimulated through pacing. In animal models, stimulation of the ventral surface of T1–T3 resulted in maximal inspired volumes, and when combined with bilateral phrenic nerve pacing resulted in tidal volumes that approached the inspiratory capacity. However, when applied to a group of spinal cord injury patients with phrenic nerve damage; very little volumes were generated with stimulation of the ventral aspect of T1–T3, and subjects were unable to breathe without mechanical ventilation for short time periods (20 min to 2.45 h). This discrepancy between animal and human studies may be secondary to the different shape of the human thoracic cage or the reduction in rib cage and lung compliance in those with tetraplegia. Additionally, stimulation of T1–T3 resulted in the movement of several nonrespiratory muscles, which led to hypertrophy of the upper trunk musculature.[150] A follow-up trial that combined intercostal pacing with unilateral diaphragm pacing in a small group of patients had unilateral phrenic nerve injuries in addition to spinal cord injury. All these patients were able to have significant periods of time free from mechanical ventilation.[154] The main limitations to this approach remain contraction of nonrespiratory muscles, which makes the process metabolically inefficient and can lead to uncontrollable muscle activity.

Those who appear to benefit from diaphragmatic pacing are ventilator-dependent patients following high cervical cord injury. Approximately one-third of patients with high cervical spinal cord injuries may be suitable for this type of treatment. Although short-term improvements are noted in terms of ventilator independence and improvement in functional status, no long-term studies demonstrating efficacy have been published to date.

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PART 12

Occupational and Environmental Disorders

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CHAPTER 85

Asbestos-Related Lung Disease

William N. Rom
Jun-Chieh J. Tsay

INTRODUCTION

Asbestos is a fibrous hydrated magnesium silicate with commercial use due to its indestructible nature, fire resistance, and easy transformability into industrial products from yarn to insulation block to brakes. Asbestos fibers are generally defined as long, thin fibers with a length-to-width ratio (aspect ratio) of 3:1. There are six commercial forms of asbestos: chrysotile, crocidolite, amosite, anthophyllite, actinolite, and tremolite. Most of the asbestos used in the United States has been chrysotile, a serpentine form of asbestos. Other asbestos types are the amphiboles—notably amosite, mined in South Africa, and crocidolite, mined in the Cape Province of South Africa and in Western Australia. These asbestos fiber types have strikingly different physical characteristics: chrysotile tends to be wavy and long and occurs in bundles; crocidolite is needle-shaped with many long fibers; and amosite is similar to crocidolite but generally thicker. Asbestos fibers accumulate in the interstitium of the lung and are coated by iron and hemosiderin in a beaded, clubbed fashion referred to as ferruginous or asbestos bodies.

Initially, asbestos was widely used in fireproof textiles and later as insulation for boilers and pipes. Thereafter, asbestos was used in yarn, felt, paper, millboard, shingles, paints, cloth, tape, filters, wire insulation, cement pipes for potable water, gaskets, friction materials including brake linings, and roofing and floor products. Asbestos was extensively used for ship construction during World War II. Occupational exposure to asbestos in the United States now primarily occurs during maintenance activities or remediation of buildings containing asbestos. The Occupational Safety and Health Administration (OSHA) has estimated that 1.3 million workers in general industry continue to be exposed to asbestos, and the National Institute for Occupational Safety and Health (NIOSH) estimates that 44,000 mine workers might be exposed to asbestos fibers or amphibole cleavage fragments, especially tremolite. Although the European Union and 55 countries have banned imports and use of asbestos, approximately 2 million tons are used worldwide. Asbestos is mined in Eastern Europe and Asia where asbestos products are manufactured for use in insulation, roofing, and construction. Globalization has resulted in export of asbestos to developing countries for manufacture and export to other developing countries with concomitant increase in asbestosis and mesothelioma.[1] In 2004 the WHO estimated 107,000 global deaths from asbestos-related diseases. However, current estimate suggest that asbestos causes 255,000 deaths annually (3500 asbestosis, 30,000 mesothelioma, and 184,000 lung cancer), and an estimated $410 billion loss due to occupational cancer and $340 billion due to asbestos exposure at work.[2]

TYPES OF EXPOSURE

Primary asbestos exposures occurred in miners and millers. Secondary exposures occurred in manufacturing plants using asbestos in the production of textiles, friction materials, vinyl tiles, and insulation materials. Epidemiologic studies focused on cohorts in these plants, since asbestos fiber type was often specified, and dust measurements were obtained. These studies demonstrated that intensity and duration of exposure play an important role in the prevalence of asbestos-related disease. Common trades with asbestos exposure include sheet metal work, plumbing, pipefitting, insulation, railroad and utility power plant work, and school or building custodians. Prevalence of radiographic opacities in asbestos insulation workers exposed prior to the 1970s reached 50% in long-term workers and was approximately 15% in sheet metal workers. There is a long latency period between exposure and manifestation of asbestos-related disease, making identification and intervention difficult.

Although measurements of airborne asbestos fibers were seldom made, the most significant exposures appear to have occurred in the construction trades. These trades included asbestos insulators (called "laggers" in the United Kingdom), who mixed asbestos cement on site to insulate joints and elbows on pipes; boilermakers and sheet metal workers, who worked adjacent to the asbestos workers; and electricians, carpenters, plumbers, and others who worked in the vicinity of work requiring asbestos exposure. These exposures were mainly to chrysotile asbestos, since practically no crocidolite was imported into the United States, and only small amounts of amosite were admixed. Asbestos workers and other construction workers wore their asbestos-covered clothes home, exposing their wives and children when greeting them or while washing their garments. These household contact exposures are often referred to as *indirect exposures,* and those exposed while working near asbestos workers are called *bystander exposures.*

Current estimates suggest 35,000 U.S. lung cancer deaths per year are related to asbestos exposure, while the National Occupational Respiratory Mortality System, which has been tracking asbestosis and mesothelioma deaths since 1968, showed that death rates have peaked at 1400 death/year and 3100 death/year, respectively. Asbestosis is the cause of about 11% of deaths in asbestos workers; interestingly, the most important determinant is radiographic profusion score, with rates increasing from 2.4% to 10.98% and 35.4% with profusion category increasing from 1 to 3.[3] Profusion of irregular opacities is categorized into four levels ranging from 0 to 3, with 12 subcategories (0/0 to 0/1 to 1/0 up to 3/4) for the most dense fibrosis according to a scale agreed to by the International Labor Organization. Dyspnea, a low FVC, and/or physical examination findings typical of interstitial fibrosis (rales, clubbing, or cyanosis) raise the risk of death from asbestosis two- to sixfold.[3]

NONMALIGNANT PLEURAL MANIFESTATIONS

Pleural disease is the most common manifestation of asbestos exposure. The nonmalignant manifestations of asbestos exposure in the pleural space include circumscribed pleural plaques, diffuse pleural thickening, rounded atelectasis, and asbestos-related pleural effusions.[4]

Pleural Plaques

Important pathogenetic and clinical features of pleural plaques are discussed below.

Pathology

Pleural plaques are the most common manifestation of asbestos exposure. They are focal, irregular, raised white lesions found on the parietal and, rarely, the visceral pleura. The plaques may be small or extensive; commonly they occur in the lateral and posterior midlung zones, where they may follow rib contours and the diaphragm. They commonly enter lobar fissures and can invade the mediastinum or pericardium; rarely do they invade the apices or costophrenic sulci. Histologically, asbestos-related pleural plaques are characterized by a paucity of cells, extensive collagen fibrils arranged in a basket-weave pattern, and a thin covering of mesothelial cells. The parietal pleura is uniformly involved, with minimal thickening of the visceral pleura. The two pleural surfaces are free of adhesions. Pleural calcifications frequently develop in these fibrohyaline lesions as the length of time from exposure increases. Exposure to asbestos is the most frequent cause of pleural plaques.

Pathogenesis

Two theories have been proposed for the pathogenesis of pleural plaques. The most plausible is based on the direct effects of fibers that reach the pleural space. Asbestos fibers—the short, thin ones in particular—have been shown to be transported by subpleural lymphatics to the pleural space. In the pleural space, it is believed that they scratch, injure, and irritate the pleural surface, leading to hemorrhage, inflammation, and eventually fibrosis. The plaques are submesothelial. Mesothelial cells appear to play an important role in the pathogenesis of these lesions: they internalize asbestos fibers via an integrin receptor that recognizes vitronectin; in vitro pleural mesothelial cells also can synthesize collagens (types I, III, and IV), elastin, laminin, and fibronectin. In keeping with the submesothelial location of the plaques, cultured mesothelial cells can organize these macromolecular connective tissue components into an assemblage of extracellular matrix that is limited to the base of the cell.

Epidemiology and Natural History

Hyaline and calcified pleural plaques have been noted to be an index of exposure to asbestos. In shipyard workers, the frequency of pleural abnormalities was approximately 10 times that of parenchymal disease. The greater the exposure, the more likely the worker was to have extensive calcified pleural plaques as well as parenchymal fibrosis. The intensity of the exposure has been noted to be an important determinant of the prevalence of these abnormalities. For example, among British shipyard workers, 36% of those with continuous exposure as "laggers" developed pleural plaques, while extensive pleural thickening and pulmonary fibrosis were seen in 5% and 7%, respectively. In contrast, those with intermittent exposure had a 6% prevalence of plaques and no pulmonary fibrosis. On average, the latency time for the appearance of plaques is 30 years, but the time can vary greatly. This variation can also be appreciated from studies of British shipyard workers in whom the prevalence of pleural plaques increased from 17% at 10 years after the first exposure to 70% at 30 years among those with continuous exposure; for those with intermittent exposures, the prevalence increased from 1% at 10 years to 16% at 30 years.

All asbestos fibers are equally capable of inducing pleural plaques: Pleural plaques are found in U.S. insulators or shipyard workers exposed to chrysotile or amosite, as well as miners in Western Australia who were exposed to crocidolite.

In addition to occupational exposures, environmental, domestic and residential exposures have been implicated in the production of pleural plaques. Evidence for the latter is the remarkably high rates of pleural calcification (up to 45%) in some rural areas of Greece, Corsica, Cyprus, and Turkey where outcroppings of tremolite asbestos have been used to whitewash houses. Pleural plaques have been noted from environmental exposure to tremolite asbestos fibers contaminating vermiculite mining and milling in Libby, Montana.

Clinical and Physiologic Features

In the absence of concomitant asbestosis or obliteration of the costophrenic angle, pleural plaques are usually asymptomatic. Most often they are incidental findings on chest radiographs. In addition, they do not cause significant abnormalities such as pleural rubs, rales, or rhonchi on auscultation of the chest.

Pleural disease has been recognized as a cause of reduced pulmonary function since the 1970s. Among 998 shipyard workers in Groton, Connecticut, who had 15 or more years of asbestos exposure, 17% of those with pleural changes had a forced vital capacity (FVC) under 80% of predicted; for those with normal chest radiographs, 9% had decreased vital capacities. In those with normal chest radiographs, the values were significantly reduced only among smokers and ex-smokers. Recent studies that have applied stepwise regression analysis to data from insulation workers have disclosed a significant inverse relationship between FVC and an integrative pleural index for patients with circumscribed pleural plaques.[5] Even among those with pleuroparenchymal abnormalities, the pleural index was found to make a significant contribution to decrements in FVC, independent of that due to parenchymal abnormalities.

In nonsmoking asbestos workers with circumscribed or diaphragmatic pleural plaques, flow rates (FEV_1, $FEF_{25\%-75\%}$) have been reported to be reduced. In an epidemiologic study of 1211 sheet metal workers, pleural fibrosis was detected in 334 and was related to age, duration of exposure, pack-years of smoking, and the presence and degree of interstitial fibrosis.[6] After controlling for these confounders, multivariate regression analysis found that both plaques and diffuse thickening were independently associated with decrements in FVC, but not with decrements in the FEV_1/FVC ratio. Furthermore, diffuse pleural thickening was associated with a decrement in FVC twice as great as that seen with circumscribed pleural plaques. After confounding variables such as age, height, smoking status, and the presence of parenchymal abnormality as assessed by chest radiography and gallium scintigraphy were taken into account, there was a significant decrease in FEV_1 and FVC (222 and 402 mL, respectively) among workers who had pleural plaques or diffuse pleural fibrosis.[6] Meta-analyses of 20 studies estimated a summary effect of the decrements in percent predicted forced vital capacity (FVC 4.09% predicted; 95% confidence interval [CI], 2.31–5.86) and forced expiratory volume in 1 s (FEV_1 1.99% predicted; 95% CI, 0.22–3.77) associated with the presence of pleural plaques.[7]

Radiographic Features

The visualization of plaques on digital chest radiography depends on their thickness, their location, and the orientation of the radiographic beam.[8] As a result, they can be viewed in profile along the lateral chest wall or on en face with a rolled or holly-leaf pattern, especially if calcified (Fig. 85-1). Only a modest proportion of plaques detected at autopsy can be seen on digital chest radiography. Computed tomographic (CT) scanning increases plaque detection (increase in sensitivity and specificity).

The CT scan can recognize plaques at a much earlier and less well-defined state than digital chest radiography. The CT scan is particularly useful for perivertebral and pericardiac plaques, and high-resolution CT scanning (HRCT) helps to establish the presence of diaphragmatic lesions. In all cases, the CT scan can help to differentiate plaques from extrapleural fat pads and can detect concomitant parenchymal abnormalities that may be difficult or impossible to see on the PA chest radiograph.

Diagnosis

Pleural plaques due to asbestos exposure are usually bilateral (80% of the time), whereas unilateral pleural plaques may be due to trauma, previous tuberculosis, or, rarely, other causes, such as

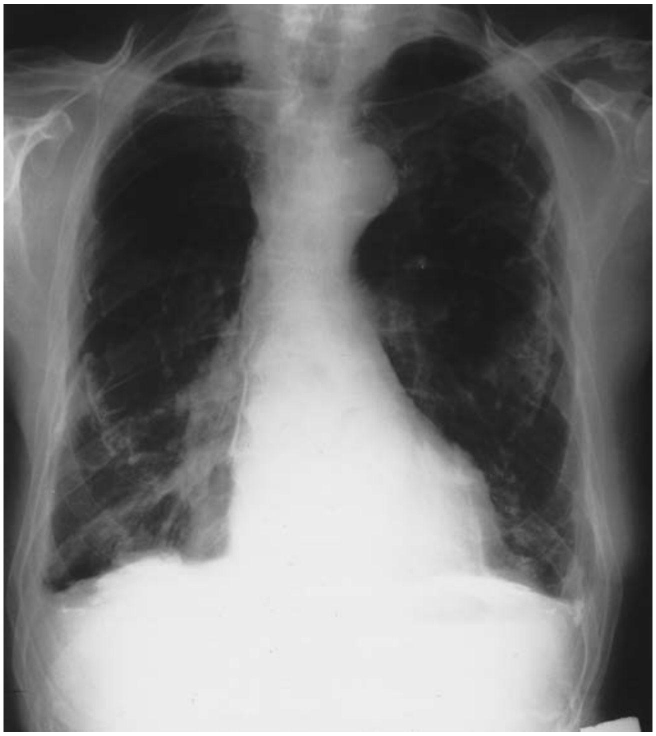

Figure 85-1 Posteroanterior (PA) chest radiograph of a 75-year-old man who worked in a shipyard during World War II insulating ships. The radiograph shows bilateral calcified pleural plaques en face and on top of the diaphragm. The pleura is diffusely thickened bilaterally and the costophrenic angles are blunted. Mediastinal pleural calcification is present on the right. *(Reproduced with permission from Dr. Timothy Harkin.)*

collagen vascular disease. The lesions are usually stable and remain the same size for months. This helps to differentiate plaques from pleural tumors. Histologic tissue examination is not necessary for diagnosis the vast majority of the time.

Treatment

No specific treatment is required for asbestos pleural plaques. Since they are markers of asbestos exposure and identify patients at risk for other asbestos-related disorders, medical surveillance, including periodic CT scans and blood biomarkers, is recommended.[9]

■ Diffuse Pleural Thickening

Pleural thickening, another common manifestation of asbestos exposure, is discussed below.

Pathology

Pleural fibrosis in persons who have been exposed to asbestos has been well described. The fibrotic responses can be localized or diffuse and either unilateral or bilateral. Macroscopically, the lesions vary in thickness from a whitish discoloration of the lung surface to a thick white peel that can encase significant pulmonary structures. Diffuse pleural thickening is most often seen as a continuous sheet that is 5 to 10 cm in craniocaudal extent, and in 90% of patients it affects the costophrenic angle. Interlobar and interlobular fissures are commonly involved. Whereas pleural plaques predominantly affect the parietal pleura, diffuse pleural fibrosis occurs most commonly as part of a fibrotic process of the visceral pleura and subadjacent interstitium.

Pathogenesis

Diffuse pleural thickening has been proposed to result from three different mechanisms. The first is the confluence of large pleural plaques, and the second is the extension of subpleural fibrosis to the visceral pleura. The most common pathogenic mechanism is thought to be the fibrotic resolution of a benign pleural effusion, producing diffuse pleural thickening. The importance of this mechanism is highlighted by the finding that about one-third of patients with diffuse pleural thickening have had a prior benign asbestos-related pleural effusion diagnosed by thoracentesis or on serial chest radiographs. The pathogenic mechanisms differentiating diffuse pleural thickening from circumscribed pleural plaques are not well defined. However, the fundamental mechanism of asbestos fibers activating macrophages and mesothelial cells to release growth factors and stimulate collagen formation is likely to be important in both. In the case of diffuse pleural responses, these fibers are deposited mainly in the parenchymal subpleural areas of the lung.

Clinical and Physiological Manifestations

Diffuse pleural fibrosis most often occurs long after short-term heavy exposure to asbestos. When mild, diffuse pleural fibrosis can be asymptomatic and discovered as an incidental finding on a chest radiograph obtained for another reason. The diffuse nature of the lesion, however, may lead to pulmonary symptoms, including dyspnea on exertion, chronic dry cough, and chest pain. As noted earlier, diffuse pleural thickening can cause a restrictive physiologic abnormality. The degree of physiologic abnormality varies with the degree of fibrotic response. On rare occasions, in patients with severe bilateral disease, respiratory insufficiency has occurred. Diffuse pleural fibrosis can increase in severity over time.

Radiographic Features

On the routine chest radiograph, diffuse pleural fibrosis presents as a continuous pleural opacity usually blunting the costophrenic angle. It can be unilateral or bilateral and seen in the presence or absence of concomitant asbestosis and pleural calcifications. Rarely, the pleural fibrosis will produce a fibrotic pseudotumor with a pleural basis (rounded atelectasis) (see below). CT scanning is particularly useful in delineating the relationship between diffuse fibrosis and other pleural abnormalities and differentiating pleural fibrosis from fat deposits.

Diagnosis

The diagnosis of diffuse pleural fibrosis is usually based on the clinical presentation and chest radiograph. The lesions of diffuse pleural fibrosis are not unique to asbestos-exposed persons and can represent old inflammatory reactions from tuberculosis, thoracic surgery, or hemorrhagic chest trauma. Differentiation among these causes is frequently based on a careful clinical history. Radiographic patterns are also helpful since bilateral interstitial changes in the lower lung zones in association with pleural plaques or calcifications strongly support a diagnosis of asbestos exposure. A biopsy may be required when the thoracic lesion is progressing or when malignancy is in the differential.

Treatment

As seen with circumscribed pleural plaques, there are no specific therapies for asbestos-related diffuse pleural fibrosis. Medical surveillance is required to detect disease progression, lung cancer, and mesothelioma.

■ Rounded Atelectasis

Rounded atelectasis is a rare complication of asbestos-induced pleural disease. It is caused by scarring of the visceral and parietal pleura and the adjacent lung, with the pleural reaction folding over on itself. The pleural surfaces then fuse to one another, trapping the underlying lung and leading to atelectasis. As a result of this alteration, a mass lesion that mimics lung cancer can be seen on the PA chest radiograph (Fig. 85-2). This lesion is most easily appreciated to be a pseudotumor with use of CT scanning. HRCT can noninvasively demonstrate continuity to areas of diffuse pleural thickening, evidence of volume loss in the adjacent lung, or a characteristic comet tail of vessels and bronchi sweeping into a wedge-shaped mass (Fig. 85-2).

CT scanning can also demonstrate stability over time (from months to years), which supports the diagnosis of a benign lesion, and pleural plaques or parenchymal changes, which support a diagnosis of asbestos exposure. In one clinical series of 74 patients with rounded atelectasis, 64 had significant asbestos exposure, and the lingula or right middle lobe was affected in 49 of the patients.[10]

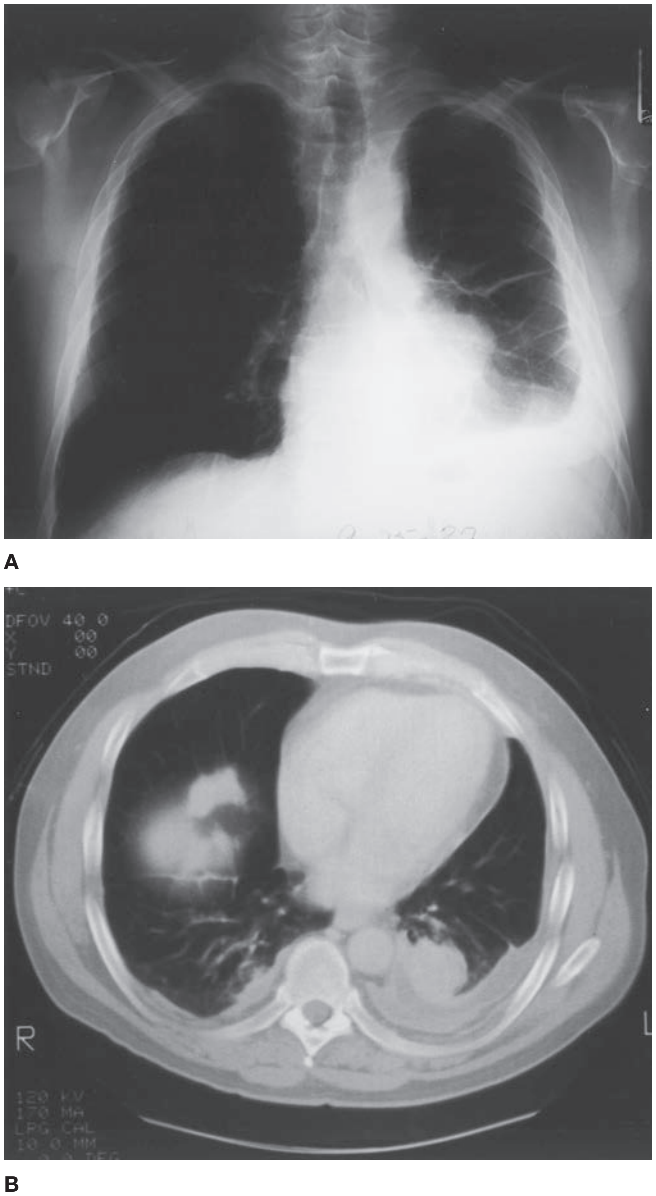

Figure 85-2 Rounded atelectasis and other pleural abnormalities in an asbestos worker. The chest radiograph (**A**) shows a left-sided pleural effusion, bilateral pleural thickening, greater on the left than on the right, and a mass in the left midlung field. HRCT (**B**) demonstrates the mass to be rounded atelectasis, with bronchovascular structures entering the trapped lung. It also reveals the pleural effusion, bilateral pleural thickening, and pleural plaques, one of which is on the right hemidiaphragm. *(Reproduced with permission from William M. Rom, MD, MPH.)*

HRCT scans localized most cases of rounded atelectasis to the lower, posterior portion of the lung; moreover, in one-third of the patients, the lesions were multiple. In most patients, rounded atelectasis occurs suddenly on a background of only plaques or a normal chest radiograph. In others, a slowly increasing pleural effusion may precede its appearance.

■ Acute Benign Pleural Effusions

Acute benign pleural effusions are common pleural manifestations in asbestos-exposed persons between 20 and 40 years of age. The latency period for these effusions is shorter than for pleural plaques, malignant mesotheliomas, or pulmonary malignancies. Benign pleural effusions generally occur earlier after exposure than do other asbestos-related processes. The latency is shorter—for example, 12 to 15 years rather than >20 years after the first asbestos exposure compared to pleural plaques or asbestosis.

About 50% of the patients with acute benign pleural effusions are asymptomatic. When patients are symptomatic, the manifestations may be those of a pleurisy (chest pain, chest tightness, dyspnea, cough, and fever). Physical examination reveals the signs of a pleural effusion; a pleural friction rub may be heard. The effusions are exudative and often bloody; glucose concentrations are normal. Mesothelial cells in effusions are found in about 50% of patients. In about 25% of patients, the fluid is eosinophilic. Rarely are asbestos bodies found even though they may be present in underlying lung tissue.

The designation “benign” refers to the lack of evidence of malignancy. The collections may persist for 6 months or more. They frequently clear spontaneously, only to recur on the contralateral side. However, a benign asbestos pleural effusion is a risk factor for the development of pleural thickening, especially diffuse pleural fibrosis. The diagnosis of acute benign pleural effusions is one of exclusion. Thoracentesis is essential. Pleural biopsy is frequently required to rule out other causes of pleural effusions, including mesothelioma. The usual pathologic findings are a chronic fibrous pleurisy with minimal cellularity. Diffuse malignant pleural mesothelioma invariably presents as a pleural effusion, but pleural mass lesions are usually seen on CT scan, which are absent in benign asbestos effusions.

ASBESTOSIS

Important pathologic and clinical aspects of asbestosis are discussed below.

■ Pathology

Asbestosis is the interstitial pneumonitis and fibrosis caused by exposure to asbestos fibers.[4] Early lesions are characterized by discrete areas of fibrosis in the walls of respiratory bronchioles. The septa adjacent to the respiratory bronchioles are often thickened, and the fibrosis sometimes appears to spread outward from the bronchioles. In addition to the peribronchiolar fibrosis, there is an intense peribronchiolar cellular reaction that may narrow and obstruct the airway lumen. Macrophage accumulation is a prominent feature of this cellularity. Proliferation of type II alveolar epithelial cells is enhanced. The interstitium may contain collections of lymphocytes; smooth muscle proliferation may be prominent in areas of remodeling; and buds of loose connective tissue may be seen within the alveoli (Fig. 85-3).[11] Initially, the disease usually involves first-order bronchioles; subsequently, second- and third-order bronchioles are affected. As the disease progresses, the fibrosis becomes diffuse, the architecture of the lung undergoes extensive remodeling, and honeycombing supervenes. In contrast to other pneumoconioses, lymph node enlargement and progressive massive fibrosis do not occur. Pathologically, the alterations seen

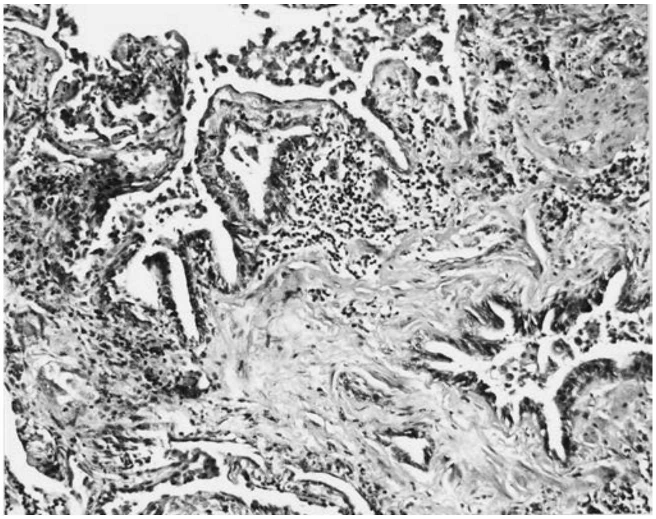

Figure 85-3 Lung tissue from a 64-year-old asbestos insulator with 46 years of exposure to asbestos while insulating pipes. His chest radiograph revealed extensive irregular opacities and bilateral pleural thickening. The figure illustrates peribronchiolar fibrosis, interstitial chronic inflammation, accumulation of macrophages in the airspaces, and proliferation of type II pneumocytes. *(Reproduced with permission from Rom WN, Travis WD, Brody AR. Cellular and molecular basis of the asbestos-related diseases. Am Rev Respir Dis. 1991;143(2):408–422.)*

in asbestosis cannot be differentiated from many other interstitial fibrotic disorders except for the presence of asbestos bodies and uncoated asbestos fibers.

■ Pathogenesis

Asbestos fibers are deposited at airway bifurcations and in respiratory bronchioles and alveoli by impaction, sedimentation, and interception. Fibers then migrate into the interstitium, in part via an uptake process involving type I alveolar epithelial cells. This causes alveolar macrophages to accumulate in the alveolar ducts, peribronchiolar interstitium, and alveolar spaces, constituting an alveolar macrophage alveolitis.[12] Following this initial macrophage alveolitis, most fibers are cleared, leaving the lungs unscarred. If clearance is incomplete, fibrosis can ensue. The degree of fibrosis in asbestosis relates, in general, to the lung dust burden. If the retained dust load is great, tissue reaction and macrophage alveolitis are proportionately more intense, greater injury occurs, and chronic and progressive lung disease can develop.

The macrophage alveolitis that is seen in early stages of asbestosis results from monocyte recruitment from the blood and in situ macrophage replication. These cells appear to play an important role in the pathogenesis of the inflammation and fibrosis seen in this disorder. Morphologically, they express an activated phenotype characterized by cellular multinucleation and a striking increase in membrane ruffling, surface blebbing, and lysosomes and phagolysosomes.[13] These macrophages are presumably attempting to engulf and clear the asbestos fibers. This process is not uniformly successful, however. First, the fibers induce apoptosis in the cells. Although the coating of asbestos fibers to form asbestos bodies makes them less toxic, the vast majority of fibers in the lung remain uncoated. Second, the long fibers cannot be completely phagocytosed. Finally, chrysotile asbestos fibers tend to split longitudinally. This generates additional fibers that can multiply the asbestos effect even after exposure has ceased. As a result, asbestos has a prolonged residence, surprising mobility, and penetrates the interstitium of the distal lung.

These characteristics probably contribute to the pathogenesis of the disease, since—in contrast to inert particles, which can be ingested by macrophages and cleared without generating a significant response—asbestos fibers stimulate macrophages to produce a variety of important cytokines and growth factors.[14] Both asbestos and silica are phagocytosed by alveolar macrophages, which then activates them to release cytokines, growth factors, and oxidants. These include platelet-derived growth factor (PDGF); insulin-like growth factor 1 (IGF-1); transforming growth factor β; the cytokines interleukin 1β (IL-1β), tumor necrosis factor α (TNF-α), and IL-8; the matrix molecule fibronectin; oxygen free radicals; and matrix metalloproteinases.[11–15] The oxygen radicals contribute to tissue injury via direct cell cytotoxicity and lipid peroxidation of membrane components. IL-8 recruits neutrophils to sites of disease activity. PDGF, IGF-1, IL-1β, TNF-α, and fibronectin contribute to tissue fibrosis by stimulating fibroblast proliferation and chemotaxis and collagen biosynthesis.[10] In vitro exposure of mononuclear phagocytes to silica, asbestos, or coal activates transcription factors including AP-1 and NF-κB, with subsequent release of cytokines and growth factors.

Bronchoalveolar lavage (BAL) in asbestosis has demonstrated an alveolar macrophage alveolitis with a modest increase in neutrophils.[12] This neutrophilia correlates with the finding of rales on physical examination and oxygenation parameters and is apt to be more pronounced in patients with advanced disease. In patients with asbestosis, ^{67}gallium lung scans may also be positive. Clinically apparent asbestosis occurs only after a significant latent period. However, studies using BAL, CT scanning, and ^{67}gallium scanning have demonstrated that inflammatory events occur well before the onset of clinical disease. Thus, it is likely that the initial exposure induces inflammation and injury that persist through the latent or subclinical phase and develops into the clinical disease diagnosed by classic radiography and other techniques. Current concepts of the pathogenesis of the disease link inflammation and fibrosis in a causal fashion.[11]

■ Epidemiology

The prevalence of parenchymal asbestosis among asbestos workers increases as the length of employment increases. This is illustrated in an early report in which investigators analyzed the chest radiographs of 1117 New York and New Jersey asbestos insulation workers. They found asbestosis in 10% of the workers who had been employed for 10 to 19 years, in 73% of those who had worked for 20 to 29 years, and in 92% of those who had worked 40 or more years.[16] A similar dose–response relationship was found in the asbestos cement industry. Among "bystanders" (i.e., among sheet metal workers who worked in close proximity to insulation workers) the overall prevalence of asbestos-related changes was 31%, including 9% who had only pleural abnormalities and 12% who had parenchymal abnormalities.[17] Among those who had been in the trade for 40 years or more, 41.5% had radiographic signs of asbestos-related disease.

Cigarette smoking can affect the expression of asbestosis.[18] Smokers without dust exposure may have a few irregular radiographic opacities, probably representing acute or chronic bronchitis or bronchiectatic changes in the lung parenchyma. Both smokers and ex-smokers have a higher frequency of asbestos-related irregular opacities on their chest radiographs than do their nonsmoking colleagues. Smoking does not alter the expression of asbestos-induced pleural fibrosis. However, cigarette smoking may interfere with the clearance of inhaled asbestos, thereby potentiating the effects of the dust in the lung.

■ Natural History

Following asbestos exposure, asbestosis becomes evident only after an appreciable latent period. The duration of exposure and its intensity influence the prevalence of radiographically evident parenchymal pulmonary fibrosis. Because work sites around the world increasingly meet recommended control levels, high-level exposure to asbestos is now uncommon and clinical asbestosis is becoming a less severe disease that manifests after a longer latent interval. In Western Australian crocidolite workers, a median of 14 years elapsed before asbestosis was detectable radiographically (range, 2–34 years). In retired Quebec chrysotile miners and millers, the frequency of pleuroparenchymal lesions was 31%, and progression of parenchymal opacities occurred in 9.3%; progression was confined to the more heavily exposed group.[19]

One approach to the study of low-level exposure is to evaluate the outcome from short-term exposure. In such a study in an amosite asbestos factory, employment for even as little as 1 month resulted in a 20% prevalence of parenchymal opacities: one-third of the participants had pleural abnormalities after 20 years of follow-up; it is significant that both "first attacks" and progression of established radiographic abnormalities occurred 20 and more years after exposure had ceased.[20]

Radiographic asbestosis, once established, may remain static or progress. Rarely has regression been recorded. The factors that determine the outcome are poorly understood. The level and duration of exposure (i.e., cumulative exposure) appear to be prognostic factors. Progression is also considerably more common in persons who already have radiographic abnormalities. This fact provides the basis for the advice that further exposure is to be avoided once the diagnosis of parenchymal asbestosis has been made.

Clinical and Physiologic Features

Dyspnea on exertion is the earliest, most consistently reported, and frequently the most distressing symptom of asbestosis. Often dyspnea is accompanied by a persistent cough, which can be spasmodic, with sputum production. Chest tightness is not uncommon, and wheezing also can occur. In a cross-sectional survey of 816 asbestos-exposed workers using a respiratory symptoms questionnaire, cough, phlegm, wheeze, and dyspnea were inversely related to pulmonary function.[21] Cough, phlegm, and chronic bronchitis were associated with a 2% to 8% reduction in FVC and FEV_1; the reduction in these measurements was more significant with wheeze and dyspnea, which caused an 11% to 17% reduction. Similarly, the prevalence of dyspnea on the level less than one block among asbestos insulators increased in stepwise fashion from 19% in patients with category 1 chest radiographic abnormalities to 35% in patients with category 2 chest radiographs and to 49% in patients with category 3 radiographic abnormalities.[22]

Rales are a distinctive feature of asbestosis. They are usually bilateral, late to pan-inspiratory in timing, heard best at the posterior lung bases, and not cleared by coughing. They differ in quality and timing from the crackles of bronchitis, which tend to be fewer and earlier. The crackles of asbestosis appear first at the bases in the midaxillary line and tend to spread toward the posterior bases. In prevalence surveys, approximately 83% of patients with higher radiographic categories of asbestosis had bilateral rales. In a study of 42 patients with a clinical diagnosis of asbestosis, in 40 the chest radiograph showed at least 1/0 profusion of irregular opacities, 36 had rales, 36 had dyspnea, and 22 had digital clubbing.[23]

The characteristic pulmonary function changes of asbestosis are a restrictive impairment with a reduction in lung volumes (especially FVC and total lung capacity), decreased lung diffusing capacity ($D\textsc{l}_{CO}$), and arterial hypoxemia.[24] Large-airway function, as reflected in the FEV_1/FVC ratio, is generally well preserved. Among the 1117 asbestos insulators in New York and New Jersey, the frequency of an abnormal FVC increased to more than 50% as follow-up was prolonged. In a larger cohort of 2611 asbestos insulators, the FVC percent predicted decreased as the profusion of irregular opacities on the chest radiograph increased; pleural thickening exaggerated the decrease for each category of profusion. For each category of profusion, diffuse pleural thickening caused a further decrease (at least 10%) in FVC percent predicted compared with circumscribed plaques.[25]

Mild airway obstruction can also be seen in nonsmokers with asbestosis.[26] These patients usually have a restrictive pattern of lung function, increased isoflow volume, and increased upstream resistance at low lung volumes. Open lung biopsies from a limited number of these patients suggest that these obstructive findings may be due to peribronchiolar fibrosis, since they revealed peribronchiolar infiltrates with macrophages and fibrosis that extended into the adjacent interstitium. Therefore, it is not surprising that lesser grades of asbestosis can show a mixed restrictive and obstructive abnormality.

Long-term medical surveillance is recommended for all asbestos-exposed persons, especially those with radiographic abnormalities. Periodic physiologic assessments play an important role in these evaluations. Prospective assessments of asbestosis should include spirometry as most useful, and diffusing capacity to assess alveolo–capillary function.

Radiographic Features

In asbestosis, digital radiography reveals bilateral diffuse reticulonodular opacities, predominantly in the lower lung zones. The International Classification of the Radiographs of the Pneumoconioses uses the term *small irregular opacities* to describe the irregular linear shadows that develop in the lung parenchyma and obscure the normal bronchovascular branching pattern seen in disease-free lungs. This schema categorized the irregular or rounded opacities found on conventional PA chest radiographs according to size and expressed them on a 12-point scale. Category 0 was defined as a normal radiograph and category 1 as mild asbestosis. Typically, a profusion of irregular opacities at the level of 1/0 is taken as the break point between normal and abnormal.[4] Moderate asbestosis and advanced asbestosis were defined as category 2 and 3 chest radiographs, respectively. As duration from onset and intensity of exposure increase, there is an increase in prevalence and severity of asbestosis as reflected in the chest radiograph.

CT scanning has improved the sensitivity for detecting asbestos-related lesions (Fig. 85-4). It eliminates a common problem with digital chest radiographs—that is, the superimposition of pleural abnormalities over parenchymal lesions. It also enhances the attenuation discrimination for parenchymal opacities. As a result of more than 300 HRCT evaluations of persons with asbestos exposure, five HRCT features of asbestosis have been identified: (1) curvilinear subpleural lines, (2) increased intralobular septa, (3) dependent opacities, (4) parenchymal bands and interlobular core structures, and (5) honeycombing. These changes have been corroborated by histologic examination.[27] In asbestos-exposed workers, abnormal HRCT has been shown to correlate with restrictive physiologic abnormalities and abnormal diffusing capacities. HRCT is also extremely sensitive in documenting the asbestos-related pleural abnormalities discussed earlier. The presence of pleural plaques (particularly if they are bilateral) provides useful evidence that the parenchymal process is asbestos-related. Hilar node enlargement is not a feature of asbestosis, and progressive massive fibrosis also is uncommon. In a CT scanning trial for the early detection of lung cancer, a comparison was made between smokers with asbestos exposure ($n = 359$) to those without asbestos exposure ($n = 1038$).[28] Asbestos-exposed smokers had decreased FVC (76% vs. 85%; $p < 0.01$) and FEV_1 (64% vs. 85%; $p < 0.01$), and those with >20 years' asbestos exposure had a further reduction. Those with isolated pleural plaques had a significant reduction in FVC% predicted compared to those with no pleural plaques or radiographic abnormalities.

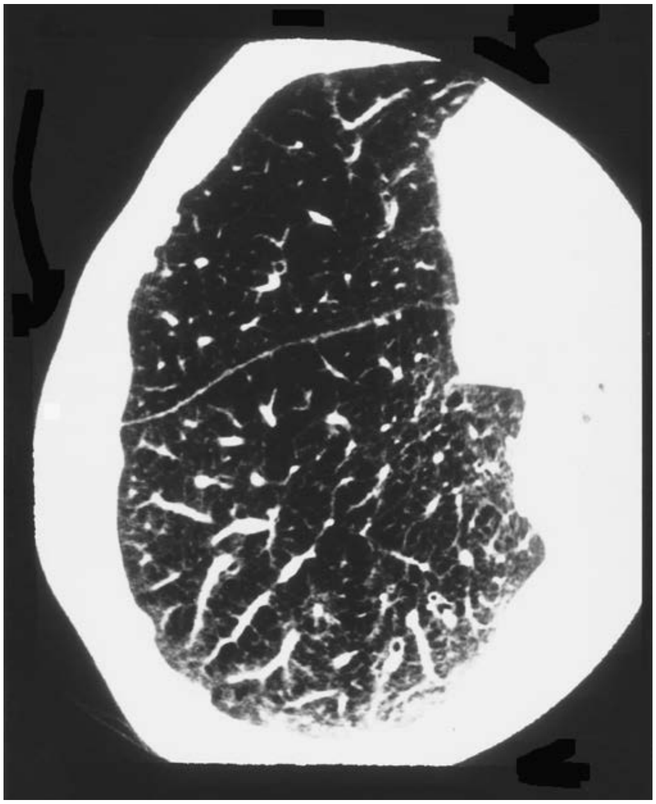

Figure 85-4 HRCT scan with irregular opacities of the lung parenchyma and interlobar structure. The PA chest radiograph was graded 2/1 on the ILO International Classification of the Radiographs of the Pneumoconioses. *(Reproduced with permission from Dr. David Naidich.)*

■ Diagnosis

Asbestosis is defined as parenchymal fibrosis, with or without pleural thickening, usually associated with dyspnea, bibasilar rales, and pulmonary function changes. To diagnose this disorder, one must establish the presence of pulmonary fibrosis and determine whether exposure has occurred of a duration and intensity sufficient to put the person at risk. A profusion of irregular opacities at the level of 1/0 is used as the break point between normal and abnormal in the evaluation of lung fields on the chest radiographs of asbestos-exposed persons. When radiographic or lung function changes are marginal, CT scanning often reveals characteristic parenchymal abnormalities as well as pleural plaques and/or pleural fibrosis. These lesions, particularly when bilateral, are strongly suggestive of asbestosis. The diagnosis of asbestosis must always be based on the chronologic occupational history with potential exposures. The features of the history that need to be defined include the duration, onset, type, and intensity of exposure. In taking the occupational history, it is important to keep in mind that intensity of exposure can be heavy even if duration of exposure is short. For example, heavy exposures were experienced by shipyard workers engaged in insulation application or removal in contained areas for brief periods aboard ship and by asbestos insulators during their apprenticeship when they unloaded asbestos sacks into troughs and mixed asbestos cement. Short, intense exposures of this sort, which lasted from several months to 1 or 2 years, can be sufficient to cause asbestosis. Exposures over 10 to 20 years are, however, usually necessary. The timing of the exposure also is relevant. Industrial hygiene controls in the 1960s and 1970s, especially in the construction trades, were not widely applied or enforced. Cohort studies have identified latency to be an important factor, with the prevalence of asbestosis increasing with time since the onset of exposure.

The specificity of the diagnosis of asbestosis increases with the number of consistent findings on chest film, the number of clinical features present (e.g., symptoms, signs, and pulmonary function changes), and the significance and strength of the history of exposure. The more significant the asbestos exposure the greater accuracy is the diagnosis. The more trivial the asbestos exposure, the less likely it is to be causal. Misclassification and diagnostic difficulty occur in patients with a heavy cigarette smoking history and concurrent emphysema (which also reduces the diffusing capacity). Patients with idiopathic pulmonary fibrosis (IPF) may have a history of asbestos exposure. These patients tend to be younger, however, and their asbestos exposure is usually casual, brief, and recent and can often be discounted. If an open lung biopsy is available, one or more asbestos bodies per high-power field (Fig. 85-5) or an asbestos fiber count per milligram of dry lung can be helpful to distinguish from IPF. In the absence of an adequate exposure history or in the presence of a confusing clinical presentation, biopsy material may be helpful in identifying the nature of the disease. It allows the pulmonary interstitial process to be compared to the known features of asbestosis and other interstitial disorders. Uncoated asbestos fibers are much more common than asbestos bodies, exceeding the frequency of coated fibers by anything from 5- to 10,000-fold. Although other inhaled particles may also become coated, most coated fibers found in human lungs have an asbestos core. Thus, the presence of asbestos bodies or asbestos fibers is considered the hallmark of exposure, past or current. Asbestos bodies can also be

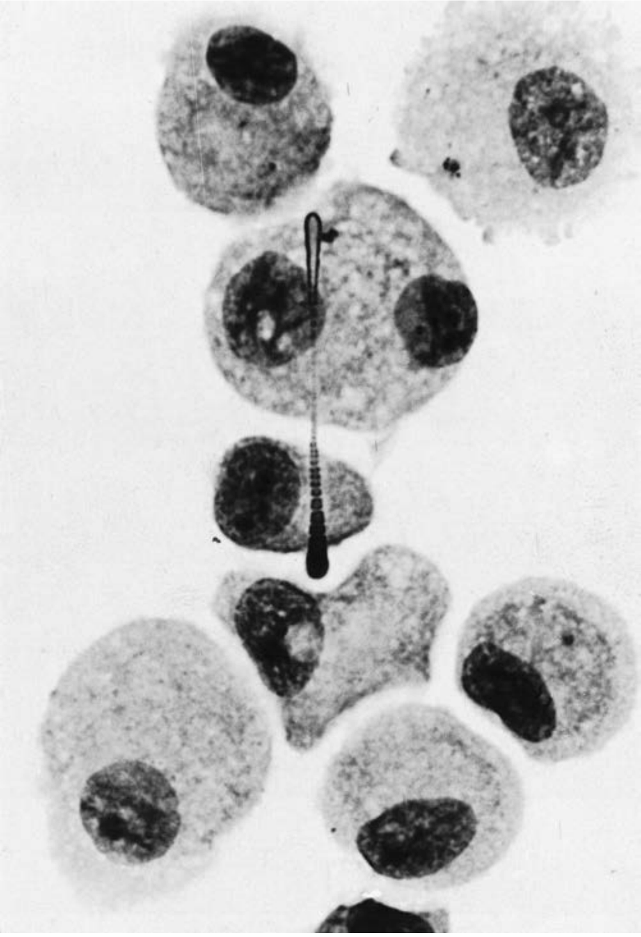

Figure 85-5 Light microscopic appearance of an asbestos body in a cytocentrifuged preparation of alveolar macrophages lavaged from a nonsmoking asbestos insulator (Wright–Giemsa stain, ×400). *(Reproduced with permission from William M. Rom, MD, MPH.)*

detected in BAL samples. Asbestos bodies in BAL correlate with heavy exposure, reduced lung function consistent with interstitial lung disease, and asbestosis.[29] This is illustrated in a large series of 563 patients: Those with asbestosis had a mean of 120 asbestos bodies per milliliter; those with pleural disease, 5 asbestos bodies per milliliter; and those with malignant mesothelioma or lung cancer, 8 asbestos bodies per milliliter of lavage fluid.[30] Of 49 patients with more than 100 asbestos bodies per milliliter of lavage fluid, 30 had asbestosis, 8 had pleural disease, 13 had mesothelioma or lung cancer, and 3 had an exposure history only. Others have estimated that one asbestos body per milliliter of BAL fluid correlates with 1000 to 3000 asbestos bodies per gram of dry lung tissue. Importantly, the Helsinki criteria guide the diagnosis of asbestosis and cancer with emphasis on a structured occupational history, clinical and radiographic findings, and recommendations for analysis of lung tissue for asbestos fibers and asbestos bodies.[31] These latter recommendations were as follows: greater than 0.1 million amphibole fibers >5 μm per gram dry lung tissue or greater than 1 million >1 μm using electron microscopy, greater than 1000 asbestos bodies per gram dry lung tissue, and greater than 1 asbestos body per milliliter of bronchoalveolar lavage fluid by light microscopy.

Treatment and Prognosis

Major causes of morbidity and mortality in patients with asbestosis include the progression of the underlying lung disease and the development of lung cancer and malignant mesothelioma. Longitudinal observations of asbestos-exposed trade workers have demonstrated accelerated declines in pulmonary function. In a study of 77 workers with a mean of 31 ± 1 years of occupational exposure, linear regression demonstrated a mean annual decline of 92 ± 28 mL/year in FVC, 66 ± 22 mL/year in FEV_1, and 14 ± 53 mL/year in total lung capacity.[32] At present, there is no established treatment for this disorder. Because of the risk of lung cancer and mesothelioma, medical surveillance with CT scans for those who also smoke more than 30 pack-years and age greater than 55 years on an annual basis is recommended.[33]

MALIGNANT MESOTHELIOMA

Malignant mesothelioma is an important complication of asbestos exposure, as discussed below. The reader is referred to Chapter 78 for additional detailed discussion of mesothelioma.

Pathology

Malignant pleural mesothelioma occurs in persons who have an exposure history to asbestos fibers, with 85% of men and 50% of women having an occupational history. In its early stage, the mesothelioma appears as multiple, small, grayish nodules on the visceral and parietal pleura that evolve to coalesce and form larger masses of tumors. These tumors then invade thoracic and other structures by direct extension. Fewer than 25% of malignant mesotheliomas are peritoneal in origin.

Mesotheliomas are conventionally classified into three histologic patterns: epithelial, sarcomatous, and mixed or biphasic; these patterns account for 50%, 20%, and 30%, respectively. The epithelial variant—in which neoplastic cells are arranged in papillary, tubular, or solid nest configurations—is most easily confused with metastatic adenocarcinoma. The sarcomatous variant has spindle-shaped cells that may be pleomorphic, with considerable mitotic activity.

The pathologic diagnosis of malignant mesothelioma may be difficult. In particular, the differentiation of malignant mesotheliomas, adenocarcinomas, and other tumors may be problematic. Histochemistry and immunohistochemistry may be helpful in making the distinction. Thus, in contrast to mesotheliomas, adenocarcinomas contain neutral mucin that stains positive with the periodic acid–Schiff stain and is often resistant to diastase. Hyaluronic acid, the major acid mucopolysaccharide in mesotheliomas, can be identified with the Alcian blue or colloidal iron stain. Removal by prior digestion with hyaluronidase increases the specificity of the reaction. In contrast, adenocarcinomas are negative for Alcian blue and colloidal iron. Mesothelial cells contain cytoskeletal filaments, including cytokeratin and vimentin; staining for these structures is not specific, since other tumor types are also positive. Carcinoembryonic antigen is absent in malignant mesothelioma but is present in up to 90% of adenocarcinomas. Similarly, the monoclonal antibody B72.3, generated against a membrane fraction of human metastatic breast cancer, was positive in 19 of 22 pulmonary adenocarcinomas but none of 20 mesotheliomas. Monoclonal antibody Leu MI is frequently positive in lung carcinomas and nonreactive with mesotheliomas.[34] Thyroid transcription factor 1 (TTF-1) is a marker for lung adenocarcinoma and is a positive prognostic factor.[35]

The ultrastructural features of malignant mesotheliomas also are noteworthy. Malignant mesotheliomas contain abundant tonofilaments, often organized into perinuclear bundles, and long, sinuous, slender surface microvilli. The microvilli sometimes show secondary and tertiary branching and may interdigitate with stromal collagen. Malignant mesothelial cells produce collagen, a prominent feature of the sarcomatous variant.

Malignant mesotheliomas are locally invasive, spreading along the pleural wall and invading the lung, mediastinal lymph nodes, and other thoracic and nearby structures. At autopsy, tumor may be found in the diaphragm, heart, liver, spleen, adrenals, gastrointestinal tract serosa, bone, pancreas, and kidneys. Between 50% and 80% of patients also have metastases.

About 10% of patients with a malignant mesothelioma are alive at 24 months. Survival is significantly longer for patients with an epithelial subtype or with a pleural rather than a peritoneal mesothelioma, and for those under 65 years of age.

The incidence of mesothelioma is increasing because of the cohort exposed to asbestos between 1940 and 1970. Incidence rates vary from a low of 11 to 13 per million per year in the United States to 33 per million per year in South Africa and to 66 per million per year in Western Australia.[36] These rates reflect mining and manufacturing industries and the location of crocidolite mines. Although the peak incidence in the United States may have passed since imports decreased after 1945, imports of asbestos in the United Kingdom reached their peak in the 1960s to 1970s. Thus, the peak of mesothelioma deaths in the United Kingdom is expected to occur in 2020, when up to 1% of men may die of the disease. Chrysotile was the major asbestos import to the United Kingdom, and half of this material went into the construction industry. Amosite was the leading amphibole import, and most of it went into insulation board. Thus, workers in the construction industry in the United Kingdom seem to be at greatest risk.

Epidemiology

In 1960, Wagner et al.[37] published a landmark paper demonstrating an association between malignant mesothelioma and asbestos exposure. They reported on 33 patients from South Africa, 28 of whom were exposed in the crocidolite mining region and 4 of whom were exposed in asbestos factories. They observed that mesotheliomas occurred 20 to 40 years after exposure to asbestos dust and found asbestos bodies in lung tissue from 8 of 10 patients from whom lung tissue was available for study. Subsequently, the importance of direct asbestos exposure was confirmed and the potential importance of indirect exposure to asbestos was recognized.

Evaluations of asbestos fiber content have shown a clear association between asbestos exposure and the occurrence of mesothelioma.[33] Epidemiologic studies have shown crocidolite to be a potent fiber type among South African and Western Australian asbestos miners and millers. Most mesotheliomas have occurred from chrysotile–amphibole mixtures, since chrysotile is the most common fiber in commercial use. The incidence of malignant mesotheliomas among chrysotile workers who came before the Workers' Compensation Board of Quebec was similar to that in western Australian crocidolite miners. Studies of Canadian cohorts have also indicated that high concentrations of chrysotile, or tremolite, are required to cause mesothelioma, and further suggest that chrysotile has weaker biopersistence than does tremolite, which is merely a contaminant in most ores. In the United States, amosite is the predominant amphibole found in lung tissue: in one study it was identified in 81% of 90 patients with mesothelioma; in this population, it accounted for 58% of all fibers at least 5 μm in length.[38] Finally, there is no association between smoking and malignant mesothelioma.

An epidemic of mesothelioma was reported in the Cappadocia region of Turkey where 40% of deaths were caused by the disease in several villages.[39] The exposure was to erionite, an aluminum silicate fibrous zeolite, and villagers used the stone to build their homes and whitewash their walls, and they carved rooms in the soft volcanic tuft. There also appeared to be a family concordance beyond the household exposure.[40] These villages have been abandoned to control the epidemic of mesothelioma.

Low levels of asbestos exposure can increase the risk of mesothelioma, for example, European case-control studies have shown that increasing exposure to ≥1 fiber/mL-year doubles or triples the risk.[41] Odds ratios of 4.8 for domestic exposure to asbestos (95% CI, 1.8–13.1) and 11.5 for neighborhood exposure to asbestos (95% CI, 3.5–38.2) have been reported.[41] There is a strong dose–response relationship with no lower threshold or safe level. The scientific basis for the mesothelial carcinogenicity of chrysotile has been established with epidemiologic studies, animal carcinogen assays, and pleural fiber burden studies.[41] Suzuki and Yuen used transmission electron microscopy to measure lung fiber burden in 168 cases of mesothelioma and found chrysotile to be the sole asbestos type in mesothelioma tumor tissue (73%) and in the lung (26%), and found that only 1% of the chrysotile fibers were ≥5 μm in length.[42] Cancer registries exploring mesothelioma have identified statistically significant occupations associated with asbestos exposure not previously recognized, including chemical engineers, machine operators, automobile mechanics, railroads, plumbers, welders, metal molders, coremakers, cabinetmakers, and postal workers.[43]

Pleural plaques have been recognized as a risk factor for mesothelioma and lung cancer probably because they represent a marker of significant asbestos exposure. In Sweden, a review of 1596 male radiographs with pleural plaques fulfilling strict radiologic criteria upon more than 20 years of follow-up found 50 lung cancers with 32.1 expected (O/E 1.6) and 9 mesotheliomas with 0.8 expected (O/E 11.25).[9] In France, CT scan screening for lung cancer among 5287 male subjects with past asbestos exposure and follow-up over 7 years identified 17 pleural mesotheliomas; a statistically significant association was observed with pleural plaques (hazard ratio [HR], 6.8 [95% CI, 2.2–21.4] after adjustment for time since first exposure and cumulative exposure index to asbestos).[44] In addition, there were 36 deaths from lung cancer that was also associated with pleural plaques (HR, 2.41 [95% CI 1.21–4.85] after adjustment for smoking and asbestos cumulative exposure index).[45] However, in two Australian cohorts including crocidolite miners and millers, the asbestos exposure was associated with lung cancer and mesothelioma (pleural thickening was associated with peritoneal mesothelioma) and not pleural disease.[46] Asbestosis was diagnosed in 32% of the Australian subjects, whereas only 0.7% had asbestosis in the French cohort consistent with the importance of significant asbestos exposure and association with asbestos-related diseases.[47] The high prevalence of asbestosis in the Australian cohorts is consistent with greater asbestos exposure overwhelming the signal from pleural plaques as an independent risk factor.

Pathogenesis

Insight into the pathogenesis of malignant mesothelioma has come from experiments in which asbestos fibers were introduced into the pleural space of animals. These studies have demonstrated that amosite, anthophyllite, crocidolite, and Canadian chrysotile can all cause these pleural malignancies. Studies of fiber size in animals have shown that the most carcinogenic fibers are biopersistent, 0.1 to 1.0 μm in diameter, and more than 8 μm in length. Inspection of electron micrographs of asbestos fibers has shown that crocidolite and amosite possess needlelike characteristics, whereas anthophyllite has a more boxlike appearance and chrysotile has a long, curly appearance. These variations in size are also consistent with epidemiologic studies indicating that crocidolite and amosite may have greater risk for mesothelioma than do other types of asbestos. Becklake et al. have stated that there is a fiber gradient in toxicity, with chrysotile exhibiting lower toxicity than the amphiboles, and amosite exhibiting lower toxicity than crocidolite.[48]

One theory concerning the mechanism of asbestos-induced carcinogenesis focuses on the observation that asbestos fibers become entangled in the mitotic spindle during interphase, thereby causing chromosomal abnormalities. Electron microscopic evaluations have shown fibers penetrating between multiple lobes of the nucleus and associating, along their length, with the outer surface of the nuclear envelope. Structural chromosomal abnormalities in mesothelioma are clonal and complex and include both chromosomal gains (chromosome 22) and losses (chromosome 7). Deletions of the short arm of chromosome 3, the break point 1p11 to p22, chromosome 17, and structural and numeric changes in chromosome 7 have been described.[49] In asbestos insulators, sister chromatid exchanges in circulating lymphocytes are increased: larger chromosomes are more susceptible, and in the largest chromosome group, there is a significant interactive effect between asbestos exposure and cigarette smoking.

Cell lines established from malignant mesotheliomas have been shown to constitutively upregulate the PDGF B-chain gene and, to a lesser extent, the PDGF A-chain gene. High levels of transforming growth factor and IGF-1 bioactivity have been reported for cell lines derived from malignant mesotheliomas. These growth factors contribute to the considerable matrix formation that accompanies mesothelial tumors and promote mesothelioma cell proliferation.

Clinical and Radiographic Features

Pleural mesotheliomas are found mainly in males (ratio, between 3 and 4 to 1) and are most commonly diagnosed in patients between 50 and 70 years of age. Chest pain is the most common symptom experienced by patients with mesotheliomas. Dyspnea is next in frequency. Less common symptoms are cough, weight loss, and fever. A pleural effusion is usually present and can be massive. The effusion is an exudate, can be hemorrhagic, and may have high levels of hyaluronic acid (Fig. 85-6). Malignant mesothelioma is locally invasive, spreading along the pleural wall and invading the lung and nearby structures. Metastases are less common but can give rise to symptoms due to tumor in the diaphragm, heart, liver, spleen, adrenals, gastrointestinal tract, bone, pancreas, and kidneys. The paraneoplastic syndromes of inappropriate antidiuretic hormone secretion, clubbing, or hypoglycemia are reported. Thrombocytosis is common (90% in one series), and thromboembolic complications can occur. Ascites and weight loss are characteristic features of peritoneal mesothelioma.

A variety of radiographic abnormalities are found in malignant mesothelioma. They include a thick pleural peel along the lateral

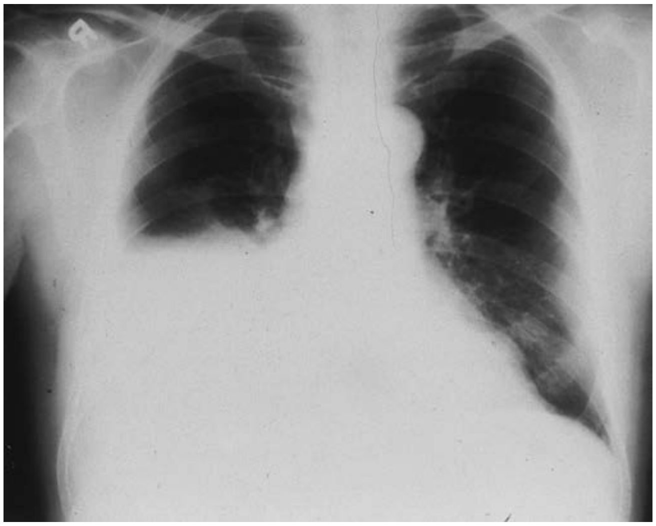

Figure 85-6 Large pleural effusion in an asbestos-exposed worker with an underlying malignant mesothelioma. *(Reproduced with permission from Dr. J. Elias.)*

chest wall that can extend to the apex with an irregular nodular surface, multiple pleural nodules or masses, plaque-like opacities, and pleural effusion(s). As the disease progresses, the lung parenchyma may be involved, the affected hemithorax may decrease in size, and the mediastinal or hilar nodes may be invaded. Pericardial thickening or effusion, abdominal extension, and chest wall invasion are common. The HRCT can help in differentiating pleural effusion from tumor and in determining the extent of tumor progression. The presence of asbestosis or of pleural plaques on the opposite side can assist in establishing the diagnosis of malignant mesothelioma.

■ Diagnosis

The diagnosis of malignant mesothelioma requires cytologic and immunohistologic validation. Calretinin, cytokeratin 5/6, and WT1 are the best positive markers for differentiating mesothelioma from pulmonary adenocarcinoma, and the best negative markers are TTF-1, CEA, MOC-31, and B72.3.[50] Obtaining a cytologic diagnosis from the pleural exudate is difficult because reactive mesothelial cells and malignant cells are not easy to distinguish. Biopsy is required. Because mesothelioma has been shown to invade the needle track, open biopsy is preferable. Thoracoscopy is the procedure of choice in establishing the diagnosis of mesothelioma.

Noninvasive biomarkers include plasma soluble mesothelin, osteopontin, and fibulin-3.[51,52] The receiver operating curve (ROC) for plasma fibulin-3 levels had a sensitivity of 96.7% and a specificity of 95.5% at a cutoff value of 52.8 ng of fibulin-3 per milliliter, and blinded validation revealed an area under the curve (AUC) of 0.87 for plasma specimens from 96 asbestos-exposed persons compared with 48 patients with mesothelioma. An AUC of 0.5 is no different between the groups, and an increased AUC greater than 0.7 is increasingly more sensitive toward 1.0, which is perfect sensitivity and specificity for the test in question. These blood tests can distinguish patients with malignant mesothelioma from asbestosis and pleural plaques as well as other causes of malignant pleural effusion such as lung and breast cancer.

■ Treatment and Prognosis

Median survival time is approximately 8 to 12 months for all patients with malignant mesothelioma. Overall, fewer than 10% of patients are alive at 5 years. Extrapleural pneumonectomy, combined with radiation therapy, may improve survival. Chemotherapy with gemcitabine and carboplatin or pemetrexed and cisplatin also may improve survival. Immunotherapy with intrapleural gene therapy with interferons has produced occasional complete or partial responses.[53–55] A promising area of research is intrapleural administration of adenoviral IFN-α2b, which resulted in tumor regression in five patients including one dramatic example of partial tumor regression at sites not in contiguity with vector infusion.[55] A detailed discussion of treatment options is provided in Chapter 78.

LUNG CANCER

In addition to mesothelioma, lung cancer is another well-recognized malignant complication of asbestos exposure.

■ Epidemiology

The association between asbestos exposure and the development of lung cancer was highlighted by Sir Richard Doll's 1955 epidemiologic cohort study of 113 men exposed to asbestos for 20 years, which reported 11 deaths due to lung cancer (compared with 0.8 expected).[56] All the individuals who died of lung cancer had evidence of asbestosis. In 1965, a retrospective cohort study in two asbestos insulator unions in the United States reported that deaths from lung cancer were 6.8 times the expected rate and that the incidence of lung cancer increased with time after exposure. In 1968, a follow-up of men in this cohort demonstrated an important synergy between asbestos exposure and cigarette smoking, since the risk of lung cancer was almost entirely borne by those who had a history of cigarette smoking.[57]

The largest survey of asbestos-related deaths evaluated a North American asbestos insulator cohort that reported a threefold excess of lung cancer deaths.[58] Comparatively few of these excess deaths were observed among those less than 25 years after the start of exposure. Lung cancer peaked at 30 years from exposure and mesothelioma at 45 years. In contrast, death rates from asbestosis increased progressively with time. This study confirmed the multiplicative effect of smoking plus asbestos exposure on the risk of lung cancer. Moreover, it showed that deaths from lung cancer dropped by almost two-thirds for asbestos insulators who subsequently stopped smoking. A recent follow-up of the North American insulator cohort from 1981 to 2008 found the following: 19% of the deaths were caused by lung cancer; the rate ratio of lung cancer in nonsmokers was 3.6 (95% CI, 1.7–7.6) and by asbestosis in nonsmokers was 7.40 (95% CI, 4.0–13.7); the joint effect of smoking and asbestos alone was additive (rate ratio, 14.4) and with asbestosis, supra-additive (rate ratio, 36.8).[59] Insulator lung cancer mortality halved within 10 years of smoking cessation and converged with that of never-smokers 30 years after smoking cessation.

Additional insights were provided by a study of amosite workers who were exposed to concentrations of 50 fibers per milliliter.[60] These patients experienced a fivefold increase in lung cancer. Long-term follow-up showed (1) a latency period of about 20 years before the increase in cancer occurred; (2) the greater the dose or the longer the exposure, the greater risk of developing lung cancer; and (3) the greater the dose or exposure time, the shorter the latency period before the tumor developed. Malignancies were also noted in the wives and children of these workers who were exposed to asbestos in the household, primarily on work clothes. In addition, men employed for less than 1 month between 1941 and 1945 developed lung cancer at an increased rate. Studies of a variety of other cohorts have confirmed the increased incidence of lung cancer in asbestos-exposed populations. They have also demonstrated an increased frequency of cancer of the larynx; in the latter, asbestos has been found in laryngeal tissue. As in the case of cancer of the lung, cigarette smoking has a strong association with the occurrence of these laryngeal malignancies.

Epidemiologic studies have also provided information about dose–response relationships and about the importance of asbestos-processing techniques and fiber type in the pathogenesis of pulmonary malignancies. The exposure–response relationship is considered to be approximately linear with higher level of lung cancer risk increment per fiber/mL-year for relatively low levels of asbestos exposure.[41,61] Differences in asbestos-processing techniques alter this relationship—for example, studies of a South Carolina plant demonstrated a steeper dose–response relationship in textile weavers versus chrysotile miners—probably due to the manufacturing process, which resulted in high levels of brief exposure during the opening of asbestos bags and the sudden separation of the asbestos fibers.[62] Similarly, differences in lung cancer mortality in asbestos cement product plants in Louisiana were found to be associated with the addition, in one of these plants, of crocidolite to the asbestos cement pipe mixture. The risk of lung cancer increases most clearly with cumulative asbestos exposure.

Pathology

Asbestos-related lung cancers are not distinct from lung cancers that occur in cigarette smokers and otherwise normal persons in type, nature, or location. All histologic types of lung cancer occur with increased frequency, but adenocarcinoma has the highest incidence. In the vast majority of patients, there is histologic evidence of asbestosis and asbestos bodies are frequently found. Asbestos-related lung cancer can occur in the absence of asbestosis.

Pathogenesis

Animal experiments using several types of asbestos have succeeded in reproducing pulmonary malignancies. In one study, approximately one-third of rats exposed by inhalation to asbestos (amosite, anthophyllite, crocidolite, Canadian chrysotile, or Rhodesian chrysotile) for periods ranging from 1 day to 24 months developed adenocarcinomas or squamous cell carcinomas of the lung.[63] In these experiments, a clear dose–response relationship existed between asbestos dose and the occurrence of tumors. In addition, available data indicate longer, thinner fibers having the strongest association with lung cancer, while fiber burden studies show that short fibers, especially chrysotile, are very frequently present.[41]

The mechanisms responsible for the induction of these malignancies include DNA adduct formation and poor repair, activation of nuclear transcription factors and driver cancer mutation, inhibition of tumor suppressor genes, reactive oxidant species, and chromosomal damage. The aldehydes acrolein and acetaldehyde are the predominant forces inducing DNA damage and inhibiting DNA repair using the TP53 gene in tobacco smoke carcinogenesis.[64] Crocidolite asbestos causes double-strand DNA breaks in small airway epithelial cells, which is the site for asbestos-induced fibrosis and carcinogenesis.[65] Reactive oxygen species also may play an important role in this process, since chrysotile asbestos, along with cigarette smoke, synergistically increases the number of breaks in DNA strands. Asbestos also induces nuclear factor-κB DNA binding in tracheal epithelial cells in vitro. NF-κB is an important transcription factor for cytokines, growth factors, and proto-oncogenes that could contribute in a variety of ways to malignant transformation. Alveolar macrophages also release TNF-α after phagocytosis of asbestos fibers, and TNF-α induces NF-κB in human mesothelial cells leading to increased survival (antiapoptosis).[66] These mesothelial cells exhibit increased mitotic index, and metaphases have prematurely separated chromatids or other chromatid abnormalities in in vitro cell culture.

The genomic understanding of early tumor development and progression has been further elucidated with deep next-generation sequencing of DNA extracted from adenocarcinoma in situ, minimally invasive adenocarcinomas, and fully invasive adenocarcinomas.[67] There were 21 of 347 cancer genes mutated among the 3 groups, and mutations in K-RAS, TP53, Jak-Stat, MAPK, cell cycle, and PI3K-AKT were found to increase in frequency from adenocarcinoma in situ to minimally to fully invasive adenocarcinoma. Deletion events were noted in chromosome 3p21 and 9q13, and KRAS and EGFR pathways were mutually exclusive, with the former pathway mainly seen in smokers. Yoshida et al. sequenced single cells from 632 bronchial epithelial colonies derived from bronchial brushings from children, never smokers, ex-smokers, and current smokers (n = 16).[68] They reported that current smokers' cells had a mean of 5300 mutations, ex-smokers 2230, never-smokers 290, and children 140 mutations per cell.[68] Smokers' genomes also had extensive insertions, deletions, and substitutions, and the number of mutations in different cells from the same individual could vary tenfold in smokers, a much higher variability than was found in nonsmokers. The most common smoking-dependent signature consisted of guanine-to-thymidine mutations, a signature that is characteristic of most smoking-associated lung cancers. In current smokers, at least 25% of cells carried driver mutations, including TP53 and NOTCH1, and specific TP53 mutations were found in multiple cells from the same individual suggesting that these mutations occur early. Driver mutations were double in smokers compared with ex-smokers and increased with age. Interestingly, in 5 of 6 ex-smokers, 20% to 50% of the cells had a low mutation burden that was similar to the profile of nonsmokers of the same age range. These cells had longer telomeres, suggesting they might have arisen comparatively recently from divisions of previously dormant stem cells.

Clinical Features

The patterns of presentation of lung cancer among asbestos workers are similar to those of high-risk patients: cough, chest pain, dyspnea, hemoptysis, recurrent bouts of pneumonia, and localized wheezing. However, patients can also be asymptomatic at the time of initial discovery, the abnormality being noted on a routine or screening CT scan. Other manifestations of carcinoma—such as rib invasion, shoulder–arm pain, and paraneoplastic syndromes—can also occur in asbestos-related malignancies.

Individuals with asbestosis have an increased risk of lung cancer.[69] Most patients with lung cancer in the Quebec asbestos mining district had small parenchymal opacities on the chest radiograph before death. In amphibole miners from South Africa with carcinoma of the lung who were evaluated by stepwise regression analysis for exposure variables, asbestosis was by far the most striking variable. Moreover, a dose–response relationship was found between the severity of asbestosis and the frequency of lung cancer. In the North American insulator cohort, 18% of the patients who died of lung cancer did not have radiographic evidence of parenchymal fibrosis.[70] Similarly, in a case control study of 271 patients with lung cancer, a small but definite increase in cancer risk was noted in patients whose chest radiographs were not definitely abnormal (0/1 or less).[71] This study indicated that asbestos exposures that do not cause small opacities on the chest radiograph may nevertheless increase the risk of lung cancer. Lung cancer mortality rate was 3.6 (95% CI, 1.7–7.6) times higher among long-term asbestos insulators who had never smoked and had no radiographic evidence of asbestosis compared with blue-collar controls; lung cancer risk doubles with asbestosis in smokers and nonsmokers among insulators.[41]

Radiographic Features

The radiographic manifestations of asbestos-induced lung cancers do not differ, per se, from those of lung cancers associated with other carcinogens. Mass lesions, atelectasis, post-obstructive pneumonia, and pleural effusions are all seen. As noted earlier, these lesions are frequently superimposed on a background of asbestosis or asbestos-induced pleural abnormalities. Confusion with lung cancer may arise from en face pleural plaques or rounded atelectasis. In contrast to lung cancer, however, these abnormalities are stable over time. The helical CT scan, which can evaluate the chest in a single breath, can increase the early detection rate of lung cancer in this high-risk patient population.

Diagnosis

The principles employed in the diagnosis of lung cancer in asbestos workers are identical to those in the diagnosis of pulmonary malignancies in patients exposed to other carcinogenic agents. Appropriate cytologic or histologic specimens are required. This can be accomplished by sputum analysis or by bronchoscopy with brushings, biopsy, or lavage. Transthoracic needle aspirates, thoracoscopic parenchymal biopsies, or open lung biopsies may be required for definitive diagnosis.

Treatment and Prognosis

The therapeutic approaches utilized for asbestos-related lung cancers are similar to those employed for lung cancers induced under other circumstances. When one is dealing with non–small-cell malignancies, patient operability and resectability need to be evaluated and, if appropriate, surgical extirpation undertaken. The impact of other asbestos-related pulmonary processes must always be taken into account. For example, severe asbestosis may limit operability, and diffuse pleural thickening may make surgical intervention problematic.

EFFORTS AT ASBESTOS CONTROL

In order to control the risk of exposure to asbestos, the Occupational Safety and Health Administration's Permissible Exposure Level not to be exceeded is 0.1 fiber/mL over an 8-h time-weighted average. As a public health measure and to protect children as well as workers, the United States should follow the rest of the world in banning the commercial use of asbestos.

Industrial hygiene efforts to control exposure have focused on engineering controls, including enclosure of the process lines, especially all sites where asbestos is introduced into a system, increasing ventilation, and the use of wet manufacturing methods. Personal respirators are used as a last resort in achieving control of exposure in the workplace; however, personal protective equipment including N95 or full-face respirators are required for removal of asbestos in place including demolition. Most of the insulation-manufacturing industry has switched to alternative materials, especially fibrous glass, rock and slag wool, and refractory ceramic fibers. Animal experiments have generally shown these asbestos substitutes to be safe, although refractory ceramic fibers have been shown to produce mesotheliomas in hamsters.

CONCLUSIONS

The asbestos-related diseases should be confined to history with the banning of asbestos in many countries and substitution of other insulating products. The Occupational Safety and Health Administration (OSHA) estimates that 2 to 3 excess lung cancers per 1000 workers exposed to the current standard of 0.1 fiber/mL for 45 years will occur and mandates work practices and engineering controls to lower exposure to asbestos. However, Nielsen et al. systematically reviewed the literature concluding that the increase in lung cancer risk was from 1% to 4% for each year of exposure to 1 fiber/mL (i.e., fiber/mL-year); we have the legacy of past exposures and the continuation of exposures during renovation and destruction of asbestos-containing buildings and products.[72] It continues to be an important area of compensation for workers developing mesothelioma, and for continued research on the mechanisms of fibrosis and carcinogenesis. Low-dose CT screening for asbestos-exposed workers can detect thoracic malignancies early and enable successful surgical treatment. The National Comprehensive Cancer Network recommends low-dose CT for people 50 years and older who have at least 20 pack-years of cigarette smoking and one additional risk for lung cancer, including occupational exposure to asbestos.[41]

Biomarkers for detection of lung cancer and mesothelioma are important for early diagnosis. Blood-based biomarkers based on plasma proteins ($n = 13$) have achieved negative predictive values of 90% in differentiating malignant nodules from benign.[73] Pathway analysis demonstrates that these proteins are involved in transcription regulators that are associated with cancer, lung inflammation, oxidative stress networks, and immunologic pathways. Gene panels and microRNAs can be differentiated in peripheral blood mononuclear cells or whole blood that are associated with lung cancer versus smokers with normal CT scans, and following surgery, the tumor influences are reversed.[74] Many of the genes that have altered expression in lung cancer are also found in the adjacent small-airway epithelium and proximal-airway epithelium consistent with an altered transcriptome in field carcinogenesis. Improving the performance of bronchoscopy with a bronchial brushing from the mainstem bronchus, a 23-gene classifier increased sensitivity to 96% in a series of 639 rule/out lung cancer patients achieving a receiver-operating-characteristic area under the curve of 0.78.[75]

Finally, the global control of asbestos should be a priority for international organizations since there is no further reason for asbestos to remain in commerce.

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CHAPTER 86

Chronic Beryllium Disease and Hard-Metal Lung Diseases

Shweta Sood
Mary Elizabeth Kreider

INTRODUCTION TO BERYLLIUM

Beryllium is the lightest metal and has an atomic number of 4. Beryllium, as an element, was first discovered in 1798 by the French chemist Vauquelin and reduced to its metallic form. Subsequently, it was named beryllium in 1828 by the German metallurgist Wohler. Beryllium became a commercial product when it was used as an alloy first with aluminum and later with cooper, nickel, and cobalt after World War I. This commercial product was used in communications (telephones and telecommunication) and medicine (x-ray devices). The industry grew in the 1930s due to the increased use of beryllium–copper products during World War II in defense (military equipment), nuclear energy (nuclear reactors), and household items (fluorescent lamp industries).

With an increased industrial need for beryllium, acute chemical pneumonitis was first described by Weber and Engelhardt[1] in Germany in 1933 and in the United States by van Ordstrand et al. in 1943.[2] This condition was usually limited to the upper respiratory tract, although it could extend to the bronchi, bronchioli, and alveoli if there was sufficient exposure. The condition peaked in the 1940s. The last reported possible case in the United States occurred in the early 1980s. Acute pneumonitis due to beryllium is now rare and expected to be seen due to large-scale disasters such as beryllium plant explosions or other serious lapses in procedures.[3]

A second pulmonary complication of beryllium exposure was first described by Hardy and Tabershaw in 1946.[4] The disease differed from the acute chemical pneumonitis because of the delayed onset, granulomatous response, and chronic course. Now known as chronic beryllium disease (CBD), the condition is a hypersensitivity reaction, or sensitization to beryllium, and is the major hazard facing beryllium workers today.

In the modern era, acute manifestations of beryllium disease (such as acute pneumonitis) tend to be rare due to stricter governmental regulations that limit exposure in most developed countries. However, beryllium continues to be produced in high quantities in several countries, and exposure occurs in individuals working in select occupations, including primary beryllium factory workers, workers processing beryllium (foundry workers, furnace tenders, machinists, welders), individuals working with beryllium products (dental technicians, golf club manufacturers, bike parts manufacturers), and select industries (e.g., aerospace, automotive, defense, electronics, energy, telecommunications).[5,6] It is estimated that as many as 60,000 workers in the United States are still exposed to beryllium.[5,6] However, other studies suggest the prevalence of beryllium exposure is as high as 130,000 workers.[7]

Immunopathogenesis of CBD

There are three important characteristics of CBD.

First, this disease is usually associated with industrial exposure to beryllium. The only cases that have been described in nonindustrial workers have been in individuals who lived near beryllium plants and were exposed to the airborne emissions from the plant or from family members who brought contaminated work clothes into the home.[8,9] In addition, workers not directly handling beryllium may be exposed from processes occurring near them. A recent study showed that workers exposed to environmental concentrate dust from a nearby plant tested positive for beryllium sensitization at a higher-than-expected rate, suggesting that perhaps environmental factors in the absence of occupational exposure may play a role in the development of BeS.[10] The majority of cases have been described in individuals who have been involved in the heating, grinding, abrading, or handling of beryllium metals, alloys, salts, or oxides. Modern industrial hygienic practices include efforts to remove potential airborne beryllium at the source to prevent beryllium from becoming airborne, limiting the number of workers with potential exposure to beryllium, limiting skin exposure, and trying to keep the airborne levels as low as possible.[7] In 2017, updated Occupational Safety and Health Administration (OSHA) guidelines reduced the beryllium permissible exposure limit (PEL) to 0.2 μg/m^3 of air averaged over 8 h and set a new short-term exposure limit (STEL) of 2.0 μg/m^3 of air over a 15-min sampling period.[6,11]

A second important characteristic of CBD is the long time interval or latency that occurs between initial exposure and the onset of disease.[8] The average time to the onset of clinical symptoms is 10 years. This fact, combined with the lack of a clear-cut dose–response relationship to CBD, has hampered efforts to determine a safe level of beryllium. Thus, it is uncertain whether a peak exposure level or a total accumulated dose is more important for the development of CBD. Individuals have been described (e.g., secretaries with apparently little exposure) who have worked in industry for less than 1 year and yet still develop disease years to decades later.

A third important characteristic of CBD is that not all exposed workers will develop the disease. A minority of individuals exposed to beryllium will develop sensitization (estimated to be <20%).[12–14] Furthermore, only about 1% to 8% of exposed workers will ever develop the disease.[8,14] This percentage appears to have remained the same despite dramatic efforts by industry to reduce the potential exposure in their workers. The last characteristic of CBD is most likely due to a genetic predisposition.

The suspicion that an immunologic reaction to beryllium caused CBD was based on the following observations: (1) Beryllium painted on the skin (patch testing) could elicit delayed-type hypersensitivity reactions in patients with CBD.[15] However, because of the concern that patch testing could sensitize individuals to beryllium, skin testing has not been widely used. (2) CBD was associated with "immunologic granuloma." (3) Finally, animal studies demonstrated that a hypersensitivity could be demonstrated in animals and that this could be passed with cells.[16]

In vitro studies that simulated patch testing were developed in the 1970s and applied to patients with CBD.[17,18] The blood cells from a large percentage of patients with CBD had positive proliferative responses to beryllium. In addition, after stimulation with beryllium, blood cells from many patients with CBD could release a lymphokine: macrophage migration inhibition factor. However, all patients with CBD did not have positive responses with their blood cells.[19]

The confirmation that CBD was due to a cell-mediated response to beryllium came in the 1980s when cells harvested from the bronchoalveolar lavage fluid (BALF) from patients with CBD were examined.[20] There was a marked increase in the number and percentage of CD4+ T lymphocytes in the BALF noted. In addition, a positive proliferative response of bronchoalveolar lymphocytes to beryllium was observed. Positive proliferative responses to beryllium were observed in all cases of CBD, while negative responses were noted in beryllium workers with biopsy-proven, non-beryllium lung disease, patients with sarcoidosis and no history of beryllium exposure, and normal volunteers.[21,22] Notably, not only did all patients with CBD have a positive proliferative response of their bronchoalveolar cells to beryllium, the response was more pronounced in lung cells than in blood. The accumulation of beryllium-specific cells in the lungs of patients with CBD has been confirmed and shown to be due to effector memory T cells[23] that produce TH1 cytokines (interleukin 2 [IL-2], interferon γ [IFN-γ], tumor necrosis factor α [TNF-α]).[24,25] The T-cell response to beryllium is oligoclonal;[26] the response can be blocked by anti-HLA DP antibodies and requires the presence of HLA-DP2 antigen-presenting cells.[27]

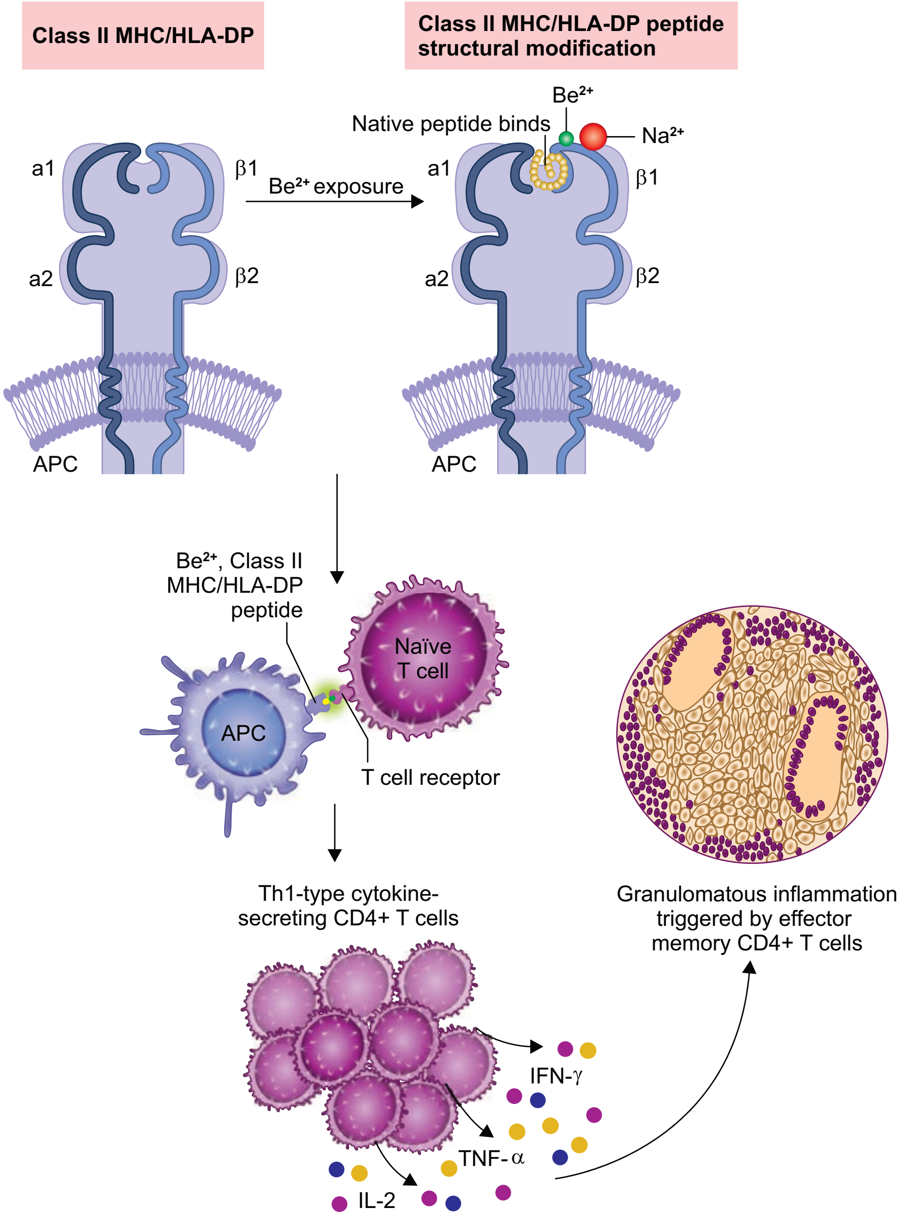

Class II MHC/HLA-DP
Class II MHC/HLA-DP peptide structural modification
a1
β1
a2
β2
APC
Be²⁺ exposure
Native peptide binds
Be²⁺
Na²⁺
a1
β1
a2
β2
APC
Be²⁺, Class II MHC/HLA-DP peptide
Naïve T cell
APC
T cell receptor
Th1-type cytokine-secreting CD4+ T cells
Granulomatous inflammation triggered by effector memory CD4+ T cells
IFN-γ
TNF-α
IL-2

Figure 86-1 Beryllium pathogenesis for CBD. Beryllium is inhaled and deposited in lungs. Antigen-presenting cells (APCs) present beryllium to T cells, triggering inflammatory response that can ultimately lead to granuloma formation over time.

The CD4+ T-cell response to beryllium suggested that specific HLA class II molecules might be involved in CBD, since HLA class II molecules present antigenic peptides to CD4+ T cells. A strong association of CBD with the marker HLA DPB1-glu 69 was first shown by Richeldi et al.[28] and subsequently confirmed in three other laboratories.[29–31] However, rather than just a marker for CBD, this haplotype appears to be associated with the ability to develop an immune response to beryllium. The less frequent alleles that code for DPB1-glu 69 appear to be more associated with beryllium sensitization and disease than the more common alleles.[32,33] The crystal structure of HLA-DP2 has been solved and helps to explain the association with beryllium disease.[34] β Glu 69 lies in a pocket that is accessible to beryllium. In addition, two additional acidic amino acids, βGlu 26 and βGlu 68, lie in this pocket. Mutation of any one of these three amino acids eliminates the ability of the molecule to present beryllium to sensitized T cells.[35] A similar molecule on DR may be responsible for the development of beryllium sensitization in those who do not have HLA DPB1-glu 69.[32]

Additional genes probably account for the progression from beryllium sensitization to disease. Polymorphisms on a number of genes, including IL-1 A,[35] CC chemokine receptor 5,[36] NTNL2 in HLA-DPB1*Glu69 negative individuals,[37] and TGFb1[38] have been identified as a possible progression factor for the development of CBD. No association has been found with TNF-α promoter regions[39] or the TNF-α gene.[40]

The previously mentioned studies suggest the following model for the pathogenesis of CBD. Beryllium is inhaled and deposited in the periphery of the lung. Beryllium, either alone as a crystal or combined with a normal lung protein(s), is bound by glu 69–containing DPB1 molecules and presented to beryllium-specific T cells. The beryllium protein or beryllium crystal is poorly digestible and cannot be removed by the immune response. Persistent inflammation leads to granuloma formation. The cells of the granuloma secrete enzymes that cause tissue destruction and fibrosis (Fig. 86-1).[41]

■ Beryllium Exposure, Beryllium Sensitization, and Chronic Beryllium Disease

Recent clinical guidelines have emphasized the importance in distinguishing individuals with beryllium exposure from patients with beryllium sensitization (BeS) and chronic beryllium disease (CBD), as shown in Fig. 86-2.[42] Beryllium exposure typically occurs in individuals working with beryllium after inhalation or skin contact. In a select group of individuals, exposure can trigger a delayed hypersensitivity response called beryllium sensitization. Individuals with BeS develop an immune-specific response but do not have clinical evidence of lung disease. BeS is defined by a positive beryllium lymphocyte proliferation test, or BeLPT. A small group of patients with BeS can progress to developing clinical signs and symptoms of CBD.

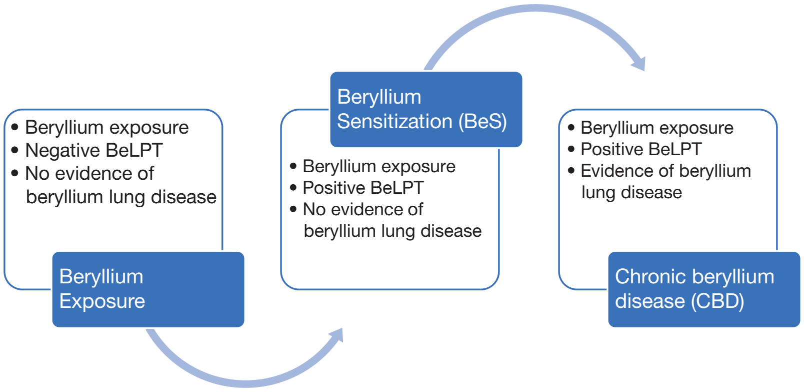

• Beryllium exposure
• Negative BeLPT
• No evidence of beryllium lung disease
Beryllium Exposure
Beryllium Sensitization (BeS)
• Beryllium exposure
• Positive BeLPT
• No evidence of beryllium lung disease
• Beryllium exposure
• Positive BeLPT
• Evidence of beryllium lung disease
Chronic beryllium disease (CBD)

Figure 86-2 Distinguishing between beryllium exposure, beryllium sensitization (Bes), and chronic beryllium disease (CBD). In beryllium exposure, patients are not sensitized to beryllium (negative BeLPT) and have no evidence of beryllium disease. BeS is defined by a positive BeLPT but no evidence of lung disease. CBD patients tend to have exposure history, positive BeLPT, and clinical evidence of lung disease. Classically, CBD patients have granulomas on lung biopsies. In patients unable to undergo lung biopsy safely, a probable CBD diagnosis can be made using noninvasive testing (history, imaging, PFT, etc.) after other differential diagnoses have been excluded. BeLPT, beryllium lymphocyte proliferation test. It is suspected that only about 1% to 8% of exposed workers will ever develop the disease.

In contrast to individuals with BeS, patients with CBD develop both immune-specific response (a positive BeLPT test result) *and* clinical evidence of lung disease. The specific diagnostic tests for distinguishing BeS from CBD are discussed subsequently. Notably, management can be different for patients with beryllium exposure and sensitization compared to those with beryllium disease. Thus, understanding the features of beryllium exposure, BeS, and CBD is crucial for diagnosis and management.

■ Clinical Presentation of Chronic Beryllium Disease

CBD is primarily a pulmonary granulomatous disorder (Table 86-1). Although involvement of other organ systems has been reported (e.g., lymph node, skin, liver), the lungs are the principal organ affected and account for the morbidity and mortality of this disease.[43,44] Extrapulmonary manifestations of CBD have been reported but are rare. In the early stages, CBD may be asymptomatic or have mild pulmonary symptoms. A positive blood proliferative response to beryllium (a positive BeLPT test) may be the earliest sign of CBD.[12,45] Radiologic changes can be detected on routine chest imaging in asymptomatic individuals.

Symptomatic disease usually begins with nonspecific respiratory complaints, such as dyspnea and cough. Early in the disease process, routine chest radiography may not be helpful. Pulmonary function testing early in the disease may be normal or have an isolated abnormality of the diffusing capacity ($D_{L_{CO}}$).[46] As the disease progresses, symptoms become more characteristic for chronic interstitial lung disease (ILD) with a nonproductive cough, substernal burning pain, and progressive exertional dyspnea. At this stage dry bibasilar crackles can be observed on physical examination. A rare patient may have asthmatic-type complaints and physical findings.

With advanced disease progressive weakness, easy fatigability, dyspnea at rest, anorexia, and weight loss may occur, and acrocyanosis and clubbing may be observed. As cor pulmonale develops, peripheral edema, hepatomegaly, and distended neck veins are seen.[47] Fever is unusual but can be seen. Hypercalcemia and nephrocalcinosis, hyperuricemia, joint pains, and severe cachexia have been described. Severe liver involvement has not been seen, but liver granulomas with mild elevation of the liver function tests occur. Skin involvement may occur in 10% to 30% of cases and frequently involves small granulomatous nodules on the hands, arms, and chest.[43]

■ Radiography of Chronic Beryllium Disease

Radiographic changes in CBD are nonspecific and cannot be differentiated from sarcoidosis (Table 86-2 and Fig. 86-3). The most common radiographic abnormalities are diffuse round and reticular abnormalities.[48,49] While most patients have both round and reticular nodules, opacities may be only round or only reticular. These opacities are usually present diffusely throughout the lungs but may be confined to the upper lobes. Hilar adenopathy similar

TABLE 86-1 Clinical Features of Beryllium Exposure, Beryllium Sensitization, and Chronic Beryllium Disease[a]

	Beryllium Exposure or Beryllium Sensitization (BeS)	Chronic Beryllium Disease (CBD)
Clinical presentation	Usually asymptomatic	Non-specific. Can be asymptomatic in early stages. In later stages, can present with cough, dyspnea, chest pain tachycardia, tachypnea, crackles, hypoxia
PFTs	Usually normal	Nonspecific. Normal, restrictive, and obstructive patterns can all occur. $D_{L_{CO}}$ can be reduced or normal.
Imaging	Usually normal	Indistinguishable from sarcoidosis. Typically, mid-to-upper lobe nodules or fibrotic changes with lymphadenopathy. In early disease, thoracic imaging can also be normal.
Lung biopsy	Not necessary in almost all individuals since patients tend to be asymptomatic	Non-caseating granulomas indistinguishable from sarcoidosis[a]
Follow-up/ treatment	Avoid or limit beryllium exposure. Surveillance: Follow patients at least every 1–3 years.	Avoid or limit beryllium exposure. Surveillance for asymptomatic individuals: Follow patients at least annually. Treatment (usually steroids and/or steroid-sparing agents) can be considered for symptomatic patients.

[a] *The presence of a positive blood or BAL fluid BeLPT distinguishes chronic beryllium disease from sarcoidosis in patients with appropriate occupational exposure history.*

Data from Balmes JR, Abraham JL, Dweik RA, et al. An official American Thoracic Society statement: diagnosis and management of beryllium sensitivity and chronic beryllium disease. Am J Respir Crit Care Med. 2014;190(10):e34–e59.

to what is commonly observed in sarcoidosis may also be seen in up to 50% of cases. However, the large "potato type" node involvement is not seen. The computed tomographic appearance of CBD includes upper lobe or diffuse fibrosis, pulmonary nodularity, and hilar and mediastinal adenopathy. However, in biopsy-proven CBD the computed tomographic findings may be normal or demonstrate ground-glass changes.

As the disease advances, radiologic evidence of scarring and retraction can be seen. The hila are retracted upward, and conglomerate mass and emphysematous bullae may be present. Gross architectural distortion can occur from severe fibrosis. Pleural thickening can be seen in the presence of long-standing disease.

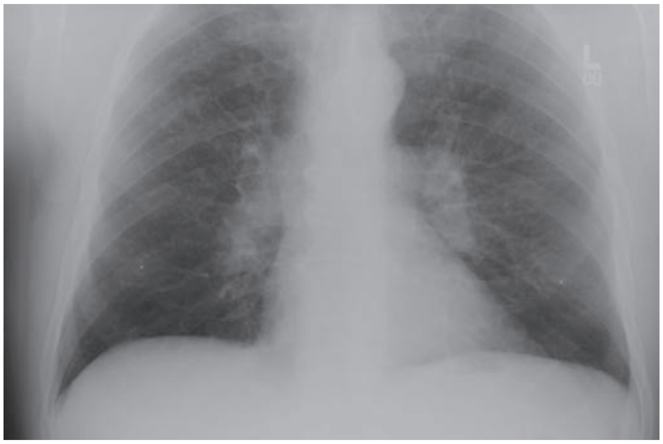
Radiographic changes can occur in CBD patients after therapy is initiated. In early disease, complete resolution of radiographic abnormalities can occur secondary to corticosteroid therapy and may recur as the corticosteroids are tapered.[50] Complete spontaneous disappearance of the radiographic lesions has not been observed.

Diagnosis of Chronic Beryllium Disease

A confirmed *definitive* diagnosis of CBD requires both demonstration of a granulomatous reaction on biopsy and evidence of

TABLE 86-2 Comparison of Chronic Beryllium Disease and Sarcoidosis

Manifestations	Sarcoidosis	Chronic Beryllium Disease
Erythema nodosum	10–20%	Absent
Hilar adenopathy	50–75%	<50%
Peripheral adenopathy	Occasional	Rare
Hypercalcemia	Occasional	Rare
Nephrocalcinosis	Rare	Rare
Bone changes	In chronic disease	Absent
Parotid involvement	Occasional	Absent
Posterior uveitis	Occasional	Absent
Liver involvement	Common	Frequent
Splenomegaly	Rare	Rare
Skin	Uncommon	Unusual
CNS	Occasional	Absent
Response to steroids	Only active disease	Only active disease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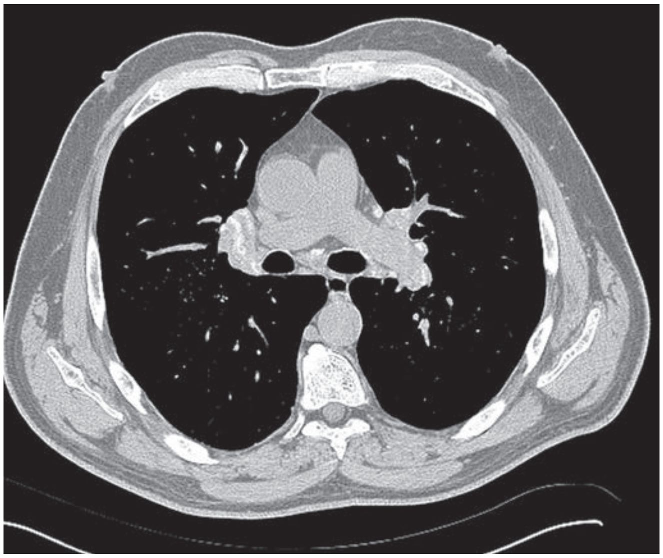
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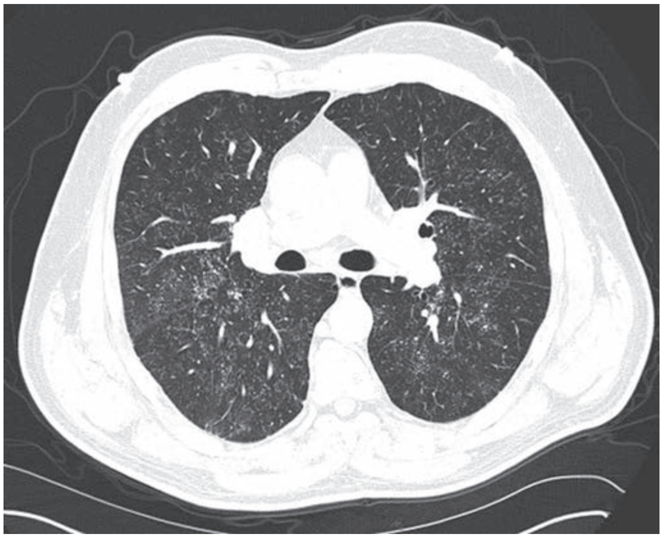
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Figure 86-3 A 61-year-old male smoker who had worked at a beryllium processing facility for 20 years. He had a productive cough for 10 years but denied any shortness of breath. He had a positive response of both his blood and BAL cells to beryllium (stimulation index [SI] for blood beryllium lymphocyte proliferation test [BeLPT] = 13.8 [Nl < 3.0], SI for BAL BeLPT = 306 [Nl < 5.0]). His BAL also demonstrated a marked lymphocytosis (cell yield = 6 × 105 cells/mL [Nl < 3.0 × 105 cells/mL], lymphocytes = 55.2% [Nl <20%]). **A.** Chest radiograph demonstrating nodular interstitial disease with adenopathy. **B.** Chest CT mediastinal window demonstrating calcified bilateral hilar and mediastinal lymph nodes. **C.** Chest CT lung window demonstrating a diffuse fine nodular pattern of interstitial lung disease that was most prominent in the mid and upper lung zones.

beryllium hypersensitivity assessed via positive BeLPT on either bronchoalveolar lavage fluid or with a blood sample. In nearly all cases, transbronchial biopsy is sufficient to detect the presence of granulomatous inflammation characteristic in CBD and surgical lung biopsies are not needed. In some patients, bronchoscopy is not safe or feasible for several reasons including patient preference. Therefore, a diagnosis of *probable* CBD can be assigned to patients with a classic exposure history, positive blood BeLPT, and radiographic findings consistent with beryllium disease as long as other differential diagnoses can be excluded.[42] Select laboratories perform BeLPT including Cleveland Clinic Foundation (Cleveland, OH), National Jewish Center for Immunology and Respiratory Medicine (Denver, CO), and Oak Ridge Institute for Science and Education (Oak Ridge, TN). A positive BeLPT is defined in several ways: (1) two abnormal blood BeLPT, *or* (2) one abnormal blood BeLPT plus a borderline result for a blood BeLPT, *or* (3) one abnormal BAL BeLPT, *or* (4) positive skin patch test to beryllium (skin patch tests are rarely done in the modern era).

The sensitivity and specificity of BeLPT are estimated to be approximately 68% and 97% respectively.[42,51] In patients undergoing bronchoscopy, bronchoalveolar lavage fluid should be sent for cell count (lymphocytosis can be seen in CBD), cultures (bacterial, fungal, and mycobacterial to exclude infectious etiologies that can mimic CBD), BeLPT (a positive BeLPT result from BAL fluid can be present in patients with negative blood BeLPT result), and transbronchial biopsies from affected areas (to detect the presence of granulomas characteristically seen in CBD).

BeLPT in screening beryllium workers can be used.[42] Because immunologic tests of beryllium hypersensitivity have been available only since the late 1980s, their use for screening worker populations is not clear. However, studies to date indicate that blood proliferative response to beryllium is the most sensitive screening test for CBD. The major difficulty with using the blood proliferative response to beryllium as a screening tool is that not all individuals with beryllium sensitization go on to develop CBD. In addition, the number of workers with beryllium sensitization that ultimately develop symptomatic CBD that requires treatment also is unknown but may be relatively low and is probably less than 10%.[45]

The justification for a screening test requires that there must be some action that will alter the course of the disease. Although it is generally believed that early treatment of CBD will alter the natural course of this condition, this is not certain.[52] In addition, removal from further exposure, a prudent but unproven practice, is possible for current workers but would not be applicable to former workers. Thus, the strongest recommendation for use of the beryllium lymphocyte proliferation test as a screening test can be made for current workers. Recommendations for screening former workers and residents of communities with past beryllium exposure from the ambient air are less certain. Nevertheless, because the risk of developing CBD is lifelong, the question of appropriate screening for exposed individuals' remains unclear.

Differential Diagnosis for Chronic Beryllium Disease

The major challenge to making the diagnosis of CBD is to think of the possibility of beryllium exposure. Most cases of CBD that are misdiagnosed are diagnosed as sarcoidosis because either the exposure to beryllium was not known by the patient or the physician failed to elicit an occupational history. In 84 cases of sarcoidosis with a history of possible beryllium exposure, a final diagnosis of CBD was made in 34 with a mean delay from the diagnosis of sarcoidosis of 4 years.[53] A similar search for cases of beryllium disease in a cohort of sarcoidosis patients failed to identify any cases of beryllium disease.[54] Because the radiographic and clinical presentation of CBD (Table 86-2) is similar to sarcoidosis,[55] the differential diagnosis includes upper-lobe fibrotic processes (Table 86-3). In addition, as for sarcoidosis, other causes of granulomatous disease must be searched for and eliminated. The differential between sarcoidosis and CBD depends upon the result of the proliferation test to beryllium. Patients with sarcoidosis do not respond to blood proliferation to beryllium, while CBD patients do. A negative blood or BAL proliferation test can identify cases of sarcoidosis in those exposure to beryllium. However, caution should always be used, and repeatedly negative blood and lung tests should be determined before accepting a case of granulomatous lung disease in a beryllium worker as sarcoidosis.

TABLE 86-3 Differential Diagnosis of Chronic Beryllium Disease

Sarcoidosis
Hypersensitivity pneumonitis
Tuberculosis
Histoplasmosis
Silicosis
Talc granulomatosis
Eosinophilic granuloma
Idiopathic pulmonary fibrosis

Treatment of Chronic Beryllium Disease

Treatment for chronic beryllium disease includes removing exposure, as well as corticosteroid and steroid-sparing agents. Small studies suggest that inhaled corticosteroids reduce symptoms but often do not improve pulmonary function test or radiographic findings.[56] No standard approach to the use of oral corticosteroids has been adopted in the treatment of CBD; however, guidelines suggest that a dose and duration mimicking treatment for sarcoidosis may be helpful (prednisone, 20–40 mg daily, followed by a taper to lowest tolerable dose over several weeks or months).[42,57–59] Because of the side effects, corticosteroids should be reserved for patients with documented pulmonary impairment or those with progressive deterioration. Doses of corticosteroids should be tapered to the lowest dose that controls the signs of active disease. Monitoring of patients with chest radiographs, pulmonary function tests, and exercise tests may be useful. Most cases of CBD are arrested with corticosteroid treatment. In cases of corticosteroid resistance or end-stage disease discovered at initial diagnosis, lung transplantation may be a reasonable approach.

Little data are available on the use of steroid sparing medications.[60] A trial of the anti–TNF-α antibody showed no significant clinical response in a very small cohort.[61] The long-term prognosis for CBD is uncertain. Follow-up of cases that were diagnosed in the 1940s and 1950s suggest that the mortality of the disease might be as high as 30%.[43] Whether a similar mortality will be present in patients with disease diagnosed since the 1990s is not certain. Newer techniques to diagnose CBD (immunologic testing) enable the disease to be detected earlier. The natural history of this condition detected at the presymptomatic stage is unknown. Two major remaining questions are whether disease that is detected early is inevitably progressive, and whether the disease will be responsive to corticosteroid therapy.

Beryllium and Lung Cancer

Many animal studies clearly indicated that beryllium is carcinogenic for several years. A National Institute for Occupational Safety and Health (NIOSH) study suggests that a small increase in lung cancer (SMR, 1.17)[62] may occur in beryllium workers. However, this finding has been challenged because of the poor data with regard to cigarette smoking.[63,64] This issue has remained controversial, however. In a report published in 2012, the International Agency for Research on Cancer stated that there was *sufficient evidence* in humans for the carcinogenicity of beryllium (Group 1).[65]

HARD-METAL LUNG DISEASE

Hard metal lung disease (HMLD) is a rare disorder that occurs in patients with exposure to hard metal. Hard metal is an alloy of tungsten carbide in a matrix of cobalt into which smaller amounts of other metals (chromium, molybdenum, nickel, niobium, tantalum, titanium, and/or vanadium) may be added. These components are milled to a fine powder, mixed together, pressed into the desired shape, and heated under pressure between 800° and 1000°C, yielding a product with a chalk-like consistency. The material may then undergo additional machining before being baked at 1500°C, which is above the melting point of cobalt and leads to the formation of an alloy. Once tungsten is intermixed with cobalt at high temperatures, the resulting metal has a hardness equivalent to $\sim$95% of diamond—hence the name "hard metal."[66] Because of this property, hard metal is an important component in cutting tools, drill bits, armor plate, jet engine parts, golf clubs, bike parts, and many other products.

Hard metal was developed in the 1920s, and ILD was first reported in hard-metal workers in 1940.[67] Lung disease has been noted to occur in those working in both the initial production of hard metal and the machining and maintenance of hard-metal tool components. In addition, although hard metal is not used in the diamond-polishing industry, a similar spectrum of disease has been reported in diamond polishers using steel polishing disks whose cutting surfaces consist of microdiamonds cemented into a fine cobalt mesh.[68] In contrast, workers in the cobalt-producing industry (who are more likely to be exposed to cobalt alone) may develop occupational asthma but appear to be much less likely to develop ILD. Cobalt lung disease has also been reported in individuals using e-cigarettes.[69]

The industrial processes associated with hard-metal lung disease produce respirable fine metallic dust particles. They also produce metallic ions that accumulate in the coolants used in the metalworking procedure and are absorbed through the skin or inhaled in vaporized coolant fluids. To counteract these exposures, the American Conference of Government Industrial Hygienists (ACGIH) has established current permissible exposure limits for cobalt metal, dust, and fumes at an 8-h threshold-weighted average (TWA) of 0.02 mg/m^3. NIOSH recommends an exposure limit of 0.05 mg/m^3 as a TWA for a 10-h workday and a 40-hour workweek, and OSHA requires an 8-h TWA of 0.1 mg/m^3.[70]

Clinical Manifestations in Hard Metal Lung Disease and Cobalt Disease

A variety of respiratory syndromes have been associated with exposure to hard metal, most commonly (1) asthmatic reactions, (2) a form of hypersensitivity lung disease, and (3) interstitial pulmonary fibrosis. The last two may be a continuum of the same process with subclinical or unrecognized hypersensitivity alveolitis proceeding to the development of fibrotic lung disease.

Over several decades, HMLD has been referred to as *hard metal pneumoconiosis*, *tungsten carbide pneumoconiosis*, *cobalt lung, and giant cell interstitial pneumonia.*[71] In the modern era, HMLD has been used to describe all types of lung disease, but it is most often used to reference the parenchymal or ILD, rather than the airway-related manifestations of hard-metal inhalations. While the nomenclature can be challenging, the key concepts to emphasize include the following: (1) hard metal is tungsten and cobalt mixed together; (2) only a select group of patients with exposure to cobalt or tungsten or both (exposure to hard metal) will develop lung disease for unclear reasons; (3) individuals with predominantly cobalt exposure may have markedly different symptoms than patients with predominantly tungsten exposure; (4) most studies suggest that workers exposed only to cobalt (no tungsten exposure) do *not* develop ILD but usually tend to develop airway-related disease or occupational asthma; (5) in contrast, workers exposed to tungsten (with or without cobalt) usually appear to develop ILD (Table 86-4).

TABLE 86-4 Comparison of Patients with HMLD and Primarily Cobalt or Tungsten[a] Exposure

Predominant Substance	Cobalt Alone	Tungsten (with or without Cobalt)
Typical Presentation	Workplace asthma type (cough, dyspnea, wheeze; symptoms may improve on non-work days)	Acute: Similar to pneumonitis (fever, cough, dyspnea, anorexia) Chronic: Mimics fibrotic ILD (chronic cough, dyspnea)
Diagnostic studies	Reduced peak flow. Positive bronchoprovocation test	Non-specific PFT and HRCT results; hence, occupational exposure history important. Pathology may reveal GIP.
Treatment	• Reduce workplace exposure • Bronchodilators • Inhaled corticosteroids • Oral corticosteroids rarely required	• Reduce workplace exposure • Often require oral corticosteroids

[a] *Patients with hard metal lung disease (HMLD) can have predominately cobalt exposure or tungsten exposure. Classically, HMLD is reserved for patients who develop ILD. Tungsten exposure seems to cause ILD more frequently. Cobalt-related lung disease is used to identify patients with asthma type of symptoms since ILD caused by cobalt disease is rare. (Cobalt ILD has been reported in very rare instances such as the diamond industry.) Since presentation varies between cobalt- and tungsten-related lung disease, diagnosis and treatment vary.*

Interstitial Lung Disease in Hard Metal Lung Disease

ILD has been seen in hard-metal workers. Studies have attempted to determine the prevalence of ILD among hard-metal workers. The studies have been frequently limited by lack of appropriate control groups, loss of former workers who may have left the plant due to illness, inconsistent disease detection/definitions, and small numbers. However, despite these limitations, it is clear that ILD develops in a small minority of exposed workers. Estimates range from 0.7% to 12.9% in cross-sectional studies.[72–77] A longitudinal study found no ILD in its cohort, but it was a small study with more recent exposure and may represent the effects of limiting exposure levels.[78] Reports of exposure intensity, duration, and immediacy have varied a great deal. For instance, in one review of 100 cases of HMD the duration of exposure varied from 1 to 30 years, and 1 case was diagnosed 40 years after a 3-year exposure had ceased.[79] Nonsmokers and former smokers also appear to be at higher risk.[80]

Interestingly, most studies suggest that workers exposed to cobalt alone without tungsten and other metals do not appear to develop ILD (Table 86-4). A few cases of diamond polishers exposed to cobalt alone who have developed ILD have been reported, but this appears to be fairly rare.[81] In some patients, HMLD presents as a hypersensitivity pneumonitis or allergic alveolitis. These patients manifest fever, anorexia, cough, dyspnea, inspiratory crackles, and fine reticulonodular infiltrates on chest radiograph. Pulmonary function testing typically shows a restrictive pattern, with a reduced DL_{CO}. Symptoms may resolve when exposure is discontinued but may recur with re-exposure.[82]

Over time, progressive dyspnea, lung function impairment, and interstitial fibrosis may develop. Fibrosis may also occur in the absence of antecedent symptoms. Patients with advanced disease exhibit weight loss, hypoxemia, digital clubbing, pulmonary hypertension, and cor pulmonale. The histopathologic manifestations of the interstitial disease in these patients can be varied, with findings consistent with bronchiolitis, desquamative interstitial pneumonitis, usual interstitial fibrosis, and giant-cell interstitial pneumonitis (GIP). Granuloma formation is infrequent. Lung biopsies may show heterogeneous patchy involvement with foci of active alveolitis, fibrosis, and normal parenchyma. Bronchiolitis may be seen in areas with and without active alveolitis. Infiltration with eosinophils also has been described. GIP is characterized by lymphoplasmacytic infiltration, epithelial desquamation, and the presence of numerous multinucleated giant cells in the alveolar spaces.[83] These giant cells are formed by both actively phagocytic alveolar macrophages and type II pneumocytes and are referred to as "cannibalistic giant cells." Notably, GIP has been seen in individuals without hard metal exposure; however, these cases appear to be rare.[84,85] At the present time, the presence of GIP in patients with hard metal exposure strongly suggests a diagnosis of HMLD.

Analysis of BALF may demonstrate hypercellularity with increased numbers of macrophages and giant cells. A relative or absolute increase in the number of lymphocytes with a reduced CD4/CD8 ratio, and increased numbers of neutrophils, eosinophils, and mast cells, also may be seen. In addition, the multinucleated giant cells can also be found in the BALF, which may be diagnostic of HMLD and obviate the need for a surgical lung biopsy.[86,87] One study found that a high number of eosinophils in the BAL that persisted after cessation of exposure and while on therapy was associated with a poorer outcome.[87] Electron microscopy with energy-dispersive x-ray analysis (EDAX) of the particulate material present in biopsy specimens may demonstrate the presence of the elements used to form hard metal. Because of its high solubility, significant amounts of cobalt are often not present.[79]

Naqvi et al. reviewed 100 cases of HMD identified either by the histologic presence of GIP or with a quantitative EDAX analysis containing tungsten at concentrations greater than 2×10^6 particles per cm^3 of lung tissues.[79] Of these, 59 had changes diagnostic of GIP. In more advanced cases, there were changes of end-stage fibrosis and honeycombing, with or without characteristic GIP lesions. Only 4 cases demonstrated granulomas, and of those, 2 also had changes of GIP. They examined 746 cases of ILDs examined by EDAX and found a striking correlation of tungsten with the finding of GIP, with higher levels of tungsten more likely to be associated with GIP. Cobalt was detected in only 36 patients in the larger cohort. Only those who had tungsten present in addition to cobalt had GIP findings on pathology. The investigators concluded that the presence or absence of cobalt was not useful in diagnosing or excluding HMLD.

Few studies have looked at the radiography of HMLD. Many of the screening studies of cobalt workers rely on plain chest radiographs and use the profusion score of the International Labour Office (ILO). However, a consistent description of the typical findings has not been offered. More recently, with the advent of computed tomography (CT) scans, a few case reports have described the CT findings of patients with HMLD. Like the pathology, these findings show a wide variability and can include end-stage honeycombing with cystic changes and traction bronchiectasis, to less impressive reticulation and even areas of ground-glass opacities.[88] No pathognomonic finding has been described.

Treatment for this disease consists of discontinuation of exposure and administration of systemic corticosteroids. A case report describes a patient who responded to a high dose of inhaled corticosteroids alone.[89] Although no clinical trials have been performed, dosage and duration of treatment similar to those used in other forms of active alveolitis or fibrosis should be considered. Patients with active alveolitis may show a dramatic response to steroids, whereas patients with more prominent fibrosis may show minimal response, despite prolonged steroid treatment.[66] Fibrosis may progress despite cessation of exposure. GIP has been observed to recur after lung transplantation, despite cessation of occupational exposure.[79,90,91]

■ Occupational Asthma in Cobalt Exposed Patients

In contradistinction from ILD, asthma can occur in workers exposed to cobalt alone without tungsten (Table 86-4).[92,93] The reported prevalence of asthma or wheezing related to cobalt or hard-metal exposure is low and ranges from 6.6% to 10.9%.[77,92,94] This variation may be attributed to different levels of exposure and the criteria used by various authors to define occupational asthma. As with other forms of occupational asthma, patients may note cough, wheezing, dyspnea, chest tightness, conjunctivitis, and rhinitis. Throughout the workday, symptoms may increase in severity, and a progressive decline in peak flow may be demonstrated. Symptoms usually abate during weekends or vacations and often resolve when exposure is discontinued.

Upper-airway symptoms may result from either direct airway irritation or atopic responses. In addition to demonstrating an association between workplace exposure and symptoms, the diagnosis may be confirmed by bronchoprovocation testing (BPT) with cobalt or cobalt salts. Testing with cobalt salts is preferable, as it is much easier to control dosage and delivery of soluble ion solutions than those of particulate substances. Immediate or delayed airway reactivity to cobalt chloride may be observed after BPT.[95] Tungsten carbide has not been shown to produce bronchoconstriction. A positive radioimmunosorbent test (RAST) to cobalt-conjugated human serum albumin also has been reported in some patients, suggesting a type I allergic response. Skin patch testing with cobalt salts does not appear to be of use in diagnosing hard-metal asthma.[95] Serum or urinary cobalt levels can be measured; however, false positives can be seen in smokers, patients taking multivitamins, or individuals with certain hip prosthesis. Furthermore, the cobalt levels may be elevated only for a short time after exposure.[71]

There is no clear dose-dependent relationship between cobalt exposure and spirometry abnormalities. Some studies have suggested a dose–response relationship between higher levels of cobalt exposures and lower forced expiratory volume in 1 s (FEV_1) on spirometry and symptoms of asthma.[77,93,96] A twofold increase in the relative odds ratio for work-related wheezing was noted when cobalt exposure exceeded 0.05 mg/m^3.[77] However, asthma and reductions in FEV_1 have been seen at levels below the allowable limit of 0.05 mg/m^3.[97,98] This suggests that the current permissible exposure limit may not protect all workers against the development of cobalt-induced asthma.

Since there is no direct link between exposure and asthma development in patients with cobalt exposure, baseline evaluations and employee screenings should be performed in workers exposed to hard-metal dust or cobalt alone. A reasonable strategy would include assessments for symptoms (rhinitis, conjunctivitis, wheezing, dyspnea, or chest tightness) and the relationship of symptoms to work hours, smoking history, physical examination, pulmonary function testing, and chest radiography. In patients with symptoms or findings suggestive of occupational asthma, peak flow monitoring during working and nonworking hours should be performed and other causes of pulmonary function deterioration ruled out.

Specific BPT and RAST results may provide additional positive criteria for diagnosis. Personal employee air sampling and measurement of urinary cobalt levels can provide information about ongoing exposure.[99] The workplace should also be examined for levels of cobalt exposure and employee protective practices. However, there may also be long-term respiratory health effects independent of the development of asthma. One recent longitudinal study found that those smokers with higher exposure had a greater fall in their FEV_1 over 10 years than those with less exposure. However, the contribution of the cobalt exposure to the overall expected decline was relatively modest (103 mL in addition to 518 mL from smoking alone in the highest exposure group).[78]

Treatment for occupational asthma related to cobalt includes control of exposure, as well as medical therapy with bronchodilators and inhaled corticosteroids. Systemic corticosteroid treatment is usually not required.[66]

■ Cobalt, Hard Metal, and Lung Cancer

Cobalt and cobalt-containing compounds have been shown to cause cancer in rats after local injection and intratracheal instillation.[100] Researchers reviewed the evidence for the carcinogenicity of cobalt in 1991 and concluded that although there was sufficient evidence for the carcinogenicity of cobalt metal powder and cobalt oxide in experimental animals, there was inadequate evidence for the carcinogenicity of cobalt and cobalt compounds in humans.[100]

Since that publication, however, there have been studies suggesting a relationship. One study of 709 French hard-metal workers found an excess of lung cancer mortality in their workers, and the excess was greater in workers with the highest levels of exposures although no relationship with duration of exposure was found.[101] However, this study was not powered to examine the effect of smoking as well, so firm conclusions could not be drawn. A second study by the same group of researchers found a twofold higher risk of lung cancer among subjects exposed to both tungsten and cobalt, and the odds ratio increased with cumulative exposure.[102] The study was able to adjust for smoking and found that the relationship between hard metal and lung cancer held.

A more recent study of one of the same plants was published in 2000 and examined mortality again from lung cancer with greater adjustment for smoking and exposure by job matrix.[103] Investigators found an elevated standardized mortality rate that increased with increasing duration, intensity, and cumulative dose of exposure to hard-metal dust. The excess was almost exclusively in subjects exposed to unsintered hard-metal dust. Ultimately, in a 2006 publication, the International Agency for Research on Cancer stated that cobalt with tungsten is *probably* carcinogenic to humans (Group 1A) and cobalt without tungsten is *possibly* carcinogenic to humans.[104]

■ Mechanisms of Injury in Hard Metal Lung Disease

The pathogenesis of the hard-metal–associated lung diseases is poorly understood. There are two predominant hypotheses for the pathogenesis of hard-metal lung toxicity: (1) hypersensitivity with lymphocyte-driven toxicity and (2) free-radical and cytokine-mediated injury.

Several authors point out the similarities of hard-metal lung disease and hypersensitivity lung disease, including the ability of cobalt to function as a hapten in complex with albumin and to cause a contact dermatitis.[105] BAL studies of both exposed workers and those with HMD have shown increased lymphocytes with reduction of the helper/suppressor T-cell ratios.[106] In addition, in at least one subject with HMD, a lymphocyte transformation test was found to be positive in the presence of cobalt.[107] Finally, a recent report suggests an association between a glutamic acid residue in position 69 of the HLA-DP beta chain and susceptibility to HMD.[108] This is similar to CBD, a known hypersensitivity disorder.

Notably, however, there are features of this disease that do not suggest a hypersensitivity reaction as the mechanism for the disease. Perhaps most obvious is the fact that granulomas, the hallmark of chronic hypersensitivity pneumonitis, are not typically found on biopsy. In addition, the finding that both cobalt and tungsten are required for most cases of hard-metal lung disease requires explanation. In vitro studies using peritoneal and alveolar macrophages from rats and mice have demonstrated that the combination of tungsten carbide and cobalt is highly cytotoxic, while cobalt and tungsten carbide alone produce minimal or no cytotoxicity.[109] In addition, the acute lung toxicity of tungsten carbide plus cobalt is much higher than that of each component after intratracheal instillation in rats.[110]

Lison[105] has proposed a mechanism that might explain this interaction. He suggests that tungsten carbide can act as an electron carrier to transfer electrons from cobalt to oxygen. This leads to the production of free radicals and reactive oxygen species, which, in turn, cause pulmonary damage. Differences in susceptibility to disease would, therefore, be due to differences in subjects' antioxidant defenses. Further research is required to elucidate the pathophysiology behind hard-metal lung disease.

SUMMARY

This chapter addresses two metals that cause lung injury usually due to an occupational exposure. Both beryllium and hard metal can cause interstitial pulmonary inflammation that is immune mediated. Beryllium results in a chronic cell-mediated response that is mediated by CD4+ T cells and results in granuloma formation. The mechanism of hard metal's interstitial inflammatory response is less clear but results in a giant-cell interstitial pneumonia, although other histopathologic findings can be seen. Both metals may cause disease in a minority of patients, and its development is not dose-dependent. Both metals have also been implicated in cancer. Chronic beryllium disease is indistinguishable from sarcoidosis unless a positive beryllium lymphocyte proliferation test is performed. Hard metal lung diseases may be associated with asthma-like reactions or interstitial lung disease. The presence of GIP on biopsy in patients with hard metal exposure is nearly diagnostic of HMLD. Improved diagnostic approaches to these conditions have resulted in earlier diagnosis and recognition of harmful workplace exposures.

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CHAPTER 87

Coal Workers' Lung Diseases and Silicosis

Robert C. Stansbury
Rahul G. Sangani
John E. Parker

COAL WORKERS' LUNG DISEASES

Coal miners are at risk for developing several distinct clinical illnesses in relation to their occupational exposures. Historically, some names applied to these conditions were miners' asthma, phthisis, anthracosis, and in Scotland, miners' black lung. It was recognized early that these afflictions were related to the occupation of mining; however, it was not until the development of specialized techniques such as chest radiography, pulmonary function testing, the discovery of the tubercle bacillus, and sophisticated histologic examination of tissue that respiratory diseases affecting miners could be separated and defined. Advances in the understanding of respiratory health issues in coal miners have focused on the spectrum of disease caused by inhalation of coal mine dust, termed coal mine dust lung disease (CMDLD).[1]

CMDLD includes the classic occupational interstitial lung diseases, such as coal worker's pneumoconiosis (CWP), silicosis, mixed dust pneumoconiosis, and dust-related diffuse fibrosis (DDF).[1] CMDLD is a preventable occupational disease that results from inhalation of coal mine dust into the lungs leading to parenchymal and airway damage, from not only the foreign material itself but also the tissue's reaction to the dust.[1,2] This disease process was identified as early as the 1800s but became much more prevalent as coal production increased during the industrial revolution. Unfortunately, disability from coal mine dust exposure went mostly unrecognized by medical authorities in the United States through the first part of the 20th century. Congress finally passed comprehensive legislation with the Federal Coal Mine Health and Safety Act of 1969. This Act went above and beyond previous legislation by providing for the first mandatory standards for working conditions in U.S. mines, a system for enforcement, and ongoing monitoring of miner health, as well as a mechanism for seeking financial compensation for coal miners who could demonstrate total disability arising from their dust exposure (aka "black lung").[3]

Since the time of this landmark legislation, further acts by Congress and enforcement agencies have improved miners' working conditions, which now fall under the purview of the Mine Safety and Health Administration (MSHA). Much of our improved understanding of the nature and extent of lung disease associated with mining coal in the United States over the past half century comes from the large number of studies performed by the National Institute for Occupational Safety and Health (NIOSH). Despite increased understanding of CWP and reports of stable or improved dust levels in mines, dust-related respiratory disease remains a significant burden. Most worrisome are recent data suggesting that contemporary dust exposure is leading to rapidly progressive pneumoconiosis particularly in young miners, with a significant impact on pulmonary function and premature death.[4]

■ Coal and Coal Mining

Coal is not a pure mineral. It is a spectrum of carbonaceous rocks derived from the accumulation of vegetation sedimented under swampy conditions and subjected to extreme pressure over long periods of time. Coals are characterized by rank, which relates to geologic age, hardness, carbon content, and the amount of heat released (BTUs) when they are burned. Thus, peat is the lowest rank (softest) coal, being geologically the newest, and anthracite is the highest rank (hardest) and oldest type of coal.

Coal may be found in outcroppings and in seams that vary from a few feet to several thousand feet below the surface. Surface or strip mining, which currently accounts for the majority of U.S. coal production, involves removal of the overburden and mining the coal seams with large earth-moving equipment. In some areas of the eastern United States, mountaintop removal mining has become a dominant form of mining. Mountaintop mining involves first removal of all vegetation and soil, and then drilling and blasting through hundreds of feet of strata to access the coal seam. The excess rock and soil are placed in the steep stream beds along the mountainsides, creating areas called valley fills. Occasionally, surface mining is also performed by boring into coal outcrops with an auger. Dust levels measured in the air at surface mines have generally been lower than in underground mines, with a few notable exceptions, but miners who work exclusively at surface operations may still develop advanced forms of pneumoconiosis (discussed below).[5,6] Coal outcrops of sufficient size can be mined deep into the hillsides. Deep seams are accessed through vertical shafts drilled from the surface to the coal seam where the mining process then follows the seam through a series of more or less horizontal tunnels. Shaft drilling, which is frequently performed under contract for mine operators, may present an important silicosis hazard. A majority of the approximately 92,000 coal miners in the United States work at underground mines,[3] although deep mines produce somewhat less than half of the coal mined; in China, there are about six million underground miners.[1]

Respirable dust concentration, coal rank, types of mining work, mining category, and duration of exposure are known risk factors for the development of pneumoconiosis.[7] Dust exposure varies significantly between specific tasks within the mines. In underground mining, airborne dust is generally highest during work at the coal-cutting face, where coal is removed from intact seams. Miners involved in roof support (termed roof bolters; see Fig. 87-1), miners who do not use protective respiratory equipment, workers exposed to explosive blasting fumes, and those who use stored mine water for dust suppression spray are all at increased risk for accelerated loss of lung function.[8]

Many miners also have exposure to respirable crystalline silica, placing them at risk for silicosis and/or concurrent CWP/silicosis.[9] In particular, silicosis has been recognized among miners performing roof bolting and drilling operations, as well as motormen who operate underground coal trains and use sand for traction on the rails.[10,11] Workers in some aboveground coal mining operations also may have important exposure to dusts.[5,12] These include workers at tipples and preparation plants, where crushing, sizing, washing, and blending of coal is done, and coal is stored or loaded onto ships, railroad cars, or river barges. At surface coalmines, drilling rigs are used to bore holes in which explosives are placed. Equipment operators may be exposed to silica and silicate dusts from the rock strata, representing a risk for silicosis or mixed dust pneumoconiosis, rather than CWP (Fig. 87-1).

■ Epidemiology of Lung Diseases in U.S. Coal Miners

Results of radiographic surveillance from the 1970s through the mid-1990s showed a marked decline in the prevalence of CMDLD.[13,14] This decreased prevalence was a source of great optimism that

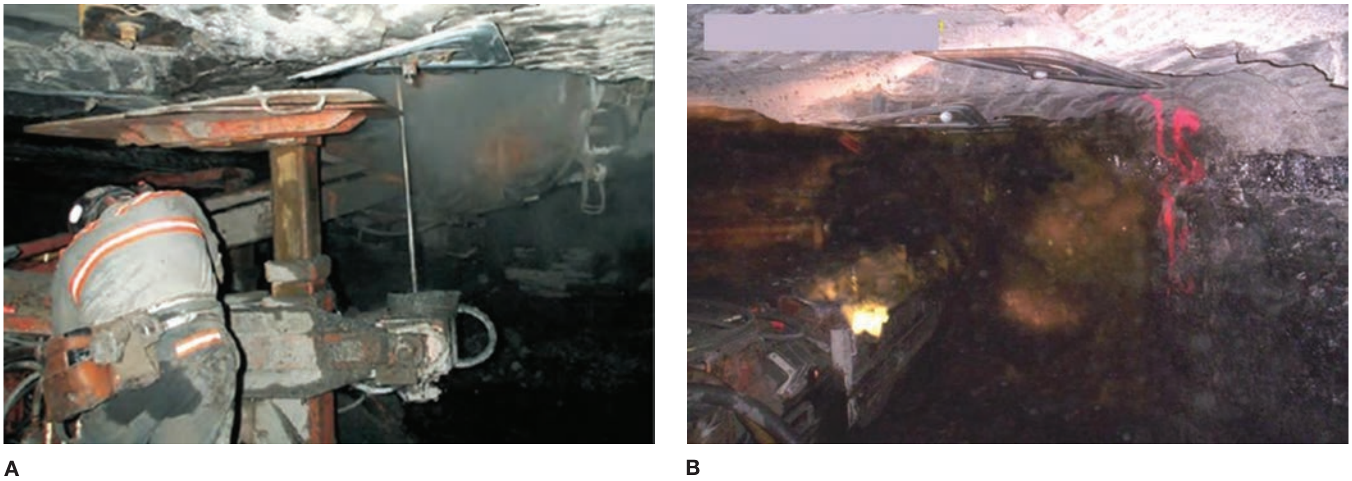

Figure 87-1 Photographs illustrating underground coal mining. In (**A**), miner is engaged in drilling before placing a roof bolt. In (**B**), the gray area above the black coal seam indicates where the mining equipment has pulverized a layer of silica-bearing rock. *(Reproduced with permission from Anita Wolfe, National Institute for Occupational Safety and Health, Morgantown, WV.)*

government regulations and oversight were resulting in improvement in miners' respiratory health. Often support for surveillance programs is decreased/eliminated when disease prevalence rates show such a significant decline. Fortunately for U.S. miners, continued work by institutions such as NIOSH have identified alarming changes in disease patterns (Fig. 87-2).[15] The most consequential findings of this contemporary work are the increased frequency and severity of disease in younger miners, higher prevalence rates of CMDLD, and a higher proportion of the most severe and often lethal form of CMDLD, progressive massive fibrosis (PMF).[16–18] In response to these trends the United States has lowered the permissible coal dust exposure limits (1.5 mg/m^3), expanded surveillance, and addressed several loopholes in dust sampling methodology.[19] While these interventions are promising, worrisome trends in miners' health remain and the efficacy of these interventions will not be apparent unless longitudinal surveillance programs are continued.[17,18] Despite a gradual shift into renewable energy, coal remains a critical source of energy production worldwide, accounting for 30% of global energy needs.[20] Coal mining employment in the United States and other countries around the world will remain high for years to come. Thus, continued surveillance by the public health sector and familiarity with the various manifestations of CMDLD by healthcare professionals will be necessary for miners' wellbeing through the 21st century.

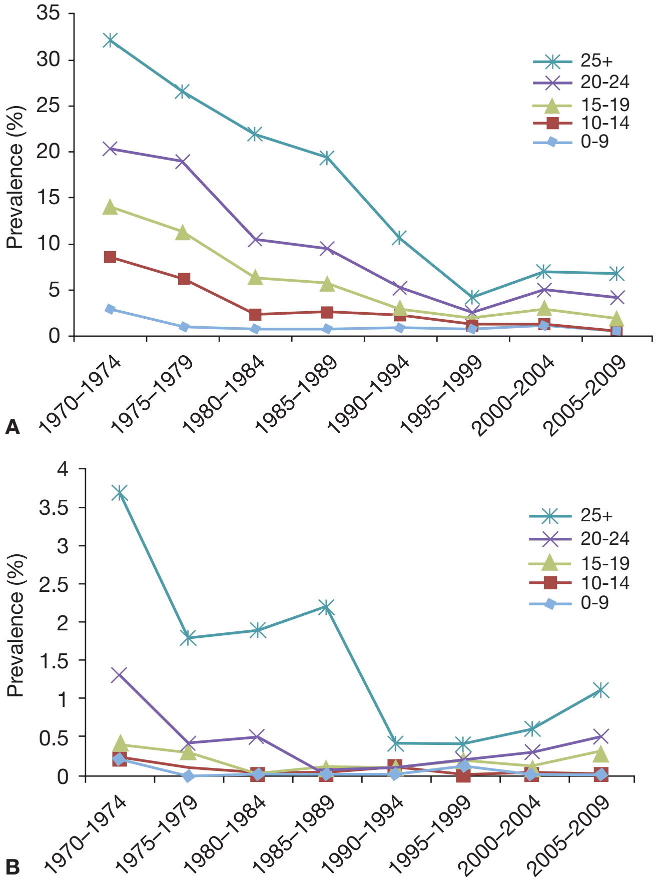

Figure 87-2 Proportion of miners examined in the NIOSH Coal Workers' X-ray Surveillance Program from 1970 to 2009 with coal workers' pneumoconiosis category 1 or greater (**A**) or progressive massive fibrosis (**B**), by tenure in underground coal mining. *(Reproduced with permission from Attfield MD. Centers for Disease Control and Prevention: Current Intelligence Bulletin 64: Coal Mine Dust Exposures and Associated Health Outcomes—A Review of Information Published Since 1995. DHHS (NIOSH) Publication No. 2011–172.)*

■ Radiographic Findings

Radiographic epidemiologic studies have been one of the cornerstones for surveillance of coal miners' health reported over the last four decades. As part of these activities, each miner's chest radiograph is independently interpreted by at least two qualified physicians, using the International Labour Office (ILO) pneumoconiosis classification system (Table 87-1).[21] Radiographic data from the initial health surveys showed an overall prevalence of simple and complicated CWP of nearly 30%. There was variation in prevalence by region of the country and the type (rank) of coal mined.[22] Enforcement of dust control measures in the United States, fully enacted in 1973, resulted in a declining pneumoconiosis attack rate. This decreased prevalence was confirmed through the federally mandated chest radiographic surveillance program for underground U.S. miners.[13,14] Between 1973 and 1978, CWP was found in about one-third of the miners who participated in the program and had worked 25 years or more underground.[14] By 1995 to 1999,

TABLE 87-1 Definitions of Terminology Used by the International Labour Office Classification to Describe Pneumoconiotic Opacities

ILO Term	Opacity Width	Opacity Type
P	≤1.5 mm	Small rounded
Q	1.5–3 mm	Small rounded
R	≥3–10 mm	Small rounded
S	≤1.5 mm	Linear/irregular
T	1.5–3 mm	Linear/irregular
U	≥3–10 mm	Linear/irregular
A	≥10–50 mm	Large
B	≥50–RUZ mm	Large
C	≥RUZ	Large

RUZ, Right upper (lung) zone.
Data from International Labour Office. Guidelines for the use of the ILO international classification of radiographs of pneumoconiosis. Revised edition 2011. Geneva, Switzerland: International Labour Office; 2011.

only 1 in 25 (4.2%) of these miners showed radiographic evidence of CWP.[14]

Regrettably, continued surveillance by NIOSH has revealed a continued increase in the prevalence of radiographic pneumoconiosis (to 10%) for miners with more than 25 years' tenure, since hitting its nadir around the turn of the century.[18] The rate of progressive massive fibrosis (PMF) has tripled to 1.1% after reaching its low point over a decade ago.[23]

Perhaps the most concerning findings of ongoing surveillance studies have been the frequency of rapidly progressive radiographic disease in certain mining populations. During their 2005 analysis, Antao et al. found that in miners with pneumoconiosis, about 35% had rapidly progressive disease. This rapid progression was defined as an increase of greater than one ILO subcategory over 5 years.[24] More worrisome is the fact that 15% developed PMF, the most advanced and debilitating form of the disease. By 2015, the prevalence of PMF in Central Appalachia reached the highest levels ever recorded.[25]

Radiographic analysis has been complemented by ventilatory lung function testing as an integral component of respiratory health studies of the mining population. Early reports strived to identify a relationship between radiographic disease and spirometry results. Multiple studies in the United States and abroad have subsequently evaluated the relationship between radiographically evident CMDLD and lung function.[26–28] Although several earlier studies did not associate lung function impairment with uncomplicated CWP, recent analysis has identified significant ventilatory deficits among coal miners with small radiographic opacities, in addition to the important decrements in lung function that have been observed in miners with the large radiographic shadows (>10 mm) of PMF.[4,28,29]

Studies in the United States and Great Britain evaluated lung function with respect to the miners' cumulative dust exposure and have helped to clarify the adverse effect of dust on coal miners' lung function.[30–32] Miners show a progressively greater risk of lung function loss with increasing cumulative dust exposure, independent of the chest radiographic findings of CWP. The forced expiratory volume in 1 s (FEV_1) loss is most severe in those who work for many years at the dustiest jobs. Among smoking miners, the effects of tobacco smoke appear to be additive and of similar magnitude to the dust effect. Studies of FEV_1 decline have demonstrated essential equivalence between 1 year of work in a job at the coal face and 1 year of cigarette smoking: no disproportionate dust effect has been noted in relation to tobacco use. Also, there is evidence that miners experience a more rapid loss in spirometric function parameters during their first few years of mining, with slower dust-related declines after that time.[25]

In summary, the epidemiologic evidence has shown that coal miners experience ventilatory lung function loss with increasing exposure to dust, in the presence or absence of radiographic CWP. Among smoking miners, the effects of tobacco and dust appear to be additive. Although, on average, the functional losses associated with either dust or smoking are small, it is estimated that after 35 years of work at the current permissible limit, dust exposures will cause a clinically important FEV_1 loss in 8 out of 100 nonsmoking coal miners. Higher exposures result in greater losses. When chronic bronchitis is present, there is an additional FEV_1 reduction averaging 200 to 250 mL.[7,33] With simple CWP, and especially when PMF is present, an additional ventilatory deficit is likely.

Investigations into miner mortality have been completed in both the United States and Britain. Findings from both countries have been generally consistent and reveal that the miners experience increased mortality attributable to pneumoconiosis, emphysema, chronic bronchitis, and ischemic heart disease.[34–39] Radiographic findings of advanced CWP (PMF) consistently affect mortality, especially in categories B and C (see Table 87-1 for definition of ILO terminology), whereas among miners with simple CWP, decreases in survival were smaller. Accelerated FEV_1 decline is also associated with increased mortality from both cardiovascular and respiratory causes.[36] Miners' risks of dying from the obstructive airway diseases of emphysema and chronic bronchitis exhibit a different geographic pattern than the mortality from CWP, suggesting that these dust effects have different mechanisms.[37] Attfield and Kuempel[38] analyzed the mortality experience over 22 to 24 years among 8899 working coal miners. Their results revealed increased mortality from nonviolent causes, nonmalignant respiratory disease, and accidents, and confirmed previous results indicating that exposure to coal mine dust leads to increased mortality in the absence of tobacco smoke exposure.

Troubling recent data regarding miners with both rapidly declining lung function and rapid progression of radiographic disease seem to have had mortality implications as well. A NIOSH report from 2018 revealed a substantial increase in years of potential life lost (YPLL) attributable to CWP between 1996 and 2016.[40] A study in 2011 reviewed a decade of data (at current exposure levels). Investigators found rapidly progressive pneumoconiosis and massive fibrosis in relatively young West Virginia coal miners that led not only to important lung dysfunction but also to premature death.[4] More documentation for the high risk of contemporary coal mine exposures comes from investigations into mining accidents. Lung tissue analysis was performed on 24 victims of a recent mine explosion. Of the 24 victims, 17 (71%) had autopsy evidence of CMDLD; 16 of the 17 miners with CWP had started working after the modern dust limits were put into effect.[41] Unfortunately these concerning trends continue, particularly in Appalachia.[42] The implications of these new studies are incompletely understood, but it is obvious that contemporary miners are still developing severe and fatal CMDLD.

Pathology of Coal Miners' Lung Diseases

Heppleston[43] identified the coal macule as a fundamental histopathologic finding in CMDLD in 1953 (Fig. 87-3). In his discussion, he described the macule as consisting of a focal collection of coal dust in pigment-laden macrophages around the respiratory bronchioles and tapering off toward the alveolar duct. A fine network of reticulin is present in the early stages and may include

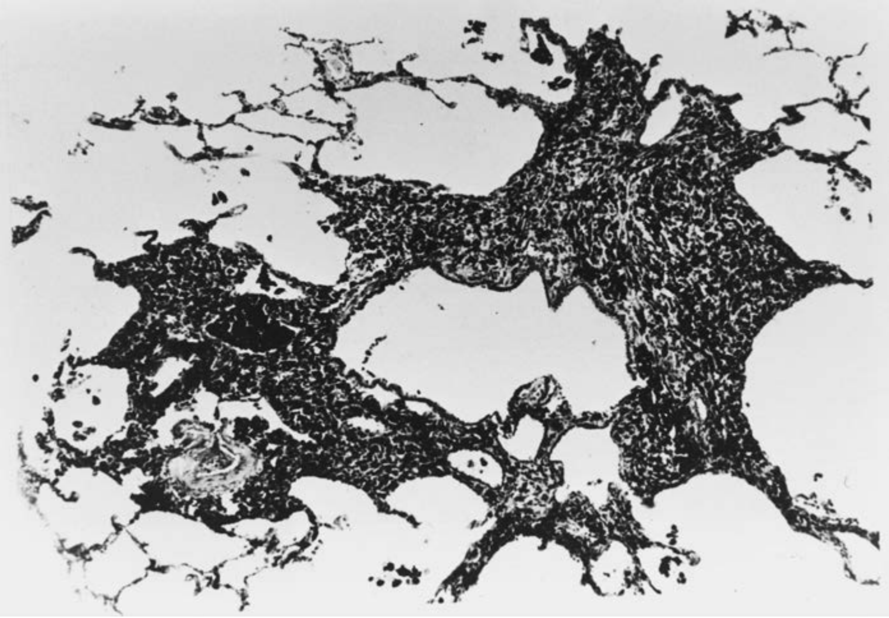

Figure 87-3 A coal macule, microscopic section. *(Reproduced with permission from Dr. Val Vallyathan, National Institute for Occupational Safety and Health, Morgantown, WV.)*

a small amount of collagen depending upon the character of the dust.[44] Centriacinar emphysema, the dilation and injury of lung gas exchange units, is observed with increased prevalence in the lungs of coal miners. Focal emphysema is the form of centriacinar emphysema that is seen as an integral part of the lesion of simple CWP. It is characterized by enlargement of the airspaces immediately adjacent to the dust macule. The pathologic severity of the emphysema is proportional to the miner's cumulative dust exposure and increases with increasing lung dust retention.[45–47] Muscular thickening of pulmonary arteries, in conjunction with hypertrophy of the right ventricle, can be observed with both simple and complicated CWP and is increasingly prominent when CWP is associated with other lung disorders.[48] The development of pulmonary hypertension secondary to these changes may have a profound adverse effect on miner mortality.[49] Pathologic changes in the airways consistent with chronic bronchitis, including enlargement of mucus glands, have also been documented in miners' lungs.[50]

Central to the biology of CMDLD (discussed below) is the alveolar macrophage.[51–53] Dust particles that travel to the distal airways (beyond the mucociliary escalator) are engulfed by alveolar macrophages and removed from the airways and lung parenchyma via lymphatics. With extended excessive dust exposure, this system is overwhelmed and coal mine dusts as well as dust-laden macrophages begin to accumulate in the airway walls and interstitium. Recent evidence suggests that important lung functional losses observed during coal mining work may at least in part be related to this dust reaction in the small airways.[54–56] With ongoing dust deposition and inadequate clearance mechanisms, these lung lesions increase in size and number. These larger fibrotic lesions are called coal nodules and are palpable in lung specimens, whereas coal macules are not. Palpable coal nodules are classified as micronodular up to 7 mm in diameter and macronodular from 7 mm and larger.[57]

A less common form of CMDLD and silicosis labeled DDF has been increasingly recognized. This finding had previously been interpreted as representing the development of usual interstitial pneumonitis (UIP) in miners. Recognition of a pulmonary fibrosis pattern related to CMDLD has been supported by case reports and several studies.[58–60] In their position paper the Industrial Injuries Advisory Council (IIAC) found "there is good evidence for a form of interstitial fibrosis which is really part of the disease process of CWP and is not typical of cases of interstitial fibrosis in noncoal workers." DDF has been described in pathologic terms as a bridging fibrosis connecting various stages of CMDLD lesions and/or lesions of silicosis and has been found in approximately 12% of coal miners at autopsy.[61] An occupational history is of utmost importance to the proper clinical recognition of DDF as opposed to UIP.[62] This distinction is of importance both from a prognostic and management standpoint.

At autopsy, complicated CWP (PMF) is confirmed when one or more nodules in a lung specimen are noted to attain a size of 2 cm or greater in diameter.[57] The 2 cm is an arbitrary choice of a minimal diameter that permits better correlation with clinical and radiographic measurements. (In fact, when radiographic pneumoconiotic shadows are >1 cm, PMF is said to be present.) Lesions are solid, heavily pigmented, and rubbery to hard. They tend to occur symmetrically, but they may be asymmetrical and may cavitate.[61,62] Airways and vessels adjacent to the lesions may be distorted, and within the lesions, they are destroyed. PMF generally occurs in association with background pathologic changes of simple CWP.[63]

■ Biology of Coal Workers' Pneumoconiosis

Numerous studies have evaluated the relationship of coal mine dust exposure and activation of immunologic and inflammatory mechanisms. Soutar et al.[64] reported a study of serum antinuclear antibodies (ANA) and rheumatoid factor (RF) among 109 miners with radiographic evidence of pneumoconiosis attending the London Pneumoconiosis Panel. They reported positive ANA in 17% and RF in 10% of the miners, whereas about 2% to 3% positive ANA was expected in a healthy male population. The prevalence of ANA was 9% in simple CWP and 27% in those with category C (PMF). A similar trend was seen with RF, ranging from 6% in simple CWP to 18% in category C. Combining both ANA and RF resulted in positive results in 13% of the miners with simple CWP and 45% of those with category C CWP.

Studies of serum immunoglobulins were conducted by Hahon et al.[65] among 155 U.S. coal miners with chest radiographs demonstrating simple CWP, Caplan syndrome (an atypical clinical presentation of pneumoconiosis associated with features of rheumatoid arthritis), or PMF. Among miners with PMF, those mining anthracite coal had significantly higher serum concentrations of C3, α1-antitrypsin, IgA, and IgG compared with miners from bituminous regions. Compared to normal controls, the miners had elevated C3,

α1-antitrypsin, and IgG values. There were few differences in these serum proteins among the miners with simple CWP. The authors did not find any association between the elevated immunoglobulins and FEV_1.

Significant research has been undertaken to understand the biologic mechanism(s) of CMDLD. Compared to controls, miners with CMDLD have been shown to have elevations in both serum and bronchoalveolar lavage (BAL) levels of several cytokines, which play an important role in lung inflammation and fibrosis, including IL-1β, IL-6, and TNF-α.[66,67] Inflammation resulting from oxidative stress has also been suggested in both human and animal data.[68,69] One potential contributor to miners' increased oxidative stress is the level of bioavailable iron. Iron has the known potential to catalyze oxidant formation through its interaction with oxygen or hydrogen peroxide. The potential of bioavailable iron to induce oxidative stress has been associated ecologically with regional variations of CMDLD prevalence.[70]

Although immunomodulation and inflammation play an important role in the development of CMDLD, the underlying host susceptibilities that lead one miner to develop severe disease in a given environment while another miner may have a relatively minimal disease burden remain elusive. Genetic studies have been unable to confirm specific markers of susceptibility to CMDLD. Small studies have suggested that certain polymorphisms including those involving IL-18 may be protective.[71–73] A recent study in Chinese miners suggests that single nucleotide polymorphisms in the H19 gene are correlated with a decreased risk of CWP.[74] Continued studies on the mechanisms of CMDLD and understanding of disease susceptibility are important, given recent trends in CMDLD epidemiology.

■ Clinical Features of Coal Workers' Lung Diseases

Reflecting the diverse lung pathology associated with coal mine dust exposure, it is not surprising that the clinical presentation of the disease may be quite variable. Miners with simple CWP, perhaps detected through a screening radiograph, may deny significant respiratory symptoms. With increased dust exposures, chronic cough and sputum production are more common, regardless of the presence or absence of simple pneumoconiosis.[75] These symptoms are likely related to bronchitic changes in the large airways, including thickening of the airway wall with mucus gland enlargement and hypersecretion that result from continued inhalation of dust particles presenting a chronic burden to the mucociliary escalator.[50,76] A study by Henneberger and Attfield[77] reported symptoms of chronic bronchitis in 35% of seasoned U.S. miners.

Emphysema has been shown to be more common in miners than nonminers, even after controlling for smoking status, and increases with increasing cumulative dust exposure.[45] As would be expected, with more severe airflow obstruction or advanced pneumoconiosis, dyspnea, cough, and sputum production are frequent. The physiologic importance of the small airway lesions from dust exposure has been debated. A pathologic label of mineral dust–related airway disease has been used to describe a lesion of pigmentation and fibrosis specific to walls of the respiratory bronchioles among workers exposed to mineral dusts.[78]

Less commonly, edema of the lower extremities, and findings consistent with cor pulmonale/pulmonary hypertension, may occur.[48,49,78] An exceedingly rare but unique clinical manifestation of CMDLD is melanoptysis (expectoration of black sputum). Melanoptysis may be a very worrisome symptom for patients but is the harmless result of excavation and liquefaction of a PMF lesion.[80]

Clubbing and crackles have not generally been considered features of coal miners' lung diseases and, if noted, should prompt further studies. For instance, a case series of 38 miners described atypical findings including crackles, finger clubbing, restrictive impairment, diffusion block, and neutrophilic BAL. Ultimately these miners were found to have chronic interstitial pneumonia.[81] Studies have not associated CWP with an increased risk for development of coexisting mycobacterial infection, in contrast to silicosis, where the risk is well documented. However, in a minority of coal miners, the lungs show classic silicotic nodules.[82] Certainly, coal miners with progressive infiltrates or cavitary lesions in PMF should undergo thorough sputum examination for typical and atypical mycobacteria.[83]

■ Radiology of Coal Workers' Pneumoconiosis

The diagnosis of CWP can be made with confidence based on the classic radiographic findings and the presence of an adequate history (at least 10 years) of coal mine dust exposure without the need for histologic confirmation.[1] The radiographic opacities of CMDLD have been well described and are classified according to the ILO system.[21] This system includes a set of standard radiographs, which can facilitate an accurate and consistent approach to recognizing and categorizing the radiographic changes associated with dust exposure. Traditionally analog chest films were used in the classification scheme. This practice changed in 2011 to include classification of digitally acquired images on a high-resolution medical viewing system.[84] Digital systems can provide equivalent results in the recognition and classification of the pneumoconioses when applied according to professional recommendations.[84,85] The radiograph in simple pneumoconiosis shows small pneumoconiotic opacities, ranging in size from pinhead up to 9 mm in diameter. In a study of working U.S. coal miners with radiographic small opacities, 62% showed mainly rounded small opacities while 38% had predominantly irregular opacities.[86] Irregular opacities were more common in lower lung zones. PMF is characterized by one or more opacities in the lung fields greater than 1 cm. Complicated pneumoconiosis is more commonly seen in the upper lung zones, but is confined to the middle and/or lower zones in about one-fourth of cases.[87,88] Although there are some limitations to the use of standard posteroanterior CXR in the diagnosis of simple CWP and of PMF, standard radiographic evaluation of CMDLD remains important for diagnosis, surveillance, compensation, and disease prevention.[82]

Computed tomography (CT) scanning in coal miners may reveal parenchymal nodules and emphysema when standard radiographs are normal.[89,90] In atypical cases, CT scans may show ground-glass opacities and honeycombing, at times without nodular findings typical of CWP.[91] Radiographic evidence of bronchiectasis has also been reported in coal miners, particularly among those with CWP.[92] CT scanning is currently not recommended in the surveillance of exposed miners, but it is likely of use in symptomatic miners with normal plain chest radiography or in miners where alternate diagnoses are being considered.[93] A pneumoconiosis classification scheme for CT has shown good reliability but has yet to be widely adopted.[94]

Several schemes have been used for classifying the radiographic shadows of pneumoconiosis in epidemiologic studies; currently the ILO 2011 Classification of Radiographs of the Pneumoconioses is the most widely accepted (Table 87-1).[21] When using the ILO system, simple pneumoconiosis is divided into major categories 0, 1, 2, and 3 according to the profusion of small opacities (number per unit area) in the lung fields. Each major category, including 0, is subdivided into 3 subcategories, providing a full range of 12 categories of simple CWP. A reading of category 1/0 indicates the definite presence of opacities consistent with pneumoconiosis. Complicated pneumoconiosis (PMF) is divided into categories A, B, and C, based on the size of the large opacities. The classification also permits documentation of other findings that may be associated with the shadows of simple or complicated pneumoconiosis, such as tuberculosis, cor pulmonale, collapse, consolidation, and emphysema. A system of training and examinations (*www.cdc.gov/niosh/topics/chestradiography/breader.html*) is available for physicians who wish to document competence in application of the ILO Classification.

The clinician may be presented with the diagnostic dilemma of distinguishing primary or metastatic lung neoplasia from an unusual presentation of PMF or Caplan syndrome. When typical large opacities of PMF occur symmetrically and bilaterally on a background of simple CWP, one can be confident that the lesions are unlikely to represent neoplastic disease. Prior radiographs from medical screening programs are often obtainable and can help confirm stability or progression over a long time interval. Positron emission tomography with fluorodeoxyglucose (FDG-PET) scanning may be useful in differentiating PMF lesions from malignancy when the mass lesion has a low level of glucose metabolism, although some massive pneumoconiotic lesions may demonstrate an uptake of fluorodeoxyglucose similar to neoplasms.[95] On magnetic resonance imaging (MRI) with contrast enhancement, the pattern of change over time in signal intensity has been reported to be a differential criterion in this setting.[95,96] When the imaging workup is equivocal, the differentiation of PMF from neoplasm may be impossible without a biopsy. In this case, patients with CMDLD who are deemed potential candidates for therapy should undergo biopsy of the suspicious lesion. Hemorrhagic complications may occur during biopsy of PMF lesions due to their vascular nature.

■ Lung Function and Respiratory Impairment in Coal Miners

As discussed earlier, CMDLD encompasses a spectrum of diseases caused by inhalation of coal mine dust that results in several pathologic processes (simple and complicated CWP, silicosis, DDF, chronic bronchitis, mineral dust airway disease, emphysema, and dust-related airflow limitation), each of which may contribute to adverse physiologic consequences. In an individual miner, the pattern and severity of impairment found will be related to such recognized factors as the intensity and duration of respirable dust exposure, geologic factors (e.g., coal rank, silica content), residence time of dust in the lung, and exposure to other respiratory hazards (e.g., tobacco smoke).[7,8,26–33,37] In miners with airway hyperresponsiveness, greater functional deficits and an increased risk of symptoms may be expected.[97,98] Several other mining exposures may also contribute to lung function loss in coal miners, including gases from underground explosive blasting and aerosols of potentially contaminated water used for dust control.[8] Additional factors implicated in underground coal miners' accelerated lung function declines include weight gain, childhood pneumonia, and childhood environmental smoke exposures.[8]

Ventilatory Function

As CMDLD can manifest pathologically as disease of the lung parenchyma, small airways, and/or large airways, the corresponding physiologic defects appreciated on lung function testing may include obstructive, restrictive, or mixed defects.[56,99] The predominant functional abnormality in a given exposed miner will depend on the relative contribution of emphysema, airway disease, and fibrosis in the individual. Epidemiologic studies, as discussed earlier, have extensively documented the occurrence of exposure-related deficits in FEV_1 and forced vital capacity (FVC) in coal miners.[7,30–33,100,101] Although the magnitude of dust-related decline has varied between studies, an important subgroup of miners with accelerated decrements in lung function (FEV_1 decrease of >60 mL/year) has been identified. These miners were found to have more chest illnesses, more respiratory symptoms, and a greater risk of death from cardiovascular or nonmalignant respiratory disease than their cohorts with more stable lung function.[36] Airflow obstruction developing during coal mining has been associated with physiologic evidence of increased resistance to airflow in small (<2 mm internal diameter) airways, including abnormal airflow at low lung volumes and reduced density dependence of maximum expiratory flows.[54–56] Not surprisingly, deficits in lung function have also been documented in U.S. surface coal miners.[15]

Gas Exchange

Diffusing capacity has been studied in relation to radiographic changes of coal worker's pneumoconiosis.[101–103] The small, rounded opacities seen in miners with simple CWP have not generally been associated with measurable reductions in diffusion capacity, and large opacities of complicated CWP are not predictably associated with decreased diffusion. In contrast, miners with irregular opacities may have significant impairment in diffusion capacity, and abnormalities of gas exchange have been associated with increasing coal mine dust exposure independent of radiographic changes. Investigators have demonstrated a significant correlation between subjective measures of breathlessness and measurements of diffusion capacity, which may not be consistently observed with other pulmonary function parameters including FEV_1.[102] Gas exchange on exercise has also been investigated in coal miners.[48,49,104–106] Many reports have been based on patients referred for disability evaluations, and thus these reports suffer from ill-defined selection biases. Exposure–response relationships also are unclear with respect to findings in these series. Exertional hypoxia, pulmonary arterial hypertension, and excess ventilation have frequently been observed in miners, particularly those with complicated CWP or airflow obstruction.[1] However, the proportion of miners who show exertional gas exchange abnormalities in the absence of either PMF or clinically important airflow obstruction is still a topic of investigation.

■ Special Studies

BAL has been used in studying pathogenetic mechanisms in the pulmonary pathology in CWP. Rom et al.[107] reported BAL results for 15 symptomatic, nonsmoking coal miners with simple CWP. They found no significant difference between miners and controls in the number of cells recovered, the percentage distribution, and the release of superoxide anion or hydrogen peroxide. This contrasted with the findings in subjects with asbestosis and silicosis, whose values for spontaneous release of superoxide and hydrogen peroxide were significantly higher than controls. With regard to fibronectin and alveolar macrophage–derived growth factor, the miners with CWP had values that were elevated above controls and not different from the values obtained in subjects with asbestosis and silicosis.

Wallaert et al.[52] demonstrated significantly increased total number of lung cells recovered from 25 miners with simple and complicated CWP, as well as increased percentages of alveolar macrophages, lymphocytes, and neutrophils. Alveolar cells from miners with simple and complicated CWP spontaneously released significantly more superoxide, demonstrated by chemiluminescence, than controls.

■ Management of Coal Workers' Lung Diseases

There is no specific therapy for CMDLD. Whole lung lavage has been evaluated, but studies to date have not adequately defined the risks, benefits, and role in CMDLD management.[108] Thus, the crux of management is directed toward prevention, early recognition, and treatment of complications. The major clinical challenges are the recognition and management of airflow obstruction, respiratory infection, hypoxemia, respiratory failure, cor pulmonale, arrhythmias, and pneumothorax.

The recent epidemiologic findings of significantly increasing prevalence and rapid progression to severe disease in CMDLD should motivate workers to assure continuous control of dust, participate in medical surveillance programs, and exercise their rights to frequent dust measurements and job transfer when necessary. Previous surveillance programs have monitored worker lung health with chest radiographs every 5 years. The current health risks for coal workers necessitate not only chest imaging but also spirometry (every 1–3 years), to provide an opportunity to protect lung health through early detection of rapid functional declines. Identification of rapidly declining lung function or worsening radiographic disease should prompt strict dust controls and transfer to low-dust jobs when available. These workers should also be carefully advised about the risks of further dust exposures. Mine management and workers must assure that ventilation systems, water sprays, and other dust capture devices that are mandated by federal law are operating throughout the workshift and their effectiveness is continuously monitored.

Workers presenting with respiratory symptoms should have careful evaluation. Initial history and examination should be supplemented by a chest radiograph, spirometry with bronchodilators, diffusing capacity, electrocardiogram, and resting arterial blood–gas measurement as indicated. A comprehensive initial evaluation of the pulmonary system allows accurate assessment of the worker's respiratory health status and serves as a starting point for documenting the response to therapy or progression of disease. For miners who smoke, cessation is important regardless of symptoms, radiographic abnormalities, or functional status. Physician encouragement to stop smoking should be supplemented by support from smoking cessation groups, use of nicotine replacement, pharmacologic aids, and behavior modification techniques.[109]

Symptomatic reversible airflow obstruction may benefit from treatment with inhaled and oral bronchodilators. Patients with severe obstruction and inadequate improvement from the usual measures should be considered for a monitored trial of corticosteroids. If improvement is objectively documented, continuation of inhaled and, rarely, oral steroids may be of benefit. Hypoxemia can be a serious complication in advanced pneumoconiosis. It may be present at rest, with exercise, or during sleep. Chronic hypoxemia can lead to additional complications including polycythemia, pulmonary hypertension, cor pulmonale, and cerebral dysfunction. Therapy with low-flow oxygen is indicated when arterial oxygen tension is 55 torr or less. Oxygen therapy in this setting may improve exercise tolerance, reduce dyspnea, and prevent arrhythmias, polycythemia, and heart failure.[110] Patients with functional abnormalities and/or radiographic CWP should receive appropriate immunization with influenza and pneumococcal vaccines.[111] Bacterial and viral episodes of bronchitis or pneumonia should be promptly recognized and appropriately treated.

Patients with complicated pneumoconiosis, especially those who have been exposed to silica as well as coal mine dust, deserve special attention with regard to mycobacterial infection.[83] These patients are considered at higher risk of TB than the general U.S. population; thus a purified protein derivative test with >10 mm of induration is considered positive.[112] Patients with a history of weight loss, fever, sweats, or malaise should be promptly investigated with chest radiographs and sputum examination for acid-fast bacilli stains and cultures. Occasionally, the sputum may be negative and mycobacterial infection can only be documented by fiberoptic bronchoscopy with brushings and washings. Active tuberculosis in patients with CWP can, in general, be successfully treated with the usual drug regimens provided rifampin is one of the drugs used. However, some authorities would recommend that in coal miners with a significant history of concurrent silica exposure (such as motormen, roof bolters, drillers, and shaft development workers), the treatment regimens for tuberculosis should be more prolonged, and long-term follow-up is indicated in view of several reports of recurrent pulmonary tuberculosis in patients with PMF after completion of apparently adequate therapy.[113]

Respiratory failure may complicate advanced disease in coal miners, as it does in other chronic respiratory diseases. Ventilatory support measures are indicated when the failure is precipitated by a treatable complication. The application of ventilatory support measures should be clarified in advanced directives before the need arises.

Clinicians need to assess the contribution of occupational dust exposures to ventilatory impairments in their patients with a history of coal mine exposure. Factors that can assist in this include a careful work history with documentation of the mining region, duration, and categories of coal mine employment, as well as the duration and intensity of any tobacco smoking. Factors associated with an increased risk of a clinically important dust effect are a history of prolonged exposures in dusty jobs, exposures to higher rank coals, a younger age at first employment, and the finding of radiographic changes of CWP. Physicians should assist their patients with job-related impairments in obtaining appropriate compensation through state and national programs.[114]

Although there is no specific therapy for CMDLD, improved understanding of lung biology offers hope for interventions that address the mediators of this disease. Over the past decade, evidence has demonstrated the clinical benefits of antifibrotic treatment in moderate to severe idiopathic pulmonary fibrosis (IPF).[115] Pathways that may play a role in lung inflammation and fibrosis in IPF may overlap with those related to fibrosis in coal dust exposure. Nintedanib inhibits growth factor–stimulated migration and proliferation of fibroblasts and attenuates markers of TGF-β–induced transformation to myofibroblasts.[116] Pirfenidone inhibits TGF-β, collagen synthesis, and fibroblast proliferation, and mediates tissue repair.[117] Studies are underway that will elucidate the potential role of this agents in CMDLD. A trial is currently recruiting patients evaluating the safety and efficacy of Nintedanib in progressive fibrosing CMD-ILD, majority of which will constitute PMF patients (https://clinicaltrials.gov/ct2/show/NCT05067517). Similarly, there's an international effort evaluating the utility of antifibrotics in both coal and silica dust induced lung diseases (https://australianclinicaltrials.com/study/new-trial-into-treatment-of-silicosis-asbestosis-black-lung-or-coal-workers-pneumoconiosis-and-other-dust-diseases-the-nips-or-nintedanib-in-pneumoconiosis-trial/).

SILICOSIS

Silicosis is a fibrosing disease of the lungs caused by the inhalation, retention, and pulmonary reaction to crystalline silica.[118] Despite knowledge of the cause of this disorder (inhalation of dust containing respirable crystalline silica), this serious and potentially fatal occupational lung disease remains prevalent throughout the world.[119] Silica, or silicon dioxide, is the predominant component of the Earth's crust. Occupational exposure to silica particles of respirable size (aerodynamic diameter of 0.5–5.0 μm) has classically been associated with mining, quarrying, drilling, tunneling, and abrasive blasting with quartz-containing materials (sandblasting).[120–122] Many other occupations (Table 87-2) have potential for silica exposure and development of disease.[122] Because silica sand is inexpensive, accessible, and versatile, millions of workers throughout the world are at risk of disease. Occasionally, silicosis is reported from nonoccupational environmental exposures.[123] The disease is often unrecognized and underreported, and thus its true prevalence is substantially underestimated.[119] Fatal cases of silicosis and multiple cases from the same worksite continue to be recognized.[123,124]

■ Definition

Silicosis is an occupational lung disease attributable to the inhalation of silicon dioxide, commonly known as silica, in crystalline forms, usually as quartz, but also as other important crystalline forms of silica (i.e., cristobalite and tridymite).[125] These forms are also called "free silica" to distinguish them from the silicates. The silica content in different rock formations, such as sandstone, granite, and slate, varies from 20% to nearly 100%.

■ Workers in High-risk Occupations and Industries

Silicosis is considered the oldest occupational lung disease (alluded to by Hippocrates and Pliny), while new cases are still reported in

TABLE 87-2 Top 10 Industries and Occupations with Significantly Elevated Proportionate Mortality Ratios for Silicosis, 26 States, 1985–1999 (CDC/NIOSH National Occupational Respiratory Mortality System)

Industries	Occupations
Metal mining	Miscellaneous metal and plastic-processing machine operators
Miscellaneous nonmetallic mineral and stone products	Hand molders and shapers, except jewelers
Pottery and related products	Hand molding, casting, and forming occupations
Nonmetallic mining and quarrying, except fuel	Crushing and grinding machine operators
Iron and steel foundries	Molding and casting machine operators
Structural clay products	Mining engineers
Coal mining	Mining machine operators
Miscellaneous fabricated metal products	Mining occupations, not elsewhere classified
Miscellaneous retail stores	Supervisors, extractive occupations
Blast furnaces, steelworks, rolling, and finishing mills	Construction trades, not elsewhere classified

Data from Centers for Disease Control and Prevention: Silicosis mortality, prevention, and control—United States, 1968–2002. MMWR—Morbidity Mortality Weekly Report. 2005;54(16);401–405.

both the developed and developing world.[126–130] Workers' respiratory health is at risk whenever the Earth's crust is disturbed, or silica-containing rock or sand is used or processed. An estimated 2.3 million U.S. workers are potentially exposed to repairable crystalline silica.[131] Without adequate dust controls, silica exposures in many mechanized industrial processes can be a major cause of morbidity and mortality.[132] For instance, after introduction of pneumatic tools in the early 1900s, Vermont granite workers experienced "appallingly high mortality from silicosis and silicotuberculosis," which prompted the state government to enforce dust exposure limits in this industry.[133,134] The type of silica exposure appears to affect the risk of disease—processes such as drilling or sandblasting represent an increased risk of silicosis.[135,136] Even brief periods of exposure to high levels of freshly fractured silica can result in a lifetime of increased risk for disease.[137] Silicosis frequently develops or progresses after exposures have ceased.[138] In both developed and developing nations, workers in mining, quarrying, tunneling, abrasive blasting, construction, and foundry work continue to develop silicosis. Silicosis also continues to be diagnosed among workers from industries not previously recognized to offer a risk, reflecting the nearly ubiquitous presence of silica.[124,139] Example of newly identified work settings include artificial stone benchtop fabricators (also known as engineered, reconstituted, or manufactured stone and agglomerated quartz), denim jean sandblasters, jewelry polishers, and dental supplies. Workers in these modern industries are at risk for acute and accelerated silicosis over a short period of time due to high-intensity silica concentrations, oxidative stress from freshly fractured silica, and a rapid proinflammatory and profibrotic response.[140] In addition, artificial stone–associated silicosis poses significantly higher mortality risk than natural stone–associated silicosis.[141]

Forms of Silicosis: Exposure History and Clinicopathologic Descriptions

Chronic, accelerated, and acute forms of silicosis have been well characterized.[142] These clinical and pathologic expressions of the disease reflect differing exposure intensities, latency periods, and natural histories. The chronic or classic form usually follows 15 or more years of exposure to respirable dust-containing quartz.[143] Accelerated silicosis results from heavier exposures and develops more rapidly than the chronic form, often with a latency of 5 to 10 years.[144] It generally progresses inexorably even after exposure is interrupted. The acute form of silicosis is a consequence of exposures to high levels of respirable dust that contains silica.[145] The exposure period is usually from several months up to about 5 years, and the clinical course one of rapid progression.

Chronic (or classic) silicosis may be asymptomatic or result in insidiously progressive exertional dyspnea or cough (often mistakenly attributed to the aging process).[124,142] Radiographs show small (<10 mm) rounded opacities predominantly in the upper lung zones.[95] The pathologic hallmark in the lungs of patients with the chronic form is the silicotic nodule. The lesion is characterized by a cell-free central area of concentrically arranged, whorled, hyalinized collagen fibers, surrounded by cellular connective tissue with reticulin fibers (Fig. 87-4).[145] When examined under polarized light, the silicotic nodule shows birefringent particles, most prominent in the periphery.[146] Electron microscopy using specialized techniques can identify the specific mineral content of the particles but is rarely needed for routine diagnostic purposes.[147] Silicotic nodules in the visceral pleura, regional lymph nodes, and occasionally in other organs, may also result from exposure.[148] The small lung nodules of chronic silicosis may coalesce and result in larger shadows on the chest radiograph (>10 mm), heralding the onset of complicated or conglomerate silicosis (often referred to as PMF) (Fig. 87-5).[149] This progressive illness may begin after dust exposure has ceased.[150]

PMF is frequently associated with a clinically important compromise of lung structure and function—and as a consequence, symptoms of exertional dyspnea and reduced functional status.[151,152] Common laboratory findings include a diminished carbon monoxide diffusing capacity, reduced arterial oxygen tension at rest or with exercise, and classically a restrictive pattern on spirometry and lung volume measurement.[153,154] Concomitant dust-induced bronchitis or distortion of the bronchial tree may also result in productive cough, and multiple studies have now confirmed the presence of airflow obstruction in many patients with silica exposure with or without radiographic silicosis.[153–156] Recurrent bacterial infections may occur.[157] Weight loss and cavitation of the large opacities may herald tuberculosis or other mycobacterial infection.[124] Pneumothorax may be a life-threatening complication, since the lung may be difficult to reexpand.[158] Hypoxemic respiratory failure, cor pulmonale, and congestive heart failure are common late findings.

Accelerated silicosis results from exposures that are more intense and of shorter (5–10 years) duration than in the chronic form, while symptoms, radiographic findings, physiologic measurements, and lung pathology are similar.[159] Deterioration in lung function is more rapid, and mycobacterial infection more common. Findings consistent with autoimmune diseases, including scleroderma, rheumatoid arthritis, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, autoimmune hemolytic anemia, dermatopolymyositis, or systemic lupus, may be seen in association with silicosis, more often in the accelerated type.[160–163] The progression of radiographic abnormalities and functional impairment can be very rapid when autoimmune disease occurs with silicosis.[157]

Acute silicosis develops within a few months up to about 5 years after a massive inhalation of silica.[161] Dramatic dyspnea, weakness, and weight loss are often presenting symptoms.[159] Unlike chronic forms of silicosis, chest radiographs show diffuse alveolar filling,

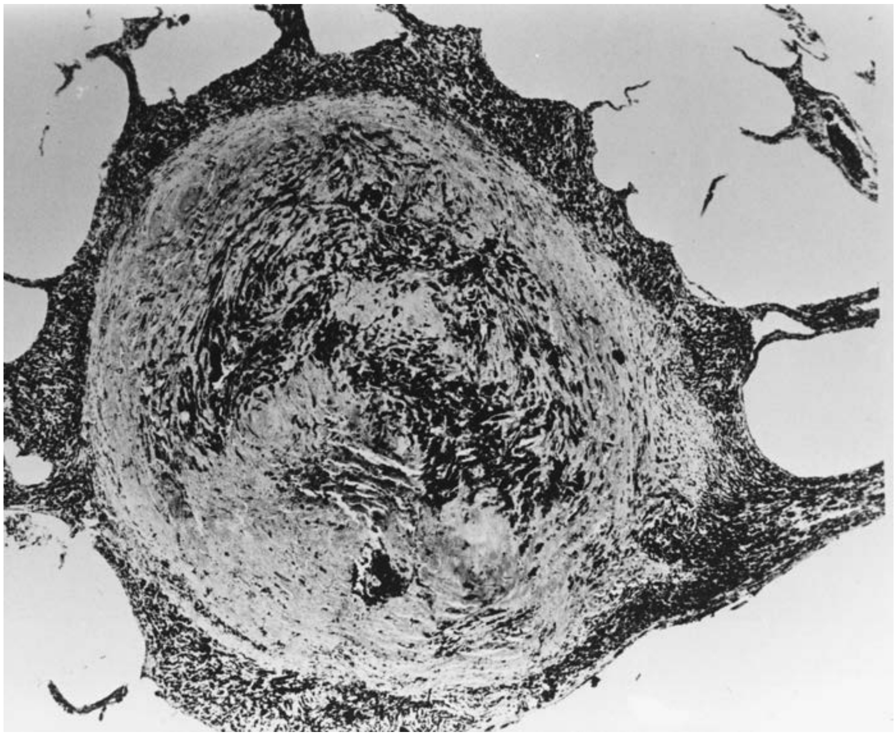

Figure 87-4 Lung pathology showing a classic silicotic nodule. (See text for description.) *(Reproduced with permission from Dr. Val Vallyathan, National Institute for Occupational Safety and Health, Morgantown, WV.)*

with a lower lung zone predominance.[164,165] Air bronchograms may be present. Histology resembles pulmonary alveolar proteinosis, with occasional extrapulmonary (renal and hepatic) abnormalities.[161,166–168] The usual clinical course is rapid progression to severe hypoxemic respiratory failure and death.

Tuberculosis may complicate silica exposure alone, and all forms of silicosis, but risk is greatest with acute and accelerated disease.[169,170] Both tuberculosis and nontuberculous (atypical) mycobacterial infections are seen.[143,171]

Even in the absence of radiographic silicosis, silica-exposed workers may also develop other diseases associated with occupational dust exposure, such as chronic bronchitis and associated emphysema. Progressive declines in lung function have been documented in workers from inhalation of silica and other occupational mineral dust exposures.[155]

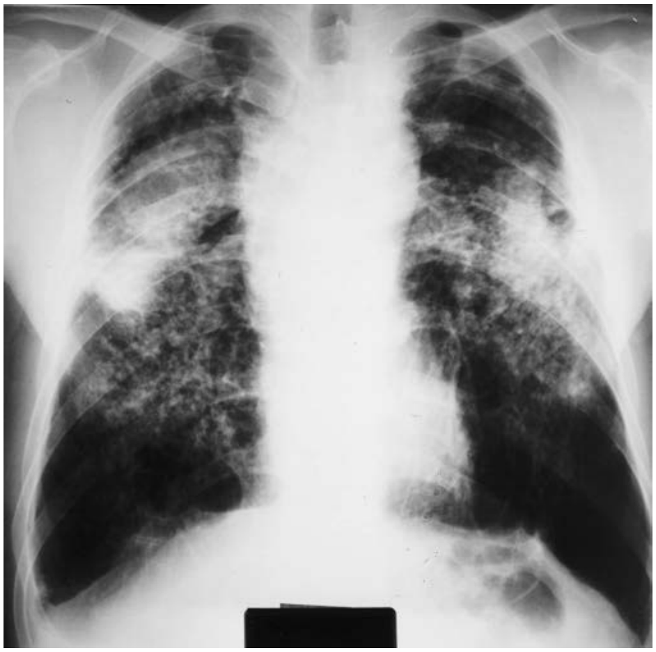

Figure 87-5 Radiographic changes of progressive massive fibrosis in a worker with complicated silicosis.

■ Pathogenesis and the Association with Tuberculosis

The precise mechanism of silica toxicity is uncertain, but it is thought to be mediated by generation of reactive oxygen species, both by the surface of silica particles themselves and by activation of alveolar macrophages.[136,172–174] Disease risk is related to the intensity and duration of the exposure; however, there is growing evidence that freshly fractured silica is more toxic than aged silica-containing dusts, perhaps related to reactive groups on the surface cleavage plane.[175] An abundance of evidence implicates the interaction between the pulmonary alveolar macrophage and silica particles deposited in the lung. Release of chemotactic factors (particularly the IL-1 signaling pathway) and inflammatory mediators, such as tumor necrosis factor, result in recruitment of polymorphonuclear leukocytes, lymphocytes, and additional macrophages.[118,125,176,177] The result of this cascade is chronic lung inflammation and eventually fibrosis. The central acellular zone of the silicotic nodule is surrounded by whorls of collagen and fibroblasts, and an active peripheral zone composed of macrophages, fibroblasts, plasma cells, and silica particles (Fig. 87-5).[161] Silica induces macrophage apoptosis, allowing the phagocytosed silica particle to be reintroduced into lung tissues and generate another cycle of phagocytosis and inflammation.[125,178] A large number of mediators have been implicated in the ongoing inflammation and fibrosis associated with silica exposure. These include IL-1B, TNF-α, TGF-β, fibronectin, and a family of inflammatory cytokines known as chemokines.[179–185] For instance, a study by Sellamuthu et al.[185] investigated mechanisms of crystalline silica–induced pulmonary toxicity by evaluating global gene expression in a human alveolar basal carcinoma epithelial cell line. Their results confirmed the involvement of previously identified molecular targets involved in silica toxicity, but also identified novel molecular pathways likely involved in toxicity. Upregulation of genes encoding for inflammatory cytokines/chemokines that function as chemoattractants and recruit inflammatory cells (especially PMNs) into the lungs appears to provide mechanisms for propagation and acceleration of initial silica-induced tissue damage. In addition, a recent meta-analysis has shown that a genetic polymorphism affecting TNF-α 308A/G and 238A/G is associated with increased susceptibility to silicosis in an Asian population.[186]

In acute silicosis, in contrast to the chronic forms, the alveolar space is filled with amorphous, lipoproteinaceous material that stains with periodic acid–Schiff (PAS) regent,[167,168] possibly related to abnormal handling and accumulation of pulmonary surfactant.[187–189]

As mentioned earlier among coal miners, DDF has been described in pathologic terms as a bridging fibrosis connecting various lesions of silicosis. This interstitial fibrosis appears to be a unique response in some silica-exposed individuals and is not thought to represent the concurrent development of UIP.

Immune system dysfunction is well described in association with silicosis, including increased prevalence of circulating immune complexes as well as increased production of serum autoantibodies, such as antinuclear antibody and RF.[190,191] The susceptibility of silicotic workers to infections, including tuberculosis and *Nocardia asteroides*, is likely related to the toxic effect of silica on pulmonary macrophages.[157,192] Thus, silica appears to activate humoral immunity (in a dysregulated manner), while impairing cell-mediated immunity.

Chen et al.[193] studied three cohorts of miners in different industries all with silica exposure. These researchers observed differences in the exposure-related risk of silicosis across the three cohorts. This epidemiologic finding lends support to the basic science literature suggesting that silica dust characteristics, in addition to cumulative respirable silica dust exposure, may affect the risk of silicosis.

Clinical Picture of Silicosis

When silicosis is symptomatic, the primary symptom is usually dyspnea, first noted with activity or exercise and later at rest. However, in the absence of other respiratory disease, shortness of breath may be absent, and the presentation may be an asymptomatic worker with an abnormal chest radiograph. The radiograph may at times show quite advanced disease with only minimal symptoms. The appearance or progression of dyspnea may herald the development of complications including tuberculosis, airway obstruction, PMF, or cor pulmonale. Productive cough is often present, secondary to chronic bronchitis from occupational dust exposure, tobacco use, or both. Cough may at times also be attributed to pressure on the trachea or mainstem bronchi from large masses of silicotic lymph nodes.

Other chest symptoms are less common. Hemoptysis is rare and should raise concern for complicating disorders, such as pulmonary neoplasms or mycobacterial infection. Wheeze and chest tightness may occur in silicosis but are usually associated with bronchitis or airflow obstruction. Chest pain and finger clubbing are not typically features of silicosis. Systemic symptoms, such as fever and weight loss, suggest complicating infection or neoplastic disease. Advanced forms of silicosis are associated with progressive respiratory failure with or without cor pulmonale. Few physical signs may be noted unless complications are present; inspiratory crackles are often absent.

Radiographic Patterns in Silicosis

The earliest radiographic signs of uncomplicated silicosis are generally small, rounded opacities. These can be categorized using the ILO International Classification of Radiographs of Pneumoconioses by size, shape, and profusion category.[21] In silicosis, rounded opacities of the "q" and "r" type dominate (Table 87-1). Other patterns also have been described, including linear or irregular shadows. The opacities seen on the radiograph represent the summation of pathologic silicotic nodules and associated changes. They are usually found to predominate initially in the upper lung zones and may progress to involve other zones.[95] Hilar lymphadenopathy is also noted, sometimes before nodular parenchymal shadows.[95] Eggshell calcification of the lymph nodes is strongly suggestive of silicosis in the appropriate clinical context, although this feature is uncommon.[194] The development of PMF is indicated by large radiographic opacities, which are categorized by size as A, B, or C (Table 87-1), using the ILO classification.[21] PMF lesions tend to contract to the upper lung zones, leaving areas of compensatory emphysema at their margins and in the lung bases.[95] The contraction process causes small pneumoconiotic opacities that previously were evident on the radiograph to become less visible or at times disappear. Pleural abnormalities are occasionally observed on routine chest radiographs with silicosis; however, CT scanning often documents localized pleural thickening, particularly in association with conglomerate lesions.[195] Pleural effusions are less frequently noted. The radiographic distinction between large pneumoconiotic lesions and lung malignancies may be difficult, particularly if no earlier radiographs are available. As in complicated CWP, FDG-PET scanning may sometimes be helpful in this distinction, but false positives occur.[196–198] Cavitation or a rapid change in the radiographic appearance of a large silicotic lesion may be due to ischemic necrosis but should always prompt a vigorous search for mycobacterial disease. Acute silicosis may present with an alveolar filling pattern and rapid development of complicated mass lesions.[164]

Lung Functional Abnormalities in Silicosis

Pulmonary function tests, including spirometry and diffusing capacity, are helpful in the clinical evaluation of individuals with suspected silicosis. Spirometry may also be of value in early recognition of the health effects from occupational dust exposures, as it may detect physiologic abnormalities that may precede radiographic changes.[199] No specific or characteristic pattern of ventilatory impairment is present in silicosis. Spirometry may be normal, or when abnormal, the tracings may show obstruction, restriction, or a mixed pattern.[199] Numerous studies have investigated the impact of silica dust exposure and lung function.[200–202] These data suggest that obstruction may indeed be the more common finding. Silica and mixed dust exposures may lead to clinically important airflow limitation independent of radiographic abnormality; however there is some evidence that lung function deficits are more associated with silica-related emphysema than nodularity on imaging.[151] Functional changes tend to be more marked with advanced radiologic categories.[151] However, no good correlation exists between radiographic abnormalities and ventilatory impairment, and workers experience lung function loss proportionate to the duration and intensity of silica dust exposure.[153] Diffusing impairment may also occur in the absence of ventilatory impairment. In acute and accelerated silicosis, functional changes generally occur earlier, are more marked, and progress more rapidly.[165,203–205] Reduced six-minute walk distance (6MWD) was noted to be a prognostic factor for both hospitalization and mortality in silicosis patients suggestive of its utility for monitoring of their health.[206] In acute silicosis, radiographic progression is accompanied by increasing ventilatory impairment and gas exchange abnormalities, which leads to respiratory failure and eventually to death from intractable hypoxemia.[157]

Complications and Special Diagnostic Issues in Silicosis

With a history of sufficient exposure and a characteristic radiograph, the diagnosis of silicosis is generally not difficult to establish. Challenges arise when the radiologic features are unusual or the history of exposure is not recognized. Lung biopsy is rarely required to establish the diagnosis. However, tissue samples may be helpful in some clinical settings when complications are present or the differential diagnosis includes tuberculosis, neoplasm, or PMF. Biopsy material should be sent for culture, and in research settings, dust analysis may be a useful additional measure. When tissue is required, open or thoracoscopic lung biopsies are generally necessary for adequate material for examination, to assure satisfactory hemostasis, and due to concern about life-threatening pneumothorax in the fibrotic lung. Some evidence suggests BAL and transbronchial biopsy may be of diagnostic aid in some cases where the diagnosis of silicosis is not straightforward.[207] Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) can be a useful diagnostic tool in suspected silicosis patients with mediastinal lymphadenopathy.[208]

Vigilance for infectious complications, especially tuberculosis and other mycobacteria, cannot be overemphasized. Any fever, weight loss, worsening symptoms, or radiographic changes should trigger a workup to exclude this treatable problem. In acute silicosis, *Nocardia* and fungal infections must be considered.[157]

In 1997, the International Agency for Research on Cancer (IARC) reclassified crystalline silica as a group I carcinogen. This new designation indicates IARC found "sufficient data" to determine that crystalline silica in the form of quartz or cristobalite dust is carcinogenic to humans.[209] Uncertainty remains over the pathogenic mechanisms for the development of lung cancer in silica-exposed populations, and the relationship between silicosis (or lung fibrosis) and cancer continues to be studied. IARC noted that a link to carcinogenicity was not detected in every type of industrial exposure and may be related to an interaction between the silica dust and other environmental factors.[209,210] Regardless of the mechanism, there is ample evidence confirming a causal link between occupational exposure to silica and lung cancer.

A relationship between renal complications and silica exposure has been suspected since the early 20th century.[211] A 2002 study reported a 5.1% excess risk of end-stage renal disease (ESRD) and a 1.8% excess risk of death from kidney disease in individuals exposed to silica.[211] Glomerulonephritis and nephrotic syndrome have been described in association with silica exposure.[160,212–214] The specific mechanisms of renal injury are not completely understood, but evidence suggests injury may occur by both direct (silica particulate in the kidney) and indirect insults (immunologic injury by immune complex formation).[160,214]

Several autoimmune diseases are clearly linked with silica dust exposure.[215] Perhaps the most well-known of these is scleroderma, first reported in the 1910s and subsequently described by Erasmus (sometimes referred to as Erasmus syndrome) in 1957 from investigations into South African gold miners.[216,217] A study analyzing the prevalence of connective tissue disease in silicosis between 1985 to 2006 reported a 24-fold risk of developing scleroderma among silicotics compared to the general population.[160] This study also found two- to eightfold risks for rheumatoid arthritis and systemic lupus erythematosus, as well as a striking increased prevalence of ANCA-associated vasculitis. A Finnish study also suggested a strong association between silica exposure and rheumatoid arthritis.[218] An earlier NIOSH review of the health implications of silica exposure cited the most commonly associated autoimmune diseases to be scleroderma, systemic lupus erythematosus (lupus), rheumatoid arthritis, autoimmune hemolytic anemia, and dermatomyositis or dermatopolymyositis.[159] An animal model has suggested a multi-hit model of autoimmunity where exposures to silica and virus exposure act synergistically to induce autoimmunity.[219]

Prevention of Silicosis

Prevention remains the principal goal in dealing with this occupational lung disease. Despite the current OSHA PEL for respirable crystalline silica of 100 μg/m^3 as an 8-h time-weighted average, silica-exposed workers continue to develop disease.[220,221] NIOSH since 1974 has recommended the PEL be reduced to 50 μg/m^3 as a time-weighted average for up to 10 h/day.[220] Workers with longer exposure at a lower concentration were noted to be at higher risk for silicosis than those with the same cumulative exposure for a shorter period of time at higher concentrations. In addition, the rate of disease progression was related to subsequent concentration of silica dust exposed to the workers.[222] Effective exposure controls are available for most processes and include process enclosure, wet abrasive techniques, and local exhaust ventilation, combined with a comprehensive approach to personal protection. Where possible, less hazardous agents should be substituted for silica. Unfortunately, noncompliance with the current permissive exposure limit appears common in many work environments.[223,224] Both employers and workers must remain vigilant regarding the hazards of silica dust exposure and control measures.

If silicosis is recognized in a worker, termination of any continuing exposures is advisable. Unfortunately, the disease often will progress even without further silica exposure. The finding of a case of silicosis is a "sentinel health event" and should prompt a thorough evaluation of workplace exposures and control measures by a competent authority, with the goal of recognizing the sources of the hazard and protecting other workers who may continue to be at risk.

Medical Screening and Surveillance in Silicosis

Workers exposed to silica and other mineral dusts should be monitored on a regular basis for adverse health effects as a supplement to, but not a substitute for, exposure monitoring and control. Health screening commonly includes periodic evaluation of respiratory symptoms, spirometric abnormalities, and radiographic changes. There is evidence that, if silicosis subsequently develops, workers who have participated in periodic health monitoring experience reduced severity of disease.[225] Evaluation for tuberculosis infection also should be performed. Historically, this was done using intradermal skin testing, although new diagnostic techniques useful in the screening and diagnosis of TB termed interferon gamma release assays (IGRAs) have come to market. While not specifically studied in the silica-exposed population, studies in general populations suggest equal if not greater specificity and sensitivity in comparison with standard dermal screening for TB. The advantages offered by these tests are as follows: (1) there is no interference with the BCG vaccine, (2) subjective interpretation is avoided, (3) a second appointment for reading the results is avoided, and (4) the test incorporates a positive control that provides valuable information for interpreting an apparently negative test as either a true negative or indeterminate as a result of technical errors or immunosuppression.[226] In addition to reporting of health surveillance results to the individual workers, health data from all workers at a plant or operation should be periodically analyzed (e.g., every 1–3 years) to assess the adequacy of prevention activities.

Several biomarkers have been investigated to aid early identification of silicosis, including higher levels of serum nephronectin (extracellular matrix–related ligand) and high-mobility group box 1 (HMGB-1).[227,228] However, their application remains limited to research settings and is largely investigational.

Therapy, Management of Complications, and Control of Silicosis

When prevention has been unsuccessful and silicosis has developed, therapy is directed largely at detecting and treating complications. Therapeutic measures are similar to those commonly used in the management of airflow obstruction, infection, pneumothorax, hypoxemia, and respiratory failure complicating other pulmonary disease. Historically, there have been a number of unsuccessful attempts to find a drug treatment that can reverse silicosis.[229,230] Whole lung lavage has been attempted with the hope of removing dust, inflammatory cells, and other mediators to potentially ameliorate disease progression.[108] Currently, there are no data to confirm that this or any other therapy alters the natural progression of human silicosis. Because of the high prevalence of disease in some countries, investigations of combinations of drugs and other interventions continue.

For workers with a diagnosis of silicosis, further exposure to silica-containing dusts is undesirable. If the disease is advanced or has occurred after a relatively short exposure (i.e., <15 years), then further dust exposure should be assiduously avoided. Advice on job reassignment should be considered in the context of the worker's age, symptoms, functional status, and the current working conditions and measured silica exposures. Patients with silicosis may have few symptoms or findings early in the disease; however, physicians should be aware that many states have a strict time limit, dating from the physician's recognition of findings of silicosis, regarding application for workers' compensation and reimbursement of medical costs.

In the medical management of silicosis, vigilance for complicating infection, especially tuberculosis, is critical. The use of bacillus Calmette-Guérin (BCG) vaccine in the tuberculin-negative silicotic patient is not recommended, but the use of preventive isoniazid (INH) therapy in the tuberculin-positive silicotic patient is advised.[231] The diagnosis of active tuberculosis infection in patients with silicosis can be difficult. Clinical symptoms of weight loss, fever, sweats, and malaise should prompt radiographic evaluation and sputum acid-fast bacilli stains and cultures.[232] Radiographic changes with infection may be subtle and atypical. Enlargement or cavitation in conglomerate lesions or nodular opacities is of particular concern. Bacteriologic studies on expectorated sputum are indicated but may not be reliable in silicotuberculosis because expectoration may produce only scant numbers of active organisms. Fiberoptic bronchoscopy for additional specimens for culture and study may be helpful in establishing a diagnosis of active disease. The use of multidrug therapy for suspected active disease is justified at a lower level of suspicion in silicotics compared to the nonsilicotic patient, due to the difficulty in firmly establishing evidence for active infection. To obtain satisfactory results in the presence of silicosis, antituberculous treatment must be more prolonged, with regimens lasting at least 8 months.[113] A multiplicative increase in risk of mycobacterial infection is associated with the combination of silicosis and human immunodeficiency virus (HIV) infection, as has been encountered in South African gold miners.[233] Coinfection with HIV and tuberculosis may also have an adverse impact on progression of silicosis and lung function decline.[234] These infections represent major clinical and public health challenges.[235] Prolonged treatment is essential, and there is potential for both adverse drug reactions and interactions between antiretroviral and antituberculous therapy. Recommended approaches continue to evolve, and clinicians should consult the latest authoritative recommendations.

Ventilatory support for respiratory failure may be indicated when precipitated by a treatable complication. Pneumothorax, spontaneous and ventilator related, is usually treated by chest tube insertion. Bronchopleural fistula may develop, and surgical consultation and management should be considered.

Acute silicosis may rapidly progress to respiratory failure. When this disease resembles pulmonary alveolar proteinosis and severe hypoxemia is present, aggressive therapy has included massive whole lung lavage with the patient under general anesthesia in an attempt to improve gas exchange and remove alveolar debris. Although appealing in concept, the efficacy of whole lung lavage has not been established.[236] Glucocorticoid therapy also has been used for acute silicosis; however, it also is of unproven benefit.[237,238]

Some younger patients with end-stage silicosis may be considered candidates for lung or heart–lung transplantation by centers experienced with this expensive and high-risk procedure.[239] Early referral and evaluation for this intervention may be offered to selected patients.

The discussion of an aggressive and high-technology therapeutic intervention such as transplantation serves to dramatically underscore the serious and potentially fatal nature of silicosis, as well as to emphasize the crucial role for primary prevention. The control of silicosis ultimately depends upon the control of workplace dust exposures. This is accomplished by rigorous and conscientious application of fundamental occupational hygiene and engineering principles, with a commitment to the preservation of worker health.

PREVENTION STRATEGIES FOR COAL WORKERS' LUNG DISEASES AND SILICOSIS

The control of coal workers' lung diseases and silicosis in both the developed and developing world requires comprehensive prevention strategies, including exposure control, medical surveillance, research, and education. Example approaches include the following:

- Major efforts must be directed to installation of effective engineering controls and improvements in work practices to progressively reduce dust exposures to recommended levels. These efforts are labeled primary prevention. In selected situations, personal respiratory protection also can play a role, particularly during short-term operations or unusual/emergency conditions, and while engineering controls are being modified or improved. The use of respirators will only be effective when part of a professionally managed comprehensive respiratory protection program and should never be relied upon outside of such a program.
- Primary prevention should involve ongoing dust exposure monitoring and include mechanisms for feedback to modify and improve working conditions if exposures are measured above recommended levels. Even exposure at currently permissible levels has been recognized to represent a risk of disease.
- Secondary prevention through medical screening and surveillance should be designed to benefit the individual worker and other potentially exposed workers. Illness identified through medical screening represents a failure of primary prevention, and thus should trigger feedback to those responsible for environmental monitoring, exposure controls, and work practice evaluations.
- Education about the respiratory health hazards from uncontrolled exposures to silica and coal mine dust must be available to workers, employers, managers, and healthcare providers.
- Information on the cumulative burden of disease should be monitored over time for both silica and coal mine dust.
- Research into mining-related lung diseases should be encouraged to improve recognition, monitoring, exposure reduction, and therapy, and to increase understanding of pathogenesis. Research efforts should supplement, not displace, attention to dust control.
- Clinicians who recognize coal-related diseases or silicosis in their patients should attempt to determine whether ongoing workplace exposures present a continuing risk to current workers, while maintaining the confidentiality of the patient–physician relationship. Assistance in this can often be obtained through local or state health departments, occupational medicine groups, and federal agencies. Reporting of occupational diseases is required in many states.

CONCLUSIONS

Although much is known about the causes, pathogenesis, natural history, and prevention of dust-related respiratory diseases, the pneumoconioses remain important causes of morbidity and mortality in the United States and throughout the world. Healthcare providers need to maintain medical vigilance and familiarity with the clinical features and management of these disorders, especially those whose clinical practice includes persons with significant mining or industrial employment. When patients are exposed to occupational lung hazards, they should be provided effective workplace protections, respiratory health monitoring, timely and accurate recognition and management of dust diseases and their complications, and referrals for public health evaluations and equitable compensation whenever appropriate.

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CHAPTER 88

Occupational Asthma, Byssinosis, and Industrial Bronchitis

Shu-Yi Liao
David C. Christiani

INTRODUCTION

Workplace inhalational hazards such as dust, fumes, and organic substances can cause various nonmalignant respiratory diseases. These occupational exposures may cause airway diseases and parenchymal diseases. Occupation-related lung parenchymal diseases, such as hypersensitivity pneumonitis, obliterative bronchiolitis, and chronic beryllium disease are considered elsewhere. In this chapter, we discuss occupational asthma, byssinosis, and industrial bronchitis.

OCCUPATIONAL ASTHMA

Below we describe important aspects of occupational asthma, including its epidemiology, causative agents, risk factors, pathogenetic mechanisms, clinical presentations, diagnosis, and management.

■ Epidemiology

Work-related asthma is the most common *occupational lung disease*. There are two categories: (1) occupational, or work-related, asthma that is caused de novo by work, and (2) work-exacerbated asthma, which implies a work-related worsening in the setting of preexisting asthma.[1] The prevalence of work-related asthma is difficult to determine. An international estimate attributes 15% to 20% of adult-onset asthma to workplace exposure.[2] A recent systemic review indicated the overall occupational population attributable fraction was 16%, with wide 95% confidence intervals between 3.8 and 27.1%.[3] The incidence of occupational asthma is 3% to 36% and varies among different industries, based on international studies in workers with different occupations[4] (Table 88-1).

TABLE 88-1 Incidence of Occupational Asthma in Main Occupations

Occupation/Exposed Antigen	Number of Cases	Incidence (%)	Country
Snow crab processors	303	15.6	Canada
Guar gum (natural polysaccharide)	151	3.0	Canada
Painters (isocyanate)	730	7.1 (all subjects were non-smokers)	Italy
Poultry workers	134	11.0	South Africa
Rat allergens	113	4.4	France
Natural rubber latex (health care workers in general hospital)	196	7.1	Italy
Florists	128	14.1	USA
Supermarket bakery workers	66	9.0	UK
Strawberry growing industry workers	43	4.7	Japan
Oyster shucker (sea squirt)	250–417	18.0–36.0	Japan

Data from Mapp CE, Boschetto P, Maestrelli P, et al. Occupational asthma. Am J Respir Crit Care Med. 2005;172(3):280–305.

■ Agents That Cause Occupational Asthma

Many agents cause occupational asthma. Two categories of agents can be classified based on molecular weight and differing mechanisms causing disease: high-molecular-weight (HMW) compounds (>5 to 10 kDa), and low-molecular-weight (LMW) compounds. A list of causative compounds and occupations at risk is provided in Table 88-2. The website *www.occupationalasthma.com* also provides up-to-date information on agents known to cause occupational asthma.

■ Risk Factors

Risk factors include exposure to a respiratory sensitizer, high intensity of exposure, genetic predisposition, smoking status, and preexisting atopy.

It has been shown that the major histocompatibility complex class II proteins are important for occupational asthma susceptibility if the occupational exposure is due to acid anhydrides, diisocyanates, western red cedar, platinum salts, latex, and/or animal proteins.

Genotypes of glutathione S-transferase[5] and N-acetyltransferase[6,7] also are associated with development of occupational asthma. A large gene–environmental study consisting of 2599 European participants showed a gene–environmental interaction between the exposure to LMW agents/irritants and genes associated with oxidative stress, such as *PLA2G4A*, *PLA2R1*, *PRKCA*, *PRKD1*, and *RELA*.[8] Susceptible genotypes may differ based on the occupational exposure types (HMW vs. LMW) and are shown in Table 88-3.[9]

Smoking is a risk factor for sensitization to HMW compound–related occupational exposures, such as coffee, castor beans, snow crab, or shrimp, and some LMW-related occupational exposures, such as platinum salts and phthalic anhydride.[10] In these instances, smoking may interact with atopy, another risk factor for occupational asthma, to increase the risk of antigen sensitization in atopic smokers.[11,12] However, sensitization to an agent is not equivalent to the development of occupational asthma, and further epidemiologic studies are needed to verify a causal relationship between smoking, atopy, and susceptibility to occupational asthma.

Atopy is also associated with sensitization, especially to the HMW compounds that induce an immediate antibody response, such as production of IgE.[13,14] While atopy can increase the risk of sensitization, the positive predictive value of atopy per se for development of asthma symptoms is low.[15,16]

■ Mechanism and Pathogenesis

The mechanism and pathogenesis of developing occupational asthma can be divided into immunologic and nonimmunologic (irritant) processes. However, some agents, such as diisocyanates, can induce asthma through both mechanisms.

Immunologic Mechanisms

Immunologic occupational asthma is characterized by a latent period; in general, a small quantity of the insult can induce severe

TABLE 88-2 Causes of Occupational Asthma

Categories	Occupations at Risk	Major Putative Component
High-molecular-weight compounds		
Animal products	Animal handlers Veterinarians	Pelt or urinary proteins
Seafoods	Crab or prawn processors Oyster farmers	Water-extractable proteins
Insects	Entomologists Grain workers Laboratory workers River workers Flight crews	Insect proteins
Plants	Grain handlers Bakers Tea workers Brewery chemists Tobacco manufacturers	Extractable plant proteins
Biologic enzymes	Detergent industry workers Bakers Pharmaceutical workers	*Bacillus subtilis*, trypsin, pancreatin, papain, pepsin
Latex	Health care workers Doll manufacturers Glove makers	Latex rubber extract
Gums	Printers Gum manufacturers	Gum acacia Gum tragacanth
Low-molecular-weight compounds		
Diisocyanates	Polyurethane workers Plastic workers Foundry workers Spray painters	Isocyanate-protein complex
Anhydrides	Epoxy resin workers Plastics workers	Phthalic anhydride–protein complexes
Wood dust	Carpenters Sawmill workers	Plicatic acid (western red cedar) Wood dust extracts
Fluxes	Aluminum solderers Electronics workers	Aminoethylethanolamine
Pharmaceuticals	Pharmaceutical manufacturers	Antibiotics, psyllium, piperazine
Fixatives	Hospital workers	Formaldehyde, glutaraldehyde
Diesel exhaust	Farmers, diesel mechanics	Nitrogen oxides, sulfur dioxide, particulates

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symptoms. This immunologic mechanism may be IgE-mediated or non-IgE-mediated. For occupational asthma, most of the immunologic reactions are IgE-mediated. HMW compounds (e.g., animal protein, flour, and latex) usually cause occupational asthma via IgE-mediated processes. This accounts for the observations that serum IgE antibodies to the specific agent can sometimes be identified and skin tests may be positive using the offending substance extracts. Consequently, atopic individuals are at a higher risk of developing occupational asthma from exposure to HMW agents.

LMW compounds, on other hand, tend to cause occupational asthma though non-IgE-mediated immunologic reactions. Notable exceptions are platinum salts and some acid anhydrides that can induce specific IgE antibodies. The mechanisms of non-IgE-mediated immunologic process with exposure to LMW agents remain unclear, although there is some evidence that the pathogenesis of red cedar, cobalt, nickel salts, or isocyanate-related asthma may involve T cell–mediated responses.[17,18]

Nonimmunologic Mechanisms

Occupational asthma caused by nonimmunologic mechanisms has no latency period. Several mechanisms are at play. Accidental exposure to high doses of ammonia, smoke, or chlorine may cause acute airway injury (irritant-induced reactive airways dysfunction) through the mechanism of loss of epithelial-derived relaxing factors, leading to neurogenic inflammation and cytokine release from mast cells.[19] Other agents, such as organophosphates,[20] may cause bronchoconstriction through anticholinergic effects, and diisocyanates[21] by blocking β2-adrenergic receptors.

■ Clinical Presentations

Occupational asthma may be more severe than non-work-related asthma and may result in higher medication use, worse asthma control, and more rapid lung function decline.[22] Clinical symptoms of occupational asthma overlap with non-work-related asthma. Common symptoms include wheezing, shortness of breath, and cough. Physicians should suspect potential occupational causes, especially in patients with adult-onset asthma.

Two main types of occupational asthma with different time frames for symptom onset after exposure should be considered: (1) occupational asthma with a latency of weeks or months after the exposure (generally immunologically mediated) and (2) occupational asthma without latency (i.e., irritant asthma), which is usually not immunologically mediated.[20]

Occupational Asthma with Latency

Patients with this type of occupational asthma develop symptoms weeks or months after the exposure as a result of sensitization. The offending agents include HMW and LMW compounds. Since this is an anamnestic response, the amount of the offending agent can be low and still cause severe bronchoconstriction. Symptoms may differ depending on the offending agents. HMW agents usually cause more conjunctivitis and rhinitis compared with LMW agents.[23]

Occupational Asthma Without Latency (Irritant Asthma)

Symptoms in irritant asthma develop within hours of exposure (<24 h). The exposure level usually is a high concentration. Patients may encounter symptoms similar to those of traditional asthma attacks, such as acute shortness of breath and wheezing. Symptoms typically persist for a couple of months, although some patients develop chronic asthma.[24]

■ Diagnosis

Three key components should be considered when thinking about the diagnosis of work-related asthma: (1) workers with de novo asthma or exacerbation of previously quiescent asthma, (2) exposure to a sensitizer or irritant that is known to cause occupational asthma, and (3) a causal relationship between agents and the worker's symptoms.

To facilitate diagnosis, the National Institute for Occupational Safety and Health (NIOSH) has created a worksheet: Decision

TABLE 88-3 Susceptible Genotypes of Occupational Asthma Based on Occupational Exposure Types

Genetic Marker	Occupational Exposure	Molecular Weight	Population
HLA-DQB1	TDI/red cedar sawmill	Low	Caucasian
HLA-DRB1-DQB1-DPB1	TDI	Low	Korean
CTNN3	TDI	Low	Korean, Caucasian
GSTP1	TDI/DI	Low	Caucasian
GSTM1	TDI/DI	Low	Caucasian
SOD2	DI	Low	Caucasian
EPHX1	DI	Low	Caucasian
NAT2	DI	Low	French Canadian Caucasian
TNFα	DI	Low	French Canadian Caucasian
PTGS2	DI	Low	French Canadian Caucasian
TGFB1	DI	Low	French Canadian Caucasian
PTGS1	DI	Low	French Canadian Caucasian
IFN-γ	DI	Low	Caucasian
TLR2-	Endotoxin	High	Canadian Caucasian
CD14-	Endotoxin	High	Caucasian
mEH	Endotoxin	High	Chinese
ADRB2	Wheat flour	High	Korean
TLR4	Wheat flour	High	Korean
IL4RA	Wheat flour	High	Korean
CD14	Wheat flour	High	Italian Caucasian
HLA-DRB1	Rat proteins	High	Caucasian
HLA-DRB1		High	Finish Caucasian
DQB1	Cow dander (Bos d 2)	High	Finish Caucasian

TDI, toluene diisocyanate; DI, diisocyanate.
Data from Dominguez-Ortega J, Barranco P, Rodríguez-Pérez R, et al. Biomarkers in Occupational Asthma. Curr Allergy Asthma Rep. 2016;16(9):63.

Logic for Work-Related Asthma Surveillance Case Identification and Classification (*www.cdc.gov/niosh/topics/surveillance*). The first step in the process is establishing a diagnosis of asthma and an association between the symptoms and work. If the patient has asthma, and symptoms are related to the work, a diagnosis of work-related asthma is made. The next step is differentiating work-exacerbated asthma from new-onset, work-related asthma. If the patient has no recent history of asthma (i.e., is asymptomatic and not on asthma treatment for 2 years prior to entering the new occupational setting), a diagnosis of new-onset work-related asthma can be made. Differentiation between occupational asthma without latency and occupational asthma with latency is based on the time between the exposure and onset of symptoms. As noted previously, irritant asthma develops within 24 h after a one-time, high-level inhalation exposure to an irritant gas, fume, smoke, or vapor, and symptoms persist for at least 3 months.

In addition to the history, several diagnostic tests may provide objective evidence for the diagnosis of occupational asthma. These include (1) work-related changes in serially measured forced expiratory volume in 1 s (FEV$_1$) or peak expiratory flow rate (PEFR); (2) work-related changes in bronchial responsiveness, as measured by serial, nonspecific inhalation challenge tests; and (3) a positive response to a specific inhalation challenge test with an agent to which the patient has been exposed at work. Details of diagnostic tests are given below.

Diagnostic Tests

Three main diagnostic tests may offer objective evidence for the diagnosis of occupational asthma: (1) pulmonary function tests, (2) bronchial provocation tests, and (3) immunologic tests. The overall sensitivity, specificity, pros, and cons of each are shown in Table 88-4. In addition, recent studies have discovered several biomarkers for occupational asthma that are discussed below.

Pulmonary Function Tests FEV$_1$ or PEFR are the two most commonly used measurements for the diagnosis of occupational asthma. Workers may present with normal spirometry while not in the workplace. Therefore, the timing of this pulmonary function test is important, and pre- and post-work measurements are needed.

Peak flow monitors are easy to use on the job. Four measurements each day are usually recommended: (1) upon awakening, (2) at the beginning of the workday, (3) at the end of the workday, and (4) prior to bed. The measurements should be performed daily for at least 4 weeks. Some experts have proposed more intense and frequent measurements with a 2-h interval, but this approach may not be practical with a busy work schedule.[26] The limitation of the PEFR measurement is that it is effort-dependent; however, it can still be used as a screening tool. If suspicion of occupational asthma remains high after the PEFR measurement, confirmatory measurements of FEV$_1$ and FVC by a trained technician in the workplace may be needed.

Bronchial Provocation Tests A nonspecific bronchial provocation test is useful to establish an initial diagnosis of asthma, although it cannot differentiate occupational asthma versus general asthma. The most commonly utilized agent in the United States is methacholine, but histamine also can be used. A positive test is defined as a provocative concentration producing a 20% decline in FEV$_1$ (PC$_{20}$) of less than 8 mg/mL of methacholine (8–16 mg/mL considered

TABLE 88-4 Diagnostic Tests for Occupational Asthma

Test	Sensitivity	Specificity	Comment
Immunologic testing	Good	Intermediate	HMW and some LMW compounds (IgE response needed)
Spirometry before and after work	Intermediate	Poor	Objective and simple
PEFR monitoring	Intermediate	Poor	Patient cooperation needed, inexpensive
MCh Challenge	Good	Poor	Test for asthma, not OA
Specific inhalation challenge	Good	Good	Gold standard, expensive and can be dangerous

borderline).[27] The test is safe, and there are performance guidelines elaborated by the American Thoracic Society and European Respiratory Society.[27,28]

A specific inhalation challenge test can be performed for the diagnosis of occupational asthma and determining whether a patient's symptoms are due to a particular agent. However, risks associated with the test include prolonged bronchospasm requiring clinical intervention. The test needs to be closely monitored and performed under a physician's supervision, usually in a hospital-based setting. The test is generally considered the gold standard for the diagnosis of occupational asthma, but it is rarely performed in the United States[29] due to the cost and high risks.

Immunologic Tests Immunologic tests can be used in immunologically mediated occupational asthma (mostly due to HMW compounds). A skin prick test using a panel of allergens can be useful in determining sensitization. Immunologic tests using an extract of the suspected specific offending agent can be useful in establishing the diagnosis. According to a systemic review of studies using specific inhalation challenge as the gold standard, sensitivity and specificity for the skin prick test are 80.6% and 59.6%, respectively.[25] Several extracts, such as flour, coffee, and animal protein, have been used for skin testing.[17]

Serum-specific IgE antibodies are another test used to facilitate the diagnosis of occupational asthma (using specific inhalation challenge as the gold standard); overall sensitivity and specificity are 73.3% and 79.0%, respectively.[25] However, immunologic tests only indicate sensitization and need to be considered in conjunction with the history and other diagnostic tests to make a definitive diagnosis of occupational asthma. Moreover, extracts are not available for the majority of chemicals implicated in causing asthma (Table 88-2).

Other Diagnostic Biomarkers In the past several decades, studies have addressed identification of biomarkers in occupational asthma. In a review by Brooks,[30] the percentage of eosinophils in induced sputum is noted to increase after specific inhalation challenge in patients with occupational asthma. Exhaled nitric oxide may also be compared before and after work as an aid in diagnosis, although confounders, such as infection and smoking, may complicate interpretation of findings, making use of this test controversial in the diagnosis of occupational asthma. Finally, elevated systemic biomarkers, such as interleukin 6 and tumor necrosis factor α in serum, nasal lavage fluid, or bronchoalveolar lavage, also may offer evidence of occupational asthma;[30] however, the findings are nonspecific.

■ Management

Removing workers with occupational asthma from offending environments is the first and an essential step. In some scenarios, an exposure reduction in the workplace may allow workers to continue working without progressive respiratory symptoms. If changing jobs is unrealistic or not feasible, and the offending agent or process cannot be eliminated, the use of personal protective equipment may reduce attacks, although it is rarely sufficient to protect sensitized workers. HMW compounds generally can be avoided through use of a high-efficiency particulate air mask, while helmet respirators with an isolated air source may be needed in workers who work with LMW compounds. Continued exposure, even with PPE, is associated with worse outcomes.

Notably, avoiding exposure is not enough. A study of refinery workers exposed to platinum salts showed that 77% of workers continued to suffer from asthma, and 86% had airway obstruction or bronchial hyperresponsiveness despite job relocation and passage of several years (median, 67 months) after the initial diagnosis.[31] Currently, there is no specific treatment for occupational asthma; however, treatment of general asthma is warranted if the patient has persistent asthma symptoms despite removal from the exposure.

BYSSINOSIS

Over 60 million people worldwide work in the textile and clothing industry.[32] In some workers, respiratory symptoms developed after exposure to cotton, flax, or hemp dust. These adverse respiratory effects were first described more than 100 years ago as a syndrome now known as *byssinosis*. Over the past years, byssinosis has been referred to as cotton worker's lung, brown lung disease, and Monday morning fever (as workers commonly have a fever and respiratory symptoms after not having worked over the weekend).

■ Epidemiology

The Centers for Disease Control and Prevention (CDC) published mortality data for byssinosis that showed a significant decline in the number of deaths between 1979 and 2014.[33] While the number of cases may have decreased in the United States, increases throughout the rest of the world, especially in countries where cotton industries have grown (such as India, Pakistan, Nepal, Sri Lanka, and Bangladesh) are not surprising. Besides cotton-based industries, flax, hemp, and jute exposures may also cause byssinosis.

Despite modernization and better work environment, byssinosis is still common. The prevalence of byssinosis in textile workers is difficult to estimate, especially since the timing of the survey may affect the prevalence estimate. For example, in a cotton textile worker cohort in Shanghai, China, examined from 1981 to 1996, 15.3% of workers reported byssinosis in the most recent survey (after 15 years) versus 7.6% at baseline.[34] Another study in Pakistan showed that 26.6% of workers had frequent sputum production, and 16.7% of works had frequent cough.[35] Not all workers in the cotton industries have the same risk of developing bronchitis. Ginning, opening, or carding work carries a higher risk than other jobs. Cleaning work, such as performed by strippers and grinders (who maintain the carding machinery), carries a particularly high risk for developing byssinosis.

■ Risk Factors

The length of employment and the intensity of cotton dust exposure are well-known risk factors for developing higher grades of byssinosis. Beyond cotton dust exposure itself, the endotoxin level in the workplace can potentiate the pathogenesis of the disease. In a 15-year Chinese longitudinal cohort study, endotoxin was an independent predictor of FEV_1 and FVC decline among cotton workers.[34]

Gene–environmental interaction also may play a role in disease pathogenesis. Workers with an A allele of TNF–308G/A polymorphism have a greater FEV_1 decline with endotoxin exposure.[36] Cigarette smoking also has been thought to have an additive effect with cotton exposure in developing byssinosis.[37] This may also explain why in southern Asia byssinosis is more prevalent, since workers in these countries also smoke heavily, which may exacerbate symptoms.

■ Mechanism and Pathogenesis

Cotton dust alone may cause airway inflammation—a phenomenon that can be seen in a tobacco smoker's airways; however, the endotoxin level in cotton dust or work environment may also play an important role in the pathogenesis of byssinosis. Endotoxin is a lipopolysaccharide found in gram-negative bacteria. The gram-negative bacterial endotoxins in cotton dust are probably the causative agent for airway obstruction and inflammation.[34,38] Findings supporting this conclusion include the following: (1) endotoxin can be detected in cotton dust; (2) animal and human studies support the concept that endotoxin inhalation can induce airway inflammation; and (3) ambient concentrations of endotoxin correlate with reduction in airway flow rates.[39]

■ Clinical Presentations

Patients usually present with frequent cough, chest tightness, dyspnea, and wheezing. Symptoms mostly happen within a few hours of exposure or re-exposure ("Monday fever"). Schilling first classified the severity of byssinosis solely based on symptoms, designating grades 0 to 3, with grade 3 the most severe.[40] The classification is shown in Table 88-5. In 1983, the World Health Organization proposed a modified classification system that incorporates spirometry; however, the revised classification has not been broadly adopted in current practice.[41]

TABLE 88-5 Clinical Grading of Byssinosis as Proposed by Schilling

Grade 0	No symptoms on first day of work
Grade 1/2	Occasional chest tightness or irritation of respiratory tract on the first workday of week
Grade 1	Chest tightness on every first day of work week
Grade 2	Chest tightness on first and other days of work week
Grade 3	Chest tightness on first and other days of work week and physiologic evidence of permanent disability

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■ Diagnosis

Unfortunately, there are no specific diagnostic tests for byssinosis. A detailed occupational history that establishes the timing of exposure and the onset of symptoms is essential. Physical examination may show fine basilar rales, and chest radiographs may show hyperinflation of the lung. However, these findings can also be seen in asthma or other pneumoconioses. Pulmonary function tests before, after, and between work shifts may be very helpful (e.g., a decline in FEV_1 noted on the day of return to work after an absence[42]).

■ Management and Prognosis

The most important elements in management are removing the symptomatic worker from the work environment and dust exposure reduction,[42] which can be done through a change in cotton processing (e.g., steam-cleaning cotton while it is still in the bale). Use of an inhaled bronchodilator with either short- or long-acting beta-agonist activity may improve respiratory symptoms. Treatment may be needed chronically. With severe and acute symptoms, a short course of corticosteroids may help. Most patients recover after the treatment and removal from exposure. For those patients with chronic cotton exposure, persistent airway inflammation may lead to obstructive lung disease.[43] Finally, in a 30-year longitudinal study of textile workers, cotton dust was found to be associated with increased cancer mortality, especially due to gastrointestinal cancer.[44]

OTHER ORGANIC DUST–RELATED DISEASES

Organic dust toxic syndrome (ODTS or pulmonary mycotoxicosis) results from exposure to mycotoxins or endotoxins.[45–47] The syndrome has been associated with exposure to grains, moldy hay, and cotton contaminated with the fungus *Fusarium*.[48] Symptoms of ODTS include fever, chills, dyspnea, cough, myalgias, and nausea that occur 4 to 6 h after exposure. Pulmonary function tests may show a restrictive ventilatory defect and a reduction in diffusing capacity. Desquamative interstitial pneumonitis also may be seen.[48] A specific clinical manifestation seen with grain dust exposures are skin reactions, which are not seen in byssinosis.[49]

OCCUPATIONAL EXPOSURE, COPD, AND CHRONIC BRONCHITIS

In the most recent American Thoracic Society and European Respiratory Society statement on COPD from 2019, the estimated occupational burden for COPD is 14% and 13% for chronic bronchitis.[3] Distinct from occupational asthma, COPD does not include a clinical subentity, such as "occupational COPD." This may be due to the fact that COPD develops slowly and is irreversible, even after avoidance of occupational exposure.[50]

Organic dust toxin syndrome and byssinosis are sometimes misclassified as COPD; however, work-related airflow limitations often have asthma-like symptoms and may become poorly reversible with chronic exposure.[50] A distinction between lung disease related to occupational exposure to organic dust and COPD is important.

In addition to COPD, emerging literature addresses occupation-related chronic cough or chronic bronchitis, especially in the context of the collapse of the World Trade Center in 2001. Chronic bronchitis has been reported in firefighters and first responders in the aftermath of collapse of the World Trade Center.[51,52] Several studies have found an association between chronic cough and occupational exposure in mines, cement workers, construction workers, and those employed in farming and the food, chemical, and wood industries.[53]

The diagnosis of occupation-related COPD or chronic bronchitis can be difficult, as the two diseases can also be caused by nonoccupational factors, such as tobacco smoking—the predominant risk factor for COPD. As noted previously, occupational risk is likely an independent risk factor, and the physician must take a detailed occupational history to explore the potential occupational etiologies of the patient's obstructive airway disease or chronic cough. Identifying occupational risks early may prevent worsening of the disease and initiation of a proper public health surveillance program and worker's compensation.

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CHAPTER 89

Indoor and Outdoor Air Pollution

Coralynn Sack
Joel D. Kaufman

INTRODUCTION

Exposure to air pollution is ubiquitous and a major cause of global morbidity and mortality. This chapter provides a broad introduction to indoor and outdoor air pollution, beginning with a brief review of the emergence and recognition of air pollution as a major public health concern. The chapter then reviews general principles and concepts related to inhalation injury, exposure, and health outcomes. The health consequences of indoor and outdoor air pollution are covered separately, although this distinction is largely artificial, given the significant overlap in exposure between pollutants found in indoor and outdoor locations. While the emphasis of the chapter is on respiratory health effects, the extrapulmonary effects of air pollutants are briefly discussed. The chapter concludes with a discussion of susceptible populations and different control strategies, aimed both at public health and individual levels.

OVERVIEW

Air pollution is now considered the largest environmental cause of disease and premature death in the world, responsible for an estimated seven million deaths per year.[1] Exposure to air pollution is a significant cause of cardiopulmonary disease and likely increases the risk of neurodevelopmental disorders, poor birth outcomes, metabolic disease, and malignancy. While a global problem, air pollution disproportionately affects the poor with the highest exposure levels occurring in low- and middle-income countries. Several of the principal air pollutants also act as greenhouse gases, contributing to global warming and the additional health risks associated with climate change.

The sources and concentration of pollutants have changed throughout history, as societies develop and as the climate warms. The use of fire for heating and cooking created exposure to smoke, a problem that persists for the billions of people who still use biomass fuels today. The rise of cities concentrated the emissions of pollutants from dwellings and manufacturing facilities within restricted locales. Industrialization introduced localized or point sources of pollution, such as power plants, which generate immense emissions of combustion byproducts in areas where people live and work. During the 20th century, mobile sources, including cars, trucks, and other fossil fuel–powered vehicles, created a new type of pollution: photochemical pollution, or “smog.” The unprecedented growth of some urban areas to form “megacities,” such as Mexico City, São Paulo, and Shanghai, has led to unrelenting air pollution from massive vehicle fleets, standstill traffic, polluting industries, and power plants.

Increasingly, there is recognition that the problem of air pollution extends into the indoor environment. In low- and middle-income countries, exposure to smoke from biomass fuel combustion for indoor cooking and heating is still widespread. In the more developed countries, indoor pollutants can be either generated by human activities or released from building and construction materials. Buildings designed to optimize energy conservation by reducing the exchange of indoor and outdoor air can seal pollutants within and result in unhealthy concentrations.

For centuries, people have recognized that air quality has health consequences. Classical writings from Roman times contain references about poor air quality linked to health. In the late 1200s, King Edward I attempted to ban the burning of “sea coal” in open furnaces to limit the emissions of sulfurous smoke.[2] However, the modern era of air pollution research and regulations did not begin until the mid-20th century, when dramatic pollutant events in the United States and England caused a clear increase in mortality. Perhaps the most striking of these episodes was the London Fog of 1952, when a temperature inversion caused the accumulation of a dense layer of coal-related toxic air, resulting in more than 3000 excess deaths observed over the next month. More recent analyses suggest that the actual mortality toll attributable to the event was probably closer to 12,000 and was associated with a persistent increase in death for more than 1 year.[3]

These catastrophes sparked the passage of environmental legislation, including the Clean Air Acts of 1956 and 1968, which laid the foundation for modern control measures.[4] They also motivated research to characterize pollutants, toxicologic investigations aimed at uncovering biologic mechanisms, and epidemiologic studies to quantify health effects in the community. These research approaches are fundamental to our understanding of the public health impact of air pollution and have resulted in a large body of scientific evidence over the past half century. The synthesized findings from this research have formed the foundation for a legal framework of regulations to limit emissions and control concentrations of key pollutants in outdoor air. These evidence-driven regulations have had substantial impact on air quality in the United States, driving down levels of the most prominent pollutants (Fig. 89-1).[5]

In spite of these improvements in air quality, air pollution remains a significant public health concern. Epidemiologic studies show that adverse health effects still occur at concentrations frequently observed and at the upper end of the range of the National Ambient Air Quality Standards (NAAQS). In addition, billions of people worldwide are exposed to levels of ambient air pollutants far above recommended levels.[6] As a consequence of the anthropogenic release of pollutants into the atmosphere, climate change has become an increasingly dire issue with a multitude of direct and indirect consequences.[7] Indoor air pollution continues to be a concern and, unlike outdoor air pollution, is not regulated by the EPA.

The literature on air pollution is now voluminous and has been published in a broad array of journals and technical reports. Of necessity, this chapter is selective in its review and emphasizes the most relevant findings for clinicians as well as newer literature. The documents prepared by the EPA on the six “criteria” pollutants (sulfur dioxide [SO_2], particulate matter, NO_2, carbon monoxide [CO], ozone [O_3], and lead) offer encyclopedic reviews that are updated periodically (Table 89-1). Key documents on specific pollutants are cited within the appropriate sections of this chapter.

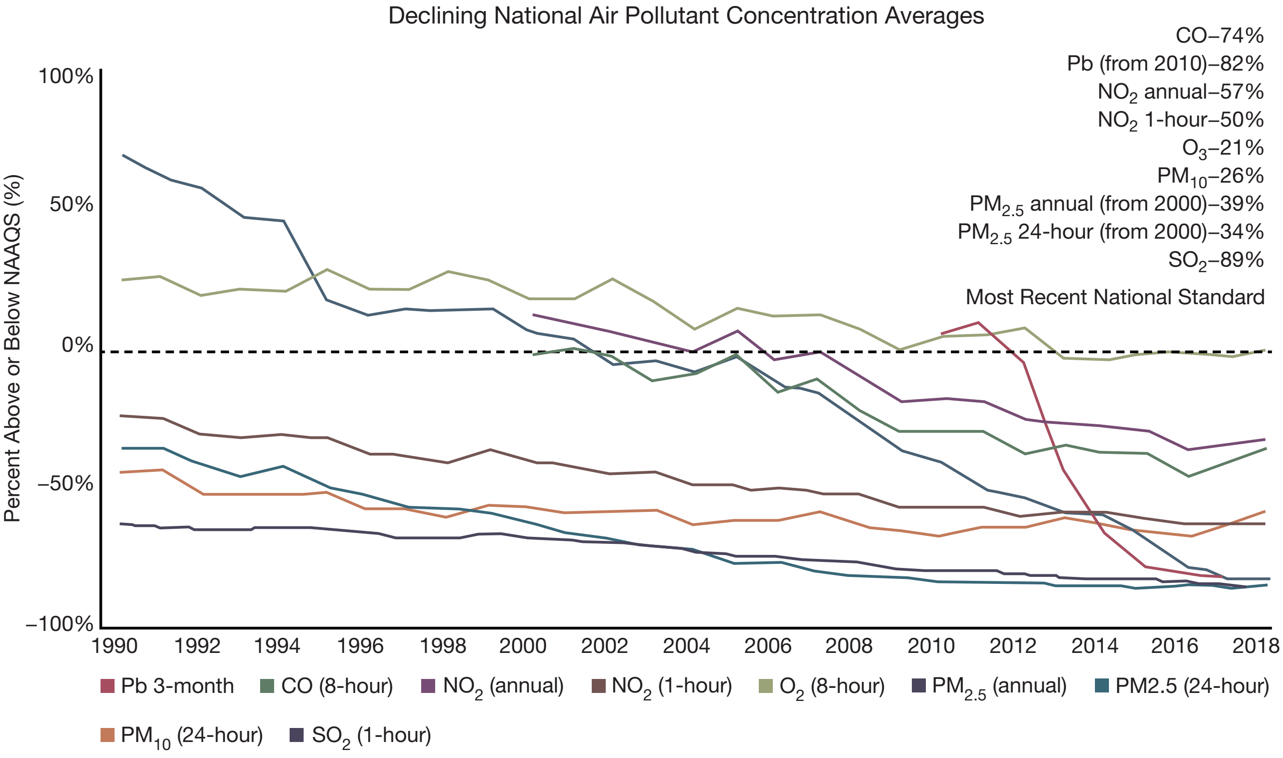

Figure 89-1 Comparison of national levels of the six common pollutants to the most recent National Ambient Air Quality Standards, 1990–2018. National levels are averaged across all monitors with complete data for the time period. *(Reproduced with permission from Our Nation's Air. Air Quality Improves as America Grows. Status and Trends Through 2019. https://gispub.epa.gov/air/trendsreport/2020.)*

TABLE 89-1 Criteria Pollutants, Sources, and National Ambient Air Quality Standards (NAAQS)

Pollutant	Outdoor Sources	Primary Standards	Averaging Time[a]
Sulfur dioxide	Coal and petroleum combustion, smelting, and other manufacturing	75 ppb	1 h
PM_{10}	Coal and petroleum combustion, vehicles, industry, surface dust	150 μg/m^3	24 h
$PM_{2.5}$	Fuel combustion from automobiles, power plants, wood burning, industrial processes, and diesel-powered vehicles	35 μg/m^3 12 μg/m^3	24 h Annual (arithmetic mean)
Nitrogen dioxide	Motor vehicles, coal and petroleum combustion, industry	100 ppb 53 ppb	1 h Annual mean
Carbon monoxide	Motor vehicles, coal and petroleum combustion	35 ppm (40 μg/m^3) 9 ppm (10 μg/m^3)	1 h 8 h
Ozone	Secondary formation from NO_2 and hydrocarbons	0.070 ppm	8 h
Lead	Gasoline, lead-containing dust	0.15 μg/m^3	Rolling 3-month average

[a] *Averaging time denotes the defined time period over which concentration is measured and averaged.*

GENERAL PRINCIPLES AND CONCEPTS

Air pollution is defined as the presence of hazardous chemicals or compounds in the air, at levels that pose a threat to human health, damage other living organisms, or adversely affects the natural environment.[8] In humans, adverse responses to air pollutants are a reflection of the exposure, target site of injury, and downstream effects of pollutants (Fig. 89-2). This section of the chapter covers principles of inhalation injury, proposed mechanisms of action, and the related spectrum of adverse health effects. It also reviews the research methods that have been developed to characterize the effects of air pollutants.

■ Principles of Inhalation Injury

Atmospheric pollutants exist as a complicated mixture of gaseous, liquid, and solid particles. The health effects from inhalation depend on a complex interplay between host and exposure characteristics. The substance's physical state, concentration, solubility, and aerodynamic dimensions partially determine the site of deposition and retention within the lung.[9] Water-soluble gases, such as SO_2, are almost completely removed in the nasopharynx while less soluble gases, such as NO_2 and O_3, can penetrate deep within the lung. Smaller particles (0.1–5.0 μm) are more likely to reach the alveoli, whereas larger particles (≥10 μm) are typically trapped and removed by the mucus and cilia of the upper respiratory tract. Ultrafine particles ($PM_{0.1}$) can pass through the alveolar–capillary membrane to reach the bloodstream and travel to other end organs.

The rate and depth of inhalation also greatly affect the total dose of pollutants delivered to the lung. Exercise increases the dose by directly increasing minute ventilation and by stimulating a switch from nasal to oral breathing, bypassing more efficient pollutant removal in the nasal passages. Airway anatomy, including branch structure and caliber, contribute by influencing aerodynamic

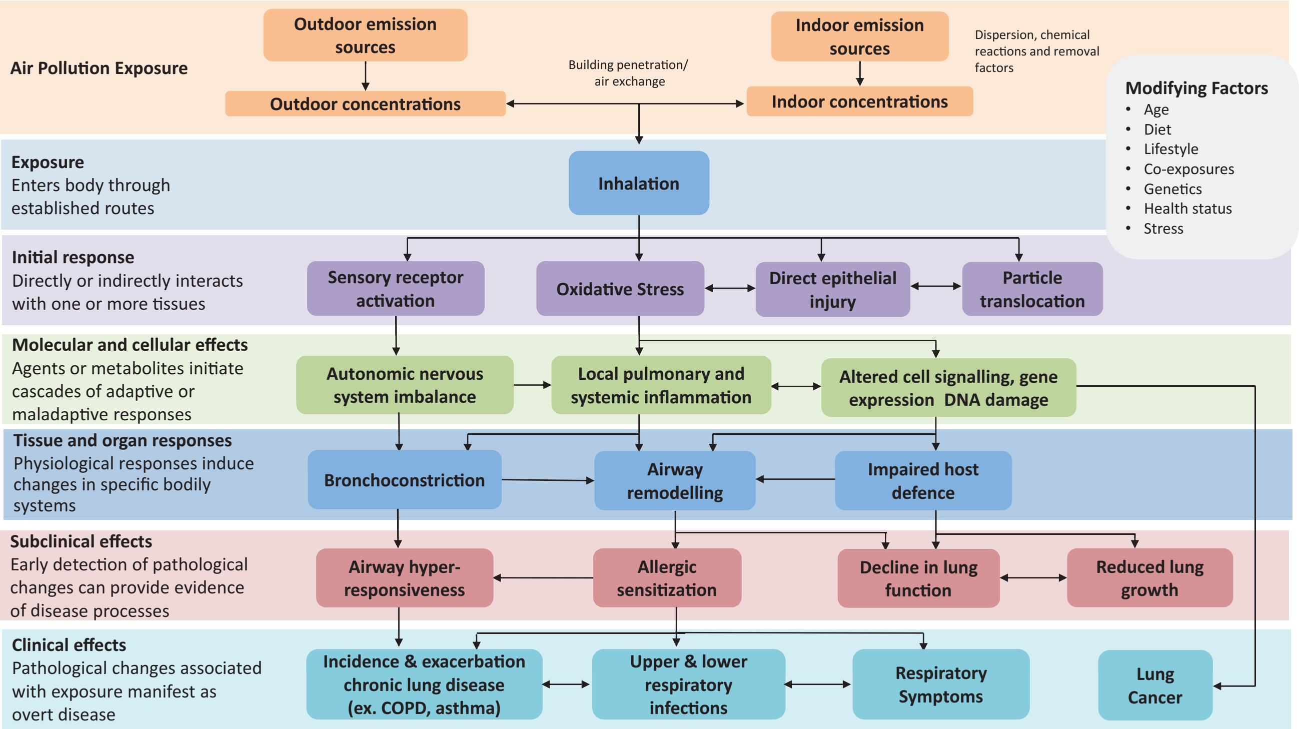
Air Pollution Exposure
Outdoor emission sources
Outdoor concentrations
Building penetration/ air exchange
Indoor emission sources
Indoor concentrations
Dispersion, chemical reactions and removal factors
Modifying Factors
• Age
• Diet
• Lifestyle
• Co-exposures
• Genetics
• Health status
• Stress
Exposure
Enters body through established routes
Inhalation
Initial response
Directly or indirectly interacts with one or more tissues
Sensory receptor activation
Oxidative Stress
Direct epithelial injury
Particle translocation
Molecular and cellular effects
Agents or metabolites initiate cascades of adaptive or maladaptive responses
Autonomic nervous system imbalance
Local pulmonary and systemic inflammation
Altered cell signalling, gene expression DNA damage
Tissue and organ responses
Physiological responses induce changes in specific bodily systems
Bronchoconstriction
Airway remodelling
Impaired host defence
Subclinical effects
Early detection of pathological changes can provide evidence of disease processes
Airway hyper-responsiveness
Allergic sensitization
Decline in lung function
Reduced lung growth
Clinical effects
Pathological changes associated with exposure manifest as overt disease
Incidence & exacerbation chronic lung disease (ex. COPD, asthma)
Upper & lower respiratory infections
Respiratory Symptoms
Lung Cancer

Figure 89-2 Framework for conceptualizing exposure, dose, and respiratory health effects from outdoor and indoor air pollution. *(Reproduced with permission from Cosselman KE, Navas-Acien A, Kaufman JD. Environmental factors in cardiovascular disease. Nat Rev Cardiol. 2015;12(11):627–642.)*

transportation and deposition mechanics in the lungs. Other factors that impact susceptibility include genetic factors related to oxidative stress and inflammation, the ability to clear substances from the respiratory tract, the presence of other comorbidities, and effects of concomitant exposures such as tobacco smoke.

The physiologic mechanisms by which inhaled gases and particles cause injury are diverse and only partially understood. Deposited particles can cause direct damage, activate sensory receptors, induce reactive oxygen species and inflammatory responses, or cross the permeable epithelial barrier to enter the systemic circulation. The oxidant gases O_3 and NO_2 also cause inflammation of the respiratory epithelium, presumably through the production of toxic oxidant species and release of potent mediators.

Oxidative stress occurs when the body's innate antioxidant capabilities are overwhelmed by reactive oxygen species, resulting in lipid peroxidation and activation of proinflammatory signaling, such as mitogen-activated protein kinase (MAPK) and nuclear factor–kappa beta (NF-κβ). This cascade can result in increased cytokine production as well as elevations in CRP, fibrinogen, and circulating leukocytes with both pulmonary and systemic effects. Epigenetic changes mediated through DNA methylation result in modified gene expression and activity. Ultimately, these can contribute to an alteration in endothelial function, platelet activation, autonomic dysregulation, and changes in the innate and adaptive immune system (Fig. 89-3).

ADVERSE HEALTH EFFECTS OF AIR POLLUTION: CLINICAL AND PUBLIC HEALTH CONCERNS

The spectrum of adverse effects of air pollution is broad, ranging from the consequences of acute, dramatic exposures to more subtle effects on disease risk resulting from chronic exposures. This spectrum has been conceptualized as a pyramid with mortality at its tip and an increasingly common set of morbidities as the base.[10]

To interpret the scientific evidence on the effects of air pollution, clinicians need a framework for determining whether an effect is "adverse." If a broad construct of health is used that includes a state of well-being as a component, adverse effects of air pollution include not only clinically evident disease but also more subtle symptom responses and physiologic effects that may compromise well-being or increase the risk of disease. In a 2016 report, a committee of the American Thoracic Society (ATS) revised guidelines for defining adverse health effects in epidemiologic studies of air pollution.[11] The committee recommended that various biomarkers, intermediary outcomes, and preclinical diseases should be labelled as adverse health effects when they are linked to a clinical condition, pathologic change, or pathway to these changes. As an example, they cite the transient increase in sputum leukocytes observed after ozone exposure. While not deleterious by itself, this finding should be considered as adverse when interpreted in the context of its known association with airway inflammation, decrement in lung function, and increased risk of exacerbation in individuals with chronic respiratory disease (Table 89-2; Fig. 89-4).

■ Concepts of Time–Activity and Total Personal Exposure

Definitions of concentration, exposure, and dose are fundamental to considering the health effects of air pollution and steps used to reduce risk.[12] *Concentration* refers to the amount of material present in air. *Exposure* constitutes contact with a material at a portal of entry into the body—the respiratory tract, gastrointestinal tract, and skin—and is calculated as the unit of concentration multiplied by time. In the lung, exposure would constitute the time spent in contaminated air. *Dose* refers to the amount of material that enters the body; *biologically effective dose* is the amount of material reaching target sites for injury—for example, the mass of respirable particles delivered to the small airways.

When considering health impacts, *total personal exposure* to a pollutant is the relevant index of exposure, not the exposures received separately within indoor and outdoor environments. The total personal exposure to a pollutant can be conceptualized as the sum of time-weighted average pollutant concentration in different

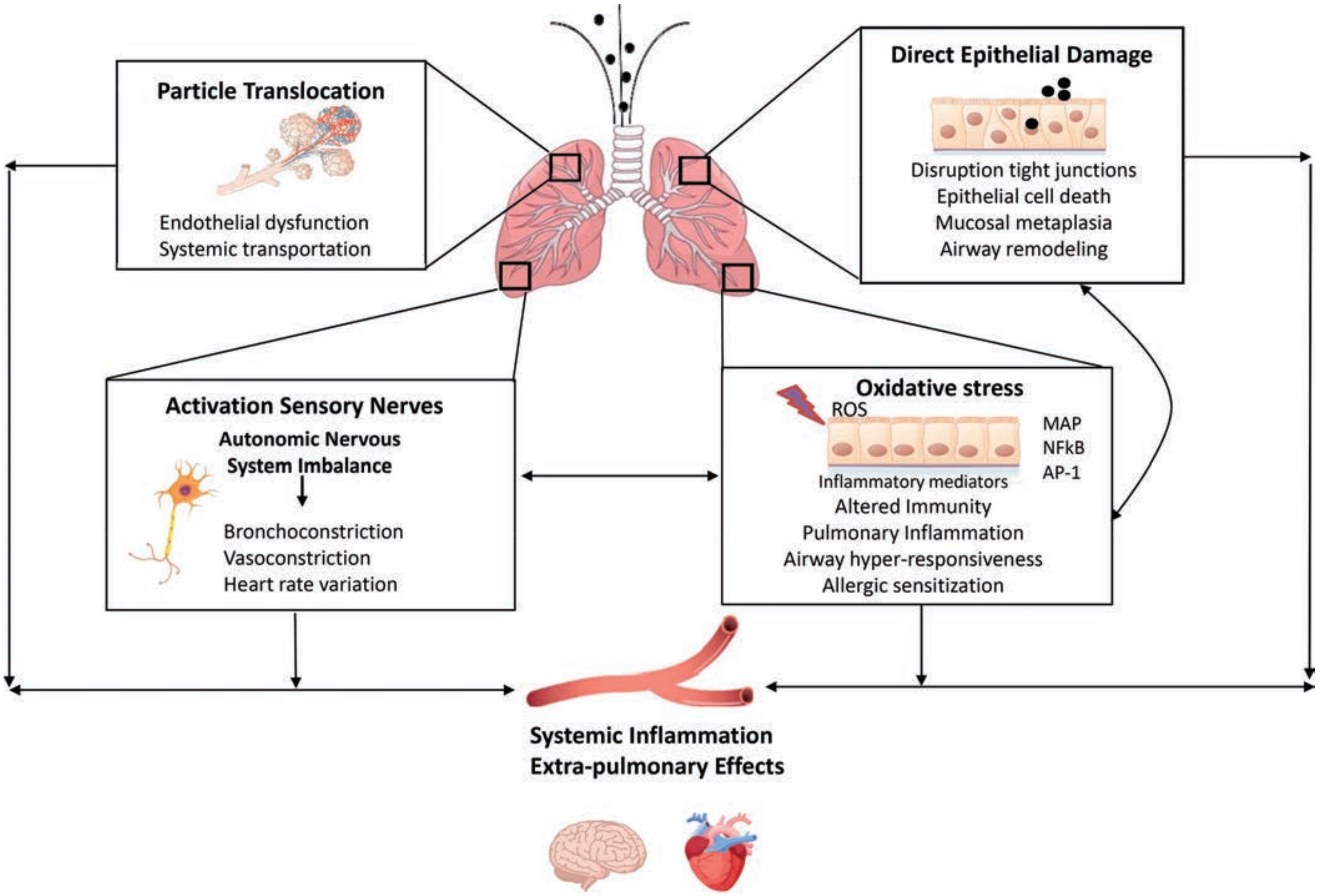
Particle Translocation
Endothelial dysfunction
Systemic transportation
Direct Epithelial Damage
Disruption tight junctions
Epithelial cell death
Mucosal metaplasia
Airway remodeling
Activation Sensory Nerves
Autonomic Nervous
System Imbalance
Bronchoconstriction
Vasoconstriction
Heart rate variation
Oxidative stress
ROS
MAP
NFkB
AP-1
Inflammatory mediators
Altered Immunity
Pulmonary Inflammation
Airway hyper-responsiveness
Allergic sensitization
Systemic Inflammation
Extra-pulmonary Effects

Figure 89-3 Major proposed pathophysiologic mechanisms of air pollution.

TABLE 89-2 Respiratory Effects Associated with Air Pollution

Respiratory mortality
Malignancies of the respiratory tract
Increased incidence, prevalence or frequency of exacerbations of chronic pulmonary disease: e.g., asthma, COPD, cystic fibrosis, interstitial lung disease
Increased incidence and severity of upper and lower respiratory tract infections
Respiratory symptoms affecting quality of life: e.g., cough, phlegm, wheezing, dyspnea, nasal drainage
Increased incidence of preterm birth, low birth weight, or growth restriction leading to adverse respiratory outcomes
Reduced growth of lung function in children
Transient reduction in lung function associated with symptoms in healthy individuals
Transient reduction in lung function without symptoms in susceptible individuals
Persistent/chronic reductions in lung function

Modified with permission from Thurston GD, Kipen H, Annesi-Maesano I, et al. A joint ERS/ATS policy statement: what constitutes an adverse health effect of air pollution? An analytical framework. Eur Respir J. 2017;49(1): 1600419.

"microenvironments."[13] Microenvironments are locations that have relatively constant levels of pollutants during the time spent there. The principal microenvironments contributing to total personal exposure are either those with relatively high concentrations or in which relatively large amounts of time are spent. For example, for particulate matter exposure, key microenvironments may include an office where smoking is allowed or the indoor residential environment. New sensing approaches are facilitating refined studies of activity levels and air pollution concentrations, which will help clarify an understanding of where and when the most-risky exposures take place.

Studies of time use in a number of countries show that people spend an average of 65% to 75% of their time inside their residences, and more than 90% of their time indoors, when including contributions from home, work, and recreational activities.[14] Consequently, personal exposures to many pollutants take place largely in indoor microenvironments. However, many pollutants generated by outdoor sources can penetrate indoors and contribute to the indoor microenvironment. Other pollutants, such as O_3, have low indoor levels so that outdoor exposures are the predominant determinants of personal dose.

■ Research Approaches to Air Pollution

Our understanding of the health effects of air pollution derives from a multipronged research approach, aimed at characterizing atmospheric pollutants and exposures, in vitro and in vivo toxicologic studies, and epidemiologic studies of "real-world" effects. These different approaches are complementary, each with their own advantages and disadvantages. Together, they provide the evidence used to define threshold levels for adverse effects due to air pollutants and are the basis on which air pollution standards are set.

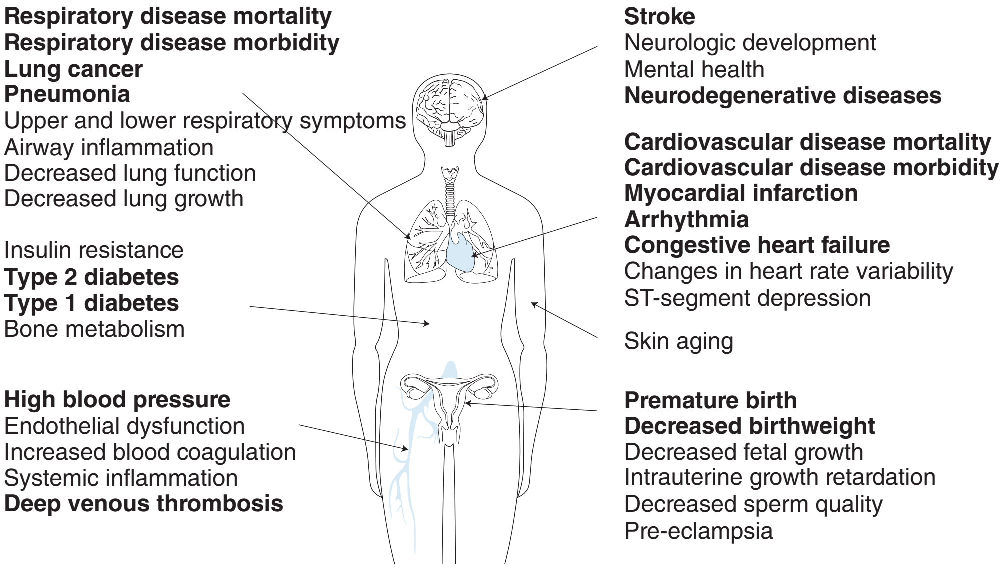
Respiratory disease mortality
Respiratory disease morbidity
Lung cancer
Pneumonia
Upper and lower respiratory symptoms
Airway inflammation
Decreased lung function
Decreased lung growth
Insulin resistance
Type 2 diabetes
Type 1 diabetes
Bone metabolism
High blood pressure
Endothelial dysfunction
Increased blood coagulation
Systemic inflammation
Deep venous thrombosis
Stroke
Neurologic development
Mental health
Neurodegenerative diseases
Cardiovascular disease mortality
Cardiovascular disease morbidity
Myocardial infarction
Arrhythmia
Congestive heart failure
Changes in heart rate variability
ST-segment depression
Skin aging
Premature birth
Decreased birthweight
Decreased fetal growth
Intrauterine growth retardation
Decreased sperm quality
Pre-eclampsia

Figure 89-4 Spectrum of adverse effects that have been associated with ambient air pollution. Bold type indicates conditions that are included in the Global Burden of Disease categories. *(Reproduced with permission from Thurston GD, Kipen H, Annesi-Maesano I, et al. A joint ERS/ATS policy statement: what constitutes an adverse health effect of air pollution? An analytical framework. Eur Respir J. 2017;49(1):1600419.)*

There is a significant body of literature on the physical and chemical properties of the different air pollutants. Exposure assessment has emerged as a distinct research discipline that uses questionnaires to capture activities and time use, personal and area monitoring of air pollution levels, statistical models to estimate exposures, and sophisticated biomarkers of exposure and dose.[13] New high-throughput technologies are being developed that will facilitate data-rich measurements of "the exposome," conceptualized as the totality of exposures that individuals experience over their lifetime.

Toxicologic studies are useful to characterize the hazards of air pollutants, explore pathophysiologic mechanisms, and assess patterns of injury and disease risk. In vitro studies of cell cultures, including human respiratory epithelial and alveolar cells, allow for rigorous control of experimental conditions to study biologic pathways of injury. Predictive toxicology methods that leverage advances in systems biology, engineered tissue, and mathematical modelling have the potential to rapidly identify and characterize emerging toxins.

Animal studies can be conducted in both healthy and diseased animals over a range of well-defined exposure levels and conditions. This allows the assessment of serious and permanent health conditions that are not possible in human studies. Animal studies also provide important insights into the impact of pollution on lung structure, both at the earliest signs of injury and at end stages of disease. By using larger numbers of animals and sensitive species or models of disease, animal toxicology studies can increase the likelihood of detecting adverse effects.[15] Despite these advantages, large interspecies variations can make findings difficult to extrapolate to human exposure and disease.[16]

In controlled human-inhalation exposure (CHIE) studies, volunteers are intentionally exposed to pollutants in controlled experimental conditions, such as an exposure chamber or sealed room. To be ethically acceptable, these studies are of brief duration and limited to levels of exposure to produce only acute fully transient effects. CHIE studies have the advantage of allowing a randomized controlled design and isolating the effects of specific laboratory-generated pollutants or mixtures, such as O_3, PM, or diesel exhaust particles (DEP). In addition to healthy volunteers, sensitive populations can also be selected for investigation, such as individuals with asthma, chronic obstructive pulmonary disease (COPD), coronary artery disease, or specific genetic polymorphisms. By producing transient changes in biomarkers, physiologic parameters, or other subclinical endpoints, CHIE studies have helped to elucidate mechanisms of injury, understand concentration-response functions in the species of primary interest, and inform air-quality standards.[17]

Epidemiologic studies use statistical methods to analyze the association between "real-world" exposure to air pollution and various health effects.[13] The findings of epidemiologic studies of air pollution have direct public health and regulatory relevance. Exposure concentrations and mixtures are representative of those received in the community. A range of participants can be studied, from those who are expected to be most susceptible or vulnerable to a more representative selection of the general population.

There are some limitations to observational studies, including the difficulty in concluding that an observed relationship is caused by the exposures. Epidemiologic studies having inadequate sample size and, therefore, limited statistical power, may supply imprecise and uninformative estimates of risk and may not be able to answer public health questions. *Confounders* are factors that are correlated with air pollution, the exposure of interest, and are also predictors of the health outcome. If these factors are not appropriately measured and adjusted for in the analysis, the results can be biased.

Exposure to pollutants is also difficult to measure accurately in epidemiologic studies, and it is often inferred from a participant's home address through a variety of different approaches. These estimates range in accuracy, from using pollutant levels from the nearest regulatory air quality monitors to calculating exposure via sophisticating spatiotemporal models. All these techniques can have some error, both random and systematic, that may not reflect individual exposure through day-to-day activities. Exposure to pollutants rarely occur singly, and disentangling the effects of individual pollutants from complex mixtures is challenging. Because many pollutants track together, adjusting for co-pollutants within statistical models is limited by collinearity.

OUTDOOR AIR POLLUTION

This section begins with a review of the sources and then considers the effects of the principal outdoor pollutants, grouped according to their designation by the EPA (Tables 89-1 and 89-3).

TABLE 89-3 Criteria Pollutants, Key Mechanisms, and Established Health Effects

Pollutant	Key Mechanisms	Established Health Effects
Sulfur dioxide	Highly soluble Generation ROS Activation sensory nerves	Upper airway injury Bronchoconstriction Increased asthma incidence and exacerbations
PM_{10}	Deposits in upper airway	Increased respiratory symptoms Asthma and COPD exacerbations
$PM_{2.5}$	Deposit in lower airway/alveoli Direct epithelial injury Generation ROS Translocation to bloodstream	Increased incidence and exacerbation of chronic lung diseases Reduced lung function Lung cancer Increased cardiopulmonary mortality Increase in neurocognitive disease
Nitrogen dioxide	Less soluble Oxidant gas	Bronchial and bronchiolar injury Impaired lung defense Enhanced response to allergens
Carbon monoxide	High affinity with hemoglobin Tissue hypoxia	Increase myocardial ischemia Neurologic effects
Ozone	Less soluble Highly reactive Simulation C-fibers	Bronchial and bronchiolar injury Reduced lung function Asthma and COPD exacerbations

Overview: Sources and Classification of Outdoor Air Pollution

Outdoor air pollutants originate from many diverse sources that can be classified as either natural or anthropogenic. While many naturally occurring pollutants, such as pollen and fungi, have well-recognized pulmonary effects, this chapter focuses predominantly on pollutants that arise from human activities. The major causes are fossil fuel combustion from mobile sources (such as motor vehicles), heat and power generation, industrial facilities (such as oil refineries and chemical manufacturing), municipal and agricultural waste sites, and residential cooking and heating.

In the United States, the principal outdoor pollutants are classified within the framework provided by the Clean Air Act, which identifies two sets of air pollutants, "criteria" pollutants (Table 89-1) and "toxic" air pollutants. The term *criteria* refers to the standard-setting process for these pollutants, which requires preparation of a criteria document reviewing all relevant evidence every 5 years. The criteria pollutants include primarily combustion-related pollutants: sulfur dioxide (SO_2), nitrogen dioxide (NO_2), particulate matter (PM), and carbon monoxide (CO); they also include the secondary pollutant ozone (O_3) and lead. The toxic pollutants are a diverse group of chemicals with serious health effects, including carcinogens, teratogens, and mucosal irritants. Examples of these pollutants are benzene, chlordane, ethylene oxide, hydrochloric acid, methane, parathion, propylene oxide, toluene, and vinyl chloride.

The regulations for these two groups of pollutants are designed to set maximum concentrations that provide an "adequate margin of safety" to the entire population, including those with heightened susceptibility. The National Ambient Air Quality Standards (NAAQS) sets standards for the six criteria pollutants, while the National Emissions Standards for Hazardous Air Pollutants (NESHAP) establishes maximum emission concentrations for the other toxic pollutants. Despite existing federal standards for ambient air quality, excesses are common in many areas of the country, particularly for O_3. Although the pollutants are considered in the following section on an individual basis, it should be re-emphasized that exposures of the population occur most often to mixtures, and synergy among individual pollutants may increase the effects of the mixture beyond the expected effect based on the components.

Outdoor Air Pollutants: Exposures and Health Effects

Important outdoor air pollutants are discussed individually below.

Particles

Perhaps the largest body of literature on the adverse effects of air pollution focuses on particulate matter (PM), which has repeatedly been shown to be associated with significant pulmonary morbidity and mortality as well as an increasing number of other extrapulmonary toxicities. PM refers to the diverse mixture of suspended liquid and solid particles found in the air and generated through a variety of anthropogenic and natural sources. Fossil fuel combustion and biomass burning accounts for approximately 85% of global ambient particles.[6] In urban areas, the most important contributors are fuel combustion for electrical production, industrial processes, and motor vehicle emissions. Particles can also arise from crushing/grinding processes or resuspension of crustal materials, such as road and tire byproducts, agricultural dust, and industrial waste sites.

The toxicity of PM likely reflects a combination of particle source, chemical composition, size, and shape. PM exists both as primary particle emissions from specific sources and as secondary compounds, formed through physical and chemical reactions in the atmosphere. Because of the diversity of sources, particles can have heterogeneous compositions that vary in both spatial and temporal dimensions. The pollutant mix reflects both local sources and those contributing to the regional background pollution (i.e., pollution generated elsewhere but transported to this and other locations via prevailing winds). In the Eastern United States, for example, much of the regional background of $PM_{2.5}$ comes from transport of power plant emissions from the central portion of the country. Hypotheses proposed on the chemical determinants of particle toxicity have focused on issues related to surface acidity, ability to exert oxidative stress, content of transition metals, organic compounds on particles (e.g., diesel particles) and presence of biologically derived agents, such as pollens or endotoxin.[18]

PM is typically divided into size categories based on mean aerodynamic diameter, as PM_{10} (particles with aerodynamic diameter <10 μm), coarse particles or $PM_{2.5-10}$ (aerodynamic diameter between 2.5 and 10 μm), fine particles or $PM_{2.5}$ (aerodynamic diameter <2.5 μm), and ultrafine particles (UFP, particles with aerodynamic diameter <0.10 μm, sometimes also referred to as nanoparticles) (Fig. 89-5). As reviewed earlier in the chapter, particle size is a determinant of inhalability and penetration within the lung. Particles larger than 10 μm tend to deposit in the nasopharynx while particles smaller than 2.5 μm can reach the gas-exchange region of the lung. The smallest particles (generally <200 nm) can be translocated across the respiratory epithelium and have been identified in multiple other organs, such as the CNS and placenta.[19,20]

The limitations of national air pollution monitoring programs make it difficult to discern differences in health effects among PM size fractions. The most complete monitoring data exist for $PM_{2.5}$, for which extensive monitoring was launched in 1999 in the United States; limited coarse PM monitoring was instituted in 2011, and there is no current national monitoring for UFP. Consequently, most epidemiologic studies have focused on PM_{10} or $PM_{2.5}$, with the strongest effects attributable to $PM_{2.5}$ exposure.

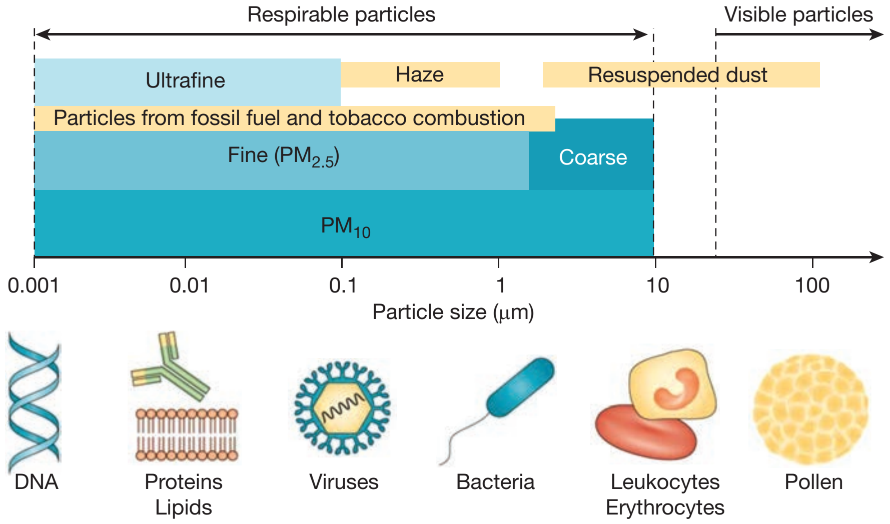

Figure 89-5 Size categorization of particulate matter. *(Reproduced with permission from Cosselman KE, Navas-Acien A, Kaufman JD. Environmental factors in cardiovascular disease. Nat Rev Cardiol. 2015;12(11):627–642.)*

Upon deposition, PM can cause direct epithelial injury, activate irritant receptors, generate reactive oxidative stress, and stimulate pulmonary inflammation and injury. Alveolar macrophages ingest PM, leading to the release of interleukin 6 (IL-6) and other proinflammatory cytokines. The accumulation of these carbon particles in macrophages can also overload the cells, resulting in impaired function and the buildup of anthracotic deposits in the lymphatic system and lung interstitium. UFP may have higher oxidative potential than other size fractions due to their increased surface area with a greater concentration of reactive oxygen species. In addition, UFP can cross the epithelial border to enter the bloodstream, and ultimately deposit in other organs where they cause disease direct damage or localized inflammation. The downstream effects of these interconnecting pathways can result in local and systemic inflammatory responses, altered immunity, endothelial dysfunction, and platelet aggregation.

Exposure to PM is a well-established cause of adverse respiratory outcomes. Both short-term and chronic exposures can result in decreased lung function, exacerbation of chronic lung disease, and increased morbidity and mortality from respiratory diseases. As opposed to the immediate effects associated with gaseous pollutants, the acute effects of PM often lag 0 to 5 days after exposure. Toxicology studies with animal models demonstrate impaired lung development with both pre- and postnatal exposure, allergic phenotypes, and increased airway hyperresponsiveness. While associations are strongest and most consistent with exposure to $PM_{2.5}$, short-term exposure to PM_{10} also is associated with ED visits and hospitalizations for worsening respiratory disease.

The global burden of disease resulting from PM exposure is significantly higher for cardiovascular rather than respiratory diseases, due to the higher underlying incidence of cardiovascular disease. While the proposed pathways that mediate this response are complex and beyond the scope of this chapter, they involve activation of the autonomic nervous system, altered endothelial function, accelerated atherosclerosis, and decreased LV contractility.[21] PM is strongly associated with increased risk of myocardial infarction, arrhythmia, stroke, and hospital admission for congestive heart failure. Multiple studies have demonstrated that $PM_{2.5}$ results in excess cardiovascular mortality, even in areas where levels are below 20 μg/m^3 or even less than 12 μg/m^3.

In addition to the clear risk of increased cardiopulmonary disease, PM is also associated with a variety of other extrapulmonary diseases in epidemiologic studies. In particular, there is a growing body of evidence demonstrating that PM has central nervous system effects, including neurodegenerative disease, cognitive effects, and impairment in neurodevelopment.

Although there is some uncertainty regarding the shape of the dose–response curve, current evidence supports that there is no threshold for adverse effects. Studies to date suggest a nonlinear dose–response relationship, with a sigmoidal or S-shaped curve: the lowest concentrations elicit a less toxic response, followed by a steeper relationship over which smaller increases in concentration cause more dramatic effects, and finally a leveling off at high concentrations.[22] These findings suggest that the present NAAQS for particulate matter may not protect against adverse health effects with the "adequate margin of safety" mandated by the Clean Air Act.

Nationally, PM levels have declined by nearly 10% since 1999 with the largest reductions in the regions of the country that initially had the highest concentrations, such as the Southeast, Southern California, and industrial regions of the Northeast.[23] A study analyzing this improvement in air quality demonstrated a concomitant increase in life expectancy of approximately 0.61 years for each 10-μg/m^3 reduction in $PM_{2.5}$.[24] Other observational studies have reported similar findings with improvement in morbidity and mortality accompanying reductions in PM.[25]

Sulfur Dioxide

The major source of sulfur oxides is the combustion of sulfur-containing fuels, mainly coal-fired power production, crude petroleum, and smelting of some ores. While there are naturally occurring sources as well, these contribute to less than 1% of ambient air concentrations, except in areas such as Hawaii where volcanic emissions are important.[26] Most exposure to SO_2 in outdoor air results in simultaneous co-exposure to other combustion-related pollutants, including NO_x and particles. Tall smokestacks for power plants, used to control local pollutant concentrations, release sulfur oxides and NO_x high into the atmosphere, where residence time is prolonged. Through a series of oxidizing chemical reactions, sulfur oxides and NO_x form sulfuric acid and nitrate particles, which are subsequently converted to clouds, fog, and eventually acid rain.[27] These pollutants can undergo long-range transportation, creating regional air problems across large portions of Central and Northeastern United States.

Due to changing patterns of fuel use and regulations, such as the Environmental Protection Agency's Acid Rain Program, which mandated ultra-low-sulfur fuels and improved controls of smokestack discharges, emissions of SO_2 have declined by approximately 79% from 1990 to 2014.[26] While there has been significant progress in reducing national emission, local sources, such as power plants or metal processing facilities, can still result in plumes with high exposures and significant spatial heterogeneity.

SO_2 is a water-soluble gas that is effectively absorbed by nasal passages and upper airway. The fate of SO_2 in the upper airways is dependent upon a series of chemical reactions, resulting in the formation of sulfite and S-sulfonates, which are readily absorbed into the blood. Overall sulfite levels in the body are heavily influenced by endogenous production and by the ingestion of food with sulfur-constituents. Consequently, inhaled SO_2 contributes little to the total body dose and most adverse health effects are related to localized effects within the respiratory tract. With exercise, there is an increase in the inhaled dose to the lower airways, both due to the rise in minute ventilation and the switch from nasal to oral breathing.

SO_2 inhalation results in immediate bronchoconstriction in both healthy adults and in individuals with asthma. The response is primarily mediated by the activation of sensory nerves, such as the vagus nerve.[28] In asthmatics, bronchoconstriction occurs at a lower concentration through an additional pathway that involves allergic inflammation. Human controlled exposure studies demonstrate that deep breathing of SO_2 for 5 to 10 min results in lung function decrement and respiratory symptoms.[29] While evidence is not definitive, there is also some suggestion that these acute exposures could lead to extrapulmonary effects from stimulation of sensory nerves resulting in changes to heart rate variability.[30] The evidence documenting an association between short-term exposures and respiratory effects motivated the current NAAQS SO_2 primary standard with 1-h average concentration of 75 ppb.[26]

Chronic respiratory effects also have been observed in animal studies, where repetitive exposure is associated with airway inflammation, remodeling, and airway hyperresponsiveness. These mechanisms suggest that SO_2 exposure can lead to both new incident disease and worsening of pre-existing asthma.

Although it is difficult to separate out the effects of SO_2 exposure from co-pollutants, epidemiologic studies have mirrored the effects observed in toxicology experiments. Acute exposure to SO_2 is associated with urgent care visits and hospital admissions for respiratory illnesses, particularly in children, asthmatics, and the elderly. Some studies have also suggested that long-term exposure is associated with incident asthma. Epidemiologic studies from Hong Kong have examined the consequences of a major reduction in sulfur content in fuels over a very short period of time. The investigators found an associated substantial reduction in health effects, specifically for childhood respiratory disease and all-age mortality outcomes.

Nitrogen Dioxide

NO_2 is the criteria pollutant regulated by the EPA that serves as an indicator of the larger group of reactive gases, collectively known as oxides of nitrogen (NO_x). This group of gases are primarily emitted in the form of nitrogen monoxide (NO) but rapidly react with oxygen to form NO_2 and other oxidized nitrogen-forming compounds. NO_x is readily transformed to secondary pollutants and is a precursor for O_3.

NO_2 is considered a proxy of near-road pollutants, as motor vehicle emissions are the largest contributor to outdoor concentrations within the United States. Other traffic-related pollutants, such as particulate matter, black carbon, and CO, highly correlate with concentrations of NO_2, which can make it difficult to separate out effects from these co-pollutants. Other sources include power plants, industrial facilities, wildfires, and other forms of transportation. Due to variation in the emission source and photochemical transformations, NO_2 has significant spatial and temporal variation within neighborhoods. Levels largely vary along with distance to road and are highest at times of peak traffic and in the winter.

In addition to outdoor sources, substantial personal exposure in the United States occurs in indoor microenvironments contaminated by unvented gas stoves and space heaters. These exposures can be higher than those typically found in outdoor air and are discussed in more detail in the subsequent section on indoor air.

NO_2 is an oxidant gas of low solubility that penetrates to the small airways and alveoli of the lung. Within the airways, it hydrolyzes with water on mucosal surfaces to form nitric and nitrous acid, which can lead to direct damage of the epithelial border, free radical generation with local and systemic inflammation, alteration of immune function, and impaired lung defenses.[31] After high-level acute exposures—such as those seen in industrial settings—NO_2 can cause acute pulmonary edema, ARDS, and subsequent bronchiolitis obliterans (Chapter 90). At the much lower concentrations observed in the typical indoor and outdoor environment, NO_2 can result in respiratory symptoms, increased airway hyperresponsiveness, and the development of allergic responses.

Data from human controlled-inhalation studies demonstrate that NO_2 can cause increased airway hyperresponsiveness in asthmatics within 1 h of inhalation. Combined with results from epidemiologic studies, this supports the evidence that acute exposure to NO_2 is a risk factor for asthma exacerbations, respiratory infections, and other adverse pulmonary outcomes. During the EPA's last review of NO_2 in 2016, they established a new 1-h standard for daily maximum NO_2, reflecting the consistent evidence of these acute adverse effects.[32]

There is also evidence that chronic exposure is associated with incident asthma. An increasing number of studies also suggests an association between NO_2 exposure and cardiovascular disease, adverse birth outcomes, diabetes, and total mortality. Individuals with asthma, children, and the elderly are most susceptible to health effects of exposure.

Ozone

Ground-level, or tropospheric, O_3 is a secondary pollutant produced by the action of sunlight on NO_x and other carbon-containing compounds, such as VOCs, CO, and methane. It is the primary component of smog, the photochemical pollution that reduces visibility in many urban and mountainous areas. Ground-level O_3 is distinct from stratospheric O_3, which is found higher in the atmosphere—above 10 km (6 miles)—and has the beneficial effect of acting as a protective layer, blocking the surface of the Earth from UV radiation.

Anthropogenic emissions, particularly from motor vehicles, are the most significant precursors of ground-level O_3, although there are some contributions from natural sources, such as wildfires, biogenic emissions (e.g., vegetation-released isoprene), and stratospheric O_3 exchange. Given the role of sunlight and heat in its formation, O_3 levels are seasonal and generally highest in the afternoon, during the spring and summer months. One exception is that some western U.S. mountainous basins experience high concentrations in the winter, where snow creates temperature inversions that trap emissions from oil and gas activity close to the ground.

While U.S. anthropogenic emissions have decreased over the past 10 to 15 years, O_3 levels in many areas can still regularly exceed the NAAQS.[33] Due to high chemical reactivity, outdoor O_3 does not readily infiltrate into buildings. Indoor concentrations are largely driven by O_3-producing appliances, such as electrostatic or ionic air purifiers, some vegetable washers, and water treatment devices.

O_3 is a pungent, blue-tinged gas that is water insoluble but highly reactive. The nasopharynx and upper airway can remove approximately 50% of the inhaled dose, while much of the remaining gas is transported deep within the lungs to act at the centriacinar region, the junction between terminal bronchioles and the alveoli. Given its oxidant properties, O_3 reacts with lipids, proteins, and antioxidants in the epithelial lining, leading to oxidative stress, direct cellular injury, and altered cell signaling. Secondary oxidation products stimulate nociceptive pathways, which reduce lung function, cause pain with deep inhalation, and may contribute to bronchoconstriction. The downstream effects include activation of inflammatory responses, alteration of the epithelial barrier function, bronchial sensitization, and modified immunity.[34]

Animal toxicology, human controlled inhalation studies, and epidemiologic studies have demonstrated that acute exposure to ozone causes respiratory morbidity and mortality. Volunteers exposed to O_3 at concentrations that are often present during pollution episodes experience transient reductions in lung function. Normal subjects have a range of responsiveness that is broad but repeatable for individuals: for example, some individuals exposed to 80 ppb O_3 for 6.6 h with 5 h of moderate activity will have no response, while others demonstrate up to 50% decrease in FEV_1. While the reduction in lung function is largely reversible after exposure to O_3 ceases, there is evidence of a persistent inflammatory response and biochemical changes in BAL fluid for up to 18 h after acute experimental exposure. Epidemiologic studies have consistently documented an association between short-term concentration and a range of pulmonary outcomes, including increased respiratory symptoms, respiratory infections, and exacerbations of obstructive airway disease.

The progressive decrements in pulmonary mechanics during exposure, coupled with the persistent biochemical changes many hours after cessation of exposure, indicate the potential for chronic effects from repeated inhalation. Chronic, low-level exposures cause damage to the small airways of experimental animals, including airway remodeling, subtle fibrosis, and permanent structural alteration. While epidemiologic studies have been somewhat mixed, there is convincing evidence that long-term exposures are associated with new-onset asthma, progression of COPD, and respiratory mortality.[35]

There is also increasing evidence linking O_3 exposure to metabolic and cardiovascular morbidity and mortality. Animal studies demonstrate impaired fasting glucose, increased triglycerides, and hepatic gluconeogenesis through activation of central neuroendocrine stress responses. These changes provide a biologically plausible connection between O_3 exposure and worsening IHD/HF, myocardial infarction, and stroke.

Carbon Monoxide

CO is an invisible gas formed by incomplete combustion of fossil fuels and other organic materials. The most prominent outdoor source is vehicle exhaust, leading to highly variable outdoor concentrations that track with traffic patterns and density. Since the passage of the Clean Air Act, there has been more than an 80% decrease in ambient CO levels, predominantly reflecting controls on vehicle emissions.[36] The most significant sources of indoor CO, which are discussed in greater detail in the section entitled indoor air pollutants, are cooking stoves, heating devices, and tobacco smoke.

The toxicity of inhaled CO is related to its high affinity for hemoglobin, resulting in tissue hypoxemia. The binding of CO to hemoglobin as carboxyhemoglobin (COHb) displaces oxygen and causes an allosteric change in the hemoglobin molecule, which also reduces the ability of hemoglobin to offload oxygen to the peripheral tissues. The COHb complex is very stable with a half-life of 2.5 to 4 h, depending on ambient levels of CO, level of activity, and lung function. The rate of accumulation of ambient CO in the body above endogenous levels is affected by ambient CO concentrations, alveolar ventilation, lung diffusivity, total hemoglobin mass, and COHb level.[37] People with impaired gas exchange (e.g., persons with COPD) have compromised ability to excrete CO.

The level of CO in the blood is a useful biomarker of dose, and the health effects of exposure to CO can be related to COHb levels. In nonsmokers who are not exposed to CO in the environment, COHb levels are approximately 0.5%. This endogenous COHb comes from catabolism of hemoglobin and heme-containing enzymes of the liver. In comparison, COHb levels of cigarette smokers average about 4% and may reach up to 10% to 15%.[38] Frank CO poisoning, manifesting as headache, loss of motor control, and coma, generally occurs with COHb levels greater than 20%.

Individuals with cardiovascular disease are considered to be at the greatest risk from CO exposure. Standard exercise tests on subjects with ischemic heart disease have demonstrated a decreased time interval to the onset of angina at COHb levels ranging from 2% to 6%.[39] At COHb levels of 6%, patients with coronary artery disease have an increased incidence of arrhythmias.[40] These studies are relevant to the urban environment, where concentrations of ambient CO may be sufficient to cause blood COHb levels in this range. The 1-h 35-ppm and 8-h 9-ppm federal standards for outdoor air (Table 89-1) were selected to prevent COHb levels from rising above 1.5%, thereby protecting persons with coronary artery disease from aggravation of myocardial ischemia.

Panel studies of health individuals from the 2008 Beijing Olympics demonstrated a potential role of CO and other pollutants in inducing adverse changes in cardiorespiratory biomarkers. Due to government restrictions on emissions and traffic during the Olympic Games, levels of CO decreased 48% (together with similar-sized reductions in $PM_{2.5}$, SO_2, NO_2, and other pollutants) from pre-Game concentrations. These pollutant changes were associated with significant reductions in inflammatory and coagulation biomarkers as a proxy of endothelial dysfunction and pulmonary and systemic oxidative stress.[41]

Pollutant Mixtures

Much of the health effects research in this chapter are distilled down to the effects of individual pollutants. While it may be possible to isolate specific components, such as O_3, in a laboratory or controlled human inhalation study, this is an artificial distinction. Real-world exposures consist of a heterogeneous mixture of gases, liquids, and solid aerosols; for example, power plants release particles, NO_x, and sulfur oxides, and vehicle exhaust contains CO, NO_x, particles, and hydrocarbons. Many of these components may interact to synergistically augment or counteract pathophysiologic mechanisms of disease.

One alternative to characterizing pollutant health effects by individual component is to characterize health effects by pollutant source. Two pollutant sources that have received increased attention are traffic-related air pollution (TRAP) and wildfire smoke.

Traffic-Related Air Pollution Traffic is a major global source of pollution, with a significant portion of the population living less than 500 m (considered to be in close proximity) from a major roadway. Many of those who live further from these major arterials still spend a significant amount of time in vehicles as part of their daily routines, engaging in activities such as commuting. In the United States, the average adult spends approximately 55 minutes per day in traffic.[42]

The complex emissions from motor vehicles, broadly referred to as TRAP, include large quantities of CO_2, CO, hydrocarbons, NO_x, PM, and mobile-source air toxins, such as benzene, formaldehyde, and 1,3-butadiene.[43] Studies often look either at single traffic-related pollutants (most commonly NO_2 or elemental black carbon [BC]), or at residential distance to the nearest road as a surrogate for exposure to TRAP. Panel studies of commuters have also used extensive in-vehicle and on-road exposure monitoring to capture the emission profile.

Epidemiologic studies have shown an association between acute TRAP exposure, on the scale of 30 min to several hours, and increased risk of myocardial infarction or ventricular arrhythmia. Repeated health measurements demonstrate an increase in endothelial and cardiovascular biomarkers.[44–46] Individual pollutants measured as markers of traffic pollution have repeatedly been associated with both cardiovascular and respiratory events, and also with adverse changes in these biomarkers of mechanisms thought to underlie the cardiorespiratory response to pollution. While evidence clearly suggests that TRAP has adverse health effects, there is concern that coincidental exposures, such as stress and road noise, may confound these associations.

Both as a component and as a model of TRAP used in controlled inhalational exposures, diesel exhaust particles (DEP) have also been extensively studied. Diesel exhaust is an irritant to which some people are highly sensitive. It has been classified as a human carcinogen by the International Agency for Research on Cancer (IARC) based on the elevated risk for lung cancer.[47]

Wildfire Smoke Over the past decades, the world has seen an increase in the severity and frequency of wildfires. The most significantly affected areas cover a broad range of topography from boreal forests in Canada, Russia, and China; savannah grasslands in Africa; tropical rainforests including Brazil, Indonesia, and Nigeria; and temperate forests in the United States and Europe. Large forest fires are five times more frequent in the western United States than they were 50 years ago.[48] As traffic- and urban-related pollutants levels have decreased in response to regulations, wildfire smoke contributes to a larger portion of overall emissions. For example, wildfires in the United States contributed to more than 50% of estimated methane emissions and 20% of all fine particulate matter in 2012.[49]

This increase in wildfires is due to a combination of factors with large contributions from climate change, historic fire suppression policies, and a rise in population density near fire-prone areas—known as the human–wildfire interface. As temperatures rise, droughts intensify and the annual snowpack decreases, leading to drier forests that are more susceptible to burning. Historic forest management has caused an unnatural accumulation of understory trees and woody debris that provide fuel for wildfires. By one estimate, anthropogenic contributions to climate change account for approximately half of the increase in fuel aridity and have doubled the forest fire activity in the western United States.[50]

Wildfire smoke is a byproduct of combustion, principally composed of water vapor, CO_2, CO, and methane. Smoke also contains PM, VOCs, NO_x, hydrocarbons, trace metals, and thousands of other chemicals. The exact constituents are unique to the burn site—dependent on the type of vegetation, whether any buildings or synthetic material are consumed, and flame intensity. During the flaming stage of combustion, there is rapid release of CO_2 and H_2O, while smoldering fires cause incomplete combustion with dirtier emissions. As the plume disperses there is photochemical aging and formation of secondary pollutants, such as O_3. Smoke plume distribution and duration are affected by meteorologic conditions, including the ambient temperature, wind speed, and local topography. Wildfire smoke can traverse large distances, affecting communities that are located thousands of miles away from the source. For instance in 2015, Maryland had a large spike in O_3 caused by a wildfire that was burning in Canada.[51]

Levels of pollution observed during wildfire smoke events can reach staggering concentrations that can be sustained for days. Many of the gases and particles in smoke can act as mucosal and epithelial irritants, resulting in headache, sinus congestion, eye irritation, pharyngitis, and cough. Much of the morbidity and mortality due to wildfire smoke exposure is thought to be caused by ultrafine and fine PM, which precipitates a similar cascade of oxidative damage and inflammation as has been observed with other sources of ambient PM.

There is consistent epidemiologic evidence of an association between wildfire smoke exposure and acute respiratory outcomes, specifically emergency department visits and hospitalizations for respiratory infections, COPD, and asthma exacerbations. There is a mixed but growing body of literature demonstrating an association between acute exposures and cardiovascular outcomes, such as MI, arrhythmia, and acute coronary syndrome.[52] Most of the studies to date have focused on the effects immediately following a smoke event, but the chronic impact of repetitive, high exposures over multiple years remains unknown.

Inferred from knowledge about ambient air pollution, it is likely that chronic exposures to wildfire smoke will have a significant impact on overall morbidity and mortality. This presumption has been echoed in some early studies that examine the delayed impacts of smoke exposure. In wildland firefighters, there is a small decline in lung function that persists after the wildfire season.[52] A recent study in Montana also demonstrated an increase in influenza severity and mortality following a season with high wildfire smoke exposure.[53]

Toxic Air Pollutants

Approximately 200 “hazardous pollutants” are listed as air toxins in the 1990 Clean Air Act amendments. These substances include a wide variety of volatile organic compounds, pesticides, herbicides, and radionucleotides that are known to cause serious health effects in humans. For example, formaldehyde, a VOC that is commonly found in indoor and outdoor air, causes nasopharyngeal and lung cancer, irritation of the respiratory tree, and asthma exacerbations. Polycyclic organic matter (POM), a broad range of compounds that are byproducts of combustion and commonly found in diesel exhaust, also are known carcinogens. Importantly, approximately 1500 new chemicals are introduced into commerce each year.[54] Many of these substances have not undergone sufficient toxicologic assessment to determine whether they pose potential health risks and should be further regulated.

INDOOR AIR POLLUTION

Indoor environments are contaminated by numerous air pollutants, including those that have penetrated from the outdoor air and those generated from indoor sources. This section reviews exposures and health effects of the principal indoor pollutants. Similar to outdoor air pollution, indoor air pollutants typically occur as exposures to mixtures, rather than as single agents.

Overview: Sources and Classification of Indoor Air Pollution

There are many sources of indoor air pollution, including building materials and furnishings, appliances, household products, heating and cooling systems, excessive moisture, biologic agents, secondhand smoke, and outdoor sources (Table 89-4). Outdoor air can enter buildings by infiltrating through cracks or other leaky structures, natural ventilation through windows and doors, or mechanical ventilation systems. The amount of infiltration depends on the building type, insulation, window-opening behavior, weatherproofing, and climate conditions. In low- and some middle-income countries, the major source of indoor pollutants, often referred to as household air pollution (HAP), is incomplete combustion from biomass (plant or animal products) or coal fuels for heating and cooking.

The concentration of an indoor contaminant depends on the strength of its source, the rate of removal, the volume of the space, and the rate of air exchange between the space and outdoors. This *mass–balance* formulation indicates that the concentration of a contaminant can be reduced by limiting emissions from the source, increasing removal rate, or increasing exchange between indoor and outdoor air. In the typical modern building, the exchange of indoor with outdoor air is accomplished by a central heating, ventilating, and air-conditioning (HVAC) system. These systems are diverse, although all have the same purpose: the delivery of air of acceptable

TABLE 89-4 Sources of Common Indoor Air Contaminants

Exposure Category	Common Sources	Specific Exposures
Combustion byproducts	Biomass burning Gas stoves and appliances Propane engines Fireplaces/wood-burning stoves	Carbon monoxide Nitrogen dioxide Sulfur dioxide Particulate soot Nitrogenated compounds
Tobacco products	Cigarettes Pipes Cigars E-cigarettes	Particulate matter Carbon monoxide Nitrogen dioxide Carbon dioxide Hydrogen cyanide Nitrosamines Aromatic hydrocarbons
Building Material and Furnishing	Asbestos-containing insulation and fire-retardant material Furniture and paneling made of pressed wood Glues and resins Coating and cleaning agents Carpeting	Asbestos Volatile organic compounds, such as formaldehyde, benzene, terpenes
Outdoor sources	Infiltration of outdoor air Soil vapor intrusion Well water	Outdoor air pollution Pesticides Radon gas and progeny
Biologic organisms	Water-damaged surfaces Humidifiers with stagnant water Condensing coils and drip pans in HVAC system Animal dander Dust mites	Fungal spores Molds and mycotoxins Bacteria and endotoxins Virus Pollens Arthropods Allergens

quality to building occupants.[55] The volume of air to be delivered follows the recommendation of standards set by the American Society of Heating, Refrigerating, and Air-Conditioning Engineers (ASHRAE).

Indoor air quality is a qualitative metric of contaminants in indoor air that can affect the occupant's health, comfort, and sense of well-being. Insufficient ventilation can lead to a perception of poor air quality and an increase in respiratory symptoms. As a by-product of respiration, CO_2 is a marker of the balance between the generation from building occupants and the removal through ventilation system and serves as a proxy for fresh-air ventilation in office buildings. In general, when indoor CO_2 concentrations exceed 1000 ppm, occupants have complaints indicative of insufficient ventilation.[56] Relative temperature and humidity also effect indoor air quality and individual perceptions of comfort. Temperatures over 71.6 to 73.4°F (22–23°C) are associated with mucosal irritation and fatigue, particularly during the colder season. Dry air is also associated with mucosal, ocular, and skin symptoms, while excess humidity can promote mold and dust mite growth. OSHA recommends that humidity be controlled between 30% and 60%.[57]

■ Indoor Air Pollutants: Exposures and Health Effects

Below we consider a variety of indoor air pollutants, including those derived from indoor combustion, organic compounds, radon, asbestos, artificial fibers, and biologic agents.

Indoor Combustion

Principle sources of pollutants related to indoor combustion include household air pollution, gas and wood-burning stoves, secondhand smoke, and aerosols from e-cigarettes.

Household Air Pollution Household air pollution (HAP) refers to emissions from the incomplete combustion of biomass burning from plant or animal products, and solid fuels such as coal or charcoal. Approximately one-third of the global population uses biomass burning or solid fuels for cooking, cleaning, and/or lighting. Women, young children, and infants are the most heavily exposed due to traditional gender roles, with women performing most of the cooking duties while often caring for children inside the home.[58] In addition to being the major source of indoor air pollution for a significant portion of the globe, HAP also is also responsible for approximately 14% of ambient air pollution and for approximately 3.5 to 4 million deaths per year.[6]

The sources of biomass fuel and pollutant by-products vary widely according to geographic area, local culture, and socioeconomic status. For example, coal is the primary source of fuel in China, while wood and charcoal are more heavily used in much of Africa, and animal dung is the major source available in rural communities or those at high altitude, such as Nepal.[58] Many of the hazardous components of HAP are similar to traffic-related pollutants and include PM, CO, SO_2, PAH, and endotoxins. In contrast to the PM from wildfire smoke, larger particles may be more important in HAP due to the high proportion of absorbed endotoxins. The emissions from these fuels are often smoky and reach high concentrations, with PM levels up to 1000 $\mu g/m^3$, due to use in poorly ventilated indoor areas with inefficient chimneys.[59]

The proposed pathophysiology of HAP is comparable to that of ambient air pollution with epithelial injury, oxidative stress, and local and systemic inflammation. In vitro and animal studies demonstrate that exposure to HAP is associated with airway hyperresponsiveness, decreased lung function, and altered immunity. The greatest increase in mortality from exposure to HAP is due to childhood PNA. HAP is also associated with increased incidence and severity of other respiratory infections, chronic lung disease and respiratory cancers. Epidemiologic studies indicate that early life exposures may lead to increased predisposition to develop asthma. There is growing evidence that HAP may also be linked with cardiovascular outcomes.

Exposure to HAP can be reduced through the introduction of improved fuels, cookstoves, heaters, and ventilation. Pellet fuels, liquid fuel such as propane, liquified petroleum gas (LPG), and biofuel are more efficient, and solar stoves can nearly eliminate emissions. The RESPIRE trial, which randomized families in Guatemala to improved chimney stoves versus traditional stoves, demonstrated a significant decrease in childhood pneumonia in the intervention group.[60] Despite these promising findings, other studies in low- and middle-income countries have more mixed findings. One explanation for the lack of clear health benefits in these epidemiologic studies is that the adoption of improved, new, efficient technology is challenging due to cultural and economic sustainability. Even in areas where national programs or research studies have introduced improved cookstoves and heaters, "stacking" often occurs, where traditional stoves are used concurrently with improved cookstoves.

While exposure to HAP may be somewhat reduced, it is unclear how much emissions need to be lowered to effectively decrease the risk of adverse effects.[61]

Gas and Wood-burning Stoves As opposed to HAP in low and middle-income countries, the major sources of indoor combustion byproducts in developed countries are gas cooking stoves, unvented space heaters, wood stoves, and tobacco smoke. Although vented to the outside by building codes, gas furnaces and water heaters may pollute residences because of flue gas spillage and back-drafting caused by improper installation, maintenance, device malfunction/wear, and weather conditions.

CO, a by-product of fuel combustion, is released indoors by cooking appliances, home heating systems, portable generators, and space heaters. Surveys of residential indoor concentrations have demonstrated that CO levels are typically low (2–4 ppm), even in the winter when windows are often closed and homes heated.[37] However, levels can increase precipitously in buildings with faulty, unvented, or improperly ventilated combustion sources. There are approximately 15,000 emergency department visits and 500 accidental deaths annually due to CO asphyxiation, with approximately 20% of the nonfatal cases attributable to malfunctioning heating appliances.[62]

In addition to CO emissions, gas cooking stoves can result in brief but high levels of exposure to NO_2, reaching up to 1000 ppb while the stove is in use. A number of epidemiologic studies have compared the occurrence of respiratory outcomes in children in homes having gas stoves to those living in homes with electric stoves. There is limited evidence that suggests gas cooking stoves are associated with increased respiratory infections, worsening of asthma symptoms, and decreased lung function.[63–65] Findings of these studies have been inconsistent, largely because of the methodologic complexities of investigating this association.

The use of wood for residential heating has become more prevalent in developed countries due to increasing energy prices and an emphasis on renewable fuels. Interestingly, in developed countries, studies of community wood smoke exposure have demonstrated more consistent evidence of adverse respiratory effects than studies of individual household wood smoke exposure.[66] While this may be attributable to study design with different exposure metrics, data suggest that the routine operation of a properly installed, maintained, and vented wood stove does not greatly affect indoor air quality. However, vented smoke may significantly affect ambient air quality and infiltrate neighboring homes. During cold periods in the winter, when there are more frequent stagnant air masses and temperature inversions, outdoor wood smoke particulate matter concentrations may remain elevated for extended time-periods. This impact on outdoor air quality may be responsible for the health effects demonstrated in studies of community wood smoke exposure.

Secondhand Smoke and E-cigarette Aerosol While the prevalence of smoking in the United States has decreased among adults to 13.7% in 2018, exposure to tobacco smoke remains common in public places and homes.[67] Additionally there is concern regarding the emergence and growing use of novel inhalation products, such as electronic cigarettes. The aerosols created from these electronic devices generally are at lower concentrations than traditional tobacco products but still contain many of the same air contaminants.

Secondhand smoke (SHS) refers to the combination of mainstream smoke exhaled by the smoker and sidestream smoke, released from the burning tobacco product end. Survey and biomarkers data on SHS exposure for nonsmokers and children have documented steady decreases over time. Among nonsmoking participants in the National Health and Nutrition Examination Survey (NHANES), measurable blood levels of cotinine, the nicotine biomarker, dropped from 87.9% in 1988 to 1991 down to 25.3% in 2011 to 2012.[68]

Hundreds of chemical compounds have been identified in cigarette smoke, but the indicators most often used to quantify its presence in the environment are total suspended PM, $PM_{2.5}$, CO, and nicotine.[69] Concentrations of PM measured over 24 h are generally two or more times higher in homes with active smokers compared to nonsmoking households. Nicotine is present as a gas in SHS and is a highly specific marker for tobacco smoke, with no other sources in indoor air. Several biomarkers of nicotine and tobacco specific carcinogens can also be measured in the blood, urine, saliva, and hair. As with other indoor air pollutants, SHS and e-cigarette aerosol exposure vary considerably depending on the number of active smokers, use patterns, size of room, and proximity to smoker.

The adverse effects of SHS have been assessed in the context of the voluminous evidence on active smoking and health, as well as detailed characterizations of the composition and toxicology of mainstream and sidestream cigarette smoke. Numerous studies have demonstrated that SHS is associated with a variety of malignant and nonmalignant diseases in nonsmokers. Household smoking, particularly maternal smoking, is associated with increased risk of lower respiratory tract infections, middle ear effusions and infections, chronic respiratory symptoms, and reduced lung function in children. Children with asthma whose parents smoke have heightened airway responsiveness and increased morbidity, as documented by indexes of medical care utilization. Exposure to SHS is also a suspected cause of asthma, and infants of smoking parents have increased airway responsiveness shortly after birth.[69]

Exposure to SHS was first linked with lung cancer in never-smokers in two reports published in 1981.[70] Subsequent epidemiologic studies have replicated these findings, demonstrating a consistent positive association between living with a smoker and the risk of lung cancer. The risk of lung cancer is increased by approximately 20% for never-smoking women married to smokers. Based on epidemiologic and toxicologic evidence, SHS is classified as a group I carcinogen, a designation applied to agents causally linked to cancer.[71]

There is also robust evidence supporting an association between SHS exposure and cardiovascular disease, particularly acute coronary syndrome. A number of epidemiologic studies demonstrate that marriage to a smoker increases the risk for ischemic heart disease.[69] SHS causes an estimated 23,000 and 70,000 cardiovascular disease–related deaths annually. A Cochrane review of the health impact of legislative smoking bans across multiple countries shows that the accompanying reduction in SHS is associated with improved CVD outcomes and a decrease in hospital admission for ACS.[72]

"Thirdhand smoke" refers to surface-deposited components (e.g., on clothing, furniture, and other surfaces) of tobacco smoke and metabolic by-products of these components.[73] Thirdhand smoke is neither smoke nor a pollutant present in the air; rather, it is composed of various compounds, many that are volatile or semivolatile, that may have a long-lived presence following deposition. Experimental research and field specimens show that these compounds may be long lived and undergo chemical transformations. Thirdhand smoke components may be absorbed via the skin or through ingestion of components on the hands or on contaminated objects that young children put into their mouths.

Organic Compounds

Organic compounds are ubiquitous indoors, where they are released from furnishings and equipment, construction materials, and consumer and office products.[74] The organic compounds found in indoor air can be grouped by boiling point range as volatile (0–240°C), semivolatile (240–380°C), and particulate (>380°C). The volatile and semivolatile organic compounds are most relevant to human health. VOCs exist as vapors over the normal range of air temperatures and pressures, whereas semivolatile organic compounds are liquids or solids but also evaporate.

Indoor concentrations of organic compounds are typically the main determinants of personal exposure, even in areas in close proximity to outdoor point sources. For example, while benzene is a byproduct of gasoline, oil refineries and chemical plants, the main contribution to personal exposure is either mainstream cigarette smoke or passive SHS.[75]

Formaldehyde is one of the most common VOCs, found in a variety of household products, paints and varnishes, preservatives, fertilizers, and wood products. The largest use of formaldehyde is in preparation of urea and phenol-formaldehyde resins, used to bind laminated wood products and particleboard. These products are widely used as shelving, counters, cabinets, and floor and wall coverings in buildings. Formaldehyde can act as a sensitizer and cause of immune-mediated asthma, as well as a potent mucosal irritant with ocular, airway, and neurologic effects. Formaldehyde is classified as a group I carcinogen by IARC and is associated with nasopharyngeal cancer and leukemia.[76]

The health risks associated with organic compounds are diverse and include carcinogens and mutagens (e.g., benzene), irritants (e.g., formaldehyde, terpenes), and neurotoxins (e.g., aromatic compounds). Despite these potential adverse effects, the exposure-disease associations are often poorly characterized due to the difficulty in characterizing indoor air exposures.

Radon

Radon is a naturally occurring, radioactive gas that is odorless and ubiquitous in the environment. Radon-222 and its parent, radium-226, are the decay products of uranium-238 and undergo further disintegration through a series of short-lived progeny. Alpha particles, beta particles, and gamma rays are released during each stage of decay until the formation of a stable atom of lead. Irradiation of respiratory epithelial cells by alpha particles damages cellular DNA and can cause lung cancer.[77]

The principal source of radon in buildings is naturally occurring gas in soil, that seeps in through openings in sump pump wells, drains, utility access holes, or other cracks.[78] The driving pressure for entry of soil gas into a building is the pressure gradient established by a structure across the soil. In most locales, building materials and water used in the home do not contribute significantly to concentrations of radon indoors.

Extensive data on radon concentrations in homes in the United States show that the average value is about 1.5 picocuries per liter (pCi/L).[79] Homes with high concentrations have been identified in all states, although the proportion exceeding the EPA's action guideline of 4 pCi/L is heterogeneous and varies with local geology. In a national survey conducted from 1988 to 1991, the EPA measured radon concentration in 6000 randomly selected homes in the United States. About 6% of homes were estimated to exceed the guideline of 4 pCi/L annual average.[80]

The risks associated with residential exposure to radon are extrapolated from studies in underground workers, in particular uranium miners, who are exposed to the highest concentrations of radon.[81] These studies consistently show an association between radon exposure and lung cancer, with a synergistic effect due to cigarette smoking. Pooled case-control studies from residential exposures confirm that these lower-dose exposures are still associated with lung cancer. Current risk models assume a linear dose-response with no threshold, implying that values under current guidelines cause a significant number of lung cancer cases. Based on these models, radon is considered to be the most common environmental cause of lung cancer after tobacco smoke, and may be responsible for approximately 12% of lung cancer deaths in the United States.[82]

The substantial lung cancer burden attributed to indoor radon has led to programs for reduction of exposure. The program in the United States, conducted by the EPA, calls for voluntary measurement of radon levels in single-family homes and mitigation if the annual concentration exceeds the agency's guideline level of 4 pCi/L.[83] Simple measures, such as sealing basement cracks and sump holes, can be effective at lowering radon levels. Other approaches include ventilating the basement to the outside and, for homes built on concrete slabs, by providing a system to exhaust the soil gas from beneath the slab. In areas that have high background levels of radon, "radon-resistant" construction techniques are used as a preventative measure.

Asbestos and Artificial Fibers

Asbestos (Chapter 85) is a group of naturally occurring inorganic fibers that are resistant to heat and corrosion, leading to its extensive use in building products in the 1900s. Due to recognition of asbestos-related health effects, its use was banned in the 1970s. Many buildings, however, still have asbestos-containing materials in thermal and acoustic insulation, fire protection, and reinforcement of building products. Despite the frequent presence of large amounts of asbestos in buildings, indoor exposure occurs only when fibers are aerosolized through disturbance of friable asbestos building materials.

Air monitoring shows extremely low average asbestos concentrations under the conditions of normal building use.[84] There is little concern that building occupants could develop asbestosis or other diseases that require high cumulative exposures, although there may be elevated risks for conditions where there is no safe threshold of exposure, such as mesothelioma or lung cancer. In addition, custodial and maintenance workers could be exposed to higher levels of asbestos in their cleaning duties, re-suspending settled dust from friable building materials. Several studies have shown that custodial and maintenance workers may have increased risk of developing pleural plaques and possibly asbestosis.

Biologic Agents

The indoor biologic agents include a variety of allergens and microbes, including bacteria, molds, pollen, animal dander or urine, cockroach feces, and mites. Levels may increase through the accumulation of materials indoors (such as human and animal dander), or by growth (such as fungi and bacteria on interior surfaces or in air-conditioning systems). Other biologic agents, such as pollen and fungal spores, enter the indoor environment predominantly via outdoor sources: through air infiltration, or as inadvertent travelers on people, animals, or objects.

The growth of microorganisms on interior surfaces causes some of the most prevalent and severe problems due to indoor biologic pollution. Any substrate that can provide a source of both carbon and water can support the growth of microorganisms, including leaks from water pipes and roofs, prior floods, and condensation in rooms with high relative humidity (>70%). Humidifiers, vaporizers, and air conditioners also can become contaminated and distribute fungal fragments, spores, and dissolved allergens into room air.

Fungi are present in the air of virtually all indoor environments and can be detected by visual inspection or odor. Commonly isolated genera include *Cladosporium*, *Penicillium*, *Alternaria*, *Epicoccum*, *Aspergillus*, and *Drechslera.* Molds and other fungi may adversely affect human health through allergy, infection, or immunologic reactions. Mycotoxins, naturally occurring secondary metabolites produced by certain fungal species, also are associated with a range of biologic effects, including some acute poisonings. The mycotoxins produced by *Stachybotrys chartarum*, also known as black mold, have been popularized as a cause of "idiopathic pulmonary hemorrhage" and remains a controversial topic in the scientific community. Recent critical reviews of the literature have concluded that indoor airborne levels of microorganisms are only weakly correlated with human disease or building-related symptoms—and that a causal relationship has not been established between these complaints and indoor exposures to *S. chartarum*.[85]

The presence of dampness and mold, determined by questionnaire, has been associated with upper respiratory symptoms and eye irritation in large cohort studies of children. These associations persist after adjustment for known determinants of respiratory symptoms, including maternal smoking, city, child's age and sex, and parent education. Similar findings have been reported in adults, and a systematic review concluded that dampness in buildings contributes to adverse health effects in persons with and without atopy.[86] The evidence on dampness was reviewed by an Institute of Medicine committee, which did not find the evidence to be sufficient to conclude that dampness causes respiratory symptoms or asthma.[87] While it seems likely that the mechanism underlying the effects of dampness is via microbiological growth and subsequent evolution of allergenic or toxic agents, the current literature is inconclusive and does not clearly implicate any agents.

Specific allergens of concern include those of dust mites (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, and *Euroglyphus maynei*), pests such as cockroaches and mice, and domestic animals, such as cats and dogs. Levels of antigen can often persist in indoor environments for long periods, even after the source is gone.[88] Airborne and dust concentrations of allergens probably have limited value for assessing the contribution of a particular allergen in causing disease. Levels of allergens and other microbial particles are highly variable and affected by activities such as vacuuming, sweeping, dusting, making beds, scrubbing contaminated surfaces, and using electric fans. Factors such as aerodynamic behavior, respirability, solubility, and cross-reactivity with other allergens are also important in the process of immunologic sensitization and the development of allergic disease.[89]

Biologic agents in indoor air may cause disease through various mechanisms, including direct toxicity, infections, and immune hyperresponsiveness. A complete review of these diverse effects is beyond the scope of this chapter, but selected elements are addressed briefly in the section below.

■ Clinical Syndromes Associated with Indoor Environments

During the last 20 years, complaints attributable to indoor environments have generally been classified into one of two broad groups: specific building-related illnesses and sick building syndrome (SBS).

Building-related illnesses have a number of etiologies and pathophysiologic mechanisms, but the specific agent responsible for causing the disease is present in the indoor environment. Examples include hypersensitivity pneumonitis caused by fungi in the ventilation system, and Legionnaires' disease resulting from transmission of the organism that grows in cooling tower water. Building-related allergic respiratory disease and epidemic asthma have been reported in office buildings in association with air-handling systems and humidifiers contaminated with bacteria and fungi.

SBS refers to nonspecific health problems related to indoor air quality, often in nonindustrial buildings where known toxic exposures would be considered atypical. From a medical perspective, these problems often do not constitute easily recognized diagnoses and are more notable due to the clustering of nonspecific symptoms in relationship to one location. Irritation of mucosal surfaces and neurotoxic effects may contribute to the nonspecific symptom complex that often includes headache, fatigue, and difficulty concentrating. Atopic individuals have been shown to have lower irritant thresholds than non-atopics. Multiple factors, including specific exposures, inadequate ventilation, and poor building maintenance have been linked to SBS. Panel studies in Denmark have found that complaints were most often attributed to the ventilation system, SHS, office machines, and other sources.[90]

Building-related symptoms that occur in the context of the workplace may be particularly challenging. The healthcare provider needs to establish the connection between the workplace and the occurrence of symptoms and then seek a solution that includes identifying and remediating the responsible factors in the workplace. The investigation requires sufficient awareness of the possible causal role of the indoor environment, as well as the potential contribution of psychosocial, organizational, or labor-management issues. Resolution may require an evaluation and intervention by indoor air quality professionals, but extensive and expensive exposure assessment is frequently unrevealing. The physician evaluating an individual patient in these situations may be unable to resolve the patient's symptoms without recognizing the underlying problems. Guidance for the clinician has been offered by the ATS.[91,92]

SUSCEPTIBLE POPULATIONS

Exposure to air pollution is ubiquitous. To fully understand the health consequences of exposure, it is important to recognize the disproportionate variation in risk among different populations, both at the individual and community level. Susceptibility refers to the intrinsic factors that can alter risk, such as life stage, ethnicity, sex, underlying health status, and genotype. Vulnerability is the term used to describe the external factors that can increase the potential for exposure to air pollution, such as outdoor laborers or communities that live next to point sources of pollution. Susceptibility and vulnerability factors are often intertwined, further compounding risk. For instance, low socioeconomic status is often associated with higher exposure to air pollution, diminished baseline health, and lack of resources to mitigate adverse effects.[93] The confluence of susceptibility and vulnerability factors that lead to a disproportionate impact of air pollution on populations of lower socioeconomic status is usually framed as "environmental justice" and often has roots in historic segregation or structural racism.

The legislative history of the Clean Air Act mandated that the primary NAAQS were to be set low enough to protect the health of all susceptible groups within the population except those requiring life-support systems. While only asthma and emphysema were specifically identified as susceptible populations in the Clean Air Act, recent epidemiologic evidence suggests that additional populations need to be considered, including persons with pre-existing coronary artery disease, those with other chronic lung diseases, infants and fetuses, and the elderly.

In this section, we consider the evidence concerning these susceptible groups (Table 89-5). Pulmonologists are likely to be asked about the consequences of pollution exposures by persons with chronic lung diseases. Patients may report being adversely affected by exposures and may request guidance concerning control measures—for example, purchase of an air-cleaning device or additional medication use when exposed.

■ Clinical Studies in Susceptible Populations

Epidemiologic studies provide much of the evidence on the acute effects of pollutants in susceptible populations. There have also been several controlled laboratory studies of volunteers with preexisting disease, such as asthma or coronary artery disease, which have attempted to identify specific effects of individual pollutants in susceptible groups.

A large body of evidence demonstrates that individuals with COPD and asthma are at high risk of exacerbations from air pollution, as determined by respiratory symptoms, medication use, urgent care visits, and hospitalizations. Recent studies have focused on groups with other underlying chronic lung disease. These have

TABLE 89-5 Populations Considered Susceptible to Air Pollution

Population	Potential Mechanism	Consequences
Persons with chronic lung disease Asthma COPD Cystic fibrosis Interstitial lung disease Post–lung transplant	Increased airway responsiveness Increased pulmonary and systemic inflammation Impaired respiratory defenses Reduced level of lung function	Increased risk for exacerbation and respiratory symptoms Increased lung function decline Increased mortality
Persons with coronary heart disease	Impaired myocardial oxygenation	Increased risk for myocardial ischemia
Cigarette smokers	Impaired defense and clearance, lung injury	Increased damage through synergism
Elderly	Impaired respiratory defenses Reduced functional reserve	Increased risk for respiratory infection Increased risk for clinically significant effects on function
Infants and fetuses	Immature defense mechanisms of the lung	Increased risk for respiratory infection Increased incidence of asthma

demonstrated that pollution is associated with an increased risk of exacerbations in individuals with cystic fibrosis and non-CF-related bronchiectasis,[94] faster progression and exacerbations in patients with idiopathic pulmonary fibrosis,[95,96] and higher odds of developing chronic lung allograft dysfunction in persons who are post–lung transplant.[97]

Persons with coronary heart disease also have been identified as a group at risk from increased levels of air pollution. Studies conducted at relatively low COHb levels demonstrate significant effects of CO exposure on exercise capacity, the occurrence of myocardial ischemia, and ventricular ectopy. Controlled exposure studies have also shown that acute exposure to diesel exhaust results in exercise-induced ST-segment depression in individuals with stable coronary artery disease.[98]

Individuals at the extremes of age may also be at a heightened susceptibility to the effects of air pollution. Cells may be particularly sensitive to the oxidative damage caused by pollutants during certain stages of growth and development, leading to alterations in organogenesis, immune system development, and epigenetic programming with long-ranging consequences. Increasingly, studies have linked gestational exposures to an increased risk of childhood asthma, low birth weight and poor fetal growth, and neurodevelopmental delay.[99–101] On the other end of the spectrum, older individuals also have been classified as particularly sensitive to the health effects of pollution exposure. The mechanisms for this heightened susceptibility are incompletely understood, but may be, in part, attributable to weakened defense mechanisms, existing comorbid conditions, diminished reserves, and higher cumulative exposures.[102,103]

Several studies have attempted to understand genetic susceptibility to pollutant effects. While these investigations primarily are useful to inform a mechanistic basis for these effects, studies have examined whether several genetic polymorphisms either protect or give an individual increased susceptibility to these cardiorespiratory health effects. For example, individuals without a polymorphism to protect against oxidative stress (e.g., glutathione S-transferase mu 1 [GSTM1] null) may be more responsive to air pollution health effects than individuals with wild type GSTM1.[104] Similarly, variants in nociceptive receptors, such as TRPV1, seem to affect the subsequent vascular response to air pollutants.[105] More work is needed, however, before we understand whether genetic markers of susceptibility have a role in improving prevention of pollutant-related health effects.

In summary, existing respiratory and cardiovascular conditions may make a patient susceptible to air pollution–mediated health effects, as several mechanisms thought to be involved in mediating a cardiovascular health response to air pollution may already be activated.

■ Control Strategies

Efforts to mitigate the health effects of indoor and outdoor air pollution requires a multipronged approach, with strategies aimed at the population level and individual guidance. While emission reduction and improvement in air quality is the ultimate goal, personal strategies to diminish the risk of adverse effects are particularly important in susceptible individuals or during high-pollution events. Clinicians should be familiar with practical recommendations and guidance to individuals that can minimize the effects of air pollution. Clinicians may serve as consultants or as advocates in seeking to reduce the effects of indoor and outdoor air pollutants through population-oriented control approaches.

Community-oriented Strategies

Government policies aimed at emissions reduction through regulations and laws are some of the most effective mechanisms used to achieve lasting improvements in air quality. Since the passage of the Clean Air Act amendment in 1970, there has been approximately a 70% reduction in the aggregate emissions of the six criteria air pollutants across the United States, despite a growing population and economy.[106] Similarly, climate change policy directed toward limiting CO_2 and greenhouse gas emissions has the co-benefit of reducing fossil fuel consumption and the production of toxic air pollutants. The promotion of alternative energy sources, clean vehicles with improved fuel efficiencies, and green building techniques not only can improve the trajectory of a warming climate, but also has the immediate benefit of cleaner air.[107]

On a more local scale, redesigning land use can be an effective conjunctive measure to mitigate the public health effects of air pollution exposure.[93] Traditional urban design places densely populated areas and key community resources near major traffic arteries with the highest levels of traffic-related air pollution. Intentional urban design of infrastructure can promote physical separation of sensitive populations from mobile and point sources of pollution. For example, the California Air Resources Board made formal distance recommendations for building healthcare facilities, schools, day cares, and residences away from freeways, rail yards, and other pollution sources.[108] While such forward-thinking urban design strategies are not yet the standard, they have significant potential to reduce exposures in the most vulnerable populations.

TABLE 89-6 Air Quality Index and Activity Recommendations

Index Values	Levels of Health Concern	Cautionary Statement
0–50	Good	None
51–100	Moderate	Unusually sensitive people should consider reducing prolonged or heavy exertion outdoors
101–150	Unhealthy for sensitive groups	Active children and adults, and people with lung or heart disease, should reduce prolonged or heavy exertion outdoors
151–200	Unhealthy	Active children and adults, and people with lung or heart disease, should avoid prolonged or heavy exertion outdoors; everyone else should reduce prolonged or heavy exertion outdoors
201–300	Very unhealthy	Active children and adults, and people with lung or heart disease, should avoid all outdoor exertion; everyone else should avoid prolonged or heavy exertion outdoors
301–500	Hazardous	Everyone should avoid all physical exertion outdoors

Data from Air Quality Index (AQI): A Guide to Air Quality and Your Health. Triangle Park, NC: U.S. Environmental Protection Agency Office of Air Quality Planning and Standards Outreach and Information Division Research; 2014. EPA-456/F-14-002.

While changes in regulations and community infrastructure are instrumental for long-term air pollution mitigation, governmental and environmental agencies also play an important role in monitoring and public reporting of air quality. Pollution forecasting websites, such as Air Now, can be used to track the level of pollution on a fine spatial and temporal scale. The Air Quality Index (AQI) (Table 89-6) is communication tool used by governmental agencies to illustrate current pollutant levels based on national air quality standards. The AQI is color coded into six categories indicating increasing levels of health concern, with a level below 50 indicating good air quality and level over 300 corresponding to hazardous air quality. Users should be aware that the AQI is an imperfect tool, that people frequently confuse AQI levels with pollutant concentrations, that the AQI attempts to provide guidance about the pollutant of most concern on a particular day, and that different countries set their own levels of concern and their own language regarding guidance—a level that is "unhealthy" in one country may be considered acceptable in another.

Patient-oriented Strategies

Where levels of pollution exceed standards, individual actions to reduce person-level exposure may be beneficial. Potential interventions to reduce personal-level exposure to air pollution can be categorized as behavioral, technologic, physical, and pharmaceutical (Table 89-7). While there is a paucity of studies investigating the effectiveness of clinical strategies based on the AQI, behavioral modifications aimed at limiting time-activity patterns in areas with high pollution are considered to be the most effective strategy.[109] These could include reducing exercise in urban areas, selecting travel routes that minimize near-road exposure, or staying indoors during periods with high pollution concentrations. In general, concentrations of ambient pollutants are lower indoors, and the EPA advises the public to remain inside during periods of high air pollution to reduce the risk of acute health effects. It is important to qualify this recommendation, as the infiltration rate can vary widely depending on building structure, weather conditions, and the ventilation system. Additional actions, such as closing all windows and recirculating the indoor air through existing HVAC systems, may further reduce the infiltration of ambient pollutants.[110]

Technologic solutions for reducing personal exposure to pollution include the use of portable or central air cleaning systems. High Efficiency Particulate Air (HEPA) filters mechanically remove greater than 99.9% of particles with a diameter of 0.3 μm from filtered air. Studies have shown that HEPA filtration can reduce indoor $PM_{2.5}$ concentration between 40% and 70%, and it may have associated mortality benefits during high-pollution events, such as

TABLE 89-7 Personal Strategies to Mitigate Effects of Air Pollution Exposure

Intervention	Examples	Comments
Monitor local air forecast	• Automated air pollution networks that provide warnings (e.g., AirNow) • Personal pollution monitors	• May be particularly helpful for susceptible populations
Activity modification to reduce exposure to pollutants	• Stay indoors during high pollutant events • Reduce exercise in areas with high pollutants • Select transportation routes to avoid high pollutant zones	• Consider variable infiltration of outdoor pollutants into buildings • Trade-off between health benefits of physical exercise and adverse health effects of pollution
Clean indoor air	• Portable air filters, such as HEPA air purifiers • Central air cleaning systems	• Must be appropriately sized for room • Filters must be maintained • Can be expensive
Personal protective equipment	• Negative-pressure air-purifying respirators (APR), such as N95 • Positive-pressure APR	• Must have correct filter • Negative-pressure APR must have appropriate seal/fit to be effective • May be uncomfortable or difficult for individuals with chronic cardiopulmonary disease to wear
Medications or dietary supplements	• Antioxidants, omega 3-fatty acids, targeted therapy to proposed pathophysiology	• Mixed evidence of benefit, not currently recommended

wildfire smoke exposure.[111] To be effective at exposure reduction, air purifiers should be placed in rooms where participants spend most of their time, and they need to be appropriately sized to the area of the space filtered. While HEPA filters capture particles on fibrous material, electrostatic air cleaners use electrostatic forces to capture particles and may produce harmful byproducts, such as ozone. Due to their potential to produce O_3, many agencies recommend against the routine use of ionizers and other electrostatic air cleaners. There is no role for O_3-based air cleaners in settings with human occupants.

The use of personal protective equipment, such as negative-pressure filtering face masks, to physically reduce pollutant exposure has been variably adopted by different countries. In some heavily polluted cities, such as Beijing, face masks are commonly used outdoors. Respiratory protective equipment has been developed for use in the workplace to minimize exposure to toxic gases and particles. However, the efficacy of respirator is dependent on the pollutant, filter material, respirator design, and user fit. Many of these devices, particularly those likely to be most effective, add to the work of breathing and may be poorly tolerated by persons with respiratory disease. Cloth and dust masks may be able to decrease large irritant particles from entering the nasopharynx but do little to reduce $PM_{2.5}$ and hazardous gases. Negative-pressure respirators, such as N95s (defined as masks able to reduce 95% of PM <0.3um), can effectively reduce the concentration of contaminants depending on the quality of the individual's face seal. While there is controversy whether widespread use of respiratory protection should be recommended, many guidelines advocate for use of an N95 or other tight-fitting respirator when exposure to high levels of ambient air pollution is unavoidable. Under most circumstances, healthcare providers should not suggest respiratory protection as a method for reducing the risks of ambient air pollution.

By targeting the proposed pathophysiologic mechanism, various medications have also been investigated as a means to block adverse pollutant effects. Overall, the results of these studies have been disappointing with negative or mixed results.[112] For example, some randomized control trials of antioxidant supplementation showed improvement in diesel exhaust–mediated health outcomes, while others showed null or even augmented responses.[105] Currently there is little compelling evidence to suggest that pharmaceutical or dietary interventions can help reduce the health risks associated with air pollution exposure.

Guidance to patients related to ambient particulate air pollution calls for tracking when pollution levels are high, by weather forecasts, EPA alerts, or visible haze and reduced visibility. At such times, it is reasonable to advise patients to reduce outdoor activity, particularly with exercise, and avoid locations where pollution levels may be particularly high, for example, adjacent to busy roadways. Such guidance is particularly appropriate for people susceptible to health effects of air pollution (e.g., people with asthma, COPD, coronary artery disease, and/or hypertension). Although mechanisms of toxicity are not completely understood, avoiding air pollution exposure can only help reduce air pollution-related cardiorespiratory morbidity and mortality.

Susceptible patients should be counseled concerning the nature and degree of their susceptibility. The use of medication should follow the usual clinical indications, and therapeutic regimens should not be adjusted because of the occurrence of a pollution episode without evidence of an adverse effect on symptoms or function. In the laboratory, inhalation of cromolyn sodium and bronchodilating agents blocks the response to some pollutants, but use of these drugs solely because of exposure to air pollution cannot be advised. Similarly, although there have been investigations of antioxidant agents in preventing some air pollutant effects, the evidence is not sufficient to conclude that these are safe and effective.

TABLE 89-8 Questions and Answers About Indoor Air Pollution

Question	Answer
Do air cleaners work?	There is increasing evidence that filter-based air purifiers are helpful, particularly for susceptible populations or during high pollution events. People should avoid ozone-generating air purifiers.
Should the radon concentration in my home be measured?	Yes, radon can be readily measured at relatively low cost, and mitigation is feasible.
Should the air ducts in my home be cleaned?	There is no evidence of health benefits for cleaning air ducts.
Will controlling mites be beneficial?	Controlling mite levels is beneficial for persons with mite-sensitive asthma.
Should my home be humidified?	Humidification may increase allergen levels.

Pulmonologists may be concerned with diverse issues related to the control of indoor air pollution, ranging from answering patients' questions about pollutant health effects and control, to management of complex problems in large buildings. Some commonly asked questions and answers that reasonably reflect the state of the evidence are provided in (Table 89-8). The clinically relevant microenvironments are numerous, including the home, the workplace, public buildings, and places where leisure time is spent.

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CHAPTER 90

Acute and Chronic Responses to Toxic Inhalations

Austin J. Jolly
David A. Schwartz

INTRODUCTION

The lungs and airways are in constant contact with the outside world and are especially vulnerable to toxic substances present in the environment. Within seconds of exposure to an inhaled toxin, pathologic events occur that may cause immediate distress, produce illness lasting days, or even lead to the development of chronic lung disease. In this chapter we discuss the pathology and pathophysiology that can result from various inhaled toxins and highlight the role of several common and medically significant toxic inhalants that are known to cause acute and chronic pathophysiologic responses in the lung. We also describe several systemic syndromes caused by acute toxic inhalations. The scope of this chapter does not include chronic exposure to low levels of toxins.

DETERMINANTS AND MECHANISMS OF IRRITANT-INDUCED PULMONARY INJURY

Inhaled toxins exist in many forms and may be categorized by considering their physical properties. General categories include gases, vapors, fumes, aerosols, and smoke. A variety of factors determine the pathologic results of a toxic inhalation: the size of inhaled particles, the water solubility of the inhaled substance, the concentration of the inhalant in ambient air, the duration of exposure, the presence or absence of ventilation, and relevant host factors (age, smoking status, comorbid diseases, use of respiratory protection, and perhaps even genetic susceptibility). While toxic inhalants provoke a broad range of chemical and biologic activities that contribute to pathogenesis, their physical properties, namely, their particle size and water solubility, are of fundamental importance in determining the site and severity of pulmonary injury. Tables 90-1 to 90-3 and Fig. 90-1 summarize the physical properties of the discussed inhalants that substantially affect the resulting pathogenesis of these agents.

The size of aerosolized particles is of critical importance in inhaled toxin pathogenesis. In general, larger aerosolized particles are more likely to deposit on the nasopharynx via impaction and not gain access to the lower airways, while smaller particles are able to penetrate smaller airways and effect toxicity at the level of the alveolus. Aerosolized particles larger than 30–80 μm are not inhalable through the nose,[1] and particles larger than 5 μm typically do not reach the alveoli.[2] Ultrafine particles (those <0.1 μm) are able to remain airborne long enough to reach the alveoli where

TABLE 90-1 Definitions of Types of Inhaled Substances

Gas: a formless state of matter in which molecules move freely about and completely occupy the space of enclosure
Aerosol: a relatively stable suspension of liquid droplets or solid particles in a gaseous medium
Coarse particles: particles between 1 and 10 μm
Fine particles: particles between 0.1 and 1 μm
Ultrafine particles: particles less than 0.1 μm
Vapor: the gaseous form of a substance that normally exists as a liquid or solid and that generally can be changed back to a liquid or solid by either increasing ambient pressure or decreasing the temperature
Fume: an aerosol of solid particles generally less than 0.1 μm in size that arises from a chemical reaction or condensation of vapors, usually after volatilization from molten materials
Smoke: the volatilized gaseous and particulate products of combustion; particles generally less than 0.5 μm in size and do not settle readily

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TABLE 90-2 Water Solubility and Mechanisms of Lung Injury of Gaseous Respiratory Irritants

Irritant Gas	Water Solubility	Mechanism of Injury
Ammonia	High	Alkali burns
Chlorine	Intermediate	Acid burns, reactive oxygen species, reactive nitrogen species
Hydrogen chloride	High	Acid burns
Oxides of nitrogen	Low	Acid burns, reactive oxygen species, reactive nitrogen species
Ozone	Low	Reactive oxygen species, reactive nitrogen species
Phosgene	Low	Acid burns, reactive oxygen species, protein acetylation
Sulfur dioxide	High	Acid burns, reactive oxygen species

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TABLE 90-3 Water Solubility and Site of Initial Impact of Toxic Irritants

Water Solubility	Initial Level of Impact	Inhalant
High	Nose	Ammonia
	Pharynx	Chlorine
	Larynx	Sulfur dioxide
Medium	Trachea	Ozone
	Bronchi	
Low	Bronchioles	Nitrogen dioxide
	Alveoli	Phosgene

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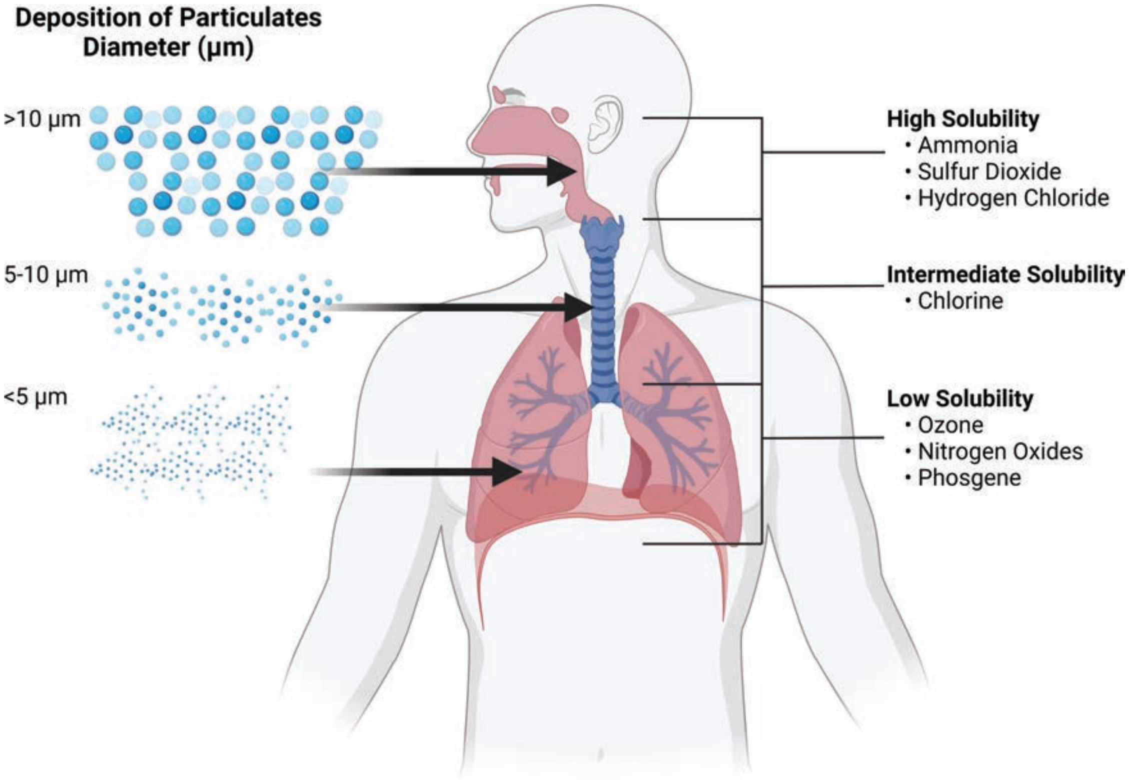

Figure 90-1 Artist illustration depicting relative water solubility and particle diameter in relation to site of initial impact within the respiratory tree.

they can transcellularly diffuse across the alveolus–capillary interface or be retained in surfactant, evading mucociliary or immune cell–mediated clearance mechanisms.[3] Inhaled particles may have direct toxic effects themselves, or they may function as vehicles for adsorbed gaseous agents that are toxic to terminal bronchioles and alveolar cells.

In addition to particle size, the relative water solubility of an inhalant determines where along the respiratory tract toxicity will occur. Substances with high water solubility, such as ammonia, sulfur dioxide, and hydrochloric acid, provoke immediate and evident injury to the conjunctiva and mucosal surfaces of the upper airways; they are largely absorbed by mucus lining the pharynx and larynx and often react there to form caustic acids and alkalis. The provoked symptoms quickly prompt exposed individuals to flee the area or contain the source of exposure, reducing the duration of exposure. These compounds can also activate irritant receptors in the upper airways, provoking a bronchoconstrictor reflex that may further limit access of the inhalant to lower airways.[4] In contrast, compounds like phosgene and ozone have low water solubility and thus fail to cause immediate irritation, promoting longer exposure to the inhalant and deeper penetration of the lower airways. Compounds of intermediate solubility, for example, chlorine gas, typically have pathologic effects throughout the respiratory tract. These differences in solubility can be overcome by differences in concentration and duration of inhalant exposure: virtually any inhaled toxin (even the most soluble agents) can cause diffuse damage of the respiratory tract by overwhelming the absorptive capacity of the upper respiratory tract. Furthermore, adsorption of a toxic gas on particulate matter may permit a toxin access to otherwise unreachable airways.

Host factors also play a significant role in predicting an individual's response to a toxic inhalation. Underlying pulmonary or extrapulmonary disease may worsen a patient's response to an exposure. Children deposit a smaller fraction of inhaled particles in their nasopharynx than adults and thus may be at elevated risk of lower airway exposure and pathology.[5] Moreover, as some gases (such as chlorine and sulfur dioxide) are heavier than air and stay closer to the ground, children may be subjected to a longer duration and higher concentration of gas than adults near the same site of toxin release. With particles greater than 0.5 µm, breathing through one's nose increases upper airway particle deposition compared to mouth-breathing; this difference is absent with particles smaller than 0.5 µm.[6] Tobacco smoking impairs ciliary clearance and cellular defense, limiting the exposed patient's ability to clear inhaled particles and prolonging exposure. Patients with increased minute ventilation (such as those panicking at the scene of an irritant gas release) are at elevated risk of increased exposure and toxicity. Experiments with inbred strains of mice suggest that genetic variants may alter the risk of responding to various inhaled toxins.[7] For example, investigators exposed a panel of 43 genetically diverse mouse strains to phosgene gas to induce acute lung injury followed by genome-wide association studies (GWAS) using a high-density single nucleotide polymorphism assembly. These findings revealed candidate genes such as *Alox5* (involved in leukotriene production) and *Itga9* (linked to TGF-β signaling) are associated with increased susceptibility to toxin-induced acute lung injury in mice.[8]

Injury from toxic inhalation may occur via several mechanisms. If the concentration of the inhalant is high enough and if ventilation is inadequate, simple asphyxiation due to displacement of atmospheric oxygen may occur. The reflex bronchoconstriction triggered by upper-airway irritant receptor activation may itself cause inadequate oxygen inhalation. Cell injury from acute toxin exposure typically occurs via nonimmunologic mechanisms of injury and inflammation, generally via formation of an acid (chlorine, oxides of nitrogen, phosgene, and sulfur dioxide), an alkali (ammonia), or reactive oxygen or nitrogen species (ozone, oxides of nitrogen and chlorine). Acid formation results in coagulative necrosis of underlying tissue, while alkali exposure causes a liquefaction of mucosa and characteristically deep lesions within the respiratory epithelial tissue. Reactive oxygen and nitrogen species and their derivatives achieve local tissue damage via lipid peroxidation and protein oxidation, which can compromise the integrity of cell membranes leading to cytotoxicity.[9] Free radicals may be direct derivatives of inhaled substances, or they may be released by alveolar macrophages that are activated by inhalant exposure.[10] All three types of tissue damage generally lead to an increase in expression of proinflammatory cytokines that can perpetuate the acute injury and may be responsible for the development of later sequelae. Disruption and repair of injured airway epithelial tissue may compromise host defenses against further infectious or irritant substances. A role played by the innate immune system in disease progression is evident in the case of endotoxin exposure in organic dust toxin syndrome (ODTS, below), and may be a host factor in the response to ozone and nitrogen dioxide.[7,11]

PATHOGENESIS AND CLINICAL PRESENTATION OF TOXIC INHALATION INJURY

Mechanisms of disease and clinical manifestations based on respiratory site exposure are considered below.

Upper Airway

Effects of toxins on the upper airways are typically sudden and short-lived compared to those more distal along the respiratory tract; chronic pathology in this region is unusual. Compounds that provoke a response in the nose, pharynx, and larynx tend to be particulates with relatively large average particle size or gases with high water solubility. Acids, alkalis, and reactive oxygen and nitrogen species may all cause tissue injury in this region depending on the inhaled compound and its reactions along airway epithelium. Characteristic tissue injury depends on dosage and ranges from slight edema of the nasopharynx and larynx to epithelial ulceration and frank hemorrhage. Once the airway epithelia are compromised, it fails to function as a protective barrier against the environment. Underlying inflammatory cells, nerves, muscles, and blood vessels become exposed, which may exacerbate the inflammatory response. The nasopharynx contains abundant vascular beds underlying the mucosa, and these vascular beds are highly responsive to neurohumoral stimuli. Due to their sensitivity, these vascular beds are largely responsible for toxin-induced upper airway constrictive reflexes that can compromise patency of the airway.[12] An obstructive response to some irritants starts to occur at concentrations only barely perceivable as irritating.[13] Irritant exposure to the upper airway can affect nonrespiratory structures such as the eustachian tube leading to otitis media.[12]

The typical presentation of patients with acute exposure of irritant substances to the upper airways includes burning sensations of the nasal passages and throat, copious sputum production, coughing, and sneezing. Extrapulmonary manifestations include burning of the eyes, profuse lacrimation, headache, and dizziness. The most serious risk in the exposed patient is airway obstruction due to reflex bronchospasm or laryngospasm, mucosal edema, increased secretions, and sloughed epithelial cells. Patients presenting with hoarseness or stridor should be carefully observed for further evidence of airway compromise. Although inhalational injury confined to the upper airways tends to be self-limited with no or few long-term sequelae, a chronic rhinitis following irritant exposure, *reactive upper airway dysfunction syndrome* (RUDS), has been described[14] and was observed among World Trade Center rescue workers following the attacks of September 11, 2001.[15] Similarly, it has been reported that workers exposed to irritants or organic dusts can develop a chronic rhinitis termed *occupational rhinitis* characterized by persistent sneezing, itching, and rhinorrhea.[16]

Patients with acute toxic exposure to the upper airways should be immediately removed from the source, which may require removal of the patient's clothes. The patient's airway should be secured and monitored; racemic epinephrine may be used for bronchodilation, but it should not delay endotracheal intubation if necessary. Frequent suction may be required. Profuse amounts of water should be irrigated over exposed surfaces. Supplemental oxygen should be provided if appropriate. Patients with extensive upper airway edema may benefit from corticosteroids,[17] but this is unsupported by clinical trials. Ophthalmologic pathology such as conjunctivitis can develop after exposure; consultation should be sought for management of eye complications.[18]

Conducting Airways

Acute or chronic effects on the airways may be observed.

Acute Injury

As is the case with the upper airways, the conducting airways protect their submucosal structures with epithelium that may be compromised by acute inhalational injury. The resulting edema, inflammation, and bronchoconstriction may be life-threatening if it results in an obstructed airway, and without its epithelial barrier the airway is vulnerable to infections and other environmental pathologies. This damage to the epithelium appears to occur at the tight junction interface between cells,[19–21] resulting in increased epithelial permeability to other irritants, which gain direct access to effector cells within the subepithelial mucosa. Resulting bronchospasm may cause ventilation–perfusion mismatch.[22] The smooth muscle of the airways can be hyperresponsive in the hours and days following irritant exposure, an effect probably mediated by the neutrophilic and eosinophilic inflammatory response inhalational injury provokes.[23,24]

Conducting airway injury may manifest as intrathoracic airflow obstruction hours after the initial insult. Patients with histories of exposure who present with any evidence of respiratory compromise should be hospitalized for observation, even if asymptomatic. Findings of concern include expiratory wheezing, decreased airflow on peak expiratory flow measurement or spirometry, abnormalities of gas exchange, or an abnormal chest x-ray. Likewise, patients with complaints of dyspnea or chest tightness should be observed carefully and treated symptomatically with inhaled steroids and bronchodilators, even in the absence of objective findings. When significant airflow obstruction is present, systemic steroids may be of some utility.

Chronic Injury

Two forms of chronic injury include reactive airways dysfunction syndrome and vocal cord dysfunction.

Reactive Airways Dysfunction Syndrome

A persistent asthma-like disease following acute exposure to an irritant inhalant, known as *reactive airways dysfunction syndrome* (RADS, or "Brooks syndrome") was named in 1985 based on a cohort of 10 previously healthy individuals who developed chronic asthma-like symptoms after acute exposure to gases and fumes; all 10 patients demonstrated a positive methacholine challenge suggesting hyperreactive airways.[25] These findings were previously observed among World War I soldiers exposed to war gases.[26] Investigation and diagnosis of the disease is generally limited by the absence of spirometry results in patients prior to exposure and any notable confounding factors (e.g., cigarette smoking), but numerous reports exist of previously asymptomatic patients experiencing hyperreactive airway disease presenting soon after a single toxic exposure and persisting for months or years.[25,27–34] RADS is distinguished from immunologic occupational asthma because it directly follows an acute, single exposure with a minimal-to-nonexistent latency period after inhalation of the offending substance.[35]

The pathogenesis of RADS likely begins with the initial injury to and desquamation of the epithelium exposing underlying nervous and vascular tissue resulting in hemorrhage and edema. Neurogenic inflammation from exposed nerve endings is likely involved. Long-term structural remodeling of the airways culminates in epithelial regeneration and fibrosis resulting in chronic changes in the tissue.[36–38] Airway narrowing may be due to mucosal edema, inflammation, or structural changes to the architecture of the bronchial wall.[39]

RADS typically presents abruptly within 24 hours following exposure with the classic symptoms of obstructive airway disease: wheezing, chest tightness, dyspnea, and cough. The symptoms and obstructive findings on exam and spirometry are relieved by bronchodilators, although not as effectively as in other types of reactive airway disease (perhaps due to chronic fibrotic remodeling of the conducting airways). The disease can persist for months and may, in some instances, be permanent.[40] A recent case report shows that a patient with severe unremitting symptoms of RADS for 5 years following an ammonia exposure responded to high-dose oral vitamin D supplements.[41] These findings were consistent with a more recent case report describing a patient who was acutely exposed to high levels of ammonia during a spill and developed severe symptoms of RADS that affected the patient's quality of life leaving the patient virtually housebound for 5 years. Aggressive vitamin D supplementation was initiated; when serum levels of vitamin D reached 200 nmol/L the patient's symptoms resolved.[35] Anecdotally, inhaled corticosteroids have shown benefit in relieving airflow obstruction.[36] Systemic corticosteroids have been proven beneficial in an animal model of RADS.[42]

Vocal Cord Dysfunction

Vocal cord dysfunction may also follow a single acute irritant exposure and may be confused with RADS.[43,44] The disorder may be caused by reflex response to nerve stimulation by irritants.[45] Patients suspected of having RADS who do not respond appropriately to bronchodilators should be evaluated for vocal cord dysfunction; direct laryngoscopy is the gold standard of diagnosis.[44]

■ Lower Airways and Pulmonary Parenchyma

While the upper and conducting airways are certainly at risk for inhalant exposure, the lower airways and lung parenchyma are primary sites for inhalational injury. Effects may be acute or chronic.

Acute Injury

Although all toxic inhalants are capable of producing distal airway disease at extreme concentrations and durations, the gases most likely to do so are those with low water solubility like phosgene and nitrogen dioxide, which bypass reflex bronchoconstriction and absorption by upper airway mucous (Fig. 90-2). The initial pathologic events in distal airways are caused by direct cellular toxicity of an inhaled agent and its derivatives, which compromise the alveolar–capillary interface.[46] Some of this cytotoxicity may be derived indirectly from reactive oxygen species released from activated inflammatory cells.[10] In the absence of an intact alveolar–capillary interface, profound pulmonary edema may develop that impairs gas exchange and can prove fatal. The severity of this pulmonary edema, which typically presents after a latent period of several hours following the initial insult, is likely dose related. This process may cause no more than slight dyspnea and cough with a mild alveolar infiltrate, or it may progress via diffuse alveolar damage to adult respiratory distress syndrome (ARDS).[47] For this reason, patients with exposure to gases capable of causing distal airway disease should be hospitalized and monitored for symptoms of respiratory distress and with serial chest x-rays for at least 24 hours following exposure. Development of ARDS from toxin exposure likely shares a common pathway with other causes of acute lung injury, and management is similar: supportive care with mechanical ventilation at lower tidal volumes,[48] careful control of blood glucose, surveillance for infection, and deep vein thrombosis prophylaxis. Diuresis, IV corticosteroids, prone positioning, nitric oxide inhalation, and exogenous surfactant are all unsupported by clinical trials but potentially confer some benefit.[49] Diffuse bronchiolitis also has been reported following acute exposure.[50]

Chronic Injury

Two forms of chronic injury include bronchiolitis obliterans and cryptogenic organizing pneumonia.

Bronchiolitis Obliterans Bronchiolitis obliterans (BO) is a well-documented but infrequent long-term sequela of toxic gas exposure, especially of nitrogen dioxide,[51,52] but also to ammonia,[53] mercury,[54] and sulfur dioxide.[55,56] BO is an inflammatory-mediated obstructive lung pathology of the smallest airways characterized by injured epithelium and excessive fibroproliferation.[57] Histopathologically, the involved tissue may show peribronchiolar smooth-muscle cell hypertrophy, inflammatory infiltrates surrounding the terminal bronchioles, and bronchiolar fibrosis.[58] The disease typically presents 1 to 3 weeks following the initial lung injury and pulmonary edema (Fig. 90-3). The interim is often free of symptoms. When BO does develop, patients may present with dyspnea on exertion or obstructive findings on spirometry. Physical exam may be either unremarkable or remarkable only for early inspiratory crackles. Chest x-ray will either be normal or demonstrate hyperinflation. Pulmonary function tests typically demonstrate airflow obstruction that may in some cases also be associated with restrictive defects. On biopsy, granulation tissue will be seen in the lumen of small airways and bronchiole walls may be obliterated by fibrous scarring. Corticosteroids may be of benefit in preventing or alleviating BO if administered early in the course of the disease,[59] although this is controversial.

Cryptogenic Organizing Pneumonia Cryptogenic organizing pneumonia, COP (formerly known as bronchiolitis obliterans organizing pneumonia, BOOP), is another observed delayed sequela of toxic inhalation.[60,61] COP is a form of interstitial lung disease with alveolar invasion of inflammatory cell infiltrates followed bFGF-mediated organization of fibroblasts leading to pulmonary fibrosis.[62] *Masson bodies* are the term given to accumulating intraluminal granulation tissue that can be visualized by H&E stain. Although not reproduced in other case studies, there has been a report of a previously healthy 20-year-old male who developed COP after acute exposure to a jalapeño grease fire.[63] Capsaicin and other jalapeño-derived compounds are known causes of bronchiolar inflammation and epithelial mucosal damage, but this case marks one of the first accounts of the development of COP from these specific inhalants. This example expands on what is currently known about inhalant exposure and COP and emphasizes the value of taking a comprehensive exposure history in patients with lung injury of unknown etiology.[63] Patients with inhalant-induced COP present in the weeks following exposure with fever, a persistent and nonproductive cough, sore throat, and malaise. Late inspiratory crackles may be observed. Chest x-ray may reveal bilateral patchy "ground-glass" densities that start as focal lesions but may coalesce with time. Pulmonary function tests generally reveal a restrictive process with decreased diffusion capacity. COP responds well to corticosteroids,[64] although a small number of patients may develop progressive fibrosis. Duration of therapy should be guided by the patient's clinical status.

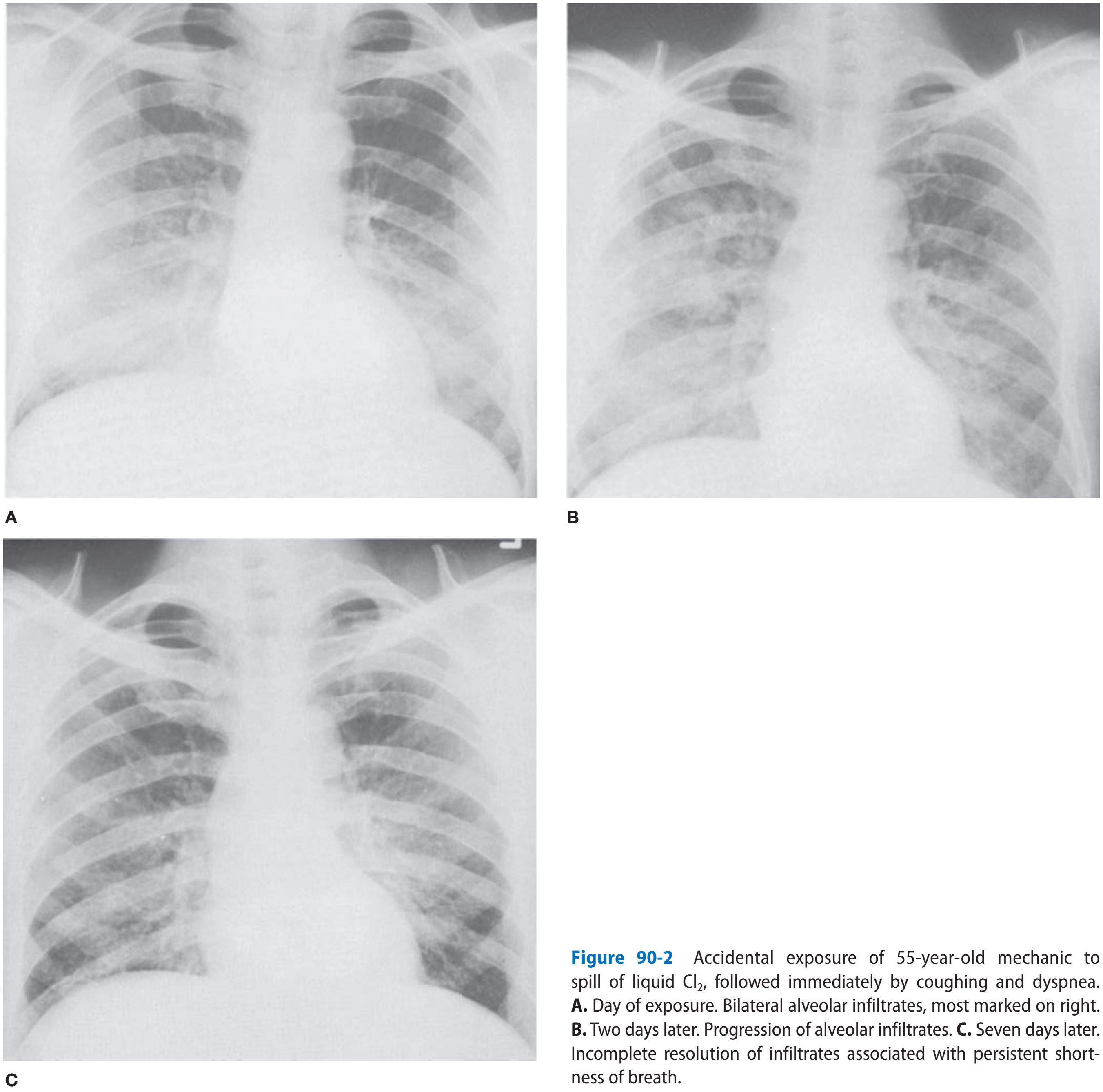

Figure 90-2 Accidental exposure of 55-year-old mechanic to spill of liquid Cl_2, followed immediately by coughing and dyspnea. **A.** Day of exposure. Bilateral alveolar infiltrates, most marked on right. **B.** Two days later. Progression of alveolar infiltrates. **C.** Seven days later. Incomplete resolution of infiltrates associated with persistent shortness of breath.

EFFECTS OF SPECIFIC INHALED TOXINS ON THE RESPIRATORY SYSTEM

The respiratory consequences of inhalation of commonly encountered toxins are discussed individually below.

■ Ammonia

Anhydrous ammonia (NH_3) is a stable colorless gas at room temperature. Ammonia is a hygroscopic nitrogen-containing compound typically dissolved in water at 5% to 10% (weight:volume) concentration for household cleaning products or upward of 25% concentration for commercial products,[65] making ammonia rank among the most commonly spilled hazardous substances (Table 90-4).[66] Familiar to all as a household cleaner, it also has countless uses in industry: as a chemical coolant used for refrigeration, as a fertilizer, as a fixative in photocopiers and in the manufacture of polymers and explosives. Small amounts are naturally present in the atmosphere as products of the putrefaction of vegetable and animal proteins. The pungent, suffocating smell of concentrated ammonia (as low as 5 ppm) is immediately recognizable. Due to the prevalence of ammonia in household cleaners and to its use in smelling salts (which exploit the noxious effect of ammonia on nasal membranes to arouse consciousness), the odor threshold may extend to over 50 ppm because of the olfactory fatigue and adaption.[67,68] Ammonia is frequently dissolved into water for storage and transportation and vaporizes readily on exposure to air. Most inhalation exposures are the result of accidental releases, including tank leaks and transportation mishaps,[69–71] and most exposures occur in the industrial workplace.[72] A reported source of exposure is via fumes produced in clandestine methamphetamine laboratories.[73] A more recent example from 2019 highlights how ammonia exposure can affect public health at a community-level. In Beach Park, a suburb of Chicago, an agriculture tractor was towing 2-ton containers that were leaking ammonia. A gas cloud quickly covered

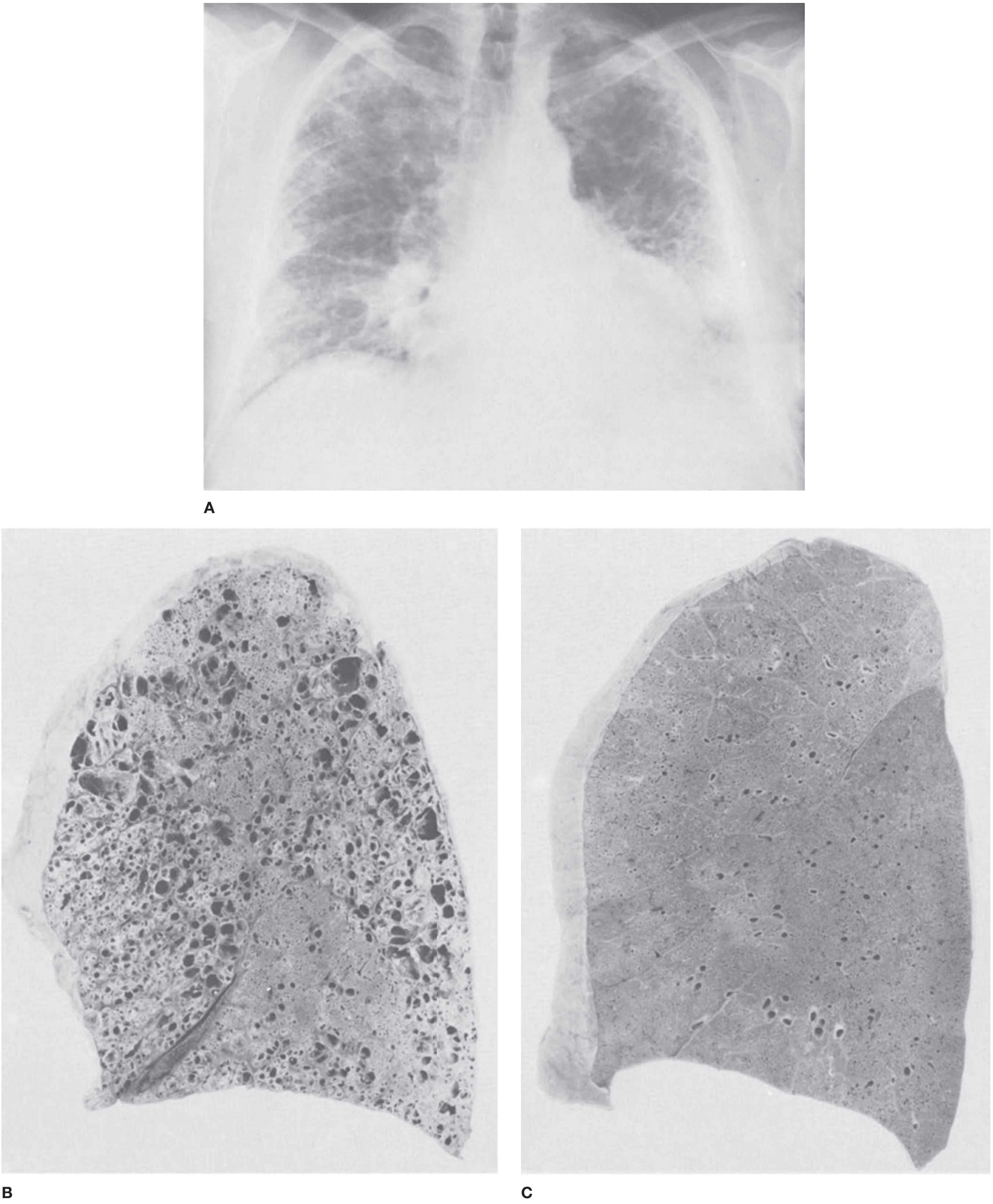

Figure 90-3 Bronchiolitis obliterans in a 63-year-old man who had been exposed to a wide variety of unidentified fumes in his jobs, which included welding. **A.** Chest radiograph. Diffuse pulmonary fibrosis and honeycombing, most marked in the peripheral portions of the lungs. **B.** Sagittal section of lung from same patient showing markedly dilated airspaces. Microscopic sections revealed bronchiolitis obliterans and chronic interstitial pulmonary fibrosis. **C.** Normal lung from a 43-year-old man who died suddenly. The difference between B and C in the alveolar portions of the lungs is striking. *(Reproduced with permission from Dr. R. Ochs.)*

TABLE 90-4 Pulmonary Manifestations of Toxin Inhalation

		Acute Clinical Manifestations		Chronic Clinical Manifestations	
Substance	**Onset**	**Upper Airway Irritation**	**Pneumonitis, ARDS**	**Bronchiolitis Obliterans, BOOP**	**RADS**
Irritant gases					
Ammonia	Minutes	Severe	+	+	+
Chlorine	Minutes to hours	Moderate	+	−	+
Hydrogen chloride	Minutes	Severe	+	−	+
Oxides of nitrogen	Hours	Mild	+	+	+
Ozone	Minutes to hours	Mild	+	−	−
Phosgene	Hours	Mild	+	−	+
Sulfur dioxide	Minutes	Severe	+	+	+
Metals					
Cadmium	Hours	Mild	+	−	−
Mercury	Hours	Mild	+	+	−
Zinc chloride	Minutes	Mild	+	−	+
Zinc oxide	Hours	Mild	+	−	−

+, exposure reported to be associated with clinical entity; −, exposure as yet not reported to be associated with clinical entity.

the suburban area and lingered for several hours. Thirty-seven people were hospitalized, 7 of whom in critical condition.[74]

The mechanisms of toxicity to the respiratory system involve both direct irritation and alkaline chemical burns. Due to its hygroscopic nature, ammonia tends to affect the proximal airways, where it reacts rapidly with the water present on mucosal surfaces to form ammonium hydroxide, causing tissue liquefaction. This necrosis liberates formerly intracellular water, which serves as further reactant for ammonia, perpetuating the reaction. In addition to the alkali burns caused by the generated ammonium hydroxide, thermal burns can result from the heat generated by this exothermic reaction. The resulting injury, typical of alkali burns, penetrates deeply. The initial injury to the mucosa of the oropharynx can cause edema, hemorrhage, sloughing of tissue, and increased secretions that can bring about fatal upper airway obstruction. Ammonia is directly caustic to airways at concentrations of 1000 ppm and higher.

Although concentrated at the proximal airways, the effects of ammonia have been observed at all levels of the respiratory tract. The penetration of the gas to the smaller airways and alveoli is a function of its concentration and the duration of exposure. Reported acute conditions associated with ammonia exposure include pulmonary edema, laryngitis/tracheobronchitis, bronchiolitis, and bronchopneumonia; reported chronic sequelae include bronchiectasis, bronchospasm/asthma (termed *reactive airways dysfunction syndrome*), and chronic obstructive pulmonary disease.[75] There are several reports of interstitial lung disease following a single exposure to ammonia.[72] A biphasic pattern of pulmonary response to ammonia inhalation has been reported, characterized by initial, acute pneumonitis that may clear over the next 2 to 3 days, followed in some individuals by the gradual development of airway obstruction and respiratory failure.[69] There may be a correlation between the development of a bacterial superinfection after exposure with the ensuing emergence of bronchiectasis.[76] In one review of published case reports, 21% of patients with acute ammonia inhalation died within 60 days of exposure.[75] The most common causes of death were laryngeal edema and obstruction, noncardiogenic pulmonary edema, and extensive pneumonic complications.

Management of a patient who has experienced ammonia inhalation requires removing the patient from the source of the irritant, securing the airway, and immediately irrigating all exposed surfaces (especially the eyes) with copious amounts of water. Humidified oxygen should be administered early. Airway management aggressiveness depends on the extent of complications such as laryngeal edema, pulmonary edema, hemoptysis, or respiratory failure that occur.[77] Rales detected on physical exam are predictive of the subsequent hospital course, even in the absence of hypoxemia and chest x-ray abnormalities.[69] Medical management is largely supportive. Aerosolized bronchodilators together with corticosteroids can be administered to treat bronchospasm. Corticosteroids and antibiotics are both frequently used, but both are unproven in human trials.

■ Chlorine, Chloramines, and Hydrochloric Acid

Chlorine (Cl_2) is a greenish-yellow gas that is heavier than air and is a common gas of intermediate water solubility. Although it has a distinct bleach-like odor, patient exposure to it may be prolonged compared with other toxic gases due to its delayed and gradual irritation of mucosal surfaces and its high density, which keeps it low to the ground. The first reports of its toxicity followed its use as an agent of chemical warfare in World War I, and war gassings remain the largest historic source of chlorine gas exposure.[78] Most exposures since then have occurred in the industrial setting, where chlorine is used in the manufacture of paper, cloth, antiseptics, and other products.[79] More common in the household is the liberation of chloramines and other toxic chlorine derivatives from the reaction of chlorine-containing products (such as hypochlorite bleach) with ammonia or products containing hydrochloric or phosphoric acid. Numerous exposures to chlorine gas have occurred near swimming pools, where chlorine-releasing agents (e.g., calcium hypochlorite and chlorinated isocyanuric acids) are used in water purification.[50]

The pathogenicity of chlorine gas derives directly from elemental chlorine's effects on the respiratory tract and indirectly from its reaction with water to form hydrochloric acid (HCl) and hypochlorous acid (HOCl). The character and distribution of injury from chlorine exposure varies according to duration of exposure and the relative concentrations of elemental chlorine and its derivative compounds. HCl and HOCl possess considerable water solubility and are responsible for the tissue damage sustained by the upper airways and ocular conjunctivae. Irritation to trigeminal nerve endings caused by these compounds can cause a reflex bronchoconstriction that may contribute to compromise airway diameter.[80] In addition to causing the tissue coagulation typical of acid exposures (described above), these compounds ionize and enter cells, where they may form reactive oxygen species. HOCl has been shown to react with nitrite (NO_2^-) to produce reactive nitrogen-containing compounds able to nitrate, chlorinate, and dimerize phenolic amino acids.[81] As nitrite and nitric oxide (its parent compound) levels are elevated at sites of tissue inflammation, this potentially is another mechanism of injury.[82] Although lower respiratory tract irritation has been reported following high-level exposures, less than 5% of inhaled chlorine gas penetrates beyond the upper airways.[83] Fatal dosages from chlorine inhalation have ranged from 50 to 2000 ppm.[50]

The immediate clinical manifestations of acute chlorine exposure are typical of irritants of its solubility: rhinitis, cough, dyspnea, wheezing, and chest tightness, along with conjunctivitis and skin irritation.[84] When chlorine gas exposure has resulted acutely in death, autopsies have revealed diffuse ulcerative tracheobronchitis, pulmonary edema, thrombi within pulmonary vessels, and denudation of respiratory tract epithelium.[85] Acute respiratory symptoms are more prevalent and severe among patients who already have chronic respiratory disease. In 2005, a derailment train released 40 to 60 tons of chlorine gas near a small town in South Carolina. Nine people died and 71 were hospitalized. The majority of people (>90%) had respiratory symptoms including wheezing, rales/crackles, cough, decreased breathing sound, rhonchi, and labored breathing. Autopsy findings revealed the causes of death to include asphyxia, lactic acidosis, and acute respiratory failure.[86]

The lasting respiratory sequelae of chlorine gas exposure have been described since the years following use of the gas in World War I.[87] Reported long-term pulmonary diseases following exposure have included both restrictive and obstructive processes, frequently resolving to normal function within a month and almost always before 2 years following exposure. Reactive airways dysfunction syndrome may be an infrequent sequela of high-level exposures to chlorine.[27,88] Other chronic sequelae from chlorine exposure include airway hyperresponsiveness and epithelial remodeling. ARDS may develop if chlorine bypasses the proximal airways and reaches the lower lung fields, and it is estimated that there is up to 1% mortality in individuals with severe chlorine exposure.[89]

Patients who have been exposed to chlorine gas should be managed according to the severity of their presenting symptoms similarly to other victims of irritant inhalation. The treatment for lung injury is primarily supportive care including humidified oxygen administration, lung protective mechanical ventilation, and pharmacologic therapeutics. Nebulized sodium bicarbonate has shown promise as a useful treatment[90,91] but lacks supporting clinical trials and showed no outcome benefit in a relatively large observational study of chloramine gas exposure.[92] Beta-agonist bronchodilators and corticosteroids are frequently used and are probably of benefit. The reported benefit of corticosteroid administration is anecdotal[85] and unconfirmed by clinical trial.

■ Sulfur Dioxide

Sulfur dioxide is a heavy, colorless, and highly water-soluble gas that has the distinct, pungent odor of burnt matches. It is generated in the combustion of coal and petroleum and is often used as a preservative in alcoholic beverages and fruit. Industrial exposures have occurred around ore smelting, metal smelting, oil refining, sugar refining, and the bleaching of wool and wood pulp. In 1930, 63 people died and thousands became ill in the narrow Meuse River Valley of Belgium due to the trapped high concentrations of sulfur dioxide from the waste products of industry resources (United States Environmental Protection Agency). Sulfur dioxide is among the most harmful gases released to the atmosphere during volcanic eruptions;[93] in 1986 the gases emitted from Lake Nyos killed nearly 2000 people in Cameroon.[94] Sulfur dioxide's great density keeps it low to the ground and slow to dissipate from sites of release; thus, children may be at an increased risk of exposure.

Sulfur dioxide reacts with water present on mucus membranes to form sulfuric acid, which, like other acids, causes tissue coagulation underlying exposed surfaces. Sulfuric acid also further dissociates into hydrogen ions, sulfite, and bisulfite,[95] which can then react with oxygen to produce reactive oxygen species; ensuing lipid peroxidation may be a contributing mechanism of injury to immediate tissues and elsewhere.[9,96] In an animal model of chemical-induced lung injury, rats were exposed to a single dose of 2200 ppm sulfur dioxide and subject to analysis for acute and chronic respiratory responses to sulfur dioxide (Fig. 90-4). Five hours post-exposure revealed abundant macrophage and neutrophil airway infiltrates associated with epithelial damage. The rats demonstrated an exaggerated methacholine response 24 hours post-exposure, suggesting the development of hyperresponsive airways. Histopathologic analysis and molecular assays demonstrated collagen deposition and increased TGF-β signaling 14 days post-exposure.[97] These results suggest sulfur dioxide is sufficient to induce proinflammatory and profibrotic responses in the acute and chronic phases, respectively.

Sulfur dioxide is detectible to humans at 3 to 5 ppm and is lethal at levels exceeding 400 ppm for 1 minute.[98] High water solubility makes sulfur dioxide primarily an upper airway irritant. The direct irritant of bisulfate iron inhibits mucociliary transport.[99] The irritation-induced parasympathetic stimulation leads to smooth muscle contraction and mucosal secretion. Exposures of high enough intensity can irritate both upper and lower airways. Patients exposed typically present with dyspnea, burning of the nose and throat, rhinorrhea, cough, and airway obstruction.[100] Proximal airway injury is characterized by acute denudation of the airway mucosa without inflammatory cell infiltrates. When lower airways are exposed, alveoli fill with fluid due to noncardiogenic pulmonary edema and the clinical picture is consistent with ARDS. Alveolar architecture is generally preserved. Extremely high-intensity acute exposures can lead within minutes to death from respiratory failure due to a combination of alveolar hemorrhage and edema, possible reflex vagal stimulation, and the asphyxiating effect of high concentrations of sulfur dioxide.[101] Reactive airways dysfunction syndrome has been reported following single sulfur dioxide exposure;[34] bronchitis also has been observed.[102] One pattern of postexposure progression reported is a rapid recovery followed several weeks later by the onset of irreversible airflow obstruction due to bronchiolitis obliterans.[101] Care for patients who have been exposed to sulfur dioxide is supportive: humidified supplemental oxygen, bronchodilators, and intubation and ventilation if necessary. The use of corticosteroids in the setting of ARDS following sulfur dioxide exposure has not been shown to be of benefit, but a trial is not unreasonable. Antibiotics may be reserved for use upon evidence of infectious complications.

■ Nitrogen Oxides

Nitrogen oxides are ubiquitous air pollutants, released from automobile engines and the combustion of coal and petroleum and present in cigarette smoke. High-level acute exposure is most likely to occur in industrial settings, including mining, acetylene welding, and explosives manufacturing. A well-known form of exposure occurs in "Silo-filler's disease," in which farmers inhale concentrated nitrogen dioxide (NO_2) gas released within silos by decomposing nitrogenous biomaterial.[51,103] Exposures to high levels of nitrogen dioxide have been attributed to blast furnaces,[50] anesthetic gases,[104] military incidents,[105,106] and ice hockey arenas (secondary to combustion byproducts from ice-resurfacing machines).[107–110] Nitrogen dioxide is a liquid at room temperature and a reddish-brown gas above 70°F. The acrid smell of nitrogen dioxide makes the inhalation exposure to be avoided at low concentration. Thus, short term (1-hour peak) nitrogen dioxide concentration outdoor is unlikely to exceed 0.2 ppm.[111] However, low concentrations at 4 ppm may anesthetize the nose, resulting in overexposure.

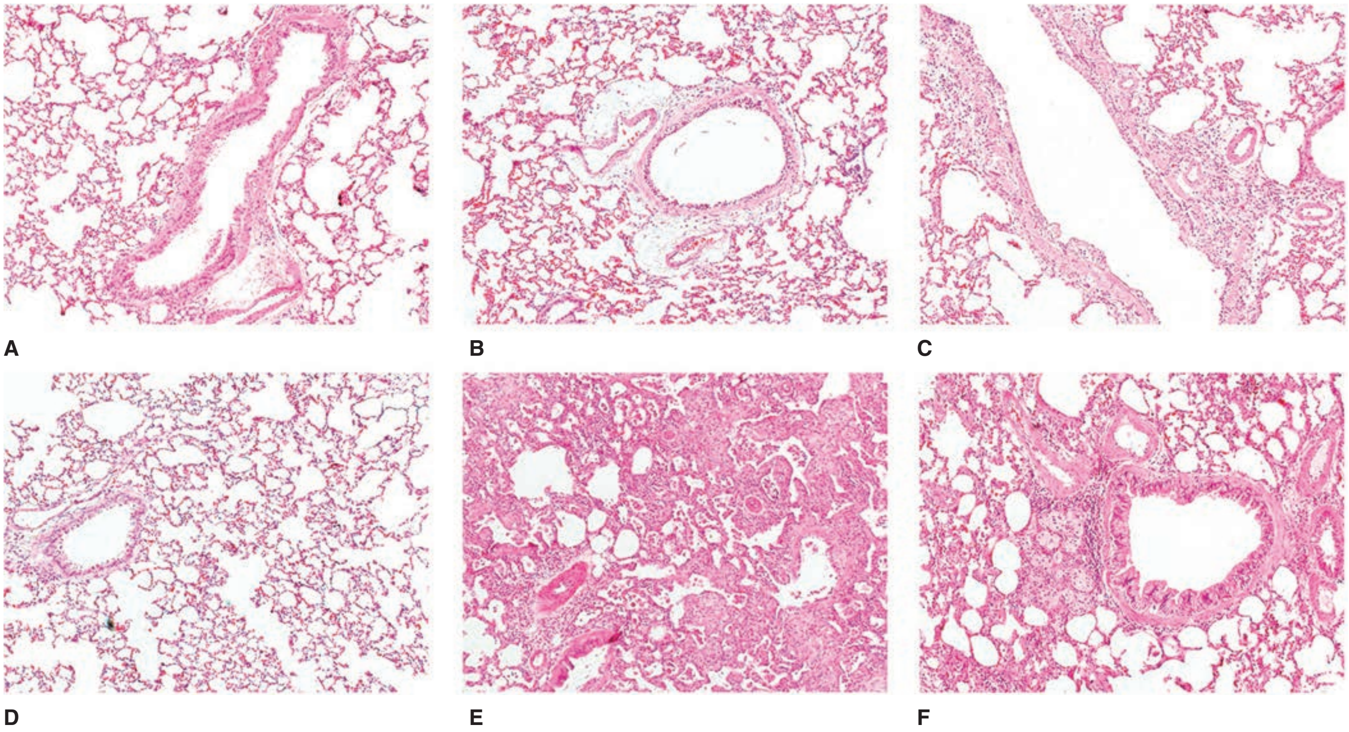

Figure 90-4 Histopathologic changes subsequent to sulfur dioxide exposure in rats. **A.** Healthy control rats not exposed to sulfur dioxide. **B–E.** Experimental rats were exposed to 2200 ppm sulfur dioxide to assess histopathologic changes after 5 h (**B**), 24 h (**C**), 14 days (**D** and **E**), and 28 days (**F**). Tissue sections were stained with hematoxylin–eosin and photos were taken at 40× magnification using light microscopy. *(Reproduced with permission from Wigenstam E, Elfsmark L, Bucht A, et al. Inhaled sulfur dioxide causes pulmonary and systemic inflammation leading to fibrotic respiratory disease in a rat model of chemical-induced lung injury. Toxicology. 2016;28–36.)*

Nitrogen dioxide (NO_2) inevitably forms when patients are administered inhaled nitric oxide (NO) via compressed gas delivery systems. The nitric oxide can react with the oxygen-rich compressed gas to form nitrogen dioxide, which can directly damage respiratory epithelial tissue.[112] Once inside the respiratory tree, nitrogen dioxide is hydrolyzed by the water on mucosal surfaces to form nitric and nitrous acids, which cause direct tissue damage. However, much of its toxicity is explained via the free radical activity of nitrogen dioxide itself and the nitrites and nitrates that derive from it.[113] Although the predominant site of toxicity from nitrogen dioxide exposure is the interface of the terminal bronchioles and alveolar membranes,[114] the relative insolubility of nitrogen dioxide in water ensures that enough gas penetrates the upper airways such that injury can occur virtually anywhere along the respiratory tract.[115] Nitrogen dioxide itself is a reactive nitrogen species that, along with other reactive derivatives, is capable of lipid peroxidation and protein oxidation,[116] both of which may be significant contributors to the gas's toxicity via disruption of the cell membrane. Mice with defective Toll-like receptor 4 expression exhibit a lessened response to nitrogen dioxide exposure compared to wild type mice,[11] suggesting that the patient's innate immunity may play a role in disease development. There is also evidence that nitrogen dioxide exposure is mutagenic to lung cells.[117]

The initial effects of nitrogen dioxide exposure are relatively benign at all but very elevated concentrations, that is, cough, fatigue, and occasionally nausea. Recent studies suggest that exposure of nitrogen dioxide in the first year of life increases the risk of persistent cough and developing asthma.[118,119] With high-intensity exposure, patients may also experience headache and chest tightness, although even these symptoms tend to resolve promptly. Nitrogen dioxide is less irritating to mucosal surfaces than other toxic inhalants. Symptoms typically abate for a period of hours before an intense pulmonary edema consistent with ARDS occurs due to increased capillary permeability following extensive damage to vascular and airway epithelium.[120] Patients who survive this are at risk for the development of bronchiolitis obliterans and cryptogenic organizing pneumonia 1 to 4 weeks following exposure.[52]

The clinical course of nitrogen dioxide toxicity demands vigilant monitoring on the part of medical personnel. Patients who are relatively asymptomatic following exposure may rapidly progress to ARDS within hours or severe obstructive bronchiolitis obliterans within weeks. Treatment is largely supportive. In animal studies, antioxidant administration has proved protective against lung injury following nitrogen dioxide exposure,[121] suggesting that aerosolized antioxidant medications are potentially of some utility in humans. Interestingly, nitric oxide (NO) has been used successfully as a pulmonary vasodilator in the treatment of ARDS following acute nitrogen dioxide toxicity.[103] Individuals who survive the initial lung injury still require close following with serial assessment of pulmonary mechanics and gas exchange over the ensuing several weeks. Patients exhibiting evidence of progressive airflow obstruction may benefit from corticosteroids to prevent or decrease the severity of BO.[122]

■ Phosgene

Phosgene (carbonyl chloride, $COCl_2$), like nitrogen dioxide, has relatively low water solubility and penetrates deeply into the alveolar spaces. It is colorless, lacks a strong odor (in high concentrations it is reported to smell like moldy hay), and is not irritating to the nasal and oral mucosa. These traits were notoriously exploited in World War I, when phosgene was used by both sides of the conflict as a weapon, resulting in tens of thousands of fatalities.[123] Modern uses include the production of pesticides, polyurethane resin, toluene diisocyanate, pharmaceutical products, and dyes. It can also be produced accidentally via the heat decomposition of various solvents, paint removers, dry cleaning fluids, and methylene chloride.[124,125] Small amounts can naturally occur from the breakdown and combustion of organochlorine compounds, such as those used in refrigeration systems.

Phosgene reacts with water to form hydrochloric acid and carbon dioxide, but its limited solubility results in little hydrolysis in the upper airways. In the relatively moist alveolar air spaces, however, the resulting acid is destructive of alveolar walls and small vessels, resulting in epithelial necrosis. In a rat model of phosgene-induced acute lung injury, stimulation of nociceptive vagal receptors was detected followed by marked decreases in minute ventilation, V/Q mismatch, and progressive pulmonary edema.[126] Phosgene's lack of irritability in the upper airways precludes the reflex bronchoconstriction provoked by other toxic gases, ensuring open passage of the gas to the alveoli. Phosgene also causes tissue damage by rapidly acetylating the amino, hydroxyl, and sulfhydryl groups of proteins, resulting in protein denaturation and structural compromise of cell membranes,[127] leading to a breakdown of the blood–air interface. Lipid membrane breakdown can occur in erythrocytes as hemolysis has been demonstrated in a mouse model of phosgene toxicity; release of intracellular erythrocyte proteins such as heme has been proposed as a potential biomarker for phosgene toxicity.[128] Lipid peroxidation also has been shown to occur, and antioxidant therapy has been shown to attenuate phosgene's effects in animal models.[129]

On exposure to phosgene, patients may experience chest tightness, wheezing, or cough; some victims experience no immediate symptoms. Following exposure, the patient experiences a latent period of 30 minutes to 8 hours before the onset of symptoms. The duration of this latent period is thought to be inversely proportional to both the severity of exposure and the ensuing severity of disease.[130] The latent period is typically followed by pulmonary edema: the patient experiences dyspnea, cough, and respiratory distress, and rales and cyanosis are appreciable on physical exam. Although survival for patients with acute phosgene exposure is good, numerous long-term sequelae have been reported, including prolonged exertional dyspnea, chronic bronchitis, and emphysema.[131]

During the latent period following exposure, numerous therapeutic options exist that may prevent or lessen the severity of pulmonary edema. Early intervention with antioxidant (N-acetylcysteine) has been shown to be beneficial in animal models by reducing free radical species and preventing biologic mediator–induced inflammation.[129] Ibuprofen, aminophylline, and isoproterenol have all proved beneficial in animal models.[132] Corticosteroids are frequently used but are of unproven benefit.[130] There is no benefit from nebulized steroid when administered 1 hour after exposure, or methylprednisolone if administered intravenously $\geq$6 hours after exposure. Intravenous bolus of high-dose corticosteroid (e.g., methylprednisolone 1 g) may be considered if presentation is <6 hours, although no experimental data are available.[133] The experiments from animal models suggested nebulized furosemide for pulmonary edema should be avoided following phosgene exposure.[134] Nebulized salbutamol treatment following phosgene also is not recommended.[135]

■ Ozone

Ozone (O_3) is a colorless, odorless gas of low water solubility. It is found throughout the atmosphere and occurs in greatest concentrations in the stratosphere, where it is protective against ultraviolet radiation. It is the main oxidant pollutant in smog and can reach hazardous levels at ground levels on days with elevated atmospheric temperature. Atmospheric levels are known to aggravate chronic lung diseases such as asthma[136] and chronic obstructive pulmonary disease.[137] Acute toxic exposures are associated with its uses in industry, including bleaching of fabrics, disinfecting water and surfaces, and the manufacture of plastics. Reports of acute ozone exposure have been reported in an airplane cabin on a high-altitude flight.[138]

Ozone is extremely reactive, and is almost entirely consumed before crossing a single bilayer membrane.[139] It results in the formation of reactive nitrogen species[140,141] and probably causes toxicity via the oxidation of membrane lipids.[142] Pre-exposure to ozone resulted in enhanced airway hyperresponsiveness, increased concentrations of total protein and proinflammatory cytokines in whole-lung lavage, and reduced inflammatory cell recruitment to the lower airways. Molecular mechanisms include enhancement of LPS and LTA-mediated signaling in lung tissue.[143,144] Animal studies suggest age-dependent effects of ozone toxicity as well as TLR-4 mediated inflammation. The cytokine CXCL5 was consistently upregulated in mice exposed to ozone, and TLR-$4^{-/-}$ mice demonstrated attenuated ozone-induced neutrophil recruitment.[145] Studies in humans have shown that exposure to ambient levels of ozone can selectively impair epithelial permeability,[146] and that this loss of epithelial integrity is parallel to, but not necessarily coupled with, increased inflammation in the lower respiratory tract.[147,148] Ozone induces epithelial necrosis and airway inflammation[148] and in severe exposures can cause dyspnea, cyanosis, and pulmonary edema. A genetic component to the response to ozone through innate immune signaling has been reported.[149] Treatment is supportive and no specific therapies have been shown to be beneficial.

■ Cadmium

Cadmium is a highly corrosion-resistant metal with many industrial applications. Most cadmium is used in nickel-cadmium batteries, but it is also found in alkaline accumulators, electroplating, bearings, solder, and as a barrier around nuclear fission generators. It is present in many metal ores, and cadmium-containing pigments are used in paints, artists' colors, rubber, plastics, printing inks, wallpaper, leather, glass, and enamels. Most inhalations occur in workers who are involved with soldering, brazing, smelting, and refining.[150] The heating of sheet metal electroplated in a cadmium cyanide bath has been reported to cause cadmium toxicity.[151] It is also important to point out that cadmium can be found in cigarettes—the heavy metal naturally accumulates in the tobacco leaf, upwards of 1 to 2 μg per gram dry weight resulting in 0.5 to 1.0 μg per cigarette.[152] Therefore, smokers may be at an elevated risk for cadmium toxicity.

The mechanisms involved with the acute lung injury due to cadmium inhalation are not well defined. Some studies suggested that cadmium-induced alveolar cell apoptosis is mediated by FasL and caspase-dependent mitochondrial apoptosis pathways in animal models.[153] Decreased adhesion of molecular E-cadherin in epithelial cells of the alveoli and small bronchioles and of VE-cadherin in vascular endothelial cells were found in mice models post exposure to cadmium.[154] *In vitro* experiments demonstrated that human fibroblasts express proinflammatory cytokines (CXCL3, CXCL3, IL-8, and IL-6) after 7 μM cadmium exposure for 7 hours.[155] Postmortem examinations of individuals who died after accidental acute inhalation exposure have revealed tracheobronchitis, consolidated lungs, denuded bronchial epithelium, intra-alveolar hemorrhage, and the presence of macrophages in the alveolar spaces.[156] It is known that cadmium inhibits the synthesis of plasma α1-antitrypsin,[157] which may explain the correlation between cadmium exposure and the later development of emphysema.[158] Rats exposed to cadmium fumes and cadmium chloride aerosols develop pulmonary edema and on necropsy show increased numbers of alveolar type II cells.[150]

When cadmium-containing materials are heated, cadmium vapors and cadmium oxide fumes are released. Patients who are exposed initially present similarly to those with metal fume fever (see below): they are asymptomatic for several hours before developing fever, malaise, and myalgias.[150] These constitutional symptoms are often accompanied by, or shortly followed by, respiratory distress, including cough, chest tightness, and dyspnea. Cadmium may be detected in the urine if the identity of the toxin is uncertain.[159] Acute cadmium toxicity has been shown to cause interstitial pneumonitis,[160] and fatal cases have been remarkable for initial pneumonitis that relentlessly progresses to ARDS and eventual death from respiratory failure.[156] Management is supportive; there are no specific treatments for cadmium inhalation. Formoterol and ipratropium bromide have been shown to partially protect the lungs against inflammation by reducing neutrophilic infiltration in rats.[161]

■ Mercury

Although mercury is poorly soluble in distilled water, its solubility increases in contact with plasma or whole blood, as at the blood–air interface. Sources of mercury gas exposure are primarily industrial and include ore smelting, cement production, fur and felt hat manufacture, fossil fuel combustion, and gold extraction. Mercury is found within the silver amalgam used by dentists, and a number of exposures, including several with fatal outcomes, have occurred in the home during amateur attempts to extract precious metals from amalgams that also contain mercury.[162,163] There is literature to support reports of people developing acute lung injury after being exposed to spilled mercury from breaking a thermometer in the home setting.[164]

Like phosgene and cadmium, mercury vapor has little or no immediate upper airway or mucosal surface irritant effects, and as a result exposed individuals may inadvertently remain in an area where the harmful vapors are present. The fatal level of mercury vapor to humans is not known. An exposure to more than 1 to 2 mg/m^3 of elemental mercury vapor for a few hours causes acute chemical bronchiolitis and pneumonitis.[158] Typical clinical presentations include symptoms of cough, dyspnea, and respiratory distress that develop 12 to 24 hours post-exposure. These initial symptoms are sometimes accompanied by fever, nausea, vomiting, diarrhea, and a metallic taste in the mouth, similar to what is often experienced by individuals with metal fume fever and associated transient pneumonitis. In fact, mercury vapor inhalation can be mistaken for metal fume fever or influenza. Symptoms of mercury vapor inhalation do not, however, spontaneously resolve as with metal fume fever. Instead, the pneumonitis may progress to ARDS; death has been preceded in several reports by tension pneumothorax.[163,165] The toxicity of mercury vapors within the lung is thought to be due in part to the irritant effects of oxidized mercurous and mercuric ions[166] and to the disruption of enzyme systems containing sulfhydryl groups.[163] Mercury coagulates protein, blocks cellular metabolism of carbohydrates at the pyruvic oxidase level, and as a result produces a metabolic acidosis.[162] Lung pathology following acute exposure reveals pulmonary edema, capillary damage, and the desquamation and proliferation of airway epithelium followed by an obliteration of airspaces.[167] Early CT imaging in patients with acute mercury poisoning reveals ground-glass opacification, alveolar consolidation, and ill-defined nodules. These abnormalities were resolved in follow-up CT scans after 30 days of exposure.[168] Inhaled mercury vapor is absorbed rapidly into the blood, where it can achieve systemic toxicity; renal, hepatic, and nervous system pathology have been reported.[169,170] Patients surviving the acute injury typically experience resolution of their symptoms within a week following onset, but some have also progressed to develop interstitial fibrosis.[171,172] Mortality due to exposure may be increased in children.[173]

Blood levels of mercury may reflect acute uptake, and urine levels can monitor chronic stores. Treatment of mercury inhalation is supportive and addresses the acute lung injury. Mechanical ventilation, including positive pressure and high-frequency oscillating ventilation, may be beneficial in the treatment of mercury-induced ARDS.[173] Early vigorous administration of steroids can decrease the inflammation and delay or prevent the progression to severe interstitial pulmonary fibrosis in mildly affected patients.[174] Chelating agents, such as dimercaprol and D-penicillamine, are frequently used to increase the rate of mercury excretion after ingestion but have not been shown to affect the outcome of the acute lung injury.[163,174]

■ Zinc Chloride

Zinc chloride ($ZnCl_2$, or hexite) is odorless, a major ingredient of smoke bombs and smoke-generating devices and has been responsible for numerous toxic and fatal exposures.[175–178] The compound forms when zinc oxide is ignited with hexachloroethane. Toxic inhalations have occurred in settings in which individuals have inhaled smoke in confined spaces, in most instances without a functional protective breathing apparatus. The smoke effect tends to contribute to the duration of exposure by obscuring vision, sometimes resulting in directional disorientation and the inability to quickly escape the area of exposure.

When inhaled, zinc chloride is in particulate form with an average particle size of 0.1 μm, small enough to allow large amounts of it to penetrate through to the lower respiratory tract. After depositing on the airway and alveolar surfaces, zinc chloride reacts with water to form hydrochloric acid and zinc oxychloride. This directly causes irritation of exposed mucosal surfaces and is the probable mechanism behind the diffuse lung injury observed on exposure.[179] The irritation of the mucous membrane of the respiratory tract leads to symptoms that include burning sensation, coughing, wheezing, laryngitis, shortness of breath, headache, nausea, and vomiting.

Zinc chloride inhalation is commonly followed by tracheobronchitis and pneumonitis, reflecting the sites of particle deposition. Patients experience cough, dyspnea, and chest tightness followed by a period of relative stabilization before progressing to ARDS.[176–178] Chest imaging may be initially normal but can reveal pleural effusions, pneumomediastinum, and bilateral infiltrates consistent with pneumonitis. There is evidence that prominence of ground glass opacities observed on high-resolution CT imaging is predictive of both severity of exposure and length of hospital stay.[178]

A urine zinc level may confirm the diagnosis of zinc inhalation toxicity. There is evidence that measuring serum zinc levels may be of prognostic value for patients who have inhaled zinc chloride from smoke bombs.[180] Patients should be monitored for progression to ARDS and treated with supplemental oxygen and mechanical ventilation if indicated. The administration of high doses of N-acetylcysteine may accelerate systemic zinc clearance[181] and thereby spare some oxidant-induced lung injury, but this is unsupported by clinical experience.[176] Since zinc inhalation is locally deposited in the respiratory tract rather than in systemic zinc overdose, the effect of N-acetylcysteine is questionable.[181] Corticosteroid use is similarly controversial. The aim to reduce overwhelming inflammation by early administration of intravenous steroid was offset by the risk of ARDS in patients with sepsis.[182]

■ Mace and Tear Gas

"Tear gas" is actually not a gas, but rather, a compound of toxic chemical irritants collectively given the names chloroacetophenone (CN or "chemical mace"), *ortho*-chlorobenzylidene malononitrile (CS), and oleoresin capsicum (OC or "pepper spray"). All three agents are used by military and law enforcement agencies to control crowds and individuals because of the irritants' intense and immediate effects on mucus membranes and lacrimal glands. Exposure to any of them results in immediate rhinorrhea, mucositis, chemical conjunctivitis, and profuse lacrimation.[183,184] Immediate pulmonary effects include an intense burning sensation in the upper airways, reflex airway constriction, chest tightness, dyspnea, and cough. Exposure may also provoke nausea, headache, and photophobia. Delayed contact allergy, leukodermia, or exacerbation of pre-existing dermatitis also have been described in case reports.[185] Severity of response depends on the concentration of the agent used, the duration of exposure, and the presence or absence of ventilation and protective breathing apparatus.

The effects of tear gas are predominantly due to its upper airway irritant effects, and thus, lower airway injury and parenchymal disease are rarely observed. Auscultation of the chest is typically clear, and the chest radiograph is usually without abnormality. Case reports of severe pulmonary disease exist, describing pneumonitis, pulmonary edema, reactive airways dysfunction syndrome, and acute bronchospasm in an asthmatic.[186–189] These cases have in common prolonged periods of exposure with poor ventilation. A fatal hypersensitivity reaction to CS has been reported.[190]

Due to the possible secondary contamination of healthcare staff, the initial medical management of patients exposed to tear gases consists primarily of nonspecific chemical decontamination and symptomatic therapy.[191] The most immediate concern in the treatment of tear gas exposure is maintenance of a patent airway. Mucosal surfaces should be irrigated profusely, and suction may be useful in clearing the copious oral and nasal secretions that may compromise the airway. Humidified O_2 should be administered. Beta-agonists and ipratropium aerosols should be used in the presence of bronchospasm;[192,193] no benefit from corticosteroids has been observed. Patients with prolonged or intense exposure should be monitored carefully for evidence of progression to significant respiratory disease.

ELECTRONIC CIGARETTES AND VAPING

Electronic cigarettes are one of the fastest growing tobacco products used in America today. E-cigarettes entered the market in 2007 and offered an attractive alternative to the conventional cigarette, which generates combustion-dependent toxins and is known to cause lung cancer.[194] Since 2014, e-cigarettes have become the most popular tobacco product used among the youth population, with more than 3.6 million youth using vaping products, including 1 in 5 high school students.[195] Initially thought to be the safer alternative to traditional combustible cigarettes, an emerging epidemic that was recognized in 2019 has curbed expectations regarding the safety of e-cigarettes and vaping products.

E-cigarette or vaping product–associated lung injury (EVALI) is the official term coined by the CDC to describe the clinical syndrome that was first reported to involve an unusual cluster of cases in Wisconsin of young adults with nonspecific respiratory symptoms and abnormal radiologic findings, all of whom reported vaping use in their clinical history.[195] Thereafter, new clusters arose in Utah; by January of 2020, 2711 cases of EVALI had been reported across all 50 states.[196] Sixty-four deaths were confirmed by the CDC within this time period.[197]

Although e-cigarettes were initially developed for the consumption of nicotine, e-cigarettes or vaping products are also made to aerosolize tetrahydrocannabinol (THC), the psychoactive ingredient of marijuana. Vaping has become a popular way to consume THC among the youth population, especially males. More than 85% of e-cigarette users report using products for THC consumption.[198] In a large survey of 4631 participants who use vaping products, the prevalence of THC-based product use was greatest among respondents aged 18 to 24 years (36%) and decreased with age.[198] Retrospective studies of patients with EVALI show a higher odds ratio of exclusive use of THC-containing products. In a smaller study of 51 patients with a clinical diagnosis of EVALI, 47 had detectable THC from bronchoalveolar lavage or reported using THC-based devices.[199] These studies suggest that THC-based products are at least as dangerous for developing EVALI as nicotine-based devices.

The components of an electronic cigarette include a battery that powers a heating coil and an atomizer that transforms the e-liquid into an inhalable aerosol.[200] The aerosolized particles are on the order of nanoscale diameter ranging from 11 nm to 25 nm but may be as large as 96 nm to 175 nm.[201] The aerosolized particles are sufficiently small to reach the alveoli, where they can diffuse across the alveolar–capillary interface and enter the bloodstream.

The e-liquid typically contains high levels of nicotine, explaining the incredible addiction potential, as well as flavoring products and humectants. Propylene glycol and glycerol are ingredients added in the e-liquid to act as a vehicle to deliver the active ingredients in solution to the user. However, the additional components in the e-liquid are numerous. Tobacco-specific nitrosamines (TSNAs), aldehydes, metals, volatile organic compounds (VOCs), phenolic compounds, polycyclic aromatic hydrocarbons, flavorings, and tobacco alkaloids represent the potentially hazardous materials found in e-cigarettes that are capable of causing pulmonary disease.[200]

TSNAs are generated during the curing process of the tobacco plant and are known carcinogens.[202] Studies have utilized mass spectrometry to measure specific TSNAs, such as *N′*-nitrosonornicotine, and have reported low levels (60 μg/L) in e-cigarette products.[203] When the e-liquid is superheated, toxic carbonyl-containing compounds are produced, including formaldehyde and acetaldehyde, which have been shown to be carcinogens by the International Agency for Research on Cancer.[204] Other carbonyl-containing compounds, such as acrolein, can be produced and have been shown to cause nasal irritation and respiratory epithelial lung damage.[200] Volatile organic compounds include alcohols and phenols that can be a health hazard to the user.

Investigators have analyzed commercially available e-cigarettes and detected concentrations of benzene, methanol, and ethanol that exceeded their authorized maximum limits as residual solvents, as defined by pharmaceutical product guidelines.[205] Additional VOCs reported to be found in e-cigarettes include toluene, xylenes, and ethyl acetate.[205]

Heavy ionized metals are also found in the inhalable aerosols of e-cigarettes. Mass-spectrometry experiments using several brands of e-cigarettes revealed that cadmium, chromium, lead, manganese, and nickel are all present in e-liquids.[206] Additionally, metals from the heating coil such as aluminum, lead, nickel, cadmium, chromium, and tin can be liberated and aerosolized during inhalation.[207] It has been reported that urine and saliva samples can be collected for detection of nickel and chromium as noninvasive biomarkers of heavy metal toxicity from e-cigarette use.[208]

More than 7000 diverse e-liquid flavors are available for users, yet many sellers of e-cigarettes fail to include the flavoring ingredients on the package labels.[209] Flavorings are a popular modification to e-cigarettes that users report as being more enjoyable than traditional tobacco cigarettes.[210] Compounds such as saccharides can be added to the e-liquid to generate a sweet taste; however, when the saccharides are heated by the coil they may produce furans and carbonyl-containing aldehydes leading to respiratory epithelial damage.[211] Specific compounds such as diacetyl and acetoin are used in industry to make unique flavor variants such as butterscotch, caramel, and piña colada flavors. Volatile diacetyl compounds have previously been reported to cause bronchiolitis obliterans in a microwave-popcorn production plant.[212]

The exact compounds directly responsible for the EVALI epidemic that arose in 2019 are not completely clear. Clinical data analysis of bronchoaveloar gavage samples from people with EVALI revealed that vitamin E acetate (VEA), a compound commonly found in dietary supplements and skin creams, was detectable in 94% of patients with EVALI.[199] To determine if there is a causal link between VEA and EVALI, investigators developed a mouse model of VEA exposure in an aerosolized form. Compared with the control group, bronchoaveloar gavage samples from mice exposed to VEA for 2 weeks demonstrated increased albumin, suggesting epithelial damage, increased CD45$^+$ leukocyte abundance, and increased lipid-laden macrophages consistent with bronchoaveloar gavage samples taken from patients with EVALI.[197] These studies strengthen the argument that VEA may be a specific factor driving the development of EVALI, but it is likely that a combination of factors contribute to the clinical syndrome in its entirety.

The underlying pathogenesis of vaping-induced lung injury is incompletely understood. Several studies have identified mechanisms that are likely to be directly involved in respiratory tissue damage. Redox imbalance and inflammation have been consistently shown to be a mediator of lung damage attributed to e-cigarettes. *In vitro* studies exposing human airway epithelial cells to e-cigarette aerosols showed increased production of proinflammatory cytokines such as IL-6 and IL-8.[218] Mice exposed to aerosols from popular e-cigarette products demonstrated depleted lung-specific glutathione levels, which are critical for maintaining redox balance.[213] A separate study reported that free radicals are detected at upward of 7×10^{11} per puff.[219] Furthermore, mice exposed to e-cigarette aerosols for 2 weeks developed macrophage-mediated inflammation and markers of oxidative stress. The mice exposed to e-cigarette aerosols also demonstrated impaired bacterial clearance of intranasal infection using *Streptococcus pneumoniae* compared with mice breathing room air, suggesting that e-cigarettes can affect the immune system.[214]

Mitochondrial oxidative stress and direct DNA damage also are implicated in the pathogenesis of e-cigarette aerosols. Human lung fibroblasts exposed to e-cigarette aerosols containing copper nanoparticles demonstrated increased mitochondrial reactive oxygen species and subsequent instability of the electron transport chain protein complex IV, as well as fragmentation of genomic DNA.[215] While more studies are needed to fully delineate the pathogenesis of lung injury caused by e-cigarette aerosols, it is clear that inflammation, oxidative stress, and immune dysregulation are implicated in the cellular pathophysiology.

The clinical course of EVALI consistently involves shortness of breath, dry cough, chest tightness, pleuritic chest pain, and occasionally hemoptysis.[195,216] Gastrointestinal complaints are not uncommon—abdominal pain, nausea and vomiting, and diarrhea were described by 77% of patients from medical chart abstraction reviews completed by the CDC.[216] Constitutional symptoms, such as fever, chills, and weight loss, may be complaints described by patients with EVALI as well.

Radiologic findings typically show diffuse hazy infiltrates or areas of consolidation by chest radiograph.[195] CT imaging reveals a pattern consistent with acute lung injury and, possibly, organizing pneumonia (Fig. 90-5).[217]

Bronchoalveolar lavage typically demonstrates neutrophilic and eosinophilic infiltrates, but these findings can be nonspecific.[218] Biopsy specimens demonstrate peribronchiolar inflammation accompanied by foamy macrophages (Fig. 90-6).

EVALI is considered a diagnosis of exclusion. A careful patient history and thorough physical examination are critical to make the diagnosis of EVALI. Treatment of EVALI typically includes initiation of empiric antibiotics to cover for community-acquired pneumonia, which is much more common than EVALI. Corticosteroids, such as methylprednisolone, have been used to treat patients with EVALI, although the efficacy of this treatment has not been formally studied[218] and is not recommended.

SYSTEMIC ILLNESS FROM INHALED TOXINS

While most of this chapter has focused on local effects within the pulmonary system, systemic, flu-like illness has been observed in patients exposed to organic dusts and fumes of heated metals and fluorocarbons. The disease course is self-limited and, in all cases, appears to be cytokine-mediated.

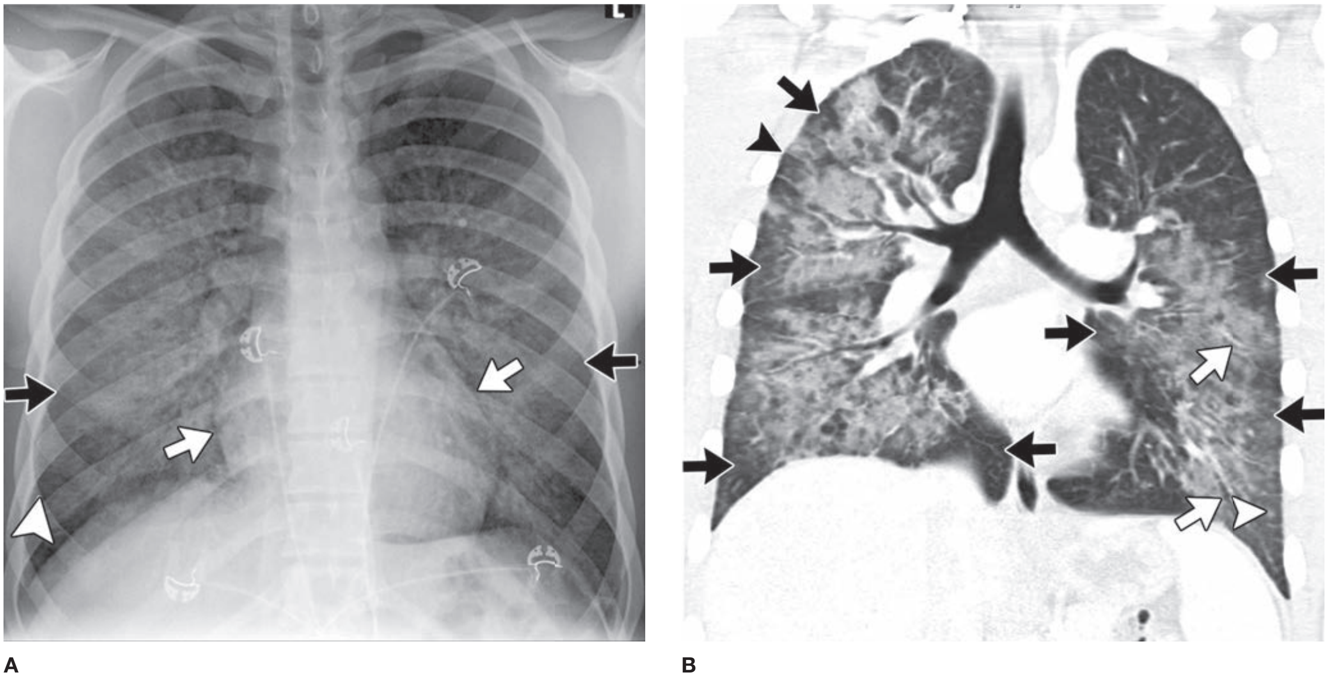

Figure 90-5 Radiologic images from an 18-year-old presenting with fever of 103°F and vomiting for 3 days. History notable for nicotine and tetrahydrocannabinol vaping. The findings demonstrate EVALI complicated by an organizing pneumonia pattern. **A.** Posteroanterior radiograph reveals perihilar hazy opacities with sparing of the heart border *(white arrows)* and periphery *(black arrows)*. Septal thickening is remarkable *(arrowhead)*. **B.** Corresponding CT image shows perihilar ground-glass opacities with prominent sparing of subpleural interstitium, both peripherally and centrally *(black arrows)* and intermixed areas of lobular sparing. There is also sparing of peribronchovascular interstitium *(white arrows)*. Septal thickening *(black arrowhead)* and scattered centrilobular nodules are present *(white arrowhead)*. Corticosteroid administration rapidly improved the patient's condition. *(Reproduced with permission from Kligerman S, Raptis C, Larsen B, et al. Radiologic, Pathologic, Clinical, and Physiologic Findings of Electronic Cigarette or Vaping Product Use-associated Lung Injury (EVALI): Evolving Knowledge and Remaining Questions. Radiology. 2020;294(3):491–505.)*

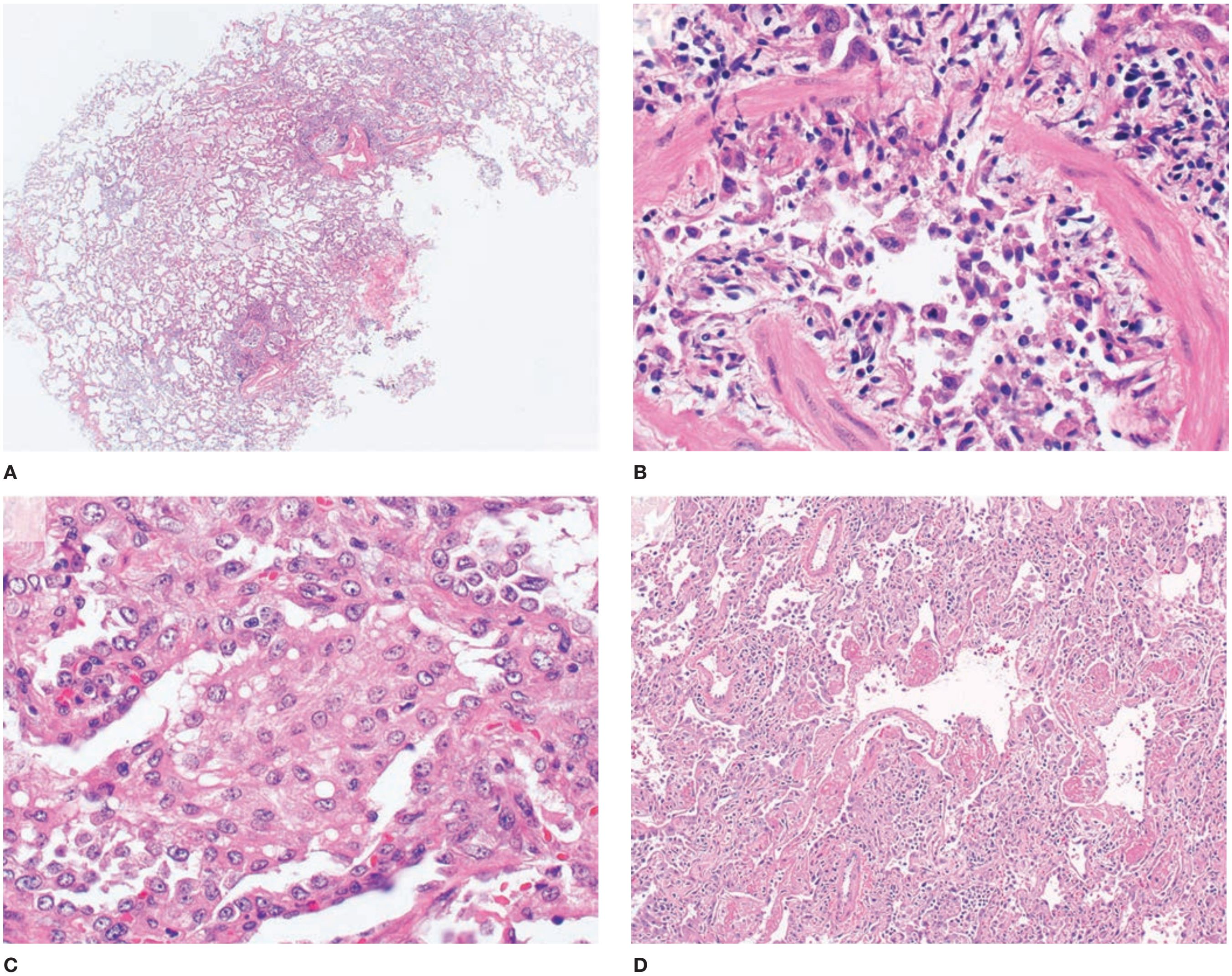

Figure 90-6 Representative biopsy specimen from a patient with EVALI. **A–B.** Cases predominantly show airway-centered acute lung injury co-presenting with severe bronchiolitis accompanied by mucosal edema, sloughing of bronchiolar epithelium, and peribronchiolar organization. **C.** All cases demonstrated foamy or vacuolated macrophage accumulation in peribronchiolar airspaces accompanied by pneumocyte vacuolization. **D.** In some instances, severe injury with diffuse alveolar damage and hyaline membranes is observed—a finding associated with a poor outcome. *(Reproduced with permission from Butt YM, Smith ML, Tazelaar HD, et al. Pathology of Vaping-Associated Lung Injury. N Engl J Med. 2019;381(18):1780–1781.)*

■ Metal Fume Fever

Since its first description by Potissier in 1822,[219] metal fume fever has been known by a number of other names: brazier's disease, spelter shakes, brass chills, zinc chills, welder's ague, copper fever, foundry fever, and Monday morning fever. It is a self-limited, flu-like syndrome characterized by the delayed onset of fever, chills, myalgias, and generalized malaise following exposure to fumes that contain metal oxides. Specific fumes that have been implicated include those of beryllium, cadmium, copper, magnesium, nickel, silver, and zinc. Metal fume fever is an occupational disease; welders are at the highest risk for developing metal fume fever, although it has been reported in other metalworking occupations including soldering, brazing, cutting, metallizing, forging, melting, and casting.[220] Episodes of varying severity of metal fume fever may be experienced by between 20% and 35% of all welders.[221,222] Exposure is typically associated with confined spaces and poor ventilation. It is estimated that 1500 to 2500 cases of metal fume fever occur each year in the United States.[220,223]

The typical course of metal fume fever begins with sensations of dry throat and a sweet or metallic taste. Fever, chills, and myalgias develop from 4 to 8 hours after exposure and spontaneously resolve within 48 hours. Respiratory-related symptoms of chest tightness, nonproductive cough, and dyspnea are sometimes observed. Laboratory findings are remarkable for transient leukocytosis; chest x-ray is typically normal, although findings consistent with pneumonitis have been observed. Pulmonary function tests are usually normal, but obstructive and restrictive deficits, as well as abnormalities of diffusion, have been reported.

Repeated exposure appears to lead to tachyphylaxis; however, this tolerance is transient and only persists through the work week. The name "Monday morning fever" refers to the recurrence of acute disease on return to exposure following a short period of absence.[224] A proposed mechanism of the observed tolerance to metal fumes involves the increased synthesis of the toxic metal-binding protein metallothionein in exposed patients.[225] The disease has been mistaken for influenza, atypical or community-acquired pneumonia, and a malaria-like illness because of overlapping presenting symptoms. The diagnosis is based primarily upon a history of exposure to metal oxide fumes. Metal fume fever is generally thought to have no long-term sequelae. An association between it and the later development of occupational asthma has been observed,[222] but a prospective study failed to show that a history of metal fume fever is predictive of later bronchial hyperresponsiveness.[226]

The pathogenesis of metal fume fever appears to involve an increase in proinflammatory cytokine activity in the lung; increased bronchoalveolar lavage fluid concentrations of tumor necrosis factor (TNF), interleukin 6 (IL-6), and IL-8 have been reported in subjects exposed to zinc oxide fumes,[227] probably produced by pulmonary macrophages.[228] Following exposure, bronchoalveolar lavage TNF-α levels peak earlier than other cytokines, suggesting that its role may be central to disease progression.[229] Of the numerous components of metal fumes, it appears to be the soluble transition metal particles, which generate reactive oxygen species and deplete glutathione stores, that are responsible for the fumes' cytotoxicity.[230] Recent studies used whole-blood assay (WBA) to more reliably understand the blood-immune response to metal fumes from a systems level. Using whole-blood samples, these results support earlier studies as they show dose-dependent increases in levels of IL-6, IL-8, TNF-α, and IL-1β after 24 hours of exposure to copper- and zinc-containing fumes.[231] These data support the hypothesis that metal fume fever is an acute systemic inflammatory reaction. *In vitro* studies show that inhibition of protein tyrosine phosphatase 1B (PTP1B) demonstrated enhanced increase in cytokine levels; PTP1B was identified as a pathway that can be attributed to the effects of zinc and copper welding fumes and therefore can explain some of the mechanisms underlying welding fume fever.[231] Gene expression profiling of lung injury following welding fume exposure in a monkey model has been reported to aid in understanding the inflammatory response of lung tissues.[232]

Treatment of metal fume fever is supportive, including bedrest, antipyretics, and analgesics. Metal fume fever must be distinguished from acute metal fume toxicity, as with cadmium or mercury, which can present similarly to metal fume fever but fails to resolve and instead progresses to respiratory distress. Prevention of metal fume fever involves provision of adequate ventilation, fume removal devices, and respiratory protection for workers in environments where metal oxide fumes are generated.

■ Polymer Fume Fever

A syndrome similar to but less common than metal fume fever, polymer fume fever was first reported in 1951.[233] Fluorocarbon polymers are a class of compounds that are commonly used as nonstick coatings on cooking equipment (polytetrafluoroethylene [PTFE, or Teflon] is a famous example) but are also used as mold-release sprays, lubricants, and fabric or leather treatments.[234] When fluorocarbon polymers are heated to greater than 300°C, fumes are produced that include carbonyl fluoride, perfluorinated alkanes, hydrofluoric acid, and carbon dioxide.[234] Extremely small particles capable of reaching alveolar units also may contribute to disease progression.[235]

Polymer fume fever presents similarly to metal fume fever: initial symptoms include dry throat, rhinitis, chest tightness, and conjunctivitis. Constitutional symptoms (fever, chills, myalgias) typically follow exposure by about 4 to 8 hours and spontaneously resolve within 1 day. As with metal fume fever, a leukocytosis is observed concurrent with the patient's constitutional symptoms. Individuals with preexisting obstructive lung disease may experience worsening obstruction after recurrent exposures to polymer fumes.[236] Notable differences between metal fume fever and polymer fume fever are important to consider. Pneumonitis is more frequently observed in polymer fume fever than with metal fume fever, perhaps due to release of hydrofluoric acid. Tachyphylaxis, a hallmark observation of metal fume fever, is not observed in polymer fume fever, suggesting that different mechanisms are responsible for the two diseases.[236] As with metal fume fever, the systemic response to particle inhalation appears to be cytokine-mediated.[237]

Although exposure to pyrolyzed fluoropolymers occurs mainly in industrial settings, it also occurs in homes and via less obvious means of exposure. In one report, within an hour of an empty PTFE-coated pan being heated on a stove, five exposed pet birds died and their owner contracted polymer fume fever.[238] A similar report from 2012 describes an individual who left a PTFE-coated pan on a stove for 5 h and, after noticing, quickly ran the pan under cool running water from the sink. This generated an explosive vapor of polymer fumes that was subsequently inhaled by the individual leading to constitutional symptoms hours later.[239] Numerous reports have suggested that workers with skin exposed to fluoropolymers may have contracted polymer-fume fever via smoking their self-contaminated tobacco.[240–242] Others may have contracted the disease via igniting their marijuana with cotton that had previously been impregnated with hairspray.[243] Several episodes of polymer fume fever have occurred following exposure via the waterproofing spray used on horse rugs.[244]

Treatment of polymer fume fever is supportive. Workers exposed to fluoropolymers should be provided adequate ventilation and instructed of the risk of indirect exposure via skin contamination. Strict handwashing should be required, and tobacco smoking should be especially discouraged after exposure.

■ Organic Dust Toxic Syndrome

The final systemic illness caused by inhalational exposure described here is organic dust toxic syndrome (ODTS), also known as silo unloader's syndrome, atypical farmer's lung, pulmonary mycotoxicosis, and toxic pneumonitis. As with metal fume fever and polymer fume fever, ODTS is a self-limited disease that presents with fever, chills, and myalgias several hours after exposure to the offending agent followed by spontaneous resolution within 48 hours.[245,246] However, underlying lung conditions may lead to incomplete or delayed recovery.[247]

Organic dusts are dissimilar from the fumes produced from extreme heating as seen in metal fume fever and polymer fume fever. Rather, organic dusts describe biomaterials found in agricultural settings and include hay or corn silage-containing silos, molds, spoiled animal feed, and swine confinement facilities. Agricultural workers are at the highest risk for contracting ODTS. Other settings of ODTS have included a college fraternity party in which hay was laid on the floor;[248] a storehouse containing moldy oranges;[249] a waste-sorting plant;[250] a print shop in which an air humidifier was colonized with Gram-negative bacteria, fungi, and amoebae;[251] following exposure to woodchip mulch;[252] and previously asymptomatic seafood factory workers who were exposed to shrimp shell powder containing bacterial endotoxin.[253] Lifetime risk of contracting ODTS may be around 19% for farmers with exposure to organic dust.[254]

The specific agent or agents within organic dust responsible for ODTS have not been fully characterized. An epidemiologic study in 2007 suggested contaminated mulch was implicated as the source of presumed ODTS among urban landscape workers, highlighting that ODTS is not limited to rural agricultural settings.[255] Bacterial cell wall components, endotoxin, and peptidoglycan are thought to play prominent roles.[256,257] Specifically, the polysaccharide component of the bacterial cell wall β-glucan has been demonstrated to induce Th1- and Th2-driven immune responses and may be implicated as a central antigen in ODTS.[258] Workers handling grass, cereal, or vegetable seeds are at risk of exposure to high levels of endotoxin-containing seed dust.[259] Fungal spores and *Actinomyces* also are likely contributors to pathogenicity,[260] and an ODTS-like response can be provoked with endotoxin-free grain extracts.[261] Like metal fume fever and polymer fume fever, the disease process is likely initiated or provoked by activation of the patient's innate immune system by organic dust components, such as endotoxin's activation of TLR-4. Cytokine expression increases following organic dust exposure, especially of proinflammatory cytokines such as TNF-α and IL-6,[262] suggesting a means by which local activation of innate immunity may provoke the observed systemic manifestations. IL-1 also is thought to play a critical role in ODTS development.[263] An intriguing correlation has been observed between patients with celiac disease and the development of ODTS,[264] suggesting that some underlying disorder, perhaps a hyperactivity of innate immunity, may increase a patient's susceptibility to both.

Patients with ODTS frequently present with no findings on chest exam, although bibasilar crackles and scattered wheezes may be appreciated. A neutrophil-predominant leukocytosis is frequently found, and mild hypoxemia and bilateral infiltrates on chest x-ray have been reported. Although bronchoalveolar lavage may initially reveal a predominance of neutrophils, a lymphocytic response may come to dominate the cellular population.[246]

ODTS needs to be clinically distinguished from hypersensitivity pneumonitis (HP), which is also provoked by inhaled organic dust. HP typically follows low levels of exposure after a period of sensitization, while ODTS is an acute reaction to high levels of organic dust, potentially on first exposure. HP is a restrictive process detectable by pulmonary function testing, while ODTS sometimes presents with transient airflow obstruction and often with no appreciable functional abnormality. The early bronchoalveolar gavage findings in ODTS are overwhelmingly neutrophilic, unlike the lymphocytic findings in HP.

Treatment of ODTS is supportive. Unlike with HP, corticosteroids appear to be of only marginal benefit in the treatment of ODTS.[265]

SUMMARY

Toxic inhalations can arise from numerous agents and produce a broad spectrum of pulmonary and systemic injuries. Treatment is largely supportive and should be guided by the patient's clinical status. Specific attention should be paid to the patency of the airway following acute upper airway exposures, and providers should be aware of the risk of the development of severe pulmonary disease following an asymptomatic latent period. Given the unpredictable clinical course of these exposures, a good exposure history should be taken, and cautious monitoring of exposed patients is prudent. Materials safety data sheets and the National Library of Medicine's TOXNET (*www.nlm.nih.gov/toxnet/*) are excellent information resources for specific toxins.

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CHAPTER 91

High-Altitude Physiology and Clinical Disorders

Kingman P. Strohl
Cynthia M. Beall
Nikolaus C. Netzer

INTRODUCTION

Altitude is an environmental state of elevation >760 m (~2500 ft) above sea level and is a continuous physiologic stressor of hypobaric hypoxia (Fig. 91-1). Altitudes are subdivided into very high (3500–5500 m or ~11,500–18,000 ft) and extreme (>5500 m or >18,000 ft). Eighty million people live at altitude around the world, and 40 million people per year travel to an altitude ≥2500 m (~8000 ft).[1] Many more work in mines, the military, or border operations at high altitude. Clinical encounters specific to altitude result from hypoxemia (FIO_2 equivalent to ~17% O_2 at 2500 m, and ~8% O_2 at the summit of Everest), which leads to physiologic responses and illnesses. Such illnesses have been recognized and empirically treated in prehistoric native populations.[2] Birthweights are generally lower, and the rates of small-for-gestational-age babies and congenital heart defects are higher than in lowland populations.[3] With a hurried ascent, ~80% of lowlanders will report a transient headache (high-altitude headache [HAH]), and some will develop an acute high-altitude illness: acute mountain sickness (AMS). Fewer will develop high-altitude cerebral edema (HACE) and high-altitude pulmonary edema (HAPE).[3,4] HAH and AMS are annoying and interfere with activity and work; however, HACE and HAPE can be fatal, with mortality rates approaching 30%.[5–7] Some residents at altitude exhibit chronic mountain sickness (CMS) and right ventricular hypertrophy, developing over months to years of residence at altitude. Cold air and extreme exercise also may contribute to illness. Other environmental features may include UV radiation, trauma, and infections (which are not covered in this chapter). Finally, managing illness in a remote altitude location can be challenging, as evacuation to a lower altitude as a primary treatment may be limited or not feasible.

CONSIDERATIONS OF EXPOSURE AND TIME COURSE

Individual responses to low-barometric-pressure hypoxia may be conceptualized along a time continuum of interrelated phases: acute (immediate to 3–5 days in which acute illnesses present), subacute (over weeks leading toward acclimatization), chronic (years), and lifelong residence (Fig. 91-2). The reduction in environmental oxygen as result of altitude exposure lowers the oxygen available for gas exchange in the lungs (PA_{O_2}), arterial oxygen (Pa_{O_2}), and cellular oxidative phosphorylation for adenosine triphosphate (ATP) production.

Single-cell and multicellular organisms have been exposed to oxygen since the origins of life; over the past 600 million years, oxygen levels have varied from as low as ~12% to as high as ~30%.[8,9] All multicellular organisms have genetically encoded oxygen homeostasis pathways—that is, there are interacting feedback controls of cellular and organ system adaptations to oxygen availability and need. Archaic responses to hypoxia appeared several billion years ago, and elements continued, some with adaptations, to contribute to physiology and altitude fitness in modern living organisms, as well as the human ancestral tree. People moved to live at high altitudes in the past 100,000 years, and in three continents evolutionary forces have resulted in different patterns of adaptation in different indigenous populations.[10,11]

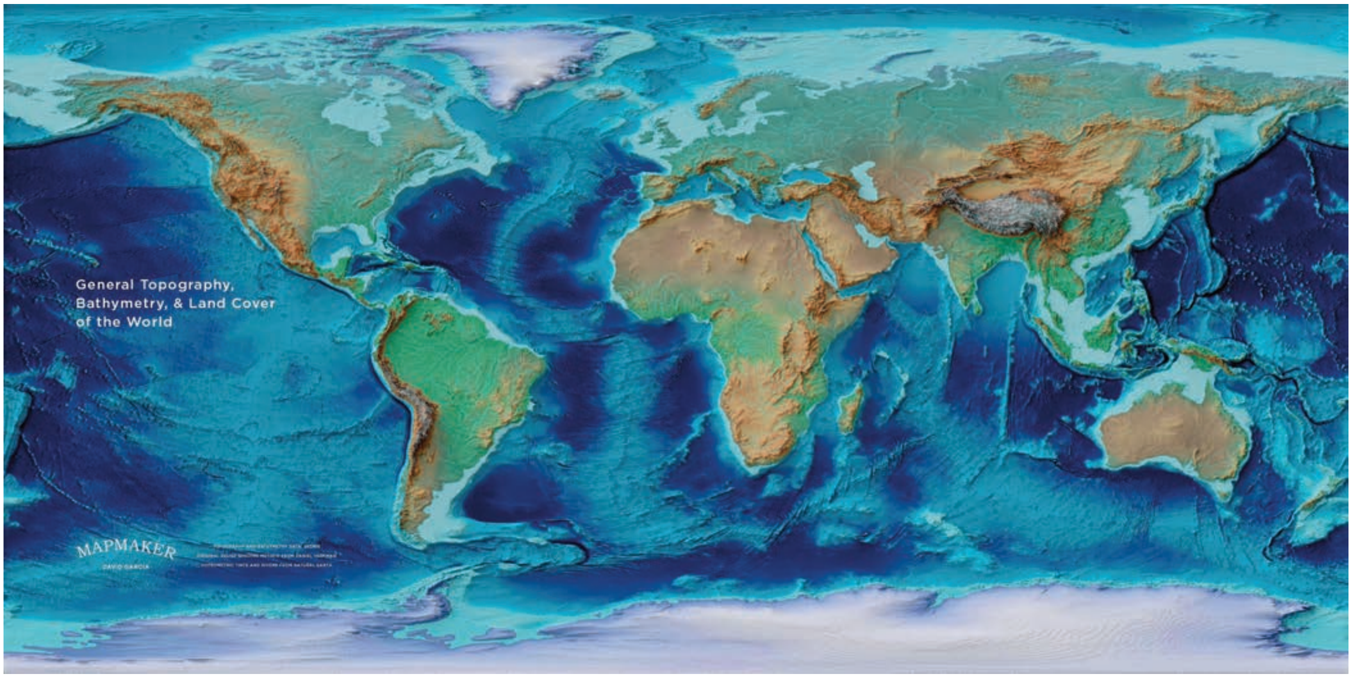

Figure 91-1 Land topography of the surface of the Earth. *(This topographic map is made from data collected from three sources: NASA's Space Shuttle, Canada's Radarsat satellite, and topographic maps made by the U.S. Geological Survey (NASA Earth Observations). Available at neo.sci.gsfc.nasa.gov/view.php?datasetId=SRTM_RAMP2_TOPO.)*

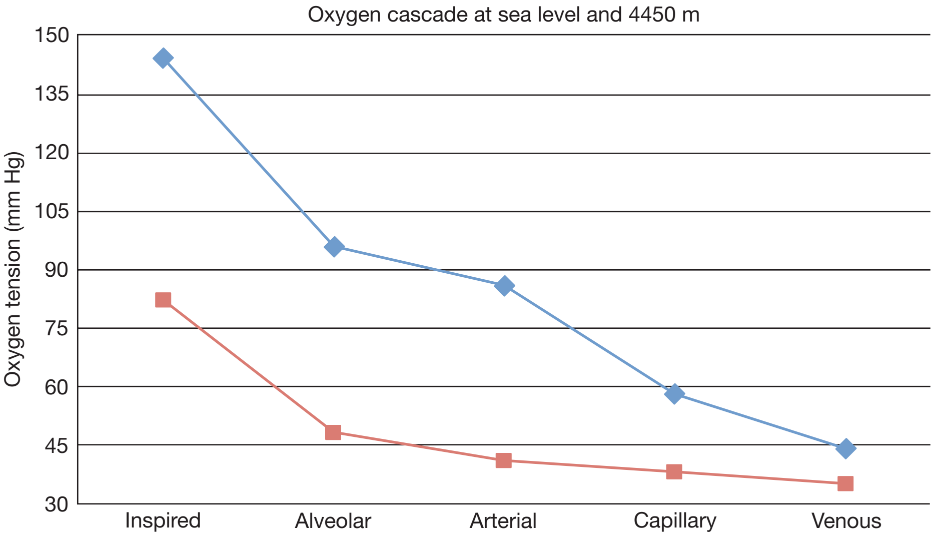

Figure 91-2 Oxygen tension is lower along the axis of oxygen delivery at 4540 m or ~15,000 ft *(red)* compared with sea level *(blue)*.

■ Responses to Hypobaric Hypoxia

The physiologic responses to hypobaric hypoxia involve adaptations in many organ systems, as discussed below.

■ Ventilatory Adaptations

An increase in ventilation is an immediate, vital, mammalian response. It results in a decrease in alveolar CO_2 in order to increase PA_{O_2}, thus mitigating decreases in vascular oxygen delivery at altitude compared with sea level (Fig. 91-2).

The sensor initiating the acute response is the carotid body, located at the bifurcation of the internal and external carotid arteries. Ablation of the carotid body attenuates the acute response to altitude exposure.[12] Blood flowing through the carotid body comes from the lungs via the carotid artery, where the oxygen pressure is typically 80 to 100 mm Hg. Carotid body afferent activity rises significantly as arterial oxygen pressure falls below 60 mm Hg.[12] However, oxygen pressure in the mitochondria is much lower, as oxygen has to diffuse across vessels and interstitial spaces and is extracted by cells for a number of metabolic processes.

In the microvessels of the carotid body, the average oxygen pressure is about 50 mm Hg with minimal values likely near 20 mm Hg. It is reasonable to expect an average mitochondrial oxygen pressure of about 40 mm Hg and a minimum of about 15 mm Hg. Although these values may seem low, in the liver and spleen average tissue values are measured at <12 to 15 mm Hg.[13] Thus, interstitial tissue in the carotid body may be exposed to a lower oxygen pressure than arterial oxygen pressure, which is typically about 80 mm Hg (Fig. 91-3).

The oxygen level is a major driver of carotid body response. Respiration is stimulated by decreasing the [ATP]/[ADP][Pi] ratio; as a result, the rate of respiration does not decrease until oxygen saturation is severe enough (~40 mm Hg) to produce central hypoxic depression leading to gasping, cardiorespiratory failure, and death.[13] At a cellular metabolic level, a sublethal decrease in availability of oxygen first affects the ability of mitochondria to maintain the ratio of [ATP]/[ADP][Pi], which is a measure of energy available when ATP is hydrolyzed to adenosine diphosphate (ADP) and inorganic phosphate (Pi). Mitochondrial ATP synthesis is tightly coupled to oxygen consumption—that is, mitochondria respire only fast enough to replenish ATP as it is used. However, other responses to lowered oxygen levels are engaged depending on the duration and severity of the oxygen deprivation. A slow downward trend in oxygen triggers a fall in cellular and organismal oxygen consumption, and cellular oxygen-sensor responses activate short- and long-term energy savings and cellular protection mechanisms.[14]

A remodeling of ventilatory control begins soon after acute exposure through changes in gene expression. In blood vessels, growth factors such as vascular endothelial growth factor (VEGF) are produced (Fig. 91-4). The exemplary pathway for such responses is mediated by the hypoxia-inducible transcription factor 1 alpha (HIF-1α). HIF-1α is the oxygen-dependent subunit of the HIF-1 heterodimer, considered the master regulator of oxygen homeostasis that initiates transcription of more than 100 hypoxia-inducible genes that have hypoxia-response elements.[15,16] Under normoxia, HIF-1α is formed continuously and degraded in the cytoplasm. HIF-1α is hydroxylated by enzyme prolyl hydroxylases (PHDs) prior to its degradation. The prolyl hydroxylases have a relatively high Km for oxygen; hydroxylation leads to degradation under physiologic conditions. Decreased oxygen pressure results in significant accumulation of HIF-1α in less than 2 min; HIF-1α is rapidly degraded upon reoxygenation.

Central controllers of ventilatory neuromuscular output can be affected directly and indirectly by oxygen availability, but over time, neurotransmitter expression correlates with changes in gain and changes in gene expression, with some additive epigenetic changes.[17] Within days of exposure there is a progressive increase in sensitivity, but there is a downregulation of the magnitude of the ventilatory response by the brainstem networks that integrate afferent information.[18] At 4300 m, hyperventilation increases over the first few days and then over 1 to 2 weeks despite metabolic compensation to the respiratory alkalosis.[19] The acclimatized person continues to hyperventilate when he or she returns to normoxia, a phenomenon not observed during the very first hour of hypoxic exposure. The ventilatory response to chronic hypoxia consists of both respiratory frequency and tidal volume changes. Acclimatized individuals return to nearly normal arterial acid–base status within 24 to 48 h of normoxia following acclimatization to 4300 m.

Hence, a transition occurs from acute to subacute to full acclimatization in the ventilatory domain.[20] Acclimatization is the

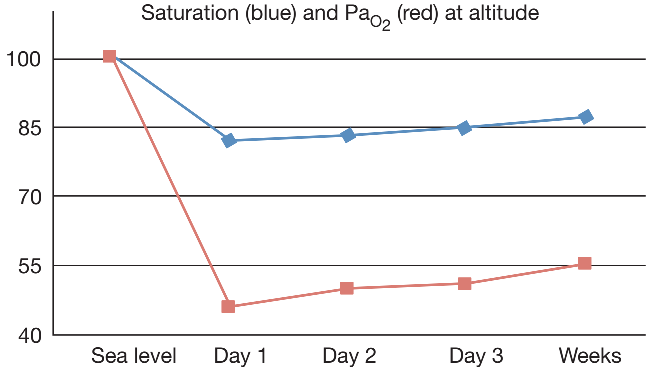

Figure 91-3 The figure illustrates the problem with hypoxemia encountered with acute altitude exposure. Values of arterial oxygen saturation *(blue)* and arterial oxygen tension (Pa_{o_2}, *red*) before, during the first few days at altitude, and after weeks of residence.

physiologic response at cellular and system levels that acts to improve oxygen delivery. Ventilatory responses are complemented by hematologic, cardiovascular, and systemic adaptations. Erythrocytosis and the formation of new blood vessels occurs, reducing the diffusion distance to further assist in increasing oxygen delivery to peripheral tissues. HIF-1α is considered the starting point for activation of "hypoxic response elements" with downstream effects on classic proteins, including erythropoietin.[21] Some actions of erythropoietin result in increases in hemoglobin levels, thereby affecting oxygen-carrying capacity in the blood, an effect that lasts weeks to months. People with a mutation limiting HIF1 degradation have high baseline ventilation and an exaggerated ventilatory response to hypoxia, as well as chronic polycythemia.[22]

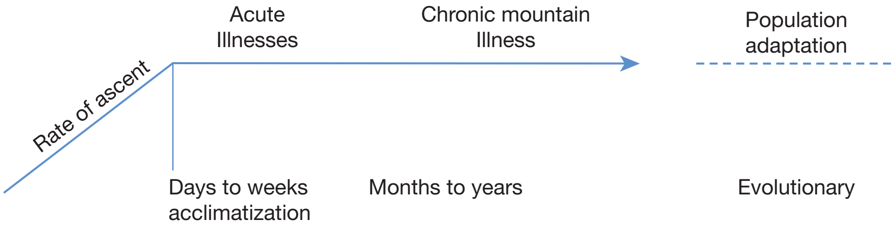

Figure 91-4 Individuals respond to altitude with time-dependent acclimatization and illness expression, and populations living at altitude exhibit adaptations that differ according to population ancestry.

■ Sleep and Periodic Breathing

Healthy persons at altitude experience patterns of regularly recurring periods of hyperpnea and apnea. This phenomenon results from a dynamic interaction among elements in two separate feedback loops—one through peripheral, and another through central, chemoreceptor reflexes, including contributions from changes in cardiac output and brain blood flow.[23] Periodic breathing occurs during wakefulness but is especially evident in sleep, and apneas and hypopnea of the nonobstructive type are reported as occurring almost equally in non-REM and REM sleep in healthy subjects.[24]

Recurrent central apneas occur during sleep at modest altitude (>2000 m) and are a manifestation of increased alveolar ventilation (hyperpnea) from hypoxia producing hypocapnia, and competing with a normal elevation in the apneic (carbon dioxide) threshold during sleep.[25] With increasing altitude, the number of apneic events increases, and hypopneas are often replaced by apneas in healthy individuals.[26] Apneas or hypopneas produce a fall in arterial oxygen and a rise in carbon dioxide that lead to sleep arousals during the hyperpneic phase.[27] The alternating hyperpneas and apneas produce an oscillatory pattern of oxygen saturation, with the nadir of oxygen saturation playing some role in susceptibility to HAPE and HACE.[28]

At altitudes above 3000 m, the quality of both REM and non-REM sleep is impaired by arousals often associated with periodic breathing;[29] at extreme altitude (above 5500 m), the length and number of apneas decrease due to a high frequency of breathing. The reason for this phenomenon may represent a greater relative influence of central oxygen-chemosensitive sites over afferent information than peripheral hypoxia and hypocapnia.[30,31] Fractured and arousal-impaired sleep at altitude may have an effect on cognitive function.[32] With acclimatization, the sleep pattern tends to become more normal; however, periodic breathing during non-REM sleep may persist over a week or more.[28]

■ Pulmonary Circulation

Moderate or severe pulmonary hypertension (both systolic and diastolic) are common in all altitude-related diseases.[3] Although pulmonary blood vessels are extensively supplied with sympathetic (vasoconstrictor) fibers and parasympathetic (vasodilator) fibers, regulation of vasomotor tone is largely due to the local effects of oxygen and carbon dioxide. At altitude, the entire lung is hypoxic and CO_2 levels are low as a consequence of hyperventilation. Indeed, altitude is a model of whole-lung hypoxic, hypocapnic, pulmonary vascular vasoconstrictive responses.[3] Acute vasoconstriction over a few hours is a physiologic response and can be reversed as soon as the hypoxia is reversed. With days to weeks of hypoxic exposure there occur a structural remodeling of pulmonary arterioles and an increase in resting pulmonary arterial pressure and pulmonary vascular resistance; hence pulmonary artery pressure does not decline immediately with restoration of normoxia. With return to sea level after weeks to months, right ventricular hypertrophy and pulmonary vascular pressures return to normal over several weeks.[3]

Andean highlanders have high pulmonary artery pressures and do experience restoration of pulmonary artery pressure or right ventricular hypertrophy to normal levels after inspired oxygen levels are reestablished to normal. In contrast, in a small study, Tibetan highlanders had a minimal elevation of pulmonary artery pressure and did not exhibit the vascular changes seen in the Andean highlanders.[33]

The pulmonary circulation is a high-flow, low-pressure system.[34] Based upon a balance of hydrostatic and oncotic pressure gradients across pulmonary capillary microvessels, and through the action of sodium ion pumps, the pulmonary interstitium and alveolar spaces are maintained in a "dry" state. At high altitude, while respiratory mechanics do not change appreciably, changes in hemodynamics due to vasoconstriction, high shear stress, and vascular injury in certain individuals lead to acute presentations of pulmonary edema.[3,35]

■ Fluid Homeostasis

Dermal edema is seen in the faces of many, but not all, mountaineers at high altitude,[36] and in the retinal vessels of almost all individuals.[37] Lung edema, cerebral edema, and peripheral edema are the hallmarks of disease. Extravasation also may result from loss of tight channels due to oxidative stress and free radicals, or as a direct effect of hypoxia on ion channels.[38] Local dysregulation of the renin-angiotensin-aldosterone system is proposed to play a role in this generalized response.[39,40]

■ Erythropoiesis and Hemoglobin Affinity for Oxygen

An increase in the number of red blood cells occurs with acute altitude exposure owing to an increase in EPO synthesis in response to HIF.[41] This acclimatization response takes between 1 and 3 weeks and is reversible upon return to low altitudes as the "excess" red blood cells die. With chronic hypoxia, increases in the number of erythrocytes and in oxygen content are seen among upward migrants, such as Colorado residents, and among Andean highlanders. Tibetan highlanders have minimal or no erythrocytosis due to the high frequencies of variants in EPAS1 (HIF-2α) associated with a lower hemoglobin concentration.[42–44]

Several studies have assessed the potential for a change in oxygen affinity with altitude. The increase in ventilation with ascent results in decreases in alveolar and arterial PCO_2 and arterial [H^+]; concomitantly, serum levels of 2,3-diphosphoglycerate (2,3-DPG) are increased. While the reductions in Pa_{CO_2} and [H^+] increase hemoglobin affinity for O_2, increases in 2,3-DPG diminish the affinity; loading and unloading of O_2 from hemoglobin depends upon the balance of these factors.[45] Humans native to the Andes or Himalayan mountains may also demonstrate increased O_2 affinity, not because of a fundamental difference in hemoglobin structure or function, but because of extreme hyperventilation and alkalosis; whether this is categorically true has been questioned.[46]

Exercise Physiology and Training

Hypoxic exposure has an been an intriguing subject in studies of physiology of cardiovascular performance and athletic training. The 1968 Mexico City Olympics, which were conducted at 2240 m, highlighted interest in this line of research. On one hand, hypoxia at sea level is known to reduce maximal exercise capacity by reducing oxygen availability;[47] however, exposure to altitude results in an increased red blood cell mass and, therefore, enhances oxygen delivery.

Hemoglobin mass in endurance athletes is not influenced by sea-level training, but it is possible to increase hemoglobin mass temporarily by 5% to 6%, provided that the athlete spends >400 h at altitudes above 2300 to 2500 m. However, this effect size is smaller than the reported 10% to 14% higher hemoglobin values of endurance athletes living permanently at 2600 m.[48] The phrases "train low and sleep high" and "train high and sleep low" both capture the extremes of the conceptual approaches.[49] There are rational effects of different training models currently employed; however, athletes who train high, like others who go to altitude, are susceptible to acclimatization illnesses, weight loss, immune suppression, and sleep disturbances that, if not managed correctly, are likely to limit athletic performance.[50]

In comparisons among exposures, a 3- or 4-week training camp at altitude may initially reduce performance, but after a period of recovery at sea level results in improved performance, even in elite swimmers. Living high and training both high and low for the same period improves swimming performance above and beyond that achieved at altitude and sea level.[51] Studies do not explain the mechanisms involved in training and living at altitude living versus sea level.

Echocardiographic studies have shown evidence for right ventricular dysfunction and pulmonary hypertension, but no change in left ventricular ejection fraction in training at altitude. Approximately 10% of athletes are susceptible to pulmonary hypertension and high-altitude pulmonary edema.[52] Intermittent training could produce repeated, transient episodes of pulmonary hypertension and right ventricular dysfunction, and the long-term effects are not known. Performance athletes are not at higher risk for ventricular arrhythmias when training or competing at increased altitudes, but persons with preexisting cardia arrhythmia are.[53] At the present time, the "live high, train low" approach appears to have the most traction.[52]

COMMON CLINICAL DISORDERS OF HIGH ALTITUDE

Altitude-related clinical disorders are well recognized. They may be observed occasionally at altitudes as low as 8000 feet (2500 m); however, their frequency increases with increasing altitude. A clinical practice review is available from the Medical Commission of International Mountaineering and Climbing Federation (UIAA).[54] Information about high-altitude travel for those with pulmonary disease also is available.[55]

High-Altitude Headache (HAH)

HAH is very common and is exacerbated by insufficient hydration in the setting of increased water loss with hyperventilation, overexertion, and insufficient energy intake, particularly in those who have experienced HAH on a previous visit to altitude. Vasodilation from hypocapnia also may contribute, but there is little evidence for brain edema in those without neurologic symptoms.[56,57] Acetaminophen or ibuprofen and hydration improve symptoms.[58,59]

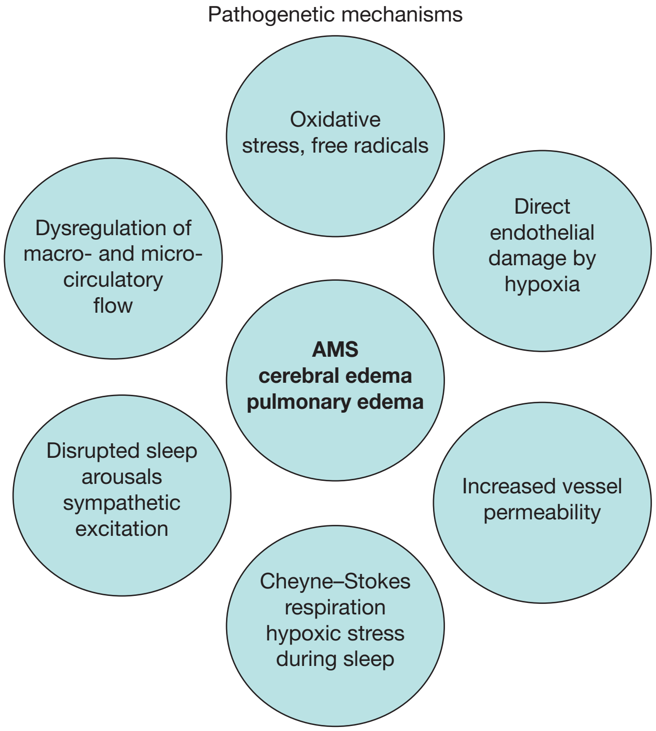
Pathogenetic mechanisms
Oxidative stress, free radicals
Direct endothelial damage by hypoxia
Dysregulation of macro- and micro-circulatory flow
AMS cerebral edema pulmonary edema
Disrupted sleep arousals sympathetic excitation
Increased vessel permeability
Cheyne–Stokes respiration hypoxic stress during sleep

Figure 91-5 There is evidence for several mechanisms for AMS, HACE, and HAPE.

Acute Mountain Sickness (AMS)

AMS occurs after 4 to 36 h of altitude exposure. Symptoms include headache (usually frontal), nausea, vomiting, irritability, malaise, insomnia, and poor climbing performance. Symptoms frequently occur initially, or are more severe, the morning after the first night at altitude. Sleep-disordered breathing contributes to the severity of AMS in the morning after the first night at high altitude.[60] AMS is usually self-limited but can be ameliorated by drug therapy (see below).

Many mechanisms have been proposed (Fig. 91-5). Studies target one or another potentially identifiable marker or therapeutic pathway, but few experts believe that only one factor produces one or more of the illnesses.

Incidence

The incidence of AMS is altitude- and time-dependent[61] and is approximately 30% on same-day, several-hour car trips to the Hawaiian or Colorado mountains (3000–4300 m).[7,62] It occurs in 10% of those at 2500 m and 51% at 4500 to 5000 m on multiday trips.[7] A survey of alpine walkers at overnight huts noted an incidence of 9% at 2850 m, 13% at 3050 m, 34% at 3650 m, and 53% at 4559 m.[63] Among trekkers en route to an Everest base camp, the incidence was 43% at 4300 m and was higher in those who had flown into an airstrip at 2800 m (49%) than those who had walked all the way (31%).[64]

The Lake Louise Symptom Score Questionnaire (Table 91-1) is the most common and useful self-administered tool to determine the severity of AMS and provides a score for the five signature symptoms, rating them from 1 (mild) to 4 (severe). A score of 4 and more is considered AMS; a score of 10 and more is considered severe and requires immediate intervention. The Lake Louise Score has recently been revised and excludes in its newest version symptoms of sleeplessness.[65] Copies should be included as equipment of any trekking group to high altitude.[66] Confounders affect such scoring systems; for instance, a hangover will give a positive AMS score even at sea level. Thus, there is a need for context and allowance for

TABLE 91-1 Lake Louise Symptom Score Self-report Questionnaire

Fill out before and each morning upon exposure to altitude or on a trek.

Symptoms	Severity	Points
Headache	• None at all	0
	• Mild headache	1
	• Moderate headache	2
	• Severe headache, incapacitating	3
Gastrointestinal	• Good appetite	0
	• Poor appetite or nausea	1
	• Moderate nausea or vomiting	2
	• Severe nausea or vomiting, incapacitating	3
Fatigue and/or weakness	• Not tired or weak	0
	• Mild fatigue/weakness	1
	• Moderate fatigue/weakness	2
	• Severe fatigue/weakness, incapacitating	3
Dizziness/ lightheadedness	• Not dizzy/lightheaded	0
	• Mild dizziness/lightheadedness	1
		2
		3

Add the responses to each question. A diagnosis of AMS is based on a recent rise in altitude, the presence of a headache with the presence of at least 1 other symptom, and a total score of ≥3 with no evidence for other reason of symptoms.

confounding factors. On the other hand, day-trippers, trekkers, and physicians unaware of the high prevalence of AMS may erroneously assign symptoms and signs to viral illness, food intolerance, poor sleep, intense exercise, or jet lag.

Risk Factors

For novices, the altitude and speed of ascent on a previous trip should be considered, as rapid ascent to altitude appears to affect everybody.[3,66] Women may be less likely to get AMS than men,[67] and there are hints that teenagers and young adults have a higher incidence of AMS as they try to get there first and fastest.[68] Other clinical features reported in the literature include history of migraine, persistence of a patent foramen ovale, Down syndrome, congenital pulmonary abnormalities, perinatal pulmonary vascular insult, and Holmes-Addie syndrome, a rare disorder of autonomic control.[69] Exercise, or at least intense physical effort, does not by itself increase AMS; however, the symptoms of gastrointestinal discomfort are associated with exercise intensity.[70]

Response to challenge with hypoxia improves risk assessment, but it is not routine.[71] A recent report on a fairly large cohort found that factors independently associated with severe high-altitude illness included (1) a previous history of acute illness, (2) ascent greater than 400 m/day, (3) history of migraine, (4) ventilatory response to hypoxia at exercise less than 0.78 L/min, and (5) desaturation at exercise in hypoxia ≥22%.[72] Chemosensitivity parameters (high desaturation and low ventilatory response to hypoxia at exercise) improved discrimination in this prediction model.

While AMS is an environmentally mediated disorder, there are individual differences in risk. The concept is that AMS is a polygenic disorder in which genotype contributes to one's capacity to rapidly and efficiently acclimatize to altitude.[73]

Prevention

Common medical disorders like diabetes, hypertension, mild COPD, hyperlipidemia, mild coronary artery disease, and renal insufficiency are generally not reasons to cancel a trip to high altitude if the same preventive and treatment measures are taken during the travel as they are at home and the traveler is aware of his or her symptoms and how they might change during the trip.[54] Exercise-induced asthma can be anticipated at altitude due to increased ventilation (increased heat exchange), but susceptibility to severe asthma should give one pause in suggesting pleasure trekking, in part because of the lack of medical facilities.[74] Known disease of more than mild severity (COPD, sleep apnea, heart failure, etc.) may be a relative contraindication for travel for pleasure,[55] although there are reports of the successful use of supplemental oxygen for these disorders during ascent. The arterial hypoxemia at high altitude poses a risk of faster disease progression in those with pre-existing kidney disease. An inability to diurese increases the risk of developing acute altitude illness in patients with chronic kidney disease.[75]

Drug interactions require consideration.[58] Acetazolamide is the most widely used pharmacologic intervention for AMS or HACE[1] (Table 91-2). It can cause problems for patients with renal failure (e.g., reduced urine output and increased metabolic acidosis), hepatic insufficiency (ammonium ion toxicity), and COPD (dyspnea) and for pregnant women (accumulating effect with natural higher progesterone levels followed by dyspnea). Patients taking aspirin (acetylsalicylic acid) on a regular basis have reduced acetazolamide elimination and increased central nervous system penetration and toxicity. Use of the phosphodiesterase inhibitors sildenafil and tadalafil should be undertaken with caution because of the danger of serious hypotension in those also treated with nitrates.[38] In one study patients on beta blockers had significantly reduced oxygen saturation and increased cardiac workload with reduced exercise tolerance during hypoxia compared with controls.[76] A change in the antihypertensive drug regimen should be considered.

Pre-acclimatization in a hypobaric chamber has been explored as a way to reduce the risk of altitude illness on a trek or a move to altitude. One study suggested that this may be a useful approach if utilized within a week before the trip.[77] The approach is predicated on a "preconditioning paradigm." However, a recent study suggested that repeated exposure has little effect.[78]

Simple, submaximal exercise testing in an hypoxic environment may be helpful. Exercise tolerance during acute exposure to high altitude can be predicted by a lower individual heart rate response to submaximal exercise assessed at low altitude.[47] Hence, pre-acclimatization could become a method of prevention for the leisure or work traveler, especially those who reach high altitude by plane.

A key element in mitigating altitude-related illness is limiting the rate of ascent to less than 400 m/day.[72,79] A slow rate of ascent is the best way to prevent AMS. A suggested rule is that above 3000 m (10,000 ft), ascent should be at a rate less than 300 m (1000 ft) per day, with a "rest" day (i.e., no additional ascent) every 3 days. This rate will be too fast for some and unnecessarily slow for others.[66] For direct travel to an altitude between 2500 m and 3000 m, the traveler should stay at that altitude for 2 days and then ascend at a rate of 300 m per day.[38] Well-trained individuals ascend too fast and are more vulnerable. The need for acclimatization also implies that those embarking on a "Kilimanjaro in 5 days tour" have no chance for safe acclimatization and are at a high risk for acute altitude illnesses.

An additional rule is, "If symptoms of AMS develop, go no higher. If they become severe, go down." Individuals who ascend to high altitude should be advised to limit their activity for the first few days upon ascent. Adequate hydration should be encouraged, and 2 L of extra fluid per day is a common rule of thumb.

TABLE 91-2 Pharmacologic Therapy for Altitude Illnesses

Syndrome	Medication	Preventive Dose	Therapeutic Dose	Side Effects
Acute mountain illness	Acetazolamide	125 mg at night (adult); 2.5 mg/kg q 12 h (children)	250 mg q 12 h (adult); 2.5 mg/kg q 12 h (children)	Diuresis, paresthesia, metallic taste, nausea, malaise
	Dexamethasone	2 mg q 6 h or 4 mg q 12 h	4 mg q 6 h (oral, IV, or IM)	Hyperglycemia, mood disturbance
	Theophylline	250 mg SR q 12 h		Nausea, headache, drug interactions
	Ibuprofen		400 mg q 8 h	Nausea, GI bleeding
	Acetaminophen		1 g q 8 h	Dose-related liver toxicity
High-altitude headache	Acetaminophen	1 g q 8 h	1 g q 8 h	Dose-related liver toxicity
	Ibuprofen	400 mg q 8 h	400 mg q 8 h	Nausea, GI bleeding
Sleep complaints	Acetazolamide	125 mg qhs x 3 days		Diuresis, paresthesia, metallic taste, nausea, malaise
	Temazepam	5–7.5 mg qhs	5–7.5 mg qhs	Confusional arousals, next-day drowsiness and dizziness
High-altitude pulmonary edema	Nifedipine	30 mg SR q 12 h or 20 mg SR q 8 h	30 mg SR q 12 h or 20 mg SR q 8 h	Dizziness, headache, palpitations
	Dexamethasone	2 mg q 6 h or 4 mg q 12 h		Hyperglycemia, mood disturbance
	Tadalafil	10 mg q 12 h		Dizziness, hypotension, headache, vision disturbance
	Sildenafil	50 mg q 8 h		Dizziness, hypotension, headache, vision disturbance
	Salmeterol	Inhaler 125 μg q 12 h		Tremor, tachycardia; hypokalemia (in African Americans)
High-altitude cerebral edema	Dexamethasone	2 mg q 6 h or 4 mg q 12 h (not indicated for prophylaxis in children)	8 mg once then 4 mg q 6 h (oral, IV, or IM adult); 0.15 mg/kg q 6 h (children)	Hyperglycemia, mood disturbance

Prophylactic administration of acetazolamide is advisable for anyone with a prior history of AMS. Use of acetazolamide (250 mg at bedtime or 125 mg twice daily) for several days after arrival may improve sleep and ability to function during the day. Some suggest starting the drug 2 to 3 days before arrival.[54] Corticosteroids (e.g., dexamethasone at a dose of 4 mg every 6 h) is recommended as an alternative for individuals unable to take acetazolamide (e.g., those with sulfa allergy).[54] The drug is continued for a few days at altitude. In a study of a comparison between acetaminophen and ibuprofen on the incidence of AMS, the drugs were equivalent, despite their different pharmacology. Multifactorial drug effects, that is, anti-inflammatory versus other analgesic mechanisms, appear to be operative.[80] Other therapies either have little support or, at best, supplement this approach.[81]

Treatment

Mild AMS is self-limiting and usually lasts about 3 days, so treatment is not mandatory. A placebo-controlled trial indicated ibuprofen is useful, while the information on aspirin or acetaminophen is anecdotal.[54] If symptoms progress, the traveler should descend (Fig. 91-5). If descent is delayed, acetazolamide is generally considered first-line treatment; dexamethasone can be used in sulfa-allergic individuals. A combination of the two agents can be used for rapidly evolving symptoms. For sleep disturbances, temazepam is effective in reducing recurrent central apnea and arousals and appears to be safe, without any measurable adverse effects the next day.[82] Based on the ability of iron to influence cellular oxygen sensing pathways, one randomized, double-blind, placebo-controlled trial found that intravenous iron supplementation protected against the symptoms of AMS in healthy volunteers.[83] This is, however, impractical for common use.

■ High-Altitude Cerebral Edema (HACE)

If the "mild" edema in the brain worsens toward compression of brain structure, the status of HACE is reached. HACE can occur even in the relative absence of symptoms of AMS.[84] Signature symptoms are dizziness; severe, almost unbearable headache; and vomiting. Ataxia is common;[85] some propose that a positive Romberg sign, the inability to stand straight with the feet together and the eyes closed, is an essential feature.[86] Somnolence, stupor, and changes in pupillary responsiveness mark the onset of a fatal stage. Concurrent signs of pulmonary edema also may be noted. In the absence of treatment, the condition will progress to coma and carries a high mortality.

Descent is critical. While awaiting evacuation, supplemental oxygen should be given. Every 1% increase in oxygen concentration above 21% reduces the equivalent altitude by about 300 m. Several hours in a portable hyperbaric chamber may buy time and be potentially useful as a life-saving measure while descent is arranged;[69] however, the beneficial effects of the portable chamber (Fig. 91-6) may evolve more slowly in HACE than in HAPE, especially in severe cases.[6] Administration of intramuscular dexamethasone (4 to 8 mg) in severe cases, or orally in less severe cases, helps reduce cerebral edema and should be given while awaiting evacuation; doses can be repeated every 6 h.[4]

■ High-Altitude Pulmonary Edema (HAPE)

The typical patient who develops HAPE is a fit young man who has climbed rapidly and is energetic on arrival.[87] Moderate symptoms of AMS may be present initially as the individual becomes more breathless (Fig. 91-5). A cough develops, which is initially dry, then productive of frothy white sputum, later becoming blood tinged. The climber may complain of chest discomfort. The pulse and respiratory rate are increased, and auscultation of the chest reveals crackles at the bases. An elevated jugular venous pressure and peripheral edema may be seen, and a right ventricular heave and accentuated pulmonary component of the second heart sound may be detected. Over a few hours, the patient's condition may deteriorate further, with additional increases in pulse and respiratory rate. As breathing becomes "bubbly" due to pulmonary edema, cyanosis develops. In the absence of definitive treatment, hypoxemia progresses to respiratory failure, and coma and death ensue.

HAPE may occur independently of AMS. The symptoms are like those of pulmonary edema at sea level. HAPE requires a substantial medical intervention (see below). Prevalence estimates are 0.5% to 2.0% of those rapidly ascending to altitude. Individuals with a previous history of HAPE are at greater risk of all altitude-related disorders.[3,4] Some demonstrate a "threshold" effect in which repeated ascents to a particular altitude are associated with development of HAPE, but lower altitudes are not. Individuals residing at high altitude who descend and then return to high altitude are susceptible.

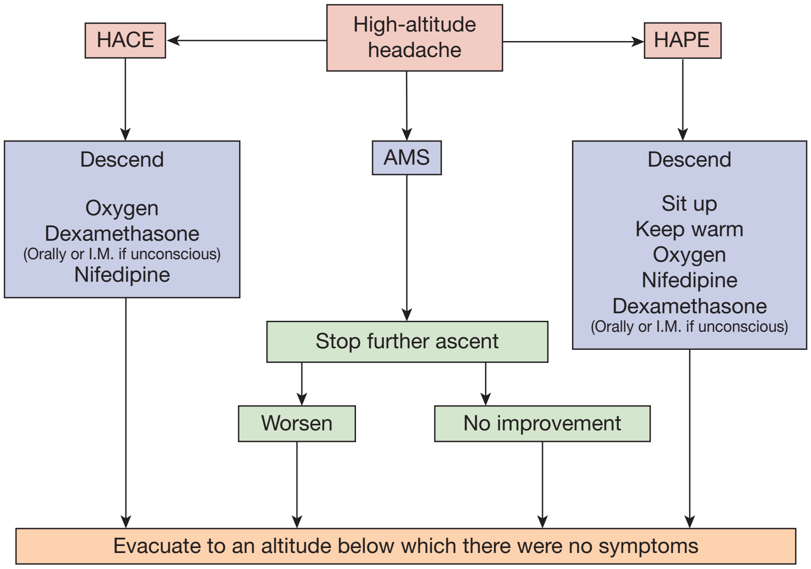

Figure 91-6 Overview of the pathway for management of acute altitude illnesses.

Mechanism

HAPE is caused by migration of fluid into extravasal space through endothelial damage along with shear stresses produced by increased cardiac output and pulmonary artery pressure. The most popular hypothesis is that susceptible subjects experience a hypoxic pulmonary artery vasoconstrictor response that is uneven throughout the lung.[4] In some areas, where there is a greater degree of vasoconstriction, blood flow is reduced, and the areas are protected from development of pulmonary edema. In those areas in which vasoconstriction is less marked, increased blood flow is associated with edema formation, perhaps through flow-related capillary damage, or sheer stress on vessel walls, increased intracapillary pressure, or oxygen radical formation in regions of the lung where blood flow is uneven. In addition, various kinins that have been identified in the edema fluid are likely to increase permeability and to recruit leukocytes.[55]

Prevention

In those who have experienced HAPE previously, use of nifedipine prophylactically (slow-release formulation, 20 mg twice daily prior to ascent, then three times daily) appears to lower significantly the incidence of HAPE.[4,69] Mean systolic pulmonary artery pressure is lowered with this approach, suggesting effects on smooth muscle relaxation. The drug appears to be ineffective in preventing AMS. Prophylactic use of an inhaled beta agonist may reduce the risk of HAPE.[54,55]

Treatment

Descent is critical for survival. Initial medical treatment while the subject awaits descent includes strict rest and supplemental oxygen (Fig. 91-6). Although not yet studied in a well-controlled trial, nifedipine (10 mg sublingually) may be used. If clinically significant hypotension does not occur with the first dose of nifedipine, its administration can be repeated every 15 to 30 min.[4,69] The phosphodiesterase inhibitors sildenafil and tadalafil are becoming fashionable drugs in the treatment of HAPE,[38] but a consensus of efficacy is not available.[4,69] There is a report of the use of nitric oxide and oxygen for this condition.[88] Anecdotally, there appear to be beneficial effects from use of a portable hyperbaric chamber[6] or positive pressure delivered via helmet,[89] constituting temporary measures while descent is arranged.

■ Chronic Mountain Sickness (CMS)

In the 1920s, Carlos Monge reported cases of polycythemia in high-altitude residents of the Andes (Monge disease), and in 1942, Hurtado published detailed observations of eight cases, including symptomatology and hematologic changes.[90] The defining feature is occurrence in a previously well-adapted, asymptomatic high-altitude resident of dyspnea and extreme polycythemia, with hemoglobin concentrations as high as 23 g/dL and hematocrits as high as 83%. Patients may have vague neuropsychological complaints, including headache, dizziness, somnolence, fatigue, difficulty in concentration, and loss of mental acuity. Irritability, depression, and even hallucinations are reported. Dyspnea on exertion is not common, but poor exercise tolerance is. The condition of chronic mountain sickness (CMS) is quite different from AMS.[91] Excessive erythrocytosis associated with a lower oxygen saturation and hypoxic ventilatory response with relative hypercapnia are the main features of CMS, followed by right ventricular enlargement, pulmonary hypertension, and remodeling of pulmonary arterioles.

Risk Factors

Age, sex, and obesity are risk factors in Andean, but not Tibetan, populations. In an ecologic study of 108 Chinese highland military units stationed in Tibet for months to years, the rate of CMS ranged from ∼1% to ∼37% and was higher among rural construction units or those with poorer medical facilities.[92] CMS is more common in males, and in civilian populations it may develop in middle and later life.[90] There may be some risk to children born at altitude with low birth weight for age or whose mothers had problematic pregnancies.[93]

Residence at sea level is the definitive treatment. However, for those who wish to remain at altitude for family or economic reasons, phlebotomy and administration of supplemental oxygen are beneficial.[90] Phlebotomy improves many of the neuropsychological symptoms, and in some patients, pulmonary gas exchange and exercise performance also are improved.

The foundation underlying therapeutic agents for CMS, as well as the clinical evidence that exist to date on their usefulness in the treatment of CMS, is sparse, compared with the work on acute illness.[90] In the Andes, ACE inhibition can effectively and safely ameliorate altitude polycythemia, while also reducing proteinuria.[94] Literature exists on respiratory stimulants, but the studies are not rigorous. Medroxyprogesterone has been employed with some success; side effects, including loss of libido, limit its use.[90] Although acetazolamide has been used in prevention of acute mountain sickness, trials addressing its use in CMS are lacking. However, the drug may be useful in improving oxygen saturation during sleep and, by this mechanism, reducing hematocrit. Further studies are necessary in establishing the role, if any, of sildenafil and related compounds, as well as phlebotomy, in patients with CMS, as used in acute illnesses.

■ Disorders of Altitude Residence

Pulmonary arterial hypertension may develop over months to years of residence at altitude. There is an interesting literature on susceptibility factors. One line of research has identified genetic polymorphisms in the ACE pathway associated with increased hypoxic responses and/or development of pulmonary hypertension.[95] Another line of work has focused on receptor functions, in particular a downregulation in the function of the β-adrenergic receptor system, found in populations at altitude but not at sea level (e.g., pulmonary hypertension in the setting of mitral stenosis).[96] A third invokes a series of dysfunctions in vascular regulation.[97] A fourth may involve a perinatal predisposition for development of high-altitude chronic illnesses in a way that some adult chronic diseases at sea level also have perinatal origins.

An intriguing publication suggested that gestational age, preterm birth, preeclampsia in the mother, or a diagnosis of neonatal hypoxia and impaired growth in utero raise susceptibility to adult disease through a reduced fetal growth of pulmonary vessels and/or an epigenetic effect of perinatal hypoxia.[93] Medications (phosphodiesterase inhibitors and prostaglandins) have been shown to alter pulmonary artery pressures in those born at high altitude and susceptible to pulmonary hypertension, but most of these studies are in smaller groups in a single population.[98–101]

Studies in permanent residents suggest that altitude may aggravate complications of pregnancy and prenatal life. Examples include fetal growth retardation and an increased incidence of the complications of pre-eclampsia and neonatal hyperbilirubinemia, the last noted in Colorado.[102] Mechanisms are not well understood, and interventions in this population have not been performed.[103] Presumably, measures such as prenatal care, vitamin supplements, attention to birth weight, and identification of known risk factors can be implemented in these populations, which often do not appear in Western, lowland health systems.

■ Preparation of Individuals with Cardiopulmonary Comorbidities for High Altitude

The lungs constitute an interface between the atmosphere and the lungs, which provide for oxygen uptake and delivery to the cells and mitochondria.[104] In COPD, ventilatory–perfusion mismatch results in impaired pulmonary gas exchange during wakefulness at sea level that worsens with altitude. For instance, eight patients with COPD and an average FEV_1 of 1.27 L were brought to 1920 m; the Pa_{O_2} fell from a sea-level average of 66 mm Hg to 54 mm Hg within 3 h of arrival at altitude.[105] The lowered oxygenation in patients with COPD poses a possible additional risk for acute mountain sickness.[106] Emphysematous bullae are a low risk for expansion with ascent to altitude, in contradistinction to their risk of expansion with ascent during scuba diving.[107] Interestingly, high altitude may have positive respiratory training effects in patients with COPD, but only if there is a short time of exposure to hypoxic conditions. Respiratory muscle strength also may improve, and it has been suggested that functional improvements in nonventilated lung areas may be seen.[108] Notably, while living at high altitude may have a harmful effect on patients with COPD, there may be a protective effect in ischemic heart disease, resulting in no net effect on anticipated life expectancy.[109]

Patients with COPD whose baseline FEV_1 is <1.5 L should be assessed prior to high-altitude travel to determine the need for supplemental oxygen. Since data suggest that the resting sea-level Pa_{O_2} alone fails to identify a significant number of patients whose Pa_{O_2} falls to 50–55 mm Hg at high altitude, prediction of the Pa_{O_2} at altitude should be based on the regression equation of Dillard: $Pa_{O_2}Alt = 0.519 \times (Pa_{O_2}SL) + 11.85 \times (FEV_1) - 1.76$, where $Pa_{O_2}Alt$ is the Pa_{O2} at altitude and $Pa_{O_2}SL$ is the Pa_{O_2} at sea level. Subjects with a predicted Pa_{O_2} of 50–55 mm Hg should travel to high altitude with supplemental oxygen.[55,110]

Management of patients with COPD at altitude is informed by very few studies. In one study, during travel to 1650 m and 2590 m, those with moderate to severe COPD experienced a mild reduction in exercise performance; however, about 25% of patients subsequently required supplemental oxygen or descent to lower altitude because of adverse health effects.[111] Another study addressed sleep-induced deterioration in gas exchange. In this randomized controlled trial, in lowlanders with COPD in Central Asia travelling to a high altitude, preventive treatment with dexamethasone improved nocturnal oxygen saturation, sleep apnea, and subjective sleep quality.[112]

For patients with asthma, changes of well-being and clinical symptoms at high altitude are inconsistent. Allergic asthma symptoms may decrease because of the lower allergen burden. House dust mites do not exist at altitudes above 2000 m, and concentrations of several classic allergens, like birch pollen, are significantly decreased.[113–115] However, in contrast to symptom improvement related to reduced allergen exposure, hypoxia and reduced air density requiring a higher minute ventilation may worsen respiratory symptoms in asthma. Furthermore, hypoxia constricts airways and increases airway hyperresponsiveness.[116,117] Dry, cold air and increased ventilation may cause exercise-induced asthma, even in those without such a history at sea level, where air is warmer and has higher humidity; the additive effects of intense exercise and "thin" air may well uncover airway hyperresponsiveness.[118]

Despite these pathophysiologic concerns, patients with mild to moderate persistent asthma have successfully travelled to altitudes up to 5000 m. They should be advised to carry a reserve of their regular inhalers, as well as oral prednisone. An additional recommendation is that asthmatics use a peak flow meter to monitor measurements each morning and evening, preemptively increasing therapy if a large drop from evening to morning values is observed. Of course, the absolute value of the measurements is not reliable in the less-dense air at altitude, so changes in measurements over time are the important measurements.

Patients with obstructive, mixed, and central sleep apnea seem to have a significantly increased number of events upon ascent to moderately high altitudes.[30,119] It is reasoned that hypoxia increases the gain of the system to produce recurrent apneas, and as the oxygen saturation is already low, there is a more prolonged and deeper oxygen desaturation. Collapse of the upper airway is more likely to occur in the low-drive portion of the periodic breathing cycle and produce obstructive and hypopneic events. Thus, snorers and patients with diagnosed sleep apnea are likely to experience symptoms.[59]

Patients with sleep apnea should use their Auto-CPAP (Self-adjusting Continuous Positive Airway Pressure) or ASV (Assisted

Servo Ventilation) devices at moderate to high altitude. If PAP treatment is not possible at certain locations, patients should take acetazolamide. Use of acetazolamide has been proven better than no sleep apnea treatment at all.[119]

Those with, or at high risk for, cardiovascular disease need preventive measures for high-altitude sojourns. Because arterial blood pressure and heart rate rise at high altitude and stay increased for at least 7 days after arrival, without nocturnal dipping, the effects provide an additional cardiovascular stress.[120] Pulmonary vasoconstriction in hypoxia stresses the right ventricle, and hypoxia alone can lead to left ventricle alterations. Despite such concerns, the European Society of Cardiology states that patients with heart failure up to level NYHA III can safely ascend to altitudes up to 3000 m if they perform only light physical activity.[121] This position is supported by observations that supervised patients with heart failure NYHA II were able, without cardiovascular events, to exercise at almost 3500 m altitude.[122] Hiking to, and at, high altitude also appears to have a positive training effect for patients with cardiovascular diseases by lowering BP by increasing in left ventricle contractility and improving myocardial oxygenation.[123,124]

The physician must carefully balance pros and cons in advising patients with cardiovascular diseases on high-altitude sojourns. Based on the recommendations of the European Society of Cardiology, blood pressure should be well controlled before ascent to altitude.[121] ACE inhibitors and selective beta blockers are preferred over nonselective beta blockers for the treatment of high BP; acetazolamide should be considered as add-on therapy, both as a diuretic and as a way to reduce periodic breathing. Patients with myocardial infarction or prior coronary stenting should wait 12 months after the event or intervention before considering travel to high altitude. However, patients with mild to moderate stable coronary artery disease (CCS, Canadian Heart Society class I–III) may ascend to altitudes of 2500 m with light physical exercise; patients with CCS 1 are allowed to hike up to 4200 m. In patients with high-risk CCS IV, the recommendation is not to ascend to high altitude.

CONCLUSIONS

Altitude illnesses are the result of acute and chronic residence above 2500 m. With a hurried ascent, many healthy people will report a transient headache (high-altitude headache or HAH), and some will develop one of three forms of acute high-altitude illness: acute mountain sickness (AMS) with or without high-altitude headache (HAH), high-altitude cerebral edema (HACE), or high-altitude pulmonary edema (HAPE). In some resident highlanders, chronic mountain sickness (CMS) and right ventricular hypertrophy develop over months to years. Altitude-associated exposure to cold and UV radiation, exercise, trauma, and infection are important considerations and may affect performance; however, the syndromic presentations are primarily due to hypoxemia and its physiologic responses. Rapid descent is first-line, optimal treatment, although there are some medications that might temporize declining health status. These syndromes and their biologic pathways are not well defined, and the actions of drugs currently employed are empiric and do not directly address hypoxemia. As a result, major gaps in our understanding of high-altitude medicine remain.

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CHAPTER 92

Diving Physiology and Dysbarism

Christopher E. Winstead-Derlega
Richard E. Moon

INTRODUCTION

Several million people worldwide participate in diving activities, including recreational, commercial, military, and competitive breath-hold diving. This chapter provides an introduction to the physiology of diving and clinical presentations of dysbarism (i.e., medical conditions arising from changes in ambient pressure), as well as an outline of fitness-to-dive principles for medical screening.

THE FIELD OF DIVING

Breath-hold diving was undoubtedly first performed thousands of years ago, and it continues today during international competitions and commercial pearl diving, mostly in the Asia-Pacific region. The maximum depth of breath-hold diving is limited predominantly by the depletion of oxygen and the mechanical effects of pressure on the thoracic contents, as is discussed in more detail below.

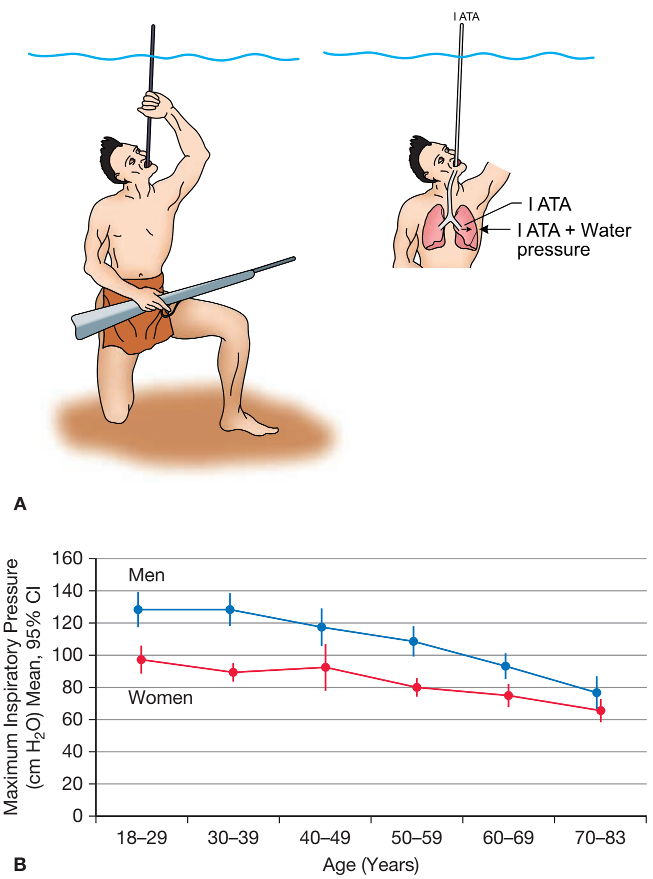

Figure 92-1 Limits of snorkel. **A.** The average adult is limited to a functional depth of 1 m due to limited strength of the inspiratory muscles to overcome the hydrostatic pressure applied to the chest. **B.** Maximum inspiratory pressure in males and females as a function of age. *(Data from Sclauser Pessoa IM, Franco Parreira V, Fregonezi GA, et al. Reference values for maximal inspiratory pressure: a systematic review. Can Respir J. 2014;21(1):43–50.)*

Breathing at shallow depth can be performed using a snorkel; however, the maximum depth is constrained by the degree to which the inspiratory muscles can breathe against the transthoracic pressure imposed by the hydrostatic pressure of the water column. Maximum inspiratory pressure varies with age and sex; for a healthy young adult it is impossible to inhale through a snorkel at depths greater than one meter[1] (Fig. 92-1). Prolonged excursions underwater can, therefore, only be performed by delivering compressed gas to the diver at the ambient pressure of the environment.

In 1942 Jacques Cousteau and Emile Gagnan designed the Aqua-Lung, an open-circuit, self-contained underwater breathing apparatus (SCUBA). With this system, the diver breathes from a regulator that delivers gas at ambient pressure. Breathing gas is stored in pressurized steel or aluminum tanks and is delivered by a series of first- and second-stage regulators, which reduce the gas pressure to the ambient pressure of the diver; exhaled gas is released into the environment.

An alternative technology, developed by naval forces at about the same time, is the closed-circuit rebreather. This device allows the diver to rebreathe expired gas, thus eliminating bubbles, increasing efficiency, and maintaining secrecy. Carbon dioxide is removed by a chemical absorbent, while oxygen is replenished from a pressurized oxygen tank. In the 1940s, rebreathers used 100% oxygen, which was discovered to produce fatal central nervous system oxygen toxicity due to seizures at depths beyond 8 to 9 meters (25–30 ft). Today's rebreathers rely on complex sensors to deliver gas at a desired partial pressure, thus allowing deeper dives. Surface-supplied diving, or hookah diving, allows for an individual diver with an enclosed helmet to be connected to a surface-supplied air source via an umbilical line that carries air, heat, and communication (Fig. 92-2).

During and after surfacing from a dive, excess tissue inert gas (e.g., nitrogen) can form bubbles, causing *decompression sickness* (DCS).[2] DCS symptoms most commonly include joint pain, numbness, paresthesias, and skin rash (Fig. 92-3) but may be more serious with involvement of the spinal cord (motor weakness, paraplegia/quadriplegia), brain (confusion, difficulty concentrating, memory loss), and inner ear (vertigo, hearing loss). Low levels of gas bubbles in the venous blood (venous gas emboli [VGE]) are usually filtered by the pulmonary circulation and may occur after a dive without

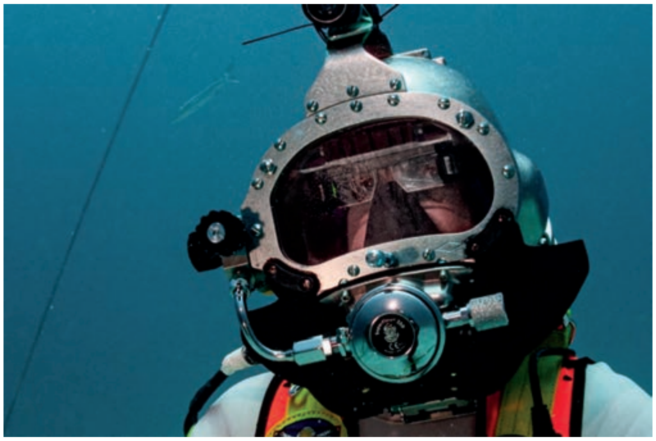

Figure 92-2 A hard hat surface-supplied Navy diver. A camera is affixed to the diver's helmet to provide information to the topside. *(Reproduced with permission from Naval Sea Systems Command Supervisor of Salvage, and the Office of Naval Research.)*

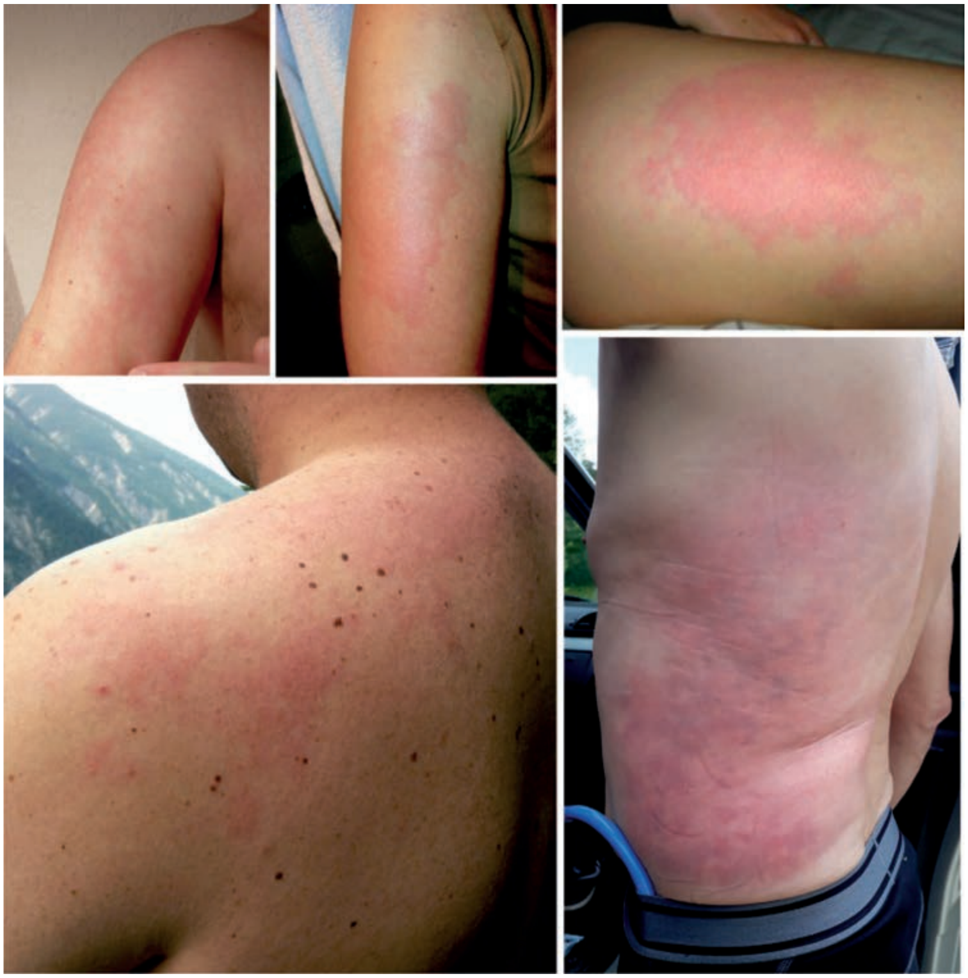

Figure 92-3 Livedo racemosa. A characteristic dermatologic sign sometimes seen in patients with decompression illness. *(Reproduced with permission from Hartig F, Reider N, Sojer M, et al. Livedo Racemosa—The Pathophysiology of Decompression-Associated Cutis Marmorata and Right/Left Shunt. Front Physiol. 2020;11:994.)*

symptoms. However, large amounts of VGE can injure the vascular endothelium, causing plasma loss, shock, and pulmonary edema (known as "chokes"). Reduction of DCS risk may require scheduled "stops" during decompression to allow orderly inert gas washout from tissues and off-gassing (Fig. 92-4). Arterial bubbles (arterial gas embolism [AGE]) also can occur due to pulmonary barotrauma (see below). Treatment of both DCS and AGE consists of general supportive measures, supplemental oxygen (even in the absence of hypoxemia), and hyperbaric oxygen.[2–4]

In order to perform underwater tasks at deep depths, such as those needed for commercial purposes, the required decompression time may grossly exceed the time at maximum depth. For such

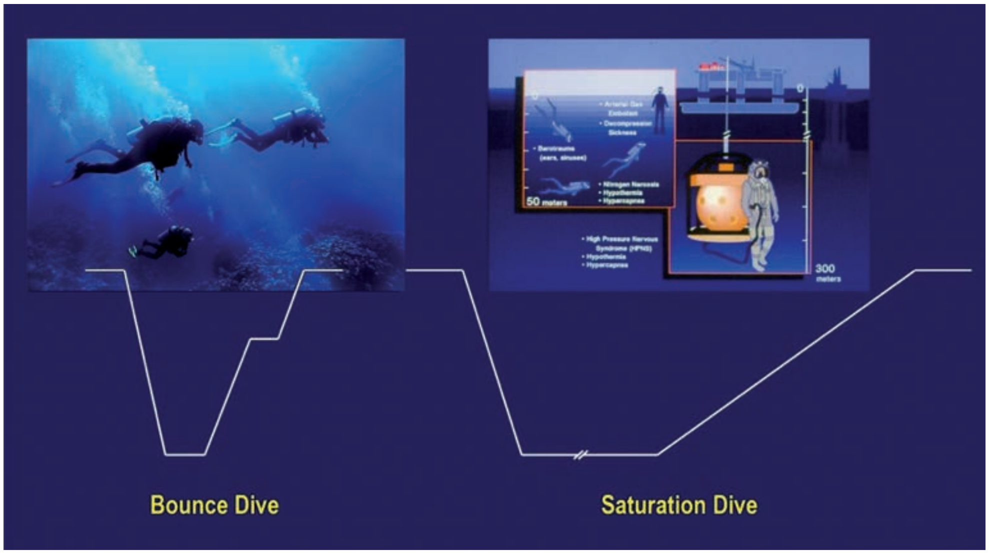
0
• Arterial Gas Embolism
• Decompression Sickness
• Barotrauma (ears, sinuses)
• Nitrogen Narcosis
• Hypothermia
• Hypercapnea
50 meters
0
• High Pressure Nervous Syndrome (HPNS)
• Hypothermia
• Hypercapnea
300 meters
Bounce Dive
Saturation Dive

Figure 92-4 Dive profiles for bounce *(left)* and saturation *(right)* dives. Notice the prolonged decompression required for saturation diving. *(Reproduced with permission from Adobe Stock Photos.)*

scenarios, the technique of *saturation diving* is often used, in which a group of divers live in a hyperbaric environment on a dive support vessel and "commute" to work on the ocean floor, usually in pairs, in a pressurized diving bell. After a "shift" they then return to the living environment, at which time two other divers travel to the worksite. Oxygen fraction must be reduced such that the ambient P_{O_2} is not toxic. Tissue inert gas partial pressures are at equilibrium ("saturated") with the environment. To avoid dysbarism, decompression at the end of the time at depth must be performed at a very slow rate (Fig. 92-4).

PHYSIOLOGICAL EFFECTS OF DIVING

Below we consider the wide variety of physiologic effects that occur with diving.

■ Toxic Effects of High Ambient Pressure

Partial pressures of component gases, such as nitrogen and oxygen, increase linearly with ambient pressure and are associated with pharmacologic or toxic effects, including inert gas narcosis and oxygen toxicity. The effects may require an adjustment of the breathing gas mix (Fig. 92-5) or replacement of nitrogen with helium, which has no narcotic effects. Ultra-high pressures (e.g., 15–20 atmospheres absolute, ATA, or greater) can induce a syndrome consisting of nausea, tremor, and ataxia known as *high pressure nervous syndrome* (HPNS).[5]

■ Immersion Effects

Because blood and water have similar densities, the tendency for blood to pool in splanchnic and lower-extremity veins in the upright position due to gravity is eliminated during immersion. As water level rises relative to the body during immersion, there is a progressive tendency for blood to redistribute into the cardiac and pulmonary vessels, which is enhanced in cold water immersion.[6] The resulting engorgement of the central veins, cardiac, and pulmonary vessels causes intravascular pressures, including pulmonary artery wedge pressure, to increase.[7,8] Lung volumes are, therefore, reduced;[9,10] total lung capacity (TLC) typically decreases by 10%, functional residual capacity (FRC) by 50%, and expiratory reserve volume (ERV) by 73% (Fig. 92-6).

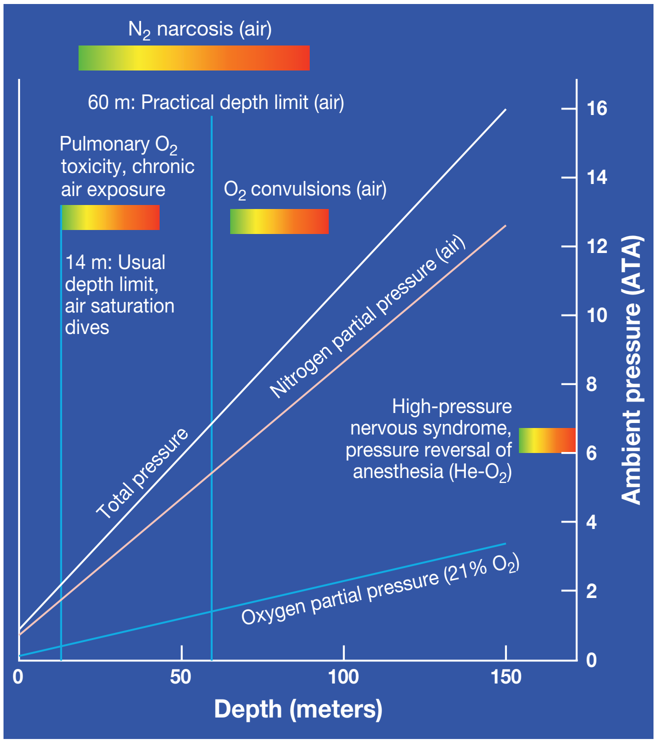

Figure 92-5 Pressure and gas partial pressure as a function of depth. Depicted are depth ranges (green-to-red: increasing severity) while breathing air for occurrence of nitrogen narcosis, pulmonary and central nervous system oxygen toxicity. Depth range for high-pressure nervous syndrome is shown for helium-oxygen breathing. See text for details.

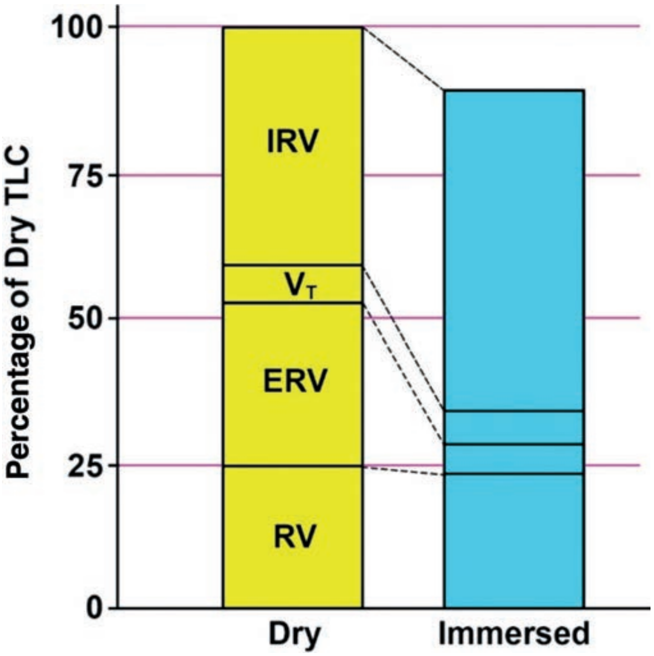

Figure 92-6 Effects of immersion on lung volumes. TLC, FRC, and ERV decrease with immersion, while RV is largely unchanged. These changes are due largely to the shift of intrathoracic blood volumes and compression of the chest wall. *(Data from Agostoni E, Gurtner G, Torri G, et al. Respiratory mechanics during submersion and negative-pressure breathing. J Appl Physiol. 1966;21(1):251–258.)*

■ Mechanical Load

During a dive, mechanical changes occur in load parameters, including *flow resistance*, *lung elastance*, and *respiratory inertance*. Gas density increases linearly with pressure, causing airway resistance to increase, particularly in large airways where turbulent flow occurs.[11] During expiration, collapsing airways can induce flow limitation.[11] These effects cause reductions in forced expiratory volume in 1 s (FEV_1), peak expiratory flow (PEF), and maximum voluntary ventilation (MVV).[12–16] MVV at high gas density (ρ) can be approximated by the following formula:

$$MVV = MVV_0(\rho/\rho_0)^{-k}$$

where MVV_0 is MVV at 1 ATA; ρ is gas density at the ambient pressure of the dive; ρ_0 is gas density at 1 ATA; and k is a constant with the value 0.4 to 0.5. A similar equation has been verified for the relationship between airway conductance and gas density.[17] This relationship becomes important during underwater exertion, where levels of ventilation appropriate to the CO_2 production rate may exceed mechanical limitations of MVV.

In addition to airway resistance, resistive properties in underwater breathing apparatus add to the overall respiratory load. Theoretically, changes in viscosity could affect laminar gas flow patterns in small airways; however, within the pressure range to which humans can be exposed, viscosity is unchanged.

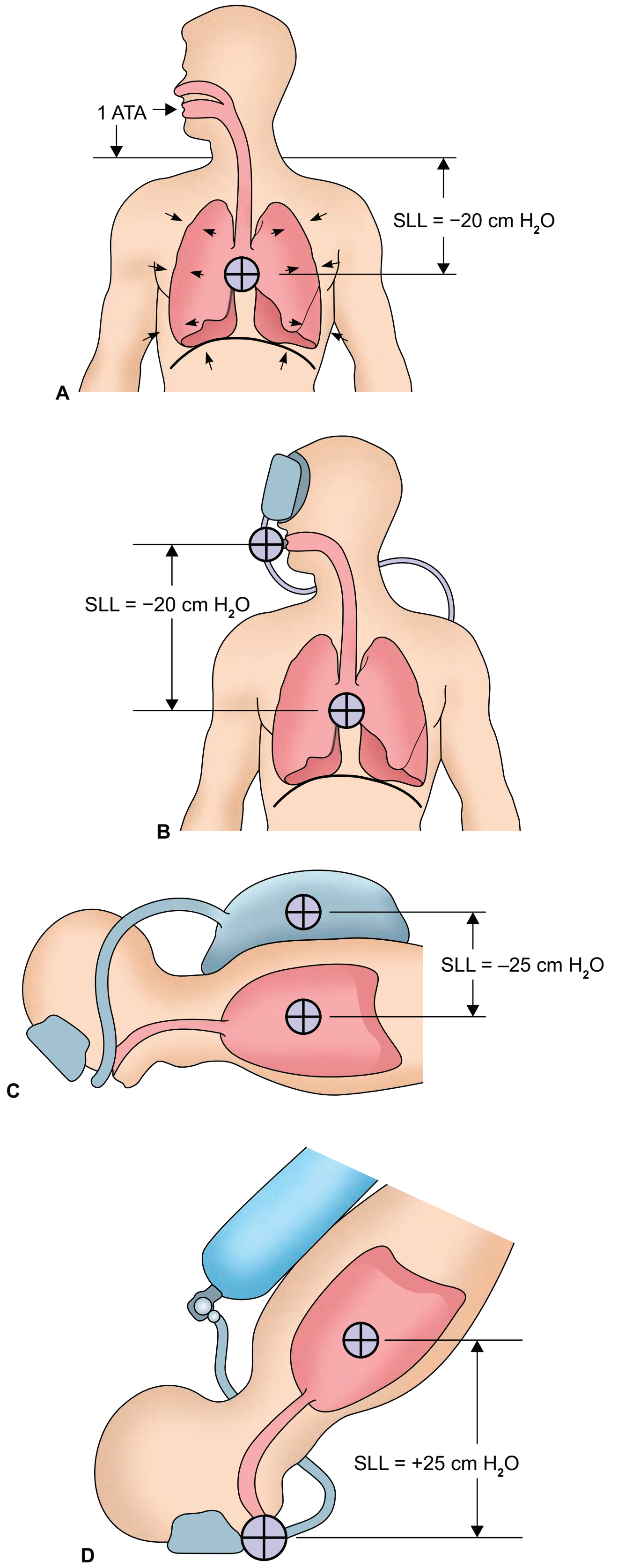

Figure 92-7 Static lung load (SLL), transrespiratory pressure gradient, changes with relative position of the breathing regulator apparatus and lung centroid. The face-down diving position offers divers a positive pressure due to greater ambient pressure at the regulator when compared to the lung. *(Reproduced with permission from Lundgren CE, Miller JN: The Lung at Depth. New York, NY: Marcel Dekker; 1999.)*

Mechanical load during diving may also be affected by thoracic *elastance*. Chest wall compliance does not change; however, redistribution of blood into the thorax and vascular engorgement caused by immersion may increase lung elastance.[18] Differences in hydrostatic pressure between the lung and the mouth (transthoracic pressure) also may increase elastic load[19,20] (Fig. 92-7). The immersion-related increase in elastic load reduces MVV by an additional 10% over that caused by high gas density.[21]

High gas density increases *inertance*, which is the tendency to resist acceleration. Inertance is a function of the mass of the chest wall, the gas flowing within the airways, the breathing apparatus, and, to a minor extent, the water surrounding a diver's torso, which must be accelerated and decelerated with breathing. At 1 ATA respiratory system inertance is typically 0.01 cm $H_2O \cdot L^{-1} \cdot sec^{-2}$, which increases in direct proportion to gas density.[22,23] Due to the normally reduced respiratory rate in divers, inertial impedance affects respiratory effort minimally. In an exercising diver, breathing a gas with a density of 10 $g \cdot L^{-1}$ and assuming a peak acceleration of 30 $L.s^{-2}$, the transrespiratory pressure due to inertance would be only approximately 3 cm H_2O.[24]

The net effect of this increase in mechanical load is relative hypoventilation[25] and hypercapnia.[16,26–31] High external breathing resistance may cause incapacitating CO_2 retention, even without dyspnea or other symptoms.[32,33] The effects of increased mechanical load may also be augmented by inadequate respiratory muscle performance due to poor function or fatigue.

■ Ventilatory Drive

Ventilatory drive (hypercapnic ventilatory response [HCVR]) can be a factor in determining the effect of diving on ventilation and, hence, in determining arterial P_{CO_2}.[30,34–38] While HCVR is mostly an intrinsic phenotypic property, it can be affected by *hyperoxia*, *narcosis*, and *respiratory muscle training* (RMT). Hyperoxia, which is ubiquitous in diving, attenuates the ventilatory response to hypercapnia;[24] however, only extreme values for P_{O_2} in inspired gas (1.75 ATM) have been shown to have even a minimal effect on the increase in P_{CO_2}.[31]

Nitrogen narcosis, via a similar mechanism, could also contribute to hypercapnia during diving. While HCVR is, indeed, attenuated at increased ambient pressure, studies using nonnarcotic gases have demonstrated that the reduction is due to the effect of increased gas density on resistive load.[30,39,40] HCVR varies several-fold within the normal population, and RMT has been reported to have no effect on average HCVR. However, RMT tends to increase the HCVR of those with low C_{O_2} ventilatory response and decrease HCVR of those with high response.[41]

■ Intrapulmonary Gas Exchange

Other factors related to the lung itself may influence both oxygen and carbon dioxide exchange, including *gas mixing and diffusion*, *distributions of blood flow and ventilation*, *ventilation/perfusion* ($\dot{V}_A/\dot{Q}$) *matching*, and *hemoglobin-oxygen affinity*.

Gas Mixing and Diffusion

Mixing of inspired and alveolar gas is determined by *convective mixing* (dependent partly on cardiogenic oscillations), *Taylor dispersion*, and *diffusion*,[42] all of which could be affected by an increase in gas density. Higher gas density promulgates turbulent flow to more distal airways and enhances cardiogenic mixing, thus improving the efficiency of gas exchange.[43] On the other hand, a high gas density could diminish Taylor dispersion (and worsen gas exchange) due to increased turbulent flow and reduce gas phase diffusivity in distal airways and alveoli.[44] While it is not possible to individually assess the effects of these phenomena, the overall effect of diving on pulmonary gas exchange can be assessed by measurement of arterial blood gases, as discussed below.

Distributions of Ventilation, Blood Flow, and $\dot{V}_A/\dot{Q}$

Distribution of ventilation during normal respiration depends on regional mechanical properties of the lung. At normal atmospheric pressure (and breathing gas density) time constants of different lung units are similar; thus, ventilation of different lung regions is reasonably uniform. However, at increased gas density the geometry of the lung is no longer optimal, and heterogeneity of ventilation is increased, leading to more disperse constants and asynchronous ventilation.[24,45,46] If these inequalities of ventilation are appropriately matched by regional changes in perfusion, $\dot{V}_A/\dot{Q}$ matching is preserved. Most studies have shown evidence of impaired CO_2 transport (increased physiologic dead space),[16,27,29,30,47,48] implying impaired pulmonary exchange of CO_2, although immersion appears to attenuate this effect except at extremely high P_{O_2} (1.75 ATA).[49] On the other hand, analysis has suggested that increased breathing gas density improves pulmonary oxygen exchange (i.e., a reduced alveolar–arterial difference, $PA_{O_2} - Pa_{O_2}$) due to promotion of intraregional convective mixing and, hence, reduced $\dot{V}_A/\dot{Q}$ dispersion.[47] Lung perfusion is not temporally uniform but rather varies cyclically with respiration, which may also improve alveolar–pulmonary capillary oxygen exchange.[50,51]

Hemoglobin-Oxygen Affinity

Increased affinity of hemoglobin for oxygen (decreased P_{50}, "shift to the left" in the oxyhemoglobin dissociation curve) has been observed at 50 to 100 ATA in vitro[52–55] and in vivo in humans during a saturation dive to 69 ATA.[56] This effect is most likely due to pressure-induced conformational changes in hemoglobin and, to a lesser extent, inert gas binding. However, small changes in hemoglobin P_{50} of the magnitude described are unlikely to have a significant effect on pulmonary gas exchange or exercise capacity, particularly at common diving depths.[57]

Effect of Diving on Arterial Blood Gases

The net effect of the processes described above has been tested by measurements of arterial blood gases during hyperbaric chamber studies.[16,27–30,49,58,59] Despite mild or moderate hypercapnia during exercise, adequate blood oxygenation occurs at gas densities up to 17g/L[29] and exercise performance (thus presumably oxygenation) at densities up to 25 g/L.[14]

PATHOLOGIC EFFECTS OF DIVING

A number of important pathologic consequences of diving may occur and are discussed in the following sections.

Pulmonary Barotrauma and Arterial Gas Embolism

Pulmonary barotrauma during a dive occurs when the diver ascends at a rate at which intrapulmonary gas expansion due to the reduction in ambient pressure exceeds the rate at which gas is exhaled. This typically occurs during breath-holding, but it can also occur due to regional hyperexpansion secondary to lung pathology, including lung cysts, bullae,[60] and obstructive lung disease.[61]

Lung parenchyma ruptures at transthoracic pressures of 70 to 80 mm Hg (95–108 cm H_2O),[62] which can be generated by a breath-hold ascent from a depth of 1 m. The most common presentation is pneumomediastinum and subcutaneous emphysema; pneumothorax is rare (Fig. 92-8). Gas entry into pulmonary capillaries can result in *arterial gas embolism* (AGE), which most commonly manifests as rapid onset of stroke-like symptoms (motor weakness, confusion, impaired consciousness). AGE can also result from VGE crossing into the systemic circulation via either intrapulmonary or intracardiac shunts.

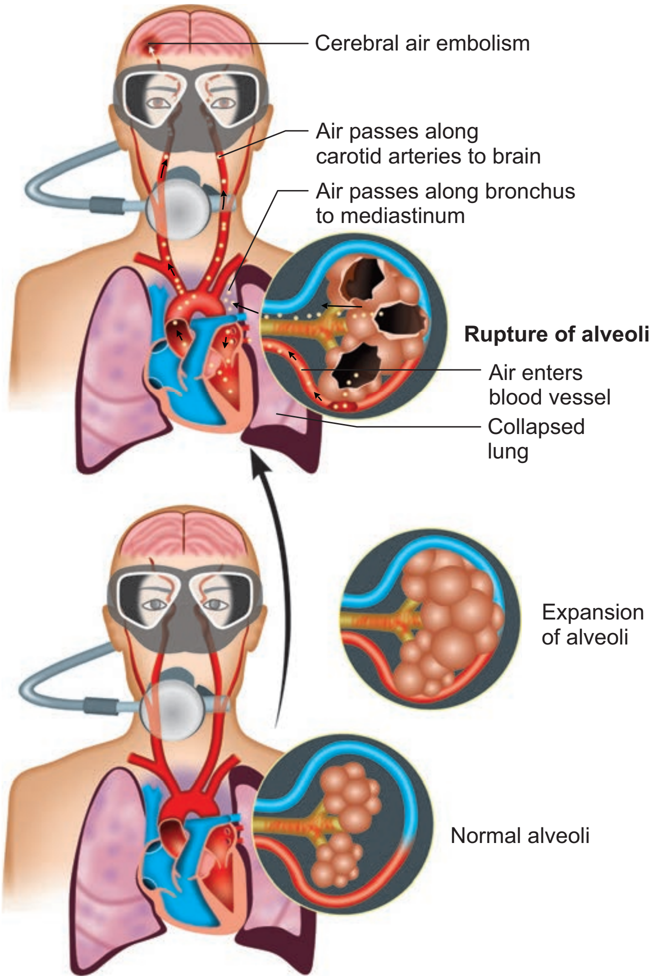

Figure 92-8 Pulmonary barotrauma. Gas trapped in the alveoli expands on ascent. As pressures increase alveoli will rupture and air will enter the mediastinum, pulmonary veins, and arterial circulation. Pneumothorax is rare. Cerebral air embolism can cause loss of consciousness and death.

Impaired Gas Exchange After Saturation Dives

During saturation dives, divers remain in a hyperbaric environment for many days or weeks where they are exposed to higher-than-normal ambient P_{O_2} (typically 0.4–0.5 ATM). During this time they may experience mild lung toxicity, in addition to the pulmonary effects of prolonged low-level venous gas embolism during decompression, which often lasts several days. After a saturation dive to 37 ATA, divers have reduced $\dot{V}O_{2max}$ and carbon monoxide transfer factor and increased respiratory dead space.[63–65]

Immersion Pulmonary Edema

Immersion pulmonary edema (IPE, often termed *swimming-induced pulmonary edema* [SIPE]) is a condition in which cough, hemoptysis, dyspnea, and hypoxemia develop after surface swimming or diving, often in young, healthy individuals,[66–68] including exceptionally fit military divers, triathletes, and other competitive swimmers.[69] Risk factors include cold water, older age, female sex, nonsteroidal anti-inflammatory drug (NSAID) use, depth of dive greater than 20 m, physical exertion, and hypertension. Left ventricular dysfunction,[70–72] including Takotsubo cardiomyopathy,[73–75] also is a risk factor.

Invasive studies during submersed exercise in individuals with a history of SIPE have revealed higher than normal pulmonary artery and pulmonary artery wedge pressures, consistent with hemodynamic pulmonary edema.[76] Pre-swim sildenafil administration may reduce the risk of SIPE;[76,77] however, for divers breathing hyperoxic mixtures (P_{O_2} >1 ATM), sildenafil may increase the risk of CNS oxygen toxicity and seizures underwater.[78]

The diagnosis of SIPE can be made on clinical grounds with, in addition to the manifestations listed above, typical pulmonary signs. It is notable that the distribution of fluid is predominantly anterior, and physical examination reveals abnormal lung sounds predominantly over the anterior chest.[69,79] Fatal cases have been reported,[80–83] although the condition usually resolves spontaneously after removal of the patient from the water, which immediately reverses the hemodynamic conditions that produced pulmonary edema. General supportive measures may be appropriate, including administration of supplemental oxygen and aerosolized β-adrenergic agonists. Diuretic therapy is rarely required.

Gas Toxicity

Nitrogen narcosis, or "rapture of the deep," is the intoxicating effect of breathing inert compressed nitrogen gas.[84] Narcotic effects are similar to those of alcohol intoxication (the "Martini effect"); symptoms are progressive and are initially seen at a depth of around 30 m. Narcosis may present with changes in behavior, memory, and cognition. These effects are quickly reversed by ascending to shallower depths. While some divers report a pleasurable effect of nitrogen narcosis, it can lead to diving error, injury, and subsequent death.

Breathing oxygen at oxygen partial pressures greater than 1.4 to 1.6 ATM places divers at risk for central nervous system oxygen toxicity. Symptoms are of sudden onset and include headache, twitching, nausea, tinnitus, and seizures. Donald's early studies in navy divers set a limit to diving on 100% O_2, concluding that dives below 8 m (25 ft) are dangerous and potentially fatal if a seizure were to occur during submersion.[85] Various mitigation strategies for CNS oxygen toxicity, including ketone diets and antiepileptic medications, are being researched.

Pulmonary oxygen toxicity occurs more gradually, with a rate that is dependent on the $P_{O_2,}$ and demonstrates a more consistent dose–response relationship. At P_{O_2} values greater than 0.5 to 0.6 ATM, tracheobronchitis (causing burning chest pain) and then pulmonary edema develop, for which a reduction in vital capacity has been used as a marker.[85,86] These changes are usually reversible when P_{O_2} is promptly reduced to normal.

Toxicities of contaminant gases, such as carbon monoxide, are also related to their partial pressures. Thus, subtoxic concentrations of contaminants at sea level pressure may become toxic during a dive.

BREATH-HOLD DIVING

Unlike SCUBA divers who breathe compressed gases at ambient pressures, breath-hold divers explore the undersea environment on a single breath of air. For thousands of years, coastal communities have employed this technique for sustenance hunting and food collection. Modern Ama, or "sea-women," in Korea and Japan continue to practice breath-hold diving as a commercial occupation. Over the last decade, competitive breath-hold diving, or "free diving," has provided venues for extreme pulmonary physiology research.[87] The deepest dive in no-limits free diving was made by Herbert Nitsch (214 m or 702 ft) in 2007.

The breath-hold diver experiences lung compression in direct relation to the increase in ambient pressure. When TLC is reduced to residual volume, the additional lung volume reduction induced by further descent is accomplished by blood redistribution into the pulmonary vessels. However, once pulmonary capillaries reach their elastic limit, additional descent can result in rupture, hemoptysis, and pulmonary edema.[88] Fatal cases of arterial gas embolism after shallow breath-hold dives are reported due to entry of gas into disrupted pulmonary capillaries.[89]

Initial lung volume (and, hence, deepest dive depth) is often increased beyond TLC pre-dive by competitive breath-hold divers by "lung packing" via glossopharyngeal insufflation. Elite divers can raise their vital capacities to 114% to 181% of predicted values,[90] which transiently decreases lung compliance.[90] Transpulmonary pressures of 43 to 80 cm H_2O have been observed in breath-hold divers practicing glossopharyngeal insufflation.[90] Glossopharyngeal insufflation allows for larger volumes of air in the lungs and chest, effectively extending dive times. This practice impedes venous return and cardiac preload, and may lead to loss of consciousness and, in one case reported, pneumomediastinum.[90]

Pre-dive behaviors alter the diver's physiologic state and dampen hypoxia signals. Hyperventilating or "pre-breathing" is common. Breath-hold divers increase minute ventilation to reduce levels of carbon dioxide.[91] The elevated pH of the blood causes a left shift in the oxygen hemoglobin dissociation curve, which favors oxygen binding. The mechanism of shallow water blackout involves a diminished hypercapnic triggered urge to breathe, while succumbing to cerebral hypoxia (Fig. 92-9).

Alveolar gas partial pressures increase as the diver descends in the water column. The highest partial pressures of oxygen are predicted to be at maximum depth. Bosco et al. demonstrated this in a breath-hold diving study in which arterial blood samples were obtained at maximum depth during a 40-m breath-hold dive.[92] Interestingly, two of six divers demonstrated a lower P_{O_2} than predicted, which was thought to be due to alveolar collapse and right-to-left intrapulmonary shunting due to atelectasis[96] (Fig. 92-10). Hypoxia of ascent occurs as a result of the diver's metabolic consumption of oxygen and a reduction of partial pressure of oxygen during surfacing. As the breath-hold diver approaches the surface, the oxygen partial pressure can drop below the level required to sustain consciousness. Compared with P_{O_2}, changes in P_{CO_2} are much less due to the higher solubility of carbon dioxide, allowing changes in P_{CO_2} to be buffered within plasma and extravascular water.

FITNESS-TO-DIVE ASSESSMENT

According to the Sports and Fitness Industry Association, there are an estimated 2.4 million recreational SCUBA divers in the United States[93] who are required to complete a medical screening form

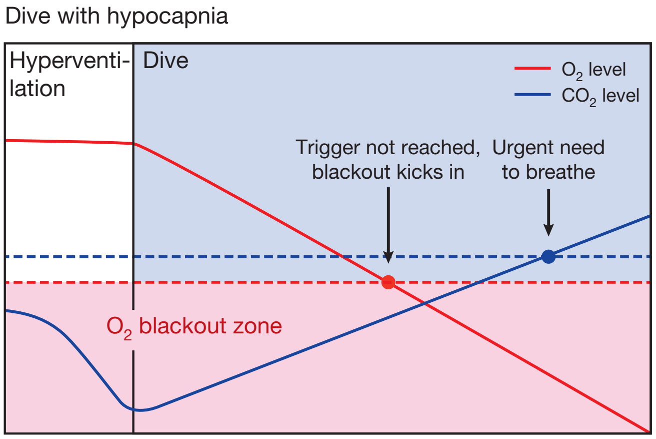

Figure 92-9 Oxygen and carbon dioxide levels in blood during a breath-hold dive. The dashed blue line represents the arterial P_{CO_2} level at which there is an urgent need to breathe; the dashed red line is the oxygen saturation at which loss of consciousness (LOC) occurs. During breath-holding, P_{CO_2} rises and blood oxygen saturation falls. Generally the urge to breathe occurs before LOC. However, if the diver hyperventilates before the breath-hold the urge to breathe is delayed and LOC may then be the initial event, causing drowning. Red line, O_2 saturation; blue line, Pa_{CO_2}.

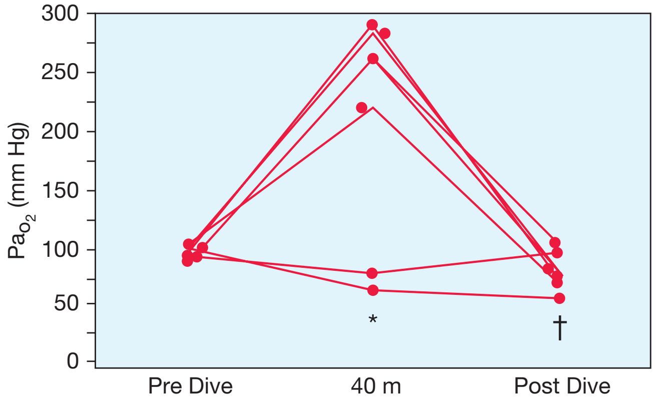

Figure 92-10 Pa_{O_2} in the breath-hold diver. Individual Pa_{O_2} measurements before, at maximum depth (40 m), and after a breath-hold dive. For the majority of divers, Pa_{O_2} increased with depth. $^{*}p < 0.05$ vs. pre-dive; $^{\dagger}p < 0.05$ vs. 40 m. *(Reproduced with permission from Bosco G, Rizzato A, Martani L, et al. Arterial Blood Gas Analysis in Breath-Hold Divers at Depth. Front Physiol. 2018;9:1558.)*

prior to participation. A preexisting condition may require consultation with a physician, preferably one with diving medicine expertise. Employed divers or volunteer divers working for a scientific or public health organization are required to complete more rigorous medical screening, a physical examination, and testing prior to clearance.[94]

Pulmonary conditions, such as bullae, lung cysts, chronic obstructive pulmonary disease, asthma, lung scarring, and pulmonary fibrosis can cause air trapping and pulmonary barotrauma during ascent. Pulmonary barotrauma may cause pneumothorax, air embolism, and/or pneumomediastinum. A history of spontaneous pneumothorax is an absolute contraindication to diving activity, as recurrence is common and unpredictable.[95]

Diving-related conditions that may exacerbate or strain preexisting pulmonary pathology also need to be taken into account, including effects of cold dry air, increased airway resistance, increased gas density, regulator breathing resistance, and heavy exertion. For individuals with a history of asthma, a consensus panel[96] recommended that fitness to dive should include absence of asthma-related symptoms, normal spirometry, and absence of airways hyperreactivity on a provocation test (later formalized by the American Thoracic Society to consist of exercise breathing dry air).[97] Mild asthma can often be controlled with inhaled corticosteroids such that these criteria can be met. Studies have documented up to 12% of divers with airflow obstruction on spirometry without apparent ill effect.[98] Nevertheless, documented instances of arterial gas embolism after shallow dives in asthmatic patients indicate some degree of risk.[61] Therefore, it is prudent for asthmatic divers to avoid diving when symptomatic, and the conservative approach outlined above is most likely the safest.

Appropriate pulmonary screening in asymptomatic patients for anatomic anomalies is controversial. Pulmonary structural abnormalities, including cysts or bullae, can lead to air trapping and alveolar barotrauma.[99] Inspiratory and expiratory CT scans with volumetric image acquisition can detect subtle gas trapping in high-risk individuals, although expiratory CT scans can demonstrate gas trapping in patients with normal lungs.[100]

Radiologic screening for lung anomalies in all divers is impractical and costly and will reveal incidental findings that are unlikely to pose additional risks. Commercial divers, given their frequent exposure and commercial liability, require initial and routine chest radiograph.[94] The limitations of chest radiograph were demonstrated in a cohort of 101 military divers undergoing screening with both plain chest radiograph and high-resolution computed tomography (HRCT).[101] Chest radiographs in 7 of the 101 divers (7%) detected bullae or blebs. Follow-up HRCT failed to identify pathology in 3 of the 7 positive studies.[101] Of the 94 divers with normal chest radiographs, 7 (7%) had bullae or blebs and 23 (24%) had other pulmonary or extrapulmonary findings; findings on HRCT were disqualifying in half of the cases.[101] The authors concluded that a routine screening chest radiograph is not reliable in asymptomatic patients; furthermore, while HRCT increases sensitivity, it detects anomalies that may lead to undue disqualification.[101] For divers who wish to return to diving after chest wall trauma, intrathoracic surgery, or traumatic pneumothorax, HRCT and pulmonary spirometry are usually performed.

For divers previously infected by COVID-19, return-to-dive guidelines have been developed, with examinations focused on cardiac and pulmonary function and exercise tolerance.[102]

FITNESS FOR HYPERBARIC EXPOSURE ASSESSMENT

Similar to divers, patients and attendants of hyperbaric chambers require fitness-to-dive assessments. Hyperbaric oxygen therapy centers treat a variety of specific indications.[103] Hyperbaric physicians, and physicians referring to these centers, should review patient medical histories, as certain medical conditions, implanted devices, and pharmaceutical therapies are contraindications for hyperbaric oxygen exposure. Pulmonary barotrauma is rare in hyperbaric chambers, likely due to the absence of immersion physiology effects and slow controlled decompressions. Patients with lung conditions that may be disqualifying for diving can usually safely complete hyperbaric chamber therapy, although a patient with severe cystic lung disease experienced pulmonary barotrauma and fatal cerebral and cardiac gas embolism after a hyperbaric treatment following 19 previous uneventful treatments in a hyperbaric chamber.[104] Such instances are extremely rare; however, radiographic imaging is recommended for individuals with clinical lung disease.

Chamber attendants are repetitively exposed to hyperbaric environments. Occupational safety and health concerns related to increased ambient pressure and fire risk are unique;[105] attendants require similar fitness-to-dive assessments. Pulmonary pathologies leading to air trapping are disqualifying.[106] Occupational exposures to dysbarism pathologies are rare, although DCS and otic barotrauma are reported.[107]

CONCLUSION

Decompression illness occurs in only a small number of divers but is an international problem that few physicians are trained to recognize or manage. Although its manifestations are often mild, the potential for permanent injury exists in severe cases, especially if unrecognized or inadequately treated. Emergency medical personnel should be aware of manifestations of decompression illness in the setting of a patient with a history of recent diving or other exposure to substantial pressure change and should contact an appropriate consultation service for advice.[108]

Divers and diving-related illness are relatively few in number, although there is a constant need for physicians to evaluate individuals wishing to participate in either recreational or professional diving. Physicians should be aware of the signs and symptoms of pulmonary barotrauma, arterial gas embolism, and decompression sickness and should be prepared to administer urgent first aid and refer patients for definitive care as rapidly as possible. Immersion pulmonary edema appears to be increasingly common, and physicians should be aware of how to evaluate subsequent risk in patients with a suggestive history.

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CHAPTER 93

Thermal Lung Injury and Acute Smoke Inhalation

Perenlei Enkhbaatar

INTRODUCTION AND EPIDEMIOLOGY

Smoke inhalation is a serious medical problem and continues to have a significant impact on the morbidity and mortality of patients with flame burns. According to the American Burn Association repository, inhalation injury is one of the most lethal characteristics of burn patients, and its presence is associated with an overall mortality rate of 20% between 2009 and 2018; mortality is only 2.9% in those patients without smoke inhalation.[1] Inhalation injury is present in 17% of patients with flame burns,[2] and its presence prolongs the length of hospital stay 2.5-fold compared to those without smoke inhalation injury (24 days vs. 10 days).[2]

Similar percentages of fire victims who have sustained smoke inhalation appear in several other countries.[3–6] In patients with combined injury, the lung is the critical organ, and the progressive respiratory failure associated with pulmonary edema is a pivotal determinant of mortality.[7–9] Although not as lethal, smoke inhalation alone is a serious problem. It is estimated by the World Health Organization that there are more than one billion people who develop airway and pulmonary inflammation as a result of inhaling smoke from indoor cooking fires, forest fires, and burning of crops.[10,11]

The inhalation of smoke has been of interest for a number of years, especially as the result of the use of gas warfare. In the 1940s there were two very large fires that focused interest on the inhalation of smoke in fire victims. The first was a fire at a nightclub in Boston called the Cocoanut Grove, where a large number of people were trapped in a burning building and consequently sustained severe inhalation injury.[12,13] It is interesting that in recent times a similar fire occurred in a nightclub near Boston in Rhode Island. The second occurred in Texas City across the bay from Galveston, Texas.[14] Here a ship exploded in a harbor and set off a chain of explosions and fires among some 50 refineries and chemical plants, resulting in more than 2000 hospital admissions of patients with smoke inhalation alone, as well as those with burn injuries, many of whom who had simultaneously inhaled smoke as well. These two disasters led to the establishment of centers for the care of burn victims and to research into the pathophysiology of burn injury. In many ways, the burn victims of the 9/11 disaster were similar to these individuals since the burns and inhalation involved combustion of petroleum products.[15,16] Approximately half (49%) of 790 victims who survived the World Trade Center attack had an inhalation injury.[16,17]

THE FIRE ENVIRONMENT: TOXIC SMOKE COMPOUNDS

Inhalation injury is caused by steam or toxic inhalants such as fumes, gases, and mists. Fumes consist of small particles dispersed in air with various irritants or cytotoxic chemicals adherent to the particles. Mists consist of aerosolized irritant or cytotoxic liquids. Smoke consists of a combination of fumes, gases, mists, and hot air. Heat, toxic gases, and low oxygen levels are the most common causes of death in a fire scene. A large variety of toxic gases and chemicals can be generated depending on the fire environment (Table 93-1).

Many of these compounds may act together to increase mortality—especially carbon monoxide and hydrogen cyanide,[18,19] for which a synergism has been found to increase tissue hypoxia and acidosis[19] and, perhaps, decrease cerebral oxygen consumption and metabolism.[20,21] Hydrogen sulfide would also be predicted to synergize with carbon monoxide since both cyanide and hydrogen sulfide are inhibitors of mitochondrial cytochrome oxidase. Victims may be incapacitated by the blinding and irritating effects of smoke, as well the decreasing oxygen concentration that occurs with combustion and results in progressive hypoxia.

Inhalation injury can be classified as follows: (1) upper airway injury, (2) lower airways and pulmonary parenchymal injury, and (3) systemic toxicity.

The extent of inhalation damage depends on fire environment: the ignition source, temperature, concentration, and solubility of the toxic gases generated. For instance, thermal and chemical compounds usually cause upper airway injury. The water-soluble materials, such as acrolein and the other aldehydes, damage the proximal airways and set off reactions that are inflammatory to the bronchi and parenchyma, whereas agents with lower water solubility such as chlorine, phosgene, nitrogen oxide, and nitrogen dioxide or N_2O_3, or even N_2O_4, are more likely to cause insidious injury.[22] Toxic gases such as carbon monoxide and cyanide rarely damage the airway but affect gas exchange, producing more systemic effects. Thus, it is important to obtain information relative to the source of the fire and the combustion products generated when treating a fire victim (Table 93-1). It is also important to know the duration of exposure and the extent to which the fire victim was in an enclosed area because this relates to the dose of toxic materials presented.

■ Carbon Monoxide

Carbon monoxide (CO) is an odorless, colorless gas that is produced by incomplete combustion of many fuels, especially cellulolytic (cellulose products) such as wood, paper, and cotton.[23] Carbon monoxide toxicity remains one of the most frequent immediate causes of death following smoke-induced inhalation injury. There are 50,000 estimated annual visits to emergency departments in the United States as result of CO poisoning.[24] The predominant toxic effect of CO is its binding to hemoglobin to form carboxyhemoglobin (COHb). The affinity of CO for hemoglobin is ~200 to 250 times higher than that of oxygen.[25] Inhalation of a 0.1% CO mixture may result in generation of a COHb level as high as 50%. The correlation of inhaled CO and COHb levels is summarized in Table 93-2.

Competitive binding of CO to hemoglobin reduces delivery of oxygen to tissues, leading to severe hypoxia, especially of the most vulnerable organs such as brain and heart. The oxygen–hemoglobin dissociation curve loses its sigmoid shape and is shifted to the left, thus further impairing tissue oxygen availability.[18] In addition, ability of CO to bind to intracellular cytochromes and to other metalloproteins contributes to CO toxicity. This competitive inhibition with cytochrome oxidase enzyme systems (most notably, cytochromes a and P-450) results in an inability of cellular systems to use oxygen.[28] Shimazu et al. have shown that extravascular binding of CO to cytochromes and other structures accounts for 10% to 15% of total body CO stores, which explains the two-compartment elimination of CO from the circulation.[29] CO also inhibits cytochrome c oxidase activity in lymphocytes. The electron chain dysfunction by CO may cause electron leakage, leading to superoxide production and mitochondrial oxidative stress. Additionally, excessive nitric oxide (and its byproduct peroxynitrite), lipid peroxidation, apoptosis, and delayed inflammation[30–33] contribute to CO toxicity at both systemic and cellular levels.

■ Symptoms and Diagnosis

The symptoms predominantly manifest in organs and systems with high oxygen utilization. The severity of clinical manifestations is

TABLE 93-1 Origin of Selected Toxic Compounds

Gases and Chemicals	Material	Source
Carbon monoxide	Polyvinyl chloride	Upholstery, wire/pipe coating, wall, floor, furniture coverings Clothing, fabric
	Cellulose	Wood, paper, cotton
Cyanide	Wool, silk	Clothing, fabric, blankets, furniture
	Polyurethane	Insulation, upholstery material
	Polyacrylonitrile	Appliances, engineering, plastics
	Polyamide	Carpeting, clothing
	Melamine resins	Household and kitchen goods
Hydrogen chloride	Polyvinyl chloride	Upholstery, wire/pipe coating, wall, floor, furniture coverings
	Polyester	Clothing, fabric
Phosgene	Polyvinyl chloride	Upholstery, wire/pipe coating, wall, floor, furniture coverings
Ammonia	Wool, silk	Clothing, fabric, blankets, furniture
	Polyurethane	Insulation, upholstery material
	Polyamide	Carpeting, clothing
	Melamine resins	Household and kitchen goods
Sulfur dioxide	Rubber	Tires
Hydrogen sulfide	Wool, silk	Clothing, fabric, blankets, furniture
Acrolein	Cellulose	Wood, paper, cotton, jute
	Polypropylene	Upholstery, carpeting
	Acrylics	Aircraft windows, textiles, wall coverings
Formaldehyde	Melamine resins	Household and kitchen goods
Isocyanates	Polyurethane	Insulation, upholstery material
Acrylonitriles	Polyurethane	Insulation, upholstery material

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varied depending on the concentration of CO. For instance, the central nervous system symptoms such as headache, confusion, and collapse may occur when the blood COHb level is 40% to 50%. Symptoms such as unconsciousness, intermittent convulsions, and respiratory failure may occur if the COHb level exceeds 60%, eventually leading to death if exposure continues. The cardiovascular manifestations result in tachycardia, increase in cardiac output, dysrhythmias, myocardial ischemia, and hypotension, depending on the severity of poisoning. The correlations of clinical manifestations and severity of CO poisoning are summarized in Table 93-3.[34,35]

Blumenthal et al. correlated the clinical signs and symptoms of CO poisoning with the concentration of inhaled CO: headache,

TABLE 93-2 COHb Levels at Various Concentrations of Inhaled CO[26,27]

CO in Atmosphere		Estimated Carboxyhemoglobin in Blood (%)
%	ppm	
0.001	10	2
0.007	70	10
0.012	120	20
0.022	220	30
0.035–0.052	350–520	40–50
0.08–0.122	800–1220	60–70
0.195	1950	80

TABLE 93-3 Symptoms and Signs at Various Concentrations of COHb

COHb %	Symptoms
0–10	None
10–20	Tightness over forehead, slight headache dilation of cutaneous blood vessels
20–30	Headache and throbbing in the temples
30–40	Severe headache, weakness, dizziness, dimness of vision, nausea, vomiting
40–50	As above; greater possibility of syncope, increased pulse and respiratory rate
50–60	Syncope, increased pulse and respiratory rate, coma, intermittent convulsions, Cheyne–Stokes respirations
60–70	Coma, intermittent convulsions, depressed cardiac and respiratory function, possible death
70–80	Weak pulse, slow respirations, death within hours
80–90	Death in less than one hour
90–100	Death within minutes

Reproduced with permission from Einhorn IN: Physiological and toxicological aspects of smoke produced during the combustion of polymeric materials. Environ Health Perspect. 1975;11:163–189.

dizziness—up to 100 ppm, 0.01% air concentration; loss of judgment, confusion, disorientation—up to 200 ppm, 0.02%; and nausea, vomiting, fatigue, confusion, disorientation, visual disturbance, and syncope, up to the onset of coma—800 ppm, 0.08% to 12,800 ppm, 1.28%.[36]

Diagnosis should be based on direct measurement of COHb levels in arterial or venous blood by co-oximetry. Portable breath analyzers may be used at the scene. Inability to differentiate oxyhemoglobin from COHb limits the use of pulse oximeters. Although there are some controversies on its reliability, fingertip pulse CO oximetry, a technology available since 2005, can be used at the scene of the fire for measurement of COHb.[37] The use of blood gas analyzers that estimate SO_2 based on measurement of dissolved PO_2 should be avoided. The measurements of acid–base balance, plasma lactate levels, and bicarbonate are helpful in management of CO poisoning with accompanying lactic or metabolic acidosis. It is important to note that high oxygen concentrations are usually administered to the victim in transit to the hospital, and some delay from cessation of exposure to measurement of CO may limit evaluation of the true extent of exposure.[38] A nomogram has been developed that relates the COHb levels of a patient to the values that may have been present at the time of smoke inhalation; this tool can be used to estimate the true degree of inhalation injury.[39]

■ Treatment

The half-life of COHb is 320 min (adult male) in room air and ~74 min in a person breathing normobaric 100% oxygen at 1 atmosphere.[40,41] These values are 30% shorter in females.[42] Therefore, all fire victims should be isolated from the fire site and given 100% oxygen en route to the hospital. Oxygen inhalation via face mask allows delivery of an inspired oxygen concentration of 50% to 60%, which is usually adequate.

To adequately treat a CO poisoning it is important also to establish COHb level as early as possible. In patients with loss of consciousness, cyanosis, or an inability to maintain the airway, 100% oxygen should be delivered via mechanical ventilation through endotracheal tube until COHb levels drop below 10% to 15%. The alternative method to rapidly decrease COHb is hyperbaric oxygen therapy (HBOT). HBOT allows CO to dissociate from cytochrome a and a3 and to increase PO_2 despite impaired hemoglobin function.[43,44] Chou et al. reported that children with CO poisoning alone who are treated with HBOT are at low risk for dying regardless of initial COHb level.[45] However, there is some debate on use of HBOT, especially in patients with burn injury. Because of the difficulty of physiologic monitoring and providing emergency procedures in small chambers, unstable hemodynamic conditions, and other complications such as seizures or aspiration of severely burned patients, the use of hyperbaric oxygen therapy is limited.[46] In severe cases, extracorporeal membrane oxygenation (ECMO) may be considered. McCunn et al. published a case report on the use of ECMO; they noted immediate reduction in the level of COHb, as well as improved oxygenation. Cardiovascular failure was reversed.[47]

Additionally, the use of pharmacologic antidotes may be of interest for efficient disassociation and elimination of CO. Some agents have been tested in preclinical studies. Roderique et al. reported that combined hydroxocobalamin and ascorbic acid efficiently converted CO to CO_2, thus reducing COHb half-life time from 33 min to 17.5 min.[48] In another study, Kitagishi et al. reported that an O_2-bound form of an iron(II) porphyrin, cyclodextrin supramolecular complex, captured CO and promoted excretion in the urine.[49] However, efficacy and safety of these agents should be further investigated to be translated to clinical practice.

■ Hydrogen Cyanide

Hydrogen cyanide is a colorless gas with the odor of bitter almonds. However, it is difficult to detect it at the site of the fire. Cyanide is a likely weapon for terrorists because of its notoriety, lethality, and availability. Hydrogen cyanide is produced in fires involving nitrogen-containing polymers (upholstery, furniture, nylon, wool, silk, and acrylics) and may produce rapid and lethal incapacitation of a victim at the fire source.[50]

Toxicity of cyanide is produced by inhibition of cellular oxygenation with resultant tissue anoxia, which is caused by reversible inhibition of cytochrome c oxidase.[51] It is toxic to a number of enzyme systems. The mechanism includes combination with essential metal ions, formation of cyanohydrins with carbonyl compounds, and sequestration of sulfur as thiocyanate. However, the main target enzyme is cytochrome c oxidase, the terminal oxidase of the respiratory chain, and involves interaction with the ferric ion of cytochrome a_3.

■ Symptoms and Diagnosis

Diagnosis at the fire scene may be difficult. Poisoning leads to central nervous system, respiratory, and cardiovascular dysfunctions resulting from inhibition of oxidative phosphorylation and may result in dyspnea, tachypnea, vomiting, bradycardia, hypotension, coma, and seizures. Electrocardiographic S-T segment elevation, which mimics an acute myocardial infarction, may be suggestive.[52] Laboratory findings of anion gap metabolic acidosis and lactic acidemia aid in confirming the diagnosis.[51] A lactic acidosis that is not rapidly responsive to oxygen therapy may be a good indicator of cyanide poisoning.[39,53] Also, an elevated mixed venous saturation is suggestive of cyanide toxicity. Cyanide increases ventilation through the carotid body by increasing peripheral chemoreceptor stimulation. Increasing ventilation may augment toxicity in the early stages. Correlations of blood cyanide concentrations with clinical symptoms are summarized in Table 93-4.[34,54]

Hydrogen cyanide is found routinely in low levels in the blood of healthy individuals (0.02 μg/mL in nonsmokers and 0.04 μg/mL in smokers). Toxicity occurs at a level of 0.1 μg/mL, and at 1.0 μg/mL death is likely.[55]

■ Treatment

Fire victims suspected to have cyanide poisoning should be removed from exposure and fully decontaminated. All victims should be

TABLE 93-4 Hydrogen Cyanide Concentrations in Air and Associated Symptoms in Humans

HCN Concentration ppm	Symptoms
0.2–5.0	Threshold of odor
10 (maximum allowed concentration)	Mild irritation of mucus membranes
18–36	Slight symptoms (headache) after several hours, irritation of throat
45–54	Tolerated for 0.5–1 h without difficulty of breathing
100	Death in 1 h
110–135	Fatal in 0.5–1 h
181	Fatal in 10 min
280	Immediately fatal

Data from Einhorn IN. Physiological and toxicological aspects of smoke produced during the combustion of polymeric materials. Environ Health Perspect. 1975;11:163–189 and Kimmerle G. Aspects and methodology for the evaluation of toxicological parameters during fire exposure. In: Polymer Conference Series: Flammability Characteristics of Materials. Salt Lake City, UT: University of Utah; 1973.

given pure oxygen (100%) and resuscitated properly if cardiopulmonary failure is present. Oxygen therapy appears to have strong beneficial effect; however, hyperbaric oxygen therapy is not recommended for the reasons previously mentioned.[51,55]

Cyanide is metabolized by hepatic rhodanese, which catalyzes the donation of sulfur from the sulfane pool to cyanide to form nontoxic thiocyanate. The half-life time of cyanide is approximately 1 to 3 h in humans.[43,56] Although there is still controversy surrounding the treatment of cyanide poisoning, there are few antidotes available that can be used by first responders. Kelocyanor (dicobalt edetate) may be useful, but is dangerous and requires experts to administer it.[57] The following agents may be considered in an intensive care setting.

Methemoglobin Generators

The therapeutic goal is to convert the ferrous ion of hemoglobin to ferric ion. The resultant methemoglobin chelates cyanide to form cyanmethemoglobin. (Cyanide has a greater affinity for binding with methemoglobin and thus is displaced from cytochrome oxidase.) The drugs of choice in this group are sodium nitrite (intravenously) and amyl nitrite (inhaled). These drugs reduce oxygen-carrying capacity; therefore, they should be used with caution, especially in patients with concomitant CO poisoning which induces COHb that may further compromise oxygen transport. These drugs should be also used with precautions in patients with shock, because they are also vasodilators and can cause hypotension. In addition, there is little evidence to suggest these measures are effective, and cardiac toxicity in people with heart disease may be problematic.[58] Thus, the methemoglobin generators should be used with extra precautions, carefully weighing patient conditions and comorbidities.

Sulfur Donors

The therapeutic goal is to convert cyanide to thiocyanate. The drug of choice in this group is sodium thiosulfate (administered intravenously). Toxicity is minimal, other than an osmotic diuretic action, which may be beneficial. However, the onset of action is quite slow. Therefore, it should be used as a second-line therapy.[18,59]

Direct Binding Agents

These are based on cobalt chemistry and chelate the cyanide ion directly. Hydroxocobalamin is the precursor of vitamin B_{12} and has very little toxicity.[18,55] Minor adverse effects include transient chromaturia, alterations in renal function, reddish skin discoloration, hypertension, and, rarely, allergic reactions.[60,61] The agent detoxifies cyanide by binding with it and forming cyanocobalamin, which is then excreted in the urine. The drug is currently approved for use by the U.S. Food and Drug Administration (FDA). However, there is controversy around its efficacy.

PATHOPHYSIOLOGY

Below we consider thermal injuries to the tracheobronchial tree and the lung parenchyma.

Tracheobronchial Tree

In normal conditions, the airway provides a protective barrier against toxic agents and bacteria, maintaining a sterile lung environment.

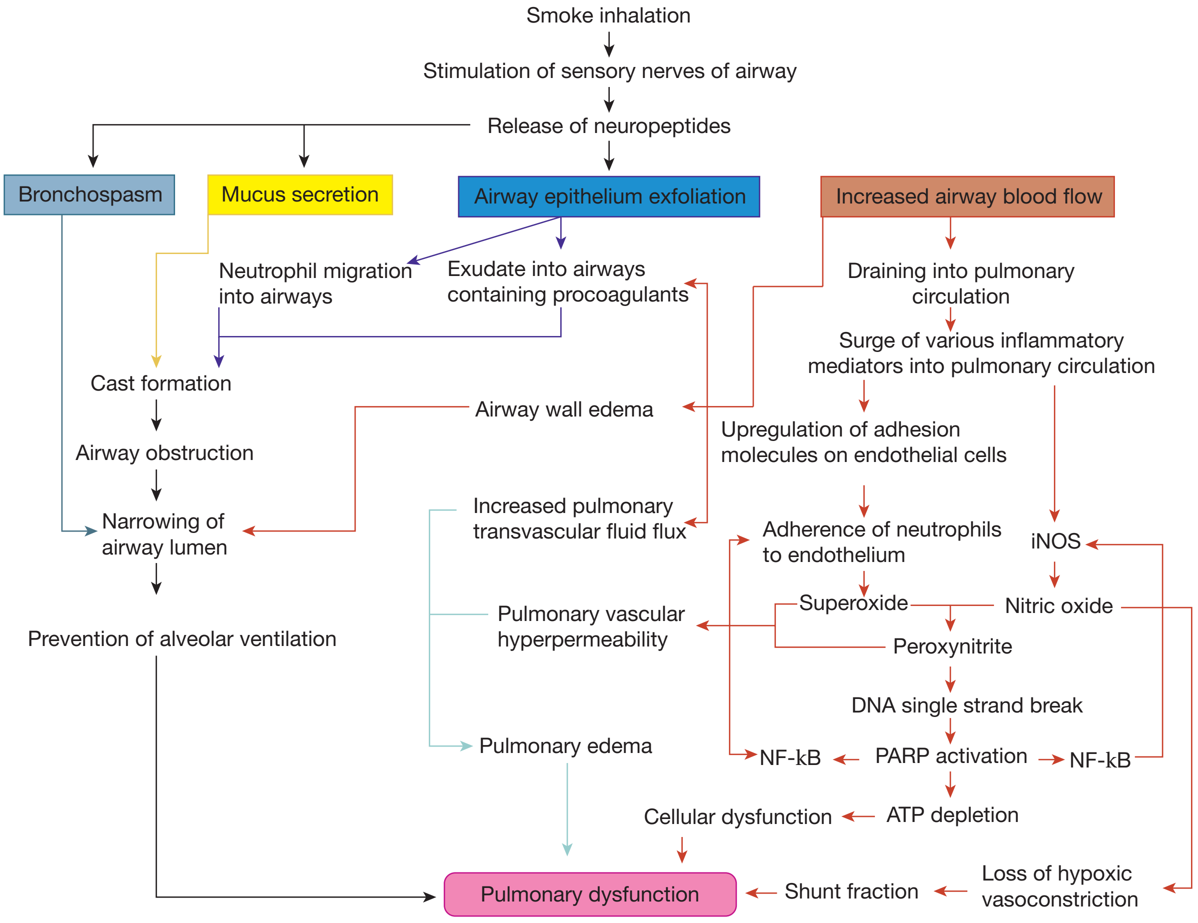
Smoke inhalation
Stimulation of sensory nerves of airway
Release of neuropeptides
Bronchospasm
Mucus secretion
Airway epithelium exfoliation
Increased airway blood flow
Neutrophil migration into airways
Exudate into airways containing procoagulants
Draining into pulmonary circulation
Surge of various inflammatory mediators into pulmonary circulation
Cast formation
Airway wall edema
Upregulation of adhesion molecules on endothelial cells
Airway obstruction
Narrowing of airway lumen
Increased pulmonary transvascular fluid flux
Adherence of neutrophils to endothelium
iNOS
Superoxide
Nitric oxide
Prevention of alveolar ventilation
Pulmonary vascular hyperpermeability
Peroxynitrite
DNA single strand break
Pulmonary edema
NF-kB
PARP activation
NF-kB
Cellular dysfunction
ATP depletion
Pulmonary dysfunction
Shunt fraction
Loss of hypoxic vasoconstriction

Figure 93-1 Mechanisms of lung parenchymal damage and the role of airway changes following smoke inhalation injury. ATP, adenosine triphosphate; iNOS, inducible nitric oxide; NF-kB, nuclear factor kappa B; PARP, poly(ADP-ribose) polymerase.

It also facilitates airflow within the lung to ensure efficient gas exchange. Following smoke inhalation, the normal function of the airway is compromised. With rare exceptions, such as inhalation of steam, injury to the airway is usually from the chemicals in smoke. The heat capacity of air is low, and the bronchial circulation is very efficient in warming or cooling the airway gases so that most gases are at body temperature as they pass the glottis.[62] Flames must be in almost direct contact with the airway to induce thermal injury.[63]

The chemicals in smoke are dependent on the materials that are being burned; however, for the most part the host response is similar. In most instances, biologic materials such as cotton fabric, wood, or grass, or their products such as cattle feces (commonly used as fuel in developing countries) are the fuel for the fire. These contain caustic materials, such as reactive oxygen (ROS) and nitrogen species (RNS), as well as organic acids and aldehydes.[64] The chemicals interact with the airway to induce an initial response to trigger an inflammatory response.

Although the degree of airway dysfunction may vary depending on the severity of inhalation injury, it can generally be characterized by a few major pathologic alterations that lead to the narrowing/occlusion of the airway lumen, reducing or preventing the normal alveolar gas exchange. The factors leading to the airway lumen narrowing are (1) airway hyperemia; (2) formation of an airway obstructive cast; (3) increased mucus secretion; and (4) bronchospasm (Fig. 93-1).

Airway inflammation plays a major role in the overall response to inhalation injury.

Hyperemia of the airway is such a consistent bronchoscopic finding in smoke inhalation that it is used to diagnose the injury.[65,66] Other variables that are used to establish a diagnosis include injury in an enclosed space, singed nasal hair, and soot in sputum. However, although these findings may be present, the subject may still not develop signs of pulmonary edema characteristic of inhalation injury.

The normal bronchial blood circulation is about 1% of cardiac output. Following smoke inhalation, airway blood flow rapidly increases, resulting in airway wall edema and a leak of protein-rich plasma into the airways. The data presented in Fig. 93-2 highlight the dramatic (10- to 15-fold) increase in tracheal (A) and bronchial (B) blood flow following smoke inhalation that leads to airway wall edema, as confirmed by the macroscopic picture. This illustrates severe edema formation in the tracheal soft tissue compared with the trachea of an uninjured sheep (C).

Many of the studies on the bronchial circulation following smoke inhalation injury have been performed in sheep because these animals have a single bronchial artery[67] and a single lymphatic that drains the lung, allowing for measurement of pulmonary transvascular fluid flux.[68] Abdi et al. reported a 10-fold increase in bronchial blood flow within 20 min of smoke inhalation in sheep.[69] These

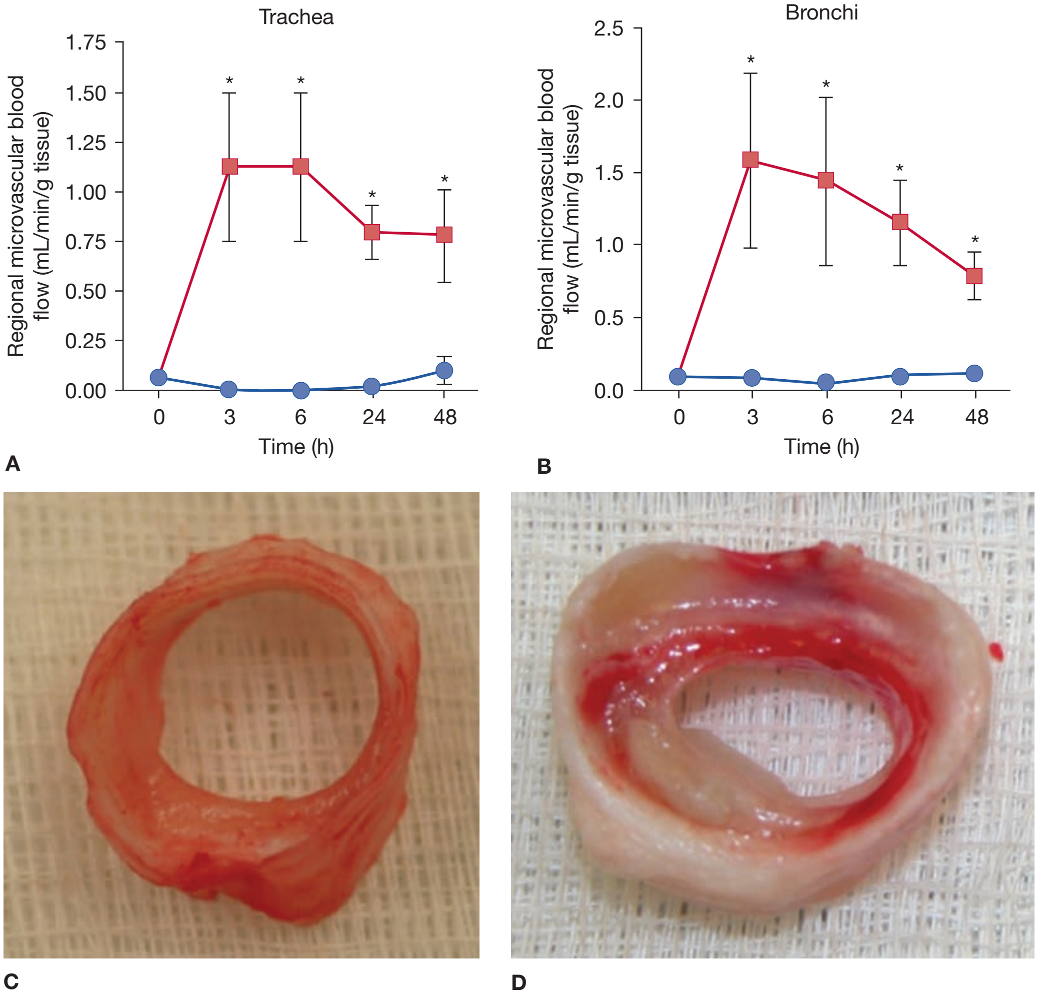

Figure 93-2 Time changes in tracheal (**A**) and bronchial (**B**) blood flow in sheep following cotton smoke inhalation (48 breaths) injury. Blood flow was determined by microsphere injection technique. Data are expressed as ± SEM. $^*p < 0.05$ vs. sham. *Closed circles* represent sheep without injury (sham smoke), and *closed squares* represent sheep with smoke inhalation. **C.** Macroscopic picture of trachea taken at 48 h after sham smoke; and **D.** Macroscopic picture of trachea taken at 48 h after smoke inhalation.

same animals demonstrated a sixfold increase in pulmonary transvascular fluid flux and a fall in $Pa_{O_2}/Fi_{O_2} \leq 300$, but these findings were delayed (24 h).

Similar findings have been reported in patients with smoke inhalation alone, or with the combination of a large cutaneous thermal injury and smoke inhalation.[70] A few investigators have also demonstrated ~10- to 20-fold increases of airway blood flow, depending on the anatomic localization of the airways, using the same model.[71–73] These changes in blood flow are associated with increased bronchial microvascular permeability to protein and small particles[74] and increased pressure.[75] The ablation of bronchial blood flow, by either a ligation of the bronchial artery or the nebulization of adrenergic agonist epinephrine, significantly improved pulmonary gas exchange in the sheep smoke inhalation and burn injury models.[71,73,76,77] Simultaneous with the changes in the function of the bronchial microvasculature, there is a loss or shedding of the bronchial columnar epithelium.[78,79] As noted, these changes result in the formation of a transudate with a protein content similar to an ultrafiltrate of plasma.[80]

The augmented airway circulation not only leads to the airway wall edema, but it also contributes to the formation of airway obstructive casts. In conditions where the basement membrane is impaired due to smoke inhalation, the increased airway blood flow leads to the massive airway transudation. The transudate, containing procoagulants, combines with copious secretions from goblet cells and leukocytes[81] to form a solid airway obstructive cast. Airway obstructive casts not only reduce or prevent normal air passage, they also become a perfect culture media for bacterial growth. In Fig. 93-3, massive airway obstructive casts from human following smoke inhalation injury are shown. The airway obstructive casts, positive for submucosal gland mucus 5B (MUC5B), occupy most of the airway lumen and prevent normal aeration of the alveoli (Fig. 93-4A,B).

Early in the response these secretions are fluid and form a foamy material in the airway that many mistake for severe pulmonary edema in humans.[82] After several hours, this transudate/exudate solidifies or clots in the presence of fibrin, forming firm obstructive materials in the airways. Figure 93-4C shows a presence of fibrin in the airway as a part of the obstructive cast. The mechanism of airway obstructive cast formation is illustrated in Fig. 93-5. These obstructive materials formed in the upper airway may migrate to the lower airways and alveoli.[81] The material is problematic from several stand points. In some rare instances of severe airway injury, the materials can induce total airway obstruction—a life-threatening problem (Fig. 93-3).

The presence of fibrin makes the removal of airway obstructive cast extremely difficult. Occlusion of some of the bronchi or bronchioles in association with high production of NO can lead to

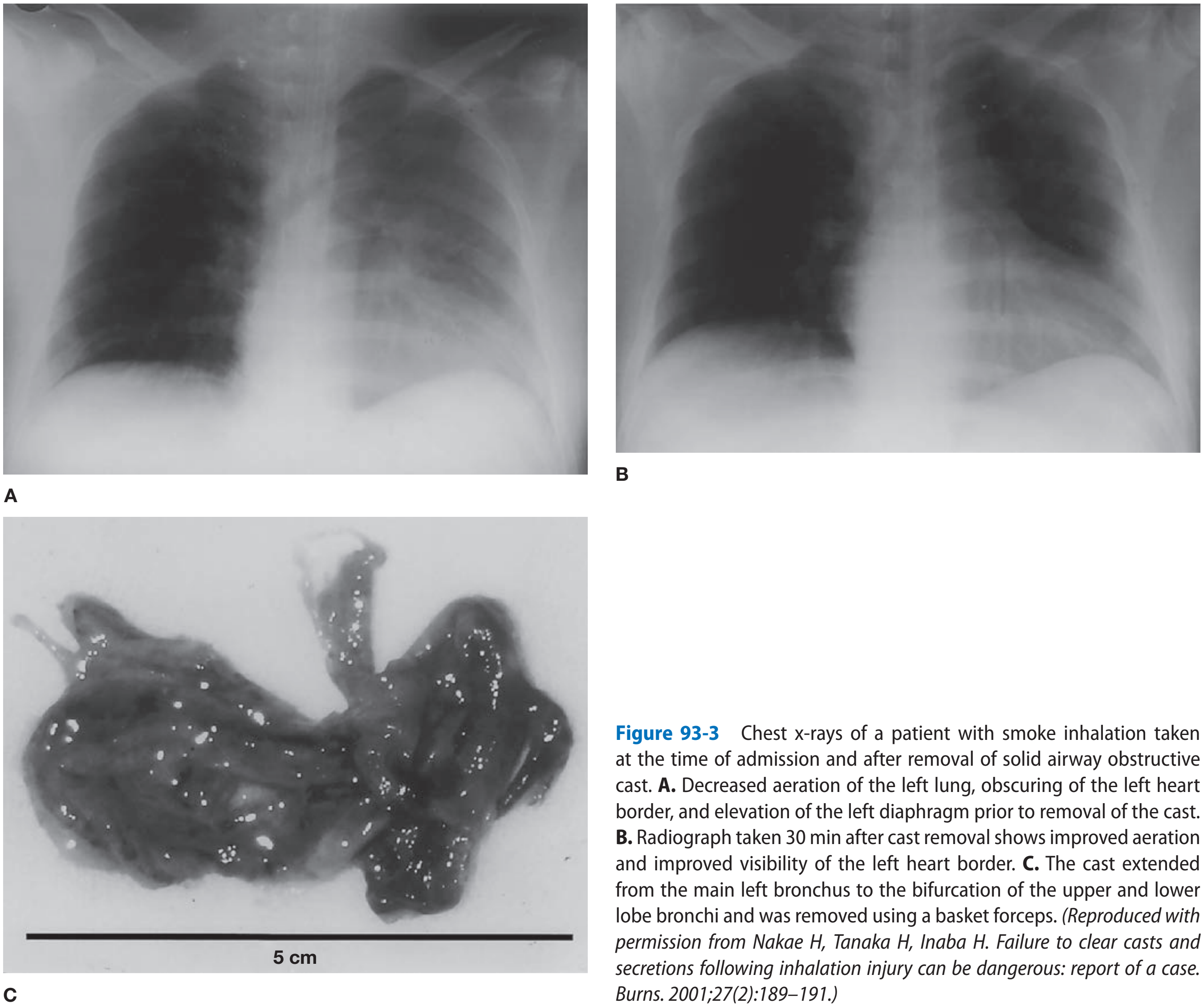

Figure 93-3 Chest x-rays of a patient with smoke inhalation taken at the time of admission and after removal of solid airway obstructive cast. **A.** Decreased aeration of the left lung, obscuring of the left heart border, and elevation of the left diaphragm prior to removal of the cast. **B.** Radiograph taken 30 min after cast removal shows improved aeration and improved visibility of the left heart border. **C.** The cast extended from the main left bronchus to the bifurcation of the upper and lower lobe bronchi and was removed using a basket forceps. *(Reproduced with permission from Nakae H, Tanaka H, Inaba H. Failure to clear casts and secretions following inhalation injury can be dangerous: report of a case. Burns. 2001;27(2):189–191.)*

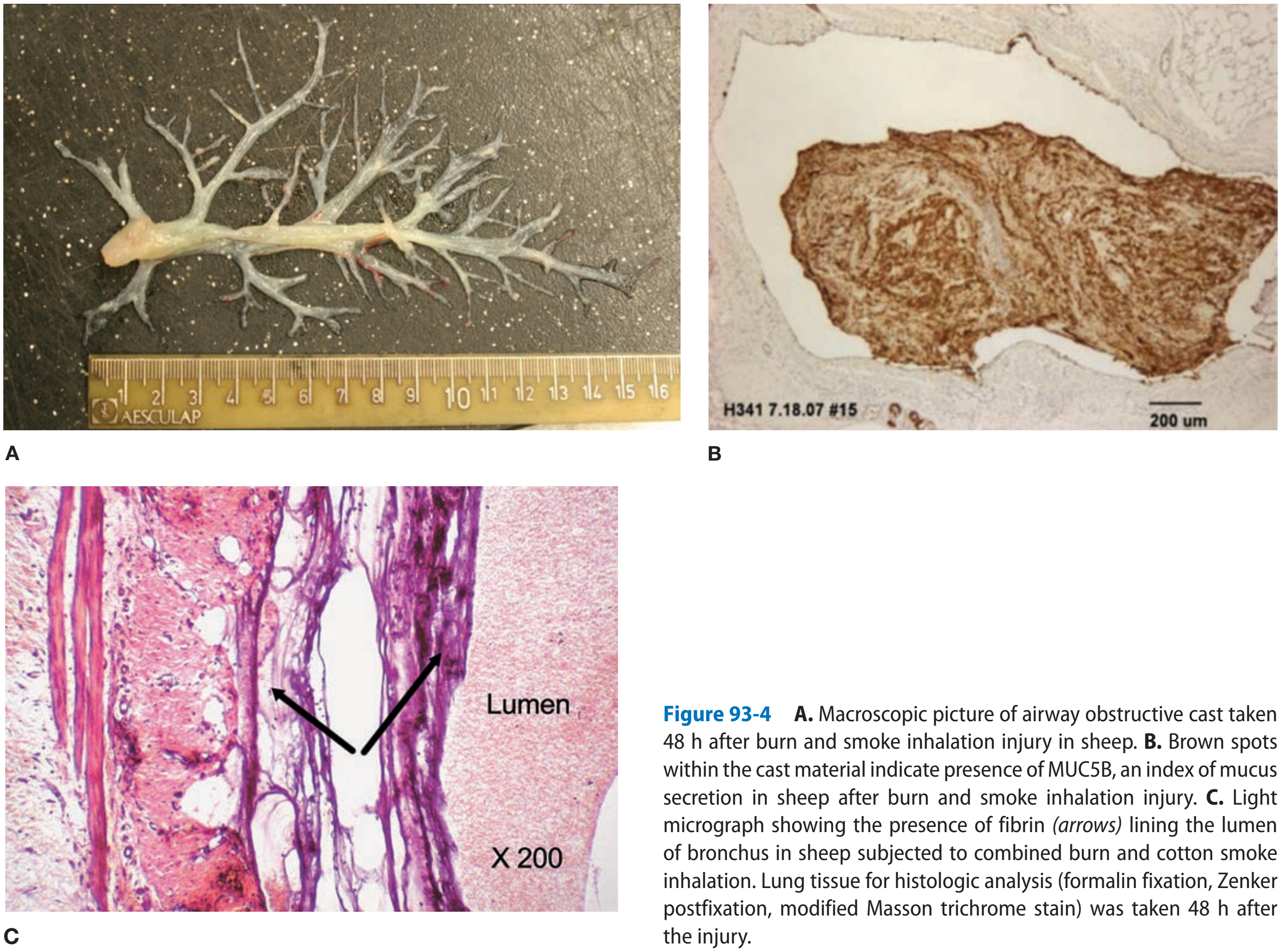

Figure 93-4 **A.** Macroscopic picture of airway obstructive cast taken 48 h after burn and smoke inhalation injury in sheep. **B.** Brown spots within the cast material indicate presence of MUC5B, an index of mucus secretion in sheep after burn and smoke inhalation injury. **C.** Light micrograph showing the presence of fibrin *(arrows)* lining the lumen of bronchus in sheep subjected to combined burn and cotton smoke inhalation. Lung tissue for histologic analysis (formalin fixation, Zenker postfixation, modified Masson trichrome stain) was taken 48 h after the injury.

a loss of hypoxic pulmonary vasoconstriction and increased shunt fraction. In addition, loss of hypoxic pulmonary vasoconstriction with inhalation injury has been reported.[83] Lastly if single bronchi are occluded while the patient is on a volume-cycled ventilator, there could be overstretch and barotrauma to the alveoli of the nonoccluded portion of the lung. In Fig. 93-6, high-resolution computed tomographic *(upper panel)* and magnetic resonance *(lower panel)* images illustrate massive airway obstructive casts and edema surrounding the trachea, main bronchi, and great vessels.

The airway is also richly innervated with vasomotor and sensory nerve endings.[84] It is known that these fibers release neuropeptides in response to caustic materials.[85] Neuropeptide release can cause activation of nitric oxide synthase, stimulate chemokine activity, and change microvascular permeability.[86] The resultant activities lead to formation of reactive oxygen and nitrogen species. Some of the latter are very potent oxidants that can damage DNA. Damage to DNA causes the activation of a repair enzyme poly (ADP-ribose) polymerase (PARP). This enzyme depletes the cell of high-energy phosphates and causes the activation of nuclear factor kappa B (NF-kB). Activation of the nuclear factor causes the upregulation of iNOS and IL-8, creating accelerated production of reactive oxygen and nitrogen species (Fig. 93-1).[44]

NO and 3-nitrotyrosine, an index of reactive nitrogen species, as well as iNOS mRNA and protein have been reported to be elevated in the airway after smoke inhalation.[87] PAR, the product of the constitutive enzyme PARP, was identified in lung tissue following smoke inhalation combined with burn[88] and pneumonia.[89] Inhibition of PARP prevented the formation of PAR, the upregulation of NF-kB, and the formation of 3-nitrotyrosine.[90] Airway inflammation is not

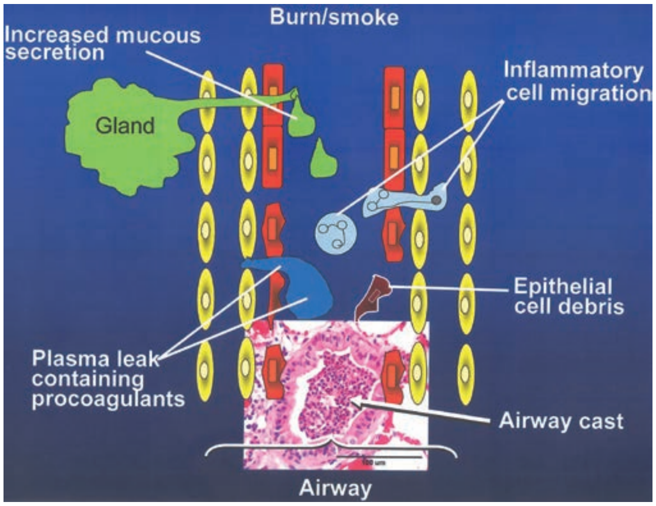
Burn/smoke
Increased mucous secretion
Gland
Inflammatory cell migration
Epithelial cell debris
Plasma leak containing procoagulants
Airway cast
Airway

Figure 93-5 Pathophysiologic process involved in the formation of obstructive airway material following thermal injury. At the bottom is a microscopic picture of a bronchiole almost completely blocked by airway obstructive material containing mostly mucus/fibrin and inflammatory cells. Sheep lung tissue was taken for histologic analysis 48 h after combined burn and smoke inhalation injury.

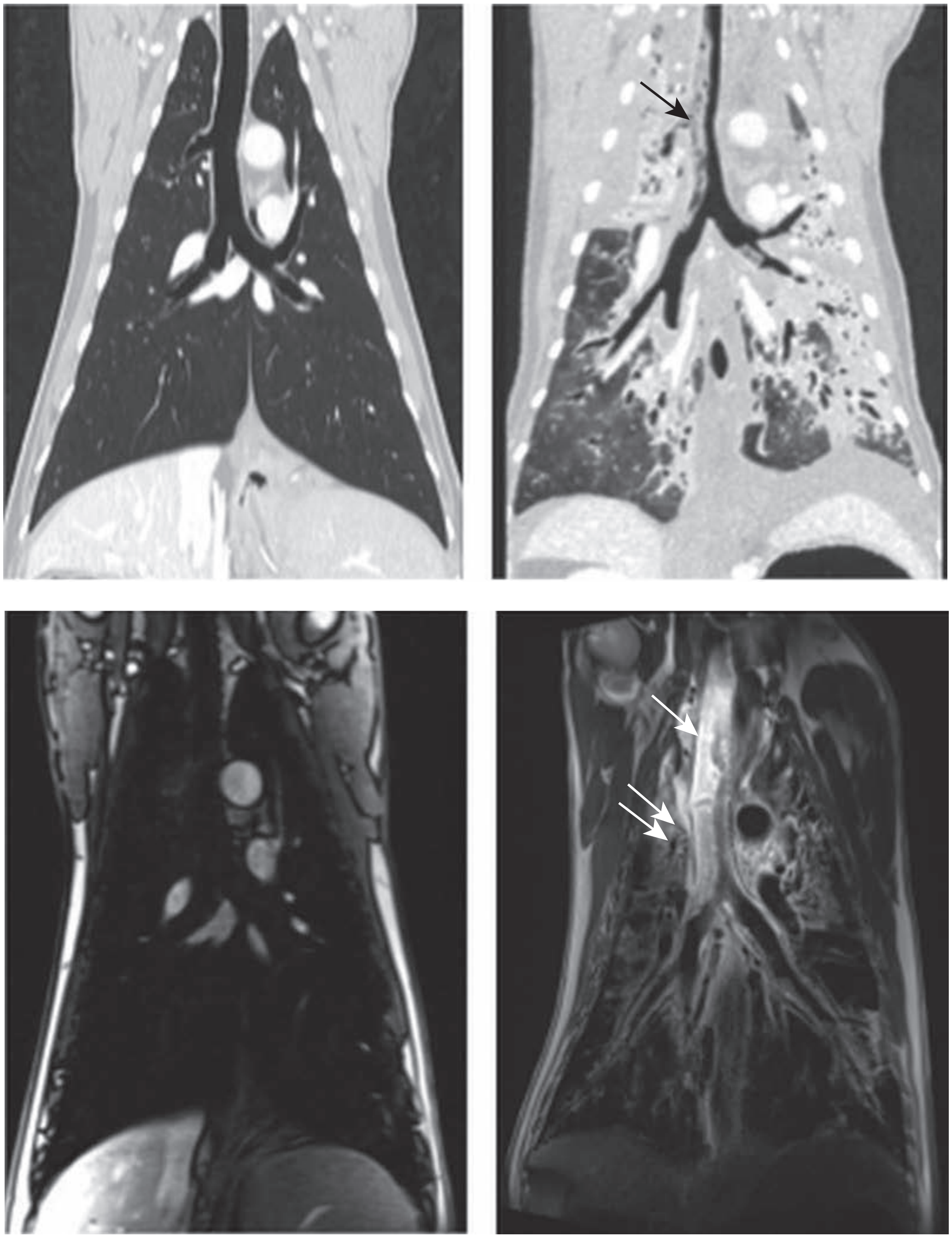

Figure 93-6 Coronal reformatted computed tomographic *(upper panel)* and magnetic resonance *(lower panel)* images obtained before and after (24 h) cotton smoke inhalation in sheep. Shown are casts in the upper airway *(single black arrow)*, including accessory right upper lobe causing its collapse. Severe edema surrounding the trachea, main bronchi, and great vessels is present in a craniocaudal gradient. *Double black arrows:* consolidative collapse of the right upper lobe.

seen in a typical asthma model in the presence of a PARP inhibitor or in mice lacking the PARP gene.[90]

■ Lung Parenchyma

As noted above, lung parenchymal changes, as reflected in reduced Pa_{O_2}/Fi_{O_2}, reduced lung compliance, and increased edema formation, are delayed. The delay is dependent on the severity of airway injury.

Lung injury is associated with an increased pulmonary transvascular fluid flux.[87] The degree of transvascular fluid is proportional to the duration of smoke exposure and is independent of the levels of CO in the inhalant gas.[91] The factors responsible for fluid leak are codified in the Starling–Landis equation.[23,92] The variables of this equation relate fluid movement to pressure and permeability variations. With inhalation of smoke there is a reduction in reflection coefficient (permeability to protein), an increase in filtration coefficient (permeability to small particles), and an increase in pulmonary microvascular pressure.[93–95] Figure 93-7 demonstrates that pulmonary transvascular fluid flux in sheep following smoke inhalation is due to changes in both microvascular permeability and pressure. It appears that microvascular changes are responsible for the early event.

Animals that have been exposed to smoke inhalation injury are also noted to have reduced Pa_{O_2}/Fi_{O_2}. The change in this variable

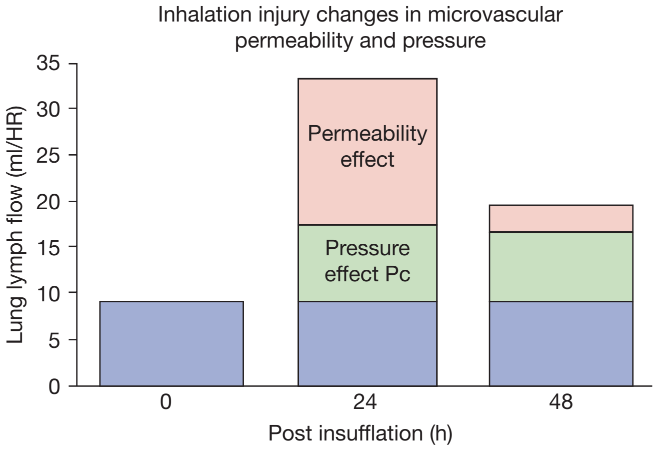

Figure 93-7 Diagram showing portion of edema resulting from either changes in pulmonary microvascular permeability or pressure at 24 and 48 h after inhalation injury. *(Data from Isago T, Fujioka K, Traber LD, et al. Derived pulmonary capillary pressure changes after smoke inhalation in sheep. Crit Care Med. 1991;19(11):1407–1413.)*

shows correlation with the histology injury scores and changes in transvascular fluid flux.[88] In addition, loss of hypoxic pulmonary vasoconstriction in the injured animals helps explain the poor oxygenation seen.[89]

As in the airway, lung parenchymal injury is markedly reduced by administration of iNOS or PARP inhibitors and is associated with the reduction of PAR and 3-nitrotyrosine.[72,87,96]

The venous outflow of the bronchial circulation drains into the pulmonary microcirculation at the precapillary level.[97] The fact that initial damage to the airway appears to drive the pathophysiology of the parenchyma led investigators to hypothesize that the bronchial blood flow might deliver cytotoxic materials or cells into the pulmonary microcirculation. To test this hypothesis, several investigators have tied off the bronchial artery of sheep and then exposed the animals to smoke.[74,71,98] The hypothesis was affirmed in these studies: Lung parenchymal changes were reduced.

Recently, Lange et al. demonstrated that nebulized epinephrine attenuated smoke inhalation–induced increases in both tracheal and bronchial blood flow and improved pulmonary gas exchange.[73] What could be the linkage among the airway, the bronchial venous drainage, and parenchymal injury to the lung? Neutrophils activated in the bronchial circulation flow out into the bronchial venous drainage. Activated polymorphonuclear cells (PMNs), especially neutrophils, are "stiff." The diameter of neutrophils that have been fixed is approximately 7 μm.[99] Since these cells have been dehydrated in alcohol as part of the fixation process, unfixed cells are much larger (on the order of 12 μm). The pulmonary capillary is small, with an average diameter of 6 μm.[99] Normally, the large neutrophil can traverse the pulmonary capillary by changing shape. However, when many neutrophils have been activated in the bronchial areas, their F-actin is activated, and the stiff cells cannot deform. The cells are carried to the pulmonary microvasculature, where they are impaled by the narrow pulmonary capillaries. The activated neutrophils release ROS and proteases that damage the parenchyma.

The following evidence supports this concept of neutrophil cytotoxicity. Oxidative processes are well known following inhalation injury. There is lipid peroxidation and release of proteolytic enzymes following injury.[100–102] Administration of protease inhibitors or scavengers of ROS reduces the response to smoke inhalation[100,103,104] when activated PMNs lose the L-selectin on their surface. This L-selectin shedding is prevented by treatment with an L-selectin antibody.[105] Treatment of the cells with an antibody to L-selectin prevents the changes in transvascular fluid flux and other aspects of parenchymal damage.[106] The final proof of this hypothesis was based on depletion of the animals' neutrophils to determine its effect on the inhalation injury. In studies of sheep depleted of leukocytes, a high percentage of the parenchymal response to smoke inhalation was blocked.[107]

In addition to depletion of antioxidants, it also has been reported that burned patients are depleted of arginine.[108] When arginine levels are low, nitric oxide synthase produces superoxide rather than nitric oxide.[109] Administration of arginine may assist in reducing the oxidation that occurs with inhalation injury. However, the need to administer the arginine as arginine hydrochloride (because of solubility) limits the amount that may be given intravenously without producing acidosis. Efficacy of arginine supplementation was demonstrated in animal models of burn and smoke inhalation injury.[110]

Smoke inhalation injury, especially when it is combined with cutaneous burns, causes both local airway and systemic coagulopathy.[111–114] The hypercoagulable state in burn patients during the initial 24 h is associated with high levels of activated factor VII (FVIIa), thrombin-antithrombin complex (TAT), and PAI-1, and low levels of antithrombin.[115] In concert, the results of these studies may suggest that a high rate of fibrin or thrombin formation and its diffuse deposition in the microvasculature during the first days following injury, along with a relatively ineffective fibrinolysis due to excess PAI-1, may play an important pathophysiologic role in the development of organ dysfunction.

■ Treatment

Treatment of smoke inhalation is complex. There is no defined and uniformly accepted standard, and the therapeutic approach varies among burn centers. An example of an evidence-based protocol for patients (0–18 years) with smoke inhalation injury at Shriners Hospitals for Children at Galveston[116] is summarized in Table 93-5.

The airway is a major concern immediately after the inhalation injury. Airway management is very difficult in patients with combined burn and inhalation injuries. Intubation of patients with burns of the soft tissues of the face, oropharynx, and neck is challenging. Burn injury to these areas results in almost immediate and severe edema and swelling.[117] Intubation in such an individual requires great skill. Securing the tube also is difficult. Accidental removal of the endotracheal tube can easily happen and may be

TABLE 93-5 Example of an Evidence-based Protocol for Patients (0–18 years) with Smoke Inhalation Injury

- Titrate humidified high-flow oxygen to maintain SaO_2 >90%
- Cough, deep breath exercises every 2 h
- Turn patient side to side every 2 h
- Chest physiotherapy every 2 h
- Nebulize 20% N-acetylcysteine (3 mL) every 4 h for 7 days; co-nebulize with a bronchodilator (albuterol) if wheezing
- Alternate aerosolizing 5000–10,000 units of heparin (in 3 mL normal saline) every 4 h for 7 days
- Nasotracheal suctioning as needed
- Early ambulation
- Sputum cultures for intubated patients every Monday, Wednesday, and Friday
- Pulmonary function studies at discharge and at outpatient visits
- Patient and family education about the disease process

lethal. Often burns and/or the chemicals in smoke can damage the larynx, and placement of the tube may cause damage and delay healing. Tracheostomy is sometimes performed but may be difficult if the tube has to be placed through burned skin on the neck. For information on this, the reader is referred to chapters in Herndon's *Total Burn Care*.[118,119]

To prevent airway obstruction, vigorous airway toilet should be performed. The airway cast material contains fibrin. Experimentally, use of heparin has been reported to be effective in reducing airway obstruction.[120] Many burn units nebulize heparin into the airways of patients with inhalation injury.[121] Of note, heparin requires the presence of antithrombin to be effective, and this factor has been reported to be deficient following burn injury.[113,122] Consequently, antithrombin has been reported as effective in these situations in animal studies.[113,114,123–126] Intravenous administration of antithrombin has also been shown to reduce mortality and morbidity in burn patients.[127] Antithrombin may also act as an anti-inflammatory agent.[128] Because concomitant use of heparin prevents antithrombin's anti-inflammatory effects, administration of these compounds by different routes was suggested in large animal, translational studies (i.e., heparin administration via nebulization and systemic administration of antithrombin, to achieve maximum local [airway] anticoagulant and systemic anti-inflammatory effects).[113,129] Tasaki et al. also reported beneficial effects of nebulized heparin combined with intravenous infusion of anti-inflammatory agents.[130]

Once obstructive materials have formed in the airway, anticoagulant therapy (heparin and antithrombin) is ineffective in their removal. Animal studies have demonstrated that tissue plasminogen activator can be effective.[112] Aerosolized tissue plasminogen activator has also been reported to be useful in removing bronchial obstructive material in patients who have had Fontan procedures for complex congenital heart diseases.[131,132]

To alleviate airway smooth muscle spasm, nebulized albuterol has been used successfully both in an animal model of smoke inhalation and in burn patients with concomitant smoke inhalation.[133,134] Other bronchodilators, such as nebulized tiotropium bromide and epinephrine, have been shown to be beneficial in an animal model of inhalation injury.[73,135]

Because of almost immediate airway hyperemia following smoke inhalation, use of nebulized agents that modulate augmented airway blood flow may be of particular importance. Lange et al. recently reported that nebulized epinephrine, a nonspecific adrenergic agonist, reduced both tracheal and bronchial blood flow and improved arterial oxygenation in a sheep model of cotton smoke injury.[69] Lopez et al. confirmed the latter result that nebulized epinephrine reduced airway mucosal and pulmonary parenchymal edema in sheep with combined burn and smoke inhalation.[136]

Nebulized epinephrine may be of particular interest in management of inhalation injury since it has both alpha (vasoconstriction) and beta (bronchodilation) effects. Recently, Fukuda et al. reported superior effects of nebulized epinephrine versus nebulized albuterol, as well as nebulized phenylephrine (specific α1-adrenergic receptor agonist) in ameliorating severity of acute lung injury in an ovine model of combined burn and smoke inhalation,[137] confirming that both alpha and beta agonist effects are required for more efficient management of airway dysfunctions. The safety of the nebulized epinephrine was also tested in a pilot clinical study involving pediatric burn patients with concomitant smoke inhalation injury.[138] However, further larger clinical studies are needed to assess the safety and efficacy of such therapy.

The importance of reducing airway hyperemia has been repeatedly shown in animal models by ablating the bronchial artery.[71,74,76,77,98] Local administration of various compounds to the bronchial artery that attenuate inflammation prevents many pathologic changes following smoke and burn injury in sheep.[139–141] Although such therapies (ligation and cannulation of bronchial artery for drug infusion) are not feasible in clinical practice, these findings strongly suggest the critical role of airway dysfunction (hyperemia, inflammation) in the pathophysiology of lung injury after smoke inhalation. The findings also suggest the crucial importance of efficient airway management in alleviating severe lung injury following smoke inhalation.

Many other drugs have also proved effective in reducing the injury to the lung parenchyma of animal models of inhalation injury, including cyclooxygenase inhibitors,[142] iNOS inhibitors,[72] PARP inhibitors,[23] and free radical scavengers,[103] as well as the anticoagulant factors[113,129] mentioned above. However, only the last noted are in clinical use and/or have been studied in clinical trials.[129,143]

Recent preclinical studies propose the use of cellular therapy. Ihara et al. demonstrated efficacy of intravenously administered adipose-derived mesenchymal stem cells (MSCs) in sheep with severe smoke inhalation injury.[144] Asmussen et al. reported beneficial effects of human bone marrow–derived MSCs in an ovine acute lung injury model induced by smoke inhalation and pneumonia.[145] Further studies are needed to investigate possible long-term safety issues related to possible malignancy.

Optimal dose-determining studies in patients with or without concomitant skin burns should be performed. A recent report by Baljinnyam demonstrated that skin burns diminish the beneficial effects of MSCs on smoke-induced lung injury by promoting migration of MSCs from the pulmonary tissue to the injured skin area, possibly via expression of Sdf-1 protein.[146]

Mechanical ventilation is indicated in cases of respiratory failure. However, mechanical ventilator management is challenging. Because of severe airway pathology, including massive airway obstructing casts, airway mucosal edema, and the presence of chest wall thermal injuries, in many instances, conventional methods of ventilation can no longer sustain pulmonary function. Sousse et al. retrospectively compared the effects of high (15 mL/kg) and low (9 mL/kg) tidal volume ventilation in pediatric burn patients and concluded that high tidal volume ventilation significantly decreased ventilator days, PEEP requirements, and the incidence of atelectasis, despite an increased incidence of pneumothorax.[147] The results of this study suggest that burn patients with smoke inhalation may require mechanical ventilation with higher tidal volumes than usually recommended. However, a prospective, multicenter clinical trial is needed to carefully weigh benefits versus harm.

To overcome the conventional ventilation challenges in burn patients with smoke inhalation, alternative methods, including percussive ventilation, have been proposed.[148] High-frequency percussive ventilation (HFPV) has been shown to improve oxygenation,[149] decrease the incidence in pneumonia, and improve survival.[148] In addition, it has been suggested that HFPV is superior to other methods of percussive ventilation, for example, high-frequency oscillatory ventilation and high-frequency jet ventilation.[150]

Hale et al. reported that independent of ventilatory method, simple prone positioning improves oxygenation in adult burn patients with severe acute respiratory distress syndrome, inducing a prompt increase in the Pa_{O_2}/Fi_{O_2} ratio. The authors concluded that prone positioning can be safely used in a burn intensive care unit to achieve an increase in Pa_{O_2}/Fi_{O_2} ratio.[151]

Extracorporeal membrane oxygenation (ECMO) has been used in burn patients with some success.[152] Techniques have now been developed in animal models of inhalation injury that involve a unique form of CO_2 removal called arteriovenous CO_2 removal or AVCOR. Off-the-shelf CO_2 removal devices used in extracorporeal bypass and cardiopulmonary bypass have been modified to enable the devices to be driven by the subject's own arterial pressure.[153] The devices were tested in animal models and shown to be very successful in reducing pathophysiologic measures, morbidity, mortality, and days of ventilatory support in models of inhalation injury.[154–156]

Finally, some pretreatment for smoke inhalation should be considered. People who are chronically exposed to smoke, such as farmers who burn crops, individuals with fires in their huts, and fire fighters may benefit from pretreatment. For example, there are reports that individuals who are chronically exposed to smoke are depleted of antioxidants.[157] Consequently, supplementation of antioxidants should be considered.[157]

CONCLUSION

The diagnosis and treatment of smoke inhalation injury are complex. Standardized criteria for the diagnosis of smoke inhalation injury and recommendations for use of specific pharmacologic agents are lacking. Multicenter, prospective, randomized, large-scale clinical trials are needed to test the efficacy and safety of promising pharmacologic agents identified in basic and translational studies (e.g., nebulized fibrinolytics, anticoagulants, beta or mixed beta- and alpha-adrenergic agonists, antioxidants).

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Dedicated to the memory of Dr. Daniel L. Traber, who was my mentor and the coauthor of this chapter in the previous edition.

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PART 13

Pulmonary Complications of Nonpulmonary Disorders

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CHAPTER 94

Noninfectious Pulmonary Complications of Hematopoietic Stem Cell and Solid Organ Transplantation

Hemang Yadav
Steve G. Peters
Robert M. Kotloff

HEMATOPOIETIC STEM CELL TRANSPLANTATION

Hematopoietic stem-cell transplantation (HSCT) is a potentially curative treatment option for hematologic and lymphoid cancers, selected solid tumors, and nonneoplastic diseases, including autoimmune disorders, amyloidosis, and aplastic anemia.[1] Since the first HSCT was performed in 1956, there has been a steady increase in the number performed worldwide, with more than 35,000 autologous and 30,000 allogeneic HSCTs now performed annually.[2] In the United States in 2018, a total of 9028 allogeneic and 14,006 autologous HSCTs were performed.[3] As peritransplant management strategies have improved, HSCTs are being performed increasingly often for a wider range of conditions, and in patients who are older and with more comorbidities.

During HSCT, patients undergo high-dose conditioning chemotherapy and/or radiation therapy with a view to eradicate their immune system along with any residual malignant cells. Stem cells are collected beforehand and are administered after conditioning is complete to reconstitute the immune system. HSCT may be autologous (where the donor stem cells are the patient's own) or allogeneic (where the donor stem cells are from an appropriately matched donor). The main indications for autologous transplant include multiple myeloma and lymphomas. The main indications for allogeneic transplants include acute and chronic leukemia, lymphoma, and myelodysplastic syndrome. Stem cells are typically harvested from peripheral blood after mobilization with agents such as G-CSF, cyclophosphamide, and plerixafor, but they can also be harvested directly from bone marrow or from cord blood.[3]

Autologous HSCT is always myeloablative: the conditioning regimen needs to eradicate any malignant cells that remain after induction chemotherapy, so no residual marrow remains. Allogeneic HSCT has intrinsic graft-versus-tumor effect, where the donor bone marrow attacks residual tumor cells. This allows for the option of nonmyeloablative and reduced-intensity conditioning regimens. These regimens are lower intensity so may leave residual tumor cells behind, but they are also easier to tolerate for older patients and those with more comorbidities.

Following HSCT, the immune system recovers along predictable patterns depending on the underlying disorder, type of transplant, stem cell source, and posttransplant complications.[4] Recovery occurs faster in autologous transplant recipients, in those who receive peripheral blood stem cell grafts, and in those allogeneic transplant recipients who receive nonmyeloablative conditioning. The posttransplant period is classically divided into three phases: peri-engraftment, early posttransplant, and late posttransplant.[5] The peri-engraftment phase (0 to 30 days) is characterized by neutropenia and breaks in the mucocutaneous barriers with a high burden of sepsis, pneumonia, aspiration, and critical illness. The early post-engraftment phase (30–100 days) is characterized by impaired cell-mediated immunity. The impact of this cell-mediated defect is greater in allogeneic transplant recipients who are prone to the development of GVHD, often resulting in the initiation of immunosuppressant medications further increasing their risk of opportunistic infection. The late posttransplant phase (>100 days) is characterized by defects in cell-mediated and humoral immunity, as well as dysfunction of the reticuloendothelial system in allogeneic transplant recipients.

While the development of noninfectious pulmonary complications is traditionally divided into this characteristic triphasic temporal pattern, it represents a dynamic, individualized spectrum of risk (Fig. 94-1).[6,7] Peri-engraftment respiratory distress syndrome (PERDS) occurs by definition in the first 30 days of transplant, typically in the few days prior to neutrophil engraftment (defined as the first of 3 consecutive days where absolute neutrophil count exceeds 500 cells per mm).[3,8] During this early posttransplant period, patients are also more susceptible to pulmonary edema, acute respiratory distress syndrome (ARDS), and diffuse alveolar hemorrhage.[9] Idiopathic pneumonia syndrome (IPS), a form of idiopathic posttransplant ARDS, can occur at any time after transplant.[10] Bronchiolitis obliterans syndrome (BOS), a form of lung GVHD, occurs in the late posttransplant phase.

Although HSCT survivorship has steadily improved in the last two decades, mortality after transplant remains substantial and is dependent on a number of factors.[3] The underlying disease affects both the type of transplant received and the likelihood of survival. For example, a patient with aplastic anemia undergoing allogeneic HCT would have a 3-year survival of 80% compared with 51% for a patient undergoing the same type of transplant for myelodysplastic syndrome. The disease status at the time of transplant also is important. A patient with early-stage AML has a 3-year survival of 58%, but this drops to 29% in those with advanced-stage AML at the time of transplant. Similarly, a chemosensitive lymphoma typically has survival 10% to 15% higher at 3 years than a chemoresistant lymphoma. Autologous transplants are done selectively in certain diseases, most commonly myeloma and amyloidosis. Patients who have disease relapse after autologous HSCT are eligible for repeat HSCT. However, survival after a second transplant is substantially lower (3-year survival, 58%) compared with patients undergoing first-time transplant (3-year survival, 76%).

Early posttransplant mortality (within 100 days) is due to disease relapse in approximately one-third of those who die. The other common causes are infection, organ failures, and GVHD (in allogeneic transplant recipients). Late posttransplant mortality (after 100 days) is due to disease relapse in the vast majority (~80%) of autologous transplant recipients. In allogeneic transplant recipients, disease relapse is responsible for ~60% of deaths, with 15% due to GVHD, 10% due to graft rejection, and 15% due to infection.[3] The likelihood of infection after allogeneic transplant is typically higher than after autologous transplant due to both a longer posttransplant period of neutropenia and the need for long-term immunosuppressive medications for GVHD treatment.

■ Frequency of Pulmonary Complications

Pulmonary complications are common after HSCT (Table 94-1). In a prospective series of 175 patients undergoing HSCT published

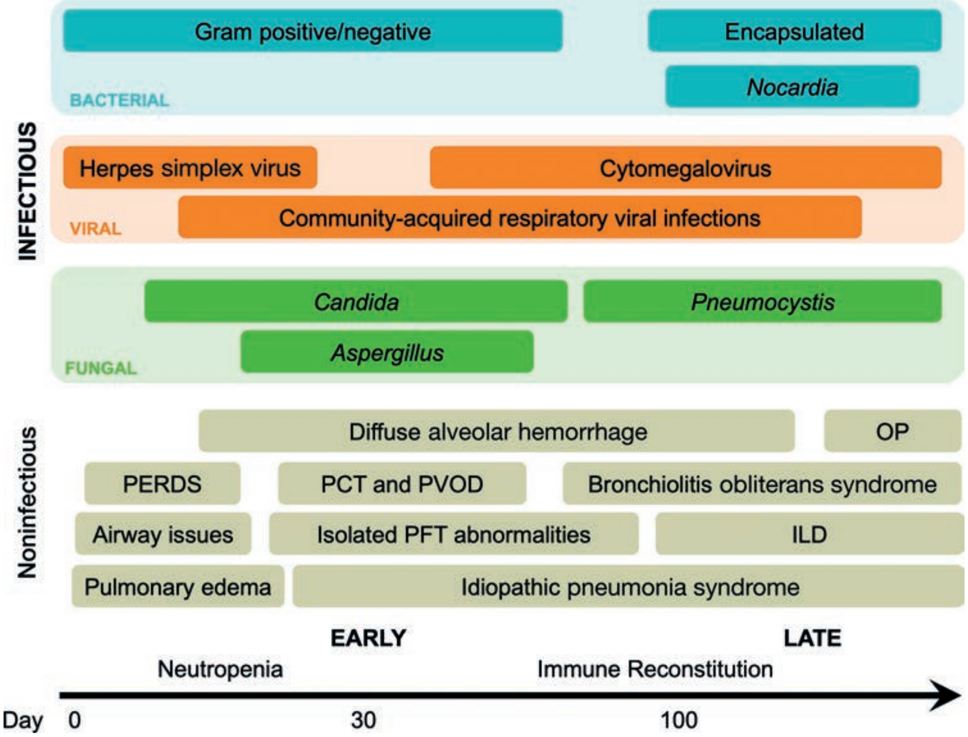
INFECTIOUS
BACTERIAL
Gram positive/negative
Encapsulated
Nocardia
VIRAL
Herpes simplex virus
Cytomegalovirus
Community-acquired respiratory viral infections
FUNGAL
Candida
Pneumocystis
Aspergillus
Noninfectious
Diffuse alveolar hemorrhage
OP
PERDS
PCT and PVOD
Bronchiolitis obliterans syndrome
Airway issues
Isolated PFT abnormalities
ILD
Pulmonary edema
Idiopathic pneumonia syndrome
EARLY
LATE
Neutropenia
Immune Reconstitution
Day
0
30
100

Figure 94-1 The temporal pattern of major pulmonary complications following hematopoietic stem cell transplantation. ILD, interstitial lung disease; OP, organizing pneumonia; PCT, pulmonary cytolytic thrombi; PERDS, peri-engraftment respiratory distress syndrome; PFT, pulmonary function test; PVOD, pulmonary vascular occlusive disease.

in 2014, 73 pulmonary complications were observed in 51 (30%) patients.[11] Of these events, 21 (29%) were noninfectious complications. Allogeneic transplant recipients were more likely to have pulmonary complications than autologous transplant recipients (58% vs. 24%). Interestingly, in a 1986 series of 130 allogeneic HSCT recipients, 69 of 130 patients (53%) developed pulmonary complications. The remarkably similar rates of pulmonary complications after allogeneic HSCT over an almost 30-year period highlight not only the severe impact of pulmonary complications on post-HSCT outcomes but also the need for further research in this area.

TABLE 94-1 Noninfectious Pulmonary Complications in the HSCT Recipient

Early (usually <100 days)
Upper airway complications
Pulmonary edema
Diffuse alveolar hemorrhage
Peri-engraftment respiratory distress syndrome
Idiopathic pulmonary syndrome
Acute respiratory distress syndrome
Late (usually >100 days)
Bronchiolitis obliterans syndrome
Organizing pneumonia
Delayed pulmonary toxicity syndrome
Eosinophilic pneumonia
Interstitial lung disease
Pulmonary alveolar proteinosis
Pleuroparenchymal fibroelastosis
Any time
Isolated abnormality in pulmonary function
Pulmonary veno-occlusive disease

The lower rates of pulmonary complications after autologous transplantation compared with allogeneic HSCT are supported by other series. For example, in a series of 1243 autologous HSCT recipients, 383 patients (27.6%) developed pulmonary complications, with noninfectious diagnoses in 10.2%.[12] In this series, the hazard ratio for death in those who had pulmonary complications was more than 30 times higher than those who did not.

Pulmonary complications appear to be similarly common in the pediatric HSCT population, although the epidemiology is less well characterized. For example, in a series of 363 pediatric HSCT recipients, 90 (25%) developed pulmonary complications.[13] Late-onset noninfectious pulmonary complications described include BOS and IPS.[14]

Impact of Pulmonary Complications on Patient Outcomes

As overall transplant survivorship has improved, there is an increased focus on identifying ways to reduce nonrelapse mortality.[3,15] Pulmonary complications remain a major threat to the survival of the transplant recipient. In a prospective series, pulmonary complications were the most common cause of mortality within the first year of transplant and represented 41% of nonrelapse mortality.[11]

Early pulmonary complications often necessitate urgent hospital or ICU admission, and a substantial number of patients need invasive and noninvasive ventilatory support. The etiology of these early complications is varied (Table 94-2) and sometimes cannot be identified. In a cohort of 2635 patients, 133 (5.0%) developed ARDS.[9] ARDS developed typically within the first 3 months of transplant and was associated with an in-hospital mortality of 57%. Although prognosis of such severe respiratory failure after HSCT is grim, overall mortality appears to have decreased over time.[16–18] Disease-specific outcomes are addressed in the relevant sections of this chapter.

Late-onset pulmonary complications are often noninfectious and include BOS, interstitial lung diseases, and pulmonary vascular diseases. These conditions often initially present subacutely in the outpatient setting. The impact of late-onset noninfectious pulmonary complications is substantial, including reduced exercise

TABLE 94-2 Risk Factors for Pulmonary Complications in HSCT Recipients

Preexisting lung disease
Older age
Underlying disease leading to transplant
Type of stem cell transplant (autologous vs. allogeneic)
Previous infections
Cytomegalovirus serology positive in recipient or donor
Current and prior immunosuppressant medications
Pretransplant conditioning regimen
Total body irradiation
Time interval between underlying diagnosis and transplant
Time elapsed since transplant
Graft-versus-host disease

capacity, oxygen dependence, and mortality in excess of 50%.[19–25] In patients who survive more than 2 years after transplant, pulmonary complications accounted for 5% of the subsequent deaths, and patients with pulmonary complications had a 15-fold increased risk of death.[26]

Approach to the Diagnosis of Noninfectious Pulmonary Complications

The diagnostic approach to the HSCT recipient with suspected noninfectious pulmonary complications should follow a systematic approach.[7] Recipients with respiratory symptoms and signs usually are evaluated with a chest radiograph followed by high-resolution computed tomography (HRCT). If the radiographic evaluation fails to reveal pulmonary infiltrates, especially in allogeneic recipients, PFT should be performed to assess for BOS. For patients with pulmonary infiltrates, noninvasive tests should be performed for infections and other causes. Noninvasive approaches include multiplex nasopharyngeal swab PCR assays,[27] sputum for microbiology studies, blood culture, galactomannan and β-D-glucan assays,[28,29] cytomegalovirus (CMV) viral load testing, and urine antigen testing for *Legionella pneumophila* and pneumococcal pneumonia.[30] If noninvasive testing is nondiagnostic, invasive techniques should be considered, balancing the risk-benefit ratio. The invasive approach usually relies on fiberoptic bronchoscopy with bronchoalveolar lavage (BAL) and occasionally transbronchial lung biopsy. Other invasive procedures such as image-guided transthoracic needle aspiration and video-assisted thoracoscopic biopsy rarely may be needed.[31]

Pulmonary Function Testing

Pulmonary function testing is part of the routine pretransplant evaluation performed when determining eligibility for both autologous and allogeneic HSCT. Since both the chemotherapy agents and radiation therapy used for pretransplant conditioning have pulmonary toxicities,[32] having baseline pulmonary function testing can be valuable when monitoring for drug- and/or radiation-induced lung injury. Baseline pulmonary function testing can also be helpful when evaluating for specific post-HSCT lung injury syndromes such as BOS.

In addition to serving as a baseline, there appears to be prognostic value in assessing pulmonary function testing.[33] Multiple series have demonstrated that poorer pretransplant PFTs are associated with an increased risk of posttransplant pulmonary complications and mortality.[34–36] In one such series, authors developed a pretransplant Lung Function Score incorporating forced expiratory time in 1 s (FEV_1) and diffusing capacity (DL_{CO}).[33] Using this score, they found impairments in pretransplant pulmonary function were associated with a greater probability of post-HSCT pulmonary complications, and that risk appeared to increase with increasing impairment of pretransplant pulmonary function. As a result, the widely used hematopoietic cell transplant (HCT)-specific version of the Charlson Comorbidity Index (HCT-CI) incorporates pretransplant FEV_1 and DL_{CO} in its composite risk score.[37] Increased HCT-CI scores are associated with reduced overall posttransplant survival, especially related to nonrelapse mortality.[38–40] Pulmonary function testing is typically performed routinely for all patients since some patients can have pulmonary function abnormalities in the absence of respiratory symptoms.[41]

Pretransplant pulmonary function studies may also have prognostic implications for developing *specific* posttransplant noninfectious pulmonary complications. For example, in a cohort of patients undergoing HSCT, pretransplant FEV_1 and DL_{CO} were associated with developing posttransplant IPS.[42] Those with severe pretransplant impairment in pulmonary function had increased risk of mortality from IPS.

Pulmonary function testing can also be used as a method for detection of posttransplant pulmonary complications. The development of pulmonary function test abnormalities after HSCT is associated with increased post-HSCT mortality.[43–46] For example, in a series of allogeneic HSCT recipients, most patients had normal pulmonary function after HSCT.[46] However, those with impaired post-HSCT pulmonary function parameters (FEV_1 and DL_{CO}) at 80 days post-HSCT had increased risk of nonrelapse mortality. A low FEV_1 was specifically predictive for developing chronic GVHD. HSCT recipients with IPS or organizing pneumonia (OP) present with restrictive pulmonary function impairment, and those with BOS demonstrate airflow obstruction.[47]

Risk factors for the development of pulmonary function abnormalities following HSCT include smoking history, pretransplant pulmonary infection, viral infection in the early posttransplant period, older age, underlying disease, pretransplant chemotherapy and conditioning regimen, GVHD, and HLA mismatch.[48–51] Respiratory muscle weakness, an alternative cause of restrictive pulmonary function abnormalities, was reported in 52% of allogeneic HSCT recipients in a retrospective study.[52] Risk factors for respiratory muscle weakness include chemotherapy, total body irradiation, high dose corticosteroids, immobility, and GVHD.[52]

Early Noninfectious Pulmonary Complications

HSCT recipients are prone to numerous pulmonary complications in the early (<100 days post-HSCT) transplant period (Table 94-3). These are broadly divided into infectious and noninfectious, and all patients with suspected noninfectious syndromes should have some form of evaluation for infection. Those presenting with acute hypoxemic respiratory failure present along a spectrum of severity, and many meet criteria for ARDS. While the underlying etiology is often not known at the time of initial presentation, the principles of ARDS management and prevention apply in this population. Specifically, this includes lung-protective mechanical ventilation with low tidal volumes as well as use of neuromuscular blockade and prone positioning where appropriate.[53–57] In addition, there should be a focus on preventing further iatrogenic injury through judicious fluid and blood product administration, aspiration precautions, and early focus on mobilization and ventilator liberation.[55,58] Several specific post-HSCT noninfectious syndromes have been described, and these are outlined below. Importantly, the post-HSCT lung injury syndromes of ARDS[9]—PERDS,[59] IPS,[10] and DAH[60]—are all overlapping in their clinical presentations, and likely also in their pathophysiologic underpinnings.

TABLE 94-3 Definitions of the Early Post-HSCT Lung Injury Syndromes

Post-HSCT Complication	Definition
Peri-engraftment respiratory distress syndrome	1. Development of new bilateral pulmonary infiltrates 2. Hypoxemia 3. Clinical syndrome not fully explained by an infectious process, fluid overload, or heart failure 4. Occurring within 5 days of either side of the neutrophil engraftment date; this is defined as the first of three consecutive days in which the absolute neutrophil count surpasses 500 cells/mm^3 following transplantation
Diffuse alveolar hemorrhage	1. Respiratory failure requiring supplemental oxygen or noninvasive or invasive ventilation 2. Evidence of bilateral pulmonary infiltrates on chest x-ray or lung CT 3. The presence of (a) progressively hemorrhagic return with serial aliquots during bronchoalveolar lavage, and (b) ≥20% hemosiderin-laden macrophages on cytopathology Definite DAH: criteria (1), (2), and both criteria in (3) Probable DAH: criteria (1), (2), and one criterion in (3)
Idiopathic pneumonia syndrome	1. Multilobar opacities on chest radiograph or computed tomography 2. Signs and symptoms of pneumonia 3. Evidence of abnormal pulmonary physiology manifested by an increased alveolar–arterial oxygen gradient or the need for supplemental oxygen 4. Absence of lower respiratory tract infection, as determined by a negative bronchoalveolar lavage 5. Clinical syndrome not fully explained by fluid overload or heart failure
Acute respiratory distress syndrome	1. Bilateral pulmonary opacities on chest imaging. 2. PF ratio <300 mm Hg with a minimum of 5 cm H_2O positive end-expiratory pressure (can be with invasive or noninvasive ventilation) 3. Clinical syndrome cannot be fully explained by cardiac failure or fluid overload 4. Occurring over 1 week or within 1 week of an inciting event

Pulmonary Edema

Acute pulmonary edema is relatively common during the neutropenic phase. In a review of more than 1200 autologous HSCT recipients, pulmonary edema was felt to be present in 4.7% of patients.[12] Patients may have preexisting cardiac dysfunction due to chemotherapy (especially cyclophosphamide and anthracyclines) or radiation therapy. Since echocardiography is routine during pretransplant evaluation, this is usually known ahead of time. Direct injury from therapies, such as total body irradiation and induction chemotherapy, may lead to endothelial injury, making pulmonary edema more likely. Patients often receive intravenous fluids due to reduced oral intake, mucositis, or increased insensible losses from fevers or diarrhea. Patients also receive numerous intravenous infusions such as antibiotics and sometimes total parenteral nutrition. Lastly, patients receive red blood cell and platelet transfusions for chemotherapy-induced cytopenias. Blood products can predispose patients to both transfusion-associated circulatory overload (TACO) and transfusion-associated acute lung injury (TRALI).[61–63] Taken together, all these factors can combine to leave patients at increased risk of pulmonary edema in the immediate posttransplant period. Importantly, while some of these factors are unavoidable, pulmonary edema is largely an iatrogenic complication that can usually be prevented.

Upper Airway Complications

Significant injury to the mucosal barrier occurs in about 75% of HSCT recipients, and oral mucositis represents a major source of early post-HSCT morbidity.[64] Mucositis typically peaks between days 6 and 12 after HSCT[65] and is associated with patient discomfort, impaired nutrition, increased hospitalization, and higher post-HSCT mortality.[66,67] Total body irradiation, allogeneic transplant, delayed neutrophil engraftment, higher chemotherapy doses, and increased weight are all risk factors for mucositis.[68,69] Upper airway inflammation due to mucositis may lead to laryngeal edema, dysphagia, and aspiration pneumonia. Life-threatening upper airway complications can occur and are more common in children.[70,71] Use of narcotics to manage mucositis-related pain can further increase the risk of aspiration, and requirement for parenteral nutrition can increase the risk for bloodstream infections.[69,68] Upper airway injury in HSCT recipients is usually managed with supportive care, including local symptomatic therapy. Endotracheal intubation is typically only needed when mucosal sloughing represents an acute airway threat. Intubation in this setting can be highly challenging and should be done by experienced airway specialists with appropriate advanced airway backup.

Peri-engraftment Respiratory Distress Syndrome

The engraftment syndrome is an incompletely understood condition that occurs during the early posttransplantation period following autologous HCT.[59,72,73] The clinical features of engraftment syndrome include noninfectious fever, skin rash, hypoxemia, pulmonary infiltrates, weight gain, and hypoalbuminemia, all occurring around the time of neutrophil recovery. When engraftment syndrome has pulmonary manifestations, it is referred to as the peri-engraftment respiratory distress syndrome (PERDS). Precise estimates of incidence of engraftment syndrome are difficult to determine due to the nonspecific nature of the syndrome and heterogeneity in diagnostic criteria, with reports indicating incidence of anywhere between 7% to 53% of HSCT recipients.[59,72,74,75] Mild cases may be subclinical and thus not detected. Although most of the studies reporting engraftment syndrome are in autologous HSCT recipients, it has been rarely reported after allogeneic transplantation as well.[76,77]

Frequency, Risk Factors, and Pathogenesis The incidence of PERDS is estimated to be between 4% and 5% after autologous HSCT, with the largest series showing an incidence of 4.8% in a cohort of more than 3500 autologous HSCT recipients.[8,12,78] PERDS occurs at time of neutrophil engraftment, typically between 9 and 16 days after autologous HSCT (median, 13 days).

Several risk factors have been identified for the development of PERDS. These include POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes) syndrome, female sex, a more rapid time to engraftment, use of G-CSF, and increased platelet transfusions in the immediate posttransplant period.[72,77–81]

The pathogenesis of PERDS is not well defined but is believed to represent an interaction between conditioning-related endothelial damage and the cytokine release associated with neutrophil and lymphocyte recovery.[8] Tissue infiltration by neutrophils has been shown to occur earlier than their appearance in the peripheral blood, and radiographic changes precede diagnosis in the majority of cases.[78,82] The association between PERDS and POEMS also supports the proinflammatory hypothesis, as patients with POEMS are known to have elevations of a variety of circulating cytokines.[79] It is possible that this proinflammatory state makes patients more vulnerable to the consequences of cytokine release during neutrophil engraftment, resulting in a greater risk of PERDS.

Clinical Findings and Diagnostic Evaluation Patients with PERDS present with nonspecific pulmonary symptoms (dyspnea, cough), typically accompanied by hypoxemia. While other features of engraftment syndrome may be present, PERDS may be the initial or only feature in some patients.[8,72,83] The majority of patients with PERDS require hospitalization. Over 50% require ICU admission and 20% require mechanical ventilation.[78]

The diagnostic criteria for PERDS are not standardized, but the diagnosis should be considered in autologous transplant recipients who develop new bilateral pulmonary opacities on chest imaging and hypoxemia within 5 days on either side of the neutrophil engraftment date (defined as the first of 3 consecutive days in which the absolute neutrophil count surpasses 500 cells/mm^3 following transplantation). The radiographic changes may precede engraftment by several days.[78] Although attempts should be made to rule out infection, most patients do not undergo BAL unless they are already on mechanical ventilation.[12] This is largely due to the self-limited nature of the disease and the invasive nature of the procedure. Biopsy is prohibitively high risk due to thrombocytopenia and not considered necessary for the diagnosis. Lung histology from patients with PERDS shows diffuse alveolar damage.[8]

Treatment Unlike other post-HSCT lung injury syndromes, PERDS appears to be relatively responsive to steroid therapy, but this is based on low-quality evidence derived from observational case series, with substantial risk of bias. For example, in one study, 40 of 41 patients with engraftment syndrome who received steroids demonstrated symptomatic or clinical improvement.[8,72] Steroid courses are typically 1 to 2 mg/kg methylprednisolone twice daily for 3 days, followed by a rapid taper.

Outcomes and Prognosis While there is considerable morbidity associated with PERDS, the prognosis is substantially better than for other post-HSCT lung injury syndromes (e.g., DAH, IPS, ARDS). PERDS is associated with increased rates of ICU admission compared with autologous HSCT recipients who do not develop PERDS (47% vs. 10% in one series).[78] Patients diagnosed with PERDS are more likely to require ventilatory support and have longer ICU and hospital lengths of stay. Case-fatality rates have decreased from greater than 20% nearly two decades ago to less than 5% in the current era.[8,78]

Diffuse Alveolar Hemorrhage

Although alveolar hemorrhage can occur in the setting of pulmonary infection, the syndrome of DAH typically refers to alveolar hemorrhage where no infectious etiology is identified.[84]

Diagnosis There are no standardized or widely accepted diagnostic criteria for DAH after HSCT. In an attempt to standardize the definition, we have recently proposed the following criteria, which are extrapolated from clinical practice and other alveolar hemorrhage syndromes.[85] Definite DAH requires the presence of all three of the following: (1) respiratory failure requiring supplemental oxygen or noninvasive or invasive ventilation; (2) evidence of bilateral pulmonary infiltrates on chest x-ray or chest CT; (3) the presence of progressively hemorrhagic return with serial aliquots on BAL and ≥20% hemosiderin-laden macrophages on cytopathology.[84] Probable DAH is defined by the presence of (1) and (2) above and *either* one of the criteria in (3). In a recent single-center retrospective review of 99 HSCT recipients with DAH, 39% met criteria for definite and 61% for probable DAH.[85] In the latter group, 40% had progressive bloody return on BAL and 60% met cytologic criteria, highlighting the importance of sending the latter study in order to capture patients without the classic findings at time of bronchoscopy. Two limitations to these diagnostic criteria should be kept in mind. First, hemosiderin-laden macrophages do not appear for 24 to 72 h after an acute bleed. Second, these criteria lack specificity and, in particular, do not distinguish bland DAH due to acute lung injury from DAH triggered by underlying infection.[84]

Incidence and Time Course The existing evidence base for DAH is limited, and many case series do not follow clear or consistent diagnostic criteria. Indeed, some do not even require bronchoscopic confirmation, but merely clinician suspicion of DAH based on clinical and radiographic features.[86] As such, there has been wide variability in the reports of DAH frequency after HSCT, ranging from 2% to 14% depending on criteria used.[87] However, these series include studies where DAH definition was questionable, as well as historic studies that likely do not reflect contemporary DAH epidemiology. A recent review of 4350 HSCT recipients who underwent HSCT at a single center found that 99 patients had clinical, radiographic, and bronchoscopic evidence of DAH, representing a frequency of 2.3%.[85]

Early studies indicated that the onset of DAH was most common in the first 30 days after HSCT.[87] However, DAH also can occur as a later complication of HSCT, and more recent studies suggest that the time to DAH development is longer than what was previously reported.[85,88] In the recently published cohort of 99 DAH cases, the median time to DAH identification after transplant was 126 days. The finding that DAH is encountered later in the post-HSCT period may reflect the overall improvement in peritransplant care, including better antimicrobial prophylaxis, improved identification and treatment of infectious syndromes, and improvements in the management of critical care syndromes, such as sepsis and ARDS. Many of the early-onset DAH cases seen in historic reports may have been infection-related and, as these complications have reduced, there has been a shift toward developing DAH later after HSCT.

Risk Factors High-quality epidemiologic studies evaluating risk factors for developing DAH are lacking. Pretransplant radiation (either total body irradiation for conditioning or history of thoracic radiation), higher-intensity chemotherapy/conditioning regimens, older age at transplant, and severe GVHD have been associated with DAH.[88–93] The majority of patients with DAH have thrombocytopenia, but DAH is not corrected by platelet transfusion.[85,87,93] Although some data are conflicting, DAH appears to be more common after allogeneic HSCT than autologous HSCT with up to a sevenfold increase in some reports.[85-87,93] Pretransplant PFTs do not appear to have any association with DAH development.[93]

In those who develop DAH, risk factors for mortality include a longer time from HSCT to DAH development, need for invasive mechanical ventilation, thrombocytopenia, and elevated INR. It is possible that those who develop DAH later after HSCT have additional complications such as disease relapse and GVHD that affect both the ability to withstand the course of critical illness and the aggressiveness of care options chosen.

Pathogenesis The pathogenesis of DAH in the HSCT recipient is not known. Lung injury, inflammation, and cytokine release are implicated but meaningful mechanistic studies are lacking.[87] Pretransplant chemotherapy, radiation, and infections may be responsible for the initial lung injury, and subsequent "second hits" may predispose patients to the DAH syndrome. Indeed, several autopsy studies of DAH show diffuse alveolar damage indicating there may be a component of bland hemorrhage complicating diffuse lung injury.[85,91,94]

Inflammation may play a role in the development of DAH. In one study, 123 patients underwent bronchoscopy with BAL before HSCT. Those who went on to develop DAH (14 in this series) had higher neutrophil counts in BAL. It was hypothesized that bronchial inflammation preceded alveolar inflammation and subsequent alveolar hemorrhage.[95,96] However, this is ultimately speculative. As indicated above, autopsy studies do not typically show extensive inflammation or alveolitis. However, in many of these reports there can be considerable time between DAH development to autopsy, and lung pathology findings could evolve over time from the initial DAH diagnosis. Obtaining transbronchial or surgical lung biopsies in this setting is typically not possible due to both coagulopathy and degree of respiratory failure. It is not known if GVHD is a major contributing factor to DAH development, but patients with GVHD are more likely to develop DAH.[88] Many patients with DAH have concomitant respiratory infection, with 43% having a presumed pathogenic organism identified in a recent series. Of those with infection, the majority (54%) had fungal infection.[85]

Clinical Findings Patients with DAH have nonspecific symptoms, most commonly dyspnea and cough.[87,93] Hemoptysis is rare, occurring in less than 15% of cases.[85,90,93,97] In recent reports, about 50% of patients required mechanical ventilation at the time of diagnosis while less than 10% were on room air.[85] Patients may have other coexistent post-HSCT respiratory failure syndromes such as ARDS and PERDS, emphasizing that these syndromes may have overlapping pathophysiologic underpinnings.[9]

Diagnostic Evaluation DAH is a syndrome with nonspecific clinical and radiologic features.[87] Chest radiograph shows diffuse interstitial and alveolar infiltrates, primarily central, and involving predominantly lower and middle lung zones.[98] The earliest radiographic manifestation is the presence of bilateral fine reticular opacities. In the later phase of DAH, 70% of patients develop an alveolar pattern, and the interstitial pattern persists in 30%. Although chest CT may be helpful in patients in whom a focal source of bleeding is suspected, chest CT has a limited role in DAH. The most common CT finding is bilateral ground-glass attenuation or consolidation.[99] Bronchoscopic evaluation is the cornerstone of diagnosis, and all patients who undergo BAL after HSCT should have serial aliquots performed and examined for the presence of progressively hemorrhagic return. In addition, all samples should undergo cytopathologic evaluation for hemosiderin-laden macrophages. It is also important to send microbiologic studies to assess for the possibility of an infectious trigger for DAH.

Treatment The practice of prescribing high-dose corticosteroids (often ≥1 g methylprednisolone daily) is extrapolated from the treatment of alveolar hemorrhage from immune-mediated conditions such as anti–glomerular basement membrane disease.[100] Although corticosteroid therapy is the standard of care for patients with post-HSCT DAH, consistent evidence of benefit is lacking.[92,100,101] There are no prospective, randomized clinical trials addressing the treatment of DAH in HSCT recipients.

In a retrospective observational study from the 1990s, 12 patients who received no steroids were compared with 10 patients who received low-dose steroids (30 mg methylprednisolone or less) and 43 patients who received higher-dose steroids (>30 mg methylprednisolone). The mortality rate was lower and fewer patients required invasive mechanical ventilation in the high-dose methylprednisolone group.[101] However, more recent data are equivocal. In a retrospective series of 119 HSCT patients with possible DAH, patients were divided into those who received low-dose, medium-dose, and high-dose steroid therapy.[86] Those patients with low-dose (<250 mg/d methylprednisolone) steroid therapy demonstrated improved outcomes compared to those with medium-dose (250–1000 mg/d methylprednisolone) or high-dose (>1000 mg/d methylprednisolone) steroid therapy. However, this series was limited by the nature of DAH case definition. The authors included those patients who had a diagnosis of DAH based on clinician impression, sometimes without supporting bronchoscopy data. All studies are retrospective, observational, and with high risk of bias. Although evidence remains weak, given the lack of effective therapeutic options and grave overall prognosis, corticosteroids remain standard of care for patients with DAH after HSCT. However, moderate-dose corticosteroids (e.g., 125 mg or 250 mg methylprednisolone) may be adequate in lieu of the very high doses that are often prescribed.

In addition to corticosteroids, it is reasonable to provide blood product support to reverse any coagulopathy. However, this has not been associated with improved outcomes.[102] Some groups have also advocated the use of aminocaproic acid in this setting, but evidence for benefit is again lacking.[86] Given that the risks of aminocaproic acid are low, this may be a reasonable option to consider. There are reports of allogeneic HSCT recipients with DAH treated with recombinant factor VIIa,[94,103,104] but this cannot be routinely recommended.

Prognosis DAH is a major complication of HSCT, contributing significantly to morbidity and mortality. The majority of HSCT recipients with DAH require mechanical ventilator support for respiratory failure.[87] The reported mortality rate of DAH in historic series was close to 80%.[87] More recent series suggest that the mortality rate may be closer to 60%, lower than previous reports but still unacceptably high.[85,105] Although the initial presentation of DAH in HSCT recipients may be with respiratory failure, the most common causes of death are multiple organ failure and sepsis. Respiratory failure with active pulmonary hemorrhage is responsible for fewer than 15% of the deaths.

Idiopathic Pneumonia Syndrome

IPS is an umbrella term for lung injury without an infectious etiology in HSCT recipients. It was first described in 1985 as idiopathic pneumonia in a review of pulmonary complications of 4500 HSCT recipients.[12,106] Diagnostic criteria were initially addressed in 1993 by a workshop sponsored by the National Heart, Lung, and Blood Institute.[107] This workshop defined IPS as widespread alveolar injury and hypoxemic respiratory failure in the absence of lower respiratory tract infection.[10,107] The criteria were updated in 2011 to additionally require exclusion of cardiac dysfunction, renal failure, and iatrogenic volume overload as the etiology for pulmonary dysfunction.[10]

Frequency The incidence of IPS varies between 2% and 17% across studies.[10,108–117] The most recent large epidemiologic study of IPS reported an incidence of 3.7% in a cohort of 1829 HSCT patients.[42]

Similarities with ARDS IPS is similar to ARDS in its clinical presentation and management. The key differences are (1) ARDS requires an inciting event within 7 days of syndrome development, whereas IPS does not; (2) ARDS has specific requirements with regard to the magnitude of hypoxemia (Pa_{O_2}/Fi_{O_2} ratio <300 mm Hg) and ventilatory support (invasive or noninvasive ventilation requiring positive end-expiratory pressure >5 cm H_20); and (3) IPS requires that infection has been excluded, whereas ARDS encompasses both infectious and noninfectious lung injury. IPS and ARDS share the common criteria that diffuse bilateral pulmonary infiltrates must be present, and the clinical syndrome should not be fully explained by cardiac failure or fluid overload.[118] Patients with IPS and ARDS can both have diffuse alveolar damage on histology.[10] Given the similarities and overlapping features noted, the principles of ARDS management can be extrapolated to management of IPS.

Risk Factors Several risk factors have been associated with IPS.[42,116] Allogeneic transplant, myeloablative conditioning therapies, use of total body irradiation for conditioning, and the presence of GVHD have all been associated with increased IPS risk.[42,119] Patients with poorer pretransplant pulmonary function are at increased risk of IPS development.[42] Patients transplanted for aplastic anemia typically have a lower risk for IPS.[120] CMV status (recipient and donor), HLA matching, and underlying malignancy do not appear to alter IPS risk.

Pathogenesis Although the pathogenesis of IPS is not well defined, lung injury, inflammation, and cytokine release are all implicated.[119] Pulmonary vascular endothelial cell damage, mediated by tumor necrosis factor (TNF)-α, is linked to the development of IPS in experimental animal models.[10,121] The occurrence of IPS after autologous BMT suggests that the pretransplant conditioning regimens, rather than GVHD and CMV infection, are likely to be culprits.[93] Similar to ARDS, infections and systemic activation of inflammatory cytokines during sepsis may also be responsible for lung injury.[111,122–125] Cell-mediated immune injury during GVHD and free-radical oxidant-mediated injury also have been hypothesized as contributing factors.[111,126,127]

Clinical Findings and Evaluation The median time to IPS onset is typically within 30 days of HSCT, and most patients will develop the syndrome within 120 days.[10,42,111,112] In a recent large cohort series, the median time to IPS onset after allogeneic HSCT was 25 days (range, 4–118 days).[42] Clinical features include dyspnea, dry cough, hypoxemia, and nonlobar radiographic opacities.[107] The spectrum of severity is broad, ranging from acute respiratory failure to incidental radiographic abnormalities.

Because IPS mimics infectious pneumonia, most patients receive antibiotics and evaluation for infection is routine. If permitted by the patient's respiratory status, bronchoscopy is performed to exclude infection and to evaluate for DAH. When pursued, lung biopsies of patients with IPS show diffuse alveolar damage, organizing or acute pneumonia, and/or interstitial lymphocytic inflammation.[110,111]

Treatment The treatment of IPS is primarily supportive.[55] The majority of patients require invasive ventilation,[128] and low stretch protocols similar to those employed in ARDS should be utilized. There is little evidence supporting any specific pharmacotherapies. Several groups have reported experience with corticosteroids. While some small series suggested benefit,[110,129] larger series did not.[109,128] Despite lack of evidence of benefit, most patients with IPS receive a trial of corticosteroids. Dosing is not clearly established and ranges from 1–4 mg/kg/day of methylprednisolone.[42]

Based on the observation that patients with IPS tend to have high cytokine expression in BAL, there was substantial interest in TNF-α inhibition with etanercept, usually in conjunction with corticosteroids.[10,130–133] This was ultimately evaluated in a randomized clinical trial in which 34 patients with IPS were randomized to receive either corticosteroids (2 mg/kg/d methylprednisolone) with etanercept (0.4 mg/kg twice weekly × 4 weeks) or corticosteroids alone.[134] There was no observed benefit with the addition of etanercept. Of note, this trial fell substantially short of planned enrollment (120 patients) and as such may have been underpowered to detect any differences. Although etanercept continues to be prescribed in patients with IPS, its use is not supported by any evidence. While lung transplant offers a potential therapeutic option for patients, reports are rare.[135]

Prognosis Early studies reported mortality rates between 60% and 86%, with a 1-year survival of less than 15%.[111,112,116,117,120,136] Many of those who develop IPS develop nonpulmonary organ failure that contributes to the high mortality rate.[111,136] There is some indication that the overall prognosis has improved in recent years.[42,133,134] For example, a recent series reported those who developed IPS had a mortality rate of 46% within 120 days of HSCT and 30% of patients with IPS were alive at 1 year post-HSCT.[42]

■ Late, Noninfectious Pulmonary Complications

Late-onset noninfectious pulmonary complications of HSCT are a major contributor to long-term morbidity and nonrelapse mortality in HSCT survivors who may otherwise be cured of their underlying hematologic disease. Although the definition is variable, any process occurring more than 100 days after HSCT typically is considered a late-onset complication. Bronchiolitis obliterans is the best recognized long-term complication, but there is increasing recognition of a wide spectrum of persistent pulmonary disease post-HSCT that includes pleural disorders and interstitial lung disease.

Bronchiolitis Obliterans

Bronchiolitis obliterans (BO) is an inflammatory and fibroproliferative process primarily affecting the small airways that leads to the development of airflow limitation.[137,138] The term *bronchiolitis obliterans syndrome (BOS)* is used when there are clinical, radiographic, and physiologic features of BO in the absence of histologic proof. BO is a common and problematic complication that is seen exclusively in allogenic HSCT recipients.

Frequency Since histopathologic confirmation is uncommon, the majority of series report the incidence of BOS instead.[49] The incidence of BOS after allogeneic HSCT approximates 5% based on pooled estimates from multiple series, although there is substantial heterogeneity in this estimate.[22,23,139–142] The median time to diagnosis is between 6 months and 1 year, and most patients who develop the disease are diagnosed within 2 years of HSCT. Importantly, these series may underestimate the true incidence. Patients who have mild disease may be asymptomatic and may not have CT imaging or PFTs performed (measurement bias). Transient declines in FEV_1 are common in the first 6 months post-HSCT, and typically the diagnosis of BOS is not made until at least 3 months have elapsed after HSCT. This can introduce implicit survival bias. Lastly, the NIH consensus diagnostic criteria proposed for BOS have good specificity but relatively low sensitivity.[143,144] As such, they may underestimate the incidence of BOS after HSCT.

Risk Factors Several risk factors for development of BOS have been identified, predominantly in retrospective studies, sometimes with conflicting results.[119,145] The one risk factor shared across all studies is concomitant extrathoracic chronic GVHD.[21,23,44,140,141,146–149] For example, in a series of 63 BOS patients in a cohort of 1145 allogeneic HSCT recipients, 100% of patients had chronic GVHD.[22] However, this also may be a reflection of bias, as the BOS diagnosis may be considered only in patients with preexisting GVHD. Other

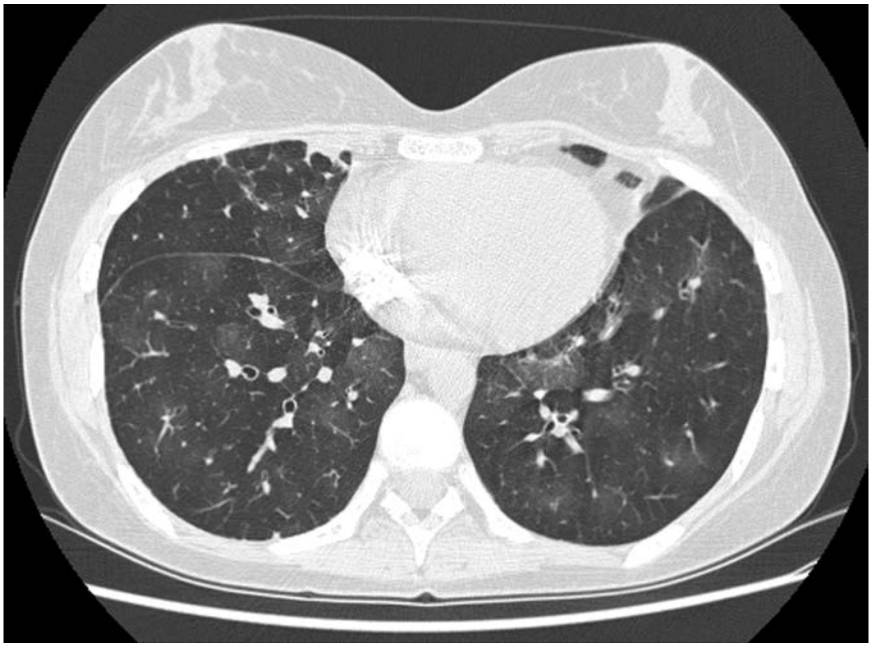

Figure 94-2 Computed tomography scan with expiratory views of a patient with bronchiolitis obliterans following hematopoietic stem cell transplantation. Mosaic attenuation associated with of air trapping (darker areas), bronchial thickening and mild bronchiectasis are evident.

risk factors identified across various studies include older age of both donor and recipient, busulfan-based conditioning, a time from disease diagnosis to transplant of 14 months or longer, methotrexate use, peripheral blood stem cell source, transplant from female donor to male recipient, and acute GVHD.[21,23,44,140,141,146–149] While pulmonary infections are common in patients with BOS, it is not clear whether they are causally related or result from associated immunodeficiency. Factors identified as potentially protective for BOS development include T-cell depletion with antithymocyte globulin and use of cord blood for the donor.[148–151]

Pathogenesis Little is definitively known about the pathogenesis of BO, although the strong association with GVHD suggests a shared pathogenesis. Early in the syndrome, bronchiolar inflammation can be seen.[152,153] Specifically, it is hypothesized that in response to some injury mechanism (e.g., chemotherapy, radiation therapy, infection) there is lymphocyte inflammation around small vessels and the respiratory epithelial lining of the small airways, followed by epithelial cell necrosis and mucosal denudation.[147] The association between BO and chronic GVHD has led to the hypothesis that host bronchiolar epithelial cells serve as a target for donor cytotoxic T lymphocytes, a hypothesis supported by the relative absence of BOS in T cell–depleted grafts.[151,154] Although a CD8 T-cell response appears to be important in pathogenesis, B-cell and humoral immune mechanisms also are likely required. In an animal model of post-HSCT BO, mice incapable of secreting IgG alloantibodies demonstrated substantial reductions in both BO and GVHD.[155] Alternative explanations for BOS development include recurrent aspiration of oral material due to esophagitis associated with GVHD, abnormal local immunoglobulin secretory function in the lungs, and unrecognized infection.[154,156] The variations in histopathology, bronchoalveolar cell differential, clinical course, and frequency of associated pulmonary infection suggest that the pathogenesis is multifactorial.[154,157] BOS in HSCT recipients resembles chronic allograft rejection in lung transplant recipients at immunologic, pathologic, and physiologic levels.[25] Similar to the mechanisms outlined above, T cell–mediated recognition of alloantigens expressed in the lung tissue plays a central role.[147]

Clinical and Radiographic Features The clinical features of BOS are nonspecific and include dyspnea, cough, exercise intolerance, and wheezing.[24,158,159] However, as many as 20% of patients with BOS lack respiratory symptoms at the time of the first abnormal pulmonary test.[160] Wheezing can be detected on physical examination in about 40% of patients.[24]

Chest radiographs are usually normal or may show hyperinflation.[24,25,161–163] Inspiratory and expiratory HRCT should be included as part of the evaluation process for BOS.[160] HRCT typically shows mosaic attenuation due to air trapping (most pronounced on expiratory images), often accompanied by vascular attenuation, bronchiectasis, and bronchiolectasis (Fig. 94-2).[25,162,164–166]

Diagnosis The diagnosis of BO is based on histologic evaluation of lung tissue demonstrating bronchiolar wall thickening, fibrosis, and narrowing of the airway lumen (Fig. 94-3).[25,152,159,167,168] Peribronchiolar inflammatory cellular infiltrates consisting of neutrophils and lymphocytes may be present.[169] Given that transbronchial lung biopsies rarely contain sufficient bronchiolar tissue to establish a histologic diagnosis and that surgical lung biopsy is invasive and carries substantial procedural risk, most patients are diagnosed based on the clinical, radiographic, and physiologic criteria for BOS. Diagnostic criteria for BOS were established by the National Institutes of Health (NIH) in order to standardize enrollment for clinical trials (Table 94-4).[144] The advantage of these criteria is that they can be satisfied with a noninvasive evaluation consisting of CT scan and PFTS, as long as the patient has no clinical evidence of respiratory infection and has at least one other organ system affected by chronic GVHD. On the other hand, the requirement that in the absence of extrathoracic GVHD, a surgical lung biopsy is required for diagnosis is impractical and unnecessary in most clinical settings. Furthermore, the sensitivity of these criteria is too low for clinical use.[170] Many patients with BOS may not meet all these criteria and such stringent criteria may miss those in the early stage of the disease when diagnosis may be most important.

The particular set of normative values utilized in interpretation of PFTs also can have a significant impact on the ability of these criteria to detect cases. In one study, utilization of the National Health and Nutrition Examination Survey (NHANES) III normative values in place of an older system increased the percentage of allogeneic HSCT recipients who met BOS criteria from 17% to 25%.[171] Ongoing research is needed to determine earlier, more sensitive, and more specific markers of BOS development. Monitoring decline in FEV_1 with routine post-HSCT PFT screening may be of value in early diagnosis.[172,173]

Based on the magnitude of decline in FEV_1, BOS is classified into stages: stage 1 (FEV_1 66%–80% of peak posttransplant baseline), stage 2 (FEV_1 51%–65% of baseline), and stage 3 (FEV_1 <50% of baseline).[174] This classification scheme was initially developed exclusively for lung transplant recipients and has not yet been widely applied to the HSCT population. Thus, its utility in defining severity or prognosis in this population remains to be established.

Treatment No therapy has been shown to be effective for the treatment of BOS, and the predominant focus of treatment is to prevent further declines in lung function.[137,145,147] Extrapolating from the treatment of chronic GVHD, the standard initial therapy for BOS

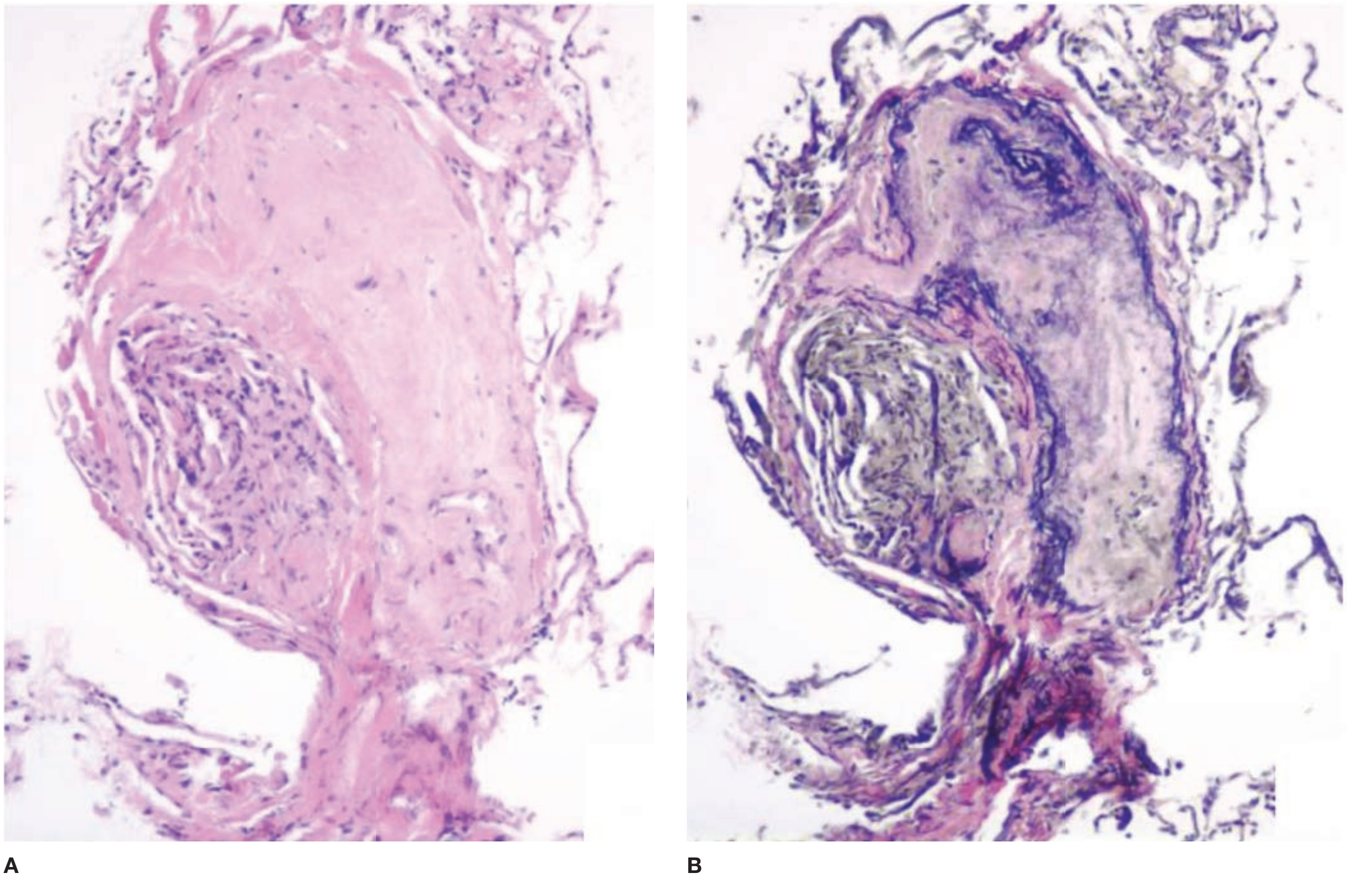

Figure 94-3 Lung pathology in bronchiolitis obliterans, showing inflammation and obliteration of the airway lumen, associated with fibrous connective tissue. **A.** Hematoxylin and eosin stain. **B.** Verhoeff–Van Gieson elastic stain.

TABLE 94-4 National Institutes of Health Consensus Clinical Definition of Bronchiolitis Obliterans Syndrome After Hematopoietic Stem Cell Transplantation (2005)

Pulmonary function testing	$FEV_1/FVC < 0.70$ *and* $FEV_1 < 75\%$ predicted *or* $RV > 120\%$
Imaging	Evidence of air trapping or bronchiectasis on lung computed tomography
Demonstrated graft-versus-host disease	Chronic graft-versus-host disease in another organ system *or* Lung biopsy demonstrating changes compatible with bronchiolitis obliterans
Evaluation for infection	Acute changes not attributable to an acute infectious process

FEV_1, forced expiratory time in 1 s; FVC, forced vital capacity; RV, residual volume.

Data from Filipovich AH, Weisdorf D, Pavletic S, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. Biol Blood Marrow Transplant. 2005;11(12):945–956.

is with systemic corticosteroids. Some patients may already be on immune suppression for preexisting GVHD. Prednisone 1 to 1.5 mg/kg/d, or its equivalent, is given for 4 to 6 weeks. If respiratory status remains stable, therapy is tapered and discontinued over several months. While several series have reported outcomes with steroids (often coupled with other medications), there have been no controlled trials, and evidence for efficacy of corticosteroids in BOS is lacking.[24,25,147,162,166,175,176] Immunosuppressive steroid-sparing drugs such as cyclosporine, tacrolimus, and mycophenolate mofetil also are used in BOS, but again this is limited to uncontrolled series without meaningful evidence for benefit.[47,137,145,154,177] Several other therapies have been studied for BOS, and the experience with these is outlined below.

Macrolides have immunomodulatory effects, and it has been hypothesized that this may halt disease progression in BOS.[81] Based on small studies in post-HSCT BOS, there was substantial interest in azithromycin specifically.[177] However, a subsequent meta-analysis of these studies suggested no benefit of azithromycin for the treatment of BOS.[178] To evaluate whether azithromycin may prevent BOS, the ALLOZITHRO trial randomized 480 allogeneic HCT patients to either placebo or three-times-weekly azithromycin at the time of conditioning chemotherapy.[179] These results showed substantial harm from macrolide therapy in the treatment group. Those receiving azithromycin had worse airflow decline–free survival, increased rate of hematologic relapse, and worse overall survival than placebo. As a result of these data, many centers no longer routinely administer azithromycin for the prevention of BOS.

Part of the drug "cocktail" that was initially studied in BOS alongside azithromycin included the inhaled corticosteroid (ICS) fluticasone and the leukotriene antagonist (LTA) montelukast, collectively termed FAM.[180] The rationale was to combine anti-inflammatory effects (ICS), immunomodulation (macrolides), and theoretical antifibrotic effects (LTA).[181] Multiple small observational studies suggested that ICS and LTA (either combined or in isolation) may have a role in stabilizing or even improving FEV_1 in patients with BOS.[180,182–185] However, these studies had substantial methodologic limitations and high risk of bias. Based on the limited data supporting its efficacy, montelukast is not routinely recommended for patients with BOS. A clinical trial evaluating ICS enrolled 32 patients with BOS, randomizing patients to either budesonide/formoterol or placebo for 6 months. The primary endpoint was change in FEV_1 at 1 month. This study found that the median FEV_1 increased by 260 mL in the budesonide/formoterol arm compared with 5 mL in the placebo arm ($p = 0.012$), and this improvement was sustained for 6 months in the 13 of 25 patients who received ICS. Although promising, conclusions from this study are limited due to small sample size and substantial crossover between treatment and placebo arm. Nonetheless, combination ICS/LABA should be considered in patients with BOS.

A promising emerging therapy for BOS is extracorporeal photopheresis (ECP). In this procedure, white blood cells are removed through apheresis and exposed to ultraviolet radiation after pretreatment with a psoralen derivative, leading to T-cell death. ECP was initially developed for the treatment of cutaneous T-cell lymphoma and adapted to chronic severe GVHD.[186] In a literature review of 735 patients with steroid-resistant, steroid-intolerant, or steroid-dependent chronic GVHD, ECP resulted in response rates of 50% to 65%, and complete response in 30% to 35% of patients.[187] Between 25% and 35% of patients were able to taper or discontinue systemic steroids. Several observational studies have reported potentially favorable results with ECP.[186,188,189] In one multicenter observational study, 26 patients with BOS who underwent at least 3 months of ECP were propensity matched 1:1 with 26 patients with BOS who did not undergo ECP.[19] The group undergoing ECP had improved overall survival, improved functional status (as measured by Karnofsky score), and lower corticosteroid use compared with non-ECP controls. However, the two groups did not differ in any pulmonary function test parameters. This may indicate that survival benefit conferred by ECP is independent of PFT measures, and the corticosteroid-sparing effect may be responsible for the improved survival. To better determine the role of ECP in this setting, a phase 2 clinical trial of ECP in steroid-refractory GVHD is currently underway (NCT03007238).

ECP is a relatively specialized procedure and may not be available in all centers. The regular need for apheresis means patients will require long-term indwelling central venous access. Given targeted T-cell depletion, patients should be considered immunosuppressed. Until further data are available, ECP is a reasonable therapy to consider for patients with severe BOS after HSCT, especially if there is concomitant steroid-refractory, extrathoracic GVHD.

Another emerging therapy for BOS is the Janus kinase (JAK) inhibitor ruxolitinib. JAK signaling is thought to be important in the pathogenesis of both acute and chronic GVHD.[190] A phase 3, randomized, controlled trial compared ruxolitinib to standard care in patients with steroid-dependent or steroid-refractory GVHD. Patients receiving ruxolitinib had significantly greater overall response to GVHD treatment (49.7% vs. 25.6%; odds ratio [OR], 2.99; $p < 0.001$) and symptom control (24.2% vs. 11.0%; OR, 2.62; $p = 0.001$) than controls.[191] However, response to patients with BOS was poor in both groups: 8.6% response in the ruxolitinib group and 6.1% in the control group. This highlights that BOS may be particularly difficult to treat within the post-HSCT GVHD spectrum.

Other therapies considered for BOS include TNF blockade[192] and the anti-CD20 monoclonal antibody rituximab.[193,194] Experience with these is limited to case reports and case series. The novel antifibrotic agents pirfenidone and nintedanib are being studied for BOS, but definitive data are not yet available.

Lung transplantation may be considered for patients with far-advanced BOS who are otherwise deemed to have a successful HSCT without risk of relapse of the underlying disease process. Published experience to date is largely limited to case reports.[135,195–200] In a cross-sectional study of 313 lung transplant recipients, 3 were performed for BOS in allogeneic HSCT recipients.[199] Lung transplants utilizing living donors have also been reported in this setting, but this procedure is currently rarely performed.[197,200,201]

Prognosis The clinical course of BOS is highly variable. The majority of patients have initial worsening of pulmonary function over 6 months, followed by stabilization.[202] Few patients have improvement in FEV_1 after diagnosis—likely less than 20%. The long-term trajectory of pulmonary function 1 year after diagnosis shows a rate of decline that exceeds normal aging, but is similar to an adult patient with COPD.[202] A more rapid initial worsening of pulmonary function may be associated with poor outcome.[24] Unfortunately, while pulmonary function tests can stabilize, the diagnosis of BOS is associated with considerable morbidity and mortality. Survival in historic series was poor, with 65% dying within 3 years of diagnosis.[23,140,160,176,192] However, more recent series suggest a 2-year survival of 70% to 80%, possibly due to better recognition, improved treatment of infection, and improved supportive care when critically ill.[19,202]

Organizing Pneumonia

Bronchiolitis obliterans organizing pneumonia (BOOP) had been widely recognized since Epler introduced the term in 1985.[203] The American Thoracic Society/European Respiratory Society recommended replacing BOOP with cryptogenic organizing pneumonia (COP) since it better describes the essential features of the syndrome.[204] Since organizing pneumonia (OP) is felt to be a complication of HSCT, the term cryptogenic is typically not used. OP in HSCT patients was first reported in the early 1990s,[205,206] and literature is largely limited to case series.[12,139,152,162,205–216] Risk factors for OP are not well described, although there is some evidence that it represents an atypical form of GVHD.[207,212,214]

Pathogenesis The occurrence of OP almost exclusively in allogeneic HSCT recipients with GVHD suggests that it may represent alloimmune-mediated injury to the lung.[160,202,210] However, OP has been reported in allogeneic HSCT recipients in the absence of clinical GVHD, suggesting that other mechanisms are involved as well.[205,217] There is a single report suggesting that recipient human leukocyte antigen (HLA) B35 may be a factor in pathogenesis.[218]

Clinical Features The presenting symptoms are nonspecific and include dry cough, dyspnea, and fever.[205–207,212] Some patients may present with respiratory failure.[214] The reported onset of OP is highly variable, ranging between 1 and 13 months following transplant in published series.[162,205–207,211,213,215,217,219]

Diagnostic Evaluation OP should be included in the differential diagnosis of bilateral airspace disease in HSCT recipients, especially if they do not respond to antibiotics for presumed pneumonia. Pulmonary function tests usually show a restrictive defect, decreased D_{LCO}, and normal airflow.[203,206,207] Chest radiographs and CT show patchy air space consolidation, ground glass attenuation, and nodular opacities.[99,163,205–208,220] The radiographic abnormalities usually demonstrate a peripheral distribution.[221] While chest CT findings may be suggestive of OP, confirmation requires lung biopsy. The yield of transbronchial lung biopsy is relatively low, and VATS lung biopsy is often required if definitive diagnosis is deemed essential.[207] The histologic hallmark of OP is the presence of patchy intraluminal fibrosis, consisting of polypoid plugs of immature fibroblast tissue resembling granulation tissue.[222]

Treatment Corticosteroid therapy is the treatment of choice, with reported response rates approximating 80%.[162,205–207,211,213,215,219]

Radiographic abnormalities usually clear within 1 to 3 months of initiating corticosteroids.[205,207,213] Based on the experience from non-HSCT recipients with OP, prednisone at a dose of 0.75 to 1.5 mg/kg/d, or equivalent, is typically administered for 1 to 3 months, followed by lower doses for a total duration of 6 to 12 months.[223] While typically steroid-responsive, there is a significant risk of relapse as steroids are tapered below 10 to 15 mg daily.

Prognosis OP in HSCT recipients appears to have a worse prognosis than COP in non-HSCT populations. Alasaly et al. found a case fatality rate of 40% in allogeneic HSCT recipients compared with 21% in COP.[207] Among 19 reported HSCT recipients with OP documented in other published reports, the overall case fatality rate was 21%.[162,205–207,211,213,215,217,219]

Interstitial Lung Disease

Interstitial lung disease after HSCT may represent atypical manifestations of GVHD, sequelae of prior chemotherapy and radiation therapy, or sequelae of prior lung injury (e.g., ARDS, IPS, DAH). Several of these entities are discussed below.

Pleuroparenchymal Fibroelastosis Pleuroparenchymal fibroelastosis (PPFE) is a rare interstitial lung disease characterized by upper lobe–predominant pleural and subpleural parenchymal fibrosis[224] with minimal inflammation. PPFE has been described in several populations and was first reported in HSCT recipients in 1991.[225] In a radiology-based review of 700 HSCT patients, 2 patients met criteria for PPFE, suggesting that this is a rare complication in this patient population.[226] Pulmonary function testing typically shows a restrictive pattern in the absence of underlying lung disease.[226] Diagnosis is principally based on presence of the characteristic radiographic features of bilateral apical fibrosis with adjacent pleural thickening. Prognosis is typically felt to be poor, although overall experience is limited. The pathogenesis of PPFE is unclear. Given that it is also seen as a manifestation of lung allograft rejection in lung transplant recipients, it may represent another atypical form of alloimmune-mediated GVHD. Supporting this, case reports of PPFE histology often demonstrate concurrent presence of BO.[225,227,228]

Pulmonary Alveolar Proteinosis Pulmonary alveolar proteinosis (PAP) is characterized by excessive accumulation of surfactant lipoprotein in the alveoli, leading to abnormal gas exchange.[229] It is diagnosed by the presence of periodic acid–Schiff proteinaceous material in BAL fluid and in alveolar air spaces on transbronchial lung biopsies. The occurrence of secondary PAP in HSCT recipients is rare but has been documented in case reports.[230–233] Chest radiograph and CT show characteristic diffuse ground glass infiltrates. The roles of whole lung lavage and aerosolized granulocyte-macrophage colony-stimulating factor, therapies employed in the primary autoimmune form of PAP, are not well established in the secondary form seen in HSCT recipients.

Chronic Eosinophilic Pneumonia There are rare case reports of chronic eosinophilic pneumonia occurring in both allogeneic and autologous HSCT recipients.[234–237] Response to corticosteroid therapy was favorable in most case reports, although there is a single report of a patient with a fatal course.[236]

■ Pulmonary Vascular Disorders

Pulmonary vascular disorders complicating HSCT are discussed briefly below.

Pulmonary Cytolytic Thrombi

Pulmonary cytolytic thrombi (PCT) is a noninfectious pulmonary complication of HSCT recipients occurring predominantly in children.[238,239] PCT occurs almost exclusively in patients with acute or chronic GVHD and is characterized by fever and pulmonary nodules. The time of onset ranges from 8 to 343 days (median, 72) after transplant.[239] Chest radiographic findings include nodules, interstitial prominence, and atelectasis. Chest CT shows multiple peripheral pulmonary nodules, ranging from a few mm to 4 cm in size.[238–241] Bronchoscopy is typically performed to exclude infection. Because of the peripheral and intravascular location of the nodules, transbronchial lung biopsy is unlikely to yield a diagnosis. Among 33 HSCT recipients who underwent open lung biopsy for nodular pulmonary lesions, 15 (45%) had PCT.[241] Biopsy of the pulmonary nodules shows a unique pattern of necrotic, basophilic thromboemboli with amorphous material suggestive of cellular breakdown products.[240,242] Most patients with PCT have a self-limited course without specific treatment, improving clinically within 1 to 2 weeks. Radiographic improvement typically occurs over weeks to months.[239] There have been no reported deaths attributed to PCT. In one study, 9 of the 13 HSCT recipients with PCT were alive at a median follow-up of 1.5 years.[239] All patients received broad-spectrum antibiotics and 9 were treated with systemic corticosteroids.[239]

Pulmonary Veno-occlusive Disease

Pulmonary veno-occlusive disease (PVOD) is a rare pulmonary vascular complication of HSCT with high morbidity and mortality. It should be suspected in patients with dyspnea, evidence of pulmonary hypertension in the absence of left heart failure, and imaging suggestive of pulmonary edema. Although the clinical picture is suggestive, definite diagnosis requires lung biopsy. The incidence of PVOD in HSCT recipients is not known but is likely extremely rare. Existing reports are limited to case series.[49,243] Endothelial damage from conditioning chemotherapy, radiation therapy, and certain chemotherapy agents (bleomycin, mitomycin, and carmustine [BCNU]) have been hypothesized as potentially contributing to PVOD.[244–247] There is no proven therapy for PVOD. While vasodilators are used in various forms of pulmonary arterial hypertension, they may be detrimental in PVOD. Dilating the pulmonary arterial vasculature in the setting of fixed venous resistance may precipitate pulmonary edema, leading to respiratory compromise.

SOLID ORGAN TRANSPLANTATION

This section focuses on noninfectious complications associated with the three most commonly performed solid organ transplant procedures: heart, kidney, and liver transplantation.

Noninfectious complications in lung transplant recipients are discussed in Chapter 106. Infectious complications in immunocompromised hosts, including solid organ transplant recipients, are discussed in Chapter 123.

■ Perioperative Complications

Perioperative pulmonary complications associated with liver, heart, and kidney transplantation are discussed below.

Liver Transplantation

Ventilatory support beyond 48 h is required by 25% to 36% of recipients immediately following liver transplantation.[248–250] Preoperative Model for End-stage Liver Disease (MELD) score has been identified as an important independent predictor of risk of prolonged postoperative ventilatory support, with an average MELD score of 36.4 for those with prolonged postoperative ventilator dependence.[249,250] Another study employing multivariate analysis identified the following preoperative risk factors as independently associated with an increased risk of postoperative respiratory failure following liver transplantation: diabetes mellitus, impaired renal function, preoperative ventilator support, use of a molecular adsorbent recycling system as an artificial liver support strategy, and deceased donor liver transplantation.[251] For those who are successfully extubated, reintubation at some point in the perioperative period occurs in one-third of patients who had initially required greater than 24 h of ventilatory support and 10% of those initially ventilated for less than 24 h.[248,252] Both postoperative respiratory failure and the need for reintubation are associated with significantly poorer survival.[251,252]

A number of factors contribute to respiratory failure, including impaired respiratory muscle function from extensive upper abdominal surgery, malnutrition, and debility; marked intravascular volume shifts and volume overload; aggressive blood product support; and a relatively high frequency of postoperative pneumonia. Additionally, patients undergoing liver transplantation are often critically ill at the time of transplantation and it is not unusual for patients to have been supported on mechanical ventilation for varying periods of time prior to transplantation.

Acute respiratory distress syndrome (ARDS) is a particularly lethal cause of postoperative respiratory failure following liver transplantation, with a reported incidence ranging from 4% to 16%.[253–255] In one study, three preoperative factors—encephalopathy, need for mechanical ventilation, and degree of hyperbilirubinemia—and one intraoperative factor—need for high-level pressor support—were identified as independent risk factors for development of postoperative ARDS.[254] Generic risk factors for ARDS that are commonly encountered in the liver transplant recipient include sepsis, massive blood transfusions, transfusion-related acute lung injury, and aspiration. Reported mortality rates vary, with one contemporary series documenting an 18% mortality rate at 3 months, compared to 8% for those without ARDS.[254]

Hepatopulmonary syndrome (HPS) and portopulmonary hypertension (PPH) are two pulmonary complications of advanced liver disease. Although their onset precedes liver transplantation, these disorders do not immediately or invariably correct following this intervention and they can therefore contribute significantly to morbidity and mortality intraoperatively and in the early postoperative period.

HPS is defined as the triad of liver disease, arterial hypoxemia, and abnormal intrapulmonary vascular dilatation. The vast majority of cases involve diffuse dilatation of the pulmonary microvasculature at the precapillary and capillary level. Rarely, discrete macroscopic arteriovenous communications are present. Proof of the presence of intrapulmonary vascular abnormalities is provided by demonstration of systemic uptake of technetium-labeled macroaggregated albumin on radionuclide perfusion imaging or the delayed appearance of bubbles in the left atrium by contrast echocardiography. Diffuse microvascular dilatation is postulated to cause hypoxemia by increasing the distance through which oxygen must diffuse and thereby creating a central stream of inadequately oxygenated red cells. Unlike a true shunt, this process can be partially corrected with administration of 100% oxygen, which serves to increase the pressure gradient favoring transfer of oxygen from the alveolus to the bloodstream. An unusual feature of HPS is the tendency for oxygenation to worsen in the erect as opposed to supine position (orthodeoxia), presumably due to basilar predominance of the vascular abnormalities.

Although HPS was once considered an absolute contraindication to liver transplantation, subsequent demonstration of its resolution following transplantation led to the reversal of this stance. Indeed, liver transplant candidates with severe HPS (Pa_{O_2} <60 mm Hg on room air) are granted additional MELD points and thus receive enhanced priority with regard to organ allocation. Nonetheless, because hypoxemia often does not correct immediately and may in fact dramatically worsen in the early postoperative period, excessive morbidity and mortality have been observed among these patients. In particular, severe preoperative hypoxemia (Pa_{O_2} <45–50 mm Hg on room air) has been associated with an increased risk of posttransplant mortality in multiple studies, including a multivariate analysis of the United Network for Organ Sharing (UNOS) database.[256,257] Nonetheless, contemporary case series from two experienced liver transplant centers reported no difference in mortality among those HPS patients with Pa_{O_2} <50 mm Hg compared with a less severely hypoxemic cohort.[258,259] The vast majority of patients who survive to hospital discharge ultimately achieve normal room air oxygen levels, most by 6 months following transplantation.[258] Late recurrence of HPS coincident with deteriorating allograft function has been reported.[260]

Postoperative care of the patient with persistent hypoxemia due to HPS centers on the administration of supplemental oxygen while awaiting resolution of the disorder. Based on the positional nature of hypoxemia discussed above, one group reported improvement in oxygenation in a patient with use of the Trendelenburg position.[261] With the demonstration that nitric oxide is an important mediator of the abnormal vascular dilatation that characterizes HPS, attention has turned to the potential therapeutic role of inhibitors of nitric oxide in treating hypoxemia.[262] Schenk et al. described significant improvement in oxygenation and shunt fraction for up to 10 h after administration of a single dose of methylene blue to seven patients with advanced cirrhosis and HPS.[263] Brussino et al. administered nebulized N(G)-nitro-L-arginine methyl ester—an inhibitor of nitric oxide synthesis—to a single patient with HPS and demonstrated a marked rise in arterial oxygen tension and a dramatic reduction in the magnitude of bubbles appearing in the left atrium on contrast echocardiography.[264] In contrast, administration of this agent to 10 patients with HPS did not result in an improvement in gas exchange parameters in another study.[265] Paradoxically, administration of inhaled nitric oxide can improve oxygenation in patients with posttransplant HPS, presumably by increasing perfusion to uninvolved areas of lung without increasing flow through the abnormal arteriovenous channels.[266,267] In the rare instances in which discrete arteriovenous malformations are present, coil embolization can be an effective treatment strategy.[268] Finally, successful use of extracorporeal membrane oxygenation (ECMO) for severe refractory hypoxemia due to HPS has been documented.[269] An algorithm for managing severe hypoxemia (oxygen saturation <85% despite 100% Fi_{O_2} and 10 PEEP) has been published (Fig. 94-4).[270]

PPH describes the development of pulmonary hypertension in patients with advanced liver disease and portal hypertension. The diagnosis rests on demonstration of a mean pulmonary artery pressure exceeding 25 mm Hg and a normal pulmonary capillary wedge pressure. Some authors also include the criterion of a pulmonary vascular resistance exceeding 120 $dyn/s/cm^{-5}$ to distinguish this syndrome from the more benign and common finding of elevated pulmonary pressures due solely to increased cardiac output. PPH is encountered in 1% to 2% of patients with chronic liver disease and in up to 12.5% of patients referred for liver transplant evaluation.[271]

Although mild pulmonary hypertension does not appear to adversely impact liver transplantation, more significant elevations in pressure are associated with excessive posttransplantation mortality. A retrospective review from the Mayo Clinic and a subsequent multicenter database documented perioperative mortality rates of 0% to 17% among liver transplant recipients with a preoperative mean pulmonary artery pressure below 35 mm Hg. In contrast, perioperative mortality rates were 35% to 40% for patients with a mean pulmonary artery pressure of 35 to 50 mm Hg and 40% to 100% for those with a mean pulmonary artery pressure exceeding 50 mm Hg.[272,273] Most deaths occur intraoperatively or in the immediate postoperative period and are largely attributable to progressive right heart failure and hemodynamic collapse.

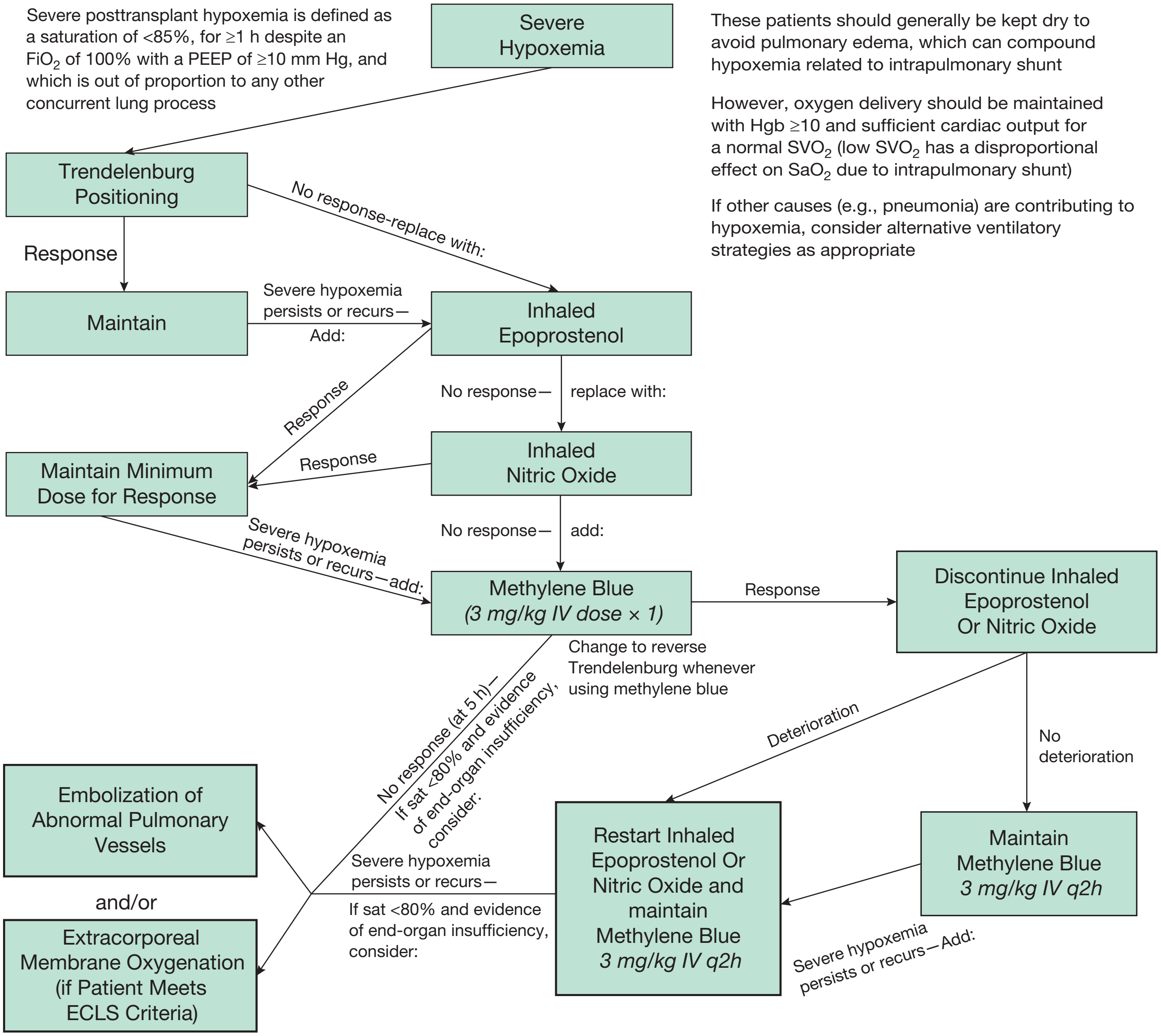
Severe posttransplant hypoxemia is defined as a saturation of <85%, for ≥1 h despite an FiO2 of 100% with a PEEP of ≥10 mm Hg, and which is out of proportion to any other concurrent lung process
Severe Hypoxemia
These patients should generally be kept dry to avoid pulmonary edema, which can compound hypoxemia related to intrapulmonary shunt
However, oxygen delivery should be maintained with Hgb ≥10 and sufficient cardiac output for a normal SVO2 (low SVO2 has a disproportional effect on SaO2 due to intrapulmonary shunt)
If other causes (e.g., pneumonia) are contributing to hypoxemia, consider alternative ventilatory strategies as appropriate
Trendelenburg Positioning
No response-replace with:
Response
Maintain
Severe hypoxemia persists or recurs— Add:
Inhaled Epoprostenol
No response— replace with:
Response
Response
Maintain Minimum Dose for Response
Inhaled Nitric Oxide
No response— add:
Severe hypoxemia persists or recurs—add:
Methylene Blue (3 mg/kg IV dose × 1)
Response
Discontinue Inhaled Epoprostenol Or Nitric Oxide
Change to reverse Trendelenburg whenever using methylene blue
No response (at 5 h)— If sat <80% and evidence of end-organ insufficiency, consider:
Deterioration
No deterioration
Embolization of Abnormal Pulmonary Vessels
and/or
Extracorporeal Membrane Oxygenation (if Patient Meets ECLS Criteria)
Severe hypoxemia persists or recurs— If sat <80% and evidence of end-organ insufficiency, consider:
Restart Inhaled Epoprostenol Or Nitric Oxide and maintain Methylene Blue 3 mg/kg IV q2h
Maintain Methylene Blue 3 mg/kg IV q2h
Severe hypoxemia persists or recurs—Add:

Figure 94-4 Proposed algorithm for management of severe hypoxemia due to hepatopulmonary syndrome in the liver transplant recipient. *(Reproduced with permission from Nayyar D, Man HS, Granton J, et al. Proposed management algorithm for severe hypoxemia after liver transplantation in the hepatopulmonary syndrome. Am J Transplant. 2015;15(4):903–913.)*

Several case series document successful transplantation of patients with severe PPH who responded favorably to the preoperative initiation of vasodilator agents.[274–276] For such patients, intravenous or inhaled epoprostenol or similar agent should be employed in the perioperative period. Since pulmonary hypertension tends to persist despite transplantation, these patients frequently require long-term therapy but can often be transitioned to oral vasodilator agents.

Heart Transplantation

Heart transplant recipients are subject to the same generic perioperative pulmonary complications encountered in the general cardiac surgical population. These include atelectasis, pulmonary edema, pleural effusions, and mediastinitis. The mean duration of mechanical ventilation following heart transplantation documented in two published series was 71.8 ± 12.6 h and 42.3 ± 59.5 h, but the need for ventilatory support beyond the initial perioperative period appears to be low.[277,278] In a series of 157 consecutive heart transplant procedures, prolonged respiratory failure requiring tracheostomy was reported in only 7 cases (4.4%), 5 of which occurred within the first 6 months following transplantation.[279]

Kidney Transplantation

Kidney transplantation is carried out with relatively few perioperative pulmonary complications, reflecting the use of a pelvic incision and the comparative good health of the recipients. The vast majority of patients are extubated in the operating room. Perioperative respiratory failure was documented in only 4% of 178 kidney transplant recipients from the University of Pittsburgh.[280] The most common noninfectious pulmonary complication is hydrostatic pulmonary edema due to impaired salt and water excretion in the setting of early allograft dysfunction or rejection. Contemporary studies of renal transplant patients admitted to the ICU with respiratory failure suggest that this is typically a late complication rather than a perioperative one. In a French multicenter study of 6800 kidney transplant recipients, the median time from transplant to ICU admission for respiratory failure was 17 months.[281] Respiratory failure was documented in 10% of a cohort of 540 consecutive adult renal transplant recipients from a center in Turkey, but the median time from transplantation was 10 months.[282] Similarly, ARDS occurs infrequently. In a retrospective review of a national kidney transplant database encompassing over 42,000 transplants, ARDS was documented in only 86 patients (0.2%) and only 1 of these cases occurred within the perioperative period.[283]

■ Pleural Effusions

Development of pleural effusions in the setting of liver, heart, and kidney transplantation is considered below.

Liver Transplantation

Postoperative pleural effusions are present in 40% to 100% of liver transplant recipients.[284–286] Effusions are exudative in up to 43% of cases and are typically right-sided or bilateral but are rarely exclusively on the left.[286] In a minority of patients, they may occupy greater than half of the hemithorax. Disruption of diaphragmatic lymphatics during hepatectomy is postulated to be the principal mechanism of fluid accumulation. Other contributing mechanisms include volume overload, hypoalbuminemia, and preexisting hepatic hydrothorax. Effusions may enlarge over the first postoperative week but typically resolve by the third week. The need for drainage because of perceived respiratory compromise has been reported in up to 31% of patients.[253,284,285] Effusions that continue to enlarge beyond the first week, persist beyond 3 weeks, or involve only the left hemithorax should be sampled to rule out other causes. Persistent or enlarging effusions should also prompt consideration of subdiaphragmatic processes including hematoma, biloma, or subphrenic abscess.

Heart Transplantation

In a series of 72 heart transplant recipients, the prevalence of pleural effusions within the first 12 months following transplantation was 85%.[287] Most of these effusions developed in the early postoperative period and were bilateral in 68%, left-sided in 14%, and right-sided in 3%. The majority of effusions were small; only 13% occupied >25% of the hemithorax. Effusions were largest between postoperative days 5 and 7, and most resolved by the end of the first year. Factors contributing to the development of pleural effusions following heart transplantation include lymphatic disruption, congestive heart failure, and postsurgical hemorrhage. Other uncommon causes that have been reported include malignancy, pericarditis, chylothorax, and idiopathic.

Kidney Transplantation

Pleural effusions in kidney transplant recipients most commonly occur in the setting of volume overload. Obstruction of the transplanted ureter causing urinothorax is a rare cause of pleural effusion; the fluid is transudative, with a pH <7.3 and a pleural fluid–to–serum creatinine ratio >1.

■ Diaphragmatic Disorders

Diaphragmatic disorders in the setting of lung, heart, and kidney transplantation are briefly considered in the sections that follow.

Liver Transplantation

Right-sided diaphragmatic dysfunction following liver transplantation is postulated to result from crush injury to the right phrenic nerve by the suprahepatic vena caval clamp placed during surgery. In one older series of 48 patients, evidence of delayed or absent right-sided phrenic nerve conduction was found in 79% of patients while the left phrenic conducted normally in all cases.[288] In 38% of patients, there was associated right diaphragmatic paralysis documented by ultrasound. Phrenic nerve injury was not associated with increased duration of mechanical ventilatory support or hospital stay. In a subset of patients followed with serial testing, abnormalities in phrenic nerve conduction and diaphragmatic excursion normalized by 9 months after surgery. Newer surgical approaches have been introduced that preserve the suprahepatic inferior vena cava, thereby minimizing the risk of phrenic nerve injury.[289]

Heart Transplantation

Diaphragmatic dysfunction due to phrenic nerve injury occurs in up to 12% of heart transplant recipients.[290] The right phrenic nerve is most prone to injury. Diaphragmatic dysfunction has been associated with an increased risk of postoperative pneumonia and a trend toward increased length of intubation.

Diaphragmatic hernias have been reported in heart transplant recipients who had left ventricular assist devices (LVAD) implanted prior to transplantation. These devices are placed either preperitoneally or intraperitoneally in the left upper quadrant. The inflow cannula penetrates the left hemidiaphragm and attaches to the left ventricle, while the outflow cannula emerges from the ascending aorta and crosses anterior to the diaphragm near the midline. At the time of heart transplantation, the LVAD is explanted and the left sided diaphragmatic defect is routinely repaired. However, repair of the anterior diaphragmatic defect is not necessarily standard practice, as it has been reasoned this would add to the operative time and that midline scarring would naturally close the rent. The incidence of diaphragmatic hernias has been reported to be as high as 16% among heart transplant recipients in whom closure of the anterior midline diaphragmatic defect was not performed, and in all cases the hernia arose at the site of the unrepaired midline defect.[291] In contrast, only 4% to 5% of patients experienced this complication when the surgical procedure was modified to include routine closure of the anterior defect at the time of LVAD explantation.[291,292]

Patients with diaphragmatic hernias can be entirely asymptomatic, experience subacute gastrointestinal symptoms (abdominal pain, nausea, vomiting), or present emergently with colonic incarceration. Chest radiographs can be nonspecific, demonstrating only an ill-defined opacity at the base of the right or left lung. More suggestive findings include the presence of air within the opacity or actual visualization of colonic haustra. The diagnosis can usually be established definitively with CT of the chest and abdomen, after administration of oral contrast. Surgical repair, either via conventional laparotomy or laparoscopically, is indicated even in asymptomatic cases because of risk of incarceration.

■ Neoplastic Disorders

Posttransplant lymphoproliferative disorder (PTLD) is second only to nonmelanoma skin cancers as a leading neoplastic complication of organ transplantation. PTLD encompasses a spectrum of abnormal B cell proliferative responses ranging from benign polyclonal hyperplasia to malignant lymphomas. Epstein-Barr virus (EBV) has been identified as the stimulus for B-cell proliferation, which proceeds in an unchecked fashion due to the inadequate cytotoxic T cell response in the immunosuppressed host. EBV-naïve recipients who acquire primary infection at the time of organ transplantation are at greatest risk of developing PTLD. A higher intensity of immunosuppression and, in particular, use of antilymphocyte antibody preparations have also been implicated as risk factors. Likely reflecting differences in the magnitude of immunosuppression employed, the incidence of PTLD is only 1% to 2% among kidney and liver transplant recipients but is in the range of 5% to 7% among heart transplant recipients.[293,294] The incidence is greatest within the first year posttransplantation. Among the non-lung organ transplant populations, heart transplant recipients are the most likely to present with intrathoracic involvement, which typically assumes the form of one or multiple pulmonary nodules occasionally accompanied by regional adenopathy or pleural effusions.

Initial treatment involves reduction in the level of immunosuppression to permit partial restoration of host cellular immunity. Such a strategy can lead to regression of tumor in up to two-thirds of solid organ recipients but carries the risk of precipitating acute or chronic allograft rejection.[295] For patients who fail to achieve a complete remission, cannot tolerate reduced immunosuppression, or have widespread disease, immunotherapy with anti-CD20 monoclonal antibodies (rituximab) is the preferred option. Experience with standard chemotherapy has been poor due to the high risk of infection during periods of neutropenia.

The mortality rate attributable to PTLD is not well defined. In multivariate analysis, increased age, elevated lactate dehydrogenase levels, severe organ dysfunction, presence of B symptoms, and multiorgan involvement are independent markers of poor prognosis.[295]

Other malignancies occasionally present in the lungs following transplantation. Bronchogenic carcinoma develops in 2% to 4% of heart transplant recipients.[296] It is unclear whether the development of lung cancer in the heart transplant population reflects an increased risk or simply represents the expected occurrence rate in a population with a high prevalence of cigarette smoking. Among liver transplant recipients with a pretransplantation history of hepatocellular carcinoma, the lung is the most common site of recurrence. Recurrence usually occurs within 2 years of transplantation and appears radiographically as single or multiple lung nodules. An elevated α-fetoprotein level provides an important clue to the possibility of recurrent disease.

Drug-Induced Lung Disease

Sirolimus, also known as rapamycin, is a potent immunosuppressive agent recently introduced into clinical practice. Since its release, numerous cases of interstitial pneumonitis developing in association with sirolimus administration have been reported.[297,298] The incidence of this complication remains unknown. Initial reports suggested that interstitial pneumonitis was largely a result of excessive sirolimus blood concentrations, but subsequent reports described this complication in the setting of therapeutic drug levels.[298,299]

Patients typically present with dry cough, progressive dyspnea, fatigue, and weakness; fever and hemoptysis are less commonly present. Radiographic abnormalities include interstitial infiltrates, alveolar consolidation, and nodular opacities. Bronchoalveolar lavage reveals evidence of a lymphocytic alveolitis and, less commonly, of alveolar hemorrhage. Reported findings on transbronchial lung biopsies include bronchiolitis obliterans with organizing pneumonia, interstitial lymphocytic infiltrates, and nonnecrotizing granulomas. Discontinuation of the drug may be sufficient treatment in many cases; corticosteroids have been given to hasten resolution, but support for this approach is anecdotal. Conversion from sirolimus to everolimus, an agent that shares similar biochemical features and mechanism of action, has led to resolution of pneumonitis in some cases.[300,301] However, interstitial pneumonitis and diffuse alveolar hemorrhage also have been reported in solid organ transplant recipients receiving everolimus.[302,303] In one study of 409 renal transplant recipients receiving an mTOR inhibitor as part of maintenance immunosuppression, the incidence of pneumonitis was 4.8% among those receiving sirolimus and 6.8% among those receiving everolimus, suggesting that pulmonary toxicity is likely to be a class effect.[304]

The interleukin 2 receptor antagonist basiliximab is commonly used as an induction agent, in part because of a generally favorable side effect profile. However, several cases of noncardiogenic pulmonary edema in renal transplant recipients have been reported in association with basiliximab infusion.[305]

Pulmonary Metastatic Calcification

Deposition of calcium in the lung parenchyma and other organs is a well-documented complication of chronic renal failure and is postulated to relate to alterations in calcium and phosphate balance and parathyroid hormone secretion.[306] Although renal transplantation should have a mitigating effect, pulmonary metastatic calcification rarely may progress despite successful transplantation[307,308] and may accelerate in association with graft failure.[309,310] Pulmonary metastatic calcification has also been described in liver transplant recipients, with a reported incidence in two series of 5.2% and 47%.[311,312] Renal insufficiency was a common but not universal feature in these patients. Secondary hyperparathyroidism, due to transient hypocalcemia induced by large volume infusion of citrate-containing blood products and, when present, to renal insufficiency, has been offered as a possible mechanism.[312]

Metastatic pulmonary calcification is most often clinically silent but rarely may lead to restrictive lung disease or fulminant respiratory failure.[309,310,313] The major import of this disorder lies in its ability to radiographically mimic more ominous processes such as infection or malignancy. Single or multiple nodular opacities or areas of alveolar consolidation are seen on plain chest radiographs, but calcification of these lesions may not be apparent. CT findings include multiple diffuse calcified nodules, diffuse or patchy areas of ground-glass opacity or consolidation, and confluent high-attenuation parenchymal consolidation. The abnormalities are typically most pronounced in the upper lung zones. Calcification is evident by CT in approximately 60% of cases. In the absence of calcification, the demonstration of high-attenuation (>100 HU) parenchymal opacities by CT scan or of increased uptake of tracer in the lung by technetium bone scintigraphy is helpful in establishing a diagnosis. In instances of diagnostic uncertainty, transbronchial or surgical lung biopsy may be necessary. There is no established treatment for pulmonary metastatic calcification but, given the overall favorable prognosis, this is rarely a consideration.

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CHAPTER 95

Pulmonary Complications of Sickle Cell Disease

Roberto F. Machado
Mark T. Gladwin

INTRODUCTION

Sickle cell disease (SCD) is one of the most common monogenetic diseases in the world.[1] Sickle cell anemia, the most common and most severe form of SCD, occurs in individuals who are homozygous for a single GAG to GTG substitution in the β-globin gene, resulting in the production of hemoglobin S (HbS). Patients with other types of SCD are compound heterozygotes, having one copy of HbS and one copy of another β-globin mutation, such as hemoglobin SC or HbS-β thalassemia.[2] The presence of concurrent α-thalassemia, which will reduce the intracellular concentration of hemoglobin, also modulates disease severity and accounts for some of the variability in the clinical presentation of patients with SCD.[3] It is estimated that approximately 250,000 children worldwide are born with homozygous sickle cell (HbSS) anemia every year.[4] Approximately 0.15% of African Americans are homozygous for SCD, and 8% have sickle cell trait. In sub-Saharan Africa, up to 40% of the population carry sickle cell trait, and up to 1% of children are born with SCD.[5]

Despite significant improvements in the life expectancy of patients with SCD, estimates of the median age at death range from 42 to 53 years for men and 48 to 58.5 years for women.[3,6–8] Within this context, pulmonary complications of SCD are common and a major threat to the well-being of patients with SCD, accounting for a large proportion of deaths among these patients.[7,9–11] According to the Cooperative Study of Sickle Cell Disease (CSSCD), a prospective multicenter study of 3764 patients, more than 20% of adults likely had fatal pulmonary complications of SCD.[7] Among the 299 patients enrolled in the long-term follow-up study of those who participated in the Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH), pulmonary disease was the most common cause of mortality, accounting for 28% of all deaths.[12] The numbers likely underestimate the importance of pulmonary disease in risk of death, as pulmonary hypertension (PH) was not diagnosed in these cohorts. Indeed, retrospective evaluation of banked plasma samples from the studies using N-terminal pro–brain natriuretic peptide (NT-proBNP) as a surrogate for the presence of PH suggested that PH was a major risk factor for death in both the CSSCD and MSH cohorts.[13,14]

When deoxygenated, HbS is much less soluble than normal hemoglobin (HbA).[15,16] Deoxygenated HbS polymerizes and aggregates inside sickle erythrocytes as they traverse the microcirculation. Rigid, dense, and sickled cells can become physically entrapped in the microcirculation, a process that is enhanced by inflammation and integrin molecule expression, causing red cell and leukocyte adhesion to endothelium. Mechanistic studies in transgenic mice expressing exclusively human HbS suggests that microvascular occlusion results in episodic interruption in blood flow, ischemia, and reperfusion injury, with secondary inflammatory, thrombotic, and oxidant stress.[17–24]

In patients, vaso-occlusion leads to the frequent episodes of bone pain and acute chest syndrome (ACS) that complicate SCD. Furthermore, the membrane of erythrocytes containing intracellular HbS polymer is constantly exposed to mechanical and oxidant injury as the red cells traverse the microcirculation. Ultimately, cumulative membrane damage shortens red cell life span, so that SCD is characterized by a chronic hemolytic anemia. Intravascular hemolysis releases cell-free hemoglobin into the plasma, which scavenges nitric oxide (NO) and releases red blood cell arginase 1 into the plasma, which, in turn, catabolizes arginine, the substrate for NO synthesis.[25–27] Hemolysis can also promote inflammasome-mediated sterile inflammation and endothelial cell death.[28–34] Hence, intravascular hemolysis produces a state of endothelial dysfunction and vascular proliferation, along with prooxidant and proinflammatory stress.[35–37] In effect, intraerythrocytic HbS polymerization leads to downstream vascular inflammation, hemolysis-related vasculopathy, and ischemia–reperfusion organ injury.

Anemia, per se, should also be considered in the evaluation of the cardiopulmonary effects of SCD, since decreasing oxygen carrying capacity of the blood related to severe anemia can impair cardiopulmonary function. The signs and symptoms induced by anemia depend on the degree of anemia, the rate at which it evolves, the oxygen demands of the patient, and the presence of chronic cardiopulmonary disease. For instance, in resting adults subjected to acute isovolemic anemia, oxygen delivery can be maintained at hemoglobin concentrations as low as 5 g/dL,[38] a finding also noted in individuals with chronic severe anemia.[39,40] Thus, anemia, even when severe, rarely causes heart failure; when it does, it is likely that the high-output failure is superimposed upon an underlying cardiac abnormality.

From the hemodynamic standpoint, as hemoglobin level decreases (particularly with hemoglobin values <7 g/dL), blood viscosity decreases, cardiac output increases, cardiac filling pressures tend to decrease, and systemic and pulmonary vascular resistances decrease substantially. As such, because of anemia, the pulmonary vascular resistance in patients with sickle cell disease without pulmonary hypertension ranges from 68 to 74 dyn • sec • cm^{-5}, as compared with the measured values in non-anemic healthy volunteers of 80 to 120 dyn • sec • cm^{-5} (or about 1 Wood Unit).[41] Anemia also lowers blood viscosity and may lead to an underestimation of the severity of pulmonary vascular disease.[42] Combined, these abnormalities may lead to an underestimation of the severity of pulmonary vascular disease in patients with SCD. Such abnormalities are readily reversible with red blood cell transfusions.[39,40,43] Finally, in severe cases, especially in patients with cardiopulmonary disease, anemic hypoxia can also occur as a consequence of reduced ability of blood to participate in gas exchange and oxygen transport. Interestingly, the severity of hemolytic anemia in patients with SCD is strongly correlated with systemic hypoxemia and decreasing arterial hemoglobin oxygen saturation, a finding that is likely related to both increased cardiac output and altered pulmonary vascular perfusion. Alterations in pulmonary vascular perfusion result in impaired ventilation–perfusion matching.[44,45]

ACUTE CHEST SYNDROME

The ACS in SCD is defined as a lung injury syndrome characterized by a new pulmonary infiltrate that (1) is consistent with alveolar consolidation, rather than atelectasis; (2) involves at least one complete lung segment; and (3) is accompanied by chest pain, fever, tachypnea, wheezing, or cough.[46]

■ Epidemiology

ACS is the second most common cause of hospitalization in patients with SCD, the leading cause of admission to an intensive care unit, and, together with PH, a leading cause of premature death, accounting for 25% of SCD-related mortality in earlier cohorts.[7,10] More recently, increased awareness, the chronic use of hydroxyurea, and the early and aggressive use of transfusion therapy have led to a decrease in ACS-related mortality.[47] For example, in a multicenter trial of inhaled NO for vaso-occlusive crisis, only 10% of patients in the study developed ACS, and none required mechanical ventilation or died.[47]

ACS can occur in any of the sickle hemoglobinopathies, but it is more common in individuals with HbSS disease. In the CSSCD, a 29% incidence of the ACS was noted in 3751 subjects over a 2-year period, representing an attack rate of 12.8 episodes per 100 patient-years for homozygous HbS disease.[7] The incidence is higher in children than in adults (24.5 vs. 8.8 events per 100 patient-years). As many as half of episodes of ACS occur in association with vaso-occlusive pain crises, and a significant proportion of patients will have a painful event within 2 weeks of the diagnosis of ACS.[48,49] Some 10% to 20% of patients admitted with an acute vaso-occlusive pain crisis develop ACS within the first 3 days of hospitalization. Recent studies suggest a much higher rate of ACS following influenza infection.[50–52]

Clinical parameters that appear to increase risk for, or are associated with, development of ACS include young age, active smoking, environmental smoke exposure,[53] major surgical procedures, acute rib infarcts, avascular necrosis of the hips, pregnancy, use of narcotics, acute anemic events, nocturnal or daytime hypoxemia, and previous pulmonary events.[48,49] In children, a number of studies suggest that asthma is a risk factor for the development of ACS.[54–56] Laboratory parameters in steady state associated with an increased risk for the development of ACS include an elevated white blood cell count, higher steady-state level of hemoglobin, and lower steady-state level of fetal hemoglobin.[48,49]

While a high steady-state level of hemoglobin is a risk factor for ACS, during acute hospitalization for a vaso-occlusive crisis, development of the ACS is often preceded by an abrupt drop in hemoglobin (mean decrease of 0.78 g/dL) and increases in markers of hemolysis—for example, lactate dehydrogenase. The platelet count also may fall prior to ACS, and platelet levels lower than 200,000 cells per mL constitute an independent risk factor for the severity of ACS, an increased risk of neurologic complications, and the need for mechanical ventilation.

A limited number of studies have addressed the role of candidate gene polymorphisms in patients with ACS. In a small cohort of 134 pediatric patients with SCD, *NOS1* AAT repeat polymorphism in intron 13 was associated with increased risk of ACS.[57] Similarly, in a study of 173 pediatric patients with SCD, individuals homozygous for an *ET-1* T8002 C polymorphism had higher rates of ACS, while those homozygous for a *NOS3* T-786 C polymorphism had lower rates.[58] Finally, in a cohort of 942 children with SCD, a highly polymorphic (GT)n dinucleotide repeat located in the promoter region of *HMOX1*, with long repeat lengths linked to decreased activity and inducibility, was evaluated. After adjusting for sex, age, asthma, percentage of fetal hemoglobin, and α-globin gene deletion, children with two shorter alleles had lower rates of hospitalization for ACS compared with children with longer allele lengths.[59]

■ Pathogenesis

The etiology of ACS is multifactorial. Although a specific cause is not identified in a substantial proportion of patients, three major pathogenetic mechanisms are involved, including infection, bone marrow fat embolization, and direct red cell intravascular sequestration, which cause lung injury and infarction (Table 95-1, Fig. 95-1).

TABLE 95-1 Causes of the Acute Chest Syndrome[a]

Cause	All Episodes (*n* = 670)	Age at Episode of Acute Chest Syndrome		
		No. of Episodes (%)		
		0–9 y (*n* = 329)	10–19 y (*n* = 188)	≥20 y (*n* = 153)
Fat embolism, with or without infection[b]	59 (8.8)	24	16	19
Chlamydia[c]	48 (7.2)	19	15	14
Mycoplasma[d]	44 (6.6)	29	7	8
Virus	43 (6.4)	36	5	2
Bacteria	30 (4.5)	13	15	12
Mixed infections	25 (3.7)	16	6	3
Legionella	4 (0.6)	3	0	1
Miscellaneous infections[e]	3 (0.4)	0	3	0
Infarction[f]	108 (16.1)	50	43	15
Unknown[g]	306 (45.7)	139	88	79

[a] *Data on one episode were excluded because the patient's birth date was not known.*

[b] *Nineteen of the episodes of pulmonary fat embolism were associated with infectious pathogens.*

[c] *This category included episodes in which Chlamydia alone was identified, but not episodes involving mixed infections or pulmonary fat embolism.*

[d] *This category included only episodes in which only Mycoplasma pneumoniae or Mycoplasma hominis was identified, but not episodes involving mixed infections, Mycobacterium tuberculosis, or pulmonary fat embolism.*

[e] *This category included two cases of tuberculosis and one case of Mycobacterium avium complex infection.*

[f] *A pulmonary infarction was presumed to have occurred when the results of the analysis for pulmonary fat embolism, bacterial studies, viral isolation studies, and serologic tests were complete and were all negative.*

[g] *The cause of episodes for which some or all of the diagnostic data were incomplete and no etiologic agent was identified was considered to be unknown.*

Reproduced with permission from Vichinsky EP, Neumayr LD, Earles AN, et al. Causes and outcomes of the acute chest syndrome in sickle cell disease. National Acute Chest Syndrome Study Group. N Engl J Med. 2000;342(25):1855–1865.

The most common etiology of ACS in both children and adults is infection by a community-acquired pathogen. It has been proposed that community-acquired respiratory infection induces an excessive inflammatory lung injury response in patients with SCD, as SCD mice that express only human HbS show increased susceptibility to inflammatory triggers (lipopolysaccharide and bacteria) and development of lung injury at lower levels of endotoxin that do not adversely affect wild-type mice.[60,61] In addition, more than 80% of adults with SCD report a history of having been admitted to the hospital for "pneumonia."[35]

The National ACS Study Group analyzed 671 episodes of ACS in 538 patients with SCD. Respiratory samples obtained from sputum and BAL were analyzed for viral and bacterial infections.[46] Among the infectious agents identified most commonly (Table 95-1) were atypical bacteria and viruses, including *Chlamydia pneumonia* (29%), *Mycoplasma pneumonia* (20%), *Legionella pneumophila* (2%), respiratory syncytial virus (10%), parvovirus (4%), rhinovirus (3%), parainfluenza virus (2%), influenza A virus (2%), cytomegalovirus (2%), Epstein–Barr virus (1%), and herpes simplex virus (1%). Community-acquired encapsulated bacteria were rarely isolated, despite the fact that patients with homozygous HbS disease rarely have normal splenic function. *Staphylococcus aureus* was isolated in 5% of cases and *Streptococcus pneumoniae* in only 4% of cases.

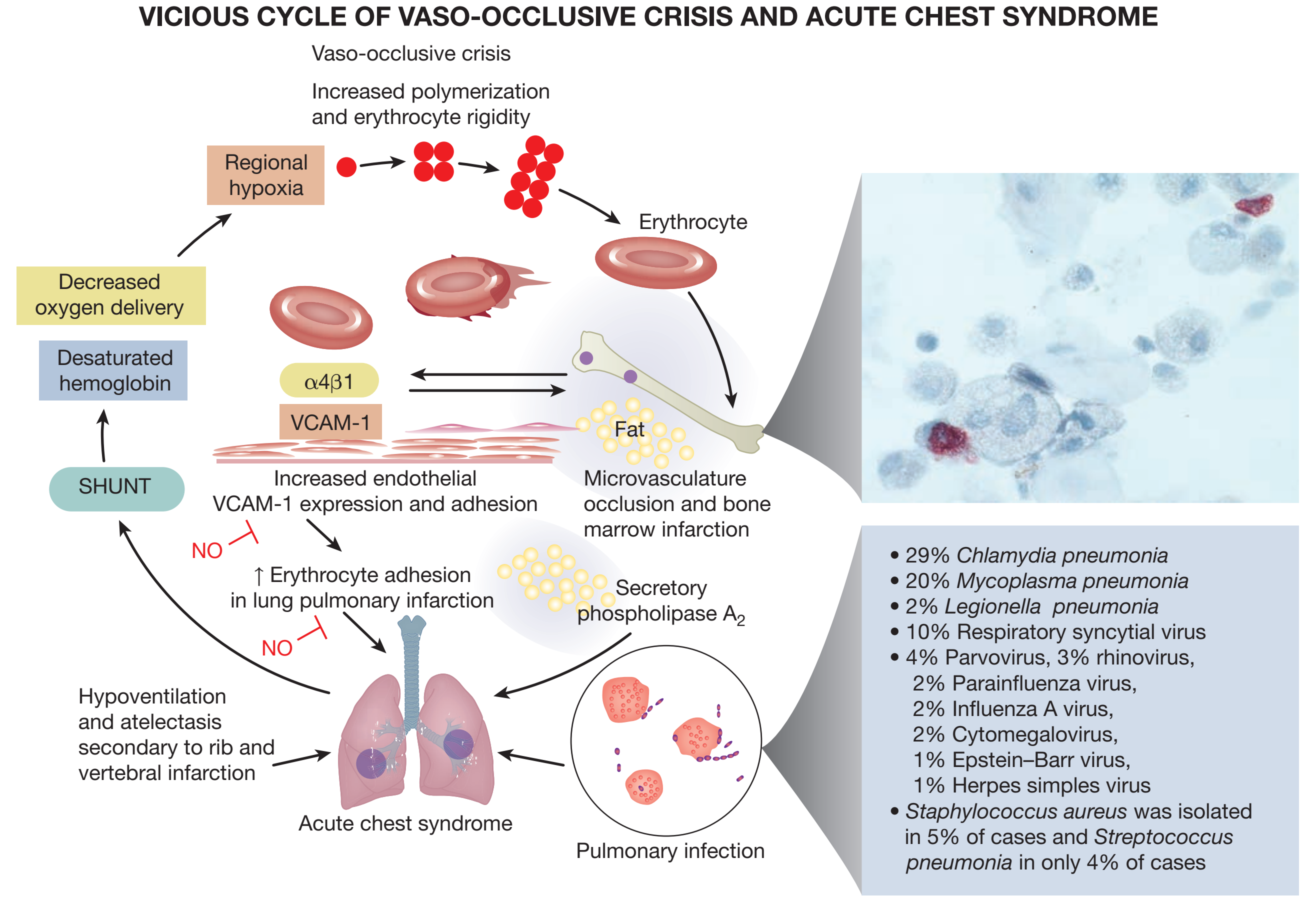

VICIOUS CYCLE OF VASO-OCCLUSIVE CRISIS AND ACUTE CHEST SYNDROME
Vaso-occlusive crisis
Increased polymerization and erythrocyte rigidity
Regional hypoxia
Erythrocyte
Decreased oxygen delivery
Desaturated hemoglobin
α4β1
VCAM-1
Fat
SHUNT
Increased endothelial VCAM-1 expression and adhesion
Microvasculature occlusion and bone marrow infarction
NO
↑ Erythrocyte adhesion in lung pulmonary infarction
Secretory phospholipase A2
NO
Hypoventilation and atelectasis secondary to rib and vertebral infarction
Acute chest syndrome
Pulmonary infection
• 29% Chlamydia pneumonia
• 20% Mycoplasma pneumonia
• 2% Legionella pneumonia
• 10% Respiratory syncytial virus
• 4% Parvovirus, 3% rhinovirus, 2% Parainfluenza virus, 2% Influenza A virus, 2% Cytomegalovirus, 1% Epstein–Barr virus, 1% Herpes simples virus
• Staphylococcus aureus was isolated in 5% of cases and Streptococcus pneumonia in only 4% of cases

Figure 95-1 Pathogenesis of the acute chest syndrome. Three major mechanisms are associated with the development of ACS: infection, bone marrow fat embolization, and direct red cell intravascular sequestration causing lung injury and infarction. Lung injury results in ventilation–perfusion mismatch and hypoxemia, which leads to increased hemoglobin S polymerization and erythrocyte vaso-occlusion. This worsens bone marrow infarction and pulmonary vaso-occlusion to promote a vicious cycle. Fat embolization can be diagnosed by Oil Red O staining of pulmonary alveolar macrophages, revealing the characteristic red lipid inclusions. Common infectious organisms identified in cases of ACS are listed. *(Reproduced with permission from Gladwin MT, Vichinsky E. Pulmonary complications of sickle cell disease. N Engl J Med. 2008;359(21):2254–2265.)*

Cases of severe ACS related to seasonal influenza also have been described.[50–52]

Fat embolization syndrome occurs as a complication of vaso-occlusive pain crisis involving multiple bones, resulting in bone marrow edema, infarction, and necrosis. Fat embolism was identified by the National ACS Study Group as the cause of ACS in 16% of patients. During fat embolization, bone marrow contents are released into the systemic circulation and are trapped in the pulmonary circulation, producing acute PH, severe lung inflammation, and hypoxemia (Fig. 95-2).[62–64] Bone marrow fat released into the bloodstream is also converted to free fatty acids by secretory phospholipase A_2, producing direct inflammatory lung injury.[65]

In approximately 20% of patients, direct adhesion of sickled cells in the pulmonary vasculature arising during lung infarction or lung vaso-occlusion is associated with the development of ACS; a small fraction of patients develop wedge-shaped infarctions, sometimes followed by central cavitation.[66] In situ pulmonary arterial thrombosis and cellular occlusion also appear to be common in patients with ACS. In a study of 144 episodes of ACS in 125 consecutive patients evaluated using CT angiography, a 17% prevalence of subsegmental thromboembolism was noted; there was no evidence of peripheral venous thrombosis.[67]

A potential role for hemolysis-derived plasma-free hemoglobin and its by-products, such as free heme, has been suggested in the pathogenesis of ACS. In children with SCD, multivariable regression analysis identified that higher plasma free heme was associated with increased odds of vaso-occlusive crisis and ACS.[68] Administration of lysed red blood cells into the circulation of sickle cell mice has been shown to increase vascular permeability in the lung without impacting permeability in other organs.[69] Furthermore, studies have demonstrated that intravenous administration of heme to sickle cell mice induces severe and lethal acute lung injury.[70] In aggregate, these data suggest that plasma-free hemoglobin or heme specifically may directly contribute to lung injury in the context of vaso-occlusive crisis and ACS. The relationship between increased intravascular hemolysis and thrombocytopenia (see below) suggests that a possible thrombotic thrombocytopenic purpura–like mechanism may occur in a subset of patients with ACS. In fact, studies have demonstrated that hemoglobin produced during hemolysis may inhibit ADAMTS13 activity.[71–73]

■ Clinical Features and Evaluation

About 80% of patients with ACS present with fever and 62% with cough; approximately 40% have chest pain, tachypnea, dyspnea, and abdominal, arm, leg, rib, or sternal pain.[46] Some of the clinical features of ACS are age dependent, which likely reflects the different disease etiologies in different age groups. Children have a higher proportion of infectious etiologies in comparison to adults, who have fat embolization as a major cause. Most adult patients present with severe extremity or chest pain and develop ACS 24 to 72 h later.

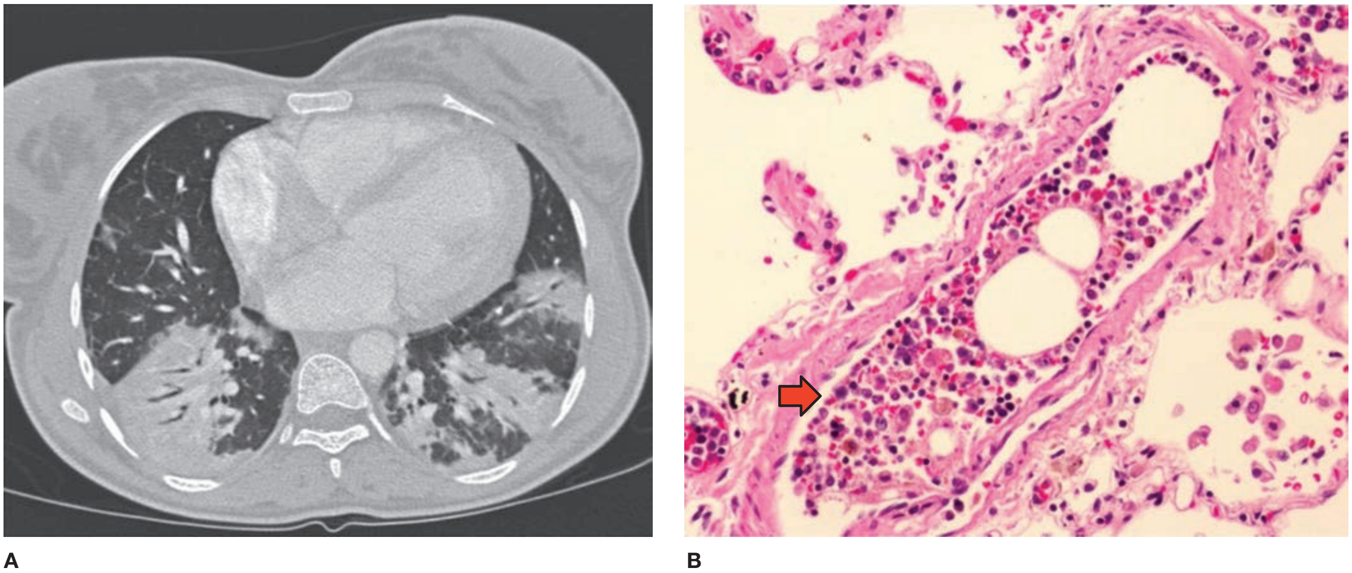


Figure 95-2 Fat embolization in acute chest syndrome. **A.** Chest CT scan of a patient with acute chest syndrome and fat embolization syndrome. **B.** Postmortem examination specimen of a patient who died suddenly during an episode of vaso-occlusive crisis and acute chest syndrome demonstrating bone marrow elements lodged in the small pulmonary artery *(arrow)*. *(Reproduced with permission from Vij R, Machado RF. Pulmonary complications of hemoglobinopathies. Chest. 2010;138(4):973–983.)*

Reactive airway disease is observed in 13% of cases and is much more common in children.[46]

ACS is associated with signs of systemic inflammation. Mean peak temperature is 38.9°C and mean white blood cell count is 23,000 cells per mL. In addition, a drop in hemoglobin level (mean decrease of 0.78 g/dL from steady-state level) and an increase in markers of hemolysis are noted.[46] Thrombocytopenia also may occur; platelet counts less than 200,000 cells per mL appear to be a marker of more severe ACS and are associated with increased risk of neurologic complications and need for mechanical ventilation.[46] Secretory phospholipase A_2 levels, which are elevated early in the course of ACS even before development of radiographic changes, have been used to predict onset of the syndrome.[74]

Some patients manifest evidence of systemic fat embolization. In these cases, ACS is part of the spectrum of the systemic fat emboli syndrome, evident as acute multiorgan system failure (MOSF) (Chapter 142). Patients with MOSF experience acute hypoxic respiratory failure, acute cor pulmonale, renal and hepatic dysfunction, alterations in mental status, seizures, thrombocytopenia, and coagulopathy.[75,76]

The diagnosis of pulmonary fat embolization syndrome is based on identification of Oil Red O–positive lipid accumulations within alveolar macrophages, as the clinical manifestations can be indistinguishable from other causes of ACS (Fig. 95-2). Bronchoscopy has been used as the diagnostic modality of choice for the diagnosis of pulmonary fat embolization syndrome. Interestingly, a study comparing the diagnostic utility of induced sputum sampling of alveolar macrophages with specimens obtained from bronchoalveolar lavage found a significant, albeit modest, correlation between the two ($r = 0.65$).[77] Patients with ACS who have lipid-laden macrophages detected in induced sputum have significantly more extrathoracic pain than those without evidence of fat emboli, more neurologic symptoms, a lower platelet count, and higher serum transaminase levels.[77]

The mean length of hospitalization for ACS is 10.5 days, compared with 3 to 4 days for uncomplicated vaso-occlusive painful crisis. Large registry studies suggest that 13% of patients require mechanical ventilation. The overall mortality is 3% for all patients and 9% for adults; however, as noted previously, these rates may be lower in experienced medical centers employing more aggressive and earlier transfusion therapy.

Risk factors for mechanical ventilation and poor outcome include a platelet count less than 200,000 per µL (likely indicative of the fat emboli syndrome), a greater number of lobes involved on the chest radiograph, and a self-reported or medical record–based history of cardiac disease.

Acute cor pulmonale also can complicate the course of ACS. In a study of 84 consecutive patients hospitalized with ACS, 13% manifested right heart failure. This subgroup had significant elevations in B-type natriuretic peptide and troponin I levels and the highest risk for needing mechanical ventilation and death.[78] PH and right heart dysfunction appear to represent major comorbidities in ACS; right heart failure should be considered in those patients presenting with shock or severe hypoxia.

■ Treatment

Since the triggers and risk factors for ACS are well known, preventive strategies in the outpatient setting, clinical surveillance, and aggressive and early therapy are likely to improve prognosis.

Patients with multiple episodes of vaso-occlusive crises or a previous history of ACS should be treated with hydroxyurea in the outpatient setting, since its use has been shown to reduce the risk of developing ACS by approximately 50%.[79,80] A chronic transfusion regimen also is effective in reducing the incidence of ACS,[81] as is preoperative blood transfusion in patients undergoing surgical procedures.[82] L-glutamine,[83] voxelotor,[84] and crizanlizumab[85] have demonstrated potential efficacy in decreasing the incidence of vaso-occlusive painful events, but a direct effect on the incidence of ACS has not been studied; thus, there is insufficient evidence to determine their efficacy for the prevention of ACS.

In acutely ill patients, specific strategies, such as aggressive pain management and incentive spirometry, can minimize chest wall splinting, mitigating development of atelectasis and alveolar hypoxia. The use of incentive spirometry has been shown to decrease the incidence of new pulmonary infiltrates in patients admitted with vaso-occlusive pain affecting the chest wall.[66]

In one small study evaluating the efficacy of prophylactic blood transfusions in patients with serum phospholipase A_2 elevations during vaso-occlusive crisis,[86] transfusion eliminated ACS in the study cohort. Larger confirmatory trials are indicated.

We recommend use of empiric antimicrobial therapy in all patients with ACS, given the high prevalence of infectious etiologies. Coverage should include agents effective against atypical bacteria and encapsulated organisms. Important to consider are alternative organisms, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and influenza viruses, especially in patients who do not respond to therapy or who develop ACS during influenza season. A recent observational cohort study suggests that a procalcitonin-guided strategy to prescribe antibiotics in patients with ACS may reduce antibiotic exposure with no apparent adverse outcomes.[87]

Although not demonstrated in randomized trials, blood transfusion remains the mainstay of ACS therapy and is considered standard of care. Acute red cell transfusion increases PaO_2 and hemoglobin oxygen saturation and may rapidly resolve the pulmonary event.[46,88] In the DeNOVO trial,[47] no episodes of ventilator-dependent respiratory failure and no deaths were noted in 30 patients with ACS receiving the current practice of early transfusion therapy. The improved outcomes compare favorably with historic data from the National ACS Study Group.

To avoid the adverse effects of increased blood viscosity and the consequent risk of vaso-occlusion, the hemoglobin level should not be raised higher than 11 g/dL with simple transfusion therapy. The National Acute Chest Syndrome Study Group found no significant differences in outcomes between patients treated with simple transfusion or red cell exchange (erythrocytapheresis), suggesting that the former approach is preferred as initial therapy.[46] Patients with high initial hemoglobin concentrations (≥9 g/dL) or those with severe or rapidly progressive disease should receive erythrocytapheresis. Most importantly, to decrease the risk of delayed hemolytic transfusion reactions related to alloimmunization against minor red blood cell antigens, all transfused blood should be matched to Rh, C, E, and Kell antigens.

Treatment with corticosteroids has been shown to reduce the severity of pain and length of hospitalization, but this therapy is complicated by a high rate of rebound pain and readmission.[89,90] An investigation of the use of a slow, tapering protocol of corticosteroids to maintain their beneficial effects while limiting rebound pain and readmission was terminated early because of slow accrual of study patients.[91]

Noninvasive mechanical ventilation (NIMV) has been studied in the setting of ACS. In a prospective, randomized, open, single-center study of 67 adult patients with ACS, use of NIMV improved respiratory rate and gas exchange but failed to significantly reduce the number of patients remaining hypoxemic by day 3 of hospitalization; in addition, use of NIMV was associated with greater patient discomfort.[92] In addition, NIMV did not change transfusion rates, pain scores, narcotic dose, or hospital length of stay. In fact, its use prolonged length of stay in the step-down unit.[92]

The DeNOVO trial explored use of inhaled NO for patients with SCD presenting in vaso-occlusive crisis. Despite two prior positive small phase 2 trials,[93,94] the DeNOVO study did not demonstrate an effect of inhaled NO therapy compared with placebo on the duration of pain crisis, narcotic use, pain scores, or development of ACS.[47]

ASTHMA AND AIRWAY REACTIVITY

Asthma is common among patients with SCD, particularly in children. In a prospective study of 291 African-American children with SCD, 17% received a clinical diagnosis of asthma.[54] Interestingly, the reported incidence of airway hyperresponsiveness in children with SCD is much higher, ranging from 40% to 77%, as measured by methacholine, exercise, or cold air challenge tests.[95–97] There is an association between elevated immunoglobulin E levels and asthma or airway hyperresponsiveness in individuals with SCD; this association supports the notion that asthma can be a separate comorbid condition in these patients.[98–100] It is important to point out, however, that data suggest that wheezing and obstructive lung disease may occur independent of a traditional diagnosis of asthma and are a marker of disease severity or an increased capillary blood volume associated with a high output state.[101,102]

Asthma has been associated with multiple complications of SCD, including ACS. Children with SCD and asthma experience almost twice as many episodes of ACS as their counterparts without asthma, even after matching for age, sex, fetal hemoglobin percentage, and lifetime average hematocrit.[54–56,103–106] Several mechanisms have been proposed for this association, including ventilation–perfusion mismatch leading to hypoxemia and sickling, and inflammation causing increased erythrocyte adhesion to vascular endothelium.[107] Asthma is an independent risk factor for mortality in children with SCD, conferring a twofold higher risk of death (hazard ratio [HR], 2.36; confidence interval [CI], 1.21–4.62; $p = 0.01$).[108] The reasons for increased mortality remain unclear but are likely related to the higher risk of vaso-occlusive crises and ACS.

Data on asthma in adults with SCD are scarce. The diagnostic and prognostic significance of the disease in adults is less clear than in children. A study of 31 adults with SCD without a clinical diagnosis of asthma showed an average TLC of 73% predicted, FVC of 79% predicted, and FEV_1 of 75% predicted.[106] Fifteen patients demonstrated bronchial hyperreactivity on methacholine provocation testing; there was evidence of a correlation between bronchial hyperreactivity and previous episodes of ACS. Another cohort study evaluated physician-diagnosed asthma and a history of wheezing in 114 adults with SCD.[109] Although self-reported severe and recurrent wheezing was associated with increased rates of pain, ACS, and risk of death, no relationship was found between a physician-established diagnosis of asthma and these complications.[110]

Although there are no controlled trials of asthma therapy in the SCD population, most experts recommend treatment following generally established guidelines for asthmatics in general.[111] Systemic corticosteroids must be used with caution, however, as corticosteroids appear to induce vaso-occlusive crises and ACS in patients with SCD. In fact, the use of corticosteroids in pediatric patients with SCD has been shown to worsen outcomes.

PULMONARY HYPERTENSION

Among the chronic cardiopulmonary complications of SCD, PH, is the major threat to the well-being and longevity of patients. A number of studies have added significantly to our understanding of the prevalence, underlying pathogenetic mechanisms, and clinical phenotype of patients with PH and SCD. Several screening cohort studies have focused on the prevalence, risk factors, and mortality rate of patients with SCD and PH diagnosed by right heart catheterization. Interestingly, recent studies in patients with many diseases suggest that even borderline values between 20 and 24 mm Hg also increase risk of death and exercise intolerance.[112,113] As a result, the 6th World Symposium in Pulmonary Hypertension has proposed to define all forms of precapillary PH as a mPAP >20 mm Hg and a pulmonary vascular resistance ≥3 Wood Units (240 dyn • s/cm^5).[114] This new definition would potentially lead to reclassification of a substantial number of patients with sickle cell disease as having PH.

■ Epidemiology

Retrospective studies using Doppler echocardiography have demonstrated that 20% to 30% of patients with SCD have an elevated estimated pulmonary artery systolic pressure (PASP) that is two standard deviations above the normal mean value (tricuspid regurgitant jet velocity [TRV] ≥2.5 m/s). Approximately 8% to 10%

have values three standard deviations above the normal mean (≥3.0 m/s).[76,115] These findings have been corroborated in several prospective studies.

In one study using echocardiographic screening, 23% of patients with SCD had borderline or mild elevations in PASP (defined by a TRV ≥2.5–2.9 m/s and corresponding to a PASP of approximately 30–39 mm Hg), and 9% had moderately to severely elevated pressures (defined by TRV ≥3.0 m/s, corresponding to a PASP of approximately 40–45 mm Hg).[35] Similar rates were found in other studies.[116–119]

In a study of patients enrolled in the MSH, plasma NT-proBNP, a prohormone released by right and left ventricular myocardium under pressure stress, was elevated in 30%, suggesting the presence of elevated pulmonary pressures and right heart strain.[13] Similarly, measurements of NT-proBNP in banked plasma from patients enrolled in the CSSCD from 1978 to 1988 revealed that 27.6% of adults had elevated levels.[14] In both studies, elevated study entry levels of NT-proBNP were independently associated with a higher risk of death in prospective follow-up.

Epidemiologic risk factors associated with an elevated TRV include a history of renal or cardiovascular complications, increased systemic systolic blood pressure, abnormalities in markers of hemolytic anemia (anemia; reticulocytosis; and increased lactate dehydrogenase, aspartate aminotransferase, and bilirubin levels), iron overload, cholestatic liver dysfunction (elevations in alkaline phosphatase), renal insufficiency, a history of cutaneous leg ulceration, and, in men, a history of priapism.[13,35] These risk factors have also been observed in studies using right heart catheterization to diagnose PH.[118,120,121] Surprisingly, in these studies development of an elevated TRV was not associated with the number of vaso-occlusive episodes, markers of inflammation, fetal hemoglobin levels, or platelet counts.[13,35] PH determined by right heart catheterization has also been shown not to correlate with episodes of vaso-occlusive crisis or ACS, suggesting that this complication arises secondary to hemolytic anemia, rather than recurrent episodes of vaso-occlusion. A large screening study of 483 patients with homozygous SS disease conducted in the United States and England reproduced these associations;[122] patients with elevations in Doppler-estimated PASP had more severe hemolytic anemia and renal insufficiency. These patients also had lower arterial oxygen saturation, higher levels of NT-proBNP, and lower 6-min walk distances. A high Doppler-estimated pulmonary artery pressure was also independent of rates of vaso-occlusive disease or ACS, providing further support to the hypothesis that this complication arises secondary to chronic hemolytic anemia and end-organ dysfunction (renal and liver disease), rather than episodes of ACS and related pulmonary fibrosis.

An elevated estimated PASP by Doppler-echocardiographic screening or right heart catheterization is a significant risk factor for death in patients with SCD. The risk appears to be linearly related to the elevation in PASP.[35] In one study, a 14% mortality rate over 2 years was reported in patients with an elevated TRV versus a 3% mortality rate in those with normal TRV.[117] Similarly, in another study, the mortality rate over 2.5 years was 25% in patients with an elevated TRV and less than 2% in those with a normal TRV.[116] Consistent with these data, in a cohort of 632 patients with SCD from the United States and England, 11.2% had TRV ≥3.0 m/s and 24.1% had NT-proBNP level ≥160 pg/mL. Of 22 deaths during follow-up, 50% had a TRV ≥3.0 m/s. At 24 months the cumulative survival was 83% with TRV ≥3.0 m/s and 98% with TRV <3.0 m/s. The hazard ratios for death were 11.1 (95% CI, 4.1–30.1; $p < 0.0001$) for TRV ≥3.0 m/s, 4.6 (1.8–11.3; $p = 0.001$) for NT-proBNP ≥160 pg/mL, and 14.9 (5.5–39.9; $p < 0.0001$) for both TRV ≥3.0 m/s and NT-proBNP ≥160 pg/mL.[123]

Several studies have provided insights into PH in SCD using the gold standard diagnostic test for the disease—right heart catheterization (Table 95-2).

TABLE 95-2 Right Heart Catheterization–based Pulmonary Hypertension Screening Studies in Sickle Cell Disease

	Parent	Fonseca	Mehari
Subjects screened (*N*)	398	80	531
Number of subjects with PH	24	8	55
Percentage of screened population	6	10	10.5
mPAP, mm Hg	30 ± 6	33 ± 9	36 ± 9
CO, L/min	9 ± 2	5 ± 2[a]	9 ± 2
PVR, dyn-s/cm^5	138 ± 58	179 ± 120[b]	227 ± 149
6MWD, m	404 ± 94	460 ± 152	358 ± 115
Number of subjects with precapillary PH	11	3	31
Percent of screened population	2.7	3.75	6.0
Number of subjects with postcapillary PH	13	5	24
Percent of screened population	3.3	6.25	4.5
Mortality in PH group	23%	38%	36%

PH, pulmonary hypertension; mPAP, mean pulmonary artery pressure; CO, cardiac output; PVR, pulmonary vascular resistance; 6MWD, 6-minute walk distance.

[a] Cardiac index (L/min/m^2).

[b] Converted mean value: PVR measured in Wood units.

In a screening study of more than 500 patients followed for up to 9 years (median duration of follow-up, 4.4 years),[121] 86 patients underwent right heart catheterization; 56 were diagnosed with PH (defined as mPAP ≥25 mm Hg) (10.5%). Similar findings were observed in another screening study of 80 patients (10% prevalence of PH using right heart catheterization).[118] A large screening study of nearly 400 patients with SCD in France[119] demonstrated a prevalence of PH (determined by right heart catheterization) of 6%.

The presence of PH, as documented by right heart catheterization, is a major risk factor for death in patients with SCD, with mortality rates ranging from 23% to 38%.[118,119,121] In one study, a 50% 2-year mortality rate was reported in patients with PH and SCD.[124] Each increase of 10 mm Hg in mean PAP was associated with a 1.7-fold increase in death rate. Autopsy studies suggest that up to 75% of patients with SCD have histologic evidence of pulmonary arterial hypertension at the time of death (Fig. 95-3).[125]

Finally, specific hemodynamic values independently associated with mortality include increases in mean PAP, diastolic PAP, diastolic PAP–pulmonary capillary wedge pressure gradient, transpulmonary gradient, and pulmonary vascular resistance.[120] These data strongly suggest that mortality in adults with SCD and PH is proportional to the severity of precapillary PH.[120]

■ Pathogenesis

An association between the development of PH and the intensity of hemolytic anemia has been observed in prospective screening studies of adult patients with SCD,[35,116,117,119,121,122] and in an expanding number of pediatric studies.[126–130] The association suggests that hemolysis is related mechanistically to PH.

Hemolysis releases plasma-free hemoglobin that inactivates the intrinsic vasodilator NO[26,27] and arginase 1, which depletes L-arginine, the substrate for NO synthesis.[25] The result of these combined pathologic processes is decreased NO bioavailability

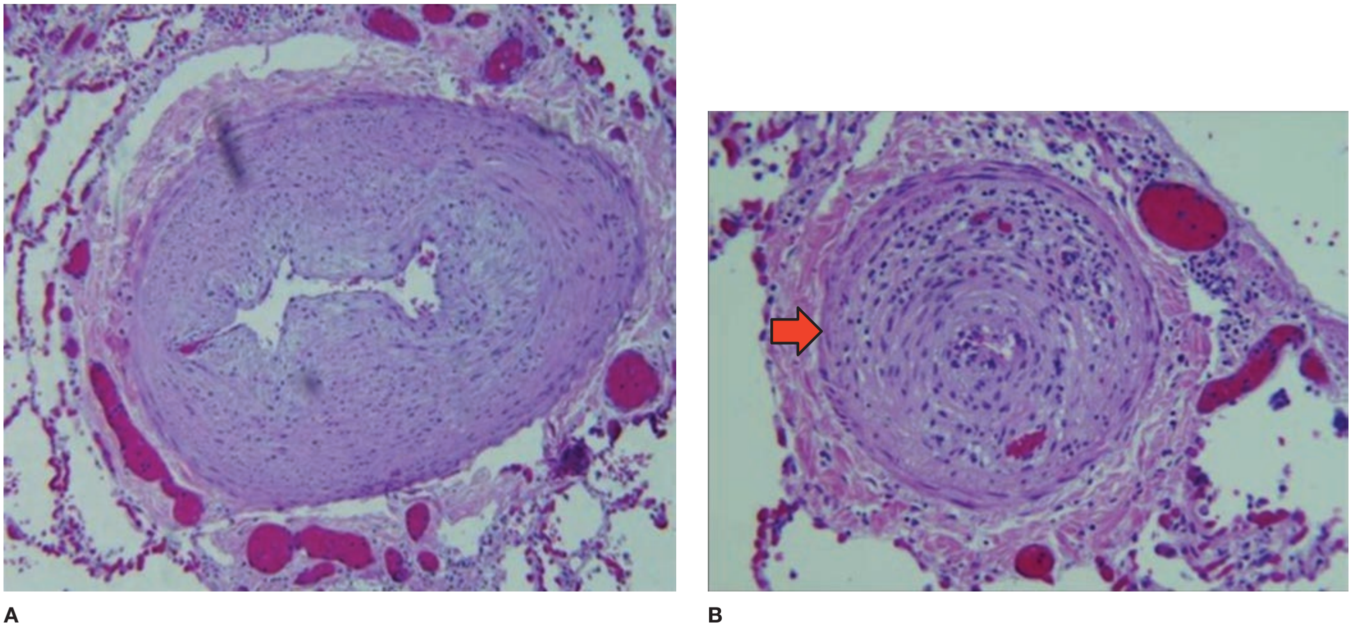


Figure 95-3 Pulmonary arteriopathy in sickle cell-related pulmonary hypertension. **A.** Low power photomicrograph demonstrating intimal and pulmonary arterial smooth muscle hypertrophy (H&E stain). **B.** Plexiform lesion (*arrow*, H&E stain).

and "resistance" to NO-dependent vasodilation.[27] In addition, the accumulation of redox-active heme and iron from lysed red blood cells contributes to the generation of reactive oxygen species that can exacerbate thrombosis and vascular proliferative responses.[131]

In situ thrombosis is well documented in patients with pulmonary arterial hypertension and chronic thromboembolism causes chronic thromboembolic PH (CTEPH). Sickle cell disease is associated with an increased risk for thrombotic complications, including pulmonary embolism[132] and, consequently, CTEPH. A correlation exists between the rate of hemolysis and levels of procoagulant factors in blood in patients with SCD.[133–135] In addition, hemolysis and decreased NO bioavailability induce platelet activation,[136] thrombin generation, and tissue factor activation, which would induce a procoagulant state.[137] Hemolysis is also associated with the formation of red blood cell microvesicles expressing phosphatidylserine, which activates tissue factor, a procoagulant mediator.[135,138] Microthrombotic and/or thromboembolic lesions are common findings at postmortem examination in patients with SCD.[139,140] Acute or organizing thrombi in the pulmonary arteries, predominantly distally, was a common finding at autopsy in a series of 11 sickle cell disease patients with the diagnosis of PH.[141] A significant association was found between the postmortem diagnoses of PH and thromboembolism in another autopsy series.[142]

Splenectomy has been reported to be a risk factor for development of PH,[143] particularly in patients with hemolytic disorders.[144–146] Thus, functional or surgical asplenia may contribute to development of PH in patients with SCD. In addition, loss of splenic function may trigger platelet activation, promoting pulmonary microthrombosis and red cell adhesion to the endothelium.[147] Patients with SCD also have increased levels of cell-free hemoglobin and red cell prothrombotic microvesicles. Following splenectomy, the rate of intravascular hemolysis increases.[135]

Additional mechanisms in the pathogenesis of PH in SCD may be operative. In patients with SCD at clinical baseline or during vaso-occlusive pain crises, plasma endothelin 1 levels are increased.[148] In vitro, sickled erythrocytes increase endothelin 1 production by cultured human endothelial cells. In addition, endothelin receptor A antagonism abolishes the vasoconstrictive effects of media obtained from pulmonary endothelial cells exposed to sickled erythrocytes on aortic rings.[149]

Chronic hypoxia and normoxic activation of hypoxia-inducible factor (HIF)-related pathways are involved in the etiology of various forms of PH.[149–154] Sickle cell disease is characterized by high circulating erythropoietin concentration (which is controlled by HIF-1α, the master regulator the response to hypoxia and which reflects tissue oxygenation status[155]) under steady state conditions,[122] suggesting that this chronic hemolytic anemia is accompanied by chronic upregulation of the hypoxic response. Confirming this hypothesis, Xu et al. compared clinical characteristics and peripheral blood mononuclear cell (PBMC) genomic profiles of subjects with sickle cell disease to those of subjects with Chuvash polycythemia, a monogenic disorder where homozygosity for *VHL*$^{\mathrm{R200W}}$ leads to posttranslational stabilization of the alpha subunits of HIF at normoxia, increased levels of HIF-1 and HIF-2 leading to altered transcription of a number of genes, and elevated systolic pulmonary artery pressures.[156–158] Results showed a strong correlation of altered gene expression profiles in SCD subjects and subjects with Chuvash polycythemia, suggesting that more than 50% of PBMC gene expression variation in hemoglobin SS patients may be related to the hypoxic response.[159] Interestingly, *MAPK8,* a hypoxia-downregulated gene that has a prominent role in promoting apoptosis,[160] appeared to play an important role in hypoxic gene regulation—and an eQTL of this gene (rs10857560) that further downregulated expression was associated with right heart catheterization–documented precapillary PH in SCD. Further, in another study, elevated levels of placental growth factor which activates HIF-1α in normoxia have been shown to be elevated and associated with elevated systolic pulmonary artery pressures in sickle cell disease mice and patients.[161,162]

Single-nucleotide polymorphisms for genes in the TGF-β superfamily—including activin A receptor, type II-like 1 (*ACVRL1*); bone morphogenetic protein receptor 2 (*BMPR2*); bone morphogenetic protein 6 (*BMP6*); the beta-1 adrenergic receptor (*ADRB1*);[163] and thrombospondin-1 (*THBS1*)[164]—have been associated with an elevated pulmonary artery systolic pressure in patients with SCD. Desai et al.[165] explored the usefulness of PBMC-derived gene signatures as biomarkers for PH in SCD. Genome-wide gene and micro-RNA (miRNA) expression profiles were correlated against estimated right ventricular systolic pressure (RVSP), yielding 631 transcripts and 12 miRNAs correlating with RVSP. Biological pathway analysis of these 631 genes revealed that pathways that have been associated with pulmonary vascular remodeling such as Wnt signaling, calcium signaling, vascular smooth muscle contraction, and cancer pathways were significantly overrepresented in subjects with elevated RVSP. Support vector machine analysis identified a 10-gene signature including *GALNT13* (encoding polypeptide *N*-acetylgalactosaminyltransferase 13, a glycosyltransferase enzyme responsible for the synthesis of O-glycan) that distinguished patients with and without increased RVSP with 100% accuracy. This finding was then validated in a separate cohort of patients who had sickle cell disease without or with PH documented by right heart catheterization, with an overall accuracy of 90%. Increased RVSP-related miRNAs revealed strong in-silico binding predictions of miR-301a to *GALNT13*, which was corroborated by microarray analyses demonstrating an inverse correlation between their expression. A genetic association study comparing patients with elevated or normal RVSP revealed five significant single-nucleotide polymorphisms within *GALNT13* associated with an elevated RVSP.

Finally, in theory, a high pulmonary artery pressure may result from the high cardiac output state associated with chronic anemia in SCD. However, this hyperdynamic state does not appear to be a major contributor to significant elevations in pulmonary artery pressure, as reports of PH associated with nonhemolytic anemias are lacking. Conceivably, a high cardiac output state, combined with hemolytic anemia and other risk factors, such as renal insufficiency and iron overload, conspire to drive pathologic pulmonary vascular remodeling.

■ Clinical Features and Evaluation

The diagnostic evaluation of patients with SCD suspected of having PH should follow the same guidelines established for other causes of PH.[166,167] Given the high prevalence of PH in this population and the associated high mortality, guidelines form the American Thoracic Society recommend universal noninvasive screening of all adults using Doppler echocardiography, measurement of steady-state plasma NT-proBNP levels, and assessment of functional capacity to assess the risk of death and of having PH for further diagnosis and intensification of sickle cell–specific therapies.[41] In patients with SCD, the echocardiographic estimation of PASP ($\text{PASP} = 4 \times \text{TRV}^2 +$ estimate of the central venous pressure) correlates well with measured PASP by right heart catheterization.[35] While no prospective data on prevalence and risk of PH are available for children, we currently recommend that children with hypoxemia, high hemolytic rate (hemoglobin values <7 g/dL and high LDH), or recurrent ACS be screened. Importantly, screening should be performed in the steady state, as pulmonary artery pressures rise during vaso-occlusive painful crises.[168]

The Doppler echocardiogram is an important tool for population screening and estimation of pulmonary artery pressure, but it cannot be used to diagnose or define PH, which is based on measurement of mPAP via right heart catheterization. In order to identify a subgroup of patients with SCD who are at a high risk for a diagnosis of PH as well as very high risk of death and hospitalization, we have analyzed data from both the NIH-PH screening study[169–171] and the Walk-PHASST cohort[123,172–174] using TRV and NT-proBNP values as noninvasive screening tests. Elevation of both of these parameters improves the positive predictive value of the echocardiogram to diagnose PH to approximately 62%[175] and identifies a group at higher risk of death. The prevalence of TRV ≥ 2.5 m/ss *and* an NT-proBNP ≥ 160 pg/mL was 19.2% in adults screened in the Walk-PHASST trial. This prevalence was 19.4% in adult patients in NIH-PH screening cohort. In the Walk-PHASST study, the 12-month mortality rate is 7.9% in this group compared with 0.5% in patients with normal TRV or NT-proBNP values. In the NIH-PH cohort these rates were 8.6% and 0.7%, respectively. This patient population is also at higher risk of hospitalization, with a risk ratio for hospitalization of 1.73. In the Walk-PHASST cohort, 12-month hospitalization risk was 78% for patients with abnormal TRV and NT-proBNP values (high-risk group) compared with 45% for patients with normal TRV or BNP values (low-risk group). This analysis suggests that a simple screening profile of TRV and NT-proBNP can identify about 19% of patients with SCD at the highest risk of death and hospitalization. Based on these data, we propose a PH-screening algorithm for adult patients with SCD (Fig. 95-4).

The diagnosis of PH in patients with SCD may be challenging (Fig. 95-5). Exertional dyspnea, the most typical presentation of PH, is also a cardinal symptom of chronic anemia and other conditions commonly present in patients with SCD, such as left ventricular dysfunction, pulmonary fibrosis, and cirrhosis. Therefore, a high index of suspicion for diagnosis is necessary.

Patients with SCD and PH tend to be older and have higher systolic arterial blood pressure, lower hemoglobin levels, higher indices of hemolysis, lower hemoglobin–oxygen saturation, greater degrees of renal and liver dysfunction, and higher numbers of lifetime red blood cell transfusions.[35] Diagnostic evaluation should also include an aggressive search for other conditions that might contribute to PH, such as iron overload, chronic liver disease, HIV infection, nocturnal hypoxemia, and pulmonary thromboembolism. A diagnostic right heart catheterization is essential to confirm the diagnosis and to exclude diastolic dysfunction.[166] The 6-min walk test is a useful surrogate for assessing functional capacity in this patient population and inversely correlates with the severity of PH.[176] In spite of this correlation, important to note is that in patients with SCD, noncardiopulmonary factors, such as concurrent pain and avascular necrosis of the hip, can interfere with test performance.

Measurement of NT-proBNP levels may be used as a PH biomarker for diagnosis and risk stratification in patients with SCD.[13] NT-proBNP levels are higher in patients with sickle cell–associated PH and correlate directly with the severity of PH and degree of functional impairment. An NT-proBNP level of 160 pg/mL or greater is associated with PH and is an independent predictor of mortality (risk ratio, 5.1; 95% CI, 2.1–12.5; $p < 0.001$).[13]

Most adult patients with SCD develop abnormal pulmonary function characterized by mild restriction (mean TLC approximately 79% of predicted), abnormal diffusing capacity, and radiographic signs of mild pulmonary fibrosis.[10,177–181] The severity of the defects seems to be slightly greater in those patients with PH.[176] However, in these patients, the degree of pulmonary function abnormalities is rarely severe enough to be a major contributor to the etiology of the PH.

A ventilation–perfusion scan is an indispensable component of the evaluation, since chronic pulmonary thromboembolic disease, if amenable to pulmonary endarterectomy, is a potentially curable form of PH in patients with chronic hemolytic disorders. In the majority of cases, observed scintigraphic evidence of thromboembolic disease is uncommon; the most commonly seen abnormalities are patchy areas of abnormal perfusion, similar to findings described in other forms of PH.[176,182] However, scintigraphic evidence suggestive of chronic thromboembolic PH occurs in approximately 5% of patients with SCD and severe PH,[168] and the PH has been successfully treated surgically in two patients (Fig. 95-6).[183] Consequently, patients should undergo imaging studies, and if findings are suggestive of chronic thromboembolic PH, additional invasive studies (i.e., angiography) are warranted to exclude a potentially surgically treatable condition.

■ Hemodynamic Profiles and Etiology of Pulmonary Hypertension in Sickle Cell Disease

Because of the different presentations, PH in the setting of sickle cell disease is currently listed in group 5 (a miscellaneous category that

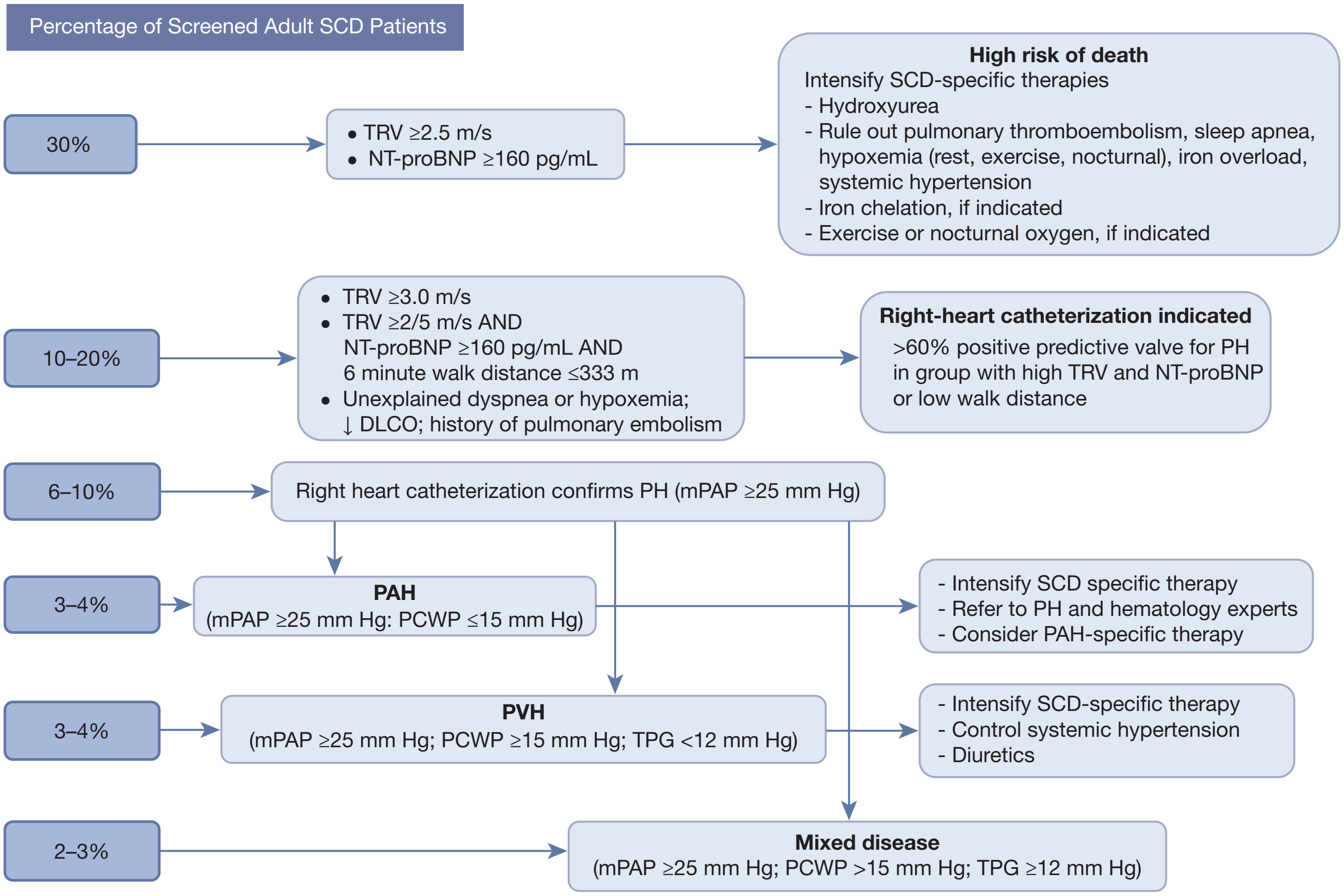

Percentage of Screened Adult SCD Patients
30%
• TRV ≥2.5 m/s
• NT-proBNP ≥160 pg/mL
High risk of death
Intensify SCD-specific therapies
- Hydroxyurea
- Rule out pulmonary thromboembolism, sleep apnea, hypoxemia (rest, exercise, nocturnal), iron overload, systemic hypertension
- Iron chelation, if indicated
- Exercise or nocturnal oxygen, if indicated
10–20%
• TRV ≥3.0 m/s
• TRV ≥2/5 m/s AND NT-proBNP ≥160 pg/mL AND 6 minute walk distance ≤333 m
• Unexplained dyspnea or hypoxemia; ↓ DLCO; history of pulmonary embolism
Right-heart catheterization indicated
>60% positive predictive valve for PH in group with high TRV and NT-proBNP or low walk distance
6–10%
Right heart catheterization confirms PH (mPAP ≥25 mm Hg)
3–4%
PAH
(mPAP ≥25 mm Hg: PCWP ≤15 mm Hg)
- Intensify SCD specific therapy
- Refer to PH and hematology experts
- Consider PAH-specific therapy
3–4%
PVH
(mPAP ≥25 mm Hg; PCWP ≥15 mm Hg; TPG <12 mm Hg)
- Intensify SCD-specific therapy
- Control systemic hypertension
- Diuretics
2–3%
Mixed disease
(mPAP ≥25 mm Hg; PCWP >15 mm Hg; TPG ≥12 mm Hg)

Figure 95-4 Pulmonary hypertension diagnostic algorithm. PCWP, pulmonary capillary wedge pressure; TPG, transpulmonary gradient. *(Reproduced with permission from Miller AC, Gladwin MT: Pulmonary complications of sickle cell disease. Am J Respir Crit Care Med. 2012;185(11):1154–1165.)*

includes the hemolytic anemias).[114] As such, patients with sickle cell disease have been shown to develop PH with primary involvement of the pulmonary vasculature (group 1 PH or pulmonary arterial hypertension [PAH]), secondary to left heart disease (group 2 PH), secondary to interstitial lung disease or pulmonary fibrosis (group 3 PH), and secondary to chronic thromboembolic disease (CTEPH or group 4 PH). From a hemodynamic and anatomic perspective groups 1, 3, and 4 PH are also defined as precapillary PH characterized by normal left heart filling pressures (pulmonary artery wedge pressure or left ventricular end-diastolic pressure <15 mm Hg), and group 3 PH is defined as postcapillary PH characterized by elevated left heart filling pressures (pulmonary artery wedge pressure or left

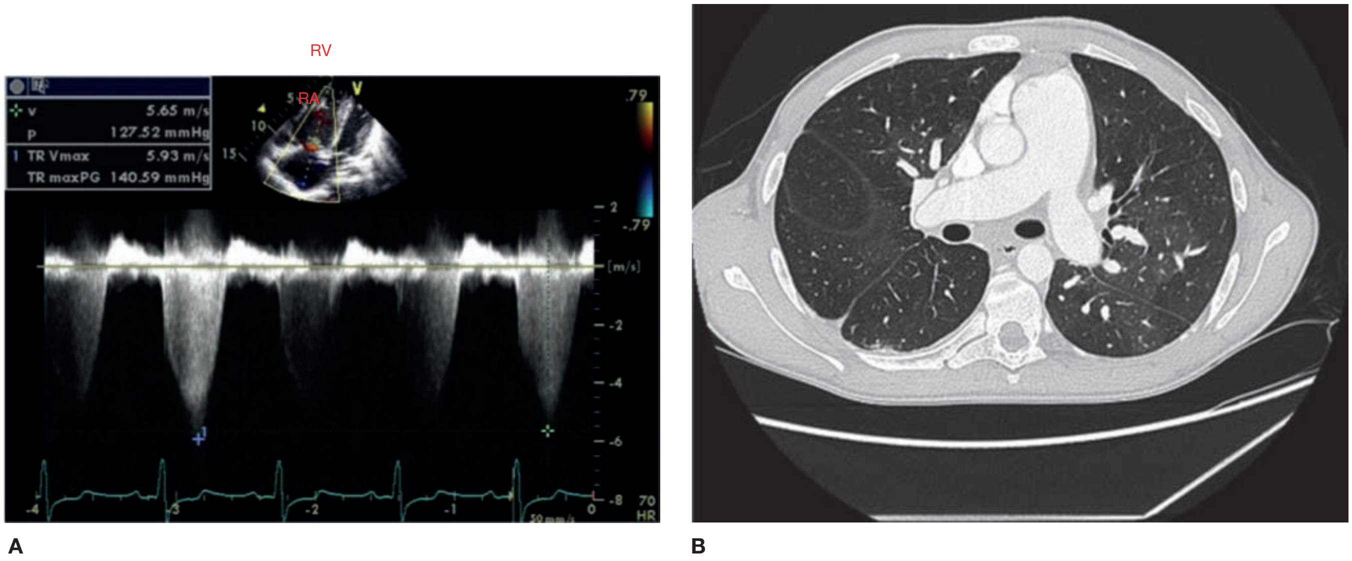
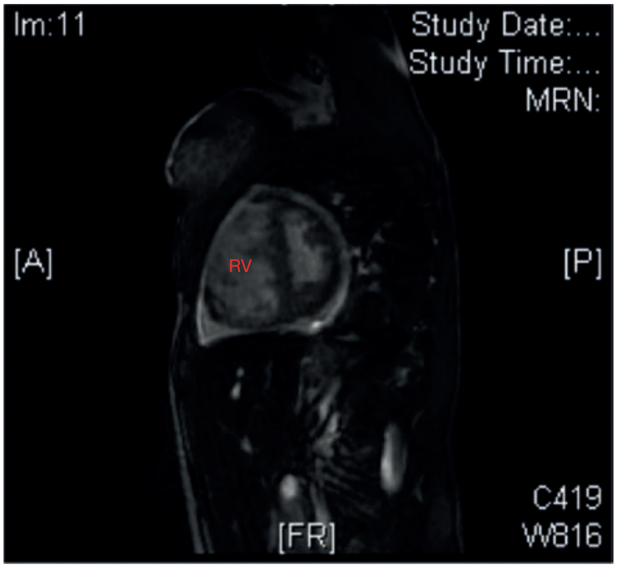

RV
RA
V
5.65 m/s
P 127.52 mmHg
TR Vmax 5.93 m/s
TR maxPG 140.59 mmHg
[m/s]
70 HR
A
B

Figure 95-5 Imaging features of sickle cell disease and pulmonary hypertension. **A.** Echocardiographic four-chamber view of the heart, illustrating severe right ventricular (RV) and right atrial (RA) dilation. Doppler tracing from a patient with severe pulmonary hypertension reveals a jet velocity of more than 5 m/s. **B.** Enlargement of pulmonary arteries in severe pulmonary hypertension.



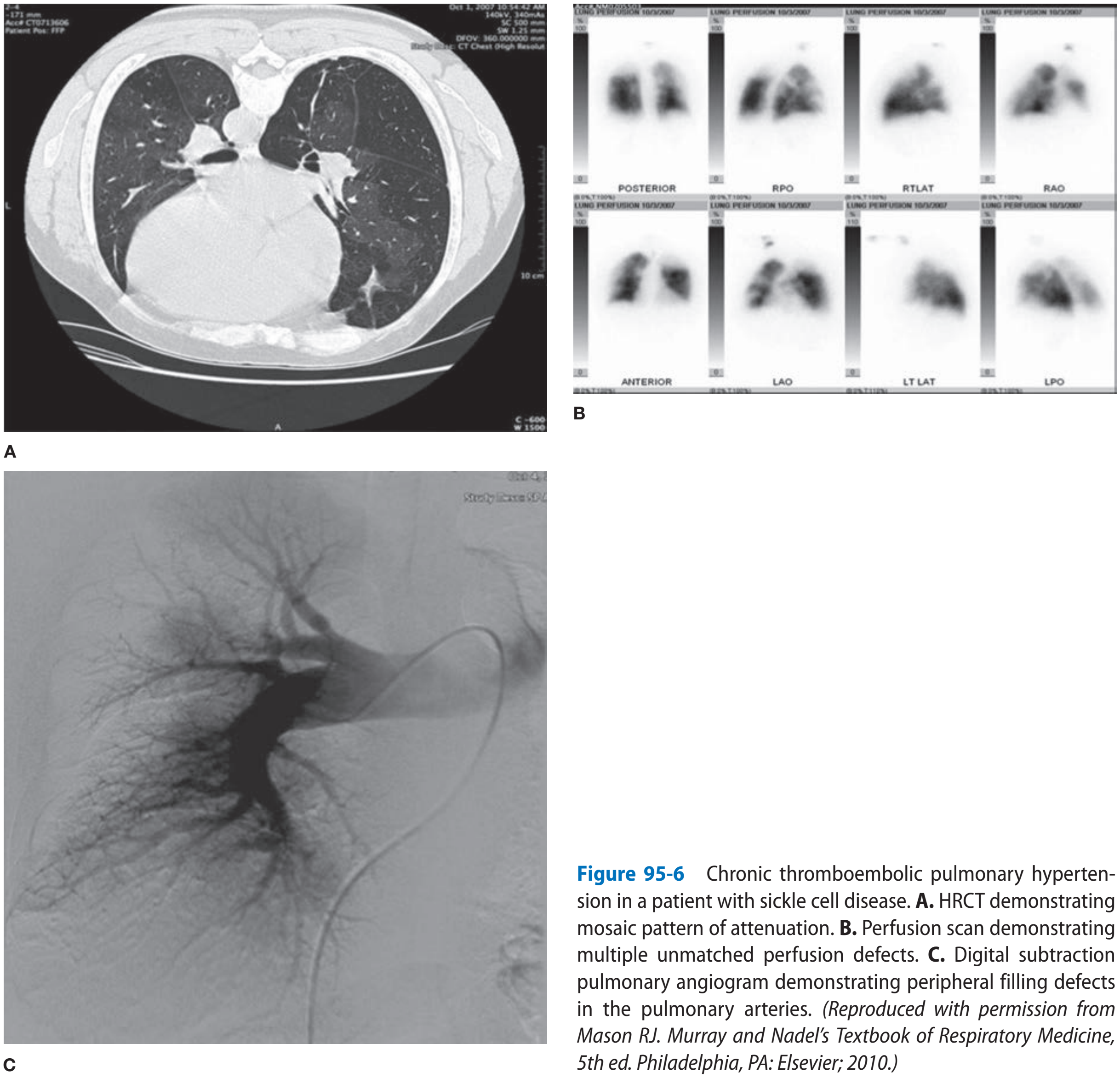
C

Figure 95-5 *(Continued)* **C.** Cardiac resonance imaging showing right ventricular (RV) dilatation in severe pulmonary hypertension.

ventricular end-diastolic pressure >15 mm Hg). Combined pre- and postcapillary PH is defined as mPAP >20 mm Hg, PAWP/LVEDP is ≥ 15 mm Hg, and pulmonary vascular resistance >3 Wood Units.

As previously discussed, as hemoglobin level decreases cardiac output increases, filling pressures tend to decrease, and systemic and pulmonary vascular resistances decrease. In studies of patients with SCD undergoing right heart catheterization, the mean cardiac output and pulmonary vascular resistance for patients without PH were 10 L/min and 59 $\text{dyn} \cdot \text{s/cm}^5$, respectively.[40,124,176] It is within the context of these data that one must consider the impact of PH in chronically anemic patients with hemolytic disorders. As such, we believe that it is appropriate to consider a lower upper limit of "normal" pulmonary vascular resistance (such as <160 $\text{dyn} \cdot \text{s/cm}^5$) in these patients.

In contrast to patients with traditional forms of pulmonary arterial hypertension (e.g., idiopathic, scleroderma associated), who are symptomatic with mean pulmonary arterial pressures in the range of 50 to 60 mm Hg, in patients with SCD the degree of elevation in mean pulmonary pressures is mild to moderate, in the range of 30 to 40 mm Hg, with mild elevations in pulmonary vascular resistance.[40,118,119,121,124,176] These patients also have coexistent mild elevation in pulmonary capillary wedge pressure, suggesting left heart failure.[40,118,119,121,124,176]



A

B

C

Figure 95-6 Chronic thromboembolic pulmonary hypertension in a patient with sickle cell disease. **A.** HRCT demonstrating mosaic pattern of attenuation. **B.** Perfusion scan demonstrating multiple unmatched perfusion defects. **C.** Digital subtraction pulmonary angiogram demonstrating peripheral filling defects in the pulmonary arteries. *(Reproduced with permission from Mason RJ. Murray and Nadel's Textbook of Respiratory Medicine, 5th ed. Philadelphia, PA: Elsevier; 2010.)*

Right heart catheterization data from these multiple studies using the previously accepted definition of PH show that the hemodynamic etiology of the PH in patients with SCD is multifactorial: precapillary pulmonary hypertension (precap PH, defined by mPAP $\geq$25 mm Hg and wedge pressure $\leq$15 mm Hg) is present in 50% of catheterized patients, while postcapillary pulmonary hypertension secondary to left ventricular diastolic dysfunction (postcap PH, defined by mPAP $\geq$25 mm Hg and wedge pressure $>$15 mm Hg) is present in 50%.

■ Heart Failure with Preserved Ejection Fraction

In response to chronic anemia, the left ventricle responds with an increase in stroke volume and chamber dilation. This response leads to increased wall stress and an increase in left ventricular mass that, in turn, leads to impaired filling, which characterizes diastolic dysfunction and a syndrome of heart failure with preserved ejection fraction. In patients with SCD, elevated systemic systolic blood pressure is an independent risk factor for the development of pulmonary hypertension, hypoxemia, diastolic heart dysfunction, chronic kidney injury, silent infarcts, and ischemic stroke.[184–187] Both anemia and increases in blood pressure are risk factors for the development of left ventricular diastolic dysfunction in patients with SCD.[185,188] Using echocardiography in a cohort of 141 patients, Sachdev et al. found that 47% had a high TRV, diastolic dysfunction, or both (29% had a high TRV alone, 11% had diastolic dysfunction and a high TRV, and 7% had diastolic dysfunction alone). An elevated TRV and diastolic dysfunction were associated with a relative risk of death of 5.1 (95% CI, 2.0–13.3) and 4.8 (95% CI, 1.9–12.1), respectively, while the relative risk of death when both were present was 12.0 (95% CI, 3.8–38.1), suggesting that both PH and diastolic dysfunction independently carry additive mortality risk.[189] In addition, in a series of 483 patients with homozygous SCD, markers of diastolic dysfunction were independently associated with a low 6-min walk distance and increased mortality.[122] A high prevalence of diastolic dysfunction has also been reported in pediatric cohorts, but mortality in all pediatric patients is exceedingly low, and it is not clear if these patients progress with age to more severe disease.[190–192]

■ Effects of Pulmonary Hypertension on Exercise Capacity

Patients with SCD appear to be poorly tolerant of even small additional increases in pulmonary artery pressure and pulmonary vascular resistance. When compared with age-, gender-, and hemoglobin-matched patients with SCD without PH, individuals with PH and mPAP of 36 mm Hg exhibit lower 6-min walk distance (435 ± 31 vs. 320 ± 20 m; $p = 0.002$) and peak oxygen consumption (50 ± 3% vs. 41 ± 2% of predicted; $p = 0.02$) and higher ventilatory equivalent for CO_2 at anaerobic threshold (31.6 ± 1.5% vs. 39.2 ± 1.6; $p = 0.035$) on cardiopulmonary exercise testing (Chapter 34).[176] In that study, the 6-min walk distance was inversely correlated with pulmonary vascular resistance and mPAP, and directly correlated with maximal oxygen consumption, supporting the contribution of increasing pulmonary artery pressures to loss of exercise capacity. A lower exercise capacity (assessed by the 6-min walk test) in patients with PH has also been demonstrated in larger cohorts of patients with SCD.[118,119,121,122] In addition, in patients with SCD, pulmonary artery pressure and pulmonary vascular resistance sharply rises with exercise, suggesting that pulmonary vascular disease contributes to functional limitation in these patients.[168] In aggregate, these data suggest that in patients with chronic anemia, mild to moderate PH has a severe adverse impact on functional and aerobic exercise capacity.

■ Treatment

There are limited data on the specific management of patients with SCD and PH, and most treatment recommendations are based on expert opinion or extrapolated from data derived from other forms of PH.[193] The general approach should include maximization of SCD-specific therapy (i.e., treatment of primary hemoglobinopathy), treatment of hypoxia with chronic oxygen therapy, and treatment of associated cardiopulmonary conditions (such as iron overload, chronic liver disease, HIV infection, nocturnal hypoxemia, thromboembolic disorders, and left ventricular disease). In patients with SCD with PAH (mean PAP $\geq$25 mm Hg and wedge pressures $<$15 mm Hg, with a relatively high pulmonary vascular resistance, e.g., $>$160 dyn • s/cm^5), PAH-specific therapy can be considered. There are no long-term data on the specific treatment of PH in SCD, and the choice of agents is largely empirical and based on the safety profile of the drugs and physician preference. Therapy should be initiated and monitored by a team composed of a PAH specialist and a hematologist specializing in SCD care.

Hydroxyurea has been shown to decrease the incidence of pain episodes and ACS, to reduce the need for transfusions, and to lower overall mortality.[12,79] It is possible that some of the decreases in pulmonary and cardiovascular deaths seen in hydroxyurea-treated patients could be related to an improvement in PH. However, these considerations have to be balanced with the lack of association between fetal hemoglobin levels and the use of hydroxyurea, and protection against the development of PH.[35] For patients with creatinine levels less than 1 mg/dL, hydroxyurea is started at a dose of 15 mg/kg/d and titrated up to a maximum of 35 mg/kg/d. Recent detailed treatment guidelines have been published.[80,194] Patients with renal dysfunction tend not to tolerate the myelosuppressant effects of hydroxyurea. In those cases, we recommend the addition of erythropoietin to the regimen. Long-term transfusion therapy lowers the risks of most complications of the disease, including the risks of pulmonary events and central nervous system vasculopathy.[195–197] It might improve cardiopulmonary function and prevent the progression of PH.[198] The same concepts and potential benefits might apply to stem cell transplantation, which has been shown to normalize pulmonary pressures and to improve short-term outcome measures in one patient.[199] There is insufficient evidence to determine the efficacy of L-glutamine,[83] voxelotor,[84] and crizanlizumab[85] in the prevention or treatment of PH associated with SCD.

The potential benefits of warfarin therapy observed in patients with idiopathic pulmonary arterial hypertension[200] have to be weighed against the risk of hemorrhagic stroke in adults with SCD or hemorrhage in chronically anemic individuals. We believe that the relatively low risk of hemorrhagic stroke (0.21 events per 100 patient-years[201]) compared with the high risk of death in patients with severe PH supports anticoagulation in patients with hemodynamic evidence of pulmonary arterial hypertension or chronic thromboembolic PH and without a specific contraindication.

Sildenafil and other phosphodiesterase 5 inhibitors function by inhibiting the metabolism of cyclic guanosine monophosphate, the second messenger that mediates the effects of NO. In a series of 7 patients with either thalassemia or sickle thalassemia and severe PH, treatment with sildenafil from 4 weeks to 48 months resulted in an improvement in TRV, New York Heart Association functional class, and 6-min walk distance.[202] In another case series, 12 patients with SCD were treated with sildenafil for a mean of 6 months. Mean PASP decreased by 9 mm Hg (95% CI, 0.3–17; $p = 0.047$), 6-min walk distance improved by 78 m (95% CI, 40–117; $p = 0.003$), and mean BNP decreased by 448 pg/mL ($p = 0.002$).[203] These preliminary data were not supported by the results of the Walk-PHaSST study.[204] This 16-week, NIH-sponsored, multicenter, double-blind, placebo-controlled trial of sildenafil in 74 patients with SCD with increased TRV and a low exercise capacity was stopped early, before enrollment of the planned 132 patients, due to a higher percentage of subjects experiencing serious adverse events in the sildenafil arm (45% of sildenafil, 22% placebo; $p = 0.022$). Subject hospitalization for pain was the predominant cause for this difference: 35% sildenafil versus 14% placebo ($p = 0.029$). Although the study was underpowered at the time it was stopped, there was no evidence of a treatment effect on 6MWD (placebo-corrected effect, −9 m; 95% CI, −56 to 38; $p = 0.703$), TRV ($p = 0.503$), or NT-proBNP ($p = 0.410$). Based on these findings, sildenafil and the other PDE5 inhibitors should not be used as first-line agents in patients with SCD and PAH. If used, sildenafil should be used only in patients on chronic transfusion therapy or very well controlled with hydroxyurea, to limit the apparent effects of these agents on increasing pain.

Riociguat is a small molecule activator of the soluble guanylate cyclase enzyme, which is approved for the treatment of pulmonary arterial hypertension and CTEPH.[205] Weir et al.[206] reported on the use of riociguat in six patients with SCD and CTEPH. In this limited series, use of riociguat was not associated with an increase in episodes of SCD-related pain, although one patient discontinued the drug due to intractable headaches. Treatment with riociguat resulted in improvements in functional class, exercise capacity, NT-proBNP levels, and estimated RVSP in three of the patients.

The published experience with endothelin receptor antagonists in the treatment of PH is also very limited. Minniti et al.[207] reported on the use of bosentan and ambrisentan in a cohort of 14 patients with SCD and PH documented by heart catheterization. Endothelin antagonist therapy either as monotherapy or in combination with sildenafil resulted in a modest improvement in 6-min walk distance (baseline 357 ± 22 vs. 398 ± 18 m 6 months posttherapy; $p < 0.05$) as well as lowered NT-proBNP levels and estimated PASP. Adverse events while on therapy occurred in 7 of 14 patients, including increased serum alanine aminotransferase (2), increased peripheral edema (4), rash (1), headache (1), and decreased hemoglobin (2). Only 2 patients required treatment discontinuation, and few patients experienced multiple side effects. Two randomized multicenter placebo-controlled studies evaluating the role of endothelin receptor antagonism in patients with SCD have been conducted. The ASSET-1 and ASSET-2 studies enrolled patients with pulmonary arterial hypertension and pulmonary venous hypertension, respectively, who were randomized to bosentan or placebo. After enrollment of 26 subjects the studies were terminated due to slow site activation and withdrawal of support by the sponsor. In that limited sample of patients, bosentan was well tolerated with no significant differences in serious adverse events or laboratory tests between patients receiving study drug or placebo, but efficacy endpoints could not be formally analyzed.[208]

Prostanoid analogs are the most effective agents for the treatment of pulmonary arterial hypertension. Acute administration of epoprostenol decreases pulmonary artery pressure and pulmonary vascular resistance and increases cardiac output in patients with PH and SCD.[124] Chronic prostacyclin-based therapy has been shown to reduce pulmonary pressures, increase 6-min walk distance, and improve functional class in a case series of patients with sickle cell disease and pulmonary hypertension.[209] A case of severe pulmonary arterial hypertension related to pulmonary veno-occlusive disease has been reported in a patient with SCD. This patient failed medical therapy and underwent a successful bilateral lung transplantation.[210]

RESTRICTIVE LUNG DISEASE

Repetitive episodes of acute lung injury related to the ACS can result in parenchymal damage and restrictive lung disease (Fig. 95-7). In a study of 310 patients with homozygous SCD, pulmonary function was abnormal in 90% of adult patients.[211] The most common abnormal pattern was a mild restrictive pattern, found in 74% of those patients (TLC of 70 ± 15% predicted). An isolated decreased $D_{L_{CO}}$ was found in 13% (57 ± 20% predicted), persisted when corrected for hemoglobin, and negatively correlated with age. Evidence of obstructive lung disease occurred in only 3% of those studied. Although patients may present with advanced interstitial lung disease, these findings suggest that pulmonary fibrosis secondary to recurrent episodes of ACS tends to be mild in most cases.

SLEEP-DISORDERED BREATHING

Sleep-disordered breathing has been reported in both children and adults with SCD.[212–214] In children, sleep-related upper airway

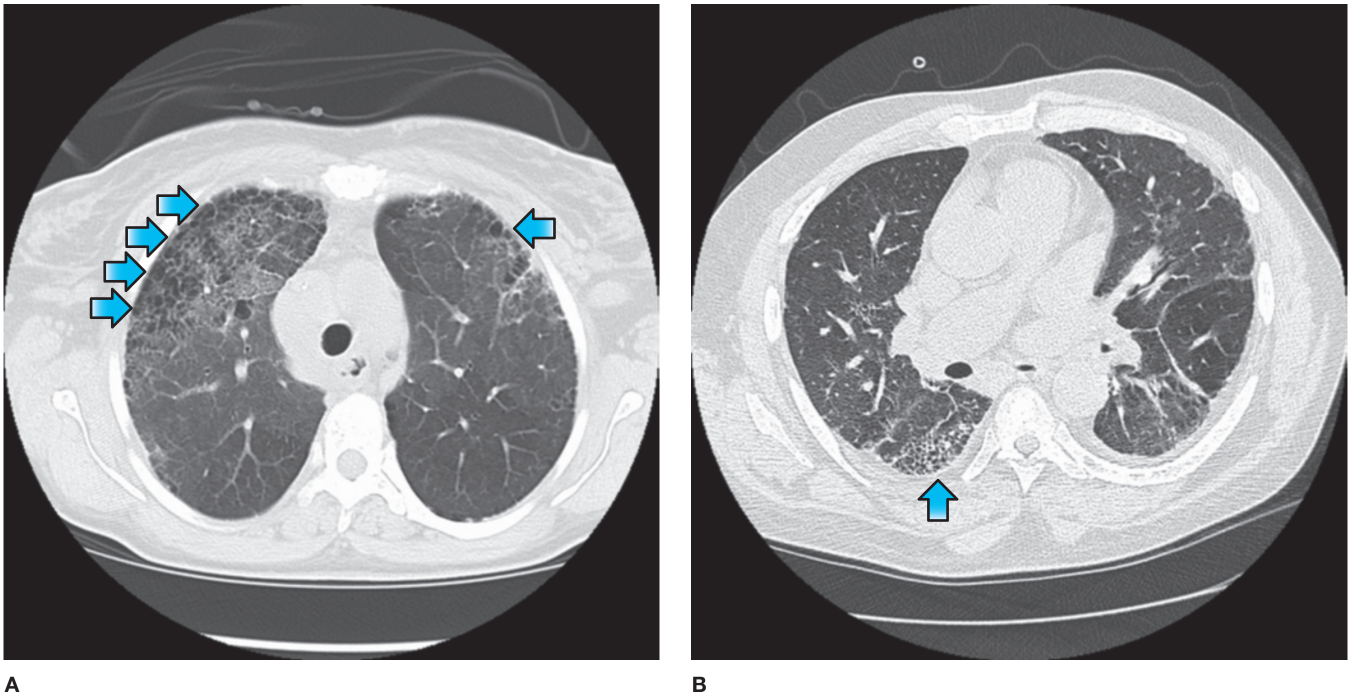


Figure 95-7 Pulmonary fibrosis *(blue arrows)* complicating multiple episodes of acute chest syndrome. **A.** Cystic changes in areas of fibrosis. **B.** Subpleural fibrosis with honeycombing. *(Reproduced with permission from Miller AC, Gladwin MT. Pulmonary complications of sickle cell disease. Am J Respir Crit Care Med. 2012;185(11):1154–1165.)*

obstruction and hypoxemia are the most common disturbances. In an uncontrolled study, adenotonsillectomy led to symptomatic improvement and amelioration of oxygen desaturation.[215,216] A small study of autoadjusting continuous positive-airway pressure (auto-CPAP) with supplemental oxygen also suggests that this therapeutic modality is well tolerated, safe, and effective in pediatric patients with SCD.[217]

Several lines of evidence suggest that nocturnal hypoxemia contributes to the development of neurologic events and vaso-occlusive crisis via mechanisms that could involve upregulation of several inflammatory endothelial adhesion molecules.[218–220] In addition, nighttime oxygen desaturation is associated with an increase in left ventricular mass and impaired diastolic function as evidenced by a study of 44 children with SCD.[221] However, in a recent prospective study of 140 children with SCD followed for a median of 4.9 years, a low nocturnal oxygen saturation, higher obstructive AHI, and higher oxygen desaturation index were not associated with increased incidence of acute severe pain episodes.[222]

SUMMARY AND CONCLUSIONS

Pulmonary complications are a major cause of morbidity and mortality in patients with SCD, and the burden of these complications is likely to become more prevalent as the life expectancy of these patients continues to increase.

Among the acute complications, ACS, which is often complicated by right heart failure, remains a major cause of death in children and adults with SCD. Fortunately, current strategies of early aggressive supportive therapy with antibiotics and red blood cell transfusion appear to have improved outcomes when compared with historic data.

PH is common and the most significant cause of death in adults with SCD. Although the etiology of PH is multifactorial in these patients, pulmonary arterial hypertension appears to be the main driver of morbidity and mortality. Additional studies evaluating pulmonary arterial hypertension–targeted therapy are needed in this complex and high-risk population.

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CHAPTER 96

Pulmonary Disorders and Pregnancy

Debasree Banerjee
Andrew T. Levinson
Jeffrey Mazer
Ghada Bourjeily

INTRODUCTION

Global fertility rates are predicted to drop significantly by 2100[1] but despite lower birth rates, there remains high maternal mortality worldwide. While the maternal mortality rate has declined since the turn of the century, approximately 810 women die of preventable pregnancy- and childbirth-related complications daily.[2] Younger women and those residing in low- and middle-income countries have a disproportionately higher risk of maternal death. Meanwhile, globally, there has been a steady rise in women becoming pregnant later in their reproductive lives,[3] particularly in higher-income countries. Together, this highlights significant inequities in the childbearing experience for women around the world. Increased maternal age is due to many factors, including more women in the workforce than ever before, and advances in assisted reproductive technology that have allowed women who might otherwise be infertile to achieve a pregnancy. Additionally, reproductive medicine now helps many women with chronic medical conditions to become pregnant. Consequently, pregnant women are now older and have more comorbid conditions than in past generations. Given the dramatic physiologic changes that occur during gestation, pregnancy can have significant clinical consequences especially among women with chronic cardiopulmonary disease.

Labor and delivery constitute a major hemodynamic and respiratory challenge; hence, women with either acute or chronic respiratory conditions need to be managed by a multidisciplinary healthcare team, which should include a pulmonologist. This multidisciplinary team should address medical and obstetric concerns, along with risks and benefits of anesthesia and analgesia, thereby ensuring appropriate management and anticipation of potential complications for both the mother and her newborn. This chapter addresses core pulmonary and cardiovascular physiologic concepts and then examines important, common clinical entities related to pulmonary and critical care diagnoses and clinical management in pregnancy.

THE PHYSIOLOGY OF PREGNANCY

While the normal physiologic changes of pregnancy are extensive, several areas are of central importance and are considered below. These include changes in respiratory and cardiovascular physiology, normal physiologic developments during labor and delivery, and determinants of fetal oxygenation and ventilation.

Respiratory Physiology

During pregnancy, the respiratory system undergoes changes throughout the respiratory tract. The effects of increasing levels of estrogen on the nasal mucosa can include edema, hyperemia, and glandular hypersecretion, which may result in gestational rhinitis, typically in the last few weeks of pregnancy.

The subcostal angle of the rib cage and the circumference of the chest wall increase[4] and the diaphragm moves cranially about 4 to 5 cm.[5] Diaphragm excursion does not decrease in pregnancy, despite the changes in chest wall configuration. However, due to the higher resting position of the diaphragm, the decreased downward pull of the abdomen, and the aforementioned chest wall changes, functional residual capacity (FRC) decreases by 20% to 30% by late gestation[6] and declines further in the supine position (Table 96-1).[7] The reduction in FRC may not be reflected when measured using body plethysmography,[8] likely due to the effect of early airway closure during tidal breathing and air trapping.[9] Inspiratory capacity increases, and therefore total lung capacity (TLC) is not significantly changed (Fig. 96-1).[10]

TABLE 96-1 Physiologic Changes in Pregnancy

Respiratory Parameter	Change	Normal Range in Pregnancy
Arterial blood gas values		
pH	↑	Mild respiratory alkalosis
Pa$_{O_2}$	↑	Average 100–105
Pa$_{co_2}$	↓	Average 28–32
HCO$_3$	↓	18–22 mEq/L
Alveolar–arterial O$_2$ gradient	↑	Increase in late gestation to approximately 20 mm Hg
Oxygen consumption	↑	20% increase, further increase during labor and delivery
Minute ventilation	↑	50% increase
Respiratory rate	↔	No change
Tidal volume	↑	40%–50% increase
Total lung capacity	↓	4%–5% decrease
Functional residual capacity	↓	20% decrease by term
Residual volume	↓	
Vital capacity	↔	
Diffusion capacity	↔	Minimal change
Forced expiratory volume in 1 s	↔	
Peak expiratory flow rate	↔	
Cardiac	**Change**	**Normal Range in Pregnancy**
Blood pressure	↓	10- to 15-mm Hg decrease in first two trimesters
Blood volume	↑	30%–50% increase
Cardiac output	↑↑	5–7 L/m^2/min (40% increase)
Central venous pressure	↔	<13 mm Hg
Colloid oncotic pressure	↓	10%–15% decrease
Ejection fraction	↔	70%
Heart rate	↑	Increases by 10–20 bpm
Pulmonary artery pressure	↔	≤25 mm Hg
Pulmonary capillary wedge pressure	↔	<13 mm Hg
Stroke volume	↑	70–100 mL/beat
Systemic vascular resistance	↓	25%–30% decrease

↑ Increase, ↓ Decrease, ↔ No change.
Modified with permission from Miller M, Bourjeily G. Management of the critically ill pregnant patient. Volume 23 (Lesson 8). Pulmonary and Critical Care Update (PCCSU). April 2014.

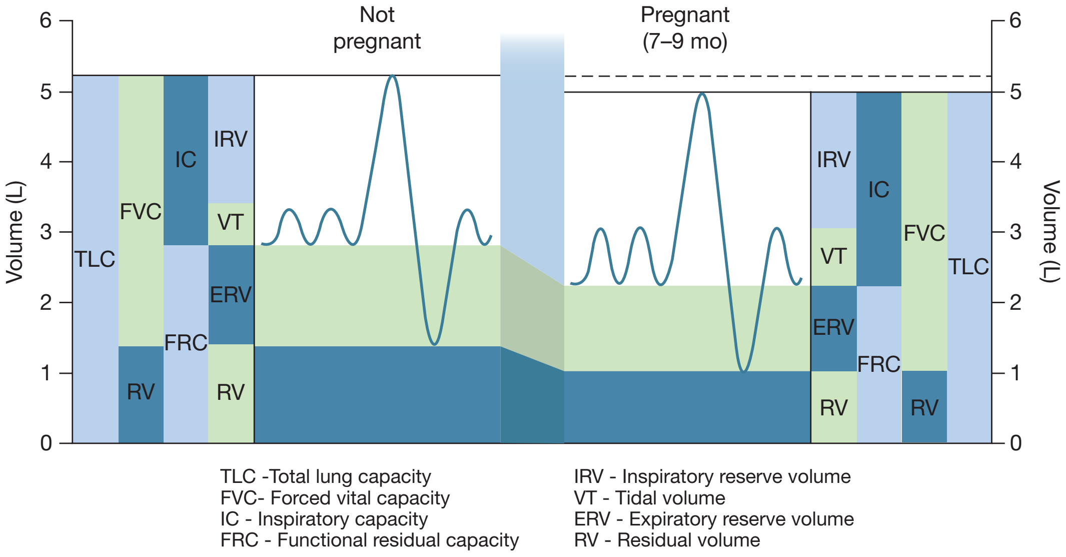
Not pregnant
Pregnant (7–9 mo)
Volume (L)
0
1
2
3
4
5
6
TLC
FVC
IC
IRV
VT
ERV
FRC
RV
TLC -Total lung capacity
FVC- Forced vital capacity
IC - Inspiratory capacity
FRC - Functional residual capacity
IRV - Inspiratory reserve volume
VT - Tidal volume
ERV - Expiratory reserve volume
RV - Residual volume

Figure 96-1 Changes in lung volumes in pregnancy. *(Reproduced with permission from Hegewald MJ, Crapo RO. Respiratory physiology in pregnancy. Clin Chest Med. 2011;32(1):1–13.)*

Despite a reduction in FRC and reduced nasopharyngeal caliber, air flow rates and airway resistance do not change in pregnancy, since pregnancy is associated with bronchial smooth muscle relaxation.[11] While the increased cardiac output of pregnancy (see "Cardiovascular Physiology," below) may increase diffusion capacity, the associated anemia of pregnancy offsets this effect. DL_{CO} is higher in the first trimester (after correcting for alveolar volume and hemoglobin), but it may decline later in pregnancy, reaching a nadir at about 24 to 27 weeks' gestation.[12]

Oxygen consumption increases in pregnancy, and minute ventilation increases by about 50%. This increase is achieved by an increase in tidal volume and mediated in part by higher levels of progesterone, a known respiratory drive stimulant. Although some studies suggest a progressive increase in minute ventilation during the course of pregnancy,[6] most studies show a sharp increase in the first trimester, with minimal rise after that.[13,14] The ratio of dead space to tidal volume (V_D/V_T) is unchanged in pregnancy, suggesting that dead space is actually also increased. While the increase in cardiac output and the resultant improved perfusion of the lung apices seen in pregnancy should result in a reduction in dead space, many studies suggest the opposite effect.[15,16]

Arterial oxygen tension increases in pregnancy to about 100 to 105 mm Hg, thereby facilitating oxygen transfer across the placenta.[16] Carbon dioxide tension decreases in pregnancy to 27 to 32 mm Hg, with a resultant increase in bicarbonate excretion and elevation in arterial pH to approximately 7.42 to 7.46. Both Pa_{CO_2} and HCO_3 are mildly lower in the third trimester compared with the first trimester.[17] The chronic respiratory alkalosis of pregnancy causes a rightward shift of the oxyhemoglobin dissociation curve, also facilitating oxygen transfer across the placenta.

■ Cardiovascular Physiology

In parallel with growth of the fetus and the accompanying increase in maternal oxygen consumption, pregnancy is accompanied by profound cardiovascular changes. Plasma volume and cardiac output progressively increase throughout gestation and are approximately 30% to 50% higher[18] at term (Fig. 96-2).[19] Heart rate also increases by 20 to 30 beats per minute. Systemic vascular resistance decreases. Historically, blood pressure has been described to decrease in the first half of pregnancy, reaching a nadir in the second trimester. However, recent large cohorts that closely monitored blood pressure in low-risk pregnancies have demonstrated no significant drops in blood pressure values.[20] Despite the increase in cardiac output, pulmonary artery pressures do not change significantly[21] due to a decrease in pulmonary vascular resistance (PVR). Oxygen consumption is increased approximately 20% above prepregnancy levels; the rate of increase in oxygen consumption is faster in pregnant women compared with nonpregnant women performing weight-bearing exercises.[22]

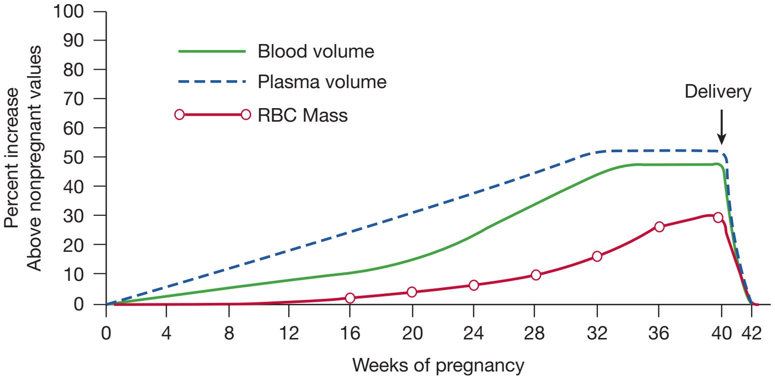

Figure 96-2 Physiologic changes in blood volume, plasma volume, and erythrocyte mass in pregnancy.

■ Labor And Delivery

Labor and delivery are associated with additional respiratory and cardiac physiologic changes. Pain, due to contractions and anxiety, leads to further increases in oxygen consumption and minute ventilation. Increased minute ventilation leads to further reduction in Pa_{CO_2}, which in cases of tenuous placental reserve may reduce placental perfusion. Pain control may help minimize these effects; however, the use of systemic opiates can lead to respiratory depression and needs to be monitored closely. Targeted regional anesthesia, which does not affect the respiratory muscles, may be a beneficial alternative and can help mitigate the stressor on the cardiorespiratory systems. In addition, in women with poor respiratory reserve, such as those with poorly controlled asthma, cystic fibrosis, or interstitial lung disease, the additional increase in minute ventilation may lead to respiratory decompensation and respiratory failure. Physiologic changes occurring in pregnancy quickly reverse in the postpartum period.

Cardiovascular changes in labor, delivery, and the postpartum period include an additional 10% to 15% increase in cardiac output in early labor, with further increases of up to 50% in the second stage of labor.[23] The changes are mediated by autotransfusion, in which 300 to 500 mL of blood is shunted into the systemic maternal circulation with every uterine contraction,[24] and by pain and anxiety.[25,26] Analgesia attenuates the changes. In addition, in the postpartum period, relief of aortocaval compression by the uterus results in an increase in venous return; autotransfusion from the contracting uterus further increases cardiac output. Women with underlying cardiac or pulmonary vascular disease may not tolerate the physiologic changes of labor and delivery. Although scheduled cesarean-section deliveries may appear to be an appropriate option for women with chronic pulmonary or cardiac disease (since they may eliminate the pain and anxiety of contractions), cesarean-section deliveries are unlikely to improve outcomes, since autotransfusion occurs with both vaginal and operative deliveries. Furthermore, the immediate fluid shifts that occur in the postpartum period are similar with both vaginal and cesarean-section deliveries. Operative deliveries are also associated with higher rates of surgical and medical complications when compared with vaginal deliveries.

■ Fetal Oxygenation and Ventilation

Uterine blood flow constitutes about 17% of the total cardiac output.[27] The placental vessels are low-resistance, high-capacitance vessels that function at maximal capacity at baseline. Therefore, when a hemodynamic insult occurs, the placental circulation cannot further vasodilate.

Supine positioning in late pregnancy may be associated with significant reduction in cardiac output and may alter the uterine circulation. Fetal oxygenation, like oxygenation of maternal organs, depends on maternal cardiac output, maternal oxygenation, and the fetal oxyhemoglobin dissociation curve. In addition, characteristics of the placenta affect diffusion of oxygen across this organ.

The fetus displays many protective mechanisms for maintaining adequate oxygenation. For example, fetal hemoglobin, which lacks beta chains, is less sensitive to the effects of 2,3-diphosphoglyceric acid than is adult hemoglobin. Consequently, the fetal oxyhemoglobin dissociation curve is shifted to the left, reflecting an increased oxygen affinity. The fetus also appears to have the ability to shunt blood to vital organs and to decrease oxygen consumption during periods of hypoxia. Despite these protective mechanisms, placental health has an important role in effecting oxygen transport to the fetus.[28]

Clinical conditions that cause a reduction in cardiac output or uterine blood flow (e.g., shock, use of vasoconstricting drugs), oxygen content (e.g., anemia, hypoxemia), oxyhemoglobin saturation (e.g., severe alkalosis, presence of carboxyhemoglobin), or placental perfusion may result in poor fetal oxygenation. Human studies on the optimal maternal oxygen level needed to achieve favorable fetal oxygenation are scarce. Based on extrapolation from available animal data, experts recommend that maternal oxygenation be maintained above a Pa_{O_2} of 70 mm Hg with an oxygen saturation of greater than 95%. However, more recent data from large cohorts suggest that maternal daytime oxygen saturation may drop as low as 93% without associated pathology.[20]

Finally, a gradient for CO_2 of approximately 10 mm Hg between fetal and maternal circulations exists (higher level in the fetus), facilitating CO_2 clearance from the fetal circulation. This fact may influence how best to use permissive hypercapnia in patients who might benefit from this ventilatory strategy. Fetal hypercapnia results in rapid fetal acidemia, increases in intracranial pressure, and a rightward shift of the oxyhemoglobin dissociation curve.

DIAGNOSTIC IMAGING OF THE PREGNANT WOMAN

Use of ionizing radiation is a major concern for most clinicians evaluating a pregnant patient. Risks that need to be considered when ordering an imaging study involving the use of ionizing radiation are the risk of malignancy and the risk of teratogenicity. A general principle in ordering diagnostic imaging should be to balance the accurate medical care of the mother with potential risks of radiation exposure to the fetus and the mother.

The risk of oncogenicity follows a stochastic (non-threshold) effect, suggesting that the risk of malignancy may occur even at low levels of exposure. This risk is not evenly distributed, as recent data suggest a lower risk of cancer when exposure occurs in utero compared with exposure in childhood.[29] The risk of teratogenicity, however, does follow a threshold effect. Based on animal and human studies of radiation exposure, a threshold has been determined for congenital malformations and miscarriage. For diagnostic tests resulting in a fetal exposure of 10 cGy or less, the risk of radiation to the embryo is very small. More conservative recommendations aim for a maximum exposure of 5 cGy. With the exception of computed tomography venography, radiation exposure from imaging procedures used for the workup of a patient with a suspected or diagnosed respiratory disorder does not exceed 5 cGy (Table 96-2).[30] As the risk of radiation below 10 cGy is miniscule, medical care of the mother takes priority over the risks of diagnostic radiation exposure to the fetus, especially when imaging is necessary for appropriate management of lung disease.[31]

Another consideration in diagnostic imaging studies includes the use of contrast agents. Iodinated contrast media are small molecules that are known to cross the placenta and carry a potential risk of thyroid dysfunction in utero. However, in a study of 350 women who received iodinated contrast in pregnancy, none of the infants had any significant thyroid dysfunction.[32] The study was, however, performed in the northeast United States, an area where iodine deficiency is rare. Use of iodinated contrast is, therefore, certainly justifiable. However, iodine reserve, timing of the study in pregnancy, and maternal renal function should be considered.

TABLE 96-2 Radiation Exposure to the Fetus Associated with Various Diagnostic Procedures

Diagnostic Test	Radiation Dose (cGy)
Chest radiography	<0.001
Ventilation scintigraphy[262]	0.028–0.051[a]
Perfusion scintigraphy[262] (half dose)	0.014–0.025
CT pulmonary angiography[263]	0.0003–0.0131
Conventional pulmonary angiography	<0.05 via brachial route; 0.2–0.3 via femoral route
CT venography	>5
Conventional venography	0.6
Chest Fluoroscopy[31]	<0.01 cGy/min
IR abdominal fluoroscopy[31]	0.6 cGy/min
PET[31]	0.8–1.6

CT, computed tomography; PET, positron emission tomography.

[a] *Dependent on agent used.*

Modified with permission from Bourjeily G, Paidas M, Khalil H, et al. Pulmonary embolism in pregnancy. Lancet. 2010;375(9713):500–512.

Gadolinium is usually used with nonionizing-radiation imaging studies (i.e., MRI) and is known to cross the placenta.[33] The effect of gadolinium on the growing fetus is unknown, as human safety data are very limited. Hence, use of gadolinium should be reserved for cases where benefit outweighs the potential unknown risk of gadolinium exposure.

Diagnostic studies involving radionuclides, such as a pulmonary ventilation/perfusion scan, expose the fetus to radiation differently than external radiation. Given that radionuclides are excreted by the kidneys and may pool in the bladder, continuous exposure to the fetus may occur after the study has been completed.

INTERVENTIONAL PROCEDURES IN PREGNANCY

Indications for interventional pulmonary procedures in pregnancy are no different than in the nonpregnant population. As with any intervention, the risk of the intervention should be weighed against the risk of an inappropriate diagnosis or untreated disease. For example, the risk of bronchoscopy in pregnancy may be related to the procedure itself, as well as to the sedatives used during the procedure. Medication effects may be even more pronounced in the pregnant patient, given the altered physiology of pregnancy, including drug distribution, response to sedatives, and decreased airway patency.

In pregnant women, an upper airway evaluation should be performed prior to every procedure, given the higher risk of intubation failure in pregnancy. Risk of aspiration also may be increased because of a decrease in lower esophageal pressures and increase in intra-abdominal pressures. To minimize the risk of hypotension and hemodynamic instability during procedures performed in the second half of pregnancy, patients should be positioned supine with a left tilt to relieve the compression of the inferior vena cava by the gravid uterus.

Given the risk of hypoxemia with bronchoscopy,[34] especially when bronchoalveolar lavage is performed,[35] oxygenation should be monitored routinely and supplemental oxygen administered as needed to keep oxygen saturation above 95%. Fetal monitoring should be discussed with the obstetric team; however, in general, fetal monitoring prior to 28 weeks of gestation can be unreliable and difficult to interpret, while monitoring prior to 24 weeks is likely unnecessary.[36] Since pregnant women may develop hypercapnia and hypoxemia more quickly than nonpregnant women,[37] smaller doses of sedation might be considered. Midazolam, meperidine, fentanyl, and lidocaine have not been reported to be associated with congenital malformations.[33]

Fluoroscopy during bronchoscopy can be used in pregnancy, given the low dose of radiation associated with its use (Table 96-2)[30] and the fact that the fetus is not in the radiation field. A discussion with the institution's medical physicist can help keep radiation exposure to a minimum. Pleural procedures also can be performed in pregnancy, but providers should keep in mind the potential 4- to 5-cm cranial displacement of the diaphragm during pregnancy. Ultrasound guidance may help minimize risks of the procedure.

PHARMACOTHERAPY CONSIDERATIONS IN THE PREGNANT PATIENT

Over-the-counter drugs and prescription medications are frequently used during pregnancy. Although a number of drugs have been clearly shown to be either teratogenic or safe in pregnancy, insufficient safety data exist for most. Most data on safety for a given drug in pregnancy are based on animal studies, case reports or series, case-control studies, or pregnancy registries. Prospective studies evaluating safety are scarce. Integral to the discussion is the patient's understanding of the limitations of the available data and the intricacies of pharmacotherapy in pregnancy.

In 2015 the U.S. Food and Drug Administration (FDA) shifted away from a designated letter classification for drugs (A, B, C, D, X) to narrative sections about drug effects on pregnancy, lactation, and fertility. Even so, these descriptions still have shortcomings, especially when drug safety data are scarce, and initiation of any medication in a pregnant woman requires a thorough discussion between the patient and the provider about risks of treatment with the drug, and the risk of untreated disease. Often the data surrounding risk of a drug are based on animal studies alone in lieu of clinical trials in humans, and thus caution should be used when extrapolating and interpreting data. Breastfeeding is associated with significant benefits to newborns, such as a lower risk of obesity, diabetes, and cardiovascular disease, among others,[38–40] and drug passage into breast milk is an important consideration. Table 96-3 summarizes data on commonly used drugs in pregnancy and lactation. Reprotox.org is an excellent source of updated information on drug safety data during pregnancy and lactation. Medications and Mothers Milk is another source of information on medication use and breastfeeding.

SMOKING DURING PREGNANCY

Estimates are that 22% of women of reproductive age in the United States smoke. Data from Europe and the United States show that 10.7% to 13.1% of fetuses are exposed to maternal smoking. Although about half of women smokers quit during pregnancy, many women start smoking again after delivery.

Smoking is associated with adverse fetal outcomes. Various mechanisms may be responsible. Placentas from smokers have reduced capillary volume and increased thickness of villous membranes.[41–43] Carboxyhemoglobin is cleared slowly from the fetal circulation and competes with fetal oxyhemoglobin. Amniocytes from smokers have an increased incidence of structural chromosomal abnormalities compared with nonsmokers.[44] In addition, nicotine promotes platelet activation, impairs estrogen synthesis, and can directly impair lung development due to interaction with nicotinic acetylcholine receptors.

Smoking is associated with placental abnormalities, premature rupture of membranes, decreased thyroid function, psychiatric illness, reduced fertility, and conception delay,[45–49] as well as decreased production of milk volume, and lower rates and shorter duration of breastfeeding.[50] Prospective[51] and retrospective[52] studies confirm an association of fetal growth restriction with smoking during pregnancy, even in the first trimester.[53] Both active and secondhand smoke exposures are associated with increased risk of first trimester pregnancy loss.[54] Smoking in pregnancy increases healthcare costs for both mothers and neonates, even after adjusting for the protective effect against preeclampsia.

Babies born to pregnant smokers are also at risk for preterm birth.[55] The association of smoking with a risk of congenital anomalies[56] is a complex issue and may be closely related to maternal genotype. Maternal smoking during pregnancy is also associated with adverse cognitive and behavioral outcomes in the offspring, such as low scholastic achievement, attention deficit and hyperactivity disorder, conduct disorder, regular smoking,[57] wheezing, and asthma.[58] Childhood exposure to secondhand smoke is associated with upper and lower respiratory tract infections, ear infections, sudden infant death syndrome (SIDS), and asthma.[59–61]

Smoking cessation at any point during pregnancy is likely associated with some benefit.[62] According to recent economic model analyses, smoking cessation in randomized trials in pregnancy was also likely to result in cost savings.[63] Pregnancy offers a unique opportunity for smoking cessation, given the mother's motivation for fetal well-being and her frequent contact with healthcare providers. Women should be screened for secondhand smoking exposure, as well as potential abuse of other substances and comorbid psychiatric illness. Women should also be followed for smoking abstinence into the postpartum period, given the high rate of smoking relapse.

TABLE 96-3 Drug Safety in Pregnancy and Lactation[33]

	Pregnancy	Lactation
Ambrisentan	Ambrisentan is expected to be teratogenic, given its mechanism of action and known teratogenicity in animal studies. No human data.	Infant risk cannot be ruled out. It is not known whether ambrisentan is excreted into human milk. **AAP:** Not reviewed
Amoxicillin/ clavulanate	Amoxicillin/clavulanate is acceptable for use during pregnancy but use peri-delivery may increase the risk of necrotizing enterocolitis in neonates. Penicillins are generally considered to be safe for use in nonallergic patients during pregnancy.	No harmful effects have been reported. **AAP:** Maternal Medication Usually Compatible with breastfeeding **Lactation Risk Category:** L1
Azathioprine	Based on human case series, azathioprine is unlikely to increase the risk of congenital anomalies.	Caution is recommended. Monitor the infant closely for signs of immunosuppression, leukopenia, thrombocytopenia, hepatotoxicity, pancreatitis, and other symptoms of 6-mercaptopurine exposure. The risks to the infant are probably low. Recent long-term data suggest that the rate of infections in treated groups is no different from nontreated controls. **Lactation Risk Category:** L3
Benralizumab	Benralizumab is a humanized monoclonal antibody (IgG) that may be used in pregnancy in uncontrolled asthma if other treatments fail. However, IgG molecules cross the placenta in the second trimester. Pregnancy and fetal outcome studies are currently underway.	It is not known if benralizumab is excreted in breast milk but is likely present.
Beta agonists	β2 agonists are not associated with congenital malformations (GINA 2020). Albuterol is listed as preferred beta agonist in 2004 NIH report on treatment of asthma in pregnancy. High doses (32 mg/d) of oral albuterol appeared to prolong gestation in a population of 132 pregnancies.[264] Various birth defects were described in association with albuterol and may have been due to chance.	Safe to use in breastfeeding mothers. Use via inhalation is recommended. **AAP:** Not reviewed **Lactation Risk Category:** L1
	Salmeterol is not expected to increase the risk of congenital malformations. Formoterol is not expected to increase the risk of malformations, but human data are inadequate.	Safe to use in breastfeeding women. Levels in breast milk very low to undetectable. **AAP:** Not reviewed **Lactation Risk Category:** L2
Bosentan	Bosentan is believed by its manufacturer to increase the risk of major congenital anomalies in humans, based on rodent studies and the known mechanism of action of the medication.	No data are available on the transfer into human milk, but based on its structure, bosentan levels in the milk compartment would probably be very low. However given 50% oral bioavailability and high incidence of liver toxicity, great caution is recommended with this product in breastfeeding mothers until we have published milk levels. **Pediatric Concerns:** No data are available. May be dosed down to children weighing at least 22 lb. **Lactation Risk Category:** L4
Budesonide inhaler	No association with congenital birth defects. Children exposed to inhaled steroids are more likely to develop endocrine, metabolic, and nutritional disorders.	Unlikely clinically relevant concentrations of budesonide reach breast milk. **Lactation Risk Category:** L1
Bupropion (Wellbutrin)	Bupropion has not been associated with an increased risk of congenital defects; however, pregnancy registry data have called attention to a possible weak association with congenital heart defects (not confirmed in other studies).	Bupropion may, in some women, suppress milk production. Some caution is recommended concerning changes to milk supply. **AAP:** Drugs whose effect on nursing infants is unknown but may be of concern
Cephalosporins	Cephalosporins may cross into the fetal circulation in small amounts, but teratogenicity has not been attributed to these agents.	As a highly protein-bound group, the cephalosporins do not pose a significant risk to the nursing infant.
Cyclophosphamide	Experimental animal studies and human case reports have shown adverse effects on fertility and embryo development. Birth defects have been demonstrated in all animal species tested.	Cyclophosphamide is excreted into human milk. It has been classified as a drug that may interfere with cellular metabolism of a nursing infant by the American Academy of Pediatrics.

(continued)

TABLE 96-3 Drug Safety in Pregnancy and Lactation[33] *(Continued)*

	Pregnancy	Lactation
Cyclosporin	Experimental animal studies do not predict an increase in congenital anomalies after pregnancy exposure to cyclosporins. A limited number of human cases are also reassuring, although premature birth and low birth weight are observed. Solid organ transplant recipients are recommended to stay on the drug, but alternatives are recommended for treatment of psoriasis and lupus nephritis if possible. Formulations may contain alcohol.	Cytotoxic drug that may interfere with cellular metabolism of the nursing infant. Close observation of the infant, including monitoring of the infants' plasma levels, is required. There should be strong consideration to discontinue the drug if breastfeeding. **AAP:** Possible immune suppression; unknown effect on growth or association with carcinogenesis **Lactation Risk Category:** L3
Dexamethasone	Glucocorticoid use in pregnancy can increase the risk of cleft palate and impaired fetal growth, but small epidemiologic studies did not demonstrate this association with dexamethasone specifically. Extended courses for pregnant women are best avoided, but the benefit may outweigh the risk.	There are no specific studies on dexamethasone, but overall corticosteroids enter human milk in small amounts. Mothers may wait 4 h after a dose to nurse. **AAP:** Prednisone/prednisolone compatible with breastfeeding
Elexacaftor/ tezacaftor/ivacaftor (Trikafta)	Based on animal studies, Trikafta is not likely to cause congenital anomalies. There is transfer of Trikafta to the fetus via fetal circulation, but anecdotal cases of pregnancy among women on Trikafta have not shown serious adverse outcomes. The European Respiratory Society and the Thoracic Society of Australia and New Zealand consider Trikafta to be "probably safe" in pregnancy.	The European Respiratory Society and the Thoracic Society of Australia and New Zealand consider Trikafta to be "probably safe" in lactation. Animal models demonstrate excretion of Trikafta in breast milk.
Epoprostenol sodium	It is unknown if epoprostenol shares any of the abortifacient properties of other prostaglandins, but the manufacturer reports no adverse events noted based on available data (limited). Overall, use should be avoided if possible.	Unknown **AAP:** Not reviewed **Lactation Risk Category:** L3
Gentamicin	Ototoxicity and nephrotoxicity in the fetus are theoretical possibilities that have not been confirmed clinically. This agent is known to cross the human placenta at term, but its use is likely justifiable in certain conditions.	**AAP:** Compatible with breastfeeding **Lactation Risk Category:** L2
Iloprost (Ventavis)	No epidemiologic studies of congenital anomalies among infants born to women who were treated with iloprost during pregnancy have been reported. Iloprost has been shown to be teratogenic in rats due to its systemic circulatory effects.	It is not known whether iloprost appears in milk. Increased mortality of nursed rat pups was reported, and the manufacturer recommends discontinuing nursing in women being treated with iloprost.
Ipratropium bromide	Based on animal studies, ipratropium is not expected to increase the risk of congenital malformations.	Transfer into breast milk in exceedingly small and clinically insignificant levels. **Lactation Risk Category:** L2
Leflunomide	Experimental animal studies demonstrated interference with embryo development and viability at high doses. Product labeling contains a warning against the use of this drug in pregnancy based on an 8% rate of congenital anomalies in human pregnancies.	Experimental studies showed >90% decrease in postnatal pup survival after exposure to leflunomide during late pregnancy and lactation; hence labeling states that this medication should not be used in nursing mothers.
Linezolid	Linezolid does not cause congenital malformations in mice and rats, even at high doses. There are no human data.	Minimal human data available. Linezolid is transferred to breast milk with a likely maximal dose of 2 mg/kg daily (with maximal dose for infants being 30 mg/kg daily). **Lactation Risk Category:** L3
Macrolide antibiotics	*Erythromycin* use during pregnancy is unlikely to increase teratogenic risk to the fetus. *Clarithromycin* may increase the risk of adverse pregnancy outcomes. In a series of observational studies, *azithromycin* did not cause an increased rate of congenital anomalies when used during pregnancy.	Pyloric stenosis has been associated with the use of erythromycin in the early postpartum period. **AAP:** Usually Compatible with breastfeeding **Lactation Risk Category:** L3
Mepolizumab	There are no human data on mepolizumab in pregnant women; however, animal studies did not show adverse fetal effects.	There are limited data on the presence of mepolizumab in human breast milk; however, it was detected in breast milk after administering to pregnant monkeys.

TABLE 96-3 Drug Safety in Pregnancy and Lactation[33] *(Continued)*

	Pregnancy	Lactation
Methotrexate	Methotrexate increases the incidence of congenital anomalies in experimental animals and appears to do so in humans as well. Methotrexate is used clinically as an abortifacient[265–267] and in the treatment of ectopic pregnancy. One study indicates a higher risk of fetal malformation in mothers who received methotrexate months prior to becoming pregnant.[268] Therefore, pregnancy should be delayed for at least 3 months following therapy if either partner is receiving methotrexate.	Methotrexate is believed to be retained in human tissues (particularly neonatal gastrointestinal cells and ovarian cells) for long periods (months). It is apparent that the concentration of methotrexate in human milk is minimal, although due to the toxicity of this agent, it is probably wise to pump and discard the mother's milk for a minimum of 2–4 d. **AAP:** Possible immune suppression; unknown effect on growth or association with carcinogenesis; neutropenia. **Lactation Risk Category:** L3
Montelukast	Montelukast is unlikely to increase risk of congenital abnormalities; however, there is currently an FDA warning related to reports of limb reduction defects. In total there are *six* cases reported of limb reduction defects, but causality is unknown.	The nursing infant is exposed to approximately 0.68% of the maternal dose, which is well below the therapeutic dose.
Mycophenolate mofetil	Mycophenolate mofetil is associated with an increased risk of miscarriage and congenital malformations. A pregnancy registry has been established by the manufacturer.	Mycophenolate is excreted in milk of rats. Human data are scarce. Product labeling recommends avoiding using the drug during lactation.
Nicotine replacement	Smoking cessation is strongly recommended in pregnancy. However, recommendations regarding nicotine replacement therapy are less clear due to known fetal toxicity of nicotine. Nicotine therapy may decrease fetal growth similarly to smoking. Nicotine metabolism is higher in pregnancy possibly requiring higher doses..	Nicotine is secreted into human milk. Use of replacement products is compatible with breastfeeding. **AAP:** Not reviewed **Lactation Risk Category:** L2
Omalizumab	Data in monkeys are reassuring, but currently, there are no human data. Pregnancy registry exists.	Omalizumab may be secreted into human milk but levels likely very low. Oral bioavailability extremely low. **AAP:** Not reviewed **Lactation Risk Category:** L3
Penicillin	Penicillins are not believed to increase adverse pregnancy outcome. Penicillins accumulate in amniotic fluid during maternal ingestion. No adverse fetal effects have been associated with this process.	Usually compatible with breastfeeding. Penicillins are excreted into human milk in small amounts with possible alterations in bowel flora and potential risk of allergic sensitization in the infant.
Penicillamine	Experimental animal studies and some case reports suggest an association with congenital connective tissue disorders including lax skin and inguinal hernia.	It is possible that copper and zinc concentrations may be reduced in breast milk of mothers taking penicillamine and possible need for supplementation. Some case reports and case series describe no complications in breastfeeding infants of mothers taking penicillamine.
Prednisone	Prednisone and other glucocorticoids are associated with fetal growth impairment in humans. Prednisone is metabolized by the placenta to a large extent, and minimal doses reach the fetus. Other steroids, such as betamethasone, are less well metabolized by the placenta and are used to enhance lung maturity in pregnancies expected to end preterm. These medications increase oral clefting in experimental animals and may do so in humans in early pregnancy exposure.	Small amounts of most corticosteroids are secreted into breast milk. With prolonged high-dose therapy, the infant should be closely monitored for growth and development. **AAP:** Usually Compatible with breastfeeding **Lactation Risk Category:** L2
Quinolones	Quinolones are avoided during pregnancy due to cartilage toxicity demonstrated in experimental animals. Human data are not supportive.	Quinolones are secreted in milk. Infants should be observed for changes in gut flora, *Candida* overgrowth, or diarrhea. The use of quinolones in the pediatric population is increasing due to minimal evidence of cartilage toxicity. **AAP:** Not reviewed **Lactation Risk Category:** L2
Remdesivir	Based on animal studies, remdesivir is not likely to cause congenital anomalies.	There are no human data on remdesivir and lactation. In animal studies, there is transfer of remdesivir and its metabolites to pups but no adverse effects.
Reslizumab	Based on animal studies, reslizumab is not likely to cause congenital anomalies. Human data are lacking. IgG molecules cross the placenta in the second trimester.	Reslizumab was present in mouse breast milk at 5%–7% of maternal concentrations with no adverse effects. There are no human data.

(continued)

TABLE 96-3 Drug Safety in Pregnancy and Lactation[33] *(Continued)*

	Pregnancy	Lactation
Riociguat	Riociguat was consistently shown to have teratogenic effects when administered to animals. Pregnancy test should be performed prior to initiating therapy and monthly while on therapy in reproductive-age women.	It is not known whether the drug transfers via breast milk in human but appears to do so in rats. Given the potential for serious adverse reactions in nursing infants, nursing should be discontinued in women on riociguat.
Rituximab	In animal studies, rituximab did not interfere with embryo development in monkeys. There was no evidence of an increase in adverse outcomes in humans in a pregnancy registry. Rituximab is present in cord blood demonstrating transplacental transfer of the agent near term, and depletion of B cells was demonstrated in an exposed neonate.	Rituximab has been demonstrated in monkey and human milk. Product labeling recommends that breastfeeding be avoided by breastfeeding women.
Sildenafil	Based on experimental animal studies, sildenafil does not appear to increase the risk of congenital malformations in exposed pregnancies.	There are insufficient data to determine the safety of sildenafil in human lactation.
Tacrolimus	Based on experimental animal studies and human case reports, tacrolimus is not expected to increase the risk of congenital anomalies. Hypertension, prematurity, and neonatal hyperkalemia have been suggested by case reports as possible adverse effects.	According to the manufacturer, tacrolimus is excreted in breast milk and should be avoided during lactation. However, studies in lactating mothers suggest the exclusively breastfed infant would receive less than 0.2% of the pediatric dosage for organ transplant rejection. **AAP:** Not reviewed **Lactation Risk Category:** L3
Tocilizumab	Based on animal studies, tocilizumab is not expected to cause congenital anomalies; however, embryofetal death was reported in monkeys. Human case series are limited, and there is an ongoing registry for pregnant mothers receiving tocilizumab.	Limited human data implies that absorption of tocilizumab by the infant via breast milk is unlikely. Small observational studies did not find adverse effects on nursing infants.
Treprostinil	Based on experimental animal studies with subcutaneous treprostinil, adverse effects in pregnancy are not anticipated. Human data and data on drug inhalation are lacking.	Manufacturer states that no reports describing the use of treprostinil during human lactation are available and the effects on the nursing infant from exposure to the drug in milk are unknown.
Vancomycin	Based on experimental animal studies, vancomycin is not expected to increase the risk of congenital malformations. Theoretical concern exists regarding ototoxicity and nephrotoxicity, but supportive evidence in humans is not available.	Only low levels are secreted into human milk. Its poor absorption from the infant's gastrointestinal tract would limit its systemic absorption. Low levels in infants could provide alterations of gastrointestinal flora. **AAP:** Not reviewed **Lactation Risk Category:** L1
Varenicline (Chantix)	Based on experimental animal studies, use of varenicline during pregnancy is not expected to increase the risk of congenital malformations. Human data are not available.	There have been no studies performed on the transfer of varenicline into human milk. **Lactation Risk Category:** L4

Various nonpharmacologic interventions for smoking cessation have been examined. Providing an incentive to encourage smoking cessation has been shown to be an effective strategy in some studies; however, the ethical framework and implications of such strategies is being questioned.[64]

Pharmacotherapy for smoking cessation in pregnancy has limited data regarding efficacy and safety. The United States Preventive Services Task Force states that the use of pharmaceuticals has not been sufficiently evaluated to determine their safety or efficacy in pregnancy.[65] Data on nicotine replacement therapy show conflicting evidence with regard to safety.[66,67] Many trials have been halted in the United States because of either adverse effects or failure to demonstrate effectiveness.[68,69] The Danish National Birth Cohort of 72,761 women showed no significant association between type or duration of nicotine product use and birth weight.[70] A recent meta-analysis demonstrated that current evidence from randomized and nonrandomized studies do not provide clear evidence of whether nicotine replacement was associated with fetal harm.[71] Overall, the risk from various chemicals in cigarette smoke likely outweighs the small risk of possible weight reduction from nicotine pharmaceuticals.

Although animal data on the safety of use of varenicline in pregnancy are available, human data are lacking. Varenicline is likely transferred through breast milk; however, data are not available. Bupropion has not been associated with an increase in congenital defects in experimental animal studies, although pregnancy registry data for bupropion calls attention to a possible association with congenital heart defects.[72] Although bupropion is passed to the fetus in breast milk, based on measurement of infant plasma levels, the dose transmitted is unlikely to be clinically significant. A recent meta-analysis examining the effect of varenicline and bupropion use in smoking cessation in pregnancy showed no major impact on congenital abnormalities, birthweight, or premature birth.[73]

MANAGEMENT OF ASTHMA DURING PREGNANCY

Asthma is the most common respiratory disease of pregnancy, affecting 2% to 13% of pregnancies worldwide.[74,75] Asthma may improve, worsen, or remain unchanged in pregnancy.[76] Predictors of disease course include prepregnancy asthma severity, race, presence of obesity, compliance with medication use, and patient difficulties in accessing antenatal care. Factors contributing to modifications of disease severity include a number of pregnancy-associated conditions: higher prevalence of gastroesophageal reflux disease,[77] nasal congestion,[78] alterations in immunity, and hormonal factors.[79] The rate of asthma exacerbations is increased between 17 and 32 weeks of gestation.[76,80] Improvement in the last few weeks of pregnancy may be related to significantly higher levels of cortisol, an anti-inflammatory hormone, compared with preconception levels.

Poorly controlled asthma may negatively impact some maternal and fetal outcomes. In a large study, asthmatic women were more likely to have pregnancies complicated by miscarriage, antepartum and postpartum hemorrhage, anemia, or depression.[81] In a retrospective cohort study performed in 12 clinical centers in the United States, asthmatics experienced increased risk of preeclampsia; gestational diabetes; preterm births, including spontaneous preterm birth; and induced preterm birth.[82] A systematic review of nine studies has shown an increased risk of preterm birth, small for gestational age, and low birthweight if the mother has asthma.[83] Babies born to asthmatic mothers may be more likely to have congenital anomalies.[84,85]

Since pregnancy does not affect air flow rates, reductions in peak expiratory flow rate (PEFR) should prompt quick medical evaluation. In a multi-institutional prospective study, lower forced expiratory volume in one second (FEV_1), but not symptom control, was associated with adverse perinatal outcomes.[86] These data may be related to the fact that, given the high prevalence of physiologic dyspnea in pregnancy, symptom interpretation by both providers and patients may be difficult without objective measures; hence, the need for close physiologic monitoring is apparent.

Most medications used to treat asthma are safe for use in pregnancy **(Table 96-3)**. An important message to patients is that good asthma control is the main goal, and the risk of medication use is lower than the risk of adverse outcomes from untreated or poorly treated disease. Recent evidence from a double-blind, randomized, controlled trial suggests that pregnant women managed according to a validated treatment algorithm based on measurements of exhaled nitric oxide (FeNO) had fewer exacerbations compared with those treated according to a symptom-based approach.[87] Despite an updated FDA warning on montelukast being possibly associated with congenital anomalies, the drug may need to be used in women whose asthma cannot be controlled without a leukotriene receptor antagonist. Newer biologics have scarce fetal safety data, but as IgG molecules they are expected to cross the placenta in the second trimester. Details regarding their appropriate dosing, efficacy, and impact on childhood vaccination have yet to be investigated.

Patients with more severe disease, or those who suffer an exacerbation close to term, require a detailed labor and delivery plan. Stress dosing with corticosteroids during labor should be considered in patients who have been on prolonged courses of systemic steroids during the pregnancy. Patients with active symptoms or more severe asthma may benefit from regional anesthesia aimed at reducing minute ventilation and oxygen consumption and preventing hyperinflation. If general anesthesia is considered, ketamine and halogenated anesthetics are preferred. Oxytocin and prostaglandin E2 are safe to use. However, other prostaglandins used for induction of labor, morphine, and meperidine should be avoided, since they may cause worsening bronchospasm.

CYSTIC FIBROSIS AND PREGNANCY

Cystic fibrosis (CF) impacts fertility in both men and women. Women with CF have various reproductive system abnormalities. Since the CF transmembrane conductance regulator (CFTR) is present in reproductive organs, cervical mucus is thicker and more tenacious, leading to obstruction of the cervical os and impaired sperm penetration. Despite these changes, fertility occurs in women with CF, and affected women should be counseled regarding contraception. Women with higher body weight and higher FEV_1 are more likely to desire and achieve pregnancy[88] and with newer generations of protein modulator therapies, more women are likely to attempt pregnancy.[89] Genetic screening of both mother and father can help assess the risk of CF in the offspring. Preimplantation genetic diagnosis can be performed during assisted reproduction and may help detect embryos affected by the disorder.

In two series reporting on 72 and 90 pregnancies in patients with CF, the need for intravenous antibiotic therapy was 65% to 77%, and higher rates of hospitalization compared to nonpregnant patients were reported.[90,91] FEV_1 may decline during pregnancy in CF, and then improve in some patients following delivery.[92] However, in larger case-controlled series, the FEV_1 decline appears similar to that experienced by nonpregnant patients with CF.[90,93] Reduced FEV_1 appears to be a predictor of adverse outcomes in pregnancy in CF,[91] including early mortality following delivery. Other predictors of decreased survival include maternal colonization with *Burkholderia cepacia* and pancreatic insufficiency.

Increased energy expenditure in pregnancy makes weight gain more challenging. Glucose intolerance and gestational diabetes occur as a result of decreased insulin production, impaired insulin sensitivity, and increased hepatic glucose production.[93,94] Multiple studies have shown an increased risk of preterm delivery,[90,95] possibly related to altered lung function. The risks of fetal demise and birth defects are likely similar to controls.[90,91,93]

Treatment of CF requires multiple chronic therapies such as antibiotics, inhaled medicines and CFTR modulators. Azithromycin, penicillins, and cephalosporins are safe to use in pregnancy. In animal studies, use of fluoroquinolones may be associated with increased risk of abnormal cartilage development; similar effects have not been observed in human studies.[96] Use of tetracyclines is hard to justify in pregnancy, since they result in tooth and bone discoloration. Rifamycins are associated with an increased risk of fetal damage and bleeding in both mother and neonate.[97] Dornase alfa use has been described in pregnancy,[98] but safety data are limited. Safety data on use of pancreatic enzyme replacement therapy also are limited,[99,100] but use is likely justifiable. Vitamin replacement can be used in pregnancy; however, vitamin A supplementation should not exceed 10,000 U daily because of teratogenic effects. Although sulfonylureas are likely safe in pregnancy, they are associated with an increased risk of fetal hypoglycemia. Insulin is the preferred glucose-lowering drug. Though the introduction of CFTR modulators has significantly impacted the outcomes of patients with CF, data on these therapies in pregnancy remain limited and more data are needed on the impact of these drugs on reproduction and contraceptives, as well as their fetal safety. Reports of the use of ivacaftor, alone, or in combination with tezacaftor or lumacaftor, did not show an association with congenital anomalies, but due to nonuniform reporting and variable exposure to the drug, these data do not establish safety.[33] The European Respiratory Society and the Thoracic Society of Australia and New Zealand have deemed the drugs as “probably safe” for use during pregnancy and lactation.[101]

Vaginal delivery is the expected mode of delivery in CF unless other indications for cesarean section exist. Epidural anesthesia may help with minimizing minute ventilation and oxygen consumption in patients with reduced lung function. Breastfeeding may not be advisable for women with poor nutritional status.

PNEUMONIA IN THE PREGNANT WOMAN

Sepsis is among the leading causes of maternal death in the world, especially in developing regions. Pneumonia in particular is one of the most common causes of non-obstetric mortality in the United States.[102,103] In addition, in a national study in Colombia examining causes for respiratory failure in pregnancy as a cause of maternal deaths between 1998 and 2009, pneumonia was the most common cause.[104] The risk of pneumonia is increased in pregnant women with comorbid conditions, such as asthma, anemia, HIV infection, and tobacco or substance abuse.[105] Pregnant women may be more susceptible than nonpregnant women to contracting viral infections, and they may have more severe disease than those who are not pregnant. Immune alterations associated with normal pregnancy may impair the response to infection and increase the risk of certain infections.

Preterm delivery appears to be the most common complication associated with pneumonia. Other potential complications include low birth weight, intrauterine growth restriction, a fetus that is small for gestational age, placental abruption, preeclampsia or eclampsia, and low Apgar scores.[106–108] Varicella infection increases morbidity and mortality in pregnancy and is associated with congenital abnormalities and poor fetal outcomes especially in the first trimester. Congenital varicella syndrome is associated with high mortality in the first 30 days of life and severe impairment related to neurologic, cardiac, gastrointestinal, and developmental delays in survivors.

In the pregnant patient with pneumonia, antibiotic therapy should be initiated empirically while awaiting confirmatory tests that may aid in narrowing the antimicrobial coverage. During influenza season, antivirals (usually oseltamivir) should be started empirically. Extensive use of oseltamivir during the 2009 H1N1 epidemic was thought not to be associated with any adverse fetal effects. Intravenous acyclovir or valacyclovir should be used in patients with a suspicion of varicella pneumonia; those suspected of varicella infection should be admitted for observation.

Case series of pregnant women with SARS-CoV-2 disease (COVID-19) have shown increased risk of preterm birth[109] and more severe maternal disease compared with nonpregnant patients. Severe maternal morbidity also may occur.[110] While vertical transmission of SARS-CoV-2 is possible, it is uncommon. The low level of vertical transmission may be explained by low levels of maternal viremia, as well as reduced expression of the angiotensin-converting enzyme 2 receptor and the serine transmembrane protease 2 in the placenta.[111,112] Antibodies formed in response to the COVID-19 infection do not appear to cross the placenta or provide immunity to the neonate; however, it is unclear whether the same is expected following vaccination.[111] Preliminary studies do not show harm in vaccinated patients who are pregnant.[113]

Women with COVID-19 may continue to breastfeed their babies while wearing a mask, and available data suggest low risk of transmission with proper hygiene and masking methods.[114]

Remdesivir, the antiviral of choice in COVID-19, has been used in pregnant women. The FDA recommends its use after weighing the potential risks and benefits for mother and fetus. Animal studies have not shown any embryofetal harm when remdesivir is administered systemically at four times the recommended human dose. It is thought that remdesivir is likely present in breast milk at lower concentrations than maternal plasma.

The use of dexamethasone, which has been shown to be beneficial in COVID-19, should be used for severe hypoxic respiratory failure in pregnant women with COVID-19, although there is a risk of suppression of the fetal adrenal function.

According to the manufacturer,[115] there are insufficient data on the safety of bamlanivimab and etesevimab in pregnancy, alone or in combination, and the risk of untreated disease needs to be weighed against the unforeseen potential risk of the drug. There are also no data on the transfer of either monoclonal antibody into breast milk in either animals or humans. Data on the use of other COVID-19 therapy such as Tocilizumab and Baricitinib are emerging. Neither drug is expected to increase the risk of congenital malformations, and as with any medication, benefit of use should be weighed against the risk of severe disease in pregnancy. Pregnancy registries exist at mothertobaby.org/ongoing_studies.

Antibiotic use in the pregnant patient with CF has been discussed previously; Table 96-3 provides additional details. Although use of aminoglycosides or vancomycin theoretically may be associated with hearing and renal dysfunction in the fetus, in most circumstances where there is an indication for one or the other agent, its benefit likely outweighs its risk.

In pregnant women with acute respiratory failure from pneumonia or other causes, decisions regarding oxygenation and ventilation should be predicated on the previously discussed physiology. Airway intubation should be anticipated and performed by the most experienced personnel available, using advanced airway devices and readily accessible equipment, given the high risk of intubation failures in pregnant women.

TUBERCULOSIS: CLINICAL COURSE AND MANAGEMENT DURING PREGNANCY

Tuberculosis (TB) is an important infection of pregnant woman. In sub-Saharan Africa, TB is the third leading cause of maternal death, following sepsis and hypertensive disorders of pregnancy.[116] In the United States, a steady overall decline in the incidence of TB has been observed, but a rise in incidence has been seen in the 15- to 45-year-old age group. As a result, an increase in the prevalence of TB among pregnant women in certain communities, for example, New York City, has been reported.[117]

The risks of TB to the mother and unborn child include intrauterine growth restriction, prematurity, and an increased risk for both maternal and fetal mortality. Transmission of TB to the fetus also is well documented[118–120] and may occur through hematogenous spread, by contiguous spread from endometrial TB, or via aspiration of TB-infected amniotic fluid. If neonatal TB is suspected, placental and endometrial tissue can be examined at the time of delivery; however, a workup of suspected active maternal TB should never be delayed until delivery. The diagnosis of TB in pregnancy often requires a high level of suspicion since fatigue and malaise can be confused with symptoms of pregnancy.

Pulmonary TB is the most common form of TB in pregnancy, accounting for up to 85% of all cases. Consequently, a chest radiograph is essential in making the diagnosis. Although tuberculin skin testing (TST) has been considered the gold standard for screening during pregnancy,[111] recent studies demonstrate that both TST and QuantiFERON-TB detection rates may be impacted by pregnancy[110] and different cut-offs may need to be considered in this population.[121]

Treatment of latent TB infection (LTBI) in pregnancy may be delayed until the postpartum period in pregnant women at low risk for reactivation.[122] This recommendation is based on a study showing a higher risk of INH-induced hepatitis in pregnant women compared with nonconcurrent controls.[123] However, in the study noted, the risk of INH-induced fatal hepatitis in both the active treatment and the control group was quite low. Conversion to active TB infection in patients coinfected with HIV is significant; therefore, immediate treatment should be initiated in coinfected patients to avoid placing the neonate, mother, and community at risk.

Pregnancy was originally believed to worsen the course of TB infection, but this has been shown not to be the case. Active, untreated TB infection in a pregnant woman is more of a hazard than the treatment. When active TB is confirmed, treatment should not be delayed. Treatment is similar to that in the absence of pregnancy. First-line therapies for TB, including rifampin, INH, and ethambutol, have been shown to be safe in pregnancy and unassociated with human fetal malformations.[124,125] INH does carry a risk of acute hepatitis, especially if the patient is treated concomitantly with rifampin. Pyrazinamide is less well studied. Although the World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease note that the use of pyrazinamide is justifiable in pregnancy, the Centers for Disease Control and Prevention (CDC) does not recommend it in pregnancy. When drug resistance is suspected, addition of pyrazinamide may be needed. Second-line agents are considered more toxic than first-line agents, and clinical experience to guide their use and safety is lacking. Streptomycin should be avoided because of its fetal ototoxicity, while amikacin and kanamycin carry known fetal nephrotoxicity. Para-aminosalicylic acid (PAS) has been used with INH in the past, and there has been no evidence of teratogenicity among babies whose mothers received the drug.[126–128]

Breastfeeding should not be discouraged in women being treated for TB, unless the mother is thought to be infectious. Since anti-TB drugs are secreted in small concentrations in breast milk, caution should be exercised when breastfeeding newborns that are also being treated for TB, since that may increase the risk of drug toxicity. Transmission of mycobacteria via breast milk is, however, quite unlikely, except for rare cases of TB mastitis.

VENOUS THROMBOEMBOLISM: DIAGNOSIS AND MANAGEMENT DURING PREGNANCY

Diagnostic and management approaches for thromboembolic disease, including pulmonary embolism (PE), in the pregnant woman merit special considerations.

Diagnosis of Venous Thromboembolism and Pulmonary Embolism

Venous thromboembolism (VTE) is one of the leading causes of maternal mortality in the developed world. As such, when suspicion for disease is high, early implementation of therapeutic anticoagulation is important. In pregnancy, the risk of VTE is as high as 7 to 10 times that of nonpregnant, age-matched controls.[129] The risk is disproportionately higher in the postpartum period, and 70% of all VTE events that happen in the postpartum period occur within the first 20 days after delivery.[130] In pregnancy, 70% to 85% of deep venous thromboses (DVTs) occur in the left leg.[131,132] This is thought to be due to compression of the left iliac vein by the right iliac artery and the gravid uterus. Isolated pelvic DVT is more prevalent in pregnancy compared with the nonpregnant population,[132,133] possibly suggesting a different pathogenesis for the disorder.

The increased risk of VTE during pregnancy is due to stasis, hypercoagulability, and vascular damage. Venous stasis in the lower extremity is secondary to the gravid uterus, as well as hormonally mediated venodilation.[134] Pregnancy is marked by many changes in the coagulation cascade, which lead to a hypercoagulable state.[135] Finally, vascular injury occurs with delivery, thereby augmenting risk in the postpartum period.

Existing clinical pretest probability tools are not validated in pregnancy, and their utility is limited by the physiologic changes of pregnancy.[136] D-Dimer performance characteristics are different in pregnant women, and its measurement in pregnancy without concomitant diagnostic imaging to exclude VTE is unreliable.[137,138] Data from the Diagnosis of PE in Pregnancy (DiPEP) decision analysis modeling showed that neither clinical features, decision rules, nor biomarkers were reliably predictive of pulmonary embolism. Emerging evidence suggests that the incorporation of D-dimers may be helpful in decreasing the need for computed tomography pulmonary angiography (CTPA) in pregnant women suspected of pulmonary embolism.[139] Other data showed more favorable outcomes,[140,141] although when tested in the DiPEP population they demonstrated poor negative predictive ability for PE.[142] Hence, current data remain limited due to sample bias, the number of protocol deviations, and power.[140,141] Use of D-dimers cannot yet be relied upon to safely exclude pulmonary embolism in pregnancy.

Testing for symptomatic DVT in pregnant and nonpregnant individuals is similar: compression ultrasonography (CUS) is the standard of care.[143] In pregnancy, the sensitivity of CUS may not be as high, given the high prevalence of isolated pelvic vein thrombosis in pregnant patients.[132] Absence of flow or need for increased pressure during CUS may be suggestive of pelvic vein thrombosis. However, the low sensitivity of CUS in detecting iliac thrombi may necessitate the use of other imaging studies, such as nonenhanced magnetic resonance venography.

In pregnant women suspected of PE who also have lower extremity symptoms, CUS is the recommended initial test in those who are hemodynamically stable. In women without lower extremity symptoms, American Thoracic Society/Society of Thoracic Radiology guidelines recommend a chest x-ray (CXR) as the next diagnostic step.[144] A CXR may provide an alternative diagnosis and also determine the utility of a perfusion scan. Using the proposed diagnostic algorithm, patients with a normal CXR are next evaluated with a ventilation–perfusion lung scan, whereas those who have an abnormal CXR undergo a multidetector computed tomography–pulmonary angiogram (MDCT-PA).[144] The main advantage of MDCT-PA over a ventilation–perfusion scan is that it provides an alternative diagnosis in 17% to 19% of pregnant women suspected of having a PE.[145] MDCT-PA may be technically limited in up to 20% of pregnant women[146] due to physiologic changes of pregnancy, including a higher plasma volume and heart rate, which affect vascular enhancement. These effects may be more pronounced in women with obesity and those with multiple gestations. Imaging protocol modifications may help reduce technical limitations of the technique.[147]

Management of Thromboembolic Disease in Pregnancy

Since the interval between diagnosis of PE and institution of therapeutic anticoagulation has been shown to be an independent predictor of death, early and appropriate treatment is essential. In pregnancy, prognostic assessment tools, such as brain (B-type) natriuretic peptide (BNP), or cardiac echocardiography for evaluation of right ventricular dysfunction, are not well validated. Furthermore, their interpretations are limited by the physiologic changes of pregnancy.[148–150] Additional work in deriving prognostic indictors for thromboembolic disease in pregnancy is needed.

Both unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) are safe during pregnancy, as they do not cross the placenta. However, LMWH is superior to UFH for all measured outcomes of VTE—risk of recurrent thrombosis, bleeding, and death.[151,152] Other advantages of LMWH over UFH include a lower risk of heparin-induced thrombocytopenia and thrombosis (HIT) and bone demineralization with subsequent fractures.[153–155]

UFH may still play a role in pregnancy, particularly around labor and delivery, given its shorter duration of action and easy reversibility. Given UFH's increased clearance and volume of distribution (and, therefore, bioavailability), its use in pregnancy should be monitored.[156] UFH administered intravenously is the treatment of choice for patients with acute renal failure or if urgent need for drug reversal may be required for delivery.

Dosing and monitoring of LMWH is controversial. The American College of Chest Physicians recommends adjusted dosing once or twice daily for enoxaparin,[157] while the American College of Obstetricians and Gynecologists recommends weight-adjusted dosing twice daily[158] and the Royal College of Obstetrics and Gynecology recommends weight-based dosing once or twice daily.[159] Twice-daily dosing is preferred by many experts, guided by anti-Xa levels obtained 3 to 6 h after a dose, especially in women with obesity. The goal for anti-Xa levels is 0.5 to 1.1 units/mL. LMWH does not appear to increase the risk of peripartum bleeding over UFH. The incidence of peripartum hemorrhage is approximately 0.9% to 1.8%, whereas the risk of antenatal hemorrhage and wound hematoma is less than 1%.[160] Although most available data were derived from the study of enoxaparin, tinzaparin likely has a similar side-effect profile.[161]

The duration of treatment for VTE in pregnancy is not well defined; consequently, recommendations for management are similar to those in the nonpregnant patient. Consensus suggests that therapy for VTE should extend for at least 6 weeks into the postpartum treatment, since this is a high-risk time for thromboembolism. The total duration beyond that is unclear, but a minimum of three months is probably warranted and should be based upon careful assessment of the risk of recurrence.[162,163]

Thrombolysis may be warranted in cases of massive PE among pregnant women. The main risk of thrombolysis in pregnancy is maternal bleeding, which is reported to occur in as many as 8.1% of patients treated; no cases of intracranial hemorrhage have been reported.[164] In one series on the use of thrombolytics in pregnancy, although no maternal bleeding was reported, the rate of fetal mortality was 8%.[165] Fetal complications may be related to thromboembolic disease severity, as well as the choice of thrombolytic agent. Alteplase (rt-TPA) does not cross the placenta and carries no risk for teratogenicity. In patients with PE who are hemodynamically stable, use of thrombolytics is controversial (even in the absence of pregnancy) and is generally discouraged. In patients who are hemodynamically unstable, but who cannot undergo systemic thrombolysis, surgical or percutaneous embolectomy are potential therapeutic options when clinical expertise for these procedures is available.[166]

Management of VTE in the peripartum period is complex and requires a detailed labor and delivery plan. The plan should take into consideration the risk of bleeding with full anticoagulation and the risk of recurrent VTE when anticoagulation is withheld. In addition, the need for regional anesthesia should be evaluated. A planned transition from LMWH to UFH near term may be considered, since UFH is more predictably reversed, has a shorter half-life, and is easily monitored.[167] A planned induction can ensure a controlled environment for delivery. However, given the unpredictable nature of labor, patients should be instructed to stop their injections at the first sign of labor and to contact their provider for further instructions.

Since a new VTE without treatment during the first month carries a 40% risk of recurrence, patients who are within two weeks of expected delivery should be considered for placement of an IVC filter.[168,169] Patients developing a clot between weeks two and four prior to delivery may be treated with intravenous UFH[170] or an IVC filter. Removable IVC filters can be placed in pregnancy, but they are usually placed above the renal veins. Intravenous UFH should be restarted postpartum as soon as possible.

Warfarin, an oral vitamin K agonist, crosses the placenta, is known to be teratogenic, and increases the risk of intracranial bleeding.[171] Use of warfarin for the treatment of VTE in pregnancy cannot be justified, given the availability of drugs with similar efficacy and better safety profiles.[30] Warfarin is detectable in breast milk, but in clinically insignificant amounts; hence, its use is considered safe in breastfeeding mothers.[172] Use of postpartum intravenous UFH or subcutaneous LMWH as a bridge to warfarin is warranted. It has been shown that use of warfarin alone, without antecedent use of heparin carries about a threefold risk of recurrent VTE.[173] Direct oral anticoagulants are not recommended for use in pregnancy or in women planning a pregnancy given a potential risk of bleeding or abortion. These drugs also are detected in breast milk, although no adverse effects were reported in the small number of exposed infants.[33]

PULMONARY ARTERIAL HYPERTENSION AND PREGNANCY

Pulmonary arterial hypertension (PAH) is an uncommon disorder that may affect women of childbearing age. PAH may present, or significantly worsen, during pregnancy. The hallmark of PAH is an increase in PVR. The increase in blood volume, cardiac output, and oxygen consumption, and the decrease in systemic vascular resistance seen in pregnancy, are poorly tolerated in patients with fixed PVR. These hemodynamic challenges are exacerbated at the time of delivery as a result of uterine contractions, autotransfusion, and increased sympathetic tone, as well as by large fluid shifts in the postpartum period. In affected patients, the normal physiologic changes of pregnancy may lead to right ventricular volume overload and, eventually, right ventricular failure and death.

Two large reviews of a total of 198 pregnancies in women with PAH revealed a mortality range from 17% in patients with idiopathic pulmonary arterial hypertension (iPAH) to 56% in women with other causes of pulmonary hypertension.[174,175] In contemporary case series in which patients were managed with pulmonary-specific vasodilators, substantially better outcomes have been reported. However, these reports may be limited due to publication biases.[176,177] Nearly all fatalities occur in the peripartum period as a result of heart failure, VTE, or sudden death. Due to the limited data and nature of the publications in this field, it remains uncertain if patients with less severe disease (i.e., lower mPAP or PVR) are at lower risk for death than are those with more severe disease, although this has been suggested in a number of reported series.[178,179] Currently, the recommendation remains that patients with even mild PAH should avoid pregnancy.[180] A decision to terminate a pregnancy or to induce delivery in the setting of PAH depends on the timing of diagnosis in gestation and the anticipated physiologic changes. In more advanced pregnancies, termination may not lessen risk of mortality or morbidity.

Use of medications for PAH in pregnancy is not well studied. Calcium channel blockers have been used successfully and are relatively safe in pregnant patients who have a vasodilator response demonstrated during right heart catheterization.[179] Unfortunately, loss of efficacy of calcium channel blockers over the long term limits their use, so pulmonary-specific vasodilators may be needed.[181] Pulmonary-specific vasodilators that have been used successfully during pregnancy include prostacyclins (treprostinil or epoprostenol) and phosphodiesterase (PDE) inhibitors (sildenafil and tadalafil).[182,183] Iloprost is teratogenic in animals, although there are reports of its use in pregnancy without teratogenicity;[184,185] however, such reports do not establish safety. Case reports describe successful use of inhaled nitric oxide (iNO) at the time of delivery, but risks to the fetus and neonate remain unclear. Since pregnancy is a prothrombotic state, anticoagulation for PAH should be used when indicated, including in those women with PAH who are on prolonged bed rest. LMWH is the preferred agent and should be continued in the postpartum period. Riociguat, an agent used for the treatment of chronic thromboembolic pulmonary hypertension, is known to be teratogenic in animals and is transferred via breast milk in animals.[186]

A multidisciplinary team that includes a PAH specialist should manage the patient throughout pregnancy and in the peripartum period. Carefully planned regional anesthesia may carry less risk than general anesthesia.[174,177] Cesarean delivery is unlikely to reduce anesthesia risk in women with PAH; in fact, cesarean delivery may be associated with a higher risk of medical complications in PAH, including VTE and atelectasis. Throughout pregnancy, close monitoring for worsening right heart failure is essential. Its development may herald the need for hospitalization, institution of bed rest, augmentation of therapy for PAH, emergent delivery, or termination of pregnancy.

Pulmonary hypertension is one of few disorders where pregnancy is a "contraindication." Hence, the best way to prevent the potentially fatal complications of PAH is to avoid pregnancy altogether. Contraception for prevention of future pregnancy is essential in patients with PAH mainly because of the high risk of mortality to both the mother and the fetus, but also because of the risk of teratogenicity in many of the drugs used to treat PAH, such as bosentan and ambrisentan. Hence, two forms of contraception are usually recommended. Options for contraception should be discussed in collaboration with a specialist familiar with both PAH and contraception. As patients with PAH are prothrombotic, estrogen-based contraception should be avoided. Similarly, intrauterine device placement carries a 5% risk of a vasovagal event, which may be fatal in patients with PAH. Thus, device implantation may require hospital admission.[163]

INTERSTITIAL LUNG DISEASES IN PREGNANCY

Only a minority of interstitial lung diseases (ILD) occur in women of childbearing age. In chronic ILD, preconception counseling is crucial to ensure appropriate disease control at the time of conception and use of medications with good efficacy and good safety profiles.[187] A multidisciplinary approach to these disorders is crucial to achieving improved outcomes.

Patients with a restrictive physiology may develop worsening symptoms in pregnancy due to a number of changes, including, for example, a significant increase in tidal volume. Outcomes often depend on the cause of restriction and disease progression during the course of the pregnancy. Patients with severe restriction should be assessed by an expert in obstetric anesthesiology prior to delivery, and a plan developed to avoid both high levels of anesthesia and use of the Trendelenburg position, when possible.

A variety of autoimmune and idiopathic systemic diseases may affect the lungs, producing pulmonary parenchymal and interstitial disease that may profoundly impact pregnancy.

Rheumatoid arthritis (RA) usually improves in the second and third trimesters[188] and flares in the postpartum period.[189] Convincing evidence that RA results in adverse pregnancy outcomes is lacking.

Systemic lupus erythematosus (SLE) may flare in pregnancy, especially in women with first pregnancies, renal involvement, and poor disease control at the time of conception.[190] The postpartum period confers a particularly high risk of lupus pneumonitis.[191] SLE increases the risk of complications of pregnancy and adverse fetal outcomes, including preeclampsia, spontaneous abortion, growth restriction, and preterm birth.[192–194]

Systemic sclerosis may have devastating consequences in pregnancy. Pregnancy planning and close monitoring can improve maternal and fetal outcomes. Renal crisis is a feared complication that is usually treated with angiotensin-converting enzyme (ACE) inhibitors. Given the high morbidity of this condition and the clear advantage of using ACE inhibitors over any other antihypertensive agents, use of these drugs can be justified, despite their known teratogenicity and the risk of neonatal renal dysfunction at birth. Pulmonary hypertension, another complication of systemic sclerosis, should be evaluated prior to pregnancy, and affected patients advised to avoid pregnancy.

Disease severity in polymyositis and dermatomyositis is likely a predictor of adverse fetal outcomes.[195] General anesthesia should be avoided in patients with polymyositis because of the risk of delayed muscle recovery, arrhythmias, heart failure, and aspiration.

Stable sarcoidosis likely has no significant effects on pregnancy outcomes. However, patients with pulmonary parenchymal disease, extrapulmonary sarcoidosis, or PAH, and those requiring drugs other than corticosteroids for disease suppression, tend to have more complicated pregnancies.[196]

Lymphangioleiomyomatosis (LAM) is a rare disorder that affects women of childbearing age. LAM is likely accelerated by exogenous hormones and pregnancy. Pregnancy in LAM is associated with a high incidence of pneumothorax and chylous effusion.[197] It is possible that LAM diagnosed during pregnancy may be a marker of disease severity.[198] The European Respiratory Society guidelines suggest that patients be informed of the risk of complications of LAM—for example, pneumothorax and chylous effusions—prior to pregnancy, as women with more severe disease may be more susceptible to these complications.[199]

The use of certain medications in pregnancy, such as corticosteroids, azathioprine, hydroxychloroquine, sulfasalazine, and intravenous immunoglobins, is necessary in certain clinical contexts. Use of tumor necrosis factor (TNF) antagonists is justifiable in rare circumstances. TNF antagonists have been implicated in cases of VATER (vertebral, anal, tracheal, esophageal, and radial anomalies) syndrome.[200] Cyclosporin A is unlikely to have teratogenic effects. Use of methotrexate, cyclophosphamide, mycophenolate mofetil, rituximab, leflunomide, and D-penicillamine should be avoided in pregnancy (see Table 93-3) and alternative agents employed in women planning a pregnancy.

PULMONARY EDEMA

Pulmonary edema during pregnancy is common, despite an overall young age of the patient population.[201] Plasma oncotic pressures decrease as gestation duration increases and decrease further in the postpartum period. Consequently, pulmonary edema may occur at lower-than-usual hydrostatic pressures during pregnancy. Given the profound hemodynamic changes at the time of labor, delivery, and the postpartum period, the vast majority of peripartum cases of pulmonary edema are reported postpartum. Intravenous fluid administration used to counteract the effect of vasodilation caused by regional anesthesia may contribute to its development. Autotransfusion of blood from the uterine circulation into the systemic circulation and the relief of inferior vena cava pressure are additional contributors.

Pulmonary edema in pregnancy can occur both with and without systemic hypertension.[202] A major cause associated with hypertension of pregnancy-related pulmonary edema is preeclampsia, which may be associated with left ventricular dysfunction, lower oncotic pressure, and possible capillary endothelial dysfunction. Tocolytic agents also have been associated with pulmonary edema. Treatment of pulmonary edema in pregnancy is essentially the same as in the nonpregnant population; however, pregnant women typically respond to lower doses of diuretics (e.g., an initial dose of 10 mg of furosemide administered intravenously). Nitroglycerine and hydralazine may be used. ACE inhibitors are known teratogens and should be avoided.

AMNIOTIC FLUID EMBOLISM

Amniotic fluid embolism (AFE), also known as anaphylactoid syndrome of pregnancy, is a rare but potentially catastrophic condition characterized by cardiopulmonary collapse and multiorgan dysfunction. An overall incidence has been reported of 1 in 40,000 births.[203] Mortality rates between 20% and 90% have been reported. Proposed risk factors for the development of AFE include advanced maternal age, complicated labor and delivery, obstetric interventions, uterine trauma, placental pathologies, and fetal distress.[204] The pathogenesis of AFE remains a subject of debate.

AFE presents as sudden hemodynamic instability, respiratory failure (cardiogenic or noncardiogenic pulmonary edema), disseminated intravascular coagulation, encephalopathy, and seizures. Detection of fetal squamous cells in the pulmonary vasculature is not a specific finding in AFE; it has been reported in asymptomatic women at term. Development of potential biomarkers to aid in timely diagnosis are being researched but are not yet validated for clinical practice.[205]

Treatment of AFE focuses on supportive measures and correction of the initial hemodynamic instability. Immediate cesarean section, which should be considered in cases of severe, refractory shock, should be promptly performed in hopes of improving maternal and fetal outcomes.[206] Use of recombinant factor VII,[207] iNO and other pulmonary vasodilators, exchange transfusion, extracorporeal membrane oxygenation (ECMO), and continuous venovenous hemofiltration (CVVH)[208,209] have been described, but little supportive evidence is available.

OVARIAN HYPERSTIMULATION SYNDROME

Severe ovarian hyperstimulation syndrome (OHSS) is an uncommon iatrogenic complication of exogenous gonadotropins used in assisted reproduction. Pulmonary complications include pleural effusions and VTE. In the severe stages, massive ovaries and ascites, large pleural effusions, oliguria, hemoconcentration, and VTE can be life threatening. Risk factors for OHSS include age older than 30 years, high serum estradiol, multiple ovarian follicles, and pregnancy.[210] Research suggests that vascular endothelial growth factor (VEGF), angiotensin II, and insulin-like growth factor play important roles in the pathogenesis of OHSS by increasing vascular permeability, which leads to vascular leakage of albumin, electrolyte imbalances, and rapid accumulation of extravascular fluid, including pleural effusions and ascites. Patients with OHSS are also at a higher risk for VTE and, in particular, a higher prevalence of upper extremity DVT, since estradiol-rich fluid drains through the thoracic duct into upper extremity veins.

Patients with severe symptoms of OHSS should have intravascular volume expansion, although the possibility of worsening intra-abdominal hypertension should be kept in mind. Current guidelines recommend paracenteses or culdocenteses for the management of symptoms as an outpatient.[211] Repeated large-volume paracenteses may improve renal perfusion by decreasing abdominal hypertension. Therapeutic thoracenteses also may be needed. Close monitoring for early signs of acute respiratory distress syndrome (ARDS), thromboembolism, and advanced renal failure is recommended. Thromboprophylaxis using UFH or LMWH should be initiated as soon as possible due to the high incidence of thromboembolic complications.[212]

SLEEP-DISORDERED BREATHING AND PREGNANCY

Sleep disruption and sleep disorders are common in pregnancy, specifically sleep-disordered breathing (SDB). While central sleep apnea (CSA) is uncommon in pregnant women, pregnancy appears to confer an increased risk for obstructive sleep apnea (OSA).

Mallampati scores[213] (relating tongue size to pharyngeal size and ease of intubation) increase as pregnancy progresses.[214] Due to the effect of estrogens and increased plasma volume, nasal patency is reduced. Upper airway size is smaller in pregnant women with[215] and without preeclampsia[216] compared with nonpregnant controls. The reduction in FRC may result in a tendency for upper airway collapse.[217] The effects of progesterone on minute ventilation may lead to a more negative inspiratory pressure, resulting in a vacuum effect on the upper airway. On the other hand, progesterone increases the electromyographic activity of the upper airway dilator muscles[218] and enhances their responsiveness to chemical stimuli.[219] In addition, reduced rapid eye movement (REM) sleep,[220] preference for assuming a lateral sleeping position in late gestation,[221] and increased minute ventilation may play protective roles. The balance of these factors favors an increased risk for SDB in pregnancy. Notably, snoring occurs in approximately 35% of pregnant women.[222] Objectively defined SDB is common even in low-risk women, occurring in 4% to 9% of all women in a multicenter sample in the United States.[223] Disease prevalence is significantly higher in pregnancies complicated by medical or obstetric conditions.[224–226] Lack of significant effort by obstetric providers in screening for SDB, even in obese patients, has been reported.[227] Hence, in clinical samples in large population-based studies that reported prevalence based on diagnosis codes, the prevalence was significantly lower at 0.1%,[228] suggesting poor screening, underdiagnosis, or underreporting.

OSA may improve in untreated women in the postpartum period;[229–231] however, it appears that at least 50% of women diagnosed with SDB in pregnancy continue to have an elevated apnea hypopnea index in the postpartum period.

Despite the high prevalence of this condition in pregnancy, screening remains complicated by the lack of a validated screening tool. The Berlin questionnaire, a widely used tool in screening the nonpregnant population, appears to have poor positive and negative predictive values in pregnancy.[232,233] Excessive daytime sleepiness correlates with other symptoms of SDB, such as snoring and witnessed apneas,[234] but Epworth Sleepiness Scale scores are not predictive of a diagnosis of SDB. Chronic hypertension, increased age, obesity, and snoring appear to have good predictive value for diagnosing OSA in high-risk populations;[235,236] however, the proposed models have not been validated in other populations including the high-risk population.

SDB is associated with a variety of medical disorders, which may have a major influence on pregnancy and its course. Gestational hypertension and gestational diabetes are associated with short-term maternal, fetal, and neonatal complications,[237–239] as well as long-term cardiovascular[240] and metabolic outcomes.[241] Hence, the association of these disorders with a modifiable disorder holds the promise of potentially preventing long-term, morbid outcomes.

Snoring and OSA have been shown to be associated with a variety of adverse pregnancy outcomes, including gestational hypertension,[222,228,242–244] gestational diabetes,[228,245–247] and cesarean deliveries.[222,248,249] Abnormalities in glucose metabolism, longer labor, and cesarean deliveries are also associated with short sleep duration.[222,246] Mechanistic studies are lacking, and the directionality of the association is not well clarified. The association of SDB with adverse fetal outcomes may be mediated by associated comorbidities. Growth restriction[243] and preterm birth[222,249,250] have been reported in association with snoring, OSA, or poor sleep in some studies. Case reports and case series suggest that fetal decelerations secondary to sleep apnea occur, but a study evaluating synchronized limited sleep studies and fetal monitors failed to show a significantly higher prevalence of late decelerations with obstructive events.[232]

A diagnosis of OSA also carries implications for labor and delivery management including upper airway patency; use of opioids peri-delivery, which may lead to respiratory depression and impact upper airway collapsibility; and monitoring in women receiving specific therapies such as magnesium sulfate, which may impact respiratory muscles.

Once diagnosed, treatment of OSA in the general population is recommended for patients with an apnea–hypopnea index (AHI) >15 or those with AHI >5, who have symptoms that respond to therapy, such as daytime sleepiness. For multiple reasons, specific guidelines on initiation of therapy in pregnancy are not available. To date, no trials have shown that treatment of OSA in pregnancy improves pregnancy or fetal outcomes, although treatment with CPAP in women with preeclampsia has shown significant hemodynamic improvement, even after one night of therapy.[251,252] This likely contributes to underscreening and underdiagnosis in this population.[227]

Alcohol and cigarette smoking avoidance carry additional pregnancy-specific benefits. Observational studies of positive airway pressure (PAP) therapy have shown improvement in daytime fatigue and daytime somnolence in pregnant women with OSA treated with CPAP which is re-titrated midpregnancy.[253] Auto-PAP may circumvent the need for repeat titration with pregnancy progression. In women with preeclampsia, small, randomized trials have shown that in-laboratory PAP therapy improves hemodynamics, uric acid, and cardiac output compared with untreated women.[251,254] Trials evaluating the effect of PAP therapy on pregnancy-specific cardiovascular and metabolic outcomes are sorely needed to help determine the "urgency" of starting PAP therapy in pregnancy.

Sleep-disordered breathing appears to improve in the postpartum period,[229] but about 50% of women with sleep-disordered breathing diagnosed in pregnancy will continue to have the disorder postpartum.[230,231] However, it is unclear whether persistence of sleep-disordered breathing in the postpartum depends on whether the disorder predated pregnancy or whether it developed in pregnancy.

PRECONCEPTION COUNSELING

Medical specialists often fail to adequately communicate and support women with chronic conditions around reproductive needs.[255] A pulmonologist's role in caring for reproductive-age women extends to preparing women with chronic lung disease for a successful pregnancy. Conversations with medical specialists need to occur in reproductive-age women with chronic lung disease who are sexually active, have a partner, and have children, regarding the possibility of and the implications of a pregnancy.[256]

According to the American College of Obstetricians and Gynecologists, the goal of prepregnancy care is to reduce the risk of adverse health effects for the woman, the fetus, and the neonate. This is achieved by working with the patient to educate her about a healthy pregnancy, optimize her health, and address potentially modifiable risk factors.[257] Since a woman's health changes throughout her lifespan, preconception counseling needs to occur multiple times during her reproductive years. Ideally, women should seek care before they attempt to get pregnant, and then as soon as they find out they are pregnant. Preconception counseling would assist in planning an optimal timing of pregnancy, avoiding unplanned pregnancies,[257] and implementing the best management strategies prior to conception and throughout pregnancy and the postpartum period.[258] Hence, periodic discussions about birth control methods are crucial.

Risk assessment includes the examination and communication of the risk of the chronic disease on pregnancy and perinatal outcomes, and vice versa.[259] Understanding and counseling patients on the risk of worsening of certain conditions (e.g., asthma, sleep apnea) during pregnancy or the recurrence of others (venous thromboembolism) can clarify expectations and assist the patient in making informed decisions about management choices and monitoring frequency.[257] Women should also be made aware of the risk of the treated or the untreated chronic condition on the health of the pregnancy and the fetus/newborn, which can guide decision-making regarding therapy choices.

Reviewing the risk of medications in pregnancy is another aim of preconception counseling.[257,260] Ideally, women would enter pregnancy on medications that are nonteratogenic. However, given the systematic exclusion of pregnant women from many interventional trials as recently as drug and vaccine trials in COVID-19, many drugs remain poorly examined for safety and efficacy in pregnancy. Hence, counseling would need to be provided with available data as well as any unforeseen potential risk.[261]

Genetic counseling is another key component of preconception counseling to properly inform the expectant mother and her family about potential risk of transmission of the disorder, and to clarify expectations for the offspring.

SUMMARY

Pregnancy constitutes a distinctive state in a woman's life that presents a number of unique physiologic, diagnostic, and therapeutic challenges. Pregnancy also offers an opportunity for many women to have meaningful interactions with the healthcare system and providers, including those focused on lung health and social habits. Prompt diagnostic and therapeutic interventions and close patient monitoring are warranted to help the pregnant woman tolerate the physiologic demands of pregnancy and the hemodynamic and respiratory stressors associated with labor and delivery. Deliberate postponement of a warranted clinical evaluation or intervention until after delivery is rarely the right approach.

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CHAPTER 97

Pulmonary Complications of Intra-abdominal Disease

Hilary M. DuBrock
Sonja D. Bartolome

INTRODUCTION

Intra-abdominal pathology may have distant effects on the pulmonary vascular bed, the pulmonary parenchyma, or the pleural space. This chapter reviews the pulmonary complications of intra-abdominal disease, focusing on the pathology, epidemiology, clinical features, and management. Topics are organized according to the primary abdominal organ system in which the disease is centered.

PULMONARY COMPLICATIONS OF HEPATIC DISEASE

A number of respiratory complications of hepatic disease are well recognized, including portopulmonary hypertension (POPH), hepatopulmonary syndrome (HPS), hepatic hydrothorax (HH), and spontaneous bacterial empyema (SBEM). Each is discussed in the subsequent sections.

■ Portopulmonary Hypertension

POPH is defined as pulmonary arterial hypertension (PAH) occurring in the setting of liver disease, or more specifically, in the setting of portal hypertension.

Epidemiology and Pathogenesis

Approximately 2% to 6% of patients with decompensated liver disease develop POPH.[1–3] Based on multicenter, case-control studies, autoimmune hepatitis and female sex are identified risk factors for the development of POPH; therefore, the role of hormonal and immunologic influences in the pathogenesis of POPH is a focus of investigation.[4,5]

Patients with POPH have measurable alterations in levels of pulmonary vasoactive substances. For example, prostacyclin is a potent pulmonary vasodilator that also has antithrombotic and antiproliferative properties; levels of prostacyclin are decreased in the lungs of patients with PH. In patients with POPH, loss of endothelial prostacyclin synthase expression compared with normal controls has been demonstrated.[6] Endothelin 1 (ET-1), a pro-proliferative and vasoconstrictive agent implicated in the pathophysiology of other types of PH, has also been shown to be increased in the circulation of patients with POPH.[7] Bone morphogenetic protein 9 (BMP9), an endothelial quiescence factor produced in the liver, is a sensitive, specific, and prognostic biomarker of POPH. Circulating levels of BMP9 are reduced in POPH as well as HPS.[8,9]

Histologically, POPH appears to be very similar to other types of PH. POPH is a precapillary pulmonary arteriopathy involving multiple layers of the vessel; specifically, POPH is characterized by smooth muscle hypertrophy, adventitial proliferation, and endothelial cell proliferation. In addition, the plexiform lesions characteristic of other types of PH have been demonstrated in patients with POPH (Fig. 97-1).[10]

The microvascular changes in POPH result in a pulmonary circulation characterized by increased resistance and low capacitance—the antithesis of the normal pulmonary vascular physiology, which is characterized by a low-pressure and high-flow state. The altered physiology constitutes an increased workload to the right ventricle (RV). Early in the disease process, the RV hypertrophies and increases its stroke volume. Over time, these changes become maladaptive, and the RV dilates and becomes dysfunctional. At this stage, the patient demonstrates progressive right ventricular failure. The clinical course of POPH is similar to that seen in other types of PH (Chapter 72), justifying its placement in Group 1 of the World Health Organization Classification (Table 97-1).[11] However, the concomitant presence of end-stage liver disease, with accompanying fluid retention, hypoalbuminemia, coagulopathy, renal dysfunction, and gastrointestinal bleeding, complicates the clinical management of patients.

Clinical Features

Patients with POPH may present with complaints of fatigue and dyspnea with exertion, which are later accompanied by signs and symptoms of right ventricular failure, such as jugular venous distension, lower extremity edema, presyncope, and syncope. The diagnosis can be particularly elusive in the cirrhotic patient, who may have edema from portal hypertension and a spectrum of hemodynamic disturbances. Consequently, the diagnostic workup must be performed carefully to avoid a misdiagnosis of POPH.

The most common hemodynamic derangement in patients with liver disease is not PH, but rather, a state of systemic vasodilation and high cardiac output (CO) induced by splanchnic vasodilation.[2] In these patients, hemodynamics are characterized by increased mean pulmonary artery pressure (mPAP), high CO, low pulmonary capillary wedge pressure (PCWP), and reduced pulmonary vascular resistance (PVR). Affected patients do not have small vessel arteriopathy, but rather, increased pressure resulting from high flow through the pulmonary circulation. This hemodynamic pattern is evident in approximately 35% of liver transplant candidates and is not associated with a poor outcome.[2]

A second abnormal hemodynamic profile present in patients with liver disease reflects volume overload or diastolic dysfunction.

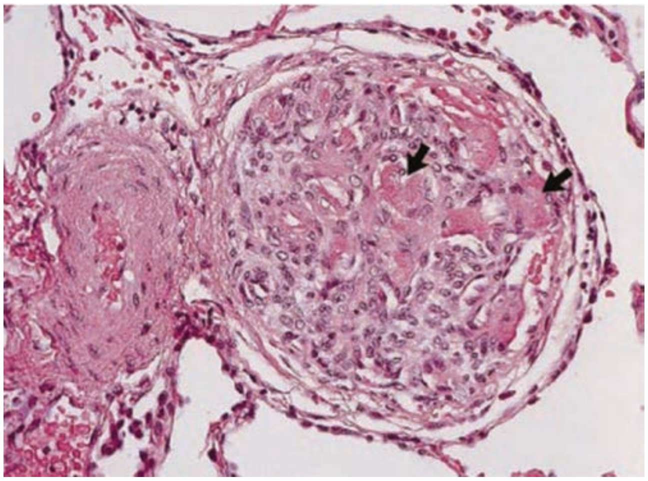

Figure 97-1 Autopsy specimen from a 55-year-old female with cryptogenic cirrhosis and portopulmonary hypertension, showing the plexiform lesion common in pulmonary arterial hypertension. The *arrows* show acute platelet-fibrin thrombi within the plexiform lesion. *(Reproduced with permission from Krowka MJ, Edwards WD. A spectrum of pulmonary vascular pathology in portopulmonary hypertension. Liver Transpl. 2000;6(2):241–242.)*

TABLE 97-1 Updated Clinical Classification of Pulmonary Hypertension (PH)

- Group 1, pulmonary arterial hypertension (PAH)
    - Idiopathic
    - Hereditable
    - Drug- and toxin-induced
    - PAH associated with:
        - Connective tissue disease
        - Human immunodeficiency virus
        - Portal hypertension
        - Congenital heart disease
        - Schistosomiasis
    - PAH long-term responders to calcium channel blockers
    - AH with overt features of venous/capillaries (PVOD/PCH) involvement
    - Persistent PH of the newborn syndrome
- Group 2, PH due to left heart disease
    - PH due to heart failure with preserved ejection fraction
    - PH due to heart failure with reduced ejection fraction
    - Valvular heart disease
    - Congenital/acquired cardiovascular conditions leading to postcapillary PH
- Group 3, PH due to lung diseases and/or hypoxia
    - Obstructive lung disease
    - Restrictive lung disease
    - Other lung disease with mixed obstructive/restrictive pattern
    - Hypoxia without lung disease
    - Developmental lung disorders
- Group 4, PH due to pulmonary artery obstructions
    - Chronic thromboembolic PH
    - Other pulmonary artery obstructions
- Group 5, PH with unclear and/or multifactorial mechanisms
    - Hematologic disorders
    - Systemic and metabolic disorders
    - Others
    - Complex congenital heart disease

Modified with permission from Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019;53(1):1801913.

With this profile, pulmonary pressures may be elevated, but CO and PCWP are also increased; in addition, PVR is low, indicating pulmonary *venous* hypertension from elevated left heart filling pressures, rather than small vessel pulmonary arteriopathy.

Finally, the third hemodynamic profile that defines POPH is characterized by an elevated pulmonary artery pressure, normal PCWP, high PVR, and high, normal, or low CO—depending on the degree of resultant right ventricular failure and liver disease (Table 97-2).

Not infrequently, patients may present with a *combination* of these hemodynamic profiles, for example, POPH with volume overload. In this case, an increased transpulmonary gradient (TPG) >12 mm Hg (TPG $=$ mPAP $-$ PCWP) may suggest existence of combined volume overload and pulmonary arteriopathy. To characterize such complexity, many have suggested that the hemodynamic definition of POPH be expanded to include mPAP >20, TPG >12, and PVR >3 Wood units.[3,11]

TABLE 97-2 Hemodynamic Patterns in Patients with Liver Disease

	mPAP	CO	PCWP	PVR	TPG
High cardiac output and vasodilated	↑	↑↑	↓	↓↓	N ↑
Fluid overload or diastolic dysfunction	↑	↑	↑↑	N	N
Portopulmonary hypertension	↑	↷	N	↑	↑

mPAP, mean pulmonary artery pressure (normal, <21 mm Hg); PCWP, pulmonary capillary wedge pressure (normal, ≤ 15 mm Hg); CO, cardiac output (normal, 4–6 L/min); PVR, pulmonary vascular resistance (normal, <3 Wood units: [mPAP–PWCP]/CO); TPG, transpulmonary gradient (normal, <12: mPAP–PCWP); N, normal.

Diagnosis

To establish a diagnosis of POPH, objective evidence (increased hepatic vein-free pressure to wedge pressure gradient) or clinical evidence of portal hypertension must be present. The presence and severity of POPH is not related to liver disease severity, and POPH can develop in patients with noncirrhotic portal hypertension. The diagnosis of POPH is often first suggested by an echocardiogram, but echocardiography is confounded by the previously noted hemodynamic changes seen in cirrhosis.[12] Therefore, an echocardiographically estimated peak pulmonary artery systolic pressure >38 mm Hg or signs of significant RV dysfunction should trigger confirmatory right heart catheterization.[13] This threshold was 100% sensitive in detecting POPH.[13]

Clinical Course

Patients with POPH appear to have worse clinical outcomes than patients with other types of PH. The French registry recorded the outcomes of 154 patients with POPH and included both treated and untreated subjects. Five-year survival was reported in 68% of patients. Multivariate analysis identified advanced liver disease severity and lower cardiac index as independent risk factors for mortality.[14]

The REVEAL (Registry to Evaluate Early and Long-term PAH Disease Management) registry for PH is a multicenter, observational study that has recorded the outcomes of 174 patients with POPH—the largest cohort to date. The data show that patients with POPH have poorer survival and higher all-cause hospitalization rates compared with patients with idiopathic or familial PH, despite the group with POPH having a more favorable initial hemodynamic profile than the others (Fig. 97-2).[15] Furthermore, when data were analyzed to derive a risk score for 1-year mortality for all patients presenting with PH, POPH demonstrated a hazard ratio of 3.6 compared to other etiologies.[16]

Management

POPH is classified as group 1 PAH, and, therefore, is a treatable category of PH using FDA-approved drugs.[11] However, POPH was excluded from the majority of clinical trials assessing use of these agents. Therefore, most data on treatment of POPH are derived from case series and single-center studies, as summarized in the following sections.

Endothelin Receptor Antagonists The endothelin receptor antagonists bosentan, ambrisentan, and macitentan are established treatments in group 1 PAH. Endothelin is a pulmonary vasoconstrictor and pro-proliferative agent, and its antagonism has been shown to improve exercise capacity and hemodynamics in patients with PH.

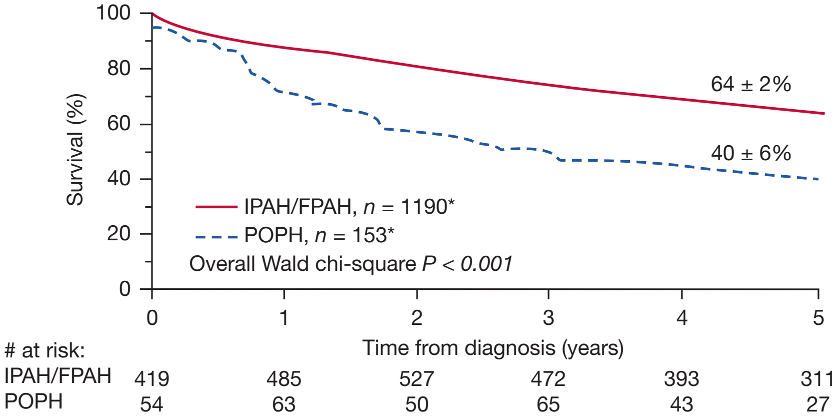

Figure 97-2 Five-year survival from the time of diagnosis of POPH versus IPAH/FPAH. *(Data from REVEAL registry. Only patients enrolled within 5 years of diagnosis were included in the 5 years survival from diagnosis curve. Chest. 2012;141(4):905–915.)*

Bosentan is a dual endothelin receptor antagonist (ET_A and ET_B). In small, single-center, uncontrolled, observational trials, POPH patients treated with bosentan have shown improvements in exercise capacity and hemodynamics.[17–19] Use of bosentan has been limited in this group due to its well-described hepatotoxicity occurring in a minority of patients (∼10%) with PH, but no underlying liver disease. The hepatotoxicity is likely related to the agent's inhibition of a bile salt transporter; the toxicity is usually reversible with drug discontinuation.[20]

Ambrisentan is a selective ET_A antagonist and is also FDA approved for the treatment of group 1 PAH. Hepatotoxicity has not been reported with this agent. A prospective, multicenter, open-label trial of ambrisentan in POPH reported a significant improvement in mPAP, PVR, and cardiac index with treatment with no significant change in 6-min walk distance.[21]

Macitentan is a newer dual endothelin receptor antagonist that is FDA approved for the treatment of group 1 PAH. A phase 4, multicenter, randomized, controlled trial found that macitentan significantly improved PVR by 35% and had a favorable hepatic safety profile but did not significantly improve 6-min walk distance.[22]

Phosphodiesterase Type 5 Inhibitors Two phosphodiesterase type 5 inhibitors (PDE5i), sildenafil and tadalafil, are currently FDA approved for the treatment of group 1 PAH. PDE5i act via the nitric oxide pathway and vasodilate the pulmonary vascular bed by inhibiting breakdown of cyclic guanosine monophosphate. Small, uncontrolled, observational trials reveal that sildenafil in POPH increases 6-min walk test distance and lowers levels of N-terminal pro b type natriuretic peptide, both of which correlate with a better prognosis in patients with PH.[23] The reported hemodynamic response has been mixed, with one observational trial reporting an improved PVR in three of five patients at 1 year,[24] and another showing improved PVR in all nine patients studied at follow-up, which ranged from 95 to 282 days.[25]

Soluble Guanylate Cyclase Stimulators Riociguat is the only soluble guanylate cyclase stimulator approved for the treatment of PAH. Mechanistically, it works by directly stimulating soluble guanylate cyclase to produce cyclic guanosine monophosphate. In PAH, riociguat improves 6-min walk distance, PVR, N-terminal pro b type natriuretic peptide levels, functional class, and time to clinical worsening. Although it was a small percentage (3%) of the cohort, this clinical trial did include POPH patients.[26]

Prostacyclin Receptor Agonists Selexipag is an oral selective IP prostacyclin receptor agonist approved for the treatment of PAH. In a multicenter, randomized clinical trial, selexipag met its primary composite endpoint of reducing mortality or a complication related to PAH primarily by reducing disease progression and hospitalization. POPH patients were not included in this pivotal trial, and there is little evidence supporting the use of selexipag in this subgroup.[27]

Prostacyclins Prostacyclin analogues are key agents in the treatment of PAH, and they are considered by many to be the agents of choice for the "sickest" patients. These drugs may be given orally, continuously via subcutaneous or intravenous routes, or intermittently in inhaled form. Current FDA-approved prostacyclins for intravenous use are epoprostenol and treprostinil. Treprostinil is also available for oral, subcutaneous, or inhalational administration. In the United States, iloprost is available only in the inhaled form, although it is given intravenously in Europe.

Uncontrolled, single-center series have consistently demonstrated that prostacyclin infusions result in significant improvements in mPAP, CO, and PVR in patients with POPH.[28–30] Furthermore, prostacyclin infusions have been used successfully to improve hemodynamics in patients with POPH in advance of safe pursuit of liver transplantation.[30–32] Limited data are available to support the use of oral or inhaled prostacyclins for POPH. Although iloprost has been shown to improve hemodynamics acutely, long-term effects are less certain.[33]

Liver Transplantation The history of liver transplantation in the setting of POPH is controversial. Early in the history of liver transplantation, the diagnosis of POPH was made in the operating room at the time of the procedure. Patients were neither previously treated for the disease nor under the care of a medical team familiar with critical care of patients with POPH. Not surprisingly, intraoperative mortality from decompensated right ventricular failure was high.[34] Long-term outcome also was adversely affected. Those with severe POPH had a 9-month posttransplant survival rate of 58%.[35] Consequently, severe POPH was considered a contraindication to liver transplantation.

With increasing clinical experience and the advent of new treatments for PH, transplant centers began to report both successful liver transplants in patients with POPH, and, in some, regression of POPH following surgery.[36,37] In 2006, a case series of eight sequential patients with POPH were treated with IV epoprostenol. Of the eight, seven had significant hemodynamic improvement. Six of the seven were listed for liver transplantation, and four of those listed were successfully transplanted. Of those transplanted, survival was 100% at 5 years.[26,32] Furthermore, in a retrospective study based on screening of patients with POPH with RHC, 5-year survival for those not transplanted or treated for PH was 15%, whereas 5-year survival for those who were treated for PH and transplanted was 64%.[33]

Because of the initial poor experiences with POPH patients undergoing liver transplantation, retrospective studies sought to identify risk factors for perioperative mortality. These series have suggested that if a patient has mPAP <35 mm Hg and normal right ventricular function, perioperative mortality approaches that of patients without POPH. However, if mPAP is >50 mm Hg at the time of transplant, mortality approaches 100%.[34,36]

Because there is a role for liver transplantation in selected patients with POPH, the United Network for Organ Sharing allows for upgrade points in the model for end-stage liver disease (MELD) score, facilitating liver transplantation. The MELD system prioritizes liver transplantation for the sickest patients, and the exception system allows extra points for those whose mortality risk is not reflected in their MELD score. Currently, the guidelines indicate that if a patient has a confirmed diagnosis of POPH and they are treated with pulmonary vasodilator therapy to attain mPAP <35 and a PVR <5 Wood units or mPAP of 35 to 45 with a PVR <3 Wood units, they are eligible for a MELD exception, or waitlist priority upgrade.[38]

Liver transplantation in these patients should be performed at a center experienced in pulmonary vascular disease, as the perioperative course may be complicated. Even in patients without POPH, a well-described "reperfusion syndrome" may occur at the time of allograft reperfusion. Reperfusion syndrome may cause acute elevations in mPAP and may induce acute, decompensated right ventricular failure in patients with POPH.[39] The use of intraoperative prostacyclin infusion, inhaled nitric oxide, or intravenous milrinone has been described in this emergent setting; results have been mixed.[3,40,41]

Limited data exist regarding the clinical course of POPH after liver transplantation. One-year posttransplant survival rates vary from 63% to 88%, while reported 5-year survival rates vary from 54% to 87%.[42] POPH progression, stability, improvement, and resolution have all been reported. In most of the cases, patients are able to wean from their prostacyclin infusion over a period of months, but some remain on oral pulmonary vasodilators. Available data suggest that 40% to 50% of patients may be able to be weaned from all pulmonary vasodilators, given enough time.[43,44]

Summary

POPH is an uncommon complication of liver disease, which is characterized by a progressive pulmonary arteriopathy, and which may result in right ventricular failure and death. Patients with POPH appear to have an increased mortality compared with those with similar levels of liver disease or with other types of PH. Specific protocols for optimal use of pulmonary vasomodulators for POPH are under investigation. However, patients exhibit improved hemodynamics and exercise capacity when receiving therapy for PH. The role of liver transplantation in this setting is arguable, but transplantation may be performed in carefully selected patients and may cure not only their liver disease, but also their POPH.

■ Hepatopulmonary Syndrome

HPS is a liver-induced pulmonary vascular disorder characterized by abnormal arterial oxygenation and a widened alveolar–arterial oxygen gradient. The widened gradient is the result of intrapulmonary vasodilation in the presence of hepatic disease or portal hypertension. Clinically, intrapulmonary vasodilation may occur with or without overt hypoxemia, depending on the severity of the disease. HPS increases mortality in patients with liver disease, is without specific therapy, and is completely curable with liver transplantation. Therefore, unlike POPH, the presence of significant HPS is considered an indication for liver transplantation.[3]

Epidemiology and Pathogenesis

The prevalence of HPS is reported as 4% to 32% in cohorts of cirrhotic patients undergoing liver transplant evaluation.[45,46] The pathogenesis is poorly understood but is thought to involve angiogenesis, as well as inadequate synthesis or metabolism by the impaired liver of pulmonary vasoactive substances, such as nitric oxide, prostaglandins, vasoactive intestinal peptide, endothelin, calcitonin, glucagon, substance P, and atrial natriuretic factor.[47] Nitric oxide has long been implicated in the pathophysiology of HPS, given its known pulmonary vasodilatory effects.[48,49] Endothelin also has been implicated in the pathophysiology of HPS. Although endothelin is often thought of as a vasoconstricting agent, and its inhibition is a common therapy for PH, endothelin's actions vary widely by the receptor to which it attaches. When endothelin 1 binds to the ET_A receptor, the effect is pulmonary vasoconstriction. However, when endothelin 1 attaches to the ET_B receptor, it enhances the activity of endothelial nitric oxide synthase and causes pulmonary vasodilation. In experimental models of HPS, the ET_B receptor has been demonstrated to be upregulated; in these animal models, the experimental HPS was reversed by ET_B receptor blockade.[50,51]

Whatever the underlying mechanism of HPS, patients develop IPVD that causes a ventilation–perfusion mismatch and diffusion limitation to oxygenation because of an increase in vascular diameter. The normal pulmonary capillary is 8 to 15 μm in diameter, but in HPS capillaries may dilate to 15 to 100 μm in diameter. Because of this alteration in the normal structure of the alveolar–capillary units, inhaled oxygen does not reach the center of the blood vessel, and some blood returns to the left heart still deoxygenated. In a very rare subset of patients the hypoxemia is the result of true shunt, and arteriovenous malformations occur with no communication with alveoli.

Clinical Features

Most patients with HPS present with symptoms of chronic liver disease, and a minority present with dyspnea as their primary symptom. Therefore, a high index of suspicion should be maintained to make a timely diagnosis. Patients may complain of platypnea (dyspnea with standing) or have the physical examination finding of orthodeoxia, which is defined as a Pa_{O_2} decrease of 5% or 4 mm Hg upon standing.[52] This combination of findings is attributed to the increases in intrapulmonary vasodilatation in the lung bases and, therefore, increased ventilation–perfusion mismatch in the standing position. Although the combination of findings is well described in HPS, it is neither common nor pathognomonic.[52]

On physical examination, patients with HPS may present with spider angiomata, clubbing on the digits, and peripheral cyanosis.[45] The chest radiograph is often normal, but it may reveal bibasilar increased interstitial markings, which may reflect vascular dilation in the bases.[53] Pulmonary function testing often reveals reduced diffusion capacity for carbon monoxide, which is out of proportion to other pulmonary function abnormalities.[54]

HPS has been reported in patients with both acute and chronic liver diseases. Most commonly, it is described in cirrhotics, but HPS has also been documented in the setting of noncirrhotic portal hypertension and acute and chronic hepatitis.[3,55] The severity of HPS does not correlate with the severity of the underlying liver disease.

Diagnosis

The diagnosis of HPS requires the presence of (1) cirrhosis or portal hypertension, (2) a widened age-corrected alveolar–arterial oxygen gradient (>15 mm Hg or >20 mm Hg if age >64), and (3) demonstration of intrapulmonary vasodilatation on a bubble contrast–enhanced transthoracic echocardiogram.

Bubble contrast–enhanced echocardiogram is the most sensitive test for the detection of intrapulmonary vasodilation. However, echocardiography is a qualitative examination in which saline is agitated and then injected into a peripheral vein. The agitation causes formation of microbubbles that are at least 15 μm in diameter. In normals, the microbubbles are trapped within the pulmonary capillary bed and absorbed. However, if intrapulmonary vasodilation is present, the bubbles traverse the pulmonary capillaries and appear in the left atrium approximately three to six cardiac cycles after their injection. Echocardiography can also identify an intracardiac shunt, in which case, the bubbles appear in the left atrium within three cardiac cycles.[56]

Intrapulmonary vasodilation may also be detected by technetium-labeled macroaggregated albumin lung perfusion scanning. In this examination, technetium-labeled macroaggregated albumin is injected intravenously and uptake is detected in the lungs and brain. In the absence of intrapulmonary or intracardiac shunt, the tracer is trapped within the pulmonary circulation and very little is observed on brain imaging. A fractional brain uptake >5% is considered abnormal. Although macroaggregated albumin scanning allows quantification of the shunt, it cannot differentiate between intracardiac and intrapulmonary shunt. One additional advantage of the macroaggregated albumin scan is that it is specific for HPS, even in the presence of intrinsic lung disease. Therefore, it may help to distinguish hypoxemia from HPS from that due to pulmonary parenchymal disease if both are present. Although macroaggregated albumin scanning is less sensitive than transthoracic echocardiography for detecting the presence of HPS, the magnitude of the shunt detected correlates poorly with the degree of hypoxemia.[56]

Arterial blood gases that quantify Pa_{O_2} and the alveolar–arteriolar oxygen gradient for HPS should be obtained with the patient seated at rest and breathing room air. Due to disease-associated alterations in ventilation–perfusion matching with positional changes, along with a propensity for increased pulmonary vasodilatation in the lung bases, hypoxemia may worsen with standing and improve in the supine position. Guidelines published in 2004 by the European Respiratory Society Task Force and recently reiterated by the International Liver Transplantation Society suggest subclassification of HPS according to level of hypoxemia: $Pa_{O_2} \geq 80$ mm Hg is considered mild; $Pa_{O_2} < 80$ mm Hg but ≥ 60 mm Hg is considered moderate; $Pa_{O_2} < 60$ mm Hg but $Pa_{O_2} \geq 50$ mm Hg is considered severe, and < 50 mm Hg is considered very severe.[3,57]

Since pulse oximetry is insufficiently sensitive as a noninvasive screening test, contrast-enhanced echocardiogram and arterial blood gas testing are needed for diagnosis.[58]

Clinical Course

The presence of significant HPS decreases exercise capacity, impairs quality of life, and increases mortality compared with patients without HPS who have a similar severity of liver disease.[52] Furthermore, the majority of patients with HPS progress over time; the average rate of decline in resting Pa_{O_2} is 5 mm Hg/year.[59] In one multicenter, prospective study, patients with HPS had a doubling in risk of death compared with patients without HPS, despite no differences in rates of listing for liver transplantation, performance of liver transplantation, age, sex, or race.[52] Guidelines recommend screening for HPS at the time of liver transplant evaluation.[3,60]

Management

No medical therapy has been shown to improve patients with HPS. Many agents have been tried unsuccessfully or with mixed results, including norfloxacin, β-blockade, nitric oxide inhibitors, nitric oxide, glucocorticoids, cyclooxygenase inhibitors, indomethacin, somatostatin, sorafenib, cyclophosphamide, and plasma exchange.[47,61,62] Supplemental oxygen is often administered in HPS and may ameliorate the symptoms of hypoxemia.

Liver Transplantation Liver transplantation is the only therapy proved to resolve HPS. Long-term follow-up reveals significant improvement or resolution of HPS in 85% of patients who undergo liver transplantation.[63–65] The time required for improvement in oxygenation is variable and may take up to 1 year or longer.

Hypoxemia due to HPS may complicate the postoperative course in liver transplantation. In a retrospective analysis of the United Network of Organ Sharing data, the finding of a preoperative $Pa_{O_2} \leq 44$ mm Hg was associated with increased postoperative mortality.[66] However, other reports suggest that liver transplantation may be safely performed in patients with HPS, including those with severe hypoxemia.[67,68]

Because of the increased mortality associated with HPS and the favorable outcome for liver transplantation, the United Network of Organ Sharing has instituted a MELD exception guideline for affected patients: if the diagnosis of HPS is confirmed with bubble contrast echocardiography and the patient's is $Pa_{O_2} < 60$ mm Hg, an application for a MELD exception may be submitted. The upgrade increases the patient's MELD score to 3 less than the median MELD score at transplant for transplant recipients within the transplant center's donor service area, regardless of the severity of liver disease.[69]

Summary

HPS is a liver-induced pulmonary vascular disorder characterized by intrapulmonary vascular dilation resulting in ventilation–perfusion mismatch and a diffusion limitation for oxygenation. No known medical treatment for HPS exists, and patients with HPS have a poorer prognosis than patients with liver disease without HPS. HPS is an indication for, and is curable by, liver transplantation.

■ Hepatic Hydrothorax

HH is defined as a pleural effusion (typically >500 mL) occurring in a patient with liver disease in the absence of an alternative cardiac or pulmonary source. HH may complicate management of cirrhosis, and it may contribute to morbidity.

Epidemiology and Pathophysiology

HH occurs in 6% to 10% of patients with end-stage liver disease. Its development is related to anatomic defects in the diaphragm, which allow fluid migration down a pressure gradient from the peritoneum into the negative pressure environment of the pleural space.[70,71] It is postulated that as ascites develops, intra-abdominal pressure increases and strains diaphragmatic tissue, which then weakens. Eventually, pleuroperitoneal blebs form and then rupture, creating a communication between the abdominal and pleural cavities. In general, these blebs are <1 cm in diameter and are more common in the right hemidiaphragm, perhaps as a consequence of the more muscular construct of the left hemidiaphragm.[72] Although HH usually occurs in the setting of ascites, HH may be present even when clinically apparent ascites is absent, making the diagnosis more challenging.[73,74]

Clinical Features

Clinical manifestations of HH include dyspnea, pleuritic chest pain, and nonproductive cough. HH is right sided in 85% of patients, left sided in 13%, and bilateral in 2%.[74] Pleural fluid analysis generally reveals characteristics consistent with ascitic fluid, with slight alterations due to the increased ability of the pleura to absorb free water. HH is transudative, with a total protein level <2.5 g/dL, lactate dehydrogenase fluid-to-serum ratio <0.5, and a total protein fluid-to-serum ratio <2.5. The serum-to-fluid albumin gradient is generally >1.1 g/dL.[70,74,75] Occasionally, patients present with hepatic chylothorax. In these cases, the fluid is also transudative, but the fluid-to-serum triglyceride level exceeds 1; in addition, the fluid-to-serum cholesterol ratio is high. Hepatic chylothorax is thought to arise from chylous ascites entering the pleural space through the previously described mechanism.[76]

Diagnosis

Diagnostic thoracentesis should be performed in the setting of hepatocellular carcinoma, fever, or pain. A prospective series investigating the clinical utility and risks of thoracentesis in the cirrhotic population demonstrated that 30% of patients have an alternative diagnosis to uncomplicated HH. The most common alternative diagnoses are SBEM (see below), pleural tuberculosis, or adenocarcinoma.[77] In another large prospective series, thoracentesis was safely performed in cirrhotic patients with mild coagulopathy (PT or PTT ≤2 × normal, platelet count of 50,000–99,000 [per μL]) without prophylactic plasma or platelet transfusion. Hence, the presence of a mild coagulopathy should not delay diagnostic evaluation.[78]

Spontaneous Bacterial Empyema

SBEM occurs when a previously existing HH becomes infected. The empyema portion of this term is a misnomer because diagnosis does not require purulent material in the pleural cavity, but rather refers to an infection diagnosed by pleural fluid cell count analysis. The diagnosis is made if the pleural fluid has a positive culture and the polymorphonuclear neutrophil count is >250 cells/mm^3, or, if the culture is negative, the fluid contains >500 polymorphonuclear neutrophils/mm^3. The sensitivity of the pleural fluid culture increases from 33% to 77% if blood culture bottles are directly inoculated at the bedside during the procedure.[77] The incidence of SBEM has been reported as 13% in hospitalized patients with cirrhosis and a pleural effusion. Simultaneous spontaneous bacterial peritonitis is a risk factor for the development of SBEM; however, up to 40% of cases are not associated with spontaneous bacterial peritonitis.[77,79] Mortality has been reported as high as 20%. Therefore, clinicians should maintain a high index of suspicion to ensure the diagnosis is made in a timely manner.

The most commonly identified bacterial pathogens in SBEM are *Escherichia coli*, *Klebsiella pneumoniae*, *Streptococcus* species, and *Enterococcus* species.[80] Third- or fourth-generation cephalosporins are the empiric treatment of choice until culture data are obtained. Chest tube insertion is not recommended unless frank pus is present in the pleural cavity, given the risks of complications from the procedure in this patient population.

Management

Medical and surgical interventions are employed in the management of HH. Each is described briefly in the subsequent sections.

Diuretics As is the case in management of ascites, the mainstay of treatment of HH is the establishment of negative sodium balance. Current guidelines for management of ascites call for a diet that entails 2 g/d sodium restriction, along with the administration of furosemide and spironolactone in a ratio of 40 mg of furosemide to 100 mg of spironolactone daily. Despite aggressive medical management, 20% to 26% of cirrhotics with ascites are refractory to medical treatment.[82]

Thoracentesis Thoracentesis can be performed safely in patients with cirrhosis, even in the face of mild coagulopathy. Therefore, therapeutic thoracentesis may be performed to relieve dyspnea in patients with HH that is refractory to dietary sodium restriction and diuretics. Traditionally, removal of no more than 2 L of fluid is recommended at one time because of the risk of re-expansion pulmonary edema and hypotension. However, whether the risks of large-volume thoracenteses apply to this population of patients is unclear. Large-volume thoracenteses have been performed safely with close patient monitoring and measurement of end-expiratory pleural pressure. The recommended goal for end-expiratory pleural pressure is >-20 cm H_2O.[84] Data in support of use of intravenous infusion of albumin to avoid hypotension during thoracentesis are lacking.

Large-volume paracentesis may also be considered for patients in respiratory distress in patients due to ascites or HH. Paracentesis improves dyspnea and lung function within 2 h of fluid removal. The procedure may provide symptomatic relief for patients with HH and a lower risk than thoracentesis.[85]

Tube Thoracostomy Although tube thoracostomy may seem an attractive option in patients with recurrent HH, multiple reports have confirmed a high complication rate. Specifically, pneumothorax, hemothorax, empyema, electrolyte abnormalities, and hepatorenal syndrome have all been reported. In one series of 59 patients with cirrhosis and chest tube placement, a complication rate of 80% and mortality rate of 27% were reported. Therefore, this intervention should be avoided.[86] Newer studies evaluating the use of indwelling pleural catheters in HH have reported lower complication rates of 36%, suggesting that indwelling pleural catheters may be considered in a select group of patients with refractory HH as a palliative treatment.[87]

Transjugular Intrahepatic Portosystemic Shunt Transjugular intrahepatic portosystemic shunt (TIPS) reduces portal pressure by creating a shunt between the portal and hepatic veins. TIPS placement is the treatment of choice for a refractory HH. In a series of 73 patients with refractory HH who underwent TIPS placement, 79% had a complete or partial response to the procedure; long-term survival rates were consistent with the severity of liver disease.[88]

TIPS placement is not appropriate for all patients, despite its success in patients with HH and ascites. Patients with severely decompensated liver disease may decompensate further following the procedure because of the shunt's negative effect on hepatic blood flow. In addition, shunting blood from the portal to hepatic vein increases right atrial and pulmonary artery pressure and may further compromise patients with right-sided heart failure or PH.[89] Therefore, moderate to severe pulmonary hypertension is considered a contraindication for TIPS placement.[90] In a high-risk patient, the option of liver transplantation should be discussed before proceeding with TIPS, since transplantation can be used as a "safety net" for clinical decompensation. In a carefully selected population with refractory HH, TIPS is the standard of care.

Surgical Intervention Small case series have documented success in treating HH using open thoracotomy or video-assisted thoracoscopy.[91,92] The procedures are based on identification of diaphragmatic defects and their closure with subsequent pleurodesis. Surgical pleurodesis has a documented success rate of 73% to 100% in preventing recurrence of HH; however, high complication rates have been noted. In one series of 18 patients, a success rate of 48% was noted, but 3-month mortality was 38.9%.[93] Therefore, although video-assisted thoracoscopy with pleurodesis may be an option for patients with refractory HH, larger trials are needed to assess safety before this procedure is considered a standard recommendation.

Liver Transplantation Liver transplantation is curative for HH and should be the primary intervention for patients with refractory disease. The presence of HH does not affect ventilator days in the immediate postoperative period, nor does it increase long- or short-term posttransplant mortality.[94]

Summary

HH may complicate the clinical course of a patient with cirrhosis. A high index of suspicion is needed to diagnose SBEM and to avoid the high mortality rate associated with this condition. Dietary sodium restriction and diuretic use are the mainstays of therapy for pleural effusion, but refractory patients may require therapeutic thoracentesis or TIPS for control. Ultimately, liver transplantation is curative for refractory HH.

PULMONARY COMPLICATIONS OF GASTROINTESTINAL DISEASE

In addition to the aforementioned pulmonary complications of liver disease, diseases of other intra-abdominal organs may have significant effects on the lungs. These include disorders of the esophagus, bowel, and pancreas. Pulmonary complications of renal disease are discussed separately, below.

Gastroesophageal Reflux Disease

Gastroesophageal reflux disease (GERD) affects up to 20% of the population.[95] GERD is characterized by reflux of gastric contents into the esophagus due to failure of the protective mechanisms of the upper gastrointestinal tract (see below) and produces symptoms of mucosal damage. In addition to the common symptom of "heartburn," reflux may be associated with a range of extraesophageal symptoms, including chronic cough, asthma, IPF, bronchiectasis, aspiration pneumonia, and COPD.[96]

Pathophysiology

Normally, several antireflux mechanisms protect the esophagus and airways from gastric contents: (1) Esophageal peristalsis allows clearance of regurgitated materials; dysmotility is associated with GERD. Abnormal peristalsis is reported in 40% to 50% of affected patients.[97] (2) The lower esophageal sphincter creates a barrier between the esophagus and the stomach. An incompetent lower esophageal sphincter is associated with reflux. (3) The diaphragm helps prevent reflux through external compression of the lower esophagus. Maintenance of a low thoracoabdominal pressure gradient may be important in minimizing reflux. Obese patients have higher incidence of GERD, which may be a reflection of the increase in intra-abdominal pressure that occurs with obesity.[98,99]

GERD-related pulmonary disease occurs with gross aspiration of large volumes of gastric contents, recurrent microaspiration, or, possibly, a GERD-induced reflex that causes an increase in vagal tone and resultant bronchospasm.[100,101]

Diagnosis

Diagnostic testing includes ambulatory esophageal pH monitoring and esophageal impedance testing.

Ambulatory Esophageal pH Monitoring Twenty-four hour ambulatory pH monitoring is considered the "gold-standard" diagnostic maneuver.[102] Until recently, this procedure required a catheter-based system, inserted through the nose and placed near the squamocolumnar junction in the esophagus. Various symptom scoring techniques allow linking of patient symptoms and reflux events to determine an association between the two and potential therapeutic intervention. However, the catheters employed are uncomfortable and external, and data suggest that the catheter itself may alter patient activity enough to impede the diagnostic accuracy. Recently, a capsule-based system with wireless data transmission has been developed, allowing increased patient comfort and incremental data collection to aid in the diagnosis of GERD. Currently, the American College of Gastroenterology recommends ambulatory pH monitoring for patients with negative findings on esophagogastroduodenoscopy who are being considered for an antireflux procedure, and for those failing therapy with a proton pump inhibitor. Symptom correlation during the procedure is recommended, although its diagnostic role is unproven for extraesophageal symptoms other than chest pain.[103]

Esophageal Impedance Testing Esophageal impedance testing measures changes in tissue resistance to electrical current generated in adjacent electrodes encompassed within an esophageal catheter assembly. The setup allows for identification of retrograde or antegrade food bolus movement along the esophagus. It does not differentiate between acidic, weakly acidic, or alkaline material; therefore, the technique is often combined with pH monitoring. Impedance testing is more sensitive than pH monitoring alone for detecting the presence of GERD, although it has not been validated for the evaluation of extraesophageal manifestations of GERD.

Clinical Features

Several potential pulmonary associations of underlying GERD should be considered, including asthma, IPF, and chronic cough.

GERD and Asthma The nature of the relationship between GERD and asthma is a subject of controversy, but GERD is common and present in 15% to 83% of asthmatics.[104–107] Several mechanisms by which acid reflux may be related to bronchoconstriction have been described in the literature. Acid reflux into the distal esophagus is postulated to cause bronchoconstriction through vagal stimulation, increased bronchial reactivity, and microaspiration.[108,109]

Declines in esophageal and tracheal pH coincide with reduced airflow, suggesting that microaspiration of gastric acid may lead to bronchoconstriction.[110] Interestingly, some studies have actually suggested the converse—that asthma exacerbations promote GERD by increasing the pleural–peritoneal pressure gradient by lowering pleural pressure,[111] by promoting lower esophageal sphincter relaxation,[112] or, perhaps, by a direct effect of bronchodilators on the lower esophageal sphincter.[113]

Asthma guidelines suggest that GERD be treated in asthmatics who have complaints of heartburn or frequent night-time symptoms. However, in a study of more than 400 patients with poorly controlled asthma who received a proton pump inhibitor, treatment had no effect on respiratory exacerbations compared with those who received placebo.[114] Proton pump inhibitor therapy is generally not indicated for patients with asthma and no GERD symptoms. Current guidelines suggest that treatment of GERD may improve asthma control, citing grade B evidence.[115] Lifestyle measures, such as weight loss and head of bed elevation, may be helpful.

GERD and Idiopathic Pulmonary Fibrosis Recently, a clinical association has been noted between GERD and IPF; the estimated prevalence of GERD in the IPF population is 90%. This association coincides with a recent shift in thought regarding the etiology of IPF, away from one of active inflammation, and toward one of alveolar injury and maladaptive repair, resulting in fibroblast proliferation and, ultimately, lung fibrosis.[116] A strong association between IPF and GERD has been documented in prior studies.[117] In addition, one retrospective review of 14 patients awaiting lung transplantation for IPF-reported stabilization, but not improvement, of lung function with laparoscopic Nissen fundoplication, but a small phase 2 study of fundoplication did not find significant clinical improvement.[118,119] The mechanistic relationship between IPF and GERD, the best diagnostic modality for assessment, and the optimal treatment are areas of active investigation. Based on the available data, the most recent IPF management guidelines recommended regular antiacid treatment in patients with IPF.[118]

GERD and Chronic Cough GERD is a well-known cause of chronic cough, and treatment of GERD is considered a mainstay in initial therapy for chronic cough. GERD was identified as a cause of chronic cough in 1981, and since then data have emerged ranking it as the second most common cause.[120,121] Twenty-eight percent of patients with chronic cough that improves with GERD therapy deny typical symptoms of GERD.[122] Although 24-h esophageal pH monitoring is considered the most sensitive test for GERD in chronic cough, it is expensive and has limitations. Therefore, the American College of Chest Physicians guidelines on the treatment of cough recommend empiric therapy for GERD in patients with GERD symptoms whose cough is likely related to reflux.[123] Recommended treatment includes a combination of weight loss in overweight or obese patients, head of bed elevation, and avoidance of meals within 3 h of bedtime and medical therapy.[123]

Treatment

The three main treatments for GERD are antacids, histamine-2 receptor antagonists, and proton pump inhibitors. Proton pump inhibitors have established efficacy over other options and are now the mainstay of therapy. Surgical therapy using Nissen fundoplication is reserved for refractory cases; it may be performed through an open incision or laparoscopically. Finally, new, less invasive procedures to improve the function of the lower esophageal sphincter are under investigation.

Summary

GERD is a common condition, affecting up to 20% of the population. The reflux of gastric contents into the esophagus may exacerbate pulmonary conditions such as IPF, asthma, and COPD, but neither a causal relationship nor a significant response to therapy has been documented in these conditions. GERD is a frequent cause of chronic cough; treatment with a PPI may ameliorate symptoms in affected patients.

■ Inflammatory Bowel Disease

Pulmonary complications associated with inflammatory bowel disease (IBD) were first described in 1976 in a small series of patients who had both IBD and chronic bronchitis.[124] Since that time, a connection between IBD and pulmonary disease has been increasingly recognized, but the pathophysiology of the relationship remains unclear. Both Crohn's disease and ulcerative colitis have been associated with a variety of respiratory problems: airway disease, parenchymal lung disease, serositis, and pulmonary vascular disease.

Airway involvement, the most common pulmonary disorder in IBD, may present as bronchiectasis, chronic bronchitis, tracheitis, subglottic stenosis, or, rarely, small airway disease.[125,126] Pulmonary parenchymal involvement is less common, but cryptogenic organizing pneumonia, eosinophilic pneumonia, granulomatous lung disease, nonspecific interstitial pneumonitis, necrobiotic nodules, and sarcoidosis have been described in IBD.[125,127,128] The association between the gastrointestinal and pulmonary "inflammation" is unclear, but the majority of these pulmonary complications appear to be steroid-responsive.[127] Finally, patients with IBD have a twofold higher incidence of thromboembolic events than do age-matched controls; the risk of pulmonary embolism does not appear to be related to disease activity.[129]

PULMONARY COMPLICATIONS OF ACUTE PANCREATITIS

Acute pancreatitis is an acute inflammation of the pancreas, which may cause both systemic inflammatory response syndrome and multisystem organ dysfunction syndrome (Chapter 142). When multisystem organ dysfunction accompanies pancreatitis, mortality is reported at 15% to 20%.[130,131] Pulmonary complications of pancreatitis are reported in 75% of cases. The most common presentations are hypoxemia without radiologic abnormalities, pleural effusions, or, in the sickest patients, acute respiratory distress syndrome (ARDS).[132,133]

■ Hypoxemia

Hypoxemia occurring early in the course of pancreatitis, even prior to development of radiologic abnormalities, is well documented and a risk factor for ARDS and increased mortality.[132,134,135] Early hypoxemia is an independent predictor of poor outcome and is included in the pancreatitis severity scores of both Ranson and Imrie.[136,137]

Several inflammatory mechanisms are implicated in development of the early lung injury of pancreatitis. Increased permeability at the microvasculature leads to alveolar filling and decreased lung compliance. In addition, nitric oxide–related endothelial cell damage occurs, with leukocyte activation and adhesion at the level of the pulmonary microvasculature. Furthermore, the systemic release of pancreatic elastase may contribute to inflammation in the lung parenchyma, and fibrinogen metabolism may allow fibrin deposition in alveoli. Collectively, these processes transform the relatively benign environment of the alveolus into an inflammatory milieu and profoundly affect gas exchange.

■ Pleural Effusion

The presence of a pleural effusion is a marker of pancreatitis severity and occurs in 84% of patients with severe disease, but only 8.6% of patients with mild disease.[143] The presence of a pleural effusion in acute pancreatitis is associated with increased in-hospital mortality.[138] Approximately two-thirds of the effusions are left sided, but they may be bilateral or right sided.[139] The effusion is usually small and may be hemorrhagic. Analysis of pleural fluid reveals a very high amylase and elevations in protein and lactate dehydrogenase levels when compared with serum.[140] Pleural effusions in acute pancreatitis may be caused by transdiaphragmatic lymphatic blockage or arise as a sympathetic effusion due to associated inflammation. A rare complication is a pancreaticopleural fistula, in which the pancreatic duct or a pseudocyst empties posteriorly into the retroperitoneum, tracking up the mediastinum and rupturing into the pleural cavity. The resulting effusions are generally massive and require evacuation and correction of the anatomic defect.[141,142] When less than massive, the effusions are treated conservatively and typically resolve with resolution of the pancreatitis.

■ Acute Respiratory Distress Syndrome

ARDS develops in approximately 15% to 20% of patients with acute pancreatitis. When present, mortality rises >50%.[143] The pathophysiologic basis of ARDS in acute pancreatitis is poorly understood, but inflammatory cytokines have been implicated (Chapter 140). Specifically, trypsin injures the pulmonary vasculature and promotes leukostasis and increased vascular permeability.[144,145] Phospholipase A2 (PLA2), which removes fatty acids from phospholipids, may act on surfactant, contributing to respiratory failure.[146,147] Multiple other mediators have been implicated, including IL-6, IL-8, NO, TNF-α, and substance P. Whatever the underlying mechanism, ARDS is the basis for 50% to 90% of deaths in acute pancreatitis.[148] Treatment is supportive and incorporates an alveolar protective ventilator strategy (Chapter 141).

Summary

Acute pancreatitis may cause a systemic inflammatory response syndrome or multisystemic organ dysfunction. One of the early signs of ensuing multisystem organ dysfunction may be hypoxemia, which is a risk factor for the later development of ARDS and early mortality. Pancreatitis is often accompanied by a pleural effusion, which is exudative and characterized by a high amylase level. In general, these effusions may be handled conservatively. ARDS occurs in 15% to 20% of patients with pancreatitis and is the cause of death in most who do not survive the bout of pancreatitis.

PULMONARY COMPLICATIONS OF RENAL FAILURE

Several notable associations exist between respiratory disease and renal failure, including PH and metastatic pulmonary calcification.

■ Pulmonary Hypertension and Renal Failure

PH associated with chronic kidney disease (CKD) is encompassed within group 5 of the World Health Organization classification of PH (PH with unclear or multifactorial causes).[11,149] CKD is defined by a reduced glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 for ≥3 months. Screening for PH in CKD is accomplished using transthoracic echocardiography and estimation of right ventricular systolic pressure. Generally, a right ventricular systolic pressure >35 mm Hg is considered "abnormal" in patients with CKD.[149] Subsequent to screening, accurate characterization and definitive diagnosis of PH in CKD requires right heart catheterization. Patients with CKD are complex with respect to the many factors, acting individually or in combination, that may contribute to PH (Table 97-3).[150,151]

The frequency of PH in CKD has been reviewed extensively; findings depend on the stage of CKD, dialysis methods and duration, and method of assessment for PH (i.e., noninvasive transthoracic

TABLE 97-3 Common Hemodynamic Profiles in Patients with Chronic Kidney Disease (CKD)

CKD Associated Condition	mPAP	CO	PCWP	PVR
Chronic volume overload	↑	N	↑↑	N
Anemia	↑	↑	N	N
Increased cardiac output due to AV fistula	↑	↑	N	↓N
Left ventricular dysfunction (usually diastolic)	↑	N	↑	N↑

mPAP, mean pulmonary artery pressure (normal, <21 mm Hg); CO, cardiac output (normal, 4–6 L/min); PCWP, pulmonary capillary wedge pressure (normal, ≤15 mm Hg); PVR, pulmonary vascular resistance (normal, <3 Wood units: [MPAP–PWCP]/CO); N, normal.

echocardiography vs. right heart catheterization).[149,151] The incidence of PH in CKD varies from 9% to 39% in non-dialysis-dependent patients and up to 82% for those on hemodialysis. Patients undergoing peritoneal dialysis appear to have a lower incidence of PH than do patients on hemodialysis.[152] Precapillary PH (increased MPAP, normal PCWP, increased PVR) complicating CKD is present in approximately 25% of patients undergoing invasive hemodynamic evaluation, suggesting some patients may have intrinsic pulmonary vascular disease.[153] Often, other comorbidities such as COPD or sleep apnea exist and may contribute to PH as well.

The finding of PH on TTE in dialysis patients has ranged from 29% to 47% and is associated with increased all-cause mortality.[154,155] Conversely, CKD is common among patients with PAH and also associated with worse survival.[16] In a study of kidney transplant candidates, pretransplant severity of PH correlated significantly with worse posttransplant survival.[156] Echocardiographic PH has also been associated with posttransplantation allograft failure.[157]

The pathogenesis of PH in the setting of CKD is not well understood but may be related to endothelial dysfunction, alterations in nitric oxide signaling, and elevations in circulating vasoconstrictors, such as endothelin 1 and angiotensin II.[158]

Summary

The pathogenesis of, and optimal treatment regimen for, PH in CKD is poorly understood. The presence of PH is associated with a poor outcome in patients on dialysis and in those who undergo renal transplantation.

■ Metastatic Pulmonary Calcification

Metastatic calcification in the lung is a well-documented complication of CKD that requires hemodialysis. It is fairly common and present in 60% to 75% of autopsy specimens of patients on hemodialysis.[159,160] Despite this common pathologic finding, patients are generally asymptomatic, and only a minority have disease visible on the chest radiograph.[159]

Metastatic calcification in patients with CKD is thought to arise from several mechanisms. Chronic metabolic acidosis from renal failure leaches calcium and phosphate from bone. In addition, when bicarbonate is used for hemodialysis, a transient alkalosis may predispose to calcium deposition in tissue.[160,161] Secondary hyperparathyroidism, which is common in CKD, results in increased calcium and phosphate release from bone. Finally, decreased clearance of phosphate due to CKD results in an increased calcium-phosphate product and further salt deposition.[162] Deposition of calcium phosphate, the primary salt, is generally benign. However, the radiographic finding may result in a workup for pulmonary infiltrates. In difficult cases, differentiating metastatic calcification from pneumonia or edema is most definitively done using ^{99m}Tc-MDP bone scintigraphy, which identifies a calcified focus in the lungs.[163] Treatment is centered on lowering the patient's calcium-phosphate product with medication and dialysis. Although the majority of cases are benign in course, some are associated with progressive dyspnea, restrictive physiology, low diffusing capacity, hypoxemia, respiratory failure, and death.[164,165]

CONCLUSIONS

Intra-abdominal pathology may have distant effects on the pulmonary vasculature, pulmonary parenchyma, or pleural space. This chapter has provided a comprehensive overview of various pulmonary complications of intra-abdominal disease. Liver disease is associated with pulmonary vascular disorders, such as POPH and HPS, two conditions that impact liver transplant eligibility and prioritization, as well as pleural disorders such as HH and SBEM. GERD may exacerbate conditions such as asthma and IPF and has been associated with chronic cough, while IBD has been associated with varied pulmonary conditions, including airways disease, parenchymal disease, and an increased risk of thromboembolic disease. Acute pancreatitis can lead to multiorgan system dysfunction, hypoxemia, pleural effusions, and ARDS. Both PH and metastatic pulmonary calcification can occur in the setting of renal failure, and the presence of PH in CKD is associated with impaired survival. This chapter highlights the importance of recognizing the diverse pulmonary complications of intra-abdominal disease.

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PART 14

Sleep and Sleep Disorders

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CHAPTER 98

Sleep Apnea Syndromes: Central and Obstructive

Grace W. Pien
Ilene M. Rosen
Barry G. Fields

HISTORY OF SLEEP-DISORDERED BREATHING

Sleep-disordered breathing (SDB) is an extremely common disorder associated with significant morbidity. Recognition of its relevance in medicine is relatively recent, although clinical reports of SDB were first made in the 19th century.[1] Likely influenced by such observations, descriptions of an entity constituting obesity and extreme somnolence were highlighted in the character narrative of Joe in Charles Dickens's series *Posthumous Papers of the Pickwick Club,* first published in 1837.[2] Dickens described Joe as a loud snorer who was obese and excessively somnolent—the classic description of Pickwickian syndrome. Sir William Osler in 1918 was credited with first linking the relationship between obesity and Pickwickian syndrome.[3] In the mid-20th century, further work led to the association of Pickwickian syndrome with alveolar hypoventilation by Burwell et al. in 1956, and periodic cessation of respiration by Drachman and Gumnit in 1962.[4,5]

Over the last 40 years, we have begun to understand the pathogenesis of sleep apnea and have developed effective diagnostic and treatment modalities for this common disorder. Gastaut et al.[6] in 1965 showed that cessation of respiration was due to obstruction of the upper airway, and obstructive sleep apnea (OSA) was recognized. In 1972, a conference organized by Lugaresi and his Bologna (Italy) group, entitled "Hypersomnia and Periodic Breathing," served as a springboard for the growth of interest and research in SDB.[7] Guilleminault et al.[8] coined the terms *sleep apnea syndrome* and *obstructive sleep apnea syndrome (OSAS)* in 1976 to underscore that airway obstruction during sleep was not restricted to obese subjects.

As the understanding of the etiology of OSA increased, treatment options began to emerge. In 1969, a case report describing treatment of OSA in a patient with tracheostomy was published.[9] The first reports demonstrating reversal of OSA with positive airway pressure (PAP) did not occur until more than 10 years later.[10,11] The role of weight loss and its shortcomings in resolution of OSA were noted by Fishman in 1972.[12]

SLEEP APNEA DEFINITIONS

Adult SDB is present when repetitive apneas (episodes of near or total breathing cessation) and hypopneas (episodes of decrement in airflow) occur during sleep, usually associated with sleep fragmentation, arousals, and/or reductions in oxygen saturation. The most recent American Academy of Sleep Medicine (AASM) Scoring Manual[13] defines an apnea as a drop in the peak respiratory signal (using an oronasal thermal sensor, PAP flow, or alternative sensor) of ≥90% from baseline; in addition, the drop must be ≥10 s in duration.

Apneas should be classified as obstructive (in which there is no airflow despite continued respiratory effort), central (no airflow and no respiratory effort), or mixed (events initially appear central in origin, with respiratory effort occurring during the latter portion of the same episode). Notably, neither an oxygen desaturation nor an arousal is required to identify an apnea.

On the other hand, desaturations and arousals *are* generally necessary to define hypopneas. In the past, hypopnea definitions varied substantially according to the degree of airflow limitation expected, the magnitude of oxygen desaturation needed, and by whether the definition included events associated with an arousal but not oxygen desaturation.[14,15] The AASM Scoring Manual[13] currently defines a hypopnea as a drop in the peak respiratory signal (using an oronasal thermal sensor, PAP flow, or alternative sensor) of ≥30% from baseline; the drop must be ≥10 s in duration, *and* there is a ≥3% (option: ≥4%) oxygen desaturation from baseline, *or* the event is associated with an arousal from sleep apparent on the electroencephalogram (EEG).

The option to invoke a 4% desaturation instead of a 3% desaturation in the hypopnea definition impacts reported disease prevalence significantly.[16,17] Although both physiologic and epidemiologic studies have demonstrated that hypopneas produce the same clinical consequences as apneas, evolving hypopnea definitions can make it challenging to compare sleep apnea severity and associated consequences across different study populations.[18] Delineating obstructive (no airflow despite continued respiratory effort) and central (no airflow and no respiratory effort) hypopneas remains optional. In addition, the term *respiratory effort–related arousal (RERA)* is sometimes used to designate a series of breaths characterized by increasing effort leading to an arousal from sleep that does not meet the criteria for apnea or hypopnea.[19]

Currently, the apnea–hypopnea index (AHI, number of apneas and hypopneas per hour of sleep) is the standard metric used to describe the severity of sleep apnea.[13] In older papers, the term *respiratory disturbance index (RDI)* was often used interchangeably with AHI. More recently, some authors have included the number of RERAs per hour of sleep in the RDI definition, that is, number of apneas, hypopneas, and RERAs per hour of sleep. Nevertheless, neither AHI nor RDI take into consideration other characteristics of SDB such as the magnitude of oxygen desaturation or duration of hypoxia. There is recent evidence that these parameters can be better predictors of cardiovascular disease than AHI/RDI.[20] Azarbarzin et al. evaluated the association of "hypoxic burden" with increased cardiovascular disease (CVD) mortality in 7854 adults age 40 and older.[21] Hypoxic burden was defined as the area under the desaturation curve from pre-event baseline during respiratory events. The authors found that elevated hypoxic burden significantly predicted CVD mortality in a dose–response manner, and it was a stronger predictor of CVD mortality than was AHI.

The respiratory event index (REI) is another metric of OSA severity being used more commonly. This terminology was introduced to differentiate respiratory indices obtained from in-laboratory polysomnography (PSG) with those derived from home sleep apnea testing (HSAT). The REI is the total number of apneas and hypopneas per hour of monitoring time[13] since, unlike PSG-defined AHI, total sleep time is only estimated using HSAT. Although more studies are using REI as a primary determinant of OSA presence and severity,[22] there is concern for OSA severity bring underestimated,[23] since total sleep time is overestimated.

■ Obstructive Sleep Apnea

OSA is defined by the presence of repetitive episodes of upper airway obstruction during sleep. An AHI of at least 5 events/h is commonly used to define OSA, with obstructive or mixed (rather than central) events accounting for more than 50% of the total.[13] OSAS is usually defined by an AHI of at least 5 events/h and persistent complaints of excessive daytime somnolence, unrefreshing sleep, or fatigue.[24] Other OSA definitions suggest that OSA be diagnosed if the AHI is at least 10 to 14 events/h, or in cases in which the AHI is between 5 and 14 events/h and documented hypertension, ischemic heart disease, history of stroke, or symptoms of excessive daytime sleepiness, impaired cognition, mood disorders, or insomnia exist.[25,26]

OSA is often classified as mild, moderate, or severe according to the AHI. A common scheme is 5 to <15 (mild), ≥ 15 to ≤ 30 (moderate), >30 events/h (severe).[27] These definitions were based on expert consensus. Some authors have suggested that severity should be defined by associations with adverse clinical outcomes rather than the event index.[28,29] Changes in clinical hypopnea definitions by organizing bodies such as the American Academy of Sleep Medicine (AASM) have also provoked debate over parameters of disease severity.[13,17,30]

In the past, the term *upper airway resistance syndrome (UARS)* has been used to describe symptoms of sleepiness and fatigue in the setting of milder SDB not meeting criteria for apneas and hypopneas.[31] Advances in detection of SDB events (e.g., with nasal pressure) and the inclusion of events associated with arousals in the hypopnea definition have likely eliminated the need to designate UARS as a separate entity.[15,32] These individuals are now likely to be diagnosed with OSA. Debate continues as to whether some nonobese individuals may have a hypersensitive arousal response to repetitive increased respiratory effort that is distinct from OSA.[33–35]

■ Central Sleep Apnea

Central sleep apnea (CSA) is much less common than OSA and is characterized by a transient cessation of rhythmic breathing. It is defined as repeated episodes of apnea in the absence of respiratory muscle effort and is observed on the polysomnogram as an absence of both nasal–oral airflow and thoracoabdominal excursion.[36] A number of etiologies for CSA have been recognized, among which congestive heart failure (CHF) and stroke are the most common.[37–39] Patients with CSA experience sleep fragmentation and can report similar daytime symptoms to those with OSA.

■ Obesity Hypoventilation Syndrome

Obesity hypoventilation syndrome (OHS), or the Pickwickian syndrome, is defined by obesity (BMI ≥ 30 kg/m^2) and hypoventilation with daytime hypercapnia in the absence of other causes for hypoventilation.[24] Thus, OHS should be regarded as a diagnosis of exclusion. Notably, while 90% of patients with OHS have been estimated to have OSA, the presence of OSA is *not* necessary for the diagnosis of OHS.[40,41] Conversely, 10% to 15% of sleep apnea patients have been noted to have daytime hypercapnia and can be classified as having concomitant OHS.[42] OHS is discussed more fully in Chapter 99.

PATHOGENESIS OF OBSTRUCTIVE SLEEP APNEA

The pathogenesis of OSA involves both anatomic and neurologic components. The upper airway is a complicated structure that performs multiple physiologic functions, including vocalization, respiration, and deglutition. The upper airway extends from the posterior margin of the nasal septum to the larynx and has a paucity of rigid bony support. It is divided into four anatomic regions (Fig. 98-1): the *nasopharynx*—the region between the nares and the hard palate; the *retropalatal oropharynx*—the region between the hard palate and the caudal margin of the soft palate; the *retroglossal oropharynx*—the region between the caudal margin of the soft palate and the base of the epiglottis; and the *hypopharynx*—the region from the base of the tongue to the larynx.

The major contributors to the airway boundaries include the soft palate and tongue anteriorly; the pharyngeal constrictor muscles, lymphoid tissue, parapharyngeal fat pads, and mandibular rami laterally; and the pharyngeal constrictor muscles posteriorly.[43,44] The soft tissue and craniofacial (bony) structures in the retropalatal and retroglossal regions contribute to the specific morphology of the airway of a given individual.[44] Collapse of the upper airway reduces its airway intraluminal diameter and increases airway resistance, leading to the apneas and hypopneas that characterize OSA.[45,46] Figure 98-1 displays a midsagittal magnetic resonance image in a normal individual in which the retropalatal and retroglossal regions are outlined. This midsagittal image also highlights the airway, tongue, soft palate, mandible, and subcutaneous fat. The lateral upper airway soft tissue structures of the retropalatal region (that is, the lateral pharyngeal walls and lateral parapharyngeal fat pads) are depicted in Fig. 98-2.

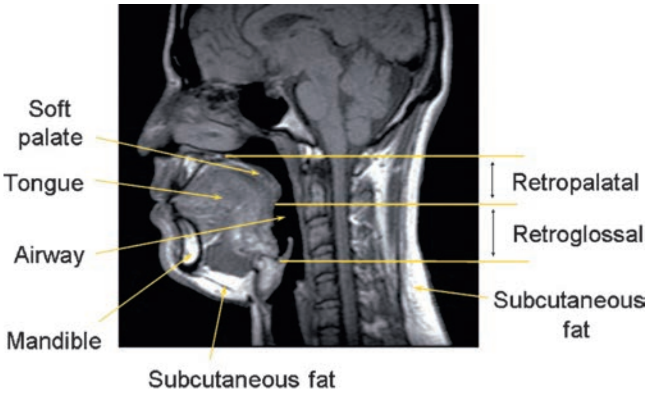

Figure 98-1 Midsagittal magnetic resonance (MR) image in a normal individual demonstrating the anatomic regions of the upper airway and relevant craniofacial and soft tissue structures. The retropalatal (RP) region is defined from the level of the hard palate to the distal margin of the soft palate; the retroglossal (RG) region is defined from the distal margin of the soft palate to the base of the epiglottis. In patients with OSA, obstruction usually occurs in the retropalatal or retroglossal levels or at both locations. *(Reproduced with permission from Schwab RJ, Gupta KB, Gefter WB, et al. Upper airway and soft tissue anatomy in normal subjects and patients with sleep-disordered breathing. Significance of the lateral pharyngeal walls. Am J Respir Crit Care Med. 1995;152(5 Pt 1):1673–1689.)*

Anatomic factors are clearly a major contributor to the propensity for airway collapse during sleep. In addition, the critical role of neuromechanical control of the upper airway in the pathophysiology of OSA is becoming increasingly well understood.

■ Anatomic Features That Predispose to Obstructive Sleep Apnea

The extrathoracic upper airway lacks a robust support framework of cartilaginous rings and therefore is at risk for collapse due to extraluminal tissue pressure exerted by circumferential craniofacial and soft tissue structures and negative pressure associated with inspiration. Changes in pharyngeal transmural pressure, defined as the difference between the pressure in the airway lumen and the pressure exerted by tissues surrounding the site of collapse, modulate upper airway size. Activity of the pharyngeal dilator muscles offsets extraluminal tissue pressure to help maintain upper airway patency.[47]

Among individuals with sleep apnea, upper airway collapse occurs most commonly in the retropalatal and retroglossal regions, reducing airway intraluminal diameter and increasing airway resistance, which leads to apneas and hypopneas.[48] Multiple sites of potential upper airway collapse have been visualized in patients with OSA and tend to be reproducible from episode to episode.[49] During

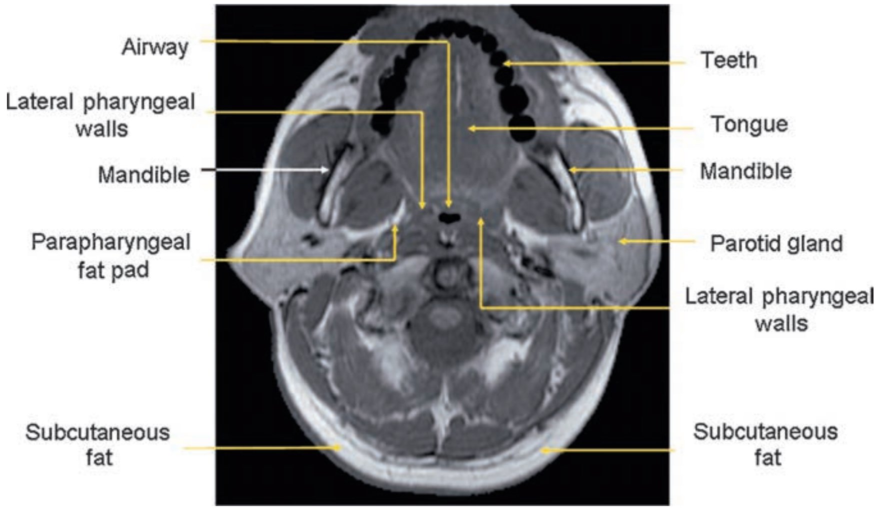

Figure 98-2 Axial magnetic resonance (MR) image at the retropalatal level in a normal subject. The relevant soft tissue and bony structures surrounding the upper airway are highlighted. The tissues immediately lateral to the airway are the lateral pharyngeal walls and the parapharyngeal fat pads. *(Reproduced with permission from Schwab RJ, Gupta KB, Gefter WB, et al. Upper airway and soft tissue anatomy in normal subjects and patients with sleep-disordered breathing. Significance of the lateral pharyngeal walls. Am J Respir Crit Care Med. 1995;152(5 Pt 1):1673–1689.)*

wakefulness, upper airway caliber is smaller in patients with sleep apnea compared with normal individuals.[50] Habitual snorers also have generalized narrowing of the pharyngeal lumen compared with normal subjects, regardless of whether they are obese.[44] Nevertheless, smaller upper airway caliber does not entirely explain OSA risk: men have larger pharyngeal airway cross-sectional area and airway volumes than women but are more likely to develop sleep apnea. Differences in airway length have been proposed to explain gender disparity in OSA risk, given observations that men have longer, and thus more collapsible, pharyngeal airways compared with women.[51] A reduction in the lateral diameter of the airway in individuals with OSA, with relative preservation of the anterior–posterior diameter, also may promote upper airway dysfunction.[52]

In population studies, neck circumference is a strong predictor of OSA.[53] Consistent with this observation, individuals with OSA demonstrate an excess of upper airway soft tissue for the space within the craniofacial structures that envelop the pharyngeal lumen. Patients with sleep apnea have larger tongues and longer soft palates than normal subjects (Fig. 98-3).[51,54–56] The larger the volume of the lateral pharyngeal walls, tongue, and total upper airway soft tissue (Fig. 98-4), the greater the likelihood of having OSA; specifically, increased thickness of the lateral pharyngeal walls may contribute to narrowing of the apneic airway.[54]

Imaging studies have demonstrated that the total volume of fat surrounding the airway is also greater in apneic individuals compared with BMI-matched normal subjects.[57] Recent evidence has highlighted the importance of tongue fat in the development of OSA. The initial identification of the role of tongue fat came from studies in mice.[58] The New Zealand Obese (NZO) mouse, which has a polygenetic abnormality that leads to morbid obesity and diabetes,[59,60] has been demonstrated to sleep upright, presumably to protect the upper airway from collapse. Imaging studies revealed a narrowed upper airway in the NZO mice with an increased tongue size compared to wild-type mice. Histologic examination revealed fat infiltration in the tongue.[58] These studies in mice have been extended to humans. In case-control analyses using Dixon imaging with MRI, individuals with OSA have more tongue fat than controls after controlling for differences in BMI (Fig. 98-5).[61]

These findings suggest that fat deposition in the neck—in the parapharyngeal fat pads, under the mandible, and particularly in the tongue—reduces upper airway caliber.[61] Increased soft tissue mass may increase tissue pressure, resulting in airway collapse and decreased airway volume.[47]

Variations in craniofacial morphology also influence upper airway configuration. For example, maxillary deficiency, mandibular retrusion, increased hyoid–mandibular plane distance, and abnormalities of the cranial base have all been associated with higher risks of sleep apnea.[62–66] The heritability of craniofacial structures associated with OSA has been demonstrated in a study examining individuals with sleep apnea and their siblings, and comparing them to controls without

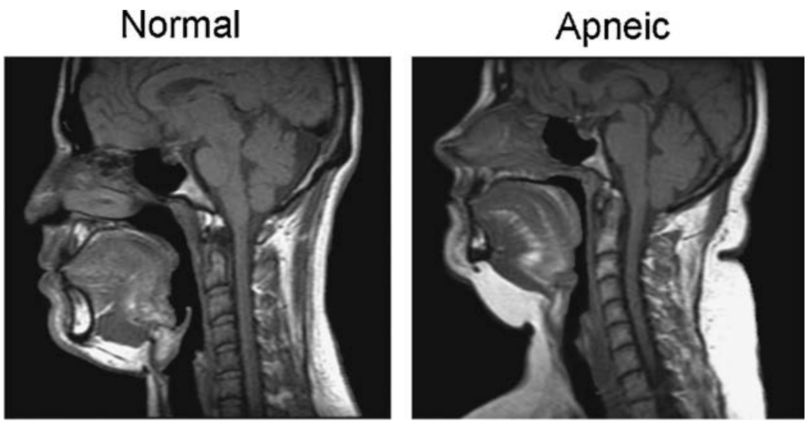

Figure 98-3 Midsagittal magnetic resonance imaging (MRI) of a normal subject on the left and a patient with sleep apnea on the right. The upper airway is smaller in both the retropalatal and retroglossal region in the apneic patient. The soft palate is longer in the apneic patient. The tongue is bigger in the retroglossal region in the patient with sleep apnea. The amount of subcutaneous fat (white area at the back of the neck) is greater in the apneic. *(Reproduced with permission from Schwab RJ, Gupta KB, Gefter WB, et al. Upper airway and soft tissue anatomy in normal subjects and patients with sleep-disordered breathing. Significance of the lateral pharyngeal walls. Am J Respir Crit Care Med. 1995;152(5 Pt 1):1673–1689.)*

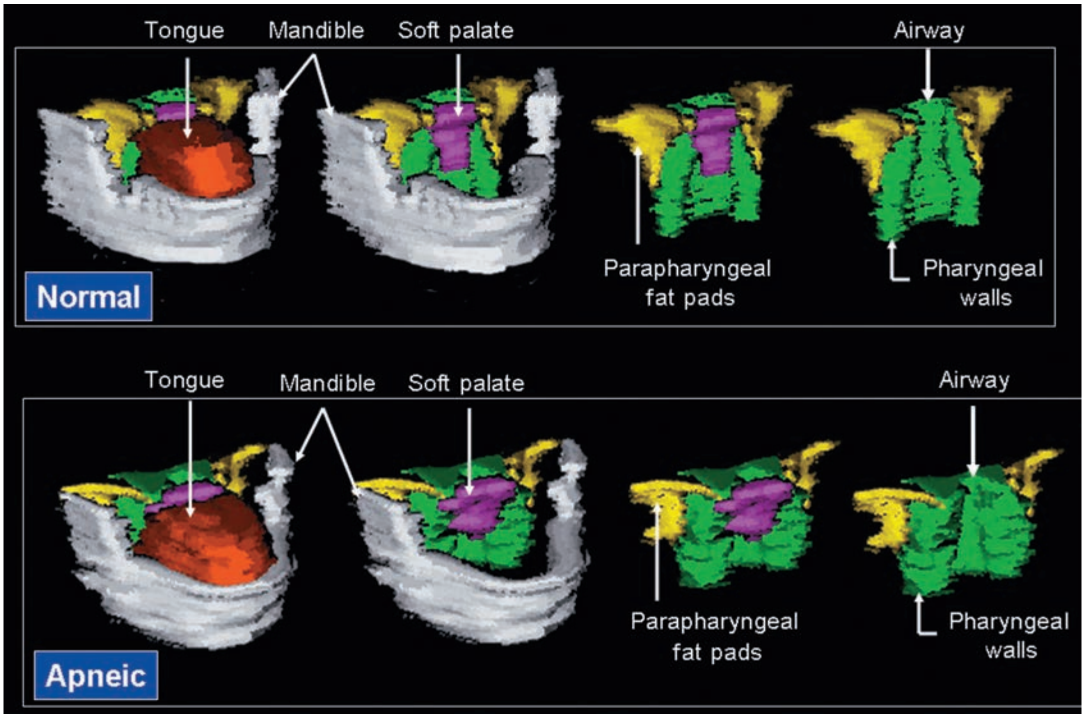
Tongue
Mandible
Soft palate
Airway
Parapharyngeal fat pads
Pharyngeal walls
Normal
Tongue
Mandible
Soft palate
Airway
Parapharyngeal fat pads
Pharyngeal walls
Apneic

Figure 98-4 Volumetric reconstruction of axial magnetic resonance (MR) images in a normal subject *(top panel)* and a patient with sleep apnea *(bottom panel)*. The mandible is depicted in gray, the tongue in orange/rust, the soft palate in purple, the lateral parapharyngeal fat pads in yellow, and the lateral/posterior pharyngeal walls in green. Both subjects had an equivalent body mass index (32.5 kg/m^2). Upper airway caliber is greater in the normal subject than in the patient with sleep apnea. The tongue, soft palate, and lateral pharyngeal walls are all larger in the patient with sleep apnea than in the normal subject. *(Reproduced with permission from Schwab RJ, Pasirstein M, Pierson R, et al. Identification of upper airway anatomic risk factors for obstructive sleep apnea with volumetric magnetic resonance imaging. Am J Respir Crit Care Med. 2003;168(5):522–530.)*

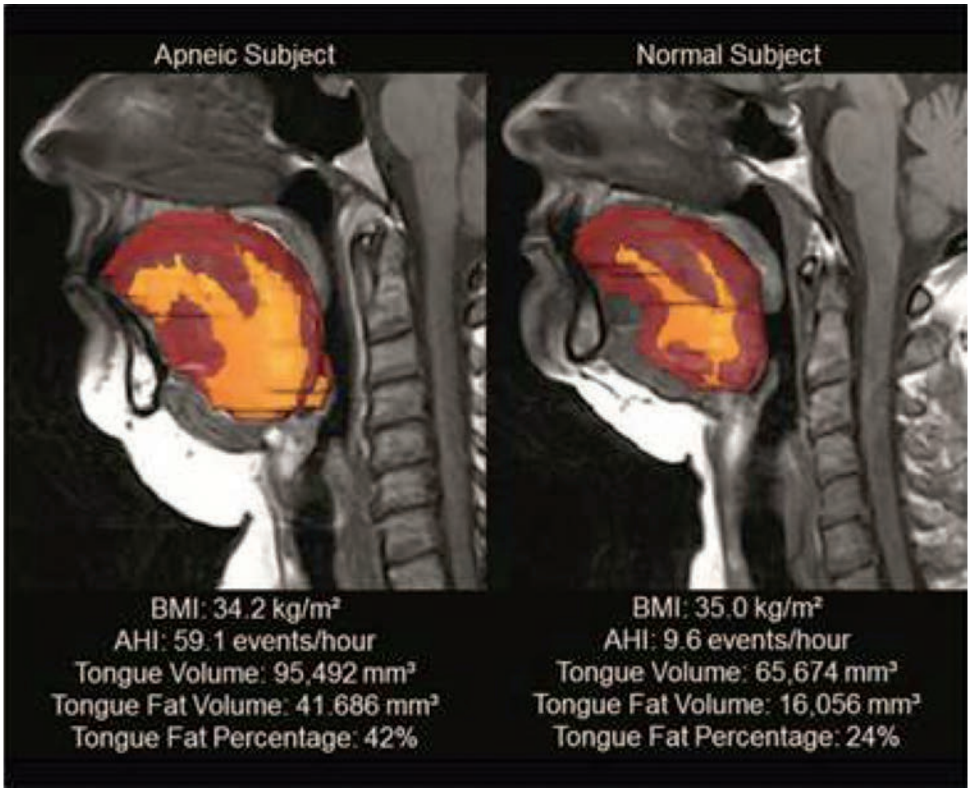
Apneic Subject
Normal Subject
BMI: 34.2 kg/m²
AHI: 59.1 events/hour
Tongue Volume: 95,492 mm³
Tongue Fat Volume: 41.686 mm³
Tongue Fat Percentage: 42%
BMI: 35.0 kg/m²
AHI: 9.6 events/hour
Tongue Volume: 65,674 mm³
Tongue Fat Volume: 16,056 mm³
Tongue Fat Percentage: 24%

Figure 98-5 Three-dimensional volumetric reconstructions in subject with sleep apnea (left) and a subject without sleep apnea (right). The tongue is in red and fat within the tongue is in yellow. The reconstruction is from series of 3-mm contiguous axial MR images superimposed on midsagittal images. The apneic tongue on the left is significantly larger with increased tongue fat compared to the non-apenic tongue on the right. Subjects were matched for age, gender, menopausal status, and ethnicity. *(Reproduced with permission from Kim AM, Keenan BT, Jackson N, et al. Tongue fat and its relationship to obstructive sleep apnea. Sleep. 2014;37(10):1639–1648.)*

OSA and their siblings.[67] Craniofacial abnormalities are more likely to be observed among nonobese persons with OSA, whereas obese individuals with OSA are more likely to have larger soft tissue structures.[42,68]

Changes in upper airway anatomy during the respiratory cycle can influence the propensity for airway collapse during both inspiration and expiration. Using dynamic upper airway imaging with CT, MRI, and nasopharyngoscopy, the airway's geometric changes have been partitioned into three phases (Fig. 98-6). During inspiration, upper airway area is relatively constant, implying a balance between muscle dilator activity and negative airway lumen pressure. In early expiration, the activity of airway dilator muscles decreases, intraluminal pressure rises, and the airway widens maximally. At end expiration, upper airway dimensions decrease. Patients with OSA have more narrowing during end expiration compared to normal controls.[52,69,70] Drug-induced sleep endoscopy (DISE), during which pharmacologic agents are used to induce a level of sedation approximating natural sleep, provides a three-dimensional evaluation of the likely site of upper airway collapse in patients with OSA.[71] During the DISE procedure, a flexible laryngoscope is used to assess the entire length of the pharynx across several cycles of airway obstruction and normal breathing. Various classification schemes such as the widely used VOTE Classification (Velum, Oropharyngeal lateral walls, Tongue, Epiglottis) are used to identify structures that contribute to pharyngeal obstruction and the degree of airway narrowing associated with each structure. Identification of the site of airway obstruction during DISE can guide the use of therapeutic alternatives to CPAP therapy[71] and is essential for determining whether patients are likely to benefit from hypoglossal nerve stimulation surgery for OSA.[72]

A number of studies have also demonstrated that redistribution of extracellular fluid from the legs to the upper body can occur during sleep and in the supine position, leading to significant increases in neck circumference and airway collapsibility, and a reduction in upper airway cross-sectional area.[73–75] The magnitude of fluid redistribution is associated with the degree of SDB, suggesting a contributory role for this mechanism in the development of OSA. However, absolute AHI fell only modestly in a small crossover study in which patients wore compression stockings during the daytime to reduce nocturnal fluid shifts, suggesting that this mechanism does not play a major role in OSA pathogenesis.[76]

■ Neural Modulation of Upper Airway Patency

During sleep, the balance in transpharyngeal pressure shifts toward upper airway collapse due to reduced upper airway dilator muscle activity. MR images suggest that even among normal individuals,

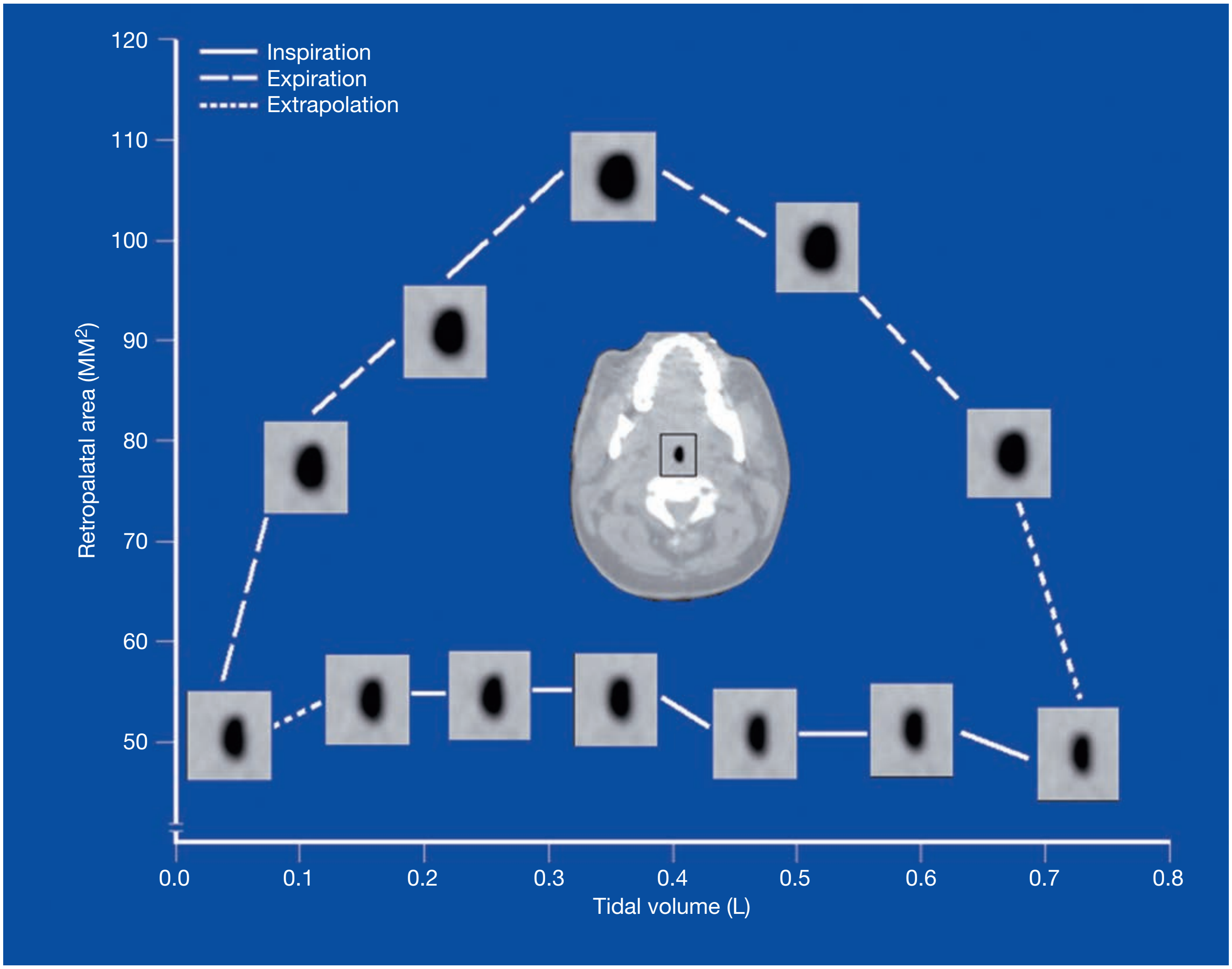

Figure 98-6 Changes in upper airway area as a function of tidal volume during the respiratory cycle using cine computed tomography (CT). Airway caliber is relatively constant in inspiration. Airway size increases in early expiration and decreases in late expiration. *(Reproduced with permission from Schwab RJ, Gefter WB, Hoffman EA, et al. Dynamic upper airway imaging during awake respiration in normal subjects and patients with sleep-disordered breathing. Am Rev Respir Dis. 1993;148(5):1385–1400.)*

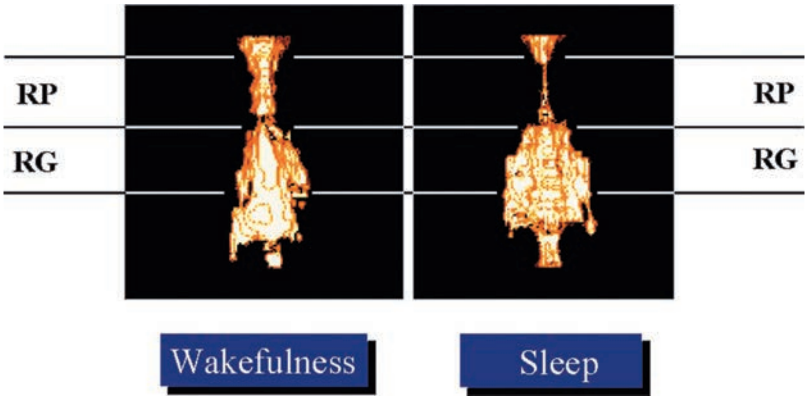

Figure 98-7 Volumetric state–dependent airway imaging in a normal subject using magnetic resonance imaging (MRI). Airway volume during sleep is smaller in the retropalatal (RP) region but not the retroglossal (RG) region. Such images suggest that the upper airway during sleep does not narrow as a homogeneous tube. Nonetheless such images indicate that the upper airway of subjects without sleep apnea narrows during sleep. *(Reproduced with permission from Schwab RJ, Pasirstein M, Pierson R, et al. Identification of upper airway anatomic risk factors for obstructive sleep apnea with volumetric magnetic resonance imaging. Am J Respir Crit Care Med. 2003;168(5):522–530.)*

the retropalatal upper airway narrows during sleep (Fig. 98-7). The neural control of the upper airway muscles is complex and involves several neurotransmitters (serotonin, norepinephrine, orexin–acetylcholine, and gamma-aminobutyric acid) that are influenced by sleep itself.[77–79] The most widely studied upper airway muscle is the genioglossus.

Three neural mechanisms have been shown to be operative with regard to genioglossus muscle activity and vulnerability to obstructive apneic events. First, negative airway pressure detected by laryngeal mechanoreceptors activates the genioglossus via increased hypoglossal nerve discharge. This reflex is diminished during non-REM sleep compared with wakefulness, and it is further reduced during REM sleep, placing the airway at risk for collapse.[80–83] A state-sensitive motor inhibitory cholinergic channel that operates at the hypoglossal motor pool has been identified as the principal mechanism of REM sleep pharyngeal motor inhibition.[84] Furthermore, patients with OSA have reduced upper airway reflexes during sleep compared with normal individuals.[85] Whether these differences occur due to individual variability in neuromuscular responses, placing some individuals at increased risk for OSA, or whether repetitive injury from snoring vibration or oxidative stress leads to neural or muscular damage has been debated.[86–88]

Second, the upper airway muscles respond to input from the respiratory control center in the medulla, with increases and decreases in activity in proportion to respiratory drive. In situations of ventilatory control instability in which respiratory drive waxes and wanes, diminished upper airway muscle activity can precipitate airway collapse, that is, obstructive apnea.[89,90] Third, neural mechanisms modulating arousal (serotonergic and noradrenergic neurons) have a tonic excitatory influence on genioglossus activity. With the onset of sleep, there is a reduction in arousal-modulated excitatory output to the upper airway musculature.[91,92] During episodes of upper airway collapse, arousal from sleep in response to respiratory activation helps to restore airway patency.[93,94] Although arousals are not always necessary for recovery from upper airway obstruction, patients with OSA have a diminished ability to restore ventilation without cortical arousal compared with nonsnorers.[95]

■ The Apneic Event

Occlusion of the airway results in a range of immediate physiologic disturbances. Episodic reductions or cessations in ventilation despite continued respiratory efforts, recurrent episodes of intermittent hypoxemia, and frequent arousals from sleep form the basis for a cascade of downstream perturbations. During obstructive apneas, breathing efforts create abrupt reductions in intrathoracic pressure that can increase atrial natriuretic peptide (ANP) release and left ventricular (LV) transmural pressure, compromise LV filling, and increase both preload and afterload.[96–100] Myocardial oxygen demand increases despite reduced coronary blood flow and decreased oxygen delivery due to apnea-related hypoxia.[101] Surges in sympathetic nervous system activity that occur due to apnea, hypoxia, hypercapnia, and arousal result in increased peripheral resistance and cardiac stimulation, which in turn lead to postapneic increases in blood pressure (BP) and heart rate.[102–105] These elevations in sympathetic activity persist during the day in individuals with OSA.[106] Moreover, individuals with the largest magnitude of change in heart rate response to apneic events have been observed to be at increased risk of nonfatal or fatal cardiovascular disease and all-cause mortality.[107] This increased risk was accentuated among those with the highest hypoxic burden.

Intermittent hypoxemia is associated with increased production of reactive oxygen species and oxidative stress, which can impair endothelially mediated vasodilation, contributing to BP elevation.[108,109] Reactive oxygen species also increase activity of the transcription factor nuclear factor kappa B (NF-κβ), a key component of the inflammatory response.[110] NF-κβ stimulates the production of inflammatory mediators (e.g., C-reactive protein, tumor necrosis factor α, and interleukins 6 and 8) and adhesion molecules (platelet endothelial adhesion molecule, intercellular adhesion molecules [ICAMs]).[111–115] These effects of intermittent hypoxia are likely to promote endothelial damage and atherosclerosis.[116,117] Many of these studies have been performed in mice exposed to chronic intermittent hypoxia, in which the ambient oxygen concentration is lowered cyclically, for example, to 5% for 60 cycles/h for 8 h/day.[118] Several of these preclinical studies suggest that visceral adipose tissue is an important source of proinflammatory mediators in OSA,[118,119] although the impact of adipose tissue on vascular inflammation in OSA is not well defined.

Termination of obstructive apneas usually occurs with a transient arousal or awakening from sleep. Arousals are coupled with respiratory effort and involve both chemical (hypoxia) and mechanical (increased respiratory effort against an occluded airway) stimuli.[120,121] Arousal mechanisms can be adversely affected by alterations in chemosensitive systems, ingestion of alcohol, or use of sedatives and hypnotics, leading to prolongation of apneic events.[122,123]

EPIDEMIOLOGY AND RISK FACTORS FOR OSA

Below we consider the epidemiology of OSA and important underlying risk factors.

■ Epidemiology of OSA

Estimates of the prevalence of OSA in the general population are variable and dependent on several factors, including the characteristics of the population studied (e.g., obesity, ethnicity), methods used to measure SDB, disease definitions (e.g., hypopnea definition), and the AHI threshold used to define OSA.[25,124,125] In the United States, a landmark community-based population study (the Wisconsin Sleep Cohort Study) published in 1993 reported the prevalence of OSA with daytime sleepiness (i.e., OSAS) to be 4% in men and 2% in women between the ages of 30 and 60.[126] In fact, current prevalence is likely to be substantially higher, given rising rates of obesity and the aging of the population worldwide.[127] The current prevalence estimate of moderate to severe sleep-disordered breathing (apnea–hypopnea index, measured as events/h, ≥15) is estimated at 10% of the adult U.S. population.[127]

A recent analysis utilizing available objective population prevalence data and data on BMI, race, age, and sex distributions in different countries estimated the worldwide number of adults between 30 and 69 years with OSA to be nearly 1 billion, with 425 million (>45%) individuals likely to have moderate or severe OSA.[128] It is important to recognize that the prevalence of OSA defined by the presence of SDB events alone, without daytime symptoms, is considerably higher than the prevalence of symptomatic OSA with excessive sleepiness.[25,126,129] For instance, 24% of men and 9% of women in the Wisconsin Sleep Cohort Study had an AHI of at least 5 events/h.[126] While the impact of milder, asymptomatic OSA on adverse health outcomes remains an area of active debate, recent evidence suggests that increased cardiovascular risk among those with OSA is strongly associated with the presence of daytime sleepiness.[130,131]

Age

The effect of age on the prevalence of OSA is complex. Population studies have demonstrated that the prevalence of OSA increases through midlife but then plateaus after age 60 to 65.[132] Furthermore, after controlling for obesity, mean OSA severity may decline with age.[25] Nevertheless, individuals between ages 65 and 100 are more than six times more likely to have OSA compared with men and women 20 to 44 years of age.[25,133] Several studies have observed that the prevalence of SDB is greater than 50% in those at least 65 years of age.[124,132,134] BMI is, however, less related to SDB in the older individuals. These findings have raised questions about whether there is a "survivor effect" for OSA among older adults (i.e., whereby those with OSA who survive to old age are relatively resistant to its adverse effects). Thus, the clinical significance of OSA in the elderly is debated, as is whether a higher threshold should be used to define OSA in this age group.[135,136]

Gender

Epidemiologic studies demonstrate that the prevalence of OSA is two to three times higher in men than women and that postmenopausal women are at an approximately threefold higher risk for OSA compared with premenopausal women.[25,126,137,138] The lower risk among premenopausal women appears to be related to the effects of reproductive hormones; however, data describing how hormone levels affect upper airway anatomy and function or the control of breathing leading to SDB remain limited.[139–141]

Gender differences in the prevalence of OSA may also be related to differences in body fat distribution. Men exhibit a more central fat distribution, including the neck, thereby increasing the risk for narrowing and closure of the upper airway.[142–144] Among women, pregnancy poses an additional period of vulnerability for SDB.[790] The prevalence of gestational sleep apnea has been estimated to be 3.6% in early pregnancy (6–15 weeks of gestation) and 8.3% during mid-pregnancy (22–31 weeks) in a large cohort of nulliparous women in a multicenter study.[145] Gestational sleep apnea is associated with important potential consequences for maternal and fetal well-being including greater risks for preeclampsia, hypertensive disorders of pregnancy and especially gestational diabetes.[145,146] A randomized trial of CPAP therapy in women with gestational sleep apnea (the CPAP for Sleep Apnea in Pregnancy [SLEEP] study) is currently being conducted by the NIH (*clinicaltrials.gov/ct2/show/NCT03487185*) to determine whether treatment reduces risks for hypertensive disorders of pregnancy.

Ethnicity

While most population-based prevalence estimates for OSA are derived from White populations, a number of recent studies have sought to characterize the burden of OSA in several Asian countries, in South America (Brazil), and among Blacks and Hispanics in the United States.[147–150] In Hong Kong, India, and Korea, the prevalence of OSA is similar to White population samples, despite the lower prevalence of obesity among Asians. In fact, after controlling the effects of age and obesity, OSA severity appears to be higher among Asians, perhaps due in part to craniofacial characteristics. In a study that matched Caucasian and Chinese patients for OSA severity, Chinese patients had more craniofacial bony restriction based on cephalometry.[151]

Among middle-aged Blacks, the prevalence of OSA is comparable to that in Whites.[132,152] A higher prevalence of OSA has been observed, however, among young Blacks (<25 years of age) compared with either Whites or Blacks in other age groups.[152,153] Data from a multiethnic study of the distribution of sleep-disordered breathing across a cohort of 2230 White, Black, Hispanic, and Chinese participants revealed that Hispanics were 2.14 times more likely to have severe SDB compared with Whites, confirming prior data suggesting a higher prevalence of OSA among Hispanics than non-Hispanic Whites.[154–157] Similarly, Chinese in this cohort study were 37% more likely to have severe SDB compared with Whites.[154]

■ Risk Factors for Sleep Apnea

Risk factors for OSA are summarized in Table 98-1.

Obesity

Worldwide, the prevalence of obesity has doubled in more than 70 countries since 1980 and has continuously increased in most other countries.[158] In the United States, by 2030, obesity prevalence is likely to approach 50% of the adult population.[159] The increase in obesity prevalence is important because numerous epidemiologic studies have shown that obesity is the strongest risk factor for OSA in adults, and that a dose–response relationship exists between excess body weight and sleep apnea prevalence, such that the prevalence of OSA is greatest among individuals in the highest BMI categories.[25,129,133,137,147–149,160] Although the majority of these investigations were cross-sectional, several longitudinal studies have demonstrated that weight gain accelerates disease progression.[161,162]

TABLE 98-1 Risk Factors for Obstructive Sleep Apnea

Obesity (BMI >30 kg/m^2)
Neck size (collar size >17 inches in males, >16 inches in females)
Gender (male/female 2–3:1)
Genetic factors/family history
Upper airway and craniofacial anatomy
Macroglossia
Lateral peritonsillar narrowing
Elongation/enlargement of the soft palate
Tonsillar hypertrophy
Nasal septal deviation
Retrognathia, micrognathia
Narrowing of the hard palate
Class III/IV modified Mallampati airway
Specific genetic disorders, e.g., Treacher Collins, Down syndrome, Apert syndrome
Endocrine disorders, e.g., hypothyroidism, polycystic ovarian syndrome, acromegaly
Alcohol, sedative, or hypnotic use

Interestingly, among the elderly, the influence of obesity is diminished compared to its effect in younger adults,[132] which may be due to accelerated mortality among obese individuals with OSA (i.e., survivorship bias) and the greater role of other age-related risk factors for OSA.

Individuals with OSA have been observed to have larger neck circumferences than those without.[53] Imaging studies have demonstrated that obese individuals with OSA have larger soft tissue structures compared with normal individuals, and BMI has been shown to correlate with the percentage of fat deposition within the tongue.[54,163] In mice, tongue fat has been shown to be a heritable trait.[164] Unlike other fat distributions, the magnitude of heritability was minimally affected when controlling for differences in body weight,[164] suggesting that there are specific genetic variants that determine tongue fat, as has been shown for pericardial fat.[165] The important role of tongue fat has been further demonstrated by studies before and after weight loss.[166] As expected, OSA severity improved with weight loss (i.e., there was a fall in AHI). Data analysis revealed that the relationship between the reductions in BMI and AHI was mediated by changes in tongue fat. Thus, tongue fat is likely to be a critical link between obesity and OSA. As noted earlier, the larger size of the tongue and other soft tissue structures may promote pharyngeal collapse during sleep by increasing tissue pressure on the pharyngeal wall.[55,57,167] In addition to biomechanical effects associated with a larger tongue, obesity is also likely to have important interactions with other risk factors, such as craniofacial characteristics.

Evidence continues to accrue that leptin, a hormone produced by adipocyte tissue that plays a major role in regulating appetite and metabolism and acts as a potent ventilatory stimulant on central respiratory control nuclei,[168] also plays an important role in the pathogenesis of OSA. In obese individuals, circulating levels of leptin are markedly elevated, but the usual stimulatory effects of leptin on respiratory drive are attenuated due to leptin resistance. Leptin is also implicated in the pathogenesis of OSA through impaired central regulation of upper airway patency and diaphragmatic control.[168] In murine models, leptin deficiency and leptin resistance are associated with a higher occurrence of flow-limited breathing and pharyngeal collapsibility.[169,170] In humans, increased leptin levels have been associated with OSA severity, independent of confounders including BMI and waist circumference.[171] Leptin-mediated increases in the production of reactive oxidative species and oxidative stress may help to explain the relationship between OSA and an increased risk of cardiovascular morbidity and mortality.[168]

Physiologic Risk Factors

Nonanatomic phenotypic traits such as a low respiratory arousal threshold, an oversensitive ventilatory control system (i.e., high loop gain, a measure of ventilatory control instability), and poor pharyngeal dilator muscle effectiveness or responsiveness during sleep also appear to be particularly important in determining whether individuals with less collapsible airways manifest OSA.[172] These physiologic factors have been identified as important contributors to the development of OSA in at least one-third of patients.[172,173]

The respiratory arousal threshold describes the level of ventilatory drive needed to trigger an arousal from sleep. Individuals with lower arousal thresholds awaken due to small changes in ventilatory drive, before the pharyngeal reflexes that activate the dilator muscles of the upper airway and thus promote stable breathing, are engaged.[94] In contrast, individuals with higher respiratory arousals thresholds may be better able to engage the pharyngeal reflexes, averting obstructive apneas.

The concept of loop gain is derived from the engineering literature and is used to characterize the stability of the negative feedback loop that controls breathing.[174] More stable systems are characterized by low loop gain, in which a smaller change in ventilation occurs in response to an apnea or hypopnea. In contrast, high–loop gain systems react to an apnea or hypopnea with a larger ventilatory change and are thus more likely to become unstable due to small disturbances.

Finally, a limited ability to activate the pharyngeal dilator muscles during sleep in response to increases in ventilatory drive, that is, poor upper airway muscle responsiveness or effectiveness, appears to promote the development of sleep apnea in a subset of patients with OSA. These physiologic factors can vary widely among patients who appear to have similar degrees of OSA when assessed using the AHI. Importantly, they may be helpful in identifying patients who are likely to benefit from targeted non-CPAP interventions such as upper airway surgery,[175] supplemental oxygen,[176] and a drug stimulating upper airway muscles.[177]

Genetic Factors

Evidence that heritable risk factors for sleep apnea exist continues to accumulate. A number of studies initially demonstrated the tendency for OSA to aggregate in families.[178,179] Subsequently, studies utilizing genetic epidemiology techniques have demonstrated increased risk for OSA, independent of obesity, among first-degree relatives in geographically diverse populations in Iceland, Israel, Scotland, and Cleveland (United States).[64,180–182] The risk for OSA increases by 30% to 58% among individuals who have one first-degree relative with OSA and two- to fourfold for those with three affected family members with OSA.[134] The heritability of both soft tissue and craniofacial structures has been recognized.[67] However, while associations between promising genetic polymorphisms and OSA have been identified in numerous candidate gene studies,[183] many of these studies had inadequate sample sizes and few results have been independently replicated.[184] In a meta-analysis of three of the available studies, the *TNF*-α (*−308G/A*) polymorphism nearly doubled the odds for OSA.[185]

In recent years, genome-wide association studies have searched for relationships between genetic polymorphisms and SDB characteristics derived from PSG. Different genetic variants associated with AHI have been identified among individuals of Caribbean descent[186] and in a larger multiethnic study combining data from seven cohort studies.[187] Two studies have identified genetic variants associated with oxygen saturations during sleep and have replicated their findings.[188,189] A genome-wide study that employed whole-genome sequencing also found several rare genetic variants associated with oxygen desaturations.[189] Finally, an analytic technique known as admixture mapping that takes advantage of migration away from relatively isolated continents has likewise identified some genetic polymorphisms associated with AHI and oximetry measurements.[190]

Genome-wide analytic techniques for identifying relevant genes are continuing to evolve. Ultimately, given the complexity of SDB, many different genes are likely to contribute.

Craniofacial Anatomy

A proportion of patients with OSA are not obese. In nonobese individuals, craniofacial features such as retroposed mandible, micrognathia, and narrowing of the hard palate are the primary risk factors for apnea.[64–66] Furthermore, heritability of craniofacial abnormalities (retroposed mandible, inferior displaced hyoid bone) and upper airway soft tissue structures (tongue volume, lateral pharyngeal walls, and total soft tissue) has been demonstrated in first-degree relatives and siblings.[64,191,192] These factors may operate in concert or alone to increase the risk of apnea. Genetic disorders associated with craniofacial and/or upper airway soft tissue abnormalities, including Treacher Collins syndrome, Down syndrome, Apert syndrome, and Pierre Robin syndrome, also confer increased risk of SDB.[193]

Endocrine Abnormalities

Individuals with specific endocrine conditions are at risk for OSA. Hypothyroidism, especially when accompanied by myxedema, is associated with both OSA and CSA due to alterations in muscle function and blunted ventilatory response.[194,195] The presence of a goiter may place the patient at risk for OSA,[196] and thyroid surgery (lobectomy or total thyroidectomy) can improve OSA symptoms including snoring and excessive somnolence.[197] Macroglossia associated with hypothyroidism also contributes to the development of OSA. OSA is common and often severe in patients with acromegaly, presumably related to both osseous and soft tissue changes narrowing the upper airway.[198]

Given the low prevalence of OSA among premenopausal women compared with postmenopausal women and men, the female reproductive hormones appear to have a protective effect on OSA risk.[199–201] Interestingly, among women with polycystic ovarian syndrome, which is characterized by hyperandrogenism, obesity, and cardiometabolic dysfunction, OSA risk is markedly higher compared with age- and/or weight-matched controls.[202,203] OSA risk among postmenopausal users of hormone replacement therapy was observed in two large cohort studies to be similar to that of premenopausal women and lower compared with nonhormone users.[25,138] However, widespread cessation of hormone therapy use occurred after the July 2002 publication of results from the Women's Health Initiative study showing increased risks for cardiovascular disease and breast cancer among women taking replacement hormones.[204] Subsequent analyses of data from the Sleep in Midlife Women Study demonstrated that the protective effect of hormone therapy against sleep-disordered breathing disappeared after the release of the WHI results, suggesting that healthy user bias was the likely reason for lower SDB rates among hormone therapy users.[205]

Other Considerations

Alcohol, which reduces upper airway tone, and sedatives or hypnotics, which reduce the arousal mechanism, also can worsen OSA.[206,207] Each potential risk factor should be considered in the patient evaluation, as it is important to address why an individual has developed sleep apnea.

Recently, a large (>81,000) international sample of individuals with and without sleep apnea was examined to identify characteristics associated with "extreme phenotypes"—that is, conferring either predisposition toward or protection against OSA in those whose disease status was not explained by known risk factors.[208] Comparisons suggested that a greater cervicomental angle increases risk for OSA in the absence of other clinical risk factors, and smaller facial widths are protective when clinical risk factors are present. More broadly, identifying extreme phenotypes may help to accelerate research into unique clinical and genetic contributors to OSA.

CLINICAL PRESENTATION AND SCREENING FOR OSA

Elements in the history and physical examination, as well as screening tools useful in establishing a diagnosis of OSA, are discussed below.

■ Clinical Presentation

Below are considered important clinical aspects of OSA, including its many heterogeneous features.

History

The diagnosis of OSA is frequently suggested by the history. Patients with sleep apnea often complain of both daytime and nighttime symptoms (Table 98-2). Bed partners are crucial informants of nocturnal events, and when available, a detailed history from the bed partner is imperative in cases of suspected OSA. Snoring is the cardinal complaint reported by the bed partner. Typically, the snoring is loud and nightly and has existed for many years. Snoring may be so disruptive that the bed partner can be driven to sleep in another room.[209] A bed partner may report a witnessed apnea that is followed by a loud snort or gasp at the end of the apneic episode. This can be extremely concerning to the partner and serve as the trigger for seeking medical attention.

TABLE 98-2 Clinical Presentation of Obstructive Sleep Apnea

Loud, habitual snoring
Witnessed apneas
Nocturnal awakening
Gasping or choking episodes during sleep
Nocturia
Nocturnal sweating
Unrefreshing sleep, morning headaches
Excessive daytime sleepiness
Automobile or work-related accidents
Irritability, memory loss, personality change
Decreased libido
Impotence

Individuals with OSA may also report snorting or gasping, choking, nocturnal diaphoresis, and restlessness related to airway obstruction.[210,211] A sensation of choking or dyspnea is reported in up to 30% of patients. Frequent nocturnal awakenings related to repetitive airway obstruction lead to sleep fragmentation. Nocturia is fairly common and has been attributed to ANP release in response to apnea-related right atrial stretch.[100] A large community-based epidemiologic study found a dose–response relationship between the severity of sleep apnea and levels of brain natriuretic peptide (BNP).[212] This relationship was not observed in a similar analysis performed in a subset of participants from the Sleep Heart Health Study,[213] who were older (median age 65) and not obese. However, nocturia has been observed to improve in patients with OSA who are adherent to CPAP therapy.[214,215]

Repetitive apneic events are not conducive to restorative sleep. Some studies have shown that untreated OSA patients have decreased slow wave sleep (non-REM stage 3) and REM sleep and more sleep stage transitions.[216,217] Thus, individuals with OSA are frequently unrefreshed upon awakening in the morning. Morning headaches are a less common manifestation of sleep apnea. When reported, the possibility of hypercapnia due to OHS should be considered.[218]

Excessive daytime sleepiness is a chief clinical consequence among patients with OSA.[219] Less commonly, patients may report insomnia, with difficulties initiating and maintaining sleep.[220,221] Interestingly, although the proportion of individuals who endorse daytime sleepiness increases with OSA severity, disease severity has proven to correlate only modestly with the degree of excessive somnolence.[222,223] Typically, the excessive daytime sleepiness of individuals with OSA occurs in sedentary situations, for example, following meals, watching television, reading, and during conversation. Driving is particularly problematic in patients with sleep apnea.[224,225] Patients may report falling asleep at red lights or stop signs, drowsiness while driving, and in extreme cases, motor vehicle accidents.[226] Thus, it is imperative to inquire about drowsy driving,

TABLE 98-3 Epworth Sleepiness Scale

In contrast to just feeling tired, how likely are you to doze off or fall asleep in the following situations? (This refers to your usual life in recent times. Even if you have not done some of these things recently, try to work out how they would have affected you.) Use the following scale to choose the most appropriate number for each situation:

0 = Would never doze
1 = Slight chance of dozing
2 = Moderate chance of dozing
3 = High chance of dozing

Situation	Chance of Dozing
Sitting and reading	____________
Watching TV	____________
Sitting inactive in a public place (i.e., a theater or a meeting)	____________
As a passenger in a car for an hour without break	____________
Lying down to rest in the afternoon when circumstances permit	____________
Sitting and talking to someone	____________
Sitting quietly after lunch without alcohol	____________
In a car, while stopping for a few minutes in traffic	____________

Reproduced with permission from Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991;14(6):540–545.

which is risky not only to the patient but also to others on the road. The Epworth Sleepiness Scale (Table 98-3), a questionnaire for assessing the degree of subjective sleepiness, is usually elevated in sleep apnea patients (scored 0–24, with >10 considered abnormal) and can be a useful tool for assessing sleepiness in clinical settings.[222] Nevertheless, it is important to appreciate that the presence of excessive daytime somnolence is neither a necessary nor a sufficient condition for making the diagnosis of OSA: Many individuals with an elevated AHI do not report daytime sleepiness, and others report sleepiness in the absence of sleep apnea (often due to insufficient sleep). Whether patients with an elevated AHI who are relatively asymptomatic should be treated continues to be debated, with recent data showing that the cardiovascular benefits of treatment likely largely accrue to symptomatic patients.[227]

OSA can also cause symptoms related to cognitive impairment.[228–231] Inattention and deficits in memory and concentration often affect the ability to function at work. Fear of falling asleep inappropriately may limit an individual's willingness to integrate socially.[232] Moreover, patients with sleep apnea and/or their spouses can report irritability, depressive symptoms, and personality change.[233,234] Sexual dysfunction, that is, either decreased libido or impotence, is another common complaint among men with OSA.[235]

OSA Is a Heterogeneous Disorder

Growing evidence that OSA is a heterogeneous disorder supports the concept that a personalized approach to diagnosis and management of OSA is required.[236,237] OSA is heterogeneous from multiple points of view. The most studied aspect is differences in symptoms. This was originally identified using data from the Icelandic Sleep Apnea Cohort.[238] Based on cluster analysis of responses to extensive questionnaires, three subtypes of OSA were recognized. These included a disturbed sleep group in which individuals' main complaints were symptoms of insomnia, that is, difficulty initiating and maintaining sleep. Patients of this type were not excessively sleepy and had a normal Epworth Sleepiness Score. A second group was minimally symptomatic. This group of patients had a normal Epworth Sleepiness Score, and the vast majority reported waking up feeling refreshed. The last was an excessively sleep group. While they are what we typically envisage sleep apnea patients to be, they comprised only 42.6% of the total clinical cohort. These individuals were very sleepy with mean Epworth Sleepiness Scores of 15.7, and they frequently fell asleep driving.[238] These groups did not differ by severity of OSA (i.e., AHI), BMI, age, or gender.

These symptom subtypes have now been replicated in multiple studies, both in population-based cohorts—the Sleep Heart Health Study,[131] the Korean Genomic Cohort,[239] and the Hispanic Cohort in the United States,[240] and in clinical cohorts of patients in sleep centers—the Sleep Apnea Global Interdisciplinary Consortium (SAGIC),[241] the Canadian National Network for Sleep and Circadian Disorders,[242] and a single center cohort in Chile[243] and France.[244] In these studies, the optimal number of clusters varied between three and five, but the subtypes originally identified in Iceland were always present.

Not surprisingly, the benefit of CPAP treatment for OSA on symptoms varies between subtypes.[245] The magnitude of change in symptoms is greatest in the excessively sleepy group but quite minimal in the relatively asymptomatic group.[245]

These subtypes have different risk of other outcomes, in particular, incident cardiovascular disease. This was originally demonstrated in a study using data from the Sleep Heart Health Study, where only the excessively sleepy subgroup had an increased risk of CV events compared to controls without OSA.[131] That the excessively sleepy group has an increased risk of CV events was confirmed in the clinical cohort in Chile,[243] but not in France.[244]

Even before the formal identification of clinical subtypes, there were studies that indicated that cardiovascular risk was greater among individuals who complained of excessive sleepiness. In the Sleep Heart Health Study, an association between OSA and hypertension was observed in those who complained of sleepiness but not in those without sleepiness.[246] Patients who were found to have OSA after a myocardial infarction had higher rates of reinfarction if they were excessively sleepy compared to those with OSA who were not sleepy.[247] This increased risk of CV events is not the result of sleepiness per se since those without OSA who are excessively sleepy do not have an increased risk of cardiovascular events.[131] Rather, it is likely that different individuals respond to OSA in dissimilar ways at a molecular level. These different responses likely lead to both excessive sleepiness and cardiovascular consequences.

The role of sleepiness in OSA is an area of considerable importance since, for ethical reasons, excessively sleepy individuals have been deliberately excluded from recent randomized control studies (RCTs) examining the impact of CPAP on future cardiovascular events. Epidemiologic studies have shown that individuals with severe OSA have an increased risk of CV events over time that is nullified if they use CPAP.[248] In contrast, recent RCTs have shown no benefit of CPAP on the rate of CV events.[249–251] It has been argued that this negative result is largely the result of exclusion of subjects with excessive sleepiness coupled with low CPAP adherence in nonsleepy subjects.[227]

OSA is also heterogeneous from a physiologic point of view. Wellman et al. have argued that there are four different physiologic risk factors for OSA.[172] The magnitude of these different risk factors varies between subjects. The four physiologic risk factors are (1) collapsibility of the upper airway; (2) overall loop gain, a measure of the instability of the ventilatory control system; (3) arousal threshold; and (4) the responsiveness of the negative pressure reflex in the upper airway that augments activity of upper airway dilator muscles.[172] Early studies to support this concept required complex protocols that included measurement of EMG activity of an upper airway dilator muscle and intraluminal pressure.[172] Recently it has been asserted that information on these four variables can be obtained from a routine sleep study based on a simple model of ventilatory control.[252,253] A cloud-based software system has been developed for clinicians to obtain these data from routine sleep study recordings.[254] This approach has been challenged since it has been argued that the model is too simple and is based on untenable assumptions.[255] Currently, data are limited regarding the reliability of the measures obtained for this simple model—for example, are the same data obtained using repeat nights of testing? Moreover, there are limited validation studies comparing results obtained with gold standard measures. Thus, this is an interesting concept, but much remains to be done before it becomes widely used in clinical sleep medicine.

There are other physiologic differences in OSA. Using cluster analysis to examine standard metrics obtained from overnight PSGs, Zinchuk et al. showed that there are different physiologic subtypes.[256] Only two of the subtypes so identified had an increased risk of CV events that was reduced with CPAP treatment. This interesting result has not, to date, been replicated in other cohorts.

There are now new metrics being obtained from sleep studies.[257,258] It is argued that the AHI is not particularly predictive of outcomes, and we need to move beyond the AHI.[258] New measures include the following: intensity of arousal on a scale of 1 to 9[259]; odds ratio product (ORP), a continuous measure of sleep depth[260]; ORP9, that is, depth of sleep 9 s after an arousal, a measure of sleep drive[261]; heart rate response to an arousal[262]; and hypoxic burden across the total sleep study.[21] Both heart rate response to arousal[107] (likely a measure of sympathetic response) and hypoxic burden[21] have been shown to be predictive of mortality from CV causes. Thus, in the future we are likely to see an increasing focus on new metrics that provide better prediction of outcomes.

Physical Examination

The examination of the patient with suspected OSAS should focus on careful inspection of the head and neck, determination of the presence of obesity (BMI >30 kg/m^2), and measurement of BP. Neck circumference greater than 17 in (43.2 cm) in men or 16 in (40.6 cm) in women indicates an increased risk for OSA.[263] The evaluation should also include assessment for abnormalities of the shape and size of the craniofacial structures (e.g., mandibular retrognathia, micrognathia, crossbite, narrowing of the hard palate, and dental malocclusion); evaluation for factors contributing to nasal obstruction including nasal asymmetry, polyps, septal deviation, and hypertrophy of the turbinates; and visualization of the pharynx to assess crowding and soft tissue dimensions (macroglossia, tonsillar hypertrophy, lateral peritonsillar wall narrowing, enlarged/elongated uvula, or a narrow, high-arched hard palate). The modified Mallampati classification is often used to describe the patency of the upper airway, with increased risk for sleep apnea observed among individuals with class III or IV airways.[264]

■ Screening for Sleep Apnea

Inexpensive tools have been developed to assess the likelihood of apnea. The ability of a number of standardized instruments, such as the Multivariable Apnea Prediction (MAP) Index and the Berlin questionnaire, to identify individuals at risk for sleep apnea has been evaluated.[210,265] The sensitivity and specificity of these questionnaires tend to vary depending on the population studied, the specific cutoffs chosen, and the severity of OSA to be identified.[266] In recent years, a straightforward eight-item questionnaire (STOP-BANG) with four self-reportable criteria (STOP: Snoring, Tiredness, Observed apnea, and high blood Pressure) and four demographic items (BANG: BMI, Age, Neck circumference, and Gender) developed for the surgical preoperative setting has been shown to have good predictive value for identifying severe OSA in surgical and sleep clinic settings worldwide, and to a lesser extent in the general population and commercial driver population.[267,268] However, by dichotomizing each variable, the STOP-BANG loses the continuous nature of the variables used, such as BMI. Other clinical situations in which sleep apnea should be considered in evaluating patients are outlined in Table 98-4.

TABLE 98-4 Conditions in Which Evaluation for Obstructive Sleep Apnea Should Be Considered

Obesity
Systemic hypertension
Myocardial infarction
Cerebrovascular accident
Type 2 diabetes mellitus
Pulmonary hypertension
Polycystic ovarian syndrome
Atrial fibrillation
Driver involved in a sleep-related automobile crash
Preoperative anesthesia evaluation

In the past, overnight pulse oximetry (Fig. 98-8) has been used to screen for OSA.[269,270] Typically, patients with OSA manifest a saw-tooth pattern on nocturnal oximetry. However, overnight oximetry does not detect apneas or hypopneas or arousals in the absence of significant oxygen desaturation, rendering the sensitivity of the test suboptimal. Furthermore, abnormal ambulatory overnight oximetry results obtained by general internists based on their initial clinical suspicion for OSA frequently fail to lead to further sleep evaluation.[271]

In recent years, the digital health revolution has produced a boom in wearable technologies, including a large consumer sleep technology family of products such as smartwatches, rings, sensor clips, wristbands, armbands, and headbands. These wearables collect data on a variety of biosignals ranging from motion to heart rate, skin conductance, and temperature; an increasing number can collect and store continuous oximetry data.[272] Thus, many of these devices can infer information about sleep and sleep-disordered breathing. There is growing recognition within the clinical and research sleep communities of the potential offered by wearable sleep trackers for advancing sleep health. Likewise, the wide availability of wearable sleep technologies can promote increased interest in and awareness of sleep health in the general population. Nevertheless, data on the validity, accuracy, and reliability of wearable sleep devices for use in screening for sleep disorders and sleep-disordered breathing are relatively sparse.[272]

DIAGNOSIS OF OBSTRUCTIVE SLEEP APNEA

While questionnaires and prediction models (i.e., Epworth Sleepiness Scale, MAP) can assist in OSA risk stratification, objective sleep testing is required to confirm the diagnosis and determine disease severity.[27] Polysomnography (PSG), still the gold standard sleep study,[273] records many parameters while the patient sleeps: electroencephalogram (EEG) to indicate sleep state, electrooculogram (EOG) to monitor eye movements, electromyogram (EMG) to measure muscle activity, oronasal thermistor and nasal pressure sensors to indicate respiratory airflow, and chest and waist bands to measure respiratory effort and arterial oxygen saturation (Fig. 98-9)

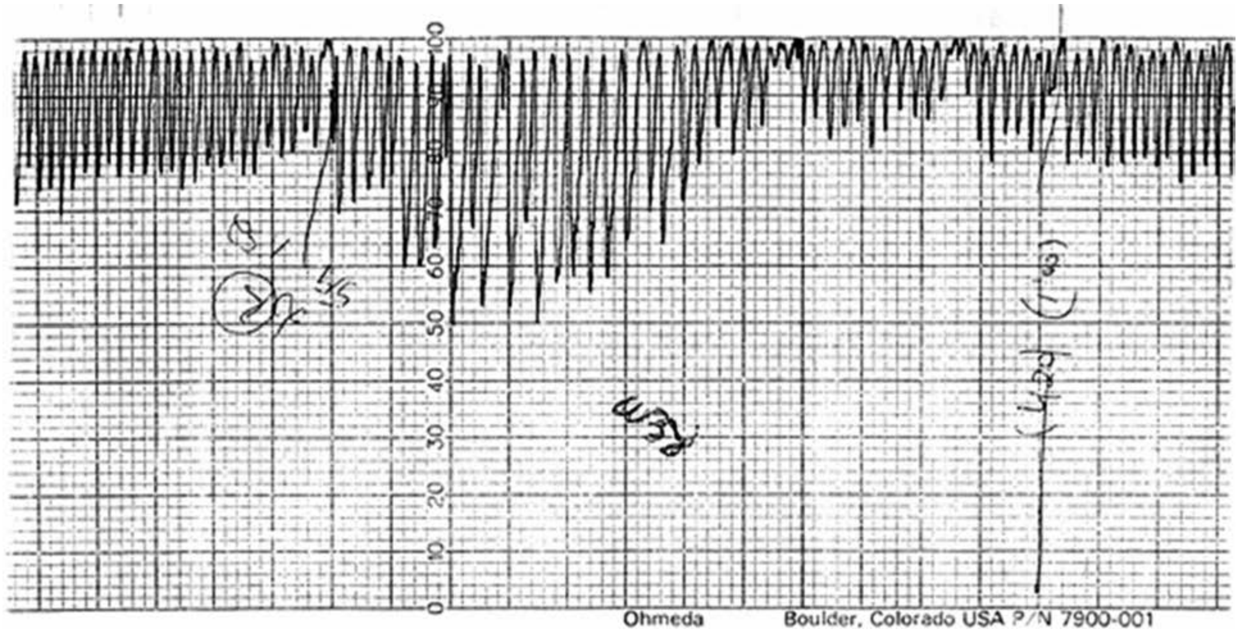

Figure 98-8 Nocturnal oximetry pattern in a patient with obstructive sleep apnea. This patient manifests recurrent oxyhemoglobin desaturations ("sawtooth pattern") that are most severe in REM sleep. Oximetry calibrated from 0% to 100%. Paper speed: each small line 1 min; each dark black line 5 min.

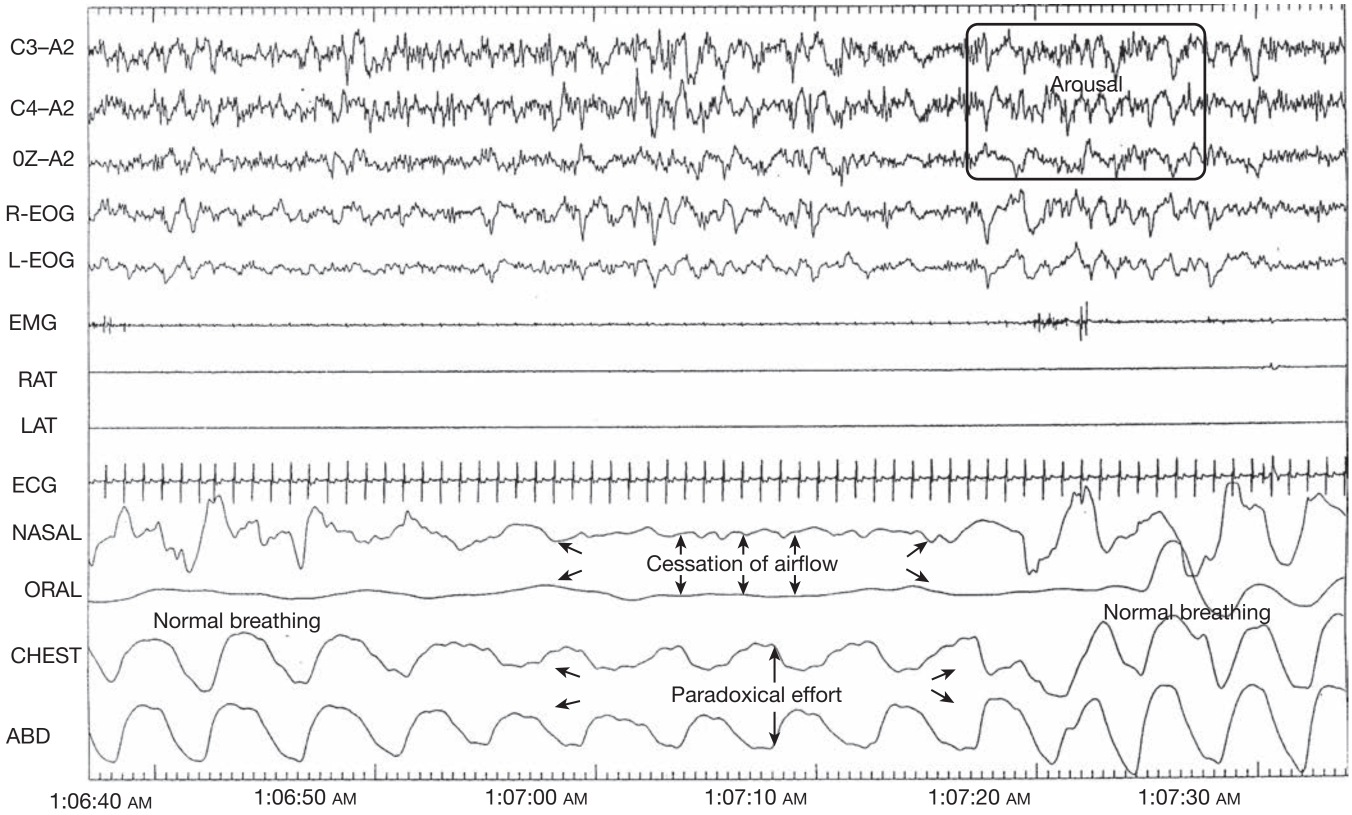

Figure 98-9 Example of an obstructive apnea in a patient with sleep apnea syndrome in stage 2 sleep. The polysomnography traces from the top down are as follows: three EEG channels *(C3–A2, C4–A2, OZ–A2)*; two EOG channels *(R and L)*; submental electromyogram *(EMG)*; right and left anterior tibialis EMG *(RAT, LAT)*, electrocardiogram *(ECG)*; nasal and oral airflow; chest and abdominal motion *(CHEST and ABD)*. During the apneic episodes, there is abnormal airflow (both oral and nasal) with paradoxical motion of the rib cage and abdomen. At the end of the apneic episode there is a burst of EMG activity at the arousal. Following the arousal, respiration resumes with synchronous movements of the rib cage and abdomen.

Video 98-1 Description and demonstration of in-laboratory polysomnography (PSG). *Video available on AccessMedicine.com.*

Video 98-2 Description and demonstration of out-of-center sleep testing (OCST). *Video available on AccessMedicine.com.*

(Video 98-1). These measurements are integrated to provide sleep staging and to indicate apneas, hypopneas, and arousals as depicted in Figs. 98-10 and 98-11.

PSG data have been used to generate the most common measure of sleep apnea severity—the AHI—for several decades. However, new analyses of the data obtained have produced new metrics that better characterize clinical impacts and mortality risk from sleep-disordered breathing. For instance, the AHI can fail to identify patients who obtain most cardiovascular benefit from OSA treatment.[258] As noted in the “Sleep Apnea Definitions” section, Azarbarzin et al. showed the hypoxic burden correlates better with cardiovascular disease mortality than the AHI.[21] The metric is easy to calculate from conventional PSG data. Other potentially useful alternatives to AHI include arousal intensity, odds ratio product (quantifying sleep depth), cardiopulmonary coupling, and apnea–hypopnea event duration.[258]

Stratifying disease severity through the AHI is important, given demonstrated linearity between increasing AHI and likelihood of adverse outcomes (e.g., hypertension, cardiovascular mortality, stroke).[248,274,275] However, despite the ubiquitous use of AHI in OSA diagnosis, the index has some limitations. First, AHI elevations often fail to correlate with sleep quality measures and clinical outcomes.[276] In addition, AHI does not capture other significant aspects of the disorder, such as the degree of oxyhemoglobin desaturation, nocturnal hypoxemia, hypoventilation (i.e., hypercapnia), or associated sleep disruption. Furthermore, variance in hypopnea definitions has led to substantial disparities in measured severity of SDB.[15,17] Despite these shortcomings, the AHI remains the primary determinant of OSA diagnosis and severity.[27] Other metrics have been suggested to better characterize disease impact and severity, and other strategies (symptom subtypes, genetics, blood biomarkers, machine learning, wearable technologies) are being developed.[258]

While in-laboratory PSG remains the gold standard to establish AHI, limited patient access and relatively high cost have led to increasing use of out-of-center sleep testing—also known as portable monitoring, unattended sleep testing, or home sleep apnea testing (HSAT) (Video 98-2). Kuna et al.[277] have established the value of HSAT in terms of patient outcomes and treatment adherence. The researchers randomized veterans to undergo sleep apnea testing either through PSG or HSAT. Patients diagnosed with OSA either were brought back to the laboratory for PAP titration (PSG arm) or underwent home auto-PAP titration (HSAT arm). After 3 months of treatment, neither functional outcome improvement nor PAP adherence was clinically inferior in the HSAT study arm compared with the PSG study arm.

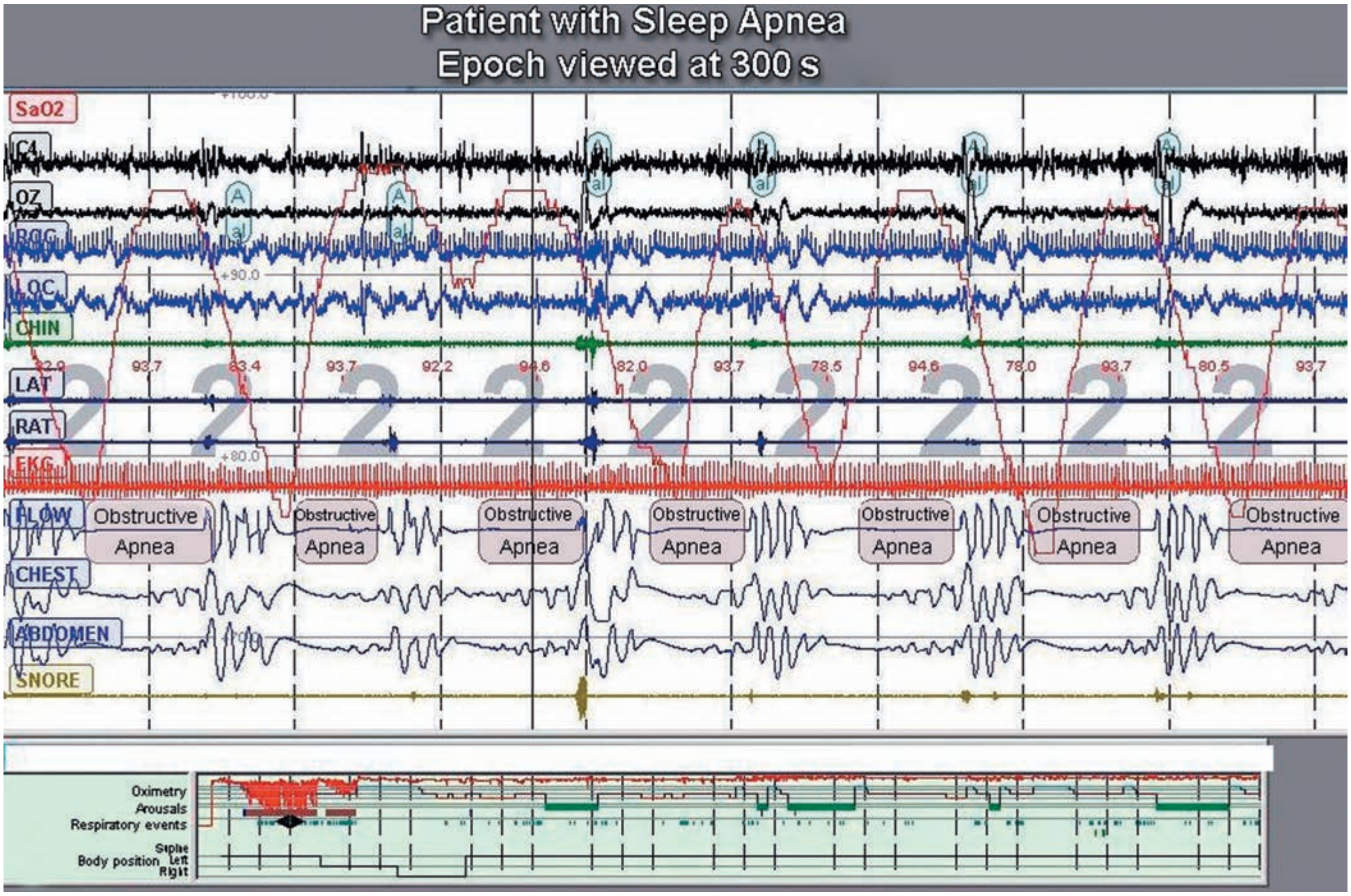

Figure 98-10 Example of a sleep study epoch from a split night sleep study in a patient with severe apnea. The epoch is viewed at 300 s. This patient has recurrent apneic events associated with oxyhemoglobin desaturations *(recurrent dips in the red line)*. At the bottom of the figure is a hypnogram displaying the sleep data from the entire night. The *black diamond* in the hypnogram shows the time frame for the specific epoch displayed in the top portion of the figure. Later on in the night the patient is started on CPAP and the recurrent apneas and oxyhemoglobin desaturations are abolished (the recurrent desaturations: *red lines* noted in the hypnogram resolve). *C4* and *OZ* are EEG leads; *ROC* and *LOC* are the right and left ocular leads; *RAT* and *LAT* are the right and left anterior tibialis electromyograms; Sa_{O_2} is the oximetry lead.

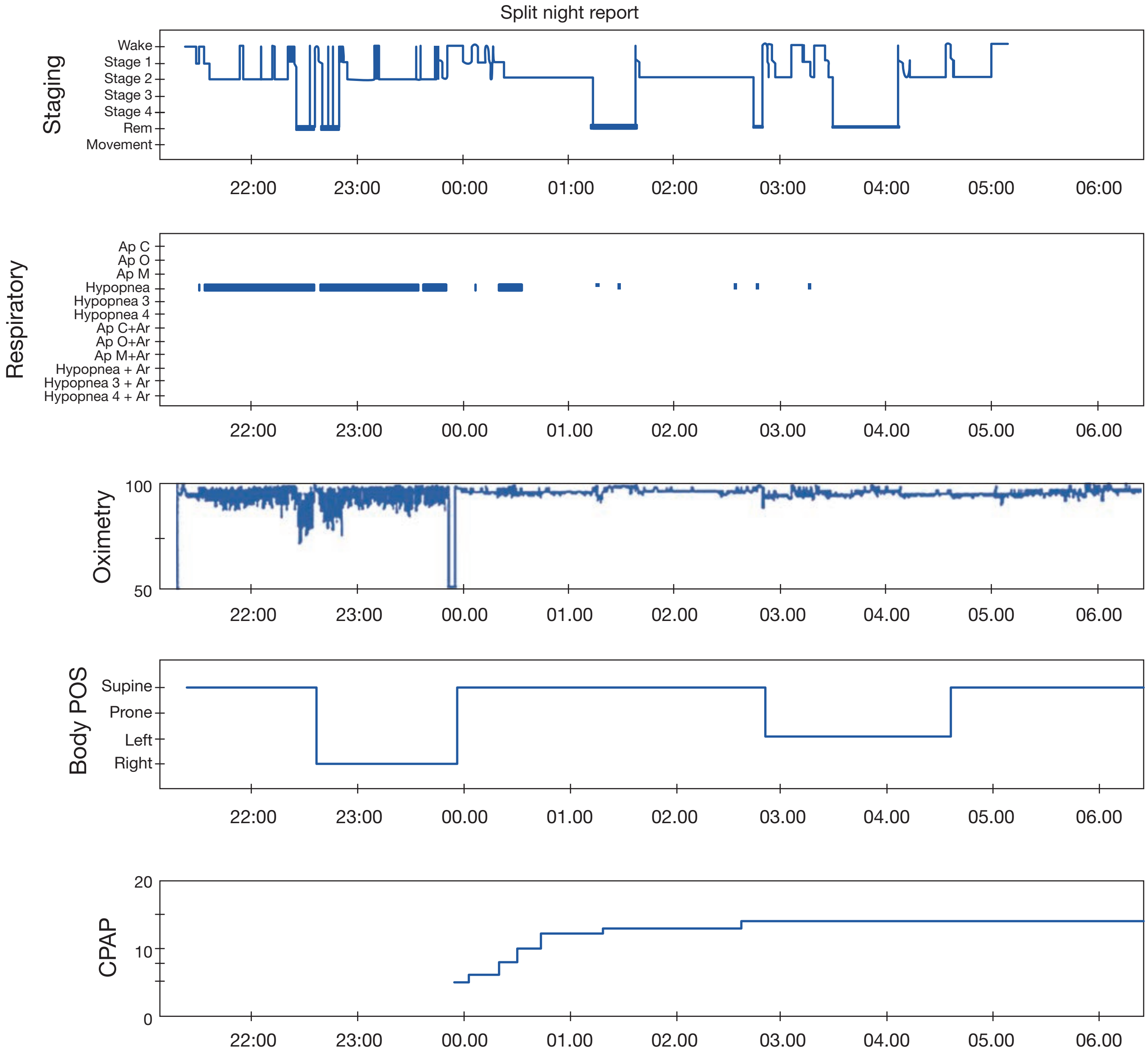

Figure 98-11 Split night hypnogram in a patient with obstructive sleep apnea. The patient has frequent hypopneas with recurrent oxyhemoglobin desaturations until he is started on CPAP at midnight. The CPAP was titrated to 14 cm H_2O, which abolished the hypopneas and oxyhemoglobin desaturations.

Typically performed in patients' homes, HSAT offers greater convenience at lower cost, and ideally replicates a usual night of sleep. The amount of data procured ranges widely, depending on the AASM-designated type of sleep testing performed (Table 98-5). An in-laboratory PSG as described earlier is designated a type I study. Overall, type II and III studies are differentiated by the number of variables measured. The former is a complete unattended home study and measures the same parameters as a type I study (PSG). Type II studies are rarely performed in clinical practice, although new devices now allow for sleep staging using strategies such as odds ratio product and delta spectral power calculations.[278] Type III studies typically include measurement of airflow, respiratory effort, pulse, and sleep position. Since EEG is not obtained, sleep stage information and stage-related events (e.g., arousals) cannot be detected. Type IV studies are limited to only one or two parameters, such as pulse rate and oximetry. The United States Centers for Medicare and Medicaid Services outlined guidelines for use of portable sleep testing for OSA diagnosis and treatment initiation in 2009.[26]

Emerging HSAT technology has challenged this type I–IV classification. For instance, some devices utilize peripheral arterial tonometry (PAT) along with oxygen desaturation and pulse rate in their diagnostic algorithms to characterize SDB events. These devices do *not* utilize direct measurements of airflow traditionally observed in type III devices (and PSGs) and have been validated against PSG to diagnose OSA.[279] An alternative HSAT categorization system, the SCOPER classification[280] takes into account Sleep, Cardiovascular, Oximetry, Position, Effort and Respiratory parameters in categorizing emerging devices. SCOPER denotation for PAT devices might appear as $S_3C_2O_{1x}P_2E_0R_0$.

Wearable consumer technologies also are challenging the traditional HSAT classification. Multiple manufacturers now sell devices purporting to track total sleep time, sleep efficiency, and even oxygen desaturations.[281] One recent study compared 4 wearable consumer devices to actigraphy and PSG in terms of sleep/wake detection and sleep stage delineation in 34 healthy young adults. Most devices performed similarly or better than actigraphy in detecting

TABLE 98-5 Diagnostic Testing Options for Sleep-disordered Breathing

	Type	Parameters Measured
	I	EEG, EOG, EMG, ECG, airflow, respiratory effort, O_2 saturation, usually video (all conducted in a sleep laboratory with a sleep professional present)
Out-of-center testing	II	Minimum of seven channels including EEG, EOG, chin EMG, ECG/HR, airflow, respiratory effort, and O_2 saturation
	III	Minimum of four channels including ECG/HR, O_2 saturation and at least two channels of respiratory movement or respiratory movement and airflow
	IV	Airflow and/or O_2 saturation[a]

[a] Centers for Medicare and Medicaid Services require measuring a minimum of three channels, at least one of which is airflow.

EEG, electroencephalogram; EOG, electrooculogram; EMG, electromyogram; ECG, electrocardiogram; HR, heart rate.

Adapted with permission from Chesson AL Jr, Berry RB, Pack A, et al. Practice parameters for the use of portable monitoring devices in the investigation of suspected obstructive sleep apnea in adults. Sleep. 2003;26(7):907–913.

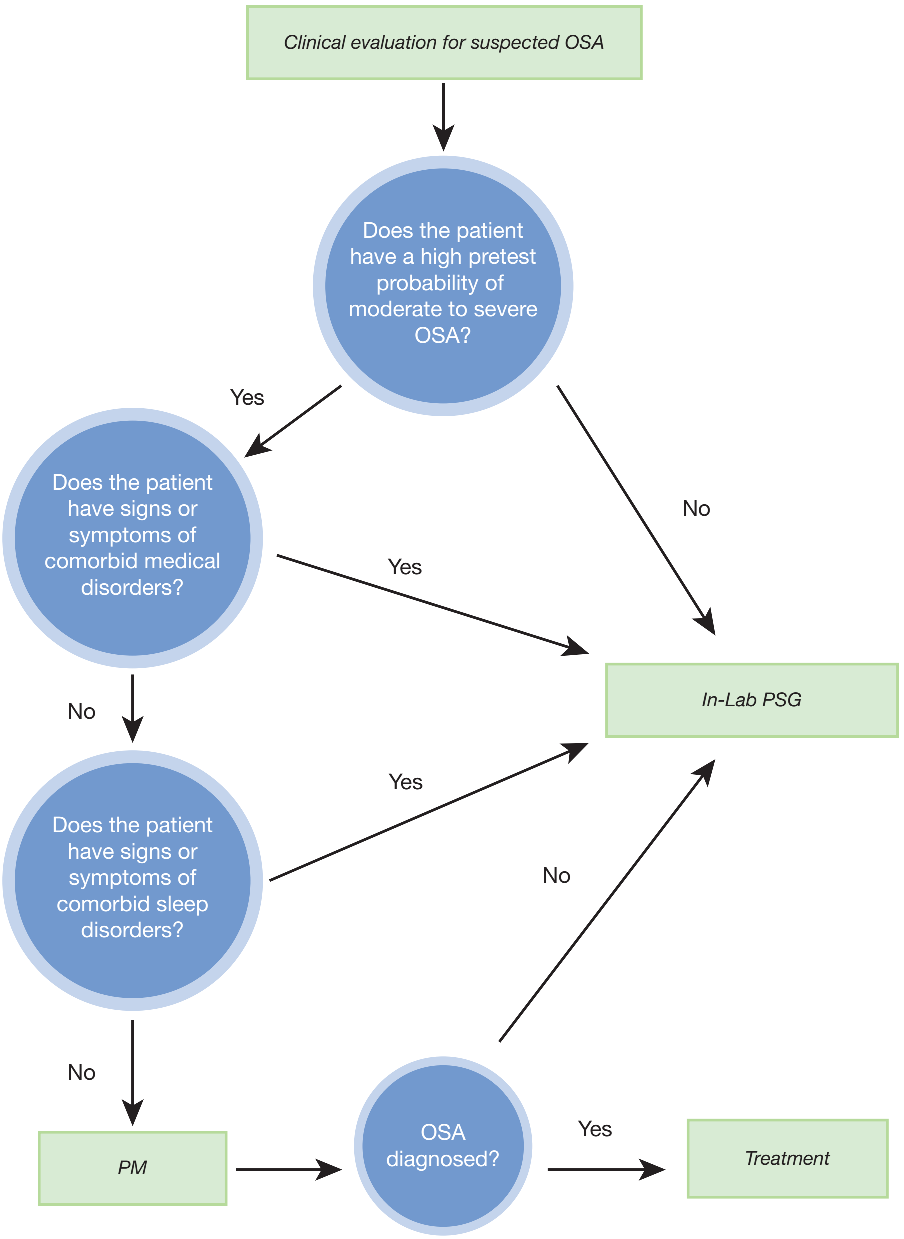
Clinical evaluation for suspected OSA
Does the patient have a high pretest probability of moderate to severe OSA?
Yes
No
Does the patient have signs or symptoms of comorbid medical disorders?
Yes
No
In-Lab PSG
Yes
Does the patient have signs or symptoms of comorbid sleep disorders?
No
No
PM
OSA diagnosed?
Yes
Treatment

Figure 98-12 Out-of-center testing decision tree. OSA, obstructive sleep apnea; PSG, polysomnography; PM, portable monitor (out-of-center sleep testing). *(Data from Collop NA, Anderson WM, Boehlecke B, et al. Clinical guidelines for the use of unattended portable monitors in the diagnosis of obstructive sleep apnea in adult patients. Portable Monitoring Task Force of the American Academy of Sleep Medicine. J Clin Sleep Med. 2007;3(7):737–747.)*

sleep, although sleep stage delineation was frequently inaccurate.[282] While not yet approved for SDB diagnosis or treatment, these devices may be useful in their potential to enhance patient engagement and patient–provider interaction in the future.[283]

In general, portable monitors' accuracy and precision relative to PSG have been easier to question than to demonstrate. Significant differences among monitor brands of the same type, inherent night-to-night variability of AHI which is also noted on in-laboratory PSG, and difficulties keeping pace with emerging technologies have all limited research in the field. AHIs determined from type III studies tend to underestimate PSG indices largely due to absence of EEG leads; PSG AHI is calculated as the number of respiratory events per hour of *sleep*, while type III monitor AHI is based on hours of *use*. In addition, hypopneas can be underdiagnosed in the absence of EEG (as arousals used to score hypopneas cannot be reliably determined). Therefore, portable monitors may have reduced sensitivity to detect OSA, especially in patients with mild disease.[284] Nevertheless, overreliance on AHI as the gold standard of measurement of disease severity is fraught with pitfalls as described above. Thus, a key measure from HSAT may not be its agreement with PSG AHI but rather that functional outcomes were not inferior when HSAT was used, compared with PSG-based assessment.[277]

Once the diagnosis is made, treatment decisions among providers (CPAP or no CPAP) are more heterogeneous for patients with portable monitor–diagnosed mild to moderate OSA compared with patients diagnosed with mild to moderate OSA through PSG.[285] Nevertheless, functional outcomes after treatment have not differed in patients with a high pretest probability for OSA diagnosed using portable monitors, compared with in-laboratory PSG.[277,286]

Guidelines were updated for portable sleep testing in 2007[287] and for all OSA testing in 2017.[273] They recommend that out-of-center sleep testing with a portable monitor be performed only in patients with high pretest probability of moderate to severe OSA without significant comorbidities including CHF, severe COPD, and neuromuscular disease, risk of CSA, or suspicion of other sleep disorders such as parasomnias or narcolepsy. Out-of-center testing is recommended when in-laboratory PSG is not feasible due to immobility, safety, or critical illness; or in patients who need assessment of responses to non-CPAP treatment (i.e., oral appliance, upper airway surgery, weight loss). If a single HSAT is negative or technically inadequate, PSG is recommended to confirm the presence or absence of OSA.[277] Kuna et al. found that, of 35 patients with inconclusive results on their HSAT, 27 (77%) were found to have sleep apnea on their PSG.

Despite these guidelines, utilization of portable sleep monitoring varies widely due to a number of factors, including local availability of in-laboratory PSG and the burgeoning number of insurers now mandating portable testing in lieu of PSG.[288] An algorithm for appropriate testing modalities for SDB can be seen in Fig. 98-12.

In summary, in-laboratory PSG represents the gold standard for diagnosing sleep apnea. Technologic advancements in portable monitors and acceptance of out-of-center sleep testing by third-party payers has led to increased access to diagnostic testing. However, excessive focus on the significance of absolute elevations in AHI can hamper the diagnosis and treatment of OSA. Patients may exhibit similar AHI but experience different quality of sleep and outcomes. Important variables such as oxygen desaturation, number of arousals, and apnea/hypopnea length are not reflected by the AHI. Furthermore, it is not the AHI itself but the consequences (hypertension, myocardial infarction [MI], stroke, cardiac arrhythmias, excessive daytime sleepiness) of sleep apnea that are of paramount importance.

CONSEQUENCES OF OBSTRUCTIVE SLEEP APNEA

The number of recognized associations with sleep apnea has increased considerably. OSA sequelae can be broadly categorized by their neurocognitive, cardiovascular, metabolic, and neoplastic effects. OSA should be seen as a systemic disorder with effects on multiple organ systems since all tissues are subjected to CIH, although this effect varies between tissues.[289] Figure 98-13 is a simplified representation of three principal disturbances associated with apnea during sleep, the proposed downstream pathophysiologic mechanisms, and reported clinical consequences. This is not a complete depiction of all that is known, and many factors operate in a complex interplay that can jointly augment health risk.

Neurocognitive Consequences of OSA

OSA-associated neurocognitive dysfunction may occur via a hypoxia/reperfusion injury mechanism whereby increased lipid peroxidation induces oxidative stress within neural tissue.[290,291] Neurovascular endothelial dysfunction has also been demonstrated in OSA patients, leading to an imbalance between vasodilation and vasoconstriction imbalance; lower nitric oxide levels in OSA patients appear to be a key mediator.[292] Dysregulated endothelium can also lead to hypercoagulability and atherosclerosis, potentially placing patients at higher risk of vascular dementia.[293] Indeed, OSA has also been linked to increased risk of developing vascular dementia and Alzheimer disease.[294–297] Patients with OSA have increased build-up of β-amyloid, a protein linked to the development of Alzheimer disease, compared to controls without OSA.[298] Data showing impact of PAP therapy on dementia progression are lacking, and recent research exploring its impact on mild cognitive impairment progression has been mixed.[299,300] Further research in this area is ongoing and greatly needed.

Excessive daytime sleepiness and sleep fragmentation associated with sleep apnea can lead to diminished cognitive function, affecting attention, memory, vigilance, and executive function.[301–304] While motor speed appears to be spared, fine motor coordination is impaired in OSA patients.[228,304,305] Despite these associations, data from the Apnea Positive Pressure Long-term Efficacy Study (APPLES) failed to show correlation between AHI and neurocognitive performance after adjusting for ethnicity, educational level, and gender in a cross-sectional cohort.[306] There were no significant improvements in neurocognition performance with CPAP therapy. However, this negative finding may reflect participant selection; participants had normal cognitive function and had attained a relatively high grade level of education (mean, 15.5 years) before entering the study. Modest relationships between oxygen desaturation and neurocognitive performance were observed in this study and in the Sleep Heart Health Study.[307,308] Although the APPLES study's methodology has been questioned, these studies demonstrate inherent difficulties in establishing the nature and prevalence of neurocognitive sequelae among OSA patients.[309]

There may be several reasons for such complexities. First, there are many facets of cognition that are difficult to capture with a single test or study protocol. For instance, broad domains of cognitive function include executive function, visuospatial planning, memory, attention, processing speed, and language. Therefore, "cognitive" effects of untreated OSA may manifest in one area but not another. Second, the cognition-OSA link can be affected by many individual factors, such as genetics, cerebrovascular adaptations to OSA, duration of presence of OSA, and experience of sleep and

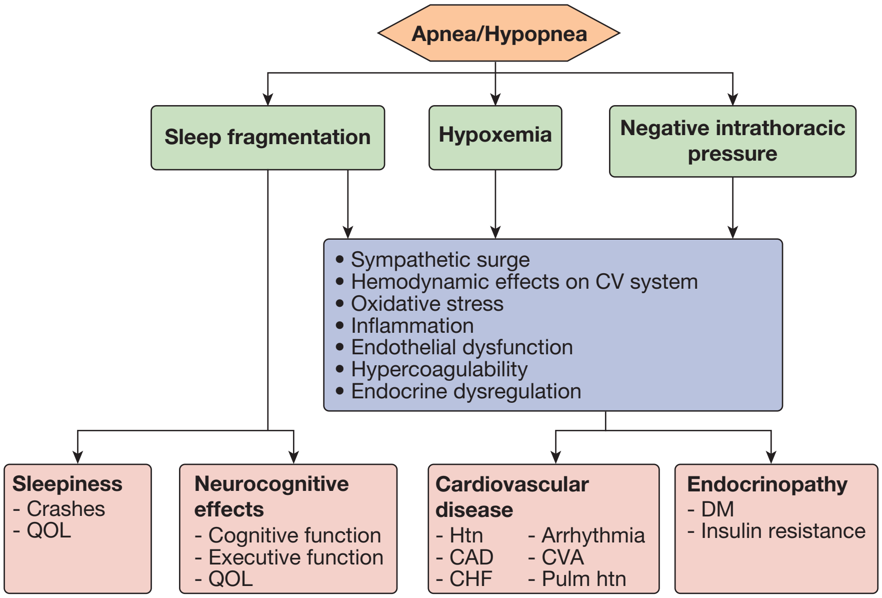

Figure 98-13 Flow chart of the proposed pathophysiologic mechanisms and consequences of obstructive sleep apnea. CHF, congestive heart failure; CV, cardiovascular; CVA, cerebrovascular accident; DM, diabetes mellitus; Htn, hypertension; Pulm htn, pulmonary hypertension; QOL, quality of life.

fatigue. Indeed, some to-be-determined patient groups may be more susceptible to cognitive effects of OSA than others. Third, studies looking at this relationship have been plagued by methodologic issues such as small sample sizes that reduce their power to find effects that may exist. Additionally, using AHI to determine OSA severity minimizes the contribution of other factors, such as arousals, respiratory event duration, and hypoxic burden, that could more closely correlate with neurocognitive impairment.[310]

OSA-related daytime sleepiness, attention lapses, and reduced vigilance are particularly salient when considering motor vehicle crashes. Several studies and a meta-analysis have shown that these patients with OSA have at least a twofold increase in relative risk of automobile accidents; up to 20% of crashes are due to sleepiness, with OSA as the most common contributing medical cause.[224,311–313] When treated with CPAP, accident rates return to those of the general population.[314] This creates an intriguing medicolegal quandary for physicians treating nonadherent OSA patients who are known to drive drowsy. Practicing physicians should understand the relevant laws in their own state for guiding decisions regarding monitoring of drivers and reporting to appropriate agencies. The American Thoracic Society has published guidelines regarding OSA and driving that support expedited diagnosis using PSG and/or out-of-center testing and rapid treatment with PAP therapy.[313] Clinicians should also consider implementation of a practice-based plan for patient education regarding drowsy driving risks and countermeasures.[313]

Special consideration should be given to commercial motor vehicle (CMV) operators with OSA given the increased risk of fatality in truck, train, and bus crashes.[315–318] Unfortunately, there is no unified regulatory mandate for OSA screening in these CMV operators.[319] The American Academy of Sleep Medicine (AASM) and Transportation Safety Awareness Task Force recommends that objective measures be used to screen all CMV operators for OSA.[320] The most common measures are body mass index (BMI), neck circumference, and the presence of hypertension; self-reported measurements of excessive sleepiness are less reliable due to their subjectivity and vulnerability to symptomatic minimization. Some major trucking companies now screen their drivers for OSA, with significant savings shown in non-OSA related medical insurance claim costs.[321–323]

Untreated OSA has also been independently associated with depression.[233] SDB should be considered in anyone suffering from this mood disorder. Beyond depressive symptoms per se, OSA also impacts quality of life as measured by the Functional Outcomes of Sleepiness Questionnaire (FOSQ) and the Sleep Apnea Quality of Life Instrument (SAQLI).[324,325] CPAP therapy has been shown to improve these measures[326] as well as more mood-specific measures such as the Hospital Anxiety and Depression scale.[327]

■ Cardiovascular Consequences of OSA

A number of cardiovascular consequences of sleep apnea have been reported. While each is discussed individually, they share common and complex pathophysiology. Obstructive apneas result in recurrent hypoxia, repetitive arousals, and large swings in intrathoracic pressure.[328] These processes lead to an array of maladaptive mechanisms: sympathetic surges, oxidative stress, inflammation, vascular endothelial dysfunction, metabolic dysregulation, hypercoagulability, and mechanical effects on the heart and vessels.[161,162,291,329–341] Each of these physiologic responses to apnea has been the focus of detailed research and requires further reading beyond the scope of this chapter. Overall, it is evident that sleep apnea induces physiologic processes conducive to the development of cardiovascular disease; results from a 10-year nonrandomized controlled observational study of patients with and without OSA showed that untreated severe OSA patients had a 2.9-fold increased rate of fatal cardiovascular events after adjusting for confounding variables (Fig. 98-14).[248]

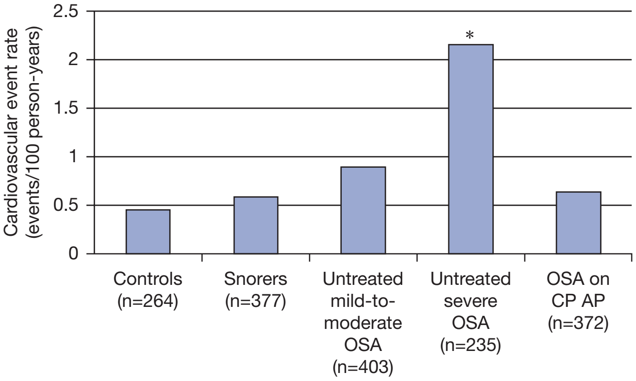

Figure 98-14 Cardiovascular event incidence during 10-year follow-up in healthy men (controls), snorers, and treated and untreated OSA patients. $^{*}p < 0.0001$ vs. healthy men. *(Data from Marin JM, Carrizo SJ, Vicente E, et al. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. Lancet. 2005;365(9464):1046–1053.)*

Hypertension

Data persuasively link OSA with systemic hypertension. About half of patients with known OSA have coexisting hypertension, and 30% to 40% of patients with hypertension have OSA.[342–344] The prevalence of OSA in patients with resistant hypertension is even higher; Logan et al.[345] studied subjects with resistant hypertension who were all taking optimal doses of at least three antihypertensive agents and found an OSA (AHI ≥10 events/h) prevalence of 83% with a mean AHI of 25 events/h.

A canine model of sleep apnea demonstrated that recurrent occlusion of a tracheostomy each time the animal fell asleep led to the development of hypertension, both acutely during the sleeping period and subsequently chronically during the wake period even though the airway was no longer occluded.[346] Implicated mechanisms behind this phenomenon in humans include alterations in output of the sympathetic nervous system and changes in the renin–angiotensin system,[39] endothelial dysfunction,[347] inflammation,[348] and metabolic dysregulation (described further below).[349]

In humans, OSA has ranked among the main causes of secondary hypertension, with several large cross-sectional studies demonstrating this relationship.[350] In the Sleep Heart Health Study, the odds ratio for the presence of hypertension in the highest category of AHI (≥30 events/h) was 1.37 compared with the lowest category AHI (<1.5 events/h) for adults younger than 65 years of age.[351] The Wisconsin Sleep Cohort Study, a prospective population-based study, demonstrated an increased risk of incident hypertension in patients with even mild OSA (AHI 5–15 events/h). Independent of BMI, the odds ratio was 2.0 for mild (AHI 5–15 events/h) and 2.9 for moderate or severe sleep apnea (AHI ≥15 events/h) over a 4- to 8-year follow-up period.[352] Among individuals in a prospective cohort of patients who were diagnosed with OSA, those patients who did not utilize therapy with CPAP had a significantly higher risk of incident hypertension compared to controls without OSA, whereas the risk for incident hypertension among OSA patients who did use CPAP was lower and similar to the control group.[353]

In several randomized trials, treatment of OSA with continuous positive airway pressure (CPAP) has been shown to reduce BP, particularly if OSA is severe. In these studies, BP was significantly lowered not only in patients with resistant hypertension, but also in patients with relatively mild hypertension. One randomized controlled trial demonstrated that several weeks to months of CPAP resulted in a significant reduction in daytime BP up to 5.1 mm Hg compared to treatment with subtherapeutic CPAP.[354] A meta-analysis of 16 randomized trials comparing CPAP users to OSA-positive nonusers found a mean net decrease in systolic pressure of 2.46 mm Hg in the former group compared with the latter.[355] This effect may appear modest, but antihypertensive literature shows a 41% decline in stroke and a 22% decline in coronary artery disease (CAD) from just a 5-mm Hg decline in diastolic BP; even a 2-mm Hg diastolic BP drop may decrease these risks by 15% and 6%, respectively.[356,357] CPAP had less effect on incident hypertension in a nonsleepy OSA population (AHI ≥20 events/h).[358]

CPAP impacts BP elevation most in patients with resistant hypertension. One study found a mean arterial pressure drop of 5.6 mm Hg in CPAP-adherent, resistant hypertension patients versus a drop of 0.8 mm Hg in CPAP-adherent patients with controlled hypertension.[359] Nearly 71% of these resistant hypertensive patients had their antihypertension regimen simplified after CPAP.[359] Other work has shown up to a 7.3-mm Hg drop in nocturnal systolic pressure in similar resistant hypertension patients using CPAP, with resumption of normal nocturnal BP dipping observed in 27% of their 33-person cohort.[360] This work was later replicated in a larger randomized trial.[361] A meta-analysis of 6 studies reveals ambulatory systolic and diastolic pressure declines consistent with these findings.[362] These beneficial effects of CPAP on hypertension, however, should not detract from emphasis on conventional pharmacologic methods of lowering BP.

Myocardial and Cerebrovascular Events

OSA has been associated with MI and stroke in cross-sectional studies, with a large longitudinal follow-up study confirming increased rates of cardiovascular events and cardiovascular mortality in patients with untreated severe OSA (Fig. 98-13).[248,363,364] One study showed increased cardiovascular event rates even in patients with moderate OSA.[365]

Specifically considering the stroke literature, OSA prevalence among these patients ranges from 50% to 70%.[366] Therefore, all stroke patients should be screened for OSA. Results from the Sleep Heart Health Study reveal that men with moderately severe OSA have an almost threefold increased risk of ischemic stroke compared to men without OSA. In fact, stroke risk in men increased 6% with every 1-unit increase in AHI between 5 and 25 events/h. The effect is not as strong in women, with risk of stroke only significantly increased at AHI >25 events/h.[275]

OSA likely leads to MI and cerebrovascular events in a variety of ways. Hypoxic events during sleep may trigger them; individuals with OSA who suffered an MI are more likely to have had their acute event between the hours of midnight and 6:00 AM than OSA-free individuals.[367] Another contributor could be OSA-related oxidative stress and proinflammatory state, leading to atherosclerosis. This has been demonstrated in a mouse model.[368] In addition, snoring is associated with plaques in the carotid arteries but not the femoral arteries, even in patients with few apneas.[369] Since rat tail vibration has been previously shown to induce blood vessel endothelial damage, snoring-related vibration may have a similar effect on the carotid arteries, increasing risk of stroke.[370] Should this concept be further demonstrated in humans, treating any patient who snores—regardless of OSA status—could become the norm.

Data demonstrating the impact of PAP therapy in this area have been conflicting. One recent meta-analysis comparing OSA patients using PAP to untreated OSA patients showed a lower rate of major adverse cardiovascular and cerebrovascular events (risk ratio, 0.46; 95% confidence interval [CI], 0.32–0.66) and all-cause mortality[371] (risk ratio, 0.40; 95% CI, 0.24–0.69). Nevertheless, two randomized trials—the Sleep Apnea Cardiovascular Endpoints (SAVE) study[249] and the Impact of Sleep Apnea Syndrome in the Evolution of Acute Coronary Syndrome (ISAACC) study[250]—failed to demonstrate similar improvements in cardio/cerebrovascular event reduction or mortality with PAP therapy.

Proposed reasons for this discrepancy include the exclusion of excessively sleepy patients and low PAP adherence in the later two trials.[372] Excluding sleepy patients leads to selection bias that may have skewed the study findings toward negative results. Sleepy adults with OSA suffer greater cardiovascular risk from the disorder than nonsleepy adults with OSA, yet this important group has been excluded from analyses; there are ethical concerns about randomizing sleepy patients to absent or “sham” PAP therapy given the increased risk of vehicle crashes.[227] Another methodologic concern about these studies is low adherence to PAP. Mean PAP use was just 3.3 h per night over the duration of the SAVE study, and median PAP use was just 2.2 h per night over the duration of the ISAACC study. Recent observational data in a clinical population revealed a median PAP adherence of 5.6 h nightly.[373] Therefore, the conclusions of these RCTS are not applicable to clinical patients who present for treatment of OSA.[374]

Other Cardiovascular Consequences of Sleep Apnea

OSA adversely impacts a number of other cardiovascular outcomes including CAD and CHF. The Sleep Heart Health Study studied men and women ≥40 years old who were free of CAD and CHF at baseline.[375] After a median 8.7-year follow-up and adjusting for multiple risk factors, they found OSA to be a significant predictor of CAD in men (but not women) ≤70 years of age. Men age 40 to 70 were 68% more likely to develop CAD if they had severe OSA than no OSA. Men were also 58% more likely to develop incident CHF when comparing these two groups. Explanations for the observed sex differences are unclear but may include less lifetime exposure to OSA in women due to their tendency to develop the disorder after menopause, and possible sex differences in physiologic response to OSA.[375]

There are several pathophysiologic explanations for higher rates of CHF in OSA patients.[376] Generation of negative intrathoracic pressure resulting from obstructive apneic events can increase the difference between extracardiac and intracardiac forces, increasing LV transmural pressure and leading to LV hypertrophy.[377] Apneic events can also distend the right ventricle, as increased filling (due to negative intrathoracic pressure) and pulmonary vasoconstriction (due to hypoxia) occur simultaneously. Leftward shifting of the intraventricular septum can occur, resulting in reduced LV filling and stroke volume.[378] OSA-associated hypoxia has also been shown to decrease systolic contractility directly while impairing diastolic relaxation.[379,380]

Cardiac arrhythmias have also been associated with OSA. Relatively benign arrhythmias (i.e., bradycardia/tachycardia [bradycardia during the apnea and tachycardia during the arousal], atrial premature contractions, and ventricular ectopy) have long been observed, but ongoing attention has focused on atrial fibrillation.[328] Data from the Sleep Heart Health Study have shown that atrial fibrillation is more common in patients with severe OSA than in those without OSA,[381] and a more recent Canadian study showed an 85% prevalence of OSA of any severity among atrial fibrillation patients.[382] In a recent randomized controlled trial of patients with moderate to severe sleep apnea and paroxysmal atrial fibrillation who were awaiting ablation, CPAP treatment did not result in a significant reduction in the percentage of time in atrial fibrillation.[383] However, as in other studies described above, patients with more significant excessive daytime sleepiness were excluded from this trial, which may have biased the results. In nonrandomized studies, patients with treated OSA who underwent cardioversion or pulmonary vein isolation have been observed to be 35% to 40% less likely to have recurrence of atrial fibrillation in the first year than patients with untreated OSA.[384] Randomized controlled trials of OSA treatment in patients after ablative therapy for atrial fibrillation are ongoing (*clinicaltrials.gov/ct2/show/NCT02727192* and *www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=369157*).

Metabolic Consequences of OSA

OSA has been proposed as an additional component of the metabolic syndrome, a multisystem disorder currently characterized by obesity, impaired fasting glucose, hypertriglyceridemia, and reduced high-density lipoprotein (HDL). In fact, OSA has been independently associated with each component of this syndrome; individuals with OSA (AHI ≥15 events/h) have about 5.9 to 9 times the likelihood of having the metabolic syndrome compared to individuals without OSA.[385–387] Specifically considering glucose tolerance, up to 86% of type 2 diabetes patients have at least mild OSA (AHI ≥5 events/h).[388] A study that followed diabetes-free men for 10 years showed that development of diabetes was independently associated with presence of OSA at baseline.[389] Similarly, recent studies show increased incidence of nonalcoholic fatty liver disease (NAFLD) among OSA patients.[390]

There is evidence of OSA as an independent risk factor for insulin resistance (controlling for obesity) in general population and sleep center cohort studies.[161,391] Results from intervention studies have been mixed, with CPAP therapy leading to improved glycemic control in one study, but having no significant impact in another.[392,393] An observational study of 1233 veterans revealed a direct relationship between increasing OSA severity and likelihood of conversion from prediabetes to diabetes, even after adjusting for age, sex, race, baseline fasting blood glucose, BMI, and weight change. PAP use attenuated the risk of incident diabetes in this population.[394] Similarly, a resistance to leptin, the satiety-signal hormone produced in adipose tissue that plays a role in glucose and fatty acid metabolism, has been observed among patients with OSA. Leptin levels increase proportionally with OSA severity, and they are recognized markers of cardiovascular risk.[349] Similarly, dyslipidemia has been associated with OSA both biochemically and clinically; oxidative stress due to intermittent hypoxia appears to be an important mediator.[395,396] Observational studies have suggested that lipid profiles improve with CPAP therapy,[397] but randomized controlled trial data suggest less of an effect.[398,399]

Mechanisms underlying the link between OSA and metabolic syndrome are likely complex and remain to be fully elucidated. Chronic intermittent hypoxia exposure and sleep fragmentation are key mediators that may trigger a systemic inflammatory response.[400] At a minimum, patients with OSA should be assessed for the presence of relevant metabolic disturbances and the metabolic syndrome. Obese patients with type 2 diabetes mellitus should be screened for OSA.

Oncologic Consequences of OSA

Intermittent hypoxia from OSA has also been implicated in the development of cancer,[401] its progression,[402] and cancer outcomes.[403] Long-term data from the Wisconsin Sleep Cohort showed cancer-related mortality rates increased directly with OSA severity, defined by AHI and degree of hypoxia during the sleep period.[404,405] Other studies have linked OSA with specific types of cancer, such as breast,[406] central nervous system cancer,[407] and lung cancer.[408] However, some studies have failed to show an OSA-cancer association. For instance, one Canadian study found no relationship between increased cancer incidence or prevalence and OSA.[409] A meta-analysis produced similar findings.[410] Hypotheses to reconcile these disparate findings include differences in observation length (longer observation times tend to favor finding an association) and measure of OSA severity utilized (stronger association with utilization of hypoxemia, rather than AHI).[403] The impact of OSA treatment on cancer incidence, prevalence, or mortality is yet to be determined.

Mortality

Several cohort studies, including the Wisconsin Sleep Cohort, Busselton Health Study, and the Sleep Heart Health Study demonstrate an association between untreated OSA and increased mortality.[274,411,412] This relationship is strongest when considering cardiovascular mortality in individuals with severe OSA.[412] A study of patients with ischemic heart disease showed a dose–response relationship between OSA severity and mortality, reinforcing the importance of OSA screening in this population.[413] Previous studies have shown that survival curves for patients with severe OSA are identical whether or not they complain of sleepiness, supporting treatment for nonsomnolent patients with OSA.[274,414] Notably, these findings may apply less to older adults (age >65). A more recent analysis within this age group has shown increased mortality in older OSA patients only if they exhibit excessive daytime sleepiness.[415] Two recent meta-analyses of observational and randomized studies have not supported a reduction in all-cause mortality in OSA patients using PAP therapy,[371,416] but evidence quality was low due to study type and imprecision regarding measures of PAP adherence that were used. Further studies are needed to delineate further whether some groups derive mortality benefits from PAP therapy.

The association between OSA and mortality is more questionable among individuals over the age of 65.[417] Indeed, Lavie et al. showed a survival *advantage* in elderly patients (≥65 years) with RDIs (similar to AHI) between 20 and 40 events/h; OSA has been hypothesized to be protective in this group due to ischemic preconditioning, leading to increased vascular endothelial growth factor (VEGF) and collateral coronary vessels.[418,419] A subsequent study observed significantly increased mortality rates are among elderly people with severe OSA (AHI ≥30 events/h), and normalization of the mortality rates with CPAP treatment.[176] Debate about whether OSA evaluation and treatment for elderly patients leads to any mortality benefit continues.

Economic Consequences of OSA

Because it is so common, sleep apnea poses a sizeable economic burden on society. OSA subjects have been demonstrated to utilize healthcare resources at approximately 1.5 to 2 times the rate of controls as far back as 10 years prior to diagnosis.[420–423] Estimates of the total economic cost that sleep apnea confers upon society are sparse. However, the financial burden of moderate to severe OSA in the United States is estimated to be $65 to $165 billion/year, which is greater than asthma, stroke, heart failure, and hypertensive disease ($20–$80 billion).[424,425] The economic burden of undiagnosed OSA patients alone is estimated at over $149 billion, highlighting the need for enhanced OSA screening and diagnosis pathways.[426] One way to ameliorate this burden may be through the use of PAP therapy. A recent analysis of Medicare beneficiaries showed that full adherence to PAP treatment (PAP use ≥4 h/night, >70% of nights) is associated with less increase in healthcare costs over time than in subjects with lower PAP adherence.[427]

Limited numbers of sleep laboratories, sleep physicians, and sleep technologists coupled with cost of equipment and reimbursement issues have created a “bottleneck” effect in which global demand for sleep medicine services exceeds capacity. Nevertheless, economic analyses have shown that addressing diagnosis and treatment of moderate to severe sleep apnea, particularly with CPAP, is economically attractive and supports the value to society relative to accepted treatment for other common conditions such as hypertension control, breast cancer screening, and comprehensive diabetes care.[428–433]

TREATMENT OF OSA

The decision to treat OSA should be based on its severity, related symptoms, and medical comorbidities. Treating moderate to severe disease (defined as AHI ≥15), particularly with PAP therapy, improves neurobehavioral performance, enhances quality of life, and may reduce cardiovascular risk.[434,435] In addition to OSA severity, disease-related sleepiness (or lack thereof) has been identified as a treatment determinant. Only sleepy patients with mild to moderate OSA show functional improvement using PAP, although the effect may be small.[436,437] Moreover, nonsleepy patients may not experience significant BP or cardiovascular event rate reduction on PAP, regardless of OSA severity.[131,243,358,438] The AASM currently recommends PAP for OSA patients with excessive daytime sleepiness, reduced sleep-related quality of life, and hypertension.[439] However, for nonsleepy adults with OSA, the AASM concluded there is insufficient evidence to either recommend or withhold PAP and recommended that the patient and clinician have a balanced discussion to decide whether treatment to potentially mitigate cardiovascular risk should be initiated.[439]

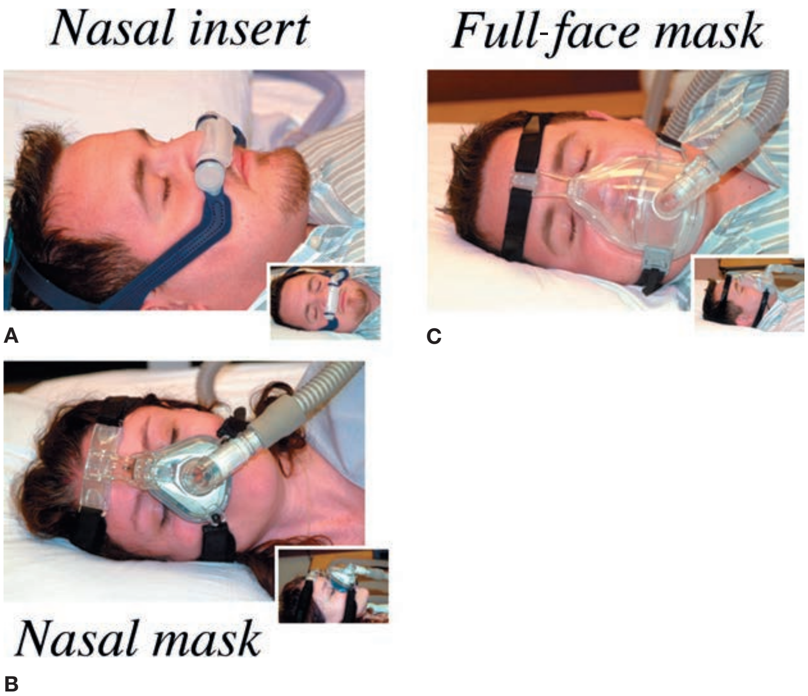

Figure 98-15 Examples of three types of CPAP interfaces. **A.** The subject is wearing a nasal pillow that fit directly into the nostrils. **B.** The subject is wearing a nasal CPAP mask. **C.** The subject is wearing a full-face mask (nose and mouth are both covered). With all three types of interfaces it is essential to ensure a good seal with minimal leaks.

Third-party payers have utilized these data in creating treatment coverage structures. The Centers for Medicare and Medicaid Services cover at least the initial 12 weeks of PAP therapy in patients whose AHI or RDI is at least 15 events/h. Patients with indices of at least 5 events/h but no more than 14 events/h must have documented excessive daytime sleepiness, impaired cognition, mood disorders or insomnia, hypertension, ischemic heart disease, or history of stroke to qualify for PAP coverage.[440] Ultimately, provider expertise should dovetail with patient preference to guide treatment choice and modality.

Options for the treatment of OSA include PAP therapy, behavioral therapies, mandibular repositioning devices, surgical treatments, and adjunctive therapies.[27] First-line therapy for sleep apnea syndrome remains medical.

■ Positive Airway Pressure Therapies

Sullivan et al.[10] first described the use of nasal CPAP to treat OSA in 1981 (see examples of subjects wearing CPAP in Fig. 98-15). Today, CPAP remains the mainstay of therapy for most patients with OSA. CPAP delivers a fixed pressure continuously throughout inspiration and expiration, providing a pneumatic splint for the airway that prevents airway collapse during sleep, when upper airway muscle dilator activity is reduced. CPAP therapy increases airway caliber in the retropalatal and retroglossal regions (Fig. 98-16); in particular, it increases the lateral dimensions of the airway and thins the lateral pharyngeal walls.[441]

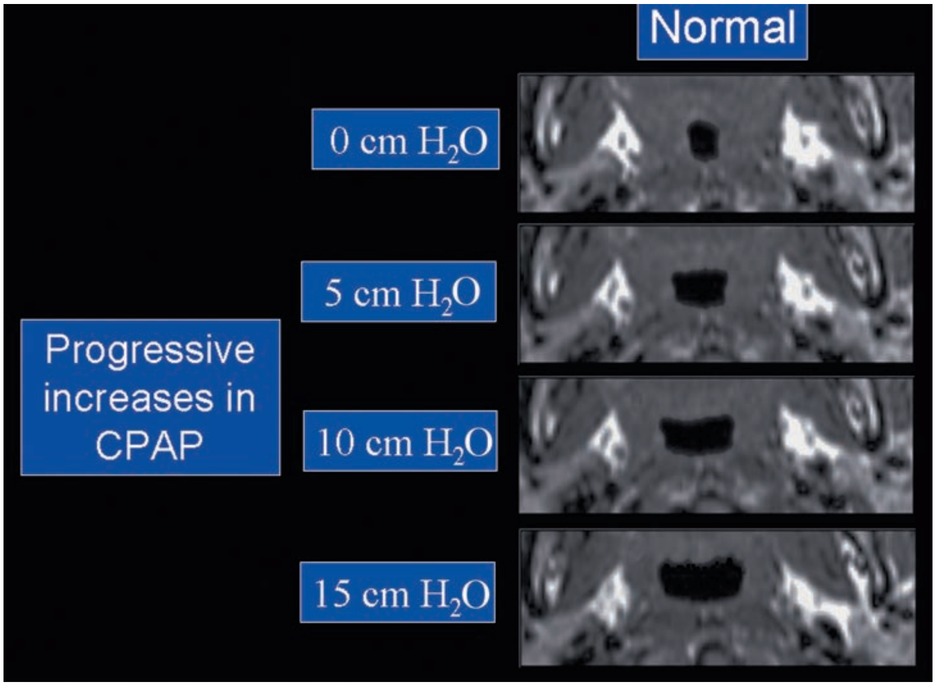

Figure 98-16 Axial retropalatal magnetic resonance imaging (MRI) in a normal individual with continuous positive airway pressure (CPAP) ranging from 0 to 15 cm H_2O. With increasing CPAP there is a progressive increase in the size of the upper airway, particularly in the lateral dimension. (The anterior–posterior dimensions of the airway do not change significantly with CPAP.) There is little movement of the parapharyngeal fat pads (white structures lateral to the airway) but progressive thinning of the lateral pharyngeal walls. *(Reproduced with permission from Schwab RJ, Pack AI, Gupta KB, et al. Upper airway and soft tissue structural changes induced by CPAP in normal subjects. Am J Respir Crit Care Med. 1996;154(4 Pt 1):1106–1116.)*

CPAP usually reduces the number of apneic episodes during sleep to the normal range and has the advantage of being noninvasive. It clearly improves daytime sleepiness in patients with OSA in numerous studies including those in which patients were randomized to CPAP or sham (subtherapeutic) CPAP therapy, with greater improvements in daytime sleepiness among those with the highest AHIs.[436,437,439,442] While there have been many randomized controlled trials published examining the effect of CPAP therapy on blood pressure,[443] CPAP use is associated with only a modest reduction in BP in the range of 2 to 4 mm Hg. This effect seems to be impacted by the underlying severity of OSA, the degree of daytime sleepiness, and the number of hours of nightly use of CPAP therapy.[355,371,444–446] In addition, drivers with OSA who are treated with CPAP have a reduced risk of motor vehicle crashes.[447]

CPAP therapy is indicated in all patients with obstructive sleep apnea (i.e., an AHI $\geq$5 events/h) who are sleepy, report sleep-related quality of life changes, and have comorbid hypertension.[371] The optimal pressure can be determined during a titration polysomnogram or using out-of-laboratory treatment algorithms with auto-adjusting CPAP.[439] Typically, pressures of 5 to 20 cm H_2O are needed to abolish apneic events, snoring, and oxyhemoglobin desaturation in all positions and during REM sleep.

CPAP can be delivered using a variety of interfaces (Fig. 98-15) including nasal masks, nasal inserts, or full-face masks (which cover the nose and mouth). It is important to ensure that the patient has a well-fitting interface with the CPAP machine absent of air leaks. Mask leak is measured directly by the PAP unit, and information on the degree of leak can be obtained from the CPAP machine and reviewed remotely by the provider. Similarly, patients can receive feedback about mask leak directly from their unit or from a mobile application to allow for adjustment to improve mask fit in real time. Mouth leaks, which often result from mouth breathing while using a nasal mask, can render CPAP ineffective, since the positive pressure generated by the CPAP unit escapes. Use of heated humidity with CPAP therapy has been shown to successfully ameliorate some of the side effects listed in Table 98-6. Some but not all studies have demonstrated improvements in CPAP adherence with the use of heated humidification.[448–450]

Over time, CPAP machines and masks have become increasingly user friendly. CPAP masks have improved profoundly, so that the prospect of using CPAP has become much less daunting. Some institutions operate “mask clinics” concomitantly with sleep clinics so that patients with OSA can be fitted for a CPAP interface immediately after the sleep specialist consultation. CPAP units are also smaller, more portable, and quieter, and they now nearly universally provide data on patient adherence patterns, mask leaks, and the effectiveness of the delivered CPAP pressure (i.e., residual SDB events with use of CPAP). Most modern CPAP devices automatically upload this usage data directly to a secure, cloud-based storage system on a regular basis. These data provide critical clinical information to be interpreted by sleep medicine providers. In addition to addressing mask leak, providers can also make pressure adjustments if the residual AHI is noted to be greater than 10 events per hour in a patient who has symptoms or if the residual AHI is greater than 20 events per hour.[451]

TABLE 98-6 Complications Associated with Positive Airway Pressure (PAP) Therapies

Nocturnal arousals
Rhinitis, nasal irritation, and dryness
Aerophagia
Mask and mouth leaks (dry mouth in morning)
Facial rash or irritation
Difficulty with exhalation
Claustrophobia

CPAP use is associated with few serious side effects.[452–455] Common side effects are listed in Table 98-6. Nasal irritation and rhinitis are treated with heated humidification and consideration of a nasal steroid spray. Claustrophobia may be relieved in some cases by changing the type of mask. Aerophagia can be ameliorated by altering body position or mask type. Serious adverse effects are uncommon but include very rare reports of severe epistaxis, meningitis, and pneumocephalus.[456–458]

Like other chronic therapies, there are issues with adherence to CPAP. Currently, insurance rules often require demonstration of adherence defined as >4 h/night for 5/7 nights/week by the 90th day of institution of therapy. With this rule in place, short-term adherence is good. A big-data study of 2.62 million patients showed that 75% met this criterion; participants used CPAP for a mean of 93% of nights.[459] The mean daily use was 5.1 ± 2.5 (SD) h across all nights and 6.0 ± 2.0 h for nights CPAP was used. Approximately 65% to 80% of patients who start CPAP therapy continue to use it after 4 years.[460,461]

While estimates suggest that patients use CPAP treatment, on average, for only 4 to 5 h per night, a dose–response relationship has been observed between longer durations of nightly use and greater likelihood of achieving normal daytime alertness and functional status.[462] Studying methods to enhance CPAP adherence has been an active area of inquiry,[463,464] and multiple methods have been employed and evaluated. Techniques employed include patient education and behavioral interventions such as motivational enhancement.[464] The latter has been studied in randomized trials.[465,466] In one study CPAP adherence was improved by an average of 99.0 min/night at 6 months after starting CPAP.[465] Authors of a Cochrane Review came to the conclusion that behavioral therapy produces a considerable improvement in adherence to CPAP.[467]

Modern CPAP machines collect CPAP adherence and efficacy information daily. This information can be obtained remotely since CPAP machines can have modem or Bluetooth capabilities. The information transmitted on a nightly basis are the hours of use, mask leak, and residual apnea–hypopnea index. CPAP manufacturers maintain cloud-based servers that store the data. These data can be accessed by providers, including the DME companies. Feeding back information on actual compliance to CPAP to patients themselves enhances CPAP use.[468] The ready availability of data from CPAP machines allows other innovative approaches. Telemedicine-automated feedback to patients based on their adherence data also improves short-term adherence to CPAP.[469] It is likely that with enhanced digital technology we will see wider application of this type of approach in the future.

In addition to fixed CPAP, PAP can be delivered via automatically titrating systems and bilevel systems. Autotitrating CPAP, or auto-CPAP, adjusts CPAP during use by detecting airway flow, snoring, apneas, and inspiratory flow limitation (Fig. 98-17). Each auto-CPAP unit uses a different algorithm for abolishing apneic events. These algorithms are currently proprietary, that is, only the manufacturers have information on the specific algorithms. These units can be utilized in several ways: for chronic treatment of OSA (e.g., for patients with difficulty tolerating fixed CPAP and evidence of variable positive pressure needs due to REM-related or positional sleep apnea); or for use in the laboratory or at home to determine the optimal setting for conventional fixed CPAP after a trial period.[470] Patient adherence does not appear to be significantly improved with chronic use of auto-CPAP compared with fixed CPAP therapy.[471]

The use of auto-CPAP for OSA titration is associated with substantially lower costs compared to in-laboratory CPAP titration, and

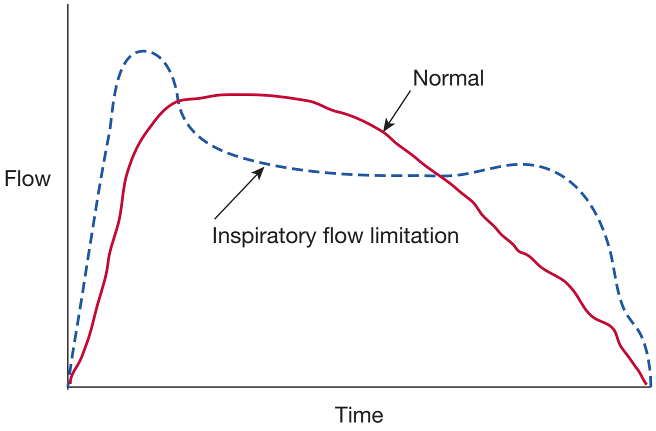

Figure 98-17 Schematic diagram showing the normal pattern of airflow during inspiration and that which occurs when there is inspiratory flow limitation. In the latter the flow quickly reaches a level that is maintained relatively constant throughout inspiration. This pattern of airflow can be detected by processors built into auto-CPAP units.

a number of studies have shown that auto-CPAP can be successfully incorporated into algorithms for diagnosis and treatment of OSA. Furthermore, with the greater implementation of out-of-laboratory treatment algorithms in which patients undergo portable monitoring for OSA diagnosis and are then started and maintained on auto-CPAP therapy, utilization of auto-CPAP has become increasingly common.[472,473] While results from one trial comparing fixed pressure CPAP to auto-CPAP suggest that fixed CPAP may be more effective at lowering 24-h diastolic blood pressure,[474] most studies to date have not demonstrated significant differences between the effects of auto-CPAP and fixed-pressure CPAP on blood pressure.[475–478]

Bilevel systems deliver higher pressures during inspiration and lower pressures during expiration and may be used when patients report difficulty with exhaling against PAP. However, bilevel systems are more expensive and evidence of better adherence and treatment outcomes when compared with CPAP is lacking.[479,480] Limited evidence suggests that patients with coexisting lung disease or respiratory acidosis demonstrate improved gas exchange with the use of bilevel PAP compared with CPAP.[481]

■ General Measures

Patients with sleep apnea should avoid alcohol, sedative hypnotics, and opioids.[482] These commonly used substances are generally thought to reduce upper airway muscle tone and increase the severity of snoring and apneas.[123,483–487] They may also depress arousal mechanisms, thereby prolonging apneas and causing more profound oxygen desaturations.[484,485,487]

Adherence to good sleep hygiene practices in order to maintain an adequate amount of sleep is also important in patients with sleep apnea. Sleep deprivation may reduce hypoxic and hypercapnic respiratory drive and prolong apnea duration.[488–491]

■ Weight Loss

Excess weight theoretically increases the propensity for upper airway collapse due to higher extraluminal pressures associated with excess soft tissue and/or fat and the encroachment of the tongue and soft palate.[54,492] Truncal obesity may also play a role by reducing chest compliance and functional residual capacity; this leads to increased oxygen demand.[493] Weight loss via dietary modification has been associated with significant reductions in SDB.[494,495] The extent of weight loss and degree of improvement are not always directly related, although it has been shown on average that a 1% change in weight is associated with a 3% change in AHI.[496] More specifically, weight loss in obese patients with type 2 diabetes mellitus is associated with a significant reduction in AHI.[497] Interestingly, AHI changes associated with weight loss (or weight gain) are stronger in men than women.[498] Weight loss effects on OSA can be beneficial well into the weight maintenance phase.[499–501]

Over the past several years, there has been progressive interest in the use of bariatric surgery to treat extreme obesity. Bariatric surgery is considered for individuals with BMI ≥35 kg/m^2 (≥32.5 kg/m^2 in Asians) who have OSA or other obesity-related conditions.[502] At present, the majority of bariatric procedures performed in the United States are sleeve gastrectomy (61%), followed by Roux-en-Y gastric bypass (17%)[503]; in randomized trials, patients undergoing these procedures manifest similar degrees of weight loss.[503] Across 24 nonrandomized controlled trials and 3 randomized controlled trials in which bariatric surgery was compared to various therapies including intensive lifestyle intervention, intensive nutritional care and CPAP, all studies consistently showed significant falls in weight and AHI following bariatric surgery both individually and when included in a recent metanalysis.[504] Over the 10 studies in which daytime sleepiness was assessed, there was also a significant improvement in Epworth Sleepiness Scale scores.[504] Nevertheless, while bariatric surgery is the most effective treatment for obesity and thus can lead to the greatest reduction in AHI among individuals with OSA, OSA did not completely resolve in the majority of patients examined 1 year after undergoing bariatric procedures.[504] Tongue fat may provide a critical link between obesity and OSA, as changes in tongue fat volume have been shown to mediate the relationship between weight loss and reductions in AHI.[166]

Given the available data, individuals who undergo bariatric surgery and experience a significant amount of weight loss should be formally reassessed for the presence of sleep apnea after maximal weight loss has been achieved. The use of autoadjusting CPAP should be considered during the postoperative period to accommodate changes in SDB during this time. Of note, increased hours of weekly physical exercise appear to have a beneficial effect on the incidence of mild to moderate OSA; this effect appears to be related to changes in body habitus.[505] It should be noted that SDB can, in turn, promote obesity via several mechanisms including physical inactivity due to sleepiness; poor dietary habits related to abnormalities in leptin, a satiety hormone; insulin resistance; and systemic inflammation.[161,333,391,506–517] Given these findings, weight loss should be recommended in all overweight and obese patients with OSA.

Of interest, a secondary analysis of data from the APPLES study revealed that individuals using CPAP experienced modest weight gain compared with those using sham CPAP,[518] an observation supported by subsequent studies.[519] An overall decrease in basal metabolic rate and increase in calorie intake have been observed among individuals who gained weight after CPAP initiation, suggesting that a positive energy balance is a possible mechanism of weight gain during OSA treatment,[520] and that untreated OSA affects energy metabolism through elevated resting metabolic rate and sleeping energy expenditure.[521]

More recently, a new medical approach to obesity has focused on the response to treatment with glucagon-like peptide 1 receptor agonists (GLP-1 Ras), particularly GLP-1 Ras with longer half-lives such as semaglutide.[522] These medications stimulate insulin secretion and reduce glucagon production from pancreatic cells and may also delay gastric emptying.[522] The mechanism of weight loss appears to be related to decreasing hunger and cravings for high-fat foods.[523] A recent, randomized, double-blind, parallel-group, phase 3a study looked at the additional benefit of semaglutide to intensive behavioral therapy and low-calorie diet. When compared with placebo, once-weekly subcutaneous semaglutide resulted in a

10.3% greater increase in body weight and more participants lost at least 5% of their body weight (86.6% vs. 47.6%).[524] This effect was sustained for 68 weeks.[525] At present, there are no data on the impact of weight loss using weekly-dosed GLP-1 Ras on OSA, but daily liraglutide demonstrated reduction in AHI (–6.1 events per hour) which was associated with the degree of weight loss in post hoc analysis.[526]

■ Intraoral Devices

Although CPAP represents the gold standard for treating OSA, adherence can be challenging for many patients.[453,455,527–529] Given this, increasing attention has focused on the use of intraoral devices, also known as oral appliances, as an alternative treatment to CPAP.

Oral devices aim to alter the position of the upper airway structures, thereby enlarging airway caliber and/or reducing airway collapsibility during sleep. Oral appliances have undergone considerable evolution in their design, comfort, and effect on airway structures. The tongue retaining device (TRD) developed in the 1980s by Samelson was designed to maintain the tongue in a forward position during sleep.[530] Given relatively sparse data on TRDs, a recent clinical guideline noted there were insufficient data to assess the efficacy of these devices for treatment of adults with OSA.[531] Two other types of devices are palatal lifting devices and mandibular advancing devices (MAD), the latter being the most studied (see example of mandibular advancing device, Fig. 98-18). The mandibular advancement devices produce downward rotation and advancement of the lower jaw during sleep.[532] These devices are fashioned out of a wide variety of materials and are available with various features. Many MADs are custom-made for the client following a dental or maxillofacial surgery consultation. In choosing an oral device, attention to its adjustability (modifiability over time) and titratability (ability to alter jaw position by adjusting the appliance) are important. In addition, provisions for temporomandibular joint support, tooth coverage, and jaw mobility are important, as side effects of the oral devices include excessive salivation, dry mouth, tooth or jaw discomfort, occlusive changes, and temporomandibular joint pain.[533] Recent advances include the ability to produce these devices using 3D printing techniques.[534]

Historically, there was no mechanism to objectively measure adherence to oral appliance therapy, but this has changed with the recent availability of commercially available temperature microsensors embedded into the device.[534] While studies using microsensor chips have indicated high rates of adherence (>80% for 1 year), sample sizes have been small.[535] Availability of this technology will allow for more robust study of the impact of successful treatment of OSA using oral appliances.

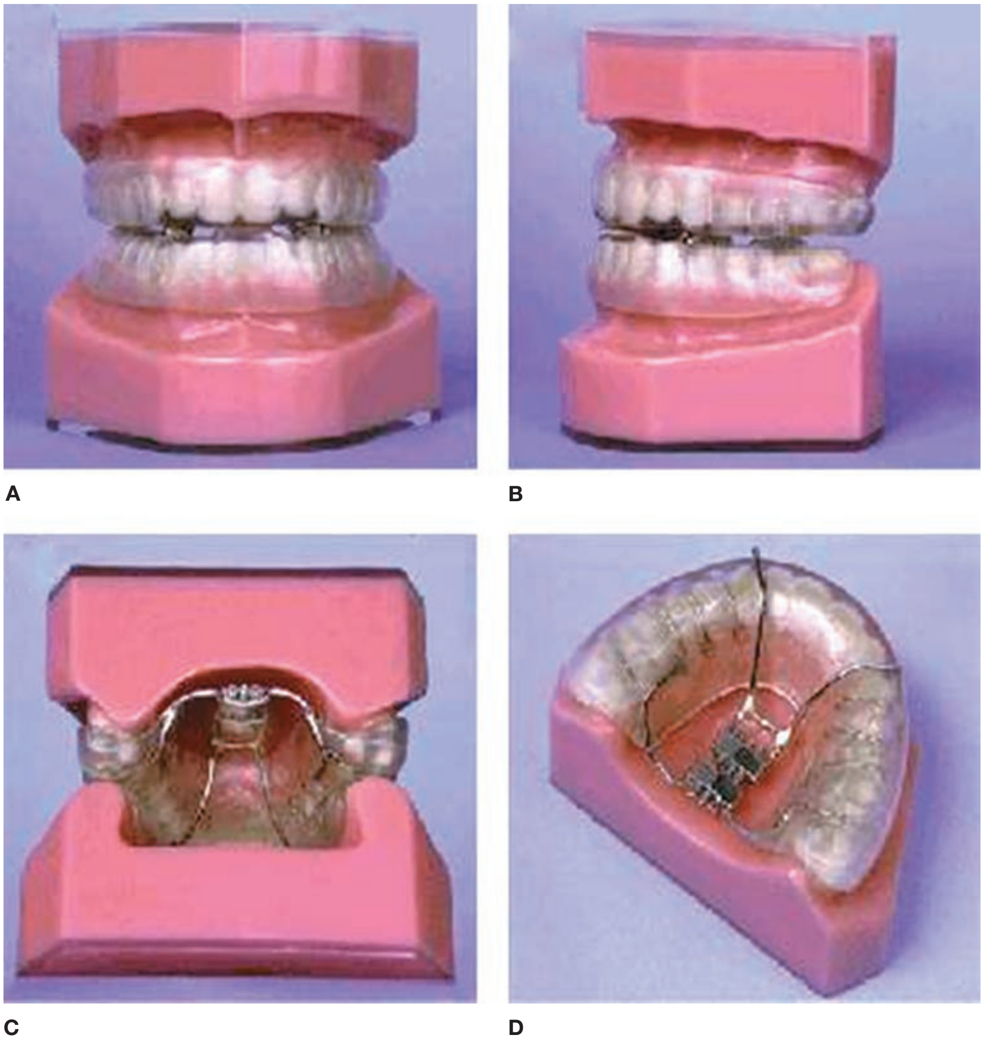

Figure 98-18 Anterior (**A**), lateral (**B**), posterior (**C**), and superior (**D**) views of an adjustable mandibular repositioning device (Klearway appliance, University of British Columbia, Vancouver, Canada). This device fits on the upper and lower teeth; it is worn during sleep and results in anterior motion of the mandible with consequent enlargement of the airway. The appliance is adjusted until the sleep-disordered breathing improves.

A recent systematic review commissioned jointly by the American Academy of Sleep Medicine and the American Academy of Dental Sleep Medicine examining the role of oral appliances (mandibular advancement devices) found that custom oral appliances reduced the frequency of sleep-disordered breathing events (AHI, RDI, REI, or ODI) and modestly improved minimum oxygen saturation in adult patients with OSA.[531] Oral appliances were also shown to reduce the arousal index and to improve daytime sleepiness and quality of life, but to have no significant effect on sleep architecture and sleep efficiency. Compared to CPAP, oral appliances were less effective at reducing SDB events, daytime sleepiness, minimum oxygen saturation, and arousal index, but nearly as effective as CPAP at improving quality of life.[531,536,537] Similarly, while the blood pressure–lowering effect associated with custom oral appliances was modest, it was deemed nearly equivalent to CPAP therapy.[445] Adherence to oral appliance therapy was observed to be higher compared to PAP therapies in a metanalysis of six trials comparing the two treatments, with four of the individual studies demonstrating higher usage of oral appliances.[538]

Based on these data, oral appliances are a reasonable alternative to CPAP, particularly for patients with primary snoring, or those with mild to moderate OSA who prefer an oral appliance to CPAP or do not respond to, are not appropriate candidates for, or fail treatment attempts with CPAP. A recent study identified phenotypic characteristics including lower age, female sex, lower BMI, smaller neck circumference, lower AHI, a retracted maxilla and mandible, a narrower airway and a shorter soft palate that were associated with a good response to oral appliance therapy, and suggested they could be used in clinical practice to identify appropriate candidates.[539] Patients with severe OSA should have a trial of CPAP first based on lower success rates with oral appliances.[531] Patients treated with an intraoral device are recommended to have follow-up sleep testing to verify efficacy, as some patients show no improvement. Importantly, the ability of oral appliances to reduce the severity of SDB to less than 10 events/h has been estimated to be approximately 50%.[533] Furthermore, based on a recently validated technique it is now possible to quantify loop gain directly from routine polysomnography as well as home sleep studies.[540] Using this technique, several studies have identified that low loop gain, higher arousal threshold, moderate pharyngeal collapsibility, and weaker muscle compensation are associated with improved efficacy of oral appliances.[541] Prospective validation suggests airflow testing may be useful for prediction[542]; further research is warranted. Patients started on mandibular advancement devices should be closely monitored by the treating physician to assess for signs and symptoms of worsening OSA. In addition, regular follow-up with the dental specialist who fashioned the device is an important component of ongoing care in patients who utilize oral appliances, to detect problems such as loosening of teeth.

■ Position Therapy

It seems intuitive that body position during sleep would have an effect on respiratory mechanics.[543–545] Sleep in the supine position would seem to be more conducive to airway obstruction by virtue of gravity's effect on the tongue along with higher collapsibility of the airway in the supine vs. nonsupine position.[546] Raising the head of bed angle to between 30 and 60 degrees has been studied; however, it is unclear if its effects reach beyond promoting airway stability to actually reducing AHI.[543,544,547] In 1984, Cartwright defined positional-dependent sleep apnea as SDB in which the AHI while asleep in the supine position was at least twice as high as in the lateral position.[548] The prevalence of position-dependent sleep apnea using this definition may be as high as 50% to 70% and may be of particular significance in patients with mild OSA.[549–554]

For patients with position-dependent sleep apnea, symptoms may be alleviated by promoting sleep in the lateral decubitus position.[552,555–560] The lateral position is associated with increased maximum cross-sectional upper airway area and lower closing pressure of the passive pharyngeal airway compared to the supine position.[545] Lateral positioning during sleep initially focused on the use of a bulky item, such as a tennis ball, placed on the patient's back.[561,562] These techniques appear to be effective in reducing the percentage of total sleep time in supine position and the overall AHI, but the long-term compliance rate is only 10%.[563–566,791] This is due to back discomfort and no improvement, or even deterioration of sleep quality and/or daytime alertness.[563,566] Next-generation position therapy in the form of a vibrational alarm worn on the trunk or neck delivers a vibrating stimulus to gently wake the patient when they move to the supine position. A meta-analysis demonstrated a reduction in both the AHI and the percentage of TST in the supine position.[567] Long-term compliance with a vibrational alarm appears to be higher at 1 year than with the bulky mass technique.[568]

Several studies have suggested that positional therapy is equivalent to CPAP in the treatment of positional-dependent sleep apnea.[552,565] However, a Cochrane review concluded that in terms of reducing the AHI and increasing oxyhemoglobin saturation, positional therapy was inferior to CPAP therapy. In addition, long-term compliance for positional therapy appears to be mediocre at best; nonetheless it is better than adherence to CPAP therapy, although there was no difference in the ESS or quality of life between the groups.[569] Interestingly, use of positional therapy in combination with another therapy for position-dependent OSA, such as a mandibular repositioning device, may be associated with a greater reduction in AHI.[570–572] Given all that is known about positional therapy, a relatively simple and inexpensive technique, consideration of its use to treat mild OSA with a positional component or as an additive measure to improve the efficacy of other treatment measures is warranted.

■ Nasal Expiratory Positive Airway Pressure

Nasal expiratory positive airway pressure (EPAP) is delivered via a novel device with a one-way mechanical valve that provides high expiratory resistance in the setting of very low inspiratory resistance. The nasal EPAP device is placed within each nostril during sleep and can be used for up to three months before needing replacement (*www.accessdata.fda.gov/cdrh_docs/pdf18/K180619.pdf*). Positive pressure resulting from the high expiratory resistance during exhalation stents open the upper airway, rendering it less likely to collapse on subsequent inhalation, and increases end-expiratory lung volumes.[573,574] Nasal EPAP appears to reduce AHI and improve subjective sleepiness in patients with mild to moderate OSA.[575–577] Nasal EPAP has not yet been compared with CPAP directly. A recent study assessing the utility of nasal EPAP as an alternative short-term therapy for patients with moderate to severe OSA already on therapeutic CPAP was unable to show a beneficial effect of nasal EPAP.[578] Given our current knowledge, it is unclear if nasal EPAP should be considered as an alternative therapy in individuals with mild to moderate SDB who are unable to tolerate CPAP therapy.

■ Surgical Treatment of OSA

A variety of surgical treatments have been employed in management of OSA and are discussed below.

Hypoglossal Nerve Stimulation

The genioglossus muscle is the largest airway dilator muscle. Electrical stimulation of the hypoglossal nerve causes tongue protrusion and stiffening of the anterior pharyngeal wall.[579] Attempts at muscle stimulation enlarged the upper airway diameter and reduced apneas and hypopneas during sleep in patients with SDB.[580–585] However, use of this technique has been limited by arousals associated with tongue protrusion.[585–587] An alternative strategy is to electrically stimulate the hypoglossal nerve to cause contraction of the genioglossus muscle, thereby increasing lower and upper airway patency during sleep in properly selected patients.[72,588–590] The branches of the hypoglossal nerve that innervate the genioglossus consist mostly of efferent (motor) fibers that activate the genioglossus muscle with minimal sensory feedback.[579] Chronic stimulation of the hypoglossal nerve as a possible treatment for OSA was initially considered more than 25 years ago, but several technical limitations led to a 10-year hiatus before enthusiasm for hypoglossal nerve stimulation (HGNS) resurfaced.[579,591–594] In a large, multicenter, prospective, single-group cohort study of carefully selected patients (STAR cohort), HGNS was associated with improvements in AHI (decreased by 68%), oxygen desaturation index (ODI; decreased by 70%), subjective sleepiness measured by Epworth Sleepiness Scale, and quality of life, as well as with high adherence (84%).[72] The primary outcome cohort study was followed by a randomized, controlled, therapy-withdrawal study consisting of the first 46 consecutive participants who were noted to have a response to therapy. Subjects were randomly assigned to the therapy-maintenance group or the therapy-withdrawal group. In this select group of responders to HGNS, therapy withdrawal was associated with a significantly higher AHI and ODI that subsequently improved when therapy was restarted.[72,589] Five-year follow-up data indicate improvements in AHI, sleepiness, and quality of life that persist in the long term.[595] Serious adverse events are uncommon. Several systematic reviews of cohort studies have demonstrated efficacy in patients with moderate to severe OSA treated with HGNS, including reduced AHI, reduced ODI, and improved sleepiness and quality of life.[588,596–598]

Early evidence indicates that HGNS may lead to improvements in downstream consequences of OSA. In the original STAR cohort, responders to HGNS were noted to have reduced heart rate variability.[599] A retrospective study comparing treatment with HGNS to PAP therapy found PAP lower mean arterial pressures in all patients, whereas HGNS lowered mean arterial pressures only among patients with elevated BP at baseline.[600] In nondiabetic patients, HGNS was associated with improved insulin resistance and oral glucose tolerance.[601]

Although current U.S. Food and Drug Administration (FDA) approval includes specific eligibility criteria (*www.fda.gov/medical-devices/recently-approved-devices/inspirer-upper-airway-stimulation-p130008s039*)—including moderate to severe OSA (AHI $\geq$15 and $\leq$65 events/h), BMI $<$33 kg/m^2, inability or unwillingness to use PAP therapy, and absence of complete concentric collapse at the palate on DISE exam—recent studies suggest that additional patients (e.g., AHI $>$65 events/h and BMI $>$32 kg/m^2) also may benefit from treatment with HGNS.[590,602–606]

Upper Airway Corrective Surgery

A variety of surgical options are available to correct abnormalities in the upper airway that lead to obstruction during sleep (Table 98-7). However, the success of these treatments, aside from tracheostomy, is less well established and generally less effective than PAP therapy.[413] The leading objective for presurgical evaluation is to identify the primary site(s) of obstruction. The level of obstructive site influences the type of surgical procedure to be performed. Fiberoptic laryngoscopy, drug-induced sleep endoscopy, or imaging can be used to classify the obstruction of the airway at the nasal, oropharyngeal, and/or hypopharyngeal level.[607,608] Surgeries aimed at reducing obstruction at the nasal, palatal, and lingual levels are referred to as phase 1 surgeries. They are typically performed first with subsequent use of a phase 2 surgery such as maxillomandibular advancement (MMA) when needed.[413]

Tracheostomy is virtually 100% effective in eliminating obstructive apneas.[609] Despite its high efficacy, it requires changes in lifestyle and is associated with negative impact on patients' quality of life. Tracheostomy is generally reserved for patients with severe OSA who have failed medical or surgical therapy and who manifest severe complications such as malignant arrhythmias without treatment.[610] Tonsillectomy and adenoidectomy is the primary therapy for children with OSA; however, it is not usually successful in adults.[611]

TABLE 98-7 Surgery for Obstructive Sleep Apnea

Nasal surgery (septoplasty, sinus surgery, and others)
Tonsillectomy ± adenoidectomy
Hypoglossal nerve stimulator implantation
Uvulopalatopharyngoplasty (UPPP)
Laser-assisted uvulopalatoplasty (LAUP)
Radiofrequency volumetric tissue reduction
Lingular tonsillectomy
Genioglossus and hyoid advancement (GAHM)
Sliding genioplasty
Maxillomandibular advancement osteotomy
Tracheostomy

Maxillomandibular advancement surgery enlarges the upper airway by physically expanding the facial skeletal framework.[612] While this invasive procedure is usually considered only for carefully selected patients whose OSA has been refractory to CPAP and other surgical interventions, a recent metanalysis incorporating data from 518 patients across 45 studies reported mean reductions of AHI and RDI of 80.1% and 64.6%, respectively, with 64.7% of patients with available AHI data demonstrating a reduction to fewer than 10 events/h.[612] Lower preoperative AHI was the only factor significantly associated with surgical cure in multivariable analyses.[612] Nevertheless, MMA should be considered only in patients with severe OSA in whom PAP therapy and oral appliance therapy are ineffective[610] and probably should be avoided in morbidly obese individuals until more information on its efficacy is available in this population.[612]

Another procedure, uvulopalatopharyngoplasty (UPPP) with tonsillectomy, was noted in a recent metanalysis to be associated with a 46.1% initial decrease in AHI. However, the surgical response rate was observed to decrease from 67.3% to 44.35% over the longer term (i.e., $\geq$34 months after surgery).[613] Another meta-analysis found that this relapse in AHI begins soon after the procedure, with a mean increase in AHI of 1.45 events/h per month over a mean follow-up period of 8.18 months. Furthermore, UPPP does not have a consistent effect on AHI when performed as a sole surgical procedure, and therefore it cannot be recommended as a standalone treatment for OSA.[614]

The role of other phase 1 therapies remains unclear. Laser-assisted uvulopalatoplasty (LAUP), a procedure involving removal of the uvula and a part of the soft palate with a carbon dioxide laser, has been associated with worsening of AHI among 44% of patients and a cure rate of only 8%[615]; it is not recommended as a treatment option for OSA by the AASM.[610] Radiofrequency volumetric tissue reduction (i.e., radiofrequency ablation [RFA]), a minimally invasive technique, has been employed to treat turbinate hypertrophy and to reduce the size of the base of the tongue. Palatal implants are intended to stiffen the soft palate and protect against upper airway collapse. Only modest improvements in symptoms and AHI were noted in one randomized controlled trial.[616] In part because of their relatively low surgical risk, RFA and soft palatal implants can be considered in individuals with mild to moderate OSA who have found CPAP and oral appliance therapy ineffective and/or undesirable.[610]

Genioglossus advancement with hyoid myotomy involves movement of the tongue forward without moving the mandible, with the aim of achieving a larger-caliber airway. The success of such combinations has been variable, ranging from 23% to 77%.[617–621] Because of inconsistent results in the setting of increased surgical risks, genioglossus advancement and related surgeries are presently not recommended therapies for OSA.

A number of recent studies have examined the value of performing UPPP and other surgical interventions for OSA compared to transoral robotic surgery.[792] In general, no significant differences have been observed in metrics including AHI, oxygen saturation nadir, ESS scores, and complication rates between patients receiving robotic surgery groups and other interventions.[622]

Other procedures listed in Table 98-7 are designed to increase airway caliber or to improve CPAP compliance. Treatment of nasal obstruction by surgical means has proved helpful in some patients, especially by allowing the patient to better tolerate CPAP. The most common nasal surgical procedure is septoplasty and turbinate reduction. These procedures can lead to subjective improvement in nasal patency and a reduction in nasal CPAP pressure requirement.

Surgery represents a viable therapeutic option for carefully selected OSA patients who cannot tolerate PAP therapy or an oral appliance. The growing use of hypoglossal nerve stimulation has further reduced the use of other surgical procedures. Meticulous preoperative assessment by examination, nasopharyngoscopy, and radiologic imaging can help to identify the likely area of upper airway obstruction. If a surgical procedure is performed, close follow-up in the immediate postoperative period to assess treatment response as well as long-term follow-up to monitor for recurrence of disease are warranted.[610]

■ Oxygen Therapy

Oxygen has a limited role in the treatment of sleep apnea syndrome. Chronic hypoxemia is associated with reduced hypoxic and hypercapnic ventilatory drives.[623] Although oxygen desaturation may be mitigated by the delivery of oxygen, there is some evidence that administration of supplemental oxygen may increase the arousal threshold and thereby prolong apneic events.[624] In this same study of three patients, supplemental oxygen use was also associated with worsening respiratory acidosis.[624] However, subsequent studies with larger numbers of subjects demonstrated that the use of supplemental oxygen reduced the degree of oxyhemoglobin desaturation and improved or did not worsen apnea frequency or duration.[623,625–628] Among patients with a relatively unstable ventilatory control system and high overall loop gain, supplemental oxygen may stabilize ventilation, reducing AHI.[629,630] The effect of supplemental oxygen alone on blood pressure in patients with OSA was examined in a randomized controlled trial of individuals with an AHI of 15–50 events/h.[631] After 12 weeks, among participants who were assigned to receive nightly supplemental oxygen (2 LPM), there were no significant differences in 24-h mean arterial pressure or C-reactive protein compared to the control group. While oxygen improves nocturnal oxygen saturation during use without significant adverse consequences, it does not have a clear role in the treatment of OSA.

■ Medications

Several pharmacologic agents have been investigated as possible therapies for primary treatment of OSA. One such intervention showing promise is the combination of atomoxetine and oxybutynin.[632] This pharmacologic pair has recently been shown to reduce AHI significantly in patients diagnosed with OSA, perhaps by enhancing genioglossal muscle responsiveness to upper airway instability. While individuals with reduced upper airway muscle responsiveness (determined by physiologic phenotyping) may be more likely to benefit from pharmacologic treatment,[177] subjects in the atomoxetine-oxybutynin study were not phenotyped. These participants reported more subjective improvement in sleep quality with higher AHI reductions, but no effect on AHI was observed if either medication was taken alone. Further investigation is needed before this combination therapy is more widely utilized.[632]

Unfortunately, few other medications have demonstrated significant effectiveness for treatment of OSA.[633] Specifically, selective serotonergic reuptake inhibitors, protriptyline, methylxanthine derivatives (e.g., theophylline), and estrogen therapy are not recommended.[27,634–636] Of notable exception, patients with hypothyroidism and acromegaly should be treated with thyroid replacement and somatostatin analogues, respectively, as such treatment does improve AHI.[27,634]

While short-acting nasal decongestants have no effect on airway patency in sleep apnea, topical nasal corticosteroids may be useful as adjunctive therapy to treat concurrent rhinitis.[27,635,636] Such treatment may be particularly helpful if rhinitis is exacerbated by PAP therapy despite the use of heated humidification. In addition, there are conflicting data regarding the use of sedative–hypnotics at the time of CPAP initiation.[637–640]

Stimulants such as modafinil can be utilized as adjunctive therapy for residual sleepiness in patients who remain excessively sleepy despite adequate treatment for SDB.[635] Doses ranging from 200 to 400 mg daily have been shown to be effective in improving excessive daytime sleepiness in several randomized trials.[641–645] Treatment with modafinil should be undertaken only after a careful search for alternative causes of residual sleepiness has been performed.[27]

CENTRAL SLEEP APNEA SYNDROMES

CSA, in which repetitive episodes of breathing cessation occur in the absence of respiratory effort, is characterized by reduced ventilatory motor output (Fig. 98-19). CSA is much less common than OSA, with one study estimating the prevalence in the general population to be <1%. Even in the clinical sleep laboratory setting, CSA is relatively uncommon.[133,646] However, small disruptions within a number of complex feedback loops in the ventilatory control system can lead to and then sustain CSA. CSA has been described as a physiologic process in normal individuals in response to an arousal (especially children and the elderly), as a manifestation of breathing instability in a number of medical conditions (e.g., Cheyne–Stokes respiration [CSR] in CHF and at high altitude), or in association with neurologic diseases such as Shy–Drager syndrome, stroke, myasthenia gravis, neuromuscular disease, bulbar poliomyelitis, brainstem infarction, and encephalitis.[647–651] It is often divided into hypocapnic and hypercapnic types.[652]

The following discussion focuses on hypocapnic CSA, as the hypercapnic CSA syndromes (e.g., OHS and congenital central hypoventilation syndrome) are discussed elsewhere (Chapter 99). The vast majority (85%–90%) of patients with OHS have concomitant OSA.[40,41] Characteristic findings observed with OHS include awake resting hypoxemia and hypercapnia, hypersomnolence, signs of cor pulmonale (right-sided heart failure and lower extremity edema), and nocturnal hypoventilation. In general, the hypocapnic CSA syndromes are associated with increased chemoresponsiveness of the ventilatory control system and are seen most commonly in individuals with heart failure or at high altitude.

During wakefulness, there is an endogenous drive to breathe that has been termed the *wakefulness stimulus*. With the onset of sleep, withdrawal of the wakefulness stimulus occurs and the chemical drive to breathe predominates.[653] Minute ventilation falls during sleep by 10% to 15% and P_{CO_2} levels rise approximately 2 to 6 Torr.[654–656]

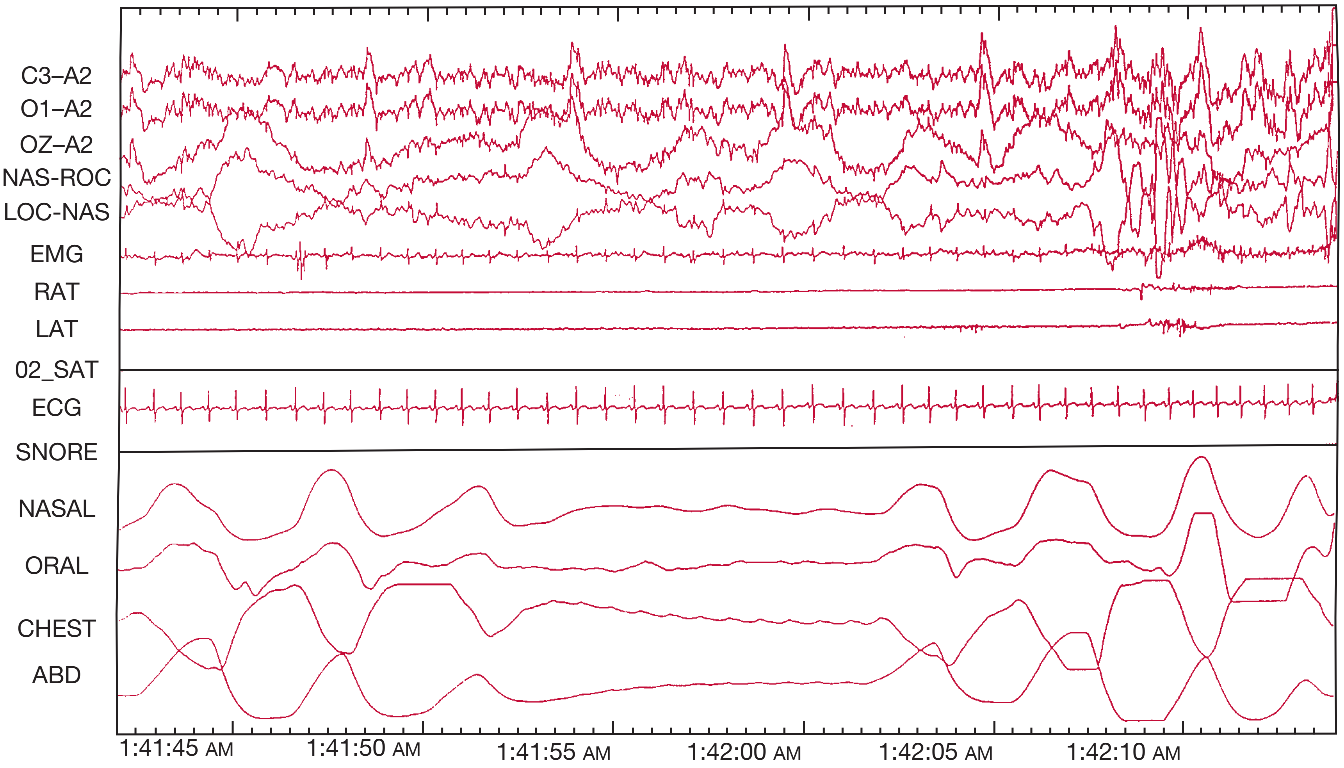

Figure 98-19 Example of central apneas. The polysomnography traces from the top down are as follows: Three EEG channels *(C3, C4, O1)*; two EOG channels *(ROC and LOC)*; submental electromyogram *(EMG)*; right and left anterior tibialis EMG *(RAT and LAT)*, oxyhemoglobin saturation *(SaO$_2$)*; electrocardiogram *(ECG)*; snoring channel *(SNORE)*; nasal airflow *(NASAL)*; oral thermistor *(ORAL)*; and chest and abdominal motion *(CHEST and ABD)*. During the apneic episodes, there is lack of airflow without rib cage or abdominal motion.

Central apneas occur if the arterial P_{CO_2} falls below the "apneic threshold," or P_{CO_2} level necessary to maintain rhythmic breathing.[657] Causes of hypocapnia include sleep-state changes, hypoxia, and fluctuations in minute ventilation related to heart failure.

Other features of the ventilatory control system can promote and sustain recurring central apneas. If the magnitude of the increase in ventilation that occurs in response to changes in P_{CO_2} is larger than is needed to achieve eupnea, self-sustaining oscillations in ventilation in which P_{CO_2} is repeatedly driven to the apneic threshold can occur and manifest as periodic breathing.[658–660] Such oscillations in ventilation can also occur when there is a lag between changes in ventilation and detection of the ensuing effects on P_{CO_2} and P_{O_2} by the central and peripheral chemoreceptors, as occurs when arterial circulation time increases.[661] Recurrent arousals from sleep can also play an important role in initiating and maintaining central apneas as the state change from sleep to wakefulness re-engages the neurogenic drive to breathe.[657,662] This can provoke ventilatory overshoot as P_{CO_2} is driven to the lower P_{CO_2} set point of wakefulness, especially in the setting of continued sleep–wake instability.

■ High-altitude Periodic Breathing

Periodic breathing with hypocapnic central apnea occurs in many healthy individuals at high altitude. At altitude, the peripheral chemoreceptors in the carotid body that sense hypoxia increase ventilatory drive.[663] As P_{CO_2} falls in response, the apneic threshold during sleep is reached, precipitating central apneas and creating a cycle of periodic breathing. Because the delay between changes in P_{CO_2} and P_{O_2} levels and detection by peripheral chemoreceptors is brief, the cycle time of periodic breathing at altitude tends to be short (12–34 s).[664] Poor sleep quality is a frequent complaint at high altitude and is likely to be related to hypoxemia and periodic breathing with frequent arousals.[665,666] Although it seems intuitive that periodic breathing would resolve as individuals acclimate to altitude, observations of decreases, increases, and lack of change in periodic breathing have all been reported.[667–670] Gender differences in high-altitude periodic breathing also have been described, with significantly fewer central sleep apnea events among women compared to men at 3400 and 5400 meters, and significantly longer respiratory cycles in women.[671] High-altitude periodic breathing can be treated using acetazolamide, which increases the magnitude of the change in P_{CO_2} required to produce central apneas, that is, it alters the apneic threshold.[672] Use of supplemental oxygen improves high-altitude periodic breathing and sleep quality and thus should also be considered.[673,674]

■ Cheyne–Stokes Respiration (CSR)

CSR is most commonly seen in individuals with systolic heart failure and, especially when present during wakefulness, is a risk factor for higher mortality in this population.[675–677] CSR is also observed in individuals with encephalopathies, stroke, and other conditions.[678–680] Among individuals with systolic heart failure, male gender, age greater than 65, atrial fibrillation, and awake hypocapnia (P_{CO_2}<38 mm Hg) all increase the risk for CSR.[681] Despite speculation that the prevalence of CSR has declined with the use of beta blockers for treatment of CHF, two studies indicate that the prevalence of SDB in general, and CSR in particular, remains high in this population.[682–684]

CSR is characterized by prolonged hyperpneas with a waxing and waning respiratory pattern and prolonged cycle duration, that is, 40 to 90 s (Fig. 98-20). Although CSR can occur during wakefulness, it is much more common during sleep, especially during non-REM sleep, when ventilation is predominantly under metabolic control and thus particularly sensitive to the apneic threshold and changes in P_{CO_2}.[685,686] Greater peripheral and central chemoresponsiveness among individuals with heart failure and CSR promotes hyperventilation and hypocapnia.[660,687] The timing and role of arousals

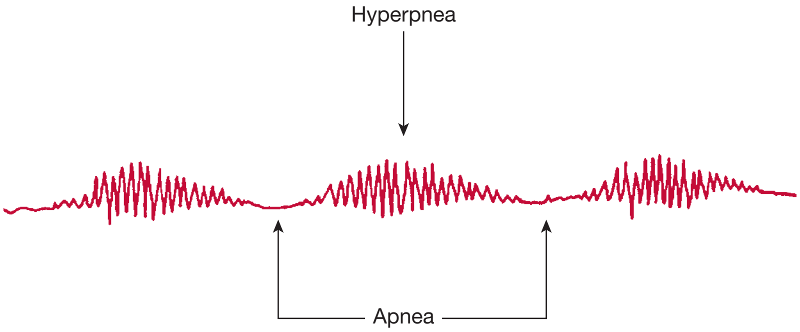

Figure 98-20 Example of Cheyne–Stokes respiration (CSR), a pattern of periodic breathing in which intervals of hyperpnea alternate with intervals of apnea. Respiration waxes and wanes in a crescendo–decrescendo pattern. Arousals during CSR tend to occur during the peak of ventilation, that is, during the hyperpneic phase rather than at the termination of the apnea. The duration of the hyperpneic phase of CSR correlates with the degree of circulatory delay.

associated with CSR, which tend to occur at the peak of ventilation, distinguish them from arousals associated with obstructive events, which occur at apnea termination. Thus, arousals during CSR provoke ventilatory overshoot and help to sustain oscillations in respiration, rather than fostering upper airway muscle activation and the resumption of airflow as occurs in obstructive apneas.[688] The cycle length in CSR generally ranges from 40 to 90 s, due in part to prolonged transit time between the lungs and chemoreceptors in the setting of reduced cardiac output and increased circulation time.[657]

The clinical presentation of patients with CSR is variable. Although some patients with heart failure and CSR complain of sleep fragmentation, daytime sleepiness, and poor nocturnal sleep, many do not.[689] The diagnosis of CSR is established by PSG demonstrating repetitive apneas in the absence of thoracic–abdominal excursion.[15] Not infrequently, a combination of obstructive and mixed apneas may be seen; central SDB events must constitute greater than 50% of total events to make the diagnosis of CSA.[688]

CSR can be treated in several ways. Aggressive pharmacologic management of heart failure, including beta blockade and angiotensin-converting enzyme inhibitors, improves heart failure status and may reduce CSA.[690,691] The use of supplemental oxygen can help to stabilize oscillations in ventilation but generally does not normalize the AHI.[692,693] Data demonstrating improved long-term outcomes with use of supplemental oxygen are lacking. However, given results from several recent trials demonstrating improvements in LV ejection fraction among patients with heart failure and CSA who received oxygen, supplemental oxygen has been recommended for this patient population.[694–697] Administering a small amount of CO_2 to patients with CSR dramatically reduces central apneas by increasing Pa_{CO_2} above the apnea threshold. This intervention has not, however, been implemented clinically due to concerns about long-term increases in Pa_{CO_2}.[698]

Although a number of initial reports demonstrated that CPAP therapy lowers AHI, reduces systolic BP, and improves LV systolic function, this treatment has proven disappointing.[676,699,700] A large, randomized trial in individuals with heart failure and CSA failed to demonstrate mortality benefit after use of CPAP for 2 years, despite improvements in the severity of CSA, nocturnal oxygenation, ejection fraction, and other physiologic measurements.[701] Furthermore, while early survival was lower among those receiving CPAP, mortality was ultimately not significantly different between the groups. Post hoc analyses demonstrated that among those individuals receiving CPAP whose CSA was reduced to less than 15 events/h, survival was improved.[702] Whether these findings represent benefit from CPAP use in this subgroup, however, or whether the reduction in AHI to less than 15 events/h identified individuals with a better overall prognosis, is unclear.

A mode of PAP therapy termed *adaptive servo-ventilation (ASV)* has been developed for use in patients with CSR and other forms of hypocapnic CSA.[703] ASV provides bilevel PAP with a fixed expiratory pressure and variable inspiratory pressure that responds to changes in the ventilatory pattern while maintaining a target ventilation based on a continuous moving window of the patient's recent average ventilation. Thus, over time, proportionate increases and decreases in inspiratory pressure occur that help to stabilize ventilation. A number of randomized trials and other studies have shown that ASV improves CSA associated with CSR due to heart failure, as well as LV ejection fraction, sleep disruption, and exercise capacity.[704–709] However, a multinational, multicenter, randomized trial of patients with symptomatic chronic heart failure with depressed LV ejection fraction (≤45%) and predominant CSA demonstrated a lack of efficacy and actually increased cardiovascular mortality among individuals assigned to ASV.[710] After assessing the available current data, the AASM has recommended the use of CPAP or oxygen for first-line treatment of CSR related to heart failure,[697] and recommended against the use of ASV to treat CHF-associated CSA in patients with low ejection fraction and moderate or severe CSA.[711]

More recently, there has been evidence supporting the use of unilateral transvenous phrenic neurostimulation in patients with central sleep apnea.[712] This novel physiologic treatment demonstrated efficacy in a multicenter, randomized, controlled trial.[712] After 6 months, improvements were noted in AHI, sleep architecture, and quality of life in CSA patients receiving phrenic neurostimulation, including those with significant comorbidities such as stage A–C heart failure, compared to those who had the device implanted at the time of randomization but not activated.[712] Once the device was approved by the FDA, all devices were activated and a pooled cohort (treatment and former control group) was followed for 36 months with similar results.[652] Fifty-two participants were followed for 5 years and were noted to have improved CSA, sleep architecture, and daytime sleepiness.[713] Importantly, phrenic nerve stimulation was well tolerated with no serious events leading to long-term harm or death.[713]

■ Idiopathic Central Sleep Apnea

An idiopathic form of CSA similar to CSR has occasionally been described in individuals with normal cardiac function. Presenting symptoms can include snoring, witnessed apneas, insomnia, and excessive sleepiness.[714–716] These individuals have an increased ventilatory response to CO_2 during sleep and wakefulness. There is no standardized treatment. While CPAP therapy has proved effective for some patients, other reported treatments have included respiratory stimulants such as acetazolamide and use of benzodiazepine and hypnotic medications to improve sleep continuity and reduce sleep state instability.[717–720]

■ Treatment-emergent Central Sleep Apnea

In recent years, the terms "treatment-emergent sleep apnea" (TECSA) or "complex sleep apnea" have been applied to the emergence of central apneas during CPAP titration for treatment of OSA.[646] The prevalence of TECSA has been estimated to be between 5% and 15% of patients undergoing CPAP titration.[646,721–724]

Individuals who manifest CPAP-emergent central apneas have been described in some studies to be more likely to be male, to be older, to have a lower BMI, and to have a history of cardiac disease compared with individuals without treatment-emergent central sleep apnea.[725]

Polysomnography in patients with TECSA may reveal recurrent central apneas occurring particularly during the lighter stages of sleep (N1 and N2), with more stable breathing during N3 and REM sleep.[726] Patients may have characteristics such as a lower arousal threshold or high ventilatory controller gain that place them at risk for ventilatory control instability.[38] Some patients report persistent sleep disruption with CPAP therapy with little symptomatic benefit.

The clinical relevance of TECSA has been vigorously debated, given evidence that CPAP-emergent central apneas may be associated primarily with CPAP initiation and are likely to resolve over time.[727,728] Among patients who were initially diagnosed with complex sleep apnea, only 20% to 25% of patients who returned for PSG after using CPAP for 1 to 3 months had persistent central apneas greater than 5/h.[721,724] Other explanations for CPAP-emergent central apneas include over- and undertitration of CPAP therapy, the presence of occult heart failure, and use of respiratory-depressant medications such as opioids and benzodiazepines.[728] Use of chronic opioid medications, which has become much more common in the past several decades, also places patients at risk for central sleep apnea events during sleep.[207,729,730]

The results of several studies that have examined the use of PAP devices for treatment of TECSA suggest that adaptive servo-ventilation appears to most effectively reduce AHI.[704,731,732] However, evidence suggests that TECSA resolves spontaneously in the majority of patients after several months of CPAP therapy.[721] Therefore, it seems reasonable to initiate a trial of CPAP therapy first and to reserve ASV for the relatively few individuals who exhibit persistent apnea, including those using opioids.

EFFECT OF SLEEP IN PATIENTS WITH PULMONARY DISORDERS

Normal sleep is associated with relative hypoventilation and hypoxemia compared to wakefulness. This may occur via a variety of mechanisms. Sleep onset has been associated with a 2- to 6-mm Hg increase in the P_{CO_2} set point for ventilation.[733,734] Hypoxic ventilatory responses can be reduced such that normal subjects may experience a decrement of up to 10 mm Hg of Pa_{O_2} during sleep; this response may be more pronounced in men compared with women.[139,735,736] Sleep is also associated with changes in respiratory mechanics, the most obvious of which are due to the posture adopted during sleep. The supine position, in particular, is associated with an additional load on inspiratory muscles due to a shifting of abdominal contents.[737] REM sleep is associated with atonia, which spares the diaphragm, but not the accessory and other muscles of respiration and can reduce functional residual capacity.[738,739] Upper airway patency is dependent on muscle activity, which can be reduced or absent in NREM versus REM sleep and by an increase in supraglottic resistance.[740]

Pulmonary disorders can deteriorate during normal sleep and especially in patients with concomitant sleep apnea. SDB is associated with exaggeration of the normal circadian changes that elicit increases in bronchial hyperresponsiveness, vagal tone, and airway inflammation, which can contribute to asthma.[741–753] The sleep disruptions and hypoxia associated with SDB can also promote insulin resistance and glucose intolerance that, coupled with daytime sleepiness and reduction in general activity, ultimately lead to weight gain.[161,324,391,510,753–755] Obesity, in turn, is a significant risk factor for asthma.[753,756–762] Furthermore, snoring or apnea is likely to worsen gastroesophageal reflux, which in turn, is known to exacerbate asthma.[763–766] Studies addressing nocturnal asthma and OSA have shown symptom improvement with CPAP use.[767–770] Given these interactions, asthmatic patients who fail to improve with optimal medical therapy or who manifest primarily nocturnal asthma should be considered for evaluation of sleep apnea, particularly if snoring is present.[753,767]

In obstructive lung diseases such as COPD, those patients who exhibit daytime hypoxemia also experience profound declines in Pa_{O_2}, especially during REM sleep.[771,772] Hypoxemia is multifactorial: Mechanisms include exaggerated changes in respiratory physiology during sleep such as reduced functional residual capacity (which decreases oxygen reserve), increased airway resistance, decreased respiratory muscle function, altered chemosensitivity, alveolar hypoventilation, and ventilation–perfusion mismatch.[773] The coexistence of COPD and OSA is relatively frequent because both disorders are so common.[774,775] In this so-called overlap syndrome, patients are at increased risk of pulmonary hypertension and respiratory failure related to progressive nocturnal hypoxemia.[716,775–777] Patients are also at increased risk of death and hospitalization due to COPD exacerbation.[778]

While oxygen is the therapy of choice in COPD patients with daytime hypoxia, its chronic use in patients with isolated nocturnal hypoxia without SDB is without clear benefit.[737,779–783] Oxygen therapy is unlikely to be sufficient in patients who suffer overlap syndrome. In patients with COPD and chronic hypercapnia, the use of high intensity nocturnal noninvasive positive pressure ventilation has been shown to reduce mortality,[784] after a series of studies suggesting noninvasive ventilation was unlikely to be of added benefit.[785–787] Patients with overlap syndrome who are treated with CPAP have also been noted to have improved survival and decreased hospitalizations due to fewer COPD exacerbations.[778] Given this observation, screening of COPD patients for clinical features indicative of coexistent OSA is warranted.[778]

It is important to recognize that a wide variety of other lung diseases, including both parenchymal lung disease and neuromuscular disease, can place patients at risk for hypoxemia during sleep. This is related to operating on the steep segment of the sigmoid-shaped oxygen dissociation curve while awake.[783] As with patients with COPD, the benefit of oxygen therapy during sleep in patients with isolated nocturnal oxygen desaturations is not clearly established; clinical judgment should be exercised before instituting such therapy, and reassessment is advised.[783] Furthermore, it is likely that OSA is common in other types of lung diseases such as idiopathic pulmonary fibrosis and sickle cell disease.[788,789] The role of CPAP has yet to be defined in these other disorders.

CONCLUSION

The past several decades have brought major advances in our understanding of normal and disordered breathing during sleep. Results from epidemiologic studies from around the world continue to illuminate our understanding of the consequences of OSA, which extend far beyond excessive daytime sleepiness to include cardiometabolic morbidity and increased mortality. Advances in basic and translational research reveal that the effects of obesity on OSA risk occur not only via anatomic and functional effects but also through effects on ventilation and neuromuscular control of the upper airway. There is likely a specific fat distribution that is important, that is, tongue fat. Evidence that effective treatment of OSA can reduce morbidity and mortality continues to accumulate. And as we learn more about the genotypic and phenotypic expression of sleep apnea, we are likely to be able to better tailor individualized therapies for patients. There is developing evidence that OSA is a heterogeneous disorder with respect to symptoms and physiologic consequences.

These advances are occurring against a backdrop of greater demand for sleep medicine services and reforms in health care that have generated growing pressure to streamline the diagnosis and management of sleep apnea patients with an emphasis on out-of-laboratory, portable testing. In response, new treatments for SDB continue to be developed and new technologies are helping providers to better understand and motivate adherence to PAP therapy. As algorithms for effective management within these systemic constraints are developed and implemented, the intensifying focus within healthcare on patient-centered, outcomes-based care demands that these principles be incorporated into successful models of care for sleep disorders. Meeting this challenge is imperative to our ability to provide optimal patient care and to make continued advances in our understanding of sleep-disordered breathing.

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CHAPTER 99

Sleep-related Hypoventilation Syndromes

Jorge I. Mora
Richard J. Schwab

INTRODUCTION

Sleep induces profound changes on the respiratory system (Chapter 100), especially in patients with underlying cardiopulmonary or neuromuscular disorders. Sleep-related hypoventilation syndromes have in common an abnormal increase in partial pressure of carbon dioxide (Pa_{CO_2}) and/or a decrease in Pa_{O_2} during sleep. A rather arbitrary threshold was chosen aiming to standardize definitions and facilitate research; in 1999 the American Academy of Sleep Medicine (AASM) included an arterial Pa_{CO_2} >45 mm Hg during wakefulness and a greater than 10 mm Hg increase in Pa_{CO_2} during sleep from awake supine values in the definition of sleep hypoventilation syndromes.[1] Similarly, the International Classification of Sleep Disorders (ICSD-3) incorporated a Pa_{CO_2} during sleep greater than 45 mm Hg or, more vaguely than the AASM definition, a disproportionate increase relative to levels during wakefulness in the diagnostic criteria for sleep-related hypoxemia/hypoventilation syndromes.[2] The AASM Sleep Apnea Definitions Task Force revised scoring of sleep hypoventilation in 2012 to include a Pa_{CO_2} increase >55 mm Hg for ≥10 min or a ≥10-mm Hg increase in Pa_{CO_2} during sleep in comparison to awake supine values to a value exceeding 50 mm Hg for ≥10 minutes.[3] These definitions are clearly subjective. While based on data that normal individuals rarely have a Pa_{CO_2} >55 mm Hg during sleep, the precise Pa_{CO_2} demarcating the transition from physiologic hypercapnia to pathologic hypoventilation remains unclear. The duration of 10 min chosen by the AASM Task Force was arbitrary and based on consensus with a lack of normative data on the amount of total sleep time at different values of Pa_{CO_2} in sleeping adults.[3] The measurement of fluctuations in Pa_{CO_2} during sleep is rather impractical and probably unattainable outside of a research setting. The determination of surrogate variables, such as end-tidal CO_2 ($ETCO_2$) or transcutaneous CO_2 ($PtcCO_2$) are more suitable for routine medical practice. However, these measurement methods are susceptible to imprecision when correlated with Pa_{CO_2} either due to sensor drifting ($PtcCO_2$) or due to altered underlying ventilatory physiology (underestimation of Pa_{CO_2} by $ETCO_2$ in the setting of increased dead-space ventilation), or because of technical inaccuracies.

Sleep is associated with stage-specific changes in ventilation covered in Chapter 100. Loss of the wakefulness drive to breathe, altered ventilatory response to hypoxia and hypercapnia, and increased upper airway resistance result in a decrease in ventilation in both non–rapid eye movement (NREM) and rapid eye movement (REM) sleep when compared with wakefulness. Consequently, there is a small normal physiologic increase in the Pa_{CO_2}, usually no larger than 6 mm Hg during sleep.

The small decrease in ventilation and increase in Pa_{CO_2} during sleep is usually of little clinical consequence in normal individuals. However, in patients with respiratory muscle weakness, altered respiratory mechanics, impaired gas exchange in pulmonary disease, and/or abnormal ventilatory drive, sleep is a vulnerable time. Nocturnal hypoventilation often precedes chronic diurnal hypoventilation and hypercarbia; a high index of clinical suspicion is necessary as the extent to which sleep can elicit and drive the clinical progression of chronic hypoventilation is often underappreciated. The benefit of early initiation of nocturnal ventilatory support in subclinical diurnal hypoventilation (daytime eucarbia in presence of sleep-related alveolar hypoventilation and episodic hypercarbia) is intuitively attractive, but the evidence supporting this intervention is currently lacking. What is clear is that nocturnal ventilatory support during sleep in clinically overt hypoventilatory syndromes (i.e., chronic daytime hypercarbia) is clinically beneficial. In this chapter we review the common causes of sleep-related hypoventilation.

CAUSES OF SLEEP-RELATED HYPOVENTILATION

The Pa_{CO_2} is determined by CO_2 production divided by alveolar ventilation—total minute ventilation or MV (total tidal volume times respiratory rate) minus dead-space minute ventilation or MVds (dead-space tidal volume times respiratory rate).

$$Pa_{CO_2} = CO_2 \text{ production}/(MV - MVds)$$

Hypercapnia results when alveolar ventilation is insufficient to meet metabolic needs and is caused by a decrease in minute ventilation, an increase in dead space ventilation, or, rarely, an increase in CO_2 production. The causes of sleep-related hypoventilation can be thought of as disorders of ventilatory drive, that is, "won't breathe," or disorders of respiratory mechanics and/or impaired gas exchange, that is, "can't breathe" (Table 99-1).[4] The ICSD-3 classified sleep-related hypoventilation/hypoxemic syndromes by etiology (Table 99-2).[2]

DISORDERS OF VENTILATORY CONTROL

Disorders of ventilatory drive may result in central apnea and nocturnal hypoventilation (hypercarbic central apnea). These disorders can be primary, including congenital central hypoventilation syndrome (CCHS) and primary idiopathic alveolar hypoventilation, where no other cause for central hypoventilation is found. Alternatively, these disorders can be acquired, usually following neurologic disorders that affect the brain stem and spinal cord, or in acute and chronic opiate use.

TABLE 99-1 The 2005 International Classification of Sleep Disorders

ISCD-2 classification of sleep-related hypoventilation/hypoxemic syndrome

- Sleep-related hypoventilation/hypoxemic syndromes
  - Sleep-related nonobstructive alveolar hypoventilation, idiopathic
  - Congenital central alveolar hypoventilation syndrome
- Sleep-related hypoventilation/hypoxemia due to medical condition
  - Sleep-related hypoventilation/hypoxemia due to pulmonary parenchymal or vascular pathology
  - Sleep-related hypoventilation/hypoxemia due to lower airway obstruction
  - Sleep-related hypoventilation/hypoxemia due to neuromuscular and chest wall disorders

Data from Medicine AAoS. The international classification of sleep disorders: diagnostic and coding manual. 2nd ed. Westchester, IL, 2005.

TABLE 99-2 Sleep-related Respiratory Abnormalities

Main Category	Subcategory	ICD-10-CM
Obstructive sleep apnea	Obstructive sleep apnea in adults	G47.33
	Obstructive sleep apnea in children	G47.33
Central sleep apnea	Central sleep apnea with Cheyne–Stokes breathing	R06.3
	Central sleep apnea due to a medical cause without Cheyne–Stokes breathing	G47.37
	Central sleep apnea due to high-altitude periodic breathing	G47.32
	Central sleep apnea due to drugs or substances	G47.39
	Primary central sleep apnea	G47.31
	Primary central sleep apnea in children	P28.3
	Primary central sleep apnea in premature infants	P28.4
	Central sleep apnea due to therapy	G47.39
Sleep-related hypoventilation	Obesity hypoventilation syndrome	E66.2
	Congenital central alveolar hypoventilation syndrome	G47.35
	Late-onset central hypoventilation with hypothalamic dysfunction	G47.36
	Idiopathic central alveolar hypoventilation	G47.34
	Sleep-related hypoventilation due to drugs or substances	G47.36
	Sleep-related hypoventilation due to a medical cause	G47.36
Sleep-related hypoxia	Sleep-related hypoxia	G47.36

■ Congenital Central Alveolar Hypoventilation Syndrome

Congenital central hypoventilation syndrome (CCHS), initially referred to as Ondine's curse, is a rare cause of central hypoventilation first described in 1970 by Mellins et al.[5] In 2003, the *PHOX2B* gene was identified as the disease-defining gene for CCHS. More than 1000 cases have been reported worldwide. The estimated incidence is 1 in 150,000–200,000 live births in France and Japan.[6] CCHS is characterized by hypoventilation and diffuse autonomic nervous system dysregulation (ANSD). Studies suggest abnormal brainstem integration of chemoreceptor afferent pathways for ventilation with demonstration of some, albeit blunted, physiologic response of both central and peripheral chemoreceptors. Abnormal central integration of chemoreceptor afferents is also thought to be responsible for the autonomic nervous system dysfunction seen in CCHS. Traditionally considered a disorder of infants and children, with advancements in knowledge and treatment, patients are now often surviving into adulthood. This lifelong disorder is rare.

CCHS is caused by a mutation in the paired-like homeobox 2B (*PHOX2B*) gene.[7,8] The *PHOX2B* gene on chromosome 4p12 encodes for a transcription factor that plays a role in the development of the autonomic nervous system and regulation of neural crest cell migration. This is shown by studies in mice in which the *PHOX2B* gene was knocked out. Such mice have abnormal development of the respiratory control system and have no ventilatory response to CO_2.[9] Approximately 90% of *PHOX2B* mutations involve polyalanine repeat expansion mutations (PARMs) producing genotypes (number of repeats) of 20/24 to 20/33, whereas the normal genotype is 20/20. The remaining 10% of cases are heterozygous for nonpolyalanine repeat mutations (NPARMs) and include missense, nonsense, or frameshift mutations. Most expansion mutations occur de novo, but in 5% to 10% of cases parents are mosaic for the *PHOX2B* mutation, with a 50% chance of transmitting the mutation.[10]

CCHS is a clinically heterogeneous disorder. Studies have demonstrated a relationship between the *PHOX2B* genotype and CCHS phenotype. A spectrum of hypoventilation severity is seen; patients with 20/27 to 20/33 genotype typically require 24-h continuous ventilatory support.[11] The syndrome is typically diagnosed in newborns with episodes of cyanosis and apnea usually requiring mechanical ventilation. After maturation of the respiratory and central nervous systems, many patients with CCHS eventually breathe adequately while awake (wakefulness stimulus to breathe) but show hypoventilation during sleep. CCHS does not resolve spontaneously. Hypoventilation in CCHS is most apparent in NREM compared to REM sleep. This is unique from other sleep-related breathing disorders and is thought to be due to an intrinsic REM-related ventilatory drive,[12] whereas during NREM sleep breathing is critically dependent on the metabolic/automatic control of breathing.

Children with CCHS lack perception of dyspnea and may not manifest signs of respiratory distress; they are unable to augment ventilation when faced with a respiratory challenge like an infection or anesthesia and, therefore, these patients may develop sudden decompensated respiratory failure. When unrecognized, children with CCHS present with complications of chronic hypoventilation, including pulmonary hypertension, cor pulmonale, seizures, or developmental delay. Patients can present outside the newborn period with late-onset central hypoventilation syndrome (LO-CCHS) (reported as late as 35 years of age) in individuals with only a minor increase in polyalanine repeats.[13] Careful review of their medical history typically reveals signs and symptoms compatible with hypoventilation and autonomic dysregulation from the newborn period. This may reflect the variable penetrance of *PHOX2B* mutations and should be distinguished from rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD) which is not associated with *PHOX2B* mutations. Patients with this syndrome typically present after the age of 2 years with hyperphagic obesity followed by hypothalamic and autonomic dysregulation, central hypoventilation, and behavioral changes. The syndrome is now considered distinct from CCHS.[10,14]

Autonomic nervous system dysfunction (ANSD) and disorders of neural crest origin are common in CCHS. Hirschsprung disease (a congenital malformation of the enteric nervous system) has been reported in approximately 16% of patients with CCHS and is often of greater severity than in the general population with Hirschsprung disease. Neural crest tumors including neuroblastoma or ganglioneuroma have been described in 5% of patients with CCHS.[15,16] Other symptoms of ANSD described in CCHS patients include diminished pupillary light response, temperature instability, sporadic profuse sweating, altered perception of discomfort and anxiety, and esophageal dysmotility. Cardiac arrhythmias, including decreased beat-to-beat heart rate variability, reduced respiratory sinus arrhythmia, and asystole, have been observed.[10,17] Children with CCHS may have a characteristic box-shaped facies that is shorter and flatter (Fig. 99-1).[18] *PHOX2B* genotype–CCHS phenotype relationships have been demonstrated for the more severe CCHS phenotypes that manifest Hirschsprung disease and tumors of neural crest origin; Hirschsprung disease is most prevalent in patients with NPARM and PARM with more than 20/27

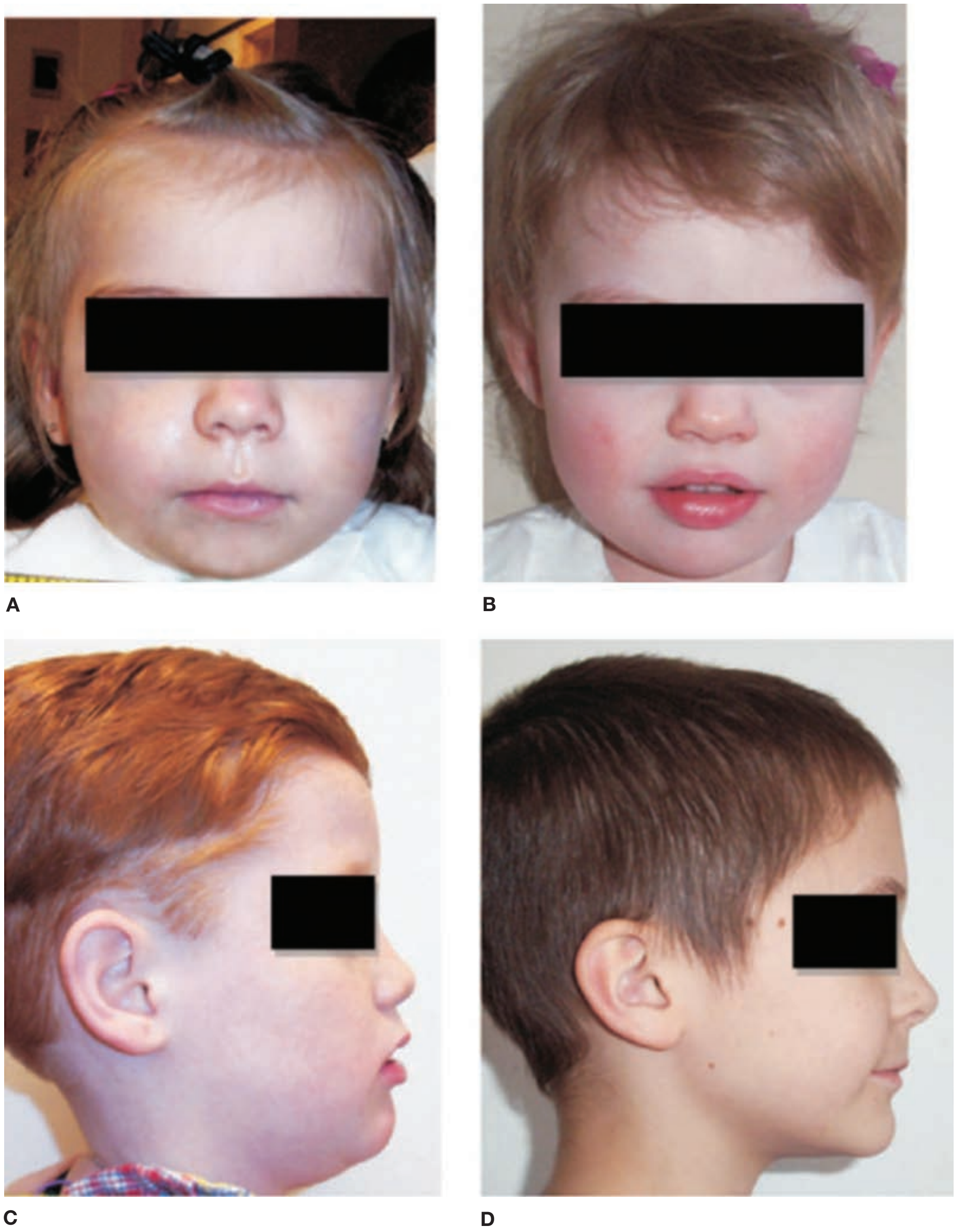

Figure 99-1 Photographs of representative congenital central hypoventilation syndrome (**A** and **C**) and control (**B** and **D**) subjects showing representative box-shaped facies of CCHS with decreases in the slope of the forehead, upper face height, upper facial inclination, nasolabial angle, upper and lower lip heights, and inferior inflection of the lateral vermillion border of the upper lip. *(Reproduced with permission from Todd ES, Weinberg SM, Berry-Kravis EM, et al. Facial phenotype in children and young adults with PHOX2B-determined congenital central hypoventilation syndrome: quantitative pattern of dysmorphology. Pediatr Res. 2006;59(1):39–45.)*

mutations.[19] Neural crest tumors have been described in 50% of NPARMs compared with 1% in controls.[10]

Diagnosis of CCHS relies on genetic testing after excluding other causes of central hypoventilation including pulmonary, neurologic, and metabolic etiologies. Genetic testing with the PHOX2B Screening Test will identify mutations in 95% of cases. If the PHOX2B Screening Test is negative but there remains a high clinical suspicion, direct sequencing of the gene can be performed to detect NPARM mutations.

Alveolar hypoventilation is the hallmark of CCHS. The severity of respiratory failure and the need for ventilatory support can be anticipated by a patient's genotype. Polysomnography (PSG) coupled with continuous CO_2 monitoring, either $ETCO_2$ or $PtcCO_2$, permits assessing ventilatory patterns and specific requirements in all stages of sleep. Further diagnostic studies are guided by the clinical evaluation and include, but are not limited to, screening for other autonomic dysfunction, including Hirschsprung with a barium enema or manometry, cardiac arrhythmias with 72-h Holter monitoring, neural crest tumors with serial chest and abdominal imaging, pupillary function with a comprehensive ophthalmologic examination, and neurocognitive testing.

Nocturnal ventilatory support can be provided by various modalities, including invasive positive-pressure ventilation via tracheostomy or noninvasive positive-pressure ventilation (NIPPV) via a nasal or face mask, ideally with a backup power source (battery) and alarm features. Volume-cycled or pressure-cycled ventilation can be used depending on patient's tolerance. The mode of ventilatory support should be guided by the needs of the patient. In infants and younger children, positive-pressure ventilation via tracheostomy is preferred.

Modern home ventilators and newer ventilatory algorithms (e.g., iVAPS or "intelligent" volume assured pressure support) make NIPPV a palatable and safe option when only nocturnal ventilatory support is required. These ventilators guarantee the delivery of a steady minute ventilation during sleep. In absence of concomitant noncentral hypoventilation, diaphragmatic pacing remains a feasible treatment option—more so in patients who require 24-h respiratory support. Monopolar electrodes are implanted on both phrenic nerves along with receivers in the abdomen or chest, which convert energy received via antennas into electrical currents that are then conducted by the phrenic nerves and result in diaphragmatic contraction. Note that novel devices for diaphragmatic pacing, such as remedē®, are not suited for CCHS. Respiratory stimulants, such as medroxyprogesterone, have not been shown to improve ventilatory drive in CCHS.[20]

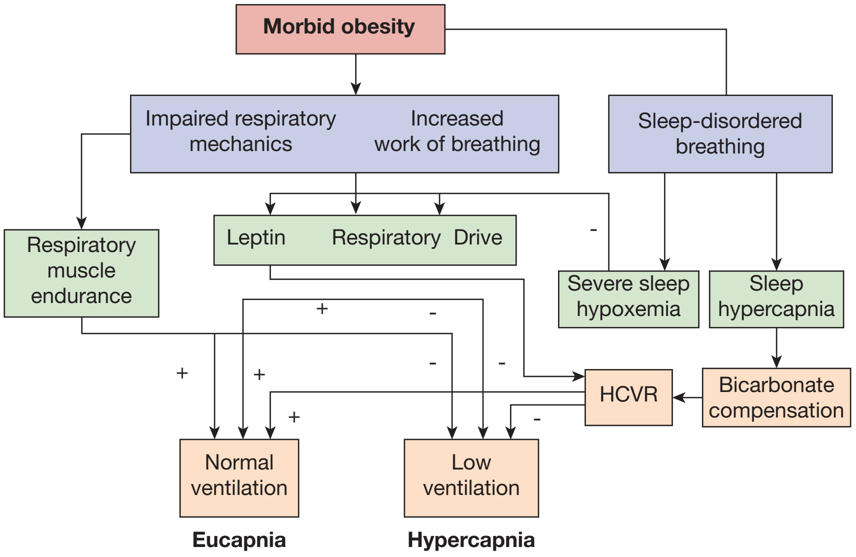

Figure 99-2 Interaction of the various pathophysiologic mechanisms implicated in the development of hypercapnia in the obesity hypoventilation syndrome. (+), positive influence on maintaining ventilation if normal or increased; (–), negative influence on maintaining ventilation if reduced or blunted; HCVR, hypercapnic ventilator response. *(Reproduced with permission from Piper AJ, Grunstein RR. Big breathing: the complex interaction of obesity, hypoventilation, weight loss, and respiratory function. J Appl Physiol. 2010;108(1):199–205.)*

With early diagnosis, close monitoring, and support, children with CCHS can be expected to function well in society and have a good quality of life, but mortality rates of 8% to 38% have been reported.[15] Genetic counseling is essential for individuals diagnosed with CCHS. *PHOX2B* gene mutation in CCHS has an autosomal pattern of inheritance with variable penetrance.[21] This results in a rather broad phenotypic spectrum, and despite most cases presenting de novo, asymptomatic parents of the affected child should be tested. Genetic counseling is imperative for individuals with CCHS and their families, as there is a 50% chance of recurrence with each child.[22]

■ Obesity Hypoventilation Syndrome

The obesity hypoventilation syndrome (OHS) is defined by the presence of obesity (body mass index [BMI] $\geq$30 kg/m^2), chronic alveolar hypoventilation with daytime hypercapnia (awake Pa_{CO_2} $\geq$45 mm Hg), and sleep-related breathing disorder in the absence of any other causes of hypoventilation. While first described in ancient Greek literature, it was not until the 1950s following case descriptions by Auchincloss et al.[23] and, later, Bickelmann et al.[24] that the syndrome gained attention and the term *Pickwickian syndrome*, from the character of Joe in *The Posthumous Papers of the Pickwick Club* by Charles Dickens, emerged.[25]

The risk of OHS increases as BMI increases. In the United States by 2018, approximately 42% of the population was obese.[26] As prevalence of obesity and in particular super obesity (BMI $\geq$50 kg/m^2) increases exponentially, OHS has become a leading cause of sleep-related hypoventilation. A prevalence of 10% to 20% has been reported in obese patients with obstructive sleep apnea (OSA), almost 50% in hospitalized patients with a BMI $\geq$50 kg/m^2, while a conservative prevalence of 0.3% has been estimated in the general U.S. adult population.[27–29] Multiple studies have reported a prevalence of OHS between 8% and 20% in obese patients referred to sleep centers for evaluation of OSA.[30–32]

Pathophysiology

The precise mechanism by which obesity leads to hypoventilation remains incompletely understood. There is likely a complex interaction[33] between (1) abnormal respiratory system mechanics and increased work of breathing due to obesity (reduced chest wall and respiratory system compliance, increased airway resistance, expiratory flow limitation, intrinsic positive end-expiratory pressure, reduced respiratory muscle efficiency); (2) sleep-related breathing disorder; and (3) blunted central hypercapnic and hypoxic ventilatory drive, including central hypothalamic "resistance" to leptin (a protein produced mainly by adipose tissue that stimulates ventilation) (Fig. 99-2).[28]

In approximately 90% of OHS patients there is an associated sleep-related breathing disorder, that is, Obstructive Sleep Apnea (OSA); nearly 70% have severe OSA (Apnea Hypopnea Index [AHI] >30 events/h).[34] In the remaining 10% the sleep-related breathing disorder is nonobstructive sleep hypoventilation characterized by sustained hypoxia and an increase in Pa_{CO_2} by 10 mm Hg above wakefulness in the absence of significant obstructive apneas or hypopneas. More recently, OHS has been suggested to result from an inadequate compensatory ventilatory response to offload the CO_2 that accumulates during apneic and hypopneic events in sleep.[35] In addition, if the bicarbonate retained by the kidneys to buffer this transient decrease in pH is slowly eliminated, there is further blunting of the ventilatory responsive to CO_2, causing progressive hypercapnia (Fig. 99-3).[36]

Clinical Presentation

OHS is associated with increased morbidity and mortality, higher rates of hospitalization and ICU admissions, increased healthcare utilization, and reduced quality of life.[27–29,37] Timely diagnosis is essential, given higher rates of systemic hypertension, angina, congestive heart failure, and cor pulmonale that are reported in OHS compared to eucapnic obese individuals.[28,37] Yet, despite the clinical consequences of OHS the diagnosis is often overlooked and a higher index of clinical suspicion is required.[29]

Typical symptoms of OSA (Chapter 98) are commonly reported by OHS patients, but additional symptoms of hypercapnia including morning headaches, and excessive daytime sleepiness despite adequate control of OSA, may be present. Dyspnea is more frequently reported than in eucapnic OSA patients. Pulmonary hypertension,

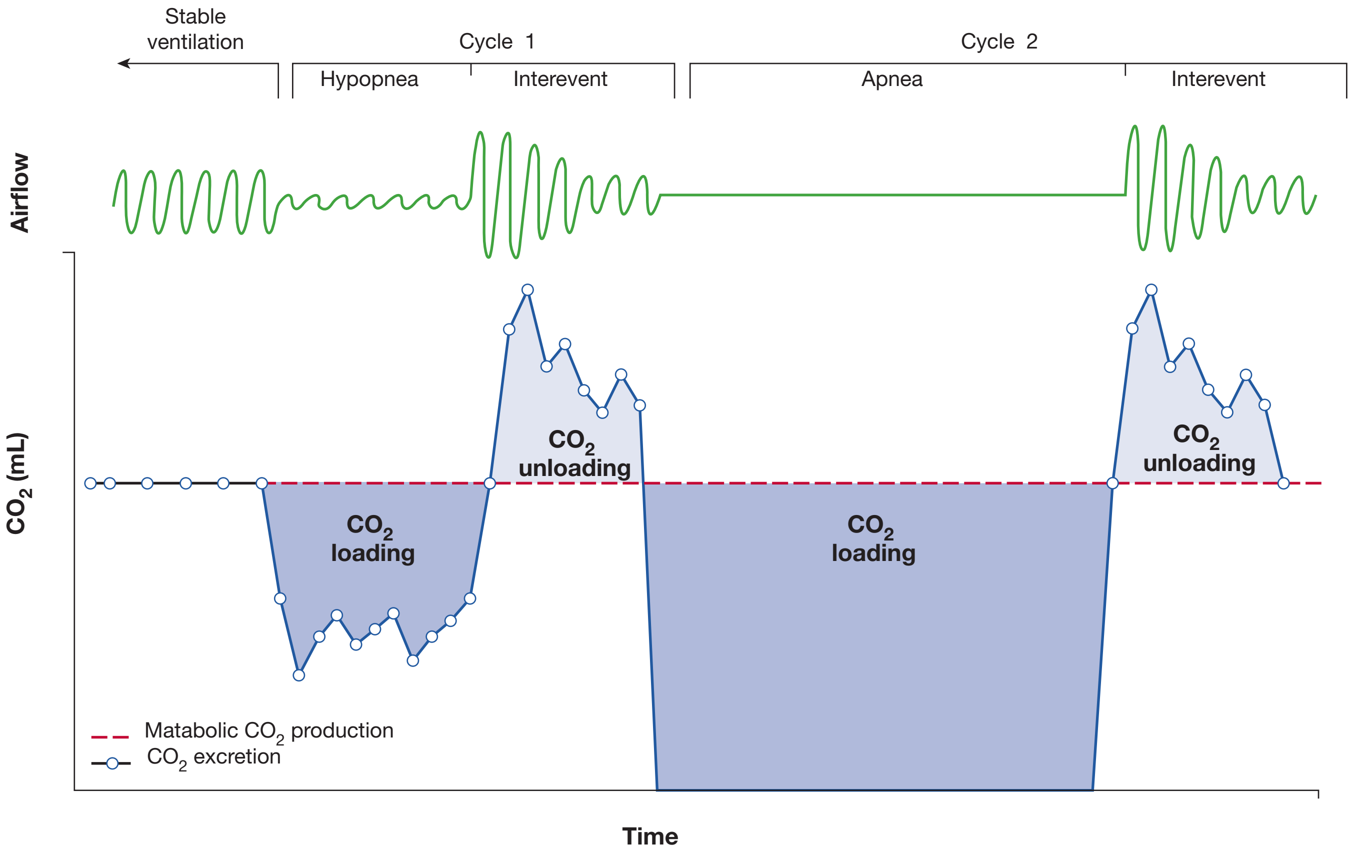

Figure 99-3 Schema depicting a proposed inadequate compensatory ventilatory response to CO_2 loading during obstructive respiratory events in the obesity hypoventilation syndrome. The dark-shaded areas depict CO_2 loading due to reduced CO_2 excretion during respiratory events, while the light-shaded areas depict CO_2 unloading due to compensatory hyperventilation between respiratory events. *(Reproduced with permission from Berger KI, Goldring RM, Rapoport DM. Obesity hypoventilation syndrome. Semin Respir Crit Care Med. 2009;30(3):253–261.)*

cor pulmonale, and polycythemia are also more common in patients with OHS compared with patients with OSA alone. It is not infrequent for patients with OHS to initially present with decompensated acute on chronic hypercapnic respiratory failure requiring the ICU and ventilatory support.

Physical examination in these patients may reveal facial plethora, injected sclera, a prominent pulmonic component of the second heart sound, and signs of right heart failure including lower extremity edema in addition to signs suggestive of OSA. Compared with eucapnic OSA patients, OHS patients commonly have awake hypoxemia typically with a Pa_{O_2} less than 70 mm Hg. Awake hypoxemia is uncommon in eucapnic OSA patients, and a pulse oximetry recording of <94% in patients with OSA should prompt consideration of an arterial blood gas (ABG) measurement.[28]

Diagnostic Approach

The diagnosis of OHS relies on demonstration of awake hypercapnia, and an arterial blood gas on room air is necessary. Chronic hypercapnia may be suggested by an elevated serum bicarbonate, and a serum bicarbonate of 27 mEq/L or greater has been shown to be highly sensitive (92%) but not specific (50%) for chronic hypercapnia.[28,38] Chronic kidney disease and the use of loop diuretics, both common in this population with multiple comorbidities, may affect bicarbonate homeostasis, limiting the role of assessment of serum bicarbonate as a screening tool. The American Thoracic Society position statement on OHS suggests that obese patients with sleep disordered breathing (SDB) who are strongly suspected of having OHS should undergo determination of Pa_{CO_2}, rather than having clinicians rely on serum bicarbonate or Sp_{O_2} to diagnose OHS.[39]

Typically, patients manifest a >10 mm Hg increase in their Pa_{CO_2} during sleep. The presence of deep nonobstructive desaturations or lack of Sp_{O_2} recovery after an obstructive event during polysomnography (PSG) suggest underlying hypoventilation. The use of $ETCO_2$ or $PtcCO_2$ monitoring during PSG should be considered in all obese patients undergoing sleep testing, even in absence of diurnal hypercarbia, as episodic hypercarbia during REM is commonly seen in these patients.

OHS is a diagnosis of exclusion. Other causes of chronic hypoventilation including significant pulmonary disease, chest wall disorders, neuromuscular disease, severe hypothyroidism, and other central hypoventilation syndromes must be excluded. However, it is likely that the pathophysiologic mechanisms underlying OHS coexist with many of these disorders, for example, COPD; they are synergistic. Further diagnostic testing should be guided by the clinical history and physical examination, but should also include pulmonary function testing, lung imaging, electrocardiography, thyroid function testing, and a sleep study, in which a characteristic pattern is often seen, including increased sleep time with Spo_2 <90%, as demonstrated in Fig. 99-4.[28,40,41]

Treatment

Continuous positive airway pressure (CPAP) and nocturnal noninvasive positive pressure ventilation (NIPPV) are currently the mainstay of treatment for OHS. Applying positive airway pressure (PAP) has been shown to improve morbidity and mortality, hypercapnia and hypoxemia, symptoms, pulmonary hypertension, and quality of life.[27,41–45] Despite the widespread adoption of PAP, the best modality remains unknown as the majority of studies are observational,

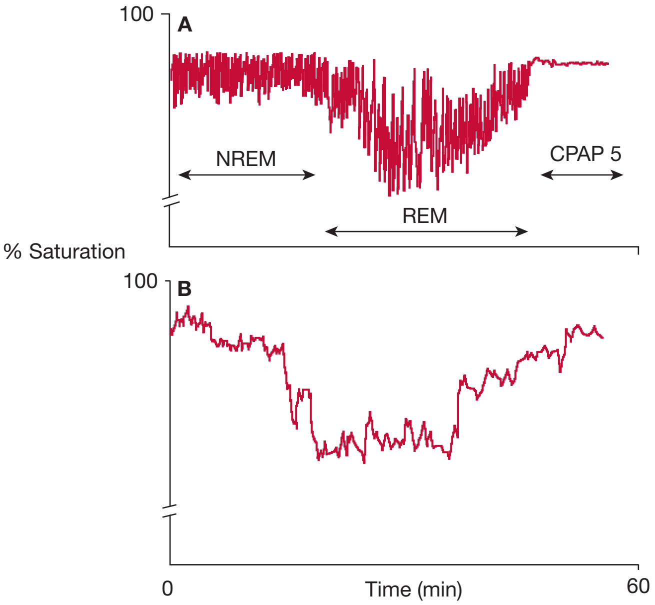

Figure 99-4 **A.** Nocturnal oximetry in a patient with severe obstructive sleep apnea demonstrating recurrent desaturations in nonrapid eye movement (NREM) and rapid eye movement (REM) sleep. Each apneic event results in an oxyhemoglobin desaturation that improves as the apnea is terminated. The degree of desaturation is greater in REM sleep and resolves when continuous positive airway pressure (CPAP) of 5 cm H_2O is applied. **B.** In contrast to **A**, this nocturnal oximetry demonstrates prolonged desaturation in a patient with obesity hypoventilation syndrome (OHS). The desaturation corresponds to periods of prolonged hypoventilation. Although not diagnostic, this pattern is highly suggestive of OHS.

rather than randomized controlled trials, and inclusion criteria in studies are heterogeneous. Improvements in awake respiratory failure, symptoms, and quality of life are similar in OHS patients treated with either CPAP or NIPPV.[39]

CPAP relieves upper airway obstruction effectively treating OSA. Although it does not increase alveolar ventilation, it can improve wake hypercarbia by means of unloading the CO_2 that builds up during repetitive episodes of flow cessation during sleep. Since OSA is present in more than 90% of OHS patients, it is not surprising that CPAP alone has been shown to be effective in treating of the 60% to 80% of patients with OHS.[38,41,46] CPAP also improves sleep quality as measured by Functional Outcome of Sleep Questionnaire and microarousal index, significantly improves daytime sleepiness, and may reduce short-term hospitalization rates without any apparent effect on long-term readmissions.[39] This seems particularly to be the case in the OHS phenotype with higher apnea-hypopnea index (AHI), that is, moderate and severe OSA. Patients of this type seem to respond better to CPAP only, and this should be tried when patients are clinically stable in the outpatient setting. Since it is not clear what features separate responders to CPAP only from nonresponders, CO_2 should be closely monitored early in therapy. A sleep laboratory titration is useful to determine if supplemental O_2 is necessary, in addition to CPAP. The readily availability of $PtcCO_2$ monitoring (in both inpatient and outpatient settings) has made serial in-lab ABG monitoring unnecessary to define adequate ventilation parameters or to evaluate the efficacy of CPAP.[47]

Early initiation of NIPPV in this group is still a common practice, as they are commonly labeled as "CPAP failure" when polysomnography PAP titration shows they unable to sustain adequate saturations on CPAP. However, there are data to suggest that the majority of patients with stable OHS may be transitioned from NIPPV to CPAP without worsening of gas exchange.[48]

The variable response to CPAP requires close monitoring to ensure that gas exchange improvement occurs and is sustained. Should hypercapnia persist, as it does in 20% to 50% of OHS patients on CPAP,[28] these patients should be transitioned to NIPPV. The percentage of failure of CPAP can be decreased by bypassing use of CPAP in those patients with low AHI, as this phenotype is unlikely to respond to CPAP. Transition to NIPPV using either bilevel PAP or volume assured pressure support (VAPS) is indicated in the low-AHI (mild OSA)/OHS phenotype and in CPAP nonresponders after 2 months of adherent therapy. VAPS aims to maintain a target tidal volume by means of an algorithm estimating the patient's tidal volume over several breaths and adjusting pressure support (IPAP-minus EPAP) to achieve that goal. For example, if patient effort and tidal volume decreases, as it occurs during REM sleep, VAPS automatically increases pressure support to maintain the target tidal volume. Successful application of VAPS in OHS has been described, but few studies have compared it to more conventional bilevel PAP modes.[49] Given the broad availability of the latter, it should be considered as a treatment option for OHS.

Independently of whcih device or ventilatory algorithm is used for treatment, it is important to understand the ventilatory mechanics behind OHS. The diaphragm is displaced rostrally by the abdominal organs and excessive intra-abdominal fat, which results in a geometric disruption of the diaphragmatic muscle fibers, making its contraction less efficient and leading to basilar atelectasis, V/Q mismatch, and hypoxemia. Ventilation also is impaired, more so in supine REM sleep when the effects of obesity on diaphragmatic function are more prominent. Additionally, the perithoracic accumulation of adipose tissue further decreases the respiratory system compliance. Atelectasis and decreased compliance mandate use of rather prolonged inspiratory times (Ti) when applying ventilatory support, as any level of PS must be exerted for a longer time in a way that the generated tidal volume (Vt) is delivered homogenously across the lungs allowing "recruitment" of atelectatic areas while avoiding excessive inflation of non-atelectatic areas (volutrauma), all of which translates to improved V/Q matching, oxygenation, and ventilation.

No standard guidelines currently exist for bilevel PAP titration in OHS. Frequently the expiratory positive airway pressure (EPAP) is increased until inspiratory flow limitation is eliminated, followed by the addition of inspiratory positive airway pressure (IPAP) to further improve alveolar ventilation. Typically, an EPAP of 6 to 10 cm H_2O, an IPAP of 16 to 20 cm H_2O, and a difference between IPAP and EPAP ADS: (or Pressure Support) of at least 8 to 10 cm H_2O is required.[27,41,50] The precise role of using a backup rate usually set at 2 breaths/min below the wake resting respiratory rate is unknown but should be used given the ventilatory control abnormalities in these patients. If we extrapolate data from NIPPV in neuromuscular disease, it is likely that "matching" patient's respiratory rate (i.e., minimizing the number of patient-triggered breaths) provides respiratory muscle rest and may translate in improved diurnal ventilatory performance; the evidence for this in OHS is, however, lacking.

In up to half of OHS patients, supplemental oxygen is needed in addition to PAP therapy to keep Spo_2 >90%, although the need for supplemental oxygen may be reduced with continued PAP usage.[47] Oxygen therapy alone, however, is inappropriate for OHS and may prolong apnea and worsen hypercapnia.[39] Oxygen should be given only in conjunction with NIPPV.

Medical weight loss should be encouraged in all patients, but this is often difficult to achieve and maintain. Strategies include exercise, diet, behavioral interventions, pharmacotherapy, or more often, a combination of them with variable and often discouraging results.

Sustained weight loss is not frequently achieved.[51] Newer drugs such as semaglutide are promising. Semaglutide, a glucagon-like peptide 1 (GLP-1) analogue, approved as a weekly subcutaneous dose for the treatment of type 2 diabetes in adults, was associated with sustained, clinically relevant reduction in body weight (14.9%) when combined with lifestyle changes.[52]

Bariatric surgery is an effective approach to achieving sustained weight loss and should be considered in all patients with OHS. Hypercapnia can improve following bariatric surgery. A recent meta-analysis of 342 patients found that 62% of patients had residual OSA with a mean residual AHI of 16 events per hour following maximum weight loss after bariatric surgery.[53] Close clinical monitoring and a repeat sleep study are indicated following this type of surgery. Worsening hypercapnia was reported by Sugerman et al.[54] 1 to 5 years following bariatric surgery despite only a small increase in BMI, thought to be due to recurrence of a sleep-related breathing disorder. While bariatric surgery should be considered in all OHS patients, it is important to recognize that the surgery is associated with postoperative risks with a reported perioperative mortality between 0.5% to 1.5%[55,56]—hence the importance of perioperative use of NIPPV, close physiologic monitoring (Sp_{O_2} and $PtcCO_2$/$ETCO_2$), and avoidance of opioids and hypnotics.

Tracheostomy was available long before NIPPV, but there are very few large studies evaluating long-term outcomes with this therapy. A tracheostomy bypasses the upper airway and has been shown to improve OSA, but correction of daytime hypercapnia is neither universal nor complete and ongoing monitoring is necessary.[57,58] Tracheostomy is now generally reserved for those who have failed all other NIPPV modalities, which is becoming increasingly uncommon. In addition, tracheostomy is often challenging in this population given the excessive neck adipose tissue in most patients with OHS. If a tracheostomy is performed, ventilation through the trachea may still be necessary to increase minute ventilation during sleep, as OSA is effectively "bypassed" but the overall ventilatory defect persists.

Finally, while there has been interest in the use of various pharmacologic respiratory stimulants including medroxyprogesterone and acetazolamide, a carbonic anhydrase inhibitor that induces metabolic acidosis thereby increasing minute ventilation, studies are few and have small sample sizes.[27] These medications should not be used in patients with OHS because of frequent side effects and a lack of demonstrated long-term benefits.

SLEEP-RELATED HYPOVENTILATION IN PULMONARY DISORDERS

Sleep-related hypoventilation occurring in chronic obstructive pulmonary disease and in the so-called overlap syndrome (i.e., chronic obstructive pulmonary disease coexistent with OSA) are discussed below.

■ Chronic Obstructive Pulmonary Disease

Patients with chronic obstructive pulmonary disease (COPD) are particularly susceptible to nocturnal hypoventilation, especially during REM sleep (Fig. 99-5).[59] Becker et al.[60] demonstrated an approximate 16% decrease in ventilation from wakefulness to NREM sleep and an almost 32% decrease during REM compared with wakefulness in patients with COPD. The greater fall in minute ventilation in patients with COPD during sleep is largely due to a decrease in tidal volume. Patients with COPD are often hyperinflated reducing diaphragmatic efficiency, which results in increased reliance on use of accessory and intercostal muscles. During REM sleep there is muscle atonia with loss of this accessory muscle contribution such that ventilation is further reduced. Hypoventilation is further augmented by a decreased ventilatory responsiveness to CO_2 during sleep. Nocturnal hypoventilation in addition to underlying O_2 diffusion defect, result in nocturnal oxygen desaturation.

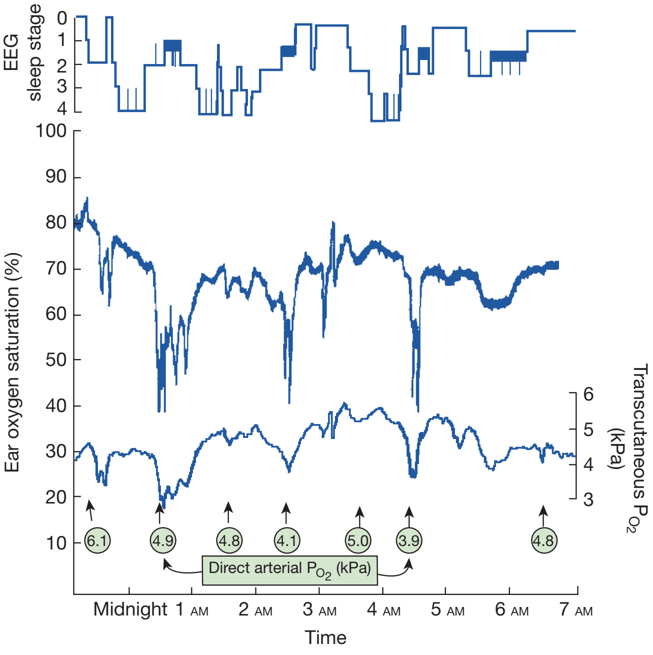

Figure 99-5 EEG sleep stage (*closed bars*, rapid eye movement [REM] sleep), ear oxygen saturation, and transcutaneous P_{O_2} in a "blue bloater" during sleep on room air depicting susceptibility to nocturnal hypoventilation, particularly during REM sleep. 1 kPa = 7.501 Torr. *(Reproduced with permission from Flenley DC. Sleep in chronic obstructive lung disease. Clin Chest Med. 1985;6(4):651–661.)*

Nocturnal oxygen desaturation is a marker of increased mortality in COPD patients.[59,61] The oxygen desaturation nadir during sleep in patients with COPD has been shown to be greater than during exercise, with Sp_{O_2} falling an average of 12.9% during sleep compared with 4.5% during maximal treadmill exercise testing.[62] The presence of hypercapnia is a determinant of mortality.[63–65] Patients with COPD with chronic hypercapnia are more likely to be admitted to the hospital; once admitted, progressive clinical deterioration often follows.[66,67]

While alveolar hypoventilation likely accounts for most of the oxygen desaturations in COPD, changes in ventilation–perfusion matching and decreased end-expiratory lung volumes also have been described.[68,69] Ventilation–perfusion mismatching is suggested by discordance between a decreased Sp_{O_2} and a stable or slightly increased Pa_{CO_2}.[70] Changes in lung volumes, including a reduction in functional residual capacity, leading to closure of small airways have been suggested but studies are conflicting.[69] In addition, as patients with COPD typically have lower wakefulness Pa_{O_2} and lie closer to the steep portion of the oxyhemoglobin dissociation curve, they are more susceptible to significant nocturnal oxygen desaturation. This is particularly relevant in the presence of coexisting OSA, as discussed below.

Nocturnal oxygen desaturation in COPD has been associated with pulmonary hypertension, cardiac arrhythmias, and impaired sleep quality.[68,70] Poor sleep has been both subjectively reported and objectively demonstrated in patients with COPD with reduced sleep efficiency, delayed sleep onset, reduced total sleep time, sleep fragmentation, and a decrease in amounts of slow-wave and REM sleep.[71,72]

Long-term oxygen therapy (LTOT) used ≥15 h per day has been shown to improve mortality and quality of life in COPD patients with chronic resting hypoxemia.[73,74] However, correction of nocturnal hypoxemia in patients with COPD with only nocturnal oxygen desaturation has not been shown to consistently improve outcomes.[75–78]

For some time, there has been significant interest in the use of NIPPV in stable hypercapnic COPD. Patients with severe COPD with chronic hypercapnia are most likely to experience rehospitalization after a life-threatening episode of acute on chronic respiratory failure.[79,80] Correcting hypercapnia is an important intervention aiming at improving the prognosis of these patients; NIPPV is increasingly being used in this group.

McEvoy et al. randomized patients with severe COPD to NIPPV (average inspiratory pressure or IPAP of 13 cm H_2O and pressure support [PS] of 8 cm H_2O) plus LTOT or LTOT alone. There was only a marginal survival benefit in the NIPPV group[81] and no changes in Pa_{CO_2}.[81] The latter observation is likely explained by the low level of PS utilized, as PS is the driving force dictating tidal volume (Vt). Subsequent data have shown that nocturnal ventilatory strategies that aim to produce eucapnia or a sizable reduction in CO_2 utilizing high IPAP and PS, and that are able to provide a backup rate (i.e., high-intensity NIPPV), improve gas exchange and respiratory muscle function,[82–85] may provide a survival benefit,[86] and may reduce readmissions.[87] Murphy et al. in the HOT-HMV trial showed that NIPPV + LTOT in patients with persistent hypercarbia (Pa_{CO_2} >53 mm Hg) 2 to 4 weeks following a hospitalization for acute or chronic respiratory failure resulted in an increased time to readmission or death.[88]

NIPPV includes pressure-targeted and volume-target ventilatory modes. Current home ventilators are able to produce hybrid algorithmic combinations of these modes in which the ventilator continuously adapts its pressure delivery to achieve a preset target Vt or MV (volume assured pressure support or VAPS). This functionality to adapt to fluctuating respiratory mechanics during sleep and disease progression over time, in addition to automatically titrating end positive expiratory pressures (EPAP) to maintain upper airway patency (e.g., decreased effort and increased airway obstruction during REM sleep), results in steady ventilation. These adaptive pressure support modalities (e.g., iVAPS, Resmed; AVAPS, Philips) have been compared with bilevel PAP, either spontaneous (S) or spontaneous/timed (S/T). Six randomized controlled trials showed minimal reduction in Pa_{CO_2} (aggregated decline, 1.95 mm Hg; confidence interval [CI], 4.9 mm Hg lower to 0.40 mm Hg higher) with VAPS, but no difference in oxygenation.[89–95] Although physiologically attractive, auto-titrating modes are substantially more costly, and it is not clear if these devices can actually deliver steady ventilation in real-life conditions, as overestimation in exhaled Vt due to leak can result in algorithm-induced hypoventilation.[96] Until more evidence becomes available, it is not clear what mode or device is optimal, and selection of ventilatory support modality should be driven by cost, clinician level of understanding of newer modes, and patient comfort and support.

■ The Overlap Syndrome

The term *overlap syndrome* was coined by David Flenley in 1985 to describe the coexistence of COPD and OSA, although the original description alludes to a broader definition of coexisting hypoxemic lung disease and OSA.[68] It is of particular clinical relevance, given that greater sleep-related hypoventilation occurs than with either COPD or OSA alone.

The prevalence of the overlap syndrome is estimated at 1% of adults, but prevalence data vary with the definitions used for both COPD and OSA.[97] There is a lack of a standardized definition for the overlap syndrome.[98] Using an OSA definition of AHI ≥5 events/h and a Global Initiative for Chronic Obstructive Lung Disease (GOLD)-based definition of stage I COPD of FEV_1 >80%, a prevalence of 4% of males has been suggested, based on an OSA prevalence of 24% of males in the Wisconsin Sleep Apnea Study.[99] Evidence suggests that there is a similar prevalence of OSA in patients with COPD compared with the general population, with no increased association between at least mild COPD and OSA.[69,100,101]

Sanders et al. found no increased prevalence of SDB in patients with mild COPD; however, oxygen desaturation during sleep was more pronounced in patients with both conditions when compared with those with either disorder alone.[102] More recent studies report a relatively increased prevalence of OSA in patients with moderate to severe COPD,[103,104] as well as a higher rate of COPD and asthma in patients with OSA when compared with a matched control population, particularly among women.[105–107]

Patients with overlap syndrome have more significant nocturnal hypoventilation, with greater hypoxemia and hypercapnia than in COPD or OSA alone.[71,100,108,109] A decreased hypercapnic ventilatory response has been shown in these patients.[110] Pulmonary hypertension is more common and more severe than in either patients with COPD or OSA alone. In the latter, severe pulmonary hypertension is uncommon.[111]

The pattern of nocturnal desaturation in patients with overlap syndrome is characterized by intermittent desaturations and baseline hypoxemia, more so during REM sleep, commonly accompanied by reciprocal hypercarbia (Fig. 99-6). Consequently, the overlap syndrome should be considered in patients with either COPD or OSA with significant hypoxemia, hypercapnia, or pulmonary hypertension disproportionate to the severity of their disease. Patients with OSA/COPD overlap may have hypercapnia with a relatively preserved lung function compared to patients with COPD alone, in whom hypercarbia is usually associated with poor lung function.[113]

The diagnosis of overlap syndrome is important, given the increased morbidity and mortality compared with either COPD or OSA alone.[69] In an observational study, Marin et al.[114] compared 213 patients with untreated overlap syndrome with 210 patients with COPD alone and demonstrated increased mortality (relative risk, 1.79; 95% CI, 1.16–2.77) in the overlap group over a median follow-up of 9.4 years. COPD has been shown to result in increased mortality in OSA in several studies.[115] Data from the 2005–2008 National Health and Nutrition Examination Survey (NHANES), which included 10,388 subjects, revealed that although having OSA/COPD overlap syndrome was associated with higher likelihood of death than COPD alone (HR, 1.5), the difference was not statistically significant.[116]

Some specific clinical features (phenotypes) in patients with COPD may help predict the likelihood of overlap syndrome. The emphysema-predominant phenotype (low BMI, hyperinflation, altered gas exchange) is less likely to have OSA, as hyperinflation

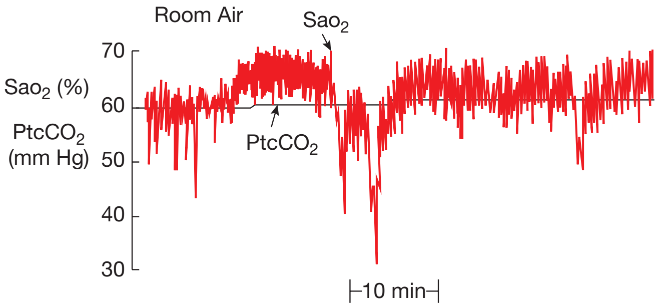

Figure 99-6 Oxyhemoglobin and transcutaneous CO_2 ($PtcCO_2$) tracing in OSA COPD overlap: note hypoxemia at baseline, cyclic desaturation due to intermittent airway obstructions, and reciprocal $PtcCO_2$ elevation. *(Adapted with permission from McNicholas WT. Chronic obstructive pulmonary disease and obstructive sleep apnoea—the overlap syndrome. J Thorac Dis. 2016;8(2):236–242.)*

reduces the critical closing pressure of the upper airway during sleep by means of mechanical tracheal traction.[117] On the other hand, the chronic bronchitis phenotype (higher BMI, altered gas exchange, cor pulmonale) has a lower respiratory drive that often leads to hypercarbia, in addition to rostral fluid shifting resulting in airway narrowing and increased prevalence of OSA.[118] The reality is that the vast majority of patients share both phenotypes, and these mechanisms often imbricate, leading to a rather broad spectrum of clinical overlap.

There are also data examining the potential overlap of systemic inflammation, oxidative stress, and leukocyte dysfunction implicated in both COPD and OSA and the resultant impact on cardiovascular disease.[98] OSA promotes lower airway inflammation in patients with COPD,[119] and chronic intermittent hypoxia contributes to inflammation and oxidative stress.[120]

Given the clinical implications of the overlap syndrome, symptoms and signs suggestive of OSA should be included in the evaluation of all patients with COPD. If there is any clinical suspicion, a full in-laboratory sleep study should be performed in eucarbic COPD. Unattended portable sleep studies have not yet been validated in the COPD population.[121] Similarly, nocturnal oximetry alone cannot reliably discriminate nocturnal oxygen desaturation secondary to COPD alone, OSA, or a combination of the two, and given differences in treatment based on the underlying pathophysiology, it is not recommended for assessment.

Treatment of the overlap syndrome is directed at the underlying disorders. Recent studies have suggested a survival benefit in patients with overlap syndrome with CPAP,[114,122] but these studies were not randomized. Nevertheless, CPAP is currently the accepted standard for the treatment of overlap syndrome. It has been suggested that CPAP, in addition to relieving upper airway obstruction, off-loads the respiratory muscles, thereby reducing hypoventilation, oxygen consumption, and CO_2 production by respiratory muscles; additionally, it may also offset intrinsic PEEP in patients with severe COPD. CPAP alone may not fully correct hypoxemia, requiring addition of supplemental oxygen; however, oxygen alone is not recommended for the overlap syndrome[123] because it can potentially worsen hypercapnia (hyperoxic hypercarbia) by relieving hypoxic vasoconstriction and shifting the pulmonary circulation to poorly ventilated lung segments, resulting in increased dead space ventilation.[124]

SLEEP-RELATED HYPOVENTILATION IN NEUROMUSCULAR DISORDERS

Sleep-related hypoventilation is common in neuromuscular disorders[125] including, but not limited to, amyotrophic lateral sclerosis (ALS), spinal muscle atrophies (SMA), post-polio syndrome, muscular dystrophies, congenital muscular dystrophy, myotonic dystrophy, metabolic myopathies, Guillain-Barré syndrome, and myasthenia gravis. The effects of neuromuscular disorders on ventilation are covered in Chapter 84. Sleep-related breathing disorders generally precede daytime ventilatory failure, and the full spectrum from obstructive and central respiratory apneas to hypoventilation is found.

The mechanisms for sleep-related hypoventilation in neuromuscular disorders are multifactorial. Respiratory muscle weakness plays a central role. The type and severity of sleep-related breathing disorders usually parallel the extent and distribution of respiratory muscle weakness. Sleep hypoventilation often develops when the supine vital capacity is $<60\%$ of the predicted value or the maximal inspiratory pressure is <34 cm H_2O.[126] Patients with diaphragmatic weakness depend on recruitment of accessory inspiratory muscles and expiratory abdominal muscles and are particularly susceptible to significant hypoventilation during REM sleep in which there is relative atonia of these skeletal muscles.

Weakness of the upper airway musculature can cause obstructive events, further exacerbated by an imbalance between the inspiratory force generated by the inspiratory muscles and activity of the muscles responsible for stabilizing the upper airway.[127] With progressive respiratory muscle weakness the number of respiratory events and the AHI may decline in ALS.[128] This may reflect an inability of the inspiratory respiratory muscles to generate pressures above the closing pressure of the upper airway, resulting in fewer obstructive events. Bulbar muscle dysfunction and aspiration risk have not been shown to be significantly associated with severity or type of sleep-related breathing disorders in ALS.[127,129,130]

Abnormalities of ventilatory control have been also described in certain neuromuscular disorders, including myotonic dystrophy and congenital myopathy.[127] The hypercapnia and bicarbonate retention caused by nocturnal hypoventilation can further depress the respiratory drive, exacerbating sleep-related hypoventilation. Sleep fragmentation with shorter total sleep time, frequent arousals, and a reduction in or complete suppression of REM sleep have been described in neuromuscular disorders.[131] This sleep fragmentation and sleep loss may further suppress the arousal response and worsen hypoventilation.

Given the pervasiveness of sleep-related hypoventilation in neuromuscular disorders, a detailed sleep history is an essential component of any clinical evaluation. Early in-laboratory polysomnography with continuous CO_2 monitoring is indicated in this patient population, as sleep-related hypoventilation may precede diurnal hypoventilation and hypercarbia. NIPPV has been shown to improve sleep quality, quality of life, and mortality in various neuromuscular disorders, and management of neuromuscular respiratory muscle dysfunction is covered in Chapter 84.[131–134] However, the optimal criteria for initiation of NIPPV for sleep-related hypoventilation in neuromuscular disorders remain uncertain. The advent of sophisticated home ventilators and improved interfaces (masks) allows providing both nocturnal and diurnal noninvasive ventilation safely to these patients. These ventilators allow transition from different modes of ventilation using one device. The use of ventilatory algorithms, such as VAPS (see above), have also improved how ventilatory support is delivered as it automatically adapts the level of support as the disease progresses. The ability to remotely monitor physiologic ventilatory outcomes through almost real-time cloud-based data generated by these ventilators allows clinicians to change parameters and predict complications (e.g., abrupt changes in Vt or RR may suggest airway obstruction or infection). $PtcCO_2$ can also be measured in the home setting in lieu of in-lab titrations.

SLEEP-RELATED HYPOVENTILATION IN RESTRICTIVE CHEST WALL DISORDERS

Chest wall deformities, in particular scoliosis, often accompany neuromuscular disorders and can contribute to sleep-related hypoventilation. Nonmuscular diseases of the chest wall are reviewed in Chapter 83.

Patients with scoliosis, a rotational deformity of the spine, have reduced chest wall and lung compliance, increased work of breathing, respiratory muscle weakness, ventilation–perfusion mismatching, and reduced respiratory drive.[135] The degree of respiratory impairment is associated with severity of spinal deformity. Respiratory failure is, therefore, uncommon if the Cobb angle (a radiographic measure of spinal curvature in the coronal plane, calculated from two lines drawn perpendicular to lines drawn through the middle of the two vertebrae at the top and bottom of the curved segment) is less than 100 degrees.[136] Sleep is a vulnerable period in patients with scoliosis, and as with neuromuscular disorders, gas exchange is worst during REM sleep.[137–140] While central hypoventilation is more common, airway obstruction also can occur. Patients with scoliosis breathe at low lung volumes, and lower airway caliber is proportional to lung volumes. In addition, secondary cervical curvature can displace the intrathoracic trachea to cause significant upper airway obstruction during sleep. Therefore, clinical evaluation for sleep-related hypoventilation is necessary in this population, followed by polysomnography when a sleep-related breathing disorder is suspected. NIPPV has been shown in small studies to improve gas exchange in restrictive chest wall disorders; however, results on changes in sleep architecture and sleep quality have been mixed.[137,138,140–142]

CONCLUSION

An understanding of normal sleep-associated changes in ventilation is essential in identifying sleep-related hypoventilation syndromes and appreciating the potential vulnerability of the sleep period for patients with underlying cardiopulmonary disorders, morbid obesity, neuromuscular disease, and restrictive chest wall disorders. Consequently, a comprehensive sleep evaluation should be incorporated in the clinical evaluation of each of these high-risk patient populations. This is particularly relevant given the recent advances in NIPPV treatment.

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CHAPTER 100

Changes in the Cardiorespiratory System During Sleep

Indira Gurubhagavatula
Susheel P. Patil

As outlined in Chapter 12, sleep occurs in distinct states classified broadly as non–rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. These states occur in a temporally organized fashion across the sleep period, with NREM dominating during the initial hours of sleep and REM during the later hours of sleep. REM sleep cycles occur in 90- to 120-min cycles, with a typical healthy adult experiencing 3 to 5 cycles during the major sleep bout. Specific alterations in autonomic regulation occur during REM sleep, which may at least partly explain the higher frequency of occurrence of myocardial infarction and ischemic stroke during early morning hours,[1–3] when REM sleep predominates. This chapter presents additional information on alterations in cardiopulmonary function during sleep.

CHANGES IN CARDIOVASCULAR CONTROL DURING SLEEP

During NREM sleep, heart rate normally slows by 5% to 10%,[4] and blood pressure drops by about 10%.[4] These changes are most prominent in the deepest stage of NREM sleep,[4] known as slow wave sleep (stage N3).[5] The mechanism for this decline was elucidated by the seminal study of Somers et al.[4] using microneurography to record sympathetic bursts in the peroneal nerve in healthy humans during wake and in the different stages of sleep (Fig. 100-1). These studies confirmed a fall in sympathetic activity during NREM sleep, which is responsible for the drop in blood pressure, cardiac output, and systemic vascular resistance.[4] The fall in sympathetic activity is accompanied by an increase in parasympathetic (vagal nerve) activity that is believed to be responsible for the bradycardia of NREM sleep.[6] Fundamental to NREM sleep is that the balance of parasympathetic/sympathetic activity is altered, with parasympathetic tone being dominant, thereby affecting heart rate variability during sleep. The high-frequency component of heart rate variability is said to reflect parasympathetic activity, while the low-frequency component is related to sympathetic activity.[4] Thus, during NREM sleep compared with wakefulness and REM sleep, there is an increase in the high-frequency component and a marked reduction in the low-frequency component of heart rate variability.[4]

Changes in cardiovascular variables in REM sleep differ from NREM sleep. During REM sleep, there are surges of sympathetic activity such that heart rate and blood pressure return to, or may sometimes even exceed, wakefulness levels.[4] This phenomenon has been shown by direct recordings of sympathetic nerve activity (SNA) in humans (Figs. 100-1 and 100-2).[4] Thus, during REM sleep the high- and low-frequency components of heart rate variability are similar to those found during wakefulness.[4]

During REM sleep there is also activity that occurs in phasic bursts associated with rapid eye movements (REMs), hence the name for the state. Phasic bursts of activity (phasic REM) can lead to brief, sudden increases in heart rate and blood pressure that are mediated by surges in sympathetic activity,[4,6–8] which are similar to or can exceed waking levels.[4] In addition to changes in SNA, denervation experiments in cats demonstrate that neural reflexes may also be at play, resulting in sudden, baroreflex-mediated periods of decrease in heart rate.[6] These changes have pathophysiologic consequences. During surges of heart rate, there are also increases in coronary blood flow.[7,8] However, increases in coronary blood flow may be insufficient to meet the additional myocardial demands that occur with the increase in heart rate, thereby compromising the myocardium. Moreover, in animal models of severe coronary stenosis, phasic decreases in coronary arterial blood flow are found when heart rate increases in REM sleep.[7] Such changes may play a role in the known diurnal rhythm of timing of reported acute cardiac events in humans.[1–3]

Episodes of abrupt heart rate decelerations can also occur during REM sleep. In addition to baroreceptor-mediated decelerations, sudden slowing of the heart rate may be a result of reduction in central autonomic input to the heart, an increase in vagal tone, or both.[9] At the extreme, brief episodes of asystole in phasic REM sleep have been described in otherwise healthy adults.[10]

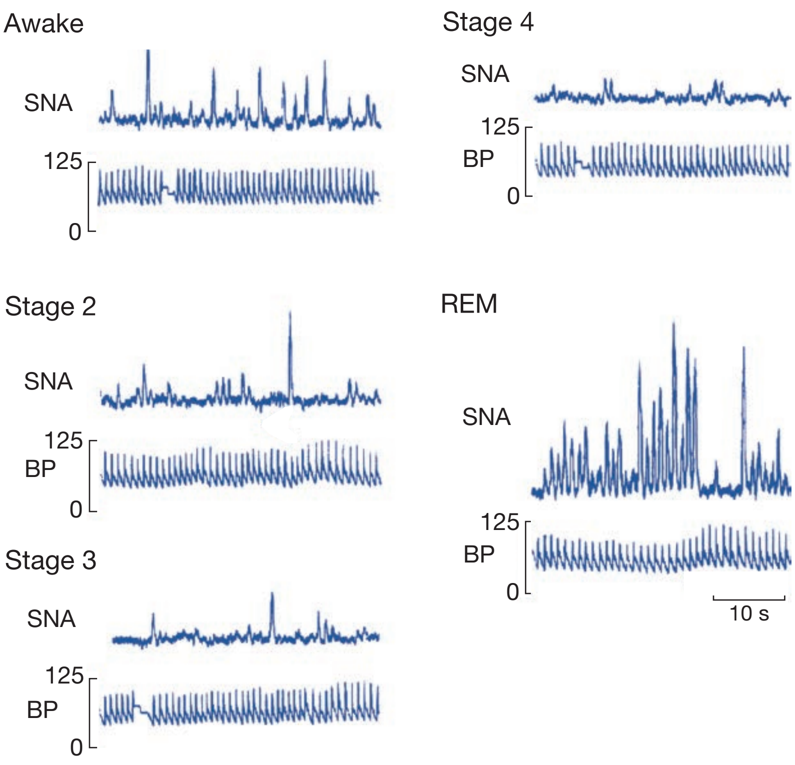

Figure 100-1 Alterations in recorded bursts of sympathetic nerve activity (SNA) and blood pressure (BP) in wakefulness, different stages of non–rapid eye movement sleep (NREM) (stages 2–4), and rapid eye movement (REM). With deepening of NREM sleep, there is progressive loss of sympathetic activity, which is virtually absent in slow-wave sleep (stage 4). Sympathetic activity returns in REM but is highly variable. *(Reproduced with permission from Somers VK, Dyken ME, Mark AL, et al. Sympathetic-nerve activity during sleep in normal subjects. N Engl J Med. 1993;328(5):303–307.)*

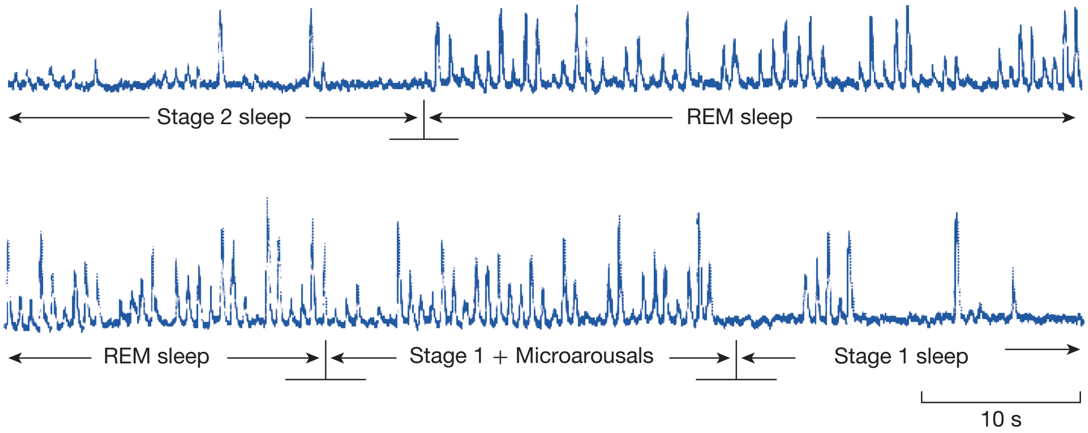

Figure 100-2 Changes in recorded sympathetic nerve bursts in a healthy human during transitions between different sleep stages. There are more bursts—that is, more sympathetic activity—in REM sleep compared with stage 2 NREM sleep (top panel) and more activity in stage 2 sleep when it is transitional with many microarousals than when fully established (bottom panel). *(Reproduced with permission from Somers VK, Dyken ME, Mark AL, et al. Sympathetic-nerve activity during sleep in normal subjects. N Engl J Med. 1993;328(5):303–307.)*

CHANGES IN VENTILATION AND ITS CONTROL WITH SLEEP

As with the cardiovascular system, there are important changes in ventilation during sleep, which differ between NREM and REM sleep.[11,12] During NREM sleep, ventilation declines. The various studies in this area have been summarized by Krieger et al.[13] All studies have reported decreased ventilation, although the magnitude of change varies from study to study (see summary in Fig. 100-3). In general, there is a decline in tidal volume while the change in respiratory rate is more variable (see Table 1 in Krieger et al., 1990).[13]

Ventilation in REM sleep is also consistently less than in wakefulness; some studies report a small increase in ventilation in REM compared with NREM sleep (0.9%–7.1%), whereas other studies report a further decrease (−1.1% to −10.8%).[13] The variability between studies is likely related to the variability of ventilation in REM sleep itself. As in the cardiovascular system, there are changes in ventilation in association with the phasic events of REM sleep.[14] Both acceleration and decelerations of respiratory rate are observed as are declines in ventilation. These effects vary between subjects (Fig. 100-4),[14] with some subjects showing large reductions in inspiratory flow and increased respiratory frequency during REMs and others showing only minor changes.[14]

The changes in NREM sleep in normal humans are largely the result of increases in upper airway resistance.[15] This resistance progressively increases from stage N1 to stage N3 NREM sleep (Fig. 100-5). This increase in resistance is associated with a decrease in upper airway muscle activity in muscles such as the genioglossus[16–20] and tensor palatini[15] in the soft palate. During REM sleep, pharyngeal muscle activity is attenuated via sleep-specific motor inhibition,[18] predisposing individuals to obstructive sleep apnea.

The neural control of upper airway motor neurons is complex and involves inputs from many premotor neurons originating in the forebrain, midbrain, pons, and medulla,[21] which communicate with upper airway motor neurons via a diverse group of neurotransmitters. Identification of the neurochemical changes that are responsible for reduced upper airway motor tone can elucidate promising pharmacologic targets for obstructive sleep apnea. Research has demonstrated that the neurochemical drive to upper airway motor neurons varies with behavioral state and in fact is quite distinct in NREM relative to REM sleep. In NREM sleep, reduced noradrenergic input from the pons[16,19,20] contributes to reduced upper airway tone. Noradrenaline as a neuromodulator may play this role by potentiating glutamatergic excitation,[16] rather than via direct excitation, as measured by masseter muscle activity. Muscarinic inhibition of the hypoglossal motor pool prevents the inhibition of genioglossus activity throughout REM sleep.[18] During REM sleep, muscarinic receptors for acetylcholine linked to G protein–coupled inwardly rectifying potassium (GIRK) channels have been shown to be important.[18] Thus, preventing apneas in both NREM and REM sleep will likely require modulation of both noradrenergic and cholinergic neurotransmitters as well as potentially specific GIRK channels.

Individuals with and without upper airway obstruction during sleep demonstrate increased Pa_{CO_2} in sleep. These findings support the concept that central ventilatory drive is altered by sleep state. Although an increase

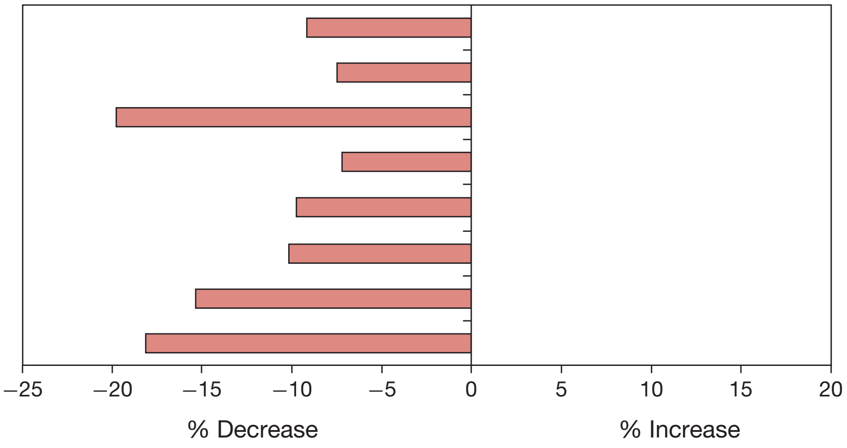

Figure 100-3 Percentage change in minute ventilation from wakefulness to NREM sleep in several different studies. There is some variation among studies in the magnitude of the drop in ventilation in NREM sleep, but all studies show a decline. *(Data from Krieger J, Maglasiu N, Sforza E, et al: Breathing during sleep in normal middle-aged subjects. Sleep. 1990;13(2):143–154.)*

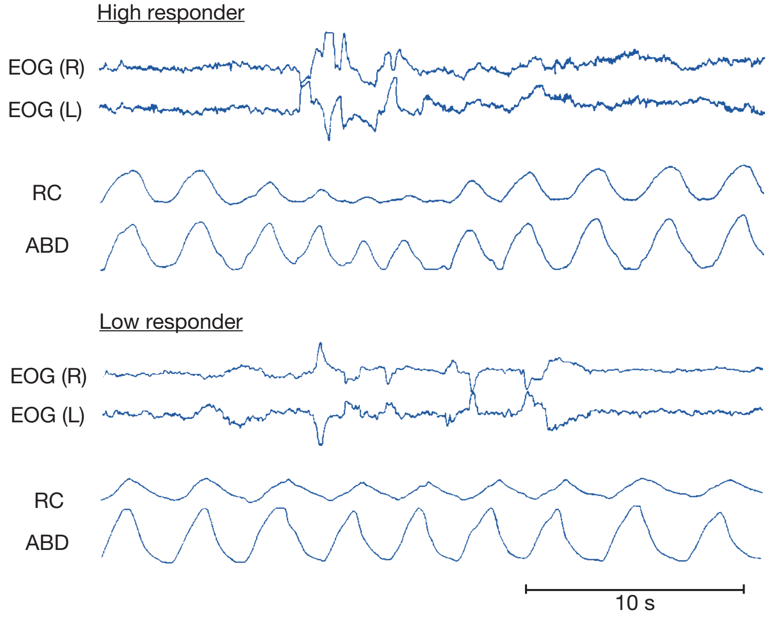

Figure 100-4 Changes in respiration during REM sleep. The data shown are for two normal healthy adults. The top traces are right and left electrooculogram [EOG (R) and EOG (L)] that show phasic eye movements during REM sleep. The bottom traces are ribcage (RC) and abdominal (ABD) motion. The subject in the top panel *(High Responder)* has a marked fall in ribcage and to a lesser extent abdominal motion in association with the eye movements. The subject in the bottom panel *(Low Responder)* has little alteration in ventilatory movements during these phasic eye movements. *(Reproduced with permission from Neilly JB, Gaipa EA, Maislin G, et al. Ventilation during early and late rapid-eye-movement sleep in normal humans. J Appl Physiol. 1991;71(4):1201–1215.)*

in upper airway resistance is the major mechanism, it is not the only mechanism, since even in laryngotomized subjects with tracheostomies, which bypass the upper airway, P_{CO_2} increases in NREM sleep compared to wakefulness.[22] During sleep, the relative importance of the increase in upper airway resistance reflects differential neural control of upper airway muscles[18–20,23,24] and respiratory pump muscles such as the diaphragm. The former is much more coupled to changes in the sleep–wake state, while the latter is more affected by chemical control rather than variations in state (Fig. 100-6). The relative balance of drive to the upper airway muscles relative to the respiratory pump muscles is partly why obstructive sleep apnea is more common than central sleep apnea.

Sleep also alters the ventilatory response to hypoxia and hypercapnia. These effects on ventilatory drive are in part sex-specific. The ventilatory response to hypoxia declines in NREM sleep compared to wakefulness in men,[25,26] but it appears to remain the same in wakefulness and NREM sleep in women.[27] This difference in ventilatory response was attributed to a higher level of ventilation during wakefulness in men than women, with comparable levels in NREM sleep.[27] The ventilatory response to hypoxia is lower in REM sleep than in NREM, in both men and women.[25–27] Likewise, the slope of the ventilatory response to carbon dioxide is reduced in NREM sleep by as much as 50%[28] compared to wakefulness and further reduced in REM sleep. However, there is no compelling evidence that there is an alteration in central neural response to chemical stimuli, as changes in upper airway resistance offset the increases in ventilation produced by increased diaphragmatic neural output.

As a consequence of the changes in ventilation with sleep onset, Pa_{CO_2} rises typically from a normal value of 40 mm Hg by a few mm Hg in NREM sleep.[29] The magnitude of increase in Pa_{CO_2} is a function of the responsiveness of the system to CO_2 during wakefulness; subjects with low ventilatory responses to CO_2 have larger increases in Pa_{CO_2} during NREM sleep than do subjects with high responsivity (Fig. 100-7).[29]

Parallel to the increase in Pa_{CO_2}, the Pa_{O_2} can fall during sleep. In healthy individuals living at sea level, the Pa_{O_2} falls by a few mm Hg but does not fall to a level where significant desaturations occur. However, in persons with low Pa_{O_2} during wakefulness who operate closer to the "knee," or inflection point of the oxygen saturation curve, the fall in Pa_{O_2} with sleep onset may lead to a significant hypoxemia. For example, patients with chronic obstructive pulmonary disease may require supplemental oxygen during sleep but not during wakefulness. The severity of sleep-related hypoxemia will also vary with sleep state–dependent changes in functional residual capacity

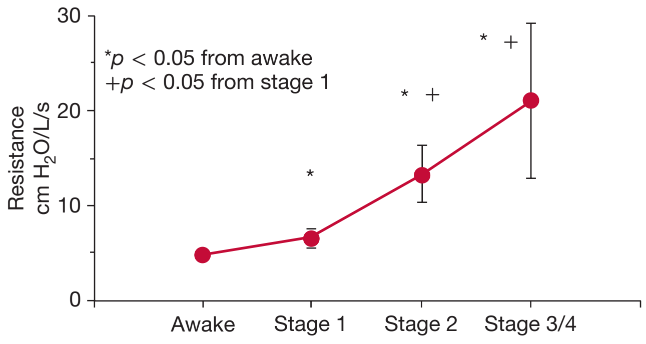

Figure 100-5 Upper airway resistance increases progressively on going from wakefulness to the deeper stages of NREM sleep. *(Data from Tangel DJ, Mezzanotte WS, White DP. Influence of sleep on tensor palatini EMG and upper airway resistance in normal men. J Appl Physiol 1991;70(6):2574–2581.)*

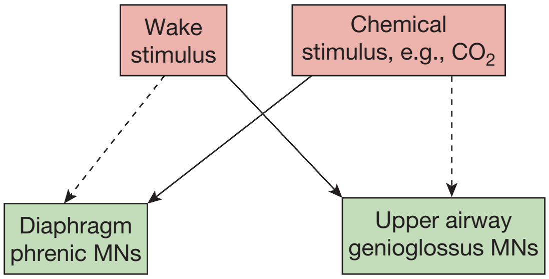

Figure 100-6 Schematic diagram illustrating the relative role of the "wakefulness drive" to breathe and that related to the chemical control system determined by Pa_{CO_2} and Pa_{O_2}. The diaphragm is only little affected by the wakefulness drive *(dashed line)* and is predominantly responding to chemical stimuli *(thick line)*. In contrast, upper airway motor neurons, such as genioglossus, are more affected by the "wakefulness stimulus" coupled to sleep state. MN, motor neurons.

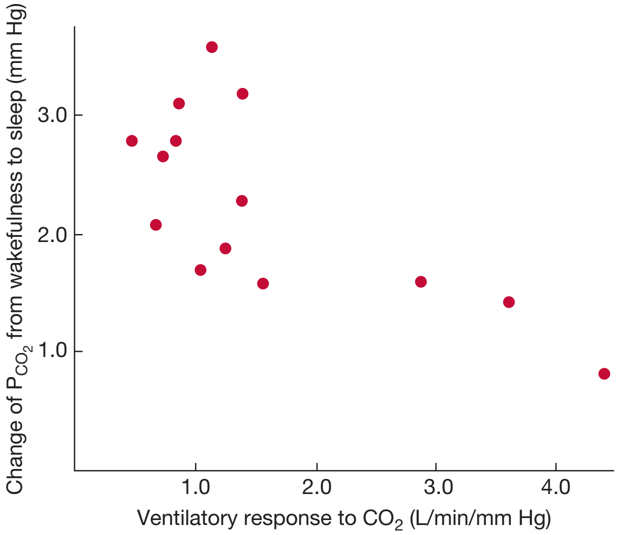

Figure 100-7 Relationship between the increase in Pa_{CO_2} that occurs in normal subjects in going from wakefulness to stages 1 and 2 NREM sleep and the CO_2 ventilatory response in wakefulness. Persons with the lowest ventilatory responses show the largest change in Pa_{CO_2} in going to sleep. *(Adapted with permission from Gothe B, Altose MD, Goldman MD, et al. Effect of quiet sleep on resting and CO_2-stimulated breathing in humans. J Appl Physiol Respir Environ Exerc Physiol. 1981;50(4):724–730.)*

(FRC). When FRC is low as a consequence of obesity or intrinsic lung disease, the fall in Pa_{O_2} will be greater than expected for the increase in Pa_{CO_2}, given the reduced reserve of oxygen in the lung.

Another major change that occurs during NREM sleep is an increase in the CO_2 apnea threshold. The apnea threshold is the Pa_{CO_2} at which there is insufficient chemical drive and ventilation ceases. During the awake state, there is a wakefulness drive to ventilation. This drive is lost during sleep, and instead, the ventilatory drive is primarily coupled to the chemical stimuli for respiration that is, increased Pa_{CO_2} and reduced Pa_{O_2}. During wakefulness, Pa_{CO_2} can be reduced by assisted ventilation to values as low as 20 mm Hg and rhythmic ventilation will be maintained;[12] thus, the CO_2 apnea threshold during wakefulness is extremely low. In contrast, during NREM sleep, the Pa_{CO_2} only needs to be reduced to values close to the normal awake Pa_{CO_2} (from 42–45 to 38–40 mm Hg) and ventilation will cease.[12] Indeed, the normal increase in Pa_{CO_2} that occurs during NREM sleep is often necessary to maintain rhythmic ventilation.

This NREM sleep–related increase in the apnea threshold has profound implications. In situations in which ventilation is stimulated—for example, by hypoxia—Pa_{CO_2} may be reduced below the apnea threshold typical for normoxic conditions, creating a state of increased vulnerability to central apneas.[12,30] It is likely that idiopathic central apnea during sleep occurs in association with hypocapnia.[30,31] This hypocapnia may be the result of chronic hyperventilation, which is probably related to augmented central and peripheral respiratory drive, which predisposes to respiratory control system instability.[30] If this is the mechanism for these apneas, increase in the Pa_{CO_2} should abolish them. This has been demonstrated by addition of small amounts of CO_2 to the inspired gas in subjects with idiopathic central apnea.[12] Relative hypocapnia is also a risk factor for the development of Cheyne–Stokes respiration in patients with congestive heart failure.[30,31] The "CO_2 reserve," which is defined as the difference between eupneic Pa_{CO_2} and the Pa_{CO_2} at the apneic threshold, has been shown to be a determinant of breathing stability during sleep. Larger reserves result in more stable ventilation, and lower reserves result in less stable ventilation.[32]

The specific cellular and neurochemical mechanisms for this NREM sleep–related change in the apnea threshold are currently unknown. Conceptually, however, it may be considered within the same category as the so-called wakefulness stimulus for breathing. Brain stem neuronal groups, such as the locus coeruleus and raphe nuclei in which the major transmitters are norepinephrine and serotonin, respectively, exhibit decreased activity with sleep.[33] Since both neurotransmitters have important excitatory effects at various levels of the central respiratory control system, these neuronal groups likely represent major components of the wakefulness stimulus and may play a role in establishing the apnea threshold.

AROUSAL DURING SLEEP

During sleep various sensory stimuli, including auditory and tactile,[34] can lead to a sudden change in sleep state to a lighter stage of sleep or complete wakefulness. Arousal can be detected with abrupt changes in the electroencephalogram.[35] Arousal also results in an increase in heart rate and blood pressure as well as an increase in ventilation,[36] a response that is independent of CO_2[37] and that decreases with age.[38] So-called subcortical or brain stem arousals—arousals with abrupt changes in cardiopulmonary variables but no change in the electroencephalogram—also can arise, sometimes observed following disordered breathing events.[39] Arousals can produce marked increases in activity of the upper airway muscles than in the diaphragm,[40] producing a ventilatory overshoot that is transiently higher than during stable wakefulness.

Respiratory stimuli, such as airway occlusion, increased upper airway resistance, hypoxia, and hypercapnia, also can lead to arousal during sleep.[34,39] Perhaps unintuitively, isocapnic hypoxia is a poor stimulus to arousal. Individuals can remain asleep without interruption even when Sa_{O_2} values fall as low as 70%.[39] The degree of respiratory effort, however, appears to be the major stimulus to arousal.[39] Increases in respiratory neural output above a threshold are closely correlated with arousal threshold for a given individual, with respiratory effort that is independent of the causes of this increased effort, whether stimulated by added inspiratory resistive load, hypoxia, or hypercapnia.[33,38] Not all arousals are identical. Azarbarzin et al. have developed a scoring approach that allows the magnitude of arousal to be quantified on a scale of 1 to 9.[41] A score of 1 indicates a "weak" arousal, while 9 is a major arousal with marked increases in muscle tone (Fig. 100-8). The heart rate response to arousal is greater with more severe arousals compared with less severe arousals.[41] The magnitude of the heart rate response to arousal is a subject-specific trait,[42] that is, the magnitude of response is stable within a subject from night to night at a fixed arousal intensity, but it varies between subjects (Fig. 100-9). Studies in twins show that this is also a heritable trait,[43] but the relevant genes have not yet been identified. This difference in response likely reflects the sympathetic response to arousals. Heart rate response to arousal has been shown to be predictive of who with obstructive sleep apnea (OSA) gets future cardiovascular events.[44] Individuals with higher heart rate response to arousals have increased cardiovascular mortality.[44]

PERIODICITIES OF VENTILATION IN LIGHT NREM SLEEP

Periodic (oscillatory) ventilation is more likely to occur during light NREM sleep (stages N1 and N2) than in slow-wave sleep (stage N3).[45–47] (Previously NREM was divided into four stages. Scoring criteria have changed such that NREM is now divided into three stages—N1, N2, and N3.) This is highly relevant to the problem of obstructive sleep apnea[47] (Chapter 98); most apneas occur in stages N1 and N2 sleep.[47] If an individual with sleep apnea is able to enter stage N3 sleep, regular ventilation resumes and apneas are less likely to occur.[47] Oscillatory ventilation is also typically observed during hypoxia, as in lung disease or at high altitude, and in certain cardiovascular diseases.[48]

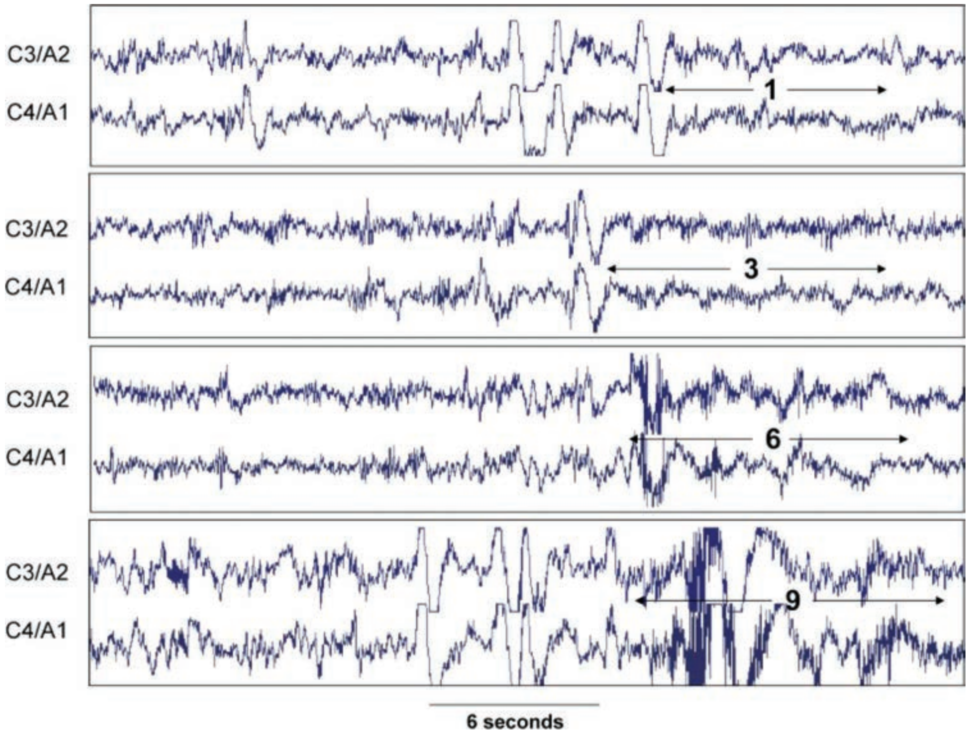

Figure 100-8 Examples of changes in EEG with arousals of different intensities. The examples shown are from the same subject and show arousals with intensity one (top panel), 3, 6, 9 (bottom panel). C31A2 and C41A1 are for control recordings of the electroencephalogram. *(Reproduced with permission from Azarbarzin A, Ostrowski M, Hanly P, et al. Relationship between arousal intensity and heart rate response to arousal. Sleep. 2014;37(4):645–653.)*

Ventilation may become periodic because of dynamic properties of the chemical feedback system that controls respiration.[46,49,50] As in any feedback system, the critical determinants of this unstable (oscillatory) behavior are the overall response (gain) of the control system and the time delay (phase lag) between the plant and the controller. For the respiratory system, the plant is the gas exchange apparatus in the lung; the controllers are the peripheral and central chemoreceptors; and the controlled variables are the arterial blood–gas tensions, Pa_{CO_2} and Pa_{O_2}. Thus, in the case of the respiratory control system, time delay is the blood circulation time between the lung and the peripheral/central chemoreceptors.[49]

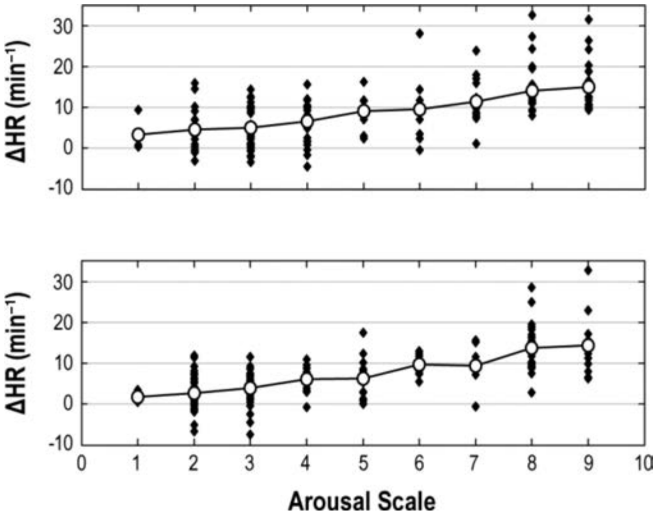

Figure 100-9 Changes in heart rate (ΔHR) with arousals of different intensities (1 to 9) in a sample subject. Data were obtained in the same subject on two separate nights of recording (top and bottom panels). Each solid dot is one or more arousal at a given intensity. The line shows the average heart rate response at arousals of different intensity. Within a subject the heart rate response to arousal is reproducible from night to night. *(Reproduced with permission from Azarbarzin A, Ostrowski M, Younes M, et al. Arousal Responses during Overnight Polysomnography and their Reproducibility in Healthy Young Adults. Sleep. 2015;38(8):1313–1321.)*

The importance of this delay is illustrated in Fig. 100-10 for a situation in which a disturbance to the ventilatory control system leads to a change in Pa_{CO_2}. In the absence of a circulatory delay, the control system responds immediately to the perturbation by adjusting ventilation to correct the change in Pa_{CO_2} (Fig. 100-10A). In contrast, with circulatory delays, the controller may act to inadvertently promote a cyclical disturbance (Fig. 100-10B) through inappropriate corrections, due to the delay in the altered Pa_{CO_2} level reaching the chemoreceptors. For example, when the Pa_{CO_2} level in the blood leaving the lung is low, the controller should respond by reducing ventilation, returning the Pa_{CO_2} to the eupneic level. If, however, the circulatory delay is significant such that the low Pa_{CO_2} signal reaches the sensor when the Pa_{CO_2} of the blood leaving the lung is already higher (e.g., due to the presence of an external perturbation or already existing oscillations, as in Fig. 100-10), the controller will act incorrectly to reduce ventilation and further increase the Pa_{CO_2}. Such a situation potentially promotes self-sustaining periodic ventilation. Thus, the circulatory time delay determines not only whether periodic ventilation will or will not occur, but also the period, that is, duration, of the oscillation.

Periodic ventilation would not occur if the control system failed to respond, or responded weakly, to breathing perturbations. Thus, the magnitude of the gain in responding to alterations in Pa_{CO_2} is also critical in determining whether ventilatory instability will occur. The key variable is overall loop gain. This is defined as the product of the controller response (the change in ventilation per unit change in Pa_{CO_2}, i.e., CO_2 sensitivity) and the plant gain (the change in Pa_{CO_2} per unit change in ventilation).[49] High overall loop gain is also one of the physiologic risk factors for obstructive sleep apnea.[51] It has been suggested that overall loop gain can be assessed from analysis of data obtained from routine sleep studies, based on a simple model of ventilatory control.[52,53] But this model has been criticized since the assumptions underlying this simple model are considered "untenable."[54] There are currently no data as to the reliability of this measure, that is, will the same result be obtained in

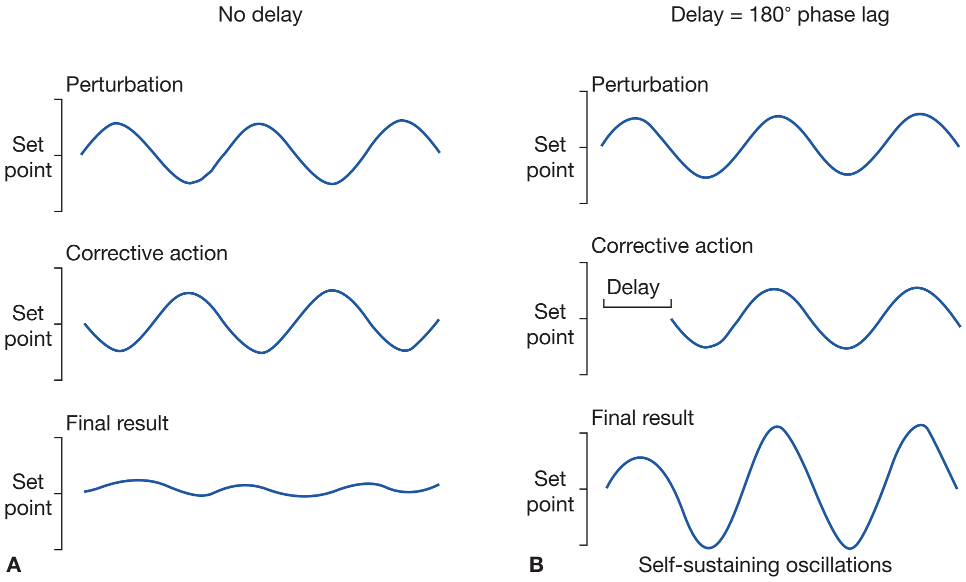

Figure 100-10 Implications for a control system with a delay between the plant and the control system. The left panel (**A**) shows how a control system will respond to a sinusoidal perturbation when there is no delay. The perturbation is essentially neutralized. The right panel (**B**) shows how a control system acts if it has a delay that results in the corrective action being 180 degrees out of phase with the perturbation. In this case, the controller's action acts to sustain, and not to neutralize, the original sinusoidal perturbation.

repeat testing of the same individual? Moreover, there are limited data validating this measure by comparison to "gold standard" measures. It has been argued that for individuals with OSA with high loop gain, use of intraoral devices for treatment is ineffective.[55,56]

Periodic breathing occurs in clinical situations, particularly in hypoxic subjects (e.g., patients with lung disease) and normal sojourners at high altitude.[57] Hypoxia increases the controller gain, increasing ventilatory instability. The period of the oscillations in ventilation induced by hypoxia is on the order of 20 s, much shorter than those typically seen in patients with obstructive sleep apnea or in Cheyne–Stokes respiration (typically 60 to 90 s). As noted earlier, abnormally prolonged circulatory time is one of several mechanisms that contribute to ventilatory oscillations that occur during sleep in patients with severe congestive heart failure (e.g., Cheyne–Stokes respiration).[58,59]

In addition to mechanisms that are related to instability of the chemical control system for ventilation, sleep–wake state instability (i.e., frequent transitions between the wake and sleep state) can produce oscillations in ventilation.[12,14,25–28,49] As discussed in the preceding section, at the onset of sleep, ventilation decreases[11,13,29] as upper airway resistance increases[15] with concomitant increases in Pa_{CO_2}; the increase in Pa_{CO_2} may, in turn, directly or indirectly interfere with the normal progression towards stable sleep. For example, an abrupt change in sleep state may occur as a result of partial airflow obstruction and increased respiratory effort, leading to a transition to a lighter stage of sleep, that is, an arousal. Upon arousal, ventilation increases, upper airway resistance decreases, and Pa_{CO_2} drops. On returning to sleep the whole cycle may repeat itself. Sleep-wake instability is more likely to arise if the ventilatory response to CO_2 is low, since the Pa_{CO_2} increases more at sleep onset and is more apt to drive the level of respiratory effort to a point at which an arousal from sleep occurs. The period of ventilatory oscillation caused by this mechanism is longer than that seen with chemical instability, at about 60 to 90 s. This mechanism likely contributes to recurrent upper airway obstruction and periodic breathing in patients with low ventilatory responses to CO_2 (e.g., patients with hypothyroidism, in whom central and obstructive apneas are common).[45,49]

CIRCADIAN CLOCKS IN THE CARDIOVASCULAR SYSTEM AND LUNG

While much is known about the physiology of cardiopulmonary changes during sleep, attention has been shifting to changes in molecular mechanisms during sleep. In the late 1990s, the discovery of the molecular components that produce circadian clocks led to the study of circadian clock genes expression in many different organs.[60] Surprisingly, functioning clocks were found not only where they were expected—in the suprachiasmatic nucleus of the hypothalamus, the site of the master circadian clock—but in most organs. In particular, functioning clocks have been elucidated in the lung and cardiovascular system.[61,62] In cardiac myocytes and vascular smooth muscle cells, clocks are intrinsic to these cells since they maintain a circadian rhythm even when the cells are isolated and in culture.[62] Many other cell types have not been as extensively tested to date, but peripheral clocks including those in the liver, kidney, heart, and adipose tissue[63,64] have been described. These clocks likely alter the temporal pattern of expression of genes in the relevant organs. Microarray studies indicate that about 10% to 15% of all genes have diurnal variation in their expression levels. In the heart, for example, diurnal variation of genes promoting fatty acid oxidation occurs. Expression of these peaks in rats during the dark phase, that is, their active period.[62] Furthermore, the expression of K+ channel genes also exhibits diurnal variation in the heart and likely contributes to the altered excitability of the cardiac myocyte across the day.[61]

These observations indicate that at a fundamental molecular level, the heart and lung at night are not the same as during the day. Molecular processes in peripheral organs are also affected by sleep and sleep deprivation,[65] and this is an area that is likely to be a fruitful area of inquiry. Currently we do not know the mechanism mediating these changes. The molecular basis of circadian rhythms and molecular functions of sleep are discussed in more detail in Chapter 12.

CONCLUSION

There are major changes in cardiopulmonary function during sleep compared with wakefulness. These changes are specific to sleep state, with differences between NREM and REM sleep. The changes in cardiopulmonary function have important pathogenetic significance. These physiologic changes can contribute to the timing across the day of acute cardiovascular events; the periodic breathing that occurs during sleep at high altitude; the anatomic and neuronal changes that lead to obstructive apnea during sleep; and the pathogenesis of Cheyne–Stokes respiration. Currently, a new understanding of circadian variation in in cardiopulmonary function at the molecular level during sleep is evolving. New observations in this area will undoubtedly lead to new insights regarding cardiopulmonary physiology that will also have implications for the pathogenesis of disease and treatment.

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CHAPTER 101

Differential Diagnosis and Evaluation of Sleepiness

Sritika Thapa
Mithu Sen
Meir Kryger

INTRODUCTION

Excessive daytime sleepiness (EDS) is a common problem affecting large segments of the general population. Although estimates depend on how sleepiness is defined (i.e., sleeping too much vs. falling asleep in the daytime), the National Sleep Foundation's annual Sleep in America poll in 2018 showed that among U.S. adults with excellent sleep health, 90% say that they feel effective at getting things done, while only 46% with poor health say they can get things done effectively; only 10% of American adults prioritize sleep over other daily activities like fitness/nutrition, work, social life, and hobbies.[1]

There is increasing evidence that sleepiness plays a part in both industrial and road traffic accidents and impaired performance. Sleepiness is most often caused by insufficient sleep or sleep disorders.

THE PHENOMENON OF SLEEPINESS

Sleepiness is both a subjective and an objective phenomenon, a constellation of sensations and a physiologic state with stereotypical behaviors. As such, it is sometimes difficult to define, and its measurement (see "Quantifying Sleepiness," below) depends on the circumstances. Sleepiness may be expressed as feeling sleepy, fatigued, or tired; sleeping too much; falling asleep inappropriately; or fighting to maintain alertness. Sleepiness can be reflected by any or all the following: heaviness of the eyelids, mild burning or itching of the eyes, difficulty keeping the eyes open, heaviness in the arms or legs, reluctance to move, loss of initiative, loss of interest in surroundings, and difficulty with concentration or memory. These sensations are accompanied by behavioral changes, such as rubbing the eyes, yawning and stretching, and nodding the head, and by generally reduced motor functions, such as speech, facial expression, and body movement. Sleep-deprived healthy individuals demonstrate attenuated facial expressions to stimuli.[2]

Sleepiness may also be considered a physiologic state like hunger or thirst. Just as hunger and thirst are physiologic states that occur with fasting and are satisfied by eating and drinking, sleepiness in individuals without a specific sleep disorder is produced by sleep restriction or deprivation and is reversed or satisfied by sleep. However, a difference between sleep and other physiologic factors is that, for example, while food may satisfy hunger, sleep quality and quantity are necessary to satiate sleep loss.

Sleep quality is impaired in individuals with specific sleep disorders, such as sleep apnea. The factors that produce and influence sleepiness are detailed below; they include such obvious factors as time since last asleep, previous amount of sleep, continuity of sleep, and normal 24-h circadian influences. Environmental stimuli influence this state and can determine, up to a point, whether this sleepy tendency will be manifested. For example, heavy meals, warm rooms, boring lectures, or monotonous tasks are usually considered soporific activities or situations. Under these circumstances, a person might feel sleepy and might fall asleep. However, the environmental factors themselves do not cause the sleepiness; they only allow it to be expressed. Equally, the same degree of physiologic sleep tendency might go unnoticed when environmental stimulation occurs in the form of a life-threatening situation. In other words, the degree to which sleepiness is experienced or evident in behavior is determined by the underlying physiologic sleep tendency (or the need for sleep) and environmental factors, which interact to manifest the sleep tendency or sleep propensity.[3]

While it is accepted that sleepiness is a physiologic state, the physiologic substrates of this state have not been identified. Neurotransmitters, such as serotonin, acetylcholine, histamine, and the catecholamines have been implicated in the sleep/wake mechanism along with a variety of other sleep-inducing substances, including adenosine through its inhibition of wakefulness-promoting neurons. While much research is ongoing, an understanding of the neurochemicals responsible for sleep, sleepiness, and loss of alertness is still evolving.[4–6]

QUANTIFYING SLEEPINESS

The sensation of sleepiness is often difficult to quantify, as are other subjective symptoms, such as pain or shortness of breath. All these subjective sensations may mean different things to different people and are modified by a variety of factors, including motivation, external stimulation, and competing needs. What constitutes extreme sleepiness for one person may be only mild sleepiness for another and depends on the situation in which it occurs. An approach is outlined in Table 101-1. Sleepiness has different dimensions, including feelings of perceived sleepiness, as well as self-estimates of sleepy behavior that are different in passive versus active situations. There exists the notion of a sleepiness trait, that is, a composite of sleep need and sleepability, which is the ability to transition into sleep rapidly.[7]

Other individual difference factors have been proposed to explain individual dissimilarities in sleepiness.[8] Sleep drive is an inherited trait.[3]

There have been initial efforts to identify gene variants associated with sleepiness using a genome-wide association study (GWAS).[9] It was conducted using data from the U.K. Biobank and based on one

TABLE 101-1 An Approach to Sleepiness

I. The Phenomenon of Sleepiness
II. Quantifying Sleepiness
    Subjective measures of sleepiness
    Objective measures of sleepiness
    Performance and vigilance tests
III. Factors Affecting Sleepiness
    Sleep quantity
    Sleep quality
    Circadian rhythms
    Medications
IV. Prevalence of Excessive Daytime Sleepiness
V. Evaluating the Sleepy Patient
    Approach and differential diagnosis

question: "How likely are you to doze off or fall asleep during the daytime when you do not mean to (e.g., when working, reading, or driving)?" Subjects indicated the frequency of occurrence of this. Investigators were able to identify 42 genome-wide significant associations. Examining the association of these variants with objective data on sleep duration led to the proposal that there were variants associated with propensity to sleep (sleep drive) and others associated with sleep fragmentation.

■ Subjective Measures of Sleepiness

Subjective reports may be used to quantify sleepiness, but statements such as "I feel sleepy" and "I feel very sleepy" often do not distinguish between feelings caused by a high physiologic sleep tendency and those resulting from muscular fatigue, depressed mood, or a general lack of energy. Thus, several subjective sleepiness scales have been developed.

The *Stanford Sleepiness Scale* (SSS), the first to receive widespread use, is a seven-point self-rating scale ranging from 1 (alert, wide awake) to 7 (almost in reverie, sleep onset soon).[10] It is brief, is simple to use, and measures current degree of sleepiness. It has been shown to correlate with the performance of mental tasks and demonstrate changes in sleepiness with sleep loss. However, there are no normative data, and results often depend on the duration of prior sleepiness. For example, unlike normal persons who are experimentally sleep deprived, patients with more chronic sleep deprivation (e.g., sleep apnea) cannot be accurately tested with the SSS. Some patients who have an obvious overwhelming physiologic sleep tendency may claim to be only mildly sleepy yet fall asleep before your eyes. This was first observed in the early 1970s, and was a stimulus for one group of investigators to develop more objective measures of sleepiness.[10] Studies have shown that continued increases in lapses in performance occur over several days of sleep restriction, but the self-reported sleepiness does not continue to get worse.[11]

It is clear that over a period of months or years, many patients with sleep apnea lose their frame of reference with regard to normal alertness and cannot distinguish major changes in sleepiness. Thus, the subjective report of sleepiness (using the SSS) by people who are chronically and severely sleep deprived is not reliable.[10]

The *Karolinska Sleepiness Scale* (KSS) is a nine-point scale ranging from 1 (very alert) to 9 (very sleepy, fighting sleep, making an effort to keep awake), with verbal descriptions of every second point.[12] Like the SSS, the KSS requires the subject to integrate and translate a number of sensations to a continuum that is fairly abstract, despite the verbal descriptions. Ratings obtained with these scales may be affected by the situation in which the scale is presented (e.g., at rest or during performance of a task) and how the subject relates his or her perception to that particular time or place. The scales reflect current sleepiness. Nonetheless, both the SSS and KSS show high correlations with performance. The KSS was also found to be strongly related to EEG and electrooculographic signs of sleepiness.[12]

The *Epworth Sleepiness Scale* (ESS; Table 101-2) was designed to measure sleep propensity in a single, standardized way and is based on questions relating to eight situations, some known to be very soporific.[13] The ESS, in contrast to the KSS and SSS, assesses symptoms of chronic sleep deprivation. The questions are self-administered, and subjects are asked to rate on a 0 to 3 scale how likely they are to doze off in the situation based on their usual habits over recent weeks to months. The ESS tries to overcome the fact that people have different daily routines, some facilitating and others preventing daytime sleep. An ESS of 10 or below is considered normal. Scores above this are considered indicative of excessive sleepiness. ESS scores have shown significant correlations with mean sleep latency in the multiple sleep latency test (MSLT, see further below) and have distinguished groups of patients with disorders of excessive sleepiness such as narcolepsy, OSA, and idiopathic hypersomnolence. The ESS score has been validated against the MSLT in a patient population with sleep disorders, specifically patients with narcolepsy, and shows 95% sensitivity and 73% specificity in comparison to the MSLT.[14] The ESS has high test–retest reliability and a high level of internal reliability in normals and patients with sleep apnea.[15] There are different dimensions to the symptoms of sleepiness. Thorarinsdottir et al. have shown that in the general population there are individuals with elevated Epworth Sleepiness Scores who do not complain of sleepiness, while there are others with normal Epworth Sleepiness Scores who complain of sleepiness on multiple days/week.[16]

■ Objective Measures of Sleepiness

The Multiple Sleep Latency Test (MSLT) has been developed and standardized as an objective, reliable, and reproducible measure of physiologic sleep tendency.[10] Performed at intervals throughout the day, the MSLT measures the time to sleep onset, as determined by the EEG. The test is based on the assumption that, given the proper surroundings, physiologic sleep tendency will be expressed by going to sleep; its appeal is intuitive in that if one patient is more sleepy than the other, the sleepier patient should fall asleep more quickly.

Patients are instrumented to record the EEG, electrooculogram (EOG), and electromyogram (EMG); they are put in a quiet, darkened, temperature-controlled room and are asked to lie quietly, close their eyes, and try to fall asleep. Naps are scheduled at 2-h intervals, with 20 min allowed for sleep to occur. If an individual initiates sleep, a mean sleep onset latency (SOL) can be measured and can support excessive daytime somnolence or a diagnosis of narcolepsy, as explained below. Thus, the average SOL of the naps represents the result of the MSLT. Both clinical and research protocols exist for conducting the MSLT.[14]

Since sleepiness follows a circadian rhythm (see "Circadian Rhythms," below), one nap is insufficient to document and quantify daytime sleepiness. Accordingly, a minimum of four and a maximum of six naps are recommended. However, pooled data from normal persons of wide age range showed a statistically significant difference in mean sleep latency with 4 or 5 naps (10.4 ± 4.3 min vs. 11.6 ± 5.2 min, respectively), while pooled reports from narcolepsy patients showed the mean sleep latency was 3.1 ± 2.9.[17] The MSLT is a reliable, reproducible test that has been validated in a number of sleep deprivation experiments in normal subjects and in a variety of clinical conditions with patients who have disorders such as narcolepsy and sleep apnea; it may be useful for documenting treatment response to a sleep disorder, such as medications in narcolepsy or CPAP in sleep apnea.

An important advantage of the MSLT is that patient motivation cannot counteract the effects of previous sleep loss on sleep latency. That is, while most people can be motivated to compensate for reduced performance after sleep deprivation, motivation cannot overcome an increased pressure for sleep, particularly when the patient is in bed in a darkened room. A mean SOL of ≤8 min is considered pathologic sleepiness. Any sleep-onset REM (SOREM) is closely observed, as it can signify a diagnosis of narcolepsy. Two or more SOREMs during the nap opportunities support a diagnosis of narcolepsy (see below).[18] Early REM on the proceeding PSG also can be considered a SOREM supporting the diagnosis of narcolepsy.

The Maintenance of Wakefulness Test (MWT) is an alternative to the MSLT. This is a variation on a theme in which subjects sit in a chair in a darkened room and are requested to remain awake for 20 (or 40) min. The test was developed on the assumption that the ability to fall asleep and the ability to stay awake are two separate phenomena. The MWT has undergone further tests of validity but has been criticized for lack of a standardized protocol, with 20-, 30-, and 40-min tests being reported. Recent practice parameters suggest

TABLE 101-2 Epworth Sleepiness Scale

Epworth Sleepiness Scale

Name: ______________________ Today's date: ______________

Your age (Years): __________ Your sex (Male = M, Female = F): __________

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired?

This refers to your usual way of life in recent times.

Even if you haven't done some of these things recently try to work out how they would have affected you.

Use the following scale to choose the **most appropriate number** for each situation:

0 = **would never** doze
1 = **slight chance** of dozing
2 = **moderate chance** of dozing
3 = **high chance** of dozing

It is important that you answer each question as best you can.

Situation	**Chance of Dozing (0–3)**
Sitting and reading	
Watching TV	
Sitting, inactive in a public place (e.g., a theatre or a meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after a lunch without alcohol	
In a car, while stopped for a few minutes in the traffic	

THANK YOU FOR YOUR COOPERATION

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that a 40-min protocol may be better than a 20-min protocol, as this is more challenging and identifies patients with real difficulty staying awake due to the longer duration of the test.[17] This is a relevant evaluation when assessing whether a patient can stay awake in a situation of personal or public safety.

While both MSLT and MWT require observer recognition of EEG changes, quantitative computerized analysis *of EEG* has been proposed as an alternate and perhaps more sensitive objective measure of sleepiness. Increased EEG delta activity with sleep deprivation and decreased alpha activity just before sleep onset are two possible metrics. However, these have yet to be translated into clinically useful tests. The Alpha Attenuation Test (AAT) has been validated in sleep-restricted normals and in patients with narcolepsy and correlates strongly with the MSLT.[14]

The *Oxford Sleep Resistance Test* (OSLER test) was designed as a low-cost alternative designed to reproduce many of the features of the MWT, but without the labor-intensive, continuous monitoring of EEG.[19]

In the OSLER test, subjects respond to a visual stimulus. A light-emitting diode mounted on the wall flashes for 1 s every 3 s in fixed intervals. If there is no response after seven consecutive stimuli, the subject is deemed to be asleep and the test is ended. The original study compared OSLER sleep latency with MWT latency in 10 patients with OSA and 10 control subjects done on separate days and showed that OSLER could be validated against the MWT in this patient population. Two other studies involving small numbers of patients in a sleep disorder center and/or normal subjects before and after sleep deprivation have demonstrated excellent agreement between the two measures and suggest that the OSLER could be an alternative to measuring sleepiness.[20] There are no large-scale studies using the OSLER; the main limitation of this test is its dependence on patient cooperation.[21,22]

One disadvantage of these tests is that it requires a whole day of testing. This has limited their widespread application.

■ Performance and Vigilance Tests

Measurements of performance after sleep loss reflect daytime sleepiness, since most people report decreased performance after a sleepless night. Previously it was felt that only performance tests that were prolonged and monotonous were sensitive to sleep loss.

However, the work of Dinges et al. (using his Psychomotor Vigilance Task [PVT]) demonstrates that if the signal rate is high and the response measure sufficiently sensitive, repetitive tasks of only 10 min duration will expose the limits of performance in sleepy persons.[23] Recently shortened versions of this test, that is, 3 min, have been applied.[24] Performance decrements resulting from sleep deprivation (or sleep disorders such as sleep apnea) can be observed with such a task if results are analyzed over time. This time-on-task or vigilance decrement may be observed as evidence of fatigue even in well-motivated subjects with adequate prior sleep, and it manifests itself as a decline in performance as time-on-task increases.

When the subject is sleep-deprived, it is impossible to sustain attention long enough to maintain peak performance throughout the entire task, and lapses in performance occur. Sleep loss increases the rate of decline in performance. The number of interrupted episodes also contributes to performance decline. The Psychomotor Vigilance Test (PVT) has become the most widely used measure of neurobehavioral performance. It has been validated with the SSS and MSLT. The test has demonstrated consistent individual differences in neurobehavioral deficits from sleep loss when repeated in the same subject, which indicate differential trait vulnerability to sleepiness.[25] Studies in monozygotic and dizygotic twins indicate that it is a very heritable trait.[3]

While the MSLT and MWT can provide helpful information, they require repeated testing every 2 h and a whole day of tests. A single administration of objective tests, in particular the PVT, can help assess sleepiness in controlled conditions that may be applied clinically.[26]

Other tests of sustained attention and performance have been developed, many to assess simulated driving performance. Using a divided attention task, in which individuals are required to pay attention to more than one aspect of the task, such as a driving task, patients with sleep apnea have been shown to perform poorly; in some cases, performance is equal to or worse than normals impaired by alcohol.[27] Nonetheless, sleepiness, as measured by MSLT, accounts for less than 25% of the variance in tracking performance. Thus, while the effects of sleepiness on performance may occur in a dose-dependent fashion in normals, performance decrements in patients who are sleepy because of an underlying sleep disorder may be accounted for by factors other than sleepiness.

Mitigating subjective “sleepiness” in patients with mild to moderate OSA, untreated with CPAP, has been shown with modafinil. The effect size was clinically important, as was the improvement on the driving simulator performance and reaction time.[28]

FACTORS AFFECTING SLEEPINESS

Sleepiness is determined by the quantity of sleep and the quality and type of sleep, interacting with circadian rhythms or drugs that patients may be taking.

■ Sleep Quantity

The amount of nocturnal sleep has a strong relationship to the degree of daytime sleepiness. A “normal” sleep duration is typically in the range of 7 to 8 h.[29] Partial or total sleep deprivation is followed by increased daytime sleepiness in normal persons. Furthermore, sleep restriction will become cumulative over time and lead to increasing daytime sleepiness.[23]

The effect of sleep restriction on sleep onset latency (SOL) is shown in Fig. 101-1. When the sleep of young adults was reduced by 2 h a night on consecutive nights, sleepiness (as measured by the MSLT) progressively increased over 7 days. Even as little as 1 h per night of sleep loss will accumulate over time and lead to daytime sleepiness—a fact generally not appreciated. Each person has a certain biologic sleep need, and the specific amount varies from one subject to the next. Regardless of cultural or environmental factors, most adults sleep 7 to 8 h per day, but the old adage that we must sleep 8 h each night is not true for everyone. Some people require more than 8 h, and others less.

There may be many contributors to the amount of sleep an individual requires, including a genetic contribution.[30,31] Gene variants associated with sleep duration have been identified using genome-wide association studies (GWAS) with both self-reported sleep durations and sleep duration estimated from accelerometry data.[32–34] In the absence of pathology, normal human sleep length varies between 6 and 9 h, although some people require less. It would be ideal to require a minimum amount of sleep to allow maximum productivity in work and adequate time for social pursuits. Indeed, some investigators believe that Western society predisposes to sleep deprivation[35] while others argue that this is not the case and the situation is more complex.[36] With economic and social constraints—the latter leading to voluntary sleep restriction—the sleep period is the time most encroached upon, potentially leading to daytime sleepiness.[37] Data from the American Time Use Survey (ATUS) show that work time, time for commuting, and time for socializing and leisure are the main determinants of sleep duration.[37]

There has been progressive reduction in sleep duration over many age ranges in the United States. There are multiple etiologies for this, including work intruding into sleep period. Overall, it appears short sleep duration is increasing in prevalence, which is associated with adverse health outcomes, such as weight gain and associated morbidities of obesity.[38] In addition, the prevalence of short sleep (<6 h) has increased in individuals who are employed full time.[31]

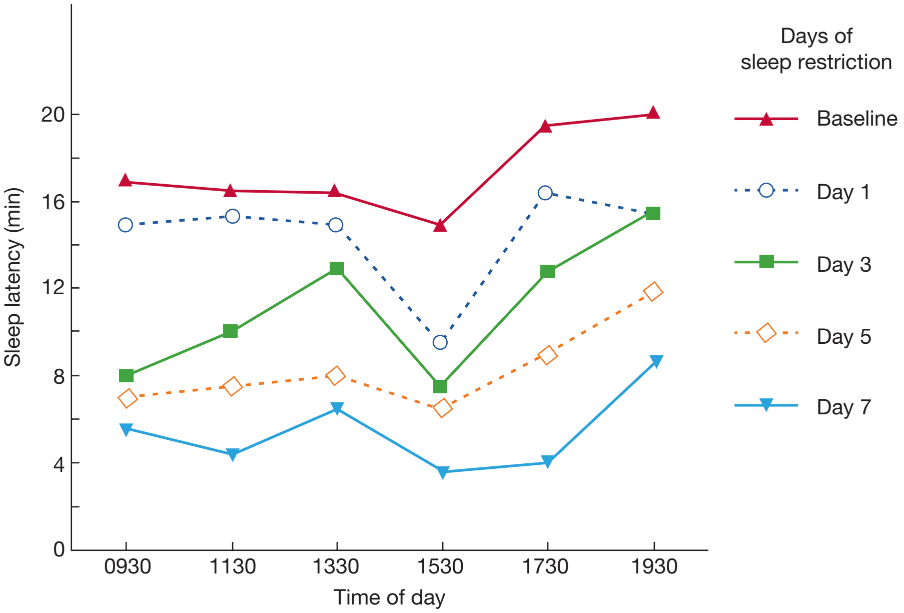

Figure 101-1 Average daily sleep latency test scores for young adults when nighttime sleep was reduced by 2 hours a night for 7 consecutive nights. *(Adapted with permission from Dement WC, Carskadon MA. An essay on sleepiness, in Boldy-Moulinier M (ed). Actualitiés en Médécine Expérimentale, en Hommage au Prof D Passouant. Montpellier, Euromed; 1981.)*

Voluntary sleep restriction or insufficient sleep causes daytime sleepiness. Among all prominent features differentiating the group of patients with insufficient sleep from those with narcolepsy is the report, obtained from the sleep history, of a disparity between the amount of sleep on weekdays and that on weekends. People with insufficient sleep typically have a much longer sleep period on weekends (by 2 h or more), often called "catch-up" sleep.

Most patients consider their weekly sleep loss trivial and assume that it is recovered on weekends. However, while recovery from a single experimental sleep restriction occurs in a couple of nights, it is not likely that repeated episodes of sleep deprivation can be compensated for in just one night. A study of a large group of normal subjects without complaints of daytime sleepiness has shown that young subjects (particularly college students) had shorter sleep latencies than did older subjects. Within the group of 120 young subjects, 12 healthy, nonsmoking men aged 21 to 35 years had a mean sleep latency of less than 6 min on MSLT testing, whereas another 12 had an MSLT of greater than 16 min.[14] These subjects had baseline testing and then extended their sleep period time from 8 to 10 h over 6 days. Repeat testing on days 1, 3, and 6 showed stepwise increases in MSLT and performance testing for both subgroups. The data support the notion that chronic voluntary sleep restriction in real life produces objective sleepiness that may or may not be perceived by the subject.

Sleep Quality

Sleep quality is perceived to be abnormal when sleep is decreased or discontinuous. Disrupting sleep continuity—that is, causing arousal from sleep, either experimentally or by sleep disorders—affects the quality of sleep and results in increased physiologic sleep tendency. An arousal can be defined as a brief (3–15 s) speeding up of the EEG, or as a burst of alpha activity occasionally accompanied by transient increases in skeletal muscle tone. These typically do not result in awakening as defined by standard sleep staging criteria or behavioral indicators.

Sleep studies can identify various causes of arousal, such as recurrent obstructive apnea, periodic leg movements, or chronic pain, in some but not all cases. A common exception is the patient with chronic obstructive pulmonary disease (COPD) who has frequent arousals from sleep in the absence of obstructive apnea or leg movements.[39] Patients with COPD often experience oxygen desaturation during sleep, and this is a potential stimulus for arousal. Nonetheless, compared with age-matched controls, patients with COPD have discontinuous sleep and poor sleep efficiency (defined as percentage of time actually asleep as a fraction of total time in bed).

Auditory stimuli presented externally to normal subjects during sleep can produce arousal; repetitive presentation of such stimuli can produce daytime sleepiness. Several studies have shown decreased performance and increased sleepiness the day after repetitive arousal, with the degree of daytime sleepiness related to the frequency of nocturnal sleep disruption. Not surprisingly, the shortest sleep latency occurred after the most fragmented nocturnal sleep. This increased sleepiness will result even if the stimulus is only sufficient to produce EEG signs of arousal, without full wakefulness. The importance of sleep disturbance from environmental noise has been reported by Basner et al.[40] There are both auditory effects such as EEG arousals, and impaired daytime alertness from lack of sleep quality and quantity that affect quality of life. There are other nonauditory effects, such as increased catecholamine release and association with cardiovascular disease. Environmental noise exposure, such as from airports and other urban environmental areas, can cause lasting damage resulting in hearing loss. Noise-induced hearing loss and tinnitus may not always be recognized in our society, but the effects on affected individuals' quality of life can be tremendous.

New metrics have been introduced to measure sleep quality. These are derived from data collected during the overnight sleep study. They provide continuous measure of sleep depth. The first measure is odds ratio product (ORP) that is derived from spectral analysis of the EEG signal.[41,42] The second is derived from the ECG and is called cardiopulmonary coupling.[43]

Circadian Rhythms

If sleep latency is measured every 2 h over a complete 24-h day, a biphasic pattern of sleep tendency becomes obvious (Fig. 101-2). This demonstrates that there are two peaks and troughs of sleepiness over a 24-h period. Not surprisingly, the times of increased sleepiness are during the nocturnal hours and during the daytime hours (in the midafternoon between 2 and 4 PM, i.e., siesta time). This circadian rhythm of sleepiness is present in all age groups, although the time of the peak rhythm may vary. This biphasic rhythm of sleepiness across the day is reflected in time of occurrence of car crashes attributed to the driver falling asleep at the wheel.[44] The circadian rhythm of sleepiness is similar to other circadian rhythms in that it possesses an endogenous periodicity that can be affected by environmental influences that fine tune or entrain the rhythm. Even in the absence of these environmental cues (i.e., awakening time, alarm clock, degree of light or darkness, food and stimulants, and social contact), rhythms show a persistent periodicity.

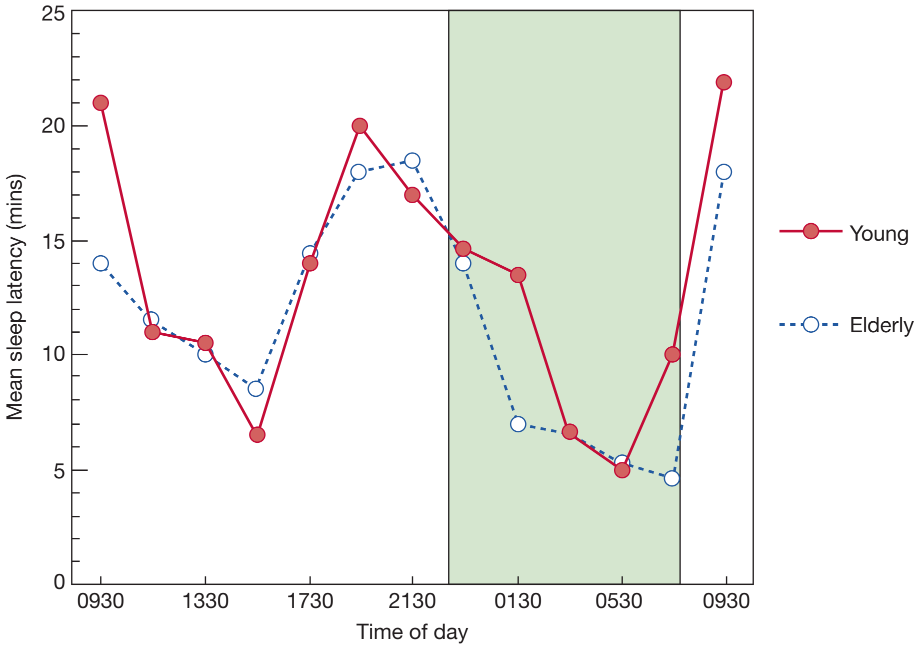

Figure 101-2 Sleep latency (mean) as a function of time of day for young subjects *(filled circles)* and elderly subjects *(open circles)*. *Stippled area* denotes nighttime sleep period. *(Adapted with permission from Richardson GS, Carskadon MA, Orav EJ, et al. Circadian variation of sleep tendency in elderly and young adult subjects. Sleep. 1982;5(Suppl 2):S82–S94.)*

The circadian rhythm of temperature is extremely stable. Temperatures falls in the late afternoon, are lowest during the middle of the sleep period, and rise before morning awakening. The temperature rhythm synchronizes most closely with sleepiness. Although the amplitude of body temperature and sleep latency rhythms differs considerably, no other biologic rhythms correlate so well in time. Circadian rhythm is discussed more extensively in Chapter 12.

Two other examples of the influence of circadian rhythms on sleepiness are obvious. The first is that associated with shift work, and the second is due to transcontinental travel (jet lag). Workers with a normal nocturnal sleep period and a previously stable circadian sleepiness rhythm suddenly will have a trough of sleepiness during the middle of their night work period. They will attempt to stay awake, while the circadian influences are promoting sleep.[45] Jet lag is similar, in that the body's circadian rhythm is out of synchrony with the clock time. As a result, performance may suffer. These differences are the result of trying to sleep at times that the clock is signaling wakefulness and is generating an arousal signal. Sleeping at inappropriate times impairs sleep efficiency (i.e., amount of sleep/time in bed) and sleep quality.

■ Medications

Drug effects on sleep can be significant and can either promote sleep and sleepiness or increase wakefulness and alertness. When assessing subjective or objective sleepiness, it is important to know whether the patient is taking a medication that may affect the degree of sleepiness, that is, the sleepiness may be a side effect of their medication.

Not surprisingly, sedative drugs increase sleepiness. Benzodiazepine hypnotics have been used to help people get to sleep at night; however, nonbenzodiazepine hypnotics also are used. Many objective studies confirm the ability of hypnotics to shorten sleep latency at bedtime through GABA_A receptor stimulation. When given during the day, they promote sleep. However, the daytime carryover effect of nocturnal sedation is not always recognized. This effect occurs most commonly with long-acting benzodiazepines, but it may occur with other medications as well. Recently, warnings have been issued from the FDA about potential sleepiness the morning after taking these medications, especially in women, and have recommended reduction in zolpidem dosages to half to increase patient safety. Second-generation antiepileptics (i.e., gabapentin, pregabalin, vigabatrin) also act as GABA agonists without interacting with the GABA_A or GABA_B receptors. Alcohol consistently shortens sleep onset and produces sedation, whether given at night or during the day. However, it also alters sleep architecture by suppressing REM sleep and contributing to sleep fragmentation through the latter portions of the night.[46]

Drugs that produce sleepiness include antihistamines, which are used in allergy and pulmonary practice. Many of the early H_1 antihistamines, such as diphenhydramine and chlorpheniramine, have been shown to reduce the MSLT. Some antihistamines, such as terfenadine and astemizole, do not produce objective sleepiness. The more lipid-soluble drugs (e.g., diphenhydramine and chlorpheniramine) penetrate the central nervous system more easily and, therefore, are more likely than less lipid-soluble drugs to produce sedation. Other medications with high lipid solubility have been reported to produce daytime sedation; the most common of these are the beta-blocker drugs. There are no controlled, objective studies of sleep latency with this type of drug, and sleepiness from these medications is based on reports of side effects or subjective questionnaires, such as the Pittsburg Sleep Quality Index (PSQI).[47]

The effect of a particular drug in producing sleepiness also depends on the background level of sleepiness or alertness. When ethanol or caffeine is given to normal-sleeping young men in the morning, one might expect ethanol to produce daytime sleepiness and caffeine to increase sleep latency during the day. Subjects are consistently sleepier after ethanol than after caffeine ingestion, but fully rested subjects (those having spent 11 h in bed) do not show sleepiness after taking ethanol. In other words, the sedative effects of drugs such as alcohol can be enhanced by increased background sleepiness. Thus, a driver who is sleepy to start with may be as vulnerable after just one or two drinks as a previously alert driver who has become legally intoxicated.[46]

Drugs that increase wakefulness or alertness include stimulants such as amphetamine, methylphenidate, modafinil, and armodafinil. These drugs are most often used in the treatment of narcolepsy but may be used to stay awake for long periods of time. Caffeine, probably the most widely used stimulant, can reduce daytime sleepiness and transiently increase alertness. Excessive caffeine intake paradoxically may also cause a degree of daytime sleepiness. This occurs when caffeine levels persist into nocturnal hours and promote difficulties with sleep onset and increased awakenings during sleep.

PREVALENCE OF EXCESSIVE DAYTIME SLEEPINESS

Prevalence rates for sleepiness depend greatly on the type of questions addressing sleepiness. For example, "Are you sleeping too much," "Are you falling asleep during the daytime," and "Does your sense of sleepiness impair your daytime activities?" all result in widely different prevalence rates. Also, men tend to report sleepy behavior whereas women report feelings of EDS, again contributing to variable prevalence. Prevalence of sleepiness also varies with the population examined.

There are many socioeconomic and demographic factors that may contribute to sleep disorders or poor sleep quality or quantity in the population. Specific associations with long SOL include being female, having black/African-American heritage, lower education level, lack of private health insurance, and food insecurity. The demographics are most associated not only with prolonged SOL, but also with nonrestorative sleep and sleep maintenance difficulties, including early morning awakenings. EDS occurs more frequently with female sex and in divorced individuals.[48]

By far, the most common sleep disorder causing excessive daytime sleepiness in sleep clinics is obstructive sleep apnea. The prevalence is 10% (95% confidence interval [CI], 7–12) among 30- to 49-year-old men, 17% (95% CI, 15–21) among 50- to 70-year-old men, 3% (95% CI, 2–4) among 30- to 49-year-old women, and 9% (95% CI, 7–11) among 50- to 70-year-old women.[49]

There are data showing that OSA is a heterogeneous disorder, including from a symptomatic point of view. Cluster analysis of responses to a comprehensive questionnaire of patients in the Icelandic Sleep Apnea Cohort (ISAC) found that there were three distinct subtypes of patients: (1) disturbed sleep, where major complaints were initiating and maintaining sleep (insomnia); (2) relatively asymptomatic; and (3) excessively sleepy.[50] The first two groups had an average or normal Epworth Sleepiness Score <10. The excessively sleepy group had marked sleepiness with an average Epworth Sleepiness Score of 15.6, and a large proportion fell asleep driving, that is, they were a very sleepy group of subjects. The existence of these subtypes has now been replicated in multiple studies: (1) in studies with data from multiple sleep centers worldwide that are part of the Sleep Apnea Global Interdisciplinary Consortium;[51] (2) in a population-based cohort in South Korea;[52] (3) in the Sleep Heart Health Study, a population-based cohort;[53] (4) in patents with OSA who are part of the recruitment by the Canadian National Network for Sleep and Circadian Disorders;[54] (5) the Hispanic Cohort study in the United States;[55] and (6) a clinical cohort of patients with OSA from Chile.[56] While in these studies the basic three subtypes were present, the optimal cluster solution varied between three and five subtypes. For example, in the Sleep Heart Health Study there was an additional subtype with moderate sleepiness.[53] While the same subtypes were present in both clinical cohorts and in population studies, the frequency of the different subtypes varied with a higher proportion of asymptomatic in the general population. These subtypes vary not only in symptoms but also in risk for cardiovascular disease.

Analysis of data from the Sleep Heart Health Study showed that it is only the excessively sleepy subtype that has an increased risk of CV events; the other subtypes do not.[53] This result has been confirmed in analysis of the data from the clinical cohort from Chile.[56]

This is an important result since it provides a potential explanation as to why recent randomized controlled trials (RCTs) for effect of CPAP on cardiovascular events were negative,[57–59] contrasting with findings from previous epidemiologic studies.[60] These RCTs excluded excessively sleepy individuals for ethical reasons.[61]

EVALUATING THE SLEEPY PATIENT

Keeping in mind the factors that determine daytime sleepiness, the sleep history can be individualized and can be very helpful in narrowing the differential diagnosis (Table 101-3).

One should always question the patient about his or her nocturnal sleep, looking specifically at sleep onset time, sleep period time, number of awakenings, and time of rising in the morning. One should also ask about when the change in sleep occurred as well as questions about sleep hygiene (e.g., when awake, reading book in dim light vs. playing games on an electronic device with bright light). Sleep onset phenomena such as sleep paralysis and hypnagogic hallucinations often suggest a diagnosis of narcolepsy, although these sometimes occur in apneics who are severely sleep deprived.[17] A history of loud snoring or stopping breathing during sleep is suggestive of sleep apnea hypopnea syndrome, particularly if the snoring is "cyclical" rather than continuous, with periods of loud snoring or snorting alternating with quiet intervals. Since insufficient sleep may be the cause of sleepiness, it is important to ask if there is any difference in the amount of sleep required during the week compared with that on weekends. Equally important is whether the patient has any changes in subjective sleepiness on weekends or holidays compared with weekdays.

In some instances, more information will be obtained from the spouse (or bed partner) or from a sleep/wake diary, since not all people are aware of the severity of their sleepiness. Moreover, patients may not understand the importance of good sleep hygiene; the diary can serve as a reminder for patients to be diligent about it.

In estimating the degree of daytime sleepiness, it is useful to ask when and during what activities the patient experiences sleepiness. Is the patient sleepy on awakening in the morning, or is it only by midday? Does the patient fall asleep while doing things or only when inactive? Driving to and from work are important times when sleepiness may become obvious, particularly while the person is waiting at a railroad crossing or stoplight. This is particularly relevant to shift workers who fall asleep on the drive home from work after their night shift. Episodes of automatic behavior, related to "microsleeps," often occur while one is driving. Do patients nap during the day, and if so, is the nap refreshing? Many patients with sleep apnea are still sleepy or foggy after a nap, whereas patients with narcolepsy most often feel refreshed immediately upon awakening after a nap.

TABLE 101-3 Common Causes of Persistent Daytime Sleepiness

Obstructive sleep apnea and other sleep-disordered breathing conditions (e.g., neuromuscular weakness with nocturnal respiratory failure)
Narcolepsy/cataplexy syndrome
Sleep-related movement disorders (periodic limb movement disorder, bruxism, etc.)
Depression
Postviral fatigue
Head injury
Metabolic, toxic, and drug-induced hypersomnolence
Idiopathic hypersomnolence
Insufficient sleep
Circadian rhythm sleep disorders

Since drugs can have a profound effect on sleep and sleepiness, a careful drug history is mandatory in the assessment of sleepiness. The clinician must remember to include queries not only about drugs that specifically affect sleep (hypnotics, sedatives, or other psychoactive medications) but also about substances that may not be considered to have any effect on sleep or waking. In particular, alcohol is a known precipitant or exaggerating factor for sleep apnea; patients often report that they feel much worse the day after ingesting alcohol despite having had a nonintoxicating dose.[62]

Apart from a general physical examination, one should pay particular attention to obesity and the size of the jaw, face, and upper airway, looking for obvious skeletal abnormalities—particularly retrognathia or micrognathia. One should carefully examine the upper airway, looking for nasal obstructions, such as a deviated nasal septum or inflammatory allergic polyps. In addition, the oropharynx should be examined, looking at the size of the tongue, the position of the soft palate, and the size of the uvula. Finally, the larynx should be assessed to rule out upper airway tumors or other obstructing lesions. While the typical patient with sleep apnea patient is an obese, plethoric man with a thick neck, it is important to remember that examination of the awake, upright airway may bear no relationship to what happens when the patient is supine and asleep. Thus, the diagnosis of sleep apnea usually is confirmed by nocturnal polysomnography or a more limited home study (Chapter 98).

The patient who has a history of snoring and daytime sleepiness but has no flow limitation, or sleep apnea or hypopnea during his or her nocturnal study, should undergo an objective measure of daytime sleepiness, because some patients who claim to have substantial daytime somnolence are simply looking for compensation.[63] Also, some patients with OSA remain sleepy despite adequate treatment of their apnea; an additional sleep disorder may coexist. There may also be residual sleepiness in patients with mild to moderate OSA despite CPAP treatment (see below). Again, daytime quantification of sleepiness will be necessary. The only disadvantage of the MSLT is that it is an inefficient test. Compared with objective measurements of airflow (e.g., FEV$_1$), which take seconds to perform and interpret, the MSLT takes almost a whole day and provides only one piece of information. Until better tests are developed and validated, however, the MSLT will continue as a standard, albeit time-inefficient, objective measure of daytime sleepiness. There are efforts to develop blood tests, that is, biomarkers, for sleepiness.[64]

It is important to remember that CNS pathology can independently contribute to EDS. While the central hypersomnias fall within the realm of sleep medicine (see below), in other neurologic diseases (e.g., Parkinson disease) or neuromuscular diseases (e.g., myotonic dystrophy), EDS can be a presenting symptom that the pulmonologist should keep in the differential diagnosis.

■ Central Hypersomnias

As mentioned above, EDS is usually associated with insufficient sleep (the most common cause, as 35.2% of American adults sleep <7 h),[65] circadian rhythm disorders, disturbed nocturnal sleep from sleep-related breathing disorders, medical or psychological disorders, or medications. Central disorders causing hypersomnolence can be diagnosed once all these conditions have been excluded. The International Classification of Sleep disorder, 3rd edition (ICSD-3), divides central disorders of hypersomnolence into eight categories (Table 101-4).

Narcolepsy type 1 (NT1) or narcolepsy with cataplexy (as previously known) is a chronic neurologic disorder with a prevalence of 0.025% to 0.05% worldwide. There is a known association with HLA

TABLE 101-4 Central Disorders of Hypersomnolence

Narcolepsy type 1
Narcolepsy type 2
Idiopathic hypersomnia
Kleine-Levin syndrome
Hypersomnia due to a medical disorder
Hypersomnia due to a medication or substance
Hypersomnia associated with a psychiatric disorder
Insufficient sleep syndrome

Data from Judd BG, Sateia MJ: The International Classification of Sleep disorder, 3rd ed. Rochester, MN: AASM; 2014.

DQB1*0602, making gene–environment interaction likely as the etiologic factor.[66] The proposed mechanism is loss of hypothalamic hypocretin-producing neurons in genetically predisposed individuals, enhanced by environmental factors such as infections or vaccines, suggesting autoimmune mechanisms.[67,68] Hypocretin (orexin) stabilizes wakefulness and sleep through modulation of other neurotransmitters; thus the disturbance in the sleep-wake system due to its deficiency leads to a dissociated state with REM intrusions into wakefulness.[68,69]

The classic tetrad for narcolepsy is EDS, cataplexy, sleep paralysis, and hallucinations. The latter occur at sleep onset (hypnagogic) or sleep offset (hypnopompic). However, only <10% present with all four symptoms, adding to the delay in diagnosis while cataplexy is present in only 65% to 75% of individuals with NT1.[70]

Cataplexy is a very specific symptom of NT1, characterized by sudden, brief loss of muscle tone (<2 min) triggered by strong, mostly positive emotions with preserved consciousness, in particular laughter. Sturzenegger et al. showed that specific questions on severity of EDS and characterization of cataplexy helped in recognizing subgroups of narcoleptics and their differentiation from nonnarcoleptic EDS patients or reporting cataplexy-like episodes.[71] Sagging of the jaw and/or trembling of the knees are the most common localizations during cataplexy, which, along with positive emotions, are more common triggers in cataplexy than cataplexy-like episodes.[71]

Sleep paralysis and hallucinations are less specific symptoms that may be present in other central sleep disorders as well. Sleep paralysis also occurs with sleep deprivation in normals, with a prevalence rate of 7.6% in the general population, and even higher rates in students (28.3%) and psychiatric patients (31.9%).[72] In addition to the classic tetrad, disturbed nocturnal sleep, mood disorders, other sleep disorders like REM behavior disorder (RBD; especially in young patients), periodic limb movements during sleep, and OSA can be associated with narcolepsy.[69]

The Ullanlinna Narcolepsy Scale (UNS) and Swiss Narcolepsy Scale (SNS) are instruments used to screen for narcolepsy with cataplexy if a patient's ESS score is >10. In addition to subjective complain of EDS, NT1 may be diagnosed by the clear presence of cataplexy and a Multiple Sleep Latency Test (MSLT) showing a mean sleep latency ≤8 min and two or more SOREMPs (one SOREMP can be replaced with a REM within 15 min of sleep onset on the preceding PSG) or cerebrospinal fluid (CSF) hypocretin-1 deficiency (<110 pg/mL or <1/3 of the mean values of normal subject with the same assay).[73] Since MSLTs may show similar findings in sleep deprivations, shift work, or secondary hypersomnia, a 2-week actigraphy or sleep log should be maintained, along with stoppage of interfering drugs (stimulants and REM-suppressing) 2 weeks prior to the MSLT.

Drakatos et al.[74,75] have suggested that REM arising directly from N1 or wake phase instead of N2 or N3 (either during MSLT or during PSG during the first REM period) increases the likelihood of NT1. This pattern of REM transition is completely absent in idiopathic hypersomnia and occurs intermediately in narcolepsy type 2; it is also associated with a worse therapeutic response.[69,74,75] HLA typing has limited use, as 20% to 30% of the general population also carries the HLA DQB1*0602 gene; thus, only its absence would help to support an alternate diagnosis.[69]

Efforts have been made to identify narcolepsy from overnight sleep recordings, for example, PSGs. Investigators used a neural network to develop a plot across the whole sleep study of the probability of different sleep stages and wakefulness (e.g., see Fig. 101-1). There was a distinct difference between normals and individuals with narcolepsy (Fig. 101-3). In narcolepsy, there was an admixture of predictions of different states at the same timepoint (Fig. 101-3).[64]

In *narcolepsy type 2* (NT2), like NT1, there is EDS and REM sleep dysregulation, but there is no cataplexy, and CSF hypocretin-1 levels are not low. NT2 is thought to be caused by localized loss of hypocretin cells, which is less severe compared with the 90% loss of hypocretin neurons in NT1.[76] While 90% of NT1 patients show low hypocretin levels, only 10% to 30% of patients with NT2 have low

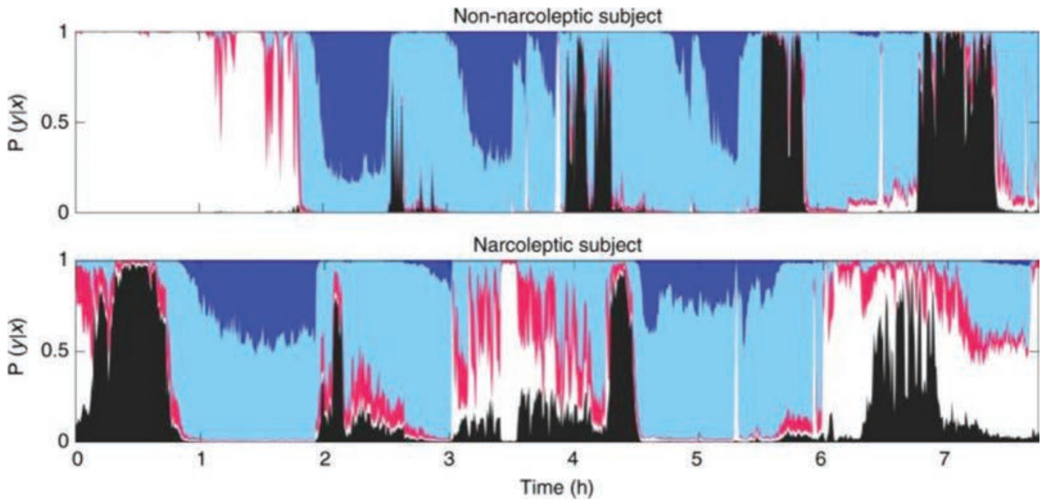

Figure 101-3 Examples of plots of probability of different sleep stages *(y axis)* and wakefulness during a full sleep study. The plot in the *top panel* is for a normal subject, while the *bottom panel* shows results for a subject with NT1 narcolepsy. Color codes: white is wake; red is N1 NREM sleep; light blue is N2; dark blue is N3; and black is REM sleep. *(Reproduced with permission from Stephansen JB, Olesen AN, Olsen M, et al. Neural network analysis of sleep stages enables efficient diagnosis of narcolepsy. Nat Commun. 2018;9(1):5229.)*

hypocretin; most patients have normal levels.[77] A study showed that among patients with NT2 who have low hypocretin, all were HLA-DQB1*06:02 positive; only 26% of those with normal hypocretin had gene positivity and those with intermediate levels (110–200 pg/mL) also had higher rates of gene positivity, suggesting a diagnostic cutoff of 200 pg/mL may be more appropriate than 110 pg/mL.[78] Diagnosing NT2 can be challenging, as there is no biomarker present and diagnostic criteria are mostly clinical. Some patients with NT2 progress into NT1 years after the onset of sleepiness. MSLT diagnostic criteria and management for NT2 are similar to those for NT1.

Idiopathic hypersomnia (IH) is less common than narcolepsy; its prevalence is unknown due to lack of diagnostic criteria and robust studies.[79] It is more prevalent in women. Age of onset ranges from 10 to 30 years. There may be a genetic predisposition, as one-third of the patients have positive family history; it is not known to be HLA-associated. The pathophysiology is unclear; some studies show normal levels CSF hypocretin 1 and others show abnormalities in melatonin secretion and the circadian system.[80] One study showed decreased histamine levels in CSF, but a subsequent study was unable to replicate the finding.[81,82]

Hypersomnolence is the key feature that is considered less “irresistible” than in NT1. Patients exhibit “sleep drunkenness” or “severe sleep inertia,” with difficulty awakening in the morning or at the end of naps, which are accompanied by confusion, poor motor coordination, disorientation, and repeated returns to sleep.[79] Naps are few, long, and nonrefreshing; patients have prolonged and undisturbed nocturnal sleep. MSLT shows MSL $\leq$8 min and fewer than two SOREMPS or no SOREMPS if the REM latency in the preceding PSG is $\leq$15 min or a 24-h sleep time is $\geq$660 min during 24-h PSG monitoring (after evaluation of sleep deprivation via actigraphy or a sleep log). High sleep efficiency on the preceding PSG is a supportive finding and, similar to NT2, the diagnosis of IH is a diagnosis of exclusion.

Kleine-Levine Syndrome is a rare and relapsing-remitting hypersomnia associated with cognitive, psychiatric, and behavioral disturbances.[73] It is estimated to affect 1 to 5 cases per million population, with male predominance, especially in the teen years, and a positive family history is common.[83] The etiology is unknown, but the first episode is usually triggered by an infection, suggesting an autoimmune mechanism. Other triggers include alcohol, stress, heat, traumatic brain injury, vaccines, or illicit drugs; the episodes recur usually more than once a year and at least once every 18 months.[69] During episodes, those affected may sleep as long as 16 to 20 h/day, waking up only to eat or void. Additional manifestations include cognitive dysfunction, altered perception, eating disorders (hyperphagia or anorexia), and disinhibited behavior (hypersexuality).[73]

Insufficient sleep syndrome (ISS) must always be considered when evaluating the sleepy patient. ISS affects a large part of the population due to current lifestyle, although the exact prevalence is unknown. Patients complain of EDS, unclear “blackouts,” cognitive symptoms, and involuntary naps with short sleep alternating with long sleep, especially during the weekends. ISS is one of the most important diagnoses in the differential diagnosis of EDS and must be ruled out by actigraphy or sleep log. PSG and MSLT may show features like other hypersomnolent disorders. There may be decreased sleep latency, increased SOREMPs (although this is unlikely from N1 and wakefulness, as in narcolepsy), high sleep efficiency, and increased slow wave sleep (due to rebound effect).[69,74,75] During PSG, when ISS is suspected, instead of ad libitum sleep on the first lab test night, an enforced and extended bedtime (i.e., 9 or 10 h) should be recommended. If no sleep disorder is demonstrated, high sleep efficiency (>90%) and excessive sleepiness on the MSLT the following day are highly suggestive of chronic sleep deprivation.[84] Also, sleep extension and documented adherence to the extended bedtime at home with improvement in symptoms confirms the diagnosis and is an effective management strategy.[84]

Residual EDS in OSA (despite adherence to therapy and normalization of AHI) is an important clinical problem. The prevalence of EDS among positive airway pressure (PAP) adherents (usage of PAP >4 h, for at least 70% of the nights) has been reported to range from 12% to 65%.[85–87] However, prior to making the diagnosis one needs to exclude poor adherence to CPAP, poor mask fit, mask leak, suboptimal pressure, nasal congestion, aerophagia, dry mouth, and treatment-emergent central sleep apnea as well as insufficient sleep. Furthermore, some of the previously mentioned conditions may be responsible for the sleepiness.[88] Even though the mechanism of persistent EDS is unclear, a variety of mechanisms may be responsible. Chronic sleep deprivation and hypoxia-reoxygenation may cause oxidative, irreversible injury in wake-promoting regions of the brain, in particular, the dopaminergic and adrenergic neurons.[88–90] Alterations in the 24-h synthesis and secretion of melatonin, along with alterations in microbiota and acquired dysbiosis, are the other purported mechanisms.[88]

CONCLUSION

Sleep is important in health and wellness. The concept of sleep health is an emerging area of interest.[91] Excessive sleepiness is a very common symptom. In patients with respiratory disease, a sleep disorder may be the presenting disease or may coexist with other disorders. Given the increasing prevalence of sleep disorders and their impact on health, it is imperative that practicing pulmonologists have a sound understanding of sleep medicine and that they can develop a differential diagnosis and orchestrate a management plan for patients with excessive sleepiness.

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PART 15

Surgical Aspects of Pulmonary Medicine

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CHAPTER 102

Perioperative Respiratory Considerations in the Surgical Patient

Horace M. DeLisser
Michael A. Grippi

INTRODUCTION

Postoperative pulmonary complications constitute a significant cause of morbidity and mortality following surgery. Managing patients at risk for postoperative pulmonary problems requires an understanding of the predictable changes in pulmonary physiology that occur with surgery and anesthesia, as well as knowledge of factors associated with development of postsurgical respiratory compromise. Despite the availability of several screening tests, a careful history and physical examination continue to be the cornerstone of preoperative pulmonary evaluation. Although a number of measures can be employed before and after surgery to minimize the risk of respiratory complications, close patient monitoring and early detection are essential.

This chapter focuses initially on changes in pulmonary function with surgery. Pulmonary risk factors before, during, and after surgery are reviewed prior to discussion of preoperative evaluation of the patient for surgery, including lung resectional surgery. Finally, recommendations are made regarding preoperative preparation and postoperative prophylactic measures. Additional discussion of the perioperative care of the patient undergoing resectional lung surgery and development of acute respiratory failure in the surgical patient are addressed in Chapter 104.

CHANGES IN PULMONARY FUNCTION WITH SURGERY

Many postoperative respiratory complications relate to exaggerations of the expected postoperative changes in pulmonary function that occur as a result of the surgery itself, anesthesia, or various pharmacologic interventions.[1,2] Hence, an appreciation of normal postoperative pulmonary physiology is useful in understanding a number of pulmonary problems seen following surgery. Five principal categories of change in pulmonary function with surgery may be considered: (1) lung volumes, (2) diaphragm function, (3) gas exchange, (4) control of breathing, and (5) lung defense mechanisms (Table 102-1).

TABLE 102-1 Changes in Pulmonary Function with Surgery

Reduction in lung volumes
Diaphragm dysfunction
Impaired gas exchange
Respiratory depression due to residual effects of anesthesia or postoperative narcotics
Impaired cough and mucociliary clearance

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Lung Volumes

The pattern of pulmonary function abnormalities following thoracic and abdominal surgery is restrictive, characterized by moderate to severe reductions in vital capacity (VC) and smaller, but more important, reductions in functional residual capacity (FRC). The degree of impairment is similar after upper abdominal and thoracic surgery[3–5] and is less for laparoscopic procedures compared with open abdominal procedures.[6] Smaller changes in VC and FRC are noted with lower abdominal surgery; superficial or extremity surgery is usually not associated with any significant or persistent changes in lung volumes.[7,8] During the first 24 h following upper abdominal surgery, VC and FRC may be reduced by more than 70% and 50%, respectively, and they may remain depressed for more than a week.[7–9] Consequently, it is not surprising that pulmonary complications are seen more often with thoracic and upper abdominal procedures than with surgery involving the lower abdomen or extremities (see “Intraoperative Risk Factors,” below).

Reductions in other lung volumes, including total lung capacity (TLC), inspiratory capacity (IC), expiratory reserve volume (ERV), and residual volume (RV) have been noted. While the forced expiratory volume in 1 s (FEV_1) is decreased, the ratio of FEV_1 to the forced vital capacity (FEV_1/FVC%) remains unchanged, indicating that major airway obstruction does not occur.[4]

Since patients undergoing superficial or extremity surgery do not experience major changes in lung volumes, residual or carryover effects from general anesthesia do not appear to play a primary role in this regard. In fact, studies have shown that in many patients, FRC in the early postoperative period is unchanged from baseline. An alternative proposal for the reduction in FRC is that postsurgical pain and associated muscle splinting impair lung mechanics. However, while processes other than pain may be operative, based on the finding that effective pain control using epidural analgesia or intercostal nerve block fails to fully restore VC or FRC to preoperative levels,[10–12] this notion has been challenged.[13] The established consensus is that diaphragm dysfunction is an important contributing factor (see below).[2]

The postoperative reduction in FRC is of major physiologic significance. Its importance can be understood when the phenomenon of airway closure and the concept of closing capacity (CC) are considered.[4]

FRC is the lung volume at the end of a normal tidal expiration. CC is the lung volume at which small airways in the lung bases begin to close during expiration because of a reduction in airway radial traction. The relationship between the two is a key factor in the development of postoperative changes in lung function (Fig. 102-1). In a normal lung, FRC is always greater than CC, and the airways remain open throughout a tidal breath. However, when CC is greater than FRC, lung volume fails to increase sufficiently during tidal breathing to open all the airways and, consequently, some alveolar units remain closed during a breath. Such regions constitute areas of atelectasis. An intermediate state exists when CC exceeds lung volume for part of the time during each tidal breath. Under these circumstances, the airways open for only a portion of the respiratory cycle, creating areas of low ventilation relative to perfusion. In summary, any circumstance that reduces FRC below CC or that increases CC above FRC produces regions of reduced ventilation and atelectasis (Table 102-2).

Diaphragm Function

Diaphragm dysfunction has been recognized as an important factor contributing to the postoperative reduction in lung volumes.[6,11–16] In patients undergoing cholecystectomy, the

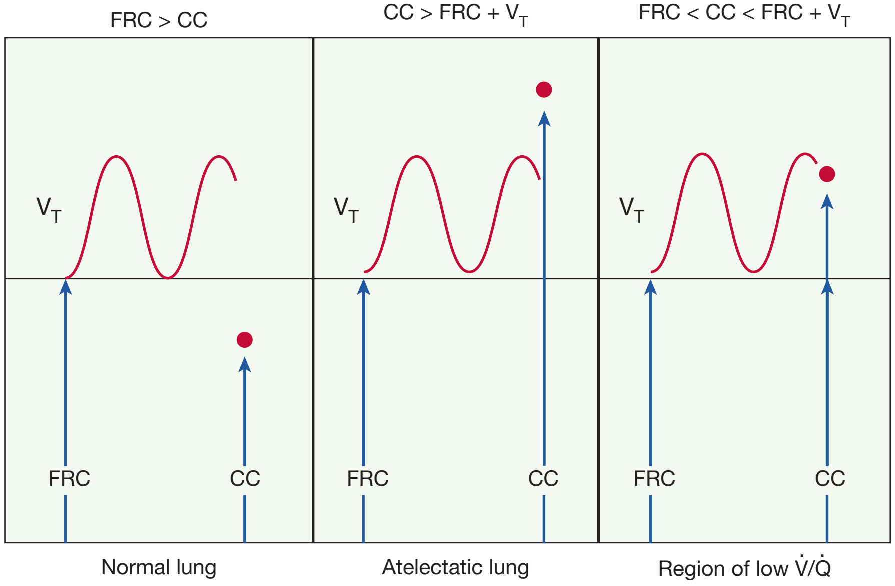

Figure 102-1 The relationship between functional residual capacity (FRC) and closing capacity (CC). V_T, tidal volume. See text. *(Reproduced with permission from Goldmann DR, Brown FH, Guarnieri DM: Perioperative Medicine. New York, NY: McGraw Hill; 1994.)*

diaphragm's contribution to quiet tidal breathing after surgery is reduced.[14] Measurements of transdiaphragmatic pressure during maximal phrenic nerve stimulation following upper abdominal surgery indicate that decreased central nervous system output to the phrenic nerves, possibly as a result of inhibitory reflexes arising from sympathetic, vagal, or splanchnic receptors, may be the important etiologic factor.[15] Studies of the role of pain in this impairment have yielded conflicting results, pointing to either a limited[10–12] or significant[13] role for pain, depending on the procedures used for analgesia.

Gas Exchange

Postoperative arterial hypoxemia occurs commonly, and two phases in its development may be described.[17,18]

The initial phase occurs in the first several hours following anesthesia and surgery. The underlying mechanisms are related largely to the residual effects of the anesthesia and include ventilation–perfusion mismatch, anesthetic-induced inhibition of hypoxic pulmonary vasoconstriction, right-to-left shunting, alveolar hypoventilation, depressed cardiac output, and increased oxygen consumption by peripheral muscles. This phase resolves within 24 h following superficial surgery.

A second phase of hypoxemia, which may persist for several days or weeks, is seen after thoracic and upper abdominal surgery. This phase correlates with reductions in FRC and changes in the FRC–CC relationship. Although alterations in the FRC–CC relationship predominate, other processes may contribute to late postoperative hypoxemia: (1) alveolar hypoventilation (see "Control of Breathing," below); (2) increased dead space ventilation due to rapid, shallow breathing; and (3) decreased mixed venous oxygen tension due to increased oxygen consumption, impaired cardiac output, and reduced oxygen carrying capacity.

TABLE 102-2 Conditions That Alter the Relationship Between Functional Residual Capacity (FRC) and Closing Capacity (CC)

Decrease FRC	Increase CC
Supine position	Advanced age
Obesity	Smoking
Pregnancy	COPD
General anesthesia	Pulmonary edema
Abdominal pain	

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Control of Breathing

Respiratory depression is a common feature of the postoperative period. Two factors are responsible. First, residual effects of preanesthetic or anesthetic agents inhibit respiratory drive and reduce the ventilatory response to hypercapnia, hypoxia, and acidosis.[19] Second, narcotics given for postoperative analgesia depress both hypercapnic and hypoxic ventilatory drives, resulting in decreased tidal volume, reduced minute ventilation, and increased Pa_{CO_2}.[20] Narcotics also alter the pattern of breathing, reducing the frequency of sighs or eliminating them entirely; in susceptible patients, narcotics may precipitate sleep apnea.

Lung Defense Mechanisms

Several mechanisms protect the lung from environmental and infectious insults. Two of the most important—cough and mucociliary transport—are compromised after surgery, contributing to an increased risk of pulmonary infection.[4,21] Postoperative pain or excessive use of narcotics may inhibit coughing; in addition, altered lung mechanics decrease the expulsive force generated with each cough. Mucociliary clearance is impaired for up to a week following upper abdominal surgery. Although an ineffective cough reflex contributes significantly to reduced mucociliary clearance, several additional mechanisms are involved. These include (1) cilia damage from endotracheal intubation and inhalation of dry, hyperoxic gas mixtures; (2) reduced tracheal mucus velocity due to the presence of an endotracheal tube; (3) anesthetic-induced inhibition of mucociliary transport; and (4) atelectasis.

PULMONARY COMPLICATIONS

The criteria used for defining postoperative pulmonary morbidity have varied considerably in published reports,[22–26] although it is clear that, from a broad perspective, six major categories of complications may be considered: (1) lung parenchymal processes (e.g., atelectasis, pulmonary edema, aspiration pneumonitis, acute respiratory distress syndrome); (2) infection, including acute tracheobronchitis and pneumonia; (3) pleural space processes such pleural effusions and pneumothorax; (4) exacerbation of underlying chronic lung disease; (5) respiratory insufficiency/failure requiring supplemental oxygen or ventilatory support; and (6) thromboembolic disease. With thoracic surgery, several additional problems may occur;[27–40] these are summarized in Table 102-3.

TABLE 102-3 Pulmonary Complications Associated with Thoracic Surgery

Procedure	Complication	Incidence (%)	References
Coronary artery bypass grafting	Phrenic nerve damage[a]	10–20	27–29
	Pleural effusions (postpericardiotomy syndrome)	10–15	30
Lung resection surgery	Pleural space complications (bronchopleural fistula, prolonged air leaks, or empyema[b])	5–20	31–36
Median sternotomy	Sternal wound infection (mediastinitis or osteomyelitis)	1–4	37,38
Esophagectomy	Anastomotic leak	3–12	39,40

[a] *Incidence for clinically significant injury with prolonged mechanical ventilation is 1% to 2%.*
[b] *Rates higher for patients undergoing resection for aspergilloma.*

TABLE 102-4 Factors Associated with Development of Postoperative Pulmonary Complications

Preoperative	Intraoperative	Postoperative
Chronic lung disease	Type of anesthesia	Immobilization
Smoking	Duration of anesthesia	Inadequate pain control
General state of health	Surgical site	
Age	Type of surgical incision	
Obesity	Nonprotective mechanical ventilation	
Nutritional status	Emergent nature of the procedure	
Antecedent respiratory tract infection		

TABLE 102-5 Relative Strength of Preoperative Risk Factors Associated with the Development of Postoperative Pulmonary Complications

Factor	Odds Ratio
General state of health (ASA class >II)	2.55–4.87
Congestive heart failure	2.93
Albumin <3.5 g/L	2.53
Age >60 years	2.09–3.04
COPD	1.79
Functional dependence	1.65–2.51
Weight loss	1.62
Impaired sensorium	1.39
Cigarette smoking	1.26
Alcohol use	1.21
Antecedent respiratory tract infection	Risk not known
Obesity	No increased risk for major morbidity

Adapted with permission from Sweitzer BJ, Smetana GW. Identification and evaluation of the patient with lung disease. Med Clin N Am. 2009;93(5):1017–1030.

The variability in defining postoperative pulmonary complications has resulted in reported incidences that have ranged widely in the literature, depending on the patient population sampled and the procedures studied. In general, a healthy, young nonsmoker of normal weight has a very low risk of postoperative pulmonary complications (1% or less).[41] However, a number of factors are associated with the development of postoperative pulmonary complications (Table 102-4).[22–26,42–47] They include preoperative factors (chronic lung disease, smoking, general state of health, age, obesity, nutritional status, and antecedent respiratory tract infection), intraoperative factors (the emergent nature of the procedure, type and duration of anesthesia, location of surgical site, type of surgical incision and nonprotective lung ventilation), and postoperative factors (inadequate pain control and immobilization). Tables 102-5 and 102-6 list, respectively, the relative strengths of preoperative and intraoperative factors associated with development of postoperative pulmonary complications based on odds ratios.[23,48]

PREOPERATIVE RISK FACTORS

A number of patient-related factors have been implicated in the development of postoperative respiratory complications.[23] They include the presence of chronic lung disease (particularly

TABLE 102-6 Relative Strength of Intraoperative Risk Factors Associated with the Development of Postoperative Pulmonary Complications

Factor	Odds Ratio
Surgical Site	
Aortic aneurysm repair	6.90
Thoracic surgery	4.24
Abdominal surgery	3.01
Neurosurgery	2.53
Head and neck surgery	2.21
Vascular surgery	2.10
Gynecologic or urologic surgery	Not a risk factor
Hip surgery	Not a risk factor
Procedure-Related Issues	
Duration of surgery >2.5–4.0 h	2.26
Emergency surgery	2.21
General anesthesia	1.83

Adapted with permission from Sweitzer BJ, Smetana GW. Identification and evaluation of the patient with lung disease. Med Clin N Am. 2009;93(5):1017–1030.

obstructive airway disease); the patient's overall state of health, age, and history of cigarette smoking; and the presence of comorbid conditions, including malnutrition, congestive heart failure, alcohol use, functional dependence, and impaired sensorium. The risk for major postoperative pulmonary complications associated with obesity appears to be modest, while the precise risk associated with recent respiratory viral infections is unknown.

■ Chronic Lung Disease

The following discussion focuses on the operative risks in patients who have one of four common categories of chronic lung disease: (1) chronic obstructive pulmonary disease (COPD), (2) restrictive lung diseases, (3) obstructive sleep apnea (OSA), and (4) pulmonary vascular diseases.

Chronic Obstructive Pulmonary Disease

Most studies addressing the impact of pre-existing lung disease on surgical risk have focused on COPD, which has been identified as a significant risk for development of postoperative pulmonary complications.[42,43,46,49–59] The reported incidence of postoperative pulmonary complications in patients with COPD varies from 10% to greater than 50% and is influenced by type of surgery, magnitude of pre-existing respiratory impairment, and criteria used to define complications. Although not precisely quantified in the literature, the risk for postoperative respiratory complications appears to increase significantly when the FEV_1 is below 65% of predicted. Evidence shows that the risk for postoperative respiratory complications in COPD may be raised further by the concomitant presence of resting hypoxemia.[60] Although an increased risk has been suggested for patients who are hypercapnic at rest,[49,61] whether hypercapnia is, in fact, an independent predictor of pulmonary complications after surgery is unclear.[62]

In patients with severe disease, an important issue is whether a critical level of lung function exists below which the risk of developing a major, potentially life-threatening pulmonary complication is so high as to make anesthesia and surgery too dangerous. In the past, such a prohibitive threshold or level was proposed. Subsequent studies, however, have failed to support this hypothesis.[63] Patients with an FEV_1 as low as 450 mL have been found to tolerate surgery safely.[61] Hence, patients should not be denied necessary operative procedures solely on the basis of marginal lung function. As with all medical interventions, the potential benefits of the operative procedure must be weighed against the operative risk.

The increased incidence of postoperative pulmonary complications in patients with COPD is due, in part, to an increase in the CC, favoring development of areas of low ventilation-to-perfusion ratios and atelectasis. In addition, in patients who continue to smoke, impaired ciliary function and chronic tracheobronchitis may be contributing factors.

Restrictive Lung Diseases

The risk of pulmonary complications in patients with restrictive lung diseases who undergo surgery is unknown. Although some experience has been reported with patients having thoracic or corrective orthopedic surgery (see below), very little data exist with regard to abdominal and extremity surgery. One might expect a higher incidence of postoperative respiratory complications in these patients for two reasons: (1) FRC is reduced, favoring the formation of areas of poor ventilation and atelectasis; (2) coughing and the ability to clear respiratory secretions are impaired.

Experience with postoperative pulmonary complications has been reported in three relatively common situations for patients with restrictive disorders: (1) sarcoidosis complicated by aspergilloma and hemoptysis, (2) corrective surgery for kyphoscoliosis, and (3) myasthenia gravis with associated thymoma.

Sarcoidosis may progress to diffuse interstitial fibrosis and cavitary changes, primarily involving the upper lobes (Chapter 53). The cavities are prone to infection with *Aspergillus* species and aspergilloma formation, with subsequent development of recurrent and, at times, life-threatening, hemoptysis. Affected patients generally have very poor lung function and, hence, are managed conservatively. However, if supportive medical therapy fails, patients may require thoracotomy and lung resection. These procedures can be done with low mortality, but they may be complicated by empyema, chylothorax, prolonged pulmonary parenchymal air leaks, or bronchopleural fistulae.[33–36]

Corrective surgery in patients with kyphoscoliosis may involve anterior or posterior spinal fusion procedures or a combination of the two.[64,65] In addition to correction of the primary orthopedic abnormality, an important indication for performing these procedures is progressive deterioration of pulmonary function. Postoperative respiratory complications have been reported in up to 20% of patients, including pleural space–related processes (e.g., pneumothorax, pleural effusion, bronchopleural fistula, and empyema) and lobar or total lung atelectasis.[65–67] Important risk factors include (1) nonidiopathic scoliosis, (2) open anterior spinal fusion procedures, (3) age greater than 20 years, (4) intellectual disability (general learning disability), (5) preoperative hypoxemia, and (6) obstructive pulmonary function tests.[66] Thoracotomy has been associated with a significant decrease in pulmonary function for up to 2 years after surgery.[65,68] Video-assisted thoracoscopic surgery (VATS) has emerged as an alternative to open thoracotomy; the outcomes of anterior fusion via VATS and thoracotomy are similar.[69,70]

The majority of patients with myasthenia gravis will, during the course of their disease, undergo thymectomy, which appears to improve long-term outcomes.[71] Surgical options for thymectomy include the long-established method of transsternal resection, a transcervical approach, a combined transsternal–transcervical procedure, and, more recently, VATS.[72,73] Video-assisted thoracoscopic thymectomy is an increasingly common approach, with outcomes equivalent or superior to more invasive procedures.[73]

Historically, up to 30% of patients undergoing thymectomy required mechanical ventilation for more than 3 days following the transsternal approach.[74,75] Reported risk factors for postoperative pulmonary complications following transsternal resection include chronic myasthenia gravis (>6 years), severe bulbar weakness, pre-existing respiratory illness, need for large doses of pyridostigmine, and reduced maximal static expiratory pressure (<50 cm H_2O or 66% of predicted).[74–76] Preoperative VC has not proved a consistent predictor of respiratory morbidity following thymectomy. More recent routine use of plasma exchange in patients with bulbar or generalized myasthenia gravis has significantly reduced the duration of postoperative ventilatory support and time in the intensive care unit following transsternal thymectomy.[72]

Virtually all patients with myasthenia gravis are treated with anticholinesterases, which are usually discontinued prior to surgery to minimize tracheobronchial secretions. Controversy exists, however, regarding whether these agents should be restarted immediately after surgery or withheld for 24 to 48 h following thymectomy.

Obstructive Sleep Apnea

OSA is common, with a prevalence of 5% or higher, depending on the population studied (Chapter 98). For many of these patients, the diagnosis of OSA is not established preoperatively.[77] Unrecognized OSA is significant because both anesthesia and surgery affect sleep architecture;[78] in addition, use of postoperative narcotics for analgesia may further blunt ventilatory chemosensitivity,[79] suggesting that postoperative respiratory morbidity is likely higher in patients with OSA than in the general population. Although initial studies were consistent with this expectation,[80] subsequent reports have failed to show that OSA is significant risk factor for development of major postoperative pulmonary complications.[81–84] Thus, while it is prudent, and in the patient's best interest to use the preoperative evaluation as an opportunity to screen for OSA, the value of preoperative screening for OSA as a means of decreasing postoperative pulmonary complications has not been established.

Pulmonary Vascular Diseases

The risk of postoperative pulmonary complications in patients with underlying pulmonary vascular disease and intact respiratory mechanics is not known. However, one might anticipate an exaggeration of, or prolongation in, the hypoxemia seen postoperatively (see "Gas Exchange," above). In addition, pulmonary reserve in these patients is usually reduced; hence, additional pulmonary insults are less likely to be tolerated.

■ Smoking History

That smoking increases the risk of postoperative respiratory complications, even among those without COPD, has long been recognized.[50,85] Given the well-documented adverse effects of smoking on respiratory epithelium and pulmonary function, the magnitudes of which correlate with the degree of tobacco consumption, such an association is not surprising.

In individuals undergoing coronary artery bypass graft surgery, the risk of smoking becomes significant when tobacco use exceeds 20 pack-years.[86] A statistically significant reduction in complications occurs only when patients discontinue smoking for at least 8 weeks prior to surgery. This finding is consistent with studies showing that abnormalities in pulmonary function may persist up to several months after smoking cessation.[87,88] Although smoking cessation of more than 2 months is associated with a decreased risk of postoperative respiratory complications, early retrospective studies actually showed a paradoxical *increase* in pulmonary complications in patients who stopped smoking only a few weeks or days prior to surgery.[89] However, more recent studies[90] and analyses[91] have failed to demonstrate increased pulmonary complications in patients who quit smoking within 2 months of surgery.

■ General State of Health

Overall clinical status, as categorized by the American Society of Anesthesiologists' (ASA) classification (Table 102-7), correlates with development of postoperative pulmonary complications.[56,92–94] Specifically, an ASA classification of II or higher is a powerful predictor of increased risk for respiratory problems after surgery.[23,46,47]

■ Age

Although increased age was previously thought to be a minor risk factor for postoperative respiratory complications,[95] more recent analyses indicate that increasing age is, in fact, a significant independent predictor, even after accounting for comorbid conditions associated with aging.[23] Advanced age, however, should not be the sole reason for withholding surgery, particularly lung resection.

In one important study, despite the finding of a higher 30-day postoperative mortality in patients over age 70 years who underwent resectional lung surgery, the incidence of postoperative pulmonary complications and hospital stay were not increased, and survival was not decreased, in the older group.[96] Further, in a nested, case-control study of patients greater than age 70 years who underwent lung resection, no significant differences were found between the elderly and younger controls in length of stay, major morbidity, or operative mortality.[97] These findings, along with other published results,[98] indicate that treatment decisions should be individualized for each patient.

TABLE 102-7 American Society of Anesthesiologists (ASA) Clinical Classification

ASA I	Otherwise healthy patient undergoing elective surgery
ASA II	Patient with single-system or well-controlled disease that does not affect daily life
ASA III	Patient with multisystem or well-controlled major-system disease that limits daily activity
ASA IV	Patient with severe, incapacitating disease that is poorly controlled or end stage
ASA V	Patient who is in imminent danger of death and is not expected to survive 24 h

■ Obesity

A number of changes in respiratory mechanics and pulmonary function occur with obesity.[99–102] The accumulation of fat in the chest wall, diaphragm, and abdomen may reduce total respiratory compliance by more than 60%—a change that is amplified when the patient assumes the supine position.[103] The reduced compliance, in turn, increases the work of breathing.[99,100] Consequently, minute ventilation, oxygen consumption, and carbon dioxide production are further increased beyond baseline values, which are already elevated as a result of increased metabolic demands imposed by the obese state. In terms of gas exchange, modest effects at rest are observed only in morbidly obese individuals: lower than predicted Pa_{O_2}, higher than predicted alveolar-to-arterial oxygen pressure difference, normal blood oxygen saturation, and normal Pa_{CO_2}.[104]

Typically, spirometry in obese patients does not indicate airway obstruction. However, a reduction in ERV is found consistently. The magnitude of the reduction correlates with the degree of obesity. Areas of low ventilation relative to perfusion and atelectasis are seen (see "Lung Volumes," above). In addition to these changes, obese patients appear to have a larger gastric volume and lower gastric pH than do nonobese patients and may be predisposed to aspiration.[105]

Morbidly obese patients may be at an increased risk for development of atelectasis, as noted on chest radiographs.[106,107] However, when bacterial pneumonia, acute respiratory failure, or prolonged mechanical ventilation are considered, and confounding factors are excluded, obese patients undergoing abdominal surgery do not show an increased incidence of clinically significant postoperative pulmonary complications compared with nonobese patients.[41,108–110] Further, respiratory complications occur in only 4% to 7% of obese patients undergoing gastric bypass surgery and appear to be declining.[111,112] Therefore, in the absence of concurrent cardiopulmonary disease, the risk of postoperative pulmonary complications associated with obesity appears not to be excessive. However, as noted previously, obesity is clearly a risk factor for OSA syndrome, which may be unmasked or exacerbated because of use of postoperative analgesics or narcotics.[113]

■ Nutritional Status

The effects of malnutrition and severe starvation on the respiratory system include a reduced ventilatory response to hypoxia, decreased diaphragmatic muscle function, impaired cell-mediated and humoral immunity, and alterations in the elastic properties of the lung. Depending on the clinical metrics examined (e.g., weight loss >10% over the previous 6 months, BMI <20 kg/m^2), the screening procedures utilized (e.g., Mini Nutritional Assessment [MNA] score <17), and the laboratory tests employed (e.g., serum albumin <36 g/L), malnutrition may be found in 50% or more of hospitalized patients.[114,115] Evidence exists that these levels of malnutrition are associated with expiratory muscle weakness (despite preservation of pulmonary function)[116] and an increased incidence of postoperative respiratory complications.[42,108,117,118] However, aggressive preoperative nutritional support has not been shown to decrease postsurgical pulmonary morbidity.[119]

Antecedent Respiratory Tract Infection

The effects of an antecedent respiratory tract infection on the incidence of respiratory complications following surgery are difficult to predict. With respiratory syncytial virus (RSV) infections, symptoms typically resolve in 7 to 10 days; viral shedding averages 10 to 13 days, but it may persist beyond 20 days.[120,121] Furthermore, enhanced airway reactivity and increased airway resistance associated with this and other viral infections may persist for weeks beyond resolution of acute symptoms.[122,123] In addition, diaphragmatic function may be impaired during viral infections.[124]

In pediatric patients, perioperative, non-life-threatening, adverse respiratory events are more common in patients with recent (within 4 weeks) upper respiratory tract infections compared with those without infections.[125,126] In an adult population, history of an acute respiratory infection in the month preceding surgery is an independent risk factor for development of a postoperative pulmonary complication.[45] Therefore, in the setting of an active or recent respiratory tract infection (in the previous 2 weeks), a 2- to 4-week delay in elective surgery is generally advised.

Other Patient-Related Factors

Other factors have been reported to be associated with an increased incidence of postoperative pulmonary complications.[23] These include congestive heart failure,[45,127,128] preoperative functional dependence, impaired sensorium (acute confusion or delirium), and active alcohol use (>2 drinks per day in the past 2 weeks).[42,43]

INTRAOPERATIVE RISK FACTORS

Several operative factors have been associated with development of pulmonary complications after surgery. These include whether the surgery is emergent or nonemergent, type of anesthesia used, length of the procedure (as determined by the duration of anesthesia), surgical site, and type of surgical incision and nonprotective mechanical ventilation.

Emergent Nature of the Procedure

Postoperative pulmonary complication rates are higher for surgeries done on an emergent basis.[42,43,45–47,53,54,127] The increased risk of emergency surgery may be significant[23] and may be related to loss of the ability to implement some of the preventative measures outlined subsequently or to deliberately plan the anesthetic strategy.

Type of Anesthesia

The pulmonary effects of general anesthesia have been implicated in the development of postoperative pulmonary complications.[42,43,56,57] They include impairment of oxygenation and carbon dioxide elimination. These effects result from anesthetic-induced changes in the shape and motion of the chest wall and diaphragm, which, in turn, lead to increases in alveolar dead space, shunt fraction, and ventilation–perfusion mismatching. Alterations in lung function may contribute to pulmonary morbidity.

Because of the effects of general anesthesia on gas exchange, regional anesthesia (spinal or epidural anesthesia) or local anesthesia with monitored anesthesia care (MAC) have been used as alternatives, particularly in patients with underlying pulmonary disease. Indeed, epidural anesthesia to a T4 sensory level does not appear to alter FRC, VC, FEV_1, the alveolar–arterial oxygen gradient, shunt fraction, or cardiac output.[129] Overall, regional anesthesia, as compared with general anesthesia, decreases the risk of postoperative respiratory complications, particularly deep-vein thrombosis.[130,131] These beneficial effects, however, appear to be most significant for abdominal and thoracic procedures[132,133] and less so for nonthoracoabdominal procedures, such as carotid endarterectomy[134,135] and hip fracture surgery.[136,137]

Duration of Anesthesia

The incidence of pulmonary complications increases significantly for procedures lasting longer than 2 to 4 h.[45,50,51,75,93] Patients whose procedures last 4 h or more are five times more likely to experience postoperative pneumonia than those whose procedures last less than 2 h.[108]

Surgical Site

Development of postoperative pulmonary complications has long been recognized to correlate strongly with the anatomic site of operation.[45,50,51,75,93] The complication rate (excluding thromboembolic disease) is less than 5% for gynecologic and urologic procedures, 5% to 10% for lower abdominal and head and neck surgeries, and 10% to 20% for upper abdominal surgeries. Abdominal aortic surgery is associated with a pulmonary complication rate of 25% or more.[23]

Reported postoperative complication rates for thoracic surgery involving lung resection vary from under 10% to 40% or higher.[138–143] Postoperative respiratory morbidity following lung resection surgery (in addition to all the factors cited earlier) also depends on a number of other issues, including (1) the presence of underlying lung disease, (2) the amount of functional lung removed, and (3) the extent to which the "bellows" function of the lung is impaired (see "Evaluation for Lung Resection," below). Furthermore, the potentially higher incidence of postoperative respiratory complications after lung resection surgery relative to other procedures also reflects the occurrence of specific problems related to entering the pleural space or resection of lung tissue (e.g., development of pleural effusion, empyema, pneumothorax, or persistent pulmonary parenchymal air leak).

Type of Surgical Incision

For abdominal procedures, vertical laparotomy incisions may carry a higher incidence of postoperative complications than do horizontal incisions,[144] although this finding has been questioned.[145] Abdominal laparoscopic procedures and thoracoscopic lung resection have gained widespread acceptance because of reduced patient discomfort, shortened length of hospitalization, and faster patient return to full activity. Since the magnitude of incisional pain is usually less, and since patients typically ambulate sooner, the incidence of postoperative respiratory complications with these less invasive procedures is likely to be lower. Laparoscopic cholecystectomy, when compared with open cholecystectomy, demonstrates better preservation and faster recovery of lung volumes, higher arterial oxygen saturations, less postoperative pain and analgesia use, and a lower incidence of postoperative pulmonary complications.[146–148] Comparable findings have been noted for minimally invasive esophagectomies compared with open procedures, and for video-assisted thoracic surgery versus open thoracotomy.[32]

Nonprotective Mechanical Ventilation

To prevent hypoxemia and atelectasis in anesthetized patients, intraoperative ventilatory support has typically involved the use of large tidal volumes (10–15 mL/kg of predicted body weight). This approach, however, may induce alveolar overdistension and lung injury and increase the risk of postoperative pulmonary complications.[149,150] In contrast, postoperative respiratory complications are decreased when an intraoperative lung protective ventilation strategy is employed, including low tidal volumes (6–8 mL/kg of predicted body weight), modest levels of positive end-expiratory pressure (PEEP) (6–8 cm H_2O), and recruitment maneuvers (periodic hyperinflation of the lungs every 30 min after intubation).[151]

POSTOPERATIVE RISK FACTORS

Inadequate pain control, prolonged bed rest, and patient inactivity contribute to development of postoperative respiratory complications.

Inadequate Postoperative Analgesia

Effective pain control is vital in the early postoperative period, since pain inhibits coughing and deep breathing and discourages early mobilization—factors that contribute to an increased risk of pulmonary complications. More importantly, there is evidence that effective analgesia after thoracic or abdominal surgery reduces the occurrences of postoperative pulmonary complications.[152–155] Obstacles to good postoperative analgesia include hesitancy of the patient to report pain for fear of being labeled a "bad" patient and anxiety of caregivers in administering narcotics because of side effects.

Immobilization

Prolonged bed rest and inactivity following surgery impact the risk of postoperative respiratory complications in several ways. FRC decreases by 500 to 1000 mL in moving from the upright to the supine position, favoring development of atelectasis.[18] Increased ambulation is associated with better clearance of respiratory secretions. Postoperative immobilization is a major risk factor for development of deep venous thrombosis and pulmonary embolism.

PREOPERATIVE EVALUATION

The principal elements in preoperative evaluation of the surgical patient are (1) the history and physical examination, (2) the chest radiograph, (3) arterial blood gas analysis, and (4) pulmonary function tests (Fig. 102-2).

History and Physical Examination

A careful history is an essential component of preoperative evaluation. The following issues should be reviewed: (1) smoking history; (2) history of respiratory symptoms (e.g., cough, chest pain, dyspnea), including symptoms of sleep apnea; (3) extent of pre-existing lung disease; and (4) history of recent respiratory tract infection. The physical examination is rarely helpful in identifying pulmonary risk factors. When the history is negative, the physical examination is typically unremarkable. However, the initial physical examination supplements the history and provides a baseline for future comparisons.

Chest Radiograph

The preoperative chest radiograph is usually unrevealing if risk factors and abnormal physical findings are absent.[156,157] Although the admission or screening chest radiograph is more likely to show an abnormality in individuals with known cardiopulmonary disease, the study usually simply confirms the presence of previously known abnormalities; only occasionally does it result in an alteration in management. Thus, a preoperative chest radiograph is indicated when there are new or unexplained symptoms or signs, when there is a history of underlying lung disease and no recent chest radiograph, or when thoracic surgery is planned.

Arterial Blood Gas Analysis

Since an elevated Pa_{CO_2} is associated with an increased incidence of postoperative respiratory morbidity in patients with significant chronic lung disease, an arterial blood gas analysis should be done preoperatively in these patients.[60] Although supportive data are lacking, it is common practice to obtain an arterial blood gas sample in all patients undergoing lung resection surgery, even those without significant underlying lung disease. The determination serves as a basis for comparison with subsequent intra- and postoperative measurements. It is also recommended that an arterial blood gas specimen be obtained in patients who, by either history or physical examination, have a new significant pulmonary process. Data do not support the use of arterial blood gas analysis as a routine preoperative screening test.[158]

Pulmonary Function Tests

An increased risk of postoperative respiratory complications has been demonstrated only with obstructive pulmonary disorders. Although theoretical reasons may prompt expectation of a higher incidence of postoperative respiratory problems in patients with restrictive lung diseases (see "Preoperative Risk Factors," above), currently, data demonstrating a correlation between the degree of restriction (as assessed by lung volumes) and postoperative pulmonary morbidity are lacking. Hence, although a complete battery of pulmonary function tests is useful in evaluating suspected restrictive lung disease, spirometry to evaluate for airway obstruction is all that is required to screen patients at risk for postoperative pulmonary complications.

Indications for preoperative pulmonary function testing include the presence of cough or unexplained dyspnea, a history of chronic lung disease, a history of cigarette smoking (>20 pack-years), or planned lung resection (see below). Current data do not support the routine use of these studies to evaluate the pulmonary risks of advanced age, obesity, malnutrition, or abdominal surgery.[159–162] Finally, normal pulmonary function tests obviously do not guarantee a complication-free postoperative course and do not lessen the need for diligent respiratory care following surgery.

EVALUATION FOR LUNG RESECTION

In evaluating patients for lung resection, the clinician must consider two broad issues: (1) What is the surgical morbidity and mortality for the patient with significant underlying chronic lung disease? (2) Will postoperative lung function be adequate to support a reasonable quality of life? Pulmonary function

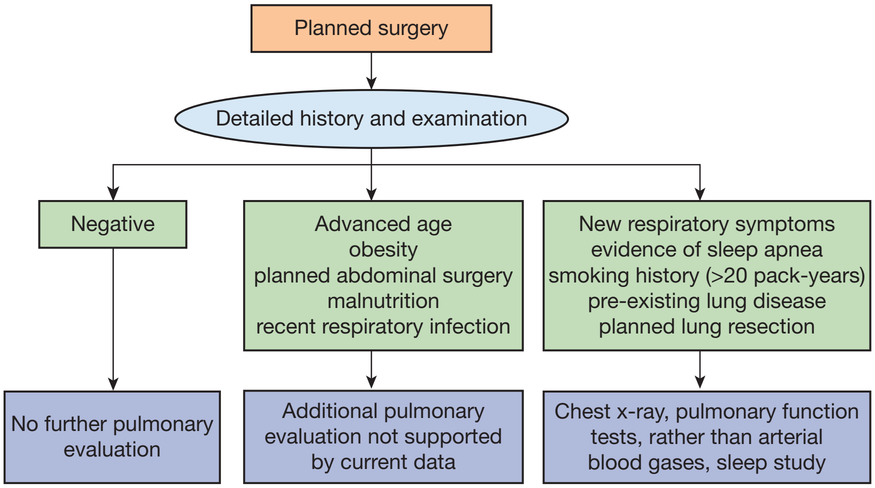

Planned surgery
Detailed history and examination
Negative
Advanced age
obesity
planned abdominal surgery
malnutrition
recent respiratory infection
New respiratory symptoms
evidence of sleep apnea
smoking history (>20 pack-years)
pre-existing lung disease
planned lung resection
No further pulmonary evaluation
Additional pulmonary evaluation not supported by current data
Chest x-ray, pulmonary function tests, rather than arterial blood gases, sleep study

Figure 102-2 Algorithm for preoperative pulmonary evaluation. See text for discussion.

testing, supplemented by exercise testing in selected cases, provides the basis for answering these questions.[163,164]

Pulmonary Function Testing

Studies dating back to the 1950s have shown that the risk of postoperative respiratory complications following pneumonectomy increases significantly when the FEV_1 is less than 2 L or 80% of predicted normal, or when the maximal voluntary ventilation (MVV) is less than 50% of predicted.[165] For a lobectomy, an FEV_1 of 1.5 L appears to be the critical threshold. The diffusion capacity for carbon monoxide (DL_{CO}) also has been identified as a predictor of postoperative complications.[166,167] Increased risk is associated with a DL_{CO} of less than 60% to 80% of predicted and appears to be independent from FEV_1 as a predictor of complications, morbidity, and death.[168–170] Therefore, predictive postoperative lung function should be estimated for patients with an FEV_1 or DL_{CO} less than 80% of predicted.[163,164]

Prediction of Postoperative FEV_1 or DL_{CO}

Ventilation–perfusion lung scans measure the relative blood flow or ventilation to one lung or lung region and can be used to predict postoperative FEV_1 or DL_{CO} using the following equation:

$$\begin{aligned}&\text{Predicted postoperative } FEV_1 \text{ or } DL_{CO} = \text{Preoperative } FEV_1\\ &\quad \text{or } DL_{CO} \times \text{(lung function remaining after resection,}\\ &\qquad \text{as determined by radionuclide imaging)} \qquad (1)\end{aligned}$$

An alternative approach to estimating the predicted postoperative pulmonary function involves a calculation based on the number segments of the lung (10 on the right and 9 on the left)[171] as follows:

$$\begin{aligned}&\text{Predicted postoperative } FEV_1 \text{ or } DL_{CO} = \text{Preoperative } FEV_1\\ &\quad \text{or } DL_{CO} \times \text{(lung function remaining after resection,}\\ &\qquad \text{as determined by radionuclide imaging)} \qquad (2)\end{aligned}$$

Studies comparing the radionuclide imaging-based technique versus the segment-based method suggest that perfusion imaging, overall, provides a better prediction of postoperative lung function, as the segment method underestimates lung function after pneumonectomy.[172,173]

In addition to the two methods noted earlier, other approaches have been employed to predict postresection lung function. However, procedures such as quantitative computed tomographic (CT) imaging[174] have failed to gain wide acceptance, and oxygen-enhanced MRI,[175] although promising, awaits further development.

A number of studies have demonstrated that the perioperative risk for lung resection increases significantly when the predicted postoperative FEV_1 or DL_{CO} is less than 40% of predicted.[166,176–179] Therefore, a predicted postoperative FEV_1 or DL_{CO} of at least 40% predicted has been proposed as useful criteria for undertaking "safe" pulmonary resection.[163,180] Finally, with recognition that most patients who undergo resectional lung surgery have lung cancer, and that this malignancy has virtually a 100% mortality without surgery (for non–small-cell tumors), caution must be exercised in applying exclusionary criteria for surgery.

Exercise Testing

A number of investigators have found measurement of maximal oxygen consumption ($\dot{V}_{O_2max}$) during cardiopulmonary exercise testing to be useful in predicting postoperative morbidity and mortality.[181–185] Specifically, a $\dot{V}_{O_2max}$ of less than 15 to 20 mL/kg/min is associated with an increased incidence of postoperative complications. Cardiopulmonary exercise testing is, therefore, used to further assess the operability of patients of who would be at high risk for surgery based on determination of predicted postoperative pulmonary function.[163]

If cardiopulmonary exercise testing is unavailable, two technologically simpler approaches, stair climbing and a walking test, can be used to assess a patient's fitness for lung resection. Although standardization of the stair climbing test may be problematic, demonstration of a patient's ability to climb five flights of stairs predicts a $\dot{V}_{O_2max}$ greater than 20 mL/kg/min; patients who are unable to climb one flight of stairs have a $\dot{V}_{O_2max}$ less than 10 mL/kg/min.[186] Furthermore, an ability to climb three flights of stairs reliably identifies patients who are likely to do well after a lobectomy, despite having a predicted postoperative FEV_1 or DL_{CO} that is <40% of predicted.[187,188]

The shuttle walk and 6-min walk tests also have been investigated as alternatives to cardiopulmonary exercise testing. For the shuttle walk, the patient walks back and forth over a distance of 25 m at a progressively faster rate. Inability to complete 25 shuttles approximates a $\dot{V}_{O_2max}$ less than 10 mL/kg/min.[189,190] A 6-min walk distance greater than 1000 ft has been reported as predictive of successful surgical outcome.[177]

Recommended Approach

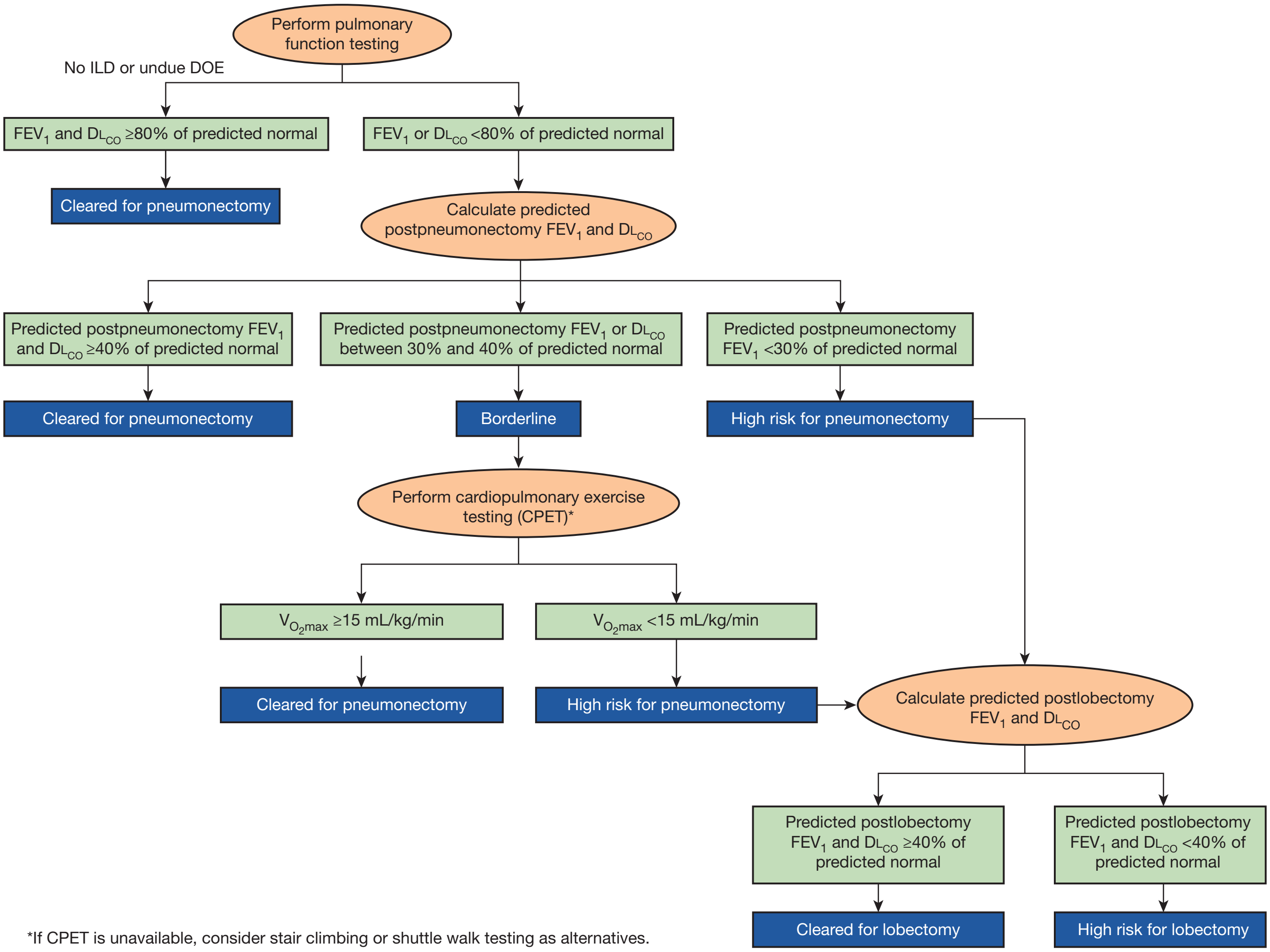
Summarized in Fig. 102-3 is a recommended sequence for evaluating patients for lung resection. The approach is adapted from recommendations of the American College of Chest Physicians (ACCP),[163] which, despite some differences, is also consistent with guidelines from several European professional societies.[164,180] The approach is predicated on determining the patient's operability for pneumonectomy, should this procedure be deemed necessary at the time of surgery (e.g., to permit complete removal of a tumor or to deal with an unanticipated intraoperative complication):

- If the preoperative FEV_1 and the DL_{CO} are greater than or equal to 80% predicted normal and the patient has no dyspnea on exertion or interstitial lung disease, the patient is cleared for pneumonectomy; no further testing is required.
- If the preoperative FEV_1 or the DL_{CO} are less than 80% predicted normal, the predicted postpneumonectomy FEV_1 and DL_{CO} should be estimated.
- If the predicted postpneumonectomy FEV_1 and DL_{CO} are greater than or equal to 40% of predicted normal, the patient is cleared for pneumonectomy and no further testing is required.
- If the predicted postpneumonectomy FEV_1 is less than 30% predicted normal, the patient is considered at high risk for a pneumonectomy.
- If the patient is considered at borderline risk for pneumonectomy (the predicted postoperative FEV_1 or DL_{CO} is less than 40% but at least 30 predicted normal), exercise testing should be done. Borderline patients with a $\dot{V}_{O_2max}$ greater than or equal to 15 mL/kg/min are cleared for pneumonectomy (no further testing is required), while patients with $\dot{V}_{O_2max}$ less than 15 mL/kg/min are considered at high risk for a pneumonectomy.
- If the patient is determined to be at high risk for pneumonectomy, the predicted postlobectomy FEV_1 and DL_{CO} should be determined to inform conversations about the risks and benefits of more limited surgical resections or nonoperative treatment options.

For selected, high-risk patients with emphysema and potentially resectable lung cancer, consideration should be given for a segmental resection[191] or combined cancer resection and lung volume reduction.[192] The latter is particularly worth considering if the emphysema is heterogeneous and primarily involves the lobe to be resected.

PREOPERATIVE PREPARATION

Relatively few studies have specifically addressed the question of whether aggressive, preoperative pulmonary preparation decreases


Perform pulmonary function testing
No ILD or undue DOE
FEV_1 and DL_{CO} ≥80% of predicted normal
FEV_1 or DL_{CO} <80% of predicted normal
Cleared for pneumonectomy
Calculate predicted postpneumonectomy FEV_1 and DL_{CO}
Predicted postpneumonectomy FEV_1 and DL_{CO} ≥40% of predicted normal
Predicted postpneumonectomy FEV_1 or DL_{CO} between 30% and 40% of predicted normal
Predicted postpneumonectomy FEV_1 <30% of predicted normal
Cleared for pneumonectomy
Borderline
High risk for pneumonectomy
Perform cardiopulmonary exercise testing (CPET)*
$V_{O_2\text{max}}$ ≥15 mL/kg/min
$V_{O_2\text{max}}$ <15 mL/kg/min
Cleared for pneumonectomy
High risk for pneumonectomy
Calculate predicted postlobectomy FEV_1 and DL_{CO}
Predicted postlobectomy FEV_1 and DL_{CO} ≥40% of predicted normal
Predicted postlobectomy FEV_1 and DL_{CO} <40% of predicted normal
Cleared for lobectomy
High risk for lobectomy

*If CPET is unavailable, consider stair climbing or shuttle walk testing as alternatives.

Figure 102-3 Algorithm for preoperative evaluation for lung resection. See text for discussion. DOE, dyspnea on exertion; ILD, interstitial lung disease.

postoperative pulmonary morbidity and mortality.[193] Although data on preoperative preparation are limited, for patients with active obstructive airway disease, intensive preoperative respiratory therapy (bronchodilators, corticosteroids, antibiotics, and chest physiotherapy) does appear to reduce the incidence of postoperative respiratory complications by more than 50%.[93,194–196]

Several preoperative prophylactic measures should be considered in patients undergoing elective surgery (Table 102-8).

Pulmonary function in patients with obstructive airway disease should be optimized. Therapy may include any or all of the following: bronchodilators, corticosteroids, antibiotics (when there is evidence of infection), and chest physiotherapy (if excessive secretions are present). When possible, these interventions should be implemented 48 to 72 h prior to surgery.

TABLE 102-8 Preoperative Pulmonary Preparation

Optimization of airway function in patients with obstructive lung disease (bronchodilators; corticosteroids, antibiotics, and chest physiotherapy when indicated)
Smoking cessation (ideally a minimum of 8 weeks prior to surgery)
Patient education (deep breathing exercises, importance of coughing and pain control, use of incentive spirometry)
Consider inspiratory muscle training

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Ideally, for at least 8 weeks prior to surgery, smoking should be discontinued. As noted previously, data indicate that complication rates are not increased by shorter periods of abstinence; therefore, even when 8 weeks of abstinence is not possible, patients should still be advised to quit smoking prior to surgery.[90,91]

A program of inspiratory muscle training for at least 2 weeks prior to surgery may reduce the incidence of postoperative pulmonary complications in patients at high risk for their development.[197]

Finally, patient education on the importance of postoperative coughing and pain control, proper use of an incentive spirometer, and deep breathing exercises should take place preoperatively.

POSTOPERATIVE PROPHYLACTIC MEASURES

Several postoperative measures may be employed in an attempt to prevent respiratory complications (Table 102-9).

Early patient mobilization and ambulation should be encouraged. As noted previously, these measures are important postoperatively in reducing the incidence of atelectasis, in promoting the clearance of secretions, and in decreasing the risk of thromboembolic disease.

Prophylactic lung expansion maneuvers should be initiated.[198,199] Two equally effective measures are deep breathing exercises and incentive spirometry.[200,201] Intermittent positive pressure breathing

TABLE 102-9 Postoperative Measures for the Prevention of Respiratory Complications

Early patient mobilization and ambulation
Prophylactic lung expansion maneuvers (incentive spirometry, deep breathing exercises, CPAP)
Provision of adequate analgesia
Prophylaxis against thromboembolism

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(IPPB) is generally ineffective and costly and is associated with several adverse effects.[198,199] Reports of intermittent continuous positive airway pressure (CPAP) applied by face mask indicate that it is at least equivalent to deep breathing exercises and incentive spirometry in preventing atelectasis and pneumonia.[202] However, while CPAP may be useful in the patient who cannot cooperate with inspiratory maneuvers, its role in the management of patients capable of taking deep breaths is unclear.

Adequate analgesia should be provided, particularly for patients undergoing major, open surgery. Traditionally, parenteral narcotics have been used for postoperative analgesia, despite the risk of respiratory depression. Unfortunately, concerns over adverse respiratory effects may lead to inadequate dosing and inadequate pain relief. To overcome this problem, alternative approaches, including use of epidural analgesia, peripheral nerve blockade, paravertebral block, and wound catheter infiltration may be employed as alternatives to the use of systemic opioids.[203] These alternative techniques provide analgesia equivalent or superior to parenteral narcotics; however, whether they are effective in reducing postoperative pulmonary complications remains unclear.

Prophylaxis for thromboembolism is an important consideration,[204] and careful monitoring for other postoperative complications constitutes a key element in all surgical patients.

Finally, several postoperative interventions have been shown to be ineffective, including chest physiotherapy in the absence of excessive secretions or sputum production,[205] and routine application of positive end-expiratory pressure in mechanically ventilated patients.[206]

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CHAPTER 103

Acute Respiratory Failure in the Surgical Patient

Robert M. Kotloff

INTRODUCTION

Advances in surgical technique, anesthesia and analgesia, and postoperative supportive care have emboldened surgeons to consider an expanding spectrum of patients for surgical interventions. In most instances, the success or failure of the surgery is defined not in the operating room, but postoperatively, when the adverse effects of surgery may first become apparent and when intercurrent complications may jeopardize the patient's recovery. The respiratory system is particularly vulnerable to the effects of general anesthesia and surgery, and postoperative respiratory impairment is common. While generally mild and well tolerated in otherwise healthy, young patients, postoperative respiratory compromise may have serious consequences in the elderly and in patients with preexisting lung disease. A number of postoperative complications, such as pneumonia, aspiration pneumonitis, and acute respiratory distress syndrome (ARDS) may lead to respiratory compromise independent of the patient's pre-surgical status.

This chapter focuses on the most serious consequence of perioperative respiratory compromise—acute respiratory failure. This complication is associated with a 30-day mortality rate in the range of 25% following major surgical procedures, compared to approximately 1% for unaffected patients.[1,2] In addition to its adverse impact on survival, respiratory failure prolongs intensive care and hospital stay, delays convalescence, and increases health care costs among survivors. Clinicians who provide preoperative evaluation and postoperative care must be able to identify high-risk patients who require a greater degree of vigilance, and to rapidly recognize and appropriately treat the complications that result in postoperative respiratory failure.

ASSESSING THE RISK OF POSTOPERATIVE RESPIRATORY FAILURE

Several calculators have been developed to estimate the risk of postoperative respiratory failure. All were constructed based on data derived from large national databases, but, notably, none has been externally validated. Furthermore, these calculators share a common definition of postoperative respiratory failure as mechanical ventilation beyond the initial 48 h following surgery or need for reintubation. This definition fails to distinguish patients requiring what most physicians (and patients) would consider to be an acceptable period of limited postoperative ventilatory support from those who truly would require prolonged ventilatory support and its attendant risks and complications. Arozullah et al. developed the first major calculator to focus specifically on respiratory failure, utilizing a database of more than 81,000 cases from 44 Veterans Affairs (VA) hospitals in their derivation cohort.[3] Respiratory failure developed in 3.4%. The type of surgical procedure was the strongest independent predictor of postoperative respiratory failure; those with the highest odds ratio for developing respiratory failure included abdominal aortic aneurysm repair, thoracic surgery, upper abdominal surgery, and neurosurgical procedures. Other independent variables included in the derived risk calculator were emergency surgery, albumin <3.0 mg/dL, blood urea nitrogen >30 mg/dL, partially or fully dependent functional status, history of chronic obstructive pulmonary disease (COPD), and age 60 or greater. Points assigned to each of these parameters are shown in Table 103-1, and the predicted risk of respiratory failure based on cumulative points is shown in Table 103-2. The generalizability of this risk calculator is limited by the exclusively male population, the high prevalence of comorbidities that typically characterizes a VA cohort, and the exclusion of cardiac surgery.

TABLE 103-1 Arozullah Respiratory Failure Risk Calculator Point System

Preoperative Predictor	Point Value
Type of surgery	
Abdominal aortic aneurysm	27
Thoracic	21
Neurosurgery, upper abdominal, peripheral vascular	14
Neck	11
Emergency surgery	11
Albumin <3 g/dL	9
Blood urea nitrogen >30 mg/dL	8
Partially or fully dependent functional status	7
History of COPD	6
Age (years)	
≥ 70	6
60–69	4

Reproduced with permission from Johnson RG, Arozullah AM, Neumayer L, et al. Multivariable predictors of postoperative respiratory failure after general and vascular surgery: results from the patient safety in surgery study. J Am Coll Surg. 2007;204(6):1188–1199.

In an attempt to render their model more broadly applicable, Johnson et al. published an updated predictive model based on cases derived from both VA hospitals and private academic centers and that included 20% women.[1] Twenty-eight variables were identified to be independently associated with increased risk and were assigned point values based on their associated odds ratio for

TABLE 103-2 Arozullah Respiratory Failure Risk Calculator Predictions

Point Total	Predicted Probability of Respiratory Failure
≤ 10	0.5%
11–19	2.2%
20–27	5.0%
28–40	11.6%
>40	30.5%

Data from Arozullah AM, Daley J, Henderson WG, et al. Multifactorial risk index for predicting postoperative respiratory failure in men after major noncardiac surgery. The National Veterans Administration Surgical Quality Improvement Program. Ann Surg. 2000;232(2):242–253.

respiratory failure (Table 103-3). Similar to their previous model, the type of procedure influenced risk, with the greatest incidence of respiratory failure associated with upper aerodigestive tract surgery, thoracic or thoracoabdominal aneurysm repair, thoracic surgery, and gastrointestinal and hepatobiliary surgery. A steady rise in risk of respiratory failure was documented with cumulative scores above 12 (Fig. 103-1). Unfortunately, the complexity of the model renders it unwieldy and has limited its widespread acceptance. Like the earlier model, it also cannot be applied to cardiac surgery patients.

TABLE 103-3 Johnson Respiratory Failure Risk Calculator: Parameters Used and Score Assigned

Parameter Set	Description	Score
1	ASA class 3	3
1	ASA class 4–5	5
2	Emergency	2
3	Work RVU 10–17	2
3	Work RVU >17	4
4	Preoperative albumin ≤3.5	1
5	Procedure: Integumentary	1
5	Procedure: Respiratory and hemic	3
5	Procedure: Heart	2
5	Procedure: Aneurysm	2
5	Procedure: Mouth, palate	7
5	Procedure: Stomach, intestines	2
5	Procedure: Endocrine	2
6	Preoperative sepsis	2
7	Preoperative creatinine ≥1.5	2
8	History of severe COPD	2
9	Ascites	2
10	Dyspnea	1
11	Impaired sensorium	1
12	Preoperative bilirubin >1.0	1
13	>2 alcoholic drinks/d in 2 weeks before admission	1
14	Bleeding disorders	1
15	Age >40 y	2
16	Preoperative white blood count <2.5 or >10	1
17	Preoperative serum sodium >145	2
18	Weight loss >10%	1
19	Preoperative acute renal failure	2
20	Male gender	1
21	Congestive heart failure <30 d before operation	1
22	Smoker	1
23	Preoperative platelet count ≤150	1
24	CVA/stroke with neurologic deficit	1
25	Wound class (clean/contaminated)	1
25	Wound class (contaminated)	1
25	Wound class (infected)	1
26	Preoperative AST >40	1
27	Preoperative hematocrit ≤38	1
28	CVA/stroke without neurologic deficit	1

ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; RVU, relative value unit.
Data from Johnson RG, Arozullah AM, Neumayer L, et al. Multivariable predictors of postoperative respiratory failure after general and vascular surgery: results from the patient safety in surgery study. J Am Coll Surg. 2007;204(6):1188–1198.

In one of the larger studies to date, Gupta et al. used the 2007 American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database of more than 210,000 patients who underwent a broad array of surgical procedures, including cardiac surgery.[2] On multivariate logistic regression analysis, five preoperative predictors of postoperative respiratory failure were identified: type of surgery (highest risk with brain, abdominal, aortic surgery), emergency cases, poor preoperative functional status, preoperative sepsis, and higher ASA class. These variables were incorporated into a predictive model that was validated in a second cohort of more than 250,000 patients from the 2008 NSQIP database. An interactive risk calculator, available at *www.surgicalriskcalculator.com/prf-risk-calculator*, was then developed to estimate the likelihood of respiratory failure for a given patient.

Pulmonary consultants providing preoperative assessment are commonly asked to specifically comment on the risk posed by a patient's history of COPD. COPD has been identified as an independent predictor of postoperative respiratory failure in numerous studies.[1,4–8] The largest and most comprehensive study utilized the NSQIP database containing more than 460,000 patients who underwent a variety of surgical procedures.[7] COPD was independently associated with an increased risk of ventilator dependence for more than 48 h following surgery (odds ratio [OR], 1.45) and reintubation (OR, 1.54). Notably, neither this study nor the others referenced above categorized patients according to preoperative pulmonary function parameters, precluding conclusions about the relationship between severity of COPD and risk of postoperative respiratory failure.

The use of preoperative pulmonary function testing to assess risk of postoperative respiratory failure in COPD patients has been most closely examined in the context of lung resection surgery for lung cancer. Studies of patients undergoing standard thoracotomy and either pneumonectomy or lobectomy have used preoperative spirometry in conjunction with quantitative ventilation/perfusion lung scans to estimate post-resection FEV_1 and diffusing capacity. While the study populations are small, published case series suggest that a predicted post-resection FEV_1 or diffusing capacity less than 40% of normal is associated with a high risk for postoperative respiratory failure and death.[9–12] In one study that examined the performance characteristics of these parameters, the probability of respiratory failure or death was 33% for those patients with an FEV_1 <40% while the probability of avoiding these complications was 90% for those with an FEV_1 ≥40%.[11] Coupling pulmonary function testing with cardiopulmonary exercise testing allows for more precise risk stratification. Those patients with peak oxygen consumption of ≥10 to 15 mL/kg/min despite predicted post-resection FEV_1 or diffusing capacity <40% appear to have a low risk of respiratory failure and death following thoracotomy and definitive lung resection procedures.[10,13] The use of video-assisted thoracoscopic surgery (VATS) in combination with lobectomy, segmentectomy, or wedge resection appears to be well tolerated by patients with severe lung disease, with only a 4% incidence of respiratory failure and a 1% mortality rate documented in one study of 100 consecutive patients with an FEV_1 <35% predicted.[14]

Studies using preoperative spirometry to assess severity of COPD in patients undergoing cardiac surgery have provided conflicting results with respect to the risk of respiratory failure. One study found that an FEV_1 <70% was an independent predictor of respiratory failure after coronary artery bypass graft (CABG), but the rather broad nature of the spirometric threshold used limits the

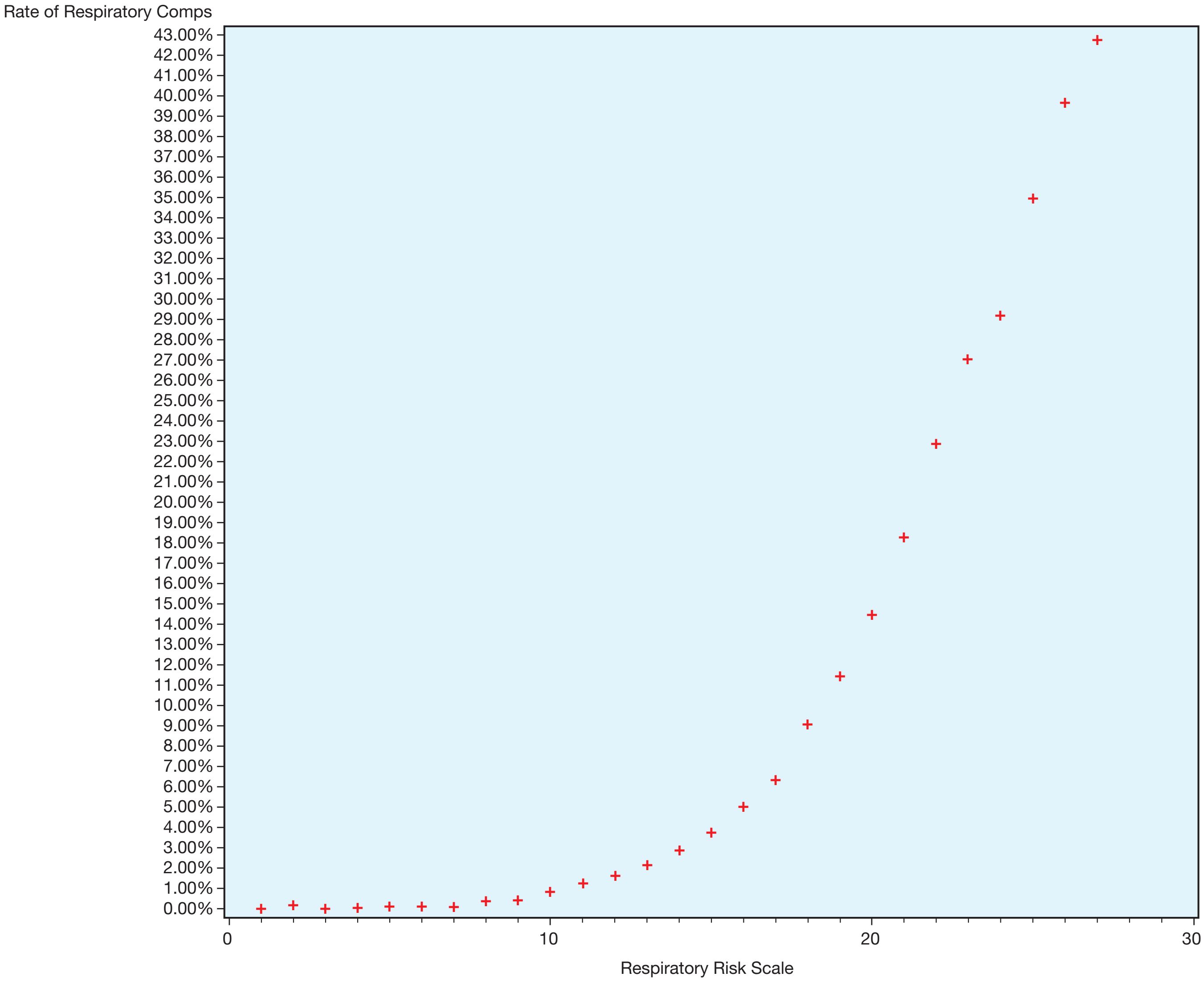

Figure 103-1 Johnson Respiratory Failure Risk Calculator. This graph plots the predicted risk of respiratory failure on the y axis against the respiratory risk score on the x axis. *(Reproduced with permission from Johnson RG, Arozullah AM, Neumayer L, et al. Multivariable predictors of postoperative respiratory failure after general and vascular surgery: results from the patient safety in surgery study. J Am Coll Surg. 2007;204(6):1188–1198.)*

utility of this finding.[4] A study of 1412 patients found that the combined incidence of prolonged postoperative mechanical ventilation (>48 h) and reintubation increased with increasing severity of COPD: 2.3% in patients without COPD compared to 0%, 13%, and 77% in patients with FEV_1 60% to 80%, 40% to 59%, and <40%, respectively. In contrast, the largest study to date utilizing a database of more than 11,000 patients did not detect an association between COPD severity and risk of prolonged postoperative mechanical ventilation even among patients with the most severe disease (FEV_1 <50%), although there was an increased risk of early mortality in this group.[15]

Data related to the use of preoperative pulmonary function parameters to stratify risk of postoperative respiratory failure in relation to noncardiothoracic surgical procedures are scant and conflicting. These data are summarized in a guideline statement issued by the American College of Physicians, which concludes that for noncardiothoracic surgery, "insufficient evidence supports preoperative spirometry as a tool to stratify risk."[16] The guideline authors caution that available studies do not define a spirometric threshold below which the risk for noncardiothoracic surgery is prohibitive.

MEASURES TO REDUCE RISK

A number of the factors associated with an increased risk of postoperative respiratory failure can potentially be addressed in order to mitigate the risk. In some cases, the surgical approach can be modified. For example, use of a transverse abdominal incision appears to carry less risk than a vertical midline incision. Cholecystectomy performed by laparoscopic technique is associated with significantly less compromise in postoperative FEV_1 and FVC and more rapid recovery of lung function compared with the conventional open approach.[17] For thoracic procedures, median sternotomy and muscle-sparing lateral thoracotomy are better tolerated than posterolateral thoracotomy. However, these approaches provide more limited access to the thorax than does the standard thoracotomy incision and they are generally inadequate for resection of the left lower lobe or for tumors involving the posterior chest wall, diaphragm, or superior sulcus. Additionally, removal of bulky tumors via the muscle-sparing approach may be problematic. VATS offers a minimally invasive alternative that is associated with a less severe decrement in respiratory muscle strength and lung function in the immediate perioperative period compared to thoracotomy.[18] A propensity-matched analysis of patients undergoing lobectomy by means of VATS versus open thoracotomy demonstrated a significantly lower rate of postoperative reintubation in the VATS cohort (1.4% vs. 3.1%).

Patients with COPD scheduled for surgery should undergo a preparatory pulmonary regimen intended to optimize lung function and minimize airway secretions. This regimen should include smoking cessation, institution or intensification of inhaled bronchodilator therapy, and use of oral antibiotics in the presence of purulent secretions or a "loose" cough. Patients should be instructed on the use of incentive spirometry or cough and deep breathing techniques prior to surgery. A short course of oral corticosteroids should be considered in patients who have a significant bronchospastic component to their disease. Other than the assurance of strict compliance with the regimen, there is no reason to believe that hospitalization is superior to outpatient preparation of the patient.

Smoking has been shown to be a risk factor for postoperative pulmonary complications in general and for prolonged ventilatory support in particular.[1] Smoking does not appear simply to be a surrogate marker of COPD; rather it poses risk that is independent of the magnitude of pulmonary impairment. Detrimental effects of smoking include bronchial irritation with resultant excessive airway secretions, impairment in mucociliary clearance, and elevation of carboxyhemoglobin levels with consequent impairment in oxygen uptake and tissue oxygen utilization. Observational studies suggest that preoperative smoking cessation is associated with a reduction in pulmonary complications, but these studies do not address the specific question of whether abstinence reduces the risk of respiratory failure.[19] A prospective, randomized trial investigated the impact of a preoperative smoking cessation program (counseling and nicotine replacement patch) on a number of postoperative complications including respiratory failure, following elective hip and knee replacement. Complete abstinence from smoking was achieved in 60% of the patients in the intervention arm compared with only 7% in the control arm. Despite this marked difference, only one patient in each group experienced postoperative respiratory failure. The obvious limitation of this trial relates to the choice of a surgical population at minimal risk for the complication under investigation. Pending additional studies, it would appear prudent to initiate smoking cessation measures in preparing patients for surgery, although the full benefit with respect to global reduction in pulmonary complications may require a minimum of 8 weeks of abstinence.[20]

IMPACT OF ANESTHESIA AND POSTOPERATIVE ANALGESIA ON PULMONARY FUNCTION

In the sections below, the impact of anesthesia and postoperative analgesia on pulmonary function is considered with regard to general anesthesia and neuraxial and postoperative analgesia.

General Anesthesia

Use of general anesthetic agents is associated with a number of well-characterized alterations in pulmonary mechanics, gas exchange, and respiratory drive.[21,22] In the controlled environment of the operating room, these physiologic derangements are clinically inconsequential and easily overcome by simple adjustments of the ventilator. However, lingering effects of general anesthesia after completion of surgery may impede efforts to extubate the patient or may precipitate respiratory failure in the recovery room.

Administration of general anesthesia, whether by the inhaled or intravenous route, results in an almost immediate loss of diaphragmatic and intercostal muscle tone, a cephalad shift of the diaphragm, and a decrease in the transverse thoracic diameter. These dimensional alterations in thoracic volume result in a 20% reduction in functional residual capacity (FRC) and in the development of compressive atelectasis. As demonstrated using computerized tomography (CT) during and after general anesthesia, patients develop crescent-shaped areas of atelectasis in dependent areas of lung within 10 min of induction.[23] Atelectatic areas constitute approximately 2% to 10% of total lung volume and disappear with the application of positive end-expiratory pressure (PEEP). Dependent atelectasis develops after administration of either inhalational or intravenous anesthetics. A notable exception is ketamine, a drug that is unique in its maintenance of respiratory muscle tone. The degree of atelectasis appears unaffected by whether the patient is breathing spontaneously or is mechanically ventilated.

Areas of dependent atelectasis perturb the normal balance of ventilation and perfusion in the lung. Persistent perfusion of nonventilated atelectatic areas results in an increase in the shunt fraction, which may approach 15%. The magnitude of shunt correlates directly with the volume of atelectatic lung and may be further magnified by impairment of hypoxic pulmonary vasoconstriction induced by certain inhalational anesthetics. Elderly patients, those who are obese, and patients with underlying COPD are most likely to develop clinically apparent hypoxemia in response to general anesthesia; the effect may persist into the early postoperative period.

The inhaled anesthetic agents in common usage are respiratory depressants that blunt the response to both hypoxemia and hypercapnia. These agents depress the ventilatory response to CO_2 in a dose-dependent fashion. They have a negligible effect on the hypercapnic response at the low concentrations encountered during emergence from anesthesia. In contrast, hypoxemic drive is markedly attenuated even at very low, subanesthetic concentrations of the volatile agents. As a result of deposition of these agents in muscle and fat, concentrations sufficient to depress hypoxic drive persist for several hours after termination of anesthesia. This can result in significant postoperative respiratory depression in patients with chronic hypercapnia who are dependent on hypoxic ventilatory drive to breathe.

Neuromuscular blocking agents are commonly administered intraoperatively along with general anesthesia. Although reversing agents are administered at the completion of surgery, between 33% and 64% of postsurgical patients arriving in the postanesthesia care unit have inadequate neuromuscular recovery as assessed by train-of-four monitoring.[24] Studies in normal volunteers have demonstrated that residual neuromuscular blockade is associated with marked attenuation of hypoxic ventilatory response, reduced upper airway dilator muscle activity, and impaired respiratory muscle strength.[24] Likely as a consequence of these effects, an association of residual neuromuscular blockade with postoperative hypoxemia and with upper airway obstruction has been shown.[24–26]

Neuraxial Anesthesia

It is common practice for those providing preoperative assessment of high-risk patients to recommend the use of neuraxial (i.e., spinal or epidural) anesthesia, predicated on the impression that this route of administration lessens the adverse impact of anesthesia on the respiratory system. Neuraxial anesthesia does possess a number of favorable physiologic features. In contrast to the effects of general anesthesia, neuraxial anesthesia preserves diaphragmatic innervation and function. External intercostal muscle paralysis is induced by thoracic levels of neuraxial anesthesia, but the level is generally two dermatomes below the sensory level because of the lesser sensitivity of motor neurons to the effects of the anesthetic agent. Hypoxic pulmonary vasoconstriction is unaffected by neuraxial anesthesia, and the ventilatory response to CO_2 is unimpaired; indeed, the CO_2 response may be heightened. A meta-analysis of trials comparing general to neuraxial anesthesia detected a significant reduction in 30-day mortality, venous thromboembolism, pneumonia, and respiratory depression.[27] Another meta-analysis restricted to patients undergoing hip fracture surgery also detected a reduction in 30-day mortality as well as a trend toward a lower incidence of postoperative hypoxemia associated with neuraxial anesthesia.[28] While these analyses suggest significant advantages associated with use of neuraxial anesthesia, they have been criticized because of the heterogeneous nature of the surgical populations and the use of older anesthetic techniques and older anesthetic agents.[29] Pending further studies, neuraxial anesthesia should not necessarily be viewed as the strategy of choice in more tenuous surgical candidates.

■ Postoperative Analgesia

Postoperative analgesia is an essential component of the care of the surgical patient. Analgesia is important not only in ensuring patient comfort, but also in mitigating the adverse effects of pain on respiratory function and airway clearance. Inadequate pain relief can lead to splinting and patient reluctance to cough and deep breathe; the end result is promotion of retained secretions, atelectasis, hypoxemia, and, possibly, pneumonia. For major surgical procedures, particularly those involving the chest and upper abdomen, administration of opiates via the parenteral or epidural route has become the analgesic method of choice.

The use of narcotic analgesia in the postoperative period is associated with a small but not insignificant risk of precipitating respiratory depression. The reported incidence of respiratory depression varies based on the criteria employed. A meta-analysis of published studies revealed an incidence of 0.3% defined by the need to administer naloxone, 3.3% defined by the presence of hypercapnia, and 17% defined by oxygen desaturation.[30] The risk may be slightly lower in association with the epidural as opposed to parenteral route of administration. When administered epidurally, hydrophilic narcotics (e.g., morphine) have a greater tendency than lipophilic compounds (e.g., fentanyl) to remain in the cerebrospinal fluid and to spread rostrally to the respiratory center located in the floor of the fourth ventricle. Elderly patients are particularly susceptible to the respiratory depressant effects of opiates, likely reflecting an impaired ability to metabolize these agents. Respiratory depression in the postoperative patient is most likely to occur during the initial 24 h following surgery. It is typically accompanied by a decreased level of consciousness and a slow respiratory rate. Treatment consists of administration of naloxone in 0.1- to 0.4-mg aliquots. Ventilation should be supported with a facemask and Ambu bag, reserving intubation for the failure of naloxone to swiftly rectify the problem.

Prospective, randomized trials examining pulmonary complications associated with epidural versus intravenous administration of perioperative analgesia following major abdominal surgical procedures have provided somewhat conflicting results. One study of 168 patients found no difference in rates of prolonged intubation or reintubation between groups receiving epidural versus intravenous postoperative analgesia.[31] A small trial involving 70 elderly patients reported no difference in duration of postoperative mechanical ventilation or major pulmonary complications (including reintubation).[32] In contrast, a larger study of 915 patients with at least one comorbidity defining them as "high-risk" surgical candidates found that epidural analgesia was associated with a significant reduction (23% with epidural vs. 30% with intravenous route) in postoperative respiratory failure, defined rather broadly as need for prolonged ventilation or reintubation or $Pa_{O_2} \leq 50$ mm Hg or $Pa_{CO_2} \geq 50$ mm Hg on room air.[33] Finally, a trial of more than 1000 patients demonstrated a significant reduction in postoperative respiratory failure (defined as the need for intubation and mechanical ventilation for >24 h postoperatively or reintubation) with use of epidural analgesia in the subset of patients undergoing aortic surgery but not those undergoing non-aortic abdominal surgery.[34]

IMPACT OF SURGERY ON POSTOPERATIVE PULMONARY FUNCTION

Surgery involving the upper abdomen and thorax results in a pronounced impairment in pulmonary function in the postoperative period. The impairment is more severe and prolonged than that due to administration of general anesthesia alone. Typically, upper abdominal and thoracic procedures are associated with a fall in lung volumes, development of atelectasis, and hypoxemia. These adverse effects commonly necessitate short-term administration of low-flow, supplemental oxygen, but when severe, or when accompanied by underlying lung disease, may precipitate respiratory failure.

■ Upper Abdominal Surgery

Within 24 h following upper abdominal surgery, vital capacity declines by 50%.[35] Although the vital capacity improves with time, marked impairment persists for as long as 7 days after the surgery. In contrast, vital capacity falls by only 25% following lower abdominal procedures; it returns to normal by the third postoperative day.[35] Underlying these profound changes after upper abdominal surgery is the development of diaphragmatic dysfunction, as reflected in a reduction in transdiaphragmatic pressure with tidal respirations and in a shift from abdominal to rib cage breathing.[36,37]

Two main theories have been proposed to explain the observed impairment in diaphragmatic function. One theory is that there is a primary alteration in diaphragmatic contractility induced by local irritation, inflammation, surgical trauma, or pain. This theory has been rendered improbable with the demonstration that external stimulation of the phrenic nerves produces normal peak transdiaphragmatic pressure in patients recovering from upper abdominal surgery.[36] In other words, when maximally stimulated the diaphragm functions in a normal fashion.

The alternative, and currently favored, theory proposes that diaphragmatic dysfunction results from diminished phrenic nerve output. The basis for the attenuation in neural drive remains a matter of speculation, although several putative pathways can be rationally eliminated. For example, general anesthesia is known to depress output from the central respiratory centers, as well as to inhibit synaptic transmission. However, as noted previously, the effects of general anesthesia on diaphragmatic tone are transient and modest. Additionally, the degree of dysfunction observed after upper abdominal procedures is not seen following general anesthesia for procedures on the lower abdomen and extremities. An inhibitory arc initiated by abdominal nociceptors for pain is unlikely, given that achievement of adequate pain control by epidural opiates fails to consistently improve pulmonary function or to normalize diaphragmatic performance. In contrast, the epidural administration of anesthetic agents such as bupivacaine does ameliorate diaphragmatic dysfunction following upper abdominal surgery. Since these agents produce sympathetic blockade in addition to pain control, it has been argued that visceral sympathetic afferents are responsible for providing an inhibitory signal that downgrades central neural drive and phrenic nerve activity, thereby leading to impaired diaphragmatic function. Supporting the notion of a reflex inhibitory arc mediated by visceral afferents is the demonstration in experimental animals that mechanical gall bladder stimulation strongly inhibits electromyographic activity and motion of the diaphragm.[38]

■ Cardiac Surgery

Although CABG—the most commonly performed cardiac surgical procedure—has been most intensively scrutinized with respect to its impact on the respiratory system, other related cardiac procedures (e.g., valve replacement) are likely to have similar effects. Lung volumes decrease by approximately 30% after CABG; the return to preoperative values may take several months.[39–41] Lung function may decline to a greater degree when internal mammary harvesting and grafting are employed.[39] Gas exchange is also impaired after CABG, as evident in the development of hypoxemia and significant widening of the alveolar–arterial oxygen gradient. In 125 patients who had daily room air arterial blood gas determinations prior to and following CABG, Pa_{O_2} fell from approximately 75 mm Hg preoperatively to a nadir of 55 mm Hg on postoperative day two.[42] The Pa_{O_2} improved but remained below preoperative values at the end of the first postoperative week. A similar pattern and magnitude of decline in oxygenation have been demonstrated in other studies, with the development of hypoxemia associated with an increase in calculated shunt fraction from 3% preoperatively to a peak of 19% postoperatively.[41] The increase in shunt fraction is readily accounted for on the basis of atelectasis, which is invariably present postoperatively, especially on the left side.

A number of factors have been implicated in the development of post-CABG pulmonary dysfunction and atelectasis. Alterations in chest wall compliance and motion may result from division of the sternum, harvesting of the internal mammary artery, and traumatic injury to the costovertebral joints and first rib induced by retraction. Intraoperative lung retraction may directly injure the left lower lobe, leading to contusion and atelectasis, and, perhaps, accounting for the predilection for radiographic infiltrates on the left side. An alternative explanation for post-CABG left lower lobe atelectasis is intraoperative injury to the left phrenic nerve and consequent diaphragmatic paralysis or paresis. The phrenic nerve is vulnerable to stretch and ischemic injury during sternal retraction, dissection of the left internal mammary artery, or prolonged distention of the pericardium. Additionally, thermal injury to the nerve may occur with the cardioplegic technique of instilling iced slush into the open pericardial sac. The actual incidence of phrenic nerve dysfunction after CABG is best defined in studies employing electrophysiologic techniques, which have documented evidence of phrenic nerve injury in 10% to 16% of patients.[43–45] This suggests that phrenic nerve injury accounts for only a minority of the observed cases of left lower lobe atelectasis.

Finally, cardiopulmonary bypass (CPB) may contribute to pulmonary impairment after cardiac surgery. The duration of CPB has been linked to the severity of postoperative atelectasis; whether this relationship is causal is unclear.[44] It has been hypothesized that the use of CPB leads to abnormal surfactant production—possibly due to ischemic, thermal, or toxic injury to the alveolar epithelium—predisposing to the development of atelectasis. More clearly established is the ability of the bypass pump to induce a capillary leak syndrome, marked by extravasation of fluid into the alveolar interstitium and, rarely, into the airspaces. This process is thought to result from exposure of blood to nonendothelial surfaces, resultant activation of neutrophils, complement, and other inflammatory cascades, and sequestration of neutrophils within the microvasculature. While this rarely may lead to full-blown ARDS (see "Acute Respiratory Distress Syndrome," below), the consequences are usually more subtle, manifesting as a widened arterial–alveolar oxygen gradient and diminished lung compliance. The recent introduction of "off-pump" CABG has permitted a greater appreciation of the adverse impact of CPB on postoperative lung function. For example, a large multicenter comparative analysis from the United Kingdom of CABG with or without CPB demonstrated significant reductions in the rates of prolonged mechanical ventilation (>24 h), reintubation/tracheostomy, and ARDS/pulmonary edema/pneumonia among the group that underwent off-pump CABG.[46]

■ Lung Resection

Unique to lung resection surgery is the immediate loss of lung function due to removal of lung parenchyma. The magnitude of the loss can be estimated reliably from preoperative quantitative lung scanning in conjunction with standard spirometry. The impact of lung resection on pulmonary function is further magnified in the perioperative period by other factors. For example, the standard posterolateral thoracotomy incision represents significant chest wall trauma, with rib retraction and resection, and transection of intercostal, latissimus dorsi, trapezius, and serratus anterior muscles. As a result, total respiratory compliance may fall by as much as 75%; work of breathing increases; and lung volumes decline dramatically, out of proportion to the surgical loss of functional lung. Following standard thoracotomy and lung resection (either lobectomy or wedge resection), FEV_1 and FVC fall to 25% of preoperative values at 1 h, and to 30% to 40% at 24 h.[47,48] When a more limited, muscle-sparing incision is used, the impact on pulmonary function is markedly attenuated.[48] Lung resection via VATS is also associated with less severe impairment in lung function.[18]

As with cardiac and upper abdominal surgery, atelectasis is frequently present after lung surgery and results in impaired oxygenation. Phrenic nerve activity remains normal and diaphragmatic function during tidal breathing is preserved, although maximal diaphragmatic strength may be reduced.

CAUSES OF POSTOPERATIVE RESPIRATORY FAILURE

The development of acute respiratory failure in the surgical patient should prompt a systematic assessment of the likely causes (Table 103-4). In approaching this life-threatening problem, one must consider the nature and magnitude of pre-existing pulmonary disease, type of surgery performed, drugs administered intra- and postoperatively, and predominant derangement in gas exchange (i.e., hypoxemia or hypercapnia). In conjunction with important information derived from the physical examination and chest radiograph, the analysis should readily identify factors responsible for or contributing to respiratory failure. The following discussion focuses on the more common or unique causes of postoperative respiratory failure in the surgical setting.

■ Atelectasis

Atelectasis is the most common pulmonary complication encountered in the surgical patient, particularly following thoracic and upper abdominal procedures. As discussed previously, anesthesia and surgical manipulation act in concert to produce regional atelectasis through incompletely defined mechanisms, including diaphragmatic dysfunction and diminished surfactant activity. The atelectasis is typically basilar and segmental in distribution,

TABLE 103-4 Causes of Postoperative Respiratory Failure

Factors extrinsic to the lung
- Depression of central respiratory drive (anesthetics, opioids, sedatives)
- Phrenic nerve injury/diaphragmatic dysfunction
- Obstructive sleep apnea

Factors intrinsic to the lung
- Atelectasis
- Pneumonia
- Aspiration of gastric contents
- Acute respiratory distress syndrome
- Volume overload/congestive heart failure
- Pulmonary embolism
- Bronchospasm/COPD

obscuring the hemidiaphragms radiographically. A distinct and less common cause of postoperative atelectasis is plugging of central airways by retained secretions. This problem is encountered in the surgical patient whose efforts to clear secretions are compromised by depressed consciousness, inadequate pain control, or a weak, ineffective cough. When situated in a mainstem bronchus, mucus plugs can result in collapse of an entire lung; more distal obstruction leads to lobar collapse. An abrupt termination of the proximal bronchial air shadow and the absence of air bronchograms within the atelectatic portion of lung are clues to the possible presence of mucus plugging.

While often clinically insignificant, postoperative atelectasis may lead to severe hypoxemia and respiratory distress. The magnitude of hypoxemia is dictated by the extent of atelectasis, the presence and severity of underlying lung disease, and the integrity of the hypoxemic pulmonary vasoconstrictive response. Impairment of hypoxemic pulmonary vasoconstriction by vasodilatory drugs, commonly administered to surgical patients for treatment of underlying hypertension or ischemic heart disease, prevents the compensatory diversion of blood flow away from nonventilated areas of lung and magnifies the shunt fraction.

Respiratory distress due to atelectasis usually evolves insidiously over the first several postoperative days. Supplemental oxygen requirements increase in association with worsening basilar infiltrates noted on the chest radiograph. The clinicoradiographic picture may be indistinguishable from that of pneumonia. While fever and leukocytosis suggest infection, these signs are common and nonspecific. When atelectasis is due to central airway occlusion by mucus plugs, hypoxemia and respiratory distress may develop quickly. A chest radiograph obtained immediately after the onset of symptoms may be surprisingly unrevealing if sufficient time has not passed to permit resorption of gas from the air spaces of the nonventilated lung. Careful examination of the patient, however, will reveal an absence of breath sounds over the involved lung, providing an important clue to the presence of central airway obstruction and obviating pursuit of other considerations, such as pulmonary embolism.

Treatment of respiratory failure due to atelectasis is directed toward the combined goals of adequate oxygenation and re-expansion of lung segments. Supplemental oxygen should be titrated to achieve an arterial oxyhemoglobin saturation of at least 90%. Refractory hypoxemia, severe respiratory distress, progressive hypercapnia, or inability of the patient to clear copious airway secretions should prompt immediate intubation and mechanical ventilatory support. This lifesaving intervention permits more efficient delivery of oxygen, secures access for suctioning of the airways, and facilitates performance of bronchoscopy should it be necessary. Moreover, the positive pressure and large tidal volumes delivered by the ventilator are often effective in rapidly re-expanding collapsed lung segments. In less dire circumstances, noninvasive ventilation may be effective, although it does not provide a conduit for airway suctioning.

Fiberoptic bronchoscopy is commonly employed in the treatment of serious atelectasis, but evidence suggests that it may be no more effective than standard chest physiotherapy. In the only randomized study directly comparing these strategies, immediate fiberoptic bronchoscopy did not result in more rapid or complete resolution of acute lobar atelectasis when compared with a regimen of deep breathing, coughing, suctioning of the intubated patient, aerosolized bronchodilator treatments, chest percussion, and postural drainage.[49] Resolution of atelectasis was dictated not by the treatment modality employed, but by radiographic evidence of central airway patency. In this regard, both chest physiotherapy and bronchoscopy were highly effective in the absence of an air bronchogram. In contrast, the presence of an air bronchogram, which indicates that the atelectasis is not due to proximal airway obstruction, was associated with minimal response to either modality. Based on this, standard respiratory therapy techniques applied to either the spontaneously or mechanically ventilated patient should be considered the mainstay of treatment for lobar atelectasis. Fiberoptic bronchoscopy should be reserved for those situations where chest physiotherapy is contraindicated (e.g., chest trauma, immobilized patient), poorly tolerated, or unsuccessful, or in the setting of life-threatening hypoxemia.

A number of other measures are commonly employed in the treatment of atelectasis. Judicious use of analgesia is an essential adjunct, permitting the patient to breathe deeply, cough forcefully, and comfortably participate in chest physiotherapy maneuvers. Care must be taken to avoid excessive sedation, which will offset the beneficial effects of pain control. Mucolytics, such as N-acetyl cysteine and hypertonic saline, are commonly administered in an effort to promote clearance of tenacious secretions; however, their efficacy in this setting has not been well documented. Nasotracheal suctioning of the nonintubated patient with a weak and ineffective cough can transiently clear secretions but can be associated with considerable patient discomfort.

■ Pneumonia

Pneumonia represents a significant cause of postoperative respiratory compromise and can precipitate acute respiratory failure, as well as complicate respiratory failure in the patient who is ventilator dependent for other reasons. The overall frequency of postoperative pneumonia approximates 2% in contemporary series but varies significantly depending on a number of identified risk factors. The type of surgery heavily influences the risk; in particular, the risk is greatest following aortic, thoracic, hepatopancreatobiliary, intestinal, and neurosurgical procedures.[50,51] Patient-specific risk factors that have been identified include advanced age, current or recent smoking, COPD, and dependent preoperative functional status.[50,51] Two risk calculators, employing a number of these patient-related and procedure-related factors, have been developed; the more recent and comprehensive calculator is available at *www.surgicalriskcalculator.com/postoperative-pneumonia-risk-calculator*.[50,51] Neither calculator has been externally validated.

Several additional risk factors are not addressed in the risk calculators cited above. The presence of a nasogastric tube and the use of gastric acid suppressive medications, commonly employed interventions in postoperative patients, have been cited as risk factors for nosocomial pneumonia in general.[52] The need for postoperative mechanical ventilatory support is also an important risk factor, as mechanically ventilated patients in general have a 6- to 21-fold increased risk of pneumonia compared with nonventilated patients.[53]

Diagnosis of postoperative pneumonia is based upon the presence of conventional clinical features—fever, leukocytosis, purulent sputum, and radiographic infiltrates. Alternative etiologies of radiographic infiltrates that must be considered in the postsurgical patient include atelectasis, pulmonary edema, infarction or hemorrhage due to pulmonary emboli, pulmonary contusion, and chemical pneumonitis. Antibiotic selection should be guided by results of sputum cultures in the nonintubated patient. In mechanically ventilated patients, semiquantitative cultures of tracheal aspirates are recommended over bronchoscopic sampling of the distal airways using either a sterile sheathed brush or bronchoalveolar lavage combined with quantitative cultures.[54] Procalcitonin levels are not recommended in the diagnosis of nosocomial or ventilator-associated pneumonia due to highly variable performance characteristics.[54] Further complicating reliance on this biomarker in the postsurgical setting is the observation that major surgical procedures as well as cardiopulmonary bypass can lead to elevation in procalcitonin levels.[55,56] While awaiting culture results (or in the absence of adequate samples), broad-spectrum antibiotics that include coverage of methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and other gram-negative bacilli should be initiated. The choice of empiric antibiotics should be informed by knowledge of the particular hospital's distribution of pathogens and their susceptibility patterns, as multidrug-resistant organisms are commonly encountered in surgical units.

■ Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome (ARDS) is defined by the constellation of hypoxemic respiratory failure, diffuse pulmonary infiltrates, and the absence of clinical evidence of elevated left atrial pressure (Chapter 141). The histologic hallmark of ARDS is diffuse alveolar damage, a widespread injury to the alveolar–capillary membrane that leads to increased capillary permeability and development of noncardiogenic pulmonary edema. ARDS represents the end result of a variety of insults that either involve the lung directly (e.g., aspiration of gastric contents) or trigger pulmonary inflammation as part of a systemic process (e.g., sepsis). Many of the risk factors associated with development of ARDS are commonly encountered in surgical patients. In decreasing order of risk, these include sepsis, massive blood transfusion, pulmonary contusion, aspiration of gastric contents, and multiple fractures.[57] Causes of ARDS of particular relevance to the surgical patient, and, in some cases, unique to this population, are described in greater detail below.

Aspiration of Gastric Contents

Aspiration of gastric contents can rapidly lead to widespread acute lung injury and is an important cause of ARDS in the surgical patient. It is the third leading cause of anesthesia-related deaths, accounting for 10% to 30% of fatal outcomes. Aspiration typically occurs when the mechanisms of glottic closure and cough, which normally protect the airway, are compromised. In the surgical patient, the period of maximal vulnerability for aspiration spans from the induction of general anesthesia to full return of consciousness postoperatively. A number of factors combine to enhance the risk of aspiration during this period. Most important is the blunting of consciousness that accompanies induction and administration of general anesthesia. Insufflation of air into the stomach during induction may cause gastric distention and promote vomiting. Vomiting may also be provoked by noxious stimulation of the posterior oropharynx during intubation or extubation. Reflux of gastric contents is facilitated by medication-induced relaxation of the lower esophageal sphincter, placement of the patient in a supine position, and manipulation of the bowel during abdominal procedures. At the completion of surgery, extubation is commonly performed at a time when the patient, while able to ventilate adequately, may not yet be capable of fully protecting the airway. Indeed, upper airway reflexes remain significantly impaired for up to 2 h after recovery from anesthesia, even at a time when mental alertness has returned. Moreover, translaryngeal intubation, even when brief, may cause residual glottic dysfunction for up to 8 h following removal of the tube. While the risk of aspiration diminishes beyond the immediate perioperative period, it remains a concern in the patient receiving narcotic analgesia, which may not only induce vomiting but also depress consciousness.

The risk of aspiration during the immediate perioperative period was delineated in a survey of more than 215,000 general anesthetic procedures performed at the Mayo Clinic.[58] Aspiration was defined as the presence of bilious or particulate matter in the airways or the development of a new infiltrate on the immediate postoperative chest radiograph. The overall incidence of aspiration was only 0.03%, but the incidence was nearly fourfold higher (0.11%) in the setting of emergency surgery. In addition to the use of general anesthesia, other predisposing factors were present in more than half of the patients who aspirated. These included gastrointestinal obstruction, swallowing dysfunction, altered sensorium, previous esophageal surgery, and a recent meal. The majority of events occurred during laryngoscopy (in preparation for insertion of the endotracheal tube) and during tracheal extubation. Of patients who aspirated, 20% required postoperative mechanical ventilation in excess of 6 h; 5% died as a direct result of this complication. The use of laryngeal mask airway devices does not appear to be associated with an increased risk of aspiration despite the fact that these devices do not isolate the larynx from the gastrointestinal tract.[59]

Acidic gastric contents introduced into the airways are rapidly disseminated throughout the bronchial tree and lung parenchyma, producing an almost instantaneous chemical burn. In addition, acid aspiration triggers a more delayed inflammatory response, with release of inflammatory cytokines and recruitment of neutrophils into the lung. The result is injury to the alveolar–capillary membrane, with flooding of the interstitium and airspaces by proteinaceous edema fluid. Surfactant levels drop precipitously due to both direct acid denaturation and diminished production, leading to alveolar instability and atelectasis. The magnitude of lung injury is directly related to the pH and volume of aspirated material. Initial studies in animals suggested that a pH of less than 2.5 and a volume in excess of 0.4 mL/kg are critical threshold values for the induction of lung injury.[60] While these values are now often quoted in the literature, their validity has been challenged by more recent studies demonstrating significant injury in association with lower volumes and higher pH. In particular, aspiration of bile is capable of inducing widespread injury even at a pH as high as 7.19. The presence of large food particles may further exacerbate the problem by causing airway obstruction and atelectasis. Notably, infection does not normally play a significant role in the initial lung injury from aspiration of acidic gastric contents, as the low pH serves to maintain relative sterility of the inoculum. However, gastric colonization with bacteria can occur in patients maintained on acid suppressive agents, those receiving enteral feeds, and those with gastroparesis or small bowel obstruction.

The diagnosis of aspiration is most firmly established in the setting of witnessed vomiting or recovery of gastric contents from the airways. More often, the diagnosis is suspected circumstantially in a patient with risk factors and a compatible clinicoradiographic picture. Massive aspiration presents with fever, tachypnea, and diffuse rales developing within several hours of the event. Wheezing is appreciated in approximately one-third of patients and may be due either to obstruction of airways by particulate matter or, more commonly, to reflex bronchospasm. Hypoxemia is universally present with massive aspiration and is sufficiently severe in the majority of patients to mandate use of mechanical ventilation. The initial presence of apnea or shock is particularly ominous and portends a high risk of subsequent death. Initial radiographic patterns vary, depending upon the volume, causticity, and distribution of the aspirated material. However, three general patterns have been described: (1) extensive bilateral consolidation resembling diffuse pulmonary edema; (2) widespread, but discrete, patchy infiltrates involving dependent areas of lung; and (3) focal consolidation usually localized to one or both lung bases.

The clinical course following massive aspiration is variable, but it typically diverges along one of several pathways. A minority of patients follow a fulminant course leading quickly to hypoxemic respiratory failure. More commonly, patients demonstrate progressive radiographic and clinical improvement over the first several days. Although most of these patients will go on to full recovery, a subset demonstrates secondary deterioration due to the development of nosocomial pneumonia. The overall mortality rate associated with massive aspiration is approximately 30% and exceeds 50% in those patients with initial shock or apnea, secondary pneumonia, or ARDS.

The treatment of respiratory failure secondary to aspiration is supportive and includes mechanical ventilatory strategies common to other forms of ARDS (Chapter 148). Bronchoscopy is indicated only when large airway obstruction by particulate matter is suspected on the basis of a localized wheeze or lobar atelectasis. Because acid is disseminated and endogenously neutralized within seconds, large-volume bronchoalveolar lavage is ineffective in attenuating the degree of injury and is not recommended. Studies of the administration of systemic corticosteroids in the treatment of aspiration pneumonitis have been inconclusive and do not currently justify their use. Similarly, use of prophylactic antibiotics is generally discouraged in the absence of supportive data and because of fear that this practice will preferentially select more highly resistant organisms. However, up to 40% of patients will develop a superimposed bacterial pneumonia within several days of the aspiration event, often heralded by a new fever, new or progressive infiltrates, and purulent sputum. Broad-spectrum antibiotic therapy is indicated at that time.

Postpneumonectomy Pulmonary Edema

Postpneumonectomy pulmonary edema describes the development of diffuse pulmonary edema in the remaining lung, in the absence of identifiable causes. While some authors apply this term exclusively in the setting of pneumonectomy, others have reported similar cases following lobectomy. Demonstration of normal pulmonary artery occlusion pressures and of protein-rich edema fluid in a small number of patients suggests that an increase in vascular permeability rather than hydrostatic pressure underlies the edema formation.[61] However, the exact mechanism responsible for lung injury remains a matter of conjecture. Mechanisms that have been advanced include hyperinflation and volutrauma resulting from single lung ventilation, endothelial injury due to hyperperfusion of the remaining lung, disruption of lymphatic drainage, and ischemia-reperfusion injury.[62]

The incidence of postpneumonectomy pulmonary edema ranges between 4% and 7%, in part reflecting variable definitions.[62] For unclear reasons, the complication is encountered more frequently following right pneumonectomy. The majority of cases develop by postoperative day 3. The observed mortality rate is in the range of 50% to 100%. Treatment is supportive, centering on lung-protective ventilator strategies. A nonrandomized trial suggested that the intraoperative administration of solumedrol was associated with a decreased incidence of postpneumonectomy pulmonary edema, but this is not considered standard of care.[63]

Cardiopulmonary Bypass

ARDS develops immediately following use of cardiopulmonary bypass (CPB) in approximately 1% of cases.[64] While factors unrelated to the use of CPB may be at play, there is evidence from both animal models and clinical studies to suggest that CPB activates a number of inflammatory pathways that could lead to acute lung injury. Activation of these pathways is thought to result in part from contact of neutrophils and platelets with the artificial surface of the bypass circuit. Additionally, during CPB, lung perfusion via the pulmonary circulation is interrupted, resulting in pulmonary parenchymal ischemia. When CPB is terminated, the resulting restoration of blood flow may produce an ischemia–reperfusion injury that triggers an inflammatory cascade.

The central role played by neutrophils in causing acute lung injury following CPB is supported by several lines of evidence: (1) bronchoalveolar lavage fluid from patients undergoing CPB contains an increased number of neutrophils; (2) plasma levels of neutrophil elastase and myeloperoxidase are increased; and (3) inhibition of neutrophil activation with pentoxifylline as well as neutrophil depletion attenuate the degree of pulmonary dysfunction.[64] Additionally, an increased expression of cell surface adhesion molecules has been demonstrated, which may promote neutrophil binding to pulmonary endothelium and release of proteolytic enzymes and reactive oxygen species. A number of other inflammatory mediators are released in association with CPB, including complement, proinflammatory cytokines, and prostaglandins.[64,65]

Demonstration of higher perioperative blood levels of interleukin 8 and neutrophil elastase when CABG is performed with CPB versus off-pump further supports the proinflammatory nature of CPB and helps to distinguish this from the effects of surgery itself.[66] Despite this, however, it is not clear that off-pump surgery mitigates the degree of perioperative pulmonary dysfunction. Perioperative oxygenation was higher in the off-pump cohort in one randomized trial,[67] but no difference was detected in another.[68]

Amiodarone

Amiodarone-induced pulmonary toxicity usually presents as a subacute illness characterized by cough, dyspnea, fever, and patchy pulmonary infiltrates. Rarely, the use of amiodarone has been linked to the development of ARDS immediately following cardiac and thoracic surgery. In most of the reported cases, amiodarone was administered preoperatively for varying periods of time for control of arrhythmias.[69] The majority of patients had no evidence prior to surgery of the more indolent form of amiodarone pulmonary toxicity. Development of ARDS also has been described in patients whose only exposure to amiodarone occurred in the postoperative period, when the drug was initiated as prophylaxis or treatment for atrial arrhythmias. In one report, postoperative ARDS developed in 11% of patients receiving amiodarone and in only 1.8% of untreated patients.[70] Notably, multiple retrospective cohort studies, prospective, randomized trials. and meta-analyses examining the use of prophylactic amiodarone in prevention of atrial fibrillation following thoracic and cardiac procedures did not detect an increased incidence of severe pulmonary complications in the treatment groups.[71–75] It has been postulated that the rarity of amiodarone-induced ARDS after the early reports in the 1990s may be due to lower cumulative doses of intravenous amiodarone and preferential use of oral administration subsequently employed in clinical practice.[76] Acknowledging the overall safety of the drug, professional society guidelines currently endorse the use of amiodarone in prevention of atrial fibrillation in high-risk thoracic and cardiac surgical patients.[76,77]

Specific perioperative factors that act in concert with amiodarone to produce acute lung injury remain to be defined. Some authors have suggested that exposure to high levels of supplemental oxygen may be a contributing factor. The diagnosis rests on exclusion of other causes rather than on specific diagnostic tests or histology. In addition to stopping the drug, high doses of corticosteroids are often given, but support for this is anecdotal at best.

Transfusion-related Acute Lung Injury

The transfusion of blood and blood products has been linked to the development of acute lung injury in two ways. An association between massive blood transfusion (>15 units/24 h) and ARDS has been noted in epidemiologic studies, but it remains unclear whether this link is truly causal or is indirect and reflective only of the critically ill nature of the patient requiring such massive transfusion support.[57] Acute lung injury can also be associated with the transfusion of a single unit of blood or blood components, an entity known as *transfusion-related acute lung injury (TRALI)*. TRALI is operationally defined as the acute development of hypoxemia and bilateral radiographic opacities during or within 6 h of a completed transfusion, in the absence of evidence of circulatory overload or alternative etiologies of acute lung injury.[78]

The mechanism underlying TRALI was initially determined to involve passive infusion via transfused blood products of donor-derived antibodies directed against recipient leukocytes. These antibodies are typically contained in blood products obtained from multiparous female donors, whose exposure to foreign human leukocyte antigen (HLA) or neutrophil antigens occurred during prior pregnancies. When transfused into a recipient with cognate antigens, these antibodies result in leukoagglutination and activation of recipient granulocytes or monocytes within the pulmonary microvasculature, triggering increased capillary permeability and the development of noncardiogenic pulmonary edema. For unclear reasons, anti–HLA class II antibodies appear to pose a greater risk than class I.[79] Less commonly, the leukoagglutinating process can be triggered by an interaction between recipient anti-HLA or antineutrophil antibodies and donor-derived leukocytes contained in the transfused blood products.[80]

While ample clinical and animal model evidence exists to support the antibody hypothesis,[78,81] several lines of evidence suggest that other factors also may be involved. First, not all patients who receive blood products containing recipient-specific anti-HLA or antineutrophil antibodies develop TRALI. Second, in a significant minority of cases, leukoagglutinating antibodies cannot be detected in either the donor or recipient. This has prompted the proposal of an alternative “two hit” mechanism, whereby an initial event is required to prime recipient neutrophils and a second event leads to activation of primed neutrophils.[78,81] Priming events that have been associated with an increased risk of TRALI include recent surgery, CPB, active infection, sepsis, and chronic alcohol abuse.[79,82,83] The second event involves transfusion of substances that trigger neutrophil activation: either antileukocyte antibodies or biologically active lipids resulting from breakdown of stored blood products.

Up to half of TRALI cases are detected in surgical patients in the immediate postoperative period, a fact that likely reflects the frequent need for transfusions in this setting and the close monitoring of cardiopulmonary function in the postanesthesia recovery area.[84–86] Cardiac surgery patients constitute the largest group, possibly due to the priming effect of CPB.[83,86] In one study of 668 patients undergoing cardiac surgery, TRALI was documented in 16 (2.4%).[83] Although virtually all blood products have been implicated, the risk of TRALI is highest in association with fresh frozen plasma and platelets.[80,81]

Clinically, TRALI is characterized by the abrupt onset of dyspnea and hypoxemia during or shortly following transfusion of blood products. Accompanying features include fever, chills, and hypotension. Respiratory distress and hypoxemia are of sufficient magnitude to require mechanical ventilatory support in up to 45% of cases.[80] The differential diagnosis includes volume overload, congestive heart failure, myocardial infarction, and aspiration. Although many cases are self-limited, with clearing of infiltrates and improved oxygenation over several days, mortality rates of 5% to 20% have been reported.[80,83]

When TRALI is suspected, the blood bank should be notified. Ideally, this should trigger testing of all donor specimens (typically retained by the blood bank) for the presence of anti-HLA and antineutrophil antibodies. However, the expense and time required often prevent blood banks from performing these studies.

Acute Exacerbations of Pulmonary Fibrosis

Patients with idiopathic pulmonary fibrosis (IPF) can experience sudden and dramatic respiratory decompensation in the absence of identifiable precipitants. Referred to as an exacerbation of IPF, this phenomenon is characterized by acutely worsening hypoxemia in association with new bilateral ground glass opacities or consolidation on chest CT not fully explained by cardiac failure or volume overload.[87] The histologic hallmark is diffuse alveolar damage, superimposed on underlying usual interstitial pneumonia.[88]

The immediate postoperative period following lung surgery is one of the settings in which acute exacerbations of IPF have been reported to occur.[89–91] Most cases have occurred following either lung resection for lung cancer or lung biopsy for diagnosis of IPF. The reported incidence ranges from 2% to 7%. The mechanism by which surgical manipulation of the lung could cause an exacerbation is currently speculative. Mortality associated with postoperative acute exacerbations is high, ranging from 50% to 100%. Steroids and other immunosuppressive agents are commonly initiated, but there is no compelling evidence for efficacy.[87,92,93] Lung transplantation may be an option in select cases.

■ Phrenic Nerve Injury and Diaphragmatic Dysfunction

Phrenic nerve injury is a well-described complication of CABG. In the past, this complication arose chiefly from the use of iced saline slush placed in the pericardium for topical cooling of the heart. Thermal injury causes both demyelination and axonal degeneration of the nerve, with slowing of conduction and impaired activation of the diaphragm. The use of topical cooling techniques has fallen out of favor largely because of this potential complication. However, the phrenic nerves can also be injured by traction, ischemia, use of diathermy, or transection during sternal retraction and harvesting of the internal mammary arteries. Unilateral phrenic nerve injury, typically involving the left phrenic, has been reported in approximately10% of patients undergoing CABG.[45,94] Bilateral phrenic nerve injury was reported to occur in 1% to 3% of cases in the era of widespread topical cardioplegia usage but is now a rare event. Phrenic nerve injury is not restricted to CABG but is also seen in association with other cardiac procedures, thoracic surgery, neck surgery, and liver transplantation.

Although typically inconsequential in the otherwise healthy patient, unilateral diaphragmatic paralysis can lead to significant respiratory compromise in patients with underlying chronic lung disease or those who are otherwise marginal. In patients with COPD, for example, the duration of postoperative mechanical ventilation and the rate of reintubation are higher for those with versus without unilateral phrenic nerve injury following CABG.[95] Bilateral diaphragmatic paralysis results in marked impairment in pulmonary function and frequently leads to respiratory failure. In the proper setting, phrenic nerve injury should be suspected when attempts to wean a postoperative patient from mechanical ventilation result in progressive hypercapnia or atelectasis. The spontaneously breathing patient will often complain of orthopnea, which may be misinterpreted by the unsuspecting clinician as indicative of congestive heart failure. However, orthopnea is actually due to further impairment in diaphragmatic function resulting from loss of gravitational assistance in the supine position. The detection of inspiratory thoracoabdominal paradox—an inward movement of the abdominal wall with simultaneous expansion of the thorax—is an important bedside clue to the presence of bilateral diaphragmatic paralysis and is best evoked in the supine position. The chest radiograph also may hold important clues, demonstrating either unilateral or bilateral elevation of the diaphragms and accompanying basilar atelectasis. However, these findings are not specific for phrenic nerve injury and may also be due to splinting or abdominal distention. A reduced maximum inspiratory pressure recorded at the mouth is another sensitive but nonspecific indication of significant diaphragmatic dysfunction.

Unilateral diaphragmatic paralysis can be readily diagnosed by fluoroscopic inspection, which reveals paradoxical upward movement of the affected hemidiaphragm with a maximal inspiratory effort (“sniff”). The situation is more problematic with bilateral diaphragmatic dysfunction. In this setting, patients often assume an altered breathing pattern marked by active contraction of the abdominal muscles during expiration, forcing the flaccid hemidiaphragms upward. With subsequent inspiration, the abdominal muscles relax and the hemidiaphragms descend briefly, potentially creating the false impression that they are functional. Because of this, fluoroscopy may not be confirmatory in these patients. Ultrasound has emerged as a simple bedside test for assessing diaphragmatic function. Thickening of the diaphragm with inspiration reflects diaphragmatic shortening, and failure to observe this sign is indicative of diaphragmatic paralysis. Ultrasound can thus be used to diagnose both unilateral and bilateral paralysis and can be performed serially to assess for recovery of function.[96]

The gold standard for confirmation of phrenic nerve injury is electrophysiologic testing, although even this methodology is occasionally flawed. The phrenic nerve is stimulated transcutaneously in the neck, and the diaphragmatic electromyogram (EMG) is recorded by surface electrodes placed in the seventh intercostal space at the costochondral junction. Demonstration of a prolonged latency between nerve stimulation and diaphragmatic action potential confirms a diagnosis of demyelinating injury. It is more difficult to interpret the significance of diminished amplitude or complete absence of the surface recording of the diaphragmatic EMG. This finding could represent either phrenic nerve injury/transection or failure to properly localize the diaphragm, which is typically shifted caudally in the postoperative patient and, therefore, away from the surface electrodes. Direct puncture of the diaphragm with a recording electrode may be employed to clarify this issue, but the technique requires a high level of expertise and carries a risk of pneumothorax.

Nontraumatic causes of phrenic nerve injury and diaphragmatic dysfunction can also lead to prolonged respiratory failure and delayed weaning in the surgical patient. Phrenic neuropathy can be a component of a more generalized polyneuropathy of critical illness, commonly encountered in the wake of an episode of severe sepsis or systemic inflammatory response syndrome. A critical illness myopathy affecting the diaphragms and other muscles of respiration can be encountered under the same circumstances. Finally, diaphragmatic dysfunction can arise as a component of a myopathy induced by the concurrent use of high-dose systemic corticosteroids and neuromuscular blocking agents.

Patients with diaphragmatic dysfunction are generally well suited for noninvasive positive pressure ventilatory support if they are awake and able to effectively handle respiratory secretions. Tracheostomy is indicated for patients with ineffective cough and those who cannot be weaned from conventional mechanical ventilation. The prognosis for patients with thermal or traction injury of the phrenic nerve is favorable; recovery is typically complete, but often protracted. In symptomatic patients with unilateral diaphragmatic paralysis due to transection of the phrenic nerve, surgical placation of the flaccid hemidiaphragm may lead to improved pulmonary function and successful liberation from mechanical ventilation.[97]

■ Pulmonary Embolism

An increased risk of pulmonary embolism (PE) accompanies a number of surgical procedures, including upper abdominal, neurosurgical, cardiac, major urologic, and lower extremity orthopedic procedures. Other, nonsurgical risk factors that predispose the patient to PE may also be present, including obesity, immobility, and underlying malignancy. Although alterations in gas exchange typify pulmonary embolism, frank hypoxemic respiratory failure is relatively uncommon and suggests massive clot burden. Lesser degrees of clot burden may produce equally devastating physiologic impairment in patients with underlying pulmonary disease.

While anticoagulation with heparin forms the mainstay of therapy for the otherwise stable patient, the presence of life-threatening hypoxemia and/or hemodynamic instability should prompt consideration of alternative or additional interventions. The use of systemic thrombolytic therapy in the postoperative period is limited by the risk of precipitating bleeding at the site of recent surgery. This risk appears to fall to an acceptable level beyond the seventh postoperative day; the exception is intracranial surgery, which contraindicates use of lytic agents for at least 2 months. Several catheter-directed options, including infusion of low-dose thrombolytics and suction embolectomy, as well as surgical embolectomy are alternative considerations in the deteriorating patient for whom systemic thrombolytics are either contraindicated or unsuccessful.[98]

■ Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is highly prevalent within surgical populations, affecting approximately 25% of adults undergoing elective general surgical procedures,[99] greater than 30% of neurosurgical patients,[100] and greater than 70% of morbidly obese patients undergoing bariatric surgery.[101] It is characterized by repetitive upper airway obstruction during sleep, resulting in arterial desaturation, hypercapnia, and arrhythmias. The perioperative period is a particularly precarious time for patients with this disorder. Because of alterations in oropharyngeal anatomy that commonly accompany obesity and OSA, orotracheal intubation at the time of induction may be difficult. The use of anesthetics, opioids, and sedatives diminishes the activity of the upper airway dilator musculature and concurrently dampens respiratory arousal mechanisms that can terminate obstructive apneas. These effects lead to an increase in the frequency and duration of obstructive apneas that, in turn, can place the surgical patient at significant risk for serious respiratory complications. A meta-analysis of 13 studies involving almost 4000 patients demonstrated that the incidence of postoperative respiratory failure was significantly higher among patients with OSA compared to those without.[100] Analysis of a national database of approximately 6 million surgical patients similarly demonstrated that OSA increased the risk of postoperative intubation and mechanical ventilation fivefold after orthopedic procedures and twofold after general surgical procedures.[102]

As many as 80% of patients with OSA are undiagnosed at the time of surgery.[99] Identification of high-risk candidates with OSA prior to surgery is thus an essential strategy in minimizing the adverse impact of OSA on postoperative outcomes. Several easily administered screening tools have been developed and validated that can be incorporated into the preoperative assessment of surgical candidates. For example, the STOP-Bang tool uses a self-administered four-item questionnaire in conjunction with assessment of four patient characteristics (Table 103-5). It has positive predictive and negative predictive values of 52% and 90%, respectively,

TABLE 103-5 STOP-Bang Scoring Model for Preoperative Assessment of OSA Risk

Snoring: Do you snore loudly?
Tired: Do you often feel tired, fatigued, or sleepy during daytime?
Observed: Has anyone observed you stop breathing during your sleep?
Blood **P**ressure: Do you have or are you being treated for high blood pressure?
BMI: BMI more than 35?
Age: Age over 50 years?
Neck Circumference: Neck circumference greater than 40 cm?
Gender: Male?

High risk of OSA: answering yes to three or more items. Low risk of OSA: answering yes to less than three items.

Modified with permission from Chung F, Elsaid H. Screening for obstructive sleep apnea before surgery: why is it important? Curr Opin Anaesthesiol. 2009;22(3):405–411.

in identifying surgical candidates with moderate to severe OSA (apnea–hypopnea index >15).[103]

A number of measures can be employed in an attempt to reduce the risk of serious pulmonary complications in surgical patients with OSA.[101] The anesthesiologist should be made aware of the potential for a difficult intubation, and emergency airway devices should be readily available. Ideally, shorter-acting anesthetic agents should be employed. Intraoperative use of opioids should be minimized; if deemed necessary, use of ultra-short-acting agents such as remifentanil is preferable. Extubation following completion of surgery should be carried out only after the patient is fully awake and residual effects of intraoperative neuromuscular blockade have fully dissipated. Application of continuous positive airway pressure (CPAP) immediately after extubation should be considered, particularly if apneic episodes are noted in the recovery area. Non-opioid analgesics should be used in an attempt to avoid or minimize use of opioids in the postoperative period.

USE OF NONINVASIVE POSITIVE PRESSURE VENTILATION AND HIGH-FLOW NASAL OXYGEN IN THE POSTOPERATIVE SETTING

For patients with respiratory failure refractory to conservative measures, endotracheal intubation is the standard means to facilitate mechanical ventilatory support. However, endotracheal intubation is associated with a number of untoward effects including airway trauma, increased risk of nosocomial pneumonia and sinusitis, and the frequent need for heavy sedation that, while addressing patient discomfort, often prolongs the process of weaning and extubation. The desire to avoid endotracheal intubation has led to the use of noninvasive positive-pressure ventilation (NIPPV), employing a tight-fitting nasal or full face mask as the interface between patient and ventilator. NIPPV has been demonstrated to reduce the risk of intubation among patients with postoperative hypoxemic respiratory failure following lung resection surgery[104] and abdominal surgery.[105] It has also been shown to reduce the risk of reintubation when used preemptively following extubation in various surgical populations.[106,107] While there has been a concern about using NIPPV following esophageal or gastric surgery, experience suggests that this can be accomplished safely.[108] In this setting, care must be taken to avoid gastric distention, using a nasogastric tube for decompression if necessary, and the magnitude of positive-pressure ventilation employed should be limited to <20 cm H_2O. Since NIPPV often requires a period of acclimation, it should not be used in unstable patients. Other contraindications to its use include depressed or agitated mental status, inability to protect the airway, and compromised airway clearance due to copious secretions or weak cough.

More recently, high-flow nasal oxygen has emerged as an alternative means of supporting patients with hypoxemic respiratory failure. A large clinical trial involving 830 cardiothoracic surgical patients who had developed acute respiratory failure or were deemed to be at risk for respiratory failure following extubation randomized patients to receive either high-flow nasal oxygen or BiPAP.[109] Rates of treatment failure (intubation, switch to the alternative treatment arm, or study-treatment discontinuation) were equivalent for the two groups, supporting the use of high-flow nasal oxygen in the postoperative setting in this particular patient population. Prophylactic use of high-flow nasal oxygen immediately after extubation was also found to decrease the risk of reintubation and escalation of respiratory support compared with conventional oxygen therapy following cardiothoracic surgery[110] but not following abdominal surgery.[111]

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CHAPTER 104

Thoracic Trauma

Seth A. Bellister
Bradley M. Dennis

INTRODUCTION

Injury to the chest and its contents occurs in nearly a quarter of all trauma patients.[1] Thoracic trauma constitutes a diverse spectrum of disease that can be rapidly progressive and that can have both immediate life-threatening consequences and the potential for long-term sequelae. This chapter addresses management of specific injuries to the thoracic contents and chest wall, many of which require intervention immediately or within the first few hours of hospitalization.

Anatomy

Due to the size of the chest, it is susceptible to injuries from both blunt and penetrating mechanisms. While lethal injuries can occur anywhere within the chest, the most concerning site of injury is classically described as "the box." The box is an area circumscribed by vertical lines drawn down from the mid-clavicle at the level of the sternal notch to the costal margin and then across. This external landmark overlies the cardiac silhouette and the great vessels of the thorax including the pulmonary hila bilaterally. However, this anatomic view oversimplifies the problem. The box must be considered as a three-dimensional structure wherein injuries to the posterior and lateral thorax can jeopardize vital structures.

It is important to emphasize that injuries outside the box also can be life threatening, both acutely and in a more chronic setting. Most specifically, tension pneumothorax can present acutely after injury well outside the box. It must not be ignored that injuries to the bony skeleton of the chest may be acutely life threatening but also may lead to long-term sequelae that compromises quality of life.

Initial Evaluation

The initial workup of all trauma patients proceeds in an organized algorithmic fashion in order to maximize early identification of life-threatening injuries and prioritize their management while minimizing missed injuries of less morbid consequence. At the time of presentation, injuries to the thorax often cause a significant amount of stress to the prehospital provider and emergency department staff. It is incumbent that providers do not develop tunnel vision and lose sight of the basic strategies of trauma management. In patients presenting with cardiovascular compromise, early definitive management of the airway should be undertaken regardless of suspected injuries. In the acute setting, with minimal history, airway management should occur with standard rapid sequence intubation practices.

Once the airway has been secured, prompt evaluation of breath sounds may simultaneously confirm proper placement of the endotracheal tube, as well as indicate life-threatening causes of cardiovascular collapse. Chest x-ray (CXR) may be ordered at this time but not performed until breath sounds have been evaluated, intravenous access secured, and resuscitation initiated. Interventions on the airway, breathing, and circulation should preclude all imaging.

Pleural Complications

Two imminently life-threatening pleural complications that require immediate intervention are tension pneumothorax and massive hemothorax. Non-life-threatening pneumothoraces and hemothoraces also are commonly encountered in the trauma patient and often require intervention, albeit less urgently.

Tension Pneumothorax

Absent breath sounds in a traumatically injured patient with hemodynamic instability should prompt immediate suspicion of tension pneumothorax. Other symptoms and signs of tension pneumothorax include chest pain, air hunger, tracheal deviation away from the side of injury, tachypnea, jugular venous distention, and hemodynamic instability. Hemodynamic instability typically manifests with tachycardia and hypotension due to decreased venous return secondary to the increase in intrathoracic pressure created by the pneumothorax. Diagnosis of tension pneumothorax should be made based on clinical findings rather than waiting for confirmation with radiographic studies.

Tension pneumothorax requires immediate and definitive treatment. Needle thoracostomy may be considered strictly as a temporizing measure and involves the use of a 14-gauge needle 5 inches in length inserted into the second intercostal space at the midclavicular line.[2] The needle may also be placed in the anterior axillary line in the fourth or fifth intercostal space. Needle thoracostomy is associated with a failure rate as high as 40%, most frequently due to failure to access the pleural cavity.[3] This has led many to question the usefulness of needle thoracostomy.[4] Failure of needle thoracostomy is more common in women than men, and the likelihood of a failed procedure may be increased by poor patient positioning.

Definitive management of tension pneumothorax is best achieved with a tube thoracostomy. Tube thoracostomy can be performed through an open surgical approach or percutaneously. The increased use of point-of-care ultrasound has allowed for the successful and reproducible identification of pneumothorax and has facilitated the safe and accurate performance of bedside tube thoracostomy. Several systems are available for percutaneous thoracostomy. The most common system is the Wayne catheter. The Wayne catheter uses standard Seldinger technique with step-up dilation to allow easy placement of a 14F pigtail catheter. Upon placement of the chest tube, a return of hemodynamic stability and breath sounds to the affected hemithorax confirm that the tension pneumothorax has been adequately addressed. Note should be made of the magnitude of any ongoing air leak and any associated bleeding.

Simple Pneumothorax

Not all pneumothoraces require emergent intervention. Simple pneumothorax presents in a hemodynamically stable patient with ipsilateral chest pain and/or shortness of breath. Some patients will have accompanying hypoxia and tachypnea. However, there is a population of patients that will present asymptomatically. Most simple pneumothoraces can be identified on chest x-ray. However, in 15% to 20% of cases, pneumothorax is not apparent on chest x-ray and only seen on CT scan.[5–7] Often, simple pneumothoraces can be managed without intervention. Indeed, regardless of blunt or penetrating mechanism, one study suggested that most pneumothoraces measuring less than 35 mm on CT scan (the radial distance between the parietal and visceral pleura in a line perpendicular to the chest wall on axial imaging) can be safely observed.[8]

Hemothorax

Large-volume blood loss into the pleural space is typically classified as more than 1.5 L immediately draining into the chest tube reservoir after tube thoracostomy. This should prompt immediate surgical exploration.[9] Additionally, the tube output should be monitored at the bedside and more than 200 mL/h over the course of 4 h should prompt surgical re-evaluation. However, the decision to operate should be based on the overall clinical picture, presumed injury, and velocity of blood loss rather than a strict output number. Indeed, regardless of output, a hemodynamically unstable patient need not wait four hours for repair to meet an arbitrary volume target.

While management of massive hemothorax is frequently surgical, smaller hemothoraces may often be managed without any intervention. Hemothorax often results from lacerated muscle and intercostal vessels after rib fractures. Small collections will often be reabsorbed. However, larger collections may organize or become infected.[10] The decision to evacuate a hemothorax should be based on clinician judgement.[11] Symptomatic hemothorax and larger collections are more likely to require drainage than small, asymptomatic ones. Thoracostomy tube drainage is the mainstay of treatment. Historically, large-bore tubes (36F and 40F) were recommended. More recent data suggest that smaller tubes are just as effective, even tubes as small as 14F.[12,13] The primary goal with any thoracostomy tube is complete hemothorax drainage. Larger retained collections (>200 mL) carry a higher risk of subsequent complications than small collections. In fact, up to 26% of patients with retained hemothoraces will develop an empyema.[14] In order to minimize complications related to retained hemothorax a defined, institution-specific algorithm should be created. By using a stepwise algorithm, the number of patients requiring operative management of retained hemothorax can be reduced.[15] Early intervention (day <7) with video-assisted thoracic surgery (VATS) can prevent development of empyema or fibrothorax with resultant entrapment of the lung. There is an evolving role for the instillation of thrombolytics via image-guided chest tubes.[16–18] However, ideal dosing, timing, and duration remain active areas of study. Randomized controlled trials comparing thrombolytic therapy to surgical treatment of retained hemothorax have not been performed. A retrospective series of 65 patients with posttraumatic retained hemothorax demonstrated that VATS led to decreased length of stay and need for subsequent thoracotomy compared to initial management with intrapleural instillation of streptokinase.[19] Based on available evidence, trauma surgery practice guidelines currently recommend VATS as first-line treatment for retained hemothorax over thrombolytics or additional thoracostomy tubes.[11,20,21] Several protocols are published; however, one has not been shown to be clearly superior to any other. Despite current approaches, as many as one in five patients will ultimately require open thoracotomy for management of retained hemothorax or subsequent empyema.[22]

Chest Tube Management

Much emphasis has traditionally been placed on chest tube position. Traditional teaching was that pneumothorax should be treated with an anteriorly placed chest tube and hemothorax should be treated with a posteriorly placed tube. There is less emphasis on tube position in contemporary management in favor of tube efficacy.[24,25] If the lung re-expands then the tube has been adequately placed and does not require further intervention or manipulation. If, however, the lung does not re-expand a second tube should be placed. Operative intervention must also be considered in the setting of failure of the lung to re-expand with an adequately placed tube. This may be due to a large lung laceration or injury to the bronchial tree. Alternatively, a chest full of clotted blood may prevent lung re-expansion, regardless of tube size or number.

■ Pneumomediastinum

Another form of barotrauma resulting from blunt trauma is pneumomediastinum, often associated with subcutaneous emphysema. This finding is seen in up to 10% of patients with severe blunt chest trauma. It is most commonly the result of the Macklin effect, a process initiated by alveolar rupture due to sudden increase in intrathoracic pressure, followed by dissection of extra-alveolar air along the bronchovascular sheaths into the mediastinum.[26] Pneumomediastinum resulting from this mechanism requires no intervention unless accompanied by pneumothorax. However, pneumomediastinum can also result from tracheobronchial or esophageal rupture—and for this reason, its presence should prompt performance of bronchoscopy and esophagoscopy or barium esophagram.

■ Pulmonary Contusion

Pulmonary contusions are often associated with chest wall injuries. These areas of contusion lose their functional capacity for gas exchange during respiration. In the setting of blunt chest injury, the effect of these injuries can be progressive and is often not apparent on initial chest x-ray. Like all contusions, this injury expands over the course of days and may ultimately compromise an initially stable patient. Treatment is largely supportive and should focus on limited utilization of crystalloid and avoiding overresuscitation to minimize the evolution of the contusion. As with supportive care of rib fractures, aggressive respiratory care including incentive spirometry, secretion clearance, and ambulation should be instituted as early as possible. When pulmonary contusions involve more than 20% of the total lung volume on CT imaging, the clinician should be mindful of impending respiratory compromise, as up to 80% of these patients will develop acute respiratory distress syndrome (ARDS) during the course of their hospitalization.[27] The need for mechanical ventilation should be determined based on usual clinical algorithms. Prophylactic intubation should not be considered in a patient with an uncompromised respiratory state. The decision to intubate often requires consideration of the number of associated rib fractures, age, and overall injury severity score rather than a single variable such as presence or absence of pulmonary contusion.

■ Tracheobronchial Injury

One rare cause of sudden cardiopulmonary compromise in both blunt and penetrating trauma is injury to the tracheobronchial tree. These injuries most commonly follow a penetrating mechanism but may be the sequelae of high speed-rapid deceleration injury. Not surprisingly, penetrating injuries occur most commonly at exposed points such as the cricoid cartilage, while blunt injuries occur most commonly within 2 cm of the carina, a relatively fixed point of the respiratory tree. Diagnosis is considered based on the presence of air in non-anatomic places such as subcutaneous tissue and mediastinum. Crepitus noted on examination of the neck should prompt investigation of a penetrating tracheal injury. Findings of blunt injury may be more subtle and include dyspnea, respiratory distress, dysphonia, hemoptysis, continuous air leak from a chest tube, and persistent pneumothorax despite adequately placed chest tube.

Tracheal injury should not preclude an attempt at endotracheal intubation, if clinically indicated, but this should be approached with caution. Emergent intubation should be reserved for patients who are in respiratory distress, for cases of impending respiratory failure, and for patients who demonstrate signs of airway compromise. For more stable patients, emergent intubation should not be performed simply because a tracheal injury has been identified. A more thoughtful and measured approach is required for this patient cohort. The location of this procedure (i.e., operating room vs. emergency department) should be chosen based on proceduralist expertise, institutional resources, and availability of resources. Intubation should be performed by a proceduralist with significant experience in difficult airway management. Surgical backup should be present for the intubation in the event that a surgical airway is needed. Fiberoptic intubation or bronchoscopic guidance may be required for more proximal injuries to ensure the endotracheal tube cuff extends below the area of injury. A prompt surgical evaluation by a trauma surgeon and/or otolaryngologist as early as possible is essential in this setting to ensure proper airway management, clinical assessment, and surgical repair.

Cardiac Tamponade

Another cause of sudden hemodynamic instability in the setting of chest trauma is cardiac tamponade. An injury within "the box" is the most common predisposing factor. While diagnostic criteria such as Beck's triad—the constellation of hypotension, muffled heart sounds, and distended neck veins—may be present to varying degrees, cardiac tamponade is often diagnosed on resuscitative thoracotomy where a simple pericardiotomy offers diagnostic and therapeutic effect. If the patient survives the primary survey, workup of pericardial effusion can be completed using point-of-care ultrasound, known as a "focused abdominal sonogram for trauma" or FAST examination (Fig. 104-1). In the setting of trauma, identifying fluid contained in the pericardium regardless of tamponade physiology should prompt rapid surgical evaluation. The approach to this problem should be a subxiphoid pericardial window. If blood is identified in the effusion, the patient should undergo an emergent median sternotomy to adequately expose the heart and offer the best approach to any injuries that are identified. In more austere settings where surgical intervention is not an option, the use of ultrasound guidance to perform pericardiocentesis remains a temporizing option. It should be clear that this is not a definitive option, but rather, a maneuver to temporarily relieve tamponade pending definitive management.[28]

Blunt Cardiac Injury

Penetrating injuries can readily reveal themselves, although small injuries may be misjudged in their severity. Blunt cardiac injuries (BCIs), on the contrary, are often subtle and at times suggested only by the new onset of an arrhythmia or conduction abnormality in the setting of blunt chest trauma. The most common form of blunt cardiac injury is myocardial contusion. Because there is no consensus on diagnostic criteria for myocardial contusion, incidence figures following chest trauma vary widely in the literature. Because of its anterior location, the right ventricle is most susceptible to injury but left ventricular regional wall motion abnormalities also have been described. In keeping with the high frequency of right ventricular involvement, the most common ECG abnormality observed in the setting of myocardial contusion is new-onset right bundle branch block.[29] Other abnormalities include ST segment depression, varying degrees of heart block, nonsustained ventricular tachycardia, and atrial arrhythmias.[30] Neither sinus tachycardia nor bradycardia is considered an indicator of myocardial contusion. In cases of severe contusion, heart failure and cardiogenic shock can ensue.

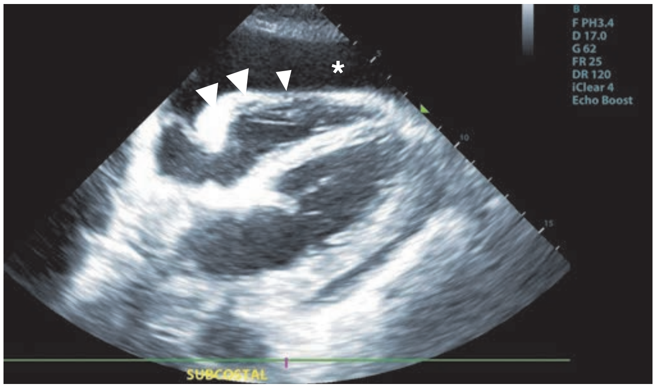


Figure 104-1 Ultrasound image showing pericardial fluid (*) and collapse of right atrium and ventricle *(white arrowheads)* consistent with cardiac tamponade. *(Reproduced with permission from Jeremy Boyd, MD.)*

Evaluation of suspected myocardial contusion from blunt cardiac injury is summarized in Fig. 104-2. Abnormalities detected on ECG often provide the first clue to the presence of myocardial contusion. If the ECG is abnormal, the next step in workup should be evaluation of cardiac enzymes. Creatine kinase has been studied extensively and found to be unreliable.[31] In contrast, troponin is specific to cardiac injury even in the setting of multisystem trauma.[32] Notably, a normal ECG is insufficient to rule out blunt cardiac injury, but the combination of a normal ECG *and* normal troponin has 100% negative predictive value for clinically significant blunt cardiac injury.[33] Persistent conduction abnormalities, high-grade arrhythmias, or hemodynamic instability should prompt further investigation with transthoracic echocardiography. In cases where significant chest wall injury, soft tissue damage, or dressings preclude transthoracic imaging, transesophageal echocardiography is advised.

The majority of blunt cardiac injuries are mild and self-resolving. Aggressive supportive care of hemodynamically significant cardiac injuries should be provided in an ICU setting. While most BCIs are nonsurgical, up to 20% of patients with BCI will require some intervention whether medical or surgical.[34]

Aortic Injury

Blunt injury to the thoracic aorta most commonly occurs at the anatomic tether points of the aorta: the root, the ligamentum arteriosum, and the diaphragm. Patients with complete transection of the aorta will likely not present to the emergency center with vital signs. However, hemodynamic stability does not preclude aortic injury.[35] Clinical suspicion for aortic injury should be elevated in patients sustaining high-velocity acceleration–deceleration injuries, for example, motor vehicle crashes, fall from height. The initial chest x-ray may suggest widening of the mediastinum. Other chest x-ray findings that may suggest thoracic aortic injury include rightward tracheal deviation, apical capping, loss of aortic knob, flattening of the left mainstem bronchus, loss of aortopulmonary window, and left hemothorax. However, these injuries are most readily diagnosed on a well-timed contrast-enhanced CT scan of the chest during the initial trauma evaluation (Fig. 104-3). This allows identification and grading of the injury.[36]

Moderate to high-grade aortic injuries almost invariably require some form of surgical intervention. The most common complications of aortic surgery are death, paraplegia, and renal failure. While renal failure rates are unaffected by the timing of repair, mortality and paraplegia rates are decreased when repair of the aorta is delayed >24 h.[37] Historically, aortic injuries were repaired in an open fashion using the "clamp and sew" technique. This technique was dependent largely on the individual surgeon's speed for good outcomes. More recently however, endovascular techniques have supplanted open surgery in the management of blunt aortic injuries.[38] These repairs require institutional and individual expertise and resources.

Skeletal Injuries of the Thorax

Below we briefly consider two common skeletal thoracic injuries: fractures of the sternum and ribs.

Sternal Fracture

Fracture of the sternum is most commonly identified on CT scan of the chest during the initial evaluation. This injury may be associated with a hematoma in the mediastinum. However, this is rarely of any significance. It was initially thought that sternal fractures may have some association with injury to the underlying heart, but more recent studies suggest that this concern is unfounded in the absence

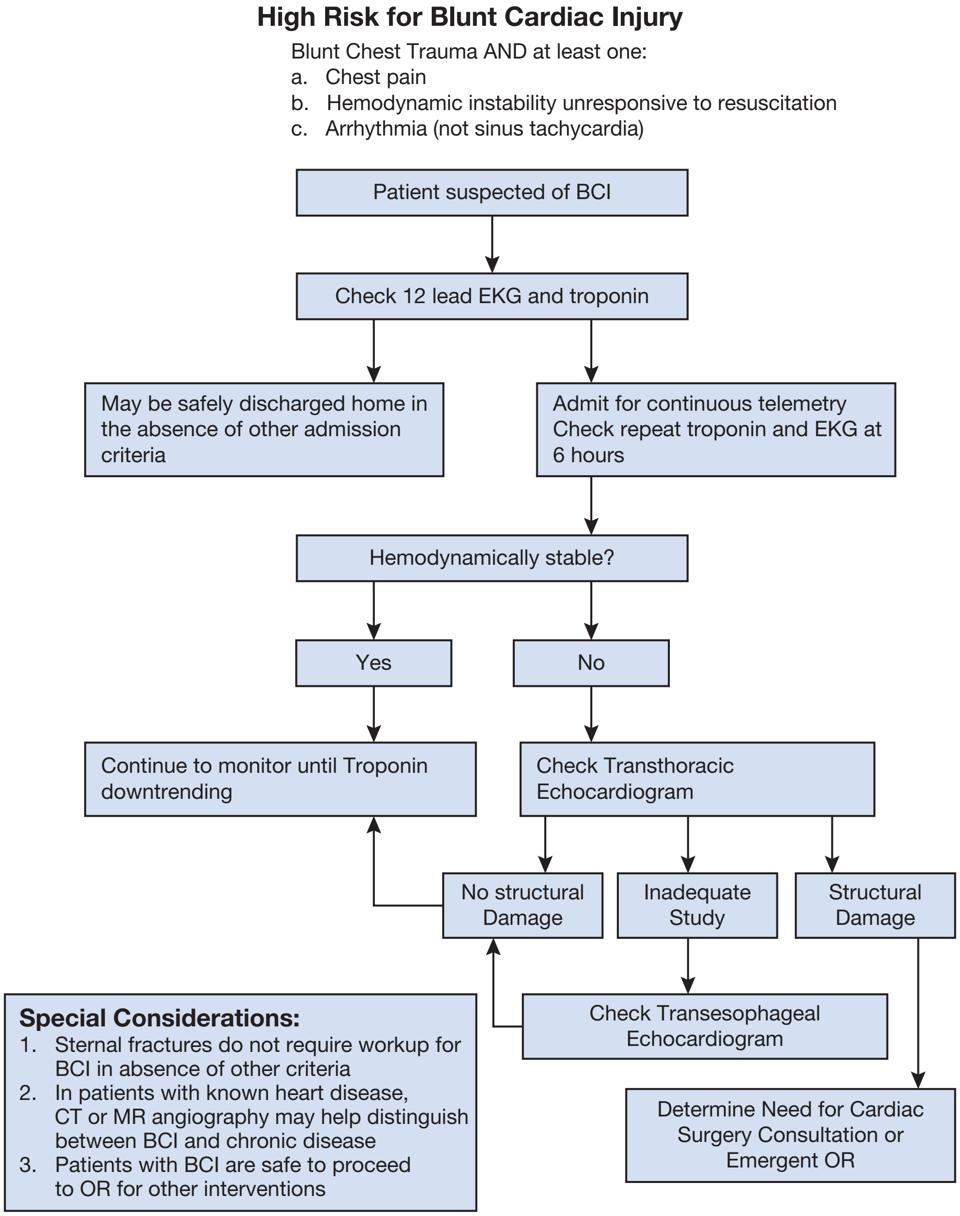

High Risk for Blunt Cardiac Injury
Blunt Chest Trauma AND at least one:
a. Chest pain
b. Hemodynamic instability unresponsive to resuscitation
c. Arrhythmia (not sinus tachycardia)
Patient suspected of BCI
Check 12 lead EKG and troponin
May be safely discharged home in the absence of other admission criteria
Admit for continuous telemetry Check repeat troponin and EKG at 6 hours
Hemodynamically stable?
Yes
No
Continue to monitor until Troponin downtrending
Check Transthoracic Echocardiogram
No structural Damage
Inadequate Study
Structural Damage
Check Transesophageal Echocardiogram
Determine Need for Cardiac Surgery Consultation or Emergent OR
Special Considerations:
1. Sternal fractures do not require workup for BCI in absence of other criteria
2. In patients with known heart disease, CT or MR angiography may help distinguish between BCI and chronic disease
3. Patients with BCI are safe to proceed to OR for other interventions

Figure 104-2 Workup for blunt cardiac injury.

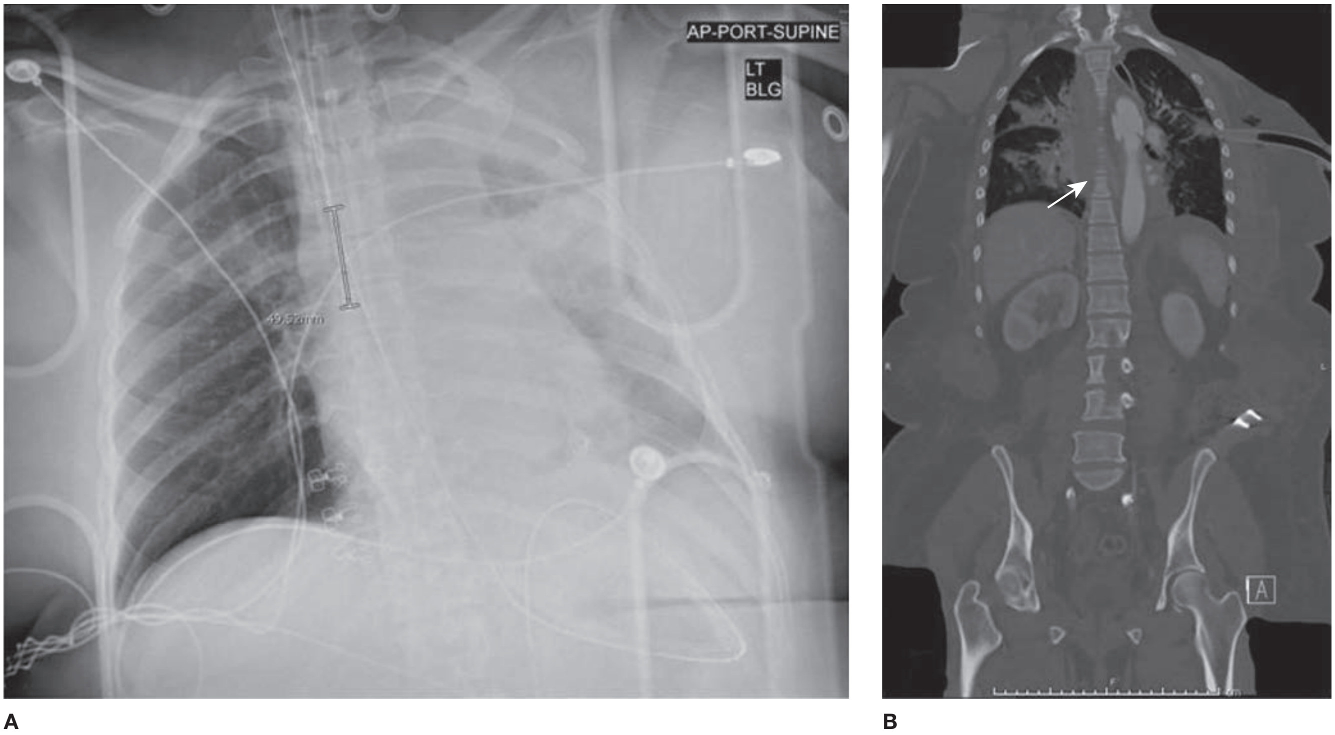
of other evidence of cardiac injury (i.e., presence of ECG changes or troponin elevations).[39]

Rib Fractures

Chest wall injury is one of the most common injury patterns in trauma, present in 10% or more of all trauma admissions. It is also a significant marker of mortality, injury severity, and associated injuries. This is particularly true in elderly trauma patients (≥65 years), for whom rib fractures were associated with increased ventilator days, pneumonia rates, ARDS, and mortality compared to younger cohorts with similar injury patterns.[40]

Initial evaluation for chest wall injury should include a chest x-ray and possibly a CT scan of the chest. It is important to note that a plain chest x-ray will miss up to 75% of rib fractures.[41] Imaging should be used to quantify the number of ribs broken, the amount of displacement, and the location of each fracture. Additionally, the volume that can be generated on a bedside incentive spirometer should be recorded during the initial evaluation.[42] Physical exam should identify any point tenderness, as well as paradoxical motion that may represent a flail segment.

Flail chest represents a particularly morbid consequence of rib fractures. It is a clinical diagnosis most commonly defined as three consecutive ribs broken in two or more places such that this segment of the chest wall moves independently of the rest of the chest. Not all patients with the fracture pattern will have a clinically significant flail segment. It is an important distinction because 80% of patients with a flail chest will be admitted to the ICU and nearly 60% will require mechanical ventilation.[43] Identification of this injury is important, as the energy required to create a flail segment will often result in laceration and contusion of the underlying lung. This underlying lung injury creates ventilation–perfusion mismatches, a major contributor to respiratory failure in patients with flail chest. Additionally, the independent motion of the flail segment relative to the rest of the chest wall prevents maximal chest wall excursion and recoil and results in less intrathoracic pressure change (Fig. 104-4). The end result is decreased oxygenation and ventilation of the lung on the injured side. These two sequelae of flail chest in combination with the pain of multiple fractured ribs result in the high rates of respiratory failure requiring mechanical ventilation.


AP-PORT-SUPINE
LT
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A
A
B

Figure 104-3 A 36-year-old female with blunt aortic injury after motor vehicle crash. **A.** Chest x-ray demonstrating widened mediastinum. **B.** Coronal CT scan demonstrating aortic pseudoaneurysm *(arrow)* at proximal descending thoracic aorta.

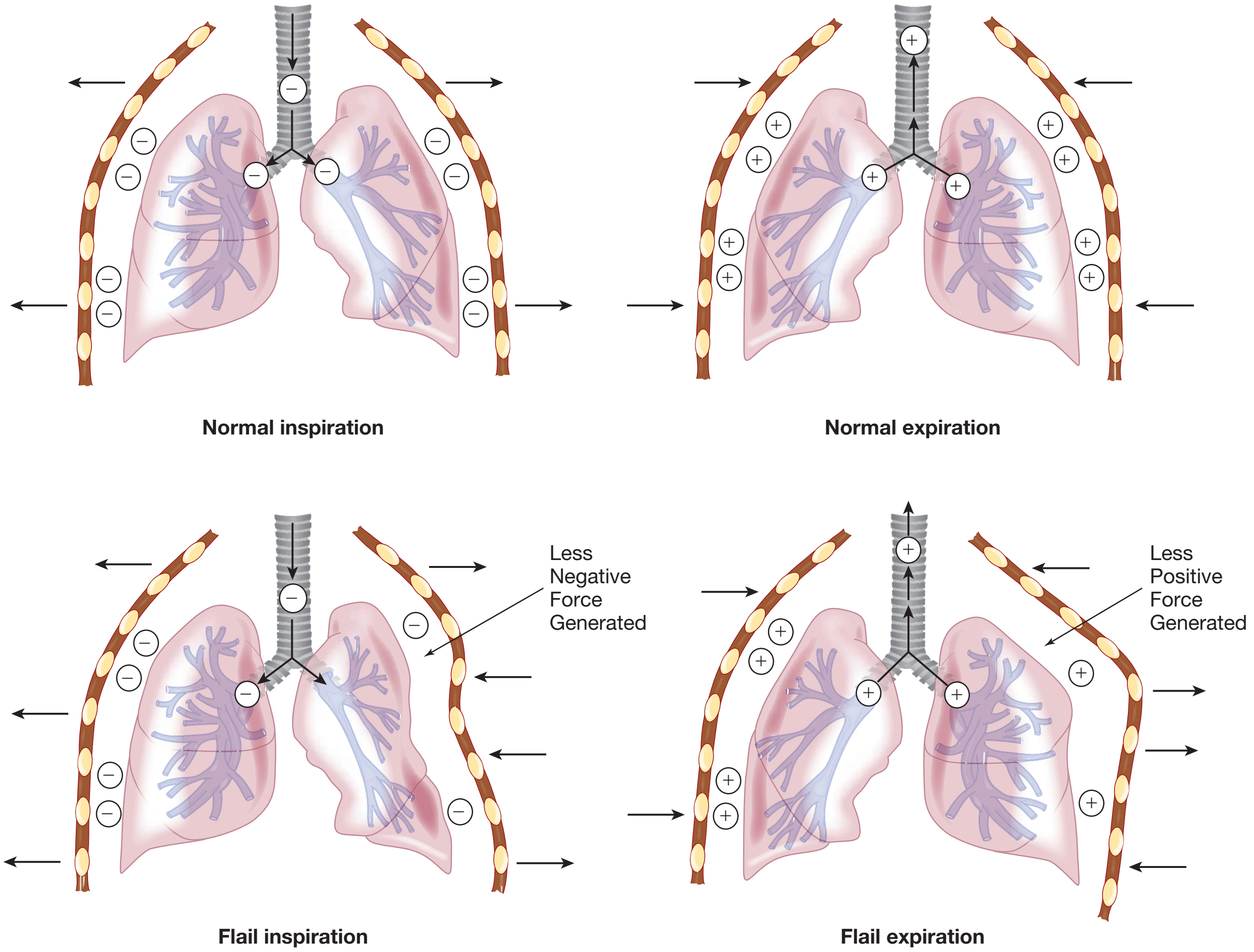
Normal inspiration
Normal expiration
Less
Negative
Force
Generated
Flail inspiration
Less
Positive
Force
Generated
Flail expiration

Figure 104-4 Comparison of inspiration and expiration in normal chest wall versus flail chest. *(Reproduced with permision from Mayberry JC, Trunkey DD. The fractured rib in chest wall trauma. Chest Surg Clin N Am. 1997;7(2):239–261.)*

TABLE 104-1 Nonsurgical Pain Control Options for Patients with Multiple Rib Fractures

	Multimodal Pain Control	Thoracic Epidural Catheter	Erector Spinae Block	Paraspinal Block
Bilateral rib fractures	Yes	Yes	No	No
Fractures above T4	Yes	No	Yes	Yes
>6 rib fractures	Yes	Yes	Yes	No
Anticoagulated	Yes	No	Yes	Yes
Unable to tolerate PO	No	Yes	Yes	Yes
Recent or anticipated T-spine surgery	Yes	No	Yes	No
Invasive	No	Yes	Yes	Yes
Associated hypotension	No	Yes	No	No

In addition to ensuring adequate oxygenation and ventilation, the initial approach to management of rib fractures focuses on pain control. There are three possible components of pain control in the setting of chest wall injury: nonregional analgesia, regional/invasive anesthesia, and rib fracture stabilization. Table 104-1 shows the various nonsurgical analgesic options for patients with rib fractures and the settings in which each may be preferred or discouraged. Pain control should focus on nonsedating, nonnarcotic pain control in the initial phase. A combination of NSAIDs, acetaminophen, gabapentinoids, and muscle relaxers, as well as topical agents, should be initiated early based on institutional expertise.[44,45] The goal of this multimodal pain regimen is twofold. First, it should provide a reduction in clinical pain scores that consequently facilitate compliance with physical and respiratory therapy exercises. Second, it should limit the overall opiate requirement during a hospitalization. Should analgesia be inadequate with this initial regimen, pain control should escalate in a standardized fashion. Some protocols may institute enteral opiates, which are preferred to intravenous administration. Should IV opiates be required, patient-controlled analgesia (PCA) is the preferred delivery modality. In some institutions, an acute pain service may be called in to monitor pain in the setting of failed nonopiate pain regimens. In situations where opiate analgesia proves inadequate, continuous infusions of ketamine (0.1–0.25 mg/kg/h) and/or lidocaine (0.2 μg/kg/h) may provide improved pain relief. These medications need to be administered in a monitored setting.[46]

Regional anesthesia, including thoracic epidural anesthesia, intercostal nerve blocks, and paravertebral and erector spinae blocks, is a second modality that can be utilized for pain control. Regional anesthesia should be reserved for patients with more severe injuries or patients whose pain is inadequately managed with standard enteral pain control. The data on epidural pain control are highly variable.[47–54] Some centers have reported excellent results while others have not been able to identify a benefit. Epidural catheters are complicated by urinary retention, hypotension, and, rarely, epidural hematomas. Care should be exercised in patients with thrombocytopenia, cirrhosis, or anticoagulation or antiplatelet therapy. Because of the variability of the data, epidural catheters are only conditionally recommended by the Eastern Association for the Surgery of Trauma.[52]

Another regional anesthetic option is intercostal nerve blocks. This technique is commonly performed by manual palpation of the individual fractured ribs, which can be problematic for the patient. Once the fractured ribs are identified, anesthetic can be infiltrated from the level above the injured rib to the level below. This procedure carries a small risk of pneumothorax, which increases with each fractured rib as each intercostal neurovascular bundle must be injected individually. Additionally, identification of bony landmarks is difficult above the seventh rib because of overlying scapulae.[55]

A third option for regional anesthesia that may provide comparable efficacy to epidural anesthesia is paravertebral block.[49] This avoids the problem of manipulating the ribs as required for intercostal blocks while achieving the dermatomal coverage similar to epidural anesthesia. Paravertebral blocks are particularly useful for unilateral fractures, as the blocks are placed in a paravertebral location where the nerve roots exit the vertebral column.

The final strategy for pain control in the setting of rib fractures is surgical stabilization of the fractured ribs. While still controversial among trauma surgeons, there is a growing body of evidence that supports decreased opiate use in patients with early stabilization of rib fractures.[54–57] In addition, there is evidence that patients may avoid intubation and have fewer ICU days with early stabilization. As with many surgical therapies, institutional experience may be the most critical factor in establishing a successful rib fixation program.[57]

In addition to pain control, the role of respiratory therapy and nursing cannot be understated in the management of rib fractures. Pneumonia and respiratory failure are the most common complications of poor pulmonary hygiene. Respiratory therapy interventions include incentive spirometry and positive expiratory pressure devices to facilitate lung expansion, and airway clearance measures. Protocols that include early ambulation, bronchodilators, and nebulizers should be developed in order to minimize respiratory decline and maximize patient success.[58–60] Multidisciplinary pathways for respiratory care may contribute to decreased length of ICU stay and hospital length of stay.[61] In addition, these pathways have been shown to decrease pneumonia rates and overall mortality.[61]

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CHAPTER 105

Developmental Disorders of the Lung

Himanshu Deshwal
Subha Ghosh

INTRODUCTION

The development of the lung starts at 4 weeks of gestation and continues through young adulthood. Any developmental abnormality during the growth of the lung may lead to anatomic and physiologic abnormalities, which in turn may lead to significant symptoms and a reduction in quality of life. Prenatal ultrasonography and Doppler technology as screening tools for fetal growth have led to early identification of most developmental anomalies, including pulmonary vascular abnormalities, and revolutionized pre-emptive management of these disorders.[1,2] Nonetheless, some developmental disorders of the lung may remain subclinical and escape diagnosis until adulthood.

Research using animal models and in vitro models has led to the identification of several genetic factors and signaling molecules that play a significant role in lung growth and morphogenesis.[3] Some lung abnormalities are part of genetic syndromes involving multiple organs that share the same molecular pathways of embryogenesis. While some lung abnormalities resolve spontaneously before birth, others persist, with a spectrum of severity ranging from asymptomatic to severe postnatal respiratory distress. Asymptomatic abnormalities often go undetected until adulthood when they are incidentally discovered on chest imaging and often misidentified as malignant or infectious lesions. Thus, an understanding of developmental defects of the respiratory system, with a clinicoradiologic approach, is critical for accurate identification and management of these patients. For ease of understanding, the developmental disorders of the lung can be classified as airway disorders, parenchymal disorders, and vascular disorders (Fig. 105-1).

DEVELOPMENT OF THE LUNG

Important considerations in lung development include stages of lung development, the role of fetal lung fluid in lung development, and associated molecular mechanisms.

Developmental Stages

Lung development starts at 4 weeks of gestation and is divided into five developmental stages known as the embryonic stage, pseudoglandular stage (5–16 weeks), canalicular stage (16–26 weeks), saccular stage (26 weeks until term), and alveolar stage (postnatal stage).

Embryonic Stage

The lung originates from the laryngotracheal groove of the endoderm located at the fourth pharyngeal arch. The splanchnic mesoderm provides the muscular and cartilaginous covering to the lung and also forms the visceral pleura, while the somatic mesoderm forms the parietal pleura.[4] The laryngotracheal groove out-pouches from the foregut, forming the respiratory diverticulum that forms the tracheal bud separating it from the esophagus. The tracheal bud further branches into the two primary bronchi (left and right), which then divide into secondary or lobar bronchi (three bronchi on the right and two on the left for each lung lobe) by 5 weeks of gestation.

Pseudoglandular Stage

The lung continues to grow laterally and caudally on exposure to the splanchnic mesoderm. The conducting airways progressively branch until terminal bronchioles (16th- to 25th-generation

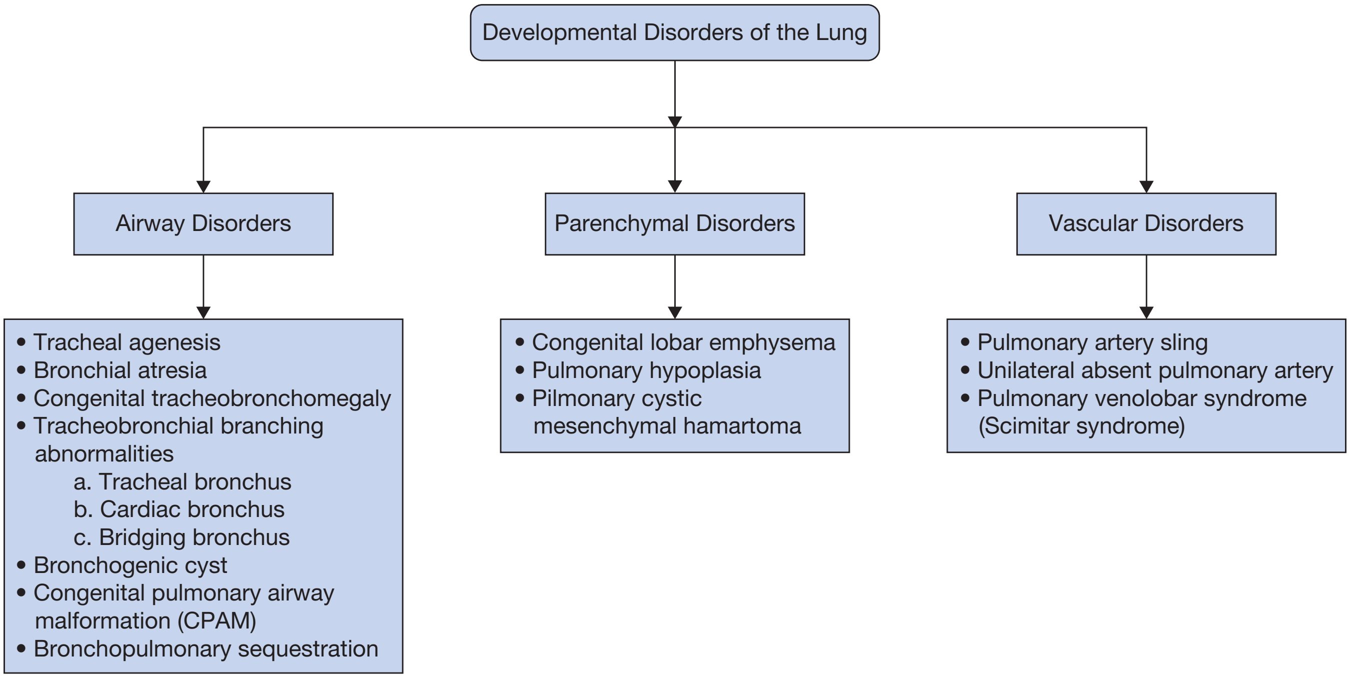
Developmental Disorders of the Lung
Airway Disorders
Parenchymal Disorders
Vascular Disorders
• Tracheal agenesis
• Bronchial atresia
• Congenital tracheobronchomegaly
• Tracheobronchial branching abnormalities
a. Tracheal bronchus
b. Cardiac bronchus
c. Bridging bronchus
• Bronchogenic cyst
• Congenital pulmonary airway malformation (CPAM)
• Bronchopulmonary sequestration
• Congenital lobar emphysema
• Pulmonary hypoplasia
• Pilmonary cystic mesenchymal hamartoma
• Pulmonary artery sling
• Unilateral absent pulmonary artery
• Pulmonary venolobar syndrome (Scimitar syndrome)

Figure 105-1 Classification of developmental disorders of the lung.

bronchioles) are formed by 16 weeks of gestation. Simultaneously, the mesenchymal tissue derived from the mesoderm starts to differentiate into ciliated columnar epithelial cells, goblet cells, and eventually type II pneumocytes.[5] This stage marks the transition between the conducting and the respiratory airways.

Canalicular Stage

Between 16 and 25 weeks of gestation, the epithelium differentiates into type I pneumocytes, also known as alveolar cells, which are the primary structural cells responsible for gas exchange.[6] There is extensive angiogenesis leading to the formation of the capillary network surrounding the alveolar cells. At the same time, lamellar bodies (inclusion bodies) start to form within the type II pneumocyte and are the primary sites for surfactant storage.[7] The conducting airways continue to elongate and grow in diameter, forming a canalicular appearance.

Saccular Stage

During this stage (26 weeks to term), there is progressive maturation of type I and type II pneumocytes and a decrease in interstitial tissue leading to the formation of air spaces. The air spaces are known as primary sacculi and are the location of future gas exchange.[8] There is an exponential growth in primary sacculi with the formation of the primary septum between each saccular unit. At this stage, the primary septa contain a double-layered capillary network.[7] The mesenchymal tissue also differentiates into smooth muscle cells and a fibroelastic network of collagen fibrils that are the foundation for the process of alveolarization.

Alveolarization Stage

This stage starts well before birth and continues into young adulthood as long as lung growth continues. The primary sacculi differentiate into alveoli, and the microvasculature continues to mature and consolidate, leading to a single-layered capillary network in the alveolar septa. This process occurs in an initial bulk alveolarization phase of rapid alveolar differentiation and microvascular maturation, and is followed by a slow continuous alveolarization phase where alveoli continue to differentiate and grow even up to the age of 20 years.[9] Interestingly, alveolarization has been observed even after pneumonectomy, explaining the compensatory growth of the contralateral lung.[10]

■ Role of Fetal Lung Fluid in Lung Development

During intrauterine lung growth, the bronchial tree is filled with protein-free, chloride-rich fluid known as fetal lung fluid. It has electrochemical properties distinct from amniotic fluid and plasma and plays a significant role in keeping the airways patent during lung development.[11] The accumulation of lung fluid provides the needed distension of 2 to 4 cm H_2O end expiratory pressure to keep the airways patent and allow for transfer of important growth factors and hormones to distant lung segments for morphogenesis and structured growth.[12]

Fetal lung fluid also plays a significant role as the fetus transitions from an intrauterine environment to the external environment. The lung epithelium switches from a predominantly secretory role to an absorptive role through alterations in sodium and chloride transporter channels. This facilitates rapid absorption of the lung fluid during birth and maturation of surfactant, thus allowing for gas exchange. A defect in absorption of lung fluid can lead to respiratory distress syndrome and transient tachypnea of the newborn.[13]

■ Molecular Mechanism of Lung Development

A complex interaction involving several growth factors and signaling molecules plays a significant role in lung morphogenesis and maturation at each stage of lung growth. The molecular pathways are tightly regulated to define right and left branching pattern, size of the airways, and the surface area participating in gas exchange. Dysregulation of any of these pathways may result in aberrant lung development.

HNF3β and homeobox genes 3 and 5 (Hoxa3 and 5) play a role in development of the laryngotracheal groove in the foregut endoderm.[14–16] Once the tracheal groove is formed, fibroblast growth factor 10 (FGF10) arising from the mesenchyme stimulates the foregut endoderm to initiate lung branching distal to the trachea. FGF10 is tightly controlled by thyroid transcriptional factor Nkx2.1, sonic hedgehog (Shh) pathway, and retinoic acid receptor (RAR).[17–19] A null mutation in these pathways may result in tracheal agenesis, tracheoesophageal fistula, and pulmonary hypoplasia.[20] A complex interplay between FGF10 and its inhibitory molecules determines the branching morphogenesis of the lung, with elevated FGF10 activity leading to airway branching at the lung tip and inhibition leading to arrest of further lung branching. Several other molecules including bone morphogenetic protein (BMP) family, epidermal growth factor (EGF), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), membrane-associated protein (MAP), and surfactant protein-C among others play crucial roles in lung growth, vasculogenesis, cartilage and smooth muscle formation, and alveolarization.[21]

AIRWAY DISORDERS

A variety of developmental disorders of the airway are well recognized and are described below.

■ Tracheal Agenesis

Tracheal agenesis is a lethal malformation that results from the arrest of the lung bud during the embryonal stage of lung development. As a result, there is either complete absence or interruption of the trachea, which is generally incompatible with life. There are three types of tracheal agenesis, as described by Floyd et al. in 1962 (Fig. 105-2).[22] Type I tracheal agenesis is associated with the absence of the proximal trachea and the development of a distal tracheoesophageal fistula. Type II is characterized by the complete absence of the trachea, with normal bifurcating primary bronchi fused at the carina (most commonly associated with an esophagocarinal or esophagobronchial fistula). Type II is the most common subtype and accounts for 50% to 60% of all tracheal agenesis. Type III also is characterized by the complete absence of the trachea, but the individual primary bronchi branch out from the esophagus.

Tracheal agenesis is a rare disorder with a prevalence of 1:50,000 cases and has a male predominance (male:female ratio of 2:1).[23] Sonic hedgehog mutations in mice demonstrate similar defects, but no specific genetic mutation has been associated with tracheal agenesis.[24] It is commonly associated with other congenital abnormalities such as VACTERL (vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula, renal and limb abnormalities) and TACRD (tracheal atresia/agenesis, cardiac defects, radial ray defect, and duodenal atresia).[25] In 70% of cases, tracheal agenesis is associated with polyhydramnios, respiratory distress, absent cry at birth, and inability to intubate beyond the vocal cords.[26]

Most neonates die within hours of birth, but temporizing methods such as esophageal intubation may be helpful in the presence of a distal tracheoesophageal fistula. With the availability of extracorporeal membrane oxygenation (ECMO), urgent cannulation and prompt surgical consultation can be considered. As a temporizing measure, tracheotomy with the insertion of a long T-tube has been described in type I tracheal agenesis.[27] Subsequently, esophageal reconstruction with colonic interposition graft can help prolong life.[27]

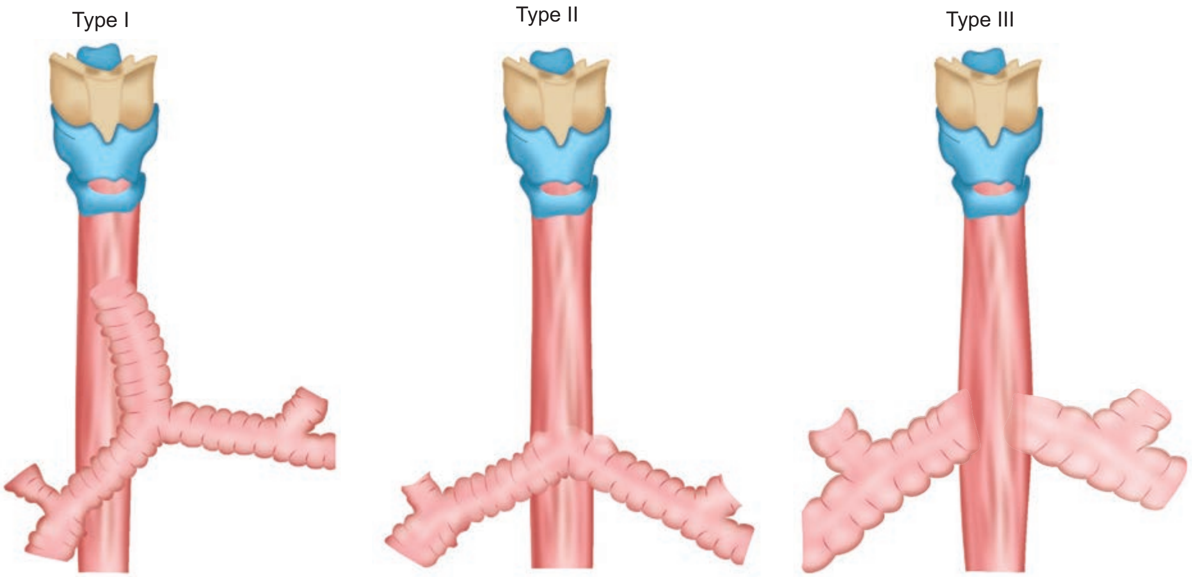

Figure 105-2 Types of tracheal agenesis. Schematic diagrams demonstrating three types of tracheal agenesis. Type I: Absence of proximal trachea with a distal tracheo-esophageal fistula. Type II: Complete absense of trachea with carina originating from the esophagus. Type III: Absence of trachea and carina with main bronchi originating directly from the esophagus.

Bronchial Atresia

Bronchial atresia is a congenital defect of a segmental or lobar bronchus leading to focal hyperinflation of the obstructed lung segment and compression of the adjacent segments. Bronchial atresia results from a defect in the vascularization of the bronchial bud and consequent termination of growth in the affected segment.[7] Collateral ventilation of the obstructed lung segment from adjacent normal lung segments via pores of Kohn leads to hyperinflation. Histopathology reveals an obstructed bronchus or bronchocele lacking communication with the bronchial tree and surrounded by hyperinflated alveoli.[28] The estimated prevalence of bronchial atresia is 1.2 cases per 100,000 and there is a male predilection.[29]

While most patients remain asymptomatic, bronchial atresia in the adult may manifest as recurrent pneumonias, atypical mycobacterial infection, or pneumothorax. The hyperinflated segment may compress the adjacent healthy segments leading to atelectasis. Recurrent infections can also lead to cavitary lung disease within the obstructed segment.[28,30]

Chest radiographs may reveal focal hyperlucency in a lung segment. A contrast-enhanced CT of the chest is the diagnostic modality of choice and demonstrates a tubular nonenhancing structure suggestive of mucus impaction in a segmental bronchus leading to an area of hyperlucent lung parenchyma (Fig. 105-3).[31] Adjacent atelectasis, cavitary lesions, and pneumothorax are other radiographic findings associated with bronchial atresia.

Management is driven by the severity of symptoms. Asymptomatic and mildly symptomatic patients can be managed conservatively with interval imaging to evaluate for complications. In patients with recurrent pneumonia or pneumothorax, surgical resection is the preferred modality. Lobectomy is preferred over segmentectomy as the hyperinflated segment often leads to chronic compressive atelectasis of the adjacent segments, which may not inflate after segmentectomy.[32,33]

Congenital Tracheobronchomegaly (Mounier-Kuhn Syndrome)

Congenital tracheobronchomegaly, also known as Mounier-Kuhn Syndrome (MKS), is a developmental disorder of the central airways characterized by pathologic enlargement of the trachea and up to fourth-order bronchi along with airway diverticula (Fig. 105-4). Generally, tracheomegaly is defined by tracheal diameter greater than 25 mm and 27 mm in transverse and sagittal sections, respectively, in men, and greater than 21 and 23 mm in transverse and sagittal sections, respectively, in women.[34] Bronchomegaly is defined as a transverse diameter greater than 21 mm for the right main bronchus (RMB) and 18.4 mm for left main bronchus (LMB) in

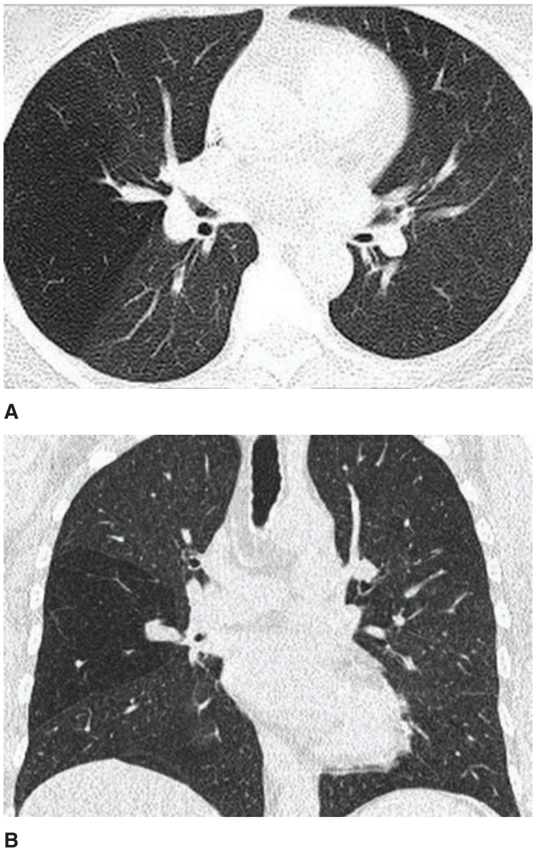

Figure 105-3 **A,B.** Bronchial atresia. Chest CT axial and coronal reformatted images show a proximal focal tubular-shaped opacity radiating from the hilum associated with a distal area of hyperlucent lung parenchyma in the right middle lobe.

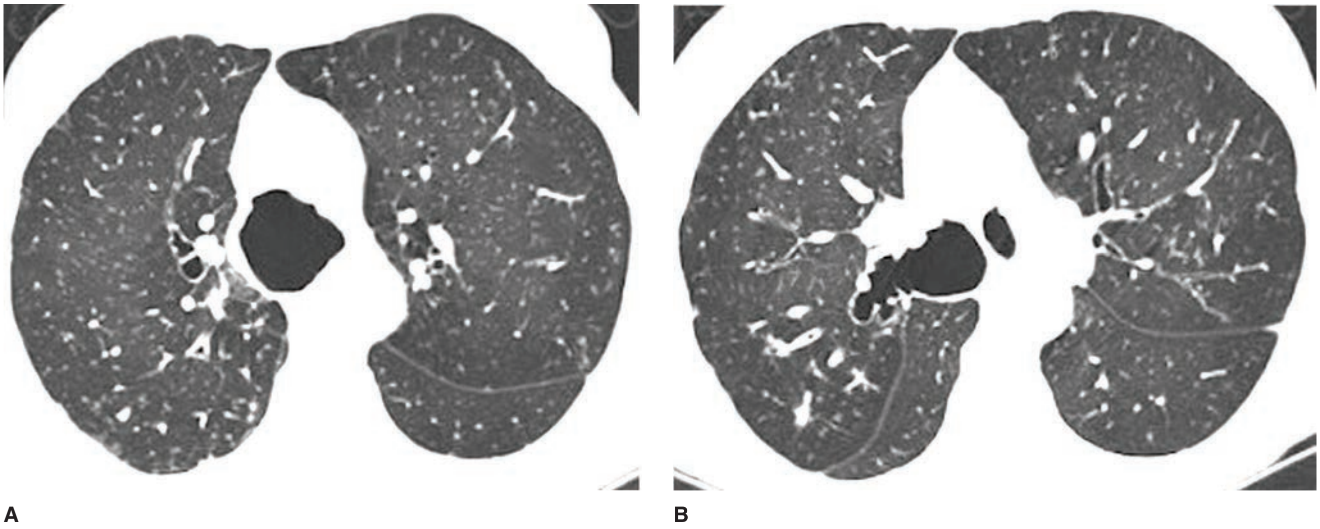

Figure 105-4 **A,B.** Mounier-Kuhn syndrome. Axial CT lung images show markedly dilated trachea and right main bronchus (left bronchus not shown).

males and 19.8 mm for RMB and 17.4 for LMB in females.[35] MKS is an extremely rare disorder with predominantly male preponderance (male:female ratio of 8:1). It is most often diagnosed in the third to sixth decade of adult life.[35,36] The pathogenesis of MKS is not well understood; however, atrophy of the smooth muscle layer and elastic cartilage have been demonstrated on histopathology, suggesting a mesenchymal defect during the saccular stage of lung development.[37] A similar congenital disorder known as William Campbell syndrome is characterized by bronchomegaly beyond the fourth order of bronchi and cystic bronchiectasis (Fig. 105-5).[38] Some familial cases of MKS have been reported in the literature suggesting a possible autosomal recessive mode of transmission.[39] Tracheobronchomegaly can also be an acquired defect in Ehlers-Danlos syndrome, Marfan syndrome, cutis laxa syndrome, Bruton disease, and Kenny-Caffey syndrome.[36]

MKS is classified into three anatomic phenotypes. Type I is characterized by mild symmetric dilation of central airways. Type II is characterized by variable dilation in the central airways along with the presence of diverticula. In type III, diverticula extend into the distal bronchi; this is usually the most severe form of MKS.[35,36]

Most patients with MKS remain asymptomatic until the third decade of life. Because of impaired airway clearance, recurrent lower respiratory tract infections are a prominent feature often leading to development of secondary bronchiectasis.[40,41] The diagnosis is often made incidentally on computed tomography (CT) of the chest. Expiratory-phase chest CT is recommended to evaluate for tracheobronchomalacia (TBM), which is common in MKS. Bronchoscopy reveals tracheobronchial dilatation, airway

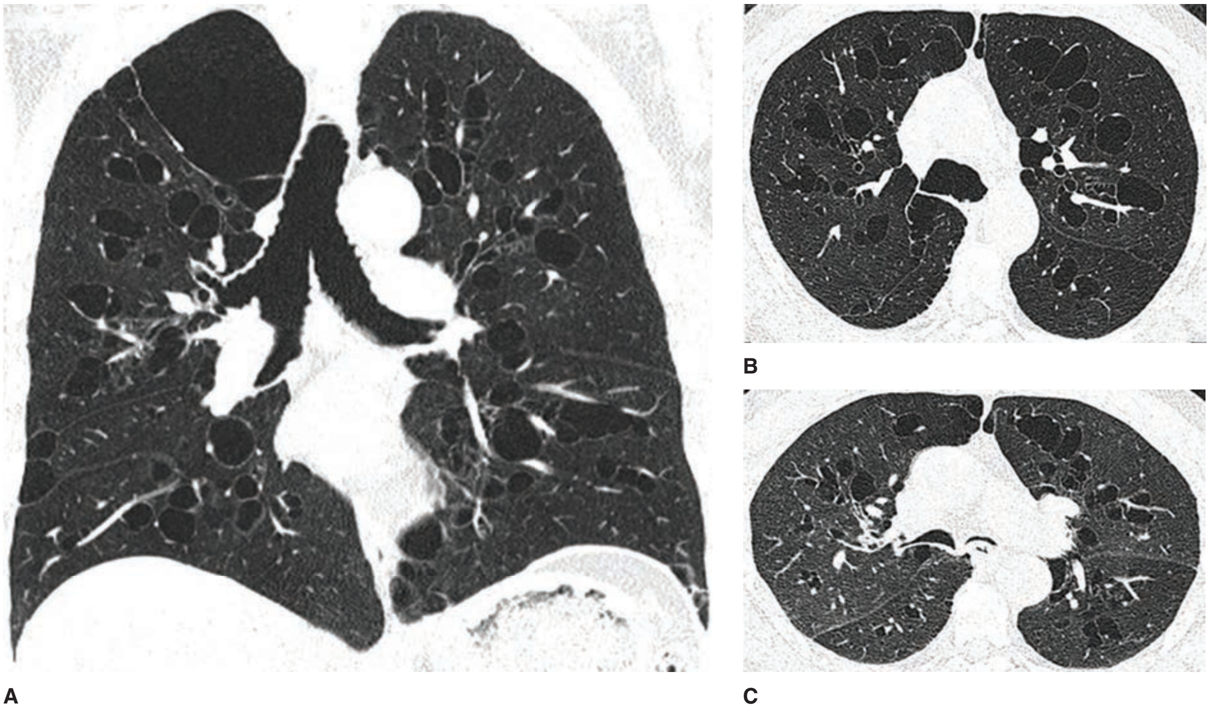

Figure 105-5 William-Campbell syndrome. HRCT of the lungs with coronal multiplanar reformation (**A**) and axial (**B**) images showing abnormally dilated middle order bronchi. Expiratory axial image (**C**) shows collapse of bronchiectatic airways. The trachea and major bronchi are normal in caliber. Note large right apical bulla (**A**).

diverticula, and expiratory collapse due to TBM but is not required for diagnosis. Pulmonary function testing may demonstrate an obstructive defect with air trapping.[40,41]

Treatment is chiefly supportive, focusing on airway clearance and antibiotics for acute respiratory tract infections. Suppressive inhaled antibiotics such as tobramycin may be effective in cases with *Pseudomonas aeruginosa* colonization and recurrent lower respiratory tract infections.[42] Since TBM is common, noninvasive positive-pressure ventilation has been used to facilitate airway clearance and treat chronic respiratory failure. In rare cases with severe TBM, silicone tracheal stents may be utilized.[43] Surgical tracheobronchoplasty for TBM and surgical resection of diverticula and sacculation have been successfully utilized in severe cases. Lung transplantation has been successfully performed in MKS patients with chronic respiratory failure.[44]

■ Tracheobronchial Branching Abnormalities

Early in fetal life, the lung bud starts to branch caudally and distally, forming segmental and subsegmental branching by the sixth week of gestation.[45] Several anomalies in tracheobronchial branching can occur and are classified according to their anatomic relationship to the ipsilateral pulmonary artery.[46] The normal right upper lobe bronchus is eparterial—that is, it arises above the point where the right pulmonary artery crosses the right main bronchus. An anomalous right bronchus arising from the right main bronchus above the point of crossing with the artery is pre-eparterial, and one that arises distal to the origin of the right upper lobe bronchus is post-eparterial. The normal left upper lobe bronchus is hyparterial, as it courses below the point where the left pulmonary artery crosses the left main bronchus. Anomalous bronchi arising from the left main bronchus above and below above the point of crossing with the left pulmonary artery are called left eparterial and pre-hyparterial bronchi, respectively, while an anomalous left bronchus that arises distal to the origin of left main bronchus is called post-hyparterial.[46,47]

The most common tracheobronchial anomalies include the tracheal bronchus, cardiac bronchus, and two types of bridging bronchi (type I and type II).

Tracheal Bronchus

The tracheal bronchus is characterized by an abnormal origin directly from the trachea (Fig. 105-6). Most tracheal bronchi are displaced upper lobe bronchi (88%) and rarely supernumerary (12%), with the ventilated lobe known as the tracheal lobe.[48] The prevalence of right tracheal bronchus is 0.1% to 2% and 0.3% to 1% for left tracheal bronchus.[49,50] The tracheal bronchus is frequently associated with congenital heart disease, Down syndrome, tracheal stenosis, or tracheoesophageal fistula.[51,52]

Both supernumerary and displaced tracheal bronchi arise directly from the trachea. A supernumerary bronchus coexists in addition to normal branching upper lobe bronchi, while a displaced bronchus is an aberrant bronchus that replaces one missing branch of the upper lobe bronchus. For example, the most common displaced tracheal bronchus supplies the apical segment of the right upper lobe, with the right upper lobe bronchus dividing into an anterior and posterior division (i.e., the apical division is absent). The supernumerary bronchus is an extra bronchus (in addition to the normal corresponding bronchi for the lobe) that may end in a blind pouch, diverticula, or ventilated or unventilated parenchyma.[47] It should be distinguished from a tracheal diverticulum. The patients may present with recurrent pneumonia of the tracheal lobe or supernumerary lobule. Most cases are identified incidentally on imaging or bronchoscopy.

Cardiac Bronchus

A supernumerary bronchus called cardiac bronchus originates from the medial wall of the right main bronchus or bronchus intermedius and is directed towards the heart and carina. A cardiac bronchus usually ends in a blind diverticular pouch but may supply an underdeveloped lobule. The cardiac bronchus is very rare, with a prevalence of 0.07% to 0.5%.[53] Most patients are asymptomatic and are identified incidentally on imaging or bronchoscopy. Symptomatic patients may experience dyspnea, recurrent lower respiratory tract infections in the underdeveloped, poorly ventilated lobule, and hemoptysis.[54] Chest CT with contrast can reveal the cardiac bronchus with contrast enhancement of unventilated lobule/tissue mass (Fig. 105-7). The ventilated lobule can be distinguished by an accessory fissure.[54]

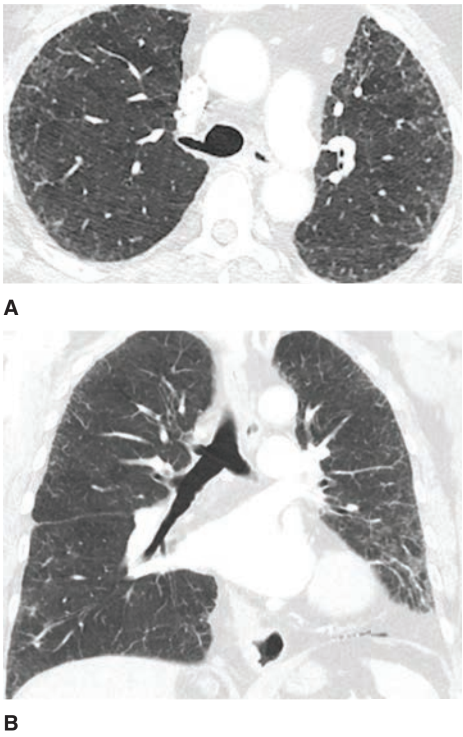

Figure 105-6 Right tracheal bronchus. Axial (**A**) and coronal multiplanar reformatted (**B**) CT images show a displaced tracheal bronchus that arises from the right lateral wall of the trachea and supplies the right upper lobe apical segment.

Intervention is rarely required, but surgical resection is a consideration in cases of massive hemoptysis or recurrent infections. Rare instances of malignancy arising from the tissue mass associated with a cardiac bronchus have been reported.[55]

Bridging Bronchus

In rare instances, the airways of the right lung may originate from the left main bronchus rather than the carina. Two types of bridging bronchi have been described (Fig. 105-8). Type I bridging bronchus originates from the left main bronchus and supplies the right middle and lower lobe, whereas the right upper lobe bronchus originates from the carina. Type II bridging bronchus is characterized by a blind right-sided pouch at the carina and the right main bronchus originating from the left main bronchus.[47] The bridging bronchus is frequently associated with left pulmonary artery sling and tracheal stenosis.[56] The outbranching of the right main bronchus from the left (pseudocarina) may be mistaken as the primary carina on bronchoscopy. A chest radiograph or CT may show the pseudocarina to be much lower (T6–T8) compared with the primary carina (usually T4–T5) and aids in diagnosis of bridging bronchus, especially type II phenotype.

The most common symptoms include wheezing and dyspnea due to tracheal stenosis.[57] Management is usually surgical if a long segment tracheal stenosis is present. Modified end-to-end anastomosis

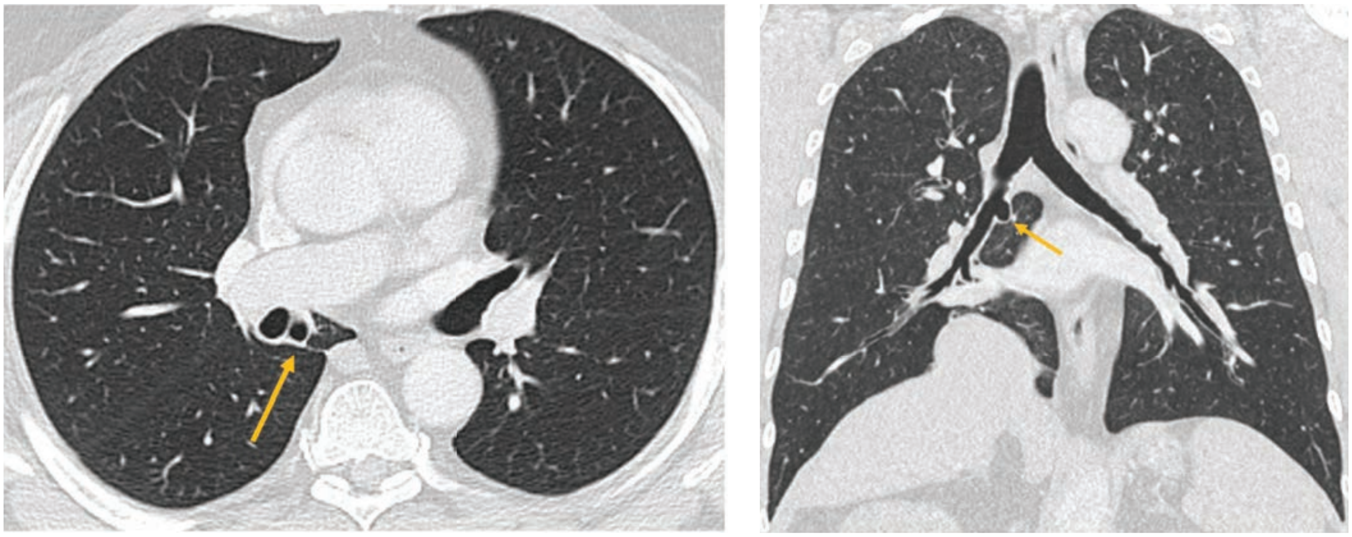

Figure 105-7 Cardiac bronchus. Axial (**A**) and coronal reformatted (**B**) CT lung images demonstrate a rudimentary bronchus *(cardiac bronchus)* that arises from the bronchus intermedius and ends in a blind pouch *(arrows)*.

technique has been described for tracheal stenosis with bridging bronchus.[58] Alternatively, slide tracheoplasty has been successfully performed for long-segment stenosis. The stenosed segment is transected at midpoint; the upper segment is incised posteriorly and lower segment anteriorly. The dissected segments are trimmed, slid together, and sutured to create a larger circumference for the trachea.[59,60]

■ Bronchogenic Cyst

A bronchogenic cyst is a congenital anomaly that is derived from the lung bud of the foregut in the embryonal stage of lung development. It is characterized by a fluid-filled blind cystic pouch, in either the mediastinum or the lung parenchyma. The location is dictated by the stage of embryonic development at which the defect occurs; defects early in lung development result in mediastinal cysts while defects in the later phase of lung development result in cysts in the lung parenchyma, predominantly in the lower lobes.[61,62] Most common locations in the mediastinum include the paratracheal, subcarinal, paraesophageal, and hilar regions. These cysts may rarely be found along the pleura, diaphragm, and neck. The incidence of bronchogenic cyst is estimated to be 1 in 42,000 to 68,000 hospital admissions and carries a male predilection.[63]

Patients are often asymptomatic, but symptoms secondary to compression of mediastinal structures can lead to superior vena cava syndrome, dyspnea, or dysphagia.[64] Postobstructive pneumonia and infection of the intrapulmonary cyst can occur in 82% of the cases who present with persistent cough, purulent expectoration, recurrent fevers, chest pain, or hemoptysis.[61,65]

A chest radiograph may demonstrate a parenchymal ovoid structure with a sharp border and occasionally an air–fluid level, resembling a lung abscess. A mediastinal bronchogenic cyst can be identified as an ovoid structure in the middle mediastinum on a lateral chest radiograph. Chest CT is the imaging modality of choice to identify bronchogenic cysts. The density (in Hounsfield units) of the cyst on CT may range from that of water to soft-tissue content and may contain calcium precipitate as well (known as milk of calcium) (Fig. 105-9).[66] Magnetic resonance imaging (MRI) may be utilized for surgical planning to differentiate surrounding structures. The bronchogenic cyst does not enhance with contrast, and the cystic content may have a variable intensity signal on T1-weighted images depending on proteinaceous debris, while T2-weighted images will demonstrate high intensity.[66] Based on imaging, the differential diagnosis may include a hydatid cyst (has typical septations within the cyst) and cystic teratomas (inhomogeneous, fat-containing, and present in anterior mediastinum) for mediastinal cysts; the differential diagnosis may include infected bullae, lung abscess, vascular malformation, and tuberculous cavity for intrapulmonary cysts.[65] Histopathology on surgically resected cyst provides the most definitive diagnosis and demonstrates characteristic respiratory ciliated pseudostratified columnar epithelial cells with the presence of occasional calcification, bronchial glands, smooth muscles, and cartilage in the cyst wall.[63]

Asymptomatic bronchogenic cysts are usually managed conservatively. Mediastinoscopy, transbronchial needle aspiration (TBNA), or biopsy of the cyst wall may be considered for diagnosis (Fig. 105-10).[67]

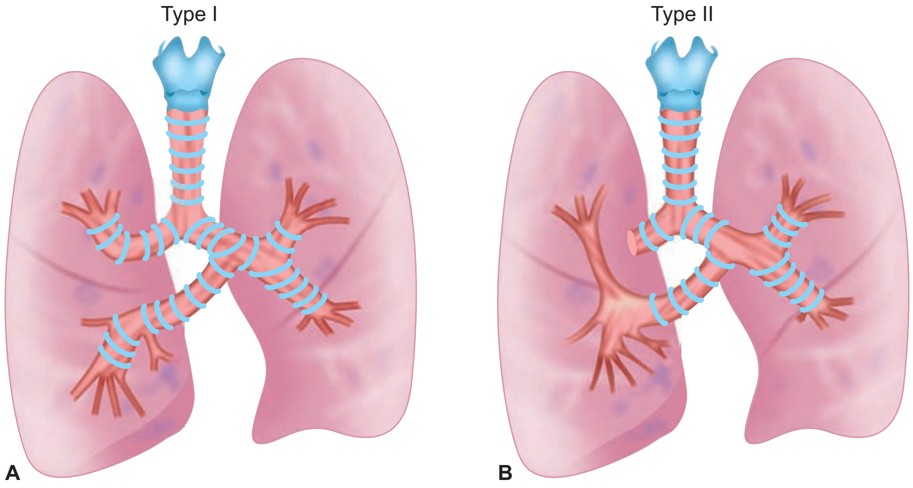

Figure 105-8 **A,B.** Two types of bridging bronchus. Schematic diagram demonstrating two types of bridging bronchus. Type I: The right bridging bronchus originates from the left main bronchus and supplies the right middle and lower lobes. The right upper lobe bronchus originates from the carina. Type II: The right bridging bronchus originates from the left main bronchus and supplies the entire right lung. The right main bronchus ends in a blind pouch.

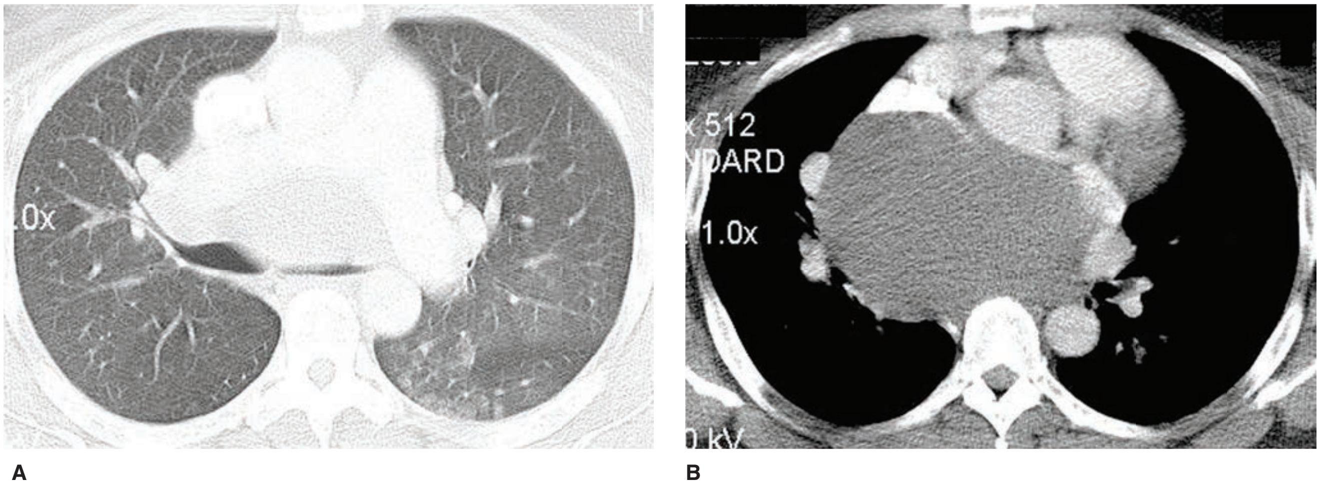

Figure 105-9 Bronchogenic cyst. Chest CT axial images at and just below the carinal level in lung window (**A**) and mediastinal window (**B**) settings show a large subcarinal cystic lesion causing mass effect on the left main bronchus and left atrium.

If the patient is symptomatic, a cyst-related complication such as postobstructive pneumonia or infected cyst must be excluded. While treatment is usually surgical excision, successful bronchoscopic drainage via transbronchial approach has been described and offers a less invasive therapeutic approach to mediastinal bronchogenic cysts.[68] Video-assisted thoracoscopic surgery (VATS) is the treatment of choice,[69,70] but posterolateral thoracotomy may be required for a large, complicated bronchogenic cyst. For intrapulmonary bronchogenic cysts, VATS cystectomy, wedge resection, segmentectomy, or lobectomy may be required depending on the size, location, and complications such as recurrent pneumonia with frequent hospitalizations.[70,71] The recurrence rate is usually low with complete resection, but cysts may recur if residual mucosa is left in the mediastinum.

■ Congenital Pulmonary Airway Malformation (CPAM)

Congenital pulmonary airway malformation (CPAM), previously known as congenital cystic adenomatoid malformation (CCAM), is characterized by cystic hamartomatous lesions in the lung. CPAM is a rare disorder with a prevalence of 9 cases per 100,000 total births.[72] The pathogenesis is believed to be due to abnormal branching of primitive bronchioles resulting in arrested development at various stages of lung morphogenesis. The primary insult appears to take place during the pseudoglandular stage but can occur as late as the alveolarization stage resulting in more distal cystic lesions.[73] Hoxb5 is required for lung branching morphogenesis during the pseudoglandular stage of lung development, and its expression subsequently decreases in advanced stages.[74] Overexpression of the Hoxb5 gene beyond the pseudoglandular stage has been implicated

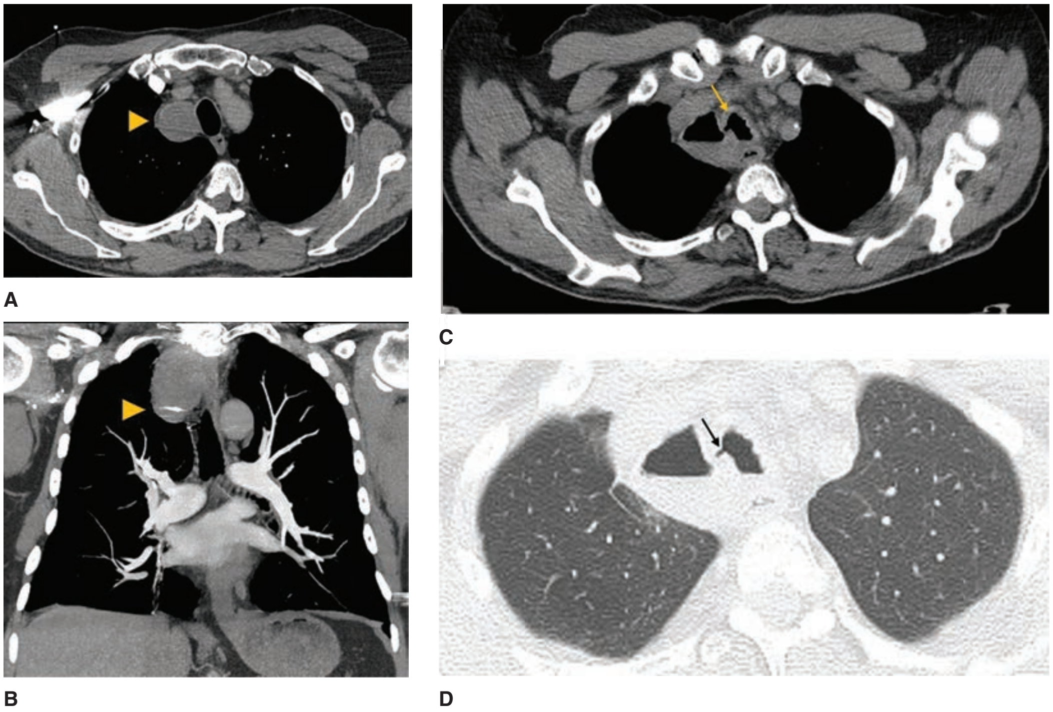

Figure 105-10 Bronchogenic cyst. Chest CT angiography axial image at the level of the great vessels (**A**) and coronal maximum-intensity projection image (**B**) show a well-circumscribed cystic mass in the right paratracheal region without any solid mural enhancing component *(arrowheads)*. Endotracheal cyst drainage was performed. Postprocedure (bronchoscopic cyst drainage) unenhanced chest CT axial images in mediastinal (**C**) and lung (**D**) window settings show an air–fluid level in the cyst with a fistulous tract to the right lateral wall of the trachea *(arrows)*.

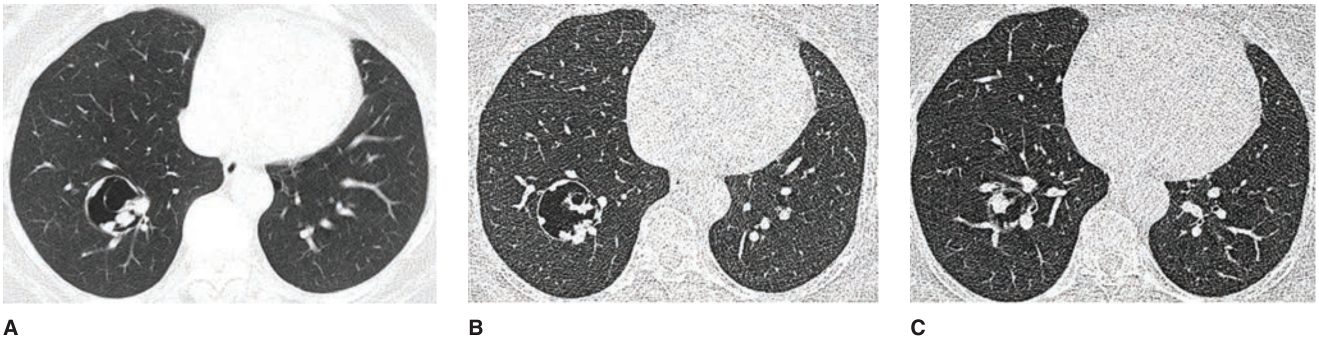

Figure 105-11 CPAM. Routine (**A**) and inspiratory HRCT (**B**) lung images show a relatively thin-walled cystic mass in the right lower lobe with mural nodular densities and a smaller cyst within the cyst, which remained stable over 10 years. Expiratory HRCT image (**C**) demonstrates partial decompression of the cyst suggestive of airway communication.

in the development of CPAM.[74] Overexpression of the human keratinocyte growth factor (KGF/Fgf7) gene and platelet-derived growth factor B (PDGFB) also have been associated with CPAM.[75,76]

Up to 70% of CPAM present as cystic lesions in distal bronchi; however, a subset may present as soft tissue masses (Fig. 105-11). As a result, the nomenclature was changed from CCAM to CPAM with classification of CPAM into five subtypes by Stocker et al.[77] Type 0 occurs at the tracheal or primary bronchial level and is often lethal. Type 1 is the most common type of CPAM, accounting for 50% to 70% of all cases, arising from distal bronchus and often presenting as a single large (3–10 cm) cyst with significant mass effects on adjacent organs (Fig. 105-12). Type 2 is the second most common, accounting for 15% to 30% of all cases. Type 2 CPAMs arise from the terminal bronchioles and typically present as evenly spaced small cysts (1–2 cm), often with solid components. Type 2 CPAM is often associated with extrapulmonary anomalies such as renal agenesis, cardiac defects, gastrointestinal atresia, and skeletal abnormalities.[78] They can be radiographically challenging to distinguish from, and indeed can be associated with, extralobar pulmonary sequestration (hybrid lesions).[78] The presence of a systemic blood supply in pulmonary sequestration helps in distinguishing the two entities.[78] Type 3 CPAM is characterized by “micro cysts” (<5 mm) consisting of cuboidal epithelium similar to fetal lung and appears largely solid on CT. Type 4 CPAM also develops from the alveolar tissue and can be indistinguishable from type 1 CPAM on imaging, characterized by very large peripheral cysts (10 cm), risk of pneumothorax, and mass effect. Malignant transformation is known to occur with CPAM. Types 1 and 2 are precursors with potential for mucinous adenocarcinoma and rhabdomyosarcoma formation, respectively.[79] Type 2 and type 4 CPAM can be associated with pleuropulmonary blastoma.[80]

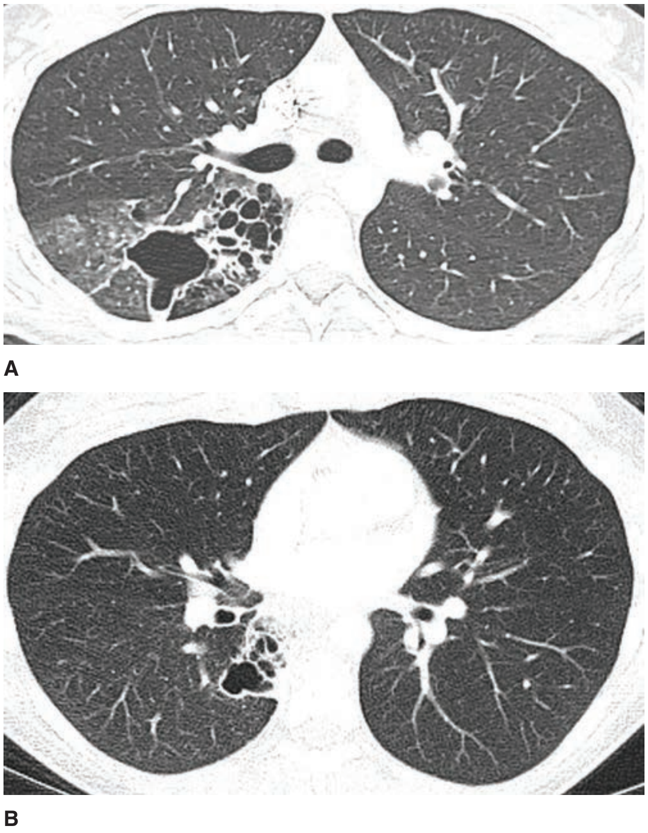

Figure 105-12 CPAM. HRCT lung images (**A, B**) demonstrate a unilocular 5.5-cm cyst surrounded by smaller cysts in the superior segment right lower lobe, suggestive of type 1 CPAM.

With the advent of frequent antenatal monitoring and obstetric ultrasound, most cases of CPAM are identified prior to birth. Without intervention, fetal hydrops in the presence of CPAM develops in up to 40% of cases and is associated with high mortality.[81] Prenatal obstetric ultrasound has a sensitivity of 93% and specificity of 32% for detecting CPAM. Fetal MRI is superior in identifying systemic feeding vessels to differentiate CPAM from BPS (sensitivity of 71%, specificity of 88%).[82] The likelihood of detection is high in the first trimester as the fetal lungs become more echogenic in later stages of development, making it challenging to identify this abnormality. Up to a third of CPAMs identified in early pregnancy resolve spontaneously before birth.[72] Up to 50% of neonates with CPAM are asymptomatic at birth and can be managed expectantly. If elective surgical resection is considered, it should be performed within 10 months of birth as it is associated with fewer complications.[83]

The decision to surgically resect a lesion in prenatal or early neonatal phase takes into account the risk of malignant transformation of existing lesions. Although type I and type II subtypes of CPAM have been associated with malignancy such as pleuropulmonary blastoma and mucinous adenocarcinoma, there is a diagnostic challenge to clinically distinguish between a malignant lesion and a benign CPAM lesion without histologic examination. Several studies have demonstrated increased mucinous cell collections in patients with type I CPAM, which may predict future risk of mucinous adenocarcinoma.[84,85] Chromosomal aberration in chromosome 2 and 4 in the atypical goblet cells and oncogenic K-ras mutations have been identified in mucinous adenocarcinoma associated with type I CPAM.[86–88] Malignant transformation is largely reported in neonates compared with adults, and the reason may be that the large lesions in type I CPAM are symptomatic early in life and often intervened in early childhood. Future risk of malignancy in adults with developmental disorders still needs to be explored.

TABLE 105-1 Types of Bronchopulmonary Sequestration (BPS)

Type of BPS	Intralobar BPS	Extralobar BPS
Origin	Originates before pleural formation, often acquired after an infection	Originates after pleural formation, associated with other congenital abnormalities
Pleural covering	Does not have its own visceral pleura	Has its own visceral pleura
Common locations	Left lower lobe, right lower lobe, and rarely upper lobes	Left hemithorax, right hemithorax, anterior or posterior mediastinum, subdiaphragmatic, and neck
Association with CPAM	Less common	More common
Lower respiratory tract infection	More common	Less common
Venous drainage	Pulmonary or systemic	Always systemic

While many cases are detected through routine prenatal screening, CPAM is occasionally encountered in adult patients. They typically come to attention as an incidental finding on imaging performed for unrelated reasons or as a cause of recurrent lower respiratory tract infections or pneumothorax. Aspergillomas can form in pre-existing cavities and can result in life-threatening hemoptysis.[89] Asymptomatic adults do not require intervention, but patients with type I or type IV CPAM should be followed closely with interval imaging as there is slightly increased risk of malignant transformation.[87] The main indication for surgical resection in the adult is recurrent infections.

Bronchopulmonary Sequestration

Bronchopulmonary sequestration (BPS) is the second most commonly identified developmental disorder of the lung, accounting for up to 6.4% of all congenital pulmonary malformation.[90] It usually presents as a lung mass that has no communication with the tracheobronchial tree and does not actively participate in respiration. BPS is supplied by systemic arterial circulation, commonly branches of the thoracic (75%) and abdominal aorta (25%).[90,91] The venous drainage can be either pulmonary or systemic. Systemic venous drainage has been associated with a higher incidence of polyhydramnios, hydrops, and congenital anomalies such as skeletal dysplasia, cardiac anomalies, and diaphragmatic hernia.[92] BPS is hypothesized to originate from a supernumerary lung bud, and the location depends on its relation to the development of the pleura.[93]

BPS is classified into two types—intralobar BPS and extralobar BPS—based on its location. If the abnormal lung bud originates before the pleural formation, it migrates caudally with the true lung bud and appears as an intralobar BPS within the lung parenchyma. If it originates in later stages after pleural formation, it presents as an extralobar BPS and has its own visceral pleura. Intralobar BPS usually appears as a lung mass, most commonly located in the left lower lung (60%), right lower lobe (38%), and rarely in the upper lobes (2%) and does not have its own pleura.[91] Extralobar BPS can present in the left hemithorax (48%), right hemithorax (20%), anterior (8%) or posterior mediastinum (6%), and subdiaphragmatic area (18%).[94] Up to 50% of extralobar BPS are associated with coexisting CPAM, commonly type 2.[94] Table 105-1 highlights the differences between extralobar and intralobar BPS.

BPS is commonly identified during the second trimester on prenatal ultrasound as solid, homogenous, well-defined lesions with increased echogenicity.[95] A color Doppler is used to identify the systemic origin of the feeding artery, which is the characteristic feature of a BPS. On MRI, it appears as a homogenous, well-defined mass with higher signal intensity than the lung but lower intensity than the amniotic fluid on T2-weighted imaging. Since most BPS (71% intralobar and 94% extralobar) decrease in size or regress before birth, they may become isoechoic on ultrasonography and isointense on MRI beyond 28 weeks of gestation.[96] In adults, a CT scan of the chest with angiography is the imaging modality of choice, demonstrating a consolidation/mass with occasional cystic or emphysematous changes predominantly in the left lower hemithorax with an easily identifiable feeding systemic artery (Fig. 105-13).[97]

Most cases are asymptomatic at birth but can present as respiratory distress. Recurrent lower respiratory tract infections are more common with intralobar BPS (71%) compared with extralobar BPS (31%).[91] Often, BPS remains undiagnosed until adolescence or adulthood, when it may present as recurrent pneumonias. Up to 50% of adults are asymptomatic, with the BPS identified incidentally on thoracic imaging.[98]

When asymptomatic, small BPS can be managed conservatively; surgical resection with minimally invasive VATS between 6 and 12 months of postnatal life should be considered for larger lesions and symptomatic patients. Antenatal intrafetal vascular laser ablation of the feeding artery is an emerging technique that led to a reduction in the size or complete resolution of BPS in 92% of cases in a small series of 12 patients.[99] In adults, the most common indication for surgical resection is recurrent infection.[98]

PARENCHYMAL DISORDERS

In addition to developmental disorders of the airways, a variety of developmental disorders of the pulmonary parenchyma have been reported and are described below.

Congenital Lobar Emphysema

Congenital lobar emphysema (CLE), also called congenital lobar overinflation, is a rare disorder characterized by overdistension of a focal segment or lobe of the lung. CLE occurs in 1 in 20,000 live births, accounting for 10.5% of all developmental disorders of the lung, and is more common in males.[100,101] Several pathogenic mechanisms have been proposed in the development of CLE, such as focal cartilage defect theory and polyalveolar theory. Focal defect or absent bronchial cartilage may result in dynamic airway collapse and air trapping, eventually leading to the formation of an overdistended lobe in up to 25% cases.[102] Morphologically there is no tissue damage; however, there is a disruption in the maturation of the acini postpartum in the affected airways leading to primitive acini with overdistended alveoli. The polyalveolar theory was proposed by Hislop and Reid in 1970 when they found a fivefold increase in the number of normal alveoli in a 17-day-old neonate without overdistension, suggesting a form of alveolar gigantism.[103] Several other case series demonstrated alveolar hyperplasia in their cohorts, supporting this pathogenetic mechanism. Demonstration of a higher-than-expected (for age) radial alveolar count has been suggested as a method for pathologic diagnosis of a polyalveolar lobe.[104,105]

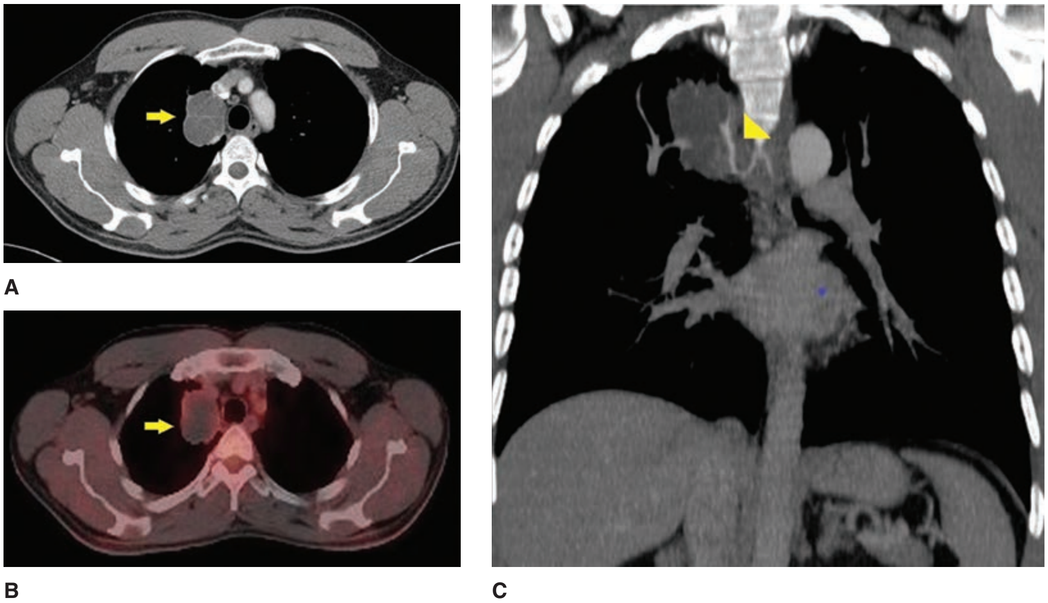

Figure 105-13 Intralobar sequestration. Contrast-enhanced chest CT (**A**) shows a well-circumscribed right paratracheal cystic mass of indeterminate etiology *(arrow)*. (**B**) PET-CT scan shows no significant FDG uptake, suggesting no hypermetabolic malignancy or active infection/inflammation. (**C**) Coronal maximum-intensity projection image shows abnormal feeding systemic artery from the descending aorta coursing into the right upper lobe soft tissues *(arrowhead)*, confirming sequestration. The feeding artery distinguishes the lesion from a bronchogenic cyst.

Other developmental disorders can mimic CLE by causing extrinsic bronchial compression and unilateral lobar hyperinflation. These include bronchial stenosis, meconium aspiration syndrome, foreign body aspiration, bronchial polyp, bronchogenic cyst, and pulmonary artery sling anomaly.[106]

Most cases of CLE are identified in the early neonatal period due to symptoms of cough, respiratory distress, or wheezing. Asymptomatic cases can go undiagnosed until adulthood and can be diagnosed incidentally on chest imaging.[107] CLE may be associated with cardiac anomalies such as ventricular septal defect, atrial septal defect, and tetralogy of Fallot.[108]

Chest radiography demonstrates focal lobar hyperlucency with contralateral mediastinal shift (Fig. 105-14).[109] The presence of bronchovascular markings within the hyperlucent area can help differentiate the overdistended lobe from pneumothorax or a cyst.[110] The left upper lobe is the most commonly affected site (42%–57%), followed by the right middle lobe (27%–35%) and right upper lobe (14%–30%).[111–113] Involvement of lower lobes or more than two lobes is rare but has been described in literature.[114,115] Chest CT demonstrates focal lobar or segmental overdistension with pulmonary vessels traversing through the affected lobe and compressive atelectasis of adjacent lung (Fig. 105-15). Mediastinal shift and, rarely, herniation of affected lung to the contralateral side also can be observed.[111] Pulmonary function tests often are normal,[105,116] but reduced forced vital capacity and forced expiratory flows at low lung volume and elevated residual volume can be demonstrated in severe cases.[117] Radionuclide ventilation–perfusion (V/Q) scan may be used for surgical planning and often shows reduced ventilation and perfusion to the affected lobe.[111]

Surgical resection is indicated for infants and children with respiratory distress. Asymptomatic or mildly symptomatic patients can be managed conservatively with close follow-up and repeat imaging.[113] Small case series have demonstrated conservative management to be noninferior to surgical treatment, as lung growth was found to be similar in both groups.[117] Since most adult patients either have mild symptoms or are diagnosed incidentally, they can be managed conservatively.

Pulmonary Hypoplasia

Pulmonary hypoplasia is a rare disorder resulting in arrested lung development. It is defined as a ratio of inflated lung volume to body weight below the 10th percentile for a given age group. Pathologically, radial alveolar count can be used to suggest pulmonary hypoplasia. Radial alveolar count is the number of alveoli from the center of the respiratory bronchiole to the nearest septal division

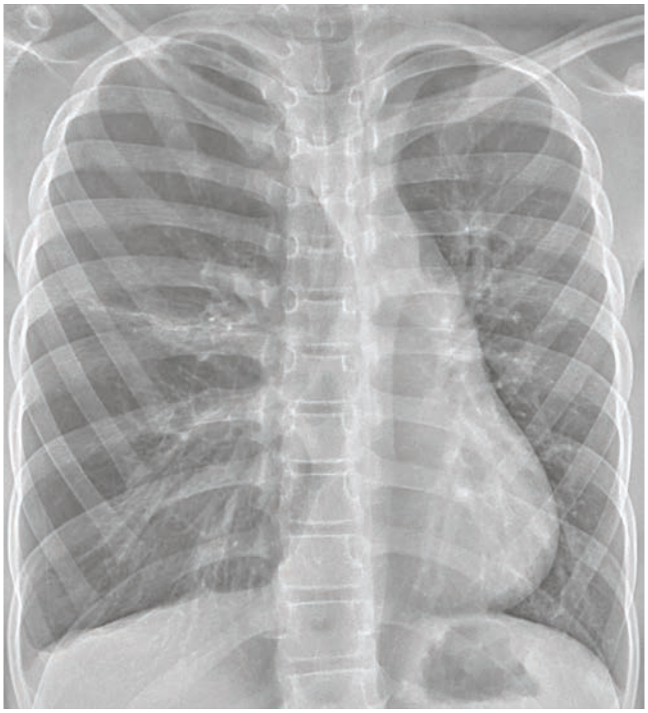

Figure 105-14 Congenital lobar emphysema. Chest radiograph demonstrates hyperlucent and overinflated right upper and middle lobe with compression atelectasis of the right lower lobe.

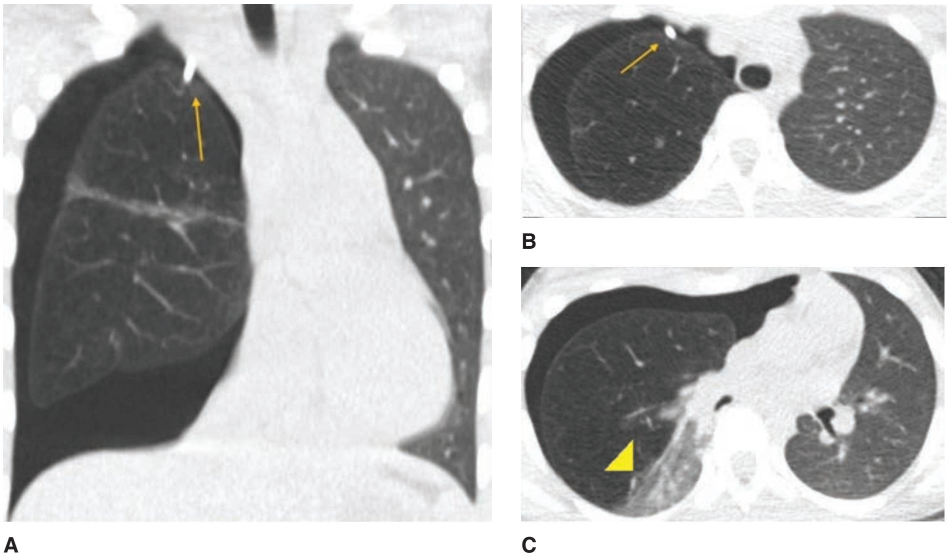

Figure 105-15 Congenital lobar emphysema (same patient as Fig. 105-14). Lung CT with coronal reformatted image (**A**) and axial images (**B, C**) shows hyperlucent and overinflated right upper and middle lobe with compression atelectasis of right lower lobe *(***C***, arrowhead)*. Note mediastinal shift. The affected right lung is larger than the normal left lung. There are decreased lung markings in the affected right lung in comparison to the normal left lung. A right pneumothorax is visualized with a pleural drain *(arrow)*.

transected by a perpendicular line. It is often used to assess lung development on biopsy samples.[118] A radial alveolar count ≤4.1 is suggestive of pulmonary hypoplasia on biopsy.[119] Previously, a ratio of lung weight to body weight less than 0.12 was also used to define pulmonary hypoplasia.[120]

The presence of lung fluid and fetal breathing movements play a significant role in lung development, and abnormalities such as oligohydramnios, decreased lung fluid, or absent fetal breaths can lead to pulmonary hypoplasia. As the elastic tissue and muscular layers develop in the airways, the lung fluid volume increases, leading to distending pressure necessary for stimulation of growth factors, cellular proliferation, and lung morphogenesis.[7] In animal models, fetal tracheostomy and lung fluid removal have resulted in pulmonary hypoplasia.[121] Oligohydramnios and premature rupture of the membrane during the canalicular phase of lung development may lead to the efflux of lung fluid due to decreased amniotic fluid. This leads to a decrease in distending pressures in the lumen of the lung and inhibition of lung growth and cellular proliferation.[122,123] Pulmonary hypoplasia is also observed in patients with congenital diaphragmatic hernia (CDH), as abdominal organs can compress the lung during pseudoglandular phase and inhibit lung branching and morphogenesis.[124] Other associated causes include renal agenesis (Potter syndrome) leading to oligohydramnios. In addition, kidneys grow in a similar fashion by branching morphogenesis and may share common signaling pathways as lungs and lead to development of renal and pulmonary hypoplasia.

With the advent of prenatal ultrasonographic screening, pulmonary hypoplasia can be diagnosed in utero. Common ultrasonographic parameters predictive of pulmonary hypoplasia include reduced thoracic circumference to abdominal circumference ratio, low lung area (correlates well with lung weight), and lung to head ratio (in cases of CDH).[125]

After birth, the most common symptoms include neonatal respiratory distress, cough, and recurrent lower respiratory tract infections. Often, patients are asymptomatic as the healthy lung compensates for the undeveloped lung. Adults with hypoplastic lung may present with chronic cough, recurrent pneumonia, and hemoptysis.[126] While most lung aplasia and agenesis do not survive to adulthood, lung hypoplasia is commonly identified incidentally on imaging. Chest imaging demonstrates a hyperexpanded healthy lung with a mediastinal shift toward the affected side. The hypoplastic lung may appear shrunken, consolidated, cystic, or bronchiectatic. In areas endemic for tuberculosis, pulmonary hypoplasia may be misdiagnosed as tuberculosis due to similarity in chest imaging.[127] Chest CT is important to distinguish between pulmonary agenesis, aplasia, and hypoplasia. The absence of any rudimentary ipsilateral bronchus and lung parenchyma suggests agenesis, while presence of rudimentary bronchus in the absence of lung parenchyma suggests aplasia. In pulmonary hypoplasia, there is a rudimentary bronchus along with a small lung parenchyma (Fig. 105-16). In addition, the reduced size of the ipsilateral pulmonary artery may point toward underlying pulmonary hypoplasia.

Proactive detection and treatment of oligohydramnios may prevent the development of pulmonary hypoplasia. Autologous amniotic fluid–derived stem cell transplantation has been shown to augment lung growth in animal models and may offer potential therapeutic benefit in pulmonary hypoplasia. A prospective, randomized, controlled pilot study demonstrated the feasibility of amnioinfusion (serial infusions of saline or lactated Ringer's to maintain amniotic fluid volume) for premature rupture of membranes, although the small sample size precluded assessment of the impact on outcomes such as incidence of pulmonary hypoplasia.[128] Lung protective ventilation and the use of inhaled nitric oxide may have a potential role in improving oxygen indices in newborns with pulmonary hypoplasia.[129,130] In adults, bronchiectasis and recurrent lower respiratory tract infections are common in the hypoplastic lung and may lead to significant symptom burden and diminished quality of life. Good airway clearance measures such as saline nebulization and chest percussion therapy are often helpful to minimize infections. In some cases, suppressive inhaled antibiotics may be needed if pseudomonal colonization is detected. In cases of recurrent pneumonia, cavitary lesions, or significant symptom burden, pneumonectomy of the hypoplastic lung may lead to improvement in symptoms and quality of life.[126]

■ Pulmonary Cystic Mesenchymal Hamartoma

Pulmonary cystic mesenchymal hamartoma is an extremely rare developmental disorder of the lung composed of immature mesenchymal cells that gradually form multiple bilateral cysts and nodules. An imbalance between respiratory endoderm and surrounding

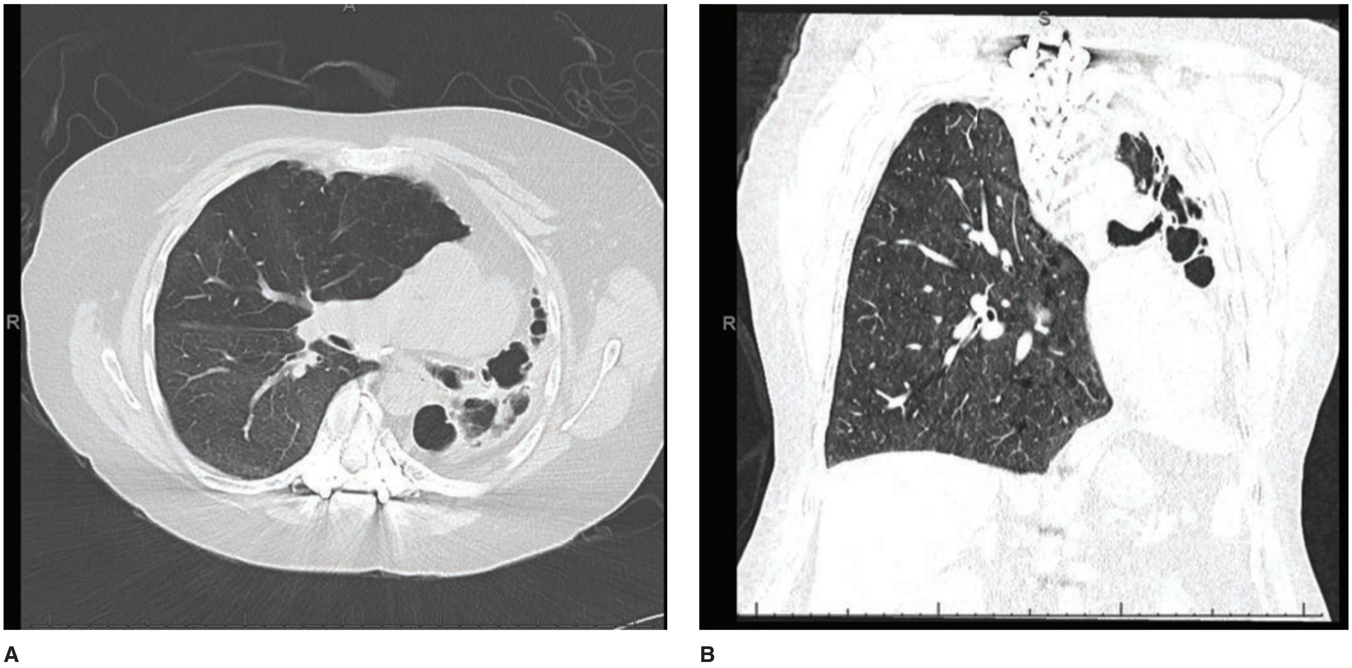

Figure 105-16 Left pulmonary hypoplasia. (**A**) Axial and (**B**) coronal reformatted CT lung images show marked volume loss with cystic bronchiectasis in the hypoplastic left lung, hyperexpanded right lung, and mediastinal shift to the left.

mesoderm during lung development is hypothesized as a possible etiology.[131] The nodules that follow are extremely slow growing and often cavitate into cystic structures exceeding 1 cm in size.[132] Due to its indolent nature, most cases are diagnosed in adults; affected individuals present with chronic cough, hemoptysis, or pneumothorax or hemothorax due to rupture of large cysts.[133]

Chest imaging reveals multiple bilateral solid nodules and large cystic lesions often 1 to 10 cm in size. Occasionally, air–fluid level may be seen in the cysts due to rupture of the adjacent bronchial artery.[133] The lesions may be indistinguishable from CPAM, bronchopulmonary sequestration, lymphangiomyomatosis, and pleuropulmonary blastoma and other malignant lesions on imaging. For this reason, histologic assessment is required for diagnosis. Biopsy demonstrates normal respiratory epithelium surrounding the cysts with an underlying layer of primitive mesenchymal cells with dark nuclei. Immunostaining may demonstrate positivity for vimentin, CD-56, and CD-10 but these findings are nonspecific.[133] The differentiating feature compared with other disorders is the low mitotic activity of the cells. In rare instances malignant transformation to rhabdomyosarcoma may be observed, highlighting the importance of histologic diagnosis.[134]

Due to the rare occurrence of this disease, no clear treatment guidelines exist. In asymptomatic cases, close monitoring with serial CT imaging to assess for enlargement of nodules and cysts is appropriate. Patients presenting with recurrent infection, hemothorax, hemoptysis, or pneumothorax should be treated with surgical excision of the culprit lesion.

VASCULAR DISORDERS

Described below are three developmental abnormalities of the pulmonary circulation: pulmonary artery sling and tracheal stenosis, unilateral pulmonary artery, and scimitar syndrome.

■ Pulmonary Artery Sling and Tracheal Stenosis

In rare instances, the left main pulmonary artery (PA) may originate from the right main PA instead of the pulmonary trunk. In order to reach the left lung, the left PA traverses between the trachea and esophagus, leading to a sling formation, hence the term *pulmonary artery sling* (PAS).[135] Left PAS can lead to posterior compression of the trachea, but the most common cause for severe symptoms is the presence of tracheal stenosis due to complete tracheal rings in up to 80% of patients with PAS.[136]

Two anatomic variants of PAS have been identified.[137] Type I left PAS is located immediately above the carina and compresses the right main bronchus and distal trachea leading to tracheobronchomalacia with resultant hyperinflation of the right lung. It is often associated with a tracheal bronchus, but tracheobronchial anatomy is otherwise normal.[138] In type II PAS, the sling is located more inferiorly (at the level of T5–T6) adjacent to an abnormally low horizontal carina and the presence of a bridging right bronchus. Type 2 PAS is subdivided into types IIA and IIB. In type IIA, there is a tracheal bronchus at the usual site of the carina that supplies the RUL; a bridging bronchus originating from the left main bronchus supplies the right middle and lower lobes. Type IIB is characterized by absence of the right upper lobe bronchus, with the right lung being supplied exclusively by the bridging bronchus. Both type II variants are strongly associated with long-segment tracheal stenosis. Other abnormalities occasionally encountered include right-sided pulmonary hypoplasia, scimitar syndrome, and foregut abnormalities.[139]

A chest radiograph may demonstrate prominent pulmonary vasculature with normal lung parenchyma in type I PAS. Posteroanterior and lateral views of the chest may show a distal T-shaped carina with difficult-to-visualize proximal trachea and atelectasis of the right lower lobe in type II left PAS.[135] In type II PAS, chest CT or MRI with angiography are excellent diagnostic tests to identify the anatomic type of PAS and length of tracheal stenosis (Fig. 105-17).[140] Three-dimensional reformatting of CT and MRI and virtual bronchoscopy can assist in surgical planning, especially for long-segment tracheal stenosis.[141,142]

Asymptomatic patients with type 1 left PAS can be monitored without intervention.[143,144] For those with respiratory symptoms, type 1 left PAS can be surgically corrected by reimplanting the left main PA into the pulmonary artery trunk anterior to the trachea. Surgical correction is often required for type II defects due to the presence of symptomatic tracheal stenosis. This most commonly involves a technique known as slide tracheoplasty in which the stenotic segment is transected at the midpoint, vertical incisions are

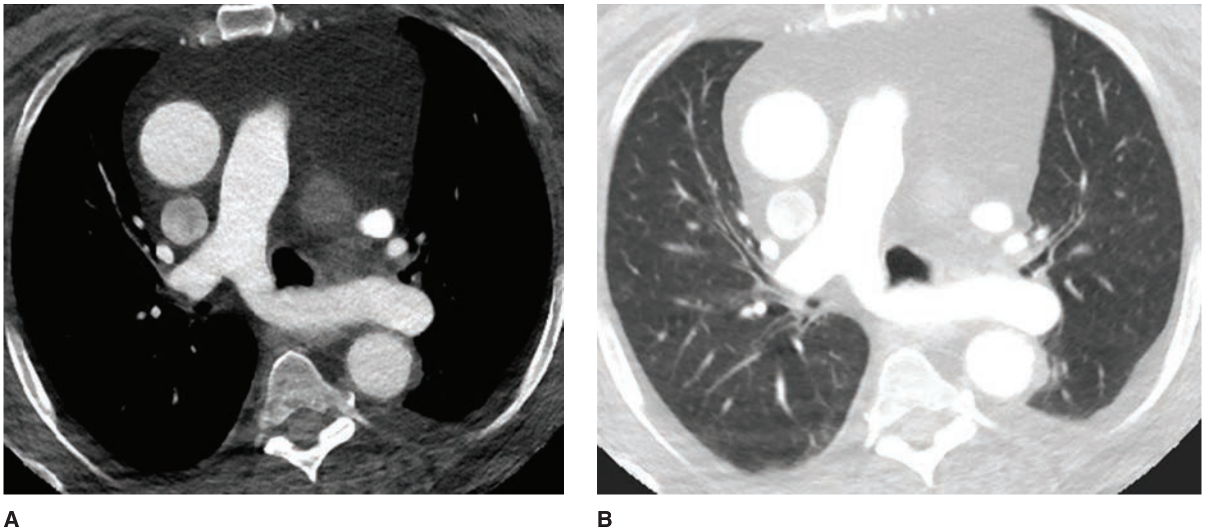

Figure 105-17 Pulmonary artery sling. Chest CT angiography images in mediastinal (**A**) and lung (**B**) window settings show an abnormal left pulmonary artery that arises from the right pulmonary artery and courses posterior to the distal trachea (just above the carina) and anterior to the esophagus. Note stretched and narrowed right upper lobe bronchus (**B**).

made in the proximal and distal narrowed segments on opposite anterior and posterior surfaces to expand them, and the two segments are slid together and sutured.

■ Unilateral Absent Pulmonary Artery

Unilateral absent pulmonary artery (UAPA) is a rare disorder with an estimated prevalence of 1 in 200,000 adults.[145] The pulmonary trunk and main pulmonary arteries arise from the sixth aortic arch, while the intrapulmonary vessels arise from the mesoderm surrounding the lung bud.[146] The involution of the ipsilateral proximal sixth aortic arch may result in UAPA with intrapulmonary vessels connecting directly to the distal sixth aortic arch and deriving blood supply from the systemic arteries. UAPA is invariably associated with a patent ductus arteriosus on the ipsilateral side with a left-to-right shunt.[147] Over time, multiple collaterals develop with bronchial, pleural, subclavian, and rarely coronary arteries.[148,149] The right pulmonary artery is absent in 60% of the cases. Absence of the left pulmonary artery is frequently associated with congenital cardiac abnormalities such as tetralogy of Fallot, coarctation of aorta, atrial septal defect, and right aortic arch.[150]

Up to 12% of patients may be asymptomatic, while 40% of patients may present with exertional dyspnea, 37% with recurrent lower respiratory tract infections, and 20% with hemoptysis.[151] Up to 44% of patients may develop pulmonary hypertension and may progress to Eisenmenger complex and right heart failure.[152]

Chest radiographs may demonstrate atrophic ipsilateral lung with elevated hemidiaphragm, hyperexpanded contralateral lung, and enlarged right heart border. CT of the chest with angiography is usually diagnostic, demonstrating an absent PA and ipsilateral atrophic lung (Fig. 105-18).[153] Bronchiectasis may also be present in cases where recurrent infection has occurred in the involved lung.[154] The peripheral pulmonary circulation in the affected lung remains intact with extensive systemic collateral blood supply. Cineangiography and MR angiography also can be used for diagnosis and are often used for preoperative assessment.

Management of UAPA depends on the severity of symptoms and complications. In cases with severe pulmonary hypertension, a trial of vasodilator therapy may be attempted as chronic high pressure in the contralateral PA and extensive systemic circulation may lead to pulmonary vascular remodeling similar to group I pulmonary arterial hypertension.[155] If identified at an early age, surgical revascularization with an aortopulmonary shunt, transposition of the interrupted pulmonary artery to the pulmonary trunk, or a modified Blalock-Taussig shunt may be performed.[146] Revascularization is not feasible in adulthood due to vascular remodeling in the contralateral lung. Patients are advised against travel to high altitudes, as they are at increased risk of high-altitude pulmonary edema (HAPE) in the hyperperfused contralateral lung.[156] Life-threatening hemoptysis may require embolization of the bleeding collateral artery. Lobectomy or pneumonectomy may be required for recurrent hemoptysis or necrotizing pulmonary infections.[157]

■ Scimitar Syndrome (Pulmonary Venolobar Syndrome)

Scimitar syndrome, also known as pulmonary venolobar syndrome, is a rare congenital disorder of the lung and pulmonary vasculature characterized by partial or total anomalous pulmonary venous return of the right lung (commonly the right lower lobe) to the inferior vena cava.[158] The anomalous pulmonary vein appears as a curvilinear shadow along the right heart border on a chest radiograph and resembles a Persian curved sword known as scimitar—hence the term scimitar syndrome.[159] It has a prevalence of 1 to 3 cases per 100,000 live births and female predominance (male:female ratio of 1:2).[160] It is frequently associated with right pulmonary hypoplasia, systemic arterial blood supply of the right lung, and congenital heart disease.[161,162] Scimitar syndrome represents only 5% of all partial anomalous pulmonary venous return abnormalities.[163]

During early embryogenesis, the pulmonary venous blood drains into the splanchnic venous circulation. Once the cardiac structures begin to develop, the pulmonary venous drainage transitions to cardiac drainage into the left atrium with regression of the systemic connection. Initially, both lungs drain into the left atrium via a common pulmonary vein, but this later divides into four separate pulmonary venous ostia in the left atrium. A defect during the transition from splanchnic drainage to cardiac drainage may lead to a total or partial anomalous pulmonary venous return of the right lung leading to scimitar syndrome.[164]

When the degree of pulmonary to systemic shunting is severe, patients may present in infancy or early childhood with tachypnea, pulmonary hypertension, and evidence of right heart failure.[165] With lesser degrees of shunting, patients may be asymptomatic or present

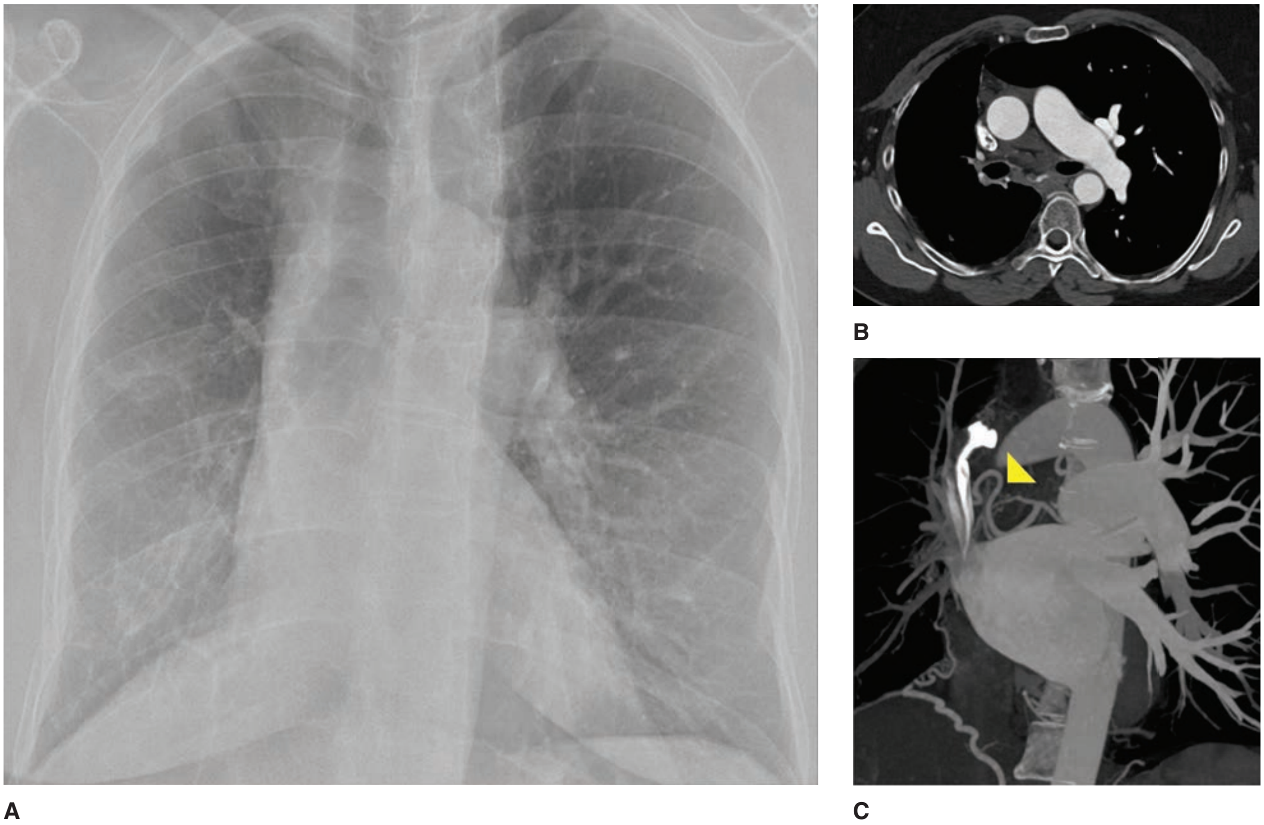

Figure 105-18 Absent right pulmonary artery. (**A**) Chest radiograph shows hypoplastic right lung. (**B**) Contrast-enhanced chest CT axial image shows absence of right pulmonary artery with normal main pulmonary trunk and left pulmonary artery. (**C**) Coronal maximum-intensity projection CT image shows multiple dilated bronchial and systemic collateral arteries supplying the right lung *(arrowhead)*.

in early adulthood with recurrent pneumonia (31%), dyspnea on exertion (19%), or hemoptysis (6%).

Chest radiographs may show the classic curvilinear right-sided opacity with right lung hypoplasia and ipsilateral mediastinal shift (Fig. 105-19). Two-dimensional transthoracic echocardiography (TTE) can be used to assess right ventricular function and estimated pulmonary artery pressure. In the suprasternal short-axis view with use of color Doppler, the left pulmonary vein can be seen entering the left atrium but not the right pulmonary vein. The parasternal short-axis view on TTE may demonstrate a small right main PA compared with normal-sized left PA. These findings can be confirmed on transesophageal echocardiogram. Lung scintigraphy with technetium-99m-labeled macroaggregated albumin can demonstrate the magnitude of blood flow to the right lung. Chest CT can accurately identify the systemic arterial supply of the affected lobe, anomalous pulmonary venous return, and site of venous drainage (infradiaphragmatic, hepatic veins, or supradiaphragmatic) (Fig. 105-20). More recently, MRI using isotropic flow-sensitive four-dimensional phase-contrast vastly undersampled isotropic projection reconstruction (PC-VIPR) has been used not only to identify anomalous pulmonary veins and cardiac morphology but also to analyze quantitated flow patterns and parameters including pulmonary-to-systemic shunt ratio without the need for angiography.[166]

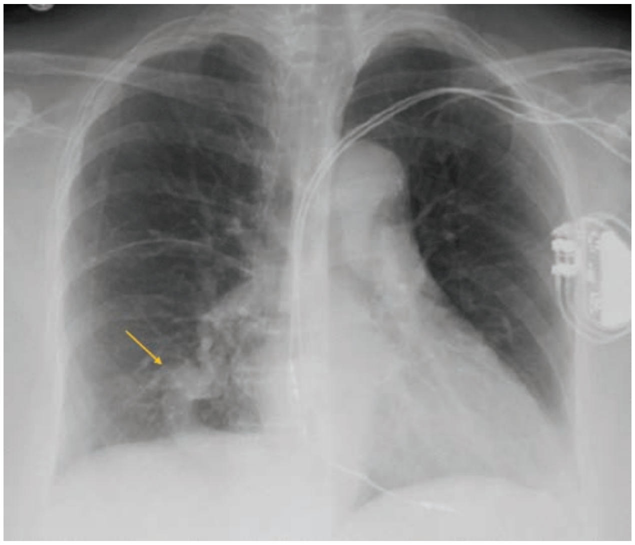

Figure 105-19 Scimitar syndrome. Chest radiograph reveals a curvilinear tubular opacity in the right lower hemithorax *(arrow)* that courses from the right hilum toward the IVC.

Management of scimitar syndrome depends on the severity of pulmonary to systemic shunting and its hemodynamic impact. Most often, the left-to-right shunt fraction decreases with age. For those with small shunt fractions and minimal symptoms, conservative management with follow-up echocardiography is recommended, and life expectancy is normal.[161] Surgical intervention is performed mainly to address a large shunt with right ventricular volume overload and pulmonary hypertension. The traditional surgical approach involves direct anastomosis of the anomalous pulmonary vein to the left atrium;[167] however, this has been associated with frequent thrombosis or stenosis of the anastomotic site.[160,161] A novel technique involves anastomosis of the anomalous pulmonary vein to a Gore-Tex vascular graft that is placed through the right atrial wall and sutured into a surgically created atrial septal defect to direct blood flow into the left atrium.[168]

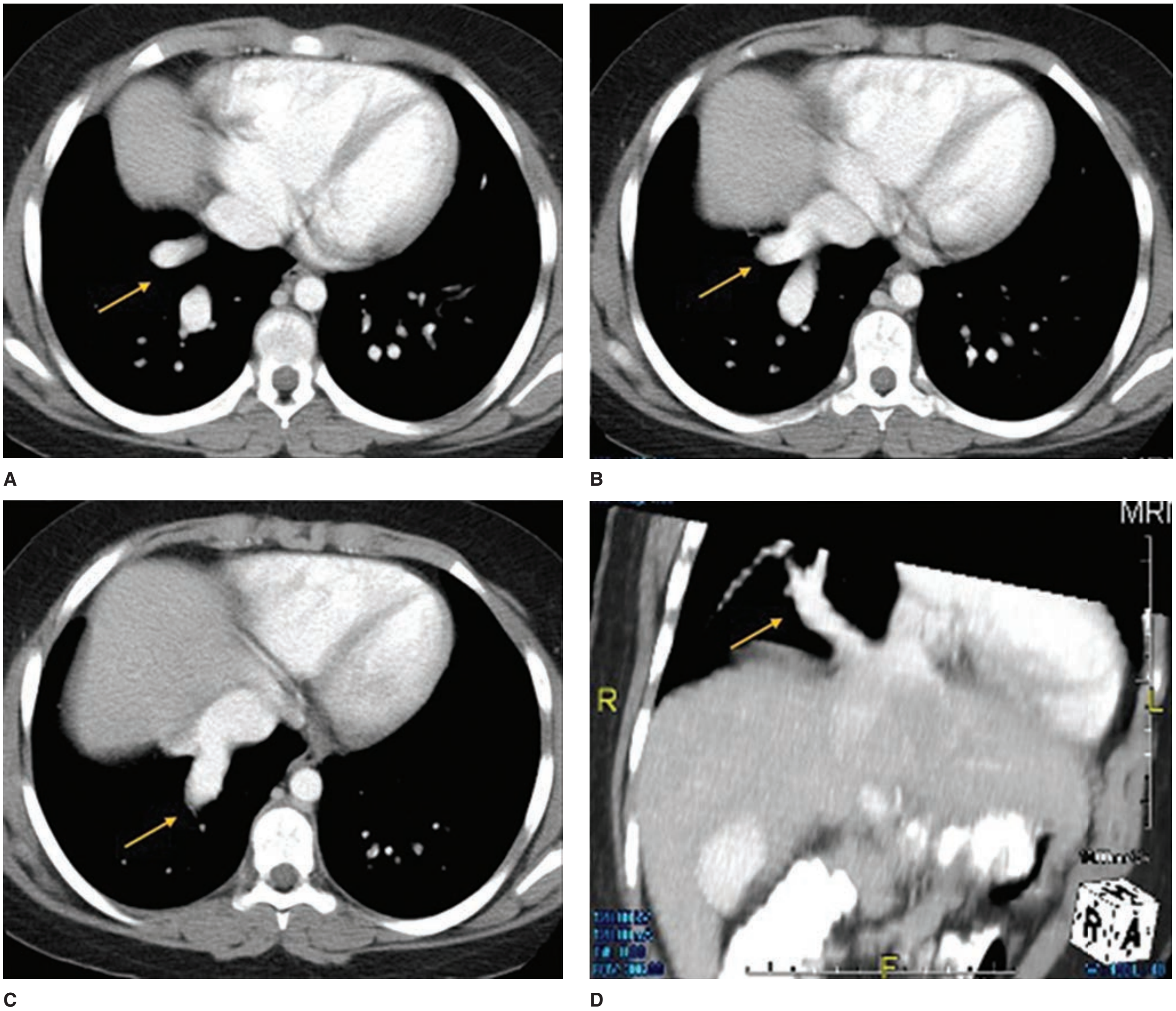

Figure 105-20 Scimitar syndrome (same patient as Fig. 105-19). Contrast-enhanced CT chest with serial axial images (**A–C**) and a coronal reformatted image (**D**) through the lower chest reveal an enhancing vascular structure in the right lower lobe that drains into the inferior vena cava and represents the anomalous draining right inferior pulmonary vein *(arrows)*.

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CHAPTER 106

Lung Transplantation

Ramsey R. Hachem

INTRODUCTION

Lung transplantation is the ultimate treatment for patients with advanced and end-stage lung diseases. The number of lung transplants performed annually has grown consistently over the past 30 years worldwide.[1] Indeed, more than 4500 lung transplants have been reported annually to the International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation (ISHLT).[1] Although donor organ availability is the primary barrier to increasing the volume of procedures performed, advances in donor selection, management, and the use of donation after circulatory death (DCD) donors and ex vivo lung perfusion (EVLP) have expanded the donor pool and allowed growth in transplant volumes worldwide.[2–7] Similarly, growing experience with lung transplantation has resulted in expansion in candidate selection. Today, lung transplant recipients are generally older, have more severe lung disease, have more comorbidities, and are more likely to be hospitalized or require life support before transplantation than 10 years ago.[2] Nonetheless, long-term survival after transplantation continues to improve compared with previous eras although the magnitude of this improvement is small on a year-to-year basis.[1,2] Indeed, long-term survival after lung transplantation remains significantly worse than after other solid organ transplants including kidney, liver, and heart transplantation.[2,8–10] Chronic lung allograft dysfunction (CLAD) has emerged as the leading obstacle to better long-term survival and the most common cause of death beyond the first year after transplantation.[1] The incidence of CLAD approaches 30% 3 years after transplantation, and the clinical course is characterized by a progressive decline in lung function culminating in severe clinical and physiologic impairment, respiratory failure, and death.[11–13] Other important complications after lung transplantation include infections, cardiovascular disease, chronic kidney disease (CKD), and malignancy.[1] Combined with episodes of rejection and the development of CLAD, these comorbidities adversely impact both quality of life and survival after lung transplantation. Better strategies and immunosuppressive regimens to prevent the development of CLAD and minimize the development of other complications are needed to improve long-term outcomes after lung transplantation. These have been the focus of basic, translational, and clinical studies, and ongoing research is critical to this mission.

HISTORY

The first human lung transplant was performed in 1963 by Dr. James Hardy at the University of Mississippi.[14] The recipient was a debilitated man with emphysema and lung cancer obstructing the left mainstem bronchus; other comorbidities included malnutrition and CKD. It was thought that a patient with a "terminal" condition was most appropriate for the first human lung transplant, which was considered an experimental treatment at the time. The patient underwent a left single lung transplant from a DCD donor. Immunosuppression consisted of mediastinal irradiation and azathioprine. The allograft functioned well with improvement in gas exchange; however, the recipient developed progressive kidney failure and ultimately died on day 18 after transplantation. In spite of the poor outcome, this early experience demonstrated that lung transplantation was technically feasible in humans, that the allograft could be physiologically functional, and that rejection could be averted at least for a brief period with the immunosuppression available at the time.

Enthusiasm for lung transplantation quickly waned after this promising but disappointing initial experience. Between 1963 and 1974, 36 lung transplants were reported.[15] The indications for transplantation spanned the spectrum of chronic lung diseases, and many recipients were moribund at the time of transplantation. Pneumonia, rejection, respiratory failure, and airway anastomotic complications were common causes of death.[15] One patient survived 6 months, and another survived 10 months after transplantation, but there were no long-term survivors. Consequently, there was a moratorium on lung transplantation although kidney, liver, and heart transplantation continued to develop clinically. The development of combined heart–lung transplantation was a key step in the progress toward successful isolated lung transplantation. After developing extensive surgical experience with primates in the laboratory, Dr. Bruce Reitz and a team of surgeons at Stanford University performed the first combined heart–lung transplant in a woman with idiopathic pulmonary arterial hypertension (IPAH).[16] The use of cyclosporin A was considered a critical component for this success, as it reduced the risk of rejection and minimized the required dose of steroids thereby promoting anastomotic healing. Initially, combined heart–lung transplantation was performed exclusively for patients with pulmonary vascular disease.[17] However, with growing experience and success, the procedure was then performed for patients with isolated lung disease, and the primary recipient's heart could be transplanted into a secondary recipient with isolated heart disease, a so-called domino heart transplant.[18,19] Lung rejection, obliterative bronchiolitis (OB), and pulmonary infections were common problems among survivors and presaged future clinical challenges in isolated lung transplantation.[17,20]

The first truly successful isolated lung transplant was performed by the Toronto Lung Transplant Group in 1983.[21] The group reported their experience with the first 2 single lung transplant recipients in 1986, both of whom were alive and well 26 and 14 months after transplantation.[21] This experience heralded the onset of the modern era of lung transplantation. The same group later reported their experience with en bloc double lung transplantation with a tracheal anastomosis in patients with bronchiectasis and emphysema.[22] However, this operation was associated with ischemic airway complications at the tracheal anastomosis and required prolonged cardiopulmonary bypass. Consequently, the operation was modified to sequentially transplant both lungs with the anastomoses at the level of the mainstem bronchi.[23] This is the currently performed surgery for bilateral lung transplants. Over time, more and more lung transplant programs were started across the world, and by 1993, more than 1000 lung transplants were reported to the ISHLT Registry.[1] Since then, transplant volumes have increased worldwide, and in 2017, more than 4500 lung transplant procedures were performed in adult and pediatric recipients.[24] In recent years, approximately 75% to 80% of all transplants are bilateral and only 20% to 25% are single lung transplants.[24]

INDICATIONS FOR LUNG TRANSPLANTATION

Lung transplantation has been performed for all benign lung diseases that progress to end stage and result in chronic respiratory failure. The most common indications for lung transplantation include chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD) from a variety of underlying causes, cystic fibrosis (CF), and pulmonary vascular disease.[1] Other benign lung diseases that are less common or less commonly progress to end stage also have been indications for lung transplantation including sarcoidosis, Langerhans cell histiocytosis (LCH), lymphangioleiomyomatosis (LAM), idiopathic bronchiectasis, and idiopathic OB. Retransplantation after graft failure has been an infrequent indication since the earliest era of lung transplantation. The most common indication for lung transplantation has changed over time. In 2000, almost 50% of all transplants reported to the ISHLT registry were performed for COPD and emphysema due to α1-antitrypsin deficiency, whereas 16% were performed for CF and 17% were performed for ILD.[24] In contrast, in 2017, only 29% of all transplants were performed for COPD and emphysema due to α1-antitrypsin deficiency, and 13% were performed for CF, while 40% were performed for ILD.[24] In the United States, this pattern is more striking. In 2018, 60% of lung transplants were performed for ILD, approximately 24% were performed for COPD, 10% for CF and other bronchiectasis, and 6% for pulmonary vascular disease.[2]

Reasons for differences in indications for transplantation in different countries are complex and include variations in clinical practice, social norms, and donor organ allocation policies. In the United States, donor lungs are allocated based on the lung allocation score (LAS), which is meant to maximize transplant benefit by accounting for risk of death on the waiting list and likelihood of survival in the first year after transplantation.[25,26] Early after implementation of the LAS, the distribution of underlying diagnoses undergoing transplantation changed significantly, favoring those with ILD, and this trend has continued over time.[2,27] The Eurotransplant International Foundation, the organization responsible for organ allocation in multiple European countries, also uses the LAS to allocate donor lungs.[28] Other countries and regions including France, Canada, the United Kingdom, and Scandinavia use different methods to allocate donor lungs and account for candidate urgency.[29–31] These systems have allowed high-urgency patients who are often critically ill to undergo transplantation.

RECIPIENT SELECTION

Identifying patients most likely to benefit from transplantation is critical because donor lungs are scarce resources and transplantation is a complex treatment with significant risks. Guidelines for recipient selection have been developed by the ISHLT.[32] In general, the ideal candidate has severe lung disease with ineffective medical therapy and a limited life expectancy yet is ambulatory and does not have significant medical or psychosocial contraindications. Transplantation should be considered if there is a high risk of death within 2 years and there is a high likelihood of survival 5 years after transplantation.[32] Clearly, making these assessments can be challenging in many cases. Furthermore, assessing the potential impact of pre-existing comorbidities on posttransplant outcomes can be very difficult. Not surprisingly, selection criteria for listing and transplantation vary among centers and countries, with some centers accepting and transplanting patients with comorbidities that other centers consider absolute contraindications. Nonetheless, comorbidities have historically been categorized as relative or absolute contraindications, and considering the overall sum of relative contraindications is critical when multiple comorbidities are present.

Comorbidities identified by the ISHLT guidelines as absolute contraindications are listed in Table 106-1.[32] However, the guidelines are not intended to be proscriptive, and some comorbidities listed as absolute contraindications are characterized using verbiage that allows clinicians and centers sufficient latitude to make individualized decisions regarding a patient's candidacy for transplantation. Among patients with a history of cancer, the risk of recurrence affects the appropriateness and timing of lung transplantation. In general, a 5-year cancer-free interval is recommended for most malignancies. However, a 2-year cancer-free interval may be appropriate with certain low-risk cancers such as prostate cancer. A large ISHLT registry study examined the impact of pretransplant cancer on outcomes after heart and lung transplantation.[33] The diagnosis of cancer before lung transplantation did not impact survival after transplantation, and no specific cancer was associated with an increased mortality after lung transplantation.[33] However, patients with leukemia, lymphoma, or myeloma had significantly worse survival after heart transplantation.[33] These findings suggest that the current approach to candidate selection for patients with cancer before lung transplantation are appropriate. Nonetheless, these may be overly conservative in some circumstances, and centers make individualized decisions in these cases. Indeed, a single-center series reported good short-term survival without a cancer-free period in some patients with prostate cancer before lung transplantation.[34]

TABLE 106-1 Absolute Contraindications to Lung Transplantation

Cancer
Acute renal failure with low likelihood of recovery
Chronic kidney disease with glomerular filtration rate <40 mL/min/1.73 m^2
Cirrhosis with portal hypertension
Acute coronary syndrome or stroke within 30 days
Septic shock
Active extrapulmonary or disseminated infection
Active tuberculosis infection
HIV infection with detectable viral load
Progressive cognitive impairment
Nonadherence to medical therapy
Uncontrolled psychiatric illness
Lack of a reliable and adequate social support system
Severely impaired functional status with limited rehabilitation potential
Substance abuse or dependence
Active tobacco smoking

Significant dysfunction of other vital organs, including chronic kidney disease (CKD), liver disease, or heart disease is generally considered a contraindication. Progressive acute renal failure, liver failure, and recent acute coronary syndrome or stroke also are considered contraindications. Similarly, chronic infection with highly virulent or resistant organisms can be a contraindication to transplantation at some centers, but this is not a uniform practice, and many patients with chronic infection with multidrug-resistant or pan-resistant *Pseudomonas aeruginosa* are suitable candidates for transplantation and have good long-term outcomes.[35,36] In contrast, chronic infection with certain genomovars of *Burkholderia cepacia* complex or *Mycobacterium abscessus* is associated with adverse clinical outcomes after transplantation.[37–40] Consequently, many transplant programs consider these infections absolute contraindications to transplantation. Historically, an unstable clinical condition was considered an absolute contraindication to transplantation at most centers. However, in the United States, approximately 15% of lung transplant recipients are in an intensive care unit at the time of transplantation, and 8% to 10% require either invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) support.[2] Indeed, the use of ECMO as a bridge to transplantation has increased worldwide over the past 10 years with acceptable long-term survival among those who are successfully bridged to transplant.[41–43] During the coronavirus disease 2019 (COVID-19) pandemic, ECMO has been used as a bridge to recovery in patients with very severe acute respiratory distress syndrome (ARDS), and a minority who would not recover have gone on to lung transplantation.[44,45] Lastly, active tobacco use, drug or alcohol dependence, nonadherence to medical therapy, uncontrolled psychiatric illness,

TABLE 106-2 Relative Contraindications to Lung Transplantation

Advanced age
Obesity with a BMI >35 kg/m^2
Severe malnutrition with a BMI <16 kg/m^2
Severe esophageal disease (e.g., esophageal dysmotility, gastroesophageal reflux)
Extensive previous thoracic surgery or pleurodesis
Severe osteoporosis
Chronic pulmonary infection with highly virulent organisms (e.g., *Mycobacterium abscessus abscessus*, *Lomentospora prolificans*, *Burkholderia cepacia* complex)
Hematologic disorders
Thoracic cage deformity that may be expected to cause severe restrictive ventilatory defect after transplant

and lack of adequate social support are considered absolute contraindications to transplantation for obvious reasons.

Relative contraindications to transplantation are listed in Table 106-2. In the earliest era of lung transplantation, age by itself was considered an important factor in candidate selection; however, over time, it was recognized that comorbidities associated with advanced age were more important than age alone. Indeed, in the United States, patients 65 years old and older have had the greatest increase in transplant volume over the past 10 years and accounted for 38.6% of all lung transplant recipients in 2020.[2,46] Likewise, hepatitis C virus (HCV) infection was previously considered a relative contraindication, but the advent of highly effective direct-acting antiviral (DAA) therapy can achieve sustained virologic response either before or after lung transplantation, making transplantation feasible with outcomes similar to those in uninfected patients.[47] Successful lung transplantation has been reported in patients infected with human immunodeficiency virus (HIV), but this is currently reserved to centers with extensive experience in both lung transplantation and HIV care.[48,49]

TIMING OF TRANSPLANTATION

For patients with progressive or advanced lung disease, early referral for transplant evaluation is ideal. The evaluation is comprehensive and often identifies comorbidities that require intervention to improve the patient's candidacy and facilitate the postoperative recovery. For example, occult coronary artery disease may be uncovered during the evaluation, and percutaneous revascularization may be necessary. Furthermore, many patients and their families face significant psychosocial stressors with transplantation including personal finances, identifying a caregiver, the logistics of moving closer to the transplant center, and the psychological trauma associated with disability and major surgery. Thus, early referral provides an opportunity for patients to better prepare for transplantation and the necessary education about the transplant process and life after transplantation. In addition, outcomes after transplantation are influenced by the patient's clinical condition immediately before transplantation, and referral before the patient becomes critically ill and transplantation becomes emergent probably improves posttransplant outcomes.

Interstitial Lung Diseases

There is often a delay in the diagnosis of interstitial lung diseases (ILD).[50] Moreover, the clinical course is typically progressive and sometimes unpredictable. This is particularly true in idiopathic pulmonary fibrosis (IPF), which is the most common ILD leading to transplantation. Furthermore, the prognosis of patients with IPF is poor in spite of available medical therapy.[51,52] Indeed, mortality on the waiting list for transplantation is highest for patients with ILD.[2,32] In the latest Scientific Registry of Transplant Recipients (SRTR) annual report, waitlist mortality for patients with ILD was 29.7 deaths per 100 waitlist-years compared with 9.4 deaths per 100 waitlist-years for patients with COPD.[2] Consequently, early referral for transplantation is crucial. For patients with IPF, referral is recommended at the time of diagnosis.[32] For any form of pulmonary fibrosis, a decline in forced vital capacity ≥10% or diffusing capacity ≥15% in the past 2 years, and resting or exertional hypoxemia requiring supplemental oxygen, are other criteria for referral for transplantation.[32] General guidelines for listing for transplantation are outlined in Table 106-3.[32]

Chronic Obstructive Pulmonary Disease

COPD generally follows a slowly progressive clinical course, and short-term survival is preserved in spite of severe physiologic

TABLE 106-3 Guidelines for Listing for Lung Transplantation

Interstitial lung diseases
Decline in FVC >10% or >5% with radiographic progression in the past 6 months
Decline in D_{LCO} >10% in the past 6 months
Oxygen saturation <88% during a 6-min walk test
Decline in 6-min walk distance >50 meters in the past 6 months
Pulmonary hypertension
Hospitalization for a respiratory indication
Chronic obstructive pulmonary disease
BODE index ≥7
FEV_1 <20% predicted
Chronic hypercapnia
History of severe exacerbations
Moderate to severe pulmonary hypertension
Cystic fibrosis
FEV_1 <25% predicted
Hypoxemia (Pa_{O_2} <60 mm Hg)
Hypercapnia (Pa_{CO_2} >50 mm Hg)
An exacerbation requiring mechanical ventilation
Need for noninvasive mechanical ventilation
Pulmonary hypertension
Frequent exacerbations requiring hospitalization
Recurrent massive hemoptysis despite bronchial artery embolization
Rapid decline in lung function
World Health Organization functional class IV
Pulmonary hypertension
ESC/ERS high risk or REVEAL risk score >10 despite aggressive therapy
Progressive hypoxemia
Progressive kidney or liver dysfunction due to pulmonary hypertension
Development of hemoptysis

FVC, forced vital capacity; D_{LCO}, diffusing capacity for carbon monoxide; FEV_1, forced expiratory volume in 1 s; ESC/ERS, European Society of Cardiology/European Respiratory Society; REVEAL, Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management.

impairment relative to other end-stage lung diseases. In the SRTR annual report, waitlist mortality is lowest for patients with COPD.[2] The BODE (Body-mass index, degree of airflow Obstruction, Dyspnea, and Exercise capacity) index is a multidimensional composite score developed to predict survival in patients with COPD, and an increasing score correlates well with survival.[53] For example, a BODE index of 7 to 10 is associated with a mortality of 80% at 52 months.[53] Some have advocated using of the BODE index to estimate or predict the survival benefit of transplantation in patients with severe COPD.[54] However, it is noteworthy that the BODE index was calculated with an older cohort of patients, and some were still smoking. These differences from patients who are being considered for transplantation raise the possibility that the BODE index may underestimate predicted survival in this cohort.[55] Nevertheless, a BODE index of 5 or 6 with frequent exacerbations, an increase in the BODE index >1 over 24 months, or a forced expiratory volume in 1 s (FEV_1) <25% are general criteria for referral for transplantation.[32] Other criteria for referral include progressive disease in spite of optimal medical therapy, supplemental oxygen, and pulmonary rehabilitation; and unacceptably poor quality of life.[32] Guidelines for listing for transplantation are outlined in Table 106-3.

Cystic Fibrosis

CF is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. CFTR modulators improve production, intracellular processing, or function of the defective CFTR protein. These have revolutionized the care of patients with CF by targeting the underlying genetic basis of the disease rather than treating the downstream effects. The combination of elexacaftor-tezacaftor-ivacaftor improves lung function, decreases the frequency of exacerbations, and improves quality of life in patients with one or more copies of the Phe508del mutation, which is the most common CF mutation.[56] The full impact of elexacaftor-tezacaftor-ivacaftor on transplantation remains to be seen. However, it should be noted that there are many patients with CF who developed advanced lung disease before the availability of highly effective modulators, and although treatment may postpone the need for transplantation, it is likely that these patients will ultimately require transplantation. Therefore, the Cystic Fibrosis Foundation recommends early referral for transplantation to optimize patients medically, psychosocially, and financially.[57] Indeed, late referral for transplantation is associated with an increased risk of waitlist mortality.[58] An FEV_1 <50% predicted associated with a 20% relative decline within the previous 12 months, or an FEV_1 <40% predicted with markers of shortened survival (reduced 6-min walk distance, hypoxemia, hypercapnia, pulmonary hypertension, low body mass index, frequent exacerbations, massive hemoptysis, or pneumothorax), or an FEV_1 <30% predicted are criteria for referral for transplantation.[57] Guidelines for listing for transplantation are outlined in Table 106-3.

Pulmonary Hypertension

Over the past 30 years, pulmonary vasodilators have revolutionized the care of patients with pulmonary hypertension. The decisions to refer and to list a patient for transplantation are difficult in this patient population. Suspected or known causes of pulmonary hypertension that are generally poorly responsive to medical therapy such as pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis are indications for early referral for transplantation. In other patients with pulmonary hypertension, use of the European Society of Cardiology/European Respiratory Society (ESC/ERS) and the Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management (REVEAL) models to risk stratify patients is recommended.[32,59,60] Patients who cannot achieve a low risk status within 6 months of aggressive therapy should be referred for transplant evaluation.[32,59,60] Guidelines for listing for transplantation are outlined in Table 106-3.[32]

DONORS

Worldwide, the vast majority of lung donors are deceased. Living donor lobar lung transplantation is an operation in which two people donate their lower lobes to one recipient. This operation was popularized in the mid-1990s and was feasible for adolescent or small-statured adult recipients who could gain sufficient lung function and fill their thoracic cavity with a right and a left lower lobe from two donors. However, by the mid-2000s, this operation fell out of favor in the United States although it remains a common lung transplant surgery in Japan.[61] Most deceased donors are brain-dead, but non–heart beating donors, or DCD donors, account for a growing proportion of donors in many parts of the world including Europe and Australia.[62] In the United States, DCD donors accounted for 4.8% of all lung donors in 2018.[2] Lungs are recovered from approximately 20% of all deceased organ donors because they are more susceptible to injury related to brain death, aspiration, and ventilator-induced lung injury. In fact, in the United States, there were 2577 lung donors in 2020 compared with 3761 heart donors, 9702 (9211 deceased and 491 living) liver donors, and 17,162 (11,925 deceased and 5237 living) kidney donors.[63]

Donor Selection

The original criteria for donor selection were derived from expert opinion and experience rather than studies to identify variables associated with clinical outcomes. Not surprisingly, these early criteria were fairly stringent and focused on minimizing risk rather than maximizing donor utilization. Indeed, in 1990, there were fewer than 500 people on the waiting list for lung transplantation in the United States, and the median waiting time was 217 days.[64] So, a conservative approach to donor selection was reasonable and expected at the time. However, it quickly became apparent that conservative donor selection criteria would not meet the rapidly growing demand as the number of people waiting for transplantation increased to nearly 3500 by 1999, and the median waiting time approached 2 years.[64] In 2003, an ISHLT consensus report defined an ideal lung donor as having the following characteristics: age <55 years, smoking history <20 pack-years, clear chest x-ray, absence of purulent secretions on bronchoscopy, absence of chest trauma, and a Pa_{O_2}:Fi_{O_2} ratio >300.[65] Furthermore, the group recognized the limitations of using such stringent and conservative criteria for donor selection and the benefits of expanding the donor pool with the use of marginal or extended-criteria donors.[65] There is no widely accepted definition for marginal or extended-criteria donors; these are generally defined as not meeting all of the criteria of an ideal donor. The term *marginal* is a misnomer as it implies inferior quality. However, multiple centers reported good outcomes after transplantation from extended-criteria donors as early as the mid 1990s.[66–68] Clearly, there is a balance between expanding the donor pool to meet the demand of the increasing number of patients on the waiting list and minimizing the risk of death while waiting and having good outcomes after transplantation. A number of lung donor scoring systems have been developed to make donor acceptance more objective.[69–72] These have generally predicted outcomes including donor acceptance and recipient survival reasonably well. However, an inherent limitation to the clinical use of a donor score to decide about donor acceptance is that the scoring systems do not account for recipient characteristics and their impact on outcomes. For example, a donor may be perfectly acceptable for a recipient at low risk for severe primary graft dysfunction (PGD) (e.g., a patient with COPD who does not have pulmonary hypertension), but the same donor may not be acceptable for a recipient at high risk for severe PGD (e.g., a patient with severe pulmonary hypertension or obesity). Interactions between donor and recipient factors are complex, and these have an important impact on outcomes. Future research in donor selection will need to account for recipient factors and these interactions to maximize the donor pool and improve outcomes.

Traditionally, only donors who were not infected with HCV were accepted for lung transplantation. However, the advent of highly effective DAA has made transplantation from hepatitis C viremic donors into uninfected recipients a clinical possibility.[73–75] Small case series have reported good short-term outcomes and early resolution of HCV infection among recipients who became viremic in the posttransplant period with DAA.[73–75] In one study, placing HCV-infected donor lungs on EVLP and irradiating the perfusate with ultraviolet C before transplantation reduced the viral load that would be transmitted to the recipient.[74] However, a recent study of HCV-infected heart donors identified an increased risk of acute cellular rejection (ACR) associated with hepatitis C viremia, but this has not been reported in lung transplantation.[76] The long-term impact of these early episodes of ACR on graft function and patient survival remains to be seen. Clearly, the use of HCV-infected lung donors will expand the donor pool, and highly effective DAA appears to prevent long-term infection in the recipient. Whether this will result in a higher incidence of ACR or other unexpected complications after lung transplantation remains to be seen as experience with this approach grows.

■ Donor Management

The donor's premortem clinical condition can result in lung injury due to brain injury, aspiration of gastric or oropharyngeal secretions, pneumonia, and mechanical ventilation. Additionally, aggressive fluid resuscitation can exacerbate this lung injury by increasing extravascular lung water. Careful donor management strategies aimed at maximizing lung donor utilization can be successful without adversely affecting other organ retrieval (e.g., kidney). Multiple studies of donor management protocols have been published.[77–79] These consistently show that relatively simple donor management protocols increase the number of donor lungs suitable for transplantation without adversely impacting clinical outcomes after transplantation. The main aspects of these protocols include recruitment maneuvers, careful attention to fluid balance, bronchoscopy to clear retained secretions, and techniques to prevent aspiration such as elevating the head of the bed and adequate inflation of the endotracheal tube balloon.[77–79] Lung-protective ventilation with low tidal volume mitigates the risk of ventilator-induced lung injury and other pulmonary complications in patients with and without acute respiratory distress syndrome (ARDS) and those undergoing abdominal surgery.[80–82] A randomized controlled trial demonstrated that lung-protective ventilation with a tidal volume of 6 to 8 mL/kg resulted in increased donor lung utilization.[5] More recently, prone ventilation for 12 h or longer to decrease atelectasis was shown to improve gas exchange and increase donor utilization.[83]

■ Ex Vivo Lung Perfusion

Traditionally, lungs are flushed with a cold low-potassium dextran solution antegrade and retrograde after they are explanted from the donor, then placed in a bag of cold preservation fluid on ice for transport to the recipient hospital.[84] This cold preservation strategy has been the standard approach to lung transplantation over the past 30 years. The purpose of cold preservation is to inhibit cellular metabolism through hypothermia and mitigate ischemia-reperfusion injury. However, in spite of optimal preservation, PGD remains a significant clinical problem after transplantation. More importantly, this static preservation does not permit serial assessment of the lungs once they have been retrieved from the donor. EVLP is a technique to perfuse and ventilate the lungs outside the donor's body that permits serial evaluation of lung function and may decrease pulmonary edema. EVLP was first used in clinical practice in 2006 in Lund, Sweden.[85] Lungs from 9 donors that were deemed unsuitable for transplantation were perfused ex vivo. Of these, 6 were "reconditioned" to acceptable function and were transplanted; 2 recipients died in the first year and 4 remained alive 2 years after transplantation.[85] In a subsequent landmark study, 4 h of EVLP improved gas exchange in 20 of 23 lungs from donors deemed at high risk for failure.[86] These lungs were transplanted, and recipients had outcomes similar to control patients who underwent transplantation using standard donor lungs.[86] Since that early experience, there have been numerous advances in EVLP, and multiple platforms and protocols are available in clinical practice.[87] EVLP can be portable, where donor lungs are placed on the device after they are explanted and perfused during transport to the recipient hospital. An alternative EVLP platform is static, where donor lungs are preserved in the standard fashion and transported on ice to be placed on EVLP at the recipient hospital.[87,88] Additional variabilities in platforms and protocols include the set flow, ventilation, and use of an acellular perfusate or the addition of erythrocytes to the perfusate. The optimal platform and protocol are not clear, and there have been no head-to-head comparisons of the different approaches. Instead, transplant programs have developed their local practices with a given EVLP platform. Nonetheless, EVLP has expanded the donor pool, and ongoing research is focused on reconditioning unsuitable lungs.[89]

LUNG TRANSPLANT SURGERY

Bilateral lung transplantation is currently the most commonly performed lung transplant surgery worldwide.[1] In 2017, 3727 bilateral lung transplants and 827 single lung transplants were reported to the ISHLT Registry.[24] Living donor lobar lung transplantation has not been performed in the United States since 2013 and is now mainly performed in countries with very limited access to deceased donor lungs.[61,63] Bilateral lung transplantation is associated with significantly better survival than single lung transplantation. In the ISHLT registry, bilateral lung transplantation had a median survival of 7.8 years whereas single lung transplantation had a median survival of 4.8 years.[24] However, it should be noted that patients in these cohorts were not randomized to receive a bilateral or a single lung transplant, and comorbidities that may have influenced the decision to perform a single lung transplant may also impact survival. Thus, it is unclear how much of the survival benefit seen with bilateral lung transplantation is due to the operation performed and how much is related to the underlying recipient characteristics. Single lung transplantation may expand the donor pool, but it provides less lung function and may not be appropriate with extended-criteria donors. No randomized controlled trial of bilateral versus single lung transplantation has ever been performed.

The underlying diagnosis leading to transplantation can impact the decision about a bilateral or a single lung transplant. Cystic fibrosis and other causes of bronchiectasis require a bilateral transplant to avoid spill-over infection from the remaining native lung into the allograft if a single lung transplant is performed. Otherwise, single lung transplantation can be performed for all other indications. However, pulmonary hypertension poses a unique physiologic scenario. Although single lung transplantation has been performed successfully in the past for pulmonary hypertension,[90,91] the allograft receives the majority of perfusion while ventilation is evenly distributed between the native lung and the allograft. This can result in severe ventilation–perfusion abnormalities when there are allograft complications such as PGD, acute rejection, or pneumonia. Therefore, bilateral lung transplantation is preferred for patients with pulmonary hypertension. Combined heart–lung transplantation is reserved for patients with Eisenmenger syndrome who have a congenital defect that is either uncorrectable or technically very difficult to repair in combination with lung transplantation.

What follows is a brief overview of the surgical approach to transplantation. Bilateral anterolateral thoracotomy is the most common incision during bilateral transplantation.[84] This incision can avoid dividing the sternum, or the sternum can be divided as in a clamshell incision to provide additional exposure if there is cardiomegaly or a small thoracic cavity. A median sternotomy is an alternative approach and is preferred by some surgeons. Either a posterolateral or an anterolateral thoracotomy can be performed during single lung transplantation, although the anterolateral approach generally provides better exposure to the hilum. The chest cavity is entered in the fourth intercostal space as the intercostal muscles are divided. The lung with the worst physiologic function is explanted first, as this may avoid the need for extracorporeal support (e.g., ECMO or cardiopulmonary bypass) during the transplant. Dissection of pleural adhesions can be difficult in patients with previous thoracic surgery, pleurodesis, or underlying bronchiectasis. Careful attention is made to protect the phrenic, vagus, and recurrent laryngeal nerves. The sequence of anastomoses is bronchial, arterial, then venous. The bronchial anastomosis is an end-to-end anastomosis. Similarly, the pulmonary arterial anastomosis is also an end-to-end anastomosis. The venous anastomosis is made by amputating the recipient's venous stumps to create an atrial cuff, which is then sutured to the donor atrial cuff.[84] Once hemostasis is confirmed, chest tubes are placed to drain the pleural spaces, and the chest is closed by reapproximating the sternum (if a sternotomy was done) and the ribs. Then, the muscle, fascia, and skin are reapproximated.

Approximately 30% to 50% of lung transplant surgeries require the use of cardiopulmonary bypass or ECMO support, although center and surgeon preferences are variable.[92,93] Historically, cardiopulmonary bypass was the standard platform for intraoperative support, but veno-arterial ECMO has gained popularity over the past 5 years. Indeed, observational studies suggest that ECMO is associated with less bleeding; a lower incidence of PGD; a shorter duration of mechanical ventilation, ICU stay, and hospital length of stay; and a lower incidence of renal failure.[93–95] The decision to use cardiopulmonary bypass or ECMO intraoperatively is based on severity of the underlying lung disease, the ability to support the patient with single lung ventilation and perfusion, and surgeon preferences. In general, patients with severe pulmonary hypertension and those with severe hypercapnic or hypoxemic respiratory failure require mechanical support. In addition, patients who become unstable hemodynamically during the operation require mechanical support.

MEDICAL MANAGEMENT

Early postoperative management and ongoing monitoring of the lung transplant patient are considered below.

Early Postoperative Management

Immediate postoperative care is focused on ventilatory support, hemodynamic management, analgesia, antibiotic prophylaxis, and immunosuppression. There have been no randomized controlled trials to guide early critical care practices, and clinical protocols vary across centers. Specifically, there have been no randomized controlled trials to guide ventilator management in the immediate period after transplantation, and although lung-protective ventilation is commonly used, tidal volumes are usually set based on recipient rather than donor ideal body weight even if there is a significant size discrepancy.[96,97] Transplanted lungs are susceptible to pulmonary edema because lymphatics are not re-anastomosed and PGD is common. Therefore, a negative fluid balance is favored as hemodynamics allow. Indeed, retrospective studies suggest that intraoperative fluids and a high central venous pressure are associated with an increased risk of PGD, prolonged duration of mechanical ventilation, and death.[98,99] Attempts to wean patients from mechanical ventilation are made as soon as practical. Pulmonary hygiene to clear secretions and avoid atelectasis is critical in the first few days after extubation. This is often complicated by incisional pain and the need for opiates, and thoracic epidural analgesia is an effective alternative.[100] The donor and the recipient are given empiric broad-spectrum antibiotics before the transplant, and these are continued for the first 1 to 2 weeks after transplant. The antibiotic regimen is typically adjusted based on culture results and sensitivity patterns. Prophylactic regimens against opportunistic infections are variable across centers. However, most centers implement prophylaxis in patients at risk for cytomegalovirus (CMV) (e.g., seropositive recipients or seronegative recipients of seropositive donors) with valganciclovir for the first year after transplantation.[101] Likewise, most centers use long-term prophylaxis against *Pneumocystis jiroveci*. Fungal prophylaxis is highly variable across centers, with some using universal prophylaxis against molds while others start antifungals based on culture results from bronchoscopy specimens.

Long-Term Monitoring

Long-term care after lung transplantation is complex. Patients are at risk of numerous complications including rejection, infections, and medication-associated adverse events. Furthermore, the immunosuppressive regimen has a narrow therapeutic window with significant risk of toxicity and complex drug–drug interactions. Therefore, transplant centers follow patients closely. Institutional protocols vary and depend on local resources and expertise as well as the distance of the patient's residence to the transplant center. In general, patients are seen frequently (e.g., weekly or biweekly) at the transplant center in the first 3 or 4 months after transplantation, and routine lab work including therapeutic drug monitoring is checked frequently during this period. The frequency of visits typically decreases after the first few months; at many centers, patients are seen monthly during the first year after transplantation and every 2 to 3 months thereafter. Collaboration and close communication between the transplant center and local referring physicians is essential if patients live at a distance from the transplant center. During these visits, patients are assessed for respiratory symptoms and signs and symptoms of medication side effects, and allograft function is monitored with pulmonary function tests. Home spirometry is an effective method of identifying complications early in between visits.[102,103] This has been particularly useful during the COVID-19 pandemic.

Acute cellular rejection (ACR) is a common complication early after transplantation and is often clinically silent. Bronchoscopy with transbronchial lung biopsies is the current gold standard for the diagnosis of ACR. Thus, many transplant programs use a surveillance bronchoscopy protocol to detect ACR.[104,105] The goal is to identify and treat episodes of ACR before the onset of allograft dysfunction. Furthermore, since ACR is a widely recognized risk factor for the development of CLAD, it is hoped that early treatment would mitigate this risk. However, this potential benefit has not been examined in the context of a clinical trial. Furthermore, some transplant centers have not adopted a surveillance bronchoscopy protocol, and a number of studies have reported good long-term outcomes without surveillance bronchoscopy.[106,107] Nonetheless, centers that do not perform surveillance bronchoscopy generally have a low threshold to perform a clinically indicated bronchoscopy. Indeed, at one center that stopped performing surveillance bronchoscopy, patients had a similar number of procedures whether they underwent surveillance or clinically indicated bronchoscopy.[108] There is a lack of evidence to guide clinical practice in this area, and transplant centers have developed local protocols for patient follow-up based on experience, expertise, and resources.

Over the past 10 years, there has been a growing interest in the role of humoral immunity in lung transplant rejection. The development of donor-specific antibodies (DSA) to mismatched human leukocyte antigens (HLA) has been increasingly recognized as an important risk factor for the development of CLAD.[109–112] Consequently, some have advocated for screening clinically stable recipients for DSA with the hope that early treatment may improve outcomes.[113–115] Furthermore, screening for DSA identifies patients at increased risk for CLAD who may benefit from closer monitoring and earlier diagnosis. Additionally, maintenance immunosuppression can be optimized in these patients to delay the onset of CLAD. However, although the development of DSA is common early after transplantation,[116] screening and interventions based on the screening results have not been evaluated in a randomized controlled trial, and the benefits of these approaches remain unproven. Recent work in antibody-mediated rejection (AMR) has focused on donor-derived cell-free DNA (ddcfDNA) as a biomarker.[117,118] Allograft injury results in the release of ddcfDNA into the circulation, and this appears to be a sensitive marker for injury especially due to AMR.[118] Elevated levels of ddcfDNA are noted almost 3 months before the onset of clinical AMR, making this in combination with DSA testing potentially very useful tests for clinical monitoring.[118]

IMMUNOSUPPRESSION

Immunosuppression management of the lung transplant recipient immediately following surgery, as well as over the long term, are considered below.

Induction Immunosuppression

Induction immunosuppression is given either during or immediately after transplant surgery depending on the drug. The goal is to prevent early rejection by rapidly suppressing immune responses to the allograft. According to the ISHLT registry report, more than 80% of lung transplant recipients were treated with induction immunosuppression in 2017.[24] This is significantly higher than in 2010 when approximately 50% were treated with induction.[24] The majority of patients are treated with an IL-2 receptor antagonist (e.g., basiliximab), and <10% are treated with polyclonal antithymocyte globulin (ATG) or alemtuzumab.[24] However, benefits of induction immunosuppression, and basiliximab in particular, have not been clearly demonstrated in clinical trials in lung transplantation. In the only multicenter study examining the role of induction immunosuppression after lung transplantation to date, 223 patients at 18 centers were randomized to rabbit ATG or placebo.[119] There was no significant difference in the composite efficacy endpoint of ACR, allograft loss, or death between the 2 groups.[119] There was also no significant difference in the incidence of bacterial, viral, or fungal infections between the 2 groups.[119] In the only other randomized controlled trial comparing rabbit ATG to no induction, the ATG group was significantly less likely to develop mild ACR.[120] However, in a subsequent study of long-term follow-up of the 2 groups, the ATG group only had a lower incidence of ACR in the first 6 months after transplant, but there was no significant difference in the overall incidence of ACR, BOS, or survival between the 2 groups.[121] Another single-center trial randomized patients to muromonab-CD3, equine ATG, or daclizumab (another IL-2 receptor antagonist that is no longer available) and found no significant difference in ACR, BOS, or survival between the 3 groups.[122] A smaller study randomized patients to rabbit ATG or daclizumab and found no significant difference in ACR, BOS, or infections between the 2 groups.[123] More recently, a single-center study demonstrated a significantly lower incidence of ACR with alemtuzumab compared to rabbit ATG.[124] It is noteworthy that although basiliximab is the most commonly used agent for induction after lung transplantation worldwide, there have been no randomized controlled trials to support its use and little evidence to support the use of any induction agent after lung transplantation. An important limitation of clinical trials in lung transplantation is that the sample size is often small, and studies may be underpowered to detect statistically significant differences. Indeed, the largest clinical trial examining the role of induction randomized 223 patients.[119] In an ISHLT registry analysis, which included more than 20,000 patients, induction was associated with a significant survival benefit.[124] However, this finding should be interpreted with caution as confounding variables that may influence survival but are not included in this univariate analysis are not accounted for.

Maintenance Immunosuppression

Maintenance immunosuppression is initiated either immediately before or after the transplant surgery based on institutional protocols and continued lifelong. In general, maintenance immunosuppression is most intensive in the first 6 to 12 months after transplantation and is subsequently tapered to minimize toxicity unless the patient develops late ACR or CLAD. Patients are treated with three classes of drugs: a calcineurin inhibitor (e.g., tacrolimus, cyclosporin A), a cell-cycle inhibitor (e.g., azathioprine, mycophenolate mofetil), and a steroid (e.g., prednisone). Tacrolimus and cyclosporin A inhibit T-cell proliferation by inhibiting calcineurin and decreasing transcriptional activation of proinflammatory cytokine genes, including IL-2, tumor necrosis factor α, and interferon γ. Azathioprine and mycophenolate mofetil block T- and B-cell proliferation by inhibiting purine metabolism. The most common combination reported to the ISHLT registry is tacrolimus, mycophenolate mofetil, and prednisone.[24] Indeed, more than 80% of patients are on tacrolimus and mycophenolate mofetil at the end of the first year after transplantation.[124]

Several randomized controlled trials comparing the efficacy of tacrolimus and cyclosporin A have been conducted over the past 25 years.[125–130] Different induction agents or no induction and different cell-cycle inhibitors have been used in these trials. Additionally, different recipient and donor selection criteria as well as different medical management practices have been used in these trials. Not surprisingly, the results have been somewhat inconsistent. Three trials demonstrated a statistically significant reduction in ACR with tacrolimus,[125,127,129] and 3 demonstrated no significant difference in ACR between the 2 drugs.[126,128,130] Two trials demonstrated a significantly lower incidence of BOS with tacrolimus,[126,130] 1 demonstrated a trend toward a lower incidence of BOS that was not statistically significant with tacrolimus,[129] and 1 demonstrated no significant difference in the incidence of BOS between the 2 drugs.[128] Notably, no significant difference in the incidence of infection has been identified between the 2 drugs in any of the trials, and most importantly, no significant difference in survival has been identified between the 2 drugs in any of the trials.[125–130] However, it should be noted that none of the trials was adequately powered to detect a survival difference, and survival was not the primary endpoint in any of these trials. Three clinical trials comparing the efficacy and safety of azathioprine to mycophenolate mofetil have been conducted in lung transplantation.[131–133] The earliest trial randomized 22 patients to mycophenolate mofetil or azathioprine in combination with cyclosporine A and ATG induction and showed a lower incidence of ACR in the mycophenolate mofetil group, but there was no difference in the incidence of BOS or survival between the 2 groups.[131] Two subsequent, larger studies showed no significant difference in ACR, BOS, or survival between azathioprine and mycophenolate mofetil.[132,133]

Mammalian target of rapamycin (mTOR) inhibitors, including sirolimus and everolimus, have antiproliferative effects beyond their immunosuppressive properties, and this makes them appealing for the prevention of CLAD.[134] Initial experience with sirolimus initiated early after lung transplantation was notable for wound and airway anastomotic dehiscence.[135,136] Since then, a number of clinical trials have examined the role of delayed initiation of mTOR inhibitors in combination with either cyclosporine A or tacrolimus compared to either azathioprine or mycophenolate mofetil.[11,137–139] Two studies demonstrated a lower incidence of ACR with everolimus compared to mycophenolate mofetil,[11,140] but none of the studies showed a lower incidence of BOS or better survival associated with either mTOR inhibitor.[11,137–139] Importantly, there was a high incidence of toxicity including kidney injury, hyperlipidemia, edema, and infections associated with mTOR inhibitors, and drug discontinuation was frequent.

Ideally, clinical practice would be guided by high-quality evidence and carefully designed randomized controlled trials. However, this has been challenging in lung transplantation in spite of many advances in immunosuppression. Clinical trials have been limited by small sample sizes, short duration of follow-up, frequent crossover, and drug discontinuation. Thus, clinical practice has largely been guided by experience and institutional protocols.

PRIMARY GRAFT DYSFUNCTION

PGD is a common early complication after lung transplantation that represents an acute lung injury with clinical, radiographic, and histologic features similar to ARDS.[140,141] The pathogenesis is complex, but ischemia after retrieval from the donor followed by reperfusion at the time of transplantation is the primary cause.[142] Other factors that promote this injury include noncardiogenic pulmonary edema due to donor brain death, aspiration, and ventilator-induced lung injury. In 2005, the ISHLT developed a definition for PGD to standardize the nomenclature and facilitate research at different centers.[143] The definition was subsequently refined in 2016.[140] The definition is based on the presence of radiographic evidence of pulmonary edema and impairment in gas exchange assessed by the Pa_{O_2}:Fi_{O_2} ratio.[140,143] For example, a patient with pulmonary edema on chest x-ray and a Pa_{O_2}:Fi_{O_2} ratio of 180 would have PGD grade 3. In contrast, a patient without pulmonary edema on chest x-ray would have PGD grade 0 regardless of the Pa_{O_2}:Fi_{O_2} ratio.[140,143] PGD is graded at four timepoints over the first 72 h after transplantation (time 0, time 24 h, time 48 h, and time 72 h). Inherent to this definition is the exclusion of other confounding complications that might cause allograft dysfunction including hyperacute rejection, venous anastomotic complications, cardiogenic pulmonary edema, and pneumonia. The definition has been validated in multiple studies.[144,145] The incidence of PGD grade 3 at any timepoint in the first 72 h is approximately 30%.[141] In general, PGD grades are highest immediately after transplantation and improve over the next 72 h.[146]

Treatment for PGD is largely supportive with no specific intervention to ameliorate the lung injury. Not surprisingly, PGD has a significant impact on early morbidity after transplantation. Patients with PGD have a longer duration of mechanical ventilation, a longer duration of ICU and hospital stay, and increased costs.[147] Moreover, patients with PGD grade 3 at 48 or 72 h have a significantly higher risk of death in the first 90 days and 1 year after transplantation.[141] Furthermore, even among those who survive to 1 year after transplantation, PGD grade 3 is associated with an increased risk of death in the long term.[148] Long-term survivors of PGD grade 3 have lower peak lung function and shorter 6-min walk distances after transplantation,[149,150] and this provides them limited functional reserves for later complications. Indeed, all grades of PGD have been associated with an increased risk of BOS, and the risk is highest for those with PGD grade 3.[146,149,151] Limited peak lung function and improvement in functional status, as well as the increased risk of BOS, all contribute to the increased late mortality associated with PGD.

Studies have identified risk factors for the development of PGD grade 3.[141] These include donor smoking history, use of cardiopulmonary bypass during surgery, recipient obesity, pulmonary hypertension, and an underlying diagnosis of sarcoidosis.[141] Some of these factors are potentially modifiable to reduce the risk, whereas others are inherent to the recipient's disease severity. For example, weight loss before listing or transplantation seems feasible if time allows, but secondary pulmonary hypertension reflects the severity of the recipient's disease. More importantly, the interactions between recipient and donor risk factors are complex, and how these should factor into donor selection for a given patient is the focus of ongoing research.

REJECTION

Acute forms of allograft rejection are considered below.

Hyperacute Rejection

Hyperacute rejection, due to preformed DSA to mismatched HLA between the donor and the recipient, is a fulminant form of rejection occurring within the first few hours of transplantation.[152–155] This has become a rare form of rejection in the modern era of lung transplantation, as advances in HLA antibody detection and determination of antibody specificity permits avoiding donors with the reactive HLA.[156] Nevertheless, hyperacute rejection demonstrates that antibodies can cause rejection and fulminant allograft failure. Furthermore, hyperacute rejection illustrates that the vascular endothelium is the focal point of injury and neutrophilic capillaritis is the histologic hallmark.[157] The paradigm for this form of rejection is that DSA bind to HLA on endothelial cells and activate the complement cascade, resulting in endothelial cell necrosis and recruitment of neutrophils to the capillaries with resultant diffuse alveolar damage (DAD).[157] Without aggressive treatment, hyperacute rejection results in allograft failure and death,[158,159] but a number of reports have highlighted recovery with various immunosuppressive treatments.[153,155] Identifying allosensitized patients before transplantation has decreased the incidence of hyperacute rejection. However, this approach narrows the donor pool and prolongs the waiting time for transplantation exposing patients to an increased risk of death.[160] Consequently, programs have attempted desensitization regimens to deplete HLA antibodies before transplantation or intraoperatively with varying success.[161,162]

Acute Cellular Rejection

The incidence of ACR after lung transplantation has been variable in different reports. This is not surprising considering differences in immunosuppressive regimens, patient populations, and variability in interpreting biopsy findings. In the ISHLT registry report, approximately 30% of lung transplant recipients developed an episode of ACR within the first year after transplantation.[24] In a randomized controlled trial comparing mycophenolate to everolimus, the incidence of ACR was 46% in the mycophenolate group and 38% in the everolimus group during the first year after transplantation, but the incidence increased to 54% in the mycophenolate group and 41% in the everolimus group at the end of 3 years.[11] Episodes of ACR, especially milder cases, are often clinically silent, and even if symptoms or clinical signs are present, these are typically nonspecific (e.g., dyspnea, cough, hypoxemia, radiographic infiltrates). Thus, the gold standard for the diagnosis of ACR is transbronchial lung biopsy although the procedure is invasive, and there is significant interreader variability in grading.[163] The histologic criteria for the diagnosis of ACR were originally developed in 1990 by the ISHLT and were revised in 1996 and again in 2007.[164–166] ACR manifests as circumferential perivascular mononuclear cell infiltrates, and the severity is graded based on the intensity of cellular infiltrates around small vessels and extension into the adjacent interstitium.[166] Minimal ACR (grade A1) is

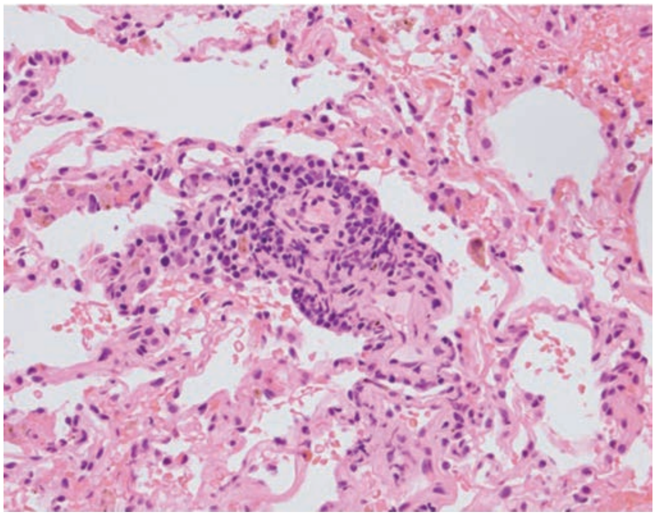

Figure 106-1 Transbronchial lung biopsy demonstrating mild acute cellular rejection (grade A2) (400×). A cuff of mononuclear cells circumferentially surrounds small vessels and expands the vascular adventitia.

characterized by scattered perivascular mononuclear cell infiltrates that are 2 to 3 cells thick and not readily visible on scanning magnification.[166] Mild ACR (grade A2) is more obvious on low power and is characterized by more frequent perivascular infiltrates expanding the vascular adventitia.[166] Figure 106-1 illustrates an example of ACR grade A2. Eosinophils and endothelialitis also may be seen. Moderate ACR (grade A3) is clearly visible at scanning magnification, and the infiltrates extend into the adjacent interstitium.[166] The infiltrating cells often include eosinophils and neutrophils in ACR grade A3. Lastly, severe ACR (grade A4) is characterized by diffuse infiltrates, necrotizing vasculitis, and DAD.[166]

ACR is most commonly seen in the first 3 to 6 months after transplantation, but late episodes beyond the first year also may occur.[167] The mainstay of treatment is bolus methylprednisolone (10–15 mg/kg daily for 3 days) and optimization of the maintenance immunosuppressive regimen because ACR is an indication of active alloimmune responses and a possible portent of poor long-term outcomes. Indeed, ACR has consistently been identified as an important risk factor for CLAD.[167–170] However, no study has demonstrated that treatment for ACR mitigates the risk of CLAD. In general, a follow-up bronchoscopy with transbronchial lung biopsies is indicated 3 to 6 weeks after an episode of ACR to exclude persistent ACR or progression to higher grade ACR. Approximately 25% of patients have persistent ACR at follow-up.[171] Treatment for persistent ACR is variable across centers, and this is often individualized based on the patient's clinical history and risk profile.

■ Lymphocytic Bronchiolitis

Airway inflammation often accompanies higher grades of ACR. Lymphocytic bronchiolitis represents an airway-focused acute rejection pathology that is associated with a high risk of subsequent BOS.[172] However, exclusion of infection as the cause of airway inflammation is necessary to consider lymphocytic bronchiolitis a form of rejection. Two grades of lymphocytic bronchiolitis are defined in the latest ISHLT criteria.[166] Grade B1R is defined as submucosal peribronchiolar mononuclear cell infiltrates without epithelial cell damage or intraepithelial lymphocytic infiltration. Grade B2R is defined as intense inflammation with activated mononuclear cells and eosinophils with epithelial cell ulceration and intraepithelial lymphocytic infiltration. There is little consensus on the optimal management of isolated lymphocytic bronchiolitis without ACR, and cases refractory to high-dose methylprednisolone have been reported to progress rapidly to BOS.[173] Progression of respiratory bronchiolar epithelial ulceration and necrosis to fibrosis and luminal obliteration, characteristic of OB, is readily understandable.

■ Antibody-mediated Rejection

Over the past 10 years, AMR has been increasingly recognized as a form of lung rejection. Although hyperacute rejection was widely accepted as a form of lung rejection more than 25 years ago, cases of AMR occurring beyond the immediate posttransplant period were not readily recognized. The diagnosis of AMR is difficult and requires a multidisciplinary approach and a high index of suspicion. While the diagnosis of ACR is based solely on pathology, the histologic features of AMR are nonspecific patterns of lung injury.[174] Although neutrophilic capillaritis raises suspicion for AMR, this is not a sensitive or consistent finding.[157] The ISHLT definition for AMR is based on experience in kidney transplantation. Definite AMR is defined as clinical allograft dysfunction, circulating DSA, pathology of acute lung injury, capillary C4d deposition, and the exclusion of other possible causes of allograft dysfunction.[174] C4d deposition indicates activation of the complement cascade, but this has been an inconsistent and nonspecific finding in pulmonary AMR.[175–177] The ISHLT definition allows that AMR may be diagnosed confidently in the absence of C4d deposition, although this is still considered probable AMR.[174] Commonly seen histologic abnormalities include DAD, acute pneumonitis, neutrophilic capillaritis, and organizing pneumonitis.[178,179] Figure 106-2 illustrates acute pneumonitis and neutrophilic capillaritis.

The management of AMR is based on experience in kidney transplantation. There is no consensus on the optimal regimen, and different centers use different protocols. In general, treatment is focused on antibody depletion and blocking the effect of antibodies on the allograft. Typically, regimens consist of multiple concomitant treatments including various combinations of plasma exchange, intravenous immune globulin, rituximab, bortezomib, carfilzomib, and eculizumab.[175,176,178–180] Studies illustrate that the acute episode of allograft dysfunction may be reversible in some cases, but there is a high incidence of CLAD and long-term survival after AMR is limited.[175,176,178–180] Additional studies are necessary to improve the management of AMR, and ideally, these would compare various treatment regimens head-to-head to better inform clinical practice.

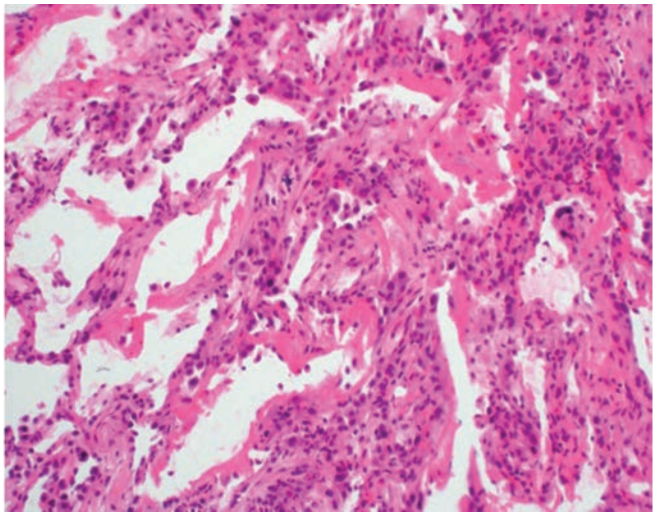

Figure 106-2 Transbronchial lung biopsy from a patient with antibody-mediated rejection showing acute pneumonitis and neutrophilic capillaritis (400×). Neutrophils are seen in the alveolar septae.

CHRONIC LUNG ALLOGRAFT DYSFUNCTION

CLAD is the leading cause of death beyond the first year after lung transplantation.[24] Chronic and progressive lung allograft dysfunction leading to respiratory failure was recognized as a serious barrier to long-term survival after combined heart–lung transplantation in the early 1980s.[181] Although histologic findings of OB and an obstructive ventilatory defect were prominent features, a concomitant restrictive ventilatory defect and diffuse interstitial and pleural fibrosis also were recognized.[181,182] These early findings from 35 years ago presage our current paradigm of CLAD after lung transplantation. Today, we recognize CLAD as chronic rejection after lung transplantation with two phenotypes: bronchiolitis obliterans syndrome (BOS) and restrictive allograft syndrome (RAS).[112,13]

■ Bronchiolitis Obliterans Syndrome

Following the recognition of CLAD after combined heart–lung transplantation, BOS received most of the attention of clinicians and researchers in lung transplantation since it was the most common and predominant form of CLAD. OB is the histologic hallmark of BOS and is characterized by fibroproliferative scarring of membranous and respiratory bronchioles. Figure 106-3 illustrates an example of OB after lung transplantation. However, histologic confirmation of OB is difficult with transbronchial lung biopsies because of the patchy nature of the lesion and the small size of biopsies. Consequently, BOS, diagnosed and staged according to decrements in spirometry, is the clinical surrogate for OB.[12,183] Baseline lung function is defined as the average of the two highest FEV_1 measurements after transplantation, and BOS is defined as a persistent ≥20% decline in FEV_1.[12,183] Progressive stages of BOS are defined according to the magnitude of decline in FEV_1 from baseline. Clinically, BOS presents with deteriorating allograft function. Symptoms may be absent during the early stages. Therefore, frequent pulmonary function testing is recommended as part of long-term monitoring of patients. When symptoms are present, they typically include dyspnea with exertion or cough. Imaging studies are usually unrevealing in the early stages, but computed tomography may demonstrate signs of air trapping or ground glass opacities. Imaging later stages of BOS may reveal bronchial wall thickening and bronchiectasis. However, standard computed tomography is an insensitive tool to diagnose or stage BOS.[184]

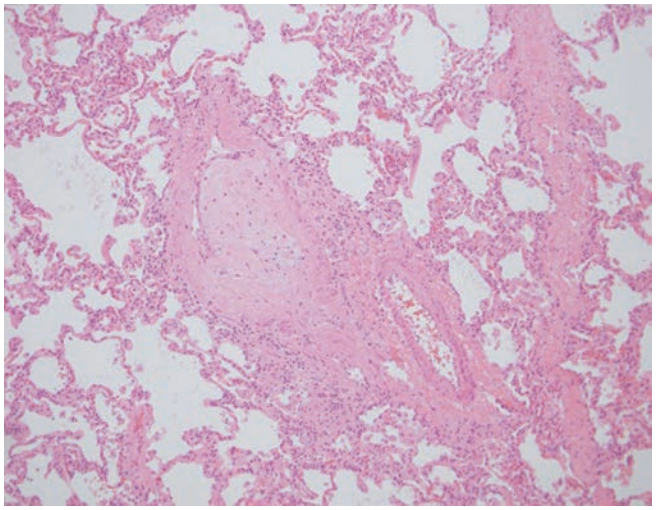

Figure 106-3 Explanted lung pathology illustrating obliterative bronchiolitis after lung transplantation (100×). The lumens of respiratory and membranous bronchioles are obliterated with fibrous connective tissue.

BOS is common, and its incidence increases over time after transplantation. In the ISHLT registry, approximately 20% developed BOS within 2 years, 30% developed BOS within 3 years, and 50% developed BOS within 5 years of transplantation.[24] Likewise, in an international multicenter randomized controlled trial comparing everolimus to mycophenolate, the incidence of BOS at 3 years was 30%.[11] Unfortunately, BOS typically follows a progressive clinical course with ongoing decline in lung function. In a recent study, the largest decline in lung function was seen in the first 6 months after diagnosis, and a ≥10% decline was associated with significantly higher risk of allograft loss.[185] Not surprisingly, BOS is associated with symptoms of anxiety and depression and decreased health-related quality of life.[186,187]

The efficacy of treatment for BOS has been largely disappointing. Long-term treatment with azithromycin has been effective in some patients. In the earliest report, 5 of 6 patients had a significant improvement in lung function after initiating azithromycin.[188] In a randomized controlled trial, 9 of 23 patients in the azithromycin group had a ≥10% increase in FEV_1 compared to none of the patients in the placebo group, although there was no significant difference in FEV_1 between the 2 groups in the intention-to-treat analysis at the end of the study.[189] Azithromycin is now widely accepted as the first-line treatment for BOS because of these results and its ease of administration and low side-effect profile. However, most patients have progressive disease. Other treatment options include ATG and extracorporeal photopheresis (ECP). Treatment with ATG for BOS dates back to the 1990s with mixed results. In a recent retrospective study, 43 of 108 patients treated with ATG had an improvement in FEV_1 in the 6 months after treatment, although the improvement was marginal.[190] ECP is an immunomodulatory treatment used for cutaneous T-cell lymphoma, graft-versus-host disease, and rarely for the prevention of cardiac allograft rejection.[191,192] Blood is separated into leukocyte-enriched and leukocyte-depleted components, and the leukocyte-enriched component is irradiated with ultraviolet light ex vivo; this results in decreases in proinflammatory cytokines, increases in anti-inflammatory cytokines, and increases in tolerogenic regulatory T cells.[193] Multiple retrospective studies have shown improvement in the rate of decline in lung function, and 1 study showed that 25% of patients have an improvement in FEV_1 in the 6 months after therapy.[193,194] Other possible interventions include total lymphoid irradiation, montelukast, and, ultimately, retransplantation.[195–199] Only a small minority of patients who have advanced BOS are candidates for retransplantation. In most cases, BOS follows a progressive clinical course ultimately resulting in chronic respiratory failure and death with a median survival of 2.5 years after the diagnosis.[200] Clearly, better treatment options for BOS are necessary to improve clinical outcomes. There are currently multiple ongoing clinical trials investigating novel treatments including aerosolized cyclosporin, nintedanib, pirfenidone, and itacitinib (a Janus-associated kinase 1 inhibitor).

■ Restrictive Allograft Syndrome

Historically, some cases of chronic allograft dysfunction did not fit the strict definition of BOS because of a predominantly restrictive ventilatory defect and fibrotic opacities on imaging studies. In 2005, a two-center study described a small cohort of patients who developed progressive allograft dysfunction characterized by upper lobe fibrosis and restrictive ventilatory abnormalities.[201] The histology was characterized by dense fibrosis with occasional OB and bronchiolitis obliterans organizing pneumonia.[201] In 2011, the Toronto Lung Transplant Program coined the term *restrictive allograft syndrome (RAS)* to characterize this unique phenotype of CLAD.[202] In this cohort, 30% of patients with CLAD had the RAS phenotype, which was characterized by a decline in total lung capacity (TLC), interstitial or ground glass opacities on computed tomography, and a pathology of DAD

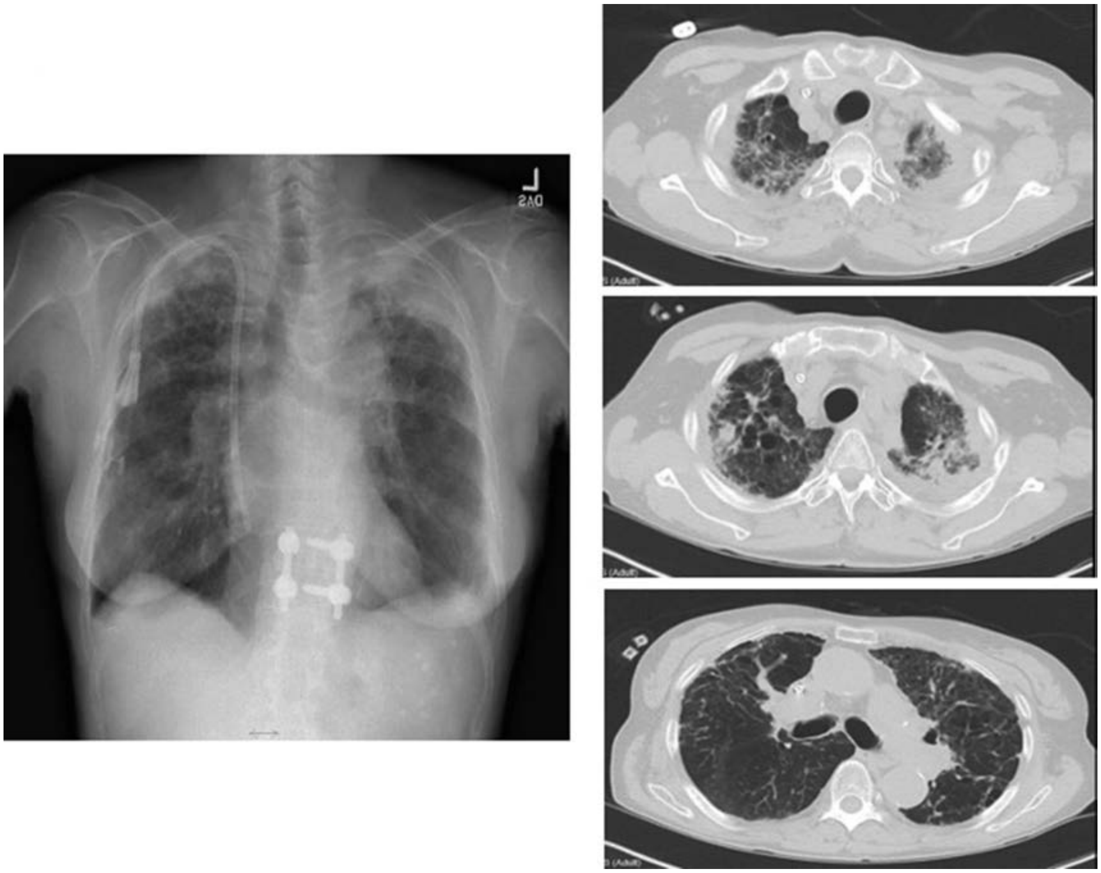

Figure 106-4 Chest radiograph illustrating coarse interstitial and airspace opacities in the upper lobes and pleural thickening in a patient with restrictive allograft syndrome. CT images of the chest show upper lobe architectural distortion, fibrosis, bronchiectasis, and pleural thickening.

and extensive fibrosis.[202] Concomitant OB was noted in some cases. Likewise, in a pathologic study of RAS, pleuroparenchymal fibroelastosis was the predominant feature in 15 of 16 patients, but notably, 14 had concomitant OB.[203] Figure 106-4 demonstrates characteristic imaging findings of RAS including upper lobe fibrosis and pleural thickening. Importantly, patients with RAS have a significantly worse survival after the diagnosis of CLAD than those with BOS; the median survival after the diagnosis of RAS was 541 days compared with 1421 days after the diagnosis of BOS.[202] Based on these findings, the ISHLT reclassified CLAD into the two current phenotypes.[12,13] Furthermore, it is recognized that some patients may have features of both BOS and RAS, and that some patients may have BOS at the onset of CLAD but evolve into a “mixed” phenotype over time as they develop signs of interstitial fibrosis and ventilatory restriction.[202] Therapeutic interventions for RAS have largely been disappointing. Not surprisingly, antifibrotic agents such as pirfenidone and nintedanib have been used with mixed results.[204–207] However, these reports have been limited to isolated cases and small case series where antifibrotics are used as a salvage therapy for refractory RAS. A randomized clinical trial using pirfenidone for RAS is currently recruiting participants. Clearly, better treatment options are necessary to improve clinical outcomes for patients with RAS.

INFECTIONS

Infections are common complications at all timepoints after lung transplantation. In fact, infections are common causes of death at all timepoints after transplantation, accounting for 15% to 30% of deaths according to the ISHLT registry.[24] Impairment in mucociliary clearance and cough, loss of lymphatic drainage, and therapeutic immunosuppression after lung transplantation increase the risk of respiratory infections. In addition, the constant exposure of the lung allograft to the environment further increases the risk of respiratory infections. In the immediate period after transplantation, donor-transmitted, recipient-derived, and nosocomial infections are most common.[208] *Pseudomonas aeruginosa* is a common cause of pneumonia in this early period after transplantation, and early nosocomial infections are associated with an increased risk of mortality.[209,210] Extrapulmonary nosocomial infections include surgical site infections, empyema, and *Clostridium difficile* colitis.[211–213] Surgical site infections are typically due to skin flora (*Staphylococcus* species or *Candida albicans*) and are associated with delayed chest closure.[214]

The risk of opportunistic infections is highest in the first 6 to 12 months after transplantation. The risk of CMV infection depends on the sero-status of the donor and the recipient, with seronegative recipients of lungs from seropositive donors having the highest risk. In general the risk of CMV infection wanes beyond the first year after transplantation, but patients with short telomeres have impaired CMV immunity and remain at increased risk of infection.[215,216] Extended prophylaxis with valganciclovir has become common practice; however, this is complicated by leukopenia in many cases.[101] Patients in certain geographic locations are at risk for endemic fungal infections, such as coccidioidomycosis, histoplasmosis, and blastomycosis. Prophylactic regimens are variable depending on local practices and risks. Invasive mold infections are uncommon but are associated with significant morbidity and mortality.[217] The lungs are the most commonly affected site, and *Aspergillus* is the most commonly isolated mold.[217] There is no consensus on the role of universal antifungal prophylaxis. Some studies suggest that this approach is superior to targeted prophylaxis, but others have not confirmed this benefit.[218,219] Thus, antifungal prophylactic regimens vary across centers. Most patients are treated with antibiotic prophylaxis against *Pneumocystis jiroveci*.

Community-acquired respiratory viral (CARV) infections are common at all timepoints after transplantation.[220] CARV infections cause a spectrum of disease in lung transplant recipients ranging from pharyngitis and rhinitis to bronchiolitis and pneumonia. Both upper and lower respiratory tract infection have been associated with a decline in lung function during the acute phase of infection, and many cases require hospitalization.[221] Beyond the acute phase of CARV infection, patients are at increased risk of acute rejection, infection with *Pseudomonas aeruginosa*, CLAD, and death following acute infection.[220–222] These serious complications indicate progressive respiratory disease following CARV infection, but the mechanism remains poorly understood. COVID-19 causes severe disease in some lung transplant recipients.[223,224] An early case series of 32 patients from New York City reported a 34% mortality during the acute phase of the infection.[224] Long-term consequences of COVID-19 infection on allograft function and survival remain to be seen.

MALIGNANCY

Therapeutic immunosuppression after solid organ transplantation is associated with an increased risk of malignancy.[225] This is especially true for malignancies linked to viral infections such as non-Hodgkin lymphoma and Epstein-Barr virus (EBV). In the ISHLT registry, the incidence of any malignancy is 5% among 1-year survivors; approximately 35% of these are skin cancers and 18% are lymphoma.[24] Among 5-year survivors, the incidence increases to 20%, and more than 70% are skin cancers, 10% are lymphoma, and 27% are other cancers.[24] Among 10-year survivors, the incidence increases to 32%, and the distribution of cancer types is similar to 5-year survivors.[24] Overall, malignancy is the cause of death of approximately 9% of lung transplant recipients who survive between 1 and 3 years, 13% of 3- to 5-year survivors, and 15% of 5-year survivors.[24] Skin cancers are primarily squamous cell carcinoma and basal cell carcinoma, and these are usually managed successfully with resection. However, recurrence or second primaries are common, and risk factors include age, white race, sun exposure, prolonged treatment with voriconazole, and a history of skin cancer before transplantation.[226–228] Some patients have a particularly aggressive clinical course, and in one report, 5% died from skin cancer.[226]

Posttransplant lymphoproliferative disorders (PTLD) are a group of abnormal lymphoid proliferations after transplantation that result from immunosuppression. B-cell proliferation and non-Hodgkin lymphoma are more common, although T-cell PTLD also is recognized. PTLD is often associated with EBV; infected B cells elicit a cytotoxic T-cell response to control the infection. This host response results in the syndrome of infectious mononucleosis. Latently infected B cells that persist may give rise to PTLD when T-cell responses wane under the influence of therapeutic immunosuppression. However, EBV-negative PTLD is increasingly recognized, and the tumor's EBV status does not appear to impact prognosis or treatment response.[229] Nevertheless, recipient EBV status is an important risk factor for developing PTLD, and EBV-seronegative recipients of lungs from seropositive donors are at significantly increased risk.[230,231] The use of induction immunosuppression also is associated with an increased risk of PTLD.[232] Approximately half of the cases of PTLD present in the first year after transplantation, and these are more likely to involve the allograft or mediastinal or hilar lymph nodes.[233,234] In contrast, later cases are more likely to be extrathoracic or disseminated.[233,234] **Figure 106-5** illustrates imaging

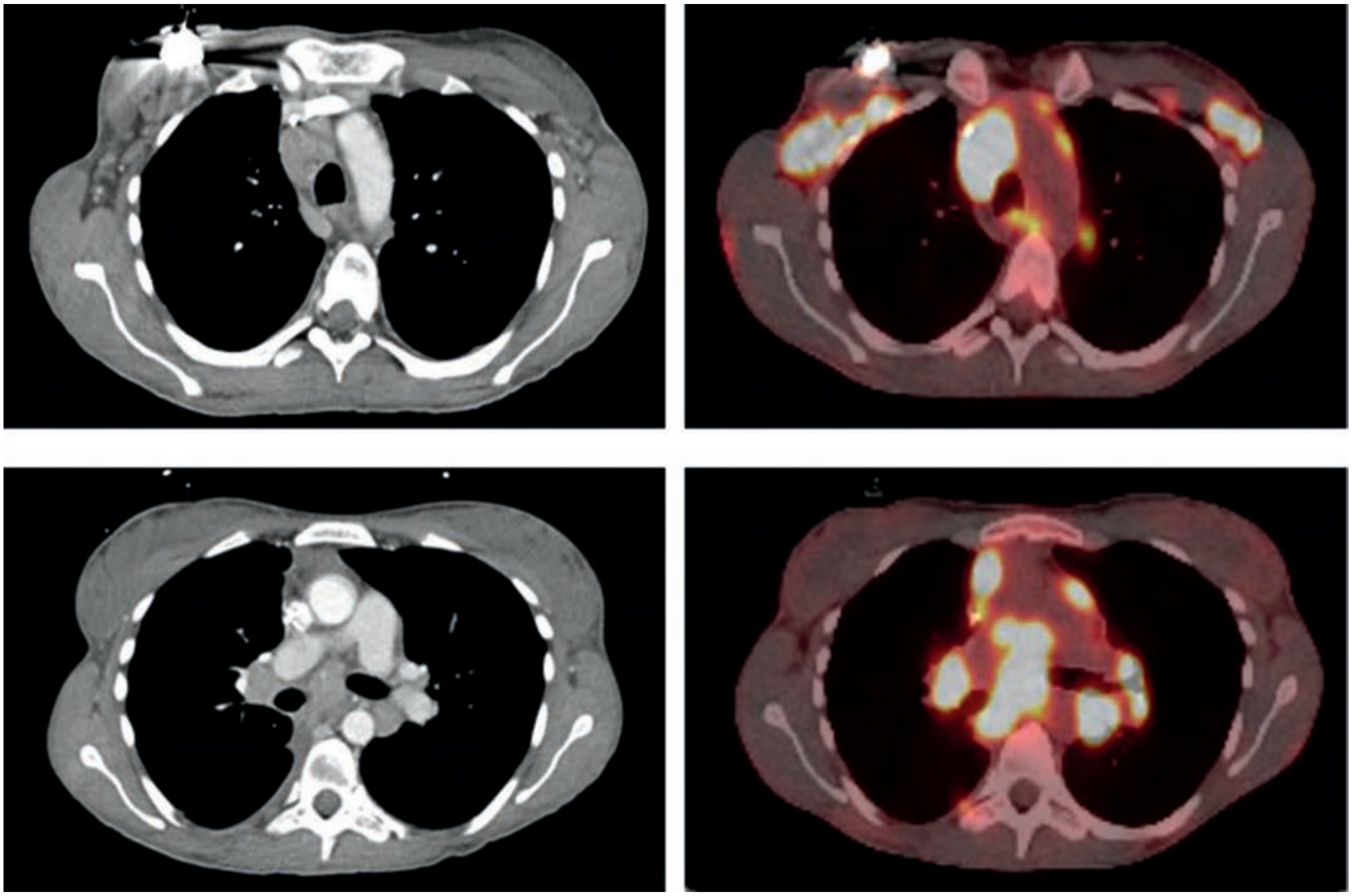

Figure 106-5 Chest CT from a patient with posttransplant lymphoproliferative disorder demonstrating lymphadenopathy in the paratracheal, subcarinal, and right hilar regions. The lymphadenopathy was fluorodeoxyglucose (FDG)-avid on positron emission tomography.

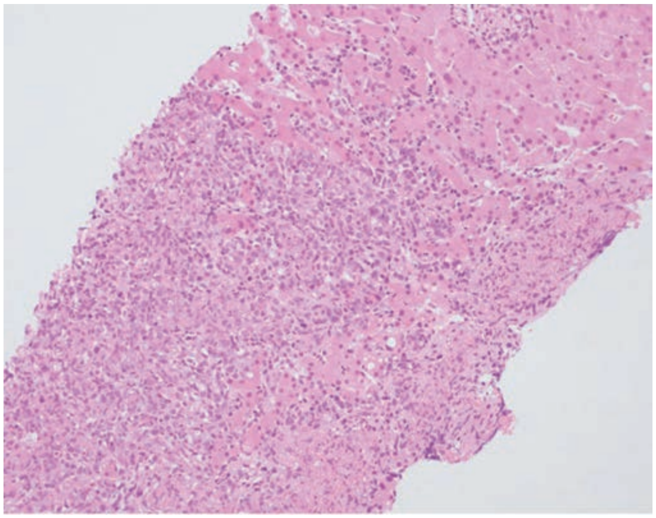

Figure 106-6 Liver biopsy from a lung transplant recipient illustrating diffuse large B-cell lymphoma, germinal center type (200×).

studies from a lung transplant recipient who presented with fever and malaise for several weeks; diffuse fluorodeoxyglucose (FDG)-avid lymphadenopathy was noted. Liver biopsy confirmed diffuse large B-cell lymphoma (Fig. 106-6).

Lung transplant recipients are at increased risk for lung cancer. This is especially true for single lung recipients who were former smokers.[235,236] Underlying diagnoses of pulmonary fibrosis and COPD are risk factors among single lung recipients, and the cancers typically develop in the native lung. Although lung cancer after lung transplantation presents at the localized stage more frequently than in the general population, the prognosis is poor.[235,237] Lung cancer in the allograft is uncommon because of stringent donor selection criteria.

SURVIVAL

Survival after lung transplantation remains disappointing. According to the ISHLT registry, which includes more than 50,000 patients worldwide, there has been steady improvement in survival over time.[24] In the most recent era between 2010 and 2017 the median survival was 6.7 years, which is significantly better than the median survival between 2002 and 2009 (6.5 years) and 1992 and 2001 (4.7 years).[24] This improvement is seen primarily in the first year after transplantation, as survival curves for each era diverge very early after transplantation but then become nearly parallel. These findings are attributed to improvements in donor and recipient selection and management, refinements in surgical techniques, and advances in intraoperative and early postoperative care. In contrast, survival beyond the first year after transplantation has been limited by persistently high incidences of CLAD and infection, which remain leading causes of death. It is noteworthy that survival in the most recent era is better than previous eras in spite of generally transplanting older and sicker patients and using more donors who were previously considered marginal. This underscores the impact of the advancements in clinical practice over the past 20 years.

The ISHLT registry analyzes predictors of survival using univariate and multivariate models.[24] However, even multivariate models only identify statistical associations, and these do not imply causation. Nonetheless, these identify clinically relevant factors that are associated with survival. Factors associated with better survival include the most recent era of transplantation, bilateral lung transplantation, and an underlying diagnosis of CF or lymphangioleiomyomatosis.[24] In contrast, CMV-seronegative recipients from seropositive donors, donor history of hypertension or diabetes, retransplantation, and poor recipient functional status before transplantation are associated with worse survival.[24] Likewise, increasing recipient age is associated with worse survival although the relationship is not linear, and the risk begins to increase beyond the age of 55 years.[24]

CONCLUSIONS

Lung transplantation evolved from an experimental surgery to the mainstay treatment for patients with advanced lung disease. Long-term outcomes remain disappointing, and patient survival is significantly lower than that of other solid organ transplant recipients. CLAD and infections are the leading causes of death beyond the first year after transplantation. A role for humoral immune responses in the development of CLAD is increasingly recognized. Clearly, better treatments are necessary to prevent and delay the development and progression of CLAD without increasing the risk of infections and other toxicities. Likewise, studies to develop a better understanding of lung rejection and CLAD are needed to improve clinical practice.

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PART 16

Cancer and Other Malignancies of the Lungs

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CHAPTER 107

Genetic and Molecular Changes in Lung Cancer: Prospects for a Personalized Pharmacologic Approach to Treatment

Howard Y. Li
Jeffrey A. Kern

INTRODUCTION

The discovery that some lung cancers harbor specific somatic mutations that are essential for malignant growth (i.e., “driver mutations”), which lead to gain of function of oncogenes or loss of function of tumor suppressor genes, and the discovery that antitumor T cell responses are regulated by immune checkpoints, have paved the way for molecularly targeted, personalized lung cancer therapy. Lung cancer is classified based on histologic features as either non–small-cell lung cancer (NSCLC; approximately 85% of all lung cancers) or small-cell lung cancer (SCLC; approximately 15%).[1] NSCLCs are further divided histologically as adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. Various chemotherapeutic regimens have been used to treat different NSCLC histologic subtypes. But with the realization that NSCLC is a collection of diseases that are identifiable by specific molecular abnormalities, personalized therapy is achievable for a subset of patients with NSCLC (Fig. 107-1).

While clearly promoting the oncogenic state, driver mutations are also commonly associated with “oncogene addiction,” or dependency of some cancers on one gene for the maintenance of the malignant phenotype. These dependencies, which are specific to an individual’s cancer, are absent in normal cells. Inhibition of “druggable” proteins coded for by driver mutations, such as the BCR-ABL fusion protein with imatinib in chronic myelogenous leukemia or human epidermal growth factor receptor 2 (HER2) with trastuzumab in breast cancer, are prime examples of successful therapeutic targeting of critical signaling nodes in cancer.

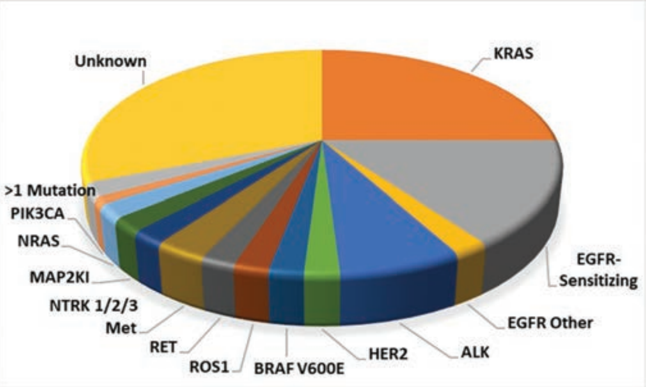

Figure 107-1 Driver mutations in lung adenocarcinoma.

Between 1980 and 2000, NSCLC oncogenic drivers that were investigated included mutations in the Kirsten rat sarcoma viral oncogene homolog (*KRAS*) and protein 53 (*p53*) genes, loss of specific chromosomal loci, loss of heterozygosity, and DNA methylation of tumor suppressor genes. In 2004, driver mutations in the epidermal growth factor receptor (*EGFR*) gene, a membrane-bound receptor tyrosine kinase (RTK) that regulates cell growth, were discovered in NSCLC, especially in adenocarcinomas.[2–4] These *EGFR* driver mutations resulted in a receptor with dysregulated signaling driving cell growth and the oncogenic phenotype, but also led to a cellular dependence on EGFR RTK signaling. Thus, these mutations were strongly associated with therapeutic sensitivity to tyrosine kinase inhibitor (TKI) drugs that inhibited EGFR’s tyrosine kinase (TK) function. In 2007, translocation of the echinoderm microtubule-associated protein-like 4 (*EML4*) translocation to the anaplastic lymphoma kinase (*ALK*) gene resulting in an *EML4-ALK* fusion gene[5] and chromosomal rearrangements of the gene encoding ROS1 proto-oncogene receptor tyrosine kinase (*ROS1*)[6] were identified in NSCLC. As with EGFR, the *EML4-ALK* translocation and *ROS1* oncogenic fusion resulted in dysregulated TK signaling, again driving cell growth and the oncogenic phenotype, as well as cellular dependencies on EML4-ALK and ROS1 signaling, respectively. Targeting ALK and ROS1 with TKIs has been shown to be highly effective in NSCLCs that express these driver mutations. BRAF^{V600E} substitution was identified in melanomas and nonsquamous NSCLC,[7] and this discovery led to the development of BRAF-targeted drugs. MET exon 14 skipping mutations and RET translocations occur in approximately 3% and 2% of nonsquamous NSCLCs, respectively. Similar to other RTK driver mutations, NSCLCs with MET exon 14 skipping mutations and RET translocations demonstrate sensitivity to TKIs. In contrast with other lung cancer patients, who tend to be older with extensive smoking history, RTK mutations are more commonly found in female never-smokers of East Asian origin with adenocarcinoma histology.

Recent advances in the understanding of T lymphocyte immunobiology have been instrumental in advancing therapeutic strategies to overcome tumor immune escape and represent a fundamental change in cancer therapy. Instead of targeting a patient’s cancer, as current chemotherapy does, immunotherapy targets the host immune cells and removes inhibitory pathways that block effective antitumor T-cell responses. A breakthrough in cancer therapy was the development of pharmacologic immune checkpoint inhibitors. Designed to interfere with naturally occurring T lymphocyte inhibitory pathways that constrain reactivity, immune checkpoint blockade releases limits on the activation and maintenance of effector T lymphocyte function. Evidence that these inhibitory T lymphocyte pathways are overactive in NSCLC led to the realization that NSCLC is an exciting target of immune-based therapies. Checkpoint inhibitors targeting programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1) yielded unprecedented and durable, long-lasting responses in a significant subset of cancer patients, leading to U.S. Food and Drug Administration (FDA) approval of these checkpoint inhibitors for multiple cancer types, including NSCLC.

These discoveries illustrate that molecular biologic findings in NSCLC and the host can be directly linked to the development of novel therapies and thereby improve the survival rates of lung cancer patients. Although 5-year survival rates for lung cancer remain low (25% for NSCLC, 7% for SCLC), overall mortality from lung cancer declined from 2013 to 2016.[8] Whereas mortality from SCLC declined almost entirely as a result of declining incidence, which has been attributed to reduced cigarette smoking rates, mortality from NSCLC decreased faster than the incidence of NSCLC.[9] The reduction in mortality from NSCLC is likely due to both reductions in incidence along with treatment advances, specifically the development and use of targeted therapies for oncogene-driven lung adenocarcinoma. Unfortunately, molecularly targeted drugs for SCLC have not been identified. Although some SCLC patients respond to PD-L1 immune checkpoint blockade, only a small subset derives prolonged benefit. Thus, a better understanding of SCLC is needed to identify therapeutic vulnerabilities that may lead to the development of rationally targeted approaches for SCLC.

As new pathways and mechanisms that drive lung cancer are identified, existing agents that have not been previously considered for lung cancer can now be tested, or new drugs targeting the affected pathways can be developed. These discoveries allow a patient's therapy to be individualized to the molecular elements that drive their disease and treatment with agents that best target the characteristics of their cancer, offering higher response rates and improvements in survival. However, hundreds of mutations occur in a cancer cell and not all of them are functionally important or suitable targets for personalized therapy. To improve the chances of success in the development of personalized medicine for lung cancer, we need to identify a functionally important target or pathway, a biomarker to identify and follow therapeutic response, the appropriate therapeutic endpoint, and the mechanisms of resistance to personalized therapy, both primary and acquired.

TUMOR MOLECULAR BIOLOGY LEADING TO TARGETED THERAPY

Lung cancer results from the dysregulation of cellular processes that control cell cycling and death, allowing unrestricted cell growth (Fig. 107-2A). Growth-promoting pathways that promote NSCLC include activating mutations in tyrosine kinases such as EGFR, ALK, ROS1, BRAF, MET, and RET; and activating mutations in intracellular guanosine triphosphatases (GTPases) such as KRAS. Although oncogenic driver mutations are critical for lung carcinogenesis, they also lead to tumor cell vulnerabilities that have paved the way for the development of targeted therapeutics.

■ Receptor Tyrosine Kinases

Membrane-bound RTKs share a common general structure composed of an extracellular region that contains a ligand-binding domain, an extracellular juxtamembrane region, a hydrophobic transmembrane domain, a cytoplasmic TK domain, and a cytoplasmic tail with tyrosine residues that serve as sites for receptor phosphorylation. Ligand binding results in receptor dimerization and activation of the receptor's TK domain, leading to phosphorylation of the receptor's tyrosine residues. This, in turn, results in recruitment of signaling molecules to the phosphorylated tyrosine residues and coupling to downstream effectors, eventually leading to biologic responses. RTK activity in nonmalignant cells is normally under tight temporal and spatial regulation by the receptor and its ligand, which safeguards against unwanted activation. Driver mutations in the membrane-bound RTKs result in dysregulated signaling or in a receptor that cannot be shut off. RTK activation in cancer may occur via overexpression of wild-type receptor due to gene amplification (resulting in excess signaling), excess ligand production with receptor overstimulation, activating mutations, translocations resulting in activated fusion proteins, or reduced receptor downregulation.

The prototypical RTKs involved in lung cancer are members of the ERBB family. The ERBB family of RTKs includes ERBB1 (EGFR; HER1), ERBB2 (HER2), ERBB3 (HER3), and ERBB4 (HER4). In the lung, these RTKs are expressed by the pulmonary

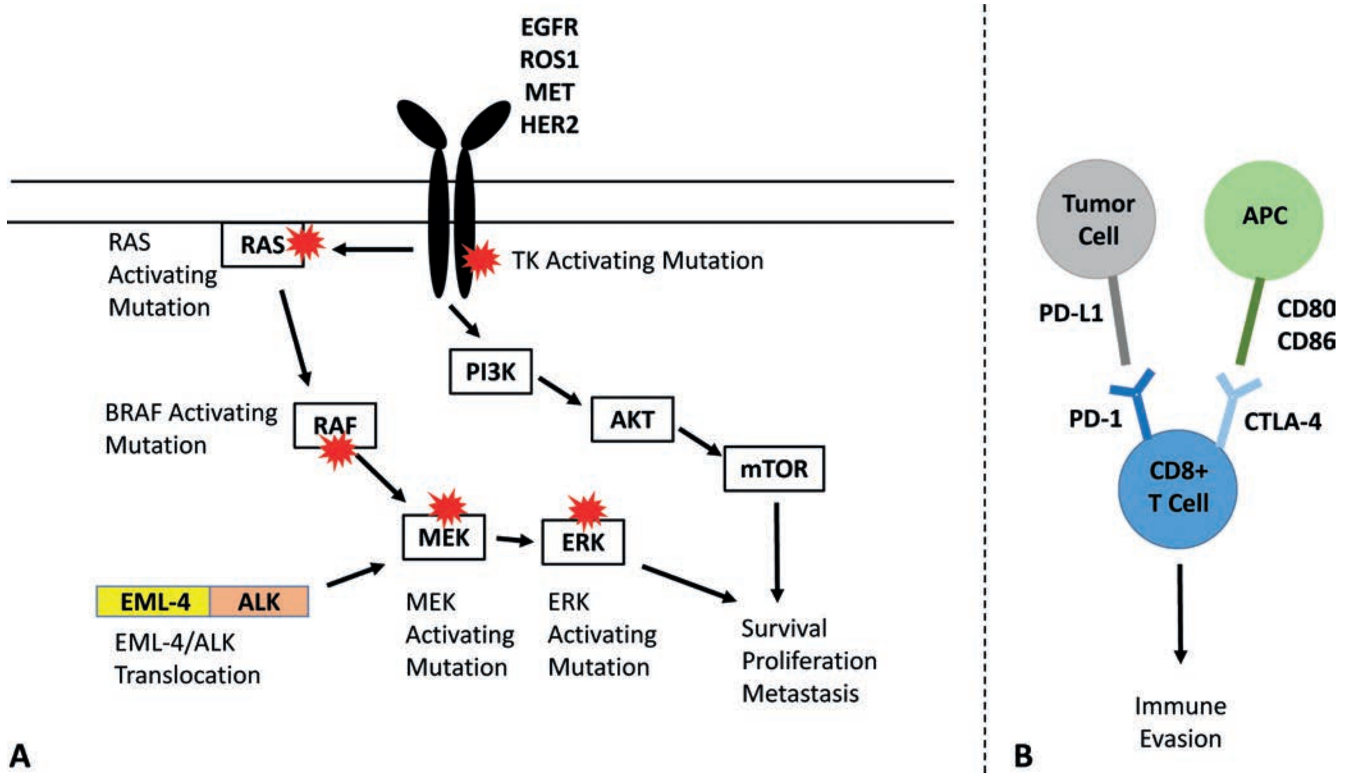

Figure 107-2 Overview of targetable pathways in lung cancer. **A.** Oncogenic driver mutations lead to ligand-independent activation of downstream signaling pathways, leading to cellular survival, proliferation, and metastasis. **B.** PD-1 and CTLA-4 are immune checkpoint receptors expressed by CD8+ T cells that are exploited by lung cancer as an immune evasion mechanism.

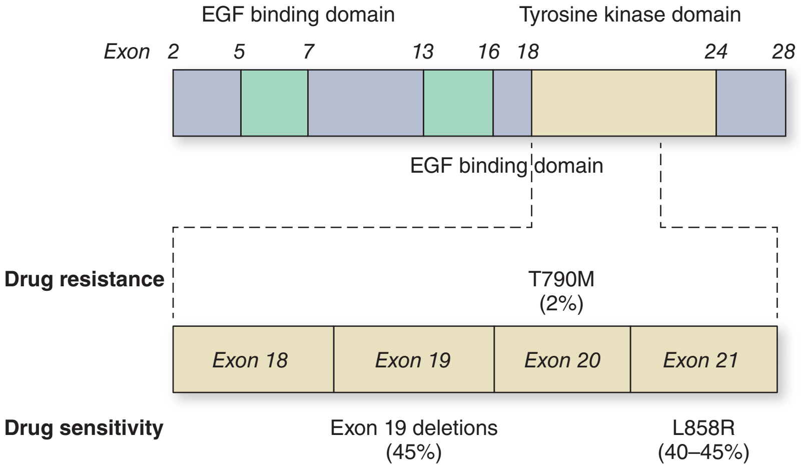

Figure 107-3 Epidermal growth factor receptor (EGFR) mutations in NSCLC. This representation of EGFR shows the distribution of exons in the epidermal growth factor ligand-binding domains and tyrosine kinase domain (TK). Exons 18–21 in the TK region where the relevant mutations are located are expanded and the most common mutations associated with EGFR TK inhibitor sensitivity and resistance are shown.

epithelium (e.g., alveolar type II cells and bronchial cells) and fibroblasts. Members of the epidermal growth factor family of peptide hormones serve as ligands for ERBB RTKs, and include epidermal growth factor (EGF), transforming growth factor α, betacellulin, and epiregulin for ERBB1; and the neuregulins for ERBB3 and ERBB4. Ligand binding activates the receptor and multiple intracellular signaling pathways that govern fundamental cellular processes including proliferation, cell migration, metabolism, and survival. For example, phosphorylation of ERBB RTKs results in activation of growth factor receptor–bound protein 2 (Grb2) and Son of Sevenless (SOS), which ultimately leads to phosphorylation and activation of RAS. Activation of the RAS/RAF/MEK/extracellular signal–regulated kinase (ERK) pathway leads to cell proliferation. In contrast, activation of the phosphoinositide 3 kinase (PI3K)/AKT pathway by ERBB RTK signaling results in prolonged cell survival via the expression of mitochondrial antiapoptotic proteins. Thus, dysregulation in an RTK pathway can give a selective growth and survival advantage to a cell, resulting in clonal expansion and tumorigenesis. Sequencing a patient's lung cancer for *EGFR* or *HER2* gene mutations can identify specific alterations in this pathway, allowing the use of targeted chemotherapy agents.

Epidermal Growth Factor Receptor

Small molecule agents have been developed to inhibit EGFR kinase signaling by blocking the intracellular TK domain. The first of these EGFR TKIs, gefitinib and erlotinib, began testing in clinical trials in the early 2000s. Both gefitinib and erlotinib are orally administered agents that bind noncovalently at the ATP-binding pocket of EGFR, competing with ATP binding, thereby suppressing EGFR phosphorylation and downstream signaling. Initial randomized studies in NSCLC with EGFR TKIs in combination with standard first-line platinum-based chemotherapy were negative. However, in the TRIBUTE trial of carboplatin and paclitaxel with erlotinib or placebo, 116 patients who reported that they had never smoked had a prolongation in survival with erlotinib treatment (22.5 months) compared to placebo treatment (10.1 months; $p = 0.01$), suggesting that treatment with erlotinib improved survival in never smokers.[10]

In 2004, as a result of basic research to understand this dramatically different response rate to EGFR TKI therapy, several groups reported the discovery of a collection of activating mutations in the TK domain of EGFR that correlated with a high likelihood of response to EGFR TKIs.[2–4] Approximately 90% of observed *EGFR* gene mutations are either small in-frame deletions in exon 19 clustered around the catalytic site of the receptor, or an amino acid substitution from a leucine to an arginine at position 858 in EGFR (L858R), which lies within the TK activation loop in exon 21 (Fig. 107-3). In cells harboring *EGFR* gene mutations, the mutated receptor leads to enhanced AKT signaling and downstream activation of antiapoptotic and prosurvival signals. The location of *EGFR* gene mutations within critical residues of the tyrosine kinase domain leads to an altered physical structure, enhanced drug binding, and sensitivity to EGFR TKIs. Virtually all EGFR inhibitors, including first-generation (gefitinib and erlotinib), second-generation (afatinib), and third-generation (osimertinib) TKIs demonstrate better responses in EGFR-mutant NSCLCs carrying exon 19 deletions compared with L858R mutations.[11,12] Other types of *EGFR* TK domain mutations have been reported. In contrast to the more common exon 19 deletions and L858R mutation, some of these minor mutations are associated with resistance to EGFR TKIs.[13]

Many of the patients harboring these mutations demonstrated rapid, nearly complete reduction of their cancers that persisted for up to several years. *EGFR* gene mutations were much more commonly found in female never-smokers of East Asian origin with adenocarcinoma histology. Whereas the incidence of *EGFR* mutations in lung adenocarcinomas among Asians is 47%, the incidence in North American and Western European patients is approximately 18%.[14] Although the strongest predictors of *EGFR* mutation status are female sex and absent or low smoking history, a large number of EGFR mutations are also found in lung adenocarcinoma tumor specimens from men and people who smoked cigarettes.[15]

The rapid and dramatic clinical responses to EGFR TKI therapy seen in patients with *EGFR* gene mutations led to the "oncogene addiction" hypothesis,[16,17] which states that because EGFR mutant lung cancers develop in a setting in which the mutated receptor is constantly transducing high levels of antiapoptotic signals, the cancer cells are "addicted" to EGFR kinase prosurvival signaling. As a result, sudden interruption of EGFR signaling by EGFR TKIs causes massive cell death. Another hypothesis, termed the "oncogenic shock" hypothesis,[18] states that proapoptotic signals are still present in EGFR mutant lung cancer cells. When receptor signaling is inhibited by EGFR TKIs, both antiapoptotic and proapoptotic signals are blocked. However, antiapoptotic signals decay much more rapidly than proapoptotic signals, leading to a temporary predominance in proapoptotic signaling and cell death.

A large number of retrospective series have demonstrated that the response rate of *EGFR* mutation–positive patients to EGFR TKIs exceeds 60%,[4] which is markedly higher than the typical 20% response rate to combination chemotherapy in NSCLC.[19] Several studies have also shown that NSCLC patients harboring *EGFR* mutations survive longer with EGFR TKI therapy compared to NSCLC patients with wild type EGFR treated with TKIs. Thus, personalized therapy targeting the specific genetic changes in a patient's lung cancer is critical for improving response rates and overall survival (OS).

Several randomized phase 3 trials comparing the first-generation EGFR TKI gefitinib to platinum-based chemotherapy in patients with advanced NSCLC have been reported. Although participants were not selected based on *EGFR* gene mutation status, the IPASS trial enriched its study population for subjects with *EGFR* mutations by selecting patients according to clinical factors known to be associated with higher prevalence of *EGFR* mutation: East Asian patients, adenocarcinomas, and never-smokers or former light smokers.[20] The IPASS trial was designed with progression-free survival (PFS) as the primary endpoint to assess the noninferiority of gefitinib compared with carboplatin/paclitaxel. The study met its primary objective demonstrating noninferiority and showed superiority of gefitinib for PFS, objective response rate (ORR), and quality of life for the entire cohort. However, results depended upon the *EGFR* mutation status. For patients whose tumors contained an *EGFR* mutation, PFS was significantly prolonged with gefitinib (9.5 months) in contrast to carboplatin/paclitaxel (6.3 months). In comparison, for those without an *EGFR* mutation, PFS was significantly shorter with gefitinib (1.5 months vs. 6.5 months). Two additional randomized phase 3 trials of patients with advanced NSCLC selected for *EGFR* mutations (either the exon 19 deletion or L858R point mutation) also demonstrated a significant increase in PFS with gefitinib compared to platinum-based chemotherapy as first-line treatment.[21,22] Similarly, a multicenter, open-label, randomized, phase 3 trial of the first-generation EGFR TKI erlotinib versus standard chemotherapy as first-line treatment for Caucasian patients with advanced-stage *EGFR* mutation–positive NSCLC (EURTAC) reported a median PFS of 9.7 months in the erlotinib group, compared with 5.2 months in the standard chemotherapy group.[23] These studies confirm that treatment of *EGFR* mutation–positive patients with first-line EGFR TKI therapy is superior to standard chemotherapy and represents one of the most promising advances in the field of lung cancer.

Unfortunately, virtually all patients who initially respond to EGFR TKI therapy will develop resistance and suffer a clinical relapse. Approximately 50% of the cases of acquired TKI resistance are attributed to a secondary *EGFR* gene mutation, the threonine-to-methionine point mutation at amino acid 790 (T790M) in exon 20 (Fig. 107-3).[24] The threonine residue at position 790 is highly conserved across the oncogenic RTKs EGFR, ABL, and KIT, and mutations of this residue often lead to resistance to kinase-targeted drugs.[25] Threonine 790 is in a key location at the entrance to a hydrophobic pocket at the back of the ATP-binding cleft. Mutation to a bulkier methionine group, the T790M "gatekeeper" mutation, leads to drug resistance by increasing the receptor's affinity for ATP at the ATP-binding pocket, allowing ATP to outcompete a TKI for the binding site, thereby minimizing the effects of the TKI.

Second-generation EGFR TKIs, such as afatinib and dacomitinib, were developed with a specific focus on overcoming resistance to first-generation EGFR TKIs induced by the T790M mutation. These second-generation EGFR TKIs are small molecules that covalently bind to the intracellular kinase domain of the EGFR protein. In addition to binding irreversibly to wild-type EGFR, HER2, and HER4, these novel agents also bind to EGFR carrying the T790M mutation. A phase 3 study comparing afatinib versus cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations demonstrated superior median PFS in the afatinib group compared to the cisplatin plus pemetrexed group (11.1 vs. 6.9 months; hazard ratio [HR], 0.58; $p = 0.001$).[26] A randomized, open-label, phase 2b trial (LUX-Lung 7) comparing afatinib to gefitinib for the first-line treatment of patients with advanced-stage EGFR mutation–positive NSCLC found afatinib treatment was associated with significantly improved PFS (median 11.0 vs. 10.9 months; HR, 0.73; $p = 0.017$) and time to treatment failure (median 13.7 vs, 11.5 months; HR, 0.73; $p = 0.0073$).[27] A randomized, open-label, phase 3 study of dacomitinib versus gefitinib as first-line treatment for patients with *EGFR* mutation–positive, advanced-stage NSCLC (ARCHER 1050) showed median PFS was 14.7 months in the dacomitinib group and 9.2 months in the gefitinib group (HR, 0.59; $p < 0.0001$).[28] Dacomitinib also showed significant improvement in OS over gefitinib (34.1 vs. 26.8 months; HR, 0.76; $p = 0.044$).[29] Thus, second-generation EGFR TKIs appear to be superior to platinum-based chemotherapy and first-generation EGFR TKIs for the treatment of *EGFR* mutation–positive NSCLC.

Although second-generation EGFR TKIs showed significant improvement in PFS, a phase 2b/3 randomized trial (LUX-Lung 1) evaluating afatinib in patients with advanced-stage lung adenocarcinoma with previous treatment failure on first-generation EGFR TKIs (likely due to the EGFR T790M mutation) failed to show improvement in OS.[30] As a result, third-generation EGFR TKIs were developed to further overcome T790M-mediated EGFR TKI resistance. Osimertinib is an oral, third-generation, irreversible EGFR TKI that selectively inhibits mutant EGFR proteins, with lower activity against wild-type EGFR. In a double-blind, phase 3 trial of patients with previously untreated, *EGFR* mutation–positive, advanced-stage NSCLC (FLAURA), median PFS was significantly longer with osimertinib than with first-generation EGFR TKIs (18.9 vs. 10.2 months; HR, 0.46; $p < 0.001$).[12] Median OS was 38.6 months in the osimertinib group and 31.8 months in the first-generation EGFR TKI group (HR, 0.80; $p = 0.046$).[31] A randomized, international, open-label, phase 3 trial compared osimertinib to platinum-based therapy plus pemetrexed in patients with T790M-positive advanced NSCLC who had disease progression after first-line EGFR TKI therapy (AURA3).[32] Median PFS was significantly longer with osimertinib than with platinum therapy plus pemetrexed (10.1 vs. 4.4 months; HR, 0.30; $p < 0.001$). As a result of these studies, osimertinib has become the standard of care for the first-line treatment of advanced *EGFR* mutation–positive NSCLC as well as for EGFR T790M-positive NSCLC. Despite its strong therapeutic effects, osimertinib-treated patients are still prone to developing resistance. Studies are being performed analyzing the effects of combining osimertinib with gefitinib to combat acquired resistance.

ROS1

ROS1 encodes an integral membrane protein RTK and was identified as a potential oncogene in NSCLC in 2007.[6] Chromosomal rearrangements result in gene fusions involving the 3' region of *ROS1*, which encompasses the kinase domain, and several different 5' fusion partners, including *CD74*, *EZR*, *SLC24A2*, and *FIG*.[33,34] ROS1 fusions lead to constitutive TK activation and resultant stimulation of the PI3K/AKT/mTOR, JAK/STAT, and RAF/MEK/ERK signaling pathways, which promote cell survival and proliferation. *ROS1* gene fusions account for 1% to 2% of NSCLC cases. Clinical characteristics of NSCLC patients with ROS1 gene fusions are similar to patients with EGFR mutation–positive NSCLC: Asian ethnicity, young age (median 49.8 years), never-smokers, and adenocarcinoma histology. *ROS1* gene fusions appear mutually exclusive of other known oncogenic drivers.

The TK domains of ALK and ROS1 share 77% amino acid identity within the ATP-binding sites.[35] This led investigators to treat advanced NSCLC patients who tested positive for *ROS1* rearrangements with the ALK inhibitor crizotinib.[35,36] Crizotinib showed marked antitumor activity in patients with advanced-stage *ROS1*-rearranged NSCLC, yielding an objective response rate of 72% and median PFS of 19.2 months.[35] Based on these results, the U.S. FDA approved crizotinib for the management of *ROS1*-rearranged locally advanced or metastatic NSCLC in 2016.

Despite successful outcomes, secondary mutations in *ROS1* can lead to acquired resistance in NSCLC patients treated with crizotinib. In addition, crizotinib's limited blood–brain barrier penetration may lead to a high incidence of CNS recurrence. Entrectinib is a multikinase inhibitor with activity against ROS1 that was designed with the ability to cross the blood–brain barrier and be retained in the CNS to overcome this problem. In an integrated analysis of three phase 1–2 trials (ALKA-372-001, STARTRK-1, and STARTRK-2), 41 (77%) of 53 patients had a response to entrectinib. Of the 20 patients with baseline CNS metastases assessed by blind independent central review, 11 (55%) had an intracranial response to entrectinib.[37] Based on these clinical trial data, the U.S. FDA approved the use of entrectinib for the treatment of metastatic ROS1-positive NSCLC in the summer of 2019. A number of other drugs have shown activity against ROS1 in phase 1–2 clinical trials, including ceritinib, brigatinib, DS-6051b, lorlatinib, and repotrectinib. Ongoing studies are needed to determine whether these drugs can be used as first-line treatment or whether they are better used after progression following crizotinib therapy. Novel drugs with strong safety profiles and the ability to overcome resistance mutations will increase treatment options for ROS1-rearranged NSCLC patients.

MET

The MET pathway is activated in a number of human malignancies, including lung cancer. MET receptor overexpression by immunohistochemistry has been reported in NSCLCs, in particular lung adenocarcinomas.[38] Using fluorescence in situ hybridization (FISH), the Lung Cancer Mutation Consortium reported that 4.1% of lung adenocarcinomas have MET gene amplification.[39] MET gene mutations have also been reported in human lung cancer, mainly clustered in the juxtamembrane domain, which enhance oncogenic signaling, tumorigenicity, cell motility, and migration. MET kinase domain mutations are also somatically selected in metastatic tumors compared with the primary tumors. Among patients with NSCLC, MET exon 14 mutations occur in 3% to 4% and MET amplifications occur in 1% to 6%.[40–43]

In preclinical studies, small molecule MET inhibitors decrease cell viability and growth, and they induce apoptosis in NSCLC cells via inhibition of MET/hepatocyte growth factor (HGF) signaling. Multiple drugs are being tested for clinical activity against *MET*-dysregulated NSCLC. A retrospective analysis using data from 12 institutions found that median OS for patients with *MET* exon 14 mutant NSCLC who were treated with a MET TKI was significantly improved compared to patients who never received a MET TKI (24.6 vs. 8.1 months).[44] A multiple cohort, phase 2 study evaluated the selective MET inhibitor capmatinib in patients with *MET* exon 14–mutated or *MET*-amplified advanced-stage NSCLC and found that ORR was 41% in pretreated patients and 68% in untreated patients.[45] The efficacy in *MET*-amplified NSCLC was higher in tumors with a gene copy number of 10 or higher than in those with low gene copy number. Tepotinib is a highly selective oral MET inhibitor that has shown promising clinical activity in patients with MET-driven tumors. In an open-label, phase 2 study in patients with advanced or metastatic NSCLC with a confirmed *MET* exon 14 mutation, the use of tepotinib was associated with a partial response in 46% of patients.[46] These trial data have led to U.S. FDA approval of capmatinib and tepotinib for advanced-stage NSCLCs containing *MET* exon 14 mutations. Other MET inhibitors under active clinical evaluation include the small molecule MET inhibitors savolitinib and cabozantinib.

RET

REarranged during Transfection (RET) is a transmembrane RTK with oncogenic characteristics and the ability to signal the PI3K/AKT, JNK, and RAS/MAPK and RAS/ERK pathways. Gene rearrangements in *RET* can lead to chimeric genes derived from the RET 3’ sequences encoding the intracellular TK domain and the 5’ sequences from another gene. These RET fusion proteins lead to a constitutively active receptor, ligand-independent signaling, and lung tumorigenesis. Several different fusion partners have been described in NSCLC.[47] Genetic rearrangements and translocations in *RET* have been identified in 1% to 2% of all lung cancers, with a higher incidence in never-smokers, females, adenocarcinoma, and poorly differentiated tumors.[48–51] Multitargeted kinase inhibitors that exhibit some degree of RET inhibition have been evaluated in prospective clinical trials.[52–55] But the use of these drugs resulted in limited clinical benefit and dose-limiting off-target toxic effects.[56,57]

Selpercatinib is a novel, ATP-competitive, highly selective small molecule inhibitor of RET kinase. The efficacy of selpercatinib was evaluated in a phase 1–2 clinical trial of patients with *RET* fusion–positive advanced-stage NSCLC (LIBRETTO-001).[58] Among patients who had previously received platinum-based chemotherapy (median of three previous systemic therapy regimens; 55% had received previous immunotherapy), 64% of the patients who received selpercatinib had an objective response. Among previously untreated patients, the percentage who had a response was even higher at 85%. Another selective RET inhibitor that is currently under investigation in advanced NSCLC is pralsetinib. These selective RET inhibitors may soon become part of the arsenal of targeted therapies available for the treatment of NSCLC.

HER2

Human epidermal growth factor receptor 2 (HER2, also known as ERBB2) is a member of the EGFR family of RTKs. HER2 has been studied extensively in breast cancer, where HER2 gene amplification has important implications for treatment with targeted therapy and prognosis. *HER2* gene amplification, HER2 protein overexpression, and *HER2*-activating kinase domain mutations also have been reported in NSCLC. Following successes in targeting HER2 in breast cancer, the monoclonal antibody trastuzumab was tested in HER2-overexpressing NSCLC. However, multiple clinical trials investigating the use of trastuzumab-based chemotherapy met with disappointing results.[59–62] The HER2 antibody–drug conjugate trastuzumab emtansine (T-DM1) also had limited therapeutic efficacy in HER2-overexpressing NSCLCs.[63,64] Thus, HER2 protein overexpression may not represent a valuable therapeutic target in advanced NSCLC. However, there is no consensus regarding how to score and classify HER2 protein overexpression in lung cancer. Two different scoring methods exist to classify HER2 protein expression: an IHC scoring system ranging between 0 and 3+, and the H-score, which is a semiquantitative assessment performed by multiplying staining intensity with the percentage of positive tumor cells. Low concordance in HER2 expression assessment by pathologists may also contribute to heterogeneous study populations.

In contrast to HER2 overexpression, targeting *HER2* mutations in NSCLC may have more therapeutic potential. Mutations within the kinase domain of *HER2* were first described in lung cancer in 2004 and occur in 1% to 3% of NSCLCs.[65] As expected, since HER2 is in the EGFR family of RTKs, clinical characteristics of NSCLC patients with *HER2* mutations are similar to those seen with EGFR mutations, including Asian ethnicity, female sex, never-smoker status, adenocarcinoma histology, and high morphologic grade. *HER2* mutations appear to be mutually exclusive of other oncogenic driver mutations, although some may be acquired as a resistance mechanism to TKIs as in EGFR mutation–positive NSCLC. Various therapeutic strategies have been developed to target *HER2*-mutated NSCLCs and have met with variable success. Pan-HER inhibitors (e.g., afatinib, neratinib, dacomitinib) have modest activity in NSCLC patients with *HER2* mutations (ORR, 0%–19%; median PFS, 2.9–5.5 months).[66–71] In contrast, trastuzumab and T-DM1 have been associated with improved outcomes, with ORR ranging between 14.8 and 50.9% and median PFS of 4.8 to 5.5 months.[64,67,72,73] Novel pan-HER inhibitors have demonstrated antitumor activity in NSCLC preclinical models and early clinical studies,[74,75] and are currently under evaluation in multiple clinical trials.

Intracellular Signaling Pathways and Targets

Various intracellular signaling pathways are activated in NSCLC and can be targeted therapeutically (Fig. 107-2A). Downstream of membrane bound RTKs is the RAS/mitogen-activated protein kinase (MAPK) pathway, which is a pivotal intracellular signaling pathway that transmits RTK signals to the nucleus via a cascade of specific protein phosphorylation events. In addition to RTKs, the MAPK pathway can also be activated by oncogenic driver mutations that lead to constitutive TK signaling, such as *EML4-ALK* rearrangements. In this section, we provide an overview of the roles of these signaling pathways and discuss how various components of these pathways are being considered as targets for lung cancer treatment.

Anaplastic Lymphoma Kinase Rearrangements

ALK is a member of the insulin receptor TK superfamily. In 2007, Soda et al. reported a new molecular abnormality involving the fusion of ALK with EML4 in lung adenocarcinoma.[5] The fusion protein results from an inversion in the short arm of chromosome 2 that fuses the N-terminal domain of *EML4* to the intracellular kinase domain of *ALK*, leading to constitutive activation of the ALK kinase, promoting cell proliferation and survival (Fig. 107-4). In the original report by Soda et al., 6.7% of unselected NSCLC patients had the EML4-ALK fusion protein. More than seven ALK rearrangements have been identified involving various EML4-ALK breakpoints, and rarely, other non-EML4 fusion partners. Similar to the clinical phenotype seen in patients with *EGFR* mutations, *ALK* rearrangements occur more commonly in younger patients who are never or former smokers and are predominantly associated with adenocarcinoma. However, patients with *ALK* rearrangements have characteristics that distinguish them from patients with *EGFR* mutations. EML4-ALK positive patients are younger than patients with *EGFR* mutations, with a median age of 52 years compared to 66 years.[36,76] Most reports show that *ALK* rearrangements are mutually exclusive of *EGFR* and *KRAS* mutations.

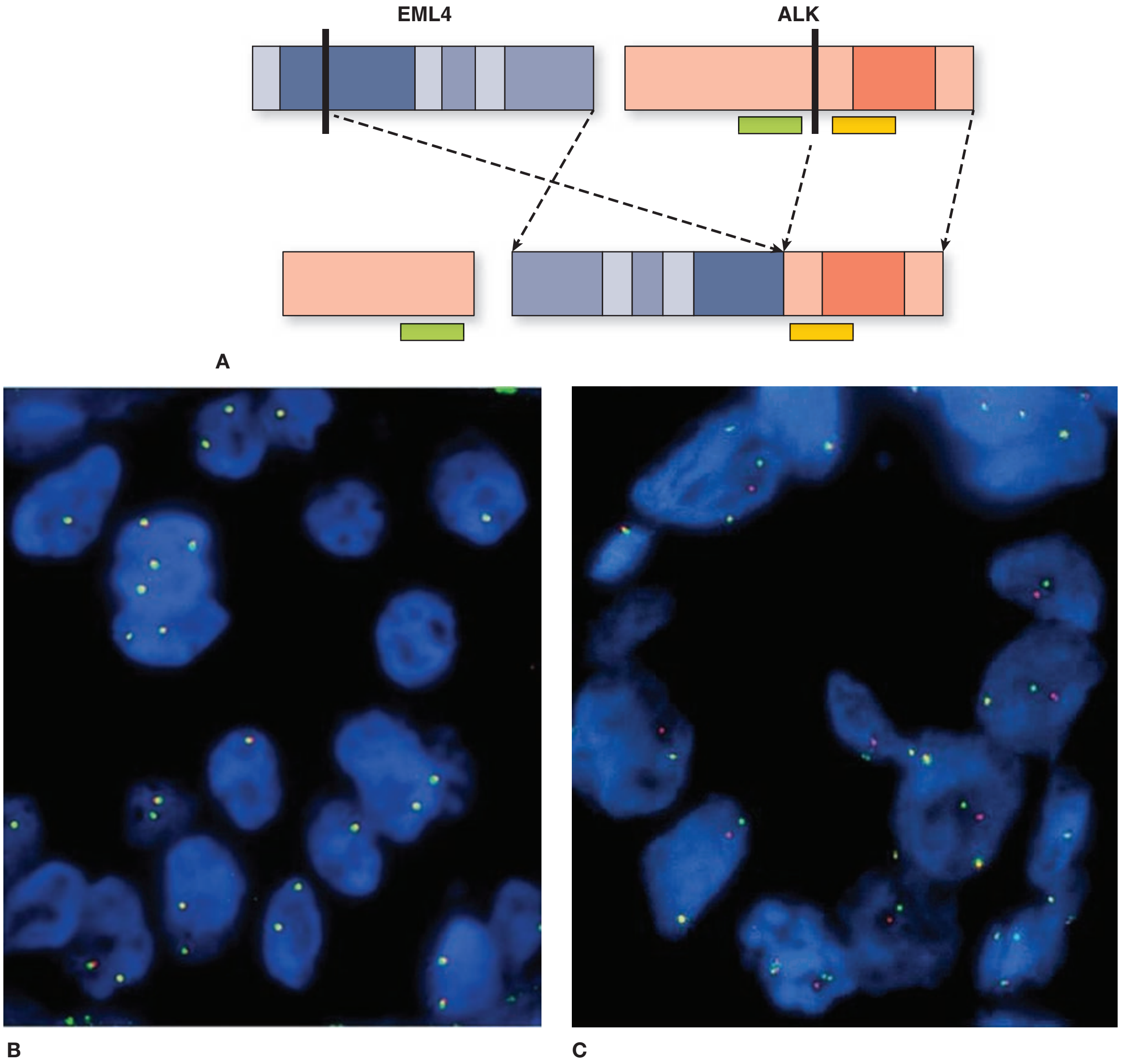

Figure 107-4 Schematic of echinoderm microtubule-associated protein-like 4 (EML4) translocation to the anaplastic lymphoma kinase (ALK) and its detection by fluorescence in situ hybridization (FISH). Both *EML4 (blue)* and *ALK (red)* genes are located on the short arm of chromosome 2 (**A**). A chromosomal inversion leads to *EML4-ALK* rearrangement and generation of a fusion protein. Green and orange bars represent DNA probes corresponding to the 5′ and 3′ fragments of the *ALK* gene. FISH detection of *EML4-ALK* rearrangement uses break-apart technology (ALK Break Apart FISH Probe, Abbott Molecular), which detects the adjacently located *EML4* and *ALK* genes in wild-type signals (**B**, *adjacent green-orange probes*) and break-apart signals caused by chromosomal inversion (**C**, *separated green-orange*). (***B** and **C:** FISH images reproduced with permission from Dr. Marileila Garcia, University of Colorado Anschutz Medical Campus.)*

In preclinical studies, the ALK kinase inhibitor TAE684 was shown to inhibit the growth of an EML4-ALK containing NSCLC cell line, both in vitro and in vivo.[5,77–80] These findings led to the testing of crizotinib, a small molecule competitive inhibitor targeted to the ATP-binding pocket of the ALK tyrosine kinase. A phase 1 study of patients with EML4-ALK–positive stage III or IV NSCLC treated with crizotinib demonstrated an overall response rate of 60.8%, including three complete responses.[36] Median time to first documented objective response was 7.9 weeks. Median PFS was 9.7 months, and estimated OS at 6 and 12 months was 87.9% and 74.8%, respectively. Based on these responses, in 2011 the U.S. FDA granted approval for crizotinib as the first ALK inhibitor for use in ALK rearrangement–positive NSCLC patients. A phase 2 study confirmed the efficacy of crizotinib in 1066 ALK rearrangement–positive NSCLC patients when used in a second-line setting.[81] In a subgroup of patients who had ALK status determined by a central laboratory using break-apart FISH (n = 908), ORR was 54%, with a median PFS of 8.4 months and a median OS of 21.8 months. Afterward, two phase 3 studies proved that targeted therapy with crizotinib in ALK rearrangement–positive NSCLC patients is superior to standard chemotherapy regimens in both first-line and second-line treatment settings.[82,83] These data show convincingly that ALK inhibition is effective in patients with NSCLC carrying an *ALK* rearrangement.

Similar to EGFR targeted therapy, resistance to crizotinib in EML4-ALK–positive NSCLC has been reported. A patient in the original phase 1 study of crizotinib developed resistance after 5 months of therapy.[84] Deep sequencing of complementary DNA comparing *EML4-ALK* translocation before and after resistance identified two independent events in the resistant cancers: point mutation of residue 1156 from cytosine to tyrosine (C1156Y), and, at residue 1196, from leucine to methionine (L1196M). In vitro, these new mutations decreased the fusion protein's sensitivity to crizotinib. Structural analysis of these mutants showed that C1156Y was close to the edge of the ATP-binding pocket. Interestingly, L1196M corresponds to the T790M gatekeeper mutation in EGFR, suggesting a common mechanism for the development of resistance in tyrosine kinases. Analysis of tissue obtained from patients with *ALK* gene–rearranged NSCLC who showed radiologic progression while on crizotinib found multiple mechanisms of resistance to crizotinib: secondary mutations in the TK domain of *ALK*, new-onset *ALK* copy number gain, and outgrowth of either *EGFR* or *KRAS* mutant NSCLC.[85]

The identification of mutations that lead to primary and secondary resistance to crizotinib fueled the development of second-generation ALK inhibitors. Ceritinib is a second-generation oral ALK inhibitor, which has been shown to overcome *ALK* mutations that lead to acquired resistance to crizotinib. In a randomized, controlled, open-label, phase 3 trial, patients with *ALK*-rearranged advanced-stage NSCLC who had received previous chemotherapy and crizotinib were randomized to ceritinib or chemotherapy (pemetrexed or docetaxel).[86] Ceritinib showed a significant improvement in median PFS compared with chemotherapy (5.4 vs. 1.6 months; HR, 0.49; p <0.001), indicating that ALK-positive NSCLC patients benefit from ceritinib after failure of crizotinib. However, no randomized clinical studies have directly compared ceritinib and crizotinib head to head. Another second-generation ALK inhibitor that has demonstrated efficacy against crizotinib-resistant mutations is alectinib. In a cohort of patients with advanced *ALK*-positive NSCLC who had progressed after crizotinib, treatment with alectinib led to an ORR of 48% and a median PFS of 8.1 months.[87] Later, several phase 3 clinical trials were conducted comparing alectinib with crizotinib in treatment-naïve patients with ALK-positive NSCLC.[88–90] Median PFS was significantly longer with alectinib than with crizotinib, leading to alectinib being recognized as a better first-line treatment option than crizotinib in several lung cancer treatment guidelines.[91–93] The second-generation ALK inhibitor brigatinib also has been compared to crizotinib in the first-line setting in ALK-positive NSCLC patients. Compared to crizotinib, brigatinib showed superiority in median PFS (24.0 vs. 11.0 months; HR, 0.49; p <0.0001), leading to the U.S. FDA approving brigatinib for the first-line treatment of patients with ALK-positive metastatic NSCLC.

Unfortunately, ALK-positive NSCLC still develops resistance to second-generation ALK inhibitors. As a result, lorlatinib, a third-generation ALK inhibitor, was designed to target mutations that drive resistance to crizotinib and second-generation ALK TKIs. Lorlatinib was also developed to cross the blood–brain barrier and facilitate CNS penetration. In a phase 2 study of patients with ALK-positive, advanced NSCLC with or without CNS metastases, lorlatinib showed substantial overall and intracranial activity, both in treatment-naïve patients and in those who had progressed on crizotinib or second-generation ALK TKIs.[94] Thus, lorlatinib represents a valid and powerful treatment strategy in heavily pretreated ALK-rearranged NSCLC patients.

RAS/MAPK Pathway

The MAPK pathway is one of the most extensively studied intracellular signaling pathways. The MAPK pathway modulates transcription factors, which in turn regulate gene expression in response to extracellular signals. In healthy cells, the MAPK signaling cascade mediates cellular growth, proliferation, and survival processes. Dysregulation of MAPK signaling in cancer is associated with evasion of apoptosis, uncontrolled cell proliferation, and resistance to chemotherapy and targeted therapies.

The MAPK pathway can be activated by multiple mechanisms, including activation of RTKs (e.g., EGFR, ROS1) in response to extracellular stimuli and mutations that lead to constitutive TK activity (e.g., EGFR mutations, *EML4-ALK* rearrangements). The canonic MAPK cascade is composed of three successive serine/threonine kinases: RAF, MEK, and ERK. Due to the alteration of the RAS/MAPK pathway in lung cancer, components of the pathway are considered to be promising drug targets for cancer therapies.

RAS

The *RAS* family of oncogenes includes neuroblastoma RAS viral oncogene homolog (*NRAS*), *KRAS*, and Harvey rat sarcoma viral oncogene homolog (*HRAS*). *KRAS* is the gene that is most commonly involved in lung cancer. *RAS* genes encode a family of membrane-bound guanine triphosphatases (GTPases or G proteins) whose signaling regulates cell growth, differentiation, and apoptosis. Similar to RTKs, G proteins can be thought of as "on/off switches" for signaling (Fig. 107-5). While in the "on" state, RAS is bound to guanosine triphosphate (GTP). A phosphate group is then transferred from GTP to a RAS effector molecule, activating the downstream signaling process. The remaining guanosine diphosphate (GDP) form of the complex is incapable of signaling and puts the RAS complex in an "off" state. Activation and inactivation of RAS and other small G proteins are thus controlled by cycling between the active GTP-bound and inactive GDP-bound forms. Activated RAS stimulates RAF protein kinases, which in turn initiates the MEK cascade leading to ERK activation and ultimately activation of transcription factors that regulate cell cycle progression. Other effectors of activated RAS include signal transducer and activator of transcription (STAT) and PI3K signaling cascades.

In 1984, a human lung cancer specimen was found to contain an activating *KRAS* mutation that was not found in corresponding normal tissue.[95] Subsequently, investigators have found that approximately 25% to 30% of NSCLCs harbor activating point mutations in *RAS* genes, with *KRAS* accounting for the majority

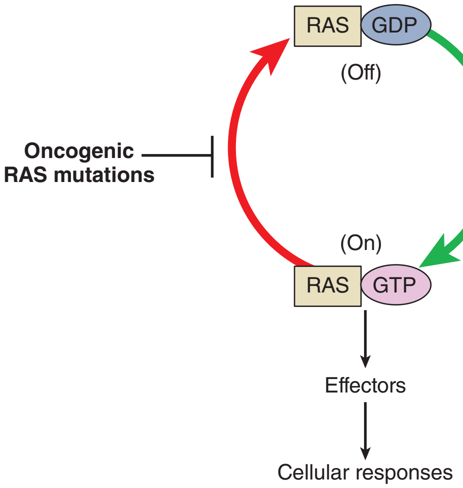

Figure 107-5 Activation cycle of RAS proteins. Growth factor stimulation leads to activation of RTKs, which causes the adaptor protein growth factor receptor–bound protein 2 (Grb2) to bind to RAS and recruit Son of Sevenless (SOS), which stimulates the conversion of RAS from the inactive guanosine diphosphate (GDP)-bound form to the active guanosine triphosphate (GTP)-bound form. Stimulation of RAS activates a mitogen-activated protein kinase cascade, leading to cell growth and differentiation. Oncogenic RAS mutations result in compromised GTPase activity, causing mutant RAS to favor its active GTP-bound state. Therefore, mutant RAS results in continuous signaling even in the absence of growth factor stimulation, conferring a proliferative advantage to tumor cells.

of *RAS* mutations (90%),[96] specifically in codons 12, 13, and 61.[97] In NSCLC, the most frequent KRAS mutations are G12C (~50%), followed by G12V and G12D.[98,99] These mutations result in compromised GTPase activity, causing mutant RAS protein to favor its active GTP-bound state. Therefore, mutant RAS protein results in continuous signaling even in the absence of growth factor stimulation, conferring a proliferative advantage to tumor cells.

Although *KRAS* mutations are the most common oncogenic driver in lung adenocarcinomas, *KRAS* mutations are uncommon in lung squamous cell carcinomas. In contrast to oncogenic driver mutations in RTKs, *KRAS* mutations are more common in NSCLC tumors from smokers than from never-smokers. A meta-analysis of 53 studies of lung cancer assessing the prognostic value of *RAS* mutations on survival found a worse survival for NSCLC with *KRAS* mutations compared to non-KRAS-mutant NSCLC, particularly in adenocarcinomas.[100] Because the RAS protein is a downstream effector of EGFR and other RTKs, *KRAS* mutations have been assessed as a primary mechanism of resistance to EGFR TKIs, and the presence of a *KRAS* mutation may predict that a patient will not respond to EGFR TKIs.

Due to the frequency of *KRAS* mutations in NSCLC, development of agents to inhibit mutated RAS proteins has been widely pursued. However, the search for RAS inhibitors has proved challenging and for decades KRAS was considered undruggable. Whereas RAS binds GTP with picomolar affinities, the concentration of GTP in cells approaches micromolar levels. Thus, targeting mutant GTP-bound RAS with nucleotide analogues has been unsuccessful due to the inability to compete with the high GTP levels. Considerable research went into the development of farnesyl transferase inhibitors to alter RAS membrane localization such as farnesylthiosalicylic acid (salirasib), which mimics the carboxy terminal amino acid of RAS and dislodges activated RAS from the membrane. However, farnesyl transferase inhibitors failed to demonstrate efficacy in clinical trials against tumors containing mutant KRAS,[101] likely due to alternate pathways for farnesyl modification of KRAS. Attempts to block RAF, one of the major downstream effectors of RAS, led to the unexpected discovery that in RAS-transformed cells, RAF inhibitors activate the MAPK pathway instead of inhibiting it.[102]

Recent breakthroughs may pave the way to developing specific therapies targeting mutant KRAS proteins. In 2013, Shokat et al. identified electrophilic compounds that interact selectively with the GDP form of oncogenic KRAS^{G12C} protein and bind covalently to a previously unknown allosteric pocket under the switch II loop region (S-IIP) near the guanosine nucleotide binding site.[103] These findings led to the discovery of the novel covalent KRAS^{G12C} inhibitor ARS-1620,[104–106] which binds covalently to the S-IIP pocket and makes KRAS^{G12C} preferentially accept GDP instead of GTP, reducing GTP-bound KRAS^{G12C} by more than 90% and locking KRAS^{G12C} in the GDP-bound off state. Importantly, ARS-1620 binds specifically to KRAS^{G12C} and has no effect on either wild-type KRAS or other mutant KRAS proteins. In preclinical patient-derived tumor models, ARS-1620 induced tumor regression, providing in vivo evidence that mutant KRAS^{G12C} can be selectively targeted.[105]

These findings have led to the development of several novel direct covalent KRAS^{G12C} inhibitors that are currently undergoing testing in clinical trials. Sotorasib (AMG 510) is a small molecule structurally related to ARS-1620, but it takes advantage of novel binding interactions with the S-IIP pocket, which improve its potency approximately 10-fold compared to ARS-1620.[107] In preclinical animal studies, treatment with sotorasib resulted in a proinflammatory tumor microenvironment and produced durable cures in combination with anti–PD-1 immune checkpoint inhibitors.[108] In a phase 1 trial of sotorasib in patients with advanced solid tumors harboring the *KRAS*^{G12C} mutation, 32.2% (19 patients) of NSCLC patients had a confirmed objective response and 88.1% (52 patients) had disease control, with median PFS of 6.3 months.[109] Another small molecule inhibitor that irreversibly binds to the KRAS^{G12C} S-IIP pocket and locks it in an inactive GDP-bound state is MRTX849.[110] In vitro, MRTX849 is a potent and selective inhibitor of KRAS^{G12C}-dependent signal transduction and cell viability. In vivo, treatment with MRTX849 inhibited KRAS signaling and induced tumor regression in multiple KRAS^{G12C} cell line and patient-derived xenograft models, and MRTX849 (adagrasib) has also advanced to clinical trials.[111] The revolutionary strategy to use covalent allosteric inhibitors that target the S-IIP pocket has provided impetus for renewed drug development efforts and has paved the way for targeted agents to treat KRAS-mutant NSCLC. The US FDA has approved both sotorasib and adagrasib for patients with KRAS G12C-mutated NSCLC who have already received at least one prior systemic therapy.

RAF

The RAF family of serine/threonine kinases, which includes ARAF, BRAF, and RAF-1 (also known as CRAF), plays a critical role in cellular growth, proliferation, and differentiation through the MAPK signaling pathway. Although RAF is activated by RAS, activation can also occur independently of RAS through other activators such as Src, c-Jun NH2-terminal kinase, interferon β, and protein kinase C-α (PKC-α), or through dimerization between RAF isoforms. In NSCLC, activating mutations of the *BRAF* gene have been reported in 3% to 5% of NSCLC tumors, most of which are adenocarcinoma.[112,113] Similar to other oncogenes, driver mutations in *BRAF* are mutually exclusive of *EGFR* mutations or *ALK* rearrangements. BRAF^{V600E} represents the most frequent BRAF mutation in lung cancer, accounting for approximately 50% of BRAF-mutant NSCLC.[114] Whereas BRAF^{V600E} mutations arise more frequently in women and are not correlated to smoking history, non-V600E BRAF mutations have been reported to be more frequent in male patients with a history of smoking.[113] BRAF^{V600E} mutations lead to constitutive activation, initiating the MAPK signaling cascade without activation by RAS, resulting in uncontrolled cellular proliferation and lung carcinogenesis.

MEK

MEK1 and MEK2 are closely related, dual-specificity tyrosine/threonine protein kinases in the MAPK signaling pathway that transmit mitogenic signals from outside the cell to the nucleus through multistage phosphorylation. MEK plays an important role in cell proliferation, differentiation, apoptosis, and stress responses. MEK1/2 have a unique pocket structure adjacent to the ATP-binding site that is an ideal target for small molecule agents.[115] The presence of small molecule inhibitors induces several conformational changes in the unphosphorylated MEK1 and MEK2 proteins that lock them into an inactive state. As MEK1/2 are the downstream effectors of RAS and RAF, MEK inhibitors have been developed as a strategy to treat NSCLC patients with *KRAS* or *BRAF* mutations. To date, four MEK inhibitors have been approved by the U.S. FDA: trametinib, binimetinib, selumetinib, and cobimetinib. Several phase 2 trials have investigated MEK inhibitors for the treatment of patients with advanced-stage NSCLC.[116–119] Unfortunately, these studies found that monotherapy with MEK inhibitors resulted in poor clinical outcomes and more toxicity for NSCLC patients compared with conventional chemotherapy.

Although MEK inhibitor monotherapy has been ineffective for NSCLC patients, the combination of MEK and BRAF inhibitors was evaluated in a phase 2, multicenter, nonrandomized, open-label, single-arm study. Patients with pretreated metastatic $BRAF^{V600E}$-mutant NSCLC treated with the combination of the oral RAF inhibitor dabrafenib and the oral MEK1/2 inhibitor trametinib had an ORR of 63.2% and median PFS of 9.7 months.[120] Similarly, in a phase 2, multicenter, nonrandomized, open-label, single-arm study, patients with previously untreated metastatic $BRAF^{V600E}$-mutant NSCLC treated with oral dabrafenib and oral trametinib had an ORR of 64% and median PFS of 10.9 months.[121] Based on these data, the U.S. FDA expanded indications for dabrafenib and trametinib to include the treatment of patients with metastatic NSCLC harboring $BRAF^{V600E}$ mutations.

ERK

ERK1 and ERK2 are structurally similar isoforms of ERK that are important effectors in the MAPK pathway. ERK is activated by its upstream effector MEK through phosphorylation. In the cytoplasm, ERK modulates key cytoskeletal proteins that affect motility, metabolism, and cell adhesion. Upon activation, ERK dimerizes and localizes to the nucleus, where it phosphorylates and activates several transcription factors that are involved in cell proliferation and survival. Although BRAF/MEK inhibitor combination therapy provides significant additional benefit beyond monotherapy, patients eventually develop resistance and disease progression. Several mechanisms of resistance have been identified, which typically lead to reactivation of ERK signaling and escape of tumor cells from combination BRAF/MEK inhibitor therapies.[122,123] Due to its aberrant expression in several cancers, including NSCLC, ERK is being studied as a potential therapeutic target in cancers with *BRAF*, *RAS*, or *MEK* mutations. Moreover, as the most distal master kinase of the MAPK signaling pathway, ERK inhibition may avoid or overcome resistance mechanisms that arise in upstream kinases.

Ulixertinib is a highly potent, selective ERK1/2 kinase inhibitor that has been shown to reduce tumor growth and induce tumor regression in *BRAF*- and *RAS*-mutant xenograft models. An open-label, dose-escalation study of oral ulixertinib was undertaken in solid tumor patients with *BRAF*, *RAS*, and *MEK* mutations.[124] In patients with *BRAF*-mutant NSCLC, partial responses were seen in 3 of 12 evaluable patients (2 with $BRAF^{V600E}$ mutations and 1 with non-V600E). Of note, CNS responses were seen in a patient with $BRAF^{V600E}$-mutant lung cancer with brain metastases. Due to concerns that ERK inhibitor monotherapy is likely to confer drug-acquired resistance, additional studies investigating ERK inhibitors in combination with TKIs or MEK inhibitors are currently being undertaken.

IMMUNOTHERAPY

The concept of mobilizing the host's immune system to treat cancer has been considered for decades. This approach represents a significant departure from chemotherapy-based cancer treatment, which targets the tumor through focusing on the host's own immune system to identify and kill cancer cells. However, therapeutically harnessing the immune system through cytokine therapy, vaccines, or interferons had limited success as a clear understanding of the tumor immune response was lacking. This changed with the discovery that the T-cell immune response is regulated not only by activation signals, but also by a plethora of inhibitory pathways called immune checkpoints, which inhibit the T-cell response and protect the host from damaging immune responses. Thus, T cell–mediated immunity consists of not only T-cell activation and proliferation, but also counterbalancing inhibitory pathways to control and ultimately abrogate T-cell effector functions. This discovery made possible the development of immune checkpoint inhibitors for cancer therapy. These drugs represent a departure in our pharmacologic approach to cancer therapy, as immune checkpoint inhibitors do not directly target tumor cells. Instead, they target the pathways that inhibit T-cell responses and enhance endogenous antitumor activity.

■ Immune Checkpoint Pathways

Immune checkpoints refer to inhibitory pathways in T cells crucial for maintaining self-tolerance. Tumors can also use these immune checkpoint pathways to inhibit T-cell response and escape immune surveillance. There are numerous immune checkpoints, and the two immune checkpoint receptors that have been most actively studied in the context of clinical cancer immunotherapy are cytotoxic T lymphocyte–associated protein 4 (CTLA-4) and programmed cell death receptor 1 (PD-1) (Fig. 107-2B). CTLA-4 regulates the amplitude of the early stages of T-cell activation by competing with the T cell CD28 receptor, whose signaling is required (co-stimulation) along with T-cell antigen receptor signaling for T-cell activation. The specific signaling pathways by which CTLA-4 blocks T-cell activation are still under investigation. Although CTLA-4 is expressed by activated CD8+ effector T cells, the major physiologic role of CTLA-4 appears to be through downmodulation of helper T-cell activity and enhancement of regulatory T (Treg) cell immunosuppressive activity. CTLA-4 blockade results in a broad enhancement of immune responses that are dependent on helper T cells and suppression of Tregs. Although currently approved only for the treatment of melanoma as monotherapy, CTLA-4 inhibitors are being investigated as treatment for a variety of cancer types, including NSCLC.

In contrast to CTLA-4, the major role of PD-1 is to interfere with signaling through the T-cell antigen receptor, acting later in the T-cell response by limiting the activity of T cells in peripheral tissues at the time of an inflammatory response (Fig. 107-6). PD-1 is expressed on tumor-infiltrating lymphocytes, and upon binding to its ligands PD-L1 and PD-L2, PD-1 inhibits kinases that are involved in T-cell activation. PD-1 is also highly expressed on Tregs and may enhance their proliferation. PD-1 ligand expression is frequently upregulated in human cancer, including NSCLC.[125] Inhibition of the PD-1 pathway has been shown to enhance intratumoral immune responses in preclinical studies, and blockade of PD-1 has introduced a new era in lung cancer treatment.

■ Pharmacologic Immune Checkpoint Inhibitors in Lung Cancer

Pharmacologic immune checkpoint inhibitors targeting PD-1, PD-L1, and CTLA-4 have been developed and tested in multiple

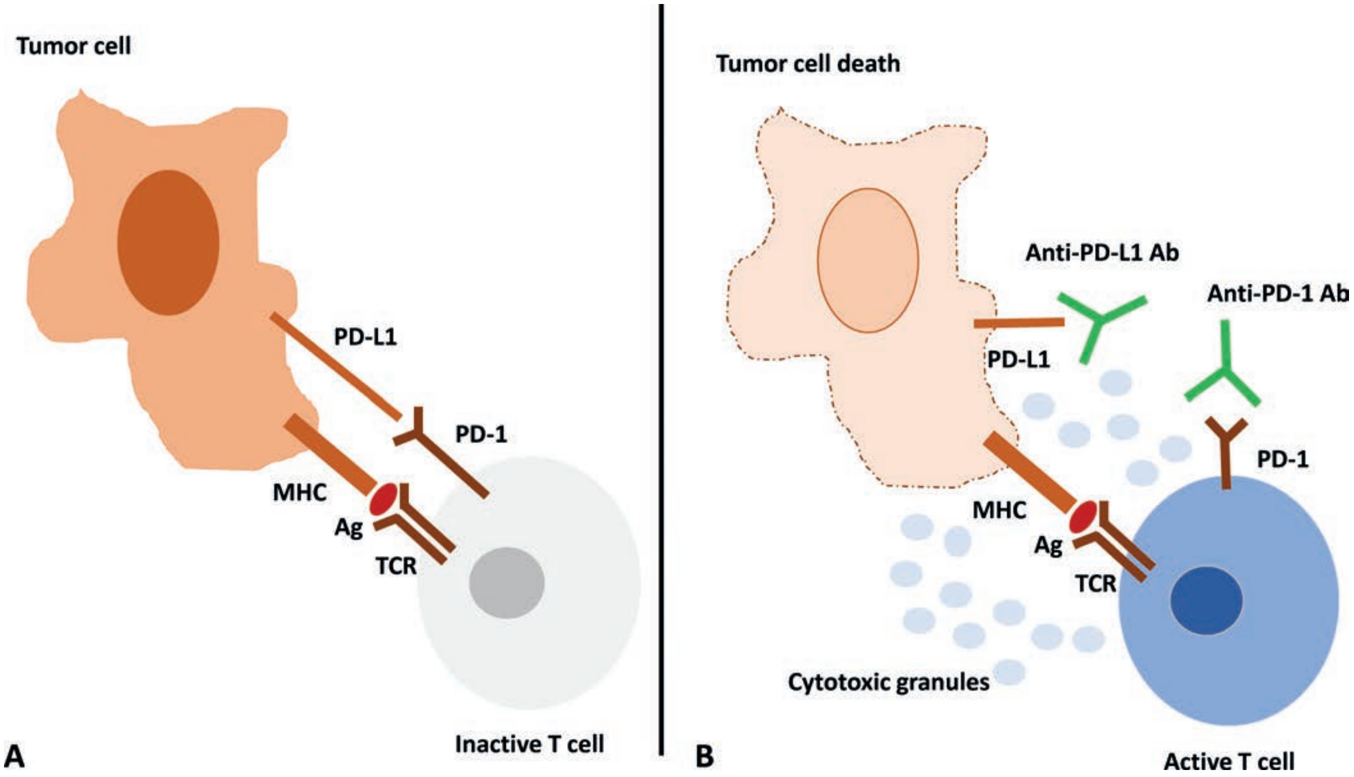

Figure 107-6 PD-1 and cancer. **A.** Ligation of T-cell PD-1 by tumor PD-L1 results in the downregulation of T-cell effector functions that destroy tumor tissue. **B.** Blockade of this pathway by anti–PD-1 or anti–PD-L1 antibodies prevents this downregulation and allows T cells to maintain their antitumor functionality and ability to mediate tumor cell death.

cancer types, including lung cancer. Whereas TKIs are typically effective only in patients with lung adenocarcinoma that express oncogenic driver mutations, immunotherapy with checkpoint inhibitors has been shown to be efficacious in both squamous and nonsquamous NSCLC patients, as well as a smaller proportion of SCLC patients. However, NSCLC patients with targetable driver mutations are unlikely to respond to immunotherapy as these cancers have a lower total mutational burden, resulting in fewer neoantigens seen by T cells.[126–128] Thus, precision targeted therapy and immunotherapy play distinct but complementary roles in the management of NSCLC.

PD-1/PD-L1 Inhibitors for NSCLC

Following successful clinical trials in the treatment of malignant melanoma, pharmacologic immune checkpoint inhibitors targeting the PD-1/PD-L1 pathway became established as a treatment for NSCLC patients. The initial trials and associated FDA-approved indications were in the second-line setting for stage IV squamous and nonsquamous NSCLC. The anti–PD-1 inhibitors nivolumab and pembrolizumab and the anti–PD-L1 inhibitor atezolizumab all showed significantly improved OS in previously treated, advanced-stage NSCLC compared with docetaxel.[129–132] Pembrolizumab and atezolizumab later proved to be superior to chemotherapy in the first-line setting for stage IV NSCLC patients with high PD-L1 expression,[133,134] and both pembrolizumab and atezolizumab have been approved by the U.S. FDA as monotherapy for the first-line treatment of PD-L1–positive metastatic NSCLC. Combinations of anti–PD-1 (pembrolizumab) or anti–PD-L1 (atezolizumab) inhibitors with platinum doublets demonstrated improved OS over chemotherapy alone[135–137] and have become standard of care for stage IV NSCLC patients without actionable oncogenic driver mutations. The PD-1 inhibitor durvalumab has also been approved by the U.S. FDA as adjuvant therapy after combined chemoradiotherapy in stage III NSCLC patients.[138]

Dual PD-1 and CTLA-4 Checkpoint Blockade for NSCLC

The combination of the anti–PD-1 inhibitor nivolumab and the anti–CTLA-4 inhibitor ipilimumab has been studied in NSCLC. CheckMate 227 included patients with previously untreated NSCLC and assigned treatment based on PD-L1 expression.[139] In the PD-L1–positive cohort, dual checkpoint blockade was superior to chemotherapy alone (median OS, 17.1 vs. 14.9 months; HR, 0.79). Dual PD-1 and CTLA-4 checkpoint blockade combined with chemotherapy as first-line treatment for NSCLC was explored in the phase 3 CheckMate 9LA trial.[140] This study included patients with treatment-naïve NSCLC, both squamous and nonsquamous, but excluded patients with *EGFR* mutations or *ALK* rearrangements. Patients were randomized to four cycles of chemotherapy alone or a combination of nivolumab, ipilimumab, and concurrent platinum-doublet chemotherapy for only two cycles. The combined chemoimmunotherapy approach improved OS, with a median OS of 15.6 months, compared to 10.9 months with chemotherapy alone (HR, 0.66). These studies led to U.S. FDA approval of nivolumab and ipilimumab as first-line treatment for patients with metastatic NSCLC with high PD-L1 tumor expression, and the approval of nivolumab plus ipilimumab and two cycles of platinum-doublet chemotherapy as first-line treatment for patients with metastatic or recurrent NSCLC.

PD-1/PD-L1 Inhibitors for SCLC

PD-1/PD-L1 inhibitors for SCLC can be considered with regard to their role in salvage chemotherapy and as part of first-line chemoimmunotherapy.

Salvage Immunotherapy In contrast with TKIs targeting oncogenic driver mutations, immunotherapy has also emerged as an effective treatment for extensive-stage SCLC. Initial efforts focused on the previously treated population. CheckMate 032 was a nonrandomized study that included 216 patients with SCLC.[141] Patients were treated with nivolumab alone or in combination with ipilimumab using various dosing schedules. Although nivolumab alone yielded an ORR of 10% and a relatively short median PFS of 1.4 months, a subset of patients achieved long-term survival with a 1-year OS rate of 33%. In the subset of patients who received nivolumab monotherapy as third-line treatment, the ORR was 11.9% with median OS of 5.6 months. While modest, the responses were durable with a median duration of response of 17.9 months and 18-month OS rate of 20%. As a result, nivolumab was granted accelerated approval by the U.S. FDA as third-line therapy for SCLC.

Pembrolizumab showed similar activity in SCLC. KEYNOTE-028 was a small, nonrandomized, phase 1b study that enrolled patients with previously treated, PD-L1–positive SCLC.[142] KEYNOTE-158 was a larger, single-arm, phase 2 trial that included patients with previously treated SCLC.[143] A pooled analysis of these trials included 83 patients who received pembrolizumab as third-line treatment.[144] In this cohort, the ORR was 19.3%. Although median PFS was limited to 2.0 months and median OS was only 7.7 months, the 24-month OS rate was 20.7%. Pembrolizumab subsequently received accelerated FDA approval as third-line therapy.

First-line Chemoimmunotherapy Combining checkpoint inhibitors with standard platinum plus etoposide chemotherapy in the first-line treatment setting has had an even larger impact on SCLC. IMpower 133 was a global, double-blind, placebo-controlled, phase 3 study that enrolled patients with previously untreated extensive-stage SCLC.[145] Patients were treated with four cycles of carboplatin plus etoposide and were randomized to receive concurrent atezolizumab followed by atezolizumab maintenance therapy or placebo. The combination of atezolizumab with carboplatin and etoposide improved both median PFS and OS and was the first treatment to improve survival for SCLC in more than three decades. The CASPIAN study was an open-label phase 3 study that randomized patients with extensive-stage SCLC to chemotherapy alone or chemotherapy with concurrent durvalumab followed by durvalumab maintenance therapy.[146] Similar to outcomes seen with atezolizumab in IMpower 133, durvalumab improved median OS from 10.3 to 13.0 months (HR, 0.73). Atezolizumab and durvalumab have since been approved with platinum and etoposide as first-line therapy for extensive stage SCLC by the U.S. FDA.

■ Clinical Assessment of Immunotherapy Response

The standard approach to assess response to cancer therapy uses Response Evaluation Criteria in Solid Tumors (RECIST) to provide a consistent approach to evaluate therapy-driven changes in tumor burden. However, tumor response to immunotherapeutic agents differs from that seen with cytotoxic agents. There can be a delayed radiographic response due to the nature of the immune response, which requires T-cell activation, expansion, tumor infiltration, and cell killing before a measurable response is detected. Patients may exhibit stable disease or progressive disease with subsequent response. A response may be mixed with variable changes in different lesions in the same host. Therefore, measurable activity at a tumor site may take longer for immunotherapies than that seen with standard chemotherapy. Four distinct patterns of response have been described: immediate response, stable disease, response after tumor burden increase, and response in the presence of new lesions. Due to the addition of novel responses, immune-related response criteria (irRC) have been developed to allow tumor assessment as a continuous variable.[147]

■ Biomarkers of Clinical Response to Immune Checkpoint Inhibition

Pharmacologic antibodies targeting PD-1 and PD-L1 have resulted in remarkable clinical responses in a subset of patients with lung cancer. However, many patients with lung cancer fail to respond to anti–PD-1/PD-L1 immunotherapy. Moreover, immune-related adverse effects associated with immune checkpoint blockade can limit its use in patients with lung cancer. Thus, it is critical to identify biomarkers that can predict efficacy to immune checkpoint inhibitors in patients with NSCLC.

PD-L1 Expression

Multiple guidelines recommend the use of immunohistochemistry methods to detect PD-L1 expression as a way to predict efficacy of anti–PD-1/PD-L1 immune checkpoint inhibitors in patients with lung cancer. However, there are multiple challenges in using PD-L1 expression as a biomarker of response. A range of commercial kits have been developed to detect different epitopes of PD-L1 utilizing five distinct antibodies on two different immunohistochemistry platforms. Whereas some kits evaluate tumor cells only, other kits evaluate both tumor cells and tumor-infiltrating immune cells. In clinical studies, each pharmacologic anti–PD-1/PD-L1 immune checkpoint inhibitor used a different antibody to evaluate PD-L1 expression in tumors: pembrolizumab used the 22C3 antibody, atezolizumab used the SP142 antibody, nivolumab used the 28-8 antibody, and durvalumab used the SP263 antibody.[148] Moreover, different cutoff values and scoring systems were used to define PD-L1 positivity. The most commonly used method for analyzing PD-L1 expression in NSCLC is the Tumor Proportion Score (TPS), which is the percentage of viable tumor cells showing partial or complete membrane staining for PD-L1 using the 22C3 antibody. In the KEYNOTE clinical trials, pembrolizumab significantly increased OS of NSCLC patients with TPS $\geq$50%.[131,133] However, there are multiple instances of PD-L1–negative NSCLC patients responding to anti–PD-1/PD-L1 immune checkpoint inhibitors, and vice versa, of nonresponders among NSCLC patients with high PD-L1 expression. In addition, PD-1/PD-L1 expression is dynamic and can change over time with therapy. The temporal and spatial heterogeneity in the expression of PD-L1 within NSCLC tumors limits its efficacy as a predictive biomarker. Ultimately, tumor cell killing is T cell–dependent. Therefore, it is likely that PD-L1 expression needs to be considered in the context of the T-cell response, as it is the T-cell functional response that is critical, not PD-L1 expression alone.

Tumor Mutational Burden

Cancer develops through the gradual accumulation of numerous somatic mutations. Although the incidence of mutations varies across tumor types, lung cancer has a high tumor mutational burden (TMB), which is defined as the number of mutations per megabase (Mb) of DNA determined using DNA sequencing. In some studies, high TMB ($\geq$10 mutations/Mb) has been shown to correlate with efficacy of immunotherapy for NSCLC irrespective of PD-L1 expression.[141,149–154] Tumors with a high TMB presumably benefit from immune checkpoint blockade therapy, because high TMB is correlated with the presence of a high number of neoantigens that could be recognized by CD8+ T cells. In theory, any acquired somatic mutation in tumor cells can be a potential neoantigen and can serve as a target for antitumor CD8+ T cells. However, only a small fraction of mutations results in neoantigens recognized by T cells. Several issues limit the utility of TMB as a biomarker of response to immune checkpoint inhibitor therapy in lung cancer. For example, TMB assessment is not standardized across research and clinical studies. Multiple factors can influence the measurement of TMB, including sample quality and quantity, sequencing platform, genome coverage, and bioinformatics analysis pipelines. Thus, TMB can vary between analyses from the same patient sample and between different samples from the same patient.

It is unlikely that a single biomarker will be able to provide all the information necessary to predict tumor response to therapy and dynamically respond to changes in T-cell activation and tumor targets. Perhaps the goal should be to develop panels of markers that will offer targeted therapies (e.g., molecular testing), monitor the tumor (e.g., TMB), and evaluate T-cell responses (e.g., immune checkpoints or other activation/inhibition markers) to guide cancer therapy.

CLINICAL PERSPECTIVE

Below we consider several key clinical areas, including molecular testing methods, the importance of adequate biopsies, acquired resistance to targeted therapy, and the role of so-called liquid biopsies.

Molecular Testing Methods

The identification of novel genetic changes in patients with NSCLC signals a new era of personalized medicine for patients with lung cancer, where it will be imperative to match the specific molecular profile of a patient's tumor with a specific therapy. An important issue to consider is which method will be used for molecular testing. Direct sequencing of PCR-amplified regions of genes that include the most common mutations is the most common method of identifying oncogenic driver mutations (e.g., *EGFR*, *KRAS*). However, testing for gene rearrangements (e.g., *EML4-ALK*, *ROS1*) is typically performed using fluorescence in situ hybridization (FISH). Finally, PD-L1 expression is based on immunohistochemistry. In addition, diagnostic lung cancer samples are frequently small biopsies. The need for multiple molecular tests, which often require distinct diagnostic platforms, is logistically complicated and difficult given the limited amount of available tumor tissue.

Next-generation sequencing (NGS) offers high-throughput sequencing capacity. Unlike PCR-based sequencing techniques, NGS does not require pre-existing knowledge of where to find a mutation. NGS can also provide information PCR-based strategies cannot, such as alternatively spliced transcripts, allele gene variants, and single-nucleotide polymorphisms. This technique provides an opportunity to analyze the entire genome to identify all medically relevant genes using one assay. NGS is already used for NSCLC diagnosis in many hospitals and clinical laboratories, and may eventually replace conventional techniques of gene analysis. NGS is capable of detecting small mutations across all regions of the analyzed genes and may increase the number of identified EGFR or BRAF mutations. However, mutations of unknown significance also may be identified. Although more complicated, NGS analysis of both genomic DNA and RNA can detect more complex alterations, such as *EML4-ALK* rearrangements, *ROS1* fusions, and *MET* exon 14 skipping mutations.[155–158] Evaluation of gene copy number variations (e.g., *MET* and *HER2* amplifications) can be achieved by comparative analysis of the number of reads. However, clinical analysis of protein expression (e.g., PD-L1) cannot be achieved by NGS and requires immunohistochemistry.

Despite obvious advantages, the use of NGS in many circumstances is impractical. NGS requires expensive, sophisticated equipment and reagents, and robust bioinformatics analysis. Thus, NGS may not be available to all medical centers around the world. Druggable mutations in NSCLC are often mutually exclusive, and simultaneous testing for all targetable mutations may not be indicated.[156] For example, the frequency of *EGFR* mutations in Caucasian females or nonsmokers approaches 30%, and in Asians may exceed 70%. Thus, it may be advisable to start testing these subsets of NSCLC patients with a simple and inexpensive EGFR test, and only evaluate for other molecular targets in EGFR mutation–negative patients. In women and nonsmokers, NGS analysis should be considered for "mutation-negative" NSCLC cases, where standard PCR-based sequencing analysis is negative for actionable mutations (i.e., EGFR, ALK, ROS1, BRAF, MET, KRAS, RET, HER2). However, because the vast majority of NSCLCs diagnosed in women and nonsmokers carry a mutation in an actionable mutation, failure to detect a targetable driver mutation may indicate either a technical laboratory error or the presence of a rare but potentially relevant genetic alteration (e.g., NTRK1/2/3, NRAS, NF1), both of which can be detected by NGS.

Importance of Satisfactory Biopsies for Molecular Testing of Lung Cancer

A satisfactory biopsy that allows for both histologic characterization and mutation analysis is becoming increasingly important, both for the diagnosis of lung cancer and for molecular testing. The analytic sensitivity of an assay dictates the quantity of tumor that must be present in the tested sample. For FISH and immunohistochemical analysis, the Molecular Assays in NSCLC Working Group recommended that a tumor tissue section should contain at least 1 to 2 mm^2 of tumor area to provide enough tumor cells for reliable interpretation.[159] FISH results should include hybridization signal counts from at least 100 to 200 tumor cells. Larger amounts of tissue may be required to ensure that sufficient DNA is obtained for mutational analysis as well as avoiding sampling errors due to tumor heterogeneity and the potential for a varying mutational landscape. However, the minimum number of cells needed for mutational analysis by direct sequencing has not been determined. Some studies have suggested a range of 100 to 400 tumor cells.[160,161] The most recent guidelines from the College of American Pathologists (CAP), the International Association for the Study of Lung Cancer (IASLC), and the Association for Molecular Pathology (AMP) recommend using sensitive analytical assays that can detect mutations with tumor cell proportions as low as 20% of the test sample.[162]

Although surgical resection remains the gold standard, the techniques most commonly used for the diagnosis of lung cancer are fiberoptic bronchoscopy and CT-guided transthoracic needle aspiration. Because the majority of patients with NSCLC have advanced disease and are not candidates for surgery, nonsurgical biopsy procedures are preferable. There are limited data on the molecular testing of samples acquired with conventional diagnostic bronchoscopy. For endobronchial tumors, four bronchoscopy biopsy specimens have been shown to be adequate for optimal diagnostic yield.[163] However, biopsy specimens are generally small, averaging approximately 300 malignant cells in aggregate biopsies. In addition, not every biopsy contains tumor cells. Although four specimens may be sufficient to make a diagnosis of lung cancer, they may not provide enough malignant tissue to perform a more detailed molecular analysis. Thus, some authors have recommended that six specimens be obtained from central, endobronchial lesions.[164] The percentage of malignant cells extracted from bronchoscopic samples obtained by bronchial forceps biopsies and endobronchial ultrasound-guided transbronchial needle aspirations (EBUS-TBNA) was compared with surgical biopsies.[165] The median proportion of malignant cells in surgical samples, bronchoscopic forceps biopsy samples, and EBUS-TBNA cell-block samples was 70%, 30%, and 20%, respectively. The frequency of activating EGFR mutations observed was similar in surgical biopsies and bronchoscopic biopsies.

Transbronchial needle aspiration (TBNA) of intrathoracic lymph nodes under endobronchial ultrasound (EBUS) has an increasingly important role in the diagnosis and staging of lung cancer. Several authors have described the successful use of EBUS-TBNA specimens for molecular analysis for *EGFR*, *EML4-ALK*, and *KRAS* gene mutations.[166–168] The concordance rate of mutation analysis between EBUS-TBNA cytologic aspirates and histologic samples obtained by surgical resection have been compared, and all mutations detected in the histologic material of primary tumors were also identified in the cytologic samples.[169] Three needle aspirates from each lymph node stage have been recommended for optimal diagnostic yield. However, the number of needle aspirates needed to obtain sufficient cellular material for molecular analysis has not been determined.

Labarca et al. reviewed the adequacy of EBUS-TBNA samples for molecular analysis in patients with NSCLC and suggested a minimum of three passes with rapid on-site examination (ROSE) or four passes without ROSE to obtain adequate samples for molecular analysis.[170] Although bronchial washes and bronchial brushes can be useful for the diagnosis of lung cancer, they often will not provide enough tumor cells for molecular testing.

For patients with peripheral lung nodules or masses, transthoracic needle aspiration and biopsy are useful procedures. Core-needle biopsy specimens usually contain enough cellular material for molecular analysis (approximately 500 cells per core biopsy). In comparison, a transthoracic needle aspirate obtained using a 21-gauge needle yields approximately 100 cells.[160] Discordance between transthoracic needle aspiration and surgical pathology in the diagnosis of lung cancer may be as high as 39%.[171]

■ Acquired Resistance to Targeted Therapy

As described above, although most NSCLC patients with *EGFR* mutations, *ALK* rearrangements, or *ROS1* fusions respond clinically and radiologically to targeted therapy, the disease always progresses due to acquired resistance. As drug-sensitive NSCLC cells are rapidly eliminated during targeted therapy, the remaining NSCLC cells become adapted to therapeutic pressure, and the molecular profile of lung tumors may significantly change over the treatment course. Thus, defining resistance to targeted therapy is critical for determining whether treatment should be changed. Jackman et al. proposed four criteria for the clinical definition of acquired resistance to EGFR TKIs: clinical exposure to an EGFR TKI, benefit from an EGFR TKI, evidence of disease progression by the RECIST criteria (an increase of 30% in summed maximum diameter or occurrence of new metastatic lesions), and lack of exposure to other drugs.[172] In patients who develop a growing lesion or new metastatic lesion on targeted therapy, we recommend that biopsies be obtained to confirm the presence of disease, and molecular testing should be repeated on these biopsy specimens to identify mechanisms of resistance, such as T790M mutations in the *EGFR* gene, and to direct further therapy. The detection of T790M mutation in TKI-resistant tumors is mandatory prior to initiating osimertinib treatment in TKI-pretreated *EGFR*-mutant NSCLC patients. In some circumstances, NSCLCs acquire TKI resistance by activating other signaling molecules (e.g., EGFR, HER2, ALK, ROS1, MET), a phenomenon that has been termed “kinase switching.” Thus, changing therapy to the appropriate TKI may downregulate the newly activated receptor and lead to clinical responses. As we learn more about the mechanisms of resistance to targeted therapy, we will be able to provide alternative therapies to patients who have disease progression.

However, there is little understanding regarding whether similar principles apply to immunotherapy. Administration of immune checkpoint inhibitors after chemotherapy typically relies on PD-L1 status determined at the time of lung cancer diagnosis (i.e., before the start of systemic treatment). It is important to recognize that second-line trials of immune checkpoint inhibitors did not account for changes in PD-L1 expression induced by chemotherapy.

■ Liquid Biopsies

Many NSCLC patients progress on therapy, developing multiple metastases and tumor foci that may demonstrate heterogeneity with regard to actionable mutations and acquired drug resistance. Obviously, repeated biopsies are not feasible. So-called liquid biopsies may therefore provide valuable insights into tumor evolution during a patient’s treatment course. Liquid biopsies represent the sampling of fluids, usually plasma, for the diagnosis or monitoring of cancer. This noninvasive approach is faster, less morbid, and, in contrast to invasive biopsies, can be performed repeatedly to follow disease. The specimen can be analyzed for soluble, cell-free DNA, some of which will come from the tumor, and circulating tumor cells. However, liquid biopsies have significant limitations, especially since high disease burden is often required for measurable levels of cell-free tumor DNA or circulating tumor cells. Hotspot mutations (e.g., EGFR T790M) can be detected in cell-free DNA or circulating tumor cells using high-sensitivity techniques such as droplet digital PCR.[173] NGS analysis, which is relatively insensitive, is required for more complex evaluations, including sequencing of *ALK* or *ROS1*, multigene tumor profiling, and TMB analysis. In addition, the inability to detect a mutation does not mean cancer is not present, as the amount of cell-free DNA in the circulation may be below detection limits or the cancer may not have a mutation to be detected. Although analysis of circulating tumor DNA will detect acquired mutations, protein expression (e.g., PD-L1) cannot be measured from plasma samples. There is significant interest in developing assays for circulating tumor cells, but it is unclear whether circulating tumor cells are representative of an entire tumor or constitute only a small fraction of cancer cells. Although liquid biopsy may play an important role in the diagnosis and management of lung cancer in the future, at present it should be used as a complementary test to tissue biopsy.

CONCLUSIONS AND PERSPECTIVES

The past two decades have witnessed dramatic success with personalized cancer therapy, and this paradigm shift has led to tremendous improvements in clinical outcomes in patients with molecularly defined subsets of lung cancer. Notably, the identification of a variety of molecular and genetic alternations in NSCLC has provided the opportunity for targeted, personalized therapy, such as EGFR TKIs for activating *EGFR* mutations in NSCLC, ROS1 inhibitors for NSCLC expressing *ROS1* fusions, and ALK inhibitors for NSCLC harboring *ALK* rearrangements. Recent discoveries have led to the development of KRAS^{G12C} inhibitors, which has led to targeted therapy for *KRAS*-mutant lung cancer. The discovery of novel “druggable” driver mutations can lead to swift development of inhibitors of these targets and improved rational combinations of agents. The development of immune checkpoint inhibitors has revolutionized therapy for both NSCLC and SCLC. Critical for their successful application is the development of biomarkers predictive of response. As we gain further understanding of the host immune response and T-cell activation, new drugs that enhance the host antitumor response will be developed. Despite initial responses to targeted therapy, the development of acquired resistance inevitably leads to treatment failure. A greater understanding of tumor resistance mechanisms will also provide additional therapeutic opportunities, leading to improved responses with targeted therapy.

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CHAPTER 108

Epidemiology of Lung Cancer

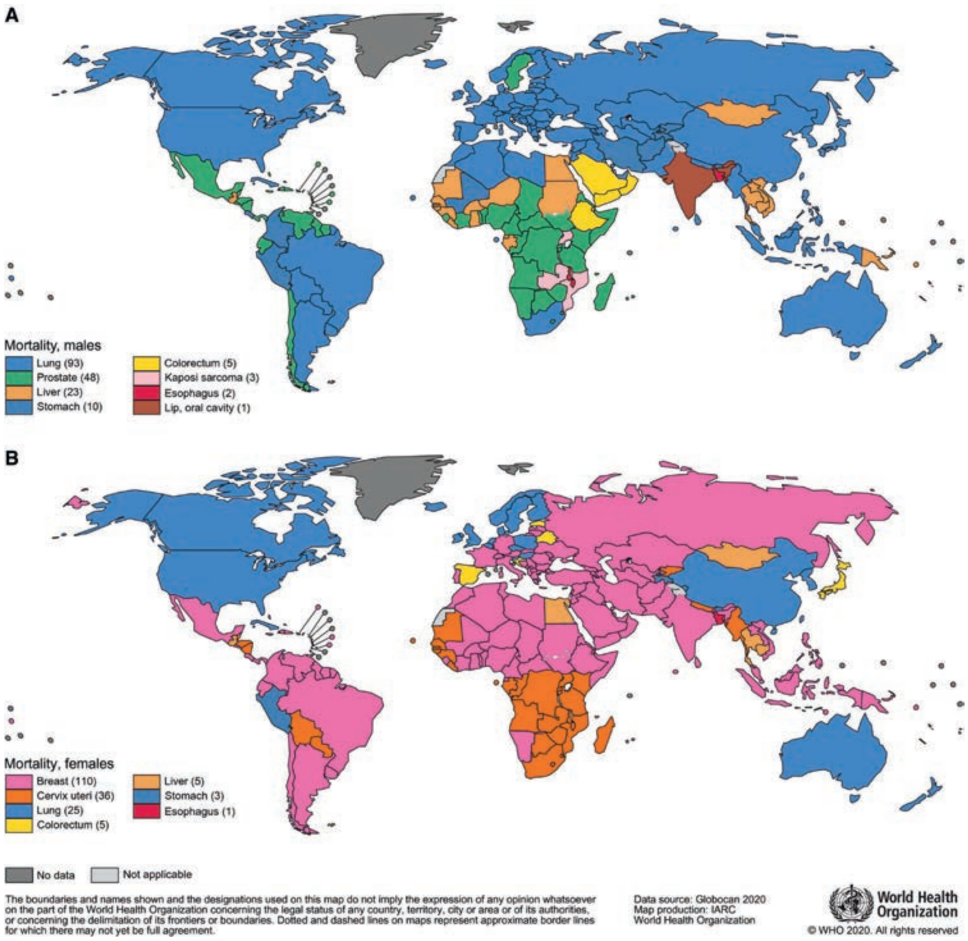
Lynn T. Tanoue
Charles S. Dela Cruz

INTRODUCTION

Lung cancer is the leading cause of cancer death in the world. The International Agency for Research on Cancer (IARC) GLOBOCAN reported a global lung cancer burden of 2.2 million new cases and 1.8 million deaths in 2020 alone.[1] These statistics emphasize the harsh reality that lung cancer is a common and highly fatal disease. Nonetheless, the past decade has witnessed remarkable advances in tobacco control, screening and early detection, and treatment, which are contributing toward progress in curtailing the global lung cancer epidemic.

Globally, lung cancer is the second most commonly diagnosed cancer. It is the leading cause of cancer incidence and mortality in men. In women, it is the third leading cause of cancer incidence after breast and colorectal cancers, and the second leading cause of mortality after breast cancer (Fig. 108-1).[2] Lung cancer is much more common in areas with a high or very high human development index (HDI), such as in Western Europe, the United States, and Japan.[2] The positive association with HDI level mirrors the maturity and extent of the tobacco epidemic in different areas and is stronger in men than in women.[3] Lung cancer incidence and mortality in both women and men in high- and very high-HDI countries historically have been several-fold higher than in countries with low or medium HDI. This will inevitably change given that 80% of current adult smokers live in low- and middle-income countries.[4] The highest lung cancer incidence rates in men are now observed in Eastern and Southern Europe, Eastern and Western Asia, and Micronesia/Polynesia, while in women the highest incidence rates are still observed in North America and Western and Northern Europe.[2] Mortality rates unfortunately closely follow incidence, reflected in an estimated global mortality incidence ratio (MIR) of 0.85.[5] Globally, some improvement has been seen in 5-year lung cancer survival rate, which in most countries is now reported in the range of 10% to 20%.[6] However, compared with the other common solid tumors—breast, colon and prostate cancers—lung cancer outcomes are poor despite the development of a wide array of new therapies, demonstration of lung cancer screening benefit, and advancements in surgical and radiation technologies. Not surprisingly, survival rates are worse in low-income countries without such resources, but poor outcomes still persist even in high-income countries, with 5-year survival in cancer registries in the United Kingdom, Germany, the United States, and Japan reported at 13%, 18%, 21%, and 33%, respectively.[6]

For the purposes of this chapter, the term *lung cancer* includes both non–small-cell lung cancer (NSCLC) and small-cell lung cancer. This distinction and further subclassification (e.g., adenocarcinoma and its subtypes, squamous cell carcinoma, etc.) should be specified in any discussion of lung cancer treatment, which is



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data source: Globocan 2020
Map production: IARC
World Health Organization

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Figure 108-1 Most common type of cancer mortality by country in 2020 among (**A**) men and (**B**) women. The numbers of countries represented in each ranking group are included in the legend. *(Reproduced with permission from GLOBOCAN 2020. © WHO 2020. All rights reserved.)*

increasingly more precisely directed by histologic type and biomarkers. From an epidemiologic perspective, many of the risk factors for the different histologic types are shared, in particular risk associated with tobacco smoking, and the distinctions are less pertinent. When relevant, specific cell types are identified in the text.

In the United States, cancer of the lung and bronchus has been the leading cause of cancer death in women since the mid-1980s and in men since the 1950s, resulting in more deaths than breast, colon, and prostate cancers combined (Fig. 108-2).[7] Lung cancer ranks second in cancer incidence in both sexes in the United States, after breast cancer in women and prostate cancer in men. In their annual 2021 report on U.S. lung cancer statistics, Siegel et al. anticipated a total of 235,760 new lung cancer cases and 137,040 deaths from lung cancer, with 119,100 new lung cancer cases in males (12% of all new cancers) and 116,660 new cases in females (13% of all new cancers).[7] The age-adjusted incidence rate of lung cancer was projected at 67.6 per 100,000 men and 51.3 per 100,000 women per year. Lung cancer will continue to be the leading cause of cancer death in both sexes in 2021, with 69,410 deaths anticipated in men and 62,470 deaths anticipated in women, accounting for 22% of all cancer deaths for each sex.

Consider that a decade ago in 2011, there were 221,130 new lung cancer cases and 156,940 deaths.[8] These figures point out that, compared to 10 years ago, more people in the United States are being diagnosed with lung cancer but fewer people are dying. The decline in mortality for lung cancer, particularly in men, accounted for nearly half (46%) of the total decline in cancer mortality in the United States observed from 2014 to 2018.[7] Incidence rates are falling for both men and women, largely reflecting reductions in tobacco consumption since the peak of the tobacco epidemic in the 1970s and 1980s. Nonetheless, the increase in annual lung cancer cases over the past decade is a reminder that the gains made in curtailing lung cancer risk have still been inadequate. Declining lung cancer mortality rates have been observed in men since about 1991 and in women since about 2005 (Fig. 108-2). By inference, more people are surviving because of a remarkable expansion of the array of effective treatments for advanced-stage disease, advancements in surgical and radiation technologies, and a growing ability to personalize treatment for individuals.

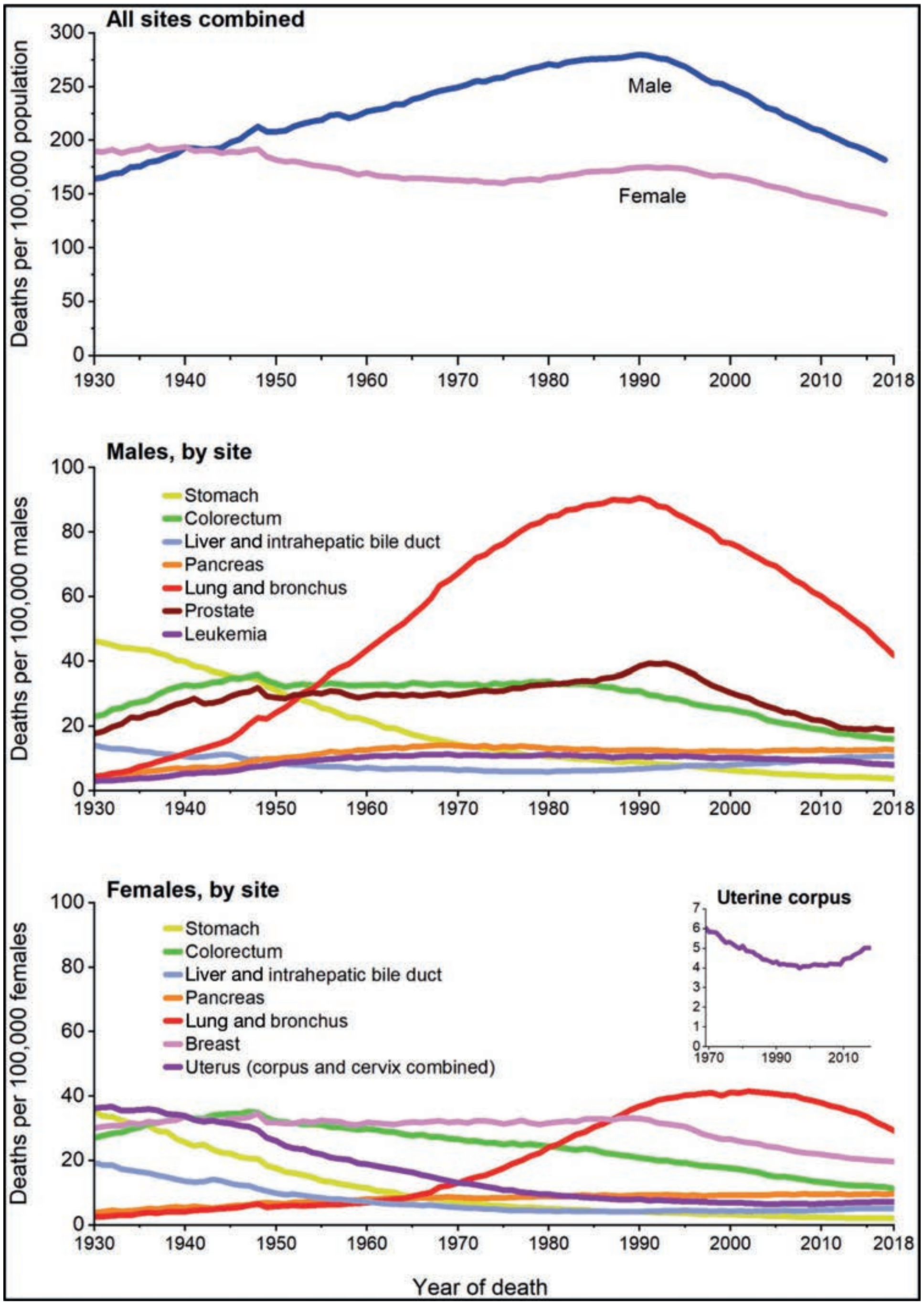

Figure 108-2 Trends in cancer mortality rates by sex overall and for selected cancers, United States, 1930 to 2018. Rates are age adjusted to the 2000 U.S. standard population. *(Reproduced with permission from Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. CA Cancer J Clin. 2021;71(1):7–33.)*

The current 5-year survival for lung cancer in the United States is 20.5%.[9] This represents substantial improvement compared to past decades, but the persistently low 5-year survival reflects the fact that more than half of lung cancers are currently identified at advanced stage, when metastasis has occurred and cure is very unlikely. Survival for these patients will be limited even with new therapies. Ultimately, significant improvements in 5-year survival will only be achieved by widespread engagement in screening and early detection.

Lung cancer screening with low-dose chest CT was approved in the United States in 2013, but at present only about 12% of eligible persons undergo screening.[10] The 2021 revision of the lung cancer screening recommendation of the U.S. Preventive Services Task Force (USPSTF) broadened criteria to include a younger population (age 50–80 years) with less intense smoking history (≥20 pack-years of smoking, currently smoking, or having quit within the past 15 years), and is estimated to nearly double the number of persons eligible for screening.[11] Ultimately, successful widespread implementation of lung cancer screening for early detection should begin shifting the preponderance of lung cancer diagnoses from advanced to early-stage disease. This, in combination with continued therapeutic advances, provides hope that substantial improvement in lung cancer mortality will be achieved.

EPIDEMIOLOGY OF LUNG CANCER

At the turn of the 20th century, lung cancer was a rare disease. In a review of autopsy reports from hospitals in the United States and western Europe in 1912, Adler reported that primary lung cancer accounted for <0.5% of all cancers identified.[12] The subsequent epidemic leading to lung cancer being the leading cause of cancer death in the world should be understood in that historic context, as it highlights the important point that lung cancer is a disease caused by modifiable risk factors. If those risk factors were to be controlled, lung cancer could again become uncommon.

■ Tobacco and Lung Cancer

Tobacco smoking is the most important modifiable risk factor for lung cancer. The World Health Organization (WHO) estimates that 1.1 billion persons over the age of 15 currently smoke.[4] Tobacco use is implicated in many cancers other than lung cancer; it has been estimated that up to 20% of all cancer deaths worldwide could be prevented if tobacco smoking were eliminated.[13] More than 90% of lung cancers in men and more than 80% of lung cancers in women develop in smokers. Several studies have reported lung cancer cumulative risk by age 75 among people who are lifelong smokers as high as 16%, compared with a lifetime risk of <1% in nonsmokers.[14,15] In other words, 1 out of 7 lifelong smokers will develop lung cancer. Moreover, smokers will also be vulnerable to excess morbidity and mortality inflicted by other smoking-related diseases, including cardiovascular disease, stroke, and other cancers.

The global lung cancer epidemic is driven largely by tobacco. Understanding the history of the excessive toll cigarettes continue to inflict on human life is a lesson that mass marketing of misinformation compounded by delays in public health interventions can inflict widespread harm. A remarkable expansion of cigarette use starting around the turn of the 20th century was made possible through industrial mechanization of cigarette production and mass advertising crafting socialization of smoking. In the early decades of the 1900s, lung cancer incidence was noted to be disproportionately increasing compared to other cancers.[16,17] Concerns in the scientific community about the deleterious effects of tobacco on longevity in general were heightened by reports that application of smoke condensed from burning of tobacco to the skin of animals produced tumors.[18,19] Subsequent studies demonstrated that tar from the burning of tobacco was carcinogenic, raising concerns that inhalation of tar from cigarettes could be an etiologic factor in lung cancer.[20] In a 1939 review of lung carcinoma, Ochsner and DeBakey stated, "it is our definite conviction that the increase in the incidence of pulmonary carcinoma is due largely to the increase in smoking."[21]

In 1950, two landmark epidemiologic studies established the causal role of tobacco smoking in bronchogenic carcinoma.[22,23] In the United Kingdom, Doll and Hill reported an association between lung cancer and cigarette smoking, including the importance of the intensity and duration of smoking.[23] In the United States, Wynder and Graham examined 605 cases of lung cancer in men and found that 96.5% of lung cancers were in men who were moderate to heavy smokers for many years.[22] They similarly concluded that excessive and prolonged use of tobacco was an important etiologic factor in lung cancer and pointed out that the clinical onset of lung cancer could occur 10 years or more after smoking cessation.

In 1964, the U.S. Surgeon General issued its landmark report on the health consequences of smoking.[24] The key elements of this report were as follows: (1) cigarette smoking was causally related to lung cancer in men; (2) the risk for lung cancer increased with duration of smoking and the number of cigarettes smoked per day; (3) cigarette smoking was associated with a 70% increase in the age-specific death rates of men as well as, to a lesser degree, an increase in the death rates of women; (4) cigarette smoking was believed to be much more important than occupational exposures in the causation of lung cancer in the general population; (5) cigarette smoking was the most important cause of chronic bronchitis in the United States; and (6) male cigarette smokers had a higher death rate from coronary artery disease than male nonsmokers. The report concluded: "Cigarette smoking is a health hazard of sufficient importance in the United States to warrant appropriate remedial action."

The 1964 Surgeon General call to action has been followed by decades of outreach, legal, and regulatory efforts intended to educate the public, curtail marketing of cigarettes to vulnerable populations, and enforce public protections against exposure to tobacco smoke. The cumulative benefit of this multipronged approach is evident in Fig. 108-3, which highlights major public health and regulatory landmarks and demonstrates that U.S. adult per-capita cigarette consumption has steadily decreased since its peak in the mid-1960s.[25] However, despite substantial and meaningful progress, 20.8% (50.6 million) of the entire U.S. adult population are tobacco consumers, 80% of whom are smoking a combustible tobacco product.[26] Fourteen percent of U.S. adults (34.1 million) smoke cigarettes, and 4.5% (10.9 million) use e-cigarettes.

Factors associated with tobacco use are multiple: male sex; younger age (≤65 years); General Educational Development (GED) as the highest level of educational attainment; annual household income <$35,000; lesbian, gay, or bisexual status; Medicaid or other public insurance or uninsured status; and the presence of a disability or anxiety.[26] Tobacco use is also higher among non-Hispanic American Indian/Alaska Native adults (29.3%), non-Hispanic White adults (23.3%), and non-Hispanic Black adults (20.7%) compared with other subpopulations, and more prevalent in those living in the U.S. Midwest and South compared to the U.S. Northeast or West. Geographic variation in lung cancer incidence rates also exposes societal norms that influence tobacco culture in both sexes. Wide variation in lung cancer incidence among states in the United States predominantly reflects the prevalence of smoking, ranging from 109.0 cases per 100,000 men and 77.5 cases per 100,000 women in Kentucky, where 1 out of every 4 residents are current smokers, to 30.2 cases per 100,000 men and 22.5 cases per 100,000 women in Utah, where only 1 out of every 10 residents are current smokers.[7,27] Effective tobacco cessation strategies will need to be designed and implemented with attention to specific factors that influence smoking behaviors in each sector.

■ Cigarettes and Lung Cancer

Lung cancer risk is related to the quantity of cigarette consumption. Factors such as the number of cigarettes smoked per day, the age of onset of smoking and its duration, the tar and nicotine content of cigarettes, the degree of inhalation, and the type of cigarette smoked all contribute to risk.[28,29] The U.S. American Cancer Society Cancer Prevention Study-II (CPS II), the largest cohort study on smoking and lung cancer risk, identified smoking duration as a much stronger predictor of lung cancer mortality than intensity (the amount smoked per day) regardless of age or sex, an observation that is consistent with IARC findings.[30,31] Individual susceptibility is further influenced by environmental and genetic factors.

Cigarette smoke is a complex aerosol composed of more than 5300 gaseous and particulate compounds.[32] *Mainstream smoke* is produced by inhalation of air through the burning cigarette and is

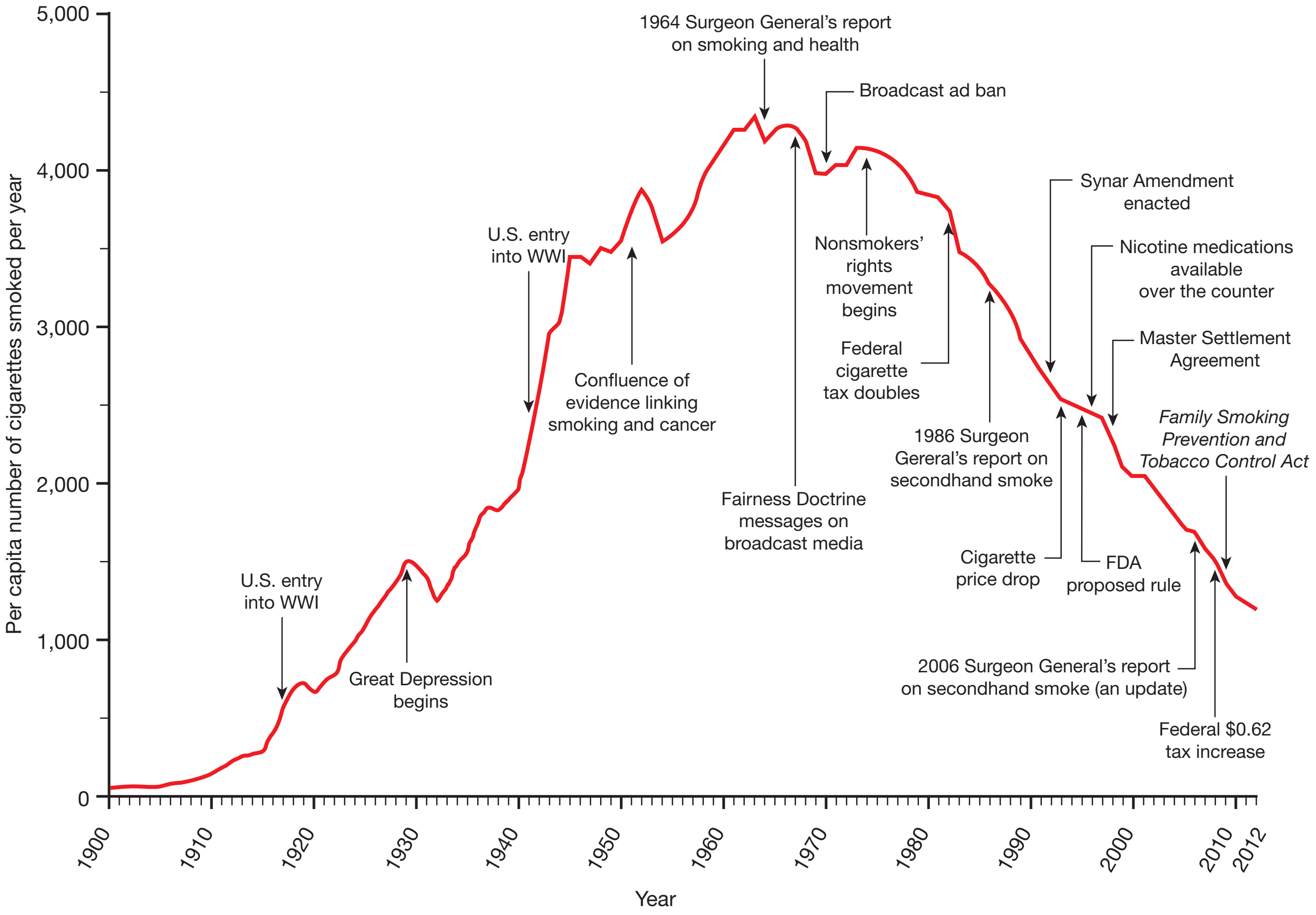

Figure 108-3 Adult per-capita cigarette consumption and major smoking and health events, United States, 1900–2012. *(Reproduced with permission from The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General. National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health. Atlanta (GA): Centers for Disease Control and Prevention (US); 2014.)*

the primary source of smoke exposure for the smoker. *Sidestream smoke* is produced from smoldering of the cigarette between puffs and is the major source of environmental tobacco smoke (secondhand smoke). The addictive property of smoking tobacco is attributed to nicotine, the principal alkaloid generated in tobacco smoke.[33] Nicotine and other tobacco alkaloids are not felt to be carcinogenic. The carcinogenic potential of cigarette smoke is related to tar, the solid and liquid residue in cigarette smoke after water and nicotine are removed. The nicotine and tar composition of mainstream smoke varies greatly depending on the tobacco curing (drying) process, chemicals that are added or created during manufacturing of the tobacco product, and the intensity of inhalation by the smoker.

There are more than 1000 different cigarette brands available for purchase in the United States.[34] Cigarette design changes including filtered, flavored, and "low tar" cigarettes do not protect smokers from inhaling carcinogens, and may themselves introduce new toxicants into inhaled smoke.[35] The primary factor determining intensity of cigarette use is the nicotine dependence of the smoker. Smokers of low-yield cigarettes containing less nicotine and tar tend to take more puffs per minute and inhale more deeply to satisfy their nicotine need. This more intensive smoking is also observed with filtered cigarettes. Deeper inhalation exposes higher-order bronchi in the peripheral lung, which lack protective epithelium, to carcinogens in smoke, rather than just the major bronchi. The ability of the smoker to more deeply inhale less irritating smoke is felt to be a contributor to the shift in the predominant lung cancer histologic type from squamous cell carcinoma to adenocarcinoma.[35,36] Moreover, cigarette design changes that decrease the noxious physical effects of inhaling tobacco smoke likely enable more individuals to initiate smoking and nicotine addiction. Public misperception that design changes such as filtration and "low tar" make cigarettes safer has impeded progress in tobacco prevention.

■ Tobacco Smoke Carcinogens

Tobacco smoke contains more than 5300 compounds, of which more than 70 have been identified by the IARC as carcinogens.[31] As early as 1939, Roffo identified the presence of benzopyrene, a polycyclic aromatic hydrocarbon known to be a carcinogenic constituent of coal tar, in cigarette smoke.[37] Carcinogens include polycyclic aromatic hydrocarbons (PAH) such as benzopyrene, N-nitrosamines, aromatic amines, aldehydes, phenols, volatile hydrocarbons such as benzene and 1.3-butadiene, and other organic and inorganic compounds such as ethylene oxide and cadmium.[32]

While many toxic and carcinogenic chemicals are artificially added during the manufacturing process, some occur naturally as tobacco is prepared for use. The agents of particular concern in lung cancer are the tobacco-specific N-nitrosamines (TSNAs) formed by nitrosation of nicotine during the process of curing tobacco and also during the smoking of burning tobacco. TSNAs are present in commercially processed cigarettes, hand-rolled cigarettes and cigars, and bidis and kreteks, which are hand-rolled cigarettes wrapped in nontobacco leaf material and smoked commonly in Southeast Asia. Multiple TSNAs are described, of which 4-(methylnitrosamino)-1(3-pyridyl)-1-butanone (NNK) appears to be the most important in lung carcinogenesis and has also been implicated in cancers of the esophagus, pancreas, and oral cavity. NNK is known to induce DNA adducts and single-strand DNA breakage, and also increases levels of other pulmonary carcinogens, such as 8-osodeoxyguanosine.[38] Failure of the normal DNA repair mechanisms to remove DNA adducts can lead to permanent mutations. NNK can mediate signaling pathway activation that includes modulation of critical oncogenes and tumor suppressor genes promoting uncontrolled cellular proliferation and tumorigenesis.[39] NNK also appears to be associated with DNA mutations resulting in the activation of *KRAS* oncogenes.[40,41] *KRAS* oncogene activation has been detected in 24% of human lung adenocarcinomas [42] and is present in lung adenocarcinoma in ex-smokers, suggesting that such mutations persist even after smoking cessation.[43] This finding may help explain the persistent elevation in lung cancer risk in ex-smokers even years after discontinuing cigarette use. Similarly, benzo(a)pyrene metabolite, a specific chemical constituent of tobacco smoke, can damage various *p53* tumor-suppressor gene loci that are known to be abnormal in approximately 60% of primary lung cancer cases.[44] Related polycyclic aromatic hydrocarbons in tobacco smoke can also target other lung cancer mutational hotspots.[45]

■ Smoking of Cigars, Pipes, and Recreational Drugs

Cigar smoking and pipe smoking are associated with increased risk for lung cancer, although with less risk than with cigarettes. To some extent this may be related to smaller amounts of tobacco being smoked. The tobacco content of a cigar can vary from 1 g to 20 g; on average, smoking five cigars is roughly equivalent to smoking one pack of cigarettes. Cigar smokers have a relative risk of lung cancer of 2.1 to 5.1 compared with nonsmokers; men who smoked five or more cigars a day have the greatest risk.[46] The risk for lung cancer in pipe smokers is similar to that in cigar smokers.[47,48]

The effects of smoking marijuana and cocaine have not been extensively studied. Marijuana smoke contains tar as well as carcinogenic polyaromatic hydrocarbons, similar to tobacco smoke. While an association has not been established between smoking marijuana or cocaine and lung cancer, metaplastic histologic and molecular changes similar to premalignant alterations have been detected in the bronchial epithelium in habitual smokers of these drugs.[49,50]

■ Tobacco Cessation

Tobacco cessation decreases lung cancer risk. Quitting smoking before the age of 40 reduces the risk of death associated with continued smoking by about 90%,[51] and cessation even into the sixth and seventh decades of life is associated with mortality benefit (Fig. 108-4).[14] Even further benefit from smoking cessation is derived from positive effects on vascular disease and nonmalignant pulmonary disease, and decreased risk of other smoking-related cancers.

In 2018, for the first time, the number of men using tobacco globally began to decline despite population growth.[4] Smoking among women worldwide has been declining since 2000.[4] These trends are unfortunately not uniform around the world. In regions where the tobacco epidemic is at an earlier stage, including China, Southeast Asia, and parts of Africa, smoking has either peaked recently or continues to increase (Fig. 108-5).[4] Barring successful interventions to accelerate smoking cessation or reduce smoking initiation, lung cancer rates will likely increase in these areas for at least the next few decades.[4,52,53]

■ Electronic Nicotine Delivery Systems

Electronic nicotine delivery systems include electronic cigarettes (e-cigarettes), e-pens, e-pipes, and e-cigars. These devices produce an aerosol by heating of a liquid containing nicotine and flavorings dissolved in glycerin or propylene glycol. Nicotine is delivered to the user by inhalation ("vaping") of the aerosol. Since around 2011, vaping has rapidly developed into a multibillion-dollar industry. Popularity and social acceptance, particularly among youth, has been fueled by unregulated marketing and chemical flavorings purposefully targeted to a younger audience.[54] In 2020 in the United States, 23.6% of high school students reported current use of any tobacco product, of which e-cigarettes were the most common.[55] Furthermore, 19.6% of students reported current active e-cigarette use compared with 9.4% reporting use of a combustible tobacco product; 8.2% reported using multiple

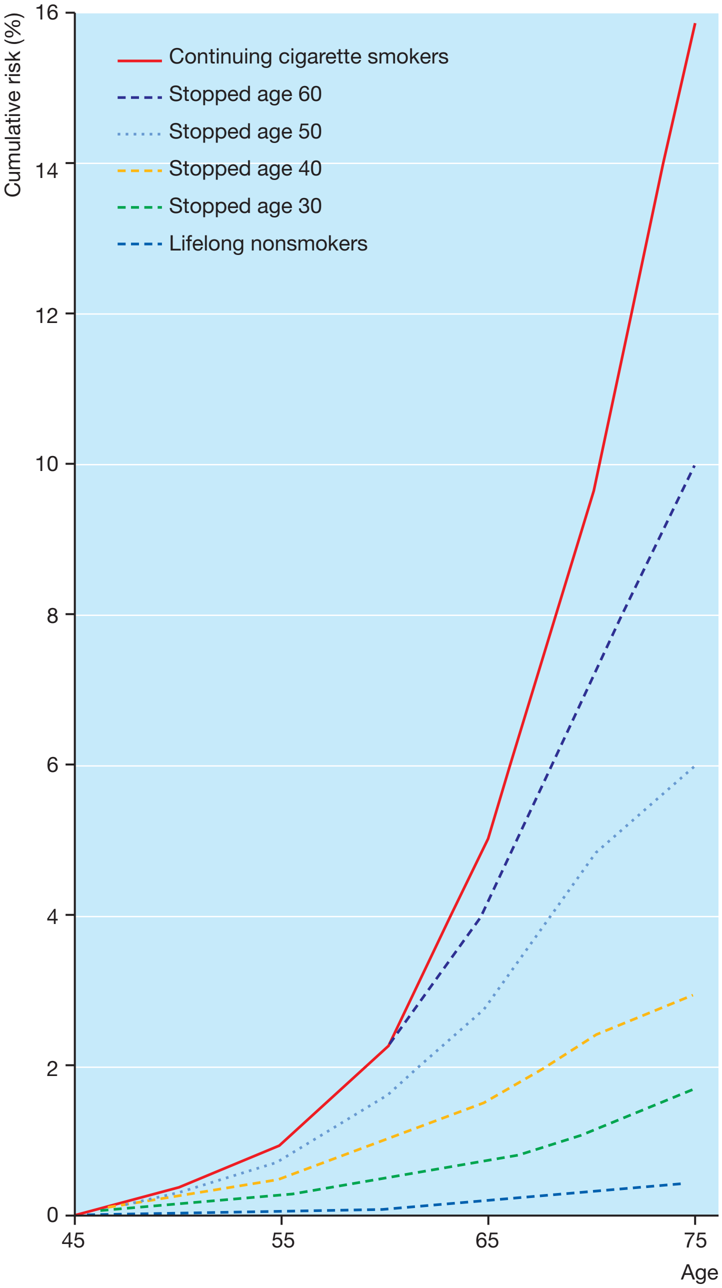

Figure 108-4 Effects of stopping smoking at various ages on the cumulative risk (%) of death from lung cancer up to age 75, at death rates for men in United Kingdom in 1990. *(Reproduced with permission from Peto R, Darby S, Deo H, et al. Smoking, smoking cessation, and lung cancer in the UK since 1950: combination of national statistics with two case-control studies, BMJ. 2000;321(7257):323–329.)*

tobacco products.[55,56] Although it is too early to know long-term consequences, vaping is clearly associated with short-term adverse respiratory outcomes.[57,58] Based on our knowledge of all the long-term health effects of cigarette smoking, it is imperative that regulatory efforts be accelerated given legitimate concerns relating to the perpetuation of future nicotine-addicted generations, the potential for conversion to tobacco cigarette consumption, and the potential for long-term health sequelae including COPD, vascular disease, and lung cancer.[59,60]

■ Never-smokers and Lung Cancer

Never-smokers are defined as persons who have smoked fewer than 100 cigarettes in their lifetime, including lifetime nonsmokers. Lung cancers in never-smokers account for a minority of the global lung cancer burden. However, the absolute number of these cases is substantial, particularly in women, with the incidence of lung cancer in never-smokers being comparable to the rates of cervical cancer in women and myeloma in men.[61,62] Worldwide, an estimated 15% to 20% of lung cancers in men and more than 50% of lung cancers in women occur in never-smokers, with wide geographic variations.[63,64] In the United States, approximately 15% to 20% of cases in women occur in never-smokers compared with 7% to 9% in men; in total, never-smokers account for approximately 10% to 15% of all cases of lung cancer.[65,66] Industrialized countries in Europe report patterns similar to the United States.[64,67–69] In contrast, countries in South Asia report the percentage of women with lung cancer who are never-smokers as high as 83%.[64]

The proportion of lung cancers in never-smokers compared with all lung cancers is increasing. However, there is controversy as to whether the incidence of lung cancer in never-smokers is actually changing, Successful tobacco control efforts, largely in high-income countries, have resulted in a decrease in lung cancer incidence and mortality among smokers, which accounts at least partly for the increase in proportion of never-smokers with lung cancer.

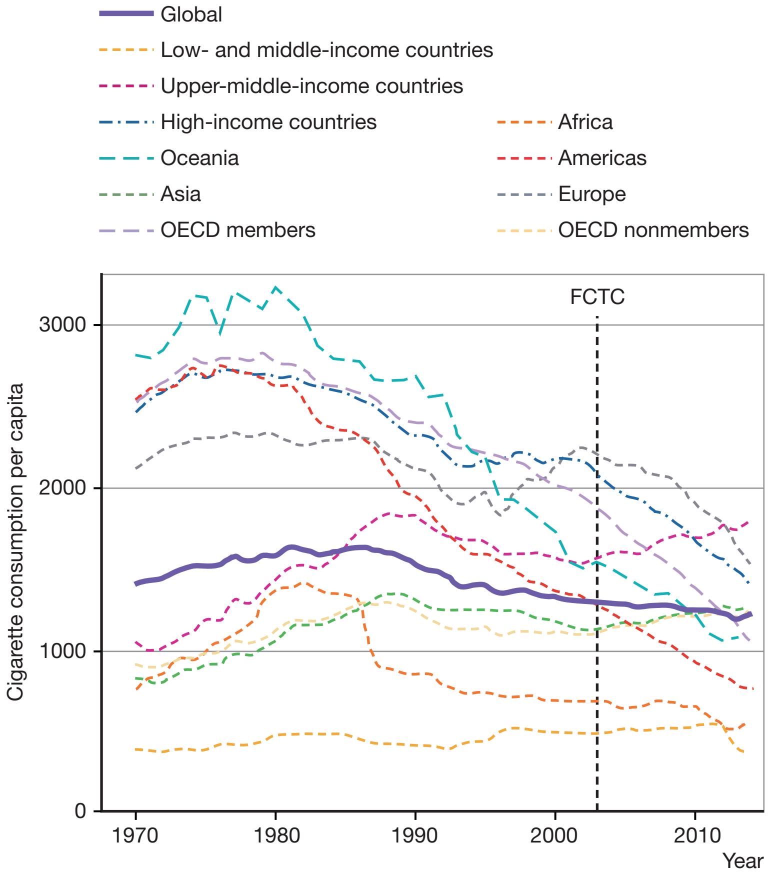

Figure 108-5 Annual population-weighted data on cigarette consumption per capita, by country income level, United Nation region, and Organization for Economic Co-operation and Development (OECD) membership status. Consumption based on number of cigarettes consumed per adult age 15 years or older per year. *(Reproduced with permission from Hoffman SJ, Poirier MJP, Rogers Van Katwyk S, et al. Impact of the WHO Framework Convention on Tobacco Control on global cigarette consumption: quasi-experimental evaluations using interrupted time series analysis and in-sample forecast event modelling, BMJ. 2019;365:l2287.)*

Adenocarcinoma is the predominant histology in never-smokers, exceeding the general trend toward an increase in adenocarcinoma across all cases of lung cancer. Never-smokers are less likely to have highly mutated cancers that are more typical of smoking-related lung cancers, and more likely to have driver mutations. For example, activating mutations in the epidermal growth factor receptor gene (*EGFR*), typically an exon 19 deletion or exon 21 mutation, are identified in 40% to 60% of lung adenocarcinomas in never-smokers, compared to approximately 15% in a general population of lung adenocarcinomas in the United States.[70–74] These and other observations suggest that lung cancer in never-smokers may have distinct biologic behavior and natural history. Microarray gene profiling studies have shown that the profiles of cancer in smokers and never-smokers are quite different.[75,76] In 2010, a genome-wide association study (GWAS) reported genetic variations in never-smoking females in chromosome 13q31.3 that altered the expression of glypican 5 (*GPC5*), a heparin sulfate proteoglycan with many known functions involving cell growth and differentiation and tissue responses.[77] Another GWAS, focusing on lung adenocarcinomas in female Han Chinese never-smokers in Taiwan, identified genetic variation in the *CLPTM1L-TERT* locus of chromosome 5p15.33 to be associated with risk for lung cancer in this population.[78] This 5p15.33 chromosome contains two genes implicated in carcinogenesis, telomerase reverse transcriptase (*TERT*) and cleft lip and palate transmembrane 1-like (*CLPTM1L*).

Risk factors considered to be important for never-smokers include environmental tobacco exposure ("secondhand smoke"), exposures to carcinogens such as radon, outdoor and indoor air pollution, asbestos, arsenic, comorbid lung disease including interstitial lung disease, and genetic factors.[79] A population-based case-control study in Canada found that occupational exposures, history of lung disease, and family history of early-onset cancer were important risk factors for lung cancer among never-smokers.[80] In this study, potential environmental sources of increased risk included exposure to solvents, paints or thinners, welding equipment, and smoke, soot, or exhaust. Other studies have also shown an association between lung cancer in never-smokers and a family history of lung cancer, a finding that suggests a role for heritable variations, for example in pathways involving the human repair gene (*hMSH2*), various cytochrome P450 enzymes, and glutathione-*S*-transferase enzymes.[81–83] Family history may be particularly important in never-smokers. A case-control study following 2400 relatives of 316 never-smokers with lung cancer cases showed a 25% excess risk for cancer in first-degree relatives.[82] Preliminary data from the Taiwan Lung Cancer Screening for Never-Smoker Trial (TALENT) also demonstrate this increased risk.[84] In Taiwan, 53% of lung cancer deaths occur in never-smokers. TALENT included 12,011 never-smoking individuals age 55 to 75 years with a high-risk feature (family history of lung cancer, history of chronic lung disease, cooking without ventilation, and cooking with high intensity of frying). Most (73.8%) study participants were female. Notably, the prevalence of lung cancer over 6 years of follow-up was 2.6%, which was higher than lung cancer detection rates in the U.S. National Lung Screening Trial (NLST) or the Dutch-Belgian Randomized Lung Cancer Screening Trial (NELSON) over similar follow-up duration.[85,86] Moreover, a positive family history of lung cancer was associated with a lung cancer detection rate of 3.2%, with even higher risk observed if the affected family member was a first-degree relation or if there was more than one family member with lung cancer.

The threshold to investigate symptoms in never-smokers is likely to be higher than in smokers because of a lower suspicion of lung cancer, contributing to diagnosis at later stages.[87] Despite this potential for delayed diagnosis, the survival rate for never-smokers is better than for smokers, independent of disease stage, treatment received, or presence of comorbidities.[88–90] A multivariate analysis of survival with lung adenocarcinoma found that never-smoking status was an independent predictor of improved survival, with an overall 25-year survival rate of 23% for never-smokers versus 16% for current smokers.[88]

■ Non-tobacco Factors and Lung Cancer

A wide variety of factors other than tobacco should be considered in the epidemiology of lung cancer, as discussed below.

Age

Lung cancer is predominantly a disease of older persons. In the United States, centralized cancer statistics are reported by the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) program, which collects data from cancer registries that include approximately 35% of the entire U.S. population. In 2020, SEER data showed that lung cancer was most frequently diagnosed among people age 65 to 74, with a median age at diagnosis of 71years.[9] Of all lung cancer cases, 70.4% occur in persons over the age of 65, with approximately half of those in persons over the age of 75. Only 7.7% of cases occur in in those less than 45 years of age.[9]

Although most cases of lung cancer occur in older persons, smoking prevalence is actually lower in the population older than 65 years than in younger cohorts. Only about 10% of current smokers are older than 65.[26,91] This difference between relatively lower current smoking prevalence and higher cancer rate in the older population in part reflects the latency between smoking exposure and clinical presentation of lung cancer. Approximately 70% of Americans responding to the 2019 National Health Interview Survey self-identified as former smokers of at least 100 cigarettes in their lifetime.[26] Demographic shifts toward older populations in countries such as the United States, Japan, and the United Kingdom and the high prevalence of prior tobacco exposure embedded in these populations imply that the relative magnitude of lung cancer burden in the elderly will continue to increase over the coming decades.[92,93]

Cancer rates in younger as opposed to older populations are felt to be indicators of cancer control efforts.[94,95] The subset of patients with NSCLC under the age of 40 constitutes less than 1% of the entire lung cancer population, but merits separate consideration as they appear to have clinical characteristics distinct from older patients. This group has a higher proportion of women, adenocarcinoma histology, and representation of Asian/Pacific Islanders, and is more likely to present with distant metastases.[94] As with the entire lung cancer population, incidence in young patients is declining. As a group, they have better all-cause and cancer-specific survival than lung cancer patients over the age of 40, although this is not uniform across the United States. Lung cancer mortality in the younger population appears to correlate significantly and inversely with individual state tobacco control efforts, highlighting the importance of regulatory efforts in curtailing tobacco use.[95]

Gender

Globally, the incidence of breast cancer is triple that of lung cancer, but nearly as many women die from lung cancer as from breast cancer.[96] Examination of the epidemiology of lung cancer in women identifies several major areas of interest and concern.

First, in industrialized regions with high HDI such as the United States and much of western Europe, lung cancer in women is largely attributable to cigarette smoking. In the United States, the cigarette smoking rate for women increased during the period from 1930 to 1960. Similar to what had previously been seen in men, a period of latency was followed by an increase in lung cancer in women starting around 1960.[97,98] By the mid-1980s and to the present day, lung cancer surpassed breast cancer as the leading cause of cancer death in women in the United States. At present, nearly twice as many American women die annually of lung cancer than succumb to breast cancer.[8] Since 2005, both lung cancer incidence and mortality in women have been decreasing but at a lesser rate than in men, with the result that the historic male-predominant gender gap is narrowing. In some countries such as the United States, Denmark, and the Netherlands, successively younger birth cohorts show higher female-to-male incidence ratios.[66,99] Anticipated continuation of current trends has resulted in a projection that lung cancer mortality in women will exceed that in men in the United States by 2045.[100]

Second, there remains controversy as to whether women are more susceptible than men to the carcinogenic effects of tobacco smoke. Several older prospective studies did not demonstrate sex-related differences in lung cancer risk related to cigarettes after adjustment for factors including age at onset of smoking, time since quitting, number of cigarettes smoked per day, or pack-years smoked.[101,102] However, more recent studies support the observations that women tend to be diagnosed with lung cancer at a younger age, with less average cigarette use, and with less consumption of non-cigarette tobacco products such as cigars or chewing tobacco.[66,103–105]

Third, women with lung cancer are more likely than men to be never-smokers. As already stated, in the United States, approximately 15% to 20% of lung cancers in women occur in never-smokers, compared with 7% to 9% in men.[65,66] Globally, 53% of lung cancers in women occur in never-smokers, compared with 15% in men. In South Asia, the proportion of female never-smokers with lung cancer has been reported in excess of 80%.[64,67,69] Female never-smokers with lung cancer have a higher likelihood of actionable *EGFR* mutations than men.[72,106,107] Women in low-HDI countries have a higher likelihood of exposures to carcinogens resulting from combustion of biomass fuels for cooking, particularly in poorly ventilated structures.[64]

Lastly, women with lung cancer have improved lung cancer survival compared with men. Multiple large population studies in different countries have demonstrated better outcomes in women than men after adjustment for age, stage of disease, histologic type, and treatment.[108–110] The reasons for this female sex-related survival benefit are not clear. Hormonal factors, in particular the estrogen signaling pathway, have generally been studied as potential contributors to an increased susceptibility of women to carcinogens.[111,112] Estrogen receptors have been demonstrated in lung cancer cell lines and lung cancer tissues, as has aromatase, the rate-limiting enzyme in estrogen synthesis.[113,114] Women over the age of 60 with lung cancer appear to have better survival than younger women, resulting in speculation that the postmenopausal state may be protective.[115] One case-control study showed that estrogen replacement therapy was significantly associated with an increased risk for adenocarcinoma (odds ratio, 1.7), whereas early menopause (age 40 years or younger) was associated with a decreased risk for (odds ratio, 0.3).[116] Sex may

TABLE 108-1 Incidence and Mortality Rates per 100,000 Population for Cancer of the Lung and Bronchus by Race and Ethnicity, United States 2013–2018 and 2008–2012

	Non-Hispanic White	Non-Hispanic Black	Asian/Pacific Islander	American Indian/Alaska Native	Hispanic
Incidence rates, 2013–2017					
Male	70.8	79.8	43.2	59.2	37.1
Female	56.4	47.9	27.9	47.9	24.3
Mortality rates, 2013–2017					
Male	49.4	57.0	28.0	38.4	23.0
Female	35.6	30.6	16.3	27.4	12.3
Incidence rates, 2008–2012					
Male	79.3	93.4	47.4	66.2	43.3
Female	58.7	51.4	28.3	52.7	26.0
Mortality rates, 2008–2012					
Male	62.2	74.9	34.0	49.1	29.5
Female	41.4	36.7	18.2	32.1	13.7

Data from Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. CA Cancer J Clin. 2021;71(1):7–33 and Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016;66(1):7–30.

also be a surrogate for other factors more common in women than men that influence lung cancer prognosis, including never-smoking status, positive *EGFR* mutational status, and lower likelihood of comorbidities.

Race and Ethnicity

Race is a complex variable. Socioeconomic inequalities in wealth are tied to race and ethnicity. It is increasingly appreciated that variations in cancer incidence and outcomes also result from deeply embedded societal structures that maintain racial inequalities and discriminatory practice differences, resulting in excess risk exposures, lower access to health care, and barriers to prevention, early detection, and treatment. Dissecting out possible biologic differences in cancer susceptibility and outcomes between racial and ethnic groups requires that socioeconomic factors be evaluated (see following section).

Table 108-1 outlines lung cancer incidence and mortality rates in the United States from 2013 to 2018 [7] and 2008 to 2012.[117] From 2013 to 2018, lung cancer incidence and mortality rates in men ranged from 37.1 cases and 23.0 deaths per 100,000 persons in Hispanics to 79.8 cases and 57.0 deaths per 100,000 persons in Non-Hispanic Blacks. In women, lung cancer incidence and mortality rates ranged from 24.3 cases and 12.3 deaths per 100,000 persons in Hispanics to 56.4 cases and 35.6 deaths per 100,000 persons in Non-Hispanic Whites. While incidence and mortality both remained higher than observed for most other cancers, it is notable that incidence and mortality decreased during the more recent time period in every racial/ethnic group in both men and women. In men, incidence is highest in non-Hispanic black and lowest in Hispanic males. Mortality is highest in non-Hispanic black and lowest in Hispanic males. In women, incidence is highest in non-Hispanic white and lowest in Asian/Pacific Islander females. Mortality is highest in non-Hispanic white and lowest in Hispanic females. These differences between racial/ethnic groups as well as sex largely reflect historic smoking patterns. Historically, men smoked more than women, and black men smoked more than men of other racial/ethnic groups. These patterns of smoking are changing. Steeper declines in lung cancer incidence and mortality rates have been seen in men compared with women; although fewer women than men smoke, they are slower to quit and an increase in smoking prevalence has been observed in some birth cohorts.[66,118] The narrowing of the disparity gap between lung cancer incidence in black and white men over the past 10 years likely reflects a substantial decrease in smoking prevalence among African-American youth since the 1970s.[119]

Smoking patterns cannot explain all the gaps in incidence and mortality observed between racial and ethnic groups, and important questions persist as to whether certain groups, and specifically African Americans, are more susceptible to lung cancer related to tobacco or other carcinogens. The prospective Multiethnic Cohort Study evaluated more than 215,000 individuals of 5 ethnic groups (African American, Native Hawaiian, Latino, Japanese American, and White) in California and Hawaii and demonstrated significant differences in the association between cigarette smoking and the risk of lung cancer between groups.[120,121] In its original report in 2006, differences were most evident in participants who smoked 11 to 20 cigarettes/day (Table 108-2). For this level of smoking after adjusting for sex, duration of smoking, and time since quitting, and with African-American participants as the reference group, the relative risk (RR) of lung cancer was similar in Native Hawaiians (RR, 0.90; 95% confidence interval [CI], 0.74–1.12) but lower in all other racial/ethnic groups: Latino (RR, 0.36; CI, 0.29–0.44; p <0.001); Japanese American (RR, 0.39; 95% CI, 0.32–0.47; p <0.001); and Whites (RR, 0.57; 95% CI, 0.49–0.63; p <0.001). An update of this study in 2019, at which time the number of lung cancers had increased from 1979 to 4993, demonstrated that these racial/ethnic differences persisted, with higher risk demonstrated in the African American and Native Hawaiian populations and more pronounced risk differences observed in moderate compared to heavy smokers.[121] Multiple other studies have demonstrated similar findings of disparities in lung cancer risk between racial/ethnic groups that cannot be fully explained by smoking patterns.

While most lung cancers are highly mutated from accumulation of somatic genetic changes resulting from cigarette smoke and other carcinogenic exposures, some differences observed between racial/ethnic groups in lung cancer incidence and mortality are likely related to diversity in germline (inherited) genetic variation.[122] This may be more evident in populations with less tobacco exposure. The ability to achieve genomic profiling for individual tumors has made more precise, personalized treatment with improved outcomes a reality for many patients. This unfortunately highlights yet another disparity, as lung tumor mutations have been much more extensively studied in White and Asian than in Black or Hispanic populations.

Racial/ethnic differences have been identified in the frequency of mutation of several genes that can “drive” carcinogenesis. Mutations in the *EGFR* gene are the most commonly identified driver mutations in adenocarcinomas and demonstrate substantial racial/ethnic variation. Actionable *EGFR* mutations are identified in approximately 35% of NSCLC patients in East Asia compared with 10% of patients in western countries.[73,123] Limited and conflicting data are available regarding the frequency of *EGFR* mutations in Black populations.[124–126] A study of 1150 NSCLC biopsies from patients in Argentina, Colombia, Mexico, and Peru showed a wide variation of *EGFR* mutations among the 4 countries, ranging from 19.3% in Argentina to 67% in Peru.[127] The Hispanic/Latinx population in countries of Latin America is likely genetically more diverse than the Hispanic population in the United States, which may account at least in part for such broad variation.[128] Anaplastic lymphoma kinase (*ALK*) oncogenic rearrangements are less commonly seen

TABLE 108-2 Relative Risks of Smoking-related Lung Cancer Among Current and Former Smokers of Five Racial/Ethnic Groups, According to the Level of Smoking[a]

Smoking Level	African American	Native Hawaiian	Latino	Japanese American	White	Global P Value
≤10 Cigarettes/day						
Relative risk (95% CI)[b]	1.00	0.88 (0.60–1.29)	0.21 (0.14–0.31)	0.25 (0.18–0.36)	0.45 (0.34–0.60)	
P value		>0.5	<0.001	<0.001	<0.001	<0.001
Cases of lung cancer	215	34	52	50	54	
No. of participants	9886	2745	12,831	8378	7650	
11–20 Cigarettes/day						
Relative risk (95% CI)[b]	1.00	0.90 (0.74–1.12)	0.36 (0.29–0.44)	0.39 (0.32–0.47)	0.57 (0.49–0.68)	
P value		0.37	<0.001	<0.001	<0.001	<0.001
Cases of lung cancer	240	65	80	136	180	
No. of participants	6514	3062	4932	10,680	9877	
21–30 Cigarettes/day						
Relative risk (95% CI)[b]	1.00	0.93 (0.72–1.21)	0.61 (0.46–0.79)	0.61 (0.49–0.74)	0.73 (0.61–0.88)	
P value		>0.5	<0.001	<0.001	0.07	<0.001
Cases of lung cancer	65	24	27	102	157	
No. of participants	1671	1419	1406	4715	6062	
≥31 Cigarettes/day						
Relative risk (95% CI)[b]	1.00	0.95 (0.66–1.35)	0.79 (0.55–1.13)	0.75 (0.57–1.00)	0.82 (0.64–1.05)	0.31
P value		>0.5	0.38	0.31	>0.5	
Cases of lung cancer	45	35	26	64	124	
No. of participants	759	788	800	2305	3970	

[a] Global P values for racial and ethnic differences in risk for each smoking level were calculated with the use of the likelihood ratio test.

[b] Relative risks were adjusted for the duration of smoking, sex, and the time since quitting. Information about the model used to estimate relative risks is provided in the Supplementary Appendix. African Americans served as the reference group. CI denotes confidence interval.

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than *EGFR* activating mutations. The most common of these, the *EML4-ALK* fusion gene rearrangement between echinoderm microtubule-associated protein-like 4 (*EML4*) and *ALK*, was originally described in a Japanese population and is observed more frequently in Asian and Latin American compared to White populations.[128,129] *KRAS* mutations, which are the most common driver mutations in lung adenocarcinoma, show a different racial/ethnic pattern than EGFR, with higher frequency in Whites than Asian or Latin American populations.[122,128] Some studies suggest that *KRAS* mutations are of similar frequency in Blacks as in Whites, but without consistent findings.[124–126]

Socioeconomic Status

Sources of wide disparities in lung cancer morbidity and mortality are multifactorial and broad ranging in scope. Factors limiting access to high-quality cancer care include lower socioeconomic or educational status, geographic barriers to tertiary care sites, neighborhood or residential segregation discrimination, lack of access to primary care, and community or cultural trust in the medical system.[130] These same factors will also negatively impact the course and outcomes of other comorbid illnesses that are common among patients with lung cancer, including cardiovascular disease and other smoking-related illnesses, leading to a further compounding of the disparities observed in overall survival.

Lung cancer rates and outcomes are inextricably linked to socioeconomic status, which is a strong determinant of smoking status. Studies in multiple countries have demonstrated that lower income, lower levels of education, and uninsured or public insurance status are associated with higher levels of smoking, higher rates of lung cancer, and worse lung cancer outcomes.[131–134] In 2019, 14% of U.S. adults age 18 or older were current cigarette smokers.[26] The smoking rate among adults with annual household income <$35,000 was 21.4%, compared with 7.1% among adults with household income >$100,000. With regard to education, 35.3% of adults whose highest level of educational attainment was a GED certificate smoked, compared with 6.9% of adults with a college degree. Adults who were uninsured or had Medicaid insurance had smoking rates of 22.5% and 24.9%, respectively, compared with adults with private or Medicare insurance, whose rates were 10.7% and 8.6%, respectively. Other groups with social, economic, and environmental stressors also have higher smoking rates, including American Indian/Alaska Natives, lesbian/gay/bisexual/transgender orientation, divorced/separate/widowed marital status, and persons with disabilities. Further, jobs generating lower income are more likely to be associated with potentially harmful occupational exposures.

Lung cancer rates are higher in Blacks and survival is worse, despite the fact that smoking rates among adults are currently lower in non-Hispanic Blacks (14.9%) than non-Hispanic Whites (15.5%).[26] Race and socioeconomic status are linked to each other and to deeply embedded structural racism that maintains the separation between races and resources and result in unequal access to both preventive and acute health care, disparities in treatment, and differences in outcomes. Several studies have shown that Black patients with early-stage lung cancer are less likely to receive surgical resection than White patients, which undoubtedly contributes to their observed lower survival.[135,136] Cultural factors may create barriers related to beliefs about harms of treatment interventions, but these too may reflect societal structures that foster distrust of the medical system.[137,138] Lower socioeconomic status has also been associated with less timely care and more advanced cancer stage at diagnosis, further contributing to worse prognosis.[136,139–141]

Genetic Factors

Heritable genetic factors influence host susceptibility to carcinogenesis with or without exposure to cigarette smoke, the type of lung cancer that may develop, and individual responsiveness to biologic therapies. A number of studies have shown an association of lung cancer risk with a positive family history of lung cancer, in both smokers and nonsmokers.[142–144] Both genetic as well as shared environmental factors may contribute to this observation. A multicenter case-control study in eastern and central Europe and the United Kingdom including 2861 cases and 3118 controls evaluated the effect of a history of cancer in a first-degree relative (parents, full siblings, children), and demonstrated an increase in lung cancer risk with odds ratio (OR) of 1.63 (95% CI, 1.31–2.01).[145] The same group performed a meta-analysis of 41 studies evaluating the association between a positive family history and lung cancer risk, which demonstrated a significant increase in risk with OR of 1.72 (95% CI, 1.56–1.88).[145] This risk was higher if two or more relatives had lung cancer (OR, 3.60; 95% CI, 1.56–8.31). If the lung cancer case was under the age of 60, the OR for a positive family history was 2.25 (95% CI, 1.61–3.16).

The influence of family history on risk is reflected in its inclusion as an independent factor in several lung cancer risk predictive models. For example, an earlier model developed by Spitz et al. incorporated family history with other significant risk variables including smoking history, exposure to environmental tobacco smoke, and occupational exposures to dusts and to asbestos.[144,146] Similarly, risk models developed from the Liverpool Lung Project (LLP) and the Prostate, Lung, Colorectal and Ovarian (PLCO) Screening Trial include family history as an independent predictive factor. The LLP risk model also identified a significantly increased risk specifically for persons with a family history of early-onset lung cancer (<60 years of age).[147]

While risk related to a positive family history of lung cancer is dwarfed by the magnitude of risk associated with smoking, individual susceptibility to carcinogenic agents can likely be influenced by polymorphisms in genes important in pathways influencing DNA damage response and repair or cell cycle events, as well as chronic inflammation related to smoking or underlying lung disease.[148–151] Genes encoding enzymes involved in repair mechanisms may be influential not only in primary carcinogenesis, but also in response to purposeful DNA damage such as is intended with cytotoxic chemotherapy. For example, the excision repair cross-complementing group 1 (ERCC1) is essential for DNA nucleotide excision repair and is one of multiple genes being studied because of their association with lung cancer susceptibility. Polymorphisms in such DNA repair enzymes may influence lung cancer risk and may also be important in response or resistance to treatment with chemotherapies such as platinum-based drugs, whose therapeutic effect depends on the induction of DNA adducts.[152,153]

Tobacco smoke carcinogens such as the PAHs and N-nitrosamines are predominantly procarcinogens that must undergo metabolic activation to become carcinogenic. Metabolic detoxification also can occur, with the balance between activation and detoxification likely influencing individual lung cancer risk.[32] Mutations and polymorphisms in genes influencing these competing processes can potentially influence an individual's tobacco-related lung cancer risk. Mutations and polymorphisms in genes encoding enzymes involved in the activation and conjugation of tobacco smoke compounds such as PAHs, TSNAs, and aromatic amines have been widely studied. Some of the frequently studied enzymes in this system include CYP1A1, the glutathione *S*-transferases (GST), microsomal epoxide hydrolase 1 (mEH/EPHX1), myeloperoxidase (MPO), N-acetyltransferase 2, and NAD(P)H quinine oxidoreductase 1 (NQO1).[32] A GWAS of tagged single-nucleotide polymorphisms (SNPs) in histologically confirmed NSCLC performed to identify common low-penetrance alleles that influence lung cancer risk identified a susceptibility locus that contains the nicotinic acetylcholine receptor genes.[154] Polymorphisms in genes involved in DNA repair enzymes active in base excision repair (XRCC1, OGG1), nucleotide excision repair (ERCC1, XPD, XPA), and double-strand break repair (XRCC3) and different mismatch repair pathways have been studied as they relate to lung cancer risks.[155,156] Chronic inflammation in response to repetitive tobacco exposure has been theorized to be involved in lung tumorigenesis.[157] Genes encoding for the interleukins (IL-1, IL-6, IL-8) or the cyclooxygenase enzymes (COX2) involved in inflammation, or the metalloproteases (MMP-1, -2, -3, -12) involved in repair during inflammation, and NFKB1 have been associated with lung cancer risk.[158] Various cell cycle–related genes also have been implicated in lung cancer susceptibility, including the tumor suppressor genes *p53* and *p73*, mouse double minute 2 (*MDM2*), and the apoptosis genes encoding FAS and FASL.[159,160] Acquired or epigenetic changes to DNA chromosome also can lead to increased lung cancer susceptibility. These events include changes such as DNA methylation, histone deacetylation, and phosphorylation, all of which can affect gene expression.[161] Moreover, interactions between genes may be as or more important than mutations or epigenetic changes in single genes, emphasizing the complexity of genetic influences in lung cancer susceptibility and development.

Diet

Diets rich in carotenoids, vegetables and fruit, and antioxidants have been proposed as chemopreventive for lung cancer based on several observational epidemiologic studies.[162–166] Conversely, diets rich in red meat, saturated fat, and nitrites have been associated with increased lung cancer risk.[167–169] Rigorous study of the effect of diet and specific chemopreventive interventions on lung cancer risk and prevention is challenging because of the large numbers of subjects and the long duration of follow-up required for such studies.

Enthusiasm for studies of cancer-preventive interventions in lung cancer was tempered in the early 1990s by unexpected harm demonstrated in both the Alpha-Tocopherol Beta-Carotene Prevention (ATBC) trial and the Carotene and Retinol Efficacy Trial (CARET).[170,171] These were large, phase 3, randomized, double-blind, placebo-controlled studies evaluating vitamin supplementation in groups at higher risk for lung cancer, based on epidemiologic evidence suggesting a benefit of dietary beta-carotene on decreasing lung cancer risk. The ATBC subjects were smokers, randomized to beta carotene and/or alpha-tocopherol (a vitamin E isoform) supplementation versus placebo. The CARET subjects were smokers or had asbestos exposure, randomized to beta-carotene and/or retinol (vitamin A) versus placebo. Both studies were terminated early because of excess incidence of lung cancer and overall mortality observed in the intervention groups. Follow-up studies confirmed the persistence for several years of an increased incidence of lung cancer and overall mortality.[172,173]

Subsequent studies, including the Physicians' Health Study and the Women's Health Study, demonstrated neither harm nor benefit with regard to beta-carotene and lung cancer.[174,175] Of note, in contrast to the ATBC and CARET studies, the subject populations of these studies were not exclusively smokers or at higher lung cancer risk, and beta-carotene supplementation doses were considerably lower. It has been postulated that supraphysiologic concentrations of beta-carotene introduced into a free radical–rich environment produced by cigarette smoke may induce oxidation products of beta-carotene, shifting the beta-carotene antioxidant:pro-oxidant balance in the lungs of smokers toward a pro-oxidant state.[176] This hypothesis is supported by a study in ferrets demonstrating that supraphysiologic doses of beta-carotene in smoke-exposed animals increased oxidative metabolites, decreased expression of retinoic acid receptor-β, facilitated the binding of cigarette smoke–derived carcinogens to DNA, and resulted in the development of squamous metaplasia.[177] These findings support concern that supraphysiologic supplementation of nutrients in a population with adequate nutritional status might not be expected to be of benefit, particularly in diseases such as lung cancer with long latency periods.[176,178]

It follows that a diet balanced in nutrients should lead to better health, whereas an unbalanced diet devoid of certain nutrients would lead to worse health, including increased cancer risk. Diets with low or no intake of fruits or vegetables have been associated with up to threefold risk for lung cancer.[179] Diets rich in fruits and vegetables are associated with decreased cancer incidence, with observed protective effects stronger in current than in former smokers.[180] Consumption of vegetables such as carrots that are rich in beta-carotene and cruciferous vegetables such as broccoli and cabbage that are rich in isothiocyanates appears to have some protective effect against lung cancer.[164,181] Raw fruits and vegetables may have better retention of important nutrients such as carotenoids.[182] A large prospective NIH-AARP Diet and Health Study showed no relation between total intake of fruit and vegetables with lung cancer risk.[183] The study did show that higher consumption of several botanical groups such as rosaceae (apples, peaches, strawberries), convolvulaceae (sweet potatoes and yams), and umbelliferae (carrots) was significantly and inversely associated with lung cancer risk in men and in former smokers.[183] Flavonoid plant metabolites have antioxidant and antiproliferative properties and can be found in foods such as berries, citrus fruits, tea, dark chocolate, and red wine. A prospective study demonstrated that risk for lung cancer was lower in men with the highest total flavonoid intake compared to those with the lowest intake.[184]

Obesity and Exercise

In 2016, the World Health Organization estimated that more than 1.9 billion adults were overweight (BMI $\geq$25 and $<$30) or obese (BMI $\geq$30) worldwide.[185] In 2018, 73.6% of the adult U.S. population were overweight and 42.5% were obese.[186] The IARC recognizes obesity as a risk factor for multiple cancers, including cancers of the esophagus, breast, uterus, and liver.[187] No association between obesity and lung cancer risk has been substantiated. One meta-analysis suggested an inverse association between BMI and lung cancer risk, and that obesity might even have a protective role.[188] However, knowing that smokers tend to have lower mean BMI than age- and sex-matched nonsmokers, any association between BMI and lung cancer would need to consider residual strong confounding effects of smoking itself.[189]

Reports on the association between physical activity and lung cancer risk have been limited. In general, positive lifestyle habits such as healthy diet, not smoking, and cardiorespiratory fitness are associated with decreased cancer risk. Several studies in women have demonstrated an inverse relationship between cardiorespiratory fitness and mortality from cancer, predominantly breast cancer.[190–192] In a prospective study of Finnish men, those in the highest tertile of exercise capacity measured by VO_{2max} had a 37% decrease in cancer mortality compared with those in the lowest tertile over an average follow-up of 16.7 years.[193] Most of the observed risk reduction was due to decreased risk of lung cancer in fit men. Whether cardiorespiratory fitness per se decreases risk or whether it is a biomarker for overall healthy lifestyle is unclear but deserves further study.

Benign Acquired Lung Disease and Lung Cancer

Several benign lung diseases are associated with increased lung cancer risk, most notably chronic obstructive pulmonary disease (COPD), interstitial lung disease, and pulmonary infections, particularly tuberculosis. The largest analysis of possible associations was performed by the International Lung Cancer Consortium and included 24,607 lung cancer cases and 81,829 controls, predominantly from Europe and North America, over the period 1984 to 2011.[194] After adjusting for age, sex, and cumulative tobacco smoking, an increased risk of lung cancer was observed with emphysema (RR, 2.44; 95% CI, 1.64–3.62) and chronic bronchitis (RR, 1.47; 95% CI, 1.29–1.68). Increased risk was also demonstrated with a history of pneumonia (RR, 1.57; 95% CI,1.22–2.01) and tuberculosis (RR, 1.48; 95% CI, 1.17–1.87). No sex-related effect was observed. A significant dose–response relation was seen, with increasing risk associated with increasing number of lung diseases.

Why the presence of COPD or any benign lung disease increases the risk of lung cancer is unknown, but it is believed to be most likely related to chronic inflammation.[195] Virchow observed in 1863 that chemical irritant–induced tissue inflammation was associated with cellular proliferation.[195,196] Inflammation may be precipitated by exposure of the airways and lung parenchyma to a variety of insults, including chemicals such as those in cigarette smoke, particulates, and microbial infections. Acute, appropriate immune responses should result in tissue repair. Chronic inflammation resulting in prolonged, persistent tissue injury may create a local microenvironment characterized by rapid local cell turnover, proliferation, and angiogenesis. Long-term chronic systemic inflammation also has been implicated in increasing the risk of lung cancer, suggesting that circulating inflammatory cells may also act as carcinogenic promoters.[197,198] Several studies have demonstrated that elevated C-reactive protein (CRP), which is released by the liver in response to systemic inflammation or tissue injury, may be a biomarker for increased risk of lung cancer and bronchial dysplasia.[198–200]

COPD is the second most common risk factor for lung cancer after smoking. Cigarette smoking is the primary cause of both lung cancer and COPD. Multiple studies have consistently demonstrated that the presence of COPD, characterized by irreversible obstruction to airflow, is associated with a higher risk of lung cancer.[201–203] While there has been debate as to whether the severity of airflow limitation correlates with the risk of lung cancer, observations from several studies support this hypothesis.[204–207] In particular, a prospective analysis of a subgroup of 18,473 high-risk cigarette smokers in the National Lung Screening Trial demonstrated a linear relationship between increasing severity of airflow limitation and risk of lung cancer.[208] Lung remodeling in general has been linked to both COPD and lung cancer Additionally, epithelial–mesenchymal transition, which is considered a precursor to many epithelial cancers including lung cancer, has been observed in patients with COPD and is associated with worsening airflow limitation.[209,210]

The understanding that chronic airflow limitation may increase the risk of lung cancer through inflammatory mechanisms led to studies examining the possible chemoprotective effect of inhaled corticosteroids (ICS). A large retrospective study of patients with COPD found that the risk for lung cancer was lower in patients who took high-dose inhaled corticosteroids than in patients taking lower doses or none at all.[211] However, subsequent randomized controlled trials and a systematic review failed to confirm this observation.[212]

Interstitial lung disease has emerged as a potential contributor to lung cancer risk. This is a very broad statement, as the interstitial lung diseases are a heterogeneous group of more than a hundred diseases with varying pathogenesis, associations, and prognosis. Repeated lung injury and lung cancer may share biologic mechanisms with carcinogenesis, for example fibroblast proliferation and epithelial–mesenchymal transition can lead to remodeling, genetic mutations, and dysplasia. Of the interstitial diseases, idiopathic pulmonary fibrosis (IPF) appears to have the most consistent association with lung cancer. While a large analysis of mortality data in the United States reported that lung cancer occurred less frequently in patients with pulmonary fibrosis compared to the general population, that conclusion is weakened by the limitations of death certificate data to reliably identify diagnoses such as interstitial lung disease, particularly if it were mild and not recognized as contributing to death.[213] Other series have reported an increased incidence of lung cancer in patients with IPF compared to the general population, predominantly in men and ever-smokers.[214–218] The strongest evidence for an independent association of IPF and lung cancer was presented in a population-based cohort study involving 890 subjects with cryptogenic fibrosing alveolitis (idiopathic pulmonary fibrosis) and 5884 control subjects in the United Kingdom, in which the incidence of lung cancer after adjustment for previous smoking was markedly increased (OR, 8.25; 95% CI, 4.70–11.48).[217]

Infections

Pulmonary infections are clearly associated with inflammation. Chronic pulmonary infection, in particular tuberculosis, may result in prolonged pulmonary as well as systemic inflammation lasting months to years. Treatment itself typically requires a duration of at least 6 months, and lung remodeling with resultant bronchiectasis and fibrosis is well described. A large population-based cohort study performed in Taiwan showed that patients with tuberculosis (N = 4480) were 10.9 times more likely to develop lung cancer compared to patients without tuberculosis (HR, 3.32; 95% CI, 2.70–4.09).[219] This study is limited by potential confounding for tobacco use, which was not reported. Other smaller case-control studies suggest that an association between tuberculosis and lung cancer risk exists with odds ratios in the 2–4 range, but this was not significant in the absence of a history of smoking.[220,221]

Acute bacterial pneumonia, for example caused by organisms such as *Streptococcus pneumoniae*, typically does not result in prolonged episodes of chronic inflammation. While there has been some suggestion of an association between prior pneumonia and subsequent lung cancer risk, in general these associations are fairly weak.[195,220,222] One exception to this may be *Chlamydia pneumoniae,* which is felt to be the cause of approximately 10% of community-acquired pneumonia. Several case-control studies have demonstrated an association of *C. pneumoniae* infection with lung cancer.[223–227] A nested case-control study within the screening arm of the PLCO Trial demonstrated that seropositivity for chlamydia heat shock protein 60 antibodies, a marker for chronic chlamydial infection, was associated with an increase in lung cancer risk (OR, 1.30; 95% CI, 1.02–1.67) independent of smoking or histology, and that risk increased with increasing antibody titers.[226] Notably, this association was not seen with seropositivity with microimmunofluorescence IgG or IgA antibodies, suggesting that the chronicity of *C. pneumoniae* infection and pulmonary inflammation might be important in contributing to lung cancer risk.

Multiple studies have demonstrated an increased risk of lung cancer in patients with HIV. At least some of the excess risk appears to be attributable to high smoking prevalence in the HIV-infected population.[228,229] However, several studies suggest that the increase in risk for lung cancer cannot be explained by smoking alone.[228–230] In a study including nearly 400,000 patients with AIDS in the United States, lung cancer risk compared to the general population was increased in all demographic groups, with the relative risk greatest in the youngest age group (standardized incidence ratio 10.4 for ages 15–29 years, 6.3 for ages 30–39 years, 3.7 for ages 40–49 years).[231] While this study did not include individual-level smoking data, an analysis based on plausible patterns of tobacco use noted a higher lung cancer risk than could be attributed to smoking alone. In a study of 2086 injection drug users including HIV-infected and HIV-uninfected groups where smoking history was known, an increased risk of lung cancer was demonstrated after adjustment for tobacco use (RR, 3.4; 95% CI, 1.6–7.4).[229] Notably, although the prevalence of smoking in the HIV-infected population is very high, there is little evidence of an increase in lung cancer in HIV-infected never-smokers.[195] This raises the possibility that HIV is a cofactor with tobacco in lung carcinogenesis. Additionally, HIV infection may invoke a likelihood of chronic inflammation, given its association with increased risk of bacterial infection and opportunistic infections, as well as a higher prevalence of coinfection with oncogenic viruses such as human herpesvirus 8, human papillomavirus (HPV), and Epstein-Barr virus.[232]

Oncogenic viruses have been proposed as potential contributors to lung carcinogenesis. Analysis of the Cancer Genome Atlas data identified viral sequences of eight viruses in lung cancers compared with paired adjacent normal tissues, including HPV16, HPV18, HPV30, HPV33, human herpesvirus 4 (Epstein-Barr virus), human herpesvirus 5 (cytomegalovirus), human herpesvirus 6, and hepatitis B virus.[233] Several of these viruses are known to be associated with other solid tumors, for example HPV16 and HPV18 with cervical cancer and cancers of the head and neck, and human herpesvirus 4 with Burkitt lymphoma and nasopharyngeal carcinoma.[234,235] Distribution of these viruses varies by sex as well as by race/ethnicity. There has not been consistent association of any of these or other viruses with lung cancer, but recognition of their etiologic role in other cancers suggests that further research in this area should be pursued.

Environmental Tobacco Smoke

Environmental tobacco smoke (ETS), also referred to as “secondhand smoke,” consists of mainstream (exhaled) smoke and sidestream (from the burning tip of the cigarette) smoke. Many organizations and governments, including the IARC, the U.S. Department of Health and Human Services, and the U.S. Environmental Protection Agency (EPA), classify ETS as containing multiple lung carcinogens.

A number of studies support the hypothesis that ETS is an important risk for lung cancer, although the magnitude of risk is problematic to measure as quantifying ETS exposure is difficult. In 1986, the U.S. National Research Council commissioned a review of the effects of ETS as a potential causal agent of lung cancer in nonsmokers exposed to household cigarette smoke.[236] Review of all the available evidence yielded an overall increase in lung cancer risk associate with ETS with OR of 1.34. In smokers, this increase in risk may be trivial. In never-smokers, this translates into an approximately 34% increase of risk for lung cancer. It important to note that since the background risk for lung cancer in a never-smoker is very low, such an increase will not substantively change that risk.[236,237] A meta-analysis including 40 case-control and prospective cohort studies evaluating the effect of secondhand smoke on never-smoking subjects showed an increased hazard ratio (HR) of 1.22 for developing lung cancer (95% CI, 1.13–1.33; $p < 0.001$).[238] Another meta-analysis evaluating lung cancer in never-smoking women exposed to a smoking spouse reported a pooled RR of 1.27 (95% CI, 1.17–1.37).[239] A case-control study done in the United States demonstrated an increased risk of lung cancer in never-smokers with secondhand smoke exposure in childhood, with OR of 1.47 (95% CI, 1.04–4.90).[240] These and other studies support the conclusion that ETS is an important risk factor for lung cancer, particularly among never-smokers.

Environmental Pollution

Outdoor air pollution is associated with lung cancer risk. Early studies involving urban-rural comparisons showed that an “urban factor" was associated with a 10% to 40% increase in lung cancer deaths.[241] Outdoor air pollution particulate matter (PM) is designated by the IARC as carcinogenic in human. Analytic methods to detect specific pollutants often use the concentration of suspended fine airborne particulates as a measure of air pollution. PM with aerodynamic diameters of <10 μm (PM_{10}) and 2.5 μm ($PM_{2.5}$) have been reported as associated with risk of lung cancer.[242] Two large U.S. cohort studies estimated a 19% excess risk for lung cancer per 10-μg/m^3 increment in long-term average exposure to fine particulates.[243,244] The Cancer Prevention II study found that fine particulate ($PM_{2.5}$) and sulfur oxide–related pollution were associated with an 8% increased risk for lung cancer mortality for each 10-μg/m^3 elevation in long-term average ambient concentration.[244] A meta-analysis of this and 17 other studies concluded that lung cancer risk increased for every 10-μg/m^3 increase in exposure to $PM_{2.5}$ (meta-analysis RR, 1.09; 95% CI, 1.04–1.14), with risk being more pronounced in former (meta-analysis RR, 1.44; 95% CI, 1.04–1.22]) and never-smokers (meta-analysis RR, 1.18; 95% CI, 1.00–1.39]).[245] Debate persists as to whether chemicals adherent to the particulates or the particulates themselves are the relevant carcinogenic exposure.[246]

It is difficult to determine the carcinogenicity of single constituents of air pollution. Combustion products of fossil fuels such as coal and oil also have potential carcinogenic components. In many parts of the world, solid fuels such as wood are burned as primary sources of domestic energy for cooking and heating. Incomplete combustion of coal in homes has been linked with lung cancer, particularly among women in Asia.[247–249] The IARC has classified indoor emission from household coal combustion as a human carcinogen and emissions from biomass fuel, primarily from wood, as a probable human carcinogen. Diesel exhaust, which is composed of a complex mixture of gases and fine particles, is also an important component of air pollution and an occupational exposure for persons in the trucking industry. Some of the gaseous components of diesel exhaust, including benzene, formaldehyde, and 1,3-butadiene, are suspected of or known to cause cancer in humans. A pooled analysis of 11 studies evaluating diesel exhaust exposure and risk of lung cancer demonstrated an increased risk with OR of 1.31 (95% CI, 1.19–1.43).[250]

TABLE 108-3 Selected Occupational Carcinogens and Associated Exposures

Carcinogen	Occupational Exposure
Arsenic	Copper, lead, or zinc ore smelting Manufacture of insecticides Mining
Asbestos	Asbestos mining Asbestos textile production Brake lining work Insulation work Shipyard work
Beryllium	Ceramic manufacture Electronic and aerospace equipment Mining
Chloromethyl ethers	Chemical manufacturing
Chromium	Chromate production Chromium electroplating Leather tanning Pigment production
Diesel	Trucking industry
Nickel	Nickel mining, refining, electroplating Production of stainless and heat-resistant steel Aluminum production Coke production Ferrochromium alloy production
Particulate matter (PM_{25})	Air pollution
Radon	Mining

Occupational Carcinogens

Lung cancer is the most common cancer associated with occupational exposures, which should be modifiable and preventable. The IARC has implicated a number of occupational carcinogens in lung cancer.[251] A selection of these agents and their associated occupations are shown in Table 108-3. An estimated 10% of lung cancer deaths in men and 5% in women worldwide could be attributable to exposure to eight occupational lung carcinogens, specifically asbestos, arsenic, beryllium, cadmium, chromium, nickel, silica, and diesel fumes.[252–255] The U.S. National Institute for Occupational Safety and Health (NIOSH) estimated that approximately 9000 to 10,000 men and 900 to 1900 women per year in the United States develop lung cancer from exposure to occupational carcinogens.[256] Given that lung carcinogenesis for smoking-related lung cancer is a multistage process, these assessments may underestimate the carcinogenic contribution of occupational and environmental exposures occurring over time.[257]

Asbestos is the most common occupational cause of lung cancer. Asbestos, a naturally occurring fibrous mineral, can be classified as serpentine (chrysotile) or amphibole (amosite, crocidolite, tremolite). Asbestos has been used in construction and as insulating material for its fire-retarding qualities and strength since the 1800s, but its role as a lung carcinogen was not established until the 1940s. While asbestos mining in the United States has ceased, asbestos per se is not banned on a federal level, and while asbestos is regulated by the EPA and some states have enacted legislative controls, asbestos can still be imported and used in the United States in small amounts. Fortunately, asbestos use has precipitously declined in the United States since the 1970s.[258,259]

Asbestos exposure is a risk factor for lung cancer as well as mesothelioma. Lung cancer related to asbestos is predominantly related to occupational exposure, with risk from nonoccupational asbestos exposure in the general environment being extremely low.[260] All commercial asbestos fiber types can be associated with lung cancer. Risk is dose-dependent without a clear minimum threshold of exposure.

It is important to recognize that cigarette smoke use contributes significantly to lung cancer risk in asbestos-exposed individuals. Debate continues as to whether exposure to the combination of smoking and asbestos results in a multiplicative or additive increase in risk, although the burden of studies suggest that the effect is more than additive.[261–266] There has also been notable controversy as to whether interstitial fibrosis related to asbestos exposure (asbestosis) is a prerequisite for lung cancer risk. In early animal studies, asbestos-exposed animals developed lung cancer only when they also developed pulmonary fibrosis,[267,268] and human studies reported that the presence of asbestosis was associated with increased likelihood of lung cancer compared to patients with asbestos exposure without associated fibrosis.[258,269] However, there is understandable dispute as to whether one, any, or all patterns of interstitial lung disease (idiopathic pulmonary fibrosis, nonspecific interstitial pneumonia, unclassified interstitial changes) can be called asbestosis in the absence of pathologic evidence of asbestos bodies. Further complexity relates to limitations imposed by the lack of pathologic evidence of asbestos bodies without an invasive procedure, or occult interstitial disease that may be subradiographic even with high-resolution chest CT scanning.[263,270]

Radon and its decay products are carcinogens associated with mining, one of the world's oldest occupations. Initially known as a wasting pulmonary disease of miners and metal smelters, radon-induced lung cancer was first attributed to exposures to dust or metals, or to infections such as tuberculosis, but was later linked to radioactive materials.[271] Uranium mining has ceased in the United States. However, radon exposure continues to be an occupational concern in non-uranium mining and underground work as well as in uranium and non-uranium mines around the world.[272] In the United States, occupational exposure to radon is strictly regulated. It has been estimated that a 40-year radon exposure at the maximum allowed level by occupational standards would increase a person's lifetime risk for lung cancer twofold.[273]

Radon is a natural decay product of radium 226, itself a decay product of uranium 238. Ultimately, radon decay produces lead 210, which has a half-life of 22 years. Both uranium and radium are ubiquitous in soil and rock, in highly variable concentrations. At usual temperatures, radon is released as an inert radioactive gas. Radon has a half-life of 3.82 days and decays into radioisotopes known as radon decay products (or radon daughters) that have half-lives measured in seconds to minutes. These products include polonium 218 and polonium 214, which emit alpha particles. It is the alpha radiation that is highly damaging to tissues including the respiratory epithelium. Inhalation of these radon decay products and subsequent alpha particle emission in the lung can cause damage to cells and genetic material. Evidence from epidemiologic studies of underground miners shows a linear relationship between radon exposure and lung cancer risk.[274,275] Uranium miners exposed to radon and its decay products have an increased risk for lung cancer, peaking 15 to 24 years after exposure.[276] A pooled analysis of 11 cohort studies including 2700 lung cancer deaths occurring in 65,000 miners concluded that the relative risk for lung cancer was linearly related to cumulative radon progeny exposure, and that 40% of all lung cancer deaths in their cohort might be due to such exposure.[277] In never-smokers, 70% of lung cancer deaths were thought attributable to radon progeny exposure.[277] Other studies support an increased risk of lung cancer in never-smokers with higher levels of uranium exposures.[277,278] The combination of uranium exposure and smoking appears to have a synergistic effect in increasing lung cancer risk in miners.[279–281]

Radon is a ubiquitous domestic indoor air pollutant and is classified by IARC as carcinogenic to humans. The U.S. National Council on Radiation Protection and Measurements has identified radon and its decay products as the largest component of environmental radiation to persons living in the United States.[275] Case-control studies identify domestic radon as increasing the risk of lung cancer.[282,283] A meta-analysis including 8 studies with 4263 lung cancer cases and 6612 controls concluded that higher residential radon levels were associated with an increase in lung cancer risk with RR of 1.14 (95% CI, 1.0–1.3).[272] In the United States, the EPA estimates that approximately 21,000 lung cancer deaths annually are attributable to radon.[284]

The concentration of radon gas in an environment depends on the richness of the source of radium and the degree to which the air around that source is ventilated. The primary factor determining radon gas concentration in homes is the concentration of radium in the soil and rock beneath those structures.[279] Building materials, well water, and natural gas are less common sources, usually contributing only minimally to indoor radon concentrations. Radon mitigation can usually be accomplished by installation of ventilation systems that exhaust radon from the home to the outside environment.

PERSPECTIVE AND CONCLUSIONS

Seven decades have passed since cigarettes were linked causally to lung cancer. What was a rare disease at the turn of the 20th century now causes 1.8 million deaths each year. Each decade has witnessed new understanding about other exposures that contribute to lung cancer risk. The knowledge that lung carcinogenesis is in most cases a cumulative process of genetic and epigenetic changes caused by largely preventable exposures provides a roadmap for mitigation.

Insights into the epidemiology and causal factors of lung cancer provide a sound foundation for disease prevention. The most important preventive strategy is to aggressively curtail cigarette consumption. The WHO Framework Convention on Tobacco Control (FCTC) treaty developed the MPOWER policy package, with the intention that countries would implement individual policies to (1) monitor tobacco use, (2) protect people from tobacco smoke, (3) offer help to quit tobacco use, (4) warn about the dangers of tobacco, (5) enforce bans on tobacco advertising, promotion, and sponsorship, and (6) raise taxes on tobacco products.[285] These policies acknowledge that tobacco control requires interventions at public health, legislative, regulatory, and personal behavioral levels. Whether the FCTC per se has changed the international agenda on tobacco, such policies alone and in combination have led to declining tobacco use in high-HDI countries, and provide a strategy for low- and middle-income countries where tobacco use is still on the rise.[286]

Our knowledge of lung cancer epidemiologic factors also identifies groups at particular risk. Lung cancer is a significant women's health issue; lung cancer incidence rates are declining more slowly in women than in men, with a worrisome narrowing of the gender gap in lung cancer mortality. Groups that live under structural bias related to race and ethnicity or subject to socioeconomic and environmental stressors are more likely to smoke and less likely to have access to preventive or primary care as well as to state of the art precision treatments. Vaping of nicotine is still largely unregulated. Occupational and domestic carcinogens, including air pollution, are prevalent. Populations with these demographics and exposures warrant specific attention, further study, and targeted interventions.

Tobacco control remains a global imperative. Predictive models for lung cancer risk developed over the past 15 years acknowledge the influence of non-tobacco factors, but it is clear that risk is overwhelmingly dominated by tobacco exposure.[146,147,287] High HDI nations are beginning to emerge from the peaks of their individual lung cancer epidemics. Other nations should not be held hostage to tobacco or subjugated to the health and economic consequences of tobacco-related diseases such as lung cancer. Primary prevention curtailing tobacco use must be an international priority.

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CHAPTER 109

Lung Cancer Screening

Humberto K. Choi
Peter J. Mazzone

INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths in the United States,[1] in part because most cases are diagnosed at advanced stages when the prognosis is poor.[1] The development of tools to detect early-stage lung cancer has the potential to dramatically impact lung cancer outcomes.

Screening refers to testing an individual at risk for a disease before they have symptoms or signs of the disease in order to detect the disease at an earlier stage, when curative intent treatment is more successful. Over the past few decades, large clinical research studies have evaluated lung cancer screening tests. Screening with chest radiography (CXR) and sputum cytology failed to demonstrate a reduction in lung cancer mortality. Early cohort studies evaluating screening with low-dose computed tomography (LDCT) were more promising, prompting controlled trials that have shown reduced lung cancer–related mortality in a group at high risk for developing lung cancer.[2,3] Low-dose computed tomography is now an accepted lung cancer screening test.[4] More than just a lung scan, screening involves appropriate patient selection, consideration of benefits and potential harms, performance and interpretation of the LDCT, and management of screen-detected findings. Lung cancer screening is a complex task requiring a multidisciplinary, comprehensive program. Additional discussion of this topic is provided in Chapter 28.

LUNG CANCER SCREENING EVIDENCE BASE

Chest radiography and sputum cytology have been evaluated as lung cancer screening tools.[5–7] Despite improved survival of screen-detected lung cancers in cohort trials, controlled trials failed to demonstrate a reduction in lung cancer mortality in the screening arms. Advances in chest imaging shifted the interest toward LDCT as a screening test given its higher sensitivity to detect small tumors.

The Early Lung Cancer Action Project and other cohort studies demonstrated that LDCT could detect more lung nodules and early-stage lung cancers than CXR.[8] These promising results led to the development of controlled trials to investigate whether LDCT could reduce lung cancer mortality (Table 109-1).[2,3,9–15] The National Lung Screening Trial (NLST) and Dutch-Belgian lung cancer screening trial (Nederlands-Leuvens Longkanker Screenings Onderzoek [NELSON]) are the only trials published to date that were powered to detect differences in lung cancer–specific mortality.[2,3]

The NLST was conducted between 2002 and 2009 at 33 medical centers in the United States. It was the first lung cancer screening randomized controlled trial to report a significant reduction in lung cancer mortality.[2] The inclusion criteria were an age of 55 to 74 years, a smoking history of at least 30 pack-years, and either current smokers or former smokers who had quit within the past 15 years. The trial enrolled 53,456 participants who were randomized to LDCT or to CXR screening with a baseline test followed by two annual LDCT or CXR rounds. Participants had 6 to 7 years of follow-up. LDCT scans that revealed any noncalcified nodule measuring at least 4 mm in diameter and CXR images that revealed any noncalcified nodule or mass were classified as positive. Screening with LDCT resulted in a 16% to 20% relative reduction in the rate of death due to lung cancer. The trial also showed a 6.7% reduction in all-cause mortality with LDCT screening. In absolute terms, for every 320 subjects screened with LDCT 1 death due to lung cancer was prevented.

The NELSON trial started in 2000 and enrolled participants age 50 to 74 years who smoked 15 or more cigarettes a day for more than 25 years or 10 or more cigarettes a day for more than 30 years, and smoked within the past 10 years. More than 13,000 male participants were enrolled and randomized to 4 rounds of screening with LDCT (baseline and years 1, 3, and 5.5) or to no screening. Participants were followed for 10 years. The trial used semiautomated software to segment lung nodules and determine the nodule volume. Based on the volume of the nodule, a screening scan could be negative, indeterminate (requiring a 3-month follow-up scan to assess for volume doubling time), or positive. The trial demonstrated a significant lung cancer–specific mortality reduction of 24% with LDCT screening. The primary analysis included only men, as a small number of women were enrolled. Women were included in a subgroup analysis that revealed a reduction in lung cancer mortality of 33% (not statistically significant).

ELIGIBILITY

The positive results from NLST led to enthusiasm to bring LDCT screening into clinical practice. Several professional societies endorsed LDCT screening based on the NLST eligibility criteria (Table 109-1).[16–19] In 2013, the U.S. Preventive Services Task Force (USPSTF) recommended annual LDCT screening for individuals between 55 and 80 years who have at least a 30-pack-year smoking history and who currently smoke or who have quit within the last 15 years.[4] The recommended expansion of the age criteria from 55–74 years to 55–80 years was based on simulation models that estimated long-term harms and benefits of screening.[20] Of the 576 scenarios simulated (different starting and ending ages, pack-years, years since quit, and frequency of screening), annual screening of individuals with at least 30 pack-years of smoking who have smoked within the past 15 years and are between the ages of 55 and 80 years was selected from among the scenarios that demonstrated the most efficient balance of benefit and harms.[20] Separately, the Centers for Medicare and Medicaid Services (CMS) evaluated the evidence for coverage of lung cancer screening in the Medicare population, establishing similar eligibility criteria (upper age limit 77 years instead of 80). The health policies that resulted from these evaluations fostered the implementation of lung cancer screening programs.[21]

In March 2021, the USPSTF has issued an updated recommendation statement.[22] The updated eligibility criteria, based on additional modeling incorporating evidence generated since the 2013 statement, expands the prior criteria to include adults between 50 and 80 years of age who have a 20-pack-year smoking history and currently smoke or have quit within the past 15 years.[22]

In an effort to expand eligibility to others at risk for developing lung cancer who do not meet the above age and smoking history risk factors, some professional societies proposed eligibility criteria that include the presence of additional risk factors for lung cancer such as environmental exposures (e.g., radon, asbestos).[17,18] Another approach to identify individuals for screening that has been proposed is to estimate their risk of developing or dying from lung cancer, or their potential to benefit (gain life-years) from screening, by using validated prediction models (Table 109-2).[23–31] The variables included in risk models favor older individuals with more comorbidities and thus may result in the selection of individuals with a lower net mortality reduction benefit from screening. To mitigate this, estimates of life expectancy may be combined with risk models

TABLE 109-1 Trials That Evaluated CT Scanning for Lung Cancer Screening[2,3,9–15,49]

	Country	Recruitment Period	Sample Size	Screening Method	Interval	Inclusion Criteria Smoking Cessation	Lung Cancer Mortality RR/HR (95% CI)
NLST	United States	2002–2004	53,454	LDCT vs. CXR	Three annual screens	55–74 ≥30 pack-years <15 years	0.85 (0.75–0.96)
NELSON	Netherlands/ Belgium	2003–2006	15,822	LDCT vs. usual care	Four screens with different intervals: 1 year, 2 years, and 2.5 years	50–75 ≥15 cigarettes per day for ≥25 years or ≥10 cigarettes per day for ≥30 years ≤10 years	0.76 (0.61–0.94)
DLCST	Denmark	2004–2006	4104	LDCT vs. usual care	Five annual screens	50–70 ≥20 pack-years ≤10 years	1.03 (0.66–1.60)
MILD	Italy	2005–2011	4099	LDCT vs. usual care	Annual and biennial for 5 years	≥49 ≥20 pack-years ≤10 years	Annual: 2.48 (0.98–6.29) Biennial: 1.24 (0.42–3.70)
UKLS	United Kingdom	2011–2014	4055	LDCT vs. usual care	Single-screen LDCT	50–75 Predicted risk of lung cancer ≥5% ≤10 years	NR
LUSI	Germany	2007–2011	4052	LDCT vs. usual care	Annual screen for 5 years	50–69 ≥15 cigarettes per day for ≥25 years or ≥10 cigarettes per day for ≥30 years ≤10 years	0.74 (0.46–1.19)
ITALUNG	Italy	2004–2006	3206	LDCT vs. usual care	Annual screen for 4 years	55–69 ≥20 pack-years ≤10 years	0.70 (0.48–1.04)
Depiscan	France	2002–2004	765	LDCT vs. CXR	Three annual screens	50–75 ≥15 cigarettes per day for ≥20 years	NR
DANTE	Italy	2001–2006	2450	LDCT vs. clinical review	Annual screen for 4 years	60–74 >20 pack-years ≤10 years	1.01 (0.70–1.44)

CXR, chest x-ray; LDCT, low-dose computed tomography; NR, not reported.

or included in a model of benefit. The application of these models may improve the accuracy of selection of screening candidates and lead to greater equity in eligibility for lung cancer screening. It is important to note that the screening eligibility criteria recommended by the USPSTF, based on age and smoking history, are the criteria used for insurance coverage. In addition, the use of risk-based or life-gained models to identify those eligible for screening is more cumbersome and challenging to implement.

It is important to consider the presence of comorbidities that might limit an individual's life expectancy when offering screening. Screening should be discontinued once an individual develops a health problem that significantly limits life expectancy or the ability or willingness to have curative intent treatment.[4] The NLST and the NELSON trial enrolled healthier individuals than a real-world screening program might encounter.[2,3] The NLST did not include individuals with history of lung or other cancer within 5 years.[2] The NELSON trial had a longer list of exclusions: moderate or severe health problems and an inability to climb two flights of stairs; a body weight of more than 140 kg; current or past history of renal cell carcinoma, melanoma, or breast cancer; and diagnosis of lung cancer or treatment related to lung cancer within 5 years. In general, older patients with more comorbidities are at higher risk for harms related to screening, such as complications related to procedures needed to evaluate screen-detected findings. On an individual level, it is challenging to distinguish those who are likely to have a net benefit from LCS despite their comorbidities from those who are more likely to be harmed by screening.

MANAGEMENT OF SCREEN-DETECTED LUNG NODULES

In the NLST any noncalcified nodule measuring at least 4 mm in any diameter was classified as positive. Abnormalities such as adenopathy or pleural effusions could be classified as positive as well.[2] The trial radiologists reported the findings to participants and their health care provider. They also developed management guidelines, but a specific approach to the evaluation of nodules was not mandated. Among the potential harms related to screening, the management of screen-detected lung nodules poses the greatest risk of harm to the individuals being screened. It is important to standardize lung cancer screening results reporting and management recommendations to minimize harms from overimaging and potentially avoidable invasive testing when LDCT screening is implemented in clinical settings.

TABLE 109-2 Clinical Risk Prediction Models That Estimate the Risk of Developing Lung Cancer, Dying from Lung Cancer, or Gaining Life-years from Screening

Model	Estimation	Projection Period	Variables
Bach (2003)	Lung cancer risk	1–10 years	Cigarettes per day, duration of smoking, duration of quitting, age, asbestos exposure, gender
Spitz (2007)	Lung cancer risk	1 year	Emphysema, hay fever, family history of any cancer, family history of cancer related to smoking, exposure to asbestos, exposure to dust, smoking status, pack years, age quit smoking
LLP (2008)	Lung cancer risk	5 years	History of pneumonia, history of cancer, family history of cancer, exposure to asbestos, duration of smoking
Hoggart (2012)	Lung cancer risk	1–5 years	Smoking status, cigarettes per day, duration of smoking, years quit smoking
$PLCO_{M2012}$ (2013)	Lung cancer risk	6 years	Age, race, level of education, BMI, history of COPD, history of cancer, family history of lung cancer, smoking status, cigarettes per day, duration of smoking, years quit
LLPi (2015)	Lung cancer risk	8.7 years	Age, gender, history of COPD, history of cancer, family history of lung cancer, duration of smoking
Pittsburgh (2015)	Lung cancer risk	6 years	Age, smoking status, cigarettes per day, duration of smoking
LCRAT (2016)	Lung cancer risk	1–10 years	Age, gender, race, level of education, BMI, emphysema, family history of lung cancer, pack-years, cigarettes per day, duration of smoking, years quit
Kovalchik (2013)	Lung cancer death		Age, BMI, emphysema, family history of lung cancer, pack-years, years quit smoking
LCDRAT (2016)	Lung cancer death	1–10 years	Age, gender, race, level of education, BMI, emphysema, family history of lung cancer, pack-years, cigarettes per day, duration of smoking, years quit
LYFS-CT (year)	Life-years gained from screening	—	Predictors of overall mortality (sex, race, BMI, pack-years, years since quitting, diabetes, stroke, hypertension) and predictors off risk for lung cancer death (age, sex, race, BMI, pack-years, duration of smoking, smoking intensity, years since quitting, emphysema, family history of lung cancer)

BMI, body mass index; LCDRAT, Lung Cancer Death Risk Assessment Tool; LCRAT, Lung Cancer Risk Assessment Tool; LLP, Liverpool Lung Project; LLPi, LLP incidence risk model; LYFS-CT, Life Years gained From Screening–CT

The American College of Radiology developed a tool called Lung-RADS that standardizes the reporting of screening findings and recommends an approach to nodule management based on nodule size and risk, with goals of minimizing testing for benign nodules, expediting treatment of malignant nodules, and facilitating monitoring for quality assurance.[32] Scans with no lung nodules or nodules with specific patterns of calcification (e.g., central, popcorn) are categorized as Lung-RADS 1. Noncalcified nodules detected are assigned a risk category (2–4) according to their average size, attenuation on LDCT (solid vs. nonsolid), evidence of stability or growth, presence of calcification, and location (e.g., perifissural). Category 4 is further divided in 4A “suspicious” and 4B “very suspicious.” Category 4X is assigned for nodules with additional features or imaging findings that increase the suspicion of malignancy. Solid lung nodules should be measured as the average of long- and short-axis diameter on the same sagittal, coronal, or transverse image. Measurement of part-solid nodules is based on the size of the solid component. The most recent version (version 1.1) incorporates volumetric analysis as well. Each category is associated with management recommendations. For example, a solid nodule that has an average diameter of 5 mm on the baseline scan would be categorized as Lung-RADS 2 (Fig. 109-1). The risk of malignancy of this nodule is less than 1% based on NLST data, and the recommendation would be to continue annual screening in 12 months. A solid nodule with an average size of 20 mm on the baseline scan would be categorized as 4B (risk of malignancy more than 15%), and the recommendation would be to consider a diagnostic CT scan, positron emission tomography (PET) scan, or tissue sampling.

Notably, Lung-RADS raised the size threshold for solid lung nodules to be labeled positive on the baseline scan to 6 mm from the 4-mm threshold used in the NLST.[2] The adoption of a larger size threshold helps decrease the false-positive rates at the expense of a small reduction in sensitivity. Lung-RADS also recommends the provider consider repeating LDCT 1 month later for new large nodules that develop on an annual screening study. These nodules would be categorized as Lung-RADS 4; however, they may be caused by infectious or inflammatory conditions and may decrease in size or resolve during short-term follow-up.

The main goals of the management of screen-detected lung nodules are to expedite the evaluation and treatment of malignant nodules, and to avoid unnecessary procedures for benign nodules. It is important that each screening program develops a system that ensures high-quality lung nodule management. This may include the documentation of management care pathways, the formation of a multidisciplinary team, and the development of a quality assurance process. Nodules may be managed by locally available resources (e.g., referring clinician or consultant) or by establishing connections with lung nodule management programs. The evaluation of concerning nodules, where invasive procedures are being considered, should start with an estimation of the malignancy risk based on clinical experience or by using a validated clinical prediction model. For example, the Brock model, derived from a lung cancer screening population, has been validated to have excellent discrimination with an area under the curve of more than 0.90 for all screen-detected nodules even when applied for nodules 10 mm or smaller in size.[33] This can be a helpful tool in clinical decision-making and can assist with patient communication.

POTENTIAL HARMS

There are several potential harms from LDCT screening. Harms include physical harms related to the evaluation of screen-detected findings, psychological distress associated with knowledge of the results, overdiagnosis and overtreatment, and the risks related to radiation exposure.

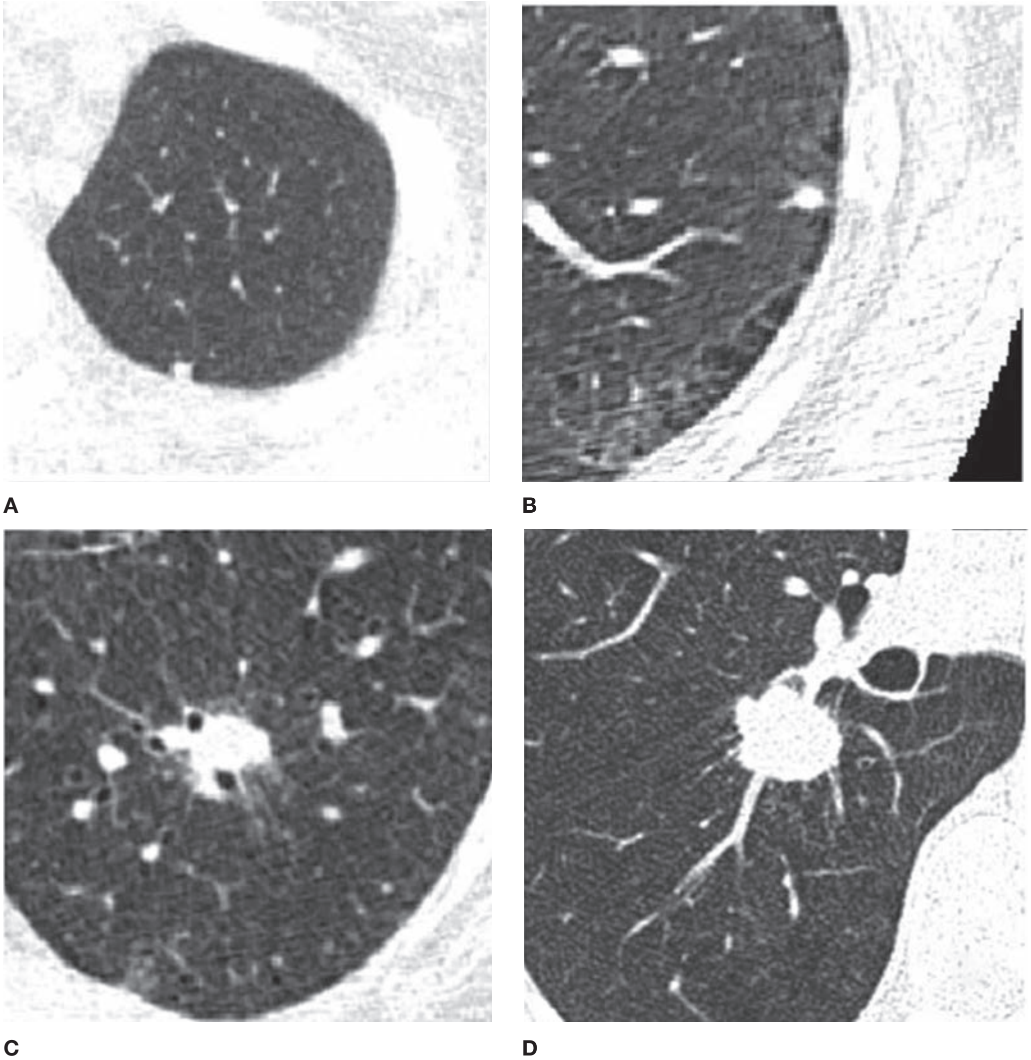

Figure 109-1 Examples of nodules and their Lung-RADS classification. **A.** Category 2: left upper lobe nodule with average size of 5 mm. Recommendation was to continue annual screening. **B.** Category 3: left upper lobe nodule with average size of 6.7mm. Recommendation was to follow in 6 months with LDCT. **C.** Category 4A: left lower lobe nodule with average size of 9.5 mm. The nodule was followed with LDCT after 3 months, which showed resolution of the nodule. It was likely an inflammatory nodule. **D.** Category 4B: spiculated right lower lobe nodule with average size of 21 mm (21 mm × 21 mm). The nodule was evaluated with a PET scan and diagnosed as squamous cell carcinoma by bronchoscopy. The tumor was treated with radiation ablative therapy.

Lung nodules, commonly found on screening LDCT, may prompt evaluation with additional chest imaging or invasive procedures for tissue diagnosis such as bronchoscopy, transthoracic needle biopsy, or surgical resection. In the NLST, 96% of positive scans (nodules ≥4 mm) were not malignant and 20% of all surgical resections were performed for nodules ultimately proven to be benign.[2] The frequency of major complications and death from a diagnostic evaluation of an LDCT screen-detected finding was 33 per 10,000 individuals and 5 per 10,000, respectively.[2]

Lung cancer screening may also cause psychological harms. Being screened for lung cancer may lead to anxiety, and learning that the scan detected a nodule may cause or increase psychological distress.[34,35] Although the early psychological impact may be significant, it is often transient and does not adversely impact longer-term quality of life.[34,35] Preparing those being screened for the possible results during a shared decision-making visit, prior to the screening LDCT, may help to mitigate the distress. A standardized approach to managing screen-detected nodules should be flexible enough to incorporate a patient's concerns and values in the management plan.

Overdiagnosis and overtreatment refer to the identification and management of a lung cancer that would not have impacted the well-being or survival of the patient if never detected. Some lung cancers are so indolent that they may never affect quality of life or be a cause of death. Overdiagnosis can also occur if a patient with severe comorbid conditions dies from one of these conditions before even a non-indolent lung cancer would have affected them. The NLST estimated overdiagnosis rates to be around 18% in the population studied with their protocol.[2]

The average effective dose of radiation from a screening LDCT is 4 to 5 times lower than a diagnostic chest CT scan (1.5 vs. 8 mSv).[36,37] The risks of developing a radiation-related cancer are felt to be low. The risk may be influenced by the age at which screening started, the sex of the patient, the numbers of LDCT scans, and exposure to other sources of radiation related to the evaluation of screen-detected findings (e.g., diagnostic imaging). It is challenging to quantify the effects of radiation exposure. One study estimated that 1 in 2500 patients screened may die of radiation-related malignancy from the cumulative radiation over the 3 years of LDCT screening in NLST.[37] Another study estimated a risk of 0.05% of developing a serious malignancy after 10 years of screening with radiation dose 40% lower than that used in NLST. This translates theoretically to 1 radiation-induced cancer for every 108 lung cancers detected over 10 years.[38]

NON-NODULE FINDINGS

Incidental pulmonary and extrapulmonary findings are common on screening LDCT.[39] Their prevalence can be as high as 94% depending on how they are defined and whether they are routinely described on the scan report. The most frequently reported findings are in the respiratory and cardiovascular systems. In a cohort of screening individuals, incidental pulmonary and cardiovascular findings were present in 69% and 67% of the scans, respectively.[39] Emphysema and coronary calcifications were the most common findings. Most non-nodule incidental findings are not clinically significant. In a systematic review, 14% of scans had findings that merited some form of additional evaluation.[40] Serious diagnoses can be found including severe coronary artery disease that requires intervention, and extrapulmonary malignancies.[39]

The potential to identify significant non-lung nodule findings should be discussed during shared decision-making visits considering their high prevalence. Each screening program should develop an approach to their management. Clinical guidelines exist to help establish an approach to the most common findings.[41,42]

IMPLEMENTATION OF LUNG CANCER SCREENING PROGRAMS

Lung cancer screening requires a dedicated multidisciplinary team and effective communication among all stakeholders. A high-quality screening program requires a robust infrastructure to meet regulatory mandates and clinical demands. There are multiple aspects of the screening process that a program needs to orchestrate, including the selection of screen-eligible individuals, shared decision-making, LDCT performance and reporting, management of screen-detected findings, provision of smoking cessation guidance, and tracking compliance with annual screening.

The adoption of lung cancer screening in the United States is growing, but it remains low.[43] Programs should educate clinicians and the general public about the eligibility criteria for lung cancer screening. There are a spectrum of program designs ranging from decentralized to completely centralized. In decentralized programs the referring provider is responsible for all aspects of the individual's care, from identifying them as screening candidates, engaging in shared decision-making, managing the screening findings, assisting with smoking cessation, and ensuring compliance with annual screening. The screening program can develop and provide resources for the provider to assist with these tasks. In a centralized program, providers make a referral to the program, and the screening program is primarily responsible for most of these functions. The screening program communicates patient management plans with the referring provider.

Given that there are potential benefits and harms from lung cancer screening and that those eligible are by definition otherwise feeling well, it is important that programs engage in shared decision-making with those considering screening. In addition, a dedicated visit for shared decision-making is currently mandated by CMS before the baseline screen.[21] The goal of shared decision-making is to inform individuals about the tradeoffs of screening versus not screening and to help them make a choice that is aligned with their preferences and values. The visit is an opportunity for patients to learn about their individual risk of developing lung cancer and the potential benefits and harms from screening. There is no mandated format for the visit, and the most effective method has not been determined. Risk or benefit prediction calculators and decision aids are helpful tools.[44] The net benefit of screening varies based on the risk of developing lung cancer and the individual's other health issues. By understanding these variables it may be possible to shape the shared decision-making discussion based on the estimated net benefit of screening.

The LDCT scans should be acquired with the use of multidetector helical CT scanners with at least 16 detectors.[16] The acquisition variables should maintain a CT dose–volume index ≤3.0 mGy for average-size patients.[2] This leads to an average effective dose of 1.5 mSv, more than 5 times lower than the effective dose with diagnostic CT scans of the chest.

FUTURE DIRECTIONS

The emergence of lung cancer screening as standard of care represents a major advance in mitigating lung cancer mortality. There are opportunities to optimize the balance of benefits and harms of lung cancer screening. Doing so will allow for the expansion of eligibility, providing access to screening for more at risk individuals, and improving equity in the provision of this service. The incorporation of risk and benefit prediction tools into screen-eligibility criteria may help with this goal. Early-detection molecular biomarkers from a variety of sources have been studied including sputum, saliva, nasal and bronchial airway epithelial cells, exhaled breath, blood, and urine.[45] Advances in the development and validation of molecular biomarkers capable of identifying those at high risk of developing lung cancer, or those that have an early stage lung cancer, may improve the efficiency of candidate selection for screening, expand access to screening, and minimize the potential harms by accurately characterizing screen-detected nodules.[45]

Automated systems using artificial intelligence (AI) may increasingly assist in the management of lung nodules detected by screening. Commercially available software is already in clinical use for automated nodule detection and size measurement.[46] AI tools help radiologists identify more nodules and improve the efficiency of reading scans.[47] These tools may assist with high-quality image interpretation in areas where well-trained radiologists are scarce. In addition to detection and measurement, advances have been made in nodule characterization and risk classification. A deep learning algorithm with an end-to-end approach with both detection and lung cancer risk categorization showed promising results, with the potential to reduce false-positive and false-negative results compared with radiologists.[48] Population health management systems will assist with results tracking and the ability of programs to track and encourage compliance with screening recommendations. Advances in shared decision-making processes, smoking cessation assistance, and the expansion of access to high-quality screening programs will improve access to screening that optimizes the net benefit for individuals and for the population.

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CHAPTER 110

Approach to the Patient with Pulmonary Nodules

Moiz Salahuddin
David E. Ost

INTRODUCTION

The radiographic finding of a pulmonary nodule, formerly known as a *coin lesion*, has long challenged the clinician. At the heart of the dilemma, the question remains unchanged: "Is it malignant or benign?" When faced with a pulmonary nodule, the clinician and the patient usually have one of three choices: (1) observe it with serial chest computed tomography (CT), (2) perform additional diagnostic tests, or (3) remove it surgically.

The proper choice depends on epidemiology, radiographic appearance, assessment of surgical risk, and patient preferences. For malignant lesions, early surgical resection still represents the best chance for cure. On the other hand, unnecessary resection of benign nodules exposes patients to the morbidity and mortality of a surgical procedure. The aim of this chapter is to review what is known about the pulmonary nodule to formulate a diagnostic approach to this often controversial problem. The goal will be to arrive at a systematic approach that will promptly identify and bring to surgery all patients with operable malignant nodules while avoiding thoracotomy in patients with benign nodules. To do this, we need to have a clear definition of pulmonary nodules, information on their incidence and prevalence, the causes of malignant and benign nodules, the available imaging techniques, a method of estimating the probability of cancer, the strengths and weakness of serial CT imaging versus different biopsy techniques, and the impact of surgical risk and comorbidities on diagnostic strategies. These various considerations can then be integrated into an algorithm providing a unified approach to diagnosis and management.

DEFINITION

Pulmonary nodules should be characterized on the basis of number, size, and density as determined by CT. A solitary pulmonary nodule is defined as a single discrete pulmonary opacity that is surrounded by normal lung tissue that is not associated with adenopathy or atelectasis.[1,2] Previously there was controversy as to what constituted the upper size limit for defining a solitary pulmonary nodule. Some early series included lesions up to 6 cm in size.[3,4] However, it is now recognized that lesions larger than 3 cm are almost always malignant, so current convention is that solitary pulmonary nodules must be 3 cm or less in diameter.[5–7] Larger lesions should be referred to as pulmonary masses and should be managed with the understanding that they are most likely malignant; prompt diagnosis and resection is usually advisable.[7]

The term *solitary pulmonary nodule* was originally used when most nodules were detected incidentally by chest radiography. Today, most nodules are detected by CT, which greatly enhances nodule detection and characterization. However, we now recognize that many nodules that would have been characterized previously as "solitary" by chest radiograph are actually not solitary, since there may be other small nodules present. Thus, the classic definition of pulmonary nodules needs to be revised to take into account data from more recent CT-based studies.[1,7] As such, the term *solitary* should not be used for nodules accompanied by additional nodules or associated findings, or for nodules not completely surrounded by aerated lung.

CT has also increased awareness of subcentimeter nodules, which are defined as those ≤8 mm in diameter.[1,8–10] Subcentimeter nodules may be spherical or nonspherical, and malignant nodules may have either shape.[10] CT has also led to a more precise and nuanced classification of nodules according to their density. Nodules may have a pure solid appearance, a pure ground-glass appearance, or a mixed ground-glass and solid appearance. These characteristics can be used to help estimate the probability of cancer in the nodule.

INCIDENCE AND PREVALENCE

The incidence of pulmonary nodules and the probability of malignancy in those nodules vary widely, depending on the patient population; thus, many case series may not be directly comparable. This is a critical distinction when reviewing the literature. It is essential, therefore, to consider the clinical context that led to nodule detection. Surgical case series, in which the denominator consists entirely of resected lung nodules, have a much higher prevalence of malignancy compared with studies that include all nodules detected by chest radiograph or CT. Note that the prevalence of cancer seen in these surgical case series is not the same as the pretest probability of cancer for a newly identified lung nodule. Cancer prevalence in surgical series is high because the population being studied consists entirely of patients in whom the clinical suspicion of cancer based on prior testing has been deemed high enough to warrant the risk of surgery. Nodules unlikely to be malignant tend to be excluded from surgical case series. Given these limitations, surgical case series data can still be useful to gain insight into the factors that impact the probability of cancer.

The frequency with which a pulmonary nodule is identified on chest radiography is on the order of 1 to 2 per 1000 chest radiographs.[11] Most of these are clinically silent, and about 90% are noted as an incidental finding on radiographic examination. Younger patients from areas where granulomatous diseases such as tuberculosis, histoplasmosis, and coccidioidomycosis are endemic can be expected to have a lower malignancy rate. In an Air Force Medical Center study from Illinois of 137 patients, only 22 (16%) had a malignancy.[12] Granulomas were diagnosed in 103 (75%) patients; 53 of them were attributable to histoplasmosis endemic to the area. Most of these patients (77%) were under age 45, and no malignant nodules were diagnosed in patients less than 35 years of age. This series predated the use of chest CT.

Importantly, the incidence of nodules and the probability of malignancy in the nodules are very different in more recent studies of low-dose CT screening for lung cancer among high-risk patients than in surgical case series. The prevalence of noncalcified nodules in observational studies of low-dose CT screening ranges from 13% to 51%.[13–15] Among nodules that are identified on the first screening study, the prevalence of cancer ranges from 3% to 12%.[16] On follow-up CT imaging of the same population (i.e., incidence screens), the probability of new noncalcified nodules has varied widely, from 2.5% to 13%. The probability of cancer in these incidence nodules has varied from 5% to 23%.

MALIGNANT PULMONARY NODULES

Risk factors for malignancy have been identified from studies of pulmonary nodules and include patient age, smoking history, nodule size, and prior history of malignancy. Age is one of the most consistent risk factors. In a series of 370 resected indeterminate solitary pulmonary nodules, the incidence of malignancy increased from 63% for patients age 45 to 54 to 74% for ages 54 to 64 and continued to rise with age to 96% for those above the age of 75.[17] Since this was a surgical case series, in which the denominator consists of resected lung nodules, the prevalence of malignancy is much higher compared with studies of nodules detected by chest radiograph or during lung cancer screening. These findings correlate with those of previous studies, which also show that malignancy is very rarely found in patients under the age of 35.[12,18,19]

Smoking is closely correlated with the development of lung cancer, particularly squamous and small cell carcinoma. The Surgeon General's report of 1964 and subsequent studies have demonstrated that the risk of lung cancer increases with the duration of smoking and the number of cigarettes smoked. Average smokers have about a 10-fold risk and heavy smokers a 20-fold risk of developing lung cancer when compared with nonsmokers. Smoking is responsible for about 85% of the cases of bronchogenic carcinoma. Cessation of smoking will reduce this risk after 10 to 20 years, but it now appears that former smokers have a slightly higher risk of cancer throughout their lifetimes.

Nodule size is closely correlated to risk of malignancy. Several series have demonstrated an increased incidence of malignancy with increasing nodule size. Lesions larger than 3 cm (i.e., pulmonary masses) will be malignant 80% to 99% of the time. In seven studies of nodules detected in lung cancer screening trials, the prevalence of malignancy was 0% to 1% in patients with nodules <5 mm in diameter, 6% to 28% for 5- to 10-mm nodules, 33% to 64% for 11- to 20-mm nodules, and 64% to 82% for nodules measuring >20 mm.[12,17,20–23]

Primary bronchogenic carcinoma is the most common malignant tumor that presents as a pulmonary nodule.[5,17,21,24] Histologically, adenocarcinoma and squamous cell carcinoma make up the majority; of the two, adenocarcinoma is the more common (Table 110-1). Of note, tumors that used to be called bronchioloalveolar cell carcinoma (BAC) have now been reclassified and the term *adenocarcinoma in situ* is used for BAC tumors once they have been confirmed by surgical resection. Small-cell carcinoma presenting as a solitary pulmonary nodule is rare. Other rare primary lung tumors that may present as solitary pulmonary nodules are bronchial carcinoids, lymphomas, hemangioendotheliomas, and sarcomas.

Metastases may present as solitary pulmonary nodules in patients who have known primary malignancies or in whom the presence of primary malignancy is unknown. In up to 40% of such patients, who manifest only a single nodule on chest radiograph, CT scan may show other nodules that are not disclosed by plain chest radiograph.[25,26] Even though a lesion is solitary, 33% to 95% of nodules in patients with an established diagnosis of cancer will be malignant.[27–31] The most common histologic types of metastatic nodules are adenocarcinomas of the colon, breast, and kidney; head and neck tumors; sarcoma; and melanoma. Because of the high likelihood of malignancy, a nodule in a patient with an established diagnosis of cancer should be treated differently from other solitary nodules. Assuming no other obvious metastatic spread, one should consider proceeding directly to biopsy. Even in the presence of a known lung cancer, some of these nodules may represent a second primary pulmonary malignancy that is similar in histologic appearance. Immunohistochemistry and other confirmatory marker studies may be indicated to determine the nature of the nodule. A solitary pulmonary nodule in a patient with a history of solid organ malignancy should be considered for resection as long as there is no other evidence of recurrent or metastatic disease.

BENIGN PULMONARY NODULES

Benign pulmonary nodules are more common in the young and in nonsmokers. Causes include benign tumors such as hamartomas, both infectious and noninfectious granulomas, vascular lesions, and rare miscellaneous conditions (Table 110-1).

TABLE 110-1 Differential Diagnosis of Solitary Pulmonary Nodules

Malignant Tumors
- Bronchogenic carcinoma (adenocarcinoma, large cell, squamous, small cell)
- Carcinoid
- Pulmonary lymphoma
- Pulmonary sarcoma
- Plasmacytoma
- Solitary metastases (colon, breast, kidney, head and neck, germ cell, sarcoma, thyroid, melanoma, others)

Benign Tumors
- Hamartoma
- Adenoma
- Lipoma

Infectious Granulomas
- Tuberculosis
- Histoplasmosis
- Coccidioidomycosis
- Mycetoma
- Ascaris
- Echinococcal cyst
- Dirofilariasis (dog heartworm)

Noninfectious Granulomas
- Rheumatoid arthritis
- Granulomatosis with polyangiitis (formerly known as Wegener granulomatosis)
- Sarcoidosis
- Paraffinoma
- Others

Miscellaneous
- Bronchiolitis obliterans organizing pneumonia
- Abscess
- Silicosis
- Fibrosis/scar
- Hematoma
- Pseudotumor
- Spherical pneumonia
- Pulmonary infarction
- Arteriovenous malformation
- Bronchogenic cyst
- Amyloidoma

Hamartomas are the most common benign tumors presenting as solitary pulmonary nodules. They are believed to be developmental malformations composed mainly of cartilage, fibromyxoid stroma, and adipose tissue. A review of 6 series with 3802 resected solitary pulmonary nodules found that 5% were hamartomas.[12,17,19,32–34] In a series of 215 hamartomas resected at the Mayo Clinic, the peak incidence was in the seventh decade of life; male-to-female ratio was 1:1; and the average size was 1.5 cm, although some were as large as 6 cm.[35] Most hamartomas were asymptomatic (97%), and 17% were noted to grow slowly on serial radiographic examination. They may be identified radiographically by a pattern of "popcorn" calcification, which is often intermixed with areas of low attenuation on CT

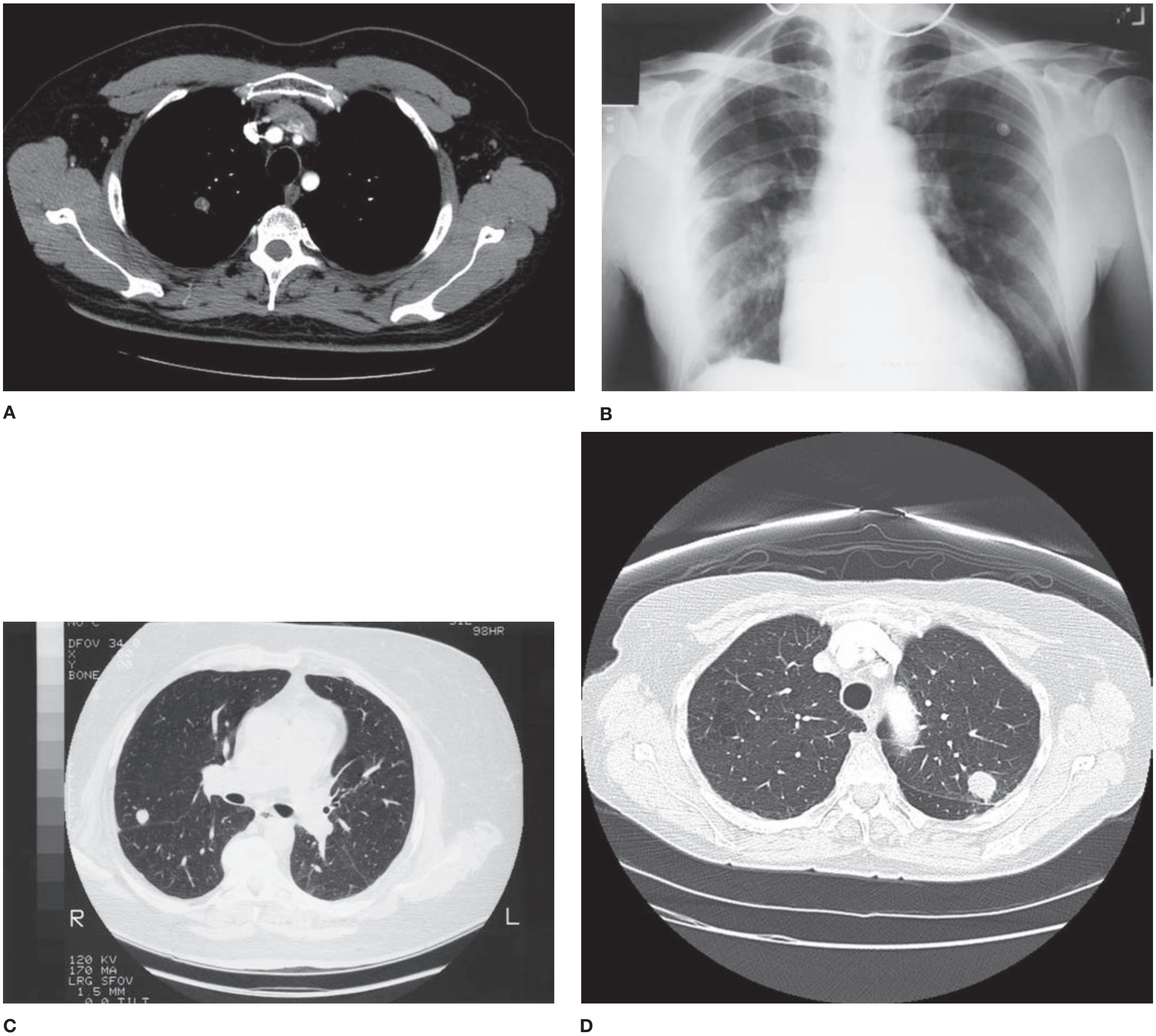

Figure 110-1 Benign pulmonary nodules and their radiographic patterns: **A.** Hamartoma with fat density within the nodule. **B.** Pseudotumor due to fluid in a fissure, the result of both pleural disease and fluid overload, has the appearance of a pulmonary mass. **C.** Noncontrast CT shows a round 1-cm nodule, with relatively high radiographic density, proven on resection to be a granuloma. **D.** Nodule with smooth border, diagnosis histoplasmosis.

scan representing fat deposits within the nodule. CT appearance is diagnostic in about 50% of hamartomas, with the finding of fat attenuation between −40 to −120 Hounsfield units (Fig. 110-1).[36]

Infectious granulomas make up more than 90% of all benign nodules. They arise as a result of healing after infection from a variety of organisms. The offending agents will vary, depending on geographic location. Among the most common causes are histoplasmosis, coccidioidomycosis, and tuberculosis. Other, less common infectious causes of infectious granulomas are dirofilariasis (dog heartworm), mycetoma, echinococcal cyst, and ascariasis. A history of exposure is important in establishing a possible infectious origin. Clues such as tuberculosis exposure history and skin test results, prior travel history, places of residence, occupation, and pets may be invaluable in some instances.

A variety of inflammatory diseases can also cause benign pulmonary nodules. Noninfectious granulomas sometimes present as pulmonary nodules in systemic diseases such as sarcoidosis, in which nodules are not invariably accompanied by hilar adenopathy. Necrobiotic nodules are pulmonary nodules with granulomatous inflammation and central necrosis on histopathology. These nodules can be seen in patients with active rheumatoid arthritis and inflammatory bowel disease. In rheumatoid arthritis, patients may also have concurrent subcutaneous nodules. Granulomatosis with polyangiitis (formerly known as Wegener granulomatosis) can also present with pulmonary nodules, which are often cavitary. In such cases there are usually multiple nodules and there may be concurrent renal or sinus disease.

Miscellaneous causes of benign pulmonary nodules include rounded pneumonia, pseudotumor (which represents fluid in an interlobar fissure) (Fig. 110-1), hematomas after thoracic trauma or surgery, and fibrosis or scars resulting from the resolution of infectious or inflammatory process. Rarer conditions presenting as pulmonary nodules include silicosis, bronchogenic cyst, amyloidosis, pulmonary infarct, and arteriovenous malformations.

Arteriovenous malformations may grow slowly and have a characteristic appearance on contrast-enhanced CT scan, with identification of afferent and efferent vessels emanating from and heading toward the hilum, respectively.

IMAGING TECHNIQUES

Imaging techniques are often helpful in distinguishing benign from malignant causes of pulmonary nodules, and as such they play a key role in their evaluation and management. During the last decade, rapid advances in both CT and positron emission tomography (PET) have dramatically changed the diagnostic approach to pulmonary nodules. However, this does not mean that these techniques should be used indiscriminately. Cost-effective strategies to manage pulmonary nodules require that we understand the performance characteristics, strengths, and weaknesses of each of these technologies, so that they can be applied properly.[37] The primary technologies that need to be considered are plain chest radiography, CT, and PET (Chapter 28).

■ Plain Chest Radiography

Many pulmonary nodules are discovered on routine plain chest radiograph while asymptomatic. Nodules are usually identifiable on chest radiograph by the time they are 0.8 to 1 cm in diameter, although nodules 0.5 to 0.6 cm can occasionally be seen.[11] Most will be identified on posteroanterior (PA) projection, but some will be seen only on lateral projection, so standard PA and lateral chest radiography should be obtained whenever possible. When a nodule can be seen only on one projection, the clinician should question whether it is truly in the lung parenchyma. Structures overlying the lungs, such as leads used for cardiac monitoring, nipple shadows, breast calcifications, skin lesions, and rib lesions can all mimic a pulmonary nodule, as can pulmonary vessels viewed end-on. If in doubt, a CT should be obtained. Once it has been ascertained that a true nodule exists, the first step is to make every effort to obtain previous radiographs for comparison. A solid nodule that has remained stable with no increase in size for 2 years by CT is very likely benign and warrants no further investigation. Similarly, a nodule that was not present on a comparable radiograph within the past 2 months is unlikely to be malignant, having grown so rapidly.

■ Computed Tomography

Chest CT should be part of the evaluation of all lung nodules, either alone or as part of a combined PET-CT. As with chest radiography, comparison with prior CT imaging is critical, since it can provide an estimate of the growth rate over time. CT can pinpoint the exact location of the nodule and provide three-dimensional images of the lesion. Thin-section high-resolution CT can better define the borders and the nodule's relation to adjacent structures, such as vessels and the pleura.[23,38] CT is also more sensitive than standard chest radiographs in detecting calcifications and can quantify calcification in nodules even when they are not readily visible to the naked eye.[23,39] Nodules with higher radiographic density are more likely to be benign (Fig. 110-1).

Calcification is generally an indication of benignity in a pulmonary nodule. Infectious granulomas tend to calcify with central, diffuse, or stippled patterns (Fig. 110-2). Laminar or concentric calcification is characteristic of granulomas caused by histoplasmosis. A popcorn calcification pattern is typically seen in hamartomas and when coupled with fat density within the same nodule is highly specific. Calcification is seen in 6% to 14% of malignant nodules, with a punctate or eccentric pattern. Benign patterns of calcification (central, diffuse, laminar, or popcorn) are very rare in malignant nodules. In one study of 1267 solitary pulmonary nodules, only 7 malignant nodules (0.6%) had a benign calcification pattern.[40] Most nodules with a benign calcification pattern can be observed with serial CT scans.

The edge characteristics of nodules can also offer insight into whether or not a lesion is malignant. Benign lesions are often well circumscribed with a round appearance, whereas malignant nodules tend to have irregular or lobulated borders (Fig. 110-3). CT imaging characteristics that suggest malignancy include spiculated margins (likelihood ratio [LR], 5.5)[23,24,38] and pleural retraction (LR, 1.9). Lobulated margins (LR, 1.1) are associated with malignancy, but the predictive value is low.[41] Other patterns that have been reported to be associated with malignancy include vascular convergence (presence of vessels abnormally angled toward the nodule),[42] a dilated bronchus leading into the nodule,[43] pseudocavitation ("bubbly" appearance thought to represent air bronchiolograms),[38] and true cavitation associated with a thick and irregular wall.[44] Squamous cell cancers can lead to a cavitary pulmonary nodule. Up to 95% of cavitary nodules with a wall thickness greater than 15 mm are malignant, and 92% of cavitary nodules with a wall thickness less than 5 mm are benign.[45] However, none of these radiographic signs is entirely specific for malignancy. Malignancy is somewhat less likely if an air bronchus sign is present although its predictive value is low. An air-bronchus sign can be seen in primary pulmonary lymphoma, but this is a very rare disease, accounting for less than

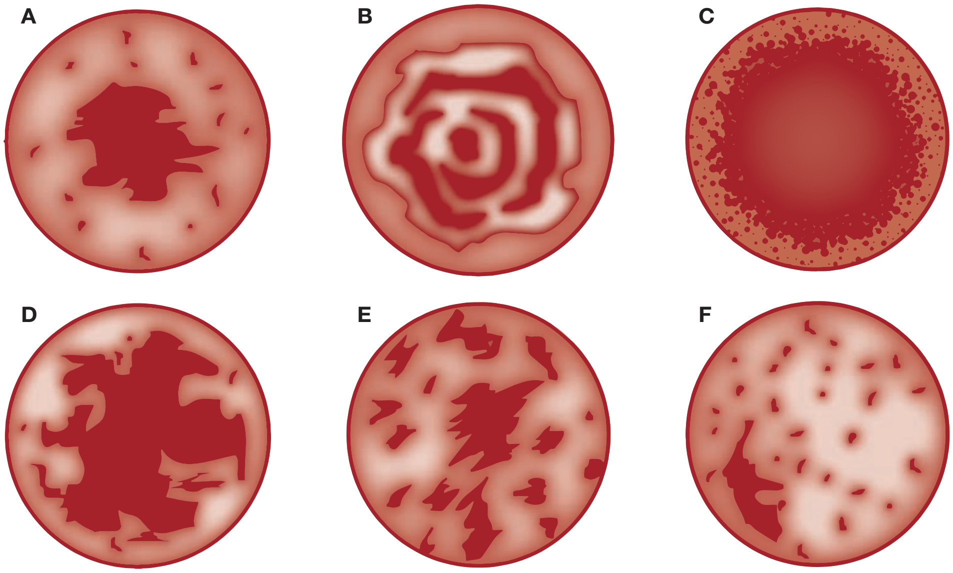

Figure 110-2 Patterns of calcification in nodules. **A.** Central. **B.** Laminated. **C.** Diffuse. **D.** Popcorn. **E.** Stippled. **F.** Eccentric. Patterns A, B, C, and D generally indicate a benign process; E and F suggest malignancy. *(Data from Lillington GA. Management of solitary pulmonary nodules. Dis Mon. 1991;37(5):271–318.)*

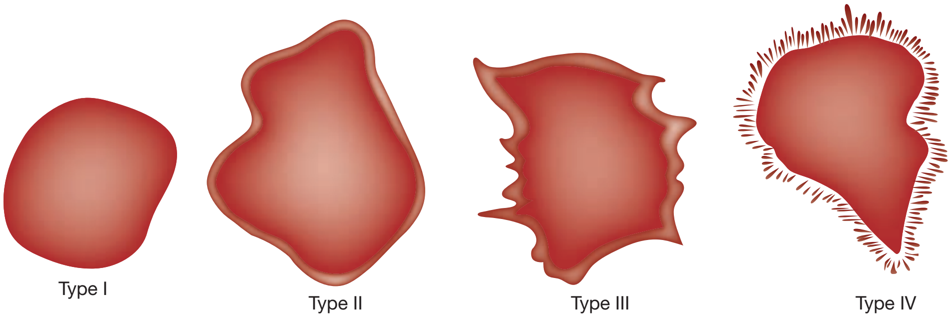

Figure 110-3 Characteristic appearance of nodule edges. Type I is sharp and smooth, type II is lobulated, type III has irregular undulations, and type IV is grossly irregular with many spiculations. *(Data from Siegelman SS, Khouri NF, Leo FP, et al. Solitary pulmonary nodules: CT assessment. Radiology. 1986;160(2):307–312.)*

1% of all lung cancers. Malignancy is much less likely if a nodule has smooth or polygonal margins (LR, 0.2).[46]

Rapid advances in CT technology have also led to more precise characterization of the density of lung nodules. It is now appreciated that nodules may be characterized as solid, partly solid, or pure ground-glass opacities (defined as focal densities in which underlying lung morphology is preserved) (Fig. 110-4). This is particularly useful for categorizing small nodules (<1 cm) since these categories can help to distinguish benign from malignant nodules. The percentage of pure ground-glass opacities that are malignant varies significantly in the literature, from 18% to almost 60%.[47–49] For subcentimeter nodules, the likelihood of malignancy is similarly high in partly solid lesions, but much lower (<10%) in solid nodules.[47,49]

Ground-glass nodules may represent either atypical adenomatous hyperplasia (AAH) or adenocarcinoma in situ (formerly BAC).[42,50–56] In contrast, partly solid or solid nodules usually represent adenocarcinoma but can also be caused by squamous cell carcinoma or small cell carcinoma. When pure ground-glass opacities start to grow and become more solid, demonstrating a replacement growth pattern, this should be considered highly suspicious for adenocarcinoma.[1,57,58] Of note, observed growth rates are often very slow for malignant ground-glass opacities, intermediate for partly solid nodules, and relatively fast for solid nodules.[59]

The superior resolution of multidetector scanners has also facilitated the development of volumetric CT. Volumetric CT may allow growing lesions to be identified earlier than conventional transverse CT. Preliminary studies demonstrated that three-dimensional volume analysis enabled tumor growth to be detected in 5-mm diameter nodules as early as 30 days after the initial CT.[60,61] Volumetric CT was successfully used to guide evaluation of small lung nodules in the NELSON trial.[8,62] In that trial, the investigators used serial volumetric CT measurements to calculate the doubling time of indeterminate lung nodules. CT volume doubling time of <400 days or a new solid component in a previously nonsolid nodule was defined as positive.[8] Follow-up imaging could detect growth as early as 6 weeks after imaging of an indeterminate nodule. The second-round screening to detect lung cancer had a sensitivity of 96.4%, specificity of 99.0%, positive predictive value of 42.2%, and negative predictive value of 99.9%.

A complementary technique is dynamic CT, which uses iodinated IV contrast to look for enhancement of nodules.[63] Although malignant nodules enhance more than benign ones, benign lesions, such as hamartomas and tuberculomas, also may enhance. Median sensitivity and specificity for detecting malignant nodules from seven studies in a systematic review were 96% and 75%, respectively.[20,63–69] In a multicenter trial using dynamic CT, the negative predictive

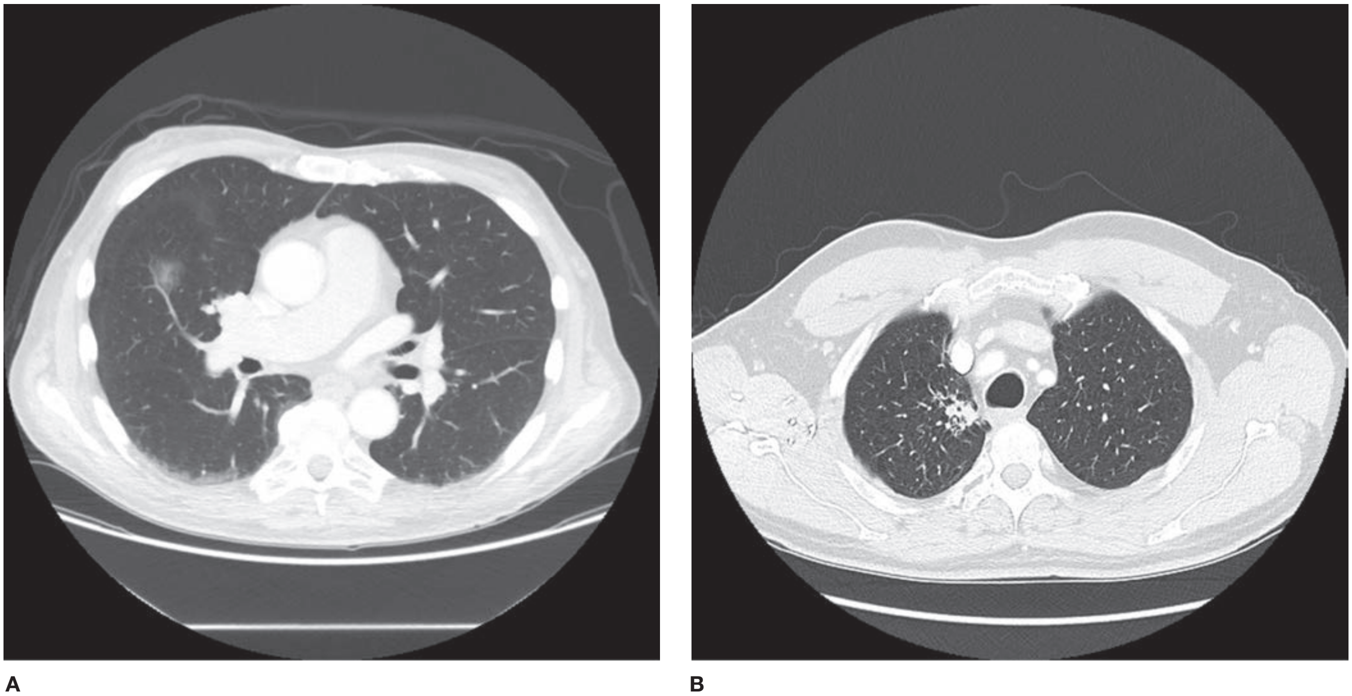

Figure 110-4 Malignant nodules with different densities and borders: **A.** Ground-glass nodule, right middle lobe, diagnosis adenocarcinoma in situ. **B.** Air bronchogram with semisolid nodule, diagnosis adenocarcinoma. *(continued)*

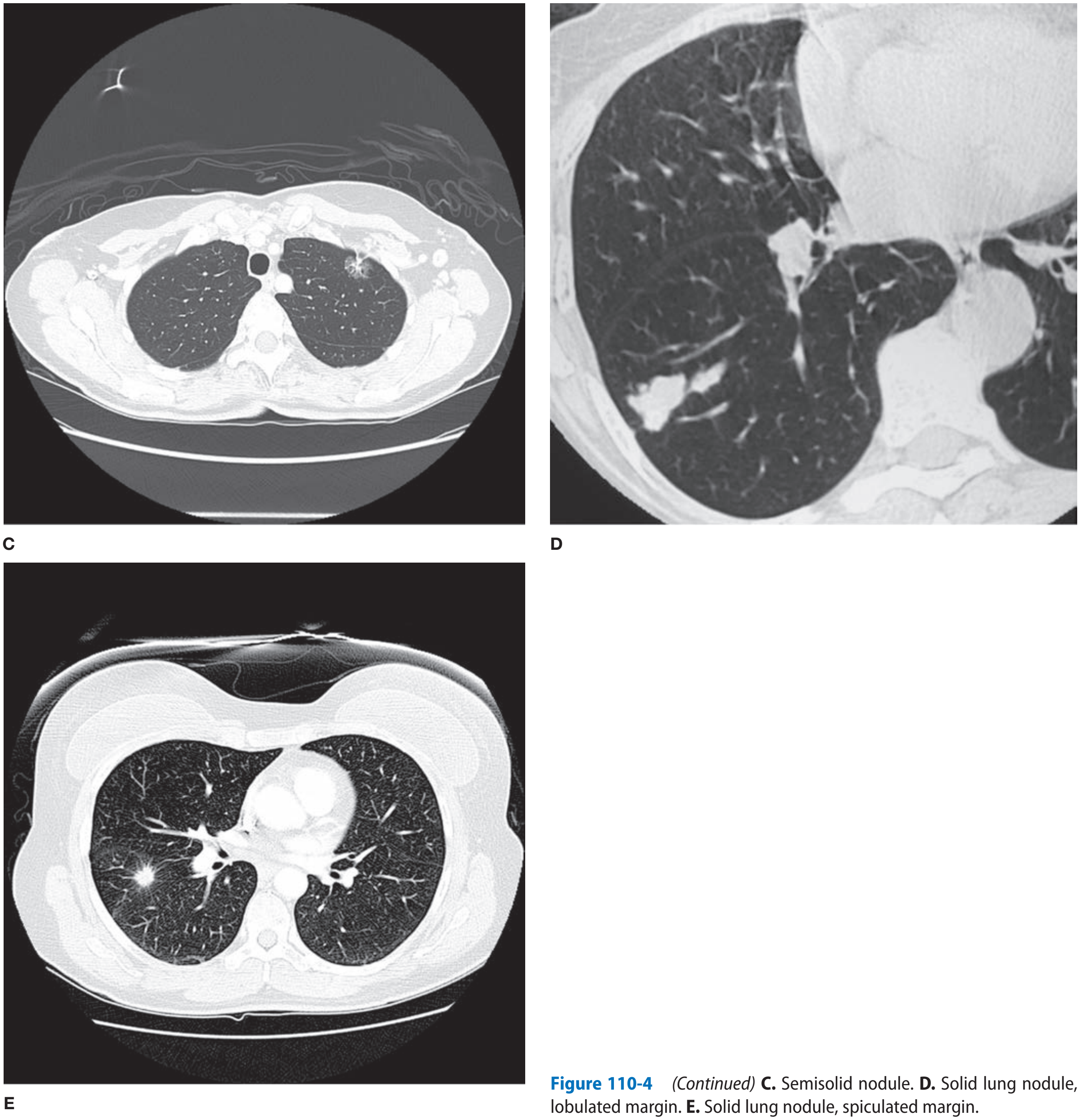

Figure 110-4 *(Continued)* **C.** Semisolid nodule. **D.** Solid lung nodule, lobulated margin. **E.** Solid lung nodule, spiculated margin.

value was 97%. However, lack of specificity has limited the utility of this test, since it cannot reliably distinguish between malignant and active inflammatory or infectious nodules. As a result, few centers at the present time are using this approach.

■ Positron Emission Tomography (PET)

PET can be used to help differentiate between malignant and benign nodules. PET takes advantage of the fact that tumor cells have increased glucose uptake and metabolism. A D-glucose analogue labeled with a positron-emitting fluorine-18 radioisotope (FDG) is injected into the patient, and uptake by the nodule is then measured. Malignant nodules have a higher uptake of FDG. Sensitivity of PET in systematic reviews has ranged from 87% to 95%.[2,61,70] Integrated PET-CT scanners combine the CT and FDG imaging gantry, allowing more precise anatomic localization of areas of FDG uptake than dedicated PET imaging alone.[71–73] PET imaging also provides useful information regarding lung cancer staging, since it will occasionally detect unsuspected regional lymph node and distant metastases.[74]

It is important to recognize that most studies of PET have used a single threshold level for discriminating malignant from benign nodules, typically a standard uptake value (SUV) of 2.5.[2,74] However, PET images actually provide a range of possible results, depending on the amount of uptake in the nodule compared with that of the mediastinal blood pool. In a study of 344 patients undergoing PET-CT, the likelihood ratios for benign, probably benign, indeterminate, probably malignant, and definitely malignant were 0.03, 0.15, 1.01, 3.2, and 9.9, respectively.[75] When FDG uptake was slightly greater than the mediastinal blood pool, this was considered as probably malignant. Substantially greater uptake was considered as definitely malignant. Indeterminate readings were rare (1%). This study suggests that greater FDG uptake is more strongly associated with malignancy. Clinically, the implication is that physicians should not only consider whether a PET scan is positive, but also consider the degree of FDG uptake when estimating the posterior probability of disease after PET imaging.[76]

PET appears to be less sensitive for lesions less than 8 mm in size, so its use should be limited to those lesions ≥8 mm in size.[2,77] While there is limited preliminary evidence that PET may be useful for lesions less than 8 mm in size, there are still too many false negatives reported to make PET useful for smaller lesions outside of a clinical trial at the current time.[78–80] False-negative findings have also been seen in patients with minimally invasive adenocarcinoma, adenocarcinoma in situ, mucinous adenocarcinomas, and carcinoids.[80,81] In one study, 18% of PET-negative solid pulmonary nodules were ultimately found to be malignant at an average of 37.6 months following detection.[82] On the other hand, false-positive results have been seen in patients with granulomatous infections, such as tuberculosis, atypical mycobacterial disease, and endemic mycoses, as well as in patients with inflammatory conditions, such as rheumatoid arthritis and sarcoidosis.[83,84] Because false-negative results can also be caused by uncontrolled hyperglycemia, blood glucose levels should be <200 mg/dL immediately prior to performing the PET scan.[85]

DISTINGUISHING BETWEEN BENIGN AND MALIGNANT NODULES

Important elements in the diagnostic approach in distinguishing benign from malignant nodules are considered below.

Estimating Probability of Malignancy

Epidemiology, knowledge of the different causes of malignant and benign nodules, and the imaging characteristics of the nodule all serve to inform the physician as to the probability of malignancy in a given nodule. While physicians often estimate pretest probability of cancer intuitively, several investigators have attempted to develop mathematical models to estimate the probability of malignancy of indeterminate pulmonary nodules.[86–89] Using clinical and radiographic characteristics of malignancy derived from the literature, these authors have analyzed some combination of the following risk factors by Bayesian, neural network, and other methods to obtain a mathematical estimate of the probability of malignancy: nodule size, location, growth rate, margin characteristics, older age, smoking history, prevalence of malignancy in the community, prior history of malignancy, interstitial lung disease, emphysema, and occult calcification on CT densitometry.[86–88,90–94] Calculators for pretest probability of malignancy have been designed where patient-specific risk factors are incorporated and a numeric probability of malignancy is obtained. The commonly used calculators are the Brock model, the VA model, and the Mayo clinic model. These calculators can help to quantify the probability of malignancy. However, these models may overestimate or underestimate the risk of malignancy when applied to other populations.[95] Other studies have shown that calculator predictions may be similar to expert clinical judgement.[96,97] These models inform and supplement decision-making but are not a substitute for clinical judgement.[96]

Assessment of the pretest probability of malignancy is central to optimal strategy selection when managing pulmonary nodules.[1,2,37,57,98] While these formulas and neural networks may lack precision on an individual patient level, they can serve to inform decision making as to what risk factors to pay attention to and how important they are relative to each other.[5] Risk factors associated with a low probability of malignancy include diameter less than 1.5 cm, age less than 45 years, absence of tobacco use, having quit for 7 or more years, and a smooth appearance on radiographic imaging. Risk factors associated with a moderately increased risk of malignancy include diameter 1.5 to 2.2 cm, age 45 to 59, smoking up to 20 cigarettes per day or being a former smoker within the last 7 years, and a scalloped edge appearance on radiography. Risk factors associated with a high risk of malignancy include a diameter of 2.3 cm or greater, age greater than 60 years, being a current smoker of more than 20 cigarettes per day, a history of prior cancer, and a corona radiata or spiculated appearance on radiography.[4,5,90,99–101]

After consideration of these risk factors and, possibly, use of one of the validated models to arrive at an estimate of the pretest probability of malignancy, physicians must then choose between alternative strategies. The main alternatives are (1) careful observation with serial CT imaging, (2) diagnostic testing with molecular assays or CT-guided biopsy or bronchoscopy, or (3) surgery. The results of each strategy help to further refine the probability of malignancy, either up or down. As such, it is important to consider the strengths and weaknesses of each of these approaches.

Careful Observation with Serial CT Imaging

Careful observation with serial CT is predicated on the ability of the imaging technology to detect nodule growth. The fundamental assumption is that by comparing serial images over time a nodule's growth rate can be determined, and this in turn can be used to help distinguish between benign and malignant nodules. Squamous and large-cell tumors have an average doubling time (i.e., the time for a nodule to double in volume) of 60 to 80 days. Adenocarcinomas double at about 120 days, and the rare small-cell carcinoma that presents as a solitary pulmonary nodule can have a doubling time of less than 30 days.[27] A nodule that has doubled in weeks to months is probably malignant and should be removed when possible.[5] Benign nodules have doubling times of less than 20 days or more than 400 days. A nodule that doubles in size in less than 20 days is usually the result of an acute infectious or inflammatory process, while those that grow very slowly are usually chronic granulomatous reactions or hamartomas. Nodules with doubling times of more than 400 days can be observed with serial radiographs.[1,2,5] This is the basis for the clinical axiom that 2-year radiographic stability is strong presumptive evidence that a solid nodule is benign.

It should be noted that controversy remains regarding how long follow-up should be continued. While traditional teaching has recommended observing lesions for a maximum of 2 years, it is now recognized that for some lesions longer follow-up may be warranted. Long doubling times have been observed in malignant lesions that presented as ground-glass nodules or as partially solid nodules.[50,55,59] Due to the concern for adenocarcinoma in situ in subsolid nodules, the recommendation is for them to be followed for up to 5 years with CT imaging.[102] The NELSON trial showed that the likelihood of malignancy in subsolid nodules is 6%; in all instances, they were stage 1 adenocarcinomas in situ.[103] However, for most solid nodules, 2 years of follow-up without evidence of growth is sufficiently long to warrant discontinuation of CT imaging.

Determination of nodule growth is based on the assumption that nodules are more or less spherical. Growth of a sphere must be considered in three-dimensional volume, not in two-dimensional diameter. The formula for volume of a sphere is $4/3(\pi)r^3$, or $1/6(\pi)d^3$, where $r =$ radius and $d =$ diameter. A nodule originally 1 cm in diameter whose diameter is now 1.3 cm has actually more than doubled in volume. Similarly, a 2-cm nodule has doubled in volume by the time its diameter reaches 2.5 cm. A nodule that has doubled in diameter has undergone an eightfold increase in volume. When old radiographs are available, growth rate and nodule doubling time can be estimated. If the diameter of a nodule is measured at two different points in time (first t1 and later at t2), then doubling time in days $= (t \times \log 2)/[3 \times \log (d2/d1)]$. In this formula, t is the number of days between t2 and t1; d1 and d2 are the diameters of the nodule at times t1 and t2, respectively. It is therefore critical that old radiographs and CT scans be obtained for comparison when evaluating pulmonary nodules, since they can provide valuable insights into the doubling time and natural history of the nodule.

Accepting the assumption that a tumor arises from serial doublings of a single cancerous cell, we can estimate that it will take 27 doublings for it to reach 0.5 cm. By the time a nodule is 1 cm in diameter, it represents 30 doubling times and about 1 billion tumor cells. Depending on the exact growth rate, this theoretical 1-cm nodule has probably existed for years before it is detected, as malignant bronchogenic tumors have doubling times estimated at between 20 and 400 days. The natural history of a tumor usually spans about 40 doublings, whereupon the tumor is 10 cm in diameter and the patient has usually died.[104]

Nodule growth rate and doubling times become clinically relevant when deciding how often to order follow-up imaging when observing a pulmonary nodule. The question often arises whether observing a pulmonary nodule for an extra 3 to 6 months increases the likelihood of metastatic disease, since that nodule has probably been growing for years. There is no convincing empiric evidence to support this hypothesis. Whether delays longer than 3 to 6 months are safe is unknown. However, estimating this risk is clinically relevant, since the optimal frequency of serial CT follow-up imaging to monitor nodules for growth is predicated on limiting this hazard of delay while containing costs and avoiding excessive radiation exposure.

The ability to detect nodule growth is a function of image resolution. CT imaging greatly improved the ability to detect nodule growth compared with conventional chest radiographs. This has made the careful observation strategy with serial imaging more effective, since it limits the hazard of delay by allowing earlier detection of growth. However, the accuracy of size measurements is still a problem when nodules are small. There is poor inter- and intraobserver variability when size differences of <1.5 mm are being assessed with two-dimensional (2D) CT.[105,106] As a result, 2D measurements of small nodules may not always be reliable. The presence of growth was incorrectly assessed in 27% to 37% of CT scan pairs when diameters or cross-sectional areas were used as compared to a reference standard of volumetric measurement.[2,107–109] Limited data suggest that volumetric measurements may provide a better alternative. When evaluated retrospectively, volumetric measurements using two CT scans performed a median of 3.7 months apart with a threshold volume doubling time >500 days were found to be 91% sensitive and 90% specific for malignancy. Another small study of predominantly solid nodules found that volumetric imaging changed management strategy in 10% of cases.[110] Volumetric imaging and doubling times were also used successfully to guide management in the NELSON lung cancer screening trial.[8] Unfortunately, volumetric measurement is time consuming and labor intensive and therefore has not yet become the standard of care.

Given this framework, it is reasonable to apply more recent expert consensus-based guidelines to help guide the frequency of follow-up CT imaging for the pulmonary nodule.[2,111,112] For follow-up studies, imaging should be performed without contrast with thin sections using low-dose techniques.[2] Where available, volumetric CT may further facilitate growth detection and limit the hazard of delay. In all cases patients should be informed about the potential benefits and harms including the hazard of delay versus the risks of unnecessary testing.

TABLE 110-3 Schedule for Conducting Serial CT Imaging on Non-Solid Nodules

	Nodules <6 mm (<100 mm^3)	Nodules >6 mm (>100 mm^3)
Single ground glass	No routine follow-up	CT 6–12 months, repeat every 2 years until 5 years have passed
Single partly solid	No routine follow-up	CT 3–6 months, then annual CT till year 5 if lesion unchanged
Multiple	CT 3–6 months, repeat at 2 years and 4 years if stable	CT 3–6 months, then management for most suspicious nodule

Data from MacMahon H, Naidich DP, Goo JM, et al. Guidelines for Management of Incidental Pulmonary Nodules Detected on CT Images: From the Fleischner Society 2017. Radiology. 2017;284(1):228–243.

Decisions about the frequency and duration of follow-up for patients with pulmonary nodules need to consider multiple dimensions of the problem, including clinical risk factors, nodule size, radiation dose, surgical risks, patient preferences, cost, and the limits of imaging technology resolution (especially at sizes less than 5 mm).[107,113,114] All of these can affect the optimal frequency of CT follow-up. The Fleischner society provides guidelines to standardize the management of these nodules. These guidelines were updated in 2017 and give recommendations on solid or subsolid pulmonary nodules found on CT chests with thin cuts (<1.5 mm). Solid pulmonary nodules are labelled as high-risk or low-risk and then divided into <6 mm, 6 to 8 mm, or >8 mm (Table 110-2), and the subsolid nodules are divided as <6 mm or >6 mm (Table 110-3). The main purposes of these guidelines are to standardize follow-up of pulmonary nodules and to decrease unnecessary CT imaging and use of resources.[102] The Fleischner guidelines do not include patients who are immunocompromised, who have known malignancies, or who are undergoing lung cancer screening.

The Lung CT Screening Reporting and Data System (LUNG-RADS) recommended by the American College of Radiology is the tool used to standardize imaging follow-up and management for pulmonary nodules in patients who undergo lung cancer screening. The classification assigns the nodule a category from 1 to 4 based on probability of malignancy, with category 1 being benign and category 4 being suspicious for malignancy. For lung cancer screening, a low-dose CT chest scan is indicated for screening of lung cancer for patients who are between ages 55 and 80, have a >30-pack-year smoking history, and are current smokers or quit <15 years ago. For patients identified with a solitary pulmonary nodule from a screening

TABLE 110-2 Schedule for Conducting Serial CT Imaging on Solid Nodules

	Nodules <6 mm (<100 mm^3)	Nodules 6–8 mm (100–250 mm^3)	Nodules >8 mm (>250 mm^3)
Single low risk	No routine follow-up	CT 6–12 months then repeat 18–24 months	CT at 3 months or PET/CT or tissue sampling
Single high risk	Optional CT at 12 months	CT 6–12 months then repeat 18–24 months	CT at 3 months or PET/CT or tissue sampling
Multiple low risk	No routine follow-up	CT 3–6 months then repeat 18–24 months	CT 3–6 months then repeat 18–24 months
Multiple high risk	Optional CT at 12 months	CT 3–6 months then repeat 18–24 months	CT 3–6 months then repeat 18–24 months

Data from MacMahon H, Naidich DP, Goo JM, et al. Guidelines for Management of Incidental Pulmonary Nodules Detected on CT Images: From the Fleischner Society 2017. Radiology. 2017;284(1):228–243.

low-dose CT, the chance of that nodule being malignant varies from 3.7% to 5.5%.[115] In the National Lung Cancer Screening trial, 24.2% of patients who underwent low-dose screening CT had a nodule, of which 11% underwent further invasive testing. Therefore, it is important that we screen, risk-stratify, and intervene on the appropriate patient population to reduce patient harm and improve outcomes (Table 110-4).

In patients with a solid indeterminate nodule or a part-solid, part ground-glass nodule that shows evidence of growth on serial imaging, a nonsurgical biopsy or surgical resection should be considered. Similarly, any patient with a pure ground-glass nodule that grows or develops a solid component should have a nonsurgical biopsy or surgical resection. If a nonsurgical biopsy is chosen, then either a specific benign diagnosis (e.g., hamartoma) or a diagnosis of malignancy must be made. If the biopsy is nonspecific (e.g., inflammation), then surgical resection should be considered.

■ Molecular Tests

For patients who are at low to intermediate risk (pretest probability of cancer $\leq$50%), proteomics may be used to inform the decision on whether to follow a serial CT strategy or to proceed to a nonsurgical biopsy of some type. Based on the PANOPTIC study, a venous blood sample can measure the relative abundance of two plasma proteins (LG3BP and C163A). The ratio of these proteins is determined and combined into a model with five clinical/imaging factors (age, smoking status, nodule size, edge characteristics, and location) to generate a risk classifier. In the PANOPTIC trial, patients who had a likely benign result had a 98% probability of not having cancer. In select patients with a pretest probability $\leq$50% in which this test demonstrates a likely benign etiology, serial CT imaging may be the best strategy. Conversely, an indeterminate result from the test suggests that a nonsurgical biopsy be pursued.[116] However, there has only been one study so far to validate these findings, so these results should be interpreted cautiously. Other blood biomarkers are being evaluated and may have a role to play in the management of pulmonary nodules in the future. Another tool that has been studied is a genomic classifier collected from a bronchial brush of a normal-appearing mainstem bronchus to assess the probability of lung cancer. In patients with intermediate pretest probability of lung cancer and a nondiagnostic bronchoscopy, a negative genomic classifier result may help in pursuing a strategy of repeat imaging compared with a nonsurgical biopsy. The weakness of this strategy is that it requires a bronchoscopy to be done, as opposed to other molecular diagnostics that can be done using a blood test. Currently, this test is not widely used in practice.

■ Nonsurgical Biopsy Techniques: CT-Guided Transthoracic Needle Biopsy

CT-guided transthoracic needle biopsy is most useful for peripheral lesions in the outer third of the lung. The sensitivity of CT-guided transthoracic needle biopsy for malignancy is 90%.[117] The major limitation of CT-guided transthoracic needle biopsy is its high rate of pneumothorax, with reported rates ranging from 10% to 35% overall.[42,118] In a recent cross-sectional analysis of 15,865 patients, the rate of any pneumothorax was 15% and the rate of pneumothorax requiring a chest tube was 7%.[119] Risk factors associated with pneumothorax include older age, smoking, emphysema, smaller lesions, deeper locations, lateral puncture site, proximity to fissures, and low entry angle to the pleura.[1,120,121] Because of the high rate of pneumothorax and its possible complications, the following patients should not undergo percutaneous needle aspiration: those with severely limited pulmonary reserve, those with bullous emphysema or blebs in the needle path, and postpneumonectomy patients. Other relative contraindications are bleeding diathesis, inability to hold breath, and severe pulmonary hypertension.

TABLE 110-4 Lung CT Screening Reporting and Data System (LUNG-RADS) for Screen-detected Nodules

LUNG-RADS Score	Findings	Management	Risk of Malignancy
0—Incomplete	Incompletely imaged lung fields or prior CT being located	Obtain additional images or compare with prior CT	—
1—Negative	• No lung nodules • Nodule with complete, central, popcorn, or concentric calcification	Annual LDCT in 12 months	<1%
2—Benign Appearance	• Perifissural nodule <10 mm • Solid nodule <6 mm • Part-solid nodule <6 mm Ground glass nodule <30 mm or >30 mm unchanged	Annual LDCT in 12 months	<1%
3—Probably Benign	• Solid nodule ≥6 to <8 mm • Part-solid nodule ≥6 mm with solid part <6 mm • Ground glass nodule ≥30 mm	LDCT in 6 months	1%–2%
4A—Suspicious	• Solid nodule ≥8 to <15 mm *or* growth <8 mm Part-solid nodules ≥6 mm with solid part ≥6 mm to <8 mm • Endobronchial nodule	LDCT in 3 months or PET/CT if solid component >8 mm	5%–15%
4B—Suspicious	• Solid nodule ≥15 mm *or* growth ≥8 mm • Part-solid nodule with solid part ≥8 mm *or* growth ≥4 mm	Chest CT, PET/CT, or tissue sampling	>15%
4X—Suspicious	Category 3 or 4 nodules with additional features that increase suspicion for malignancy	Chest CT, PET/CT, or tissue sampling	>15%

Data from Lung-RADS® Version 1.1. American College of Radiology. 2019.

Importantly, CT-guided transthoracic needle biopsy does not always provide a specific benign or malignant diagnosis. Such nondiagnostic results occur in 4% to 41% of cases.[2] Because of this, if the pretest probability of cancer is high, then a nondiagnostic result does not necessarily rule out malignancy and additional testing or observation with serial CT may be warranted.

■ Nonsurgical Biopsy Techniques: Bronchoscopy

Traditionally, conventional bronchoscopy has been regarded as a procedure of limited usefulness in the evaluation of pulmonary nodules.[122,123] Studies have shown variable success rates, with an overall diagnostic yield of 36% to 68% in nodules greater than 2 cm with bronchoscopic biopsy, brushings, and washings.[124,125] In general, the yield for specific benign diagnoses has ranged from 12% to 41%.[32,124] Complication rates are low at about 1% to 2%, with most of the risk being associated with the transbronchial biopsy component of the bronchoscopy.[126,127]

Factors to consider when deciding on the suitability of bronchoscopy for diagnosis of a pulmonary nodule include the size of the nodule, its location, the presence of air bronchograms, and the availability of new bronchoscopic technologies. In terms of nodule size, the sensitivity of conventional bronchoscopy is significantly worse for smaller lesions. The overall sensitivity when performing bronchoscopy with cytology brushing, bronchoalveolar lavage, and transbronchial biopsy under fluoroscopic guidance was 34% for lesions <2 cm and 63% for lesions >2 cm.[117,126,128,129] Location also matters: nodules located in the inner or middle one-third of the lung have the best diagnostic yield, whereas nodules in the outer one-third have a much lower diagnostic yield and as such are often best approached with CT-guided transthoracic needle aspiration. Another characteristic of pulmonary nodules to consider is the relation of the nodule to neighboring bronchi.[117] Tsuboi et al. described four types of tumor–bronchus relationships: (1) the bronchial lumen is patent up to the tumor; (2) the bronchus is contained in the tumor mass; (3) the bronchus is compressed and narrowed by the tumor, but the bronchial mucosa is intact; and (4) the proximal bronchial tree is narrowed by peribronchial or submucosal spread of the tumor or by enlarged lymph nodes[130] (Fig. 110-5). The presence of types 1 or 2, a bronchus leading to or contained within the body of a nodule or mass on CT, has been termed a positive bronchus sign. When a bronchus sign is present on CT, the diagnostic yield of bronchoscopy can be as high as 60% to 90%.[20,117,131,132] With a negative bronchus sign, the yield drops to 14% to 30%. Signs and symptoms of airway involvement (cough, hemoptysis, localized wheezing), although rare in pulmonary nodules, will increase diagnostic yield when present.

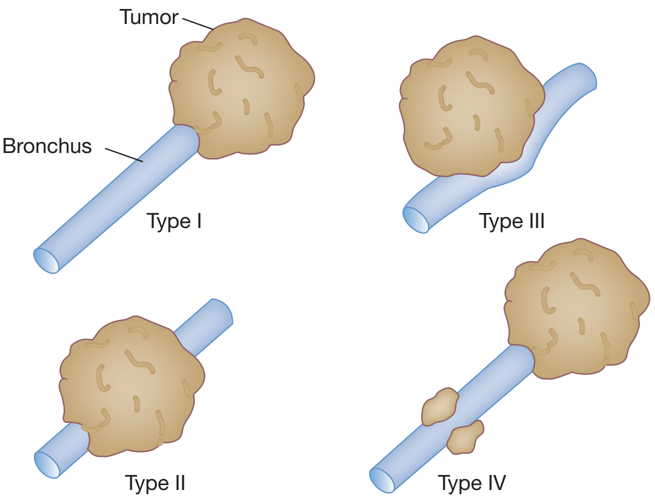

Figure 110-5 Schematic illustration of tumor–bronchus relationships (see text). *(Data from Tsuboi E, Ikeda S, Tajima M, et al. Transbronchial biopsy smear for diagnosis of peripheral pulmonary carcinomas. Cancer. 1967;20(5):687–698.)*

Newer bronchoscopic technologies include electromagnetic navigation and guidance (EMN), radial endobronchial ultrasound (r-EBUS), ultrathin bronchoscopy, guide sheath techniques, and virtual bronchoscopic navigation (Chapters 33 and 34). EMN uses navigation software that provides bronchoscopic guidance to reach the target peripheral nodule. Once the bronchoscope is within vicinity of the nodule, a transbronchial forceps biopsy, transbronchial needle aspiration, or cytologic brushings can be performed. R-EBUS uses real-time ultrasound to provide a 360-degree image of the airways. Once an abnormal lesion is identified with the radial probe, biopsies of the lesion can be performed with or without the guide-sheath. R-EBUS and EMN can also be used together.

In meta-analyses of EMN, the pooled sensitivity for malignancy was found to be 70.7% to 77%.[126,133–135] Meta-analyses of r-EBUS with transbronchial biopsy demonstrated an overall diagnostic sensitivity of 70.6% to 72%.[133,136,137] Note that in many of the studies cited, investigators would use multiple modalities concurrently—for example, a study using r-EBUS with a guide sheath and virtual bronchoscopy would be included in all three categories. As such, it is difficult to tell the contribution of individual system components, since what is truly relevant is overall aggregate system performance. In addition, many of the studies did not report on the method of patient selection, but it is clear that proper patient selection is vital if high diagnostic yields are to be obtained with these technologies, since they are not suitable for all patients. The meta-analyses also found significant heterogeneity between studies, and therefore sensitivity may vary significantly across institutions. The main risk with EMN and r-EBUS is pneumothorax; however, that risk is only around 0.7% to 2%.[136,137] Studies have found that size greater than 2 cm, presence of an air bronchus sign on CT scan, and use of rapid on-site cytologic evaluation are associated with an increase in the diagnostic yield of r-EBUS and EMN.[136–138] It does appear that the time required to reach the lesion is less when using both modalities together compared to when either is used alone.[139]

Emerging modalities such as robotic bronchoscopy and cone-beam CT-guided bronchoscopy are being investigated for sampling of peripheral lung nodules. Preliminary data suggest that they are feasible and their safety data are encouraging, but their diagnostic sensitivity is not yet well measured.[140–143] Further studies of these modalities are needed before they can become standard of care.

On balance, EMN, EBUS, and VB appear to increase the diagnostic sensitivity of bronchoscopy in select centers with the appropriate expertise, although the magnitude of the benefit for each of these technologies is difficult to quantify and there is a paucity of randomized controlled data. In cases in which there is an air-bronchus sign or very central lesions abutting the large airways, bronchoscopy may be of use. Similarly, if there is a suspicion for an infectious etiology (e.g., tuberculosis or fungal infections), then bronchoscopy may be warranted.

■ Surgery: Thoracotomy and Thoracoscopy

Surgical biopsy can be achieved with video-assisted thoracoscopic surgery (VATS), traditional thoracotomy, or a combination of both. If the frozen section demonstrates a benign lesion, then only a wedge resection may be required—and if that is the case, then operative mortality will be low (~0.5%).[57] Conversely, if the lesion is malignant and the patient has sufficient pulmonary reserve a lobectomy using either open thoracotomy or VATS with systematic lymph node sampling remains the standard of care.

Lobectomy mortality is 1% to 4%.[1] Mortality is higher in patients over age 70 and in patients with malignancy. These patients will often have other coexisting illness, such as chronic obstructive pulmonary disease (COPD) or coronary artery disease. The mortality risk increases with the extent of the procedure. In one series, the mortality was 1.4% for wedge resection, 2.9% for lobectomy, and 6.2% for pneumonectomy.[144] A more recent observational study of lung cancer surgery reported similar 30-day mortality rates.[145] Of note, this study indicated that there may be a relationship between volume of surgeries performed and outcome. Hospitals that performed the highest volume of lung cancer surgeries had lower 30-day mortality than those that had the lowest volume (3% vs. 6%).

VATS uses fiberoptic telescopes and miniaturized video cameras to facilitate biopsies and resection. VATS represents a complementary approach to traditional thoracotomy and can be very useful in some patients. This approach still requires general anesthesia but does not require a full thoracotomy incision or spreading of the ribs. VATS allows the experienced surgeon to identify and wedge out peripheral nodules in many cases with minimal morbidity and mortality. In a series by Mack et al., 242 nodules were resected with no mortality and minimal morbidity.[146] Average hospital stay was 2.4 days. VATS can spare some patients with benign nodules the risks of open thoracotomy and can be useful for wedging out nodules in patients who have limited pulmonary reserve who cannot otherwise tolerate a lobectomy. However, in up to 12% of cases conversion from VATS to a minithoracotomy will still be required.[147–151]

Whether resection is performed by VATS or by thoracotomy, lobectomy with systematic lymph node sampling remains the procedure of choice for malignant solitary pulmonary nodules.[152] Wedge excisions or segmental resections for smaller cancers have been evaluated, but the role of these limited pulmonary resections in the management of lung cancer remains controversial. The Lung Cancer Study Group evaluated this in a study of 276 patients with T1N0 lesions that were strictly staged to prove N0 status. Patients were randomized to lobectomy or limited resection.[153] In patients undergoing limited resection, there was an observed 75% increase in recurrence rates ($p = 0.02$) attributable to an observed tripling of the local recurrence rate ($p = 0.008$), an observed 30% increase in overall death rate ($p = 0.08$), and an observed 50% increase in death with cancer rate ($p = 0.09$) compared to patients undergoing lobectomy. Because of the higher death rate and locoregional recurrence rate associated with limited resection, lobectomy stands as the surgical procedure of choice for patients with peripheral T1N0 non–small-cell lung cancer.

For patients with insufficient pulmonary reserve to tolerate a lobectomy, segmentectomy or wedge resection remains a viable alternative. In addition, whether very small malignant lesions, less than 2 cm in size, can be managed with segmentectomy, radiation, or some combination thereof, remains controversial and is the subject of ongoing research. The original randomized trial used both wedge resections and segmentectomy, but more recent data suggest that segmentectomy is superior to wedge resection for tumors less than 2 cm in size.[154–156] At the present time, it is reasonable to recommend lobectomy with systematic lymph node dissection for all patients with malignant solitary pulmonary nodules who have sufficient pulmonary reserve to tolerate the procedure, with consideration of segmentectomy for those patients with inadequate pulmonary function to tolerate a lobectomy.

THE IMPACT OF SURGICAL RISK ASSESSMENT ON DIAGNOSTIC STRATEGY

For patients with pulmonary nodules, the probability of malignancy should be assessed. If the probability is close to 0, then a strategy of careful observation with CT is recommended. If the probability of malignancy is close to 1, then directly proceeding to surgery after staging work-up will be the best strategy. For patients with an intermediate probability for malignancy, a nonsurgical biopsy should be pursued. The probability at which the strategy changes from observation to nonsurgical biopsy is the "observation threshold," and the probability at which the strategy changes from nonsurgical biopsy to surgical resection is the "surgical threshold" (Fig. 110-7, Table 110-5). These decision thresholds are determined by the sensitivity and specificity of the available tests as well as the treatment threshold. The treatment threshold is the probability of disease at which the expected outcome of treatment and no treatment are exactly the same (Table 110-5).

Algorithms for pulmonary nodules assign a probability of 5% to the "observation threshold" and a probability of 60% for the "surgical threshold."[1,2] However, these numbers vary significantly from patient to patient based on their surgical risks, comorbidities, and personal preferences (Fig. 110-6). The surgical threshold will be higher for patients with a higher surgical risk and multiple comorbidities compared to a patient with the same pulmonary nodule without those risk factors. It is also important to recognize that the decision thresholds of 5% and 60% are based on the assumption that a surgical wedge resection for the pulmonary nodule is possible. A wedge resection serves to limit the harm of surgery in benign nodules, since morbidity and mortality are much lower than with a lobectomy. If a wedge resection of a nodule is not possible because of nodule location such that a lobectomy is required for access, then the harms increase and thus treatment and decision thresholds increase.[1,157] Other factors, such as competing risks from comorbidities and patient preferences, will also change the decision thresholds as shown in Fig. 110-7.

SYSTEMATIC APPROACH TO THE PULMONARY NODULE

The goal is to promptly identify and bring to surgery all patients with operable malignant nodules while avoiding thoracotomy in patients with benign nodules. Based on the previous discussion, the systematic approach to the pulmonary nodule should begin with a history and physical. The history and physical should focus on addressing the following questions: (1) What is the pretest probability of cancer? (2) What is the patient's surgical risk? This should include a detailed history of relevant comorbidities that impact surgical risk as well as severe competing diseases (e.g., severe Alzheimer disease) that significantly limit life expectancy independent of cancer and surgical risk.

Surgical risk assessment should include spirometry and diffusion capacity for carbon monoxide (DL_{CO}). If pulmonary function is not normal, then quantitative perfusion scans may be warranted to calculate the projected postoperative FEV_1 and DL_{CO}. If the projected postoperative FEV_1 and DL_{CO} are at least 40% of predicted, the risk of pulmonary complications following surgery is acceptable. If one of the two measures is less than 40% while the other is at least 40%, pulmonary exercise testing may be useful to further risk-stratify the patient. A $\dot{V}O_{2max} \geq 15$ mL/kg/min is associated with a low risk of pulmonary complications following lobectomy. Other factors to consider include the location of the nodule. If the nodule is very peripheral and easily reached by VATS and wedge resection is feasible, then the potential harm of resecting a benign lesion will be relatively low. Conversely, if the nodule is very central, such that the only way to obtain a surgical biopsy is to do a lobectomy, then the potential harm of resecting a benign lesion will be high. These considerations in turn will impact the treatment threshold and hence optimal strategy.

A chest CT should be ordered if not already available and compared with all old chest radiographs and CT images (if available). A pretest probability of cancer should be estimated, based on clinical and radiographic features. If the lesion is a solid nodule and has demonstrated radiographic stability for 2 or more years, no additional evaluation is warranted—but a period of 5 years of stability is necessary for pure ground-glass nodules to be deemed to be benign.

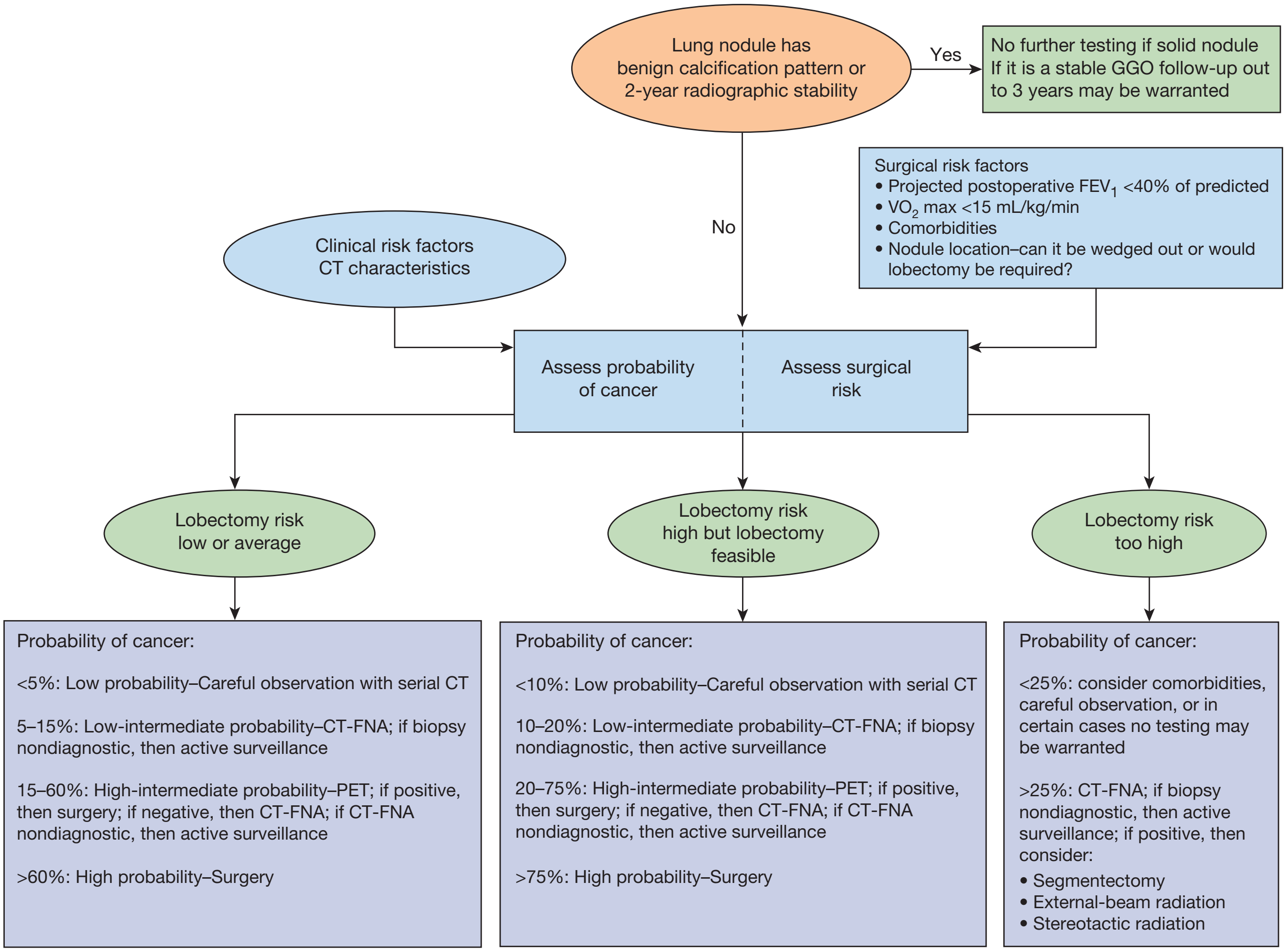
Lung nodule has
benign calcification pattern or
2-year radiographic stability
Yes
No further testing if solid nodule
If it is a stable GGO follow-up out
to 3 years may be warranted
No
Surgical risk factors
• Projected postoperative FEV$_1$ <40% of predicted
• VO$_2$ max <15 mL/kg/min
• Comorbidities
• Nodule location–can it be wedged out or would lobectomy be required?
Clinical risk factors
CT characteristics
Assess probability of cancer
Assess surgical risk
Lobectomy risk low or average
Lobectomy risk high but lobectomy feasible
Lobectomy risk too high
Probability of cancer:
<5%: Low probability–Careful observation with serial CT
5–15%: Low-intermediate probability–CT-FNA; if biopsy nondiagnostic, then active surveillance
15–60%: High-intermediate probability–PET; if positive, then surgery; if negative, then CT-FNA; if CT-FNA nondiagnostic, then active surveillance
>60%: High probability–Surgery
Probability of cancer:
<10%: Low probability–Careful observation with serial CT
10–20%: Low-intermediate probability–CT-FNA; if biopsy nondiagnostic, then active surveillance
20–75%: High-intermediate probability–PET; if positive, then surgery; if negative, then CT-FNA; if CT-FNA nondiagnostic, then active surveillance
>75%: High probability–Surgery
Probability of cancer:
<25%: consider comorbidities, careful observation, or in certain cases no testing may be warranted
>25%: CT-FNA; if biopsy nondiagnostic, then active surveillance; if positive, then consider:
• Segmentectomy
• External-beam radiation
• Stereotactic radiation

Figure 110-6 Systematic approach to the pulmonary nodule.

TABLE 110-5 Definitions and Formulas for Decision Analysis of Solitary Pulmonary Nodules

Harm	Difference in outcome between similar patients *without* the disease who do not receive treatment and those who receive treatment
Benefit	Difference in outcome between similar patients *with* the disease who receive treatment and those who do not receive treatment
Treatment threshold	*Harm/(harm* + *benefit)* = 1/(1 + [*benefit/harm*])
Observation threshold	*(Harm x false — positive ratio)/(harm x false — positive ratio)* + (*benefit x true — positive ratio*) Probability at which the strategy changes from observation to nonsurgical biopsy
Surgical threshold	(*Harm x true — negative ratio)/(harm x true — negative ratio*) + (*benefit x true — false negative ratio*) Probability at which the strategy changes from nonsurgical biopsy to surgical resection

True-positive ratio, sensitivity; false-positive ratio, (1 – specificity); true-negative ratio, specificity; false-negative ratio, (1 – sensitivity).

At this point the physician should integrate the probability of cancer with the relative consequences of treatment. Treatment consequences should be considered by comparing the benefits of surgery if the patient has cancer with the potential harm of surgery if the patient does not have cancer. This determines the treatment threshold, which is the point around which the decision centers. These thresholds vary significantly between patients depending on their cardiopulmonary reserve, comorbidities, and individual preferences. Patient preferences for certain outcomes can play an important role in strategy selection, so physicians should discuss the risks and benefits of alternative strategies and elicit patient preferences.[2,37,91,158] Management strategies can then be selected based upon the patient's surgical risk, probability of disease, and patient preferences (Fig. 110-7).

There have been many decision analysis studies of solitary pulmonary nodules published over time, and the probability of cancer that defines low-, intermediate-, and high-probability risk groups varies between studies.[37,91,159,160] In part, this is because diagnostic tests and treatments have changed over time so the underlying probability thresholds will of course vary over time. As new diagnostic and treatment alternatives become available, these thresholds need to be periodically reassessed.[161] However, even if technology were unchanging, patient characteristics and preferences vary significantly, so defining a single "optimal answer" for all patients is not feasible. Given these constraints, all of the decision analyses published are fairly consistent, with low probability being approximately 5% to 12% or less, and high probability being approximately 60% to 72%.[57,91,159,160] When the

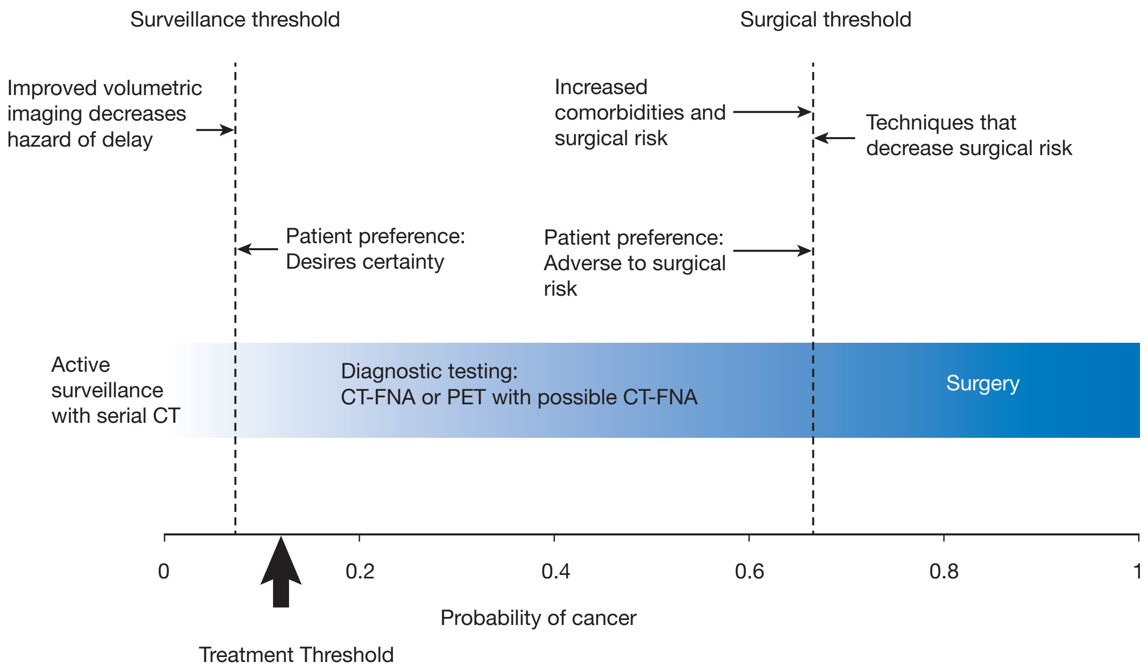
Surveillance threshold
Surgical threshold
Improved volumetric imaging decreases hazard of delay
Increased comorbidities and surgical risk
Techniques that decrease surgical risk
Patient preference: Desires certainty
Patient preference: Adverse to surgical risk
Active surveillance with serial CT
Diagnostic testing: CT-FNA or PET with possible CT-FNA
Surgery
0
0.2
0.4
0.6
0.8
1
Probability of cancer
Treatment Threshold

Figure 110-7 Decision and treatment thresholds for diagnostic strategy of pulmonary nodules. The observation and surgical thresholds vary depending on individual patient comorbidities, surgical risk factors, patient preferences, and the availability of diagnostic tests and treatments. For example, increased comorbidities and surgical risk increase the surgical threshold. Improved detection of nodule growth with volumetric CT increases the observation threshold. *(Reproduced with permission from Ost DE, Gould MK. Decision making in patients with pulmonary nodules. Am J Respir Crit Care Med. 2012;185(4):363–372.)*

pretest probability is low, a PET scan will not be as useful because the specificity of PET is only 83%.[20,57] A positive PET scan increases the posttest probability of cancer, but the posttest probability of cancer will not be above the surgical threshold so it is not high enough to make a definitive treatment decision. We can use the same approach to understand why PET is preferred when the pretest probability is in the high-intermediate range. Imagine that the pretest probability is just below the surgical threshold. The pretest probability is so high that any single negative test will not result in a posttest probability below the observation threshold. Thus, a second negative test would be needed to lower the probability below the observation threshold. However, PET carries much less risk to the patient than CT-FNA. If PET is performed first when the pretest probability of cancer is high, the posttest probability will be high enough to warrant surgery and the risks of CT-FNA will be avoided.

Keeping this in mind, we can gain some useful insights of a more general nature from a careful examination of Fig. 110-7. While decision thresholds for individual patients vary because of the surgical risk, and hence the potential benefit and harm of surgery vary, the order of the preferred strategies is the same when going from lowest to highest pretest probability of cancer: careful observation with serial CT, then CT-FNA or peripheral bronchoscopy, then PET with possible CT-FNA or peripheral bronchoscopy, and then surgery. The decision between pursuing bronchoscopy compared to CT-FNA is based on location, size, availability of equipment, and expertise. CT-FNA is the most sensitive test for obtaining a definitive diagnosis; however, it has a pneumothorax complication rate of approximately 20%. The sensitivity of bronchoscopy improves as size increases, and since the complication rate of bronchoscopy is lower, bronchoscopic options are more competitive for larger lesions and select lesions with an air bronchus sign.

For most patients with peripheral pulmonary nodules without mediastinal adenopathy on PET-CT who are surgical candidates, conventional bronchoscopy will not play a major role since the sensitivity of CT-guided biopsy is considerably higher. However, in patients with emphysema or concerns of not tolerating CT-guided biopsy, peripheral bronchoscopy techniques such as EMN, r-EBUS, and robotic bronchoscopy can be considered since they are safer than CT-guided biopsy with the caveat of a lower sensitivity. In patients with a radiographically negative mediastinum and a pulmonary nodule in the inner one-third of the lung, c-EBUS of the mediastinum should be performed. This should be followed by peripheral bronchoscopy if the mediastinum is negative for malignancy on rapid on-site cytology examination. For patients with a peripheral pulmonary nodule less than 3 cm located in the outer two-thirds of the lung, performance of bronchoscopy for the additional purpose of staging the mediastinum is not essential if the patient is being considered for resection.[122,123] However, for patients being considered for stereotactic body radiation therapy, mediastinal staging with c-EBUS with concurrent peripheral bronchoscopic biopsy if needed should be performed, since stereotactic body radiation is contingent on not having any nodal disease (including N1).

SUMMARY

Evaluation of pulmonary nodules should begin with estimating the pretest probability of cancer. For patients with a very low probability of cancer, careful observation with serial CT is warranted. For those with a very high probability of cancer, surgery is preferred. For patients with an intermediate probability of cancer, either CT-FNA or peripheral bronchoscopy is best. Patient preferences should be considered because individual patients vary significantly in terms of their risks, potential for benefit, and preferences.

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CHAPTER 111

The Pathology of Bronchogenic Carcinoma

Leslie A. Litzky

INTRODUCTION

The development of new classes of drugs and targeted therapy for lung cancer prompted an extensive reevaluation of the pathologic classification of bronchogenic carcinoma but did not diminish the significance and impact of the histologic classification of bronchogenic carcinoma. Rather than marginalizing the traditional role of the pathologist in lung cancer treatment, the advent of what has been termed “personalized” or “precision” medicine has only made pathologic assessment more crucial to patient management.[1,2] The clinical necessity of providing rapid and concurrent molecular/immunologic analysis along with a histologic diagnosis has placed the anatomic pathologist in the additional central strategic management role of tumor tissue processing and evaluation, in addition to frequent consultation on optimal sample acquisition. This chapter focuses on the major histologic subtypes of malignant pulmonary epithelial tumors and includes carcinoid tumors, sarcomatoid carcinoma, and salivary gland tumors. Other unusual tumors, both benign and malignant, are covered in a separate chapter, and there is another chapter on the genetic and molecular changes in lung cancer. The extremely rapid pace of developments in molecular diagnostics and therapy makes it quite difficult to make enduring summary statements about the prognostic and therapeutic implications for specific histologic subtypes. New molecular and immunologic insights are leading to entirely new classes of drugs that are continuously impacting, and in some cases dramatically improving, overall survival statistics. The intent of this chapter, therefore, is to provide a broad overview of the current histologic classification and to provide a deeper understanding of the critical issues regarding the preanalytic steps of sampling, processing, and evaluating lung cancer specimens for molecular analysis.

GENERAL CONSIDERATIONS IN HISTOLOGIC CLASSIFICATION AND THE CURRENT CLASSIFICATION OF LUNG TUMORS

Pathologic assessments are continually refined to reflect changes in surgical and medical management, as well as to incorporate an improved understanding of basic tumor biology. Once the diagnosis of malignancy had been made, the pathologic evaluation of lung cancer had traditionally focused on histologic subtyping and, for the selected subset of patients undergoing surgical resection, determining the pathologic stage of disease. Histologic classification is essentially predicated on the assumption that the quantitative predominance of a particular histologic pattern reflects distinctive biologic characteristics. It has been gratifying to note that concurrent developments in other disciplines such as molecular biology have substantiated many aspects of the currently accepted framework for histologic classification. The 2004 World Health Organization (WHO) classification of lung tumors was the first edition to extensively summarize the molecular biology of different tumor subtypes.[3] Nevertheless, the main purpose of the 2004 WHO classification was to provide reproducible criteria to pathologists worldwide by using recognizable architectural patterns and individual cellular features that can be appreciated by routine light microscopy and standard hematoxylin- and eosin-stained slides. The use of ancillary techniques, such as immunohistochemistry or molecular biology, was not required in most instances, thereby making the classification accessible to all pathologists for diagnosis and fostering consistency in treatment and research protocols. Although this approach might seem antiquated, it should be noted that the incorporation of data from ancillary studies such as immunohistochemistry or molecular analysis has broad implications, not the least of which is the expense of the laboratory tests, which require additional time, special equipment, technical expertise, and the possibility of exhaustion of small tumor samples that are then no longer available for future testing. By the time of the 2015 WHO classification, the requirement for immunohistochemistry in the accurate diagnosis and subclassification of many lung tumors was clearly inescapable.[4] The WHO classification was traditionally based on a detailed histologic examination of resection specimens, despite the unfortunate fact that the majority of lung cancer patients present with advanced disease and never undergo resection. Personalized treatment, especially in patients with advanced lung cancer who often have limited samples, required histologic classification to be as precise as possible. The most recent 2021 WHO classification directly addresses in detail the issue of pathologic classification of small biopsy samples and cytopathology specimens.[5]

Tumor classification and associated generalizations pertaining to tumor type are often made to seem relatively straightforward but, in practice, it is always a challenge for any proposed scheme of histopathologic classification to ensure the reproducible recognition of tumor subtypes. The degree to which histologic heterogeneity is recognized and tumors classified depends to some extent on sampling techniques, and that may, in turn, have implications for protocol design and data evaluation. The effects of prior therapy must also be considered in subsequent biopsies. It is a fundamental fact of lung tumor classification that small samples taken from advanced-disease patients may not be entirely representative of the tumor—either in terms of histology or in molecular alterations. The histologic subtyping of pulmonary carcinomas on the basis of morphology alone is even more challenging in small samples. With the advent of targeted therapies for non–small-cell carcinoma, further pathologic subclassification beyond the traditional distinction between small-cell carcinoma and non–small-cell carcinoma is now considered critical for selecting appropriate treatment for patients.[1] Subsequent sections will address the expanded use of immunohistochemical stains for further histologic subclassification as well as the competing priority of preserving sufficient tumor for molecular analysis.

Lung carcinomas are classified according to the best differentiated component, and pathologists assign a degree of differentiation to tumors that show differentiation, such as squamous cell carcinoma and adenocarcinoma. This is also known as histologic grading, and it is used in tumor pathology as a way of attributing prognostic significance to a specific histologic pattern. It is an assessment as to how much the tumor cells phenotypically resemble a normal cell type, such as a squamous cell or a glandular cell. Histologic grading should not be viewed as a histogenetic determination, that is, that a tumor is derived from a specific cell of origin, such as a squamous cell, or that the tumor cell has “dedifferentiated” from a cell of origin. Traditionally, there have been three histologic degrees of differentiation: well differentiated, moderately differentiated, and poorly differentiated. Many lung tumors show a wide variation in differentiation. If a tumor is largely undifferentiated but contains recognizable foci of squamous cell carcinoma or adenocarcinoma, it is classified as a poorly differentiated squamous cell carcinoma or adenocarcinoma, respectively. Some tumors, such as small-cell carcinoma or sarcomatoid carcinoma are, by definition, poorly differentiated. In recent years, the most intense focus has been on developing an improved and more standardized histologic grading system that is more prognostically robust, particularly for pulmonary adenocarcinomas, and these efforts will be summarized in the subsequent section on adenocarcinoma.

INVASIVE ADENOCARCINOMA, INCLUDING ADENOCARCINOMA IN SITU AND MINIMALLY INVASIVE ADENOCARCINOMA

Adenocarcinoma is the most common histologic subtype in the United States and in most countries.[6] Adenocarcinoma is also the most frequently diagnosed subtype in nonsmokers.[7] The classification of pulmonary adenocarcinoma has long been a source of controversy—not only because of its diversity in histologic appearance but also because of a wide spectrum of clinical behavior, radiographic findings, and molecular characteristics associated with the entity. It is worth reviewing a concise history of the revisions in lung adenocarcinoma classification to understand the conceptual framework of the current 2021 WHO classification. The inherent histologic heterogeneity of many primary pulmonary adenocarcinomas has always made reproducible subclassification difficult, and even small adenocarcinomas (<2 cm) can contain more than one histologic pattern.[8] This practical problem was addressed by the 1999 WHO revision, which introduced for the first time a *mixed* subtype to the four previously recognized subtypes of *acinar*, *papillary*, *bronchioloalveolar*, and *solid*.[9] In addition, a strict definition for bronchioloalveolar carcinoma (BAC) was adopted in the 1999 revision and retained in the 2004 classification. The definition required that the tumor have a pure lepidic growth pattern without evidence of stromal, vascular, or pleural invasion.[3,9] The term *lepidic* means that the proliferation of tumor cells should line the alveolar walls in a uniform manner, using the alveolar walls as a supporting scaffold. It should be noted that prior to the 1999 revision, pathologists widely varied in their assessments. Adenocarcinomas with a minor, usually central, and often more poorly differentiated invasive glandular component along with a peripheral bronchioloalveolar pattern are frequently encountered. In instances in which the peripheral BAC component predominated, it had been a common practice to designate the tumor either as a BAC or an "adenocarcinoma with a BAC pattern/features." The stricter definition of BAC prevailed in the revisions because of evidence demonstrating that small (<2 cm) solitary tumors with a pure lepidic growth pattern had a 100% 5-year survival.[10] Histologically, BACs were divided into two major subtypes, *nonmucinous* and *mucinous*, and were grouped together because of a similar "lepidic" growth pattern along alveolar septa. The more common nonmucinous type consists of cuboidal, columnar, or so-called hobnail cells with apical nuclei. The mucinous type consists of tall columnar cells with abundant apical pale mucinous cytoplasm and basally located nuclei, sometimes resembling goblet cells. A rare *mixed nonmucinous and mucinous* or *indeterminate* subtype was also recognized in the 1999/2004 revisions.

While this classification of BAC made sense from a histologic pattern perspective, it did not really encompass the variability in clinical presentation, radiographic features, or prognosis. Although practice patterns changed somewhat after these revisions, the diagnosis of BAC continued to be used for both small and well-differentiated adenocarcinomas as well as for more advanced-stage tumors with obvious diffuse pneumonic spread or lymph node involvement. Moreover, in the years following the publication of the 2004 WHO classification, it became increasingly apparent that the nonmucinous and mucinous cell types have distinctive clinical, radiographic, immunophenotypic, and molecular correlations.[11,12] In 1995, Noguchi et al. had suggested that even small foci of invasion in what would otherwise be a pure BAC were associated with a 100% disease-free survival, and following the publication of the 2004 WHO classification, there were a number of other studies that similarly supported quantitation of the lepidic growth pattern and the area of invasion within these "mixed" type adenocarcinomas. These studies focused on a cutoff of 5 mm or less of invasion as a way of defining a "minimally invasive adenocarcinoma" (MIA) with an excellent survival.[13,14]

The 2015 WHO classification completely discarded the term *BAC* in favor of *adenocarcinoma in situ* (AIS). For small (≤3 cm) solitary adenocarcinomas with predominant lepidic growth and small foci of invasion measuring ≤0.5 cm, the term *minimally invasive adenocarcinoma* was recommended.[4] By definition, MIA can be applied only to a solitary and discrete lesion unless it is clear, in the instance of multiple tumors, that they are synchronous primaries. Although the new terminology was a bit unsettling to pathologists and clinicians who have long been used to the entity of BAC, the terms *AIS* and *MIA* were favored because they more accurately reflect both the histologic growth pattern and survival statistics. AIS and MIA will typically present as pure ground-glass opacities without a solid component or with a very small solid component on computed tomography (CT) scans.[15] The majority of AIS and MIA cases are nonmucinous, although some cases of mixed nonmucinous and mucinous MIA have been reported (Fig. 111-1).[16] Most lesions with a mucinous "BAC" histologic pattern, if carefully examined and sampled, will have invasive foci and, therefore, are classified as "invasive mucinous adenocarcinoma" (Fig. 111-2A,B).

The 2021 WHO classification recommends that invasive nonmucinous adenocarcinomas be characterized by a predominant subtype and recognizes five major patterns: lepidic predominant, acinar predominant, papillary predominant, micropapillary predominant, and solid predominant.[5] The introduction of a "predominant" pattern was intended as a practical way to evaluate the characteristic heterogeneity of many adenocarcinomas and to allow for better stratification than the previous "mixed subtype." The recommendation was based on studies in stage I tumors that suggested that these different histologic patterns had prognostic value in a grading system and that these different patterns can be reproducibly recognized.[16–18] Other studies have further validated the prognostic significance of the predominant histologic pattern using this classification system or have evaluated other potential parameters for

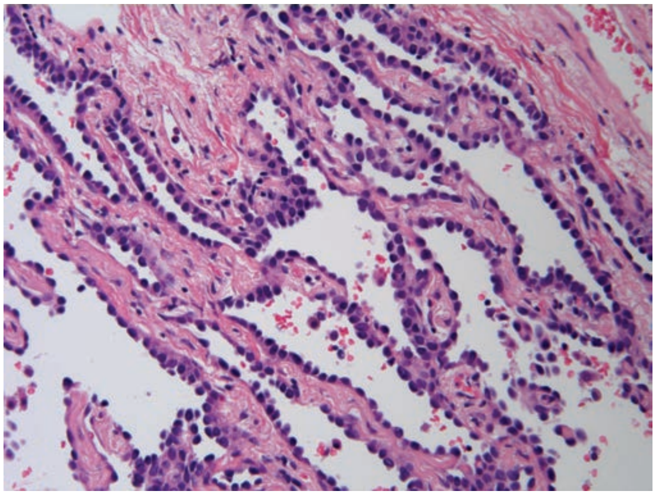


Figure 111-1 Adenocarcinoma in situ, nonmucinous. Uniform proliferation of atypical nonciliated columnar cells with apical nuclei. The tumor cells are growing along the alveolar septa without invasion. (H&E, 200×).

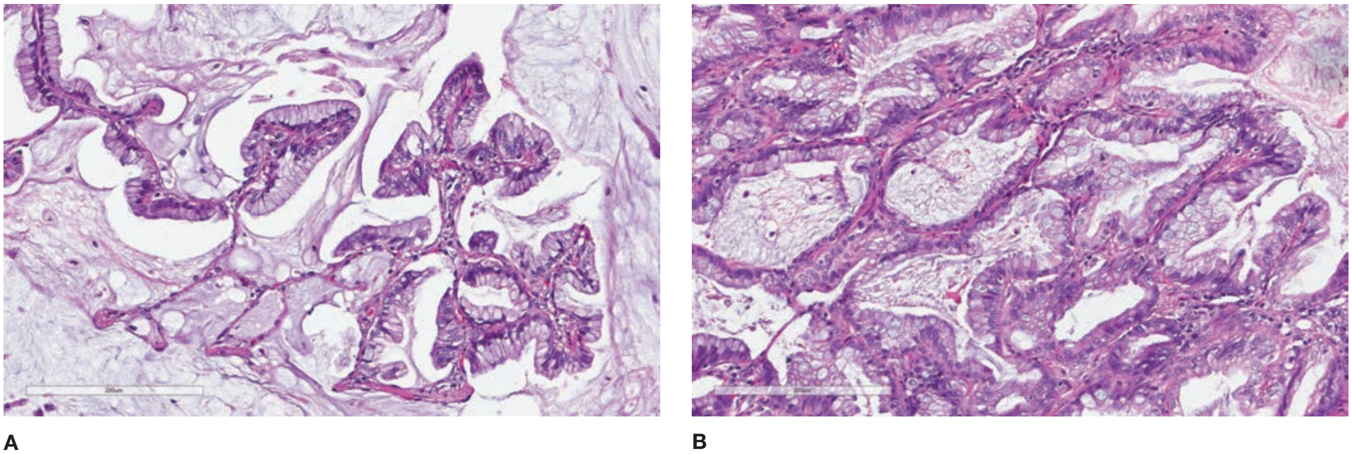


Figure 111-2 Invasive mucinous adenocarcinoma. **A.** Tall columnar cells with abundant mucinous cytoplasm line the alveolar septa (former mucinous bronchioloalveolar carcinoma). **B.** Invasive pattern in same tumor. (H&E, 200×).

a grading system.[19–22] The 2021 WHO classification further recommends that any pattern present in a resected specimen be estimated in a semiquantitative fashion and recorded in 5% to 10% increments totaling 100% pattern (although this has been variably adopted in past and current practice). The practice of estimating percentages for each component has been incorporated into a new proposed grading scheme for pulmonary adenocarcinoma that redefines the traditional well, moderate, and poorly differentiated criteria with a significantly improved predictive model for early-stage resected adenocarcinomas (see subsequent discussion).[23] *Lepidic predominant adenocarcinoma* consists mainly of tumor cells growing along alveolar septae (previously referred to as a nonmucinous BAC pattern) but with greater than 5 mm invasion. *Acinar predominant adenocarcinoma* consists of irregularly contoured but nonetheless recognizable glandular structures and is often associated with a desmoplastic stroma (Fig. 111-3A). Within the acinar group, there is a subgroup of complex glandular patterns that are considered to be high-grade. These include *cribriform* (defined as nests of tumor cells with sieve-like perforations) and fused gland (defined as poorly formed fused glands without intervening stroma or in a ribbon-like formation with irregular borders and single cells infiltrating a desmoplastic stroma).[5] *Papillary predominant adenocarcinoma* consists of malignant cuboidal or columnar cells that line the surface of fibrovascular cores (Fig. 111-3B). *Micropapillary predominant adenocarcinoma* consists of small papillary clusters of glandular cells growing within airspaces (Fig. 111-3C).[5] To this classic description of micropapillary adenocarcinoma has been added a newly recognized *filigree* pattern. The filigree pattern is characterized as tumor cells growing in delicate, lace-like, narrow stacks of cells without fibrovascular cores.[24] *Solid predominant adenocarcinoma* consists of sheets of tumor cells without an acinar, papillary, micropapillary, or lepidic growth pattern (Fig. 111-3D). The tumor cells have abundant cytoplasmic and mostly vesicular nuclei with prominent nucleoli. Multiple tumor cells have basophilic cytoplasmic vacuoles that suggest intracytoplasmic mucin, which then may be confirmed by a special stain for mucin. The 2015 WHO classification required that be there five or more mucin-positive cells in at least two high-power fields (0.4 mm^2) for the diagnosis of *solid adenocarcinoma.* This criterion was adopted because it is not uncommon for squamous cell or large cell carcinomas to have rare mucin droplets. However, the use of TTF-1 immunohistochemistry is more sensitive than mucin and is preferentially used wherever immunohistochemical stains are easily available. Supporting evidence for glandular differentiation also can be provided by a positive napsin A stain and/or a negative p40 stain.

The general acknowledgment that there should be a more comprehensive grading system for pulmonary adenocarcinomas led to efforts to define a supplemental grading system within the parameters of the current classification. One recent study based on carefully staged resection specimens matched with clinical outcome data suggested a combination of the predominant plus high-grade histologic pattern (with a cutoff of 20% for the high-grade pattern) that was both practical and prognostic for invasive pulmonary adenocarcinomas.[23] In this model, lepidic predominant is grade 1. Grade 2 consists of acinar or papillary predominant tumors with no or less than 20% of high-grade patterns. Grade 3 is any tumor with 20% or more of high-grade patterns (solid, micropapillary, or complex gland patterns).

There are four other variants of invasive adenocarcinoma in the 2021 WHO classification: *invasive mucinous adenocarcinoma* (formerly mucinous BAC), *colloid adenocarcinoma*, *fetal adenocarcinoma*, and *enteric adenocarcinoma*.[5] The historically recognized variants of *signet-ring adenocarcinoma* and *clear cell adenocarcinoma* were discarded as discrete entities and are now viewed as cytologic changes that can occur in association with multiple histologic patterns and are therefore not included in the comprehensive histologic description, although it is useful to document these patterns for comparison of histologic features with tumor recurrence or metastasis.[5]

Invasive mucinous adenocarcinoma is a primary pulmonary adenocarcinoma with tumor cells that show goblet cell or columnar cell morphology with abundant intracytoplasmic mucin.[5] There is also a less common variant of *mixed invasive mucinous and nonmucinous adenocarcinoma*. There is no established grading system for invasive mucinous adenocarcinoma, and it is often the case that the tumor cells are deceptively bland in appearance. Although much of the tumor can appear noninvasive and grow in a lepidic manner, careful sectioning usually reveals invasive foci that can appear as acinar, papillary, micropapillary, or solid patterns. Invasive mucinous adenocarcinomas are peripheral tumors and frequently present as multifocal, multilobar, and/or bilateral tumors, that may reflect aerogenous spread. This tumor often grows in a pneumonic-like pattern, producing consolidation that is initially misinterpreted as infection. Radiographic presentation as a part-solid or solid nodule also occurs, and particularly with multilobar and bilateral involvement, the question of an extrapulmonary primary is often raised. Without careful clinical and radiographic correlation, it can be exceedingly difficult to distinguish a pulmonary primary from other extrapulmonary primary sites including the pancreaticobiliary system, gastrointestinal tract, and ovary on a morphologic and even immunohistochemical basis.

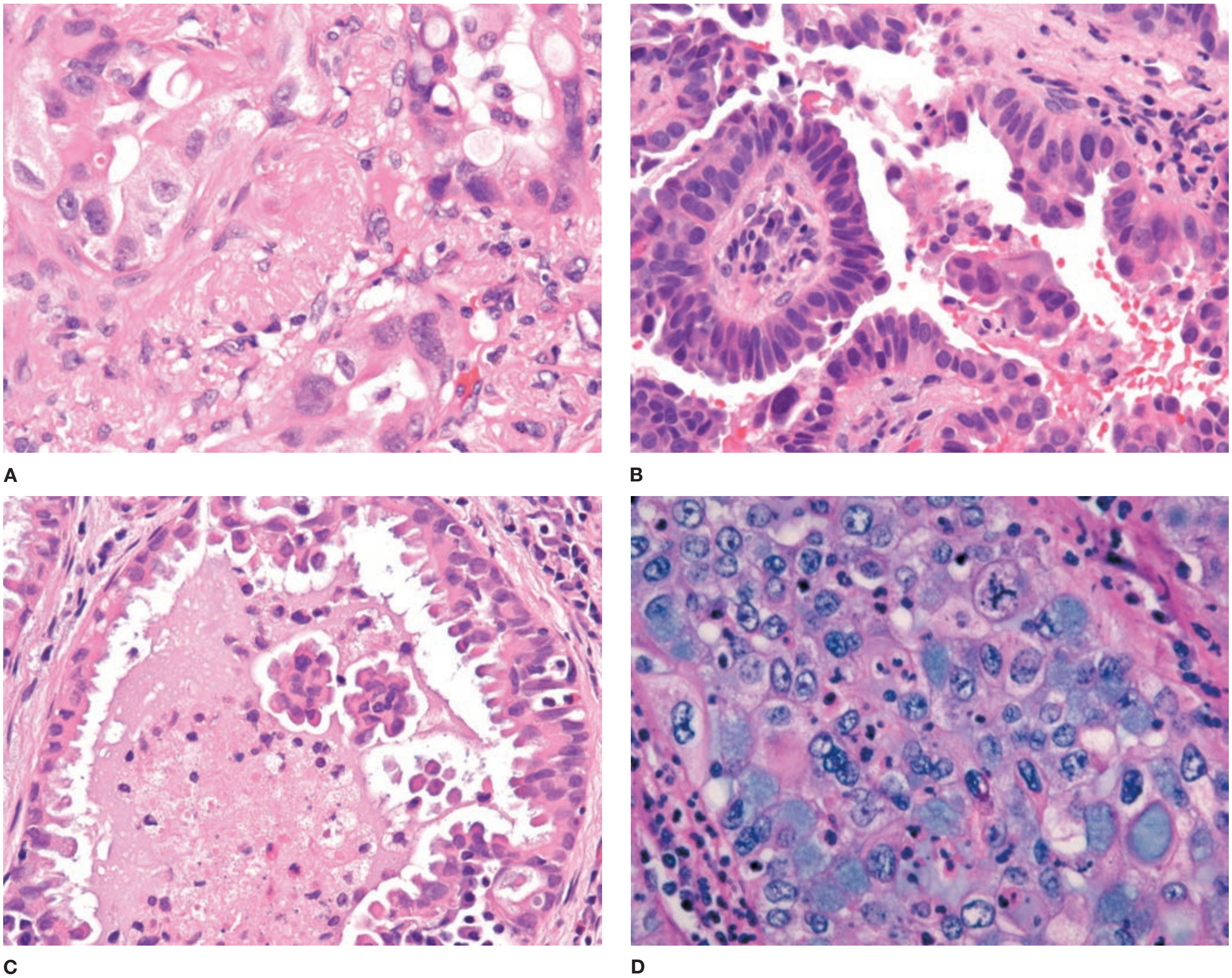


Figure 111-3 **A.** Invasive pulmonary adenocarcinoma, acinar predominant. Small, irregularly shaped glands within a desmoplastic stroma (H&E, 400×). **B.** Invasive pulmonary adenocarcinoma, papillary predominant. Malignant cells are arranged on the surface of fibrovascular cores (H&E, 400×). **C.** Invasive pulmonary adenocarcinoma, micropapillary predominant. Small papillary clusters without fibrovascular cores (H&E, 400×). **D.** Invasive pulmonary adenocarcinoma, solid predominant. Solid nests of cells with mucin (H&E, 400×).

Enteric adenocarcinoma is an important variant because of its morphologic and immunohistochemical overlap with colorectal adenocarcinomas, thereby necessitating a clinical evaluation to exclude a gastrointestinal primary.[5] The need to exclude a metastatic mucinous adenocarcinoma from other primary sites such as the GI tract, pancreas, and breast is a similar concern when diagnosing a primary pulmonary *colloid adenocarcinoma. Fetal adenocarcinoma* is a rare entity that resembles the developing fetal lung in its pseudoglandular stage. There are both low-grade and high-grade variants.

The reproducibility of histopathologic subtype and invasion in pulmonary adenocarcinomas has been studied.[25] In pulmonary adenocarcinomas with classic morphology, there is good reproducibility in identifying a predominant pattern but only fair reproducibility in distinguishing invasion from in situ (purely lepidic) patterns. Specifically recognizing stromal invasion is still somewhat problematic in practice, even among expert thoracic pathologists. Many adenocarcinomas have areas of fibrosis due to alveolar wall collapse or septal fibrosis, with some observers interpreting an individual case as tumor-related stroma with fibroblasts (desmoplastic stroma) and others interpreting as benign fibroelastotic scarring. Histologic criteria for true invasion include single cell infiltration, a fibromyxoid stromal response, high-grade cytology, and a cribriform or acinar growth pattern.

Most adenocarcinomas arise in the periphery of the lung and are often associated with parenchymal scarring or puckering of the overlying pleura (Fig. 111-4). It is now a standard recommendation for accurate staging to use elastin stains in the evaluation of visceral pleura invasion in any lesion that approaches the visceral pleura (Fig. 111-5).[26,27] Histologic subtype alone cannot be used to replace molecular analysis in predicting which lung cancers have mutations and are likely to respond to targeted therapy. The current recommendation is to submit a sample for molecular testing whenever the sample is sufficient.[28]

The histologic heterogeneity of adenocarcinomas is such that the exclusion of metastatic disease or malignant mesothelioma is often an important consideration. As mentioned previously in the enteric variant of adenocarcinoma, the exclusion of a colorectal primary (among others) may be important. Other features such as signet-ring cytology raise the possibility of a gastric or appendiceal tumor as well as other primary sites. Mucinous carcinomas, particularly of pancreatic or ovarian origin, may metastasize to the lung and mimic a mucinous adenocarcinoma. All the classic growth patterns—acinar, papillary, micropapillary, or solid—may be seen in any number

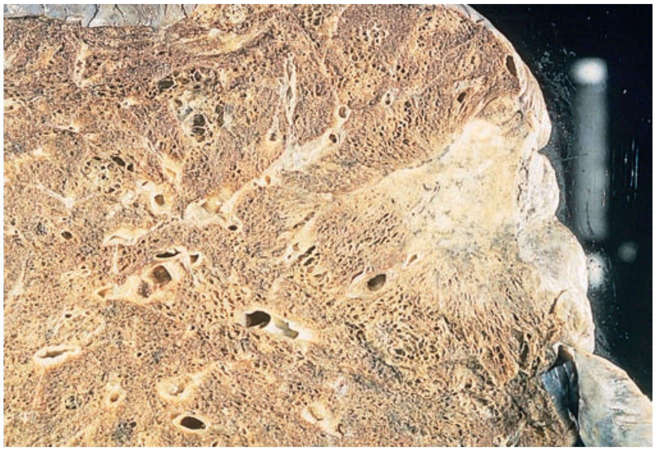


Figure 111-4 Peripheral adenocarcinoma of the lung with pleural puckering.

of extrapulmonary primaries, and clinicoradiologic correlation is always essential. The distinction between peripheral adenocarcinomas with extensive pleural involvement, diffuse carcinomatous involvement of the pleura by metastatic tumor, and malignant mesothelioma may be similarly problematic. Some carcinomas grow in a manner virtually identical to malignant mesothelioma, with extensive pleural involvement and limited parenchymal invasion.[29] Clinically, radiographically, and macroscopically, these tumors are indistinguishable from malignant pleural mesothelioma. The histologic appearance may be equally confusing, requiring the use of immunohistochemical stains. As will be discussed further in the general section on immunohistochemistry, there are multiple antibodies that will stain adenocarcinomas of the lung. Many of these antibodies (CEA, MOC31, B72.3, LeuM1, and BerEP4) recognize glycoproteins and are not specific for the lung. Surfactant protein A (SP-A), TTF-1, and Napsin A are the three commercially available markers that can be useful in the diagnosis of lung adenocarcinomas, with the latter two markers having higher sensitivity for lung adenocarcinomas.[30,31] It is important to recognize that neither TTF-1 nor Napsin A are entirely specific for lung adenocarcinomas and pathologists must still consider within the differential diagnosis a number of extrapulmonary tumors, depending on the clinical circumstances. The combined use of TFF-1 and Napsin A does result in improved sensitivity and specificity for identifying primary pulmonary adenocarcinomas.[32]

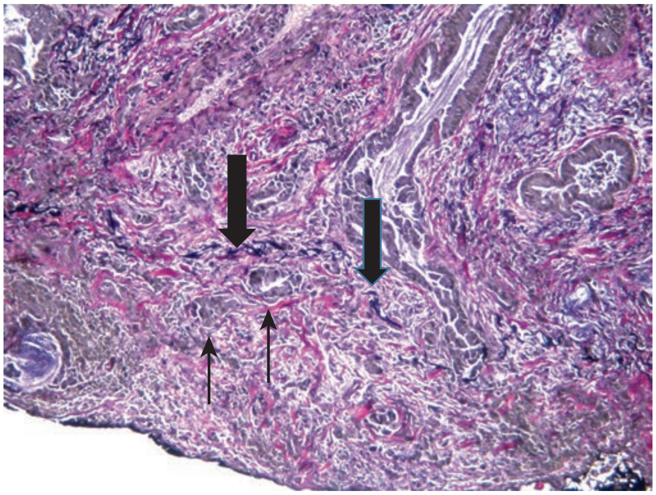


Figure 111-5 Visceral pleural invasion. Tumor cells *(thin black arrow)* are present beyond the black elastic layer of the visceral pleura *(thick black arrow)*. (Elastin, 100×).

SQUAMOUS CELL CARCINOMA

Despite its replacement as the leading lung cancer cell type among both men and women in the United States and in many other countries, squamous cell carcinoma remains an important histologic subtype. Squamous cell carcinoma is still very strongly correlated with cigarette smoking. About two-thirds of squamous cell carcinomas occur centrally, where involvement of a mainstem, lobar, or segmental bronchus may be demonstrated, but squamous cell carcinoma may also present as a peripheral mass and the incidence of this appears to be increasing—especially in patients with underlying interstitial lung disease[33] (Fig. 111-6A,C). As would be expected from an endobronchial growth pattern, squamous cell carcinomas often are associated with bronchial obstruction and postobstructive pneumonia. Cavitation with superimposed infection can be seen in peripheral tumors[5] (Fig. 111-6B).

In the 2021 WHO classification, squamous cell carcinoma is defined as a malignant epithelial tumor characterized by the presence of keratinization, intercellular bridges, or immunohistochemical markers of squamous differentiation (with p40 being the most recommended and specific immunohistochemical stain).[5] This latter criterion represents a significant departure from the traditional reliance on morphologic characteristics alone to classify these tumors. There are two major entities in the 2021 WHO classification of squamous cell carcinoma: squamous cell carcinoma and lymphoepithelial carcinoma (see separate section). Within squamous cell carcinoma, there are three subtypes: keratinizing, nonkeratinizing, and basaloid. On occasion, a tumor may consist entirely of one of these subtypes, but mixed tumors with both a basaloid and keratinizing or nonkeratinizing component do occur. A familiarity with these variant patterns is useful for the practicing pathologist, but at the current time there is no evidence that these variant patterns have any clinical significance. Keratinization may be in the form of squamous pearls or individual cells with dense eosinophilic cytoplasm. Intercellular "bridges" are seen in paraffin sections due to cell shrinkage caused by fixation and correspond to the desmosomal attachments that can be appreciated ultrastructurally (Fig. 111-7B,C). A desmoplastic (i.e., fibrotic) response is often associated with the invasive nests of tumor cells (Fig. 111-7A). The nonkeratinizing variant requires the use of immunohistochemistry to separate it from large-cell carcinoma in both small biopsies and resections. In the basaloid variant, the nests of tumor cells have prominent peripheral palisading and have less cytoplasm toward the periphery, but the more centrally located cells have more obvious keratinization. The basaloid histologic features in lung carcinomas are similar to those also seen in other extrapulmonary sites such as the head and neck or cervix. Squamous cell carcinomas with a greater than 50% basaloid component should be classified as basaloid carcinoma. Basaloid cells are typically described as relatively small monomorphic cuboidal to fusiform cells with moderately hyperchromatic nuclei, finely granular chromatin, absent or focal nucleoli, scant cytoplasm, and a high mitotic rate. Intercellular bridges and/or individual cell keratinization may be seen but are often absent or inconspicuous. The tumor cells are usually arranged in lobular, trabecular, or palisading growth patterns (Fig. 111-8). Since these types of histologic patterns can also be seen in neuroendocrine tumors, immunohistochemical stains for neuroendocrine markers should be negative or extremely focal. The basaloid variant of squamous cell carcinoma, in particular, can pose a diagnostic dilemma in small, poorly preserved biopsies when the relatively scant cytoplasm mimics small-cell carcinoma. In this instance, a panel of immunohistochemical stains that includes markers of

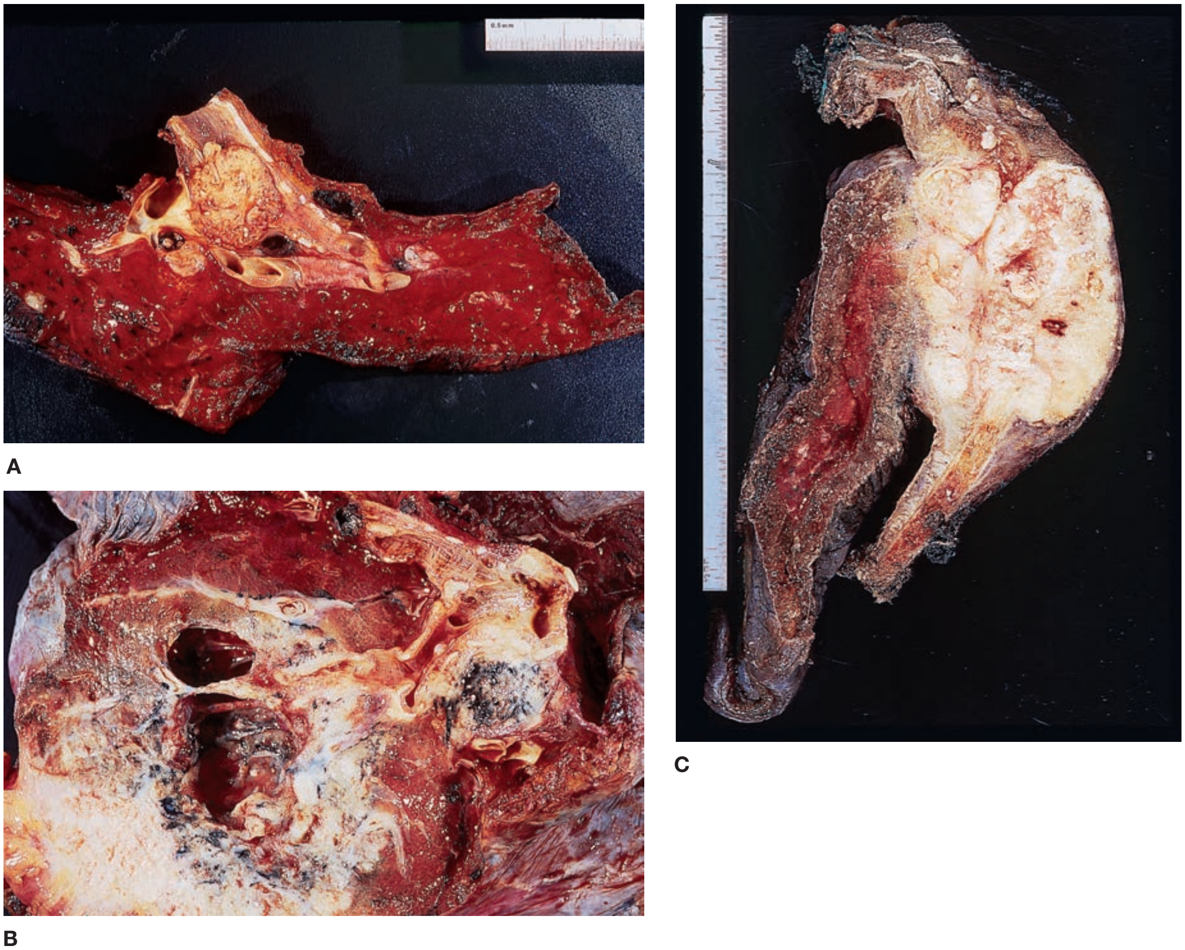


Figure 111-6 **A.** Large endobronchial squamous cell carcinoma with atelectasis and obstructive pneumonitis. **B.** Cavitation within a squamous cell carcinoma. **C.** Right upper lobectomy with chest wall resection for squamous cell carcinoma.

squamous and neuroendocrine differentiation is essential for interpretation.

Although not invariably demonstrated, it is easiest to identify a trend in tumor progression with the squamous cell histologic subtype. Sampling of a resected specimen may show changes in the adjacent bronchial mucosa ranging from squamous metaplasia to dysplasia to carcinoma in situ. If identified, the presence of an in situ component helps to differentiate a primary squamous cell carcinoma from a metastatic lesion. Aside from a clear-cut transition from in situ to invasive squamous cell carcinoma, there is no other conclusive morphologic means of differentiating a primary pulmonary squamous cell carcinoma from a metastasis. There is a tendency for metastatic tumors from the head and neck to be better differentiated (i.e., show more extensive keratinization) than their primary pulmonary counterparts, but reliably distinguishing a primary squamous cell carcinoma of the lung from other primary sites, particularly from the head and neck, continues to be an ongoing issue. Although availability may be regionally limited or not clinically indicated, multigenic panels and human papillomavirus (HPV) testing/genotyping can be helpful in defining the primary site of some cases of squamous cell carcinomas when the clinicopathologic data are equivocal and when the distinction is critical for treatment or prognosis.[5] Separation from a urothelial or thymic primary also can be problematic with immunohistochemical panels being of limited utility.

ADENOSQUAMOUS CARCINOMA

This tumor consists of squamous carcinoma and adenocarcinoma components, with each component composing at least 10% of the whole tumor.[5] The areas of glandular and squamous differentiation may be located in different areas of the tumor or may be intimately admixed. In the past, different criteria had been used for this histologic subtype, and these differences in definition, in addition to its low incidence, have made it extremely difficult to compare survival rates with other non–small-cell carcinomas. The tumor is more common in smokers but does occur in nonsmokers, and the incidence is estimated at 2% to 3%.[5] The tumor is more common in the periphery but also occurs centrally. Studies support a worse prognosis with adenosquamous carcinoma when compared to other non–small-cell carcinomas of the lung.[5] Molecular data show that the two components contain similar driver mutations, thereby suggesting a clonally identical tumor and not a "collision" tumor. Targeted therapy selection is currently based on the genetic abnormalities found in lung adenocarcinomas.

LARGE CELL CARCINOMA

The widespread use of immunohistochemistry in addition to the generation of a significant amount of genomic data has markedly reduced the incidence of large cell carcinoma from its traditional proportion of about 10% of all lung cancers to about 1.5%.[5,35] The tumor, like other non–small-cell lung cancers, is much more common in current or former smokers. Large cell carcinoma is defined in the 2021 WHO classification as "an undifferentiated non-small-cell carcinoma malignant epithelial tumor that lacks the cytologic, architectural, and immunohistochemical features of small-cell carcinoma, adenocarcinoma, or squamous cell carcinoma, in addition to giant cell, spindle cell, or pleomorphic carcinoma." The tumor cells typically have large

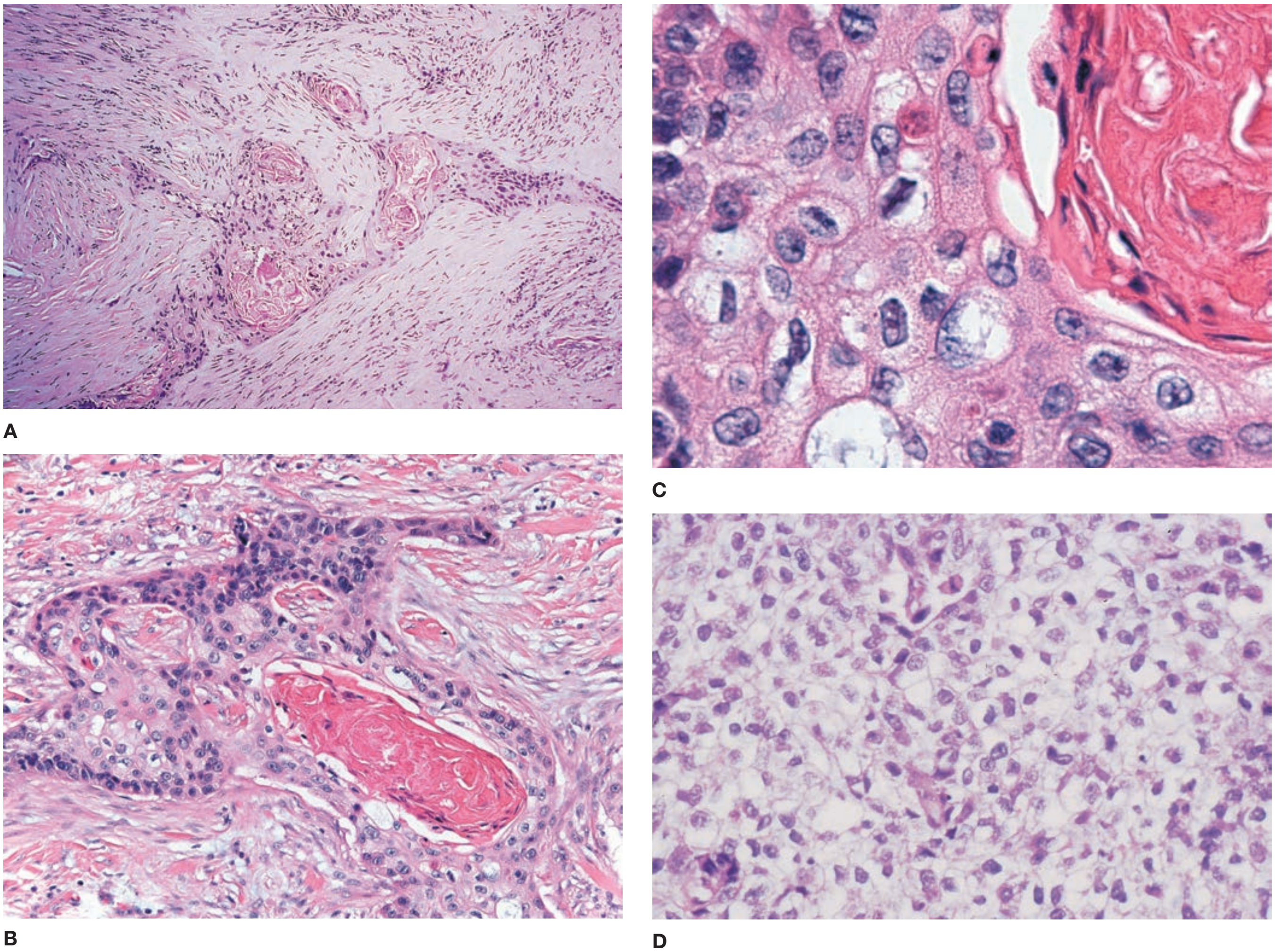


Figure 111-7 **A.** Desmoplastic response with nests of infiltrating squamous cell carcinoma (H&E, 200×). **B.** Squamous cell carcinoma with keratinization and intracellular bridges (H&E, 200×). **C.** High-power view of keratinization and intercellular bridges (H&E, 400×). **D.** Tumor cells with clear cytoplasm from a squamous cell carcinoma (H&E, 400×).

nuclei, prominent nucleoli, and a moderate amount of cytoplasm (Fig. 111-9). As is evident from this description, this tumor is defined more by what it is not than what it is. For practical purposes, it is a diagnosis of exclusion, and the diagnosis of large cell carcinoma requires morphologic examination of the resected tumor as well as immunohistochemistry. Besides other types of non–small-cell carcinoma, melanoma, malignant large cell lymphomas, and epithelioid sarcomas also can mimic large cell carcinoma, typically requiring the use of immunohistochemistry to exclude these diagnoses. Several entities that were previously included under the large cell carcinoma

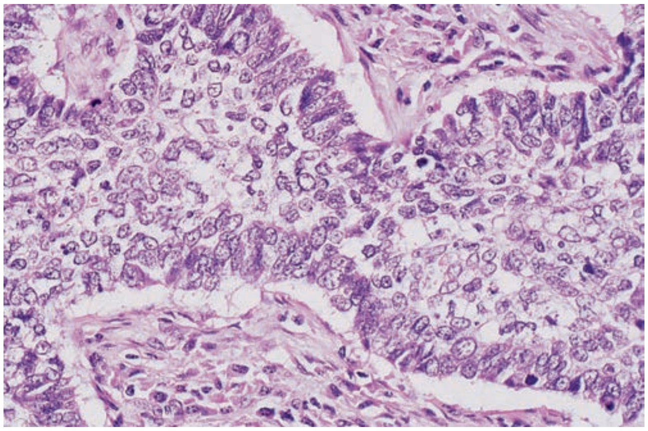


Figure 111-8 Basaloid carcinoma of the lung. The tumor cells are relatively small with hyperchromatic nuclei and scant cytoplasm. Note the tendency of the tumor cells to palisade at the periphery of the tumor nest (H&E, 400×).

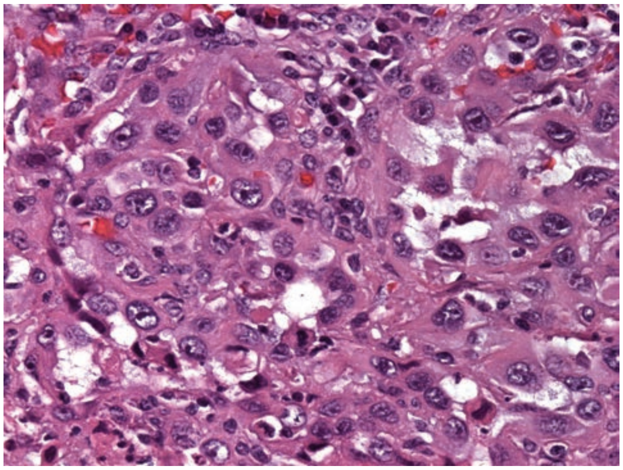


Figure 111-9 Large-cell carcinoma of the lung. There is no obvious squamous differentiation in the form of keratinization or intercellular bridges, and a mucin stain was negative (H&E, 400×).

category are now classified elsewhere in the 2021 WHO classification. *Large cell neuroendocrine carcinoma* is now part of the neuroendocrine tumor classification and *lymphoepithelioma-like carcinoma (now renamed lymphoepithelial carcinoma)* is classified as a separate entity under squamous cell carcinoma (see subsequent section).[5] Tumors with clear cell or and rhabdoid features are not considered variants, although these features should be noted.

It had long been known and generally acknowledged that the majority of large cell carcinomas represented either very poorly differentiated adenocarcinomas or squamous cell carcinomas. By electron microscopy, many large cell carcinomas had shown focal ultrastructural features consistent with adenocarcinoma or a poorly differentiated squamous cell carcinoma.[36] Similar subsets within large cell carcinoma can be defined using the same immunohistochemical stains that are routinely employed to distinguish between adenocarcinoma and squamous cell carcinoma, and the distribution of targetable mutations can be generally correlated with the immunophenotyping profile.[37] After having separated out poorly differentiated adenocarcinomas and squamous cell carcinomas, there still remains a small subset of tumors that are not classifiable as anything other than marker-null large cell carcinomas.[35] Multivariate analysis has demonstrated that these marker-null subsets of large cell carcinoma, though rare, are associated with clinically aggressive behavior. The current paucity of actionable molecular alterations has significant implications for predictive molecular testing strategies and individualized therapy.

■ Lymphoepithelial Carcinoma (Formerly Lymphoepithelioma-Like Carcinoma)

In the 2021 WHO classification, *lymphoepithelial carcinoma* is defined as a poorly differentiated squamous cell carcinoma admixed with variable amounts of lymphoplasmacytic infiltrate, frequently associated with Epstein-Barr Virus (EBV). Lymphoepithelial carcinomas are extremely rare (<1% of non–small-cell lung carcinomas), and predominantly affect younger, Asian, nonsmokers (median age of about 50 years).[5] This rare pulmonary tumor was first reported in the lung in 1987 and the morphologic features are identical to undifferentiated nasopharyngeal carcinoma of the head and neck.[38] Large malignant cells with prominent nucleoli are arranged in nests within a lymphoid-rich stroma (Fig. 111-10). In Asian patients, EBV is found in >90% of cases but occurs at a much lower rate in patients of European descent. Survival rates are better than in patients with conventional non–small-cell carcinomas, stage for stage.[5]

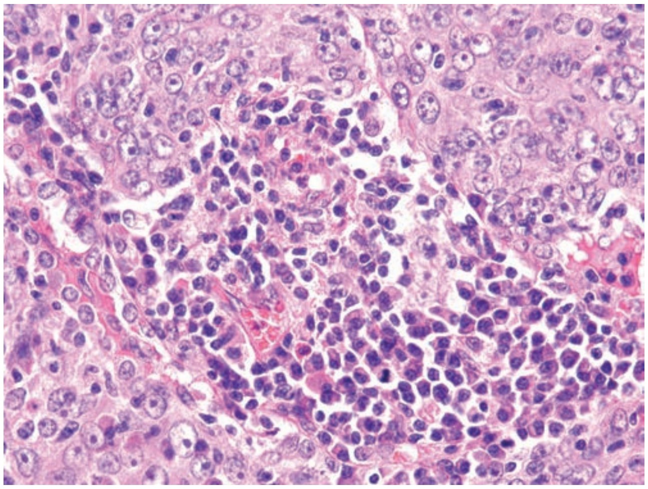


Figure 111-10 Lymphoepithelial carcinoma. Large malignant cells with prominent nucleoli are arranged in nests within a lymphoid-rich stroma (H&E, 400×).

SARCOMATOID CARCINOMA

Tumors that have sarcoma-like elements such as malignant spindle or giant cells or have a sarcomatous component that consists of a neoplastic but differentiated connective tissue phenotype such as neoplastic bone, cartilage, and striated muscle have been described in many primary organ sites, including the lung. The proliferation of terms in past literature and even the variations in nomenclature that have characterized revisions in the WHO classification has generated a disproportionate degree of confusion when compared with the actual incidence of these relatively rare lung tumors. Various terms in the literature have included spindle cell carcinoma, sarcomatoid carcinoma, carcinosarcoma, pleomorphic carcinoma, giant cell carcinoma, and pulmonary blastoma. The current 2021 WHO classification variants of sarcomatoid carcinoma include *pleomorphic carcinoma*, *carcinosarcoma*, and *pulmonary blastoma.*[5] It is now accepted that these variants are phenotypic variations that can occur within the spectrum of epithelial-derived lung tumors and the term *sarcomatoid carcinoma* can be used as an encompassing term for these tumors. Careful sampling of these tumors will often demonstrate an identifiable component of squamous cell carcinoma, adenocarcinoma, or large cell carcinoma. As with other entities in the WHO classification, the diagnosis of sarcomatoid carcinoma cannot be made on the basis of a cytology or small biopsy specimen. Features suggestive of the tumor in a small sampling may be mentioned on a descriptive basis, that is, non–small-cell carcinoma, not otherwise specified (NOS) with a comment on the sarcomatoid features.[5] Any additional identifiable component (adenocarcinoma or squamous cell carcinoma) also should be mentioned, as this might affect treatment.

Pleomorphic carcinoma is defined as a poorly differentiated non–small-cell carcinoma, including adenocarcinoma, squamous cell carcinoma, and/or large cell carcinoma containing at least a 10% component of spindle cells and/or giant cells, or a carcinoma that consists entirely of spindle and/or neoplastic giant cells[5] (Fig. 111-11). The incidence of these tumors in resected specimens is about 2% to 3%.[5] They are frequently large and peripheral, often with chest wall invasion. Most patients are former or current smokers. The giant cells in this tumor are bizarre, dyscohesive, and multinucleated. The spindle cells may be overtly cytologically malignant or may be deceptively bland. The tumor is, by definition, poorly differentiated. *MET* exon 14 skipping mutations have been identified in some tumors.[5]

Carcinosarcoma is a malignant tumor consisting of non–small-cell components combined with at least one sarcomatous heterologous

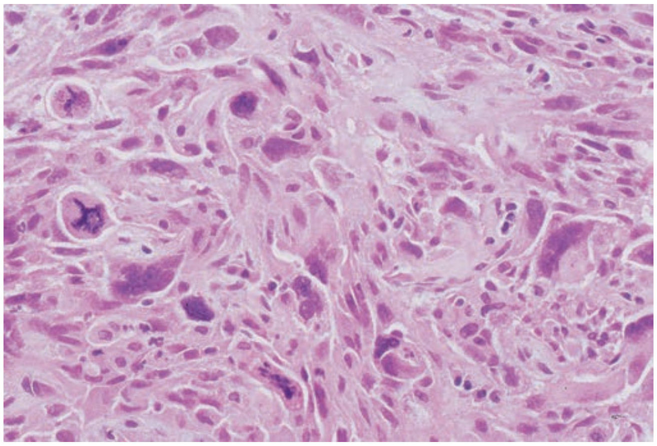


Figure 111-11 Pleomorphic carcinoma of the lung. The spindle cell and giant cell component in this large-cell carcinoma constitute at least 10% of the tumor (H&E, 400×).

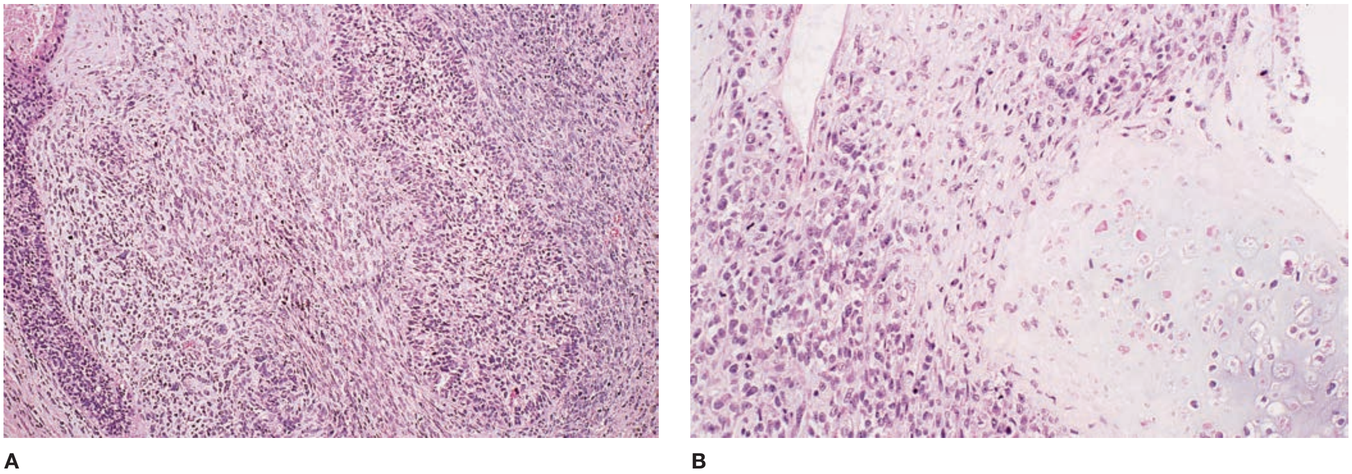


Figure 111-12 **A.** Carcinosarcoma showing a mixture of sarcoma (center) and carcinoma (periphery) (H&E stain, 100×). **B.** Tumor includes a malignant cartilaginous component (H&E stain, 100×).

element.[5] In the pathology literature, tumors that contain cells with a neoplastic but differentiated connective tissue phenotype are said to have "heterologous elements." Recognizable heterologous elements include rhabdomyosarcoma, osteosarcoma, or chondrosarcoma (Fig. 111-12). Rather than terminology, the more significant issues confronting the pathologist are exclusion of metastasis from another site and avoiding the misdiagnosis of a primary pulmonary sarcoma. The incidence of these tumors in resected specimens is <0.2%.[5] The tumor can be central, endobronchial, or peripheral. Most patients are former or current heavy smokers. Like other sarcomatoid carcinomas, these tumors have a poor prognosis.

Pulmonary blastoma is a biphasic tumor that consists of a low-grade fetal adenocarcinoma/well-differentiated fetal adenocarcinoma and primitive mesenchymal stroma. Foci of osteosarcoma, chondrosarcoma, or rhabdomyosarcoma are occasionally present.[5] It is a rare tumor with an incidence of <0.1% of resected lung cancers.[5] It mainly occurs in adults, and smoking does appear to be an important risk factor.[5] The histologically distinct, malignant glandular component resembles the developing fetal lung at an early gestational age with tumor cells that have been compared to an endometrioid carcinoma. The malignant cellular stromal component similarly has an embryonic appearance (Fig. 111-13). These tumors may have missense mutations in exon 3 of *CTNNB1*, which may be useful in diagnosis.[5] The prognosis is poor and correlates with stage.

PULMONARY NEUROENDOCRINE TUMORS—OVERVIEW

The 2021 WHO classification includes four tumor subtypes with neuroendocrine differentiation: carcinoid tumor (typical), carcinoid tumor (atypical), large cell neuroendocrine carcinoma, and small-cell carcinoma.[5] Collectively, these neuroendocrine tumors represent about 25% of all primary pulmonary carcinomas, with small-cell carcinoma being by far the most common (nearly 80% of neuroendocrine tumors). Typical carcinoid tumors, despite their low incidence, are well represented in surgical series but the relative rarity of atypical carcinoid tumors (<1% of all lung cancers) and the lower incidence (<20%) and inadequate representation of large cell neuroendocrine carcinoma in surgical series have made it more difficult to establish treatment guidelines and prognosis for those entities. Historically, the recognition of "neuroendocrine differentiation" was based on morphologic characteristics as assessed by traditional light microscopy and hematoxylin and eosin sections. The subsequent introduction of electron microscopy and then the widespread use of immunohistochemistry (which is the current standard in routine clinical practice) led to a broader identification of "neuroendocrine differentiation" and, inevitably, debates about classification, therapeutic implications, and prognosis ensued. As is to be expected with any framework for classification, the WHO classification for neuroendocrine tumors is not without some controversy and practical difficulties. Although it has been intellectually appealing to view the pulmonary neuroendocrine tumors

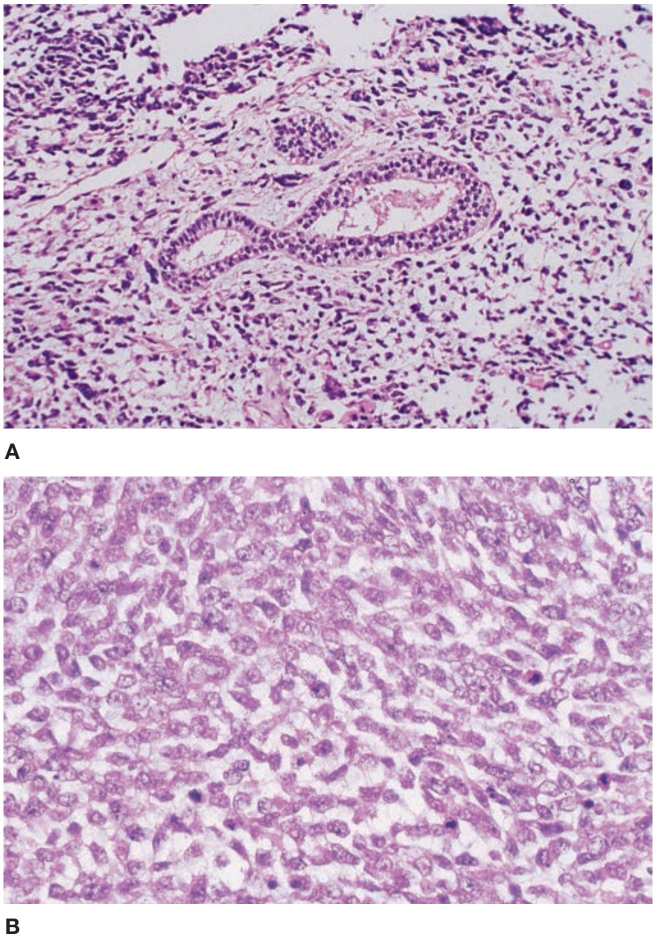


Figure 111-13 **A.** Pulmonary blastoma, showing a characteristic endometrioid-type gland, composed of cells with clear cytoplasm and basally oriented nuclei (H&E, 200×). **B.** Malignant stroma in a pulmonary blastoma (H&E, 400×).

along a continuous spectrum from low grade (typical carcinoid) to intermediate grade (atypical carcinoid) to high grade (large cell neuroendocrine carcinoma and small-cell carcinoma), the data indicate that there are major epidemiologic, clinical, histologic, genetic, and prognostic differences between carcinoid tumors and the high-grade neuroendocrine carcinomas.[5,39] Large cell neuroendocrine carcinoma is defined as a non–small-cell carcinoma with a distinct morphologic appearance and immunohistochemical evidence of neuroendocrine differentiation.[5] Leaving some occasional issues in diagnostic reproducibility aside, this entity challenges the traditional separation of the two high-grade neuroendocrine tumors into small-cell carcinoma and non–small-cell carcinoma (large cell neuroendocrine carcinoma) for treatment purposes, as some authors have suggested that treatment paradigms for small-cell carcinoma be similarly applied to the management of large cell neuroendocrine carcinoma.[40,41]

It is also important to note, based on surgically resected series of small-cell lung carcinoma and large cell neuroendocrine carcinoma that up to about 25% of these tumors will have other histologic components of non–small-cell lung carcinoma such as adenocarcinoma or squamous cell carcinoma. These tumors are designated as "combined" small-cell lung carcinoma or large cell neuroendocrine carcinoma.[5]

CARCINOID TUMORS

The overall incidence of carcinoid tumors is less than 2% of all lung cancers.[5] The 2021 WHO classification recognizes two distinct subtypes of carcinoid tumor—typical carcinoid tumor and atypical carcinoid tumor.[5] Both tumors are recognized by their low-power architectural pattern and characteristic cytologic features that are familiar to pathologists and are similar in appearance to carcinoid tumors that occur in other primary sites such as the gastrointestinal tract. However, in contrast to the terms low-grade or intermediate-grade or well-differentiated neuroendocrine carcinoma that are now used in extrapulmonary sites, carcinoid tumor has been retained in the lung tumor nomenclature because of its familiarity to clinicians and because of the well-established clinical behavior associated with the terminology and criteria for diagnosis. Although ki-67 has been incorporated into the diagnosis of neuroendocrine tumors in extrapulmonary sites, mitotic count and the presence of necrosis have proved to be the most robust and reliable features for classification of pulmonary carcinoid tumors. The mitotic activity is expressed as the number of mitoses per 2 mm^2. Since mitotic count and the consequent tumor classification are based on a resection specimen, it is not possible to reliably separate an atypical carcinoid from a typical carcinoid tumor on the basis of a small biopsy or to apply this criterion to a cytology specimen. The distinction may not affect subsequent prognosis if the tumor is amenable to surgical management, but it may impact subsequent prognosis if the patient is not resected and the tumor remains largely unsampled. The 2021 WHO classification recommends the generic topline diagnosis of "carcinoid tumor NOS" for any small sample or sampling from a metastatic site with a notation of mitotic count and ki-67. Although these criteria cannot be used for definitive classification, it is felt that treating oncologists might find the information of some utility.

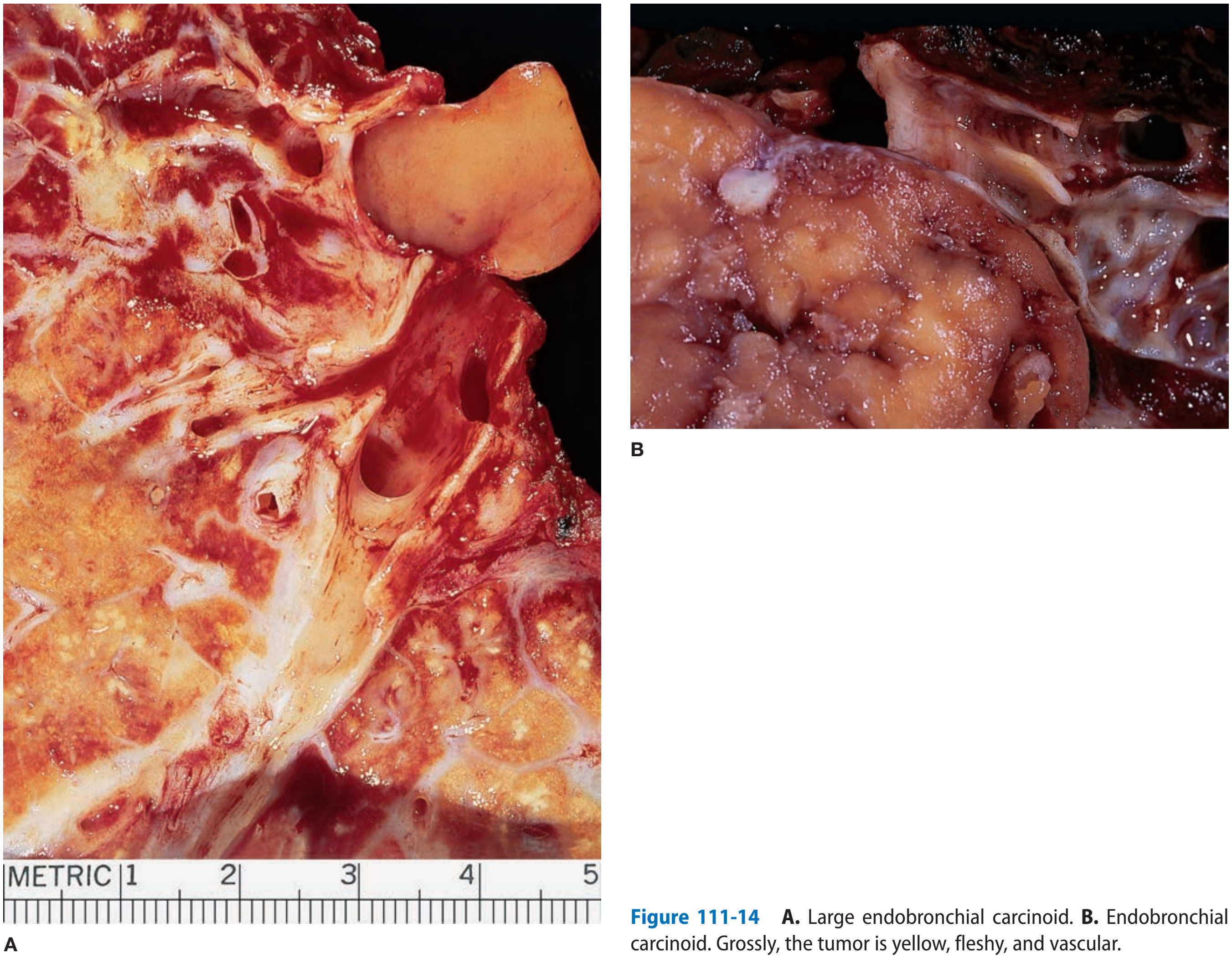


Figure 111-14 **A.** Large endobronchial carcinoid. **B.** Endobronchial carcinoid. Grossly, the tumor is yellow, fleshy, and vascular.

Typical Carcinoid

Typical carcinoid tumors can be divided into central and peripheral variants. Both variants can be asymptomatic, but central carcinoids, which characteristically grow as an endobronchial mass, may present clinically with recurrent pneumonias or hemoptysis. Typical carcinoid tumors are not associated with tobacco use, but there is an association with multiple neuroendocrine neoplasia (MEN)1 syndrome in about 5% of cases, and screening for pulmonary carcinoids with CT imaging is recommended in patients with MEN1.[42] The incidence of bronchial carcinoid tumors with carcinoid syndrome at presentation is low (1%–3%), usually occurring in the presence of metastatic liver disease.[43] Cushing syndrome due to ectopic production of ACTH is similarly rare.

Central carcinoids grossly appear as yellow or fleshy polypoid masses (Fig. 111-14). The tumor usually has a significant exophytic endobronchial component, but the tumor can infiltrate between cartilaginous rings to extensively involve the bronchial submucosa. The tumor cells form diverse patterns such as organoid nests, trabeculae, insular islands, ribbons, or rosette-like arrangements. Carcinoids can also have papillary, sclerosing, follicular, and glandular patterns. The tumor cells are generally uniform in appearance and have a low nuclear:cytoplasmic ratio with round to oval nuclei and eosinophilic cytoplasm (Fig. 111-15). The tumor cells have characteristic neuroendocrine tumor chromatin that is finely granular or classically described as "salt and pepper."

Peripheral carcinoids are frequently subpleural and can be associated with a scar (Fig. 111-16A). Unlike the cells of central tumors, which are usually round or polygonal in shape, the tumor cells of peripheral carcinoids tend to have prominent spindle cell features (Fig. 111-16B). These fusiform cells have less cytoplasm than central tumors, but this feature should not be considered a sign of atypia. There is a subset of patients with one or more peripheral carcinoid tumors who have multiple tumorlets (defined as small neuroendocrine cell proliferations <0.5 cm) and diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH). This neuroendocrine cell hyperplasia represents a preneoplastic condition. In addition, a significant complication for this subset of patients is airway fibrosis, which can progress to severe obstructive lung disease.

The pathologic attributes of typical carcinoid tumors have been examined in numerous histologic, immunohistochemical, and molecular studies. The only consistent prognostic indicators have proved to be mitotic rate and necrosis. The current 2021 WHO criteria for the diagnosis of typical carcinoid tumor require less than 2 mitoses per 2 mm^2 of viable tumor and no necrosis. Cytologic atypia, increased cellularity, and lymphovascular invasion are not predictive features. Although typical carcinoid tumors have a generally excellent prognosis, with the majority presenting as early-stage tumors that can be completely resected, it is critical to understand that typical carcinoids are low-grade but malignant tumors. The incidence of lymph node metastasis is in the range of 10% to 15%, with a 3% to 5% incidence of distant metastasis at presentation.[44] The presence of lymph node metastases, however, is not used for classification of typical versus atypical carcinoid tumor. The current TNM classification is used for staging bronchopulmonary carcinoid tumors.

Atypical Carcinoid

The term *atypical carcinoid* was first introduced by Arrigoni and colleagues in 1972.[45] Twenty-three tumors were described that appeared to have a general resemblance to carcinoid tumors but that also had a focally disorganized growth pattern, areas of tumor

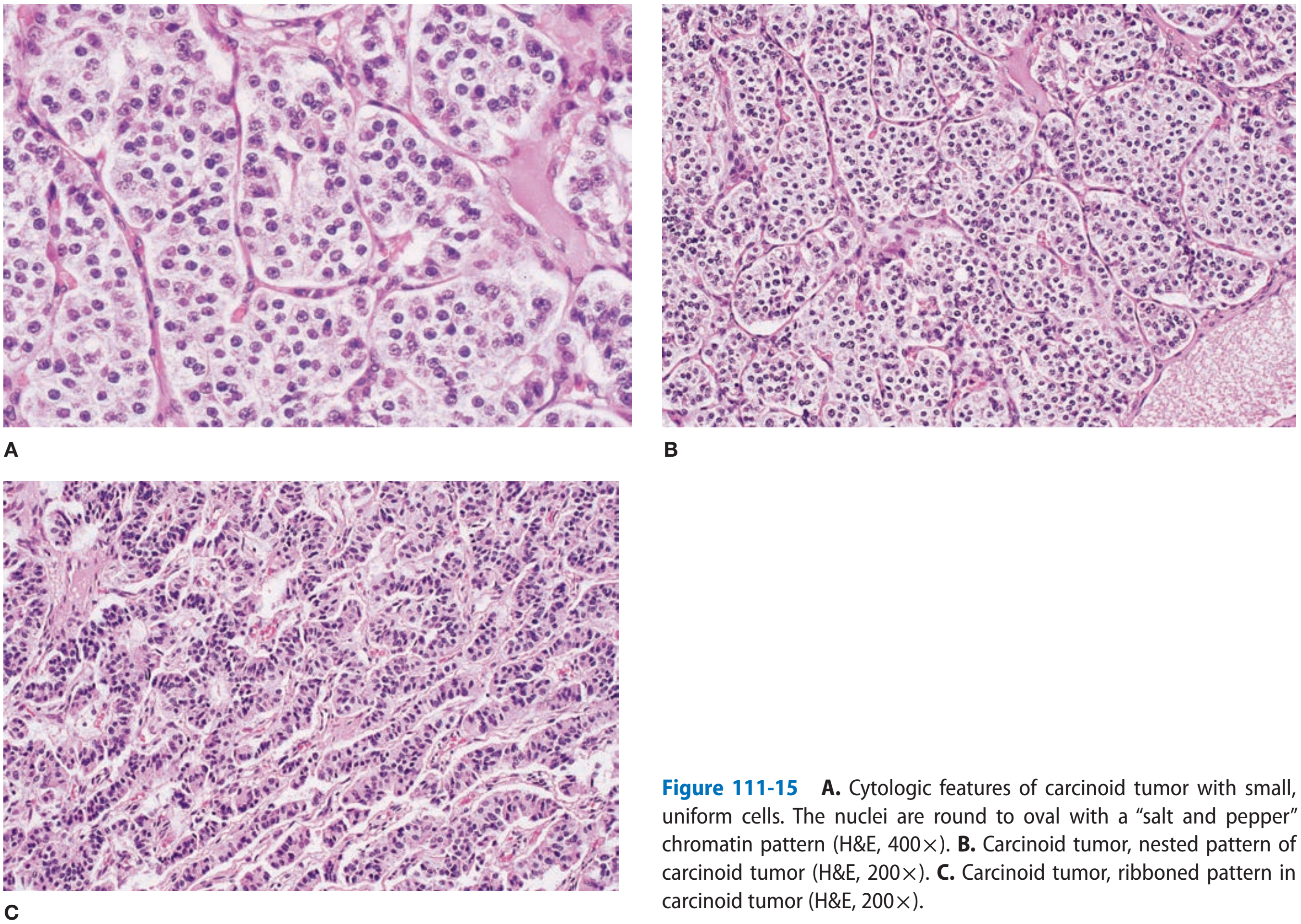


Figure 111-15 **A.** Cytologic features of carcinoid tumor with small, uniform cells. The nuclei are round to oval with a "salt and pepper" chromatin pattern (H&E, 400×). **B.** Carcinoid tumor, nested pattern of carcinoid tumor (H&E, 200×). **C.** Carcinoid tumor, ribboned pattern in carcinoid tumor (H&E, 200×).

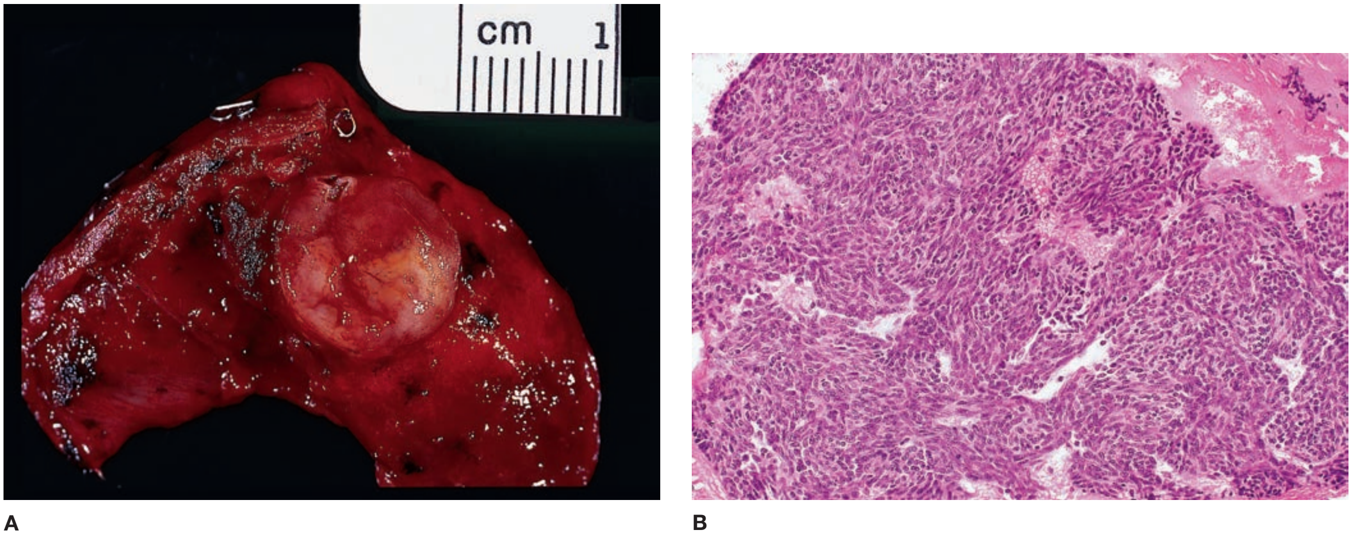


Figure 111-16 **A.** Peripheral carcinoid. **B.** Peripheral carcinoid with prominent spindle cell features (H&E, 200×).

necrosis, increased mitoses, and cellular pleomorphism. Dissension was immediately generated by the use of the word "atypical," given the aggressive biologic behavior in their series. Many other terms were introduced into the literature in the 1980s as more published reports detailing this entity appeared. The tumors described in these initial papers were a heterogeneous group, in part due to the subjective interpretation of features such as "architectural distortion." In defending atypical carcinoids as a distinct clinicopathologic entity, Travis et al.[46] emphasized that the overall architecture should be that of a recognizable carcinoid tumor with a predominantly organoid growth pattern. In the 2021 WHO classification, an atypical carcinoid tumor is defined as a carcinoid tumor with between 2 and 10 mitoses per 2 mm^2 and/or with foci of necrosis.[3] The necrosis in these tumors is usually punctate (Fig. 111-17), and one should be careful to exclude the possibility of a large area of necrosis that is secondary to a previous fine-needle aspiration or needle biopsy. Although cytologic atypia, lymphovascular invasion, nucleoli, increased cellularity, and disorganized architecture may be seen, these features are not a part of the classification system. Like typical carcinoid tumors, atypical carcinoid tumors can occur centrally as well as in the periphery. It is appropriate to consider atypical carcinoid tumors as an intermediate-grade malignant tumor with an increased capacity for progression. Atypical carcinoids have a higher incidence of lymph node metastases at presentation (about 50%) and of distant metastases at presentation (about 20%) than typical carcinoid tumors.[44]

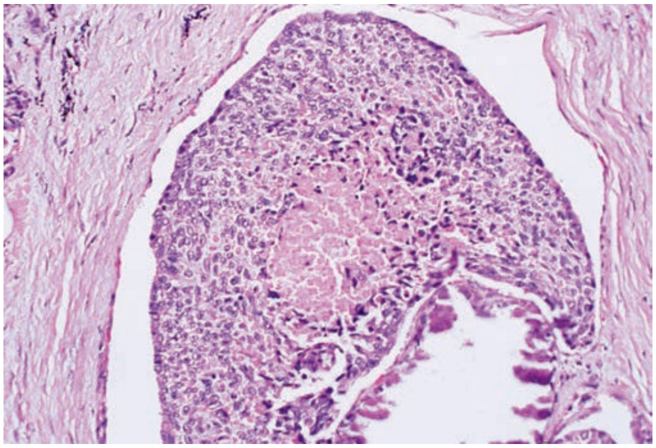


Figure 111-17 Central necrosis in an atypical carcinoid tumor (H&E, 200×).

Small-Cell Carcinoma of the Lung

The 2021 WHO classification defines small-cell carcinoma as a malignant epithelial tumor consisting of small cells with scant cytoplasm, finely granular nuclear chromatin, and absent or inconspicuous nucleoli, with a high mitotic count and frequent necrosis.[5] The tumor cells can be round, oval, or spindle shaped with poorly defined cell borders. The criterion for cell size is given as "usually less than the size of three small resting lymphocytes," but there is no absolute criterion for cell size and cell size can vary from less than the diameter of three resting lymphocytes (10 µm) to that of a larger tumor cell (45 µm) depending on the type of specimen, the quality of fixation/processing, and inherent tumor heterogeneity.[47–49] Nuclear molding is commonly seen, as is crush artifact with basophilic nuclear DNA encrustation of the vessel walls (Azzopardi effect). There is usually a high mitotic rate, averaging over 60 mitoses per 2 mm^2, but a significant mitotic rate may not be discernible in some small biopsy cases.[50] Extensive necrosis and numerous apoptotic cells are frequently seen but again may be absent in smaller biopsies (Fig. 111-18). While this definition

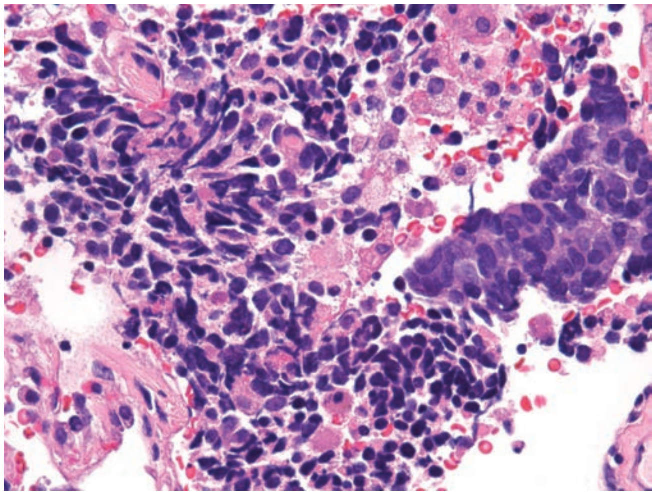


Figure 111-18 Small cell carcinoma. Classic tumor cell appearance with scant amounts of cytoplasm, hyperchromatic nuclei, nuclear molding, crush artifact, and necrosis. (H&E, 400×).

can be simply summarized, and the most classic appearance of small-cell carcinoma easily recognized with a high degree of interobserver agreement, diagnostic difficulties and issues of reproducibility do occur even among experts.[51] Some of these difficulties are related to the sampling problems inherent in the small biopsies that are obtained by fiberoptic bronchoscopy, and are further discussed in the section on small biopsies. Some of these difficulties are related to the qualitative rather than quantitative criteria that have been set forth as distinguishing features between small-cell carcinoma and large cell neuroendocrine carcinoma and will be further discussed in the section on large cell neuroendocrine carcinoma.

Small-cell lung carcinoma has decreased in incidence in the United States but it is still the most common of the pulmonary neuroendocrine tumors.[44] A significant smoking history is present in the vast majority of cases, such that the diagnosis of small-cell carcinoma should be seriously reconsidered in a patient without current or former heavy tobacco use. There are several different presentations that are familiar to most clinicians. Patients may present with pulmonary symptoms related to a large central mass that include cough, wheezing, dyspnea, and hemoptysis. Mediastinal extension may cause superior vena cava syndrome, recurrent laryngeal nerve paralysis, or dysphagia. Constitutional symptoms such as pain, decreased appetite, and weight loss are also common. A significant number of patients present with widespread metastases involving the liver, brain, bone, and adrenal glands. Paraneoplastic syndromes include the syndrome of inappropriate secretion of antidiuretic hormone, Eaton–Lambert syndrome, and ectopic Cushing syndrome. Despite the fact that less than 10% of patients with small-cell carcinoma limited to the lung are surgical candidates, the International Association for the Study of Lung Cancer (IASLC) staging project recommends and adopted the TNM staging system rather than the traditional limited- versus extensive-stage disease that has been used for staging small-cell carcinoma.[52] The College of American Pathologists (CAP) protocol for the examination of resected pulmonary specimens includes small-cell carcinoma and can be used as a template for pathologic evaluation as with non–small-cell carcinomas.

Small-cell carcinoma can present as a solitary pulmonary nodule, and early-stage small-cell carcinomas are occasionally resected. In the descriptions of surgically resected small-cell lung carcinomas, the gross appearance does not differ significantly from many other lung carcinomas.[49] The tumors are described as well circumscribed and often lobulated, with others as endobronchial and some as subpleural. The cut surface is described as white to tan to yellow and gray, with necrosis recorded in only a small number of cases.

In addition to other neuroendocrine tumors, the differential diagnosis of small-cell carcinoma might include nonspecific chronic inflammation, other small "round blue cell tumors," and poorly preserved, often necrotic non–small-cell lung carcinomas. The general use of immunohistochemistry in the differential diagnosis of lung tumors is discussed in a separate section, but two points deserve to be emphasized here. One point is that a positive TTF-1 stain cannot be used to support a diagnosis of a primary pulmonary small-cell carcinoma or to exclude a metastatic small-cell carcinoma from an extrapulmonary primary.[53] The second point is that it is a mistake to rely on neuroendocrine markers alone for the diagnosis of small-cell carcinoma. Not only are neuroendocrine markers negative in about 10% of small-cell carcinomas, but other tumors within the differential diagnosis may be positive for neuroendocrine markers. The difficulties that can be encountered in separating small-cell carcinoma from carcinoid tumors and other non–small-cell carcinomas in a small biopsy are discussed in greater detail in a separate section, as is the distinction from large cell neuroendocrine carcinoma. But in general, it might be considered that the name itself, "small-cell" carcinoma, has led to a relative overemphasis on cell size in comparison to other criteria. From a therapeutic point of view, the recognition of any small-cell component has significant clinical implications, but interpretative disagreements as to whether the tumor is a combined small-cell carcinoma (small-cell carcinoma mixed with any type of non–small-cell carcinoma component) or a pure small-cell carcinoma may not.

LARGE CELL NEUROENDOCRINE CARCINOMA OF THE LUNG

In 1991, Travis and colleagues[54] first proposed criteria for this entity, which was considered to be histologically distinct from atypical carcinoid tumor or small-cell carcinoma. A great deal of controversy ensued over that following decade and continues to some extent to the current time, although rapid advances in the molecular classification of lung tumors have shifted the focus away from pure morphologic characterization as the basis for treatment. As mentioned in the introduction to this section on pulmonary neuroendocrine tumors, one controversy centers on the reproducibility of the diagnosis of large cell neuroendocrine carcinoma. One study has demonstrated substantial agreement, at least among experienced lung pathologists.[51] In this study, a majority consensus diagnosis was achieved for 50% of the cases of large cell neuroendocrine carcinoma, which is no worse than other categories of lung tumors. However, there are a number of other studies that question the reproducibility of the diagnosis and have highlighted the considerable overlap in cell size and the substantial degree of subjective interpretation that is required for categorization.[49,55–58] Also problematic, as it is for other WHO lung tumor entities, is that the definition of large cell neuroendocrine carcinoma applies to resected tumors and not to smaller samples. A third controversy has focused on the clinical significance of the diagnosis, particularly in relationship to small-cell carcinoma. From an epidemiologic perspective, both tumors are associated with heavy tobacco use and both tumors can occur in combination with other non–small-cell lung cancers. Both tumors are aggressive high-grade neuroendocrine tumors and have a very poor prognosis.

Large cell neuroendocrine carcinoma is defined as "a high-grade non–small-cell carcinoma with neuroendocrine morphology and a mitotic count of >10 mitoses/2 mm^2, that expresses one or more neuroendocrine immunohistochemical markers."[5] Histologic features that suggest neuroendocrine differentiation include organoid nesting, trabecular, rosette-like, and palisading patterns. The cells are relatively large in size, often polygonal in shape, with moderate to abundant cytoplasm. The nuclear chromatin ranges from vesicular to finely granular. Nucleoli are frequent and often prominent (Fig. 111-19A). The presence of nucleoli tends to be a critical feature in the separation from small-cell carcinoma (Fig. 111-19B), but some large cell neuroendocrine carcinomas lack this criterion. As mentioned previously, neuroendocrine differentiation must be demonstrated by ancillary techniques such as immunohistochemistry. CD56, chromogranin, and synaptophysin are the three stains that are most frequently used together if there is sufficient tissue and are considered to be more specific than neuron-specific enolase, which is not recommended to use. For a tumor to be designated as a large cell neuroendocrine carcinoma, the tumor must have both neuroendocrine morphology and positive staining. Tumors that otherwise look like squamous cell carcinomas, adenocarcinomas, or large cell carcinomas but have focal neuroendocrine staining are not included in this definition and are not formally part of the WHO classification. *Combined large cell neuroendocrine carcinoma* refers to a large cell neuroendocrine carcinoma with components of another non–small-cell carcinoma such as, for example, squamous cell carcinoma or adenocarcinoma.

The low incidence of the tumor (estimated as 3% of non–small-cell carcinomas) has resulted in a lack of robust evidence for

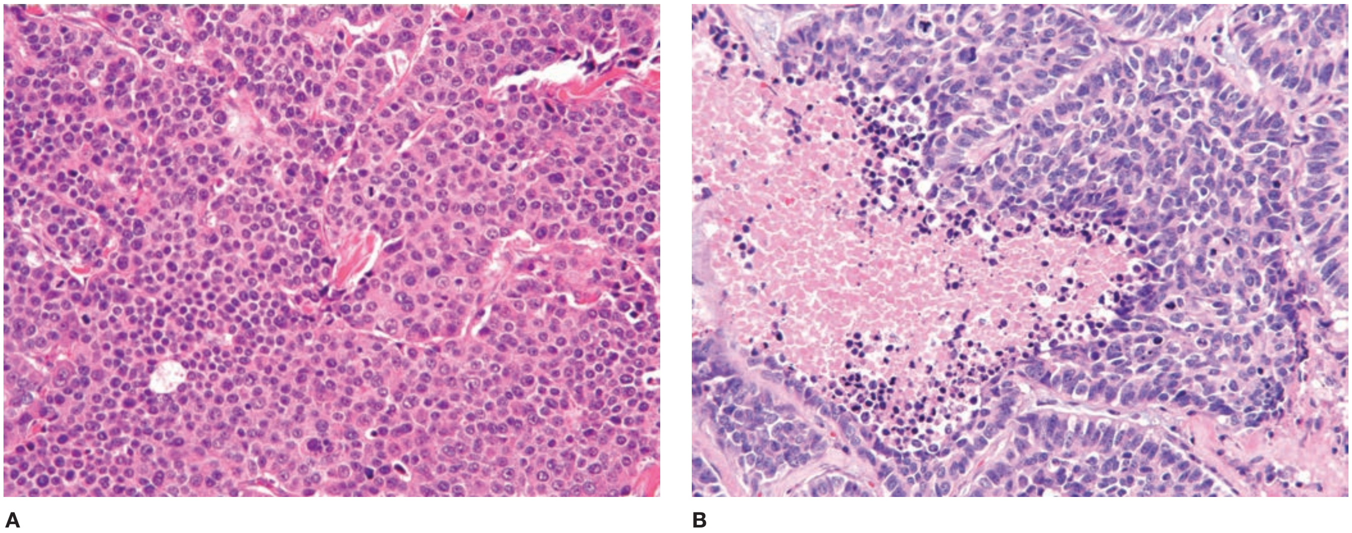


Figure 111-19 Side-by-side comparison of large cell neuroendocrine carcinoma **(A)** with small cell carcinoma **(B)**. The large cell neuroendocrine tumor cells have more cytoplasm and there are more prominent nucleoli. The small cell carcinoma tumor cells have less cytoplasm and the nuclear chromatin is finely granular. (H&E, 200×).

stage-based treatment strategies.[44] What can be concluded is that the molecular genotype and phenotype of large cell neuroendocrine carcinoma and small-cell carcinoma in some data subsets are similar enough to support at least consideration of extrapolation from treatment paradigms for small-cell carcinoma and, as has been suggested, to include unresectable disease large cell neuroendocrine carcinoma patients within clinical trials for small-cell carcinoma to obtain prospective data. It is anticipated that in the future these data may further clarify the clinical and pathologic distinction between these two high-grade neuroendocrine carcinomas.

SALIVARY GLAND–TYPE TUMORS

Mixed seromucinous glands are found in the tracheal and large bronchial submucosa and are believed to give rise to a variety of salivary gland–like tumors, histologically indistinguishable from their major salivary gland counterparts. The 2021 WHO recognizes six subtypes of malignant salivary gland tumors in the lung: pleomorphic adenoma, adenoid cystic carcinoma, epithelial–myoepithelial carcinoma, mucoepidermoid carcinoma, hyalinizing clear cell carcinoma, and myoepithelioma (as well as myoepithelial carcinoma).[5] Other salivary gland–like tumors such as acinic cell carcinoma or carcinoma ex pleomorphic–mixed tumor do occur in the lung but are exceptionally rare. Salivary gland carcinomas represent less than 1% of all lung carcinomas, with mucoepidermoid carcinoma and adenoid cystic carcinoma being the most common subtypes.[5] Although uncommon, their distinctive morphology, growth pattern, and clinical presentation make these salivary gland–type tumors of the lung an important subgroup of malignant epithelial tumors of the lung. In all instances of suspected primary salivary gland–type tumors, it is important to exclude metastasis from an extrathoracic primary, particularly from the head and neck.

■ Adenoid Cystic Carcinoma

Adenoid cystic carcinoma is the most common of the tracheobronchial gland tumors but is still quite rare, representing less than 1% of all primary lung tumors.[5] There is no association with smoking. The vast majority of cases originate within the bronchial lumen, and the typical presenting symptoms such as wheezing, progressive dyspnea, stridor, cough, and hemoptysis reflect this intraluminal tumor growth. Unlike carcinoid tumors and mucoepidermoid carcinomas, which usually present as intraluminal endophytic masses, adenoid cystic carcinomas have a more variable growth pattern. Some tumors are grossly nodular with minimal invasion of the bronchus, whereas others have a mixed nodular/infiltrative or predominantly infiltrative growth pattern (Fig. 111-20A,B). More infiltrative tumors appear as small nodules within the airway or cause a generalized constriction of the airway. There may be lymph node involvement, usually by direct extension, and higher-grade tumors have a tendency to radially spread into the adjacent parenchyma rather than along the airways.

The microscopic level of invasion nearly always exceeds that which is grossly apparent. Negative resection margins often are difficult to achieve. Complete resection may be quite difficult and can require multiple frozen sections to confirm clear surgical margins. The tumor cells are small with a relatively high nuclear:cytoplasmic ratio, but nuclear pleomorphism and mitoses are rare. Characteristic mucinous cysts of varying size are present within the tubular and cribriform patterns (Fig. 111-20C). Poorly differentiated tumors have a significant component of solid tumor nests. As is characteristic of their salivary gland counterparts, adenoid cystic carcinomas are notorious for perineural spread. Long-term survival can be achieved with adequate resection, but local recurrence may occur even late (>10 years) following resection. The most common site of disseminated disease is the lung parenchyma, but extrathoracic metastases do uncommonly occur.[59] As with adenoid cystic carcinomas of the head and neck, *MYB-NFIB* gene fusion testing can be used to support the diagnosis.[60,61]

■ Mucoepidermoid Carcinoma

Mucoepidermoid carcinomas account for <1% of lung cancers.[5] Patients with this tumor may be asymptomatic, but it is far more common for patients to present with symptoms of bronchial obstruction due to the tumor's characteristic endobronchial location.[62] These symptoms include wheezing, cough, and hemoptysis, and patients may present with postobstructive pneumonia. The age at presentation varies, but almost half of the cases of mucoepidermoid carcinoma occur in patients under 30 years of age and it is common in the pediatric population. There is no significant association with tobacco use. Although the radiographic findings may be subtle and identified in retrospect, a solitary, centrally located mass with distal pneumonia or atelectasis is typical.

Mucoepidermoid carcinomas usually arise from segmental and subsegmental bronchi but can involve the trachea as well. The

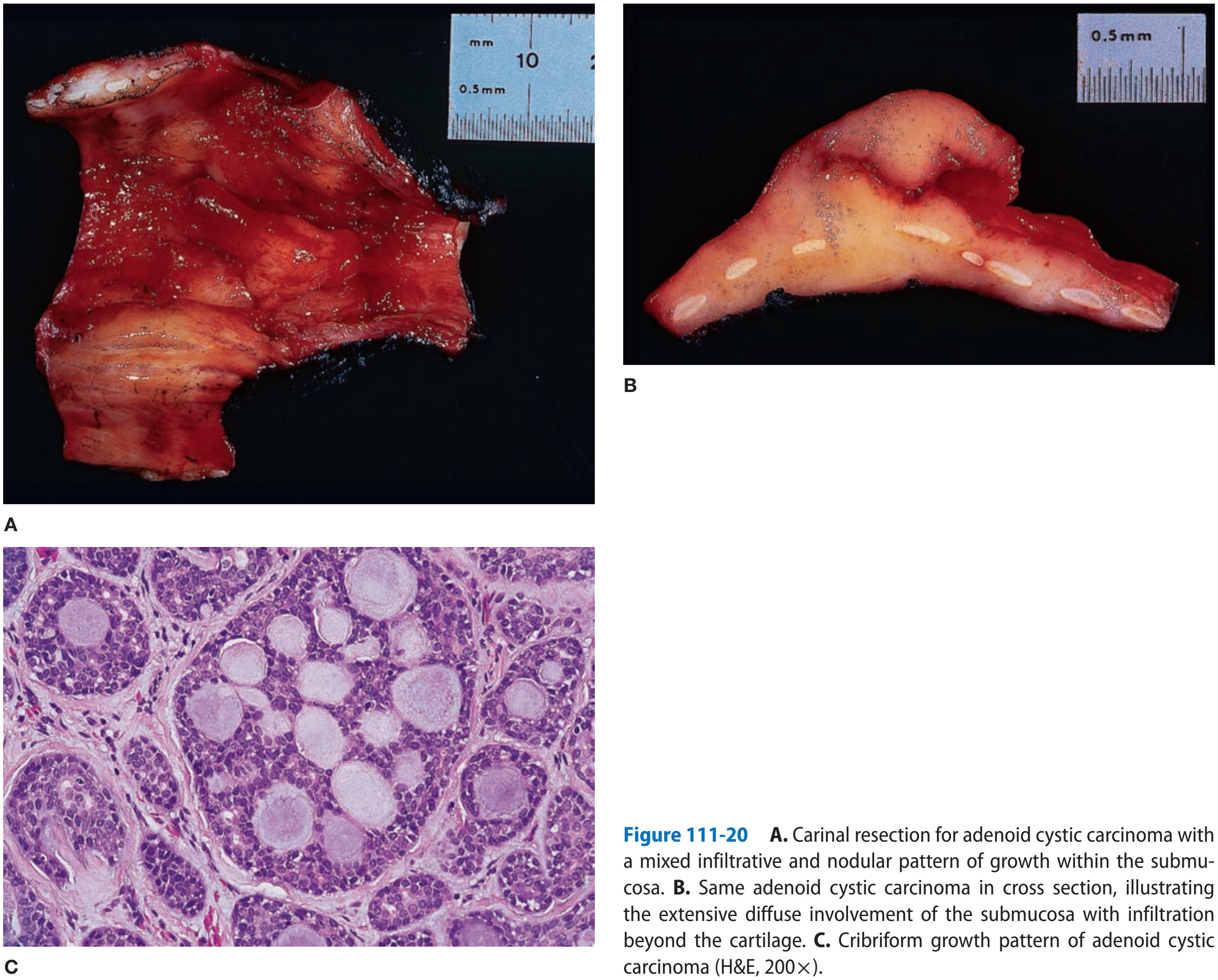


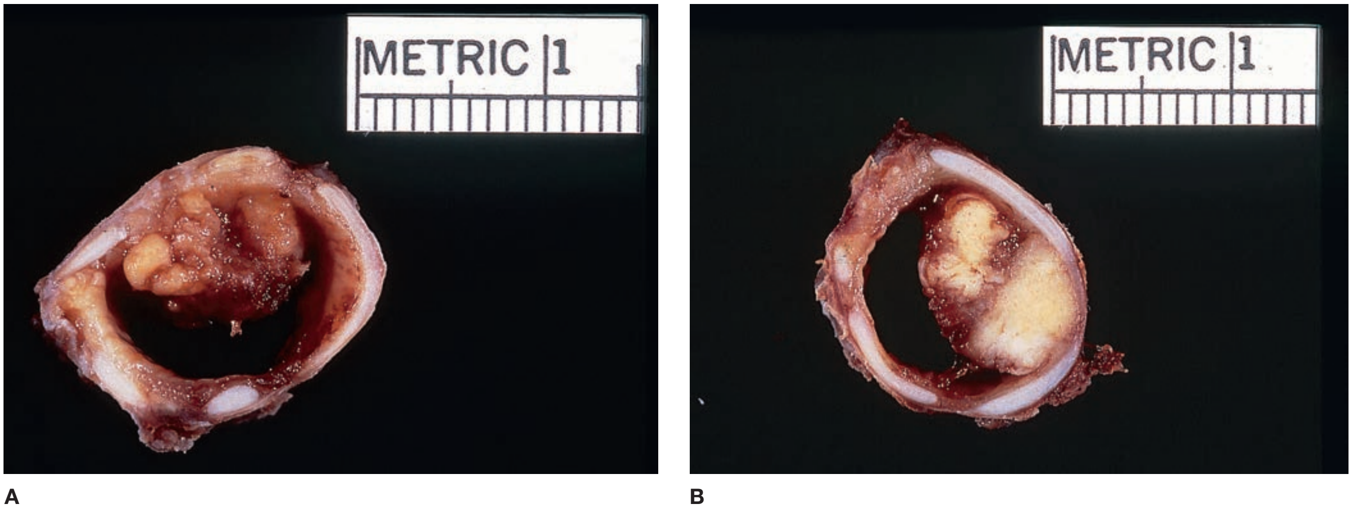
Figure 111-20 **A.** Carinal resection for adenoid cystic carcinoma with a mixed infiltrative and nodular pattern of growth within the submucosa. **B.** Same adenoid cystic carcinoma in cross section, illustrating the extensive diffuse involvement of the submucosa with infiltration beyond the cartilage. **C.** Cribriform growth pattern of adenoid cystic carcinoma (H&E, 200×).

average size is about 3 cm, and the tumor grows as a polypoid mass with a tan or gray surface (Fig. 111-21A,B). On cross section, the tumor may appear more mucoid or cystic than the more common non–small-cell carcinomas of the lung. Histologically, mucoepidermoid tumors of the lung are separated into low- and high-grade tumors.[63,64] An "intermediate grade," which is used for tumors within the salivary gland, is not normally recognized within the WHO lung classification. The tumors are composed of a mixture of mucin-secreting cells, squamous cells, and what are termed "intermediate cells." The intermediate cells have a polygonal shape and eosinophilic cytoplasm but lack obvious squamous or glandular differentiation. The mucinous component consists of well-differentiated glands, with both intracellular and extracellular mucin (Fig. 111-21C). These tumors are TTF-1 negative. In low-grade tumors, the cells have minimal pleomorphism, rare mitoses, and minimal necrosis. Criteria for high-grade tumors include frequent mitoses, necrosis, and nuclear pleomorphism. High-grade mucoepidermoid carcinomas still retain a characteristic admixture of mucin-containing cells, squamoid cells, a central endobronchial location, and transitional areas from low-grade mucoepidermoid carcinoma. There should be no keratinization, squamous pearl formation, or in situ squamous cell carcinoma. These features, if present, are more consistent with a diagnosis of squamous or adenosquamous carcinoma. *CRTC1-MAML2* gene fusion testing can be used to support the diagnosis.[65]

The clinical behavior of these neoplasms had been controversial, mainly due to past ambiguities regarding the definition of high-grade mucoepidermoid carcinomas and their distinction from adenosquamous carcinomas. Low-grade tumors, which are usually confined to the bronchus, have an excellent prognosis following complete excision. High-grade tumors, which tend to invade the adjacent lung parenchyma, carry a worse prognosis and tend to behave in a manner similar to more common non–small-cell carcinomas. The data suggest that long-term clinical follow-up is indicated for these patients. Lymph node metastasis and incomplete resection are associated with a poor prognosis.[5]

■ Epithelial–Myoepithelial Carcinoma

The 2021 WHO classification defines epithelial–myoepithelial carcinoma as a biphasic tumor that consists of an inner layer of epithelial cells forming duct-like structures and an outer layer of myoepithelial cells (Fig. 111-22).[5] The tumor is extremely rare, accounting for less than 4% of primary salivary gland-type tumors of the lung.[5,66–68] Endobronchial tumors are most common, but the tumor may also arise within the lung parenchyma. There is a wide reported age range, and there are no known risk factors. Grossly the tumor is well circumscribed but unencapsulated, with a size range of 1.2 to 5.0 cm. Microscopically, the tumor consists of duct-like structures that are lined by a double layer of cells with an inner layer of cuboidal cells with eosinophilic cytoplasm and an outer layer of cells with predominantly clear cell cytoplasm. There is often eosinophilic material in the luminal spaces. The outer layer of cells and more solid components typically stain positively for SMA, S-100, p63, and



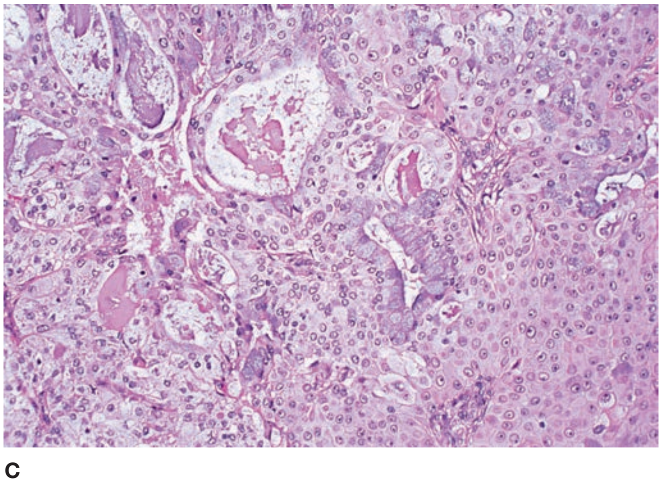


Figure 111-21 **A.** Left mainstem bronchus resection for endobronchial mucoepidermoid carcinoma. **B.** Same mucoepidermoid carcinoma tumor in cross section, demonstrating an attachment to the bronchus but invasion is limited to the superficial portion of the submucosa. **C.** Mucoepidermoid carcinoma. There are both well-differentiated mucinous glands *(left)* and intermediate cells *(right)* that have a polygonal shape and abundant eosinophilic cytoplasm (H&E, 200×).

calponin, which is characteristic of myoepithelial cells. The inner layer of tumor cells stains positively with cytokeratins (CAM5.2, AE1/3, CK7, and CK903) as well as EMA and TTF-1.[5] The positive TTF-1 staining is of interest in that other salivary gland–type tumors such as adenoid cystic carcinoma and mucoepidermoid carcinoma are reported to be TTF-1 negative. Most cases are low grade, with patients free of disease following complete surgical resection, but a minority of cases demonstrate lymph node involvement or recurrent disease.[66–68]

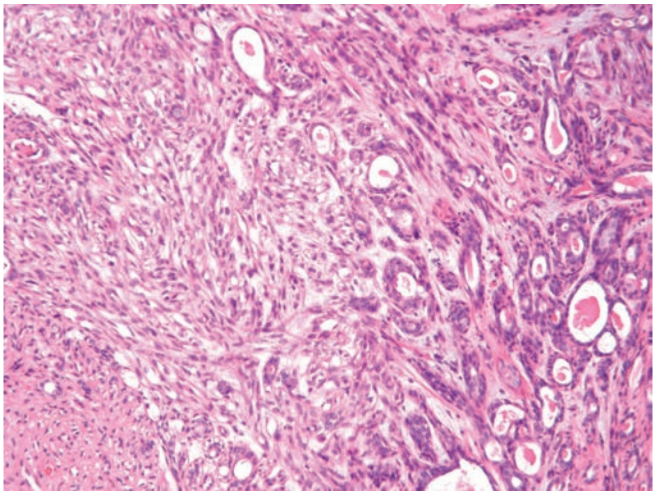


Figure 111-22 Epithelial–myoepithelial carcinoma. Tumor is composed of duct-forming epithelium and myoepithelial cells with a spindle cell morphology (100×).

ANCILLARY STUDIES

The lung is a common site for both primary tumors and metastases, and the pathologist must consider a broad differential diagnosis when analyzing a cytologic or tissue preparation. Ancillary studies typically are used to narrow the differential diagnosis or demonstrate differentiation. The appropriate use of ancillary studies is grounded in a well-formulated differential diagnosis based on the tumor's histologic appearance. The clinician contributes greatly by providing the details of a complete clinical history, thorough physical examination, and high-quality radiographic imaging. This helps direct the diagnostic work-up and avoids unnecessary tests that will delay the diagnosis or exhaust the tumor contained in that specimen. This latter consideration is particularly critical in the current era of molecular testing when the results are often needed in an expedited manner and *prior* to initiating treatment.

■ Histochemical Stains

The most commonly used histochemical stains in tumor evaluation are those that demonstrate intracellular mucins—periodic acid–Schiff (PAS) after diastase and mucicarmine—characteristic of adenocarcinomas. Mucin stains are typically performed on poorly differentiated carcinomas that appear as solid carcinomas lacking glandular differentiation but prove to have numerous mucin-positive tumor cells and therefore would be best classified as adenocarcinomas, solid type (Fig. 111-23). While helpful in some instances, mucin stains have a low sensitivity for glandular

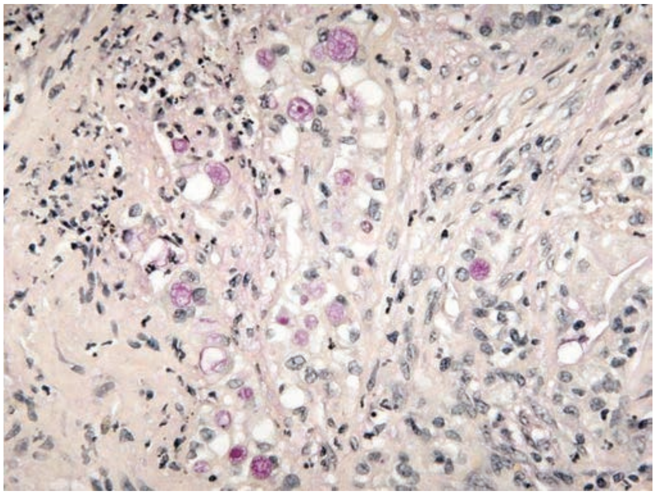


Figure 111-23 Positive mucin stain in a poorly differentiated non–small cell carcinoma with clear cell change, supporting the diagnosis of adenocarcinoma (400×).

differentiation (about 30%).[69] Although practice patterns vary somewhat, pathologists will often forego a mucin stain in small biopsies in an effort to preserve as much tissue as possible and do a limited panel of immunohistochemical stains instead. Alcian blue staining with hyaluronidase treatment can be used to distinguish the acid mucin of mesothelial cells from the epithelial mucin associated with adenocarcinomas, but its use has been supplanted by immunohistochemistry.

■ Immunohistochemistry

Immunohistochemistry is based on a primary antigen–antibody reaction and a secondary antibody–enzyme complex that interacts with a chromogen for a microscopically visible color reaction. Since its introduction into diagnostic pathology in the early 1980s, immunohistochemistry has become an integral part of tumor diagnosis. Unfortunately, there are very few antibodies that approach 100% sensitivity and specificity. As experts on immunohistochemistry have emphasized, it is diagnostically irrelevant to speak of overall sensitivity and specificity for a particular antibody. Rather it is more appropriate to speak of relative sensitivity and specificity within a particular differential diagnosis. This requires clinical interaction and morphologic expertise in generating a differential diagnosis in addition to critical assessment of the immunohistochemical results with appropriate controls. New antibodies are developed, evaluated, and introduced at a fairly constant rate. The following summary remarks are meant only as broad overview of current practice with the understanding that the field is constantly evolving and that all of the markers mentioned have utility both in and outside of the lung.[70]

Immunohistochemistry is often used in the work-up of an undifferentiated large cell carcinoma, usually to exclude melanoma and lymphoma, which can mimic a highly pleomorphic epithelial tumor. Within this differential diagnosis of an undifferentiated tumor composed of large cells, cytokeratin antibodies such as AE1/3, CAM5.2, and pancytokeratin are used to support the diagnosis of carcinoma. Cytokeratin antibodies will at least focally stain most non–small-cell carcinomas of all histologic subtypes, in addition to a wide variety of carcinomas from other primary sites. There are, however, potential pitfalls. Cytokeratin antibodies stain benign bronchial and alveolar epithelia, which can be entrapped within tumors and lead to a false-positive interpretation. Reactive mesothelial cells and malignant mesotheliomas are cytokeratin positive as well. Cytokeratin positivity, usually focal, also has been demonstrated in sarcomas and melanomas. S100, HMB45, SOX10, melan-A, MITF, and tyrosinase are markers of melanocytic differentiation; a panel using at least two or three of these is often employed when malignant melanoma is a strong consideration. Although sensitive, S100 is less specific for melanoma and stains other tumors, including those of neural origin and some adenocarcinomas of both primary pulmonary and extrapulmonary origin, such as the breast. The range of markers used to evaluate lymphoid neoplasms is extensive but include leukocyte common antigen (LCA), CD30, and B and T cell markers. There are antibodies to glycoproteins such as CEA, MOC31, and BerEP4, which stain a high percentage of adenocarcinomas, including adenocarcinomas of the lung. Recommended guidelines on the use of immunohistochemistry when the differential diagnosis includes malignant mesothelioma have been published and updated.[71] When the differential diagnosis centers on an epithelioid malignant mesothelioma versus adenocarcinoma, a panel of at least two affirmative markers for malignant mesothelioma and two affirmative markers for adenocarcinoma is recommended.

Immunohistochemistry is similarly used in the work-up of an undifferentiated small-cell carcinoma, usually to exclude melanoma and other "small round blue cell tumors" such as lymphoma, Merkel cell carcinoma, and other primitive neuroectodermal tumors. In this instance, attention to subtle differences in nuclear cytology, chromatin pattern, and mitotic activity is essential, as is a targeted immunohistochemical panel that might include (depending on the circumstances) pancytokeratin, synaptophysin, chromogranin, CD56, TTF-1, CK7, CK20, CD99, S-100, desmin, WT-1, LCA, myogenin, and TLE. Unusual clinical circumstances or radiographic imaging, particularly but not limited to a younger patient or a nonsmoker, should prompt consideration of a broad immunohistochemical workup as well as molecular tests for characteristic cytogenetic abnormalities for tumors such as a synovial sarcoma, desmoplastic small round cell tumor, NUT carcinoma, thoracic SMARCA4-deficient undifferentiated tumor, Ewing sarcoma, and rhabdomyosarcoma.

The use of immunohistochemistry has not eliminated the challenges of distinguishing a primary lung carcinoma from metastatic disease. There are only a limited number of instances in which immunohistochemical stains are useful in differentiating a pulmonary primary from a metastatic tumor. With the exception of thyroglobulin for the majority of thyroid tumors and prostate-specific antigen or NKX3.1 for the majority of prostatic adenocarcinomas, many other antibodies have too much overlap in specificity to be conclusive. There has been some qualified success in instances when the differential diagnosis includes other common solid organ malignancies such as breast or gastrointestinal carcinomas. Staining with a panel of antibodies to bolster one's diagnostic certainty in the differential diagnosis of primary lung carcinoma versus metastasis can certainly enhance diagnostic accuracy. Fundamentally, however, this type of immunohistochemical analysis remains an exercise in probabilities and may not be sufficient for certain clinical circumstances. It is most often the case that new markers are introduced into the literature with initial reports of high sensitivity and specificity. After a time, with additional studies and incorporation into daily practice, more exceptions appear. A good example is TTF-1. On average, TTF-1 stains about 75% of primary pulmonary adenocarcinomas, although the percentage is lower in more poorly differentiated tumors, some subtypes of adenocarcinoma, and better-differentiated neuroendocrine tumors.[31] It was initially believed that the only extrapulmonary tumor that was as frequently positive for TTF-1 was thyroid carcinoma. Now there are reports of TTF-1 positivity in extrathoracic tumors that would not be expected—such as ovarian epithelial tumors—making the marker less specific than was initially asserted although often still useful.[31] The same can be said of gastrointestinal profile panels that use CK7, CK20, TTF-1, Napsin A, and CDX2 to support a luminal GI primary. Although many GI primaries will have a CK20, CDX2 positive and CK7, TTF-1, Napsin A negative staining pattern, a small subset of primary lung tumors with an "enteric" differentiation will show an overlapping staining pattern.[72] Whether "molecular profiles" will be able to improve diagnostic accuracy or supplant the relatively rapid turnaround time and low cost of immunohistochemistry remains to be seen.

As discussed in the section on pulmonary neuroendocrine tumors, the artifacts that are often present in small samples can make it difficult to separate out small-cell carcinoma from other non–small-cell carcinomas or to apply the criteria for separating out carcinoid tumors from the higher-grade neuroendocrine carcinomas. In addition to some of the other immunohistochemical stains mentioned for supporting neuroendocrine differentiation (synaptophysin, chromogranin, CD56, and INSM1), an extended panel might also include CK5/6, p40, and TTF-1 to exclude the possibility of a basaloid or small-cell variant of squamous cell carcinoma.[73] The proliferation marker ki-67 is routinely used in smaller specimens as a surrogate for identifying mitoses, which may be absent or infrequent. Although not completely standardized or reproducible, an increased proliferation index can be helpful in favoring a lower- or higher-grade neuroendocrine tumor.[50,74]

The need for a more precise classification of poorly differentiated non–small-cell carcinoma into squamous or nonsquamous histology has further expanded the use of immunohistochemistry within pulmonary pathology. A significant proportion of small biopsies (and some large resections) will not have obvious evidence of squamous differentiation, as defined by keratinization or intercellular bridges, or obvious features of adenocarcinoma, as defined by gland formation or intracellular mucin. In these instances when the tumor cells are arranged in solid nests and there is no specific evidence of differentiation, a panel of immunohistochemical stains can be used for further subclassification. There are numerous studies that have looked at the utility of immunohistochemistry in reducing the category of "non–small-cell lung carcinoma, not otherwise specified" and the minimum number of stains needed for evaluation. The latter point, of using the least number of stains with the most specificity and sensitivity, is not a trivial issue in the usual case of an advanced-disease patient who will have an initial biopsy that will likely be triaged for targeted therapy. At the current time, the data support at minimum a panel that includes TTF-1, CK5/6, and p40, with addition of stains such as Napsin A or CK7 if there is sufficient tissue (Fig. 111-24A–D).[68,75–77] Beyond using evidence to construct the best limited immunohistochemical panel to determine differentiation, other techniques such as dual-antibody staining cocktails can reduce the amount of tissue used (Fig. 111-25). As discussed in greater detail in the following section, processing decisions must be

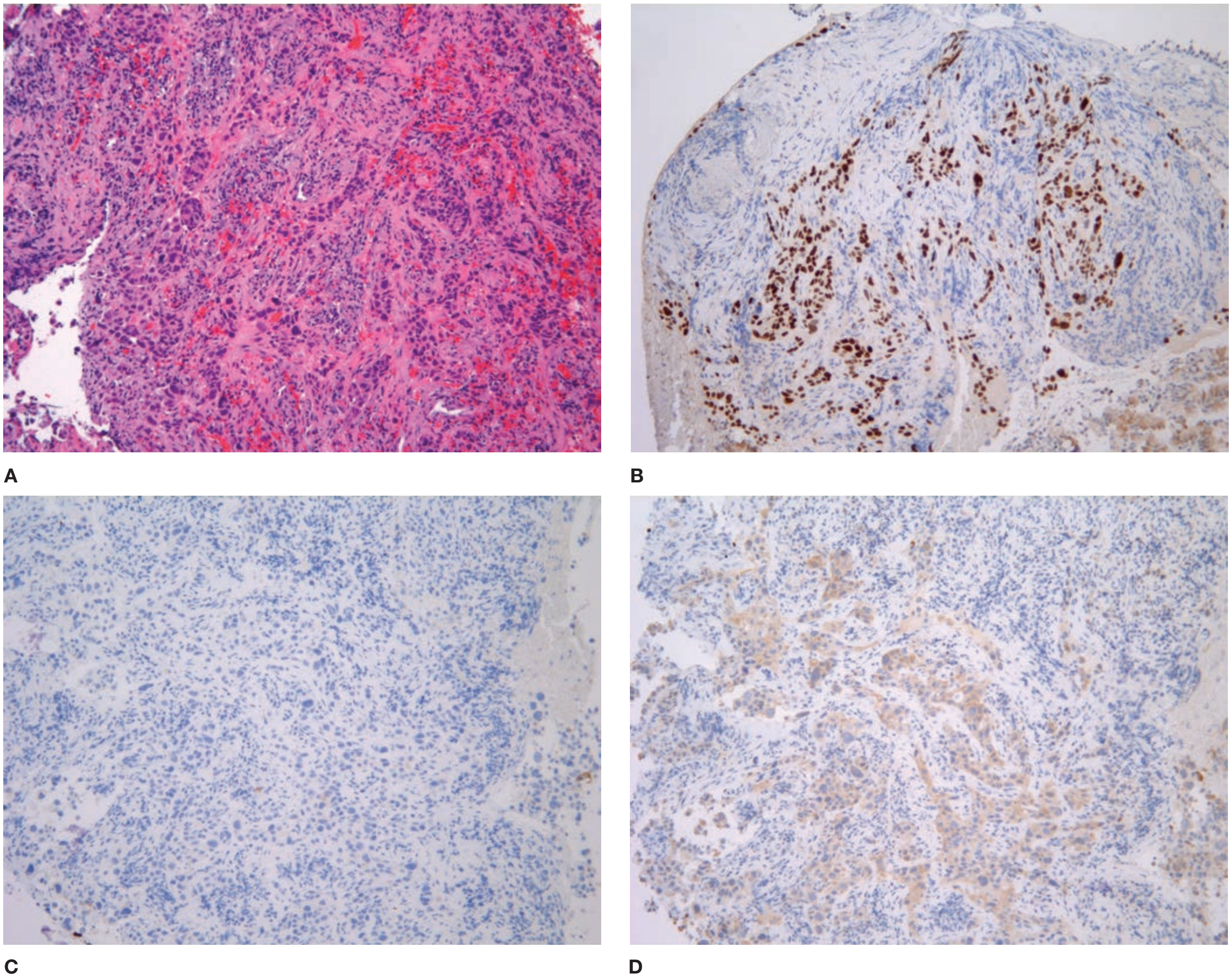


Figure 111-24 Small biopsy showing poorly differentiated non–small cell carcinoma and immunohistochemical stains supporting the diagnosis of pulmonary adenocarcinoma. **A.** H&E (100×). **B.** TTF-1 antibody positive (100×). **C.** CK5/6 antibody negative (100×). **D.** p63 antibody negative in tumor nuclei (100×).

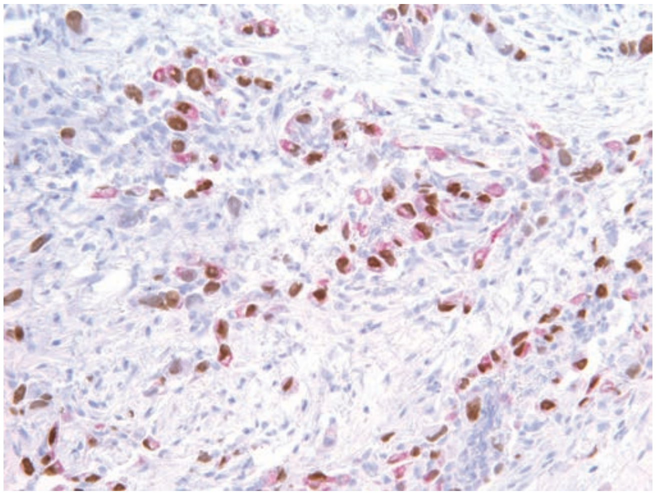


Figure 111-25 Poorly differentiated non–small-cell carcinoma with squamous differentiation demonstrated by positive dual antibody immunohistochemical staining for CK5/6 *(pink)* and p63 *(nuclear brown staining)* (200×).

made up front to ensure that there is sufficient material for diagnosis, immunohistochemical stains if necessary, and residual tissue for molecular testing.

The increased use of immunohistochemistry for histologic subclassification has generated debate, particularly in the context of clinical trials for advanced disease patients, as to what exactly it means—biologically, therapeutically, and prognostically—for a tumor to have only immunohistochemical evidence of differentiation. These issues were further complicated by the conspicuous historic lack of any standard nomenclature for small biopsies. The 2021 WHO classification includes terminology for small biopsies/cytology specimens in these instances that should help in the adoption of standardized terminology in general practice and within academic medical centers.[5]

ADEQUACY OF SMALL SPECIMENS FOR DIAGNOSIS, TREATMENT, AND MOLECULAR ANALYSIS

Small specimens occupy a central role in the majority of patients with lung cancer—often at multiple time points during the course of their disease—and the clinical relevance of these small specimens has led to a “paradigm shift” in the way these small specimens are processed and interpreted.[78] Bronchoscopic biopsies with or without endobronchial ultrasound guidance, fine-needle aspiration, and body fluid cytologic examination are all acceptable as minimally invasive procedures for the initial diagnosis of a primary lung carcinoma or to document metastasis. With the emerging emphasis on the importance of histologic subtyping in non–small-cell lung cancer and the need for molecular analysis for “personalized” or “precision” medicine, the debate in recent years had focused on whether small specimens are adequate for these purposes. Numerous studies have now established that a variety of specimens, ranging from small biopsies to cytology cell blocks to cytology touch imprints or aspirates, are potentially suitable for molecular testing and the practical considerations for testing have been recently and comprehensively reviewed.[79] The essential point is that small diagnostic specimens must be handled carefully from the outset of any procedure with the understanding that the specimen may be the only specimen available for molecular analysis. Within each specific practice setting, an algorithm should be established that emphasizes the need for communication between the pathologist and the clinical care team *before* the specimen is processed.[80] This clinical information should include such information as whether the biopsy is for initial diagnosis, whether the patient is a candidate for surgical resection, whether the patient is a candidate for targeted therapy, whether the biopsy is for molecular prioritization in a patient with an established diagnosis of lung cancer, or whether the biopsy is a repeat biopsy for resistance testing. All of this information will in turn allow the pathologist to communicate with molecular and histology laboratories to ensure that the specimen is appropriately triaged and that the optimal material is selected for diagnosis, ancillary immunohistochemical testing, and molecular prioritization.

CONCLUSION

In addition to the clinicopathologic features and histologic subtyping of primary pulmonary carcinomas, recent changes in tumor classification and sample evaluation have been reviewed. The pathologist makes a critical contribution to the management and treatment of lung carcinoma, but the final pathologic interpretation should not be rendered in a clinical vacuum. It is incumbent upon the clinician caring for the patient to be sure that the pathologist has the benefit of complete clinical information. Nowhere is this clinical information and communication more critical than in the processing of small specimens in this era of personalized medicine. The inclusion of the pathologist as an integral part of what is now a multidisciplinary evaluation team for a thoracic malignancy enhances the quality of care for the individual patient and refines the general practice of thoracic oncology.

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CHAPTER 112

Clinical Evaluation, Diagnosis, and Staging of Lung Cancer

A. Cole Burks
M. Patricia Rivera

INTRODUCTION

Patients who present with suspected lung cancer require a detailed clinical evaluation followed by noninvasive testing and invasive procedures to establish both the histopathologic diagnosis as well as disease stage. Historically, great emphasis has been placed upon the differentiation of small-cell lung cancer (SCLC) from non–small-cell lung cancer (NSCLC). SCLC, which accounts for 13% of bronchogenic carcinomas, is histologically and clinically distinct from NSCLC.[1] NSCLCs comprise clinically, pathologically, and molecularly diverse tumors that respond to different therapeutic agents based on specific histologic phenotypes and molecular characteristics.

The clinician evaluating the patient with suspected lung cancer must take into account several factors, including the likelihood of SCLC versus NSCLC, probability of metastatic disease, comorbid illness, functional status, presence of paraneoplastic syndromes, and treatment preferences of the patient. Good decision-making regarding appropriate diagnostic test selection must incorporate (1) careful assessment of pretest probabilities based upon clinical evaluation and initial radiographic features, and (2) understanding of specific test characteristics. The main objectives of the diagnostic and clinical staging evaluation are to obtain adequate tissue to establish the histopathologic diagnosis and, when indicated, molecular and diagnostic biomarker testing screening for actionable oncogenic driver mutations and programmed death ligand 1(PD-L1) expression, and to ascertain the extent of disease to determine candidacy for specific therapies. These twinned goals should be accomplished in the safest, least invasive, and most cost-effective manner possible.

INITIAL CLINICAL EVALUATION

A detailed history and physical examination are of key importance in the assessment of the patient's overall health status and medical appropriateness for specific therapies.[2] Certain comorbid conditions may reduce therapeutic options. Limited cardiopulmonary reserve may preclude surgical intervention. A thorough history can also assist a physician in determining the overall extent of disease. At the time of presentation, it is most useful to consider the clinical stage using the International Association for the Study of Lung Cancer (IASLC) 8th edition of the tumor, node, and metastasis (TNM) classification system (Table 112-1); pathologic stage is established only after surgical resection.[3]

TABLE 112-1 TNM Staging System for Lung Cancer

Primary tumor (T)	Tis	Carcinoma in situ
	T1	Tumors ≤3 cm that do not invade the lobar bronchus and do not invade the visceral pleura
	T1a(mi)	Minimally invasive adenocarcinoma
	T1a	Tumors ≤1 cm
	T1b	Tumors >1 cm but ≤2 cm
	T1c	Tumors >2 cm but ≤3 cm
	T2	Tumors >3 cm but ≤5 cm *or* • Invades the visceral pleural • Invades the mainstem bronchus but not involving the carina • Is associated with atelectasis or obstructive pneumonia extending from the hilum
	T2a	Tumor >3 cm but ≤4 cm
	T2b	Tumor >4 cm but ≤5 cm
	T3	Tumors >5 cm but ≤7 cm *or* • Direct invasion of chest wall, phrenic nerve, mediastinal or parietal pleural, parietal pericardium • Superior sulcus tumors • Satellite tumor nodules within same lobe
	T4	Tumors >7 cm *or* • Invade any of the following: mediastinum, trachea, recurrent laryngeal nerve, carina, vertebral body, diaphragm, great vessels, or esophagus • Satellite tumor nodule within a different lobe of the ipsilateral lung
Regional lymph nodes (N)	N0	No regional lymph node metastases
	N1	Metastases or involvement by direct extension of ipsilateral peribronchial, intrapulmonary, or hilar nodes
	N2	Metastases to ipsilateral mediastinal or subcarinal lymph node
	N3	Metastases to any scalene or supraclavicular lymph node or to contralateral mediastinal or hilar nodes
Distant metastases (M)	M0	No distant metastases
	M1	Distant metastases present
	M1a	Satellite tumor nodule(s) in contralateral lung, pleural or pericardial nodules, or malignant pleural or pericardial effusion
	M1b	Single extrathoracic metastasis
	M1c	Multiple extrathoracic metastases in one or more organs

Adapted with permission from Goldstraw P, Chansky K, Crowley J, et al. The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. J Thorac Oncol. 2016;11(1):39-51.

More than 75% of patients are symptomatic at the time of initial diagnosis due to the vast majority of lung cancer presenting at a later stage.[4,5] The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program database survey of patients diagnosed with lung cancer demonstrates that the majority of patients continue to have either locally advanced (stage III) or metastatic disease (stage IV) at the time of diagnosis. Only ~25% of patients have

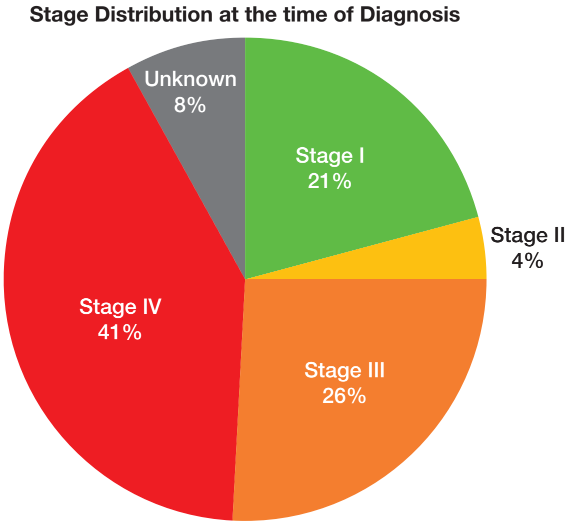

Figure 112-1 Stage distribution at the time of diagnosis.

stage I or stage II, whereas ~26% have stage III disease and ~41% have metastatic disease (stage IV) (Fig. 112-1).[6,7]

Patients often have had symptoms for months before diagnosis.[1,8,9] Symptoms, particularly those associated with localized disease such as cough, wheezing, and dyspnea, are often attributed to comorbid illnesses by both patients and their physicians. In one study in the United Kingdom of newly diagnosed lung cancer patients, symptom duration ranged from 4 to 24 months with a median of 12 months.[10] In one of the earliest series describing the relationship of presenting symptoms to stage and prognosis, about a third of patients (27%) presented with symptoms related to primary tumor only (Table 112-2), another third (34%) presented with nonspecific symptoms concerning for metastatic disease, and the final third (32%) presented with symptoms attributable to a distant metastatic site; only 6% were asymptomatic.[11]

Local symptoms can include cough, hemoptysis, dyspnea, chest pain, and wheezing.[12,13] Cough is the most frequently encountered presenting symptom and can be the result of endobronchial or parenchymal involvement by the primary tumor, regional lymph node enlargement, or postobstructive complications. Hemoptysis is the symptom that typically results in the most expeditious evaluation; about 5% of patients with hemoptysis and a normal chest x-ray will ultimately be diagnosed with lung cancer.[14] Chest discomfort and pain may indicate pleural involvement or direct tumor invasion of the chest wall or thoracic cage. Hoarseness, which can occur in up to 5% of lung cancer patients at presentation, suggests laryngeal nerve palsy, which can occur in 2% to 18% of lung cancer patients.[12] This is more commonly seen with left-sided tumors, which can involve the recurrent laryngeal nerve as it loops under the aortic arch.[13] Lung cancer accounts for up to 75% of all cases of superior vena cava (SVC) syndrome due to local compression or invasion.[15] Signs and symptoms of SVC syndrome include swelling of the face, neck, upper torso, and arms; and dyspnea. Up to 4% of patients with NSCLC and 10% of patients with SCLC develop SVC syndrome. Dysphagia suggests extrinsic compression of the esophagus due to bulky mediastinal disease, particularly involving the subcarinal lymph node, or it can result from direct esophageal invasion. Central tumors such as squamous cell carcinoma may cause airway obstruction resulting in a localized or unilateral wheeze, atelectasis, or postobstructive pneumonia.[16,17] Cancers arising in the lung apex (superior sulcus tumors) can present with Pancoast syndrome, an assortment of clinical manifestations due to invasion or compression of local structures.[18] Characteristic signs and symptoms include shoulder pain due to invasion of the brachial plexus and/or ribs and vertebrae, upper extremity weakness and paresthesia, and Horner syndrome (unilateral ptosis, miosis, and lack of facial sweating on the involved side) due to compression or invasion of the sympathetic chain.[18,19]

TABLE 112-2 Initial Signs and Symptoms of Lung Cancer

Signs and Symptoms	Range of Reported Frequencies (%)
Cough	8–75
Weight loss	0–68
Dyspnea	3–60
Chest pain	20–49
Hemoptysis	6–25
Bone pain	6–25
Fever	0–20
Weakness	0–10
Superior vena cava obstruction	0–4
Dysphagia	0–2
Wheezing	0–2

Data from Andersen HA, Prakash UBS. Diagnosis of symptomatic lung cancer. Semin Respir Med. 1982;3:165–175; Grippi MA. Clinical aspects of lung cancer, Semin Roentgenol. 1990:25:12–24; Hyde L, Hyde CI. Clinical manifestations of lung cancer. Chest. 1974;65:299–306; Cromartie RS III, Parker EF, May JE, et al. Carcinoma of the lung. Ann Thorac Surg. 1980;30:30–35; Karsell PR, McDougall JC. Diagnostic tests for lung cancer. Mayo Clin Proc. 1993;68:288–296; American Thoracic Society, European Respiratory Society. Pretreatment evaluation of non-small-cell lung cancer. Am J Respir Crit Care Med. 1997;156:320–332.

Focal symptoms of metastatic disease are fairly common at presentation: 25% of patients present with bone pain, 20% of patients present with symptoms associated with bulky mediastinal adenopathy such as cough and hoarseness, and 10% of patients have neurologic symptoms that may include headache, nausea and emesis, seizures, and/or mental status changes at the time of diagnosis.[12,13] Lung cancer accounts for approximately two-thirds of the cancers that first present as symptomatic brain metastases.[20] The presence of nonspecific constitutional symptoms (weakness, weight loss, fever, and anorexia) is worrisome for metastatic disease. Standard laboratory testing should include a complete blood count as well as chemistries that include liver function testing. Anemia (hematocrit <40% in men and <35% in women) may indicate a higher likelihood of metastatic disease. Similarly, elevated liver function tests are concerning for hepatic metastases.

Hooper et al.[21] have enumerated a standard set of clinical features found to be associated with metastatic disease (Table 112-3). A systematic review suggests that absence of all of these features makes metastatic disease highly unlikely with a negative predictive value exceeding 90%.[22,23]

Initial clinical evaluation of the patient with suspected lung cancer should also include an assessment for paraneoplastic syndromes (Table 112-4), clinical disorders associated with malignant disease that are not directly attributable to the physical effects of the tumor (Chapter 118). They may be seen in up to 10% of patients with lung cancer.[12] The most commonly recognized paraneoplastic syndromes are hormonally mediated; tumor cells secrete hormones or hormonal analogues. The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is seen in 10% to 45% of patients with SCLC and 0.7% to 1% of patients with NSCLC (squamous cell and adenocarcinoma), although symptoms related to hyponatremia are present in just 1% to 5% of patients.[24,25] Hyponatremia is associated with decreased survival in SCLC.[26] Ectopic production of adrenocorticotropin hormone (ACTH) can be found in up to 50% of patients with

TABLE 112-3 Features of a Standardized Evaluation for Metastatic Disease

Symptoms	• Weight loss >10 lb • Focal skeletal pain • Neurologic symptoms: headaches, syncope, seizures, focal extremity weakness, altered mentation
Signs	• Palpable lymphadenopathy (>1 cm) • Hoarseness or SVC syndrome • Bone tenderness • Hepatomegaly (>13 cm) • Focal neurologic signs • Soft tissue mass
Laboratory testing	• Hematocrit <40% in men or <35% in women • Elevated alkaline phosphatase, liver function tests

Data from Feinstein AR, Wells CK. A clinical-severity staging system for patients with lung cancer. Medicine. 1990; 69:1–33; Hooper RG, Tenholder MF, Underwood GH, et al. Computed tomographic scanning of the brain in the initial staging of bronchogenic carcinoma. Chest. 1984;85:774–776.

TABLE 112-4 Paraneoplastic Syndromes Associated with Lung Cancer

System	Syndrome
Endocrine	SIADH Hypercalcemia Cushing syndrome Gynecomastia Hypercalcitoninemia Elevated LH and FSH Hyperthyroidism Carcinoid syndrome
Neurologic	Subacute sensory neuropathy Mononeuritis multiplex LEMS Encephalomyelitis Necrotizing myelopathy Cancer-associated retinopathy
Skeletal	Hypertrophic osteoarthropathy Clubbing
Renal	Glomerulonephritis Nephrotic syndrome
Metabolic	Lactic acidosis Hypouricemia
Systemic	Anorexia Fever
Rheumatologic	Dermatomyositis and polymyositis Vasculitis SLE
Cutaneous	Acquired hypertrichosis lanuginosa Erythema multiforme Tylosis Erythroderma Exfoliative dermatitis Acanthosis nigricans Sweet syndrome Pruritus and urticaria
Hematologic	Anemia Leukocytosis and eosinophilia Thrombocytosis Thrombocytopenia purpura Thrombophlebitis Disseminated intravascular coagulation

Data from Scagliotti G. Symptoms, signs and staging of lung cancer. Eur Respir Mon. 2001;17:86–119; Carbone PP, Frost JK, Feinstein AR, et al. Lung cancer: perspectives and prospects. Ann Intern Med. 1970;73:1003–1024.

lung cancer, but true Cushing syndrome is seen in only 1% to 5% of patients with SCLC.[12,24] Ectopic Cushing syndrome is also associated with a poor prognosis in SCLC, in part related to an increased susceptibility to opportunistic infection in patients given chemotherapy.[24,27–29] Hypercalcemia is seen in 2% to 6% of all lung cancer patients at presentation, and in up to 10% to 25% during their clinical course.[12,30] Etiology of hypercalcemia can be due to direct tumor effect on local osteolytic activity when there are bony metastases. However, in a substantial fraction of patients, typically those with squamous cell histopathology and less commonly in SCLC, hypercalcemia is due to tumor cell–elaborated parathyroid hormone–related peptide (PTHrP).

Digital clubbing and hypertrophic osteoarthropathy (HOA) are two paraneoplastic syndromes of the musculoskeletal system commonly associated with NSCLC (Chapter 27). Clubbing manifests as enlargement of the terminal tufts of the fingers and toes. It results from the proliferation of connective tissue beneath the nail matrix and can be seen in up to 29% of patients with adenocarcinoma or squamous cell carcinoma histopathology.[31] HOA, which occurs in fewer patients (<4%), presents as painful symmetric arthropathy, usually involving the ankles, wrists, and knees, and is caused by new periosteal bone formation at the distal long bones, resulting in vascular hyperplasia and edema. It is postulated that HOA occurs due to overexpression of vascular endothelial growth factor (VEGF).[32]

Other paraneoplastic syndromes associated with lung cancer occur due to the development of autoantibodies that can cause neurologic disease or rheumatologic disease. Dermatomyositis and polymyositis are autoimmune inflammatory myopathies characterized by progressive symmetrical proximal muscle weakness associated with various malignancies. Patients with dermatomyositis additionally may have Gottron papules and a heliotrope rash with poikiloderma. In two series, lung cancer accounted for 17.4% and 18%, respectively, of new cancer diagnoses within the first year of diagnosis of dermatomyositis.[33,34] The diagnosis can be confirmed by muscle or skin biopsy. Polymyositis is similarly associated with an increased risk of malignancy, with lung cancer accounting for 20% of newly diagnosed cancers during 5-year follow-up.[33]

There are a large number and variety of paraneoplastic neurologic syndromes (PNS) (Table 112-3).[35] Approximately 17% of paraneoplastic neurologic syndromes are due to lung cancer.[36] In 80% of cases, the neurologic disorder presents before the cancer is diagnosed; less than half will have detectable autoantibodies.[37] Although PNS are rare (<1% of all cancer patients), up to 3% to 5% of SCLC develop a PNS.[38] Lambert Eaton myasthenic syndrome (LEMS) is one of the better defined syndromes; it occurs due to the development of autoantibodies against presynaptic voltage-gated calcium channels. These circulating autoantibodies can be found in up to 5% to 8% of patients with SCLC although clinical LEMS occurs in only 1% to 3% of patients.[39,40] Other paraneoplastic neurologic syndromes occur due to the presence of circulating neuronal autoantibodies (including anti-Hu, anti-Yo, and anti-Ri antibodies) and have a myriad of clinical manifestations.[24] Up to 20% of patients with SCLC have circulating anti-Hu antibodies, although paraneoplastic syndromes do not occur in the majority.[41] The related syndromes can include autonomic overactivity, corticocerebellar degeneration, brainstem encephalitis, limbic encephalitis, myelopathy, and peripheral nerve palsies. Autopsy studies have revealed that patients suffering from these syndromes have lymphocytic inflammatory infiltration in areas of the nervous system corresponding to their neurologic deficits.

While paraneoplastic syndromes manifest systemically, they are not always indicative of advanced malignant disease. In one study, more than 40% of patients with SCLC-associated PNS had limited-stage disease at the time of diagnosis.[37] PNS may regress with appropriate treatment of the tumor.

IMAGING EVALUATION

Following the initial intake evaluation, further noninvasive and invasive workup should be undertaken with paired goals of (1) definitive establishment of histopathologic diagnosis and, when indicated, molecular and diagnostic biomarker testing, and (2) determination of disease stage in the most cost-effective and least invasive manner possible. Given the myriad of diagnostic modalities available, it is often advisable that patients suspected of having lung cancer undergo this phase of the evaluation at an established multidisciplinary lung cancer center.

Unless a patient is not a candidate for any treatment, all patients should undergo a chest computed tomography (CT) scan appropriately modified for lung cancer assessment. The lung cancer CT scan includes the chest and the upper abdomen such that the liver and the adrenal glands are visualized in their entirety. The administration of intravenous contrast facilitates better characterization of hilar and mediastinal lymph nodes by differentiating them from vascular structures and also helps to better characterize hepatic and adrenal lesions. CT is most useful in delineating the key features of the primary tumor (size, presence of satellite nodules, associated atelectasis and infection, and invasion of adjacent structures); these features are essential in establishing the clinical T stage (Chapter 28).

Regional lymph node involvement can also be evaluated on chest CT. Lymph nodes are deemed to be pathologically enlarged when they measure greater than 1 cm in short-axis diameter on transverse images. The likelihood of metastatic involvement increases with the degree of lymph node enlargement: 62% of lymph nodes measuring 10 to 15 mm are malignant versus 90% of nodes measuring >15 mm.[42] However, in most patients, lymph node staging cannot be accurately undertaken based upon CT findings alone. In a meta-analysis of 35 studies (5111 patients, 28% of whom had mediastinal metastases), the pooled sensitivity of CT scanning for mediastinal nodal metastases was found to be 51% and pooled specificity, 86%.[43] About 20% of nodes deemed to be benign on chest CT were malignant and 40% of nodes deemed abnormal on chest CT were benign.

On occasion, there are CT findings that demonstrate mediastinal tumor invasion convincingly enough that further staging is unnecessary. These findings include extensive infiltration of mediastinal structures such that discrete anatomic landmarks are lost, matting of nodal tissue such that boundaries become indistinct, and encircling of mediastinal structures by infiltrating tumor. In the absence of these findings, further studies need to be undertaken to adequately stage the mediastinum.

Chest CT scan can also often demonstrate findings that may be suggestive of metastatic disease. CT may delineate pleural effusions, the majority of which are malignant. Also, CT may reveal pericardial effusion, pleural nodularity, or nodules in the contralateral lung, all of which may indicate metastatic disease. Bony involvement of the thoracic cage may be seen. Adrenal lesions can be identified in 4% to 18% of patients; however, up to 50% of these are ultimately found to be benign.[44]

Positron emission tomography (PET) with 18-fluoro-2-deoxyglucose (FDG) has a prominent role in the initial noninvasive evaluation of the patient with suspected lung cancer.[45] Metabolically active tissues avidly take up the glucose analogue FDG and appear bright on PET scan. Strongly hypermetabolic activity raises suspicion of malignancy. However, hypermetabolic activity can also be seen in inflammatory processes related to infections, sarcoid, vasculitis, recent surgery, or reaction to immunotherapy, limiting the specificity of PET to ~85%.[46] False negatives can also occur with low-grade malignancies or small foci of malignancy, leading to a sensitivity of 96%.[46] Lesions less than 0.8 to 1.0 cm may be too small for accurate assessment.[47] High-level physiologic uptake within the brain, heart, gastrointestinal, and genitourinary tracts may compromise precise evaluation of tumor invasion or metastasis in these areas. In addition, the presence of hyperglycemia can interfere with the uptake of FDG and thus increase the likelihood of false-negative examinations.[48] The PET scan is more sensitive and specific than CT in regional lymph node assessment with a pooled sensitivity of 74% and specificity of 85% in the identification of mediastinal lymph node metastases.[45] In patients with enlarged mediastinal nodes, the sensitivity has been estimated to be as high as 100% with a specificity of 78%.[46] Thus the false-positive rate ranges between 13% and 25% in patients with nodal enlargement. In those with normal-sized nodes on CT, PET sensitivity is 82% but specificity is higher at 93%. Approximately 20% of patients with normal mediastinal nodes on CT and PET will have malignant disease within the mediastinum.[46]

PET scanning can disclose unsuspected metastatic disease (M1) in 6% to 37% of cases, depending on clinical pretest probability. Rates are lower in earlier-stage disease: 1% to 8% in clinical stage I disease and 7% to 18% in patients with clinical stage II disease.[45] Liver metastases, adrenal metastases, and bone metastases can be diagnosed with good accuracy. A recent study of PET-CT in the evaluation of adrenal lesions detected in patients with lung cancers reported an overall sensitivity and specificity of 97% and 94%, respectively.[49] Two systematic reviews suggest that PET scanning has a higher diagnostic value than bone scintigraphy for the detection of bone metastases from lung cancer, with >90% sensitivity and specificity for PET-CT.[50,51]

PET-CT has been the most helpful in decreasing the frequency of understaging in patients at risk for advanced lung cancer. Clinical trials have suggested that the addition of PET-CT imaging to the evaluation results in a reduction of the rates of noncurative surgery for NSCLC from 40% down to 20%.[52–54] The frequency of understaging disease decreases from 30% to 15%. The beneficial impact of PET diminishes in a patient with early-stage disease. PET correctly detects N2, N3, or M1 disease in 7% to 10% of patients with clinical stage I disease.[55] However, this comes at a cost of increased false-positive rate of up to 14%. PET should not be used alone to confirm advanced-stage disease as patients may be erroneously directed away from curative therapies.

MRI scanning is the test of choice when assessing for intracranial metastatic disease. It is more sensitive than a CT scan of the brain.[56] Staging brain MRI should be considered in patients who present with locally advanced or advanced NSCLC on chest CT or PET scanning (clinical stage IB through IV); patients with neurologic signs or symptoms; patients presenting with nonspecific constitutional symptoms of fevers, weight loss, anorexia, and weakness; and all patients with SCLC.[57–59] MRI scanning is also often the test of choice for focused examination for the extent of chest wall invasion, diaphragmatic involvement, superior sulcus tumors, brachial plexus invasion, or invasion of the spine (TNM T4 disease).[60]

Any extrathoracic lesion detected on imaging studies in a patient suspected of having lung cancer should be biopsied first, if feasible.

This will accomplish not only tissue diagnosis but also confirmation of advanced disease in both SCLC and NSCLC.

ESTABLISHING THE TISSUE DIAGNOSIS

Methods employed in establishing a tissue diagnosis SCLC and NSCLC are discussed below.

■ Small-cell Lung Cancer

Specific imaging characteristics on chest CT can be indicative of SCLC. In particular, the findings of massive lymphadenopathy, direct mediastinal invasion, or hilar masses can suggest SCLC. The suspicion should be raised if the clinical evaluation is worrisome for SIADH, ectopic ACTH production, or PNS. If SCLC is suspected, then tissue diagnosis should be established utilizing the least invasive test feasible.

In 1989, the International Association for the Study of Lung Cancer (IASLC) modified the Veterans Administration Lung Study Group (VALSG) two-stage classification of SCLC; this modified classification system is currently the widely accepted clinical staging system for SCLC.[61] Patients with limited-stage disease have disease confined to one hemithorax, the mediastinum, and ipsilateral supraclavicular lymph nodes. In other words, limited-stage defines a primary tumor and regional nodes that can be incorporated into a reasonably safe radiation port. Patients with extensive-stage disease have malignant pleural and pericardial effusions, contralateral hilar or supraclavicular nodes, and/or distant metastases. Given the high likelihood of extensive disease at the time of presentation, all patients should undergo a full staging evaluation that traditionally included a contrast-enhanced CT of the chest and abdomen, bone scan, and MRI or contrast-enhanced CT scan of the brain. MRI scanning, the preferred imaging modality, will detect brain metastasis in 10% to 15% of asymptomatic patients with SCLC at the time of diagnosis, and in 12% of patients with otherwise limited-stage SCLC.[40,62] Routine bone marrow aspiration is not indicated. The use of PET scan in the initial staging of SCLC has been evaluated in several small studies.[50–54,63–67] Because SCLC is a highly metabolic malignancy, PET scan is 100% sensitive for the detection of the primary tumor. Also, PET is superior to standard imaging in both sensitivity and specificity for detection of non-CNS metastatic foci. In a systematic review, PET/CT changed binary SCLC staging in 15% of patients.[68] In patients with radiographic evidence of extensive-stage SCLC, tissue diagnosis and stage confirmation should be accomplished by biopsy of a metastatic focus if feasible.

■ Non–small-cell Lung Cancer

In the case of NSCLC, the primary goals in tissue sampling selection are more complicated. These goals are (1) to obtain a tissue specimen adequate for histopathologic subtyping, molecular biomarker testing to identify actionable mutations, and diagnostic biomarker testing (PD-L1 expression), and (2) to establish the clinical stage of disease in the least invasive manner feasible. If imaging tests suggest a site of distant metastatic disease, then that site should be sampled first, if accessible.

Sputum cytology is the least invasive way of achieving a histologic diagnosis. However, it is also the least accurate and least useful for therapeutic analysis. For these reasons, it has largely been replaced by other methods and is generally of historic interest only. Thoracentesis is indicated as the initial test for tissue acquisition when a pleural effusion is present in a patient suspected of having lung cancer. Malignant pleural effusion (MPE) is common at the time of presentation—11% and 16% to 26% in patients with SCLC and NSCLC, respectively.[69,70] Additionally, up to 40% will develop a MPE during the disease.[71] Positive pleural fluid cytology not only establishes the diagnosis but also establishes stage IV (M1a) disease in NSCLC and extensive-stage SCLC. Due to the decrease in complications, improvement in procedure success rates associated with ultrasound guidance, and ubiquitous nature of ultrasound equipment, ultrasound-guided thoracentesis is the standard of care.[72,73] Furthermore, ultrasound imaging can reveal findings that raise the suspicion for malignant disease, including pleural thickening and nodularity.[74] Pleural fluid cytology sensitivity for malignancy overall is approximately 60% to 72% when a volume of at least 50 mL is sent; diagnostic yield does not appear to increase with larger volume of fluid analyzed.[75–77] If the initial thoracentesis is negative, a second thoracentesis should be performed, as it can increase the diagnostic yield by an additional 27%; additional samples add little to the diagnostic yield.[78] Sensitivity of pleural fluid cytology can be as high as 72% when at least two separate specimens are sent.[79]

When pleural disease is present and thoracentesis is negative, additional diagnostic strategies include non-image-guided closed pleural biopsy, percutaneous image-guided biopsy, and thoracoscopic biopsy. Non-image-guided closed pleural biopsy using an Abrams needle is uncommonly employed as it increases diagnostic yield over thoracentesis by only 7% to 27%.[79] Percutaneous image-guided pleural biopsy has clear advantages in diagnostic yield, particularly when there are abnormal pleural findings on ultrasound or chest CT, with a sensitivity of 84%.[79] Thoracoscopy has a reported sensitivity of 80% to 99% in the diagnosis of malignant pleural disease.[79] However, when there is CT evidence of pleural thickening or nodules, the diagnostic yield of image-guided percutaneous biopsy is similar to thoracoscopy. Thus, medical or surgical thoracoscopy should be reserved for patients with pleural fluid but without a discrete target for image-guided pleural biopsy.[80]

HISTOLOGIC SAMPLING OF THE PRIMARY TUMOR

There are numerous procedures presently utilized to sample the primary tumor with varying diagnostic yields depending on tumor characteristics and adjunct technologies (Table 112-5). Bronchoscopy enables sampling of the primary tumor as well as the mediastinum for regional lymph node staging (Chapters 33 and 34). The overall sensitivity of endobronchial forceps biopsy of directly visualized central tumor is 74%, with yield increasing with the number of biopsy passes.[79] It is recommended that at least three biopsies be taken. The yield of endobronchial washes and brushes is lower (sensitivity 47% and 61%, respectively) but may have additive benefit.[79] Endobronchial needle aspiration further increases yield, as forceps biopsies of endobronchial lesions can sometimes sample areas of necrosis and may result in nondiagnostic biopsies.[81–83] When all techniques are utilized, the reported yield of bronchoscopic sampling of endobronchial lesions can be as high as 91% to 96%. Bronchoscopic visualization of endobronchial disease is also the best way to estimate the extent of proximal tumor invasion, aiding in differentiating the T stage of centrally located tumors. Specifically, if the tumor invades the mainstem bronchus but spares the carina, it is a T2 lesion while involvement of the carina or trachea designates a T4 lesion.

Advanced bronchoscopic techniques such as electromagnetic navigational (EMN) bronchoscopy and radial probe endobronchial ultrasound (R-EBUS) have improved the diagnostic armamentarium for peripheral lung cancers. R-EBUS permits direct real-time ultrasound imaging of target lesions; early studies suggested R-EBUS can increase the overall sensitivity of bronchoscopic biopsy of peripheral lesions up to 73%.[84] EMN bronchoscopic technology creates a real-time virtual thoracic map that helps the bronchoscopist steer electromagnetically tracked tools through subsegmental airways toward the target lesion, with initial reports and subsequent meta-analysis suggesting that EMN increases the diagnostic yield of bronchoscopic biopsy of peripheral lesions from 57% overall to 70%.[85] Despite the early reports of diagnostic

TABLE 112-5 Sampling of Primary Tumor

Tumor Characteristics	Procedure	Sensitivity (%)	Comments
Directly visualized endobronchial tumor	Bronchoscopy with forceps biopsy	74	
	Bronchoscopic washes	47	
	Endobronchial brush	61	
	Needle aspiration	75–96	
Peripheral lesions	Transbronchial biopsy		Yield increases with number of biopsy passes: 45% for one sample and 70% for six samples[75]
	Overall	57	
	Lesions <2 cm	34	
	Lesions >2 cm	63	
	Transbronchial brush	54	
	Bronchoalveolar lavage/wash	43	
	Transbronchial needle aspiration	65	
	Combination of all modalities	78	
	Radial EBUS	50–57	Yield increases with "bronchus sign"—subsegmental bronchus leading to lesion on chest CT[96,97]
	Overall	31	
	Lesions ≤2 cm	58	
	Lesions >2 cm		
	EMN bronchoscopy	50–57	
	Transthoracic needle aspiration	90	Pneumothorax rate 20%
	CT guided	92	Core biopsy similar to FNA for malignancy but better to determine benign diagnoses[99]
	Fluoroscopically guided	88	

yields and sensitivity greater than 70%, more recent, large, multicenter registries and prospective randomized trials suggest guided bronchoscopy (R-EBUS, EMN, or both) results in an overall yield for peripheral lesion biopsy of 50% to 57%.[86–88] Some factors that increase the yield and sensitivity of guided bronchoscopy are as follows: (1) when CT scanning demonstrates that a subsegmental bronchus leads directly into the lesion (bronchus sign), yield increases up to threefold;[85,89] and (2) the addition of needle aspiration has been suggested to improve the yield up to twofold.[86,90,91] Lesion size, as with fluoroscopically guided procedures, continues to influence test performance, with a diagnostic yield between 50% and 67% for lesions less than or equal to 2.0 cm, increasing to 71% to 79% for larger lesions.[86] Procedural complications are minimal, with an overall rate of pneumothorax of 1% and pneumothorax requiring catheter drainage of 0.4%.[85]

Image-guided transthoracic needle biopsy (TTNB) has excellent sensitivity for peripheral lesions, with a pooled sensitivity of approximately 90%.[79] However, a negative biopsy does not rule out malignant disease. The false-negative rate can range between 20% and 30% depending on patient population and disease characteristics.[79] CT guidance is superior to fluoroscopic guidance. The addition of transthoracic core biopsy has a sensitivity equivalent to fine-needle aspiration biopsy (FNAB) but increases the ability to establish a specific histopathologic diagnosis by improving tissue acquisition for immunohistochemical staining and molecular characterization in up to 98% of cases. In addition, a core biopsy improves the diagnostic yield of specific benign etiologies from 52% with FNAB to 91%.[92] The complication rate of TTNB is higher than that associated with bronchoscopy. The incidence of pneumothorax is ∼20% and the incidence of severe hemorrhage is 1%.[93] Risk factors for complications include underlying chronic obstructive pulmonary disease, small lesion size, long needle path, repeated pleural puncture, and proximity to pleural fissures and diaphragm.[94] In addition to the higher complication rate associated with TTNB compared to bronchoscopy, TTNB cannot provide mediastinal staging. Therefore, TTNB is recommended as the first line for biopsy of peripheral lung lesions in intermediate to high lung cancer likelihood patients when (1) the lesion is peripheral; (2) the lesion is less than 3 cm in size; (3) there is no CT/PET evidence of mediastinal lymph node or extrathoracic metastasis; and/or (4) the patient is a poor surgical candidate.[79]

Video-assisted thoracoscopic surgery (VATS) wedge resection followed by definitive anatomic resection (e.g., lobectomy) as indicated is the gold standard for peripheral lung biopsy with the highest sensitivity and specificity (Chapter 35). Because of the invasive nature of the procedure, it requires hospitalization and carries a higher attendant risk. It can be combined with bronchoscopic mediastinal staging or mediastinoscopy; however, as described in the next section, bronchoscopic mediastinal staging is less invasive, more cost-effective, and equally sensitive and specific for mediastinal staging. Furthermore, unnecessary surgery can be avoided in 29% to 66% of patients presenting with clinical early-stage lung cancer who undergo mediastinal lymph node staging.[95–97] Therefore, in patients who have an acceptable surgical risk profile, a peripheral lesion less than 3 cm, and no CT/PET evidence of metastatic disease (lymph node or extrathoracic), definitive VATS resection is preferred, as it provides both diagnosis and cure in one procedure.[45,98] Otherwise, despite overall lower yield, bronchoscopic sampling has become the preferred biopsy method in centers where advanced bronchoscopy technologies, including R-EBUS and EMN, are available for the following situations: (1) when combined with mediastinal staging in patients with central lesions, peripheral lesions at least 3 cm, and/or CT/PET evidence of mediastinal lymphadenopathy; (2) in low-intermediate or indeterminate cancer likelihood patients to establish a nonmalignant diagnosis; (3) in poor surgical candidates with lesions greater than 2 cm being considered for stereotactic body radiation (SBRT) as fiducials can be placed at the time of biopsy.[79]

TABLE 112-6 Classification of Mediastinal Disease by Radiographic Characteristics

Group	Description
A	Mediastinal infiltration: tumor invasion such that normal anatomic boundaries cannot be distinguished
B	Enlarged discrete mediastinal lymph nodes: lymph nodes measuring ≥1 cm in short-axis diameter on transverse CT scan
C	Clinical stage II or central stage I tumor: normal-sized mediastinal lymph nodes but enlarged N1 nodes or central tumor
D	Peripheral clinical stage I tumor: normal mediastinal and hilar nodes with a peripheral tumor

Adapted with permission from Detterbeck FC, Jantz MA, Wallace M, Vet al. Invasive mediastinal staging of lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). Chest. 2007;132(3 Suppl):202S–220S.

MEDIASTINAL STAGING

Lung cancer staging is based upon the tumor node metastasis (TNM) staging system last updated on January 1, 2018 (Table 112-1) by the International Association for the Study of Lung Cancer. Extent of disease is categorized by the characteristics of the primary tumor (T), the involvement of regional lymph nodes (N), and the presence or absence of distant metastases (M).[3] Disease stage is the key determinant of candidacy for tumor resection. Patients with stage I and II diseases and otherwise adequate cardiopulmonary reserve should undergo surgery. Unfortunately, only about one-third of patients present as stage I or II and therefore would benefit from surgery after thorough clinical staging.[7,99,100]

Nearly a quarter of patients with lung cancer have locally advanced disease with mediastinal involvement (N2 or N3) at the time of presentation.[4,6] Mediastinal staging is crucial in determining the stage of disease and candidacy for surgical resection once metastatic disease has been ruled out, as 29% to 66% of noncurative surgeries for lung cancer can be avoided with adequate mediastinal staging.[95–97] Tissue confirmation of mediastinal nodal metastasis becomes unnecessary only in the following situations: (1) where distant metastatic disease has already been confirmed; (2) when the patient is not a candidate for any treatment; (3) in a peripheral lesion, less than 3 cm in size, with no radiographic evidence of lymph node metastasis.

Patients with NSCLC fall into four categories concerning the approach to clinical staging of the mediastinum based on the radiographic findings (Table 112-6).[96] Radiographic group A includes patients who have imaging characteristics that are unequivocally consistent with malignant invasion of the mediastinum (mediastinal infiltration with loss of normal tissue boundaries, nodal tissue is no longer discrete and can be matted together, and vascular structures are often encircled) (Fig. 112-2). In this group of patients, the goal is

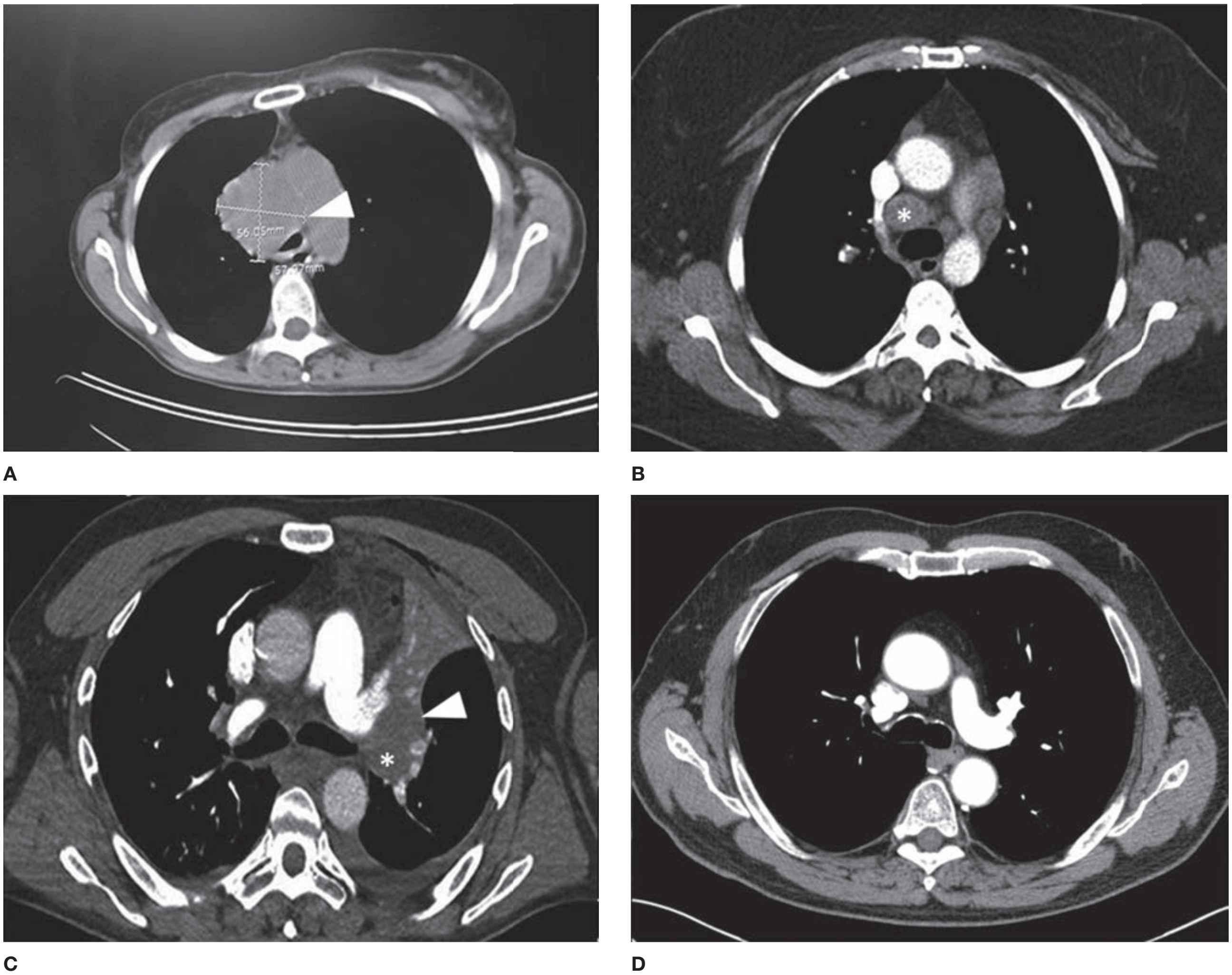

Figure 112-2 Example of radiographic group A disease: mediastinal infiltration with loss of normal anatomic boundaries.

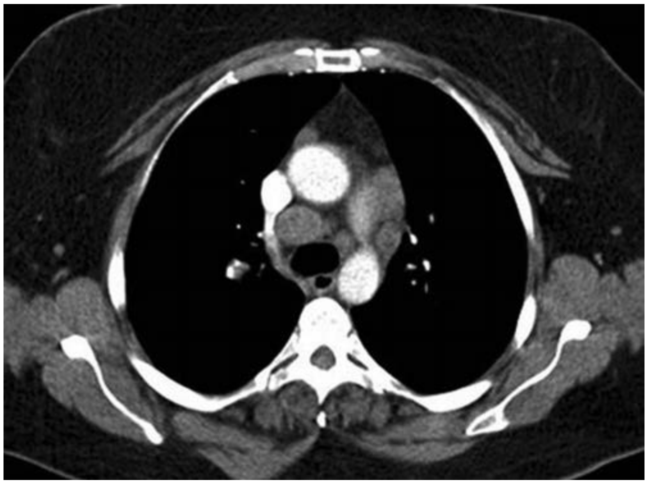

Figure 112-3 Example of radiographic group B disease: discrete mediastinal (4R) nodal enlargement.

to obtain tissue by the least invasive procedure to establish the diagnosis. Group B includes patients with discrete lymph node enlargement (Fig. 112-3). Discrete enlargement of lymph nodes on a CT scan, even massive enlargement, is inadequate evidence for mediastinal metastases as up to 40% of these nodes are benign.[43] Conversely, group C includes patients with central lesions or N1 disease with radiographically normal mediastinal lymph nodes (Fig. 112-4). In this group, 20% to 25% are found to have nodal involvement.[43] Finally, the last group of patients, group D, includes those with peripheral clinical stage I lesions with radiographically normal mediastinal and hilar lymph nodes. These patients have a sufficiently low pretest probability for mediastinal involvement that invasive mediastinal sampling becomes unnecessary. In patients with radiographic group B or C disease, adequate staging of the mediastinum is mandatory.

Mediastinal staging procedures include transthoracic needle aspiration (TTNA), transbronchial needle aspiration (TBNA) with or without EBUS, endoscopic ultrasound (EUS) needle aspiration, cervical mediastinoscopy, anterior mediastinoscopy, and thoracoscopy. Selection of appropriate procedure is made based upon nodal station (Table 112-7), the pretest probability of disease, and medical appropriateness for surgical resection.[96] The diagnostic yield of each procedure (Table 112-8) should also be taken into account.

TTNA of mediastinal nodal tissue is possible when anterior mediastinal lymph nodes (anatomic stations 3a and 6) are enlarged. A recent systematic review reported a pooled sensitivity of 94%.[45] As with TTNA of peripheral lesions, the risk of pneumothorax is fairly high. Chest tubes are required for evacuation of pneumothorax in 10% of procedures.[96] TTNA of the mediastinum is primarily utilized in patients with fairly bulky anterior mediastinal lymph node enlargement.

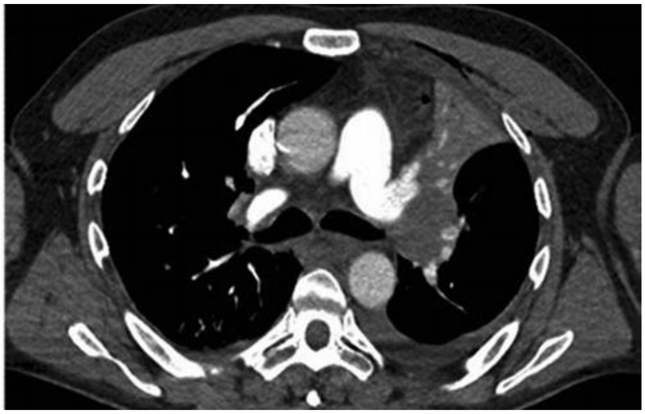

Figure 112-4 Example of radiographic group C disease: central lesion with N1 disease but no enlarged mediastinal lymphadenopathy.

TABLE 112-7 Regional Lymph Node Stations (International Association for the Study of Lung Cancer)

Zone	Lymph Node Station	
Supraclavicular zone	1	Low cervical, supraclavicular, sternal notch
Superior mediastinal nodes	2R	Right upper paratracheal
	2L	Left upper paratracheal
	3a	Anterior mediastinum—prevascular
	3p	Posterior mediastinum—retrotracheal
	4R	Right lower paratracheal
	4L	Left lower paratracheal
Aortic nodes/aortopulmonary window nodes	5	Subaortic
	6	Para-aortic
Inferior mediastinal nodes	7	Subcarinal
	8	Paraesophageal nodes
	9	Pulmonary ligament
Hilar nodes	10	Hilar nodes
	11	Interlobar nodes
Peripheral nodes	12	Lobar nodes
	13	Segmental nodes
	14	Subsegmental nodes

Data from Rusch VW, Asamura H, Watanabe H, Giroux DJ, Rami-Porta R, Goldstraw P. The IASLC lung cancer staging project: a proposal for a new international lymph node map in the forthcoming seventh edition of the TNM classification for lung cancer. Journal of Thoracic Oncology. 2009;4(5):568–577.

Bronchoscopic sampling of mediastinal lymph nodes with TBNA without image guidance can potentially access stations 2, 4, 7, 10, and 11 with variable yield.[101] The availability of rapid on-site cytologic evaluation improves diagnostic yield and decreases the number of biopsy passes needed.[102] However, the widespread adoption of convex probe EBUS (CP-EBUS) to guide TBNA has largely supplanted "blind" sampling. The advent of CP-EBUS has significantly improved the diagnostic yield of TBNA sampling of the mediastinum. EBUS allows for real-time visualization of the target nodal tissue with a pooled sensitivity on a systematic review of 87% compared to 86% with video-assisted mediastinoscopy. It is now recommended as the first procedure, if available, for sampling the hilar and mediastinal nodes.[45,103] EBUS-TBNA provides access to nearly all lymph node stations (2, 4, 7, 10, and 11), combines diagnosis and staging in a single procedure, and results in equivalent diagnostic yield when compared with mediastinoscopy.[104–106] Performance is best in patients with positive CT or PET results, with a sensitivity of 94% in that population, for whom the false-negative PET rate remains substantial at 24%.[105] Evaluation of tissue adequacy for immunohistochemical testing and molecular characterization suggests that EBUS-TBNA can result in satisfactory sampling for both tumor subtyping and molecular markers in >94% of cases.[107] When assessed for adequacy for immunohistochemical subtyping, next-generation genetic sequencing,

TABLE 112-8 Mediastinal Staging

Procedure	Lymph Node Stations	Sensitivity (%)	Comments
TBNA	4, 7, and 10	78	
EBUS-TBNA	2, 4, 7, and 10	88–93	Sensitivity 94% in PET positive lymph nodes.
EUS-FNA	5, 7–9	83, overall 90, enlarged nodes 58, normal-sized nodes	
CT-guided TTNA	3a, 5, 6	92	Requires bulky disease in 5–6.
Mediastinoscopy	1, 2R, 2L, 3, 4R, 4L, anterior subcarinal (7)	81	
Thoracoscopy	4, 7–10	99	Typically, only one side of the mediastinum is sampled. Right side is more easily accessible than the left.

and ALK molecular testing, EBUS-TBNA was sufficient in 82% of 112 patients in one study, and 90.6% of 85 patients in another.[108,109] Diagnostic yield and sample adequacy are related to the expertise of the bronchoscopist and cytopathologist, respectively, and there is significant heterogeneity in yield across hospitals.[110] Therefore, negative sampling in patients with high pretest probability for lymph node metastasis should be followed by mediastinoscopy in patients who are candidates for surgical resection.[45]

EUS fine-needle aspiration (EUS-FNA) can access the inferior mediastinal nodal stations as well as nodal tissue in the subaortic stations: 9, 8, 7, and 5. Like bronchoscopy, EUS-FNA is minimally invasive and is an outpatient procedure. In addition, the left adrenal gland, celiac lymph nodes, and lesions involving the left lobe of the liver can be sampled utilizing this technique. The sensitivity for accessible mediastinal lymph nodes is excellent at 83% with an overall false-negative rate of 19%.[111] Yield is highest with enlarged nodes with a sensitivity of 90% and a false-negative rate of 22%.[111] In the hands of expert endoscopists, normal-sized nodes may also be sampled with a reported sensitivity of 58% for metastatic disease.[111] While a negative test impels further testing, a positive study obviates the need for more invasive evaluation.

When EUS is combined with EBUS, the mediastinum can be more extensively sampled than with either modality alone. In the studies investigating this combined approach, sensitivity ranged between 72% and 100% with 98% to 100% specificity.[112–118] Negative predictive values ranged between 80% and 100%. This combined approach requires highly specialized expertise and is available only at selected centers.

Cervical mediastinoscopy is typically a same-day surgical procedure in which an incision is made just above the suprasternal notch and a mediastinoscope inserted. It is a low-morbidity procedure with complication rates of 2% and mortality of 0.08%.[96] The high and low paratracheal nodes (2R, 2L, 4R, and 4L), pretracheal (1 and 3), and anterior subcarinal (7) nodal stations can be sampled. Mediastinoscopy is the procedure of choice to demonstrate node negativity before surgical resection of the primary tumor in cases where FDG avid mediastinal nodes are found to be negative for malignancy on EBUS-TBNA staging. Test sensitivity has been reported to be overall 80% with a false-negative rate as high as 10%.[96] The lymph nodes identified as false negatives are often located in nodal stations not accessible to the mediastinoscope. The addition of video mediastinoscopy may further improve test performance with sensitivity increasing to 80%.[96] A Chamberlain procedure (i.e., anterior mediastinoscopy) can be performed to sample aortopulmonary and anterior mediastinal nodal stations (stations 5 and 6), commonly involved with left upper lobe cancers that are not accessible by EBUS-TBNA, to rule out N2 disease.

VATS can be utilized to sample multiple lymph node stations, including the right paratracheal (station 4R) nodes, stations 5 and 6 nodes, paraesophageal nodes, and stations 9 and 10 nodes, and is guideline-directed care at the time of curative intent surgery for clinical/radiographic stage I or II NSCLC when there are no enlarged lymph nodes on CT and there is no FDG uptake in lymph nodes on PET/CT.[98] The left paratracheal lymph nodes are much more difficult to access. VATS sampling also provides the most reliable information short of full thoracotomy regarding the extent of primary tumor invasion of the chest wall and mediastinal structures as well as pleural and pericardial involvement.

TISSUE ACQUISITION FOR HISTOPATHOLOGY AND MOLECULAR AND DIAGNOSTIC BIOMARKER TESTING

NSCLC encompasses a heterogeneous group of cancers with not just different histologies but also different genetics. In addition, NSCLCs respond differently to therapeutic agents depending on histology and molecular characteristics. Significant positive outcomes have been reported when certain adenocarcinomas are combined with specific chemotherapy agents (e.g., pemetrexed) and tyrosine-kinase inhibitors (e.g., erlotinib), while patients with squamous cell histology are clearly at higher risk of toxicity from bevacizumab.[119,120]

Molecular translational research has resulted in identification of genetic alterations in oncogenes and tumor suppressor genes critical to tumor growth, leading to significant improvements in treatment of metastatic NSCLC, as these somatic mutations are clinically actionable with targeted agents. Oncogenic mutations are detected in roughly 64% of NSCLC and include mutations in the epidermal growth factor receptor (*EGFR*), rearrangements of the anaplastic lymphoma kinase (*ALK*) gene or c-ROS oncogene 1 (*ROS1*) gene, mutations in human epidermal growth factor receptor 2 (*HER2*), high-level MET amplification, and *MET* exon 14 and *RET* gene rearrangements.[121–125] Targeting with a specific therapy has, in some cases, resulted in dramatic response rates and improvement in survival compared with cytotoxic chemotherapy.[126] In addition to targeted therapies, inhibition of immune checkpoints has shown promise and has become integrated into the clinical management of metastatic NSCLC.[127] Immunotherapy results in superior survival with less toxicity compared with cytotoxic chemotherapy in patients with a high level of PD-L1 expression, with estimated 5-year overall survival rates of 23.2% and 15.5% in treatment-naïve and in previously treated patients, respectively.[128]

Guidelines recommend routine molecular biomarker testing (*EGFR*, *ALK*, *ROS-1*, *BRAF*, *HER2*, *MET*, *RET*, and *KRAS*) in all patients with advanced-stage adenocarcinoma, large cell carcinoma, and NSCLC otherwise not specified, and in select patients with squamous NSCLC.[129,130] Testing for molecular biomarkers should ideally be done in laboratories that perform next-generation sequencing panels.[130] Guidelines also recommend that diagnostic biomarker testing (PD-L1 expression) be performed in all patients with advanced-stage NSCLC.[129]

The emergence of individually tailored therapy based on histology and molecular and diagnostic biomarkers serves to emphasize how important adequate tissue acquisition is when diagnosing lung cancer. It has become incumbent upon clinicians who perform diagnostic studies to obtain sufficient tissue to perform immunohistochemical and molecular analysis to accurately ascertain the histologic subtype and molecular characterization of NSCLC. The impetus to obtain larger pieces of tissue can often seem discordant with the other objective of tissue acquisition, which is to achieve diagnosis and staging in the least invasive manner possible. In an era of minimally invasive procedures, several studies have reported high feasibility (range, 67%–100%) of performing immunohistochemical staining and molecular analysis and PD-L1 testing on specimens obtained via EBUS-TBNA.[131–135] Given the excellent performance of smear preparations, guidelines support performing molecular and diagnostic biomarker testing on any cytology sample with adequate cellularity and preservation.[136] Preservation of material from needle aspirates in cell block can store tumor cells for future immunohistochemical and molecular studies. How much tissue is needed to accurately diagnose the lung cancer histologic type and assess molecular markers has not been formally studied. It has been reported that one aspiration per lymph node station during EBUS-TBNA without rapid on-site cytology results in sample adequacy of 90% compared with 100% for three aspirations.[137]

SUMMARY

- Initial clinical evaluation of a patient with suspected lung cancer should focus upon presenting symptomatology as well as signs and symptoms suggestive of advanced-stage disease. History and laboratory testing may also be revealing for paraneoplastic syndromes.
- Initial imaging evaluation should include a chest CT scan for all patients who may be candidates for treatment. Integrated PET-CT scanning is indicated for the majority of patients, particularly for those who are at risk for mediastinal involvement as well as those patients with advanced thoracic disease and thus are at risk for distant metastatic disease. CT with contrast or MRI of the brain should be performed to assess for intracranial metastases in patients with neurologic symptoms or to screen for intracranial metastases in patients with locally advanced or advanced NSCLC, and those with SCLC.
- When SCLC is suspected, tissue diagnosis should be obtained in the least invasive manner possible. Staging classification is either limited-stage or extensive-stage disease and if feasible, a suspicious metastatic lesion should be biopsied first to confirm diagnosis and stage. In selected cases, staging can be accomplished through imaging evaluation alone (e.g., patient with multiple brain lesions or multiple bone lesions).
- Multiple diagnostic modalities are available to establish tissue diagnosis and to confirm the clinical stage. Selection should be based upon diagnostic yield, procedure safety, and ability to simultaneously establish stage. Thus, priority should be given to procedures that sample foci of metastatic disease detected on imaging evaluation (e.g., thoracentesis when pleural effusions are present, biopsy of PET-CT avid adrenal, bone, or hepatic lesions).
- Tissue sampling from the primary tumor can be accomplished percutaneously, bronchoscopically, and surgically. Yield of bronchoscopic biopsy for peripheral lung lesions is still not as high as that seen with TTNA. However, the advent of new techniques such as R-EBUS and EMN has improved test performance. Bronchoscopy remains the procedure with the lowest complication rate and should be strongly recommended as the procedure of choice in centers with local expertise.
- EBUS-TBNA is the procedure of choice for sampling hilar and mediastinal lymph nodes.
- In the absence of M1 disease, clinical staging of the mediastinum becomes crucial unless the patients have radiographic findings of mediastinal invasion or the patient has a sufficiently low pretest probability of mediastinal metastasis (peripheral T1N0 lesion). Ultrasound-guided bronchoscopic and endoscopic techniques have resulted in much improved diagnostic yield with excellent procedural safety. However, negative results should prompt surgical mediastinal sampling.
- The emergence of targeted therapies and immunotherapy has resulted in a greater emphasis on adequate tissue acquisition for molecular and diagnostic biomarker analysis.

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CHAPTER 113

Treatment of Non–Small-Cell Lung Cancer: Surgery

John K. Waters
Scott I. Reznik

INTRODUCTION

Lung cancer is the deadliest malignancy, accounting for more annual deaths than breast, prostate, and colorectal cancer combined. In 2018, 1.7 million people died worldwide from this disease, which accounts for 18.4% of all cancer deaths.[1] In 2020, it will claim the lives of 135,0000 Americans.[2] Lung cancer was a rare disease until the early part of the 20th century. In 1879, lung cancer represented only 1% of cancers identified at autopsy compared with 14% in 1927.[3]

The link between tobacco use and lung cancer is indisputable. Some of the carcinogenic chemicals found in cigarette smoke include NNK (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone) and benzo(a)pyrene diol epoxide,[4–6] affecting first- and second-hand smokers.[7] Other toxins that increase the lung cancer risk include arsenic, asbestos, nickel, cadmium, beryllium, silica, and diesel fume exposure.

Lung cancer treatment is multimodal. Physicians diagnosing and treating this disease must collaborate to determine the best treatment for an individual patient.

DIAGNOSIS

Lung cancer is often diagnosed during work-up of an abnormal chest x-ray or CT scan. These studies are often performed in response to a symptom a patient may be experiencing or as a screening examination. Common imaging findings include a lung nodule (solid pulmonary tumor ≤3 cm), mass (tumor >3 cm), or ground glass opacity.

The estimated risk that the nodule represents a cancer guides the evaluation and work-up.[8] Externally validated models can provide patients and physicians with an initial cancer risk assessment.[9,10] Lung nodule management is guideline driven, principally via the widely adopted Fleischner Society guidelines.[8] Generally, low-risk (<5% risk of malignancy) solid nodules between 6 and 8 mm should undergo imaging surveillance. Management options for solid nodules larger than 8 mm in low-risk patients include radiographic surveillance, ^{18}F-FDG PET-CT, or biopsy, depending on nodule size and morphology, assessment of cancer risk, and patient comorbidities. For high-risk patients (≥5%), radiographic surveillance is discretionary for solid nodules smaller than 6 mm, and endorsed for nodules 6 to 8 mm. Solid nodules larger than 8 mm with high malignancy risk should be managed with radiographic surveillance, ^{18}F-FDG PET-CT, and/or biopsy, depending on individual nodule and patient characteristics. Subsolid nodules (ground glass or part solid) at least 6 mm should be followed with serial CT imaging for 5 years independent of patient risk assessment, and biopsied or resected if growth is demonstrated.

Nonsurgical biopsy can be performed through the airway or chest wall. Central nodules or those fed by a nearby airway are amenable to bronchoscopic biopsy often with use of computer-assisted navigation or endobronchial ultrasound. Peripheral nodules may be addressed via transthoracic needle biopsy. The diagnostic yield of electromagnetic navigational bronchoscopy approximates 75% to 85%,[11] while the accuracy of CT-guided biopsy can be as high as 93.5%.[7] Risks of both procedures include bleeding and pneumothorax.[8] The decision to obtain a nonsurgical biopsy is based on the nodule's size and location, the preoperative likelihood of malignancy, and the patient's ability to tolerate operative intervention. A peripheral speculated nodule in an otherwise healthy patient with a significant tobacco history can be managed without preoperative tissue confirmation.

A negative nonsurgical biopsy in a suspicious lung nodule typically necessitates surgical biopsy, such as a wedge resection or rarely an incisional biopsy. For benign nodules, resection is diagnostic and therapeutic. Malignant nodules identified on frozen analysis following wedge can be treated definitively with anatomic lung resection and lymph node sampling in a single operative setting.

Lung masses (i.e., lesions >3 cm) should be strongly considered for expeditious nonsurgical biopsy and invasive mediastinal staging. It is important to consider, however, that other diseases may present with a lung mass: pulmonary infections, inflammatory and autoimmune conditions, lymphoma, and solitary fibrous tumors.

Ground glass opacities (GGOs) are triaged based on their number, their size, and the presence of a solid component within ground glass tissue.[12] An enlarging subsolid (>20 mm) or solid (>6 mm) component should lead to nonsurgical biopsy or surgical resection. ^{18}F-FDG PET-CT is typically performed prior to resection; however, a lack of ^{18}F-FDG uptake does not rule out malignancy in these circumstances.

STAGING

Lung cancer staging is performed clinically and pathologically according to the American Joint Commission on Cancer Staging Manual, which is currently in its eighth edition. Clinical staging is preliminarily based on noninvasive imaging studies. Pathologic staging is driven by histologic results from invasive procedures and is considered definitive.

T, N, M (tumor, node, and metastasis) features drive cancer stage, with a trend toward upstaging as tumor size, nodal status, and metastatic disease burden increase. Particular attention is paid to the mediastinum, as cancers deeply invading the mediastinum (c/pT4) or mediastinal lymph nodes (N2, N3) are typically not amenable to upfront surgery.

Imaging studies have demonstrated good accuracy for predicting mediastinal disease. CT sensitivity, specificity, and accuracy approximate 83%, 82%, and 80% respectively, while ^{18}F-FDG PET-CT yields a sensitivity, specificity, and accuracy of 88%, 92%, and 91%, respectively.[13] A caveat to both tests, however, is that suspicious results do not always correlate with positive disease. Enlarged mediastinal lymph nodes (>1 cm in minor axis) or mediastinal ^{18}F-FDG avidity may represent nonmalignant processes such as inflammatory, granulomatous, or infectious conditions.

There are several methods for invasively staging lung cancer: endobronchial ultrasound (EBUS), endoscopic ultrasound (EUS), cervical mediastinoscopy, anterior mediastinotomy, and video-assisted thoracoscopic exploration and biopsy. EBUS and cervical mediastinoscopy are typically performed when there is mediastinal adenopathy on CT, increased mediastinal FDG uptake on PET-CT, clinical evidence of N1 disease, a lung mass greater than 3 cm, a central lung cancer, or evidence of bilateral lung tumors.[14,15] Anterior mediastinotomy is performed when there are bulky station 5 and/or 6 lymph nodes and there are concerns about a patient's ability to tolerate single-lung

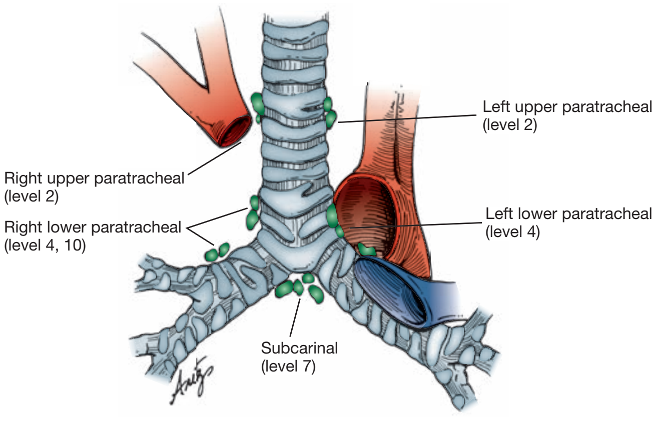

Figure 113-1 Lymph node stations accessible by cervical mediastinoscopy. For consistency the levels should be labeled with the appropriate number when submitted to surgical pathology.

ventilation and thoracoscopic exploration. Thoracoscopic exploration is performed when there is concern for metastatic disease, particularly in the presence of a pleural effusion with negative fluid cytology or evidence of pleural studding. It can also be used to sample station 5/6 lymph nodes or determine mediastinal invasion.

At our institution, EBUS is the initial diagnostic test for mediastinal staging. EBUS with rapid on-site evaluation proceeds logically from N3 to N2 locations, minimizing the need for sampling nodal stations and reducing upstaging risk through needle contamination.[14]

Should EBUS be negative in a patient with suspicious imaging who is a candidate for resection, cervical mediastinoscopy is performed at the time of planned resection. EBUS followed by mediastinoscopy improves sensitivity and reduces sampling error.[16]

■ Cervical Mediastinoscopy

Cervical mediastinoscopy is performed through a small (2.5 cm) transverse neck incision, 1 cm above the sternal notch. The platysma is divided, strap muscles split in the midline, and the pretracheal fascia incised. Blunt dissection is performed over the trachea to create a space for the mediastinoscope. Both nonvideo and video mediastinoscope systems are available (Figs. 113-2 and 113-3). Standard exploration of the mediastinum is performed, assessing the upper and lower paratracheal and subcarinal lymph node stations (2R, 2L, 4R, 4L, and 7). Nodes are harvested and sent for pathologic analysis.

Mediastinoscopy requires a general anesthetic and surgical training to perform correctly and safely. Morbidity and mortality of mediastinoscopy are low: 0% to 5.3% and 0% to 0.05%, respectively.[17] Operators must be able to identify the esophagus, recurrent laryngeal nerve, pulmonary artery, aorta, innominate artery, vena cava, and azygous vein in the process of harvesting lymph nodes (Fig. 113-4).

■ Chamberlain Procedure

The Chamberlain procedure, that is, anterior mediastinotomy, is performed via an incision made over the left second costal cartilage, which is excised. The pleural reflection is swept laterally to access the aortopulmonary window in an extrapleural plane. If this plane is maintained, tube thoracostomy is rarely needed and the procedure can be performed as an outpatient.

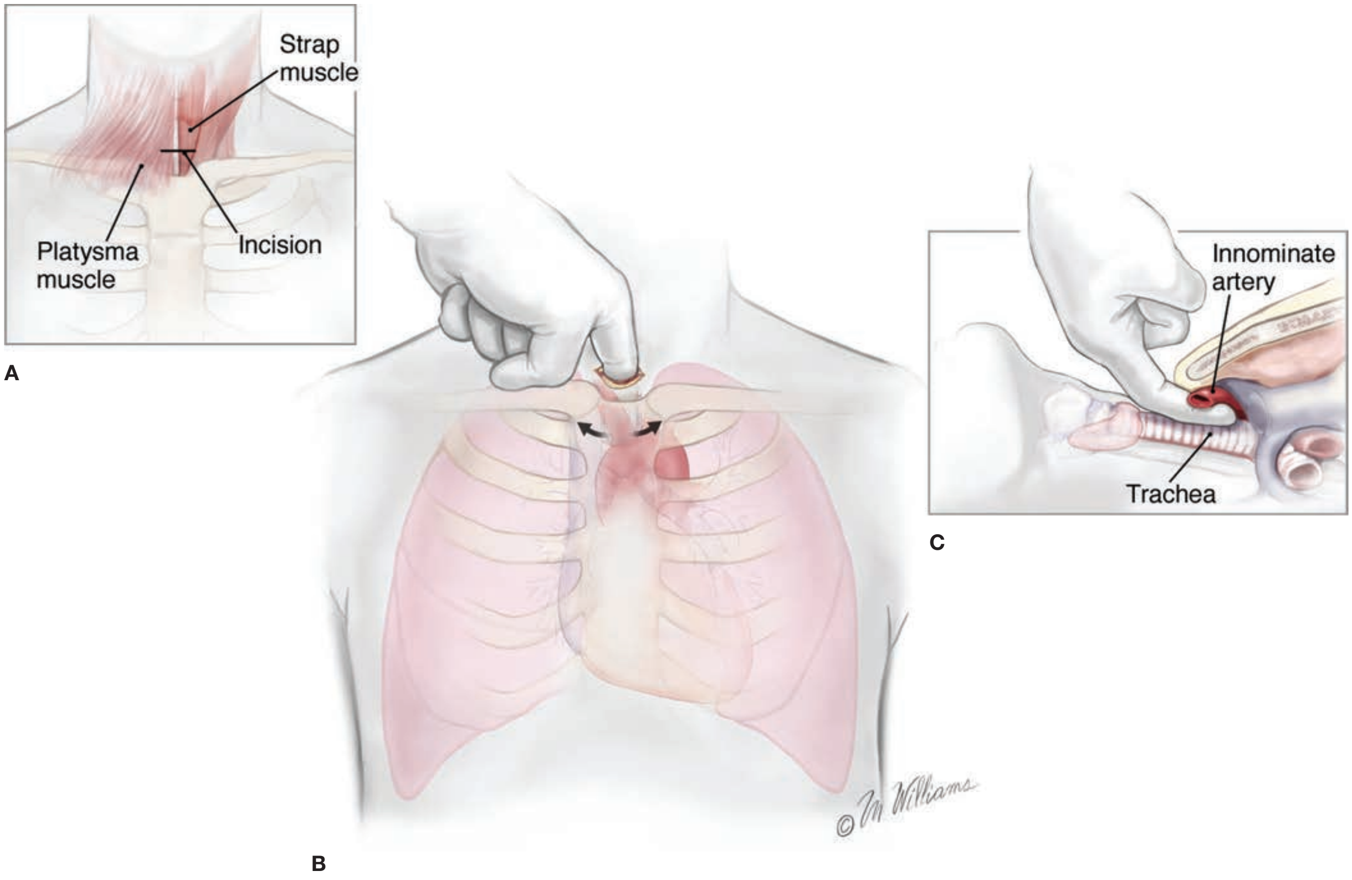

Figure 113-2 Technique of cervical mediastinoscopy. **A.** A 3-cm incision in the midline one fingerbreadth above the sternal notch. **B.** Pretracheal tunnel fashioned with blunt dissection using the index finger. **C.** Dorsal aspect of the finger remains on the trachea while the volar aspect comes in contact with the innominate artery. *(Reproduced with permission from Marcia Williams.)*

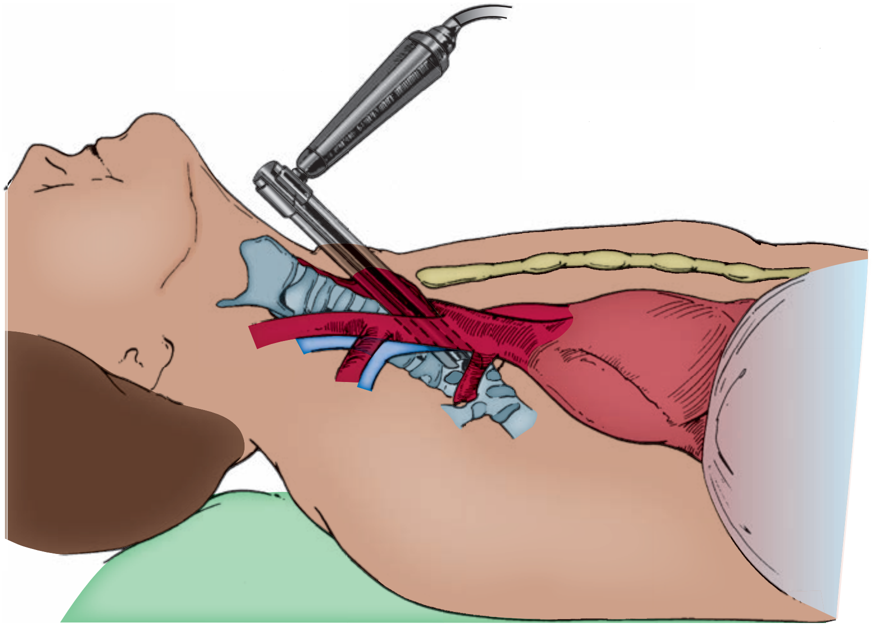

Figure 113-3 Mediastinoscope in place demonstrating the superior mediastinal plane.

Thoracoscopic Surgery

Video-assisted thoracoscopic surgery (VATS) or robotic-assisted thoracoscopic surgery (RATS) can be performed with limited incisions on both sides of the chest. This requires a brief period of single-lung ventilation and may require short-term chest tube drainage. Many patients can undergo this procedure as an outpatient. The benefit of this procedure is excellent visualization of the inside of the chest. The downside is postoperative pain, potential need for a chest tube, and overnight stay in the hospital. Thoracoscopic staging can be performed to evaluate the pleura, level 5 or 6 lymph nodes, right paratracheal nodes, subcarinal nodes, paraesophageal nodes (level 8), and nodes in the inferior pulmonary ligament (level 9) as well as to assess for chest wall or mediastinal invasion.

SURGICAL TREATMENT OF LUNG CANCER

Surgery remains the most durable and thorough method of treating localized lung cancer. Additional benefits of resection include availability of the entire tumor mass for pathologic and molecular testing and provision of more detailed staging information from extensive lymph node sampling. Types of surgical resection include anatomic procedures—segmentectomy, lobectomy, bilobectomy, and pneumonectomy—and nonanatomic wedge resection.

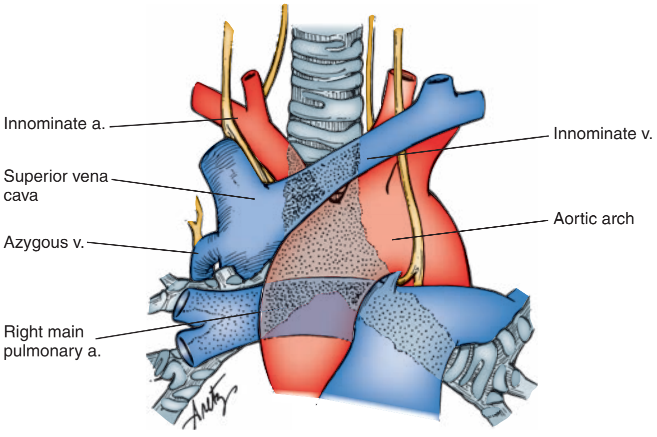

Figure 113-4 The relationship of major vascular structures potentially encountered during mediastinoscopy to the trachea and main bronchi.

When a patient with lung cancer is evaluated for resection, three criteria must be met: surgery must be oncologically beneficial, technically feasible, and physiologically possible. Oncologic benefit and technical feasibility are driven by staging studies and intraoperative findings. A patient's ability to tolerate surgery is determined preoperatively. As critical care and anesthetic techniques continue to improve and minimally invasive surgery advances, all patients with lung cancer should be considered for therapy by the treating specialists. Age bias against treatment including chemotherapy, radiation, and surgery has been documented across many fields of medicine.[18] Age alone should not be the basis for ruling out definitive treatment, and each patient must be evaluated individually.

Patients with advanced disease, who may be candidates for resection after induction therapy, should be referred early in the process so that decisions about potential fitness for operation from oncologic, medical, and technical perspectives can be made.

Tests commonly used to determine a patient's physiologic reserve include ECOG assessment, frailty index calculation, stair climbing, pulmonary function testing, transthoracic echocardiogram, and cardiac stress test.[19] Functional testing, such as stair climbing or shuttle walking, are easily performed in the office and are associated with minimal cost. The height climbed or speed at which the patient climbs a set number of stairs can predict postoperative complications.[20,21] Marginal surgical candidates may be referred for advanced testing such as cardiopulmonary exercise testing.[18,19] Physiologic reserve may be improved by smoking cessation therapy and dedicated exercise programs.[22] Quantitative perfusion lung scans are ordered when advanced pulmonary resections such as bilobectomy or pneumonectomy may be required or for patients with marginal pulmonary function and heterogeneous emphysema.

Anatomic resection involves individual ligation of feeding pulmonary arteries, vein, and bronchus to the region of the lung to be removed. Wedge resection involves removing lung tissue by dividing the lung parenchyma without ligation of the feeding vasculature or airway. Extended resections include anatomic resection with associated structures involved with cancer. These can include the chest wall, vertebral body, diaphragm, pericardium, left atrium, superior vena cava, main bronchus, and pulmonary artery. Resection choice is multifactorial based on tumor location, tumor stage, and a patient's physiologic reserve.

Open Versus Minimally Invasive Surgery

Most pulmonary resections are performed by thoracotomy, but the number of procedures performed by VATS or RATS is rising.[23,24] Open surgery is time-proven and safe, typically performed for central tumors or complex resections, or when VATS/RATS technology or experience is unavailable. VATS procedures were first performed in the early 1990s and have been associated with decreased length of stay, complication rate, and need for blood transfusion.[25–29] RATS has demonstrated similar benefits to VATS and has been performed since the early 2000s. It is estimated that approximately 30% of pulmonary lobectomy procedures are performed in a minimally invasive fashion.[23–25,31] There is increasing evidence that patients who undergo VATS lobectomy are better able to tolerate adjuvant chemotherapy and receive a greater proportion of the planned dose.[28,29]

Type of Resection

A variety of resection techniques must be considered, including lobectomy, segmentectomy, wedge resection, pneumonectomy, sleeve resection, and extended resection.

Lobectomy, Segmentectomy, Wedge Resection

Regardless of the resection modality used, the technical and oncologic principles of lung resection remain the same:[22,23] dissection and individual ligation of the relevant pulmonary arterial, venous, and bronchial branches combined with thorough mediastinal and regional lymph node sampling.[30–32] Lobectomy is the gold standard technique for removing most lung cancers. Segmentectomy is appropriate for invasive cancers less than 2 cm (cT1a–b) with no evidence of lymphatic invasion or for patients with limited pulmonary function. Wedge resection is appropriate for stage 0 lung cancers (adenocarcinoma in situ, adenocarcinoma with lepidic growth pattern, and minimally invasive adenocarcinoma with pure lepidic growth).[33–35]

Segmentectomy represents a more favorable treatment option than wedge resection, providing a wider parenchymal margin and removing regional lymphatic tissue.[39] A prospective randomized trial (CALGB 140503) is being performed to address the issue of lobar versus sublobar resection for peripheral tumors less than or equal to 2 cm. Long-term data are not available yet, but preliminary analysis shows relatively equal perioperative outcomes between lobectomy and segmentectomy.[36] Segmentectomies are often more technically demanding to perform compared to lobectomy. Many surgeons who do not perform a high volume of pulmonary surgery may not possess the expertise required to perform this procedure. Segmentectomy can be performed by open, robotic, or thoracoscopic techniques. Any of the pulmonary segments can be resected individually or in groups. The prototypic segmental resection is the superior segment of the lower lobe. Often, the basilar segments of either lower lobe are resected as a unit. Both segments of the lingula or the upper division of the left upper lobe are often resected together. Posterior or anterior segmentectomy of the right upper lobe also are commonly performed. Once the segmental artery, vein, and bronchus are divided, the lung parenchyma is divided along the intersegmental plane. Techniques for identifying the intersegmental plane include differential inflation and near infrared fluorescence thoracoscopy with indocyanine green injection either intravenously or endobronchially.[37] Three-dimensional CT reconstruction can assist in identifying the segmental anatomy and in localizing tumors near the intersegmental plane[38] (Fig. 113-5).

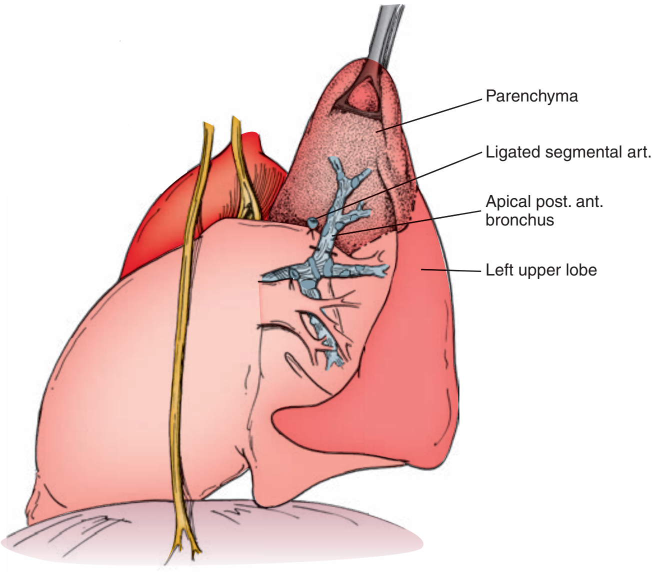

Figure 113-5 Segmental resection. The example shown here is the resection of the apical–posterior segment of the left upper lobe. The segmental pulmonary arterial branch is shown ligated and divided. The segmental bronchus has been dissected out and is the next structure to be divided.

Wedge resection represents the most limited extent of resection. It should be reserved for patients who cannot tolerate an anatomic resection or for patients with known adenocarcinoma in situ or minimally invasive adenocarcinoma. Wedge resection crosses lymphatic channels, does not remove the originating bronchus, and does not permit adequate regional lymph node resection, and parenchymal margins may be limited. These factors limit the value of wedge resection as a planned curative procedure for most primary lung cancers. Anytime a wedge resection is planned for physiologic reasons, nonoperative therapy such as stereotactic body radiotherapy (SBRT) should be considered. A randomized prospective trial of high-risk operable patients deemed not to be candidates for lobectomy is currently accruing patients. The STABLE-MATES trial will compare sublobar resection with SBRT.[39] Adjuvant radiation following wedge resection has been studied in high-risk patients for treatment of early-stage non–small-cell lung cancer (NSCLC).[40] The trial, CALGB 9335, prospectively accrued 58 patients to undergo local radiation treatment with 56 Gy following thoracoscopic wedge resection. Results were mixed: 17% of patients required conversion from VATS to thoracotomy, there were positive resection margins in 13% of patients with T1 and 31% with T2 tumors, and severe dyspnea and pneumonitis occurred in 11% and 14%, respectively, of patients receiving radiation.

Several groups have reported decreased local recurrence with adjuvant brachytherapy at the time of wedge or sublobar resection.[41,42] In these cases, ^{125}I seeds embedded in an absorbable mesh are applied to the line of resection on the lung.[42] This treatment, however, did not result in a meaningful clinical benefit in a randomized clinical trial (ACOSOG Z4032).[43]

Nonoperative therapy should be considered for patients who are not candidates for surgical resection.[44–46] A recent prospective study has shown that SBRT in medically inoperable early-stage cancers was associated with a 3-year locoregional control rate of 87.2% and overall survival of 56%.[46] Drawbacks of radiation therapy include lack of pathologic evaluation of the tumor and local lymph nodes and reduced local control rates.

Pneumonectomy, Sleeve Resection, and Extended Resections

Extended lung resections may be required for larger, locally invasive tumors. Whenever possible, attempts are made to preserve lung tissue using bronchoplastic and arterioplastic surgical techniques. Pneumonectomy is considered a last-resort operation due to a perioperative mortality rate of approximately 5% to 7%. Indications for pneumonectomy include tumor involvement of the main pulmonary artery, extensive endobronchial tumor precluding sleeve resection, involvement of the confluence of the pulmonary veins or a large portion of the left atrium, or long-segment invasion of the interlobar pulmonary artery.

Sleeve resections (bronchoplastic procedures) are more technically demanding but preserve lung tissue. Sleeve resection is possible for each of the lobes. Right upper lobe sleeve resection is the most commonly performed bronchoplastic resection, in which the right main bronchus is divided proximal to the right upper lobe takeoff and the bronchus intermedius is divided distal to the right upper lobe orifice (Fig. 113-6). The right upper lobe (and tumor at the lobar orifice) is removed with a portion of the mainstem bronchus and bronchus intermedius. With any lung-conserving procedure, the margins of the resection should be sent for frozen section for confirmation that no tumor is present. The bronchus intermedius and right main stem bronchus are then anastomosed and usually bolstered with a pedicled autologous flap such as intercostal muscle. Bronchoplastic resections result in lung conservation and are associated with long-term survival rates equivalent to pneumonectomy, with lower morbidity and mortality.

Proximal involvement of the pulmonary artery may also be amenable to arterial sleeve resection. Patch angioplasty with pericardium can be performed to reduce the risk of arterial stenosis. Alternatively, a segment of the artery can be removed and an end-to-end anastomosis performed with or without an interposition graft. Bronchoplastic resections and arterial resections with angioplasties are performed using minimally invasive techniques in many specialized centers.[47–49]

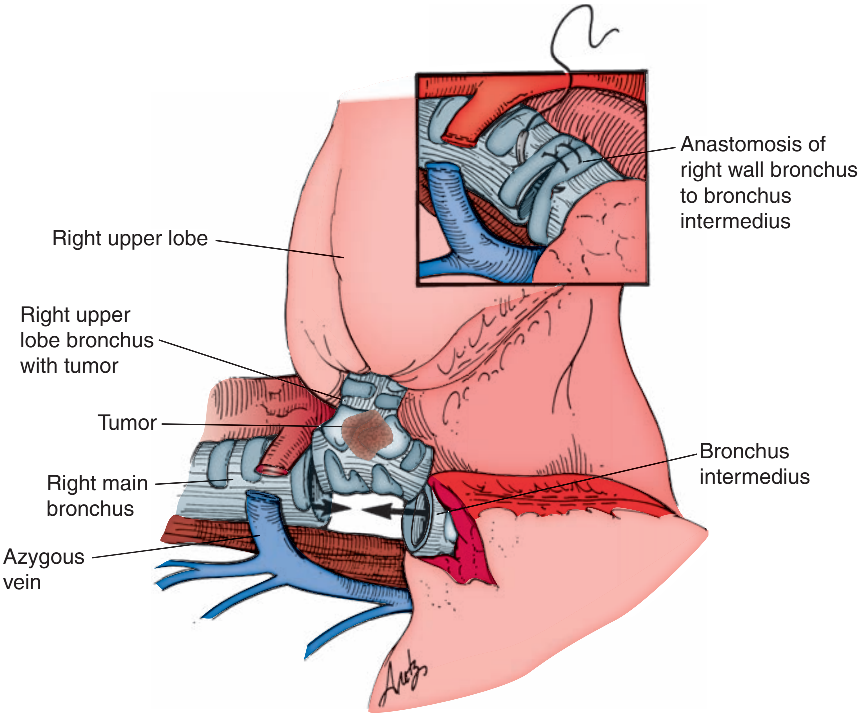
Anastomosis of right wall bronchus to bronchus intermedius
Right upper lobe
Right upper lobe bronchus with tumor
Tumor
Bronchus intermedius
Right main bronchus
Azygous vein

Figure 113-6 Right upper lobe sleeve resection. The right main bronchus has been divided just proximal to the right upper lobe takeoff where the tumor is located. The bronchus intermedius has been divided just distal to the right upper lobe bronchus. The bronchus intermedius is anastomosed to the right main bronchus *(inset)*.

■ Lymph Node Assessment

Lymph node removal is an important part of operative therapy for lung cancer. The extent of lymph node harvest, ranging between systematic sampling and dissection, has been a subject of debate. A 2011 randomized trial among 1000 patients with T1 or T2 tumors showed no significant survival advantage to lymph node dissection as long as systematic and thorough lymph node sampling was performed.[50] It is important to sample stations 2R, 4R, 7, and 10R for right-sided cancers and stations 5, 6, 7, and 10L for left-sided tumors. Failure to include mediastinal lymph nodes as part of a resection results in incomplete information with a risk of understaging and therefore undertreating.

During anatomic resection, multiple inter- and intralobar lymph nodes are encountered; these N1 nodes are labeled by their anatomic location and sent for pathologic examination. During segmentectomy, many surgeons perform frozen section analysis on N1 nodes. If these are positive for cancer, the operation is converted to lobectomy to reduce local recurrence rates.

N2/N3 Disease

Involvement of ipsilateral paratracheal or subcarinal lymph nodes (N2) classifies lung cancer as stage IIIA. These patients are best treated with induction (neoadjuvant) therapy followed by lobectomy or definitive chemoradiation. Contralateral mediastinal disease (N3, stage IIIB) carries a worse prognosis and usually renders a patient oncologically inoperable.

Treatment controversies for stage IIIA disease arise from disagreements about the appropriate role for surgery in this low-volume, heterogenous cancer stage. Questions remain regarding whether bulky, nonbulky, and microscopic nodal disease and single- and multistation lymphatic disease have similar natural histories following induction therapy and whether surgery can improve survival in select patients.

The history of stage IIIA treatment has evolved from surgery alone to induction therapy followed by surgery to definitive chemoradiation. In 1987, Martini et al. demonstrated complete resection in 151 of 500 patients with N2 disease. Complete resection resulted in 28% 5-year survival and 26% absolute survival.[51] Due to 0% survival in patients identified to have N2 disease prior to surgery, Martini subsequently showed that complete resection was possible in 65% of patients after induction therapy. Survival of complete versus incomplete tumor removal was 44% versus 28%, respectively, at 3 years and 26% versus 17%, respectively, at 5 years. Median survival was 27 versus 19 months, respectively.[52]

Subsequent studies confirmed the benefit of induction therapy with surgery in stage IIIA disease. Roth et al. randomized 60 patients with N2 disease to receive 3 cycles of chemotherapy (cyclophosphamide/etoposide/cisplatin) followed by surgery or surgery alone.[53] Preoperative therapy resulted in better outcomes than surgery alone, with median survival of 64 months versus 11 months, respectively. Rossell et al. similarly randomized 60 patients with N2 disease to chemotherapy followed by surgery or surgery alone.[54] A significant survival benefit was seen in the group that received combination therapy: median survival was 26 months versus 8 months, respectively.

A phase 3 trial (Intergroup 0139) was performed to compare induction chemoradiation followed by surgery with definitive chemoradiation.[55] Overall survival was similar in the two groups, but progression-free survival was significantly improved with the combined use of chemoradiation and surgery. When the analysis was restricted to patients who underwent lobectomy as opposed to pneumonectomy, overall survival was improved in the surgical group. Despite this latter result, many centers treat stage IIIA patients definitively with chemoradiation (Fig. 113-7).

In recent years, the pendulum has swung toward considering surgery more seriously as a treatment modality following induction for stage IIIA disease. Koshy et al. retrospectively reviewed 39,000 patients from the National Cancer Database with clinical stage IIIa–N2 disease, reporting improved survival in patients receiving neoadjuvant chemoradiation followed by lobectomy.[56] These results have been replicated by European and North American trials, including SAKK (16/00) and RTOG 0229.[57,58]

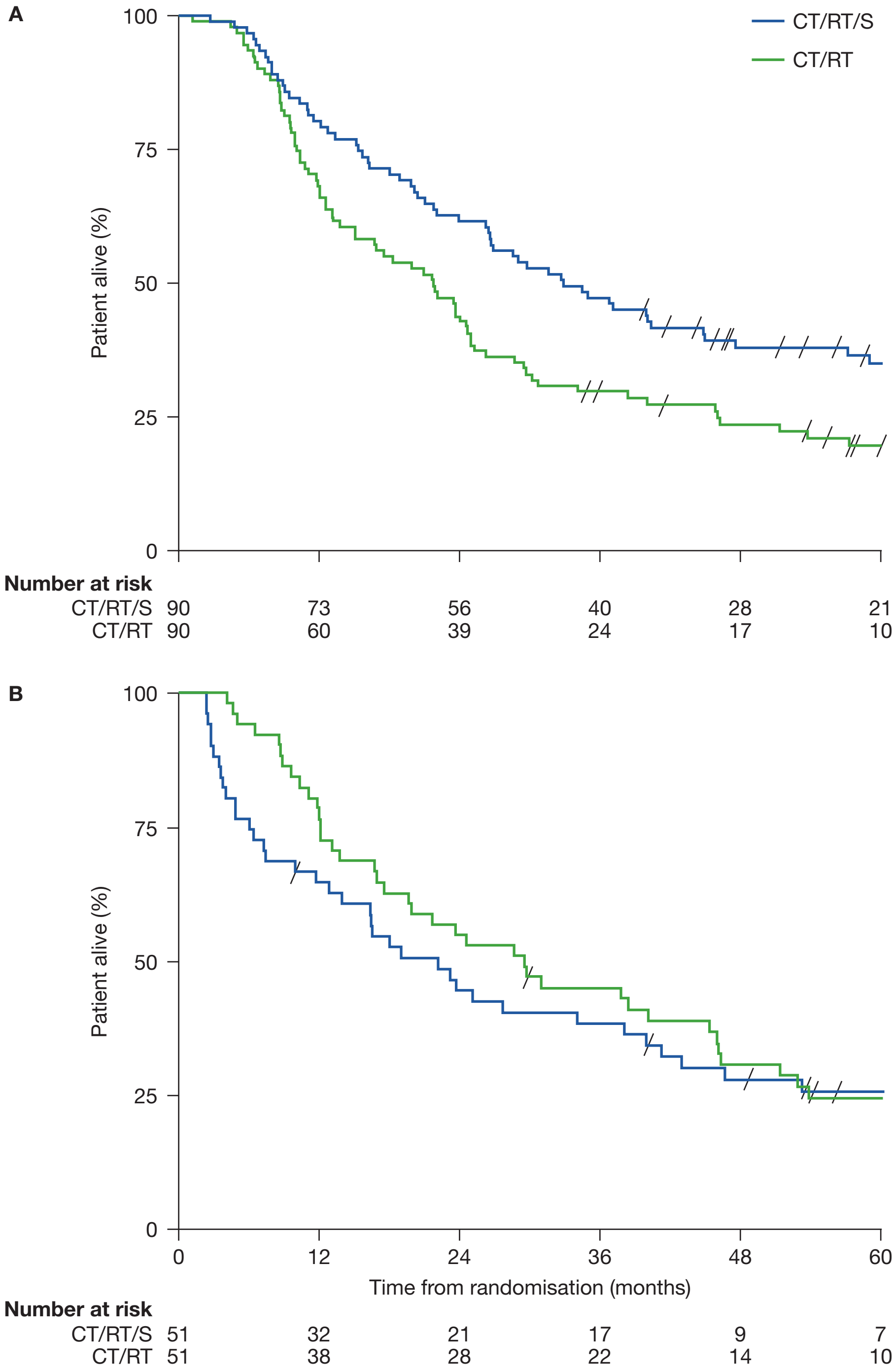

Figure 113-7 Overall survival of a subset of patients from the Intergroup 0319 trial: the intention-to-treat population given lobectomy (**A**) or pneumonectomy (**B**) in group 1 versus matched cohorts in group 2. *Slash marks* represent censored results. CT/RT/S, chemotherapy plus radiotherapy followed by surgery (group 1, *n* = 202); CT/RT, chemotherapy plus radiotherapy (group 2, *n* = 194). *(Reproduced with permission from Albain KS, Swann RS, Rusch VW et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. Lancet. 2009;374(9687):379–386.)*

Fibrosis that results from induction chemotherapy and radiation can pose technical challenges. This is especially challenging when involved lymph nodes become intimately associated with the pulmonary artery and its branches. It is important to consider obtaining proximal control of the pulmonary artery before attempting resection in these cases. The patient's physiologic reserve, extent of resection, and tumor burden should be carefully considered prior to embarking on a strategy of induction therapy followed by resection.

Pneumonectomy as treatment for stage IIIA disease following induction therapy remains controversial. Despite reported mortality rates as low as 5%, this has not been universally observed.[59–61] Many groups avoid pneumonectomy after induction due to the higher-risk nature of the procedure. Most centers recommend vascularized flap coverage of the bronchial stump in this setting.[60]

■ Chest Wall Resection

Approximately 5% of lung cancers involve the chest wall by direct extension (T3). Involvement may be limited to the parietal pleura or may include the endothoracic fascia, intercostal muscle, and/or ribs. Chest wall involvement by direct extension is *not* a contraindication to resection unless multiple vertebral bodies are invaded; even then, under some circumstances resection may still be completed with concurrent spinal stabilization.

Chest wall pain is the most sensitive predictor of chest wall involvement in a patient with a peripheral lung lesion. Neither CT, MRI, PET-CT, nor bone scan can distinguish between abutment and invasion unless there is gross invasion of bone. Optimal treatment for tumors involving the chest wall (not superior sulcus) is resection followed by adjuvant therapy.[62,63] Metastatic and mediastinal lymphatic disease must be ruled out prior to performing chest wall resection. Three-year survival approaches zero in patients with chest wall and mediastinal lymph node involvement. Greater than 50% 5-year survival can be expected in patients with chest wall involvement with negative mediastinal lymph nodes.

Surgery performed in a patient with suspected chest wall involvement begins with mediastinoscopy to rule out N2/N3 disease. If this is negative, thoracoscopic exploration is often performed on the side of the tumor. This rules out diffuse pleural disease and defines whether the chest wall is invaded; it also allows for lung hilum to be examined to ensure that a clear vascular margin can be obtained.

Resection begins in the extrapleural plane, separating the parietal pleura from the endothoracic fascia in the area of the lesion. If this plane is easily developed, it may be that the parietal pleura is not invaded but affected by inflammatory adhesions. If there is any question about rib invasion when developing the extrapleural plane, then chest wall resection is performed (Fig. 113-8).

The chest wall is resected in continuity with the lung parenchyma. The portion of chest wall removed remains attached to the underlying lung and the specimen is removed en bloc. The chest wall resection should include at least one rib and preferably two ribs above and below the area of invasion. Three- to 5-cm margins

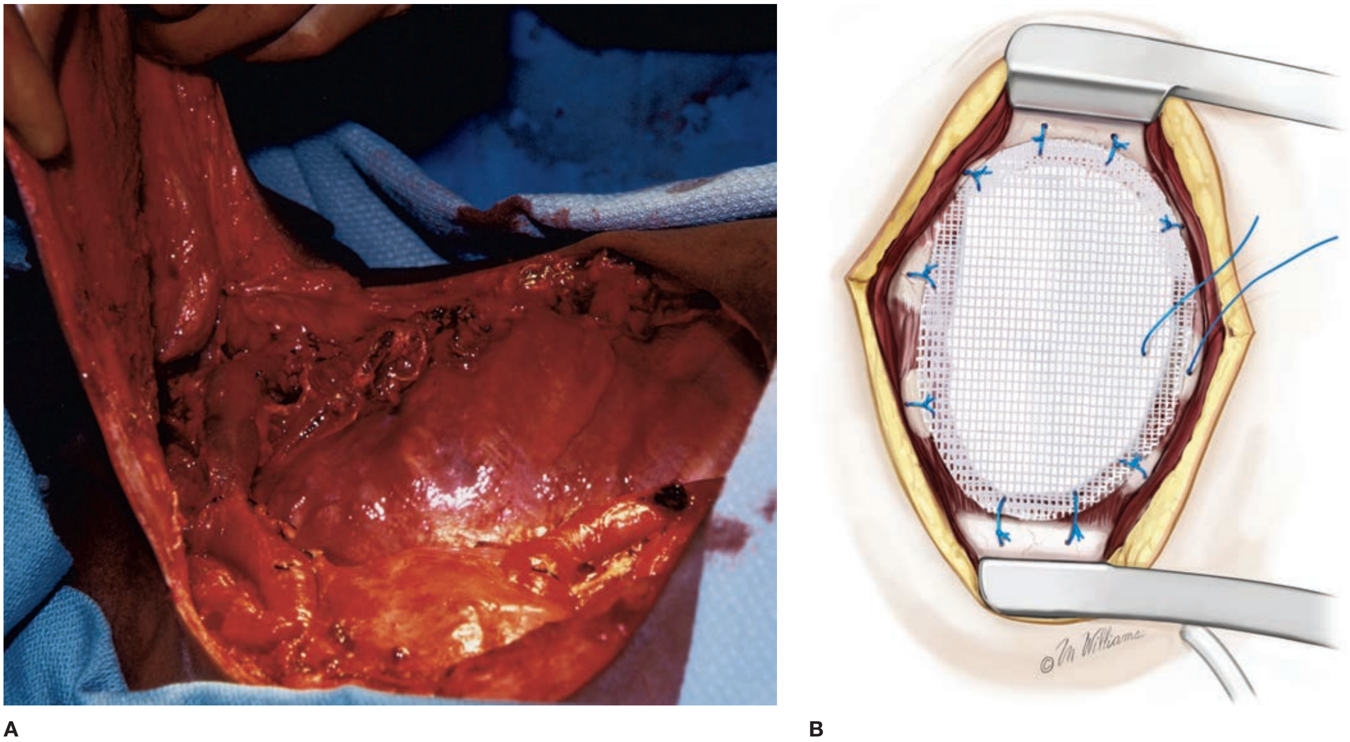

Figure 113-8 **A.** Operative photograph showing the defect left after resection of the left upper lobe in continuity with the anterior chest wall. **B.** This anterior defect requires reconstruction with prosthetic mesh and methyl methacrylate cement. *(**B.** Reproduced with permission from Marcia Williams.)*

should be taken anteriorly and posteriorly. For posterior tumors, the rib should be disarticulated and nerve root ligated.

Once the chest wall bloc is mobilized, it is dropped into the chest and lobectomy with lymph node sampling or dissection completed. Posterior and anterior chest wall defects greater than 5 cm are reconstructed to preserve chest wall function and protect the thoracic viscera. There are multiple prosthetics used for reconstruction, including polypropylene mesh, expanded polytetrafluoroethylene (ePTFE), a sandwich of methyl methacrylate cement and polypropylene mesh, titanium mesh, titanium or stainless steel rib prosthetic plates, and custom 3D-printed prostheses.[64–66] Bioabsorbable prostheses also are available for reconstruction, which have the advantage of being radiolucent.[67] The ideal material for reconstruction has yet to be identified, as the technology does not exist to recreate the rigidity and flexibility of the native chest wall. Posterior defects covered by the scapula may not need reconstruction. Care must be taken to ensure that the scapula tip does not drop into a chest wall defect, causing scapular entrapment.

Chest wall resection, reconstruction, and anatomic resection can be accomplished in selected patients without formal thoracotomy, using thoracoscopic and robotic techniques and low-profile bone-cutting instruments.[68]

Interestingly, en bloc resection of the chest wall increases neither postoperative pain nor overall morbidity of a pulmonary resection. Adjuvant chemotherapy is provided for margin-negative disease.[63] Radiation therapy is provided for positive chest wall margins that cannot be re-resected.[63]

■ Superior Sulcus Tumors

Tumors of the superior sulcus present an oncologic and surgical challenge. Therapy for these tumors has evolved from upfront surgery to palliative care to induction chemoradiation followed by surgery with curative intent.[69] Patients with superior sulcus tumors may present with Pancoast syndrome, which includes shoulder pain, Horner syndrome, and neurologic deficits in the ipsilateral upper extremity usually in the ulnar nerve distribution.[70] MRI of the thoracic inlet, spinal imaging, MRI of the brain, and invasive mediastinal staging must be performed on these patients. N2 disease, C8 root involvement, and motor loss in the ipsilateral hand are contraindications to surgery.

Typical treatment regimens include induction chemoradiation with cisplatin/etoposide and 45 Gy of radiation followed by resection and adjuvant chemotherapy.[71] These tumors may be approached using an anterior cervicothoracotomy, an extended posterolateral thoracotomy, or a combined anterior and posterior approach.[69,70,72] Involved vertebral bodies may be resected and reconstructed at the time of surgery.[73] Reconstruction of the subclavian artery may be required and is associated with good long-term survival provided a complete resection is achieved.[74] Hybrid approaches using minimally invasive techniques have been reported.[75]

■ Tumors Extending into the Mediastinum

Some centrally located primary tumors may invade mediastinal structures (Fig. 113-9). Assessment of the mediastinum is best determined intraoperatively. Without evidence of frank invasion of the mediastinum, we favor evaluation for aggressive resection, provided mediastinal nodal and metastatic disease are ruled out.

Invasion of the heart, great vessels, esophagus, and recurrent laryngeal nerve are contraindications to surgery. Direct involvement of the carina, superior vena cava, and left atrium are not strict contraindications to surgery. The superior vena cava can be partially or completely resected and reconstructed with patch angioplasty or interposition grafting. Autologous or bovine pericardium can be used to reconstruct a portion of the left atrium. Carinal resection and reconstruction usually combined with a right upper lobectomy or right pneumonectomy is performed using similar techniques to sleeve lobectomy with cross-table ventilation of the contralateral

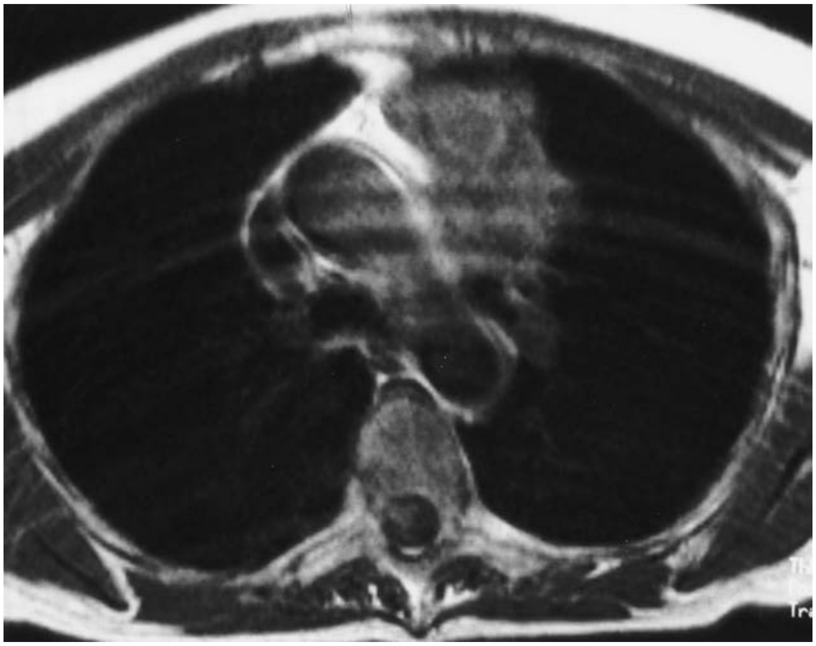

Figure 113-9 MRI scan showing a primary lung tumor involving the aorta by direct extension (T4 primary). The distinction between abutment and invasion often cannot be made until the findings are seen at operation. MRI is no better at delineating invasion than CT.

lung.[76] T4N0–N1 tumors are staged as IIIa and should be evaluated and treated as such.[77]

Vertebral body invasion is not a contraindication to resection. Transverse process or anterior vertebral body involvement can be removed with partial resection of the vertebral body. Extensive involvement of one or more vertebral bodies can be managed with vertebral corpectomy and spinal stabilization with neurosurgeons or orthopedic spine surgeons in one or two stages. These procedures are preferably performed after induction therapy in specialized centers[78,79] (Fig. 113-10).

Involvement of the recurrent laryngeal nerve is a contraindication to surgery. The only exception to this is the occasional situation in which the primary tumor involves the left vagus nerve as it crosses the aortic arch. Such instances merit exploration to determine whether resection is feasible.

■ Palliative Resections

There is a limited role for palliative resections in the modern era of NSCLC. Bleeding or infection of primary tumors usually can be managed with bronchoscopic debulking, airway stenting, external beam radiation, or endobronchial brachytherapy. Chest wall pain can be effectively palliated by radiation therapy.

OUTCOMES

Below we briefly consider postoperative complications, as well as postoperative morbidity and mortality.

■ Postoperative Complications

Major improvements in perioperative thoracic surgical care have led to decreased morbidity and mortality. More sophisticated preoperative patient evaluation has allowed for identification of modifiable risk factors. Increased use of lung-conserving procedures, use of minimally invasive surgical techniques, and increasing number of specialty-trained thoracic surgeons have allowed surgery to be offered to greater numbers of patients. Innovations in pre- and postoperative respiratory care and pain management have contributed to a decrease in perioperative respiratory complications. The introduction of enhanced recovery after surgery (ERAS) protocols has decreased perioperative length of stay, cost, and complications.[80,81] "Prehabilitation" may hold promise in further decreasing perioperative complications and allow more patients to undergo surgery.[22]

Despite these advances, thoracic surgery remains a significant physiologic stress. Patients may not achieve full physiologic and psychological recovery for several months after surgery.[82–86] Additionally, postthoracotomy incision pain—even after minimally invasive procedures—may persist for several weeks after surgery. Patients requiring narcotics beyond the first 6 weeks after surgery should be referred back to the operating surgeon to ensure no organic reason exists for their symptoms. For patients with pure pain-related issues, nonnarcotic analgesics such as gabapentin and referrals to pain management specialists may be helpful adjuncts.

■ Postoperative Mortality

Lobectomy and lesser resections have a mortality rate between 1% and 2%; pneumonectomy mortality approximates 5% to 7%.[66,67] Respiratory complications are the most common cause of

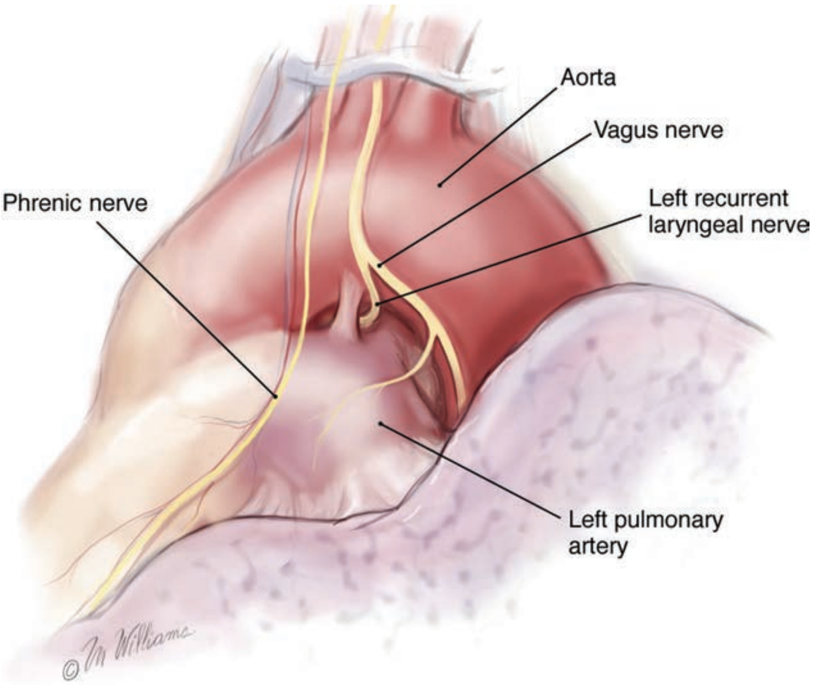

Figure 113-10 The anatomy of the aortopulmonary window showing the relationship of the left recurrent laryngeal nerve to the aortic arch and ligamentum arteriosum. The nerve is easily damaged in this location. Hoarseness may result from tumor involvement of the nerve in this location or from involvement of the vagus nerve at the level of the aortic arch proximal to the location where the recurrent laryngeal nerve originates. *(Reproduced with permission from Marcia Williams.)*

postoperative mortality. Cardiac complications and technical issues such as bleeding hemorrhage, bronchopleural fistula, and empyema account for a small but significant portion of mortality.

Postoperative Morbidity

Approximately 30% to 40% of patients undergoing pulmonary resection experience a postoperative complication. Two-thirds of these are minor, and one-third are nonfatal major.[87] The most common is supraventricular arrhythmia, which occurs in up to 20% of patients. Most respond to simple pharmacologic manipulation and are self-limited. Other minor complications include postoperative air leaks lasting greater than 5 days and atelectasis. Major nonfatal events are typically respiratory related, principally aspiration pneumonitis and nosocomial pneumonia. A small percentage of patients require reintubation for respiratory failure.

There are no definitive predictors of postoperative pulmonary complications, although increasing age, FEV_1 less than 2 L, and diminished diffusing capacity ($\mathrm{DL}_{\mathrm{CO}}$) have been associated with worse outcomes.[88–90] Oxygen consumption ($\dot{V}\mathrm{O}_{2\max}$) less than 10 mL/kg/min on preoperative cardiopulmonary exercise testing is associated with an increased risk of death.

Use of VATS or RATS may decrease pulmonary complications, particularly in patients with limited pulmonary reserve.[91] Chest physiotherapy, nebulized and mucolytic therapies, and patient education have assisted with mucociliary clearance and reduced mucus plugging events following surgery.

Pneumonectomy-specific complications include postpneumonectomy pulmonary edema, postpneumonectomy syndrome, and empyema with or without a bronchial stump leak. Postpneumonectomy edema is characterized by tachypnea, low-grade fever, noncardiogenic pulmonary edema, and hypoxemia in the absence of pneumonia. Supportive care, gentle diuresis, and protective ventilation strategies are the mainstays of care; mortality approximates 50%.[92]

Hemodynamic instability immediately after pneumonectomy may be the result of acute mediastinal shift to the ipsilateral side obstructing venous return. Acute management includes placing the patient in the decubitus position with the operated side elevated and prompt return to the operating room. Postpneumonectomy syndrome is due to anatomic kinking of the contralateral bronchus resulting from excessive mediastinal shift and rotation. It is unclear exactly why this complication develops, but it appears to be due to fibrosis of the mediastinum following pneumonectomy combined with progressive shift of the mediastinum toward the surgical side. Symptomatic patients may be helped by stabilizing the mediastinum with insertion of sterile saline implants or Lucite balls into the pneumonectomy space, which repositions the mediastinum closer to the midline and relieves the functional obstruction.

Postpneumonectomy empyema may occur in the perioperative period from contamination at the time of surgery or a bronchial stump leak. It can occur late, from local recurrence, instrumentation, or bacteremia, or its source may be idiopathic. A sudden decrease in the height of the air–fluid level on chest radiograph, signifying a bronchopleural fistula, and a cough productive of thin brownish sputum should trigger prompt investigation. Treatment involves prompt pleural drainage, initiation of broad-spectrum antibiotics, and evaluation of the bronchus via flexible bronchoscopy. Pleural drainage should be instituted with the affected side in a dependent position. Additionally, the operator must be cognizant of the anatomic derangements after pneumonectomy such as an elevated diaphragm and mediastinal shift that may put thoracic or abdominal viscera at risk during pleural drainage. Decisions regarding the need for definitive drainage via window thoracostomy versus autologous pedicled flapping and chest closure or nonoperative therapy remain challenging.

TABLE 113-1 Overall Survival by Clinical Stage

Stage	24-Month Survival	60-Month Survival
IA1	97%	92%
IA2	94%	83%
IA3	90%	77%
IB	87%	68%
IIA	79%	60%
IIB	72%	53%
IIIA	55%	36%
IIIB	44%	26%
IIIC	24%	13%
IVA	23%	10%
IVB	10%	0%

Data from Goldstraw P, Chansky K, Crowley J, et al. The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. J Thorac Oncol. 2016;11(1):39–51.

PROGNOSIS

Outcomes following pulmonary resection for lung cancer are dictated by TNM stage. In the absence of stage IV disease, lymphatic involvement drives prognosis. Histology also has prognostic significance—in particular, the presence of neuroendocrine carcinoma/small-cell lung cancer and micropapillary adenocarcinoma with extensive spread through the air spaces portend a worse prognosis. Survival estimates vary among surgical series. The current staging system divides stage IA disease into stages IA1, IA2, and IA3 to allow for granular discrimination of outcomes. In the validation of the most recent staging system, 17,477 clinically staged and 31,836 pathologically staged patients were analyzed.[93] Survival estimates, which include patients treated with both surgical and nonsurgical interventions, are shown in Table 113-1.

Sites of Recurrence

Patients with lung cancer frequently die of disseminated disease. A study from Memorial Sloan Kettering reported recurrence patterns in patients with initially localized lung cancer: 44% distant sites, 30% distant and locoregional sites, and 26% locoregional.[94] More than 30% of patients with adenocarcinoma develop brain metastasis. Other sites of metastasis include bone, lung, liver, and adrenal glands. Patients with higher-stage disease at diagnosis have a greater likelihood of developing disseminated disease. This recognition has led to routine administration of adjuvant treatment regimens following surgical resection for patients with stage IIA and above disease.

Local recurrence may be amenable to repeat resection. Sites of local recurrence include the chest wall, adjacent lung tissue, mediastinum, and great vessels of the chest. Determination of resectability is made in a multidisciplinary setting, with consideration of a patient's performance status and ability to obtain a complete resection. SVC syndrome and recurrent laryngeal nerve invasion are not amenable to surgery, but radiation and chemotherapy may be helpful.

POSTSURGICAL FOLLOW-UP

Postresection follow-up is dictated by pathologic cancer stage. Generally, stage IA and IB disease, treated with surgery alone, should be followed with history, physical examination, and chest

CT with contrast every 6 to 12 months for 2 years. Should there be no evidence of recurrent disease, annual examination and noncontrast CT should be performed for an additional 3 years.[43] Patients receiving adjuvant chemotherapy for stage IB–IIIA disease typically undergo similar surveillance, with a provisional recommendation to undergo initial CT imaging every 3 to 6 months for the first 2 years following treatment completion. The American Association for Thoracic Surgery surveillance protocol recommends an annual low-dose screening CT for lung cancer survivors between the ages of 50 and 79 years who have completed 4 years of standard follow-up.[95,96] PET and MRI are not routinely ordered but may be required if additional nodules or metastatic lesions require assessment.[96]

FUTURE DIRECTIONS

Continued refinement in surgical technique and perioperative management will allow greater numbers of patients to benefit from surgical intervention. Ongoing collaboration between surgeons, medical and radiation oncologists, and basic scientists will continue to expand treatment options for this virulent disease. Immunotherapy and targeted therapies are showing promise in treating patients with disseminated disease with molecular mutations. While surgery remains the standard therapy for fit patients with localized NSCLC, risk factor modification is the best way to prevent disease. The importance of smoking cessation efforts and improved occupational environmental controls cannot be overemphasized.

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CHAPTER 114

Treatment of Non–Small-Cell Lung Cancer: Chemotherapy and Immunotherapy

Laurie L. Carr

INTRODUCTION

Although lung cancer remains the leading cause of cancer death in the United States, a reduction in smoking rates and recent medical advances have improved the overall mortality rate. The decline in lung cancer mortality rates has accelerated from a 3% decrease (2008–2013) to 5% (2013–2017).[1] Noted medical advances driving the decrease include lung cancer screening and stereotactic body radiotherapy. However, improved systemic therapy with immune checkpoint inhibitors and targeted agents also have had an impact. These improvements have led to prolonged survival in those with metastatic disease. Treatment with targeted agents or immunotherapy has led to a significant percentage of these patients surviving 5 years or more.[2–4] These novel therapies have emerged to make lung cancer therapy better tolerated and more effective, even among those with significant comorbidities. Thus, although the morbidity and mortality of lung cancer remain high, novel approaches to therapy have begun to make a substantial impact.

Chemotherapy is used for three main reasons in the treatment of non–small-cell lung cancer (NSCLC): (1) as adjuvant therapy in early-stage disease, either preceding or following potentially curable, surgical resection to prevent disease recurrence; (2) as concurrent therapy with radiation in locally advanced disease to radiosensitize the tumor for improved local response and prevent metastatic disease recurrence; and (3) as palliative therapy in the setting of advanced disease to ease symptoms and prolong survival. Immunotherapy has emerged as an important addition to conventional chemotherapy for treatment of advanced disease. This chapter focuses on the role of systemic chemotherapy and immunotherapy in the treatment of NSCLC in each of these settings.

ADJUVANT THERAPY FOR NON–SMALL-CELL LUNG CANCER

Surgery remains the standard of care for patients with early-stage disease who do not have medical contraindications. In this setting, surgery provides definitive treatment and allows for more accurate pathologic staging. Staging is central to the therapeutic approach to NSCLC and entails determination of the extent of invasion of the mediastinal lymph nodes. Mediastinoscopy or fine-needle aspiration (FNA) of lymph nodes by endobronchial ultrasound (EBUS) can be used to sample mediastinal lymph nodes before surgical resection. As for all surgical interventions for thoracic malignancy, complete nodal sampling or lymph node dissection is an integral part of the procedure. Reliance on noninvasive imaging alone may be inadequate for an accurate assessment of the mediastinum (Fig. 114-1).

Adjuvant Chemotherapy

It is well recognized that despite complete resection, most patients with NSCLC will develop disseminated disease. The risk of developing disseminated disease can be predicted, with some accuracy, based on the stage of the disease determined at the time of the initial resection. However, the value of the staging information depends on the completeness of the staging procedures carried out at the time of resection. Even with stage I disease, as many as 20% of patients die of disseminated disease within 5 years. With stage II disease, less than 60% of patients are alive at 5 years; with stage IIIA disease, at best, 41% of patients are alive at 5 years.[5] These numbers illustrate the need for additional therapy to improve the overall survival (OS) achieved by surgery.

To this end, a body of data has emerged to define the role of chemotherapy in the adjuvant setting. The rationale behind this approach is to treat patients who are deemed to be at high risk for recurrence and dissemination of disease in the hope of eliminating micrometastatic disease. Multiple trials randomizing patients to surgery versus surgery followed by platinum-based chemotherapy have been conducted. More recently, molecular targeted agents have been studied in the adjuvant setting to determine the impact of these agents in early-stage disease (Table 114-1).

International Adjuvant Lung Cancer Trial

The International Adjuvant Lung Cancer Trial (IALT) randomized 1867 patients with stage I, II, or III NSCLC to observation or chemotherapy after surgical resection.[6] Due to the lack of consensus regarding the use of adjuvant radiotherapy, the choice of a specific radiation regimen was made by each participating institution at the time of protocol development. The chemotherapy regimens used consisted of cisplatin 80, 100, or 120 mg/m^2 offered on 1 of 4 different schedules with vindesine, vinblastine, vinorelbine, or etoposide. Patients were treated with 3 or 4 cycles. Of the various choices, the combination of cisplatin and etoposide was used to treat nearly 50% of the patients. When offered, radiation was given after chemotherapy in the group randomized to postoperative treatment. Overall, the results favored the use of adjuvant chemotherapy, with

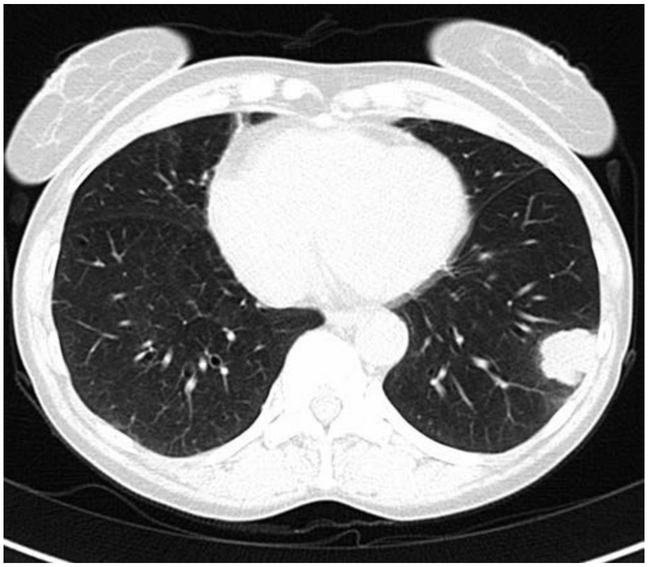

Figure 114-1 CT scan of a 59-year-old female with ongoing smoking and chronic cough. The image shows a large nodule in the left lower lobe extending into the pleura. The patient underwent a mediastinal lymph node dissection and left lower lobectomy. She was found to have several hilar lymph nodes involved with tumor at the time of resection (stage IIA). She received four cycles of cisplatin-based adjuvant chemotherapy following surgical resection.

TABLE 114-1 Randomized Trials of Adjuvant Therapy

	Overall						
					Survival (%)		
Trial	Number of Patients	Stage	Therapy	Survival (Months)	2 Years	3 Years	5 Years
International Adjuvant Lung Cancer Trial[6,7]	1867	IA, IB, II, III	Observation	45	66.7		40.4
			Chemotherapy	54	70.3		44.5
CALGB 9633[8]	344	IB–T2N0	Observation	78[a]	84	73	58[a]
			Chemotherapy	95[a]	90	80	60[a]
NCIC JBR 10[9]	482	IB, II (no T3N0)	Observation	73			54
			Chemotherapy	94			69
ANITA[10]	840	IB, II, IIIA	Observation	43.7			
			Chemotherapy	65.7			
LACE	4584	IA, IB, II, III	Observation			Absolute improvement	
Meta-analysis[12]			Chemotherapy			3.9%	5.4%
ADJUVANT/	222	II, IIIA	Chemotherapy	79.2		67.5	52.4
CTONG1104[16]			Gefitinib	75.5		68	53.8
ADAURA[17,18]	682	IB, II, IIIA			Disease-free survival		
			Placebo		52[a]		
			Osimertinib		89[a]		

[a] Statistically significant.

CALGB, Cancer and Leukemia Group B; NCIC, National Cancer Institute of Canada; ANITA, Adjuvant Navelbine International Trialist Association; LACE, Lung Adjuvant Cisplatin Evaluation; CTONG, Chinese Thoracic Oncology Group.

a hazard ratio (HR) for death of 0.86 (0.76–0.98). At 5 years, the group that received chemotherapy had a statistically significant improvement in survival of 44.5% versus 40.4%. The toxicities associated with chemotherapy included the expected risks of neutropenia and nausea/vomiting. However, 7 patients (0.8%) died due to chemotherapy-related acute toxicities; this was predominantly seen in those who received cisplatin at 120 mg/m^2. This positive trial demonstrated an absolute benefit at 5 years and provided support for the use of cisplatin-based treatment in the adjuvant setting.[7]

NCIC JBR 10

In this intergroup study, 482 patients with stage IB or II (excluding T3N0) NSCLC were randomized to either surgery or surgery followed by 4 cycles of chemotherapy.[8] Again, the treatment studied included cisplatin (50 mg/m^2 days 1 and 8) and vinorelbine (25 mg/m^2 weekly); 1 cycle was 4 weeks. NCIC JBR 10 was a positive study, with 5-year survival favoring the chemotherapy group (69% vs. 54%), as well as a statistically significant improvement in disease-free survival (DFS) and OS. Toxicity was associated with this regimen with 2 treatment-related deaths and more than 70% of patients experiencing either grade 3 or 4 neutropenia.

ANITA

The Adjuvant Navelbine International Trialist Association (ANITA) study randomized 840 patients with stage IB, II, or IIIA NSCLC to 4 cycles of chemotherapy or observation after surgery.[9] Similar to the other trials, the chemotherapy regimen consisted of cisplatin (100 mg/m^2, day 1) and vinorelbine (30 mg/m^2, weekly) for a 4-week cycle. The choice of radiotherapy was left to the discretion of the treating physicians. In the final analysis, 24% of patients in the chemotherapy arm and 33% of patients in the observation arm received radiation. Patients randomized to chemotherapy had a significant improvement in median survival to 66 months, compared with 44 months in the control group. At 5 years, the absolute benefit in survival was 8.6%, and in a subset analysis, this benefit seemed to be mainly noted in stage II and IIIA patients.

TREAT Study

More recently, the Trial on Refinement of Early-Stage NSCLC Adjuvant Chemotherapy (TREAT) randomized patients to cisplatin (75 mg/m^2) and pemetrexed (500 mg/m^2) every 3 weeks versus cisplatin (50 mg/m^2 days 1 and 8) and vinorelbine (25 mg/m^2 days 1, 8, 15, and 22) every 4 weeks. The study was designed to determine if substitution for the vinca alkaloid could improve upon side effects and dose delivery in the adjuvant setting. In all, 132 patients (stages IB–IIIA) were randomized to 4 cycles of either regimen. Ninety-five percent of those in the pemetrexed arm vs. 75% in the vinorelbine arm received all cycles of therapy without significant dose-limiting toxicity. The hematologic grade 3 or 4 toxic effects were significantly less with pemetrexed, yet no difference was seen in progression-free survival (PFS). This regimen is recommended for adjuvant therapy in resected adenocarcinoma.[10]

Lung Adjuvant Cisplatin Evaluation Meta-analysis

In 2008, the Lung Adjuvant Cisplatin Evaluation (LACE) Collaborative Group published results of a pooled analysis of large trials (>300 subjects) investigating the use of cisplatin-based adjuvant chemotherapy versus no further therapy following complete resection of NSCLC.[11] The individual data from more than 4500 subjects was analyzed with a median of 5.2 years follow-up. The investigators found an absolute benefit of 5.4% improvement in OS at 5 years in the treatment group. There was no interaction seen in regard to gender, age, histology, or type of surgery. However, the degree of benefit varied with stage; the HR for stage IB was 0.93 (95% confidence interval [CI], 0.78–1.10), for stage II the HR was 0.83 (95% CI, 0.73–0.95), and for stage III the HR was 0.83 (95% CI, 0.72–0.94). This analysis confirmed the benefit of cisplatin-based adjuvant chemotherapy following complete resection in fit patients with stage II and III NSCLC. Currently, the National

Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO) guidelines recommend cisplatin-based adjuvant chemotherapy for stage II and IIIA NSCLC. Unfortunately, the addition of bevacizumab, an antiangiogenesis agent, to adjuvant chemotherapy did not improve outcomes and is not recommended in this setting.[12]

CALGB 9633

The Cancer and Leukemia Group B (CALGB) conducted a trial to test the benefit of carboplatin-based adjuvant chemotherapy exclusively in stage IB (T2N0) patients.[13] Other studies included these patients along with those with more advanced disease, and in subset analyses, the true benefit of chemotherapy after surgery in this population was questioned. Originally, this study was intended to enroll 500 patients. However, due to poor accrual, this number was modified and in the final analysis, 344 patients were treated. Patients randomized to the chemotherapy arm received carboplatin dosed to a target area under the curve (AUC) of 6 mg/mL/min and paclitaxel 200 mg/m^2 every 3 weeks for 4 cycles. After 74 months of mean follow-up, the difference in 5-year survival between the chemotherapy and observation arms (59% vs. 57%; HR, 0.83) was not statistically significant. Therefore, the routine practice of treating patients with stage IB disease is no longer recommended. However, in a subset analysis of patients with tumors greater than 4 cm in size who received chemotherapy there was a statistically significant benefit overall (HR, 0.69; $p = 0.43$). This benefit was not shared in those with tumors less than 4 cm in size. Thus, in practice, many oncologists choose to treat patients with large-stage IB tumors with adjuvant chemotherapy based on this subset analysis.

In summary, multiple randomized studies of adjuvant chemotherapy demonstrated improved disease-free survival when four cycles of cisplatin-based doublets are administered following surgical resection. This benefit is greatest in those with stage II and III disease; however, in stage IB disease with high-risk features (i.e., >4 cm in size), adjuvant therapy is also recommended. In those with contraindications to cisplatin (i.e., hearing loss or chronic kidney disease), carboplatin is used.

■ Adjuvant Molecular Targeted Therapy

The use of oral agents that inhibit driver mutations in metastatic NSCLC, such as epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitors (TKIs), has made a substantial improvement in survival and quality of life for patients with advanced disease driven by activating mutations. Efforts to integrate targeted therapy into the treatment of early-stage disease are ongoing, including in the adjuvant setting.

RADIANT

RADIANT was the first large, randomized trial of EGFR inhibition following surgical resection in NSCLC. In this study, patients with stage IB–IIIA NSCLC who had undergone surgical resection and platinum-based adjuvant chemotherapy were randomized to two years of erlotinib versus placebo. A total of 973 patients whose tumors expressed EGFR protein by immunohistochemistry (IHC) or EGFR amplification by fluorescence in situ hybridization (FISH) were enrolled. Although not required for enrollment, tissue was also tested for EGFR activating mutations. The study was negative for the primary endpoint of improved DFS (HR, 0.90; 95% CI, 0.74–1.10; $p = 0.324$). Among the 161 patients (16.5%) in the EGFR mutation–positive subgroup, DFS favored erlotinib with a median of 46.4 months versus 28.5 months (HR, 0.61; 95% CI, 0.38–0.98; $p = 0.039$). However, this was not statistically significant due to hierarchical testing. Also of concern, only 40.6% of those in the erlotinib arm completed the planned 2 years of treatment; the authors noted patients had a low tolerance for prolonged treatment in the adjuvant setting due to side effects.[14]

SELECT

The Surgically Resected EGFR-Mutant Lung Cancer with Adjuvant Erlotinib Cancer Treatment (SELECT) study was a nonrandomized, open-label trial of patients with stage IA–IIIA NSCLC who had completed planned adjuvant chemotherapy and radiotherapy as needed. This small, single-arm study of adjuvant erlotinib therapy in 100 patients with EGFR mutations was able to demonstrate improvement in 2-year DFS compared with historic controls. Although this was a small nonrandomized study, several important outcomes were observed. First, with appropriate dose reductions, 69% of subjects were able to complete 2 years of erlotinib therapy. Second, although 40 patients had disease recurrence in the 5.2 years of median follow-up, only four occurred while on erlotinib. The median time to recurrence was 25 months after stopping erlotinib. Importantly, when retreated with erlotinib upon disease recurrence, the median duration of response was still 13 months. Larger, randomized trials were needed to determine if adjuvant therapy with an EGFR TKI changes the natural course of disease and improves survival or merely delays recurrence.[15]

ADJUVANT/CTONG1104

One such large, randomized, phase 3 study was performed in China in which 222 stage II–IIIA patients, whose lung cancer expressed mutated EGFR, were enrolled in the ADJUVANT/CTONG1104 study comparing 2 years of gefitinib to 4 cycles of cisplatin and vinorelbine. The study was positive for longer median DFS of 28.7 months in those treated with gefitinib versus 18 months (HR, 0.60; 95% CI, 0.42–0.87; $p = 0.0054$). However, the 2 groups had similar 3-year DFS, and the OS was not significantly improved at 75 months versus 62 months (HR, 0.92; $p = 0.674$). Thus, in this study, adjuvant gefitinib delayed disease recurrence but did not increase the number cured.[16]

ADAURA

The most exciting data in the use of TKIs in the adjuvant setting are the initial results of a large, placebo-controlled, phase 3 trial of patients with stage IB–IIIA NSCLC who had undergone surgical resection and adjuvant chemotherapy for EGFR-mutated disease.[17,18] In this study, a third-generation EGFR TKI, osimertinib, or placebo was given for 3 years. The trial was unblinded early due to notable improvement in DFS, the primary endpoint. The 2-year DFS was 89% with osimertinib versus 53% with placebo (HR, 0.21; $p < 0.0001$). The OS data are immature. As osimertinib is well tolerated, these data may change the standard of care, particularly for stage III disease due to the high recurrence rates. These data have also changed recommendations expanding molecular testing to early-stage disease.

■ Future Directions in Adjuvant Therapy for NSCLC

Adjuvant cisplatin doublet chemotherapy is currently the standard of care for stage II and IIIA patients. The role of adjuvant treatment of stage IB patients has yet to be defined more clearly, but based on subset analyses, patients with tumors greater than 4 cm may benefit from chemotherapy. For those with EGFR-mutated disease, there are compelling data regarding improved 2-year DFS with adjuvant osimertinib. We are awaiting the overall survival data from this study. Additional large trials of targeted therapy in the adjuvant setting are ongoing, including ALCHEMIST, the Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial, which includes a study of an adjuvant TKI in ALK translocated disease. For those without driver mutations, the future of adjuvant therapy lies in understanding the role of immune checkpoint inhibitors. Currently, four phase 3 randomized studies are underway to determine if adjuvant immunotherapy can improve outcomes in early-stage disease.

LOCALLY ADVANCED NSCLC

The term *locally advanced* includes several different presentations of primary lung cancer, but all have in common the absence of disease outside of the chest. Included in this category are those with stage IIIA–IIIC disease. These tumors involve mediastinal lymph nodes, either ipsilateral (N2) or contralateral (N3), or large primary tumors that directly invade important thoracic structures. For example, T3 tumors involve the chest wall or the phrenic nerve, or are greater than 5 cm in size. T4 tumors invade the mediastinum and affect structures that are not usually considered resectable (e.g., aorta, esophagus, vertebral bodies). Mediastinal lymph node invasion should be determined before surgical resection by way of mediastinoscopy or EBUS with FNA, which also allows contralateral mediastinal lymph nodes to be sampled.

About 40,000 cases of stage III disease occur per year in the United States. The best treatment approach to locally advanced disease has not yet been determined. A wide array of combined modality approaches has been used in stage IIIA patients (particularly those with N2 nodes). These include varying combinations of chemotherapy, radiation, and surgery. More recently, the introduction of immune checkpoint inhibitors into the treatment of locally advanced disease has led to changes in treatment plans and improved outcomes. Integrating immunotherapy into the treatment of locally advanced disease is an active area of research in NSCLC.

■ Locally Advanced Resectable NSCLC

The roles of sequential chemotherapy followed by surgery and concurrent chemoradiation followed by surgery in treating locally advanced, resectable NSCLC are described below.

Chemotherapy Followed by Surgery

Neoadjuvant therapy, also referred to as *induction therapy*, has been applied to the treatment of NSCLC. It entails treating patients with chemotherapy even though there is no clinical evidence that the primary cancer has spread. Lung cancers are particularly attractive targets for neoadjuvant therapy, as many present as locally advanced disease confined to the chest, and patients run a considerable risk of developing distant disease within a short time. Neoadjuvant therapy affords a unique opportunity to assess the sensitivity of the cancer to the drug regimen. This information may be useful in the postoperative period when the possibility of adjuvant therapy is under consideration. Assessing response to neoadjuvant therapy can also more rapidly translate into clinical research findings, particularly if pathologic response is used as a surrogate marker for survival. Another consideration is that the required dose-intensive regimens are apt to be better tolerated before surgery and may improve drug delivery due to the preserved vasculature of the tumor, thus decreasing the prospect of developing drug resistance. However, the possibility that adverse effects of induction chemotherapy could lead to a delay in surgery or a postoperative complication must be considered.

There have been two phase 3 randomized trials of neoadjuvant chemotherapy in patients with locally advanced NSCLC (stage IIIA). Some patients had N2 disease alone, while others had T3N0 disease (now considered stage IIB by the American Joint Committee on Cancer 8th edition TNM staging).[19,20] In contrast to results in patients with disseminated NSCLC, in whom the response to chemotherapy at best approaches 30%, 60% to 70% of patients with locally advanced disease responded favorably. Importantly, in both trials, the median survival was improved in patients who received neoadjuvant treatment. The study of neoadjuvant chemotherapy was expanded to earlier stages (IB–IIIA) in several additional trials.[21,22] Although several of these studies were closed early due to the adoption of adjuvant therapy during this time, an improvement in OS was seen in those with stage II/IIIA disease. For example, in a randomized study of surgery alone or surgery plus preoperative cisplatin and gemcitabine, the subgroup of stage IIB/IIIA patients had an improvement in 3-year PFS (36.1% vs. 55.4%; $p = 0.002$).[22] These data are consistent with results seen in studies of adjuvant chemotherapy.

As described above, one potential advantage of neoadjuvant therapy is timely outcome data through assessment of pathologic response at the time of surgical resection. In a 2012 study of histopathologic response to neoadjuvant chemotherapy, the percentage of residual viable tumor cells was associated with OS and DFS in a multivariate analysis.[23] Five-year OS and DFS were significantly longer in patients with $\leq$10% viable tumor cells after neoadjuvant therapy compared to those with $>$10%. To facilitate the adoption of new treatment for patients with resectable tumors, it has been proposed to use "major pathologic response" (MPR) (10% or less residual viable tumor after neoadjuvant therapy) as a primary endpoint for drug development in this area.[24] Current immunotherapy trials in the neoadjuvant setting have incorporated MPR as a surrogate endpoint for survival.

Early trials of immunotherapy in the neoadjuvant setting have used immune checkpoint inhibitors alone, either programmed death 1 (PD-1) or programmed death ligand 1 (PD-L1) inhibitors. A pilot study of single-agent nivolumab (PD-1 inhibitor) in 21 patients prior to surgery demonstrated a MPR of 45% with few side effects and no delay in surgery.[25] Early results of a single-arm study of neoadjuvant atezolizumab (PD-L1 inhibitor) revealed an MPR of 24% (95% CI, 7–50) among the first 21 subjects. Again, the treatment was well tolerated with no delay in planned surgery.[26] Other trials have combined immune checkpoint inhibitors with cytotoxic chemotherapy in the neoadjuvant setting. In a 30-patient, single-arm, phase 2 trial of atezolizumab (PD-L1 inhibitor) combined with carboplatin and nab-paclitaxel prior to resection, 57% of patients (95% CI, 37–75) had an MPR. Additional phase 2 studies of combined chemoimmunotherapy in the neoadjuvant setting have demonstrated high MPR rates, leading to the initiation of multiple, randomized, phase 3 studies with the potential to change the treatment of locally advanced, resectable NSCLC.[27]

Concurrent Chemoradiation Followed by Surgery

Various theoretical considerations have led to trials of chemotherapy and radiation followed by surgery (trimodality therapy): (1) Tumor cell subpopulations in locally advanced NSCLC may respond differently to radiation and chemotherapy, and cells resistant to one treatment method may be sensitive to the other. (2) Chemotherapy may promote the emergence of radiosensitive cells, thereby increasing the total number of cells killed by continued radiation treatments. (3) Induction of cell cycle synchronization by certain drugs may increase cell killing by radiation and induce recruitment of tumor cells in G_0.

The Southwest Oncology Group (SWOG) conducted a trial using the cisplatin/etoposide regimen they had developed with concurrent radiotherapy; the trial included both stage IIIA and IIIB patients.[28] All 126 patients underwent mediastinoscopy for histologic evaluation of mediastinal lymph nodes. The response rate to the preoperative therapy was 59%, with 29% having stable disease. The resection rate was 85% in the stage IIIA patients and 80% in the stage IIIB patients. The 3-year survival was similar in both stage IIIA and IIIB patients at 27% and 24%, respectively. The absence of tumor in the mediastinal nodes at the time of surgery was associated with improved survival. Failure was more common in distant, rather than locoregional, sites with relapse occurring in 26 patients.

It remains to be proven that surgery is a necessary part of the treatment of these patients. The high response rate to chemoradiotherapy in the high-performance patients entered into these clinical trials raises the question of whether chemotherapy and radiation might be able to achieve a similar endpoint with regard to local control. A large intergroup study addressed this question.[29] In this trial, 396 patients with stage IIIA, pathologic N2 disease were randomized to either concurrent chemotherapy with cisplatin/etoposide and radiation to 4500 cGy followed by surgery or the same chemotherapy regimen with radiation to higher doses of 6100 cGy. The patients who were randomized to surgery had a statistically significant improvement in progression-free survival (12.8 vs. 10.5 months); although there was a trend toward an improvement in OS in the surgery group, this was not statistically significant. In an unplanned subset analysis, patients who seemed to do better were those who had a lobectomy rather than a pneumonectomy, as well as those who had obtained a pathologic response in the mediastinal nodes. Although there was no significant benefit in OS, surgery is often offered to medically fit patients after induction chemoradiotherapy.

■ Locally Advanced Inoperable or Unresectable Stage III NSCLC

Below are considered treatment approaches based on sequential or concurrent chemotherapy and radiation therapy to manage locally advanced, inoperable, or unresectable stage III NSCLC.

Chemotherapy Followed by Radiation Therapy

Several prospective, randomized studies have compared radiation therapy alone and radiation therapy in sequence with chemotherapy in the setting of unresectable stage III disease. Le Chevalier et al.[30] randomized 353 patients to radiation alone (6500 cGy) or cisplatin-based chemotherapy followed by radiation; 1-, 2- and 3-year survival rates all favored the combined therapy arm (51%, 21%, and 12% vs. 41%, 14%, and 4%, respectively). However, using repeat biopsies, the study found only a 17% incidence of local control in the radiation arm and a 15% incidence of local control in the chemotherapy and radiation arm.

In a trial conducted by CALGB, 155 patients were randomized to either radiation alone (6000 cGy) or a cisplatin-based regimen followed by radiation.[31] The median survival favored the combination therapy arm (13.8 vs. 9.7 months). The 3- and 5-year survival rates also favored combination therapy (25% and 19%) over radiation therapy alone (11% and 7%). Unfortunately, the study was limited to patients with a high performance status and less than 5% weight loss in the 6 months before enrollment in the trial. Limiting a study to the most favorable patients begs the question of the applicability of the results to the general group of patients with locally advanced lung cancer, many of whom have a decrease in their performance status and have lost considerable weight.

A study seeking to confirm the CALGB report was initiated by the Radiation Therapy Oncology Group (RTOG), which randomized patients to the same two arms, in addition to a third arm using hyperfractionation radiation (69.6-cGy twice-daily fractions) as the only treatment modality.[32] This study demonstrated that chemotherapy given prior to radiation was superior to radiation alone in the patients with good performance status (i.e., loss of weight of $<5\%$ in the previous 3 months). Analysis at 1 year showed the median survival to be statistically longer for those in the combined chemotherapy and radiation arm. However, at 3 years follow-up, no difference in survival (14%) was observed between the chemotherapy and radiation arm and the hyperfractionated arm. Both of these treatment regimens were better than standard radiation alone.

Concurrent Chemotherapy and Radiation Therapy

The rationale for concurrent therapy, that is, chemotherapy given during a course of radiation therapy, is based on the concept that some drugs or drug combinations (notably, cisplatin) may increase the radiosensitivity of tumor cells. However, the trade-off is an increase in toxicity and a regimen that is not well tolerated by all potentially eligible patients. A meta-analysis of randomized trials directly comparing platinum-based chemotherapy given concurrently with thoracic radiation to chemotherapy given sequentially with thoracic radiation was performed in 2010.[33] Data from 6 trials (1205 individual patients) were analyzed. There was a significant benefit to concurrent therapy with an absolute OS benefit of 5.7% at 3 years (HR, 0.84; 95% CI, 0.74–0.95; $p = 0.004$). The primary effect was seen in control of locoregional disease, with no difference in risk of distant recurrence compared to sequential therapy. The risk of severe esophagitis was increased with concurrent therapy, although pulmonary toxicity was not different. Concurrent platinum chemotherapy and radiation therapy is the treatment of choice for patients with locally advanced, inoperable disease, provided their performance status and comorbidities do not limit their ability to withstand the toxicities associated with this approach. Based on small phase 2 trials conducted by SWOG, a favored regimen for concurrent therapy utilizes cisplatin (days 1, 8, 29, 36) and etoposide (days 1–5, 29–33) with conventional RT.[28,34] For those patients unable to receive cisplatin due to renal insufficiency or hearing loss, weekly carboplatin and paclitaxel has demonstrated activity in this setting. The OS seen with carboplatin and paclitaxel treatment is less than the control arms of the cisplatin/etoposide studies, although these 2 chemotherapy regimens have not been directly compared in a randomized trial.

PROCLAIM is a phase 3 study of concurrent chemotherapy with radiation followed by two additional cycles of chemotherapy given in consolidation to those with unresectable NSCLC. In this study, patients were randomized to pemetrexed, cisplatin, and concurrent radiation with additional cycles of pemetrexed as consolidation or the standard regimen of cisplatin and etoposide with concurrent radiation and two additional cycles of cisplatin and etoposide as consolidation. This study attempted to improve upon the toxicity seen with the concurrent approach.[35] For patients with nonsquamous NSCLC, the use of pemetrexed did not improve overall survival. However, there was a significant decrease in grade 3 to 4 adverse events, including neutropenia. Thus, the NCCN has added this regimen to recommended chemotherapy for concurrent chemoradiation. For those unable to tolerate a concurrent approach, sequential chemotherapy followed by radiation is a reasonable alternative.

Induction or Consolidation Chemotherapy in Addition to Concurrent Chemoradiation

Although the addition of concurrent platinum-based chemotherapy to thoracic radiation for unresectable stage III NSCLC has been proven to improve local control and OS, disease recurrence at distant sites remains high. With concurrent therapy, only two cycles of chemotherapy are given during the course of radiation. This is fewer than the four cycles of cisplatin-based chemotherapy that has proven benefit to lessen disease recurrence in the adjuvant setting. This led to an interest in increasing the amount of chemotherapy given for patients receiving concurrent therapy in locally advanced disease by adding additional chemotherapy cycles either prior to (induction) or after (consolidation) the concurrent chemoradiation.

Multiple clinical trials have studied each of these approaches. In a nonrandomized phase 2 study, concurrent chemoradiation was followed by two cycles of consolidation cisplatin and etoposide, resulting in a median survival of 15 months and a 5-year survival of 15%.[34] A subsequent trial used the same combined treatment regimen but then switched to docetaxel for consolidation.[36] This yielded a median survival of 26 months and a 3-year survival of 37%. However, a randomized study performed by the Hoosier Oncology Group in which patients received cisplatin, etoposide, and radiation, either with or without consolidation docetaxel, failed to show a benefit from consolidation treatment.[37] Another favored regimen utilizes low-dose carboplatin and paclitaxel with radiation, followed by consolidation therapy with the same agents. Noncomparative phase 2 studies of this regimen demonstrated a median survival of 16 months.[38] CALGB published findings of a phase 3 randomized study of two cycles of induction chemotherapy with full-dose carboplatin and paclitaxel followed by concurrent weekly dosing with radiation versus concurrent therapy alone.[39] OS was not significantly improved with induction therapy (14 vs. 12 months; $p = 0.3$).

New Approaches to Concurrent Chemoradiation

Due to poor outcomes and limitations of adding further chemotherapy to locally advanced disease, a different approach was needed. A pivotal trial in improving the survival outcomes of these patients was the PACIFIC trial. This study of locally advanced, nonresectable NSCLC included a unique approach to consolidation with an immune checkpoint inhibitor. The PACIFIC trial is a randomized, phase 3 trial of consolidation with durvalumab (PD-L1 inhibitor) versus placebo following concurrent radiation and chemotherapy.[40] Patients who had no signs of disease progression following completion of thoracic radiation and at least 2 cycles of platinum-based chemotherapy were eligible for enrollment. A total of 713 patients underwent randomization to 12 months of durvalumab or placebo, with PFS and OS as coprimary endpoints. The median PFS from randomization was 16.8 months (95% CI, 13.0–18.1) with durvalumab versus 5.6 months (95% CI, 4.6–7.8) with placebo. The recently updated OS demonstrated an HR of 0.69 (95% CI, 0.55–0.86), with the median survival not reached for durvalumab (95% CI, 38.4 months to not reached) and 29.1 months (95% CI, 22.1–35.1) with placebo.[41] Thus, the addition of durvalumab as consolidative immunotherapy improved survival of patients undergoing concurrent, definitive chemoradiation. The PACIFIC trial has changed the standard of care for patients with unresectable, locally advanced NSCLC.

In summary, significant issues remain concerning the sequence and type of treatment for locally advanced disease. Although some permutation of combined modality treatment is needed in patients with locally advanced disease, we currently do not have data in the form of randomized controlled studies that compare the efficacy of the varying combinations of chemotherapy, immunotherapy, radiation, and surgery. In patients who can tolerate the added toxicity, concurrent chemoradiotherapy is more effective than sequential therapy. Although it has not been proven that surgery after induction chemoradiotherapy confers a survival benefit compared to definitive chemoradiotherapy, surgery is still a preferred approach in many institutions if patients can tolerate trimodality treatment. It remains unclear how definitive chemoradiotherapy compares to induction chemotherapy followed by surgery or chemoradiotherapy followed by surgery, particularly with the addition of immunotherapy. At the present time, this is a matter of institutional preference, as well as the particular characteristics of individual patients.

METASTATIC NSCLC

The first-line treatment for metastatic NSCLC has been redefined due to the introduction of immune checkpoint inhibitors and an increasing number of targeted agents for oncogenic drivers of disease. Currently, personalized treatment plans can be developed for each patient within several cohorts: (1) those with drug targeted driver mutations, (2) those with immune biomarkers predictive of durable response to single-agent PD-1 or PD-L1 inhibitors, (3) those who lack both and require a combination of chemotherapy with immunotherapy, and (4) those with contraindications to immunotherapy and who are treated with chemotherapy alone. Because the treatment of metastatic NSCLC is based upon driver mutations and immunotherapy biomarkers, prompt molecular testing of the tumor is of increasing importance. Currently, in addition to immune biomarkers for all NSCLC, the NCCN recommends testing all newly diagnosed nonsquamous-cell NSCLC (and all cell types in never-smokers) for an increasing number of activating mutations.[42] In metastatic lung cancer, the goals of therapy are to extend survival and to palliate the symptoms of disease. The decision to use cancer-directed therapy in the setting of incurable disease is based on patient preference, comorbidities, and performance status and requires an ongoing dialogue between the patient and physician throughout the disease course.

■ First-line Chemotherapy

Chemotherapy alone is recommended for those with metastatic NSCLC and contraindications to PD-1 or PD-L1 inhibitors, with no activating mutations in EGFR, ALK, c-ros oncogene 1 (ROS1), or the serine/threonine kinase B-raf (BRAF). For patients with adequate performance status, the standard first-line chemotherapy recommendations currently consist of a platinum doublet, with several reasonable nonplatinum combinations as alternatives. Although there are several cisplatin or carboplatin backbone doublets to consider, carboplatin tends to be favored in the palliative setting due to its better toxicity profile. A large study conducted by the ECOG randomized 1207 patients with advanced disease to cisplatin/paclitaxel, cisplatin/gemcitabine, cisplatin/docetaxel, or carboplatin/paclitaxel.[43] The median survival among all 4 treatment groups was 7.9 months, with a 1-year survival of 33% and a 2-year survival of 11%. There was no clear survival benefit with any one regimen compared with the others.

Pemetrexed, an antifolate, is a cytotoxic agent, unique in that efficacy varies by the histology of the NSCLC. It is labeled by the U.S. Food and Drug Administration for use in nonsquamous-cell NSCLC only. This labeling is based on a phase 3 trial in which newly diagnosed patients with advanced NSCLC were randomized to either cisplatin/gemcitabine or cisplatin/pemetrexed in the first-line setting.[44] This trial was designed as a noninferiority study and demonstrated that the cisplatin/pemetrexed doublet was noninferior to a standard doublet with a median OS of 10.3 months. When given with the appropriate folic acid and vitamin B12 supplementation, the cisplatin/pemetrexed doublet was associated with less cytopenia and decreased the need for growth factors and blood transfusions. A prespecified histology stratification was performed comparing nonsquamous NSCLC (including adenocarcinoma, large cell carcinoma, and others) versus squamous cell NSCLC. Median OS for the nonsquamous NSCLC histology was 11.0 months for those who received cisplatin/pemetrexed versus 10.1 months for cisplatin/gemcitabine (HR, 0.84; 95% CI, 0.74–0.96). However, for those with squamous cell histology, cisplatin/pemetrexed had an inferior median OS of 9.4 months versus 10.8 months with cisplatin/gemcitabine (HR, 1.22; 95% CI, 0.99–1.5). As pemetrexed is well tolerated and not associated with alopecia, carboplatin with pemetrexed is a widely used first-line regimen in nonsquamous cell NSCLC.

Albumin-bound paclitaxel (also called nab-paclitaxel) is a novel formulation with a reduced risk of hypersensitivity compared with other taxanes (paclitaxel and docetaxel). A large randomized study of carboplatin with either paclitaxel given every 3 weeks or nab-paclitaxel given weekly demonstrated an improved response rate with nab-paclitaxel (33% vs. 25%; $p = 0.005$) with less peripheral neuropathy.[45] No change in OS was noted among the different paclitaxel formulations: median OS 12.1 months versus 11.2 months

($p = 0.271$). The use of nab-paclitaxel with carboplatin is particularly useful in those with a history of hypersensitivity to docetaxel or paclitaxel or those with a contraindication to high-dose corticosteroids as premedication. Carboplatin and weekly nab-paclitaxel is an additional platinum-based doublet that can be used in the first line.

Two randomized phase 3 studies have addressed the use of non–platinum-based regimens as first-line treatment. The first randomized patients to paclitaxel and gemcitabine versus paclitaxel and carboplatin.[46] The study showed similar efficacy with respect to median survival, 1-year survival, and response rate. Both regimens were well tolerated. The largest study to address the role of nonplatinum doublets randomly allocated 929 patients to carboplatin/paclitaxel, carboplatin/gemcitabine, or gemcitabine/paclitaxel.[47] Again, the results indicated similar efficacy in all 3 arms. There were differences in toxicities in that anemia and thrombocytopenia were more common in the carboplatin/gemcitabine arm, although peripheral neuropathy and alopecia were more common in the paclitaxel containing groups. For chemotherapy-naïve patients, treatment choices tend to be heavily dependent on a patient's comorbidities and each regimen's toxicity profile.

The monoclonal antibody bevacizumab, which targets the vascular endothelial growth factor (VEGF), is approved for first-line treatment of NSCLC when combined with cytotoxic chemotherapy. VEGF, a circulating ligand that promotes angiogenesis, is not mutated in NSCLC, and this therapy, although molecularly targeted, is not specific to the tumor. A large randomized phase 3 study published in 2006 demonstrated an improvement in OS—12.3 versus 10.3 months (HR, 0.79; $p = 0.003$)—for those patients who received bevacizumab in addition to carboplatin and paclitaxel for advanced NSCLC.[48] Additional studies demonstrated equal efficacy when bevacizumab is combined with carboplatin and pemetrexed.[49] Due to the high risk of life-threatening hemoptysis seen in early clinical trials, patients with squamous-cell lung cancer or a history of hemoptysis were excluded from this study. As an antiangiogenesis agent, bevacizumab has several unique adverse effects, including hemoptysis, hypertension, and proteinuria.[50] When carefully used in patients with advanced lung cancer, bevacizumab is a novel targeted agent that can improve survival.

■ Immunotherapy as First-line Therapy

The biggest impact of immunotherapy in NSCLC has been in the metastatic setting. Clinical trials have shown significant improvement in PFS and OS with a combination of cytotoxic chemotherapy and an anti PD-1 or PD-L1 monoclonal antibody. This improvement has been observed in multiple studies independent of histology, and across all levels of PD-L1 expression[51] (Table 114-2). Immunotherapy is often well tolerated and able to produce a durable response. Therefore, immune checkpoint inhibitors are continued as maintenance therapy providing a subset of patients benefit over long periods. The development of immunotherapy biomarkers identifies patients predicted to have high objective response rates and PFS with the use of immune checkpoint inhibitors as a single agent, thus reducing the toxicity of adding cytotoxic chemotherapy in the first line. To date, validated biomarkers in this setting include PD-L1 expression by IHC staining of tumor cells and tumor mutational burden, a standardized number of somatic mutations within the tumor.

TABLE 114-2 Randomized Trials of Immune Checkpoint Inhibitors in First-line Treatment of Advanced NSCLC

Clinical Trial	Histology	PD-L1 TPS	Treatment	Median PFS	Median OS
Keynote 042[51]	NSCLC (EGFR and ALK neg)	≥1%	Pembrolizumab	5.4	16.7
			Chemotherapy	6.5	12.1
Keynote 189[52,53]	Nonsquamous NSCLC (EGFR and ALK neg)	0%–100%	Pembrolizumab and pemetrexed with carbo/cisplatin	9.0	22.0
			Pemetrexed with carbo/cisplatin	4.9	10.7
Keynote 024[56,57]	NSCLC (EGFR and ALK neg)	≥50%	Pembrolizumab	10.3	30.0
			Chemotherapy	6.0	14.2
Keynote 407[55]	Squamous cell carcinoma	0%–100%	Pembrolizumab and (nab) paclitaxel with carboplatin	6.4	15.9
			(nab) Paclitaxel with carboplatin	4.8	11.3
Checkmate 227[59]	NSCLC (EGFR and ALK neg)	≥1%	Nivolumab and ipilimumab	5.1	17.1
			Nivolumab	4.2	15.7
			Chemotherapy	5.6	14.9
IMpower 110[58]	NSCLC	TC 3 or IC 3 (TC1/2/3 or IC1/2/3)	Atezolizumab		20.2 (17.5)
			Chemotherapy		13.1 (14.1)
IMpower 130[54]	Nonsquamous NSCLC (EGFR and ALK neg)	0%–100%	Atezolizumab and carboplatin with (nab) paclitaxel	7.0	18.6
			Carboplatin with (nab) paclitaxel	5.5	13.9
IMpower 150[60]	Nonsquamous NSCLC (EGFR and ALK neg)	0%–100%	Atezolizumab and carboplatin/paclitaxel and bevacizumab	8.3	19.2
			Carboplatin/paclitaxel and bevacizumab	6.8	14.7

PD-L1 TPS, programmed death ligand 1 tumor proportion score; PFS, progression-free survival; OS, overall survival; NSCLC, non–small-cell lung cancer; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; TC, tumor cells; IC, tumor-infiltrating immune cells.

The current recommendation for patients with newly diagnosed, metastatic, nonsquamous NSCLC is a combination of PD-1 or PD-L1 inhibitor with a carboplatin-based doublet. This recommendation is based on 2 large, randomized studies, Keynote-189 and IMpower130. Both studies enrolled patients without an activating mutation in EGFR or ALK. The Keynote-189 study enrolled 616 patients randomized to carboplatin or cisplatin and pemetrexed with or without pembrolizumab (PD-L1 inhibitor).[52] Combined therapy was given for 4 cycles, followed by maintenance therapy with either pemetrexed alone or combined with pembrolizumab. The median PFS was 9.0 months (95% CI, 8.1–9.9) in the pembrolizumab group versus 4.9 months (95% CI, 4.7–5.5) in the placebo group. HR for death or disease progression was 0.48 (95% CI, 0.40–0.58; $p < 0.001$). Median OS was 22.0 months (95% CI, 19.5–25.2) in the pembrolizumab combined group versus 10.7 months (95% CI, 8.7–13.6) with HR of 0.56 (95% CI, 0.45–0.70).[53] This benefit was seen across all levels of PD-L1 expression, including <1%. The IMpower130 study had a similar design with 723 patients randomized to carboplatin and nab-paclitaxel (given weekly) plus atezolizumab (PD-L1 inhibitor) or placebo.[54] Combined therapy was given for 4 to 6 cycles followed by maintenance atezolizumab or placebo if no progression was seen. Median PFS was 7.0 months with atezolizumab (95% CI, 6.2–7.3) versus 5.5 months (95% CI, 4.4–5.9) with HR of 0.64 ($p < 0.001$), and median OS was 18.6 months (95% CI, 16.0–21.2) versus 13.9 months (95% CI, 12.0–18.7) with HR of 0.79 ($p = 0.033$). In both studies, the combined therapy was well tolerated.

Keynote-407 investigated a combined chemotherapy and immunotherapy approach in 599 patients with advanced squamous-cell carcinoma, regardless of PD-L1 expression level.[55] Again, pembrolizumab or placebo was added to a combination of carboplatin and either paclitaxel or nab-paclitaxel. The combination was given for 4 cycles with maintenance pembrolizumab or placebo for those without disease progression. The median PFS was 6.4 months with pembrolizumab (95% CI, 6.2–8.3) versus 4.8 months (95% CI, 4.3–5.7) with HR of 0.56 ($p < 0.001$). Median OS was 15.9 months (95% CI, 13.2–NR) in those with pembrolizumab versus 11.3 months (95% CI, 9.5–14.8) with placebo, with HR of 0.64 ($p < 0.001$). Thus, a combination of chemotherapy with an immune checkpoint inhibitor is now recommended first-line treatment for all histologic types of metastatic NSCLC.

The development of PD-L1 expression as a biomarker is most useful in determining if single-agent immune checkpoint inhibitors will produce a high response rate and PFS for individual patients, without the need to combine with chemotherapy. The Keynote-024 study was designed to determine if patients with newly diagnosed, advanced NSCLC and high PD-L1 tumor expression (PD-L1 expression on ≥50% of tumor cells), without an activating mutation in EGFR or ALK, would benefit from pembrolizumab alone. A total of 305 patients were randomized to pembrolizumab alone versus platinum-based chemotherapy. This study demonstrated that those with high PD-L1 expression had an improved PFS and OS with fewer adverse effects when given pembrolizumab alone in the first line compared to chemotherapy.[56] At 25 months of follow-up, the OS for pembrolizumab was 30 months (95% CI, 18.3–NR) versus 14.2 months for chemotherapy alone (95% CI, 9.8–19), with HR of 0.63 (95% CI, 0.47–0.86).[57] This improvement in OS was seen despite a high rate of crossover from the chemotherapy group to pembrolizumab upon progression. Subsequent studies have shown similar efficacy with other immune checkpoint inhibitors (atezolizumab) in this select group.[58] At this time, there are no data directly comparing immune checkpoint inhibitors alone to combined therapy for those with high PD-L1 expression. In patients with a large tumor burden or suffering complications of disease, a combination of chemotherapy and immunotherapy may provide faster disease response and may be necessary even in the setting of high PD-L1 expression.

Another approach to first-line therapy is the combination of different immunotherapies without the addition of chemotherapy. In Checkmate-227, patients were randomized to chemotherapy alone or a combination of nivolumab (a PD-L1 inhibitor) with ipilimumab (a cytotoxic T-lymphocyte–associated protein 4 [CTLA-4] inhibitor).[59] In those with PD-L1 expression ≥1%, the combination of nivolumab and ipilimumab produced a longer OS than chemotherapy alone—17.1 months (95% CI, 15.0–20.1) versus 14.9 months (95% CI, 12.7–16.7). This combination provides an alternative first-line therapy to the use of cytotoxic chemotherapy.

Nearly all of the first-line studies of immunotherapy alone or in combination with chemotherapy have excluded those with EGFR-activating mutations or translocations in ALK. Early studies of immune checkpoint inhibitors in the second line showed a low response rate to immunotherapy in these patients, despite PD-L1 expression on tumor cells. This led to a question of the appropriate therapy for these patients once resistance to targeted agents has developed. The current recommendations are for chemotherapy alone or combined with bevacizumab. The IMpower150 study enrolled patients with known EGFR mutations into a randomized trial of three arms: chemotherapy with bevacizumab, chemotherapy with atezolizumab, or a combination of chemotherapy with bevacizumab and atezolizumab. A total of 1202 patients were enrolled; 124 had known EGFR mutations. Analysis of the EGFR-mutated subgroup showed a trend toward improved OS with the combination of immunotherapy, chemotherapy, and bevacizumab compared to chemotherapy and bevacizumab alone (HR, 0.31; 95% CI, 0.11–0.83).[60] The authors believed this warranted further study of this immunotherapy combination in EGFR-mutated disease.

The introduction and now widespread use of immune checkpoint inhibitors in the treatment of advanced NSCLC has required that clinicians recognize and manage immune-related adverse events. These adverse events are often distinct from those associated with cytotoxic chemotherapy and may involve a wide range of organ systems. Commonly these are low-grade adverse events involving the skin, thyroid, and GI tract. However, moderate to severe adverse events—for example, pneumonitis or hepatitis—may develop, requiring permanent discontinuation of immune therapy and prompt treatment with corticosteroids and additional immunosuppressive agents.[61] The use of immune therapy in those with a history of autoimmune disease is particularly high-risk, and careful consideration and discussion with the patient is needed prior to use.

■ Elderly Patients with Advanced NSCLC

The median age at diagnosis for patients with NSCLC is 65 years; therefore, a significant number of patients diagnosed with advanced disease are elderly (≥70 years). Chemotherapy has been demonstrated to improve survival in the elderly with advanced disease to the same extent as those who are young.[62] Although there is an increase in side effects, particularly cytopenias, advanced age is not a contraindication to chemotherapy. Randomized studies dedicated to the treatment of elderly patients with advanced NSCLC are few, but several have provided needed data for this group. A randomized trial using a carboplatin-based doublet for elderly patients randomized patients to single-agent vinorelbine or gemcitabine versus carboplatin and weekly paclitaxel.[63] Those who received the platinum-based doublet had a higher response rate (27% vs. 10.2%; $p < 0.0001$) and better OS (10.3 vs. 6.2 months; $p < 0.001$). Higher rates of febrile neutropenia were seen with the doublet therapy. This study supports the use of carboplatin and weekly paclitaxel in elderly patients with good performance status with close monitoring for associated cytopenia. More recent clinical trials of immunotherapy in advanced NSCLC have removed exclusions based on age. These studies have enrolled significant subpopulations of patients ≥75 years of age with good performance status. Outcomes in this older population of fit patients are consistent with that seen in the overall population.

Patients with Poor Performance Status

Patients with poor performance status represent another common group in need of treatment for advanced lung cancer but are underrepresented in randomized clinical trials. Patients with ECOG performance status grade 2—defined as "ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours"—if included in first-line trials, represent a small proportion of those enrolled. A randomized clinical trial dedicated to first-line treatment of patients with ECOG performance status grade 2 randomized patients to pemetrexed alone versus carboplatin and pemetrexed.[64] Those who received the platinum-based doublet had an improved response rate (24% vs. 20%) and improved median OS (9.1 vs. 5.6 months; $p = 0.001$). For those patients with ECOG performance status grade 3—"capable of only limited self-care, confined to a bed or chair more than 50% of waking hours"—cytotoxic chemotherapy is of no known benefit, and best supportive care is recommended. Unfortunately, modern studies of immunotherapy, including those described above, routinely exclude patients with an ECOG performance status grade 2, leaving a gap of knowledge in the best first-line therapy for this group of patients.

Maintenance Therapy for Advanced Disease

Historically, first-line chemotherapy for NSCLC was given for four to six cycles and then held, as there was no proven benefit to extending treatment with a doublet past six cycles. If the disease was under control (responded to therapy or stable), all treatment was held, and the patient was followed clinically until disease progression. At that time, the patient would be considered for second-line chemotherapy. The availability of drugs that are better tolerated, such as pemetrexed and immune checkpoint inhibitors, has enabled investigators to reevaluate this approach and consider maintenance therapy for those with disease control following first-line treatment. Maintenance therapy is given to keep cancer from progressing after response to initial treatment. Recent clinical studies have demonstrated an OS benefit with the use of maintenance therapy, and it has become the standard of care in advanced NSCLC treatment.

Continuation maintenance is "the use of at least one of the agents given in the first line, beyond four to six cycles, in the absence of disease progression."[42] Several agents originally approved for use in the first line have been used in this fashion. For example, all studies of first-line immune checkpoint inhibitors continue the immunotherapy as maintenance until disease progression or serious adverse event. In clinical trial ECOG 4599, bevacizumab was continued until disease progression even after the carboplatin and paclitaxel were held after four to six cycles. Pemetrexed also has been studied as a single agent given as continuous maintenance therapy when used as part of a platinum-based doublet in the first line.[65] PARAMOUNT, a randomized trial of continuous maintenance pemetrexed following first-line treatment with cisplatin/pemetrexed, demonstrated an improvement in progression-free survival when compared with placebo: 4.1 months versus 2.8 months ($p < 0.001$) after randomization.[66] There are also data to suggest an OS advantage to the continuous use of pemetrexed (13.9 vs. 11.0 months).[67] As a result, the current recommendation in those with disease control following cisplatin (or carboplatin) with pemetrexed is to continue pemetrexed until disease progression. In a similar design, the clinical trial AVAPERL randomized patients to bevacizumab/pemetrexed versus bevacizumab alone as continuous maintenance following disease response to first-line cisplatin, pemetrexed, and bevacizumab. Data from this trial showed that the use of pemetrexed and bevacizumab together in the maintenance setting was associated with superior PFS (10.2 vs. 6.6 months; HR, 0.58; $p < 0.001$) and a trend toward improved OS (17.1 vs. 13.2 months; HR, 0.87; $p = 0.32$).[68] Thus, when disease response is seen with cisplatin, pemetrexed, and bevacizumab in the first line, consideration for continuation with pemetrexed and bevacizumab is recommended. POINTBREAK, an open-label, randomized, phase 3 study comparing carboplatin, paclitaxel, and bevacizumab with bevacizumab as maintenance to carboplatin, pemetrexed, and bevacizumab with bevacizumab and pemetrexed as maintenance found no difference in OS.[49] Due to less toxicity associated with the carboplatin, pemetrexed, and bevacizumab therapy, this is the preferred regimen for those with nonsquamous-cell NSCLC.

As previously described, due to increased risk of hemoptysis with bevacizumab, and decreased efficacy with pemetrexed, patients with squamous-cell NSCLC are not able to receive these drugs as maintenance therapy. A clinical study with a significant number of patients with squamous-cell NSCLC investigated the use of gemcitabine as continuous maintenance following cisplatin/gemcitabine induction chemotherapy.[69] Progression-free survival was significantly improved in those who received gemcitabine versus placebo following induction chemotherapy. An overall survival benefit was seen in those who received gemcitabine after an objective response to induction therapy, but not those with stable disease. This suggests that gemcitabine is a reasonable agent to use as continuous maintenance in patients with squamous-cell carcinoma with response to platinum-gemcitabine in the first line.

Second-line Therapy

Ultimately, patients with advanced disease will progress after receiving first-line therapy, with or without maintenance treatment. There are several options to consider in the second-line setting, and the selection of the appropriate agent depends on histology, ECOG performance status, and previous treatment. Docetaxel was one of the first agents approved for this indication. In the first trial of interest, 104 previously treated patients were randomized to docetaxel every 3 weeks at 100 mg/m^2, 75 mg/m^2, or supportive care.[70] Docetaxel therapy improved median survival (7.5 vs. 4.6 months) and 1-year survival (37% vs. 11%). The lower dose of docetaxel was better tolerated. Further improvement in second-line therapy has been studied with drugs in combination with docetaxel. The REVEL study investigated the addition of ramucirumab, a monoclonal antibody that inhibits VEGF receptors, to docetaxel in the second line, regardless of histology. Median OS was longer in those who received ramucirumab with docetaxel, 10.5 months versus 9.1 months, with HR of 0.86 (95% CI, 0.75–0.98; $p < 0.023$).[71] However, patients in this study had a high rate of serious adverse events (>70%) in both the control arm of docetaxel and with the ramucirumab combination. Due to the high incidence of adverse events, the administration of docetaxel in second-line NSCLC requires careful follow-up and supportive care.

In a phase 3 trial of pemetrexed in NSCLC, 571 patients were randomized to docetaxel or pemetrexed in the second-line setting.[72] Survival was similar in each arm with a median survival of 8.3 and 7.9 months for pemetrexed and docetaxel, respectively. The 1-year survival was 29.7% in both groups. Although survival with pemetrexed was not improved compared to docetaxel alone, pemetrexed was better tolerated with a significant decrease in the incidence of grade 3 or 4 neutropenia and febrile neutropenia events.

The majority of patients with advanced NSCLC receive immunotherapy in the first line, either as a single agent or combined with chemotherapy. For those who did not receive an immune checkpoint inhibitor in the first line, multiple studies have demonstrated improved outcomes for single-agent immune checkpoint inhibition therapy compared to docetaxel. Nivolumab and atezolizumab have been approved for use regardless of PD-L1 expression level, while pembrolizumab is recommended for those with PD-L1 ≥1% based on the Keynote-010 study.[73] In this randomized study, patients previously treated for NSCLC and known PD-L1 $\geq 1\%$ were randomized to pembrolizumab (at two different dosing levels: 2 mg/kg and 10 mg/kg) versus docetaxel. The median overall survival was 10.4 months with pembrolizumab 2 mg/kg, 12.7 months with pembrolizumab 10 mg/kg, and 8.5 months with docetaxel. Each pembrolizumab arm had a significant prolongation of overall survival compared to docetaxel. Notably, serious treatment-related adverse events are less common with immune checkpoint inhibitors than docetaxel in the second line.

■ Molecular Targeted Therapy

Advances in molecular biology have enabled the search for novel molecular abnormalities in lung cancer that provide insights into tumorigenesis as well as potential therapeutic targets. The identification of "driver mutations," those mutations that drive neoplastic transformation and contribute to tumor progression, has accelerated and led to multiple recent drug approvals for targeted therapy in advanced NSCLC (Table 114-3). As the identification of driver mutations significantly impacts the selection of first-line therapy, thorough and timely molecular testing is of growing importance. Due to the small tissue samples often obtained in NSCLC, acquiring sufficient material for extensive histologic and molecular testing often requires a repeat biopsy, further delaying treatment. The use of circulating tumor DNA testing (liquid biopsy) can aid in the detection of driver mutations when the tissue sample is insufficient or the patient is too high-risk to undergo a diagnostic procedure. Although the specificity of a liquid biopsy assay is high, the sensitivity remains low. Thus, a tissue biopsy should be used for molecular testing whenever possible.[42] Current recommendations are for molecular testing in all patients with adenocarcinoma, adenosquamous carcinoma, a small biopsy sample, or limited smoking history. In addition to IHC for PD-L1 expression, the current recommended testing includes EGFR mutations, ALK genes fusions, ROS1 gene fusions, BRAF V600E mutations, ret proto-oncogene (RET) rearrangements, hepatocyte growth factor receptor (MET) exon 14 skipping mutations, and neurotrophic tyrosine receptor kinase (NTRK) gene fusions. As the advancement in targeted therapy of NSCLC continues, the number of biomarkers is expanding. A broad panel of next-generation sequencing (NGS) is often used to ensure that all molecular variants are identified.

EGFR was the first driver mutation to introduce personalized medicine for NSCLC. It was also the first to demonstrate improved outcomes for a TKI over chemotherapy in the first-line treatment of advanced adenocarcinoma.[74] EGFR mutations have been reported in 10% to 15% of Western and 25% to 30% of Asian lung cancer patients. These mutations are significantly more common in women and nonsmokers. Current testing should include molecular techniques to identify activating mutations in EGFR exons 18 to 21. This includes high-frequency L858R point mutations, exon 19 deletions, and less common mutations with at least 1% prevalence.[75] The presence of an activating EGFR mutation strongly predicts response to TKI therapy. There are now three generations of EGFR TKIs available for clinical use. First-generation TKIs bind reversibly to the kinase and include erlotinib and gefitinib. Second-generation TKIs bind irreversibly and include afatinib and dacomitinib. Finally, third-generation TKIs also bind irreversibly with additional activity against the T790M mutation; osimertinib is one example. The recommended first-line treatment for advanced, EGFR-mutated NSCLC is osimertinib, based on the phase 3 FLAURA trial. This clinical trial randomized previously untreated patients with EGFR-mutated NSCLC to osimertinib versus a first-generation EGFR TKI (either gefitinib or erlotinib). Osimertinib had a superior median PFS of 18.9 months compared to 10.2 months for first-generation inhibitors (HR, 0.46; 95% CI, 0.37–0.57; $p < 0.0001$).[76] Upon further follow-up, median OS was also superior with osimertinib: 38.6 months versus 31.8 months (HR, 0.80; 95% CI, 0.64–1.0; $p = 0.46$).[4] This improvement was attributed to improved control

TABLE 114-3 Targeted Therapy in Advanced Non–Small-Cell Lung Cancer

Molecular Target	Genetic Alteration	First-line Therapy	Subsequent Therapy	Reference
EGFR epidermal growth factor receptor	L858R/exon 19del[a]	Osimertinib,[b] erlotinib, gefitinib, afatinib, or dacomitinib	Osimertinib[b] if T790M mutation identified	76 80–84
	T790M	Osimertinib		
ALK anaplastic lymphoma kinase	Gene rearrangement	Alectinib[b] or brigatinib[b] Ceritinib	Lorlatinib	77,79,85,86
ROS1 ros proto-oncogene 1	Gene rearrangement	Crizotinib or entrectinib Ceritinib	Lorlatinib	87–90
BRAF serine/threonine-protein kinase Braf	V600E	Dabrafenib with trametinib		91
RET ret proto-oncogene	Gene rearrangement	Selpercatinib or pralsetinib Cabozantinib or vandetanib		92,93 94,95
NTRK (1/2/3) neurotrophic tyrosine receptor kinase	Gene rearrangement	Entrectinib or larotrectinib		96,97
MET hepatocyte growth factor receptor	Exon 14 skipping mutation	Capmatinib or tepotinib Crizotinib		98–100

[a] *Other rare mutations may respond: exon 19 insertions, L861Q, G719X, and S768I.*

[b] *NCCN recommended category 1.*

of CNS metastatic disease, fewer serious adverse events leading to dose reduction, and expanded coverage of the T790M resistance mutation with osimertinib. Unfortunately, several EGFR mutations are associated with resistance to TKI treatment, for example, exon 20 insertions. Over time, almost all TKI-responsive lung cancers acquire secondary mutations rendering them resistant to further treatment and relapse is inevitable.[44] Mechanisms of resistance are being studied to provide future targeted therapy in this setting.

Another clinically relevant molecular subset of NSCLC is driven by the echinoderm microtubule–associated protein-like 4 (EML4) and ALK translocation.[49] The EML4–ALK translocation in NSCLC leads to the constitutive activation of the ALK kinase domain and promotes cell growth and survival. More recently, additional fusion partners have been identified with ALK. ALK translocations are found in approximately 2% to 5% of NSCLC, most commonly in never-smokers or light smokers with adenocarcinomas. The preferred first-line therapy for ALK-translocated, advanced NSCLC is the second-generation TKI alectinib. The recommendation is based on a phase 3 randomized trial, ALEX, of alectinib versus crizotinib, a first-generation TKI approved for treatment of ALK-mutated NSCLC. In this large trial of first-line treatment, alectinib had an improved median PFS of 34.8 months vs. 10.9 months (HR, 0.43; 95% CI, 0.32–0.58).[77,78] Alectinib had superior CNS control, fewer severe adverse events, and higher response rates. Several other second-generation ALK TKIs are approved for first-line therapy (brigatinib and ceritinib). Lorlatinib, a third-generation ALK inhibitor, has been shown to have activity in ALK-translocated NSCLC that has become resistant to previous ALK TKIs.[79] It is now recommended as a subsequent treatment for patients with resistance to previous ALK TKIs and is being studied as first-line treatment (Figs. 114-2 and 114-3).

EGFR mutations and ALK translocations are the most common driver mutations found in advanced NSCLC. However, multiple additional mutations have been identified and targeted as therapy. Current guidelines include recommendations for targeted therapy for the following driver mutations: ROS1 rearrangements, BRAF V600E mutations, NTRK fusions, MET 14 exon skipping mutations, and RET rearrangements. This list continues to expand as studies of targeted therapy for EGFR exon 20 insertions, KRAS G12C mutations, and HER2 amplifications are ongoing. Remarkable advances have been made in using oral targeted agents to treat advanced NSCLC with driver mutations. These include (1) broadening the number of unique driver mutations identified and treated with novel targeted agents, (2) expanding treatment of TKI-resistant disease to second-line therapies, and (3) improving agents used in the first line for previous targets (such as EGFR and ALK). Advances in targeted therapy have had a large impact on survival and quality of life for patients with advanced disease.

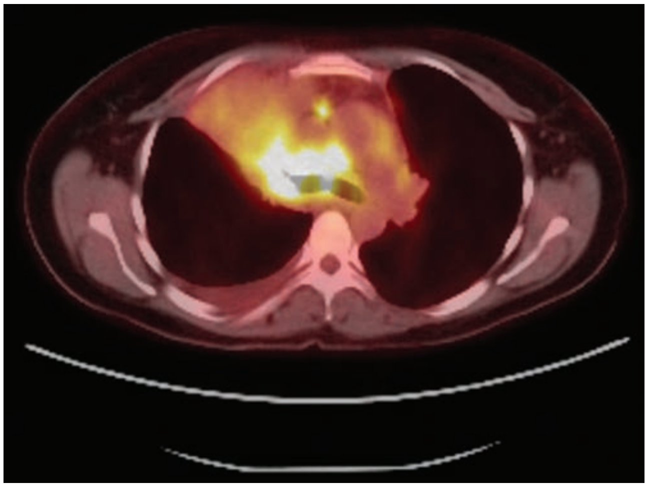

Figure 114-2 CT scan combined with fluorodeoxyglucose positron emission scan (FDG-PET) of a newly diagnosed metastatic lung adenocarcinoma in a never-smoker. This tumor was found to have an echinoderm microtubule–associated protein-like 4 (EML4) and anaplastic lymphoma kinase (ALK) translocation upon fluorescence in situ hybridization (FISH) analysis.

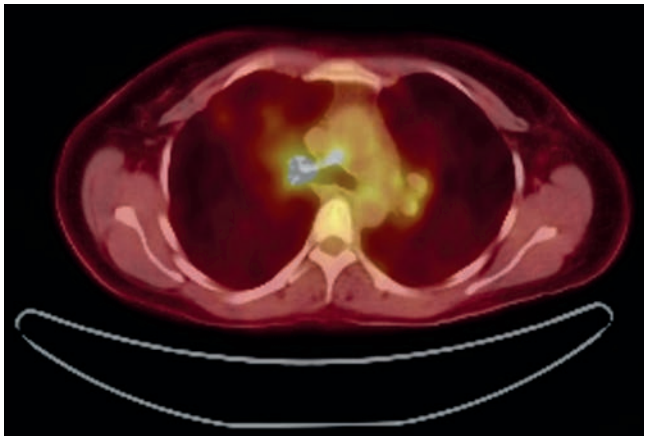

Figure 114-3 CT/FDG-PET scan of the same patient after 3 months of treatment with crizotinib, an oral tyrosine kinase inhibitor. The imaging shows marked disease response.

CONCLUSION

Chemotherapy has an established role in the adjuvant therapy of stage II and IIIA NSCLC. Randomized clinical trial data demonstrate improved median and long-term survival when antineoplastic agents are used with surgical resection. The next step in the development of adjuvant regimens will integrate molecular targeted agents and immunotherapy. These trials are already underway and showing promise. Multimodality therapy is necessary to treat locally advanced disease. The role of systemic treatment with chemotherapy and immunotherapy is essential to improve survival rates of those treated with radiation and surgery. Questions that need to be addressed in future and ongoing trials include the optimal sequence for various modalities in locally advanced disease as determined by biomarkers. For advanced-stage NSCLC, there is now a growing list of active agents. For those treated with targeted therapy for specific driver mutations or immunotherapy for high PD-L1 expression, remarkable advances in the durability of disease control have been seen. Further clinical studies are eagerly awaited with novel classes of immunotherapy beyond PD-L1, PD-1, and CTLA-4 inhibitors. However, there is still considerable room for improvement, particularly in those with poor performance status and heavily pretreated patients. Cost/benefit analysis is another consideration, as the newer agents are especially expensive. With the development of novel therapeutic agents and the future potential to select treatment options based on genomic and proteomic profiles, there is renewed optimism that the treatment of NSCLC will continue to improve in the future.

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CHAPTER 115

Treatment of Non–Small-Cell Lung Cancer: Radiation Therapy

Joseph A. Miccio
Mitchell Machtay

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INTRODUCTION

Approximately 85% of lung cancers are non-small cell lung cancers (NSCLC), a heterogeneous group that is further divided into squamous cell and adenocarcinoma, the latter of which has numerous clinicopathologic–biologic subtypes. Unlike the situation for systemic treatment of NSCLC, presently, radiotherapy (RT) management differs very little among the various subtypes. It is anticipated that this will change in the future, as clinically useful predictive biomarkers for RT emerge but currently, and disappointingly, they do not yet exist. Conversely, however, this means that RT is a predictable, highly broad-spectrum agent against NSCLC. Most NSCLC patients receive RT at some point in the course of their illness; this may be thoracic RT and/or RT against metastatic sites, including though not limited to brain or bone metastases. Thoracic RT can be used for one of three treatment indications: (1) Definitive: An attempt at cure without surgery, using radiation as the primary local modality. (2) Palliative: Efforts directed toward short-term and/or long-term relief of cancer-related symptoms. (3) (Neo)-adjuvant: The integration of radiation prior to (neoadjuvant) or after (adjuvant) surgery, to improve the chance for permanent locoregional control.

There can be considerable overlap among these categories, and goals of treatment may change based on the patient's trajectory and disease course. A major example of this is the evolutionary use of stereotactic RT for patients with selected (oligometastatic or oligoprogressive) stage IV NSCLC who are doing well with systemic therapy; we describe this is as a hybrid between definitive and palliative treatment. Table 115-1 summarizes the different types of RT for lung cancer, with the typical associated radiation doses, treatment time, and other considerations.

The decision to use thoracic RT should usually occur in a multidisciplinary "tumor board" process in order to optimize integration of RT with other modalities. The factors most important in determining RT utilization are cancer stage and tumor size, along with the patient's pulmonary reserve and performance status. Consideration must also be given to psychosocial and logistic factors, such as the ability of the patient to cooperate with RT planning, delivery, and follow-up care. Table 115-2 illustrates the general (strong relative) contraindications to definitive intent thoracic RT.

Although there have been tremendous advances in the quality and safety of thoracic RT and multimodality treatment of lung cancer, it must be remembered that most NSCLC patients referred for RT have a poor prognosis for 5-year survival with standard-of-care therapy. As a result, consideration should be given to encouraging appropriate patients to participate in clinical trials.

DEFINITIVE RT FOR LOCALLY ADVANCED (INOPERABLE, BUT NONMETASTATIC) NSCLC

Patients without demonstrable distant metastases after thorough workup but who have locally advanced disease that precludes surgery are usually candidates for definitive RT. This includes most patients with stage III NSCLC and some stage II NSCLC. Workup

TABLE 115-1 Summary of Radiotherapy for NSCLC

Type	Stage/ Indication	Typical Radiation Dose	Radiation Time Course	Integration of Other Therapy	Comments
Definitive medically inoperable early stage	Stage I (and select stage II T3N0)	45–60 Gy	1–2 weeks	None	Stereotactic technology with ultra-accelerated fractionation
Definitive inoperable/ locally advanced	Stage III (and select stage II)	60–66 Gy	6–6.5 weeks	Concurrent chemotherapy and post-RT durvalumab	Pts not suitable for systemic therapy may be considered for moderately hypofractionated RT alone
Preoperative/ neoadjuvant	Select stage IIIA and Pancoast	45 Gy	5 weeks	Concurrent chemotherapy	
Postoperative/ adjuvant	Select stage IIIA	50 Gy (60 Gy if gross residual disease)	5 weeks	Start systemic therapy before adjuvant RT	
Palliative	Stage IV; select stage III	20–45 Gy	2–3 weeks	Systemic therapy as appropriate	Concurrent immunotherapy is OK, but generally not chemotherapy
Oligometastatic (quasi-definitive)	Select stage IV	30 to 60 Gy (stereotactic ultra-accelerated RT)	1–2 weeks	Systemic therapy as appropriate	Stereotactic technology with ultra-accelerated fractionation

TABLE 115-2 Relative Contraindications to Definitive (Curative Intent) RT for Lung Cancer

Contraindication(s)	Comments
Prior high-dose RT with field overlap	Length of time since previous RT and anatomic location of field overlap are important considerations when considering reirradiation
Autoimmune/active connective tissue disease and/or idiopathic pulmonary fibrosis (IPF)	
FEV_1 <800 cc	FEV_1 (or other PFTs) are generally not a contraindication to SBRT for peripheral stage I lung cancer
Tracheobronchial–esophageal fistula	
Tumor size/geometry so extensive that RT fields will include >37% of the patient's normal lung parenchyma, even with maximal technology RT	Generally analyzed as V20 (percent of total lung receiving 20 or more Gy); consider reduction in total prescribed RT dose and/or reduced treatment margins
Tumor size/geometry so extensive that RT fields will include >50% of the patient's heart/pericardium, even with maximal technology RT	Generally analyzed as V30 (percent of total heart receiving 30 or more Gy); consider reduction in total prescribed RT dose
Performance status (Zubrod) of 3 or 4	
Anticipated noncompliance with treatment or follow-up	It is important not to be "biased" in making this highly subjective judgment to deny someone potentially curative therapy

should include chest CT scan, FDG-PET/CT scan, brain MRI, and cytology of pleural effusion (if present). In many cases, pathologic staging of lymph nodes via endobronchial ultrasound (EBUS), endoesophageal ultrasound (EUS), or mediastinoscopy is appropriate before RT.

For patients who are medically fit, the current standard of care is a complex multimodality therapy regimen consisting of concurrent radiotherapy and chemotherapy (CCRT), followed by maintenance immunotherapy. (As of the writing of this chapter, the only FDA-approved immunotherapeutic for this purpose is durvalumab.)[1,2] Suitability for CCRT requires a Zubrod performance status of 0 or 1 (roughly corresponding to Karnofsky score of 70 or above). Significant weight loss is a relative contraindication based upon historic clinical trials showing this to be a poor prognostic factor.[3] Relatively advanced age is not an absolute contraindication for this approach,[4] although it should be noted that the pivotal clinical trials establishing the treatment have a median age of about 60 and few patients greater than or equal to 75 years old.

The conventional dose/fractionation schedule for definitive RT as part of CCRT is typically 60 Gy in standard fractionation (2 Gy once daily × 30 fractions over 6 weeks). A major randomized trial comparing 60 Gy/6 weeks with 74 Gy/7.4 weeks, with all patients receiving concurrent systemic therapy, not only failed to show benefit from the more intensive RT dose but demonstrated *worse* survival with 74 Gy.[5] It is hypothesized that toxicity (cardiopulmonary and/or immunologic) led to this paradoxical outcome. A secondary analysis of the trial suggested that patients treated with intensity-modulated radiation therapy (IMRT) had improved outcomes compared with "standard" conformal RT.[6] It is uncertain whether next-generation IMRT and/or proton beam RT with modestly intensified RT dose will perform better in newer trials. When patients are treated with RT alone for inoperable NSCLC, RT dose intensification may be more effective than standard 60 Gy/6-week therapy; this is important to keep in mind for patients who are not candidates for chemotherapy.[7]

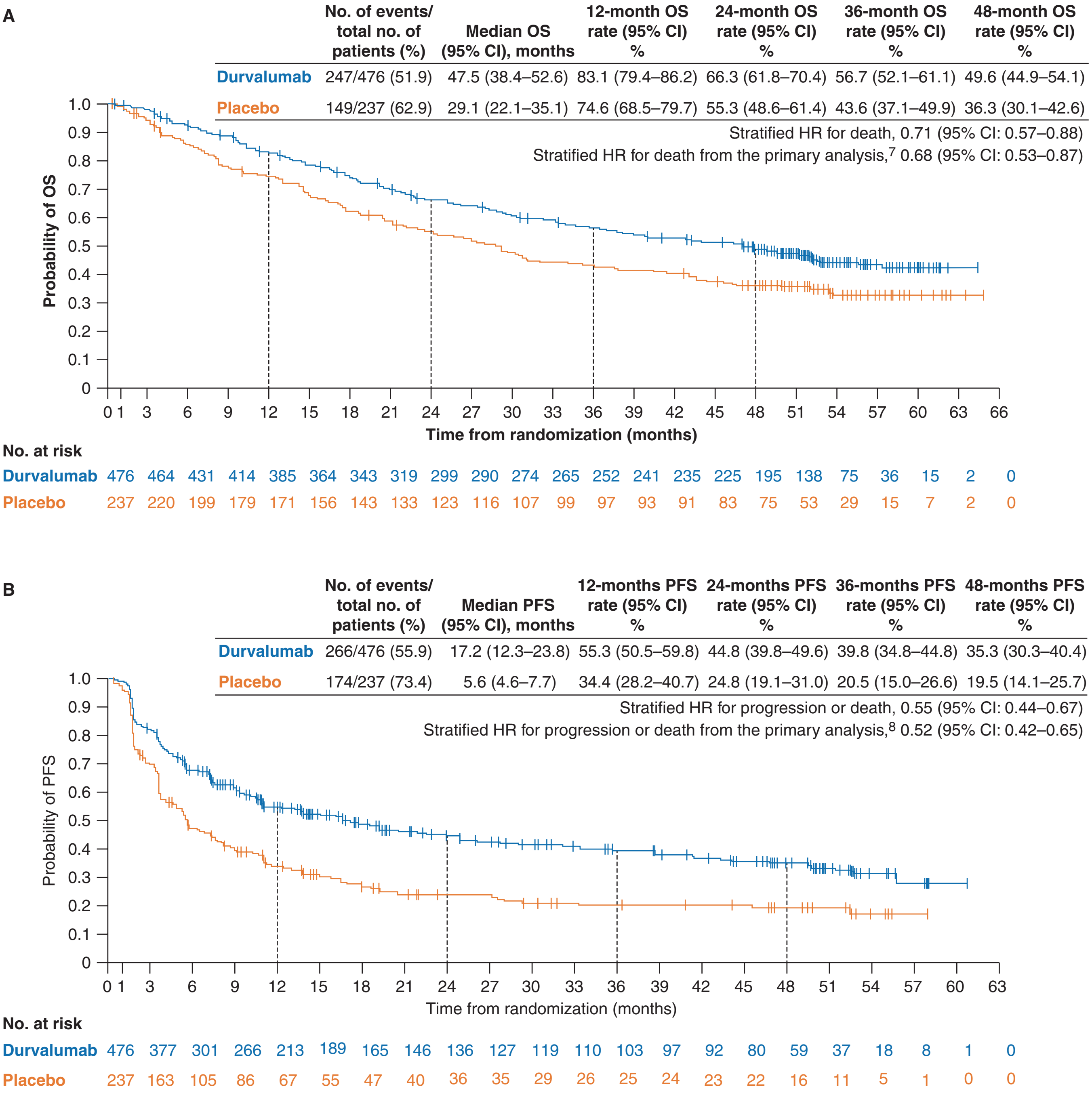
The most commonly used CCRT regimen consists of weekly concurrent carboplatin/paclitaxel, although other regimens that combine a platinum (cisplatin or carboplatin) with a second agent such as etoposide, vinorelbine, docetaxel, or (for nonsquamous disease) pemetrexed also are well accepted. There are no conclusive studies showing an advantage (or major disadvantage) to any one of these platinum-based doublet regimens. There does not appear to be benefit from continuing chemotherapy after RT is completed.

The benefit from consolidation durvalumab was demonstrated in the PACIFIC trial to be strikingly positive (Fig. 115-1), and secondary analyses suggested that (1) a shorter interval between the completion of RT and the start of durvalumab was better; and (2) patients whose tumors were enriched in high levels of PDL1 had greater benefit.[1,2] It should be noted that the study only enrolled patients who were doing well after CCRT, without any major pulmonary toxicity and with no evidence of early disease progression.

The topic of pulmonary toxicity from RT is discussed later in this chapter. The transition from "large field" thoracic RT (i.e., fields that include the tumor plus elective nodal stations) to "involved field" RT lessened the risk and intensity of high-grade radiation pneumonopathy. Furthermore, this reduction in radiation field size has not negatively impacted survival.[8,9,] Current standard of care for most patients is to identify the gross tumor volume based on high-resolution and up-to-date imaging (CT, FDG-PET/CDT) and other data (e.g., results of EBUS when performed) and to limit the size of the RT fields. Figure 115-2 displays an example of a patient with stage III lung cancer treated with definitive chemoradiotherapy. Figure 115-3 illustrates the dose–volume histogram for this patient.

Sometimes, even with involved field RT planning and optimal technology, the gross tumor volume is so large that the safety of full-dose CCRT is questionable. In these scenarios, there are three options: (1) abort the plan for CCRT and treat the patient as if they have stage IV NSCLC (systemic therapy alone); (2) proceed with CCRT but reduce the prescribed dose of RT to a dose felt to be acceptable with respect to lung/heart tolerance metrics; (3) delay RT in favor of induction systemic therapy in the hopes that tumor shrinkage will then allow smaller and safer RT fields in several months. Each strategy has its pros and cons, and each case of this type should undergo thorough consultation with other team members in an effort to achieve a consensus.

Overall, there has been a steady improvement in the prognosis for stage III/inoperable NSCLC over four decades, as shown in Table 115-3. This results both from improvements in staging/diagnosis (i.e., stage migration) as well as better treatment. There is still much room for improvement, and patients with this category of lung cancer should be strongly encouraged to join therapeutic clinical trials.



	No. of events/ total no. of patients (%)	Median OS (95% CI), months	12-month OS rate (95% CI) %	24-month OS rate (95% CI) %	36-month OS rate (95% CI) %	48-month OS rate (95% CI) %
Durvalumab	247/476 (51.9)	47.5 (38.4–52.6)	83.1 (79.4–86.2)	66.3 (61.8–70.4)	56.7 (52.1–61.1)	49.6 (44.9–54.1)
Placebo	149/237 (62.9)	29.1 (22.1–35.1)	74.6 (68.5–79.7)	55.3 (48.6–61.4)	43.6 (37.1–49.9)	36.3 (30.1–42.6)

Stratified HR for death, 0.71 (95% CI: 0.57–0.88)

Stratified HR for death from the primary analysis,7 0.68 (95% CI: 0.53–0.87)

No. at risk

Durvalumab	476	464	431	414	385	364	343	319	299	290	274	265	252	241	235	225	195	138	75	36	15	2	0
Placebo	237	220	199	179	171	156	143	133	123	116	107	99	97	93	91	83	75	53	29	15	7	2	0

	No. of events/ total no. of patients (%)	Median PFS (95% CI), months	12-months PFS rate (95% CI) %	24-months PFS rate (95% CI) %	36-months PFS rate (95% CI) %	48-months PFS rate (95% CI) %
Durvalumab	266/476 (55.9)	17.2 (12.3–23.8)	55.3 (50.5–59.8)	44.8 (39.8–49.6)	39.8 (34.8–44.8)	35.3 (30.3–40.4)
Placebo	174/237 (73.4)	5.6 (4.6–7.7)	34.4 (28.2–40.7)	24.8 (19.1–31.0)	20.5 (15.0–26.6)	19.5 (14.1–25.7)

Stratified HR for progression or death, 0.55 (95% CI: 0.44–0.67)

Stratified HR for progression or death from the primary analysis,8 0.52 (95% CI: 0.42–0.65)

No. at risk

Durvalumab	476	377	301	266	213	189	165	146	136	127	119	110	103	97	92	80	59	37	18	8	1	0
Placebo	237	163	105	86	67	55	47	40	36	35	29	26	25	24	23	22	16	11	5	1	0	0

Figure 115-1 These figures show the 4-year overall survival (**A**) and progression-free survival (**B**) in the PACIFIC trial comparing the immune checkpoint inhibitor durvalumab versus placebo following standard chemoradiotherapy for inoperable stage III NSCLC. *(Reproduced with permission from Faivre-Finn C, Vicente D, Kurata T, et al. Four-Year Survival With Durvalumab After Chemoradiotherapy in Stage III NSCLC-an Update From the PACIFIC Trial. J Thorac Oncol. 2021;16(5):860–867.)*

DEFINITIVE RT FOR EARLY-STAGE, INOPERABLE NSCLC

Surgical resection for early-stage NSCLC remains the gold standard of care for patients with stage I disease. However, many patients with early-stage NSCLC are elderly and have significant lung disease, heart disease, and/or other relative or absolute contraindications to thoracic surgery. It has long been understood that some of these “medically inoperable” patients can be cured with RT alone. Their prognosis with respect to the lung cancer is significantly better than that for patients with stage III/technically inoperable NSCLC, and this argues in favor of early diagnosis and intervention with RT.

Historically, RT for medically inoperable early-stage NSCLC was given with large fields and a dose of 60 to 70 Gy over 6 to 7 weeks (standard fractionation), with fair results.[10] However, advances in RT hardware and planning software allow these relatively small tumor volumes to be treated with a technique called stereotactic body radiotherapy (SBRT). SBRT is analogous to gamma knife or other forms of intracranial stereotactic radiosurgery. A great many narrowly collimated radiation beams from multiple geometric angles converge on the tumor. The small tumor volume allows for a very precise and high dose of radiation to be delivered, with much lower RT doses outside of the tumor volume to the lung, heart, and other organs. SBRT dose/fractionation is usually 50 to 60 Gy given in three to eight treatments (i.e., daily dose of radiation between 7.5 and 20 Gy per fraction).

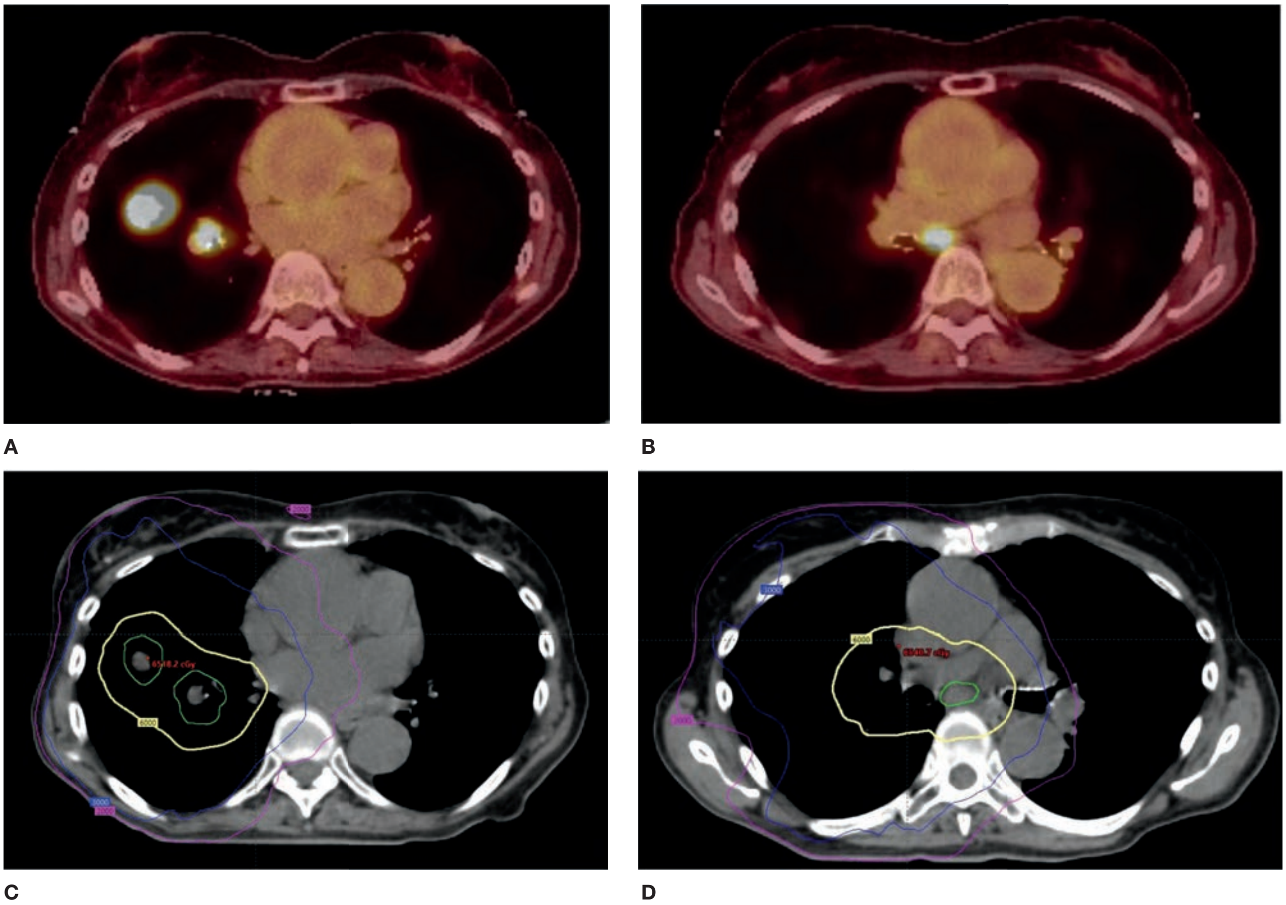


Figure 115-2 A 77-year-old female with an extensive smoking history was found to have a 2.6-cm spiculated mass in the right upper lobe on CT scan when she presented to the hospital with bronchitis. PET/CT scan showed an intensely avid primary tumor in the RUL with avid hilar adenopathy (**A**) as well as subcarinal adenopathy (**B**). She proceeded with EBUS and biopsy of the subcarinal lymph node confirming adenocarcinoma (cT1cN2; stage IIIA). She was treated with concurrent chemoradiation with carboplatin/paclitaxel. Radiation prescription was 60 Gy in 30 fractions *(yellow isodose line)* encompassing the target volume *(green contour)* with appropriate margin for microscopic disease extension and patient setup variability (**C** and **D**). The 30-Gy *(blue)* and 20-Gy *(pink)* isodose lines also are shown. The "hot spot" for the radiation plan at this axial slice is shown in *red*.

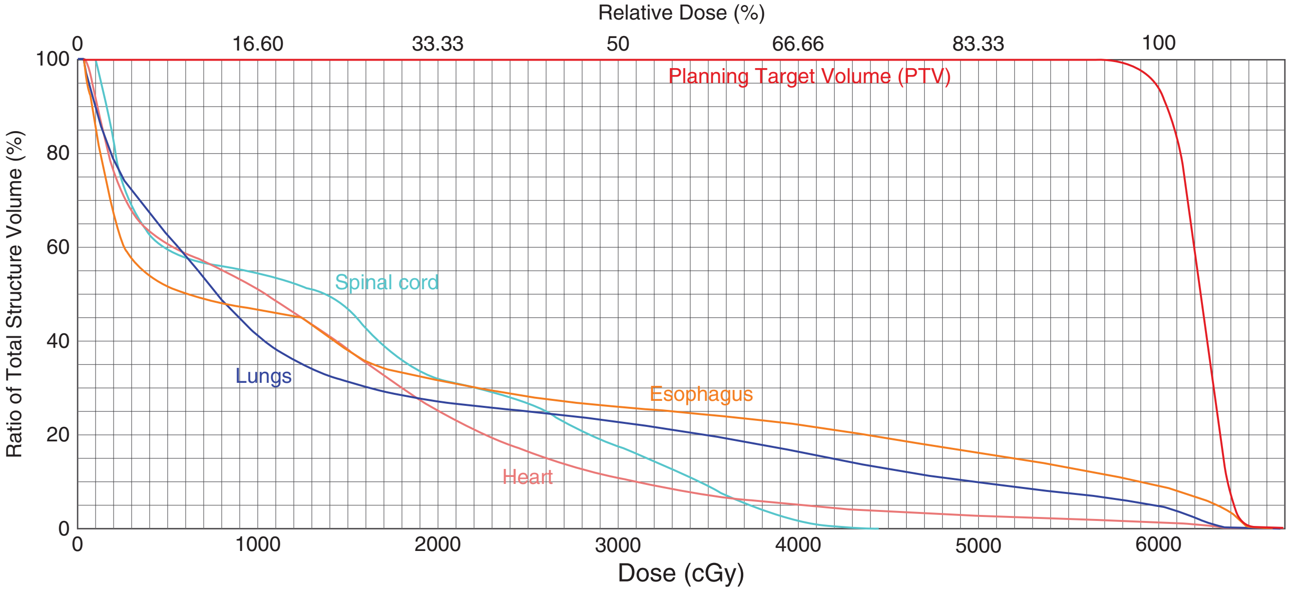


Figure 115-3 Radiation therapy dose–volume histogram (DVH) of the patient described in Fig. 115-1. On a single graph, radiation dose *(x-axis)* is plotted against the total volume of the target volume and several normal organs *(y-axis)*. As shown in this DVH, 95% of the planning target volume is receiving the prescribed dose of 60 Gy. The normal organ dose constraints that are achieved in this DVH include spinal cord maximum dose of 50 Gy, lung V20 <35%, esophagus V60 ≤15%, and heart V30 ≤25%.

TABLE 115-3 Improvement in Survival in Clinical Trials for Stage III Inoperable Lung Cancer

Treatment	Approximate Median Survival	Approximate 3-Year Survival
RT alone: 40- to 60-Gy standard fractionation/techniques[43]	10 months	10%
RT alone: 70+ Gy (or biologically equivalent accelerated techniques)[46]	12 months	15%
Sequential chemotherapy followed by RT[3]	14 months	25%
Concurrent chemoradiotherapy (technology circa 2000)[44]	17 months	35%
Concurrent chemoradiotherapy (technology circa 2010[a])[5]	29 months	50%
Concurrent chemoradiotherapy followed by immunotherapy[b,2]	47 months	65%

[a] *Modern technology includes FDG-PET–based staging and RT treatment planning, as well as higher-precision and safer RT techniques including IMRT.*

[b] *The trial documenting these results did not include patients who suffered progression and/or severe toxicity during their course of chemoradiation.*

Radiobiologically, only extremely radioresistant cells can survive this dose intensity of radiation; for typical epithelial malignancies SBRT doses are considered "ablative." A typical case of medically inoperable stage I NSCLC treated with SBRT is shown in Fig. 115-4.

Pilot studies showed not only safety, but local tumor control rates for stage I NSCLC of 85% to 95%, comparable to surgery.[11] Randomized trials showed its superiority over older standard therapy.[12,13] SBRT is now rightfully considered standard of care for inoperable stage I NSCLC. There are increasing data to suggest that

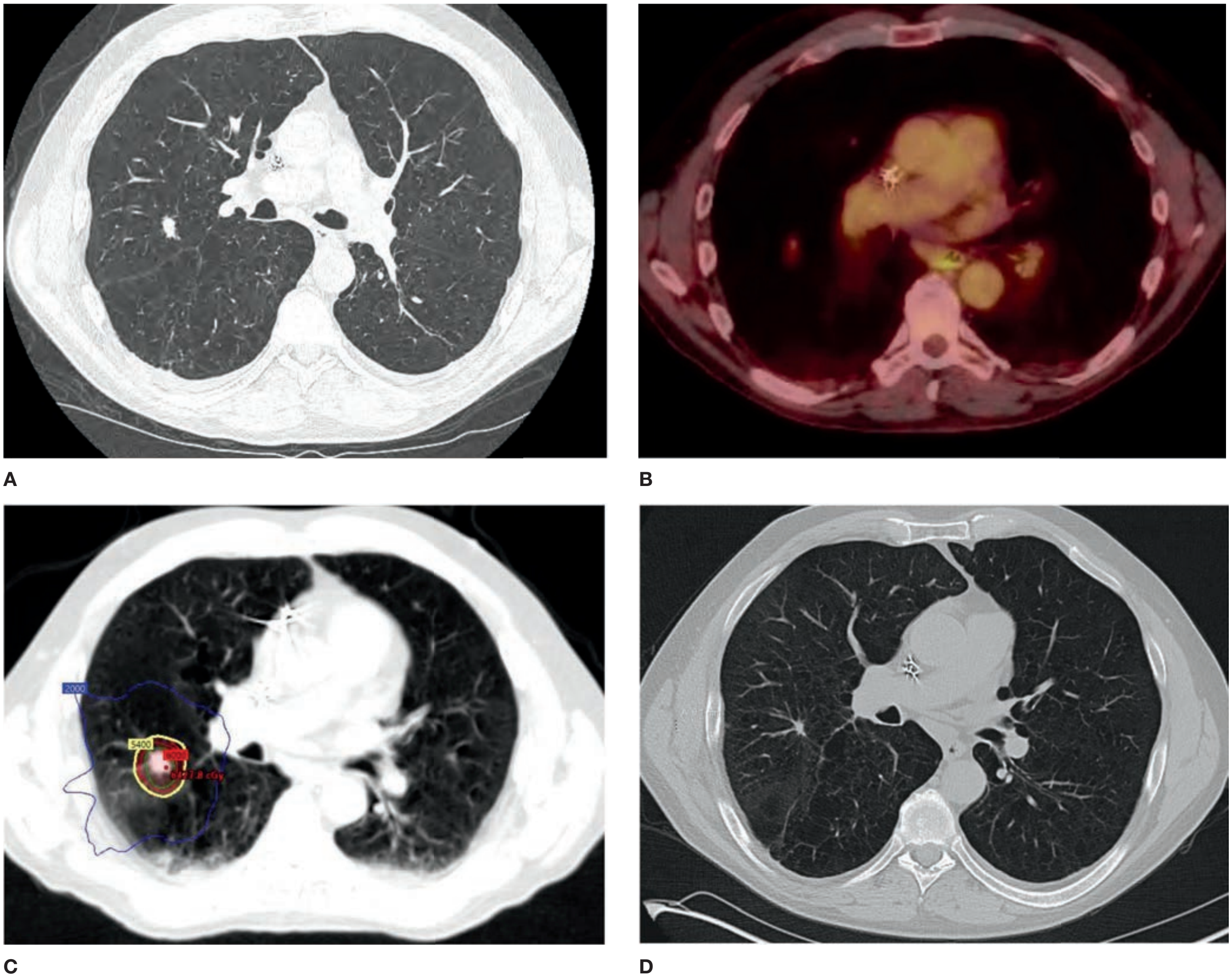


Figure 115-4 A 61-year-old man with an extensive smoking history and COPD was found to have a 1.2-cm spiculated mass in the right upper lobe on CT screening for lung cancer (**A**). A PET scan showed FDG uptake (**B**), and subsequent biopsy of the mass showed adenocarcinoma (cT1bN0, stage IA2). The patient was evaluated by a cardiothoracic surgeon, and it was determined that he was not an appropriate surgical candidate. He was treated with stereotactic body radiation therapy (SBRT) to 54 Gy in 3 fractions. The treatment plan (**C**) shows the target volume *(green)* well covered by the 54-Gy prescription isodose line *(yellow)* with further dose escalation to the target *(60-Gy isodose line in red)*. The 20-Gy isodose line *(blue)* is shown as well. CT scan 4 months after SBRT (**D**) shows a decrease in size of the treated tumor.

(1) SBRT offers results similar to surgery for patients with borderline operable NSCLC or patients with patently operable NSCLC who decline surgery;[14] (2) SBRT can be safely used for patients whose imaging data is highly consistent with stage I NSCLC but for whom biopsy was nondiagnostic and/or considered unsafe;[15] and (3) selected patients may be candidates for single-fraction SBRT (i.e., "radiosurgery") with 30 to 34 Gy.[16] Extra caution is advised when treating central tumors adjacent to the mainstem or lobar bronchi and/or great vessels.[17] At present, there is no proven role for neoadjuvant or adjuvant systemic therapy (immunotherapy or otherwise) to reduce the risk of regional or distant recurrence, although studies are underway.

PALLIATIVE RT FOR LOCAL AND/OR METASTATIC SYMPTOMATIC NSCLC

Palliative-intent RT can be extremely valuable in situations where the patient's quality of life is or may soon be substantially compromised by a localizable malignant tumor, whether in the chest or elsewhere. It has often been said that the best time to start palliative RT is "one day before the patient develops serious symptoms." Obviously, it is not possible to identify this day for any given person. Thus, the radiation oncologist—and the entire multidisciplinary team together—must use their enlightened judgment on when to intervene with RT. With more severe situations—for example, whole lung atelectasis or excruciating bone pain—the benefits of RT are low. Conversely but similarly, patients are unlikely to greatly benefit from RT to a completely asymptomatic mass that is unlikely to cause acute harm between regular follow-up/imaging intervals. Table 115-4 summarizes approximate response rates to radiotherapy for intrathoracic symptoms, recognizing that for any individual patient the likelihood of benefit is unpredictable. Unfortunately, there are no biomarkers of individual tumor radiosensitivity to predict the likelihood of benefit. The intrathoracic situations most likely to benefit from RT include low to moderate degrees of hemoptysis, pain, superior vena cava syndrome, and obstruction of central bronchi and/or pulmonary vessels. The efficacy of palliative RT in NSCLC, using moderate doses and schedules, can be profound, particularly when compared with cytotoxic chemotherapy. A variety of RT doses and schedules can be used, with no clearly shown benefit of any one schedule, at least with respect to survival.[18] A commonly used regimen in the United States is 30 Gy in 10 fractions (3 Gy per day), although shorter or slightly longer schedules are also used. These schedules commonly have temporary acute toxicities (e.g., esophagitis, fatigue) but are unlikely to cause high-grade or long-term injury to critical organs, and it is often possible to offer a repeat course when needed later in the patient's life.

For metastatic sites (e.g., painful bone, adrenal, soft tissue metastases), palliative RT can be given using similar dose/fractionation as for thoracic palliative RT. In some cases of uncomplicated bone metastases, a single 8-Gy fraction can be effective, although this may be associated with an increased likelihood of recurrence and the need for additional RT.[19] Complex bone metastases with larger volume, soft tissue extension, and/or neuropathic pain component are more commonly treated with 20 to 30 Gy over 2 to 3 weeks. SBRT, with its high-precision delivery and higher biologic dose, appears to have value for certain lesions and may improve the chance for complete pain relief and tumor control.[20]

Brain metastases from NSCLC are a special and increasingly common situation, for which a detailed discussion is beyond the scope of this chapter. Historically, the diagnosis of brain metastases would prompt an immediate course of whole-brain RT, often followed by hospice referral given the low response rate of systemic therapies. However, there have been dramatic changes in the treatment of brain metastases, including a significant increase in the number and diversity of systemic agents that cross the blood–brain barrier and have some efficacy in the brain. Whole-brain RT (WBRT) has largely been replaced by focal stereotactic radiosurgery (gamma knife and other platforms), as radiosurgery causes significantly less radiation-induced cognitive dysfunction, while simultaneously being capable of delivering ablative doses of RT to metastatic foci similar to surgery.[21,22] Although the data in favor of radiosurgery are strongest for treating one to three brain metastases, there is now substantial evidence supporting its use in much larger numbers, as long as the overall volume of metastatic disease remains modest.[23] In cases where WBRT is indicated, an IMRT technique that spares the hippocampus from high-dose RT appears to improve cognitive outcomes.[24]

TABLE 115-4 Approximate Response Rate to Radiotherapy for Common Thoracic Symptoms from Lung Cancer

Symptom	Approximate Response Rate (%)
Vocal cord paralysis	5%
Atelectasis	20%
Weight loss/anorexia	30%
Dyspnea	40%
Cough	50%
SVC syndrome	60%
Pain	70%
Hemoptysis	80%
Overall symptomatic response	**60%–75%**

NEOADJUVANT/ADJUVANT THORACIC RT

The indications for thoracic RT prior to or following definitive surgery for NSCLC are decreasing. Historically, RT was used for many cases of node-positive, resected, stage II or III NSCLC based upon the strong efficacy of RT to improve local control. However, prospective randomized trials have not demonstrated improved survival; thus, the increased local control must be weighed against the risks of RT, particularly short- and long-term cardiopulmonary risks. A detrimental effect of postoperative RT for resected, margin-negative, stage I and II (pathologic N1) NSCLC is well documented.[25] The situation in stage IIIA/N2+ NSCLC is less clear and remains controversial.[26,27] Two recent studies randomized patients with mediastinal node–positive (N2) cancer who underwent surgery and adjuvant chemotherapy to postoperative RT or no RT. There was no demonstrable benefit to postoperative RT with respect to survival, although mediastinal relapse was reduced by nearly 50%.[28,29]

Similarly, a randomized study from Switzerland showed that the addition of RT to neoadjuvant chemotherapy for "resectable" IIIA/N2 NSCLC did not improve survival despite showing trends toward improved R0 (no cancer cells seen microscopically at the primary tumor site) resection, downstaging, and pathologic complete response.[30] This study can be critiqued for being underpowered; moreover, chemoradiation was not concurrent, and the study did not employ optimal (i.e., IMRT) RT techniques. Arguably, a more important question than whether RT should be added to preoperative chemo for IIIA NSCLC is whether these patients should instead undergo nonsurgical therapy with definitive CCRT plus durvalumab. Given the prolonged accrual period needed to complete trials that address whether there is benefit to inclusion of surgery versus a nonsurgical approach, a randomized trial to address this question would be difficult to perform, as demonstrated in the 1990s/early 2000s.[31]

There are several special circumstances for adding RT to definitive surgery. The first is the important use of RT (and chemotherapy) for positive margins/residual cancer after surgery.[32,33] The sequencing of chemotherapy vis-à-vis RT in this setting remains unclear.[34] The second important indication for chemo/RT plus surgery is for superior sulcus (Pancoast) NSCLC. Failure to achieve local control for this type of lung cancer causes a devastating and often uncontrollable pain syndrome due to tumor invasion of adjacent structures such as the brachial plexus. Thus, trimodality therapy (neoadjuvant chemoradiation followed by surgery) to maximize local control is suggested.[35,36]

CONSOLIDATION (QUASI-DEFINITIVE/PALLIATIVE) RT FOR OLIGOMETASTATIC NSCLC

As noted in an earlier section, SBRT is a major advance for the treatment of stage I medically inoperable NSCLC. It is a relatively nontoxic, highly effective, and convenient treatment for small-volume lesions in the lung. These features of SBRT, and the many improvements in systemic therapy for NSCLC, have led radiation oncology investigators to expand the use of SBRT to treatment of stage IV NSCLC. The working hypothesis is that systemic therapies (whether cytotoxic, biologic-targeted, or immunotherapeutic) are most effective against microscopic subclinical metastases, while grossly evident lesions are highly likely to harbor resistant foci of cancer and/or harbor a microenvironment hostile to these systemic therapies. It has been known for decades that some patients with a single brain metastasis from NSCLC can be cured with neurosurgical resection plus brain RT, analogous to resection or radiofrequency ablation for limited liver metastases from colorectal cancer.

This line of reasoning has promoted the use of local RT for "oligometastatic" (usually defined as 1–5 metastatic foci) cancer. Several clinical trials have demonstrated the value of RT not only in controlling the irradiated lesion(s), but with regard to metrics like progression-free survival and overall survival. For example, the SABR-COMET trial, which included patients with oligometastatic disease from a number of primary sites including lung, demonstrated a 5-year survival rate of 42% among patients receiving SBRT plus systemic therapy versus 18% among patients receiving systemic therapy alone.[37] A limitation is that these trials are small and include not just lung cancer but breast, colorectal, and other cancers; SABR-COMET had 99 patients (18 with lung cancer). The NCI-supported NRG Oncology cooperative group is conducting the largest randomized study on this topic, which is extremely difficult to operationalize due to rapid changes in backbone systemic therapies (clinicaltrials.gov/ct2/show/NCT03137771).

RADIATION-RELATED TOXICITY

Toxicity from radiotherapy occurs both as acute side effects, generally defined as occurring during or within 90 days from a course of irradiation, and late effects, which become manifest 3 months or later (up to decades) after RT. Although acute and late effects of RT tend to have similar risk factors, acute effects themselves do not necessarily lead to late complications. Conversely, some patients who had minimal acute toxicities may develop significant late toxicity.

As with systemic therapy, radiation toxicity is graded on a 1 to 5 scale, with grade 1 representing mild effects (e.g., mild dyspnea on exertion) and grade 5 representing fatal toxicity. Radiation toxicities differ from systemic therapy in that the effects almost universally occur only in the irradiated tissue volumes. Some effects of radiation are more generalized, including fatigue and immunosuppression. In the treatment of thoracic malignancies, where high radiation doses and large fields are often needed, the organs of greatest concern for both acute and late complications are the lung, heart, and esophagus. Significant dermatologic toxicity is rare with modern megavoltage equipment, and likewise with modern treatment planning technology the risk to the thoracic spinal cord is low. Other structures prone to injury from high-dose radiation include the brachial plexus, the tracheobronchial tree, the great vessels, and bones; concern about these organs has become of greater interest in the era of high-dose SBRT. Although many complications of RT are manageable, the most important strategy is prevention through sophisticated treatment planning and appropriate patient selection.

■ Lung Complications

Radiation-induced lung injury (pneumonitis and fibrosis) is the most common serious complication of thoracic irradiation. It usually appears between 1 and 4 months after irradiation, but it may occur during a course of particularly intensive (chemo)radiotherapy. Dyspnea is the hallmark symptom, along with cough, low-grade fever, malaise, and sometimes pleuritic chest pain. See Figure 115-5 for a classic case example of radiation pneumopathy after aggressive, curative-intent thoracic chemoradiotherapy. Most cases are more subtle and require computed tomography imaging to assist in the differential diagnosis and followup.

The differential diagnosis is broad, and radiation pneumonitis should not automatically be assumed solely because of temporal relationship. A key feature of radiation pneumonitis is its general confinement to the irradiated lung volume, and comparison between CT opacities and the radiation port is an essential step in making the diagnosis. In addition to chest CT imaging, bronchoscopy may be indicated to rule out infection or tumor recurrence/progression.

Radiation pneumonitis is often but not invariably steroid responsive. For more severe cases, a high dose (60 mg prednisone per day or equivalent) for 1 to 2 weeks is initiated followed by a slow taper over 3 to 12 weeks.[38] In contrast, the long-term phase of radiation-induced lung injury, radiation fibrosis, has no known effective treatment.

Given the limited treatment options for radiation-induced lung injury, the main strategy is minimization of the risk. The most significant risk factor for high-grade radiation pneumonitis is the volume of lung irradiated. Other factors associated with a higher risk include radiation dose and dose per fraction (larger dose per fraction increases risk) and tumor location (lower lobe lesions appear to have a higher risk). Poor pulmonary function before treatment also increases the risks of serious lung injury; in particular, pre-RT idiopathic pulmonary fibrosis predisposes to high-grade radiation pneumonitis and is a relative contraindication to thoracic RT.[39] Connective tissue diseases like systemic lupus erythematosus or scleroderma also raise concerns.[40] Certain chemotherapy agents, especially anthracyclines, methotrexate, bleomycin, and mitomycin, have long been recognized as exacerbating radiation lung injury, and these drugs are rarely used with thoracic RT today. Concurrent administration of carboplatin/paclitaxel has been associated with increased risk compared with cisplatin/etoposide.[41] The data are still evolving on the use of immunotherapy concurrent with radiation.

In radiation treatment planning, particular attention is given to the "V20"—the percent volume of the patient's total lung volume irradiated to 20 Gy or more.[41] Radiation planning should prioritize achieving V20 levels less than 30%. As the V20 rises above 37%, the risk of grade 3 pneumonitis exceeds 15%, and the risk of grade 4 to 5 (acute respiratory distress syndrome and/or death) increases significantly.

Modern radiation techniques like IMRT or proton beam therapy offer better lung V20s and appear safer than classic conformal RT fields.[42] With SBRT for a small stage I NSCLC, lung toxicity is remarkably mild, particularly if the irradiated lung field is peripheral and already mostly nonfunctional. There is no measurable biomarker to predict radiation-induced lung injury; research has focused on measuring cytokine profiles (e.g., TNF-α, TGF-β, IL-6), but these hypotheses have not yet been validated.

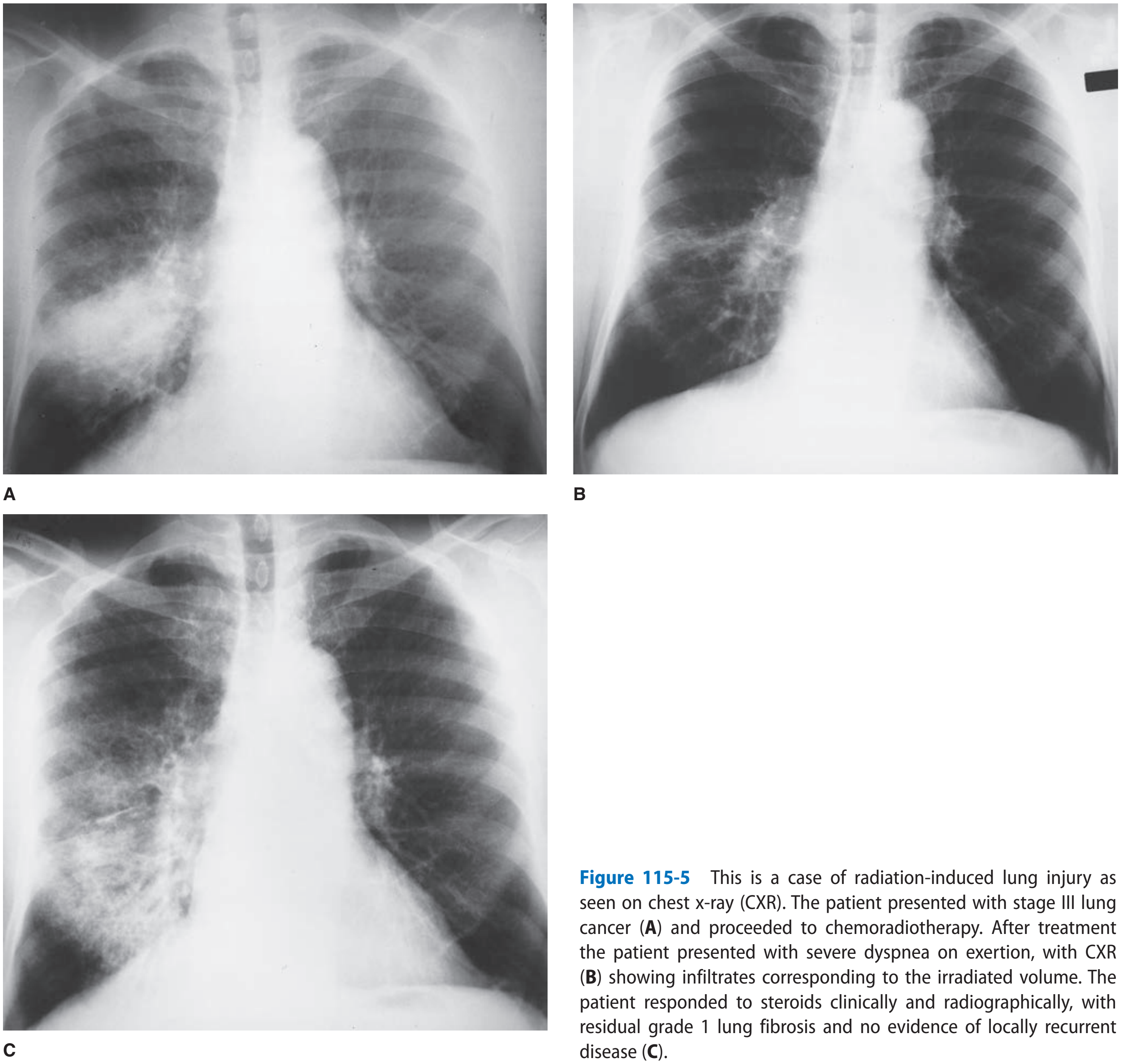


Figure 115-5 This is a case of radiation-induced lung injury as seen on chest x-ray (CXR). The patient presented with stage III lung cancer (**A**) and proceeded to chemoradiotherapy. After treatment the patient presented with severe dyspnea on exertion, with CXR (**B**) showing infiltrates corresponding to the irradiated volume. The patient responded to steroids clinically and radiographically, with residual grade 1 lung fibrosis and no evidence of locally recurrent disease (**C**).

■ Cardiac Toxicity

In addition to lung toxicity, there is increased recognition of the importance of cardiac toxicity from radiation in lung cancer patients[43] This is not unexpected based upon longstanding experience in breast cancer and lymphoma patients and is likely to become an increasing challenge as lung cancer patients are living longer. Indeed, cardiac injury is hypothesized as a reason ultra-high-dose (74 Gy) radiotherapy for stage III cancer or postoperative radiotherapy for resected stage II cancer may be more detrimental than beneficial.[5,25]

Cardiac events occurring during a course of RT are more likely to be related to the tumor itself (e.g., atrial fibrillation due to tumor invasion of the pericardium) and/or underlying cardiac disease. Acute cardiac complications (during or within several months post-RT) such as radiation pericarditis and associated dysrhythmias occur in about 5% of patients. Most cases are self-limited and treated with appropriate medications. Pericardiocentesis or other invasive procedures are rarely required.

As with lung toxicity, the risk of cardiac complications from RT is highly dependent upon the radiation dose and volume of heart irradiated. Longer-term cardiac complications include accelerated atherosclerosis, valvular disease, and cardiomyopathy. There is no clear threshold radiation dose/volume relationship to cardiac toxicity, although metrics of interest include V30 (percent of total cardiac volume irradiated to 30 Gy or more) and mean heart dose. This is somewhat analogous to radiation planning to minimize lung injury. However, it has added complexity because certain substructures of the heart (e.g., left anterior descending coronary artery) are more critical than others. Proton irradiation appears to be associated with improved radiation dosimetry for the heart, but this has not yet been shown to translate into better outcomes.[42]

■ Esophageal Toxicity

Esophageal toxicity from RT is primarily an acute problem. It is a nearly universal side effect of RT when treating mediastinal nodes and is significantly worse with chemoradiation than RT alone.[44] However, it is usually self-limited, and the risk of long-term complications like stricture approximates 10% with the standard RT dose of 60 Gy. Acute radiation esophagitis usually responds well to topical anesthetics and oral pain medications, and strictures can be managed with endoscopic dilatation. With ultra-high-dose radiotherapy to the mediastinum (70+ Gy), or with overlapping reirradiation, there is a risk of tracheoesophageal fistula, particularly in the presence of active tumor in this region.

Other End-organ Toxicities

No organ is completely resistant to radiation injury. One of the most feared complications from radiation therapy is spinal cord myelopathy. Fortunately this is rare today (<1% risk), with modern technology to reliably limit cumulative spinal cord dose to less than 50 Gy. Similarly, brachial plexopathy is uncommon with RT doses of 60 Gy or less, although patients irradiated for superior sulcus tumors are particularly susceptible.

A more recent phenomenon is the occurrence of chronic localized chest wall pain and/or rib fracture following SBRT for peripheral lung cancers.[45] This may occur years following radiation and can mimic pathologic fracture from tumor recurrence/metastasis.

With the use of higher-dose RT, including SBRT, patients are at risk for serious complications to critical structures in the mediastinum and hilum, including the tracheobronchial tree and great vessels. Patients treated with high-dose SBRT for central stage I cancers (within 2 cm of a lobar bronchus) are at risk for massive fatal pulmonary hemorrhage. Although this is uncommon (<5%), this has led to caution with the use of SBRT for such patients.

SUMMARY

RT plays a major role in the treatment of NSCLC. It is the primary treatment (with systemic therapy) for inoperable, nonmetastatic NSCLC and there have been considerable improvements in local control and other outcomes in recent decades. Of particular note, patients with medically inoperable early-stage NSCLC have a good chance for durable disease control with appropriately planned and delivered SBRT. In addition to its value as definitive therapy, RT benefits selected patients when given as adjuvant or neoadjuvant therapy. There are also a number of patients with oligometastatic stage IV NSCLC for whom RT may improve survival when added to systemic therapy. Finally, RT is of critical importance as part of palliative treatment for advanced incurable disease, both in the chest and at distant metastatic sites.

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CHAPTER 116

Small Cell Lung Cancer: Diagnosis, Treatment, and Natural History

Jonathan E. Dowell
Benjamin J. Drapkin
David E. Gerber
David H. Johnson

INTRODUCTION

Small-cell lung cancer (SCLC) is, in many ways, a unique tumor. Untreated, it is a highly virulent malignancy, with a life expectancy best measured in weeks. Conversely, it displays exquisite chemosensitivity, resulting in partial or complete responses in the majority of cases. For the first time in more than 30 years, the standard of care for advanced SCLC has changed with the addition of immune checkpoint inhibitor therapy to standard chemotherapy. Unfortunately, even with this advance, durable tumor responses are rare, and as a result, more than 95% of SCLC patients die from their disease. This chapter reviews the biology, epidemiology, diagnosis, clinical presentation, staging, and current management of this difficult disease.

EPIDEMIOLOGY

Lung cancer remains the leading cause of cancer death in men and women in the United States. In 2021, estimates call for 235,760 cases of newly diagnosed lung cancer (119,100 men and 116,660 women) and 131,880 deaths (69,410 in men and 62,470 in women).[1] Smoking tobacco products is the leading cause of lung cancer, conferring a 20-fold increase in risk and accounting for approximately 90% of all cases,[2] and smoking cessation reduces this risk substantially.[3] The prevalence of smoking in the United States peaked in 1964 at 42.7% with the landmark surgeon general's report on Smoking and Health. Since that report, the percentage of ever-smokers who have successfully quit smoking, or "quit ratio," has steadily increased to 61.7% in 2017, meaning that are currently more former smokers than current smokers, and the prevalence of smoking has declined below 18%.[4] The incidence of lung cancer lagged behind smoking cessation by just under three decades, but it has steadily declined by nearly 30% from its peak in 1982.[5] One study predicts that continued decline in smoking prevalence will reduce lung cancer deaths to 50,000 annually by 2065, a 60% reduction, despite increasing population and life expectancy.[6]

SCLC is more tightly associated with smoking than any other histologic subtype of lung cancer, with only 2% of cases occurring in never-smokers[7–9] and a relative risk that increases sharply with duration and intensity of exposure.[10] COPD is an independent risk factor for SCLC and mediates a small proportion of the smoking risk effect.[11] Other proposed risk factors include exposure to bis(chloromethyl) ether, nickel, vinyl chloride, asbestos, cadmium, radon, arsenic, and radiation, but the impact of each of these agents is not well quantified.[12] Due to the tight association between SCLC and tobacco use, smoking cessation had a greater impact on SCLC than other types of lung cancer, decreasing proportional incidence from a peak of 17% of all lung cancer in 1986 to 13% in 2002, where it has remained as of 2017.[5,13] SCLC mortality has declined in parallel with incidence and can be attributed almost entirely to smoking cessation, as survival following diagnosis has remained brief. In contrast, non–small-cell lung cancer (NSCLC) mortality decreased twice as rapidly as incidence (6.3% vs. 3.1% annually), reflecting a marked improvement in survival following diagnosis attributable to advances in therapies.[14]

PATHOLOGY

In 1926 William George Barnard published the first report of SCLC, in which he described mediastinal tumors of epithelial origin that he called "oat cell sarcoma" due to the histologic resemblance of the cells to oat grains.[15] Following this initial description, a series of classification systems were developed to divide SCLC into a variety of subtypes, but these were of limited clinical utility. In 1999 the WHO revised the classification of neuroendocrine lung tumors into four diagnoses by histologic grade: low-grade typical carcinoid (TC), intermediate-grade atypical carcinoid (AC), and two high-grade tumors, SCLC and large cell neuroendocrine carcinoma (LCNEC) (Table 116-1).[16]

This system has remained largely intact in the most recent WHO classification of lung tumors, published in 2015, in which only two subtypes of SCLC are recognized: pure SCLC and combined SCLC, in which another NSCLC component is present.[17] If the combined NSCLC component is LCNEC then it must be present in at least 10% of the tumor due to histologic similarity, but for

TABLE 116-1 Features of Neuroendocrine Lung Tumors

	Typical Carcinoid	Atypical Carcinoid	LCNEC	SCLC
NE features	Well differentiated	Well differentiated	Poorly differentiated	Poorly differentiated
Cell size	Intermediate	Intermediate	Large to intermediate	Small to intermediate
Mitotic rate	Low <2 mitoses/2 mm^2	Intermediate 2–10 mitoses/2 mm^2	High median 70 mitoses/2 mm^2	High median 80 mitoses/2 mm^2
NE markers by IHC	+++	++-+++	+-+++	±
Necrosis	—	+ (focal)	+++	+++
Ki-67 index	≤5%	5–20%	50–100%	80–100%
5-year survival	90–95%	60–70%	10–40%	≤5–10%

IHC, immunohistochemistry; LCNEC, large cell neuroendocrine carcinoma; NE, neuroendocrine; SCLC, small cell lung cancer.
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mixed adenocarcinoma or squamous cell carcinoma there is no fractional requirement.[18] Approximately 20% of SCLC is combined with NSCLC, most frequently LCNEC, but this estimate is based on surgical and autopsy series,[19,20] whereas the majority of diagnostic SCLC samples are small biopsies in which combined histology is difficult to recognize.

SCLC usually arises as a perihilar tumor, but in 95% of cases it presents as disseminated disease with mediastinal lymph node metastases that are often more prominent than the primary tumor.[21] Because there is no curative role for surgical resection in these cases, the vast majority of SCLC pathology samples are small biopsies or cytologic specimens from sites of metastasis. In the 2015 WHO classification of lung tumors, a specific approach to diagnosis using cytologic specimens was proposed, and although biopsy specimens are ideal, cytology alone is 60% to 90% sensitive and more than 95% specific for SCLC.[22,23]

The hallmark features of SCLC can be discerned by light microscopy, and although immunohistochemistry may be helpful for the diagnosis in some cases, the most important stains are hematoxylin and eosin (H&E). On H&E slides at low power, SCLC appears blue owing to the high nuclear-to-cytoplasmic (N:C) ratio, relatively basophilic cytoplasm, and scant extracellular matrix, which immediately distinguishes it from the more eosinophilic NSCLCs.[24] At higher magnification, tumor cells are small (<3 lymphocyte diameters, or ~ 20 μm) and round or spindle-shaped; they have scant cytoplasm, poorly defined borders, granular evenly distributed chromatin ("salt and pepper") and absent or inconspicuous nucleoli.[25] Nuclei are often deformed by adjacent tumor cells and structures, termed "nuclear molding" **(Fig. 116-1)**.

The predominant architecture of SCLC is dense sheets of cells with extensive areas of crush artifact and necrosis, and samples lack the glandular architectures of adenocarcinoma or keratinization of squamous cell carcinoma. Architecture is not entirely absent, as isolated areas may organize into rosettes (nuclei surrounding an eosinophilic cell-free center), trabeculae (ribbons of adjacent interlocking cells slightly overriding one another), palisades (parallel rows of cells), or nests (clumps of cells surrounded by stroma).[26]

Both apoptotic and mitotic figures are frequent, with an average of 60 mitoses per 2 mm^2 (8–10 high-powered fields).[24] Mitotic counts distinguish SCLC and LCNEC from the lower-grade pulmonary carcinoid tumors, with a threshold of at least 11 per 2 mm^2 required for diagnosis.

Although immunohistochemistry is not required for diagnosis of SCLC, it reduces interobserver variability by confirming expression of neuroendocrine markers and ruling out non-neuroendocrine lineages.[27] Immunohistochemistry is particularly useful in small biopsies and cytology specimens with crush artifact to distinguish SCLC from crushed carcinoid or lymphoma, as Ki-67 staining should be high (80%–100%) and lymphoid markers negative.[25,28] The classic neuroendocrine markers include synaptophysin, chromogranin A, and neural cell adhesion molecule (NCAM, CD56). Synaptophysin and chromogranin A are components of neurosecretory granules and synaptic vesicles, respectively, and are specific markers of neuroendocrine differentiation in lung tumors. CD56 is more sensitive for SCLC—positive in more than 90% of cases—but is not as specific, as CD56 is expressed in skeletal muscle and leukocyte subsets, as well as in 5% to 15% of NSCLC excluding LCNEC and more than 70% of mesotheliomas.[29–32] A fourth neuroendocrine marker, insulinoma-associated protein 1 (INSM1), has recently entered clinical practice and may have greater sensitivity and specificity than the other three markers alone or in combination.[30,33–36] INSM1 is a transcription factor expressed in developing neuroendocrine tissue during embryogenesis, and its nuclear localization may aid in straightforward diagnosis of SCLC.[29,37] All four neuroendocrine IHC markers (synaptophysin, chromogranin A, CD56, INSM1) may be negative or low in 10% of SCLC cases that nevertheless meet morphologic criteria for diagnosis.[29] Emerging research suggests that a substantial fraction of these neuroendocrine-low SCLC cases may be driven by POU domain class 2 transcription factor 3 (POU2F3), a transcription factor that normally regulates chemosensory tuft cell development, but this tuft-cell variant has not yet impacted diagnosis or clinical management.[38,39]

Non-neuroendocrine lung tumors that may mimic the cellular morphology and tissue architecture of SCLC include basaloid squamous cell carcinoma, poorly differentiated adenocarcinoma, NUT carcinoma, melanoma, lymphoma, Ewing sarcoma, and desmoplastic small round cell tumor (DSRCT).[24] In addition to absence of neuroendocrine markers, positive immunohistochemical markers may be used to exclude these diagnoses. Pure SCLC lacks expression for p40 or Napsin A, which mark squamous cell carcinomas and adenocarcinomas, respectively.[40,41] In contrast, TTF-1 (thyroid transcription factor 1, NKX2.1) is positive in the majority (>80%) of both SCLC and adenocarcinoma and does not distinguish these entities.[42–44] SCLC tumors express low-molecular-weight cytokeratins and stain positively with broad-spectrum antibody cocktails such as AE1/AE3. Low or absent cytokeratin staining supports non-epithelial diagnoses such as lymphoma, sarcoma, or melanoma, which may be further distinguished by positive CD45 immunohistochemical staining in lymphoma,

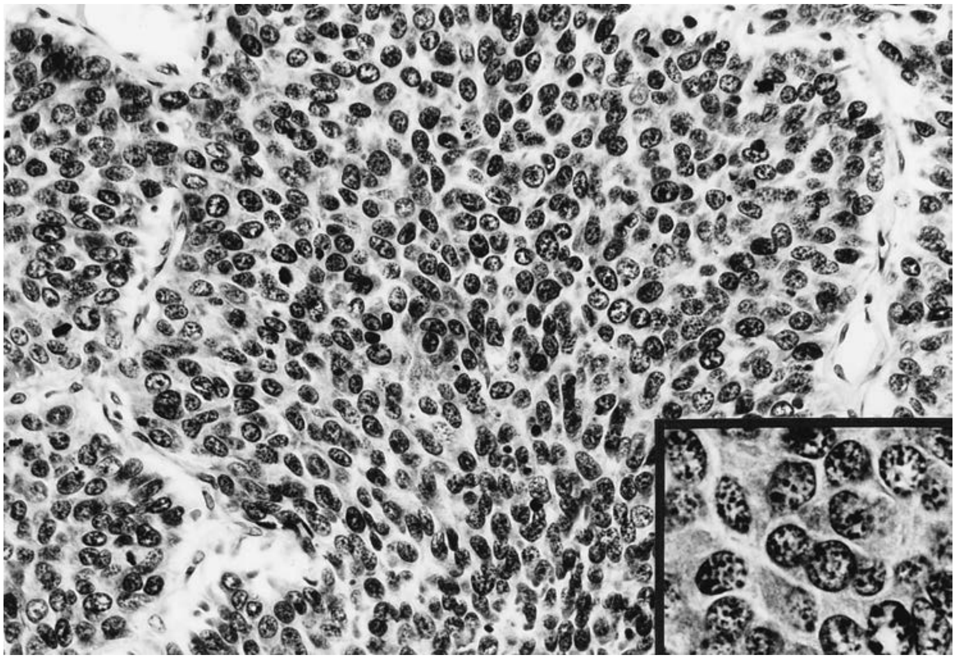

Figure 116-1 Photomicrograph of pure small-cell carcinoma, demonstrating a homogeneous cell population with salt-and-pepper chromatin and moderately prominent nucleoli (H&E, 250×; *inset* 400×). *(Reproduced with permission from Dr. Michael T. Lomis, Vanderbilt University.)*

CD99 in Ewing sarcoma or DSRCT (with desmin), or melanocytic markers such as S-100 in melanoma.[18,45,46] Strong uniform nuclear staining of NUT protein is diagnostic for NUT carcinoma, and this can be confirmed by fluorescence in-situ hybridization (FISH) detection of the *NUTM1* rearrangement.[47] Merkel cell carcinoma is a neuroendocrine skin cancer that may first present as a cancer of unknown primary with bulky mediastinal metastases, mimicking SCLC. These cases may be distinguished by expression of the high-molecular-weight cytokeratin CK20 and absence of TTF-1.[48]

TUMOR BIOLOGY

The genomic drivers of SCLC tumorigenesis have been identified though complementary efforts to discover recurrent alterations in human tumors and cell lines, and to test the tumorigenic potential of these alterations in genetically engineered mouse models (GEMMs). The first SCLC genome was reported in 2010 and sequenced from a cell line established at the National Cancer Institute Navy Medical Oncology Branch in 1979, NCI-H209.[49,50] This cell line demonstrated the three genomic hallmarks of SCLC: (1) a high tumor mutational burden with a predominant C>A transversion signature due to tobacco carcinogens, (2) biallelic loss of Retinoblastoma 1 (*RB1*), the first gene ever identified as a tumor suppressor, and (3) biallelic loss of tumor protein 53 (*TP53*), the most commonly mutated gene in human cancer.[18,51–53] In mice, pulmonary neuroendocrine cells engineered for deletion of *RB1* and *TP53* produce SCLC tumors with a 10- to 12-month latency, confirming that these alterations drive tumorigenesis.[54]

SCLC is almost never surgically resected or biopsied after diagnosis, and the scarcity of fresh-frozen specimens has restricted genomic profiling. Despite a higher incidence than glioblastoma, acute myeloid leukemia, or diffuse large B-cell lymphoma, SCLC is not represented among the 37 cancers sequenced in the Cancer Genome Atlas.[5,55] The NCI-H209 genome was followed by two small studies of primary tumors, representing 36 and 29 patients.[56,57] The largest effort to date, published in 2015, scoured global tissue repositories to obtain 110 fresh-frozen samples suitable for whole genome sequencing.[58] For these studies, tumor samples were obtained almost exclusively from untreated patients and enriched for early-stage disease. These studies confirmed the near-universal loss of *RB1* and *TP53* observed in cell lines, but these mutations cannot be targeted by current therapies and are so prevalent that they do not define SCLC subclasses that might respond to different therapies. Mutations in *RB1* and *TP53* are both tumor-defining and clinically inert.

Genomic profiles of SCLC have not revealed targetable oncogenic drivers, such as the activating mutations in *EGFR* and rearrangements in *ALK* that began the era of targeted therapy in NSCLC.[59–62] However, recurrent genomic alterations that occur in subsets of cases have been demonstrated to drive SCLC tumorigenesis or promote tumor growth in laboratory models, and may serve as future targets for new therapies. These include amplifications in MYC family genes (*MYC, MYCL1,* and *MYCN*), *BCL2, SOX2,* and *FGFR1*; inactivating mutations in the RB-related genes *RBL1* (p107) and *RBL2* (p130); mutations in histone modifying enzymes *CREBBP*, *EP300*, *MLL,* and *KMT2D;* inactivation of NOTCH family receptors *NOTCH1-4*; activating mutations in the PI3 kinase (PI3K) catalytic subunit *PIK3CA* or deletion of the opposing phosphatase *PTEN*; and dominant negative mutations in the tumor suppressor *TP73*.[56–58,63–79] None of these genomic alterations is present in more than 15% of cases, and only the MYC family amplifications and NOTCH family mutations are mutually exclusive, with the caveat that these relationships are imprecise due to the small number of samples.

Gene expression profiles of SCLC have provided more fertile ground for development of new treatment strategies. Differential expression of PARP1 (poly-ADP-ribose polymerase 1) between SCLC and NSCLC led to the discovery that SCLC cells are exquisitely sensitive to PARP inhibitors in vitro, and promising early-phase trials of PARP inhibitor combinations have been reported or are accruing as of 2021.[80–82] Similarly, the cis-acting NOTCH inhibitor DLL3 (delta-like ligand 3) is not expressed outside the central nervous system and is both sensitive and specific for SCLC. Initial attempts to target DLL3 with antibody–drug conjugates proved highly effective in laboratory models but toxic in patients and remain an active area of translational investigation.[83–85] A molecular subclassification for SCLC has been proposed based on dominant expression of one of four lineage-defining transcriptional regulators: ASCL1, NEUROD1, POU2F3, and YAP1.[86] This subclassification is currently in rough-draft form and undergoing frequent experimental revision, but when more mature it may help to focus development of new therapies on the patients most likely to benefit.[18]

NATURAL HISTORY

The natural history of untreated SCLC is characterized by early dissemination and death. Unlike NSCLC, it is always considered a systemic disease at diagnosis, even if it appears clinically confined to the chest. Postmortem examinations performed on patients who died from other causes shortly after the "complete" surgical resection of their SCLC have demonstrated identifiable metastases in up to 70% of cases.[87] Evidence of distant spread can be found in virtually any organ system. The most common sites of involvement, however, are the liver, bone and bone marrow, and central nervous system (CNS) (Table 116-2).[88] This pattern of spread dictates how the search for metastatic disease is undertaken (see "Staging and Pretreatment Evaluation," below).

Patients with SCLC have a short life expectancy if therapy is not initiated in a timely fashion. The median survival for untreated patients is 4 to 6 months if they have disease that is apparently confined to the chest (limited stage [LS]), and 5 to 9 weeks if they present with metastatic disease. With therapy, survival improves significantly (see "Treatment," below). Chemotherapy with or without irradiation can extend median survival to an average of 14 to 20 months for those with thorax-confined disease and 7 to 10 months for those with more extensive spread. Recent trials indicate that 2-year survival may be as high as 40% for aggressively treated LS patients. Two- to three-year survival remains under 5% for those with metastatic disease.

TABLE 116-2 Involvement of Extrathoracic Sites at Diagnosis After Pretreatment Staging Studies in Small Cell Lung Cancer

Extrathoracic Site	Patients with Finding (%)
Final stage	
Limited stage	30–40
Extensive stage	60–70
Bone	19–38
Liver	17–34
Bone marrow	17–23
Brain	0–14
Lymph nodes	7–25
Soft tissue	3–11

Data from Abrams J, Doyle LA, Aisner J. Staging, prognostic featurs and special considerations in small cell lung cancer. Semin Oncol. 1988;15:261–277 and Ihde DC. Staging evaluation and prognostic factors in small cell lung cancer In Aisner J, ed. Lung cancer. New York, NY; Churchill Livingstone; 1985:241–268.

SCREENING

Lung cancer screening with annual low-dose computed tomography (LDCT) was endorsed by the United States Preventive Services Task Force (USPSTF) in 2013 and first covered by the Centers for Medicare and Medicaid in 2015. Eligible individuals are age 50 to 80 years (USPSTF) or 55 to 77 years (Medicare), have smoked 20 pack-years, and if former smokers have quit within the prior 15 years. In the National Lung Screening Trial (NLST) and in the European NELSON trial, LDCT-based lung cancer screening reduced lung cancer and overall mortality.[89,90] Nevertheless, it remains largely underutilized, with fewer than 5% of eligible patients in the United States undergoing screening.[91]

Although heavy smokers have the greatest likelihood of developing SCLC, the benefit of lung cancer screening appears tied almost exclusively to early detection of NSCLC. In an analysis of 5134 individuals enrolled in 2 lung cancer screening trials, 10 cases of SCLC were reported, accounting for only 6% of the lung cancer cases identified.[92] Notably, these patients had median cumulative tobacco consumption of 82 pack-years, compared to 39 pack-years for the overall study population and 46 pack-years for subjects diagnosed with NSCLC. At diagnosis, stage distribution was as follows: IV (70%), III (20%), I (10%). None of the patients survived 3 years. This experience mirrors that in the NELSON trial, where SCLC accounted for only 7% of reported tumors, and only half of these cases were initially detected by LDCT.[90]

STAGING AND PRETREATMENT EVALUATION

Staging a cancer defines the anatomic extent of the tumor, helps determine prognosis, and guides treatment options. The official staging for SCLC is the same as for NSCLC and utilizes the American Joint Cancer Commission staging system, which defines stage based on the extent of the primary tumor, the degree of nodal involvement, and the presence or absence of distant metastasis (TNM staging). Virtually all clinicians, however, prefer the original staging system for SCLC proposed several decades ago by the Veterans Affairs Lung Cancer Study Group as it better segregates patients into two groups with clearly different prognoses and treatment options. In this system, disease confined to one hemithorax that is able to be encompassed by a single, tolerable radiation port is considered LS.[93] This typically includes patients with hilar, mediastinal, and ipsilateral supraclavicular lymphadenopathy. There is debate regarding whether patients with contralateral hilar and supraclavicular lymphadenopathy or those with ipsilateral pleural effusion should be placed in the LS category. However, most clinical trials for LS disease exclude these patients. Any spread of disease beyond the extent described earlier is defined as extensive-stage (ES) disease. A third stage ("very limited-stage [VLS] disease") has been proposed by some to define those patients with small primary tumors and no identifiable regional lymphadenopathy or distant metastases, as this group of patients may be considered for surgery (see "Treatment," below). In most modern series, the majority of patients (60%–65%) present with ES disease, with LS (30%–35%) and VLS (<5%) making up the remainder.[13,94]

Once a diagnosis of SCLC is established the initial pretreatment evaluation should include a complete history and physical examination, and basic laboratory studies including a complete blood count (CBC), serum electrolytes, and liver and renal function tests. A serum lactate dehydrogenase (LDH) level may provide additional prognostic information (see "Prognostic Factors," below). Current guidelines call for CT scans of the chest (including the liver and adrenal glands) as initial imaging. Some 10% to 18% of SCLC patients have brain involvement at presentation,[95,96] and it is therefore recommended by many that all patients with SCLC undergo imaging of the brain at diagnosis, preferably magnetic resonance imaging (MRI). Certainly, those patients with symptoms suggesting brain involvement require prompt evaluation.

Bone metastases from SCLC are also frequent at presentation. Historically, bone scan was the study of choice to evaluate those patients with bony symptoms or an elevated alkaline phosphatase suggesting possible spread of disease to the bone. Fluorodeoxyglucose positron emission tomography (FDG-PET) has supplanted bone scan at most centers. SCLC is a highly metabolically active tumor and is therefore typically quite FDG avid at both the primary and metastatic sites. Case series suggest that PET scan can improve staging accuracy in SCLC and that PET will correctly upstage as many as 19% of patients previously thought to have LS disease.[97–102]

Another staging procedure of historic interest is bone marrow biopsy and aspiration. SCLC is one of a few cancers known to commonly cause bone marrow metastases, and as a result, bone marrow evaluation was standard in SCLC patients for many years. However, most patients with bone marrow involvement have significant abnormalities on their CBC (notably leukoerythroblastosis), and exceedingly few patients have bone marrow as the only site of metastasis. Therefore, the utility of this test appears limited to those few patients with LS disease after complete radiographic staging who have an abnormal CBC.

In general, with the possible exception of brain imaging to rule out occult disease, once the presence of metastatic SCLC has been established, further radiographic evaluation to identify additional sites of metastatic disease is not warranted. In that setting, subsequent evaluation should be symptom guided.

CLINICAL PRESENTATION

No aspect of the clinical presentation of SCLC distinguishes it from NSCLC or even from neoplasms metastatic to the lungs. However, the duration of time from the development of symptoms to the diagnosis of SCLC tends to be very short, due to the rapid dissemination of the disease. The typical patient is a middle-aged or elderly smoker who presents with symptoms attributable to pulmonary and mediastinal disease: cough, dyspnea, chest pain, hoarseness, and/or hemoptysis. Because of the usual endobronchial location of the tumor, patients often have accompanying postobstructive pneumonia.

Constitutional symptoms may include weakness, anorexia, weight loss, and, rarely, fever. Symptoms may also arise from distant metastases, including headache or seizures in patients with CNS disease, and abdominal or bone pain with hepatic and osseous metastases. Symptoms may also reflect regional spread with attendant superior vena cava obstruction, manifesting as facial fullness, upper extremity swelling, headache, and dysphagia. In rare instances, patients present with symptoms from a paraneoplastic syndrome. The more common of these rare presentations are syndrome of inappropriate antidiuretic hormone secretion (SIADH) and other causes of hyponatremia, Cushing syndrome, Lambert–Eaton syndrome, and other paraneoplastic neuropathies or neurologic disorders (see "Paraneoplastic Phenomena," below).

Physical examination may yield only the stigmata of chronic obstructive pulmonary disease, or it may demonstrate lymphadenopathy, hepatomegaly, bone tenderness, or neurologic findings. Signs of the superior vena cava syndrome include venous distention of the neck and chest wall, cyanosis, facial plethora, and upper extremity edema.

Radiographic studies typically demonstrate a central mass (75% of patients) with or without hilar nodal involvement (Figs. 116-2–116-4). Postobstructive atelectasis and pneumonia are very common with SCLC, but cavitation is rare and suggests the alternative diagnosis of squamous cell lung cancer.

Laboratory evaluation reveals an elevated LDH in about 50% of patients. Liver function tests may be abnormal in those with

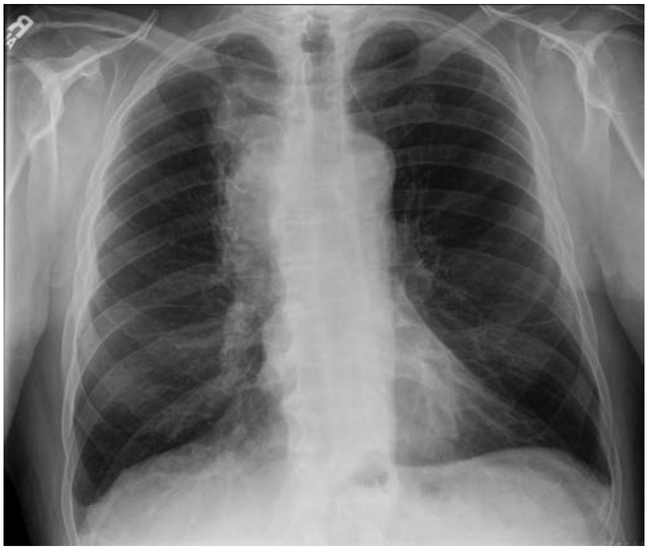

Figure 116-2 Chest radiograph of a patient with SCLC demonstrating increased right paratracheal soft tissue prominence. Note that the right paratracheal line is greater than 3 mm. *(Reproduced with permission from Dr. Matthew J. DeVries, University of Nebraska Medical Center.)*

extensive liver metastases, and isolated elevation of the alkaline phosphatase is seen in patients with bone involvement. In some instances, SCLC infiltrates the bone marrow. In such cases, the CBC reveals pancytopenia with evidence of myelophthisis on the peripheral blood smear (a left shift, nucleated red blood cells, and tear drop cells).

PARANEOPLASTIC PHENOMENA

Certain cancers cause symptoms not attributable to direct tumor invasion or compression. Labeled *paraneoplastic syndromes* in the 1940s, these conditions are primarily due to tumor secretion of functional peptides and hormones (as occurs in endocrine paraneoplastic syndromes [Table 116-3]) or immune cross-reactivity between tumor and normal host tissues (as occurs in neurologic paraneoplastic syndromes [Table 116-4]). Paraneoplastic syndromes may be seen in any type of cancer but historically are most frequently associated with SCLC.

■ Paraneoplastic Endocrinopathy Syndromes

Because paraneoplastic endocrine syndromes are generally due to tumor production of hormones or peptides that lead to metabolic derangements, successful treatment of the underlying tumor often improves these conditions. These disorders are typically detected after a cancer diagnosis. Development of a paraneoplastic endocrine syndrome does not necessarily correlate with cancer stage or prognosis.[103]

Syndrome of Inappropriate Antidiuretic Hormone Secretion

SIADH is characterized by hypo-osmotic, euvolemic hyponatremia. Although it affects only 1% to 2% of all patients with cancer, SCLC accounts for most of these cases, with approximately 10% to 45% of all patients with SCLC developing SIADH.[104] In SIADH, tumor cells produce ADH (also known as arginine vasopressin or vasopressin) and atrial natriuretic peptide.[105,106]

The symptoms of SIADH depend on the degree and rapidity of onset of hyponatremia. Mild symptoms include headache, memory difficulties, and weakness. More severe symptoms (altered mental status, seizures, coma, respiratory collapse, death) may be seen with serum sodium levels less than 125 mEq/L, especially if developing within 48 h.[107] If hyponatremia develops over a longer time period, neurologic complications may not develop.

The time course of hyponatremia also impacts treatment. With symptomatic hyponatremia developing within 48 h, the serum sodium level may be raised 1 to 2 mEq/L/h and usually no more than 8 to 10 mEq/L in the first 24 h. With chronic hyponatremia, due to the brain generating endogenous osmoles to minimize intracellular swelling, rapid correction may lead to water egress, brain dehydration, and central pontine and extrapontine myelinolysis. This condition, which may be irreversible, features lethargy, dysarthria, spastic

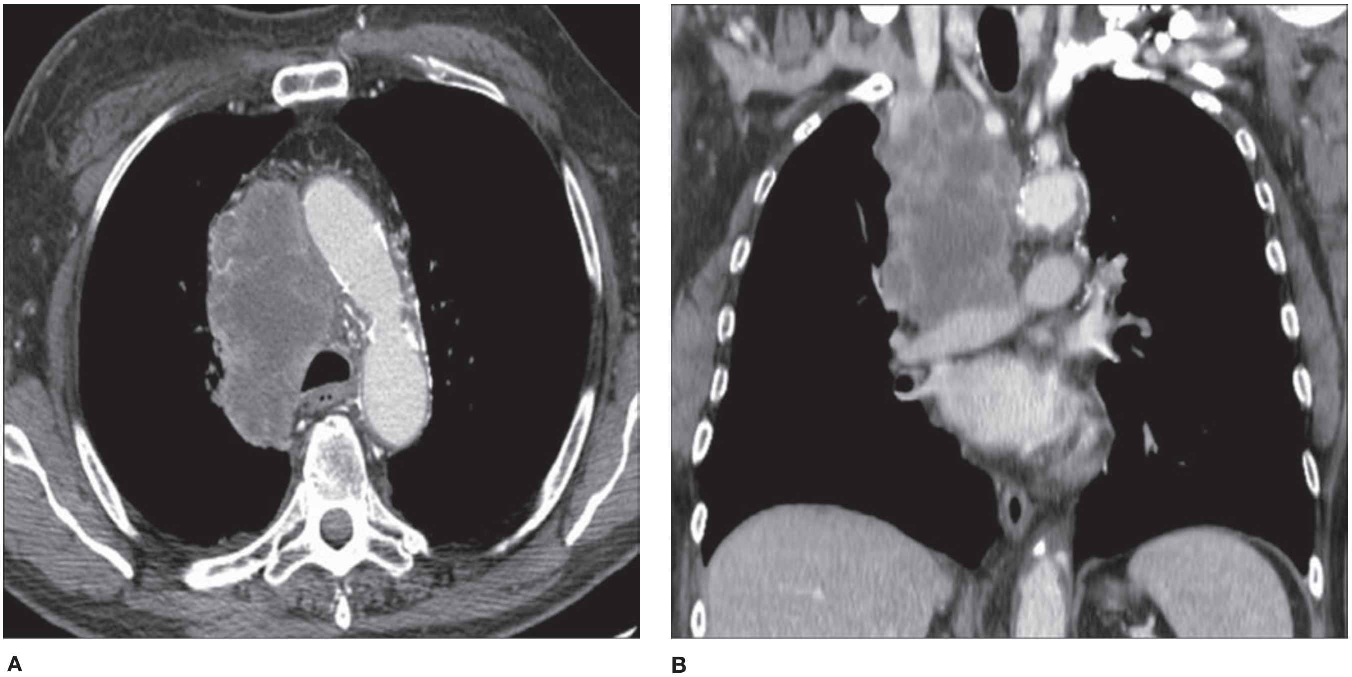

Figure 116-3 Axial (**A**) and coronal (**B**) CT images of the chest of a patient with SCLC demonstrating a large, heterogeneous mass extending through the right mediastinum. *(Reproduced with permission from Dr. Matthew J. DeVries, University of Nebraska Medical Center.)*

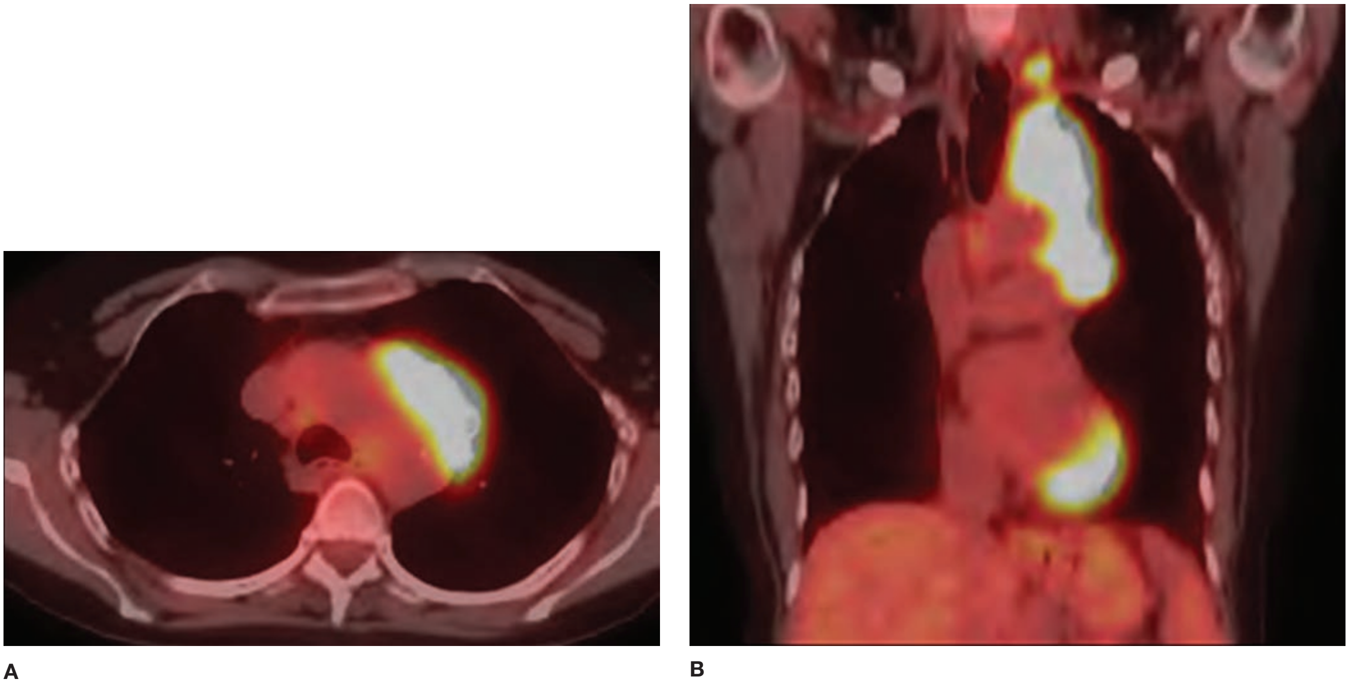

Figure 116-4 Axial (**A**) and coronal (**B**) fused PET/CT images of a patient with SCLC show increased glucose avidity along the left mediastinal boarder. *(Reproduced with permission from Dr. Matthew J. DeVries, University of Nebraska Medical Center.)*

quadriparesis, and pseudobulbar palsy. Accordingly, a correction goal of 0.5 to 1.0 mEq/L is recommended for these patients.[104,107]

Successful treatment of the underlying tumor (which is frequently attainable given the chemosensitivity of SCLC) may normalize sodium levels in days to weeks.[104] In the short term, free water restriction (usually <1000 mL/d) along with adequate dietary protein and sodium (with the use of salt tablets if needed) may be implemented. In many instances, administration of standard intravenous fluids may exacerbate SIADH. Normal (0.9%) saline has an osmolality of 308 mOsm/kg, which is often less than urine osmolality in SIADH. Thus, normal saline infusion will result in free water retention and worsening of the hyponatremia. By contrast, hypertonic (3%) saline has an osmolality of 1026 mOsm/kg, which almost always exceeds that of the urine. The primary pharmacologic treatment of SIADH is demeclocycline (usually given at a dose of 300–600 mg per day, but can be increased to 1200 mg per day), an antibacterial agent that interferes with the renal response to ADH. In patients on demeclocycline responding to chemotherapy, careful monitoring is required to ensure against overcorrection and resulting hypernatremia.

TABLE 116-3 Selected Paraneoplastic Endocrine Syndromes Occurring in Small Cell Lung Cancer

Syndrome	Presentation/Symptoms	Laboratory Values	Management/ Treatment[a]
SIADH	Gait disturbances, falls, headache, nausea, fatigue, muscle cramps, anorexia, confusion, lethargy, seizures, respiratory depression, coma	Hyponatremia Mild = serum sodium 130–134 mmol/L Moderate = serum sodium 125–129 mmol/L Severe = serum sodium <125 mmol/L Increased urine osmolality (>100 mOsm/kg in the context of euvolemic hyponatremia)	Fluid restriction (and encourage adequate salt and protein intake) Discontinuation of offending drugs Demeclocycline Vasopressin-receptor antagonists Conivaptan Tolvaptan Hypertonic (3%) saline *(if acute onset)*
Cushing syndrome	Muscular weakness, peripheral edema, hypertension, weight gain	Hypokalemia typically <3.0 mmol/L Elevated baseline serum cortisol >800 nmol/L Normal to elevated midnight serum ACTH (not suppressed with dexamethasone) >100 ng/L	Ketoconazole Octreotide Aminoglutethimide Metyrapone Mitotane Etomidate Mifepristone

[a] *In addition to treating the underlying malignancy.*

ACTH, adrenocorticotropic hormone; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

Adapted with permission from Pelosof LC, Gerber DE. Paraneoplastic Syndromes: an Approach to Diagnosis and Treatment. Mayo Clin Proc. 2010;85(9):838–854.

TABLE 116-4 Selected Paraneoplastic Neurologic Syndromes Occurring in Small Cell Lung Cancer

Syndrome	Clinical Presentation	Associated Antibodies	Additional Diagnostic Studies	Management/ Treatment
Limbic encephalitis (LE)	Mood changes, hallucinations, memory loss, seizures, less commonly hypothalamic symptoms (hyperthermia, somnolence, endocrine dysfunction); onset over days to months	anti-Hu (ANNA-1) anti-CRMP5 (anti-CV2) anti-Ma anti-amphiphysin	**EEG** epileptic foci in temporal lobe(s); focal or generalized slow activity **FDG-PET** increased metabolism in temporal lobe(s) **MRI** hyperintensity in medial temporal lobe(s) **CSF** pleocytosis, elevated protein, elevated IgG, oligoclonal bands	IVIG Corticosteroids Plasma exchange Cyclophosphamide Rituximab
Paraneoplastic cerebellar degeneration (PCD)	Ataxia, diplopia, dysphagia/dysarthria; prodrome of dizziness, nausea, vomiting	anti-Hu (ANNA-1) anti-Yo anti-CRMP5 (anti-CV2) anti-Ma anti-Tr anti-Ri anti-VGCC anti-mGluR1	**FDG-PET** increased metabolism (early stage) and then decreased metabolism (late stage) in cerebellum **MRI** cerebellar atrophy (late stage)	IVIG Corticosteroids Plasma exchange Cyclophosphamide Rituximab
Lambert–Eaton myasthenic syndrome (LEMS)	Lower extremity proximal muscle weakness, fatigue, diaphragmatic weakness, bulbar symptoms (usually milder than in myasthenia gravis); later in course, autonomic symptoms (ptosis, impotence, dry mouth) in most patients	anti-VGCC (P/Q type)	**EMG** low compound muscle action potential amplitude; decremental response with low-rate stimulation but incremental response with high-rate stimulation	3,4-Diaminopyridine (DAP) Guanidine Pyridostigmine Corticosteroids Azathioprine IVIG Plasma exchange
Subacute (peripheral) sensory neuropathy	Paresthesias/pain (typically upper extremities before lower) followed by ataxia; multifocal/asymmetric distribution; all sensory modalities decreased but especially deep sensation/pseudoathetosis of hands; deep tendon reflexes decreased/absent; onset over weeks to months	anti-Hu (ANNA-1) anti-CRMP5 (anti-CV2) anti-amphiphysin	**NCS** reduced/absent sensory nerve action potentials **CSF** pleocytosis, high IgG, oligoclonal bands	Corticosteroids Cyclophosphamide IVIG Plasma exchange
Autonomic neuropathy	Panautonomic neuropathy, often subacute (weeks) onset, involving sympathetic, parasympathetic, and enteric systems: orthostatic hypotension, GI dysfunction, dry eyes/mouth, bowel/bladder dysfunction, altered pupillary light reflexes, loss of sinus arrhythmia *Chronic gastrointestinal pseudo-obstruction* *(CGP):* Constipation, nausea/vomiting, dysphagia, weight loss, abdominal distension	anti-Hu (ANNA-1) anti-CV2 (CRMP5) anti-nAchR anti-amphiphysin	**Abdominal x-ray/barium studies/ CT** GI dilatation but no mechanical obstruction (for CGP) **Esophageal manometry** achalasia or spasms (for CGP)	*For orthostatic hypotension:* Water, salt intake Fludrocortisone Midodrine Caffeine *For pseudo-obstruction:* Neostigmine

ANNA, antineuronal nuclear antibody; CRMP, Collapsin Response Mediator Proteins; CSF, cerebrospinal fluid; CT, computed tomography; EEG, electroencephalogram; EMG, electromyography; FDG-PET, fluorodeoxyglucose positron emission tomography; IVIG, intravenous immunoglobulin; mGluR1, metabotropic glutamate receptor subtype 1; MRI, magnetic resonance imaging; nAchR, nicotinic acetylcholine receptor; NCS, nerve conduction study; VGCC, voltage-gated calcium channel.

Adapted with permission from Pelosof LC, Gerber DE. Paraneoplastic Syndromes: an Approach to Diagnosis and Treatment. Mayo Clin Proc. 2010;85(9):838–854.

Cushing Syndrome

Approximately 5% to 10% of cases of Cushing syndrome (hypercortisolism) are paraneoplastic, and 50% to 60% of these paraneoplastic cases occur with neuroendocrine lung tumors (SCLC and bronchial carcinoids).[108] Paraneoplastic Cushing syndrome is due to tumor secretion of adrenocorticotropic hormone (ACTH) or corticotropin-releasing factor (CRF). In turn, this results in adrenocortical hyperplasia and release of cortisol. Clinical features include hypertension, hypokalemic metabolic alkalosis, hyperglycemia, edema, and muscle weakness. Compared to Cushing disease (i.e., hypercortisolism due to a pituitary adenoma) onset is often more abrupt and weight gain with centripetal fat distribution is less common.

Ectopic (i.e., paraneoplastic) Cushing syndrome is distinguished from a pituitary source by failure to respond to high-dose dexamethasone suppression. For this test, 2 mg of dexamethasone is administered orally every 6 h for 72 h. Levels of urine 17-hydroxycorticosteroid (an inactive product of cortisol metabolism) are measured at 9:00 A.M. and midnight of days 2 and 3 of the test. The test is considered positive if 17-hydroxycorticosteroid levels are reduced by 50% or more. Due to the distinct biochemical profile of paraneoplastic Cushing syndrome, inferior petrosal sinus sampling (to rule out a pituitary etiology) is generally not required.[108]

Therapy includes treatment of the underlying tumor and agents that inhibit steroid production. These include ketoconazole, mitotane, metyrapone, and aminoglutethimide. Ketoconazole is usually the best tolerated of these options, despite nausea, hepatotoxicity, and potential for drug–drug interactions. Supportive care includes antihypertensive agents and diuretics, with careful monitoring of serum potassium. Adrenalectomy may be considered when medical therapy is not successful.

Other Paraneoplastic Endocrine Syndromes

Although paraneoplastic hypercalcemia can be seen with several malignancies (including squamous NSCLC, breast, renal, and lymphoma), it is extremely unusual in patients with SCLC, even among cases with skeletal involvement. Similarly, tumor-associated hypoglycemia, a rare paraneoplastic phenomenon occurring most commonly in sarcomas, mesothelioma, and gastrointestinal cancers, also is unusual in SCLC.

■ Paraneoplastic Neurologic Syndromes

Immune cross-reactivity between tumor cells and components of the nervous system gives rise to paraneoplastic neurologic syndromes. Onconeural antibodies are produced by a patient in response to a developing cancer. Due to antigenic similarity, these onconeural antibodies and associated T lymphocytes inadvertently attack the nervous system as well.[109] Although paraneoplastic neurologic syndromes occur in less than 1% of cancer patients overall, they are seen in up to 5% of patients with SCLC.[110] The potential for immune cross-reactivity with SCLC is apparent through its immunophenotypic profile. CD56, which is positive in the majority of SCLC cases, is also known as neural cell adhesion molecule (NCAM).

In direct contrast to paraneoplastic endocrine syndromes, more than 80% of cases of paraneoplastic neurologic syndromes are detected prior to a cancer diagnosis.[103] Because most patients diagnosed with an apparent paraneoplastic neurologic syndrome will not have known cancer at the time, screening for an underlying tumor is indicated. This process includes complete history and physical examination, as well as imaging studies. If chest, abdomen, and pelvic CT scans are negative, FDG-PET or combined PET-CT may identify the underlying tumor, particularly in the case of an early central SCLC, which may be difficult to identify anatomically amid surrounding mediastinal structures.[111]

Because tumor cells do not directly produce the causative agents (i.e., onconeural antibodies) and because these antibodies may cause permanent neuronal damage, successful cancer treatment does not necessarily result in neurologic improvement. Immunosuppressive therapy—including corticosteroids, other agents, intravenous gamma globulin, and plasma exchange—is a principal component of therapy.

Establishing a diagnosis of a paraneoplastic neurologic syndrome may require imaging, serologies, electroencephalography, electromyography, nerve conduction studies, and cerebrospinal fluid (CSF) analysis for signs of inflammation. Onconeural antibodies lack both sensitivity and specificity, as up to 30% of patients with apparent paraneoplastic neurologic syndromes do not have detectable antibodies and well-defined onconeural antibodies may be detected in individuals with no neurologic illness.[112]

The impact of these conditions on prognosis is complex and multifactorial. Development of a paraneoplastic neurologic syndrome may result in diagnosis of a cancer at an otherwise clinically occult and highly treatable stage. Conversely, the syndrome itself may cause substantial morbidity, independent of the underlying malignancy. Finally, onconeural antibodies may indicate an antitumor immunologic effect; patients with SCLC who have anti-Hu antibodies are more likely to have complete response to therapy and have longer survival than patients without anti-Hu antibodies.[113] While such observations raise the question whether treatment of paraneoplastic neurologic syndromes with immune modulation could lead to cancer progression, this hypothetical scenario has not been reported clinically.[103]

The autoimmune etiology of these paraneoplastic syndromes raises the hypothetical concern that immunotherapy therapy might increase the incidence or severity of these conditions. However, in phase 3 clinical trials, the addition of immune checkpoint inhibitors to platinum-etoposide chemotherapy did not result in increased autoimmune paraneoplastic syndromes, and rates of immune-related adverse events overall were comparable to those in NSCLC and other oncology patient populations.[114,115]

In SCLC, well-described paraneoplastic neurologic syndromes include limbic encephalitis (LE), cerebellar degeneration, Lambert–Eaton myasthenic syndrome (LEMS), subacute (peripheral) sensory neuropathy, optic neuropathy, and autonomic neuropathy.

Limbic Encephalitis

LE features mood changes, hallucinations, memory loss, seizures, and less commonly hypothalamic symptoms (hyperthermia, somnolence, endocrine dysfunction), with onset over days to months. In SCLC, which accounts for 40% to 50% of LE cases, the associated antibody is usually anti-Hu (also known as antineuronal nuclear antibody 1 [ANNA-1]). Characteristic findings may also be seen on electroencephalogram, MRI, and CSF analysis.[116]

Paraneoplastic Cerebellar Degeneration

Paraneoplastic cerebellar degeneration (PCD), manifesting with ataxia, dysarthria, and diplopia, is seen with SCLC (incidence approximately 2%), as well as with gynecologic malignancies and lymphomas. Antibodies that react against cytoplasmic proteins of cerebellar Purkinje cells are often found in these patients. One such antibody, anti-Yo, attacks the cdr2 proteins in the Purkinje cells. Treatment may include steroids, plasmapheresis, and chemotherapy.

Lambert-Eaton Myasthenic Syndrome

LEMS is a result of IgG autoantibodies directed against presynaptic P/Q-type voltage-gated calcium channels. These antibodies are estimated to occur in 5% of patients with SCLC. Clinically, the syndrome presents with proximal muscle weakness, usually in the lower extremities, occasional autonomic dysfunction, and rarely with cranial nerve symptoms. As contrasted with patients with myasthenia gravis, strength *improves* with serial effort, and the weakness associated with LEMS improves over the course of the day. Plasma exchange and intravenous immunoglobulin can provide short-term benefit, whereas 3,4-diaminopyridine (which enhances the release of acetylcholine from presynaptic terminals), prednisone, and azathioprine can provide limited long-term benefit. Some patients who respond to chemotherapy have resolution of the neurologic abnormalities.

Subacute Peripheral Sensory Neuronopathy

With onset over weeks to months, this syndrome initially features paresthesias and pain (typically multifocal, asymmetric, with upper extremities involved before lower), followed by ataxia. Nerve conduction studies demonstrate reduced or absent sensory nerve action potentials. A number of onconeural antibodies, including anti-Hu, may be seen. Lung tumors (principally SCLC) account for 70% to 80% of cases.

Optic Neuropathy

Paraneoplastic optic neuropathy (PON) also has been reported in association with SCLC. The most common presentation is painless visual loss in association with optic disc edema. It may occur in isolation or along with other neurologic syndromes (often neuropathic disorders, limbic encephalitis, or cerebellar degeneration). Many PON patients have antibodies to collapsin response mediator protein 5 (CRMP-5 or anti-CV2), often in conjunction with other paraneoplastic autoantibodies. Clinical improvement has been described with treatment of the underlying cancer and with steroids.[117]

Autonomic Neuropathy

Paraneoplastic autonomic neuropathy typically has a subacute onset over weeks and may involve sympathetic, parasympathetic, and enteric systems.[118,119] Symptoms include orthostatic hypotension, gastrointestinal dysfunction (pseudo-obstruction), and dry eyes and mouth. A number of onconeural antibodies, including anti-Hu and anti-CRMP5 (anti-CV2), may be detected.[120] Other findings suggestive of this condition are loss of sinus arrhythmia (naturally occurring variation in heart rate that occurs during a breathing cycle) on ECG, GI dilation without obstruction on abdominal imaging, and achalasia or spasms on esophageal manometry. Supportive care may include fludrocortisones, midodrine, caffeine, and neostigmine (for pseudo-obstruction).[121]

EXTRAPULMONARY SMALL-CELL CARCINOMA

The knowledge that small cell cancers can arise from tissues other than the lungs has existed since 1930.[122] Extrapulmonary small-cell cancer (EPSCC) remains relatively rare, accounting for <5% of diagnosed small-cell cancers.[123] EPSCC can arise from a variety of primary sites, including the female genital tract (commonly the uterine cervix), the genitourinary organs (primarily bladder and prostate), the head and neck, the gastrointestinal tract, and breast.[124,125]

Staging of EPSCC is similar to that of SCLC. LS is defined as disease confined to the primary site and regional lymph nodes. Any spread beyond the regional lymph nodes is ES disease. It is recommended to perform the same staging evaluation on these patients as in those with SCLC.

Due to the rarity of this entity, the optimal treatment of EPSCC is not clearly defined. Most case series are from single institutions and include EPSCC from a variety of primary sites. In general, the treatment approaches have been adapted from those utilized in SCLC. Surgery has been shown to be curative in selected patients with organ-confined disease. Unfortunately, as with SCLC, EPSCC is often characterized by early metastasis and a fairly aggressive course. Combined chemotherapy and radiation can be utilized for LS disease. ES EPSCC responds to platinum-based chemotherapies in approximately 75% of the cases, but these responses are typically short-lived. In a large retrospective single institution review from Australia, those EPSCC patients with LS disease had a median survival of 1.4 years and a 1-year survival rate of 63%, while those with ES stage disease had median and 1-year survivals of 0.7 years and 24%, respectively.[125] In their cohort, patients with a primary lesion in the female genital tract or the head and neck had superior outcomes when compared with other primary sites. Given the recent approval of immune checkpoint inhibitors given with platinum-based chemotherapy in ES SCLC (see “Immunotherapy,” below), it is reasonable to utilize a similar approach in ES EPSCC.

PROGNOSTIC FACTORS

A variety of pretreatment factors have been reported to have value in predicting therapeutic outcomes for patients with SCLC. Since the aggressiveness of therapy may depend on this perceived outcome, it is important to determine before treatment how a patient is likely to do. The strongest prognostic factors for SCLC are stage of disease (limited vs. extensive) and performance status at presentation. The importance of stage has already been mentioned. ES patients have a lower chance of achieving a complete response to chemotherapy and a much shorter survival than those with LS disease. The performance status or ability of the patient to carry out normal daily activities has a profound effect on both the ability to tolerate chemotherapy and the efficacy of the drugs that are administered (Table 116-5). In general, SCLC patients with a poor performance status have a lower chance of response to chemotherapy, a higher probability of experiencing clinical toxicity, and a worse overall survival.[126–128] However, as opposed to NSCLC patients, poor performance status does not automatically exclude SCLC patients from receiving aggressive treatment. Occasionally, SCLC patients with significant functional impairment can experience improvement with chemotherapy.

Beyond stage and performance status, for treatment-naïve SCLC the clinical features that impact prognosis are presence of a paraneoplastic syndrome, continued use of tobacco, and serum LDH. As mentioned above, LEMS is the most common paraneoplastic neurologic syndrome, developing in 3% to 4% of SCLC patients,[129–131] and in both retrospective and prospective studies LEMS correlates with a marked and significant increase in overall survival.[130,132–134] The only serum marker consistently shown to be of prognostic value in SCLC is the serum concentration of LDH, a nonspecific marker of cell turnover and pulmonary inflammation. Baseline LDH is elevated in 33% to 57% of all SCLC patients and in as many as 85% of patients with ES disease. In a contemporary population of 397 SCLC patients treated from 2004 to 2008, LDH proved to be a strong prognostic marker independent of stage and performance status.[136] In this study, median overall survival was 12 months versus 18 months for LS patients with elevated and normal LDH, respectively; it was 7 months versus 12 months for ES patients with elevated versus normal values. Finally, in addition to its primary role in SCLC tumorigenesis, continued cigarette smoking after diagnosis is an adverse prognostic factor. In a study of 284 patients with LS SCLC treated from 1997 to 2008 at the Mayo Clinic, smoking cessation was at least as significant as performance status, reducing risk of death by 45%.[136]

Treatment-naïve SCLC is remarkably sensitive to chemotherapy—so much so that there was initial optimism that cure could be achieved by escalating drug combinations and regimen dosages, as with some lymphomas.[137] First-line therapy with etoposide-platinum with or without atezolizumab has an overall response rate of 50% to 70%,[138] approximately twice that of first-line therapy for NSCLC.[139] However, relapse is nearly inevitable, at which point

TABLE 116-5 Performance Status Scales

KARNOFSKY			ECOG	
Able to carry on normal activity and to work; no special care needed	100	Normal no complaints; no evidence of disease	0	Fully active, able to carry on all predisease performance without restriction
	90	Able to carry on normal activity; minor signs or symptoms of disease	1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
	80	Normal activity with effort; some signs or symptoms of disease		
Unable to work; able to live at home and care for most personal needs, varying amount of assistance needed	70	Cares for self; unable to carry on normal activity or to do active work	2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
	60	Requires occasional assistance, but is able to care for most of his personal needs		
	50	Requires considerable assistance and frequent medical care	3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly	40	Disabled; requires special care and assistance		
	30	Severely disabled; hospital admission is indicated although death not imminent	4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
	20	Very sick; hospital admission necessary; active supportive treatment necessary		
	10	Moribund; fatal processes progressing rapidly		
	0	Dead	5	Dead

Data from Schag CC, Heinrich RL, Ganz PA. Karnofsky performance status revisted: reliability, validity, and guidelines. J Clin Oncology. 1984;2(3):187–193; Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649–655.

SCLC often becomes resistant to further DNA damaging agents; response rates in the second line plummet to approximately 20%, and benefit is brief (~3 months). Following relapse, the strongest known prognostic factor is the duration of response to first-line therapy—significantly stronger than performance status. Disease progression within 90 days of etoposide-platinum portends a dismal outcome (15% response rate, 5.5-month survival) regardless of regimen.[140] Consequently, relapsed SCLC can be reasonably divided into platinum-sensitive versus platinum-resistant disease.

TREATMENT

The roles of surgery, chemotherapy, and radiation in the treatment of SCLC are considered below. In addition, special circumstances, including treatment in the elderly and in those with poor performance status, are discussed.

■ Surgery

Surgery was abandoned as a standard treatment modality for the majority of patients with SCLC in the 1970s following the publication of the results of a trial by the British Research Medical Council randomizing patients with LS disease to single-modality treatment with radiation or surgery. Although outcomes were poor in both treatment arms, the 5- and 10-year survival rates were significantly inferior with surgery.[141] A subsequent Lung Cancer Study Group trial also failed to demonstrate a benefit to surgery when compared with radiation in 340 LS patients following induction chemotherapy.[142] A legitimate criticism of these trials is that patients were inadequately staged when compared with modern standards. In addition, in both trials, only a small fraction of eligible patients had clinical stage I and II disease, which are the groups theoretically most likely to benefit from resection.

Over the past decade, there has been a renewed interest in surgery as a potential treatment modality for highly selected patients with VLS SCLC. A number of primarily retrospective single institution series have reported outcomes with surgery followed by adjuvant chemotherapy (and sometimes radiation) in patients with VLS SCLC. In patients with pathologic stage I disease, the 5-year survival ranged from 40% to 86%.[143–145] In addition, analyses of the Surveillance, Epidemiology, and End Results (SEER) database and the National Cancer Database have shown improved outcomes for those patients with VLS SCLC who are treated with surgery.[94,146,147] Unfortunately, interpretation of these retrospective series and database reviews is hampered by inherent selection bias as well as by the heterogeneity of adjuvant treatment (chemotherapy and radiation) utilized.

Current guidelines suggest that surgical resection should be considered only in patients with clinical stage I (T1 or T2, N0, M0) SCLC and with adequate cardiac and pulmonary function to tolerate a thoracotomy. Patients should undergo rigorous staging, including invasive evaluation for mediastinal nodal disease as well as extensive radiographic assessment for distant metastases. Following complete resection, it is recommended that patients without nodal metastases receive adjuvant chemotherapy and that those with nodal metastases receive concurrent chemotherapy and radiation. Prophylactic cranial irradiation (PCI) can also be considered in selected patients (see "Prophylactic Cranial Irradiation," below). At most centers, fewer than 5% of SCLC patients (primarily those who cancers were discovered incidentally) are considered candidates for a surgical approach.[143]

■ Chemotherapy

Chemotherapy for SCLC can be considered with regard to first-line and second-line regimens.

First-Line Chemotherapy

In contrast to NSCLC, SCLC is classically associated with exquisite chemosensitivity, which may reflect its rapid doubling time and high growth fraction. In reality, the difference in treatment outcomes is modest with comparable median survivals in SCLC and NSCLC following chemotherapy for metastatic disease. Numerous chemotherapeutic agents have demonstrated activity in SCLC (Table 116-6). Untreated, patients with SCLC rarely survive more than a few months. Chemotherapy markedly prolongs survival compared to best supportive care.[148] In LS disease, chemotherapy combined with thoracic radiation achieves a response in 80% to 90% of patients, and a complete response in the range of 40% to 60%. In LS disease, median survival in treated patients is 15 to 20 months, with 5-year survival rates of 10% to 13%. In ES disease, the response rate is 60% to 80%, with a complete response rate around 15% to 35%. The median survival for ES patients treated with chemotherapy remains 7 to 9 months, with few long-term survivors. Patients with bulky or ES disease may be considered at risk for tumor lysis syndrome, although this event is quite rare in clinical practice. Prophylaxis against this complication, which generally includes hydration and allopurinol, may be considered.[149] It should also be noted that systemic chemotherapy frequently yields intracranial responses in patients with brain metastases, with response rates ranging from 27% to 85%.[150,151]

The earliest treatments for SCLC included alkylating agents, such as nitrogen mustard and subsequently cyclophosphamide, given as monotherapy. As responses to single agents were rare, the focus changed to combinations of drugs, each with independent activity against SCLC. When given in combination, these drugs had synergistic activity and lowered the likelihood of complete tumor resistance. Until the mid-1980s the combination of cyclophosphamide, doxorubicin (Adriamycin), and vincristine (CAV) was commonly used as first-line therapy. For the past three decades, platinum-based regimens have become the most frequently used combinations. A meta-analysis of 19 randomized trials encompassing more than 4000 cases demonstrated an increase in response rates and decrease in risk of death for patients receiving cisplatin-containing chemotherapy.[152]

Currently, the two-drug regimen of cisplatin and etoposide is considered the standard of care for SCLC chemotherapy. In randomized trials, this combination appears to be at least as effective as CAV and has less toxicity.[153,154] The cisplatin-etoposide regimen is typically given over 3 days (cisplatin on day 1, etoposide on days 1–3) every 3 weeks for four to six cycles. Modifications to the cisplatin-etoposide regimen have included the substitution of carboplatin for cisplatin, replacing etoposide (a topoisomerase II inhibitor) with irinotecan or topotecan (topoisomerase I inhibitors), adding other agents, increasing dose intensity, and prolonging the duration of chemotherapy.

TABLE 116-6 Chemotherapeutic and Immunotherapeutic Agents with Activity in Small Cell Lung Cancer

Chemotherapeutic Agents
Platinum compounds (cisplatin, carboplatin)
Podophyllotoxins (etoposide, teniposide)
Camptothecins (irinotecan, topotecan)
Alkylating agents (ifosfamide, cyclophosphamide, lurbinectedin)
Anthracyclines (doxorubicin, epirubicin, amrubicin)
Taxanes (paclitaxel, docetaxel)
Vinca alkaloids (vincristine, vinorelbine)
Nitrosoureas (lomustine [CCNU])
Antimetabolites (methotrexate, gemcitabine)
Immunotherapeutic Agents
Check point inhibitors (atezolizumab, durvalumab, nivolumab, ipilimumab, pembrolizumab)

Carboplatin has a more favorable toxicity profile than cisplatin, with less nephrotoxicity, ototoxicity, neurotoxicity, and emetogenicity. Because pre- and posthydration are not required, its administration is also more convenient (typically 45 min for carboplatin vs. 4–6 h for cisplatin, including hydration). In a randomized trial comparing the two agents, cisplatin demonstrated slightly higher overall and complete response rates than did carboplatin: overall response 64% versus 50%; complete response 16% versus 10%. However, there was no significant difference in overall survival.[155] Based on a more favorable toxicity profile, most clinicians in the United States employ carboplatin–etoposide for the treatment of ES SCLC, with cisplatin–etoposide preferred for the treatment of LS SCLC due to the possibility of a higher response rate.

Cisplatin plus irinotecan has been compared to cisplatin plus etoposide in a number of clinical trials. In a Japanese study, the irinotecan-containing arm demonstrated a significantly higher response rate (84% vs. 68%), longer median survival (12.8 months vs. 9.4 months), and higher 2-year survival rate (19.5% vs. 5.2%).[156] However, three larger studies performed in Western populations did not confirm these findings, raising the possibility of pharmacogenomic differences between the populations.[157–159]

Three- and four-drug regimens, in which agents such as paclitaxel, ifosfamide, cyclophosphamide, and epirubicin are added to etoposide-platinum, have yielded mixed results. Some studies have demonstrated higher response rates and modest prolongation of survival, but often at the cost of increased toxicity, including higher rates of treatment-related mortality in some instances.[160–162] Administration of non–cross-resistant regimens such as etoposide-platinum and CAV in alternating or sequential fashion has not consistently demonstrated a survival benefit.[163] Several studies have explored increasing chemotherapy dose intensity via dose escalation, shortening the interval between cycles, and providing hematopoietic support through growth factor administration or stem cell transplantation.[164–66] None of these approaches has demonstrated consistent benefit.

Maintenance chemotherapy, which has emerged as a new standard of care for advanced NSCLC, has also been studied in SCLC. In these trials, patients with nonprogressing disease after four cycles of combination induction therapy immediately proceed to maintenance monotherapy with agents such as topotecan or etoposide.[167,168] Individual trials have not demonstrated a significant increase in overall survival. Although a meta-analysis has suggested a modest survival advantage,[169] few if any oncologists employ this approach in the management of SCLC.

Based on the extant literature, it appears the optimal therapy for a majority of SCLC patients is etoposide-platinum, with the addition of thoracic radiotherapy for those with LS disease (see below). Treatment beyond four to six cycles is unwarranted in the first-line setting. There is little support for the use of dose intensification or so-called "dose-dense" therapy as a course of routine treatment.

Immunotherapy

FDA approvals for immune checkpoint inhibitor therapy alone or in combination with conventional chemotherapy represent one of the few recent advances in the medical treatment of SCLC. These monoclonal antibodies, which target programmed death 1 (PD-1), PD-1 ligand (PDL-1), or cytotoxic T-lymphocyte antigen 4 (CTLA4) "release the brakes" on the immune system, resulting in enhanced antitumor immunity. Immune checkpoint inhibitors are now approved for numerous common solid tumors and lymphoma, with an estimated 45% of patients with advanced malignancies eligible for these treatments.[170]

Given the promising effects of immune checkpoint inhibitors in NSCLC one might anticipate even greater efficacy in SCLC. Patients with SCLC tend to have greater smoking history, which may be associated with heightened tumor mutational burden and, in turn, antigenicity.[171] Furthermore, the heightened incidence of autoimmune paraneoplastic phenomena reflecting immune cross-reactivity between SCLC and normal tissues suggests an underlying antitumor immune response against SCLC.

While immune checkpoint inhibitors have indeed improved outcomes in this disease, their relative benefit appears less than that achieved in non–small-cell lung cancer. The addition of the anti-PD1 agent atezolizumab to carboplatin–etoposide as first-line treatment of extensive-stage SCLC resulted in an improvement in medial overall survival from 10.3 months to 12.3 months (hazard ratio [HR], 0.70; 95% confidence interval [CI], 0.54–0.91; $p = 0.007$).[114] Similarly, the addition of the anti-PDL1 agent durvalumab to first-line platinum–etoposide increased median overall survival from 10.3 to 13.0 months (HR, 0.73; 95% CI, 0.59–0.91; $p = 0.005$).[115] With both of these regimens, if patients are continuing to benefit from and tolerate treatment after four cycles of combination therapy, the immune checkpoint inhibitor is continued as maintenance monotherapy until disease progression or intolerable toxicity. Unfortunately, compared to NSCLC, it is less clear whether a proportion of patients treated with these new regimens will truly be long-term survivors or potentially cured.

Notably, despite the high mutational burden of SCLC, relatively few cases are PD-L1 positive, a biomarker associated with checkpoint inhibitor efficacy in NSCLC. Specifically, in SCLC, approximately 20% of cases have tumor PD-L1 expression ≥1%, compared to approximately 70% of NSCLC cases.[172] This observation serves as a reminder that these biomarker populations have only partial overlap, with 20% of high-mutational-burden tumors having high PD-L1 expression and 30% of PD-L1–high tumors also having high mutational burden.[173]

Due to low prevalence and limited predictive capacity, PD-L1 is not used as a clinical biomarker for treatment decisions in SCLC, although it may be used in NSCLC for consideration of first-line checkpoint inhibitor monotherapy and combination immunotherapy regimens. Indeed, in SCLC, tumor mutational burden may be a more useful predictive biomarker for anti-PD1 or combined anti-CTLA4 regimens. Radiographic response to nivolumab (anti-PD1) is 5% in low tumor mutation burden, versus 21% in high-mutation-burden cases. Similarly, with combination nivolumab and ipilimumab (anti-CTLA4), response rates are 22% and 46% for low and high mutation burden, respectively.[173] To date, however, tumor mutation burden is not a formally approved biomarker for routine clinical care in SCLC or any other malignancies treated with checkpoint inhibitors.

Second-Line Chemotherapy

Although the majority of SCLC patients treated with first-line chemotherapy demonstrate tumor response, most eventually relapse. Response to first-line therapy tends to be brief, with a median duration of 6 to 8 months. Along with performance status and tumor extent (i.e., limited vs. extensive), the time to relapse after first-line therapy is among the most important prognostic factors in SCLC.[126] The timing of relapse also has implications when considering further treatment options. Patients who relapse greater than 6 months after completion of first-line therapy are often re-treated with etoposide–platinum. Patients with earlier disease progression can be categorized as *sensitive relapse* (tumor progression >90 days after last day of initial treatment), *resistant relapse* (tumor progression ≤90 days after last day of initial treatment), or *refractory* (tumor progression during initial therapy or unresponsiveness to initial therapy). For patients with sensitive relapse, response rates to second-line chemotherapy are 30% to 40%, and median survival is approximately 6 months. For those with resistant relapse or refractory disease, responses occur in less than 10% of cases.

For many years in the United States, the topoisomerase I inhibitor topotecan was the only FDA-approved drug for second-line treatment for SCLC. Oral and intravenous topotecan formulations used as a single agent exhibit response rates of 11% to 37%.[174–176] These responses are rarely durable, with median time to progression of 12 to 13 weeks and resultant median survival of 6 to 7 months. In 2020, the alkylator lurbinectedin was granted accelerated FDA approval based on a single-arm phase 2 trial in relapsed/refractory SCLC that reported a tumor response rate of 35% and a median response duration of 5.3 months.[177] Comparative trials against topotecan are underway to determine if lurbinectedin offers a survival advantage.

■ Radiation Therapy

The role of radiation in treatment of SCLC may be considered with respect to thoracic radiation and prophylactic cranial irradiation.

Thoracic Radiation Therapy

SCLC is a malignancy that is sensitive to radiation. Thoracic radiation therapy (TRT) as a single modality results in an objective tumor response rate of 75% in LS disease, and may cure as many as 5% of these patients.[141] Initial clinical trials combining TRT with chemotherapy yielded mixed results. For the most part, these early trials demonstrated a decrease in local recurrence but no clear survival benefit. However, two meta-analyses published in 1992 reported a statistically significant 5% improvement in overall survival with the addition of radiation to chemotherapy in SCLC patients with LS disease.[178,179] These reports established concurrent chemotherapy and radiation as the standard of care for fit patients with LS SCLC. Significant questions remained regarding the optimal timing, dose, and fractionation of radiation. A number of trials have evaluated early (typically <30 days after initiation of chemotherapy) versus late radiation and have yielded conflicting results. Both a subsequent meta-analysis and systematic review of the available data concluded that early radiation resulted in a small but significant improvement in overall survival and have established early TRT as the preferred approach for patients with LS disease.[180,181]

The optimal fractionation and dose of TRT also are unknown. The Eastern Cooperative Oncology Group conducted a randomized trial in LS SCLC patients comparing twice-daily TRT to 45 Gy with the prior standard of once-daily TRT to 45 Gy. Both treatment arms received standard etoposide–platinum chemotherapy. They reported a significantly improved median (23 vs. 19 months) and 5-year survival (27% vs. 11%) favoring twice-daily TRT.[182] Despite these results, this strategy has not been widely adopted, presumably due to the inconvenience of administering twice-daily TRT. A criticism of this trial is that the radiobiologic dose of 45 Gy twice daily is significantly higher than once daily to 45 Gy, and therefore daily radiation to a higher dose may produce comparable results. However, a European randomized phase 3 trial (CONVERT) failed to demonstrate a survival advantage for once-daily radiation to 66 Gy over twice daily to 45 Gy, although numeric outcomes and toxicity between the two arms were similar.[183] A second randomized trial comparing twice-daily to 45 Gy with once-daily to 70 Gy is ongoing. At present, both strategies (twice daily to 45 Gy and once daily to 60–70 Gy) are utilized in clinical practice.

Consolidative chest irradiation is beneficial in selected patients with ES SCLC who respond to initial chemotherapy. Trials demonstrate decreased progression in the chest as well as improved survival in some patients, although the patients most likely to benefit are those with residual chest disease after chemotherapy and limited extrathoracic metastases.[184,185] Of note, the safety of administering chest radiation in patients receiving immune checkpoint inhibitor therapy (see above) has not been evaluated in any prospective trial. Radiation also plays a palliative role in ES disease, and can be used for symptomatic control in bony, pulmonary, and brain metastases.

Prophylactic Cranial Irradiation

As detailed earlier, the brain is a frequent site of metastatic spread in SCLC. Some 10% to 18% of patients have brain involvement at presentation, and 60% to 80% of SCLC patients who survive at least 2 years will develop brain metastases.[95,96,186] The prevailing assumption is that micrometastases in the brain are relatively protected from systemic chemotherapy by the blood–brain barrier. Given these facts, a number of randomized trials evaluated PCI in LS SCLC patients who had a complete or near-complete response with chemotherapy and TRT. These studies reproducibly showed significant reductions in the incidence of brain metastases with PCI but had conflicting results regarding the impact of PCI on overall survival. In 1999, an individual patient data meta-analysis of all available randomized trials reported a 5.4% increase in overall survival at 3 years (15.3% vs. 20.7%) favoring PCI. PCI also reduced the cumulative risk of brain metastases at 3 years from 58.6% to 33.3%.[187]

PCI in ES SCLC similarly reduces brain metastases, but the impact on survival is debated. In a European trial, patients with ES disease who experienced at least a partial response to chemotherapy were randomized to PCI or observation. The primary endpoint, symptomatic brain metastases, was reduced from 41.3% in the observation arm to 16.8% with PCI. Median survival (6.7 months vs. 5.4 months) and 1-year survival (27.1% and 13.3%), both secondary endpoints, were significantly improved with PCI.[188] A criticism of this trial is that it did not perform routine surveillance for asymptomatic brain metastases. In a trial from Japan, ES SCLC patients who responded to initial chemotherapy were randomized to PCI or routine MRI surveillance for brain metastases (allowing for early treatment of asymptomatic metastases). No difference in overall survival was seen between the two groups.[189]

Current guidelines recommend consideration of PCI for all LS patients with a good performance status who have attained a complete or near-complete response after chemotherapy and radiation. In ES SCLC patients who respond to initial chemotherapy, routine MRI surveillance or PCI are acceptable options. Concern has been raised about long-term neurocognitive impairment from PCI, which includes potential effects on communication and memory that may be dose dependent.[190,191] Therefore, before undergoing PCI, patients should be counseled regarding the expected risks and benefits of this intervention. In addition, strategies such as hippocampal sparing PCI and the use of memantine are considerations to mitigate these effects.

■ Treatment in the Elderly and Patients with a Poor Performance Status

In most patients with metastatic solid tumors and a poor performance status, chemotherapy is felt to be of limited benefit given the high likelihood of severe toxicity and the low chance of a significant durable tumor response. As noted earlier, given the relative chemosensitivity of SCLC, an impaired performance status does not necessarily preclude treatment. Some SCLC patients with functional impairment can experience significant tumor response and resultant modest improvements in their performance status after treatment with chemotherapy.

Similarly, age should not be the sole criterion by which treatment decisions in SCLC are based. In recent series, the median age at diagnosis in SCLC is >65 years and approximately 40% of patients are ≥70 years.[94] Clearly, elderly (typically defined as >70 years old) patients with SCLC will be encountered frequently in clinical practice. Treatment of these patients is complicated by underlying comorbidities as well as decreased organ function that may lead to poor tolerance of treatment. Unfortunately, the elderly are typically underrepresented in clinical trials in SCLC, and therefore there is little definitive prospective evidence on the appropriate management of this group. The available information suggests that elderly patients who are able to tolerate standard treatment for SCLC fare as well as their younger counterparts.[192] In addition, prospective randomized trials of "less intensive treatment" in those felt to be at risk for excess toxicity from standard therapy found inferior survival and palliation on the "less intensive" treatment arms.[193] Current recommendations are to consider comorbidities and functional capacity, rather than age alone, when making treatment recommendations for these patients.

COMPLICATIONS

Both radiotherapy and chemotherapy cause side effects specific to the agent used. Irradiation can have early (esophagitis, pneumonitis, superficial skin burns) and late (pulmonary fibrosis, late cardiac disease, myelitis) toxicities. Chemotherapy toxicities depend on the specific regimen used, but they generally include alopecia, nausea and vomiting, and myelosuppression. Bone marrow suppression can lead to life-threatening bleeding episodes (from thrombocytopenia), but more commonly it is associated with neutropenic fevers, and occasionally fatal infections. Published series in SCLC patients have demonstrated that episodes of febrile neutropenia occur in roughly 30% of treated patients, documented infection in 5% to 15%, and fatal infection in 7%. Prevention of infection in patients treated with chemotherapy with or without irradiation has received significant attention. Measures have included prophylactic use of antibiotics and granulocyte colony-stimulating factor (GCSF). Recently, a large, randomized trial showed that GCSF in addition to chemotherapy led to a reduction of the number of episodes of neutropenic fever and documented infections. Many oncologists do not agree that this is a cost-effective measure, however.

Immune checkpoint inhibitors convey risk of immune-related adverse events. These autoimmune toxicities may affect almost any organ system, including skin, thyroid, lungs, pituitary, GI tract, liver, kidney, joints, and, in rare cases, heart or central nervous system. These toxicities may be severe or potentially permanent, and they may occur at almost any point during (or occasionally even after) immunotherapy.

The estimated incidence of immune-related pulmonary toxicities varies widely, from approximately 5% to 20% of treated patients.[194,195] Clinical manifestations are nonspecific and include cough, dyspnea, hypoxia, chest discomfort, and fever. Radiographic features may include ground-glass opacities, consolidations, interlobar septal thickening, pleural effusions, and lymphadenopathy, findings that may overlap with infection, other toxicities (e.g., radiation pneumonitis), or disease progression.[196] Bronchoalveolar lavage may show a lymphocyte-predominant differential, and bronchoscopic biopsy may demonstrate cellular interstitial pneumonitis, organizing pneumonia, or diffuse alveolar damage.[197] Management of immune-related pulmonary events and other autoimmune toxicities centers on immunosuppression, most commonly corticosteroids. For moderate to severe cases, steroid tapers over several weeks may be required. Occasionally, other immunosuppressants such as mycophenolate, anti-TNF antibodies, or IVIG may be required. Unlike chemotherapy, there is no role for dose reduction with immune checkpoint inhibitors. These agents are either given at full dose, temporarily withheld, or permanently discontinued.

Given that the majority of patients with SCLC are older and have extensive smoking histories, it is not surprising that cardiovascular, cerebrovascular, and pulmonary diseases are extremely common in this population. Thus, a large portion of long-term survivors of SCLC succumb to these other diseases. Up to one-third of all long-term surviving patients, especially those who continue to smoke, have recurrence of their SCLC or, more rarely, develop a new SCLC. Other aerodigestive cancers, particularly NSCLC, are extremely common, leading some investigators to propose trials of chemoprevention agents in long-term survivors of SCLC. Finally, patients with SCLC have an increased risk of developing a hematologic malignancy. Secondary leukemias are believed to be related to treatment, especially if chemotherapy with alkylating agents was employed. Some of these posttreatment leukemias have also shown a deletion of chromosome 3, suggesting an underlying predisposition or common ancestor cell to both cancers, instead of a secondary leukemia arising from alkylating chemotherapy–induced genetic damage. Overall, 2-year survivors of SCLC face a 3.5-fold increased risk of a second cancer (mostly NSCLC) compared with the general population. The risk of a second lung cancer is increased 13-fold among those patients who received TRT and 7-fold among those who did not undergo radiation, with ongoing smoking further escalating risk.[198] Accordingly, long-term surveillance is mandatory in these otherwise cured patients.

CONCLUSION

SCLC is distinct from the other three major histologic varieties of pulmonary malignancies, which tend to behave similarly and are lumped together under the generic rubric "NSCLC." It is biologically more active, secreting multiple hormones and neural markers, resulting in a number of paraneoplastic syndromes. It is thought of as a systemic disease, and treatment nearly always includes chemotherapy and, more recently in ES patients, immune checkpoint inhibitors. Although the tumor is highly responsive to initial therapy, and survival is significantly prolonged with systemic treatment, the complete eradication of SCLC remains a relatively rare event. Long-term survivors are subject to a host of cardiopulmonary conditions, as well as second malignancies and recurrence of their SCLC. In the era of tumor genomic profiling and molecularly targeted therapies, there is hope that new insights into tumor biology and novel therapies may show promise in the treatment of this aggressive and often fatal cancer.

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CHAPTER 117

Uncommon Tumors of the Lung

Karen Rodriguez
Gerald F. Abbott

INTRODUCTION

Although lung cancer is the most common primary pulmonary neoplasm, a variety of uncommon or rare primary pulmonary tumors may occur, including both benign and malignant entities. This chapter reviews the most frequently encountered uncommon tumors of the lung.

BENIGN TUMORS

Benign lung tumors include hamartomas, chondromas, papillomas, and inflammatory myofibroblastic tumors, each of which is discussed below.

■ Hamartoma

Pulmonary hamartoma is the most common benign pulmonary neoplasm, accounting for 6% of all solitary pulmonary nodules. Hamartomas are composed of varying amounts of at least two mesenchymal tissues, such as cartilage, fat, bone, connective tissue, and smooth muscle, in combination with entrapped respiratory epithelium.[1–6] Most hamartomas occur as solitary nodules in the periphery of the lung (Fig. 117-1), and affected patients are asymptomatic. However, approximately 10% of hamartomas may involve the airways and produce symptoms and imaging signs of bronchial obstruction. Affected patients may present with cough, dyspnea, or pneumonia. Hamartomas occur more often in men than women, with a peak incidence in the sixth decade. They should be considered in the imaging diagnosis of pulmonary nodules that exhibit intrinsic fat and calcification on CT.[7–10] MRI in-phase and out-of-phase imaging can also be used to demonstrate the presence of macroscopic fat.[1,12]

Small, slow-growing hamartomas can be managed conservatively. If the diagnosis is uncertain or if larger lesions or endobronchial lesions cause postobstructive findings, then surgical resection is often performed.[13–15]

Multiple hamartomas may occur in Cowden syndrome, an autosomal dominant disorder that may affect multiple organs, including the skin, thyroid gland, and gastrointestinal tract. In addition to its association with benign hamartomas, the syndrome carries an increased risk of breast and thyroid cancers.[16]

Pulmonary chondromas are benign cartilaginous tumors that consist entirely of cartilaginous components that may calcify.[17] Chondromas may be associated with Carney triad, which is defined by the coexistence of extra-adrenal paragangliomas, gastric gastrointestinal stromal tumors (GIST), and pulmonary chondroma and is typically seen in young women.

■ Solitary Papilloma/Papillomatosis

Squamous cell papilloma is a benign papillary tumor that arises from the wall of a mainstem, secondary, or tertiary bronchus as an exophytic “cauliflower-like” growth. The tumor consists of delicate connective tissue fronds formed by arborizing fibrovascular cores covered by stratified squamous epithelium. A solitary papilloma is very rare, accounting for <1% of all pulmonary neoplasms.[18–21] Multiple papillomas may involve the larynx, trachea, bronchial tree, and lung parenchyma as laryngotracheal papillomatosis, also known as recurrent respiratory papillomatosis (RRP).[22–28] Juvenile laryngeal papillomatosis affects children (18 months to 3 years of age) and may remain localized to the larynx or resolve spontaneously. However, in 5% of patients involvement spreads to the trachea and remains limited to that airway.[29,30]

Approximately 1% of patients develop lung disease as papillomatosis spreads to involve the main bronchi and, subsequently, to bronchi, bronchioles, and the alveolar airspaces. Patients with mild involvement may be asymptomatic or present with hoarseness due to laryngeal involvement. Lung involvement typically occurs 10 years after laryngeal disease.

On imaging studies tracheobronchial papillomatosis is manifest as airway wall nodularity that may be sessile or polypoid, with

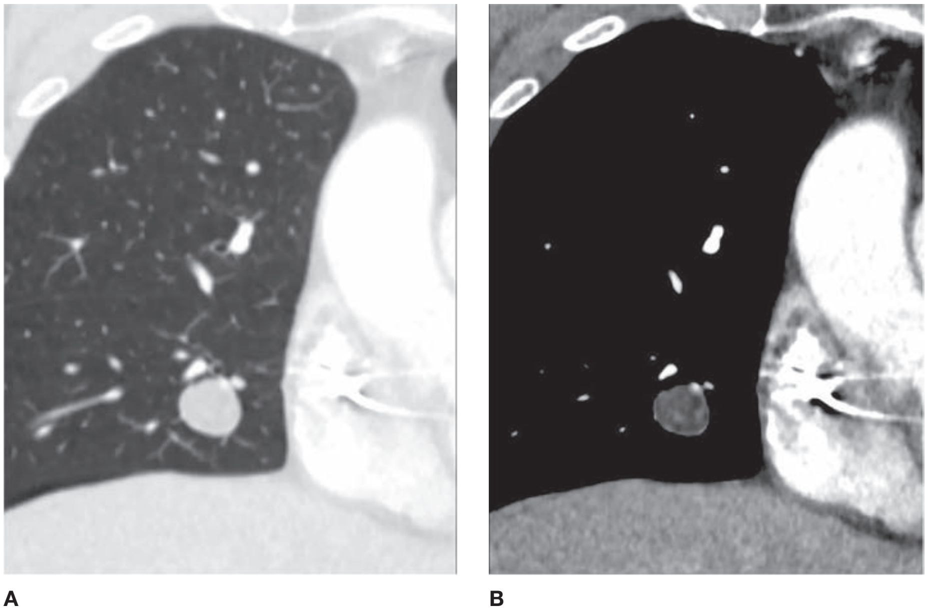

Figure 117-1 Hamartoma. Contrast-enhanced coronal CT images in lung window (**A**) and mediastinal window (**B**) demonstrate a well-circumscribed peripheral pulmonary nodule in the right lower lobe. The mediastinal window image (**B**) reveals macroscopic fat manifesting as low attenuation within the nodule. Most hamartomas occur as peripheral nodules in asymptomatic patients, but 10% occur as central lesions that may be endobronchial and cause obstructive symptoms and imaging findings. The CT demonstration of macroscopic fat within a pulmonary nodule is considered diagnostic of pulmonary hamartoma.

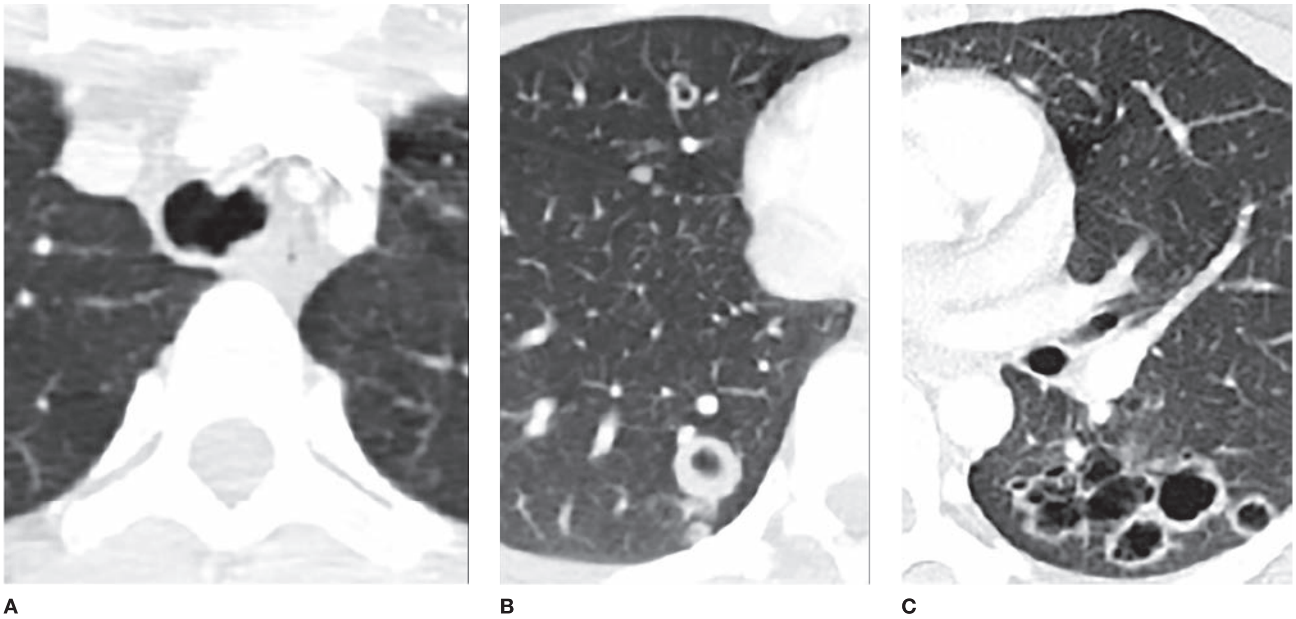

Figure 117-2 Papillomatosis. Composite CT image shows mural nodules in the trachea (**A**), cavitary nodules in the right middle and lower lobes (**B**), and thick-walled cystic lesions in the left lower lobe (**C**). The nodular and cystic lesions demonstrate predominant involvement of the posterior, dorsal aspects of both lungs—a characteristic distribution of lung involvement in tracheobronchial papillomatosis, suggesting that aspiration may play a role in the pathogenesis of papillomatosis.

the upper airways more commonly affected. Multiple pulmonary nodules and masses may evolve into cavitary nodules with irregular walls and subsequent cystic lesions, all of which have a predominantly posterior distribution in both lungs (Fig. 117-2).[22–28] Most nodules are slow growing and benign; however, rapid growth may occur in up to 2% of cases and undergo malignant transformation to squamous cell carcinoma. Multiple risk factors predispose to a higher risk for squamous cell carcinoma, including cigarette smoking, a history of prior radiation exposure, and infection with human papillomavirus (HPV) types 6 and 11.[18]

Solitary papilloma can be managed conservatively. For patients with RRP, surgical resection using laser therapy may be utilized for lesions causing airway obstruction or hoarseness.

Inflammatory Myofibroblastic Tumor

Inflammatory myofibroblastic tumor (IMT) is a spindle cell neoplasm with low malignant potential. It usually occurs in children and young adults and typically manifests as a well-defined mass. Patients are usually symptomatic with nonspecific constitutional symptoms, such as fever and malaise.[31–34] Histologically, IMT consist of spindle cell (myofibroblast) proliferation and inflammatory cells, including plasma cells and lymphocytes, within a background of granulation tissue.[32,33] Tumors are classified based according to varying degrees of mitosis, necrosis, and vascular invasion. Anaplastic lymphoma kinase (ALK) oncogene mutation is seen in up to 60% of IMT. On cross-sectional imaging, IMT typically manifests as a heterogeneously enhancing nodule or mass; central calcification or necrosis may occur (Fig. 117-3). On MRI, IMT may demonstrate T2 hypointensity due to the tumor's fibrous stroma.

IMT often have a good prognosis following complete surgical resection, but incomplete resection may result in recurrence. Chemotherapy along with steroids and radiation therapy are considered when surgical resection is not feasible.

MALIGNANT TUMORS

Uncommon malignant tumors of the lung include bronchial carcinoid (both typical and atypical), adenoid cystic carcinoma, mucoepidermoid carcinoma, lymphoma, and carcinosarcoma, each of which is considered below.

Bronchial Carcinoid (Typical and Atypical Carcinoid)

Bronchial carcinoids are low-grade, malignant neuroendocrine tumors that arise from tracheobronchial Kulchitsky cells.[35–40] The

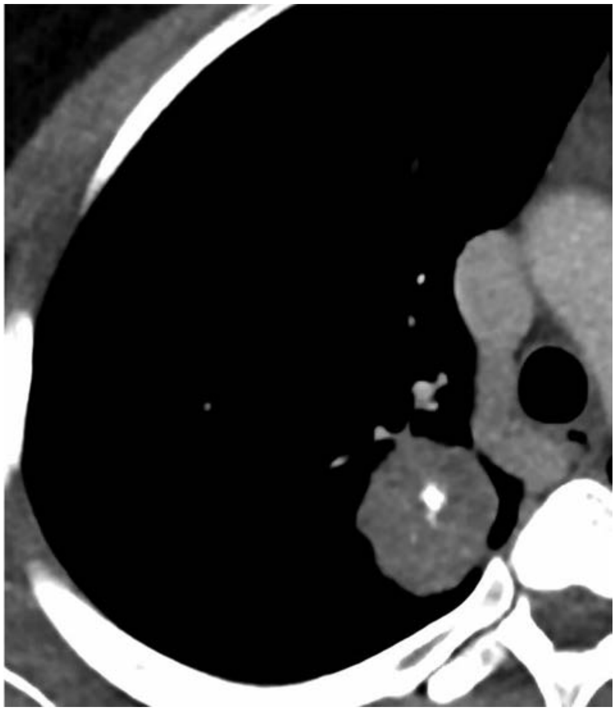

Figure 117-3 Inflammatory myofibroblastic tumor. Axial CT of a 38-year-old nonsmoker demonstrates a peripheral pulmonary nodule with lobulated margins and a focal area of eccentric calcification. Differential diagnostic considerations include bronchial carcinoid tumor, granuloma, and lung cancer.

World Health Organization has classified these tumors based on mitotic activity and necrosis into typical carcinoids (TC) and atypical carcinoids (AC).

Typical carcinoids have rare mitotic figures (<2 mitoses per 10 high-power fields), and necrosis is absent. Atypical carcinoids tend to be larger than typical carcinoids. Atypical carcinoids have increased mitotic activity (2–10 mitoses per 10 high-power fields) and may demonstrate tumor necrosis.[41,42] Carcinoid tumors typically occur in young and middle-aged patients, with a mean age of 55 years and equal female–male distribution. The average age for patients with atypical carcinoids tends to be about a decade older than those with typical carcinoids. Affected patients often complain of cough and may report episodes of hemoptysis.

Some patients may present with postobstructive pneumonia due to air trapping from endobronchial ball-valve obstruction. A rare presentation is a paraneoplastic syndrome, such as Cushing syndrome due to ectopic production of adrenocorticotropic hormone (ACTH), which occurs more often in patients with AC than those with TC. Carcinoid syndrome is rare in cases of bronchial carcinoid tumors, but it has been reported in patient with AC and liver metastases.[43,44]

Macroscopically, bronchial carcinoid tumor typically manifests as a smooth red polypoid endobronchial nodule or mass. Most arise within central bronchi. Microscopically, bronchial carcinoids are characterized by uniform cells separated by a fibrovascular stroma.

Neuroendocrine neoplasms (NE) form a spectrum with varying grades and aggressiveness, ranging from low-grade TC, to intermediate grade AC, and to more aggressive large-cell neuroendocrine carcinoma (LCNEC) and small-cell lung cancer (SCLC). Histologic analysis of NE also demonstrates a spectrum in the number of mitotic figures detected per 10 high-power fields (HPF), ranging from less than 2 in TC to at least 2 in AC, and greater than 10 in NEC and SCLC. AC and TC may not always be reliably distinguished from each other on small biopsy specimens.[41,42]

Typical and atypical carcinoids demonstrate similar features on imaging studies. Most carcinoids occur as a central hilar or perihilar nodule or mass (>3 cm) with 85% in the mainstem, lobar, or segmental bronchi (Fig. 117-4A, B). Bronchial carcinoids may be completely endobronchial, but often they are manifest as an "iceberg" growth pattern, with the bulk of tumor outside of the airway and a smaller endobronchial component within forming the "tip of the iceberg" (Fig. 117-4C, D). Most affected patients present with postobstructive symptoms. Up to 20% of carcinoids may occur as a peripheral, solitary pulmonary nodules, and patients may be asymptomatic.[39,40] On CT, carcinoid tumors may exhibit calcification, typically demonstrate intense enhancement on contrast-enhanced studies, and often reveal their airway relationship and related findings of atelectasis and/or postobstructive pneumonitis (Fig. 117-4E).

Complete surgical resection is the most effective treatment. Recurrence-free survival is common in patients with TC. Tumor histology and nodal status are the main predictors of mortality. Five-year survival rates following complete resection of TC and AC are 87% to 100% and 44% to 77%, respectively.[42] Survival decreases in the presence of nodal metastases. There is no correlation between tumor size and the presence of nodal involvement.

Multiple carcinoid tumorlets or carcinoid tumors are suggestive of diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH). DIPNECH has been described predominantly in older women, typically nonsmokers. CT characteristics include lower lobe–predominant nodules and mosaic attenuation on expiratory imaging. DIPNECH has a generally good prognosis, with very slow growing tumorlets.[45]

■ Adenoid Cystic Carcinoma

Adenoid cystic carcinoma (ACC) is a slow-growing neoplasm that arises from submucosal gland myoepithelial cells.[46–54] ACCs typically arise in the trachea and mainstem bronchi and are the second most common malignant tracheal neoplasms. The average age of affected patients is 30 to 50 years, with equal gender distribution. Patients may present with nonspecific respiratory symptoms, such as dyspnea, cough, and stridor and are often misdiagnosed as having asthma.[47] Microscopically, ACC demonstrates a high nuclear-to-cytoplasmic ratio and an infiltrative pattern of uniform tumor cells. Perineural extension is a histologic hallmark of ACC.[51]

The characteristic imaging features of ACC are annular airway thickening and polypoid or broad-based endoluminal nodules or masses in the trachea or mainstem bronchi (Fig. 117-5).[47] ACCs more frequently involve the distal two-thirds of the trachea. CT demonstrates homogenous soft tissue thickening with variable degrees of airway luminal narrowing. ACC may involve a long tracheal segment due to longitudinal submucosal extension of tumor and may demonstrate local invasion into the adjacent mediastinal fat.[47–50] Some patients present with advanced disease, most commonly mediastinal lymphadenopathy and hematogenous pulmonary nodular metastases.

ACC have a good prognosis following complete resection with end-to-end anastomosis of the trachea; 5- and 10-year survivals are 65% to 100% and 50% to 60%, respectively.[46] Tumors with local invasion of the adjacent mediastinal fat may require extensive resection. Local recurrence or residual disease may respond well to radiation but may pose a risk of tracheoesophageal fistula.

■ Mucoepidermoid Carcinoma

Mucoepidermoid carcinoma (MEC) is less common than ACC; it also arises from bronchial glands in the tracheobronchial tree. MEC affects young patients, typically less than 30 years of age, with an equal gender distribution. These tumors are typically ovoid, endoluminal, well-circumscribed nodules that primarily affect the main or lobar bronchi and much less commonly the trachea. Affected patients usually present with cough and postobstructive pneumonia.[55,56] MECs are classified as low- or high-grade, based on their microscopic features; both display solid collections or sheets of squamous cells. A propensity of mitoses and necrosis characterizes the high-grade MEC. The characteristic imaging features of MEC are a nodule or mass involving the main or lobar bronchi, often accompanied by obstructive atelectasis or pneumonia (Fig. 117-6).

The prognosis for low-grade MEC is usually good; complete resection is curative. High-grade MEC may present with mural invasion and lymph node metastasis.

■ Lymphoma

Lymphoma comprises a diverse group of malignant neoplasms arising from lymphocytes.

Non-Hodgkin lymphoma (NHL) is the most common type of lymphoma (80%–90% of all cases). Hodgkin lymphoma (HL) represents 10% to 20% of all lymphomas.[57] Both NHL and HL frequently involve the chest, most often as lymph node malignancies that primarily involve the mediastinum; however, both may affect the lung with primary or secondary involvement that may be a manifestation of systemic disease.[58]

Primary pulmonary lymphoma (PPL) represents less than 1% of all pulmonary malignancies and is defined as malignant lymphoma originating from pulmonary parenchyma or bronchi, with or without hilar lymph node involvement, in a patient with no evidence of extrathoracic lymphoma for at least 3 months after the initial diagnosis. The most common type of PPL is mucosa-associated lymphoid tissue (MALT) lymphoma (70%–90%), and less commonly diffuse large B-cell lymphoma (DLBCL) and lymphomatoid granulomatosis (LYG).[57] Secondary pulmonary lymphoma (SPL) is more common than PPL and refers to a secondary involvement of the lung from a

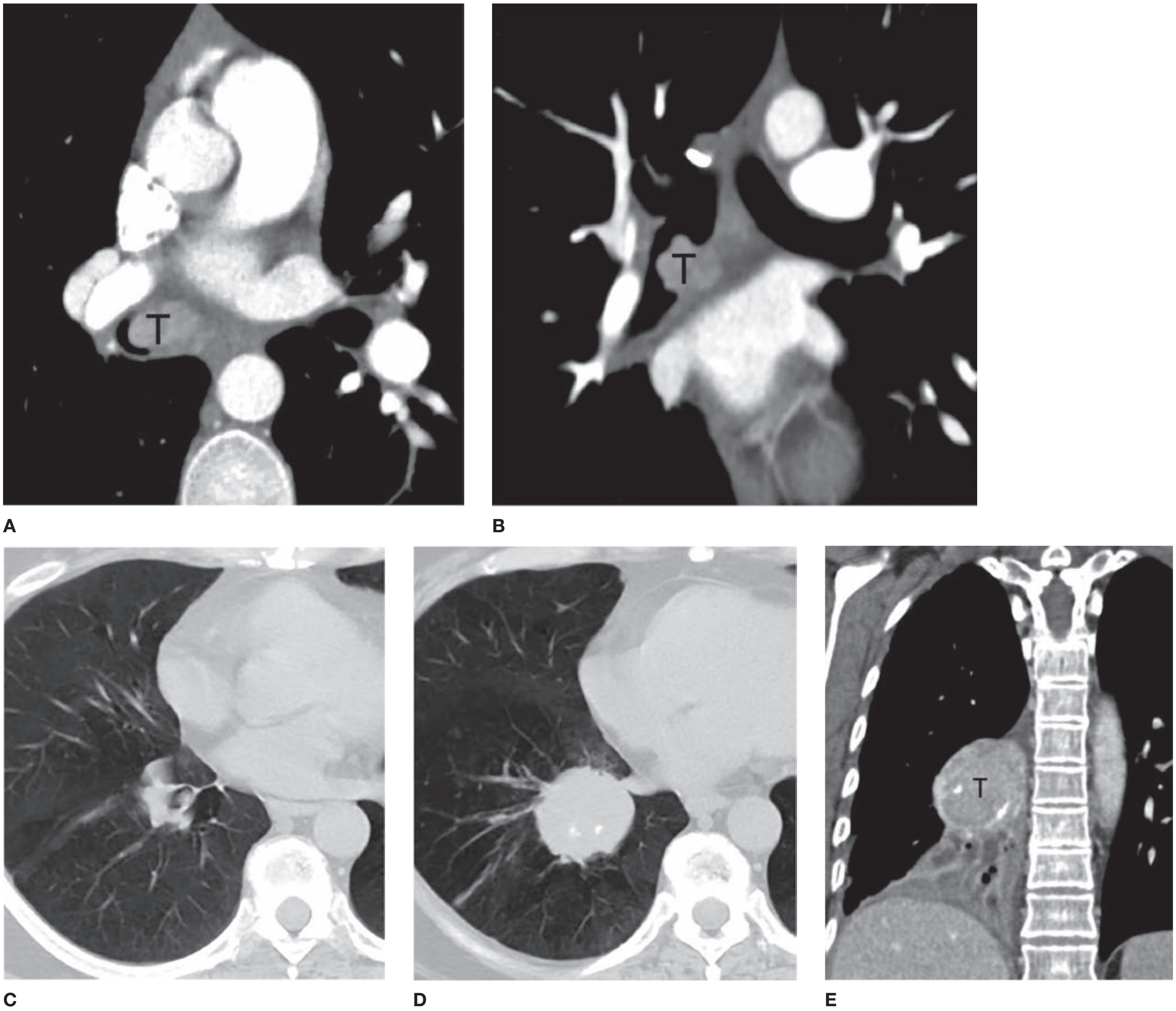

Figure 117-4 Bronchial carcinoid. Composite of axial (**A**) and coronal (**B**) CT images demonstrates an enhancing endobronchial carcinoid tumor (**T**) in the bronchus intermedius with lobulated contours and without distal effects. Bronchial carcinoid tumors typically demonstrate contrast enhancement on CT, likely a manifestation of their underlying fibrovascular stroma. Note the focal penetration of tumor through the medial bronchial wall, a characteristic feature of bronchial carcinoid tumors. Axial CT images demonstrate the characteristic "iceberg" growth pattern of bronchial carcinoid tumors, with the tip of the iceberg manifesting as a focal endobronchial lesion in the right lower-lobe bronchus (**C**) and the bulk of the tumor outside of the airway (**D**). The larger tumor component (**D**) also demonstrates eccentric foci of calcification, a frequent imaging finding in bronchial carcinoid tumors. The imaging features of typical and atypical carcinoid tumors are indistinguishable. That determination is made by pathologists, based on the number of mitotic figures per 10 high-power fields. Coronal CT (**E**) of a bronchial carcinoid involving the right lower-lobe bronchus demonstrates a large central enhancing carcinoid tumor (**T**) that obstructs the airway with resultant lobar atelectasis and distal bronchiectasis with dilated, fluid-filled airways with foci of air. There are eccentric and peripheral areas of calcification within the tumor. Bronchial carcinoid tumors typically involve the central airways and may cause distal atelectasis and pneumonitis.

known extrapulmonary lymphoma. These two origins of pulmonary lymphoma are pathologically distinctive but may share the same mediastinal manifestations with similar imaging features.[58]

In 2016, the World Health Organization published a revised classification scheme that grouped lymphomas by cell type and by their molecular, cytogenetic, and phenotypic characteristics.[59–62]

On chest CT primary malignant lymphoma manifests as bilateral pulmonary nodules or masses that may be focal or multifocal, and unilateral or bilateral, with ill-defined or well-defined borders, and, frequently, air bronchograms (Fig. 117-7A, B). Other imaging manifestations include areas of lobar or segmental consolidation and endobronchial lesions with postobstructive changes. Less common manifestations include miliary pulmonary nodules or a lymphangitic pattern of tumor spread. Direct chest wall invasion also may occur.[58]

Surgery has been suggested as the preferred treatment in cases of localized PPL when complete resection may be achieved. Patients with SPL are typically treated with chemotherapy. Prognosis varies based on the subtype and clinical stage of disease.[57]

■ Carcinosarcoma

Pulmonary carcinosarcoma is a rare tumor that typically occurs in older men (50–80 years old) with a history of heavy cigarette

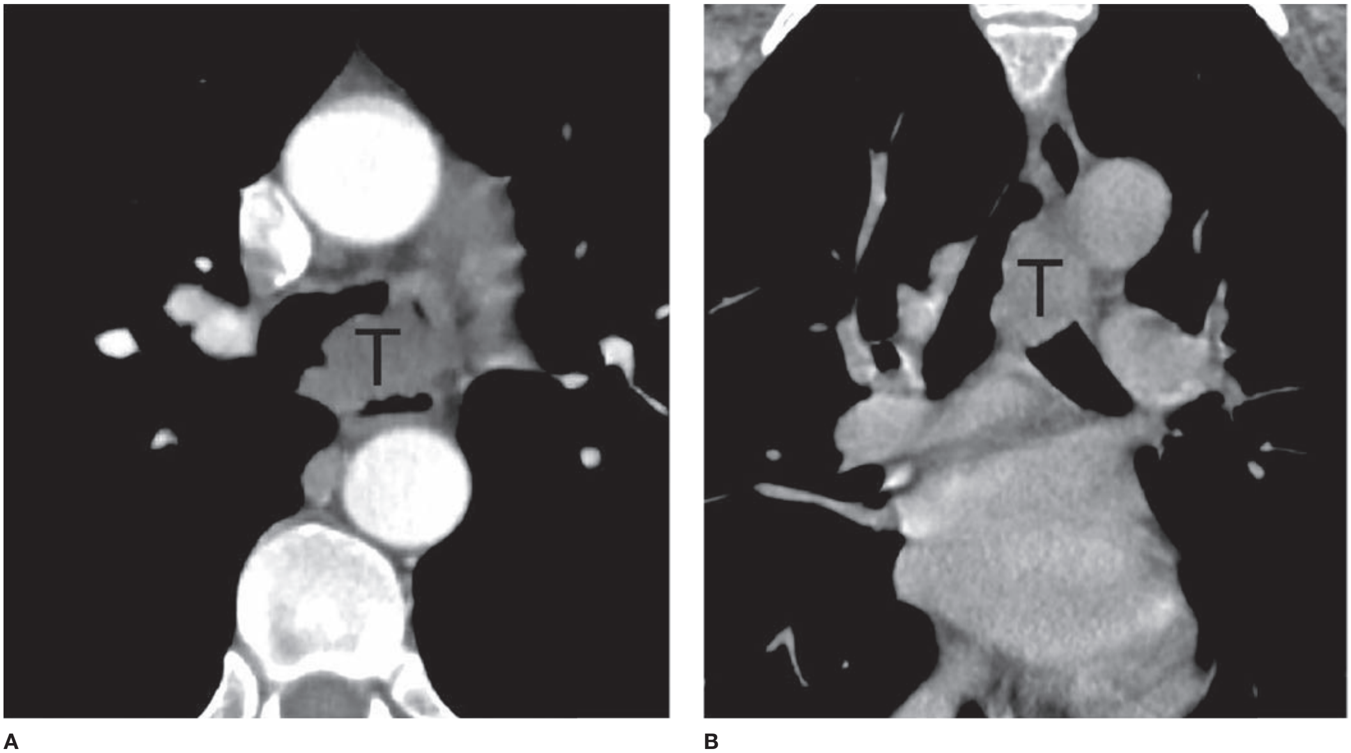

Figure 117-5 Adenoid cystic carcinoma. Composite CT image in the axial **(A)** and coronal **(B)** planes demonstrates an endobronchial tumor **(T)** with nodular and annular mural components involving the distal trachea and proximal left main bronchus. Biopsy revealed an adenoid cystic carcinoma. The combination of nodular and annular growth pattern is characteristic of adenoid cystic carcinoma, but differential diagnostic considerations include squamous-cell carcinoma and mucoepidermoid carcinoma.

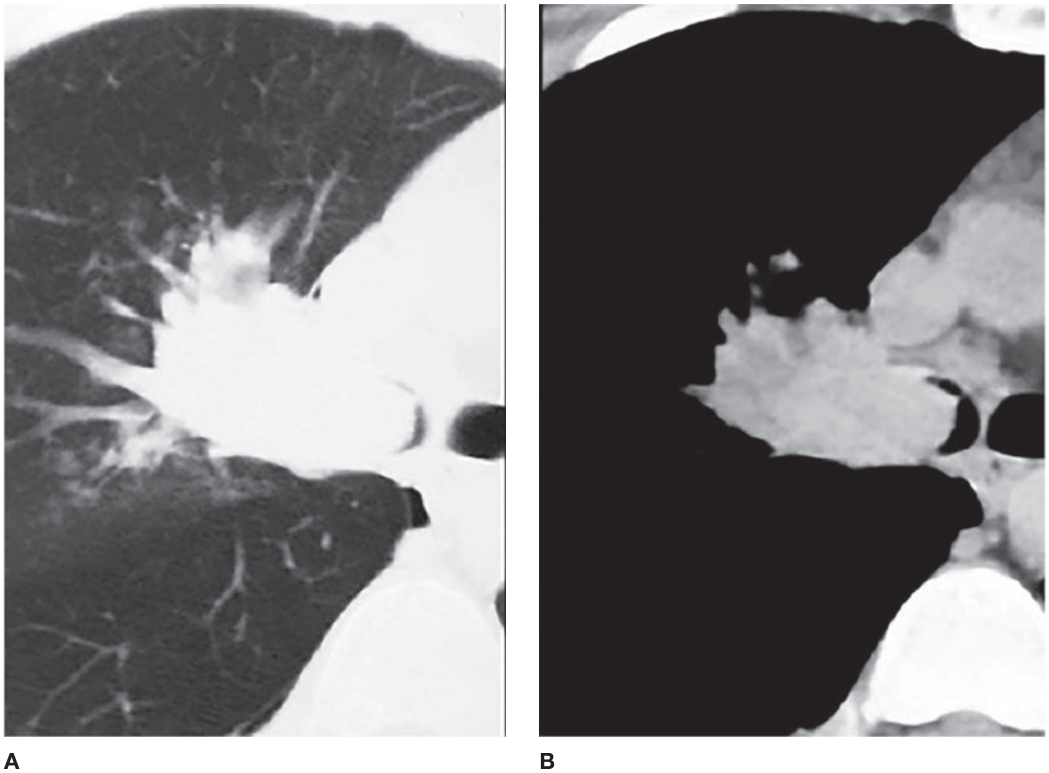

Figure 117-6 Mucoepidermoid carcinoma. Composite of axial CT image shown in both lung window (**A**) and mediastinal window (**B**) demonstrates a mucoepidermoid carcinoma involving the right main and right upper-lobe bronchi with distal patchy ground-glass opacity and several small centrilobular nodules as a manifestation of obstructive pneumonitis. Mucoepidermoid carcinomas affect primarily the lobar and segmental bronchi.

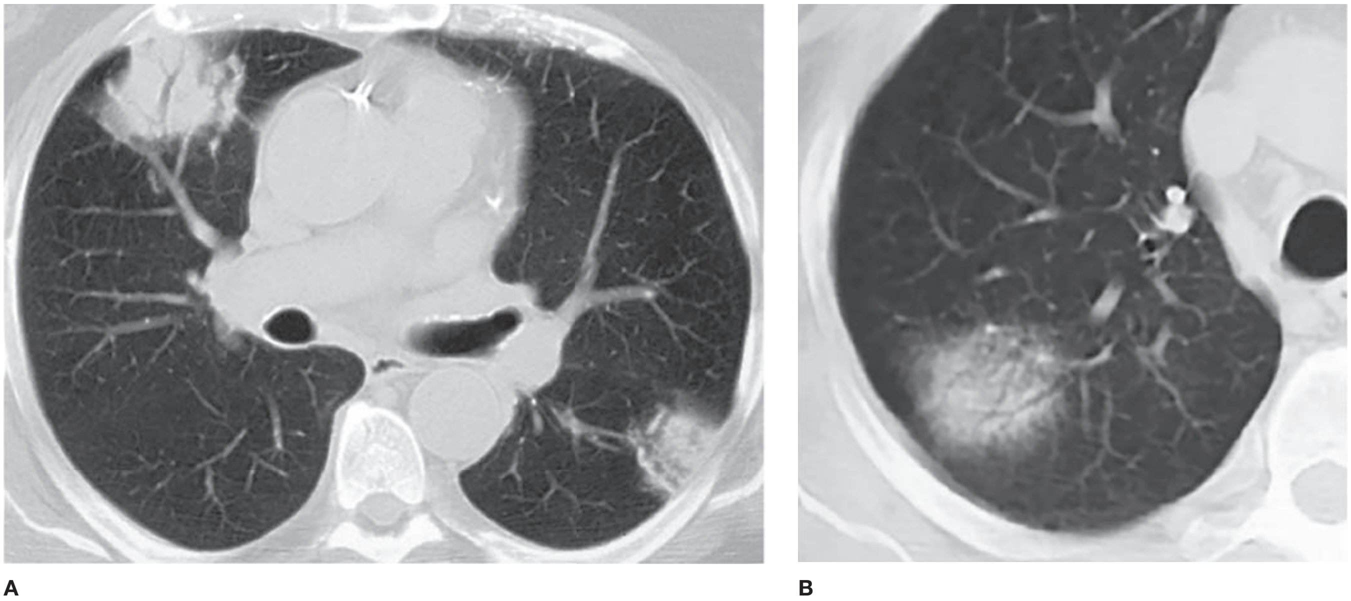

Figure 117-7 Lymphoma. Axial CT images of two patients demonstrate multifocal **(A)** and focal **(B)** pulmonary lymphoma manifesting as rounded consolidative opacities that exhibit air bronchograms, a characteristic appearance of pulmonary lymphoma. Other imaging manifestations include areas of segmental or lobar consolidation and less frequently endobronchial lesions. Chest wall invasion may also occur.

smoking.[63] Carcinosarcomas, often referred to as mixed tumors, are composed of a mixture of epithelial and mesenchymal components that are both malignant. Either of the malignant components may predominate—the carcinomatous (squamous cell carcinoma, adenocarcinoma, or undifferentiated carcinoma) or the sarcomatous (spindle cell, rhabdomyosarcoma, chondrosarcoma, or osteosarcoma).[63]

The characteristic gross pathologic features of carcinosarcoma are a large mass (average diameter 6 cm) with an upper lobe predominance, frequently with associated areas of necrosis and hemorrhage. Direct tumor extension may occur to the pleura, chest wall, and mediastinum.

Microscopically, the carcinomatous elements are often displaced to the tumor periphery, suggesting rapid growth of the central sarcomatous elements that form the bulk of the tumor. Immunohistochemical staining for keratin is positive for both the epithelial and mesenchymal components, suggesting that carcinosarcomas are of a monoclonal epithelial origin that has undergone sarcomatoid metaplasia.

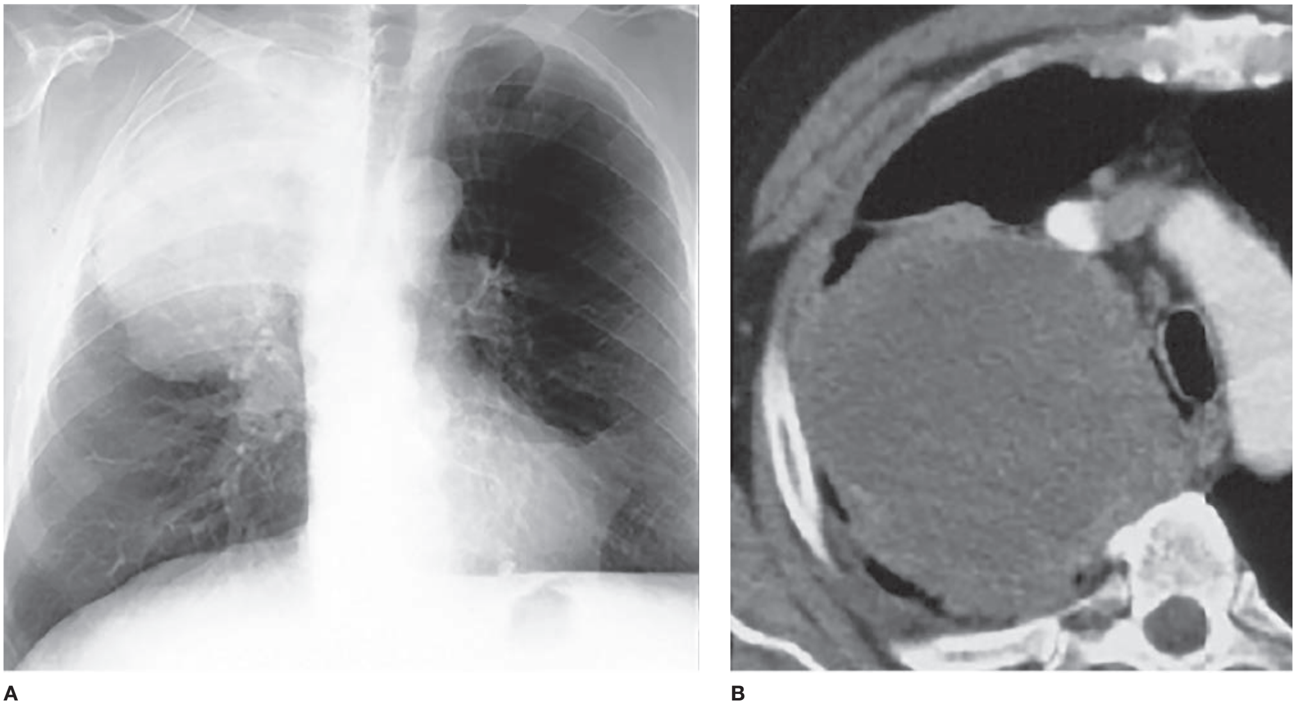

Figure 117-8 Carcinosarcoma. Composite image of PA chest radiograph (**A**) and axial CT (**B**) demonstrate a large in the right upper lobe of an elderly man with a 40-pack-year history of cigarette smoking. The mass abuts the mediastinal and costal pleural surfaces and exhibits heterogeneous low attenuation, suggestive of necrosis. While lung cancer was the most likely diagnosis to consider, histologic evaluation revealed carcinosarcoma.

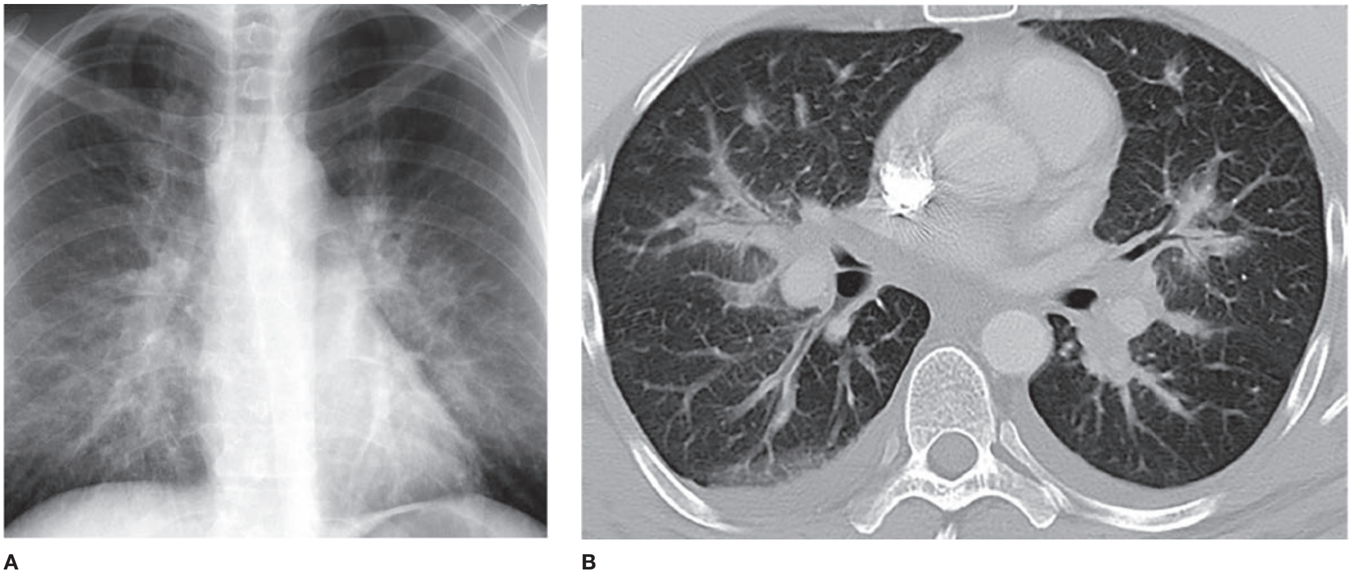

Figure 117-9 Kaposi sarcoma. PA chest radiograph (**A**) of a 38-year-old man with AIDS-KS demonstrates bilateral perihilar and midzone patchy opacities that appear to extend along the bronchovascular structures. Axial chest CT (**B**) reveals indistinct patchy and nodular opacities extending along the bronchovascular structures and within the lung parenchyma. The peribronchovascular opacities have been described as flame-shaped, some with peripheral halos of ground glass opacity. There are additional findings of bilateral pleural effusions and bilateral hilar lymphadenopathy, characteristic findings in Kaposi sarcoma.

On imaging, carcinosarcoma typically manifests as a large mass, predominantly involving an upper lobe, that may manifest signs of mediastinal and/or chest wall invasion, often with associated findings of atelectasis and pneumonia (Fig. 117-8).

Clinically, carcinosarcoma is characterized by aggressive growth, local invasion, widespread metastases, and rapid death.[63]

■ Kaposi Sarcoma

Kaposi sarcoma (KS) is a low-grade mesenchymal neoplasm of blood and lymphatic vessels that is associated with human herpesvirus type 8.[64,65] Four distinct types include iatrogenic KS, endemic KS, classic or Mediterranean KS, and AIDS-KS. AIDS-KS is the most common AIDS-related neoplasm. Affected patients typically present with dyspnea and cough, especially those patients with CD4 lymphocyte counts less than 200 cells/mm^3.

On imaging, AIDS-KS typically manifests as ill-defined nodules in a mid- to lower-zone-predominant pattern, with nodules typically in a symmetric perihilar and peribronchovascular distribution (Fig. 117-9). The consolidative nodules have been described as having a "flame-shaped" appearance, often with a halo of ground-glass opacity.[65] Associated findings of interlobular septal thickening, nodularity along interlobar fissures, lymphadenopathy, and pleural effusions are common. The treatment for AIDS-KS is highly active antiretroviral therapy and chemotherapy.

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CHAPTER 118

Extrapulmonary Syndromes Associated with Lung Tumors

Nicholas J. Pastis
Nichole T. Tanner
Gerard A. Silvestri

INTRODUCTION

A wide variety of extrapulmonary syndromes have been reported with lung cancer. This chapter focuses primarily on paraneoplastic syndromes, a heterogeneous group of disorders associated with cancer but not due to direct invasion, obstruction, or metastasis.[1,2] As many paraneoplastic syndromes share similar underlying mechanisms, they may be classified according to the system in which they cause disease (endocrine, hematologic, dermatologic, rheumatologic, or neurologic syndromes). More broadly speaking, they are either hormonally or immunologically based.

Paraneoplastic syndromes affect up to 8% of patients with cancer,[3] and of all malignancies, lung cancer is most commonly associated with these syndromes. The subtype of lung cancer most commonly associated with paraneoplastic syndromes is small-cell lung cancer (SCLC),[4] but some syndromes such as hypertrophic pulmonary osteoarthropathy (HPO) and hypercalcemia are more common in non–small-cell lung cancer (NSCLC).[5]

Endocrine and hematologic syndromes associated with lung tumors are listed in Table 118-1. The endocrine syndromes are characterized by the ectopic production by tumor cells of biologically active peptide hormones that bind to receptors in adjacent or distant organs, giving rise to a clinical syndrome. Hematologic syndromes develop in patients with lung cancer through the production by tumor cells of cytokines that activate progenitor cells in the bone marrow. Neurologic syndromes, such as encephalomyelitis and subacute sensory neuropathy, are caused by the induction of antibodies directed against proteins expressed by the lung cancer cells and directed against antigens present on cells in the nervous system.

In clinical practice, an understanding of the extrapulmonary syndromes is important for several reasons: (1) recognition of a syndrome may serve as a harbinger of an occult malignancy or may signify disease recurrence; (2) the course of the endocrine and hematologic syndromes usually parallels the course of the lung cancer, although the neurologic syndromes frequently do not; and (3) appropriate treatment of the extrapulmonary syndrome often reduces the patient's morbidity and may allow definitive treatment of the cancer. In general, definitive treatment of the underlying tumor is the most effective form of therapy for the paraneoplastic syndromes, so their presence should not preclude treatment of lung cancer with curative intent as most syndromes are reversible once the patient receives treatment.

HYPERCALCEMIA OF MALIGNANCY

Hypercalcemia is commonly seen in cancer patients,[6,7] and lung cancer is the most common solid tumor associated with it, occurring in up to 20% of patients.[8,9] It is overall the most common of the paraneoplastic syndromes. It occurs most frequently in patients with squamous cell lung cancer but is occasionally seen in patients with adenocarcinoma and very rarely in patients with SCLC.[10]

Biology

Etiologic mechanisms for hypercalcemia in patients with lung cancer include tumor secretion of parathyroid hormone–related peptide (PTHrP), tumor production of the active metabolite of vitamin D (calcitriol, also called 1,25-dihydroxyvitamin D_3), and localized osteolytic hypercalcemia due to osteolytic metastasis with release of cytokines including osteoclast activating factors.[6,11] Most cases of hypercalcemia in patients with lung cancer are caused by the ectopic production of PTHrP by tumor cells (referred to as humoral hypercalcemia of malignancy).[12–14] The PTHrP gene expresses three messenger RNAs (mRNAs) that encode three distinct peptides, each differing at the COOH-terminal region (Fig. 118-1). Eight of the first 13 amino acids in PTHrP are homologous with PTH, so similar functional activity is shared between the 2 peptides. PTHrP mRNA and peptides have been demonstrated in cancer cells from patients with lung cancer and hypercalcemia. PTHrP has been shown to bind to PTH receptors in the bone and kidney, which causes increased osteoclastic bone resorption, decreased bone formation, and decreased calciuria, leading to hypercalcemia.[15,16] Levels of 1,25-dihydroxyvitamin D_3 are suppressed in patients with PTHrP-induced hypercalcemia, but are raised in patients with primary hyperparathyroidism. This difference occurs because renal α-hydroxylase activity is low in PTHrP-induced hypercalcemia, unlike primary hyperparathyroidism.[17] PTH production by lung

TABLE 118-1 Endocrine and Hematologic Syndromes Associated with Lung Tumors

Syndrome	Tumor	Proteins/Cytokines
Hypercalcemia of malignancy	Non–small-cell	Parathyroid hormone–related peptide
		Parathormone
Hyponatremia of malignancy	Small-cell	Arginine vasopressin
	Non–small-cell	Atrial natriuretic peptide
Ectopic ACTH syndrome	Small-cell	Adrenocorticotropic hormone
	Carcinoid tumors	Corticotropin-releasing hormone
Acromegaly	Carcinoid tumors	Growth hormone–releasing hormone
	Small-cell	Growth hormone
Carcinoid syndrome	Carcinoid tumors	Serotonin
	Large-cell	
	Small-cell	
Granulocytosis	Non–small-cell	G-CSF
		GM-CSF
		IL-6
Thrombocytosis	Non–small-cell	IL-6
	Small-cell	
Thromboembolism	Non–small-cell	Unknown
	Small-cell	

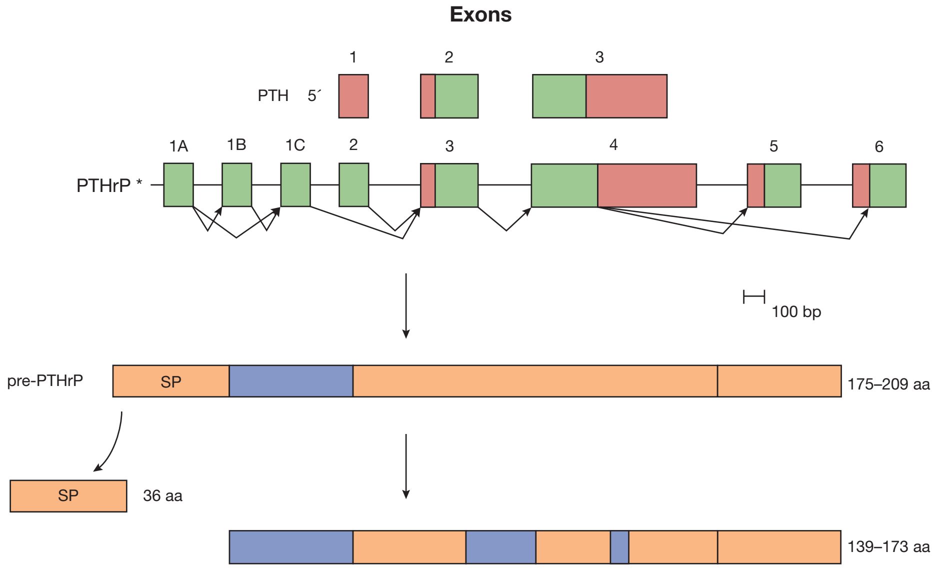

Figure 118-1 Parathyroid hormone and parathyroid hormone–related peptide. The human PTH gene has three exons, which constitute the protein-coding segments. Three exons are represented by 3 boxes for PTH and 8 exons are represented by 8 boxes for PTHrP. The PTHrP gene is more complex, with eight exons. Through alternative splicing, three different isoforms of mRNA can be produced. These isoform mRNAs encode the pre-PTHrP proteins, which vary in size from 175 to 209 amino acids (aa). Thirty-six amino acids are removed from the amino terminal end as the signal peptide. Three different PTHrP molecules are produced, with 139 to 173 aa. The rectangular region at the carboxy terminal represents the different lengths of PTHrP. The N-terminal region (1-34aa) mimics the classic PTH-like function (*purple box on left*). The midregion of the peptide stimulates placental calcium transport (*orange and purple box*). The C-terminal region (107-111 aa) inhibits osteoclast bone resorption (*orange, purple, orange boxes before box at carboxy terminal*).

cancer cells also has been described, but it is a very rare cause of hypercalcemia of malignancy.[18–20] Other factors that cause bone resorption have been identified in the plasma of patients with lung cancer, including transforming growth factor α and a vitamin D metabolite. These are very rare, however, and their causative role in hypercalcemia has not been shown conclusively.

Diagnosis

The early symptoms of hypercalcemia include thirst, malaise, fatigue, anorexia, polyuria, constipation, nausea, and vomiting. As hypercalcemia becomes increasingly severe (>14.0 mg/dL), confusion, lethargy, coma, and death can occur. The demonstration of a suppressed intact parathyroid hormone (iPTH) level and a low or normal calcitriol level along with an increased concentration (>10.5 mg/dL) of calcium in the serum of a patient with NSCLC should suggest this paraneoplastic syndrome. This is in contrast to the findings of elevated iPTH and calcitriol levels in primary hyperparathyroidism, which may occur in up to 10% of patients with cancer. A complete diagnostic evaluation includes measuring serum concentrations of iPTH, PTHrP,[21] 1,25-dihydroxyvitamin D, 25-hydroxyvitamin D, calcium, albumin, magnesium, and phosphorus. Other potential causes of elevated serum calcium also should be excluded. Thiazide diuretics, vitamin D or lithium administration, hyperthyroidism, and sarcoidosis are potential causes.[22] Bone scintiscan should be obtained to exclude bone metastases. An elevated PTHrP level in the absence of bone metastases establishes the diagnosis of humoral hypercalcemia of malignancy caused by ectopic PTHrP.[16,21]

Treatment

As with other paraneoplastic syndromes, treatment of the underlying cancer is the most effective method of treating the humoral hypercalcemia associated with lung cancer. Until this can occur, medical management of hypercalcemia must be considered. If asymptomatic or mildly symptomatic, hypercalcemic patients with calcium levels less than 12 mg/dL (3 mmol/L) do not require immediate treatment. Similarly, a serum calcium level of 12 to 14 mg/dL (3–3.5 mmol/L) may be well tolerated chronically and may not require immediate treatment. However, an acute rise to these concentrations may cause a marked change in sensorium and an oncologic emergency requiring urgent intervention.[23] Patients with a serum calcium concentration greater than 14 mg/dL (3.5 mmol/L) require treatment, regardless of symptoms.[24,25] Treatment includes intravenous normal saline. The addition of furosemide diuresis should not be routine and should occur only after correction of intravascular volume depletion. Loop diuretics may be needed in patients with renal insufficiency or heart failure. Subcutaneous calcitonin has a rapid onset of action and is most useful in severe cases. Bisphosphonates, such as pamidronate, are effective for long-term control of hypercalcemia.[26] In patients in whom bisphosphonates are contraindicated (severe renal impairment), denosumab can be administered. Corticosteroids exert their effect through inhibition of dihydroxyvitamin D_3 synthesis and therefore have less effect in patients with elevated PTHrP. There may be circumstances requiring hemodialysis when serum calcium concentrations are 18 to 20 mg/dL with neurologic symptoms or in severe cases when patients cannot be safely hydrated due to renal insufficiency or heart failure.[27]

Humoral hypercalcemia usually develops in patients with advanced progressive cancer and is associated with a median survival of about 1 month.[28,29] Nonetheless, in some cases, treatment of hypercalcemia serves an important palliative role by improving symptoms and allowing patients to be discharged from the hospital. Hypercalcemia is often a sign of metastatic non–small-cell lung cancer, so early palliative care consultation is recommended.[27]

HYPONATREMIA OF MALIGNANCY

Hyponatremia is a frequent complication in patients with cancer. It occurs at presentation in approximately 15% of patients with SCLC and 1% of patients with NSCLC.[30] The ectopic production of arginine vasopressin (AVP) by cancer cells plays a causal role in the majority of cases.[30] This form of hyponatremia is recognized

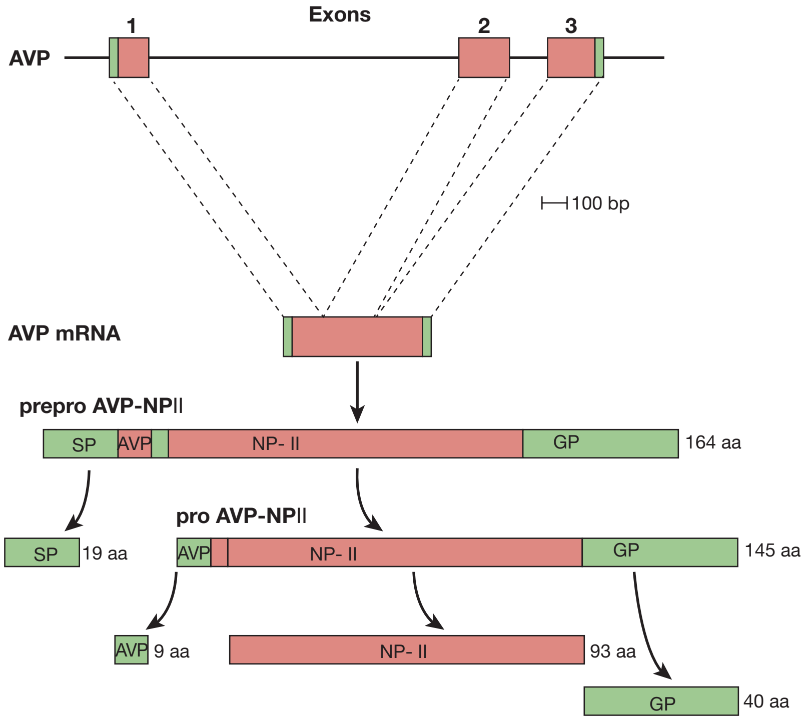

Figure 118-2 Arginine vasopressin. The three exons of the human AVP gene rise to a 700-base arginine vasopressin mRNA. The mRNA is translated into a 164-amino-acid (aa) preprohormone with a 19-aa amino terminal signal peptide (SP). The SP is cleaved, giving rise to a 145-aa prohormone. This prohormone is processed into the nonapeptide AVP, a 93-aa neurophysin (NP), and a 40-aa glycoprotein (GP). The black line divisions in each box represent the protein-coding portions of the gene and mRNA.

as the *syndrome of inappropriate antidiuretic hormone* (SIADH). Up to one-third of patients with lung cancer and hyponatremia do not demonstrate elevation of AVP in their tumors or plasma.[31–33] In these patients, the ectopic production of atrial natriuretic peptide (ANP) has been implicated, but the exact contribution of this hormone remains to be defined.[31]

■ Biology

AVP is a nine-amino-acid peptide normally produced by the neurohypophysis. The peptide binds to receptors in the kidney to reduce the excretion of free water. When plasma osmolality exceeds 280 mOsm/kg, the release of AVP from the pituitary increases, causing the kidney to retain more free water and maintain fluid and osmolar balance. In patients with SCLC, ectopic production of AVP causes hyponatremia by inhibiting free-water excretion in the distal tubule of the kidney. AVP mRNA is expressed in SCLC cells and the peptide is translated and secreted (Fig. 118-2). Measured levels of AVP in plasma are often increased.[34]

There is a subgroup of patients with SCLC and hyponatremia, however, who have no detectable levels of plasma AVP.[35] Similar findings have been shown in SCLC cell lines.[36] The tumors from these patients express ANP mRNA and secrete the peptide, resulting in high levels of circulating ANP in plasma.[37] ANP is the leading candidate to be the natriuretic factor that Bartter and Schwartz proposed in their original description of SIADH. Further investigation into the precise role of ANP in patients with SCLC and hyponatremia of malignancy is ongoing.

■ Diagnosis

In patients with lung cancer, hyponatremia is most frequently diagnosed as a laboratory abnormality in the absence of significant symptoms. The symptoms of acute hyponatremia do not typically occur because the syndrome develops over a prolonged period in concert with the growth of the lung cancer. When symptomatic, mild hyponatremia (serum sodium <135 mmol/L) can cause headache, difficulty concentrating, nausea, weakness, and fatigue. Severe hyponatremia (serum sodium <125 mmol/L), especially when it develops rapidly, can lead to serious symptoms including confusion, hallucinations, seizures, coma, respiratory arrest, decerebrate posturing, and death.[38]

The diagnosis of SIADH is based on the following criteria: (1) plasma hypo-osmolality (<280 mOsm/kg); (2) osmolality of urine greater than serum (usually >500 mOsm/kg); (3) persistent urinary excretion of sodium in the absence of diuretics (>20 mEq/L); (4) absent signs of volume depletion; and (5) normal renal, adrenal, and thyroid function.[39]

In patients with lung cancer, nonmalignant causes of hyponatremia should be considered in the initial evaluation. These include diuretic use, renal disease, cardiac dysfunction, hypoadrenalism, thyroid disease, and dilutional hyponatremia. Medications as a cause for hyponatremia also should be addressed. Patients with lung cancer are commonly treated with cisplatin, selective serotonin reuptake inhibitors, and narcotics, which can cause SIADH.

■ Treatment

The initial therapy for hyponatremia caused by lung cancer is treatment of the underlying malignancy. This often involves multimodality therapy with surgical excision, radiation, and/or chemotherapy. Even with tumor response to therapy, hyponatremia often persists or may recur following tumor progression. In SCLC, there are data to suggest that those patients who do not fully regain normal values of plasma sodium have a poorer survival than those patients who do.[40,41]

Asymptomatic patients with chronic hyponatremia are at low risk for serious neurologic sequelae but are at risk of developing osmotic demyelination with rapid correction of the serum sodium concentration.[42] Treatment is therefore aimed at gradual correction. Fluid restriction, which can be estimated by urinary and plasma electrolytes, but is usually started at 500 mL per day, is a cornerstone of therapy.[43] Pharmacologic therapy may be indicated when fluid restriction is ineffective or poorly tolerated. Demeclocycline blocks the action of AVP on the renal tubule, thereby reducing urine osmolality and increasing serum sodium levels; however, its effects can be variable, and it can cause nephrotoxicity.[38] Lithium and phenytoin also inhibit the effects of AVP on the renal tubule but are no longer recommended for treatment. A more recent option for the treatment of hyponatremia is vasopressin receptor antagonists. Conivaptan is a nonselective vasopressin receptor antagonist indicated for patients with moderate to severe hyponatremia with no severe symptoms and is administered intravenously.[44] Tolvaptan is an orally active, selective AVP receptor 2 (V2) antagonist that has a similar indication. By blocking AVP effects in the renal collecting duct, aquaresis is promoted, leading to a controlled increase in serum sodium levels.[45]

For patients who present with severe, symptomatic hyponatremia characterized by seizure, delirium, or coma, rapid treatment is warranted.[46] The widely accepted goal of therapy is to correct the serum sodium by 1 to 2 mmol/L per hour through the infusion of 3% saline. The administration of concomitant furosemide also is recommended. The magnitude of correction within the first 24 h is suggested to be no more than 8 to 10 mmol/L and no more than

18 to 25 mmol/L in the first 48 h to avoid osmotic demyelination. An alternative approach is to treat until acute symptoms resolve and then adjust the correction rate.[47]

ECTOPIC ADRENOCORTICOTROPIC HORMONE (ACTH) SYNDROME

Lung cancers are the most common neoplasms that cause ectopic ACTH production and Cushing syndrome, accounting for 50% of all cases. SCLC accounts for 80% to 90% of cases associated with lung cancer. Carcinoid tumors (10%) and bronchial adenocarcinomas (5%) also have been reported to produce biologically active ACTH. While biochemical abnormalities suggestive of ectopic ACTH production are reported in 30% to 50% of SCLC, Cushing syndrome is clinically present in only 1% to 5% of SCLC.[48–53] Hypercortisolism is important to recognize as it increases the risk of therapy-induced complications[54,55] such as opportunistic infections and venous thromboembolism (VTE).[56–58]

Biology

Most cases of Cushing syndrome associated with lung cancers are caused by ectopic production of ACTH by the tumor.[59] The precursor gene, proopiomelanocortin (POMC), is expressed in the cancer cells, and a 241-amino-acid prohormone is translated and then cleaved into ACTH (39 amino acids), melanocyte-stimulating hormone, and opiate-like hormones (Fig. 118-3). The ACTH binds to receptors in the adrenal gland, causing them to produce excessive glucocorticoid and mineralocorticoid hormones.[60]

Ectopic production of corticotropin-releasing hormone (CRH) has been reported as a cause of Cushing syndrome in a small number of patients with SCLC or bronchial carcinoids.[52] CRH is a 41-amino-acid peptide normally produced in the paraventricular nuclei of the hypothalamus that stimulates the release of ACTH from the pituitary.

Clinical Presentation and Diagnosis

Ectopic ACTH production occurs with equal frequency in males and females, but Cushing syndrome has an 8:1 female preponderance. Patients who have slow-growing carcinoid tumors often present with the clinical features of Cushing syndrome: truncal obesity, moon facies, striae, polyuria, and polydipsia. In contrast, patients with SCLC often present with other signs of mineralocorticoid and glucocorticoid excess due to the rapidity of tumor growth: edema, weakness, hypertension, and hypokalemic alkalosis.

The diagnostic evaluation of ectopic ACTH syndrome starts by excluding iatrogenic Cushing syndrome in order to avoid unnecessary chemical testing. Once iatrogenic disease has been excluded, initial testing should include the following: 24-h urinary free cortisol, late-night salivary cortisol, and the low-dose dexamethasone suppression test.[61–64] The diagnosis of Cushing syndrome is established when at least two of these tests are unequivocally abnormal. Demonstration of an increased plasma ACTH level (>22 pg/mL) confirms that the hypercortisolism is ACTH-dependent. Finally, persistently elevated serum cortisol in response to a high-dose dexamethasone suppression test differentiates ectopic ACTH syndrome from a pituitary source (high-dose dexamethasone will suppress pituitary but not ectopic source of ACTH).[61,65,66] Bronchial carcinoids are an exception, because in some tumors ACTH and cortisol levels have been suppressed by dexamethasone.[67,68]

In patients with clinical features of Cushing syndrome in whom the dexamethasone suppression test is equivocal, a CRH stimulation test or bilateral inferior petrosal vein sampling will provide the definitive diagnosis. After CRH infusion, pituitary tumors release increased amounts of ACTH, whereas pituitary-independent lung tumors should not. Similarly, in pituitary-dependent Cushing syndrome, petrosal vein sampling will reveal a gradient between the level of ACTH in the petrosal vein and the peripheral concentration. In contrast, patients in whom ACTH is ectopically produced demonstrate no gradient between the petrosal vein and the peripheral blood.[69,70]

Treatment

Management of a patient with lung cancer and ectopic ACTH syndrome requires therapy directed at both the underlying tumor and the hypercortisolism. The treatment for a patient with ectopic ACTH production is to remove the source of the ACTH. This requires combination chemotherapy, with or without irradiation, for patients with SCLC and surgical resection and/or radiation for patients with carcinoid tumors. Chemotherapy for patients with SCLC and ectopic ACTH syndrome has been problematic. Patients often have a poor response to chemotherapy and are susceptible to

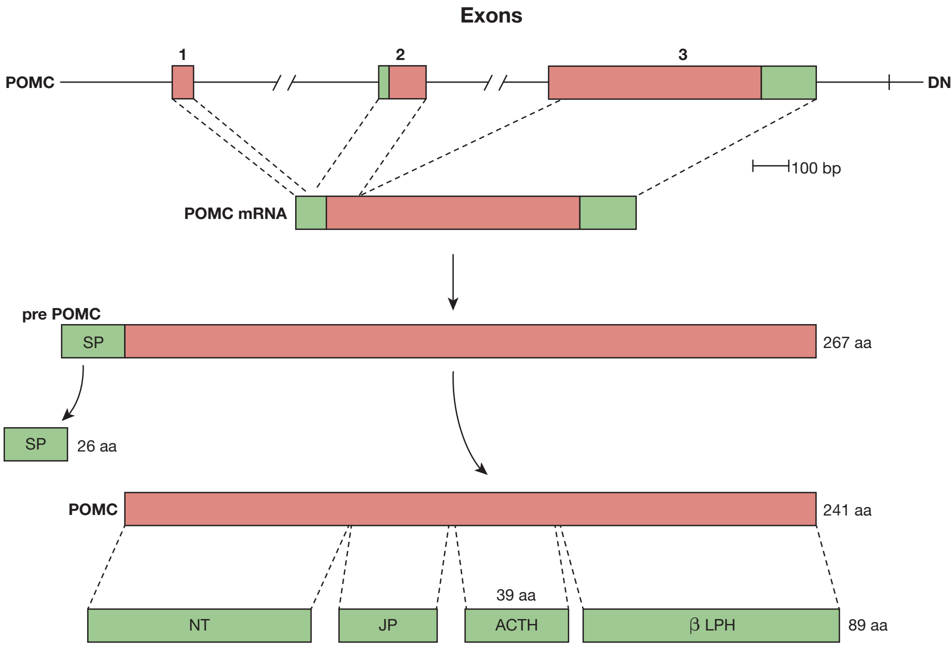

Figure 118-3 Proopiomelanocortin. The three exons of the POMC gene give rise to a 1072-base POMC mRNA. The mRNA is translated into a 267-amino-acid pre-POMC with a 26-amino-acid amino terminal signal peptide (SP). The SP is cleaved, creating the 241-amino-acid POMC. The POMC peptide is cleaved into many products, including the N-terminal peptide (NT), the joining peptide (JP), a 39-amino-acid mature ACTH, and β-lipotropin (β-LPH). The molecules can also undergo further processing. The black portions of the exons represent the protein-coding portion of the gene and mRNA.

early infection and death. Early control of a patient's glucocorticoid excess is beneficial and may reduce the morbidity of treatment.

When removal of the ectopic source of ACTH is not possible, pharmacologic agents directed at blocking adrenal cortisol production may be successful. These drugs include ketoconazole, mitotane, metyrapone, and aminoglutethimide. Ketoconazole is an imidazole derivative that inhibits steroidogenesis at both adrenal and gonadal sites; it may be the most effective and least toxic agent available.[71,72] Metyrapone and aminoglutethimide also have shown limited success by inhibiting adrenal steroid synthesis. Octreotide, a somatostatin analogue, can suppress ectopic ACTH production and has been reported to be useful in some of these patients.[71] Bilateral adrenalectomy should be considered in patients who fail medical therapy.[65,73]

In some patients, the clinical signs and symptoms of ectopic ACTH production develop before the development of a clinically obvious lung cancer. In these cases, symptomatic management of hypercortisolism is undertaken and periodic imaging studies are performed because these patients may have a slow-growing carcinoid tumor that will be amenable to surgical resection.[67,74]

ACROMEGALY

Only 1% of acromegaly is caused by ectopic production of growth hormone–releasing hormone (GHRH) or growth hormone (GH) by tumors.[75] Of these, the majority are caused by carcinoid tumors of the lung and intestine.[76]

Biology

The ectopic production of GHRH or GH by lung cancers has been demonstrated to cause acromegaly. In most cases, the GHRH gene is expressed by the cancer cells, and a 40- or 44-amino-acid peptide is produced.[77] Circulating GHRH peptide binds to receptors in the pituitary gland resulting in the production of excessive amounts of GH.[78] GH then mediates its effects through GH receptors in soft tissue and by stimulating the production of insulin-like growth factor 1 (IGF-1).

Although many carcinoid tumors express immunoreactive GHRH and result in abnormal GH secretion,[79–81] most patients with these tumors are not clinically acromegalic. It has been suggested that the observed high incidence of GHRH expression and low incidence of clinical acromegaly may be due to inadequate tumor production of GHRH or due to the impaired bioactivity of the circulating GHRH.[78]

Diagnosis

The earliest features of GH excess are hypertrophy of the extremities and face (often manifest as increased glove, shoe, and ring size), thickened leathery skin, prominent skin folds, hyperpigmented skin, and hair growth. Bony changes, hypertension, and diabetes mellitus are later, less common findings.

The presentation of a patient with a lung mass and signs of acromegaly should raise suspicion of ectopic acromegaly especially if the mass is found to be carcinoid. The diagnosis of ectopic acromegaly is established by elevated serum levels of GHRH or GH, the absence of a pituitary tumor, complete recovery following lung tumor resection, positive GHRH immunostaining, detection of GHRH mRNA, positive bioassay (cultured rat pituitary cells produce GH in response to tumor extract), or GHRH extraction from the tumor tissue.[82] Because coincidental pituitary tumors and solid tumors have been described, patients who have lung cancer in association with low GHRH levels and high GH and IGF-1 levels should undergo magnetic resonance imaging (MRI) to exclude a pituitary tumor.

Treatment

Management of ectopic acromegaly involves surgical resection of the tumor and is often curative in those with lung carcinoid. In those with unresectable or metastatic cancers, medical therapy with somatostatin analogues, such as octreotide and bromocriptine, has been shown to be effective.[83,84] Bromocriptine acts by inhibiting GH release by the pituitary; octreotide lowers both GH and IGF-1 levels in plasma and also appears to inhibit GHRH release by tumors. Clinical abatement of acromegalic features has been reported in patients treated with octreotide.

CARCINOID SYNDROME

Ectopic serotonin production is rare in lung neoplasms, occurring in 1% to 5% of patients with pulmonary neuroendocrine tumors (NETs).[85] Hallmarks of the syndrome include flushing of the skin of the upper thorax, secretory diarrhea, and bronchoconstriction. It is important to recognize an acute carcinoid crisis in patients with lung cancer as it can be precipitated by chemotherapy, biopsy, anesthesia, surgery, or the use of adrenergic drugs. It is a result of a massive serotonin release and can lead to cardiopulmonary failure.[86]

The evaluation for carcinoid syndrome begins with a 24-h urine collection for the main metabolite of serotonin, 5-hydroxyindoleacetic acid (5-HIAA). This test has a specificity of approximately 90%.[87] Detection of occult NETs in patients presenting with a carcinoid syndrome may be aided by testing for serum biomarkers of NETs such as neuron-specific enolase (NSE) and chromogranin A.[88] When these serum biomarkers are negative in a patient with high clinical suspicion of a NET, radionuclide-labeled octreotide scintigraphy is useful as up to 80% of pulmonary NETs express somatostatin receptors.

In patients who are surgical candidates, surgery is the optimal treatment of carcinoid syndrome. Otherwise, control of symptoms should be the goal via somatostatin analogues, serotonin receptor blockers, interferon, and antidiarrheal medications. In addition, carcinoid crisis can be prevented or treated with intravenous octreotide acetate.[86]

HEMATOLOGIC SYNDROMES

Most hematologic syndromes associated with lung tumors are not as well characterized as the endocrine syndromes, and an ectopic hormone responsible for the syndrome has not been identified in most tumor tissues. In many of the hematologic syndromes, such as granulocytosis and thrombocytosis, clinical sequelae are often absent. As with the endocrine paraneoplastic syndromes, the most appropriate therapy for the hematologic syndromes is the treatment of the underlying neoplasm.

Granulocytosis

NSCLC is the most common cancer associated with granulocytosis. Some 15% to 20% of patients with NSCLC have granulocytosis, with absolute white blood counts ranging from 10,100 to 25,000 (normal range, 4000–10,000). Its presence is associated with a poorer prognosis compared to patients without granulocytosis.[89–91] Although granulocyte colony–stimulating activity can be demonstrated in serum and/or urine in 80% of affected patients, tumor production of granulocyte colony–stimulating factor, granulocyte-monocyte colony–stimulating factor, or interleukin 6 (IL-6) has been shown in only a minority of patients.[92,93]

Virtually all patients with lung cancer who present with tumor-associated granulocytosis are asymptomatic from the excess white blood cells. The diagnosis is suggested by the presence of an increased white blood count in which neutrophils predominate without immature forms, in the absence of nonneoplastic causes. An increased leukocyte alkaline phosphatase score and a normal bone marrow are consistent with this diagnosis.

Thrombocytosis

Thrombocytosis is common in patients with lung cancer, afflicting 16% to 32% of patients with both NSCLC and SCLC.[94,95] The pathogenesis of thrombocytosis in patients with lung cancer has not been definitively elucidated. IL-6, which is a cytokine for megakaryocytes, has been demonstrated in cell lines from patients with lung cancer and thrombocytosis, and increased levels of IL-6 have been demonstrated in the plasma of such patients. Thrombopoietin is increased in patients with lung cancer and thrombocytosis but is decreased in patients with essential thrombocytosis. The identification of the thrombopoietin gene may lead to a better understanding of the role of this protein in paraneoplastic thrombocytosis.

Patients with thrombocytosis are nearly always asymptomatic and do not have an increased incidence of thromboembolism. The diagnosis of cancer-associated thrombocytosis is suggested by an increased platelet count (>500,000/mm^2) in a patient with newly diagnosed lung cancer, and it is associated with advanced disease and worse clinical outcomes.[96,97] A primary myeloproliferative disorder can be excluded by a bone marrow biopsy.[98] In addition, the presence of the JAK2 V617F mutation may indicate essential thrombocytosis (present in 50% of cases) since it is not present in cases of reactive thrombocytosis.[99]

■ Thromboembolism

Of all disease states, lung cancer is known to have one of the strongest associations with VTE.[100] The incidence of VTE in patients with lung cancer is approximately 40 to 100 cases per 1000 person-years compared to 1 to 2 cases per 1000 person-years in the general population. It is also notable that 20% of patients who present with recurrent idiopathic venous thrombosis are found to have an underlying diagnosis of cancer.[101] The spectrum of causes of thrombosis in patients with lung cancer is broad, including disseminated intravascular coagulation (DIC), Trousseau syndrome (recurrent migratory venous thrombophlebitis), nonbacterial thrombotic endocarditis, and obstruction of great vessels.[102,103] Surgical procedures and chemotherapy also have been demonstrated to increase risk of thrombotic complications among cancer patients.[104]

Cancer cells are able to directly activate the clotting cascade via two procoagulants: tissue factor and cancer procoagulant. Increased expression of human tissue factor has been shown in NSCLC tissue, and active tissue factor–bearing microparticles, which may originate from tumor cells, have been demonstrated in the circulation of cancer patients.[105,106] Microparticle-associated tissue factor activity has been proposed as a mechanism for the prothrombotic state in cancer patients.[107]

The treatment of VTE associated with active lung cancer differs from standard treatment of VTE as the increased risk of recurrent thromboembolism must be balanced with the increase risk of bleeding. It was previously shown that for recurrent thromboses (as in Trousseau syndrome), long-term subcutaneous heparin is more efficacious than warfarin.[108] A meta-analysis of six randomized controlled trials in cancer patients being treated with long-term anticoagulation for VTE found a statistically significant reduction in VTE with LMWH compared to warfarin, with no significant difference in bleeding.[109,110] In addition, a large multinational randomized controlled trial showed that the direct oral anticoagulant apixaban (without a previous course of heparin) is an effective and safe alternative to dalteparin (an LMWH) for VTE associated with malignancy.[111] LMWH is contraindicated with creatinine clearance <30 mL/min. Direct oral anticoagulants have not been adequately studied in patients with renal insufficiency; dose adjustments and monitoring of anti-factor Xa levels may be necessary if used in this setting.[112]

NEUROLOGIC SYNDROMES

There are a number of paraneoplastic neurologic syndromes associated with lung cancer. Encephalomyelitis, cerebellar degeneration, retinopathy, opsoclonus/myoclonus, and the Lambert–Eaton syndrome have all been described and are most commonly associated with SCLC. The majority of these syndromes are a result of an autoimmune response directed at shared antigens present in both cancer cells and normal neural tissue. The autoantibodies associated with each neurologic syndrome are listed in Table 118-2.

■ Encephalomyelitis/Subacute Sensory Neuropathy

The paraneoplastic syndrome of encephalomyelitis/subacute sensory neuropathy was first described in a patient with SCLC. More than 70% of cases of paraneoplastic encephalomyelitis are diagnosed in patients with SCLC, with a wide range of clinical presentations. A specific antibody, anti-Hu, which reacts with the HuD antigen expressed by lung cancer cells and neuronal tissues, has been identified in many patients who develop this syndrome. Approximately 20% of patients with SCLC are seropositive for anti-Hu, but only a few will develop a paraneoplastic neurologic disorder.[113]

Biology

Anti-Hu is an IgG antibody found in the sera and cerebrospinal fluid of patients with sensory neuropathy and encephalomyelitis. Patients with anti-Hu have an immune response targeting a family of proteins known as Hu, which are expressed in both neurons and SCLC cells. They are RNA-binding proteins involved in the post-transcriptional regulation of RNA in neurons.[114] The *HuD* gene has been mapped to the chromosome 1p region and appears to be a marker of neuroendocrine differentiation in these cells.

Diagnosis

The location and severity of neuronal loss predict the patient's clinical symptoms. Neuronal loss may be limited to one area of the nervous system but more frequently involves multiple areas over time.[34] Onset of symptoms is subacute and precedes the diagnosis of SCLC in greater than 70% of cases, thus warranting a complete diagnostic evaluation for occult malignancy in those presenting with encephalomyelitis or subacute sensory neuropathy. One-half of patients undergo progressive sensory loss in the hands and feet. Others present with a limbic encephalopathy characterized by memory loss, behavioral changes, and seizures. Focal myelopathy with weakness, brain stem signs (nystagmus, dysarthria), and autonomic nervous system dysfunction also occur in patients with this syndrome. CT scans are typically normal in these patients, but MRI studies may show increased T2 signal in affected areas of the brain.

TABLE 118-2 Neurologic Syndromes Associated with Lung Cancer

Syndrome	Tumor	Antibody	Antigen
Encephalomyelitis/subacute sensory neuropathy	Small-cell	Anti-Hu	Hu-D antigen: 35- to 40-kDa neuronal nuclear protein
Cancer-associated retinopathy	Small-cell	Antirecoverin	23-kDa protein specific to photoreceptor cells (recoverin)
Lambert–Eaton syndrome	Small-cell	Anti-P/Q channel	P/Q-type calcium channel

Pathologic examination demonstrates neuronal loss and inflammatory infiltrates in areas of the nervous system including the brain stem, hippocampus, spinal cord, and dorsal root ganglia.[115] Serum and cerebrospinal fluid from patients with paraneoplastic encephalitis will often reveal the anti-Hu antineuronal antibody.

Treatment

Early diagnosis and treatment of the underlying tumor offers the best chance for stabilizing the neurologic syndrome.[116] Alternative therapies with immunosuppressive agents and plasmapheresis, with the goal of clearing the responsible antibody, have been shown to be effective in only 10% to 20% of patients. Patients with anti-Hu positive neurologic paraneoplastic syndromes are more likely to die of neurologic causes including respiratory muscle failure, autonomic failure, and progressive diffuse encephalopathy rather than from metastatic cancer.[117,118]

■ Paraneoplastic Cerebellar Degeneration

Paraneoplastic cerebellar degeneration is manifested by symptoms including ataxia, nystagmus, dysarthria, mental status changes, muscular and sensory deficits, and diplopia. This disorder accounts for 12% of cases of paraneoplastic neurologic syndromes secondary to lung cancer.[119] Pathologically, there is the diffuse loss of Purkinje cells accompanied by thinning of the molecular and granular layers, and degeneration of the long tracts of the spinal cord.[120] In patients with SCLC, paraneoplastic cerebellar degeneration can occur with or without the presence of Hu antineuronal antibodies, indicating that the syndrome can develop via different immunologic mechanisms.[117]

■ Opsoclonus and Myoclonus

Opsoclonus is a disorder consisting of involuntary rapid conjugate eye movements in vertical and horizontal directions. It is often associated with myoclonus in patients with solid tumors. This syndrome of opsoclonus/myoclonus has been identified in both SCLC and NSCLC. Opsoclonus/myoclonus is the main presentation of paraneoplastic cerebellar degeneration associated with anti-Ri antibodies.[121] Anti-Ri binds to two proteins (55 and 80 kDa) expressed in the dentate nucleus.[122] Anti-Ri antibodies have also been identified in those presenting with a broad variety of neurologic symptoms.[123] The anti-Hu antibody has been identified in some patients with SCLC and opsoclonus/myoclonus.

■ Cancer-associated Retinopathy

Cancer-associated retinopathy is a rare paraneoplastic syndrome that occurs predominantly in patients with SCLC. Autoantibodies have been identified in patients with this disorder that bind to a photoreceptor-specific protein called recoverin.[124,125]

Biology

Retinal ganglion cells and their processes are characteristically lost in this disorder because of the autoantibodies that bind to recoverin, a 23-kDa photoreceptor-specific protein found in rods and cones as well as in SCLC cells. The autoantibodies that cause the cancer-associated retinopathy specifically bind to the recoverin protein and do not recognize other retinal proteins.[89,90,126,127]

Diagnosis

The clinical triad of photosensitivity, ring-scotoma visual field loss, and attenuation of retinal arteriole caliber is considered highly suggestive of cancer-associated retinopathy. The typical patient presents with symptoms of rapid visual loss, night blindness, and color loss. On physical examination, most patients demonstrate visual field deficits, disk pallor, and cells in the vitreous body, along with arteriolar narrowing.

Demonstration of the anti-recoverin antibody in a patient with signs of retinopathy establishes the diagnosis. As with paraneoplastic cerebellar degeneration, cancer-associated retinopathy is often the first sign of an occult carcinoma. Therefore, an evaluation for lung cancer should be performed in all patients who present with this syndrome.[91,128,129]

Treatment

In contrast to those with the other paraneoplastic neurologic syndromes, more than half of patients with cancer-associated retinopathy have been reported to respond with visual improvement after systemic steroid therapy. Treatment of the primary tumor without immunosuppressive therapy has not been shown to result in visual improvement in patients with cancer-associated retinopathy, and most of these patients develop progressive visual loss and blindness within 18 months.[130]

■ Lambert–Eaton Syndrome

The Lambert–Eaton syndrome afflicts fewer than 2% of lung cancer patients but has been reported in up to 5% of patients with SCLC. Conversely, 50% to 60% of all patients with Lambert–Eaton syndrome will be diagnosed with SCLC.[131]

Biology

Lambert–Eaton syndrome is a consequence of the development of antibodies to P/Q-type voltage-gated calcium channels in motor and autonomic nerve terminals, leading to inhibition of acetylcholine release.[132] The resulting weakening of the neuromuscular signal results in neurologic dysfunction. This antibody also binds to the 58-kDa synaptic vesicle protein synaptotagmin, which is present in SCLC cells.[133] These antibodies have been detected in 85% to 90% of patients with Lambert–Eaton syndrome and some reports cite close to 100% detection in those with SCLC.[134]

Diagnosis

Lambert–Eaton syndrome is diagnosed based on clinical signs and symptoms, electrophysiologic studies, and antibody testing. The classic clinical triad is proximal muscle weakness (usually the first symptom noted), autonomic dysfunction, and areflexia.[135] While symmetric muscle involvement is most common, some patients present with isolated weakness (e.g., only proximal legs, isolated limb, ocular, oropharyngeal, or respiratory muscles).[136,137] Physical examination reveals decreased or absent tendon reflexes. Because there is a short-term return of reflexes following muscle contraction in 40% of patients, these should be tested after a period of rest.[138] Electrophysiologic studies with repetitive nerve stimulation are often diagnostic of Lambert–Eaton syndrome. A decrement in the amplitude of the muscle action potential of at least 10% is considered abnormal, a finding seen in the overwhelming majority of patients with Lambert–Eaton syndrome. Nerve stimulation after exercise demonstrates an amplitude increase, which has a high sensitivity and 100% specificity for Lambert–Eaton syndrome and distinguishes this entity from myasthenia gravis.[139,140]

Treatment

Treatment of the underlying SCLC with chemotherapy often can effectively treat Lambert–Eaton syndrome. Should symptoms persist, the first choice of treatment is 3,5-diaminopyridine, which results in functional improvement the majority of the time. There are two proposed mechanisms of action. First, by blocking voltage-gated potassium channels, the action potential at the motor nerve terminals is prolonged and the opening time of the voltage-gated calcium channels is lengthened.[141] Second, neuromuscular transmission is potentiated by targeting a subunit on the voltage-gated

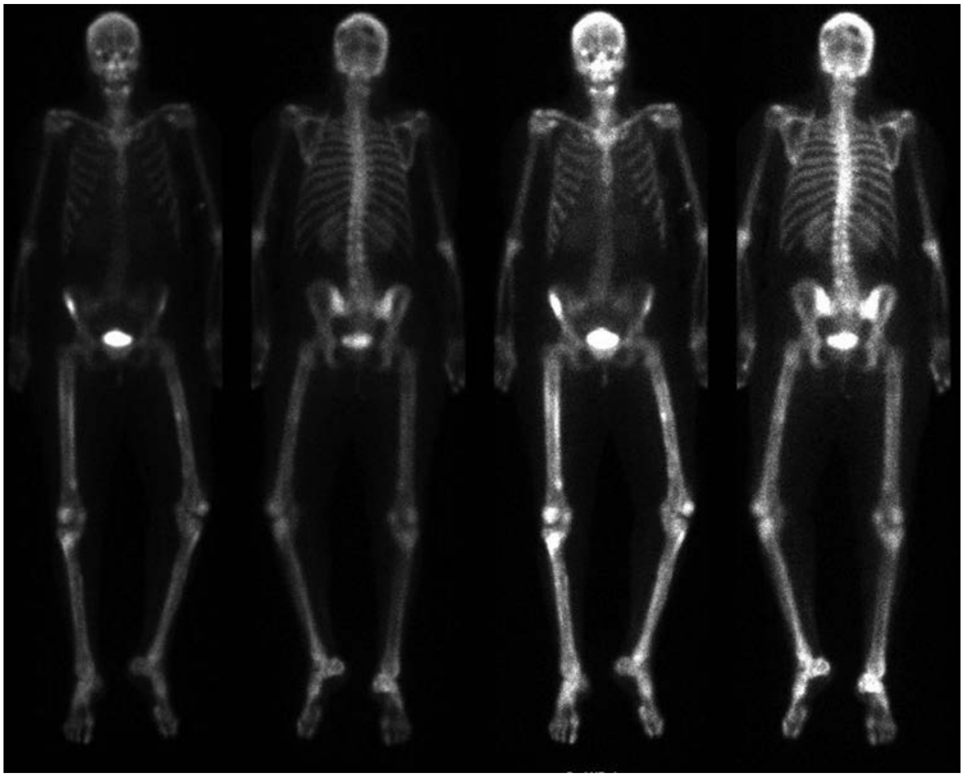

Figure 118-4 Tc99 bone scintigraphy reveals symmetric diffusely increased uptake mainly along the cortical margins of both femurs (seen best in the two delayed phase images on the right).

calcium channel directly.[142] In those with severe weakness and impairment that develops gradually over time and fails to improve despite treatment of the underlying cancer and a trial of 3,5-diaminopyridine, combined therapy with prednisone and azathioprine has been shown to be effective.[143] For those with severe weakness and severe impairment that develops rapidly, treatment with intravenous immunoglobulin or plasmapheresis is indicated as it can provide marked, albeit transient, improvement in strength while treatment for SCLC is started.[144]

HYPERTROPHIC PULMONARY OSTEOARTHROPATHY

HPO is characterized by the abnormal proliferation of the cutaneous and osseous tissues at the distal parts of the extremities. While any intrathoracic malignancy may be associated with HPO, the disease is secondary to primary lung cancer in 80% of cases.[145] HPO is estimated to occur in 0.7% to 4.5% of patients with lung cancer.[145–148]

■ Biology

While the exact mechanisms of HPO have not been elucidated, there are a number of theories. One theory suggests that arteriovenous shunting within the tumor allows platelet clumps and megakaryocytes that are usually cleared by the pulmonary endothelium to enter the systemic circulation and deposit in the distal vasculature, causing the local release of growth factors including platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF).[149] PDGF causes proliferation of fibroblasts and an increase in vascularity and permeability resulting in connective tissue changes that are the hallmark of clubbing.[150] VEGF leads to vascular hyperplasia, osteoblastic differentiation with new bone formation, and edema; all are features of HPO.[151] Ectopic production of these growth factors by the lung cancer is an alternative hypothesis.[152] Finally, there is a neurogenic hypothesis that proposes a vagally-mediated alteration in limb perfusion. This is supported by experimental and clinical observation of resolution of HPO symptoms following unilateral vagotomy.[153]

■ Diagnosis

Diagnosis of HPO is based on clinical symptoms, physical examination, and radiographic findings. The classic triad consists of digital clubbing, arthritis, and bilateral, symmetrical periosteal formation of new bone. The latter finding is often present on plain films of the long bones but bone scintigraphy is the most sensitive method for the detection and evaluation of the extent of HPO-associated periostitis (Fig. 118-4). With its ability to delineate the subtleties of the disease, scintigraphy often reveals abnormalities that precede plain radiograph changes.[154] Scintigraphy findings range from symmetrical increased "bracelet-like" uptake to diffuse uptake in the juxta-articular regions and distal portions of the long bones.[155] There are case reports documenting the ability of fluoro-18-deoxyglucose positron emission tomography (PET) to detect periosteal new bone formation of HPO and it is more sensitive and specific than bone scintigraphy for detecting bone metastasis as an alternative cause of long bone pain.[156–158]

■ Treatment

With resection and/or treatment of the primary tumor, the symptoms of HPO will improve and often resolve completely.[148,159,160] When the primary tumor cannot be eliminated, there are a variety of symptomatic treatments for HPO, based largely on the postulated pathogenetic mechanisms, that anecdotally have been demonstrated to be effective.[161] Performance of unilateral vagotomy on the ipsilateral tumor side has led to complete resolution of pain and radiographic regression of HPO.[162,163] There are a number of case reports to support the use of nonsteroidal anti-inflammatory drugs including ketorolac, indomethacin, and the COX-2 inhibitor rofecoxib.[149,164,165] Prostaglandin E is effectively reduced with these medications, thereby decreasing periostitis and HPO symptoms. The somatostatin analogue octreotide has also been used with success in

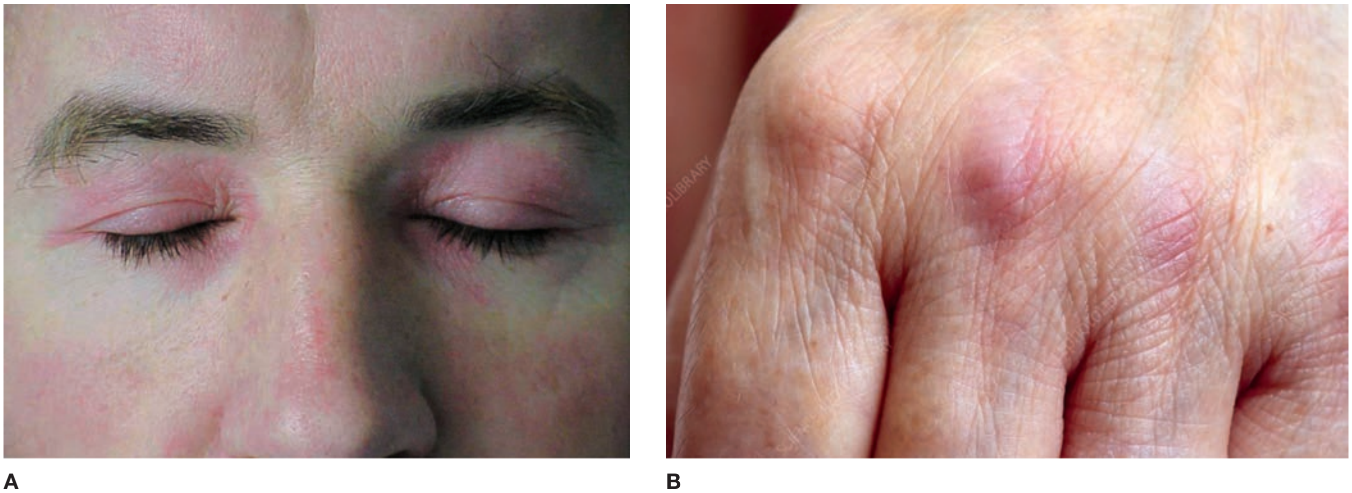

Figure 118-5 Dermatomyositis periorbital heliotrope rash and Gottron's papules on hands. *(**A.** Reproduced with permission from Jaeschke R, Gajewski P, O'Byrne PM: McMaster Textbook of Internal Medicine 2019/20. Kraków, Poland: Medycyna Praktyczna; 2019. **B.** SPL/Science Source.)*

the treatment of HPO and is thought to be efficacious due to inhibition of VEGF and endothelial proliferation.[166,167] Bisphosphonates are potent inhibitors of bone metabolism and also decrease the levels of VEGF, and symptomatic improvement has been demonstrated with both pamidronate and zoledronic acid.[168,169]

INFLAMMATORY MYOPATHIES

Polymyositis (PM) and dermatomyositis (DM) are autoimmune inflammatory myopathies that can manifest as paraneoplastic syndromes in the setting of lung cancer, though they are more common in association with other malignancies.[1] DM has a stronger association than PM with malignancy and about 10% to 25% of cases are paraneoplastic.[170,171] SCLC is more commonly associated with DM.[172–174] Painless proximal muscle weakness is a hallmark. DM is associated with a heliotrope rash (purple periorbital discoloration), Gottron papules (purple papules and plaques on the dorsum of both hands) and erythematous rash on the face, neck, back, chest, and shoulders (Fig. 118-5).[175] The diagnosis of DM is suggested by an elevated level of creatine phosphokinase, characteristic findings on electromyography, and muscle biopsy findings demonstrating a mixed B- and T-cell perivascular inflammatory infiltrate and perifascicular muscle fiber atrophy.[176] The mainstay of management of these syndromes consists of cancer-directed therapy. Standard treatments of inflammatory myopathies may also be necessary, such as high-dose glucocorticoids or other immunosuppressive medication. In general, these syndromes are less responsive to immunosuppressive medications than when not paraneoplastic.[177]

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CHAPTER 119

Lymphoproliferative Diseases Involving the Lung

Venerino Poletti
Sara Piciucchi
Silvia Asioli

INTRODUCTION

Nomenclature and classification schemes of lymphoproliferative disorders have undergone changes over the past 20 years. Malignant lesions are now best classified according to the current World Health Organization (WHO) schemes.[1,2] In the lung and pleura, primary lymphoproliferative disorders represent a wide and overlapping spectrum of conditions from reactive polymorphous and polyclonal processes to various entities of malignant lymphomas. The natural history of these diverse conditions is variable, and further heterogeneity is recognized within distinct disease entities. Primary pleuropulmonary lymphoproliferative diseases are rare, whereas lymphomas secondarily affecting the lungs occur in up to 20% of autopsy cases. Although most diagnoses are based on light microscopy, immunohistochemical and molecular investigations have assumed a vital role. A schematic classification of lymphoid disorders involving primarily the lung and pleura is shown in Table 119-1.

ANATOMY AND HISTOLOGY OF THE PULMONARY LYMPHOID SYSTEM

Pulmonary lymphatics originate in superficial and deep plexuses; the interalveolar septa and the alveolar ducts and sacs have no lymph vessels.[3] The superficial plexus lies deep to the visceral pleura and in the fibrocollagenous interlobular septa, and its efferents pass around the margins of the lung and its fissures, eventually reaching the bronchopulmonary (hilar) nodes. The deep lymphatics originate at the bronchiolar level and follow the divisions of the bronchial tree and pulmonary vessels up to the lung hilum, ending in the same nodes as the superficial plexus. The lymphatics communicate at lobar, lobular, and pleural boundaries and, thus, serve each other as potential collaterals. These channels ultimately flow into the intrathoracic lymphatic duct, which then typically empties into the left subclavian vein.[4,5] Lymphatics are not usually obvious in histologic sections of normal lung, but they are prominent and open in some of the disorders that manifest with specific lymphatic involvement, such as cardiogenic edema and lymphangitic carcinomatosis. In the latter, lymphatic channels distended with malignant cells are apparent within the visceral pleura, interlobular septa, and adventitia of arteries, veins, and bronchioles. All lymphatics contain valves and extremely thin, flat endothelial cells lining a rudimentary basement membrane. These endothelial cells express characteristic markers, such as podoplanin (a mucin-type transmembrane glycoprotein), lymphatic vessel endothelial hyaluronan receptor 1 (LYVE-1, a CD 44 homolog), products of the homeobox gene PROX1, vascular endothelial growth factor receptor 3 (VEGFR-3), and fibrillin 1 and 2. Larger lymphatics contain smooth muscle cells and collagen.[6]

Small submucosal aggregates of lymphoid cells are often prominent at bronchial bifurcations and near distal respiratory bronchioles (pulmonary microtonsils) and represent bronchus-associated lymphoid tissue (BALT)[7] (Fig. 119-1). Whether humans are born with this specialized secondary lymphoid system, or whether the aggregates of B lymphocytes, T lymphocytes, HLA-DR+ interdigitating cells, follicular dendritic cells, and lymphoid follicles with overlying flattened and attenuated specialized epithelium develop in response to antigenic stimulation is still controversial.[7–11] Viruses, connective tissue disorders, tobacco use, bronchiectasis, and obstructive pneumonia are just a few of the pathologic processes known to induce BALT. Unlike typical lymph nodes that rely on afferent lymphatics for antigen retrieval, BALT is integrated into lung tissue, and antigen is sampled directly from the bronchial and bronchiolar lumens through specialized "lymphoepithelium." This specialized pseudostratified bronchial epithelium is depleted in cilia and goblet cells and infiltrated by T lymphocytes, and it is capable of specific phago-pinocytosis and antigen presentation. Immunoglobulins, most notably IgA, are synthesized and secreted by lymphocytes directly into airway lumens. Amazingly, this system appears capable of mounting a competent adaptive immune response. In addition, BALT B lymphocytes circulate and "home" to other mucosal sites, such as the conjunctiva, salivary glands, stomach, and intestines, to

TABLE 119-1 Classification of Lymphoid Disorders Affecting Only or Mainly Lung and Pleura

Benign Hyperplastic Disorders
Reactive pulmonary lymphoid hyperplasia (nodular)
Follicular bronchitis/bronchiolitis (FBB)
Lymphocytic interstitial pneumonia (LIP)/pulmonary diffuse lymphoid hyperplasia
Common variable immunodeficiency (granulomatous and lymphocytic interstitial pneumonia [GLILD])
Autoimmune lymphoproliferative syndrome
Atypical Lymphoid Hyperplasia
Castleman disease (unicentric, multicentric)
IgG4-related disease
Primary Pulmonary Lymphoid Neoplasms
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
Follicular lymphoma
Diffuse large B-cell lymphomas (DLBCL) as a group
(Variants: lymphomatoid granulomatosis, intravascular lymphoma, primary effusion lymphoma, DLBCL associated with chronic Inflammation)
Plasmacytoma
Amyloidosis
Light chain disease
Extranodal natural killer–T cell lymphoma (nasal type)
Peripheral T-cell lymphoma not otherwise specified
Anaplastic large cell lymphoma
Classic Hodgkin lymphoma
Posttransplant Lymphoproliferative Disorders (PTLDs)
PTLD—early (plasmacytic hyperplasia, infectious mononucleosis–like)
PTLD—polymorphic PTLD—monomorphic (classify according to lymphoma classification)

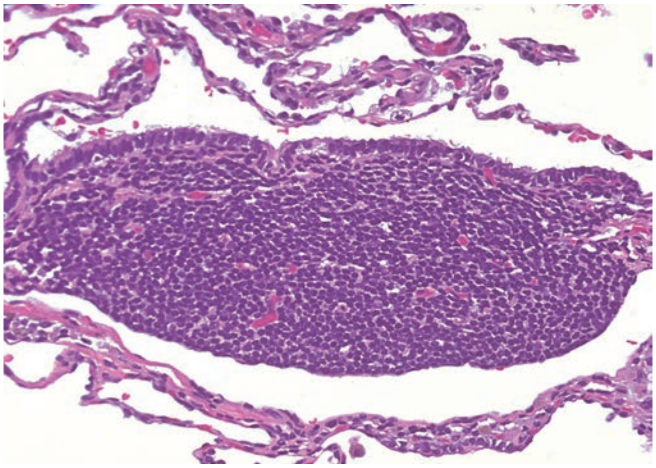

Figure 119-1 Bronchus-associated lymphoid tissue. The submucosal collection of lymphoid cells is intimately associated with overlying bronchiolar epithelium. Hematoxylin and eosin, 40× original magnification.

create a common mucosal immune system—the mucosa-associated lymphoid system (MALT).[12] Thus, responses induced in one location can be replicated at other sites.

Intrapulmonary lymph nodes (IPLs) may be part of the pulmonary immune system and may also be induced by antigenic stimuli, rather than through normal embryologic development.[13] Autopsy studies suggest a prevalence of 18%, and although many are related to bronchi of the first few orders, peripheral subpleural locations are not uncommon. In this age of high-resolution computed tomography (HRCT) and lung cancer screening programs, up to 80% of reported cases of IPLs occur in men with histories of tobacco use, and almost 35% of cases are multiple.[12] They appear as round or angulated, sharply circumscribed subpleural opacities up to 2 cm in diameter and are found along interlobular septa or within major and minor fissures. IPLs histologically resemble classic lymph nodes with well-developed cortical and medullary areas.[13,14] Sinus histiocytes frequently contain abundant anthracosilicotic pigment, and silicotic nodules with calcifications may form. In patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), IPLs may be involved and, rarely, primary lung carcinoma or carcinoma from a nonpulmonary site can metastasize to IPLs.

GENERAL CONSIDERATIONS

Although pulmonologists often diagnose pulmonary diseases on the basis of clinical and radiographic findings and rely on tissue samples merely for confirmation, definitive diagnosis of lymphoid lesions of the lung almost invariably is based on histology. Yet clinical and radiologic features often provide essential clues that narrow the differential. For example, a history of Sjögren syndrome and/or the presence of cysts on HRCT should raise suspicion for the presence of lymphoid interstitial pneumonia (LIP).

Bronchoalveolar lavage fluid analysis by flow cytometry or molecular biology techniques may be diagnostic in cases of B-cell lymphomas (mainly MALT lymphoma), especially when the process presents with alveolar consolidations. Endobronchial ultrasound (EBUS)-directed fine-needle aspirates/biopsies of intrathoracic lymph nodes,[15] large core transthoracic biopsies, and transbronchial biopsies supplemented with ancillary studies may suffice for a diagnosis of malignant lymphoma. Transbronchial cryobiopsy may represent a valid diagnostic approach because samples so obtained are significantly large and without crush artifacts. Peripheral structures of the secondary pulmonary lobules may be captured by this approach, and a "lymphangitic distribution" of the lesions may be proven. Furthermore, cryobiopsy provides ample material for immunohistochemistry and molecular biology analyses.[16] However, surgical wedge biopsies may be required for a precise and definite diagnosis, mainly in primary pulmonary Hodgkin lymphoma (HL) and T-cell lymphoma or when the process manifests with scattered nodules in the lungs. Pleuroscopy or video-assisted thoracoscopic surgery (VATS) are the first-choice techniques in cases of pleural effusion when cytologic analysis of the fluid (using morphology, flow cytometry, and molecular biology investigations) obtained by thoracentesis fails.

In addition to histologic examination, immunophenotyping is routinely performed and has become indispensable in diagnosing and classifying lymphoid lesions of the lung.[1,2] Immunohistochemical studies, fluorescence in situ hybridization (FISH), or other molecular biology techniques can be reliably performed on formalin-fixed, paraffin-embedded tissue, whereas flow cytometry is useful for demonstrating immunoglobulin light-chain restriction in fresh tissue. Aberrant antigen expression by either method also allows for subclassification. Polymerase chain reaction (PCR) may be required in up to 20% of cases to prove clonality.[1,2] Either rearrangement of the immunoglobulin heavy-chain gene joining region (*JH*) or the T-cell receptor γ-chain gene (TCR-γ) can be investigated. Lastly, chromosomal abnormalities indicative of specific lymphomas, such as t(14;18) translocation in follicular lymphoma or t(11;14) translocation in mantle cell lymphoma, may be helpful. Because of the strict links between some kinds of malignant lymphoma and viral infections (Epstein-Barr virus [EBV], human herpesvirus 8 [HHV-8], Human Immunodeficiency Virus [HIV], Hepatitis C Virus [HCV], Human T-Lymphotrophic Virus type 1 [HTLV-1]), specific testing for these agents in biopsy samples is part of the diagnostic workup. Lastly, although clonality indicates malignancy, clonality in pulmonary lymphoid lesions may not predict clinical outcome.[17,18]

REACTIVE LYMPHOID PROCESSES

Although the terminology used to describe inflammatory processes of the lung has remained relatively static over the past 25 years, immunohistochemistry and molecular genetic analysis have redefined diagnostic criteria. Processes arising from BALT include nodular lymphoid hyperplasia (NLH), follicular bronchitis/bronchiolitis (FBB), diffuse lymphoid hyperplasia (DLH), and LIP. Common variable immunodeficiency (CVID) and other genetic disorders also may manifest as lymphoid lesions in the lungs.

■ Nodular Lymphoid Hyperplasia

Known to previous generations of pulmonologists and hematopathologists as "pseudolymphoma," this reactive process was recognized as a form of BALT hyperplasia in the mid-1980s. Although NLH was once considered to be quite common, ancillary studies have convincingly demonstrated that most cases were actually low-grade lymphomas. Thus, true NLH is now considered a legitimate, but exceedingly rare, polymorphous nodular lymphoid lesion of the lung. Interestingly, immunohistochemical studies have documented B-cell lymphomas within pre-existing reactive masses of BALT, such that one could, in the most general sense, consider NLH a precursor lesion.

Most affected individuals are middle aged with a nearly equal gender incidence. Patients are usually asymptomatic, although a small percentage may have autoimmune diseases such as systemic lupus erythematosus or Sjögren syndrome, or polyclonal hypergammaglobulinemia. Lesions usually appear as solitary subpleural radiographic nodules with air bronchograms, but several nodules or localized infiltrates can be seen, the latter finding serving as a reminder that the distinction between nodular and diffuse processes is arbitrary. Up to one-third of cases feature regional lymphadenopathy. Excised tan-white rubbery to firm nodules measure from 0.6 to 6.0 cm. Histologically, the well-demarcated lesions may

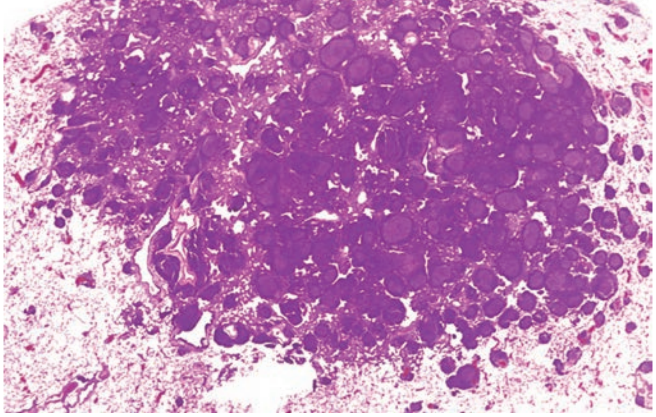

Figure 119-2 Nodular lymphoid hyperplasia. The lesion is composed of benign reactive germinal centers. Although radiographically nodular, germinal centers spill out into surrounding lung. Immunohistochemistry is required to exclude a diagnosis of malignant lymphoma. Hematoxylin and eosin, 1× original magnification.

feature slight extension along alveolar septa and central scarring. Normal lung parenchyma is overrun by large reactive germinal centers with well-preserved mantle zones. Interfollicular areas are filled with plasma cells and mature lymphocytes (Fig. 119-2). The follicles are clearly reactive with a variety of cell types, mitoses, and macrophages. Regional lymph nodes often feature reactive follicular hyperplasia. Histologic diagnosis may be supported by findings observed even in small samples (e.g., regular transbronchial biopsy, transbronchial cryobiopsy, percutaneous guided biopsy).

Immunohistochemical studies demonstrate a mixture of B and T cells. The B cells express both κ and λ light chains without light chain restriction. Aberrant B-cell staining for CD5, CD23, or CD43 is not seen, and the germinal centers do not stain with bcl-2. Immunoglobulin heavy chain gene rearrangement or evidence of t(14;18) breakpoints is not observed. These ancillary findings are of the utmost importance since light microscopy alone may not differentiate NLH from an extranodal marginal zone B-cell lymphoma of MALT. The latter usually features infiltrative growth but may have reactive follicles and polytypic plasma cells with only a focal monotypic cell population. Bronchoalveolar lavage may document an increase of lymphocytes (mainly CD3+ T lymphocytes, but also CD19/CD20+ B lymphocytes without monotypic light chains restriction as assessed in flow cytometry). Positron emission tomography (PET) shows a very low metabolic activity, and surgical excision is done in a significant minority of cases when the suspicion of malignancy is high.

■ Follicular Bronchiolitis

Diffuse lymphocytic lung hyperplasia restricted to the walls of airways and peribronchial tissue is referred to as follicular bronchiolitis (FB).[19–21] FB is often seen in individuals with bronchiectasis, chronic infections, and chronic obstructive pulmonary diseases, including asthma. The entity may also be seen in association with connective tissue diseases, congenital or acquired immunodeficiencies, or bone marrow transplantation, or as a manifestation of a hypersensitivity reaction. FB may also be seen in some occupational exposure settings, for example, nylon flocking workers.[22] Idiopathic forms have been reported.

Patients with FB in association with connective tissue disease are usually in their forties and most often suffer from Sjögren syndrome or rheumatoid arthritis (RA). Rarely it is associated with primary biliary cirrhosis or with chronic hepatitis C virus infection. Patients may also suffer with chronic low-grade infections, such as mycoplasma, chlamydia, adenovirus, or EBV.

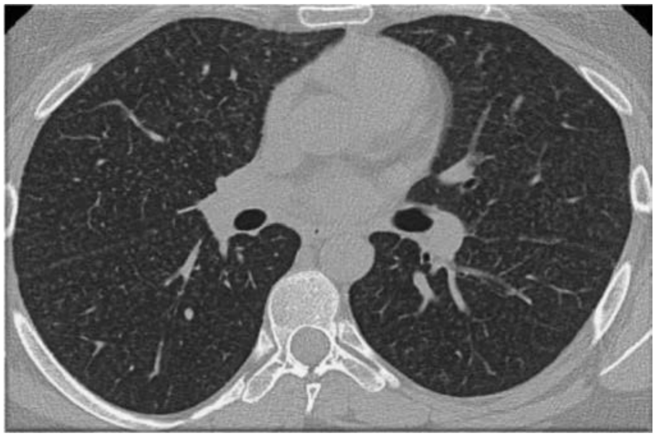

Figure 119-3 CT scan from a patient with Sjögren syndrome demonstrating centrilobular nodules consistent with follicular bronchiolitis.

Individuals with FB present with dyspnea and cough; some may have fever, recurrent pneumonia, or weight loss. Pulmonary function tests reveal restrictive, obstructive, or normal patterns, sometimes with reduced diffusing capacity ($D_{L_{CO}}$). Those with RA often have a very high rheumatoid factor. Peripheral eosinophilia may be noted in those with hypersensitivity syndromes. Chest radiographs feature bilateral diffuse reticular and nodular opacities, whereas HRCT shows up to 12-mm centrilobular and peribronchial nodules, with or without areas of ground-glass opacities[23] (Fig. 119-3). Air trapping also may be a prominent feature. Rarely, cysts as the main feature have been described.[24] Microscopically, nodular aggregates of B cell–rich lymphocytes and plasma cells with reactive germinal centers expand the bronchial and/or bronchiolar submucosa and bulge into, and permeate, overlying epithelium (Fig. 119-4). Rare

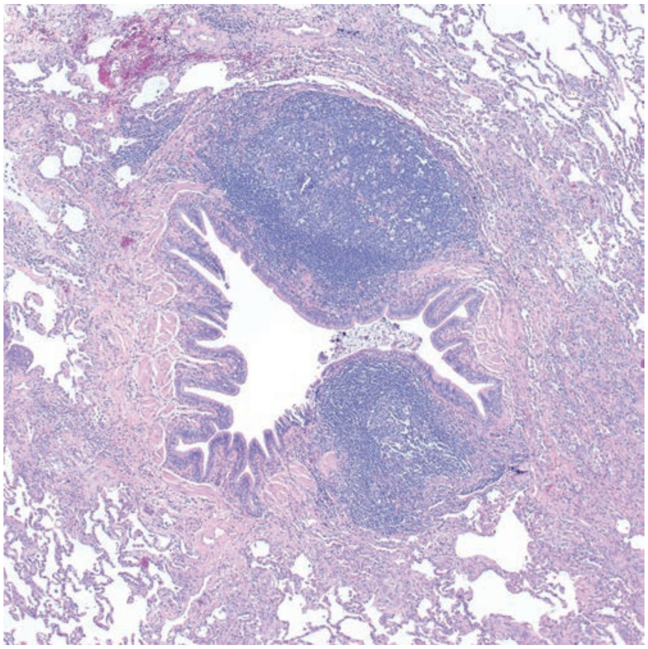

Figure 119-4 Follicular bronchitis/bronchiolitis. Reactive germinal centers expand airway submucosa and compress the lumen. Mucus accumulation often leads to infection and bronchiolectasis. Alveolar parenchyma is spared. Hematoxylin and eosin, 4× original magnification.

T cells wander beyond the follicles into adjacent alveolar septa.[21] Smaller airway lumens are distorted and narrowed, predisposing to mucostasis and subsequent infections. Lymphoid follicles along interlobular septa and beneath the pleura represent a more diffuse form of lymphoid hyperplasia and warrant the descriptive diagnosis of DLH. Bronchoalveolar lavage (BAL) may document an increase of CD3+ lymphocytes and, to a lesser degree, polyclonal B lymphocytes. Lung biopsy (cryobiopsy, VATS) offers definitive diagnosis.[25]

Treatment of FBB with corticosteroids has variable results. Those with peripheral eosinophilia are reportedly steroid-responsive. A prolonged course of low-dose macrolides (after having excluded a mycobacterial infection) may be beneficial.[26]

■ Lymphocytic Interstitial Pneumonia (Diffuse Lymphoid Hyperplasia)

Although LIP is included in the American Thoracic Society/European Respiratory Society (ATS/ERS) classification of idiopathic interstitial pneumonias, this multifactorial, but rarely idiopathic, process represents the most florid form of BALT hyperplasia and may be difficult to differentiate from florid FB and low-grade malignant lymphoma. The morphologic distinction between LIP and diffuse lymphoid hyperplasia is arbitrary.[27] Almost all patients with LIP have immunologic disorders (Sjögren syndrome, systemic lupus erythematosus, RA, Hashimoto thyroiditis, myasthenia gravis, hemolytic anemia, pernicious anemia, chronic active hepatitis, primary biliary cirrhosis), dysproteinemias, or viral infections including EBV and, especially in children, human immunodeficiency virus (HIV).[28,29] LIP may also represent a pulmonary manifestation of chronic graft-versus-host (GVHD) disease in hematopoietic stem cell transplant recipients, or it may be a manifestation of drug-induced lung injury.[30,31]

The clinical presentation includes cough and/or dyspnea in addition to symptoms and signs related to underlying diseases. More than 60% of patients have dysproteinemias, which may precede the onset of LIP or occur any time during the clinical course.[32,33] Most of these cases are associated with hypergammaglobulinemia; only 10% of cases are associated with hypogammaglobulinemia. A monoclonal spike seen with serum immunoelectrophoresis suggests a diagnosis of lymphoma rather than LIP. Pulmonary function tests reveal reduced lung volumes and $\mathrm{DL_{CO}}$, and hypoxia is common. Bronchoalveolar lavage (BAL) analysis shows an increased percentage of lymphocytes, mainly CD3+, but also an increase of polyclonal B cells.

The lungs are typically firm and tan-gray, and end-stage cases feature honeycomb change with subpleural cysts. Although the radiographs and gross appearance suggest parenchymal consolidation, histologically LIP shows a diffuse prominently interstitial infiltrate of small lymphocytes, plasma cells, larger mononuclear cells, and histiocytes (Fig. 119-5). Although the infiltrates are centered on airways, vessels, and interlobular septa, and include peribronchiolar lymphoid follicles, infiltration into alveolar septa is always present and distinguishes LIP from FB. Small nonnecrotizing granulomas, reactive germinal centers, and infiltration into overlying respiratory epithelium are often seen, whereas lymphocytes frequently spill into alveolar spaces. In long-standing lesions, honeycomb changes may be superimposed. HIV-infected patients may show few plasma cells, while occasional cases of LIP are so rich in plasma cells that they have been termed "lymphoplasmacytic pneumonia" or "plasma cell interstitial pneumonia." The lymphoid follicles largely consist of cytologically bland B cells, whereas the interstitial lymphocytes are mostly T cells. Immunoglobulin heavy chain restriction or gene rearrangement is lacking. In addition to malignant lymphoma, nonspecific interstitial pneumonia (NSIP) (the boundaries between these two entities are not always clear), hypersensitivity pneumonitis, and infections, including pneumocystis, should be excluded.

CT demonstrates <3.0-cm thin-walled cysts (Fig. 119-6). They are usually limited in number. Tiny and numerous cysts with a peribronchovascular distribution have been described. Other findings reported are small, ill-defined centrilobular nodules, ground-glass opacities, bronchovascular and interlobular thickening, mosaic attenuation, and enlarged hilar lymph nodes.[34] Cysts may be the only CT scan finding and may be confused with lymphangioleiomyomatosis (LAM) or other cystic lung disorders.[35] The presence of larger calcified nodules suggests the coexistence of nodular amyloidosis.

Given the rarity of LIP, controlled treatment trials have not been undertaken. Corticosteroids are the primary therapy, in addition to other immunosuppressive agents, such as cyclophosphamide and chlorambucil and azathioprine; results are variable. One-third of patients have resolution, one-third stabilize, and the remaining third progress. Nonresponders often die of therapy-related infections, but occasional individuals die of end-stage pulmonary fibrosis. Lymphomatous transformation is very unusual.

In patients with HIV infections or acquired immunodeficiency syndrome, LIP is part of a spectrum of lymphoid proliferations and demonstrates a virtually identical morphology; however, clinical

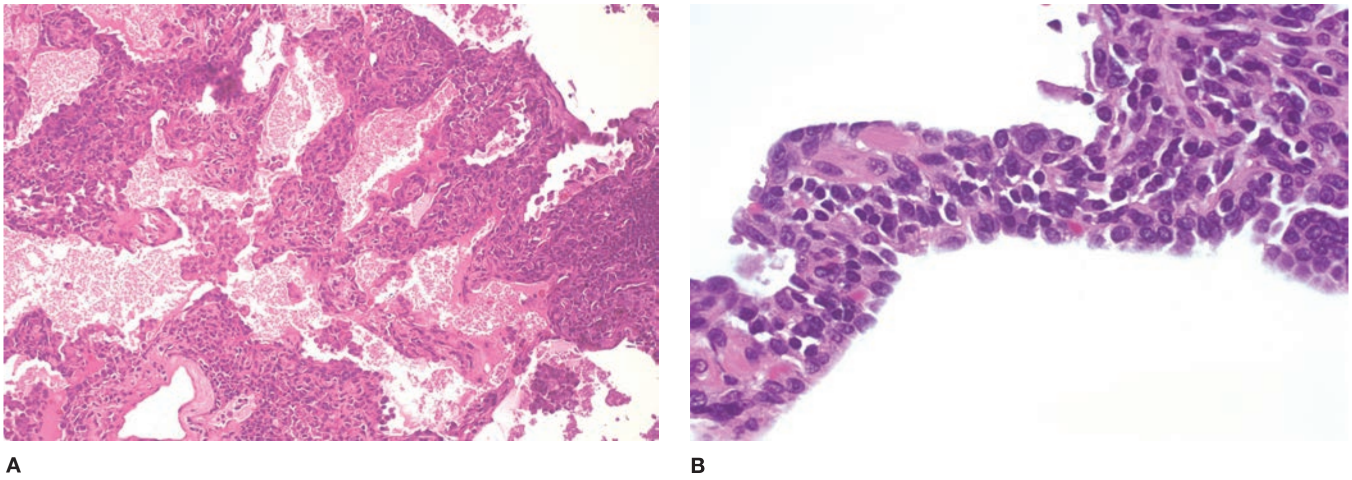

Figure 119-5 **A.** Diffuse alveolar septal expansion with lymphocytes and plasma cells. Hematoxylin and eosin, 50× original magnification. **B.** Higher-power view demonstrating interstitial accumulation of lymphocytes and plasma cells. Hematoxylin and eosin, 60× original magnification.

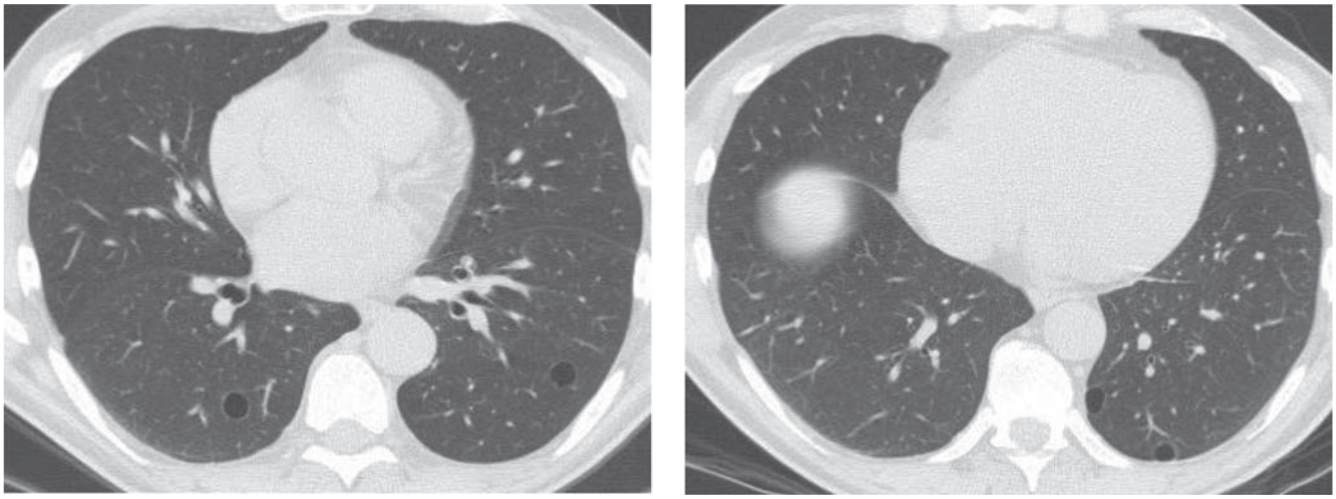

Figure 119-6 Representative CT images from a patient with lymphocytic interstitial pneumonia demonstrating scattered thin-walled cysts.

presentations may differ. Individuals with so-called diffuse infiltrative lymphocytosis syndrome (DILS), featuring sicca syndrome with increased numbers of circulating CD8+ T cells in the blood, generalized lymphadenopathy, and enlarged parotid glands, are at high risk of developing LIP.[36]

■ Granulomatous and Lymphocytic Interstitial Pneumonia

Common variable immunodeficiency syndrome (CVID) is a primary immune disorder with functional abnormalities of the B-cell lineage. Two broad categories of monogenic genetic defects have emerged: mutations in genes that are involved in various stages of B-cell activation, survival, and maturation to plasma cells, and defects in genes that control general immune regulation.[37] There are similarities with a number of other monogenic antibody deficiency syndromes that present with interstitial lung disease having pathology similar to that seen in patients with CVID. These include patients with gain-of-function mutations of PI3KD that develop a CVID-like syndrome defined by lymphoid hyperplasia, which can affect the airways and lung parenchyma.[38]

As a consequence of humoral immune deficiency, patients with CVID suffer from recurrent bacterial infections of the respiratory tract, sepsis with encapsulated organisms, and infections from *Ureaplasma urealyticum*, *Giardia* species, and enteroviruses. Additionally, variable dysfunction of T-cell immunity results in a subset of patients suffering from noninfectious, autoimmune manifestations (cytopenia, hemolytic anemia, neuropathy, endocrinopathies, skin disease, liver disease, uveitis, pernicious anemia), lymphoid lymphoproliferative lesions, and malignancy. In this "autoimmunity" context, lung involvement is characterized by peribronchial and interstitial lymphocytic infiltration, granulomatous inflammation, and organizing pneumonia (so called granulomatous and lymphocytic interstitial pneumonia, or GLILD). Granulomas are also present in hilar and mediastinal lymph nodes.[39] Bronchoalveolar lavage demonstrates a profile very similar to that observed in sarcoidosis. HRCT findings demonstrate a lower lobe predominance and include nodules, smooth thickening of interlobular septa, bronchiectasis, and multifocal pulmonary consolidation (Fig. 119-7). Thoracic adenopathy is consistently present, and splenomegaly is a common feature. PET scan demonstrates hypermetabolic activity in the parenchymal lesions and lymph modes. Diagnosis may be confirmed by transbronchial cryobiopsy or VATS lung biopsy. However, the combination of two clinical parameters (splenomegaly and autoimmune cytopenia), one lung function index ($D_{L_{CO}}$, % predicted), and one immunologic variable (percentage of circulating $CD21^{low}$ B cells) has been recently shown to be a promising tool for early identification of CVID patients with interstitial lung disease, potentially limiting the use of invasive diagnostic procedures.[40]

Milder cases of GLILD may respond to treatment with corticosteroids. For more severe cases, studies have demonstrated a dramatic

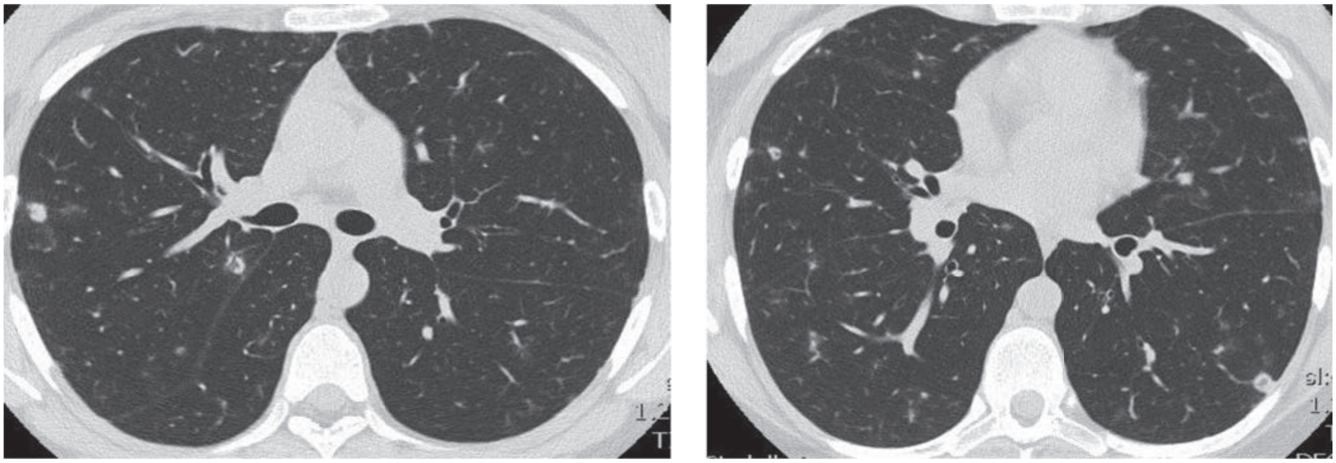

Figure 119-7 HRCT images demonstrating scattered nodules in a 25-year-old female with CVID and GLILD.

response with prolonged remission of disease when a combination of anti-CD20 monoclonal antibody (rituximab) and azathioprine or mycophenolate mofetil was used.[41]

Autoimmune Lymphoproliferative Syndrome

Autoimmune lymphoproliferative syndrome (ALPS) is a rare inherited disorder characterized by nonmalignant T- and B-cell lymphoproliferation causing splenomegaly and enlarged lymph nodes; 70% of patients also display autoimmune manifestations, such as autoimmune cytopenias, Guillain-Barré syndrome, glomerulonephritis, uveitis, and hepatitis.[42] A hallmark of ALPS is the presence in peripheral blood of mature alpha/beta T cells that are negative for CD4 and CD 8 (so-called alpha/beta double-negative T cells). Hypergammaglobulinemia, consisting of IgG and IgA, also is frequently observed. The syndrome is caused by a defect in Fas-mediated apoptosis of lymphocytes due to somatic or germline mutation, either heterozygous or homozygous, in FAS, FASLG, or CAPS 8 or 10. ALPS with undetermined genetic defect (ALPS-U) is a term to categorize patients who fulfill the diagnostic criteria of ALPS but who do not have an identifiable mutation despite detailed genetic analysis. ALPS may predispose to malignancies (both non-Hodgkin and Hodgkin lymphomas). Lung abnormalities may be detected mainly in the ALPS-U subtype, and clinical investigation is mainly undertaken when there is suspicion of lymphoproliferative disorders or infections. Patients are asymptomatic or present with dyspnea. Pulmonary function testing often reveals a significant reduction of D_{LCO}. CT scan features are diverse, including ground-glass opacities, large nodules or consolidation, tree-in bud pattern, bronchiectasis, septal thickening, cysts and cavities, and mediastinal adenopathy. BAL fluid lymphocytes are significantly increased. Histopathologic features are a mix of mucosal lymphoid hyperplasia/follicular bronchiolitis, bronchiectasis, interstitial lymphocytic infiltration, interstitial fibrosis, organizing pneumonia, acute inflammation, and granulomatous changes.

Recently the mTOR inhibitor rapamycin (sirolimus) was shown to be highly effective in amelioration of ALPS-related refractory cytopenias in a small multicenter clinical trial.[43]

Castleman Disease

Castleman disease (CD) is the eponymous term used to describe a group of at least four disorders that share a spectrum of characteristic histopathologic features but have a wide range of etiologies, presentations, treatments, and outcome.[44,45] The clinical presentation is divided into unicentric (UCD) and multicentric (MCD) subtypes. Histologic features clearly defined in lymph nodes specimens range from forms characterized by numerous follicles with regressed germinal centers, prominent vascularization (a peculiar feature is represented by vessels penetrating germinal centers conferring a “lollipop appearance”), and large dysplastic cells with vesicular nuclei expressing markers of follicular dendritic cells (CD21+, CD23+ cells) (the hypervascular end of the spectrum) (Fig. 119-8) to forms in which hyperplastic and, occasionally, regressed germinal centers with prominent monotypic or polyclonal plasmacytosis in the interfollicular areas are evident (plasma cell variant) (Fig. 119-9). Overlapping features of both types represent mixed histopathology. Recently, the Castleman Disease Collaborative Network proposed a classification system that retained the UCD and MCD nomenclature, but further divided MCD by etiologic driver (HHV-8–associated MCD, POEMS-associated MCD, idiopathic MCD [iMCD], and within iMCD, by phenotype, iMCD-TAFRO [thrombocytopenia (T), anasarca (A), fevers (F), reticulin myelofibrosis (R), organomegaly (O)], and iMCD not otherwise specified).[45] Each variant is associated with a wide range of clinical features; histopathology should be used to determine whether a patient has CD, but it does not alone guide clinical management.[46]

UCD is an uncommon form of lymphoid hyperplasia in young to middle-aged individuals of either gender that primarily affects mediastinal, retroperitoneal, and cervical lymph nodes (Fig. 119-10). Pleural, chest wall, and extrathoracic involvement have been reported, but pulmonary parenchymal disease is a true rarity, and most reported cases likely represent nodal, rather than true pulmonary, disease.[47,48] UCD lesions are usually asymptomatic or rarely cause compression-related symptoms. Rare severe complications, such as polyneuropathy, autoimmune hemolytic anemia, and paraneoplastic autoimmune multiorgan syndrome with severe obstructive pulmonary impairment, however, may be observed. Laboratory tests are usually normal, but anemia, hypergammaglobulinemia, and elevated sedimentation rate may be present. PET may be positive with low SUV. Some 70% of UCDs feature hyaline-vascular morphology (HV-CD), whereas the remainders are the plasma cell variant. UCD is considered most likely to be a clonal neoplastic process with the follicular dendritic cell as the progenitor. In fact, secondary follicular dendritic cell sarcomas are not an uncommon complication.[2]

Surgical excision is the treatment of choice and results in the disappearance of associated symptoms.[49] Neoadjuvant therapy with rituximab or siltuximab/tocilizumab (if evidence of acute

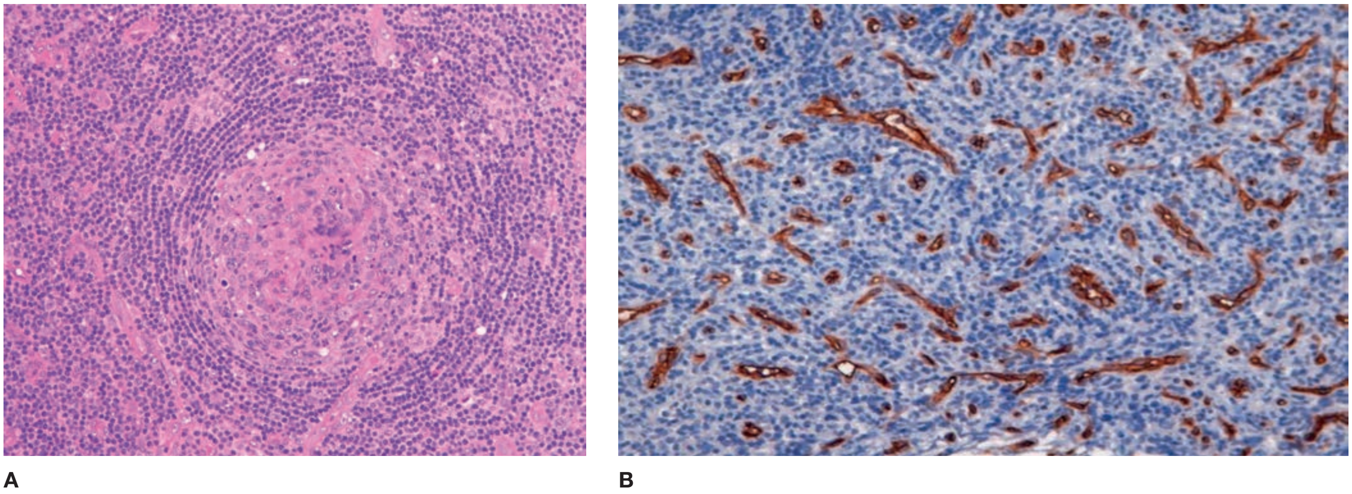

Figure 119-8 Hyaline-vascular Castleman disease. **A.** Biopsy demonstrating prominent mantle lymphoid cells with characteristic “onion-skin” pattern around the atrophic germinal center with hyalinized penetrating venules resulting in “lollipop” appearance (H&E, × 10). **B.** Vascular proliferation with increased numbers of high endothelial venules marked by CD34 monoclonal antibody (× 20)

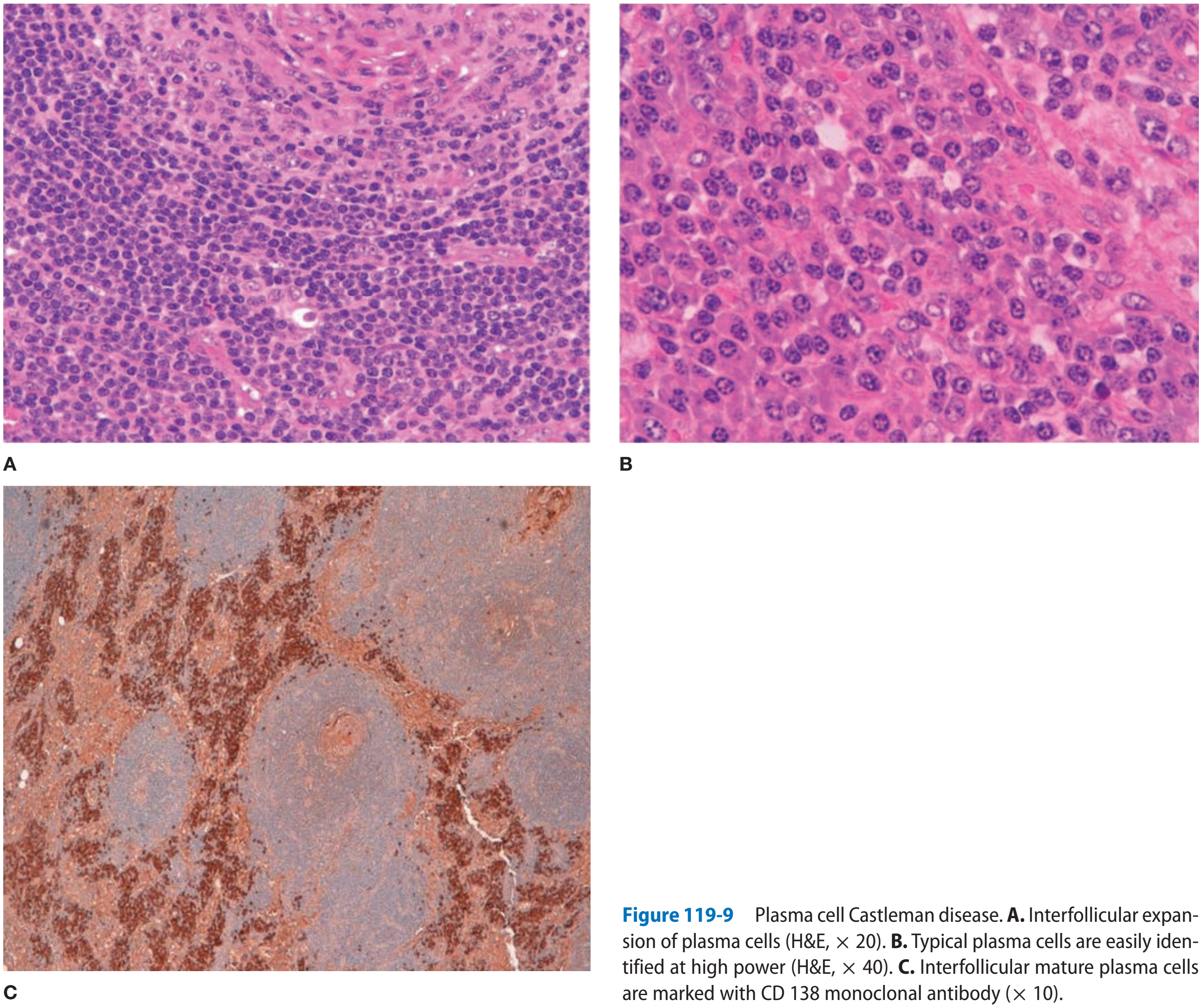

Figure 119-9 Plasma cell Castleman disease. **A.** Interfollicular expansion of plasma cells (H&E, × 20). **B.** Typical plasma cells are easily identified at high power (H&E, × 40). **C.** Interfollicular mature plasma cells are marked with CD 138 monoclonal antibody (× 10).

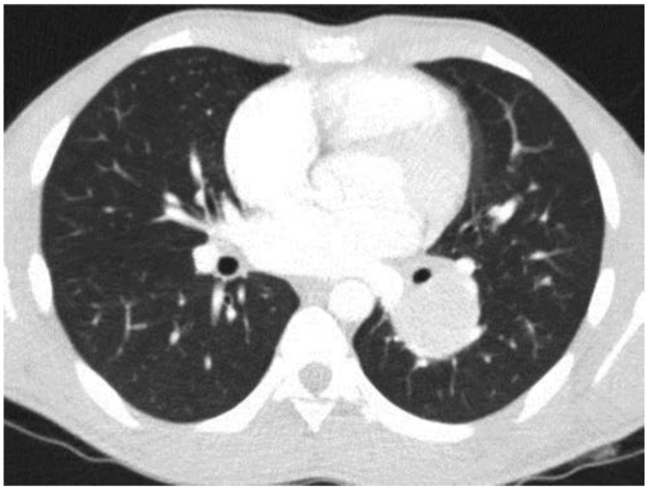

Figure 119-10 CT scan demonstrating well-circumscribed mass in left hilum, found on surgical resection to be due to unicentric Castleman disease.

inflammatory state is documented) may be considered.[49] Radiation also may be effective as primary therapy.[49]

MCD is, as already mentioned, a heterogenous group of disorders. Inclusion (major and minor) criteria and exclusion criteria to formulate a diagnosis have been formalized.[45] Uncontrolled HHV-8 infection is the etiologic driver in HHV8-MCD, with viral-induced transcription of homolog interleukin 6 (IL-6) that subsequently incites lymph nodes, extranodal pathology, and signs and symptoms.[50] HHV8-MCD is quite common in HIV-positive subjects. Monoclonal plasma cells are the likely etiologic drivers of polyneuropathy, organomegaly, endocrinopathy, skin changes (POEMS)-MCD.[51] Excessive VEGF and IL-12 production are pivotal pathogenetic steps in this subtype. The etiology and pathogenesis of idiopathic MCD are less well understood. IL-6 is a critical disease driver in most patients. Recently, a key role of activated T cells and mammalian target of rapamycin pathway activation has been observed.[52]

Patients with MCD exhibit a wide spectrum of clinical and laboratory abnormalities that sometimes follow a waxing and waning course. Symptoms and signs include fever and asthenia; ascites and peripheral edema; cytopenias; hemophagocytic syndrome; liver and kidney dysfunction, including secondary amyloidosis and membranoproliferative glomerulonephritis; peripheral neuropathy; and skin abnormalities (rash, hyperpigmentation, cherry angiomata).

TABLE 119-2 Diagnostic Criteria for iMCD-TAFRO

Histopathology (all needed):

- Typical lymph node pathology (atrophic germinal centers with enlarged nuclei of endothelial cells)
- Proliferation of endothelial venules
- Small numbers of mature plasma cells
- Negative LANA-1 for HHV-8

Major clinical-laboratory criteria (need 3 of 5):

- Thrombocytopenia
- Anasarca
- Fever
- Reticulin fibrosis in bone marrow biopsy
- Organomegaly

Minor criteria (need at least one):

- Hyper/normoplasia of megakaryocytes
- High alkaline phosphatase without markedly elevated transaminases

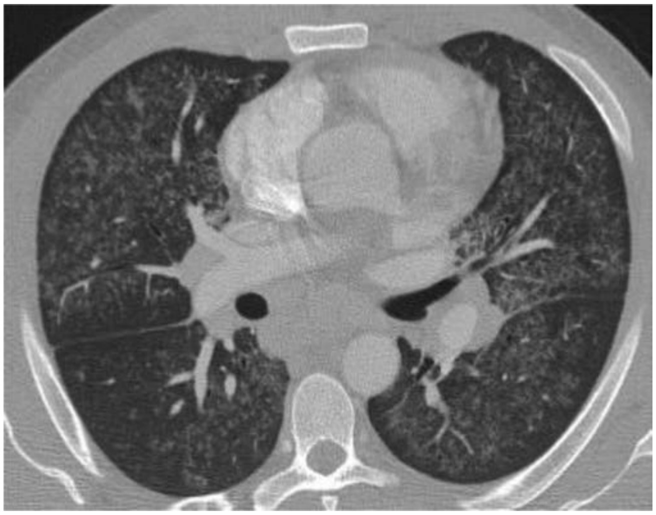

Figure 119-12 HHV-8–associated multifocal Castleman disease in a 37-year-old male with HIV. Axial CT scan demonstrates bilateral, extensive centrilobular and peribronchovascular ground glass nodules, mainly in the mid and upper zones, with subpleural sparing. Mediastinal and hilar adenopathy also is present.

Positive testing for HHV8 by LANA-1 on biopsy specimens and/or polymerase chain reaction for HHV8 in blood establish the diagnosis of HHV8-MCD. iMCD is clinicopathologically similar to HHV8-MCD, but the viral agent is not detectable. iMCD-TAFRO is an aggressive clinical subtype. Diagnostic criteria for iMCD-TRAFO are reported in Table 119-2.

Lung involvement in MCD is characterized by marked accumulation of lymphocytes and plasma cells (with sheets of plasma cells without intervening lymphocytes), lymphoid follicles, and dense fibrosis mainly in the alveolar area adjacent to interlobular septa, bronchovascular bundles, and pleura and the absence of obstructive vasculitis or eosinophilic infiltrates[53] (Fig. 119-11). A pattern mimicking LIP is more frequently observed in HHV8-MCD.

CT scan findings of lung involvement are usually characterized by septal and peribronchovascular thickening, intralobular reticulation, and centrilobular nodules with ground glass attenuation (Fig. 119-12). Nodules and cysts also have been reported. Bilateral pleural effusions are typically observed in TAFRO syndrome. Enlarged lymph nodes in the hila and mediastinum are almost always documented.

The main therapeutic options for treatment of MCD include corticosteroids, immunosuppressive drugs (cyclosporine A, cyclophosphamide, thalidomide, bortezomib, lenalidomide), rituximab, rituximab combined with etoposide or liposomal doxorubicin, and anti–IL-6 drugs (e.g., siltuximab, tocilizumab). Sirolimus may be useful in cases of mTOR activation.[54,55] JAK inhibitors could be considered in siltuximab nonresponders. In bronchiolitis obliterans, a severe complication mainly observed in the stroma-rich variant of the hyaline vascular Castleman disease subtype, lung transplantation may represent a therapeutic option.[56]

■ Immunoglobulin G4–Related Lung Disease

IgG4-related disease (IgG4-RD) is an immune-mediated disorder associated with fibroinflammatory mass–forming lesions that can occur at nearly any anatomic site. It follows a biphasic progression characterized by an "inflammatory" phase that eventually

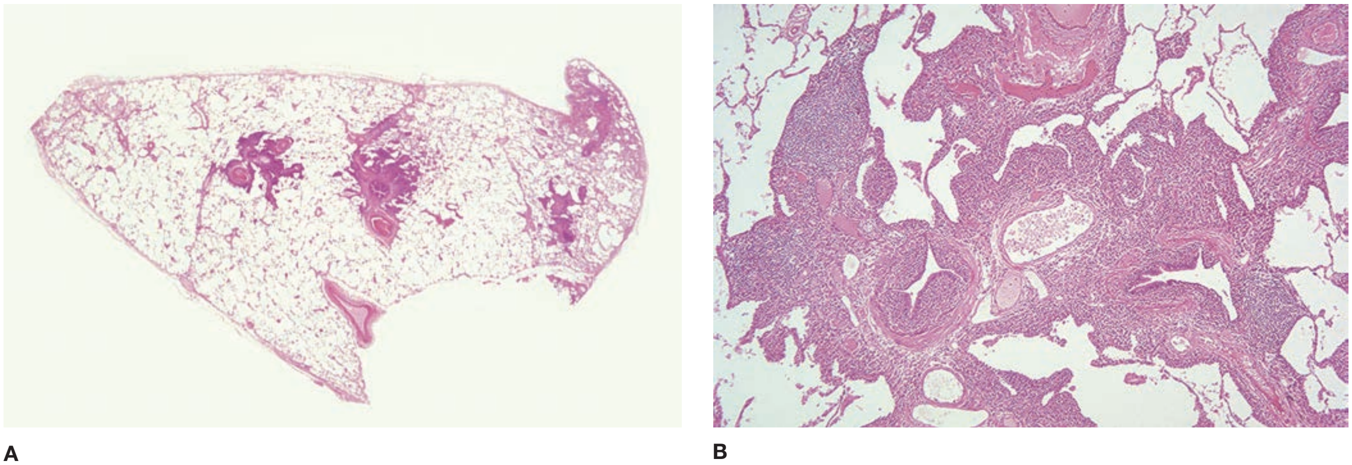

Figure 119-11 Multicentric Castleman disease. **A.** The bronchocentric nature of this KSHV/HHV8-driven systemic process is apparent at scanning microscopy. Hematoxylin and eosin, 1× original magnification. **B.** The lymphoplasmacytic infiltrate is confined to the pulmonary interstitium. Honeycomb-like changes may develop. Hematoxylin and eosin, 10× original magnification. *(Glass slides reproduced with permission from Dr. J. English, University of British Columbia and Vancouver Hospital, Vancouver, BC.)*

TABLE 119-3 Diagnostic Criteria for IgG4-RD

Clinical and radiologic features compatible with IgG4-RD
Characteristic histopathologic and immunostaining features
• Dense lymphoplasmacytic infiltrates
• Storiform pattern of fibrosis
• Obliterative phlebitis
• Increased number of IgG4+ plasma cells and IgG4+/IgG+ cell ratio >40%
Other supportive findings
• Serum IgG4 level >135 mg/dL
Exclude other identifiable diseases with overlapping clinicoradiologic and/or histopathologic features

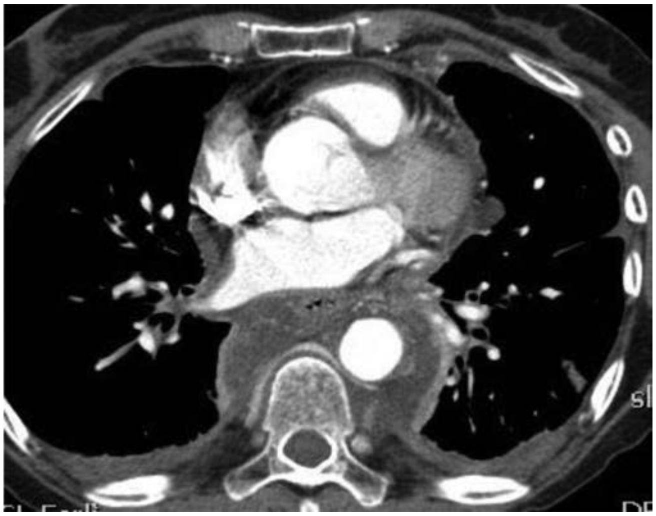

Figure 119-13 IgG4-related lung disease. CT scan with contrast showing soft tissue enlargement of the retromediastinal and pleural space.

culminates in a “fibrotic” outcome and often presents as a multiorgan disease that may be confused with malignancy, infection, or other immune-mediated conditions, such as Sjögren syndrome, ANCA-related vasculitides, or rarer autoinflammatory disorders. Although the pathogenesis of IgG4-RD is still poorly understood, there is a growing body of evidence that indicates an antigen-driven process requiring T-cell and B- cell interaction in which autoantibodies, plasmablasts, follicular helper T cells, and CD4+ cytotoxic T lymphocytes participate.[57,58]

Well-characterized IgG4-RD manifestations include relapsing pancreatitis, sclerosing cholangitis, retroperitoneal fibrosis/aortitis, hypertrophic pachymeningitis, and chronic sialadenitis. According to the main clinical manifestations, laboratory profile, and sites involved, four clinical phenotypes have been identified: pancreato-biliary; retroperitoneal/aortitis; head and neck limited; and Mikulicz/systemic. Males predominate in all but the head and neck phenotype that more frequently is observed in Asian females.

Criteria for diagnosis and classification have been recently revised[59] (Table 119-3). Definitive diagnosis requires rigorous clinicopathological correlations because clinical assessments, laboratory tests, and imaging studies are often insufficient.[60] Erythrocyte sedimentation rate, LDH, and soluble IL-2 receptors may be elevated; C-reactive protein is usually normal. Peripheral blood eosinophilia and increased serum IgE levels occur in almost 30% of patients.[61] Circulating autoantibodies, such as antinuclear antibodies and rheumatoid factor, may be present. An increase of serum IL-6 has been described. Although useful for initial screening, elevation of serum IgG4 has poor diagnostic utility because it may occur in a variety of neoplastic, infectious, and autoimmune disorders. Increased ratios of serum IgG4 to total IgG (>10%) or IgG1 (>24%) have been shown to improve diagnostic specificity, especially when IgG4 concentrations are only slightly raised. Ultimately, pathologic examination plays a pivotal role in achieving a definite diagnosis.

Lungs, pleura, and large airways are affected mainly in the Mikulicz/systemic phenotype.[62] Lung/pleural/large airways involvement may represent the first manifestation of the disease. Most patients are males with an average age of 69 years. One-half of patients have respiratory symptoms such as cough, exertional dyspnea, and chest pain. Very rarely recurrent wheezing or inspiratory stridor are the first manifestations. Low-grade fever and weight loss may be less frequently observed. No risk factors are recognized.

Radiographic presentation varies considerably. Major subtypes of CT features have been identified:[61] solid nodular lesions; round-shaped ground-glass opacities; alveolar-interstitial type with honeycombing, bronchiectasis, and diffuse ground glass; and bronchovascular type with thickening of the bronchovascular bundles and interlobular septa. Masses and large nodules are usually solitary, whereas small nodules are multiple. Most patients have more than one abnormality. Hilar and mediastinal adenopathy may be seen. Pleural thickening and/or effusion and thickening of the wall and stenosis of the lumen of the larger airways also have been reported (Fig. 119-13). Abnormal uptake on 18-fluorodeoxyglucose PET is usually present. Bronchoscopic inspection of the airways is usually unremarkable, but multiple white nodular protuberances, along with mucosal hyperemia and edema or subglottic stenosis, have been described.

The three major histopathologic features defined in soft tissue, pancreas, or other sites are (1) dense lymphoplasmacytic infiltrate; (2) fibrosis, arranged, at least focally, in a storiform pattern; and (3) obliterative phlebitis.[63] IgG4-related pulmonary disease may lack all the distinct storiform fibrosis, while pulmonary arteries, in addition to veins, may be involved. Notably, lung biopsy interpretation of this condition is often challenging because of a relative paucity of pathognomonic features and the presence of a plethora of findings overlapping with other fibroinflammatory processes.[64] The most notable and consistent histopathologic finding in lung biopsies is a prominent lymphangitic distribution of plasma cell–rich inflammatory infiltrates, with involvement of visceral pleura, interlobular septa, and bronchovascular stroma. Additionally, vascular changes without vessel lumen obliteration, concentric bronchiolar inflammatory infiltration with germinal centers, and organizing pneumonia and/or prominent eosinophilia may be seen.

Tissue and serum IgG4 and IgG levels serve as supplemental diagnostic data. Immunohistochemical stain evaluation requires counting the three 40× microscopic fields with the highest number of IgG4+ plasma cells, in addition to counting the number of IgG+ plasma cells in those same areas. According to the consensus statement, more than 50 IgG4+ cells per high-power field and more than 20 IgG4+ cells per high-power field are adequate cutoffs in surgical and nonsurgical lung biopsies, respectively.[65] The IgG4+/IgG+ plasma cell ratio should be greater than 40%. However, other lung processes, including idiopathic NSIP, usual interstitial pneumonia, Rosai Dorfman disease, and connective tissue disease–associated interstitial pneumonias, as well as inflammatory myofibroblastic tumor, may have increased IgG4+ cell counts in biopsy specimens.

Glucocorticoids (0.6–1 mg/kg daily of oral prednisone or equivalents) represent the cornerstone for inducing disease remission in patients with active IgG4-RD, both at disease onset and with disease flare. Although no consensus exists on the optimal duration of steroid treatment and on the pace of steroid tapering, one accepted

TABLE 119-4 Classification of Primary Pulmonary Lymphoid Malignancies

Lymphomas involving mainly the lungs
MALT lymphomas of the lung
Follicular lymphoma
Diffuse large B-cell lymphomas
Lymphomatoid granulomatosis
Intravascular large B-cell lymphoma of the lung
Plasmacytoma
Amyloidosis
Light chain disease of the lung
Extranodal natural killer T-cell lymphoma (nasal type)
Peripheral T cell lymphoma, not otherwise specified (NOS)
Anaplastic large cell lymphoma (ALCL)
Hodgkin lymphoma
Pleural lymphomas
Primary effusion lymphoma
Pyothorax-associated lymphoma

approach is to maintain the starting dose for 2 to 4 weeks and then gradually reduce by 5 mg every 2 weeks over a period of 4 to 6 months. Immunosuppressive drugs such as azathioprine, methotrexate, cyclophosphamide, leflunomide, mycophenolate mofetil, cyclosporine, and tacrolimus have been used. Emerging treatment options include rituximab, bortezomib, belimumab, abatacept, and elotuzumab.[66]

PRIMARY PULMONARY LYMPHOID MALIGNANCIES

Primary lymphoid neoplasms are classified according to the general WHO classification system (Table 119-4). Although more than half of patients with nodal lymphoma have lung involvement, primary pulmonary lymphomas constitute less than 0.5% of primary lung neoplasms.[67,68] Furthermore, the most common primary lung lymphoma, marginal zone non-Hodgkin lymphoma of MALT origin, represents less than 10% of extranodal lymphomas.[69] Hodgkin lymphomas (HL) are only rarely considered lung primaries, even when the lung is the principal site of organ involvement.[70,71] Furthermore, mainly in primary MALT pulmonary lymphoma, if in-depth investigations are done, other extranodal sites (e.g., stomach, colon, thyroid, bone marrow) may be identified as sites of subclinical clonal lymphoid proliferation.[1,2]

■ Extranodal Marginal Zone B-Cell Lymphoma of MALT Type

MALT lymphoma is the most common type of primary pulmonary lymphoma, accounting for 70% to 90% of all cases.[72,73] It usually affects patients in their seventh decade of life with a slight female predominance. Autoimmune diseases, mainly Sjögren syndrome, are present in approximately one-third of cases. Approximately 40% of patients are asymptomatic, with the remaining presenting with systemic or organ-related symptoms, such as fever, night sweat, malaise, cough, dyspnea, and even less frequently, hemoptysis and chest pain. Serum findings include monoclonal gammopathy detected in up to 60% of patients. Other nonspecific laboratory findings are elevated LDH, C-reactive protein, and beta-2 microglobulinemia. CT findings vary and include alveolar consolidation with air bronchograms, areas of ground-glass attenuation, nodules, cysts, or thickening of the interlobular septa (Fig. 119-14A).[74] Areas of calcification/ossification indicate the coexistence of amyloid deposits (Fig. 119-14B). Bronchiectasis often can be seen in larger lesions. These abnormalities are frequently multiple and bilateral. The disease may rarely appear as a submucosal lesion in the large airways or as a pleural effusion. Hilar and mediastinal lymphadenopathy is not a prominent radiologic finding, and only 30% of cases exhibit nodal involvement at pathologic analysis. PET-CT is often positive.

Under light microscopy, pulmonary MALT lymphoma shows lymphocytes disrupting the lung architecture.[1,2,72] Such lesions display a spectrum of architectural patterns, ranging from discrete nodular lesions with variably defined borders to a lymphangitic-type distribution along the visceral pleura, interlobular septa, and around bronchovascular bundles (Fig. 119-15). Rarely, it may manifest predominantly as an endobronchial lesion.

The classic histologic "triad" of MALT lymphoma consists of reactive germinal centers, diffuse infiltration by centrocyte-like lymphocytes, and lymphoepithelial lesions (lymphocytes in nests infiltrating the bronchiolar epithelium). The neoplastic cells are heterogeneous and are thought to derive from a single precursor cell

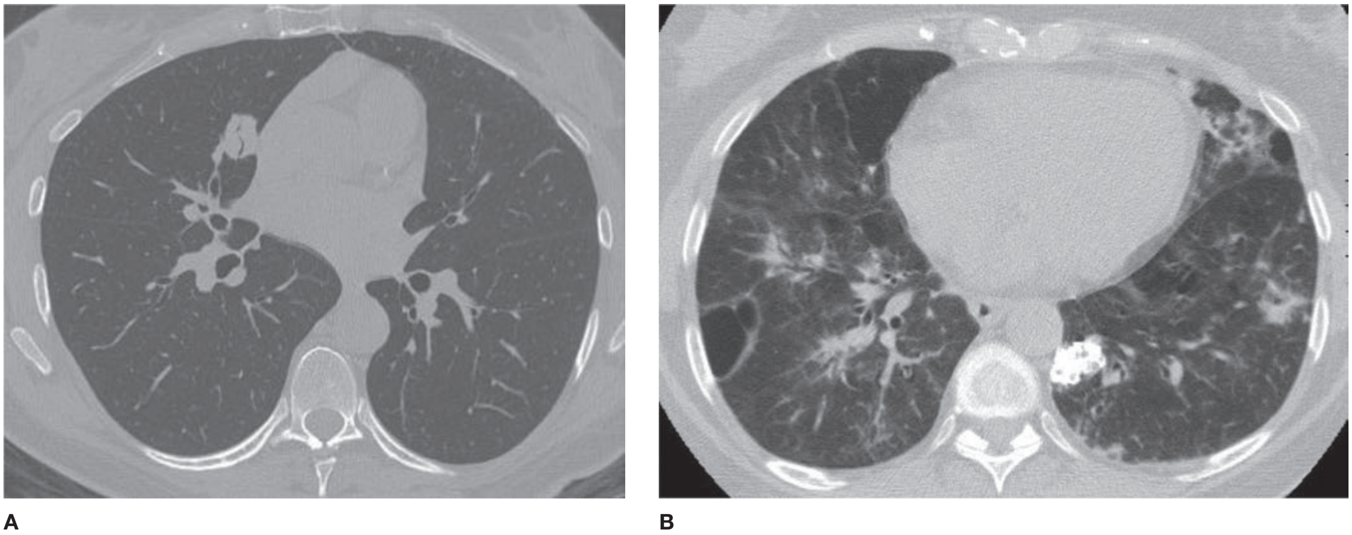

Figure 119-14 Primary pulmonary MALT lymphoma. **A.** Axial CT scan demonstrating a nodule with air bronchogram. **B.** Scattered bilateral areas of alveolar consolidation accompanied by cysts and a calcified nodule representing an amyloid deposit.

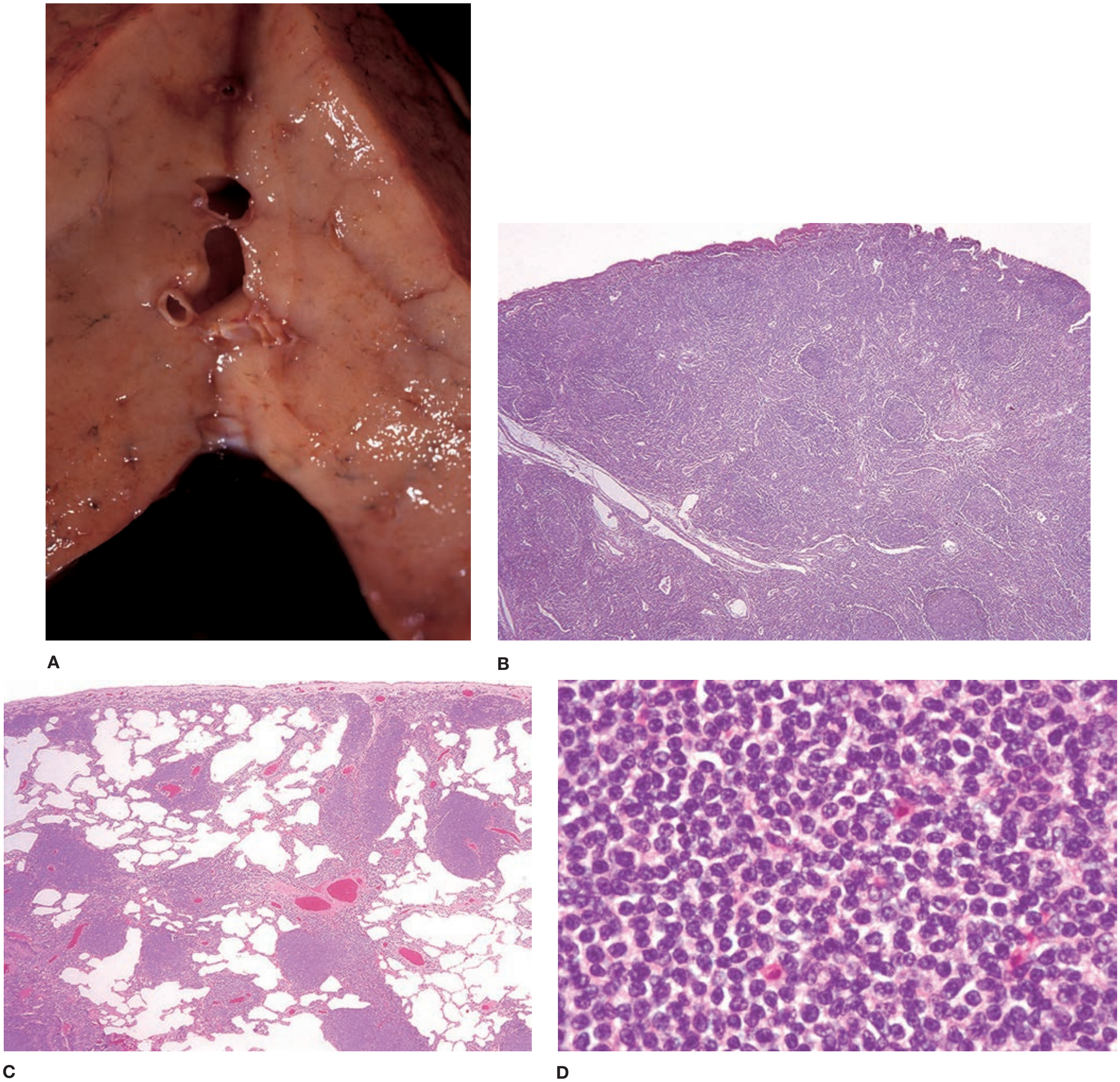

Figure 119-15 Extranodal marginal zone B-cell lymphoma of MALT type. **A**. Tan fleshy tumor fills alveolar spaces but preserves lobular architecture. **B.** Malignant lymphoid cells overrun lung tissue. Germinal centers are usually prominent. Hematoxylin and eosin, 4× original magnification. **C.** Malignant lymphoma often tracks along lymphatic pathways beyond the dominant mass lesion. Involvement of visceral pleura suggests the malignant nature of the process. Hematoxylin and eosin, 4× original magnification. **D.** Most pulmonary marginal zone B-cell lymphomas of MALT type are composed of small monotonous round (centrocyte-like) B-lymphocytes. Hematoxylin and eosin, 40× original magnification.

with multilineage potential. They include (1) small centrocyte-like lymphocytes with round, regular to indented, "cleaved" nuclei, evident nucleoli, moderately dispersed chromatin, and scant cytoplasm; (2) monocytoid lymphocytes with moderately condensed chromatin, inconspicuous nucleoli, and more abundant amphophilic-to-pale eosinophilic cytoplasm forming a perinuclear halo; and (3) a variable amount of plasmacytoid lymphocytes and plasma cells. Erosion of the bronchial cartilage and vascular involvement are frequent findings. Nonnecrotizing epithelioid granulomas, occasional massive crystal-storing histiocytosis, mostly in overt plasmacytic differentiation, large lamellar bodies (rings of eosinophilic proteinaceous material) within the spared alveoli, and multinucleated giant cells may be observed.

Pulmonary MALT lymphomas with prominent plasmacytic differentiation show a frequent association with amyloidosis, paraproteinemia, and light and/or heavy chain deposition. This MALT lymphoma subset is most common in elderly women (mean age, 70 years) with underlying autoimmune disorders, such as Sjögren syndrome or RA. Typically, MALT lymphoma cells express CD19, CD20, CD22, and CD79a and are negative for CD3, CD5, CD10, CD23, BCL6, and cyclin D1. A small immunohistochemistry panel is desirable to exclude follicular lymphoma, mantle cell lymphoma, and chronic lymphocytic leukemia. BCL2 staining is an adjunct in distinguishing neoplastic cells from reactive monocytoid lymphocytes. Cytokeratin immunostaining supports the identification of lymphoepithelial lesions. The Ki-67 proliferation index is low in the neoplastic cells (<10%) but is typically higher in residual germinal centers. Kappa and lambda light chain restriction of plasma cells and/or B lymphocytes by flow cytometry, immunohistochemistry, or in situ hybridization may be necessary to support the diagnosis.

Up to 50% of MALT lymphomas carry a chromosomal translocation resulting in the production of a chimeric protein (BIRC3-MALT1) and in transcriptional deregulation of BCL10, MALT1, and FOXP1, with variable frequencies, depending on the site of occurrence. In both pulmonary and gastric MALT lymphoma, the most common cytogenetic abnormality is t(11;18)(q21;q21) (present in 31%–53% of cases), which generates a fusion transcript, resulting in activation of the NF-kB pathway, which is a potential therapeutic target. Trisomy 3 (20% of cases), t(14;18)(q32;q21) (IGH-MALT1) (up to 10%), and trisomy 18 and t(1;14)(p22;q32) (BCL10-IGH) (both up to 7%) may occur with decreasing frequency. Other genetic alterations, such as abnormalities of TNFAIP3 on chromosome 6q23, which may include deletions, mutations, and promoter methylation, have been reported in 15% to 30% of cases. MYD88 L265P mutations may occur in a minority of cases of MALT lymphoma (6%–9%) at different sites, including lung. Additional genetic alterations assessed by next-generation sequencing analysis, involving chromatin remodeling, BCR/NF-kB and NOTCH pathways, and recurrent inactivations of TET2, have been recently described.

Diagnosis of MALT lymphoma usually requires biopsy; transbronchial cryobiopsy, or percutaneous CT- or echo-guided core biopsy are often sufficient. In cases in which alveolar consolidation is present, bronchoalveolar lavage may document a B-cell lymphocytosis consisting of atypical cells with light chain monotypic restriction on flow cytometry.[75] Surgical lung biopsy is the definitive approach when less invasive techniques have failed to provide a diagnosis.

Treatment includes surgical resection of localized lesions and radiotherapy, chemotherapy, or immunotherapy in nonresectable cases, depending on patient comorbidities.[72] Administration of rituximab may result in long-term remission, yielding a response rate as high as 70%, but it is associated with disease recurrence in up to 36% of cases. The combination of rituximab plus chemotherapy yields higher response rate and event-free survival according to some studies.[76] Systemic therapy is the current treatment of choice for advanced or multicentric primary pulmonary MALT lymphoma. Novel therapeutic strategies include ibrutinib, a Bruton tyrosine kinase inhibitor, and the PI3K inhibitors copanlisib and umbrasilib.[72] The presence of confluent sheets or large aggregates of large B cells points toward a transformation to diffuse large B-cell lymphoma (DLBCL) in up to 20% of cases and is associated with a poorer prognosis, prompting a change in the treatment protocols.

Major prognostic factors associated with survival are age, performance status, disease stage, presence of systemic symptoms, coexistence of autoimmune disorders, number and location of pulmonary lesions, presence of paraproteinemia, and type of treatment. An associated pleural effusion or amyloid portends a poorer prognosis. An elevated β2-microglobulin level and stage IV classification have been reported as independent predictors of prognosis for MALT lymphoma occurring at all sites.

■ Follicular Lymphoma

Follicular lymphoma is generally an indolent B-cell lymphoproliferative disorder of transformed follicular center B cells. It is characterized by diffuse lymphadenopathy, bone marrow involvement, splenomegaly, and, less commonly, other extranodal sites of involvement such as gastrointestinal tract, lung, skin, and other sites.[1] It affects adults (median age, 59 years) and it is more frequent in females (male:female ratio, 1:1.7). In general, cytopenias can occur but constitutional symptoms of fever, night sweats, and weight loss are uncommon. Primary lung involvement is rare and usually asymptomatic. HRCT scan shows ground-glass opacities sometimes with a "crazy paving" pattern or nodules. The differential diagnosis includes minimally invasive or in situ adenocarcinoma. Diagnosis is based on histology and often requires large biopsy specimens. Immunohistochemical staining is positive in virtually all cases for cell-surface CD20 and CD10, nuclear staining for Bcl6 and monoclonal immunoglobulin, as well as membrane expression of bcl-2 protein. The overwhelming majority of cases have the characteristic translocation t(14;18)(q32;q21) involving the IgH/bcl-2 genes. The majority of patients are treated with chemotherapy plus rituximab, which has improved response rates.

■ Diffuse Large B Cell Lymphoma

Diffuse large B-cell lymphoma (DLBCL) as a group is the second most common type of primary pulmonary lymphoma, usually affecting older adults in the sixth and seventh decades.[1,2,76] Morphologic, biologic, and clinical studies have subdivided DLBCL into morphologic variants, molecular subtypes, and distinct disease entities.[77] The main morphologic variants are centroblastic, immunoblastic, and anaplastic. The molecular subtypes are germinal center, B cell, and activated B cell. However, there remain many cases that may be biologically heterogeneous.

The centroblastic variant is characterized by cells with oval to round vesicular nuclei, multiple nuclear membrane–bound nucleoli, and scanty pale cytoplasm. The immunoblastic variant contains large lymphoid cells with round to oval vesicular nuclei and a single centrally located prominent nucleolus with scant to moderate basophilic cytoplasm (Fig. 119-16A). In some cases, plasmacytic differentiation may be seen, with eccentrically located nuclei. The anaplastic variant is characterized by large pleomorphic cells with bizarre irregular nuclei, often with multinucleated forms, and variable amounts of cytoplasm. Lymphoma cells are positive for CD20, CD79a, PAX5, CD10 (30%–50% of cases), BCL6 (60%–90% of cases), MUM1 (35%–65% of cases), BCL2 (47%–84% of cases), and CD5 (5%–10% of cases). Some DLBCL cases, especially the anaplastic variant, are positive for CD30. Ki67 staining is usually positive in greater than 40% of neoplastic cells (and in some cases, this value may exceed 90%). Cases that are CD10+ are classified as a germinal center B-cell subtype; this also applies to cases that are CD10− but BCL6+ and MUM1−. BCL6(3q27) rearrangement is seen in ≤30% of DLBCL. Approximately 20% to 0% of DLBCL cases have t(14;18) involving the BCL2 gene. MYC rearrangement occurs in approximately 8% to 14% of DLBCL cases. Cases with MYC and BCL2 and/or BCL6 rearrangement are called "double/triple-hit lymphomas" and are classified in a separate category of "high-grade B-cell lymphoma with MYC and BCL2 and/ or BCL6 rearrangement." In a minority of cases, markers for EBV infection may be detected (EBV-positive DLBCL not otherwise specified).

DLBCL manifests as a primary lung disease, most frequently with a nodule or a large mass, sometimes occupying most of a lobe and often accompanied by foci of necrosis. The pattern of growth is intraparenchymal or endobronchial (Fig. 119-16B), although it may appear with pleural effusion and pleural masses. PET positivity is the rule. Symptoms include cough, hemoptysis, low-grade fever, and asthenia. Laboratory tests are nonspecific, and diagnosis requires a biopsy; small samples are usually enough. Treatment is with an R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and steroids) regimen; the 5-year progression-free and overall survival rates were found to be approximately 60% and 65%, respectively. Chimeric antigen receptor (CAR) T-cell immunotherapy has been recently found to be an effective treatment in relapsed and refractory patients.[78]

■ Lymphomatoid Granulomatosis

Lymphomatoid granulomatosis (LYG) is characterized by an angiocentric/angiodestructive polymorphous lymphoid infiltrate composed of EBV-positive B cells admixed with a large number of

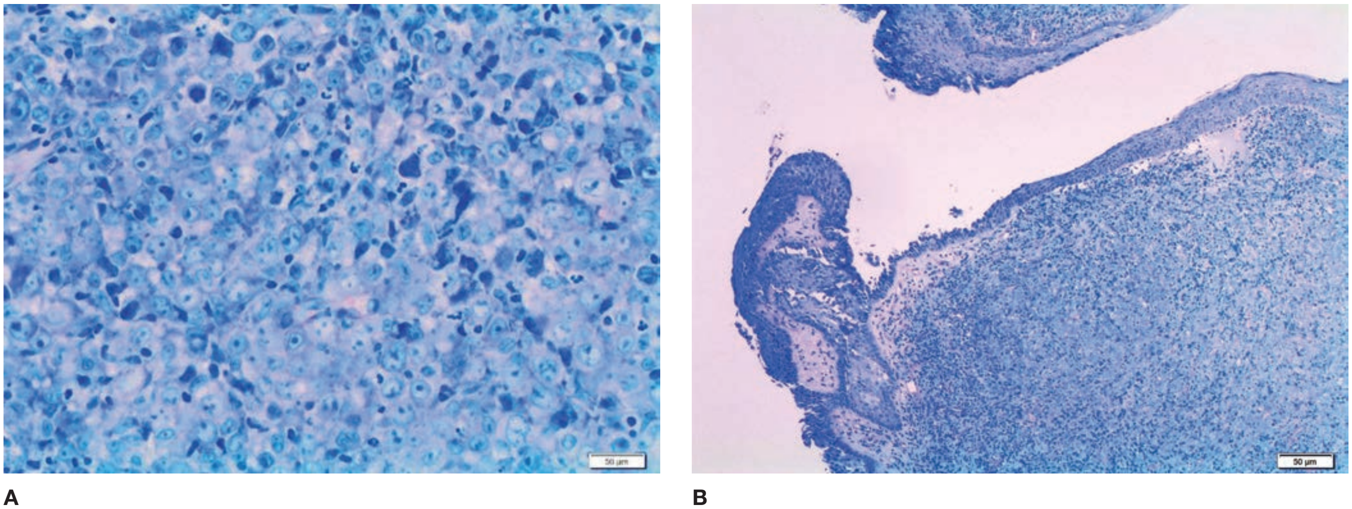

Figure 119-16 Pulmonary diffuse large B-cell lymphoma, immunoblastic variant. **A.** Sheet of large lymphoid cells with round to oval vesicular nuclei and a single centrally located prominent nucleolus with scant to moderate basophilic cytoplasm (Giemsa, × 40). **B.** Pulmonary diffuse large B-cell lymphoma arising in a large airway. Neoplastic cells infiltrating the submucosa (Giemsa, × 10).

reactive T cells. LYG is considered an EBV-driven B-cell lymphoproliferative disorder arising in individuals with either obvious or clinically undetected defects in cell-mediated and, perhaps, also humoral immunity.[1,2,72] Predisposing conditions include Wiskott–Aldrich syndrome, HIV infection, and X-linked lymphoproliferative syndrome. LYG has been reported in patients with autoimmune disorders who underwent long-term methotrexate or azathioprine therapy. Patients presenting without evidence of underlying immunodeficiency usually manifest reduced immune function on careful clinical or laboratory analysis.

Although quite rare, LYG has characteristic clinical features.[79–81] Patients usually present in the fifth or sixth decades of life, but children and the elderly can be stricken. Men are affected two to three times as often as women. Dyspnea, cough, and chest pain, along with fever, malaise, and weight loss, are the most common presenting complaints; up to 40% of patients also have skin nodules, ulcers, rashes, peripheral neuropathies, or symptoms referable to central nervous system involvement. Other sites that may be involved are adrenal glands, prostate, liver, and kidneys. Gastrointestinal, splenic, musculoskeletal, or nodal involvement is uncommon.

Laboratory findings include either leukocytosis or leukopenia and elevated serum IgG or IgM. Cerebrospinal fluid may have abnormal protein and glucose levels. Serologies for autoimmune diseases are negative, but serologic evidence of EBV infection may be present.

The imaging findings of LYG in the lung are fairly well established.[82] In greater than 80% of cases, multiple nodules are found in a bronchovascular distribution, usually in both lungs, with a basilar predominance (Fig. 119-17). Cavitation is seen in around 30% of cases (Fig. 119-17). Nonspecific reticulonodular infiltrates, as well as solitary infiltrates or masses, are less common. Ground-glass opacities and small pulmonary nodules with a predominant peribronchovascular distribution and sparing of the periphery are rarely reported. Cases initially presenting with bilateral ground

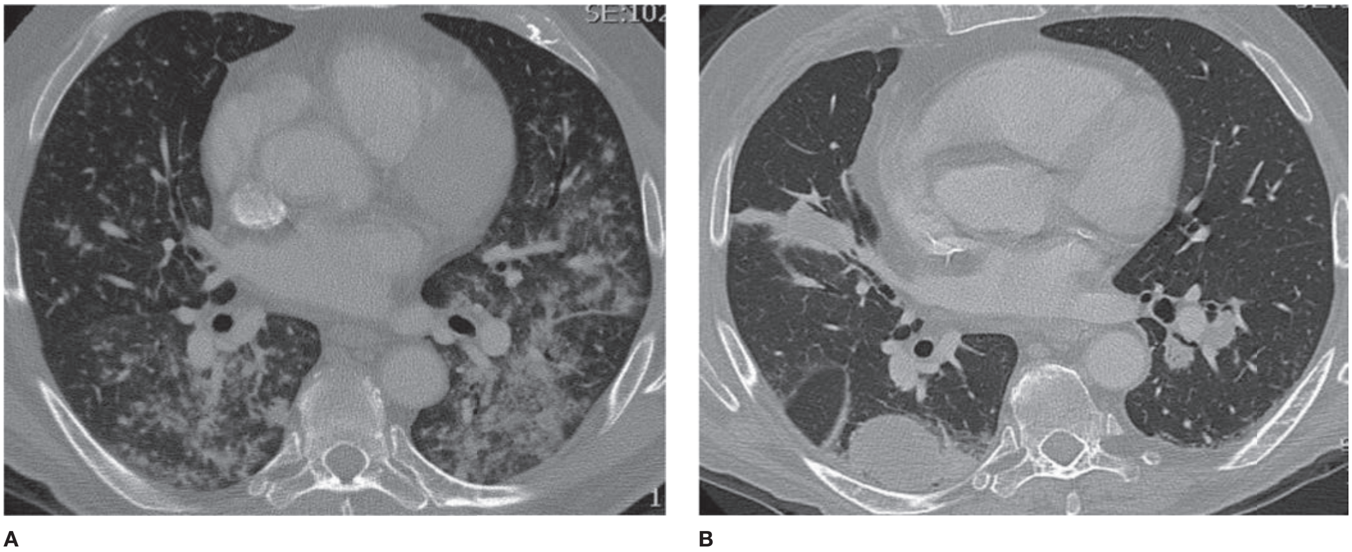

Figure 119-17 Lymphomatoid granulomatosis. **A.** CT scan shows numerous poorly defined ground glass and solid nodules throughout the lung, mainly in a peribronchovascular distribution, with areas of coalescence. **B.** CT scan from another patient demonstrating nodular mass in right lower lobe. *(continued)*

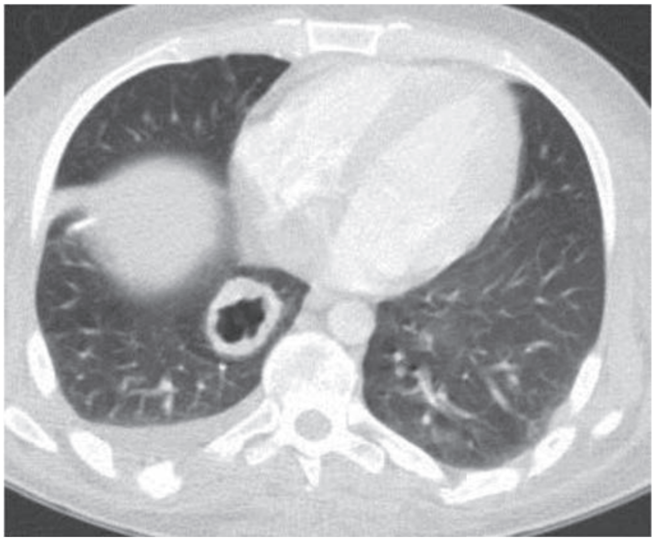

Figure 119-17 *(Continued)* **C.** Nodules are often cavitary and thick-walled.

glass opacities and respiratory failure responding in part to corticosteroids (organizing pneumonia–like manifestation), but eventually progressing to overt nodular lesions, have been observed. Pleural effusion is present in up to one-third of patients. PET is useful in documenting lesions in the lungs and in other sites. Cases with a prominent endobronchial manifestation have been reported. CT scan of the brain should always be part of the diagnostic workup. The differential diagnosis of LYG includes infections, primary pulmonary or metastatic neoplasms, cryptogenic organizing pneumonia, granulomatosis with polyangiitis, nasal-type extranodal T/NK cell lymphoma, and IgG4-related fibroinflammatory disorder.

Macroscopically the lungs and other affected organs contain yellow–white well-demarcated masses, with either solid or granular textures. Microscopically LYG is characterized by nodules containing a polymorphous lymphoid infiltrate with an angiocentric distribution (Fig. 119-18). The majority of the cells are T cells (predominantly CD4+ lymphocytes) admixed with a variable number of histiocytes, plasma cells, and immunoblasts. Central necrosis is often present to a variable extent. The larger cells are B cells (CD20+ and CD79a+), which are EBV-infected according to PCR and in situ hybridization studies (Fig. 119-19). CD30 positivity is also noted in infected monoclonal cells. EBV-positive cells vary in size and may show cytologic atypia. They may have an appearance of immunoblasts but can rarely resemble Reed-Sternberg cells with multinucleated forms. Despite the name of the disorder, well-formed granulomas are absent.

LYG is graded by comparing the proportion of EBV-positive B cells and their degree of cytologic atypia to the background population of reactive T cells. Grade 1 lesions are composed of polymorphous lymphoid infiltrate without significant atypia; necrosis may be focal or absent. Large EBV-positive lymphoid B cells are rare. Some of the cases previously included in the now obsolete classification of benign lymphocytic angiitis are likely grade 1 LYG. In grade 2 lesions, large EBV-positive cells are easily identifiable (5–50 per high-power field [HPF]), and necrosis is more common. Grade 3 lesions are characterized by a greater number of EBV-positive cells (>50 per HPF), and necrosis is common and often extensive. The large, atypical cells may occur in clusters. However, if there is a uniform population of large, atypical cells, a diagnosis of EBV-positive B-cell lymphoma is more appropriate. Given the complex histologic features of LYG and the need to identify scattered large cells in an inflammatory mass, diagnosis and accurate grading almost always requires generous biopsy samples. Immunohistochemistry is fundamental for a precise diagnosis. Clonal immunoglobulin gene rearrangements may be identified in most grade 2 and grade 3 lesions. B-cell clonality may not be detected in grade 1 lesions, most likely due to the paucity of EBV-positive cells. Clonal T cell receptor gene rearrangements are usually not present, although restricted patterns may be observed.

The natural history of LYG is variable, and clinical behavior ranges from indolent to aggressive. Histologic grade correlates with outcome. Most patients have either grade 1 or 2 disease; one-third of those with grade 1 lesions progress to grade 3/malignant lymphoma, whereas two-thirds of those with grade 2 lesions develop grade 3/malignant lymphoma. Asymptomatic patients, or those with minimal disease and grade 1 or 2 histology, may be observed. Clinically aggressive grade 2 and all grade 3 lesions are treated as DLBCL with chemotherapy plus rituximab or with stem cell transplantation. In more indolent cases, therapies targeting EBV-bearing B cells (interferon-α2β) or reactive T cells (cyclosporine) have been reported. As many as 63% of patients die, with a median overall survival of 14 months.

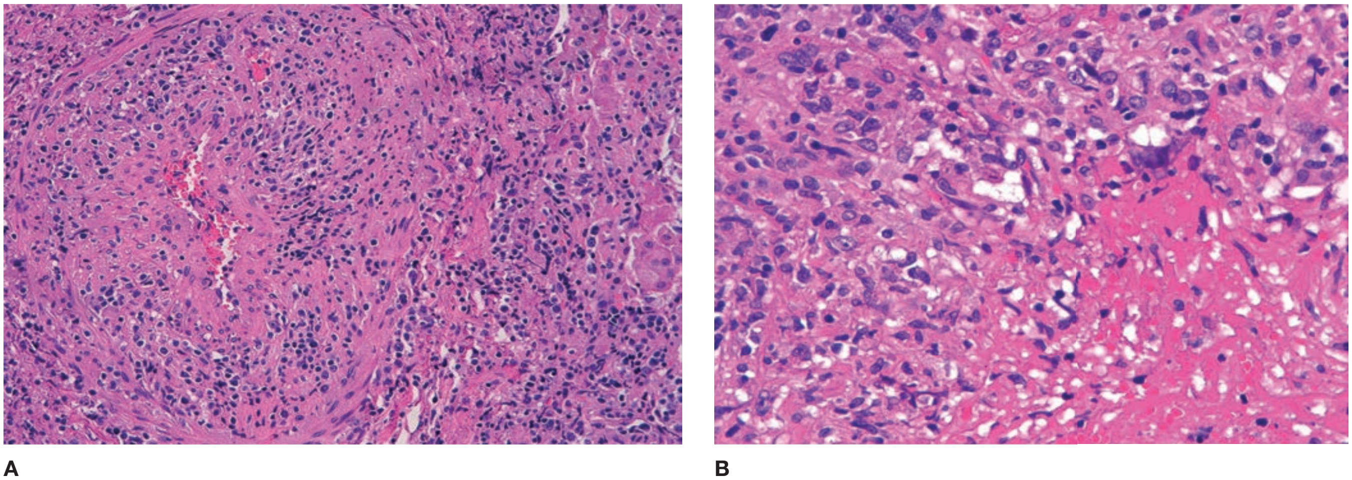

Figure 119-18 Lymphomatoid granulomatosis (video-assisted thoracoscopic biopsy). **A.** Dense infiltrate of large lymphoid cells with angiocentric distribution and destruction of normal lung architecture (H&E, × 20). **B.** Higher power demonstrating area of diffuse coagulative necrosis (H&E, × 40).

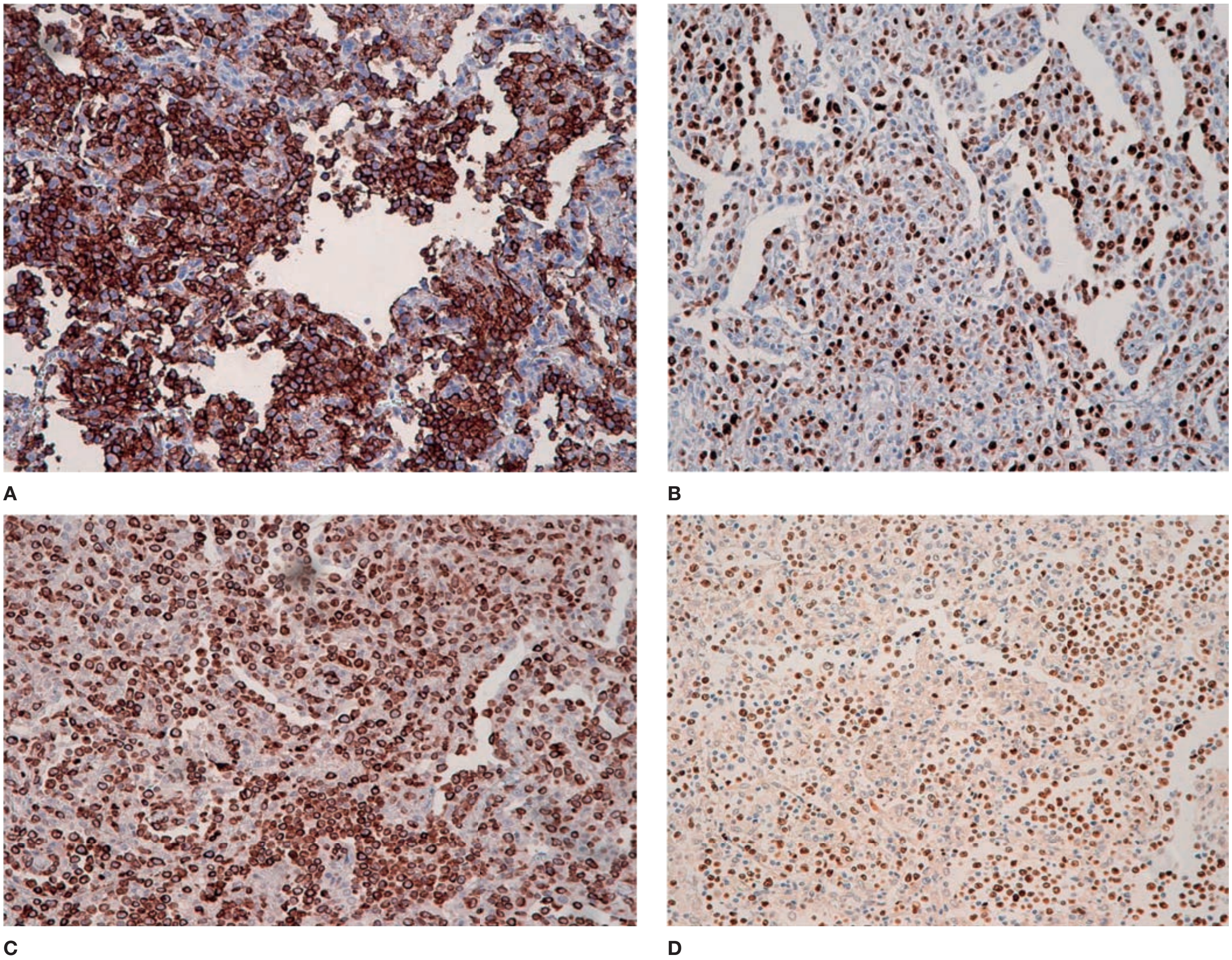

Figure 119-19 Lymphomatoid granulomatosis. Immunohistochemical profile: large lymphoid cells are positive for CD20 **(A)**, MUM1/IRF4 **(B)**, and Bcl2 **(C)**. **D**. In situ hybridization for EBV-encoded small RNA (EBER) demonstrates positive staining.

Intravascular Variant of DLBCL

An intravascular variant of DLBCL has been identified, characterized by the selective growth of malignant cells within the lumen of vessels, particularly capillaries;[1,2,72] it presents without adenopathy, organomegaly, or mass-forming lesions in solid organs. The vessels are filled with aggregates of large cells with coarse chromatin and a high nucleus-to-cytoplasm ratio that is clearly different from resting lymphocytes or monocytes (Fig. 119-20). Scattered extravascular atypical lymphoid cells may be detected as well. The neoplastic cells express mature B cells markers and frequently also CD5 and PD-L1; they characteristically have a defective expression of adhesion molecules.[84]

While there may be a prominent pulmonary component, the disease is never restricted to the lung and should be regarded as an aggressive, systemic lymphoma from the outset. Two major patterns of clinical presentation have been recognized: the so-called classic form (mostly present in Western countries), which is characterized by symptoms related to the main organ involved, predominantly neurologic or cutaneous, and a hemophagocytic syndrome–associated form, originally documented as an Asian variant, in which patients present with multiorgan failure, hepatosplenomegaly, and pancytopenia. B symptoms, particularly fever, are very common in both patterns of presentation. When the lungs are mainly involved, the differential diagnosis includes a thromboembolic event or an interstitial pneumonia. Pulmonary function tests document a preservation of lung volumes, along with a significant decrease of $\mathrm{DL_{CO}}$. Echocardiography usually shows an increased pulmonary artery systolic pressure. CT features include ground-glass opacities (occasionally associated with reverse halo sign), multiple centrilobular nodules, interlobular septal thickening, interstitial shadows and thickening of bronchovascular bundles, mosaic attenuation, intraparenchymal linear calcifications, and pleural effusion (Fig. 119-21). Serum LDH is markedly elevated, and hypercalcemia may be rarely observed. A random skin biopsy of normal-appearing skin and lung biopsy are often helpful in making the diagnosis.[85] Treatment is usually R-CHOP, combined with high-dose methotrexate and intrathecal chemotherapy, which is of benefit when a diagnosis is made in the early phases.[86]

Plasmacytoma

Extraosseous (extramedullary) plasmacytomas most often affect the upper respiratory tract. Primary plasmacytomas of the lung are exceedingly rare; patients are usually in their fifth and sixth decades and are asymptomatic. Cough, dyspnea, and hemoptysis have been reported. Unlike multiple myeloma, individuals may lack a serum M-protein or Bence Jones light chains in the urine. Radiographs most commonly demonstrate a midlung or hilar solitary mass, but peripheral lesion occur.[2,87]

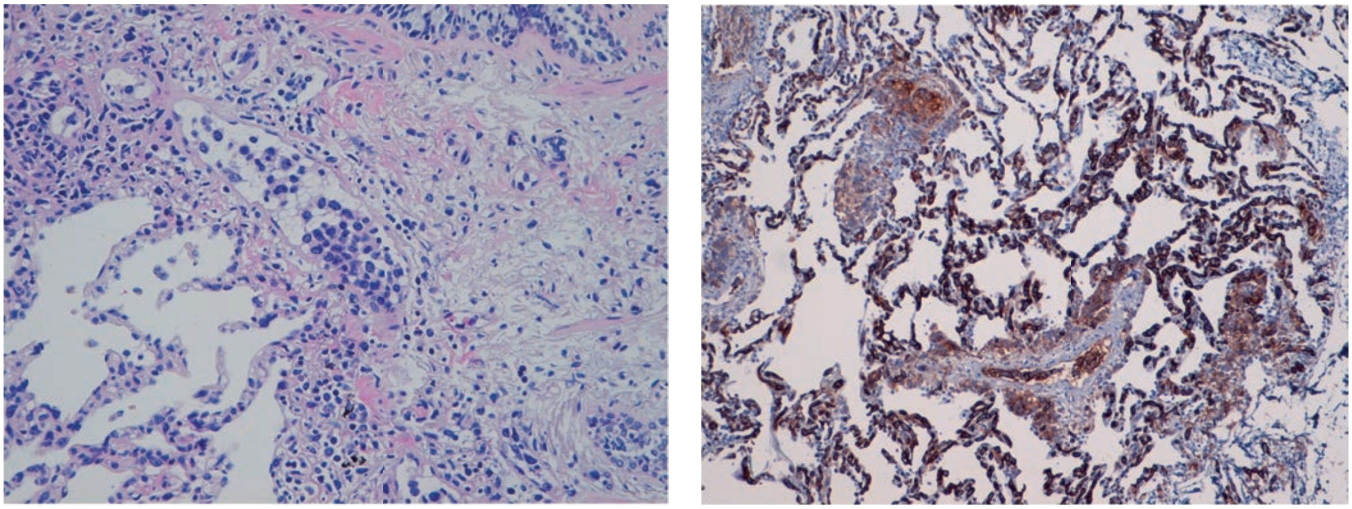

Figure 119-20 Intravascular large-B cell lymphoma of the lung. **A.** Large lymphoid cells are observed within pulmonary capillaries and small vessels (H&E, × 10). **B.** Immunohistochemistry for CD20 expressed by neoplastic cells highlights the vascular network of the alveolated lung (× 10).

Tumors range from 2.5 to 8.0 cm and most often involve a major bronchus, with occasional involvement of regional lymph nodes. Histologically, sheets of plasma cells, including binucleate forms, overrun lung parenchyma and bronchial cartilage. Fibrous bands course through the tumor, and amyloid or light chains may be associated with the neoplasm. κ and λ light chains, as well as IgG, IgA, and IgD, can be expressed immunohistochemically or produced as M-proteins by the tumor. The pathologist must discriminate between plasmacytoma and marginal zone lymphoma with plasmacytoid features, as well as inflammatory myofibroblastic tumor. Although the natural history of this rare tumor is not well delineated, surgical excision or radiation therapy may be curative, although some cases evolve into multiple myeloma. The presence or absence and amount of M-protein may mirror tumor burden, while an increase or decrease in levels may be associated with recurrence or successful treatment, respectively. An overall 5-year survival of 40% has been reported.

■ Amyloidosis

Amyloidosis related to B-cell lymphoproliferative disorders may involve the lower respiratory tract in three distinct forms: diffuse alveolar septal amyloidosis, nodular amyloidosis, and tracheobronchial amyloidosis.[1,72] Immunoglobulin light chains, typically λ light chains, represent the protein present in the fibril. Diffuse alveolar septal amyloidosis is characterized by the presence of amyloid deposits in the alveolar septa. Most cases represent pulmonary manifestations of systemic AL amyloidosis. Pleural effusion may be a manifestation of AL amyloidosis. Nodular amyloidosis is defined as one or more tumorlike amyloid deposits that involve the pulmonary parenchyma (Fig. 119-22). The process is rarely associated with systemic diseases, such as plasma cell myeloma; it is usually related to a localized lymphoproliferative process, such as MALT lymphoma, even if the process is subtle. It typically appears as solitary or multiple nodules with calcification (Fig. 119-23). Cavitation is rare; however, cysts are not infrequently observed. In tracheobronchial

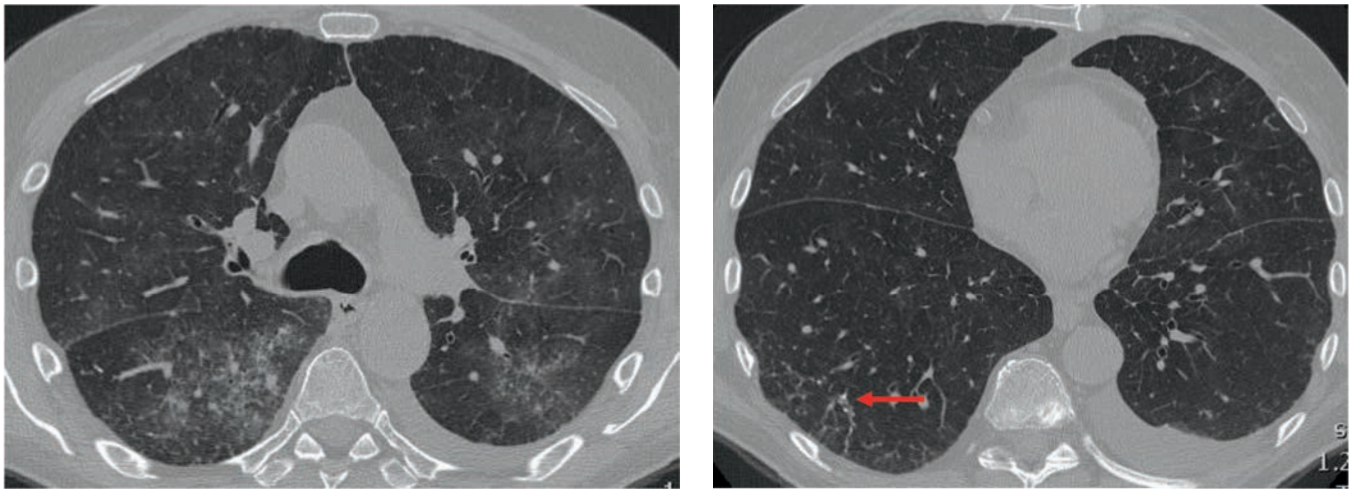

Figure 119-21 Intravascular large-B cell lymphoma of the lung. **A.** Axial CT scan shows patchy ground glass opacities associated with focal areas of septal thickening and consolidation. **B.** Scattered calcifications are present along the secondary lobular margins in the right lower lobe *(red arrow)*.

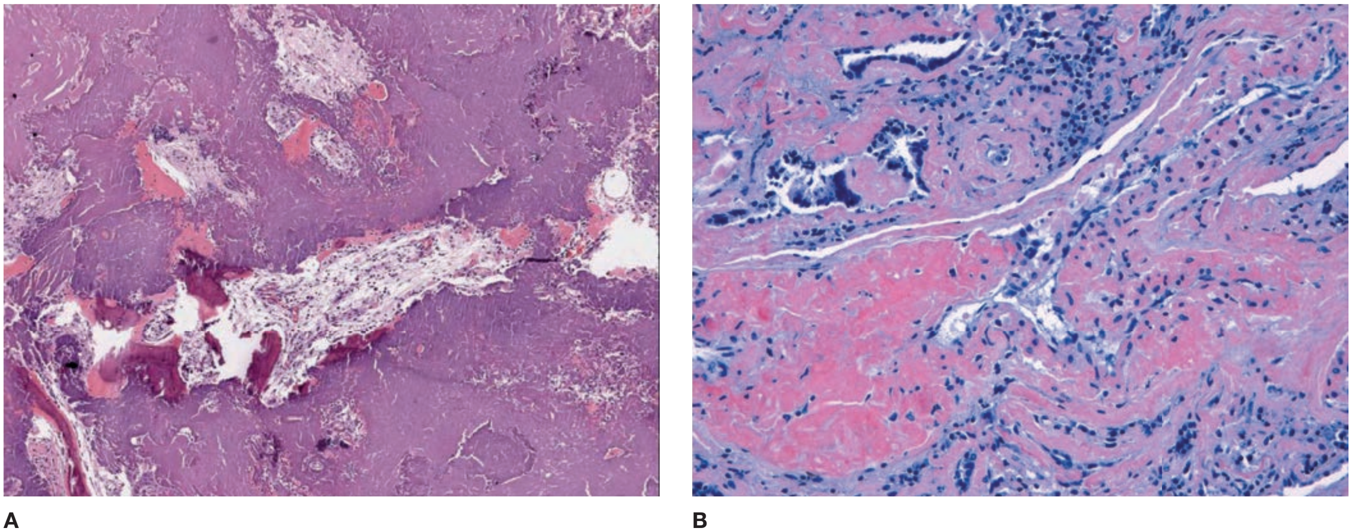

Figure 119-22 Pulmonary AL amyloid. **A.** A large deposit of amorphous, eosinophilic material entrapping a bronchiole (H&E, × 10). **B.** The Congo red–stained section shows that the amorphous material appears red (× 20).

amyloidosis, amyloid is deposited in various segments of the trachea and bronchi; the B-cell clones may be hidden and difficult to document, even using molecular tests. Bronchoscopy may document irregular whitish deposits, most often diffuse, which narrow the airway lumen. Three patterns of involvement have been described: proximal, mid-, and distal airway. Subglottic stenosis may mimic Granulomatous with Polyangiitis (GPA) or other rare forms of tracheal involvement. A daratumumab–bortezomib combination can be used in cases of diffuse lung involvement. Stenosis of large airways may be treated by bronchoscopic debulking and stent insertion.[88]

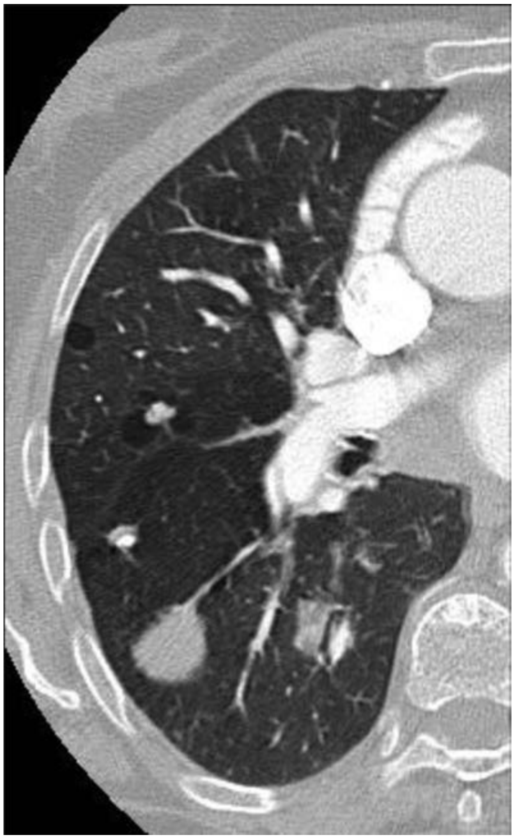

Figure 119-23 Nodular AL pulmonary amyloidosis. Axial CT showing large nodules, some partially calcified, and scattered cysts.

■ Light Chain Deposition Disease

Colombat et al. reported a very rare form of light chain deposition disease that presents as a diffuse cystic lung disorder and, in their original series, led to respiratory failure and need for lung transplantation[89] (Fig. 119-24). It was hypothesized that monoclonal light chain synthesis occurs within the lungs. This was based on the absence of disease recurrence after bilateral lung transplantation and serum-free light chain ratio normalization after the procedure.[28] Histologic examination of the explanted lungs identified diffuse, non-amyloid κ light chain deposits associated with a mild lymphoid infiltrate composed of aggregates of small CD20(+), CD5(−), CD10(−) B lymphocytes, reminiscent of BALT. A dominant B-cell clone may be identified using PCR. The deposits appear crimson red with a Masson trichrome stain and salmon pink with a sulfated Alcian blue stain; they do not stain with Congo red and do not demonstrate apple-green birefringence under polarized light. These characteristics are helpful in differentiating these deposits from those detected in amyloidosis[90] (Fig. 119-25). A very few cases manifesting with thin walled bronchiectasis have been reported.

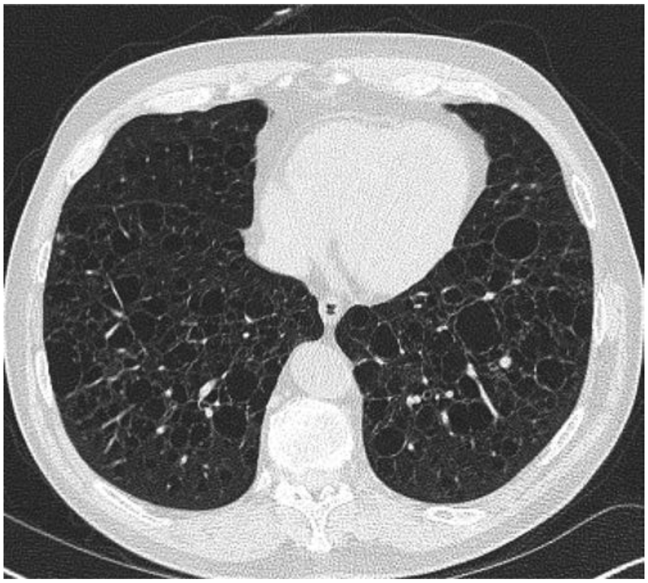

Figure 119-24 Pulmonary light chain deposition disease. HRCT shows innumerable thin-walled cysts.

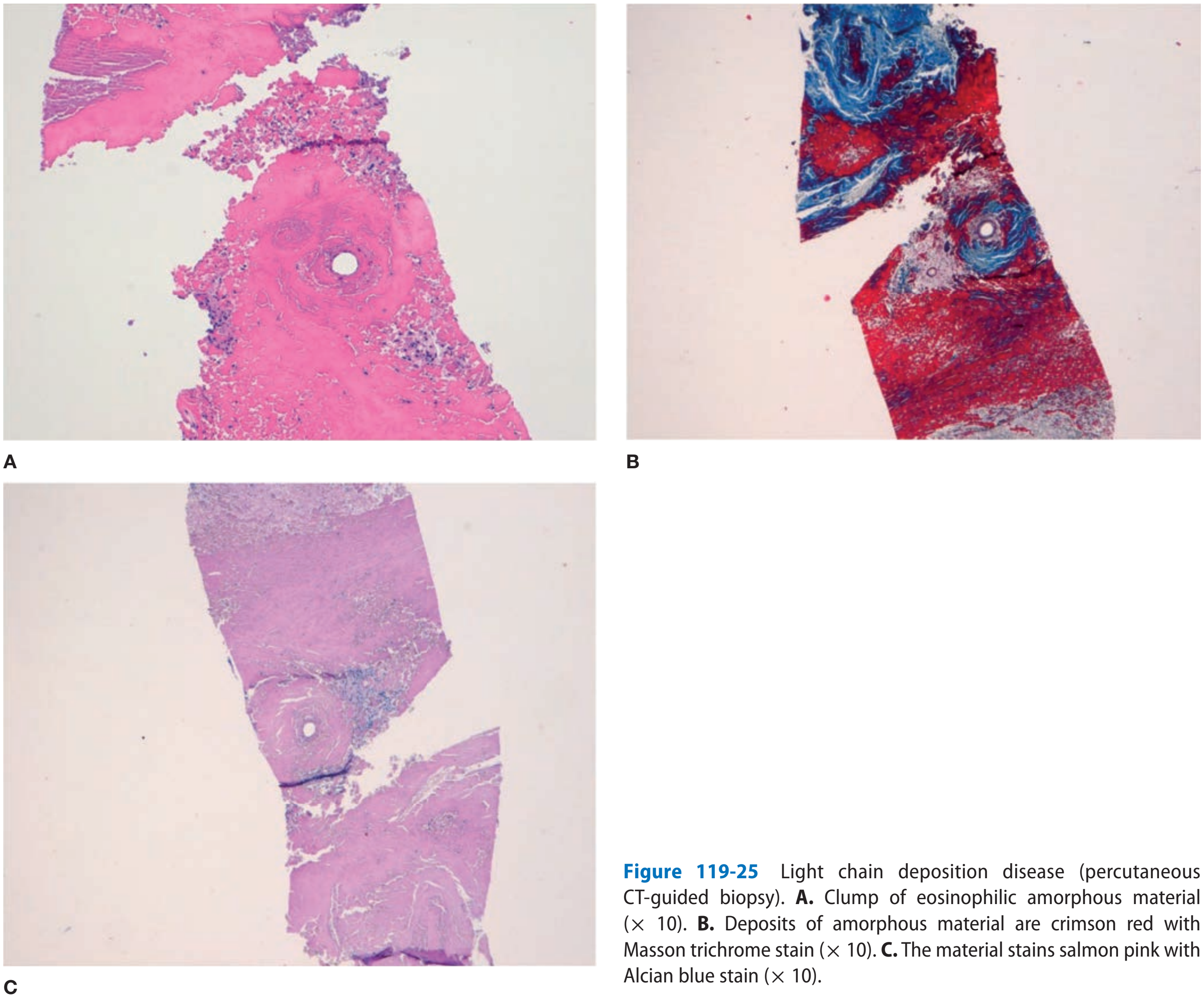

Figure 119-25 Light chain deposition disease (percutaneous CT-guided biopsy). **A.** Clump of eosinophilic amorphous material (× 10). **B.** Deposits of amorphous material are crimson red with Masson trichrome stain (× 10). **C.** The material stains salmon pink with Alcian blue stain (× 10).

■ Extranodal Natural Killer T-Cell Lymphoma (Nasal Type)

Extranodal natural killer T-cell lymphoma (ENKTCL), nasal type, is a predominantly extranodal lymphoma of NK-cell or T-cell lineage characterized by vascular damage and destruction, prominent necrosis, cytotoxic phenotype, and association with EBV. It is predominantly seen in middle-aged men from Asia, Mexico, and South America, but it has also been reported in Western countries.[1,2] It presents as tumors or destructive lesions in the nasal cavity, maxillary sinuses, or palate; it may also appear mainly localized to the lungs. Pulmonary (hemoptysis, chest pain) and systemic symptoms (fever, asthenia) are common. The first symptoms may be due to coexisting pulmonary infections (fungal, viral) or to hemophagocytic syndrome.[72] Laboratory tests may document CD4+ lymphocytopenia in peripheral blood.[72] CT scan shows nodules or masses with an important necrotic component. ENKTCL ranges from monomorphic, small/medium-sized cell lymphomas to large cell lymphomas and is characterized by frequent features of angioinvasion and angiocentrism, as well as necrosis. The neoplastic cells usually express cytoplasmic CD3, are CD2+, CD5+, CD7+CD16 +/−, and CD56+ and have an activated cytotoxic profile. By definition, all cases are associated with expression in the neoplastic cells of EBV-latent infection markers (EBERs, latent membrane protein 1, and EBNA2). Recent studies have documented consistent programmed death ligand 1 (PD-L1) expression by ENKTCL neoplastic cells, suggesting that checkpoint inhibitors may represent a therapeutic option for patients who are refractory to standard lines of chemotherapy.[91,92]

■ Peripheral T Cell Lymphoma, Not Otherwise Specified

Peripheral T-cell lymphoma (PTCL), not otherwise specified (NOS), constitutes a heterogeneous category of nodal and extranodal mature T-cell lymphomas that do not correspond to any of the specifically defined entities of mature T-cell lymphoma in the current WHO classification.[1,72] Excluded from this category are tumors with a T follicular helper cell phenotype, as defined by the expression of at least two (ideally, three) of the following markers: CD10, BCL6, PD1, CXCL13, CXCR5, ICOS, and SAP. PTCL, NOS nearly always presents in adults and has an aggressive clinical course. Expression in the neoplastic cells of EBV-latent infection markers may be documented in a minority of cases. Natalizumab, an anti-integrin alpha-4 monoclonal antibody used for treatment of multiple sclerosis, has been reported to be associated with PTLC.

Rarely, PTLC, NOS may present as a localized lung lesion. Patients usually present with cough, dyspnea, chest pain, fever, and hemoptysis. Not infrequently a superimposed pulmonary infection (bacterial, fungal or even viral) may be the first manifestation of the underlying lymphoma. Laboratory tests may document lymphopenia and eosinophilia. Serum autoantibodies (such as proteinase-3 antineutrophil cytoplasmic antibodies) may be detected. Hemophagocytic syndrome is a rare but ominous complication.

CT features include alveolar consolidation and large nodules with or without cavitation. Areas of ground glass and/or crazy paving are rarely reported. These features may be explained in part by the presence of organizing pneumonia around the lymphoid neoplastic infiltrates. Pleural effusion as first manifestation is very rare.

The cytologic spectrum is extremely broad, ranging from polymorphous to monomorphic. Most cases consist of numerous small/medium-sized and/or large cells with irregular, pleomorphic, hyperchromatic, or vesicular folded nuclei, prominent nucleoli, and many mitotic figures. Clear cells and Reed-Sternberg-like cells also can be seen. Rare cases have a predominance of small lymphoid cells with atypical, irregular nuclei. Neoplastic cells express T-cell markers, such as CD3 and CD2 with a CD4 or CD8 phenotype, with frequent downregulation of CD5 and CD7. A CD4/CD8 double-positivity or double-negativity is sometimes seen. CD15 may be positive and may be coexpressed with CD30 in rare instances. CD15 expression is associated with an adverse prognosis. The neoplastic cells infiltrate the lung parenchyma with a perivascular/perilymphatic distribution. Infection of neoplastic cells by EBV is reported in a small number of cases. The background consists of a mixed inflammatory infiltrate (small lymphocytes, frequent eosinophils, plasma cells, and a variable number of epithelioid histiocytes, with loosely formed granulomas, mainly in the lymphoepithelioid or "Lennert" variant). Organizing pneumonia features may be prominent around the neoplastic infiltrate. In areas of necrosis a superimposed infection may be documented. Diagnosis requires a generous biopsy sample, and if less invasive approaches fail, surgical lung biopsy is mandatory.

Anthracycline-based combination chemotherapy remains the most frequently used frontline strategy. However, prospective studies have shown that consolidation with high-dose chemotherapy and autologous stem cell transplantation results in a better progression-free survival.[93,94]

■ Anaplastic Large Cell Lymphoma

Anaplastic large cell lymphoma (ALCL) is a rare non-Hodgkin T/NK cell lymphoma. The WHO 2017 Classification defined ALCL as a CD30+T/NK cell neoplasm that is further subdivided in two distinct entities by ALK protein expression (ALK-positive ALCL and ALK-negative ALCL). A chromosomal translocation involving the ALK gene (2p23) is present.[1,95] The lung is a common site of secondary involvement by systemic T cell-ALCL, but rare cases of primary pulmonary ALCL of T or NK cell type have also been reported.

Lung parenchymal masses or single nodules are the features observed on CT scan. Rarely, ALCL may appears as a large airways endoluminal mass. Morphologically it is characterized by large anaplastic, pleomorphic cells with "horseshoe-shaped" nuclei and abundant cytoplasm. In some cases, the nuclear indentation is in the plane of view, such that the nucleus appears as an "O" (donut cells). The majority of these cases are positive for a pan–T cell marker, such as CD2, CD3, or betaF1, although some may be negative for these antigens (null cell phenotype) or negative for leukocyte common antigen. Neoplastic cells express CD30.

Because ALK is essential for the proliferation and survival of ALK-positive ALCL cells, it provides a unique therapeutic target. Promising clinical results have been achieved in small case series of ALK+ ALCL with small molecule inhibitors of ALK kinase. CD30-targeting with antibody/drug conjugates and brentuximab vedotin also has been utilized. The clinical outcome of ALK-negative ALCL with conventional therapy is poorer. However, approximately 30% of cases harbor DUSP22 rearrangements, and this subtype has a favorable prognosis similar to that seen in ALK-positive ALCL.[95]

■ Hodgkin Lymphoma

Classic Hodgkin lymphoma (HL) rarely can appear as a primary lung disorder.[2,96–98] This occurs more frequently in females, and patients are usually older than those with primary nodal disease. Cases of primary pulmonary HL occurring in patients treated with methotrexate for autoimmune diseases have been reported.[99] Reticulonodular infiltrates, single or multiple nodules (frequently cavitary), and alveolar consolidation are the main radiographic manifestations. Patients are usually symptomatic with cough, fever, weight loss, night sweat, dyspnea, fatigue, anorexia, chest pain, and/or pruritus. The "nonclassic" or lymphocytic-predominance subtype has not yet been reported a primary lung tumor.

Diagnosis of the "classic" HL requires the identification of Reed–Sternberg cells or its variants. These cells are CD30+ in nearly all cases and CD15+ in most. The B-cell nature of the Hodgkin-Reed Sternberg cells is demonstrable by the expression of the B cell–specific activator protein PAX-5. The prevalence of EBV in HL cells varies according to the histologic subtype and epidemiologic factors. EBV-infected neoplastic cells express LMP1 and EBNA1 without EBNA2, a pattern characteristic of type II EBV latency. In the lung the mixed inflammatory milieu of HL may overlap substantially with reactive conditions.

Central necrosis, granulomatous inflammation, and vascular and bronchial infiltration by the polymorphous infiltrate are commonly seen. The morphologic differential diagnosis includes inflammatory and malignant processes, infections, GPA, sarcoidosis, poorly differentiated carcinomas, inflammatory solitary fibrous tumor, inflammatory myofibroblastic tumor, LYG, and a variety of non-Hodgkin lymphomas.

The prognosis for patients with primary pulmonary HL is variable. Relapses occur in the lung and elsewhere and appear associated with multiple lobe involvement, pleural invasion, cavitation, and presence of B symptoms. Treatment is with the ABVD regimen. However, in patients with methotrexate-related HL, use of bleomycin can result in an increased lung toxicity, and an alternative regimen consisting of brentuximab vedotin, in combination with doxorubicin, vinblastine, and dacarbazine, has been adopted.[100] PD-L1 antibody therapy is beneficial in relapsed/refractory HL.[101,102]

■ Pleural Lymphomas

Two major types of lymphoma involve the pleura as primary neoplasms: primary effusion lymphoma (PEL) in the setting of HIV infection, and pyothorax-associated lymphomas (PAL), with a strong Epstein-Barr virus (EBV) or pyothorax association.[1,2] A rare form of microscopically proliferation of large B cells found incidentally with fibrin in pleural or other confined anatomical spaces has been recently reported and called fibrin-associated diffuse large B cell lymphoma.[1,2]

Primary Effusion Lymphoma

Primary effusion lymphoma (PEL) is a peculiar form of malignant lymphoproliferative disorder. According to the WHO classification,[1,2] classic PELs present as serous effusions with or without mass lesions over the entire course of the disease. Extracavitary PELs are less common, representing approximately one-third of the cases.[2,103] PEL occurs in HIV-infected patients, but also rarely in the setting of transplantation and in elderly patients. Neoplastic cells exhibit a range of appearances, from large immunoblastic to anaplastic, and their nuclei are positive for HHV-8 latent proteins. Most cases (usually those manifesting in HIV patients) are coinfected with EBV. The malignant cells express CD45 and CD30, but pan–B cell markers are not expressed. However, terminal B-cell differentiation markers, such as MUM1, CD38, and CD138, are expressed. Eventually, aberrant expression of T-cell markers (CD2, CD3, CD4, and CD5) may be detected.[104] Cytologic analysis of fluid, along with PCR to identify HHV-8, is usually diagnostic. Treatment options for PEL include cyclophosphamide, doxorubicin, vincristine, and prednisone-based chemotherapy regimens alone or in combination with immunomodulatory agents (e.g., lenalidomide) and proteasome inhibitors (e.g., bortezomib).[105] Several case reports have shown prolonged complete remission with brentuximab vedotin.[104] Highly active antiretroviral therapy should be initiated or continued in patients with associated HIV infection. Prognosis, however, remains grim.

Pyothorax-Associated Lymphoma

Pyothorax-associated lymphoma (PAL) is a lymphoid neoplasm that develops in the pleural cavities of immunocompetent patients with chronic suppurative pleuritis; it is linked with EBV.[1,2,72,106,107] Most cases arise decades after artificial pneumothorax for treatment of tuberculosis or tuberculous pleuritis. Approximately 2% of individuals with chronic pyothorax develop PAL. Patients, more often males, are usually in their sixth to eighth decades of life and usually present with chest pain, back pain, shoulder pain, and dyspnea. Radiographic studies demonstrate an intense ^{18}F fluorodeoxyglucose PET–positive visceral or parietal pleural mass that may invade the chest wall, lung, pericardium, or diaphragm in the setting of pleural fibrosis and calcification.[108,109]

Biopsy and resection specimens show masses composed of sheets of large atypical lymphoid cells with prominent nucleoli and basophilic cytoplasm. Mitotic figures and apoptotic bodies, as well as necrosis, abound. Immunohistochemical studies distinguish this high-grade lymphoma from PEL. Typically, lymphoma cells associated with PAL stain for B-cell antigens CD20 and CD79a; plasma cell markers CD38 and CD138; and, on occasion, a T-cell marker such as CD2, CD3, CD4, or CD7. Immunohistochemistry is positive for EBV, whereas KSHV/HHV8 is absent.

Treatment options include chemotherapy (e.g., CHOP), rituximab, and/or radiotherapy. Combination chemotherapy and radiotherapy may induce a complete response and prolong survival, with overall 5-year survival rates of 20%. Those who demonstrate a complete response to chemotherapy and/or radiotherapy achieve a more prolonged survival, with 5-year survival rates approaching 50%. Pleuropneumonectomy has been advocated for selected patients.[110]

SECONDARY LUNG INVOLVEMENT FROM EXTRATHORACIC LYMPHOMA

Secondary lung involvement due to nodal and extranodal lymphomas is significantly more common than primary pulmonary lymphoma. Lung and pleural involvement with common nodal and disseminated lymphomas surpasses 50% during life and at autopsy.[111] Clinical and radiologic features may mimic an infectious process.

Morphology does not usually allow for distinction between primary and secondary lung disease. For example, pulmonary involvement with nodal marginal zone lymphoma is indistinguishable from primary pulmonary extranodal B-cell lymphoma of MALT. Thus, clinical history and review of previous diagnostic material are necessary for proper diagnosis. Secondary lymphomas involving the lung can also transform to more aggressive histology with increased numbers of large cells. This phenomenon is not infrequently seen in samples from patients with chronic lymphocytic leukemia/small lymphocytic lymphoma.

Particular systemic lymphoproliferative disorders that may present with significant lung pathology warrant additional discussion. Mycosis fungoides may involve the lung after dissemination of cutaneous disease or as part of Sézary syndrome. Indeed, the lung is the second most common extracutaneous site after lymph nodes. Clinical and radiographic features often mimic pneumonia, or even acute respiratory distress syndrome, with nodular and diffuse disease. Tissue samples demonstrate air space and interstitial infiltrates along lymphatic routes in addition to occasional granulomas.

The lungs are also frequently involved with angioimmunoblastic T-cell lymphoma.[1,111] Neoplastic cells have a T follicular helper (TFH) cell gene expression signature and express many of the TFH cell-associated markers, such as CD10, CXCL13, BCL6, ICOS, CXCR5, SAP, MAF (also called c-MAF), and (in most cases) CD200. Cytologically, the neoplastic T cells are small- to medium-sized lymphocytes, with clear to pale cytoplasm, distinct cell membranes, and minimal cytologic atypia. Patients exhibit immunodeficiency secondary to the neoplastic process, and expansion of EBV-positive B cells may be observed in the majority of patients. This aggressive disease in the lung can be mistaken for interstitial lung disease or infectious pneumonia.

Chronic lymphocytic leukemias (B-cell type) can appear as a diffuse symptomatic lung disease mimicking nonneoplastic forms of interstitial lung disease or chronic bronchiolitis.[112] BAL with flow cytometry and/or transbronchial biopsy are usually diagnostic.[112] T-cell large granular lymphocytic leukemia may appear as a cystic lung disease.[113]

POSTTRANSPLANT LYMPHOPROLIFERATIVE DISORDER

Posttransplant lymphoproliferative disorder (PTLD) occurs after solid organ transplantation or hematopoietic stem cell transplantation.[113,114] Among adults, patients receiving renal allografts have the lowest frequency of PTLD (generally <1%); those with hepatic and cardiac allografts have an intermediate risk (approximately 1%–5%); and those receiving heart–lung, lung, or intestinal allografts have the highest frequency (≥5%). In general, allogeneic hematopoietic stem cell recipients have a low risk of PTLD (~1%–2%). These disorders constitute a spectrum of lymphoproliferative entities, including early lesions (which are also defined as "mononucleosis-like" and are always EBV-positive), polymorphic PTLDs (which are characterized by a mixture of B lymphocytes with infiltrating T lymphocytes, without necrosis), and a group of monomorphic PTLDs (which includes all non-Hodgkin lymphoma histologies).[2,111,115] EBV-associated lesions with histopathologic features of LYG also have been reported. Other rare monomorphic subtypes of PTLD are multiple myeloma, plasmacytoma, Hodgkin lymphoma, and EBV-negative PTLD.[114]

Lymphoid proliferations are related to a T-cell dysfunction, which results from the administration of immunosuppressive agent and, in virtually almost all cases, the presence of EBV.[116] The interval between transplantation and the onset of PTLD varies widely (from 2 to 128 months); it usually manifests 2 to 6 months after lung transplant.[114,115,117,118]

The majority of cases of pulmonary PTLD occur in lung transplant recipients. Individuals may be asymptomatic or present with constitutional or respiratory symptoms. CT scan demonstrates solitary or multiple nodules or masses, sometimes with surrounding ground glass ("halo sign"); regional lymphadenopathy also may be present. Endobronchial lesions as a manifestation of PTLD have been reported.[119] Treatment strategies consist of response-adapted risk-stratified methods using immunosuppression reduction (as permitted), immunotherapy (rituximab in CD20+ lesions), and chemotherapy. Chemotherapy is reserved for CD20− lymphomas and for cases refractory to the above measures but is often poorly tolerated in immunocompromised transplant recipients.[120,121] The combination of brentuximab vedotin given concurrently with rituximab is a promising approach.[122]

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PART 17

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CHAPTER 120

Pulmonary Clearance of Infectious Agents

Theodore J. Standiford
Gary B. Huffnagle

INTRODUCTION

The primary function of the lungs is the exchange of gases at a rate required to support tissue metabolism. During gas exchange, the lung is continuously exposed to a varied burden of foreign substances, including infectious agents. In addition, microbes immigrate into the lower respiratory tract via subclinical microaspiration of oropharyngeal microbiota.[1,2] The lung has the difficult task of defending itself against this potentially hostile environment while maintaining the alveolar architecture required for adequate gas exchange. This group of nonrespiratory antimicrobial functions has been collectively termed *pulmonary host defenses*.[3]

MECHANICAL DEFENSES

Mechanical defenses of the respiratory system include those in the nasopharyngeal airway as well as those in the conducting airways.

Nasopharyngeal Airways

Nasal hairs remove most particulates larger than 10 μm. Brisk airflow and rapid changes in direction of the airstream within the nose promote inertial deposition of large particulates, which are cleared primarily by swallowing, sneezing, or coughing. Mucociliary clearance participates in the removal of particulates from the nasopharynx. Ciliated mucosa is present on the nasal septum and turbinates; mucociliary action sweeps mucus toward the posterior pharynx, where secretions are either swallowed or expelled from the throat.[4–6]

Conducting Airways

Important functional aspects of the conducting airway defense mechanisms include the mucociliary escalator and airway secretions, as discussed below.

Mucociliary Escalator

Most particulates larger than 2 μm in diameter affect the conducting airways of the lower respiratory tract. Mucociliary clearance and coughing are the principal means of mechanical defense.[5,7] The mucosa of the conducting airways is lined with mucus secreted by goblet cells, bronchial glands, and club cells (previously termed Clara cells). The mucous blanket is composed of two distinct layers: a watery periciliary layer, which provides lubrication for ciliary movement, and an upper more viscous layer that is just penetrated by the ciliary tip.[4,6–9] Mucus is propelled cephalad within the respiratory tract by the terminally differentiated pseudostratified ciliated epithelium that lines the conducting airways. Each ciliated cell has approximately 200 cilia, which are approximately 5 to 6 μm in length and have a beat frequency of 12 to 14 beats per second. Beat frequency is regulated by both environmental factors and pharmacologic agents. Particulates can be cleared from the trachea and distal airways within minutes to hours.

Airway Secretions

Secretory cells of the airway epithelium, including serous, club, and goblet cells, secrete a broad array of antimicrobial molecules.[10–13] Mucus is comprised of a complex mix of mucin glycoproteins, diverse antimicrobial peptides, and metabolites. Mucus functions to ensnare microbes for removal and protects the respiratory epithelium from microbial invasion. MUC5B and MUC5AC are the predominant mucins present in mucus, and MUC5B in particular is essential for effective mucociliary clearance.[14] Mucins have also been shown to display antimicrobial, antiprotease, and antioxidant properties.

Lysozyme is secreted in abundant quantities in human airways (10–20 mg per day). This enzyme catalyzes the hydrolysis of peptidoglycan constituents of the cell walls of most bacteria and some fungi. Airway secretions contain both serum-derived antiproteases (α1-antitrypsin, α_2-chymotrypsin, and α_2-macroglobulin) and airway epithelial cell–derived antiproteases (secretory leukocyte proteinase inhibitor [SLPI] and elafin).[8] Iron is essential for survival of many microbes.[15] Iron is sequestered in cells or firmly complexes to transport proteins. Microbes compete for this iron with their own transport proteins, known as siderophores. Lactoferrin, transferrin, and lipocalin 2 are host-derived molecules that effectively complex free iron in mucosal secretions, limiting iron required for bacterial growth.[16–18] Lactoferrin also exerts direct antimicrobial effects by disrupting microbial plasma membranes and has immunomodulatory properties on innate and adaptive immune cells.[18]

Airway secretions and alveolar lining fluid also contain the small cationic antimicrobial peptides β-defensin and cathelicidin.[8,19–22] These proteins exert broad antimicrobial activity against bacteria, fungi, and viruses through hydrostatic interactions with cell membranes resulting in cell rupture.[19,23] Cathelicidins also exert immunomodulatory properties that augment local antimicrobial responses, including stimulation of inflammatory cytokine production and induction of neutrophil extracellular trap (NET) release from neutrophils.[24] Different classes of antimicrobial molecules can function in a synergistic fashion to markedly enhance microbial killing.[25] For instance, sub-MIC concentrations of lysozyme and lactoferrin can substantially enhance the bacterial killing activity of β-defensins and cathelicidins. The respiratory epithelium also has the ability to generate reactive oxygen species at bactericidal concentrations. Hydrogen peroxide is produced in the airway via the dual NADH oxidase/peroxidase (Duox) system, which is induced during infection.[9,26] The bactericidal activity of H_2O_2 is greatly enhanced in the presence of lactoperoxidases produced in abundance by the airway epithelium.

LUNG INNATE IMMUNITY

Host immune mucosal defenses against invading microbial pathogens consist of two distinct but integrated components: innate immunity and adaptive immunity. Innate immune recognition occurs via germline-encoded receptors that recognize conserved molecular features common to multiple microorganisms (Fig. 120-1).

Innate Immune Recognition

Microbial recognition is complex because microbes display molecular heterogeneity and have high mutation rates. The innate immune system detects a broad spectrum of pathogens using a repertoire

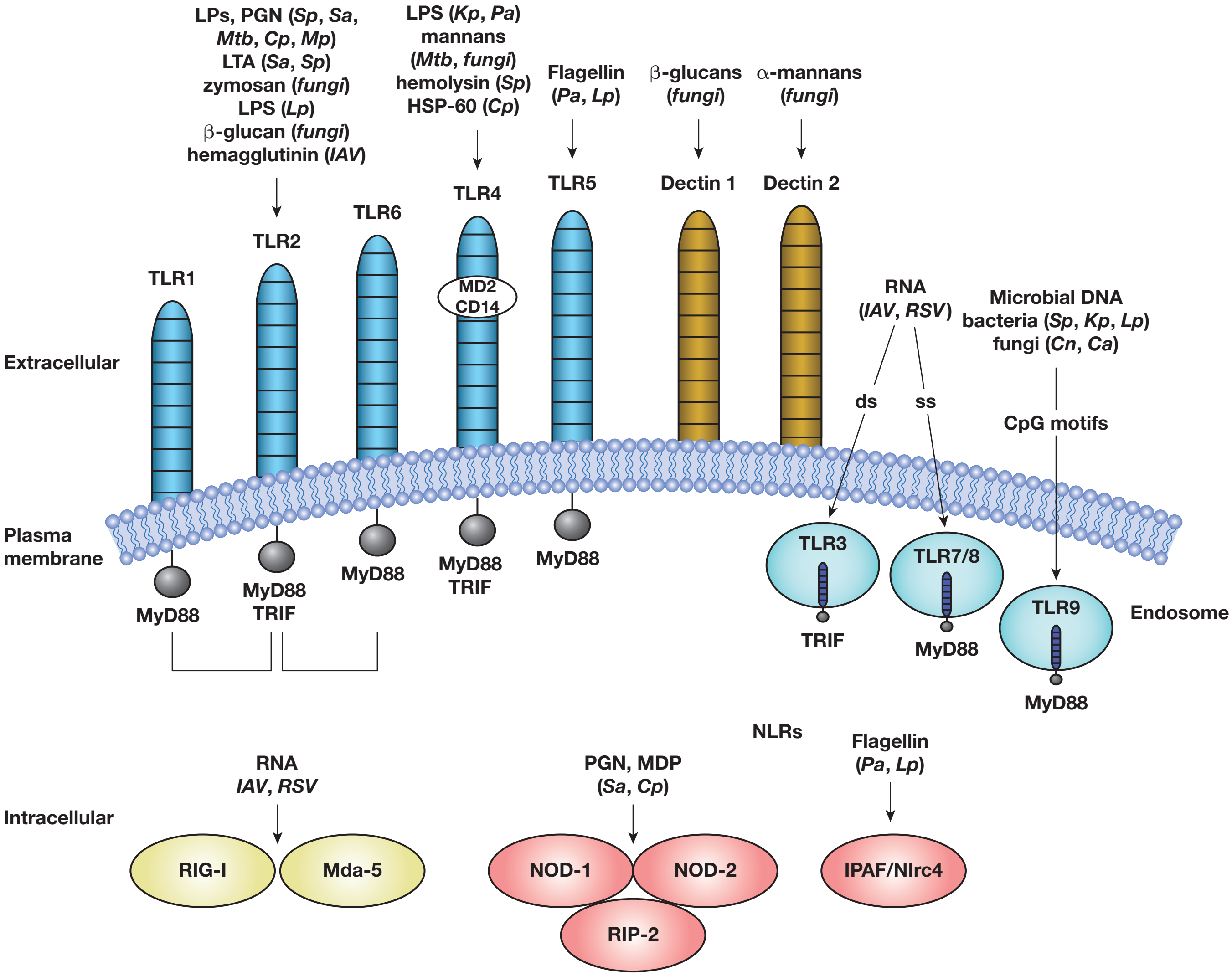
LPs, PGN (*Sp*, *Sa*, *Mtb*, *Cp*, *Mp*)
LTA (*Sa*, *Sp*)
zymosan (*fungi*)
LPS (*Lp*)
β-glucan (*fungi*)
hemagglutinin (*IAV*)
LPS (*Kp*, *Pa*)
mannans (*Mtb*, *fungi*)
hemolysin (*Sp*)
HSP-60 (*Cp*)
Flagellin (*Pa*, *Lp*)
β-glucans (*fungi*)
α-mannans (*fungi*)
TLR1
TLR2
TLR6
TLR4
MD2
CD14
TLR5
Dectin 1
Dectin 2
RNA (*IAV*, *RSV*)
ds
ss
Microbial DNA
bacteria (*Sp*, *Kp*, *Lp*)
fungi (*Cn*, *Ca*)
CpG motifs
Extracellular
Plasma membrane
MyD88
MyD88
TRIF
MyD88
MyD88
TRIF
MyD88
TLR3
TRIF
TLR7/8
MyD88
TLR9
MyD88
Endosome
NLRs
RNA
IAV, *RSV*
PGN, MDP (*Sa*, *Cp*)
Flagellin (*Pa*, *Lp*)
Intracellular
RIG-I
Mda-5
NOD-1
NOD-2
RIP-2
IPAF/Nlrc4

Figure 120-1 Pathogen recognition receptors: TLRs, NLRs, C-type lectin receptors, and RIG-I system for detection of extracellular and intracellular PAMPs. TLRs 1, 2, and 4–6, and C-type lectin receptor are extracellular; TLRs 3, 7/8, and 9 detect PAMPs within endosomes; NLRs and RIG-I detect intracellular PAMPs. All are signaling receptors. ds, double stranded; HSP, microbe-derived heat shock protein; LPS, lipopolysaccharide; LTA, lipoteichoic acid; ss, single stranded.

of invariant extracellular and intracellular receptors that recognize highly conserved microbial molecules including combinations of sugars, proteins, lipids, and distinct nucleic acid motifs. The receptors that recognize these molecular patterns are termed pathogen recognition receptors (PRRs). The microbial ligands recognized by PRRs are referred to as pathogen-associated molecular patterns (PAMPs). PAMPs share certain features. Specifically, PAMPs are invariant structures shared by classes of pathogens, are produced only by microbes, and are essential for microbial pathogenicity or microbial survival.[27] PRRs also recognize certain host-derived signals released in the setting of cellular stress or injury, referred to as danger-associated molecular patterns or DAMPs.[28,29]

PRRs can be divided into two general classes: endocytic and signaling receptors. Macrophage scavenger receptors (MSR), including SR-AI/II, MARCO, and CD36 have broad specificity for varied polyanionic molecules, including environmental particles, apoptotic cells, and microbial components.[30,31] Microbial ligands for scavenger receptors include double-stranded RNA, LPS, and lipoteichoic acid, and these scavenger receptors mediate binding and internalization of nonopsonized bacteria such as *Escherichia coli* and *Staphylococcus aureus* and some viruses.[32] While not considered classic signaling receptors, scavenger receptors can stimulate respiratory burst but generally not inflammatory cytokine production.[33] Signaling PRRs induce expression of inflammatory cytokines, chemokines, and other innate effectors molecules following binding of PAMPs. Signaling PRRs include Toll-like receptors (TLRs), nucleotide binding oligomerization domain (NOD)-like receptors, the RNA helicase retinoic acid–inducible gene I (RIG-I) system, and C-type lectin receptors.

Toll-like receptors are critical elements of innate immune recognition.[29,34–37] Ten TLRs have been described in humans and are expressed by both professional immune cells (macrophages, dendritic cells [DCs], mast cells, neutrophils, eosinophils, innate lymphoid cells [ILCs]) and lung structural cells (epithelial cells, fibroblasts, and endothelial cells).[38–42] Pattern recognition receptors (PRRs) differ from one another in ligand specificity, expression patterns, and the genes they induce. TLR1, TLR2, TLR4, TLR5, and TLR6 are expressed on the cell surface, whereas TLR3, TLR7, TLR8, and TLR9 are intracellular, primarily localized to the endosomal compartment. Several TLRs exist in both transmembrane and soluble forms serving as sinks to bind PAMPs and DAMPs. TLR2 recognizes a wide range of microbial constituents expressed primarily by Gram-positive bacteria, mycobacteria, fungi, and certain viruses such as influenza.[43–50] These PAMPs include lipoproteins, peptidoglycan, lipoteichoic acid, lipoarabinomannan, hemagglutinin, and zymosan.[51] TLR2 also forms heterodimers with other TLRs such as TLR1 and TLR6, substantially increasing the repertoire of ligands recognized by TLR2. TLR3 recognizes double-stranded RNA (dsRNA) expressed by most viruses during replication, including influenza and coronavirus.[52,53] TLR4 is the primary receptor for LPS recognition and is required for clearance of many Gram-negative bacteria, including *E. coli*, *H. influenzae*, and *K. pneumoniae*.[54,55] This TLR is also speculated to interact with the spike protein of SARS-CoV-2.[56] In addition to PAMPs, TLR4 also recognizes endogenous ligands released from activated or stressed cells, such as high-mobility group box 1 (HMGB1), heat-shock proteins, and the S100 proteins (calprotectins), as well as matrix components, surfactant proteins, and β-defensins.[28] TLR5 is activated by flagellin, the principal component of bacterial flagella.[57] TLR7 and TLR8 recognize single-stranded RNA (ssRNA) from viruses such as human immunodeficiency virus and influenza A virus (IAV).[58] TLR9 is activated by unmethylated CpG motifs present in bacterial, mycobacterial, and fungal DNA but not mammalian DNA.[59,60] This TLR mediates DC activation that is required for innate and adaptive responses to bacteria (*S. pneumoniae*, *K. pneumoniae*, *L. pneumophila*) and fungi (*Candida albicans*, *Cryptococcus neoformans*).[60–62] Most TLRs require the adaptor molecule MyD88 for downstream signaling, whereas TLR3 utilizes the adaptor TRIF. Several TLRs, including TLR2 and TLR4, can signal through both MyD88- and TRIF-dependent pathways, with the MyD88 pathway serving as the dominant pathway in innate mucosal antimicrobial responses to bacterial challenge.[63–65]

Another class of signaling PRRs is the NOD-like receptors (NLRs).[66] NLRs exist within the cytosol and function to recognize intracellular PAMPs or DAMPs. NLRs activate the inflammasome, an intracellular multimeric protein complex that regulates the maturation and release of proinflammatory cytokines of the IL-1 family (IL-1β, IL-18). NLRs are activated by a diverse group of PAMPs, including the bacterial cell wall components peptidoglycan and muramyl dipeptide (MDP), bacterial flagellin, and several bacterial toxins.[67,68] NLRs and their adaptor molecules contribute to protective immunity against diverse respiratory pathogens, including extracellular (*S. aureus*, *S. pneumoniae*, *K. pneumoniae*) and intracellular bacteria (*L. pneumophila*, *Chlamydia pneumoniae*), and viruses such as RSV.[69–71] NLRs can act cooperatively with TLRs to amplify innate responses. For instance, TLR5 and the NLR IPAF/Nlrc4 function cooperatively to optimally eradicate flagellated bacteria such as *P. aeruginosa* and *L. pneumophila* from the alveolus.[72]

RNA helicase retinoic acid–inducible gene I (RIG-I) is a complimentary cytosolic system to sense and respond to pathogen-specific 5′-di- or -triphosphate RNA.[58,73,74] RIG-I and family member MDA5 are expressed most prominently by myeloid (conventional) DCs and respiratory epithelial cells, and are major drivers of virus-induced type 1 interferon production. During influenza infection, both TLR7 and RIG-1 are required for maximal antiviral IFN-α/β responses, with TLR7 mediating IFN production from plasmacytoid DCs, and RIG-I necessary for myeloid DC IFN responses.[75] RIG-I can also sense bacterial mRNA that translocates to the cytosol, although the requirement of this PRR in control of bacterial infection has not been defined.

C-type lectin family are signal-transducing type I and II transmembrane proteins that are expressed mainly in DCs, macrophages, and neutrophils.[76–79] This family contains one or more carbohydrate recognition domains that allow for recognition of glucans present in most classes of human pathogens, including bacteria, fungi, and viruses. The family of C-type lectin receptors includes the mannose receptor, DC-specific ICAM3-grabbing non-integrin (DC-SIGN), macrophage-inducible C-type lectin (Mincle), and the Dectin receptors. Like TLRs, C-type lectin receptors can exist in both soluble and transmembrane forms. The mannose receptor (CD206) interacts with Gram-positive and Gram-negative bacteria and fungal pathogens and mediates phagocytosis. DC-specific intracellular adhesion molecule 3–grabbing non-integrin (DC-Sign) is a type II membrane C-type lectin expressed predominantly by DCs and resident alveolar macrophages (AMs).[80] This PRR recognizes galactomannans of diverse pathogens, including bacteria, mycobacteria, fungi and viruses.[81] Mincle is expressed by myeloid cells and senses glycolipids primarily from mycobacterium, but also certain fungal and bacterial pathogens.[79] Dectin-1 recognizes β-glucans, whereas dectin-2 is activated by α-mannans. Both β-glucans and α-mannans are major cell wall components of fungi, including *Pneumocystis jiroveci*, *Aspergillus fumigatus*, and *C. albicans*.[77,78,82,83] Dectins are key receptors for antifungal host defense. Activation of C-type lectin receptors can induce reactive oxygen species, production of cytokines and chemokines (CXCL1, CXCL8, IL-23, IL-17A, and IL-22), and influx of PMNs required for effective innate antimicrobial responses.

■ Resident Lung Innate Immune Cells

Cells resident in the lung that are important in immune defense include macrophages, lymphoid cells, and alveolar epithelial cells.

Alveolar Macrophages

Resident alveolar macrophages (AMs) are a heterogeneous population of phagocytes that constitute the first line of defense against microbes that reach the alveolus.[50,84,85] These cells are embryonically derived and self-renewing from precursors present within the lung. Alveolar macrophages are also derived from circulating monocytes during inflammatory conditions. Alveolar macrophages have a life span of months to years. Other resident macrophage populations exist in the lung, including within the airway, interstitium, pleura, and intravascular space. These various macrophage populations are phenotypically distinct for one another and from macrophages that reside in the alveolar space. Under basal conditions, resident AMs produce low levels of inflammatory cytokines, maintain high phagocytic capability, and generally function to suppress inflammation and adaptive immunity within the lung.

The antimicrobial function of AM is dependent on four essential attributes. Macrophages recognize host- and microbe-derived signals, migrate in response to stimuli, secrete mediators, and ingest and kill invading microbial pathogens.[50] Macrophages recognize signals in their microenvironment via PRRs and surface receptors capable of binding specific ligands, including complement proteins, immunoglobulins, cytokines, apoptotic cells, PAMPS, and DAMPS (Fig. 120-2). Ligation of TLRs induces transcriptional activation of inflammatory cytokines (TNF-α, IL-6, and the IL-1 family members IL-1α/β and IL-36 α/γ), chemokines, and signals that regulate the differentiation and activation of lymphocytes, such as IL-10, IL-12, and type 1 IFNs. Early response cytokines produced by AMs network with structural cells of the alveolar-capillary membrane, including alveolar epithelial cells (AECs).[86–89] Alveolar macrophages also communicate with AECs via the release of membrane-encapsulated microvesicles containing bioactive cargo and by direct cell–cell calcium-dependent signaling through connexin 43–containing gap junction proteins.[90,91] Compared with monocytes and macrophages in other tissue compartments, AMs preferentially produce 5-lipoxygenase rather than cyclooxygenase products, including LTB_4 and LTC_4, resulting in robust PMN recruitment and activation.[92] During their quiescent state, resident AMs present antigen poorly. However, PRR ligation results in upregulation of costimulatory molecules (CD80, CD86) and transform these cells into capable antigen-presenting cells.[50]

Alveolar macrophages migrate within the alveolar space in response to both endogenous signals and mechanical stimuli.

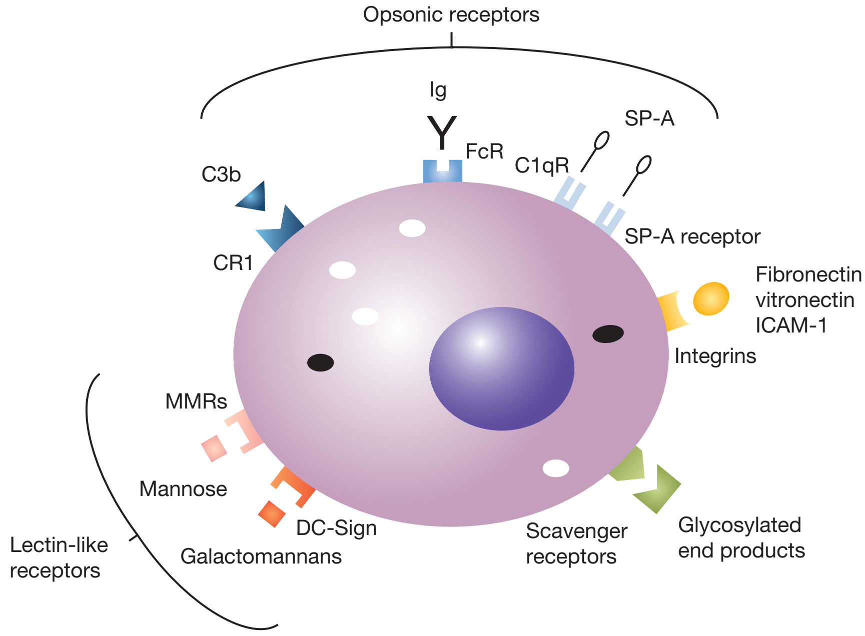

Figure 120-2 Cell surface receptors expressed by resident AMs mediating adherence, movement, and pathogen internalization. Opsonic receptors mediate attachment and phagocytosis of pathogens opsonized with C3b, immunoglobulin, or SP-A. C-type lectin receptors and scavenger receptors mediate attachment and internalization of nonopsonized microbes expressing specific carbohydrate moieties. Integrins mediate alveolar macrophage binding to and migration along matrix components or alveolar epithelium.

The movement of these cells in response to bacteria is dependent upon chemotactic signals, including surfactant proteins (SP-A), chemokines (CCL2), and adhesion molecule (ICAM-1) expression by AECs.[93–95] Mechanical stretch of the alveolus can also stimulate directed movement of AMs.

Alveolar macrophages are highly phagocytic cells. The opsonization of microbes by the complement component C3b or immunoglobulin binding greatly facilitates phagocytosis. Macrophages express two distinct receptors for C3b. Complement receptor 1 (CR1) preferentially binds C3b, whereas the complement receptor 3 (CR3, Mo-1, MAC-1, CD11b/18) is a member of the β_2 integrin family required for cell–cell and cell–substrate adhesion. Three Fcγ receptors recognize the Fc domain of immunoglobulin G (IgG). All FcRs function as signal-transducing molecules. FcγRI, FcγRII, and FcγRIII trigger both phagocytosis and cytolytic responses, with FcγRII and FcγRIII the most indispensable.

Alveolar macrophage also expresses multiple cell surface receptors that promote binding and internalization of nonopsonized particulates, including microbes. The macrophage mannose receptor binds mannose and mediates phagocytosis of yeasts, zymosan particles, and *P. jiroveci* (Fig. 120-2). Scavenger receptors bind apoptotic cells and acellular debris, and they serve as a major mechanism to internalize nonopsonized Gram-positive and Gram-negative bacteria, such as *S. aureus*, *S. pneumoniae*, and *E. coli*.[30,31] SP-A-opsonized microorganisms binds to specific high-affinity receptors and C1q receptors, triggering internalization and increased cell-surface expression of macrophage Fc receptors, mannose receptors, and scavenger receptors. Binding of microbes to DC-SIGN can signal an IL-10–predominant anti-inflammatory response, thus subverting from a killer to a permissive phenotype in responding cells.

Phagocytosis requires sequential, circumferential interaction of phagocyte surface receptors with complementary ligands on the surface of the particle. The ingested microbe is initially contained within a phagosome that subsequently fuses with lysosomes to form phagolysosomes. TLR stimulation is linked to phagosomal maturation. The killing capacity of resting resident AM is low, and these cells require activation signals from the microenvironment for intracellular killing to occur. Activation stimuli include microbial products, inflammatory cytokines, and plasma proteins. Most notable is IFN-γ, the primary activator of macrophage antimicrobial effector responses, leading to skewing toward an M1 or classically activated phenotype. Other activating cytokines include TNF-α, IL-1, IL-18, and GM-CSF, which provides a priming signal to augment AM differentiation and microbicidal activity.[96–98] Emerging evidence indicates that resident AMs display some degree of phenotypic plasticity, in that these cells can simultaneously display features of M1 and M2 (or alternative) activation during the evolution of inflammatory responses.[99]

Both oxidative and nonoxidative processes are used to kill ingested microbes. Alveolar macrophages display considerably less potent antimicrobial activity compared with blood monocytes and recruited exudate macrophages. Loss of granular peroxidase and a more modest respiratory burst account for reduced microbicidal activity. Resident AMs contain very little myeloperoxidase (MPO), and as a consequence the MPO-H_2O_2-halide system is less robust in resident AMs than in recruited macrophages. Microbes are also killed by macrophage-dependent nonoxidative mechanisms, including proteases, lysozyme, nitric oxide products, defensins, and cathelicidins. Late-phase killing of certain internalized bacteria, including *S. pneumoniae* and *H. influenzae*, ultimately requires induction of apoptosis in infected AMs.[100]

For effective killing of intracellular pathogens such as *M. tuberculosis* and certain fungi, resident AMs require cytokine signals elaborated by antigen-specific T cells during the adaptive immune response. Resident AMs can also develop long-term modifications of their immune phenotype after recovery from a prior infection, rending the host resistant to subsequent challenge by related or heterologous microbes, a form of trained immunity leading to "memory" AMs.[101,102] For example, recovery from *S. pneumoniae* results in enhanced long-term regional innate immunity to other pneumococcal serotypes, which is associated with augmented resident AM MHC class II expression, metabolic activity, and inflammatory cytokine production.[101] Conversely, prior exposure to viruses such as influenza can induce prolonged AM dysfunction, including impaired TLR signaling and reduced cell-surface C-type lectin and scavenger receptor expression.[103,104]

Innate Lymphoid Cells

A population of resident lymphoid cells, referred to as innate lymphoid cells (ILCs), are present in the respiratory tract.[41,42,105,106] These cells produce large amounts of cytokines early in response to microbial invasion and can be activated directly by microbial signals

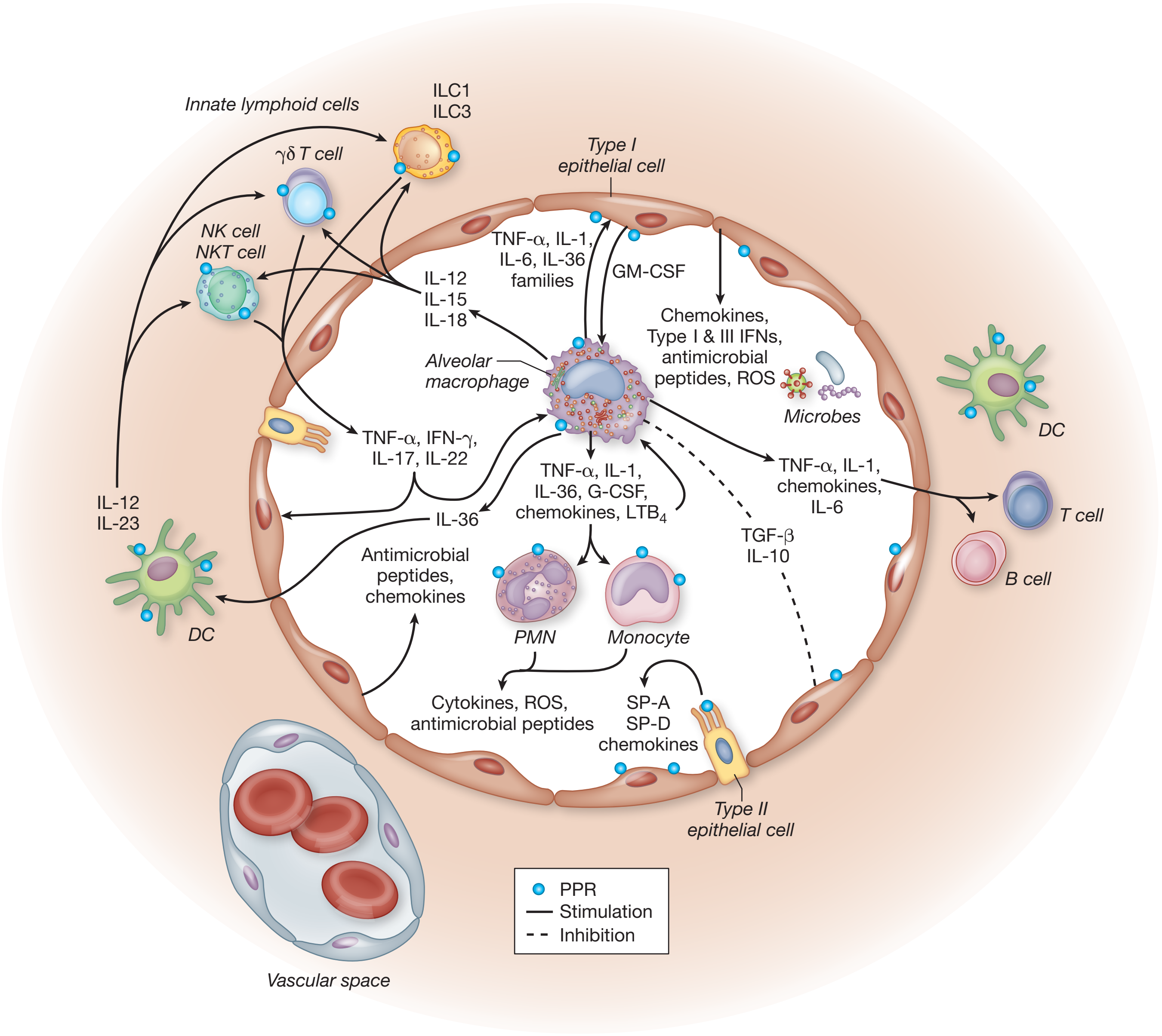
Innate lymphoid cells
ILC1
ILC3
γδ T cell
Type I
epithelial cell
NK cell
NKT cell
TNF-α, IL-1,
IL-6, IL-36
families
GM-CSF
IL-12
IL-15
IL-18
Chemokines,
Type I & III IFNs,
antimicrobial
peptides, ROS
Alveolar
macrophage
Microbes
DC
TNF-α, IFN-γ,
IL-17, IL-22
TNF-α, IL-1,
IL-36, G-CSF,
chemokines, LTB4
TNF-α, IL-1,
chemokines,
IL-6
IL-12
IL-23
IL-36
T cell
TGF-β
IL-10
Antimicrobial
peptides,
chemokines
B cell
DC
PMN
Monocyte
Cytokines, ROS,
antimicrobial peptides
SP-A
SP-D
chemokines
Type II
epithelial cell
● PPR
— Stimulation
- - Inhibition
Vascular space

Figure 120-3 Initiation and regulation of innate antimicrobial responses in the lower respiratory tract. PAMPs stimulate resident AMs to produce inflammatory cytokines and eicosanoids, including TNF-α, IL-1β, chemokines, and leukotriene B4, leading to the recruitment and activation of PMNs and exudate macrophages. Proximal cytokines induce gene expression and production of chemokines and growth factors by alveolar epithelial cells and other lung parenchymal cells. Microbes stimulate DCs and/or resident AMs to produce activating cytokines including TNF-α, IL-12, IL-23, IL-15, IL-18, and type I IFNs, leading to elaboration of IFN-γ, IL-17, and IL-22 by ILCs. Macrophage-derived signals can stimulate cytokine production from resident or recruited DCs. ILC can also be directly activated by PAMPs or DAMPs. Immunoregulatory molecules are released by AMs, ILCs, AECs, and myeloid-derived suppressor cells (MDSCs) to finely tune the magnitude of the innate response.

or host-derived cytokines without classic antigen presentation. Innate lymphoid cells, including NK, NKT, γδ T cells, and type 1, 2, and 3 innate lymphoid cells, drive protective local innate and adaptive immune responses in the lung (Figs. 120-3 and 120-4).

NK cells are present in large quantities within the lung, making up approximately 10% of the entire lymphocyte population. NK cells are also rapidly recruited to the lung in response to infection, where they are activated by cytokines, such as IL-12, IL-15, IL-18, TNF-α, and type 1 interferons produced by lung macrophages, DCs, and AECs.[107–109] Upon activation, NK cells produce robust quantities of TNF-α, IL-17, and IFN-γ, which are required for optimal cellular recruitment and pulmonary macrophage microbicidal activity during bacterial, mycobacterial, and fungal infection.[110] NK cells also mediate protective immunity during influenza infection via perforin-mediated lysis of virally infected cells and stimulate antimicrobial peptide release and epithelial regeneration via the elaboration of IL-22.[111] Overzealous innate responses by NK cells can sometimes be detrimental to the host, as is the case in respiratory syncytial virus (RSV) or influenza pneumonia.[108,112,113] The elaboration of IL-10 by NKs can paradoxically impair immunity against virulent bacterial pathogens such as *S. pneumoniae*.[114] Genetic deficiencies in NK cell function are associated with recurrent viral and bacterial infections, including those involving the respiratory tract.

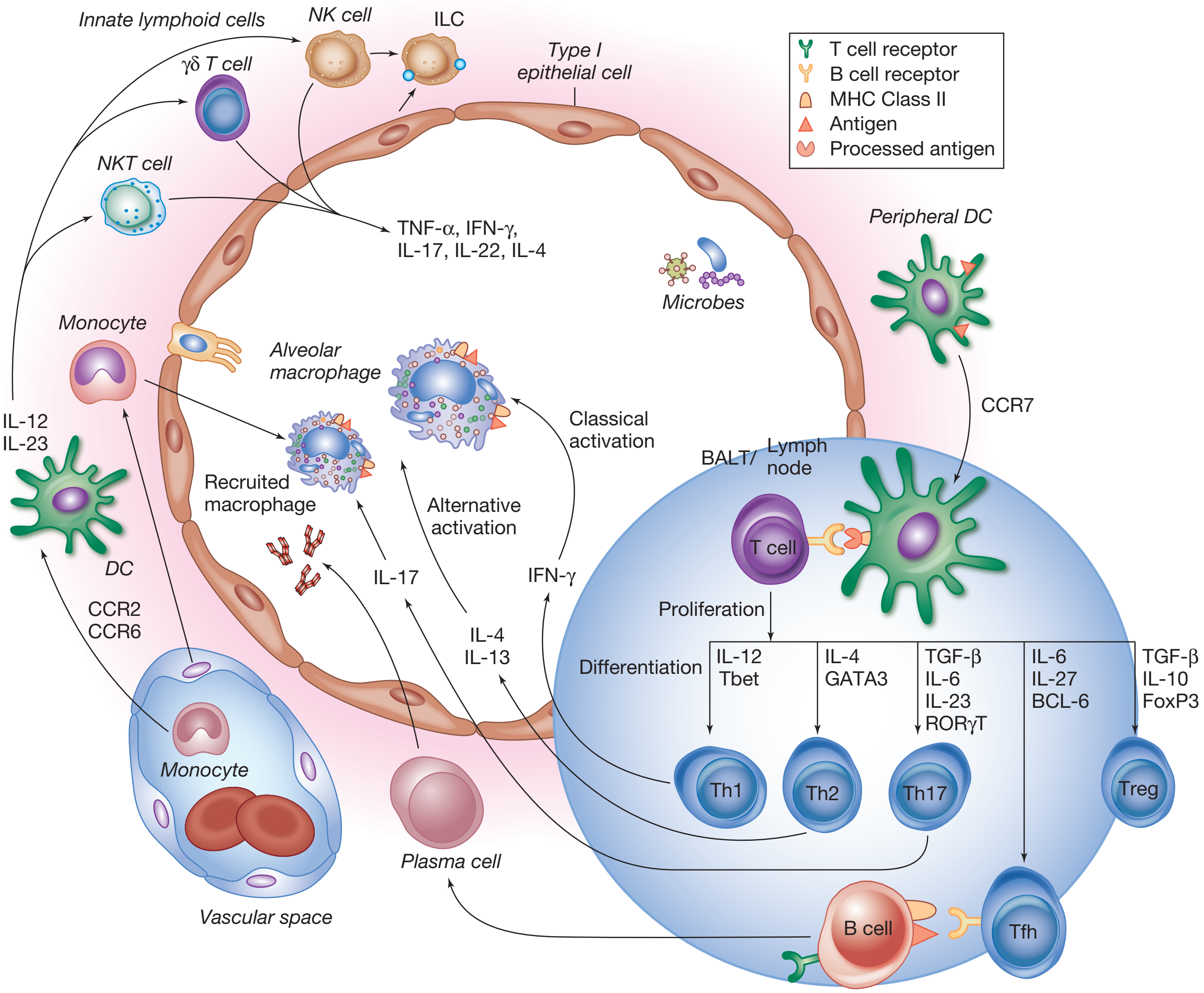
Innate lymphoid cells
NK cell
ILC
γδ T cell
Type I epithelial cell
T cell receptor
B cell receptor
MHC Class II
Antigen
Processed antigen
NKT cell
TNF-α, IFN-γ,
IL-17, IL-22, IL-4
Peripheral DC
Microbes
Monocyte
Alveolar macrophage
IL-12
IL-23
Classical activation
CCR7
Recruited macrophage
Alternative activation
BALT/ Lymph node
T cell
DC
IL-17
IFN-γ
CCR2
CCR6
Proliferation
IL-4
IL-13
Differentiation
IL-12
Tbet
IL-4
GATA3
TGF-β
IL-6
IL-23
RORγT
IL-6
IL-27
BCL-6
TGF-β
IL-10
FoxP3
Th1
Th2
Th17
Treg
Monocyte
Plasma cell
Vascular space
B cell
Tfh

Figure 120-4 Adaptive immune responses in the lungs develop in the draining lymph nodes and mucosa-associated lymphoid tissues, such as the bronchial-associated lymphoid tissue (BALT), both of which are organized into unique inductive and effector sites. DCs, macrophages, and B cells are the major APCs in the lungs. Monocytes contribute to the pool of newly recruited DCs through transendothelial migration in which peripheral blood monocytes differentiate into tissue DCs after crossing the vascular endothelium. Antigens in the airways and lung parenchyma are rapidly taken up and processed for antigen presentation by APCs on MHC class II to CD4+ T helper lymphocytes, which results in T cell proliferation. ILCs produce large amounts of cytokines early in a response that drive the polarization of Th1, Th2, Tfh, Th17, and Treg responses. By producing a distinct set of cytokines, each CD4$^+$ Th-cell subset helps shape the adaptive immune response, such as macrophage activation. With the "help" of Tfh cells, activated B cells in germinal centers undergo isotype switching and differentiation into plasma cells that secrete large amounts of antigen-specific effector antibodies.

NKT cells are a subset of unconventional αβ-T lymphocytes that recognize glycolipid rather than protein antigens that are presented by CD1d, a nonpolymorphic MHC class I–like antigen.[42,115,116] CD1d-restricted NKT cells can be activated directly by bacterial (*Streptococcus* spp.) or viral (IAV) glycolipids resulting in expression of TNF-α, chemokines, IFN-γ, and IL-17 required for microbial clearance.[117,118] In the lung parenchyma, NKT17 cells predominate. NKT cells can also be activated by host-derived cytokines, including IL-12, IL-18, IL-23, and type 1 interferons. Similar to NK cells, NKT cells can directly kill bacterial or virally infected cells in a perforin- and granzyme-B–dependent fashion. NKT cells have been shown to play a pivotal role in mucosal responses to viral (IAV, RSV), bacterial (*P. aeruginosa*, *Chlamydia* spp., *S. pneumoniae*), and fungal (*C. neoformans*, *A. fumigatus*) infection.[118,119] Importantly, different subsets of NKT cells can either augment or suppress the development of innate and acquired immunity, suggesting an important regulatory role of these cells during lung infection.

Mucosal-associated invariant T (MAIT) cells are a subset of predominantly CD8+ T cells that the recognize small molecules derived from the riboflavin metabolic pathway of bacteria, mycobacteria, and fungi and presented by the nonpolymorphic MHC class I molecule MR1.[42] MAIT cells are abundant in lung tissue, and these cells are major producers of type 1 and especially IL-17-related cytokines. Similar to NKT, MAIT cells can efficiently kill pathogen-infected cells. While the biologic role of these cells in human disease has not been well characterized, MAIT cells have been implicated in respiratory infections due to bacteria (*S. pneumoniae*), mycobacteria, and viruses (IAV).[120–122]

Gamma-delta T cells are a unique innate T-cell subset that are small in number (approximately 1%–2% of the total lung lymphocyte population) and localized to mucosal and epithelial surfaces. However, during respiratory infection the numbers of γδ T cells in the lung increase considerably (>30-fold), a process that is due primarily to local expansion rather than recruitment.[123,124] Upon activation by bacteria (*S. pneumoniae*, *K. pneumoniae*) and viruses, γδ T cells function as a rich and early cellular source of TNF-α, chemokines, IFN-γ, IL-17, and IL-22. The population of γδ T cells is rather heterogeneous, with specific subsets functioning to control the magnitude of DC and macrophage recruitment and activation during the resolution phase of pulmonary inflammation.[125] This nuanced response by γδ T cells is necessary to maintaining the immune and structural integrity of the lung during infection.

A subgroup of tissue-resident innate lymphoid cells (ILCs) has been more recently described that require the common γ chain of the IL-2 receptor and transcriptional repressor inhibitor of DNA binding 2 (Id2) for their development.[41] These lymphocytes lack the recombination-activating gene (RAG) and can be directly activated by cytokines released in the microenvironment during infection. There are three groups of ILC based on their predominant cytokine secretion profiles: group 1 ILCs produce the type 1 cytokine IFN-γ; group 2 ILCs produce type 2 cytokines such as IL-5 and IL-13; and group 3 ILCs produce IL-17 and IL-22. However, ILCs display considerable phenotypic plasticity, in that signals present in the lung microenvironment can skew the cytokine profile of ILC from one type to another. For example, during certain lung infections, resident or recruited ILC2s can convert to ILC1s by the myeloid-derived cytokines IL-12 and IL-18. ILC1s produce large amounts of IFN-γ and are thought to contribute to host defense against viral and bacterial pathogens.[126] ILC2s are activated by IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) and participate in immunity against parasites. In addition, these cells secrete amphiregulin, a molecule that may contribute to respiratory epithelial repair during viral infection.[127] The prodigious production of IL-17 and IL-22 by ILC3s facilitates pathogen clearance and cytoprotection in lung infections due to bacteria such as *S. pneumoniae* and *K. pneumonia* and fungi (*C. albicans*).[128,129]

Alveolar Epithelial Cells

The alveolar–capillary membrane is a dynamic assembly of nontraditional innate immune cells that generate cytokines and chemokines required to recruit and activate specific inflammatory cells during microbial insults. In particular, alveolar epithelial cells (AECs) are key participants in the innate mucosal response to microbial challenge.[15,130] These cells express an array of both extracellular and intracellular signaling PRRs, including TLRs, NLRs, C-type lectins, and RIG-I. These PRRs trigger the release of a variety of inflammatory cytokines (IL-1, IL-6, IL-36 α/γ, type I and III interferons, GM-CSF) and chemokines (CXCL1, CXCL2, CXCL5, CXCL8, CCL2, CCL20) that regulate the engagement and activation of resident and recruited phagocytic cells.[11,38,96,97,130–132] AECs also highly express RAGE, which serves as a signaling receptor for the DAMPs HMGB1 and S100 proteins.[133] Like airway epithelial cells, AECs secrete molecules that directly mediate antimicrobial killing, include large antimicrobial proteins (lysozyme, lactoferrin, calgranulins A and B, SLPI) and small antimicrobial peptides (β-defensins, cathelicidins).[12,21] Type II AECs produce surfactant protein (SP)-A and SP-D, members of the collectin family of lectins. SP-A contains a carbohydrate recognition domain that binds to exposed carbohydrate residues on the surface of microbes, serving as an opsonin to promote internalization of diverse pathogens (Gram-positive and -negative bacteria, fungi, and viruses) by AMs and type II AECs.[93] SP-A also stimulates secretion of GM-CSF, promotes directed migration of AMs, and regulates macrophage oxidant production.[93,134] SP-D mediates agglutination of bacteria, fungi, and influenza virus, facilitating uptake by PMNs and other phagocytic cells.[135]

To maintain immune homeostasis, AECs function to tonically suppress potentially damaging inflammatory responses in the airspace. Immune suppression occurs through multiple mechanisms. Cell-surface CD200 expression by AECs functions to directly inhibit AM activation.[136] Trans-acting soluble factors secreted by AEC also exert suppressive effects on cells within the alveolus in a paracrine fashion. Inhibitory and cytoprotective molecules include cytokines such as IL-33, TGF-β, leukemia inhibitory factor, prostaglandins, lipoxins, resolvins, and surfactant proteins.[13,88,137,138]

AMPLIFICATION AND REGULATION OF THE INFLAMMATORY RESPONSE TO MICROBIAL INVASION

A dual phagocytic system involving resident and recruited macrophages and recruited PMN is required for the clearance of bacteria from the lower respiratory tract (Fig. 120-3). Neutrophils ingest microbes by phagocytosis.[139] Effective killing requires products of granule constituents and molecular oxygen. Hydrogen peroxide and reactive oxygen intermediates are involved in neutrophil-mediated killing. The MPO-H_2O_2-halide system is a crucial participant in oxygen-dependent killing by neutrophils. Granule components also are crucial in PMN-mediated microbial killing. Microbicidal molecules found in azurophil granules include lactoferrin, lysozyme, cathepsin G, elastase, and cationic proteins such as α-defensins and cathelicidins. Neutrophil extracellular traps (NETs) are complex structures composed of nuclear chromatin, histones, and a variety of granular antimicrobial proteins.[140,141] NETs are released from azurophilic granules during infectious challenge and are capable of physically ensnaring bacteria. These structures facilitate the interactions between bacteria and antimicrobial effectors, ultimately leading to enhanced bacterial killing.[142] NETosis (this regulated form of neutrophil cell death) is stimulated by both microbial components and endogenous molecules, including the antimicrobial peptide LL37, the DAMP HMGB1, and reactive oxygen species.[24] While NETosis in general enhances the containment and killing of pathogens, uncontrolled NET formation can mediate collateral damage to lung structures, as has been observed in severe H1N1 and SARS-CoV-2 pulmonary infection leading to ARDS.[143] Moreover, certain extracellular bacterial pathogens such as *S. aureus* and *S. pneumoniae* can subvert the microbicidal effects of NETs by inhibiting NET formation and elaboration of pathogen-derived protease that degrade NETs.[144]

Recruitment of PMNs from the blood into the alveolus is initiated by upregulation of selectins and β-integrins on the surface of leukocytes and endothelium, concurrent with the establishment of chemotactic gradients within the lung interstitium and alveolar space.[87] Chemotactic gradients are established in part by matrilysin-mediated shedding of syndecan–chemokine complexes into the alveolar space.[145] Early recruitment of PMNs to the lung (<4 h) is directed by cytokines, chemokines, and leukotrienes secreted by resident AMs, whereas sustained neutrophil influx (24 h) appears to be driven by chemokines produced by lung structural cells, including AECs.[146] CXC chemokines that mediate PMN influx during lung infection include CXCL1, CXCL2, and CXCL5 in the rodent and CXCL8 in humans.[87,146,147]

Recruited or exudate macrophages represent an essential arm of the innate response in bacterial and fungal infection of the respiratory tract. The recruitment of these cells to the lung requires specific chemokines and chemokine receptors. In particular, CCL2 and its receptor CCR2 mediate the influx of exudate macrophages in bacterial pneumonia.[148] CCL2 also serves as an autocrine inducer of cytokine (G-CSF) and CXC chemokine (CXCL1, CXCL2) production from AMs, further amplifying the neutrophilic response during pneumonia.[149] CCL3 participates in both exudate macrophage and PMN recruitment during bacterial infection.[150] Recruited macrophages represent a heterogenous group of inflammatory cells, with a distinct pool of exudate macrophages displaying a highly activated phenotype, function as antigen-presenting cells, and produce robust amounts of inflammatory cytokines. In addition to direct antimicrobial properties, these inflammatory macrophages network with resident lung cells, including ILCs and AECs via elaboration of proximal cytokines such as TNF-α.[129] Exudate macrophages can also network with recruited PMNs to optimize type 1 cytokine responses in bacterial pneumonia.[151] A separate pool of recruited macrophages exhibit enrichment of genes involved in protein processing and proteolytic activity and are believed to function in a reparative role during resolution of inflammation.[99]

Sentinel DC and macrophages produce IL-12, IL-15, IL-18, IL-23, and type 1 interferons within minutes to hours after exposure to LPS and other microbial products. IL-12, IL-15, and IL-18 induce the release of IFN-γ from ILCs early in the innate response and antigen-specific T cells later in the adaptive response. IL-23 triggers rapid (hours) production of IL-17 and IL-22 from tissue-resident γ/δ, NKT, MAIT, and ILC3.[41,42,152] IL-17 promotes production of IL-1, IL-6, TNF-α, CXC chemokines, IL-22, and antimicrobial peptides from ILCs, AMs, and cellular constituents of the alveolar–capillary membrane.[152,153] IL-1 family members, including IL-1 and IL-36α/β, also serve as relevant proximal signals leading to DC activation and induction of cytokines and chemokines from myeloid and structural cells of the lung.[154]

Robust innate responses are required for effective control of pathogens at mucosal sites of invasion. However, these responses need to be tempered to allow for protection and restoration of lung architecture. Deleterious innate immune activation within the lung is characteristic of infections due to certain viruses (H1N1, avian influenza, SARS-CoV-2) and bacteria (cytotoxic strains of *P. aeruginosa*).[155] The cytokine storm that occurs in response to viral infections such as SARS-CoV-2 may be mediated, in part, by inhibition of autophagic responses in immune cells, leading to inflammasome activation and release of inflammatory cytokines.[156] Specific cells and soluble factors present within the lung microenvironment contribute to the fine-tuning of innate responses. For instance, surfactant proteins A and D and soluble forms of PRRs can antagonize binding of DAMPs and PAMPs to toll like receptors or C-type lectin receptors, hence reducing inflammatory mediator release.[157–159] Inhibitors of downstream TLR signaling, such as IRAK-M, suppress deleterious inflammation in influenza infection.[160] Anti-inflammatory molecules, including IL-10 and IL-1 receptor antagonist, produced by NKT, $\gamma\delta$ T cells, exudate macrophages, and myeloid-derived suppressor cells, contribute to the resolution of inflammation.[161,162] Finally, the update of apoptotic neutrophils and other cells by lung macrophages signals an anti-inflammatory program that facilitates tissue repair.[163]

LUNG ADAPTIVE IMMUNE RESPONSES

Adaptive immune responses consist of two major effector systems, antibody- and cell-mediated immunity, which are generated by antigen specific B and T lymphocytes, respectively. B and T lymphocytes rearrange their immunoglobulin and T-cell receptor (TcR) genes to generate upward of 10^{11} and 10^{14} different clones of B and T lymphocytes that each express a distinct antigen receptor. The antigen receptors on B lymphocytes recognize native antigens including carbohydrates, proteins, and simple chemical groups, while the antigen receptors on T lymphocytes recognize only peptides derived from protein antigens bound to cell-surface proteins from the major histocompatibility complex (MHC) on antigen-presenting cells (APCs). Antigen-specific immune responses require at least 7 to 10 days for their development; this time is required for the proliferation and differentiation of antigen-specific T and B lymphocytes. During the development of specific immune responses, pathogens may continue to grow in the host or be held in check by innate and inflammatory mechanisms.

Adaptive immune responses in the lungs develop in the draining lymph nodes and mucosa-associated lymphoid tissues, both of which are organized into unique inductive and effector sites. Inductive sites include specialized lymphoid follicles underlying the epithelium, such as nasopharynx-associated lymphoid tissue (NALT) and bronchial-associated lymphoid tissue (BALT) in the upper and lower airway, respectively, and Peyer's patches and isolated lymph follicles in the gut, and downstream lymph nodes, including cervical and mediastinal lymph nodes (LN) draining the respiratory mucosa and mesenteric LN draining the intestinal mucosa.[164,165] Clones of lymphocytes are triggered by APCs to proliferate and differentiate into effector cells. Antigen-specific lymphocytes remain expanded after elimination of an infection (memory lymphocytes). Memory lymphocytes provide a much more rapid response to a second exposure to antigen.

Antigen Presentation and Antigen-Presenting Cells

Antigen-presenting cells (APCs) and innate lymphoid cells (ILCs) provide an essential link between innate and adaptive immunity (Fig. 120-4).[166–174] Antigens in the airways and lung parenchyma are rapidly taken up and processed for antigen presentation by one of two pathways.[175] The endocytic pathways process protein antigens obtained from the extracellular space in phagolysosomes converting them to small polypeptides. The polypeptides are loaded onto MHC class II molecules to prime APCs for further presentation to MHC class II–restricted CD4+ T helper lymphocytes. The endogenous pathway processes peptides from the intracellular environment and loads them onto MHC class I molecules for presentation to MHC class I–restricted CD8+ T cells.

Dendritic cells, macrophages, and B cells are the major APCs in the body. Immature DCs have very active constitutive macropinocytosis, a nonspecific process through which the cell can internalize extracellular material, and this is believed to be a major mechanism of antigen acquisition by DCs.[176] As a result, DCs are very efficient APCs.[177] In contrast, B cells have little macropinocytic activity and rely almost exclusively on receptor-mediated endocytosis for antigen uptake. B cells with antigen-specific surface-bound immunoglobulin (B cell receptor, BCR) are 1000 times more efficient in processing and presenting antigens to T cells than B cells encoding BCRs for an irrelevant antigen.[178] B cells and macrophages also have cell-surface Fc receptors for IgG (FcγRs), as well as complement receptors, that are involved in both clathrin-dependent and -independent antigen internalization, processing, and presentation.[176] Macrophages, DCs, and B cells also express lectin receptors, such as the mannose receptor and DEC205, that bind carbohydrate residues on some microbes and target them for uptake either by clathrin-dependent endocytosis or by phagocytosis. For macrophages and some subsets of DCs, phagocytosis is an important mechanism of foreign antigen uptake. However, plasmacytoid DCs (pDCs) have severely compromised phagocytosis compared with conventional DCs (cDCs).[176] As noted above, phagocytosis can also be mediated by receptors such as C-type lectins, Fc receptors, complement receptors, scavenger receptor A, and CD36, which recognize ligands on pathogens and apoptotic cells. More recently, there has been interest in the role of macroautophagy in internal Ag acquisition by MHCII on APCs. Mutation of autophagy gene 5 (ATG5) in DCs render them unable to activate virus-specific CD4+ T cells, which suggests a role for macroautophagy in APC activity by DCs. Thus, DCs, macrophages, and B cells use various different cellular processes to capture and deliver diverse antigens as APCs.

Dendritic cells are the most potent APCs for T cells. DCs are bone marrow–derived cells that take up residence in peripheral tissues at epithelial borders throughout the mammalian host, where they become specialized for recognition of pathogens and microenvironmental tissue damage during antigen uptake and presentation. Following antigen uptake, they migrate to lymph nodes or mucosa-associated lymphoid tissue. Two broad subsets of DC have been identified:[166,179,180] conventional DC (cDCs) and plasmacytoid DC (pDCs). mDC express CD11c, CD11b, and varying levels of MHC class II and costimulatory molecules (CD40, CD80, and CD86). Human pDCs express blood DC antigen (BDCA)-2, whereas murine pDCs express CD11c, GR-1, and B220. cDCs contribute to a variety of T-cell responses or tolerance, and pDCs have been implicated in antiviral immunity and in murine models of asthma. The predominant DC subset involved in host defense against pathogens is the cDCs.

DCs exist in both immature and mature forms.[181] Immature DCs are concerned mainly with antigen capture. DCs are mobilized from bone marrow precursors to peripheral blood in response to pulmonary inflammation. Monocytes contribute to the pool of newly recruited DCs through transendothelial migration in which peripheral blood monocytes differentiate into tissue DCs after crossing the vascular endothelium. CCR2 is a critical receptor in the recruitment of DCs during inflammatory responses. CCR6 mediates recruitment of DCs specifically to the airways and alveolar space in response to CCL20 secreted by respiratory epithelial cells.[182] DC maturation is dependent on sensing of infection,[166,179,180] which may occur directly by detection of pathogen products using PRRs, activation by inflammatory signals such as TNF-α, or indirectly through exposure to DAMPs. Mature DCs upregulate MHC class II and costimulatory molecules allowing a phenotype focused on antigen presentation and the stimulation of naïve T cells.

DC maturation is accompanied by changes in the expression of chemokine receptors.[166,179,180] CCR1, CCR2, CCR5, and CCR6 are downregulated. CCR7 expression is enhanced, allowing DCs to respond to chemokine gradients of CCL21 and CCL19 emanating from local lymphatics and draining lymph nodes. Mature DCs leave the local inflammatory environment carrying their antigenic load to draining lymph nodes. DC–T-cell interactions within the draining lymph node are complex.[183] T-cell stimulation, proliferation, and activation result if antigen recognition occurs. Induction of Th1, Th2, Th17, Tfh, or T-regulatory responses may be the end result.[170,172,184]

The engagement of PRRs on DCs leads to increased expression of MHC-peptide complexes and costimulatory molecules as well as the production of immunomodulatory cytokines, all of which have a profound effect on T-cell priming and differentiation.[166,179,180] Triggering of the T-cell receptor (TCR) occurs following an interaction with an antigen/MHC complex and provides “signal one” to the T cell. T-cell maturation results in upregulation of important costimulatory molecules. Specifically, DCs increase the expression of B7.1 (CD80) and B7.2 (CD86), which bind CD28 on T cells providing “signal two” to activate antigen-specific T cells.

■ T Cells and Adaptive Responses

For decades, CD4 Th cells were believed to be the most significant sources of regulatory cytokines shaping the development of immune responses in the lung; however, ILCs produce large amounts of cytokines early in a response that drive the polarization of Th1, Th2, Tfh, Th17, and Treg responses.[185–187] These cells produce many of the same cytokines as CD4 Th cells, but they do not express a T cell receptor or cell surface markers associated with other lineages. Thus, they are not antigen-specific. Activation of ILCs is an important step in the development of adaptive immunity and polarization of T-cell responses.

$CD4^+$ T cells coordinate antigen-specific immune responses against inhaled antigens.[170–174,179] Separate, distinct subsets of $CD4^+$ T helper (Th) cells mediate a variety of distinct adaptive immune response “programs” (Fig. 120-4). Antigen exposure can initiate the afferent phase of the adaptive immune response that includes all subsequent events that lead to the formation of a poised antigen-specific response. The priming of $CD4^+$ Th cells from naïve precursor $CD4^+$ T cells is a critical component of the afferent phase. $CD4^+$ Th cells aid B cells in the production of antibodies that mediate components of the hypersensitivity reaction. Endowed with antigen-specific receptors, T cells and antibodies mediate the efferent phase of the adaptive immune response that encompasses all the immune activities directed at the antigen source. APCs acquire antigen at the site of introduction and migrate to draining lymph nodes and BALT to prime naïve $CD4^+$ T cells. Naïve $CD4^+$ T cells undergo multiple rounds of division and progress through multiple stages of differentiation along the pathway to becoming effector $CD4^+$ Th cells.[188–190]

$CD4^+$ Th cells differentiate into one of several distinct subsets that in turn mediate a distinct adaptive immune response “program.”[185–187] Each program has a genetic foundation in $CD4^+$ Th cells. Master regulation by a specific transcription factor promotes the acquisition of a particular Th phenotype at the expense of the other phenotypes. Tbet (Tbx21) promotes Th1 development, GATA3 promotes Th2 development, and RORγT promotes Th17 development. Likewise, $CD4^+$ T regulatory (Treg) cells that inhibit $CD4^+$ Th activity to limit harmful inflammation are specified by the transcription factor Foxp3. During $CD4^+$ Th cell activation, the cytokine milieu present (from DCs and ILCs early in the response and other inflammatory cells during chronic inflammation) guides cellular differentiation along one of the particular pathways. IL-12 along with IFN-γ promotes Th1 cell development, IL-4 promotes Th2 cell development, and the combination of TGF-β and IL-6 promotes Th17 development. IL-23 drives the expansion of the Th17 cell population. The presence of TGF-β alone supports the differentiation of Treg cells.

Cytokine production represents a key effector function by which $CD4^+$ Th cells coordinate adaptive immune responses.[185–187] By producing a distinct set of cytokines, each $CD4^+$ Th cell subset coordinates a distinctive adaptive immune response program that likely developed evolutionarily to counter a particular pathogenic threat. Th1 cells produce IFN-γ, along with IL-2 and TNF-α, and help protect against intracellular pathogens, but also mediate delayed-type hypersensitivity. Th2 cells produce IL-4, IL-5, and IL-13 and promote a response to parasite infection and responses where mucus shedding and expulsion are beneficial, as well as humoral immunity. Th17 cells produce IL-17 required for protection against several extracellular pathogens.

Th2 cells have long been regarded as the main providers of help for isotype switching, cellular proliferation, and antibody production by B cells.[185–187] However, it is now appreciated that Tfh cells are the primary “helper” cells for B cells in vivo. Tfh and Th2 cells share numerous features and signaling pathways and may develop from a common precursor, as exemplified by studies that demonstrated impaired development of both types of T cells in mice with targeted knockouts of the genes encoding MaF, ICOS, and IL-21R. However, Tfh cells can be clearly distinguished from Th2 cells by their increased expression of both CXCR5 and BCL-6 and by their reduced expression of BLIMP1 and CCR4; the latter is a Th2 cell–associated chemokine receptor. Similar to Th2 cells, Tfh cells can express IL-4.

■ B Cells and Adaptive Responses

The antigen specificity of an antibody molecule is generated by the rearrangement of heavy and light chain gene segments, which ultimately encode the amino-terminal domains of the heterodimeric antibody protein. Each B cell secretes a single type of antibody molecule as a result of these genetic rearrangements within that cell, which recognizes a single epitope on a microbial Ag. Antibodies are proteins that readily move from the circulation through tissues and into lymphatic drainage. It is not inaccurate to describe the lung tissue as being bathed in circulating antibodies. Antibody isotype and effector functions are determined by the carboxy-terminal domain of the protein, known as the Fc region. Each of the antibody isotypes (IgM, IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, or IgE) binds to one or more receptors, via Fc region binding to an Fc receptor, expressed by an effector cell of innate immunity (such as AMs or recruited neutrophils). This has the effect of pointing the antigen-binding site away from the cell and "imparting" microbial Ag specificity to an effector cell. This makes it possible for different microbial antigens to activate different effector functions of innate immunity such as phagocytosis, degranulation, complement activation, or transcytosis across the epithelium. Antibodies are also critical for blocking binding of microbial toxins and viruses to cells in the vasculature, lungs, and other organs. Some antibody isotypes are more closely associated with allergic and antiparasitic responses (IgE), mucosal protection (IgA), anticapsular bacterial responses (IgM), and antibacterial and antiviral responses (IgG).

Antibodies can be either secreted or surface-bound, which is dependent on the differentiation state of the B cell. The surface-bound immunoglobulin molecule on a B cell and its intracellular signaling complex is often termed the B-cell receptor (BCR). B cells differentiate from hematopoietic stem cell precursors, initially becoming immature B cells (expressing IgM and IgD isotype antibodies on their surface) that emerge from the bone marrow and circulate through the peripheral blood, lymphoid organs, and tissues (such as the lungs). If B cells specifically bind to a microbial Ag via their BCR in the periphery, these B cells become activated and can proliferate to form discrete structures called germinal centers in secondary lymphoid tissues or BALT. Most Tfh cells and most IL-4 production is localized to germinal centers.[185,187,191,192] The processes of somatic hypermutation, class switch recombination, and affinity maturation of activated B cells all occur in germinal centers, as well as differentiation of memory B cells and plasma cells.

After interaction with Ag-primed DCs, Tfh cell precursors migrate to the T cell–B cell border in the white pulp of secondary lymphoid organs to form germinal centers to provide help for B cell maturation. Tfh cells home to B cell follicles owing to their expression of CXCR5, and CXCR5$^+$ Tfh cells isolated from secondary lymphoid tissue can produce cytokines that support B cell differentiation. In the absence of T cell help during B cell priming, B cells will undergo apoptosis, rather than differentiation into germinal center B cells or plasma cells. Tfh cells also express high levels of inducible T cell costimulator (ICOS), programmed cell death 1 (PD1), the transcriptional repressor B cell lymphoma 6 (BCL-6), and cytokines that influence B-cell differentiation and antibody production such as IL-21 and IL-4. Human Tfh cells have also been reported to express IL-10, which also plays a role in the differentiation of human B cells, and high levels of the chemokine CXCL13.

With the "help" of Tfh, activated B cells in germinal centers undergo isotype switching, which enables them to utilize a different immunoglobulin constant region for the same antigen-binding specificity, resulting in production of a different antibody isotype (e.g., IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgE). Long-lived B cells are a critical arm of durable immunity to respiratory pathogens.

As mentioned previously, B cells can act as APCs. B cells endocytose whole antigen (via their BCR) and then present degraded peptide fragments to antigen-specific T cells in association with MHCII. B cells are less efficient APCs than DCs and other myeloid cells;[193] however, B cells are highly selective APCs because the endocytosed Ag must be bound by the Ag-specific BCR to initiate the process. Thus, in Tfh–B and Th2–B interactions, the T cells recognize the same antigen as the B cell, which can significantly amplify an antigen-specific response.[194]

Efferent Immune Responses and Regulatory T Cells

Antigen-specific T cells must migrate via the bloodstream to peripheral sites of ongoing infection.[174,195] Chemokine–chemokine receptor and adhesion molecule–ligand interactions are involved. While DCs often migrate to local lymphoid tissue after activation, a subset of recruited DCs remains in the lung rather than migrating to draining lymph nodes.[171,179,196] These recruited nonmigratory pulmonary DCs present antigen to newly recruited T cells to drive T-cell polarization and stimulate cytokine release. Cytokines produced by specific CD4 and CD8 lymphocytes play a central role in the ongoing recruitment of inflammatory mononuclear phagocytes and other effector lymphocytes.

Viruses including influenza, parainfluenza, RSV, Hantavirus, coronavirus, herpesvirus, and CMV cause significant pulmonary disease. Viruses are intracellular pathogens; the killing of virally infected cells by MHC class I–restricted cytotoxic CD8 T lymphocytes (CTLs) is required. CTLs kill target cells by two mechanisms (Fig. 120-5). Cytolytic mediators, including perforins and granzymes, are released from cytoplasmic granules. Perforins induce pore formation and osmotic cell lysis, and granzymes are proteases that activate cell caspases, resulting in apoptosis. Killing of virally infected cells can also result from the direct induction of apoptosis by Fas–Fas Ligand binding, which is upregulated and present on CTL.

The development of cell-mediated immunity to viral infections precedes by mechanisms presented earlier but may also precede locally within the lung. Priming can occur in bronchus-associated lymphoid tissue (BALT), a submucosal lymphoid tissue found in the major bronchi.[164,165] Localized priming of the cell-mediated immune response may play a crucial role in viral host defense.

Memory T-cell responses are important in certain viral illnesses and following administration of antiviral vaccines.[173,174,190] Subsets of memory T cells have been defined.[197] Effector memory T cells are found within the lung, are short lived, retain markers of activation, and have effector functions; these cells lack expression of lymphoid trafficking molecules CCR7 or CD62L. Central memory T cells reside predominantly within lymphoid organs, persist for long periods of time, and express CCR7 and CD62L.

The immune system possesses various mechanisms to control and regulate inflammation and adaptive responses to prevent and minimize reactivity to self-antigens or an overexuberant response to a pathogen. One of these mechanisms is through the generation of Treg cells.[198,199] CD4+CD25+ T reg cells are the best-characterized subset. These cells represent 5% to 10% of the CD4+ T lymphocytes in healthy adult mice and humans. CD4$^+$ Treg cells are recognized for the production of cytokines with anti-inflammatory activity, including IL-10 and TGFβ, and are able to limit CD4$^+$ Th responses.

There are a number of subsets of Treg cells, with the major distinction being (1) Tregs that are induced in the periphery following antigen encounter (inducible Tregs, iTreg) and (2) Tregs that arise from normal T-cell thymic development (naturally occurring Tregs, nTreg).[200–202] Both types of regulatory T cells have been shown to play a role in mucosal inflammation and infection. Activated Treg cells can suppress not only antigen-specific responses but also unrelated immune responses in a non-antigen-specific manner either through cell contact or through the regulatory cytokines they produce—a mechanism known as bystander suppression.

nTreg cells can prevent immunopathology in a variety of infections, and the mechanisms by which nTreg cells regulate inflammation appear to vary between stimuli and include cell contact and soluble mediators.[200–202] Activated nTreg cells efficiently control self-reactive T cells and innate responses (thereby limiting tissue damage)

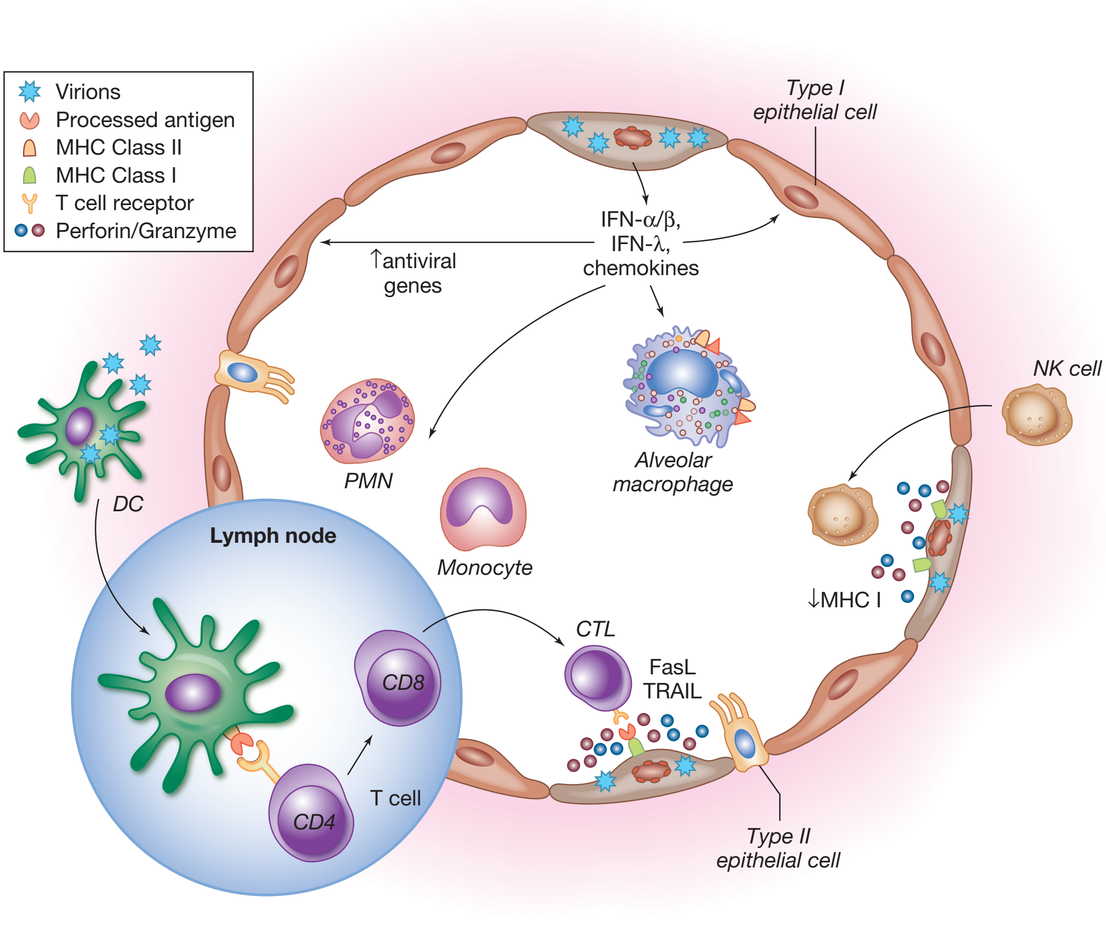

Figure 120-5 Viral infection of the lower airways initiates a cascade of events leading to antiviral immunity. One of the earliest steps is the production of type I interferons (IFN-α/β) by infected epithelial cells, as well as other cytokines, that can activate alveolar macrophages, uninfected epithelial cells, recruited inflammatory cells, and DCs. Virus antigen uptake by DCs in the lungs, along with inflammatory signals, results in migration of DCs to the draining lymph nodes or BALT where viral Ag is processed and presented to Ag-specific CD4 Th1 cells that become activated and clonally expand. These Th1 cells provide additional signals for the proliferation and activation of virus-specific CD8 cytolytic T cells (CTLs). These CTLs can lyse cells in the lungs that are virally infected by targeting MHCI molecules that have bound processed viral Ag (viral peptides). If a CTL is activated, it can lyse a virally infected cell using perforin- and granzyme-mediated mechanisms or by inducing apoptosis. To evade detection, some viruses cause a downregulation of MHCI expression on cells. However, NK cells specifically target cells that have lost MHCI expression and lyse them through similar mechanisms as CTLs.

in mouse models of chronic infection and inflammation. nTreg cells, however, can also inhibit allergen-induced airway hyperreactivity through IL-10–dependent mechanisms or by inhibiting antigen presentation by DCs. The antigen specificity of iTreg cells is largely microbial or environmental antigens, whereas the nature of the antigens recognized by nTreg cells is not clear. nTreg cells are believed to recognize a wide array of self-antigens as a consequence of their development and selection in the thymus. During the onset of acute disease, nTreg cells have the potential to recognize self-antigens that are released by tissue damage; however, evidence from chronic infection suggests that nTreg cells can also recognize microbial antigens.

iTreg cells are generated in the periphery during an immune response and act in an antigen-specific manner.[200–202] Several subsets of iTreg cells have been defined, and iTreg cells do not constitutively express Foxp3 or CD25 but can express high levels upon activation. Foxp3 appears to act as a cell lineage differentiation factor because it correlates closely with suppressor activity, irrespective of CD25 expression. iTreg cells are often the most potent source of IL-10 in downregulating inflammatory responses to infections or allergens.

Depending on their stage of differentiation, B cells can be activated to perform an array of cellular functions, in addition to antibody production and antigen presentation. B cells can be induced to express costimulatory molecules, such as CD80, CD86 and CD40, which promote the interaction with T helper cells, including activation of proinflammatory cytokine secretion. Subsets of B cells also produce a number of cytokines, including lymphotoxin-α, IL-6, and TNF-α, which can help create the inflammatory milieu in the lungs and GCs that promotes local polarization of Th1 and Th17 cells.[203] Other subsets of B cells (regulatory B cells) produce anti-inflammatory cytokines, such as IL-10 and IL-35.[204] Ultimately, B cells that develop during infection in the lungs and draining lymph nodes can play a role in promoting or damping inflammation in the lungs.

Long-term B cell immunity to respiratory infection involves both plasma cells (typically found in the bone marrow) and memory B cells in the lungs and other peripheral sites, both of which require T-cell help in germinal centers for their development.[192,205] B cells can stop proliferating in a germinal center, differentiate into memory cells, and migrate to mucosal surfaces in preparation for subsequent encounter with their microbial antigen.[206] There is tissue-specific selectivity for memory B cell homing, and lung-resident B cells have hallmarks of resident memory cells, such as the expression of CD69, and respond more quickly to reinfection than those from lymphoid organs.[206] It has recently been demonstrated in a murine influenza infection model that influenza-specific resident memory B cells develop early after infection and are phenotypically distinct from memory B cells in secondary lymphoid tissue.[207] The development of these lung-resident memory B cells is dependent on the presence of Ag and CD40 signaling, and these cells appear to develop in the germinal centers of the BALT of influenza-infected mice. In terms of timing of the response, germinal centers develop in the draining lymph nodes very rapidly after infection, whereas germinal centers develop more slowly in lung tissue because it takes time to form inducible BALT.[208] Ultimately, the presence of resident memory B cells in the lung allows for a rapid secondary response (antibody secretion) in the lung following subsequent infection.

Lung-resident memory T cells are also a critical element of long-term pulmonary immunity, and these T cells must physically interact with MHC-expressing cells (either as target cells or APCs) in a secondary response in order to exert their effector functions.[209] Thus, both resident memory T cells and resident memory B cells in the lung contribute to protection against secondary pulmonary infections. Immunoglobulins are clearly present in the epithelial lining fluid of the lower respiratory tract. Serum IgG can clearly gain access to the alveolar space in normal subjects and during inflammation when large changes in alveolar permeability occur. Systemic immunization enhances pulmonary clearance of many bacteria in animal models, and enhanced clearance correlates with the appearance of antibodies in serum and bronchoalveolar lavage fluid that are directed against the organisms. Thus, it seems likely that alveolar antibodies can be derived from the serum. However, there is one intriguing hypothesis about optimal antibody production from the previously discussed research,[207] which is that for respiratory infections by influenza, SARS-CoV-1, SARS-CoV-2, and others, optimized vaccines designed to elicit highly effective, long-lived protection against respiratory viral infections may need to have some level of antigen sequestration in the respiratory tract, as would be seen in recovery from a live infection.

Circulating antibody (immunoglobulin) is the most widely recognized effector molecule produced by B cells. Immunoglobulins are a major protein constituent of the fluid that lines the luminal surface of conducting airways and alveolar lining fluid. Effector functions for antibodies include opsonization, complement fixation, antibody-dependent cellular cytotoxicity (ADCC), agglutination, and neutralization. Approximately 20% of the total protein present in bronchoalveolar lavage fluid consists of IgG, IgM, and IgA. IgA is the predominant immunoglobulin in secretions of the trachea and major bronchi, while both IgG and IgE are present as well. IgG is the predominant immunoglobulin in alveolar lining fluid. Antibodies function as (1) opsonins that allow phagocytes to recognize and ingest microbes via the involvement of Fc receptors; (2) activators of complement, which enhances opsonization and leads to direct lysis of some bacteria; and (3) neutralizing antibodies that neutralize pathogens or their toxins by binding to microbes or their products, thereby preventing injury to cells. Specific antibody is an important component in lower respiratory tract defenses against extracellular microbes. Many extracellular bacteria possess polysaccharide capsules that allow them to evade phagocytic cells.

Numerous species and strains of bacteria and fungi have evolved the capacity to invade and survive within host leukocytes, primarily macrophages, to evade recognition and elimination by innate immune responses. Cell-mediated immunity is required to successfully eradicate these microbes. Cytokines produced by CD4 and CD8 T lymphocytes play a central role in the activation of microbicidal function in phagocytic cells (Fig. 120-4). IFN-γ produced by both CD4 and CD8 T lymphocytes is the most important macrophage-activating factor. Macrophage activation is further enhanced by TLR stimulation and by inflammatory cytokines such as TNF-α and GM-CSF. Activated macrophages kill intracellular microbes by exposure to toxic acid hydrolysis and cationic peptides in phagolysosomes, enhanced nitric oxide and reactive nitrogen intermediate production, and induction of the respiratory burst. Macrophage apoptosis in response to intracellular infection has been shown to be of importance in blocking cell-to-cell spread of certain intracellular infections.

Granuloma formation is an important mechanism of host defense to intracellular microbes.[210,211] The recruitment of monocytes and lymphocyte populations to the site of infection is required for granuloma formation. Macrophages coalesce into large, epithelioid, and multinucleated giant cells. DCs, CD4+ T lymphocytes, and CD8+ lymphocytes form a loose meshwork that serves to contain microorganisms. Granulomas are sites of ongoing production of inflammatory cytokines, including TNF-α, IFN-γ, and chemokines capable of recruiting additional effector cells.

CONCLUSION

Infections are the evolutionary force for the development of a complex system of pulmonary host defenses. A coordinated response of many different cells is required for the lung to clear pulmonary pathogens. An increasingly complex and potentially injurious cascade of host responses is mobilized following pulmonary microbial challenges. Although the interactions of microbes in the host are invariably complex, models of pulmonary infection have provided crucial information regarding the regulation of inflammatory and immune responses. These insights should eventually allow the development of rational strategies regarding vaccination and immunotherapy. The use of animal models offers the possibility of understanding the mechanisms that regulate immune responses sufficiently well so that the response to a specific antigen could be controlled. A more complete understanding of host defense will allow the stimulation of deficient responses and the suppression of harmful responses to microbial pathogens and other antigens that enter the lung.

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CHAPTER 121

The Lung Microbiome

John E. McGinniss
Joshua M. Diamond

INTRODUCTION

The use of novel methods to study the microbiome has revolutionized our understanding of the microbial communities that reside on mucosal surfaces. While culture-based methods and Koch's postulates produced advances in medicine that moved the field into the modern era through development of antimicrobials and an understanding of microbial pathogenesis, these methods are inherently biased and reductive in scope.

This chapter constitutes an introduction to the methods used in microbiome research. Highlighted are specific considerations for lung research, as well as what is known about the lung microbiome in health and selective disease states. Table 121-1 outlines terms used in this chapter and commonly employed in the microbiome literature. Since this is a rapidly evolving field, inevitably, we will witness advances in a variety of areas. Understanding microbiome composition in disease states, identifying predictive microbiome features, and establishing prognostic biomarkers, host–microbiome interactions, and, potentially, therapeutics that affect the microbiome or that are microbially derived, are reasonable goals. Given the dynamic nature of the field, our objective is to provide an overview of foundational principles, to highlight considerations for understanding the microbiome in the lung, and to suggest future directions in lung microbiome research.

METHODS OF STUDYING THE LUNG MICROBIOME

Advances in sequencing technology ("next-generation" or "deep sequencing") and computational methods have enabled wide application of comprehensive, unbiased, culture-independent approaches to the study of the lung microbiome.[1] The earliest and most widely used approach amplifies the bacterial 16S rRNA gene.[2–5] PCR amplification uses primers targeting conserved sequences; within the 16S rRNA gene are hypervariable regions whose sequences vary between bacteria. Therefore, sequencing data allows identification of the various bacterial members of the community.[1,5] Sequence-based approaches are quantitative and capture both recognized pathogens and commensals. Targeted 16S rRNA gene analysis also captures archaea, which are scant in the lung and generally understudied. Fungi (the "mycobiome") are studied using analogous targeting of regions shared by all fungi, such as the 18S rRNA gene or internal transcribed spacer (ITS) sequence in the ribosomal gene locus. In contrast, viruses have no such universally shared sequences. Figure 121-1 outlines the main steps in conducting a microbiome study.

A complementary approach is *shotgun metagenomic sequencing*, which sequences all the DNA (or RNA, depending on sample preparation) in a specimen. Thus, shotgun sequencing can be used to profile viruses (the "virome"), as well as fungi and bacteria. Another benefit of shotgun sequencing is that it captures microbial gene content that enumerates the genetic potential for microbial functions (e.g., metabolic activity, virulence factors, antimicrobial resistance). Large amounts of host DNA relative to microbial DNA in many lung samples often results in increased cost of data acquisition and complexity of analysis,[6] although with recent advances, shotgun metagenomics enjoys broader use in lung microbiome research.[6–9] Table 121-1 lists selected key elements in microbiome investigation relevant to this review.

SAMPLE TYPES

The human respiratory tract has been studied using a variety of techniques. Generally, the gold standard in evaluating the lower respiratory tract is bronchoalveolar lavage (BAL). Obtaining a BAL sample requires bronchoscopy and provides specimens from the small segmental airways and alveolar compartment. However, BAL samples a relatively large surface area of the lung and, in heterogeneous lung disease, likely samples both normal and diseased areas. An early concern in obtaining BAL for microbiome analysis was "carryover" from the upper airways during bronchoscopy. Studies have used sampling via protected brushes and other high-stringency methods to confirm that the taxa are authentically present in the lung and do not reflect procedural carryover from the upper respiratory tract.[10–12]

TABLE 121-1 Microbiome Terminology

- Microbiome: the community of microbes and their gene content in an environmental niche
- Microbiota: the community of microbes in a given niche
- Mycobiome: the fungal microbiome
- Virome: the viral microbiome
- 16S rRNA: gene commonly used for targeted sequence analysis of bacteria and archaea
- 18S rRNA: gene commonly used for targeted sequence analysis of fungi
- Internal transcribed spacer (ITS) sequence: region in the rRNA locus commonly used for targeted sequence analysis of fungi
- Operational taxonomic unit: closely related sequences grouped together to represent a unit of bacteria ("taxon")—for example, 16S sequences clusters sharing 97% sequence identity
- Amplicon sequence variant (ASV): amplified 16S sequences that are binned together based on 100% identity
- Richness: number of different taxa present in a community
- Evenness: equality of distribution among taxa in a community
- Alpha diversity: the within-sample diversity that incorporates both richness and evenness
- Beta diversity: compositional differences between two or more microbial communities
- Dysbiosis: deviation from the normal, optimal, or healthy microbiome in a particular niche
- Relative abundance: proportion of sequences that align with a taxon within a sample; this does not necessarily represent the absolute abundance of that bacteria in a sample
- Shotgun sequencing: sequencing of the entire DNA content in a sample based on generation of random fragments and alignment of these fragments to a database to generate annotations to specific bacteria, fungi, or viruses and their respective genes
- Metagenomics: the study of genetic material recovered directly from an environmental niche without ex vivo culture or perturbation
- Metatranscriptomics: analysis of all the RNA (typically messenger RNA) of a sample to understand functional capacity
- Taxon (plural, taxa): a grouping of microbes at a taxonomic level such as family, genus, or species

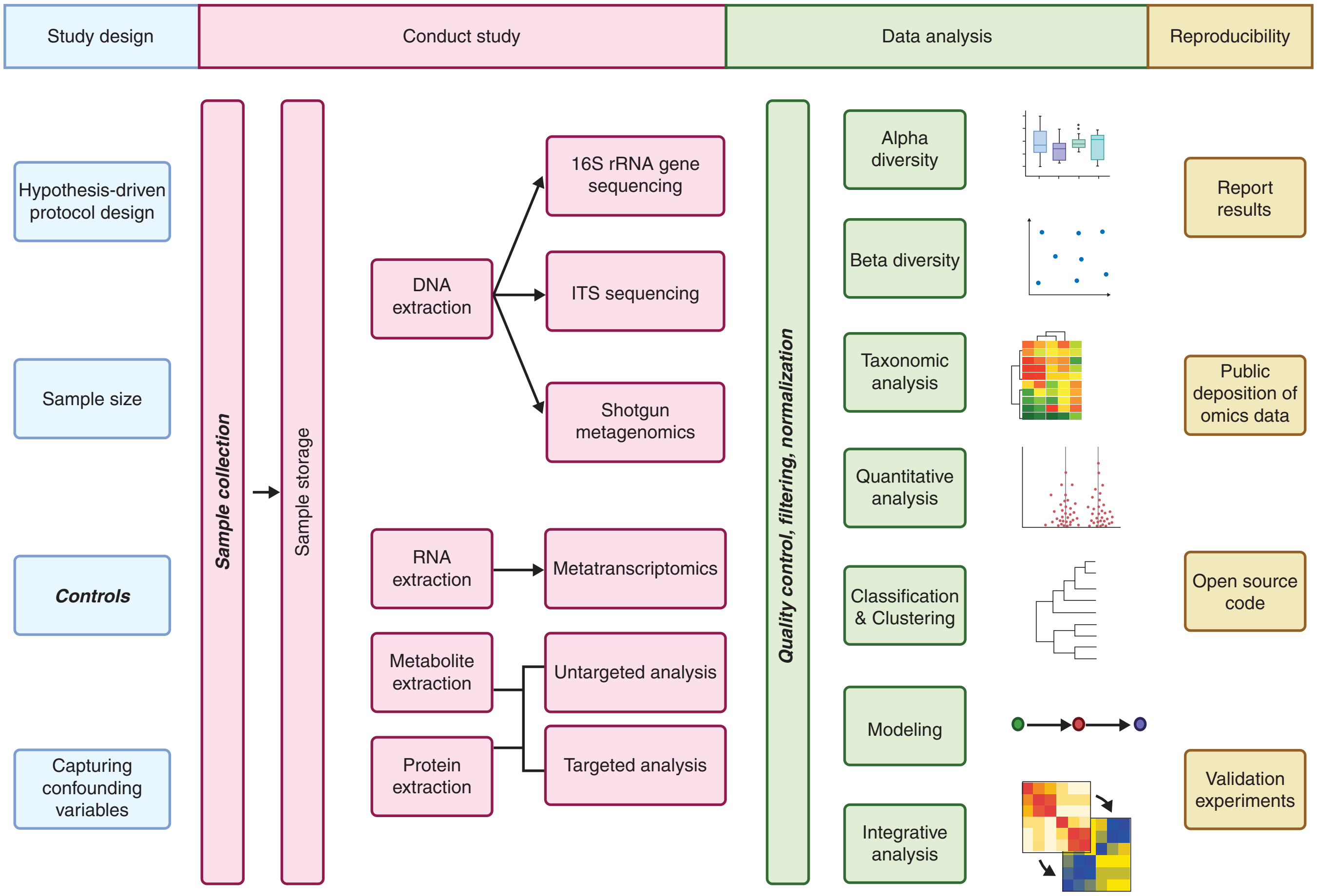
Study design
Conduct study
Data analysis
Reproducibility
Hypothesis-driven protocol design
Sample size
Controls
Capturing confounding variables
Sample collection
Sample storage
DNA extraction
16S rRNA gene sequencing
ITS sequencing
Shotgun metagenomics
RNA extraction
Metatranscriptomics
Metabolite extraction
Protein extraction
Untargeted analysis
Targeted analysis
Quality control, filtering, normalization
Alpha diversity
Beta diversity
Taxonomic analysis
Quantitative analysis
Classification & Clustering
Modeling
Integrative analysis
Report results
Public deposition of omics data
Open source code
Validation experiments

Figure 121-1 Overview of microbiome study methodology. There are multiple phases in the execution of a microbiome study. Those in bold need particular attention in the conduct and evaluation of lung microbiome studies, given the unique features of this niche: low-biomass status, dynamic nature, and close relation to the upper respiratory tract.

Sputum samples are commonly used, noninvasively obtained, and readily available. These are attractive features for microbiome analysis in the nonintubated patient. Challenges include quality control of the sample and the fact that sputum is inevitably an admixture of upper and lower airway microbiota. Furthermore, the proportions of these two compartments is dynamic and difficult to predict.[13] Interestingly, in more severe disease, sputum may more accurately reflect the microbiota of the lower airways.[14]

Other sampling methods used to study the respiratory tract include tissue samples,[15] tracheal aspirates,[16] induced sputum,[13] and exhaled breath condensates.[17] Each has its advantages and shortcomings and, importantly, tends to produce results that are not completely overlapping.[18–20] Therefore, in interpreting respiratory tract microbiome studies, it is imperative to note the sampling method. Combining analysis of the lower respiratory tract microbiome with samples or swabs from the upper airway (oropharynx or nasopharynx) and/or gastrointestinal tract is a powerful tool in placing complex, within-subject dynamics and host–microbiome interactions in proper context.

MICROBIOME ANALYSIS

Sequencing of whole microbial communities yields rich and dense data. To date, there is no consensus on the best pipeline or analytical tools,[18] but there are emerging best practices.[20] After careful quality control and filtering of data (which is beyond the scope of this chapter),[21] the basic output is a table of the relative abundances of each microbial taxa in a given sample. Key features of microbiome data that require careful statistical approaches are as follows: (1) the data are *wide*, with many more microbial features than samples in a typical study, (2) the data are *sparse*, with most taxa having an abundance of zero in a given sample,[22] and (3) the data are *compositional*, in which all the relative abundances of a microbial taxon sum to one in a sample.[23] The lung is a low-biomass system, and therefore extra care must be taken in assessing the quality of the data sequencing. In addition, concerted effort is needed to tease apart the relatively smaller signal from the inevitable noise introduced by sampling contamination and bacterial sequence contamination from instruments and reagents.[20,24]

After data processing, one important data output is a summary of the diversity of the complex communities. The approach is an ecologic one, and methods initially developed to understand diversity of outdoor environs[25] have been adapted for human microbial study.[26] One elemental metric is known as *alpha diversity*. This is a within-sample measurement of how many distinct microbes are present and how evenly are they distributed. *Richness* is the measure of the number of taxa per sample; other indices, such as the *Shannon index*, account for both richness and evenness.[27]

Alpha diversity provides an overall portrait of the health of a community; generally, higher diversity is considered healthier. There are notable exceptions reported in the literature, such as in the vaginal microbiome[28] and the bronchial microbiome in asthma.[29] *Beta diversity* is the measure of the difference in composition between two samples; a greater difference means a more distinct microbiome. Two of the most commonly used metrics of diversity are the Bray-Curtis dissimilarity and UniFrac distance measures.[30] An extension of beta diversity analysis is creation of *clusters* of similar samples to create "microbiome types," generally through machine learning clustering methods."[31–33]

In addition to microbial diversity, *abundance of bacteria* is an important metric. This measure has traditionally been assessed using 16S rRNA qPCR to determine the bacterial biomass. More recently, *droplet digital PCR*, which has much higher sensitivity, has been used to quantify bacterial burden in a sample.[34] This technique holds great promise, as multiple studies have linked biomass to outcomes in idiopathic pulmonary fibrosis[35] and lung transplantation.[36]

Microbial function can be either inferred or measured directly. A common computational approach uses *imputed metagenomics*[37] to infer the functional potential of the microbes discovered in a given community based on marker gene sequencing. More directly, the bacterial DNA genes can be quantitated during shotgun metagenomic sequencing, and the transcribed RNA measured using metatranscriptomic study.[21,38] These study types are computationally difficult, and the sequencing is costly.

In addition to measuring functional potential of a microbial community through DNA and RNA sequencing, the downstream intermediaries of the host interaction, namely, metabolites and proteins, constitute an active area of investigation. While complex, these approaches hold the promise of identifying networks of interaction that mediate disease.[31,39,40] One such study identified that metatranscriptomics of BAL best predicted short-chain fatty acid (SCFA) production, as measured by mass spectrometry, and captured dynamic microbial SCFA metabolism using a murine model.[38]

THE HEALTHY LUNG MICROBIOME

Below we consider important attributes of the healthy lung microbiome.

■ The Normal Lung Microbiome: Scant, Dynamic, and Largely Derived from the Upper Respiratory Tract

Traditionally, healthy lungs were thought to be sterile, but work in the last decade has definitively disproved that notion. Healthy lungs harbor low levels of bacteria—a finding based on molecular detection and, to a more limited extent, high-sensitivity culture.[10,12] Given that the lung is contiguous with the microbe-rich upper respiratory tract, coupled with the fact that we inhale multiple liters of air per minute from the nonsterile external environment, this is, perhaps, not surprising. Applying rigorous approaches, we now know healthy lung composition significantly overlaps with the upper respiratory tract and glottic region.[10] The most prevalent taxa in the healthy lung are from the Firmicutes and Bacteroidetes phyla, a finding that has been remarkably consistent across studies and geographic sites.[10,11] The most common genera within these phyla are *Prevotella*, *Streptococcus*, and *Veillonella*.

These findings indicate that the main source of lung microbes is microaspiration from the upper respiratory tract,[11,41] an event that is known to occur in all healthy people.[12] In the normal lung, the bacterial populations are transient because of efficient clearance by mechanical and innate immune defenses.[42] Aspirated bacteria immediately encounter airway mucus and mucociliary action, alveolar macrophages and neutrophils, and the airway epithelium as first lines of defense against bacterial colonization.[42] There are subtle regional differences within the lung and from upper respiratory communities, suggesting that differential clearance and/or local replication occur even in healthy people.[11]

An important limitation of 16S rRNA is its inability to distinguish live from dead bacteria. However, other methods have identified that a proportion of these lung-derived bacteria are viable and transcriptionally active.[43] These characteristics of the healthy lung microbiome as transient and dynamic stand in contrast to the higher-biomass, locally replicating, resident gut microbiome. Hence, vastly different ecologic forces are applied to the microbial communities of the two niches.[44]

■ The Lung Microbiome: Surveilled by the Immune System and a Regulator of Local Immune Tone

Despite the relatively low biomass and dynamic nature of the lung bacterial microbiome, it has important effects on the immune environment in the lung. In healthy humans, the presence of microbial sequences in the lung that mirror those in the oropharynx correlate with higher basal Th17 lymphocytes when compared with those whose lung bacteria cluster with control samples.[45] This suggests that entry of upper respiratory–derived microbiota regulates immunity in the lung.

At the same time, it is well established that the gut microbiome, with an exponentially higher biomass, determines, in part, the systemic immune "tone" that may impact the local lung immune milieu—the so-called gut–lung axis.[46] A murine study found that while both local lung and gut microbiota influenced lung immune profiles, the lung microbiome was the much stronger influence.[47] Hence, both the lung–lung axis and gut–lung axis seem to contribute to the lung immune setpoint in health.

THE LUNG VIROME AND MYCOBIOME

The viral and fungal components of the lung microbiome are less well studied than the bacterial microbiome. Apart from acute infection with community-acquired viruses, sequence-based analysis has identified Anelloviridae as the most common and abundant component of the lung virome, along with bacteriophages; more variable has been the detection of other eukaryotic viruses, including Herpesviruses and Papillomaviruses.[48,49] Anelloviridae are small, single-stranded, DNA circular-genome viruses found in blood and many tissues. Their prevalence is nearly 100% in humans, although they have not been associated with disease.[50]

Fungal constituents of the microbiome in health also are understudied and present unique challenges.[6,10,49,51–54] In addition to upper respiratory tract and background contamination with fungi, many respiratory samples have very low fungal biomass and low numbers of fungal taxa.[55] In addition, fungal cell walls are difficult to lyse, and there are biases in 18S and ITS primers. Finally, nonstandardized nomenclature and poor annotation of fungal databases complicate classification.[49] Limited small studies in healthy lungs show low fungal biomass and interindividual heterogeneity; fungi from the Ascomycota phylum are most common, followed by Basidiomycota. The main genera are *Candida*, *Saccharomyces*, *Penicillium*, *Cladosporium*, and, occasionally, other environmental taxa; *Aspergillus* and *Pneumocystis* are inconsistently identified at low levels in health.

GUT–LUNG AND ORAL–LUNG AXES

Evidence has emerged that the oropharynx and gastrointestinal tract influence the lung microbiome. The influence arises from direct effects from anatomic contiguity of the oropharynx and the airways[10,45,56–58] and, potentially, from gut–lung translocation of bacteria (mostly described in the context of critical illness[59] and severe immunosuppression[60]). Indirect influence arises through a shaping of the inflammatory milieu and host response in the lung.[61] Studies have revealed that microaspiration is likely the predominant source of lung bacteria.[12]

In children, the oropharyngeal microbiome overlaps more with the lung in those with impaired swallowing mechanisms; more overlap is seen in the lung and gastric aspirates in those children with intact swallowing mechanisms.[62] Interestingly, horses and other quadrupeds likely have a relatively greater contribution from the nasopharynx than the oropharynx because of the attenuated effect of gravity.[63] Therefore, the oropharynx and supraglottic space are important to understanding the sources of lung communities. This is clearly important in health when lung microbiome communities constitute low biomass and are dynamic. The extent to which this is true in advanced lung disorders, in which there is more local proliferation in the lung, remains to be determined.

The gut microbiome has been shown to regulate systemic immunity in multiple ways.[64,65] The high biomass of gut microbiota interacts with the gut mucosal immune system, and these numerous, dynamic interactions influence systemic immune tone.[66] In addition, the gut microbiome is a source of metabolites that enter the systemic circulation and influence distant targets.[67–69] Finally, in critical illness and advanced HIV the gut barrier function is impaired, and gut bacteria and/or their products may access the circulation.[70–72] The extent to which this impacts lung microbiome function is an open area of investigation. Therefore, in general, it is important to consider the lung microbiome not in isolation, but in conjunction with other mucosal niches.

DISEASE ASSOCIATIONS

Table 121-2 includes selected findings regarding the associations between the lung microbiome and common lung diseases. In this section we highlight two clinical states: interstitial lung disease and post–lung transplantation. These scenarios represent the diversity of microbiome investigations and highlight the promises and challenges of determining the role of the lung microbiome.

■ Microbiome in Interstitial Lung Disease

Significant radiographic, pathologic, and clinical heterogeneity exists across the numerous forms of interstitial lung disease. Microbiome analysis is an ideal tool to actively assess potential differential etiologies and markers of risk for disease progression. Additionally, microbiome assessment allows for potential development of novel therapeutic modalities. Two disease states highlight the innovative role of microbiome analysis: sarcoidosis and idiopathic pulmonary fibrosis.

Microbiome in Sarcoidosis

Given the complicated interplay of genetic susceptibility and environmental exposure, combined with the central pathologic finding of granulomas in sarcoidosis, significant efforts have been aimed at identifying an underlying infectious etiology or microbial biomarker for aiding in the diagnosis and prognosis for sarcoidosis.

Whole blood gene expression studies utilizing machine learning to identify patterns demonstrate significant overlap with tuberculosis gene expression signatures.[73]

A 2013 meta-analysis identified a significantly increased risk of sarcoidosis associated with *Propionibacterium acnes* identification.[74]

Small, single-center studies have focused on further assessing the causal role of the microbiome in sarcoidosis. A study comparing 31 patients with sarcoidosis and 19 controls with non-sarcoidosis-related ILD demonstrated no difference in microbial richness or alpha diversity and no difference in specific operational taxonomic unit composition between the two groups.[75] Notably, 20% of the identified operational taxonomic units could not be assigned to a specific genus, limiting the studies' capacity to potentially identify a sarcoidosis-associated organism.

A study of 93 patients compared those with sarcoidosis to controls using environmental samples to assess the microbiome, mycobiome, and virome of lymph nodes, BAL, and spleen specimens, as well as Kveim reagent, to assess for lineages enriched in sarcoidosis.[6] While there were tissue-specific enriched organisms identified, including *Cladosporiaceae* fungal isolates in lymph node tissue and *Aspergillus* in BAL, no organism was shared across tissue types after false discovery rate correction. This study also highlighted the importance of assessing environmental admixture when assessing low microbial biomass sites.

A study of 19 patients with ILD, including 10 with sarcoidosis, did not identify a specific microbial signature for sarcoidosis, although the study was limited by small sample size.[76]

When excluding oral taxa, a study of 21 patients with sarcoidosis identified *Erythrobacteraceae*, a group of organisms without known human disease pathology, to be enriched in patients with sarcoidosis.[77]

Accumulating data, combined with ongoing interest in an unknown microbial trigger for sarcoidosis, led to the design and implementation of the National Institutes of Health–funded Genomic Research in Alpha-1 Antitrypsin Deficiency and Sarcoidosis (GRADS) study, the primary objective of which is identification of patterns in the lung microbiome associated with sarcoidosis severity and disease phenotypes.[78] With a planned enrollment of 400 subjects, the study has the potential to greatly improve our understanding of the complex interplay between the microbiome and sarcoidosis, and the sample size may enable identification of novel sarcoidosis-related or sarcoidosis-specific organisms.

Microbiome in Idiopathic Pulmonary Fibrosis

The impact of lung microorganisms on idiopathic pulmonary fibrosis (IPF) has been highlighted over the last several years in multiple clinical trials and observational studies.[79,80] The role of the lower respiratory tract microbiome in pathogenesis of IPF can be considered with regard to several disease phases, including early disease, acute exacerbation of IPF (AE-IPF), and late, advanced disease.

Clear differences exist in the microbiome of patients with IPF compared with healthy controls. Indirect evidence for a role for microbial populations includes a statistically significant increased risk of death associated with immunosuppression, as well as a decrease in mortality and improvement in quality of life among patients treated with trimethoprim-sulfamethoxazole (TMP-SMX).[81,82] While not statistically significant in a study with limited overall sample size, bacterial diversity, as measured by richness and Shannon diversity, was lower in patients with idiopathic interstitial pneumonia compared with patients with other lung diseases or healthy controls.[83] An early study evaluating the culture-independent composition of the lower respiratory tract of IPF and other patients with ILD identified numerous, noncultured organisms, including *Actinobacterium*, *Neisseria*, *Haemophilus influenzae, Streptococcus*, and *Moraxella,* (predominantly components of oral flora).[84]

Multiple studies have implicated specific organisms or changes in the microbiota with acute exacerbations of IPF. A case control study of 20 patients with AE-IPF and 15 stable patients with IPF revealed (1) increased total microbial load in the BAL of patients with AE-IPF; (2) higher relative abundance of *Campylobacter* and *Stenotrophomonas* spp. in those with AE-IPF; and (3) lower relative abundance of *Veillonella* spp.[85]

Using a subgroup of patients from the prospective observational cohort study COMET-IPF, investigators identified *operational taxonomic unit*s matching *Staphylococcus* and *Streptococcus* to be strongly associated with rapid disease progression.[86] Relative threshold levels of 3.9% for *Streptococcus* and 1.8% for *Staphylococcus* also strongly correlated with differential survival.

A study using TGF-β1–overexpressing mice demonstrated increased growth of *Staphylococcus nepalensis* and identified a novel proapoptotic peptide, corisin, that induced lung epithelial cell apoptosis.[87] Furthermore, inhibition of corisin with polyclonal anti-corisin antibody prevented apoptosis; instillation of either corisin or *S. nepalensis* exacerbated fibrotic disease in the mouse model. Furthermore, corisin levels are significantly elevated in the BAL fluid of patients with AE-IPF compared to healthy controls.[87] These studies highlight the potential utility of microbiome analysis for

TABLE 121-2 Select Lung Microbiome Disease Associations

Disease State	Microbiome Associations	References
Lung cancer	Increased Proteobacteria in lung cancer.	Greathouse et al., 2018[125]
	Acidovorax identified by fluorescent in situ hybridization and 16S sequencing (significant increase in squamous cell carcinoma cases with TP53 mutations).	
	Elevated Proteobacteria in squamous cell carcinoma compared to adenocarcinoma and increased diversity in BAL.	Gomes et al., 2019[126]
	PI3K pathway upregulated with oral taxa enrichment in airway brushes of cancer cases.	Tsay et al., 2018[127]
Cystic fibrosis	Ivacaftor significantly decreased bacterial burden and *P. aeruginosa* (but did not eradicate) burden and markers of inflammation.	Hisert et al., 2017[128]
	Lung function declines correlated with increase in potential pathogen dominance and decreased diversity over time.	Cuthbertson et al., 2020[129]
	Under 2 years of age, patients with CF have abundant *Streptococcus*; this becomes replaced with pathogens in older children and adults.	Zemanick et al., 2017[130]
Chronic obstructive pulmonary disease (COPD)	Neutrophilic endotype of COPD had a *Haemophilus*-predominant (clinically stable, high IL-1b, TNF-α) and balanced microbiome (clinically dynamic, elevated IL-17a) subgroups. Eosinophilic endotype had enrichment of nondominant taxa.	Wang et al., 2020[131]
	Longitudinal increases in *Moraxella* and *Actinobacillus* most strongly correlated with exacerbations.	
	Elevated *Staphylococcus* relative abundance and low alpha diversity increased risk of mortality when found after a hospitalization for an acute exacerbation of COPD.	Filho et al., 2019[132]
	Lung tissue microbiome in mild to moderate COPD found enrichment of nasal and oral taxa.	Pragman et al., 2018[133]
	More within subject similarity of bronchial and lung microbiome than between types across subjects.	
Asthma	Asthmatic subjects had higher diversity than healthy controls or those with atopy without asthma in protected bronchial brushings.	Durack et al., 2017[29]
	Baseline Streptococcaceae, Fusobacteriaceae, and Sphingomonadaceae predicted response to inhaled corticosteroids (ICS).	
	No significant differences in sputum microbiome in high- versus low-dose ICS asthma treatment. *H. parainfluenzae* enriched in high-dose fluticasone versus budesonide.	Martin et al., 2020[134]
	The bedroom environmental mycobiome and sputum mycobiome have significant overlap during asthma exacerbations and contain clinically significant fungi.	Vandenborght et al., 2020[135]
Acute respiratory distress syndrome (ARDS)	The lung becomes enriched with gut bacteria (Bacteroidetes) in ARDS, implicating translocation as a possible mechanism.	Dickson et al., 2016[59]
	Higher bacterial burden and composition with gut-associated bacteria on admission to the ICU in intubated patients predicted fewer ventilator-free days and ARDS.	Dickson et al., 2020[136]
	Mechanically ventilated patients with low alpha diversity and enrichment with potential pathogens and high inflammation, longer duration on mechanical ventilation, and lower 30-day survival.	Kitsios et al., 2020[137]
HIV-related pulmonary disease	*Tropheryma whipplei* is prevalent in the lungs of persons living with HIV (PLWH).	Lozupone et al., 2013[138]
	No difference in lung bacterial composition between PLWH and healthy controls in well-controlled and early disease.	Beck et al., 2015[139]
	In advanced HIV, there is a reduction over time of alpha diversity and differences in bacterial composition compared with non-HIV controls.	Twigg et al., 2016[140]
Lung infection	An integrated approach with metagenomic sequencing and transcriptomics was able to differentiate infectious versus noninfectious causes of respiratory failure.	Langelier et al., 2018[141]
	Oral taxa such as *Prevotella* may drive progression to active TB through production of short-chain fatty acids that activate anti-inflammatory regulatory T cells in the lung. These cells in turn reduce IL-17a and IFN-γ needed to control TB infection.	Segal et al., 2017[142]
	16S rRNA sequencing is less sensitive than culture in detecting nontuberculous mycobacteria (NTM). NTM culture–positive patients who were enriched in oral taxa had increased inflammatory biomarkers.	Sulaiman et al., 2018[13]
IPF	*Campylobacter* and *Stenotrophomonas* are associated with risk of acute exacerbation of IPF.	Molyneaux et al., 2017[85]
	Staphylococcus and *Streptococcus* are strongly associated with rapid disease progression in IPF.	Han et al., 2014[86]
	Murine model of IPF using TGF-β1 overexpression demonstrated *Staphylococcus nepalensis*—release of the proapoptotic peptide corisin resulted in progressive pulmonary fibrosis.	D'Alessandro-Gabazza et al., 2020[87]
Sarcoidosis	Erythrobacteraceae, a group of organisms without known human disease pathology, are enriched in patients with sarcoidosis.	Fukui et al., 2020[77]
	National Institutes of Health–funded Genomic Research in Alpha-1 Antitrypsin Deficiency and Sarcoidosis (GRADS) study is ongoing.	Moller et al., 2015[78]

identifying patients at risk for AE-IPF, although the lack of consistent findings across studies and among populations of patients with IPF and the small number of patients studied precludes generalization of results.

In a study utilizing explanted lung tissue samples from end-stage, transplanted patients with IPF, the total microbial load identified was indistinguishable from negative controls, indicating that the honeycombed portions of the lung with IPF contain no inherent microbiome.[15] A similar study of explanted lungs with advanced IPF demonstrated higher bacterial burden in the airways compared to lung parenchyma of patients with IPF.[88] Investigators identified a cluster of samples with high bacterial load, low alpha diversity, and increased typical airway organisms, including *Streptococcus*, *Veillonella*, or *Prevotella*. This cluster was also associated with higher rates of death, use of antibiotics, and incidence of AE-IPF.

Similar to the earlier indirect evidence for bacterial involvement in IPF, there is indirect evidence for a role for viral infection. Case reports and small, open-label trials of ganciclovir administration demonstrate stabilized lung function.[89,90] Multiple studies have implicated herpesviruses in the potential pathogenesis of IPF as well.[91]

The association of altered or different microbiomes or viromes with advanced IPF is also intriguing. However, as for associations with AE-IPF, correlations themselves are not evidence of causation; they require further investigation. For example, despite prior evidence that TMP-SMX improved IPF outcomes, a recent, randomized trial of 342 patients with IPF showed no difference in time to death, transplantation, or nonelective hospitalization compared with placebo.[92] At present, causative microbial organisms or obvious new novel targets for therapy based on non-culture-based identification remain elusive.

■ The Post–Lung Transplantation Microbiome

Below we consider the bacterial microbiome, the virome, and the mycobiome in lung transplant recipients.

Bacterial Microbiome

Multiple studies have revealed an elevated bacterial burden in lung transplant recipients compared with healthy controls, ranging from 15-fold to 1000-fold higher.[51,93–96] Across studies, a subset of posttransplant patients maintains a lung microbiome composition predominantly of oral-type flora,[51,94,96,97] while most have a marked decrease in alpha diversity accompanied by an outgrowth of specific taxa. Quantitative comparison of lung versus upper respiratory tract communities shows outgrowth in the lung of commensals and potential pathogens, such as *Pseudomonas*, *Enterobacteriaceae*, *Staphylococcus*, as well as anaerobes.[51]

In longitudinal studies, upper respiratory tract flora usually are the predominant taxa in the lung microbiome in the first year after transplant;[94,97] this profile is also seen after the first posttransplant year.[96,98] The most abundant phylum is Bacteroidetes, followed by Firmicutes, then Proteobacteria and Actinobacteria.[94,97] A smaller proportion of samples exhibit outgrowth of *Corynebacterium* and potential pathogens such as *Pseudomonas*, *Staphylococcus*, and *Stenotrophomonas*. In cystic fibrosis (CF), two main types of posttransplant lung bacterial communities have been described: one typical of oral bacteria (particularly *Streptococcus* and *Veillonella*) and one dominated by *Pseudomonas*.[98]

Thus, across studies, the posttransplant lung microbiome has a higher biomass and is dysbiotic (i.e., deviates from normal lung composition), but the specific nature of the dysbiosis tends to be patient-specific. In addition, variability based in space and time is noted. In transplant patients, differences have been reported between proximal and distal airway samples[99,100] and between native lungs and allografts in single lung transplant recipients.[95] This could result from regional differences in organism entry, clearance, or local replication. In addition, there are complex dynamics at the time of transplant and in the first posttransplant year. Early on, donor microbiota persists in some subjects post-transplant, while in others, it is rapidly replaced.[98,101] In CF, *Pseudomonas* strains derived from the transplant recipient populated the allograft within days.[102,103] After the first year, extensive change occurs over time in bacterial composition at lower taxonomic levels, although more stability is noted at higher taxonomic levels.[104] These considerations preclude broad generalizations about a homogenous, "posttransplant lung microbiome" composition. It is this very heterogeneity that suggests distinct outcomes may be linked to microbiome profiles.

The Bacterial Microbiome and Outcomes

Chronic lung allograft dysfunction (CLAD) is the chronic loss of allograft function and is the primary cause of late morbidity and mortality in lung transplantation.[105,106] Bronchiolitis obliterans syndrome (BOS), the more common obstructive form of CLAD, has had variable associations with the lung microbiome. An early study found that the presence of *Pseudomonas* species in CF subjects post-transplant appeared protective against BOS, particularly if the patient had *Pseudomonas* previously identified.[98] In contrast, enrichment with oral taxa increased the incidence of BOS. This did not hold true for non-CF subjects. Furthermore, decreased diversity over time within an individual increased the risk of BOS. These findings raise the hypothesis that the stability of the microbiome over time increases BOS risk.

Subsequent studies have reported different microbiome correlations with BOS. A small, uncontrolled study found enrichment of *Actinomyces* and Xanthomonadaceae in BOS.[104] Another found that Actinobacteria dominance (*Propionibacterium* and *Corynebacterium*) at 3 months post-transplant had lower rates of BOS, less inflammation in BAL, and lower rates of acute cellular rejection.[107] However, this association did not hold for later time points, suggesting a time-dependent association with outcomes. In an examination of topographic features of the posttransplant lung microbiome, microbial and inflammatory profiles differed in proximal and distal airways, and BOS was linked to specific taxa from three phyla (Proteobacteria, Bacteroidetes, Firmicutes) in distal, but not proximal, specimens.[100]

In summary, emerging data suggest a complex relationship between the lung transplant bacterial microbiome and BOS. Unraveling this complexity must account for temporal, spatial, and patient-specific factors. In addition, cross-kingdom interactions with the virome and mycobiome, as well as an integration with the multifaceted host response after lung transplantation, warrant further study.

The Virome and Mycobiome

Herpesviruses, particularly cytomegalovirus and herpes simplex virus, are important pathogens after lung transplantation and are targets of prophylactic antiviral regimens.[108] Community-acquired respiratory viruses, such as influenza, enteroviruses, and rhinoviruses, lead to acute morbidity and increased risk of later CLAD.[109–111] These viruses are typically identified using targeted PCR methods. While there is a burgeoning literature probing the human virome through sequence-based methods,[48,111–114] only a few have focused on the lung, and even fewer on lung transplantation.

The most abundant eukaryotic viruses in lung transplant BAL are of the Anelloviridae family—small circular DNA viruses (such as torque teno virus [TTV]).[48,111–114] Despite their prevalence and abundance, Anelloviridae effects on the host are not well understood. Altered peritransplantation dynamics of Anelloviridae have been associated with primary graft dysfunction,[113] in which subjects had smaller increases in Anelloviridae levels, suggesting that the robust immune activation may lead to both acute lung injury and inhibition of viral replication. Lung Anelloviridae levels remain elevated after transplant and correlate with the degree of bacterial dysbiosis, indicating interkingdom covariation.[48,112] The consequences of persistent Anelloviridae elevations and allograft/recipient virome intermixing remain to be determined.

Bacteriophages (or phages) are abundant in the lungs of transplant recipients, particularly phages that infect bacterial inhabitants of the human respiratory tract.[113] Phages can influence bacterial pathogenesis in the lung, particularly in CF.[115] Also, emerging data suggest that phages may directly interact with human cells and modulate innate immune function.[116] However, what role phages play post-transplantation is unknown. Phages have also garnered interest as treatments for multidrug-resistant bacterial infections, such as *Pseudomonas* and *Mycobacterium* species, including in lung transplant recipients.[117,118]

A limitation in interrogating the virome using deep sequencing is the incomplete nature of viral databases that do not identify many of the viral sequences—so-called viral dark matter. Recent contributions have chipped away at this dark matter. One such study identified a novel viral family termed Redondoviridae (named for their small, circular DNA genome).[119] Future studies are needed to determine what role these and other newly discovered members of the human virome have in lung health and disease.

Based on fungal culture, *Aspergillus* and *Candida* are commonly identified in lung samples after transplantation.[51,55] *Aspergillus* is associated with early anastomotic complications, as it grows in ischemic anastomotic tissue.[120] Several studies have linked *Aspergillus* infection or colonization to later CLAD,[121,122] although one large cohort study found no association.[123] Invasive *Candida* infections are common after lung transplantation and usually involve the bloodstream, pleural space, or surgical site.[108,124]

The first posttransplantation metagenomic analysis found that fungi were highly variable among patients in absolute quantity and composition.[51,55] *Candida* was the most prevalent taxon and, when abundant in the lung, was also abundant in the oropharynx. This contrasted with healthy controls, in whom *Candida* was prevalent in oral samples but scarce in lung. *Aspergillus* was seen in BAL, sometimes at high levels, while other subjects had *Cryptococcus* and environmental fungi. Additionally, there was significant interkingdom covariation between *Candida* and *Rothia*, *Streptococcus*, and *Veillonella*.[55]

CONCLUSION

Study of the lung microbiome is a relatively new and evolving field that applies advanced computational approaches to dissect host–microbe interactions. Advances in technology and analytical methods have illuminated our understanding of the complex microbial communities that inhabit the lung in health and disease—yet methodologic limitations and hurdles remain. Future lung microbiome research will attempt to overcome these barriers and advance our knowledge of host–microbe interactions increasingly from the lab to the bedside in the form of improved prognostic, diagnostic, and therapeutic capabilities.

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CHAPTER 122

Approach to Pulmonary Infection in the Immunocompetent Host

Megan Rose Curtis
Tulip Ajit Jhaveri
Camille Nelson Kotton

OVERVIEW

Pneumonia is defined as inflammation of the pulmonary parenchyma caused by an infectious agent. In the fifth century BC, Hippocrates and his pupils first observed the cardinal symptoms of pneumonia: productive cough, fever, and dyspnea. He pioneered the use of auscultation, comparing the oscillations between the hemithoraces to diagnose lower respiratory tract infections.[1] Despite millennia of medical advances, pneumonia continues to cause significant morbidity and represents the leading cause of infection-related mortality worldwide.[2] Clinicians still rely primarily on history and physical examination when caring for a patient with suspected pneumonia. The clinical presentation of pneumonia is vastly heterogenous and may include fever or hypothermia; sweats; rigors (chills); pulmonary symptoms such as cough, sputum production, dyspnea, or pleurisy; and pulmonary lesions observed on radiographic examination. Nonspecific symptoms are common, including loss of appetite, fatigue, and confusion. The classic findings on physical examination include "crackles" or "rales"; however, the accuracy of clinical signs and symptoms alone have been shown to be ineffective in successfully diagnosing pneumonia.[3] Radiographs assist in identifying a pulmonary lesion; however, findings may be nonspecific. Because there are no diagnostic tests available to identify the microbiologic etiology immediately upon presentation (besides those for viral causes), initial antibiotic treatment is empiric and should be started as soon as pneumonia is suspected.

Management of pneumonia is complicated by changing epidemiology. Widespread administration of the conjugate pneumococcal vaccine has significantly decreased the incidence of pneumococcal pneumonia. Additionally, there has been increased recognition of viral pathogens as molecular diagnostic tests have become more advanced.[4] Viral pathogens may cause coinfections or precede a subsequent bacterial superinfection. Outbreaks of novel pathogens, such as SARS-CoV-2, pose a unique and unheralded layer of complexity to the microbiologic epidemiology of pneumonia. Despite an expanding array of antimicrobial options for treatment, none can be used empirically to treat all possible pathogens, and overuse of broad-spectrum antibiotics has led to increasing antimicrobial resistance.[5] Pneumonia represents an important and demanding clinical challenge. Successful management requires synthesis of epidemiologic, clinical, laboratory, microbiologic, and radiographic data, as well as swift clinical decision-making.

The purpose of this chapter is to assist the clinician at any step of the diagnostic and treatment algorithms when caring for a patient with suspected pulmonary infection. The first portion of the chapter provides broad guidance for initial patient evaluation and establishes a basic framework for clinical assessment; common viral and bacterial pathogens are emphasized (Table 122-1). The next portion focuses on diagnostics available to the clinician, including laboratory, radiographic, and microbiologic studies. The focus is on creating a framework to assist in guiding the workup and evaluating data as they become available. The last portion of the chapter explores the details of viral, atypical, fungal, and parasitic pneumonias.

THE ROLE OF HOST DEFENSES

The presence of pneumonia should be taken as evidence of an immune defect relative to the epidemiologic pressure of the microorganisms (Chapter 120). Organisms of high native virulence (due to adhesion properties, presence of invasive enzymes, motility characteristics, or intracellular presence) may cause infection with a small inoculum size in an immunologically normal host (Chapter 124). Organisms of low virulence should cause infection only if there is an immune or anatomic predisposition to infection or a high burden of organisms.[6] Microorganisms may reach the lungs via the airways, bloodstream, or lymphatics. Defects in specific components of the immune system (innate and acquired) predispose to specific types of infection, as shown in Table 122-2.

An important first step in the pathogenesis of many infections is colonization of the upper airway via adhesion of organisms to epithelial surfaces. These surfaces are normally protected by mechanical clearance of organisms from the nose or oropharynx, local production of complement and IgA, the presence of saliva, sloughing of epithelial cells, and bacterial interference by "normal flora." Changes in these surfaces (diminished IgA secretion, changes in production of adhesins or fibronectin, and altered lectin binding) predispose to adhesion of microorganisms. Organisms carrying enzymes that can degrade IgA exotoxins, adhesion proteins, or pili more readily colonize the respiratory epithelium. Mucociliary clearance may be disrupted by cigarette smoking or prior infections with viruses, *Haemophilus influenzae*, or *Mycoplasma pneumoniae*.

Aspiration may result from altered glottic closure (e.g., due to neurologic injury, sleep apnea, airway intubation, alcohol consumption, or administration of anesthesia). Once bacteria or viruses traverse the glottis, most are small enough (<2 μm) to reach the alveoli, unless impeded by alveolar lining fluid containing surfactant, IgG, complement, and other proteins. Surfactant includes a variety of components that serve to activate alveolar macrophage and neutrophil functions and may serve as an opsonin (e.g., SP-A and SP-D) for many organisms. Organisms surviving the upper airway defenses are subsequently addressed by the cellular components of the lower airways, including T and B lymphocytes, macrophages, and dendritic cells.

Pulmonary defense mechanisms are also disrupted by systemic infections (including sepsis), hyperglycemia and diabetes, acidoses, hypoxemia, pulmonary edema, malnutrition, uremia, age, and acute respiratory distress syndrome (ARDS). Endotoxin and lipopolysaccharide diminish clearance of bacteria from the lungs. Viral infections may diminish neutrophil and macrophage functions, including phagocytosis, chemotaxis, and oxidative metabolism.

The microbiome of the lung may play an important role in pneumonia pathogenesis (Chapter 121). Innovations in culture-independent microbial identification has highlighted the presence of diverse communities of organisms within the lung parenchyma, traditionally thought to be "sterile."[7] Microbes in the alveoli may exert an effect through modulating the host immune response or directly by overgrowth of the lung parenchyma. Dysbiosis has been identified in obstructive pulmonary disease, idiopathic pulmonary fibrosis, cystic fibrosis, and bronchiectasis, all of which are risk factors for development of pneumonia.[8] More research is needed to better understand the role of the microbiome in pneumonia, as little is known about the interaction between the host immune system and microbes, including viruses, fungi, and bacteria.

TABLE 122-1 Routine Evaluation of Patients with Suspected Pneumonia

History	
Age	
Community (respiratory viruses, antimicrobial resistance) vs. hospital (ventilator)	
Pace of onset, dyspnea	
Recent infections (post–viral pneumonia, endocarditis, aspiration)	
Recent hospitalization or exposure to medical facilities (extended care)	
Underlying conditions (mental status, immunity, cardiopulmonary, medications)	
Exposures (illness, children, institutions, animals, gardens, travel)	
Antimicrobial therapies, home infusion therapy, vaccinations	
Duration of hospitalization or endotracheal intubation	
Physical Examination	
Laboratory	
Complete blood count with differential counts	
Electrolytes, liver function tests, BUN, creatinine	
HIV	
Radiology	
PA and lateral chest radiograph (depending on host and severity of illness)	
Consider: Chest CT with contrast, echocardiogram, thoracentesis, rarely biopsy	
Microbiology *(adapted to clinical setting and severity of illness)*	
Gram stain and culture	All typical bacteria—*S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, *S. aureus*, enteric Gram-negative bacilli
Blood cultures (two sets)	All typical bacteria, some fungi and mycobacteria
Acid-fast smear and culture	*M. tuberculosis*, atypical mycobacteria, aerobic actinomycetes such as *Nocardia*
Fungal wet mount and culture	Molds (*Aspergillus* and mucormycosis), endemic mycotic agents (*Histoplasma*, *Blastomyces*, and *Coccidioides*)
Direct fluorescent antibody	*Pneumocystis*, *Legionella*, pertussis, and influenza and other respiratory viruses
Antigens	
–Bacterial	Pneumococcal urinary antigen, *Legionella* urinary antigen
–Viral	Influenza, SARS-CoV-2, RSV, parainfluenza, adenovirus, metapneumovirus
–Fungal	*Cryptococcus* serum antigen, *Blastomyces* urine antigen, *Histoplasma* urinary antigen, BDG, galactomannan
Molecular assays (NAAT)	
–Bacterial	*C. pneumoniae*, *M. pneumoniae*, *Legionella*, *Bordetella*, MRSA
–Viral	SARS-CoV-2, influenza, RSV, HSV, CMV, EBV, adenovirus
–Fungal	*Pneumocystis*, *Aspergillus*
–Mycobacteria	*M. tuberculosis,* nontuberculous mycobacteria
Serologic tests	
–Bacterial	*Mycoplasma*, *Chlamydophila*, Q fever, tularemia, anthrax
–Viral	Influenza, SARS-CoV-2, RSV, adenoviruses, parainfluenza
–Fungal	*Histoplasma*, *Coccidioides*, sporotrichosis, toxoplasmosis

BUN, blood urea nitrogen; HIV, human immunodeficiency virus; PA, posteroanterior; CT, computerized tomography; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; RSV, respiratory syncytial virus; BDG, 1,3-B-D-glucan; NAAT, nucleic acid amplification test; HSV, herpes simplex virus; CMV, cytomegalovirus; EBV, Epstein-Barr virus

GENERAL GUIDELINES IN EVALUATING PATIENTS WITH PNEUMONIA OR OTHER RESPIRATORY INFECTIONS

A patient with pulmonary infection often presents in an ambulatory setting. The clinician's goal is to distinguish infectious from noninfectious processes, to initiate appropriate antimicrobial therapy quickly, and to define the microbiology. Achieving these goals is crucial to reduce unnecessary exposures to antimicrobial agents and to provide optimal care.

Evaluation of the patient with possible pneumonia depends on a series of questions that provide clues that guide the workup and inform selection of empiric antimicrobial agents. Broadly, the evaluation includes assessing disease severity, identifying risk factors for drug-resistant organisms, and appreciating comorbidities or underlying immunosuppression that confer increased risk of poor outcome.

Frequently, pneumonia is divided into categories that *may* reflect the epidemiology of the process and possible causative organisms (Table 122-3): aspiration pneumonia, lung abscess (Chapter 127), community-acquired pneumonia (CAP) (Chapter 128), nosocomial pneumonia (Chapter 129), the immunocompromised host (Chapter 123), and atypical pneumonia. These categories have been employed historically when choosing an empiric antibiotic. In the United States, recent Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) Guidelines for Diagnosis and Treatment of CAP suggest that local epidemiologic data may be more useful than these categories when choosing antibiotics[9] (Chapter 125).

Initial antimicrobial therapies should be considered as therapeutic trials and given adequate time to demonstrate effectiveness; they should be subject to revision if ineffective. Subsequently obtained

TABLE 122-2 Infections Associated with Specific Immune Defects

Defect	Common Causes	Associated Infections
Granulocytopenia	Leukemia, cytotoxic chemotherapy, AIDS, drug toxicity, Felty syndrome	Enteric Gram-negative, *Pseudomonas*, *S. aureus*, *S. epidermidis*, streptococci, *Aspergillus*, *Candida*, and other fungi
Neutrophil chemotaxis	Diabetes, alcoholism, uremia, Hodgkin disease, trauma (burns), lazy leukocyte syndrome, CT disease	*S. aureus*, *Candida*, streptococci
Neutrophil killing	CGD, myeloperoxidase deficiency	*S. aureus*, *E. coli*, *Candida*, *Aspergillus*
T-cell defects	AIDS, congenital causes e.g., DiGeorge (22q11.2 deletion) syndrome, autosomal dominant hyperimmunoglobin E/Job syndrome, and IL-12 receptor deficiency, lymphoma, sarcoidosis, viral infection, CT disease, organ transplants, steroids	Intracellular bacteria (*Legionella*, *Listeria*, mycobacteria), HSV, VZV, CMV, EBV, parasites (*Strongyloides*, *Toxoplasma*), fungi (*P. jirovecii*, *Candida*, *Cryptococcus*)
B-cell defects	Congenital/acquired agammaglobulinemia, burns, enteropathies, splenic dysfunction, myeloma, ALL	*S. pneumoniae*, *H. influenzae*, *Salmonella* and *Campylobacter* spp., *Giardia lamblia*
Splenectomy	Surgery, sickle cell, cirrhosis	*S. pneumoniae*, *H. influenzae*, *Salmonella* spp., *Capnocytophaga*
Complement	Congenital/acquired defects	*S. aureus*, *Neisseria* spp., *H. influenzae*, *S. pneumoniae*
Anatomic	IV/Foley catheters, incisions, anastomotic leaks, mucosal ulceration, vascular insufficiency	Colonizing organisms, resistant nosocomial organisms

AIDS, acquired immunodeficiency syndrome; ALL, acute lymphocytic leukemia; CGD, chronic granulomatous disease; CT, connective tissue disease; IV, intravenous.

microbiologic data provide the basis for adjusting antimicrobial therapy.

The clinician should pose a series of questions when caring for a patient with suspected pneumonia.

Is the process life-threatening and does the patient have risk factors for severe disease? Related questions are as follows: What is the rate of progression of the process? Is it rapidly progressive or gradual? Does this patient meet criteria for severe pneumonia? Does the patient have chronic heart, lung, liver, or kidney disease? Does the patient have diabetes mellitus, alcoholism, malignancy, asplenia, or underlying immunodeficiency? Table 122-4 highlights key risk factors for severe disease. Could the process be underestimated based on the absence of normal inflammatory responses (see Section 3: Lung Immunology)?

Which pathogens are most likely to be causing disease? In the past, it was helpful to resort to clinical categories of infections: community-acquired, nosocomial (hospital-acquired, ventilator-associated, acquired in a healthcare facility), or pneumonia in the immunocompromised patient. Such groupings have been used to provide a guide to empiric therapy while evaluation is underway. Additionally, it is important to understand the incidence of HIV, pattern of respiratory viral infections, and prevalence of antimicrobial-resistant organisms (e.g., *Pseudomonas aeruginosa*,

TABLE 122-3 Categorization of Pneumonia by Clinical Setting

Community-acquired pneumonia
- Typical (i.e., classic) pneumonia
- Atypical pneumonia
- Aspiration pneumonia
- Pulmonary abscess and empyema

Nosocomial pneumonia
- Hospital-acquired pneumonia (HAP)
- Ventilator-associated pneumonia (VAP)

Pneumonia in immunocompromised hosts
- Immunoglobulin and complement deficiencies
- Granulocyte dysfunction or deficiency (cyclic neutropenia, chronic granulomatous disease, leukocyte adhesion defects, myeloperoxidase, or G6PD deficiency)
- Innate immune defects (NK deficiency, defects of interleukin/interferon-γ pathways, pattern recognition receptor pathway defects)
- Cellular and combined immune deficiencies
  - Neoplastic disease (notably hematopoietic malignancy and therapies)
  - Solid-organ and hematopoietic transplant recipients
  - Untreated HIV infection
  - Immune reconstitution syndromes (IRIS)
  - SCID and congenital deficiencies
  - Autoimmune and connective tissue disorders
  - Other immunocompromised patients

Cystic fibrosis and anatomic disorders (bronchopulmonary sequestration, tracheomalacia, or bronchomalacia)

TABLE 122-4 Underlying Conditions Contributing to Adverse Outcomes from Pneumonia

- Alcohol consumption
- Increasing age
- Leukopenia
- Congestive heart failure
- Coronary artery disease
- Diabetes mellitus
- Immune compromise
- Neurologic disease
- Active malignancy
- Clinical signs including dyspnea/tachypnea, hypothermia, chills, hypotension, confusion or altered mental status
- Laboratory tests: hyponatremia, hyperglycemia, azotemia, hypoalbuminemia, liver function test abnormalities
- Radiographic infiltrates and pleural effusions, postobstructive pneumonia
- Microbiology: Gram-negative bacilli, *S. aureus*, mixed flora (aspiration), bacteremia

Staphylococcus aureus) in the community or institution. If available, clinicians should consult their local antibiogram. Dual infections are common (e.g., viral plus bacterial), and initial therapy must be directed at both common bacterial and "atypical" pathogens (i.e., *Mycoplasma*, *Chlamydophila*, and *Legionella* species) (Chapter 125). Inquiry about exposures to specific pathogens also is important, as is asking about prior residence in, or travel to, a region endemic for TB (Chapter 130). Knowledge of whether the patient ever presented with methicillin-resistant *S. aureus* (MRSA) or pseudomonal infection is important,[10,11] as is a history of the patient being previously hospitalized or having received parenteral antibiotics.

What are the gross radiologic features of the pulmonary process? Broad categories include frank pneumonia, with or without sputum production; focal infiltrates; lung abscess; chronic cavitary lesions; bronchiectasis; and miliary lesions. These distinctions can be helpful in diagnosing pneumonia; however, findings may be nonspecific. As a corollary, since pulmonary infections are occasionally generated by the hematogenous, rather than bronchogenic, route, possible extrapulmonary processes in the pathogenesis of pulmonary infection must be considered.

For ambulatory patients, does the patient need to be admitted to the hospital for management? Important determinants include whether the patient has social support in the community, whether he or she can manage oral medications, other therapies, and follow-up visits from home. Also to be considered are the need for supplemental oxygen, assisted ventilation, surgery, blood products, monitoring, or isolation.

CLINICAL EVALUATION

Pulmonary infections are often included in the differential diagnosis for a patient presenting with respiratory complaints.[12] Symptoms commonly associated with pneumonia include fever, cough, sputum production, dyspnea, and chest pain. Gastrointestinal symptoms, including abdominal pain and diarrhea, may be noted as well. The clinician should assess for evidence of alternative diagnoses and conduct a thorough medical history. For example, orthopnea and lower extremity edema may suggest congestive heart failure, while a history of malignancy may predispose toward pulmonary embolism, and a recent bout of vomiting or loss of consciousness (e.g., due to a cerebrovascular accident, seizure, or administration of anesthesia) may implicate aspiration pneumonitis rather than true infection.

Epidemiologic history is crucial and should include recent travel, contacts, exposures, history of vaccination, prior infections, and hospitalizations (Table 122-5). Treatment should be reserved for those patients for whom there is a reasonable suspicion of infection or who are seriously ill. Even the most thorough history may not help distinguish an infectious versus noninfectious process; antibiotics are frequently initiated empirically while additional workup is underway. Consideration of the epidemiology is crucial when evaluating a patient with suspected pneumonia.

■ Epidemiology

Streptococcus pneumoniae has long been considered the most common bacterial etiology of CAP, accounting for about 80% of cases before the advent of antibiotics.[13] However, the frequency with which *S. pneumoniae* is identified as the etiologic agent of CAP has been gradually declining. In the United States, *S. pneumoniae* has been isolated in 5% to 15% of cases.[4,14] Globally, *S. pneumoniae* accounts for an estimated 27% of cases.[15] In addition to *S. pneumoniae*, *Haemophilus influenzae*, *Legionella pneumophila*, *Moraxella catarrhalis*, *Mycoplasma pneumoniae*, *Staphylococcus*

TABLE 122-5 Epidemiologic Exposures Associated with Pneumonia

Pathogen	Epidemiology
Anthrax	Bioterrorism, animals, hides, raw wool, goat hair
Brucella sp.	Domestic animals, unpasteurized dairy products, abattoir, veterinarian
Chlamydophila psittaci	Birds: parrots, budgerigars, cockatoos, pigeons, turkeys
Coxiella burnetii (Q fever)	Goats, sheep, cattle, domestic animals (feces, amnionic fluid, placenta, milk)
Legionella	Contaminated aerosols, pooled water
Leptospirosis	Rodents, animals, water contaminated by animal urine
Melioidosis	West Indies, Australia, Southeast Asia, South Central America
Pasteurella multocida	Dogs, cats
Neisseria meningitidis *Mycoplasma pneumoniae*	Close living quarters such as university dormitories
Plague *(Yersinia pestis)*	Bioterrorism, squirrels, chipmunks, rabbits, prairie dogs, rats
Rhodococcus	Horses, soil, farms
Tularemia	Rabbits, squirrels, foxes, horses, soil, farms, bites from infected flies or ticks
Hantavirus	Rodent droppings/urine (predominantly in Southwestern United States, virtually all states)
SARS, avian influenza	Southern China
Middle Eastern respiratory syndrome (MERS): Coronavirus	Endemic regions (Saudi Arabia)
Coccidioidomycosis	Southwest United States
*Cryptococcus neoformans (*including var. grubii*)*	Birds (pigeons), caves, bats
Cryptococcus gattii	Eucalyptus trees
Histoplasmosis	Bird/bat droppings, endemic in central and eastern United States and Central America; also found in parts of South America, Africa, Asia, and Australia regions
Paracoccidioides	South America (Brazil)

aureus, and gram-negative bacilli account for a substantial portion of other bacterial pneumonias.

In recent studies, *S. pneumoniae* has been replaced as the most common cause of CAP by viruses and a broad array of bacteria. The Etiology of Pneumonia in the Community (EPIC) study was a large epidemiologic study undertaken by the U.S. Centers for Disease Control and Prevention to detect presence of pathogens in patients hospitalized with pneumonia in the United States. A virus was isolated in 27% of adults with radiographically confirmed cases of pneumonia. Bacterial pathogens were identified in 11% of patients, and *S. pneumoniae* accounted for only 5% of cases.[4] Similar findings were reported from a study identifying respiratory pathogens in more than 323 patients from the United Kingdom. This analysis identified viruses in 30% of patients. *S. pneumoniae* was isolated in only 5% of participants.[16] In both studies, rhinovirus, influenza A/B, parainfluenza virus, human metapneumovirus, respiratory syncytial virus (RSV), adenovirus, and endemic coronaviruses were the most commonly identified viral pathogens.[4,16] The decreasing incidence of *S. pneumoniae* likely reflects identification, using advanced techniques, of other organisms not identified in earlier studies, a reduction in the detection of the *S. pneumoniae* due to successful empiric therapy, and shifts in "community flora" through use of antimicrobial therapies. Reductions in smoking (a known risk factor for pneumococcal pneumonia), herd immunity through mass immunization of children with the pneumococcal conjugate vaccine, and recommendations for vaccination of adults at older age also are thought to play key roles in this epidemiologic shift.

Specific pathogens are associated with certain special populations or predisposing conditions. Hospitalized patients are at risk of *S. aureus*, *Klebsiella*, *Enterobacter*, and *E. coli*. *Acinetobacter*, *Stenotrophomonas*, and *Pseudomonas* are found in highest frequency among patients who are mechanically ventilated.[17] Age is an important epidemiologic factor. Gram-negative bacterial pneumonias are seen more frequently in older patients, whereas younger patients are more likely to present with pneumonia due to *M. pneumoniae*.[12] Nontypeable *H. influenzae* is seen in older adults, particularly those with underlying structural lung disease, such as chronic obstructive pulmonary disease (COPD) and cystic fibrosis. Pneumonia due to *Pseudomonas aeruginosa*, *Stenotrophomonas* spp., *Burkholderia* spp., *Achromobacter xylosoxidans*, and atypical mycobacteria are common among patients with cystic fibrosis (Chapter 123). HIV has been shown to be a risk factor for bacterial pneumonia. *S. aureus*, *Legionella*, *S. pneumoniae*, and *Pseudomonas* have been shown to be more prevalent in patients with HIV.[18] Additionally, *S. pneumoniae* is commonly seen at the extremes of age, in patients with alcohol use disorder, or in those with asplenia, multiple myeloma, or sickle cell disease.

Details of the clinical history also may provide a clue as to the underlying pathogen. Pneumococcal pneumonia may be associated with a single severe rigor with fever and has been associated with symptomatic outbreak of herpes labialis. The abrupt onset of illness with recurrent (over several days) shaking chills, particularly if associated with mild diarrhea for 1 or 2 days, may suggest Legionnaires' disease. Gastrointestinal symptoms and confusion may be seen with any infection, but they are particularly notable in pneumococcal pneumonia and Legionnaires' disease.

The pace and timing of the patient's illness is important to consider. A patient with delayed presentation and underlying risk factors for aspiration or esophageal fistula should prompt consideration of anaerobic organisms, including *Bacteroides* spp., *Fusobacterium* spp., *Peptostreptococcus* spp., *Peptococcus* spp., and *Prevotella* spp. (Chapter 127). Prior mild respiratory illness ("the flu"), followed by improvement and then rapid deterioration, is suggestive of bacterial superinfection of viral pneumonitis and is consistent with *S. aureus* or other bacterial infection, especially in the patient with known prior respiratory colonization or with positive nasal swab screening.

■ Physical Examination

Physical examination may provide very important clues regarding the etiology of pulmonary infection. Skin lesions may suggest underlying pathogens, such as ecthyma gangrenosum, which is associated with Gram-negative infections (in particular, *Pseudomonas*). Erythema multiforme and bullous myringitis are associated with *M. pneumoniae* infection. Evidence of injection drug use, such as cutaneous abscesses, or evidence of needle injury ("track marks") may suggest bacteremic pneumonia. Additionally, Janeway lesions, Osler nodes, and splinter hemorrhages are signs that suggest endocarditis.

Endovascular infection may be complicated by septic pulmonary emboli if the disease is based in the right side of the heart or venous circulation, or if there is a left-to-right intracardiac shunt. Retinal examination may support bacteremia as the underlying pathogenesis if there is evidence of endophthalmitis.

Periodontal disease or absent gag reflexes are risk factors for aspiration pneumonia. Chest splinting may impair clearance of pulmonary secretions and increase risk of infection. Neurologic symptoms can be easily overlooked, but they may provide valuable clues. The elderly patient with pneumonia often presents with a globally depressed mental status, while an immunocompromised host may have focal neurologic deficits consistent with embolic or invasive disease (Chapter 123).

Dullness to percussion, bronchial breath sounds, and egophony ("E to A changes") are suggestive of pulmonary consolidation. Patients infected with *Pneumocystis jirovecii*, *Mycoplasma*, or viruses may have a normal chest examination despite abnormal chest radiographs (or vice versa) and marked hypoxemia.

■ Routine Laboratory Tests

Many systemic processes are reflected in abnormalities of blood counts, urinalysis, or routine blood chemistries. Most patients with bacterial pneumonia have an elevated white blood cell count and increased neutrophils. Viral pneumonia may depress the white blood cell count, particularly the number of lymphocytes. Mixed hematologic pictures are common. Hyponatremia has been associated with Legionnaires' disease; however, any pulmonary infection can cause SIADH leading to hyponatremia.[19] Mild liver function abnormalities may suggest Q fever, tularemia, miliary tuberculosis, or Legionnaires' disease, but are commonly seen with systemic infection. The presence of pigmented casts in the urine and markedly elevated serum levels of creatine phosphokinase may focus attention on possible influenza virus pneumonia, Legionnaires' disease, or pulmonary infiltrates associated with injection drug use.

■ Biomarkers of Infection

Because of the inflammatory milieu of infection, interest has arisen in assays measuring blood levels of cytokines to predict severity of disease and to aid in diagnosing pneumonia.

Procalcitonin has received much attention as a biomarker. Procalcitonin is released into the blood when systemic inflammation is mediated by a bacterial infection. This phenomenon has been shown to be triggered by bacterial toxins, as well as cytokines, including TNF-α, IL-1β, and IL-6.[20] Procalcitonin release into the bloodstream has not been shown to occur in the context of viral infection. Thus, procalcitonin shows promise as a biomarker for early detection of bacterial infections and for distinguishing these infections from other infectious or inflammatory disorders.

Currently, clinical understanding of optimal use of procalcitonin is evolving. Given its hypothetical utility to differentiate between viral and bacterial processes, enthusiasm has grown about using procalcitonin in the decision process of when to initiate antibiotics. Some institutions have begun to use a procalcitonin level <0.25 mg/mL as a threshold for discontinuing antibiotics in clinically stable patients in whom an alternative and more likely diagnosis has been made, or in those with probable viral infection (based on testing). However, it should be noted that the thresholds for discontinuing antibiotics have not been rigorously studied, and clinically useful ways to deploy the test continue to evolve. Furthermore, pneumonia secondary to infection with *Mycoplasma* spp. and *Chlamydia* spp. has not been shown to be associated with increased procalcitonin levels. Lastly, procalcitonin is only useful when laboratory infrastructure allows for a quick turnaround time.[21] Current U.S. Guidelines from the IDSA/ATS make a strong recommendation against withholding antibiotics in patients with clinically suspected and radiographically proven pneumonia, regardless of the procalcitonin level.[9] In short, procalcitonin should supplement, rather than supplant, clinical judgment.

■ Management

In practice, initial therapy in community-acquired pneumonia is empiric and based primarily on available clinical clues. The selection of drug(s) for empiric therapy depends on the clinical setting and the gravity of the pulmonary process. Selection of specific antimicrobial agents is considered in detail elsewhere (Chapter 125).

In addition to the choice regarding empiric antibiotics, another key decision is whether the patient with suspected pneumonia merits hospitalization. In practice, this is often a function of a judgment as to whether appropriate therapy is available in the community, including adequate social support to care for the patient's needs (e.g., medications, food, comfort), and the ability to bring the patient back for further care, if indicated. Multiple semiquantitative methods have been developed to assist in this process.

■ Pneumonia Severity Stratification

Pneumonia severity stratification tools have been developed to aid to estimate the predicted mortality of a patient presenting suspected pneumonia. There have been a number of scores to assist clinicians in making this decision using predicted mortality. One of the earliest is the PORT (Pneumonia Patient Outcomes Research Team) score, also known as the Pneumonia Severity Index (PSI). This index stratifies patients according to 20 variables organized by age, presence of medical comorbidities, vital signs, specific laboratory results, and imaging findings. Using a point system, patients are assigned to one of five prognostic categories, with group I associated with the lowest and group V the highest predicted mortality. Groups I and II are often managed as outpatients. Group III is considered "borderline." Lastly, groups IV and V are admitted to the hospital or ICU. The PSI has been widely validated and endorsed; however, it is limited by its complexity and number of inputs.[22,23]

In response to the complexity of the PORT, new scorings systems have been developed that are simpler and utilize more accessible parameters. These include the CURB score, the CURB-65 score, and the CRB-65 score. The CURB score uses just four variables: **C**onfusion of new onset, **U**rea >7 mmol/L (19 mg/dL), **R**espiratory rate ≥30 breaths per minute, and **B**lood pressure <90 mm Hg systolic or <60 mm Hg diastolic.[24] In calculating the score, one point is assigned per variable present, and the presence of two or more points signifies increased risk of mortality.[25] The CURB-65 was later developed and added age >65 to the scoring system, defining severe pneumonia and increased mortality risk as presence of three or more parameters.[26] CRB-65 omits the blood urea nitrogen as a factor, thereby obviating the need for a blood draw, and is sometimes used in the outpatient setting.[27]

More recently, scoring indices have been developed to identify cases of severe pneumonia and patients who may require transfer to the intensive care unit once admitted to the hospital. These include the severe community-acquired pneumonia (S-CAP) score, the SMART-COP, and the Risk of Early Admission to the Intensive Care Unit (REA-ICU) index.[28–30] Additionally, the IDSA/ATS has developed criteria to define severe pneumonia and to guide the decision to admit to the ICU. The IDSA/ATS guidelines have been independently validated and include major and minor variables to identify the sickest patients who may ultimately require intensive care–level support. Major criteria include septic shock requiring vasopressors and respiratory failure requiring mechanical ventilation; the presence of one major criterion dictates transfer to an ICU (Table 122-6).[31] There are limited data to suggest that any of these indices is superior in predicting the need for ICU level care.[32] In conclusion, although scoring systems can bolster clinical decision-making, they should not supersede clinical judgment.

TABLE 122-6 Definition of Severe CAP

Requires 1 major criterion or ≥3 minor criteria
Major Criteria
Hypotension from sepsis requiring pressor support
Respiratory failure requiring mechanical ventilation
Minor Criteria
Tachypnea (respiratory rate ≥30 breaths/min)
$\text{Pa}_{\text{O}_2}/\text{Fi}_{\text{O}_2} \leq 250$
Multilobar infiltrates
Altered mental tatus
Leukopenia (white blood cell count <4000 cells/μL) not otherwise explained
Thrombocytopenia (platelet count <100,000/μL)
Hypothermia (temperature <36°C)
Hypotension requiring intravenous fluid resuscitation

RADIOGRAPHIC FEATURES OF PNEUMONIA

In general, identification of infiltrates on chest radiograph is considered the gold standard for diagnosing pneumonia in a patient presenting with clinical signs and symptoms of a pulmonary infection (productive cough, pleuritic chest pain, dyspnea, and fever), as described earlier.[33] According to consensus guidelines, a chest radiograph should be obtained in all patients presenting with suspected pneumonia.[31] However, no radiologic pattern provides a specific etiologic diagnosis (Chapter 28). The radiographic pattern, combined with clinical and epidemiologic information, *may* allow narrowing of the diagnostic considerations while microbiologic data are assembled. Additionally, the severity of radiographic findings or pattern of findings may identify patients at risk of decompensation who require closer monitoring or inpatient admission (Table 122-7).

Interpretation of chest radiographs should be undertaken within the clinical context of the patient's presentation. If a patient presents with a syndrome highly suggestive of CAP, a clear radiograph may represent a false-negative result. In this case, it is reasonable to initiate empiric treatment (Chapter 125). Factors associated with a false-negative radiograph include presentation early in the course of the illness, neutropenia, hypovolemia, or *Pneumocystis jirovecii* pneumonia. In these instances, repeating the chest radiograph is reasonable; computed tomography (CT) of the chest may provide increased sensitivity.

Several radiographic patterns may be helpful to note. These include (1) lobar consolidation, (2) bronchopneumonia, (3) interstitial pneumonia, (4) nodular or cavitating lesions, and (5) a miliary or micronodular pattern. The chest imaging of a particular patient may not fit neatly into one or another of these categories, and multiple patterns may suggest different etiologies or progression of a disease process. The patterns are generally best defined by

TABLE 122-7 Radiographic Features and Differential Diagnosis of Pneumonia in the Immunocompetent Host

Consolidation/focal opacity	*Streptococcus pneumoniae*, *Mycoplasma pneumoniae*, *Haemophilus influenzae*, *Chlamydophila pneumoniae*, *Legionella* species, *Staphylococcus aureus*, *Mycobacterium tuberculosis* and "atypical" mycobacteria (*M. avium* complex)
Cavitation	*S. aureus*, anaerobic bacteria, *M. tuberculosis*, Gram-negative aerobic bacteria, *Aspergillus* species, geographic/endemic fungi (*Histoplasma capsulatum*, *Coccidioides immitis*, *Blastomyces dermatitidis)*
Interstitial infiltrates	Viruses, *M. pneumoniae*, *M. tuberculosis*, geographic/endemic fungi, *Chlamydophila psittaci*, drug-induced
Miliary	*Mycobacterium tuberculosis*, geographic/endemic fungi, viruses, *M. pneumoniae*
Lymphadenopathy	*M. tuberculosis*, viral (EBV, CMV, rubella), geographic/endemic fungi, *Chlamydophila psittaci*, cat-scratch disease

CT scanning, which may also detect patterns within a pulmonary process, including lung necrosis; bronchial obstruction (e.g., due to hilar lymphadenopathy or endobronchial tumor); underlying parenchymal disease that accounts for a pleural effusion, empyema, or loculated fluid collection; bronchiectasis; or fungus balls within cavitary lesions.[34] Subtle changes, including interstitial patterns or infections in immunocompromised hosts (e.g., *P. jirovecii*), are often better assessed using CT scanning (Chapter 123). CT scanning can also assist in determining the best invasive diagnostic approach (e.g., needle aspiration, bronchoalveolar lavage, or open lung biopsy).

■ Lobar Pneumonia

The radiographic infiltrate of lobar pneumonia occurs when organisms induce inflammatory edema in alveoli. When the consolidation involves an entire lobe, the result is classic *lobar pneumonia*. An air bronchogram, or outline of an airway made visible by filling of the surrounding alveoli by fluid or inflammatory exudates, is characteristic of lobar pneumonia. Loss of volume is absent or minimal during the acute stage of consolidation, but some atelectasis may develop due to obstruction of bronchi by exudate. It is generally thought that lobar pneumonia indicates a bacterial process, whereas interstitial infiltrates are more likely to be related to viruses and pneumocystis. However, studies have highlighted significant interobserver variation among radiologists' interpretations of chest radiographs in differentiating bacterial and nonbacterial pneumonia based on radiographic features.[35,36]

A large lobar pneumonia with associated pleural effusion is suggestive of a bacterial process. Most cases of lobar pneumonia are due to *S. pneumoniae*; however, this organism can also present with a variety of radiographic patterns. *K. pneumoniae* is another common cause of CAP, which, like pneumococcal pneumonia, shows homogeneous parenchymal consolidation containing air bronchograms (Fig. 122-1). Although *K. pneumoniae* classically affects the right upper lobe and produces a dense, homogeneous lobar consolidation with bulging of the fissure, these features are not pathognomonic and cannot be relied on for diagnosis without supportive bacteriologic data. The propensity for *K. pneumoniae* to produce tissue destruction and abscess formation may result in a shrunken, rather than an expanded, lobe. Pneumococcal pneumonia may also cause bulging of the fissure, albeit less commonly and less prominently than in *K. pneumoniae*. Extensive alveolar consolidation may occur in a variety of other bacterial causes of pneumonia, including those due to mixed anaerobes of aspiration pneumonia and a variety of Gram-negative bacilli implicated in nosocomial infections.

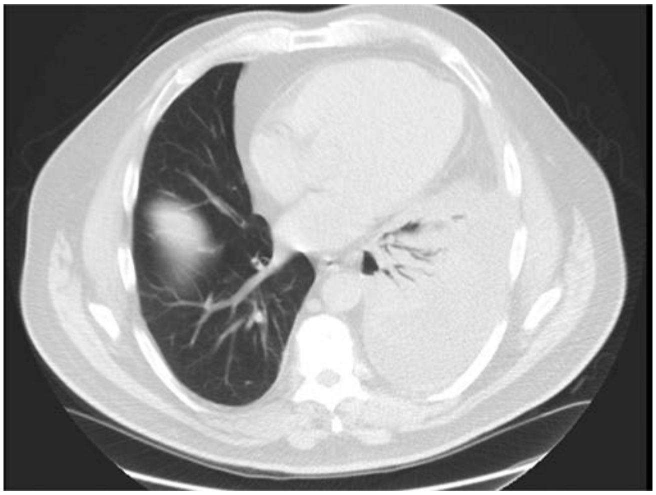


Figure 122-1 CT scan of a patient with CAP, consistent with left-sided lobar pneumonia. Note the evident air bronchograms signifying dense filling of alveoli. *(Reproduced with permission from Dr. M. Kavanaugh.)*

Occasionally, airspace consolidation appears spherical, with rounded edges, and is termed *spherical pneumonia*. Notably, the finding occurs in children. The underlying pathogenesis leading to spherical infiltrates is thought to be mediated by passage of exudate into adjacent alveoli via the pores of Kohn. The most frequent organisms implicated include *S. pneumoniae* or *H. influenzae*. The finding has also been reported with Q fever (*C. burnetii*).

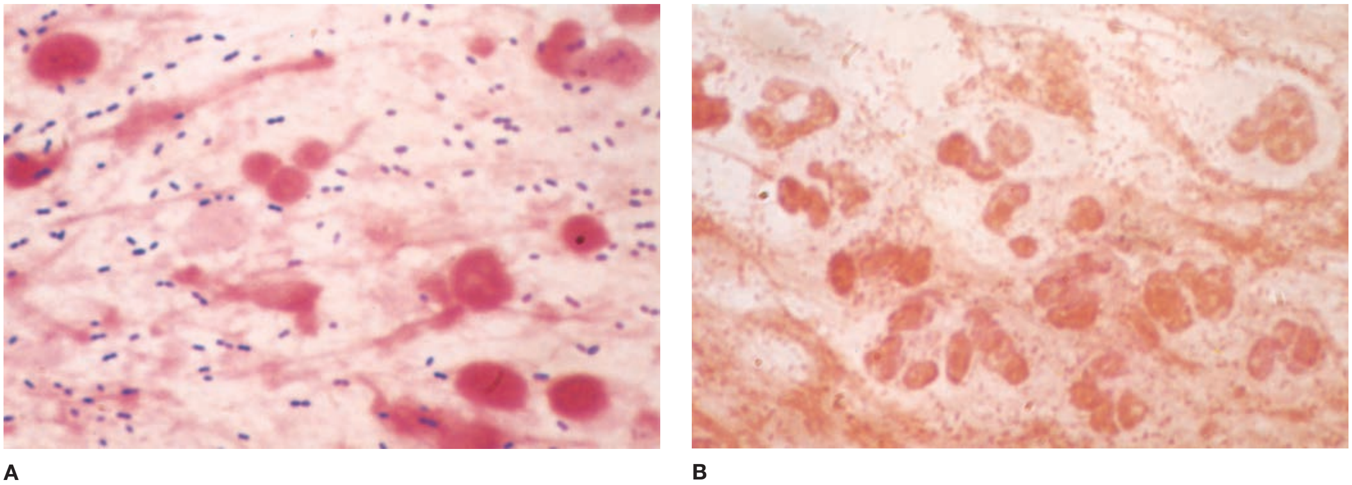
■ Bronchopneumonia

In bronchopneumonia, the focus of infection and the inflammatory response result in epithelial ulceration of the walls of the bronchi and fibrinopurulent exudate filling surrounding peribronchiolar alveoli. This typically occurs in a segmental, patchy, multifocal distribution. Segmental involvement may become confluent, producing a more homogeneous pattern. Bronchopneumonic patterns are commonly observed in pulmonary infections due to *S. aureus* or nonencapsulated *H. influenzae*. Figure 122-2 *shows a Gram stain of common organisms that cause a bronchopneumonic pattern radiographically.*

A bronchopneumonic, rather than lobar, pattern of consolidation is commonly observed when CAP follows viral infection or pneumonia occurs in the setting of underlying bronchiectasis or chronic bronchitis. In the presence of underlying emphysema, the radiographic pattern of pneumococcal pneumonia may also be altered from its usual homogeneous pattern to one characterized by multiple radiolucencies (representing nonconsolidated emphysematous areas) that may be misinterpreted for abscesses.

Segmental bronchopneumonia is the typical radiographic pattern seen with *Chlamydophila pneumoniae* (Taiwan Acute Respiratory Agent [TWAR]), *M. pneumoniae*, and many viral pneumonias. Any of the bacterial species that cause nosocomial pneumonia may produce a radiographic pattern of bronchopneumonic consolidation.

Noninfectious etiologies of bronchopneumonia include aspiration of gastric contents, bronchioloalveolar cell carcinoma, granulomatous disease in pneumoconiosis, sarcoidosis, hypersensitivity



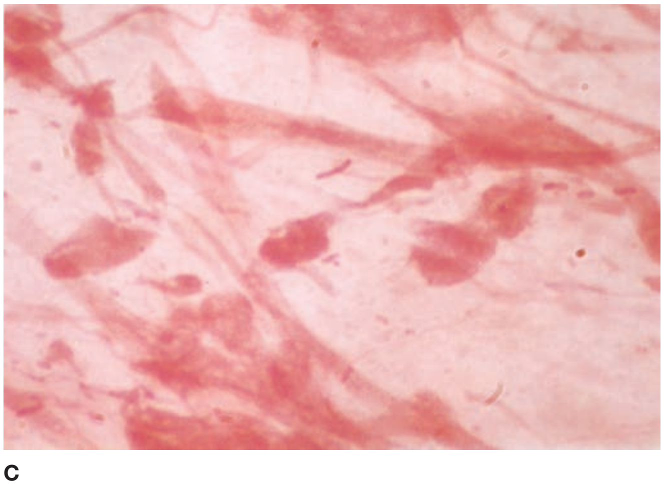


Figure 122-2 **A.** Gram-stained smear of sputum from patient with pneumococcal lobar pneumonia ×1000. In this field there are numerous Gram-positive lancet-shaped diplococci and polymorphonuclear leukocytes. **B.** Gram-stained smear of sputum from patient with bronchopneumonia superimposed on chronic bronchitis. The field (×1000) is teeming with Gram-negative coccobacilli. Many polymorphonuclear leukocytes are present. *H. influenzae* was isolated from sputum as predominant organism. **C.** Gram-stained smear of sputum from patient with lobar pneumonia due to *K. pneumoniae*. In this field (×1000) there are moderate numbers of polymorphonuclear leukocytes and large, thick, Gram-negative bacilli. *(Reproduced with permission from H. Provine.)*

pneumonitis, cryptogenic organizing pneumonia (COP), autoimmune diseases, and bronchiolitis obliterans.

■ Interstitial Pneumonia

A reticular or reticulonodular pattern of infiltration is the radiographic representation of interstitial inflammation—that is, a peribronchovascular infiltrate. In otherwise healthy persons, *M. pneumoniae* is high on the list of community-acquired causes of a radiographic pattern of interstitial pneumonia. In some instances, interstitial infiltration progresses to patchy consolidation of airspaces, most often in the lower lobes. Pneumonia due to respiratory viruses sometimes has an interstitial pattern that progresses to patchy segmental consolidation or to diffuse airspace disease that resembles pulmonary edema. This can appear as ground-glass opacities on CT (Fig. 122-3). *Legionella*,

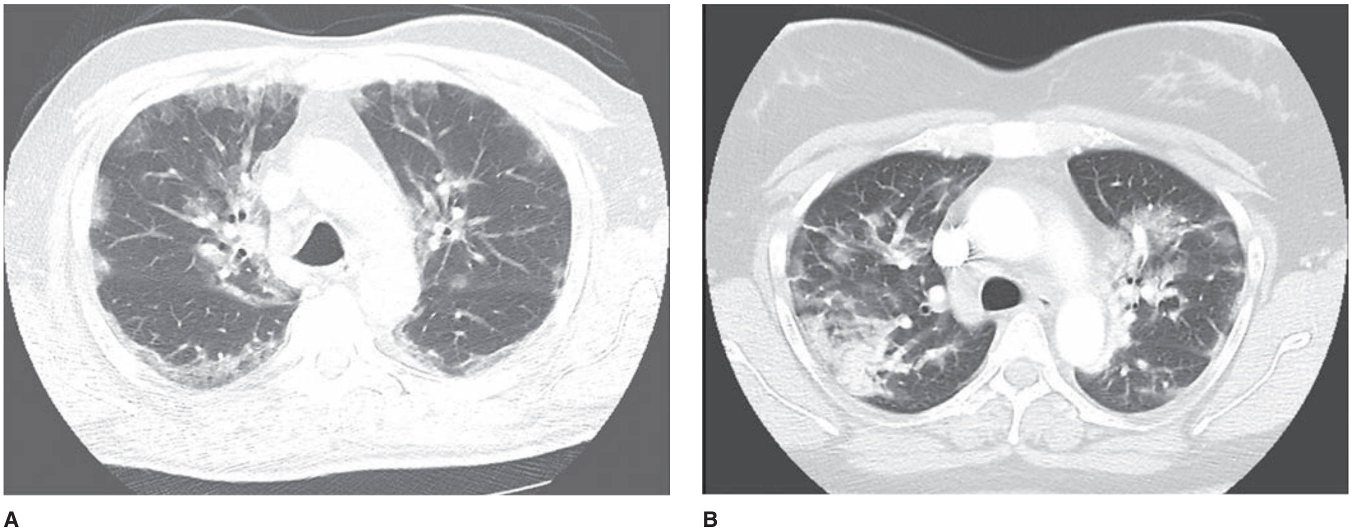


Figure 122-3 Computed tomography of viral pneumonia. **A.** Peripheral ground-glass opacities in a patient with influenza. **B.** Ground-glass opacities and consolidation in a patient with COVID-19. *(Reproduced with permission from Dr. M. Kavanaugh.)*

Pneumocystis, and primary viral pneumonias may manifest as bilateral, diffuse disease. A variety of noninfectious causes of interstitial lung disease (e.g., hypersensitivity lung disease, collagen vascular disease, and sarcoidosis) may also produce a reticular pattern on the chest radiograph (Fig. 122-4).

■ Nodular Infiltrates, Cavitation, and Pneumatoceles

In the current discussion, nodular infiltrates are considered as well-defined, large (>1 cm on the chest radiograph), round, focal lesions. A nodular infiltrate may represent a small abscess secondary to aspiration (without air–fluid levels), a fungal or tuberculous granuloma, or a lesion of pulmonary nocardiosis. Multiple nodular infiltrates may also represent necrotic lesions secondary to septic vasculitis produced by staphylococcal or pseudomonal bacteremia, or the consequences of fungemic spread of *Candida* from an infected intravascular catheter. Infected nodular pulmonary lesions are sometimes caused by septic pulmonary infarcts produced by infected emboli that originate from right-sided bacterial endocarditis, septic thrombophlebitis of pelvic veins, or septic jugular vein phlebitis. Cavitation may be caused by ongoing necrosis of nodules associated with *S. pneumoniae*, *K. pneumoniae*, or *P. aeruginosa* (Fig. 122-5).

S. aureus may cause necrosis of the lung, bronchopleural fistulae, and empyema. Macro- and micro-abscess formation may occur rapidly in cases of *S. aureus* pulmonary infection. Panton-Valentine

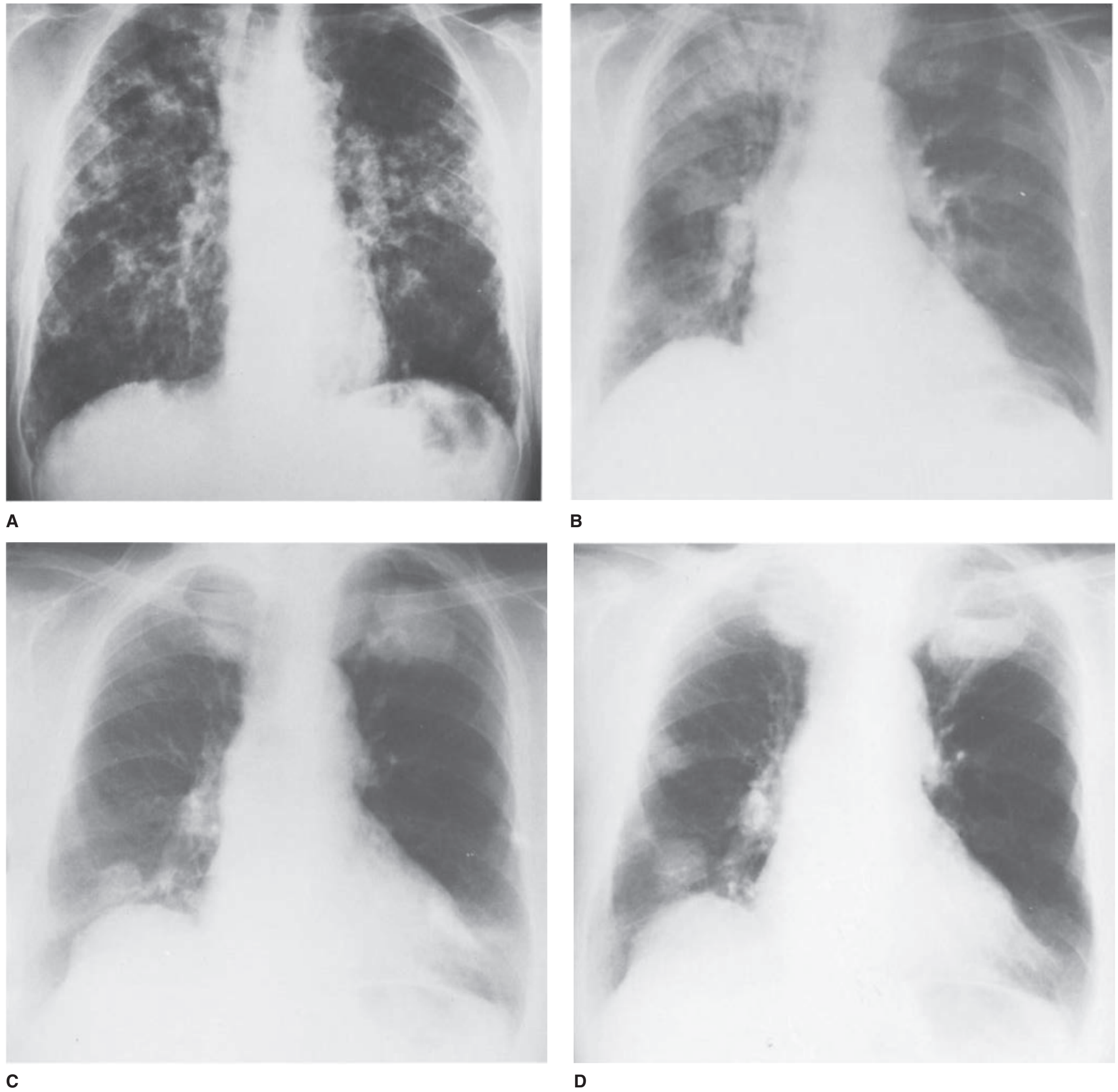


Figure 122-4 Granulomatosis with polyangiitis. **A.** Onset with chills and fever in a previously healthy 64-year-old man. Lung biopsy was interpreted as granulomatosis with polyangiitis. Partial clearing in response to combined chemotherapy (cyclophosphamide and prednisone). **B.** Onset with malaise, headaches, and fever in a previously healthy 62-year-old woman. Bilateral maxillary sinusitis. Widespread nodular pulmonary infiltrates are most marked on the right. **C.** Same patient as **B** after 3 years of intermittent combined chemotherapy. Bilateral large masses. **D.** Same patient as **C**, 2 months later. Necrosis within mass in left upper lobe has produced a fluid level.

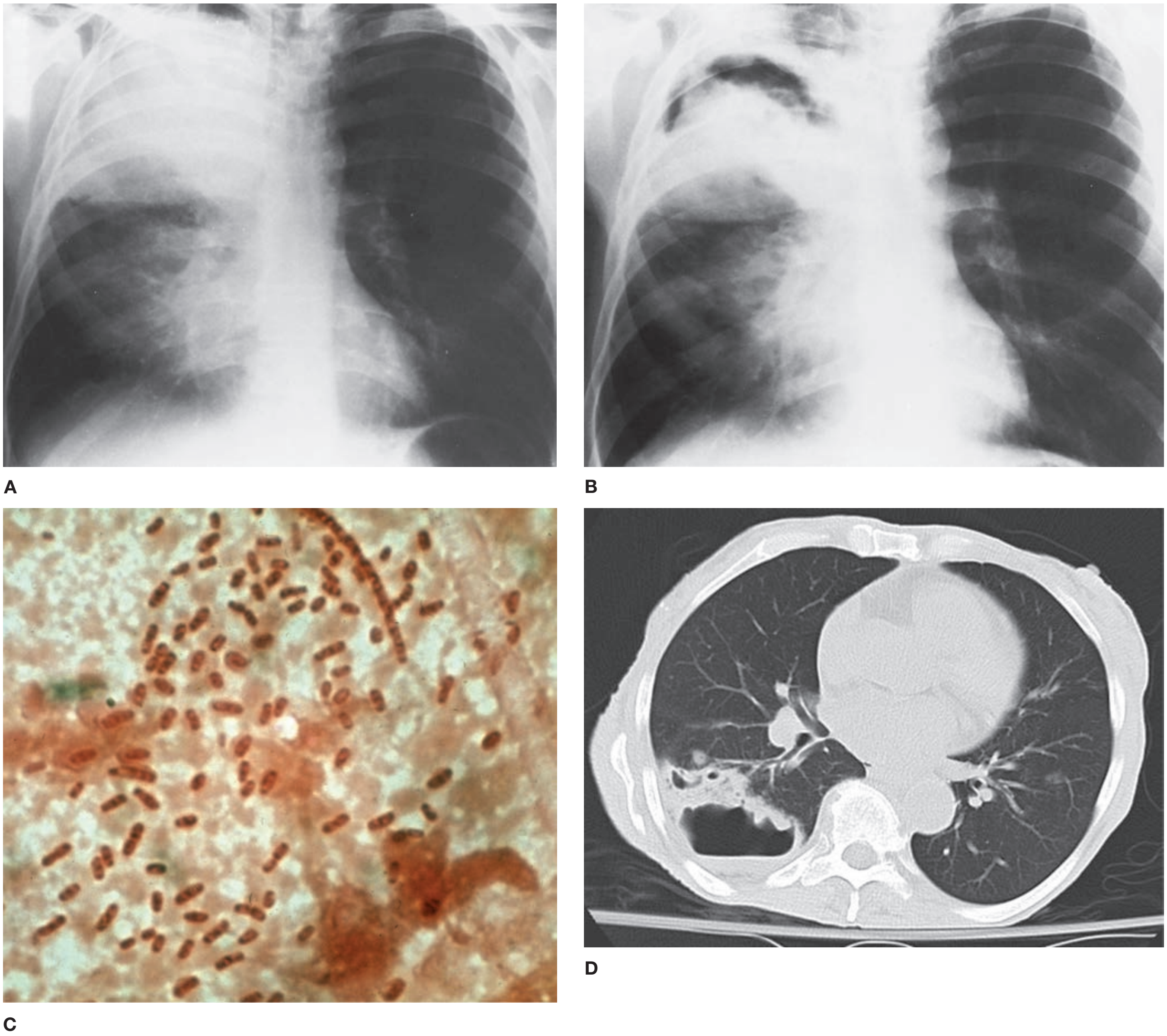


Figure 122-5 **A.** Dense lobar consolidation involving right upper lobe and right middle lobe in an alcoholic patient with *Klebsiella pneumoniae* pneumonia. The minor fissure is bulging downward. **B.** Same patient 7 days later. Despite antibiotic therapy, *K. pneumoniae* pneumonia progressed to become a necrotic process with formation of multiple abscesses. **C.** Sputum Gram stain from patient with *K. pneumoniae* infection reveals Gram-negative rod forms with trace of a surrounding capsule. **D.** A different patient with necrotizing *K. pneumoniae* pneumonia; note the cavitary lesion with air-fluid level. *(**C.** Reproduced with permission from Dr. R. Greene; **D.** Reproduced with permission from Dr. M. Kavanaugh.)*

leucocidin produced by *S. aureus* is associated with necrotizing pneumonia and multilobar involvement. Pneumatoceles occur early in the course of about half of children with *S. aureus* pneumonia. These cystic spaces are believed to be the consequence of a check-valve opening between a peribronchial abscess and an adjacent bronchus. Figure 122-6 illustrates a prominent pneumatocele. Pneumatoceles may also be seen with other causes of pneumonia, including *K. pneumoniae*, *S. pneumoniae*, *H. influenzae*, and *P. jirovecii*.

Aspiration pneumonia may additionally cause cavitation, necrotizing pneumonia, and empyema (Chapter 127). This commonly involves the basilar or superior segment of the lower lobes or the posterior segments of the upper lobes. This predilection depends on the patient's position at the time of aspiration; the lower lobes are involved more frequently when the patient is upright, and the posterior upper lobes are more commonly involved if aspiration occurred while supine.

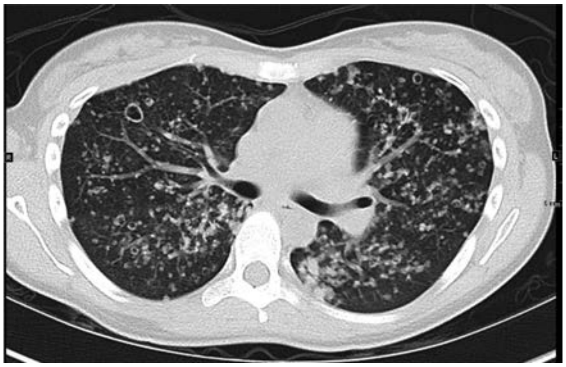


Figure 122-6 Thin-walled, cystic pneumatoceles characteristic of *Pneumocystis jirovecii* pneumonia. *(Reproduced with permission from Dr. M. Kavanaugh.)*

When chronic, cavitary pulmonary disease is most often caused by tuberculosis (Chapter 130). Tuberculosis commonly begins with a focus of pneumonitis, usually in the subapical posterior portion of an upper lobe. This patch of pneumonitis occurs at a latent site of earlier metastatic infection (called a *Simon focus*), produced by lymphohematogenous or hematogenous spread from primary pulmonary tuberculous lesions. Progressive caseation necrosis at the site, followed by drainage of caseous material through the bronchial tree, produces a cavity, as seen in Fig. 122-7. The cavity is encased in a rigid wall of fibrous tissue.

In addition to pyogenic lung abscess and pulmonary tuberculosis, other pulmonary infections may produce chronic cavities. These include infections with *Nocardia*, *Rhodococcus equi*, actinomycosis, and chronic primary pulmonary mycoses (particularly histoplasmosis, occasionally coccidioidomycosis, and, uncommonly, blastomycosis). Sporotrichosis may affect the lung and produce thin-walled cavities. Parasitic infestation of the lung (paragonimiasis, echinococcosis) also may form cavities.

Pulmonary cavities may also occur in noninfectious disorders (e.g., granulomatosis with polyangiitis, lymphoma or bronchogenic carcinoma, bland pulmonary infarcts, and intrapulmonary nodules of rheumatoid lung disease). Pneumatoceles may also be caused by noninfectious processes, including hydrocarbon ingestion, trauma, and positive-pressure ventilation. Cavitary and cystic lesions occur in chronic pulmonary sarcoidosis and in the markedly dilated bronchi of saccular bronchiectasis. Cavities may become superinfected with *fungus balls*. These represent tangled masses of fungal hyphae and debris lying freely within pulmonary cavities. Typically, they represent noninvasive saprophytic growth in the immunologically normal host. The most common organism is *Aspergillus* (usually *A. fumigatus*), and the fungus ball is called an aspergilloma. Invasion of the cavity wall may occur with immune compromise; hemoptysis originating from the cavity wall is common and may be severe. This hemorrhage leads to the classic "halo sign" on CT (Fig. 122-8).

■ Miliary and Micronodular Pulmonary Disease

Disseminated miliary lesions of an infectious nature suggest tuberculosis, nontuberculous mycobacteria, or endemic fungi (e.g., histoplasmosis or blastomycosis) in either the normal or immunosuppressed host. Hematogenous dissemination of tuberculosis may follow initial infection in children or adults. It may also result from breakdown of formerly quiescent sites of pulmonary or extrapulmonary infection. Clinically unexplained fever may be accompanied by small lesions seen on the chest radiograph (so-called "millet seed" pattern); histologically, these lesions are foci of granulomatous reaction and appear as areas of fine nodularity (Fig. 122-9). Similar radiographic lesions occur in the course of hematogenously disseminated bacterial and

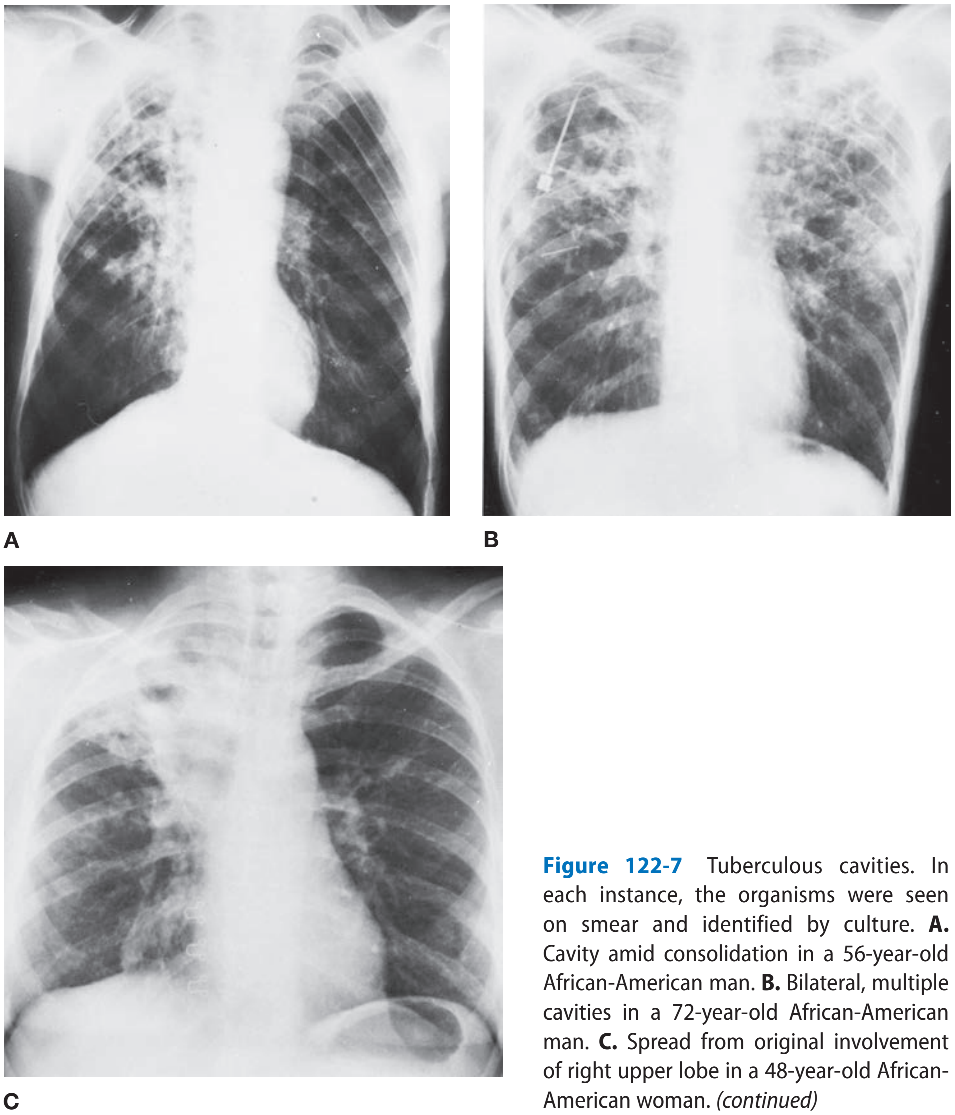
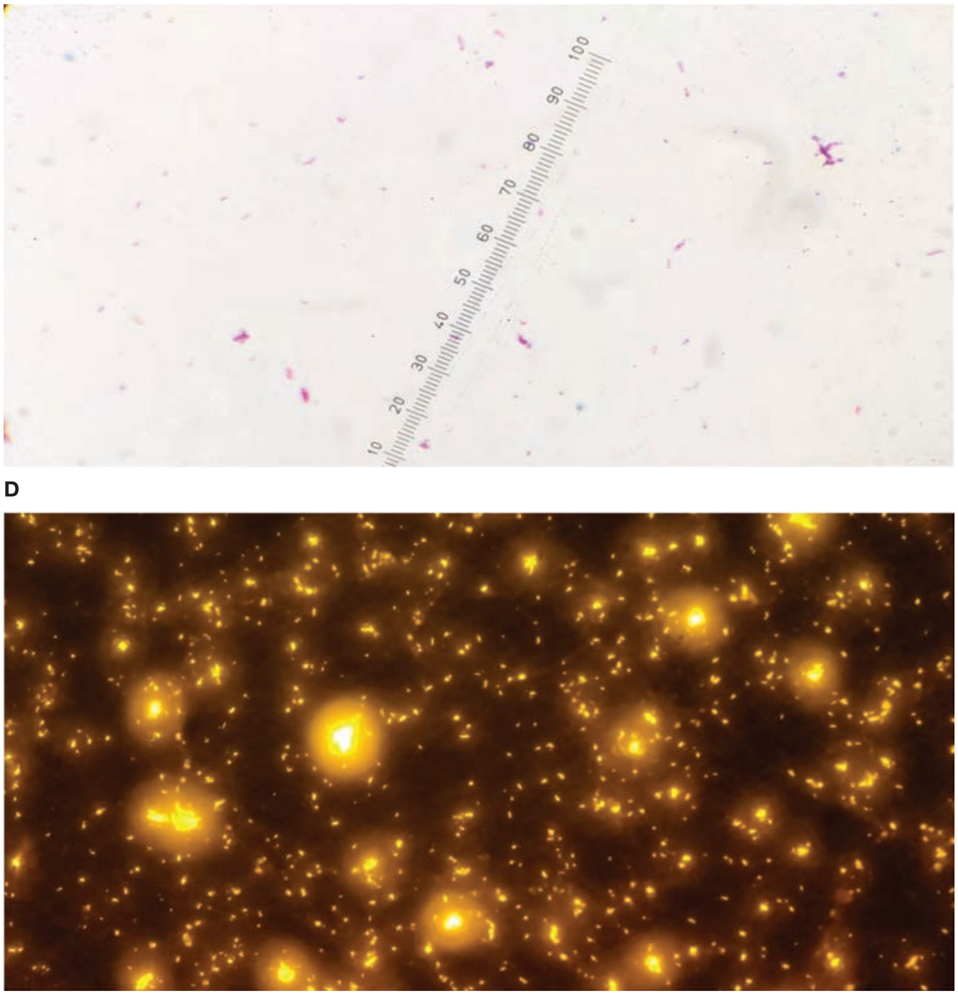


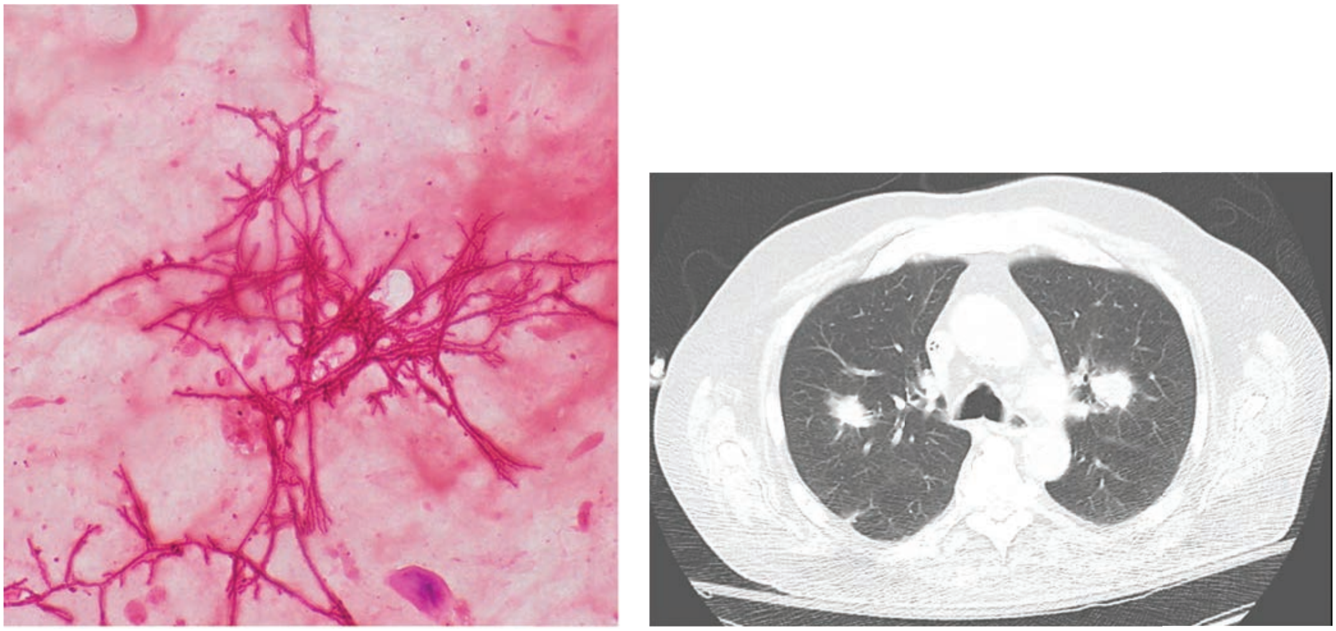
Figure 122-7 Tuberculous cavities. In each instance, the organisms were seen on smear and identified by culture. **A.** Cavity amid consolidation in a 56-year-old African-American man. **B.** Bilateral, multiple cavities in a 72-year-old African-American man. **C.** Spread from original involvement of right upper lobe in a 48-year-old African-American woman. *(continued)*



D

E

Figure 122-7 *(Continued)* **D.** Positive AFB smear—Kinyoun stain. **E.** Positive AFB smear—auramine rhodamine stain.



A

B

Figure 122-8 **A.** Gram stain showing the acute angle branching of *Aspergillus*. **B.** Angioinvasive aspergillosis on computed tomography with the characteristic halo-sign representing hemorrhage into surrounding alveoli. *(Reproduced with permission from Dr. M. Kavanaugh.)*

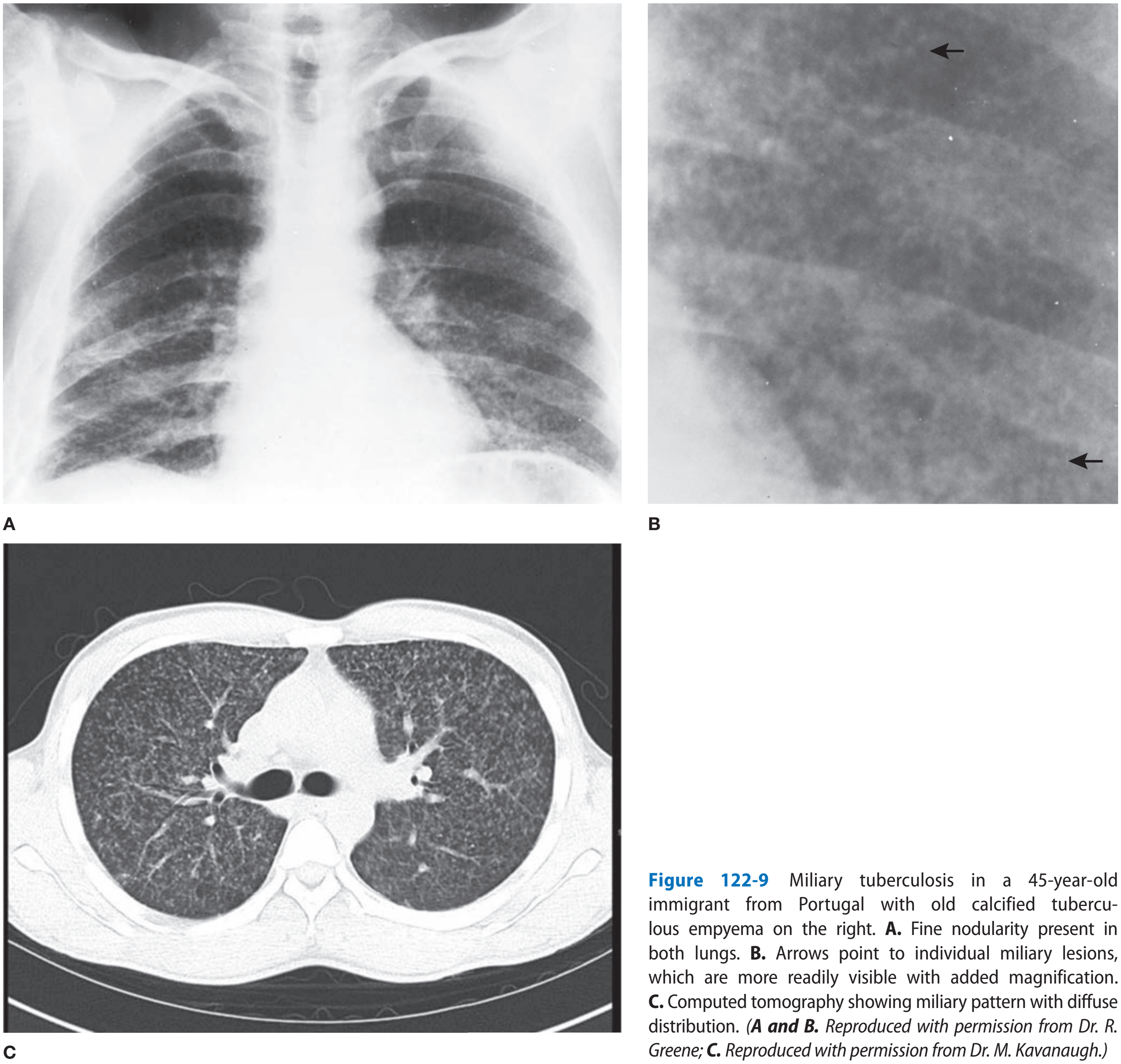


Figure 122-9 Miliary tuberculosis in a 45-year-old immigrant from Portugal with old calcified tuberculous empyema on the right. **A.** Fine nodularity present in both lungs. **B.** Arrows point to individual miliary lesions, which are more readily visible with added magnification. **C.** Computed tomography showing miliary pattern with diffuse distribution. *(**A and B.** Reproduced with permission from Dr. R. Greene; **C.** Reproduced with permission from Dr. M. Kavanaugh.)*

mycotic infections, including cryptococcosis and histoplasmosis. In the immunosuppressed patient, a miliary pattern may be seen in disseminated cryptococcal infection or with hematogenous spread of bacterial or *Candida* infection (Chapter 123).

APPLICATION OF RADIOGRAPHIC TECHNIQUES TO THE CLINICAL DIAGNOSIS OF PNEUMONIA

A consistent approach to the incorporation of radiographic imaging in evaluating a patient with suspected pneumonia is helpful. One such approach includes the following four steps.

Comparison of the radiograph with prior studies. Is the process old or new? Are there multiple processes? Has the patient had surgery in the intervening period? Is the spleen enlarged or absent?

Note the presence or absence of an infiltrate. Chest radiograph findings can be helpful in distinguishing which patients will benefit from antibiotic therapy. Absence of radiographic findings of a lower respiratory tract infection can be used to withhold antibiotics in a patient who is not severely ill, and in whom the presenting features are not highly consistent with pulmonary infection. Determining whether the pattern is more consistent with an interstitial or lobar process may be helpful.

Consider confounding variables. If there is no infiltrate, assessment of the probability of a false negative radiographic is useful. Is this patient early in the disease course? Are they dehydrated? Does the patient have risk factors for *Pneumocystis* pneumonia (advanced HIV or prolonged steroid use)? Are the radiographic findings more consistent with a noninfectious etiology (e.g., diffuse pulmonary edema in a patient with decompensated heart failure)?

Consider obtaining a CT scan. CT scanning is highly sensitive to discerning changes unrecognized in plain radiographs and may be useful in guiding invasive procedures.

EXAMINATION OF CLINICAL SPECIMENS AND ESTABLISHMENT OF A MICROBIOLOGIC DIAGNOSIS

The traditional clinical approach to pneumonia places great emphasis on establishing a specific microbiologic diagnosis. An appropriately stained smear of sputum or pleural fluid, bronchoalveolar lavage (BAL) fluids, blood buffy coat, skin lesions, or throat swabs *may* provide a provisional diagnosis and allow deployment of more targeted antimicrobial therapy.[37]

In practice, most patients with pneumonia are treated empirically. Examination of sputum samples should not delay treatment. For community-acquired pneumonia in the outpatient setting, pretreatment blood cultures and sputum cultures are not recommended routinely. Indications for obtaining microbiologic data include patients with severe disease, hospitalized patients, patients at risk of multidrug-resistant organisms (such as patients with cystic fibrosis or immunosuppressed patients), and patients empirically treated for *Pseudomonas aeruginosa* and MRSA.[9]

Noninvasive studies may provide information indicating the specific microbial cause of a pulmonary infection or may narrow the field of likely etiologic agents. Culture of sputum, blood, or pleural fluid may provide a specific diagnosis when evaluation of sputum smears have not, either because the infecting agent cannot be distinguished from components of the normal upper respiratory tract flora incorporated in the specimen, or because the particular microorganism is not visible on Gram-stained smear (e.g., *Mycobacterium*, *Mycoplasma*, *Legionella* species). The availability of rapid culture–independent microbiologic assays for viral respiratory infections and for some common pathogens (e.g., antigen detection for pneumococcal or *Legionella* infections, rapid viral screens) has, to some extent, reduced the need for other modalities of diagnosis.[38]

Tests of Respiratory Specimens

A variety of laboratory tests may be performed on respiratory specimens and are considered below.

Specimen Quality

Adequate quality of samples of expectorated or induced sputum for staining and culture is very important. Poor-quality specimens typically have high numbers of squamous epithelial cells due to contamination with oropharyngeal secretions. A microorganism isolated from deeply coughed sputum cultures obtained before the initiation of antimicrobial therapy is considered clinically relevant if detected in respiratory specimens, blood, or both, and the specimen is of good quality, that is, contains >25 leukocytes and <10 squamous epithelial cells per low-power field. The presence of 10 or more squamous epithelial cells (normally exfoliated from the oropharynx) per low-power (×100) magnification field indicates that the specimen is unsatisfactory; culture of such a specimen correlates poorly with results from culture of a transtracheal aspirate (Fig. 122-10).

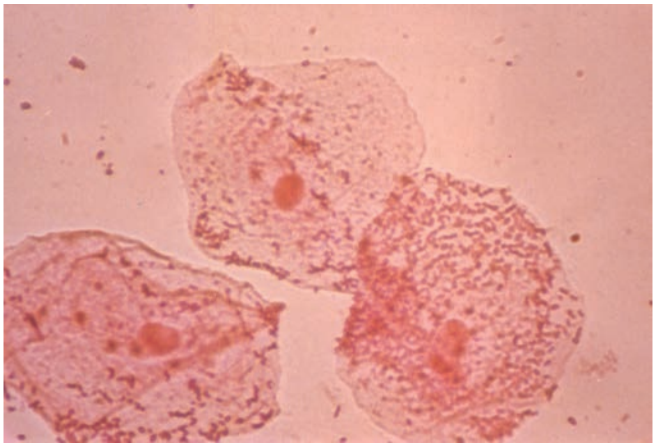


Figure 122-10 Three large oropharyngeal epithelial cells from a specimen of "sputum" that is inadequate for Gram stain analysis and culture because of its origin in the upper respiratory tract. Note the large number of organisms agglutinated on the surface of the squamous epithelial cells (×400).

The presence of numerous polymorphonuclear neutrophils on a Gram-stained smear (10–25 neutrophils or more per low-power microscopic field) in the absence of an excessive number of squamous cells (see above) is indicative of a good specimen for bacteriologic evaluation. One study demonstrated that, in contrast to sputum of low quality, where culture positivity was 14.5%, sputum of good quality was associated with culture positivity of 63.2%.[39]

Some laboratories reject inadequate sputum specimens and notify clinicians to request a repeat specimen, whereas other laboratories never reject a sputum, but abbreviate the quality of the specimen on the result report. Specimens should be plated for cultures within 2 h of receipt or stored at 4°C until plated. In practice, many patients with pneumonia (~30%) cannot produce good sputum samples, and many have had prior therapies that alter the success of microbial cultures (15%–30%); 40% to 60% of cultures are negative.[40,41] A specific etiology can be established in fewer than 50% of cases using routine studies (sputum and serologies). Sputum induction using inhaled nonbacteriostatic saline mist and chest percussion may increase the yield for *Pneumocystis*, mycobacteria, and malignancy on cytologic examination. Cytologic assessment is not necessary for screening specimens for detection of *Legionella*, mycobacteria, or any specimens obtained using induced sputum.

Examination of Gram-stained Smears for Bacteria

Initial examination of Gram-stained sputum smears can be of major value in pinpointing a bacterial cause of pneumonia and guiding initial and subsequent therapy, especially when a single morphologic type of bacteria predominates. In clinical practice, therapy is generally initiated prior to the availability of sputum examination.

Many bacterial respiratory tract pathogens have characteristic morphologies and strongly suggest an etiologic role when present in a suitable respiratory specimen containing inflammatory cells (in the absence of neutropenia). Such organisms include *S. pneumoniae* (Gram-positive oval or lancet-shaped diplococci), *H. influenzae* (small, pleomorphic Gram-negative bacilli), *M. catarrhalis* (Gram-negative, biscuit-shaped diplococci), or the similar-appearing *Neisseria meningitis*, enteric Gram-negative bacilli (indistinguishable from one another with respect to species, except for large encapsulated rods that are suggestive of *Klebsiella*), and *S. aureus* (large Gram-positive cocci in small groups or clusters) (Fig. 122-11). Since normal oral flora includes a variety of streptococcal species that are morphologically somewhat similar to *S. pneumoniae*, sputum smears may be misinterpreted. Thus, a predominance of Gram-positive diplococci in multiple oil immersion fields needs to be observed to implicate *S. pneumoniae*.[42] A quantitative aspect to the evaluation has been suggested: at least 10 Gram-positive, lancet-shaped diplococci per oil immersion field predicts the isolation of *S. pneumoniae* from sputum cultures with a specificity of 85% and sensitivity of 62%. A systematic review and meta-analysis of 24 studies, including 4533 patients with sputum Gram stains for diagnosing bacterial pathogens in community-acquired pneumonia, has been published. It demonstrated a specificity of 91% and sensitivity of 69% for detecting *S. pneumoniae*, and a specificity of 97% and sensitivity of 76% for detecting *H. influenzae* in good-quality sputum specimens. Bacterial pathogens were identified in 73% of good-quality specimens and in 36% of all specimens, regardless of quality.[43]

In appropriate clinical and radiographic settings, Gram-stained smears may be helpful not only in the etiologic diagnosis of community-acquired bacterial pneumonia due to the usual respiratory pathogens, but also in supporting a diagnosis of atypical pneumonia when sputum examinations repeatedly show neither neutrophils nor bacteria (*Mycoplasma* or *Legionella*). Uncommon bacterial species may be implicated in a pulmonary infection on the basis of unusual morphology. Figure 122-12 shows a Gram-stained smear

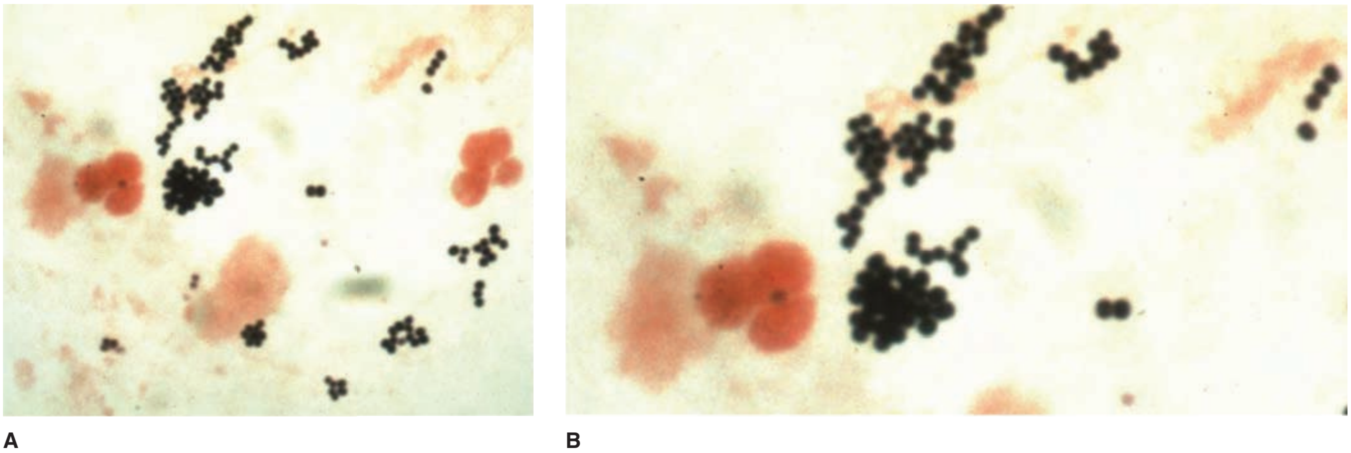


Figure 122-11 *S. aureus* on Gram-stained smear from patient with history of injection drug use with right-sided bacterial endocarditis. There are polymorphonuclear leukocytes and clusters of Gram-positive cocci. *(Reproduced with permission from H. Provine.)*

of irregularly staining, beaded, delicate, Gram-positive, branching filaments that suggest either *Nocardia* or *Actinomyces* (Chapter 137). Several organisms that are uncommon causes of pulmonary infection have morphologic characteristics that may mimic other, more common respiratory pathogens. *Pasteurella multocida* and *Acinetobacter* species, both small Gram-negative coccobacilli, have each been mistaken for either *H. influenzae* or *M. catarrhalis* in sputum of patients with pulmonary infections.

Sputum or pleural fluid with foul odor suggests the presence of anaerobic organisms and underlying lung abscess, aspiration pneumonia, empyema, or occasionally, bronchiectasis. In these settings, findings on Gram-stained smear may corroborate the

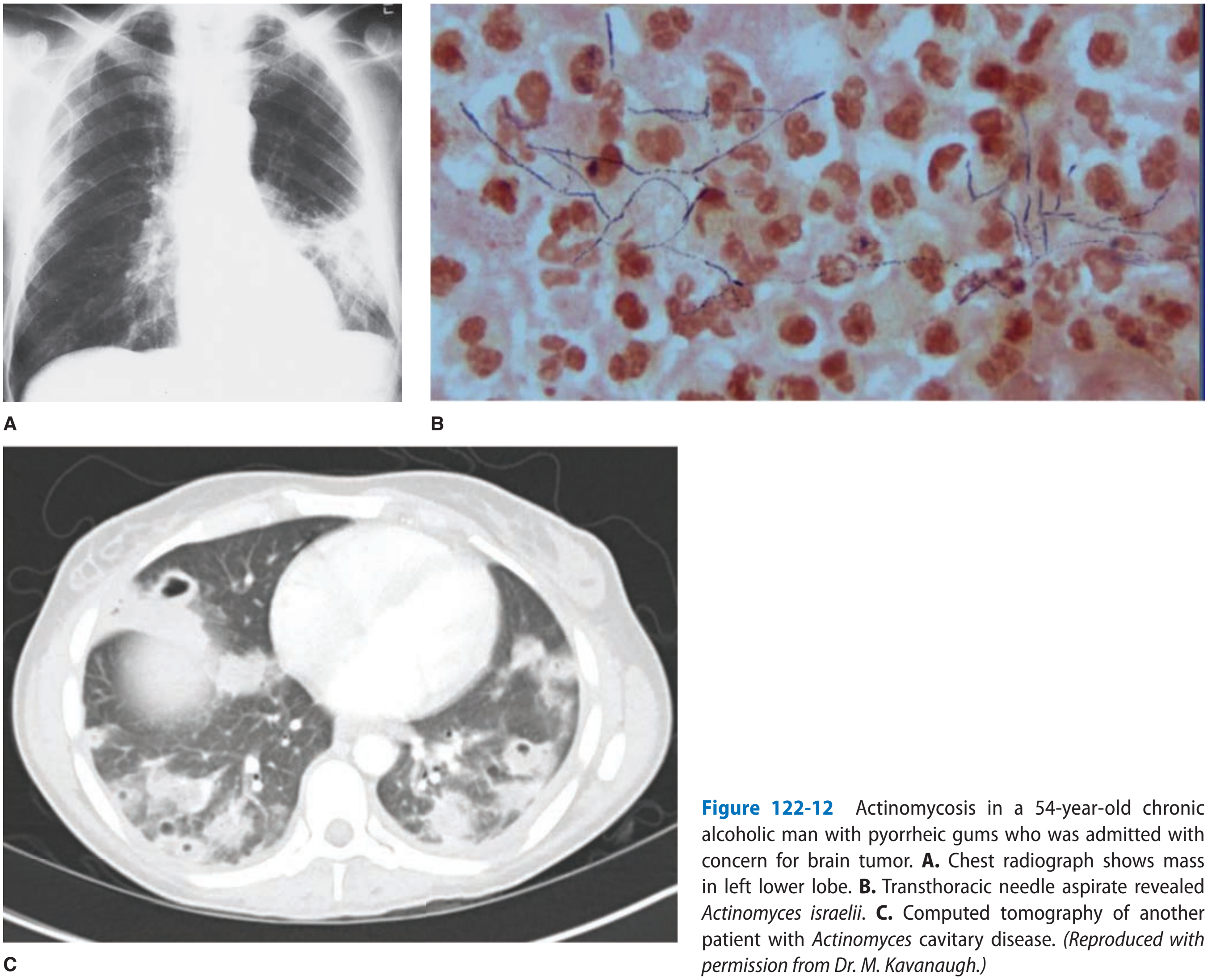


Figure 122-12 Actinomycosis in a 54-year-old chronic alcoholic man with pyorrheic gums who was admitted with concern for brain tumor. **A.** Chest radiograph shows mass in left lower lobe. **B.** Transthoracic needle aspirate revealed *Actinomyces israelii*. **C.** Computed tomography of another patient with *Actinomyces* cavitary disease. *(Reproduced with permission from Dr. M. Kavanaugh.)*

preliminary diagnosis. Organisms of the *Bacteroides melaninogenicus–Bacteroides asaccharolyticus* group are small, Gram-negative coccobacilli. *Fusobacterium nucleatum* is a long, tapering, pale-staining, Gram-negative bacillus with irregular, Gram-positive internal granules. Purulent secretions or pus from such anaerobic infections contains numerous neutrophils and, usually, a mixture of bacterial species, including anaerobic and microaerophilic streptococci seen on stained smear.

Examination of Acid-fast Stained Smears for Mycobacteria

Acid-fast stains include fluorescent stains, such as auramine-rhodamine, and carbol-fuchsin-based stains, such as Kinyoun and Ziehl-Neelsen, which are viewed by light microscopy. Kinyoun cold staining is a modification of the classical Ziehl-Neelsen method that excludes the heating step during staining and, therefore, uses a higher concentration of carbol fuchsin.[44] Most laboratories currently employ a fluorochrome stain with auramine–rhodamine (Mycobacteria fluoresce orange-yellow) for initial examination of sputum or other body fluids, as it is easier to visualize fluorescent rods on a dark background than pink rods on a blue background.[44] Although less sensitive than culture (50%–65% vs. 80%–85%) for the diagnosis of tuberculosis, acid-fast smears are performed on direct specimens because the positive predictive value is very high, particularly in respiratory specimens. A positive smear indicates that a species of mycobacteria is present, although not necessarily *M. tuberculosis*. Molecular diagnostics (e.g., polymerase chain reaction [PCR]) for *M. tuberculosis,* available for direct application to clinical specimens, provide great promise in reducing the global burden of tuberculosis by offering a rapid and accurate diagnosis.

Atypical mycobacteria may be demonstrated on sputum smears of patients whose pulmonary disease is usually characterized by slow progression, or who have underlying immunocompromise (Chapter 131). Disseminated *M. avium complex* infection in patients with advanced HIV is usually diagnosed by isolation of the organism from AFB isolator blood cultures or by histopathologic diagnosis on biopsy. The organism may be demonstrated on acid-fast smears and culture of respiratory secretions, however, even with little radiographic evidence of pulmonary infection directly attributable to its presence. Improved culture techniques are available to more rapidly isolate mycobacteria from clinical specimens. Modified Ziehl–Neelsen–stained smears are helpful in detecting *Nocardia*, which appear as a partially acid-fast, filamentous, branching rod with beaded appearance. Their appearance sets them apart from *Actinomyces* and *Streptomyces*, which may appear similar on Gram stain, but are not acid-fast.

Fungal Wet Mount Preparations

Fungal wet mount preparations using potassium hydroxide (KOH) or smears stained with the Calcofluor white chemifluorescent agent are employed when epidemiologic considerations suggest community-acquired pulmonary mycoses (particularly coccidioidomycosis and blastomycosis). Fungi are fairly refractory to the activity of KOH, while human tissues are dissolved, clearing the specimen and making the microscopic demonstration by Calcofluor staining of the fungi much easier. Calcofluor white binds to chitin; hence, it is particularly useful for highlighting the cell wall of fungi in clinical specimens.[45] The sensitivity of Calcofluor-KOH examination of sputum ranges from 50% to 90% in patients with pulmonary blastomycosis. The examination should be a routine part of evaluation of respiratory secretions and lung biopsy specimens from immunocompromised patients in whom additional fungal pathogens (e.g., *Aspergillus* and mucormycosis) may be present. In patients with allergic bronchopulmonary aspergillosis (ABPA), or in whom *Aspergillus* is unexpectedly detected in sputum, the presence of fungal hyphae must be interpreted in the appropriate clinical context.

Rapid Detection by Direct Immunofluorescent Microscopy

Direct fluorescent antibody (DFA) staining may be useful in rapid diagnosis of respiratory tract pathogens. Rapid viral diagnosis by DFA (turnaround time, ∼2 h) may be applied to a variety of specimens, including bronchial lavage or brushings and nasopharyngeal swabs or washings. The technique uses a pool of monoclonal antibodies to influenza and other common respiratory viruses to directly detect infected cells obtained from clinical specimens. DFA sensitivity and specificity are dependent on the skill of the personnel performing the test.[46]

Besides the molecular diagnostics used to evaluate for P. jirovecii nucleic acids, immunofluorescence with monoclonal antibodies against *P. jirovecii* is the most widely used diagnostic technique for diagnosis, demonstrating a sensitivity of 69% to 92%.

Some caveats of DFA staining should be noted. Use of DFA staining for *L. pneumophila* is not recommended in examination of sputum specimens because of the presence of cross-reacting species (e.g., *Bacteroides* species, *Pseudomonas* species, *Bordetella pertussis*) in the upper respiratory tract. However, biopsy specimens of lung (obtained via needle, bronchoscopic, or surgical techniques), bronchoscopic aspirates, BAL washings, and pleural fluid samples are suitable for DFA staining for *L. pneumophila*. Although DFA was one of the first diagnostic tests developed for *Legionella*, due to its technical complexity and modest sensitivity, DFA testing of respiratory samples is rarely used.[47] In addition, although anti–*B. pertussis* DFA may be used on nasopharyngeal aspirate smears in a presumptive case of pertussis, because of its poor sensitivity (only 50%–65%), DFA is no longer in the CDC's diagnostic algorithm for pertussis.

Special Stains for the Diagnosis of *Pneumocystis* Infection

Historically, a variety of stains (toluidine blue O, methenamine silver, Wright–Giemsa, Diff-Quik, Calcofluor) have been useful in identifying *P. jirovecii* cysts in induced sputa or BAL specimens, or on imprint smears of lung tissue specimens. Due to limited sensitivity and specificity of these stains, we prefer use of DFA, as described previously; however, in resource-limited settings, these stains are still used.[48] Toluidine blue O and methenamine silver stain only the cyst (typically <10% of the organism burden), not the trophozoite forms of *P. jirovecii*. Giemsa and Diff-Quik stain trophozoites and intracystic sporozoites.

Sputum Cultures

In most patients with common types of community-acquired and nosocomial bacterial pneumonias, the etiologic diagnosis can be made based on the combined results of a sputum Gram stain and culture of a freshly obtained sputum specimen (see earlier discussion).

Like the Gram stain, sputum cultures can be difficult to interpret. Culture preparation generally entails streak dilution on chocolate agar, blood agar, and MacConkey agar. Expectorated sputum should not be cultured anaerobically, since contamination with oral anaerobes is inevitable. Many pathogens are fastidious, and normal flora may overgrow them. A time delay of >2 h from collection to incubation is associated with substantial loss of pathogen detection. Blood agar best supports the growth of Gram-positive cocci and most Gram-negative rods and is especially useful for evaluation of the colony morphology and hemolysis of streptococci. MacConkey agar is selective for Gram-negative bacteria and is used to determine bacterial ability to ferment lactose (lactose-positive or -negative organisms). Chocolate agar allows recovery of *H. influenzae* and other fastidious organisms. Because patients with Legionnaires' disease often have little sputum production, and since growth requires special media, most attempts to isolate *Legionella* entail procurement of specimens obtained by sputum induction, fiberoptic bronchoscopy, lung biopsy, or thoracentesis. Cultures of materials obtained are plated on buffered charcoal-yeast extract (BCYE) agar. Occasionally, *Legionella* species can be isolated from sputum with the use of a semiselective medium—either BCYE or BCYE-containing cefamandole, polymyxin B, and anisomycin. Culture sensitivity ranges from 15% to 95%; higher sensitivities are seen in severely ill patients.[47] Culture is the most definitive method for diagnosis of *Legionella* infection. Unfortunately, colonies may take 5 or more days to appear.

Cultures for mycobacteria are undertaken when clinical circumstances raise the possibility of pulmonary infections due to *M. tuberculosis* or atypical mycobacteria. The use of solid culture medium, such as Lowenstein-Jensen (LJ) medium, is more cost-effective in resource-poor settings.[49] Similarly, cultures of sputum for primary invasive mycotic agents (e.g., *Histoplasma capsulatum*, *Blastomyces dermatitidis*, and *Coccidioides immitis*) are dictated by clinical and epidemiologic circumstances. The yield of cultures of bronchial washings in patients with pulmonary blastomycosis approaches 100%, but the confirmation of a diagnosis may take up to 5 weeks.[50] In immunosuppressed patients, cultures of sputum are also directed toward a variety of opportunistic fungi, including *Cryptococcus neoformans*, *Aspergillus* species, and Mucoraceae. Given its superior yield, a fungal-specific medium, for example, Sabouraud dextrose agar, should be included at the time of initial specimen setup in clinical scenarios in which *Aspergillus* spp. (or other molds) are considered possible pathogens.[51]

Most hospitals do not have facilities for isolating viruses by tissue culture. This poses little problem in dealing with most community-acquired viral pneumonias, for which viral isolation is not necessary and the cost prohibitive. Viral isolation from throat washings is warranted in exceptional circumstances, for example, to understand the pathogenesis and infectivity of a specific novel viral agent, such as SARS-CoV-2.

Cultures may be grown in cell lines susceptible to the viral infections under consideration in either standard "tube cultures" or "shell vial" cultures. (Rapid culture within 24–48 h is achieved by centrifugation of specimens against the cultured cells.) Viral replication in tissue culture can be confirmed within 48 h after inoculation using fluorescent monoclonal antibodies. Because CMV and herpes simplex are frequently present in the oral and respiratory secretions of immunosuppressed patients, isolation of these viruses tends to include many false positives. In practice, diagnostic cultures (e.g., for CMV, other herpesviruses, and adenovirus) have been replaced by quantitative molecular amplification assays (e.g., nucleic acid amplification tests [NAATs] and PCR) or antigen detection systems that are more rapid and cost-efficient than culture systems (Table 122-8).

Molecular Diagnostic Testing

A variety of NAATs are available for the direct detection of pulmonary pathogens. These tests are more sensitive and specific than traditional antigen tests or viral cultures. Using an array of diagnostics, likely pathogens may be detected in 67% to 89% of cases of CAP. *S. pneumoniae* remains the most common pathogen at 38% and is more often detected by molecular and urinary tests than sputum

TABLE 122-8 Assays for Viral Agents of Adults

Virus (Type)	Season	Culture/Specimen	Culture Days to Positive	DFA/Serology/ Antigen	Molecular Amplification+
Influenza A/B (RNA)	Winter	Nasopharyngeal wash/BAL	3–5	+/+/+	Qual (rapid, sensitive, specific)
RSV (RNA)	Fall, Winter	Nasopharyngeal wash/BAL	5–7	+/+/–	Qual
Parainfluenza (RNA)	Fall, Spring	Nasopharyngeal wash/BAL	5–7	+/+/–	Qual
Human metapneumovirus (RNA)	Late winter	Nasopharyngeal wash/BAL	10–14	+/+/–	Qual
Adenovirus (DNA)	All	Nasopharyngeal swab, stool	3–5	+/+/–	Qual/quant
Measles (RNA)	All	Conjunctiva, nasopharynx; BAL, blood, urine	2–15	–/+/–	Qual
EBV (DNA)	All	PBL–PCR, mono spot, serum	1–7	–/+/–	Qual/quant (new WHO standards)
CMV (DNA)	All	Blood, urine, BAL saliva	2 (shell vial)–14	+/+/–	Qual/quant PCR (WHO standards) antigenemia pp65
VZV (DNA)	All, especially Spring	Vesicle, throat, BAL, blood	Slow	+/+/–	Qual/quant
HSV1, HSV2 (DNA)	All	Vesicle, BAL, blood	1–2	+/+/–	Qual/quant (HSV1/2)
SARS-CoV-2 (RNA)	All	Nasopharyngeal wash, oropharyngeal wash, sputum, BAL, anterior nares, saliva	N/A	+/+/+	Qual (rapid, sensitive, specific)
MERS-CoV (RNA)[a]	All	BAL, sputum	N/A	+/+/–	Qual (RTPCR)

[+] *Quant, quantitative assay; Qual, qualitative assay; RTPCR, real-time reverse-transcription polymerase chain reaction assays.*

[a] *Testing of multiple specimens including lower and upper respiratory samples, serum, and stool samples.*

culture and examination.[52] Most clinical laboratories have employed NAAT for rapid identification of influenza viruses, as this is the diagnostic gold standard in clinical virology. A recent meta-analysis investigating rapid viral NAAT for influenza showed a pooled sensitivity of 90.9% and specificity of 96.1%.[53] Testing has been shown to reduce unnecessary antibiotics, improve appropriate use of antivirals, decrease hospital stay, and improve infection control efforts. As seen during the global SARS-CoV-2 pandemic, these assays can be used to identify emerging pulmonary pathogens as well.

In some major medical centers, PCR assays for the detection of *C. pneumoniae* and *M. pneumoniae* on nasopharyngeal or throat swab specimens are available. They markedly shorten the time required to isolate organisms by culture (by up to 3 weeks). These new testing capabilities have been entered into new guidelines—for example, the IDSA recommends MRSA nasal screening in patients with HAP or VAP with the intent that a negative test will allow for narrowing of the antibiotic regimen.[9] NAAT assays may be incredibly useful to clinicians; however, they must be used in the context of sound clinical judgment and only when results will impact treatment decisions. For example, IDSA recommends testing for influenza using NAAT assays during periods of high prevalence of the virus within the community.[9]

PCR tests can detect *M. tuberculosis* (as distinct from nontuberculous mycobacteria) directly in sputum and BAL specimens. The World Health Organization endorsed the use of Xpert MTB/RIF (Cepheid, Sunnyvale, California, United States) in 2010 and has since published policies for its global implementation, based on its ease of use in the field, its provision of a result while a patient is waiting, and its diagnostic accuracy. The Xpert MTB/RIF test provides results in about 2 h. Its sensitivity in smear-positive respiratory specimens is 98% to 99% and in smear-negative specimens is 68% to 90%, depending on the number of specimens tested. In countries with a higher prevalence of multidrug-resistant tuberculosis, rifampin resistance is a useful predictor of this finding. The Xpert test also screens for the most common rifampin resistance mutations by interrogating the rifampin resistance–determining region of *rpoB* in *M. tuberculosis*.[54,55]

Molecular detection of herpes simplex virus, adenovirus, cytomegalovirus, Epstein-Barr virus, and other pathogens is used primarily with blood specimens, but it may also be used in samples of BAL or CSF.

In immunosuppressed patients with pneumonia, a broad array of opportunistic viral infections (e.g., CMV, RSV, varicella-zoster virus, herpes simplex) are diagnostic considerations. Strict criteria for CMV pneumonia include demonstration of the virus, typical cytologic and pathologic changes, and absence of other evident pathogens.[56] These criteria are applicable in non-immunocompromised patients, in whom CMV is frequently isolated (likely due to shedding), but in whom CMV rarely causes pneumonia. Isolation of CMV from BAL fluid or blood in bone marrow transplant recipients with pneumonia may be sufficient to establish a presumed diagnosis and to institute treatment, particularly in view of the high frequency and mortality of CMV pneumonia in these patients. Commercially available molecular amplification tests for other pulmonary pathogens include *P. jirovecii*, *L. pneumophila*, and *Aspergillus* spp. In patients with severe immunocompromise who are suspected of having invasive pulmonary aspergillosis, the American Thoracic Society (ATS) recommends the inclusion of *Aspergillus* PCR in BAL and serum testing as part of the evaluation (as well as other diagnostics).[51] One drawback with all PCR testing is that it is overly sensitive—that is, the test may detect organisms even in absence of clinical illness and, hence, does not differentiate between colonization and infection.

Recently, highly sensitive and specific multiplex molecular assays for numerous possible respiratory pathogens using the same specimen have been adopted by some clinical laboratories.[57] Until recently, these included respiratory viruses and some "atypical" pathogens, for example, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Bordetella* spp. The Flu SC2 Multiplex Assay (Centers for Disease Control and Prevention, Atlanta, Georgia, United States), used to diagnose infection with influenza A, influenza B, or SARS-CoV-2, is now commercially available.[58] Appropriate specimens for testing include nasopharyngeal swabs, nasal washes, sputa, and bronchoalveolar lavage.

An additional, culture-independent technique includes metagenomic next-generation sequencing (mNGS). Briefly, mNGS is a molecular diagnostic that sequences all nucleic acid in a clinical specimen. The sequences are then referenced against a database of organism genome sequences. The technique has been described as the "needle in a haystack" approach and is generally less sensitive and specific than targeted molecular diagnostics. Usefully, genotypic resistance profiles are generated through mNGS and may impact antimicrobial choices. Given that a causative pathogen is not often identified, the technique may be useful under selected circumstances.

■ Nonmicrobiologic Clues to Pulmonary Infection

Occasionally, in the setting of apparent pulmonary inflammation and features atypical for infection, microscopic examination using stains other than Gram stain may be indicated. For example, Wright-stained smears may show the presence of eosinophils in allergic pulmonary aspergillosis or in other causes of pulmonary infiltrates accompanied by eosinophilia. Birefringent calcium oxalate crystals (needle-like in rosettes or arranged like sheaves of wheat) in sputum cytologic specimens have been reported as suggestive of pulmonary infection with *Aspergillus* (including aspergilloma and, occasionally, invasive aspergillosis).

In the intubated or tracheotomized patient, whose tracheobronchial secretions commonly contain neutrophils and often some bacteria on Gram-stained smears, it may be difficult to distinguish between colonization and nosocomial pneumonia.[59] The presence on light microscopy (×400) of characteristic elastin fibers with split ends (seen in a tracheal aspirate to which a drop of 40% KOH has been added), in the appropriate clinical setting, is a strong indicator of a necrotizing pulmonary infection.

■ Tests from Nonrespiratory Specimens

A variety of nonrespiratory specimens may be useful in the evaluation of patients with suspected underlying pneumonia.

Blood Cultures

Blood cultures should be performed prior to initiation of antibiotics in hospitalized patients with suspected bacterial pneumonia.[60] Bacteremia occurs in approximately 30% of patients with pneumococcal pneumonia, who represent up to two-thirds of those with positive blood cultures.[61] Blood cultures are more often positive in sicker patients, including those with hypotension, renal and liver dysfunction, pleurisy and tachypnea, and thromboembolic disease. Bacteremia in patients with pneumonia may indicate that the pulmonary infection is secondary to a focus of infection elsewhere (e.g., acute right-sided *S. aureus* endocarditis or *Pseudomonas aeruginosa* infection of thermal burns). *Legionella pneumophila* has been isolated with some frequency from automated radiometric blood culture bottles, but blind subculture onto BCYE agar is necessary because growth in the liquid medium does not achieve detectable levels. In patients with AIDS and disseminated *M. avium-intracellulare* infection, mycobacterial blood cultures are almost always positive. The lysis centrifugation technique permits rapid isolation of the mycobacterium and quantifies the intensity of bacteremia.

Antigen Testing

The quellung reaction was extensively used in the pre–antimicrobial agent era to identify *S. pneumoniae* in sputum.[13,62] It entails the use of light microscopy to detect capsular swelling (*Quellung* is the German word for swelling) after pneumococcal antiserum has been added to a loopful of sputum. The occurrence of the quellung reaction was shown to correlate closely with the presence of *S. pneumoniae* in sputum culture in about 90% of the patients. Pneumococcal antigens may also be detected in the sputum of patients with pneumococcal pneumonia using ELISA, latex particle agglutination, or counterimmunoelectrophoresis; none of these techniques is commonly used at present. Antigen detection in sputum may have a sensitivity as high as 70% to 90%; however, specificity is a problem, with about 20% false positives, probably due in part to the difficulty in distinguishing oropharyngeal contamination from colonization.

In many patients, a sputum-based diagnosis is not easy; either an etiologic diagnosis cannot be made based on initial smears or cultures, or antimicrobial therapy may have been initiated before cultures were obtained or adequate sputum samples available. For adults with severe CAP, urinary antigen tests for *S. pneumoniae or Legionella* may be helpful.[9] In adults hospitalized with CAP due to *S. pneumoniae*, generally without bacteremia (the presence of which increases sensitivity), the sensitivity of the pneumococcal urinary antigen assay is 71% and specificity 96%.[63,64] The *L. pneumophila* antigenuria test is easy to perform, is rapid, and is positive despite prior antimicrobial agent administration. Antigenuria may persist for weeks or months after recovery from pneumonia.[65] The assay is available only for *L. pneumophila* serogroup 1, which is responsible for about 80% of *L. pneumophila* infections.

When respiratory viruses are circulating in the community, nasal swabs for viral antigens (influenza, parainfluenza, metapneumovirus, adenovirus, RSV) are often helpful, particularly in the immunosuppressed patient. Rapid, more accessible, point-of-care antigen tests for influenza and SARS-CoV-2 have good specificity but only 50% to 70% sensitivity; retesting using more sensitive assays may be required if clinical suspicion is high.[66,67] For infection control purposes, repeat screening of individuals in high-risk congregate settings may be useful in identifying individuals with SARS-CoV-2, thereby enabling isolation.[66]

In certain patients, the epidemiologic history may suggest other risk factors that indicate the need for specific testing, for example, for *Histoplasma* (urinary antigen), viral infections (serum antigenemia or nucleic acid testing) (Tables 122-1 and 122-8), or cryptococcal infection (serum cryptococcal antigen assay). Cryptococcal antigenemia is detectable by latex particle agglutination in patients with cryptococcal pneumonia or disseminated cryptococcal infection. Serum cryptococcal antigen detection is sensitive for the diagnosis of pulmonary infection, more so in immunocompromised than immunocompetent patients. If the clinical suspicion for cryptococcal pneumonia is high, the test should be performed. The CMV antigenemia assay detects CMV matrix protein pp65 and can be detected with use of fluorescent or peroxidase-labeled antibody staining of peripheral blood neutrophils. The assay is semiquantitative, but it is not standardized and is labor-intensive due to the liability of blood cells. The test has largely been replaced by molecular amplification methods, such as viral load measurement for detecting CMV in peripheral blood. Similar assays are available for most clinically important viruses.

Serologic Testing

Serologic (antibody) tests may be useful in establishing the cause of a variety of pulmonary infections when the causative agents are difficult to isolate. The approach requires demonstration of a fourfold or greater rise in titer between acute and convalescent samples. Serologic testing neither enables rapid diagnosis nor aids in initial selection of antimicrobial therapy. Rather, testing is useful in confirming the diagnosis in retrospect, in most instance.

Microimmunofluorescence serologic tests are of limited value in supporting the diagnosis of infections caused by *Chlamydia psittaci (psittacosis)* and *Chlamydia pneumoniae*. Similarly, for Legionnaires' disease, the indirect immunofluorescent antibody test may provide a retrospective diagnosis in epidemiologic investigations, although the antibody rise occasionally may not be demonstrable for 4 to 6 weeks after the clinical onset. Antibodies may persist for months or up to a year or more.

Cold agglutinins (IgM antibodies against I antigen on RBC membranes) develop in about half of patients with *M. pneumoniae* pneumonia, but such antibodies occur in other conditions; complement fixation testing is the preferred diagnostic procedure. For Q fever pneumonia, the complement fixation (CF) test is usually used to confirm the diagnosis, but microimmunofluorescence, microagglutination, and enzyme-linked immunosorbent assays have been used to diagnose acute *Coxiella burnetii* pulmonary infection. In acute Q fever, the phase II antibody is usually higher than the phase I titer, often by fourfold. In chronic Q fever, the reverse situation is generally seen. Tularemic pneumonia may be diagnosed serologically using an agglutination test for *Francisella tularensis*.

Serologic tests are also helpful in the diagnosis of invasive infection due to the primary pulmonary fungal pathogens. Serum IgM precipitins (latex agglutination, immunodiffusion) appear in primary coccidioidomycosis within 2 weeks of symptom onset. Abnormally high complement fixation titers (at least 1:32) are present in most patients who have disseminated infection due to *Coccidioides immitis*. Increasing complement fixation titers in serial specimens are considered diagnostic of active disease. A fourfold increase in complement fixation titer to yeast and to mycelial phases of *H. capsulatum* (or, possibly, a single titer of 1:32 or higher) and the simultaneous appearance of H and M precipitin bands on immunodiffusion test strongly suggest histoplasmosis.

Complement fixation tests for blastomycosis lack sensitivity and specificity. However, titers of at least 1:8 suggest recent or active disease, particularly if precipitins to the A antigen on immunodiffusion test also are present. In patients with suspected blastomycosis, serum antibody testing specifically directed against the anti–BAD-1 (anti–*Blastomyces* adhesin 1) antigen for blastomycosis can be used together with clinical and epidemiologic data to establish the diagnosis.[51] Sporotrichosis can be diagnosed using a serologic agglutination test when the titer is 1:8 or greater. Pulmonary toxoplasmosis is uncommon in seronegative individuals, although acute toxoplasmosis is seen in endemic regions (e.g., the Caribbean, France) following organ and bone marrow transplantation.

Serologic tests may be helpful for the retrospective diagnosis of respiratory viral infections due to influenza A and B, SARS-CoV-2, RSV, adenoviruses, and parainfluenza viruses. In a systematic review of 38 studies that evaluated the sensitivity of serologic testing by time from symptom onset in patients with COVID-19, IgM was detected in 23% by 1 week, in 58% by 2 weeks, and in 75% by 3 weeks; the corresponding detection rates for IgG were 30%, 66%, and 88%, respectively.[68] Per IDSA recommendations, serologic testing should not be used to diagnose SARS-CoV-2 infection during the first 2 weeks following symptom onset. In diagnosing COVID-19 infection in symptomatic patients with a high clinical suspicion of the infection and repeatedly negative NAAT results, SARS-CoV-2 IgG antibody or total antibody tests are preferred over IgM antibody, IgA antibody, or IgM/IgG differentiation tests because of their greater accuracy.[69]

Fungal Biomarkers

Fungal pneumonia is generally observed in the setting of anatomic abnormalities (e.g., fungus ball in a pulmonary cavity) or immune dysfunction or suppression. Cryptococcal pneumonia or disseminated cryptococcal infection may be diagnosed with high sensitivity and specificity using serum cryptococcal antigen.

Two fungal antigen tests, 1,3-β-D-glucan (BDG) and galactomannan (GM), have been developed as screening tools to assist in the detection of fungal infection in high-risk patients. Both tests are based on distinct carbohydrates found in abundance in fungal cell walls and released during invasive infections; each can be detected in BAL fluid and blood. Serum assays for BDG are recommended for diagnosing invasive aspergillosis (IA) in high-risk patients (e.g., those with hematologic malignancy or allogeneic HSCT) but are not specific for *Aspergillus*.[70] *Candida* species, while frequently isolated in respiratory specimens, rarely cause pneumonia other than in infarcted lung or as a result of embolic disease (e.g., endocarditis in injection drug users). A positive BDG assay in the immunocompromised host is likely a reflection of infection due to *Pneumocystis*, *Fusarium*, dermatophytes, and endemic fungi, in addition to *Aspergillus* spp.;[71,72] notable exceptions include *Cryptococcus* spp. and zygomycetes.[73] The sensitivity for proven or probable invasive fungal infection in various hosts is generally in the 50% to 77% range (often lower in practice) and the specificity 80% to 95%. The specificity is altered due to false-positive results from prior administration of intravenous immunoglobulin or albumin, use of cellulose hemodialysis membranes, and prior exposure to glucan-containing gauze (e.g., the packing used after surgery). BDG testing exhibits poor specificity and reproducibility in BAL; hence, assays to detect BDG typically use serum.[74]

For *Aspergillus* species, galactomannan can be measured by enzyme-linked immunoassay and has been shown to correlate with the burden of fungal disease[70–72] (Chapter 132). Serum and BAL GM are recommended as accurate markers for the diagnosis of invasive aspergillosis in adult and pediatric patients when used in select patient subpopulations (e.g., those with hematologic malignancy, HSCT).[51,70]

A meta-analysis of the performance characteristics of the assay in serum demonstrated a sensitivity of 0.71 (95% confidence interval [CI], 0.68–0.74) and specificity of 0.89 (95% CI, 0.88–0.90) using an index cutoff of 0.5 in immunocompromised patients with proven invasive aspergillosis.[75] Individual studies reveal variability in assay performance. In a meta-analysis of 16 studies involving 783 adults with hematologic malignancies, summary estimates of the overall accuracy of BAL-GM for diagnosing invasive aspergillosis were derived. BAL-GM had a reported sensitivity of 0.92 (95% CI, 0.48–0.99) and specificity of 0.98 (95% CI, 0.78–1.0) using an index cutoff of 1.5.[76] BAL-GM conferred greater sensitivity, but lower specificity, than the serum GM testing and similar specificity as the PCR assay.[76] False-positive GM results may be seen in patients undergoing chemotherapy or who are at risk for mucositis, in whom cross-reactive epitopes from other fungi or bacteria (e.g., *Bifidobacterium* spp. in neonates) may penetrate the intestinal mucosa, causing a positive test result.[51]

■ Other Tests from Nonrespiratory Specimens

High-grade bacteremia sometimes accompanies pulmonary infections, and the etiologic agent may be demonstrable on stained smears of the buffy coat of centrifuged blood. Pneumococci have been identified in Gram-stained or Wright–Giemsa–stained smears of buffy coats from a patient who has undergone splenectomy; occasionally, *M. avium-intracellulare* has been found intracellularly in acid-fast stains of buffy coats from patients with advanced HIV. Additional special microscopic examinations may be indicated for immunocompromised patients who have patchy pulmonary infiltrates on the chest radiograph. For example, the presence of the hyperinfection syndrome of strongyloidiasis (often accompanied by *Escherichia coli* bacteremia) can be established by the finding of filariform larvae in the stool suitably prepared by concentration techniques. Although eosinophilia is often present in patients with strongyloidiasis, it may be absent in the hyperinfection syndrome or in patients on corticosteroids.

■ Skin Tests of Delayed Hypersensitivity

The tuberculin skin test (TST) is of great importance in the evaluation of a pulmonary infection of unknown origin. The intermediate (5 tuberculin units) purified protein derivative (IPPD) test should be used if no information is available about previous testing. A positive test does not distinguish between prior and current infection. A negative second-strength PPD skin test in a patient who is not anergic is evidence against a tuberculous origin of a pulmonary process in a normal host. Several caveats are noteworthy: since it may take 4 to 6 weeks for the skin test to become positive, the TST may be initially negative in progressive primary pulmonary tuberculosis, and in the patient who was infected long ago, cutaneous hypersensitivity may wane. In elderly patients in whom waning has occurred, repeat testing several weeks later may show a positive result (booster effect), even if the original PPD skin test was negative. A PPD reaction of at least 5 mm is considered positive in HIV-infected patients, organ-transplant recipients, and other immunosuppressed hosts; for those with recent exposure; and in some cases of x-ray–positive, remote tuberculosis. A PPD of at least 10 mm is considered positive for individuals from an endemic region, intravenous drug users, TB laboratory personnel, group-housing residents, patients less than 5 years of age, and those with a low body weight and comorbidities that place them at high risk for TB, such as diabetes, severe kidney disease, and certain types of cancer. PPD tests should be considered positive when at least 15 mm induration in other hosts with no known risk factors for TB.[77]

Interferon-γ release assays (IGRAs) carry a 70% to 90% concordance with PPD testing and can be used in all circumstances in which TST is currently used.[78–80] The IGRA is more specific than TST, but it is more expensive and requires whole blood testing.

Fungal skin tests do not distinguish between current and past infection; indeed, active disease is often accompanied by a negative skin test. The coccidioidin skin test is the best of the available tests, but the diagnosis of coccidioidomycosis is not excluded by a negative test. Blastomycin and histoplasmin skin tests are of little value because of frequent false-negative results and cross-reactions. Also, application of the histoplasmin skin test may falsely elevate antibody levels to the *H. capsulatum* mycelial antigen.

A negative skin test response to a specific antigen must be interpreted in the light of possible anergy. A battery of control antigens (mumps, *Candida*, *Trichophyton*, streptokinase–streptodornase) serves to detect such anergy, but these reagents are increasingly unavailable and costly.

INVASIVE DIAGNOSTIC PROCEDURES

Examination of respiratory specimens should always begin with sputum examination; however, this test may not be adequate for a presumptive diagnosis in all patients. Immunocompromised patients, those on mechanical ventilation, or patients in whom there is a broad microbiologic differential diagnosis may require more invasive procedures to obtain a respiratory specimen to guide management. Such techniques avoid potential contamination of sputum samples with upper airway flora; however, they are not without risk (Chapters 33, 34, and 35).

Important considerations include the type and location of the pulmonary lesion, the ability of the patient to cooperate with the required manipulations, the presence of coagulopathies, and experience of the operator in performing the procedure. For patients who are critically ill or unlikely to tolerate invasive procedures (e.g., immunocompromised hosts, those with recent major surgery, underlying heart or liver or renal failure, or COPD), it is reasonable to consider more invasive diagnostic procedures early in the clinical course, bearing in mind the risks inherent to invasive tests. In such patients, empiric antimicrobial therapies carry the risk of obscuring a specific microbiologic diagnosis, as well as drug-associated toxicities. Such an approach may also be required if the patient's condition continues to deteriorate, despite empiric antimicrobial therapy. The selection of an invasive procedure should be based on the nature of the illness and the likelihood of success for each procedure at the institution. Imaging is also a crucial consideration, as specific procedures may be better suited for lesions in specific intrathoracic locations.

The clinician should take into account the patient's immune status and the pathogenesis of the organism under consideration when devising a diagnostic strategy. For example, *P. jirovecii* pneumonia is an alveolar process, so examination of routinely collected expectorated sputum samples for *P. jirovecii* is not often diagnostic in immunosuppressed patients without HIV. However, in patients with advanced HIV, examination of induced sputa employing aerosolized, hypertonic saline may be helpful, since the number of organisms is high in these patients. Additionally, specimens can be evaluated using a tiered approach. If results of examination of induced sputa are negative, and clinical circumstances warrant further attempts at diagnosis, follow-up bronchoscopy with transbronchial biopsy or BAL may be performed to increase diagnostic sensitivity.

■ Fiberoptic Bronchoscopy

Fiberoptic bronchoscopy allows visualization of the tracheobronchial tree and collection of lower respiratory tract cultures through the use of protected brush catheters, bronchoalveolar lavage (BAL), and transbronchial biopsy (Chapter 33).

Endobronchial brushing involves use of a protected specimen brush, which is a brush enclosed within a catheter sheath to avoid contamination with oral flora. Insertion of a bronchoscope permits advancement of the brush out of the sheath and into the airway, allowing sampling of the involved area under direct visual guidance. After the specimen is obtained, the brush is withdrawn into its protective sheath and the sheath removed from the bronchoscope. The sample from the distal end of the brush can be sent for microbiologic testing as detailed above. Transbronchial biopsy increases the diagnostic yield and helps rule out noninfectious etiologies. It is indicated in diagnosis of pulmonary infections in the immunocompromised host and can be particularly helpful if fungal or mycobacterial infection is suspected.

BAL, performed during flexible bronchoscopy, is a method for evaluating processes at the alveolar level. This procedure involves instillation of sterile normal saline into a bronchial segment or subsegmental orifice, followed by suction and collection of the fluid for analysis. BAL allows sampling of a larger portion of the lung than transbronchial biopsy or brushing—sampling approximately 100 million alveoli.[12]

■ Diagnostic Testing in Ventilator-associated Pneumonia

Both bronchoscopic and noninvasive methods are employed for use of evaluating the lower respiratory tract in cases of suspected VAP (Chapter 129). Bronchoscopic BAL provides the highest diagnostic accuracy in diagnosing VAP. However, this requires expertise in performing the procedure and incurs risk associated with a more invasive procedure, including worsening hypoxemia and barotrauma.

Alternatives to use of BAL include the "mini-BAL" and endotracheal suctioning. The mini-BAL is performed by advancing a catheter through the endotracheal tube blindly until meeting resistance, at which time sterile saline is infused and aspirated. Mini-BAL may be used for patients in whom bronchoscopy is considered too dangerous. Endotracheal suctioning (sometimes called endotracheal aspirate) is performed by advancing a catheter through the endotracheal tube until resistance is encountered, at which time suction is applied to obtain a microbiologic specimen. Some prefer obtaining an endotracheal aspirate as the initial test in patients with suspected VAP, as this method is considered inexpensive and low risk. The ATS/IDSA 2016 Guidelines for VAP recommend use of endotracheal aspirate for diagnosis of VAP, given that it is inexpensive, provides rapid results, and is relatively lower risk than more invasive methods.[81] However, none of these methods has proved superior in diagnosing VAP, and the diagnostic approach is often dictated by institutional practices.[82]

■ Percutaneous Transthoracic Needle Lung Biopsy

Percutaneous needle biopsy, guided by radiology, is often the invasive diagnostic procedure of choice for a sizable (>1.0 cm) pulmonary nodule or cavity that is located peripherally. The small core of tissue and aspirated fluid is examined by stained smear and culture for various infectious agents. Cytologic examination should be done for neoplastic cells. Occasionally, fungal hyphae are seen. Because of the small volume of the specimen, however, histopathologic examination is generally less diagnostic. In patients with a tenuous respiratory status, or in whom lymph node biopsy or sampling of pleural fluid may be desired, video-assisted thoracoscopic surgery (VATS) or open biopsy may be preferred (Chapter 35).

■ Lung Biopsy

Open lung biopsy and VATS constitute the most definitive procedures for histopathologic diagnosis in the immunocompromised host. The procedures provide the highest yield for obtaining sufficient lung tissue for diagnosis and enable sampling of multiple sites. Surgical lung biopsy is particularly suitable for evaluating processes that may not be infectious (e.g., neoplasms, such as Kaposi sarcoma; antineoplastic drug toxicity; drug hypersensitivity; and lymphocytic interstitial pneumonia). However, the need for general anesthesia, inherent delays in preparing the patient for the procedure, the requisite intubation, the common need for placement of a chest tube, and postoperative splinting due to incisional pain may be significant challenges for the patient.

For the patient in whom the pace of the illness does not allow a sequential diagnostic approach, surgical lung biopsy may be the procedure of choice. Processing of lung biopsy specimens should include special stained imprint smears for *P. jirovecii*, bacteria (including *Nocardia* and mycobacteria), fungi, and viral inclusion bodies; cultures for bacteria, viruses, fungi, and mycobacteria; if available, NAAT for suspected organisms; and tissue sections for histology and for infectious agents.

PULMONARY INFECTIONS ACCORDING TO ETIOLOGY: VIRUSES, ATYPICAL PNEUMONIA, FUNGI, AND PARASITES

Thus far, discussion has focused on the approach to a patient with a suspected pulmonary infection and for whom a specific microbiologic diagnosis may not be known. The following discussion addresses the patient with a pulmonary infection due to a specific class of pathogen.

■ Viral Infections

Respiratory viral infections are a major cause of morbidity worldwide. Findings may occur in either the upper or lower respiratory tract. A more detailed discussion appears in Chapter 126. With upper tract disease, patients present with cough, sore throat, bronchoconstriction, fever, rhinitis, and suffusion of mucus membranes. The majority of these infections are isolated upper respiratory infections and of significance as causes of discomfort and as predisposing conditions for lower respiratory infections. Spread is via aerosolized droplets and inoculation of mucous membranes from hand contamination. The most prominent viral pathogens are rhinovirus and coronavirus, followed by adenovirus, parainfluenza virus, RSV, and influenza viruses. Less commonly, reovirus, enteroviruses, metapneumoviruses, and picornaviruses may cause the same symptoms.[83,84] Infections with respiratory viruses occur predominantly in the winter and early spring.

In considering lower respiratory infections, the most common viral pathogens include influenza, adenovirus, parainfluenza, respiratory syncytial virus, and human metapneumovirus. Viruses have the ability to undergo antigenic shift—thought to be related to interacting with animals and leading to a "jump" from animal species into humans. When antigenic shift occurs, most of the population will have little immunity to the new virus, allowing for development of a pandemic—as dramatically illustrated with the 2019 SARS-CoV-2 pandemic.

Influenza viral pneumonia usually occurs in the setting of an outbreak of influenza infections. Patients with underlying heart disease (mitral stenosis), those with chronic pulmonary disease, or those who are pregnant, as well as immunocompromised individuals, are disproportionately impacted. Unlike secondary bacterial pneumonia after influenza (a complication that occurs 1 to 4 days after improvement following typical upper respiratory illness), primary influenza pneumonia is part of the initial clinical presentation. In general, about 90% of infections are due to influenza A, and about 10% due to influenza B; variations are noted in any given year. Outbreaks of pandemic influenza (e.g., avian influenza, 2004–2007, A/H5N1) most likely arise from birds. In 2009 to 2010, the pandemic A/H5N1 was the result of avian, human, and swine influenza viruses in Mexico and was associated with significant mortality, particularly in those with underlying comorbidities, including diabetes, COPD, and obesity.

A novel Hantavirus, Sin Nombre virus, emerged in 1993 in the Four Corners area of New Mexico, Arizona, Colorado, and Utah. Although cases were reported worldwide, they occurred primarily in the west and southwestern United States.[85] The case fatality rate for the Hantavirus pulmonary syndrome is 50%.

Severe acute respiratory syndrome (SARS) is a viral respiratory illness that first appeared in southern China in 2002 before spreading globally. Its cause is a SARS-associated coronavirus (SARS-CoV). Between November 2002 and July 2003, a total of 8098 people worldwide developed SARS, and 774 died. No new cases were reported after July 2004. A related infection emerged in Saudi Arabia in 2012—Middle Eastern Respiratory Syndrome (MERS), caused by a coronavirus called MERS-CoV. MERS is a severe acute respiratory illness that presents with fever, cough, and shortness of breath following exposure in or near the Arabian Peninsula. Spread occurs by close contact, but sustained spread has not been identified. From 2012 until January 2020, the total number of deaths associated with MERS-CoV was 866 out of 2519 cases globally.[86] At the end of 2019, genomic sequencing identified a novel coronavirus SARS-CoV-2 as the cause of cluster of pneumonia cases in Wuhan, China. Infection spread rapidly, ultimately leading to the global COVID-19 pandemic.

Human metapneumovirus (HMPV) is a ubiquitous virus (Pneumovirinae subfamily, Paramyxoviridae family) that is a major cause of acute respiratory infection, particularly in children and in immunocompromised individuals. The virus has phenotypic and clinical characteristics similar to those of RSV, often presenting with bronchiolitis. The virus may coinfect individuals with other viral pathogens.

Atypical Pneumonia

Historically, so-called atypical pneumonia has been characterized as an indolent disease with a gradual onset. When referring to a bacterium as atypical, the implication is that the organism is not easily identified on routine smears (e.g., Gram stain, Ziehl–Neelsen stain) or cultures (including cultures for mycobacteria or *Legionella* species) and is resistant to β-lactam antibiotics. The syndrome was first described in the 1930s when physicians noted that a number of patients had milder symptoms than patients with the "typical" presentation attributed to *S. pneumoniae*, *H. influenzae*, *S. aureus*, and gram-negative rods.[87] Typically, the patient's cough is described as "dry," with minimal sputum production. Extrapulmonary symptoms, such as malaise, headache, and myalgias, are frequently reported.

TABLE 122-9 Causes of "Atypical Pneumonia"

Mycoplasma	
	M. pneumoniae
Chlamydophila	
	C. psittaci (psittacosis), *C. pneumoniae*
Bacteria	
	Legionella spp., *F. tularensis*, *Y. pestis*, *B. anthracis (agents of bioterrorism)*
Fungi	
	Histoplasma, *Blastomyces*, *Coccidioides*, *Pneumocystis*
Aspiration pneumonitis	
	Sterile or mixed upper respiratory and oral flora
Viral agents	
	Respiratory tract viruses: influenza, adenovirus, respiratory syncytial virus (RSV), parainfluenza virus, metapneumovirus
	Varicella-zoster, measles, Epstein–Barr virus (EBV), cytomegalovirus (CMV), Hantavirus
Rickettsia	
	C. burnetii (Q fever)

The etiologies of atypical pneumonia are heterogeneous and include bacteria, viruses, and fungi (Table 122-9). *M. pneumoniae* is the most common pathogen associated with atypical pneumonia and accounts for up to 15% of cases treated on an outpatient basis.[88] In adults, *M. pneumoniae* pneumonia often begins insidiously with malaise, fever, and prominent headache. Sore throat is common, but coryza is minimal or absent. Nonproductive cough, developing over a few days, is the hallmark of the disease. Small outbreaks of *M. pneumoniae* infection in households, schools, and military camps may not be appreciated because of the long incubation period and variation in clinical presentation.

Legionella accounts for 1% to 10% of cases of community-acquired pneumonia and is notable given its ability to cause severe disease that frequently necessitates care in an intensive care unit.[4,25,89] Respiratory viruses are responsible for another 30% of cases and should be considered in the initial evaluation. *Chlamydia pneumoniae*, *Chlamydia psittaci*, *Coxiella burnetii*, *Francisella tularensis*, *Yersinia pestis* (plague pneumonia), *Bacillus anthracis* (anthrax pneumonia), and endemic mycoses have all been described as causes of community-acquired pneumonia, albeit less frequently than the agents previously noted.

Fungal Pneumonia

Fungal pneumonia occurs most often in immunocompromised hosts. In the normal host, infection due to the endemic or geographic fungi (i.e., *Histoplasma capsulatum*, *Coccidioides immitis*) or to *Cryptococcus neoformans* may be asymptomatic or present with systemic signs. The diagnosis is often confused with acute bronchitis, viral infection, mycobacterial infection, or aseptic meningitis. Otherwise, fungal infection of the lungs is most commonly associated with anatomic defects (e.g., aspergilloma in a pulmonary cavity); it is otherwise rare in individuals without immune defects.

Pneumocystis jirovecii causes pneumonia in immunocompromised individuals, particularly those on corticosteroids. Hypoxemia is prominent and often accompanied by few physical or radiologic findings. As this infection is easily prevented, consideration should be given to prophylaxis in any individual receiving chronic immunosuppressive therapy, or who has HIV infection or AIDS unresponsive to antiretroviral therapy.

Traditionally, aspergilloma has been considered to represent noninvasive colonization of pulmonary cavities, although gross hemoptysis may complicate management, and dissemination may occur at the time of surgical resection. Immunosuppression may convert benign disease into invasive infection. Aspergillosis is among the more common and aggressive pneumonias seen after bone marrow and organ transplantation.

Mucormycosis (due to the *Mucoraceae*) causes rapidly progressive sinus and lung infection that requires surgical resection for cure. This infection is most common in diabetics and other immunocompromised hosts. Fusarium species typically disseminate via the bloodstream, producing diffuse pulmonary infiltrates that are often accompanied by skin lesions (Chapter 123).

■ Endemic Mycoses

The principal clues to the presence of pulmonary mycoses are epidemiologic (Chapter 133). The principal endemic areas for histoplasmosis are in the midwestern United States, Central and South America, and Africa. Disease may be found in other locales and after travel. The organism is present in high concentrations in soil sites where avian, chicken, or bat excrement has accumulated. Movement of soil in such endemic areas by cleaning chicken coops or bird roosts, in old attics, or caves may expose people to high concentrations of airborne spores that, when inhaled, produce an acute pneumonia.

Blastomycosis is endemic in the southeastern United States, and regions of note extend north into eastern Canada. Rural exposure to soil contaminated with animal excrement appears to be a risk factor. Skin lesions, either verrucous or ulcerative, are the most common extrapulmonary manifestations of blastomycosis and offer a clinical clue to diagnosis (Chapter 27).

Coccidioidomycosis is endemic in the southwestern United States (California, particularly the San Joaquin Valley, and Arizona) and in neighboring portions of Mexico. Infection is usually acquired in these areas by inhalation of highly infectious arthrospores. Occasionally, major dust storms carry the arthrospores considerable distances from their soil source and produce unexpected outbreaks of infection. Archeologic digs sometimes cause infection in those living elsewhere who have received an artifact uncovered in the explorations. Erythema nodosum may be associated with any of the primary pulmonary mycoses, but most often with coccidioidomycosis. The coincidence of this hypersensitivity skin lesion and an atypical pneumonia syndrome in a person from an endemic area suggests the possibility of one of these pulmonary mycoses.

Paracoccidioidomycosis (South American blastomycosis) is endemic to Brazil and is found in Colombia, Venezuela, and Argentina. The disease is caused by *Paracoccidioides brasiliensis*. In adults, the manifestations of the disease are mainly pulmonary; radiographs show patchy or confluent areas of consolidation, often bilateral. Cases have occurred in North America and Europe, but in those instances, the patients had previously resided in endemic areas where initial infection presumably had been acquired.

■ Parasitic Pneumonia

Parasitic pneumonias are rare and require endemic exposures (Chapter 135). Pneumonias occur when the organism lifecycle includes the lungs. Pulmonary infections due to migrating worms include Loeffler-like syndrome with *Ascaris lumbricoides*; post-obstructive pneumonitis and polymicrobial systemic sepsis and meningitis due to *Strongyloides stercoralis*; cysts and nodules due to *Echinococcus granulosus*, *Paragonimus westermani,* and *Schistosoma* species; and pulmonary eosinophilia with filariasis. Infection by *Entamoeba histolytica* causes pleuropulmonary disease as a result of (1) *sympathetic* reaction to an unruptured abscess within the liver; (2) empyema, after rupture of the liver abscess into the pleural space; or (3) parenchymal involvement with abscess, consolidation, or hepatobronchial fistula after the rupture of a liver abscess.

Acute infection due to *Toxoplasma gondii* in the immunocompetent host is generally asymptomatic, with cervical lymphadenopathy as the hallmark of disease. It may be confused with mononucleosis caused by Epstein–Barr virus or CMV. Fever, malaise, sore throat, and hepatosplenomegaly also are seen, and the peripheral blood may manifest atypical lymphocytosis. Rarely, acute disease may present with severe dissemination, marked by pneumonitis, hepatitis, encephalitis, polymyositis, or myocarditis.

FAILURE OF THERAPY

Nonresolving pneumonia may be a result of inappropriate antibiotics, superinfection, inadequate host response, airway obstruction, empyema, noninfectious processes, or recurrent infection.[90] Inappropriate antimicrobial therapy includes inadequate dosing, use of agents that fail to penetrate infected lung tissue (e.g., aminoglycosides or daptomycin), or use of agents to which the organisms are resistant.[91] Common examples of resistance include use of a β-lactam, such as amoxicillin in the case of β-lactamase–producing *H. influenzae*; use of azithromycin or doxycycline for resistant *S. pneumoniae;* or infection with *Pseudomonas* or MRSA, which are not adequately treated with empiric regimens for outpatient CAP. Failure to respond could represent progression of a viral pneumonia to bacterial superinfection, often with MRSA. Empyema or loculated infection may evolve during appropriate therapy for pneumonia. Relapsed infection is common in intubated patients colonized with resistant microorganisms. Unresolving pneumonia may also result from infections with mycobacteria (*M. tuberculosis* and nontuberculous mycobacteria), endemic mycoses (*Blastomyces dermatitidis*, *Histoplasma capsulatum*), or less common bacteria, including *Nocardia* and *Actinomyces israelii.* These infections are more difficult to diagnose and treat. *Nocardia* and *Aspergillus* should be considered in the immunosuppressed host. Untreated endovascular infections, intraabdominal abscess, or septic pulmonary emboli may cause persistent, evolving lung infections.

In the immunocompromised host, reduction of exogenous immunosuppression, repletion of antibodies through the use of intravenous immunoglobulin, normalization of low neutrophil counts (via use of colony-stimulating factor), treatment of concomitant viral infections (HIV, CMV), and repeat culturing may assist in management. Airway obstruction or empyema must be addressed to promote source control and resolution of infection. Recurrent infection may be observed when there are mechanical issues at play, for example, if there is ongoing aspiration or sinusitis, if the patient has a misplaced feeding tube or has airway narrowing, or if a pulmonary embolism with infarction has occurred. Additional cultures and radiologic studies (e.g., CT scans) may assist in defining lung processes failing to respond to therapy. Bronchoscopic evaluation and, in selected patients, lung biopsy also may assist in further diagnosis and management.

NONINFECTIOUS PROCESSES MIMICKING PULMONARY INFECTIONS

The list of noninfectious disorders that mimic pulmonary infections is extensive (Table 122-10). These diagnoses should be considered

TABLE 122-10 Noninfectious Causes of Febrile Pneumonitis Syndrome (Mimics of Pulmonary Infection)

- Drug-induced pulmonary disease
- Hypersensitivity pneumonitis
- Injury due to inhaled toxic gases, dusts, chemicals
- Acute eosinophilic pneumonia
- Chronic eosinophilic pneumonia
- Interstitial lung disease associated with autoimmune/connective tissue disorders
  - Systemic lupus erythematosus
  - Polymyositis–dermatomyositis
  - Mixed connective tissue disease
- Interstitial lung disease associated with pulmonary vasculitis
  - Granulomatous polyangiitis (formerly known as Wegener granulomatosis)
  - Lymphomatoid granulomatosis
  - Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)
  - Polyangiitis overlap syndrome
- Interstitial lung disease associated with airway disease
  - Allergic bronchopulmonary aspergillosis
  - Bronchocentric granulomatosis
  - Bronchiolitis obliterans (OB) and bronchiolitis obliterans with organizing pneumonia (BOOP)
- Acute or subacute interstitial pulmonary fibrosis (AIP)
- Idiopathic interstitial pneumonia
  - Usual interstitial pneumonia (UIP)
  - Nonspecific interstitial pneumonia (NSIP)
  - Desquamative interstitial pneumonia (DIP)
  - Respiratory bronchiolitis interstitial lung disease (RB-ILD)
  - Acute interstitial pneumonia (AIP)
  - Cryptogenic organizing pneumonia (COP)
  - Lymphoid interstitial pneumonia (LIP)
- Pulmonary neoplasms
- Sarcoidosis
- Pulmonary infarction
- Acute chest syndrome in sickle-cell crisis
- Radiation pneumonitis
- Lipoid pneumonia (exogenous or endogenous)
- Acute respiratory distress syndrome (ARDS)
  - Extrapulmonary sepsis
  - Oxygen toxicity, chemical inhalation or aspiration, or aspiration of gastric contents
  - Pancreatitis
  - Fat embolization (surgery, trauma)
  - Shock of various etiologies
  - Drug overdose (aspiration)
  - Chest trauma
- Transfusion-related acute lung injury (TRALI)
- Pulmonary alveolar proteinosis
- Plasma cell granuloma
- Eosinophilic granuloma
- Idiopathic pulmonary hemosiderosis
- Goodpasture syndrome—GBM disease
- Miscellaneous

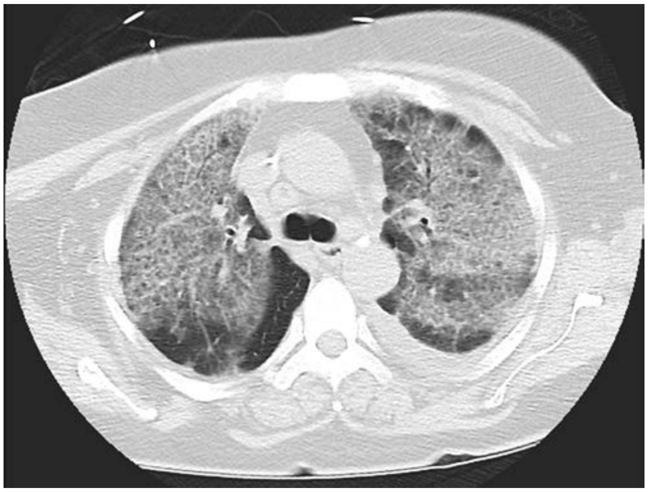


Figure 122-13 Bilateral ground-glass opacities on computed tomography in patient eosinophilic pneumonia. *(Reproduced with permission from Dr. M. Kavanaugh.)*

in the course of taking the initial history and reviewed again if the initial diagnosis does not improve with seemingly appropriate treatment.

The likelihood of noninfectious etiologies of pulmonary disease increases if the Gram-stained smear and culture of sputum are unrevealing, if the initial response to empiric antimicrobial therapy proves unsatisfactory, or if radiographic findings are atypical. Similar histologic appearances result from both infectious and noninfectious etiologies. The presence of a maculopapular skin rash, generalized lymphadenopathy, joint or rheumatologic symptoms, or peripheral eosinophilia should suggest hypersensitivity or a rheumatologic etiology, such as eosinophilic pneumonia (Fig. 122-13).

As noninfectious and infectious processes often coexist, it is essential to exclude infectious causes of pulmonary dysfunction before treating. Immunosuppressive agents, notably corticosteroids, will reduce inflammation due to both infectious and noninfectious causes, and may contribute to progression of untreated infection. Noninfectious etiologies such as sarcoidosis, granulomatosis with polyangiitis, or pulmonary emboli may masquerade as a respiratory infection. A chest radiograph of a patient with sarcoidosis is shown in Fig. 122-14. Findings could be mistaken for an infectious process on initial evaluation. Patients who present repeatedly with symptoms suggestive of pneumonia that do not improve with antibiotics should be evaluated for noninfectious processes.

CONCLUSION

Pulmonary infections include a broad array of disease entities with varying degrees of severity. This chapter provides a general approach to caring for a patient with a suspected pulmonary infection. Successfully diagnosing and treating a patient with pneumonia requires a thorough history and physical examination, as well as obtaining multiple diagnostic studies to better characterize the underlying pathology. Radiographs allow the practitioner to assess the severity of pneumonia and to distinguish this process from acute bronchitis. Unfortunately, no radiographic findings are specific enough to define the microbial origin of a given pneumonia or pulmonary infiltrate. The only definitive way to obtain a specific etiologic diagnosis is through demonstration of the infecting organism. With varying sensitivity and specificity, this can be achieved by examination of stained smears of sputum and pleural fluid or other biologic materials, culturing respiratory secretions and blood, demonstrating nucleic acids or proteins from an infecting microorganism, or demonstrating an increase in antibody titer against

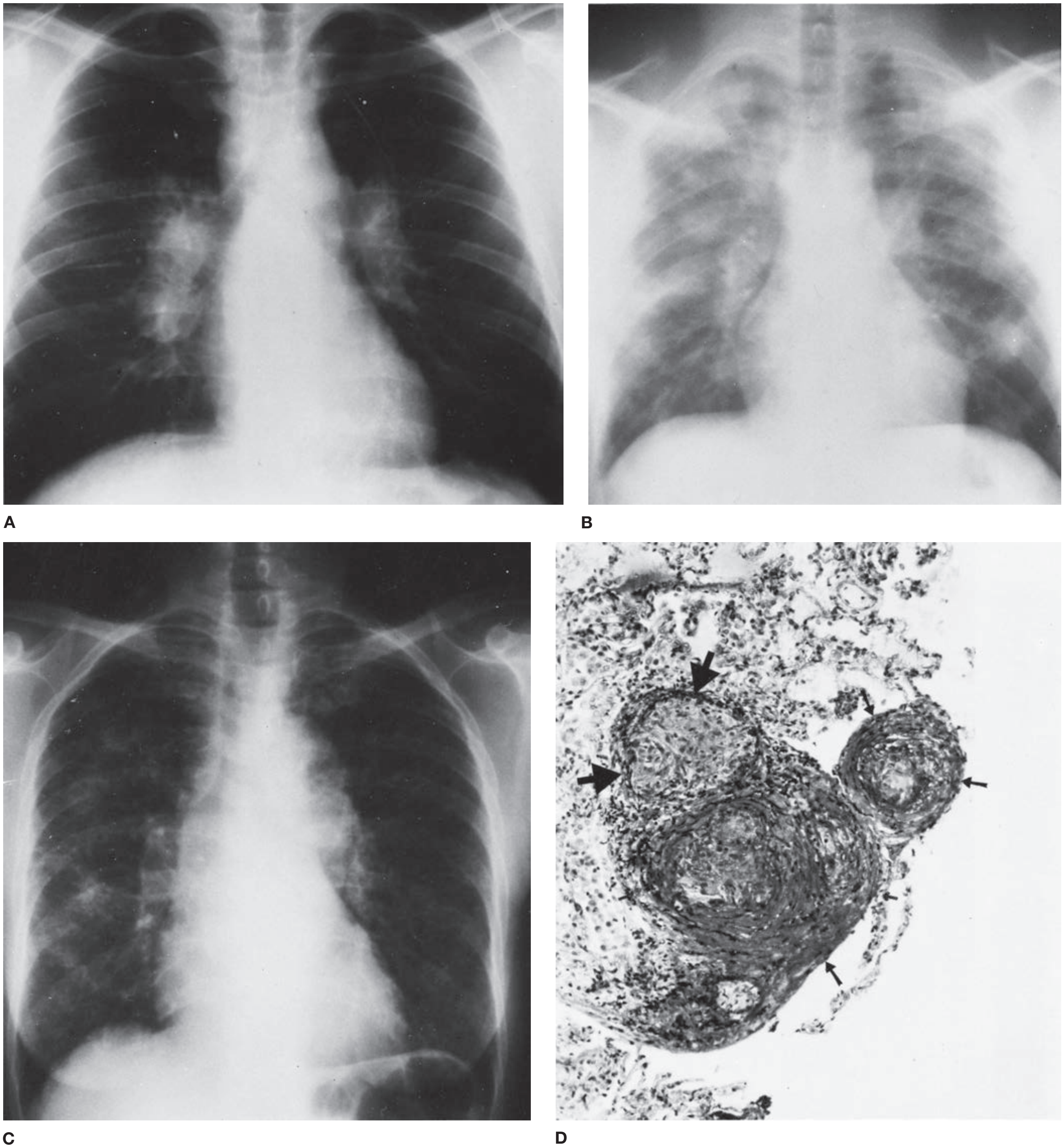


Figure 122-14 **A–C.** Chest radiographs illustrating the various stages of sarcoidosis. **A.** Stage I, bilateral hilar adenopathy. **B.** Stage II, bilateral hilar adenopathy with parenchymal infiltrates. **C.** Stage III, parenchymal infiltrates without hilar adenopathy. **D.** Transbronchial lung biopsy from a patient with sarcoidosis. *Small arrows* indicate granuloma with a surrounding rim of collagen (confirmed by positive trichrome staining). The *large arrows* indicate a granuloma without a surrounding rim of collagen. Original magnification ×10.

the infecting microorganism. Notably, these microbiologic studies are recommended only for severely ill patients, immunosuppressed patients, or those being started on antibiotics for resistant organisms (such as MRSA and *Pseudomonas*). Often, the microbiologic etiology is not identified at the time of presentation, and treatment must be initiated empirically. It is important to follow the patient's clinical arc, changing antibiotics if necessary, and discontinuing them when an alternative diagnosis becomes more apparent. Ultimately, pulmonary infections are among the most common and serious challenges a clinician will face. Having a solid framework for obtaining information and synthesizing a clinical plan to facilitate swift action when caring for these patients is crucial.

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CHAPTER 123

Approach to Pulmonary Infection in the Immunocompromised Host

Matthew B. Roberts
Camille Nelson Kotton

OVERVIEW

Immunocompromised host is a term encompassing a growing group of individuals with a variety of immunocompromising conditions and varying degrees of immunodeficiency.[1] The group includes persons with human immunodeficiency virus (HIV), solid organ transplant (SOT) recipients, hematopoietic stem cell transplant (HSCT) recipients, those on chemotherapy for malignancies, those receiving medications for autoimmune conditions, those with primary immune deficiencies, and those with acquired or intrinsic immune deficiencies.

This large and diverse group is expanding as medical therapies improve and evolve. Similarly, the medical complexity of the immunocompromised host is rising with new therapeutic agents, use of immunosuppressive agents later in life as immunosenescence occurs,[2] and prolonged survival of immunocompromised individuals. This prolonged survival is frequently due to improved management of infectious complications of immunodeficiency.[3]

Pulmonary infections encompass a major category of infectious complications affecting these individuals.[4–8] Pulmonary infections in immunocompromised hosts have a spectrum beyond that of immunocompetent hosts, with greater variety of presentations and the potential for both multiple infections *and* noninfectious processes to occur simultaneously. Opportunistic infections (those infections that do not usually occur in immunocompetent individuals, or that do so with increased virulence) are an important group of infections in immunocompromised hosts, but common or "typical" infections continue to constitute the majority of infections occurring in immunocompromised hosts, albeit often with more severe or prolonged manifestations.

While some infections are more common with specific immune deficits (Table 123-1), this is not always the case. Similarly, many patients have multiple simultaneous immune deficits, making an immune deficit approach alone inadequate for clinical management.

This chapter aims to provide an adjunct to the preceding chapter on pulmonary infection in the immunocompetent host (Chapter 122) in order to provide a framework with which clinicians can approach the wide variety of presentations immunocompromised patients with possible pulmonary infection may have, rather than specific details about individual disease states or infection, which can be found in later chapters of this text.

GENERAL PRINCIPLES OF MANAGEMENT OF OPPORTUNISTIC INFECTION

Opportunistic infection is defined as infection occurring as a result of compromised immune function and that would not be expected to occur, or would otherwise cause disease of lesser intensity in the presence of normal immune function. Thus, immunocompromised individuals are subject to infections commonly present in the community; however, these infections are likely to be of greater frequency or severity than in the immunologically normal host. In addition, infection in these patients may be caused by organisms of low native virulence or that cause insignificant disease in the normal host, including such organisms as *Pneumocystis jirovecii* or cytomegalovirus (CMV).

The risk of infection in any patient is determined by the interaction of two factors: the potential pathogens to which the individual is exposed (epidemiologic exposures), and a measure of

TABLE 123-1 Infections Associated with Specific Immune Defects

Defect	Common Causes	Associated Infections
Granulocytopenia/ neutropenia	Leukemia, cytotoxic chemotherapy, HIV, drug toxicity, Felty syndrome	Enteric Gram-negative bacteria, *Pseudomonas*, *S. aureus*, *Staphylococcus epidermidis*, streptococci, *Aspergillus*, *Candida*, other fungi
Neutrophil chemotaxis	Diabetes, alcoholism, uremia, Hodgkin disease, trauma (burns), lazy leukocyte syndrome, CT disease	*S. aureus*, *Candida*, streptococci
Neutrophil killing	Chronic granulomatous disease, myeloperoxidase deficiency	*S. aureus*, *E. coli*, *Candida*, *Aspergillus*
T-cell defects	HIV, congenital, lymphoma, sarcoidosis, viral infection, HSCT, solid-organ transplants, steroids, purine analogues (fludarabine)	Intracellular bacteria (*Legionella*, *Listeria*, mycobacteria), HSV, VZV, CMV, EBV, parasites (*Strongyloides*, *Toxoplasma*), fungi (*P. jirovecii*, *Candida*, *Cryptococcus*)
B-cell defects	Congenital/acquired agammaglobulinemia, burns, enteropathies, splenic dysfunction, myeloma, acute lymphocytic leukemia, use of anti-CD20 agents (e.g., rituximab)	*S. pneumoniae*, *H. influenzae*, *Salmonella* and *Campylobacter* spp., *Giardia lamblia*, Gram negative (*E. coli*, skin)
Splenectomy	Surgery, sickle-cell anemia, cirrhosis, use of eculizumab	Encapsulated bacteria (*S. pneumoniae, H. influenzae, N. meningitidis*), *Salmonella* spp., *Capnocytophaga canimorsus*
Complement	Congenital/acquired defects	*S. aureus*, *Neisseria* spp., *H. influenzae*, *S. pneumoniae*, *Capnocytophaga*
Anatomic defects/ compromise	Intravenous or urinary catheters, incisions, anastomotic leaks, mucosal ulceration, vascular insufficiency	Colonizing organisms, resistant nosocomial organisms

TABLE 123-2 Factors in the "Net State of Immunosuppression"

- Immunosuppressive therapy
  - Dose
  - Duration
  - Temporal sequence
- Underlying immune deficiency
  - Autoimmune disease
  - Functional immune deficits
- Mucocutaneous barrier integrity
  - Catheters
  - Epithelial surfaces
  - Devitalized tissue
  - Fluid collections
- Neutropenia, lymphopenia
- Metabolic conditions
  - Uremia
  - Malnutrition
  - Diabetes
  - Alcoholism with cirrhosis
- Viral infection
  - Cytomegalovirus
  - Epstein–Barr virus
  - Hepatitis B and C
  - Human immunodeficiency virus
  - Respiratory viruses

the individual's susceptibility to infection, termed the "net state of immunosuppression" (Table 123-2).[9–11]

The occurrence of infection in an individual at a time when the immune status of the patient is thought to be nearly normal is evidence that either an excessive environmental exposure has occurred or that the immune status of the individual is depressed. Conversely, even minimal environmental exposures may cause invasive infection in an individual who is maximally immunosuppressed.

Several key concepts help guide the approach to pulmonary infection in the immunocompromised host:

- The combination of epidemiologic exposures and net state of immunosuppression provides guidance as to the spectrum of pathogens that many be encountered.
- The timing of illness onset relative to commencement of the immunocompromised state can be a useful guide to likely infection in some hosts, such as those with HIV, solid organ transplant recipients, bone marrow transplant recipients, and those receiving chemotherapy for cancer.
- Clinical and radiographic features at presentation are often vague or atypical compared with immunocompetent hosts.
- Specific and accurate microbiologic diagnosis is essential for diagnosis and successful management.
- Immune reconstitution syndrome can occur with institution of antimicrobial therapy or reduction in immunosuppressive state.
- Multiple infectious and noninfectious processes can occur simultaneously in immunocompromised hosts.

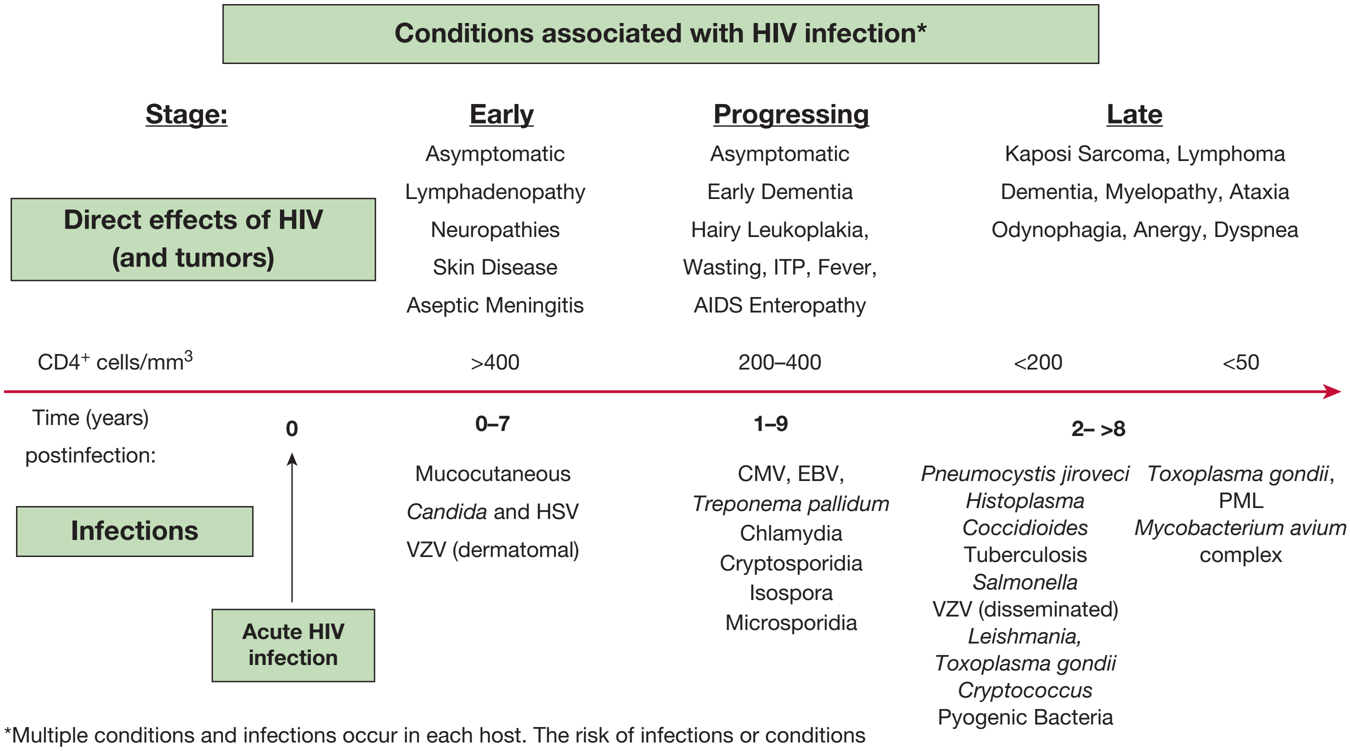
■ The Net State of Immunosuppression

The *net state of immunosuppression* (Table 123-2) is a conceptual framework for the host factors that contribute to infectious risk.[10] These include the dose, duration, and temporal sequence in which immunosuppressive drugs are deployed; injuries to the primary mucocutaneous barrier to infection (e.g., indwelling catheters and drains); leaks and fluid collections (hematoma, effusions, ascites); ischemic tissues; surgical anastomoses; neutropenia or lymphopenia; underlying immunodeficiency; pulmonary aspiration injury; metabolic problems including protein–calorie malnutrition, uremia, and hyperglycemia; and infection with immunomodulating viruses (CMV, Epstein–Barr virus [EBV], hepatitis B and C, influenza, and human immunodeficiency virus [HIV]). These viruses predispose to other opportunistic infections and also to graft rejection and to graft-versus-host disease (GVHD). Foreign materials (e.g., vascular grafts, heart valves, sutures) provide a nidus for infection for an organism that would not be capable of causing infection under normal conditions.

The sum of the congenital, metabolic, medication, and surgery-related factors is the patient's net state of immunosuppression.[10] Generally, more than one factor is present in each host; the identification of the relevant factors, and correction when possible, is central to the prevention and treatment of infection in these hosts. For example, in the lung transplant recipient with CMV infection and thoracic fluid collections, the net state of immunosuppression includes the immunosuppression used to maintain graft function; diminished immunologic responsiveness due to CMV; the risk of empyema and bacteremia from fluid collections at surgical sites; exposure to, and colonization with, community-acquired and nosocomial organisms; and new infections (e.g., aspiration, *Clostridium difficile* colitis) that may occur during the prolonged waiting period for a compatible organ. When the organ for transplantation becomes available, it may carry latent infection (e.g., CMV, EBV, *Mycobacterium tuberculosis*) or organisms acquired by the donor during hospitalization (e.g., bacteremia) or procurement. The recipient is often critically ill and is subjected to a major surgical procedure. After surgery, the lungs are apt to be compromised, recovery of function in the allograft is often slow, immunosuppressive drugs are initiated, intravenous and urinary catheters and drains are placed, and major incisions need to heal. Drug toxicities are common and may result in renal dysfunction, confusion, or neutropenia. The sum of the underlying, operative, medication, and transplant-related factors is the net state of immunosuppression.

Pulmonary defense mechanisms are compromised to varying degrees in immunocompromised hosts (Chapter 122). Structural defects (fibrosis, airway or lymphatic obstruction by tumor, emphysema) interfere with normal clearance mechanisms. Clearance mechanisms are further impaired by excess mucus and ciliary defects, as in cystic fibrosis, congenital defects, and after lung transplantation, including those due to recent viral or bacterial infections. For example, *Mycoplasma* shears off epithelial cilia, incapacitating the mucociliary elevator.[12] Viral infections may immobilize pulmonary macrophages (CMV), produce local or systemic immunosuppression, and disrupt the local cytokine network.[13] These effects are amplified in the lung transplant recipient in whom the impact of systemic immunosuppression is added to the possible effects of tracheal anastomotic narrowing and tissue ischemia, an impaired cough reflex, progressive bronchiolitis obliterans syndrome, decreased pulmonary T-cell and macrophage functions, hypogammaglobulinemia, and disrupted lymphatic drainage. Thus, in the solid-organ transplantation recipient, the immunosuppression used to prevent graft rejection, as well as technical factors, the diminished host immune responses in the major histocompatibility–mismatched organ, and the impact of immunosuppressive viral infections are the main mediators of susceptibility to infection.

In the stem cell recipient, the intensity of immunosuppression varies with the degree of histocompatibility mismatch between donor and recipient. Nonmyeloablative regimens have reduced the duration of the initial period of neutropenia. Susceptibility


Conditions associated with HIV infection*
Stage:
Early
Progressing
Late
Direct effects of HIV (and tumors)
Asymptomatic
Lymphadenopathy
Neuropathies
Skin Disease
Aseptic Meningitis
Asymptomatic
Early Dementia
Hairy Leukoplakia,
Wasting, ITP, Fever,
AIDS Enteropathy
Kaposi Sarcoma, Lymphoma
Dementia, Myelopathy, Ataxia
Odynophagia, Anergy, Dyspnea
CD4+ cells/mm3
>400
200–400
<200
<50
Time (years) postinfection:
0
0–7
1–9
2– >8
Infections
Acute HIV infection
Mucocutaneous
Candida and HSV
VZV (dermatomal)
CMV, EBV,
Treponema pallidum
Chlamydia
Cryptosporidia
Isospora
Microsporidia
Pneumocystis jiroveci
Histoplasma
Coccidioides
Tuberculosis
Salmonella
VZV (disseminated)
Leishmania,
Toxoplasma gondii
Cryptococcus
Pyogenic Bacteria
Toxoplasma gondii,
PML
Mycobacterium avium complex

*Multiple conditions and infections occur in each host. The risk of infections or conditions from early in the course of disease will persist without specific therapy or prophylaxis. *Mycobacterium* tuberculosis may occur at any point in the continuum. HIV-2 may have slower progression than HIV-1.

Figure 123-1 Timeline of infections in untreated HIV with typical CD4+ T-cell count.

to infection in both autologous and allogeneic HSCT recipients, however, persists despite immune reconstitution.[14] Innate immune function is reduced early (first 6 months) as NK cells and alveolar macrophages suffer dysregulation of cytokine, eicosanoid (leukotrienes, prostanoids), and intracellular signaling, and alterations in scavenger receptors, resulting in reduced phagocytosis and bacterial and fungal killing. Over time, persistent reductions are observed in multiple T- and B-cell lineages and maintained in the setting of chronic GVHD.[15] T-cell functions are suppressed by the immunosuppressive agents used to prevent or treat GVHD.

The Timeline of Infections

Certain immunocompromising states have a "typical" timeline of infections that have been well characterized and are an important clinical tool when evaluating these patients.[14,16,17] With standardized immunosuppressive and chemotherapeutic regimens, specific types of infections often occur in a predictable pattern as a reflection of the specific risk factors present at each phase of the immunosuppressed state. This is best illustrated in patients with HIV (Fig. 123-1) and patients who have had HSCT or SOT (Fig. 123-2). These timelines are altered by specific immunosuppressive regimens, use of antimicrobial prophylaxis, and individual factors (e.g., underlying immune deficits, microbial colonization, organ dysfunction, epidemiologic exposures), but they are useful in considering the "likely" etiology of infectious syndromes in immunocompromised hosts.[5,14]

Timelines (Figs. 123-1 and 123-2) are used in a number of ways:

- To develop a *differential diagnosis* for infectious syndromes by time posttransplant—what type of infections are most likely at various times after transplantation.
- To develop prophylactic strategies for each patient population based on general considerations (e.g., duration of neutropenia or of T-cell defects) and patient- or institution-specific patterns (e.g., microbial resistance, drug allergies).
- To identify *excess epidemiologic hazards*, including *nosocomial hazards*—for example, *Aspergillus*, methicillin-resistant *Staphylococcus aureus,* and vancomycin-resistant enterococci, which may be clustered in time and space, by inpatient unit, by procedures, or by surgical suite; *community exposures*—for example, respiratory viruses, *Legionella*, other outbreaks (SARS-CoV-2); and *individual risks*, including unique exposures (e.g., hobbies), travel, and occupational hazards.
- *To assess excessive immunosuppression*—too many infections or unusual severity and/or at the wrong time on timeline suggesting that a problem exists with routine immunosuppressive regimens.

The patterns are altered by antimicrobial prophylaxis, antiviral therapies for HIV, CMV, and hepatitis B and C viruses, the broader range of immunosuppressive and chemotherapeutic agents, and the use of nonmyeloablative conditioning regimens for HSCT. However, the general concepts and major determinants of infection remain the same: the epidemiology of the patient and the intensity of immunosuppression coupled with mucosal injuries and other individual risk factors. Superimposed viral infections will increase the risk of opportunistic infection at any point along the timeline.

In immunocompromised hosts, the risks of infection may be *relatively stable* over time, as in the diabetic with vasculopathy and neuropathy who is prone to skin and soft tissue infections. The risks of infection may be *time-limited*, as in the postsurgical patient without complications. The risk of infection may be *cumulative and progressive*, as in the untreated patient with HIV, in whom infection is a function of declining immune function and immune memory, falling CD4+ lymphocyte counts, rising viral loads, and the effects of persistent infections (CMV, *Cryptosporidium*) (Fig. 123-1).[17,18] In these individuals, the occurrence of new types of infection suggests the progression of immunocompromise.

The risks of infection may also *change predictably with time* as a function of relatively standardized immunosuppressive regimens

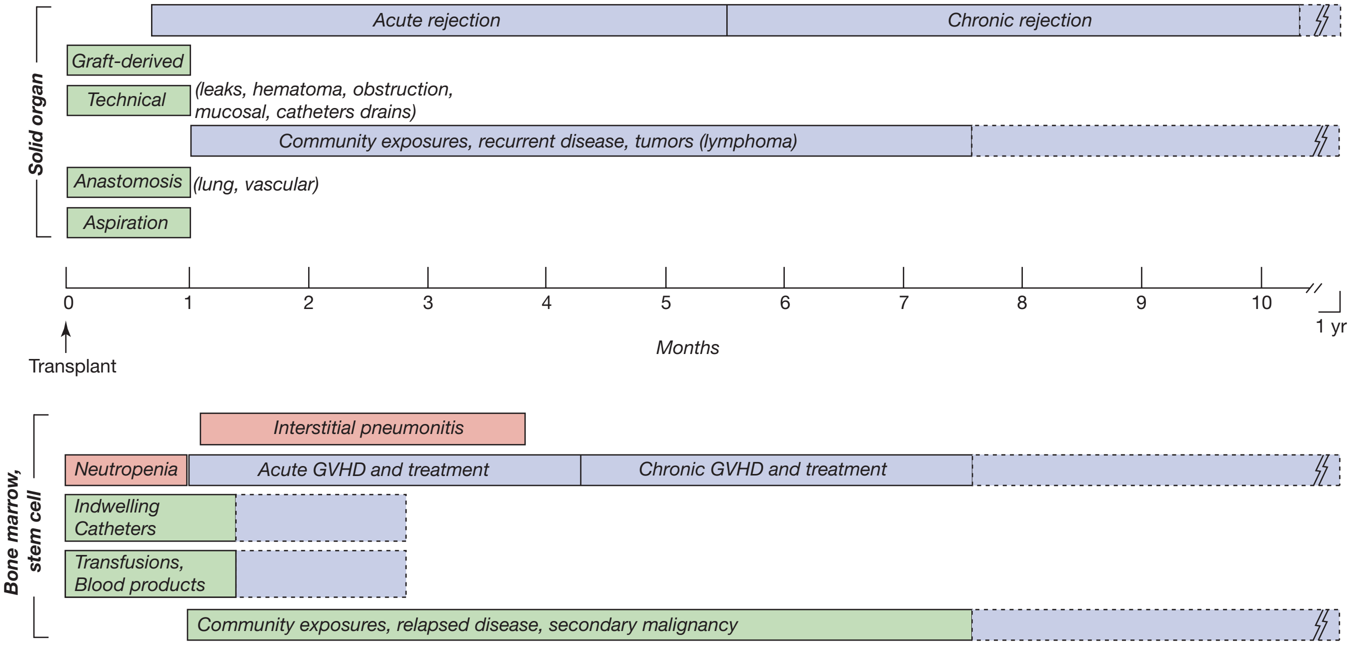


Figure 123-2 The timelines of conditions predisposing to infection in solid-organ transplantation *(above the timeline)* and in bone marrow and stem cell transplantation *(below the timeline)*. Patients vary in individual susceptibility patterns and with regard to prophylactic therapies.

and the evolving condition of the patient, as in allogeneic HSCT or solid-organ transplantation.[14,16] For example (Fig. 123-2), in the early phase after HSCT or the "pre-engraftment phase," the risk for infection is driven by neutropenia and mucositis and is generally related to nosocomial or endogenous exposures (Gram-negative and Gram-positive bacteria, *Candida* and *Aspergillus* species).[19] With nonmyeloablative preparative regimens, this period is generally 14 to 21 days, but it may be significantly longer. This reflects microbial colonization, pre-existing infections, and the impact of vascular access catheters, as well as defects in innate immune function and in mucosal barriers. Subsequently, following marrow engraftment (the "early post-engraftment phase" lasting approximately 3 weeks to 3–6 months), with continued immunosuppression and the absence of full cellular immune function, viral infections predominate, including pneumonitis or colitis (herpes, shingles, CMV, respiratory and enteric viruses), as well as encapsulated bacteria, *Pneumocystis*, and *Aspergillus*.[14] In this period, unusual infections (toxoplasmosis) and endemic pathogens also must be considered. Thus, "common" pathogens might be dengue virus and *Mycobacterium tuberculosis* in Southern Asia, or *Paracoccidioides* and *Mycobacterium tuberculosis* in Brazil. Full immune recovery is not achieved before 12 to 24 months, and gaps in immune function may persist for longer periods. During the development of and treatment for acute and chronic GVHD, susceptibility to infection is a function of the intensity of immunosuppression and mucosal injuries (from GVHD, chemotherapy, radiation, or infections such as *C. difficile* colitis). In patients with GVHD in particular, bronchiolitis obliterans, posttransplant lymphoproliferative disorders, and idiopathic pneumonitis syndrome may be observed.[20] Nonmyeloablative conditioning has reduced the rate of diffuse alveolar hemorrhage (early), hepatic veno-occlusive disease, and idiopathic pneumonitis syndrome.[20]

In the solid organ transplant recipient, immunosuppression is most often continued for the life of the transplanted organ. Early (first month) nosocomial infections (surgical and nosocomial) and donor-derived infections are observed, but opportunistic infections are not generally seen as the full impact of immunosuppression is not yet appreciated.[16] After a month, as the effects of immunosuppression are maximized, viral infections predominate (CMV, EBV, other herpesviruses, BK polyomavirus, respiratory viruses), and opportunistic pathogens (*Nocardia*, *Toxoplasma*, *Cryptococcus*, *Pneumocystis*, mycobacteria, and endemic species) are observed.[16] The endemic species include community-acquired infections, such as geographically restricted fungi (*Histoplasma*, *Coccidioides*, *Blastomycosis*, *Paracoccidioides*) and parasites (*Trypanosoma cruzi*, *Leishmania*, *Strongyloides*).

Because each risk factor renders the patient susceptible to infection by new groups of pathogens, infections occurring with the "wrong" pathogen or at the wrong time suggest an undiscovered "immune deficit" (fluid collection, neutropenia) or an unusual epidemiologic exposure (Table 123-1). The occurrence of specific infections can be prevented by the use of antimicrobial prophylaxis, vaccines, and behavioral modifications (e.g., no raw vegetables or digging in gardens without masks). This may result in a "shift to the right" of the timeline in that infections are delayed but incompletely prevented unless the intensity of immunosuppression is reduced.[5,16]

PREVENTION OF PULMONARY INFECTION

A key requirement for clinicians prescribing immunosuppression is consideration of whether screening and/or treatment for latent or active infection are required *prior* to immunosuppression and whether antimicrobial prophylaxis needed. When there is uncertainty, consulting an expert or a consensus guideline will often provide useful tools to guide the clinician. Consideration must also be given that guidelines cannot cover all scenarios and at times. For instance, a patient with systemic lupus erythematosus on hydroxychloroquine and 15 mg of prednisone would not usually reach a threshold in most guidelines to require *Pneumocystis* prophylaxis. However, should that patient develop new lupus nephritis, require dialysis, and commence cyclophosphamide then the "net state of immunosuppression" has changed, and *Pneumocystis* prophylaxis should be reconsidered.

Given the often predictable occurrence of many infections in particular hosts, for example *Pneumocystis* in people with HIV and CD4+ counts below 200 cells/μL, the potential to prevent infection with prophylaxis is a key consideration in any immunosuppressed host. The inability to objectively measure the "net state of immunosuppression" means providing universal guidelines for screening and prophylaxis that apply to all hosts is not possible. This lack of a "global guideline" has necessitated numerous international and regional guidelines based on patient group.[21–33]

Pre-immunosuppression Assessment

Pre-immunosuppression assessment including management of active and latent infection can prevent considerable morbidity and mortality. Pre-immunosuppression screening varies by patient, exposures, and treatment group, but should at a minimum include HIV, hepatitis B virus, hepatitis C virus, *Treponema pallidum* (syphilis), *M. tuberculosis*, and *Strongyloides stercoralis*. Additional screening may be required based on epidemiologic, patient, and treatment factors (e.g., *Coccidioides* sp., malaria, *Toxoplasma gondii*, *Trypanosoma cruzi*). Ideally, any active infections are treated prior to initiation of immunosuppression.

Pre-immunosuppression assessment for *M. tuberculosis* should be undertaken in all patients, given its high global prevalence, capacity for prolonged latency, and potential for high morbidity and mortality with reactivation. In the those without active tuberculosis, careful questioning on potential exposure, previous testing results, and previous treatment should be undertaken in order to determine level of risk. In addition to history, screening for latent tuberculosis typically involves a test of T-cell memory to *M. tuberculosis* exposure with either tuberculin skin test (TST) or interferon-γ (IFN-γ) release assay.[34] Both tests can be falsely negative, particularly in those already on immunosuppression or with active tuberculosis. IFN-γ release blood assays are more sensitive than TST, while maintaining high specificity for *M. tuberculosis* exposure.[35] In high-risk individuals with a negative IFN-γ release assay, chest CT is another tool to examine for previous *M. tuberculosis* exposure. Of note, previous vaccination with bacillus Calmette-Guérin may lead to false-positive TST (but not IFN-γ release assay); clinicians should exercise great caution before discounting a positive TST in vaccinated individuals, as vaccination does not provide universal protection from *M. tuberculosis* infection and true latent infection may still be present. As both TST and IFN-γ release assays are imperfect, results must be interpreted in context of the patient's epidemiologic risk. Where uncertainty exists, expert consultation is recommended, even if TST and/or IFN-γ release assay is negative. Treatment guidelines for latent tuberculosis are widely available;[34] of particular importance is the need to exclude active tuberculosis before treating for latent tuberculosis (Chapter 130). *Strongyloides* screening should be undertaken in those with epidemiologic risk or unexplained eosinophilia. *Strongyloides stercoralis* is a problematic pathogen in immunocompromised hosts and is ideally treated pre-emptively prior to any immunosuppression, given the risk of hyperinfection syndrome and associated high mortality.

Prevention of infection in immunocompromised hosts also includes patient education on measures to minimize epidemiologic exposure to potential pathogens and comprehensive vaccination.[36] Ideally, vaccines are given prior to onset of any immunosuppression to maximize likelihood of lasting immunogenic response. Allogeneic HSCT recipients should also undergo a process of re-vaccination following engraftment, usually beginning at 3 to 6 months post-HSCT.[1,37] Yearly influenza vaccine and up-to-date *B. pertussis* and *S. pneumoniae* vaccines are important for preventing pulmonary complications of immunosuppression.[1] Of note, live vaccines should not be given in the setting of immunosuppression.

Primary Prophylaxis for Pulmonary Infections

In general, commonly targeted organisms for prophylactic antimicrobials include herpes simplex virus, varicella zoster virus, CMV, hepatitis B virus, *Pneumocystis jirovecii*, and *Toxoplasma gondii*. The following focuses on prevention of pulmonary infection in immunocompromised hosts and does not consider all the prophylaxis that may be required for nonpulmonary infections.

Viruses

Prophylaxis of viral lung infection is usually reserved for those with hematologic malignancies as well as SOT and HSCT recipients, and is targeted towards herpes viruses, particularly reactivation of herpes simplex virus, varicella zoster virus, and, in those at risk, CMV.[21,27,28,32,33] Oseltamivir prophylaxis might be given to an individual at high risk for severe influenza after a significant influenza contact.

Bacteria

Antibacterial prophylaxis for lung infection is rarely used as antimicrobial resistance readily emerges, which can impair future treatment for bacterial infection. Lung transplant recipients occasionally receive prolonged antibacterial prophylaxis following perioperative prophylaxis based on specific transplant center and patient factors, including prior colonization and risk of bronchial anastomosis infection. Prophylaxis for *Mycobacterium avium* complex is employed occasionally for people with HIV and CD4+ T-cell count below 50 cells/μL.[23]

Fungi

Antifungal prevention is predominantly employed to prevent *Pneumocystis*. Unfortunately, *Pneumocystis* prophylaxis can be inadvertently omitted by inexperienced clinicians when immunosuppression is used infrequently, despite clear guidelines.[38] Indications for *Pneumocystis* prophylaxis are broad, and clinicians should consider the net state of immunosuppression when being interpreted. Trimethoprim/sulfamethoxazole is a unique prophylactic agent; it is the most effective agent for preventing *Pneumocystis* but also has efficacy in preventing *Toxoplasma gondii* reactivation, some *Nocardia* sp. infections, *Listeria monocytogenes*, and many other Gram-positive and Gram-negative bacteria (although susceptibility patterns many change over time, making prevention of Gram-positive and Gram-negative infections less effective). Second-line options for *Pneumocystis* prophylaxis include atovaquone, dapsone, and pentamidine.[38]

Anti-mold prophylaxis is used following HSCT, lung transplant, and liver transplant in some centers depending on local epidemiology and patient-specific characteristics.[25] Potential benefits of anti-mold prophylaxis must be determined based on local epidemiology and balanced against cost and risk of driving antifungal resistance. Prophylaxis for reactivation of *Coccidioides* sp. is employed in those with previous exposure following SOT.[26]

Parasites

Antiparasitic prophylaxis for pulmonary infection is rarely required except for *Toxoplasma gondii* in HSCT recipients and patients with HIV and CD4+ less than 100 cells/μL.[23] A course of ivermectin may be given for those at risk for strongyloidiasis.

EVALUATION OF AN IMMUNOCOMPROMISED INDIVIDUAL WITH POSSIBLE PULMONARY INFECTION

Bedside evaluation of the immunocompromised patient includes taking a thorough history, performing a detailed physical examination, and undertaking a targeted laboratory assessment.

History

There are several features of the clinical history of particular importance to the immunocompromised host. As noted above, establishing the net state of immunosuppression is vital in evaluation of an immunocompromised host to determine their likelihood of

TABLE 123-3 Geographic Considerations for Pulmonary Infections in Immunocompromised Hosts

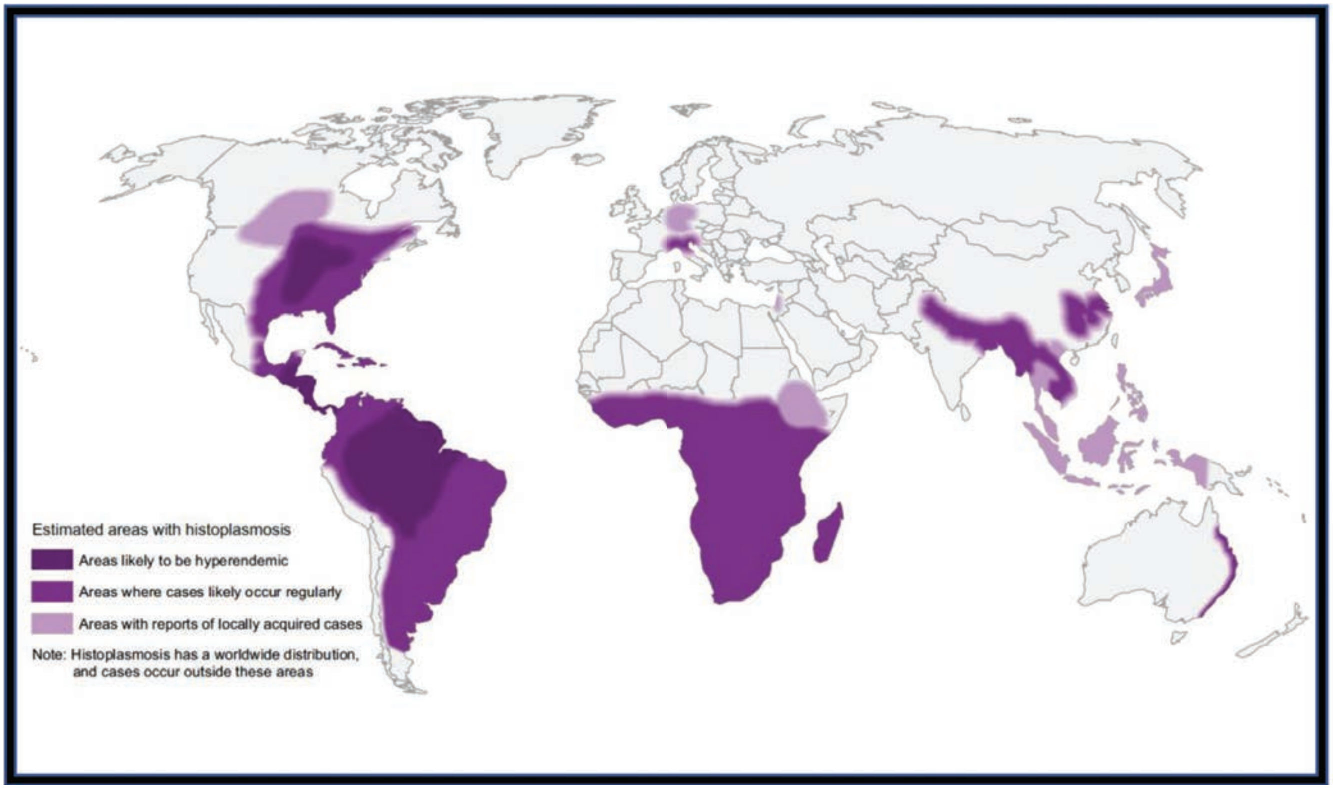
Disease	Organisms	Most Common Regions
Melioidosis	*Burkholderia pseudomallei*	Southeast Asia, northern Australia
Anthrax	*Bacillus anthracis*	South America, central and southwestern Asia
Histoplasmosis	*Histoplasma capsulatum*	Eastern United States, sub-Saharan Africa
Coccidioidomycosis (valley fever)	*Coccidioides immitis*	Southwestern United States, Central and South America
Cryptococcosis	*Cryptococcus gattii*	Australia, U.S. Pacific Northwest, Canada (Vancouver Island, British Columbia), Papua New Guinea
Paracoccidioidomycosis	*Paracoccidioides brasiliensis*	Central and South America
Talaromycosis (previously called penicilliosis)	*Talaromyces marneffei*	Southeast Asia, northeastern India, southern China
Blastomycosis	*Blastomyces dermatitidis*	Eastern United States and Canada, Africa
Strongyloidiasis	*Strongyloides stercoralis*	Southeast Asia, Africa, Western Pacific and Northern Australia

particular infections. This consideration is frequently overlooked, and treating clinicians as well as the patient may not recognize its importance. A clear understanding of the patient's medical history, timeline of immunomodulatory medications received, and previous infections is vital.

Establishing the nature and time course of epidemiologic exposures is of the utmost importance in immunocompromised hosts, where even very remote exposure to an infectious agent can be relevant (e.g., childhood exposure to tuberculosis, or remote exposure during the Vietnam war to *Strongyloides*).[39] The immunocompromised state predisposes to infections that can manifest in immunocompromised hosts that may otherwise have been quiescent, or that may manifest more severely or in an atypical manner. As with all hosts, consideration of prior travel history is important for understanding potential exposures in endemic regions of particular infections (Table 123-3). Some of these exposures are environmental, such as endemic fungi[40] (Fig. 123-3), *Burkholderia pseudomallei*, and *Legionella*; some are zoonotic, such as *Coxiella burnetii* or Middle East Respiratory Syndrome; and some are human-related, such as *Mycobacterium tuberculosis*, influenza, and SARS-CoV-2. In solid organ transplant recipients, consideration of epidemiologic exposures of the organ donor may be required, particularly with regard to the risk of transmission of tuberculosis, coccidioidomycosis, and strongyloidiasis.[41–43]

Animal exposures pose greater health risks to immunocompromised hosts than immunocompetent hosts. Examples of potential pulmonary pathogens due to animal exposure are shown in Table 123-4.

Several diseases warrant specific note due to their epidemiology and potential for prolonged latency from exposure that can reactivate in the setting of commencing immunosuppressive medication or developing immunocompromised state, including


Estimated areas with histoplasmosis
Areas likely to be hyperendemic
Areas where cases likely occur regularly
Areas with reports of locally acquired cases
Note: Histoplasmosis has a worldwide distribution, and cases occur outside these areas

A

Figure 123-3 Approximate global distribution of endemic fungi: (**A**) *Histoplasma capsulatum*,

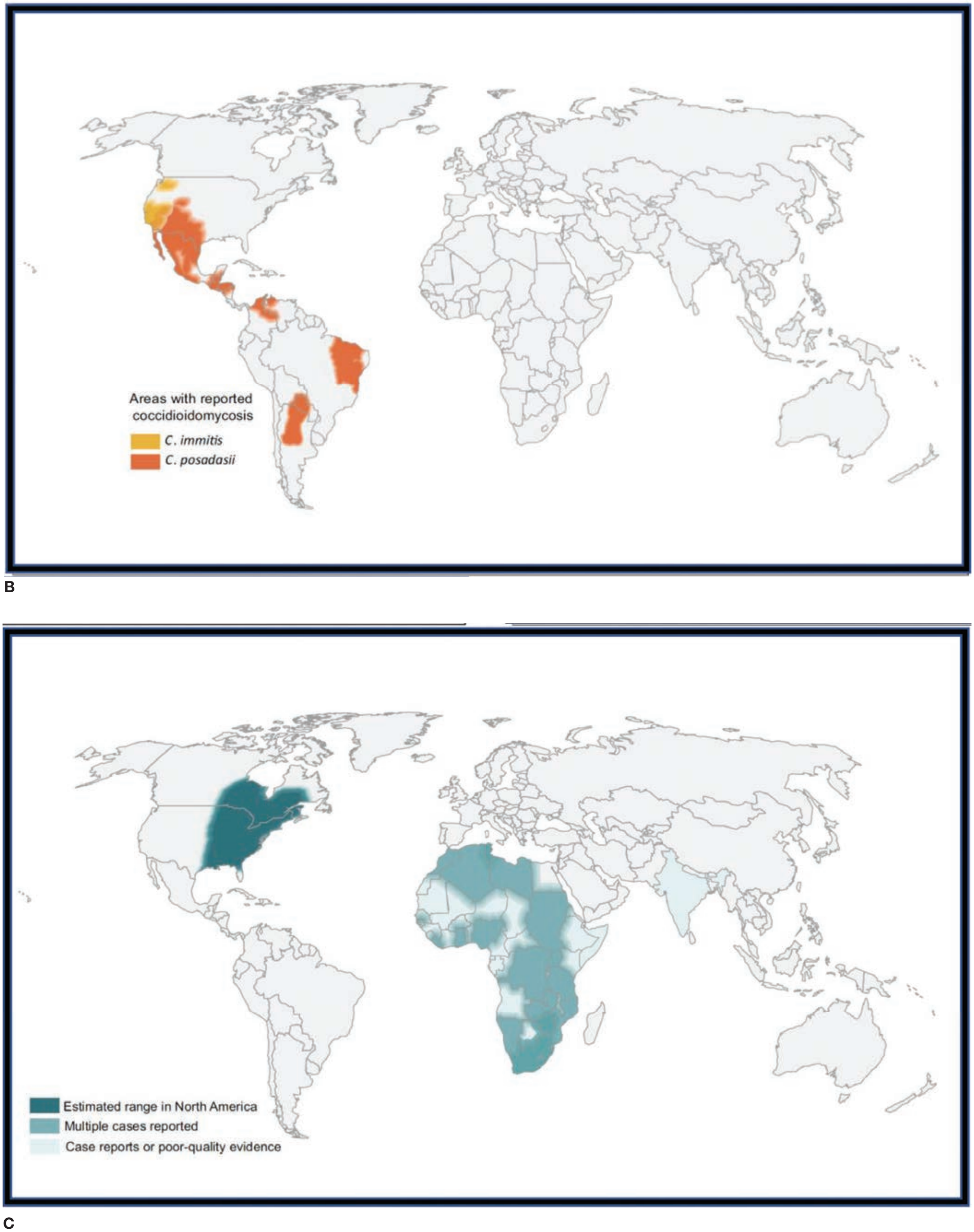

Areas with reported coccidioidomycosis
C. immitis
C. posadasii
B
Estimated range in North America
Multiple cases reported
Case reports or poor-quality evidence
C

Figure 123-3 *(Continued)* (**B**) *Coccidioides* sp., (**C**) *Blastomyces dermatitidis*. *(Reproduced with permission from Ashraf N, Kubat RC, Poplin V, et al. Re-drawing the Maps for Endemic Mycoses. Mycopathologia. 2020;185(5):843–865.)*

TABLE 123-4 Animals with Potential Pulmonary Pathogens

Animal	Potential Pulmonary Pathogen
Dogs	- *Pasteurella* sp. - *Bordetella bronchiseptica* - *Coxiella burnetii* - *Brucella* sp.
Cats	- *Pasteurella* sp. - *Bartonella henselae* - *Toxoplasma gondii* - *Francisella tularensis* - *Bordetella bronchiseptica*
Birds/poultry	- Cryptococcus (*Cryptococcus gattii*, *Cryptococcus neoformans*) - Psittacosis (*Chlamydophila psittaci*, *Chlamydia psittaci*) - *Histoplasma capsulatum* - Avian influenza - *Aspergillus* sp. (environmental)
Horses	- *Rhodococcus equi* - *Coxiella burnetii*
Rabbits	- *Bordetella bronchiseptica* - *Francisella tularensis* - *Pasteurella multocida*
Rodents	- *Francisella tularensis* - *Yersinia pestis* - *Hantavirus* - *Leptospirosis*
Bats	- *Histoplasma capsulatum*
Other	- Camel: Middle East respiratory syndrome (MERS) - Various (cattle, sheep, goats, sloths, kangaroos, etc.): *Coxiella burnetii*, *B. anthracis*, *Brucella* sp.

tuberculosis,[44–47] strongyloidiasis,[48] coccidioidomycosis,[49,50] toxoplasmosis,[51,52] melioidosis,[53] paracoccidioidomycosis,[54] and penicilliosis (*Talaromyces marnefei*).[55,56] Most recent exposures should be considered for all hosts, especially for immunocompromised patients, where apparently trivial exposure can lead to infection and cause disease. Frequently, potential exposure to such pathogens can be determined from a thorough epidemiologic history with common risk factors, as shown in Table 123-5.

Understanding the effects of immunosuppressive medication is essential, including the potential duration of their effect on the immune system.[57] Some drugs have prolonged half-lives with intermittent infusions separated by many months. Clinicians should be mindful in considering the prolonged effects of these medications on the host immune system. Examples include many monoclonal antibodies (for example, anti-CD20, anti–TNF-α, anti–IL-6) and antithymocyte globulin. Additionally, the immune effects of many medications may linger for weeks beyond medication cessation due to long drug half-life—for example, leflunomide and methotrexate.

Many immunocompromised patients are prescribed antimicrobial prophylactic agents including agents targeted to *Pneumocystis jirovecii* (trimethoprim-sulfamethoxazole, atovaquone, dapsone, pentamidine), herpes simplex and herpes zoster (acyclovir, famciclovir, valacyclovir, valganciclovir), cytomegalovirus (valganciclovir, letermovir), fungi (fluconazole, voriconazole, posaconazole, itraconazole, isavuconazole, amphotericin [inhaled/systemic]), and other bacteria (ciprofloxacin, amoxycillin, doxycycline). Importantly, the efficacy of each of these agents toward their target varies and relies on adequate dosing, absorption, and patient adherence. Thus, prophylaxis may not always exclude an organism being implicated in a pulmonary presentation. For example, atovaquone is frequently substituted for trimethoprim-sulfamethoxazole for *Pneumocystis jirovecii* prophylaxis; however, atovaquone is less effective than trimethoprim-sulfamethoxazole and may lead to breakthroughs.[58] Similarly, prophylaxis may change the organisms encountered. For instance, antifungal prophylaxis with voriconazole among high-risk HSCT recipients may reduce aspergillosis but increase the risk of mucormycosis.[59]

Consideration should be given to vaccination history. The efficacy of vaccines in immunocompromised hosts is often reduced.

TABLE 123-5 Risk Factors for Exposures to Organisms with Potential to Reactivate Following Immunosuppression

Disease	Organism	Risk Factors for Exposure
Tuberculosis	*Mycobacterium tuberculosis*	Relative or close contact with tuberculosis Health care workers Residency/prolonged travel in an endemic country Prison workers/previous incarceration Homelessness
Coccidiomycosis	*Coccidioides* sp.	Residency or travel to Southwestern United States, Mexico, Central America (Fig. 123-3)
Strongyloidiasis	*Strongyloides stercoralis*	Residency/prolonged travel in an endemic region (includes much of Asia, Africa, South America, Pacific Island, Northern Australia), including military service
Toxoplasmosis	*Toxoplasma gondii*	Feline/animal exposure, consumption of contaminated foods or undercooked infected
Melioidosis	*Burkholderia pseudomallei*	Residency/prolonged travel in endemic region (Southeast Asia especially Thailand, Vietnam, Cambodia, Myanmar, Philippines, Malaysia, Indonesia, Papua New Guinea; Northern Australia)
Paracoccidioides	*Paracoccidioides* sp.	Residency in Central and South America
Talaromycosis (previously called penicilliosis)	*Talaromyces marneffei*	Residency/prolonged travel in Southeast Asia

Hence, the presence of a previous vaccine does not exclude the possibility of disease in many vaccine-preventable diseases and may alter the clinical presentation.

As with all hosts, timeline and constellation of symptoms is important to understand. When taking a history from an immunocompromised host, several aspects are worth noting:

- Fever may not be recognized or may not be present.
- Purulence may be less than expected—for example, purulent sputum may be minimal in bacterial pneumonia.
- Clinical course may be different or vague compared with that which typically occurs in immunocompetent hosts.
- COVID-19 may have shorter prodrome, with a more rapid onset of hyperinflammatory phase. Alternatively, some patients may have a prolonged prodrome and the hyperinflammatory phase may not occur until much later than expected.
- Some opportunistic infections have "typical" presentations, such as *Pneumocystis* pneumonia in patients with HIV and low CD4+ T-cell count (Chapter 134).

Physical Examination

Systematic and thorough bedside examination has the potential to yield important information. Clinicians should be mindful that clinical signs may be altered in the setting of some immunocompromised states, including diminished or absent fever and reduced signs of inflammation, with absent or minimal purulence or erythema than would otherwise be anticipated (Fig. 123-4). In solid organ transplant recipients, transplanted organs are denervated and may not exhibit typical signs of infection or inflammation.

The importance of examination beyond the respiratory system is vital given the potential for many pulmonary pathogens to have disseminated or metastatic foci. For example, the presence of a skin rash or nodule may be key to the diagnosis of disseminated *Fusarium*, *Nocardia*, or *Cryptococcus*. Similarly, focal neurologic findings may give a clue to *Nocardia* or *Aspergillus* brain infection. All recent and former surgical sites should be examined carefully, even if remote, as such sites may provide a site of least resistance (*locus minoris resistentiae*) for entry and/or establishment of an infectious process. Joints should be examined carefully given the potential for pulmonary pathogens to involve bones and joints—for example, *Streptococcus pneumoniae* and *Mycobacterium tuberculosis*. A detailed physical examination may also help elicit processes that mimic pulmonary infection.

Diagnostics

A key principle of the approach to an immunocompromised host is the importance of specific and accurate diagnosis. The breadth of potential infectious agents that may contribute to pulmonary disease are too broad to accurately cover empirically in many circumstances, necessitating rapid and definitive measures to obtain

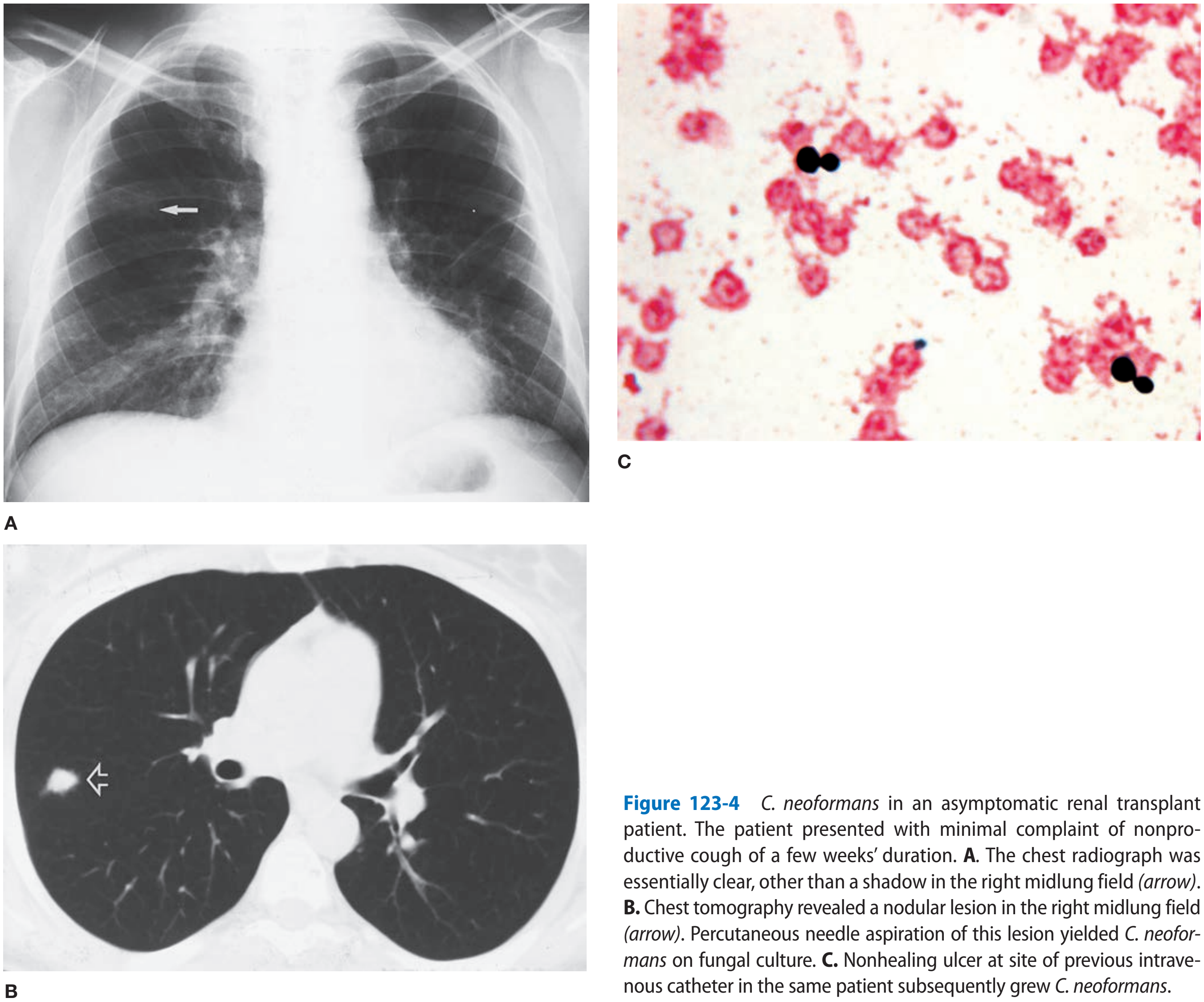


Figure 123-4 *C. neoformans* in an asymptomatic renal transplant patient. The patient presented with minimal complaint of nonproductive cough of a few weeks' duration. **A.** The chest radiograph was essentially clear, other than a shadow in the right midlung field *(arrow)*. **B.** Chest tomography revealed a nodular lesion in the right midlung field *(arrow)*. Percutaneous needle aspiration of this lesion yielded *C. neoformans* on fungal culture. **C.** Nonhealing ulcer at site of previous intravenous catheter in the same patient subsequently grew *C. neoformans*.

TABLE 123-6 Causes of Neutropenia

- Iatrogenic
    - Cancer chemotherapy
    - Drug toxicities (TMP–SMX, chloramphenicol, ganciclovir, AZT, allopurinol)
- Infection
    - Viral (cytomegalovirus, HIV, Epstein–Barr virus, hepatitis B)
    - Parasitic *(Leishmania)*
    - Bacteria *(Clostridium)*
    - Acute neutropenia of sepsis/endotoxemia (Gram-negative sepsis)
    - Bone marrow failure of neonatal sepsis
- Immune
    - Drug-induced autoimmunity (haptenic: penicillins, sulfa drugs)
    - Aplastic anemia (includes idiosyncratic reactions: phenothiazines, chloramphenicol)
    - Alloimmune neonatal neutropenia (maternal–fetal incompatibility)
    - Congenital autoimmune neutropenia
    - Primary autoimmune (systemic lupus erythematosus, Felty syndrome, rheumatoid arthritis)
    - Transfusion-induced
    - Antineutrophil antibody–mediated
    - Cyclic neutropenia (CD57 lymphocyte expansion)
- Hereditary
    - Infantile genetic agranulocytosis
    - Familial neutropenia
    - Cyclic neutropenia (autosomal dominant)
    - Advanced age

diagnostic samples in order to promptly make a diagnosis and guide appropriate therapy.

Basic Investigations

In general, initial diagnostic testing is similar to that of an immunocompetent host. Initial testing includes chest x-ray and basic laboratory markers including complete blood examination and biochemistry. Lymphopenia may be a function of immunosuppressive agents rather than viral infection. Nonetheless, considering relative lymphopenia compared with previous results can be useful. In patients on more than 5 mg prednisone or equivalent, eosinophil count should almost always be very close to 0. If not, pathology causing elevated eosinophil lineage should be considered, most commonly drug reactions or parasitic infection. In organ transplant recipients, allograft rejection should always be considered in the differential of elevated eosinophil count.[60] Neutropenia is an important consideration given its association with bacterial and fungal infections, especially if prolonged. Potential causes of neutropenia are outlined in Table 123-6.

Radiology Radiology is an essential component of diagnostic workup for immunocompromised hosts with suspected pulmonary infection. While often nonspecific, pulmonary imaging can aid considerably in the creation of a differential diagnosis. The chest x-ray may be falsely reassuring in immunocompromised hosts. Thus, a low threshold is required for cross-sectional imaging with CT (ideally high resolution if indicated, and with intravenous radiocontrast when needed). High-quality cross-sectional imaging may provide important clues to the implicated organism and more accurately target diagnostics. Common differential diagnoses based on radiographic appearance are shown in Table 123-7.

Similar to inflammatory biomarkers markers (below), radiology may be less dramatic than anticipated for severity of infection owing to a lack of inflammatory response. Further, following institution of appropriate antimicrobial therapy, reduction of immunosuppression, or recovery of neutrophil count there may be an apparent radiographic worsening that may be paradoxical to clinical response (see “Immune Reconstitution Syndrome: a Diagnosis of Exclusion,” below).

While radiographic findings may assist in creation of a differential diagnosis list, no individual radiographic finding is sufficient to confirm a diagnosis. Each radiographic appearance (Table 123-7) is associated with a broad list of differential diagnoses. An example is a “halo sign” (Fig. 123-5), which is commonly associated with invasive pulmonary aspergillosis. However, numerous infectious and noninfectious etiologies can produce this sign, leaving the radiographic feature as suggestive but not diagnostic.[61–69] The presence of a “reverse halo sign” is commonly associated with mucormycosis but also is not diagnostic.[65,70,71] Both signs provide clues and may guide empiric therapy, but they do not obviate the additional necessary investigations to arrive at a specific diagnosis.

Ground-glass opacities are a frequent radiographic finding in immunocompromised individuals with pulmonary symptoms (Figs. 123-6 and 123-7). Once again, the differential diagnosis of

TABLE 123-7 Infectious and Non-infectious Differentials for CT Chest Findings

	Potential Infectious Causes	Potential Non-infectious Causes
Nodular lesion	*Aspergillus* sp. *Mucorales* *Cryptococcus* sp. *Nocardia* sp. *Toxoplasma gondii* *Legionella* sp. *M. tuberculosis* Nontuberculous *Mycobacteria* Endemic fungi Septic emboli	Malignancy - Primary - Metastatic - Hematologic Autoimmune - Sarcoidosis - Organizing pneumonia - Rheumatoid arthritis - Granulomatosis with polyangiitis Arteriovenous malformation Rounded atelectasis Amyloidosis Benign neoplasms

TABLE 123-7 Infectious and Non-infectious Differentials for CT Chest Findings *(Continued)*

	Potential Infectious Causes	Potential Non-infectious Causes
Cavitary lesion	*M. tuberculosis* Nontuberculous *Mycobacteria* Pyogenic bacteria *Aspergillus* sp. *Mucorales* *Cryptococcus* sp. *Nocardia* sp. *Rhodococcus equi* Septic emboli *Pneumocystis jirovecii*	Autoimmune - Sarcoidosis - Granulomatosis with polyangiitis - Rheumatoid arthritis Malignancy - Primary - Metastatic - Hematologic Cystic lung diseases
Consolidation	Bacterial pneumonia Viral pneumonia Aspiration Fungal pneumonia *M. tuberculosis* and nontuberculous *Mycobacteria* *Nocardia* sp.	Malignancy Pulmonary hemorrhage Pulmonary edema Hypersensitivity pneumonias Alveolar proteinosis Chronic aspiration
Ground-glass opacities/ pulmonary infiltrates	Viral pneumonia (e.g., influenza, SARS-CoV-2) Atypical bacterial pneumonia *Toxoplasma gondii* *Pneumocystis jirovecii* *M. tuberculosis* and nontuberculous *Mycobacteria* *Histoplasma capsulatum*	Pulmonary edema Diffuse alveolar hemorrhage Malignancy Drug toxicity (sirolimus, methotrexate, bleomycin) GVHD Lung transplant rejection Radiotherapy Aspiration Hypersensitivity pneumonias Cryptogenic organizing pneumonia Pulmonary alveolar proteinosis
Pleural effusion	*M. tuberculosis* and nontuberculous *Mycobacteria* Bacterial or fungal empyema	Drug related (imatinib) Malignancy Pulmonary embolism Nephrotic syndrome Hepatic failure Cardiac failure Pancreatitis Autoimmune - Rheumatoid arthritis - Systemic lupus erythematosus - Granulomatosis with polyangiitis - Systemic sclerosis Radiation
Mediastinal lymphadenopathy	Bacterial pneumonia Viral pneumonia Fungal pneumonia *M. tuberculosis* Nontuberculous *Mycobacteria* HIV infection	Malignancy Sarcoidosis Reactive to pulmonary process

this finding is broad, including infectious etiologies like viral pneumonia and pneumocystis, but also noninfectious etiologies like lung transplant rejection, pulmonary edema, and drug hypersensitivity.[9]

Thus, while radiology is a helpful aid, it is rarely able to provide specific diagnosis of a causative pathogen in isolation. This highlights the importance of obtaining specific microbiologic diagnoses in patients with potential pulmonary infection as much as possible.

When considering the immunocompromised host with pulmonary infection, care should be taken to consider the need to

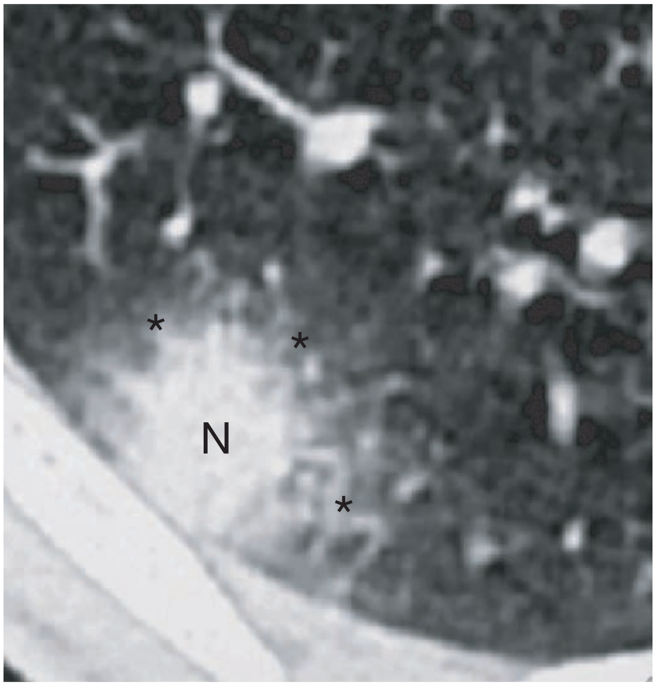


Figure 123-5 "Halo" sign in angioinvasive aspergillosis. CT scan of patient with fever and prolonged neutropenia during therapy for hematopoietic malignancy demonstrates a macronodule *(N)* surrounded by a halo of ground-glass opacity *(*)*.

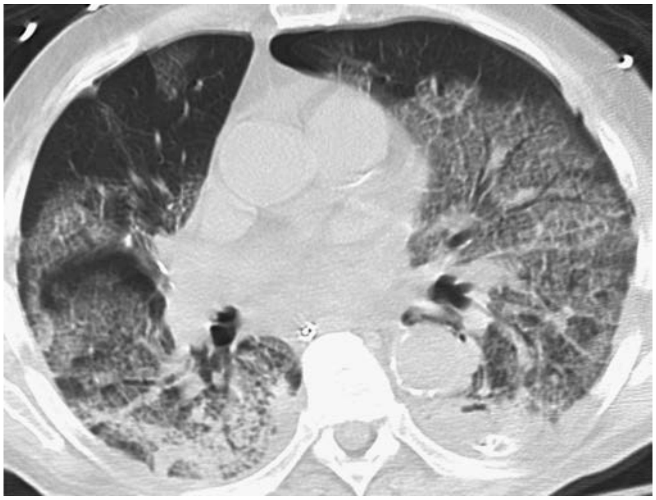


Figure 123-6 Diffuse ground-glass opacity of *P. jirovecii* pneumonia in advanced HIV at the time of initial presentation predominantly involved the subpleural lung and spared the central lung.

image other areas—in particular, areas such as the brain in pulmonary cryptococcosis, aspergillosis, nocardiosis, or toxoplasmosis (Fig. 123-8).

Inflammatory Biomarkers The measurement of inflammatory biomarkers, such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and procalcitonin should be undertaken only with knowledge of their limitations in immunocompromised hosts, particularly those on immunosuppressive medications. CRP and ESR are nonspecific markers of inflammation and can be falsely low in immunocompromised patients with severe bacterial infection due to a muted inflammatory response. Furthermore, immunocompromised hosts frequently have reasons for noninfectious elevations of CRP/ESR, such as underlying malignancy, an autoimmune disorder, or organ transplant rejection.[72–76]

Procalcitonin is a novel biomarker studied in immunocompetent hosts and has an evolving role that may allow discrimination between bacterial and viral infection or noninfection. In immunocompromised hosts, especially those on immunosuppressive medications, the role of procalcitonin remains understudied. While procalcitonin may be more useful than CRP or ESR in predicting bacterial infection, studies have not demonstrated superiority to bedside clinical judgement.[77–83] The test may have some value in distinguishing bacterial infection from organ transplant rejection,[80,81] but procalcitonin has also been shown to increase readily following induction immunosuppression with antithymocyte globulin in solid organ and hematopoietic stem cell transplant recipients.[82]

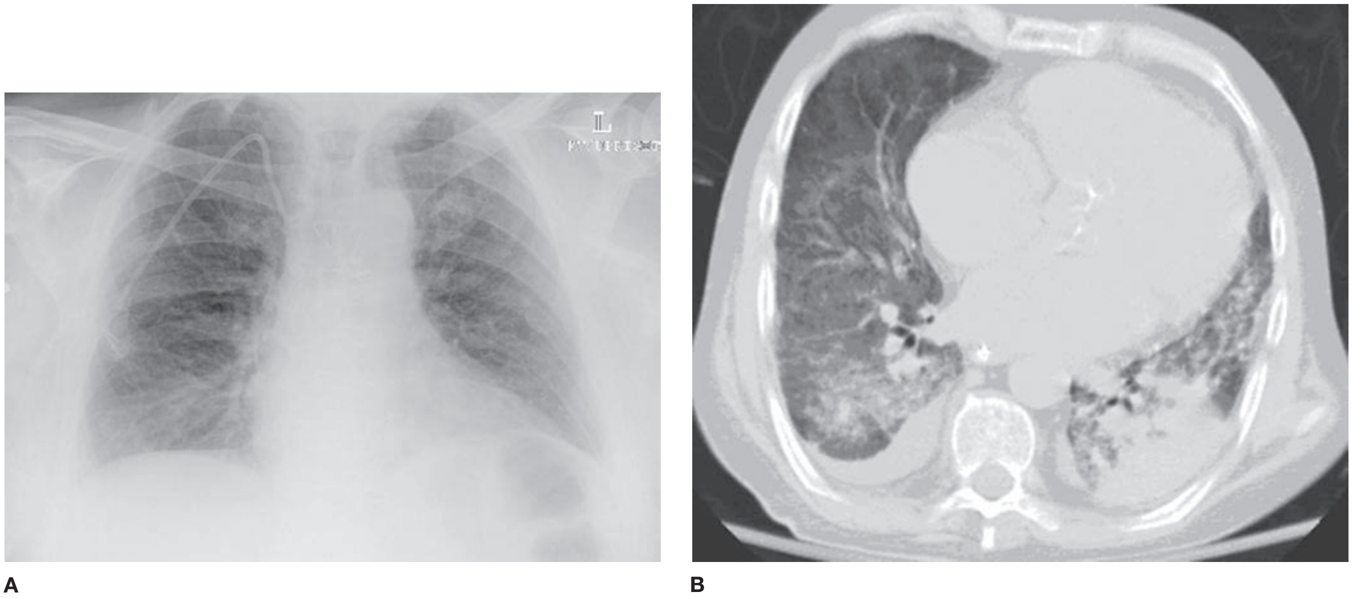


Figure 123-7 Diffuse process on plain radiograph (**A**) of *Pneumocystis* pneumonia 8 weeks following hematopoietic stem cell transplantation for T-cell lymphoma. CT scan (**B**) revealed pattern most consistent with aspiration pneumonia. Bronchoalveolar lavage revealed *Pneumocystis* and antimicrobial-resistant *K. pneumoniae*. Treatment of both processes resulted in resolution of infection.

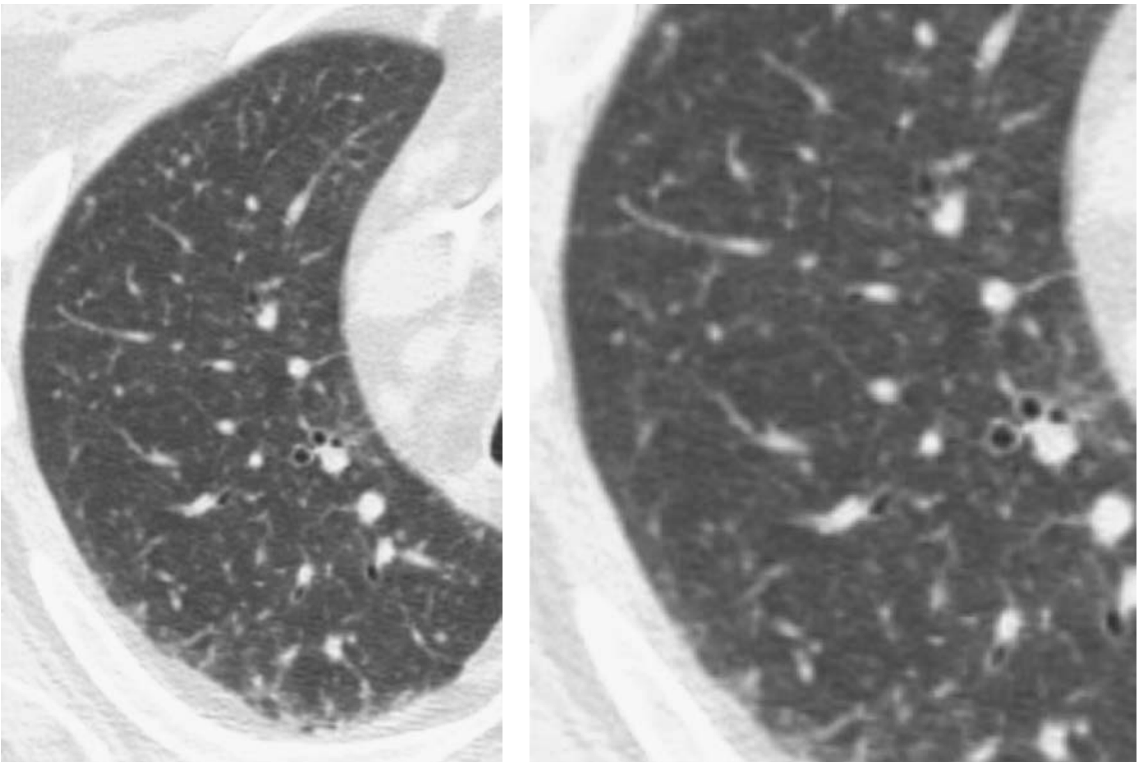


Figure 123-8 Miliary cryptococcal pneumonia in a 62-year-old man undergoing intensive chemotherapy for pancreatic cancer. *C. neoformans* was isolated from bronchoalveolar lavage specimens and cerebrospinal fluid (CSF). Cryptococcal antigen was positive in serum and CSF at titers greater than 1:1024. CT scan demonstrates diffuse 1- to 3-mm micronodules in both lung fields, often difficult to distinguish from small blood vessels on end. This requires review of serial CT cuts to distinguish nodules from tubular vessel structures.

Overall, elevated CRP, ESR, or procalcitonin should raise consideration of a potential bacterial or fungal infection in immunocompromised hosts, but a low value does not reliably exclude the possibility of infection.

Non-culture-based Microbial Diagnostics Non-culture-based microbial diagnostics include molecular tests, serologic tests, specific antigen tests, nonspecific fungal markers, and metagenomic sequencing.

Molecular Tests Viral polymerase chain reaction (PCR) from upper respiratory tract or lower respiratory tract specimens are useful tests for many common respiratory illnesses, including those in immunocompromised hosts (Chapter 122). Viral infections such as respiratory syncytial virus, influenza, human metapneumovirus, and parainfluenza can cause severe disease in many immunocompromised hosts, particularly solid organ transplant recipients (especially lung transplant recipients) and following HSCT.[84,85] Similarly, the occurrence of a viral infection may increase the risk of developing chronic lung allograft dysfunction or bronchiolitis obliterans syndrome in lung transplant recipients and chronic lung dysfunction following HSCT.[86–88] Depending on local epidemiology, PCR testing for SARS-CoV-2 also should be considered. Common multiplex panels include respiratory syncytial virus, human metapneumovirus, parainfluenza, enterovirus, rhinovirus, influenza, and adenovirus, and increasingly, SARS-CoV-2.[89,90] Adenovirus is of particular importance in HSCT and SOT recipients, where it has the ability to cause disseminated disease with multiorgan manifestations (Fig. 123-9). PCR testing may also be undertaken for atypical pathogens, such as *Mycoplasma pneumoniae* and *Bordetella pertussis*, which can cause severe disease in immunocompromised patients.[89,91,92] PCR testing sensitivity and specificity vary by assay and organism; thus, the clinician should have knowledge of particular test characteristics of the local laboratory. The site of sampling can also alter test sensitivity. Typically, in patients with pulmonary manifestations of any of these infections, the most sensitive samples are those obtained from the lower respiratory tract, such as sputum or BAL.[93,94]

Peripheral blood samples for PCR can be useful for diagnosis of a number of pulmonary-based infections, including CMV, adenovirus, and, rarely, primary EBV infection. CMV pneumonitis is a rare manifestation of CMV disease occurring primarily in HSCT and lung transplant recipients. Rarely, CMV pneumonitis can occur in lung transplant recipients with negative peripheral blood PCR, although this phenomenon is much less common in the era of high-sensitivity CMV assays. Where suspicion of CMV pneumonitis persists despite a negative peripheral blood PCR, pulmonary tissue for PCR or via immunohistochemical staining is the preferred method of diagnosis, as BAL CMV PCR may reflect asymptomatic viral shedding.[21]

Pneumocystis jirovecii PCR is increasing in availability and can be performed on induced sputa and BAL specimens. A positive *Pneumocystis* PCR must be interpreted in conjunction with clinical syndrome and other markers, as it is unable to distinguish airway colonization from true infection. In a vulnerable host (see "The Net State of Immunosuppression," above) with a compatible clinical syndrome and radiologic findings, elevated LDH and 1,3 Beta-d-glucan are useful adjunctive markers that support a diagnosis of *Pneumocystis* infection over colonization when *Pneumocystis* PCR is positive but direct visualization methods are negative.[22,95–97] The use of quantitative PCR may further enhance our ability to differentiate colonization from infection.[98,99]

Aspergillus PCR (Chapter 132) has been studied in blood/serum and BAL samples; BAL testing has a higher overall sensitivity.[100–102] PCR on BAL specimens lacks the ability to differentiate between colonization and infection, especially in lung transplant recipients. Furthermore, while some assays can detect some genes responsible for azole resistance, the lack of phenotypic antifungal susceptibility data means this test currently serves primarily as an adjunct to culture data.[89]

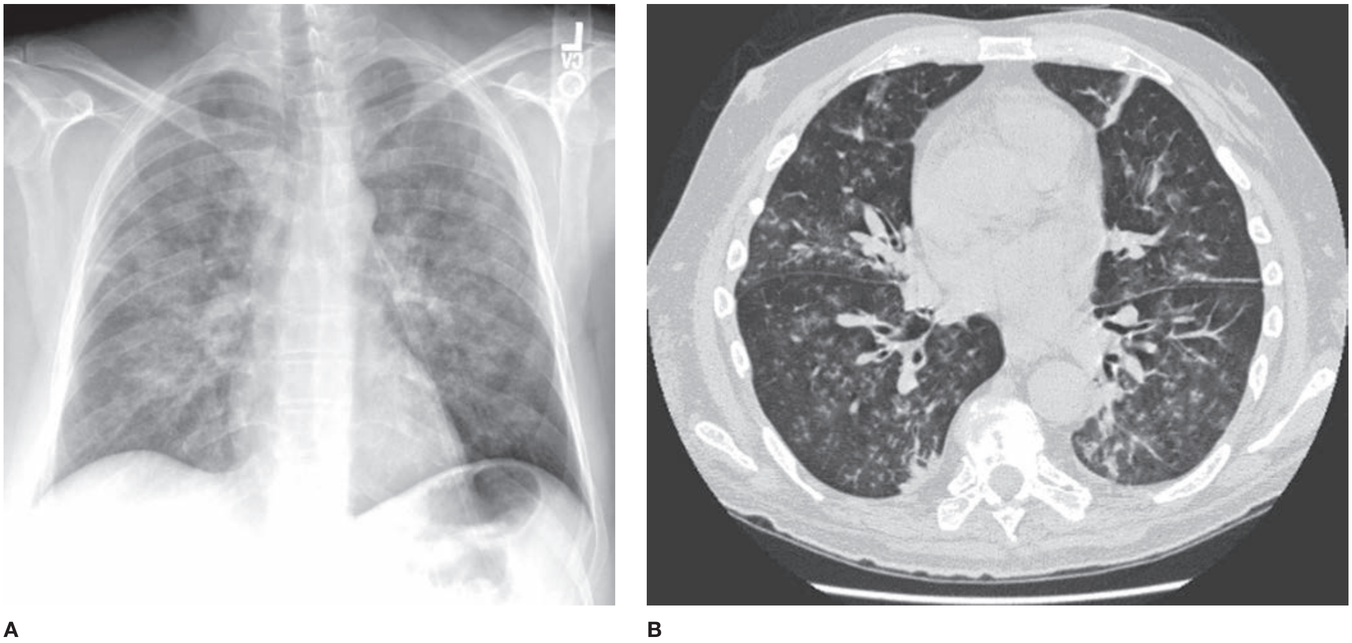


Figure 123-9 Adenovirus pneumonia during week after marrow engraftment following allogeneic hematopoietic stem cell transplantation for acute myelogenous leukemia. Routine chest radiograph (**A**) reveals diffuse pneumonia while CT scan (**B**) demonstrates bronchiolitis. The patient failed to respond to cidofovir therapy but cleared infection after infusion of autologous stem cells.

Serology Serologic testing is rarely useful in the acute phase of a respiratory illness, especially in immunocompromised hosts who may have impaired antibody responses to infection. Serologic testing may be useful for a select few set of infections with prolonged prodrome. Potential serologic tests that may be of use in diagnosis of chronic infection include tests for *Coccidioides*,[103] *Paracoccidioides*,[104] *Histoplasma capsulatum*, *Toxoplasma gondii*, and *Burkholderia pseudomallei.* Sensitivity of serologic testing is particularly poor in immunocompromised hosts and may only establish a history of possible exposure and the potential for the organism to reactivate. Thus, the utility of serologic testing is limited in diagnosing acute infection. In the setting of HSCT and SOT, pretransplant serology for CMV of donor and recipient can help define the risk of CMV disease following transplantation, as shown in Table 123-8.[21,32] EBV-seronegative SOT recipients are at risk of primary EBV and post-transplant lymphoproliferative disorder, especially if the donor is EBV IgG-positive.[105] EBV-related PTLD can occur following HSCT, particularly with EBV mismatch between donor and recipient.[106]

Specific Antigen Testing Serum cryptococcal antigen (Chapter 133) has high specificity and sensitivity in patients with disseminated *Cryptococcus*, particularly in patients with HIV, but may be negative in patients with isolated pulmonary disease.[107–109] Care should be taken for patients with potential neurologic disease, where lumbar puncture and CSF cryptococcal antigen are still required where clinical suspicion remains, even if peripheral blood cryptococcal antigen is negative. This noninvasive test rarely represents a false positive (although this may occur with disseminated infection due to *Trichosporon asahii*, or some rare bacterial species). The timeline for decay of this marker is long and remains positive following successful treatment completion of cryptococcosis for months to years.[110,111] Thus, it has limited role in monitoring treatment response. Referral of the clinical specimen to an experienced laboratory is required to in order to minimize risk of a false negative from inappropriate handling or failure to assess for a prozone effect.[112,113] In HIV-infected individuals, some guidelines include screening for *Cryptococcus* with serum cryptococcal antigen when the CD4+ count is less than 100 cells/µL.[114] However, screening is not recommended in other populations unless disease is suspected. This is a useful test in a number of immunocompromised hosts with suspected cryptococcosis.

As in immunocompetent hosts, urinary and serum antigen testing should be considered for coccidiomycosis, histoplasmosis, and blastomycosis in those with epidemiologic risks and a compatible clinical syndrome. There is cross-reactivity among the endemic fungi assays, and limited sensitivity means a negative test does *not* exclude infection with either of these organisms.[26,115]

Urinary antigen tests are often limited by sensitivity. The most useful test is a urinary *Legionella* antigen, although this does not test for all serotypes relevant to a given geographic region, further reducing sensitivity.[116] The utility of a *Streptococcus pneumoniae* urinary antigen test is questionable among immunocompetent adults, in whom standard antibiotic regimes may not be altered by a positive or negative result. Similarly, the role of this test is also not clear in immunocompromised hosts.

Nonspecific Fungal Markers There are several nonspecific markers that can be utilized in immunocompromised patients with potential fungal infection.

TABLE 123-8 Risk of CMV in SOT and HSCT Recipients by Serostatus of Donor and Recipient

CMV Status	Donor IgG Pretransplant	Recipient IgG Pretransplant	Risk Category
SOT	+	–	High risk
	+/–	+	Moderate risk
	–	–	Low risk
HSCT	–	+	High risk
	+	+/–	Moderate risk
	–	–	Low risk

1,3 Beta-D-glucan is a component of cell walls of *Candida* species, *Aspergillus* species, and *Pneumocystis jirovecii*. Several assays measuring 1,3 Beta-D-glucan have been developed. Test results can be elevated with localized or systemic infections due to any of these organisms, and testing can be performed in serum and BAL samples. However, detection of 1,3 Beta-D-glucan has poor specificity, limiting its ability to accurately guide diagnostic and therapeutic decisions.[117–122] False positives are also problematic.[123–127] The role of 1,3 Beta-D-glucan in distinguishing *Pneumocystis jirovecii* colonization from infection is emerging; however, its ability to incrementally improve diagnostic accuracy beyond clinical acumen is untested.[96,128] Furthermore, it is not typically elevated due to infection with other fungi, such as mucormycosis and cryptococcosis (which do not contain 1,3 Beta-D-glucan in their cell walls). Hence, this test does not perform as a "pan-fungal marker,"[120,129] and the diagnostic role of 1,3 Beta-D-glucan remains unclear.

Galactomannan (*Aspergillus* antigen) is another fungal marker that may be measured in peripheral blood or BAL specimens and is specific for *Aspergillus* species (Chapter 132). Utility of peripheral blood galactomannan is predominantly limited to patients with hematologic malignancy or HSCT recipients, particularly when they are neutropenic and are not taking mold-active antifungal prophylaxis.[130,131] In other immunocompromised patients, such as solid organ transplant recipients and those with chronic granulomatous disease, sensitivity of blood galactomannan for invasive aspergillosis is poor.[132–135] Sensitivity may also be lower with isolated pulmonary aspergillosis without angioinvasion.[136] Some institutions have adopted a strategy to serially monitor blood galactomannan in HSCT recipients to "screen" for invasive *Aspergillus* infection, as serum galactomannan positivity may precede clinical diagnosis of invasive *Aspergillus* infection[137,138] in those not prescribed mold-active antifungal prophylaxis.[139] Galactomannan on BAL fluid has improved test characteristics compared with peripheral blood galactomannan and is a suitable test for any immunocompromised patient with suspected invasive pulmonary aspergillosis. Sensitivity remains highest in those with hematologic malignancy and following HSCT and is reasonably high in other immunocompromised patient groups with suspected invasive pulmonary aspergillosis, particularly solid organ transplant recipients.[119,140,141] BAL galactomannan maintains higher performance characteristics, even in those receiving mold-active antifungal prophylaxis.[142] In lung transplant recipients, BAL galactomannan is not able to distinguish between airway colonization and invasive aspergillosis.[143,144] False positives can occur, in addition to cross-reactivity with other infections,[145–150] underlining the importance of continuing to pursue specific diagnosis with sampling and culture in patients with positive galactomannan. In all patient groups, BAL galactomannan sensitivity is not high enough to exclude pulmonary aspergillosis when used in isolation.

Metagenomic Sequencing Metagenomic sequencing is an emerging technology with an evolving role in clinical practice.[89] Currently, clinical use is generally limited to circumstances where standard microbiologic, molecular, and pathologic methods have failed to yield a causative organism.

Data are emerging from studies addressing earlier institution of this technology.[151] Sequencing can be performed on blood, tissue, and respiratory specimens, although sensitivity and specific of such samples vary widely.[152–155] In the future, this technology may prove a powerful tool in specific diagnosis among immunocompromised patients in whom standard diagnostic methods are often negative.

Culture-based Diagnostics: Sampling and Microbiology Those with respiratory presentations will generally have culture-based diagnostics targeted toward samples obtained from the respiratory tract. The suggested flow of sampling is shown in Fig. 123-10 and covered in Chapter 31. Where possible, a sufficient sample volume should be obtained to undertake all necessary tests, ideally those listed

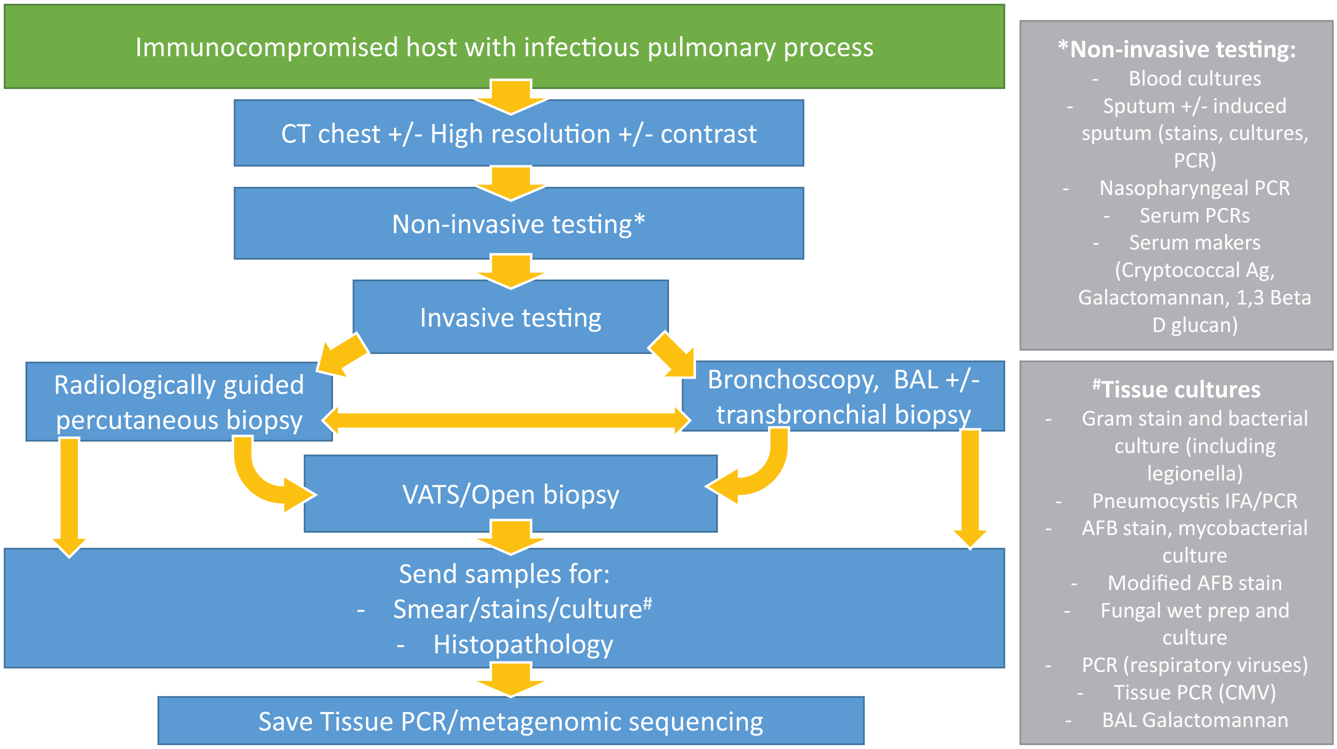

Immunocompromised host with infectious pulmonary process
CT chest +/- High resolution +/- contrast
Non-invasive testing*
Invasive testing
Radiologically guided percutaneous biopsy
Bronchoscopy, BAL +/- transbronchial biopsy
VATS/Open biopsy
Send samples for:
- Smear/stains/culture#
- Histopathology
Save Tissue PCR/metagenomic sequencing
*Non-invasive testing:
- Blood cultures
- Sputum +/- induced sputum (stains, cultures, PCR)
- Nasopharyngeal PCR
- Serum PCRs
- Serum makers (Cryptococcal Ag, Galactomannan, 1,3 Beta D glucan)
#Tissue cultures
- Gram stain and bacterial culture (including legionella)
- Pneumocystis IFA/PCR
- AFB stain, mycobacterial culture
- Modified AFB stain
- Fungal wet prep and culture
- PCR (respiratory viruses)
- Tissue PCR (CMV)
- BAL Galactomannan

Figure 123-10 Suggested diagnostic workup of pulmonary infection in immunocompromised host. Choice of invasive test depends on patient and technical factors; multiple methods may be required if initial approach fails. Tissue for sequencing/metagenomics may only be required if diagnosis has not been established by traditional methods. AFB, acid-fast bacilli; Ag, antigen; BAL, bronchoalveolar lavage; CMV, cytomegalovirus; IFA, indirect fluorescent antibody; PCR, polymerase chain reaction; VATS, video-assisted thoracoscopy.

TABLE 123-9 Routine Laboratory Evaluation of Bronchoalveolar Lavage and Biopsy Specimens in Immunocompromised Hosts

- **Tissue pathology**[a]
  - Wright–Giemsa stain
  - Papanicolaou stain
  - Silver stain
  - Modified Jimenez stain (or other suitable for detecting *Legionella*)
  - Fluorescent antibody stain for *Pneumocystis*
  - Organism-specific PCR: CMV, HSV, VZV, adenovirus, influenza, other respiratory viruses
  - Save specimen for 16S/18S PCR or metagenomic sequencing
- **Microbiology**[a]
  - Stains:
    - Gram stain
    - Wet mount KOH or calcofluor white
    - Acid-fast smear ± *M. tuberculosis* PCR
    - Modified acid-fast
    - Fluorescent antibody stain for *Pneumocystis*, *Legionella* (respiratory viruses if PCR unavailable)
  - Antigen/molecular:
    - Respiratory viral PCR testing: influenza, parainfluenza, rhinovirus, human metapneumovirus, SARS-CoV-2, adenovirus (antigen testing if PCR unavailable)
    - *Mycoplasma* and *Bordetella pertussis* PCR
    - *Pneumocystis PCR*
    - *M. tuberculosis PCR*
    - Galactomannan (BAL)
  - Culture:
    - Bacterial (aerobic), semi- or quantitative method
    - *Legionella* sp. (chocolate yeast extract)
    - Fungal—consider epidemiology: *Aspergillus*, *Cryptococcus*, *Histoplasma*, mucormycosis (do not grind when mucormycosis being considered)
    - Mycobacterial culture (tuberculosis and nontuberculous)
    - Nocardia/actinomyces

[a] *Available testing and stains will vary by laboratory. In all cases, close liaison with clinical microbiologists and pathologists regarding potential infective organisms will assist in ensuring that appropriate tests are performed. Test rationalization may be required where sample is limited.*

in Table 123-9. Communication directly with the microbiology laboratory regarding the most likely pathogen is helpful to ensure expeditious and efficient use of specimen, in addition to allowing specific sample processing requirements to be followed.

Sputum cultures can be useful and should be an initial test in all patients, although the yield is highest for bacterial pathogens. This simple, rapid test should be considered in all immunocompromised patients presenting with respiratory illness. Induced sputa have particular importance for *M. tuberculosis* and *Pneumocystis*, where there is greater yield than standard expectorated specimens.[156,157] Importantly, negative induced sputa does not exclude either of these diseases, especially *Pneumocystis* in HIV-negative patients.[158]

Bronchoscopy should be consider in all immunocompromised patients with unexplained respiratory presentations and suspected infection.[159] Whether bronchoscopy is required depends on the exact clinical circumstance and radiologic findings. However, this intervention is frequently necessary in patients with otherwise unexplained pulmonary presentations, given the variety of possible diagnoses (which can occur concurrently) and the difficulties associated with empiric therapy for opportunistic infections. Transbronchial biopsy should be considered, when risks are acceptable, as there is a potential increased yield in immunocompromised patients.[160–163]

Radiologically guided (usually via CT) percutaneous biopsy of lung or pleural lesions is an important intervention in immunocompromised patients with suspected pulmonary infection for whom a diagnosis has not been established using the previously described studies. This investigation is most commonly used to diagnose invasive fungal infection, but it also has important discriminatory power for differentiating fungal from other infections, including those due to mycobacterial disease and *Nocardia*. Additionally, percutaneous biopsy can aid in the diagnosis of malignancy and other noninfectious lung diseases.[164–169]

Open and video-assisted lung biopsy are final diagnostic tests that have the potential to obtain the most representative tissue, although potential risks must be carefully evaluated, as yield is variable.[170–177] These interventions have become less necessary as interventional radiologic techniques have improved.[178]

Blood cultures are useful in the majority of immunocompromised patients presenting with pulmonary infection, especially in acute presentations, where blood cultures are essential. In more subacute presentations, blood cultures positive for fungi (*Cryptococcus*, *Fusarium* sp., *Talaromyces marneffei*) or mycobacteria (both *M. tuberculosis* and nontuberculous mycobacteria) have significant therapeutic implications. When seeking to isolate tuberculosis or nontuberculous mycobacteria, specific mycobacterial blood cultures should be obtained and incubated long-term, given the potential slower growth of these organisms.

In all scenarios, a close working relationship with the microbiology and pathology laboratories provides the highest likelihood of success in identifying the causative organism. Laboratories have differing capabilities; liaison with microbiology and pathology colleagues regarding likely pathogens will assist in improving yield and turnaround time. Frequently, samples obtained may be limited and require rationing of testing to provide the highest yield.

SPECIFIC PULMONARY SYNDROMES IN IMMUNOCOMPROMISED HOSTS

While there is significant overlap of clinical syndromes between immunocompetent and immunocompromised hosts with a pulmonary presentation, some syndromes are more commonly encountered in immunocompromised hosts and warrant specific mention.

The combination of pulmonary and neurologic manifestations in immunocompromised hosts is notable. Findings may include a clear pneumonic process with concurrent meningitis, or a more subacute presentation of concurrently developing pulmonary and CNS mass lesions with minimal symptoms. Infectious causes of a "brain–lung" syndrome are outlined in Table 123-10. In such cases, diagnostics and imaging should be directed toward both sites, as a single diagnosis cannot always be presumed. Pulmonary investigations have been previously outlined and may provide a unifying diagnosis for both pulmonary and CNS manifestations. Specific, high-quality CNS imaging should always be considered in these presentations, including brain MRI, preferably with gadolinium contrast. In some circumstances, lumbar puncture for cytologic and microbiologic analysis of CSF may be useful, particularly if meningoencephalitis is suspected. When diagnostic uncertainty persists, biopsy of CNS lesions may be helpful, although the increased risks of the procedure must be considered.

In patients with concurrent pulmonary and skin manifestations, a broad differential diagnosis should be considered (Table 123-10). Skin biopsy is a generally safe and readily undertaken procedure

TABLE 123-10 Organisms Associated with Brain–Lung Syndromes and Skin–Lung Syndromes in Immunocompromised Hosts

Syndrome	Infectious Causes	Noninfectious Causes
Brain–lung syndrome	Disseminated viral infection (VZV, HSV, adenovirus, CMV) *M. tuberculosis* Nontuberculous *Mycobacteria* *Burkholderia pseudomallei* *Streptococcus pneumoniae* *Nocardia* sp. *Rhodococcus equi* *Coccidioides* sp. *Histoplasma capsulatum* *Cryptococcus* sp. *Aspergillus* sp. *Toxoplasma gondii* *Strongyloides stercoralis* (with Gram-negative meningitis)	Malignancy Autoimmune - Sarcoidosis - Granulomatosis with polyangiitis - Vasculitides Aseptic/thrombotic emboli
Skin–lung syndromes	Disseminated viral infection (VZV, HSV, adenovirus, CMV) Nontuberculous *Mycobacteria* *Burkholderia pseudomallei* *Nocardia* sp. *Rhodococcus equi* *Fusarium* sp. *Mucorales* *Cryptococcus* sp. *Coccidioides* sp. *Histoplasma capsulatum*	Malignancy Autoimmune - Sarcoidosis - Systemic lupus erythematosus - Connective tissue disorders - Vasculitides Drug reactions (including DRESS)

that can provide a rapid and specific diagnosis in many patients with rash and concurrent pulmonary pathology. In patients with vesicular or pustular lesions, a swab of vesicles or a pustule for Gram stain, culture (including bacterial, mycobacterial, *Nocardia*, and fungal cultures), and viral analysis (varicella zoster/herpes simplex via direct fluorescent antigen or PCR) can be particularly useful.

In both syndromes, the clinician must always consider the possibility that the processes occurring in separate organ sites are different and unique and may be infectious or noninfectious. This is especially true in immunocompromised hosts, in whom concurrent processes are common.

PULMONARY INFECTION IN LUNG TRANSPLANT RECIPIENTS

Lung transplantation is reviewed in detail in Chapter 106. When considering pulmonary infection, lung transplant recipients constitute a unique set of immunocompromised patients. As a group, they are often managed with more immunosuppression compared with other solid organ transplant recipients. In addition, their transplanted organ is a common site of infection and is constantly exposed to the environment. Lung transplant recipients with underlying cystic fibrosis are frequently heavily pretreated with antibiotics and, as a result, are colonized with multidrug-resistant bacteria and fungi. Thus, pretransplant colonizing organisms should be considered when designing prophylaxis and when considering potential pathogens.

The importance of establishing a specific diagnosis for a pulmonary process in lung transplant recipients cannot be overstated. The differential diagnosis almost always includes infection and rejection, with differentiation of the two guided mostly by histology and microbiological sampling. Atypical nonpulmonary pathogens also should be considered in lung transplant recipients. For example, pulmonary or disseminated infection with *Ureaplasma* species is associated with development of hyperammonemia syndrome after lung transplant and requires specific cultures or molecular testing for detection. This diagnosis can be challenging to recognize clinically, as the primary disease manifestations are those of hyperammonemia rather than infection.[179] Since prophylaxis is used more frequently, and often for prolonged periods in lung transplant recipients, empiric therapy must address the likelihood of breakthrough infection or development of resistant organisms.

Importantly, the surgical bronchial anastomotic site is highly susceptible to infection with potentially devastating consequences; hence, prophylaxis is often broad following lung transplantation. The bronchial anastomotic site is immediately exposed to the patient's environment and respiratory secretions. In addition, its blood supply is potentially impaired. Bronchial anastomotic infection is often diagnosed on routine bronchoscopy early in the posttransplant course. Later presentations include features of airway obstruction or bleeding. Commonly implicated organisms include fungi, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*.[180] Early debridement and aggressive antibiotic therapy are the mainstays of therapy.

Chronic lung allograft dysfunction is a disabling and irreversible cause of lung function decline in lung transplant recipients and includes two phenotypes: bronchiolitis obliterans syndrome (BOS) and restrictive allograft syndrome.[181] Respiratory viral infections and cytomegalovirus may be implicated in the etiology of chronic lung allograft dysfunction.[182–185] However, data are conflicting, and mechanisms are still being elucidated.[186] Clinical implications are currently unclear, although it appears reasonable to emphasize minimizing exposure risk and vaccinating when possible. Although treatment of viruses with effective therapy has yet to be proven effective in preventing chronic lung allograft dysfunction, treatment has been generally recommended when effective agents are available.[187] Reduction in immunosuppression is also limited in lung transplant recipients, for whom onset of rejection can be a life-threatening event. The importance of multidisciplinary care between pulmonary and infectious disease specialists cannot be overemphasized.

NONINFECTIOUS PULMONARY SYNDROMES

Immunocompromised hosts, for example, lung transplant recipients, patients with newly diagnosed acute myeloid leukemia, or chronically immunosuppressed patients with rheumatoid arthritis, are frequently complex. These patients have heightened risks not only for infection, but also for noninfectious pulmonary processes including malignancy, thrombosis, cardiac or renal failure, autoimmune phenomena, and drug toxicity (Chapter 94).

The occurrence of multiple, simultaneous infections or conditions often complicates and delays appropriate therapy. For example, CMV infection may complicate treatment of graft rejection or GVHD and contribute to the pathogenesis of *Pneumocystis* or *Toxoplasma* pneumonia. In the compromised host with fever and pneumonitis, chest radiographs may be difficult to interpret. Noninfectious causes of pulmonary infiltrates may coexist with infection, and atypical patterns predominate. Drug toxicities (e.g., bleomycin, cyclophosphamide, sulfa drugs), leukoagglutinin reactions, engraftment or immune reconstitution syndromes, radiation injury, pulmonary emboli, and lesions of metastatic cancer may coexist with opportunistic infection. The "typical" evolution of pulmonary infection may be altered by the presence of underlying (e.g., interstitial) pulmonary disease, as well as by diminished inflammatory responses. Commonly, laboratory tests may need to be repeated, CT scans performed, or invasive diagnostic modalities (including biopsy) utilized in the evaluation of patients unresponsive to therapy. Furthermore, complications of treatment may contribute to development of new infections or other complications. For example, trimethoprim/sulfamethoxazole may cause pneumonitis, hepatitis, or Stevens–Johnson syndrome; ganciclovir may cause neutropenia; transfusion reactions may cause pulmonary infiltrates and hemolysis; tacrolimus and cyclosporine may cause hemolytic–uremic syndrome; and antimicrobials may contribute to the development of thrush and *C. difficile* colitis.

EMPIRIC ANTIMICROBIAL THERAPY

Empiric therapy for pulmonary infection is covered in detail in Chapter 125. Exact regimens for empiric therapy are beyond the scope of this chapter, but a framework for determining empiric regimes is discussed. Although the literature is still somewhat limited, some professional societies have published guidelines regarding empiric antimicrobial therapy in immunocompromised hosts.[188,189] Figure 123-11 describes a common approach to empiric therapy.

When considering empiric therapy in immunocompromised patients, epidemiologic exposures, prior colonization or history of infection, and the net state of immunosuppression should be considered in developing a list of potential pathogens. Clinical presentation, imaging, and initial diagnostics can be used to refine the list of potential pathogens. At this point, a risk stratification can be performed to determine to what extent organisms on the list need to be treated empirically.

Patients should be stratified into two groups: (1) those with low initial severity and low risk for decompensation without any, or with narrow, empiric coverage, and (2) those with high initial severity of disease or high risk of decompensation. By design, those with higher initial severity or risk of decompensation are likely to require broader initial empiric therapy.

In an era of rapid molecular diagnostics, many infections can be confirmed or excluded quickly. Despite this, risk stratification is necessary, since the need to ensure adequate initial antimicrobial coverage increases with illness severity and risk of decompensation. This approach is balanced against the underlying need to ensure sufficient opportunity to collect adequate initial samples and allow a reasonable chance of specific microbial diagnosis. This is particularly true for bacterial and nonviral infections, where diagnostic yield may be reduced following empiric therapy, and when empiric therapy may be associated with substantial toxicity. Notably, many prospectively

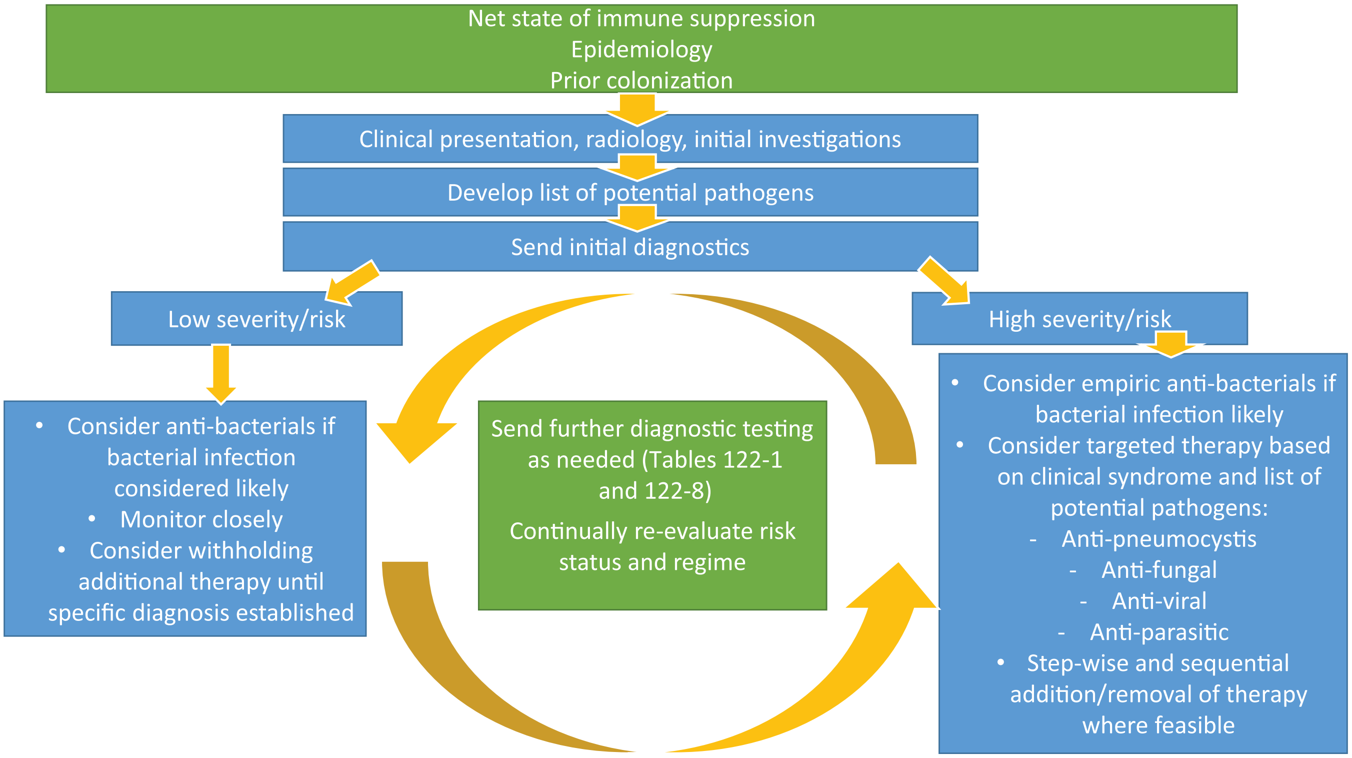

Net state of immune suppression
Epidemiology
Prior colonization
Clinical presentation, radiology, initial investigations
Develop list of potential pathogens
Send initial diagnostics
Low severity/risk
High severity/risk
• Consider anti-bacterials if bacterial infection considered likely
• Monitor closely
• Consider withholding additional therapy until specific diagnosis established
Send further diagnostic testing as needed (Tables 122-1 and 122-8)
Continually re-evaluate risk status and regime
• Consider empiric anti-bacterials if bacterial infection likely
• Consider targeted therapy based on clinical syndrome and list of potential pathogens:
- Anti-pneumocystis
- Anti-fungal
- Anti-viral
- Anti-parasitic
• Step-wise and sequential addition/removal of therapy where feasible

Figure 123-11 Approach to empiric therapy for pulmonary infections in immunocompromised hosts. Following consideration of the patient's net state of immunosuppression, prior colonization, and epidemiologic exposures, a list of potential causative pathogens can be developed. Initial diagnostics should be sent as soon as possible, including blood cultures, sputum cultures, serum/urine testing, and molecular testing. Patients can be categorized as high- or low-risk, based on severity of current illness and risk of further deterioration. Empiric therapy should be targeted to most likely causative pathogens. In low-severity/risk patients, consider delaying or narrowing empiric therapy to maximize likelihood of achieving a specific diagnosis. In high-severity/risk patients, it may be less feasible to delay empiric therapy while diagnostics are underway, and broader empiric therapy may be required. In all patients, the goal of specific microbiologic diagnosis is paramount (Fig. 123-10); yield may be higher in low-severity/risk patients, in whom empiric therapy is delayed or narrower. In both high- and low-severity/risk patients, constant re-evaluation of regimen efficacy and safety is warranted, as is regimen refinement as diagnostic tests return. Where feasible, stepwise and sequential introduction and withdrawal of agents may prove useful.

TABLE 123-11 Factors Involved in Determining Risk Category for Empiric Therapy

Considerations when determining pulmonary infection severity and risk for decompensation

- Hemodynamic status
- Oxygenation, respiratory rate, and pulmonary reserve
- Background patient "frailty" (malnutrition, deconditioning, age, etc.)
- The net state of immune suppression
- Degree of systemic compromise (confusion, renal failure, liver failure, cardiac failure)
- Recent hospitalization or surgical intervention, including transplantation
- Neutropenia
- Degree of inflammatory response by bedside, laboratory, and radiographic criteria
- Previous infections, including with opportunistic pathogens ("susceptibility" to infection)
- Recent epidemiologic exposures to respiratory pathogens

validated measures of pneumonia severity (e.g., Pneumonia Severity Index [PSI], CURB-65), have excluded many immunocompromised hosts, including solid organ and stem cell transplant recipients.[190–192] Thus, risk stratification is in the hands of the bedside clinician, and formal criteria do not exist. Factors to consider when determining risk stratification are listed in Table 123-11.

Once patients are categorized as low- or high-risk, the urgency and breadth of empiric therapy can be determined. The underlying principle of striving to obtain a specific diagnosis should be held paramount in "low-risk" patients, in whom tailoring empiric therapy to the most likely pathogens can be undertaken with minimal negative consequences. In higher-risk patients, the threshold for initiating empiric therapy is lower and may supersede the goal of establishing a specific diagnosis or initiating empiric therapy prior to diagnostic evaluation.

Frequently, a clinician's approach to empiric therapy is "step-wise and sequential." Initial therapy may be targeted toward the most likely pathogens, based on the previously described approach. These pathogens are frequently bacteria. Once the initial empiric regimen is instituted, clinical progress should be carefully monitored. As the patient progresses and diagnostic test results return, additional therapeutic agents (e.g., antiviral, antifungal, or antiparasitic drugs) can be added. The threshold for adding a new agent depends on the patient's risk category and clinical progress, and the clinician's diagnostic certainty.

Finally, utilization of previous antimicrobial exposure, including prophylaxis regimens, must be considered. Generally, infection emerging while a patient is on a prophylactic agent indicates drug resistance, and the agent should be avoided in empiric regimens.

■ Antibacterials

The threshold for initiating empiric therapy for bacterial infection should be low, given the risk of rapid deterioration due to bacterial sepsis and the ability to rapidly obtain blood and sputum cultures. Empiric antibiotic regimes should be selected based on local antibiograms and consideration of the patient's own microbial flora. Immunocompromised hosts are regularly "healthcare exposed" and are at higher risk for multidrug-resistant organisms. In addition, a documented history of these infections should further inform antibiotic selection.[189] Atypical pathogens (e.g., *Mycoplasma*, *Legionella*) should be considered when community acquisition of bacterial pneumonia is likely.

The initial antibiotic regimen design must also take into account special clinical circumstances. For example, the presence of neutropenia should prompt broader empiric coverage consistent with a "febrile neutropenia" addressed in local clinical guidelines. Typically, such regimens include an antipseudomonal agent. Similarly, a regimen for a patient with concurrent pulmonary and neurologic components may warrant antibiotics suitable for empiric treatment of meningitis or encephalitis, including drugs that cross the blood–brain barrier.

Typically, antimycobacterial agents are withheld until sufficient diagnostic testing has been performed. Sufficient diagnostic evaluation prior to initiation of antimycobacterials is vital to successful management of these patients, given the need for prolonged therapy and the potential for drug resistance. Frequently, test results may not be available for weeks, and empiric therapy may be initiated in a patient with a high pretest probability for a mycobacterial infection. Finally, empiric therapy for *Nocardia* and *Toxoplasma* may be clinically indicated based on the patient's clinical or microbiology specimen stains, ideally after sufficient diagnostic specimens have been sent.

While tempting, empiric antibacterial therapy must not be excessively broad, given the risks that prolonged use of such agents can pose. The risk of *Clostridioides difficile* and emergence of multidrug-resistant pathogens is already heightened in many immunocompromised patients, owing to multiple hospital admissions, increased antibiotic use, and immunosuppressive medications. The delicate balance between early, empiric, broad-based antibiotic coverage and the hazards of such an approach underscores the importance of determining a specific diagnosis as expeditiously as possible.

■ Antivirals

Empiric antiviral therapy is less commonly required, since rapid and accurate molecular testing allows relatively prompt diagnosis or exclusion of many pathogenic viruses in immunocompromised hosts. When diagnostic results are delayed, pretest probability is high, or the patient is very ill, empiric antiviral therapy for likely pathogens may be required. Empiric therapy for influenza is frequently started in suspected cases, pending molecular testing. SARS-CoV-2 represents a potentially severe respiratory infection, treatment of which entails evolving therapeutic options that may be warranted empirically as evidence emerges. Empiric therapy for herpes simplex, varicella zoster, or CMV is occasionally required, depending on the clinical circumstances. Other antiviral therapy options are limited and are frequently associated with greater initial toxicity; hence, empiric therapy in the absence of a clear diagnosis may be unwarranted.

■ Antifungals

Institution of empiric antifungal therapy is a complex decision, and involvement of an expert is usually necessary. Careful consideration via the approach outlined in Fig. 123-11 is recommended.

The risk of reducing the yield of diagnostic cultures is balanced against the risk of clinical deterioration and progression of infection. The complexity of decision-making is intensified, as many fungal infections require prolonged treatment (sometimes for months or even years) with drugs that are often associated with toxicities and drug interactions. These factors warrant a timely diagnostic investigation, including establishing a specific diagnosis and antifungal susceptibilities. Higher-risk patients, or those with fungal infections that appear rapidly progressive or disseminated, warrant earlier empiric therapy, regardless of the timeline for results of diagnostic tests. Conversely, some fungal infections may have a subacute course. In lower-risk patients, delaying antifungal treatment until diagnostics are performed may be reasonable. An example of an infection that requires urgent empiric antifungal therapy is mucormycosis; another is cryptococcal meningitis. Mucormycosis has the potential for rapid progression and dissemination and must be treated as a medical emergency using a combination of medical and surgical approaches. The clinical presentation of cryptococcal meningitis is dominated by neurologic features and is rapidly diagnosed using cryptococcal antigen testing.

Empiric treatment for *Pneumocystis jirovecii* is often required, particularly in patients with untreated HIV infection or other forms of profound immunosuppression (especially those not on prophylaxis). Frequently, patients with *Pneumocystis* present with severe pneumonia and require urgent treatment prior to results of testing. The decision to start empiric anti-*Pneumocystis* therapy must take into account the net state of immunosuppression (the "right" host for *Pneumocystis*), the clinical presentation (e.g., hypoxia disproportionate to other respiratory findings; a large arterial–alveolar oxygen gradient; an elevated LDH), and compatible imaging (i.e., diffuse ground-glass opacities). An appropriate combination of findings in a patient at risk usually creates a pretest probability high enough to warrant empiric therapy prior to a establishing a definitive diagnosis.

DRUG INTERACTIONS AND DISTRIBUTION

When prescribing antibiotics, possible drug interactions are an important consideration, particularly in immunocompromised hosts, who frequently take medications with numerous interactions (e.g., calcineurin inhibitors [tacrolimus, cyclosporine], ritonavir). Azole antifungals are commonly used in immunocompromised hosts; other antibiotics, such as clarithromycin and rifampicin, also are problematic. The involvement of an experienced clinical pharmacist is invaluable. Consideration of antimicrobial penetration to the site of action is important in regime selection. Some antibiotics have poor activity in the lung (e.g., daptomycin, which is inactivated by alveolar surfactant), have poor clinical efficacy for blood stream infection (e.g., tigecycline), or do not cross the blood–brain barrier easily (e.g., cefazolin).

Some antimicrobials should be prescribed only in conjunction with a plan for therapeutic drug monitoring. This is especially true for oral agents (for which absorption may be variable) and agents with narrow therapeutic indices. Vancomycin, aminoglycosides, flucytosine, voriconazole, and posaconazole are commonly used antimicrobials whose therapeutic drug levels inform guidance on drug dosing.

ALLERGY AND DRUG INTOLERANCE

Immunocompromised hosts are frequently exposed to healthcare settings and antimicrobial agents. Consequently, antibiotic and drug allergies are frequently reported among this population.[193,194] Adequate investigation and documentation of the precise nature of the drug reaction, including possible allergy testing, is vital to ensuring that adequate antimicrobial therapy is available, if needed. Ideally, clinicians should perform an allergy evaluation when the patient is well, thereby obviating the need for testing in the setting of acute illness.[194]

IMMUNOSUPPRESSION REDUCTION AS THERAPY

An improvement in the "net state of immunosuppression," either by reduction of immunosuppressive medications or by restoration of immune function (e.g., via initiation of antiretroviral therapy for HIV) may represent important primary or adjunctive therapy in immunocompromised hosts with infection. The timing and degree of immune reconstitution must take into account potential risks and benefits.[57]

For infections without availability of high-quality antimicrobial therapy, immunosuppression reduction may be potentially lifesaving (e.g., mucormycosis). However, reduction of immunosuppression carries risks in some hosts—for example, triggering a flare of an underlying autoimmune condition that may ultimately require *more* immunosuppression to control. The risk is especially great in transplant recipients, in whom immunosuppression reduction may precipitate allograft rejection or graft-versus-host disease that can be life-threatening.

Another risk of immunosuppression reduction is the emergence of immune reconstitution syndrome, as described below.

Thus, for some infections, reduction in "net state of immunosuppression" may be warranted until specific antimicrobial therapy is given, for example, treatment of cryptococcal meningitis in patients with HIV infection and decreased CD4 count who are not already on antiretroviral therapy.[23] In all cases, complex treatment decisions should be made following discussion with experts in management of the underlying condition and infectious disease consultants.

IMMUNE RECONSTITUTION SYNDROME: A DIAGNOSIS OF EXCLUSION

Immunocompromised hosts may experience an inflammatory syndrome that complicates therapy for infection or unmasks a new infection with immune recovery. *Immune reconstitution inflammatory syndrome* refers to a vigorous immune response to a pathogen and is typically associated with some degree of recovery in immune function. The syndrome has been described in patients with HIV infection as they begin antiretroviral treatment and experience a rise in CD4+ T cells.[195,196] However, it has also been described in patients recovering from neutropenia, solid organ transplant recipients, and others undergoing withdrawal of immunosuppression.[195,197,198]

A classic example is a patient with HIV infection who presents with a low CD4+ T cell count and concurrent tuberculosis. With commencement of antituberculous therapy, improvement or stabilization of symptoms may be noted. However, as antiretroviral therapy–related effects develop, recovering T cells recognize the tuberculosis pathogen and generate an immune response, manifest as fever, constitutional symptoms, and radiographic worsening of pulmonary infiltrates. In addition, local inflammation may occur at sites of infection that were previously unrecognized or that had stabilized or improved.

Other examples of immune reconstitution inflammatory syndrome include recovery of neutrophil counts with engraftment following hematopoietic stem cell transplant or with reduction of immunosuppression following solid organ transplant.

Key to patient management in these circumstances is consideration of the patient's entire clinical course to date. Careful bedside assessment is required to ensure that the diagnosis is correct (which may require repeat clinical evaluation and laboratory sampling) and reassessment for development of new processes (infectious and noninfectious, including drug reactions). The clinician must consider the possibilities that a new process has developed, or a new process *and* immune reconstitution are present. In some circumstances, additional immunosuppression may be warranted if immune reconstitution is the predominant clinical problem.[199]

OCCAM'S RAZOR MAY NOT APPLY

Immunocompromised hosts may experience multiple concurrent processes, some of which are infectious and others noninfectious. Additionally, *multiple concurrent* infections may be observed. For example, consider a hematopoietic stem cell recipient with graft-versus-host disease involving the lungs who develops CMV infection, followed by a fungal lung infection. All three issues are important and require therapy. A clinician managing such a patient must be mindful that establishing one diagnosis does not exclude all others. Careful monitoring of the patient's progress is required, as multiple diagnoses may emerge through the course of an illness.

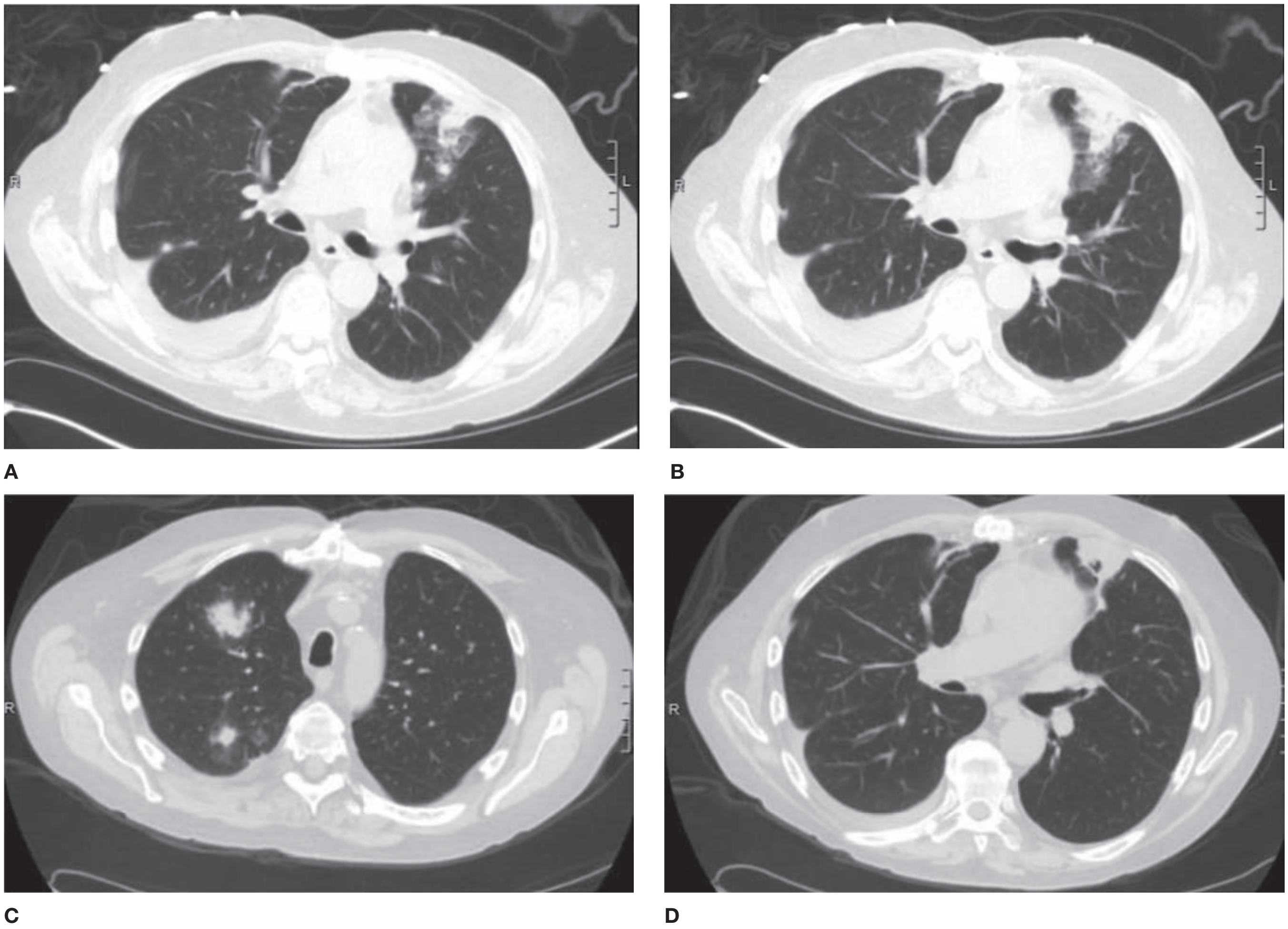


Figure 123-12 A recent cardiac transplant recipient developed CMV DNAemia, quickly followed by left lower lobe pulmonary aspergillosis with *Aspergillus flavus* (**A** and **B**). While on valganciclovir and voriconazole (therapeutic drug levels), a new right upper lobe pulmonary lesion developed on surveillance CT chest at 4 weeks (**C**), while the left lower lobe lesion was improving and starting to cavitate (**D**). Bronchoscopy showed a necrotic bronchial lesion. Bronchial biopsy demonstrated aseptate fungi. Lobectomy pathology demonstrated abundant septate and aseptate fungi, as well as CMV viral inclusions. Cultures grew *Scopulariopsis* species, *Nocardia nova*, and multidrug-resistant *Enterobacter*. Fungal polymerase chain reaction of pulmonary tissue demonstrated *Rhizopus oryzae* and *Aspergillus niger*. The patient was treated for pulmonary infection with CMV, multidrug-resistant *Enterobacter cloacae*, *Nocardia nova*, *Scopulariopsis* species, *Aspergillus*, and *Rhizopus oryzae*; immunosuppression was reduced. The patient eventually made a full recovery. This case demonstrates that multiple simultaneous process may occur, and that specific microbial diagnosis is key to successful management.

Constant vigilance is vital to the management of the immunocompromised host with infection (Fig. 123-12).

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CHAPTER 124

Microbial Virulence Factors in Pulmonary Infections

Carl D. Britto
Gregory P. Priebe
Gerald B. Pier

GENERAL CONSIDERATIONS

Beginning at birth, microbial organisms enter and leave the human body, primarily through external and mucosal surfaces. Some of these predominantly commensal organisms become resident; others are transient; and still others establish latent foci in various tissue spaces. Over a lifetime, the host–pathogen interactions that take place in an average human determine colonization, microbiome composition, and susceptibility to infections as well as immune-related events such as vaccine responses, autoimmunity, and malignant transformation. The human host is a reservoir for hundreds of strains of viruses, thousands of bacterial species, and a scattering of fungi and parasites. When these organisms violate their niche, invade, or produce toxic products, and at the same time overcome innate and adaptive host defenses, virulent interactions take place and can lead to disease. Organisms have evolved a variety of strategies to overcome host defenses, evade the immune system, scavenge for nutrients, eradicate competing bacteria, and survive to spread to other hosts. At the macro level, infection in the lung is the culmination of a disruption in the epidemiologic triad comprising host, agent, and environment. At the molecular level, new mechanistic insights into the interactions between host susceptibility, pathogen virulence, and environmental risk factors continue to be discovered.

The immune system maintains surveillance for organisms that invade phagocytes, propagate, and resist killing, and also for organisms that invade nonphagocytic cells. Means by which microbes can be controlled range from physical clearance mechanisms, to phagocytosis (followed by oxidative or nonoxidative killing), to nutritional depletion (e.g., sequestration of iron, which is an essential nutrient for bacterial growth). The existence of heavy colonization or infection in the upper airways increases the potential for infection in the lungs by a variety of mechanisms, mostly by a simple dose effect, whereby a large burden of potentially pathogenic organisms overwhelms the clearance mechanism of the lungs. Although the alveolar spaces are generally sterile, low levels of microorganisms are continually inhaled into the lungs. Inoculation of the lungs can occur from a variety of sources, including aspirated oropharyngeal secretions, directly inhaled from ambient air (airborne) or as droplet nuclei, particularly in closed environments, where density is great and infected individuals can deposit organisms into the air. Although not common, organisms can also gain entry into the lung via hematogenous spread from the bloodstream to the lungs, perhaps most notably in Lemierre disease related to septic thrombophlebitis due to the Gram-negative anaerobe *Fusobacterium necrophorum*.

The quantity and species diversity of many of the organisms colonizing the upper airways can be stable over long periods, although transient colonization with a variety of microbes also occurs with some frequency, and these changes are often correlated seasonally and/or with concomitant infections with respiratory viruses. For example, *Streptococcus pneumoniae* (pneumococcus) and *Neisseria meningitidis* (meningococcus) are more frequently isolated from the nasopharynx or throat during the winter months.[1–4]

Whether these inhaled or aspirated microbes cause disease depends on the intersection of multiple factors, one of which is whether the microbe possesses and expresses virulence factors. The regulation of the expression of bacterial virulence factors is tightly controlled by the interplay of pathogen factors including a complex network of two-component regulatory systems and pathogenicity islands. In *Pseudomonas aeruginosa*, quorum sensing (cell density–dependent gene expression) via small organic molecules called acyl homoserine lactones has been shown to be important for virulence in pneumonia models both by regulating expression of secreted toxins and by inducing inflammation.[5] *Staphylococcus aureus* strains control virulence through regulatory peptides involved in activating and suppressing the accessory gene regulator *(agr)* network, with similar systems found in other Gram-positive pathogens as well.[6] Interfering with these systems with appropriate inhibitors holds promise for future therapeutic interventions in bacterial pneumonia.

Most of the initial host response to pathogens in normally sterile sites, indicative of infection, involves the basic inflammatory responses of innate immunity. The microbes generally initiate this response by activating complement, binding quasi-specific host molecules such as mannose-binding lectin, and generating other tissue signals via cell-associated pattern-recognition molecules such as the TLRs[9,10] that lead to an influx of inflammatory cells and serum factors into the site of infection (Chapter 120). Inflammation leads to clinical symptoms such as sore throat, sneezing, coughing, malaise, and so on. Some particularly virulent microbes can rapidly produce much more serious disease as the organisms spread and cause inflammation diffusely throughout the respiratory tract. The balance between the host inflammatory response and microbial growth is the key factor in the disease process. As is often the case with microbial infection, inflammation is a double-edged sword, critically important for resolution of infection but also responsible for tissue damage.

THE ROLE OF THE MICROBIOME

The respiratory tract harbors distinct communities of microbes, with multiple discrete ecologic niches (e.g., nasal cavity, oropharynx, upper airways, lower airways) that vary in terms of temperature, pH, oxygen tension, mucus production, and other factors. With advances in sequencing technologies and bioinformatic capabilities, novel paradigms in understanding susceptibility to infections in relation to the microbiome continue to emerge. Perhaps the most important source of organisms causing pneumonia is the flora of the upper respiratory tract. A large microcosm of organisms that includes both pathogenic and nonpathogenic bacteria and fungi normally resides in the upper airways. These organisms are in a state of dynamic equilibrium and influence the susceptibility of infections based on the changing composition of the microbiome (Chapter 121). Bacteria colonizing the nasopharynx are often associated with the concurrent presence of certain viruses and bacteria—for example, *S. aureus* is associated with influenza but not rhinoviruses or pneumococcus; and pneumococcus with rhinoviruses, *Haemophilus influenzae*, and *Moraxella catarrhalis*.[7] The detection of rhinovirus together with *M. catarrhalis* has been associated with more severe manifestations of bronchiolitis. Human respiratory syncytial virus (RSV) infection predisposes to a respiratory microbiota that is *Streptococcus*-dominant, while infection with rhinovirus predisposes to a *Haemophilus*-dominant profile.[8] RSV infection has been shown to be enhanced by preceding *S. pneumoniae* infection both in vitro and in vivo,[9] but preceding RSV infection induces antibacterial effects by overexpression of proteins with known antibacterial activity.[10] In mice, colonization of the upper respiratory tract with *S. aureus* drastically reduces influenza-induced acute lung injury and mortality by recruiting a C-C chemokine receptor type 2+ (CCR2+) monocyte subset to the lungs and inducing an M2 macrophage phenotype.[11] However, increased diversity of the nasopharyngeal microflora may increase influenza severity, and severe influenza can decrease the abundance of *S. aureus* while increasing the abundance of *Prevotella*, *Streptobacillus*, *Porphyromonas*, *Granulicatella*, *Veillonella*, *Fusobacterium*, and *Haemophilus*.[11]

Organisms that make up the normal microbial flora in other parts of the body can be transferred to the lung, where they can cause infection. In early-onset group B streptococcal pneumonia and sepsis in neonates, the organisms are transferred during birth from the vaginal canal of the mother to the respiratory tract of the infant. In some cases, as long as a potential pathogen confines itself to a local site in the upper respiratory tract, no disease will ensue. At other times, growth at the local site and/or elaboration of toxins can cause frank disease; this is the mechanism of group A streptococcal pharyngitis and whooping cough caused by *Bordetella pertussis.* In general, the nasopharynx and throat readily tolerate the presence of a dynamic bacterial population, comprising mostly nonpathogenic strains along with potential pathogens that often come and go quietly, not spreading to other tissues or causing disease except when other factors intersect, such as a respiratory viral infection or other types of host stressors. While the microflora of the anterior nares and the nasopharynx are distinct, there is considerable overlap between the bacterial community compositions from these two anatomic sites, and microflora disease predictor associations from the nasopharynx are recapitulated in the anterior nares.[12]

OVERCOMING INHERENT PHYSIOLOGICAL AND CHEMICAL BARRIERS

Organisms gain access to the lower airways, either alone or in association with particles of mucus. They are generally either cleared by mucociliary flow or scavenged by phagocytes (Chapter 6). Particulates greater than 10 μm in diameter settle in the larger airways. Particles less than 5 μm that are not cleared within the larger airways reach the alveoli. Most particulate matter is not infectious, and only viable spores or organisms can cause infection. Prior to entering the lower respiratory tract, an organism must overcome a number of inherent mechanical and chemical barriers in the nasal passages and upper respiratory tract. The mucous lining of the respiratory tract possesses a variety of protective entities that act as physical barriers as well as immune mediators of protection. Pathogens, through natural selection, have evolved mechanisms to evade these innate barriers. The capsule present on bacteria such as *S. pneumoniae*, *H. influenzae*, and *N. meningitidis* reduces entrapment in the mucus and prevents adherence to epithelial cells to avoid activation of innate immune pattern recognition molecules such as toll-like receptors (TLRs). Thus, while there are studies using cell cultures that have shown that microbial adhesin factors such as choline-binding protein A (CbpA, also referred to as PspC or SpsA) promote pathogen binding to epithelial cells, and levels of pre-existing cross-reactive immunoglobulin to SpsA correlate with susceptibility to the establishment of pneumococcal carriage,[13] in vivo studies point to avoidance of epithelial binding and activation of innate immunity as correlates of pathogen virulence. For invasive pathogens, such as *S. pneumoniae*, the cell-wall phosphorylcholine has been shown to bind to the G protein–coupled platelet-activating factor receptor (PAFr) following inflammatory activation of human cells.[24] While this mechanism has been reported to lead to escape through the lung epithelium via the vascular endothelium into the circulation to cause sepsis, in vivo studies in mice showed that inhibition of binding of *S. pneumoniae* to PAFr by a receptor antagonist gave a contradictory outcome, increasing levels of *S. pneumoniae* in the lung and blood. It has been reported that type 1 and type 3 fimbriae of *K. pneumoniae* can extend beyond the capsular matrix and mediate D-mannose–sensitive adhesion to host epithelial cells, immune cells, and abiotic surfaces.[14] However, as was found with *S. pneumoniae* in vivo, *K. pneumoniae* avoids epithelial cell adherence to facilitate pathogenesis. *P. aeruginosa* possesses a protein called FliD at the tip of the flagellum that mediates adherence to respiratory mucin,[15] and *H. influenzae* similarly uses its pilus to bind to mucins[16] and anchor the cells within the respiratory tract. Most viruses and intracellular bacteria require attachment onto cells and subsequent intracellular invasion via structures that determine species and tissue tropism, transmissibility, and replication as typified by the viral hemagglutinin molecule on the surface of the influenza virus, the spike protein of SARS-CoV-2, the nucleocapsid of RSV, and the knob domain of adenovirus.[17,18] In contrast, intracellular nonviral microbes such as *Chlamydia* are taken into cells nonspecifically by phagocytosis or endocytosis.

Other extracellular pathogens that cause lung infections establish themselves in tissues by binding to factors in the mucus, notably mucin. Several bacterial pathogens that frequently cause pneumonia—including *P. aeruginosa, H. influenzae, S. aureus, S. pneumoniae, K. pneumoniae,* and some *Escherichia coli* strains—bind specifically to terminal or internal GalNAc-β (1–4)-Gal sequences lacking sialic acid residues commonly found on cellular glycolipids in the respiratory tract. *P. aeruginosa* has been prominently studied in regard to binding to respiratory mucins as a mechanism to establish and maintain infection in the lung. Nontypeable *H. influenzae* also appears to utilize pilus-mediated adherence to human respiratory mucins to establish chronic infections in the lung. *Bordetella pertussis* binds exclusively to the cilia on ciliated respiratory epithelium, using at least two bacterial cell surface factors, designated pertactin and filamentous hemagglutinin (FHA). A fraction of the organism's cell wall, the muramyl dipeptide, is then extensively produced and secreted, and this factor is toxic to the ciliated tracheal cells. These cells are extruded from the epithelial surface, perhaps in an attempt to clear the bacteria from the respiratory tract. With viruses, factors such as the neuraminidase and hemagglutinin proteins on the coat of the influenza virus are needed to promote viral shedding from infected cells followed by binding to uninfected cells, which leads to subsequent cellular invasion, viral replication, inflammation, and disease.

Microbes become "parasitic" when they express the requisite *virulence determinants* to gain entry and overcome or evade host defenses. In the absence of inherent host defenses, as seen with cystic fibrosis, in immotile cilia syndrome, and during prolonged endotracheal intubation, organisms are able to gain entry as well as colonize the respiratory tract more efficiently. Once these host barriers are breached, the downstream host immune responses are deployed to fend off infection.

SUBVERSION OF THE INNATE AND ADAPTIVE IMMUNE SYSTEM

The innate arm of the immune system is the evolutionary result of millions of years of exposure to pathogenic organisms. A variety of nonspecific innate immune mechanisms are potently activated by microbial binding to epithelial surface or, following binding and internalization, binding to intracellular Toll-like receptors (TLRs) and other conserved pattern-recognition molecules such as the complement system. Along with induction of cytokine synthesis and release there is a rapid activation of beneficial inflammation and clearance. Since the rates of evolution and natural selection of pathogenic organisms are infinitely greater than the innate immune system of humans, pathogens have evolved methods to evade these innate immune mechanisms. Thus, the microbes have a clear genetic advantage leading to selection of microbial factors that enhance virulence and survival.

Most of the initial host response to pathogens in normally quiescent tissues, indicative of infection, involves the basic inflammatory responses of innate immunity. The microbes generally initiate this response by activating complement, binding quasi-specific host molecules such as sugar-specific lectins, and generating other tissue signals via cell-associated pattern-recognition molecules such as the TLRs[19,20] that lead to an influx of inflammatory cells and serum factors into the site of infection (Chapters 19 and 120). Even the complement system can be inhibited by pathogen-specific effectors. For example, a staphylococcal complement inhibitor acts directly on C3 convertases (C4b2a and C3bBb), decreasing phagocytosis and killing by neutrophils,[21] and *N. meningitidis* produces a factor H binding protein to inhibit the killing activity of the complement system. Notably, this family of proteins accounts for part of the two available vaccines for the serogroup B strains of *N. meningitidis*.

Once a microorganism gains access to the lower respiratory tract, it must be able to resist clearance from this space, remain viable, and multiply. Organisms will either multiply locally, resisting local defenses, or spread to other body sites by traversing epithelial barriers that normally inhibit microbial spread. In order for extracellular organisms to multiply, they must scavenge for nutrients. Of particular note is the universal requirement for iron, which must be extracted from iron-binding molecules such as transferrin. Bacteria such as *K. pneumoniae* produce iron-binding substances known as siderophores that have an affinity for iron of greater than 10^{18} M and bind to high-affinity receptors on the bacterial surface. Organisms must also resist opsonophagocytosis or be able to survive and multiply within phagocytes. Viruses and obligate intracellular parasites, such as *Chlamydia*, usually must find their way to the lower respiratory tract and invade a specific cell in order to start growing. Some bacterial pathogens, such as *Legionella pneumophila* and *Mycobacterium tuberculosis*, need to encounter alveolar macrophages where they are ingested but resist destruction within these cells in order to establish infection and cause disease. *Mycobacterium tuberculosis* enters these cells in the lower and middle airways with high airflow, as it is an obligate aerobic organism (Chapter 130). Bacterial ligands and cellular receptors involved in this process are not fully characterized, although dendritic cell–specific intercellular adhesion molecule-3 grabbing nonintegrin (DC-SIGN) on dendritic cells and macrophages appears to play a role.[22] Following inhalation, most individuals will effectively clear or contain the tubercle bacilli, while in a minority the bacteria escape from the macrophage phagolysosome, or prevent its formation in the first place, leading to bacterial growth and host inflammation and resulting in lesions typical of tuberculosis. On the opposite side of the time spectrum from *M. tuberculosis*, inhaled spores of *Bacillus anthracis* as well as the *Listeria monocytogenes* and *Yersiniapestis* organisms are phagocytosed by alveolar macrophages but then escape from phagosomes, replicate within the cytoplasm, and emerge from the macrophage to enter the lymphatics or the bloodstream, with rapid development of clinical symptoms.[23]

Disease entities that result in the deficits in the innate arm shed light on host–pathogen interactions at this level. For example, in neutropenic mice, the infectious dose of *P. aeruginosa* applied to the nose of an anesthetized animal that produces a lethal pneumonia and sepsis can be in the range of 10 to 50 bacterial cells, whereas in a neutrophil-sufficient setting usually 107 to 108 bacterial cells are needed to initiate infection.[24] Clearly, avoiding polymorphonuclear leukocyte (PMN)-mediated clearance initiated by innate immunity is essential for serious pulmonary disease due to *P. aeruginosa*.

Many bacterial respiratory pathogens, particularly *B. pertussis*, *P. aeruginosa*, and *S. aureus*, produce very potent toxins. *P. aeruginosa* secretes elastase, an enzyme that can interfere with innate immunity in the lung by cleaving surfactant protein D, thereby abrogating its role in bacterial clearance.[25] Secreted toxins can act locally and/or systemically spread to cause clinical symptoms. The pertussis toxin is composed of two subunits, designated A and B; the B subunit binds to receptors on host cells, allowing the A subunit to enter the cell. The A subunit transfers the ADP-ribosyl part of NAD to a membrane-bound, GTP-binding protein that normally inhibits the enzyme adenyl cyclase. This leads to increased synthesis of cAMP and inhibition of neutrophil recruitment, thereby delaying antibody-dependent clearance of the bacterium even in immune hosts.[26]

The potential for epithelial injury to initiate tissue destruction can be a devastating consequence of microbial growth in normally sterile lung sites. In addition to toxins secreted extracellularly, protein effectors of the type III secretion system of *P. aeruginosa* can be directly injected into host cells, injuring the alveolar epithelium and subsequently allowing the release of proinflammatory cytokines such as TNF-α into the circulation, resulting in septic shock. *P. aeruginosa* also possesses a type VI secretion system that lyses nearby bacteria, allowing it to dominate its local environment.[27] The emergence of strains of community-acquired methicillin-resistant *S. aureus* (MRSA) associated with severe cases of necrotizing pneumonia appears to be related to elaboration of high levels of the alpha-hemolysin toxin (also called α-toxin), which injures epithelial cells after binding to a specific receptor, the zinc-dependent metalloprotease ADAM10.[28] The increased virulence of these MRSA strains was initially attributed to the Panton–Valentine leukocidin (PVL),[29] a pore-forming toxin specific for white blood cells, but subsequent work has shown that the PVL-producing strains are relatively rare causes of systemic infection[30] and these genes are mostly a marker for strains causing skin and soft-tissue infections with no real role in pneumonia.[31,32] The Gram-negative endotoxin, also called lipopolysaccharide (LPS), can cause serious damage to lung tissues, although the lung seems relatively resistant to the effects of inhaled endotoxin when compared with the systemic response to circulating LPS.

Many respiratory bacterial pathogens are encapsulated—a critical factor in promoting bacterial resistance to phagocytic killing. Neutralization of this antiphagocytic property by specific antibody results in high-level host immunity. Successful vaccines against *S. pneumoniae*, *H. influenzae* type b, and certain serogroups of *N. meningitidis* have been developed by engendering capsule-specific immunity via immunization, and comparable vaccines and monoclonal antibodies against *P. aeruginosa*, *K. pneumoniae*, group B streptococcus, and *S. aureus* are in various stages of development and testing in humans. Bacterial capsules are antiphagocytic and can reduce the total amount of complement that is deposited on the bacterial surface and the number of pneumococcal cells that are confined in neutrophil extracellular traps.[13]

The innate immune system works in concordance with the adaptive system to encompass a variety of defenses against a broad range of pathogenic mechanisms. The immune system attempts to recognize the pathogen and develop an effective adaptive immune response involving T cells and antibodies to prevent reinfection. These responses are considerably more rapid in onset and evolve swiftly through somatic hypermutations and T cell maturation to effectively neutralize pathogens and also develop memory responses.

Pathogens have evolved a series of mechanisms to avoid immune detection, including local interference with immune processes, antigenic variation, avoidance of inducing immune responses, or inducing ineffective immune responses.[33] The mechanisms by which pathogens display antigenic variation include varying copies

TABLE 124-1 Steps and Molecular Factors for Infectious Microorganisms to Cause Lung Disease

Step	Molecular Factors	Result
Attachment to or entry into the body	Pili, flagella, surface proteins, LPS, specific ligands for receptors on host cells or mucins	Establish organisms in a host
Multiplication	Iron-binding factors; quorum-sensing signals, biofilm matrix	Increase microbial numbers; activate other virulence systems; initiate clinical symptoms
Local spread in the lungs	Capsular polysaccharides, antiphagocytic factors, motility (pili and flagella), toxins	Evade defenses and the natural barriers to spread
Damage to lung tissue, dissemination to bloodstream	Exotoxins (including type III secretion system), LPS, cytotoxins, immunosuppressive factors	Inflict pathology due to the infectious agent, cause systemic evidence of infection (sepsis, septic shock)
Shedding (exit) from the body	None identified	Leave body at site and on a scale that ensures spread to a new host

of an antigenic molecule regulated by an on/off operon, posttranscriptional modification of antigenic genes, and highly variable binding sites. *Neisseria meningitidis* and *K. pneumoniae* use all three of these mechanisms during colonization in the upper respiratory tract as well as in the pathogenesis of their respective diseases. The capsule of pneumococcus and other capsulated organisms prevents antibody as well as complement deposition on its surface.[33] As alluded to earlier, the exotoxin of most organisms is a key virulence factor—but this is also a prime target of the adaptive immune response. Toxin expression in pathogens such as *B. pertussis*[34] and *Corynebacterium diphtheriae*[35] has evolved to escape immune detection by vaccine-induced memory responses and is in part the reason for the resurgence of pertussis particularly in teenagers. CMV causes downregulation of MHC class I and II molecules thereby preventing effective T-cell signaling, and the nucleoprotein of RSV has been shown to inhibit the immunologic synapses between dendritic cells and T cells during infection, resulting in inefficient T cell activation.[33]

The pathogenesis of microbial infections of the lung thus entails complex interactions between the microorganisms and a variety of host defense mechanisms. The general steps and molecular factors involved in the pathogenesis of microbes causing lung infections are summarized in Table 124-1.

UNIQUE ATTRIBUTES

Another mechanism for pneumonic infection can result from conditions that perturb the specific and/or nonspecific mucosal defenses, leading to respiratory infection as a sequela of another pathogenic process. *S. pneumoniae*, *H. influenzae*, and *S. aureus* are the most commonly reported bacteria associated with secondary infections following influenza virus infection. The neuraminidase of influenza virus has been shown to play a synergistic role in pneumococcal pneumonia models by cleaving the sialic acid residues on host glycoconjugates, thereby leading to increased adherence of the bacterium.[36] Denuded epithelial surfaces do provide sites for microbial binding via virulence factors such as SpsA, serine-rich repetitive proteins, and MSCRAMM (microorganism surface components that recognize adhesion matrix molecules) of *S. aureus*.[37] Also, virus-mediated inflammation upregulates certain molecules and apical receptors, including ethylenated glycans (such as GalNacβ1-4Gal) or α5β1 integrin, which promotes binding for organisms like *S. aureus* or *P. aeruginosa*. The exposed collagen and superimposed fibrin deposition stabilizes the adhesion of *S. pneumoniae*, *H. influenzae*, and *S. aureus* to respiratory tissues.[37] Activation of the innate immune response to viral RNA, modeled by polyI:C-mediated stimulation of the TLR3 and RIG-I pathways, which induce type I interferons, can also increase susceptibility of mice to pneumococcal and staphylococcal pneumonia.[38] During the adaptive immune response to influenza in mice, interferon γ can interfere with alveolar macrophage phagocytic function and heighten susceptibility to *S. pneumoniae* pneumonia.[39]

S. aureus infection can aid influenza infection by increasing the infective potential of influenza as the virion is being transduced into host cells within an endosome. The acidic pH within the endosome causes a conformational change to the viral hemagglutinin (HA[0]) allowing cleavage by host proteases into two subunits (HA[1] and HA[2]), thus activating HA, mediating viral-endosome fusion with subsequent opening of the M2 ion channel for viral ribonucleoproteins (vRNP) to be released into the host cell followed by viral RNA. Several strains of *S. aureus* produce proteases that assist in cleavage of influenza HA, allowing for more vRNP to enter host cells with subsequent transcription and viral replication.[40] This aspect contributes to the increased severity of disease caused by co-infection.[41] The stark decrease in staphylococcal pneumonia following measles vaccine programs in sub-Saharan Africa provides a good example of the importance of diminishing initial infections in order to prevent secondary infections. More recently, *S. aureus* pneumonia has been reported after RSV infection and SARS-CoV-2 infection.[42,43]

The human host response to invading pathogens differs across human genotypes, nature of antigenic stimulation, quantity of infectious dose, and route of infection. Some respiratory pathogens, of which measles is the best studied, induce unusual immune effects including its propensity to “reset” the immune systems of infected patients. The acute phase of infection induces immune suppression through a process called immune amnesia by replacing clonal-specific memory cells with new, measles virus [MV]-specific lymphocytes resulting in strong MV-specific immunity but with compromised defenses to many other pathogens.[44,45] MV enters host cells by fusing with the host plasma membranes in a receptor-dependent manner and subsequently infects alveolar macrophages possessing signaling lymphocytic activation molecule (SLAM), circumventing destructive phagocytosis. These infected macrophages then interact and infect memory T cells, memory B cells, and naïve B cells. Clearance of MV requires the abolition of these virally infected lymphocytes via immune-mediated elimination of past memory T cells and B cells, indirectly also creating immune amnesia. Restoration of protective immune memory takes about 2 to 3 years following initial MV infection.[44]

The acute inflammatory response in severe viral pneumonias such as SARS-CoV-2, MERS, and SARS is marked by the activation of proinflammatory cytokines or chemokines leading to the recruitment of inflammatory cells and increased expression of inflammatory, antiviral, and apoptotic genes, which are accompanied by abundant immune cell infiltration and tissue damage.

The magnitude of inflammation associated with an immunologic phenomenon termed the cytokine storm leads to diffuse alveolar damage, hyaline membrane formation, fibrin exudates, and fibrotic healing, which clinically manifests with signs of severe capillary damage, ARDS, and organ dysfunction when these cytokines/chemokines spill over into the circulation. An optimal inflammatory response begins when the pathogen-associated molecular patterns (PAMPs) from the virus are recognized by the pattern recognition receptors (PRRs) of innate immune cells. Specific proinflammatory cytokines are then expressed after the downstream signaling cascades of PRRs are triggered by stimuli. Polymorphisms of PRRs are thought to be the mechanism by which some individuals, but not others, seem relatively resistant to a cytokine storm in the setting of SARS-CoV-2, MERS, and SARS.[46] SARS-CoV-2 causes some degree of lymphopenia with cytotoxic T-cell exhaustion in association with evoking a cytokine storm in susceptible individuals.[46]

SPECIAL CONSIDERATIONS

Chronic bacterial lung infections can be caused by a variety of pathogens, many of which occur in persons with underlying lung disease. Patients with chronic obstructive pulmonary disease (COPD) are particularly susceptible to chronic infection with nontypeable *H. influenzae*. Beyond the propensity of *H. influenzae* to bind to respiratory mucins,[16] the molecular basis for infection and disease are mostly unclear. Interestingly, co-colonization experiments with *H. influenzae* and *S. pneumoniae* in mice have found that *H. influenzae* predominates due to *H. influenzae*–induced complement-dependent phagocytic killing of *S. pneumoniae*.[47]

Among patients with cystic fibrosis (CF), 80% to 90% will become chronically infected with *P. aeruginosa* (Chapter 48). This pathogen is currently the major factor limiting their life expectancy. Of note, while use of newer technologies that identify the complex mixtures of microbial DNA in samples of human tissues and secretions has greatly expanded our insights and understandings into the microbial communities or microbiomes present in the GI and vaginal tracts, skin, and oropharynx, the role they play in chronic respiratory infections is still under assessment. In CF, increasing concurrence with the concept of a community of microbes being associated with disease has to be placed in the context of findings that, when examining tissues from autopsies or lung transplants, only traditional CF pathogens such as *P. aeruginosa* are found by either culture or DNA analysis. In contrast, microbiome community DNA is found in oropharyngeal swabs and expectorated sputum that must come through the oropharynx in order to be collected,[48] likely confounding the conclusion that these organisms are truly present in the lung and contributing to disease pathogenesis.

Thus, *P. aeruginosa* remains the major infectious entity associated with pulmonary decline in CF, and a large research effort has focused on understanding how this pathogen infects the vast majority of patients with a genetic defect that does not appear related to chronic bacterial lung infection. In patients with CF, mutations are found in the CF transmembrane conductance regulator (CFTR) gene, which codes for a large protein that regulates chloride ion secretions directly and also appears to affect the flow of glutathione and bicarbonate. Some 70% of persons carry at least one mutant CFTR allele that lacks the codon for the phenylalanine at position 508 (ΔF508 mutation), making one-half of affected persons (∼49%) homozygous for this mutation. The lack of phenylalanine at position 508 leads to an inability of the mature protein to get into the cell membrane.

The relationship of mutant CFTR and hypersusceptibility to chronic *P. aeruginosa* infection is undergoing intensive study. Pier et al. have proposed that clearance of *P. aeruginosa* from the lung following inhalation of bacteria is critically dependent on CFTR-controlled internalization of the bacterium by lung epithelial cells followed by rapid activation of innate immunity involving NF-κB nuclear translocation and production of inflammatory cytokines such as IL-6, IL-8, and CXCL1.[48,49] The combined effects of epithelial cell internalization and shedding, along with rapid activation of innate immunity that most likely brings in neutrophils to phagocytose and eliminate additional extracellular bacteria, can lead to efficient microbial clearance. Resolution of this response via apoptosis has also been shown to be important in the CFTR-dependent response of the lung to *P. aeruginosa*. The CFTR protein has been identified as the actual cellular receptor for clearance of *P. aeruginosa* from the lung. In a neonatal mouse model of clearance of *P. aeruginosa* from the lungs after nasal inoculation of bacteria, it was found that blocking of CFTR-mediated epithelial cell ingestion of *P. aeruginosa* led to higher bacterial burdens in the lung. Similarly, in transgenic CF mice there is reduced epithelial cell uptake of *P. aeruginosa* and increased overall bacterial burdens in the lung. Of note, there appeared to be little to no binding of bacteria to tracheal epithelial cells in the infected CF mice, whereas extensive binding, ingestion, and shedding of *P. aeruginosa* by epithelial cells could be seen in tracheas of infected wild-type mice. Thus, in vivo, *P. aeruginosa* binding to CF epithelial cells is not observed, a situation completely consistent with results from histopathologic examination of lungs taken at transplant or autopsy from CF patients, where *P. aeruginosa* also is not seen binding to the epithelium but rather encased in mucus plugs within the airways. Overall, the initial establishment of *P. aeruginosa* infections in the lungs of CF patients can be directly attributable to the lack of functional CFTR in cell membranes to bind to this microbe and initiate appropriate innate immune responses, which overall prevents efficient bacterial clearance from the lung. Additional factors in the CF lung, such as reduced airway surface pH, as noted in the recently developed CF pig model,[50] may also play a role in impaired innate defenses against *P. aeruginosa* and other bacteria.

The pathogenic mechanisms leading to chronic *P. aeruginosa* lung infections in CF patients are more extensive. After avoiding initial clearance, the bacteria adhere to mucins and become embedded in mucus plugs within the airways[51] and eventually undergo a phenotypic conversion wherein they both lose their ability to produce the long O-polysaccharide side chains that are usually on the LPS and acquire the ability to elaborate copious quantities of a bacterial exopolysaccharide called alginate. The hypermutable phenotype seen in *P. aeruginosa* strains from CF patients likely speeds this adaptation.[52] Alginate is unable to provoke a protective antibody response in the host[53] and encases the bacteria in microcolonies within a hypoxic microenvironment in the lung.[54] Within this protective coating, phagocytes such as neutrophils are unable to ingest and kill the microorganisms. This leads to a vicious cycle of additional but ineffective inflammation and bacterial growth, the result of which is tissue destruction subsequent to the chronic inflammatory process. Alterations in the lipid A structure of the *P. aeruginosa* LPS in strains isolated from CF patients appear to confer resistance to antimicrobial peptides and a hyperinflammatory response.[55] For most of the patient's life, *P. aeruginosa* infection appears to remain confined to endobronchial surfaces, which become plugged with mucus while the airway tissues are being destroyed, although recently reported histopathologic results from lungs of CF patients who died in the 1970s also showed extensive alveolar involvement, prior to more modern medical management with aggressive anti-*Pseudomonas* antibiotic therapy.[56] The finding of quorum-sensing signals in the CF lung suggests that *P. aeruginosa* may exist as a biofilm (defined as a structured community of bacteria encased in a self-produced matrix), which likely contributes to the recalcitrance of this infection to antibiotics,[57] as does the recently described ability of *P. aeruginosa* to produce the gases hydrogen sulfide and nitric oxide in order to resist the oxidative stress induced by antibiotics.[58,59] Thus, the pathogenesis of chronic *P. aeruginosa* infection in CF involves at least two components: an initial phase of hypersusceptibility to infection that is predicated on an inability of CF patients to kill or clear inhaled *P. aeruginosa* cells, and a subsequent phase directly related to the bacterium's ability to elaborate alginate, which allows the organism to resist host defenses while continuing to provoke inflammation that damages lung tissues.

From this example of chronic lung infection, we garner some important insights into mechanisms whereby bacterial pathogens cause lung infections. Many of the principles apply to other types of pathogenic microbes that follow the basic scenario of entry, attachment, multiplication and survival, elicitation of inflammation, and ultimately tissue damage and compromise of respiratory function. Although each of these steps can often be characterized at a highly specific molecular level, usually using isolated factors such as toxins to elicit clinical symptoms of disease, the overall pathogenesis of disease requires that elaboration of molecular factors of pathogenesis be coordinated and that each step in the process occur under the proper circumstances and at the right time. Research in identifying and understanding the microbe's genetic and molecular factors that control and coordinate pathogenesis is still in its infancy. Presumably, greater understanding of particular factors and the interactions among both the factors and host tissues will lead to development of better vaccines and other therapies that will minimize the occurrence of microbial infections in the lung.

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CHAPTER 125

Principles of Antibiotic Use and the Selection of Empiric Therapy for Pneumonia

Girish B. Nair
Michael S. Niederman

INTRODUCTION

Antibiotics are the foundation of therapy for respiratory tract infections. The approach to use varies with the type of pneumonia, age of the affected patient, presence of various comorbid illnesses, risk factors for infection by specific pathogens, and severity of the acute illness. For most patients, initial therapy is empiric, aimed at a broad spectrum of potential pathogens. Once culture data become available, therapy can be pathogen-specific making it possible to de-escalate to fewer drugs with a narrower antimicrobial spectrum.[1] In some cases, initial empiric therapy must be continued because no etiologic pathogen is identified.

The transformation of modern medicine over the last century can be attributed in part to the discovery and development of antibiotics. However, with widespread use of antibiotics, antimicrobial resistance in bacterial pathogens has become rampant, and once easily treatable conditions, such as pneumococcal pneumonia, are becoming deadly again.[2] The Presidential Executive Order 13676 for Combating Antibiotic-Resistant Bacteria (CARB) released in 2014 recognizes the importance of curbing antimicrobial resistance and sets forward a set of principles to help tackle this emerging issue.[1]

When a pathogen is defined, the term "appropriate" refers to the use of at least one antimicrobial agent that is active in vitro against the etiologic pathogen. The term "adequate" includes not only appropriate therapy, but also the use of that agent in the correct dose, via the right route, given in a timely fashion, and with penetration to the site of infection. Timely and appropriate antibiotic therapy can improve survival in patients with community-acquired pneumonia (CAP) and nosocomial pneumonia or hospital-acquired pneumonia (HAP), and the benefits are most evident in patients who are not otherwise terminally ill.[3,4] Ventilator-associated pneumonia (VAP) is nosocomial pneumonia that develops after at least 48 h of preceding mechanical ventilation, and thus some ventilated HAP patients may not have VAP, since they do not satisfy this definition of prolonged preceding mechanical ventilation.

In the setting of CAP, effective initial antibiotic therapy is associated with a marked improvement in survival, compared with ineffective therapy, particularly in patients with severe illness.[3,5] In several studies, identification of the pathogens causing severe CAP did not lead to an improved survival rate, while the use of a broad-spectrum, empiric regimen directed at likely pathogens reduced mortality. Further, patients with CAP have reduced mortality if initial antibiotic therapy is provided within 4 h of arrival to the hospital. In the treatment of VAP, data show that appropriate therapy should be given as soon as the infection is clinically identified, and lower respiratory tract samples have been collected for culture. Delay of even 24 h in starting therapy is an important mortality risk factor in VAP.[4] In general, with severe illness, those receiving antibiotics earlier in their course have a lower mortality than those receiving delayed therapy, with the risk of death rising 7% to 8% for each hour of delay of therapy during the first 6 h of septic shock and hypotension.[6]

Even with the use of correct agents, not all patients recover. The fact that some HAP patients die in spite of microbiologically appropriate therapy is a reflection of the degree of antibiotic efficacy, as well as a reflection of host response capability (which may in part have a genetic determinant). Antibiotic effectiveness and clinical success are a complex system-level process, sensitive to environmental factors after drug administration, such as protein binding, intrapulmonary penetration, drug distribution, pharmacokinetic and pharmacodynamic properties, and host characteristics, such as the presence of comorbid conditions, immune related lung damage, and nonpulmonary complications.[7] In some HAP patients, death is the result of the serious underlying illness; the percentage of deaths that occur because of infection, termed "attributable mortality" of HAP, has been estimated to be as high as 50% to 60%, but timely use of appropriate antimicrobial therapy can reduce this attributable mortality to 20% or lower.[8,9]

The American Thoracic Society and Infectious Diseases Society of America (ATS/IDSA) have updated both CAP and HAP/VAP guidelines recently.[3,4] These guidelines emphasize the importance of timely, appropriate, and adequate antibiotic coverage to decrease mortality and avoid drug resistance. In the case of CAP, the emergence of penicillin-resistant pneumococcus, community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA), and epidemic viral illness (influenza, SARS, and SARS Coronavirus-2) may affect the selection of initial therapy. The "PES" pathogens (*Pseudomonas aeruginosa*, Enterobacteriaceae that are extended-spectrum β-lactamase–positive, and methicillin-resistant *Staphylococcus aureus*) account for up to 6% of hospitalized CAP and require specific therapy different from standard CAP therapy.[10] In the setting of HAP, each hospital, and each ICU within that hospital, has unique flora and antimicrobial susceptibility patterns; knowledge of such patterns is essential for selection of the optimal agents.

The majority of data establishing "standard" antibiotic doses are derived from studies in healthy volunteers or non–critically ill hospitalized patients, which have been extrapolated to a wide range of patients, including the elderly, the obese, and the critically ill, with differing clearances of these agents. Critically ill patients may manifest significantly altered end-organ function, whereas those with sepsis may have a hyperdynamic circulation and augmented renal clearance (ARC), necessitating higher than normal doses of antibiotics to achieve effective serum and intrapulmonary concentrations. In these patients, as well as in obese individuals who have an altered volume of distribution (Vd) of some drugs, subtherapeutic concentrations may result in treatment failure or in selection of antimicrobial-resistant organisms.[11] Several novel antibiotics with different mechanisms of action have recently been approved and may offer broad-spectrum coverage—particularly for those who are intolerant of, or not responding to, standard treatment, including those who harbor drug-resistant pathogens.[12]

In this chapter, the principles underlying antibiotic use are examined, followed by a discussion of the commonly used antibiotics for respiratory tract infections, the principles of empiric therapy of both CAP and HAP, and an overview of newer antibiotic choices for treatment of pneumonia. Further, pharmacokinetic and pharmacodynamic considerations are a theoretical way to optimize the delivery of antibiotics. To preserve antibiotics for future use, it is necessary to understand mechanisms of antibiotic resistance and to practice antimicrobial stewardship by focusing on proper antibiotic dosing, de-escalation therapy, and the development of local protocols for antibiotic choice, but not necessarily by restricting access to potentially effective broad-spectrum agents for seriously ill patients.

PRINCIPLES OF ANTIBIOTIC USE

Antibiotics interfere with the growth of bacteria using various mechanisms, including undermining the integrity of their cell wall and interfering with bacterial protein synthesis or common metabolic pathways. The mechanism of activity can be used to define whether an agent is bacteriostatic or bactericidal, terms discussed in "Mechanism of Action," below.

MECHANISM OF ACTION

Bactericidal antibiotics kill bacteria, generally by inhibiting cell-wall synthesis or by interrupting a key metabolic function of the organism. Agents of this type include the penicillins, cephalosporins, aminoglycosides, fluoroquinolones, vancomycin, daptomycin, colistin/polymyxin, rifampin, and metronidazole. *Bacteriostatic agents* are antibiotics that inhibit bacterial growth but generally do not interfere with cell-wall synthesis and rely on host defenses to eliminate microbes. Agents of this type include the macrolides, tetracyclines, sulfa drugs, chloramphenicol, linezolid, and clindamycin.

The terms *bactericidal* and *bacteriostatic* are broad categorizations and may not apply for a given agent relative to all organisms, with certain antimicrobials being bactericidal for one bacterial pathogen but bacteriostatic to another.[13] The use of a specific agent is dictated by the susceptibility of the causative organism(s) in a given anatomic location to individual antibiotics. However, a meta-analysis evaluating categorization of antibiotics did not show differences in clinical cure rate or mortality rate between patients treated with bacteriostatic or bactericidal antibiotics.[14] When neutropenia or immune compromise are present or if there is accompanying endocarditis or meningitis, the use of bactericidal agents is preferred. Thus, for most patients with pneumonia, it is not essential to choose a bactericidal agent. One additional consideration is that certain organisms such as *S. aureus* can produce toxins, and the optimal agent must be able to kill the bacteria and also to inhibit the production of disease-mediating toxins. Agents that inhibit bacterial toxin production include clindamycin, rifampin, and linezolid.

The *minimum inhibitory concentration (MIC)* is the minimum antibiotic concentration necessary to inhibit the growth of 90% of a standard sized inoculum, leading to no visible growth in a broth culture. The MIC is used to define the sensitivity of a pathogen to a specific antibiotic, under the assumption that the concentration required for killing (the MIC) can be reached in the serum in vivo. This term must be interpreted cautiously in the treatment of pneumonia, because the clinician must consider the MIC data in light of the penetration of an agent into lung tissues, with some agents achieving higher than serum levels at respiratory sites of infection and others reaching lower levels.[15,16]

The *minimum bactericidal concentration (MBC)* is the minimum concentration needed to cause a 3-logarithmic decrease (99.9% killing) in the size of the standard inoculum, and generally all pathogenic bacteria are killed at this concentration.

The *mutation prevention concentration (MPC)* is the lowest concentration of an antimicrobial agent that prevents bacterial colony formation from a culture containing greater than 1010 bacteria.[15] At lower than MPC concentrations, spontaneous mutants can persist and be enriched among the organisms that remain during therapy. The concept has been most carefully studied with the pneumococcus and fluoroquinolones. In general, the MPC is higher than the MIC, implying that it is possible to use an antimicrobial to successfully treat a clinical infection but with inadequate levels to eradicate the bacteria. These remaining organisms may provide a basis for the emergence of antimicrobial-resistant bacteria.

IMPORTANT PHARMACOKINETIC–PHARMACODYNAMIC VARIABLES

Pharmacokinetics refers to the absorption, distribution, and elimination of a drug in the body, which can be used to describe the concentration of a drug in the serum. *Pharmacodynamics* refers to the physiologic and biochemical effects of a drug on the body or any organisms within the body, the mechanisms of action, and the relationship between a drug's concentration and effect. Bacterial killing is affected by the way in which an antibiotic reaches the site of infection considering the frequency of administration and dose administered, thus defining a close relationship between pharmacokinetic and pharmacodynamic.[15,16]

There are three types of bactericidal antibiotics. First, are those that kill in relation to the duration in which the non-protein-bound free concentration of the agent stays above the MIC of the target organism, $f\mathrm{T} > \mathrm{MIC}$ *(time-dependent killing)*.[13] Examples include the β-lactams, carbapenems, aztreonam, macrolides, and linezolid. For maximal efficacy, β-lactam concentrations should be maintained at four times the MIC, for approximately 40% to 70% of the dosing interval, depending on the agent being employed.[16] Generally, carbapenems should exceed the MIC for at least 40% of the dosing interval, penicillins for 40% to 50%, and cephalosporins for 60% to 70% of the dosing interval. Second are agents that kill in relation to how high the peak concentration is, relative to the MIC, defined by the C_{max}:MIC ratio *(concentration-dependent killing)*.[16] Examples include the aminoglycosides and fluoroquinolones, as well as the ketolides. Finally, agents like the glycopeptides (vancomycin), daptomycin, linezolid, colistin, tigecycline, and the fluoroquinolones are bactericidal by *both concentration and time-dependent killing mechanisms*, and have efficacy defined by the area under the concentration–time curve divided by the MIC (AUC: MIC ratio, or AUIC).[17]

To optimize time-dependent killing, dosing should be chosen to achieve the maximal time above the MIC of the target organism; this can be done with continuous or prolonged (over 3–4 h) infusions. The rate of killing is saturated once the antibiotic concentration exceeds four times the MIC of the target organism. In spite of these considerations, for many organisms, the concentration of a carbapenem only needs to be above the MIC for 40% of the dosing interval.[15]

The target AUIC for Gram-negative bacteria is 125 or greater, whereas for most antibiotics that treat the pneumococcus, the target value is at least 30. Some studies have shown that aiming for C_{max}/MIC target of 12 for fluoroquinolones against pneumococcus is optimal. Appropriate use of these agents would entail infrequent administration but with high doses, which is the underlying principle behind the once-daily administration of aminoglycosides.

The *post-antibiotic effect (PAE)* maintains the efficacy of the antibiotic after the serum (or lung) concentrations have fallen below the MIC of the target organism. Thus, with once-daily aminoglycoside dosing regimens, the patient achieves a high peak concentration (maximal killing), and a low trough concentration (minimal nephrotoxicity) with the PAE achieving continued antimicrobial effects. While most agents exhibit a PAE against Gram-positive organisms, prolonged PAEs against Gram-negative bacilli are achieved by the aminoglycosides and fluoroquinolones.[15,16] For pneumococcus, a PAE exists for the macrolides/azalides, clindamycin, vancomycin, quinupristin/dalfopristin, tetracyclines, and the oxazolidinones (such as linezolid). Most of the agents that kill in a concentration-dependent fashion have a prolonged PAE. Agents with little or no PAE against Gram-negatives are generally also agents that kill in a time-dependent fashion and are administered several times daily. The β-lactams (including the penicillins, cephalosporins, and monobactams) generally have little or no PAE against Gram-negatives; one notable exception is imipenem, which has a modest

PAE against *Pseudomonas aeruginosa*. In clinical practice, the use of once-daily aminoglycoside dosing has had variable benefits in both efficacy and toxicity, but the advent of this type of dosing regimen follows from an understanding of pharmacodynamic principles. *Post-antibiotic leukocyte enhancement (PALE)* refers to the ability of functioning leukocytes to kill organisms in the post-antibiotic phase of growth. Thus, when the patient has functioning neutrophils, the PAE of some agents is extended by their PALE.

Some investigators have suggested that antibiotics should be selected based on whether they stimulate *inflammation* and cytokine production in response to the presence of the bacterial cell-wall lysis products.[13] Certain antibiotics liberate bacterial cell-wall products that interact with cytokine-producing cells, stimulating the production of high levels of cytokines such as tumor necrosis factor. In theory, this could lead to the development or the worsening of sepsis syndrome. This may be a consideration in patients with *Pneumocystis jiroveci* pneumonia or pneumococcal meningitis who may benefit from the use of corticosteroids with antimicrobial therapy in these infections. In general, the clinical role of cytokine release is uncertain, but bactericidal antibiotics tend to produce a greater host inflammatory response than bacteriostatic agents. Antibiotics that are cell wall–active, and that kill slowly, have been associated with the greatest cytokine release.

As noted previously, the use of antibiotics that inhibit protein synthesis (linezolid, clindamycin) may have an advantage in toxin-mediated illnesses, such as those caused by certain strains of *S. aureus*, when compared with cell wall–active bactericidal antibiotics.[18]

FACTORS AFFECTING ANTIBIOTIC CONCENTRATIONS

Alterations in lung penetration, protein binding, and changes in drug volume of distribution (Vd) and clearance (Cl) can significantly influence antibiotic concentrations achieved at a site of infection and, therefore, the probability of microbiologic success.[11] Furthermore, in critically ill patients, drug elimination is likely to be markedly different from healthy volunteers, and thus it is challenging to define optimal dosing in these patients.[11,19,20] In critically ill patients, concentrations may be higher or lower than in other patients. For example, with sepsis, and hyperdynamic cardiac function, patients may have augmented renal clearance (ARC), defined as a creatinine clearance >130 mL/min; the serum concentrations may be lower than expected, with normal dosing. In those with volume overload, Vd may increase and lead to lower serum drug levels, while altered renal and hepatic function can reduce drug clearance and cause higher than normal levels.[21] Organ support, such as renal replacement and extracorporeal membrane oxygenation (ECMO), may raise or reduce serum concentrations, depending on the agent being used.

Beyond the immediate threat of treatment failure, subtherapeutic antibiotic concentrations are a risk factor for the selection of drug-resistant organisms.[22] In critically ill patients, it is common to underdose antibiotics, and in one study it was common for patients not to achieve adequate time of β-lactam therapy above the target MIC, with at least 20% not achieving even a conservative target of having serum concentrations exceed the MIC of the target pathogen for at least 50% of the dosing interval.[23] Tigecycline resistance was identified within months of the commercial release of this antibiotic, and this may have been related to suboptimal concentrations at the site of infection.[24] In this respect, accurately identifying patients at risk of suboptimal drug exposure for a given causative pathogen remains a difficult clinical problem. Those most at risk for underdosing have a history of recent surgery, reduced creatinine clearance, and use of β-lactams by intermittent infusion. While therapeutic drug monitoring (TDM) provides the most robust means of identifying subtherapeutic concentrations, its availability for all classes of antibiotic is largely limited to specialized centers.[25] In addition, changing organ function during the course of critical illness will affect antibiotic PK parameters, necessitating a regular review of dosing requirements. TDM has shown its greatest value with aminoglycosides, voriconazole, and ribavirin, but a consensus statement suggested that if available, TDM should also be done for β-lactams, vancomycin, and linezolid.[26] Currently, empiric dosing can be done by computer-based nomograms that use input from population pharmacokinetics and individual patient factors.[27]

PENETRATION INTO THE LUNG

A key requirement for the successful treatment of pneumonia is the achievement of therapeutic drug concentrations at the site of infection; in pneumonia, the targets are the lung parenchyma and alveoli (Table 125-1).[28] The drug concentration within the epithelial lining fluid (ELF) has been the most commonly used surrogate in pneumonia therapy. Research over a number of years has established that there is wide variability both within and between antibiotic classes in terms of ELF penetration.[16,29] The physiochemical properties that govern drug movement across biologic membranes include the degree of ionization, fat solubility, molecular weight, and protein binding. Despite accounting for such characteristics, many of the differences between antibiotics in ELF to plasma concentration ratios (C_{ELF}:C_{Plasma}) remain poorly understood.[29] Sputum and bronchial concentrations may be the most relevant measurements for bronchial infections, whereas the concentrations in lung parenchyma, ELF, and cells such as macrophages and neutrophils may be more important for pneumonia. The localization of the pathogen also may be important; intracellular organisms such as *Legionella pneumophila* and *Chlamydophila pneumoniae* may be best eradicated by agents that achieve high intracellular concentrations in macrophages.

Macrolides have good penetration into ELF (e.g., C_{ELF}:$C_{Plasma} > 10$ for azithromycin),[29] whereas β-lactams have varying penetration ratios[30] without a predictable pattern. Vancomycin demonstrates limited lung penetration (C_{ELF}:$C_{Plasma} < 1$),[31] while both linezolid and fluoroquinolones are reported to have ELF concentrations equivalent to or greater than those in plasma (C_{ELF}:$C_{Plasma} \geq 1$).[32,33] Specific

TABLE 125-1 Penetration of Antibiotics into Respiratory Secretions

Good Penetration: Lipid Soluble, Concentration Not Inflammation Dependent
Quinolones
New macrolides: azithromycin, clarithromycin, solithromycin
Ketolides (telithromycin)
Tetracyclines
Doxycycline
Tigecycline
Omadacycline
Clindamycin
Trimethoprim-sulfamethoxazole
Poor Penetration: Relatively Lipid Insoluble, Inflammation Dependent for Concentration in the Lung
Aminoglycosides
β-lactams
Penicillins
Cephalosporins
Monobactams
Carbapenems

data from critically ill subgroups are generally limited, and in those where results have been reported, significant interpatient variability has been noted.[34] Another glycopeptide, daptomycin is inactivated by pulmonary surfactant and should not be used for treatment of lower respiratory tract infections but is used to treat bacteremia due to susceptible pathogens.

The quinolones kill in a concentration-dependent fashion allowing optimal antibacterial activity with infrequent dosing and high peak concentrations and high ratios of AUC/MIC or C_{max}/MIC. In addition, because quinolones have a post-antibiotic effect against both Gram-positive and Gram-negative organisms, killing is maintained after local concentrations fall below the MIC of the target organism. These properties allow the fluoroquinolones to be infrequently dosed, often once daily, particularly given the longer half-life of the newer compounds. The factor limiting once-daily dosing for all quinolones is the toxicity associated with higher doses of some agents such as ciprofloxacin, with neurotoxicity and possible seizures.

Two features of quinolones that make them well suited to respiratory infections are good oral bioavailability and excellent penetration into respiratory secretions and inflammatory cells within the lung, achieving local concentrations that often exceed serum levels; similar serum and tissue levels can be reached with oral or intravenous administration. Given good lung penetration, the quinolones may be clinically more effective than predicted by MIC values and may be better than other agents in prolonging the "disease-free" interval between exacerbations of COPD, a finding that has been demonstrated for moxifloxacin.[35] High bioavailability allows some "borderline" patients (such as nursing home patients) with pneumonia to be managed with outpatient oral therapy and maintain high therapeutic levels in the serum. In addition, these agents permit an easy transition from intravenous to oral therapy of inpatients with pneumonia.

The local concentration of an antibiotic must be considered in light of the activity of the agent at the site of infection, as well as the presence of bacterial resistance mechanisms. For example, antibiotics can be inactivated by certain local conditions. Aminoglycosides have reduced activity in acidic pH, which may be present in infected lung tissues. In addition, some bacteria develop resistance by producing destructive enzymes (such as β-lactamases), by altering the permeability of the outer cell wall, by changing the target site of antimicrobial action, or by pumping (efflux) of the antimicrobial from the interior of the cell. In these conditions a high local concentration of antimicrobial may help to offset bacterial resistance mechanisms.

The concentration of an antibiotic in lung parenchyma depends on the penetration through the walls of the bronchial capillaries, which have a fenestrated endothelium. Antibiotics penetrate in proportion to their molecular size and protein binding with small molecules that are not highly protein bound passing readily into the lung parenchyma. When inflammation is present, penetration is increased. Antibiotics reaching the ELF must pass through the pulmonary vascular bed with a nonfenestrated endothelium. This presents an advantage for lipophilic agents, which are generally not inflammation-dependent.

Lipophilic agents include chloramphenicol, the macrolides (including the azalides and ketolides), linezolid, clindamycin, the tetracyclines, the quinolones, and trimethoprim-sulfamethoxazole (TMP-SMX). Agents that are poorly lipid soluble are inflammation-dependent for entry into the ELF; these include the penicillins, cephalosporins, aminoglycosides, vancomycin, carbapenems, and monobactams.

Active transport can facilitate antibiotic entry into lung tissue and phagocytes. Agents that are concentrated in phagocytes in this manner include the macrolides, clindamycin, and the fluoroquinolones. Antibiotics, such as the β-lactams, that are not concentrated in phagocytes by active transport remain in the extracellular space, which constitutes 40% of the weight of bronchial tissue; thus, penicillins achieve only about 40% of the serum level in lung tissue.

Drugs that penetrate well into the sputum or bronchial tissue include the quinolones, the newer macrolides and azalides (azithromycin and clarithromycin), the ketolides (telithromycin), the tetracyclines, clindamycin, and TMP-SMX. On the other hand, the aminoglycosides, vancomycin, and to some extent the β-lactams, penetrate less well into these sites. With the use of once-daily aminoglycoside dosing, high peak serum concentrations can be achieved, but the alveolar lining fluid concentration in patients with pneumonia is only 32% of the serum level over the first 2 h; the two sites have more similar concentrations later in the dosing interval.[36] Since aminoglycosides require high peak concentrations for optimal killing, their poor penetration with systemic administration often impacts efficacy, suggesting a potential role for delivery by the aerosol route.

VOLUME OF DISTRIBUTION

The Vd describes the relationship between the dose administered to the concentration of the drug that is measured in blood or plasma. Values exceeding 3 L imply a distribution outside the plasma. Hydrophilic drugs that are poorly lipid soluble diffuse freely into interstitial fluid but do not penetrate cells. Thus, only the free, non-protein-bound drug can be distributed outside the plasma. Aminoglycosides and β-lactams are hydrophilic and will distribute into the extracellular space (~0.6 L/kg).[37] Lipophilic agents such as the macrolides and quinolones are extensively distributed in body tissues, and serum levels underestimate the effect at the site of infection. This observation explains the efficacy of azithromycin, which achieves relatively low serum levels with high intracellular concentrations, yet can treat pneumonia.

Vd is also affected by obesity. Dosing based on ideal body weight may lead to underdosing in general, while for hydrophilic antibiotics, dosing based on total body weight may result in excessive drug levels. In critical illness, the Vd of many agents can differ from that in healthy subjects, primarily as a reflection of changes in microvascular function. Volume resuscitation, a ubiquitous intervention in critical illness, may also increase Vd for hydrophilic agents in the face of increased capillary permeability and interstitial edema.[38,39] Sánchez et al.[40] described the hemodynamic changes observed after fluid resuscitation for septic shock, showing that antibiotics such as the β-lactams, aminoglycosides, and glycopeptides "go where the water goes," meaning that in critical illness, these drugs will be preferentially "dragged" into the interstitial space by extravascular movement of free fluid. The Vd of such drugs is much higher than in the absence of "leaky" capillaries. This effect is associated with decreased serum concentrations for any given dose; thus a larger dose is required to compensate for the increased Vd. As patients improve, fluid redistribution from tissues into the vascular space occurs, resulting in a significant decrease in the Vd. Thus, for drugs that distribute into extravascular interstitial fluid, an initial loading dose[41] is required to adequately "fill" these compartments and the Vd will change in parallel with each patient's physiology. This may explain why higher doses of vancomycin were needed to reach target serum concentrations in ICU patients in whom standard "ward" doses are likely to be inadequate. A larger Vd is also well described for β-lactams.[42]

PROTEIN BINDING

Many antibiotics demonstrate plasma protein binding, to either albumin or alpha-1-acid glycoprotein (AAG),[37] which can be disturbed in critical illness with many patients manifesting hypoalbuminemia.[43] The free fraction of the drug is eliminated with low plasma protein concentrations, resulting in an increase in Vd and clearance (CL) for highly protein-bound agents such as flucloxacillin, ertapenem, ceftriaxone, and teicoplanin.[43] Measuring the free drug concentration can be technically difficult; thus most published research has focused on total serum levels without correction for protein binding based on data from healthy volunteers.

DRUG CLEARANCE

Drug clearance represents the volume of plasma cleared of a specific pharmaceutical per unit time, and it can involve organ-independent enzymatic degradation, hepatic metabolism, or renal elimination of the parent compound or metabolites. During critical illness many aspects of these elimination pathways are disturbed. There are changes in major organ blood flow, saturation of enzyme systems, or complex drug–drug interactions.[37] Few data are available that describe the impact of changes in hepatic function on antibiotic pharmacokinetics and pharmacodynamics.

For many antibiotics (such as the aminoglycosides, β-lactams, and glycopeptides), renal drug clearance is directly proportional to creatinine clearance (CrCl).[37] With the administration of large volumes of fluid and the use of vasoactive agents in critically ill patients with sepsis, trauma, or burns, and in neurosurgery patients, there is often an increased cardiac output and organ perfusion with enhanced delivery of solute to drug-eliminating organs leading to the phenomenon of augmented renal clearance (ARC).[44] With ARC, serum creatinine concentrations are almost always within the "normal range," while measured creatinine clearance is elevated, even as high as 200% of normal. This may lead to suboptimal trough β-lactam concentrations in critical illness, thereby impacting the likelihood of achieving the necessary amount of time that the drug reaches an adequate concentration above the MIC targets.[44] ARC is mostly seen in male patients age 50 to 55 years with a higher mean diastolic BP and having fewer comorbidities, lower Sequential Organ Failure Assessment scores, and lower Acute Physiology and Chronic Health Evaluation (APACHE) II scores. In such patients the use of an isolated serum creatinine concentration to extrapolate GFR is not possible; dosing derived from noncritically ill patient populations may fail to account for ARC. In this setting, a timed urinary CrCl provides a simple, cheap, and repeatable estimate of renal drug elimination[45] and affords an alternate means of identifying such patients. From an antibacterial prescribing perspective, ARC will lead to an increased rate of drug elimination and may necessitate more frequent intermittent doses or administration by continuous or extended infusion.[46]

A paucity of data to guide dose selection is also present when patients receive extracorporeal renal replacement therapy (RRT, such as continuous veno–venous hemofiltration, hemodialysis, and hemodiafiltration). In such instances, native renal drug elimination is limited (although not completely absent), whereas nonrenal mechanisms may assume a greater role in total body clearance. As a consequence, highly variable antibiotic concentrations have been observed in patients receiving RRT.[47] The variety of RRT modalities available further complicates such determinations due to variations in the parameters employed (including blood flow rates, effluent flow rates, and membrane pore size) and the unique physiochemical characteristics of each drug.

Drugs that are hydrophilic have good clearance with dialysis. Although not similar to those with normal renal function, comparatively smaller molecules such as β-lactam and aminoglycosides are cleared with dialysis, whereas large molecules such as vancomycin are not cleared with dialysis.[11] Not surprisingly, optimal dosing strategies in RRT remain largely uncertain. Lately, extracorporeal membrane oxygenation (ECMO) has resulted in increased Vd with decreased CL, but limited data are available for pharmacokinetic and pharmacodynamic of antibiotics in these patients.[11]

The role of continuous infusion dosing (CD) for time-dependent antibiotics has been extensively studied as a means to optimize *concentration of drug as function of time over MIC*, with numerous studies suggesting an improved ability to achieve the required pharmacokinetic and pharmacodynamic targets,[48,49] particularly with more virulent bacteria. In the BLISS trial, an open-label, randomized study including 140 severe sepsis patients, CD was associated with higher clinical cure rates compared with intermittent dosing (ID) in those patients not receiving RRT with no overall difference in mortality.[50] Dulhunty et al.,[51] using three commonly prescribed β-lactams, showed that CD was associated with a significantly improved ability to achieve optimal pharmacokinetic–pharmacodynamic targets along with higher clinical cure rates; however, no difference was identified in ICU-free days or hospital survival. In a recent meta-analysis of 3 randomized controlled studies, including 632 patients with severe sepsis, Roberts et al. reported a significantly better in-hospital mortality (19.6% vs. 26.3%; $p = 0.045$) and clinical cure (55.4% vs. 46.3%; $p = 0.021$) with CD compared to ID.[52] Other factors such as ARC could pose unique challenges on drug dosing and reinforce the need to further investigate optimal dosing strategies in those with critical illness.[19]

ANTIMICROBIALS USED IN THE THERAPY OF RESPIRATORY TRACT INFECTIONS

A variety of classes of antibiotics are used in the treatment of respiratory tract infections. Each is discussed below.

■ Macrolides (Including Azalides)

Macrolides are bacteriostatic agents that bind to the 50S ribosomal subunit of the target bacteria and inhibit RNA-dependent protein synthesis. They have good activity against pneumococci as well as "atypical" pathogens (*C. pneumoniae*, *Mycoplasma pneumoniae*, *Legionella*). Older macrolides including erythromycin are not active against *Haemophilus influenzae* and have poor intestinal tolerance, so prolonged therapy is difficult. The newer agents in this class include azithromycin (also referred to as an azalide), clarithromycin, and solithromycin. Among the macrolides, azithromycin is more active than clarithomycin against *H. influenzae* (including beta-lactamase-producing strains), *M. catarrhalis*, and *M. pneumoniae*, whereas clarithromycin has shown to be more active against *Legionella*, *C. pneumoniae* and *Streptococcus pneumoniae*.

Both azithromycin and clarithromycin have better intestinal tolerance than erythromycin and penetrate well into sputum, lung tissue, and phagocytes. Clarithromycin, which has an active 14-hydroxy metabolite that is antibacterial, is administered twice a day orally at a 500-mg dose for 7 to 10 days in the treatment of CAP and acute exacerbations of chronic bronchitis (AECB). Azithromycin has a longer half-life than clarithromycin, and concentrates in tissues, achieving very low serum levels when administered orally. The dosing regimen for CAP is usually 500 mg for 1 day, followed by 250 mg daily for 4 days. An extended-release preparation allows the administration of 2000 mg as a one-time dose for CAP. For the hospitalized patient, an intravenous preparation of azithromycin is available and is dosed as 500 mg daily, with the duration defined by the clinical course of the patient, but usually for 7 to 10 days.[3] Because of its intravenous administration, the serum levels achieved have been adequate for the therapy of bacteremic pneumococcal pneumonia.[53] During inpatient CAP therapy, the fluid infusion volume of erythromycin is greater with erythromycin than azithromycin and has occasionally led to more volume overload and cardiac complications with erythromycin.

Solithromycin is a novel fourth-generation macrolide effective against *S. pneumoniae*, *H. influenzae*, and atypical pathogens. In two recent, double-blind, randomized, controlled, noninferiority trials, solithromycin was comparable to oral moxifloxacin in patients with mild to moderate CAP (Pneumonia Severity Index classes II–IV).[54,55] Elevated liver enzymes were seen in the first trial, SOLITAIRE-ORAL (800-mg oral loading dose then 400 mg for 5 days), but not with the follow up study, SOLITAIRE-IV (400 mg IV with option of switching to oral dose as with SOLITAIRE-ORAL). Because of concerns about hepatic toxicity, this drug is not currently approved for use in the United States or Europe.

Clinical studies of CAP have consistently shown a benefit of using macrolide therapy, usually in conjunction with a β-lactam, but the mechanism for this favorable effect is not known.[3,56] The addition of a macrolide to a β-lactam has reduced mortality for hospitalized CAP patients, including those with pneumococcal bacteremia and those with pneumococcal pneumonia and a high level of inflammation. Speculation has included the possibility of coverage for atypical pathogen coinfection, a possibility supported by studies that have found the benefit of the addition of a macrolide to vary year to year.[50] Another explanation is the anti-inflammatory effects possessed by macrolides, which may account for their benefit in improving quality of life in patients with cystic fibrosis and bronchiectasis. Macrolides have a myriad of other effects, including interference with "quorum sensing" between bacteria, which could inhibit the in vivo proliferation of *P. aeruginosa* after colonization has occurred.[57]

Although macrolides remain an important therapeutic option for community respiratory tract infections, pneumococcal resistance is becoming increasingly common, especially in patients who have received an agent of this class in the past 3 months.[58,59] In addition, macrolide resistance can also coexist with penicillin resistance with up to 30% to 40% of penicillin-resistant pneumococci also erythromycin-resistant. The clinical relevance of these in vitro findings remains to be defined, particularly if macrolides are used in combination with a β-lactam antibiotic. However, there are two forms of pneumococcal macrolide resistance, one involving efflux of the antibiotic from the bacterial cell and the other involving altered ribosomal binding of the antibiotic. The former mechanism is associated with much lower levels of resistance than the latter and is present in two-thirds of the macrolide-resistant pneumococci in the United States. The latter form of resistance is less common and, when present, makes macrolide therapy for pneumococcal infection ineffective.

Clindamycin

This agent inhibits bacterial protein synthesis by binding to the 50S ribosomal subunit, and can be either bactericidal or bacteriostatic depending on the target pathogen site of infection and drug level achieved. Available both orally and intravenously, clindamycin is approved for use in the therapy of sepsis and intra-abdominal infections, but it may be valuable in the therapy of CAP in specific patient populations. It is active against anaerobes and can be used in some patients with aspiration pneumonia and lung abscess. It is active against pneumococcus and *S. aureus* and can be used in patients with penicillin allergy. It is also effective at inhibiting bacterial toxin production and can be added to vancomycin to inhibit toxin production in patients with necrotizing pneumonia due to community-acquired methicillin-resistant *S. aureus*. The most common side effects are nausea, vomiting, diarrhea, and an increased risk of *Clostridium difficile* infection.

■ Tetracyclines

The tetracycline and doxycycline are bacteriostatic agents that act by binding the 30S ribosomal subunit and interfering with protein synthesis. These agents can be used in CAP because they are active against *H. influenzae* and atypical pathogens, but in the United States, pneumococcal resistance to tetracyclines may be approaching 20% and may exceed 50% among organisms with high-level penicillin resistance. Photosensitivity is the major side effect, limiting the use of these agents in sun-exposed patients. This drug still remains as a good alternative to treat patients with suspected atypical pneumonia infection in those with electrocardiographic QT prolongation.

Omadacycline is a recently approved aminomethylcycline with structural modifications to the tetracycline scaffold allowing it to withstand the tetracycline efflux and ribosome protection mechanisms of resistance. In a recent, randomized, double-blind trial in CAP patients (Pneumonia Severity Index risk class of II, III, or IV) comparing omadacycline (100 mg IV every 12 h for two doses, then 100 mg IV every 24 h) to moxifloxacin (400 mg intravenously every 24 h), there was a similar early clinical response with both antibiotics.[60]

Tigecycline is a glycylcycline, which is structurally similar to the tetracyclines, and contains a central four-ring carbocyclic skeleton but is a derivative of minocycline. Tigecycline is bacteriostatic and is a protein synthesis inhibitor that acts by binding to the 30S ribosomal subunit of bacteria, thereby blocking entry of aminoacyl-tRNA into the ribosome during prokaryotic translation.

This drug is approved to treat complicated skin and skin-structure infections and complicated intra-abdominal infections, but it can also be used in CAP caused by *S. pneumoniae*, *H. influenzae*, and *L. pneumophila*. With the exception of gastrointestinal adverse events, tigecycline is generally well tolerated. It is not approved for the therapy of MRSA pneumonia or HAP. Freire et al.,[61] in a randomized, double-blind study including 945 HAP patients, found tigecycline 100 mg per day to be noninferior to imipenem/cilastatin in a modified intent-to-treat analysis but not in the clinically evaluable population and not in VAP. Tigecycline should not be used as monotherapy of VAP, but could be part of a combination when treating resistant *Acinetobacter* strains.[62] Some data suggest that a higher dose (100 mg every 12 h) could be more effective, but this is not approved for clinical use.

■ Trimethoprim–Sulfamethoxazole

This combination antibiotic has been the mainstay of therapy against *Pneumocystis* pneumonia and *Pneumocystis jirovecii*. In the past, given its antimicrobial spectrum, ease of use, and low cost, it was an effective agent for CAP and AECB. It has bactericidal activity against the pneumococcus, *H. influenzae*, and *M. catarrhalis*, but not against atypical pathogens. Recently, it has become less popular because of the emergence of pneumococcal resistance at rates of at least 30%, since 80% to 90% of organisms that are penicillin resistant are also resistant to TMP-SMX. The sulfa component of the drug inhibits the bacterial enzyme responsible for forming the immediate precursor of folic acid, dihydropteroic acid. Trimethoprim is synergistic with the sulfa component and inhibits the activity of bacterial dihydrofolate reductase. TMP-SMX is available in a fixed combination of 1:5 (TMP:SMX), and is dosed as either 80/400 mg or 160/800 mg orally twice a day for 10 days, but the dosage should be adjusted in renal failure. An intravenous preparation also is available. Side effects generally result from the sulfa component and include rash, GI upset, and occasional renal failure (especially in elderly patients).

■ β-Lactam Antibiotics

β-Lactam antibiotics are bactericidal agents that interfere with the synthesis of bacterial cell-wall peptidoglycans by binding to bacterial penicillin-binding proteins. They share a β-lactam ring with structural modifications determining classification: (a) penicillins with the β-lactam ring bound to a five-membered thiazolidine ring; (b) cephalosporins with the β-lactam ring bound to a six-membered dihydrothiazine ring; (c) carbapenems with modifications in the thiazolidine ring (imipenem, ertapenem, doripenem, and meropenem); (d) monobactams with absence of a second ring structure found in the carbapenems (aztreonam). These agents can also be combined with β-lactamase inhibitors such as sulbactam, tazobactam, vaborbactam, relebactam, avibactam, or clavulanic acid to create the β-lactam/β-lactamase inhibitor drugs, which may overcome the bacterial resistance mechanism of β-lactamase production.

The penicillins used for respiratory tract infections include the natural penicillins (penicillin G and V), the aminopenicillins (ampicillin, amoxicillin), the antistaphylococcal agents (nafcillin, oxacillin), the antipseudomonal agents (piperacillin, ticarcillin), and the β-lactam/β-lactamase inhibitor combinations (ampicillin/sulbactam, amoxicillin/clavulanate, piperacillin/tazobactam, and ticarcillin/clavulanate). Among the antipseudomonal penicillins, piperacillin is the most active agent.

Imipenem, doripenem, and meropenem are the antipseudomonal carbapenems, the broadest-spectrum agents in this class, active against Gram-positives, anaerobes, and Gram-negatives including *P. aeruginosa*. They have shown efficacy for patients with severe pneumonia, both community-acquired and nosocomial. A nonpseudomonal carbapenem, ertapenem also is available and has been used effectively in the therapy of CAP and HAP. Several new preparations have added β-lactamase inhibitors to carbapenems to expand their spectrum of activity against resistant bacteria, including imipenem/relebactam and meropenem/vaborbactam. Aztreonam is a monobactam that is antigenically distinct from the β-lactams and can be used in penicillin-allergic patients. It is only active against Gram-negative organisms, having a spectrum very similar to the aminoglycosides.

The earlier cephalosporins were generally active against Gram-positive bacteria without activity against the more complex Gram-negatives or anaerobes and were susceptible to destruction by bacterial β-lactamases. The newer-generation agents are generally more specialized, with broader-spectrum activity and with resistance to breakdown by bacterial enzymes. The second-generation and newer agents are resistant to bacterial β-lactamases, but cefuroxime may not be an optimal pneumococcal agent if resistance is present.[63] The third-generation agents such as ceftriaxone and cefotaxime are active against penicillin-resistant pneumococci, while ceftazidime is not reliable against the pneumococcus but is active against *P. aeruginosa*. The third-generation agents may induce β-lactamases among certain gram-negatives (especially the *Enterobacteriaceae* spp.) and thus may promote the emergence of resistance during monotherapy. The fourth-generation agent cefepime is active against pneumococci and *P. aeruginosa* and is also less likely to induce resistance among the *Enterobacteriaceae* than the third-generation agents. Ceftaroline is a new, advanced-generation cephalosporin that has been approved for the therapy of CAP with in vitro activity against MRSA. It has bactericidal activity against Gram-positive and -negative pathogens, but also against MRSA and particularly against DRSP. In a meta-analysis of three randomized studies, ceftaroline (600 mg every 12 h) was superior to ceftriaxone (1–2 g every 24 h) for 5 to 7 days in an intention-to-treat analysis in patients with severe pneumonia (odds ratio [OR], 1.66; 95% confidence interval [CI], 1.34–2.06).[64] In another meta-analysis of 5 randomized controlled studies of CAP patients, ceftaroline was superior to ceftriaxone for clinical cure rate (OR, 1.61; 95% CI, 1.31–1.99).[65]

In the last few years, several new therapeutic options have become available for pneumonia, particularly HAP/VAP, with a focus on treating MDR pathogens, including the following:

1. Ceftobiprole, a fifth-generation cephalosporin with extended-spectrum activity against Gram-positive pathogens including methicillin-sensitive *S. aureus* (MSSA), methicillin-resistant coagulase-negative staphylococci, penicillin, and ceftriaxone-resistant *S. pneumoniae* and Gram-negative pathogens such as *P. aeruginosa* and *Enterobacteriaceae*, but limited efficacy against MRSA, *Acinetobacter*, and extended-spectrum β-lactamase (ESBL)-producing Gram-negatives.[66] It is approved in Europe for the treatment of HAP/VAP but not approved in the United States for use in pneumonia. In a randomized study including 706 CAP patients, use of ceftobiprole (500 mg every 8 h) was not inferior to ceftriaxone as monotherapy (2 g every 24 h) or combined with linezolid (600 mg every 12 h) in microbiologic cure rates.[67] In another study including 781 HAP/VAP patients, ceftobiprole 500 mg every 8 h showed similar efficacy to ceftazidime 2 g every 8 h plus linezolid 600 mg every 12 h (49.9% vs. 52.8%; 95% CI for the difference, −10.0 to 4.1).[68] Dose adjustments are needed in patients with moderate to severe renal impairment. In clinical trials, ARC may have led to some patients doing less well with ceftobiprole than with comparator agents.
2. Ceftazidime-avibactam (CEF/AVI) is a combination of a third-generation cephalosporin with a semisynthetic β-lactamase inhibitor. CEF/AVI is active against *P. aeruginosa* as well as a variety of MDR Gram-negatives producing β-lactamases, including Ambler class A (*K. pneumoniae* carbapenemases and ESBL-type enzymes), Ambler class C (AmpC), and some Ambler class D serine enzymes (e.g., oxacillinase OXA-48). This agent is not active against metallo-β-lactamases (MBL) or *Acinetobacter* OXA-like carbapenemases. CEF/AVI is approved by the FDA and EMA for use in HAP/VAP, having been shown to be noninferior to meropenem in a randomized controlled trial of carbapenem-resistant, non-Enterobacteriaceae pneumonia.[69] That trial included 726 nosocomial pneumonia patients, comparing 2000 mg ceftazidime and 500 mg avibactam to meropenem 1000 mg IV every 8 h. Both therapies had similar clinical cure rates (68.8% vs. 73.0%; difference, −4.2%; 95% CI, −10.8 to 2.5).[70] CEF/AVI could also be considered as an alternative to colistin in the treatment of carbapenem-resistant Enterobacteriaceae infections.[71]
3. Ceftolozane-tazobactam (CTZ/TAZ) is a cephalosporin and β-lactamase inhibitor with in vitro activity against multidrug-resistant *P. aeruginosa* and ESBL-producing Enterobacteriaceae. In a randomized controlled trial of CTZ/TAZ in mechanically ventilated patients with Gram-negative nosocomial pneumonia,[72] CTZ/TAZ (2 g ceftolozane plus 1 g tazobactam infused for 1 h every 8 h) was compared with meropenem (1 g infused for 1 h every 8 h). In the study, CTZ/TAZ was highly effective and well tolerated in mechanically ventilated patients with Gram-negative nosocomial pneumonia, with a mortality advantage in those with ventilated HAP and in those with prior unsuccessful antibiotic therapy of the current episode of nosocomial pneumonia. Bacteremic patients and those with *P. aeruginosa* infection had a higher rate of clinical cure if they were treated with CTZ/TAZ. This agent has been approved for HAP treatment by the FDA and EMA. Caution needs to be exercised in patients with impaired renal function.
4. Cefiderocol is a siderophore cephalosporin that binds to iron and enters the bacterial cell using the iron transport system. It is active against many carbapenem-resistant pathogens including *Enterobacteriaceae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*. In addition, it has activity against *Stenotrophomonas maltophilia*. Cefiderocol is approved for nosocomial pneumonia, including VAP, but showed no survival advantage or higher cure rates compared to meropenem. In another study, patients with VAP had a lower survival than with best available therapy.[73,74]
5. Meropenem-vaborbactam is a combination agent containing an existing β-lactam antibiotic (meropenem) with a cyclic boronate, non–β-lactam/β-lactamase inhibitor (vaborbactam). It has activity against Gram-negative microorganisms, including those with extended-spectrum β-lactamases and *K. pneumoniae* carbapenemases. However, it does not have activity against metallo-β-lactamase- and oxacillinase-producing strains. Although not approved for VAP, in a trial that included mechanically ventilated

patients, with carbapenem-resistant Enterobacteriaceae (CRE), meropenem-vaborbactam was compared with best available therapy (usually colistin) and showed an advantage for clinical cure with the new agent.[75]

6. Imipenem-relebactam (IR) is a combination agent containing an existing β-lactam antibiotic (imipenem-cilastatin) with a non–β-lactam/β-lactamase inhibitor (relebactam) and activity against Gram-negative microorganisms, including Ambler class C, extended-spectrum β-lactamases, and *K. pneumoniae* carbapenemases. However, it does not have activity against metallo-β-lactamase- and oxacillinase-producing strains. In a phase 3 trial comparing IR to piperacillin-tazobactam in 537 patients with nosocomial pneumonia, half being mechanically ventilated, the two therapies were equivalent for clinical cure and mortality.[76] Among the subgroup of those mechanically ventilated at baseline, survival was higher with IR.

■ Fluoroquinolones

Fluoroquinolones are bactericidal agents that act by interfering with bacterial DNA gyrase and/or topoisomerase IV, leading to impaired DNA synthesis repair and transcription and other cellular processes resulting in bacterial cell lysis. The earlier quinolones (such as ciprofloxacin and ofloxacin) are active primarily against DNA gyrase, which accounts for efficacy against Gram-negative bacteria. The newer agents (levofloxacin and moxifloxacin) bind both DNA gyrase and topoisomerase IV, accounting for efficacy against even drug-resistant Gram-positive organisms, including drug-resistant *S. pneumoniae* (DRSP). Resistance to fluoroquinolones can occur via a variety of mechanisms including mutations in the topoisomerase enzymes, altered permeability of the bacterial cell wall, or efflux of the antibiotic from inside of the bacteria.[77]

The fluoroquinolones are active against β-lactamase–producing organisms like *H. influenzae* and *M. catarrhalis,* making them very useful for patients with AECB.

Both levofloxacin and moxifloxacin have extended the activity of the quinolones with enhanced Gram-positive activity as well as by being more active against *C. pneumoniae* and *M. pneumoniae* when compared with the older agents. They are also highly effective against *L. pneumophila* and may be the drug of choice for this organism. For *P. aeruginosa*, as in certain patients with CAP, AECB, and HAP, only ciprofloxacin (750 mg twice daily orally or 400 mg every 8 h IV) or levofloxacin (750 mg orally or IV daily) are active enough for clinical use. Since some agents (e.g., ciprofloxacin) have borderline activity against the pneumococcus, if they are used for AECB or CAP, the dose should probably be optimized to either 750 mg twice daily of ciprofloxacin for AECB or 750 mg once daily of levofloxacin for CAP or AECB.

Levofloxacin and ciprofloxacin, but not moxifloxacin, are renally excreted and thus require dosage adjustment in patients with renal insufficiency. These agents also differ in the degree of protein binding. The relevance of this feature to clinical outcome is uncertain, but agents like levofloxacin and moxifloxacin are not highly protein bound and have higher free serum concentrations. Although the newer agents are highly active against both penicillin-sensitive and -resistant pneumococci, there is concern that widespread use may increase pneumococcal resistance to these agents. Up to 20% of pneumococcal strains have quinolone resistance–determinant genes present but have not developed full resistance.[77] Risk factors for quinolone resistance among pneumococci are recent hospitalization, recent quinolone therapy, and residence in a nursing home.

Several new quinolones are in development. Nemonoxacin is a novel nonfluorinated quinolone; in a phase 3 study of CAP patients randomized to nemonoxacin ($n = 356$) or levofloxacin ($n = 171$) there was no difference in clinical or microbiologic cure rates between the groups at 7 to 10 days, with comparable adverse side effects.[78] In a meta-analysis including 3 randomized controlled studies, cure rates, microbiologic response, and treatment-emergent adverse effects were similar in CAP patients treated with nemonoxacin (500 or 750 mg) compared to levofloxacin.[79] Major side effects are QTc interval prolongation and myelotoxicity. Delafloxacin is another novel fluoroquinolone with activity against MRSA, *Enterococcus faecalis*, *C. pneumoniae*, *Mycoplasma* spp., and *Legionella* spp. In a phase 3 study in CAP patients, there was a 16-fold greater activity with delafloxacin compared to moxifloxacin for Gram-positive and fastidious Gram-negative pathogens, with retained activity against resistant phenotypes found in *S. pneumoniae* (penicillin-, macrolide-, and multiple-drug resistant), *Haemophilus* species (β-lactamase–producing, macrolide-nonsusceptible), and *S. aureus* (MRSA, fluoroquinolone-nonsusceptible MSSA).[80] Zabofloxacin is another oral fluoroquinolone with greater in vitro activity against Gram-positive agents than moxifloxacin. In a phase 3 trial, zabofloxacin 367-mg tablet orally once daily for 5 days (plus 2 days placebo) was noninferior (86.7% vs. 86.3%) to moxifloxacin 400 mg once daily for 7 days for patients with chronic obstructive pulmonary disease exacerbation.

■ Aminoglycosides

The aminoglycosides are bactericidal agents that act by binding to the 30S ribosomal subunit of bacteria, thus interfering with protein synthesis. Aminoglycosides have primarily a Gram-negative spectrum of activity and are usually used in combination with other agents targeting difficult organisms such as *P. aeruginosa* or other resistant Gram-negative bacteria. When combined with certain β-lactam agents they can achieve antibacterial synergy against *P. aeruginosa*. Amikacin is least susceptible to enzymatic inactivation by bacteria, whereas tobramycin is more active than gentamicin against *P. aeruginosa*. Aminoglycosides penetrate poorly into lung tissue and can be inactivated by the acidic environment of pneumonic lung tissue, and are primarily used as part of combination therapy. Because of poor penetration, some investigators have used nebulized aminoglycosides for the therapy and/or prevention of Gram-negative pneumonia, but clinical data showing efficacy are limited for this application. Clinical trials conducted for nosocomial pneumonia therapy revealed that the use of an intravenous aminoglycoside with a β-lactam antibiotic compared to a β-lactam monotherapy alone was not more effective and the combination did not prevent the emergence of *pseudomonal* resistance.[81] In the treatment of bacteremic *pseudomonal* pneumonia, aminoglycoside combination therapy may be more effective than monotherapy.

As discussed above, aminoglycosides kill in a concentration-dependent fashion and can be dosed once daily to optimize killing while minimizing toxicity (primarily renal insufficiency). In clinical practice, this has not been proven to occur, and once-daily dosing is comparable in efficacy and nephrotoxicity to multiple-dose regimens. When aminoglycosides are used, it is necessary to monitor serum levels to minimize the occurrence of acute renal failure. Peak concentrations correlate with efficacy but only have meaning with multiple daily doses, and their utility in once-daily regimens has not been established. Trough concentrations are monitored to minimize toxicity and probably should be followed regardless of dosing regimen.

A semisynthetic aminoglycoside (referred to as a neoglycoside), plazomicin, may become a therapeutic option for pneumonia, but it is currently approved only for complicated urinary tract infections. It is also a bactericidal agent, with concentration-dependent killing, acting to inhibit bacterial protein synthesis at the 30S ribosomal subunit, after binding to the 16S subunit.[82] It has broad activity against Gram-negatives and Gram-positives, including MRSA, *P. aeruginosa* (more active than amikacin), Enterobacteriaceae, *K. pneumoniae*, and some *Acinetobacter* spp. For all these pathogens, plazomicin is more active than other aminoglycosides. It has similar concerns about nephrotoxicity and limited data for therapy of VAP, being similar in efficacy to colistin.

■ Therapy of Methicillin-Resistant *S. aureus* Infections

Vancomycin and Other Older Agents

MRSA has emerged as an important pathogen in patients with nosocomial pneumonia, particularly VAP, and also in association with necrotizing post-influenza community-acquired pneumonia. In the past, vancomycin was the agent used most commonly against this pathogen. However, there have been concerns about the limited efficacy of vancomycin, primarily because of poor penetration into respiratory secretions. In addition, vancomycin is dosed intermittently with the goal of maintaining trough concentrations between 15 and 20 μg/mL; in critically ill patients this level may be associated with nephrotoxicity and may not be effective for organisms with MIC values >1 μg/mL. Vancomycin is often underdosed in critically ill patients with pneumonia and ARC.[83] Higher doses may be required in those receiving RRT. Use of a weight-based loading dose (approximately 35 mg/kg, using actual body weight) followed by continuous infusions (adjusted according to the CrCl) has been advocated by some investigators to rapidly achieve therapeutic vancomycin concentrations in critical illness, but without proven benefit. In patients with community-acquired MRSA, necrotizing pneumonia may develop due to damage caused by bacterial exotoxins. Toxin inhibition does not occur with vancomycin and can be achieved by adding clindamycin—or alternatively by monotherapy with linezolid (below), which can inhibit bacterial toxin production.

Quinupristin/dalfopristin has been tested in patients with VAP and was not as effective against MRSA as vancomycin in spite of good in vitro activity. There are several other agents in various stages of development that have activity against MRSA that have not been proven to be useful for the therapy of respiratory tract infections (see below). This includes daptomycin, which is inactivated by pulmonary surfactant, thus explaining a lack of efficacy in pneumonia therapy trials (and which is never recommended for pneumonia). Tigecycline and ceftaroline are available, but efficacy of these agents in the therapy of MRSA pneumonia is not known.

Linezolid

Linezolid is the first agent in a newer antibiotic class, the oxazolidinones, which act by inhibiting bacterial protein synthesis and have activity against MRSA. Oxazolidinones bind to the 50S ribosomal subunit, preventing binding to transfer RNA and blocking formation of the 70S initiation complex. Oxazolidinones inhibit production of antibacterial toxins such as the Panton-Valentine leukocidin, which can be produced by community-acquired MRSA strains. Linezolid is active against MRSA as well as against DRSP and vancomycin-resistant enterococci (VRE) (both *Enterococcus faecium* and *Enterococcus faecalis*). This agent has a high bioavailability with similar serum levels with oral or intravenous therapy. Renal and nonrenal clearance occurs, and dosing adjustments are not needed for patients with renal failure.

Given the increased recognition of the unique pharmacokinetic–pharmacodynamic changes in critical illness, empiric use of linezolid instead of high-dose vancomycin has a theoretical advantage for the treatment of MRSA pneumonia. One prospective, double-blind, controlled trial involving patients with confirmed MRSA pneumonia—randomized to receive either linezolid (600 mg 12 hourly) or vancomycin (15 mg/kg every 12 h with dose adjustment on the basis of trough levels) for 7 to 14 days—showed higher clinical success with linezolid and similar 60-day mortality rates between groups.[84]

Linezolid is a reasonable alternative for patients with treatment failure while receiving vancomycin, for MRSA isolates with vancomycin MIC values >2 μg/mL, for patients with allergic reactions, or for those with high risk of vancomycin-induced nephrotoxicity.[85] Side effects are not common and include nausea, diarrhea, anemia, and thrombocytopenia (especially with prolonged use). It is a weak monoamine oxidase inhibitor. Tedizolid is a synthetic oxazolidinone active against MRSA, linezolid-resistant MRSA, and VRE. It is approved for acute bacterial skin and soft tissue infections, but its use is being explored for patients with HAP/VAP.[86] It may cause less thrombocytopenia than linezolid.

Telavancin

Telavancin is a new lipoglycopeptide with rapid, concentration-dependent killing activity, adequate lung penetration, and bactericidal action against Gram-positives including VRE and MRSA. In a prospective, randomized, double-blind trial, telavancin was compared against vancomycin in the treatment of MRSA HAP in 1503 patients.[87] Higher cure with monomicrobial *S. aureus* infection was seen with telavancin, and it was more effective than vancomycin for MRSA with vancomycin MIC values >1 μg/mL. The ATTAIN studies comparing telavancin (10 mg/kg every 24 h) versus vancomycin (1 g every 12 h) for the treatment of HAP/VAP reported similar mortality and safety profile with both drugs, except higher mortality in the telavancin arm for those with moderate to severe renal impairment.[88] Thus, telavancin is an alternative for vancomycin in treatment of MRSA nosocomial pneumonia except in those with renal impairment.

■ Polymyxins

Polymyxins are bactericidal antibiotics used in the treatment of Gram-negative bacterial infections that work in a concentration-dependent fashion, and include polymyxin B and E—the latter known as colistin. After binding to lipopolysaccharide (LPS) in the outer membrane of Gram-negative bacteria, polymyxins disrupt both the outer and inner membranes, causing increased permeability of the bacterial cell wall to other antibiotics. Gram-negative bacteria can develop resistance to polymyxins through various modifications of the LPS structure that inhibit the binding of polymyxins to LPS.

Polymyxins can be used for pneumonia caused by strains of MDR *P. aeruginosa*, *Acinetobacter* resistant to carbapenems, or carbapenemase-producing *Enterobacteriaceae*.[89] Polymyxins are not absorbed from the gastrointestinal tract, and therefore they are administered intravenously or by inhalation. Elimination is primarily renal, and they are 50% protein bound. Major side effects include nephrotoxicity and neurotoxicity (neuromuscular block, confusion, ataxia, visual disturbances, and dizziness).

A retrospective matched case-control study comparing IV colistin or aerosolized (AS) plus IV colistin in the treatment of VAP by MDR pathogens, in which *A. baumannii* was the most common pathogen, followed by *Klebsiella pneumonia* and *P. aeruginosa*, showed no significant differences between the groups for eradication of pathogens, clinical cure, and mortality.[90] Optimal pneumonia dosing is not fully established. Colistin dosing is from 3 million (240 mg colistimethate) units to 5 million (400 mg colistimethate) units every 8 h. In the therapy of *Acinetobacter*, polymyxins may be more effective when combined with sulbactam.

■ Lefamulin

This agent is in the new pleuromutilin class of antibiotics and is a novel semisynthetic compound. It has activity against MRSA, VRE, DRSP, *L. pneumophila*, *C. pneumoniae*, and *Mycoplasma pneumoniae*. It was approved for use in CAP based on the phase 3 LEAP 2 randomized clinical trial examining early clinical response in CAP patients (Pneumonia Severity Index risk class of II, III, or

IV) receiving 5 days of oral lefamulin, where it was noninferior to 7-day oral treatment with moxifloxacin.[91]

Aerosolized Antibiotics for Respiratory Tract Infections

Lung penetration of many intravenous antibiotics, including aminoglycosides and colistin, is limited despite appropriate antibiotic administration. Increased dosages and prolonged duration of therapy used to treat resistant organisms can be associated with greater systemic toxicity with an increased risk of development of antimicrobial resistance.[92] Aerosolized antibiotics might address these concerns by direct delivery to the site of respiratory infection, particularly for agents that penetrate poorly into the lung with systemic administration. Direct delivery of antibiotics is usually achieved by nebulization, which achieves high intrapulmonary concentrations with generally low systemic absorption, reducing the risk of systemic toxicity. The majority of studies of inhaled antibiotics have been done in nonventilated patients with cystic fibrosis, and chronic bronchial infection with *P. aeruginosa*, including patients with bronchiectasis.[93]

The use of this approach in mechanically ventilated patients has been reported for patients with either infectious tracheobronchitis or VAP, particularly when the infections involve highly resistant Gram-negative bacteria (*P. aeruginosa*, *Klebsiella* spp., and *Acinetobacter* spp.) and in whom topical delivery of antibiotics might allow effective therapy of pathogens that cannot be eradicated by systemic therapy. The appropriate dose of aerosolized antibiotics is uncertain but can be calculated using the intravenous dose for that particular medication and adding to it the amount of extrapulmonary drug deposition. When concentration-dependent killing antibiotics are administrated, higher peak tissue concentration is associated with greater bactericidal activity, while time-dependent antibiotics are required to maintain lung tissue concentrations above the MIC of the target organism for a prolonged period.[94,95]

Antibiotics can be administered using ultrasonic, jet, or vibrating mesh nebulizers. Jet nebulizers generate aerosols by using compressed gas, ultrasonic nebulizers use a piezoelectric crystal to agitate a solution at high frequency, and mesh nebulizers use a high-frequency vibrating mesh to pump a solution through tapered holes.[94] Factors that influence lung deposition of nebulized antibiotics during mechanical ventilation include aerosol particle size, type of nebulizer, physical characteristics of the carrying gas, respirator settings, pneumonia severity, and degree of lung aeration.[94] (Penetration of antibiotic into areas of bronchopneumonia differs from consolidation.) Aerosolized particles with median mass aerodynamic diameter of 1 to 5 μm can reach the distal bronchioles and alveolar space. A volume control mode of mechanical ventilation has been used with a constant inspiratory flow but may require sedation during aerosol administration. Nebulization should be synchronized to the inspiratory cycle, while the inspiratory to expiratory ratio is maintained at 1:1, and the nebulizer can be placed in the inspiratory tubing or in line between the endotracheal tube and the Y connector.[96,97] Conventional humidifiers need to be used in the ventilator, but humidification is discontinued during nebulization. While the optimal method of administration of aerosol therapy is unknown, most studies have shown that nebulization can be effective and achieve more uniform distribution than direct instillation and, with modern delivery methods, more than 50% of the nebulized dose is retained in the lung. In experimental studies, it has been shown that the alveolar capillary membrane permeability is markedly increased during lung parenchymal infection.[94] Thus, inhaled antibiotics like aminoglycosides and cephalosporins, but not colistin, could be absorbed into the systemic circulation, with some potential for toxicity.

Several studies have shown that inhaled antibiotics can be used as either sole therapy or adjunctive (to intravenous) therapy for MDR Gram-negative VAP.[90,98] Cure rates greater than 60% have been reported, especially with the use of the vibrating mesh plate, small-particle nebulizer. Aerosolized antibiotics have shown efficiency in studies to treat the lung infection as well as the bacterial reservoir within the biofilm of the endotracheal tube. One randomized trial compared nebulized amikacin and ceftazidime (without systemic therapy) in the treatment of *pseudomonal* VAP to intravenous treatment with the same medications. The study showed that nebulized medications were able to treat VAP but prevented treatment-related acquisition of antibiotic resistance that was seen in patients receiving intravenous antibiotics.[99] Another prospective randomized trial examined the impact of adjunctive inhaled amikacin, using a vibrating mesh plate nebulizer in patients with VAP, many of whom had MDR Gram-negative infection, and showed that inhaled therapy led to less systemic antibiotic use and more de-escalation than adjunctive inhaled saline.[100]

In a meta-analysis including 11 studies, the authors found that aerosolized colistin or aminoglycosides led to a higher resolution rates for patients with resistant pathogens, but not in those with sensitive pathogens.[101] In a more recent, randomized, placebo-controlled study of adjunctive inhaled amikacin/fosfomycin (300 mg amikacin, 120 mg fosfomycin inhaled every 12 h for 10 days) in 143 patients with Gram-negative VAP, the authors found no difference in the Clinical Pulmonary Infection Score (CPIS), mortality, or clinical cure between the standard of care arm and the adjunctive inhaled treatment arm.[102] Another large, randomized, blind study of 712 patients with Gram-negative VAP compared adjunctive inhaled amikacin (BAY41-6551) to inhaled placebo and demonstrated no impact on mortality at 32 days.[94] In both of the studies mentioned above, *Acinetobacter baumannii* and *P. aeruginosa* were the predominant respiratory isolate with a trend showing decreased need for antibiotic escalation with inhaled treatment.

The most recent IDSA/ATS guidelines on nosocomial pneumonia gave a weak recommendation for the addition of inhaled colistin and aminoglycosides to systemic antibiotics for patients with nonresponding Gram-negative VAP with MDR pathogens.[4] In mechanically ventilated patients, even though local antibiotic administration has been successful, there has been concern about the emergence of MDR Gram-negatives with nebulized antibiotic therapy. Most current studies of VAP using either aminoglycosides or polymyxin B have not shown resistance to emerge. One side effect of aerosolized antibiotics has been bronchospasm, which can be induced by the antibiotic or the associated diluents present in certain preparations.

PRINCIPLES OF THERAPY FOR RESPIRATORY TRACT INFECTIONS

Principles of therapy underlying treatment of community-acquired, healthcare-associated, and hospital-acquired pneumonia are considered below.

Community-Acquired Pneumonia

Empiric therapy for CAP is selected by categorizing patients on the basis of the presence or absence of cardiopulmonary disease or other specific "modifying" factors that make certain pathogens more likely, severity of illness, and place of therapy (outpatient, inpatient, ICU). Table 125-2 describes the common pathogens causing CAP in specific patient populations. Figure 125-1 describes antibiotic preferences for the treatment of CAP in an outpatient setting, based on patient characteristics and risk factors. Unlike prior guidelines, newer guidelines allow for β-lactam monotherapy in low-risk outpatient CAP patients. Figure 125-2 describes the antibiotic preferences for the treatment of pneumonia for non-ICU hospitalized patients (hemodynamically stable) based on risk factors and allergy status.

Modifying factors that increase the risk for infections with specific pathogens include the following:

TABLE 125-2 Common Pathogens Causing CAP in Specific Patient Populations (in Order of Decreasing Frequency)

Outpatient, No Cardiopulmonary Disease or Modifying Factors	*S. pneumoniae*, *M. pneumoniae*, *C. pneumoniae* (alone or as mixed infection), *H. influenzae*, respiratory viruses, others (*Legionella* sp., *M. tuberculosis*, endemic fungi)
Outpatient, with Cardiopulmonary Disease	All of the above plus DRSP, enteric Gram-negatives, and possibly anaerobes (with aspiration)
Inpatient, with Cardiopulmonary Disease and/or Modifying Factors	*S. pneumoniae* (including DRSP), *H. influenzae*, *M. pneumoniae*, *C. pneumoniae*, mixed infection (bacteria plus atypical pathogen), enteric Gram-negatives (which can include *P. aeruginosa*), anaerobes (aspiration), viruses, *Legionella* sp., others (*M. tuberculosis*, endemic fungi, *Pneumocystis jirovecii*)
Inpatient, with No Cardiopulmonary Disease or Modifying Factors	All of the above, but DRSP and enteric Gram-negatives are not likely. These patients are rarely admitted to the hospital.
Severe CAP, with No Risks for *P. aeruginosa*	*S. pneumoniae* (including DRSP), *Legionella* sp., *H. influenzae*, enteric Gram-negative bacilli, *S. aureus*, *M. pneumoniae*, respiratory viruses, others (*C. pneumoniae*, *M. tuberculosis*, endemic fungi)
Severe CAP, with Risks for *P. aeruginosa*	All of the pathogens above, plus *P. aeruginosa*

MDR: Hospitalization for 2 or more days in the past 90 days, broad-spectrum antibiotics within the past 3 months, immune suppression, poor functional status, admission to an ICU with a high rate of MDR organisms, residence in a nursing home or long-term care facility, or regular visits to a hospital clinic or hemodialysis center. In newer guidelines, an important risk factor is prior respiratory tract isolation of MRSA or *P. aeruginosa*.[3]

DRSP: Age >65 years, β-lactam therapy within the past 3 months, alcoholism, immunosuppressive illness (including therapy with corticosteroids), multiple medical comorbidities, and exposure to a child in a day care.

Enteric Gram-negative bacteria: Residence in a nursing home, underlying cardiopulmonary disease, multiple medical comorbidities, and recent antibiotic therapy. Specific risks for *P. aeruginosa include* structural lung disease (bronchiectasis), corticosteroid therapy (>10 mg prednisone/day), broad-spectrum antibiotic therapy for more than 7 days in the past month, and malnutrition. Oral anaerobes occur in the presence of poor dental hygiene.

Post-influenza pneumonia can be caused by *S. aureus* (including community-acquired MRSA), *H. influenzae*, *or* pneumococcus.

From the available data, either a fluoroquinolone or a β-lactam/macrolide combination regimen is therapeutically equivalent in nonsevere CAP. Although not proven, it may be useful to use these two types of regimens interchangeably, striving for “antibiotic heterogeneity” and being sure to select an agent in a different class from those the patient received in the past 3 to 6 months. If patients have received a macrolide, fluoroquinolone, or penicillin in the past 3 months, then a subsequent infection with pneumococcus is more likely to be resistant to the agent received in the past than to other agents.[3] Although oral quinolones may be as effective as intravenous quinolones for admitted

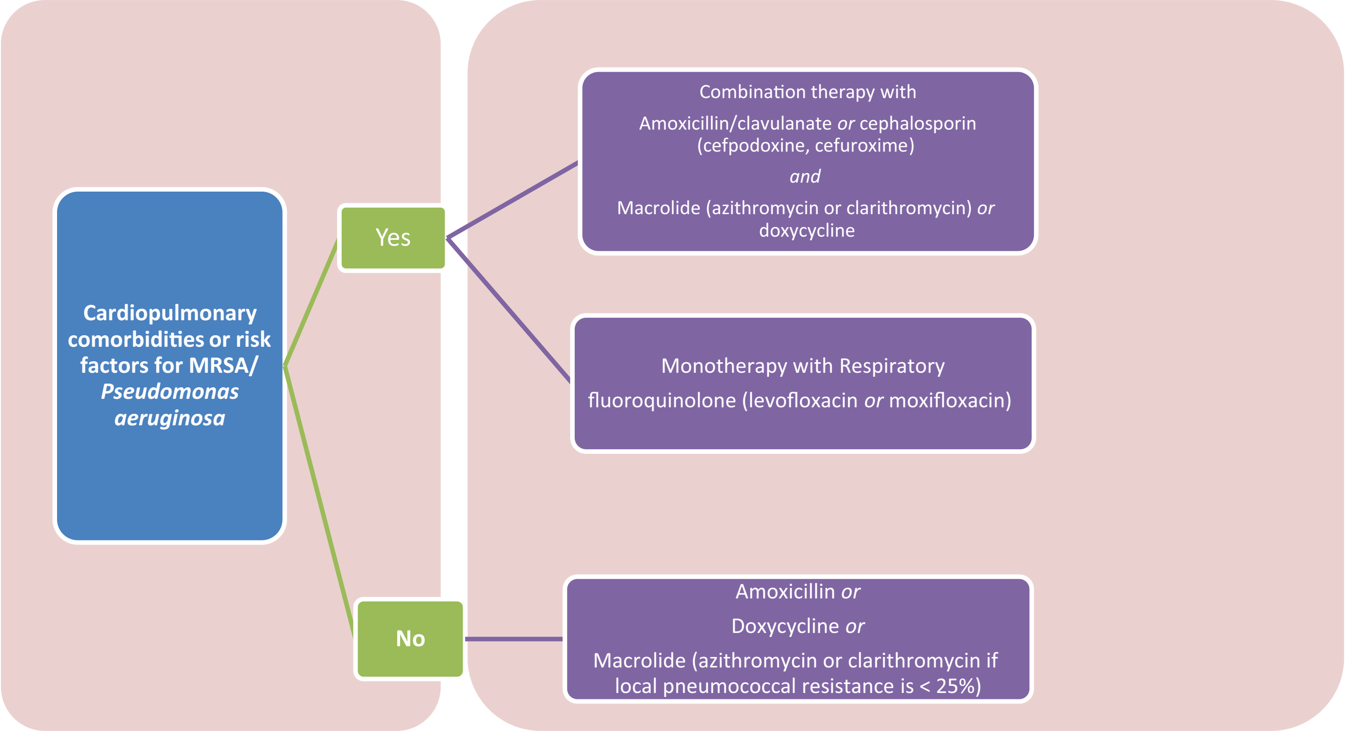
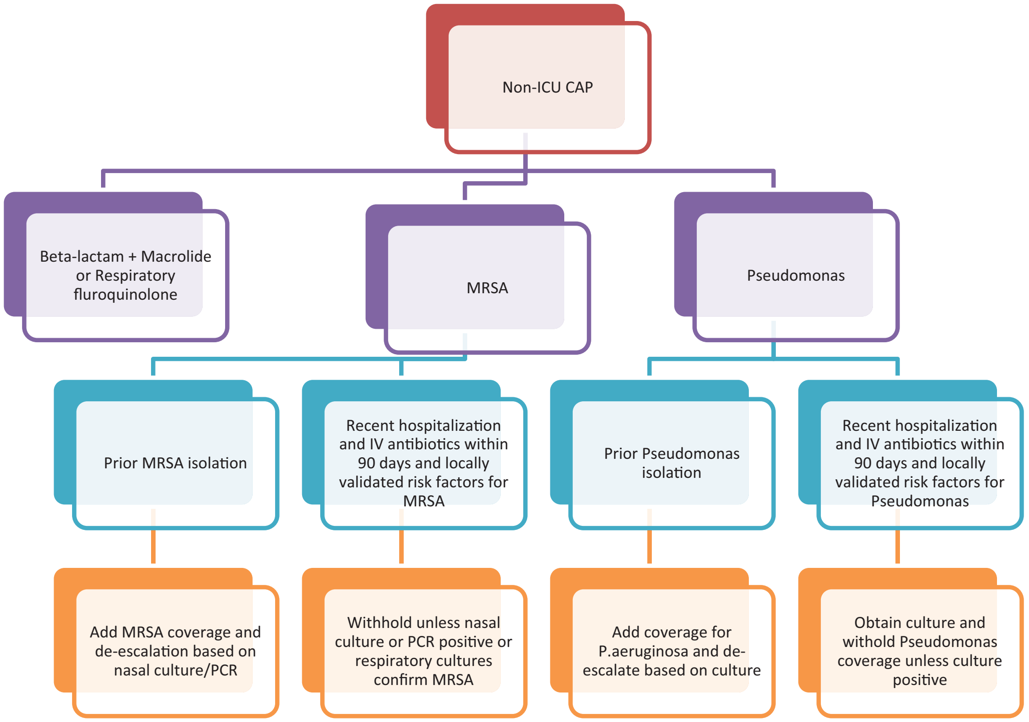

Cardiopulmonary comorbidities or risk factors for MRSA/ *Pseudomonas aeruginosa*
Yes
No
Combination therapy with
Amoxicillin/clavulanate *or* cephalosporin (cefpodoxine, cefuroxime)
and
Macrolide (azithromycin or clarithromycin) *or* doxycycline
Monotherapy with Respiratory fluoroquinolone (levofloxacin *or* moxifloxacin)
Amoxicillin *or*
Doxycycline *or*
Macrolide (azithromycin or clarithromycin if local pneumococcal resistance is < 25%)

Figure 125-1 Antibiotic preferences for outpatient CAP management based on patient risk factors. Risk factors include prior respiratory isolation of MRSA or *P. aeruginosa*, recent hospitalization, and IV antibiotics within 90 days. Comorbid conditions are chronic heart, lung, liver, or renal disease, as well as alcoholism, malignancy, asplenia, or diabetes mellitus. **Approach to antibiotic selection and dosage for outpatient CAP therapy:** Amoxicillin 1 g three times daily, amoxicillin/clavulanate 500 mg/125 mg three times daily, amoxicillin/clavulanate 875 mg/125 mg twice daily, 2,000 mg/125 mg twice daily, cefpodoxime 200 mg twice daily, cefuroxime 500 mg twice daily, doxycycline 100 mg twice daily, azithromycin 500 mg on first day then 250 mg daily, clarithromycin 500 mg twice daily, or clarithromycin ER 1,000 mg daily, Levofloxacin 750 mg daily, moxifloxacin 400 mg daily.


Non-ICU CAP
Beta-lactam + Macrolide or Respiratory fluroquinolone
MRSA
Pseudomonas
Prior MRSA isolation
Recent hospitalization and IV antibiotics within 90 days and locally validated risk factors for MRSA
Prior Pseudomonas isolation
Recent hospitalization and IV antibiotics within 90 days and locally validated risk factors for Pseudomonas
Add MRSA coverage and de-escalation based on nasal culture/PCR
Withhold unless nasal culture or PCR positive or respiratory cultures confirm MRSA
Add coverage for P.aeruginosa and de-escalate based on culture
Obtain culture and withold Pseudomonas coverage unless culture positive

Standard regimen: Beta-lactams + Macrolide or Respiratory fluroquinolone. Penicillin allergy - aztreonam 2 g every 8 h. Ampicillin/sulbactam 1.5–3 g every 6 h, cefotaxime 1–2 g every 8 h, ceftriaxone 1–2 g daily, or ceftaroline 600 mg every 12 h, AND Azithromycin 500 mg daily or clarithromycin 500 mg twice daily Or Levofloxacin 750 mg daily or moxifloxacin 400 mg daily.
MRSA: vancomycin 15 mg/kg every 12 h and adjusted to trough 15–20 or linezolid 600 mg every 12 h.
Pseudomonas: piperacillin- tazobactam 4.5 g every 6 h, cefepime 2 g every 8 h, ceftazidime 2 g every 8 h, imipenem 500 mg every 6 h, meropenem 1 g every 8 h, aztreonam 2 g every 8 h.

Figure 125-2 Antibiotic preferences for hospitalized CAP management (non-ICU) based on patient risk factors and allergies.

patients with moderately severe illness, most of these patients should receive initial therapy intravenously to be sure that the medication has been absorbed. Once the patient shows a clinical response, oral therapy can be initiated. Selected inpatients with mild to moderate disease can initially be treated with the combination of an intravenous β-lactam and an oral macrolide, switching to exclusively oral therapy once the patient shows a good clinical response.

The most recent updated IDSA/ATS guidelines recommend the use of dual antibiotics: a β-lactam plus either a macrolide or a respiratory quinolone (levofloxacin or moxifloxacin) for patients with severe pneumonia in the ICU with no risks for drug-resistant organisms.[3] Figure 125-3 shows antibiotic preferences to treat CAP in ICU patients based on risk factors and allergy status. In the ICU population, all individuals should receive combination therapy directed at DRSP and atypical pathogens; only those with appropriate risk factors should have coverage for *P. aeruginosa*. Monotherapy should not be used in any ICU admitted CAP patient. In the therapy of *P. aeruginosa*, combination therapy is often needed, but a quinolone may not always be a good choice, given antimicrobial resistance patterns at many hospitals.

In the empiric therapy of CAP, there is a limited need for routine therapy against MRSA; however, a strain of this organism (community-acquired [CA] MRSA) has been described to cause a severe, necrotizing form of CAP after influenza.[18] Although the frequency of this organism is currently low, vigilance is needed for identifying this organism. Optimal therapy for CA-MRSA is uncertain, but the organism produces exotoxins and may be best treated by using both an antibiotic and a toxin production inhibitor. This can be done using linezolid alone or vancomycin with clindamycin. The IDSA/ATS 2019 guidelines recommend empiric coverage for *Pseudomonas aeruginosa* and MRSA based on locally validated epidemiologic risk factors and data about prior isolation of either pathogen. However, for those without prior isolation of either pathogen, empiric therapy directed at them is withheld in those outside the ICU, even with risk factors, pending culture data—but for those in the ICU, empiric therapy for these pathogens is recommended for those at risk, but then adjusted depending on culture data.[3]

These algorithms suggest that all patients should receive empiric therapy that provides coverage for atypical pathogens, based on outcome studies showing improved survival with this approach, and may reflect a high frequency of coinfection by atypical pathogens. Quinolones are preferred over macrolides if *Legionella* is suspected.[103] The current IDSA/ATS 2019 guidelines do not recommend adding additional anaerobic coverage for suspected aspiration pneumonia, as the majority of aspiration pneumonia episodes are caused by Gram-negative pathogens.[3]

Prior studies have shown that combination therapy with a macrolide appeared to have a modest mortality benefit in *S. pneumoniae* bacteremia.[104–107] Sligl et al. found in a meta-analysis of severe CAP patients that combination therapy with a macrolide and β-lactam was associated with reduced mortality compared to other regimens.[108] However, more recent data in non-ICU patients, comparing β-lactam monotherapy to β-lactam–macrolide and fluoroquinolone monotherapy strategies, found no statistical difference in 90-day mortality with the addition of a macrolide.[109] Similarly, another systematic review including 16,884 patients found no difference in outcomes between the use of a β-lactam plus macrolide versus β-lactam plus fluoroquinolone.[110] In general, monotherapy is avoided in ICU

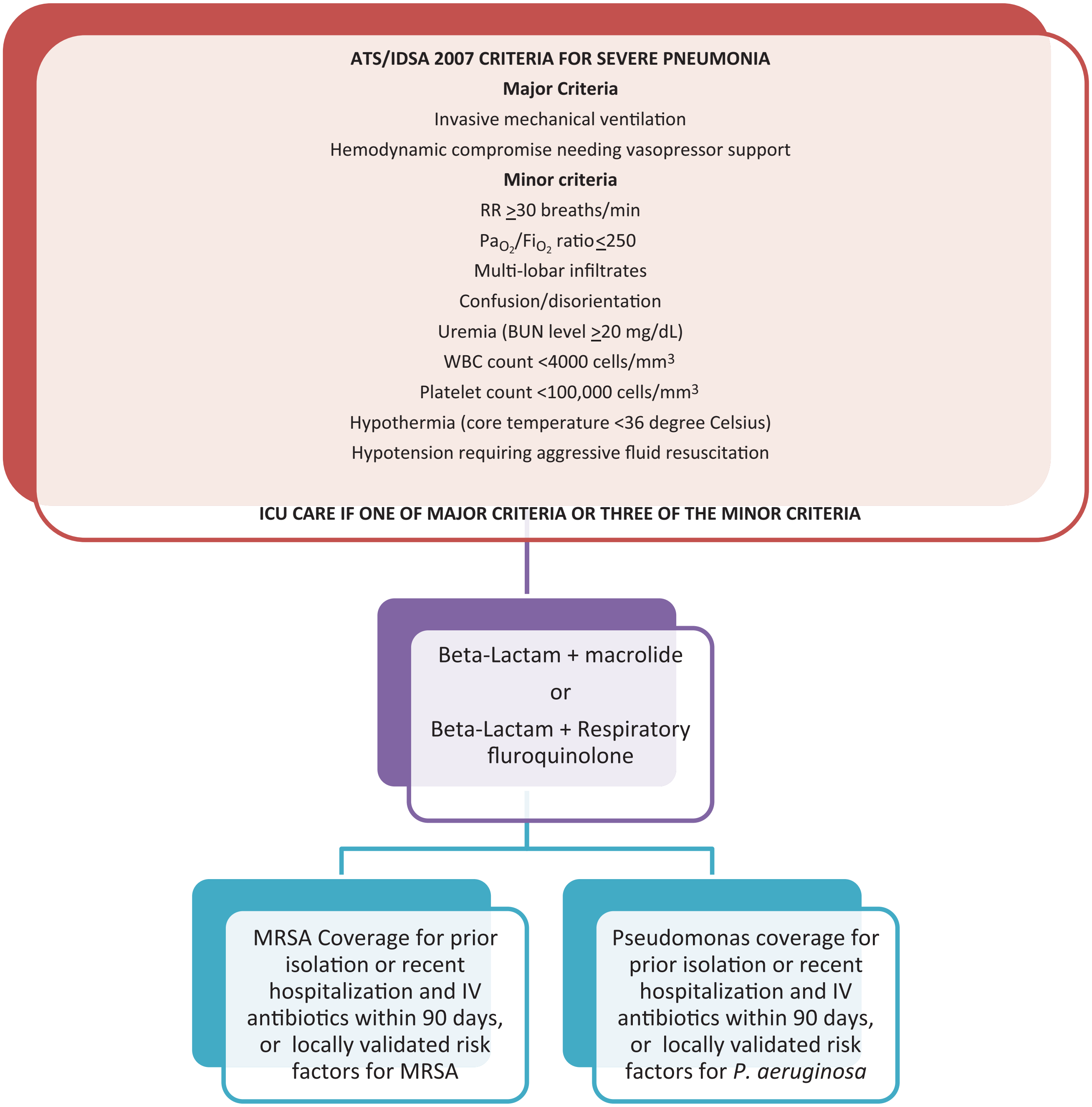

ATS/IDSA 2007 CRITERIA FOR SEVERE PNEUMONIA
Major Criteria
Invasive mechanical ventilation
Hemodynamic compromise needing vasopressor support
Minor criteria
RR ≥30 breaths/min
Pa_{O_2}/Fi_{O_2} ratio ≤250
Multi-lobar infiltrates
Confusion/disorientation
Uremia (BUN level ≥20 mg/dL)
WBC count <4000 cells/mm3
Platelet count <100,000 cells/mm3
Hypothermia (core temperature <36 degree Celsius)
Hypotension requiring aggressive fluid resuscitation
ICU CARE IF ONE OF MAJOR CRITERIA OR THREE OF THE MINOR CRITERIA
Beta-Lactam + macrolide
or
Beta-Lactam + Respiratory fluroquinolone
MRSA Coverage for prior isolation or recent hospitalization and IV antibiotics within 90 days, or locally validated risk factors for MRSA
Pseudomonas coverage for prior isolation or recent hospitalization and IV antibiotics within 90 days, or locally validated risk factors for *P. aeruginosa*

Figure 125-3 Antibiotic preferences for inpatient-ICU-admitted CAP management based on patient risk factors and allergies.

CAP patients, as effective dosing and the safety of a single agent have not been established and guideline-concordant treatment has been consistently effective in reducing CAP mortality.[111]

■ De-Escalation of Antibiotic Therapy in Cap Patients

The IDSA/ATS 2019 guidelines recommend de-escalation of antibiotics in those with no evidence of bacterial superinfection and clinical stability after 48 to 72 h of initiation of antibiotics.[3] Biomarkers such as procalcitonin have been employed to help aid antibiotic de-escalation without an increase in either mortality or treatment failure.[112–115] In a recent meta-analysis of CAP patients, there was no difference in clinical cure rates between short course treatment defined as ≤6 days versus treatment for ≥7 days irrespective of patient setting or severity of pneumonia.[116] Thus, the current guidelines endorse clinicians to continue antibiotics until the patient achieves clinical stability and the duration is not less than 5 days.[3]

■ Hospital-Acquired Pneumonia

Prompt empiric therapy should be initiated as soon as there is clinical suspicion of hospital-acquired infection, since mortality is increased if incorrect antibiotics are used or if a delay in antibiotic initiation occurs (Table 125-3).[4] The updated ATS/IDSA 2016 nosocomial pneumonia guidelines recommend noninvasive sampling with semiquantitative cultures (sputum, endotracheal aspirate) to diagnose VAP, rather than invasive sampling (protected brush, BAL) with quantitative cultures prior to initiation of antibiotic therapy.[4] The guidelines also endorse antibiotic dosing to be determined using pharmacokinetic and pharmacodynamic data based on antibiotic blood concentrations and weight-based dosing rather than manufacturer's prescribing information.[4]

Ideally, each ICU should have a tailored antibiogram, based on local data, for the initial antimicrobial therapy to be effective and account for local bacteriologic patterns. Recent exposure to a

TABLE 125-3 Principles of Antibiotic Therapy for Hospital-Acquired Pneumonia

Prompt empiric therapy: initiate when there is clinical suspicion of infection.
Obtain a lower respiratory tract culture (sputum, endotracheal aspirate) prior to initiation of antibiotic therapy.
Refer to local antibiogram and prevalence of MDR pathogens. Consider MRSA coverage if local resistance pattern for methicillin resistance is >10%–20% and double pseudomonal coverage if local resistance pattern of Gram-negatives shows >10% resistance to any of the antibiotics used for monotherapy.
Use a narrow-spectrum agent for patients only at risk for infection with "core pathogens," and with no risk factors for MDR pathogens. Options include ceftriaxone, ampicillin/sulbactam, ertapenem, levofloxacin, or moxifloxacin. For penicillin allergy, use a quinolone or the combination of clindamycin and aztreonam.
Use combination therapy with a broad-spectrum regimen, containing at least two antimicrobials in patients with risk factors for MDR pathogens. Specific choices should be guided by a knowledge of local microbiology patterns. Use an aminoglycoside or an antipseudomonal quinolone (ciprofloxacin or high-dose levofloxacin), *plus* an antipseudomonal β-lactam such as cefepime, ceftazidime, ceftolozane/tazobactam, imipenem, meropenem, or piperacillin-tazobactam. If there is concern about MRSA, add either linezolid or vancomycin.
Use the correct therapy in recommended doses (see text).
Choose an empiric therapy that uses agents from a different class of antibiotics than the patient has received in the past 2 weeks.
Try to de-escalate to monotherapy after initial combination therapy, after reviewing culture data and clinical response. If *Pseudomonas aeruginosa*, consider stopping the aminoglycoside after 5 days and finish with a single agent to which the organism is sensitive. If a nonpseudomonal infection, switch to a single agent that the organism is sensitive to, using imipenem, meropenem, cefepime, ceftolozane/tazobactam, ceftazidime/avibactam, piperacillin/tazobactam, ciprofloxacin, or high-dose levofloxacin.
The drug of choice for *Acinetobacter* is a carbapenem, but colistin should be considered if there is carbapenem resistance.
Consider linezolid as an alternative to vancomycin in patients with proven MRSA VAP, those with renal insufficiency, and those receiving other nephrotoxic medications (e.g., an aminoglycoside).
Consider adjunctive aerosolized aminoglycosides in patients with highly resistant Gram-negative pathogens.

class of antibiotics can predict subsequent resistance to a variety of agents, usually to the same class but occasionally to other classes of agents as well.[117] The 2016 ATS/IDSA nosocomial guidelines emphasize that in patients with suspected HAP (non-VAP), treatment should be modified to the results of microbiologic cultures rather than being treated empirically if culture data are available. On the other hand, if empiric treatment is to be started, it should be based on a local antibiogram and the prevalence of MDR pathogens in that hospital. The risk factors for MDR-specific pathogens in VAP include use of IV antibiotics within 90 days, septic shock at time of VAP, acute respiratory distress syndrome preceding VAP, late-onset VAP, and need for renal replacement therapy prior to VAP onset.[4] Risk factors for MRSA and *Pseudomonasaeruginosa* HAP/VAP include prior IV antibiotic use within 90 days.

The European guidelines for HAP do not endorse all these risk factors and emphasize a high rate (>25%) of local MDR pathogens, a mortality risk of >15%, recent antibiotic therapy for >5 days in the hospital, recent colonization by MDR pathogens, and the presence of septic shock.[118]

When treating patients with HAP/VAP, empiric coverage should include *S. aureus*, *Pseudomonas aeruginosa*, and other Gram-negative bacilli. MRSA coverage should be included if the local prevalence of *S. aureus* isolates is greater than 10% to 20% methicillin resistant by American guidelines and greater than 25% by European guidelines. Two antipseudomonal antibiotics from different classes are used in patients with risk factors for MDR pathogens or if the locally prevalent Gram-negative isolates have more than 10% resistance to any of the antibiotics used for monotherapy, or if a local antibiogram is not available.[4]

A narrow-spectrum regimen can be used for patients at risk for infection with the "core pathogens" (nonresistant enteric Gram-negatives, pneumococcus, *H. influenzae*, and methicillin-sensitive *S. aureus*) and with no risk factors for MDR pathogens, although very few patients fall into this category. Antimicrobial options include ceftriaxone, ampicillin/sulbactam, ertapenem, levofloxacin, or moxifloxacin. For penicillin allergy, a quinolone or the combination of clindamycin and aztreonam can be selected.

Combination therapy with a broad-spectrum regimen containing at least two antipseudomonal agents should be used for patients with risk factors for MDR pathogens. Specific choices should be guided by knowledge of local microbiology patterns and should include an aminoglycoside or an antipseudomonal quinolone (high-dose ciprofloxacin or levofloxacin) and an antipseudomonal β-lactam such as cefepime, ceftazidime, ceftolozane/tazobactam, imipenem, meropenem, or piperacillin/tazobactam. If there is concern about MRSA, a third agent can be added using either linezolid or vancomycin. Linezolid may be the preferred in patients with proven MRSA VAP and renal insufficiency or in those receiving other nephrotoxic medications (such as an aminoglycoside). The newer agents ceftazidime-avibactam, ceftolozane-tazobactam, imipenem-relebactam, meropenem-vaborbactam, and cefiderocol can be used as the β-lactam agent in patients with risk factors for drug-resistant pathogens that are particularly susceptible to these agents, as outlined above. For those with carbapenem-resistant Enterobacteriaceae, the newer agents such as ceftazidime-avibactam, imipenem-relebactam, and meropenem-vaborbactam may be the most effective choices. For organisms that produce metallo-β-lactamases, the most effective choices may be ceftazidime-avibactam and cefiderocol.[119] For those with highly resistant *P. aeruginosa*, the most effective choices may be ceftolozane-tazobactam, ceftazidime-avibactam, and imipenem-relebactam.

Initial therapy should be given in full recommended doses adjusted as needed for renal function: cefepime 2 g every 6 h; imipenem 500 mg every 6 h or 1 g every 8 h; meropenem 1 g every 8 h; piperacillin/tazobactam 4.5 g every 6 h; levofloxacin 750 mg daily or ciprofloxacin 400 mg every 8 h; vancomycin 15 mg/kg every 12 h leading to a trough level of 15 to 20 mg/L; linezolid 600 mg every 12 h; and for aminoglycosides, 7 mg/kg per day of gentamicin or tobramycin and 20 mg/kg of amikacin.[4] Dosing for the newer agents is listed in Table 125-4. As discussed above, these agents should also be dosed using pharmacokinetic and pharmacodynamic principles of prolonged or continuous infusion of β-lactams, particularly if there is concern about organisms with potential drug resistance.

When choosing empiric therapy, it is important to select agents from a different class of antibiotics than the patient has received in the past 2 weeks, with a plan to de-escalate to monotherapy once culture and clinical response data are available. If *P. aeruginosa* is present, consider stopping the aminoglycoside after 3 to 5 days and finish with a single agent to which the organism is sensitive. If it is a

TABLE 125-4 Newer Antibiotics for Treatment of Pneumonia

Drug	Class	Mechanism of Action	Major Pathogens Covered	Dosage	Major Side Effects
Omadacycline	Aminomethylcycline	Inhibits ribosomal proteins and prevents efflux pumps	MRSA, DRSP, atypical pathogens	100 mg IV once daily 200 mg once daily oral	GI side effects
Solithromycin	Fourth-generation macrolide	Binds to 23S ribosomal RNA, preventing bacterial translation	*S. pneumoniae*, *H. influenzae*, atypical pathogens	800-mg loading dose IV followed by 400 mg once daily IV	Hepatotoxicity
Telavancin	Lipoglycopeptide	Cell wall synthesis inhibitor	Gram-positive including MRSA and VRE	10 mg/kg every 24 h IV	Moderate to severe renal impairment
Nemonoxacin	Novel nonfluorinated quinolone	Inhibits DNA gyrase and topoisomerase IV	Gram-positive, Gram-negative, atypical pathogens, MRSA and VRE	500 mg once daily for 7 days	QT prolongation, myelotoxicity
Delafloxacin	Quinolone	Inhibits topoisomerase IV	MRSA, *Enterococcus faecalis*, *C. pneumoniae*, *Mycoplasma* spp., and *Legionella* spp.	300 mg IV q12h for 5–10 days *or* 300 mg IV q12h, then switch to a 450-mg tablet PO q12h for 5–10 days *or* 450 mg PO q12h for 5–10 days	Tendon rupture, peripheral neuropathy, central nervous system effects, exacerbation of myasthenia gravis
Lefamulin	Pleuromutilin	Bacterial protein synthesis inhibition by binding to peptidyl transferase of 50S bacterial ribosome	MRSA, MSSA, VRE, DRSP, *L. pneumophila*, *C. pneumoniae, and Mycoplasma pneumoniae;* Gram-positives, -negatives, and atypicals	150 mg twice daily IV or oral dose of 600 mg twice daily	Hepatotoxicity
Ceftobiprole	Fifth-generation cephalosporin	Inhibits transpeptidase activity and binding of PBPs	MSSA, MRCNS, *H. influenzae*, *M. catarrhalis*, *K. pneumoniae*, *E. coli*, *P. aeruginosa*, and Enterobacteriaceae	500 mg IV every 8 h	Hepatic enzyme elevation, hyponatremia
Ceftaroline	Fifth-generation cephalosporin	Inhibits transpeptidase activity and binding of PBPs	MRSA, MRCNS, DRSP	600 mg IV every 12 h	Infusion-site reactions
Cefiderocol	Siderophore cephalosporin	Binds to iron and enters bacteria through iron channels	Carbapenem- and colistin-resistant *Acinetobacter* and other Gram-negatives	2 g over 3 h, every 8 h × 7–14 days	Allergic reactions, increased all-cause mortality in MDR Gram-negative infection
Ceftolozane-tazobactam (CToZ + TAZ)	Cephalosporin/BLI	Cell wall synthesis inhibitor and binding of PBPs	Gram-negatives, ESBL, AmpC β-lactamases in *Pseudomonas*; no KPC activity	3 g (2000 mg CToZ + 1000 mg TAZ) IV every 8 h	Hypertension, diarrhea
Ceftazidime-avibactam (CAZ-AVI)	Cephalosporin/BLI	Cell wall synthesis inhibitor, binding of PBPs	Gram-negatives, *Pseudomonas* including KPC, AmpC, OXA-48 enzyme, and ESBL-producing organisms	2.5 g (2000 mg CAZ + 500 mg AVI) every 8 h	Abdominal pain, infusion-site reaction
Meropenem/vaborbactam	Carbapenem/BLI	Inhibits serine β-lactamases	Gram-negatives including ESBL and KPC Enterobacterales, AmpC β-lactamase–producing *P. aeruginosa*	4 g (2000 mg meropenem + 2000 mg vaborbactam) IV every 8 h	Infusion-site reactions, headache
Imipenem/relebactam	Carbapenem/BLI	Cell wall synthesis inhibitor combined with β-lactamase inhibitor	Gram-negatives, including Ambler class C, extended-spectrum β-lactamases, and *K. pneumoniae* carbapenemases	1.25 g (0.5 g imipenem + 0.5 g cilastatin + 0.25 g relebactam) IV every 6 h	Allergic reaction, neurotoxicity, diarrhea

ESBL, extended-spectrum β-lactamases; PBP, penicillin-binding protein; CRE, carbapenem-resistant Enterobacterales; MRSA, methicillin-resistant Staphylococcus aureus; MRCNS, methicillin-resistant coagulase-negative staphylococci; VRE, vancomycin-resistant enterococci; KPC, Klebsiella pneumoniae carbapenemase.

nonpseudomonal infection, it is best to switch to a single agent that the organism is sensitive to, using imipenem, meropenem, cefepime, piperacillin/tazobactam, a newer β-lactam/β-lactamase inhibitor combination, ciprofloxacin, or high-dose levofloxacin.

The drug of choice for *Acinetobacter* spp. is a carbapenem, but colistin should be considered with carbapenem resistance. Tigecycline monotherapy is not recommended, but this agent can be combined with a carbapenem, colistin, or sulbactam. Aerosolized aminoglycosides or colistin can be added as adjunctive therapy in patients with highly resistant Gram-negative pathogens.

The use of empiric combination therapy in VAP is controversial, and there are few data to suggest that use of an aminoglycoside with a β-lactam is more effective than β-lactam monotherapy. Dual therapy may have value if the patient is neutropenic or if pseudomonal bacteremia is present, but both situations are uncommon. Thus, the most compelling reason for using empiric combination therapy in patients with suspected MDR pathogens is to provide a broad enough spectrum of agents to increase the likelihood that the initial therapy is appropriate. Once the organism is identified, it is possible to de-escalate therapy. In patients with pneumonia and sepsis, dual adequate therapy is more effective than single effective therapy, possibly because of more rapid bacterial eradication.[120]

■ De-Escalation of Antibiotic Therapy for HAP/VAP

Antibiotic overuse causes bacterial resistance, which can in turn lead to inappropriate empiric therapy. To minimize this risk, it is necessary to de-escalate after an initial broad-spectrum therapy, which can involve using fewer drugs, drugs of a narrower spectrum, and short durations of therapy. Chastre et al., in a multicenter, randomized, controlled trial, demonstrated that patients who received appropriate initial empiric therapy of VAP for 8 days had outcomes similar to those patients who received therapy for 14 days.[121] Short-duration therapy was associated with a trend toward relapse if the etiologic agent was *P. aeruginosa* or *Acinetobacter* spp. In another study, investigators prospectively randomized VAP patients to receive 15 days ($n = 109$) versus 8 days ($n = 116$) of therapy,[122] finding no difference in mortality, ICU length of stay, and mechanical ventilation days between both the groups. It is possible to effectively treat VAP with 6 to 8 days of therapy, provided that the initial therapy is appropriate.[4] The optimal duration of therapy for infections caused by *P. aeruginosa* and MRSA is still uncertain, but prolonged therapy may be no better than short duration therapy, in the absence of bacteremia.

In clinical studies of VAP, the rate of de-escalation has varied from 16% to 74%, with the highest rates being in those who are treated with a protocol for de-escalation, when initial therapy is appropriate, when initial cultures are positive (although it can be done with negative cultures), when the therapy involves broad-spectrum agents and multiple agents, and if the frequency of MDR pathogens is not high.[123] However, one recent study of 1495 ICU patients found that de-escalation was done in only 16% within the first 3 days, despite half getting empiric combination therapy and a quarter involving a carbapenem.[124] De-escalation does not appear to be dangerous and may be associated with reduced mortality, compared with no change in antibiotics. The decision to change antibiotics is made by assessing clinical features such as fever, leukocytosis, purulence of secretions, radiographic patterns, and oxygenation. In general, the best clinical predictor of response is improvement in oxygenation, which usually occurs by day 3 in survivors of VAP, but not in nonsurvivors. If the patient is improving, then cultures should be checked and efforts made to de-escalate and shorten duration of therapy. In some instances, all signs of pneumonia are gone by day 2 to 3, respiratory cultures are negative, and, in retrospect, the diagnosis was heart failure or atelectasis—and antibiotics can be completely stopped. Serial measurement of biomarkers such as procalcitonin (PCT) can help guide therapy discontinuation for VAP and help decrease the number of days on antibiotic, without having an adverse effect on mortality.[115,125] In several large studies, de-escalation guided by a PCT-based algorithm, primarily in ICU patients with HAP and CAP, has been safely done and led to reduced overall mortality due to fewer antibiotic-associated side effects.[126]

ANTIMICROBIAL STEWARDSHIP

Antimicrobial control or stewardship programs involve a number of interventions and require a committed champion and a good knowledge of local antibiotic usage patterns. The principles of antimicrobial stewardship have been compiled into a guideline, the focus of which is on prospective audit and feedback of antibiotic use, de-escalation of broad-spectrum therapy, proper dosing, and the development of local guidelines for antibiotic use based on knowledge of local microbiology.[59] Antibiotic restriction was not a highly recommended strategy, nor was restricting access to specific antibiotics.

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CHAPTER 126

Viral Infections of the Lung and Respiratory Tract

John Treanor

GENERAL PRINCIPLES

Viral infections of the upper and lower airways have a major impact on health. Acute respiratory illnesses, caused largely by viruses, are the most common illness experience for otherwise healthy adults and children. Past data from the National Health Interview Survey suggested that such illnesses are experienced at a rate of 85.6 illnesses per 100 persons per year, and account for 54% of all acute conditions exclusive of injuries.[1] A total of 44% of these illnesses require medical attention and result in 287 days of restricted activity, 94.4 days lost from work, and 182 days lost from school per 100 persons per year. Estimates from family-based surveillance suggest that approximately one-fourth of these illnesses result in consultation with a physician. Illness rates for all acute respiratory conditions are highest in young children; children below the age of 9 are estimated to experience between 5 and 9 respiratory illnesses per year, whereas adults experience between 3 and 5 such illnesses.[2,3]

Mortality due to acute viral respiratory infection in otherwise healthy individuals in economically developed countries is relatively rare, with the exceptions of influenza and the recently emergent coronavirus. However, acute respiratory infection is a major cause of childhood mortality in developing countries, and it is estimated that 4.5 million children under 5 years of age die annually from acute respiratory infection.[4] Viruses are identified in about 3% to 40% of cases of respiratory disease in this setting and are estimated to play a contributing role in approximately 20% to 30% of deaths. In addition, new and emerging respiratory viruses such as hantavirus, emerging coronaviruses, and transmission of influenza viruses from avian or swine sources to humans pose a continuing threat.

Epidemiology

Many of the viruses associated with acute respiratory disease display a significant seasonal variation in incidence. Although the exact seasonal arrival of each virus in the community cannot be predicted with precision, certain generalizations are useful diagnostically and in planning control strategies. For example, influenza and respiratory syncytial virus epidemics both occur predominantly in the winter months, with a peak prevalence in January to March in the northern hemisphere. Parainfluenza virus type 3 (PIV-3) infections show a predominance in the spring, whereas types 1 and 2 (PIV-1 and PIV-2) cause outbreaks in the fall to early winter. Rhinoviruses may be isolated throughout the year, with increases in frequency in the spring and fall. The peak prevalence of enteroviral isolations is in late summer and early fall, whereas adenoviruses are isolated at roughly equal rates throughout the year. The herpes viruses also do not show significant seasonal variation in incidence, except for varicella, which occurs throughout the year but more commonly in late winter and early spring.

The reasons for these seasonal changes are not entirely clear. One mechanism may involve seasonal effects on virus transmissibility either because of more favorable environmental conditions for virus survival[5] or because of behavioral changes that increase transmission, such as indoor crowding. Effects of season on host susceptibility or response to infection also could play a role. All these factors could determine the eventual seasonal pattern of SARS-CoV-2.

Characteristics of the Viruses

Viruses of importance in the respiratory tract include both those considered to be principal respiratory viruses, whose replication is generally restricted to the respiratory tract, and others in which respiratory involvement is part of a generalized infection. The classification of these viruses depends in part on the type and configuration of the nucleic acid in the viral genome, the characteristics of the viral structural proteins, and the presence or absence of a lipid-containing envelope surrounding the virus particle (Table 126-1). The number of distinct antigenic types in each of the virus families varies. For example, the adenovirus and rhinovirus groups are composed of large numbers of antigenically (i.e., serotypically) distinct immunotypes, but other groups, such as paramyxovirus and respiratory syncytial virus, are composed of only a limited number of immunotypes. The degree of antigenic stability of the virus is an important factor in determining frequency of reinfection. This characteristic is particularly important for influenza type A virus, which periodically undergoes both minor and major changes in its surface antigens.

Transmission

The routes by which the different respiratory viruses spread from person to person are still not established with certainty. Rhinovirus and respiratory syncytial virus spread, at least in part, by direct hand contact with contaminated skin and environmental surfaces. This is followed by self-inoculation of infectious virus onto the nasal mucosa or conjunctiva. Others, including influenza, measles, and varicella-zoster viruses, spread at times in small-particle aerosols. Many viruses may spread by means of large-particle aerosols over short distances (<1 m). The relative importance of the various transmission routes under natural conditions for each virus can be quite variable.[6]

Pathogenesis of Infection

The initial sites of infection and pathogenesis differ for the various virus groups. Some, such as rhinovirus, are associated mainly with upper respiratory tract involvement. Others, such as influenza and coronavirus, commonly invade the lower airways and sometimes pulmonary parenchyma in addition to causing upper airway disease. The viruses also differ in the amount of damage produced in the cells lining the respiratory tract. Extensive damage to the respiratory epithelium is a characteristic feature of influenza virus infection, but biopsy studies show little evidence of nasal epithelial damage in persons with rhinovirus colds. Instead, colds are related both to virus damage to the respiratory tract and to the host responses to infection, including immunologic events, release of mediators of inflammation, and neurogenic reflexes.

An additional important feature of respiratory virus infections is their effect on the resident bacterial flora of the upper airways. Respiratory virus infections have been found to alter bacterial colonization patterns, increase bacterial adhesion to respiratory epithelium, and reduce mucociliary clearance and phagocytosis.

TABLE 126-1 Common Respiratory Viruses

Virus	Family	Genome	Seasonality	Diseases	Vaccine	Antivirals
Influenza virus	Orthomyxoviridae	ss RNA (–)	Yes (Winter)	Influenza, croup, bronchitis, pneumonia	Yes	Yes (oseltamivir, zanamivir, pimodivir, baloxavir)
Respiratory syncytial virus (RSV)	Paramxyoviridae	ss RNA (–)	Yes (Winter)	Bronchiolitis, pneumonia	No	Yes (ribavirin is available but not routinely recommended)
Metapneumovirus (hMPV)	Paramxyoviridae	ss RNA (–)	Yes (Winter)	Bronchiolitis, pneumonia	No	No
Parainfluenza virus (PIV)	Paramyxoviridae	ss RNA (–)	Yes (Winter)	Croup (PIV1), pneumonia (PIV3)	No	No
Measles	Paramyxoviridae	ss RNA (–)	No	Croup, pneumonia	Yes	No
Rhinovirus	Picornaviridae	ss RNA (+)	Yes (Spring, Fall)	Common cold	No	No
Seasonal coronavirus (hCoV)	Coronaviridae	ss RNA (+)	Some (Winter)	Common cold (OC43), pneumonia (HuCoV)	No	Yes (interferon α?)
Pandemic coronavirus	Coronaviridae	Ss RNA (+) ss RNA	No	SARS (SARS-CoV) MERS (MERS-CoV) COVID-19 (SARS-CoV-2)	Yes	Yes (remdesivir, nirmatrelvir/ritonavir [Paxlovid], molnupiravir)
Sin Nombre virus	Bunyaviridae	ss RNA (+/–)	No	Pneumonia	No	No
Adenovirus	Adenoviridae	ds DNA	No	Croup, pneumonia	Yes	No
Herpes simplex	Herpesviridae	ds DNA	No	Pneumonia	No	Yes (acyclovir, famciclovir)
Varicella zoster virus	Herpesviridae	ds DNA	No	Pneumonia	Yes	Yes (acyclovir, famciclovir)
Cytomegalovirus	Herpesviridae	ds DNA	No	Pharyngitis, pneumonia	No	Yes (ganciclovir, cidofovir)
Epstein-Barr virus	Herpesviridae	ds DNA	No	Pharyngitis	No	No
Bocavirus	Parvoviridae	ss DNA (+/–)	No	Bronchiolitis, colds	No	No

These impairments of host defenses by virus allow colonization by pathogenic bacteria and invasion of normally sterile areas, such as the paranasal sinuses, middle ear, and lower respiratory tract, resulting in secondary infection.

A summary of the specific viral etiologies most commonly associated with syndromes of upper respiratory tract infection is given in Table 126-2. The following sections briefly summarize the important points of viral respiratory tract infections.

THE COMMON COLD

The clinical features of the extremely common upper respiratory tract infection known as the "common cold" are discussed below.

TABLE 126-2 Virus-associated Respiratory Tract Infections

Clinical Syndrome	Associated Viruses
Common cold	Rhinovirus, other picornaviruses, RSV, PIV, coronavirus, adenovirus
Pharyngitis	Rhinovirus, influenza, EBV, CMV, HSV, HIV
Tracheobronchitis	Influenza, adenovirus, rhinovirus
Croup	PIV1, PIV2, influenza, adenovirus, measles
Bronchiolitis	RSV, hMPV, HuCoV-NL63, bocavirus
Pneumonia	
Adults	Influenza, adenovirus, RSV, PIV, measles, VZV, Sin Nombre virus, CoV-SARS, CoV-MERS, CoV-SARS-2
Children	RSV, PIV, influenza, measles, adenovirus, rhinovirus, CMV
Immunocompromised	CMV, HSV, VZV, adenovirus, RNA viruses

Clinical Features

The term "cold" really does not constitute a single entity, but rather a group of similar illnesses of differing cause. However, all colds include symptoms of rhinitis with variable degrees of pharyngitis. Predominant associated symptoms include nasal stuffiness, sneezing, runny nose, and sore throat. Patients often report chills, but fever is not a typical feature of uncomplicated colds. Cough and hoarseness are variably present and may be more frequent in the elderly,[7] but other lower respiratory tract signs and symptoms are not typical of colds and should raise suspicion of other entities.

Physical findings are nonspecific and most commonly include nasal discharge and pharyngeal inflammation. More severe disease, with higher fever, may be seen in children. Although colds are generally self-limited, symptoms may last for a surprisingly long period of time, with a median duration of illness of approximately 9 to 10 days in adults.[8] Recognized complications of colds include secondary bacterial infections of the paranasal sinuses and middle ear, and exacerbations of asthma, chronic bronchitis, and emphysema. Colds are frequently associated with involvement of the middle ear, likely due to eustachian tube dysfunction. Colds are associated with symptomatic otitis media in approximately 2% of cases in adults, and in a higher proportion in young children.

Colds are also associated with detectable abnormalities of the paranasal sinuses, which may or may not be evident clinically. Mucosal thickening and/or sinus exudates have been observed in as many as 77% of subjects with acute colds.[9] These abnormalities are transient and usually not associated with symptoms, although they may persist 21 days or longer. Colds are associated with symptomatic otitis media in approximately 2% of cases in adults[10] and in a higher proportion in young children.[11] Rhinoviruses and other common cold viruses have been detected in middle ear fluids in approximately 20% to 40% of cases of otitis media with effusion in children.[12] Infections with RSV, influenza, and adenoviruses are often also associated with otitis media.[11] However, clinically manifest acute sinusitis is seen in a small (0.5%–5%) proportion of individuals with naturally occurring colds.

Clinical colds in atopic individuals may be more severe or more likely to result in wheezing than in normal individuals, and rhinoviruses have been identified as major causes of asthma exacerbations in children and adults.[13] Rhinovirus colds may increase asthma by augmenting airway allergic responses such as histamine release and eosinophil influx after antigen challenge. Rhinoviruses have also been identified as important causes of exacerbations of chronic obstructive pulmonary disease (COPD).[14,15]

Viral Etiologies and Differential Diagnosis

Epidemiologic studies have established that the great majority of common colds are associated with infection with the human rhinoviruses or other picornaviruses. Other agents frequently associated with common colds include seasonal coronaviruses, parainfluenza, and respiratory syncytial virus, with a variety of other agents implicated occasionally. The clinical characteristics of illness due to each of these viruses are similar, and a specific viral etiology generally cannot be deduced on clinical grounds alone. Epidemiologic studies have indicated that on an annual basis, any one antigenic type of virus is responsible for less than 1% of all colds.

The differential diagnosis of individuals presenting with typical signs and symptoms is not extensive. However, in the presence of additional signs or symptoms that are not part of this clinical description, such as high persistent fever, signs of respiratory distress, or lower respiratory tract disease, alternative diagnoses should be sought. Allergic causes should be considered in individuals who present with recurrent symptoms restricted to the upper respiratory tract.

Pathogenesis

Studies of the pathogenesis of the common cold have largely focused on rhinoviruses, which constitute the most commonly implicated viral etiology. In situ hybridization studies of nasal biopsy specimens from rhinovirus-infected subjects demonstrate that infection is largely confined to relatively small numbers of ciliated nasal mucosal epithelial cells , although occasional nonciliated cells are also infected.[16] Sloughing of these epithelial cells is seen in naturally occurring colds, but the epithelial lining remains intact, with structurally normal cell borders. Infection is associated with significant increases in the numbers of polymorphonuclear leukocytes in nasal mucosa and secretions, probably due to elaboration of IL-8 by infected cells.[17] Although rhinoviruses are not able to grow efficiently at body temperature, virus can be detected within cells of the lower airway even in uncomplicated colds in healthy subjects.[18]

In general, the number of infected cells appears to be quite limited, even in fairly symptomatic individuals, and there is no clear correlation between the level of virus replication or the number of cells infected, and the level of symptomatology. These results have suggested that virus-induced cellular injury is not the direct cause of symptoms in rhinovirus colds, but rather that inflammatory mediators play an important role. Analysis of the nature of the mucosal exudate during rhinovirus colds suggests that the nasal secretions during the initial response to rhinovirus infection are predominantly the result of increased vascular permeability, as demonstrated by elevated levels of plasma proteins in nasal secretions,[19] whereas later glandular secretions (lactoferrin, lysozyme, and secretory IgA) predominate. Similar observations have been made in allergic rhinitis. However, in contrast to the situation in allergic rhinitis, histamine does not appear to play a role in the induction of symptoms in colds, as nasal histamine levels do not increase and therapy with selective H1 antihistamine is not effective.[20,21] Nasal secretion kinin levels do correlate with symptoms in natural and experimental colds, and intranasal administration of bradykinin mimics the induction of signs and symptoms in the common cold,[21,22] including increased nasal vascular permeability, rhinitis, and sore throat.

Diagnostic Tests

Molecular diagnostic tests have been developed for many of the viruses associated with the common cold. Since there is no specific therapy and the clinical characteristics of colds due to different viruses are similar, use of techniques for specific viral diagnosis in the common cold is generally limited to the research setting.

Treatment and Prevention

The recommended treatment for colds is to use individual remedies to treat specific symptoms. Symptoms of sneezing and rhinorrhea can be alleviated with nonselective sedating antihistamines,[23,24] although a recent meta-analysis suggested only short-term benefit.[25] Studies of pseudoephedrine have demonstrated measurable improvements in nasal air flow consistent with a decongestant effect. In previously healthy children and adults, there is no danger from the routine use of cough suppressants, although they should be used cautiously in patients with serious underlying COPD. Cough syrups containing expectorants are of unproved value in common colds, although guaifenesin may reduce the cough reflex.

Symptomatic therapy with systemic anticholinergic drugs or anticholinergic–sympathomimetic combinations has not been shown to confer any benefit, and is associated with significant side effects, especially in children.[26,27] In addition, the use of the decongestant phenylpropanolamine is associated with an increased risk of hemorrhagic stroke,[18,28] and this drug has been removed from over-the-counter cold remedies.

Topical application of vasoconstrictors such as phenylephrine or ephedrine provides relief of nasal obstruction but may be associated with a rebound of symptoms upon discontinuation if used for more than a few days. Thus, nasal sprays containing decongestants should be used for no more than 3 days. Topical application of ipratropium, a quaternary anticholinergic agent that is minimally absorbed across biologic membranes, reduces rhinorrhea significantly in naturally occurring colds.[29] This agent probably exerts its major effect on the parasympathetic regulation of mucous and seromucous glands. Over-the-counter use of oral zinc for treatment of common colds has not been associated with significant efficacy.[30] It has also not been possible to demonstrate substantial benefit of *Echinacea*, an herbal remedy based on the purple coneflower for either treatment or prevention of colds.[31]

There has been considerable interest in the development of antiviral agents for the common cold. Several problems confront the successful development of such an antiviral agent. Because of the numerous etiologic agents, the ideal drug would require a wide spectrum of activity. In addition, many drugs that appear to have excellent in vitro activity have failed in clinical trials, apparently because they did not reach sufficient levels within the nasal mucosa where virus replication occurs. Finally, because symptoms in colds are not clearly related to the level of virus replication, a successful treatment strategy may also require use of drugs to antagonize the effects of inflammatory mediators.[32]

LARYNGITIS AND PHARYNGITIS

The viral etiologies and clinical manifestations of laryngitis and pharyngitis are considered below.

Clinical Features

Pharyngitis is a common complaint of both adults and children and is one of the most common reasons for seeking outpatient medical care. In general, this syndrome refers to individuals who present with the primary complaint of sore throat and should probably be reserved for those individuals who manifest some objective evidence of pharyngeal inflammation as well. The clinical manifestations of pharyngitis are dominated by the specific causative agent. However, generally the syndrome can be divided into those cases in which nasal symptoms accompany pharyngitis, which are predominantly viral in nature, and those cases without nasal symptoms, which have a somewhat more diverse spectrum of etiologic considerations, including both group A and nongroup A streptococci, *Chlamydia* (strain TWAR), *Mycoplasma*, and other agents.[33]

Viral Etiologies and Differential Diagnosis

Rhinovirus colds are frequently accompanied by pharyngitis, although objective signs of pharyngeal inflammation are uncommon. Adenovirus infections are frequently associated with pharyngitis, and a specific syndrome of pharyngoconjunctival fever, consisting of fever, pharyngitis, and bilateral conjunctivitis is associated with adenovirus types 3 and 7. A variety of enteroviral serotypes are associated with febrile pharyngitis. Herpangina is a specific Coxsackie virus–induced pharyngitis in which small (1- to 2-mm) vesicular lesions of the soft palate rupture to become small white ulcers. Pharyngitis is a typical component of acute influenza in which individuals experience the sudden onset of systemic symptoms of fever, myalgias, and malaise accompanied by upper respiratory signs and symptoms, including pharyngitis. Primary oral infection with herpes simplex virus may present with pharyngitis, typically with vesicles and shallow ulcers of the palate, and cervical lymphadenopathy.

Pharyngitis may be the presenting or predominating symptom in more generalized viral infections. Pharyngitis is a significant complaint in approximately one-half of cases of the acute mononucleosis syndrome due to Epstein-Barr virus. Pharyngitis in this syndrome is generally exudative and can be accompanied by cervical and generalized lymphadenopathy, as well as fever, hepatosplenomegaly, and other systemic symptoms. The heterophile antibody test (Monospot) is typically positive in the second week of illness. Cytomegalovirus can cause an identical syndrome that is Monospot negative. Cytomegalovirus may be associated with pharyngitis more commonly in children than in adults. An acute mononucleosis-like syndrome with pharyngitis may also be the presenting manifestation of primary HIV infection and toxoplasmosis. Viruses in the hemorrhagic fever group produce an acute pharyngitis that occurs early in the disease, before skin lesions appear. Also, exudative pharyngitis is a common clinical manifestation in Lassa fever.

The differential diagnosis of acute pharyngitis generally centers upon the differentiation of streptococcal from viral etiologies. Features suggestive of streptococcal pharyngitis include tonsillar swelling, moderate to severe tenderness on palpation, enlargement of lymph nodes, presence of scarlatiniform rash, and absence of coryza. The presence of nasal symptoms or of conjunctivitis favors a viral etiology, and as described, some viral syndromes may present with distinguishing characteristics that help in their identification. Generally, acute pharyngitis in children less than 3 years of age is predominantly viral in origin. The presence of exudate is suggestive of bacterial etiology, but exudates may also be seen with adenovirus or Epstein-Barr virus.

Pathogenesis

As described, pharyngitis in the common cold is probably the result of chemical mediators of inflammation, which are potent stimulators of pain nerve endings. Potentially similar mechanisms may account for pharyngitis in other viral syndromes as well. Direct viral damage and other host inflammatory responses also may contribute. Pharyngitis occurs most often as part of the common cold syndrome and thus is usually associated with the same viruses that cause colds. In some cases, pharyngeal symptoms predominate to a degree that overshadows other complaints. The kinins are potent stimulators of pain nerve endings, and high levels of bradykinin and lysyl bradykinin are present in nasal secretions of patients with rhinovirus colds. Intranasal application of bradykinin promotes sore throat and nasal symptoms in volunteers, supporting a role for these agents in the pathogenesis of cold symptoms.

Diagnostic Tests

Rapid antigen detection tests are available for respiratory syncytial virus and influenza A virus. Rapid diagnostic tests are widely available for the office identification of group A streptococci and are indicated in most cases in which the etiology is uncertain. When highly sensitive tests are used, backup cultures are generally not necessary. Routine studies for other bacterial and nonbacterial pathogens are usually not obtained. Identification of viral causes of pharyngitis is generally possible through isolation in cell culture but is seldom attempted in clinical practice. Use of guideline recommendations for the selective use of throat cultures combined with antibiotic treatment based only on positive rapid test or throat culture can reduce unnecessary use of antibiotics for treatment of pharyngitis.[34]

Treatment and Prevention

The treatment of most cases of viral pharyngitis is symptomatic, as noted in the section on common colds. Patients suspected of having influenza pharyngitis who are seen within the first 2 days of illness can be treated with antiviral therapy (see “Influenza Virus,” below). In immunosuppressed patients with chronic herpetic pharyngitis or normal hosts with primary gingivostomatitis, acyclovir therapy is recommended (see “Herpes Simplex Virus,” below).

Treatment of group A streptococcal infections with antimicrobial agents is generally initiated to prevent rheumatologic complications of this infection, and because treatment of acute streptococcal pharyngitis is associated with more rapid resolution of symptoms,[35] although the absolute benefits are rather modest.

CROUP

Croup represents an important clinical entity, especially in children, as discussed below.

Clinical Features

Croup, or viral laryngotracheobronchitis, is a clinically distinct illness that predominantly affects children under the age of 3. The illness typically begins with upper respiratory tract symptoms of rhinorrhea and sore throat, often with a mild cough. After 2 or 3 days, the cough deepens and develops a characteristic brassy, barking quality, which is similar to a seal’s bark. Fever between 38°C and 40°C is common, although those with croup due to respiratory syncytial virus may have normal temperatures. The child may appear apprehensive and most comfortable sitting forward in bed. The respiratory rate is elevated, but usually not over 50; this contrasts with bronchiolitis, in which more severe tachypnea is often seen. Chest wall retractions, particularly in the supraclavicular and suprasternal areas, may be observed. Children with this finding on presentation have a higher risk of hospitalization or of requiring ventilatory support.

The characteristic physical finding of croup is inspiratory stridor. Inspiration is prolonged, and in very severe cases, some degree of expiratory obstruction also may be seen. Rales, rhonchi, and wheezing, which reflect the characteristic involvement of the lower respiratory tract, may be heard on physical examination. A fluctuating course is typical for viral croup, and the child may appear to worsen or improve within an hour. The typical duration of croup is 3 to 4 days.

Hypoxemia occurs in 80% of children with croup severe enough to require hospitalization. The degree of hypoxia is generally difficult to ascertain clinically, but pulse oximetry provides a reliable and noninvasive means to monitor the state of oxygenation. Children who develop respiratory insufficiency as a result of increasing fatigue may also have elevations of Pa_{CO_2}.

Children with croup characteristically exhibit subglottic narrowing of the tracheal air shadow on PA films of the neck, the "steeple" sign. This finding may be useful in differentiating croup from epiglottitis. However, radiographs are limited in accuracy, and when the diagnosis is uncertain, radiologic and pharyngeal examination should be avoided because of the risk of cardiorespiratory arrest in acute epiglottitis. Emergency assessment by an otolaryngologist or an anesthesiologist is indicated in this situation. Chest x-rays may reveal parenchymal infiltrates, which are part of the characteristic involvement of the lower respiratory tract in this syndrome.

■ Viral Etiologies and Differential Diagnosis

Parainfluenza viruses type 1 and 2 are the most common viruses responsible for croup, accounting for about 75% of cases,[36] and the seasonal incidence of croup reflects the seasonal variations in parainfluenza virus incidence. Less common causes of croup include respiratory syncytial virus, influenza A or B viruses, measles, rhinoviruses, and adenoviruses as well as *Mycoplasma pneumoniae.* Parainfluenza virus type 2, influenza A viruses, and measles are associated with more severe disease, but generally, the clinical presentation of the croup syndrome due to individual agents is similar.

The majority of cases of inspiratory stridor in children are caused by viral croup. However, it is critical to distinguish these syndromes from other, potentially more serious causes of airway obstruction such as bacterial epiglottitis and tracheitis early in clinical management. Epiglottitis is an acute cellulitis of the epiglottis and surrounding structures. Patients present with acute respiratory distress and drooling, but the barking cough of croup is absent. Since the introduction of effective vaccines for the major bacterial cause or epiglottitis, *Haemophilus influenzae* type b (Hib), the incidence of epiglottitis in children has also declined considerably. In adults, and rarely in children, epiglottitis may be caused by a variety of other bacterial agents such as *Haemophilus parainfluenzae* or α-hemolytic streptococci, which may spread from a contiguous focus of infection. Bacterial tracheitis is a relatively rare syndrome that mimics croup. Abundant purulent sputum is often present. Bacterial tracheitis is usually caused by *Staphylococcus aureus* or Hib; other bacteria such as *Streptococcus pneumoniae* also have been associated with this syndrome. Other infectious causes of stridor, including peritonsillar or retropharyngeal abscess, or diphtheria, should be considered. Evidence of noninfectious causes of stridor, such as trauma or aspiration of a foreign body, also should be sought in the history and physical examination.

■ Pathogenesis

The severity of clinical symptoms in parainfluenza virus croup appears to be directly related to the level of virus replication.[37] The viral infection in croup produces inflammation both in the upper respiratory tract and in the lung parenchyma. The classic signs of croup, including barking cough and inspiratory stridor, arise mostly from inflammation occurring in the larynx and trachea. Inflammatory changes are seen by histology in the epithelial mucosa and submucosa of the larynx and trachea. The cellular infiltrate includes histiocytes, lymphocytes, plasma cells, and polymorphonuclear leukocytes. The inflammation and obstruction are greatest at the subglottic level, which is the least distensible part of the airway because it is encircled by the cricoid cartilage. Consequently, localized inflammation and edema lead to obstruction of airflow. The impeded flow of air through this narrowed area produces the classic high-pitched vibration. Obstruction is greater during inspiration because it occurs in the extrathoracic portion of the airway and is enhanced in small children because the walls of the airways in these individuals are relatively compliant. Obstruction of airflow results in an initial decline in tidal volume, which is compensated by an increase in respiratory rate to maintain adequate alveolar ventilation. However, if the obstruction increases, the work of breathing may increase until the child tires, and as the respiratory rate declines, the child develops hypercarbia and respiratory failure.

Involvement of the lower respiratory tract with resulting hypoxia is integral to the pathophysiology of croup.[38] Inflammatory changes are noted throughout the respiratory tract, including the linings of the bronchi, bronchioles, and even the alveoli. Although some degree of hypoxia can be explained on the basis of hypercarbia, the major pathophysiologic mechanism is ventilation–perfusion mismatching.

Pulmonary edema may complicate severe croup and upper airway obstruction. The onset of pulmonary edema often is immediately following intubation. Pulmonary edema in these cases does not appear to be due to pulmonary artery hypertension, but to local hypoxia and increased alveolar–capillary transmural pressure.

In addition to these anatomic pathophysiologic events, immunologic mechanisms also may play a role in some manifestations or in determining the severity of disease. Virus-specific IgE responses appear earlier and are of greater magnitude in patients with parainfluenza virus-associated croup than in age-matched controls with simple upper respiratory illness. Histamine is also detectable in upper respiratory tract secretions in this condition. There also appears to be a relationship between croup and subsequent reactive airways disease.[39]

■ Diagnostic Tests

Parainfluenza viruses and other viruses associated with croup can be isolated in cell culture, and specific viral diagnosis can be made by PCR, but the clinical syndrome is sufficient for diagnosis, and management generally does not depend on identification of the specific agent.

■ Treatment and Prevention

Because most hospitalized children are hypoxic, oxygen is the mainstay of treatment for severe disease and should be given to all hypoxemic patients. Use of helium as the carrying gas, rather than air, has been suggested as a method to decrease the work of breathing. However, this approach requires use of 70% helium to be effective and limits the amount of oxygen that can be delivered.[40] Humidified air or mist therapy is commonly used and has several potential roles. Desiccation of the inflamed epithelial surfaces is decreased, and the viscosity of the exudate is reduced. However, the value of mist therapy has not been proven, and it should be recognized that water from the standard home-use vaporizer cannot reach the lower respiratory tract because of the large particle size. In addition, removal of the child from the parents and placement in a mist tent can be more distressing to the child than beneficial.

Administration of nebulized racemic epinephrine generally gives rapid, symptomatic relief in croup.[41] It is believed that α-adrenergic stimulation by this drug causes mucosal vasoconstriction, leading to decreased subglottic edema. Several randomized trials have demonstrated a rapid beneficial effect on airway obstruction.[42,43] The onset of action is rapid, often within minutes, but the duration of relief also is limited, lasting 2 h or less. Therefore, treated subjects should be observed closely for clinical deterioration. Although symptomatic relief is considerable, use of epinephrine is not associated with improvements in oxygenation, probably because the defect in oxygen is associated with ventilation–perfusion mismatching due to lower respiratory tract involvement. In addition, tachycardia may occur. Thus, inhaled epinephrine is generally reserved for children who fail to respond to more conservative management,[44] although some centers use it routinely.

Steroids have been shown to confer significant benefits in the management of mild, moderate, and severe croup,[45] including more rapid improvement in symptoms, reduced length of hospital stay, and reduced rates of intubation. Administration of intramuscular, oral, or nebulized steroids appears to be equally effective,[46,47] and low-dose dexamethasone or prednisolone equally effective as standard dose.[48] Administration of single-dose steroid therapy in this setting has not been associated with significant side effects[49] and should probably be used in any patient with illness significant enough to require an emergency room or clinic visit.

Antiviral agents effective against some of the viruses responsible for croup are available but have not been tested for efficacy in this situation. However, the potential benefit of the use of antiviral agents in the typical self-limited course of croup would likely be limited. Since croup is a viral illness, antibiotic therapy is of no benefit. Vaccines are currently available for both measles and influenza, but there are currently no vaccines available for parainfluenza virus.

TRACHEOBRONCHITIS

Tracheobronchitis is an extremely common disorder with diverse etiologies.

Clinical Features

In addition to causing croup and bronchiolitis, viral infection of the trachea and bronchi may cause tracheitis or tracheobronchitis. The diagnosis of acute bronchitis is usually applied to cases of acute respiratory disease with severe and prolonged cough that continues after other signs and symptoms of the acute infection have subsided. Cough occurs during the first week of illness in 30% of rhinovirus colds in young adults and in 80% or more of cases of influenza A virus infection, in which it is often prolonged. Adenovirus infections characteristically involve the tracheobronchial tree, with resultant bronchitis that in military populations is part of the syndrome of acute respiratory disease. Tracheitis is characterized by tracheal tenderness, which can be elicited by gentle pressure on the anterior trachea just below the cricoid cartilage. Substernal discomfort on inhalation, and nonproductive paroxysmal cough, are noted. Paroxysmal nonproductive cough also is characteristic of tracheobronchitis and is usually much more severe at night. Later in the course of illness, small amounts of clear or whitish sputum may be produced. Accompanying symptoms may include fever, headache, myalgias, malaise, and anorexia. After several days of coughing, chest wall or abdominal discomfort that is muscular in nature may be noted. Physical findings are generally nonspecific; examination of the chest may reveal no adventitious sounds, but more commonly diffuse rhonchi and occasional wheezing. Physical signs such as egophony, pleural friction rubs, or areas of dullness to percussion are not present.

Pathogenesis

The mechanisms of cough production in viral infection are not well understood but may include direct damage to the respiratory mucosa, release of inflammatory substances in response to the infection, increased production and/or decreased clearance of respiratory secretions, and stimulation of airway irritant receptors. Intranasal application of several prostaglandins also produces cough in uninfected volunteers.[50] Infection may also enhance airway reactivity, leading to increased sensitivity to cold air and pollutants such as smoke.

Viral Etiologies and Differential Diagnosis

Tracheobronchitis is most typically caused by influenza A or B virus. In adults, other common respiratory viruses such as parainfluenza virus or respiratory syncytial virus may present with prolonged cough. Herpes simplex has been associated with necrotizing tracheobronchitis in nonimmunocompromised hosts. This syndrome is often accompanied by refractory bronchospasm.

The differential diagnosis of acute bronchitis includes nonviral infections and noninfectious etiologies such as cough-variant asthma. *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* infections cause prolonged cough. *Bordetella pertussis* infection also should be considered in the differential diagnosis. In otherwise healthy persons, workup of acute cough should be directed toward determining whether pneumonia is present, which would be more clinically concerning.

Diagnostic Tests

Many of the viral pathogens associated with tracheobronchitis can be detected in multiplexed nucleic acid–based diagnostics, but specific viral diagnosis is generally not necessary for appropriate management.

Treatment and Prevention

Treatment in adults is best effected by prescribing rest, aspirin for headache and fever, cold water vapor inhalation, and a cough syrup such as guaifenesin with dextromethorphan. For children, a cough suppressant may be helpful. In the absence of signs of pneumonia, treatment of prolonged cough with antibacterial agents is of no benefit and not recommended.[51,52]

BRONCHIOLITIS

Bronchiolitis is an important entity with significant clinical manifestations, the hallmark of which is airflow obstruction.

Clinical Features

Bronchiolitis is a fairly characteristic syndrome whose presenting symptoms are dominated by the major pathophysiologic defect, obstruction to expiratory air flow.[53] The onset of lower respiratory symptoms is usually preceded by rhinitis, often with nasal congestion and discharge. More severe symptoms characteristically occur 2 to 3 days later but in some cases are concurrent with the onset of upper respiratory symptoms.

The hallmark of disease is wheezing, which can be quite marked, with flaring of the nostrils and use of accessory muscles of respiration. Cough may or may not be prominent initially, and when cough is present, it may be paroxysmal in nature. Bronchiolitis may be complicated by apnea as well.[54] Slight cyanosis is often observed, but the presence or absence of cyanosis is not a reliable indicator of the degree of oxygenation or of the severity of disease. Physical findings are generally confined to the chest, with development of rales, which are usually musical in the beginning and then become moister. Hyperresonance of the chest may be observed, and the liver may be displaced downward. The respiratory rate is elevated, with rates of 50 to 80 breaths per min. Fever is frequently present at the beginning of the illness but may no longer be present at the time lower respiratory tract involvement develops. Among hospitalized infants, one-third or more are afebrile but have marked lower respiratory tract disease. Thus, the presence or absence of fever does not indicate the severity of the child's illness. Mild conjunctivitis is noted in about one-third of cases, with pharyngitis of varied severity in about one-half, and otitis media in 5% to 10%. The hospital course is variable, but most infants show improvement in 3 to 4 days.[55]

Radiologic findings are generally nonspecific, with reported findings including air trapping, consolidation, and collapse.[56] However, there is no correlation between the chest x-ray findings and the clinical course,[57] and in general, chest x-rays are not necessary in the evaluation of bronchiolitis.[58] Results of routine laboratory tests are generally unremarkable. Electrolyte disturbances, most notably hyponatremia, may be seen with severe disease, particularly if excessive amounts of hypotonic fluid are administered. Acute disease may be associated with elevations in pulmonary artery pressure, but echocardiographic studies are usually unremarkable in infants with structurally normal hearts.

Bronchiolitis is a disease predominantly of infancy, and the peak age incidence is between 2 and 6 months of age, with more than 80% of cases occurring in the first year of life. The risk of hospitalization and severe bronchiolitis is particularly high in infants with congenital heart disease, chronic lung disease, or immunodeficiency. In addition, infants born prematurely, and those who are less than 6 weeks of age at the time of presentation, also are at increased risk of hospitalization. More severe disease has also been documented in children with a family history of asthma, and in those exposed to cigarette smoke in the family setting.

Viral Etiologies and Differential Diagnosis

Respiratory syncytial virus (RSV) causes most cases of bronchiolitis. During the RSV season, essentially all cases are due to this virus. In the northern hemisphere, RSV season usually ranges from October to May, with a peak number of cases in December through February. Overall, RSV is recovered from about three-fourths of all infants admitted to the hospital with bronchiolitis.[53] Several other respiratory viruses are associated with bronchiolitis, including parainfluenza viruses, influenza virus, mumps, and rhinoviruses, and coinfections are common.[59]

The epidemiology and pathophysiology of parainfluenza bronchiolitis are similar to those of RSV, and particularly severe disease may be associated with parainfluenza virus type 3. Adenoviruses types 3, 7, and 21 are relatively uncommon causes but may be associated with more severe disease, including the development of bronchiolitis obliterans. Rhinoviruses represent a small but significant proportion of cases of bronchiolitis[60] and may mimic RSV infection in infants with bronchopulmonary dysplasia. Rhinoviruses and *Mycoplasma pneumoniae* become more important causes of infection-induced wheezing as children become older. Surveys of bronchiolitis in various parts of the world have suggested a similar pattern of viral etiologies.

A significant number of cases are associated with the human metapneumovirus (hMPV).[61] The clinical picture most closely resembles that of RSV, and bronchiolitis is the major manifestation in children. Clinical features include wheezing and hypoxia. There are no clinical features that can distinguish between disease caused by hMPV and RSV, although generally those due to RSV may be more severe. Seasonal human coronaviruses also have been associated with lower respiratory tract disease in infants.[62] Human bocavirus, a human parvovirus, has been found in as many as 20% of cases of acute wheezing in young children, often in conjunction with other viruses. The exact role it plays in this syndrome has not been determined completely.[63]

The differential diagnosis of diseases characterized by expiratory airflow obstruction in infants is relatively small. Pertussis can occasionally be confused with bronchiolitis; however, more frequent vomiting and more paroxysmal cough would be clues to the diagnosis. Anatomic defects such as vascular rings can cause obstruction of the airway. Foreign bodies should be considered strongly, especially in young infants. Gastroesophageal reflux is an additional consideration. The major differential diagnostic consideration is asthma, which is uncommon under the age of 1 year.

Pathogenesis

The pathophysiology of infectious bronchiolitis has been described most completely in the case of infection with RSV.[53] The average incubation period is 4 to 5 days, with a range of 2 to 8 days. Virus replication is limited to the respiratory tract mucosa, which may be involved through its entire length. Involvement of the lower respiratory tract probably occurs by cell-to-cell spread through the respiratory epithelium or aspiration of upper respiratory secretions. Pathologic findings in RSV bronchiolitis include necrosis of bronchiolar epithelium, loss of ciliated epithelial cells, and marked peribronchiolar mononuclear inflammation. Virus-induced cytopathology and associated submucosal edema leads to obstruction of smaller bronchioles, particularly in infants, with distal collapse or air-trapping.

Viral infection of epithelial cells of the bronchioles leads to destruction and necrosis of the ciliated epithelium. Lymphocytes can be seen in increased numbers in the peribronchial tissues. The submucosa becomes edematous, and there is increased production of mucus. Ultimately, dense plugs of alveolar debris and strands of fibrin form within small bronchi and bronchioles, which may partially or completely obstruct airflow. The pathogenic basis for respiratory difficulty in bronchiolitis is related to obstruction of these small airways. Hypoxemia is the major abnormality of gas exchange, with ventilation–perfusion imbalance the major cause of the hypoxemia. In addition to hypoxia, hypercarbia and respiratory acidosis have been observed in some severely ill infants.

Infants are particularly susceptible to the consequences of viral infection for several reasons. The peripheral airways are disproportionately narrow in the early years of life. In addition, collateral channels of ventilation, such as the pores of Kohn, are deficient in both number and size in the infant lung. Finally, the airways of infants are intrinsically more reactive to bronchospastic stimuli than are the airways of older children.[64]

The possibility that immune responses are involved in the pathogenesis of RSV bronchiolitis has received considerable attention. The presence of preexisting infection-induced antibody does not appear to play a role in enhancing the severity of disease because maternal antibody, or passively transferred antibody, is protective. It has also been postulated that cellular immune responses may be involved in the pathogenesis, since infants infected with RSV who have clinical bronchiolitis have higher levels of cell-mediated immunity to RSV than those with uncomplicated upper respiratory tract disease. Immediate hypersensitivity type reactions also have been postulated to play a role in the pathogenesis of wheezing in bronchiolitis. Production of virus-specific IgE and subsequent release of mediators of bronchoconstriction have been documented with RSV and PIV bronchiolitis. Leukotriene C4, a potent stimulant of airway smooth muscle constriction and mucus secretion, also is released into the airway in acute bronchiolitis.[65] Elevated levels of histamine and prostaglandin $F_2\alpha$ metabolite have been found during acute bronchiolitis and increased levels of eosinophilic cationic protein in nasopharyngeal secretions, suggesting that release of chemical mediators of inflammation in response to viral antigens is one factor contributing to the development of severe bronchiolitis.

The innate immune response also plays an important role in the pathogenesis of RSV disease in infants, and it has been recognized that single-nucleotide polymorphisms in several genes that control the inflammatory response have an important impact on the severity of RSV disease.[66] Examples include polymorphisms in the genes for IL-4, IL-8, and IL-13, and in TLR-4 and the CCR5 receptor, among others.

Following recovery from acute bronchiolitis, some children experience continued episodes of wheezing, especially during viral upper respiratory infections. Estimates are that 5% to 50% of children diagnosed as having bronchiolitis in infancy go on to develop recurrent episodes of wheezing. Generally wheezing episodes wane in frequency over the next several years. After clinical bronchiolitis, some individuals may also demonstrate increased bronchial responsiveness to histamine or cold challenge, which generally decreases over time. The mechanism by which RSV or other viral infection might lead to increased episodes of wheezing is unclear. Some individuals develop elevated levels of viral specific IgE, which may play a role in triggering bronchospasm upon re-exposure. In some studies, persistent wheezing correlates with a family history of asthma and with higher levels of IgE.

■ Diagnostic Tests

Specific viral diagnosis is possible by either detection of viral antigens or viral nucleic acid in nasopharyngeal secretions. However, routine virologic testing in bronchiolitis is not recommended because it does not impact management.[58] In transplant patients with suspected RSV pneumonia, samples of the lower respiratory tract by bronchoalveolar lavage are more sensitive than throat swabs for detection of RSV.

■ Treatment and Prevention

Recommendations regarding the treatment and prophylaxis of bronchiolitis have been summarized recently.[58] Oxygenation should be monitored by pulse oximetry, and oxygen administered to infants whose oxygen saturation consistently falls below 90%. Since bronchiolitis is a viral disease that is infrequently complicated by bacterial superinfection, routine treatment with antibiotics is not warranted. Because of the dehydrating effect of tachypnea and reduced oral intake in some hospitalized infants, parenteral rehydration is often needed, but care must be taken to avoid inducing hyponatremia. Fluid intake and electrolyte concentrations should be carefully monitored in all infants with severe bronchiolitis, as hyponatremia and syndrome of inappropriate secretion of antidiuretic hormone (SIADH) may occur.

There is general agreement that bronchodilators should not be administered to children with bronchiolitis. While bronchodilators may produce modest short-term improvements in clinical scores, t do not improve oxygenation, rates of hospitalization, or duration of hospital stay.[67–69] In addition, bronchodilating drugs may contribute to increased restlessness and cardiovascular stress. Because some children do respond to these drugs,[70] a reasonable strategy is a short trial of nebulized bronchodilator with continued therapy only in selected children who respond.

The majority of studies of systemic corticosteroids have also failed to demonstrate a beneficial effect in acute bronchiolitis.[71,72] A recent meta-analysis has shown that systemic steroids do not decrease admission rates.[73] Randomized trials of inhaled steroids also have not shown significant benefit in bronchiolitis.[74]

Ribavirin (1-β-D-ribofuranosyl-1,2,3-triazole-3-carboxamide) is a broad-spectrum antiviral agent with antiviral activity against multiple respiratory viruses including RSV in a variety of cell culture systems and animal models. It does not achieve suitable levels in respiratory secretions when administered systemically, so aerosolized drug has been used for treatment of bronchiolitis. Although initial randomized placebo-controlled trials of ribavirin given as a small-particle aerosol showed benefit in treatment of bronchiolitis, subsequent experience with use of the drug in clinical practice did not confirm this clinical benefit. The primary use of ribavirin currently is in treatment of RSV pneumonia in immunocompromised patients.[75] Multiple additional antivirals directed at RSV are in clinical development, but none is currently licensed. A common problem with these agents has been the rapid selection of resistant mutants, suggesting that multidrug approaches may be necessary.[76]

Bronchiolitis due to RSV can be prevented by passive transfer of antibody against this agent. A humanized neutralizing monoclonal antibody to the RSV F protein, palivizumab has significant protective efficacy in a population of infants with prematurity or bronchopulmonary dysplasia, as well as in children with hemodynamically significant congenital heart disease. Current recommendations for the use of passive antibody prophylaxis are to consider use in infants born before 29 weeks of gestation (who would be expected to receive little placental transfer of maternal antibody), and infants with hemodynamically significant heart disease or chronic lung disease of prematurity. Infants born before 29 weeks who will be less than 12 months during the subsequent RSV season should receive up to 5 monthly doses or until the end of the season, whichever comes first.[58] Palivizumab in not recommended for use in the second year of life or beyond, except for some cases of chronic lung disease of infancy. Palivizumab is not effective for therapy of RSV disease.[77]

Vaccines are available to prevent bronchiolitis due to influenza virus and mumps, but there is no vaccine currently available for prevention of bronchiolitis due to RSV. There are multiple significant hurdles to the development of such a vaccine, including the very young age at which the disease presents, the suppressive effect of maternal antibody on vaccine responses, and the potential for enhanced disease in vaccine recipients.[78]

VIRAL PNEUMONIA

Viral pneumonia is an extremely important clinical entity that affects a wide variety of hosts, both immunologically intact and immunologically compromised.

■ Clinical Features

Although there can be considerable variety to the presentation of viral pneumonia depending on the age and immunologic competence of the host, and the specific viral pathogen, there are certain general features that are described in the following.

Viral pneumonia in adults is usually associated with nonproductive cough, although production of frothy, pink-tinged sputum is seen in some severely ill individuals. Cyanosis and hypoxemia are prominent features of severe primary viral pneumonia. Physical findings are often nonspecific. The patient may appear acutely ill, conjunctivitis and rhinitis may be noted, and the trachea may be somewhat tender if accompanied by viral tracheitis. There is an increased respiratory rate, and diffuse rales and wheezes. A variety of chest x-ray patterns have been described, including lobar infiltrates, but most typically primary viral pneumonia presents with diffuse, bilateral interstitial infiltrates. However, there are really no x-ray patterns that reliably differentiate between bacterial and viral pneumonia. The sputum is relatively scant, it generally shows few polymorphonuclear leukocytes, and gram stain reveals minimal numbers of bacteria.

The basic presentation of viral pneumonia in children is similar. The clinical presentation varies considerably with the specific causative agent but typically includes fever and lower respiratory tract signs and symptoms, such as difficulty breathing, nonproductive cough, and physical findings of wheezing or increased breath sounds. Young infants may present with apneic episodes with minimal fever. The clinical presentation may be dominated by the associated croup or bronchiolitis, which are frequently present.

Underlying cardiopulmonary diseases, such as valvular heart disease or COPD, are well-recognized risk factors for viral pneumonia in adults and children. Pregnancy, particularly in the second and the third trimester, has been recognized as a risk factor for cardiopulmonary hospitalizations associated with influenza epidemics.

Bacterial superinfection is a common complication of viral lower respiratory tract infection, particularly in influenza. The classic presentation is that of a typical episode of viral illness with more or less complete recovery, followed 2 to 14 days later by a recurrence of fever and development of cough and dyspnea.[79] CXR reveals lobar infiltrates, and the clinical course is typical of bacterial pneumonia. In addition, combined bacterial and viral pneumonia, with clinical features of each, can occur in adults and with certain viruses in children.

Pathogenesis

The pathogenesis of viral infections of the lower respiratory tract can conveniently be considered in terms of infections initiated in and primarily confined to the respiratory tract, or so-called primary viral pneumonia, such as with influenza or RSV; processes in which infection is initiated in the respiratory tract with subsequent systemic manifestations, such as in measles or varicella; and processes in which respiratory tract involvement is secondary to a systemic infection, such as with CMV. Each of these situations may lead to what is recognized clinically as a viral pneumonia. In this discussion, the general features of primary viral pneumonia are discussed using influenza as a model, and pathogenesis of other forms of viral pneumonia is discussed briefly in comparison.

In primary influenza viral pneumonia, virus infection reaches the lung either by contiguous spread from the upper respiratory tract, or by inhalation of small-particle aerosols. Infection initially occurs in ciliated respiratory mucosal epithelial cells of the trachea, bronchi, and lower respiratory tract, and leads to widespread destruction of these cells. The trachea and bronchi contain bloody fluid, and the mucosa is hyperemic. Tracheitis, bronchitis, and bronchiolitis are seen, with loss of normal ciliated epithelial cells. Submucosal hyperemia, focal hemorrhage, edema, and cellular infiltrate are present. The alveolar spaces contain varying numbers of neutrophils and mononuclear cells admixed with fibrin and edema fluid. The alveolar capillaries may be markedly hyperemic with intra-alveolar hemorrhage. Acellular, hyaline membranes line many of the alveolar ducts and alveoli.

The pathologic changes in the lower respiratory tract in children with viral pneumonia due to RSV and parainfluenza virus are nonspecific and include epithelial necrosis with bronchiolar mucus plugging and widespread inflammation and necrosis of lung parenchyma, and severe lesions of the bronchial and bronchiolar mucosa as well. In fatal cases of RSV pneumonia in children, hemorrhagic pneumonia with peribronchial mononuclear infiltration and cytoplasmic inclusion bodies in epithelial cells are seen.

Bacterial superinfection is a well-recognized complication of viral pneumonia and accounts for a large proportion of the morbidity and mortality of viral lower respiratory tract disease, especially in adults. Consequently, the spectrum of disease and pathophysiology of bacterial superinfection has been studied intensively, and a number of factors have been identified in viral respiratory disease that could play a role in increasing the risk of bacterial infection.[80] The disruption of the normal epithelial cell barrier to infection, and loss of mucociliary clearance, undoubtedly contribute to the enhancement of bacterial pathogenesis. The physiologic consequences of these alterations have been demonstrated as markedly decreased mucociliary clearance of labeled particles in human subjects with acute, naturally acquired influenza.[81] Animal models have also suggested that virally induced inflammatory responses, particularly the type I interferon response, also contribute to the downregulation of host antibacterial defense mechanisms.[82,83]

Viral Etiologies and Differential Diagnosis

The impact of viral pneumonia and the spectrum of associated viral agents is highly dependent on the age group and immune status of the host. Viruses are clearly important and frequent causes of pneumonia in young children. The role of viruses becomes less apparent in older children; in healthy adults, pure viral pneumonia is rare and is predominantly due to influenza. Elderly adults may experience more significant lower respiratory tract signs and symptoms following infection with agents that normally cause upper respiratory tract illness in younger adults, but generally have similar rates of viral pneumonia as do healthy young adults. Finally, viral pneumonia is an important cause of morbidity and mortality in individuals with compromised immune systems, with a broader spectrum of viral agents than seen in immunologically intact individuals. The following sections outline the features of the most common viruses associated with lower respiratory tract infection and viral pneumonia.

Influenza

Influenza is a prevalent infection that has wide-reaching implications for large populations of patients.

Clinical Features The onset of influenza is typically abrupt, and the illness is characterized by the predominance of systemic symptoms, including fever, prostration, myalgias, and malaise. Respiratory symptoms may be relatively minimal, particularly early in the course, and include nasal complaints, sore throat, hoarseness, and nonproductive cough. Because of the involvement of tracheal epithelium in infection, complaints of burning throat and substernal pain may be seen. Among healthy adults, the best clinical predictors of influenza virus positivity are the presence of cough and fever in patients presenting during epidemics.[84]

Other than fever, there are usually few findings on physical exam. Affected individuals may exhibit rhinitis, pharyngitis, conjunctival injection, and tracheal tenderness. The chest is usually clear in uncomplicated cases. Most acute symptoms resolve in 3 to 5 days, but complete recovery may take weeks. The clinical features of influenza A and B virus infection are similar. Symptoms of influenza in children are similar to those in adults, although children may have higher fever with febrile seizures. As described earlier, influenza may be associated with otitis media or croup in children.

Primary influenza viral pneumonia is characterized by rapid progression of dyspnea, cough and cyanosis, and development of respiratory distress syndrome acute (ARDS). Chest roentgenographs reveal bilateral interstitial infiltrates, sputum production is scanty, and Gram stain reveals few organisms. Secondary bacterial pneumonia may present 1 to 2 weeks after apparent recovery from an acute influenza episode with recurrence of fever, and signs and symptoms of typical lobar pneumonia. Many patients present with mixed viral and bacterial pneumonia. Bacterial superinfections of influenza have been postulated as a major cause of death during the pandemic of 1918.[85] The most common bacteria implicated are *Streptococcus pneumoniae*, with a significantly increased frequency of *Staphylococcus aureus*[86,87] including methicillin-resistant staph (MRSA).[88]

Influenza A and B viruses are both significant causes of pneumonia in children, especially during periods of epidemic prevalence. In infants and children, the most frequent manifestation of influenza pneumonia is an interstitial pneumonitis similar in appearance and course to those of the other predominant viral agents of pneumonia in this age group, except that a secondary bacterial pneumonia may occur more frequently than with RSV or parainfluenza viruses.

Epidemiology Influenza is typically associated with seasonal epidemics of greater or lesser severity, which occur during the winter months in temperate climates in both the northern and southern hemispheres. Outbreaks in the northern hemisphere are usually noted between the months of November and March or April, and typically last from 4 to 6 weeks in any given community. The reasons for the seasonal behavior of influenza are not known but have been the subject of much interest. Some suggested mechanisms have included the seasonal effects of heat and humidity on the viability of virus in the environment, behavioral patterns that facilitate transmission, such as attendance at schools, or sunlight effects on baseline immune function.

Seasonal influenza epidemics are regularly associated with excess morbidity and mortality,[89] and both influenza A and B can be associated with severe illness. During inter-pandemic years, influenza is characterized by a "U-shaped" epidemic curve, in which attack rates and medically attended illness rates are generally highest in infants and young children, whereas mortality is generally highest in the elderly. Young children are generally more susceptible to influenza infection than are adults, and they shed higher levels of virus for longer periods. Healthy children younger than 1 year of age are hospitalized for influenza at rates comparable to those of older children and adults with chronic high-risk conditions[90,91] and are special targets of prevention measures.

Excess morbidity and mortality are particularly high in those with underlying medical conditions, including chronic cardiovascular or pulmonary disease, chronic metabolic disease including diabetes mellitus, renal dysfunction, hemoglobinopathies, or immunodeficiency, including HIV. Recently, it has been recognized that individuals with neuromuscular conditions affecting the ability to clear respiratory secretions,[92] and persons with morbid obesity,[93] also are at high risk for influenza hospitalization. Women in all stages of pregnancy, and in the immediate postpartum period, also have increased rates of hospitalization, ICU admission, and deaths during influenza epidemics.[94,95]

Antigenic variation is the hallmark of the epidemiology of influenza, and occurs in two forms referred to as antigenic "drift" and antigenic "shift." Drift refers to the gradual accumulation of mutations, primarily in the hemagglutinin (HA) and neuraminidase (NA) proteins of the virus, that allow the virus to escape from antibody generated against previous strains. New, drifted strains generally appear every several years and tend to replace previous strains. Antigenic drift occurs in both influenza A and influenza B viruses. In addition, recent influenza B viruses have evolved into two antigenically distinct lineages termed the "Yamagata" and "Victoria" lineages,[96,97] which currently cocirculate.

Influenza A viruses exist as multiple antigenically distinct HA or NA subtypes. There are currently 17 recognized HA subtypes (H1–H17) and 9 recognized NA subtypes (N1–N9), although current seasonal viruses are restricted to the H1N1 and H3N2 subtypes. When one influenza A subtype is replaced by another, a phenomenon recognized as antigenic shift, the new virus encounters a population with little or no prior immunity. Worldwide epidemics of severe disease, referred to as pandemics, are usually the result.

Pandemics associated with antigenic shift have been noted multiple times in the twentieth and twenty-first centuries. In 1918 H1N1 viruses emerged and replaced previous H3N2 viruses, in 1957 H2N2 viruses replaced H1N1 viruses, and in 1968 H3N2 viruses replaced the H2N2 viruses. In 1977, an H1N1 virus antigenically similar to H1N1 viruses from 1950 emerged to cause disease primarily in those born after 1950 but did not replace previous H3N2 viruses. Finally, in 2009 a new H1N1 virus (the so-called pH1N1 virus) emerged that was antigenically similar to H1N1 viruses prior to 1947 and caused disease predominantly in young adults and children. Since then, both H3N2 and pH1N1 viruses have circulated in humans. Influenza A viruses are zoonotic in multiple animal species including migratory waterfowl and swine, and epidemiologic data strongly support the notion that new pandemic influenza A viruses arise from this reservoir (see below).

Pathogenesis The mechanisms responsible for transmission of influenza viruses from person to person have never been completely defined, and it is likely that both large particles (i.e., droplet) and small particles (aerosol) released from the airway during coughing and sneezing play a role. Once virus is deposited on the respiratory tract epithelium, it can attach to and penetrate columnar epithelial cells if not prevented from doing so by specific secretory antibody (IgA), by nonspecific mucoproteins to which virus may attach, or by the mechanical action of the mucociliary apparatus. The duration of the incubation period to the onset of illness and virus shedding varies from 18 to 72 h depending in part on the inoculum dose. Viral shedding in the respiratory tract is first detected just before the onset of illness (within 24 h), rapidly rises to a peak and remains elevated for 24 to 48 h, and then rapidly decreases to low titers. Usually, influenza virus is no longer detectable after 5 to 10 days of virus shedding. Both the duration and the level of virus shedding are typically longer in young children than in adults. In general, the course of the clinical illness correlates temporally with the pattern of virus shedding, and severity is correlated with the quantities of virus shed.

Bronchoscopy of individuals with typical, uncomplicated acute influenza has revealed diffuse inflammation of the larynx, trachea, and bronchi, with mucosal injection and edema. Histologic findings on autopsy of more severe cases show extensive necrotizing tracheobronchitis, with ulceration and sloughing of the bronchial mucosa, extensive hemorrhage, hyaline membrane formation, and a paucity of polymorphonuclear cell infiltration. Abnormalities of pulmonary function are frequently demonstrated in otherwise healthy, nonasthmatic young adults with uncomplicated (nonpneumonic) acute influenza. Demonstrated defects include diminished forced flow rates, increased total pulmonary resistance, and decreased density-dependent forced flow rates consistent with generalized increased resistance in airways less than 2 mm in diameter,[98] as well as increased responses to bronchoprovocation. In addition, abnormalities of carbon monoxide diffusing capacity and increases in the alveolar–arterial oxygen gradient have been seen. Of note, pulmonary function defects can persist for weeks after clinical recovery.

Diagnostic Tests Rapid viral diagnosis based on immunologic detection of viral antigen in respiratory secretions is widely used for influenza diagnosis. All these tests are designed to detect both influenza A and B, but only some of the tests differentiate between the two. Some of the tests that are minimally complex may be eligible for waivers that allow them to be used in the office setting. In general, sensitivities in adults and elderly patients tend to be lower than reported in young children, who tend to shed much larger quantities of virus in nasal secretions and therefore have much higher concentrations of antigen in their samples. Although all types of respiratory samples can be used in such tests, the sensitivity appears to be better with nasopharyngeal swabs and aspirates than with throat swabs or gargles.

Molecular diagnostic tests are also widely available for influenza diagnosis and are frequently coupled with detection of other respiratory viruses, especially RSV. Nasopharyngeal samples remain the most sensitive of samples, but it has been noted that in some patients with pneumonia, sputum samples have been positive when nasal samples were negative. As is the case for all diagnostic testing, specific influenza testing should be focused on those cases where a specific diagnosis will have implications for therapy or infection prevention.[99]

Treatment and Prevention Below are considered treatment options for influenza treatment, as well as recommendations for prevention.

Antiviral Therapy Available antiviral agents for influenza are summarized in Table 126-3. The currently most widely used antiviral agents for influenza are the neuraminidase inhibitors, selective inhibitors of the neuraminidase enzymes of both influenza A and B viruses. In cell culture, inhibition of neuraminidase function is predominantly manifested as inhibition of cell-to-cell spread of virus. Currently available neuraminidase inhibitors include orally administered oseltamivir, intravenously administered peramivir, and inhaled zanamivir. Results of clinical trials of these products have been very similar, with excellent safety profiles.

As a general principle, it is clear that early initiation of therapy is critical to the effectiveness of antiviral therapy of acute influenza. This general observation is consistent with the typical pattern of

TABLE 126-3 Antivirals Active Against Influenza

Drug	Dosage in Adults	Dosage in Children	Comments
Oseltamivir	75 mg PO bid for 5 days	≤15 kg: 30 mg twice daily >15–23 kg: 45 mg twice daily >23 kg: 60 mg twice daily >40 kg: 75 mg twice daily	• Controlled trials available in adults, elderly, and children • Approximately 1- to 2-day earlier resolution of symptoms, reduced otitis in children • Other effects demonstrated include earlier return to work, decreased diagnosis of bronchitis • Metaanalysis shows reduced hospitalization rates • Well tolerated, main adverse event is nausea
Zanamivir	10 mg via inhalation bid for 5 days	≥7 years: 10 mg via inhalation twice daily <7 years: Not recommended	• Similar safety and efficacy profile as oseltamivir, without nausea • Reports of exacerbations of reactive airways disease
Peramivir	600 mg IV once daily or, if severe, for up to 5–10 days	Infants ≥6 months and children: 12 mg/kg as a single IV dose; maximum dose: 600 mg/dose; can be used for up to 5–10 days	• For those who can't tolerate oral therapy
Baloxavir marboxil	<80 kg: 40 mg as a single dose within 48 h of onset of influenza symptoms (if >80 kg, dose is 80 mg)	Oral: 2 mg/kg once as a single dose; maximum dose: 40 mg/dose	• Emergence of resistance after a single dose raises concerns about the long-term utility of this drug as monotherapy
Amantadine	<65 years: 100 mg twice daily for 5 days	1–9 years: 5 mg/kg/d, not to exceed 150 mg/d in two divided doses 10–12 years: 100 mg twice daily	• High levels of resistance in current influenza A viruses; no longer used for treatment of influenza
Rimantadine	100 mg twice daily for 5 days	≤12 years: Not recommended	• High levels of resistance in current influenza A viruses; no longer used for treatment of influenza • Not approved for use in children

viral shedding in an immunologically primed individual in which the peak of virus shedding is in the first few days of illness and is rapidly controlled by the immune system. Therapy initiated beyond 48 h of symptoms does not appear to be useful in immunocompetent adults and children, and the greatest benefit is seen when therapy is begun within 12 or 24 h after the onset of symptoms. Relatively little controlled data are available related to the use of antivirals in immunocompromised individuals with influenza or in primary influenza infections, and it is unclear whether these same constraints would apply in these situations.

Metanalysis of results of these trials has also suggested that early treatment may reduce the frequency of influenza-related complications, with reductions in the use of antibacterials and in hospitalization.[100] However, pooled analyses of these studies of early therapy with zanamivir[101] and oseltamivir[100,102] demonstrated a significant reduction in the rate of influenza complication in treated individuals. The subsequent experience in the epidemic of pH1N1 virus has also suggested a beneficial effect of early therapy on complications. These include observations in hospitalized patients[103,104] and surveillance data suggesting that therapy as late as 5 days improved survival of hospitalized patients.[105] Surveillance data have also suggested that treated children had lower rates of complications.[106]

Resistant viruses have been detected in treated patients, most commonly in children. Beginning in 2006, spontaneously resistant H1N1 viruses carrying a specific neuraminidase mutation H274Y began to spread, and by 2008 all H1N1 viruses isolated in the United States were resistant. Of note, emergence and spread of resistant viruses was spontaneous and did not occur in the context of widespread uses of these drugs.[107] Fortunately, the emerging pandemic H1N1 virus, which subsequently replaced previous seasonal H1N1, has remained susceptible to neuraminidase inhibitors.[108]

Baloxavir marboxil is an orally administered inhibitor of the endonuclease subunit of the influenza polymerase trimer and has in vitro activity against both influenza A and B viruses. In a recent, large, randomized clinical trial, a single dose of baloxavir was as effective as a 5-day course of oseltamivir in alleviation of symptoms in H3N2-infected subjects and led to a more rapid decline in viral shedding.[109] However, viruses with reduced susceptibility to baloxavir due to specific mutations in the PA protein (I38T/M) were found frequently, and this was associated with a less rapid resolution of symptoms. Of note, such variants seemed to be most common in individuals with low baseline neutralizing antibody against the virus.[110] Since licensure, resistant viruses have been frequently detected in treated children.[111] Resistant viruses may be less fit in vitro, but human-to-human transmission of resistant variants has been identified in household contacts.[112] Baloxavir is currently approved in the United States for single-dose treatment of acute influenza of 48 h duration or less in individuals 12 years and older.

A third class of antiviral agent is the adamantanes (amantadine and rimantadine), whose mechanism of action is the result of inhibition of the viral M2 protein, an ion channel involved in viral uncoating. M2 inhibitors are active only against influenza A viruses. Although M2 inhibitors were highly effective drugs for prophylaxis and therapy of influenza A, resistant viruses were also generated quite readily in treated individuals.[113] Despite relatively infrequent use of these agents, resistant viruses emerged and spread worldwide in the 1990s, and almost all influenza A viruses are now completely resistant to M2 inhibitors[114] and they are no longer used for treatment of influenza. Along with experience with other antiviral agents, the rapid development of antiviral resistance remains an important consideration in the development of specific therapies.

Although the benefits of antiviral therapy were initially demonstrated as a shortening of illness duration in healthy adults with uncomplicated influenza, this is generally not considered the priority target group for antiviral therapy. Current recommendations

TABLE 126-4 Current Influenza Vaccines

	SD IIV-4	HD IIV-4	ccIIV4	rIV4	aIIV3	LAIV4
Formulation	Inactivated split virus or subunit	Inactivated split virus	Inactivated subunit	Recombinant HA protein	Inactivated subunit plus MF59 adjuvant	Live attenuated influenza viruses
Dose	15 μg/HA	60 μg/HA	15 μg/HA	45 μg/HA	15 μg/HA	10^7 FFU/virus
Number of HAs	4 (H1, H3, BV, BY)	4 (H1, H3, BV, BY)	4 (H1, H3, BV, BY)	4 (H1, H3, BV, BY)	3 (H1, H3, B*)	
Substrate	Eggs	Eggs	MDCK cells	Insect cells	Eggs	Eggs
Age indication	≥6 months	≥65 years	≥4 years	≥18 years	≥65 years	2–49 years

HA, hemagglutinin; BV, influenza B Victoria lineage; BY, influenza B Yamagata lineage; B, only one lineage is included.*

include the use of antivirals in individuals at risk for more severe influenza, or in individuals with severe disease or requiring hospitalization.[115] Treatment should be started as early as possible, but even delayed therapy can be of benefit in hospitalized patients. Given the totality of available data, oseltamivir is generally recommended as the first choice for seriously ill patients. For outpatients with suspected or confirmed uncomplicated influenza, oral oseltamivir, inhaled zanamivir, or oral baloxavir may all be used for treatment. In addition to those options, for hospitalized patients, intravenous peramivir would also be used.

Vaccines for Influenza Multiple formulations of influenza vaccines are currently available for prevention of influenza (Table 126-4). Influenza vaccines are designed to induce primarily serum antibody to the hemagglutinin and neuraminidase, although other mechanisms of protection also may be induced. Multiple formats of vaccines are available, including inactivated, chemically disrupted, and purified HA and NA antigens generated from viruses grown in embryonated hen's eggs or from viruses grown in cell culture, as well as purified HA recombinant protein expressed in insect cells using baculovirus technology. Virion-based vaccines are typically formulated to contain 15 μg of each HA in the final product, while the recombinant vaccine contains 45 μg, and a high-dose vaccine containing 60 μg of each HA is licensed for use in individuals 65 and older. The saponin adjuvant MF59 is included in one of the vaccines to improve the antibody response in older recipients. Current vaccines contain one example of influenza A (H1N1) and A (H3N2), based on the most current epidemiologic predictions of the likely circulating strains in the coming season, and may contain one example of influenza B or examples of both influenza B lineages. Current recommendations do not include a preference for any specific vaccine, although this may change as more data become available.

A live attenuated influenza vaccine is also available, designed to induce mucosal antibody in the respiratory tract, although specific correlates of protection have not been developed. This vaccine is generated by genetic reassortment between circulating wild-type strains and attenuated master donor viruses for both influenza A and B and is currently formulated as a quadrivalent preparation. The live vaccine is currently licensed for use in adults and children from 2 to 49 years of age.

Current recommendations for prevention of influenza in the United States[116] and several other countries call for a strategy of universal vaccination, in which vaccine is offered annually to the entire population. Efforts at vaccination should be especially targeted at persons who, for reasons of age or medical conditions, are at increased risk for developing complications, hospitalization, or death due to influenza, and contacts who may transmit infection to these high-risk individuals. Persons who may transmit to high-risk persons include family members, out-of-family caregivers, and importantly, health care providers.

Respiratory Syncytial Virus

Respiratory syncytial virus frequently causes detectably altered airway reactivity in adults, and on occasion, lower respiratory tract involvement becomes clinically manifest as pneumonia in otherwise healthy adults. RSV is being increasingly recognized as a cause of significant lower respiratory tract disease in the elderly.[117] It has been estimated that 2% to 4% of pneumonia deaths among the elderly in the United States may be due to RSV.[118]

In most series, RSV has been associated with the largest proportion of viral pneumonia in young children, particularly if accompanied by bronchiolitis. It should be noted in this regard that bronchiolitis and pneumonia represent a spectrum of lower respiratory tract involvement with RSV, frequently coexist, and are not clearly distinguishable. The most typical finding is diffuse interstitial pneumonitis (Fig. 126-1). Lobar or segmental consolidation are evident by CXR in about one-fourth of children with RSV lower respiratory tract disease.

RSV has been well recognized as a cause of pneumonia in recipients of bone marrow[119] and solid organ transplantation.[120] Nosocomial transmission of RSV in this setting has been well documented and may be the source of many infections in this susceptible population. The illness typically begins with nondescript upper respiratory symptoms that progress over several days to severe, life-threatening lower respiratory tract involvement. Mortality rates of 50% or higher are typical, particularly if disease occurs in the pre-engraftment period.

Parainfluenza Virus

The parainfluenza viruses are most typically associated with viral pneumonia in children, particularly serotype 3 (PIV3). However, occasionally these viruses may be associated with pneumonia in adults. Frequent contact with small children is probably a risk factor.

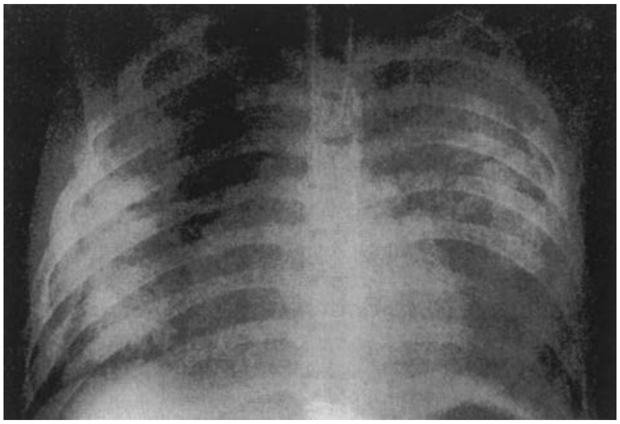

Figure 126-1 Premature infant at 3 months of age with respiratory syncytial virus pneumonia. *(Reproduced with permission from Duchin JS, Koster FT, Peters CJ, et al. Hantavirus pulmonary syndrome: a clinical description of 17 patients with a newly recognized disease. The Hantavirus Study Group. N Engl J Med. 1994;330(14):949–955.)*

Parainfluenza viruses have occasionally been reported as causes of pneumonia in adults and in the elderly.[121] Parainfluenza viruses have also been reported as an infrequent lower respiratory tract pathogen in both solid organ and bone marrow transplantation. PIV3 has been the most common serotype isolated, but all four serotypes have been implicated.

There are no licensed vaccines or antiviral agents for parainfluenza virus. DAS 181 is an inhaled sialidase linked to a respiratory epithelium–binding domain. The product can remove sialic acid from the epithelial cells of the respiratory tract, thereby inhibiting viruses that rely on such receptors. Clinical trials have not shown benefit in influenza, but there are reports of compassionate use of the drug to treat parainfluenza infections of the lower respiratory tract in lung transplant recipients.[122]

Adenovirus

Adenovirus was first recognized as a cause of viral pneumonia in military recruits and has since been recognized as a rare cause of pneumonia in civilian adults and children. Outbreaks in institutionalized populations occur. The clinical characteristics of adenovirus pneumonia are similar to those of other pneumonias, so that it is difficult to make an accurate etiologic diagnosis on the basis of clinical features. In fatal cases there has been extensive pulmonary damage, with death occurring 2 to 3 weeks into the illness. Intravascular coagulopathy has also been a late feature of some cases, and a septic shock picture has been described. Bacterial superinfection, particularly with *N. meningitidis*, may occur. Since 1996, a specific variant of adenovirus type 7 (Ad7d2) has been responsible for several civilian outbreaks and a large military outbreak. The appearance of new Ad 7 genotypes may herald a shift in the predominant strains with greater disease impact.[123] Recent reports have emphasized the emergence of a relatively rare adenovirus serotype 14 responsible for severe community acquired pneumonia in adults and children.[124]

Adenoviruses are frequently isolated from children with respiratory disease and are implicated in about 10% of childhood pneumonias. However, the true impact of adenoviruses as causes of pneumonia in this age group is difficult to assess because of the long and intermittent asymptomatic respiratory shedding of these viruses in children. Hilar adenopathy on CXR is somewhat more common with this form of pneumonia than other types.

Adenoviruses are significant causes of morbidity and mortality in immunocompromised patients, particularly after transplantation. In contrast to infection in normal hosts, infection in immunocompromised subjects tends to be disseminated, with isolation of virus from multiple body sites including lung, liver, gastrointestinal tract, and urine.[125] In addition, the spectrum of serotypes includes both those found in immunocompetent individuals as well a markedly increased frequency of isolation of higher-numbered serotypes found rarely in immunologically normal subjects.

Antiviral treatment of proven value for adenovirus infection is not available. Both the broad-spectrum antiviral agents ganciclovir and cidofovir are active in vitro. Cidofovir has also been used for preemptive therapy in high-risk immunocompromised patients.[126] Brincidofovir is an oral formulation of cidofovir that also is being evaluated as a potential therapeutic.[127]

Measles

Pneumonia is the most frequent serious complication of measles. The prodrome of typical measles lasts 2 to 8 d and is characterized by fever, malaise, anorexia, cough, coryza, and conjunctivitis. Koplik spots, which are erythematous macular lesions with central white-yellow or gray puncta, appear on the buccal or labial mucous membranes toward the end of the prodromal period. The maculopapular, erythematous eruption begins about the face and neck and progresses to involve the upper body, trunk, and extremities. The rash typically disappears after 5 to 6 d in the order in which it appeared. Defervescence and symptom improvement occur several days after the appearance of the rash, although persistent cough is common. Leukopenia is common during the prodromal and early exanthematous stages of measles. Pronounced leukopenia (less than 2000 cells/mm^3) is associated with a poor prognosis. The development of neutrophilic leukocytosis suggests the possibility of bacterial superinfection or other complications.

Measles can be complicated by clinically severe pneumonitis in a small percentage of healthy adults, and bacterial superinfection is common.[128] In patients with altered cell-mediated immune function, and rarely in apparently normal persons, infection by wild measles virus can cause a lethal giant cell pneumonia with or, in about 30% of patients, without rash.[129] Measles has largely been controlled by vaccination, but outbreaks continue to occur.

Measles giant cell pneumonia is a severe, usually fatal form of pneumonia associated with measles infection in immunosuppressed individuals. Most cases have occurred in those with hematologic or other malignancies, or individuals with AIDS. Recent outbreaks of measles worldwide, coupled with the increasing incidence of HIV infection, have increased the frequency and impact of measles giant cell pneumonia. Giant cell pneumonia also occurs in significantly malnourished individuals. Multinuclear giant cells with intranuclear inclusions are seen and may be demonstrable in fluid obtained by bronchoalveolar lavage. An important feature of measles pneumonia in immunocompromised hosts is that many patients present without rash or other typical manifestations of measles, and a high index of suspicion must be maintained. It has been speculated that such hosts may not mount the cellular immune responses involved in the pathogenesis of rash in immunologically intact individuals. In hospitalized patients, mortality rates are approximately 70% in oncology patients and 40% in HIV-infected patients.[130]

Varicella Zoster Virus

Viral pneumonia is the major complication of varicella zoster virus (VZV) in normal adults, in whom it occurs with an estimated 25-fold higher frequency than in children.[131] Smoking is a significant risk factor. Pneumonia associated with varicella is usually apparent 1 to 6 d after the onset of rash. Symptoms include cough, dyspnea, pleuritic chest pain, and hemoptysis. Physical findings other than fever and tachypnea are often modest. The intensity of the rash does not necessarily correlate with the severity of pneumonia. The characteristic radiographic pattern is that of diffuse nodular (1–10 mm) infiltrates, which may resolve with miliary calcific densities. Hilar adenopathy, pleural effusions, and peribronchial infiltrates are frequently present. Pulmonary infarction may complicate the clinical picture. Pulmonary function studies have found normal spirometric values but decreased carbon monoxide diffusing capacity, which may persist for months. One prospective radiologic study of military recruits with varicella found abnormalities in approximately one in six patients, but only one-fourth of those with radiographic changes had cough, and none experienced severe disease.[132]

VZV is an important problem in individuals with hematologic malignancies and others with iatrogenic immunosuppression, with the greatest risk seen in organ transplantation. Prolonged fever and/or recurrent crops of lesions are predictors of visceral dissemination, and pneumonia is generally seen in this setting. Pulmonary manifestations may include pleuritic chest pain due to vesicular lesions of the pleura, and, as is also true in normal hosts, the CXR may demonstrate nodular lesions.

Cytomegalovirus

CMV is frequently detected in respiratory samples from immunosuppressed individuals, particularly transplant recipients, or individuals infected with the human immunodeficiency virus

(HIV) with severe pneumonia. The highest risk in the transplant population is 1 to 3 months post-transplantation, with the peak incidence at 8 weeks post-transplant. Diffuse interstitial pneumonitis is the most frequent presentation, but multiple other CXR presentations have been reported, including nodular infiltrates resembling *Nocardia*. Multiple associated findings are present in severe infection and reflect the disseminated nature of the infection; the presence of neutropenia, abnormalities of liver function tests, and mucosal ulcerations may be clinical clues to the diagnosis.

Characteristically, patients with CMV pneumonia have sustained fever, nonproductive cough, and dyspnea. Rales and tachypnea are often present, and marked hypoxemia is an indicator of life-threatening infection. Pneumonitis may be accompanied by mild neutropenia, thrombocytopenia, and elevated liver enzymes, which may be helpful in differential diagnosis. Chest radiographic changes are usually bilateral, with diffuse or focal haziness involving the mid and lower lung fields. Both miliary and interstitial radiographic patterns have been described. Often the perihilar distribution of the infiltrate is suggestive of pulmonary edema. Common CT scan findings include small nodules, consolidation, and ground-glass attenuation.

Cytomegalovirus pneumonia is a problem predominantly in individuals with compromised immune systems, particularly after transplantation, and represents a systemic infection that involves the lung secondarily. There are several features of this disease in the transplant setting that suggest that both host and viral factors interact in pathogenesis.[133] CMV pathogenicity is enhanced in transplant recipients and frequently occurs at the site of the transplanted organ. The risk of CMV pneumonitis is highest in individuals at the highest risk for graft-versus-host disease. In transplant patients, the detection of CMV by itself does not necessarily indicate end-organ involvement. For transplant patients, it has been suggested that higher levels of CMV in pulmonary specimens may be more indicative of CMV pneumonia.[134] Assessing the role of CMV in an immunosuppressed patient can be challenging, since in HIV patients CMV is frequently detected along with other pathogens, such as *Pneumocystis*, and its role in the pneumonia can be unclear.[135]

The pathogenesis of CMV pneumonia is partly related to viral replication but is also thought to have an immunopathologic basis.[136] The development of CMV pneumonitis reflects a complex interaction between viral infection and graft-versus-host disease, particularly in marrow transplant recipients. Two patterns of histopathology have been described in the lung tissue of bone marrow transplant patients with serious pneumonia. One is a miliary pattern, with multiple focal lesions showing extensive cytomegaly with localized necrobiosis, alveolar hemorrhage, fibrin deposition, and neutrophilic response. The other is of interstitial character, with alveolar-cell hyperplasia, interstitial edema, lymphoid infiltration, and diffusely distributed cytomegalic cells.

Guidelines for reducing the risk of CMV disease in stem cell and solid organ transplant recipients have been published.[137] Transplant candidates should be screened for evidence of CMV immunity, and CMV-seronegative recipients of allogeneic stem cell transplants from CMV-seronegative donors should receive only leukocyte-reduced or CMV-seronegative RBCs and/or leukocyte-reduced platelets. In mismatched solid organ transplant recipients (donor+/recipient−), posttransplant prophylaxis with valganciclovir significantly reduces the risk of CMV disease, although late-onset disease still occurs.[137] Another strategy is preemptive therapy with valganciclovir or another anti-CMV agent when weekly screening detects early infection.

Herpes Simplex Virus

HSV infection of the lower airway may occur either as the result of direct extension of infection from the tracheobronchial tree to the lung or as the result of hematogenous dissemination of virus from mucocutaneous lesions of the upper airway or genitourinary tract. Dyspnea, cough, and hypoxemia are usually seen, but the clinical features of the pneumonia generally do not permit an etiologic diagnosis to be made antemortem. Focal or multifocal infiltrates are thought to indicate direct extension, whereas diffuse bilateral infiltrates may occur due to presumed hematogenous dissemination of virus.[138] CT scan findings include multifocal segmental and subsegmental ground-glass opacities[139] but are not distinctive. In one study, more than one-half of the patients had concomitant pulmonary infection with other microorganisms, including bacteria, *Candida* and *Aspergillus* species, and cytomegalovirus.

Isolation of HSV from lower respiratory tract secretions is common in mechanically ventilated patients and may be associated with a poor outcome.[140] However, clinical outcomes of HSV-positive patients are not significantly different from those of HSV negative patients,[141] and it can be difficult to determine whether HSV is playing a specific role in the lower respiratory tract disease.

Acyclovir is active in vitro against herpes simplex virus types 1 and 2; it is approximately tenfold less active against VZV and does not have clinically useful activity against cytomegalovirus or Epstein-Barr virus. Although controlled clinical trials of this drug in herpes simplex pneumonia have not been conducted, the drug has proven clinical efficacy in other herpesvirus infections and would be indicated in any serious HSV lower respiratory tract infection. Acyclovir is also effective in the therapy of varicella, and intravenous acyclovir has been effective when initiated early in the course of varicella pneumonia. Viruses resistant to acyclovir have been isolated from treated patients, albeit rarely, and may be susceptible to foscarnet.

Emerging Viruses

The potential for novel viruses that normally infect animal species to be transmitted to humans and spread rapidly represents a potential public health threat of increasing concern. There have been multiple examples of this phenomenon in recent years, and developing strategies to rapidly and effectively respond to such emerging threats is a critical public health goal. Examples of the emergence of highly lethal viruses that originated from animal species are briefly described below.

Novel Coronaviruses In recent years, three previously undescribed coronaviruses have emerged to cause severe lower respiratory tract illness in humans. The first epidemic to be recognized was referred to as severe acute respiratory distress syndrome, or SARS. Epidemics of SARS were initially recognized in southern China in 2003 and subsequently spread throughout the world. The etiologic agent was identified as a novel coronavirus, designated the human SARS coronavirus[142] and currently referred to as SARS-CoV. After an intense epidemic associated with 8096 cases and 774 deaths, the disease disappeared, largely due to aggressive infection control practices. Virus shedding was at its peak at the time that illness was most severe,[143] and the preponderance of transmission occurred in the hospital setting. Ultimately, this allowed the pandemic to be controlled largely by isolation and other infection prevention procedures. Then in 2012, cases of a similar severe respiratory illness were recognized in a variety of Middle Eastern countries. This illness, now referred to as the Middle Eastern respiratory syndrome, has been named MERS-CoV. In contrast to SARS, little if any sustained person-to-person transmission has been observed to date with MERS-CoV, although obviously there is concern that the virus could gain this ability at some later time.

Because of the far greater number of cases of SARS, much more is known about the presentation and clinical features of pneumonia due to this virus. The most common symptoms on presentation were fever, chills and/or rigors, and myalgias. Cough and dyspnea were the predominant respiratory symptoms but were not always present initially. Upper respiratory symptoms, such as rhinorrhea or sore throat, were infrequent. In addition, about one-third of patients had diarrhea at some point in the clinical course. Respiratory disease was progressive and became more severe over 4 to 7 d, leading to significant hypoxemia. About 20% of patients required respiratory support. The overall case fatality rate was about 10% but was much higher in older adults. In contrast, children appeared to have milder disease.[144] To date, MERS has had a similar presentation to SARS, although gastrointestinal symptoms may be more prominent.[145] Common findings on CT included ground-glass opacification and interlobular septal and intralobular interstitial thickening. Pulmonary fibrosis developed in some patients after recovery from the acute illness.[146]

Around November of 2019, a new antigenically distinct coronavirus emerged and spread rapidly around the world. The virus was subsequently named the severe acute respiratory syndrome coronavirus type 2, or SARS-CoV-2, and the resulting disease syndrome referred to as coronavirus infectious disease 2019, or COVID-19. Unlike the previous SARS and MERS coronaviruses, efficient person-to-person transmission of SARS-CoV-2 occurs prior to the development of severe disease, substantially impacting control of the spread of the virus using traditional quarantine approaches that had ultimately proved successful for control of SARS. Within just a few months, the virus had spread worldwide, with devastating public health impact.

All three of these viruses were genetically similar to coronaviruses found in bats, which may represent the population from which the viruses were ultimately derived. There is substantial interest in the ability of bats to harbor diverse varieties of viruses, including hantaviruses, Nipah viruses, influenza viruses, and others. In part this may be related to the very large and diverse species of bats, but it may also be related to unique properties of the bat immune system that allow viral infection without the development of illness.[147] However, there are significant genetic differences between closely related bat viruses and subsequent human isolates, suggesting a role for intermediate mammalian hosts. In the case of SARS, this was suggested to possibly be the palm civet, while for MERS camels clearly play an important role. The specific intermediate host for SARS-CoV-2 remains to be determined.

Clinical Features of COVID-19 A wide variety of presenting clinical symptoms have been described for COVID-19. Frequently, the illness begins with upper respiratory symptoms such as runny nose and sore throat and progresses over several days to fever, malaise, cough, and gradually increasing dyspnea and hypoxia. In initial reports of disease in Wuhan, the most common symptoms were fever, fatigue, and dry cough. Other associated signs and symptoms include loss of sense of smell or taste, diarrhea or other gastrointestinal symptoms, and development of discoloration of the fingers and toes (chilblains). Typical CT findings include bilateral patchy shadows or ground-glass opacity in the lungs typical of viral pneumonia.[148,149] Other common findings include consolidation, pleural thickening, interlobular septal thickening, and air bronchograms.[150] Respiratory failure is usually the immediate cause of death in fatal cases. Although the denominator of total cases can be difficult to ascertain, it is estimated that approximately 10% of cases require hospitalization, with a case fatality rate on the order of 1%.

A variety of serious and severe complications of COVID-19 have been described. These include pulmonary fibrosis; blood coagulation complications such as deep-vein thrombosis, pulmonary embolism, and cerebrovascular accidents; neurologic complications including transverse myelitis and encephalitis; and cardiac complications including development of myocarditis and heart failure. These effects may persist well beyond the resolution of the acute illness. Recovery from COVID-19 may also be complicated by the persistence of a variety of poorly understood effects, such as long-term difficulties with mentation (referred to as "brain fog"), chronic fatigue, and elements of posttraumatic stress disorder. The specific pathogenesis and appropriate treatment of such "long-haul" effects are unknown at this time.

Several features have been identified as risk factors for severe disease and death. These include age, with older subjects at much higher risk, and a number of medical conditions, such as obesity, diabetes, hypertension, cardiovascular disease, chronic lung disease, chronic kidney disease, and immunosuppressive illnesses. However, a substantial number of hospitalizations have occurred in young, otherwise healthy individuals as well. Rates of symptomatic disease appear to be substantially lower in young children, for unclear reasons. However, a multisystem inflammatory syndrome in children (MIS-C), resembling Kawasaki disease, has been associated with COVID-19. There is no demographic group that is not affected by the COVID-19 pandemic.

Epidemiology of COVID-19 Infection is associated with rapid viral replication, and titers of nasopharyngeal virus are typically highest early in the course of illness, facilitating the likelihood of transmission before severe illness is recognized. Transmission of virus from person to person can occur by direct contact, droplet spread, and aerosol, although the relative contribution of each mode of transmission is unclear. As a result, nonpharmaceutical control measures have included personal hygiene, social distancing, use of masks and personal protective equipment, avoiding indoor gatherings, and improving air flow in indoor spaces. Observational studies have suggested that each of these measures has reduced the rate of transmission.

Factors impacting transmission in the community are poorly understood. As the pandemic virus was introduced into various countries, the numbers of detected cases expanded rapidly, with estimates of initial reproductive number (R0) of 2 to 3 and serial interval of 4 to 7 days. Increases in hospitalizations and mortality then occurred approximately 2 to 3 weeks later. In most outbreaks, the rates of new cases slowly declined as various nonpharmaceutical control measures were put in place, schools were closed, and warmer weather encouraged more outdoor as opposed to indoor activities. It is possible that environmental conditions such as temperature and relative humidity also could impact transmission. Although virus can be detected on environmental surfaces, evidence favors predominantly respiratory transmission. Infectiousness peaks prior to symptom onset.[151]

Many communities then experienced second waves of infection occurring in the late fall and winter seasons. In part, some of these second waves were associated with relaxing of containment measures. In general, most of these surges took place in populations that did not have high enough background of previous exposure to generate significant population immunity. However, mutations in the viral stalk protein that impact binding to the ACE2 receptor, and that also effect the binding of neutralizing antibody, also have occurred and in some cases resulted in second waves in populations that had already experienced very high incidence rates. Emerging data suggest that these mutant viruses, or variants, may have increased transmissibility and may be associated with increased severity of illness and 20% to 60% increases in the case fatality rate. Antibody generated by infection or vaccination may be significantly less effective at neutralizing some variants, and continued evolution of variants could require strategies for periodic vaccination with updated vaccine components (see below), similar to the strategy used for seasonal influenza.

Pathogenesis of COVID-19 Infection is thought to primarily begin in the respiratory tract and progress to the lower respiratory tract over several days. Virus shedding can be detected prior to the onset of symptoms, and infection in healthy young adults may be largely asymptomatic.[152] As the disease progresses, it is associated with increasing hypoxia and respiratory distress, associated with increases in IL-6 and other inflammatory mediators, referred to as "cytokine storm."[153] Higher concentrations of IL-6 and D-dimer were independently associated with in-hospital mortality.[154] Disease is frequently associated with hypercoagulability with both microangiopathy and local thrombus formation, as well as a systemic coagulation defect that leads to large vessel thrombosis and major thromboembolic complications, including pulmonary embolism in critically ill hospitalized patients.[155]

Treatment and Prevention of COVID Developing effective therapies for COVID-19 that could speed recovery, reduce hospitalization rates, or within hospitalizations reduce ICU admissions and deaths, are a critical public health need. Current recommendations for treatment of COVID-19 are summarized in the IDSA guidelines.[156]

Several strategies have been pursued in this regard. The first has been the well-established approach of developing direct acting antiviral agents that inhibit the replication of the virus. A second approach has been to develop host-directed therapies designed to reduce the inflammatory response that appears to play an important role in the pathogenesis of disease. Because of the urgency of the situation, emphasis has been placed, where possible, on repurposing already existing products and evaluating their potential effectiveness for COVID. A third approach has been the administration of monoclonal antibodies, or antibody cocktails that neutralize virus and speed clearance.

A variety of potentially direct-acting antiviral agents have been evaluated for the treatment of COVID-19, and many studies are still ongoing. Of these agents, remdesivir, an inhibitor of the viral RNA dependent polymerase, has been shown to be beneficial in randomized trials. These studies have demonstrated reduced duration of illness in hospitalized patients.[157] In patients with severe COVID-19 not requiring mechanical ventilation, there were no differences between patients treated with a 5-day course compared to a 10-day course of remdesivir.[158] In another study,[159] hospitalized subjects randomized to 5 days, but not 10 days, of remdesivir had clinical improvement, although significance was unclear.

Other repurposed drugs with potential direct antiviral effects, including hydroxychloroquine and lopinavir, have had little or no effect on hospitalized patients with COVID-19, as indicated by overall mortality, initiation of ventilation, and duration of hospital stay.[160] Generally, studies have not shown benefit of hydroxychloroquine in treatment of hospitalized patients[161,162] or in prevention of disease when administered to exposed patients.[163] More recently, nirmatrelvir/ritonavir (Paxlovid) and molnupiravir have been recommended for nonhospitalized patients at high risk for severe disease (see CDC guidelines at CDC.gov).

Because severe COVID-19 is associated with a prominent inflammatory response and elevated proinflammatory cytokines, there has been considerable interest in repurposing anti-inflammatory agents, many of which are used to treat conditions such as rheumatoid arthritis, for the treatment of severe COVID disease. The most success has been seen with steroids. In patients hospitalized with COVID-19 who require oxygen or mechanical ventilation, the use of dexamethasone has been shown to result in lower 28-day mortality[164] and an increase in the number of ventilator-free days.[165] Severe COVID is also associated with high levels of the proinflammatory cytokine IL-6, but the results of therapy directed at this have been mixed. In hospitalized patients with COVID-19 pneumonia who were not receiving mechanical ventilation, tocilizumab (anti-IL6 receptor antibody) reduced the likelihood of progression to mechanical ventilation or death, but it did not improve survival.[166] Other studies have not shown benefit in treatment of moderate to severe COVID-19 pneumonia[166–169] and might be associated with increased mortality.[170] The Janus kinase inhibitor baricitinib, currently approved for treatment of RA, has been shown to be of benefit when added to remdesivir[171] and is recommended for use in patients who cannot tolerate corticosteroids or have contraindications.

A third approach has been to develop monoclonal antibodies against the spike protein to neutralize CoV-2 and use these in a therapeutic or prophylactic strategy.[172] The utility of prophylactic antibody is limited by the need for intravenous administration and expense. However, a number of monoclonal antibodies or combinations of monoclonal antibodies have been shown to be effective in preventing progression of disease.[173,174] To be effective, monoclonal antibodies should be used relatively early in the course of illness, that is, for treatment of mild to moderate disease in patients who are at risk of progressing to severe or critical disease. Convalescent plasma was not beneficial in hospitalized patients with severe pneumonia.[175]

Vaccines have been developed and deployed. In general, these approaches have been focused on generation of immunity to the spike protein, with an emphasis of generation of neutralizing antibody responses, although other functional antibody and T cell responses also may play a role in protection. Both messenger RNA (mRNA) and adenovirus vector delivery of S antigen have been used internationally, and other platforms including protein subunit and inactivated virion approaches are in development. The ultimate strategies for using such vaccines and best use of future booster doses are currently unknown.

Human Infections with Animal Influenza A Viruses Humans are susceptible to infections with influenza A viruses resident in a variety of animal species, such as swine, horses, and migratory waterfowl. The 2009 pandemic of H1N1, which originated in swine and was due to a virus with a complex genetic makeup of gene segments from human, avian, and swine influenza viruses, is the most recent example of how pandemic influenza arises from animal sources. For this reason, there has been substantial effort put into surveillance for influenza at the animal–human interface, and several small outbreaks of severe disease in humans resulting from transmission of viruses from avian sources have been recognized. The most severe cases have been due to viruses of the H5 or H7 HA subtype, but neither of these viruses has exhibited sustained human-to-human transmission to date.

The available data regarding the signs and symptoms of H5N1 infection are mostly from hospitalized patients.[176,177] Most patients present with the nonspecific complaints of cough and shortness of breath. In many patients, there is a progression of symptoms leading to respiratory failure requiring ventilation and other supportive measures. Atypical symptoms such as nausea, vomiting, encephalopathy, and bleeding gums and nose have been reported. Watery diarrhea may be present prior to the onset of respiratory symptoms. The majority of patients have an abnormal chest x-ray with diffuse and multifocal or patchy infiltration, but pleural effusions are rare.

Aberrant cytokine responses also have been implicated in the pathogenesis of H5N1 disease. Autopsy findings in humans have revealed changes of a reactive hemophagocytic syndrome, ARDS, and multiorgan failure, findings typically associated with production of high levels of cytokines like TNF-α and interferons.

H7 viruses have also caused large outbreaks in humans. In the Netherlands, an outbreak of H7N7 infection associated with a major epidemic in domestic poultry caused numerous human cases.[178,179] Most of these consisted of mild respiratory disease with conjunctivitis, but there was one death from pneumonia. Multiple outbreaks of human H7N9[180] infection have been reported over several years in China. In contrast to previous reports of H7 disease in humans, these outbreaks have been associated with significant lower respiratory tract disease and a mortality rate of approximately 30%. The majority of severe cases have been seen in older adults, many of whom had comorbid conditions.[180,181] It has been suggested that individuals born after 1968, whose first influenza exposure was likely due to H3N2 viruses, might be relatively resistant to H7 viruses because of some shared antigenicity between H3 and H7 viruses.[182] While these outbreaks have not spread widely and sustained person-to-person transmission has not been observed, human infections with novel avian viruses continue to pose a potential pandemic threat.

Hantavirus Pulmonary Syndrome Hantavirus pulmonary syndrome (HPS) was first recognized in the United States in the southwest in 1993 and was discovered to represent transmission from an animal reservoir, the deer mouse, to humans via contaminated rodent feces.[183] Since that time, a variety of hantavirus species have been recognized, and the disease has been diagnosed in both North and South America. Although person-to-person transmission has not been noted in the Northern Hemisphere, the Andes hantavirus has demonstrated such transmission in Argentina and elsewhere.[184]

Clinical features of the Hantavirus pulmonary syndrome (HPS) include onset of severe pulmonary dysfunction after a 2- to 3-day prodrome of nonspecific influenza-like symptoms of fever, myalgias, cough, gastrointestinal symptoms, and headache.[183] Laboratory abnormalities included leukocytosis, increased hematocrit due to hemoconcentration, and thrombocytopenia with coagulopathy.[185] However, clinical bleeding is unusual, in contrast to other systemic Hantavirus syndromes. Moderately elevated levels of serum lactate dehydrogenase and aspartate aminotransferase are typically seen. A variety of radiographic abnormalities have been described. Radiographic findings that may help to distinguish HPS from ARDS include early, prominent interstitial edema and nonperipheral distribution of initial airspace disease.[186]

Presentation of HPS begins with a prodrome of fever, chills, and myalgias, occasionally accompanied by abdominal discomfort and gastrointestinal symptoms, and generalized malaise. Upper respiratory symptoms are usually absent. After a variable period of several days, the patient presents with mild, nonproductive cough and progressive dyspnea resulting from leakage of high-protein edema fluid into the alveoli. On physical exam patients are febrile, with tachypnea and tachycardia with mild hypotension. Examination of the chest may reveal rales but is otherwise unremarkable.

Laboratory studies generally reveal hemoconcentration, mild thrombocytopenia, and mildly elevated lung function tests (LFTs). The triad of thrombocytopenia, left shift with circulating myeloblasts, and circulating immunoblasts is highly suggestive of HPS.[185] Multivariate analysis has identified dizziness, nausea, and the absence of cough as clinical symptoms predictive of HPS, as well as thrombocytopenia, elevated hematocrit, and decreased serum bicarbonate as features that help distinguish HPS from other causes of acute respiratory distress such as pneumococcal pneumonia and influenza.[187] Mild renal abnormalities may be detected, but unlike in hemorrhagic fever with renal syndrome (HFRS), do not progress to renal failure.

Chest radiograph typically shows both interstitial and alveolar infiltrates and resemble noncardiogenic pulmonary edema (Fig. 126-2). Pleural effusions are present in most cases. Early in the course of HPS these effusions are transudative, while later they develop higher fluid protein content and in severe cases have the protein characteristics of plasma. Cardiopulmonary manifestations in severe cases include a shock state with low cardiac index, low stroke volume index, and high systemic vascular resistance. Typically, the pulmonary artery wedge pressure is normal or low. Progression is associated with worsening cardiac dysfunction and development of lactic acidosis. The case-fatality rate averages approximately 30% to 40%. In those patients who survive, recovery is usually complete, but some patients have manifested long-term pulmonary dysfunction. The syndrome in children and adolescents is similar to that in adults.

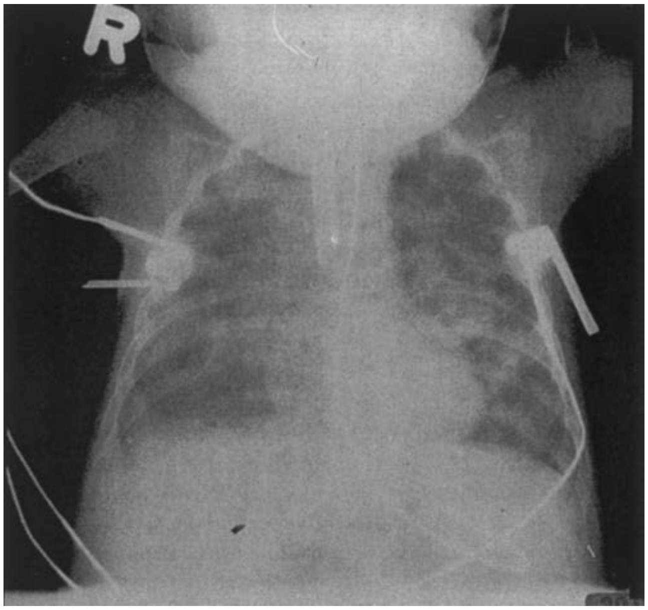

Figure 126-2 Chest radiograph showing diffuse interstitial and alveolar infiltrates in a patient with Hantavirus infection. *(Reproduced with permission from Dr. Janet Englund, Baylor College of Medicine.)*

SUMMARY

Lower respiratory tract viral infections pose an enormous public health burden on both adults and children worldwide. The clinical manifestations, pathogenesis, and laboratory abnormalities of these illnesses are quite variable, and with few exceptions are not specific enough by themselves for etiologic diagnosis. In addition, there is a very wide spectrum of viruses that cause human respiratory illness, with highly variable biology, mutable genomes, and diversity of antigenic characteristics. This wide range of pathogens and highly variable immunology poses substantial challenges to the development of specific medical countermeasures such as antiviral agents and vaccines.

An additional concern is the potential for transmission of previously unknown viral zoonotic pathogens from animals to humans, where they have the potential to spread rapidly and cause catastrophic epidemics and/or worldwide pandemics. There are multiple recent examples of such events, including hantavirus, avian and swine influenza A viruses, and novel coronaviruses. As contacts between animals and humans intensify as a result of population growth and possibly climate change, the potential for transmission of new pathogens will continue to increase.

Public health preparation and response to these events will require continued surveillance in both human and animal populations, international cooperation, and the development of countermeasures that can be very rapidly developed and deployed in response to a pandemic event. Better understanding of the pathogenesis and immunology of viral infection and best strategies for control will ultimately provide pathways forward for improved measures for both pandemic and seasonal respiratory viruses.

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CHAPTER 127

Aspiration, Empyema, Lung Abscesses, and Anaerobic Infections

Kyle B. Enfield
Costi D. Sifri

OVERVIEW

Aspiration pneumonia, lung abscess, and necrotic lung are parenchymal lung diseases. *Aspiration pneumonia* refers to the pulmonary consequences that follow abnormal entry of fluid, particulate substances, or endogenous secretions from the upper airways or gastric contents into the lower airways (Chapter 69). Aspiration pneumonia develops following the disruption of a series of formidable host defense mechanisms that normally protect the lower airways. These defenses include, among others: glottic closure via the cricopharyngeus muscle, the cough reflex, and ciliary clearance of the airway. The material aspirated must generate an inflammatory response or cause obstruction. The nature of the pneumonia that develops depends on the inoculum and the host response. Historically, anaerobic bacteria were considered the most common pathogens in this setting, reflecting both pathogenic potential and importance in the normal flora of the upper airways; however, recent data have challenged this view. Risk factors for aspiration may be transient (anesthesia, intoxication) or persistent (e.g., neuromuscular disorders, achalasia). Recurrent aspiration risk depends on recognition and resolution of the inciting defect.[1,2]

Lung abscesses reflect infection with an unusual microbial burden (e.g., acute aspiration), a failure in microbial clearance mechanisms (e.g., bronchial obstruction), or both, leading to necrosis of pulmonary tissue and formation of cavities containing necrotic debris or fluid (Fig. 127-1). The appearance of multiple smaller (<2 cm) abscesses in pulmonary tissue is occasionally referred to as necrotizing pneumonia or lung gangrene. Both lung abscess and necrotizing pneumonia are manifestations of the same pathologic processes, and the distinction is arbitrary.[3]

Empyema refers to a purulent collection in any body site but is commonly used to indicate a pleural space infection.[4] Empyema is typically associated with underlying pulmonary parenchymal infection but may also be associated with blood-borne infection, thoracic surgery, trauma, abdominal infection, or neoplasm.[3] Failure to recognize and treat either empyema or lung abscess is associated with a poor clinical outcome.[5,6] In the preantibiotic era, lung abscess was associated with mortality approaching 40%.[7] However, controversy exists over the best approaches to both processes in terms of antimicrobial selection and physical drainage.[5,6]

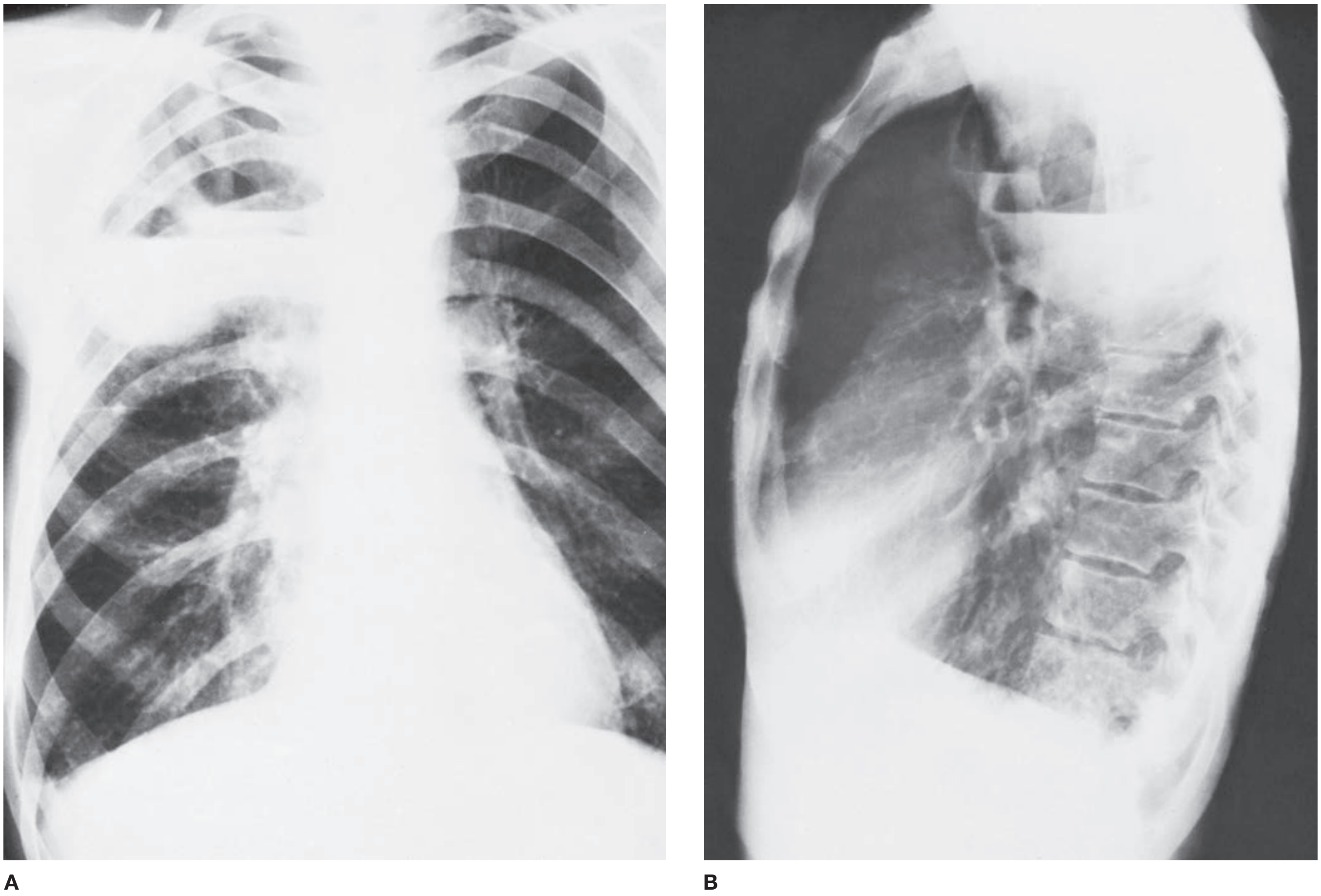

Figure 127-1 **A.** Anaerobic pneumonia with abscess formation in a 48-year-old alcoholic man. The abscesses are located in the posterior segment of right upper lobe, a dependent segment that is seen best on lateral view (**B**).

HISTORY

In 1893, Veillon published a review of "fetid infections," first marking the published record of infections due to anaerobic pathogens. However, anaerobes are now largely forgotten potential pathogens in pulmonary infection, including in both community- and health-care-associated pneumonia.[1] The clinical and bacteriologic features of anaerobic infections of the lung have been documented by extensive studies during two periods of investigation.[1] The first was at the turn of the century when anaerobic bacteria were initially reported as significant causes of empyema. This early work continued through the late 1920s when David Smith conducted classic studies on the pathogenesis of lung abscess. At that time, approximately one-third of patients with lung abscess died. Smith noted that the bacteria in the walls of the abscess at autopsy resembled the bacteria found in the gingival crevice, leading him to conclude that aspiration was the central mechanism in pathogenesis. He subsequently supported this hypothesis by inoculating the trachea of experimental animals with gingival crevice material to reproduce the sequence of pneumonitis events, followed by lung abscess formation in 7 to 10 days.[8,9] Bacteriologic studies of the inoculum showed that four bacterial species were critical, and all were anaerobic bacteria: a fusiform bacterium now recognized as *Fusobacterium nucleatum*, *Prevotella melaninogenica* (formerly *Bacteroides melaninogenicus*), *Peptostreptococcus*, and an anaerobic spirochete. This study is one of the first demonstrations of bacterial synergy, defined as the demonstration that two or more bacterial species are required to produce a pathologic process that could not be reproduced by any single component of the inoculum.[9]

In the first two or three decades of the antibiotic era, the role of anaerobic bacteria in this and other pathologic processes was largely ignored. Patients with lung abscesses often had putrid sputum and no identifiable pathogen; these infections were frequently referred to as nonspecific lung abscesses. Although the microbial cause was unknown, it was well established that these patients almost invariably responded to penicillin treatment. The role of anaerobes in empyema was also largely ignored, which can be ascribed to the paucity of laboratories capable of cultivating oxygen-sensitive bacteria at the time. Studies of anaerobic bacteria were spawned by the ability to culture anaerobes in clinical laboratories with the introduction of anaerobic gas–generating culture jars, the description of the taxonomy of these organisms, and the availability of new antimicrobial agents (clindamycin, metronidazole, cefoxitin) for the therapy. The introduction and widespread use of transtracheal aspiration (TTA) in the late 1960s made it realistic to collect uncontaminated specimens from the lower airways used for anaerobic cultures. TTAs are seldom performed today, so anaerobic bacteria are rarely established as pulmonary pathogens. However, these organisms are important in patients with aspiration pneumonia, necrotizing pneumonia, lung abscess, and empyema, and are often suspected based on the etiologic route of infection (e.g., oropharyngeal flora).[1]

PATHOPHYSIOLOGY OF ASPIRATION, EMPYEMA, AND LUNG ABSCESS

The bacteria implicated in anaerobic lung infections represent the normal flora of the oral cavity—primarily the gingival crevice, where anaerobic bacteria are found in concentrations that approach the geometric limits with which bacteria occupy space: 10^{12}/g.[10] Compromised consciousness or dysphagia is the most frequently predisposing risk factor for clinically significant aspiration. Common conditions associated with clinically significant aspiration include alcoholism, general anesthesia, seizure disorder, drug abuse, esophageal lesions, hepatic failure with a decreased level of consciousness, and neurologic deficits associated with dysphagia.[11]

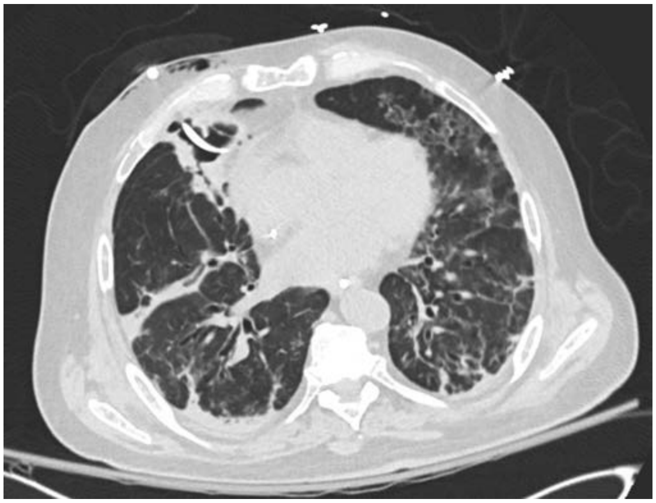

Figure 127-2 An 18-year-old man with COVID-19 pneumonia on ECMO with a bronchopulmonary fistula and polymicrobial empyema (*Escherichia coli*, *Klebsiella pneumoniae*, *Prevotella melaninogenica*, and *Fusobacterium nucleatum*).

Additional conditions that appear to predispose to anaerobic infections include pulmonary infarction, obstruction due to carcinoma or a foreign body, and bronchiectasis. These conditions are associated with stasis or necrosis of tissue, which presumably accounts for the association with anaerobic infections. The use of acid-suppressing medication has also been associated with community-acquired, hospital-acquired, and ventilator-associated pneumonia, presumably due to loss of the gastric acid barrier to bacterial growth.[12,13]

A somewhat unique feature of anaerobic lung infections is the proclivity for necrosis of tissue, resulting in abscess formation of a bronchopleural fistula associated with empyema (Fig. 127-2).[14] Virulence factors of anaerobic bacteria presumed to account for this association include the capsular polysaccharide of anaerobic Gram-negative bacilli. The most extensively studied is the polysaccharide of *Bacteroides fragilis*; however, the same observations may also apply to *P. melaninogenica* and other anaerobic Gram-negative bacilli.[15–17] The capsule of *B. fragilis* consists of a family of polysaccharides composed of oligosaccharide repeating units with sugars containing positively charged free amino groups and negatively charged carboxyl, phosphate, and amino groups.[16–19] These positive and negative charges mediate the capacity to induce abscess formation in experimental animals.[19,20] Another virulence factor possessed by most anaerobic bacteria is the production of short-chain fatty acids that inhibit phagocytic killing at low pH levels.[21,22] Short-chain volatile fatty acids are metabolic products of anaerobic bacteria used to classify these organisms taxonomically. They appear to be responsible for the putrid odor that is often a characteristic feature of infections by these organisms.[23,24]

MICROBIOLOGY

Bacteriologic findings of anaerobic lung infections from two large series are summarized in Table 127-1. Most of these infections involve multiple bacterial species, and approximately half of the patients have anaerobic bacteria combined with potentially pathogenic aerobic or facultative anaerobes. Community-acquired infections involving only anaerobes and those with mixtures of aerobic and anaerobic bacteria show common clinical features and no difference in the frequency of suspected aspiration, indolent presentation, or putrid discharge. The implication is that a putrid lung

TABLE 127-1 Bacteriology of Anaerobic Lung Infections

	Bartlett	Marina et al.
Period reviewed	1968–1975	1976–1991
Patients	193	110
Total anaerobic isolates	461	404
Major isolates		
Gram-negative bacilli		
Bacteroides fragilis group	38[a]	18
Pigmented *Prevotella*[b]	76	63
Nonpigmented *Prevotella*	—	40
Bacteroides ureolyticus	—	23
Fusobacterium nucleatum	56	34
Bacteroides spp. (other)	37	138
Peptostreptococcus/Peptococcus[c]	126	39
Gram-positive bacilli		
Clostridium spp.	18	12
Eubacterium spp.	18	22
Actinomyces	5	1
Lactobacillus	8	22
Cutibacteria (Propionibacteria)	10	9

[a] *Numbers indicate the total number of isolates. Some of the differences are due to taxonomic changes.*

[b] *Pigmented Prevotella refers to organisms previously classified as B. melaninogenicus.*

[c] *Most peptococci have been reclassified as Peptostreptococcus.*

TABLE 127-2 Incidence of Anaerobic Infection of the Lung

Number of Patients				
With Anaerobes	**Total**	**Percentage**	**Reference**	**Year**
Lung abscess				
53	57	93	Bartlett et al.[32]	1986
22	26	85	Beerens and Tahon-Castel[25]	1965
9	10	90	Brook and Finegold[112]	1980
37	41	90	Gudiol et al.[113]	1990
Aspiration pneumonia				
61	70	87	Bartlett et al.[32]	1986
17	17	100	Cesar et al.[114]	1975
29	47	62	Lorber and Swenson[84]	1974
69	74	93	Brook and Finegold[112]	1980
1	25	4	Marik and Careau[26]	1999
17	62	27	Tokuyasa et al.[27]	2009
1	193	0.5	Marin-Corral et al.[28]	2021
Empyema				
63	83	76	Bartlett et al.[32]	1986
23	45	51	Beerens and Tahon-Castel[25]	1965
28	72	39	Sullivan et al.[115]	1973
35	430	8	Maskell et al.[110]	2005
Community-acquired pneumonia				
28	89	33	Ries et al.[30]	1974
16	74	22	Pollock et al.[31]	1983
5	1709	0.3	Marin-Corral et al.[28]	2021
Nosocomial pneumonia				
56	159	35	Bartlett et al.[32]	1986

abscess with *Escherichia coli* in expectorated sputum, or anaerobic bacteria plus *E. coli* in a TTA, should usually be considered an anaerobic infection. However, caution is advised in applying these conclusions to nosocomial pulmonary infections since this is a setting in which the aerobic component of the infection is probably more important.

The establishment of anaerobic bacteria in pulmonary infections requires specimens of respiratory secretions devoid of contamination from the upper airways. Procedures satisfying this criterion are TTA, transthoracic aspiration, open lung biopsy, thoracentesis, and, more recently, bronchoscopy with quantitative cultures. In addition, there must be appropriate laboratory expertise for the cultivation of anaerobic bacteria. The incidence of anaerobic lung infections reported in published studies from the antibiotic era that satisfy both requirements is summarized in Table 127-2.

Most historic reports examining the role of anaerobic bacteria in aspiration pneumonia or lung abscess demonstrated recovery rates ranging from 62% to 100%. The typical specimens in these studies were collected by TTA and transthoracic aspiration. For example, in a study published in 1965, Beerens and Tahon-Castel[25] used transthoracic needle aspiration to characterize the flora in lung abscesses; this series showed recovery of anaerobic bacteria, usually in pure culture, in 22 (85%) of 26 cases. The major bacterial isolates in patients with anaerobic lung infections are *Peptostreptococcus*, *F. nucleatum*, and *P. melaninogenica*, often with concomitant aerobic and microaerophilic streptococci.

More recent studies, however, have shown a shift from anaerobes to bacterial pathogens typically associated with community-acquired and hospital-acquired pneumonia.[26] Indeed, modern studies have shown that anaerobic bacteria are recovered in a small minority of cases of aspiration pneumonia.[26–28] The reason for this discrepancy is not clear but could reflect that historically TTA was often performed late in the course of illness, often after patients developed complications such as lung abscess or empyema, or differences in patient characteristics in older studies, such as higher representations of chronic alcoholism.[26] Furthermore, improvement in oral health, which is associated with respiratory health, may influence the incidence of anaerobic pneumonia.[29]

There have been few studies to identify the frequency of anaerobic bacteria in unselected cases of community-acquired pneumonia. Ries et al.[30] performed TTAs in patients hospitalized with a diagnosis of pneumonia and recovered anaerobic bacteria in 29 (33%) of 89 cases. A more recent study by Pollock et al.,[31] using fiberoptic bronchoscopy with a protected catheter and quantitative cultures, showed recovery of anaerobes in 16 (22%) of 74 patients. These two reports suggest that anaerobic bacteria are relatively common pathogens among patients with community-acquired pneumonia and presumably account for a substantial proportion of cases that are considered enigmatic. In nosocomial pneumonia, Bartlett et al.[32] utilized TTA in 159 consecutive patients and showed anaerobes in 56 (35%). Nevertheless, most of these patients also showed the simultaneous presence of aerobic gram-negative bacilli or *Staphylococcus aureus*, and their clinical course was determined largely by the aerobic pathogens.

TABLE 127-3 Clinical Features of Anaerobic Pulmonary Infections[a]

	Lung Abscess (83 pts)	Empyema (51 pts)	Pneumonitis (only) (79 pts)	Total (193 (pts)
Age (median, years)	52	49	60	51
Peak temperature (mean, °F)	102.1	102.4	102.6	102.4
Peripheral leukocyte count (median/mm)	15,000	21,600	13,700	15,000
History of weight loss	36 (43%)	28 (55%)	3 (4%)	57 (30%)
Putrid discharge	41 (49%)	32 (63%)	4 (5%)	62 (32%)
Lethal outcome	3 (4%)	3 (6%)	3 (4%)	8 (4%)

[a] *Based on retrospective chart review of 193 cases established by recovery of anaerobes as dominant flora in TTA, pleural fluid, or blood culture.*

Data from Bartlett JG. Anaerobic bacterial infections of the lung. Chest. 1987;91:901–909; Bartlett JG. Anaerobic bacterial infections of the lung and pleural space. Clin Infect Dis. 1993;16:S248–S255; Marina M, Strong CA, Civen R, et al. Bacteriology of anaerobic pleuropulmonary infections: preliminary report. Clin Infect Dis. 1993;16: S256–S262.

CLINICAL FEATURES

Nearly all patients with anaerobic lung infections have the usual constitutional findings for patients with infection (Table 127-3). A review of 193 bacteriologically confirmed cases showed that the mean peak temperature for hospitalized patients was 39.1°C and all but 5 patients were febrile. The average peripheral leukocyte count was 15,000/mL[3]. Patients presenting with suppurative complications had a longer duration of symptoms before presentation; this was commonly associated with other evidence of chronic disease, including weight loss and anemia. Another common feature of patients with suppurative complications was putrid sputum or empyema fluid, which was noted in 40% to 60%. It should be emphasized that the putrid discharge in these cases is considered diagnostic of anaerobic infection since aerobic bacteria are not capable of producing this characteristic odor either in vitro or in vivo. Thus, anaerobic bacteria may cause a diverse range of pulmonary infections, which may be acute, subacute, or chronic. The anaerobic etiology is rarely established or even suspected in patients with acute pneumonitis. This compares with aspiration pneumonia, where anaerobes are presumed pathogens in most community-acquired infections and may contribute to many nosocomial cases. By contrast, anaerobic bacteria are readily recognized as potential pathogens in patients with late suppurative complications, such as lung abscess or empyema.

One review of 46 patients with anaerobic bacterial pneumonitis showed similar clinical features to those of pneumococcal pneumonia.[33] The diagnosis was established by TTA, and the results in this group were compared with those in the second group of patients in whom TTAs yielded *Streptococcus pneumoniae*. The two groups were similar in age, changes on the chest radiograph, peak temperature, and peripheral leukocyte count. Significant differences in the group with anaerobic infections were the lack of rigors, somewhat more prolonged duration of symptoms before presentation, and a more frequent association with predisposing conditions for aspiration.[33] An important point to emphasize is that patients presenting in this early stage of infection rarely have the features commonly associated with anaerobic lung infections, such as putrid sputum, tissue necrosis with abscess formation, or a chronic course. These infections presumably account for some and possibly many cases of community-acquired pneumonia in which no etiologic diagnosis is established despite extensive study; such cases account for 40% to 50% of cases in most series. Features of anaerobic infections that are nearly unique are the association with conditions that predispose to aspiration and infection in the gingival crevice, putrid discharge, and a high frequency of suppurative complications in late-stage disease.

ASPIRATION SYNDROMES

Aspiration is a relatively common event that is typically well-tolerated. Numerous studies indicate that virtually all healthy persons aspirate but that this is usually inconsequential. In one study, airway protective mechanisms were challenged by placing contrast material in the mouths of sleeping patients. The following morning, most patients had radiographic evidence of aspiration, defined as contrast material seen on imaging of the lungs, but no evidence of a disease process.[34] Similarly, dye markers placed in the stomach of postoperative patients have later been aspirated from the tracheobronchial tree, indicating aspiration of gastric contents during general anesthesia in 7% to 16%.[35,36] Scintigraphic methods have also been used to demonstrate frequent aspiration in patients with intubation of the airways or gastrointestinal tract.[37–39] None of these studies, however, has shown any clinical consequences from occult aspiration. The conclusion is that aspiration is relatively common but usually resolves spontaneously. The decisive factor for the development of lung complications depends on the frequency, volume, and character of the material in the inoculum. The aspiration of large volume or frequent aspirations leads to three distinct syndromes according to the nature of the inoculum: chemical pneumonitis, bacterial infection, and airway obstruction. The nature of the inoculum also dictates the pathogenesis of pulmonary complications, clinical presentation, and management strategies (Table 127-4).

■ Chemical Pneumonitis

Chemical pneumonitis refers to the aspiration of an inoculum that is inherently toxic to the lungs. Examples include acid, fats such as milk or mineral oil, and volatile hydrocarbons. These substances are toxic to the lower airways and initiate an inflammatory reaction. The effect of acid on the lungs was initially described in animal studies in World War I and subsequently confirmed in humans by Mendelson. His work was the first to describe gastric acid pneumonitis leading to chemical pneumonitis in humans, which came to be referred to as Mendelson syndrome.[39] This is a severe pneumonitis with fever, hypoxia, and respiratory alkalosis, which typically clears rapidly in healthy hosts within 4 to 7 days but may progress following lung injury and superinfection to pneumonia, lung abscess, or acute respiratory distress syndrome (ARDS) (Chapters 140 and 141). Factors that contribute to hypoxemia are pulmonary edema, reduced surfactant activity, reflex airway closure, hyaline membrane formation, and alveolar hemorrhage. Pulmonary function tests show decreased compliance, abnormal ventilation–perfusion, and reduced diffusing capacity.[2] The pathophysiology of gastric acid pneumonitis has been studied in experimental animals with intratracheal instillation of graded acid inocula. This work shows that the pH must be 2.5 or less, and a relatively large inoculum, usually a minimum of 0.3 to 0.6 mL/kg, is required for the inflammatory process to be initiated.[40–43] It is possible that smaller volumes create a less dramatic presentation or may go undetected.[41,43] Support for this hypothesis is the observation of frequent

TABLE 127-4 Classification of Aspiration Pneumonia

Inoculum	Pulmonary Sequelae	Clinical Features	Therapy
Acid breathing	Chemical pneumonitis	Acute dyspnea, tachypnea; tachycardia; cyanosis, bronchospasm, fever Sputum: pink, frothy Radiographic infiltrates in one or both lower lobes Hypoxemia	Supplemental oxygen, bronchodilators, mechanical ventilation as needed
Oropharyngeal bacteria	Bacterial infection	Usually insidious onset Cough, fever, purulent sputum Radiographic infiltrate in dependent pulmonary segment or lobe ± cavitation	Antibiotics
Inert fluids	Mechanical obstruction Reflex airway closure	Acute dyspnea, cyanosis ± apnea Pulmonary edema	Tracheal suctioning, supplemental oxygen, mechanical ventilation as needed
Particulates	Mechanical obstruction	Dependent on level of obstruction, ranging from acute apnea and rapid death to irritating chronic cough ± recurrent superimposed infections	Extraction of matter Antibiotics for infection

bouts of pneumonitis and otherwise unexplained pulmonary fibrosis in patients with gastric reflux or esophageal disease.[44,45]

Pathologic changes in acid pneumonia occur rapidly. Atelectasis occurs within seconds and is extensive within minutes. There is also peribronchial hemorrhage, pulmonary edema, and bronchial epithelial cell degeneration. The alveolar spaces fill with neutrophils within hours, and hyaline membranes are seen within 48 h. Resolution begins by the third day and may be complete or may result in residual scarring of the pulmonary parenchyma.[46,47] Long-term follow-up studies in patients who have gastric acid pneumonia show either complete recovery or radiographic evidence of pulmonary fibrosis with abnormal gas exchange.[48,49] Pulmonary fibrosis may also be associated with repeated, small, “silent” aspirations of gastric secretions without clinically overt pneumonitis (Chapters 56 and 57).[44,50]

The diagnosis of acid pneumonia is usually presumed on the basis of clinical observations such as the abrupt onset of dyspnea in a patient who is aspiration prone and has radiographic evidence of infiltrates, usually in the lower lobes. Other characteristic clinical features are the rapid clearing of the infiltrates and progression to ARDS.[47,51] Bronchoscopy demonstrates erythema of the bronchi, suggesting a “chemical burn.”[52] Confirmation of the acid inoculum is not possible because of rapid neutralization by pulmonary edema fluid and bronchial secretions within minutes after aspiration.

The treatment of gastric acid aspiration includes tracheal suction to clear fluids and particulate matter that may have been concurrently aspirated. Supportive care consists primarily of ventilatory support with positive-pressure ventilation and resuscitation with intravenous fluids.[47,53] While use of corticosteroids dates back to the 1950s, clinical trials have not shown them to be beneficial.[54–56] Use of prophylactic antimicrobial agents for acute aspiration pneumonitis has not been shown to reduce ICU transfer or mortality but is associated with escalation of antimicrobial treatment for those who develop pneumonia.[57,58] Supportive treatment is the mainstay, and antimicrobial therapy should be reserved for those with superinfection.

■ Aspiration Pneumonia

While not as fulminant as chemical pneumonitis,[59] bacterial infection following aspiration is associated with an increased risk of prolonged hospitalization and death.[60,61] In the preantibiotic era, the natural history of these infections could be followed. The initial presentation was similar to chemical pneumonitis, usually combined with purulent sputum. After 8 to 14 days, progression to tissue necrosis with abscess formation or extension into the pleural space may occur. This stage is marked by putrid discharge and cavitation.[62–64] The distinction between aspiration pneumonia and other forms of pneumonia is based mainly on the clinical characteristics, but clear overlaps exist. For example, healthy elderly patients with community-acquired pneumonia have a markedly higher incidence of silent aspiration than matched control patients.[65] While no gold standard for the diagnosis of aspiration exists, studies suggest that 5% to 15% of community-acquired pneumonia may be due to aspiration.[11,66,67] The incidence of aspiration pneumonia in elderly patients with community-acquired pneumonia may be much higher.[68,69] The diagnosis of aspiration pneumonia is often inferred from patient characteristics. Antimicrobials with specific anaerobic activity may only be indicated in patients with periodontal disease, patients expectorating putrid sputum, and patients with necrotizing pneumonia or lung abscess on chest radiograph.[26,47,70,71]

■ Mechanical Obstruction

Aspiration may involve fluid or particulate material. In this form of aspiration pneumonia, the inoculum is not toxic to the lung but may cause obstruction or reflux airway closure. In most cases, there is only transient, self-limited hypoxemia due to rapid clearance.[46] Some patients develop pulmonary edema, with hypoxemia and reduced compliance apparently due to an intrinsic pulmonary reflex closure.[46] Other patients suffer sequelae due to failure to clear relatively large volumes of the aspirate, such as near-drowning victims and patients with profound neurologic deficits or coma. The apparent critical intervention is tracheal suction.

Aspiration with mechanical obstruction may also be associated with solid particles. Foreign-body aspiration is most frequent in children 1 to 3 years of age.[72–74] The most common objects in the lower airways are vegetable particles, inorganic materials, and teeth.[72–74] The severity of the obstruction depends on the relative size of the material aspirated and the caliber of the lower airways. Large objects may cause obstruction at the level of the larynx or trachea, leading to sudden respiratory distress, cyanosis, stridor, and in some cases, aphonia.[75,76] This is referred to as café coronary syndrome because it often involves meat aspiration during restaurant dining and may simulate an acute myocardial infarction.[77] Aspiration of smaller particles may result in complete obstruction of more distant components of the tracheobronchial tree or partial obstruction. Chest radiographs often show atelectasis or obstructive emphysema.[78] Common symptoms include chronic cough, fever, hemoptysis, and dyspnea.[79,80] An essential clue in some cases is unilateral wheezing.[81] Bacterial infection is not present in the early stages of obstruction but is a common feature when obstruction has been present for more than 1 week.[82] The most common pathogens are anaerobic bacteria from the upper airways. These patients may respond well to antibiotics but often have recurrent infections in the same pulmonary segment.[72] The most important therapeutic intervention is removal of the foreign body, usually with bronchoscopy.[73]

Radiologic Diagnosis

Chest radiographs in patients with anaerobic lung infections typically demonstrate infiltrates (with or without cavitation) involving dependent pulmonary segments.[1,47] The favored locations are the superior segment of the lower lobes or posterior segments of the upper lobes—dependent segments in the recumbent position. The basilar segments of the lower lobes are favored in patients who aspirate in the upright position. The right lung is more frequently affected owing to the more direct takeoff of the right mainstem bronchus.

Laboratory Diagnosis

Aspiration pneumonitis is a clinical diagnosis. It is generally assumed that there is an anaerobic component to pneumonia in patients with altered consciousness or after surgical procedures. It is important to emphasize the utility of the Gram stain in making the diagnosis of anaerobic lung infection. Often culture data are not available to confirm the presence of these organisms. However, most anaerobic Gram-negative bacteria have unique morphologic features that make them relatively easy to identify or suspect on direct Gram stain. For example, peptostreptococci appear like their aerobic counterparts. Aspiration pneumonia is usually a mixed infection involving multiple bacteria; about half of the cases demonstrate mixtures of aerobic and anaerobic bacteria.[1,83,84] Thus, the detection of polymicrobial flora or bacteria with the unique morphology of anaerobes on any specimen that is devoid of contamination by normal flora represents an important clue to the probable presence of anaerobic infection.

Determination of the microbiology of anaerobic infections of the lower airways requires a specimen devoid of contamination by the flora of the upper airways or quantitative cultures that distinguish pathogens from normal flora. Uncontaminated specimens that are considered valid for anaerobic culture include pleural fluid, TTAs, transthoracic aspirates, and specimens obtained at thoracotomy or thoracoscopy. Quantitative cultures of specimens obtained at fiberoptic bronchoscopy, either by BAL or with the protected brush, also may be used for this purpose.[1] Anaerobic bacteriology should not be obtained from standard bronchoscopic aspirates. Quantitative culture of lower airway secretions improves diagnostic accuracy with virtually any specimen that is subject to contamination, including expectorated sputum and tracheostomy aspirates. Most studies employing these techniques have used them to detect aerobic bacteria; relatively few studies evaluated anaerobic cultures. Whether treatment decisions based on quantitative cultures of anaerobic pathogens improve treatment outcomes is unknown.

When possible, respiratory samples should be obtained before the inception of antibiotic treatment. In clinical practice, specimens are often not obtained for anaerobic culture until the patient has developed complications of persistent infection, which significantly reduces their yield. Thus, the anaerobic pathogens should be considered in the appropriate clinical context, even when only aerobic organisms are isolated.

It is essential that material obtained for culture be placed under anaerobic conditions promptly before transport to the laboratory. A sealed syringe provides the best container, with delivery of the specimen to the laboratory within 20 to 30 min for immediate plating. It is imperative that air bubbles be eliminated from the syringe and needle. Special anaerobic transport tubes are available for brush or liquid specimens. It is important to obtain additional pulmonary specimens for culture and antibiotic susceptibility measurements from patients failing to respond to initial therapy (Fig. 127-3). Such data may demonstrate the presence of unrecognized or antibiotic-resistant organisms. Most of these infections are polymicrobial, and many of the organisms grow slowly in vitro. Thus, it often takes several days to separate, identify, and report results of anaerobic cultures. There is great variation in the availability and quality of in vitro susceptibility tests. These factors illustrate the need for empiric decisions regarding antibiotic selection.

Prevention

The reversibility of underlying conditions predisposing to aspiration must be considered. It has recently been recognized, for example, that aspiration in lung transplant recipients is a major predisposing factor to graft injury and obliterative bronchiolitis.[85] In the general patient population, nasogastric feeding tubes, sedation, lying flat in bed while sleeping, reflux, and frequent choking are associated with aspiration and should suggest strategies for remediation.[47] Gastric surgery for obesity also has been associated with a high incidence of aspiration disease.[86]

Positioning, dietary changes, medications, oral hygiene, antiseptic oral rinses, and tube feeding, among other interventions, have been proposed to prevent aspiration in both hospitalized and nonhospitalized patients, particularly in the elderly. However, studies have failed to support specific intervention in the outpatient setting.[87] While using nectar or honey-thickened liquids decreases aspiration among patients with dementia or Parkinson disease,[88] the incidence of pneumonia is not changed.[89] Studies have also failed to demonstrate that aspiration prevention measures improved outcomes in elderly long-term care residents. In a large, multicenter study involving 36 nursing homes, the combination of oral hygiene care, semirecumbent position when eating, and chlorhexidine gluconate oral rinses had no impact on the incidence of pneumonia or the overall mortality rate.[90]

Methods to prevent aspiration have been studied most extensively in hospitalized patients, especially in those who are aspiration prone. Most important is use of semirecumbent or upright positioning.[91] Additional measures to prevent aspiration with variable efficacy include tracheostomy, reducing gastric contents by suction or metoclopramide, feeding via gastrostomy tube, and neutralization of gastric acid. Many of these procedures may alter colonization patterns and potentially may predispose to more significant infections. Neutralization of gastric acid may increase colonization of the oropharynx and thereby increase the risk of bacterial infection following aspiration of gastric contents. Tracheostomy is useful in some patients with repeated aspiration, but inflation of the balloon may occlude the esophagus and promote aspiration of upper airway contents. Patients who require nasogastric feedings are aspiration prone; percutaneous endoscopic gastroscopy (PEG) may be an alternative method to address this issue, but study results are quite variable. A recent meta-analysis of nine studies found that while PEG feeding was superior to nasogastric tube feeding in providing consistent nutritional support, the incidence of pneumonia was no different between the two groups.[92] Alternative procedures sometimes considered to prevent or limit aspiration include post-pyloric feeding jejunostomy and Nissen fundoplication. The use of intermittent oroesophageal (IOE) tube feeding has in a single-center trial shown a reduction in aspiration pneumonia compared with traditional continuous nasogastric tube feeding (16% vs. 31%). In IOE tube feeding, a tube is inserted orally into the esophagus at each

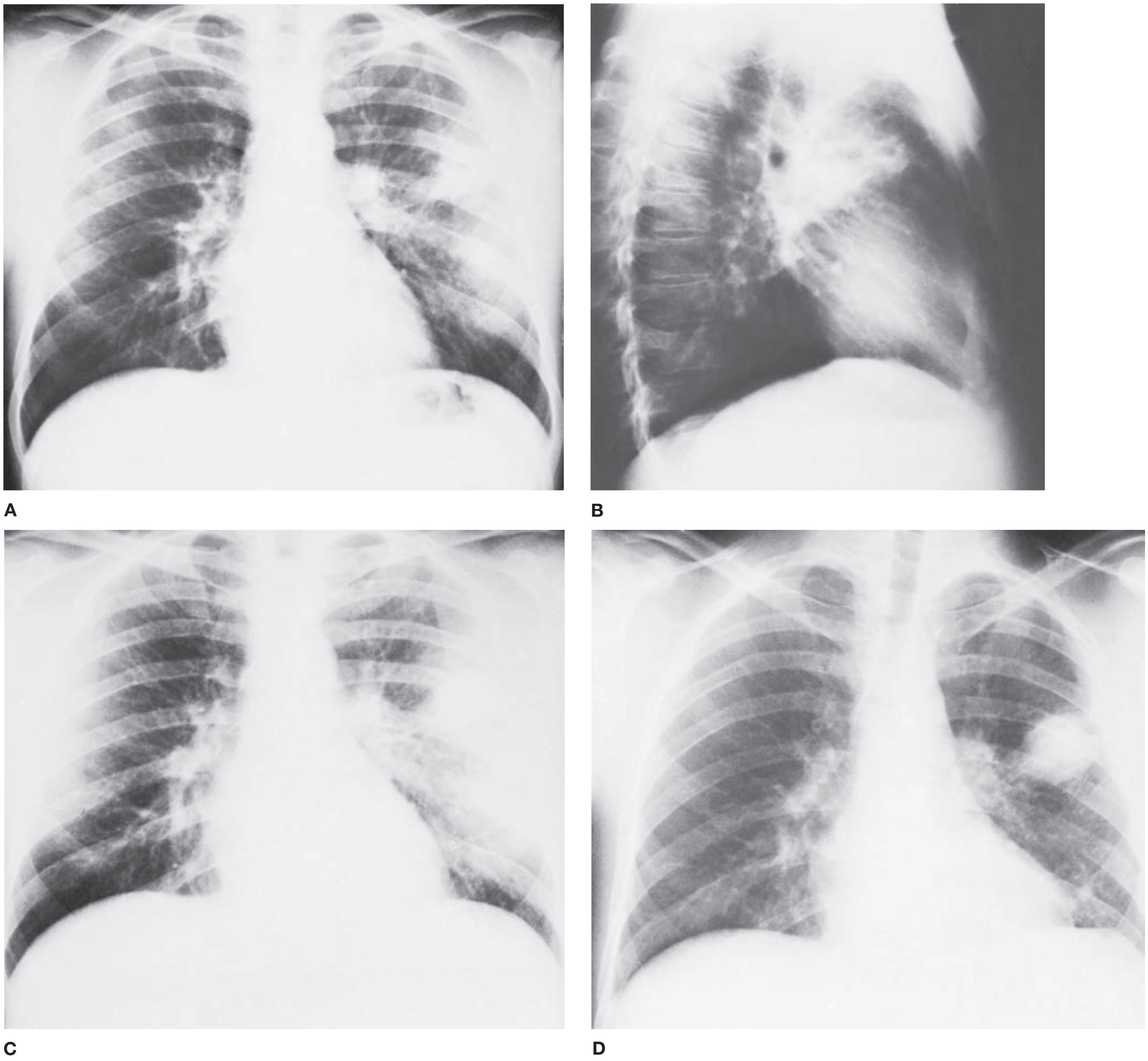

Figure 127-3 Failure of penicillin therapy for anaerobic lung abscess in a 29-year-old alcoholic man. **A.** Admission chest radiograph reveals a radiolucent area within a zone of consolidation in the left upper lung field. **B.** Lateral view demonstrates multiple cavities. The patient was treated for 5 days with penicillin (6 million units per day intravenously), followed by the same dosage orally for 10 days. **C.** Radiographic infiltrate persists, but no cavity is visible. **D.** Six weeks after the cessation of penicillin therapy, the abscess has recurred in the same area. Marked pleural reaction is noted in the vicinity of the recurrent disease.

feeding and then removed. The decrease in pneumonia is hypothetically from a reduction in the interruption of the gastroesophageal sphincter reducing reflux.[93]

Antimicrobial Therapy

It is essential, whenever possible, to obtain microbiologic samples from the lungs and blood in advance of antimicrobial therapy. As for all pneumonias, inappropriate initial therapy has an adverse impact on outcome. The initial choice of antimicrobial agents should be guided by the Gram stain and the likely bacteriology of the infection and then adjusted as culture data become available. The history and a review of previous culture results may be useful in the selection of specific antibiotics. The standard drug historically for aspiration pneumonia and lung abscess involving anaerobic bacteria has been penicillin, usually given intravenously or with high-dose oral treatment. However, in the face of increasing penicillin resistance among *S. pneumoniae* and in 40% to 60% of strains of fusobacteria and *P. melaninogenica* as well as anaerobic Gram-negative bacilli, alternatives should be considered for empiric therapy. In early therapeutic trials in patients with lung abscess involving anaerobic bacteria (Table 127-5), clindamycin proved superior to penicillin in terms of response rates and time to defervescence. Alternative regimens that have been used successfully based on anecdotal experience include amoxicillin-clavulanate and penicillin combined with metronidazole. Metronidazole should not be used as a single agent in patients with anaerobic lung infections since there is a poor response in about 50%.[94,95] The presumed explanation is the contributing role of aerobic and microaerophilic streptococci, which are resistant to this drug.

Many other antimicrobial agents are likely to be useful in anaerobic or mixed aerobic–anaerobic infections: combinations

TABLE 127-5 Antibiotic Treatment of Anaerobic Lung Infections: Results of Two Randomized Trials

Source	Treatment	# Pts	Number of Patients with Failure	Number of Patients with Relapse	Mean Days to Symptom Resolution Fever	Mean Days to Symptom Resolution Putrid Sputum
Levinson (1983)	Penicillin (6 million units/d)	21	5 (29%)	3 (19%)	7.7	7.8
	Clindamycin (1.8 g/d)	17	0[a]	0	4.7[a]	4.1[a]
Gudiol (1990)	Penicillin (12 million units/d)	18	7 (39%)	2 (11%)	7.2	7.3
	Clindamycin (2.4 g/d)	19	1 (5%)	0	6.4	3.9[a]

[a] *Difference for treatment favoring clindamycin is statistically significant.*

of a β-lactam and β-lactamase inhibitor (ampicillin-sulbactam, amoxicillin-clavulanate, piperacillin-tazobactam), carbapenems (ertapenem, imipenem-cilastatin, meropenem), and second-generation cephalosporins such as cefoxitin or cefotetan. Macrolides (erythromycin, clarithromycin, and azithromycin) offer good in vitro activity against most species except fusobacteria. Oxacillin and nafcillin are much less active. Vancomycin is active only against Gram-positive anaerobes. Drugs that have virtually no activity against anaerobes include aminoglycosides, first-generation fluoroquinolones, aztreonam, and trimethoprim-sulfamethoxazole (TMP-SMX). Moxifloxacin has broad coverage that includes anaerobes;[96] however, increasing resistance in *Bacteroides* spp. raises concerns for the suitability of moxifloxacin monotherapy.[97]

Several new antimicrobial agents may be useful for patients with mixed aerobic-anaerobic pulmonary infections involving multidrug-resistant Gram-negative pathogens, such as carbapenem-resistant *Enterobacterales* (CRE) and extensively drug-resistant (XDR) *Pseudomonas aeruginosa*. The novel siderophore cephalosporin cefiderocol and two new cephalosporin β-lactamase inhibitor combinations, ceftazidime-avibactam and ceftolozane-tazobactam, demonstrate excellent in vitro activity against multidrug-resistant Gram-negative bacilli and have received FDA approval for hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP). Ceftolozane-tazobactam—the combination of a novel, semisynthetic cephalosporin and an established β-lactamase inhibitor—demonstrates enhanced activity against strains of XDR *P. aeruginosa* as well as some extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae. The addition of avibactam, a non-β-lactam β-lactamase inhibitor, to ceftazidime restores ceftazidime activity against Gram-negative bacteria that produce serine class A or class D carbapenemases, such as *Klebsiella pneumoniae* carbapenemase (KPC) or the oxacillinase OXA-48, respectively.[98] Cefiderocol is a novel siderophore cephalosporin with a spectrum of activity that includes CRE, XDR *P. aeruginosa*, and several other highly drug-resistant Gram-negative pathogens, including *Stenotrophomonas maltophilia*, *Acinetobacter baumannii*, and *Burkholderia cepacia*.[99] However, all three have limited anaerobic activity. The addition of metronidazole is recommended when using these agents to treat nosocomial pneumonia due to both anaerobes and multidrug-resistant Gram-negative pathogens.

Two new carbapenem β-lactamase inhibitor drug combinations offer additional treatment options for patients with HABP/VABP due to a combination of anaerobic and extensively drug-resistant Gram-negative bacteria. Meropenem-vaborbactam, a carbapenem and novel cyclic boronic acid–based β-lactamase inhibitor drug combination, has received FDA approval for the treatment of complicated urinary tract infections including those caused by CRE. Given its spectrum of activity and limited clinical trial experience, meropenem-vaborbactam is predicted to be a therapeutic option for mixed aerobic–anaerobic pulmonary infections involving CRE.[100,101] However, the addition of vaborbactam to meropenem does not improve activity against *P. aeruginosa* compared with meropenem alone and therefore should not be used to treat pneumonias involving carbapenem-nonsusceptible *P. aeurinosa*.[102]

Another novel carbapenem β-lactamase drug combination, imipenem-cilastatin-relebactam, was recently approved by the FDA to treat HABP/VABP involving pathogens multidrug-resistant pathogens. Relebactam is a novel β-lactamase inhibitor that inhibits Ambler class A serine carbapenemases, including *K. pneumoniae* carbapenemase (KPC). Furthermore, relebactam can increase activity of imipenem against imipenem-nonsusceptible *P. aeruginosa*. For mixed pulmonary infections that include MDR Gram-negative bacteria like KPC-producing CRE and anaerobes, imipenem-cilastatin-relebactam may be a new option in the antibiotic armamentarium.[103]

While first-generation tetracyclines show limited activity against many anaerobic bacteria in vitro, the tetracycline analogues tigecycline (a glycylcycline) and eravacycline (a fluorocycline) have broad-spectrum antimicrobial activity against Gram-positive, Gram-negative (except *P. aeruginosa*), and anaerobic bacteria. Both have been approved by the FDA for the treatment of complicated intra-abdominal infections, and tigecycline has an approved indication for the treatment of community-acquired pneumonia due to *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Legionella pneumophila*. However, tigecycline has an FDA boxed warning against use for HABP/VABP due to increased risk of death compared with other antibiotics.[104] Correspondingly, experience with eravacycline for the treatment of healthcare-associated or aspiration pneumonia is limited and its role remains to be determined.

The appropriate duration of therapy is unclear. No clinical trials have been performed to determine optimal treatment term. Typically the duration is dependent on the clinical and radiographic response of the patient. Patients should be treated at least until fever, putrid sputum, and abscess fluid have resolved, and any fluid collections have resolved or stabilized, typically over 2 to 3 weeks. In the absence of abscess formation, a course of 7 to 10 days of antibiotics is recommended, but longer courses may be necessary. Relapse is common and may involve organisms resistant to initial antibiotic agents (Fig. 127-3).

LUNG ABSCESS

Because the most important predisposing condition for lung abscess is aspiration, lung abscesses are most often located in the posterior segment of the right upper lobe, less often in the left upper lobe, and the apical segments of the lower lobes (Fig. 127-1). Periodontal disease is highly associated with lung abscess formation; in edentulous patients, lung abscesses are uncommon and may suggest the presence of an obstructing lesion of the bronchus, pulmonary embolus, septic embolus, or unsuspected pathogen. Nosocomial aspiration often involves Gram-negative bacteria, particularly organisms with hospital-acquired antibiotic resistance patterns. Many of these infections progress to suppurative complications, with presentation as lung abscess or empyema. Usually 1 to 2 weeks are required for cavity formation.

Lung abscesses generally develop after inflammation produces tissue necrosis with cavitation. In the presence of pre-existing cavitary disease, for example, due to emphysema or old tuberculous lesions, infection may proceed without frank necrosis. The abscess cavity may become lined with regenerated epithelium. Local obstruction may produce bronchiectasis or emphysema in the surrounding lung.

The classification of lung abscesses is based on the duration and likely cause of the process. Acute abscesses are less than 4 to 6 weeks old, whereas chronic abscesses are of greater duration. Primary abscesses are infections due to aspiration or to pneumonia in the normal host; secondary abscesses are due to pre-existing conditions (obstruction, spread from an extrapulmonary site, bronchiectasis, immune compromise). Abscesses with foul odors associated with anaerobic organisms are often called putrid abscesses.

■ Microbiology

In lung abscesses, anaerobes are recoverable from up to 93% of patients.[14,15] In some patients, anaerobic organisms of presumably greater virulence (e.g., *Fusobacterium* or *Peptostreptococcus*) may be found as the sole infecting organism. In studies by Bartlett and Finegold,[3] 46% of patients with lung abscesses had only anaerobes isolated in cultures, while an additional 43% had a mixture of anaerobes and aerobic bacteria. In addition to anaerobes, among the organisms often implicated in lung abscess formation or in necrotizing pneumonia included are *S. aureus*, *Streptococcus pyogenes*, *K. pneumoniae*, and *P. aeruginosa*. Infrequently, other Gram-negative bacilli, such as *E. coli* and *H. influenzae* type B, may cause pulmonary necrosis. Uncommon but important causes of cavitating pneumonia are *Nocardia* spp., *Paragonimus westermani*, *Legionella* species, *Burkholderia pseudomallei*, *Burkholderia mallei* (glanders), and tuberculosis. Certain fungal infections may cause cavitation in diabetic and immunocompromised hosts (e.g., the Mucoraceae, *Aspergillus* species). *Entamoeba histolytica* is an important but uncommon cause of lung abscess, almost always in the basilar portion of the right lower lobe.

■ Clinical Features

The clinical presentation of lung abscess may be coincident with the initial presentation of pneumonia or other underlying condition or may occur later in the clinical course. Suspicion may be heightened by the presence of conditions predisposing to aspiration or anaerobic pneumonia: alcoholism or other causes of altered consciousness, anesthesia, dysphagia or pharyngeal dysfunction, gingivitis or pyorrhea (purulent inflammation of the gums), blunt or penetrating chest trauma or lung surgery, obstruction due to neoplasm, bronchiectasis, or pulmonary embolism. Bad breath or putrid sputum may be noted. However, the absence of a foul odor does not exclude the possibility of anaerobic infection, since certain anaerobes do not generate the end products of metabolism responsible for this type of odor, and communication may be lacking between the lesion and tracheobronchial tree. A change in sputum production, either increased or decreased, may be noted in patients with chronic bronchitis or bronchiectasis.

The patient with primary lung abscess gradually develops fever, cough, pleurisy, chest heaviness, shoulder pain, and malaise. Pneumonia may be present or suspected from history for a period of 1 to 3 weeks before the recognition of the lung abscess. By contrast, secondary lung abscesses—due, for example, to septic pulmonary emboli with infarction—can evolve over 48 to 72 h (Fig. 127-4). Clinically, the distinction between primary and secondary abscesses may be unapparent at the time of presentation but is important in the proper management of the patient. Thus, the patient with staphylococcal or streptococcal endocarditis may present with pneumonia, lung abscess, and empyema. The main clue to the presence of underlying endocarditis may be the development of new lung abscesses during the course of therapy. The patient with lung abscesses complicating subdiaphragmatic infection, for example, due to amebic abscess of the liver or pancreatic phlegmon, may have abdominal signs in addition to acute pulmonary disease. Seizures due to brain abscesses are occasionally the presenting clinical manifestation of bacteremia due to lung abscesses.

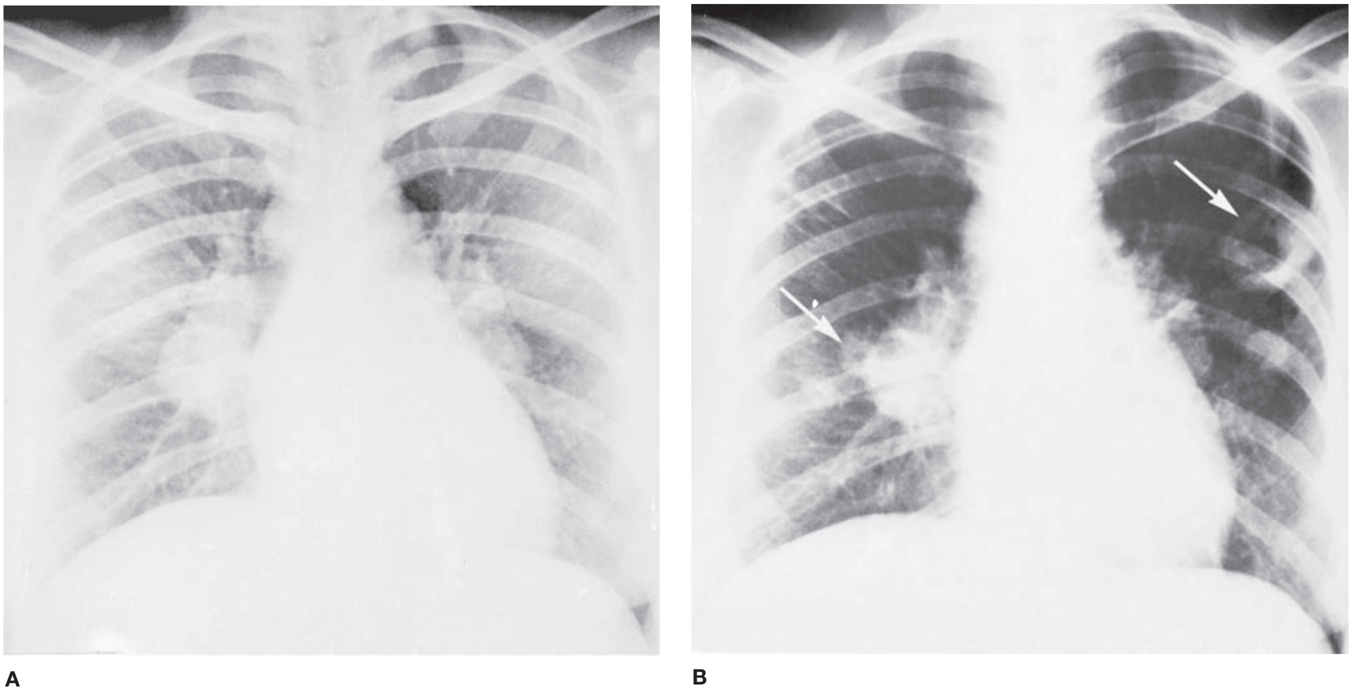

Figure 127-4 Septic emboli due to *Pseudomonas aeruginosa* in a 33-year-old woman with sarcoidosis and pyelonephritis following spontaneous abortion. The patient presented with headache, fever, backache, and purulent sputum. Pseudomonas grew from the sputum culture. **A.** Chest radiograph before present illness. Bilateral hilar adenopathy of sarcoidosis. **B.** Posteroanterior view of chest shows bilateral cavitary lesions *(arrows)*. *(continued)*

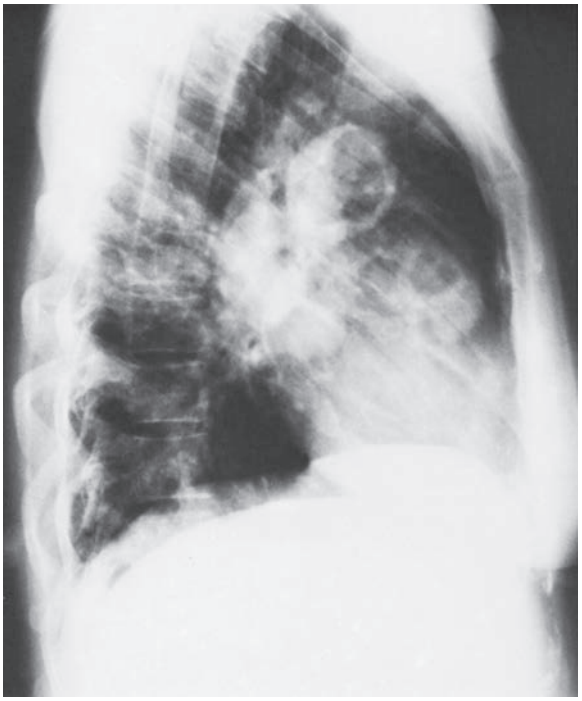

Figure 127-4 *(Continued)* **C.** Lateral view. The lesions are more dramatically seen.

Radiologic Diagnosis

The classic radiographic appearance of a lung abscess is an irregularly shaped cavity with an air–fluid level. Because the presentation is often indolent, numerous chest radiographs may be needed to follow the evolution of pneumonia into necrotizing pneumonia and then a pulmonary cavity (Figs. 127-5 and 127-6). Anaerobic infection is suggested by rapid pulmonary cavitation within a dense segmental consolidation; there may be rapidly enlarging nodular lesions, with or without cavitation. Although anaerobic pulmonary infections may be acute and fulminating, almost two-thirds have a subacute or chronic presentation. The natural progression of virulent infection, delays in appropriate therapy, or tissue infarction may allow the underlying infection to progress into pulmonary gangrene (Fig. 127-6). Seeding of infection or rupture of a lung abscess into the pleural space may cause empyema (Fig. 127-4). Up to one-third of lung abscesses may be accompanied by empyema. Solitary cavities are generally observed with primary lung infections, whereas many smaller collections may be found in metastatic infection. Chest tomography will define the size and location of abscesses and may distinguish between related processes (empyema, infarction) better than conventional radiographs (Fig. 127-7). The common organisms and conditions associated with lung abscesses are listed in Table 127-6.

Laboratory Diagnosis

Microbiologic specimens from patients with lung abscesses should be obtained, if possible, without contamination by oral flora, especially after nosocomial colonization. Thus, invasive procedures are preferred to routine sputum samples. In particular, the diagnosis of anaerobic infection is complicated by the prevalence of large numbers of anaerobes as normal flora in the mouth and upper respiratory tract (Figs. 127-8 and 127-9). However, there may also be significant colonization with nosocomially acquired pathogens in hospitalized patients.

Blood and sputum cultures should be obtained as adjunctive guides to therapy. When empyema or bacteremia complicates lung abscess, adequate specimens for microbiologic evaluation may be obtained from the pleura or blood. However, to obtain adequate specimens from the abscess, bronchoalveolar lavage, the use of a protected double-lumen catheter, or percutaneous transthoracic aspiration under radiographic guidance is recommended. The specific procedure selected depends on the location of the infection and the expertise of the institution. Specimens collected through a fiberoptic bronchoscope, using bronchoalveolar lavage or a plugged double-lumen sampling catheter with a protected sampling brush, are generally preferred; these require the use of quantitative cultures. Growth at a dilution of 10 from a protected brush represents

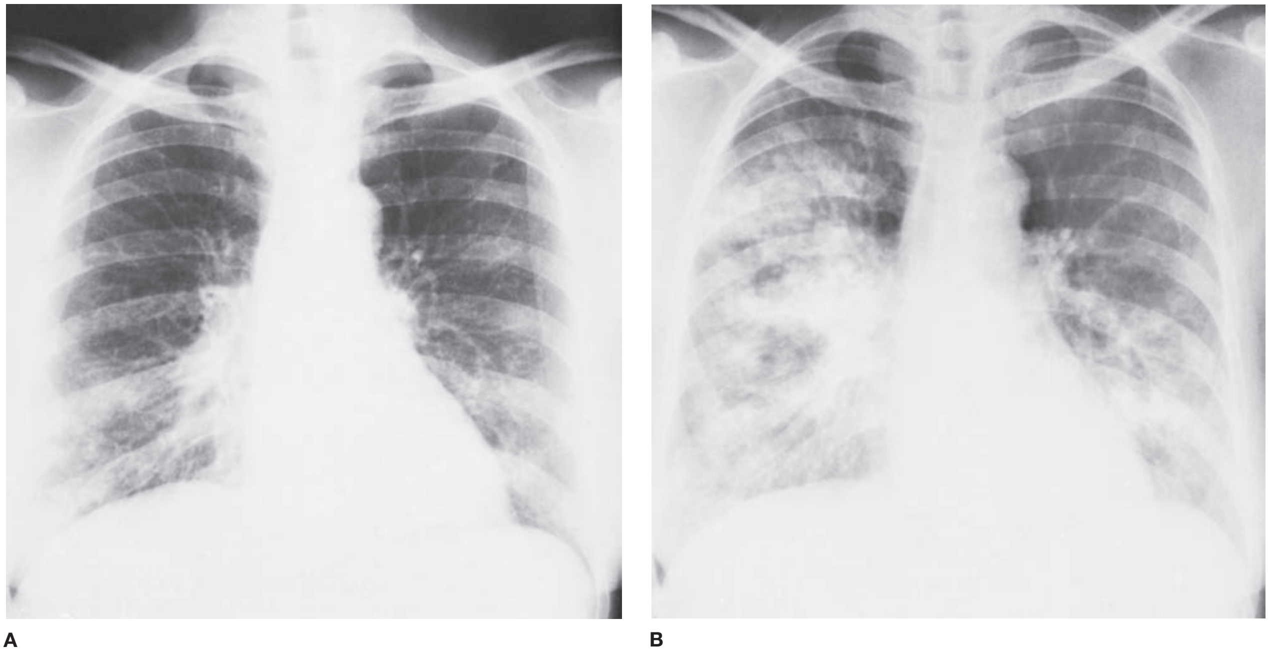

Figure 127-5 Fulminating anaerobic pneumonia in a 44-year-old woman with onset of pneumonia 6 days before admission. **A.** Day of admission. Patchy consolidation in right lower lung field and behind the cardiac silhouette. **B.** One day after admission: Extensive patchy alveolar infiltrates bilaterally with areas of rarefaction on right suggestive of cavitation. The patient died 2 days later.

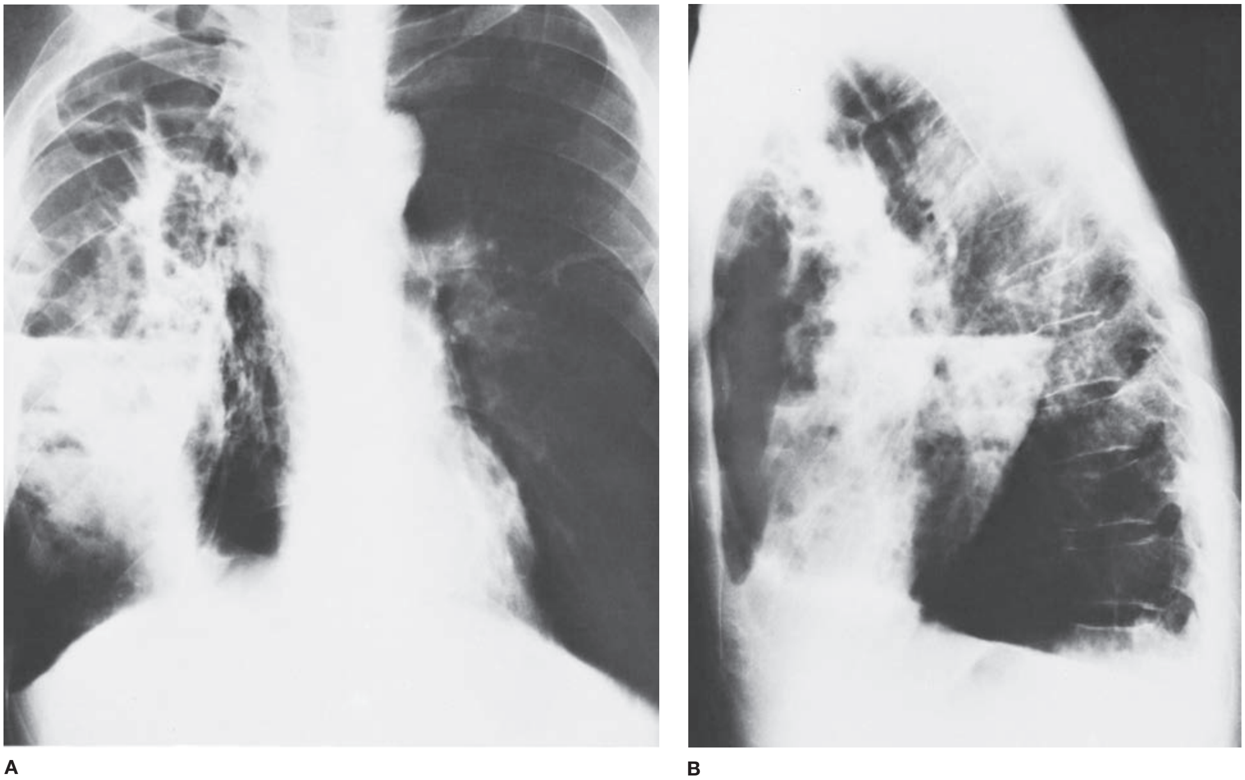

Figure 127-6 "Gangrene" of the lung after aspiration—anteroposterior (**A**) and lateral (**B**) views. Extensive cavitation following necrotizing pneumonia in a 65-year-old man.

approximately 10^{10} organisms per milliliter in the lower respiratory tract. Recovery of nonbacterial and anaerobic bacteria from these specimens has not been well standardized. Specimens obtained from blind, deep suctioning via an endotracheal tube may also be useful if cultured quantitatively and examined microscopically.

■ Treatment

The treatment of lung abscess must be guided by the microbiology and knowledge of any underlying or associated conditions that may predispose to the development of severe pulmonary infection. A small abscess in an otherwise healthy person may respond to conservative management with antimicrobial therapy and chest physical therapy. A rapidly expanding pulmonary abscess in an immunocompromised host (e.g., due to mucormycosis) requires urgent lung resection in addition to antimicrobials. Intermediate to these approaches is the use of bronchoscopic-guided or radiographically guided catheter drainage of any fluid and necrotic debris. In the absence of antibiotics, the mortality of lung abscess is approximately 33%.[105] However, up to half of patients surviving a lung abscess acutely in the preantibiotic era had significant pulmonary complications, including recurrent infections and abscesses, pleural empyema and adhesions, chronic bronchitis, and bronchiectasis. The introduction of penicillin, orally or parenterally administered, resulted in resolution or collapse of the abscess in up to 90% of patients (although long courses of treatment were often needed). Therefore, these patients could avoid surgical resection.

The role of drainage or surgery is based on serial clinical assessments of the patient. Bronchoscopic drainage may be most useful

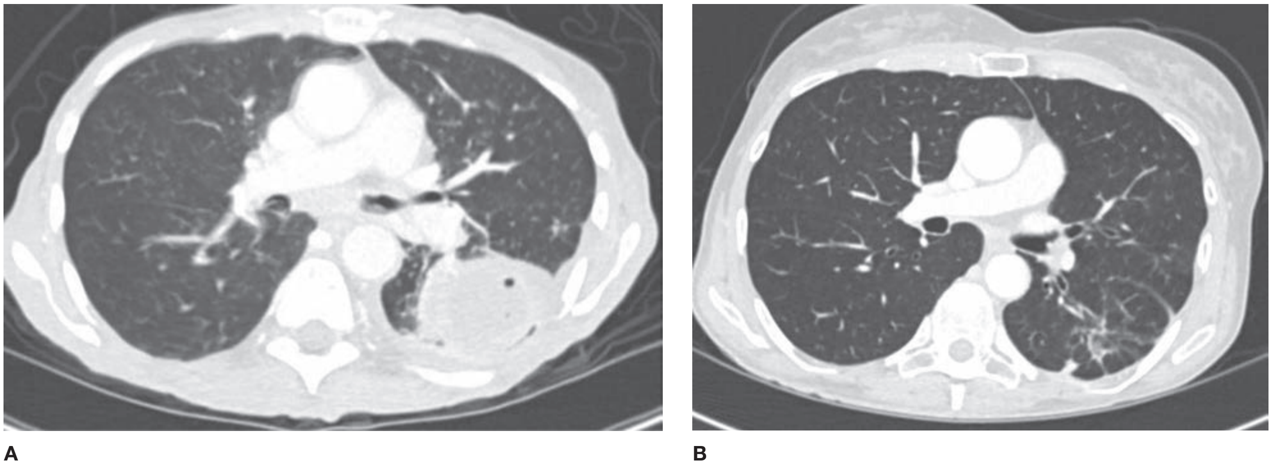

Figure 127-7 CT of a pulmonary abscess in 64-year-old with COPD (**A**) prior to antibiotics and (**B**) 2 months after antibiotics. Bronchoscopy and CT cultures were nondiagnostic.

TABLE 127-6 Organisms and Conditions Associated with the Radiographic Appearance of Lung Abscess

Infectious
Bacteria
Anaerobes, *Staphylococcus aureus*, Enterobacteriaceae (e.g., *Klebsiella pneumoniae*), *Pseudomonas aeruginosa*, *Burkholderia pseudomallei*, streptococci, *Legionella* spp., *Nocardia asteroides*, *Rhodococcus equi*, *Actinomyces* spp.
Mycobacteria (often multifocal)
M. tuberculosis, *M. avium* complex, *M. kansasii*, *M. malmoense*, other nontuberculous mycobacteria
Fungi
Aspergillus spp., zygomycetes, *Histoplasma capsulatum*, *Blastocystis hominis*, *Coccidioides immitis*, *Cryptococcus neoformans*, *Pneumocystis jiroveci*, *Penicillium marneffei*
Parasites
Entamoeba histolytica, *Paragonimus westermani*, *Strongyloides stercoralis* (postobstructive)
Miscellaneous
Empyema (with air–fluid level), septic embolism (endocarditis)
Noninfectious and Predisposing Conditions
Anatomic, fluid-filled cysts, bland infarction, bronchiectasis, vasculitis, Goodpasture syndrome, granulomatosis with polyangiitis (formerly Wegener granulomatosis), periarteritis, obstruction (neoplasm, foreign body), pulmonary sequestration, pulmonary contusion, carcinoma

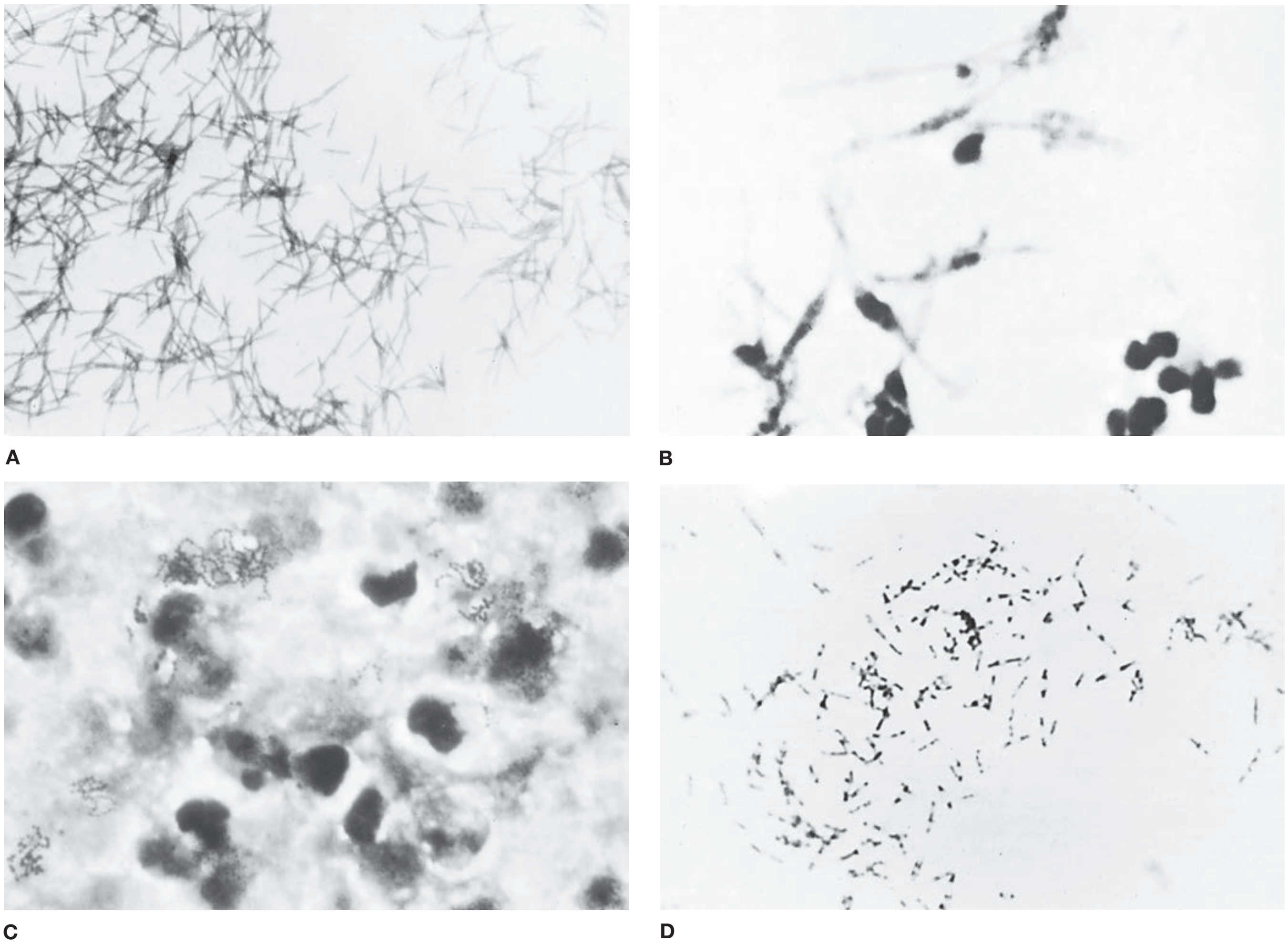

Figure 127-8 Bacteriology of empyema and lung abscess. **A.** *Fusobacterium nucleatum*, microscopic morphology. Organism is a thin and delicate Gram-negative bacillus with tapered ends (sometimes filamentous). **B.** Pleomorphic Gram-negative bacillus with filaments containing swollen portions and with large round bodies. This appearance is seen with *F. necrophorum*, *F. mortiferum*, and *F. varium*. **C.** Pus showing microaerophilic streptococcus. **D.** Microscopic morphology of *Bacteroides fragilis*. Organism is an irregularly stained, Gram-negative rod. Bipolar staining may be seen.

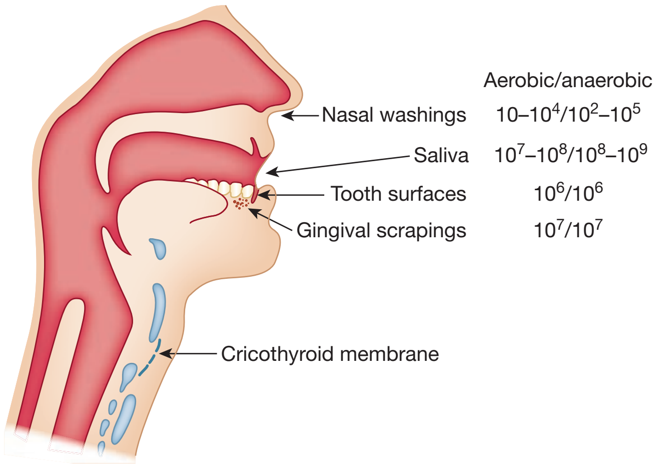
Aerobic/anaerobic
Nasal washings $10–10^4/10^2–10^5$
Saliva $10^7–10^8/10^8–10^9$
Tooth surfaces $10^6/10^6$
Gingival scrapings $10^7/10^7$
Cricothyroid membrane

Figure 127-9 Sagittal section illustrating presence of large numbers of organisms, including anaerobes, as indigenous flora in upper respiratory tract. (Values given as number of aerobic/anaerobic organisms per milliliter.) *(Reproduced with permission from PD Hoeprich.)*

in the relief of abscesses without air–fluid levels, which indicate the possibility of a persistent connection with the bronchi.[106] However, experience dictates caution with the bronchoscopic drainage of closed cavities; spillage of cavity contents into other lung segments may produce catastrophic pulmonary dysfunction. Further, there are few data to suggest that bronchoscopic drainage offers a significant advantage in terms of rapidity of recovery in the immunologically normal host. In patients with coexistent empyema and lung abscess, it is often useful to address drainage of the empyema first, stabilizing the patient and then considering further procedures for the lung abscess. In critically ill patients or those with bronchial obstruction related to the abscess cavity, bronchoscopic drainage should be considered.

Bronchoscopy and chest CT have major roles in the evaluation of the patient failing therapy. Persistence of bacteremia or high-grade fevers after 72 h, or the absence of change in sputum production or character or in the radiographic images over 7 to 10 days, suggests unappreciated anatomic or microbiologic problems. Obstruction or resistant organisms (including fungi, parasites, or mycobacteria) may be present. Multiple loculations may be present, or empyema, including drainage of the abscess into the pleural space, may develop. New sites of infection, including extrathoracic sites, may have developed in the bacteremic patient. Progression of pulmonary infiltrates may occur after the initiation of appropriate antibiotic therapy, reflecting the relatively poor activity of many antibiotics at the low pH levels of poorly ventilated and underperfused, infected lung tissues, as well as the delayed radiographic response to treatment.

Surgical resection of necrotic segments of the lung is helpful if the response to antibiotics is poor, for large abscesses, or when ventilation–perfusion scans suggest little residual lung function in a limited necrotic region. Infarcted lung or rapidly progressive infection may force surgical resection of the affected tissue. Surgery is also indicated if airway obstruction limits drainage. Such presentations are seen in the presence of a tumor or a foreign body. In patients thought to be poor surgical risks, percutaneous drainage via catheters may be a useful temporizing measure. However, leakage of the abscess contents into the pleural space in such patients may be disastrous and must be avoided.

Mortality in patients with lung abscesses reflects the quality of the host's inflammatory response and overall condition. Patients with large abscesses (over 5–6 cm), progressive pulmonary necrosis, obstructing lesions, aerobic bacteria (especially *K. pneumoniae*, *S. aureus*, or *P. aeruginosa*), immune compromise, old age, malnutrition, or systemic debility, and those with major delays in seeking medical attention have a significantly increased mortality.[107]

EMPYEMA

The microbiology, diagnosis, clinical features, and management of empyema are considered below.

■ Microbiology

Pleural infections are associated with a significant degree of morbidity and mortality, with death or surgical intervention in more than 30% of patients.[108,109] In the preantibiotic era, up to 11% of cases of pneumococcal pneumonia were associated with empyema, and 64% of all cases of empyema were associated with *S. pneumoniae*. β-Hemolytic streptococci (15%) and staphylococci (8%) were the other organisms most commonly isolated from empyema fluid. In the 1960s and 1970s, with new culture techniques, one study found only anaerobic bacteria in pleural empyema fluid in 35% of cases, and a mixture of aerobic and anaerobic bacteria in 41% in a series of 83 medical patients who had not received antibiotics or surgical intervention (Tables 127-7 and 127-8; Figs. 127-8, 127-10,

TABLE 127-7 Bacteriology of Anaerobic Empyema: Predominant Flora

Organism	Number of Isolates
Anaerobic isolates	
Fusobacterium nucleatum	19
Prevotella denticola–melaninogenica group	10
Prevotella oris	9
Prevotella intermedia–nigrescens group	8
Prevotella oralis	4
Prevotella buccae	3
Bacteroides fragilis	5
Other *B. fragilis* group	6
Unidentifiable *Bacteroides* spp.	4
Bacteroides gracilis	3
Campylobacter spp.	3
Peptostreptococcus micros	9
Peptostreptococcus anaerobius	5
Peptostreptococcus spp.	4
Peptostreptococcus magnus	3
Streptococcus intermedius	5
Eubacterium spp.	7
Lactobacillus spp.	7
Actinomyces spp.	4
Actinomyces odontolyticus	3
Cutibacterium (Propionibacterium) acnes	4
Clostridium perfringens	3
Clostridium spp.	3
Aerobic isolates	
α-Hemolytic streptococcus	21
Nonenterococcal group D streptococcus	4
Coagulase-negative staphylococci	4
Proteus spp.	3

Data from Cien R, Jousimies-Somer H, Marina M, et al. A retrospective review of cases of anaerobic empyema and update of bacteriology. Clin Infect Dis. 1995;20:S224–S229.

TABLE 127-8 Correlation of Infecting Organism and Conditions Underlying Anaerobic Pleuropulmonary Infection

Bacteria	Aspiration	Tonsillitis, Tonsillectomy	Gingivitis, Dental Extraction, Pyorrhea	Bronchiectasis	Bronchogenic Carcinoma	Chest Trauma, Thoracotomy	Peritoneal Infection or Source in Bowel	Pelvic Infection
Bacteroides fragilis group	11	1	0	3	1	3	16	1
Pigmented Gram-negative anaerobic rods	13	0	7	2	0	0	2	0
Fusobacterium nucleatum	24	2	7	4	4	4	6	1
Fusobacterium necrophorum	2	45	2	1	2	0	5	4
Peptostreptococcus	27	5	9	4	2	10	6	8
Microaerophilic streptococcus	17	0	5	0	4	0	5	1
Anaerobic, non–spore-forming, catalase-negative, Gram-positive rods	6	1	0	1	2	1	3	0
Clostridium	6	3	1	0	0	15	7	

Data from Finegold SM: Anaerobic Bacteria in Human Disease. New York, NY: Academic; 1977.

and 127-11). With the introduction of sulfa drugs and penicillins, the expansion of thoracic surgery, and the emergence of antibiotic resistance in staphylococci, the isolation of *S. pneumoniae* from empyema fluids decreased, and that of *S. aureus* and other nosocomial pathogens increased. In more recent studies of empyema, the pneumococcus accounts for only 5% to 10% of cases, whereas anaerobes are found in 25% to 40%. The highest yield reported in recent years is a collaborative study at Cook County Hospital in Chicago and two VA hospitals in Los Angeles. Anaerobes were recovered in 63 (76%) of 83 cases.[4]

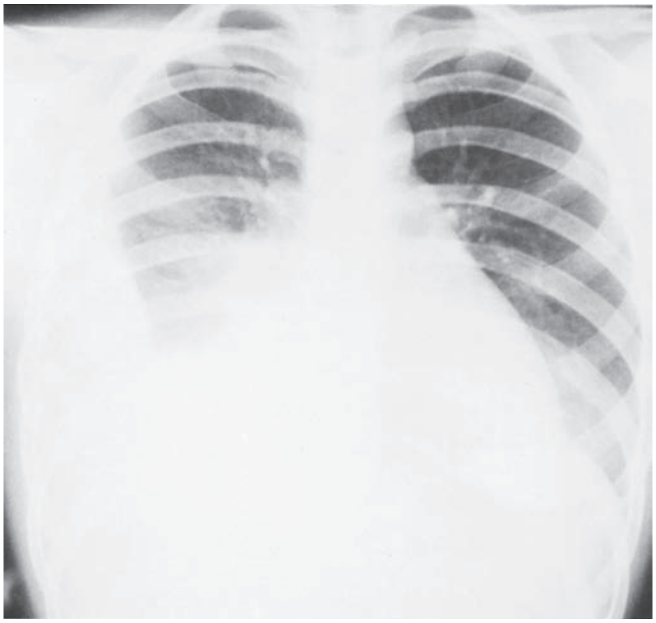

Figure 127-10 Large anaerobic empyema accompanying right middle-lobe pneumonia.

Anaerobic Bacteria in Empyema

The frequency of anaerobic infection of the lung and pleural space is a function of the colonization pattern of the individual patient, including the presence of hospital-acquired pathogens and the role of aspiration in many of these infections (Tables 127-7 and 127-8). The most frequent isolates are the anaerobes *Prevotella*, *F. nucleatum*, and *Peptostreptococcus*, and the streptococci. In early studies, the *B. fragilis* group was isolated from 15% to 20% of patients with anaerobic pleuropulmonary infections. However, later studies employing newer techniques and utilizing newer taxonomic criteria found *B. fragilis* group in only 6.8% of 46 patients with pleural empyema specimens. The *B. fragilis* group is important because of resistance to penicillin (a property shared by a number of common anaerobes) and other antimicrobial agents. Subdiaphragmatic infection may extend to the lung or pleural space by way of lymphatics, directly through the diaphragm or defects in it, or by way of the bloodstream. Anaerobic pulmonary and pleural processes rarely extend to the chest wall unless associated with actinomycosis, tuberculosis, or tumor.

Nonanaerobic Infections

In immunologically normal adults, the aerobic organisms currently most often associated with empyema and lung abscesses are *S. aureus*, β-hemolytic streptococci, and various Gram-negative aerobic or facultatively anaerobic bacilli, particularly *P. aeruginosa*, *E. coli*, *Klebsiella* species, and other nosocomial enteric Gram-negative organisms—reflecting infections associated with pneumonia treated with antimicrobial agents to which the causative organism is resistant, with thoracic surgery or high-grade bacteremias. Mixed aerobic–anaerobic infections are often related to subdiaphragmatic processes. Increasingly, *Mycobacterium tuberculosis*, *Nocardia asteroides*, and fungi have been identified. In the immunocompromised host, the infecting organisms will more often be Gram-negative bacteria (especially *Pseudomonas* and *Enterobacter)*, less virulent streptococci, *Aspergillus*, other fungi (e.g., *Mucoraceae*, *Fusarium* species, *Scedosporium* species, *Cryptococcus* species, rarely *Candida*

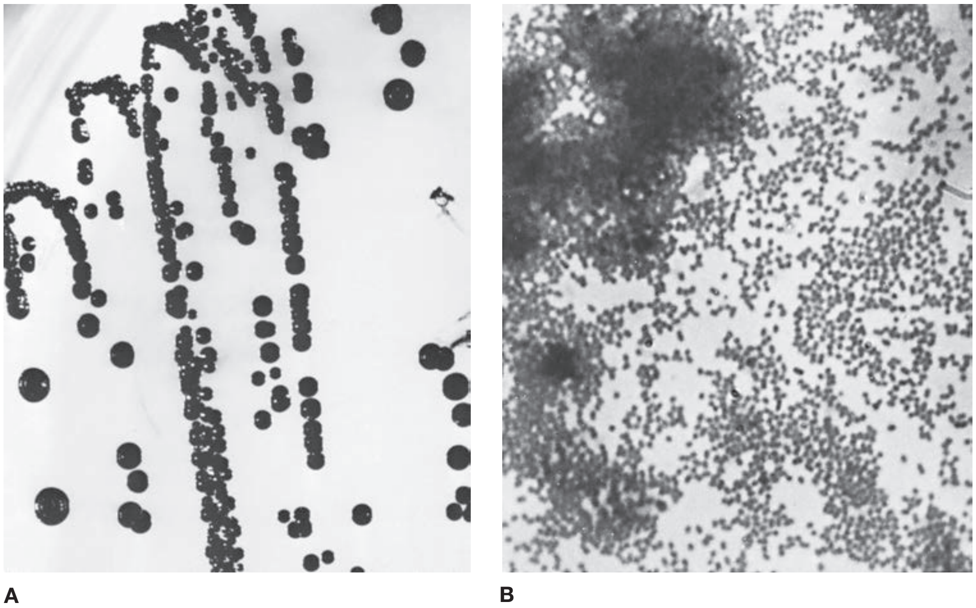

Figure 127-11 *Prevotella melaninogenica*. **A.** Distinctive black colonies (on blood-containing medium); pigment is hematin. **B.** Microscopically, the organism is a coccobacillus.

species), or will be due to reactivation of latent or subclinical infections due to *M. tuberculosis*. In all hosts, the colonization pattern of the individual will often predict the causative organisms, even if these are not easily isolated.

■ Clinical Features

The pathogenesis and presentation of both pleural empyema and lung abscesses are often indistinguishable. Shared presentations of empyema and lung abscess include the indolent development of symptoms, most often fever, sweats, cough, dyspnea, weight loss, and pleurisy; an association with conditions predisposing to aspiration events (altered consciousness, dysphagia, and gingivitis); and foul odors of sputum or breath associated with anaerobic bacteriology. Lung abscesses and empyemas often coexist. Both are generally associated with primary pneumonias.

The clinical presentation of empyema is determined by the underlying cause of infection. Empyema associated with aspiration pneumonia may develop over 1 to 3 weeks, usually with associated symptoms of pneumonia. The patient may have high fever and leukocytosis. Physical examination reveals dullness to percussion and decreased breath sounds on auscultation. These changes may be quite localized in the setting of loculated fluid. The empyema fluid is generally purulent by the time of detection, but pleural infection may be noted only after treatment for pneumonitis has failed to resolve fever or pleurisy. Empyema associated with thoracic surgery may be radiologically “hidden” in areas of the chest not drained by chest tubes or behind relatively benign pleural effusions. The patient may appear minimally toxic or severely ill, depending on the extent of the infection and organisms present. The presentation is modified by routine prophylactic antibiotic use, sedation, intubation, and antipyretics. Acute empyema may be seen in staphylococcal and streptococcal infections and following rupture of hepatic abscesses, especially those due to *E. histolytica*.

■ Radiologic Diagnosis

With empyema, chest radiographs generally reveal fluid, most often in the costophrenic angles; free-flowing effusions layer on lateral decubitus radiographs. The use of bedside ultrasound (Fig. 127-12) is useful in guiding drainage of these fluid pockets. Loculations and pleural disease are often best defined by computed tomography of the chest, which should include the neck and diaphragms to rule out extrathoracic sites of infection. Spinal disease is better detected with magnetic resonance imaging (MRI). Before invasive diagnostic procedures, a careful history and physical examination may suggest a reason for the accumulation of pleural fluid. Noninfectious causes include bland pulmonary embolus, malignant effusion, benign postsurgical changes, pericardiotomy syndrome, collagen vascular diseases (systemic lupus, rheumatoid arthritis), congestive heart disease, sympathetic effusion related to subdiaphragmatic disease (pancreatitis), leakage of ascites or peritoneal dialysis fluids, and hemorrhage (from venous access catheters or aortic tears).

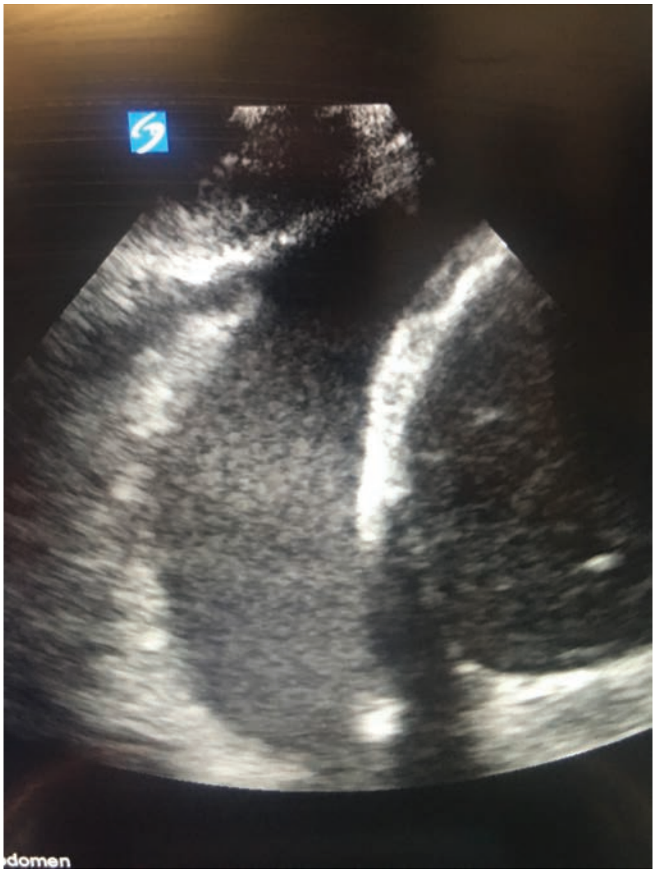

Figure 127-12 Ultrasound of pleural fluid pocket.

Infectious causes include extension of all classes of pulmonary infections from the lungs (parapneumonic), esophageal rupture, parapharyngeal space drainage, drainage, or sympathetic effusion due to hepatic or subdiaphragmatic abscesses, septic metastasis, and direct infection via thoracic defects or chest tubes used for pleural drainage. Pyopneumothorax, in the absence of bronchopleural fistula, prior surgery, or prior thoracentesis, suggests the possibility of gas formation by bacteria implicated in the infection. Although nonspecific, pyopneumothorax suggests a component of anaerobic infection.

Laboratory Diagnosis

The diagnosis of empyema is based on the characteristics of thoracic fluid. The urgency for diagnosis is due to the development of pleural scar and of loculated effusions in the presence of undrained pus. Thus, diagnostic thoracentesis should be attempted unless the nature of the pleural fluid is clear or the clinical risk to the patient is too great. Pleural fluid analysis should include Gram stain and cultures (routine, anaerobic, mycobacterial, and fungal), parasitologic examination when appropriate, fluid cell count and differential, cytology, pH, lactic dehydrogenase, total protein, and glucose measurements at a minimum (Chapter 76). Purulent fluid requires drainage. Empyema is diagnosed on the basis of the neutrophilic predominance in fluids with more than 25,000 white blood cells per milliliter. Parapneumonic effusions will generally have lower white blood counts, negative Gram stains and cultures, a pH over 7.3, and glucose greater than 50% of serum glucose levels. Parapneumonic fluids may become infected over time. Blood cultures and sputum cultures should be obtained as adjunctive guides to therapy.

Treatment

The management of empyema includes antimicrobial treatment, identification and treatment of any anatomic processes, and drainage of the infected fluid. The approach to a specific patient is based on the clinical status of the patient as well as the microbiology of the infection. For example, patients with empyema following thoracic surgery and other hospitalized patients may have useful culture data available from chest tube drainage samples or sputum cultures to assist in the selection of antibiotics. The Gram stain may indicate the predominant organism type. Mixed aerobic and anaerobic organisms may be the first suggestion of esophageal tear or parapharyngeal infection. Fastidious organisms (*S. pneumoniae*, anaerobes) may be seen on Gram stain but not isolated in culture. Antibiotic susceptibility data should be used to guide therapy, especially in nosocomially acquired infection. Local administration of antibiotics (e.g., inhaled, instilled) is unnecessary and may be irritating; intrapleural injection of antibiotics should be reserved for pleural ablation (pleurodesis), as may be achieved with erythromycin.

The decision to drain a pleural fluid collection is based on the characteristics of the fluid. In the presence of pleural fluid and unexplained fever, leukocytosis, or bacteremia, or in the postoperative patient, thoracentesis should be performed routinely. Noninfected parapneumonic pleural effusions resolve with appropriate treatment

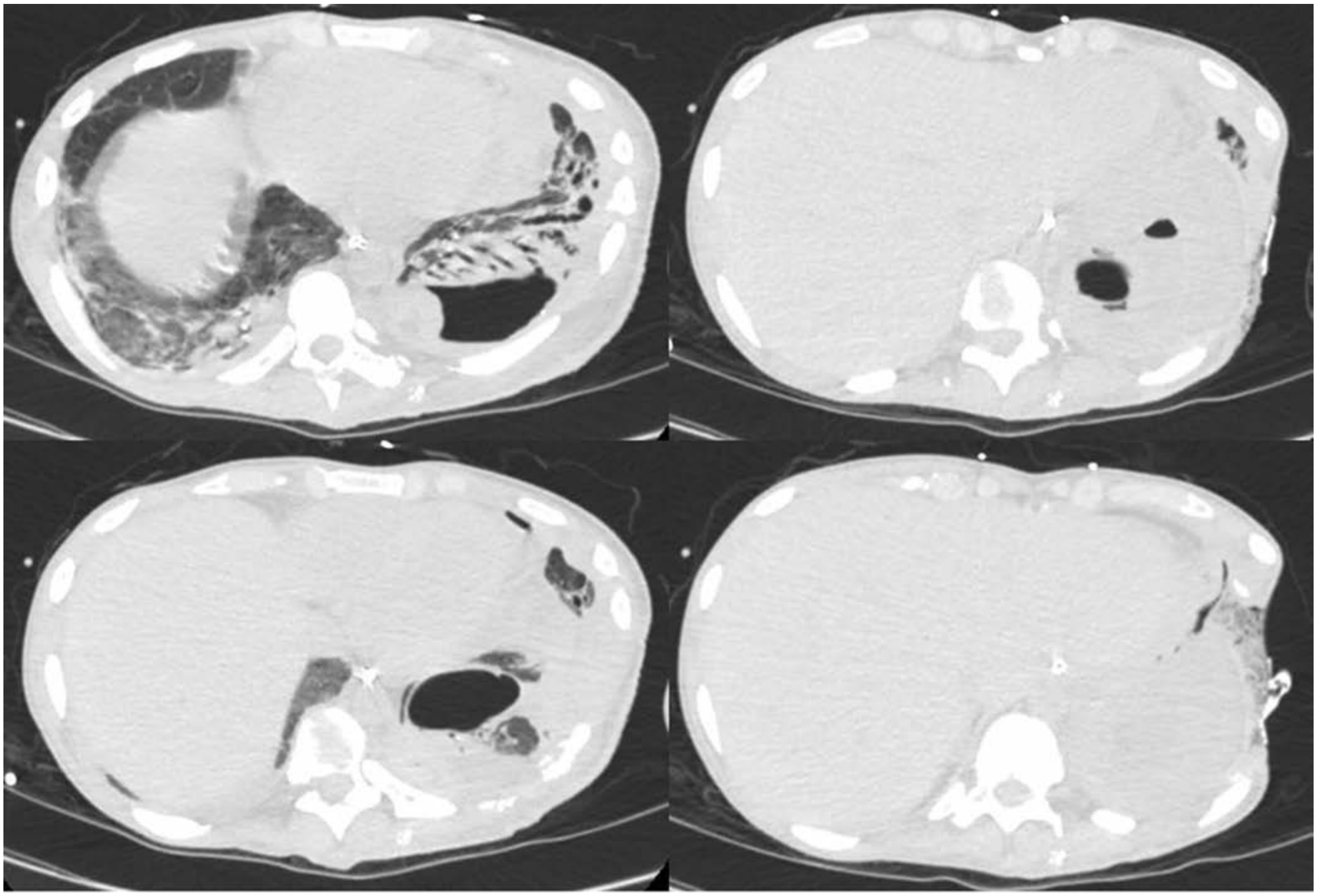

Figure 127-13 Representative cross-sectional imaging of an 18-year-old male, previously described in Fig. 127-2. The patient underwent decortication and construction of an Eloesser flap, shown here, for a right-sided empyema that led to trapped lung. At the time these images were obtained, a wound vac was in place at the flap site. Ongoing trapped lung ultimately required a second decortication procedure.

of the underlying infections. Drainage is required if infection or frank pus is present. Highly viscous or purulent fluids and fluids with acid pH also require the insertion of a chest tube via thoracostomy or the thoracoscopic drainage of the fluid. In approximately one-third of patients, however, drainage through a chest tube along with antibiotic treatment fails to cure an empyema, necessitating surgical intervention.[110] This may be improved through use of DNase plus tissue plasminogen activator (t-PA) instilled through the chest tube. The use of these two agents in combination has been shown to decrease the number of patients who require surgical intervention.[111]

In the early or exudative phase of parapneumonic effusion, the fluid is thin and serous or serosanguineous. This may resolve during appropriate antibiotic therapy either without drainage or with multiple needle aspirations. If the pH is over 7.3, this method may be preferred. If the pH is less than 7.0, however, complete drainage should be performed, often requiring closed chest tube insertion. If the pH is between 7.0 and 7.3, failure to demonstrate improvement of infection or inflammation on multiple thoracenteses over 3 to 4 days should lead to consideration of formal drainage, especially if the primary process is adequately treated. Loculation of pleural fluid or failure to respond to antimicrobial therapy may require either multiple thoracenteses guided by ultrasound or chest tomographic evaluation (CT scans) or surgical intervention. Bloody fluid or persistent parapneumonic fluid should prompt cytologic evaluation and CT scans for lung masses or undrained mediastinal or retrocardiac collections.

Empyema diagnosed later in the course, persistently infected pleural fluid, viscous fluid, or fluids with acid pH may require large-bore tube drainage. This heavily proteinaceous fluid is characteristic of the fibropurulent phase of the evolving empyema. Indications for closed chest tube placement include bronchopleural fistula with empyema, loculated fluid unresponsive to thoracentesis and antibiotics, the presence of blood clots, and rapidly accumulating empyema not otherwise manageable. Under suction, and with removal of the gel-like material, pus, and clots, the lung expands and obliterates the empyema space. Failure to expand the underlying lung, persistence of drainage beyond 7 days, inability to achieve drainage assessed radiologically, fever without change in 2 to 3 days, or pus formation with persistent infection (as opposed to colonization of the chest tubes) necessitates a search for undrained foci of infection, failure to close a bronchopleural fistula or esophageal tear, undetected rupture of a lung abscess, or antibiotic failure. As the infection enters the chronic phase, open drainage with rib resection or pleurocutaneous fistula formation (such as with an Eloesser flap, Fig. 127-13) may be needed, with or without decortication, to achieve lung expansion and healing. Open drainage is obtained by making the pleura adherent to the chest wall during the insertion of chest tubes directly into the empyema cavities. Drainage achieved too late in the course of infection may result in the development of pleural scar and fibrous peel with restrictive pulmonary physiology. Decortication may be needed to achieve sterilization of the pleural space and restore lung expansion. Thoracoscopic drainage of empyema has been used with excellent results at a number of institutions, particularly in children. Often, thoracoscopic drainage of empyema is used as a temporizing maneuver (e.g., following acute rupture of a lung abscess into the pleural space). Patients achieving rapid re-expansion of the lungs may avoid open drainage procedures while achieving limited decortication and disruption of loculations. Alternatively, once a patient is stabilized and can better tolerate open drainage or has demonstrated an inability to resolve the empyema without further drainage, surgical intervention may be needed. Early, aggressive treatment of empyema may reduce the duration of hospitalization and the risk of nosocomial superinfection.

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CHAPTER 128

Acute Bronchitis and Community-Acquired Pneumonia

James M. Walter
Richard G. Wunderink

INTRODUCTION

Acute bronchitis (or tracheobronchitis) and community-acquired pneumonia are two prevalent disorders in the general population. In this chapter we discuss important clinical aspects of these infections, including diagnostic approaches and treatment strategies.

ACUTE BRONCHITIS

Acute bronchitis is inflammation of the large airways without evidence of pneumonia. Approximately 5% of adults develop acute bronchitis in a given year, resulting in approximately 100 million ambulatory care visits in the United States.[1] Consumers in the United States spend roughly $7 billion annually on the management of cough—the most common symptom of acute bronchitis.[2]

Respiratory viruses, including rhinovirus, coronavirus, parainfluenza virus, respiratory syncytial virus, human metapneumovirus, and influenza virus, are responsible for up to 90% of cases (although many patients with acute bronchitis do not have a specific pathogen identified).[1,3] The important role of respiratory viruses in disease pathogenesis helps explain the increased incidence of acute bronchitis in the fall and winter. *Bordetella pertussis*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae* are the bacteria most frequently identified in immunocompetent adults with acute uncomplicated bronchitis in the absence of chronic lung disease.[4] *Moraxella catarrhalis*, *Haemophilus influenzae*, and *Streptococcus pneumoniae* are more common in patients with chronic obstructive pulmonary disease (COPD) and possibly in smokers without overt COPD.

Cough, with or without sputum production, is the hallmark of acute bronchitis. Although patients with purulent sputum are more frequently prescribed antibiotic therapy, sputum appearance is an unreliable surrogate for bacterial infection and does not identify patients more likely to benefit from antibiotics.[4,5] On average, cough lasts for 10 to 20 days but can persist for more than a month.[6] Patients may also endorse headaches, rhinorrhea, and mild constitutional symptoms.

Given the self-limited nature of acute bronchitis, the goal of a clinical evaluation is to exclude potentially life-threatening diagnoses whose symptoms may overlap with acute bronchitis, including pneumonia and exacerbations of asthma, COPD, and congestive heart failure (CHF). In younger patients without comorbidities, a persistent cough coupled with normal vital signs and a reassuring physical examination is sufficient to diagnose acute bronchitis.[7] For elderly patients and those with chronic health conditions, basic laboratory testing and a chest radiograph are often required to exclude more concerning diagnoses.

Although a large number of both over-the-counter and prescription pharmacotherapies are available for the symptomatic management of acute bronchitis, evidence to support the efficacy of any specific medication is minimal.[8,9] Guidelines do not recommend the routine prescription of antitussives, inhaled bronchodilators, oral corticosteroids, or other oral anti-inflammatory medications.[7] Management is, therefore, supportive, and plans should be made for clinical re-evaluation if a patient experiences persistent or progressive symptoms. The development of "red flag" symptoms including hemoptysis, worsening dyspnea, weight loss, difficulty swallowing, and persistent fever should trigger a more urgent evaluation.[10]

An ongoing challenge in the management of acute bronchitis is the recalcitrant nature of antibiotic overuse. Guidelines from professional societies and the Centers for Disease Control and Prevention (CDC) uniformly recommend avoiding antibiotics for acute uncomplicated bronchitis.[1,11] Indeed, the Infectious Diseases Society of America (IDSA) includes a recommendation to avoid antibiotics for acute bronchitis as one of their five statements for the Choosing Wisely campaign.[12]

Despite these recommendations and consistent evidence that antibiotics provide minimal benefit for patients with acute bronchitis, many patients continue to receive antibiotics.[13,14] In an analysis of ambulatory care prescription practices in the United States from 1996 to 2010, the overall antibiotic prescription rate for acute bronchitis was 71%, a rate that actually rose during the study period.[15] Similarly, in a 2020 evaluation of data from a large U.S. healthcare network, 21% of patients evaluated in the outpatient setting for respiratory conditions for which antibiotics were not indicated (including acute bronchitis) received antibiotic therapy.[16]

Reducing antibiotic use for acute bronchitis is the focus of ongoing efforts by professional societies and the CDC.[1,17] Results from a Cochrane group review suggest C-reactive protein (CRP) testing, procalcitonin-guided management, and shared decision-making may be valuable tools to aid these efforts.[18]

COMMUNITY-ACQUIRED PNEUMONIA

Pneumonia is defined as an infection of the pulmonary parenchyma from the level of the respiratory bronchioles to alveoli.[19] Clinically, pneumonia can be recognized by the presence of a new lung infiltrate coupled with any of the following: new or increased cough, dyspnea, pleuritic chest pain, purulent sputum, confusion, fever, hypoxemia, rales, leukocytosis, or leukopenia.[20]

Introduction

The diagnosis and treatment of pneumonia is guided by the setting in which it develops. Pneumonia that occurs in community-dwelling individuals is termed *community-acquired pneumonia* (CAP). *Hospital-acquired pneumonia* (HAP) is defined as pneumonia that occurs 48 h or more after hospital admission, while *ventilator-associated-pneumonia* (VAP) is defined as pneumonia occurring 48 h or more after endotracheal intubation.[21] *Healthcare-associated pneumonia* (HCAP), a categorization meant to identify community-dwelling individuals at particularly high risk of infection with drug-resistant pathogens, was removed from recent Infectious Diseases Society of America–American Thoracic Society (IDSA–ATS) clinical practice guidelines.

In this chapter we review the epidemiology, diagnosis, and treatment of adults with CAP. Pneumonia in severely immunosuppressed patients—including those with advanced human immunodeficiency virus (HIV) infection or prolonged neutropenia, solid organ transplant recipients, and patients undergoing chemotherapy—are not discussed here given the unique epidemiology and management considerations; see Chapter 123 for discussion of pneumonia in the immunocompromised host.[22]

Epidemiology

CAP imposes a sizeable burden on our healthcare system. While conditions such as myocardial infarction and stroke receive significantly more preventative resources, CAP is associated with higher rates of hospitalization and total healthcare costs.[23] In the United States, pneumonia accounts for 1.5 million annual visits to the emergency department (ED) and is a leading cause of admission to the hospital.[24,25] Due in part to an aging population, the number of patients with CAP who require care in the intensive care unit (ICU) has significantly increased, especially among the elderly and patients with comorbidities.[26]

CAP is the eighth leading cause of death in the United States.[27] Worldwide, lower respiratory tract infections including CAP are the fourth leading cause of mortality, accounting for 2.6 million annual deaths.[28] In low-income countries, lower respiratory tract infection trails only neonatal conditions as the leading cause of death.

In 2019, pneumonia caused 43,881 deaths in the United States with an age-adjusted death rate of 10.8 deaths per 100,000 persons.[29] Encouragingly, between 1999 and 2019, both the percentage of total deaths due to pneumonia and pneumonia mortality rates per 100,000 persons fell. However, the pace of this decline lags behind other infectious diseases such as HIV.[30] Additionally, deaths from sepsis, acute respiratory distress syndrome caused by CAP, or those in which pneumonia occurs as a complication of a chronic progressive illness, such as Alzheimer dementia or end-stage malignancy, are likely not captured in the above figures, given differences in coding intended to maximize reimbursement. Prospective incidence studies suggest a higher incidence of CAP-associated mortality than is noted in death certificates.[31,32]

While CAP is an acute time-limited illness, it is associated with increased long-term mortality. Nearly one-third of patients hospitalized for CAP die within 1 year.[32] For patients admitted to the ICU, 1-year mortality approaches 50%.[31] Patients hospitalized for CAP experience long-term mortality rates more than three times higher than matched population controls.[33] Interestingly, an episode of CAP has been shown to increase a patient's risk of long-term mortality irrespective of age.[34]

Several factors may explain these observations. CAP disproportionally impacts the elderly and those with chronic health conditions, groups at increased risk of death irrespective of pneumonia (Fig. 128-1). Multiple studies suggest that CAP increases the risk of both short- and long-term cardiovascular disease including myocardial infarction, cerebrovascular accidents, and heart failure.[35] Notably, even for patients without chronic health conditions at the time of hospitalization, post-CAP mortality is frequently driven by cardiovascular disease, cancer, or renal failure.[36] Evidence of subclinical inflammation at hospital discharge is common and is independently associated with death in the months that follow. These observations raise the possibility that CAP, or the subclinical inflammation that often follows, may accelerate the emergence of life-limiting medical conditions. This pattern is even more evident for CAP caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

The most rigorous recent investigation of CAP epidemiology in the United States is the University of Louisville Pneumonia Study—a 2-year population-based cohort study of adults hospitalized with CAP in Louisville, Kentucky.[32] In this study, the annual age-adjusted CAP incidence was 649 patients hospitalized per 100,000 adults. Older adults experienced significantly higher rates of CAP requiring hospitalization (2093 per 100,000 persons for adults ≥65 years of age compared with 327 per 100,000 persons for adults <65 years of age). CHF and COPD were associated with the highest risk of CAP, with rates for patients with COPD exceeding 5800 patients hospitalized per 100,000 persons.

Patients with CAP frequently require care in the ICU. In a secondary analysis of the University of Louisville Pneumonia Study, 23% of patients were admitted to the ICU.[31] The incidence of CAP requiring ICU admission was 145 cases per 100,000 adults. Not surprisingly, patients older than 75 years of age and those with CHF or COPD experienced the highest incidence of ICU admission. These findings align with data from the CDC's Etiology of Pneumonia in the Community (EPIC) study in which 21% of patients required admission to the ICU.[37]

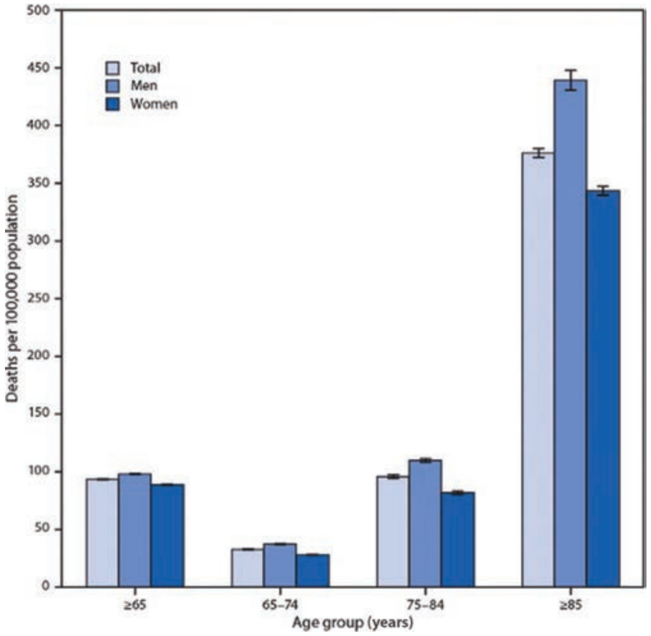

Figure 128-1 Death rates from influenza and pneumonia among persons 65 years of age or older grouped by sex and age—National Vital Statistics System, United States, 2018. *Bars* show death rates per 100,000 population within each age group; 95% confidence intervals are shown with *error bars*. *(Reproduced with permission from QuickStats: Death Rates from Influenza and Pneumonia Among Persons Aged ≥65 Years, by Sex and Age Group—National Vital Statistics System, United States, 2018. MMWR Morb Mortal Wkly Rep. 2020;69(40):1470.)*

Recognition of the important link between structural determinants of health (including but not limited to air quality, housing and food insecurity, and reduced access to healthcare services) and CAP epidemiology has been increasingly recognized.[38] When areas of Louisville were grouped according to a deprivation index, adults living in high-deprivation areas had both a higher CAP incidence and a significantly higher odds of severe CAP than adults in low-deprivation areas. These findings emphasize the need to consider socioeconomic and environmental factors when designing interventions to improve CAP prevention and treatment. The inequities observed during the coronavirus disease 2019 (COVID-19) pandemic highlight the urgency of this work.[39]

■ Microbiology

Several factors complicate an accurate characterization of CAP microbiology. Many patients who are initially diagnosed with CAP ultimately receive an alternative diagnosis. In a prospective study of 259 patients diagnosed with CAP at a Veterans Health Administration hospital, 44 (17%) were eventually diagnosed with a noninfectious cause for their symptoms including pulmonary edema, interstitial lung disease, and malignancy.[40]

Additionally, despite advances in diagnostic testing, a causative pathogen is identified for only a minority of patients with CAP. In the landmark CDC EPIC study, which performed rigorous microbiologic testing in 2259 adults hospitalized with CAP, no pathogen was identified in 62% of patients (Fig. 128-2).[37] Over the past two decades, the percentage of patients hospitalized in the United States with pneumonia who had no reported pathogen increased

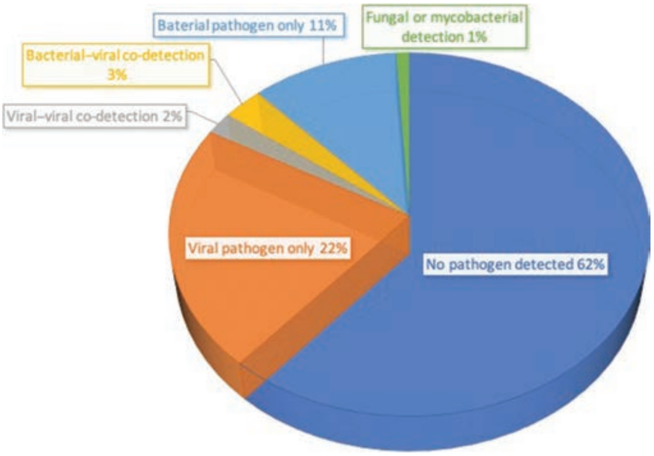

Figure 128-2 Type of pathogen detected among 2259 adults hospitalized adults with community-acquired pneumonia in the CDC-EPIC study.

by almost 20% (Fig. 128-3).[41] Factors that may contribute to the large percentage of CAP patients in whom no pathogen is identified include the widespread emphasis on prompt antibiotic administration for acutely ill patients, successful vaccination programs against *S. pneumoniae*, the variable ability of patients to provide a high-quality sputum sample, persistent limitations in our ability to distinguish "normal respiratory flora" from causative CAP pathogens, and the imperfect sensitivity of diagnostic testing of the upper airway.

Despite these diagnostic uncertainties, a clear paradigm shift in our understanding of CAP microbiology has emerged. Historically, CAP has been viewed as a bacterial disease. In the preantibiotic era, rates of *S. pneumoniae* exceeded 90%.[42] As recently as the 1990s, clinical reviews referenced *S. pneumoniae* as the etiology for between 20% and 75% of CAP.[43] Other bacteria commonly cited as "classic" CAP pathogens include *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Legionella pneumophila*, *Staphylococcus aureus*, *Moraxella catarrhalis*, and *Chlamydia pneumoniae*. Apart from influenza, common respiratory viruses were viewed as minor contributors to CAP pathogenesis in adults.

That respiratory viruses are an important, if not the predominant, cause of CAP is now clear. What accounts for this change? First, the incidence of invasive pneumococcal pneumonia has decreased due to widespread vaccination, increased awareness of the importance of early antimicrobial therapy, and decreased rates of cigarette smoking.[44] As an example, from 1998 to 2003, adults older than 50 years of age experienced nearly a 50% decline in invasive pneumococcal disease.[45] In the CDC EPIC study, only 5% of patients had documented *S. pneumoniae* infection (Fig. 128-4).[37]

Second, an aging population has resulted in an ever-increasing number of individuals particularly susceptible to severe viral infection. There are roughly 50 million adults older than 65 years of age in the United States; this number is projected to increase to more than 80 million by 2040.[46] The elderly are up to 10 times more likely to develop viral pneumonia than younger adults and experience substantially higher morbidity and mortality with viral pneumonia.[37,47,48]

Finally, ability to detect respiratory viral pathogens in clinical practice has markedly improved. Slow and labor-intensive culture-based techniques have been largely replaced by increasingly sensitive diagnostic systems that pair nucleic acid amplification with multiplex technology, allowing multiple viruses to be tested on a single sample. A single patient sample can now be simultaneously tested for up to 35 pathogens including multiple respiratory viruses, with results typically available in less than 6 h.[49]

Driven by the above trends, viral CAP is now frequently identified in clinical practice. In the CDC EPIC study, 23% of patients had a virus identified on testing, compared with just 11% with evidence of a bacterial infection.[37] Rhinovirus was the most frequently identified pathogen overall, found in 9% of patients. Similarly, in a 2016 systematic review of 31 studies, 25% of CAP patients had a viral infection detected using polymerase chain reaction (PCR)-based testing.[50] When lower respiratory tract samples are available, the prevalence of viral infection approaches 50%.[50]

Antibiotic-resistant Pathogens

An important consideration in the evaluation of patients with CAP is the accurate identification of those at risk for infection with drug-resistant pathogens including methicillin-resistant *S. aureus* (MRSA), antibiotic-resistant and multidrug-resistant (MDR) *Pseudomonas aeruginosa*, extended-spectrum β-lactamase (ESBL)-producing Enterobacterales, and *Acinetobacter baumannii* (Table 128-1).

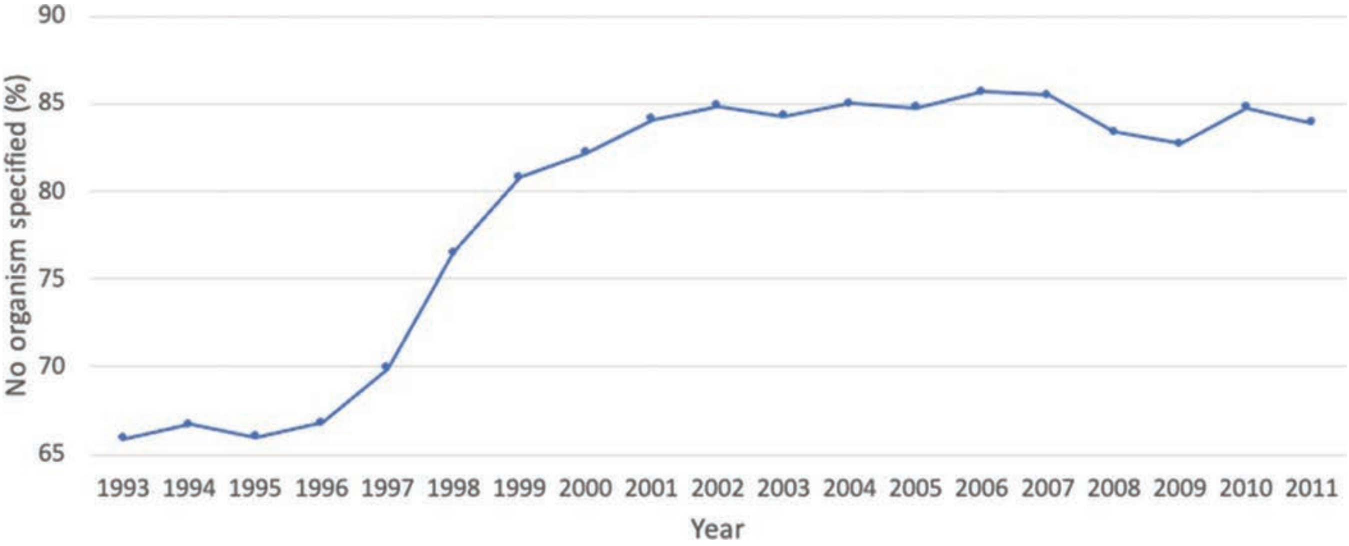

Figure 128-3 Percentage of hospital admissions for pneumonia with no pathogen identified from 1993 to 2011. *(Data from Smith SB, Ruhnke GW, Weiss CH, et al. Trends in pathogens among patients hospitalized for pneumonia from 1993 to 2011. JAMA Intern Med. 2014;174(11):1837–1839.)*

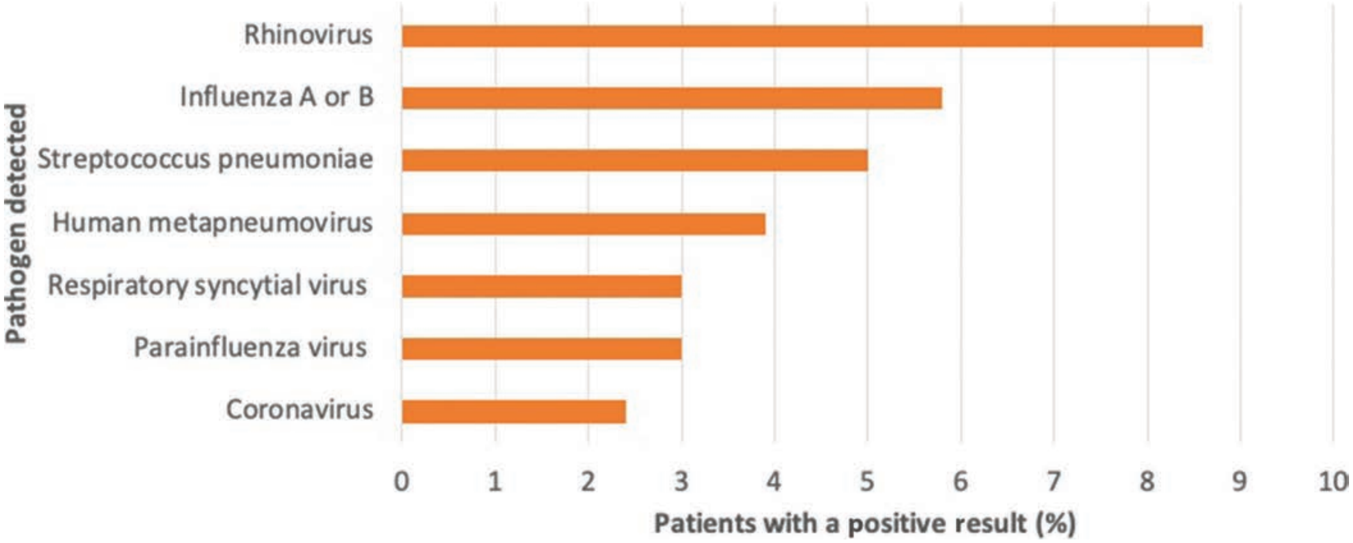

Figure 128-4 Pathogen detection among 2259 adults hospitalized adults with community-acquired pneumonia in the CDC-EPIC study. *(Data from Jain S, Self WH, Wunderink RG, et al. Community-Acquired Pneumonia Requiring Hospitalization among U.S. Adults. N Engl J Med. 2015;373(5):415–427.)*

In the Global Initiative for MRSA Pneumonia (GLIMP) study, an international multicenter point-prevalence study of 3193 patients admitted with CAP who underwent microbiologic testing within 24 h of admission, 95 (3%) were diagnosed with MRSA.[51] Among 443 patients enrolled in the United States, 22 (5%) were found to have MRSA. Risk factors independently associated with MRSA pneumonia included previous MRSA infection or colonization, recurrent skin infections, and severe disease.

In a separate analysis of the GLIMP cohort, 4.2% of patients were found to have *P. aeruginosa* while 1% were diagnosed with MDR *P. aeruginosa*.[52] In North America, 2.5% of patients were diagnosed with antibiotic-resistant *P. aeruginosa,* while 1.2% were found to have MDR *P. aeruginosa.* Independent risk factors for *P. aeruginosa* infection included prior infection or colonization with *P. aeruginosa*, tracheostomy, bronchiectasis, need for invasive respiratory support or vasopressors, and very severe COPD.

Enterobacterales were identified in 6% of the GLIMP cohort.[53] More than half these patients had an isolate resistant to at least one antibiotic, while 1.2% of the study cohort was found to have an MDR pathogen. Independent risk factors for Enterobacterales infection were male sex, severe disease, low body mass index, and prior infection with an ESBL-producing pathogen.

Although drug-resistant pathogens are an uncommon cause of CAP, early identification and timely antibiotic therapy are essential given the high mortality associated with these infections.[54] The HCAP framework was intended to aid the identification of patients most likely to benefit from empiric broad-spectrum antibiotic therapy.[55] However, the criteria's poor specificity fueled widespread antibiotic overtreatment and likely worsened outcomes.[56,57]

A number of investigators have developed prediction scores to identify patients at high risk of CAP due to drug-resistant pathogens. As an example, in a review of more than 1000 patients hospitalized with pneumonia in Japan, the strongest risk factors for infection with drug-resistant pathogens were prior hospitalization, immunosuppression, previous antibiotic use, use of gastric acid–suppressing agents, tube feeding, and nonambulatory status.[58] When 3 or more risk factors were present, the rate of infection with a drug-resistant pathogen exceeded 40%. Unfortunately, most available prediction models lack the test characteristics necessary to reliably guide antibiotic selection in high-risk patients.[59]

TABLE 128-1 Select Risk Factors for Infection with Antibiotic-resistant Pathogens in Community-acquired Pneumonia[a]

MRSA	• Prior MRSA infection or colonization • Recurrent skin infections • Severe CAP
Pseudomonas aeruginosa	• Prior infection or colonization with *P. aeruginosa* • Tracheostomy • Bronchiectasis • Need for invasive mechanical ventilation or vasopressors • Very severe COPD
Enterobacterales	• Male gender • Severe disease • Low body mass index • Prior infection with an ESBL-producing pathogen

[a]Independent risk factors for infection from the Global Initiative for Methicillin-resistant Staphylococcus aureus Pneumonia (GLIMP) study.
CAP, Community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; ESBL, extended-spectrum β-lactamase; MRSA, methicillin-resistant Staphylococcus aureus.
Data from Aliberti S, Reyes LF, Faverio P, et al. Global initiative for meticillin-resistant Staphylococcus aureus pneumonia (GLIMP): an international, observational cohort study. Lancet Infect Dis. 2016;16(12):1364-1376; Restrepo MI, Babu BL, Reyes LF, et al. Burden and risk factors for Pseudomonas aeruginosa community-acquired pneumonia: a multinational point prevalence study of hospitalised patients. Eur Respir J. 2018;52(2):1701190; Villafuerte D, Aliberti S, Soni NJ, et al. Prevalence and risk factors for Enterobacteriaceae in patients hospitalized with community-acquired pneumonia. Respirology. 2020;25(5):543–551.

■ Lung Microbiome

Pneumonia has traditionally been viewed as the result of a pathogenic species invading the sterile lower respiratory tract through either aspiration or inhalation. However, a growing body of literature suggests that the respiratory system in health is home to a complex microbial ecosystem that extends from the nares to the alveoli and may include microbes traditionally viewed as pathogenic.[60] Through this lens, pneumonia can be conceptualized as an abrupt breakdown in the homeostasis of the lung microbiome—a disruption that does not necessarily require the introduction of a new pathogen. This novel framework challenges the validity of discounting certain bacteria identified on respiratory culture as "normal flora." Indeed, interest in the role of pathogen-agnostic diagnostic platforms such as metagenomic sequencing to facilitate a more nuanced approach to pneumonia pathogen detection is growing.[61,62] For additional information, please refer to Chapter 121 on the lung microbiome.

■ Clinical Evaluation

The diagnostic hallmarks of pneumonia are a new infiltrate on chest imaging, clinical evidence of infection (e.g., fever or leukocytosis), and findings suggestive of respiratory tract involvement (e.g., cough, sputum production, dyspnea, or abnormalities on the pulmonary physical exam).[20]

While a detailed history and physical examination should be performed in every patient, neither is sufficient in isolation to reliably confirm or exclude CAP. In a systematic review of four studies, no findings on patient history had sufficient negative predictive value to obviate the need for additional testing.[63] Only fever, immunosuppression, and a history of dementia had positive likelihood ratios for pneumonia greater than two. Atypical features on presentation including confusion or the absence of hypoxemia are associated with significant delays in antibiotic administration.[64]

Conversely, historic features may suggest infection with a specific pathogen. For example, the presence of hemoptysis, erythematous rash, skin pustules, severe pneumonia during the summer months, and cavitary disease should raise concern for community-acquired MRSA.[65] Similarly, diarrhea and hyponatremia should prompt consideration of infection with *Legionella* species.[66] Additional pathogen-specific considerations are discussed later in this chapter.

While important, the pulmonary physical exam is plagued by poor interrater reliability. In a study of 52 patients presenting to an ED with symptoms of lower respiratory tract infection (of whom 24 were ultimately diagnosed with pneumonia), only the identification of rales and wheezes reached even fair levels of agreement between independent examiners.[67] "Classic" physical exam findings of pneumonia including bronchophony and egophony had markedly poor interrater reliability. In a recent meta-analysis of 11 studies, chest auscultation was found to have a sensitivity of 0.33 (95% confidence interval [CI], 0.24–0.44), specificity of 0.87 (95% CI, 0.81–0.92), positive likelihood ratio of 2.6 (95% CI, 1.9–3.4), negative likelihood ratio of 0.77 (95% CI, 0.68–0.87), and an area under the curve of 0.68 (95% CI, 0.64–0.72).[68]

■ Imaging

The chest radiograph has long been the standard imaging modality for patients with suspected CAP. However, disagreement on radiograph interpretation, even among experienced radiologists, is well described. As an example, in a study of 282 patients with clinical CAP, agreement between two university radiologists on the presence of infiltrate was only fair ($\kappa = 0.37$; 95% CI, 0.22–0.52).[69]

Evidence supports an expanding role for computed tomography (CT) in the evaluation of patients with suspected CAP. In a secondary analysis of the CDC EPIC study, 3% of patients had radiographic evidence of CAP identified only on chest CT.[70] These patients had similar illness severity scores, bacterial infection rates, and outcomes compared with patients who had infiltrates identified on chest radiograph. Similarly, in a study of 319 patients presenting to an ED with suspected CAP, 33% of those with a negative chest radiograph were found to have an infiltrate on CT.[71] Conversely, among the 188 patients with an infiltrate identified on chest radiograph, pneumonia was excluded by chest CT in nearly 30%. Across the study cohort, CT findings frequently prompted changes in antibiotic therapy. Together, these studies support the role of chest CT in the evaluation of CAP for patients where diagnostic uncertainty persists after initial evaluation.

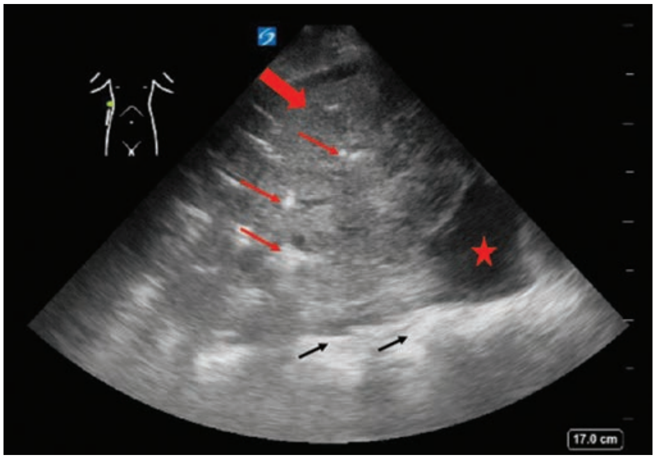

Figure 128-5 Point-of-care thoracic ultrasound image from a patient with severe community-acquired pneumonia showing dense pulmonary consolidation *(thick red arrow)*. The lung is filled with numerous hyperechoic *(bright)* areas also referred to as sonographic air bronchograms thought to represent air trapped in small airways within an area of consolidation *(thin red arrows)*. A small anechoic pleural effusion is visible *(red star)*, as are the hyperechoic spinous processes *(black arrows)*.

Enthusiasm for point-of-care ultrasound (POCUS) has increased markedly in recent years. The use of POCUS to guide safe bedside procedures and inform the rapid evaluation of patients with respiratory failure and shock is now widely considered standard of care.[72] Lung ultrasound offers a number of advantages over traditional imaging techniques including its low cost, the fact that it can be performed by the treating clinician facilitating real-time integration of imaging findings into a patient's care plan, avoidance of radiation or iodinated contrast, and the ease with which it can be performed serially over a patient's hospital stay (Fig. 128-5). A recent systematic review and meta-analysis evaluated 16 studies to determine the accuracy of lung ultrasound for diagnosing pneumonia.[73] Pooled sensitivity and specificity were not evaluated given study heterogeneity. The sensitivity of lung ultrasound ranged from 57% to 100% and specificity from 54% to 99%. While more research is needed to refine guidance on the use of lung ultrasound in pneumonia, experienced sonographers should be encouraged to incorporate lung ultrasound into their bedside evaluation, especially for acutely ill patients.[74] For additional discussion of thoracic ultrasound, the reader is referred to Chapter 29.

■ Microbiologic Evaluation

Table 128-2 summarizes IDSA–ATS guidelines on recommended diagnostic testing in CAP. Major changes between the 2007 and 2019 guidelines are summarized in Table 128-3.

Expectorated Sputum

One of the most controversial aspects of CAP diagnosis is the value of expectorated sputum. For infection with certain pathogens including *S. pneumoniae*, *H. influenzae*, and *S. aureus*, the specificity of high-quality Gram stain exceeds 85%.[75] When Gram stain shows a predominant morphotype, a causative organism is identified on culture in more than 85% of cases.[76]

TABLE 128-2 Recommendations for Diagnostic Testing from the 2019 IDSA/ATS Guidelines for Community-acquired Pneumonia

Diagnostic Test	Not Recommended	Recommend For
Pretreatment Gram stain and culture	CAP managed in the outpatient setting	• Severe CAP • Patients receiving empiric treatment for *Pseudomonas aeruginosa* or MRSA • Patients with prior infection with *P. aeruginosa* or MRSA • Patients who have been hospitalized and received parenteral antibiotics (whether during the hospitalization or not) in the last 90 days
Blood culture	CAP managed in the outpatient setting	• Severe CAP • Patients receiving empiric treatment for *P. aeruginosa* or MRSA • Patients with prior infection with *P. aeruginosa* or MRSA • Patients who have been hospitalized and received parenteral antibiotics (whether during the hospitalization or not) in the last 90 days
Legionella and pneumococcal urinary antigen testing	Most cases of CAP	• Where indicated by epidemiologic factors (such as in association with a *Legionella* outbreak or travel) • Severe CAP
Testing respiratory sample for influenza virus	CAP when there is low or no influenza circulation in the community	• When influenza is circulating in community (use of a rapid influenza molecular assay is recommended)
Procalcitonin	All patients with CAP	• Not recommended for use

ATS, American Thoracic Society; CAP, community-acquired pneumonia; IDSA, Infectious Disease Society of America; MRSA, methicillin-resistant Staphylococcus aureus.
Data from Metlay JP, Waterer GW, Long AC, et al. Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med. 2019;200(7):e45–e67.

Despite these impressive results when testing is performed in dedicated and highly experienced microbiology laboratories, clinical results fall far short of these ideal situations. In the CDC EPIC study, a high-quality sample was obtained in only 12% of patients.[37] Even for patients with bacteremic CAP, the yield of sputum culture is variable. In a study of 1669 patients with CAP, 133 (8.0%) of whom had pneumococcal bacteremia, only 39 (29.3%) produced a high-quality sputum sample.[76] Just 13 of these samples (representing 9.8% of patients with pneumococcal bacteremia) were culture-positive for *S. pneumoniae*.

At least three reasons explain these less robust results in clinical practice: (1) many CAP etiologies are not associated with a productive cough, (2) many patients are unable to expectorate an adequate volume of sputum for a high-quality sample, and (3) emphasis

TABLE 128-3 Key Changes Between the 2007 and 2019 IDSA/ATS Guidelines for Community-acquired Pneumonia

Recommendation	2007 Guidelines	2019 Guidelines
Sputum culture	Recommended in patients with severe disease	Recommended in patients with severe disease and inpatients empirically treated for MRSA or *Pseudomonas aeruginosa*
Blood culture	Recommended in patients with severe disease	Recommended in patients with severe disease and inpatients empirically treated for MRSA or *P. aeruginosa*
Macrolide monotherapy	Strong recommendation for outpatients	Conditional recommendation for outpatients based on local resistance levels
Use of procalcitonin	Not covered	Recommend against use
Use of corticosteroids	Not covered	May be considered in patients with refractory septic shock
Use of healthcare-associated pneumonia	Accepted as a categorization	Recommend abandoning this categorization; emphasis on local epidemiology and validated risk factors to determine need for MRSA or *P. aeruginosa* coverage; increased emphasis on de-escalation of treatment if cultures are negative
Standard empiric therapy for severe CAP	β-Lactam/macrolide and β-lactam/fluoroquinolone combinations given equal weight	Both accepted but stronger evidence in favor of β-lactam/macrolide combination
Routine use of follow-up chest imaging	Not covered	Recommend not to obtain; patients may be eligible for lung cancer screening, which should be performed as clinically indicated

ATS, American Thoracic Society; CAP, community-acquired pneumonia; IDSA, Infectious Disease Society of America; MRSA, methicillin-resistant Staphylococcus aureus.
Modified with permission from Metlay JP, Waterer GW, Long AC, et al. Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med. 2019;200(7):e45–e67.

on time to first antibiotic dose means that many samples are not obtained until after exposure to antibiotics. For *S. pneumoniae* and *H. influenzae*, even a single dose of antibiotic results in negative cultures. Additionally, whether sputum Gram stain and culture routinely alters management or impacts patient outcomes is unclear.[77,78]

The most recent IDSA–ATS guidelines re-emphasize the value of sputum Gram stain and culture for reasons of antibiotic stewardship. Sputum samples are recommended specifically for patients in whom broad-spectrum antibiotics are being considered due to sufficient clinical concern for infection with a pathogen resistant to usual CAP antibiotic regimens. Infection with many of these bacterial pathogens, including *P. aeruginosa* and MRSA, are more likely to result in a productive cough, are less likely to be suppressed on culture with early empiric antibiotics, and are more likely to alter management if identified on culture. Even with these recommendations, assuring that the sputum sample is free from upper airway contamination is critical. In general, fewer than 10 squamous epithelial cells per low-power field are required for an informative sample.

The equation may be changing significantly with the development of molecular diagnostics. PCR-based assays can detect pathogens killed by recently administered antibiotics and are routinely more sensitive than culture from the same sample. In addition, the clinical diagnostic standard for several bacterial pathogens that require very specialized culture media and conditions for growth, including *Legionella*, *Mycoplasma*, and *Chlamydia*, is already PCR. A multiplex PCR of high-quality specimens in the CDC EPIC study had a very high yield for a variety of bacteria, as well as viruses, missed by nasopharyngeal swab.[79] Commercially available multiplex platforms have been validated on expectorated sputum.[80,81]

Reluctance to culture should not apply to tracheal aspirates from patients with severe CAP.[82] While tracheal aspirates facilitate sampling of the lower respiratory tract, negative cultures resulting from recent antibiotics are still common. However, a negative culture from a tracheal aspirate specimen effectively rules out resistant bacterial pathogens and allows antibiotic de-escalation. Once again, multiplex PCR solves some of these issues.

Blood Cultures

The yield of blood cultures when obtained broadly in patients with CAP is low, with positivity rates ranging from 0% to 14% depending on the study population.[83] In the CDC EPIC study, 119 (5.8%) of the 2069 blood cultures obtained were positive.[37] Significantly higher positivity rates were noted when cultures were obtained prior to the administration of antibiotics. Regardless of the result, blood cultures infrequently alter management for patients with CAP.[83] Accordingly, blood cultures are recommended only for patients with severe disease or with concern for infection with a drug-resistant pathogen.

Legionella and Pneumococcal Antigen Testing

Urinary antigen testing can identify pathogen-specific capsular polysaccharides for *L. pneumophila* and *S. pneumoniae*. For *L. pneumophila*, commercially available assays only identify infection with serogroup 1. Fortunately, this serogroup is responsible for more than 80% of *L. pneumophila* infections in most areas of the United States.[84] In a systematic review and meta-analysis of 30 studies, urinary antigen testing for serogroup 1 had a pooled sensitivity of 0.74 (95% CI, 0.68–0.81) and specificity of 0.99 (95% CI, 0.98–1.0).[85] When obtained routinely in patients with CAP, positivity rates for *L. pneumophila* urinary antigen tests are low. In the CDC EPIC study, 1.6% of patients had a positive *Legionella* antigen test.[37] Similarly, in a multicenter prospective cohort of 1941 patients hospitalized with CAP, 32 (1.6%) had a positive urinary antigen test for *L. pneumophila*.[86]

Notably, in a recent large retrospective review, 23% of patients found to have *Legionella* CAP did not receive empiric antibiotics that covered *Legionella*, highlighting the potential role of antigen testing to inform early therapy, especially for patients not receiving empiric coverage for *L. pneumophila*.[66] IDSA–ATS guidelines recommend urinary antigen testing for *L. pneumophila* only for patients with severe CAP or when there are clear epidemiologic risk factors for *L. pneumophila* infection.

As with *Legionella*, urinary antigen testing for *S. pneumoniae* is highly specific. In a meta-analysis of 27 studies, urinary antigen testing for *S. pneumoniae* had a sensitivity of 74.0% (95% CI, 66.6%–82.3%) and specificity of 97.2% (95% CI, 92.7%–99.8%).[87] False positives can result from recent pneumococcal vaccination. Urinary antigen testing for *S. pneumoniae* is appealing as it is inexpensive and quick to process, and results are unaffected by recent antibiotic administration. IDSA–ATS guidelines recommend urinary antigen testing for *S. pneumoniae* only for patients with severe CAP. Notably, recent data suggest that as few as 18% of critically ill patients with pneumonia undergo urinary antigen testing for *S. pneumoniae*.[88] Narrowing this implementation gap has the potential to significantly impact antimicrobial stewardship.[89]

PCR-based Testing

As noted above, nucleic acid amplification using PCR is now the testing method of choice to identify respiratory viral pathogens in patients with CAP. PCR allows for the exponential amplification of a target DNA sequence.[90] RT-PCR (where RNA rather than DNA is used as the starting material for PCR) is used for detection of RNA viruses.

PCR-based testing is appealing for a number of reasons. With multiplex platforms, multiple patient samples can be quickly tested for clinically relevant pathogens, facilitating both rapid diagnosis and the identification of polymicrobial infections. Many platforms are semi- or even fully automated, obviating the need for more than basic laboratory personnel. Results are typically available in a matter of hours, enabling rapid pathogen detection for acutely ill patients. Perhaps most importantly, PCR-based testing is both highly sensitive and specific.[91]

Despite these advantages, how and when to incorporate molecular diagnostic testing for respiratory viruses in CAP remains a source of debate. IDSA–ATS guidelines recommend testing for influenza virus with a nucleic acid amplification assay when influenza virus is circulating in the community but do not comment on testing for other respiratory viruses.

Several challenges with PCR-based testing for respiratory viruses deserve mention. First, sensitive diagnostic platforms are unable to distinguish between true infection and asymptomatic viral carriage. Rates of asymptomatic viral carriage range from 2% to 17% depending on the patient population studied.[37,92–94] Second, results from upper and lower respiratory tract samples are frequently discordant.[50,95] In a study of patients admitted to the ICU with acute respiratory failure, 20% of patients with a severe respiratory infection had a viral pathogen identified only in the upper airway while 29% had a virus identified exclusively on tracheobronchial aspirate.[93] Third, bacterial and viral coinfection is common, occurring in more than one-third of cases.[37,96] The identification of a viral pathogen on PCR-based testing, therefore, does not guarantee the safety of withholding or discontinuing antibiotic therapy for CAP. Finally, the use of molecular diagnostic platforms has not yet been convincingly shown to improve clinical outcomes.[97]

A growing number of multiplex platforms now identify bacteria and genes associated with antibiotic resistance (e.g., *mecA* for MRSA). Early studies suggest that these tests may facilitate the detection of bacterial pathogens in CAP and aid antimicrobial stewardship.[98,99] These expanded assays may prove particularly useful in intubated patients with severe CAP where the rapid testing of lower respiratory tract specimens may aid the timely identification and treatment of drug-resistant pathogens. To date, no large trials have evaluated the safety and efficacy of diagnosing and treating severe CAP using PCR-based diagnostic platforms.

Procalcitonin

Procalcitonin, a protein produced in health by thyroid neuroendocrine cells and synthesized by most tissues during bacterial infection, is a promising biomarker to guide antibiotic therapy for patients with respiratory infections and sepsis.[100] When evaluated broadly in patients with "acute respiratory infections," procalcitonin-guided antibiotic therapy decreases exposure to antibiotics and lowers mortality.[101] However, in a recent systematic review and meta-analysis focused only on patients with CAP, procalcitonin (at a level of 0.5 μg/L) did not reliably distinguish between bacterial and viral infection.[102] A recent multicenter trial of 1656 patients presenting to the ED with suspected lower respiratory tract infection found that providing clinicians a procalcitonin level and guidance on test interpretation failed to decrease antibiotic use, although multiple protocol violations complicate interpretation of these results.[103]

IDSA–ATS guidelines recommend against using procalcitonin to guide the initiation of empiric antibiotic therapy for patients with CAP. Whether pairing procalcitonin with PCR-based multiplex testing for respiratory viruses can inform the safe discontinuation of antibiotics for patients with viral CAP is an important area for future study.[49]

■ Risk Stratification

Appropriate decisions regarding the site of care have a major impact on the cost of care and may impact mortality. Hospitalization clearly plays a major role in the cost of care, although inappropriate floor admission of critically ill patients is associated with both increased cost and mortality.

Inpatient Versus Outpatient Care

Guidelines recommend the use of a validated clinical prediction tool in addition to clinical judgment to inform which patients with CAP should be hospitalized. Of available scoring systems, the *pneumonia severity index* (PSI) has the most robust supporting evidence and is the tool recommended by the IDSA–ATS.

The PSI was developed in 1997 as a mortality prediction tool for patients with CAP.[104] Based on 20 prognostic variables, patients are grouped into one of five risk classes (Table 128-4). In general, patients in risk classes IV and V are classified as high-risk and should be hospitalized. Rigorous randomized controlled trials demonstrate that integration of the PSI into decision-making pathways increases the number of patients who can be safely managed in the outpatient setting.[105] Proponents of the PSI highlight the score's slightly superior test characteristics for identifying low-risk patients and predicting 30-day mortality.[106] Complexity at the point of care limits clinical use.

CURB-65, the major alternative scoring system, is preferred by many for its simplicity as it contains only five variables (confusion, blood urea nitrogen >20 mg/dL, respiratory rate ≥30 breaths per minute, systolic blood pressure <90 mm Hg or diastolic blood pressure ≤60 mm Hg, and age ≥65 years of age). Patients with a score of 0 to 2 are classified as low-risk and have 30-day mortality rates less than or equal to 2.1%.[105] The British Thoracic Society recommends CURB-65 over the PSI in part due to ease of use.[107] The simplicity of CURB-65 allows better integration into electronic site-of-care decision support and helps reduce admission of low-risk patients.

Regardless of the prediction tool used, clinicians should remember that these scores are meant to support rather than replace clinical judgment. Important considerations including barriers to safe longitudinal care after discharge, the severity of comorbid illness, and the magnitude of vital sign abnormalities relative to a patient's baseline may provide compelling reasons for admission irrespective of a patient's risk score.

TABLE 128-4 Pneumonia Severity Index

Patient Characteristic	Points Assigned
Demographic factors	
Males	Age (years)
Females	Age (years) – 10
Nursing home residents	Age (years) + 10
Comorbid illnesses	
Neoplastic disease	+30
Liver disease	+20
Congestive heart failure	+10
Cerebrovascular disease	+10
Renal disease	+10
Physical examination findings	
Altered mental status	+20
Respiratory rate ≥30 breaths/min	+20
Systolic blood pressure <90 mm Hg	+20
Temperature <35°C or ≥40°C	+15
Pulse ≥125 beats/min	+10
Laboratory findings	
pH <7.35	+30
Blood urea nitrogen ≥30 mg/dL	+20
Sodium <130 mEq/L	+20
Glucose ≥250 mg/dL	+10
Hematocrit <30%	+10
Partial pressure of oxygen <60 mm Hg	+10
Pleural effusion	+10

Interpretation: Patients <50 years of age who do not have any of the above comorbid illnesses or physical examination findings are risk class I; patients with a score of ≤70 are risk class II; patients with a score of 71–90 are risk class III; patients with a score of 91–130 are risk class IV; and patients with a score of >130 are risk class V. Risk classes I and II are felt appropriate for outpatient care, while risk classes IV and V should be hospitalized. Disposition for patients in risk class III should be guided by clinician judgment.

Data from Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med. 1997;336(4):243–250.

Admission to the ICU

A key limitation of both the PSI and CURB-65 is their low sensitivity and specificity for predicting the need for ICU admission.[108] As such, neither score is recommended to determine the location of inpatient care. Accurate identification of patients likely to require ICU admission is critical, as delayed admission to the ICU has consistently been associated with increased mortality.[32,109]

Several scoring systems are available to guide the need for ICU admission. Of these, the 2007 IDSA–ATS major and minor criteria for severe CAP are recommended for use in IDSA–ATS guidelines (Table 128-5). As the major criteria (need for mechanical ventilation or vasopressor support) are self-evident indications for ICU admission, the minor criteria have been proposed as a stand-alone risk-stratification tool. A large prospective validation study of 1062 patients with CAP in the United Kingdom found the presence of greater than or equal to 3 IDSA–ATS minor criteria to be predictive of the need for mechanical ventilation or vasopressors (area under the receiver operator characteristic curve [AUC], 0.85; 95% CI,

TABLE 128-5 Criteria for Severe Community-acquired Pneumonia

Minor criteria[a]	• Respiratory rate ≥30 breaths/min[b] • PaO_2/FiO_2 ≤250[b] • Multilobar infiltrates • Confusion/disorientation • Uremia (BUN ≥20 mg/dL) • Leukopenia (WBC count <100,000 cells/mm^3)[c] • Hypothermia (core temperature <36 °C) • Hypotension requiring aggressive fluid resuscitation
Major criteria	• Invasive mechanical ventilation • Septic shock with need for vasopressors

[a] *Other criteria to consider include hypoglycemia (in nondiabetic patients), acute alcoholism/alcohol withdrawal, hyponatremia, unexplained metabolic acidosis or elevated lactate level, cirrhosis, and asplenia.*

[b] *A need for noninvasive ventilation can substitute for a respiratory rate >30 breaths/min or* Pa_{O_2}/Fi_{O_2} *≤250.*

[c] *As a result of infection alone.*

Severe pneumonia is defined as the presence of at least one major or three or more minor criteria.

BUN, blood urea nitrogen; Pa_{O_2}/Fi_{O_2}*, arterial oxygen pressure/fraction of inspired oxygen; WBC, white blood cell.*

Reproduced with permission from Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. 2007;44 Suppl 2(Suppl 2):S27–S72.

0.82–0.88) and ICU admission (AUC 0.85; 95% CI, 0.82–0.88).[110] Use of these criteria to identify at-risk patients in the ED may reduce delayed ICU admission and improve clinical outcomes, although more studies are needed to confirm these findings.[111]

The development and validation of decision tools to identify patients most likely to benefit from ICU admission is complicated by a number of factors including how scores consider limitations in care (e.g., do not resuscitate orders) and the significant variation in center-specific factors that impact ICU bed utilization.[108]

■ Empiric Antibiotic Therapy

Empiric antibiotic therapy for CAP should provide robust coverage of common pathogens while minimizing the harms associated with the overuse of broad-spectrum antibiotics. Factors that inform antibiotic selection include the severity of illness and the presence of risk factors for drug-resistant pathogens. IDSA–ATS recommendations for empiric antibiotic therapy for patients with CAP are summarized in Table 128-6.

Outpatient Setting

The major change between the 2007 and the 2019 IDSA–ATS guidelines with respect to CAP managed in the outpatient setting is the downgrading of the strength of recommendation for macrolide monotherapy in healthy patients without comorbidities from a strong recommendation to a conditional recommendation informed by local resistance levels.

S. pneumoniae and *H. influenzae* are important causes of CAP in outpatients, neither of which is reliably covered by macrolides. Pneumococcal resistance to macrolides develops through either ribosomal methylation or efflux of the drug from bacteria.[112] Resistance rates vary significantly by country but have been reported to exceed 30% in U.S. isolates.[113,114] Frequent use of macrolides for both the acute and chronic treatment of chronic lung diseases like COPD may accelerate the spread of macrolide-resistant pneumococcus in the near future. Macrolides are also generally ineffective against *H. influenzae* due to the presence of an intrinsic efflux pump. IDSA–ATS guidelines suggest macrolide monotherapy should not be used when local rates of pneumococcal resistance to macrolides exceeds 25%. Some experts suggest this cutoff should be significantly lower to minimize the risk of ineffective early antibiotic therapy for patients with CAP.[115]

Single-agent amoxicillin, while lacking activity against atypical pathogens, achieves success rates comparable to other antibiotic classes in the treatment of CAP in the outpatient setting.[116] Updated IDSA–ATS guidelines include high-dose amoxicillin (1 g three times a day) as a reasonable treatment option for healthy outpatients with CAP.

Empiric antibiotic therapy should be expanded for outpatients with comorbidities including chronic heart, lung, liver, or renal

TABLE 128-6 Antibiotic Treatment Recommendations for Community-acquired Pneumonia

Group	Antibiotic Regimens

Healthy outpatients without risk factors for MRSA or *Pseudomonas aeruginosa*[a]	• Monotherapy with
	  • Amoxicillin
	  • Doxycycline
	  • Macrolide[b,c]

Outpatients with comorbidities[d]	• Combination therapy with
	  • Amoxicillin/clavulanate or cephalosporin + Macrolide[c] or doxycycline
	  • Monotherapy with a respiratory fluroquinolone[e]

Inpatients with non-severe CAP without risk factors for MRSA or *P. aeruginosa*[a]	• Combination therapy with
	  • β-lactam[f] + macrolide[c]
	• Monotherapy with
	  • Respiratory fluroquinolone[e]
	• Combination therapy with a β-lactam[f] + doxycycline can be considered if contraindications to both macrolides and fluroquinolones

Severe CAP	• Combination therapy with
	  • β-lactam[f] + macrolide[c] *or*
	  • β-lactam + respiratory fluoroquinolone[e]

Empiric treatment for MRSA	• Vancomycin or linezolid
Empiric treatment for *P. aeruginosa*	• Piperacillin-tazobactam, cefepime, ceftazidime, aztreonam, meropenem, or imipenem

[a] *Risk factors include: prior respiratory isolation of methicillin-resistant Staphylococcus aureus or Pseudomonas aeruginosa, recent hospitalization with receipt of parenteral antibiotics during the previous ninety days.*

[b] *Macrolide therapy recommended only if local pneumococcal resistance is <25%.*

[c] *Azithromycin or clarithromycin.*

[d] *Notable comorbidities include chronic heart, lung, liver, or renal disease, diabetes mellitus, alcohol use disorder, malignancy, or asplenia.*

[e] *Levofloxacin or moxifloxacin.*

[f] *Ampicillin/sulbactam, cefotaxime, ceftriaxone, or ceftaroline.*

ATS, American Thoracic Society; CAP, community-acquired pneumonia; IDSA, Infectious Disease Society of America; MRSA, methicillin-resistant Staphylococcus aureus.

Data from Metlay JP, Waterer GW, Long AC, et al. Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med. 2019;200(7):e45–e67.

disease; patients with diabetes mellitus; alcohol use disorder; malignancy; or asplenia. Patients with these conditions experience increased morbidity and mortality with infection and are more likely to be infected with methicillin-sensitive *S. aureus* and Gram-negative bacilli.

For outpatients with comorbidities, monotherapy with a respiratory fluoroquinolone continues to receive a strong recommendation in recent guidelines. This recommendation is supported by a strong body of evidence showing that respiratory fluroquinolones compare favorably with β-lactam or macrolide-based treatment regimens.[117] However, growing concerns about the adverse effects of fluoroquinolones, which range from tendinopathy and aortopathies to psychiatric diseases, hypoglycemia, and neuropathy, have tempered enthusiasm for this therapy.[118] Accordingly, a growing number of antimicrobial stewardship interventions aim to limit their use.[119] Fluroquinolones may be particularly problematic in areas with a high incidence of *Mycobacterium tuberculosis* (mTB). Fluoroquinolones are effective anti-mTB agents, and their use for suspected bacterial CAP may impede a timely diagnosis of mTB infection.[115]

Anaerobic Coverage

IDSA–ATS guidelines now explicitly recommend against the addition of anaerobic coverage for patients with aspiration pneumonia in the absence of lung abscess or empyema (conditional recommendation, very low quality of evidence). This recommendation is driven by the changing microbiology of aspiration pneumonia. While historic studies describe high rates of infection with anaerobic pathogens, confirmation of an anaerobic infection is now increasingly uncommon.[120] In a recent secondary analysis of the GLIMP study, 2606 hospitalized patients with CAP were evaluated for a diagnosis of aspiration pneumonia, the presence of aspiration risk factors, and the results of microbiologic evaluation.[121] Only 0.5% of patients with aspiration pneumonia and 0.3% of patients with CAP and aspiration risk factors had an anaerobic pathogen isolated from respiratory samples. Despite this, 16% of patients with aspiration CAP and 5% of patients with CAP and no aspiration risk factors received anaerobic coverage, highlighting an important area for improved antimicrobial stewardship.

Inpatient Setting

An ongoing debate in the management of hospitalized patients with nonsevere CAP concerns the safety and efficacy of monotherapy with a β-lactam. Indeed, the key distinction between IDSA–ATS guidelines and those from countries in northern Europe is the strong recommendation for β-lactam–macrolide combination therapy in North American guidelines.

The strongest supporting evidence for β-lactam monotherapy comes from a 2015 multicenter cluster-randomized trial of 656 hospitalized patients with nonsevere CAP in the Netherlands.[122] β-Lactam monotherapy was found to be noninferior to β-lactam–macrolide combination therapy with respect to the primary endpoint of 90-day mortality. Several caveats have been raised about the generalizability of these findings. First, many patients enrolled in the study had a low severity of illness, roughly 25% did not have radiographically confirmed CAP, and protocol deviations were high and occurred differentially among the regimens. Second, patients were hospitalized for a median of 6 days, twice as long as comparable North American trials.[123] This added period of observation may have facilitated prompt recognition of treatment failure with β-lactam monotherapy (which actually occurred in a substantially greater proportion of patients initially treated with β-lactam monotherapy). Finally, it is debatable whether empiric antibiotic selection in nonsevere CAP can impact 90-day mortality—a metric that is likely driven predominately by comorbid conditions.

In contrast, a 2014 multicenter randomized trial of 291 patients hospitalized with CAP in Switzerland found β-lactam monotherapy to be associated with lower rates of clinical stability at day 7.[124] Additionally, patients treated with combination therapy experienced lower serious adverse events while hospitalized and lower 30-day readmission rates. In a 2016 systematic review, 6 of 8 included observational studies reported lower short-term mortality rates with β-lactam–macrolide combination therapy.[125]

The addition of a macrolide to β-lactam therapy may improve outcomes through several mechanisms including coverage of atypical pathogens, nonbactericidal immunomodulatory effects, and suppression of the exotoxin pneumolysin production when infection is caused by *S. pneumoniae*.

Monotherapy with a respiratory fluoroquinolone for hospitalized patients with nonsevere CAP continues to receive a strong recommendation in IDSA–ATS guidelines despite the concerns regarding fluoroquinolones noted above. In support of this recommendation, observational studies have reported relative reductions in mortality of 30% to 45% with the use of fluoroquinolones compared to β-lactam monotherapy for hospitalized patients with CAP.[125]

Severe CAP

Empiric antibiotic therapy for patients with severe CAP remains a significant challenge. No prospective trials have studied the efficacy and safety of different antibiotic regimens for severe CAP. This paucity of data is troubling, as patients with severe CAP have high rates of infection with difficult-to-treat pathogens including MRSA, *P. aeruginosa*, and Enterobacterales. Additionally, critically ill patients are the most likely to experience significant morbidity and mortality with even small delays in administration of appropriate antibiotic therapy.[126]

In the absence of risk factors for drug-resistant pathogens, patients with severe CAP should receive combination therapy with either a β-lactam and a macrolide or a β-lactam and a respiratory fluroquinolone. These recommendations are based on the benefit of combination therapy noted in observational studies. In a 2014 meta-analysis of 28 studies involving 9850 critically ill patients with CAP, therapy with a macrolide was associated with a 3% absolute risk reduction in mortality compared with non-macrolide-containing regimens (21% vs. 24%; risk ratio [RR], 0.82; 95% CI, 0.70–0.97).[127] The addition of a macrolide appears to improve outcomes in severe pneumococcal CAP independent of macrolide resistance rates, possibly due to its antitoxin effects.[128]

Antibiotics for Drug-resistant Pathogens

As discussed above, a major change in recent IDSA–ATS guidelines is the recommendation to abandon HCAP as a clinically relevant phenotype given its unacceptably low positive predictive value for infection with drug-resistant pathogens. Instead, guidelines highlight the importance of using locally validated risk factors to identify patients likely to benefit from empiric therapy against MRSA and *P. aeruginosa*. When local risk factors are not available, guidelines recommend empiric broad-spectrum antibiotics for patients with a history of MRSA or *P. aeruginosa* infection within the past year regardless of disease severity. Additionally, broad-spectrum antibiotics should be administered to patients with severe CAP and a history of hospitalization with exposure to parenteral antibiotics within the past 90 days. Guidelines support the use of an MRSA nasal swab to inform de-escalation of MRSA coverage. In a 2018 meta-analysis, a negative MRSA nasal swab was found to have a negative predictive value greater than 98% for patients with CAP.[129] Given its much lower positive predictive value (56.8%), the implications of a positive MRSA nasal swab are less clear.

While vancomycin and linezolid are equally recommended as empiric treatment options for MRSA, linezolid therapy or inclusion of clindamycin with vancomycin for likely exotoxin-expressing strains, such as the USA300 strain, are associated with lower mortality rates.[130] Although piperacillin–tazobactam, cefepime, ceftazidime, aztreonam, meropenem, and imipenem are included as reasonable empiric options to coverage *P. aeruginosa* and other Gram-negative pathogens, a variety of studies suggest that outcomes with these broader spectrum β-lactams are less effective for more common CAP pathogens.

A limitation of current guidelines is their exclusive focus on the identification and treatment of CAP secondary to MRSA and *P. aeruginosa*. Especially for patients with severe CAP, infection with ESBL-producing Enterobacterales and *A. baumannii* also are important diagnostic considerations.[53] Better predictive tools are needed to aid clinicians in identifying patients most likely to benefit from empiric therapy that covers these pathogens. Testing of lower respiratory tract samples with multiplex PCR-based diagnostic platforms is a promising yet understudied approach that may aid the prompt identification of infection with drug-resistant pathogens and inform the safe de-escalation of empiric broad-spectrum antibiotic therapy for patients with severe CAP.

Novel Antibiotics

The increasing prevalence of drug-resistant pathogens in CAP highlights the need to expand our antibiotic armamentarium. In recent years, only one antibiotic with an entirely novel mechanism of action has been approved by the U.S. Food and Drug Administration for CAP. Lefamulin is a semisynthetic pleuromutilin that inhibits the 50S subunit of bacterial ribosomes. In a recent phase 3 clinical trial, 5 days of lefamulin was found to be noninferior to a 7-day course of moxifloxacin for the primary endpoint of early clinical response at 96 h.[131]

Other recently approved antibiotics expand upon already available drug classes. Omadacycline, a once-daily aminomethylcycline derived from the tetracycline class, was found to be noninferior to moxifloxacin for the treatment of CAP.[132] Ceftaroline fosamil, a cephalosporin with activity against MRSA and many Gram-negative pathogens, performed favorably against ceftriaxone in hospitalized patients with nonsevere CAP.[133] More research is needed to inform when and if these medications should be used in routine care.

■ Antiviral Therapy

IDSA–ATS guidelines recommend the use of oseltamivir for patients with CAP and confirmed influenza infection in both the inpatient and outpatient setting independent of the duration of illness prior to diagnosis.

The role of neuraminidase inhibitors for patients with influenza infection is controversial. A 2014 Cochrane Group review found that the use oseltamivir in healthy outpatients was associated with a 16.8-h reduction in time to first alleviation of symptoms (95% CI, 8.4–25.1) compared with placebo.[134] However, therapy did not significantly reduce hospitalization rates or serious complications of influenza and came with increased rates of gastrointestinal, renal, and psychiatric adverse effects. A patient-level meta-analysis of more than 3000 patients from 9 countries with influenza A (H1N1) virus infection found that treatment with a neuraminidase inhibitor was associated with decreased odds of hospital admission (adjusted OR, 0.24; 95% CI, 0.20–0.30).[135] A more recent meta-analysis of more than 18,000 patients with influenza A (H1N1) virus infection found that the use of neuraminidase inhibitors was associated with reduced hospital length of stay.[136] How reliably conclusions from studies evaluating the efficacy of neuraminidase inhibitors in a broadly defined population of outpatients can be extrapolated to the subset of patients with confirmed CAP is unclear.

No randomized trials of neuraminidase inhibitors in critically ill patients with CAP secondary to influenza infection exist. Pooled data from observational trials suggest that prompt therapy with neuraminidase inhibitors is associated with improved outcomes including lower mortality rates.[137]

Patients with CAP and confirmed influenza infection should still receive empiric antibiotic therapy. Rates of bacterial coinfection in patients with influenza range from 2% to 65%, with *S. pneumoniae* and *S. aureus* being the most frequently isolated pathogens.[138] More accurate diagnosis of bacterial superinfection in severe CAP patients may ultimately change this recommendation for universal antibiotics.

■ Adjunctive Therapy: Corticosteroids

The efficacy and safety of corticosteroids in patients with CAP remain a source of debate. Several randomized clinical trials have shown corticosteroids to be associated with improved intermediate clinical endpoints. A multicenter trial in Switzerland of 785 hospitalized patients with CAP found that patients randomized to receive 50 mg of prednisone daily for 7 days experienced a shorter median time to clinical stability than patients who received placebo (3.0 days vs. 4.4 days).[139] A multicenter randomized controlled trial in Spain evaluated the impact of intravenous methylprednisolone 0.5 mg/kg given every 12 h for five days versus placebo in 120 patients with CAP and a CRP greater than 150 mg/L.[140] Patients in the intervention arm experienced a significant reduction in the primary outcome of treatment failure compared with patients in the control arm (13% vs. 31%; $p = 0.02$). However, no difference was noted in hospital length of stay, time to clinical stability, or in-hospital mortality. Additionally, the reduction in the primary endpoint was driven predominantly by less radiographic progression in patients who received steroids—a finding of unclear clinical significance.

Raising concern for the use of corticosteroids in patients with mild to moderate CAP, a recent stepped-wedge cluster-randomized clinical trial of 816 patients hospitalized with CAP of varying severities found that implementation of a bundled intervention that included adjunctive prednisolone acetate 50 mg daily for 7 days did not improve clinical outcomes and was associated with increased rates of gastrointestinal bleeding (2.2% vs. 0.7% for patients who received steroids vs. placebo, respectively).[141]

A Cochrane group meta-analysis of 13 trials in adults found corticosteroid treatment to be associated with reduced mortality in patients with severe CAP (RR, 0.58; 95% CI, 0.40–0.84) but not in adults with less severe pneumonia (RR 0.95; 95% CI, 0.45–2.00).[142] However, the methodologic rigor of several of the most positive trials included in this analysis has been questioned.[143] Results of a large Veterans Affairs study specifically addressing severe CAP, which include more patients with severe CAP than the entire Cochrane meta-analysis, are available in preliminary form and demonstrate no benefit with steroid therapy.[144]

Further clouding the role of corticosteroids in CAP is conflicting evidence on the impact of corticosteroids in viral pneumonia. In patients with pneumonia and confirmed influenza infection, the use of adjunctive corticosteroids is associated with increased mortality.[145] Conversely, corticosteroids reduce mortality for critically ill patients with COVID-19 pneumonia.[146]

IDSA–ATS guidelines recommend against the use of corticosteroids for patients with CAP regardless of severity. Guidelines do endorse the Surviving Sepsis Campaign recommendation for the use of stress-dose hydrocortisone in patients with CAP and refractory shock. For clinicians who do choose to use steroids for patients with CAP, therapy should likely be restricted to those with severe disease.[147]

■ Duration of Therapy

Patients with CAP should receive antibiotics for a minimum of 5 days, with the timing of discontinuation past this point guided by markers of clinical stability. This approach is supported by a 2016 multicenter randomized controlled trial of 312 hospitalized patients with CAP where the duration of antibiotic therapy beyond day 5 was guided by either specific markers of clinical stability (intervention arm) or clinician discretion (control arm).[148] Patients in the intervention arm had equivalent clinical outcomes despite spending significantly less time on antibiotics. Despite these recommendations, upward of one-third of patients with CAP continue to receive antibiotics for days after vital signs have normalized.[149]

■ Follow-up Imaging

Routine follow-up imaging after an uncomplicated episode of CAP is not recommended. Lung-cancer screening with low-dose chest CT should be pursued for patients who meet the eligibility criteria outlined in the U.S. Preventive Services Task Force guidelines.[150]

■ Prevention

Vaccination against *S. pneumoniae*, influenza, and now SARS-CoV-2 are the major preventative interventions to decrease the risk of CAP. The CDC's Advisory Committee on Immunization Practices (ACIP) publishes guidelines on recommended immunization schedules for both children and adults.[151]

Widespread childhood vaccination with the pneumococcal conjugate vaccine (PCV13) is thought to contribute to declining rates of invasive pneumococcal disease in both children and adults. The effectiveness of this vaccine has allowed the ACIP to reverse the recommendation that all adults older than 65 years of age receive the PCV13 vaccine. Instead, the ACIP now recommends that adults should engage in shared decision-making with their provider. PCV13 is still recommended for immunosuppressed adults and those with cerebrospinal fluid (CSF) leak or cochlear implants. All children younger than 2 years of age should still receive the PCV13 vaccine in a series of four doses. More controversial is the recommendation that adults 65 years of age and older receive the less effective purified polysaccharide vaccine (PPSV23) vaccine, which contains capsular antigens for additional capsular serotypes. Adults who received PCV23 before age 65 should receive one additional dose after age 65 administered at least 5 years after the prior dose of PCV23.

All adults, including pregnant women, should be encouraged to receive an annual influenza vaccine, the most common of which is an injection of an inactivated influenza virus. Intranasal administration of a live attenuated virus is available for adults less than 50 years of age. Contraindications to the live attenuated virus include a history of severe allergic reactions to any vaccine component, immunocompromised states, close contact with severely immunocompromised persons, pregnancy, cranial CSF–oropharyngeal communications, and cochlear implants.

Smoking cessation counseling and administration of evidence-based pharmacotherapies to aid cessation efforts are important additional preventative interventions given the clear link between smoking and pneumococcal disease.[152]

The COVID-19 pandemic has illustrated the powerful role appropriate isolation of infected individuals, masking in public places, and vaccination play in pneumonia prevention. Influenza and other respiratory viral infections have virtually disappeared during this pandemic, even in countries that had few SARS-CoV-2 cases and practiced milder forms of these preventative practices.

■ Specific Pathogens

Below we discuss common specific pathogens identified as etiologic agents in CAP.

Streptococcus pneumoniae

S. pneumoniae is still thought to be the most common bacterial cause of CAP. Fortunately, due in part to declining rates of cigarette smoking and effective vaccination programs, the burden of invasive pneumococcal disease in the United States is decreasing. In the CDC EPIC study, *S. pneumoniae* was identified in only 5% of patients.[37] Whether relaxing the adult PCV13 vaccine recommendations will maintain these lower rates is unknown.

Despite these encouraging trends, the global burden of *S. pneumoniae* remains sizeable. Pneumococcal disease is responsible for more than half of lower respiratory tract infection–related deaths in children under 5 years of age.[153] Annually, pneumococcal pneumonia causes an estimated 1.5 million deaths worldwide, including nearly 700,000 deaths in adults over 70 years of age.[153] Risk factors for pneumococcal disease include advanced age (the incidence of *S. pneumoniae* infection in adults over 65 years of age is almost 5 times higher than in younger patients), smoking, chronic respiratory disease, chronic heart disease, asplenia, diabetes mellitus, alcohol use disorder, and antecedent influenza infection.[154]

S. pneumoniae is spread from person to person either by inhalation of airborne droplets or by direct contact with respiratory secretions.[155] Asymptomatic colonization of the nasopharynx, especially in children, is felt to be an important bacterial reservoir facilitating spread throughout the community. At least 97 distinct capsular polysaccharide serotypes are known.[155] Bacterial serotype appears to be an important determinant of both the symptomology and disease severity observed with infection.[156] Indeed, emergent serotypes following widespread pneumococcal vaccination may partly explain why the incidence of complicated pneumococcal pneumonia and empyema increased globally between 1990 and 2012.[157] A number of virulence factors contribute to bacterial pathogenicity, including a polysaccharide capsule that facilitates evasion of host immune cells and production of the pore-forming exotoxin pneumolysin, which induces inflammation and promotes bacterial transmission.[155]

The classic presentation of pneumococcal CAP includes fever, purulent rust-colored sputum, pleuritic chest pain, and dense consolidation on chest radiograph (Fig. 128-6). This constellation of findings is far less common with widespread attention to early antibiotic therapy. The elderly and immunocompromised patients are more likely to present with atypical features.[158] Nearly 40% of patients with pneumococcal CAP are bacteremic on presentation.[159] The presence of a pleural effusion or a CRP greater than 20 mg/dL are predictive of bacteremia.[159] Whether bacteremic patients represent a particularly high-risk group is unclear, as studies on the prognostic significance of bacteremia have reached variable conclusions.[160,161]

S. pneumoniae can be identified on Gram stain as lancet-shaped Gram-positive diplococci grouped in pairs and short chains. While findings on Gram stain are highly specific for *S. pneumoniae*, less than 30% of patients with pneumococcal bacteremia are able to produce a high-quality sputum sample.[76] In the CDC EPIC study, only 28% of *S. pneumoniae* infections were diagnosed via analysis of expectorated sputum.[37] *S. pneumoniae* grows readily on a blood agar plate, and culture of lower respiratory tract specimens remains valuable for its ability to inform antibiotic susceptibility.

Urinary antigen testing has appealing test characteristics, with a sensitivity above 70% and a specificity approaching 100% for infection with *S. pneumoniae*.[87] This diagnostic approach can be particularly helpful in patients unable to produce a high-quality sputum sample or those who have already received antibiotics, as test characteristics are unaffected by recent therapy. An important limitation is that testing does not provide information on antibiotic susceptibility.

In 2008, the Clinical and Laboratory Standards Institute revised the minimum inhibitory concentration (MIC) breakpoints that define *S. pneumoniae* susceptibility to penicillin.[162] For infections other than meningitis, susceptibility to an intravenous penicillin is now defined by an MIC of less than or equal to 2 μg/mL and

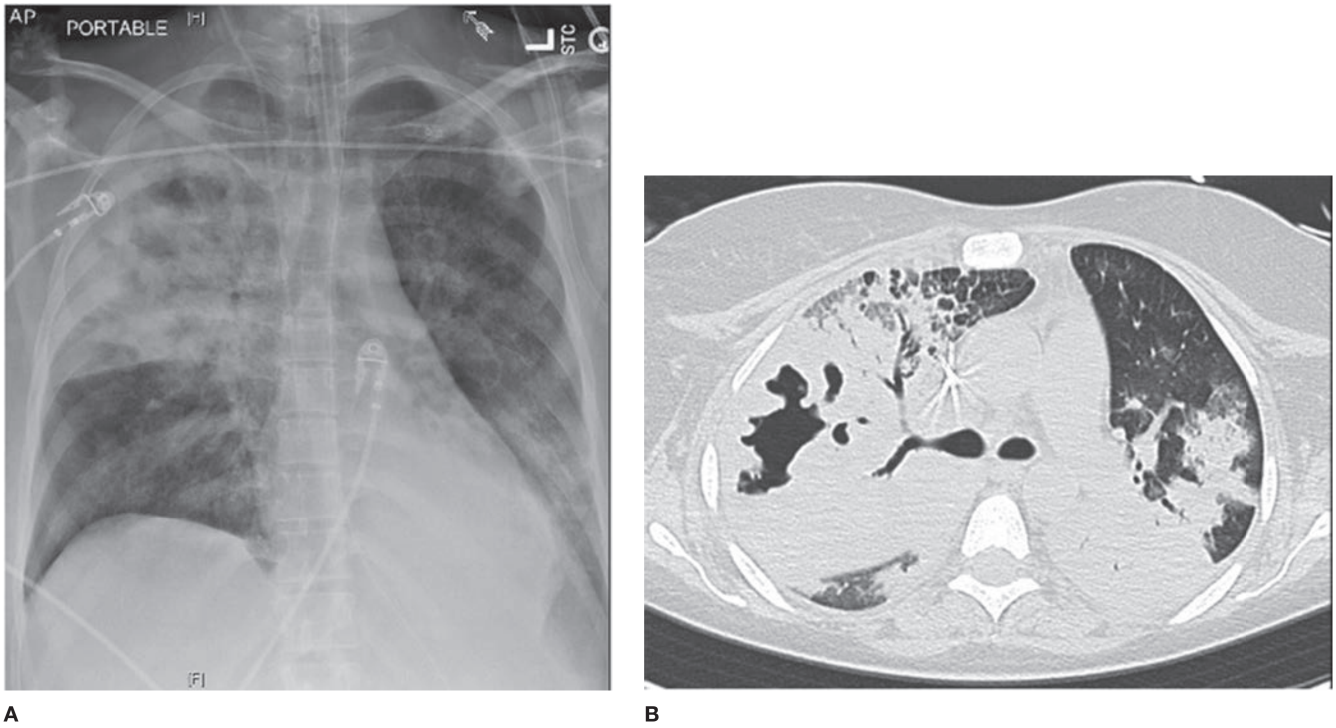

Figure 128-6 **A.** Portable chest radiograph showing dense multifocal consolidation in a patient with septic shock and hypoxemic respiratory failure secondary to *Streptococcus pneumoniae* community-acquired pneumonia. **B.** Axial chest computed tomography performed 3 days later showing persistent multifocal consolidation and evolving cavitation in the right upper lobe.

high-level resistance defined as an MIC greater than or equal to 8 μg/mL. This change has led to a decrease in the number of isolates identified as resistant to penicillin (2% in recent CDC data).[163,164]

High-dose amoxicillin is recommended as front-line therapy for healthy outpatients with CAP in recent IDSA–ATS guidelines. Ceftriaxone is the treatment of choice for hospitalized patients with pneumococcal pneumonia. In the United States, nearly 98% of pneumococcal isolates are either suspectable (MIC ≤1 μg/mL) or intermediately susceptible (MIC >1 and ≤2 μg/mL) to ceftriaxone.[164] For patients unable to receive ceftriaxone, a respiratory fluoroquinolone provides equally robust coverage although with a more concerning side-effect profile. Given the high rates of macrolide-resistant *S. pneumoniae,* studies showing a benefit to β-lactam–macrolide combination therapy in hospitalized patients with CAP suggest that the anti-inflammatory properties of macrolides may be particularly valuable. Supporting this hypothesis, in a recent study of hospitalized patients with CAP in Spain, β-lactam–macrolide combination therapy was most strongly associated with lower mortality in patients with pneumococcal pneumonia and an elevated CRP.[165]

Haemophilus influenzae

H. influenzae is a small Gram-negative coccobacillus with strains characterized as either encapsulated (serotypes a through f) or nonencapsulated/nontypeable. As a result of childhood vaccination against *H. influenzae* serotype b (Hib), the incidence of Hib disease in children has sharply declined.

In an analysis of invasive *H. influenzae* in the United States from 2009 to 2015 conducted through the CDC-supported Active Bacterial Core surveillance program, the mean annual incidence of invasive *H. influenzae* was 1.70 cases per 100,000 population.[166] The highest incidence was in very young children and adults over the age of 65, with a disproportionate burden of disease noted in American Indians and Alaska Natives. Nearly 80% of strains identified in older patients were nontypeable. During the study period, the incidence of *H. influenzae* increased, driven largely by a rise in serotype a.

No clinical features reliably distinguish *H. influenzae* CAP from CAP caused by other pathogens. In a review of more than 9000 patients with CAP enrolled in prospective cohort study in Germany, purulent sputum, receipt of a pneumococcal vaccination, and a history of chronic respiratory comorbidities were the only clinical characteristics significantly more common in patients with *H. influenzae* CAP than in those with CAP from other causes.[167]

Roughly 25% of *H. influenzae* strains produce a β-lactamase.[168] While awaiting susceptibility testing, suggested antibiotic regimens for confirmed moderate or severe *H. influenzae* CAP include second- or third-generation cephalosporins, β-lactam–β-lactamase inhibitor combinations, and respiratory fluroquinolones.

Mycoplasma pneumoniae

Mycoplasmas are the smallest self-replicating free-living organisms. More than 200 *Mycoplasma* species have been identified, of which *M. pneumoniae* is the most relevant to human disease. *M. pneumoniae* does not exist freely in nature but rather is an obligate parasite, residing primarily on the epithelial cell surface of hosts on which it relies for necessary nutrients.[169] Cytoadherence and motility are achieved in part through an elongated attachment organelle.[170] Production of a recently identified virulence factor, the community-acquired respiratory distress syndrome toxin, is an important driver of disease pathogenesis and contributes to the dry cough that characterizes infection.[171] Spread occurs through inhalation of respiratory droplets during close contact.

As the most common bacterial cause of acute uncomplicated bronchitis and a frequently identified pathogen in outpatient CAP, *M. pneumoniae* is an important cause of respiratory infections in the ambulatory care setting.[172] Community outbreaks of *M. pneumoniae* are well described.[170] In hospitalized patients, confirmed infection is less common. As an example, in the CDC EPIC study, only 2% of

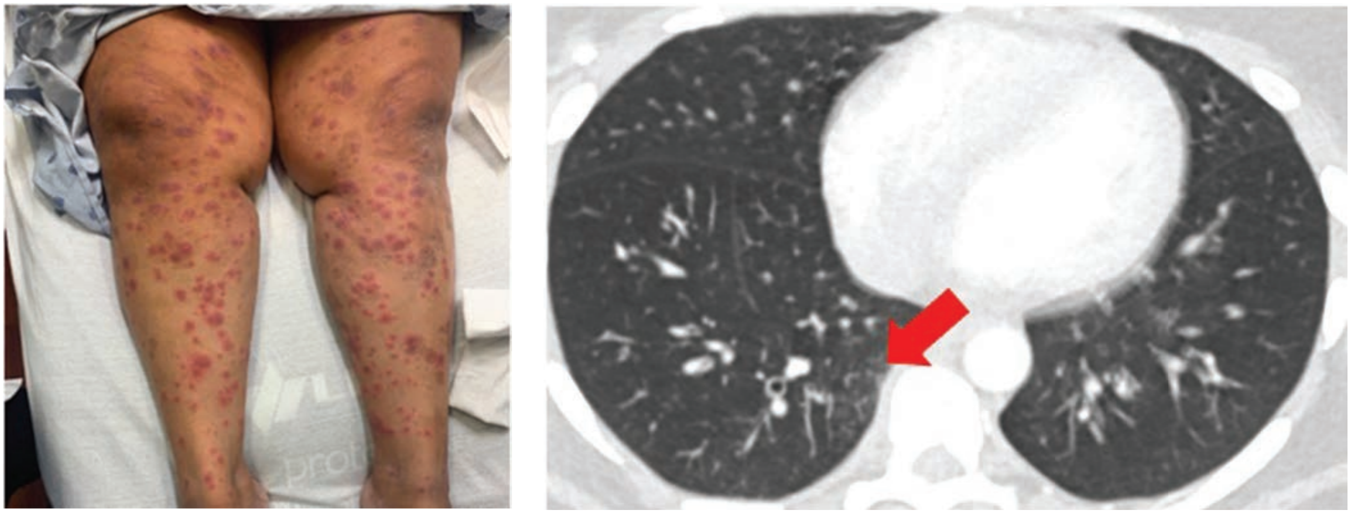

Figure 128-7 **A.** Lower extremities of a patient with community-acquired pneumonia secondary to *Mycoplasma pneumoniae* showing numerous targetoid pink papules with central dusky centers. The patient also had prominent oral and genital mucositis consistent with a diagnosis of *Mycoplasma*-induced rash and mucositis. **B.** Axial chest computed tomography from the same patient showing areas of tree-in-bud opacities and airway wall thickening *(red arrow)*.

patients had documented *M. pneumoniae* infection despite routine use of PCR-based testing of the nasopharynx.

M. pneumoniae CAP is viewed as the quintessential "atypical" pneumonia, associated with more subacute symptoms, a less productive cough, less severe disease, and more subtle radiographic abnormalities than CAP due to *S. pneumoniae*. In a comparison of CT findings between patients with *M. pneumoniae* and *S. pneumoniae* CAP, patients with *M. pneumoniae* were more likely to have bronchial wall thickening, ground-glass opacities, and centrilobular nodules.[173] Despite these broad distinctions between CAP caused by typical and atypical pathogens, there are no validated tools to reliably identify *M. pneumoniae* infection in the absence of diagnostic testing. Interestingly, bacterial co-detections can be found in 35% of *M. pneumoniae* CAP cases, especially in children.[174]

M. pneumoniae lacks a cell wall and is bounded by only a plasma membrane. As a result, it does not reliably take up Gram stain. *M. pneumoniae* is also difficult to isolate in culture, requiring several weeks of incubation with special medium. Given these limitations, PCR-based testing of respiratory samples with nucleic acid amplification is now the standard for diagnosis in acutely ill patients.

M. pneumoniae is unique in its ability to cause extrapulmonary disease including central nervous system disease (e.g., encephalitis, meningitis, and Guillain-Barré syndrome), cold-agglutinin hemolytic anemia, dermatologic disease (e.g., erythema multiform, Stevens-Johnson syndrome), pericarditis, and hepatitis (Fig. 128-7).[175]

Given its lack of a cell wall, *M. pneumoniae* is resistant to β-lactams. Macrolides or respiratory fluoroquinolones are the mainstay of therapy for documented infection. Macrolide resistance is an emerging issue for *M. pneumoniae*, with rates as high as 15% in some locales.

Legionella pneumophila

L. pneumophila is an intracellular, aerobic, faintly Gram-negative bacillus. Of at least 15 serotypes, serotype 1 is responsible for more than 80% of infections in the United States.[176] Infection with *L. pneumophila* causes two distinct syndromes: Pontiac fever, a self-limited nonpneumonic febrile illness, and Legionnaires' disease, a form of CAP named for a 1976 outbreak in Philadelphia (Fig. 128-8).

L. pneumophila is found in freshwater environments, artificial water supplies (e.g., cooling towers and plumbing systems), and moist soil. Infection occurs predominantly through inhalation of aerosolized particles and less commonly though aspiration of contaminated water. Person-to-person transmission is rare but has been recently described.[177] Nosocomial and nursing home outbreaks occur and can be triggered by inadequate cleaning of respiratory equipment.[178] Major risk factors for disease include advanced age, cigarette smoking, chronic lung disease, and immunocompromised states.

L. pneumophila CAP is uncommon, with detection rates of less than 2% in large U.S. studies.[37,66] In a retrospective review of more than 150,000 patients with pneumonia in a large U.S. healthcare network, only 26% were tested for pneumonia with 1.5% testing positive for *L. pneumophila* infection.[66] Compared to patients with negative testing, patients who tested positive for *L. pneumophila* had higher rates of tobacco use (38.0% vs. 22.0%), alcohol abuse (9.2% vs. 5.0%), diarrhea (8.9% vs. 4.1%), and hyponatremia (36% vs. 14%). The predictive value of these associations is unclear, as many patients with these characteristics did not undergo *L. pneumophila* testing.

L. pneumophila is difficult to detect on Gram stain and requires buffered charcoal yeast for growth on culture, making routine analysis of expectorated sputum an unreliable diagnostic test. Urinary antigen testing is the most clinically useful testing method given its rapid turnaround time and appealing test characteristics (a sensitivity of 74% and specificity of 99% in a 2009 meta-analysis).[85] Importantly, urinary antigen testing detects only infection with serogroup 1. While this serogroup is responsible for the vast majority of *Legionella* infections in the United States, human infection has been described with nearly all other serogroups and multiple other *Legionella* species. As an example, *L. longbeachae* is responsible for roughly 30% of infections in Australia and New Zealand.[179] As a result, a negative urinary antigen test does not definitively rule out *Legionella* infection.

The treatment of choice for *Legionella* pneumonia is either azithromycin (500 mg per day) or levofloxacin (750 mg per day). No randomized controlled trials compare these two antibiotics, although observational studies suggest both are effective.[180] No evidence suggests that combination therapy with these two agents or the addition of rifampin improves outcomes.

Duration of therapy for confirmed *L. pneumophila* pneumonia is unclear. For immunocompetent patients, discontinuation of therapy

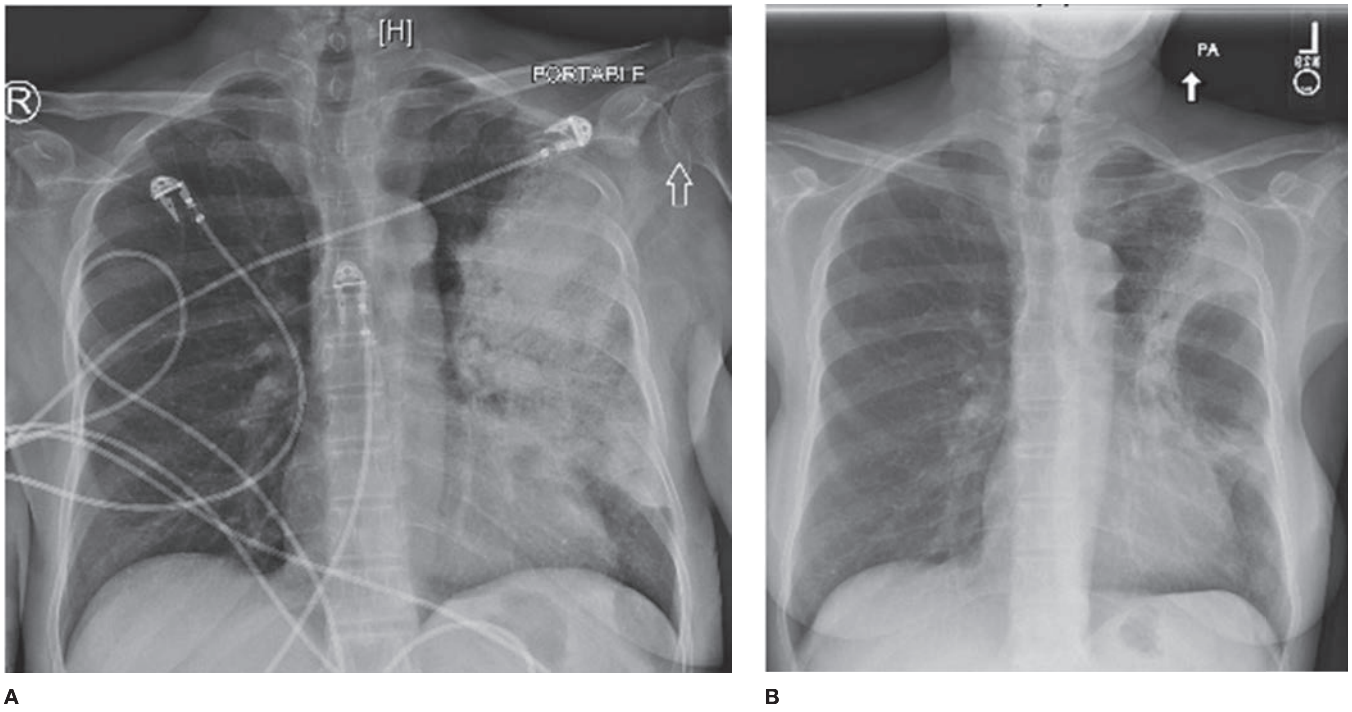

Figure 128-8 **A**. Portable chest radiograph showing dense left-sided opacities in an immunocompromised patient with community-acquired pneumonia secondary to *Legionella pneumophila* serotype 1. **B**. Posteroanterior chest radiograph performed 3 months after hospital discharge showing coalescing curvilinear opacities in the left lung.

guided by objective measures of clinical stability after a minimum of 5 days of antibiotics is reasonable. Immunocompromised patients, especially those with severe disease, may benefit from a more prolonged treatment course.

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CHAPTER 129

Nosocomial Pneumonia, Including Ventilator-associated Pneumonia

Andrew T. Roth
Marin H. Kollef

INTRODUCTION

Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) are the most frequent causes of healthcare-associated infections (HAIs) and represent significant clinical and economic burdens on healthcare systems. Definitions for each of these conditions are provided in Table 129-1. HAP and VAP are frequently associated with multidrug-resistant (MDR) microorganisms, leading to further morbidity and mortality in hospitalized patients. VAP is considered a device-associated HAI and is, therefore, reported to the National Healthcare Safety Network (NHSN), the surveillance branch of the Centers for Disease Control and Prevention (CDC). According to the latest published data from the NHSN, 10,037 cases of VAP were reported from 2015 to 2017.[1] This chapter focuses on the epidemiology of infection, the microorganisms responsible for infection, the complexities surrounding the diagnosis, and the preventive and therapeutic management strategies used to combat nosocomial pneumonia.

EPIDEMIOLOGY

HAP and VAP account for approximately 28% of HAIs and are collectively the most frequent cause of nosocomial infection.[2,3] Epidemiologic data estimate an overall prevalence of nosocomial pneumonia in hospitalized patients of 0.89%, with the burden substantially higher among patients in the intensive care unit (ICU).[2,3] While the majority of cases of nosocomial pneumonia occur in nonintubated patients, mechanical ventilation is the most important risk factor for pneumonia, increasing the incidence up to 20-fold.[2,4,5] Approximately 10% of patients undergoing mechanical ventilation develop VAP.[6] In a 1-day point prevalence study involving ICU patients from centers in 88 different countries, investigators found respiratory tract infections were the most common infection in the ICU, accounting for 60.1% of infections. Furthermore, respiratory tract infections were the most frequent reason for antibiotic prescription in the ICU. Overall, greater than 50% of the infections documented in this study were categorized as hospital-acquired or healthcare-associated, rather than community-acquired.[3] A multicenter, prospective cohort analysis conducted in Canada demonstrated a VAP rate of 14.8 cases per 1000 ventilator days, with half occurring on or before day 7. While the cumulative risk for developing VAP increased with duration of ICU stay, the daily risk increased until day 5 and then subsequently decreased.[7]

TABLE 129-1 Definitions of Nosocomial Pneumonia[a]

Pneumonia Category	Definition
HAP, hospital-acquired pneumonia	Pneumonia diagnosed 48 h or more after hospital admission Can occur in nonventilated or ventilated patients
VAP, ventilator-associated pneumonia	Pneumonia diagnosed 48 h or more after endotracheal intubation

[a] *Clinical criteria for pneumonia include new or progressive lung infiltrate and at least two of the following: hyperthermia or hypothermia, elevated white blood cell count, purulent tracheal secretions or sputum, and worsening oxygenation.*

Determining the economic impact of VAP and the associated morbidity and mortality is challenging. Critically ill patients have multiple, evolving, complex disease processes that make it difficult to isolate VAP as the sole cause of excess cost, morbidity, or death. Multiple studies have been performed with variable findings. In a recent, large, international study, patients with respiratory tract infections had an ICU mortality rate of 24.8% and an in-hospital mortality rate of 31.9%.[3] An older case-control analysis revealed a crude mortality of 54%, an attributable mortality of 27%, and a 13-day increase in ICU length of stay compared with matched controls.[8] A larger, case-matched, prospective cohort study demonstrated an attributable ICU length of stay of 4 days and an attributable mortality of 6%.[9] A retrospective, matched cohort study using a large U.S. database estimated an increase of >$40,000 in mean hospital charges per patient.[10] In addition, a more recent retrospective, matched cohort study using ICD-9 coding to identify VAP revealed mean hospitalization costs of $99,598, which was $39,828 greater than those patients without VAP.[11]

Recent advances in statistical methodology allow for the control of the effect that severity of illness can have on the attributable mortality associated with VAP, not only at the time of infection but over the course of a hospitalization during disease evolution. Employing a statistical technique from the field of causal inference, an analysis of a large French national database resulted in a lower estimation of attributable mortality associated with VAP of 1% on day 30 and 1.5% on day 60.[12] Modifiable factors, particularly the timely initiation of appropriate antibiotics, certainly affect the aforementioned estimates. Although debate continues over the attributable mortality and cost of VAP, the condition undoubtedly imposes significant clinical and economic burdens.

Multiple databases track HAIs in the United States, including HAP and VAP. The NHSN functions as the CDC's surveillance system for HAIs and collects data from more than 5000 participating healthcare facilities. The NHSN Device-Associated Module includes data from patients undergoing mechanical ventilation. Analysis of data in 2012 categorized rates of VAP based on ICU location, with the highest incidence in burn, neurologic, neurosurgical, and surgical ICUs, ranging from 2.1 to 4.4 cases per 1000 ventilator days.[13] VAP was diagnosed less frequently in medical and medical/surgical ICUs, occurring at a rate of 0.9 to 1.0 cases per 1000 ventilator days (Table 129-2).[13] Compared to its report using data from 2006, the results demonstrated an overall decrease in the rate of VAP.[14] However, it is unclear whether the incidence of VAP is truly decreasing, or whether the NHSN definition of VAP is being more rigorously applied over time.[15]

The Medicare Patient Safety Monitoring System (MPSMS) has independently collected data on VAP within the Medicare population since 2005. Independent audit of these data showed stable rates of VAP at approximately 10% of mechanically ventilated patients from 2005 to 2013, in contrast with NHSN data.[6] Additionally, analysis of survey data from the CDC's Emerging Infections Program showed that despite an overall decrease in the number of HAIs, the rate of VAP was not significantly changed when comparing data from 2011 and 2015.[2] Given that the CDC/NHSN pneumonia

TABLE 129-2 2012 National Healthcare Safety Network VAP Rates Based on ICU Location in Major Teaching Hospitals

ICU Location	VAP Cases	Ventilator Days	Rate[a]
Burn	86	19,503	4.4
Medical	396	419,123	0.9
Medical/surgical	1398	1,330,178	1.0
Neurologic	62	20,859	3.0
Neurosurgical	210	98,026	2.1
Surgical	472	223,639	2.1
Cardiothoracic	319	190,785	1.7
Trauma	508	141,314	3.6

[a] Expressed as number of VAP cases per 1000 ventilator days.

Data from Dudeck MA, Weiner LM, Allen-Bridson K, et al. National Healthcare Safety Network (NHSN) report, data summary for 2012, Device-associated module. Am J Infect Control. 2013;41(12):1148–1166.

definitions (Table 129-3) were thought to lack accuracy, objectivity, and consistency, a new surveillance algorithm was introduced to identify ventilator-associated events (VAEs) in January 2013.[1] The goal of the new algorithm is to identify complications of mechanical ventilation including, but not limited to, VAP by using objective changes in ventilator parameters indicative of worsening oxygenation (Fig. 129-1).

MICROBIOLOGY

The etiologies of HAP and VAP depend on multiple factors, including co-existing diseases, geography, ICU population, duration of mechanical ventilation, previous antibiotic therapy, and the method used to obtain respiratory cultures. More microbiologic data are available for VAP compared with HAP, as VAP is a reportable condition and microbiologic samples of the lower respiratory tract can be easily obtained.

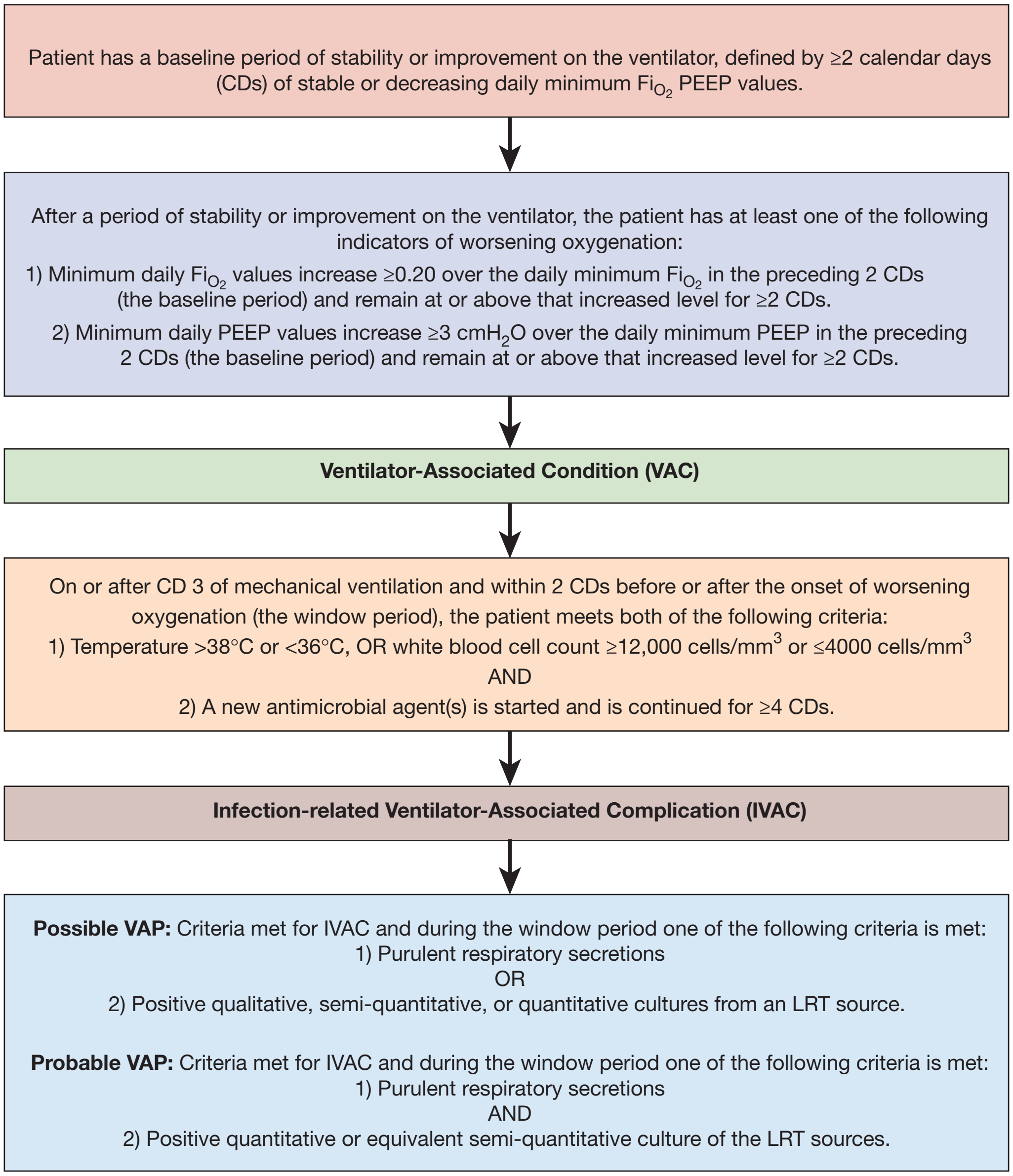
The most recent analysis of NHSN data examined microbiologic data from 9266 cases of VAP across ICUs in the USA from 2015 to 2017.[1] While Gram-negative bacilli (GNB) made up the majority of organisms, *Staphylococcus aureus*, including methicillin-resistant *S. aureus* (MRSA), was the most common pathogen, accounting for 28.8% of organisms. *Pseudomonas aeruginosa* made up 12.9%. The Enterobacteriaceae collectively accounted for 26.7% of organisms, including *Klebsiella* spp. (10.1%), *Enterobacter* spp. (8.4%), *Escherichia coli* (5.6%), *Proteus* spp. (1.4%), and *Citrobacter* spp. (1.2%). Etiologic organisms of community-acquired pneumonia (CAP) were a less frequent but significant cause of VAP, particularly *Haemophilus influenzae* (5.9%). Important GNB infections with special resistance patterns included *Stenotrophomonas maltophilia* (4.0%), *Acinetobacter* spp. (3.2%), and *Burkholderia cepacia* (0.3%) (Table 129-4).

Similar microbiologic data were seen in the 2020 Prospective Identification of Pneumonia in Hospitalized Patients in the Intensive Care Unit (PROPHETIC) study, which prospectively identified and followed hospitalized patients in the United States at high risk for developing HAP/VAP. Among the patients who developed VAP and grew bacteria on respiratory culture, *S. aureus*, including MRSA, was the most common organism, accounting for 23.5% of cases followed by *P. aeruginosa* (11.5%), *Klebsiella* spp. (10.6%), *Enterobacter* spp. (7.0%), *E. coli* (6.2%), *Stenotrophomonas maltophilia* (3.9%), *H. influenzae* (3.6%), *Acinetobacter* spp. (3.1%), and *Serratia* spp. (2.2%). No bacterial pathogens were isolated on culture in 34.2% of cases.[16]

TABLE 129-3 Centers for Disease Control and Prevention National Healthcare Safety Network Pneumonia Definitions

PNEU Type	Definition
PNU1	Two or more serial chest radiographs with at least ***one*** of the following: new or progressive and persistent infiltrate, consolidation, or cavitation and At least ***one*** of the following: • Fever (>38°C) • Leukopenia (<4000 WBC/mm^3) or leukocytosis (≥12,000 WBC/mm^3) • Altered mental status in an adult ≥70 years of age without an alternative etiology and At least ***two*** of the following: • New onset of purulent sputum or change in character of sputum or increased secretions/suction requirements • New-onset or worsening cough, dyspnea, or tachypnea • Rales or bronchial breath sounds • Worsening gas exchange
PNU2	Two or more serial chest radiographs with at least ***one*** of the following: new or progressive and persistent infiltrate, consolidation, or cavitation At least ***one*** of the following: • Fever (>38°C) • Leukopenia (<4000 WBC/mm^3) or leukocytosis (≥12000 WBC/mm^3) • Altered mental status in an adult ≥70 years of age without an alternative etiology and At least ***one*** of the following: • New onset of purulent sputum or change in character of sputum or increased secretions/suction requirements • New-onset or worsening cough, dyspnea, or tachypnea • Rales or bronchial breath sounds • Worsening gas exchange and At least ***one*** of the following: • Positive blood culture not related to another source of infection • Positive pleural fluid culture • Positive quantitative culture from minimally contaminated LRT specimen • ≥5% of BAL cells containing intracellular bacteria • Histopathologic examination revealing ***one*** of the following: abscess formation, positive quantitative culture, or invasion of lung parenchyma by fungal hyphae or pseudohyphae

PNU3 is a separate definition applied to immunosuppressed patients. Definitions can be found at www.cdc.gov/nhsn.



Patient has a baseline period of stability or improvement on the ventilator, defined by ≥2 calendar days (CDs) of stable or decreasing daily minimum Fi_{O_2} PEEP values.

After a period of stability or improvement on the ventilator, the patient has at least one of the following indicators of worsening oxygenation:

1) Minimum daily Fi_{O_2} values increase ≥0.20 over the daily minimum Fi_{O_2} in the preceding 2 CDs (the baseline period) and remain at or above that increased level for ≥2 CDs.

2) Minimum daily PEEP values increase ≥3 cmH_2O over the daily minimum PEEP in the preceding 2 CDs (the baseline period) and remain at or above that increased level for ≥2 CDs.

Ventilator-Associated Condition (VAC)

On or after CD 3 of mechanical ventilation and within 2 CDs before or after the onset of worsening oxygenation (the window period), the patient meets both of the following criteria:

1) Temperature >38°C or <36°C, OR white blood cell count ≥12,000 cells/mm^3 or ≤4000 cells/mm^3

AND

2) A new antimicrobial agent(s) is started and is continued for ≥4 CDs.

Infection-related Ventilator-Associated Complication (IVAC)

Possible VAP: Criteria met for IVAC and during the window period one of the following criteria is met:

1) Purulent respiratory secretions

OR

2) Positive qualitative, semi-quantitative, or quantitative cultures from an LRT source.

Probable VAP: Criteria met for IVAC and during the window period one of the following criteria is met:

1) Purulent respiratory secretions

AND

2) Positive quantitative or equivalent semi-quantitative culture of the LRT sources.

Figure 129-1 Abbreviated NHSN surveillance algorithm for ventilator-associated events.

Even with special attention to collection method and culture media, anaerobic bacteria do not appear to be important causes of nosocomial pneumonia outside of special circumstances, such as lung abscess or empyema. In a prospective study of 185 episodes of VAP, invasive samples were collected using a protected specimen brush and cultured in anaerobic media, yielding growth of *Veillonella parvula* in a single case.[17] Cases of *Legionella* species are uncommon causes of nosocomial pneumonia but have been reported in the context of contaminated water supply.[18] Viral infections are important and underappreciated causes of respiratory failure in the ICU and frequently require mechanical ventilation.[19] Transmission of nosocomial viral infections including influenza virus and rhinovirus has been documented.[20,21]

Antimicrobial resistance remains a critical issue in management of nosocomial pneumonia, particularly with infection due to *S. aureus* and *P. aeruginosa*. Infection with MDR microorganisms is associated with increased mortality, in part due to delayed time to appropriate antimicrobial therapy.[3] NHSN data from 2015 to 2017 showed that 36.9% of tested *S. aureus* isolates were methicillin-resistant.[1] Analysis of *P. aeruginosa* isolates from the same NHSN data showed that resistance was common across different antibiotic classes, with 16.8% of isolates showing resistance to at least one agent in three different antibiotic classes.[1] There is significant variation in the microbiologic etiology of HAP and VAP between different hospitals[22] and between different parts of a given hospital.[23] Therefore, optimal management requires knowledge of local antibiogram data and appropriate tailoring of antimicrobial therapy.

PATHOPHYSIOLOGY

Nosocomial pneumonia usually occurs through the aspiration of microorganisms colonizing the aerodigestive tract in a host with altered immunity, while direct inhalation and hematogenous dissemination of bacteria are less frequent routes of infection. Hospitalized patients are at increased risk for oropharyngeal colonization with pathogenic microorganisms due to pharmacologic and dietary alterations in gastric pH, exposure to contaminated respiratory equipment and hospital water systems, transmission of bacteria via healthcare workers, and spread of microorganisms through respiratory droplets.

Aspiration during sleep occurs in a large number of normal subjects, but the volume aspirated is small and, more importantly, the pathogenicity of the microorganisms is minimal. Hospitalized

TABLE 129-4 Distribution and Rank of 9622 Isolated Pathogens Associated with VAP in Hospital ICUs Reported to the National Healthcare Safety Network Between 2015 and 2017

Pathogen	Number of Isolates (%)	Rank
Staphylococcus aureus	2673 (28.8)	1
Pseudomonas aeruginosa	1192 (12.9)	2
Selected *Klebsiella* species	936 (10.1)	3
Enterobacter species	781 (8.4)	4
Haemophilus influenzae	550 (5.9)	5
All *Streptococcus* species	527 (5.7)	6
Escherichia coli	520 (5.6)	7
Serratia species	428 (4.6)	8
Stenotrophomonas maltophilia	372 (4.0)	9
Acinetobacter species	294 (3.2)	10
Proteus species	134 (1.4)	11
Citrobacter species	110 (1.2)	12
Moraxellacatarrhalis	71 (0.8)	13
Morganella species	32 (0.3)	14
Burkholderiacepacia	26 (0.3)	15
Other	620 (6.7)	

Data from Weiner-Lastinger LM, Abner S, Edwards JR, et al. Antimicrobial-resistant pathogens associated with adult healthcare-associated infections: Summary of data reported to the National Healthcare Safety Network, 2015-2017. Infect Control Hosp Epidemiol. 2020;41(1):1–18.

patients are considered more likely to aspirate larger volumes of virulent bacteria with greater frequency due to decreased sensorium, impaired cough mechanism, difficulty swallowing, and impaired gut motility.[24] The role of colonization of the upper respiratory and digestive tracts is well studied. Prospectively collected culture data showed that 23% of patients admitted to a medical ICU who were colonized with GNB developed a nosocomial respiratory infection compared with only 3% of noncolonized patients.[25] A more recent study utilizing genomic analysis demonstrated that strains of bacteria isolated from the lower respiratory tract (LRT) in cases of nosocomial pneumonia were identical to those strains colonizing the oropharynx and/or stomach.[26]

Alterations in gastric pH promote growth of bacteria in a normally sterile environment, increasing the risk for nosocomial pneumonia.[27–29] Critically ill patients requiring mechanical ventilation are at increased risk for developing stress ulcers and, thus, are often treated with histamine type 2 (H_2) antagonists and proton pump inhibitors for prevention.[30] While these strategies provide effective prophylaxis, use of H_2 antagonists and proton pump inhibitors is associated with increased rates of gastric colonization and pneumonia, including VAP, and therefore should only be used when there is significant risk of developing stress ulcers.[31,32] Furthermore, recent meta-analysis showed that in patients receiving enteral tube feeds, the use of H_2 antagonists was associated with increased frequency of HAP without reduction in the frequency of gastrointestinal bleeding.[29]

An endotracheal tube serves as a reservoir for bacteria from the upper airway to leak around the cuff and gain entry into the LRT. Manufacturers have developed novel endotracheal tubes with antimicrobial properties that prevent biofilm formation.[33] Humidifiers and nebulizers may be infected, thereby allowing for the transfer of microorganisms between patients by respiratory personnel. Contaminated water supply systems have led to previous nosocomial outbreaks of *Legionella* species.[18] Fungal infections have resulted from hospital renovations and construction, contaminated air supply, and poor filtration.[34]

VAP caused by MDR microorganisms is a well understood example of how alterations in the host microbiome contribute to the development and progression of nosocomial pneumonia and other infections.[35] It is increasingly apparent that microbial imbalances within the body, such as an impaired intestinal microbiome, represent important pathogenic mechanisms for the development of nosocomial lung infections. Investigators have demonstrated that critically ill subjects have lower initial diversity of their microbiota in both the upper and lower respiratory tract compared to healthy controls.[36] The presence of endotracheal tubes and antibiotic administration may promote pathogenic bacterial colonization in the airways, contributing to both lower microbiota diversity and the development of an intermediate respiratory infection termed ventilator-associated tracheobronchitis (VAT).[37]

VAT represents a compartmentalized host response associated with a better overall prognosis compared with VAP.[38,39] If the aforementioned response is not compartmentalized, progression to VAP is likely, and other organ failures, including the acute respiratory distress syndrome (ARDS), may occur. In one study, examination of the lungs of critically ill patients revealed a correlation between lung-specific microbiota and clinical outcomes.[40] Patients with increased lung bacterial burden had fewer ventilator-free days. Moreover, the investigators found that the community composition of lung bacteria, driven primarily by gut-associated bacteria, was also predictive of ventilator-free days and the presence of ARDS. Thus, both bacterial burden and community composition of the microbiota influence disease presentation and clinical outcomes, including the occurrence of nosocomial pneumonia.

The early, hyperinflammatory response that occurs in trauma and sepsis may cause multisystem organ failure and death. Improvements in the management of sepsis have decreased rates of early death, and patients now often succumb to protracted or nosocomial infections. Recent evidence suggests that a subset of patients who survive the cytokine storm associated with the proinflammatory response of sepsis develop an immunodeficient state promoting viral reactivation and nosocomial infection, including pneumonia. Immunomodulatory therapies to attempt to obviate this risk are currently being investigated.[27]

RISK FACTORS

Given the important pathophysiologic roles of aspiration and colonization of the aerodigestive tract, it is logical that the significant risk factors for nosocomial pneumonia involve these processes. A complete list of risk factors is provided in Table 129-5.

Mechanical ventilation is the single most important risk factor for nosocomial pneumonia, increasing the risk up to 20-fold.[2,4,5] Reintubation is associated with further increased risk of developing VAP.[41] Severity and type of disease are known risk factors for nosocomial pneumonia. An Apache II score of at least 16 and an organ system failure index of 3 or greater have both been linked to VAP.[5,42] Nosocomial pneumonia occurs more frequently in postsurgical patients, particularly burn and trauma victims.[43] The incidence is also higher in COPD likely due to greater colonization rates, impairment of airway clearance, and risk of ARDS as a result of prolonged mechanical ventilation.[44–46]

Aspiration occurs more frequently in the supine position and may be exacerbated by the presence of a nasogastric tube combined with early enteral nutrition.[47–50] As previously mentioned, aspiration is more frequent and the risk of macroaspiration is increased in

TABLE 129-5 Risk Factors for Nosocomial Pneumonia Determined by Regression Analysis

Aspiration	Colonization	Aspiration/Colonization	Other
Documented aspiration risk	Frequent ventilator circuit changes	Mechanical ventilation	Severity of illness (Apache, SOFA)
Supine position	Prior antibiotic use	Reintubation	ARDS
Nasogastric tube	COPD	Admission diagnosis of trauma or cerebrovascular accident	Age >60
Enteral nutrition			Transport out of ICU
Decreased endotracheal tube cuff pressure			PRBC transfusion
Neuromuscular disease			
Coma/head trauma			
ICP monitor			

Data from Cook DJ, Kollef MH. Risk factors for ICU-acquired pneumonia. JAMA. 1998;279(20):1605–16056; Bergin SP, Coles A, Calvert SB, et al. PROPHETIC: Prospective Identification of Pneumonia in Hospitalized Patients in the ICU. Chest. 2020;158(6):2370–2380.

hospitalized patients.[24] Postpyloric feeding may reduce gastroesophageal reflux, but the impact on VAP incidence is unclear. Antacids and H_2 antagonists used for stress ulcer prophylaxis are independent risk factors for nosocomial pneumonia, as alterations in gastric pH promote bacterial colonization.[51,52] In addition, prior antibiotic administration may select for infection by MDR microorganisms.[16,42]

Work is currently underway to identify patients at highest risk for nosocomial pneumonia in order to optimize its prevention, diagnosis, and treatment. The PROPHETIC study prospectively identified patients at high risk for nosocomial pneumonia based on need for supplemental oxygen or ventilatory support, followed them over time for development of infection, and then developed a multivariable logistic model in order to identify risk factors, comorbidities, and exposures associated with pneumonia. The study found increased odds of developing nosocomial pneumonia in patients receiving enteral nutrition, with documented aspiration risk, with admission diagnosis of trauma or cerebrovascular accident, and with receipt of antibiotics in the previous 90 days.[16]

In patients with CAP, determining which patients are at highest risk for infection due to MDR microorganisms is an area of active investigation. Rapid identification of these patients is important because delay in appropriate antimicrobial therapy is associated with increased morbidity and mortality.[53] Healthcare-associated pneumonia (HCAP), an entity defined in the 2004 ATS/IDSA guidelines on nosocomial pneumonia, includes a large group of patients with exposures, including treatment at outpatient dialysis and wound care centers, recent hospitalization, and recent receipt of IV antibiotics or chemotherapy, in an effort to capture patients from the community with increased risk for pneumonia due to MDR microorganisms.[54] In a review of hospital admissions for pneumonia in New York City, patients meeting criteria for HCAP had a mortality rate of 15.6% compared with 7.9% in patients with CAP.[55] Several observational studies support HCAP as an effective set of criteria to identify those with pneumonia in the community at high risk for infection due to MDR microorganisms.[56,57] However, recent prospective studies have raised doubt about whether HCAP is an effective way to identify those most at risk for infection due to MDR microorganisms and suggested that they may result in overuse of broad-spectrum antibiotics.[58,59]

Particular attention has been paid to three bacteria which make up a large share of the MDR microorganisms in CAP and result in excess mortality: *P. aeruginosa*, β-lactamase–positive Enterobacteriaceae, and MRSA (PES).[60] In order to identify at-risk patients, the PES Score was generated from analysis of an observational prospective study of patients admitted to the hospital with diagnosis of pneumonia and includes the patient's age, sex, antibiotic use, medical comorbidities, and level of consciousness on admission.[53] The inclusion of antibiotic history is further supported by the PROPHETIC study, which prospectively identified receipt of antibiotics in the previous 90 days as a risk factor for pneumonia due to MDR microorganisms. Multivariable logistic regression analysis of a large cohort of immunocompromised patients presenting to the hospital with CAP identified several factors with increased odds of *P. aeruginosa* pneumonia, including severe COPD, tracheostomy, inhaled corticosteroid use, indwelling catheter (vascular or urinary), and prior history of *P. aeruginosa* infection.[61]

VAP was previously classified as early-onset or late-onset based on data that showed significantly increased risk of infection with MDR microorganisms in patients with a diagnosis of VAP after greater than 7 days of mechanical ventilation.[62] While early-onset VAP was previously thought to confer a better prognosis due to decreased risk of infection with MDR microorganisms, more recent data have challenged this. In a retrospective review comparing VAP diagnosed before or after 5 days of initiation of mechanical ventilation, no difference was found in the incidence of MDR microorganisms.[63] A prospective observational trial also concluded that duration of mechanical ventilation alone was not predictive of risk of VAP due to MDR microorganisms.[64] Rather, assessment of risk factors, including recent antibiotic usage and local prevalence of MDR microorganisms, is needed to properly strategize treatment in patients with early-onset VAP.[65]

DIAGNOSIS

The diagnosis of nosocomial pneumonia remains challenging. Optimal use of both clinical and microbiologic data is needed to maximize diagnostic accuracy. Nosocomial pneumonia should be suspected in any patient with new or progressive radiographic opacities and clinical signs or symptoms indicative of infection, including fever, leukocytosis or leukopenia, purulent sputum, or worsening oxygenation. These clinical findings are neither sensitive nor specific, and there is no gold standard for the diagnosis of HAP or VAP; even postmortem histologic examination does not provide 100% specificity.[66] Microbiologic data can also be difficult to interpret, as false-positive and false-negative results are common.

The clinical strategy employs the previously mentioned clinical and radiographic criteria in diagnosing nosocomial pneumonia. A prospectively specified combination of two out of three clinical criteria (leukocytosis, purulent secretions, and fever) and a radiographic infiltrate yielded a sensitivity of 69% and a specificity of 75% for the diagnosis of VAP in 25 mechanically ventilated patients using histology and quantitative lung tissue culture on autopsy as the reference. Increasing the number of clinical criteria resulted in greater specificity but at the cost of lesser sensitivity.[67] However, in a postmortem analysis of 39 mechanically ventilated patients, clinical criteria did not provide a reliable positive predictive value for histologic pneumonia.[66]

The bacteriologic strategy uses quantitative cultures of the LRT via endotracheal aspirate, protected specimen brush, or bronchoalveolar lavage (BAL) to confirm or eliminate the diagnosis of nosocomial pneumonia based on thresholds of bacterial growth. These thresholds differ depending on the method of respiratory sampling and are as follows: $\geq 10^5$ colony-forming units (CFU)/mL for an endotracheal aspirate, $\geq 10^4$ CFU/mL for a BAL, and $\geq 10^3$ CFU/mL for a protected specimen brush. Results of these procedures guide decisions such as when to initiate or stop antibiotics and the drug(s) to be used against the offending agent. There are no definitive data to support the use of one sampling technique over another; however, cellular analysis of BAL fluid may provide an advantage, as a sample containing $<50\%$ neutrophils produced excellent negative predictive value in one study.[66] Also, given the multifocal nature of VAP, even mini-BAL samples obtained blindly without the use of bronchoscopy may be effective.[68–70]

A semiquantitative endotracheal aspirate culture can be used to identify a pathogen and, if positive, has been shown to correlate with quantitative cultures of the LRT obtained via protected specimen brush.[71] Also, a negative endotracheal aspirate culture has high sensitivity and good negative predictive value if antibiotics have not recently been changed.[72] However, semiquantitative cultures are not as reliable as quantitative cultures of the LRT due to an inability to differentiate between colonization and infection.

The use of clinical criteria and a reliance on semiquantitative cultures can be overly sensitive, resulting in unnecessary antibiotic use and potential delay in the identification of extrapulmonary infection. The bacteriologic strategy has resulted in less and more narrowed antibiotic use, an important point given the surge of MDR microorganisms in the ICU setting.[73–75] A major disadvantage with this approach is the concern for false negatives, which could result in cases of nosocomial pneumonia going untreated, especially in the setting of recently introduced antibiotics.[76] A recent pilot study utilized metagenomic shotgun sequencing in BAL fluid as a novel tool to identify bacterial pathogens in a highly sensitive manner, which may represent a promising future approach.[77]

Multiple studies have compared the clinical and bacteriologic strategies. Only one prospective, randomized trial demonstrated a mortality benefit at 14 days when using the bacteriologic strategy.[73] Others have failed to reproduce these findings, including a large study conducted by the Canadian Critical Care Trials Group, as well as a comprehensive meta-analysis.[78,79] In addition, the bacteriologic strategy does not seem to reduce the duration of mechanical ventilation or ICU length of stay. Ultimately, the decision to employ either strategy rests with the clinician on a case-by-case basis. If bronchoscopic sampling can be performed safely and the appropriate personnel are available, it is reasonable to utilize this approach as antibiotic decisions may change based on culture results. If the clinical strategy is used, the clinician should reevaluate the patient often for guidance on antibiotic usage. Regardless of the diagnostic strategy, an unstable patient with a high pretest probability of nosocomial pneumonia should be initiated on empiric antibiotics, as a delay in antibiotic administration leads to higher mortality.[80–85]

PREVENTION

Prevention of nosocomial pneumonia centers on minimizing mechanical ventilation and reducing aspiration and bacterial colonization. As mentioned previously, mechanical ventilation is the most important risk factor for nosocomial pneumonia.[2,4,5] Therefore, avoiding intubation and reintubation, shortening the duration of mechanical ventilation, and employing noninvasive methods to improve oxygenation and ventilation when indicated can prevent pneumonia.[41,86,87]

Multiple methods designed to reduce bacterial colonization of the aerodigestive tract have been evaluated for their impact on VAP incidence. In selective decontamination of the digestive tract, nonabsorbable antimicrobial agents are administered directly to the oropharynx and stomach to prevent colonization with GNB and *S. aureus*. While this approach has been shown to have a beneficial effect on nosocomial infection rates and even survival, potential negative effects include cost and selection for antibiotic-resistant microorganisms when utilized in ICUs with high rates of endemic antibiotic resistance.[88–91] Alternatively, selective oropharyngeal decontamination with nonabsorbable antibiotics or chlorhexidine offers a more limited approach. While this has been associated with lower VAP rates in some trials, particularly in cardiac surgery patients, meta-analysis has failed to show clear association with VAP rates in mechanically ventilated patients.[91–93] Furthermore, selective oropharyngeal decontamination with chlorhexidine has been associated with increased mortality in retrospective analyses, including a recent multicenter study, and should be used with caution.[65,94,95] While systemic antibiotics given once at the time of intubation may reduce early-onset VAP, the routine use of prolonged prophylactic, systemic antibiotics cannot be recommended.[96–98] Probiotics may reduce VAP rates; however, no studies performed to date demonstrate a survival benefit.[99,100]

Strategies to reduce aspiration also have been studied. Patients should be managed in a semirecumbent position rather than supine, particularly when receiving enteral nutrition.[101] In a meta-analysis of patients undergoing mechanical ventilation, semirecumbent positioning with the head of the bed elevated to 30 to 60 degrees reduced the frequency of clinically suspected VAP when compared with patients positioned supine.[102] Continuous drainage of subglottic secretions with specialized endotracheal tubes decreases the frequency of VAP but has not been shown to improve mortality or duration of mechanical ventilation.[103] A randomized controlled trial from 2013 showed that monitoring of gastric residual volume was a poor predictor of aspiration and did not change the frequency of VAP.[104] While postpyloric feeding may reduce aspiration, its effect on infection rates and mortality is unknown. In addition, there is no evidence favoring a specific time point for the initiation of enteral feeding.[105]

Several important trials have evaluated changes to the endotracheal tube and ventilator circuit. Silver-coated endotracheal tubes reduce the frequency of VAP, but they have not been shown to reduce mortality and are more costly when compared to standard endotracheal tubes.[33,106] An updated 2017 Cochrane review did not find a difference in mortality or frequency of VAP when comparing use of heat–moisture exchangers or heated humidifiers in mechanically ventilated adults.[107] There is no evidence that frequent changes of the ventilator circuit or early tracheostomies reduce the rate of VAP.[108–110]

Several bundles of prevention measures exist to improve the care of mechanically ventilated patients. The nonprofit Institute for Healthcare Improvement (Boston, USA) developed a programmatic bundle used by many healthcare institutions in the United States, including semirecumbent positioning with the head of the bed elevated at 45 degrees, daily sedation holidays coupled with an assessment of readiness to extubate, and daily oral care with chlorhexidine.[111]

A similar bundling strategy developed by French investigators was evaluated prospectively in a single medical ICU. Components of the bundle included hand hygiene, semirecumbent positioning, maintenance of tracheal cuff pressure, avoidance of gastric overdistention, good oral hygiene, and minimization of tracheal suction. After an initial educational program for healthcare personnel, compliance with each component increased throughout the 24-month study.[112] In a companion evaluation, total VAP rates decreased from 22.6 to 13.1 per 1000 ventilator days after implementation of the bundle.[113]

A multicenter, prospective surveillance trial of 181 ICUs in Spain used a similar strategy and demonstrated a reduction in the frequency of VAP by approximately 50%, which was sustained at 21 months.[114]

A recent meta-analysis of similar preventive bundles in the pediatric population similarly showed reduction in the frequency of VAP.[115]

Thus, the bundling strategy appears to reduce VAP rates and could potentially produce a more substantial impact with improved compliance. Table 129-6 contains a list of recommended prevention strategies.

TABLE 129-6 Strategies for the Prevention of Nosocomial Pneumonia

Recommended	Evidence Level
Shortening the duration of mechanical ventilation	1
Short-course antibiotic therapy (when clinically applicable)	1
Use of noninvasive mask ventilation	1
Oral chlorhexidine	1
Orotracheal intubation preferred for airways	1
Use of heat–moisture exchanger	1
Semierect positioning	1
Polyurethane endotracheal tube cuff	1
Subglottic secretion drainage	1
Silver-coated endotracheal tube	1
Rotational beds	1
Closed endotracheal suctioning	1
Use of protocols/bundles incorporating multiple prevention elements	2
Adequate intensive care unit staffing	2
Avoid reintubation	2
Avoid patient transports	2
Restricted (conservative) blood transfusion	2
Orogastric intubation preferred for feeding tubes	2
***Not* Recommended**	
Routine ventilator circuit changes	1
Chest physiotherapy	1
Early tracheostomy	1
Specific stress ulcer prophylaxis regimen	1
Topical iseganan	1
Oro-digestive decontamination[b] (Topical/topical plus intravenous antibiotics)	1
Aerosolized antibiotics[b]	1
Intravenous antibiotics[b]	1
Routine antibiotic cycling/rotation/heterogeneity[a]	2

Evidence levels: 1, supported by randomized trials; 2, supported by prospective or retrospective cohort studies.

VAP, ventilator-associated pneumonia.

[a] *May be useful in specific clinical circumstances (outbreaks of a multidrug-resistant bacterial infection).*

[b] *Routine antibiotic prophylaxis not recommended due to potential emergence of antibiotic-resistant bacteria.*

Reproduced with permission from Kollef M, Isakow WA, Burks AC, et al. The Washington Manual of Critical Care, 3rd ed. Philadelphia, PA: Wolters Kluwer; 2018.

TABLE 129-7 Risk Factors for MDR Pathogens

- Intravenous antimicrobials in previous 90 days
- Chronic lung disease including COPD, cystic fibrosis, pulmonary fibrosis, or bronchiectasis
- Residence in high-risk environment including LTAC or skilled nursing facility
- Tracheostomy
- Septic shock at the time of VAP onset
- ARDS prior to VAP onset
- Immunosuppressive therapy
- Hospitalization for >2 days in the previous 90 days
- Indwelling vascular or urinary catheter
- Home wound care
- Current hospitalization for 5 d or greater
- High rates of local antibiotic resistance
- Acute renal replacement therapy prior to VAP onset

Data from Bergin SP, Coles A, Calvert SB, et al. PROPHETIC: Prospective Identification of Pneumonia in Hospitalized Patients in the ICU. Chest. 2020;158(6):2370–2380; Kalil AC, Metersky ML, Klompas M, et al. Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis. 2016;63(5):e61–e111; Di Pasquale MF, Sotgiu G, Gramegna A, et al. Prevalence and Etiology of Community-acquired Pneumonia in Immunocompromised Patients. Clin Infect Dis. 2019;68(9): 1482–1493.

TREATMENT

When initiating empiric antibiotics for the treatment of nosocomial pneumonia, the clinician first needs to assess the patient's risk for infection with MDR microorganisms. Table 129-7 lists these risk factors.[48] Figure 129-2 lists appropriate empiric antibiotic management when HAP/VAP is suspected.

Failure to initiate the appropriate antibiotics in a timely fashion results in excess morbidity and mortality.[80–85] Inappropriate antibiotics are those that do not have in vitro activity against the offending pathogen. A large, multicenter study conducted in Spain demonstrated that in 565 cases of nosocomial pneumonia, a change in the initial empiric antibiotic regimen was required in 43.7% of cases. The most frequent reason for a change in therapy was inadequate antimicrobial coverage, which resulted in greater attributable mortality.[81] A multivariate analysis of 107 patients with VAP determined that a delay in appropriate antibiotics for ≥24 h was an independent risk factor for in-hospital mortality.[82] A separate multivariate analysis showed that prior antibiotic use was an independent risk factor for inappropriate antibiotic therapy; therefore, one should consider the possibility of drug resistance associated with previous antimicrobial agents.[62,85,116] A protocol-based approach to empiric antibiotics resulted in a greater rate of appropriate antibiotics and a reduction in antibiotic duration.[117] In addition, knowledge of each healthcare facility's antimicrobial drug resistance profile is of paramount importance.[22,23,118]

Choosing the correct dose of an antibiotic and the route of administration is essential in the treatment of nosocomial pneumonia. It is important to know the mechanism of action of each antibiotic. For example, β-lactam antimicrobial agents kill in a time-dependent fashion and require a serum concentration above the microorganism's minimal inhibitory concentration (MIC). This knowledge has led to the proposition of prolonged infusions, a practice that remains controversial.[119,120] On the other hand, aminoglycoside agents kill bacteria in a concentration-dependent manner, leading to newer extended-interval dosing parameters. Antibiotics

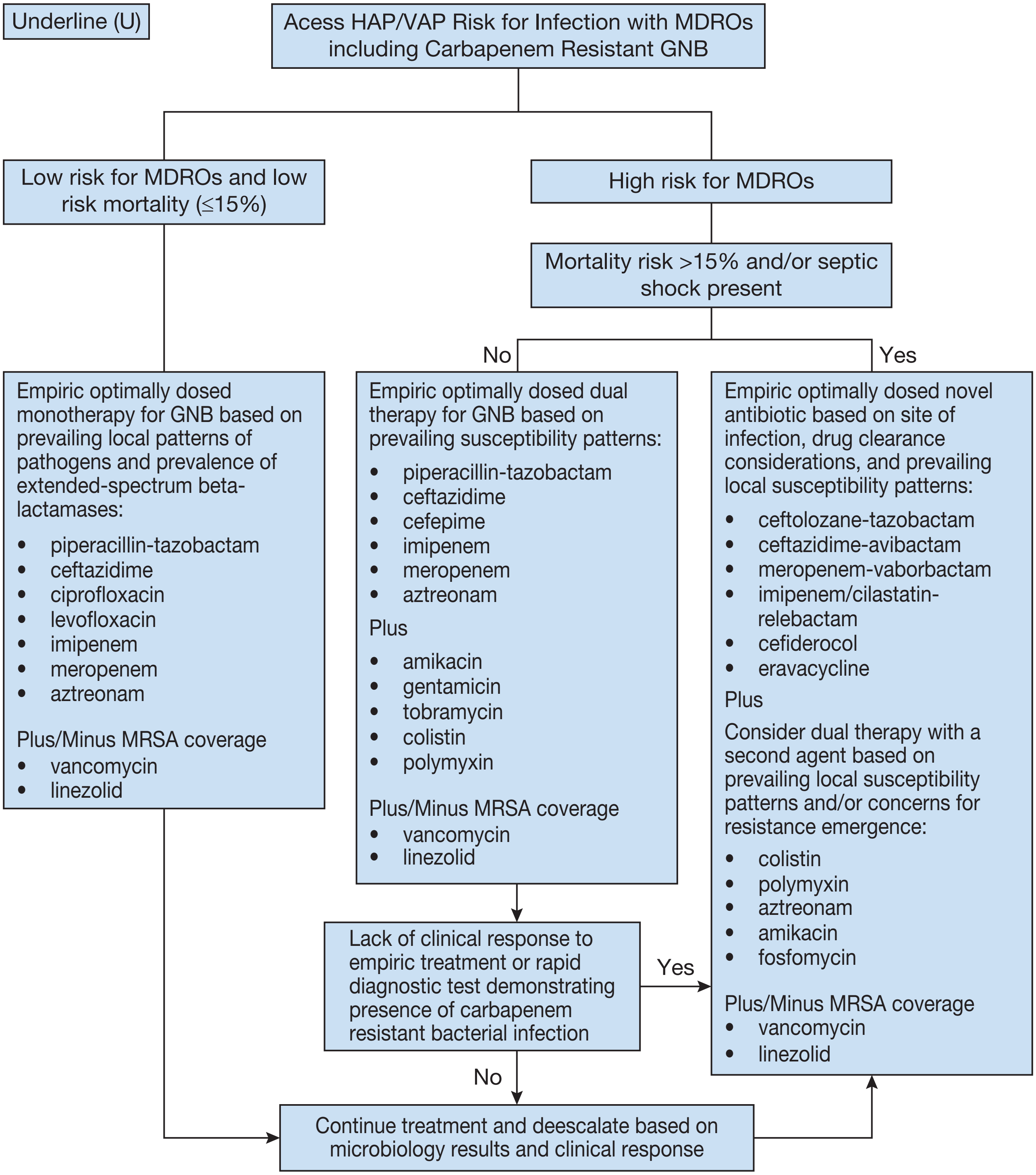

Underline (U)
Acess HAP/VAP Risk for Infection with MDROs including Carbapenem Resistant GNB
Low risk for MDROs and low risk mortality (≤15%)
High risk for MDROs
Mortality risk >15% and/or septic shock present
No
Yes
Empiric optimally dosed monotherapy for GNB based on prevailing local patterns of pathogens and prevalence of extended-spectrum beta-lactamases:
• piperacillin-tazobactam
• ceftazidime
• ciprofloxacin
• levofloxacin
• imipenem
• meropenem
• aztreonam
Plus/Minus MRSA coverage
• vancomycin
• linezolid
Empiric optimally dosed dual therapy for GNB based on prevailing susceptibility patterns:
• piperacillin-tazobactam
• ceftazidime
• cefepime
• imipenem
• meropenem
• aztreonam
Plus
• amikacin
• gentamicin
• tobramycin
• colistin
• polymyxin
Plus/Minus MRSA coverage
• vancomycin
• linezolid
Empiric optimally dosed novel antibiotic based on site of infection, drug clearance considerations, and prevailing local susceptibility patterns:
• ceftolozane-tazobactam
• ceftazidime-avibactam
• meropenem-vaborbactam
• imipenem/cilastatin-relebactam
• cefiderocol
• eravacycline
Plus
Consider dual therapy with a second agent based on prevailing local susceptibility patterns and/or concerns for resistance emergence:
• colistin
• polymyxin
• aztreonam
• amikacin
• fosfomycin
Plus/Minus MRSA coverage
• vancomycin
• linezolid
Lack of clinical response to empiric treatment or rapid diagnostic test demonstrating presence of carbapenem resistant bacterial infection
Yes
No
Continue treatment and deescalate based on microbiology results and clinical response

Figure 129-2 Algorithm for treatment of nosocomial pneumonia.

should initially be given intravenously in all cases of nosocomial pneumonia; however, transitioning to oral therapy in certain cases has been proven to be safe and effective.[121] Finally, while traditionally thought to have a synergistic effect on the eradication of Gram-negative organisms, combination therapy rather provides a greater likelihood of appropriate empiric therapy in the case of MDR microorganisms.[122]

Aerosolized antibiotics offer an appealing treatment route as direct antibiotic delivery to the airways while avoiding systemic delivery and the associated toxicities.[123] However, the challenges accompanying aerosolizing small particles through a mechanical ventilator have limited the use of inhaled antibiotics. Two randomized controlled trials have evaluated the addition of inhaled antibiotics to standard-of-care antibiotic therapy in ventilated patients with pneumonia. One study used inhaled amikacin, while the other study used a combination of amikacin and fosfomycin, with each failing to demonstrate a difference in mortality.[124,125] While routine use of inhaled antibiotics cannot be recommended in treating HAP or VAP, their use should be considered as adjuncts in cases of pneumonia due to GNB where there is limited or no in-vitro susceptibility to available antibiotics.

When determining treatment duration for nosocomial pneumonia, the goal is to eradicate the microorganism without allowing for colonization of the host with MDR microorganisms. Clinical improvement with appropriate antibiotic therapy usually occurs in 3 to 5 days, as shown in a cohort of 63 patients with VAP in whom Clinical Pulmonary Infection Scores were obtained before and after antibiotic initiation.[126] Survivors had improving scores by day 3 compared with nonsurvivors. Currently, 7 days is a reasonable duration of treatment, but prolonged therapy should be considered in the case of *P. aeruginosa*.

A large French analysis demonstrated that patients with VAP had similar mortality and infection recurrence rates when treated with 8 days of antibiotics versus 15 days. Patients infected with nonfermenting GNB who received only 8 days of treatment had a higher infection recurrence rate compared with the prolonged therapy group, but no difference in mortality was noted.[127]

A 2013 systematic review found no mortality difference between a short course of antibiotics (7–8 days) versus a longer course (10–15 days) in the management of VAP. However, there was a strong trend toward lower relapse rates when using a longer course of antibiotics, mainly limited to VAP cases caused by nonfermenting GNB.[128] Additionally, when a 7-day course of doripenem was compared to a 10-day course imipenem–cilastatin in the management of VAP due to GNB, higher rates of clinical failure and mortality were noted, particularly in those patients infected with *P. aeruginosa*.[129] Longer durations of treatment should also be considered in patients with immunocompromise, cavitation, lung abscess, empyema, and bronchiectasis.[65] Nonresponders should be evaluated for emergence of antimicrobial resistance, extrapulmonary infection, complications of pneumonia such as empyema, and noninfectious causes of fever and pulmonary infiltrates (Table 129-8).

CONCLUSIONS

Recent epidemiologic data show that the associated morbidity, mortality, and cost of nosocomial infection, and pneumonia in particular, remain stubbornly high. This is expected to continue to be a substantial problem across the healthcare system, as the number of patients with complex chronic illnesses and the use of invasive devices increase. Diagnosis remains challenging, particularly in the nonintubated patient. Further innovations are needed in the engineering of invasive devices such as mechanical ventilators and endotracheal tubes in order to minimize nosocomial pneumonia, as are innovations in diagnostic tests that can obtain a more rapid and accurate microbiologic diagnosis. Multidrug-resistant infections are on the rise; therefore, antibiotic stewardship and development of a pipeline of new antibiotics remain high priorities. Bundled prevention strategies are an area of progress and have been successfully implemented in the ICU to reduce the rate of nosocomial pneumonia. A further understanding of the cellular and molecular interactions between host cells, pathogens, microbiota, and the environment has the potential to unlock future diagnostic and therapeutic advances.

TABLE 129-8 **Noninfectious Causes of Fever and Pulmonary Infiltrates Mimicking Nosocomial Pneumonia**

Chemical aspiration without infection
Atelectasis
Pulmonary embolism
Acute respiratory distress syndrome
Pulmonary hemorrhage
Lung contusion
Infiltrative tumor
Radiation pneumonitis
Drug reaction
Bronchiolitis obliterans organizing pneumonia

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CHAPTER 130

Tuberculosis

Akash Gupta
Karen R. Jacobson

INTRODUCTION

Tuberculosis (TB) is a severe and contagious disease caused by *Mycobacterium tuberculosis* complex (MTBC). Most often involving the lungs, TB is transmitted by cough, with an infectious dose of less than 10 bacteria.[1] Case fatality rates in untreated active pulmonary TB approach nearly 60%.[2] Starting in the 1940s, major medical advances brought effective treatment capable of curing the vast majority of clinical cases.[3,4] TB continues to cause more than a million deaths worldwide every year. The morbidity and mortality burden of TB is unevenly distributed throughout the globe, disproportionately affecting those living in poverty and those from resource-limited settings.[5]

EPIDEMIOLOGY AND MICROBIOLOGY

In this section, aspects of the epidemiology and microbiology of TB are presented.

Global Burden of TB and Recent Progress

In 1990, the World Health Organization (WHO) declared TB a global emergency. In response, the WHO endorsed the directly observed therapy strategy (DOTS), promising to "Stop TB" by finding and treating infectious cases in resource-limited settings.[6,7] Within a few years of its design, the World Bank labeled the DOTS strategy the most cost-effective health intervention ever deployed.[8,9] By 2020, an estimated 60 million lives had been saved.[10] Since 2004, TB incidence has been slowly falling every year, with an estimated reduction of 2.3% between 2018 and 2019.[10] The Joint United Nations Programme on HIV/AIDS set the 90/90 goals, aiming to reach at least 90% of people with TB and ensure that at least 90% of them have a successful treatment completion.[11] However, at the current pace, it is unlikely that these goals will be met by 2030 as originally proposed. Furthermore, these gains may be set back by disruption to TB control services during the COVID pandemic.[10]

Although global TB incidence is falling, TB remains one of the leading causes of global infectious mortality, and the 10th leading cause of death worldwide.[10,12,13] In 2019, there were an estimated 10 million new TB cases, with 1.2 million deaths among HIV-negative people, and an additional 208,000 deaths among HIV-positive people. Moreover, many TB deaths occur in young, previously healthy adults, and as such, in 2019 TB was the 9th leading cause of lost disease-adjusted life years (DALYs).[7,14]

Poverty and TB

Globally, TB disproportionately impacts those with greater poverty and lower human development indices.[15–18] Population health factors such as water sanitation, childhood immunization rates, and life expectancy also independently predict TB incidence.[19,20] The vast majority of the global burden of TB is concentrated in low- and middle-income countries (LMICs), with 28 of the 30 highest-burden countries located in Africa and Asia[10] (Fig. 130-1, Table 130-1).

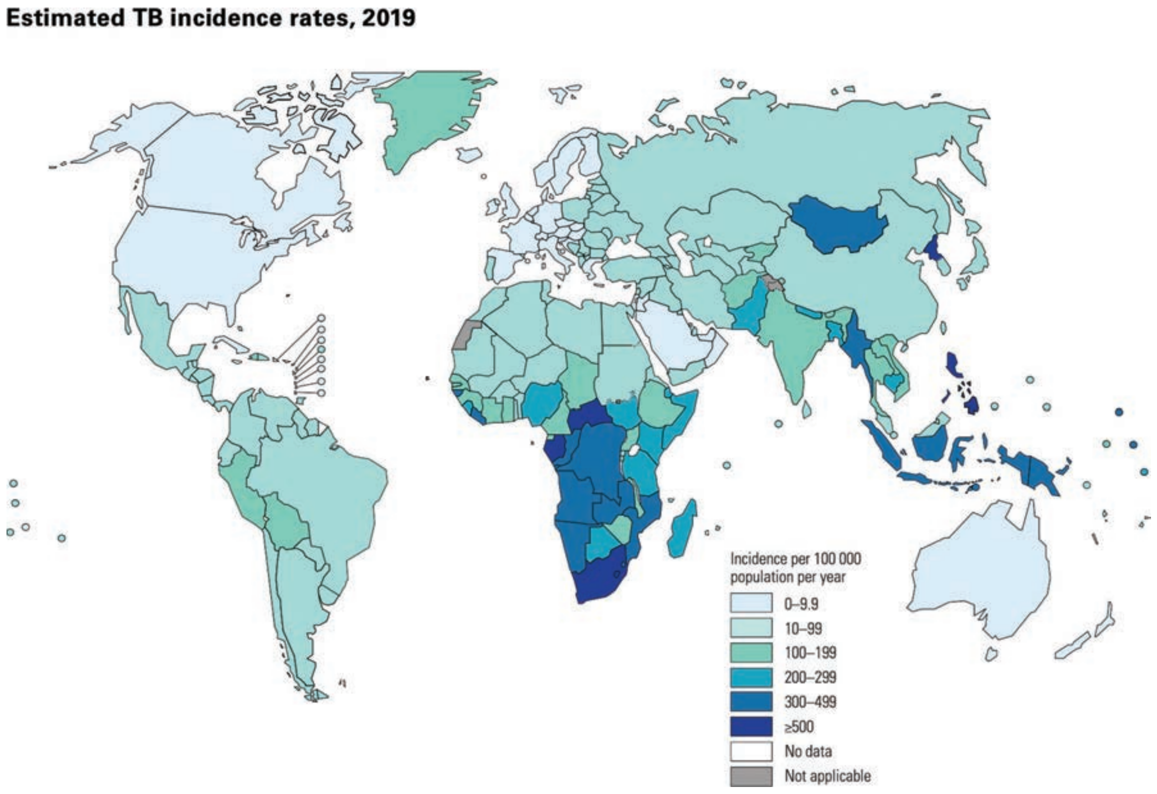
Estimated TB incidence rates, 2019
Incidence per 100 000 population per year
0–9.9
10–99
100–199
200–299
300–499
≥500
No data
Not applicable

Figure 130-1 Estimated TB incidence by Country, 2019. *(Reproduced with permission from Global Tuberculosis Report 2020, World Health Organization.)*

TABLE 130-1 TB Incidence and Incidence Rate in 2019 for the 30-High TB Burden Countries

Country	TB Incidence (per 100,000 Population) in 2019	Number of New TB Cases in 2019
Angola	351	112,000
Bangladesh	221	361,000
Brazil	46	96,000
Cambodia	287	47,000
Central African Republic	540	26,000
China	58	833,000
Congo	373	20,000
DPR Korea	513	132,000
DR Congo	320	278,000
Ethiopia	140	157,000
India	193	2,640,000
Indonesia	312	845,000
Kenya	267	140,000
Lesotho	654	14,000
Liberia	308	15,000
Mozambique	361	110,000
Myanmar	322	174,000
Namibia	486	12,000
Nigeria	219	440,000
Pakistan	263	570,000
Papua New Guinea	432	38,000
Philippines	554	599,000
Russian Federation	50	73,000
Sierra Leone	295	23,000
South Africa	615	360,000
Thailand	150	105,000
UR Tanzania	237	137,000
Vietnam	176	170,000
Zambia	333	59,000
Zimbabwe	199	29,000

Data from Global Tuberculosis Report, World Health Organization; 2020. Available at: https://apps.who.int/iris/bitstream/handle/10665/336069/9789240013131-eng.pdf.

■ HIV and TB: Co-pandemics

HIV-induced immune suppression increases the risk of progression to active TB nearly 100-fold.[21–25] Worldwide, TB is the most common opportunistic illness and the leading cause of death in patients with AIDS.[26] HIV coinfection complicates 8.2% of all TB cases worldwide as of 2019.[10] As both a potent and common risk factor, HIV contributes substantially to TB incidence, especially in Sub-Saharan Africa.[2,27]

■ Drug-resistant TB

In 2019, there were more than 360,000 cases of multidrug-resistant (MDR) TB, defined by resistance to the two most important first-line antimicrobials, isoniazid and rifampin (rifampicin).[10] MDR-TB accounted for approximately 3.3% of newly diagnosed TB cases and 18% of relapsed cases globally. These proportions have overall remained stable. Eastern European countries have particularly high rates of MDR-TB; this is a phenomenon considered linked to the underinvestment in national TB programs and the social disruption that occurred following the collapse of the Soviet Union in the 1990s.[28] These factors are believed to have led to MDR-TB strains successfully circulating in those countries. MDR-TB is much more challenging to treat than drug-susceptible TB, with long treatment courses, higher cost, and worse treatment outcomes. However, newer regimens already have reduced, and may continue to reduce, the required treatment duration, efficacy, and total cost.[29,30] Extensively drug-resistant TB (XDR-TB) until 2021 was defined as TB resistant to rifampin, isoniazid, any fluoroquinolone, and any second-line injectable agent. There were 12,350 cases of XDR-TB reported worldwide in 2019 by this older definition, with cases in all WHO regions.[10] In 2021, the World Health Organization formally introduced the definition of pre-XDR-TB as strains that are MDR or rifampin-resistant TB and resistant to any fluoroquinolone. XDR-TB was updated as MDR or rifampin-resistant TB plus resistance to any fluoroquinolone and at least one additional group A drug, which are the most potent drugs in the ranking of second-line medicines[31]. Group A drugs may change over time as more potent options are found or resistance profiles change, so specific drugs were not named. Current group A drugs include bedaquiline and linezolid.[32]

■ Newer Threats to Global TB Control

Diabetes, smoking, alcohol, and malnutrition also can impair immunologic containment of TB infection. Their prevalence continues to increase globally, and the cumulative impact threatens global TB control in the future.[9,16,33] Among HIV-negative individuals in 2015, alcohol use accounted for 11.4% of global TB deaths, diabetes accounted for 10.6%, and smoking accounted for 7.8%.[34] These comorbidities have larger population impact on TB outcomes in many of the middle income countries including India, China, and Brazil where HIV is less prevalent.

■ TB Epidemiology in the United States: Historic Perspective

In the first half of the 20th century, TB was a leading cause of morbidity and mortality in the United States. In 1920, pulmonary TB accounted for nearly 1 in 13 deaths, outranking cancer.[6,35,36] Improvements in social conditions and population health during the early 20th century led to significant reductions in TB incidence. With the introduction of effective chemotherapy in the 1950s, incidence declined even further.[4] By the 1970s, TB incidence in the United States had reached historic lows, less than 10 cases per 100,000 people, and TB seemed on the brink of elimination. Unfortunately, public health funding for TB control was then greatly reduced, and by the mid-1980s, a nationwide resurgence ensued, particularly in the major urban centers and partially driven by HIV.[6,37,38] It is estimated that this resurgence resulted in 67,000 more cases of tuberculosis than would have occurred had the strategy designed by the CDC and its Advisory Council for the Elimination of Tuberculosis been successfully implemented.[37,39]

■ Current U.S. Trends in TB Epidemiology

With renewal of government investment in the mid-1990s, TB control was reestablished, and TB rates have since declined every consecutive year in the United States (Fig. 130-2). Since 2010, TB incidence has decreased by an average of 2% to 3% annually. In 2020, there were 7163 total reported cases of TB in the United States, or 2.2 cases per 100,000 people, which was 20% lower than 2019, although this was likely driven by multiple factors including lower detection, underreporting, and lower immigration in the setting of the COVID-19 pandemic.[40]

TB remains a concern within specific demographic groups. Non-U.S.-born individuals, especially newly arrived immigrants,

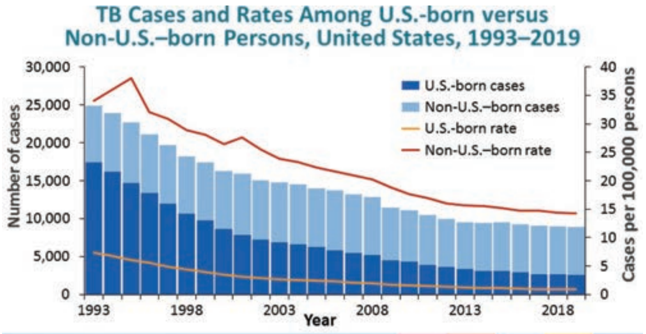

Figure 130-2 TB cases and rates among U.S.-born versus non-U.S.-born persons, United States, 1993 to 2019. *(Reproduced with permission from Tuberculosis in the United States 2019 Slide Set, Centers for Disease Control & Prevention.)*

account for the majority of TB cases in the United States, representing 71% of all U.S. cases in 2020 (Fig. 130-3). During 2019 and 2020, the most frequently reported countries of birth among non-U.S.-born persons with tuberculosis were Mexico, the Philippines, India, Vietnam, and China.[40] In non-U.S.-born residents, TB usually represents reactivation of infection acquired in TB-endemic countries prior to arrival, rather than new infection resulting from local transmission.[41] Overwhelmingly these individuals develop TB in the first years after their arrival; studies have shown that TB disease is uncommon (0.8%) more than 15 years after initial exposure.[42]

Among the U.S.-born individuals with TB disease, 36% identified as Black, 24% as Hispanic, and 4% as American Indian/Alaska Native (AI/AN).[43] Risk factors for TB in the United States include incarceration, history of alcohol or illicit drug use, and experiencing homelessness.[39,41,44–46] In these groups, "mini" outbreaks of TB resulting from recent transmission have been seen. Because TB disease in children often occurs sooner after initial infection, childhood TB incidence reflects ongoing community TB transmission and is an important indicator of TB control. In the United States, almost 80% of childhood TB occurs in U.S.-born children, although they may be in families with non-U.S.-born members.[41]

■ Microbiology of Tuberculosis

Mycobacterium tuberculosis was first conclusively demonstrated as the causal agent of TB in 1882 by Robert Koch, earning him a Nobel Prize in 1905.[47] *M. tuberculosis* is a slender, slightly curved, rod-shaped bacillus averaging 3 × 0.3 μm in size, which is visible by light microscopy. It is nonmotile, nonencapsulated, and non-spore-forming. *M. tuberculosis* is strictly aerobic.[48,49] Traditionally, mycobacteria are grown on solid, enriched media where rough, pigmented colonies generally appear 4 to 6 weeks after inoculation. MTBC can also be cultivated in specialized liquid media where characteristic "cords" visible by light microscopy are formed. Rapid liquid culture systems (e.g., BACTEC) have been adapted for use with mycobacteria and shorten time to detection of growth to as little as 9 to 16 days, depending on the initial concentration of the bacteria in the specimen tested.[50,51]

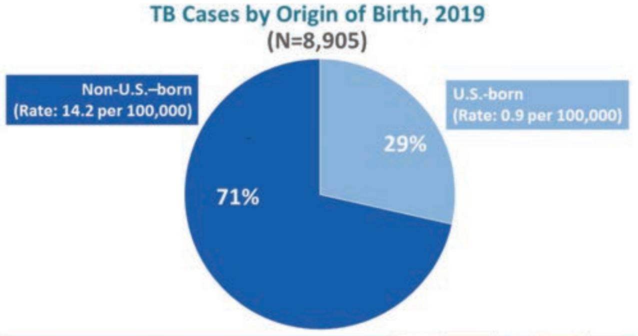

Figure 130-3 TB cases by origin of birth, 2019. *(Reproduced with permission from Tuberculosis in the United States 2019 Slide Set, Centers for Disease Control & Prevention.)*

MTBC

Eight closely related mycobacterial species capable of causing human TB have been identified and together they comprise the MTBC: *M. tuberculosis* (Koch bacillus), *M. bovis* (agent of bovine TB), *M. caprae* (bovine TB), *M. africanum* (a cause of human TB in West Africa), *M. microti* (agent of rodent TB), *M. pinnipedii* (agent of TB in seals, and a rare zoonotic disease in marine biologists attending to them), and *M. canettii* (rare cause of human TB in East Africa) (Table 130-2).[50,52,53]

Of these eight species, *M. tuberculosis* causes the vast majority of TB today. In the early 20th century, *M. bovis* accounted for up to 20% of all cases of human TB, but *M. bovis* now causes less than 2% of reported TB cases in the United States due to modern surveillance of animal herds and widespread use of milk pasteurization.[43,54,55] Sporadic outbreaks of *M. bovis* infection still occur in the United States, and ongoing surveillance is important for food-chain safety. Human-to-human transmission of *M. bovis* has been demonstrated.[56]

■ Mycolic Acid and the *Mycobacterium* Genus

The MTBC are members of the diverse *Mycobacterium* genus. The outstanding feature of the mycobacteria is their lipid-rich cell wall containing very high concentrations of mycolic acids.[48,49,51,57] This cell wall prevents reliable uptake of Gram stain. With phenol additive, mycobacteria can eventually be stained to facilitate light microscopy. Once stained, removal of dye is extremely difficult, resisting even acid alcohol wash (hence "acid-fast bacilli" [AFB]). Lipids in the mycobacterial cell wall also help resistance to drying, a property that allows MTBC to retain infectiousness even within dried droplet nuclei. The metabolic investment required to produce mycolic acids significantly slows growth rate[51] and prolongs the time to detection in incubated clinical specimens submitted to laboratory.[48] The mycolic acid–containing cell wall is also a major virulence factor, helping mycobacteria avoid innate immune defenses and intracellular killing by nonactivated host phagocytes.[58]

TABLE 130-2 Members of the Mycobacterium Tuberculosis Complex (MTBC)[a]

Species	Primary Reservoir Host	Geography
M. tuberculosis	Humans	Worldwide
M. bovis	Cattle, deer, elk, bison, badger, opossum	Worldwide
M. caprae	Goats	Worldwide
M. africanum	Human	West, Central Africa
M. microti	Vole, rodents	
M. pinnipedii	Seal, sea lion	
M. canettii	Human	East Africa

[a] *While all members of the MTBC can infect humans, some are zoonotic diseases.*

Comparison with Other Mycobacteria

The nontuberculous mycobacteria (NTM) are free-living saprophytic bacteria, commensal inhabitants of the soil and/or aquatic environments (Chapter 131). The NTM are nontransmissible from human to human under ordinary conditions, and only rarely infect humans as opportunists. In contrast, MTBC are highly transmissible, obligate primary pathogens without an environmental reservoir.[50]

Transmission

Important considerations for TB transmission are discussed below.

Droplet Nuclei

In the late 1930s, William Wells, a sanitation engineer at Harvard University, first conceived of “droplet nuclei” for airborne transmission of infectious diseases.[59] He found that forceful expiratory efforts, such as coughing and sneezing, discharge minute respiratory droplets of sputum containing viable bacilli that, when increasingly reduced in size by evaporation, become infectious droplet nuclei, each measuring less than 5 µm.[60] Certain healthcare procedures, for example, bronchoscopy, sputum induction, autopsy, and even irrigation of abscesses, also produce infectious droplet nuclei.[61]

Due to small size, droplet nuclei have an extremely slow settling rate in air (0.5 mm/s or less), permitting their transport over significant distances by air currents. Larger respiratory droplets, on the other hand, settle out of the air quickly, and travel only a few feet from the source case. The microbes suspended within droplet nuclei are highly susceptible to germicidal levels of ultraviolet light.[2,62] The small size of droplet nuclei also facilitates penetration of the bronchial defenses, allowing access to terminal alveolar macrophages. The fairly tortuous and branched path of the pharynx and bronchial tree ensures that larger respiratory droplets are instead deposited on the mucosal lining of the airway or trapped in the mucociliary elevator and expelled[60] (Table 130-3).

Airborne Transmission of TB

In the 1950s, Richard Riley, a medical student working with Wells, elegantly demonstrated that TB is near exclusively transmitted by droplet nuclei. Riley commandeered a TB ward of six rooms for his study. The air from each individual room was ventilated to an upper chamber, where caged guinea pigs were kept, sometimes passing through an adjustable UV light source.[63] Guinea pigs are considered uniquely susceptible to infection with *M. tuberculosis*, even by dilute aerosols, and their use allowed quantification of degree of patient infectiousness.

Relatively few respiratory diseases are preferentially transmitted via the airborne route; these include TB, measles, varicella, and smallpox. Most infectious respiratory diseases (including, e.g., pertussis, influenza, the common cold, and pneumococcal pneumonia) are instead transmitted by direct contact with larger respiratory droplets leading to colonization of the host nasopharynx before subsequent lung invasion. There is evidence that SARS-CoV-2, the virus that caused the COVID-19 pandemic, can be transmitted by both larger respiratory droplets and by airborne droplet nuclei.[64]

TABLE 130-4 Factors Associated with TB Transmission and Number of Infectious Droplet Nuclei per Volume of Air

Characteristics of Source Case	Environmental Factors
Sputum-smear positivity for AFB	Air circulation, ventilation
Cough strength and frequency	Room volume
Presence of lung cavitation	Humidity
Effective treatment	UV light
Delayed diagnosis	Proximity to the source case
Laryngeal tuberculosis	Duration of contact with infected air

Data from Sepkowitz KA. How contagious is tuberculosis? Clin infect Dis. 1996;23(5):954–962.

Risk Factors for TB Transmission

The risk of TB infection is a function of exposure to the tubercle bacilli. In turn, this depends on the interaction of three factors: infectiousness of the source case, a conducive environment to airborne transmission, and host susceptibility (Table 130-4).

Source Case Infectiousness

An important finding from Riley’s studies was the extreme variability in infectiousness of TB patients.[65,66] The dominant predictors of infectiousness in source cases are the presence of cough, lung cavitation on chest radiograph, and acid-fast bacilli visible in sputum by smear microscopy. Sputum-smear microscopy positive cases excrete about 108 bacilli per mL of sputum compared with less than 103 bacilli per mL of sputum in smear-negative cases.[61] About 35% of close contacts of sputum smear–positive patients will become infected, compared to less than 10% from sputum smear–negative cases[61,67–69] (Fig. 130-4).

Riley also demonstrated that effective anti-TB treatment could rapidly render patients noninfectious, usually within a few days of initiation.[70] These findings guide the discontinuation of hospital

TABLE 130-3 Key Distinguishing Features of Transmission from Droplet Nuclei and Respiratory Droplets

	Droplet Nuclei Transmission	Respiratory Droplet Transmission
Particle size	1- to 5-µm-diameter particles (dried residua of larger particles)	>100 µM-diameter particles
Time for article to settle out of air	Suspended indefinitely	Settle within seconds, 1 m from source
Number of microbes per particle	Contain few microbes	Contain many microbes
Site reached by particle in recipient airway	Alveolar deposition	Upper airway deposition
UV-light susceptibility	Susceptible	Resistant
Example pathogens	Measles, TB, varicella, SARS-CoV-2	RSV, SARS-CoV-2, influenza, *Staphylococcus*

Modified with permission from Garay S, Rom W. Tuberculosis, 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.

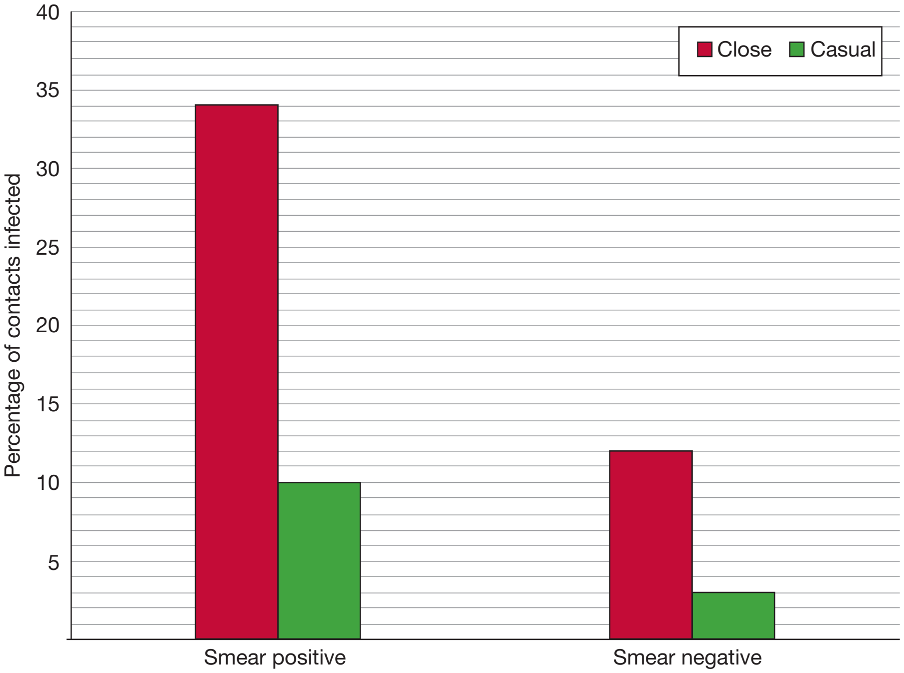

Figure 130-4 Infectiousness of tuberculosis by bacteriologic status of and proximity to source case. *(Reproduced with permission from Grzybowski S, Barnett GD, Styblo K. Contacts of cases of active pulmonary tuberculosis. Bull Int Union Tuberc. 1975;50(1):90–106.)*

isolation.[71] As a matter of convention, pulmonary TB patients are usually considered noninfectious after 2 weeks of effective chemotherapy, provided drug resistance and nonadherence are excluded.[72]

Conducive Environment

Important environmental factors influencing TB transmission include ventilation (or room air changes per hour) and ultraviolet light.[61,73,74] Proximity and duration of contact with source case are also determinants of TB transmission. Household contacts are several times more likely to be infected than are casual contacts from the community.[61,68] Thus crowded housing with poor ventilation and inadequate natural lighting—such as occurs in prisons, homeless shelters, and the large urban slums of the developing world—are particularly conducive for TB spread.[15,75] Recent data has shown that in high-burden settings, molecular epidemiology studies among household clusters show mismatch.[76] Newer models from molecular epidemiology suggest that only 8% to 19% of transmission to adults occurs within the household, or between known social contacts. The rest are thought to be from community contacts in high-burden settings.[77]

Host Susceptibility

Genetic determinants of innate immunity are likely important to host susceptibility, but they are poorly understood.[58,78] Vaccination with attenuated *M. bovis* Bacille Calmette-Guérin (BCG) strain probably does not reduce the risk of infection with MTBC, even if it does reduce the subsequent chance of developing disseminated active disease once infected.[61,78,79] Some studies suggest that previous TB infection (as manifested by tuberculin skin test positivity) may partially protect against reinfection, although the degree of protection has not been quantified.[80–82] Other studies have shown in high-TB-burden settings that having had TB previously increases individual risk of recurrent disease; it is unclear if this is still modified by some level of protection.[83]

NATURAL HISTORY AND PATHOPHYSIOLOGY OF TB INFECTION

It is estimated that about 25% of the world's population is infected with latent TB.[84] However, only a small fraction of these individuals will develop active TB; most infections remain latent without apparent ill effect on the host. Risk factors associated with progression to active disease once infected are shown in Table 130-5.

From Exposure to Infection and the Innate Immune Response

The natural history of TB infection is outlined in Fig. 130-5. Following exposure to an infectious source case, many contacts do

TABLE 130-5 Common Risk Factors for Increased Likelihood of Progression from Latent Tuberculosis Infection to Active Tuberculosis Disease

Risk Factor	Relative Risk	References
Advanced, untreated HIV infection	9.5–9.9	Moss *Am J Resp Crit Care Med* 2000 Pablos-Méndez *AJPH* 1997
Close contact with infectious TB case	6.1	Ferebee *Bibl Tuberc* 1970
Radiographic evidence of old, healed TB that was not treated	5.2	Ferebee *Bibl Tuberc* 1970
Treatment with ≥15 mg prednisone daily	2.8	Jick *Arthritis Rheum* 2006
Chronic renal failure	2.4	Pablos-Méndez *AJPH* 1997
TNF-α Inhibitor	2.0	Askling *Arthritis Rheum* 2005
Poorly controlled diabetes	1.7	Pablos-Méndez *AJPH* 1997
Weight ≥10% below normal	1.6	Palmer *Am Rev Tuberc* 1957
Smoking	1.5	Bates *Arch Intern Med* 2007

Data from Horsburgh CR Jr, Rubin EJ. Clinical practice. Latent tuberculosis infection in the United States. N Engl J Med. 2011;364(15):1441–1448.

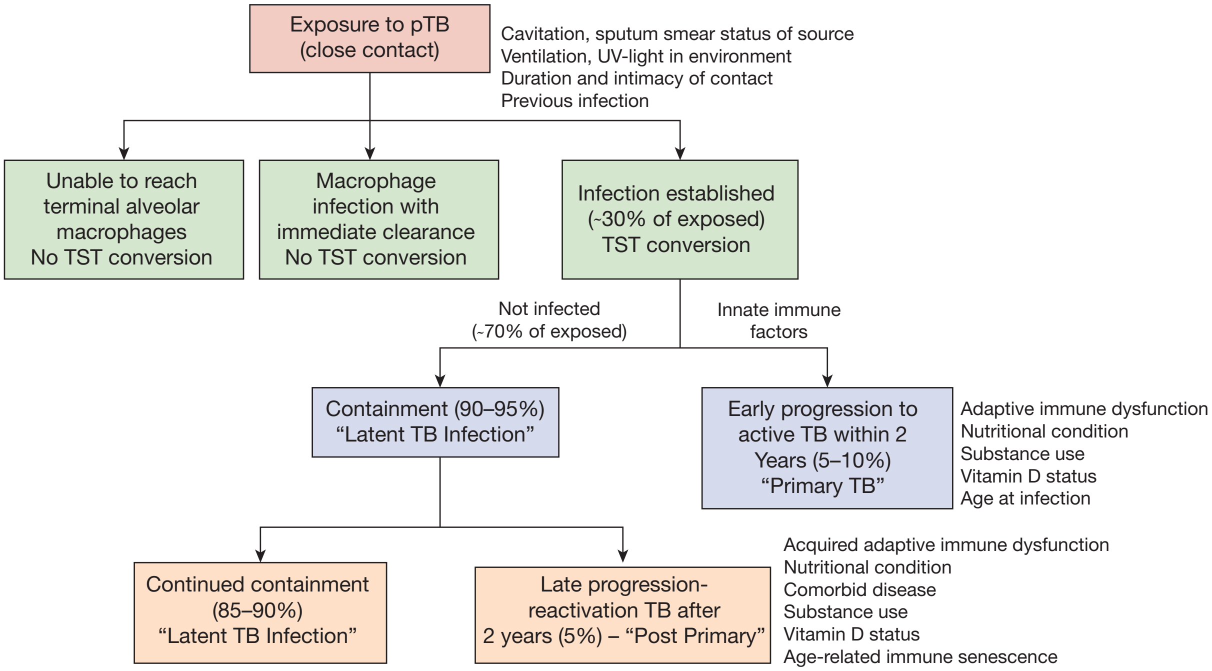
Exposure to pTB (close contact)
Cavitation, sputum smear status of source
Ventilation, UV-light in environment
Duration and intimacy of contact
Previous infection
Unable to reach terminal alveolar macrophages No TST conversion
Macrophage infection with immediate clearance No TST conversion
Infection established (~30% of exposed) TST conversion
Not infected (~70% of exposed)
Innate immune factors
Containment (90–95%) "Latent TB Infection"
Early progression to active TB within 2 Years (5–10%) "Primary TB"
Adaptive immune dysfunction
Nutritional condition
Substance use
Vitamin D status
Age at infection
Continued containment (85–90%) "Latent TB Infection"
Late progression-reactivation TB after 2 years (5%) – "Post Primary"
Acquired adaptive immune dysfunction
Nutritional condition
Comorbid disease
Substance use
Vitamin D status
Age-related immune senescence

Figure 130-5 Natural history of TB infection. pTB, pulmonary tuberculosis; TST, tuberculin skin test. *(Data from Comstock GW. Epidemiology of tuberculosis. Am Rev Respir Dis. 1982;125(3 Pt 2):8–15.)*

not become infected, and will not convert their TST—either because infectious droplet nuclei did not reach their terminal alveoli or because any successful invaders were immediately cleared by intrinsic microbicidal activity of macrophages.[3]

However, in those who become infected, invading mycobacteria engulfed by alveolar macrophages manage to evade intracellular killing. Mycobacteria bypass innate immune mechanisms and replicate without limitation, spreading to regional lymph nodes, and silently disseminate hematogenously.[1,52,78] After a few weeks, dendritic cells are activated and produce cytokines, such as tumor necrosis factor α (TNF-α), which recruit blood-borne monocytes and lymphocytes to sites of infection, setting the stage for the adaptive cellular immune response.[78]

The Adaptive Immune Response and Containment of Mycobacterial Infection

The main effectors of the adaptive, cell-mediated immune (CMI) response to mycobacteria are the CD4-positive subset of T lymphocytes. Once stimulated, T lymphocytes release their own battery of cytokines (including interferon γ [IFN-γ]) that serve to reciprocally activate infected macrophages and trigger enhanced intracellular mycobacteria killing. This is the basis for both the tuberculin skin test and IFN-γ release assays, which become positive with the development of a host CMI response. Over the next few weeks, the CMI directs necrotizing granuloma formation, which usually contains bacillary replication.[78]

Primary Disease

About 5% of immune competent individuals do not control initial mycobacterial replication and instead progress to primary TB disease, usually within 18 months. The risk of progression to primary disease is even higher in those with compromised CMI or other risk factors. Primary disease may occur at the initial site of lung entry (typically the mid and lower lung zones where greater airflow directs droplet nuclei deposition), regional lymph nodes, or rarely at metastatic sites initially seeded during early occult hematogenous dissemination.[78]

Reactivation Disease from Latent Infection

For the individuals who successfully contain the initial infection and avoid primary disease, mycobacteria lie latent within healed, fibrotic, and/or calcific granulomata. At this stage, mycobacteria cannot be cultured from host sputum or tissue specimens and symptoms are not present.

Historically, TB has been perceived to exist in one of these two states: latent or active. However, recent research has demonstrated that TB infection often exists along a continuum between these two states, based on the degree of mycobacterial activity and immune response at a given moment. Some have suggested adding "incipient TB," or TB that is likely to progress to active disease but is not yet detectable by symptoms or conventional diagnostics, and "subclinical" TB, or TB that produces abnormalities detectable by diagnostics but has not yet produced symptoms.[85,86]

Caseation and Cavitation

Differences in quality of host adaptive immune response determine clinical presentation.[52,78] Some individuals develop a particularly robust, caseating granulomatous inflammatory response with resultant tissue destruction and lung cavitation—they discharge large amounts of bacilli into airways and are highly contagious. At the other end of the spectrum, a severely weak or immature granulomatous response allows hematogenous dissemination of bacilli, accompanied by widespread inflammatory foci of poorly formed granulomas. Each focus typically enlarges to about 3 mm in size, or about the size of millet seed. This severe form of TB (miliary TB) has a high case-fatality rate.

CLINICAL MANIFESTATIONS

TB has had a number of illuminating vernacular names through history. In ancient Greece, TB was called "phthisis" meaning to waste away. In Rome, "tabes" was used, indicating wasting and overall decay. "Consumption," a term applied to TB in 19th century England is particularly evocative, referring to the observation that TB sufferers appear to be gradually "consumed" by the disease, becoming lighter and less robust over months.[87]

TABLE 130-6 Proportion of Reported TB Cases in the United States, by Predominant Site of Disease, 2019

	Site or Type of Disease	Percentage (%)
Pulmonary		79.4
Extrapulmonary	Total	20.6
	Pleural	4.0
	Lymphatic	7.6
	Meningeal	0.9
	Peritoneal	1.3
	Bone and joint	1.8
	Genitourinary	0.9
	Other	5.3

Reproduced with permission from Centers for Disease Control and Prevention. Reported Tuberculosis in the United States, 2019.

■ Site of Disease and Clinical Presentation

TB is predominantly a respiratory disease, affecting the lungs in about 80% of cases[43,88] (Table 130-6). About 30% of TB cases involve an extrapulmonary site, occurring either with or without concomitant lung involvement; this percentage is higher (generally closer to 50%) in immunocompromised patients. TB can affect virtually any organ, although peripheral lymph nodes and pleural space are the most common extrapulmonary sites.[89]

Classically TB presents insidiously over weeks, with persistent local symptoms correlating to granulomatous inflammation (e.g., cough in the case of pulmonary TB, neck mass for cervical lymph node TB), as well as constitutional symptoms that correlate to the production of pyrogenic cytokines such as TNF-α (e.g., fevers, night sweats, anorexia, weight loss). Initially the cough may be dry, but after several months it becomes productive. Fever may be absent, especially in the elderly.[90] With advancing disease, hemoptysis, anorexia, and weight loss can occur.[91–93] As discussed above, some patients are asymptomatic even with clear TB disease activity demonstrable on culture or radiography—a prospect that frustrates active case finding efforts by TB control programs.[3,94] Recent work has focused on this "subclinical" phase when an individual may become infectious but remain without symptoms or symptom unaware.

■ Physical Examination

Even when relatively extensive disease is present, pulmonary TB most often produces no detectable abnormality on physical examination.[91,94] However, it is important to examine for signs of extrapulmonary disease such as lymphadenopathy, abdominal, or bone and joint involvement, particularly in HIV-infected individuals. Tachypnea and hypoxia are relatively rare, unless there is extensive lung destruction or miliary disease.

■ Chest Radiography in Pulmonary TB

Radiographic findings of TB are well described.[94–96] Sensitivity of chest x-ray for active pulmonary TB is 70% to 80%, although it is less in patients with HIV or other severe immune compromise. Chest radiography is only moderately specific and there is generally poor agreement between chest film readers.[97–99] Chest radiography alone cannot reliably distinguish between active and healed, latent TB.[97,98,100]

Typical Chest Radiograph Patterns

Four radiographic features suggest active TB: (1) nodular opacities located in the apical–posterior segments of the upper lobes or superior segment of the lower lobes, (2) associated volume loss and fibrosis, (3) lung cavitation, and (4) endobronchial spread. Endobronchial spread to dependent lung segments fills lung acinar units, resulting in 4- to 5-mm nodular opacities on plain film (acinar shadows) and a "tree-and-bud" pattern on computed tomography (CT)[95,98,101] (Figs. 130-6 and 130-7).

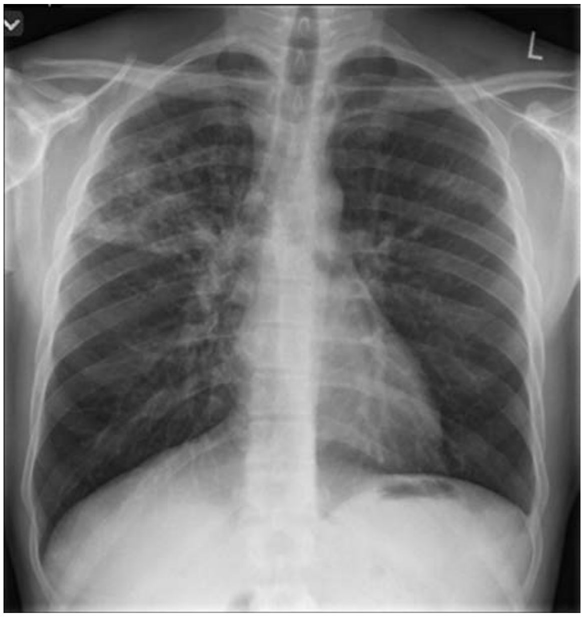

Figure 130-6 This 32-year-old male refugee recently arrived from Eritrea. He presented with persistent cough and fevers despite completing two courses of antimicrobial therapy directed against bacterial community-acquired pneumonia. Sputum sample was both smear positive and culture positive for MTBC.

Atypical Chest Radiograph Patterns

Atypical radiographic patterns are seen in children, the elderly, the immunocompromised, and those with primary disease.[96,100,102] Atypical features include lower lung zone infiltrates without cavitation, unilateral pleural effusion (Fig. 130-8), and ipsilateral hilar or

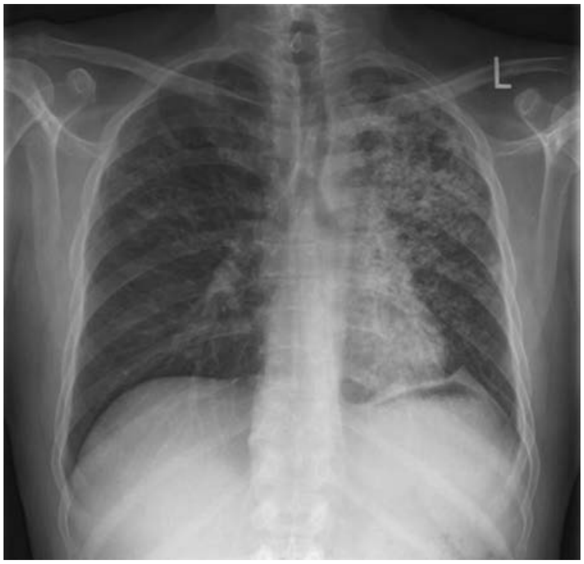

Figure 130-7 A 36-year-old man with history of homelessness. This radiograph demonstrates typical manifestations of reactivation TB: upper lobe nodular opacities, cavitation, acinar shadowing from endobronchial spread, and fibrosis.

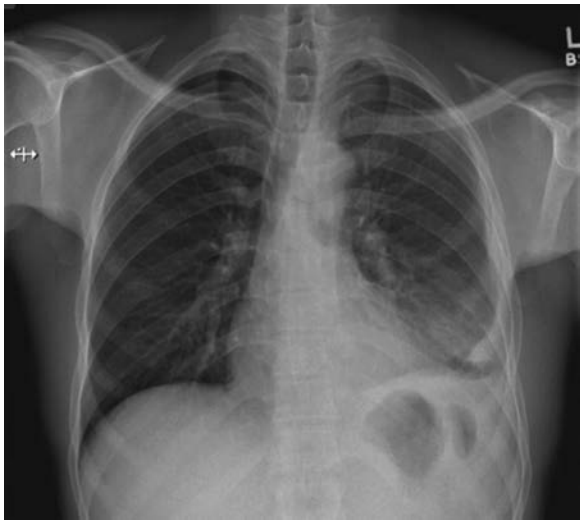

Figure 130-8 This 22-year-old man identified as a close household contact of a smear-positive case of pulmonary tuberculosis. Seven weeks later he developed fevers and cough. This radiograph demonstrates unilateral pleural effusion with compressive atelectasis. Diagnostic thoracocentesis revealed a transudate with cellular infiltrate, predominantly lymphocytic. Sputum was culture negative for mycobacteria, but pleural specimen eventually grew MTBC.

mediastinal adenopathy (Fig. 130-9). Intrathoracic TB lymphadenitis is often better appreciated on CT, with characteristic features including lymph node enlargement, rim enhancement, and low central attenuation.[95]

Miliary TB is rare; when present, it produces a distinctive, readily recognizable radiographic pattern: innumerable, interstitial nodules uniformly distributed throughout all lung fields, without reduction in lung volumes (Fig. 130-10).

DIAGNOSIS OF TB

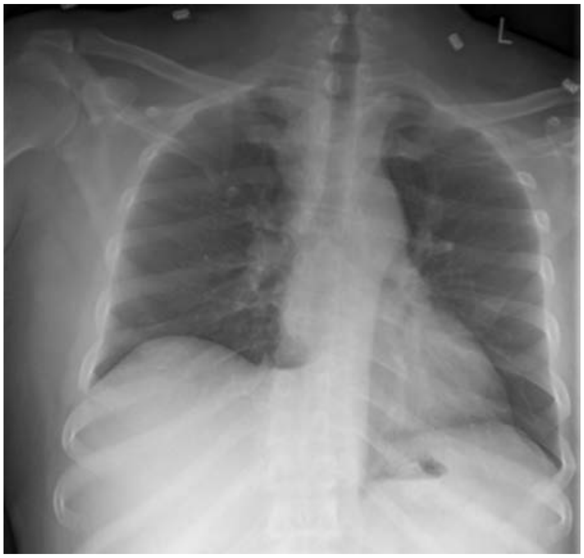

Figure 130-9 This 42-year-old HIV+ man with a CD4 count of 150 cells/mm^3 presented with cough. Significant mediastinal and right hilar adenopathy are present without apparent lung parenchymal disease. Sputum cultures were smear negative but culture positive for MTBC.

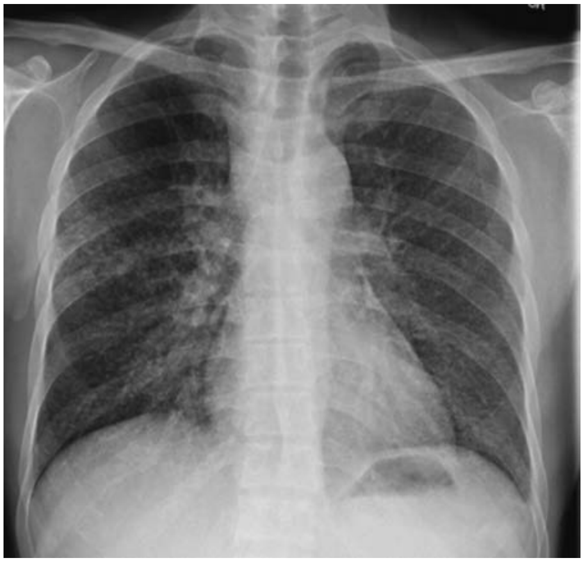

Figure 130-10 This 36-year-old HIV+ man presented with fevers. Chest radiograph identified right upper lobe infiltrate and a background miliary pattern consisting of innumerable noncalcified nodules measuring 2 to 3 mm, randomly distributed.

Most U.S. clinicians will practice for years without ever encountering a case of TB. For every 450 ambulatory visits for community-acquired pneumonia (CAP), and for every few dozen cases of lung cancer, there is on average one case of TB in the United States.[103,104] In low-incidence settings, many patients diagnosed with TB will have experienced multiple contacts with the healthcare system before the diagnosis of TB is considered.[105–107]

Thus, the diagnosis of TB requires a very high index of suspicion, considering epidemiologic risk factors and suggestive clinical–radiographic features (Fig. 130-11). Ultimately, the definitive diagnosis requires culture confirmation, although many (usually in the setting of significant risk factors) will be treated as presumed TB. In cases of high clinical suspicion due to radiologic findings, culture negative disease is the diagnosis if radiologic findings improve after treatment with tuberculosis medications.

■ Laboratory Investigations

A number of laboratory studies that constitute important elements in the diagnostic armamentarium for tuberculosis are discussed below.

Specimen Collection

Protocols to ensure proper specimen handling, storage, transport, and labeling are available.[94] Ideally, specimen collection should occur before initiation of therapy to increase yield.

For the diagnosis of pulmonary TB at least three sputum samples, each 5 to 10 mL, should be collected at least 1 hour apart. For those patients unable to expectorate spontaneously, sputum induction (with nebulized hypertonic saline) or bronchoalveolar lavage (BAL) is an alternate established method.[108] Induced sputum samples produce slightly higher yield than do BAL samples (87% vs. 73%), and sputum induction is much better tolerated, less invasive, and lower cost.[109,110] If bronchoscopy is performed to evaluate other diagnostic considerations, then an additional sputum sample collected immediately after bronchoscopy may have particularly high yield for mycobacterial identification.[108] Interestingly, recent work has suggested face-mask sampling as an additional noninvasive method for detecting exhaled *M. tuberculosis*.[111]

For diagnostic confirmation of extrapulmonary TB, tissue or fluid samples should be submitted for TB smear and cultures. Gastric aspirates performed upon awakening can be helpful for the diagnosis of pulmonary TB in certain situations.[110] Specimens should be

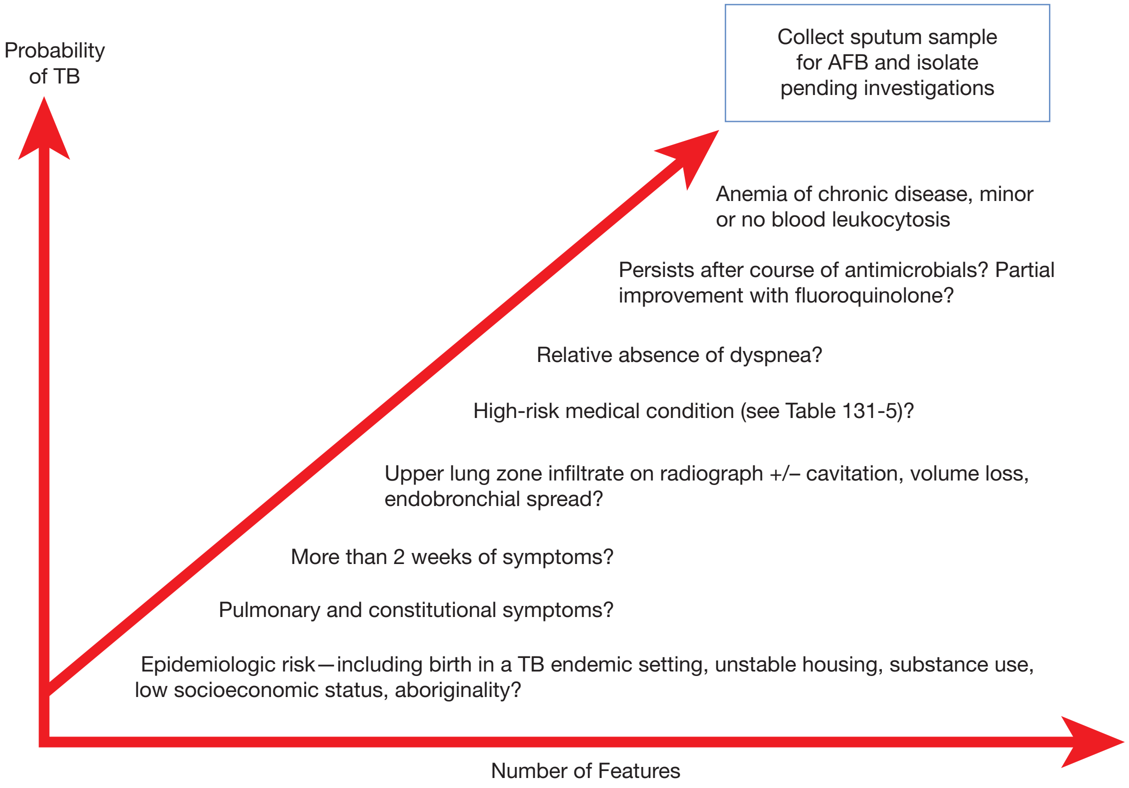
Probability of TB
Collect sputum sample for AFB and isolate pending investigations
Anemia of chronic disease, minor or no blood leukocytosis
Persists after course of antimicrobials? Partial improvement with fluoroquinolone?
Relative absence of dyspnea?
High-risk medical condition (see Table 131-5)?
Upper lung zone infiltrate on radiograph +/– cavitation, volume loss, endobronchial spread?
More than 2 weeks of symptoms?
Pulmonary and constitutional symptoms?
Epidemiologic risk—including birth in a TB endemic setting, unstable housing, substance use, low socioeconomic status, aboriginality?
Number of Features

Figure 130-11 Clinical factors increasing index of suspicion for tuberculosis. Increasing probability of TB warrants further investigation, especially collection of respiratory samples for mycobacterial stain and culture. For hospitalized patients, or those in congregate living settings, increasing suspicion warrants prompt isolation pending results of investigations. *(Reproduced with permission of Richard Long, unpublished observations.)*

submitted as fresh (or in sterile normal saline) without addition of preservative (e.g., formalin), because this will prevent subsequent identification, culture, and drug susceptibility testing in the microbiology laboratory. It is important to notify both the laboratory and clinician before collecting a specimen if extrapulmonary TB is suspected, as the laboratory must take appropriate biosafety precautions during specimen handling to prevent laboratory transmission of TB.

Direct Microscopy for AFB

Sputum-smear microscopy is more than 100 years old but remains the most widely used investigation for active TB in many high-burden countries today.[47,112] Two methods are commonly used for acid-fast staining of mycobacteria: carbolfuchsin (e.g., Ziehl–Neelsen [ZN]) and fluorochrome-based procedures (e.g., auramine–rhodamine dye). Fluorescent methods slightly improve sensitivity over ZN and allow the use of lower microscopic magnification during inspection of the slide, significantly shortening the time required to examine an entire specimen.[113]

Sputum microscopy is widely available and low cost. It is performed directly on clinical specimens with rapid turnaround time, which facilitates prompt recognition, isolation, and treatment of infectious TB cases. Microscopy also provides prognostic information: smear-positive TB cases are more infectious and have much higher case-fatality rates if untreated than do sputum smear–negative cases, reflecting high bacterial burden and more advanced disease.[68,114,115]

However, sputum-smear microscopy has limitations. Sensitivity for pulmonary TB is only about 60% to 70%, and even lower in extrapulmonary specimens and in those with HIV coinfection. NTM also stain acid-fast, which lowers the specificity of smear microscopy.[116–118] In low TB prevalence settings, NTM are recovered from up to 9.1% of AFB smear-positive sputum samples.[119]

Mycobacterial Culture

Mycobacterial culture remains the gold standard for the diagnosis of active TB. Culture methods can detect as few as 10 viable bacilli per millimeter of sample, compared with about 100 bacilli per millimeter for nucleic acid amplification (NAAT) and 5000 to 10,000 bacilli per millimeter with smear microscopy.[94] In addition, biochemical and phenotypic testing of isolated organisms provides nearly perfect specificity, distinguishing even between individual members of the MTBC. Of particular importance, isolation of the infecting organism permits drug susceptibility testing, which can be used to guide targeted therapy. Species identification can be performed using molecular subtyping (i.e., DNA/RNA fingerprinting), high-pressure liquid chromatography, biochemical testing, or mass spectrophotometry (i.e. MALDI-TOF systems).[120–122]

Culture of MTBC from clinical specimens takes, on average, between 2 to 4 weeks, but as long as 8 weeks in some specimens with low initial concentration of organism.[123] Culture requires a level III biosafety laboratory to prevent transmission to laboratory technicians, and availability of such facilities is poor in most high-burden, resource-limited settings.

Nucleic Acid Amplification

NAAT is a useful tool in the diagnosis of TB, offering higher sensitivity than microscopy and shorter turnaround times than culture.[100,124,125] Sensitivity of NAAT in AFB smear-positive respiratory samples is excellent, usually greater than 95%.[124] However, in paucibacillary specimen types, such as AFB smear-negative sputum and extrapulmonary samples, the sensitivity is reduced to 40% to 60%, with a negative predictive value inadequate to exclude a diagnosis of TB.[126–130] Specificity of NAAT methods is very high, ranging between 90% and 100% for all specimen types.

Performance of traditional NAAT requires sophisticated laboratory facilities. However, in the last decade, several automated in-cartridge assays have become available to facilitate wider use in settings without intensive laboratory facilities. The most widely adopted have been the Xpert assays by Cepheid, including initially Xpert/MTB RIF and more recently Xpert Ultra. These were developed to allow NAAT directly from unprocessed clinical specimens, without the need for a centralized reference laboratory, even in resource-limited settings.[131–133] The Xpert/MTB-RIF simultaneously detects mutations within the mycobacterial RNA-polymerase gene that correlate with rifampin resistance, thus identifying MDR cases several weeks before culture-based testing. The WHO endorsed the Xpert/MTB-RIF assay in 2011,[134] and it was approved by the FDA in 2013.[135] The Xpert MTB-RIF *Ultra* assay was then developed to improve the sensitivity of the standard Xpert/MTB-RIF assay, and it was endorsed by the WHO in 2017 to replace the standard Xpert/MTB-RIF assay.[55,136] There are some trade-offs, however, as the Xpert Ultra assay has lower specificity, given that trace MTB DNA could be residual from prior infection that is now inactive.[133]

In addition, the MTBDR*plus* by Hain Lifescience is a molecular line-probe assay designed to detect resistance to rifampin and isoniazid,[137,138] and the MTBDRs/assay can detect resistance to fluoroquinolones and injectable agents. Neither of these assays are approved by the FDA, but the WHO does recommend their use in certain situations and they have been deployed for clinical use in certain countries, such as South Africa.[139]

Urine Antigen Detection in HIV Patients

A point-of-care assay has been developed for urine detection of a mycobacterial cell wall antigen (glycolipid lipoarabinomannan, or urine LAM). This test has been validated specifically in patients with HIV.[140,141] The WHO recommends its use for HIV-infected individuals with concern for TB and CD4 <100, or for HIV-infected patients of any CD4 count if they are seriously ill.[142] The assay has not been FDA-approved for use in the United States.

Testing for Latent TB infection

There are two main tests for the identification of LTBI: (1) tuberculin skin test (TST) and (2) IFN-γ release assays (IGRAs). Both are indirect, in that they evaluate the presence of host cell–mediated immunity rather than detect actual mycobacterial organisms or antigens.[143] As such, neither can distinguish active disease from latent infection, and neither is predictive of future risk of active TB. Both tests have very poor sensitivity and predictive value for active TB, and neither can be used to exclude a diagnosis of active TB.[144,145] These tests are better used to assess candidates for LTBI treatment (discussed below). The choice of whether to use TST, IGRA, or both is dependent on the pretest probability of infection (based on risk factors), and the risk of progression to active TB (based on immune suppression and comorbidities). Other considerations include prior BCG vaccination (favors IGRA, which are not positive from BCG exposure), likelihood of patient returning to have the test read (favors IGRA over TST), and local test and laboratory capabilities (may favor TST).[146]

Other Laboratory Findings

Anemia is commonly observed in TB, usually due to chronic inflammation or malnutrition.[94] Syndrome of inappropriate ADH can complicate pulmonary or central nervous system TB.[147] Historically, disseminated TB was an important cause of adrenal insufficiency. Hypercalcemia is a relatively frequent complication of TB.[148] Activated macrophages within granulomas upregulate 1-α-hydroxylase, which can in turn activate vitamin D and lead to an increase in calcium absorption.[149–151] Hypercalcemia of TB can be symptomatic and occasionally leads to nephrocalcinosis, nephrolithiasis, or acute volume depletion. Vitamin D supplementation during TB therapy may increase the risk of hypercalcemia.[152]

MANAGEMENT OF ACTIVE TB

Prior to the availability of chemotherapy, prevailing wisdom prescribed fresh air, nutrition, sunlight, and rest for treatment of TB. In 1947, clinical outcomes of smear-positive pulmonary TB patients treated at a sanatorium in the United Kingdom were recorded: within 4 years of entry, 55% died, 20% remained chronically affected, and 25% experienced remission.[153] With the discovery of medications for treatment of TB, mortality dropped by orders of magnitude, and within a decade TB sanatoria were shuttered.[6,154]

■ Principles of TB Therapy

The aims of TB therapy are to (1) interrupt transmission by rapidly rendering patients noninfectious, (2) relieve symptoms and prevent mortality, (3) prevent the emergence of drug resistance, and (4) prevent future relapse by providing a definitive cure.

To achieve these aims, treatment regimens must include combination of potent bactericidal drugs that are provided for a minimum of 6 months based on current guidelines, although recent research suggests a possible 4-month regimen may be equally effective.[155] The choice of regimen should be guided by the results of drug susceptibility testing after they become available. TB regimens are divided into an initial intensive phase, designed to quickly reduce large bacillary burden, followed by a prolonged continuation phase that consolidates antimycobacterial killing while allowing intermittent dosing and lower pill burden. A high level of adherence is required to prevent relapse and emergence of resistance. Rifamycins (rifampin, rifampicin, rifabutin) have a critical role in preventing relapse and whenever possible should be provided throughout the treatment. Several randomized clinical trials have established standardized treatment regimens as outlined in Table 130-7. Reported success rates with these regimens approach 95% in the United States.[156]

■ First-line TB Drugs

Current first-line TB drugs include isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB) (Table 130-8).

INH, first introduced in 1952, remains a cornerstone of TB treatment. It has potent bactericidal activity and causes rapid decline of sputum bacillary load within days of administration, rapidly reducing infectiousness.[157] INH is generally well tolerated but can cause hepatotoxicity, requiring cessation of therapy in a small subset of patients. Risk factors for severe INH-related hepatotoxicity include older age and pre-existing liver diseases.[158] Peripheral neuropathy can develop in elderly, malnourished, or diabetic patients taking INH, but this risk is lowered with concomitant administration of pyridoxine (vitamin B6).

RIF revolutionized TB therapy following its introduction in 1968 and has since become a critical component of modern, short-course TB regimens.[157,159,160] RIF and other rifamycins appear to have unique relapse-preventing properties that allow the duration of chemotherapy to be shortened to 9 months or less. Until recently, without RIF, relapse rates are unacceptably high, and treatment duration must be significantly extended. New regimens do hold promise for a 6-month course with three novel agents, but those are still in trials and not yet widely available.[161]

RIF is very well tolerated in the vast majority of patients. Rarely, hypersensitivity reactions occur, including thrombocytopenia, flu-like syndrome, and neutropenia. RIF is a strong inducer of the cytochrome p450 oxidation system (CYP450) and interacts with a multitude of other medications.[162] RIF produces a benign orange-red discoloration of body fluids (urine, tears, sputum, feces, sweat) and can permanently stain contact lenses and dentures.

TABLE 130-7 Drug Regimens for Treatment of Active Tuberculosis in Adults, Caused by Susceptible Organism

	Intensive Phase (8 Weeks)	Continuation Phase	Comments
Regimen 1	INH + RIF + PZA + EMB[a] Given daily or 5×/week	18 weeks INH + RIF Given daily or 5×/week[b]	Preferred regimen for patients with newly diagnosed tuberculosis. Extend continuation phase to 7 months if risk of relapse present.[b]
Regimen 2	INH + RIF + PZA + EMB[a] Given daily or 5×/week	18 weeks INH + RIF 3×/week	Preferred alternative in situations in which more frequent DOT during continuation phase is difficult.
Regimen 3	INH + RIF + PZA + EMB[a] Given 3×/week	18 weeks INH + RIF Given 3×/week	Caution in patients with HIV and/or cavitary disease. Missed doses increase risk of treatment failure, relapse, drug resistance.[e]
Regimen 4	INH + RIF + PZA + EMB[a] Given daily × 2 weeks, followed by 2×/week for 6 weeks	18 weeks INH + RIF Given 2×/week	Not eligible for this regimen if HIV-infected, or if smear-positive and/or cavitary disease. If missed doses, equivalent of weekly therapy, which is inferior.

INH, isoniazid; RIF, rifampin; PZA, pyrazinamide; EMB, ethambutol; DOT, directly observed therapy.

[a] *EMB is given pending results of INH susceptibility testing—if isolate confirmed fully susceptible then EMB is discontinued.*

[b] *Risk factors for relapse include cavitation on chest radiograph, extensive pulmonary disease, culture positive after 2 months of therapy, poorly controlled HIV infection, diabetes, or other immunosuppressing condition.*

Note: Pyridoxine (vitamin B6), 25–50 mg/day, is given with INH to all patients at risk of neuropathy. For patients with peripheral neuropathy, experts recommend increasing pyridoxine dose to 100 mg/day.

Data from Nahid P, Dorman SE, Alipanah N, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. Clin Infect Dis. 2016;63(7):e147–e195.

Rifapentine (RPT) is also a rifamycin, but with a half-life 5 times longer than RIF, allowing the drug to be given once weekly. The prolonged half-life makes RPT an attractive agent for use in intermittent treatment regimens in order to facilitate adherence.[163] However, use of weekly dosed RPT is associated with relapse and acquired resistance in those with extensive disease, slow sputum culture conversion, or HIV coinfection.[163–165] RPT strongly induces CYP450 leading to multiple potential drug–drug interactions. Other rifamycins (e.g., rifabutin) produce lower levels of CYP450 induction. RPT is generally well tolerated, but hypersensitivity syndromes

TABLE 130-8 TB Drug Dosing and Important Adverse Reactions, Adults

Drug[a]	Daily Dose (Typical Dose)	Intermittent Dose (Typical Dose)	Selected Adverse Events
Isoniazid (INH)	5 mg/kg (300 mg)	15 mg/kg (900 mg)	Hepatotoxicity Peripheral neuropathy
Rifampin (RIF)	10 mg/kg (600 mg)[b]	10 mg/kg (600 mg)[b]	Thrombocytopenia Hepatotoxicity, often hyperbilirubinemia Drug–drug interactions[c]
Rifapentine (RPT)	—	10–20 mg/kg	Drug–drug interactions
Pyrazinamide[d] (PZA)	[e]40–55 kg: 1000 mg 56–75 kg: 1500 mg 76–90 kg: 2000 mg	Varies by weight and dosing interval	Hepatotoxicity Hyperuricemia Arthralgia
Ethambutol[d] (EMB)	[e]40–55 kg: 800 mg 56–75 kg: 1200 mg 76–90 kg: 1600 mg	Varies by weight and dosing interval	Optic neuritis
Moxifloxacin or levofloxacin[d]	400 mg 750–1000 mg	No data to support	GI upset QT prolongation Insomnia Tendinopathy

[a] *All drugs are provided orally; however, INH, RIF, and the fluoroquinolones are available as intravenous formulations.*

[b] *Higher doses of rifampin are well tolerated and associated with higher drug concentrations. However, effect on efficacy needs to be studied.*

[c] *Drug–drug interactions mediated mostly through cytochrome p450–3a4 enzyme induction.*

[d] *May require renal adjustment.*

[e] *Based on estimated lean body weight. Optimal dosing for obese patients is not established.*

Data from Nahid P, Dorman SE, Alipanah N, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. Clin Infect Dis. 2016;63(7):e147–e195.

including fever, myalgia, and cytopenias occurred in about 3% of patients in a clinical trial of LTBI treatment.[166]

PZA is bactericidal and when added to treatment regimens containing RIF permits shortening duration to 6 months.[167] Arthralgias are the most frequently reported adverse event and can be alleviated by the administration of nonsteroidal anti-inflammatories. PZA can also cause severe hepatotoxicity, especially in the elderly and those with pre-existing liver disease.

EMB is the weakest first-line agent, contributing little to early bactericidal activity or to relapse prevention. However, it is effective in preventing the emergence of resistance to isoniazid. It is generally well tolerated. Optic neuritis, the main adverse drug event, occurs infrequently with the currently recommended dosages, but is seen at higher rates with renal impairment. Clinicians should monitor for development of red–green color blindness; some use the Ishihara templates for testing in clinic and/or refer to ophthalmology for periodic monitoring while on treatment. EMB is added to the initial phase of treatment regimens pending results of susceptibility testing; if there is no drug resistance to one of the first-line agents, EMB is then discontinued.[156]

Later-generation fluoroquinolones (FQs), such as moxifloxacin and levofloxacin, are well-tolerated oral drugs with potent bactericidal activity against MTBC.[168–172] Based on accumulating clinical evidence, FQs may enter first-line treatment regimens and may allow for shorter-course regimens.[155] FQs are currently reserved for cases of resistance or intolerance to other first-line drugs.[173]

Pulmonary TB can initially be misdiagnosed as CAP and treated with FQs alone.[174] FQ monotherapy can temporarily alleviate TB symptoms and can reduce the yield of TB sputum cultures, thus significantly contributing to diagnostic delay.[175] Inadvertent monotherapy of TB initially mistaken for CAP also risks the development of FQ resistance, potentially compromising future TB treatment options.[174] FQs should be used cautiously for suspected CAP in patients at significant epidemiologic risk for TB.

■ Adjunctive Corticosteroid Use

Treatment of TB is occasionally complicated by paradoxical treatment responses whereby clinical deterioration develops a few weeks into an otherwise effective treatment.[176,177] The response is characterized by a robust inflammatory reaction, typically at the site of initial disease, without apparent microbiologic failure or bacillary replication. The paradoxical response is most commonly observed in extrapulmonary disease such as scrofula, TB in neck lymph nodes.[178] Paradoxical responses are typically self-limited, even when TB treatment is continued. Symptomatic benefit is sometimes observed following a brief course of corticosteroid treatment.[177] Important differential diagnostic considerations of paradoxical responses that should be excluded prior to treatment with corticosteroids include treatment nonadherence, inadequate dosing, drug malabsorption, or drug-resistant TB.

For disease of the CNS and pericardium, the consequences of a paradoxical response are potentially life threatening, including increased intracranial pressure and constrictive pericarditis, respectively. Meta-analyses have suggested an appreciable benefit to simultaneous initiation of corticosteroids along with TB treatment for these forms of TB.[179–182] The regimens tested in the clinical trials varied but 40 to 80 mg of prednisone per day for 6 to 12 weeks is a common prescription.

■ Direct Observation of Therapy

Direct observation of therapy (DOT) supports adherence, thus improving treatment outcomes.[183] Because physicians are poor at predicting which patients will adhere to therapy, DOT is recommended for all patients.[184]

■ Intermittent Dosing

Direct supervision of therapy by healthcare workers is facilitated by intermittent treatment regimens (e.g., 5 days per week, or Monday–Wednesday–Friday, or even twice weekly). Intermittent dosing schedules take advantage of the slow growth of MTBC and the post-antibiotic effect of TB drugs.[185,186] However, acquired drug resistance has been documented with intermittent dosing schedules, especially in patients with extensive disease or poorly controlled HIV coinfection, and many are moving away from this approach.

■ Treatment Monitoring

Bacteriologic monitoring (e.g., monthly sputum cultures until negative) is the preferred method of follow-up for pulmonary TB cases. A persistently positive sputum culture 2 months after starting effective treatment is a marker for relapse, and treatment extension is suggested. Culture positivity at 3 months is highly suggestive of treatment failure, and patients must be carefully evaluated to identify potential causes (e.g., nonadherence, malabsorption, acquired resistance, poor drug quality, drug–drug interactions). Patients should have repeat drug susceptibility testing and drug levels checked, especially for isoniazid and rifampin. Treatment failure is defined as persistently positive cultures 4 months into treatment.[156]

■ Adverse Effects

Severe side effects necessitating drug discontinuation are rare with standard TB treatment regimens. A commonly encountered adverse event is drug-related hepatotoxicity.[158,187] Transient, mild elevation in liver enzymes early in the course of therapy occurs in about 20% of patients and is usually inconsequential, usually resolving without intervention and without treatment interruption. However, for patients with symptomatic and/or marked elevation of transaminases (above 3–5× the upper limit of normal), treatment should be immediately discontinued and drugs cautiously reintroduced one at a time under close monitoring once the liver enzymes and function have returned to normal.

■ Drug-resistant TB

Among cases in the United States in 2019, resistance to isoniazid occurred in 9.5% of cases.[43] Monoresistance to INH does not appear to compromise TB treatment outcomes substantially as long as RIF, EMB, and PZA can be continued throughout.[156,188–190] It is also recommended to add a later-generation fluoroquinolone for optimal treatment success.[191]

Multidrug resistance was demonstrated in 1.5% of all TB cases in the United States in 2019.[43] Among patients with a history of previous TB treatment, MDR-TB prevalence was 5.4%. The majority (~86%) of MDR-TB cases in the United States occur in non-U.S.-born individuals.

Compared with treatment of drug-susceptible TB, treatment of MDR-TB is challenging, requiring more medications, worse side effects, and longer durations of treatment. Current U.S. and European guidelines recommend using at least five active drugs in the intensive phase, and four drugs in the continuation phase. The recommended treatment duration is 15 to 21 months after culture conversion. Drug classes used in the treatment of drug-resistant tuberculosis include fluoroquinolones, bedaquiline, linezolid, cycloserine, clofazimine, and injectable aminoglycosides now as a last resort.[191] Trials of shorter-course regimens of 9 to 12 months have had positive results,[29,192–195] including an all-oral bedaquiline-containing regimen that is now recommended by the WHO for certain patients.[32] These shorter-course regimens are not yet recommended by U.S. guidelines. Second-line TB agents and important side effects are listed in Tables 130-9 and 130-10.

TABLE 130-9 U.S./European Guidelines for Second-line TB Drugs

Group	Drugs
Strongly recommend use	Bedaquiline, fluoroquinolone (moxifloxacin or levofloxacin)
Conditionally recommend use	Linezolid, clofazimine, cycloserine, injectable amikacin, injectable streptomycin, ethambutol, pyrazinamide, injectable carbapenems w/clavulanic acid, delamanid
Conditionally recommend *against* use	Ethionamide prothionamide, injectable kanamycin, p-aminosalicylic acid, injectable capreomycin
Strongly recommend *against* use	Macrolides (azithromycin, clarithromycin), amoxicillin/clavulanate

Choice of medications further guided by prior treatment history and drug susceptibility testing.

U.S./European guideline recommends using at least five drugs in intensive phase (5–7 months after culture conversion) and four drugs in the continuation phase (15–21 months, longer if pre-XDR-TB or XDR-TB). Do not yet recommend for or against short-course 9- to 12-month regimen endorsed by World Health Organization.

Data from Nahid P, Mase SR, Migliori GB, et al. Treatment of Drug-Resistant Tuberculosis. An Official ATS/CDC/ERS/IDSA Clinical Practice Guideline. Am J Respir Crit Care Med. 2019;200(10):e93–e142.

TABLE 130-10 Second-line TB Drugs and Selected Toxicities

Agent	Important Adverse Effects
Amikacin (and other aminoglycosides)	Hearing loss, renal failure
Bedaquiline	QT prolongation, hepatotoxicity
Clofazimine	Skin hyperpigmentation, moderate QT prolongation
Cycloserine	Psychosis, depression, anxiety, seizures
Delamanid	Mild QT prolongation
Ethambutol	Optic neuropathy
Ethionamide/ prothionamide	Nausea, vomiting, hypothyroidism
Imipenem/clavulanic acid	Seizures, rash
Levofloxacin	QT prolongation, tendinitis, Achilles tendon rupture
Linezolid	Bone marrow suppression, peripheral neuropathy, optic neuritis
Meropenem/ clavulanic acid	Rash
Moxifloxacin	QT prolongation, tendinitis, Achilles tendon rupture
P-aminosalicylic acid	Nausea, vomiting, diarrhea, hypothyroidism
Pyrazinamide	Hepatotoxicity[a]

[a] *Risk factors for pyrazinamide hepatotoxicity include advanced age and underlying liver disease.*

Data from Dousa KM, Kurz SG, Bark CM, et al. Drug-Resistant Tuberculosis: A Glance at Progress and Global Challenges. Infect Dis Clin North Am. 2020;34(4):863–886.

■ Treatment Issues in Special Populations

Treatment considerations in two special patient populations—those coinfected with HIV and solid organ transplant recipients—are discussed below.

HIV Coinfection

Standard regimens used for the treatment of TB in HIV-uninfected individuals have similar efficacy in HIV-infected individuals, provided these patients are also effectively treated with antiretroviral therapy (ART).[196] However, the addition of ART to TB treatment can result in overlapping drug toxicity and intolerances including peripheral neuropathy, hepatotoxicity, and GI upset. Potent bidirectional drug–drug interactions between rifampin and several classes of antiretroviral drugs can amplify toxicity and undermine HIV virologic control. A number of studies have also found reduced serum concentrations of TB drugs in patients coinfected with HIV, thought to be due to decreased gastrointestinal absorption.[197] In turn, low serum drug concentrations may increase the risk of treatment relapse or acquired rifamycin resistance. Intermittent RPT in the continuation phase is associated with higher relapse rates and acquired rifamycin resistance in HIV-infected individuals and should be avoided.[163,165,198]

Successful HIV treatment with ART can lead to immune reconstitution and, in patients with concurrent active TB, restores the host inflammatory response to TB infection. This can clinically present as transient worsening of TB disease a few weeks following initiation of ART (a phenomenon known as immune reconstitution inflammatory syndrome or TB-IRIS). TB-IRIS can occur following ART initiation in patients already on treatment for TB (paradoxical type) or in patients with previously undiagnosed TB (unmasking type). TB-IRIS produces significant morbidity, occasionally requiring glucocorticoid therapy for symptom control.[199] However, in patients diagnosed simultaneously with HIV and TB, treatment outcomes, relapse rates, and overall mortality are greatly improved when ART is added early, within a few weeks of initiating TB treatment, even if this strategy noticeably increases risk of TB-IRIS.[156,200,201] An exception to this is for CNS TB, for which it is recommended that ART initiation be delayed by 8 weeks.[156,202] A short course of oral prednisone at the time of ART initiation in patients with HIV/TB coinfection and advanced HIV disease decreases the risk for TB-associated IRIS without increasing risk of death or complications.[203]

Solid-organ Transplantation

The majority of TB cases in solid-organ transplant recipients arise from reactivation of latent infection acquired prior to transplantation.[204] Donor-derived TB transmitted with organ transplantation is very rare. Overlapping drug toxicity and significant drug–drug interactions complicate treatment of TB in transplant recipients.[205] RIF significantly lowers serum drug concentrations of immunosuppressant medications, which can precipitate organ rejection. Rifabutin, a rifamycin with less CYP450 activity than either RIF or RPT, has good activity against MTBC and can be used instead of RIF in standard TB regimens.[206–208] Liver transplant recipients are particularly prone to hepatotoxicity from isoniazid, rifampin, and pyrazinamide, and close monitoring of liver function tests is indicated.[208]

TARGETED TESTING AND TREATMENT OF LATENT TB INFECTION

The use of anti-TB drugs in latently infected patients to prevent subsequent progression to active disease was first reported in the early 1950s.[209] Dozens of controlled clinical trials subsequently confirmed that INH reduced the risk of TB in those with positive TST by 60% to 90%, depending on the level of adherence.[210–212] An estimated 4% of the U.S. population is latently infected,[213] but currently available tests do not reliably predict which infected individuals will eventually develop active disease.[214] Furthermore, up to 5% of those treated for latent infection will experience an adverse event; rarely this can be severe hepatotoxicity and fulminant hepatic failure.[158,215,216] Thus, the decision to treat LTBI must be individualized, balancing the risk of developing active TB against the potential for adverse events.

Diagnosis of LTBI

The diagnosis of latent TB infection hinges on a positive TST and/or IGRA (discussed above). Once infected with MTBC, it is believed that the potential for reactivation persists for the lifespan of the host.

Tuberculin Skin Test

The TST is more than 100 years old.[217] The most commonly used method for administering the TST is the Mantoux technique: Here, five tuberculin units of purified protein derivative (PPD) from *M. tuberculosis* are injected intradermally on the inner surface of the left forearm. In those individuals with cell-mediated immunity to PPD, a delayed-type hypersensitivity (DTH) response will occur, manifest as a circular indurated skin reaction arising at the site of injection 48 to 72 h later.

Several factors can undermine the predictive value of the TST for latent TB infection.[143] Potential causes of false-negative reactions include immune compromise, malnutrition, chronic renal failure, improper administration, and expiration of tuberculin.[216,217] TB disease itself reduces test sensitivity, with up to 25% of TB cases TST negative. The TST is also prone to false-positive reactions. PPD is a relatively crude extract of mycobacterial antigens, many of which are conserved between mycobacterial species. Sensitization to PPD can develop after routine exposure to environmental NTM or following previous vaccination with BCG.[143]

Although technically simple, significant training and expertise is required for reliable test performance and interpretation. Roughly speaking, the larger the reaction size, the more likely is latent TB infection. The predictive value of the test varies by prevalence of LTBI and immunocompetence, and different reaction size criteria are used to define positivity in different populations[146,216] (Table 130-11).

Interferon-γ Release Assays

IGRAs are in vitro blood tests of CMI response; they measure T-cell release of IFN-γ following stimulation by synthetic peptide antigens specific to *M. tuberculosis*.

Replacing the mixture of antigens contained in PPD with specific synthetic peptides greatly improves the specificity of IGRAs compared to TST, especially in populations previously vaccinated with BCG.[218,219] The sensitivity of the IGRA is comparable to the TST, even in immunocompromised hosts, although the absence of a gold standard makes precise estimation difficult.[220–222]

IGRA appear less reproducible on repeated testing than is TST, especially when values of IFN-γ release are near the quantitative threshold for reporting positive (i.e., borderline positive).[212] This can result in spontaneous conversions and reversion on serial testing of the same individual, with uncertain clinical implications.[223]

There are two currently approved IGRA tests available in the United States: the QuantiFERON-TB Gold and QuantiFERON-TB Gold Plus assays (Qiagen, Gaithersburg, Maryland) and the T-SPOT.TB assay (Oxford Immunotec, United Kingdom).

Which Test to Use in LTBI

Either the TST or the IGRA are acceptable for the diagnosis of LTBI.[145,146] The improved specificity of IGRAs and the need for a single patient visit make this test attractive. IGRAs are associated with high testing costs and require laboratory infrastructure and significant technical expertise. The improved specificity of the IGRA might reduce the number of candidates for LTBI treatment,

TABLE 130-11 Considerations for Testing for Latent Tuberculosis Infection, Adults

Group	Testing Strategy	Considerations
Likely[a] to be infected **High**[b] risk of progression (TST ≥5 mM)	**Acceptable**: IGRA or TST Consider dual testing where a positive result from either would be considered **positive**	Prevalence of BCG vaccination Expertise of staff and/or laboratory Test availability Patient perceptions Staff perceptions Programmatic concerns
Likely to be infected **Low to intermediate**[c] risk of progression (TST ≥10 mM)	**Preferred**: IGRA where available **Acceptable**: IGRA or TST	
Unlikely to be infected (TST >15 mM)	**Testing for LTBI is not recommended** **If necessary:** **Preferred:** IGRA where available **Acceptable:** IGRA or TST **For serial testing:** **Acceptable**: IGRA or TST Consider repeat or dual testing where a negative result from either would be considered positive.	

LTBI, latent tuberculosis infection; TST, tuberculin skin test; IGRA, interferon-gamma release assay; BCG, bacille Calmette-Guérin.

[a] *Groups with increased likelihood of infection: household contact or exposure of active case, mycobacteriology laboratory personnel, immigrants from high-burden countries (>20/100,000), residents and employees of high-risk congregate settings.*

[b] *Factors conferring high risk of progression: age <5 years old, HIV infection, immunosuppressive therapy, abnormal chest x-ray consistent with prior TB, silicosis.*

[c] *Factors conferring intermediate risk of progression: diabetes, chronic renal failure, intravenous drug use.*

Data from Lewinsohn DM, Leonard MK, LoBue PA, et al. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children. Clin Infect Dis. 2017;64(2):e1–e33.

but whether this translates to cost-effectiveness is controversial.[224] The choice of whether to use TST, IGRA, or both is dependent on the pretest probability of infection (based on risk factors), and the risk of progression to active TB (based on immune suppression and comorbidities).[146]

■ Decision to Treat LTBI

The first step in deciding whether to treat for LTBI is to assess the likelihood that a positive TST or IGRA represents true TB infection. Both tests perform poorly in low-prevalence populations, and a true positive result is much more likely in those exposed to active TB or from high-risk epidemiologic groups such as foreign-born, travelers to TB endemic countries, homeless, and incarcerated populations.

The second step is to estimate likelihood of progression to active TB if actually infected[221] (Table 130–2). The third step is to evaluate potential risks for adverse reactions to treatment. The main adverse effect of LTBI treatment is INH-related hepatotoxicity. The strongest predictor of hepatotoxicity is age. Those younger than 20 years old have less than a 0.1% chance of hepatotoxicity during LTBI treatment, whereas those over 65 years are exposed to a risk around 2% to 5%. An internet-based calculator is available to assist in balancing these probabilities and informing treatment decisions.[225] However, this calculator does not take into account reinfection, and the toxicity is calibrated for INH rather than the newer rifamycin-based regimens.

Treatment of LTBI has been demonstrated to be effective only in those with a positive TST or IGRA. Several clinical trials have failed to demonstrate a benefit of treatment in immunocompromised individuals at risk but with a negative TST or IGRA.[226,227]

Before the treatment of LTBI is started, active disease must be excluded carefully by means of history, physical examination, chest radiography, and sputum culture, in order to avoid inadvertent monotherapy of active TB that could lead to resistance.

■ Treatment for LTBI

Historically, the most widely used treatment of LTBI is self-administered INH taken daily for 9 months.[212,228] However, increasing evidence has led to a shift in guidelines to now recommend rifamycin-based regimens over INH monotherapy. The three preferred rifamycin-based regimens include 3 months of weekly isoniazid plus rifapentine, 3 months of daily isoniazid plus rifampin, or 4 months or daily rifampin monotherapy.[229] Preferred and alternative regimens are shown in Table 130-12. Contacts of INH-monoresistant cases can be offered 4 months of RIF daily. Contacts of MDR-TB can be offered therapy with 6 to 12 months of a daily later-generation FQ, with or without an additional drug. This recommendation is based on observational studies, although randomized trials are underway.[191]

Patients receiving LTBI treatment should be monitored at least monthly for clinical symptoms of hepatitis. They should also be educated about the symptoms of hepatitis and instructed to stop the medication immediately and seek prompt evaluation to reduce risk for progression to severe disease.

TABLE 130-12 Preferred and Alternative Regimens for Treatment of Latent Tuberculosis Infection, Adults

Priority Rank	Duration	Frequency	Drugs
Preferred	3 months	Weekly[b]	Isoniazid[a]: 15 mg/kg (max 900 mg) + Rifapentine: if $\geq$ 50 kg[c], 900 mg
Preferred	4 months	Daily	Rifampin: 10 mg/kg
Preferred	3 months	Daily	Isoniazid[a]: 5 mg/kg (max 300 mg) + Rifampin: 10 mg/kg (max 600 mg)
Alternative	6 months	Daily	Isoniazid[a]: 5 mg/kg (max 900 mg)
Alternative	9 months	Daily	Isoniazid[a]: 5 mg/kg (max 900 mg)

[a] *Pyridoxine supplementation (25–50 mg daily) often provided to prevent INH-associated peripheral neuropathy, especially if risk factors including alcohol use disorder, diabetes, malnutrition, uremia, and HIV infection.*

[b] *Intermittent regimens should be provided under direct observation.*

[c] *Rifapentine dosing for lower weight: 10–14.0 kg (300 mg), 14.1–25.0 kg (450 mg); 25.1–32.0 kg (600 mg); 32.1–49.9 kg (750 mg).*

Data from Sterling TR, Njie G, Zenner D, et al. Guidelines for the Treatment of Latent Tuberculosis Infection: Recommendations from the National Tuberculosis Controllers Association and CDC, 2020. MMWR Recomm Rep. 2020;69(1):1–11.

TB VACCINATION

French researchers Albert Calmette and Camille Guérin experimented with laboratory attenuation of *M. bovis* by repeated subcultivations in bile acids; this work eventually led to the creation of a TB live-attenuated vaccine BCG in 1928.[230,231] This vaccine is rarely used in the United States today, but worldwide it remains one of the most commonly delivered childhood vaccines with coverage rates approaching 100% in many resource-limited settings. Despite its wide use, there remains some controversy as to its actual efficacy, and some concern that ongoing subculture to produce the vaccine is resulting in loss of activity.[232] Disseminated infection with BCG has been documented in severely immunocompromised children, and universal vaccination is therefore no longer recommended in low-prevalence settings.[233] In the Unites States, BCG is perhaps more commonly encountered as a therapeutic agent for management of bladder transitional cell carcinoma. Disseminated BCG infection has been documented in this patient group, but human-to-human transmission is not reported.[234,235]

Ongoing research is directed toward a vaccine to replace BCG, ideally with improved efficacy against both infection and progression to TB.[236] However, after millennia of coevolution, the host–pathogen relationship is extremely complex and inadequate understanding of TB immunity and correlates of protection hamper progress in vaccine development.

CONCLUSION

TB has become an uncommon but serious infection in the United States, and a high index of suspicion is required. In endemic regions, clinicians tend to consider the diagnosis more frequently. Diagnostic delay occurs frequently despite availability of accurate diagnostic technologies. In settings of chronic medical illness, immunocompromise, and social deprivation, TB can flourish. Treatment is effective and can significantly reduce a high case-fatality rate. Current research is directed to shortening the duration of therapy to facilitate adherence and treatment completion rates. New drugs are being developed and promise to improve outcomes in MDR disease. Ongoing national surveillance and funding of TB control programs is required to maintain low TB incidence. However, given that an increasing proportion of TB relates to global migration, further reduction in TB incidence will ultimately require investment in TB control globally. Even in the wealthy countries of the West, TB is not conquered but continues to smolder, threatening reemergence where social injustice prevails and where the vigilance of TB control programs is relaxed.

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CHAPTER 131

Pulmonary Diseases Due to Nontuberculous Mycobacteria

John S. Albin
Rocio M. Hurtado

INTRODUCTION

This chapter focuses on the diagnosis and management of pulmonary infections caused by nontuberculous mycobacteria (NTM), a large group of species of the genus *Mycobacterium* that can cause disease in humans and that are distinct from other classic mycobacterial pathogens, such as *M. leprae*, *M. ulcerans*, and species of the *M. tuberculosis* complex. Despite the diversity of this group of pathogens, the clinical presentation and diagnostic approach to most pulmonary NTM infections is similar, and the vast majority of disease is caused by a handful of species, including those of the *M. avium* (MAC) and *M. abscessus* (MAb) complexes, as well as *M. kansasii* and *M. xenopi*. Management differs according to species, extent of disease, and susceptibility patterns. We describe here the epidemiology and pathogenesis of pulmonary NTM infections and a general diagnostic approach. We then proceed to the treatment regimens used for common NTMs and discuss the nuances associated with management in special populations.

EPIDEMIOLOGY

There are 192 known species of the genus *Mycobacterium*.[1] Of these, several are *M. tuberculosis* complex species that cause tuberculosis in humans, while *M. leprae* causes leprosy and *M. ulcerans* causes Buruli ulcer. Most of the remainder are known as nontuberculous mycobacteria (NTM), which are environmental organisms typically found in soil and water. Together, they constitute the greatest source of pulmonary mycobacterial infection in developed nations. Most human pulmonary NTM disease is caused by species of the *M. avium* and *M. abscessus* complexes, as well as *M. kansasii* and *M. xenopi*; others, such as *M. gordonae*, are generally considered contaminants.[2] The relative contributions of each species responsible for infection may vary geographically.[3–5] Overall, prevalence has increased by up to 8.2% per year in recent decades, representing up to 48 cases per 100,000 in the United States as of 2012.[2,6]

Among risk factors for pulmonary NTM disease that predispose to infection, a common theme is underlying structural lung abnormalities that impede physiologic airway clearance or ciliary function. Notable among these underlying diagnoses are bronchiectasis, chronic obstructive pulmonary disease, pneumoconiosis, and pulmonary alveolar proteinosis. Cystic fibrosis, including the presence of cystic fibrosis transmembrane conductance regulator (CFTR) changes not associated with clinical cystic fibrosis, and α1-antitrypsin deficiency are two genetic conditions that predispose to pulmonary NTM infection.[7,8] Additional associations that have been observed are listed in Table 131-1. Although immunodeficiency is a risk factor for both pulmonary and disseminated NTM infections,[9] the vast majority of pulmonary NTM infection occurs in the absence of known immunodeficiency.

PATHOGENESIS

Abnormal airway clearance allows persistence of pulmonary NTMs that would otherwise normally be cleared. Distinguishing colonization from infection can be challenging, as more than half of patients may undergo spontaneous sputum conversion from positive to negative.[10,11] Once infection is established, pulmonary NTMs can persist within biofilms and macrophages, which may shield NTMs from antibiotic therapy.[12–16] Absent clearance, the natural history of disease is generally one of slowly progressive lung destruction over a course of years, although this course may wax and wane. Treatment success is limited, but even those who achieve sputum conversion remain susceptible to reinfection due to persistence of the abnormalities that predisposed to initial infection.[4]

DIAGNOSIS

The diagnosis of pulmonary NTM infection is based on clinical and radiographic findings, along with appropriate microbiology, in the absence of an alternative diagnosis. Guidelines have been developed to help facilitate interpretation of what can sometimes be diagnostically challenging cases (Table 131-2). Symptoms often include cough (74%–82%), dyspnea (47%–55%), hemoptysis (10%–27%), fever (24%–38%), weight loss (5%–32%), and fatigue or malaise (53%–66%).[4,5,17] A variety of imaging findings may be seen on CT, and certain patterns, such as nodular bronchiectatic or fibrocavitary changes, which may wax and wane over time, may help guide treatment.[4,8,18] Examples of several commonly encountered radiographic findings are shown in Fig. 131-1.

The microbiologic diagnosis of pulmonary NTM infection can be made by several means, including, most commonly, growth of the same NTM species in two or more sputum samples (Table 131-2).[18] Criteria may also be fulfilled by NTM growth from a single bronchoalveolar lavage sample, or the observation of typical lung pathology on biopsy, such as granulomatous inflammation or the finding of

TABLE 131-1 Common Risk Factors and Associations with Pulmonary NTM Infection

Structural Lung Abnormalities	Genetic Predispositions	Other Associations
• Bronchiectasis due to any cause (e.g., sequela of infection such as tuberculosis) • Chronic obstructive pulmonary disease • Pulmonary alveolar proteinosis • Pneumoconiosis	• CFTR changes including cystic fibrosis • α1-antitrypsin deficiency • Rare genetic variants associated with family clusters	• Gastroesophageal reflux, esophageal dysmotility • Older age • Lower BMI • Female sex • Immunosuppression • Scoliosis, pectus excavatum • Mitral valve prolapse

TABLE 131-2 Criteria for the Diagnosis of Pulmonary NTM Disease[a]

Category	Conditions to Fulfill Criteria (Must Fulfill All Three Categories)
Clinical	• Pulmonary or systemic symptoms
Radiologic	• Nodular or cavitary opacities, bronchiectasis on chest imaging
Microbiologic	• ≥2 positive sputum cultures with the same NTM species *or* • ≥1 positive bronchoalveolar lavage culture growing NTMs *or* • Lung biopsy with characteristic pathology (granulomatous inflammation or acid fast bacilli) *and* • Biopsy culture growing NTMs *or* • ≥1 or more respiratory cultures growing NTMs

[a]Data from American Thoracic Society (ATS), European Respiratory Society (ERS), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), and Infectious Diseases Society of America (IDSA) guidelines for the treatment of pulmonary NTM infections.

acid-fast bacilli accompanied by NTM growth from the biopsy sample itself or from an accompanying respiratory sample. Rapidly growing mycobacteria, such as MAb, *M. chelonae*, and *M. fortuitum*, may grow in as little as 1 week, while slowly growing mycobacteria (most of the remaining species) may require several weeks or more. Most species will grow within 8 weeks—the typical duration for which cultures are held, although certain species, such as *M. xenopi*, may take longer. Others, such as *M. haemophilum*, have specific nutrient and temperature requirements. Identification may proceed via use of rapid nucleic acid probes for some species, such as *M. kansasii*, MAC, and the common low-virulence species *M. gordonae*. Definitive identification is typically based on gene sequencing or mass spectrometry, although the latter may fail to distinguish some subspecies. PCR on fresh tissue also may be used.

In vitro susceptibility to certain agents strongly predicts clinical outcomes. Current recommendations are to test for MAC and MAb susceptibility to macrolides and amikacin. In the case of MAb, molecular methods or a 14-day hold for culture may further be necessary to evaluate for an inducible *erm* gene conferring macrolide resistance. Guidelines also support testing of *M. kansasii* for susceptibility to rifampin.[18] Standard susceptibilities may be completed in many laboratories, albeit with some variability in reproducibility;[19] extended susceptibilities may require send out to reference laboratories.

TREATMENT

Among patients with positive cultures, 14% to 43% will fulfill guideline diagnostic criteria for pulmonary NTM infection.[4,5,17] Even among patients meeting criteria, the decision to treat is nuanced and based on a longitudinal assessment of expected risks and benefits of treatment, including comorbidities, life expectancy, drug interactions and adverse effects, and the functional impact of disease progression. More than half of patients with MAC may experience progressive disease over a course of 3 years, leading to treatment.[10]

Up to one-third of patients with MAC may receive suboptimal regimens associated with emergent macrolide resistance, such as macrolide monotherapy or dual therapy consisting of a macrolide and either a fluoroquinolone or a rifamycin.[20] Therapy is further complicated by the frequency of subtherapeutic drug levels, which may be mitigated by therapeutic drug level monitoring.[21] The overall proportion of patients who improve on therapy varies by the infecting species but, overall, is about two-thirds; adverse events occur in more than one-third. Cessation of therapy is required in approximately 14%, and microbiologic recurrence, including reinfection, occurs in 17% to 48%.[4,22,23] Composite 5-year survival has been reported at 73%.[24]

Side-effects from treatment are common, particularly gastrointestinal intolerance, occurring in more than 40%.[25] Despite limitations of therapy, patients with pulmonary NTM infections suffer from diminished quality of life and may benefit from treatment, which is intended to prevent decline in lung function.[26–29] Common treatment regimens are summarized in Table 131-3. Major toxicities associated with treatment are summarized in Table 131-4 and discussed below.

■ *Mycobacterium avium* Complex (MAC)

MAC refers to a group of 12 species that are the most commonly encountered pulmonary NTM pathogens in the United States.[18] The initial therapeutic regimen used in most cases consists of the trio of a macrolide (azithromycin is preferred over clarithromycin,

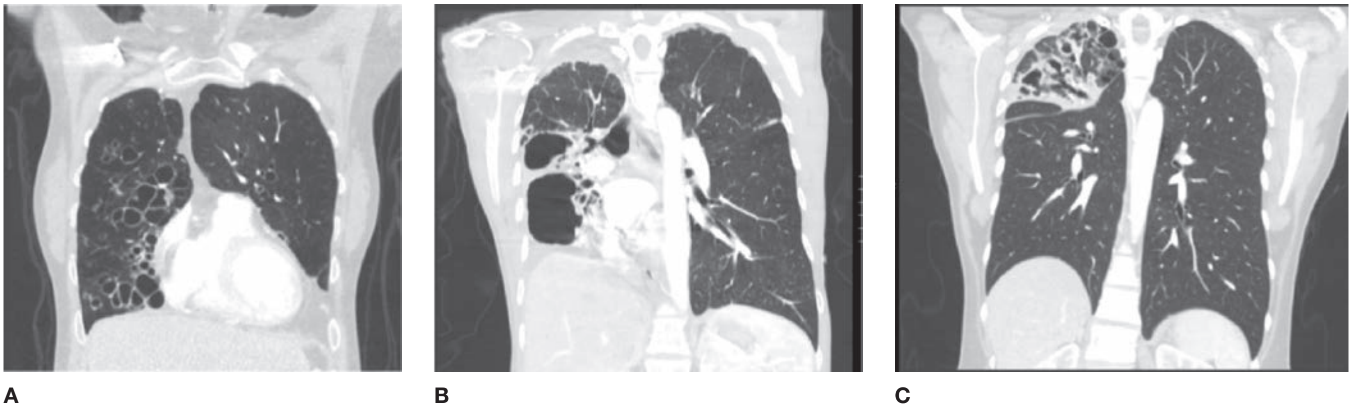

Figure 131-1 Radiographic findings in pulmonary NTM infections. Images demonstrate several radiographic patterns observed among patients with pulmonary NTM infections. **A.** Cystic bronchiectasis in a patient with cystic fibrosis and *M. kansasii* infection. **B.** Fibrocavitary disease in a patient with MAC, in this case complicated by bronchopleural fistula. **C.** Progressive right upper lobe bronchiectasis and cavitation with *M. tuberculosis* and *M. chelonae* coinfection in a patient who went on to have surgical resection.

TABLE 131-3 Preferred Treatment Regimens with Normal Renal Function[a]

NTM (Susceptibility Duration)	Disease Category	Dosing Regimen (Minimum of Three Drugs)
MAC Test: • Macrolides • Amikacin Duration: • 12 months after sputum conversion (minimum)	Nodular-bronchiectatic	Dosed thrice weekly • Ethambutol 25 mg/kg po • Rifampin 600 mg po[b] • Azithromycin 500 mg po[b]
	Cavitary, extensive, or macrolide-resistant	Dosed daily • Ethambutol 15 mg/kg po • Rifampin 450–600 mg (10 mg/kg) po[b] • Azithromycin 250–500 mg po[b] Dosed thrice weekly • Amikacin 15–25 mg/kg[b]
	Refractory	Dosed daily • Ethambutol 15 mg/kg po • Rifampin 450–600 mg (10 mg/kg) po[b] • Azithromycin 250–500 mg po[b] ***and*** • ALIS 590 mg inhaled *daily* ***or*** • Amikacin 15–25 mg/kg *thrice weekly*[b]
MAb Test: • Macrolides • Amikacin • A broader panel of potentially active agents Duration: • Variable; options include induction of several months followed by oral maintenance for 12 months after sputum conversion (minimum) versus intermittent induction	Macrolide-sensitive	Initial therapy (1–2 IV, 2 oral, ≥3 active drugs) *IV:* Amikacin 15–25 mg/kg IV thrice weekly Imipenem 500–1000 mg IV 2–3 times daily[d] Cefoxitin 2–4 g IV 3 times daily[d] Tigecycline 25–50 mg IV 1–2 times daily[e] *Oral:* Azithromycin 250–500 mg daily[b] Clofazimine 100–200 mg daily Linezolid 600 mg 1–2 times daily[e] Continuation phase (≥2 active drugs) Oral agents as above ALIS 590 mg daily inhaled
	Macrolide-resistant	Initial therapy (2–3 IV, 2–3 oral, ≥4 active drugs) *IV:* As in macrolide-sensitive strains *Oral:* As in macrolide-sensitive strains[f] Continuation phase (≥2 active drugs total) Oral agents as above[f] ALIS 590 mg daily inhaled
M. kansasii Test: • Rifampin Duration: • 12 months	All categories	Dosed daily[c] • Ethambutol 15 mg/kg po • Rifampin 450–600 mg (10 mg/kg) po[b] ***and*** • Azithromycin 250–500 mg po[b] ***or*** • Isoniazid 5 mg/kg (up to 300 mg) po[b]
M. xenopi Test: • No standard Duration: • 12 months after sputum conversion (minimum)	Nodular-bronchiectatic	Dosed daily • Ethambutol 15 mg/kg po • Rifampin 450–600 mg (10 mg/kg) po[b] ***and*** • Azithromycin 250–500 mg po[b] ***or*** • Moxifloxacin 400 mg po

TABLE 131-3 Preferred Treatment Regimens with Normal Renal Function[a] *(Continued)*

NTM (Susceptibility Duration)	Disease Category	Dosing Regimen (Minimum of Three Drugs)
	Cavitary or extensive	Dosed daily • Oral agents as in nodular-bronchiectatic ***and*** Dosed thrice weekly Amikacin 15–25 mg/kg IV[b]

[a] *Data from American Thoracic Society (ATS), European Respiratory Society (ERS), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), and Infectious Diseases Society of America (IDSA) guidelines for the treatment of pulmonary NTM infections. Dosing is adapted from guideline recommendations for normal renal function, although it is important to keep in mind that additional factors such as renal function and MICs (from susceptibility testing) may mandate different dosing or alterations in regimen. Consultation with pharmacy is recommended throughout, particularly for management of aminoglycosides. In re-treatment patients, patients with macrolide resistance, or patients failing therapy, expert consultation is recommended.*

[b] *Azithromycin, rifampin, or amikacin may be substituted by clarithromycin, rifabutin, or streptomycin, respectively. Please note, some M. xenopi strains may be resistant to rifampin.*

[c] *When a macrolide-based regimen is chosen, dosing may be thrice weekly as in MAC rather than daily.*

[d] *Only one of cefoxitin or imipenem should be used in any given regimen.*

[e] *Daily dosing (50 mg/day) is generally preferred for tolerability.*

[f] *Although a macrolide may be retained in macrolide-resistant infections for other indications such as immunomodulation, this should not be counted against the recommended number of active drugs.*

TABLE 131-4 Major Toxicities Associated with Drugs Commonly Used to Treat NTMs[a]

Drug	Toxicities	Management
ALIS	• Respiratory adverse events	• Symptomatic management of dysphonia, upper irritation; bronchodilators for cough, dyspnea; may be able to reintroduce without symptoms after a drug holiday
Aminoglycosides	• Ototoxicity	• Lower risk with thrice-weekly dosing; audiology every few weeks; cessation of drug if occurs
	• Nephrotoxicity	• Monitor drug levels; drug holiday and change in dosing in consultation with pharmacy
Bedaquiline	• QTc prolongation	• Monitor ECG; minimize QTc prolonging agents
β-lactams	• Cytopenias	• Lab monitoring, cessation if occurs
	• Seizures	• Monitor for symptoms
Clofazimine	• Skin changes	• Counseling for expectation of discoloration and xerosis
	• QTc prolongation	• Monitor ECG; minimize QTc prolonging agents
	• Intussusception	• Counseling to monitor for symptoms
Ethambutol	• Optic neuritis	• Ophthalmology evaluation every few months; cessation of therapy if occurs
Fluoroquinolones	• Tendon rupture	• Counseling to avoid strenuous activity; cessation of therapy if occurs
	• QTc prolongation	• Monitor ECG; minimize QTc prolonging agents
Isoniazid	• Hepatotoxicity	• Symptomatic and lab monitoring; cessation of therapy if occurs
	• Neuropathy	• Coadministration of vitamin B6
Macrolides	• Hearing loss	• Audiology at baseline; monitor symptoms; cessation of therapy if occurs, but may be able to tolerate clarithromycin
	• QTc prolongation	• Monitor ECG; minimize QTc prolonging agents
Oxazolidinones	• Cytopenias	• Lab monitoring; cessation of therapy if occurs; may be able to tolerate tedizolid
	• Drug–drug interactions	• Avoid serotonergic drugs; monitor symptoms[b]
	• Optic neuritis	• Monitor symptoms; cessation if occurs
	• Neuropathy	• Coadministration of vitamin B6
Rifamycins[c]	• Drug–drug interactions	• Avoid use with CYP3A4 substrates[b]
	• Hepatotoxicity	• Symptomatic and lab monitoring; cessation of therapy; if minor, may later be reintroduced
	• Cytopenias	• Cessation of therapy
Tetracyclines	• Gastrointestinal disturbance and granulomatous hepatitis	• Start tigecycline at low dose with slow dose escalation over weeks
	• Pancreatitis	• Add amylase/lipase to usual lab monitoring

[a] *All of the agents discussed in this chapter may contribute to common side effects such as gastrointestinal disturbance, rashes, and abnormalities on liver function testing. This is separately denoted for agents where this is particularly common or severe. In practice, we monitor labs on a monthly basis in uncomplicated oral regimens and weekly on IV regimens. Consultation with pharmacy is generally advisable, particularly for management of aminoglycosides.*

[b] *Details of common drug–drug interactions are discussed in the main text sections on each drug as well as the Special Populations section.*

[c] *Although not a toxicity, patients should be counseled on expected secretion discoloration.*

based on side effects), ethambutol, and a rifamycin (rifampin is preferred over rifabutin).[18,30,31] Injectable agents (e.g., amikacin or streptomycin) are included in regimens for severe, cavitary, or macrolide-resistant disease. Macrolides, particularly azithromycin, carry a low risk of potentially irreversible pan-frequency hearing loss, as well as gastrointestinal side effects and hepatitis.[32] Baseline audiology with repeat testing for symptoms may be helpful. Clarithromycin may be associated with less ototoxicity, but the drug is dosed twice daily and has more drug interactions and gastrointestinal side effects.[33]

In the context of MAC therapy, ethambutol carries a 6% risk of optic neuritis when dosed daily at 15 mg/kg (less when dosed three times weekly at 25 mg/kg); this form of toxicity commonly manifests months into therapy as blurred vision or changes to red–green color vision affecting one or both eyes. In most cases, the findings improve or resolve within several months following cessation of therapy.[34] Baseline ophthalmology examination prior to the start of therapy and every 3 months thereafter, as well as counseling the patient to hold therapy for visual changes pending evaluation, may minimize progression.

Rifampin has a number of potential adverse effects, including gastrointestinal intolerance, hepatotoxicity, and cytopenias. Relevant drug interactions are also important to recognize, including increased metabolism of anticoagulant and immunosuppressive medications via induction of CYP3A4 enzymes, which may necessitate changes in therapy. Rifampin hepatotoxicity occurs in up to 19% of MAC treatment courses. Hepatotoxicity may be monitored when mild; when severe, management centers on cessation and subsequent reintroduction, which can be accomplished in 90% of patients.[33]

Macrolide-resistant MAC portends a long duration of therapy, unfavorable outcome, and high rate of death. Resistance is associated with changes in the 23S rRNA *rrl* gene when a macrolide is used alone, with a quinolone, or without ethambutol.[35] Daily dosing of the oral regimen, along with intensification of the regimen with the addition of 2 to 3 months of an aminoglycoside, is used for severe or cavitary disease, as well as for macrolide resistance.[36] Additional agents, such as clofazimine and bedaquiline, also may be considered.

Use of long-term aminoglycosides may result in irreversible high-frequency ototoxicity, more commonly in older patients and with use of greater cumulative doses; vestibular toxicity and renal toxicity also may be seen. Typical monitoring includes audiology every few weeks, in addition to weekly laboratory tests to assess renal function. For patients who have failed 6 months of therapy, amikacin liposome inhalation suspension (ALIS) may be added to improve rates of culture conversion.

For noncavitary, nonsevere disease, three times weekly, rather than daily, therapy is associated with lower rates of drug regimen changes and similar rates of culture conversion and macrolide resistance.[37] The extent of disease and bacillary burden may be considered as additional factors in determining the need for daily regimens.

The overall rate of culture conversion has been reported at 60% (41%–74%), with 16% stopping therapy prematurely.[32] Recurrence is most commonly due to reinfection with a new strain, although true relapse may be more common among patients who do not complete a full course of therapy.[38] Guidelines recommend at least 12 months of therapy past the date of culture conversion, although this may be extended in selected patients with more severe disease, depending on clinical and radiographic evolution.[18]

■ *Mycobacterium abscessus* Subspecies (MAb)

Pulmonary *M. abscessus* infection refers to infection with any of three subspecies within the *M. abscessus* complex—*M. abscessus*, *M. bolletii*, or *M. massiliense*. The last of these three is distinguished by its nonfunctional *erm* 23S rRNA methylase, which confers inducible macrolide resistance in the former two.[39] Mutations in the 23S rRNA *rrl* gene may contribute to constitutive macrolide resistance, while 5% of isolates carry 16S rRNA *rrs* mutations that may contribute to amikacin resistance.[40] MAb as a whole are the most resistant NTMs, and outcomes are often suboptimal in the absence of surgical resection of diseased lung.[41] Cure rates approximate 50%, with 20% recurrence and lower success rates in patients with recurrent disease, or in those whose disease is due to macrolide-resistant MAb; macrolide-sensitive *M. massiliense* is more responsive to treatment.[42]

For patients with susceptible isolates, guidelines support inclusion of a macrolide in a regimen consisting of at least three active drugs.[18] A common therapeutic approach is to complete an induction course of up to several months, during which at least one oral agent and two parenteral agents (amikacin, tigecycline, and either cefoxitin or imipenem) are administered. One reported series noted the highest success rates with amikacin, and similar rates among linezolid, tigecycline, or imipenem-based regimens.[43]

Amikacin ototoxicity rates have been reported at 23% in treatment of MAb; adverse effects, such as leukopenia (51%) or transaminase elevations (15%) are also commonly associated with cefoxitin.[43,44] Tigecycline often has significant gastrointestinal side effects.

Following induction, selected patients may transition to an oral regimen to extend at least 12 months past the time of culture conversion, if achieved. Another common approach is to complete several months of induction therapy as toxicity allows, followed by medication holidays. Surgical resection may contribute to sputum conversion in carefully selected patients with localized disease and adequate pulmonary reserve.

■ *Mycobacterium kansasii*

Mycobacterium kansasii is considered one of the most pathogenic NTMs, although almost all appropriately treated patients achieve sputum conversion.[45] Guidelines support the primary use of a three-drug regimen consisting of rifampin, ethambutol, and either isoniazid or a macrolide; a major consideration is the prevention of rifampin resistance.[18] Some data support three times per week dosing of a macrolide-containing regimen for *M. kansasii*, and either daily or three times per week dosing of a macrolide-containing regimen may be used for noncavitary disease.[46] For cavitary disease treated with any regimen or for noncavitary disease treated with an isoniazid-containing regimen, however, guidelines support daily dosing.[18] When rifampin resistance occurs, guidelines favor replacement with moxifloxacin. Sputum conversion is usually achieved by 4 months; the duration of therapy is 12 months. Rates of relapse are lower than in the treatment of MAC and MAb.[47]

■ *Mycobacterium xenopi*

Another pathogenic, slowly growing mycobacterial species with a greater incidence of cavitary disease is *M. xenopi*, which has been associated with 69% mortality; it is unclear to what extent the high mortality is due to *M. xenopi* itself.[11,48] Treatment may extend survival,[49] but a limited literature informs the current guidelines supporting use of three-drug therapy, including ethambutol and rifampin, plus either moxifloxacin or a macrolide. Interim analysis from a randomized trial of moxifloxacin versus clarithromycin as the third drug in this regimen has shown no difference in outcomes to date.[50,51] Based on potential severity of outcomes, guidelines also support a total duration of therapy of 12 months past the time of culture conversion as well as inclusion of parenteral amikacin in the regimens of patients with cavitary disease. Surgical intervention may also improve outcomes.[49]

MANAGEMENT OF COINFECTION

Coinfection with multiple NTMs is seen in up to 10% of patients. In such cases, combinations of MAC, *M. kansasii*, and/or *M. xenopi* are readily addressed by use of a guideline-supported regimen consisting of ethambutol, a rifamycin, and a macrolide.[18] Coinfection becomes more complicated, however, when considering the common combination of MAC and MAb, in which case an important branch point in treatment decision-making is macrolide susceptibility. If the MAb is macrolide-resistant, we treat MAC and MAb with non-overlapping regimens optimized for each pathogen, starting with MAC therapy, which is more likely to be tolerated; subsequently, agents active against MAb are added, once MAC therapy is established. When the MAb is macrolide-sensitive, use of a macrolide for both pathogens may simplify the overall regimen but complicate the initiation process. It may then be advisable to initiate treatment for MAC and MAb simultaneously to avoid development of MAb macrolide resistance while the patient is receiving *de facto* MAb macrolide monotherapy during initiation of the MAC regimen.

ADJUNCTIVE INTERVENTIONS

A major factor underlying pulmonary NTM infection is the presence of abnormal airway clearance contributing to the pathogenetic cycle of persistence, inflammation, and infection. Interventions geared at optimizing airway clearance and bronchiectasis management, such as nebulized hypertonic saline, flutter valve devices, or high-frequency chest wall oscillation vests are an important part of an overall treatment plan formulated among a multidisciplinary team, including pulmonology and chest physiotherapy. Although such interventions are not well studied or validated in cases of bronchiectasis outside the context of cystic fibrosis, in our clinical experience, patients with pulmonary NTM infections who engage in airway clearance regimens fare better than those who do not. These adjunctive interventions may also be helpful among patients for whom antibiotic therapy is not yet indicated, or for patients who are unable to tolerate antibiotic therapy. Given the high rates of esophageal dysmotility with fibronodular bronchiectasis and pulmonary NTM infections, prevention of aspiration events and management of esophageal co-pathology is also essential.

Limited data associate surgical intervention with improved outcomes in some pulmonary NTM infections.[36,44,49] Where indicated, these procedures, most often lobectomies, may be completed with relatively low morbidity and mortality; the most common complication is bronchopleural fistula associated with a high bacillary load or with right pneumonectomy.[52] Careful selection for patients with adequate pulmonary reserve and localized, refractory disease or complications, such as massive hemoptysis or resistant NTMs, is paramount.

NOVEL THERAPIES AND APPROACHES

A number of new pharmacologic agents for treatment of NTM respiratory infections are considered below.

Amikacin Liposome Inhalation Suspension

Amikacin liposome inhalation suspension (ALIS) carries the hypothetical benefits of local delivery to minimize systemic toxicity, enhanced macrophage uptake to improve intracellular drug delivery, and biofilm penetration.[53] The phase 3 CONVERT study demonstrated that addition of ALIS in patients who had received guideline-based therapy for MAC for at least 6 months led to a fourfold improvement in culture conversion rates.[53,54] These data followed a phase 2 study in which addition of ALIS in patients with persistently positive cultures resulted in a threefold increase in the number of patients with at least one negative sputum culture, although the primary endpoint of a decrease in semiquantitative NTM cultures narrowly missed significance; treatment may be less effective for MAb than for MAC.[55,56] Monitoring suggested nontoxic serum amikacin levels with inhaled therapy. No significant aminoglycoside-related toxicities were observed. Importantly, culture conversion was seen only among patients with amikacin MICs ≤64 μg/mL.[18,55]

Although ALIS is effective as an adjunct to standard of care, it has high rates of respiratory adverse events. More than 90% of patients in each arm of CONVERT experienced treatment-associated adverse events, most commonly within the first month of ALIS; particularly notable were dysphonia, cough, hemoptysis, and dyspnea, leading to discontinuation of ALIS in 17% of patients.[53] A later survey found similar symptoms among 73% of patients on ALIS. In most cases, symptoms are amenable to conservative interventions, such as lozenges, gargling, antitussives, evening administration of the drug, bronchodilators, or a brief treatment interruption with subsequent reintroduction.[57]

■ Clofazimine

Clofazimine has been in clinical use for the treatment of leprosy since the 1950s. The drug was used subsequently in the treatment of tuberculosis. In vitro studies generally show favorable MICs for clofazimine in the treatment of NTMs, although it may be less active against rapidly growing mycobacteria and *M. kansasii*. Synergy may be seen with some agents, such as amikacin, clarithromycin, or bedaquiline.[58,59] Animal models have generally supported antimycobacterial activity, although comparisons between rifampin- and clofazimine-based regimens have shown mixed results.[60,61]

Published clinical experience suggests 50% sputum conversion with clofazimine-containing regimens for treatment of MAb, MAC, or dual infection; 14% stop therapy due to adverse reactions such as gastrointestinal side effects or common dermatologic side effects of clofazimine, including skin discoloration (63%), dry skin (32%), or sun hypersensitivity (20%).[62] Conversion rates may improve among patients with more favorable clofazimine MICs (≤0.25 mg/L) and may be comparable to rifampin-containing regimens.[63,64]

In practice, we utilize clofazimine for MAC in patients unable to take first-line agents (more commonly rifamycins rather than ethambutol). When MICs are favorable, we also deploy clofazimine as part of salvage regimens for MAC or as part of an oral regimen for MAb. Outcomes in salvage therapy tend to be modest; series including clofazimine as part of salvage therapy have shown 16% to 29% favorable outcomes.[65,66] Access to clofazimine is complicated by its investigational status in the United States; for clinicians who are not part of a hospital or clinic that has a multipatient investigational agreement with Novartis, the only option is to submit a single-patient investigational new drug (IND) application to the U.S. Food and Drug Administration. Both require ethics approval in the treating clinicians' institutions.

■ Bedaquiline

Initially approved in 2012 for use against multidrug-resistant *M. tuberculosis*, bedaquiline exerts its antimycobacterial action by inhibiting the mycobacterial ATP synthase. NTM isolates from patients naïve to bedaquiline generally demonstrate favorable MICs.[58,67] Resistance to bedaquiline can be conferred by increased efflux pump expression, as well as direct alteration of the ATPase complex; the former is of particular concern, given its ability to confer cross-resistance between bedaquiline and clofazimine.[68,69] Synergy has been observed between bedaquiline and clofazimine, amikacin, and cefoxitin. Animal models have generally supported at least some degree of bedaquiline efficacy in the treatment of NTM infections in vivo.[70]

Although clinical experience is limited, an observational study of 10 patients taking bedaquiline as part of a regimen consisting of a mean of 5 drugs showed a microbiologic response in 6 patients at 6 months.[71] The most common side effects were nausea (60%), arthralgias (40%), and anorexia and subjective fever (30%); mild QTc prolongation was noted. Treatment may be complicated by selection for resistance while on therapy, necessitating implementation of an optimized regimen to preserve bedaquiline activity.[72] Use of bedaquiline is further complicated by interactions with rifampin, which substantially decreases bedaquiline levels compared with rifabutin. A final consideration is the long terminal half-life of bedaquiline (estimated at 5.5 months), which may lead to unintentional monotherapy when stopping regimens.[73] Rules for procurement of bedaquiline differ by country and may limit availability for use in the management of pulmonary NTM infections.

Novel Tetracyclines

Tigecycline is a glycylcycline tetracycline derivative that acts at the 30S ribosomal subunit. Unlike earlier tetracyclines, it is less susceptible to common resistance mechanisms, such as binding site alteration and efflux pumps in diverse bacteria as well inactivating enzymes associated with high level tetracycline resistance in MAb.[74,75] Its use in salvage regimens for MAb pulmonary infections is supported by in vitro susceptibility among rapidly growing mycobacteria (where MICs for slowly growing mycobacteria are generally unfavorable) and animal models. In observational studies, approximately two-thirds of patients on tigecycline-containing regimens showed improvement, typically when combined with macrolides, amikacin, linezolid, clofazimine, or imipenem; adverse effects, such as nausea (63.5%) and vomiting (34.6%), were common, necessitating a dose reduction or cessation of therapy in more than half of patients.[76,77] Starting treatment with 25 mg IV daily, followed by slow escalation over weeks to a target dose of 50 mg IV daily, may improve long-term tolerability.

Later-generation tetracyclines, such oral and intravenous omadacycline, have entered clinical practice more recently and are generally better tolerated than tigecycline; these carry the potential additional advantage of improved plasma and lung concentrations.[78] In phase 3 trials of omadacycline for non-NTM infections, the most common adverse effects were nausea (14.9%) and vomiting (8.3%); transaminase abnormalities were comparable with the comparators, linezolid and moxifloxacin.[79] Both omadacycline and eravacycline typically have favorable MICs against rapidly growing mycobacteria, such as MAb, where MICs against slowly growing mycobacteria appear generally unfavorable.[80] Published clinical experience to support efficacy remains limited to a handful of case reports.[81,82] Some rapidly growing mycobacteria and *M. kansasii* may also be susceptible to the older oral agent minocycline.

Oxazolidinones

Oxazolidinones target the 50S ribosomal subunit and are broadly active against Gram-positive bacteria. Both of the approved drugs in this class, linezolid and tedizolid, have some activity in vitro against most NTMs, although tedizolid is generally more potent.[83] Resistance to linezolid in MAC is conferred by mutations in the 23S rRNA gene *rrl,* as well as the *rplD* gene encoding the L4 ribosomal protein, in addition to efflux pumps.[84,85] A small series in the literature suggested improved sputum conversion rates from 29.4% to 81.3% when linezolid was added to standard therapy, although leukopenia and transaminase elevations were commonly encountered.[86] Linezolid carries a number of side effects that are less prominent than with tedizolid, including marrow suppression in 10% of patients treated for MAb.[43] When linezolid bone marrow toxicity occurs, use of tedizolid may still be possible.[87] Other adverse effects include optic neuritis, peripheral neuropathy for which vitamin B6 is typically coadministered, and the risk of serotonin syndrome when the drug is coadministered with other agents active in the inhibition of monoamine oxidases. We frequently use these agents in oral regimens for MAb, although adverse effects, particularly with linezolid, can be limiting.

Fluoroquinolones

Fluoroquinolones exert broad-spectrum antibacterial activity by inhibiting the normal function of DNA topoisomerases. They are variably active against MAC, MAb, and *M. kansasii*, although moxifloxacin tends to be the most active.[88,89] A number of resistance mechanisms have been demonstrated in typical bacteria, including direct changes in the topoisomerases themselves, although the details of fluoroquinolone resistance in NTMs remain unclear.[88] Published clinical experience is limited. One series looking at intensification of therapy with moxifloxacin for MAC resulted in sputum conversion in 12 of 41 patients who had refractory disease.[90] Another series comparing triple therapy, with or without levofloxacin for MAC, suggested lower sputum conversion rates in the presence of levofloxacin. The use of quinolones in combination with a macrolide has emerged as a risk factor for macrolide resistance.[36,91] Common adverse effects of fluoroquinolones include QTc prolongation and tendon rupture. Aside from *M. kansasii*, *M. xenopi*, and uncommon NTM species, quinolones are of limited utility in the management of NTM infections.

Phage Therapy

The rise of resistant organisms has rekindled interest in phage therapy as an alternative to antibiotics. The first human use of mycobacteriophage was reported in 2019 in a 15-year-old female with cystic fibrosis who had been treated for MAb for 8 years prior to bilateral lung transplant. The patient suffered disseminated infection following transplant that progressed through antibiotic therapy. Infection ultimately improved with a combination of three phages.[92] A more recent report from the University of California San Diego's Center for Innovative Phage Applications and Therapeutics showed that MAb and other NTMs are among the most frequent infections for which phages are requested. Although the cases described in this series did not include MAb, experience with typical bacteria indicated that intravenous administration of phages was safe, well tolerated, and translatable to the outpatient setting.[93] Although promising, phage therapy is investigational, and regulatory barriers and lack of experience limit the scalability of the approach at present.

SPECIAL POPULATIONS

Two special clinical circumstances warrant additional discussion: cystic fibrosis and lung transplantation.

Cystic Fibrosis

Patients with cystic fibrosis are disproportionately affected by NTM lung disease, and routine annual screening for NTMs is recommended.[94] Culture positive prevalence has increased by as much as 5% per year recently, reaching 20% in one study,[95] although most patients with a single positive culture do not progress to active disease.[96] Among those meeting criteria for infection, the most common pathogens are MAb among younger patients with severe disease and MAC among older patients with lower body mass index.[95] Although the source of NTM is usually environmental, gene sequencing supports a role for person-to-person transmission among patients with cystic fibrosis.[97] When NTM infection occurs, patients are at risk for a more rapid decline in lung function.[98] Infection may complicate potential future transplant[99] for the 16% (MAC) to 24% (MAb) of infected patients who progress to end-stage lung disease.[100]

The CFTR modulators ivacaftor and tezacaftor, as well as the antimycobacterial agent bedaquiline, are substrates for CYP3A4 enzymes that are strongly upregulated by rifamycins; coadministration of rifamycins with these medications is contraindicated. Clarithromycin, by contrast, is a CYP3A4 inhibitor that may increase exposure to CFTR modulators or bedaquiline. Other potential interactions of distinct or unknown mechanisms include decreased levels of linezolid and moxifloxacin in the presence of rifampin, and increased levels of linezolid in the presence of clarithromycin.[101] QTc-prolonging drugs include macrolides, clofazimine, bedaquiline, and fluoroquinolones. Gastrointestinal tract involvement may also lead to malabsorption, which may warrant therapeutic drug monitoring.

Management of pulmonary NTM infections in patients with cystic fibrosis typically follows guidelines for the general NTM patient population,[102] although some differences exist. Patients with cystic fibrosis were excluded from the CONVERT trial and fared worse in the prior phase 2 trial, although a small case series demonstrated clearance of cultures in three patients with cystic fibrosis who were placed on ALIS monotherapy.[56] Among a group of patients with cystic fibrosis in whom prior regimens had failed to yield sputum conversion, 50% achieved sputum conversion on a clofazimine-containing regimen,[62] while the sole published evidence for the use of phages for MAb derives from treatment of a patient with cystic fibrosis.[92,99] Prophylactic use of azithromycin in patients with bronchiectasis, both with and without underlying cystic fibrosis,[103–105] may reduce the rate of NTM infection. Its use in patients with underlying cystic fibrosis appears not to be associated with an increase in the isolation of macrolide-resistant strains.[106–108] Whether use of azithromycin may ultimately select for macrolide-resistant species and strains, such as MAb, has not yet been addressed in large studies.

■ Lung Transplantation

Although most pulmonary NTM disease occurs in the absence of immunosuppression, organ transplantation and other conditions that decrease cell-mediated immunity may predispose to both pulmonary and disseminated NTM infections.[9,109] Within the specific context of lung transplantation, MAb and MAC have most commonly been isolated from <1% to 7% of patients pre-transplant, and from 4.5% to 14% post-transplant, with the incidence of post-transplant isolation increasing over time to a peak of more than 20% at 5 years.[110–113] Several series have shown comparable survival, with and without pulmonary NTM infection, in the context of lung transplantation, although patients with NTM may be at increased risk of bronchiolitis obliterans syndrome; many centers consider NTM infection due to MAb at least a relative contraindication to transplantation.[99,110,111,114–116]

As in the case of cystic fibrosis, a major consideration in the management of pulmonary NTM infection in transplant patients is the potential for drug–drug interactions. Concerns center particularly on use of the rifamycins, which may significantly decrease levels of corticosteroids, tacrolimus, sirolimus, cyclosporine, and mycophenolate.[101] Clarithromycin, by contrast, may increase corticosteroid, tacrolimus, and sirolimus levels, while tigecycline may increase cyclosporine and tacrolimus levels.[101] Guidelines for the management of NTM infections in the context of transplantation support use of azithromycin and rifabutin as the preferred macrolide and rifamycin, respectively, due to their lower potential for drug-drug interactions.[117] Potential exists also for QTc prolongation with multiple agents, and coadministration of fluoroquinolones and corticosteroids may increase the risk of tendon rupture related to the former. Care should be taken in the context of nephrotoxic medications, such as amikacin, given the potential for additional nephrotoxic effects from some immunomodulatory medications.[101] To the extent possible, reduction of immunosuppression while still preserving optimal allograft function may also be part of treatment.[9,116,118]

FUTURE DIRECTIONS

Although much progress has been made in the diagnosis and management of pulmonary NTM infections, a number of knowledge gaps remain for further research, as has been highlighted by recent consensus statements on definitions of desired treatment outcomes and research priorities.[119,120] Among these, the clearest need is for more effective, better-tolerated, and overall simpler and shorter treatment regimens based on an enhanced understanding of NTM pathogenesis. Similarly, improved diagnostics for the identification and susceptibility testing of NTM isolates may help to facilitate more timely and efficacious treatment strategies.

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CHAPTER 132

Aspergillus, Candida, and Other Opportunistic Pulmonary Mycoses

Georgios Chamilos
Dimitrios P. Kontoyiannis

INTRODUCTION

Pulmonary mycoses, mainly caused by *Aspergillus*, Mucorales, and other saprophytic molds are emerging diseases in the rapidly expanding population of immunocompromised patients. These opportunistic fungal pathogens cause a spectrum of pulmonary diseases depending on the severity of the underlying immunodeficiency. In particular, invasive mold infections are associated with considerable mortality despite appropriate antifungal therapy. Apart from improvements in establishment of timely diagnosis of pulmonary mycoses with establishment of non-culture-based diagnostic methods, there is a need to dissect the underlying mechanisms of immunopathogenesis in order to develop host directed therapies.

PULMONARY ASPERGILLOSIS

Aspergillus is a ubiquitous saprophytic mold that has a simple biologic cycle characterized by asexual reproduction and a high sporulating capacity, which results in the release of conidia at high concentrations (1–100 conidia/m^3) into the atmosphere. *Aspergillus* conidia have a diameter small enough (2–3 μm) to reach the pulmonary alveoli.[1,2] However, while humans may frequently inhale *Aspergillus* conidia, such conidia are effectively eliminated in immunocompetent individuals.[3]

Epidemiology

Infections by *Aspergillus* species cause a wide spectrum of illnesses in humans, which reflect the immune status of the host (Table 132-1). Hence, in immunocompetent hosts, isolation of *Aspergillus* spp. in respiratory secretions typically reflects colonization, not infection. In normal individuals, inhalation of *Aspergillus* spp. does not trigger immune responses because fungal spores are covered by a hydrophobic protein layer that masks recognition of immunostimulatory fungal cell wall polysaccharides by the immune system.[1–3] In atopic people, the fungus triggers robust immune reactions, including allergic rhinitis, asthma, hypersensitivity pneumonitis, and allergic bronchopulmonary aspergillosis (ABPA).[4] In patients with pre-existing cavitary pulmonary lesions (mainly as a result of prior tuberculosis), saprophytic growth of *Aspergillus* spp. can lead to aspergilloma formation or persistent inflammation, a disease entity called chronic pulmonary aspergillosis (CPA). Finally, in immunocompromised individuals, *Aspergillus* conidia may germinate in the lung to form hyphae, the invasive form of the fungus, which causes a severe, frequently fatal angioinvasive infection called invasive pulmonary aspergillosis (IPA).[5–7] The degree of fungal invasion, response to antifungal therapy, and outcome of invasive aspergillosis (IA) depend on the type and severity of immunosuppression. Thus, in patients with incompletely characterized, subtle immune defects, chronic forms of *Aspergillus* infections (CPA) in the lung have been described, which are characterized by an indolent clinical course, low-grade chronic inflammation, the development of progressive cavitary or fibrotic lesions, and minimal or no evidence of parenchymal invasion.[8] A less angioinvasive form of IA, frequently called subacute IPA, has been described in patients with genetic defects in NADPH oxidase (chronic granulomatous disease or CGD), whereas

TABLE 132-1 Spectrum of Pulmonary Aspergillosis

Clinical Manifestation	Immune Status	Underlying Lung Architecture	Degree of Tissue Invasion
Simple colonization	Normal	Chronic obstructive airway disease	None
Hypersensitivity reactions			
Allergic bronchial asthma	↑[a]	Normal	None
ABPA	↑	Excess airway mucus	None
Bronchocentric granulomatosis	↑	Excess airway mucus	None
Extrinsic allergic alveolitis	↑	Normal	None
Invasive infection			
IBA[b]	↑	Lung transplantation	++
Bronchial stump aspergillosis	Normal	Pneumonectomy	+
CPA[c]	↓[d]	Chronic obstructive airway disease	+
IPA[e]	↓↓↓[f]	Normal	+++

[a] ↑Hyperactive humoral response.

[b] Includes tracheobronchitis, pseudomembranous tracheobronchitis, and ulcerative tracheobronchitis. The latter two forms typically manifest as anastomotic infections in lung transplant recipients.

[c] Includes the following forms: aspergilloma, chronic necrotizing pulmonary aspergillosis (CNPA), chronic cavitary pulmonary aspergillosis (CCPA), chronic fibrosing pulmonary aspergillosis (CFPA). Aspergillus hyphae occasionally invade the lung parenchyma in CNPA. Significant overlap exists among these entities. Aspergilloma, previously regarded as saprophytic fungal growth, has been classified as a form of CPA.

[d] ↓Suppressed immune response.

[e] May have features of invasive disease surrounding the cavity. It occurs in two settings with distinct histopathologies and immunopathogenesis: angioinvasive IPA in profoundly neutropenic patients and nonangioinvasive IPA in immunocompromised nonneutropenic individuals, including those receiving corticosteroid-based treatment, recipients of HSCTs with severe GvHD, patients with AIDS, recipients of solid-organ transplants, and patients with CGD. Mixed forms and significant overlap exist.

[f] ↓↓↓Severely depressed immune response, neutropenia.

progressive IPA is encountered in severely immunocompromised hosts.[1,2,6,7] There is no doubt that since the first description in the 1940s, IA has emerged as the major problem of modern mycology. Currently, IA is a leading cause of death in severely immunocompromised individuals, with mortality rates up to 50% in patients with leukemia and recipients of hematopoietic stem cell transplants (HSCTs).[1,6] In addition, invasive *Aspergillus* has emerged as an important pathogen in an expanding spectrum of nonneutropenic patients with incompletely understood immunometabolic defects in myeloid phagocytes induced by prolonged receipt of corticosteroids, other immunosuppressive therapies, or underlying diseases. Thus, IPA is increasingly encountered in patients with inflammatory and autoimmune diseases, end-stage cirrhosis, chronic obstructive lung disease, and immunosuppression induced by viral or bacterial sepsis in patients with prolonged ICU stays.[1,2] At the same time, over the past two decades, we have witnessed a significant expansion in the antifungal armamentarium with the introduction of several agents with anti-*Aspergillus* activity. In addition, promising new non-culture-based diagnostic methods are being developed, and considerable progress has been made in understanding the epidemiology and immunopathogenesis of IA. As a result, a significant improvement in IA-attributable mortality has been noted. As IPA currently accounts for more than 90% of invasive *Aspergillus* infections we devote a significant portion of this chapter to this type of pulmonary aspergillosis.[1]

■ Mycology and Host Defenses

Of the nearly 200 *Aspergillus* spp., only 20 have been encountered as pathogenic in humans.[1] *Aspergillus fumigatus* is the most frequently identified of these species; however, other species, such as *Aspergillus flavus*, *Aspergillus niger*, *Aspergillus terreus*, and *Aspergillus nidulans* have emerged as important pathogens in immunocompromised individuals. Appropriate identification of *Aspergillus* species is important because of differences in epidemiology, host tropism, virulence, and susceptibility to antifungal agents. For example, *Aspergillus nidulans* is the second most encountered mold in CGD patients;[1,2] *A. nidulans* and other rare *Aspergillus* spp. cause almost exclusively invasive infections with distinct clinical features in patients with primary immunodeficiency. In addition, certain species including *A. terreus*, *A. flavus*, and *A. nidulans* are clinically resistant to AMB.[6,7] Studies using molecular identification methods discovered "cryptic" clinical isolates of *Aspergillus*, including *Aspergillus lentulus*, *Aspergillus calidoustus*, and *Aspergillus glaucus*, that had been misclassified as *A. fumigatus* and display inherent resistance to certain antifungal agents. Notably, *A. fumigatus* is nearly always the cause of allergic pulmonary disease.[4] *Aspergillus* spp. are rapidly growing, hardy molds identified by the macroscopic appearance of the colony and by microscopic examination of the spore-bearing structures.[1] Microscopically, *Aspergillus* spp. are characterized by the production of uniform 4- to 6-mm wide hyphae with parallel walls and distinct septa. Dichotomous branching of hyphae occurs at 45-degree angles.[1] However, other filamentous fungi, such as *Fusarium*, *Acremonium*, and *Scedosporium* species share the same histopathologic features with *Aspergillus* spp.[1] A wide range of microscopic appearances may be observed in clinical specimens.

Sputum specimens obtained from patients and examined by direct mounting or with KOH and ink may reveal the typical 45-degree branching hyphal fragments of aspergilli, which are often associated with eosinophils and Charcot–Leyden crystals in patients with ABPA.[1] Stained tissue sections reveal regular hyaline septate hyphae that are best observed with the use of periodic acid–Schiff (PAS) and Gomori methenamine silver (GMS) stain.[1] Fungus ball specimens obtained from cavities connected to bronchi have hyphae that often appear to be lifeless and stain poorly. Also, although seldom seen, the fruiting heads and conidia may appear to be well formed.

■ Host Immune Responses

Recent years have witnessed improvements in understanding of the immunologic mechanisms of host resistance to *Aspergillus* spp. Protection of the normal host against *Aspergillus* infection is mediated by a highly coordinated response that predominantly involves the innate immune system (Chapters 122 and 123).[1–3] IPA almost exclusively occurs in patients with defects in numbers and/or function of phagocytes. Acquired quantitative and qualitative defects in phagocytic function associated with prolonged and profound neutropenia and/or monocytopenia or corticosteroid-induced dysfunction of myeloid derived monocytes/macrophages have long been recognized as the major risk factors for IA. In addition, functional phagocytic defects due to mutations in NADPH oxidase seen in patients with CGD are associated with inflammatory immunopathology associated with inability to eliminate fungal conidia and unique susceptibility to IA.[3]

Overall, a balanced inflammatory response is required for abrogation or effective resolution of invasive *Aspergillus* infection. Thus, while an early and effective proinflammatory response is required to restrict infection, an uncontrolled inflammatory response is detrimental and may eventually facilitate fungal persistence. To that end, high-level production of IL-10 by T regs may be beneficial by contributing to resolution of the inflammatory response.[3] On the other side, IL-10 overproduction suppresses antifungal effector mechanisms and results in susceptibility for IA in human patients and mice.

Immune augmentation therapies have become a top priory in fungal immunology research.[2,3] However, in contrast to the animal studies, in severely immunocompromised patients with IPA, immune augmentation therapies have been of unclear benefit using myeloid growth factors, Th1 recombinant cytokines, or T cell–based adoptive transfer. Thus, translating recent advances in fungal immunology to novel therapeutics against IA in humans remains a challenge. In particular, translation of results of ex vivo experiments and studies in mice with genetic defects in receptors, signaling molecules, cytokines, or chemokines into clinical practice has been difficult in view of the complex and multifactorial pathophysiology of IPA in humans. Furthermore, immune augmentation strategies and vaccination-induced protective immune therapies could be suboptimal in profoundly immunocompromised individuals and should be tailored to the restoration of the underlying dominant immune defects of the individual patient. Better understanding of the immunopathogenesis of IPA at the cellular and molecular level coupled with efforts to validate research findings from mice in humans could facilitate the development of personalized immune-based augmentation therapies.

■ *Aspergillus* Virulence Factors

There is debate over which factors determine *Aspergillus* virulence and pathogenicity.[1,2] Several putative virulence factors in *A. fumigatus* have been identified, including various proteolytic enzymes (elastases, collagenases, trypsin), phospholipases, ribotoxin, hemolysin, gliotoxin, and many other enzymes and toxins.[1,2]

Importantly, tissue necrosis and angioinvasion are prominent features of IA in immunocompromised patients. Of interest, gliotoxin has been shown to block angiogenesis during invasive *Aspergillus* growth.[2,3] In fact, restoration of antiangiogenic activity of *Aspergillus* via administration of proangiogenic factors has been shown to potentiate activity of antifungal therapy in murine IPA. In addition, adaptation in the hypoxic environment during tissue necrosis is a prominent feature of invasive *Aspergillus* growth. In fact, an

Aspergillus mutant deficient in a sterol regulatory element-binding protein required for hypoxia adaptation (Δ*SrbA*) was completely avirulent in mice.[2,3] Iron metabolism is important for *Aspergillus* in vivo growth, and mutants defective in both intra- and extracellular siderophore production fail to grow in vivo and are avirulent following infection of neutropenic mice. Moreover, the melanin pigment and rigid protein coat layer composed of hydrophobic rodlet fascicles on the *Aspergillus* conidial surface confer resistance to phagocytosis and killing by the innate immune system.[2] In fact, melanin acts as a virulence factor by inhibiting calcium signaling regulating phagolysosomal fusion and killing of *Aspergillus* conidia by macrophages. On the other hand, comparative genomic analysis across filamentous fungi suggests that *A. fumigatus* virulence results from the immunosuppression or possibly genetic susceptibility of the host rather than from specific, unique fungal determinants.[2,3] Hence, *A. fumigatus* appears to be a saprotrophic fungus that only becomes pathogenic for very simple biologic reasons: it is present in high concentrations in the atmosphere, it grows faster than any other airborne fungi at physiologic mammalian temperatures (above 37°C), and it can overcome the defense of the host not because of specific virulence mechanisms but because of inefficient host innate immune responses. Taken together, these data suggest that approaches aiming at restoration of defective cellular immune responses via cytokine immunotherapy, treatment with checkpoint inhibitors, engineered effector cells, or dendritic cell vaccine–based vaccination warrant investigation as therapeutic modalities for invasive *Aspergillus* infections.[2,3]

Clinical Manifestations

The varied clinical manifestations of disease related to *Aspergillus* species are considered in detail below.

Hypersensitive Reactions

Hypersensitivity lung diseases that result from exposure to *A. fumigatus* allergens include allergic asthma, ABPA, and hypersensitivity pneumonitis.[4,6] In atopic individuals, inhalation of *Aspergillus* spores triggers an IgE-mediated allergic inflammatory response in the bronchial mucosa, leading to excessive mucus production, bronchial obstruction, and asthma.[4,6] Similarly, ABPA develops following sensitization to *A. fumigatus* allergens in a unique subset of atopic individuals and patients with cystic fibrosis (CF), who are genetically susceptible for ABPA.[4] The immune response to *Aspergillus* antigens in both patients with allergic asthma and those with ABPA is characterized by a robust Th2 polarized CD4+ response and eosinophilia, which are linked to polymorphisms in CARD9 signaling regulating IL-5 production in response to *Aspergillus*.

In nonatopic individuals, persistent airway colonization and, more rarely, a type of hypersensitivity pneumonitis called *extrinsic allergic alveolitis* can occur as a result of massive or repeated inhalation of *Aspergillus* conidia.[4,8] Hypersensitivity pneumonitis in these patients manifests with dyspnea because of pulmonary constriction and an influenza-like syndrome with fever, malaise, and fatigue. In contrast to other allergic diseases caused by *A. fumigatus*, hypersensitive pneumonitis is characterized by extensive infiltration of neutrophils in the acute phase as a result of a Th1 CD4+ response.[4,8] Early recognition of these syndromes is important for early initiation of appropriate treatment to prevent progression to permanent lung damage. Table 132-2 summarizes the hypersensitivity syndromes that result from exposure to *Aspergillus*.

Simple Colonization

Although there is not a uniform definition of colonization, it should be considered in cases of isolation of *Aspergillus* spp. from cultures of the respiratory tract in patients without evidence of invasive or allergic disease.[8] Patients with structural lung diseases such as chronic obstructive pulmonary disease (COPD) are at increased risk for persistent *Aspergillus* colonization. Furthermore, genetic susceptibility as a result of polymorphisms in the transcriptional factor ZNF77 impairs respiratory epithelial integrity and promotes *Aspergillus* colonization in patients with asthma and ABPA.[1] Tissue invasion by *Aspergillus* is not a feature of saprophytic colonization, although IPA following subsequent dysfunction of host defenses may develop. In fact, *Aspergillus* colonization has been shown to be a marker for the development of IA in immunocompromised individuals, particularly lung and bone marrow transplant recipients, and may precede invasion for up to 3 months.[7,8] Quantitative real-time polymerase chain reaction (PCR) and measurement of BAL *Aspergillus* galactomannan antigen are both highly sensitive and specific assays in distinguishing *Aspergillus* colonization from invasive infection.[1,6]

Allergic Bronchial Asthma

Asthmatic patients may become sensitized to *Aspergillus* conidia as a consequence of thick bronchial secretions that trap fungal spores.[4,8] These spores seldom germinate in the bronchial airways. Allergic bronchial asthma develops in patients who are atopic

TABLE 132-2 Hypersensitive Reactions to *Aspergillus*

	Asthma	ABPA	Extrinsic Allergic Alveolitis
Pathology	Hypertrophied mucus glands	Colonization of airways, viscid mucoid impaction, tissue eosinophilia	Lymphocytic infiltration of interstitium, noncaseating granuloma
Radiographic features			
Early	Normal, hyperinflation	Migratory peripheral infiltrates, atelectasis, bronchiectasis	Diffuse alveolar–interstitial infiltrates
Late	Normal, hyperinflation	Fibrosis	Reticulonodular interstitial opacities
Skin test reactions to *Aspergillus* antigens			
Immediate	Positive	Positive	Positive
Delayed	Negative	Positive	Positive
Peripheral eosinophilia	Negative[a]	Positive	Negative
IgG *Aspergillus* precipitins	Positive (up to 25%)	Positive	Positive
Serum IgE levels	Normal or mildly elevated	Marked elevation	Normal

[a] *Occasionally positive.*

and is perpetuated by inhalation of *Aspergillus* antigens, which typically triggers acute bronchospasm. The presence of transient infiltrates has been described during the immediate reaction but is not frequent. As is typical in asthma of other etiologies, eosinophils and serum IgE antibody are increased. Immediate skin reactions to *Aspergillus* antigens are positive, but specific precipitating antibodies (IgG) are usually negative.[4,8] Avoidance of exposure to *Aspergillus* allergens reduces asthma attacks in this group of patients. *Aspergillus* bronchitis is a rare, distinct clinical entity that has been recently described in immunocompetent individuals with structural lung disease, chronic pulmonary symptoms, and lack of response to antibiotic therapy. All of these patients had evidence of *Aspergillus* growth in their lungs, showed marked improvement following antifungal therapy, and did not fulfill criteria for asthma or other forms of invasive or chronic aspergillosis.

Allergic Bronchopulmonary Aspergillosis

The important clinical entity of allergic bronchopulmonary aspergillosis (ABPA) is discussed below. The reader is also referred to Chapters 46 and 51.

Immunopathogenesis and Risk Factors It has been recently proposed that ABPA develops in genetically susceptible patients with asthma or CF because of increased activity of *A. fumigatus*–specific Th2 CD4+ cells (Chapter 46).[4] Hence, in addition to a history of atopy, predisposing factors for ABPA include immunogenetic human leukocyte antigen (HLA)-distinct phenotypes (e.g., HLA-DR 2- and HLA-DR 5-specific alleles), mutations in the CF transmembrane conductance regulator (CFTR) gene, polymorphisms of the collagen region of the SP-A2, and/or other collectins (e.g., mannose-binding lectins), which collectively result in deregulated mucosal immune responses and chronic inflammation.[4,8] Additionally, genetic defects in epithelial integrity, associated with polymorphisms in transcriptional factor ZNF77, are associated with increased risk for ABPA.[1] Furthermore, epigenetic factors and environmental exposures may play a role in ABPA pathogenesis.[4,8]

In patients with ABPA, inhaled *A. fumigatus* conidia are able to colonize, persist, and germinate, leading to growth of hyphae in mucus plugs, which are often observed in expectorated sputum.[4] During this process, *A. fumigatus* releases a panel of proteases and other toxins that are capable of further compromising mucociliary clearance, breaching the airway epithelial barrier, and activating the immune system in the lung.[4]

IgE molecules on the surface of mast cells initially recognize *A. fumigatus* antigens. Binding of these antigens with IgE causes mast-cell degranulation, releasing mediators that cause vasodilatation and vascular leakage so that serum components, including anti-*Aspergillus* IgG, enter the bronchi and combine with *Aspergillus* antigens to form IgG-containing immune complexes.[4] These complexes activate the complement cascade leading to inflammation and pulmonary damage. Importantly, investigators have identified specific *Aspergillus* antigens capable of inducing IgE and IgG responses and aberrant immune responses selectively in patients with ABPA.[4]

Clinical Features ABPA is a hypersensitivity disease of the lung that is virtually almost always related to *A. fumigatus* (discussed in detail in Chapter 46). Some key points are highlighted here. Some 7% to 14% of patients with poorly controlled asthma and 7% to 9% of those with CF meet the diagnostic criteria for ABPA.[4] In fact, nearly all patients with ABPA have a history of chronic asthma. Rarely, patients present without symptoms or physical findings despite having radiographically detected abnormalities. Clinically, ABPA manifests with episodic wheezing, malaise, low-grade chronic fevers and cough, sputum containing brown flecks and plugs, chest pain, pulmonary infiltrates, and sputum and blood eosinophilia.[4,8] Patients may have a history of recurrent pneumonias and frequent use of antibiotic therapy. Mucus plugs form in the proximal bronchi and can progress to mucoid impaction, resulting in atelectasis with transient pulmonary infiltrates. Mucus plugs often yield aspergilli in culture (Figs. 132-1 and 132-2). As ABPA progresses, central bronchiectasis becomes a dominant feature of the disease and may result in chronic bronchorrhea and occasionally hemoptysis, development of clubbing, and fixed, characteristic radiographic abnormalities.[4,8] In patients with CF in particular, ABPA often manifests with hemoptysis and may be complicated by pneumothorax.[4]

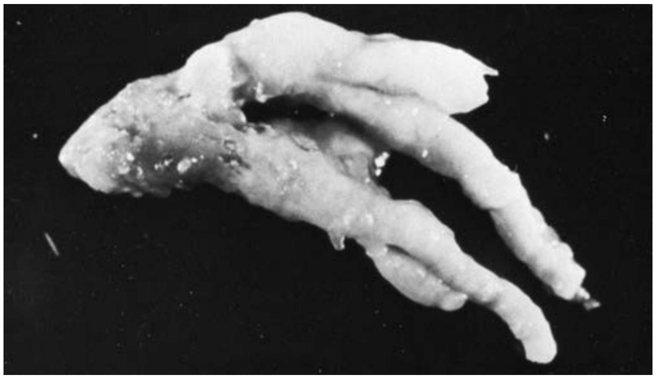

Figure 132-1 Mucus plug expectorated by a patient with ABPA. Of note is the tapering, cylindrical shape with branching characteristic of the parent bronchi. *(Reproduced with permission from Dr. Frederic Askin, Chapel Hill, NC.)*

Radiographic Findings The radiographic features of ABPA have an essential role in diagnosis, as they may distinguish ABPA from simple, chronic asthma. Pulmonary infiltrates in cases of ABPA are initially transient, but they ultimately progress to permanent radiographic changes.[4,8] In many instances, the "ring sign" indicative of bronchial wall thickening, "parallel" shadows or "tram lines" suggestive of bronchiectasis, and branching "finger-in-glove" opacification of the dilated bronchi because of mucoid impaction are seen on regular chest radiographs of patients with ABPA (Fig. 132-3).[4,8] The presence of proximal bronchiectasis (Figs. 132-3 and 132-4), which is characterized by normal filling of bronchi distal to the saccular bronchial lesion, is considered a hallmark for the diagnosis of ABPA.[4] ABPA lesions are either focal or bilateral and tend to occur more frequently in the upper lobes. Late radiographic findings in patients with ABPA include cavitation, local emphysema, contracted upper lobes, and honeycomb fibrosis.

Chest computed tomography (CT) has been a significant aid in diagnosing ABPA because it is more sensitive than regular chest radiography; however, there are no pathognomonic CT findings for this entity.[4,8] Besides central bronchiectasis, CT findings highly suggestive of ABPA include the presence of varicose or cystic bronchiectasis of segmental and subsegmental bronchi (90% in ABPA vs. 30% in simple asthma), mucoid impaction of the segmental and subsegmental airway (67% in ABPA vs. 4% in simple asthma), and small airway abnormalities such as centrilobular nodules and tree-in-bud opacities (93% in ABPA vs. 28% in simple asthma).[4,8] In patients with CF especially, CT diagnosis of ABPA is particularly challenging, as there is a significant overlap in the radiographic features of both entities.[4] In fact, the presence of high-attenuation mucus plugs because of dystrophic calcification is the only CT finding that favors the diagnosis of ABPA in patients with CF.

Diagnosis The "classic" patient with ABPA fulfills the criteria listed in Table 132-3. It has been suggested that the minimal essential criteria for the diagnosis of ABPA include the presence of (a) asthma, (b) immediate cutaneous reactivity to *Aspergillus* antigens, (c) elevated total serum IgE levels (>1000 U/mL), (d) elevated serum IgE and

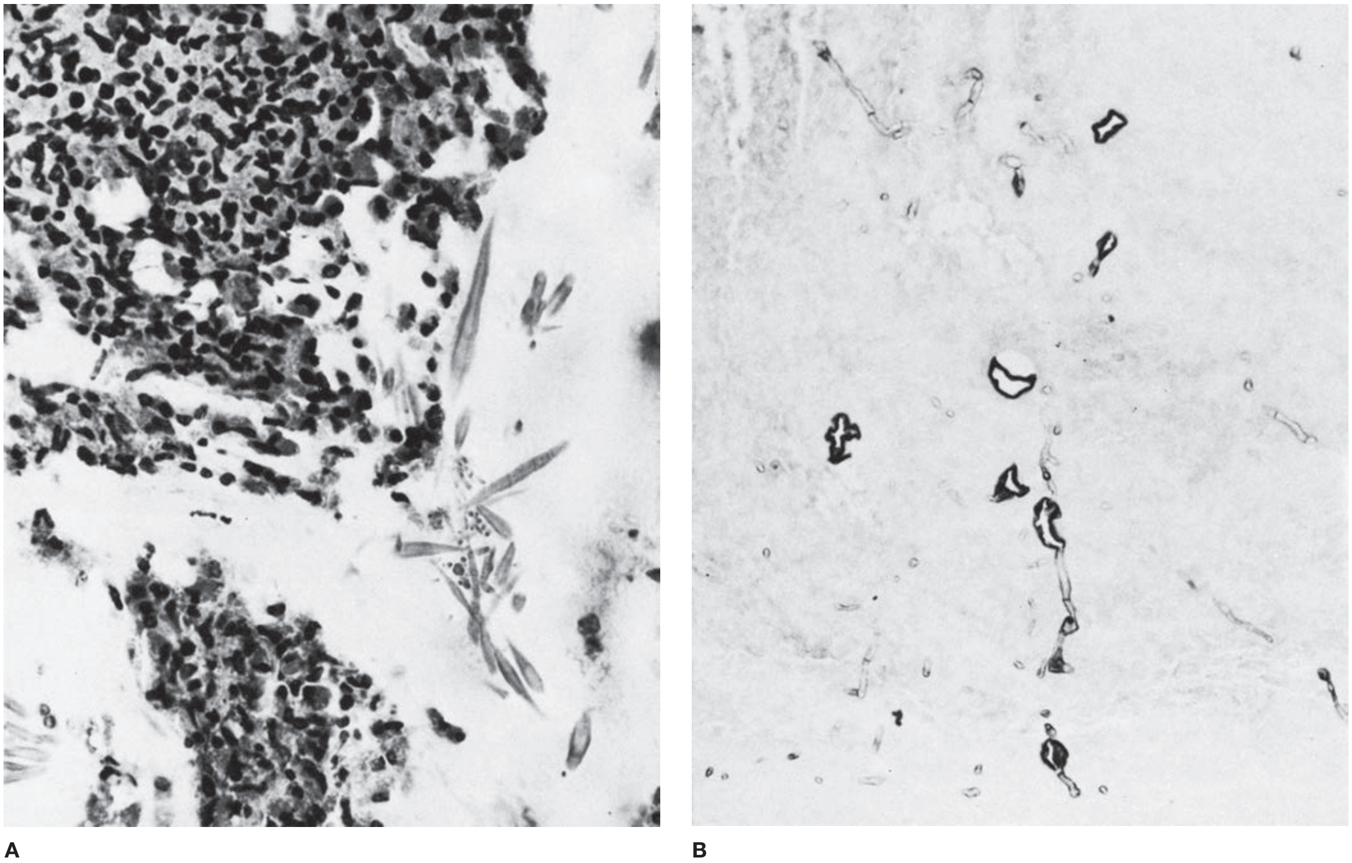
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Figure 132-2 High-magnification photomicrograph of inspissated mucus in mucoid impaction of the bronchus. **A.** Groups of Charcot–Leyden crystals adjacent to clusters of necrotic eosinophils. H&E stain, ×520. **B.** *Aspergillus* hyphae. Of note is the transition from regular, thin septate hyphae to dilated, often folded degenerating forms. H&E stain, ×354. *(Reproduced with permission from Drs. S. Albelda and G.H. Talbot.)*

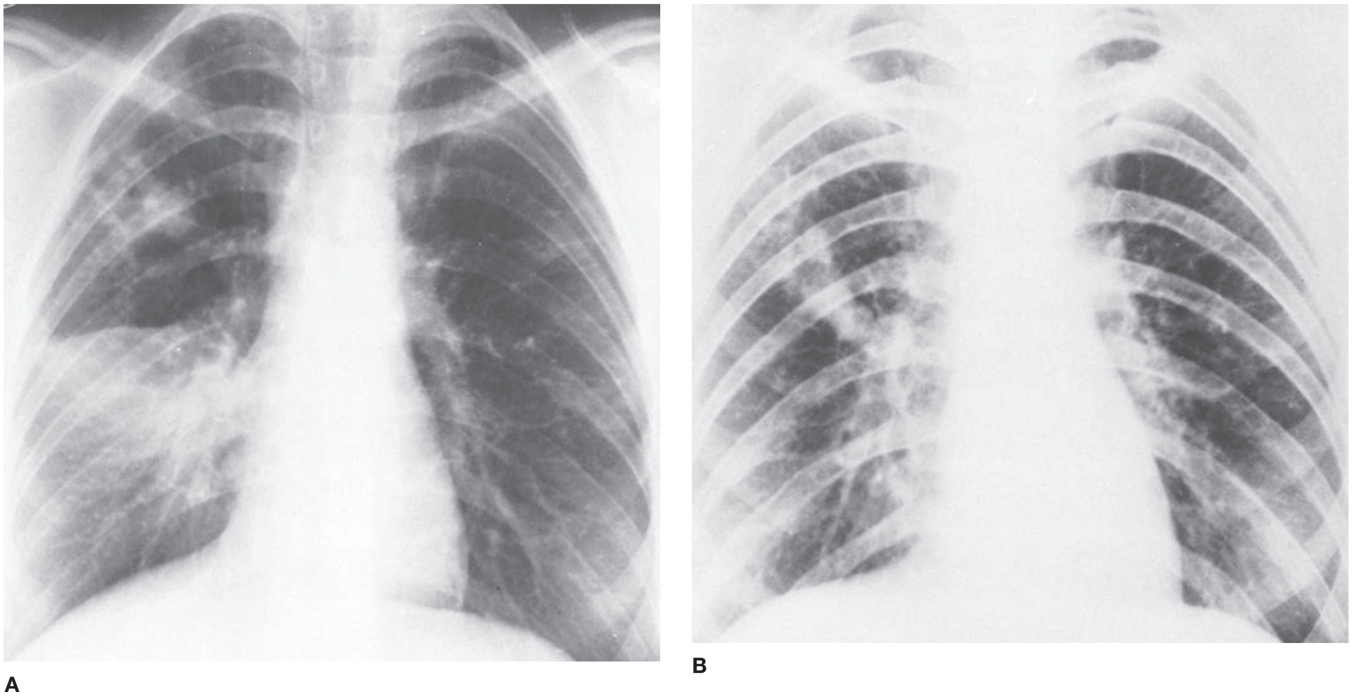
A B

Figure 132-3 A 23-year-old woman with documented ABPA. **A.** Chest radiograph showing mucoid impaction in the right upper lobe and alveolar consolidation in the right middle lobe. **B.** Eight months later, the alveolar consolidation has resolved, and the appearance of the mucoid impaction in the right upper lobe has changed.

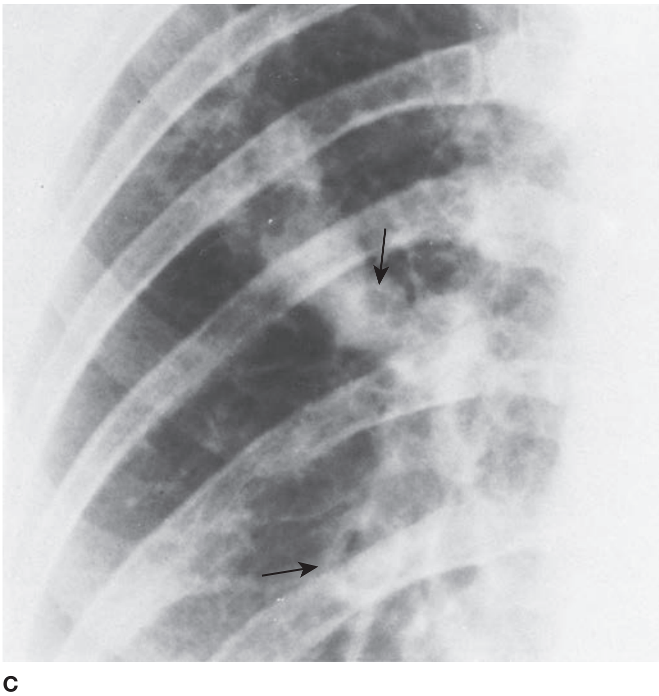

Figure 132-3 *(Continued)* **C.** Close-up of the right lung in **B** showing the "gloved finger" appearance of mucoid impaction as well as ring shadows *(arrows)* characteristic of bronchiectasis. *(Reproduced with permission from Drs. S. Albelda and G.H. Talbot.)*

TABLE 132-3 Criteria for the Diagnosis of Allergic Bronchopulmonary Aspergillosis (ABPA)

Primary
- Episodic bronchial obstruction (asthma)
- Peripheral blood eosinophilia (>1000/mm^3)
- Immediate-type skin reactivity to *Aspergillus* antigens[a]
- Precipitating serum antibodies (precipitins) against *Aspergillus* antigens[a]
- Elevated serum IgE concentrations (>1000 ng/mL)[a]
- Elevated serum IgE and/or IgG antibodies specific to *A. fumigatus*[a]
- History of pulmonary infiltrates (transient or fixed) on chest radiographs or CT scans
- Central bronchiectasis on chest CT scans

Secondary
- *A. fumigatus* in sputum (by repeated culture or microscopic examination)
- History of expectoration of brown plugs or flecks
- Arthus reactivity (late skin reactivity) to *Aspergillus* antigen

[a] *Test must be positive for serologic diagnosis in asymptomatic patients.*

Reproduced with permission from Rosenberg M, Patterson R, Mintzer R, et al. Clinical and immunologic criteria for the diagnosis of allergic bronchopulmonary aspergillosis. Ann Intern Med. 1977;86(4):405–414.

IgG levels to *A. fumigatus,* and (e) central bronchiectasis.[4,8] However, asymptomatic pulmonary involvement occurs in patients with ABPA and may lead to diagnostic uncertainty, delayed diagnosis, and irrevocable structural lung damage. Furthermore, corticosteroid-based therapy for asthma may mask the signs of ABPA, leading to a progressive decline in pulmonary function. Because the above criteria may not apply in such cases, ISHAM proposed updated criteria for diagnosis of ABPA, which have been recently validated and shown to be more sensitive for diagnosis of ABPA.[4,8] The updated criteria define asthma or cystic fibrosis as predisposing conditions and require two obligatory criteria: (1) immediate cutaneous hypersensitivity to *Aspergillus* antigen or elevated IgE levels against *A. fumigatus*, and (2) elevated total IgE levels, and the presence of at least two out of three minor criteria, for ABPA diagnosis: (1) presence of precipitating or IgG antibodies to *A. fumigatus*, (2) radiographic features in the lungs consistent with ABPA, and (3) peripheral blood eosinophilia. In addition, the diagnostic criteria for ABPA in patients with CF were recently modified because of the overlapping features between these entities. The new criteria consist of (a) clinical and/or pulmonary function deterioration from baseline status, (b) positive immediate cutaneous reaction to *A. fumigatus* antigens or elevated IgE *A. fumigatus* antibody serum level, (c) elevated serum total IgE level >1000 U/mL, (d) elevated serum IgG *A. fumigatus* antibody level or positive *A. fumigatus* precipitins, and (e) abnormal chest imaging findings or a change in baseline abnormalities.[4]

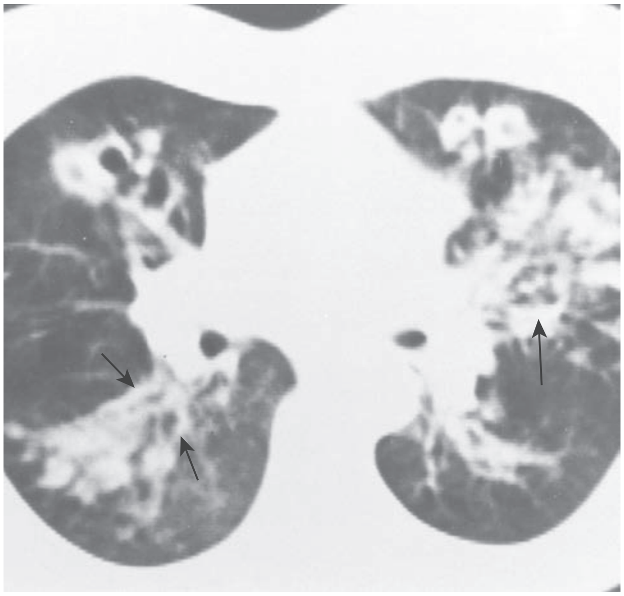

Figure 132-4 Proximal saccular bronchiectasis characteristic of ABPA. The CT scan reveals multiple rounded, dilated bronchi *(small arrows)*. Of note is the air–fluid level *(large arrow)*. *(Reproduced with permission from Drs. S. Albelda and G.H. Talbot.)*

Important clinical clues that should alert clinicians to the possibility of ABPA include refractory asthma or asthma with any of the following features: bronchiectasis, radiographic infiltrates, prominent eosinophilia, and expectorated brown plugs that may contain eosinophils or hyphae (Fig. 132-2).[4] In addition, in patients with CF, prominent wheezing is considered to be suggestive of ABPA. Rarely, ABPA may be caused by non-*fumigatus* aspergilli or other fungi; in such cases, the serological tests will be negative.

Because no single clinical or immunologic feature is diagnostic for ABPA, this disease is underdiagnosed. In the past, serologic diagnosis of ABPA was based on *Aspergillus* crude extracts, a laborious process with low specificity and reproducibility. However, the use of standardized recombinant *A. fumigatus* allergens substantially improved the specificity and sensitivity of diagnosis of *A. fumigatus*–related diseases, including ABPA.[4,8] Several recombinant *A. fumigatus* allergens, including Aspf1, Aspf2, Aspf3, Aspf4, Aspf6, and Aspf16, show high specificity for the detection of sensitization to *A. fumigatus* and for the diagnosis of ABPA and appear to be superior to crude *Aspergillus* allergen extracts.[4] However, because the sensitivity of each recombinant *A. fumigatus* allergen is suboptimal, use of a panel of recombinant allergens is favored to increase the sensitivity of the diagnosis of ABPA. Further standardization and development of commercially available immunoassays containing a combination of these allergens holds promise for improving the diagnosis of ABPA.

Because patients with CF are at high risk for ABPA, initiation of annual screening in patients with >6 years of age for ABPA with monitoring of serum total IgE levels has been recommended with further diagnostic workup for ABPA in cases with IgE levels >500 U/mL.[4] Likewise, because treatment with corticosteroids has a significant impact on disease progression, screening CT has been advocated for asthmatics with a skin-prick hypersensitivity test positive for *A. fumigatus* extracts to identify ABPA at an early stage.[4,8]

Histopathology Because the diagnosis of ABPA is based on clinical and laboratory criteria, use of lung biopsy to confirm the diagnosis is usually not required. The presentations of the hypersensitivity syndrome associated with fungi are discussed in detail in Chapter 46. Some of the histopathologic presentations associated with ABPA overlap those of invasive *Aspergillus* infection. Thus, eosinophilic infiltrates may be present in patients with a chronic invasive *Aspergillus* infection as well as in those with other allergic lung entities, such as Löffler syndrome, tropical eosinophilic pneumonia, and chronic eosinophilic pneumonia (Chapter 71).[4,8] Mucoid impaction associated with ABPA or other fungi may predispose patients to bacterial superinfection (Figs. 133-1 and 133-2). Necrotizing granulomas in association with the presence of *Aspergillus* spp. in asthmatic patients may be observed and is considered part of the ABPA syndrome.[4,8] The histopathologic distinction between ABPA, with fungal elements restricted to the airways, and semi-invasive or fully IA may be obscured by tissue necrosis or poor granuloma formation. These presentations are discussed further below.

Treatment ABPA may progress through five stages based on clinical, serologic, and radiographic findings, which are summarized in Table 132-4.[4,8] Importantly, the first four stages are potentially reversible without long-term sequelae; only the last stage, which is characterized by fibrosis and bronchiectasis, is irreversible. The goals of therapy for ABPA are to treat acute exacerbations of disease and prevent the development of fibrosis and bronchiectasis. Therefore, early diagnosis of ABPA before permanent lung damage occurs is critical. Therapeutic modalities for ABPA include oral corticosteroids, metered-dose inhaler medications, and systemic antifungal agents.[4,8] Omalizumab, a humanized monoclonal antibody against IgE that is an approved therapy for severe asthma, has been used for refractory cases of ABPA.[4,8]

Use of oral corticosteroids remains the cornerstone of the treatment of ABPA.[4,8] These agents suppress the inflammatory response provoked by *Aspergillus* infection rather than eradicate the fungus. Recent studies validate the use of a low-dose steroid regiment in management of ABPA. Recommended corticosteroid doses for acute exacerbations of ABPA are 0.5 to 1.0 mg/kg of prednisone equivalent daily for 1 to 2 weeks, followed by 0.5 mg/kg per every other day for 6 to 12 weeks. The physician should then attempt to taper the patient's corticosteroid dosage. However, some patients cannot be successfully weaned off corticosteroids and may require a daily maintenance dose of at least 7.5 mg.

Increasingly, use of itraconazole, an azole antifungal with activity against *Aspergillus* spp., has been employed as adjunctive fungal antigen–reducing therapy for ABPA, especially in patients with frequent relapses or corticosteroid dependence.[4,8] A randomized controlled study reported that oral administration of itraconazole (200 mg twice daily) was beneficial in terms of significant improvement of symptoms, pulmonary function, chest radiographic findings, and serum IgE levels in asthmatic patients with ABPA; uncontrolled studies suggested a similar benefit in patients with CF and ABPA.[4,8] However, use of itraconazole requires determination of drug levels to ensure adequate absorption and poses significant issues with long-term tolerability and drug–drug interactions.[5,6] Another important issue of prolonged itraconazole use is the emergence of azole-resistant *Aspergillus* isolates. In addition, itraconazole has a 40% failure rate in ABPA treatment.[6] The newer triazole voriconazole has improved fungicidal activity against *Aspergillus* spp. and better bioavailability when compared with itraconazole.[5,6] A recent retrospective study in 20 ABPA patients who failed or were intolerant to itraconazole and received either voriconazole or posaconazole found sustained clinical and immunologic responses and reduced corticosteroid requirements at 12 months in over 75% of treated patients.[5–7] However, high relapse rates (up to 57%) have been reported following discontinuation of azole treatment in patients with ABPA, and there are concerns for the development of secondary resistance in *Aspergillus* following prolonged courses of antifungal therapy.

Use of inhaled corticosteroids may help control the symptoms of asthma but does not prevent episodes of eosinophilic infiltration and mucus impaction and is generally thought to have no influence on progressive lung damage.[4,8] Inhaled bronchodilators such as β-agonists, anticholinergics, and leukotriene antagonists may be

TABLE 132-4 **Staging System for Allergic Bronchopulmonary Aspergillosis (ABPA)**

Stage	Symptoms	Radiographic Features	Laboratory Features	Management
I. Acute	Fever, productive cough, wheezing	Pulmonary infiltrates, mucoid impaction	Blood eosinophilia, elevated serum IgE level, positive skin test	Corticosteroids to achieve remission
II. Remission	Asymptomatic	Normal	Decrease in IgE and blood eosinophilia	Careful follow-up
III. Exacerbation	All or some of acute-stage symptoms	All or some of acute-stage findings	At least a doubling of IgE in asymptomatic patients and an increase in IgE in symptomatic patients	Retreat with steroids to induce remission
IV. Corticosteroid dependent	Symptomatic steroid-requiring asthma	Variable	Usually continued elevation of IgE	Long-term steroids to control asthmatic symptoms and keep IgE levels at baseline
V. Fibrotic	Severe dyspnea, fibrotic lung disease, as well as bronchospasm	Pulmonary fibrosis	Restrictive plus reversible and irreversible obstructive function tests; may have continued increased IgE	Long-term corticosteroid use

Data from Mendelson EB, Fisher MR, Mintzer RA, et al. Roentgenographic and clinical staging of allergic bronchopulmonary aspergillosis. Chest. 1985;87(3):334–339 and Patterson R, Greenberger PA, Radin RC, et al. Allergic bronchopulmonary aspergillosis: staging as an aid to management. Ann Intern Med. 1982;96(3):286–291.

used to treat asthma-related symptoms.[4,8] Inhaled antifungal agents such as nystatin and amphotericin B deoxycholate (AMB-D) may offer temporary suppression of colonization, but penetration of these agents into plugged bronchi is limited and recolonization rapidly occurs once therapy ends. When combined with oral steroid treatment, nebulized AMB has been an effective option to reduce ABPA exacerbations. Meticulous bronchial toilet is important for clearance of *A. fumigatus* from the airway. Thus, physical therapy with postural drainage is an important adjunctive treatment. Increased hydration, use of expectorants, and, in selected patients, bronchial lavage may aid in viscid mucus clearance. Avoidance of environmental reservoirs of *Aspergillus* spp. such as compost heaps, grain silos, and decayed organic matter may help prevent exacerbation of ABPA. In patients with CF ABPA, differentiating between a bacterial exacerbation of CF and an ABPA flare is important, because initiation of corticosteroids may have detrimental effects in patients with bacterial infection; a serologic assessment is essential as part of this evaluation.[4]

Immunotherapy with the injection of conventional allergens has not been shown to be of value for ABPA.[4,8] However, newer immunomodulatory approaches, including immune modulation toward a Th1 response by using *A. fumigatus* synthetic peptides, DNA-based vaccines, and immunostimulatory molecules such as cytosine polyguanine oligonucleotides, are being explored in animal models with promising results. Recently, a placebo-controlled study of omalizumab in a small group of patients with ABPA was associated with a significant reduction in disease exacerbations and improvement in immunologic parameters.[4]

Monitoring of treatment efficacy and toxicity is imperative. Long-term follow-up of patients with ABPA has shown that increasing serum levels of IgE is often a harbinger of a clinical flare of the disease and that the levels of IgE decline correlate with a clinical response to corticosteroids.[4,8] Thus, a prudent course of action is to determine baseline serum IgE levels when ABPA has been controlled by corticosteroid-based therapy and then monitor serum IgE levels regularly (every 1–2 months). Total serum IgE levels usually should decrease by at least one-third within 6 weeks from the initiation of corticosteroid-based treatment; infiltrates should be resolved after 1 to 2 months, and the results of pulmonary function tests should improve. Although serum IgE levels seldom return to normal, reinstitution of corticosteroids should be considered even in asymptomatic patients if the serum IgE level is double that of the baseline value.[4,8] In patients with symptomatic ABPA, chest radiographs should be obtained every 3 months during the first year of follow-up and yearly thereafter; pulmonary function tests should also be performed yearly.[4,8] However, no one has identified certain prognostic indicators for progression or regression of ABPA, and whether “pre-emptive” treatment of asymptomatic flares alters the natural history of the disease remains controversial.

Bronchocentric Granulomatosis

Bronchocentric granulomatosis is a rare hypersensitivity syndrome that is characterized histologically by replacement of bronchial mucosa with necrotizing granulomatous tissue.[8] Also, eosinophilic infiltration of bronchioles and fibrosis is prominent, whereas there is no evidence of *Aspergillus* invasion. *Aspergillus* hyphae have been demonstrated within the lesions in approximately half of the cases of bronchocentric granulomatosis. This syndrome is associated with asthma in half of the patients described and likely represents a severe exuberant focal manifestation of ABPA rather than the more generalized pulmonary pathology evident in patients with ABPA.[8] Patients typically present with chronic symptoms, such as malaise, cough, low-grade fever, dyspnea, dull chest pain, and hemoptysis associated with a focal lesion on chest radiographs, often in an upper lobe. Occasionally, radiographic findings of multiple nodular or mass-like lesions simulate metastatic carcinoma.[8] Diagnosis of bronchocentric granulomatosis is made based on biopsy or often retrospectively after removal of the lesion, which is curative. Some patients, especially those with multifocal lesions, may need corticosteroid-based therapy for ABPA.[8]

Extrinsic Allergic Alveolitis

Heavy or repeated exposure to *Aspergillus* conidia and mycelia may result in a hypersensitivity reaction affecting the alveoli in nonatopic individuals known as *extrinsic allergic alveolitis* (Chapter 58).[8] Malt workers, distillers, brewers, and others exposed to moldy straw or grain have suffered attacks consisting of cough, dyspnea, fever, chills, myalgia, and malaise 4 to 8 h after exposure to *Aspergillus* antigens.[8] Repeated exposures may lead to malt worker’s lung or farmer’s lung or to the development of granulomatous disease or interstitial fibrosis. The immunopathogenesis of extrinsic allergic alveolitis involves cell-mediated immunity (type IV response) and immune complex deposition (type III response) and likely involves an intricate interaction between these immune mechanisms.[8]

Radiographic changes in the acute syndrome include diffuse alveolar–interstitial infiltrates that may resolve with the removal of the inciting antigen. Patients with chronic extrinsic allergic alveolitis may have fine reticulonodular interstitial infiltrates that may progress to pulmonary fibrosis with honeycombing.[8] Serum IgG antibodies (precipitins) against *Aspergillus* antigens are present in patients with extrinsic allergic alveolitis; however, the serum IgE level is typically normal. Skin tests usually demonstrate an Arthus reaction at 4 to 8 h and occasionally may be preceded by an immediate wheal and flare reaction and followed by a delayed reaction (36–48 h afterward). Removal or avoidance of the source of antigen exposure is crucial in the management of extrinsic allergic alveolitis, as spontaneous recovery often ensues once exposure has ended.[8] Administration of corticosteroids is helpful in aiding the resolution of acute symptoms and reduces the likelihood of structural damage. However, corticosteroids are not helpful once fibrosis has developed.

Aspergilloma

Saprophytic colonization of a parenchymal lung cavity by *Aspergillus* is referred to as *aspergilloma*, *mycetoma*, or a *fungus ball.*[8] Spontaneous shrinkage or disappearance of aspergilloma has been reported in 7% to 10% of cases and is often associated with bacterial superinfection of the cavity.[8] Aspergillomas only rarely increase in size. Most aspergillomas are caused by *A. fumigates*, but some, especially in patients with diabetes mellitus, are caused by *A. niger*, in which case oxalic acid crystals may be seen in the sputum.[8] Rare cases of extrapulmonary sites of aspergillomas involving the skin, brain, retroperitoneal area, and sinuses have been described. Recently, aspergilloma has been classified as a form of chronic pulmonary aspergillosis (CPA).

Pathophysiology The pathogenesis of aspergilloma usually involves colonization and proliferation of the fungus in a pre-existing pulmonary cavity (secondary aspergilloma). The cause of a pre-existing cavity is most commonly prior cavitary tuberculosis; aspergilloma has been reported in 11% to 17% of patients with posttuberculosis cavities.[8] In fact, 20% of patients who recover from cavitary tuberculosis develop aspergillomas within the next 3 years. Of interest, in developing countries tuberculosis is the predisposing factor for over 90% of cases of aspergilloma. However, an aspergilloma may complicate a wide spectrum of cavitating pulmonary diseases, such as sarcoidosis, histoplasmosis, blastomycosis, AIDS (especially in cases of atypical *Pneumocystis jiroveci* pneumonia), pneumonia and/or lung abscess, pulmonary or bronchial cysts, bronchiectasis, pulmonary fibrosis, asbestosis, adenocarcinoma, ankylosing spondylitis, rheumatoid nodules, cyanotic heart disease, and pulmonary infarction.[8]

Primary aspergilloma, which arises within the bronchial tree with the proliferation of *Aspergillus* leading to a pulmonary cavity, is far less common. The clinical conditions leading to the initiation of a cavitary process and formation of a fungus ball include IPA, chronic necrotizing pulmonary aspergillosis (CNPA), and ABPA. IPA may lead to primary aspergilloma during bone marrow recovery, as the host is able to mount an inflammatory response and ward off the fungus. Pneumothorax may be a severe complication of pulmonary mycetoma that is reported as a rare occurrence in patients with hematologic malignancies.[8] ABPA may cause bronchiectasis in the chronic phase of the disease and result in aspergilloma secondary to growth of a fungus distal to a plugged bronchus.[4,8] In fact, aspergillomas have been found in 7% of patients with ABPA in one study. Thus, aspergilloma may provide a stimulus for the perpetuation of ABPA.

Typical biofilm structures have been observed in aspergillomas from patients and in a murine model of IPA. Defective extracellular matrix penetration by most antifungal agents makes them significantly less effective when *A. fumigatus* is grown under biofilm versus planktonic conditions. Thus, chronic exposure and suboptimal azole concentrations in fungal biofilms could explain the emergence of azole-resistant *A. fumigatus* isolates reported in these patients.[2,3,8]

Clinical Features/Diagnosis Hemoptysis is the typical manifestation of aspergilloma, as it is seen in 50% to 90% of patients.[8] Hemoptysis is typically infrequent and mild but can be occasionally massive or even fatal. The diagnosis is usually made based on clinical and chest radiographic features coupled with serologic evidence of precipitating antibodies to *Aspergillus* spp.

Chest radiographs reveal a solid round mass within a cavity (3–5 cm diameter) partially surrounded by a radiolucent crescent (Monod's sign) (Fig. 132-5).[8] Movement of the fungus ball within

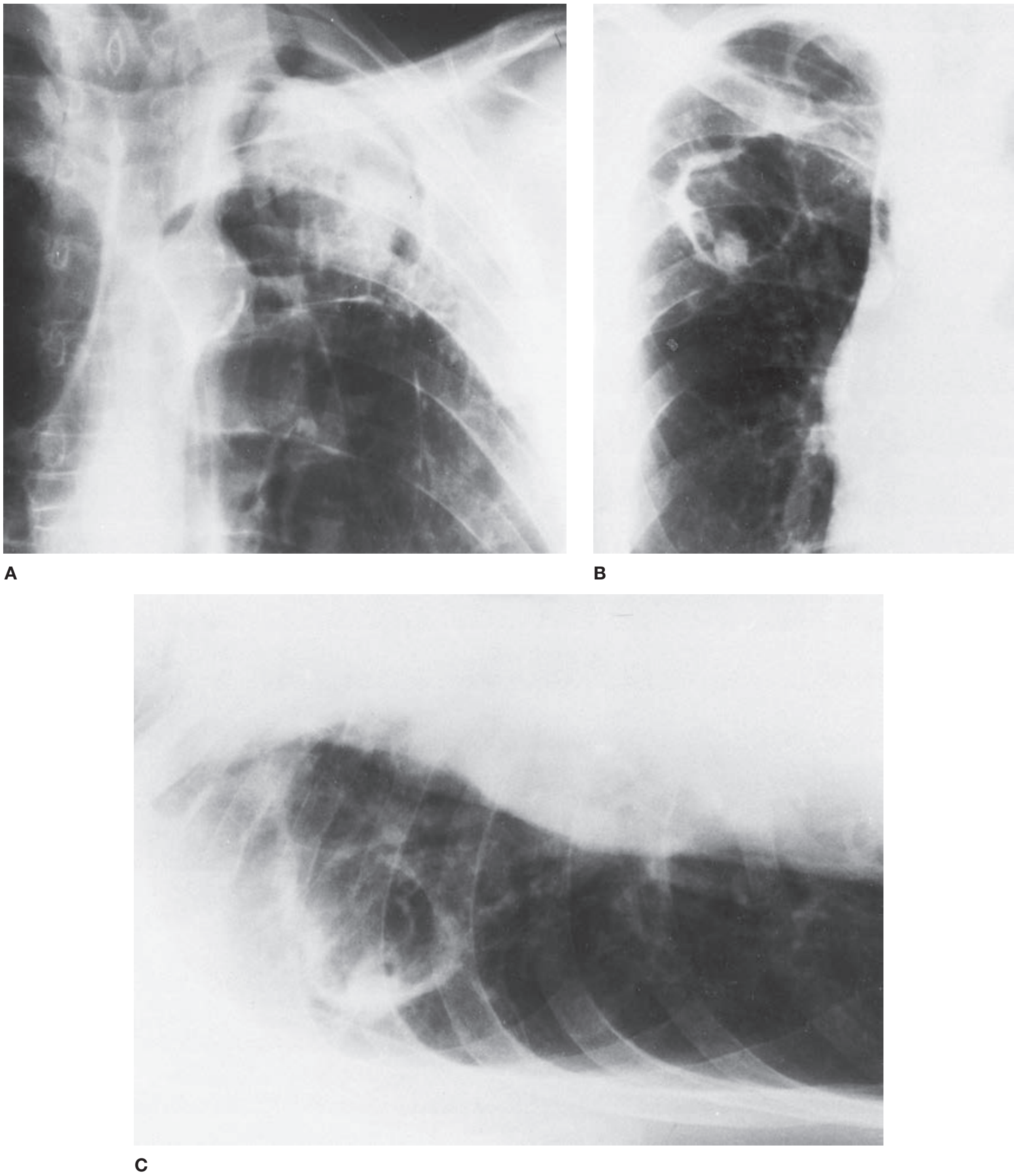

Figure 132-5 Radiographic appearances of pulmonary aspergillomas. **A.** A 51-year-old man with a history of tuberculosis showing the classic crescent-shaped patch of air (Monod's sign) as well as marked pleural thickening. **B.** A 49-year-old man with ankylosing spondylitis in whom an aspergilloma developed inside a thin-walled cavity. **C.** Decubitus film of the patient in **B** showing a fungus ball that moved when the patient changed position. *(Reproduced with permission from Drs. S. Albelda and G.H. Talbot.)*

the cavity may be appreciated when comparing upright and decubitus images. A solitary lesion in the upper lung fields is the most common radiographic feature of aspergilloma, as pre-existing tuberculosis cavities is the most common predisposing condition. However, aspergillomas can be bilateral and multiple. In many cases, chest CT may be helpful in further delineating the radiographic features of an aspergilloma that are not apparent on chest radiographs. On CT scans, globules of gas are often seen within the hyphal mass. CT angiography may also provide useful information for patients with hemoptysis by identifying hypertrophic bronchial arteries that often supply the cystic wall of aspergillomas.[4,8]

Although sputum cultures are positive for *Aspergillus* in more than half of all patients with aspergilloma, culture is not a sensitive and specific diagnostic marker.[8] Precipitating antibodies to *Aspergillus* antigens are present in the sera of more than 95% of patients with aspergilloma; however, some patients receiving corticosteroids may be seronegative.[8] Eosinophilia, IgE, and skin-test reactivity may be seen in individuals who are allergic to the fungus, but these are not consistent findings. Therefore, a positive precipitin reaction for *Aspergillus* is particularly helpful in establishing the diagnosis of aspergilloma. Clinical judgment and a low threshold for performing serologic diagnostic workup, BAL, or a lung biopsy in atypical cases are required.

Predictors of poor prognosis for aspergilloma include a progressive increase in the size and/or number of aspergillomas, severe underlying lung disease with a poor lung reserve, immunosuppressive therapy, AIDS, sarcoidosis, a rising *Aspergillus*-specific IgG titer, and repetitive episodes of severe hemoptysis.[4,8]

Treatment There is no consensus on the treatment of aspergilloma because of a lack of controlled studies. Because life-threatening hemoptysis occurs only in a minority of patients, subjecting all patients with aspergilloma to surgical therapy, which is often associated with significant morbidity and mortality, seems to be inappropriate.[8] Management options for aspergilloma currently include systemic or local administration of antifungal agents, surgical resection, and conservative management with careful follow-up without specific medical or surgical intervention.[8] Often, the best course of action for asymptomatic patients with aspergilloma is carefully repeated clinical evaluation with periodic chest radiographs without surgical intervention. Therapeutic considerations must include the individual patient's health status with attention to the potential risks of each treatment.

For patients who are unfit for surgical resection, an alternative approach is cavernostomy, which is performed under local anesthesia; however, cavernostomy is also associated with mortality and mediocre results.[6,8] This procedure should be considered as a last resort.

Intracavitary instillation of an antifungal agent is a promising alternative treatment in patients with severe pulmonary dysfunction who are poor candidates for surgery. CT-guided percutaneous instillation of AMB-D has been shown to be effective for aspergilloma in several cases of massive hemoptysis, with resolution of hemoptysis within 5 days.[8] Endobronchial instillation of ketoconazole via fiberoptic bronchoscopy also has been successful.[8]

Bronchial arterial embolization (BAE) has been extensively used in the management of hemoptysis in patients with aspergilloma.[4,8] Hence, BAE seems to be appropriate only as a "bridge" procedure in patients with massive hemoptysis until surgical resection of the aspergilloma can be performed. Also, radiation therapy has been shown to be effective for aspergilloma, even in patients with massive hemoptysis.[4,8] This modality has been recommended for cases of recurrence of life-threatening hemoptysis after BAE.

Itraconazole is an orally administered antifungal agent with activity against *A. fumigatus* and high tissue penetration into the lung. The use of itraconazole for aspergilloma has been reported in several noncontrolled studies.[4,8] Data from these studies showed that the use of itraconazole capsules at doses ranging from 200 to 400 mg/d for 6 to 18 months resulted in radiographic and symptomatic improvement in almost two-thirds of the patients and may have a place for the treatment of aspergilloma.[8] Recurrence of aspergilloma often follows discontinuation of itraconazole treatment, whereas acquisition of secondary resistance of *A. fumigatus* isolates to itraconazole has been described in patients with aspergilloma following prolonged treatment. Voriconazole has been successfully used to treat pulmonary aspergilloma caused by itraconazole-resistant *A. fumigatus* isolates, although cases of voriconazole failure in patients with aspergillomas have also been reported. There is evidence of development of secondary resistance to voriconazole during long-term treatment of patients with aspergillomas.

Invasive Bronchial Aspergillosis

The term *invasive bronchial aspergillosis* (IBA) refers to infection involving the large airways. Further subclassification of IBA based on the bronchoscopic appearance has been proposed, including tracheobronchitis, pseudomembranous tracheobronchitis, and ulcerative tracheobronchitis. In fact, these entities represent a continuous spectrum of this infection.[7,8] An alternative, more functional classification based on the depth of tissue invasion by *Aspergillus* includes (a) superficial infiltration type; (b) full-layer involvement type; (c) occlusion type (airway occlusion ≥50% of the original diameter of involved bronchi); and (d) mixed type. The potential impact of this classification system on the management of IBA has not been validated.

Aspergillus tracheobronchitis is the least invasive form of IBA and is characterized by the presence of a superficial tracheobronchial inflammation, intact mucosa with no evidence of ulcers, and pseudomembranes or other abnormalities; *Aspergillus* spp. are identified in mucus exudates.[7,8] In contrast, pseudomembranous tracheobronchitis is characterized by significant necrosis of bronchial epithelium and formation of pseudomembranous plaques, which are white, gray, or black in color. These lesions may progress and result in extensive invasion of the large airways; however, in the majority of patients, the depth of invasion does not extend beyond the bronchial cartilage.[7,8] Finally, ulcerative tracheobronchitis is the most aggressive form of IBA and manifests with endobronchial plaques, nodules, or areas of ulceration and necrosis; in addition, the infection may extend to the adjacent pulmonary parenchyma and pulmonary vasculature.[7,8] Late sequelae of ulcerative tracheobronchitis include the formation of excessive granulomatous tissue with resulting bronchial stenosis.

The pseudomembranous form of IBA is typically seen in lung transplant recipients, who accounted for almost 40% of published cases.[6,8] In fact, IBA is the most common infection within 3 months following lung transplantation, whereas IPA tends to occur much later in this patient population. Occasionally, pseudomembranous tracheobronchitis is found in various clinical settings including HSCT, hematologic malignancies, metastatic renal cell carcinoma, COPD, AIDS, systemic lupus erythematosus, metabolic abnormalities including DM, and even in immunocompetent individuals.[1,6] Influenza-associated aspergillosis typically manifests as IBA.[1] Patients may be initially asymptomatic or have symptoms attributed to the underlying illness with negative chest radiographs. However, as the infection progresses, symptoms become more pronounced, including characteristic stridor, resulting in respiratory failure and ultimately death. Persistent stridor in neutropenic or severely immunocompromised patients should raise suspicion for IBA; however this symptom occurs in less than one-quarter of all cases. Importantly, *Aspergillus* galactomannan antigen has limited value in IBA diagnosis as it is positive in only 60% of the cases.[5,6]

The ulcerative form of IBA occurs almost exclusively at the site of bronchial anastomosis in lung transplant recipients.[6] Bronchoscopically, the appearance is that of severe tracheobronchitis with multiple ulcers at the site of anastomosis. The symptoms are similar to those of pseudomembranous IBA. Complications include acute IPA, severe bronchial stenosis, anastomotic dehiscence, and bronchial necrosis with bronchoarterial anastomotic fistula.[6] Rarely, ulcerative IBA develops in patients with AIDS or solid tumors.[6] Diagnosis of all forms of IBA requires a high index of suspicion and is established only by bronchoscopic examination.

Bronchial stump aspergillosis is an unusual complication of lung resection.[6,7] The period from pneumonectomy to the onset of infection usually ranges from 6 to 12 months, although it was noted to occur after 3 years in one case. Patients may present with a productive cough and hemoptysis, sputum that may be putrid, and occasionally, expectoration of fungal material or suture thread.[6,7] Chest radiographs are usually unchanged when compared with those taken at baseline. The cause is secondary *Aspergillus* infection of silk suture material used to close the bronchus after pulmonary resection. Local inflammation, compromised tissue viability, and the use of silk sutures favor the establishment of *Aspergillus* infection. Substitution of nylon monofilament for silk sutures at surgery has significantly reduced this infectious complication.[6,7]

All of the forms of IBA, including bronchial stump anastomosis, require prompt treatment with systemic antifungals for IA (discussed in detail below). Data from controlled studies of the treatment of IBA are lacking, however. A common, although unproven practice is to combine systemic antifungal therapy, such as intravenous AMB-D or voriconazole, with aerosolized AMB-D.[6,7] Notably, most reported failures occurred following cessation of the treatment. Finally, surgical resection and stent placement may be necessary in conjunction with antifungal therapy if dehiscence of the anastomosis occurs because of tracheobronchial aspergillosis.[5–7]

Chronic Pulmonary Aspergillosis

Chronic forms of *Aspergillus* infection of the lung have been increasingly recognized.[8] CPA occurs in patients with chronic cavitary lung disease and is characterized by an indolent clinical course evolving over months to years, constitutional symptoms, serum IgG to *A. fumigatus*, elevated acute phase markers of inflammation, and an underlying immune deregulation that remain largely uncharacterized. Locally invasive (semi-invasive) *Aspergillus* infection may be evident histopathologically. However, both angioinvasion and dissemination are absent. A variety of terms have been used for CPA, including pulmonary aspergillosis with cavitation, complex aspergilloma, chronic granulomatous aspergillosis, semi-invasive pulmonary aspergillosis, and CNPA.[8]

A previously proposed subclassification of CPA based on clinical and radiographic findings included CNPA, chronic cavitary pulmonary aspergillosis (CCPA), and chronic fibrotic pulmonary aspergillosis (CFPA).[8] CNPA is a syndrome of slowly progressive cavitary lung disease, chronic respiratory symptoms, and the presence of precipitating antibodies against *Aspergillus*. Some cases of CNPA have invasion of the lung parenchyma by *Aspergillus* spp. However, in most of the described cases, there is no tissue invasion despite the presence of extensive and progressive tissue damage. CCPA refers to cases in which there is formation and expansion of multiple cavities over time, whereas CFPA refers to cases in which cavity formation is followed by a pronounced fibrotic reaction.[8] In addition, it has been recommended that any case with proven hyphal invasion of tissue should be classified as CNPA. In view of the common underlying immunopathogenesis, CPA is the preferable term used for all the aforementioned clinical entities.

Defects in mucociliary clearance, epithelial integrity, and mucosal immunity associated with structural lung disease appear to be critical factors in the pathogenesis of CPA.[8] Prior mycobacterial lung infection, emphysema and/or COPD, bullae, asthma, sarcoidosis, pneumoconiosis, lung cancer, thoracic surgery, upper lobe fibrosis complicating ankylosing spondylitis, marijuana use, and a history of *Legionella* infection have been described as predisposing conditions for CPA. In addition, chronic inflammation and fibrosis as a result of incompletely understood defects in systemic immune response to *Aspergillus* may play a role in the pathogenesis of CPA. Hence, defects in mannose-binding lectins, alterations in SP-D, certain polymorphisms in cytokine-encoding genes such as transforming growth factor β, TNF-α, IFN-γ, and IL-15, and immunometabolic defects due to corticosteroid-based therapy, diabetes mellitus, AIDS, and alcohol abuse, have all been associated with CPA in humans.[8] However, the precise pathophysiologic mechanism of new cavity formation remains uncertain.

CPA tends to affect middle-aged individuals who are relatively immunocompetent and more male than female individuals.[8] CPA has an indolent and progressive course that lasts for years. Chronic productive cough and weight loss with mild hemoptysis, dyspnea, and fatigue are the usual presenting symptoms. Pleural fibrosis and *Aspergillus* empyema appear to complicate some cases of CPA.[8]

Although the diagnosis of CPA may be suspected with a single chest radiograph, sequential chest radiographs are typically required to confirm the progressive nature of CPA lesions. CT is particularly useful in defining the precise pattern and extent of the disease. Typical radiographic findings include the presence of one or more cavities, which may or may not contain fungus balls, often located in the upper lobes.[8] New cavity formation and expansion of preexisting cavities are also characteristic of CPA. Pericavitary infiltrates and adjacent pleural thickening are frequently observed and appear to correlate with the overall disease activity.[8] With appropriate treatment, these radiographic abnormalities may regress, leaving residual thin-walled empty cavities.

The combination of characteristic clinical and radiologic findings and either the presence of *Aspergillus* precipitins or the isolation of *Aspergillus* spp. from respiratory samples is highly indicative of CPA.[8] Although the demonstration of precipitin or IgG antibodies against *Aspergillus* is the cornerstone and a prerequisite for the diagnosis of CPA, these antibodies may be negative in approximately 10% of CPA patients, especially in case of infection with non-*fumigatus Aspergillus* spp.[8] Histopathology demonstrates chronic inflammation and fibrosis, sometimes with granulomatous features with or without visible hyphae. The absence of hyphae does not exclude the diagnosis of CPA because of the paucity of high fungal burden in patients with CPA.

Differentiating CPA from other serious lung conditions that require specific therapy, such as cancer and chronic cavitary mycobacterial and endemic fungal infections, as well as other inflammatory lung conditions, is a major challenge as overlap is not uncommon. In fact, there is a strong association between CPA and atypical mycobacterial infections. In these cases, imaging is not helpful, so biopsy and comprehensive microbiologic studies must be used to exclude the coexistence of CPA with such entities. In addition, CPA differs from simple aspergilloma because of the presence of constitutional symptoms for at least 3 months, the development of persistent pericystic lung nodules or pleural thickening, consolidations or ground-glass opacities, and the development and/or progression of cavities.[8] Finally, one should always consider the possibility of a pyogenic bacterial infection in a cavity that may require drainage and appropriate antibacterial treatment.

CPA requires prolonged treatment with systemic antifungal agents. In the literature, most patients with CPA have received treatment with oral itraconazole, whereas IV AMB-D has been successfully used in refractory cases.[8] In a series of 18 patients, use of itraconazole capsules resulted in improvement or stabilization of disease in 71% of the cases.[8] Use of voriconazole has been associated with favorable responses in small case series with response rates ranging from 30% to 80% and should be considered as another treatment option. Posaconazole has also been successfully used with a 61% response rate in 79 patients with CPA. However, emerging rates of azole resistance in *Aspergillus* isolates recovered from patients with CPA have been reported, although there is controversy on whether in vitro resistance of *A. fumigatus* to azoles correlates with worse clinical outcome. In addition, serious side effects necessitating discontinuation of treatment with azoles occur in up to 27% of patients. Alternative treatment strategies include intravenous use of polyenes or echinocandins. Although the reported response to IV AMB-D (81%) appears to be slightly better than that to itraconazole, administration of AMB-D may require prolonged hospitalization and is associated with considerable toxicity, especially nephrotoxicity.[8] In a recent randomized study, treatment with IV micafungin had comparable (60%) rates of response with IV voriconazole (51%) and significantly fewer adverse effects in patients with CPA and could represent an alternative especially in cases where azole resistance in a concern.[6] Anecdotal reports of improved outcome as a result of adjunctive immunomodulating treatment with IFN-γ have also been reported based on suboptimal IFN-γ responses in a limited dataset of patients with CPA.[8]

Surgery plays a limited role in the treatment of CPA because of the poor overall lung function in many patients. Major postoperative complications, such as respiratory failure, bronchopleural fistulae, pleural extension of aspergillosis, and even dissemination of *Aspergillus* can occur.[8] Thus, surgery should be reserved for selected patients with a reasonable respiratory reserve for whom there are no other treatment options. For example, surgery may be appropriate for patients with severe hemoptysis if embolization fails.

Although systemic antifungal therapy for CPA seems to be beneficial, assessment of response to it is difficult to gauge because the activity of the disease may fluctuate over time. Weight gain and improved energy levels are the earliest and most reliable indicators of response. Inflammatory markers also improve albeit more slowly, and they usually remain elevated even during long-term therapy. Relapse months or years after discontinuation of treatment is frequently reported. In view of the suboptimal effect of antifungal therapies, understanding molecular immunopathogenesis of CPA is essential for development of host directed therapies.

Invasive Pulmonary Aspergillosis

An important clinical manifestation of *Aspergillus*-related disease is invasive pulmonary aspergillosis, discussed in detail below.

Epidemiology *Aspergillus* has emerged as one of the most common causes of infectious death in severely immunocompromised patients, with mortality rates of 30% to 50% in patients with leukemia and recipients of HSCTs.[1,6,7] Surveillance studies demonstrated a three- to fourfold increase in the frequency of *Aspergillus* infections at major cancer centers after 1990s. In fact, IPA has surpassed invasive candidiasis as the most common fungal infection found at autopsy at several institutions; approximately 15% to 20% of patients with leukemia die of fungal pneumonia caused by *Aspergillus* spp. Similarly, in allogeneic HSCT recipients, 15% to 30% of deaths are caused by refractory fungal infections, mainly caused by *Aspergillus* spp., and most of these infections occur late in the postengraftment period in the setting of graft-versus-host disease (GvHD).[1,6,7] Large prospective multicenter surveillance studies contacted by the Transplant-Associated Infection Surveillance Network (TRANSNET) and Prospective Antifungal Therapy (PATH) Alliance have furthered insights into the epidemiology of IA in the United States. From both studies, IA has emerged as the most common invasive fungal infection in HSCT and solid-organ transplant recipients (43% and 59% of all IFIs, respectively) over invasive candidiasis and mucormycosis, with a 12-month cumulative incidence of 1.6%. Overall mortality in these patients was estimated to be approximately 36% and 75% at 12 weeks and at 1 year, respectively.[6,7]

Changes in HSCT practices over the past decade have greatly impacted the epidemiology of IPA. Autologous HSCT is associated with a low risk of IPA because of shortened periods of pre-engraftment neutropenia and a lack of GvHD. On the other hand, IPA has a bimodal distribution in allogeneic HSCTs, with patients at risk before and after bone marrow engraftment. The increasing use of peripheral blood stem cells, growth factors, and nonmyeloablative conditioning regimens (minitransplants) in allogeneic HSCT has shortened the duration of pre-engraftment neutropenia and the incidence of IPA shortly post HSCT. In contrast, late (40–80 days after engraftment) and very late (80+ days after engraftment) IPA has increased.[6,7] This trend is associated with increased use of matched unrelated-donor (MUD), haploidentical allogeneic transplants and with interrelated risk factors, such as lymphopenia, chronic GvHD, corticosteroid-based therapy, new immunosuppressive regiments, and/or CMV infection.[6,7] Among HSCT recipients, IPA now predominantly occurs as a community-acquired rather as a nosocomial infection in nonneutropenic patients late after engraftment, in whom GvHD and management with increasingly intense immunosuppression have emerged as the major risk factors. Of interest, recent studies in HSCT recipients implicate geoclimatic changes, associated with high environmental spore counts following periods of high temperature and low precipitation, as a factor for the development of IPA.

In addition to the "classic" groups of patients at risk for IPA, such as those with prolonged, profound neutropenia because of a hematologic malignancy (5%–25% risk) or aplastic anemia; recipients of allogeneic HSCTs (5%–30% risk), or lung transplants (17%–26% risk); those with AIDS, severe combined immunodeficiency, or CGD (25%–40% lifetime risk); burn patients; and patients receiving chronic corticosteroids, IPA has been increasingly described in new groups of patients.[6,7] Hence, patients with systemic lupus erythematosus, patients with multiple myeloma who receive high-dose steroids, and premature neonates are prone to the development of severe IPA. Furthermore, IPA is an emerging entity in patients with low-risk malignancies of lymphoid origin, inflammatory diseases, or autoimmune diseases who receive small molecule kinase inhibitors targeting immune signaling pathways. In particular BTK inhibitors are associated with a surge of cases of IPA. IPA is less commonly encountered in patients receiving JAK/STAT signaling, ERK, or multikinase signaling inhibitors.[1] Even the use of high-potency inhaled steroids may predispose some apparently normal hosts to IPA in rare instances. IA is considered an emerging infection in patients with prolonged stay in intensive care units (ICUs) due to immunoparalysis of myeloid phagocytes.[1] ICU aspergillosis is a distinct clinical entity that is probably underreported.[5–7] Influenza associated aspergillosis and aspergillosis associated with macrophage activation due to other viral syndromes (e.g., severe fever and thrombocytopenia syndrome, COVID-19–associated aspergillosis) are emerging clinical entities.[1]

IPA caused by *Aspergillus* spp. less susceptible to antifungals than *Aspergillus fumigatus* such as *A. terreus* and *A. flavus* has also been reported in individual institutions.[1,6,7] This phenomenon may be at least partially a reflection of antifungal selection pressure determined by extensive empirical and prophylactic use of antifungal agents in high-risk patients or evolutional pressure by environmental exposure to azoles. Alternatively, because non-*fumigatus* aspergilli cause nosocomial infections more frequently than does *A. fumigatus*, an epidemiologic niche for these species may also account for their predominance in some institutions. *A. terreus* is clinically resistant to AMB, but species including *A. flavus*, *A.*

lentulus, *A. nidulans*, *A. ustus*, *A. glaucus*, and others, can also demonstrate resistance to antifungal agents.

A number of nosocomial clusters of IPA have been reported over the past three decades mostly associated with hospital construction and defects in air-handling equipment. Air and environmental surfaces have been the focus of most investigations. An outbreak of IPA after major cardiac surgery caused by abnormally high levels of fungal spores in the air of the ICU has been reported.

Pathogenetic Mechanisms Because *Aspergillus* is a saprophytic mold that colonizes in the respiratory tract of immunocompromised patients, the pathogenesis of infection depends on the host's underlying immunometabolic defects in myeloid phagocytes. In the immunocompromised host, IPA typically occurs following inhalation of *Aspergillus* conidia, although hematogenous dissemination from a cutaneous or gastrointestinal source is seen occasionally.[1–3] Damage to respiratory epithelium because of radiation therapy, chemotherapy, GvHD, or prior infection (e.g., RSV, influenza) may facilitate attachment of *Aspergillus* conidia to the respiratory epithelial surface.[1–3] Furthermore, acquired iron overload related to the underlying disease promotes *Aspergillus* invasive fungal growth and likely impairs antifungal effector pathways in phagocytes.[1]

Breach of mucosal host defense mechanisms in the setting of underlying immunodeficiency places the host at risk for invasive infection by *Aspergillus* spp.[1,3,6,7] For example, CMV infection can result in dysfunction of dendritic cells and phagocytes, which may predispose patients to IPA. Of interest, critically ill patients with prolonged ICU stay develop a systemic deactivation of the immune system following sepsis or any severe insult that has activated a systemic inflammatory response.[1–3] This sepsis-induced immune paralysis often results in superinfection with opportunistic pathogens, including *Aspergillus*. In agreement, mice recovering from sepsis remain exquisitely susceptible to *Aspergillus* and develop IPA upon pulmonary infection without the need for immunosuppression.[1–3] Although the mechanism of increased susceptibility to *Aspergillus* in sepsis-induced immunosuppression remains obscure, there is evidence of predominance of a deregulated myeloid cell function induced by cytokine hyporesponsiveness in the lung of mice that develop invasive fungal infection. Importantly, deregulated cytokine release by myeloid cells and associated susceptibility to IPA in septic mice could be restored by adoptive transfer of bone marrow–derived dendritic cells from healthy mice.[1–3]

Once germination of conidia occurs, *Aspergillus* hyphae invade pulmonary arterioles and lung parenchyma, leading to ischemic necrosis. Hematogenous dissemination with thrombosis, hemorrhagic infarction, and invasion of distant organs may result from invasion of arterioles by *Aspergillus* hyphae and is found in approximately one-third of cases of IPA at autopsy.[1,6,7,9,10] Thus, IA, in addition to pneumonia, can present with a clinical picture similar to that of other thrombotic and embolic diseases, such as pulmonary embolism, cerebral vascular accidents, Budd–Chiari syndrome, and renal papillary necrosis. In addition, IA can spread to contiguous structures, across the diaphragm to the stomach, or from the lung to the heart or superior vena cava.

Importantly, it has been recently demonstrated that IPA has different pathophysiologic mechanisms depending on the type of immunosuppression. Thus, a low *Aspergillus* tissue burden, extensive inflammatory injury, absence of angioinvasion, and localized infection have been observed in CGD, sepsis- or corticosteroid-immunosuppressed mice, largely attributed to impaired activation of ROS-dependent activation of autophagic signaling (LAP) regulating fungal killing. In contrast, minimal inflammation, extensive angioinvasive *Aspergillus* growth, and disseminated infection are characteristic of IPA in cyclophosphamide-treated neutropenic mice.[1,6,7] In mice with LAP-defective myeloid phagocytes, host immune effector cells appear to have limited activity against *Aspergillus* hyphae but cause extensive alveolar damage and exudative bronchiolitis, which appears to be more important than the *Aspergillus*-induced injury itself. This nonangioinvasive form of IPA has been increasingly recognized in a wide range of nonneutropenic hosts, including those who received corticosteroids, recipients of solid-organ transplants and allogeneic HSCTs with GvHD, and patients with CGD and immunoparalysis induced by sepsis (Fig. 132-6).[1,6,7] Similar to the animal models of IPA, histopathology in those nonneutropenic patients is characterized by extensive pyogranulomatous inflammatory reactions, inflammatory necrosis, and extensive cavitation.

Studies on genetic susceptibility to IA have been almost exclusively performed in allogenic HSCT. SNPs in PTX-3 in donor hematopoietic cells results in functional defects in phagocytosis and killing of neutrophils and confers increased risk for IA in independent gene association studies. Although deficiency of TLR adaptive protein MyD88 and Dectin-1 in humans is not associated with the development of IA, genetic polymorphisms in donor TLR-1, TLR4, TLR-6, and Dectin-1 predispose to the development of IA in allogenic HSCT recipients.[1–3] In addition, polymorphisms in IL-10 and plasminogen are associated with increased risk for IA. Thus, better understanding immunogenetics of IA in these

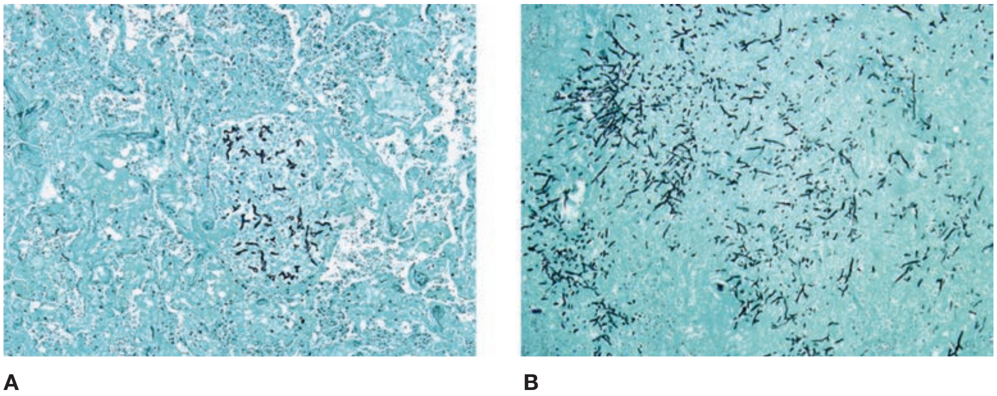

Figure 132-6 The characteristic pattern of *Aspergillus* invasion in tissue obtained from (**A**) an HSCT recipient with IPA and severe GvHD and (**B**) a patient with acute leukemia and severe neutropenia in whom IPA developed. Extensive inflammation, less *Aspergillus* burden, and absence of angioinvasion was observed in the patient with GvHD. In comparison, the histopathology of IPA in the patient with severe neutropenia was characteristic for scant infiltration by phagocytic cells, extensive coagulative tissue necrosis caused by angioinvasion, and a high fungal burden. Gomori methenamine silver stain, ×100. *(Reproduced with permission from Dr. M. Luna.)*

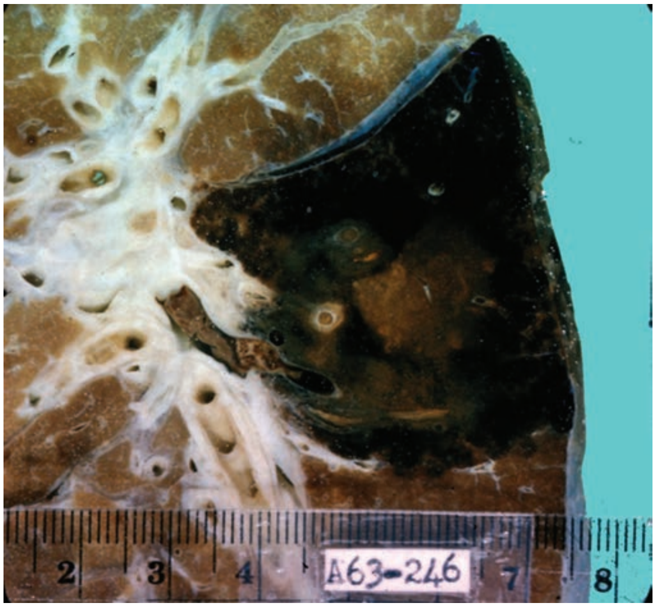

Figure 132-7 A 62-year-old man with acute leukemia in whom IPA developed. The gross appearance of the fungal lesion shows a central necrotic area surrounded by a lining of hemorrhagic infarction. *(Reproduced with permission from Dr. G.P. Bodey.)*

high-risk individuals could facilitate risk stratification and design of preventive strategies.[1–3]

Clinical Features Symptoms of IPA are subtle and atypical and occur relatively late in the disease course. IPA symptoms begin with low-grade fever (unless the patient is receiving corticosteroids), which may be followed by a mild nonproductive cough suggestive of bronchitis. Pleuritic chest pain and progression to pneumonia occur within 1 to 2 days. Cavitation tends to occur in patients if immunosuppression is decreased, such as in leukemic patients during recovery of bone marrow hematopoiesis or when steroid-based therapy is reduced significantly, and on occasion gives rise to massive hemoptysis (Figs. 132-7 and 132-8).[1,6,7] Pleuritic pain and slight hemoptysis may suggest pulmonary infarction. Patients may also expectorate necrotic tissue filled with hyphae. Cough, sputum production, and pleural effusion are either absent or minimal. IA must be strongly considered when dealing with susceptible patients in whom treatment with broad-spectrum antibiotics fails.

Extrapulmonary sites may be involved including the highly vascular organs such as the kidneys, liver, spleen, and central nervous system. Invasive disease of the nose and paranasal sinuses occurs in immunocompromised patients, and contiguous invasive spread into the orbit or into the cranial vault can result in a syndrome similar to rhinocerebral mucormycosis.

Diagnosis Substantial delay in establishing an early diagnosis remains a major impediment to the successful treatment of IPA. Chest radiographs are not sensitive in detecting early forms of bronchopulmonary IPA, and up to 10% of patients with proven IPA have "normal" chest radiographs within a week of death.[1,6,7] High-resolution CT scans of the chest may reveal small wedge-shaped subpleural lesions or nodules typically surrounded by intermediate attenuation. This halo sign correlates with hemorrhage and edema surrounding an infarct caused by thrombosis and is highly suggestive of acute IPA, especially in neutropenic patients with leukemia.[1,6,7] However, the halo sign has been documented only in 33% to 60% of patients and is transient. In fact, to be useful for the diagnosis of IA, CT must be performed within 5 days of the onset of infection, because more than 75% of initial halo signs disappear within a week.[1,7,9] With neutrophil recovery, these lesions coalesce and cavitate, forming the "air crescent" sign, a classic sign of late filamentous invasive mold infection (IMI). However, the air crescent sign does not appear until the third week of the infection, and the appearance may be too delayed to be helpful in the diagnosis of IA. Importantly, lesions frequently increase in size in the first 7 to 10 days following effective antifungal therapy. In view of the angioinvasive nature of IPA, detection of vascular occlusion by CT-based pulmonary angiography was evaluated in a recent study as an early sign of IMI. Importantly, the presence of positive vascular occlusion sign was more sensitive and specific than the halo sign and comparable to serum galactomannan test for diagnosis of IPA. Thus, CT pulmonary angiography could represent a viable diagnostic tool for IPA, especially in patients at low-risk of contrast-induced acute kidney injury.

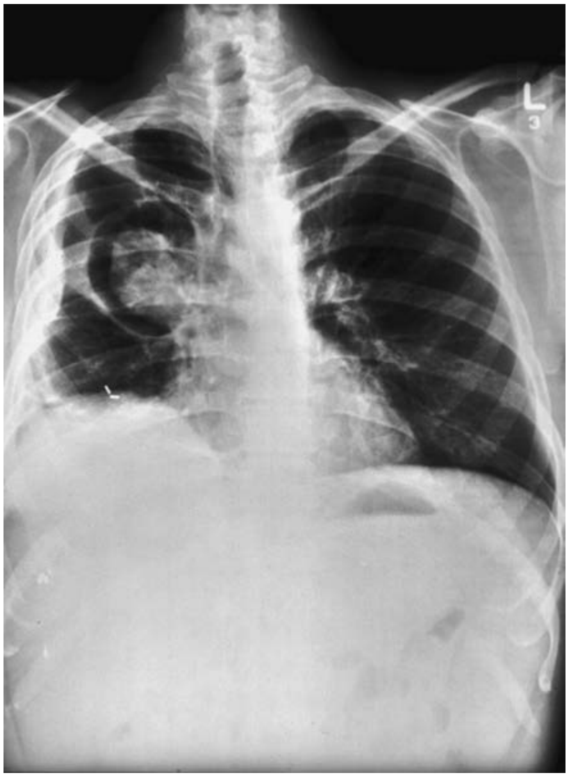

Figure 132-8 The characteristic radiographic features of IPA following neutrophil recovery illustrated in a patient with acute leukemia. A lesion has cavitated, creating the air crescent sign. *(Reproduced with permission from Dr. G.P. Bodey.)*

Persistently febrile neutropenic patients with leukemia would benefit from the use of early high-resolution chest CT to identify early radiologic signs of IPA such as the halo sign. In a study of febrile neutropenic patients, early and routine CT scanning coupled with early intensive antifungal-based treatment and surgery resulted in increased survival rates when compared with therapy initiated at the first sign of a pulmonary fungal infection.[1,6] CT also plays a critical role in determining the appropriateness of various downstream diagnostic procedures (bronchoalveolar lavage [BAL], percutaneous needle biopsy, and open lung biopsy) in patients with IPA. Nonetheless, clinical and radiologic presentations of IPA in the expanding group of nonneutropenic patients who develop infection is atypical, including cases with tree-in-bud opacities or diffuse ground-glass appearance and ARDS-like features in CT.[1,6–9] Development of novel imaging platforms based on antibody-guided positron emission tomography and magnetic resonance (immunoPET/MR) for early and specific detection of *Aspergillus* invasive growth holds promise as a future diagnostic modality for IPA.[1]

Respiratory cultures of *Aspergillus* from expectorated sputum, bronchial washings, or BAL specimens have low sensitivity (<30%) for diagnosing IA but a high positive predictive value (>60%) in heavily immunocompromised patients.[6] Early performance of CT-guided fiberoptic bronchoscopy with BAL in immunocompromised patients with pulmonary infiltrates has been shown to improve the diagnostic yield of this procedure. In addition, there is a need for the development of standardized BAL protocols in order to facilitate comparative clinical studies on the diagnosis of IPA. Blood cultures have little diagnostic value for IA but may reflect true disease cases of *A. terreus* infection. Ultimately, open lung biopsy may be required for a definitive diagnosis of IPA and may not be feasible until late in the course of infection or recovery of pancytopenia.

In recent years, efforts have been directed toward identifying non-culture-based markers for rapid, reliable diagnosis of IA.[9] Detection of anti-*Aspergillus* antibodies has very poor sensitivity for IA, especially in patients receiving immunosuppressive agents. Instead, tests based on identifying circulating polysaccharides, peptides, nucleic acids or metabolites released during fungal growth are promising.[1] To date, the two approaches that have demonstrated the greatest promise in early clinical studies are detection of antigens and measurement of *Aspergillus* nucleic acids by using PCR.

Galactomannan is a polysaccharide cell wall component of *Aspergillus* spp. that is released into the circulation during fungal growth in tissues and can be detected in the serum, BAL, and other fluids of patients with IA.[1,6,7,9] A sandwich enzyme-linked immunosorbent assay (ELISA) capable of detecting galactomannan at concentrations as low as 0.5 ng/mL is the most widely used assay for diagnosis of IPA. Initial studies evaluating the role of galactomannan serum assay in the diagnosis of IA have been predominantly conducted with profoundly neutropenic patients undergoing chemotherapy for cancer or recipients of HSCTs who were on fluconazole prophylaxis. These studies have documented sensitivity rates ranging from 67% to 100% and specificity rates ranging from 86% to 99% in these patients.[1,9] When serially monitored, the galactomannan assay preceded the diagnosis of IA by an average of 6 to 14 days and has prognostic value in response to therapy.[1,9] However, in a study that evaluated the value of the galactomannan assay in the detection of early IA, the appearance of major lesions (halo sign, air crescent sign, and cavitation) on high-resolution CT scans almost coincided with or even preceded the detection of the galactomannan antigen in serum.[6,7] Furthermore, the performance of serum GM assay is substantially compromised in other settings, including breakthrough IA to mold-active antifungal prophylaxis, pediatric populations, solid-organ transplant recipients, and other nonneutropenic patients with IPA characterized by deregulated inflammation and low fungal burden.[7] Other factors, such as the pretest probability of infection, the patient's immune status (neutropenia vs. GvHD), antifungal therapy, antibacterials, and diet may affect both the performance and interpretation of the galactomannan assay. Hence, sensitivity rates as low as 30% have been reported in nonneutropenic HSCT recipients receiving mold-active antifungal prophylaxis and lung transplant recipients.[6,7,9] In addition, false-positive results have been described in patients receiving β-lactam antibiotics, particularly piperacillin–tazobactam, as well as in those ingesting certain cereals, pastas, nutritional supplements, and soy sauce produced with fermentation products of *Aspergillus oryzae*, a fungus commonly used in food production.[6,7,9] In addition, false-positive galactomannan antigenemia has also been reported as a result of transfusion of blood products. BAL GM has substantially improved diagnostic yield compared to serum GM and is the preferably diagnostic method in high-risk patients with IPA.[9] A meta-analysis of 30 diagnostic studies with the use of BAL GM, using an optimal cutoff value of 1.0, the BAL-GM assay had 90% sensitivity and performed better compared to PCR and serum GM test although specificity was lower (89%).[1,9] Point-of-care GM detection with lateral flow device shows comparative performance with GM ELISA and holds promise as an alternative diagnostic modality especially in resource limited settings.[1,9]

A colorimetric commercially available assay that allows for batch (>20 samples) detection of 1,3-β-D-glucan in patient samples, an integral cell wall component in a number of pathogenic yeasts and filamentous fungi, has been recently endorsed in guidelines as an alternative to GM for diagnosis of IPA.[9] The sensitivity and specificity rates for this test in limited studies thus far have ranged from 67% to 100% and from 84% to 100%, respectively. Several false-positive test results have been reported in patients with cirrhosis; in patients undergoing hemodialysis, albumin infusion, or receipt of blood products; in patients following abdominal surgery; with the use of surgical gauze products; and in those receiving antimicrobials or chemotherapy with particular agents.[9] Furthermore, the 1,3-β-D-glucan assay has been reported to be less sensitive and reproducible and to become positive later in the course of IA when compared with galactomannan antigen assay. The release of a rapid test that allows for single testing of 1,3-β-D-glucan will facilitate broader use of this assay for diagnosis of IPA.[1,9]

PCR detection of *Aspergillus* nucleic acids has been recently implemented in updated guidelines for diagnosis of IA.[9] The sensitivity of PCR is excellent, but its specificity for invasive infections can be problematic, and false-positive results are common. Multiple unresolved issues accompany the use of PCR for the diagnosis of IA, including the sample type (serum, BAL fluid), amplification strategy (nested vs. conventional PCR), protocol (real-time quantitative vs. conventional PCR), primer selection (*Aspergillus*-specific or pan-mold, pan-fungal primers), method of DNA extraction, and CT cutoff values.[1,9] A meta-analysis of 19 studies comparing the value of BAL PCR with BAL GM concluded that although sensitivity and specificity of both tests were comparable, combination of both tests increased sensitivity without compromising specificity. Thus, like GM testing, PCR is likely to become an adjunctive diagnostic method alone or in combination with other biomarkers and standard microbiologic, histologic, and radiographic methods of diagnosing IA.

Novel investigational diagnostic approaches include the development of a breath test to detect volatile *Aspergillus* biomarkers that are not produced by other pathogens, and detection of circulating *Aspergillus* antigens in BAL and serum of patients with IPA by using an immunochromatographic lateral flow device.

Treatment of IPA Although the past two decades have witnessed improved outcomes of patients with IA, the mortality rate of this mycosis in severely immunocompromised patients remains high.[6] Several strategies have been applied in an attempt to improve the outcome of IA. These include the introduction of potent antifungal agents such as voriconazole and other newer triazoles, early onset of treatment triggered by CT and/or galactomannan antigen, use of delivery systems to improve the therapeutic index of currently available antifungals such as lipid formulations of AMB, and possibly combination antifungal therapy, surgical excision of sequestered necrotic lesions, and use of immunomodulating agents in selected patients.[6] There has not been a systemic evaluation of the merit of each of these strategies in the treatment of IA, however. This is not surprising in view of the complexity of IA and the paucity of organized, prospective controlled clinical studies in refractory IA.

Tables 132-5 and 132-6 list the principles of management of IPA. Until the early 1990s, AMB-D was the only drug available for the treatment of aspergillosis, and no prospective evaluations of this drug had been attempted.[6] Another major obstacle to evaluating the merit of antifungal therapy for IPA until the early 2000s was difficulty in establishing the diagnosis; hence, most patients received empiric treatment. The introduction of uniform diagnostic criteria for proven, probable, and possible IA by the European Organization

TABLE 132-5 Therapeutic Options for Invasive Fungal Infections

Regimen	Advantages	Disadvantages
Amphotericin B-deoxycholate (AMB-D)	Broad-spectrum activity, lack of frequent resistance, fungicidal activity, lower cost	Acute and chronic toxic effects, minimally effective in patients with neutropenia and with chronic disseminated candidiasis, intravenous preparations only
Lipid formulations of AMB	Broad-spectrum activity, reduced nephrotoxicity, increased doses can be administered	Only prospective randomized trial showed no advantage in efficacy over AMB-D despite higher doses, more expensive, intravenous preparations only
Fluconazole	Oral and intravenous preparation, as effective as AMB in randomized trials of nonneutropenic individuals with candidiasis, minimal toxicity, more effective for chronic disseminated candidiasis, little experience in neutropenic patients but appears to be as effective as AMB	Variable activity against *C. glabrata* and *Candida dubliniensis*, inactive against *C. krusei*, some drug–drug interactions, inactive against molds
Itraconazole	Broad spectrum of activity, lower cost, oral, and intravenous preparations	Drug–drug interactions and poor absorption (capsules) are common causes of clinical resistance, marked interpatient variability in serum levels, expensive
Voriconazole	Oral and intravenous preparations; broad-spectrum activity, including fluconazole-resistant species (e.g., *C. krusei*); fungicidal against *Aspergillus*	Drug–drug interactions, erratic pharmacodynamics, more expensive than fluconazole, inactive against *Zygomycetes*, some cross-resistance with fluconazole, need for drug level monitoring, expensive
Posaconazole	Oral and intravenous formulations; slow-release tablets show improved absorption and PK properties; broadest spectrum of activity among all azoles, including *Candida* spp., *Aspergillus*, *Mucorales* spp., and most other filamentous fungi	Drug–drug interactions, poor absorption, no intravenous formulation available yet (under development, in clinical trials), some cross-resistance with itraconazole, need for drug level monitoring, expensive
Isavuconazole	Broad spectrum of activity, including *Candida* spp., *Aspergillus* spp. and *Mucorales*. Cases of breakthrough IFIs especially in the setting of protracted neutropenia.	Excellent absorption and tolerability, fewer drug–drug interactions, predictable pharmacokinetics, less need for drug level monitoring
Echinocandins (caspofungin, micafungin, anidulafungin)	Fungicidal activity against most *Candida* spp., minimal toxicity, lack of cross-resistance with azoles, preferred regiment for candidemia, immune-modulating properties	No oral preparation, poor central nervous system and urinary penetration, narrow spectrum of activity (*Candida, Aspergillus*), limited experience in neutropenic patients
Flucytosine	Synergistic with AMB and fluconazole, combination of flucytosine and AMB may be superior to AMB alone for chronic disseminated candidiasis and *C. tropicalis* infection	No IV preparation, causes myelosuppression, often requires monitoring of serum concentrations, emergence of resistance in monotherapy

TABLE 132-6 Drug Dosages for Serious Invasive Fungal Infections of the Lung

Drug	Loading Dose	Daily Dose	Route
Amphotericin B deoxycholate (AMB-D)	—	1.0–1.5 mg/kg	IV only
Lipid AMB	—	3–5 mg/kg	IV only
Fluconazole	800 mg (12 mg/kg)	400 mg (6 mg/kg)	IV, PO
IV itraconazole	200 mg bid ×2 d	200 mg	IV
Itraconazole solution	200 mg bid × 2 d	200 mg	PO
Itraconazole caps	200 mg tid × 3 d	200 mg bid	PO
IV voriconazole	6 mg/kg bid × 2 d	4 g/kg q 12 h	IV
Voriconazole tab	—	200 mg q 12 h (≥40/kg)^{a} 100 mg q 12 h (<40/kg)	PO
Posaconazole solution	200 mg qid × 7 d	400 mg bid	PO
Posaconazole tablets	300 mg bid × 1 d	300 mg	PO
IV Posaconazole	300 mg bid × 1 d	300 mg	IV
Isavuconazole	200 mg tid × 2 d	200 mg	PO, IV
Caspofungin	70 mg	50–70 mg	IV
Micafungin	150 mg	100–150 mg	IV
Anidulafungin	200 mg	100 mg	IV

bid, twice a day; caps, capsule; d, day; h, hours; IV, intravenous; PO, oral; q, every; sol, solution; tab, tablet; tid, three times a day.

[a] *Oral daily dose may be increased up to 300 mg bid (≥40/kg) or 150 mg bid (<40 kg).*

for Research and Treatment of Cancer (EORTC)/Mycoses Study Group (MSG) consortium has been an advance.[9] These criteria are standardized and reproducible and consist of host-risk, microbiologic, clinical/radiologic, PCR, and/or galactomannan antigen criteria. Despite the fact that the EORTC/MSG criteria have been updated to incorporate biomarkers for the diagnosis of IMI, their clinical applicability was questioned in real word settings; for example, in an autopsy study more than 60% of proven cases of IA in patients with hematologic malignancies were not identified antemortem according standard definitions.[10]

The introduction of the broad-spectrum triazole voriconazole represents a major therapeutic advance in the management of IA, including IPA.[6,7] Voriconazole is available in both intravenous and oral preparations and is much better tolerated than AMB-D. In a large prospective randomized trial comparing voriconazole with AMB-D in patients with definite or probable aspergillosis, the response rate was 53% and 32%, respectively, and the survival rate at 12 weeks was 71% and 58%, respectively.[11] Improved response was seen irrespective of the underlying condition, site of infection, and presence or absence of neutropenia. Patients in whom initial therapy failed received other medications; this occurred more frequently among the AMB-D population primarily because of drug toxicity. The improved survival observed in this comparative study made voriconazole the preferred drug for first-line therapy for IA, and this has been endorsed by many guidelines. A recent study has shown that isavuconazole, a newer-broad spectrum triazole, is equally efficacious and better tolerated than voriconazole.[1] Based on this study, both isavuconazole and voriconazole have an IA indication in the management of IA. Posaconazole, a triazole with broad-spectrum activity against *Aspergillus* and other molds, is endorsed as an alternative therapeutic option in IA guidelines. An interim analysis of a recent randomized controlled study demonstrated that posaconazole was noninferior to voriconazole in terms of all-cause mortality up until day 42 in patients with documented or probable IA and was associated with a better toxicity profile.[12] This new evidence justifies the use of posaconazole as frontline therapy for IPA.

Use of lipid formulations of AMB is an attractive alternative to AMB-D because of reduced nephrotoxicity.[6,7] Although no comparative trials between the lipid formulations of AMB have been conducted thus far, they appear to be equally efficacious, although both toxic effects and costs differ. Most of the available data have been derived from indirect comparisons and suggest that all lipid formulations of AMB, when given at the standard dosage of 5 mg/kg, appear to have efficacy comparable to voriconazole.[6,7] That higher dosages of L-AMB are not necessarily equivalent to greater response rate was demonstrated in a prospective randomized study that compared two different dosages of L-AMB (3 mg/kg/d and 10 mg/kg/d) for the primary treatment of proven and probable IA in 201 patients. Importantly, survival rates and overall response rates were similar among the two study groups; however, higher dosage of L-AMB was associated with greater toxicity.[13] The dose–response relationships for ABLC and ABCD have not been well studied.

The echinocandins, including caspofungin, micafungin, and anidulafungin, belong to a new class of antifungal agents that inhibit the synthesis of 1,3-β-D-glucan, an essential component of the cell wall of many fungi.[6,7] They are all available only in intravenous preparations. In addition, caspofungin and micafungin have been used as primary therapy in noncomparative studies of IA with response rates ranging from 33% to 60% for caspofungin and 50% to 71% for micafungin. In addition, use of caspofungin as salvage therapy has been associated with response rates in 45% (37/83) of patients, including 50% of patients with IPA.[6,7]

Combination Treatment The introduction of echinocandins, a class of antifungal agents with different mechanism of action, reinforced the concept of combination therapy (e.g., azoles plus echinocandins, AMB plus echinocandins, AMB plus azoles and echinocandins) as a possible means to improve suboptimal long-term survival of high-risk patients with IA treated with monotherapy.[14] Many in vitro studies and animal models suggest that administration of an echinocandin with voriconazole may result in additive or synergistic effects, which can potentially translate into clinical benefits. This hypothesis has been supported by small clinical studies and noncomparative observations. A completed double-blind randomized clinical study in 454 patients with IA compared the efficacy of combination of voriconazole and anidulafungin versus voriconazole monotherapy with 6 weeks survival being the primary study endpoint. Importantly, treatment of IA with the combination of voriconazole and anidulafungin was associated with a clinically meaningful survival benefit in patients with hematological malignancies or after HSCT, particularly in patients with a diagnosis of IA based on GM antigen positivity and consistent radiologic findings (6 weeks mortality 15.7% for combination and 27.3% for monotherapy; $p = 0.04$).[1,6] This is the first study to demonstrate a significant impact of combination therapy in the outcome of patients with IA and a positive galactomannan assay.

In another randomized study, the efficacy of L-AMB standard dose (3 mg/kg/d) in combination with caspofungin was compared with L-AMB high dose (10 mg/kg/d) in 30 patients with hematologic malignancies and IPA.[15] The combination of caspofungin plus L-AMB demonstrated higher overall responses rates when compared with L-AMB monotherapy and 100% survival at the end of the study, although differences in responses were not statistically significant, probably because of the small size of the study.

Therapeutic Drug Monitoring A growing body of evidence suggests patient-to-patient variability in the pharmacokinetics of triazoles used for treatment or prophylaxis in IA.[6] Absorption issues (for itraconazole and posaconazole), drug–drug interactions (for all triazoles, especially voriconazole), and pharmacogenetic differences (for voriconazole) may have significant impact in the management and outcome of patients with IA under triazole treatment. Thus, plasma drug level monitoring play an increasingly important role in optimizing the safety (for voriconazole) and efficacy (for itraconazole, posaconazole, and voriconazole) of antifungals with significant interpatient pharmacokinetic variability. Isavuconazole has predictable pharmacokinetics over other triazoles, which might obviate the need for TDM.[1,6] The need to perform therapeutic drug monitoring should be individualized as determined by the clinical status of the host (e.g., specific organ function, comorbidities, and receipt of concomitant medications) and the overall treatment plans.[6]

Surgery The role of adjunctive surgery in the management of IPA also has not been demonstrated conclusively. Pulmonary infarcts and tissue sequestration are common causes of antifungal therapy failure and fatal hemorrhage in patients with IPA. Resection of infected pulmonary tissue is beneficial for selected patients.[6] Residual cavitary lesions, especially when containing fungus balls, after successful antifungal therapy may cause late exsanguinating hemorrhage or reactivation of infection during subsequent myelosuppressive chemotherapy. Removal of these lesions, if surgically feasible, should be considered and may provide survival benefit. Surgical intervention may be a life-saving procedure for patients with IPA who experience acute pulmonary hemorrhage, when performed early in the disease process. It is less evident whether early removal of well-circumscribed lesions close to pulmonary arteries is beneficial. Likewise, the value of late debulking of a pulmonary mass if the patient has multiple fungal lesions that cannot be completely resected is uncertain. Recent uncontrolled data suggest that resection of the lobe most adversely affected by IA is beneficial in treating pulmonary lesions that worsen despite the use of intense antifungal therapy.[6]

Immune Augmentation Treatment Because host immunodeficiency is the critical determinant of the outcome of IA, a large number of studies, mostly preclinical, over the past two decades have focused on strategies to augment cellular immune defenses against IMIs. The available preclinical data suggest that quantitative and qualitative deficiencies in host cellular immune responses can be corrected with adjunctive cytokine therapy, such as the use of myeloid growth factors (e.g., granulocyte colony–stimulating factor [G-CSF], granulocyte-macrophage colony-stimulating factor [GM-CSF]), IFN-γ, or a combination of these cytokines plus infusion of host effector cells (e.g., IFN-γ plus granulocyte transfusions), reversal of the underlying immune defects with checkpoint inhibitors, administration of *Aspergillus*-specific T cells or NK cells or engineered fungal-specific CAR T cells.[1,6,7] Granulocyte transfusion therapy has become more feasible since the introduction of G-CSF/corticosteroid mobilization into the donor leukocyte collection process.[6] Currently, there are no data from randomized clinical trials examining the efficacy of granulocyte transfusions for IA or other serious infections during neutropenia. Future studies in this area will likely examine the use of vaccinations and/or cellular transfer with or without adjunctive cytokines to enhance cellular immunity tailored to the underlying immune defects of the individual patient. Importantly, WBC transfusions have been occasionally associated with serious adverse reactions including transfusion-related acute lung injury (TRALI). Clearly, this is a challenging area of investigation. Carefully designed clinical trials will be required to verify results from animal models and other preclinical observations and evaluate both the efficacy and safety of these interventions. Understanding the immunopathogenesis features and underlying host immune defects in the diverse and expanding group of nonneutropenic patients with IPA is essential to design host directed effective immunomodulatory therapies.

Prophylaxis in High-risk Patients Reports on nosocomial outbreaks of IPA have linked cases to hospital construction, the absence of appropriate barriers between patients and the environment, and the presence of fungal spores in room air samples. Specialized air-handling systems such as high-efficiency particulate air (HEPA) filtration with or without laminar airflow ventilation have proved to be effective at excluding *Aspergillus* spores.[1,6,7] However, HEPA filters have not been shown to prevent *Aspergillus* infections during building renovation and may not prevent outbreaks of these infections related to building demolition or renovation. A meta-analysis of 16 controlled trials that evaluated the effect of HEPA filtration on neutropenic patients with hematologic malignancies or HSCT found that the placement of patients in protective environments appeared to be beneficial in preventing IFIs, but the data seemed insufficient to support firm conclusions. The Centers for Disease Control and Prevention guidelines for preventing opportunistic IMIs in allogeneic HSCT recipients recommend the use of HEPA filters in patient rooms (*www.cdc.gov/infectioncontrol/guidelines/isolation/*). However, highly immunocompromised stem cell transplant recipients are commonly managed as outpatients, where engineering standards of the inpatient protected environment are not feasible. More recently, hospital water systems have been implicated as potential sources of high-level spore bursts of pathogenic fungi. During bathroom activities such as showering and toilet flushing, patients may create aerosolized mists of fungal spores that increase the risk of IPA. In addition, researchers reported an association between molds (*Aspergillus* and *Fusarium* spp.) cultured on hospital sinks and water sources and IMIs in patients with leukemia.[6,7] As a result, some have recommended cleaning of patient showers and bathroom areas with a phenolic cleaning solution prior to use by severely immunocompromised patients. Although these preliminary data are intriguing, establishing a causal link between nosocomial exposure to *Aspergillus* spores and subsequent development of IA remains difficult and requires the demonstration of genetic relatedness of environmental *Aspergillus* strains and clinical isolates. In fact, one of the largest molecular epidemiologic studies of IA suggested that any *Aspergillus* strain could be pathogenic in the appropriate host background and that isolates causing invasive disease are not necessarily nosocomially derived.[1,6]

The new oral, extended-spectrum triazoles, such as voriconazole and posaconazole, have a satisfactory pharmacokinetic profile and documented efficacy in the treatment of infections, which may make them suitable for prophylaxis in HSCT recipients and neutropenic patients. Posaconazole has been endorsed by several guidelines as the prophylactic azole of choice. Antifungal prophylaxis with the echinocandin micafungin in HSCT recipients was shown to reduce the incidence of IA;[6,7] however, the fact that echinocandins are parenteral drugs limits use in extended antifungal prophylaxis during the postengraftment period, when IA is most likely to occur.

Secondary Prophylaxis Patients with a history of IA are at high risk of reactivation of the infection if they undergo further intensive chemotherapy or HSCT, with relapse rates up to 30% to 50%. Patients receiving prophylaxis have fewer relapses than do those who do not.[6,7] In an open-label noncomparative study in 45 high-risk HSCT recipients with a previous history of invasive fungal infection (mostly IA), secondary voriconazole prophylaxis resulted in 6.7% incidence of relapse rate of IFI, which is considered lower than the relapse rate reported in historic control studies. Thus, in the absence of comparative clinical trials, triazoles such as voriconazole seem to be the most appropriate agents for secondary prophylaxis.

PULMONARY CANDIDIASIS

Candida, a commensal fungus of mucosal surfaces, is the predominant fungal pathogen in humans. The spectrum of *Candida*-induced illnesses is broad, ranging from mild, chronic mucocutaneous infections to life-threatening acute invasive infections involving potentially any organ.[16] Pulmonary candidiasis is an infrequent form of invasive *Candida* infection that almost exclusively occurs in cases of aspiration pneumonia in immunocompromised patients who have heavy colonization of *Candida* spp. in the oral cavity (primary *Candida* pneumonia) or as part of disseminated candidiasis primarily in neutropenic patients.[16–19]

Candida pneumonia is a challenging infection because of a lack of established, reliable clinical criteria for making the diagnosis. *Candida* is frequently an asymptomatic colonizer, particularly among debilitated individuals who are receiving antibacterials.[16–19] Thus, cultures of sputum and/or BAL that are positive for *Candida* in a patient with a pulmonary infiltrate do not establish the diagnosis of *Candida* pneumonia. An autopsy study of patients with cancer demonstrated that whereas many high-risk patients with pneumonia had *Candida* spp. cultured from sputum and BAL specimens, the specificity (57%–60%) and positive predictive value (29%–42%) of cultures of both types of specimens were low.[16] Similarly, quantitative cultures of transbronchial lung biopsy samples in critically ill, mechanically ventilated patients have been of no predictive value for *Candida* pneumonia.[17] Therefore, only histopathologic demonstration of yeast cells or pseudohyphae in lung tissue is confirmatory of *Candida* pneumonia, which is often impossible to achieve in many patients. Of interest, in a large prospective autopsy study including 233 ICU patients there was no evidence of *Candida* pneumonia despite frequent isolation of *Candida* from the airways.[19] However, *Candida* airway colonization resulted in impaired macrophage effector function in a rat model of *Pseudomonas pneumonia* and has been associated with increased risk for ventilator associated pneumonia by MDR bacteria and overall worse clinical outcome. A recent meta-analysis also found a significant association of *Candida* airway colonization with higher mortality rates and longer ICU stay in patients with VAP. However, it is still unclear whether *Candida* colonization is causally related to poor outcomes or whether it is a marker of underlying host immunosuppression, and there are no studies to justify antifungal treatment for this entity.

Epidemiology

The true incidence of *Candida* pneumonia is unknown, and most of the data on this infection are extrapolated from autopsy series. The fact that only 55 patients with unequivocal evidence of primary *Candida* pneumonia had been reported in the literature up to 1993 emphasizes the rarity of this infection.[17] Large autopsy surveys in patients with cancer reported a prevalence of primary *Candida* pneumonia ranging from 0.2% to 0.4%.[18–21] In another autopsy study that included a general population of patients, primary *Candida* pneumonia accounted for 17% of all *Candida* infections, with an overall prevalence of 0.3%.[21] On the other hand, primary *Candida* pneumonia has been a relatively frequent finding in autopsy studies of high-risk patients, such as premature neonates (1%) and critically ill, mechanically ventilated patients (8%).[17]

In contrast with primary *Candida* pneumonia, secondary lung involvement by *Candida* spp. is a common finding at autopsy, occurring in 42% to 81% of cases of disseminated candidiasis.[18–21] However, the clinical significance of *Candida* pneumonia identified at autopsy, especially in cases of hematogenous dissemination, has been questioned. For example, a study demonstrated that almost half of such *Candida* infections were incidental autopsy findings without clinical significance.[21]

Although large surveillance studies to capture the prevalence of *Candida* pneumonia are lacking, *Candida* was the third most common fungal pathogen after *Aspergillus* and *Cryptococcus* in a series of 140 patients with biopsy-proven invasive fungal pneumonia.[20] Interestingly, an increasing number of patients with primary *Candida* pneumonia were reported during the last years of the study. However, whether these latter cases represented a true increase in the incidence of *Candida* pneumonia or simply reflected a bias because of improved diagnosis is not certain.

Mycology

Similar to the other forms of invasive candidiasis, *Candida albicans* is the predominant species in patients with primary *Candida* pneumonia, accounting for 40% to 70% of all reported cases.[18–21] Until the early 1990s, *Candida tropicalis* and *Candida parapsilosis* were the most common non-*albicans Candida* spp. in patients with primary *Candida* pneumonia. However, the widespread use of broad-spectrum azole antifungals in the 2000s has led to the emergence of less susceptible non-*albicans Candida* spp., such as *Candida glabrata* and *Candida krusei*, as important causes of *Candida* pneumonia. Hence, *C. glabrata* is currently considered the second most common *Candida* spp. in cases of primary *Candida* pneumonia in immunocompromised individuals.[17–20] In cases of secondary *Candida* pneumonia caused by hematogenous dissemination, the distribution of the species appears to follow that in bloodstream candidiasis, with *C. albicans* being the predominant species followed by *C. glabrata*, *C. tropicalis*, *C. krusei*, and *C. parapsilosis*.[18–21] Recently, sporadic cases of aspiration pneumonia by the emerging MDR *C. auris*, a species with unique epidemiologic properties that can cause outbreaks in healthcare settings, have been reported.

Pathogenesis

Most of the data on the pathogenesis of *Candida* pneumonia have been gained from analysis of histopathologic findings at autopsy and studies of animal models of aspiration-induced pneumonia. *Candida* pneumonia develops only rarely in normal hosts, and most of the reported cases of this infection occurred in heavily colonized, immunocompromised individuals. A constellation of factors suggests that primary *Candida* pneumonia has a distinct pathophysiology when compared with other forms of invasive candidiasis and develops in a particular clinical scenario.[17,18] Specifically, the mechanism of entry of *Candida* into the lungs is via aspiration of oropharyngeal contents.[18] In addition, several studies indicated that the typical risk factors for invasive candidiasis, such as chemotherapy-induced neutropenia, prolonged corticosteroid use, immunosuppressive agent use, prior antibiotic use, hyperalimentation, diabetes mellitus, and the presence of vascular devices were not significantly associated with the development of *Candida* pneumonia.[17–21] In contrast, alteration of mental status (with or without subsequent aspiration) was the most important contributing factor in the majority of these patients. Thus, individuals prone to aspiration who have heavy oral colonization with *Candida* spp., such as those with head and neck cancer receiving chemoradiation, premature neonates, and critically ill, mechanically ventilated patients, constitute the population at highest risk for primary *Candida* pneumonia.

However, a distinct type of secondary *Candida* pneumonia caused by hematogenous dissemination has been described occasionally in profoundly neutropenic patients with cancer.[18] The histopathologic characteristics of *Candida* lesions reflect pulmonary seeding from systemic bloodstream infections. Specifically, autopsy examination of these patients found evidence of pneumonia with scant inflammation and clumps of *Candida* yeast cells and pseudohyphae present in large portions of the involved lung sections in a pattern that closely resembled *Candida* growth in culture medium. Furthermore, in contrast with primary *Candida* pneumonia, destruction of lung parenchyma is subtle, whereas hemorrhage and angioinvasion by pseudohyphae are prominent. Although speculating that typical risk factors for disseminated candidiasis may apply in cases of secondary *Candida* pneumonia is reasonable, the majority of cases of clinically significant infection have been described in profoundly neutropenic patients with leukemia.[18–22]

Clinical Manifestations

The clinical manifestations of primary *Candida* pneumonia are nonspecific and include persistent fever and tachypnea.[16,17] Chest pain, cough, and sputum production occur occasionally. Also, physical examination and routine laboratory studies are nonspecific. Chest radiographs may demonstrate a local or diffuse infiltrate involving one or both lungs, which is most often associated with infection acquired by the endobronchial route. A miliary–nodular pattern is most often associated with hematogenous seeding of the lung in cases of disseminated candidiasis and often appears late in the clinical course of the disease (Fig. 132-9).[16–18]

Extrapulmonary manifestations such as skin lesions, myositis, and endophthalmitis may be the first signs of *Candida* fungemia. Multiple organ involvement prior to or concurrent with pulmonary findings, particularly liver or kidney dysfunction and myocardial failure, may indicate hematogenous seeding that warrants investigation.

Lung transplant recipients occasionally develop an early (within 2 weeks after transplantation) and fulminant *Candida* pneumonia.[17] This association is probably caused by occult aspiration of *Candida* colonizing the donor lung followed by invasive pulmonary *Candida* infection after transplantation when immunosuppression is most intense.

Asthma related to an IgE-mediated allergy to *C. albicans* or allergic bronchopulmonary candidiasis can occur, although this is uncommon. Allergic bronchopulmonary candidiasis should be considered in patients with ABPA with serologic and skin tests negative for *Aspergillus*. In addition, cases of chronic eosinophilic

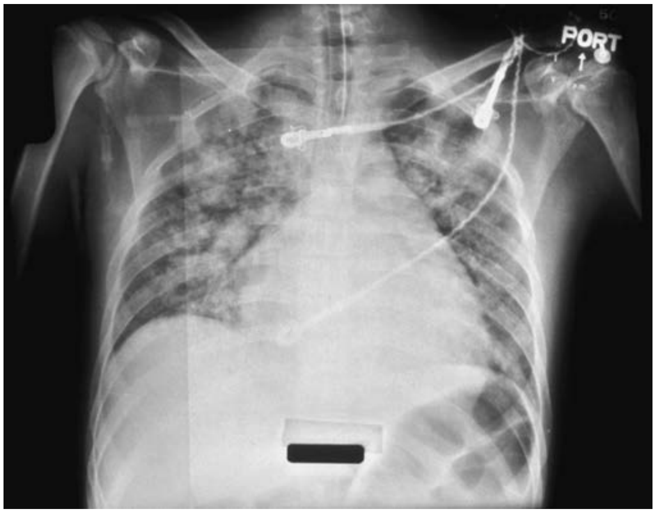

Figure 132-9 The radiographic features of *Candida* pneumonia in a patient with acute leukemia and severe neutropenia in whom disseminated candidiasis developed. Diffuse bilateral infiltrates along with the characteristic macronodular lesions are shown. *(Reproduced with permission from Dr. G.P. Bodey.)*

pneumonia with peripheral eosinophilia and selective sensitization to *C. albicans* occur rarely in the absence of asthma. Early diagnosis and corticosteroid-based therapy may prevent late fibrosis in those patients. Finally, fatal aspiration pneumonitis characterized by intense inflammatory response and lack of deep-tissue invasion has been described in alcoholic patients.

■ Diagnosis

Diagnosis of pulmonary candidiasis is challenging and depends on evidence of tissue invasion.[16–20] Isolation of yeast from sputum does not prove invasive yeast infection of the respiratory tract because of contamination by commensals from the oropharynx. *Candida* is present in the oropharynx of approximately 20% to 40% of all patients, especially those with chronic lung disease and those receiving prolonged antibacterial treatment.[15,16]

Bronchial washings and BAL specimens provide a more representative picture of the respiratory pathology compared to sputum. However, they can still be contaminated with mouth flora. At least in a selected group of patients with acute leukemia and severe neutropenia, if no other organisms are present and abundant *Candida* yeast cells and pseudohyphae are detected in the cytologic examination of BAL specimens, clinical suspicion of *Candida* pneumonia should be high.[15,16] On the other hand, cultures from lung specimens negative for *Candida* spp. have a high negative predictive value and virtually exclude *Candida* pneumonia.[15–18]

Histopathologic demonstration of tissue invasion by *Candida* spp. in open lung biopsy or CT-guided fine-needle aspiration of peripheral nodular lesions is definitive, although such biopsies are difficult to perform in pancytopenic patients with pneumonia and are prone to sampling error. Transbronchial biopsy revealing tissue invasion by *Candida* spp. is also diagnostic.

Isolation of *Candida* from the blood may be helpful in the diagnosis of disseminated candidiasis; however, the organism may not be isolated even from multiple blood culture specimens in up to 40% of patients with widespread infection demonstrated at autopsy.[15–21] The use of lysis centrifugation, the BacT-Alert system that monitors CO_2 production, and the high-volume BACTEC system with infrared detection has improved the yield of *Candida*-positive blood cultures. A variety of methodologies have been developed to detect circulating *Candida* antigens, nucleic acids, and metabolites. Among these non-culture-based diagnostic methods, PCR and β-D-glucan assays in serum hold most promise for adoption in routine clinical microbiology practice.[15] Of interest, in a recent prospective study of invasive candidiasis both PCR and serum β-D-glucan assays had higher sensitivity than blood cultures among patients with deep-seated candidiasis (88% and 62% vs. 17%, respectively); the combination of both the PCR and β-D-glucan assays resulted in 98% sensitivity. In addition, β-D-glucan levels seem to be a prognostic marker for treatment response in invasive candidiasis. The T2 *Candida* molecular diagnostic panel uses T2 magnetic resonance to detect *Candida* DNA directly within whole blood samples and shows improved sensitivity over blood cultures and other molecular detections methods especially in the setting of antifungal therapy. However, it is associated with high cost and the need for specialized equipment.[15]

In cases of disseminated candidiasis, characteristic eye lesions suggestive of *Candida* infection may develop;[15] hence, a careful ophthalmologic examination should be performed when this infection is suspected. In addition, typical maculopapular or nodular skin lesions have been described in up to 10% of patients with hematogenous candidiasis.[15] Some of these patients also have associated myositis, particularly in cases of *C. tropicalis* infection. *Candida* spp. can be identified in the dermis and cultured from about half of all biopsy samples. Finally, CT scans of the abdomen may suggest hepatosplenic candidiasis in compromised hosts with an unrevealing microbiologic evaluation.

■ Treatment

Primary *Candida* pneumonia is considered a life-threatening infection, with mortality rates approaching 70% in severely immunocompromised patients.[16–20] Therefore, rapid clinical diagnosis and prompt initiation of systemic antifungal therapy are important upon suspicion of the infection in the appropriate setting.

Given the rarity of primary *Candida* pneumonia, there are no controlled studies of its treatment. Historically, most patients with primary *Candida* pneumonia have received AMB-D (0.7–1.0 mg/kg/d) for a minimum of 2 weeks after all signs and symptoms of infection disappeared and until bone marrow recovery in those with neutropenia.[15] In cases of secondary *Candida* pneumonia associated with hematogenously disseminated infection, therapy directed at disseminated candidiasis rather than at *Candida* pneumonia is indicated.[15] Over the past two decades, several antifungal agents, including fluconazole and the newer triazoles (especially voriconazole), lipid formulations of AMB, and the echinocandins, have become available for the treatment of invasive candidiasis, showing comparable efficacy and significantly less toxicity when compared with AMB-D in several prospective randomized trials.[15]

Echinocandins are the preferred antifungal agents in the treatment of invasive candidiasis.[15] All three available echinocandins, including caspofungin, micafungin, and anidulafungin, have shown comparable, broad-spectrum fungicidal activity against *Candida* spp., including azole-resistant non-*albicans Candida* spp.[15] In fact, because of their potency, minimal toxicity, and superior activity when compared to AMB-D and fluconazole in randomized controlled studies in patients with candidemia, the echinocandins have become the drug of choice for candidemia/candidiasis in seriously ill and unstable patients.

The accumulating experience with the treatment of other invasive pulmonary mycoses with echinocandins holds promise for the use of these agents in the treatment of *Candida* pneumonia. However, because of the rarity of *Candida* pneumonia a definite treatment of choice for this entity has not been endorsed in recently published guidelines on treatment of *Candida* infections.[15] Thus, with all of the limitations of the aforementioned studies, and given the fact that fluconazole has been used extensively for prophylaxis in many institutions, initiation of therapy for *Candida* pneumonia with an echinocandin with subsequent switch to an azole may be a reasonable approach in such cases.[15] Also, using higher doses of fluconazole (800 mg/d), at least initially, may be appropriate in nonneutropenic patients.

PULMONARY MUCORMYCOSIS (FORMERLY ZYGOMYCOSIS)

Mucormycosis (formerly zygomycosis) has recently emerged as an important opportunistic mycosis in severely immunocompromised patients with hematologic malignancies and recipients of stem cell or organ transplantation.[25–27] Zygomycosis, the previous terminology for infections caused by fungi of the order Mucorales, is no longer appropriate due to a taxonomic reclassification that abolished Zygomycetes as a class. Necrotizing pneumonia is a predominant feature of mucormycosis, especially in severely immunocompromised patients.[25,27]

Fungi of the order Mucorales are distributed in six families, each of which can cause serious invasive infections (Table 132-7). Species of the family Mucoraceae are isolated more frequently from patients with mucormycosis than are species of any other family.[25,27] Among the Mucoraceae, *Rhizopus oryzae* (*Rhizopus arrhizus*) causes the vast majority (>70%) of Mucorales infections. Other less frequently encountered species of the Mucoraceae family include *Rhizopus microsporus*, *Lichtheimia* (formerly known as *Absidia* species), *Apophysomyces elegans*, *Mucor* species, and *Rhizomucor pusillus*. *Cunninghamella bertholletiae* is an increasingly reported cause of mucormycosis and appears to be the most virulent Zygomycetes species in humans.[25] All of these organisms are indistinguishable by histopathology. Various terms have been used in the past to indicate infections caused by Mucorales, such as mucormycosis, phycomycosis, and simply mucor. However, the more accurate term *mucormycosis* is used throughout this chapter to indicate opportunistic mold infections in humans caused by Mucorales, because this is the taxonomically correct description.

TABLE 132-7 Classification of Fungi in the Class Zygomycetes, Order Mucorales[a]

1. MUCORACEAE
    - a. *Absidia (Lichtheimiaceae)*
        - i. *A. corymbifera*[b]
    - b. *Apophysomyces*
        - i. *A. elegans*[b]
    - c. Mucor[b]
        - i. *M. circinelloides*
        - ii. *M. hiemalis*
        - iii. *M. racemosus*
        - iv. *M. ramosissimus*
        - v. *M. rouxianus*
    - d. *Rhizomucor*
        - i. *R. pusillus*[b]
    - e. *Rhizopus*
        - i. *R. arrhizus*[b]
        - ii. *R. azygosporus*
        - iii. *R. microsporus var. rhizopodiformis*[b]
        - iv. *R. microsporus var. oligosporus*
        - v. *R. microsporus var. microsporus*
        - vi. *R. schipperae*
        - vii. *R. stolinfer*
2. *CUNNINGHAMELLACEAE*
    - a. *Cunninghamella*
        - i. *C. bertholletiae*[b]
3. *MORTIERELLACEAE*
    - a. *Mortierella*
        - i. *M. wolfii*
4. SAKSENAEACEAE
    - a. *Saksenaea*
        - i. *S. vasiformis*
5. *SYNCEPHALASTRACEAE*
    - a. *Syncephalastrum*
        - i. *S. racemosum*
6. *THAMNIDACEAE*
    - a. *Cokeromyces*
        - i. *C. recurvatus*

[a] *Data from Ribes JA, Vanover-Sams CL, Baker DJ. Zygomycetes in human disease. Clin Microbiol Rev. 2000;13(2):236–301.*

[b] *These species are the more common etiologic agents associated with mucormycosis in humans.*

Disease Manifestations/Epidemiology/Risk Factors

The Mucorales are saprophytic fungi ubiquitous in soil and decaying organic material. Mucorales species that are pathogenic in humans grow rapidly on any carbohydrate substrate and produce abundant sporangiospores via asexual reproduction.[24] Mucorales are also capable of sexual reproduction via fusion of two hyphae and formation of thick-walled structure called zygosporangium under stress conditions. Although sexual reproduction has been linked to virulence of *Mucor circinelloides* in preclinical studies, its significance during human invasive infections remains uncharacterized. Spores produced by the fungi become airborne, and inhalation of Mucorales conidia into the respiratory tract occurs daily. Even though these fungi grow in many ecological niches, the rarity of mucormycosis reflects the low virulence potential of Mucorales in immunocompetent hosts. For unclear reasons, the incidence of Mucorales infections, particularly of *Cunninghamella*, *Absidia*, and *Apophysomyces* spp., is higher in male patients (65%) than in female patients. The most common forms of mucormycosis based on anatomic localization include (a) rhinocerebral infection (39%), (b) pneumonia (24%), (c) disseminated infection (23%), (d) cutaneous/soft tissue infection (19%), (e) gastrointestinal infection (7%), and (f) uncommon presentations (7%). When compared to other opportunistic molds, Mucorales tend to infect a broad, more heterogeneous population of human hosts, including immunocompetent individuals. Specifically, Mucorales cause acute angioinvasive infections in patients with a variety of debilitating and immunosuppressive conditions, including those with poorly controlled diabetes mellitus (especially with diabetic ketoacidosis), neutropenia, malignancies, burns, or chronic renal failure with iron overload, as well as recipients of transplants and patients with renal failure receiving the iron (and aluminum)-chelating agent deferoxamine.[24] A common denominator of the aforementioned predisposing conditions is the loss of intra- and extracellular immune effector mechanisms, including nutritional immunity, which physiologically restrict fungal growth. Professional phagocytes mediate protective immunity against all filamentous fungi. However, there are important differences in the cellular and molecular host defense mechanisms against Mucorales as compared to *Aspergillus*, which are relevant to the unique pathogenesis of mucormycosis. It is important to emphasize that dissemination may occur from any of the primary sites of

Mucorales infection, mainly in patients with profound immunosuppression.

Of note, particular host immune defects predispose to different forms of mucormycosis. For example, patients with diabetic ketoacidosis are prone to the development of the rhinocerebral form of mucormycosis but less often suffer from pulmonary or disseminated infection. In contrast, pulmonary mucormycosis typically affects severely immunocompromised individuals, including patients with high-risk hematologic malignancies and recipients of hematopoietic stem cell and organ transplants. The predominance of pulmonary infection in those patients may be a result of chemotherapy-related defects in innate pulmonary host defenses associated with neutropenia and/or chemotherapy-induced mucociliary dysfunction. Prolonged and severe neutropenia is the sole identifying risk factor in approximately 15% of all reported mucormycosis cases. Nonetheless, like aspergillosis, mucormycosis is increasingly reported as a late (1–6 months), or very late (>6 months) community-acquired infection in nonneutropenic, HSCT recipients post-engraftment, especially in the setting of multiple, overlapping, and cumulative mechanisms of immunosuppression during GvHD treatment. In these patients, severe immunodeficiency due to high-dose glucocorticosteroid therapy and/or other immunosuppressive therapies frequently coexists with other comorbidities that are interrelated and difficult to quantify, such as hyperglycemia, metabolic acidosis, renal failure, iron overload, malnutrition, advanced age, and CMV infection.

A significant increase in the rates of mucormycosis has been observed recently among severely immunocompromised individuals classically at risk for other opportunistic mold infections, such as patients with acute leukemia and transplant recipients.[24–26] An autopsy study in hematologic malignancy patients from a single cancer institution with high background rates of mucormycosis reported a significant threefold increase in prevalence of autopsy-proven mucormycosis cases from 0.9% to 3% during the study period (1989–2003). Importantly, most of these infections were diagnosed postmortem. Similarly, there was a fourfold increase in the overall incidence of mucormycosis during a period of active surveillance at 25 U.S. transplant centers from 2001 to 2006, whereas the incidence of other opportunistic molds remained constant. In the aforementioned study the overall cumulative annual incidence (CI) of mucormycosis was the highest (0.29%) in HSCT recipients, particularly those receiving transplant from an HLA-unrelated donor (0.85%). Among solid-organ transplant recipients, the overall 12-month CI of mucormycosis was 0.07%, with lung transplants and liver transplants having the highest incidence of mucormycosis, at 0.18% and 0.16%, respectively. Of note, there was a seasonal variation in incidence of mucormycosis with declining rates among the groups transplanted in the first 4 months of each year. National studies in Europe that used administrative data from hospital records to capture cases of mucormycosis also demonstrated a significant increase in incidence of mucormycosis within a 10-year period.[24–26]

Of concern, a growing proportion of pulmonary mucormycosis cases manifest as breakthrough infections in patients receiving antifungal agents with activity against aspergillosis but not mucormycosis (i.e., voriconazole, echinocandins). Case series in high-risk leukemia and allogeneic HSCT patients suggest that mucormycosis should be considered whenever fungal sinusitis develops while on *Aspergillus*-active antifungal prophylaxis (i.e., voriconazole), especially in patients with prolonged immunosuppression, underlying diabetes or malnutrition, and in the setting of negative *Aspergillus* galactomannan assay and "therapeutic" voriconazole serum levels (e.g., voriconazole levels >2 ng/mL). Animal studies have demonstrated increased virulence of *Mucorales* spp. following voriconazole pre-exposure; previous voriconazole use has been independently associated with the development of mucormycosis in leukemia and transplant patients. Other studies have reported an increase in mucormycosis cases prior to the introduction of voriconazole, and a recent randomized trial on voriconazole prophylaxis in low- to moderate-risk allogenic HSCT recipients with favorable prognostic features did not find a higher incidence of mucormycosis. Hence, additional factors including underlying host immunoparalysis, evolving transplant practices, and immunosuppressive strategies that ultimately result in improved posttransplant survival could potentiate the association of voriconazole with development of mucormycosis. Very late-onset mucormycosis, occurring 2 years or more after transplantation, has been reported in a significant proportion of HSCT (13.8%) and SOT (33.3%) recipients in a multicenter prospective surveillance study.

There are inherent problems with epidemiologic studies on mucormycosis related to challenges in establishing a diagnosis and capturing shifts in prevalence of classic or unknown risk factors of infection in high-risk populations. Furthermore, surveillance strategies to capture the true incidence of mucormycosis are imperfect given that the diagnosis is difficult to achieve antemortem. Instead of registries that create databases based on hospital coding diagnoses, development of active surveillance programs is needed with long-term follow-up in selected high-risk patient groups such as transplant recipients.

■ Mycology

Mucorales are molds characterized by growth of hyphae in the environment and in tissue. They grow rapidly—within 2 to 5 days on most culture media—as fluffy gray or brownish colonies, with many of the species demonstrating aggressive vertical growth toward the lid of the Petri dish; these species are referred to as "lid lifters."[24] As the *Mucorales* colony matures, the mycelium may darken and exhibit a black pepper–like effect as large numbers of sporangia are formed. Cycloheximide inhibits the growth of these fungi, and media that contain this compound, such as Mycosel and mycobiotic agar, should not be used. Clinical tissue samples potentially infected with the *Mucorales* should be chopped, not ground, for inoculation into microbiologic cultures. All pathologic species grow well at 37°C.[24]

Microscopic examination for the presence and location of rhizoids and apophyses and to determine the morphology of the columellae differentiates the genera. Isolating and speciating the organism is important for selection of treatment. However, morphologic identification of Mucorales species is often imprecise.

■ Immunopathogenesis

Quantitative (i.e., neutropenia) or qualitative (i.e., associated with glucocorticoids, hyperglycemia, and/or acidosis) defects in phagocytic cell activity permit unrestricted growth of the hyphal form and development of mucormycosis. In particular, both hyperglycemia and acidosis are known to impair chemotaxis and the killing activity of phagocytic cells against Mucorales by impairing oxidative and nonoxidative mechanisms.[24] Likewise, corticosteroids impair migration, ingestion, and phagolysosome fusion in human macrophages.[3] However, the molecular mechanisms that account for attenuated phagocytic function in patients with hyperglycemia, ketoacidosis, or steroids are only partially characterized.

Iron metabolism has a central role in pathogenesis of mucormycosis.[3,25] Thus, patients with iron overload states, including those undergoing chelation therapy with deferoxamine, are uniquely predisposed to mucormycosis. Deferoxamine abolishes the fungistatic effect of serum and increases in vitro fungal growth by acting as a siderophore for Mucorales species.[25] The key role of iron utilization in pathogenesis of mucormycosis is further illustrated by the fact that conditional inactivation of the *R. oryzae* high-affinity iron permease gene, FTR1, renders the fungus nonpathogenic in mice.[25] Similarly, the increased susceptibility to mucormycosis of patients with acidosis, including diabetic acidosis, is attributed to increased availability of serum iron partially due to diminished affinity of transferrin for free iron at a lower pH (<7.4). Unlike deferoxamine, the other iron chelators, such as deferiprone and deferasirox that lack xenosiderophore activity for *Rhizopus*, induce an iron-starvation effect to the fungus and have shown to be protective in animal models of mucormycosis and in anecdotal reports of human infection.

A hallmark of mucormycosis is extensive angioinvasion with resultant vessel thrombosis and tissue necrosis (Fig. 132-10). Apart from mucoricin toxin production, interaction of Mucorales spores with endothelial cells appears to play a critical role in angioinvasion. Ibrahim et al. identified glucose-regulated protein 78 (GRP78) as a novel host receptor that selectively and specifically interacts with *Rhizopus* mediating invasion and damage of human endothelial cells by the fungus.[25] Of interest, elevated glucose and iron levels upregulate GRP78 expression and promote endothelial cell invasion and damage by *R. oryzae* in a receptor-dependent manner. From the fungal perspective, Mucorales bind to GRP78 endothelial receptors via a specific class of spore surface proteins, CotH invasins, which are unique for this class of fungi. Treatment of mice with anti-CotH antibodies augments opsonophagocytic uptake of fungal conidia by neutrophils and protect mice from development of invasive disease.

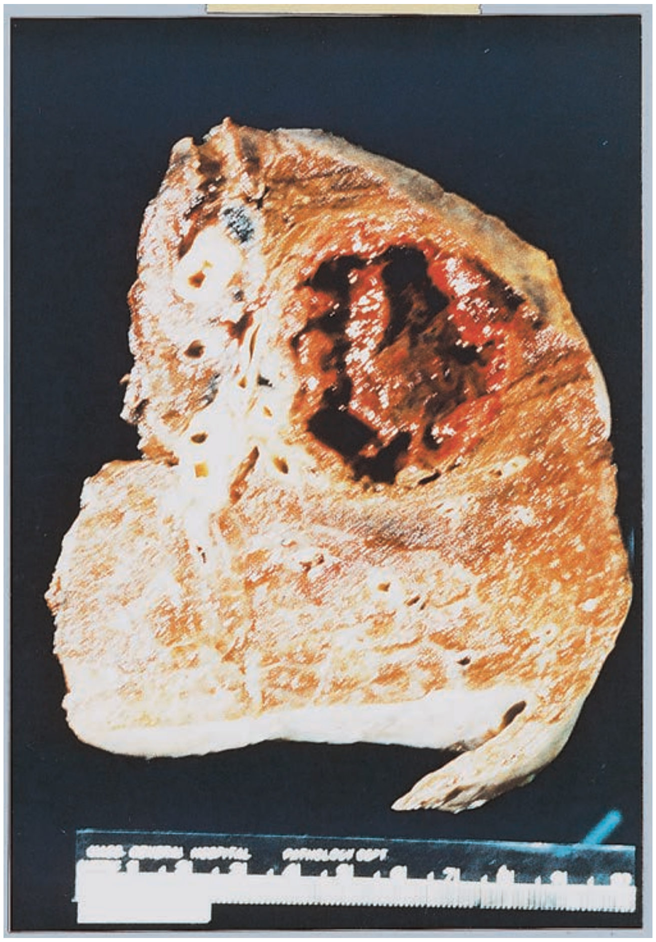

Figure 132-10 Pulmonary mucormycosis in a 63-year-old diabetic kidney transplant recipient with a rapidly expanding pulmonary mass. *(Reproduced with permission from Jay A. Fishman, Massachusetts General Hospital.)*

■ Clinical Manifestations

Although concomitant sinus infection is suggestive of pulmonary mucormycosis, the clinical manifestations of pulmonary infection are almost indistinguishable from those caused by the more common opportunistic mold *Aspergillus*.[24,26] Therefore, timely diagnosis is critical in the outcome of this infection because first-line antifungal agents typically used for aspergillosis, such as voriconazole, lack activity against Mucorales.

Clinical symptoms of pulmonary mucormycosis are subtle and nonspecific even at late stages of infection, especially in neutropenic patients and those receiving immunosuppressive therapies that dampen immune responses. Pulmonary mucormycosis frequently manifests with persistent fever on broad-spectrum antibiotics, nonproductive cough, progressive dyspnea, and pleuritic chest pain.[26] Infection has a propensity to traverse tissue planes in the lung, including the bronchi, diaphragm, chest wall, and pleura. Hyphal invasion of blood vessels results in necrosis of the surrounding parenchyma, ultimately leading to cavitation or potentially fatal hemoptysis. In patients with hematologic malignancies, clues for distinguishing pulmonary mucormycosis from IPA may include the presence of necrotic lesions in palate, severe sinusitis, rhino-orbital extension, prophylaxis with antifungals that possess activity against aspergillosis but not mucormycosis (i.e., voriconazole and the echinocandins), and possibly the repeated absence of detectable *Aspergillus* galactomannan antigen and/or b-glucan in the serum.[24,26] Unfortunately, the frequent coexistence of bacterial or mixed fungal pneumonia (up to 22% in a single-institution observational study) in high-risk hematologic malignancy patients can further complicate early diagnosis and management of pulmonary mucormycosis. Pulmonary mucormycosis rapidly spreads to the contralateral lung and distal organs if not promptly treated. While patients with pulmonary mucormycosis usually die from disseminated disease before respiratory failure occurs, dissemination is rarely detected antemortem. The overall mortality rate of pulmonary mucormycosis ranges from 50% to 70% but exceeds 90% with extrathoracic dissemination.[24,26]

A multitude of patterns may be present in a regular chest radiograph of patients with pulmonary mucormycosis, including lobar consolidation, nonspecific infiltrates, cavities, masses, and nodules. Similar to IPA, high-resolution chest CT is the best method of determining the extent of pulmonary mucormycosis and typically demonstrates evidence of the infection earlier than standard chest radiographs. While nodular opacities without an air bronchogram indistinguishable from those of aspergillosis are the most common findings on CT scan, the presence of multiple nodules (≥10) and, to a lesser degree, pleural effusions may favor the diagnosis of pulmonary mucormycosis.[24] Halo and air crescent signs are encountered less frequently in leukemic patients with pulmonary mucormycosis compared to pulmonary aspergillosis. However, the presence of air crescent sign in centrally located lesions reflects an increased risk of pulmonary artery erosion and massive hemoptysis. Small case series suggested that a reverse-halo sign, a focal round area of ground-glass attenuation surrounded by a ring of consolidation, may be a common early radiographic finding in neutropenic patients with invasive pulmonary mucormycosis versus aspergillosis, especially when accompanied by a thick (>1 cm) outer consolidation rim.[24,26]

Atypical presentations of pulmonary mucormycosis include chronic infection with constitutional symptoms that last for several months in relatively immunocompetent hosts, multiple mycotic pulmonary artery aneurysms and pseudoaneurysms, bronchial obstruction, asymptomatic solitary nodules, or even normal chest radiographs. Of interest, patients with diabetes mellitus have an apparent predilection for the development of endobronchial lesions, accounting for more than 80% of reported cases in the literature. Furthermore, pulmonary mucormycosis tends to present with a less fulminant, subacute clinical course in these patients. However, endobronchial lesions may occasionally lead to obstruction of major airways or erosion of major pulmonary blood vessels and fatal hemoptysis. In lung transplant recipients, ulcerative tracheobronchitis at the bronchial anastomotic site is rarely caused by Mucorales when compared to *Aspergillus*; however, changes in immunosuppressive and antifungal prophylaxis practices could lead to the emergence of this infection in the future.[24]

Similar to *Aspergillus* spp., Mucorales species rarely produce an asymptomatic mycetoma within a pre-existing lung cavity. Allergic *Rhizomucor* sinusitis has been reported in immunocompetent individuals. In addition, hypersensitivity pneumonitis caused by *Rhizopus* has been described in farm workers as well as in Scandinavian sawmill workers (wood trimmer's disease).[24]

■ Diagnosis

Little improvement has been made over the past few decades in the diagnosis of mucormycosis, which still relies on histopathology and traditional culture methods. Timely diagnosis of mucormycosis requires a high index of suspicion and largely depends on histopathological demonstration of tissue invasion by the characteristic hyphae or by isolation of Mucorales species in cultures of sterile tissue, which necessitates implementation of an invasive procedure. Tissue swabs, sputum, or bronchial alveolar lavage fluid cultures are usually nondiagnostic, but provide an important indication of disease and allow for the establishment of probable infection in immunocompromised patients.[24] Blood cultures rarely, if ever, grow Mucorales species despite the angioinvasive nature of these pathogens.

Mucorales stain poorly with PAS and Gram stains but stain very well with Grocott–Gomori methenamine-silver. Treatment with fluorescent stains such as calcofluor-white or Blankofluor may aid in detection of hyphal elements and improve the discrimination between septated and aseptate molds. In tissue specimens Mucorales appear as broad (10–20 μm in diameter) nonseptate hyphae with branches occurring at right angles (Fig. 132-11). Differentiation of *Aspergillus*, *Fusarium*, *Scedosporium* spp., or other hyalohyphomycetes from Mucorales hyphae in tissue involves visualizing thinner, more regularly shaped fungal elements with more frequent acute angle branching and the presence of septae in the former group.[24]

In the majority of patients with pulmonary mucormycosis, establishment of a definite diagnosis with biopsy is hampered by the presence of comorbidities, such as thrombocytopenia. Furthermore, routine laboratory cultures, even if performed from tissue specimens with abundant Mucorales hyphal growth, have a yield of less than 50%. Recovery from tissue can be improved by mincing (not homogenizing) tissue and use of culture techniques that simulate in vivo growth, including incubation at 35° to 37°C in semianaerobic conditions.[24,26]

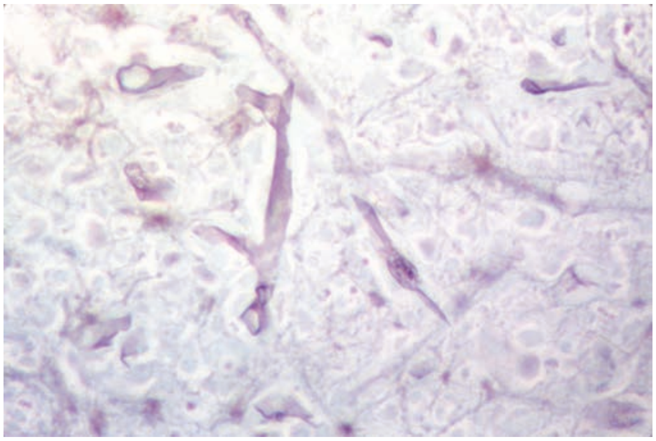

Figure 132-11 Histopathologic features of Zygomycetes hyphae in a profoundly neutropenic patient with leukemia in whom pulmonary mucormycosis developed. Of note is the characteristic broad nonseptate or rarely septate hyphae with branches at right angles. H&E stain, ×400. *(Reproduced with permission from Dr. G.P. Bodey.)*

The importance of early differentiation of pulmonary mucormycosis from other IMIs has generated considerable interest in the development of surrogate diagnostic tests such as detection of specific antigens or nucleic acid by PCR. Unfortunately, serology-based diagnostic assays such as *Aspergillus* galactomannan and b-glucan are not useful for detection of mucormycosis. Other molecular diagnostic techniques using PCR assays in serum samples or paraffin wax embedded tissue or in situ hybridization techniques are promising but remain investigational. In a prospective study of CT-guided percutaneous lung biopsy samples from high-risk patients with suspected fungal pneumonia, investigators demonstrated that early diagnosis and differentiation of pulmonary mucormycosis from IPA could be improved using a three-step analysis approach of biopsy specimens of lung lesions that included calcofluor-white staining to rapidly distinguish septated versus aseptate hyphae, *Aspergillus* galactomannan and PCR testing for rapid identification, and PCR testing of DNA in selected biopsy specimens where aseptate hyphae were observed or *Aspergillus* markers were negative.[24] These promising results require validation in a wider range of patients before PCR becomes a standardized adjunctive diagnostic test for mucormycosis.

■ Treatment

Successful treatment of pulmonary mucormycosis relies on timely diagnosis, reversal of underlying predisposing factors, early and broad surgical debridement of infected tissue (when possible), and rapid administration of effective antifungal therapy in the context of a multidisciplinary approach.[24,26] Cooperation among the primary care physicians, infectious disease consultants, surgeons, microbiologists, and pathologists is essential in the early stages of infection to avoid unnecessary diagnostic and treatment delays that increase patient morbidity and mortality.[26] For example, patient outcomes can be improved if initial treatment decisions are based on frozen tissues biopsy rather than from paraffin-embedded tissue samples. Similarly, delays in the administration of effective systemic antifungal therapy within the first few days of diagnosis increase the probability of patient death due to progressive and/or disseminated infection. In addition, rapid correction of underlying conditions such hyperglycemia, diabetic ketoacidosis or other form of acidosis, tapering of corticosteroids, and other immunosuppressive drugs is critical to outcome. Notably, there have been rare cases of pulmonary mucormycosis with spontaneous regression of infection after correction of diabetic ketoacidosis.[24]

Antifungal Treatment

With the exception of the recently completed DEFEAT *Mucor* study, there are no other prospective studies for the treatment of pulmonary mucormycosis because of the rarity and heterogeneity of the infection. Most evidence on the activity of existing antifungal agents comes from small case series, anecdotal case reports, and animal studies. Based on consensus guidelines,[24] the liposomal formulations of AMB have become the mainstay for treating mucormycosis in view of their favorable toxicity profile and comparable clinical outcomes with those historically reported for conventional AMB-based therapy. Thus, in the largest reported case series of mucormycosis including 24 patients who received a lipid complex of AMB for refractory disease or intolerance of conventional AMB, the overall response rate was 71%, without significant toxic effects even in patients with pre-existing renal disease. Animal models of pulmonary mucormycosis suggest a possible benefit for early administration of higher dosages of lipid AMB, and a phase 2 clinical study of 10 mg/kg/d liposomal AMB in mucormycosis will further address this question (*clinicaltrials.gov/ct2/show/NCT00467883*).[24,25] Recent guidance from European Confederation for Medical Mycology recommends 5 to 10 mg/kg/d liposomal AMB with a dose of 10 mg/kg/d in cases of CNS involvement.[24,25]

Alternative routes of administration of amphotericin B as an adjunct to systemic therapy have been reported in pulmonary mucormycosis, although the efficacy of this approach is difficult to discern. For example, case reports describe the successful treatment of cancer patients with pulmonary mucormycosis using systemic therapy and ABLC aerosolized with a Respirgard II nebulizer, and direct instillation of amphotericin B within pulmonary cavities or into the pleural space.

In a recent, open-label, single-arm study the efficacy of the newer triazole isavuconazole as first-line treatment was tested and found to be similar to that of a historic matched control group treated with amphotericin B formulations. This limited size study enrolled 21 patients and compared them with 33 matched patients from the FungiScope registry. As a result, isavuconazole has FDA approval for first-line treatment of mucormycosis and has been endorsed in recent guidelines. Importantly, cases of breakthrough mucormycosis in patients receiving isavuconazole secondary prophylaxis have been reported, and the activity of this antifungal is variable across different Mucorales species.[24]

Posaconazole, an orally available broad-spectrum triazole, possess reliable activity against Mucorales and was until recently the only alternative therapy for mucormycosis. In an open-label salvage trial, the overall success rate of posaconazole was 70% in 24 patients and was associated with minimal toxicity. Similarly, a retrospective review of posaconazole-based salvage therapy in 91 patients who had refractory mucormycosis indicated an overall success rate of 61%, including a success rate of 65% in the group of patients with pulmonary mucormycosis.[24] Nonetheless, posaconazole exerts limited activity against *Rhizopus* spp. in neutropenic mouse models, and cases of breakthrough mucormycosis in HSCT recipients while on posaconazole prophylaxis have been reported. Treatment with oral posaconazole has important pharmacokinetic limitations related to drug interactions and the poor absorption of the drug, especially in patients with mucositis and those with poor dietary intake, while steady-state plasma concentrations of posaconazole are not reached until around 1 week of therapy.[26] Drug interactions can be problematic, especially in patients receiving drugs that accelerate CYP P450 metabolism (i.e., rifampicin), or acid suppression therapy particularly with proton pump inhibitors. Therefore, it is preferable that patients with mucormycosis should initially receive several days of a lipid AMB formulation before being started on posaconazole therapy, and plasma drug level monitoring may be necessary in selected patients. Patients with persistently low or undetectable serum drug levels, poor oral intake, or GI dysfunction (severe nausea, diarrhea) often must be transitioned back to intravenous liposomal AMB even in the absence of obvious disease if they are receiving additional immunosuppressive therapy. Overall, posaconazole seems to be a favorable option for less severely immunocompromised patients who need to be on continuous long-term antifungal therapy given the high risk for relapse of mucormycosis. The new (IV and oral slow-release tablet) formulations of posaconazole display improved pharmacokinetics and have been recommended as an alternative first-line therapy for mucormycosis.

Echinocandins lack activity against Mucorales in vitro, and clinical experience with caspofungin in the treatment of mucormycosis is extremely limited. Nevertheless, in case reports and a study with a model of disseminated mucormycosis in diabetic mice, echinocandins appear to have some role, especially in combination with a polyene, in serious cases of mucormycosis.[24] A combination ABLC-caspofungin treatment regimen was associated with improved therapeutic success (100% vs. 45%; $p = 0.02$) in 41 diabetic patients with biopsy-proven, mostly rhino-orbital cerebral mucormycosis.[26] Recent ECMM recommendations are against the use of echinocandins in management of mucormycosis.[24]

The duration of treatment required for mucormycosis should be highly individualized. Near normalization of radiographic imaging, negative biopsy specimens, and cultures from the affected site, and recovery from immunosuppression, are indicators that a patient is a candidate for stopping antifungal therapy. Intracellular persistence of dormant Mucorales conidia inside tissue macrophages supports the use of long-term secondary prophylaxis in patients with mucormycosis.

Surgical Treatment

Because mucormycosis is a highly angioinvasive infection with resulting extensive thrombosis and tissue necrosis, antifungal agents often display poor penetration at the site of infection. Therefore, even if the causative *Mucorales* strain is susceptible to the antifungal agent in vitro, the agent may be ineffective in vivo. Surgical debridement of infected lung tissue should be performed on an urgent basis. In patients with pulmonary mucormycosis, surgical treatment in conjunction with antifungal therapy has been shown to significantly improve survival when compared with antifungal therapy alone. Hence, a comprehensive review of cases of pulmonary mucormycosis showed that the mortality in patients who received antifungal agents alone was 55% versus 27% in patients who received antifungal agents and surgery.[24] Removal of as much of the infected or devitalized tissue as possible while the infection is localized has the greatest benefit. Lobectomy is often required, and pneumonectomy may be necessary for proximal or extensive involvement. Also, repeated procedures may be needed. The benefit of pulmonary resection diminishes as dissemination occurs.

Other Adjunctive Therapies

Small case series implicate that treatment with hyperbaric oxygen (HBO) may be a beneficial adjunct to standard therapy for mucormycosis, particularly in patients with diabetes mellitus who have rhinocerebral disease.[24] HBO has pleiotropic properties by promoting wound healing, phagocytic cell function, and oxidative killing mechanisms of Mucorales by AMB and also displays direct antifungal activity. However, data on treatment with HBO of pulmonary mucormycosis are scarce, and a role in this setting remains uncertain.

The role of adjunctive cytokine therapy for mucormycosis has not been extensively studied. Cytokines that activate phagocytic activity, such as IFN-γ and GM-CSF, increase the killing efficacy of phagocytic cells against Mucorales species in vitro. Case reports indicate a favorable outcome in selected patients with rhinocerebral mucormycosis who received IFN-γ and GM-CSF adjunct salvage treatment. In selected neutropenic patients, granulocyte transfusion may be a useful bridge until neutrophil recovery, although the clinical benefit remains unproven and serious adverse effects that resemble immune reconstitution inflammatory syndrome (IRIS), including pulmonary toxicity and accelerated cavitation/bleeding, have been reported in patients with opportunistic lung mycoses.[24,26] Importantly, granulocyte transfusions contain not only neutrophils but also substantial number of lymphocytes, and HLA alloimmunization can be a major complication of granulocyte transfusions. Thus, the benefits and risks of granulocyte transfusions should be carefully assessed on an individual basis, particularly for patients who are candidates for HSCT. Adoptive T cell–based immunotherapeutic strategies are feasible and could represent an attractive future strategy in the management of mucormycosis.

The central role of iron metabolism in the pathogenesis of mucormycosis supports the hypothesis of using iron chelators without xenosiderophore activity, such as deferiprone and deferasirox, as adjunctive antifungal therapy.[26] In contrast with deferoxamine, such iron chelators induce iron starvation in the fungus, thereby inhibiting growth in vitro in the presence of iron and improving survival in a diabetic ketoacidosis animal model of mucormycosis. Case reports imply that deferasirox with antifungals may be less effective in neutropenic patients than in diabetic ketoacidosis patients. Moreover, the bioavailability of oral deferasirox in immunocompromised patients with mucositis due to chemotherapy or GvHD of the gut is unknown. Importantly, a recently completed, phase 2, double-blind, randomized, placebo-controlled trial of adjunctive deferasirox therapy failed to demonstrate a benefit of the combination regimen in 20 patients with mucormycosis (DEFEAT *Mucor* trial, NCT00419770).

EMERGING OPPORTUNISTIC PULMONARY MYCOSES

Over the past three decades, and with the ever-expanding spectrum of immunocompromised patients, we have witnessed the emergence of less common but medically important opportunistic fungal pathogens, including septate filamentous fungi such as hyalohyphomycetes (e.g., *Fusarium*, *Scedosporium*, *Lomentospora prolificans*, *Trichoderma* species), dematiaceous fungi (e.g., *Phaeohyphomycetes*), endemic dimorphic pathogens (e.g., *Penicillium marneffei*), and rare pathogenic yeasts (e.g., *Trichosporon* species).[27–30] The diagnosis of invasive fungal pneumonia caused by these uncommon filamentous fungi is challenging because of the similarity of the manifestations and histopathologic features of these mycoses with those of IA. Given the fact that most of these infections have a poor outcome because of broad-spectrum resistance to conventional antifungal agents and the severity of underlying immunodeficiency, timely diagnosis is critical for outcome. Therefore, pulmonary infections caused by hyalohyphomycetes, including *Fusarium* and *Scedosporium* and *Lomentospora prolificans* species, are discussed below.

■ Pulmonary Fusariosis

Fusarium spp. are ubiquitous filamentous fungi found in soil, water, and decaying material. Although *Fusarium* is a well-known plant pathogen, only a few of the 50 different species have been reported to be pathogenic in humans, including *Fusarium solani*, *F. oxysporum*, *F. moniliforme*, *F. verticillioides*, *F. dimerum*, and *F. proliferatum*.[27] Of these species, *F. solani* is the most virulent, causing half of all cases of invasive fusariosis reported in humans. Since the description of the first case of disseminated fusariosis in a child with acute leukemia in 1973, invasive fusariosis has emerged in some tertiary care oncology centers as an important IMI in profoundly immunocompromised patients with hematological malignancy.[29]

There seems to be a distinct seasonal peak and geographic distribution of invasive fusariosis. The vast majority of cases have been reported in the United States during the rainy summer season, when the dispersion of fusarial conidia in the air is most pronounced.[29] More than 90% of human invasive fusariosis cases occur in neutropenic patients with hematologic malignancies, especially those with acute leukemia. Another risk factor for invasive fusariosis is GvHD treated with high doses of corticosteroids during the postengraftment period in HSCT recipients.[27–31]

The skin and respiratory tract are the primary portals of entry for *Fusarium* infection. In particular, onychomycosis and paronychia are typical skin entry sites in the immunocompromised host. Inhalation of *Fusarium* conidia through the lung and paranasal sinuses by a severely immunocompromised host may lead to sinopulmonary infection characterized by angioinvasion, extensive tissue necrosis, and secondary dissemination. In addition, disruption of skin integrity because of local trauma or placement of a central venous catheter or in the setting of onychomycosis with associated cellulitis appears to be a relatively common portal of entry for disseminated *Fusarium* infection that involves the lung in immunocompromised hosts. The ability of *Fusarium* spp. to undergo adventitious sporulation with formation of microconidia in vivo facilitates dissemination and may account for the high rates of positive blood cultures and associated skin lesions in cases of fusariosis.[29] Neutrophils probably play the most critical role in the control of human *Fusarium* infections. Several studies have demonstrated that the prognosis for patients with fusariosis is associated with the prompt recovery of neutrophil counts. In fact, the mortality rate in patients with fusariosis in the setting of profound, prolonged neutropenia is essentially 100%, even with prompt administration of effective antifungal treatment, compared with a rate of approximately 30% in the setting of neutrophil recovery.[28]

Fusariosis in immunocompromised patients manifests in four major patterns: refractory fever of unknown origin, sinopulmonary infection or pneumonia, disseminated infection, and a variety of focal single-organ infections.[29] Sinopulmonary fusariosis and pneumonia occurs in more than 80% of patients and is most often clinically and radiographically indistinguishable from the much more common IA and other IMIs. Sinus involvement is also frequent, as it has been observed in up to 80% of cases in some reports.[29] One of the diagnostic challenges in immunocompromised patients with fungal pneumonia is differentiating between IA, invasive fusariosis, and mucormycosis. Hence, recovery of *Fusarium* spp. from cultures of blood (~70% fungemia) and other appropriate specimens and detection of GM antigen in serum (present in >80% of patients) is essential for a definite diagnosis.

The histopathologic picture of *Fusarium* is identical to that of *Aspergillus* and other hyalohyphomycetes (e.g., *Scedosporium* spp.) and may lead to misidentification. Even so, there are subtle differences in the histopathologic features of *Aspergillus* and *Fusarium* spp. that can facilitate differentiation between the two species based on the histopathology itself, including the presence of *Fusarium* chlamydosporia in tissue (Table 132-8).

Because hyalohyphomycetes (*Aspergillus* vs. *Fusarium* vs. *Scedosporium* spp.) have different levels of susceptibility to antifungal agents, the ability to differentiate between these molds in histopathology-positive but culture-negative cases using molecular identification methods could have significant implications on therapeutic decision-making. In situ hybridization directed against ribosomal 18 S RNA sequences was shown to rapidly and accurately distinguish *Fusarium*, *Aspergillus*, and *Scedosporium* spp. from histopathologic specimens.[28] However, further standardization of these promising molecular methods is needed. Proteomic-based approaches with the use of mass spectroscopy (MALDI-ITOF) are capable to provide rapid diagnosis of clinical isolates of *Fusarium*. These techniques are promising in diagnosis of fungal pathogens but require further standardization and are not widely available. Thus, tissue cultures remain the gold standard for differentiation between these fungi.

Despite the clinical similarities between pulmonary fusariosis and IPA, there are some characteristics that favor the diagnosis of invasive fusariosis (Table 132-8). First, *Fusarium* spp. are usually recovered from blood specimens in the setting of disseminated disease. The reported rate of positive blood cultures in patients with disseminated fusariosis ranges from 50% to 70%, and fungemia may be the only manifestation of the infection.[29] *Fusarium* is the most common mold associated with true fungemia in HSCT recipients.[31] This feature contrasts with disseminated IA and mucormycosis cases in which these molds are rarely (<5%) isolated from blood specimens, with the notable exception of *A. terreus*.

TABLE 132-8 Differentiating Features Among the Major Opportunistic Mold Infections of the Lung

Incidence	• *Aspergillus* causes the vast majority of cases of fungal pneumonia, followed by Mucorales
Predisposing factors	• Mucorales are associated with the presence of diabetes mellitus, acidosis, malnutrition, iron overload states, and voriconazole prophylaxis
Clinical features	• Skin lesions are more common in disseminated fusariosis (50%–70%) than in disseminated IA (<10%) and disseminated mucormycosis (<10%) • Skin lesions in fusariosis are different from those in IA and mucormycosis (*Aspergillus and* Mucorales skin lesions are fewer, less widespread, have a larger diameter, and present with a black eschar with a thinner erythematous halo) • Fungemia is more common in fusariosis (60%–70%) than in IA (<5%) and mucormycosis (virtually absent) • Fungemia also often occurs earlier in fusariosis than in IA (shortly before death or after death) • Mucorales *and Fusarium* spp. are highly resistant to antifungal agents and develop as breakthrough infections to antifungals with anti-*Aspergillus activity*
Histopathologic features	• Broad-based nonseptate or pauciseptate ribbon-like hyphae are pathognomonic for Mucorales • The presence of chlamydosporia in histopathology is pathognomonic for *Fusarium* spp.
CT features	• On CT scans, reverse halo sign, multiple (>10) nodules, and pleural effusions favor the diagnosis of pulmonary mucormycosis vs. IPA • Pulmonary mucormycosis has a predilection for the upper lung lobes
Serology	• Positive galactomannan antigen is virtually diagnostic for IPA; cross-reactivity of *Aspergillus* galactomannan antigen with *Fusarium* spp.

Another distinctive feature of invasive fusariosis is the high incidence (50%–70%) of necrotic skin lesions in patients with disseminated disease. This contrasts with the low incidence of skin lesions in patients with disseminated aspergillosis (<10%). In fact, skin lesions are frequently the sole diagnostic material for invasive fusariosis in a high-risk patient with presumed fungal pneumonia. Several patterns of skin lesions can be seen: subcutaneous nodules, purpura, red or gray macules and/or papules with or without progressive central necrosis, flaccid pustules, vesicles, and hemorrhagic bullae.[29] The most characteristic skin lesions encountered in cases of disseminated fusariosis are "ecthyma gangrenosum–like" lesions, which are red or gray macules with central ulceration or black eschar. *Fusarium* skin lesions are often tender, especially subcutaneous nodules, and can involve any skin site, although they appear predominantly in the extremities. Most patients have lesions at different stages of evolution. Accompanying myalgias are also common, reflecting concomitant muscle involvement.

Fusarium species are quite resistant to the arsenal of modern antifungal agents, and breakthrough infections to AMB or triazoles are common.[29] In particular, *F. solani* is the most resistant species within the genus. The mainstay in the treatment of fusariosis has traditionally been AMB-D. However, the in vitro susceptibility of *Fusarium* spp. to AMB-D is, at best, mediocre. Whether the in vitro susceptibility of *Fusarium* spp. alone can predict outcome is unclear because other factors, such as neutrophil recovery, are probably the most critical determinants of the prognosis for fusariosis. There have been reports of improved outcome of fusariosis with the use of high-dose lipid formulations of AMB. Hence, the mortality rate in patients who received high doses of a lipid complex of AMB (>5 mg/kg/d) was significantly lower (<30%) than that observed in patients who received conventional AMB-D doses (>75%) in a previous study.[29]

Among the antifungal triazoles, fluconazole and itraconazole are not active against *Fusarium* spp. However, the newer broad-spectrum triazoles voriconazole and posaconazole have variable in vitro activity against *Fusarium* spp. and may show promise in the management of fusariosis. A recent retrospective study evaluated the outcome of 73 patients with fusariosis treated with voriconazole either as frontline (22%) or salvage (78%) therapy, with an overall response rate of 47%. Another retrospective study in 21 patients with fusariosis refractory or intolerant to AMB-based therapy reported a 48% response rate in 10 patients receiving salvage posaconazole.[29] Given that AMB and the newer triazoles voriconazole and posaconazole are the most active agents against *Fusarium* spp., a strategy combining a lipid formulation of AMB with one of these triazoles is frequently employed in clinical practice. A retrospective study examined the rationale of combination therapy in 44 hematologic malignancy patients with fusariosis. The majority of these patients (73%) received combination therapy with amphotericin B and a triazole, with 41% response at 12 weeks after diagnosis. Overall, the rationale of combination therapy for fusariosis is reasonable and merits further investigation.[29] Isavuconazole displays less potent in vitro activity when compared to the other triazoles. Nonetheless, frontline isavuconazole therapy in a small case series of 7 patients (enrolled in VITAL and SECURE trials) resulted in 44% survival at 90 days.

Because the neutrophil count seems to be the most crucial prognostic determinant in fusariosis cases, a potentially beneficial adjuvant therapeutic strategy is to transfuse granulocytes obtained from G-CSF– and GM-CSF–stimulated donors.[29] Granulocyte transfusion has been suggested to result in more favorable response rates (33%–50%) in profoundly neutropenic patients by shortening the duration of neutropenia.[29]

■ Pulmonary Scedosporiosis

The genus *Scedosporium* comprises a group of filamentous fungi found ubiquitously in the environment. The two major human pathogenic species are *Scedosporium apiospermum*—the asexual state of *Pseudallescheria boydii*—and *Lomentospora prolificans* (formerly *Scedosporium prolificans* or *S. inflatum*).[27,28,30] Both of these species histologically resemble *Aspergillus* spp. with hyphae that are septate and branching at acute angles. Although *Scedosporium* infections can occasionally occur in immunocompetent individuals, the overall incidence has increased over the past decade because of improved diagnostic modalities and the expanding population of immunocompromised individuals. These fungi can cause fatal angioinvasive infections in immunocompromised hosts that manifest with sinopulmonary, central nervous system, osteoarticular, ocular, endovascular, and lymphocutaneous involvement.[27,28,30] Disseminated infection is associated with high (>75%) mortality rates. *Scedosporium* spp. are known to be remarkably resistant to most conventional antifungals, such as AMB; treatment with newer triazoles, such as voriconazole, appears to be more efficacious.[27,28,30,31]

Spores of *Scedosporium* spp. enter the respiratory tract by inhalation and the skin by direct inoculation to areas of trauma. Germination of conidia results in hyphal invasion in tissue with the potential to disseminate hematogenously to distant anatomic sites. Similar to *Fusarium* spp., dissemination may be facilitated by the ability of *Scedosporium* spp. to undergo adventitious sporulation in vivo. In general, strains of *Lomentospora prolificans* are more virulent than strains of *S. apiospermum*. *Lomentospora prolificans* produces melanin, which may be an important virulence factor contributing to in vivo protection against host defense mechanisms.[27,28,30]

Patients with AIDS, congenital or acquired immunodeficiency, or hematologic malignancies as well as recipients of stem cell and solid-organ transplants and those receiving antineoplastic or immunosuppressive medications are especially susceptible to these filamentous molds.[27,28,30] In these immunocompromised individuals, sinopulmonary disease with hematogenous dissemination to various organs most often occurs. Of interest, a recent review of 189 cases of pulmonary scedosporiosis reported that 11% of all cases were in immunocompetent patients following near-drowning. This association implies the higher virulence of *Scedosporium* spp. compared to other opportunistic molds.[27,28,30]

The spectrum of pulmonary scedosporiosis largely mimics aspergillosis, ranging from respiratory tract colonization, to allergic bronchopulmonary hypersensitivity, to saprophytic fungus ball formation in pre-existing pulmonary cavities, and, finally, to invasive pulmonary or disseminated scedosporiosis.[27,28,30] Invasive disease without pre-existing lung tissue damage caused by *S. apiospermum* generally occurs only in immunocompromised hosts during or immediately after periods of prolonged neutropenia or with intensification of immunosuppression, and fever is the most common clinical presentation. Onset of infection may also be manifested by pulmonary symptoms, maculopapular skin lesions that later may become necrotic, myalgias, and central nervous system and other organ involvement.[27] On rare occasions, pulmonary infections that spread to involve the central nervous system are reported in immunocompetent individuals after massive inoculation with *S. apiospermum* by aspiration of polluted water.[27] Fungemia is diagnosed in more than two-thirds of patients with disseminated *Lomentospora prolificans* and *S. apiospermum* infection. The radiographic appearance of pulmonary infections caused by *S. apiospermum* and *Lomentospora prolificans* is essentially indistinguishable from that of IPA. Because no radiographic findings are truly pathognomonic for *Scedosporium* infections, diagnosis relies on prompt histopathologic and microbiologic evaluation.

Histopathological features of *Scedosporium* spp. in tissue sections can be confused with those of other fungi that have acute-angle–branching septate hyphae. The melanin-specific Fontana–Masson stain may be used to confirm the presence of dematiaceous hyphae of *Lomentospora prolificans* in tissue.[27,28,30] Nevertheless, definitive diagnosis requires fungal culture and is crucial for antifungal susceptibility testing.

In general, *Lomentospora prolificans* is resistant to all clinically available antifungal agents, whereas *S. apiospermum* may be susceptible to miconazole, voriconazole, and posaconazole.[27,28,30] Both species are inherently resistant to the polyenes, including AMB. Data from clinical studies are limited. In a multicenter study of voriconazole administered as salvage therapy for scedosporiosis, the overall response rate of voriconazole for scedosporiosis outcomes of voriconazole therapy for *S. apiospermum* (33%) was somewhat better than that for *Lomentospora prolificans* (25%).[27,28,30]

Severe *Lomentospora prolificans* infections have been successfully treated with a combination of voriconazole and terbinafine.[27,28,30] In combination with azoles, terbinafine, an allylamine that blocks squalene epoxidase in the ergosterol synthesis pathway, has demonstrated synergistic interactions in vitro against clinical isolates of *S. prolificans*. Limited experience in patients with disseminated *Lomentospora prolificans* suggests that the combination of voriconazole and terbinafine is a legitimate treatment option, although the unfavorable pharmacokinetic characteristics of terbinafine preclude use as monotherapy.

Surgical debridement in cases of pulmonary scedosporiosis should be considered, especially for abscess drainage as well as for localized infections. In general, neutrophil recovery has been associated with an improved prognosis. IFN-γ and GM-CSF have been shown to enhance neutrophil oxidative mechanisms of killing against *S. prolificans* hyphae.[27,28,30] Although clinical data are scarce, in view of the dismal prognosis for patients with *Scedosporium* infections, immunomodulating therapy, including G-CSF, GM-CSF, IFN-γ, and primed white blood cell transfusions, should be considered as an adjunct treatment modality for these infections.[27,28,30]

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CHAPTER 133

Cryptococcosis and the Endemic Mycoses: *Histoplasma*, *Blastomyces*, and *Coccidioides*

Marwan M. Azar
Nathan C. Bahr
Joshua Malo
Chadi A. Hage

INTRODUCTION

The dimorphic fungi *Histoplasma capsulatum*, *Blastomyces dermatitidis*, and *Coccidioides immitis/posadasii* and the yeast *Cryptococcus neoformans* share important epidemiologic, mycologic, and clinical characteristics. With the exception of *Cryptococcus neoformans* var. *neoformans*, which exhibits no strong geographic predilection, these fungi are found in the soil and other environmental niches of certain endemic regions within the United States, particularly the Mississippi and Ohio River valleys for *H. capsulatum* and *B. dermatitidis*, the Southwestern United States for *C. posadasii/immitis*, and the Pacific Northwest for *Cryptococcus neoformans* var. *gattii* (Fig. 133-1). Beyond the United States, areas of high endemicity have been established across all six inhabited continents, lending global significance to these fungal pathogens (Fig. 133-1).[1] Additionally, due to global warming, anthropomorphic land utilization, and a world that is increasingly interconnected by the mass migration of people and goods, the geographic extent and epidemiology of endemic fungi are changing. Infection most commonly follows inhalation of aerosolized infectious particles when sites containing the organism are disturbed. Within the human host, these pathogens exist in yeast form and must be distinguished from other pathogenic yeast and from one another based on mycologic characteristics including size, wall thickness, and presence and type of budding, among others important features. Unlike many other fungi that cause disease only in immunocompromised hosts or in those with disrupted mucosal or skin barriers, the dimorphic fungi and *Cryptococcus*, especially *Cryptococcus neoformans* var. *gattii*, can lead to local and disseminated disease in the immunocompetent host. Indeed, the majority of those hospitalized due to infection with endemic mycoses in the United States and up to 20% of HIV-negative patients with *Cryptococcus* infection have no identifiable immunologic deficits.[2] In endemic areas, dimorphic fungal pathogens account for up to 30% of community-acquired pneumonia and respiratory manifestations mimic those of bacterial pneumonia leading to antibiotic misuse, diagnostic delays, and increased morbidity and mortality.[3] Both *Cryptococcus* and the endemic fungi can lead to a wide spectrum of pulmonary manifestations ranging from subclinical and mild respiratory symptoms to acute, subacute, and chronic pneumonias, mediastinal involvement, and acute respiratory failure as well as a variety of pulmonary infiltrates, including nodules, consolidations, cavities, and ground-glass opacities among others. These presentations must be distinguished from other infectious and noninfectious pulmonary processes such as bacterial pneumonia, tuberculosis, lung cancer, and sarcoidosis that may present similarly. Dissemination outside the lungs occurs more commonly in immunosuppressed hosts and is associated with high mortality. In the United States, direct healthcare costs from histoplasmosis, blastomycosis, and coccidioidomycosis alone approach $500 million annually, emphasizing the devastating impact of endemic mycoses and the need for increased awareness, early diagnosis, and effective treatment modalities.[4]

CRYPTOCOCCAL INFECTIONS

Cryptococcus neoformans is an encapsulated yeast that has a worldwide distribution. Cryptococcosis occurs when *C. neoformans* is inhaled and, after gaining entry into lungs, spreads hematogenously. Although cryptococcal meningoencephalitis is the most commonly diagnosed and most severe form of cryptococcosis, *C. neoformans* may infect numerous other systems, and the spectrum of disease varies from asymptomatic pulmonary infection to critical illness, typically due to meningoencephalitis. In 2017, it was estimated that 6% (95% confidence interval [CI], 5.8–6.2) of HIV-positive persons with a CD4 T cell count <100 cells/mm^3 had a positive cryptococcal blood antigen test, totaling 278,000 (95% CI, 195,500–340,600) cases of cryptococcosis with a positive blood antigen test and 223,100 (95% CI, 150,600–340,600) cases of cryptococcal meningitis.[5] Although most cases are associated with HIV, a number of other immune-suppressing conditions confer susceptibility to cryptococcosis, and disease may also develop in persons not known to have underlying immune suppression.[2,6,7] Mortality related to cryptococcal meningoencephalitis ranges from ~20% to as high at 70% and is heavily influenced by local resources, antifungal therapy selection, and supportive care.[8]

■ Epidemiology

C. neoformans serotypes A and D are most common in North America and Europe and are often associated with bird droppings or vegetation. Serotypes B and C are classified as *C. neoformans* var.

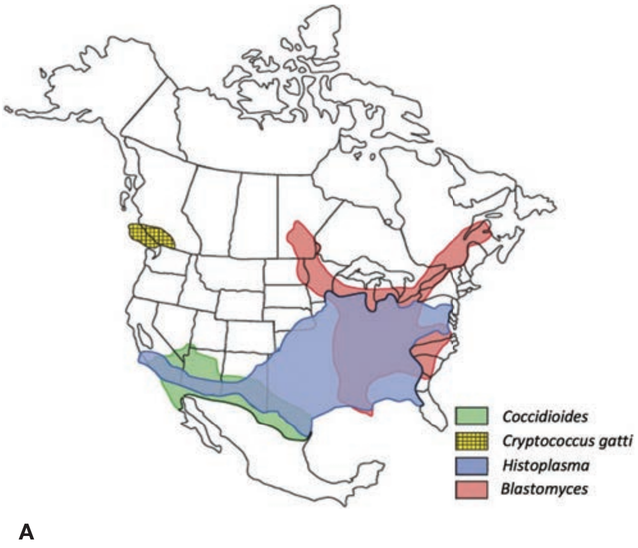


Figure 133-1 **A.** Geographic distribution of endemic mycoses in the United States. The area of histoplasmin skin test reactivity in the southwestern United States represents cross-reactivity caused by coccidioidomycosis, not endemic histoplasmosis. World map estimating regions most likely to have *(continued)*

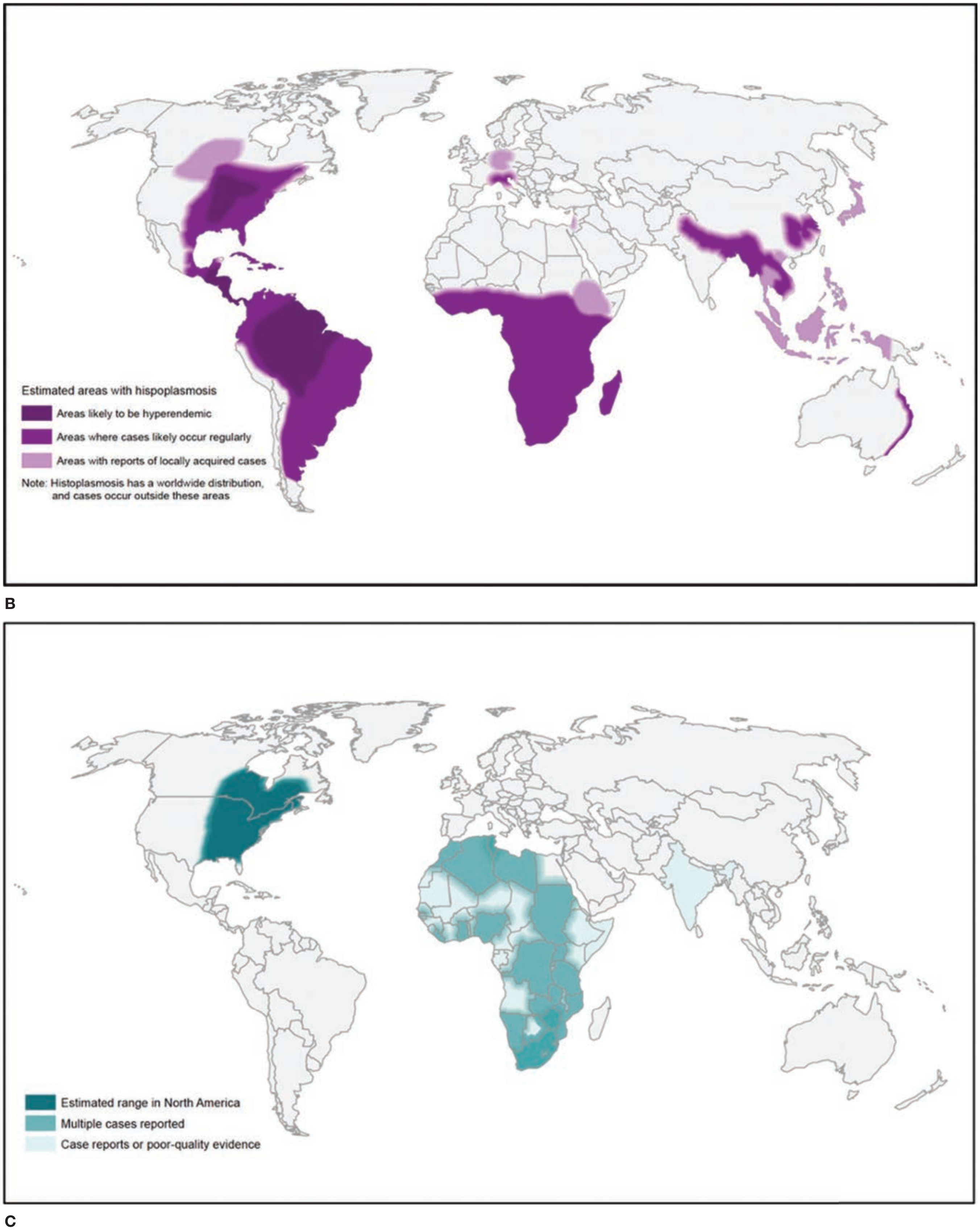
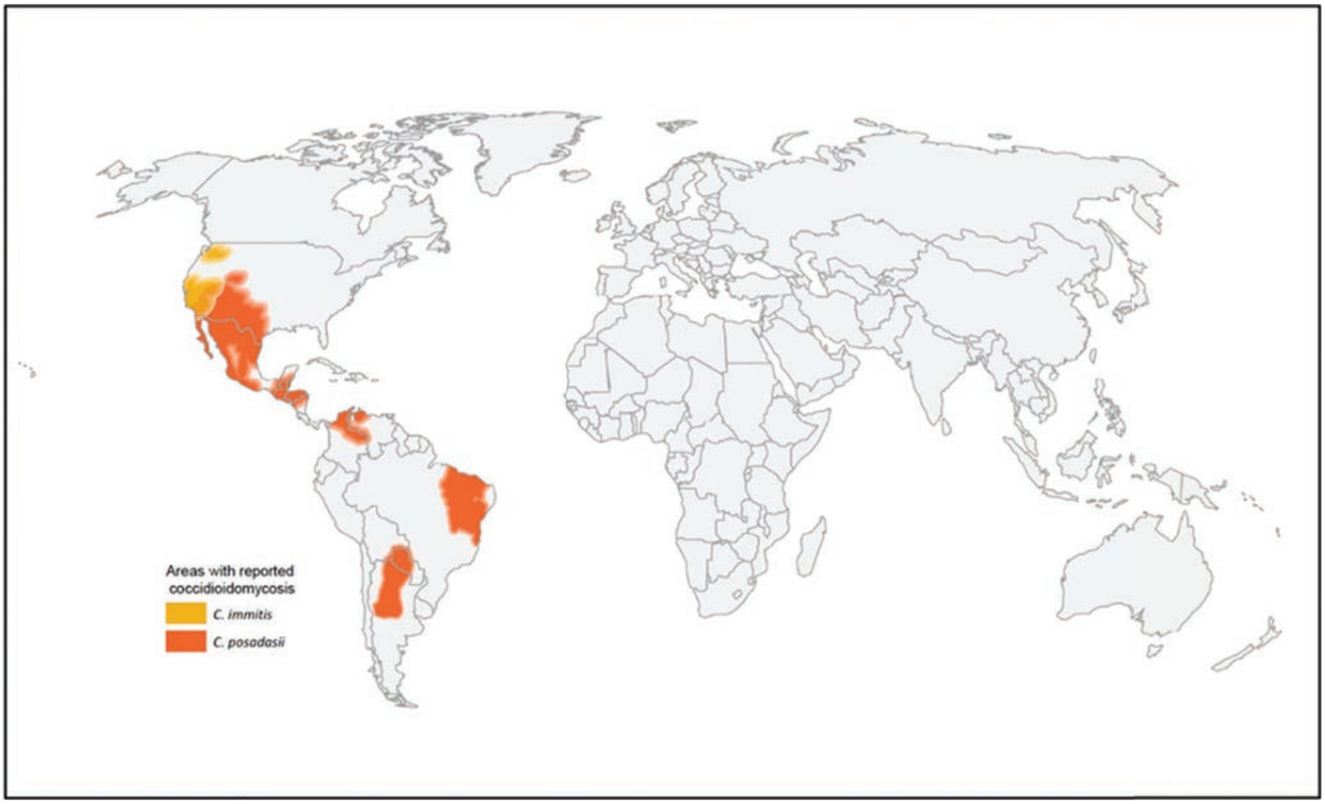

Estimated areas with hispoplasmosis
Areas likely to be hyperendemic
Areas where cases likely occur regularly
Areas with reports of locally acquired cases
Note: Histoplasmosis has a worldwide distribution, and cases occur outside these areas
B
Estimated range in North America
Multiple cases reported
Case reports or poor-quality evidence
C

Figure 133-1 *(Continued)* histoplasmosis (**B**), blastomycosis (**C**), and coccidioidomycosis (**D**) *(**B–D.** Reproduced with permission from Ashraf N, Kubat RC, Poplin V, et al. Re-drawing the Maps for Endemic Mycoses. Mycopathologia. 2020;185(5):843–865).*



D

Figure 133-1 *(Continued)*

gattii and are endemic to Australia where they are classically associated with eucalyptus trees as well as other tropical and subtropical regions.[9] Numerous outbreaks have now been reported in nontropical regions such as the pacific northwest of North America.[10] Aside from those related to *C. neoformans* var. *gattii* in recent years, outbreaks are rare. Person-to-person transmission has not been documented. While persons living with HIV (PLWH), particularly those with CD4 T cell counts <100 cells/mm^3, are at high risk for cryptococcosis, numerous other groups are at high risk, including those taking immunosuppressive medications such as tumor necrosis factor (TNF) inhibitors, ibrutinib and other tyrosine kinase inhibitors, corticosteroids, and transplant-related immune suppressive medications, as well as those with other immunosuppressive conditions such as cirrhosis, lymphoreticular malignancies, and anti–granulocyte-monocyte colony-stimulating factor antibodies.[2,6,7,11] Persons without known immunosuppressive conditions are less commonly affected by cryptococcosis.[2]

■ Mycology

C. neoformans is characterized by its thick polysaccharide capsule, which can vary from 1 to 30 or more μm, with the yeast itself measuring 4 to 6 μm in diameter (Table 133-1, Fig. 133-2). The capsule tends to be smaller in the environment, which allows the yeast to reach terminal airways when inhaled. *C. neoformans* grows readily in fungal media, allowing isolation usually in less than 48 h. *C. neoformans* can be identified by biochemical tests or

TABLE 133-1 Microscopic Characteristics of Endemic Fungi, *Cryptococcus*, and Other Similarly Sized Organisms

Organism	Size (μm)	Shape	Budding Type	Thickness of Cell Walls	GMS	PAS	Mucicarmine and Fontana-Mason
H. capsulatum var. *capsulatum*	2–4	Globose or ovoid	Narrow base	Thin	Positive	Positive	Negative
H. capsulatum var. *duboisii*	6–12 or larger	Ovoid	Narrow base	Thick, refractile	Positive	Positive	Negative
B. dermatitidis	5–15 or larger	Globose	Broad base	Thick	Positive	Positive	Negative
C. neoformans/*C. gattii*	4–6	Globose or ovoid	Narrow base	Thin	Positive	Positive	Positive[a]
Leishmania spp. (amastigotes)	<4	Ovoid	None	None	Negative	Negative	Negative
T. gondii (bradyzoites)	<4	Ovoid	None	None	Negative	Negative	Negative
T. cruzi (amastigotes)	<4	Ovoid	None	None	Negative	Negative	Negative
C. immitis/*posadasii*	10–200	Round	None	Thick	Positive	Positive	Negative

GMS, Gomori methenamine silver stain; PAS, Periodic acid–Schiff stain.
[a] *Unencapsulated strains stain negative.*

DNA probes, and four serotypes (A, B, C, D) have been described, as noted above.

Pathogenesis

C. neoformans is generally acquired via inhalation although direct inoculation of skin or soft tissues can occur as well. After inhalation, yeast may reach as far as the pulmonary alveoli despite typical physical immune defense mechanisms, such as airflow turbulence, the epithelial mucosal barrier, and mucociliary transport.[12] The innate immune response to *C. neoformans* includes alveolar macrophages, dendritic cells, natural killer cells, and the complement system.[12] In some cases granulomas form in the lungs, sequestering the organisms, and latent infection is established.

In addition, CD4+ T helper cells and a Th1 type immune response, where interferon γ (IFN-γ) plays a crucial role, are particularly important for control of cryptococcosis.[12,13] One mechanism used to evade host destruction by *C. neoformans* yeast is to promote an imbalanced immune response, skewed toward Th2. Progressive disease may occur in those with impaired cellular immunity, highlighting the close linkage of severe cryptococcosis, particularly cryptococcal meningitis, with advanced HIV.[12,13] Proposed mechanisms for central nervous system (CNS) invasion include the "trojan horse" model in which macrophages infected with *Cryptococcus* cross the blood–brain barrier (BBB) via transcytosis through the interstitial spaces of the BBB, or paracytosis, by which proteases help *Cryptococcus* to digest cells in order to cross the BBB.[14]

Clinical Findings

Cryptococcal infection has a broad range of outcomes. In persons with normal immune systems, asymptomatic or self-limited

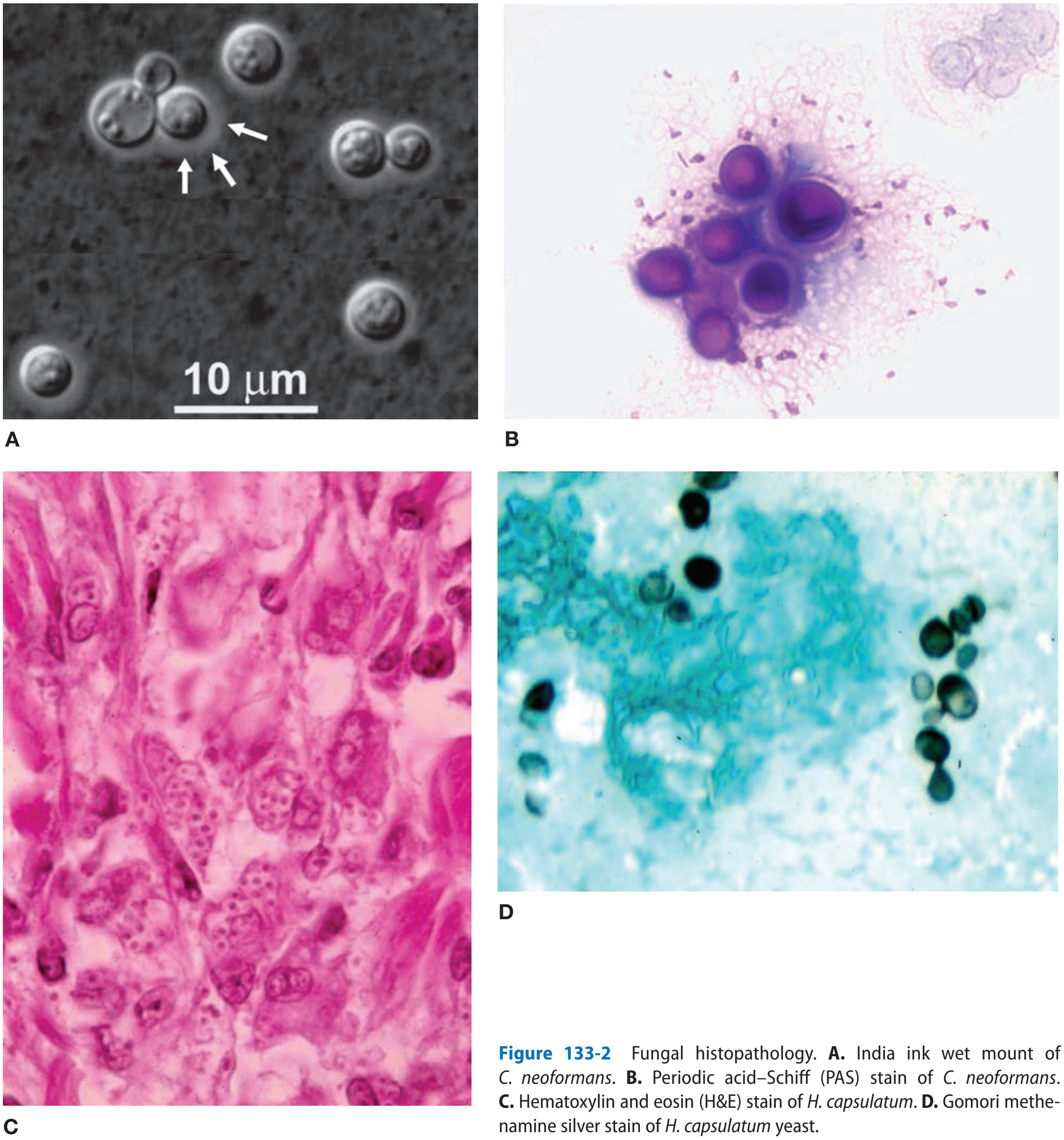


Figure 133-2 Fungal histopathology. **A.** India ink wet mount of *C. neoformans*. **B.** Periodic acid–Schiff (PAS) stain of *C. neoformans*. **C.** Hematoxylin and eosin (H&E) stain of *H. capsulatum*. **D.** Gomori methenamine silver stain of *H. capsulatum* yeast.

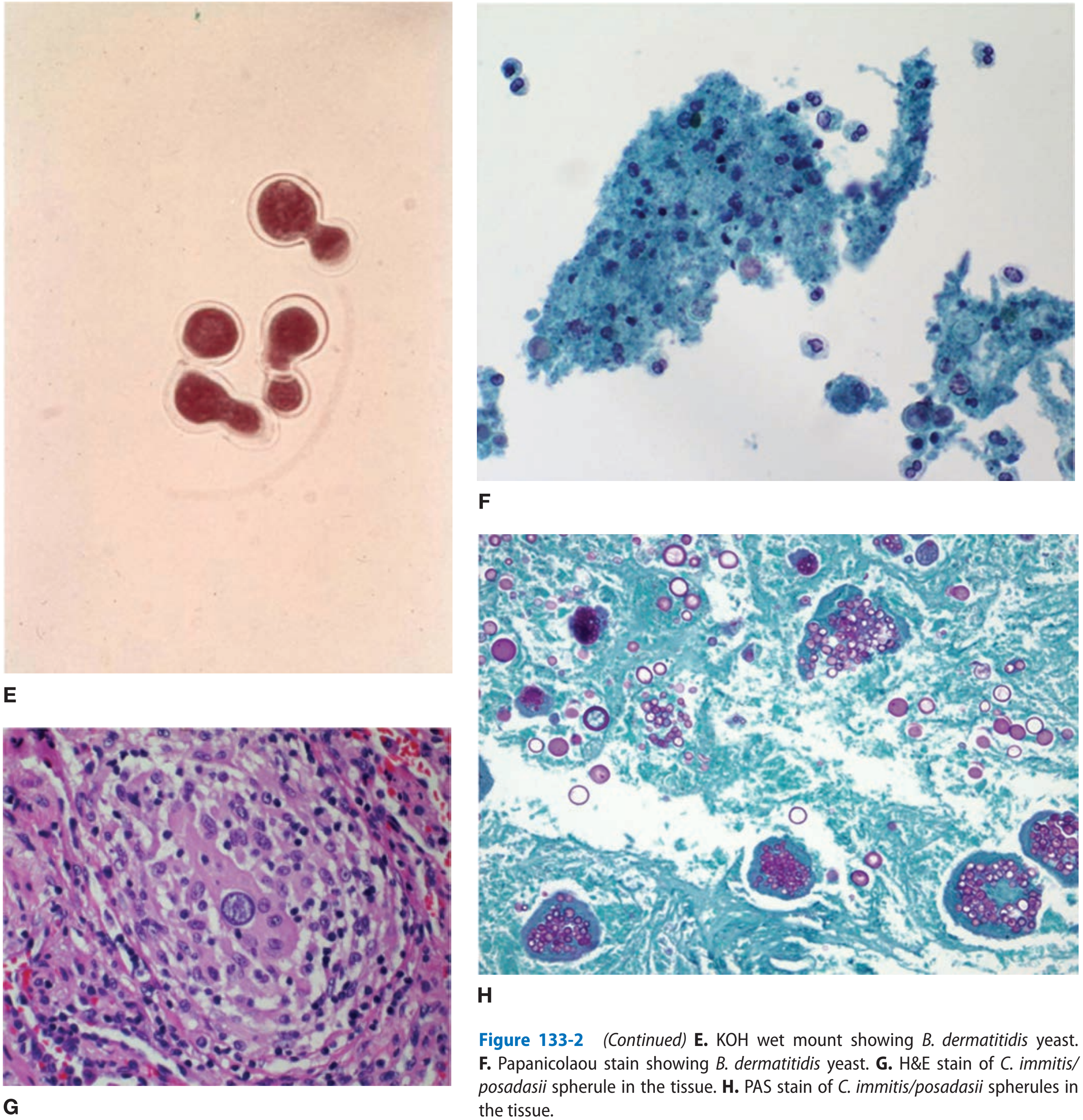


Figure 133-2 *(Continued)* **E.** KOH wet mount showing *B. dermatitidis* yeast. **F.** Papanicolaou stain showing *B. dermatitidis* yeast. **G.** H&E stain of *C. immitis/posadasii* spherule in the tissue. **H.** PAS stain of *C. immitis/posadasii* spherules in the tissue.

pulmonary infections are most common. In persons with immune deficits (particularly those within the adaptive immune system, such as PLWH), disease may be much more severe. In this population, meningoencephalitis is the most commonly recognized manifestation of cryptococcosis and the most common cause of death, although hematogenous dissemination to nearly every tissue has been reported.

Pulmonary

The lung serves as the primary portal of entry for cryptococcal infections. In hosts without immune-compromising conditions, isolated asymptomatic pulmonary infection is common. Evidence of prior infection may be noted on subsequent imaging, but findings such as nodular infiltrates (Fig. 133-3) are not specific enough to point to *Cryptococcus* as the culprit. Symptoms, when they occur, are nonspecific and may include dyspnea, cough, fever, and chest pain.[12] Symptoms generally resolve spontaneously in those who truly have a normal immune system, although progression of pulmonary findings, concurrent meningoencephalitis, or concurrent disseminated disease all occur in some cases.

Cryptococcosis in immunocompromised hosts is more likely to cause symptomatic pulmonary disease, although symptoms are similarly nonspecific, as noted above. Imaging findings may include diffuse interstitial or patchy alveolar infiltrations. In persons with less severe immune deficits, patchy alveolar or nodular infiltrates may occur (Fig. 133-3). Other rarer imaging findings may include cavitary disease, cryptococcoma, mediastinal adenopathy, and pleural effusion. The "halo sign," often considered classic for

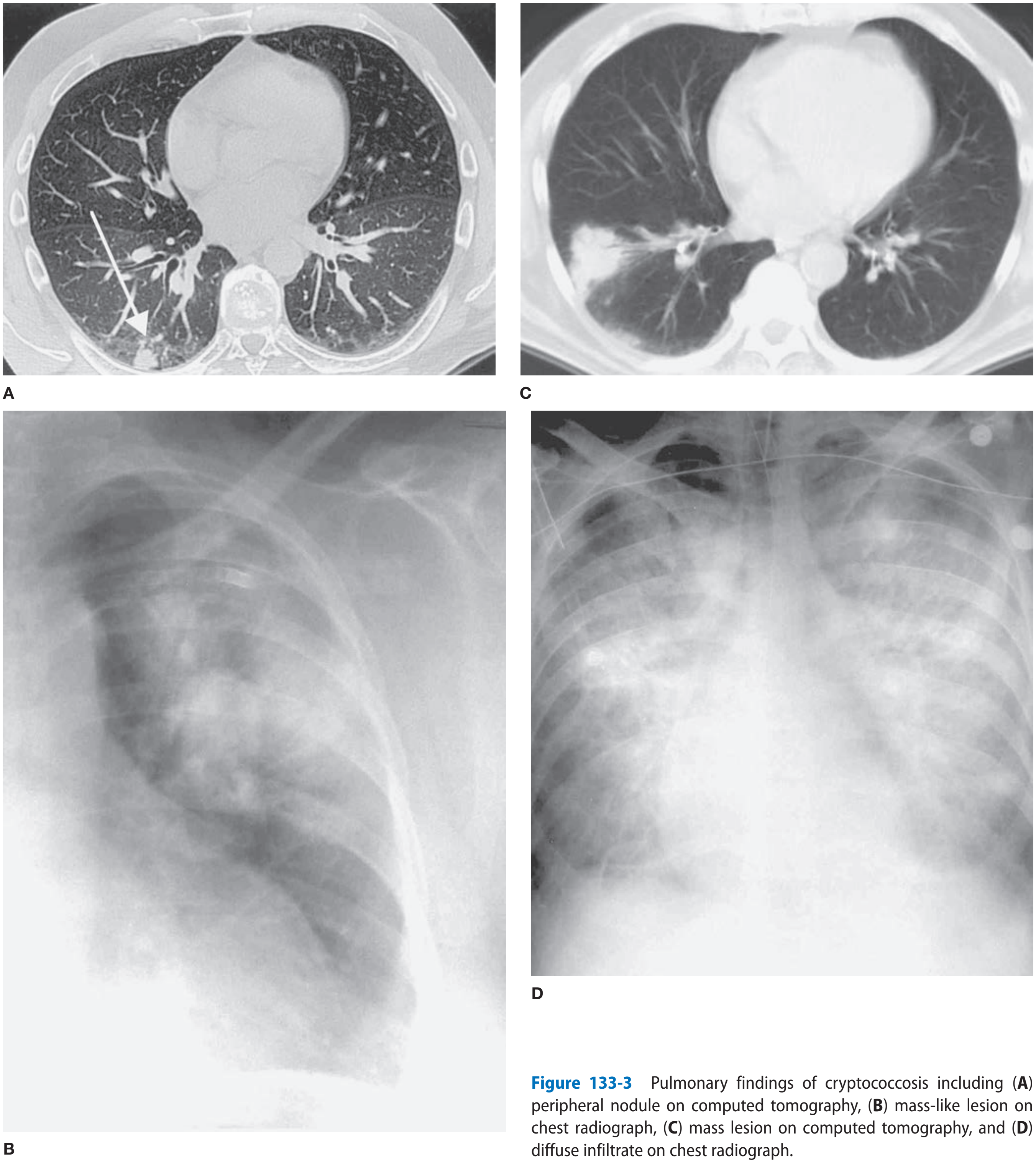


Figure 133-3 Pulmonary findings of cryptococcosis including (**A**) peripheral nodule on computed tomography, (**B**) mass-like lesion on chest radiograph, (**C**) mass lesion on computed tomography, and (**D**) diffuse infiltrate on chest radiograph.

aspergillosis, may occur with cryptococcosis as well.[12] Concomitant meningoencephalitis or dissemination is more likely to occur with more severe immune compromise; mortality is at least 20% in many settings if meningoencephalitis develops.[8]

Meningoencephalitis

Meningoencephalitis is the most severe and commonly diagnosed manifestation of cryptococcosis. Generally, cryptococcal meningoencephalitis presents as a subacute disease with symptoms worsening over 2 to 4 weeks, but a more rapid presentation may occur with severe immunodeficiency. Typical symptoms include headache, nausea, vomiting, meningismus, fever, and altered mentation; changes in mentation are associated with poor outcomes.[14] Focal neurologic abnormalities also occur, with sixth cranial nerve palsies being particularly common; seizures are seen in up to one-third of patients.[14,15] Elevated intracranial pressure is common, often persistent (even without clear symptoms), and if not managed properly, leads to poor outcomes.[15] Repeated lumbar punctures are commonly required to reduce intracranial pressure.[16] Lumbar drains or ventriculoperitoneal shunts are needed on occasion. Intracranial cryptococcomas occur more rarely and are difficult to treat.

Other Sites of Dissemination

While meningoencephalitis and pulmonary cryptococcosis are most commonly diagnosed, disseminated cryptococcosis may involve nearly any organ in the body. Skin lesions are often umbilicated, resembling molluscum contagiosum, and can be an early clue to cryptococcosis. Additional sites of involvement frequently reported include the liver, spleen, kidneys, lymph nodes, bone marrow, eyes, and bones. The prostate has been recognized as a site of cryptococcal infection and persistence after acute infection.[17] However, nearly every organ has been described as susceptible to cryptococcal disease; autopsy studies have been particularly helpful in describing disease distribution.[18]

Immune Reconstitution Syndrome

Immune reconstitution inflammatory syndrome (IRIS) commonly complicates HIV-associated cryptococcal meningitis. Although cryptococcal IRIS may occur in conditions as broadly disparate as treatment with granulocyte-colony stimulating factor and the early postpartum period, it is much more common with HIV infection.[19–21] Generally, IRIS is categorized as either "paradoxical" or "unmasking."

In HIV-associated cryptococcal meningitis, paradoxical IRIS is characterized by the patient having been diagnosed with cryptococcal meningitis, having an appropriate clinical response to treatment, and having a recurrence or worsening of symptoms after beginning antiretroviral therapy. In the same context, unmasking IRIS refers to starting antiretroviral therapy (ART) without a known diagnosis (or, presumably, symptoms) of cryptococcal meningitis, but subsequently, after starting ART, having a rapid onset of symptoms consistent with cryptococcal meningitis, and thereafter, establishment of the diagnosis. Both versions of IRIS are generally characterized by an exaggerated and often disorganized immune response.[19]

Paradoxical cryptococcal IRIS is characterized by pre-ART elevations in Th2 and Th17 type cytokines, such as interleukin (IL)-17 and IL-4, decreases in proinflammatory cytokines, such as TNF-α and granulocyte colony–stimulating factor, and higher titers of serum and cerebrospinal fluid (CSF) cryptococcal antigen (CrAg).[19,22] Clinically, IRIS mimics the presentation of the underlying phenomenon; symptoms are similar to cryptococcal meningitis, but the onset of symptoms after treatment initiation should raise the possibility of IRIS. Cryptococcal meningitis–associated IRIS has higher mortality than does IRIS outside of the CNS due to the inflexibility of the anatomic location. To prevent IRIS to cryptococcal meningitis in patients with newly diagnosed HIV, ART initiation should be delayed for 4 to 5 weeks (as opposed to immediately starting ART, which is otherwise recommended).[23] Prevention of unmasking IRIS is accomplished by screening for CrAg in asymptomatic individuals with CD4+ counts <100 cells/mm^3 prior to starting ART. This practice has become standard of care in many parts of the world and is recommended by the World Health Organization.

Diagnosis

A variety of modalities may be used in establishing a diagnosis of cryptococcal infection.

Pneumonia

Diagnosis of cryptococcal pneumonia can be difficult. In general, the fungal burden is higher in PLWH, so detection of the yeast is more easily achieved. Dissemination outside the lungs is more common in PLWH, so extrapulmonary disease should be investigated. Serum CrAg is less sensitive for pneumonia than for meningitis. Although less reliable in isolated pulmonary disease in those without HIV (as low as 23% in one study), relatively high sensitivities are achieved in PLWH, with findings as high as 100% in one small study (Table 133-2).[24–27] Bronchoalveolar lavage (BAL) CrAg use has been reported but is not routinely done. Regardless, a negative CrAg alone cannot rule out isolated pulmonary cryptococcal disease.

When biopsy is indicated, cytology and/or histopathology may be more sensitive in people without HIV, although the test is more invasive.[24–27] *C. neoformans* is most recognizable in cytology or histopathology by its large polysaccharide (Fig. 133-2). Numerous stains, including Gomori methenamine silver (GMS), periodic acid–Schiff (PAS), and India ink can readily identify *C. neoformans* yeast. Special stains for cryptococcosis include the Fontana-Masson stain, which stains the melanized cryptococcal cell wall, and the mucicarmine stain, which highlights the cryptococcal capsule. These stains can be useful in differentiating *C. neoformans* from similarly sized yeasts like *B. dermatitidis*.[28] Culture of sputum or BAL fluid may achieve similar sensitivities but may require up to 2 weeks to achieve a diagnosis.[25–27] Colonization of the airway may occur, so the diagnosis should be considered if an unexpected positive culture or histopathology result occurs.

Screening for CNS Disease in Those with Pulmonary Disease

The patient's net state of immunosuppression is crucial in understanding cryptococcal CrAg testing in particular. In PLWH with pulmonary cryptococcosis, positive serum CrAg often reflects dissemination or, at least, a high fungal burden with antigen spilling into the circulation. Thus, in such situations, CNS disease must be considered. CSF examination is indicated if the patient has any symptoms of meningitis or CNS involvement. Most experts also recommend lumbar puncture in PLWH with a positive serum CrAg test and/or evidence of pulmonary cryptococcosis, regardless of symptoms.[16,29] A positive serum CrAg is associated with a significant risk of meningitis in solid organ transplant recipients.[30] Therefore, symptoms and signs of meningitis should be investigated and a lumbar puncture considered.[31] On the other hand, for

TABLE 133-2 Diagnostic Studies in Cryptococcosis (Percent Positive Assays)

	Pulmonary, Nondisseminated		
	Nonimmunocompromised	Immunocompromised	Meningitis—Immunocompromised
India ink		55	50–80
Histopathology	5	66	NA
Antigen, serum	5	89	88–100
Antigen, BAL		86	NA
Antigen, CSF	NA	NA	98–100
Culture	72	92–100	90

BAL, bronchoalveolar lavage; CSF, cerebrospinal fluid; NA, not applicable.

putatively normal hosts with pulmonary cryptococcosis and no evidence of CNS disease, lumbar puncture is not required.

Meningoencephalitis

Although CSF culture has traditionally been the gold standard for the diagnosis of cryptococcal meningitis, CrAg is likely more sensitive and is much more rapid (~10 minutes versus up to 2 weeks).[29] The cryptococcal lateral flow assay (LFA) CrAG (IMMY Inc, Norman, OK, USA) is an improvement on the traditional latex agglutination (LA) CrAg in terms of performance (Table 133-2); the test is inexpensive, rapid, and widely available, and does not require cold-chain storage. Sensitivity of LFA for CNS disease in PLWH is 99.3% versus 97.0% for LA, 94.2% for culture, and 86.1% for India ink.[29] Although widely available and cheap, India ink testing is not helpful unless antigen testing is unavailable. In persons without HIV, performance of CSF CrAg is still excellent, although it is slightly less sensitive than for PLWH (Table 133-2).

Serum CrAg LFA testing is a highly sensitive screening tool for cryptococcal meningitis. While the presence of serum CrAg LFA doesn't confirm meningitis, it does confirm the diagnosis of cryptococcosis. One study in Uganda found that of 149 persons with positive serum CrAg, 138 had a positive CSF CrAg, while the remaining 11 were determined to have cryptococcal disease (no false positives).[32] Of note, the study found 100% agreement among plasma, serum, and fingerstick assessments of the CrAg LFA.[32] Importantly, the CrAg LFA is not an infallible test and is susceptible to false negative results due to "post-zone" effects at extremely high titers—an issue that can be remedied with serial dilution.[33] False-positive tests in persons without HIV are also a concern when dealing with low titers.[34]

In persons with a prior diagnosis of cryptococcal meningitis, decay of antigen in the blood or CSF is unpredictable; hence, following serial antigen titers is of uncertain utility. Furthermore, in a person with a recurrence of symptoms after treatment, antigen testing may not be helpful, as it may remain positive. In these situations, treatment failure must be strongly considered while awaiting culture results.

Two diagnostic tests, CSF (1–3)-B-D-Glucan and the FilmArray CSF panel (BioFire, Salt Lake City, UT, USA), which are not as sensitive as CrAg for diagnosis of cryptococcosis, may have some utility in this setting, as both tests decay more rapidly than CrAg.[35–37] Although neither test should be considered a first-line test for diagnosis of cryptococcal meningitis, (1–3)-B-D-Glucan may indeed be detectable in cryptococcal meningitis, despite the poor sensitivity of serum (1–3)-B-D-Glucan for cryptococcal infection.[37,38]

CSF lactate may be utilized as a prognostic marker of cryptococcal meningitis severity and mortality in the setting of HIV. In a study of 317 Ugandan patients with PLWH with cryptococcal meningitis, elevated CSF lactate levels were associated with altered mental status, seizures, increased CSF opening pressures, and death.[39]

Treatment

Persons with symptomatic pulmonary disease or who are asymptomatic and immune compromised, and all persons with meningoencephalitis or disseminated disease require treatment (Table 133-3).[16] Patients with profound immune suppression related to HIV and "asymptomatic antigenemia" also should be treated.[40] Whether such strategies make sense for immunosuppressed, non-HIV populations is less clear at this time. If treatment is not initiated in an asymptomatic person with pulmonary cryptococcosis without immune compromise or symptoms, he or she should be observed closely. Any increase in lesion size or number on imaging, or development of symptoms, should be considered an indication to start treatment. A situation where treatment can truly be avoided altogether is rare.

TABLE 133-3 Treatment Recommendations for Cryptococcosis Syndromes

Syndrome	Recommendation
Pneumonia (mild–moderate)	Fluconazole 400 mg daily for 6 to 12 months
Pneumonia (severe)	Same as for meningitis
Meningitis (IDSA 2010)	**Induction**: Amphotericin B deoxycholate (0.7–1.0 mg/kg/day) or liposomal amphotericin B (3–4 mg/kg/day) or amphotericin B lipid complex (5 mg/kg/day) plus flucytosine (100 mg/kg/day divided into four doses) for at least 2 weeks (4 weeks for non-HIV, nontransplant patients) **Consolidation**: Fluconazole 400 mg daily × 8 weeks **Maintenance:** Fluconazole 200 mg daily for at least 12 months total of therapy
Meningitis (WHO 2018)	**Induction**: Amphotericin B (1.0 mg/kg/day) plus flucytosine (100 mg/kg/ day, divided into four doses per day) for 1 week followed by 7 days of fluconazole 1200 mg daily **Consolidation**: Fluconazole 800 mg daily × 8 weeks **Maintenance:** Fluconazole 200 mg daily for at least 12 months total of therapy

Pneumonia

Assuming there is no CNS disease, therapy for mild to moderate pulmonary disease consists of fluconazole, 400 mg daily for 6 to 12 months.[16] The workup for sites of dissemination, including CNS, disease should be more intensive in those with suppressed immune systems. In those with severe disease, treatment should begin with amphotericin-based therapy, as for meningeal disease (see below).[16] Posaconazole, voriconazole, isavuconazole, and itraconazole are alternatives with minimal supporting evidence for their use if administration of fluconazole is not possible.

Meningitis

Currently, cryptococcal meningitis therapy is based on the combination of amphotericin B and flucytosine induction, followed by a longer consolidation regimen of high-dose fluconazole, and, finally, a long-term, lower-dose course of fluconazole for secondary prophylaxis.[16] In PLWH, the 2010 Infectious Disease Society of America (IDSA) guidelines recommend amphotericin B deoxycholate (0.7–1.0 mg/kg/d) or liposomal amphotericin B (3–4 mg/kg/day) or amphotericin B lipid complex (5 mg/kg/day), plus flucytosine (100 mg/kg/day divided into four doses) for at least 2 weeks, followed by fluconazole, 400 mg daily × 8 weeks, followed by fluconazole, 200 mg daily for secondary prophylaxis until the CD4 count is >100 cells/mm^3 and viral load suppressed for at least 3 months (at least 12 months total of therapy).[16] Recommendations for transplant recipients are similar except that liposomal or lipid complex formulations of amphotericin are explicitly preferred over amphotericin b deoxycholate.[16] Additionally, immunosuppression should be reduced concomitantly with antifungal treatment to improve therapeutic response and reduce the likelihood of relapse. Maintenance therapy should be continued for 6 to 12 months, with careful monitoring after stopping fluconazole. If symptoms recur, lifelong maintenance therapy may be required.

In non-HIV, nontransplant persons with cryptococcal meningitis, a 4-week induction period is recommended.[16] The lipid preparations of amphotericin are generally less toxic. Fluconazole monotherapy at doses as high as 1200 mg daily is used in some parts of the world where amphotericin or flucytosine are not available. However, whenever possible, amphotericin-based combination therapies are preferred, given that mortality with fluconazole monotherapy is up to 70% in some settings.[8,41]

Since the 2010 IDSA guidelines were published, large clinical trials have been completed, particularly those related to HIV-associated cryptococcal meningitis. Molloy et al. published the ACTA trial in 2018,[42] a landmark, large ($n = 721$), open-label, randomized study of HIV-associated cryptococcal meningitis at nine African centers. Participants were assigned to induction therapy of fluconazole, 1200 mg daily, plus flucytosine, 100 mg/kg/day × 2 weeks, versus amphotericin B deoxycholate, 1 mg/kg/day for 1 or 2 weeks. The amphotericin arms had fluconazole or flucytosine (at the same doses as above) randomly assigned as partner drugs, for an effective total of five arms. Ten-week mortality was lowest when one week of amphotericin B was paired with flucytosine (24%), interestingly, followed by fluconazole plus flucytosine (35%).[42] Two weeks of amphotericin led to more adverse events, likely contributing to greater attrition and higher overall mortality. Flucytosine was clearly superior to fluconazole as a combination agent for amphotericin B,[42] a particularly notable finding, given difficulties in accessing flucytosine in much of the world.[8] Based on these findings and systematic reviews of other published data,[43] the World Health Organization now recommends 7 days of amphotericin B plus flucytosine, followed by 7 days of fluconazole, 1200 mg daily as induction therapy; if amphotericin (or necessary adjunctive treatments and monitoring capability) is unavailable, oral flucytosine plus fluconazole for 2 weeks is an alternative.[44] The World Health Organization also recommends a higher dose (800 mg daily) of fluconazole for consolidation based primarily on expert opinion.[44]

In 2019, an important phase 2 study evaluated the effectiveness of single-dose liposomal amphotericin (10 mg/kg) compared with daily infusions of 3 mg/kg (both with 14 days of high-dose oral fluconazole) for HIV-associated cryptococcal meningitis in Tanzania. Among 80 participants, noninferiority was achieved for the mean rate of fungal culture clearance.[45] These findings are now being further examined in a large, phase 3, open-label study in five African countries, where a single dose of liposomal amphotericin (10 mg/kg) plus 14 days of fluconazole (1200 mg daily) and flucytosine (100 mg/kg/daily) will be compared to the new standard of care per World Health Organization guidelines (7 days of amphotericin deoxycholate [1 mg/kg daily] plus flucytosine [100 mg/kg daily], followed by 7 days of fluconazole [1200 mg daily]); this trial is ongoing.[46] When IDSA revisits cryptococcosis guidelines, changes to the induction regimen should be a strong consideration.

In addition to antifungal treatment, intracranial pressure should be closely monitored. If CSF opening pressure is greater than 25 cm H_2O, repeat lumbar punctures should be performed to drain CSF sufficiently to relieve intracranial pressure by 50% or to $<$20 cm H_2O.[16]

Additional Considerations for Treatment of Cryptococcal Meningitis

In 2014, Boulware et al. published the landmark COAT trial, which showed that in ART-naïve individuals with cryptococcal meningitis, starting ART within 1 to 2 weeks of beginning cryptococcal meningitis treatment carried a significantly higher risk of 26-week mortality (45%) than did starting ART after 5 weeks (30%); the hazard ratio for death was 1.73 (95% CI, 1.06–2.82; $p = 0.03$).[23] Most of the excess deaths in the early ART arm occurred within 2 to 5 weeks from diagnosis. A later analysis of this study found that early ART was associated with CSF pleocytosis and macrophage activation, perhaps giving insight into immune mechanisms related to increased mortality.[47] Thus, the standard of care is to wait 5 weeks from the start of induction therapy to start ART in ART-naïve persons with cryptococcal meningitis.

All amphotericin formulations are associated with nephrotoxicity, hypokalemia, and hypomagnesemia. These issues are particularly pronounced with amphotericin B deoxycholate. In 2014, Bahr et al. reduced treatment mortality compared to historic controls by implementing a uniform protocol of potassium and magnesium monitoring and universal supplementation, and additional standardized replacement when necessary.[48] Compared with historic controls, 14-day mortality improved from 62% to 78% with the universal electrolyte protocol.[48] Electrolyte monitoring and replacement, although considered routine in many locations, are not routinely available in many settings and are now part of the World Health Organization treatment recommendations for HIV-associated cryptococcal meningitis.[44]

In addition to pharmacotherapy, management of intracranial pressure is crucial. Use of therapeutic lumbar puncture is associated with improved survival.[49] Repeat lumbar punctures should be done routinely in the absence of contraindications. In some cases, where available, lumbar drain or ventriculoperitoneal shunts should be considered.[16]

Disseminated or Extrapulmonary Disease without Meningoencephalitis

There should be a high concern in persons with disseminated disease for meningitis until proven otherwise. Although rare, falsely negative CSF cryptococcal antigen testing does occur (at times due to the post-zone effect with massive fungal burden or, conversely, due to lower fungal burden in CSF, as in discrete CNS disease with cryptococcomas).[33] Thus, the safest route for the patient is likely to treat in most cases as if meningitis is present. The treatment principles related to meningitis above should be considered strongly in these situations.

Asymptomatic Antigenemia

One crucial strategy to prevent death due to cryptococcosis is to screen at-risk persons with serum CrAg. CrAg is present in 1% to 15% of asymptomatic PLWH and CD4 counts $<$100 cells/mm^3; one study from the United States found a positive rate of 2.9%.[29,50] Those with detectable CrAg and no evidence of meningitis should be treated preemptively with high-dose fluconazole.[29] One randomized controlled trial (RCT) in sub-Saharan Africa found a 28% survival benefit from this practice, which is now recommended by the World Health Organization and which has been found to be cost-effective in numerous settings.[44,51] Whether high-dose fluconazole is adequate treatment for this entity is unclear, and studies investigating amphotericin-based therapies in this setting are ongoing.

Role of Antifungal Resistance

C. neoformans resistance to fluconazole is of significant concern. In 2015, among 198 clinical isolates from Uganda, Smith et al. found the minimum inhibitory concentration (MIC) required to inhibit $>$50% of strains (MIC50) was 8 μg/mL and the MIC90 was 32 μg/mL; 31% of isolates had an MIC of ≥16 μg/mL (considered resistant in vitro). These findings were compared to an MIC50 of 4 μg/mL and an MIC90 of 8 μg/mL in isolates in two studies from 1998 to 1999, prior to widespread human use of fluconazole and agricultural use of azole fungicides.[52] The worsening resistance patterns are of significant concern and will only serve to worsen the already poor survival for cryptococcal meningitis treated with fluconazole monotherapy. Also of concern is be the potential for breakthrough fluconazole-resistant strains while on maintenance therapy.

Alternative Antifungal Agents

Alternatives to fluconazole include itraconazole, voriconazole, posaconazole, and isavuconazole. None of these agents appears to offer clear advantages over fluconazole, but they may be considerations as salvage therapy. Although *Cryptococcus* does produce relatively small amounts of (1–3)-B-D-Glucan, echinocandins are not active against *C. neoformans* in vitro and should not be considered as salvage therapy.[53]

Adjunctive Therapy

Adjunctive IFN-γ immunotherapy showed no mortality benefit when added to amphotericin B and flucytosine in a randomized controlled trial in patients with cryptococcal meningitis.[54] Generally, this therapy is not utilized, nor it is available in settings where cryptococcosis is most common. Of note, sertraline showed promising activity against *Cryptococcus* in vitro and in vivo. An open-label dose study showed faster clearance of *Cryptococcus* from the CSF when used in conjunction with amphotericin and high-dose fluconazole.[55,56] Unfortunately, a placebo-controlled RCT did not show benefit in mortality, so sertraline is not used to treat cryptococcal meningitis.[57] Similarly, there was significant interest in corticosteroids as an adjunctive therapy, given the frequency of IRIS and the drug's role in TB meningitis. Yet, a placebo-controlled RCT found that adjunctive dexamethasone not only did not improve mortality, but also increased adverse events and disability. Thus, outside of documented cryptococcal IRIS, dexamethasone is not recommended for cryptococcal meningitis.[58]

■ Prevention and Screening for Cryptococcosis

Broad antifungal prophylaxis is not currently recommended, even in persons with advanced HIV/AIDS. Rather, appropriate use of ART in all PLWH is the mainstay of cryptococcosis prevention in this setting. Secondary prevention by targeting screening for cryptococcal antigenemia in susceptible individuals is crucial and cost-effective, as discussed above. Such efforts have not been well studied in persons with other forms of immunosuppression. *Cryptococcus* is ubiquitous in the environment; avoidance of exposure is difficult, although avoiding bird droppings may be beneficial.

HISTOPLASMOSIS

Histoplasmosis is the most prevalent endemic mycosis in the Americas and a major cause of morbidity in patients who live in endemic areas.[59] Progressive disseminated histoplasmosis (PDH) is an important complication in patients with HIV/AIDS and those receiving immunosuppression for the prevention of transplant rejection[60] or treatment of inflammatory diseases,[61–63] as well as those with malignancies and immunodeficiency disorders.[64] Understanding of the clinical syndromes and untreated course of the infection is essential to the diagnosis and management of patients with histoplasmosis. Improved laboratory tests have made rapid diagnosis possible. Expanded treatment options are available using triazole antifungal agents and liposomal formulations of amphotericin B.

■ Epidemiology

H. capsulatum var. *capsulatum* is highly endemic in areas of North America,[65] (Fig. 133-1) especially in U.S. states bordering the Mississippi and Ohio river valleys, as well as a large part of Central and South America.[1,66] In French Guiana, histoplasmosis is so prevalent that it eclipses other opportunistic pathogens in frequency and is the most common AIDS-defining illness.[67] Clusters of infections are reported at increasing rates from areas outside the traditional endemic regions, including China, Thailand, and India, as well as parts of Africa and Southern Europe.[1,68–70] African histoplasmosis, caused by *H. capsulatum* var. *duboisii,* occurs exclusively in Africa, particularly in Central and Western Africa and Madagascar.[71] Bird and bat excrement enhance growth of the organism by accelerating sporulation. Cases outside the endemic regions may be acquired by exposure during travel, prior residence in endemic areas, or exposure to microfoci containing the organism within nonendemic areas. In endemic areas, between 10% and 90% of individuals exhibit histoplasmin skin test positivity as immune evidence of past histoplasmosis.[72]

■ Mycology

Histoplasma capsulatum grows as a mold in the soil and converts to a yeast in tissues (Fig. 133-2). Microconidia, measuring 2 to 4 μm in diameter, are the infectious particles in the mold phase of the organism. *H. capsulatum* also grows as a mold on fungal media at ambient temperature in the laboratory. Definitive identification of a mold as *H. capsulatum* is made by DNA probe or exoantigen detection. At temperatures above 35°C, *H. capsulatum* grows as a yeast, which is the pathogenic form found in the tissues. The yeast measures about 2 to 5 μm and exhibits narrow-based budding.

■ Pathogenesis

Infection develops when conidia are inhaled and germinate into yeast. In many cases primary infection is asymptomatic and goes undiagnosed. Clinical illness most often follows exogenous infection or reinfection. With the development of cell-mediated immunity during the first month following initial infection, IFN-γ and IL-12 activate macrophages to kill the fungus and halt progression of the disease.[73] In addition, TNF-α is very important for immune defense against *H. capsulatum.*[74,75] These defense mechanisms are sufficient to control the infection in immunocompetent individuals, accounting for the subclinical or self-limited course characteristic of acute histoplasmosis in the majority (90%) of individuals.

Reactivation of latent infection may account for some cases occurring in individuals with past histoplasmosis who become immunocompromised. Studies showing a low incidence of histoplasmosis following immunosuppression in children,[76] organ transplantation,[77] or treatment with TNF inhibitors,[61,63] however, suggest that reactivation is rare. Also, latency could not be demonstrated experimentally in calcified lung lesions identified as incidental findings at autopsy.[78]

■ Clinical Manifestations

The clinical manifestations and severity of histoplasmosis depend on the infectious inoculum, the immune state of the host, and the health status of the host's lungs.[79,80] Heavy exposure can cause severe illness, even in healthy subjects. Low-level exposure is more common, however, and usually causes asymptomatic infection or clinically self-limited infection. When the exposure occurs in a closed space such as a cave, the attack rate is relatively high (50%–100% with a mean of 74%) with symptomatic infections, even for healthy individuals.[81] The common self-limited presentations are acute and subacute pulmonary histoplasmosis, pericarditis, and rheumatologic syndromes.

Asymptomatic Infection

In endemic areas, up to 90% of residents exhibit histoplasmin skin test reactivity by age 20.[72] In most of these cases, infection was presumed to have been asymptomatic. Most asymptomatic cases are identified as an incidental finding on chest radiographs or computed tomography (CT) scans performed for other reasons. The most common findings are enlarged mediastinal or hilar lymph nodes or pulmonary nodules.[82] The main significance of such findings is the need to differentiate them from malignancy or tuberculosis.[83]

TABLE 133-4 Summary of Pulmonary and Mediastinal Histoplasmosis Syndromes

	Age (Years)	Disease Course	Chest Imaging Findings	Presence of Calcifications	Fistulization	Preferred Diagnostic Method	Treatment Indication
Pulmonary Histoplasmosis							
Acute	Any	1–2 weeks	Diffuse airspace disease, lymphadenopathy	No	No	*Histoplasma* antigen BAL cytopathology and culture	No, unless prolonged or severe illness
Subacute	Any	Weeks to months	Focal airspace disease, lymphadenopathy	No	No	*Histoplasma* serology *Histoplasma* antigen (low sensitivity) BAL cytopathology and culture	No, unless symptoms last >1 month
Chronic	>45	Months to years	Focal airspace disease, upper lobe cavitary, thick-walled bullae, underlying emphysema	Yes (calcifications)	Rare	*Histoplasma* serology BAL cytopathology and culture	Yes
Progressive disseminated	Any immunocompromised	1–2 weeks	Diffuse airspace opacities	No	No	*Histoplasma* antigen BAL cytopathology and culture Blood and bone marrow culture	Yes
Mediastinal Histoplasmosis							
Mediastinal adenitis	<20	Early complication	Homogenous mediastinal mass	No	No	*Histoplasma* serology	Obstruction of airway, esophagus, or vessels
Mediastinal granuloma	>2	Early or late complication	Heterogenous mediastinal mass	Yes	Possible (to bronchi, esophagus)	*Histoplasma* serology	Obstruction, fistula, superinfection, persistent pain
Mediastinal fibrosis	>10, usually 20–30	Late complication	Homogenous mediastinal mass obstructing nearby airways, esophagus, or vessels	Yes (extensive)	No	*Histoplasma* serology	Recurrent hemoptysis, invasion/obstruction of airways, esophagus, or vessels

Asymptomatic infection also may be identified by demonstration of seropositivity during evaluation of another condition.

Pulmonary Syndromes

A variety of pulmonary syndromes may be seen with histoplasmosis.[80] They are considered below and in Table 133-4.

Acute Pulmonary Histoplasmosis Following heavy fungal exposure, patients present with diffuse pulmonary involvement often causing respiratory compromise.[71,80] Chest radiographs usually show diffuse interstitial, reticulonodular infiltrates, nodular, or patchy airspace disease, but a miliary pattern suggestive of hematogenous dissemination may be seen (Fig. 133-4). Initial radiographs may appear normal, evolving to show infiltrates over the next few weeks. Mediastinal adenopathy is common. Extrapulmonary dissemination occurs in about 40% of cases.[84] While patients may recover without therapy,[85] convalescence may be slow,[86] respiratory failure may develop,[87] and some infections may be fatal, especially after a heavy inoculum of infection.[87,88]

Subacute Pulmonary Histoplasmosis This syndrome presents subacutely and is most likely due to exposure to a smaller fungal inoculum.[80,89] Patients present with fever, cough, and chest pain. Chest radiographs often show mediastinal lymphadenopathy with patchy infiltrates. Most patients recover in a few weeks, but some experience persistent fatigue.

Chronic Pulmonary Histoplasmosis Chronic pulmonary histoplasmosis occurs in patients with underlying lung disease and is characterized by persistent or recurrent pulmonary symptoms, progressive lung infiltrates, fibrosis, and cavitation.[90–92] Upper lobe infiltrates and cavities are characteristic, resembling the findings of pulmonary tuberculosis. Progression is manifested by cavity enlargement, formation of new cavities, spread to other areas of the lungs, and formation of bronchopleural fistulae. Bacterial pneumonia, chronic *pulmonary aspergillosis*, and malignancy must also be considered in evaluation of new masses or infiltrates.

Nodules Nodules from histoplasmosis must be differentiated from malignancy.[83,93] Calcification suggests histoplasmosis but does not exclude malignancy. Conversely, the absence of calcification does not exclude histoplasmosis. Positive positron emission tomography (PET) scan, as seen with malignancy, is common in histoplasmosis. Rarely, nodules may cavitate, but cavitation does not necessarily represent development of chronic pulmonary histoplasmosis and does not require therapy. Nodules also may rarely enlarge (up to 2 mm per year), but slow enlargement is not caused by progressive infection and is not a basis for treatment on its

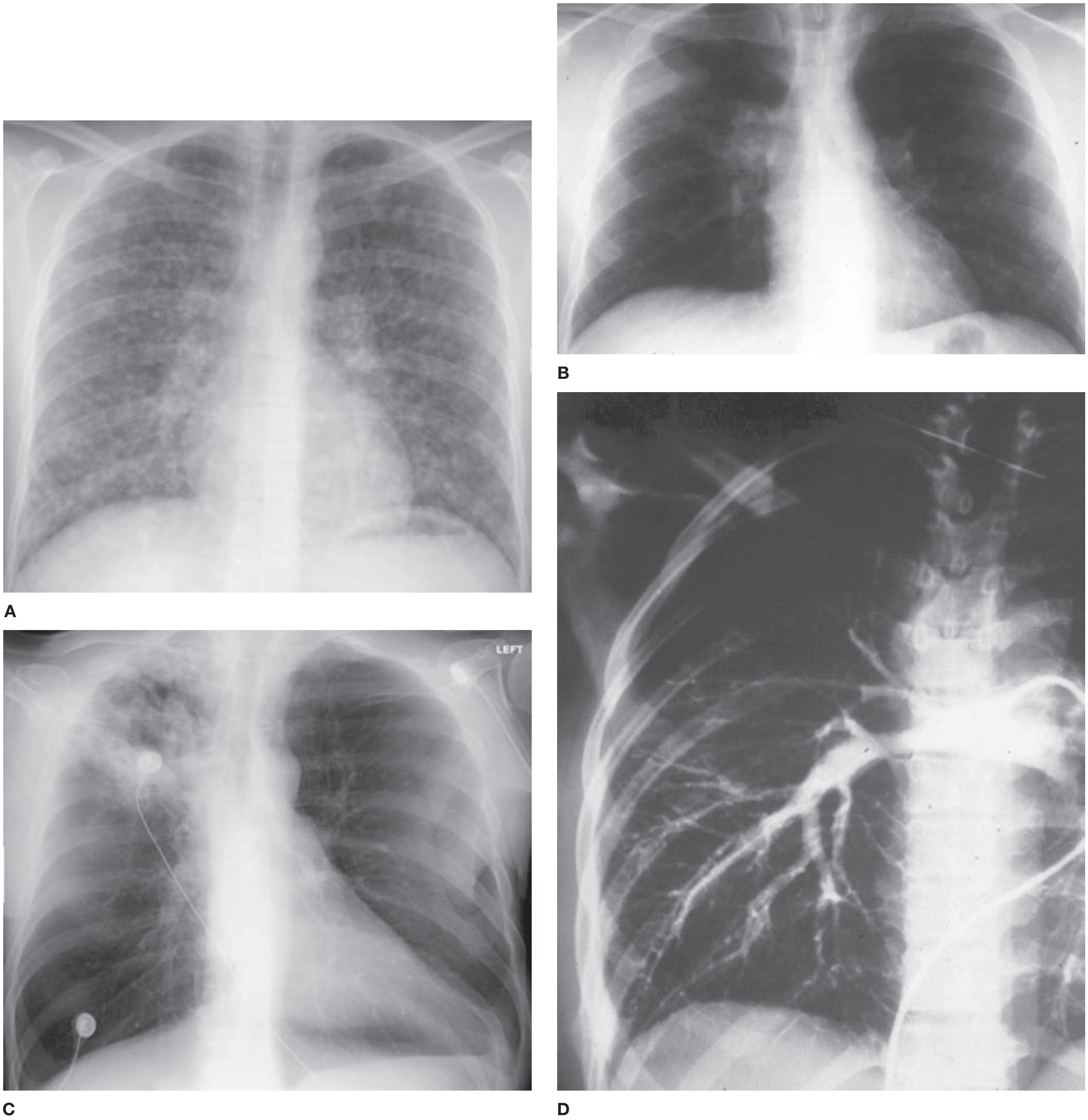


Figure 133-4 **A.** Chest radiograph of acute diffuse histoplasmosis after large inoculum exposure. **B.** Chest radiograph of subacute histoplasmosis with mediastinal adenopathy. **C.** Chest radiograph of cavitary histoplasmosis. **D.** Pulmonary arteriogram showing obstruction of pulmonary artery to right upper lung caused by fibrosing mediastinitis.

own.[94] Calcification occurs in the necrotic center and surrounding fibrous tissue.

Broncholithiasis Lymph nodes and pulmonary granulomas calcify and may erode into adjacent bronchi causing hemoptysis or obstruction.[82] Patients may expectorate stone-like particles of tissue and experience recurrent and severe hemoptysis, bronchial obstruction, or tracheoesophageal fistulae.

Relationship to Sarcoidosis Sarcoidosis and histoplasmosis share several clinical and radiographic findings.[82] Angiotensin-converting enzyme (ACE), sedimentation rate, C-reactive protein, and immunoglobulin elevations occur in both conditions.[95] Noncaseating granulomas can be seen with both, and caseation, which is more typical of histoplasmosis, may also occurs in sarcoidosis. Histoplasmosis must be excluded before the diagnosis of sarcoidosis is confirmed, to prevent administration of immunosuppressive therapy to patients with active infection.

Mediastinal Syndromes of Histoplasmosis Mediastinal adenitis, mediastinal granuloma, and fibrosing mediastinitis are three mediastinal disorders which may complicate histoplasmosis.

Mediastinal Adenitis Mediastinal lymph node involvement is present in most cases of acute and subacute pulmonary histoplasmosis.[80] Although usually asymptomatic, chest pain is the most common manifestation. Rarely, mediastinal lymph nodes can impinge upon the airways, esophagus, or superior vena cava, causing obstructive symptoms. Airway obstruction is more likely in children because their airways are less rigid.

Mediastinal Granuloma Histopathology of mediastinal granulomas shows a necrotic central core, often containing yeast surrounded by caseating and noncaseating granuloma,[80] fibrous tissue, and a thin-walled (<5 mm) capsule. The fibrosis is less exuberant than in fibrosing mediastinitis and does not invade adjacent structures. Symptoms are usually caused by compression of the superior vena cava, esophagus, or airways, and in some cases the nodes liquefy and drain into adjacent structures.[96,97] Disruption of the capsule, either spontaneous or caused by surgery, may create fistulae to the airways, pericardium, skin, or esophagus. Esophageal involvement may result in diverticulum formation.

Mediastinal Fibrosis Mediastinal fibrosis represents an exuberant scarring reaction to mediastinal histoplasmosis.[98,99] The superior vena cava is most commonly involved, but fibrosis also may occlude airways, pulmonary arteries or veins, or the esophagus, and invade the thoracic duct, recurrent laryngeal nerve, or heart in rare cases. Chest radiographs show subcarinal or superior mediastinal widening, while CT scans reveal fibrotic restriction and invasion of mediastinal structures and calcification of lymph nodes. Recurrent postobstructive pneumonias, especially of the right middle lobe, are common. Serious hemoptysis may result from lung or airway damage and vascular compromise. Fibrosing mediastinitis progresses to respiratory failure and death in up to one-third of the patients, especially if the process is bilateral and involves major vessels and airways.[100,101]

Other Inflammatory Syndromes

Inflammatory syndromes complicating histoplasmosis include rheumatologic syndromes and pericarditis.

Rheumatologic Syndromes Patients with subacute histoplasmosis may experience arthritis or arthralgia accompanied by erythema nodosum,[102] a manifestation often misdiagnosed as sarcoidosis.[103] Chest radiographs usually show mediastinal lymphadenopathy and focal pulmonary infiltrates but may also be normal. These findings represent a systemic inflammatory response rather than disseminated infection, and are managed by anti-inflammatory treatment, not antifungal therapy. The illness may recur within weeks to months after treatment is stopped.[104,105]

Pericarditis Pericarditis is another inflammatory complication of primary histoplasmosis, occurring in less than 10% of cases.[106,107] Findings include chest pain, pericardial friction rub, and occasionally, signs of pericardial tamponade. Chest radiographs usually show mediastinal lymphadenopathy and increase in the cardiac silhouette, while CT scan and echocardiogram may show pericardial effusion. These patients respond to anti-inflammatory treatment but may require drainage of the pericardial fluid for the management of tamponade. Development of constrictive physiology is rare; the reasons for this are unclear but could be because the pericardial inflammation is an autoimmune reactive process, rather than a result of direct fungal invasion of the pericardium, and tends to resolve with or without anti-inflammatory treatment.[107]

Progressive Disseminated Histoplasmosis

PDH occurs in about 1 in 2000 cases, usually in patients who are immunosuppressed or at the extremes of age. HIV/AIDS,[108,109] solid-organ transplantation,[60] and treatment with TNF-α inhibitors[61,63] are common predisposing conditions.[110] In organ transplant recipients, PDH develops during the first year after transplant in 34% of cases[60] but may occur up to 10 years after transplantation. Therefore, any signs of disseminated disease should be thoroughly investigated throughout the course of immunosuppression, especially in persons living in endemic areas or those who have new high-risk epidemiologic exposures.

Fever, weight loss, cough and dyspnea are the most common manifestations in PDH.[108,111] Examination reveals hepatomegaly or splenomegaly in about half of cases and lymphadenopathy in a third of cases. A syndrome resembling sepsis may be seen in cases with severe immunosuppression, cases in which corticosteroids are given for presumed inflammatory or autoimmune disease, or in which diagnosis is delayed. Meningitis or focal brain lesions occur in about 5% to 10% of cases.[112,113] Other common sites of dissemination include the oral mucosa, gastrointestinal tract,[114] skin, and adrenal glands in 5% to 10% of cases. Chest roentgenograms are abnormal in 70% of patients, usually showing diffuse interstitial or reticulonodular infiltrates, and less often, a miliary pattern.[111,115]

In patients who experience improvement in immune function during treatment for histoplasmosis, an immune reconstitution syndrome has been reported with a significant degree of morbidity.[61,116–118] Manifestations include respiratory failure, elevation of hepatic enzymes, hepatic or splenic abscesses, lymphadenitis, arthritis, uveitis, and intestinal obstruction in the context of effective control of the infection, decreasing antigen levels, and negative fungal cultures.[61,116–118]

Diagnosis

Diagnostic modalities for histoplasmosis are well developed and validated.[119,120] Histopathology, cytopathology, and antigen detection are the most useful modalities for rapid diagnosis in patients with moderate to severe acute pulmonary histoplasmosis and PDH (Table 133-5).[84,121] Culture results may not be available for up to 1 month due to the prolonged incubation required for growth, limiting utility in this setting. Although less useful overall for acute disease, serology may form the basis of diagnosis for subacute and chronic disease.[121–123] Chronic pulmonary histoplasmosis can also be diagnosed using culture of respiratory secretions, although serology, antigen testing and pathology are also useful.[91,92]

Antigen Detection

Detection of antigen in the body fluids offers a valuable approach to rapid and accurate diagnosis of patients with PDH and acute pulmonary histoplasmosis, providing results within 24 to 48 h.[121] Antigen can be detected in the urine of more than 90% of patients with PDH and 80% with acute diffuse pulmonary disease.[84,121] Sensitivity is improved by testing both serum and urine.[84] Antigen detection is less sensitive in subacute pulmonary histoplasmosis.[121] Detection of antigen in BAL fluid may improve the sensitivity for the diagnosis of pulmonary histoplasmosis.[124] Antigen may be found in the CSF in 50% of patients with *Histoplasma* meningitis.[112,113] Positive

TABLE 133-5 Sensitivity of Various Diagnostics in Different Histoplasmosis Syndromes

	Antigen	Antibody	Pathology	Culture
Acute pulmonary	83%	64%	20%	42%
Subacute pulmonary	30%	95%	42%	54%
Chronic pulmonary	88%	83%	75%	67%
Progressive disseminated	92%	75%	76%	74%
Mediastinal	5%	54%	44%	5%

results caused by cross-reacting antigens occur in patients with African histoplasmosis, blastomycosis, paracoccidioidomycosis, and Talaromyces *marneffei* infection.[121] Antigen levels correlate well with disease severity,[121] and trends can be used to follow disease response to antifungal therapy as they decline during treatment and increase with relapse, providing an effective tool for monitoring therapy at regular intervals (perhaps biweekly for the first month then every 1 to 2 months thereafter until negative or stable).[125–127]

Histopathology and Cytopathology

Fungal staining permits rapid diagnosis but has a lower sensitivity than antigen detection.[121] The highest yield is from bone marrow specimens. Fungal stain of BAL is positive in 70% of cases of diffuse pulmonary histoplasmosis in patients with AIDS with PDH. The sensitivity of fungal stain of sputum or BAL in patients with other types of pulmonary histoplasmosis has not been reported but appears to be low. Yeast may be seen in peripheral blood smears in patients with severe PDH. *Pneumocystis jirovecii, Candida glabrata, Blastomyces dermatitidis, C. neoformans, Toxoplasma gondii,* and *T marneffei* may be misidentified by morphology as *H. capsulatum.*

Serologic Tests

Antibodies to *H. capsulatum* measured by immunodiffusion (ID) or complement fixation (CF) develop in most patients.[120,128] Antibodies may require up to 6 weeks to become detectable following exposure.[129] In acute pulmonary histoplasmosis, antibodies can be detected in about 15% of cases during the first 2 weeks of infection, increasing to about 75% by the sixth week.[129] Outside periods of outbreaks, the background positivity for histoplasma serology in the general population in highly endemic areas is <5%, making a positive test clinically significant even in endemic settings.[123] Patients with asymptomatic or mild infection[130] and those who are receiving immunosuppressive medications following solid-organ transplantation[60,121] may not mount an antibody response. Antibody responses do not appear to be impaired by treatment with TNF inhibitors[61,63,121] and are only slightly impaired in patients with AIDS.[109,121]

Serology is most useful in patients with subacute manifestations of histoplasmosis (pulmonary, rheumatologic, pericardial, and mediastinal syndromes) and chronic pulmonary infection and is positive in 90% of such cases.[121] Sensitivity is higher, while specificity is lower using complement fixation, compared to immunodiffusion, methods. Complement fixation titers greater than or equal to 1:32 are more suggestive of active infection, but titers of 1:8 to 1:16 should not be disregarded. Cross-reactions occur in patients with other fungal diseases. Also, antibodies persisting following prior histoplasmosis may cause confusion in patients with other lung diseases. The newer enzyme immune assay (EIA)-based antibody test with IgG and IgM detection appears to offer higher sensitivity and specificity than the ID and CF in patients with acute pulmonary histoplasmosis. Furthermore, combining antigen and EIA antibody testing increases the sensitivity for diagnosis of acute pulmonary histoplasmosis.[122]

Fungal Cultures

While fungal cultures provide definitive proof for histoplasmosis, they are limited by low sensitivity in self-limited infections and delayed growth (2–4 weeks). Cultures are most sensitive in patients with chronic pulmonary histoplasmosis and PDH.[121] Sputum production is rare in patients with acute subacute pulmonary histoplasmosis, but organisms can be cultured from BAL or other bronchoscopy specimens. In chronic pulmonary histoplasmosis patients commonly expectorate sputum, and organisms can be found in sputum or bronchoscopy specimens in 60% to 85% of cases.[92,121,124] Multiple specimens must be cultured to achieve the highest yield. In PDH, the highest yield is from bone marrow or blood, with positive cultures in more than 75% of cases, and in BAL of patients with pulmonary infiltrates.[121] Cultures are usually negative in pulmonary nodules and mediastinal nodes representing subacute or old healed lesions, despite demonstration of yeast by histopathology.

Molecular Methods

Several studies report diagnosis of histoplasmosis using novel molecular methods in blood, tissues, or body fluids.[20,131] While specificity of the various platforms tend to be very high, sensitivity varies significantly among methods and specimen types.[120] Many improvements have been made over the last two decades with amplification target selection and detection methods, resulting in improved yields.[120] Most studies are limited by a small number of samples and subjects. Further systematic testing at a larger scale is needed to standardize the molecular diagnosis of histoplasmosis.

■ Exclusion of Histoplasmosis in Workup of Patients with Community-Acquired Pneumonia and Suspected Sarcoidosis

Other conditions to be distinguished from histoplasmosis include community-acquired pneumonia and sarcoidosis.

Community-acquired Pneumonia

Histoplasmosis is always community-acquired and is often initially misdiagnosed as other agents of community-acquired pneumonia.[71,132] Failure to suspect and correctly diagnose histoplasmosis may result in errors in patient care, which can lead to improper therapy, unnecessary morbidity, or even death, and higher cost for diagnosis and management. Workup for histoplasmosis should be considered in patients from endemic areas with exposure history, if other causes cannot be established, or if empiric antibiotics do not result in prompt clinical improvement, remembering that histoplasmosis can be prevalent in many areas outside known endemic regions.

Sarcoidosis

Considering the similarity between the two conditions, and the risk for progression of histoplasmosis during immunosuppression for presumed sarcoidosis, active histoplasmosis must be excluded before potent immunosuppressant therapy is initiated.[95,133] If immunosuppressive therapy is initiated in patients with clinical and laboratory findings suggestive of histoplasmosis, the patient should be followed closely for evidence of progression of histoplasmosis. Also, if patients initially respond to immunosuppressive treatment, but later relapse, testing for histoplasmosis should be repeated.

■ Treatment

Most infections (90%) are asymptomatic or clinically self-limited, requiring no therapy. Additionally, treatment has only been well studied in PDH and chronic pulmonary histoplasmosis, precluding assessment of effectiveness in the other syndromes. While treatment in cases of acute pulmonary histoplasmosis appears to be effective, studies showing that therapy hastens response or reduces morbidity have not been conducted. Antifungal therapy for the subacute pulmonary, inflammatory, and mediastinal syndromes is rarely indicated and probably has no effect on the course of the illness, as the pathogenesis appears to involve the inflammatory response and/or mass effects of the enlarged nodes rather than progressive infection.[80]

Comprehensive reviews and treatment guidelines have been published and should serve as reference for indications for the treatment, selection of antifungal agents, duration of therapy, and testing to monitor response.[80,134,135] An earlier Infectious Diseases Society

TABLE 133-6 Treatment Recommendations for Histoplasmosis Syndromes

Syndrome	Recommendation
Acute pulmonary—moderately severe or severe	Liposomal amphotericin B 3.0 mg/kg/d or amphotericin B lipid complex 5.0 mg/kg/d or amphotericin B deoxycholate 0.7–1.0 mg/kg/d for 1–2 weeks followed by itraconazole 200 mg twice daily for a total of 12 weeks Methylprednisolone, 0.5–1.0 mg/kg/d IV for 1–2 weeks
Acute pulmonary—mild to moderate	Symptoms <4 weeks: none Symptoms >4 weeks: itraconazole 200 mg once or twice daily for 6–12 weeks
Chronic cavitary pulmonary	Itraconazole 200 mg once or twice daily for at least 12 months
Progressive disseminated—moderately severe/severe	Liposomal amphotericin B 3.0 mg/kg/d, or amphotericin B lipid complex 5.0 mg/kg/d, or amphotericin B deoxycholate 0.7–1.0 mg/kg/d for 1–2 weeks, then itraconazole 200 mg twice daily for at least 12 months
Progressive disseminated—mild to moderate	Itraconazole 200 mg twice daily for at least 12 months

of America guideline summarized prior studies evaluating therapy for histoplasmosis.[136]

Acute Pulmonary Histoplasmosis

Patients with symptomatic acute pulmonary histoplasmosis manifested by diffuse infiltrates following heavy exposure appear to benefit from antifungal therapy (Table 133-6).[86,137] Adjunctive therapy with corticosteroids may hasten recovery in such patients. Lipid formulations of amphotericin B are preferred as initial therapy in patients with moderate to severe disease because of improved efficacy compared to azole-based therapy and decreased nephrotoxicity compared with amphotericin B deoxycholate. Moreover, improved survival has been reported with liposomal amphotericin B compared with conventional formulations in patients with AIDS and PDH.[138] Itraconazole is recommended in patients with milder disease and as step-down therapy following response to amphotericin B. A 6- to 12-week course is recommended in the absence of PDH, which should be excluded.

Subacute Pulmonary Histoplasmosis

Patients with subacute pulmonary histoplasmosis usually recover without treatment; there have been no studies to determine if treatment alters the course or prevents complications. Nevertheless, treatment is reasonable in patients who show no improvement of symptoms after a month of observation. Oral therapy with itraconazole for 6 to 12 weeks is appropriate.

Chronic Pulmonary Histoplasmosis

Without antifungal therapy, chronic pulmonary histoplasmosis can progress leading to further lung damage and significant morbidity.[2] Treatment improves survival, reduces symptoms, promotes radiographic healing, and eradicates *H. capsulatum* from the sputum. Most patients with chronic pulmonary histoplasmosis can be managed without hospitalization and respond well to treatment with itraconazole for 12 to 24 months. Amphotericin B in conventional or lipid formulations is recommended for initial therapy in patients with more severe respiratory insufficiency to achieve a more rapid clinical response.

Progressive Disseminated Histoplasmosis (PDH)

Treatment is indicated in all patients with PDH. The mortality of untreated disseminated histoplasmosis is greater than or equal to 80% but can be reduced to less than 10% with timely and effective therapy.[60,63,109,138] Lipid formulations of amphotericin B are preferred as initial therapy in patients with moderate to severe disease because of improved efficacy and decrease nephrotoxicity. Induction therapy with amphotericin is given for 1 to 2 weeks, followed by step-down to oral itraconazole after clinical and radiographic response. In cases of patients with milder disease, itraconazole can be effective. A total duration of 12 to 24 months is recommended in most cases. In patients who cannot tolerate prolonged courses of itraconazole, other azoles, including fluconazole, voriconazole, posaconazole, or isavuconazole, can be used (see “Alternative Antifungal Agents,” below).

Mediastinal Adenitis and Granuloma

Patients with obstructive symptoms or fistula caused by mediastinal granuloma and adenitis should be treated, but whether treatment alters the outcome remains unknown.[80] Itraconazole for 6 to 12 weeks is recommended, after which imaging studies should be repeated to assess response. If the enlarged nodes show reduction in size, therapy might be continued for a total of 3 to 6 months. Surgery should be considered if symptoms persist and are sufficiently bothersome.[139] Antifungal treatment or resection of enlarged mediastinal lymph nodes to prevent fibrosing mediastinitis is not indicated since progression of enlarged mediastinal nodes to fibrosing mediastinitis has not been documented.[98,140]

Mediastinal Fibrosis

Antifungal treatment is not thought to improve the outcome of mediastinal fibrosis, but therapy with itraconazole 6 to 12 weeks is commonly tried and is reasonable, considering the seriousness of this complication. Occasionally, patients benefit from the placement of stents in pulmonary vessels or the superior vena cava.[141] Stenting of the airways is not recommended because of the risk for growth of inflammatory tissue causing obstruction of the stent.[80] Surgery is associated with a high mortality and limited efficacy and should generally be discouraged. In patients with no other options, care should be taken to select a surgeon experienced with this rare manifestation of histoplasmosis.

Broncholithiasis

Surgical therapy is required for patients with significant hemoptysis or recurrent pneumonia and for repair of fistulae. Antifungal therapy is not expected to reduce the symptoms since active infection is uncommon in such cases.

Inflammatory Syndromes

Rheumatologic syndromes and pericarditis are noninfectious, inflammatory manifestations and respond to anti-inflammatory therapy.

Histoplasmosis-related pericarditis is treated similarly to pericarditis from other inflammatory causes, usually with nonsteroidal anti-inflammatory drugs and colchicine. Steroids should be avoided, if possible, as they are associated with an increased risk of recurrent pericarditis.[142] Antifungal therapy is not indicated unless there is evidence of yeast in bone, joint, or pericardial tissues, or if corticosteroids are used for treatment of the inflammatory syndrome.

Selection of Antifungal Agents

Amphotericin B acts more rapidly than triazole antifungal agents and is recommended for moderate or severe cases which require hospitalization and women who are pregnant.[135] Liposomal amphotericin B was shown to be superior to the amphotericin B deoxycholate formulation in patients with AIDS with histoplasmosis, with improved overall response and decreased mortality and side effects.[138] Patients who were treated with liposomal amphotericin B experienced a faster resolution of fever, higher overall response, better survival, and lower toxicity.[138] Liposomal amphotericin B, 3.0 mg/kg/d, or amphotericin B lipid complex, 5.0 mg/kg/d, is recommended for patients with moderate to severe PDH. Treatment can be changed to itraconazole after the patient improves, usually in 3 to 14 days.

Itraconazole is highly effective in most mild to moderate cases of PDH and in chronic pulmonary histoplasmosis.[60,63,109] Itraconazole capsules require an acidic gastric environment for solubilization and should be given with food or carbonated beverages. Medications that reduce gastric acidity should be avoided. Itraconazole solution is a good alternative in patients who require gastric acid suppression or who have low blood itraconazole levels while taking the capsule formulation. Itraconazole blood levels should be measured after 2 to 3 weeks of therapy with a sample obtained just before a dose, aiming for a trough concentration between 1 and 10 μg/mL when measured by high-pressure liquid chromatography (HPLC).[143] Levels measured by bioassay should generally be about two times higher than HPLC, with a the target concentration between 3 and 10 μg/mL. The solution formulation achieves concentrations that are ~30% higher than the capsule formulation.

Drug interactions can be common with itraconazole. Hepatic enzyme inducers, such as rifampin, reduce itraconazole concentrations and should be avoided. Itraconazole also inhibits intestinal and hepatic cytochrome P450 3A4, causing accumulation of several drugs and increasing associated toxicities.[144] As the list of contraindicated medications continues to evolve, physicians and pharmacists should closely review potential drug interactions before starting itraconazole and when new medications are added to the regimen. Furthermore, itraconazole is eliminated by hepatic metabolism. Itraconazole may also cause congestive heart failure and should be avoided in patients with heart disease unless the benefit outweighs the risk.[145] If itraconazole is used in patients with cardiac disease, careful follow-up for the development of heart failure is essential, and if heart failure develops, itraconazole should be stopped.

Alternative Antifungal Agents

Fluconazole, voriconazole and posaconazole are active in vitro against *H. capsulatum.*[146] Fluconazole is less active in vitro than itraconazole for histoplasmosis. Isolates from patients who failed fluconazole exhibited at least a fourfold reduction in susceptibility to fluconazole in more than two-thirds of cases.[146] In patients with AIDS and PDH treated with fluconazole, 800 mg/day for 12 weeks, followed by 400 mg/day indefinitely, failure occurred in up to one-half of patients within 6 months.[147,148]

Voriconazole MICs are higher compared to other azoles and may further increase after fluconazole exposure, leading to some concern regarding the use of voriconazole for treatment of histoplasmosis.[146] A recent study comparing outcomes of treatment for histoplasmosis with itraconazole or voriconazole reported higher mortality during the first 42 days in those treated with voriconazole.[149]

On the other hand, posaconazole was effective in an experimental model of histoplasmosis[150] and as a salvage treatment in a small series of patients with disseminated histoplasmosis.[151] In addition, extended-release formulation of posaconazole afford more reliable serum levels and are associated with a better side effect profile than voriconazole.

Isavuconazole exhibits in vitro activity against *H. capsulatum* and has been successfully used for treatment of cases of pulmonary and extrapulmonary histoplasmosis, but data remain limited.[152–154]

Echinocandins are not active in vitro or effective in murine models and have not been well studied in patients with histoplasmosis.[155] Taken together, these data suggest that posaconazole may be the best alternative if itraconazole cannot be used.

Duration of Therapy and Special Populations

Lifelong maintenance therapy was the standard of care in patients with AIDS complicated by PDH before the advent of ART. With ART, maintenance therapy can be discontinued in patients who (1) have received at least 1 year of itraconazole, (2) have antigen levels less than 2 ng/mL in urine and serum, and (3) have a CD4 count greater than 150 cells/mm^3.[109,135,156] Patients must be carefully monitored for relapse and continued response to ART. Resumption of antifungal therapy is recommended if the CD4 count falls below 100 cells/mm^3 or if antigen levels in urine or serum increase, providing evidence of relapse. In patients who develop histoplasmosis while on anti-TNF therapy, after 12 months of effective antifungal therapy with documented clearance of the infections, anti-TNF agents can be safely resumed with close clinical and microbiologic monitoring with serial antigen testing at monthly intervals.[61,63] For recipients of solid organ transplantation, immunosuppression should be reduced concomitantly with antifungal treatment to improve treatment response and reduce likelihood of relapse. Treatment should be continued for at least 12 months and until antigen levels are less than or equal to 2 ng/mL, since relapse is more likely if levels are greater than 2 ng/mL at time of treatment cessation. After stopping treatment, antigen levels should be monitored frequently (e.g., monthly) for at least 6 months.[157] Monitoring of antigen levels can be performed on both urine and serum, although serum levels have been shown to correlate more closely with treatment response.[125,127]

■ Prevention

Patients at high risk for dissemination should avoid activities that expose them to *H. capsulatum*, such as caving or remodeling old buildings inhabited by bats or birds. Hand-washing reduces the risk for acute histoplasmosis among persons exposed while crawling in a bat-inhabited cave, while use of loose-fitting paper masks does not. A placebo-controlled study using itraconazole, 200 mg daily, in persons with AIDS demonstrated reduction in the incidence of histoplasmosis.[158] However, since the introduction of ART, the incidence of these infections has declined and is too low to justify prophylaxis. Prophylaxis may be reasonable in patients with HIV/AIDS and a CD4 count of less than 150 cells/mm^3 living in areas where the combined incidence of systemic fungal infections exceeds 10 cases per 100 patient-years.[135] Screening for histoplasmosis is not recommended prior to transplantation, as the risk of reactivation post-transplant is extremely low.[157]

BLASTOMYCOSIS

B. dermatitidis, the agent of blastomycosis, is the least common and the least well-understood endemic mycosis within the United States. Although many clinical and radiographic features overlap with those of histoplasmosis and coccidioidomycosis, blastomycosis exhibits certain distinctive characteristics. These include a greater predilection for immunocompetent hosts, a tendency for pulmonary consolidations to appear mass-like, the frequent absence of mediastinal and hilar lymphadenopathy, and a greater proclivity for extrapulmonary dissemination to the skin. On microscopy, *B. dermatitidis* also differs from other North American dimorphic fungi both in terms of the characteristics of individual yeast cells as well as the histopathologic inflammatory reaction engendered. Although previously thought to be essentially restricted to the United States and Canada, cases of blastomycosis have also been reported in Africa and Southeast Asia. Moreover, *Blastomyces* quasispecies including *B. helicus*, *B. percursus*, and *B. emzantsi* are being increasingly recognized as causes of human disease in North America and Africa.

Epidemiology

Although *B. dermatitidis* has been isolated from soil enriched with animal excreta and rotting wood, particularly in areas proximate to waterways and bodies of water, the exact environmental reservoir of *B. dermatitidis* is unknown, hindering the epidemiologic characterization of blastomycosis. Additionally, *B. dermatitidis* serologic testing is characterized by poor sensitivity and specificity, lessening the utility of serosurveillance studies in characterizing the geographic extent of this fungus.[159] Furthermore, the incidence and prevalence of blastomycosis may be underestimated since many regions in the United States and Canada do not mandate public health reporting of cases of blastomycosis. Zoonotic cases of blastomycosis, particularly among dogs, often exceed and precede human cases. As such, these have served as surrogates for changes in the epidemiology of human disease and an early indicator of increases in incidence.[160]

The areas of highest endemicity for blastomycosis are located within the North American continent in states bordering the Mississippi, Ohio, and St. Lawrence River valleys, the south central and northern Midwestern states, and the Canadian provinces along the Great Lakes (Fig. 133-1). The Kenora region of northwestern Ontario in Canada has the highest reported incidence of blastomycosis in the world.[161] In the United States, the highest-incidence states are Louisiana, Arkansas, Mississippi, Tennessee, North and South Carolina, Kentucky, Missouri, West Virginia, Illinois, and Wisconsin.[1] The incidence of blastomycosis cases has steadily increased over recent years across endemic areas of Canada and the United States, as well as in regions outside the traditional geographic confines of endemicity. Following a recent rise in the number of cases in areas along the St. Lawrence River in Upstate New York, the State newly designated blastomycosis an emerging disease that is reportable to local health departments.[162] Cases of blastomycosis in persons with no history of out-of-state travel have been reported in Colorado, Oregon, Nebraska, and Florida, suggesting local acquisition in areas not known to be endemic.[163] In Canada, several cases of blastomycosis were reported in the traditionally non-endemic area of southern Saskatchewan in patients who had never traveled to endemic areas, suggesting a broader region of endemicity than previously known.[164] Outside of North America, the endemicity of blastomycosis is still less well understood, but most cases are reported from Africa, with most coming from Tunisia, South Africa, and Zimbabwe.[1] Although cases have been reported from the Asia–Pacific region, including India, it remains unclear whether these represent true local acquisition.[1]

Risk factors for blastomycosis include construction, forestry, and other occupational exposures to disrupted soil or decaying vegetation.[165] Male sex and certain races, including Black and Canadian Aboriginal races, are associated with an increased risk for blastomycosis, thought to be mainly a function of increased occupational and recreational exposures.[166] An increased genetic predilection for blastomycosis has been suggested for Asian residents of Hmong ethnicity after this group was found to be 12 times more likely than non-Asians to develop clinical blastomycosis in a Wisconsin outbreak in 2009.[167] Both limited and disseminated disease can occur in immunocompetent patients, usually as a result of exposure to large fungal inocula, but individuals with defects of cellular immunity are at increased risk for disseminated and severe disease. These include recipients of solid organ and bone marrow transplantation and patients on high-dose corticosteroids and TNF-α blockers.

Blastomyces species other than *B. dermatitidis* are increasingly recognized as causes of human disease. In a study of 20 cases of blastomycosis in South Africa, morphologic, phylogenetic, and whole genome sequencing analyses revealed that all 20 cases belonged to *Blastomyces* species that were closely related to, but distinct from, *B. dermatitidis*, including *B. percursus* and *B. emzantsi.*[168] Notably, disseminated disease to the skin and bones, including sinus track formation in some cases, was more common than isolated pulmonary disease. Additionally, fungi previously designated under the genus *Emmonsia* have been reclassified as *Blastomyces* based on genetic analyses, including *Emmonsia parva* (now *Blastomyces parvus*) and *Emmonsia helica* (now *Blastomyces helicus*). *B. helicus* was reported as a cause of severe pulmonary, systemic, and central nervous system disease, mostly among immunocompromised patients (71%) in the United States and Canada.[169]

Mycology

At body temperature (37°C), *B. dermatitidis* exists as a uniform, moderate-sized yeast (ranging from 8 to 15 μm but sometimes as large as 40 μm) with thick double-refractile walls and broad-based budding (Fig. 133-2). At room temperature (25°C) and when incubated at 30°C ± 2°C in laboratory settings, *B. dermatitidis* uptakes the form of a septated mold with round or piriform conidia at the end of conidiophores. Macroscopically, *B. dermatitidis* colonies are white or off-white with a cottony texture and a reverse that is tan in color. Microscopically, *B. dermatitidis* is distinct from *H. capsulatum* var. *capsulatum* which is much smaller (2–4 μm) and exhibits narrow-based budding, and from *C. posadasii/immitis* which exists as a much larger non-budding, endospore-containing spherule (up to 200 μm). However, several yeast and yeast-like structures can mimic *B. dermatitidis* on histology (Fig. 133-5). Immature C. *posadasii/immitis* spherules may have a similar size and appearance to *B. dermatitidis* yeast and must be distinguished by searching for characteristic mature spherules. When variable in size, *B. dermatitidis* can mimic non-encapsulated strains of *Cryptococcus,* which often exists as a mixture of smaller and larger organisms. *H. capsulatum* var. *duboisii* is a moderately-sized yeast with thick walls similar to *B. dermatitidis* but with narrow-based, hourglass-shaped budding. Finally, *Lacazia loboi*, the etiologic agent of lobomycosis, has thick, double-refractile walls like *B. dermatitidis* but often occurs in linear chains, which is a characteristic and distinguishing feature. Additionally, other rare *Blastomyces* species, including *B. percursus* and *B. helices,* with differing microscopic features must be considered.[168]

Pathogenesis

Infection primarily occurs via the respiratory route, following inhalation of aerosolized conidia from the environment into terminal alveoli of mammalian lungs. Less commonly, direct cutaneous inoculation of conidia can occur after a penetrating injury (such as with a branch contaminated with fungal spores), leading to primary cutaneous blastomycosis. After gaining entry into the human host, *B. dermatitidis* conidia transform into more pathogenic yeast forms under higher body temperature conditions, unless they are phagocytosed and destroyed by neutrophils and alveolar macrophages. In a host who is immunocompromised or when the fungal inoculum is high, the immune system is unable to fully interrupt the cascade of

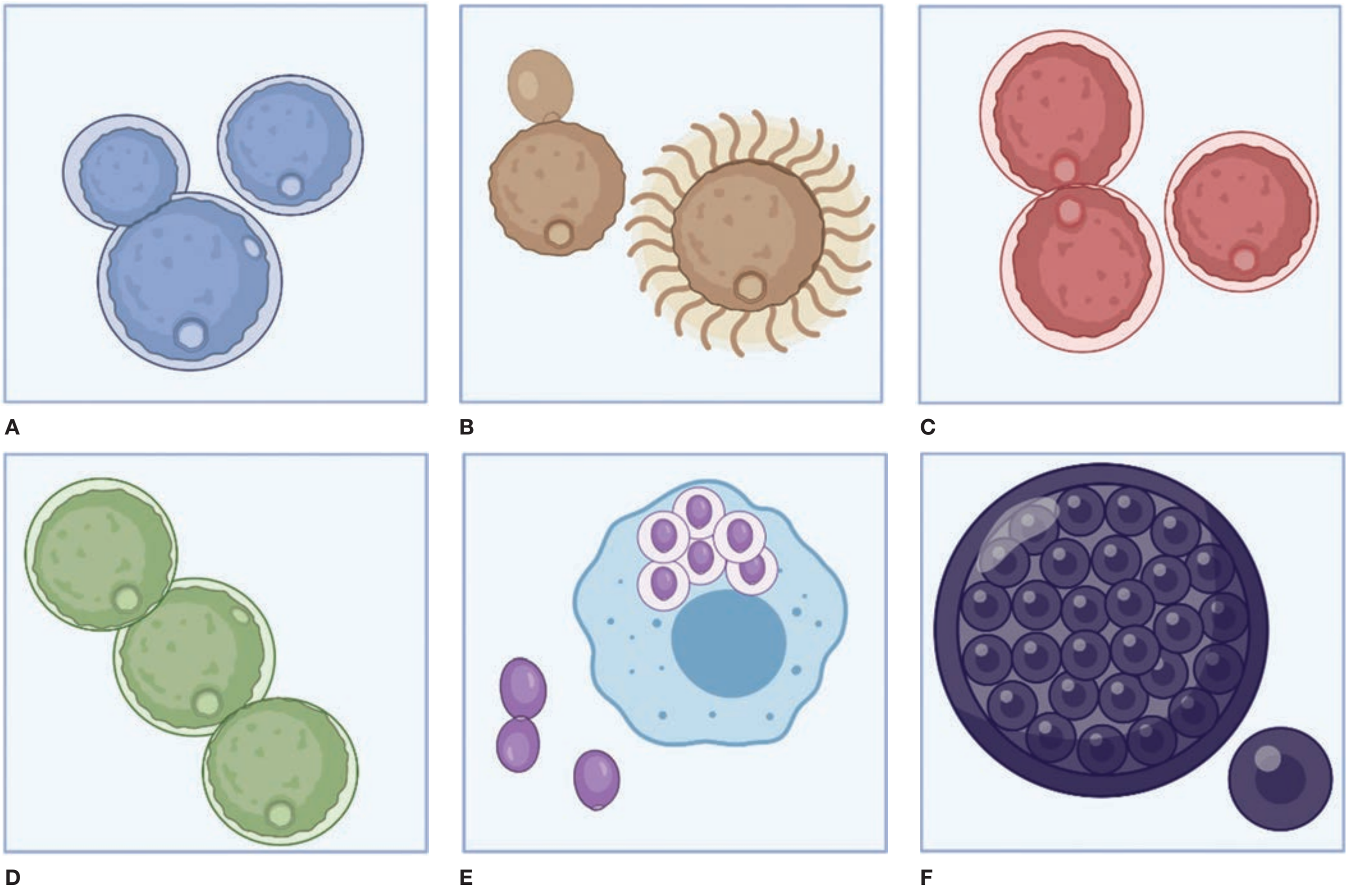


Figure 133-5 Microscopic appearance of *B. dermatitidis* (**A**) and mimics including *C. neoformans/gattii* (**B**), *H. capsulatum* var. *duboisii* (**C**), and *L. loboi* (**D**). Other important endemic fungi are shown including *H. capsulatum* var. *capsulatum* (**E**) and *C. immitis/posadasii* (**F**).

infection, allowing some conidia to evade phagocytosis and progressive infection to develop. *B. dermatitidis* yeast can successfully evade the immune system through impaired neutrophil recruitment, defensin production, macrophage priming, and granuloma formation. Several mechanisms are responsible, including inhibition of Th1 and Th17 cell activation and downregulation of (1–3)-B-D-Glucan, a fungal cell wall component that also functions as a ligand for fungal host–cell pattern recognition receptors.[170] In addition to acting as a virulence factor by decreasing host recognition, low (1–3)-B-D-Glucan cell wall content has implications for diagnostics and treatment by reducing the efficacy of glucan-targeting echinocandin antifungals and association with poor sensitivity of diagnostic assays that detect circulating (1–3)-B-D Glucan.[171]

Pathologically, blastomycosis is characterized by granuloma formation with central microabscesses. This pyogranulomatous response is in contrast to the purely granulomatous response as seen with histoplasmosis or tuberculosis, and to the often-eosinophilic granulomatous response that occurs with coccidioidomycosis. Histologic changes in the skin may resemble those of squamous-cell carcinoma or keratoacanthoma. Calcification is uncommon.

■ Clinical Manifestations

Blastomycosis most often affects the lungs with a spectrum of disease ranging from asymptomatic infection to acute and chronic pneumonia, ARDS, and disseminated disease. A greater proportion of disease is symptomatic with blastomycosis (50%) compared to histoplasmosis (10%) and coccidioidomycosis (40%).[71,172] The incubation period is a median of 45 days, with a range of 21 to 106 days; shorter incubation periods are seen in immunocompromised patients or in high-inoculum exposures.[159]

Acute and Chronic Pneumonia

Two distinct syndromes of pneumonia occur in patients exposed to *B. dermatitidis*: acute pulmonary blastomycosis with or without ARDS and chronic pulmonary blastomycosis.

Acute pulmonary blastomycosis is characterized by the abrupt onset of respiratory symptoms including productive or dry cough, dyspnea, and pleuritic chest pain and constitutional symptoms including fevers, chills, night sweats, weight loss, fatigue, and malaise. The presentation can be mistaken for bacterial community-acquired pneumonia, leading to inappropriate use of antibiotics and delays in diagnosis. The correct diagnosis is often suspected only after symptoms fail to improve with antibacterial therapy or in the context of a blastomycosis outbreaks in endemic areas. In a multicenter retrospective study of pulmonary blastomycosis cases in Minnesota and Wisconsin, the median number of visits required to make a diagnosis was 2 (interquartile range, 1–4), encompassing a median of 23 days (interquartile range, 8–36 days); the median number of prior antibiotic courses was 2.5 (interquartile range, 1.5–4.5).[173] Almost half of patients required hospitalization, including 14% in the intensive care unit. The most common radiographic findings in acute pulmonary blastomycosis include uni- or multilobar consolidation and nodular infiltrates[174,175] (Fig. 133-6). Other patterns include cavitation, focal or diffuse ground-glass opacities, and unilateral or bilateral pleural effusions.[176] Miliary nodules and interstitial infiltrates are often seen in severe disease and ARDS. Unlike histoplasmosis (>60%) and coccidioidomycosis (40%), mediastinal and hilar lymphadenopathies are much less common with pulmonary blastomycosis (10%).[71]

Chronic pulmonary blastomycosis is more common in sporadic cases than in an outbreak setting. It is characterized by the insidious

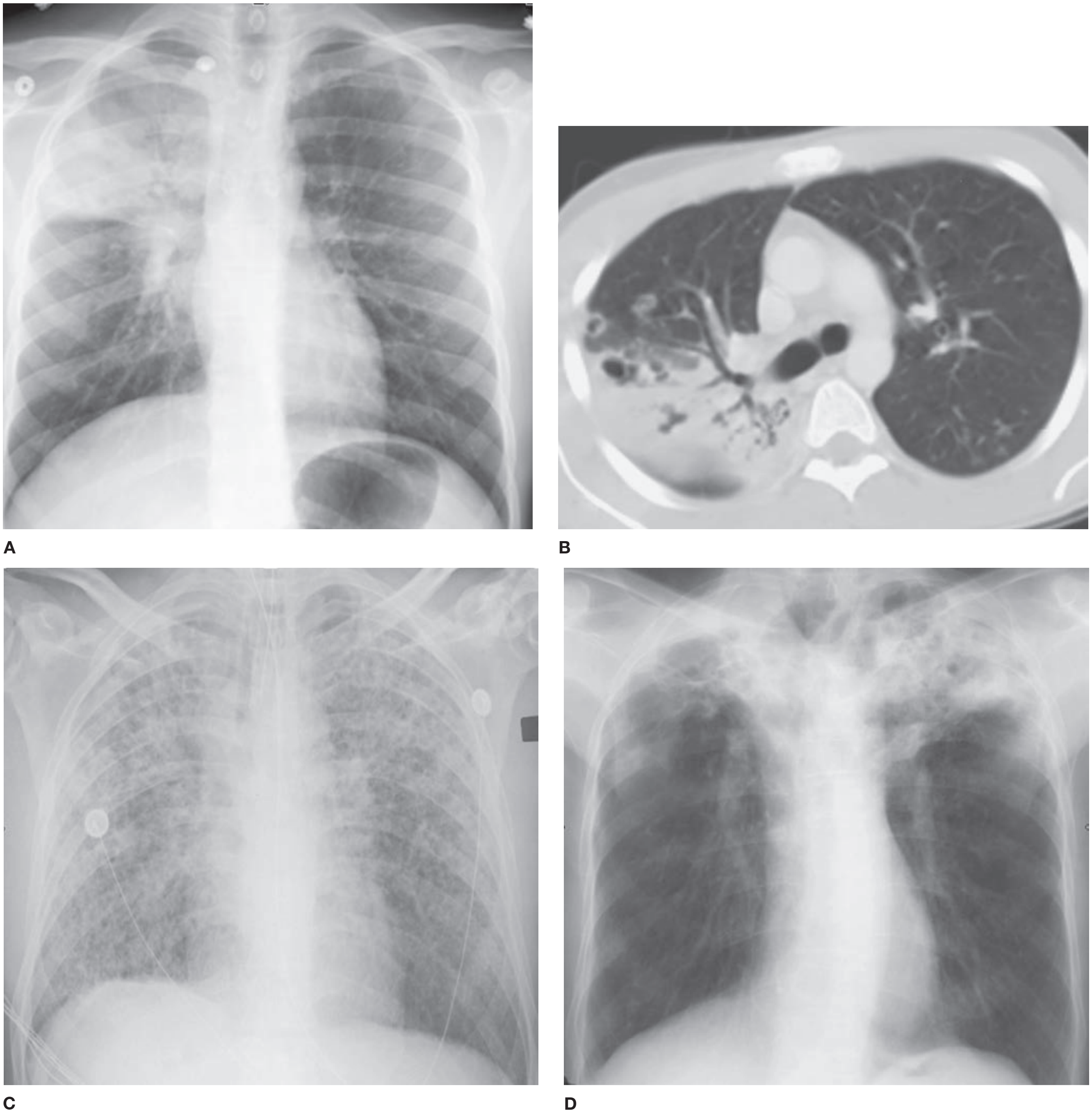


Figure 133-6 **A.** Chest radiograph of infiltrate resembling bacterial pneumonia in acute blastomycosis. **B.** Computed tomography scan showing lobar infiltrate in blastomycosis. **C.** Chest radiograph of diffuse infiltrates associated with acute respiratory distress syndrome in blastomycosis. **D.** Chest radiograph of cavitary blastomycosis.

onset of respiratory and constitutional complaints lasting weeks to months, mimicking other chronic endemic fungal pneumonias, tuberculosis, sarcoidosis, and lung cancer. The illness tends to progress if left untreated. Chronic pulmonary blastomycosis is as or more common than the acute form. In two studies from Tennessee and Arkansas, approximately 60% of patients presented with chronic pneumonia.[177,178] On imaging, consolidations, nodules, and fibrocavitary disease can be seen. Consolidations often appear mass-like, mimicking lung cancer, but PET scanning using fluorodeoxyglucose-F18 is not sensitive enough to distinguish these two conditions.[179,180] Fibrocavitary disease is less common than in histoplasmosis and coccidioidomycosis and is seen in $<10\%$ of cases. As with the acute form, lymphadenopathy is uncommon.

Acute Respiratory Distress Syndrome

Acute pulmonary blastomycosis may be complicated by the development of ARDS, which is characterized by bilateral pulmonary infiltrates and hypoxic respiratory failure requiring mechanical ventilation, without or without circulatory shock.[181] Progression to ARDS may occur and is associated with high mortality of $>50\%$, partly from delayed disease recognition and institution of appropriate antifungal therapy.[182] In one retrospective study of 114 patients with blastomycosis, 15% of patients developed ARDS; mortality in this group was 47%.

Lung pathology in ARDS is characterized by dense alveolar consolidation, microabscesses, hyaline membranes, and abundant yeasts. Although ARDS is often seen in immunocompromised patients, such as individuals with HIV/AIDS or diabetes, transplant recipients, and patients receiving treatment with TNF inhibitors, immunocompetent patients also may be affected.[182–185] In the series of cases of blastomycosis series noted above, only 50% of patients with ARDS were immunocompromised, highlighting a broad pathogenic potential that extends to normal hosts.[175] Despite appropriate antifungal therapy, the mortality rate of blastomycosis-associated ARDS remains high (47%–89%).[175,178,181,186]

Disseminated and Extrapulmonary Blastomycosis

Extrapulmonary blastomycosis occurs in a substantial number of cases (25%–40%), usually as a result of dissemination from the lungs, although direct cutaneous inoculation can occur.[171,187] Skin lesions are the most common extrapulmonary manifestation, usually occurring after resolution of acute pulmonary disease, or concurrently with chronic pulmonary blastomycosis, often on the face. In one series, 31% of patients with pulmonary blastomycosis had concurrent cutaneous involvement.[175] Skin lesions are most often verrucous or ulcerative, but nodules or pustules can occur. Ulcerative lesions may masquerade as pyoderma gangrenosum.[188] The most common extrapulmonary sites after the skin are the bones and joints (18%), genitourinary track (13%, particularly the prostate), and the central nervous system (CNS, 5%–10%).[189] CNS blastomycosis is most common in immunocompromised patients, especially in those with HIV/AIDS for whom a rate as high as 40% has been reported.[183,190] CNS infection may manifest as acute or chronic meningitis with diffuse leptomeningeal enhancement, or as focal brain lesions. In a multicenter study of 22 cases of CNS blastomycosis, manifestations included epidural abscess (n = 1), meningitis (n = 7), intracranial mass lesions (n = 10), and concomitant mass lesions and meningitis (n = 4). CNS disease is associated with a high mortality rate of ~20%.[191] Immunocompromised patients with extrapulmonary disease are more likely to have relapse after treatment cessation.

■ Diagnosis

Blastomycosis is a protean disease that requires a high index of suspicion. Even in endemic areas, the diagnosis is often delayed. Inquiry must be made about recent acute and more longstanding respiratory and systemic symptoms, as well as possible high-risk exposures through occupational or recreational activity and travel to endemic areas. Symptoms in family members or friends and even in pet dogs may serve as a clue of local outbreaks. An in-depth physical examination looking for signs of respiratory, skin, osteoarticular, and CNS disease must be performed. A definitive diagnosis requires histopathology demonstrating compatible yeast forms and growth on culture, but the detection of *Blastomyces* antigen has proved useful for rapid diagnosis of pulmonary and disseminated blastomycosis (Table 133-7).[192] Increased sensitivity may be achieved by use of several diagnostic methods.[124,159,174,175,193–195]

TABLE 133-7 Diagnostic Studies in Blastomycosis

Test	Sensitivity (%)
Antigen	93
Cytology	50–93
KOH	29–83
Histopathology	85
Culture	66–75
Serology	<50

Culture

The gold standard for diagnosis of blastomycosis requires isolation of *B. dermatitidis* on culture of various specimens including respiratory fluid (sputum, tracheal aspirate, BAL fluid), skin biopsy, and others. The yield of culture from BAL fluid is higher with blastomycosis than with histoplasmosis (92% vs. 50%).[195] A drawback of relying on culture for the diagnosis of blastomycosis is the prolonged incubation time of 1 to 4 weeks required for growth. After isolation of the fungus, a preliminary diagnosis can be done by microscopic examination of hyphal and conidial structures under light microscopy. Historically, culture confirmation was further performed by incubating mold colonies at higher temperature to achieve thermoconversion into yeast. More recently, this time-consuming practice has been replaced by culture confirmation using DNA hybridization probe applied to fungus isolated from culture (see "Molecular Testing," below).

Histopathology and Cytopathology

Direct visualization of *B. dermatitidis* yeast on tissue specimens obtained via biopsy can support a diagnosis for blastomycosis. Histopathologic examination of biopsy specimen is up to 81% sensitive.[175,191] Although yeast can be visualized on standard hematoxylin and eosin staining, detection is improved with the use of special stains including the Gomori methenamine silver and periodic acid–Schiff stains. Mucicarmine and Fontana-Masson stains allow differentiation of *B. dermatitidis* from *C. neoformans* by staining the cryptococcal capsule and cryptococcal melanin, respectively. Similarly, detection of organisms on respiratory or other liquid specimens using cytopathology can provide a rapid diagnosis when positive, although the yield is variable, ranging from 38% to 97%, contingent on specimen quality, stains type, and cytopathologist experience.[175,196] When applied to the same specimen, the combination of culture and cytology increases the sensitivity of testing.[197] A drawback of these approaches is the need for invasive procedures, including bronchoscopy and transbronchial, surgical, or percutaneous biopsy, to obtain specimens.

Antigen Testing

Blastomyces antigen can be detected in multiple body fluids, including urine, serum, BAL, and CSF and provides a rapid, noninvasive, and sensitive method for detection that has vastly improved the ability to diagnose blastomycosis. Antigen testing is overall most sensitive when applied to urine (up to 93%), although the sensitivity is lower in patients with mild and localized disease as compared to those with severe and disseminated disease. Serum and BAL antigen testing sensitivity is 5% to 20% lower than urine. Data for CSF antigen testing are limited, but the test is useful when positive. Importantly, a positive *Blastomyces* antigen cannot differentiate blastomycosis from histoplasmosis due to almost uniform cross-reactivity of antigen testing. Cross-reactivity with other endemic fungi also occurs, including *Paracoccidioides braziliensis* and *Talaromyces marneffei.*[120,131,191,194,198–200] Antigen levels can be followed (usually monthly) as a means of assessing treatment response, as is done with histoplasmosis.[127]

Serology

In contrast with histoplasmosis and coccidioidomycosis, commercially available serology for blastomycosis is not clinically useful due to poor sensitivity and specificity (immunodiffusion sensitivity, 33%–85%; complement fixation sensitivity, 33%–50%).[71] *Blastomyces* serology cross-reacts significantly with *H. capsulatum*. A laboratory-developed enzyme immunoassay targeting the *Blastomyces* A antigen (BAD-1) has been shown to be more sensitive (88%) and specific (99%) with little cross-reactivity with *H. capsulatum* (6%), but it is not yet commercially available.[200]

Molecular Testing

Based on traditionally higher sensitivity and specificity than other methods, nucleic acid–based methods promise to supersede antigen testing for the diagnosis of blastomycosis. However, in real-world practice, molecular methods are not routinely used in the direct detection of blastomycosis because of variable performance and lack of standardization. A laboratory developed real-time PCR assay applied to culture isolates and clinical specimens achieved high sensitivity and specificity and showed no cross-reactivity between *B. dermatitidis* and *H. capsulatum*, confirming the high potential of this methodology.[131] Although not yet widely used for direct specimen detection of *H. capsulatum*, molecular testing is routinely used for identification of cultured isolates in the microbiology laboratory. One such assay is the AccuProbe, which employs a single-stranded DNA probe with a chemiluminescent label complementary to a sequence of *B. dermatitidis* rRNA. Fluorescence produced by labeled DNA:RNA hybrids is subsequently measured by a luminometer to determine whether the signal crosses the threshold for positivity. Culture confirmation can also be done via PCR sequencing in reference laboratories.

■ Treatment

Unlike with histoplasmosis and coccidioidomycosis, consensus guidelines recommend treatment for all patients diagnosed with blastomycosis because of a higher likelihood of symptomatic disease, progression to severe or disseminated disease, and development of chronic blastomycosis if left untreated (Table 133-8).[134,201] In some cases, patients with mild disease restricted to the lungs and without any immunocompromising conditions may be considered for observation and expectant management. However, this requires close and long-term follow-up to ensure that chronic infection has not ensued. Transplacental transmission of blastomycosis has rarely been described. Pregnant women do not appear to be at increased risk for poor outcomes.[196] Treatment of mothers may reduce the risk of transmission to fetus and should employ amphotericin B as the triazoles are contraindicated due to teratogenicity. Although data are scarce, lipid formulations of amphotericin B appear to be safe in pregnancy.[202]

Acute Pulmonary Blastomycosis

For acute pulmonary blastomycosis of mild to moderate severity, oral itraconazole (200 mg three times a day for three days as a loading dose, followed by 200 mg twice a day for maintenance) is recommended for a duration of 6 to 12 months, along with therapeutic drug level monitoring (with a target itraconazole serum level of ≥1.0 mg/mL at 2 weeks after initiation of therapy). Itraconazole has been associated with >90% success rate in this setting.[203] Fluconazole is less effective than itraconazole for blastomycosis. Higher doses of fluconazole (800 mg daily) may be considered as an alternative when itraconazole cannot be tolerated.[201,204]

For severe pulmonary blastomycosis, a lipid formulation of amphotericin B (3–5 mg/kg/d) is recommended for 1 to 2 weeks and until there is clinical improvement. Lipid formulations are associated with lower nephrotoxicity than conventional amphotericin B (0.7–1.0 mg/kg/d). The response rates to amphotericin B in this setting range from 85% to 90%.[205] Adjunctive steroids have been suggested for treatment of severe pulmonary disease with ARDS. There are few data to guide this practice, but in one small study, mortality was lower in patients with blastomycosis-associated ARDS who received corticosteroids than those who did not (2 of 6 patients vs. 6 of 11 patients).[175] Following clinical improvement, intravenous therapy can be stepped down to oral itraconazole for a total of 6 to 12 months.

TABLE 133-8 Treatment Recommendations for Blastomycosis Syndromes

Syndrome	Recommendation
Acute or chronic pulmonary—moderate to severe	Lipid amphotericin B 3.0–5.0 mg/kg/d or deoxycholate amphotericin B 0.7–1.0 mg/kg/d for 1–2 weeks followed by itraconazole 200 mg twice daily for 6–12 months ARDS: Can consider adjunctive methylprednisolone, at around 1.0 mg/kg q6h IV for 1–2 weeks
Acute or chronic pulmonary—mild to moderate	Itraconazole 200 mg twice daily for 6–12 months
Disseminated blastomycosis with CNS involvement	Lipid amphotericin B 5.0 mg/kg/d for 4–6 weeks followed by itraconazole 200 mg twice daily or voriconazole 200–400 mg twice daily for at least 12 months

Chronic Pulmonary Blastomycosis

Chronic pulmonary blastomycosis is often symptomatically mild and is treated with oral itraconazole for at least 6 months and until there is radiographic and clinical improvement.

Extrapulmonary and CNS Blastomycosis

Treatment of extrapulmonary blastomycosis depends on severity and site of dissemination.[201] Mild to moderate disease is treated with itraconazole for 6 to 12 months (12 months for osteoarticular disease), while moderate to severe disease is treated with amphotericin B for 1 to 2 weeks, followed by itraconazole for 12 months. CNS disease always requires an induction phase with amphotericin B of 4 to 6 weeks, prior to stepdown therapy with itraconazole. There are reports of successful use of voriconazole for treatment of CNS blastomycosis, thought to be associated with its ability to achieve higher drug concentrations in CSF and brain tissue than itraconazole. In a retrospective multicenter study of 22 cases of CNS blastomycosis, 8 patients received step-down therapy after induction with amphotericin B, and of these, 7 had positive outcomes.[191] Immunosuppressed patients without CNS disease should be treated with amphotericin B for 1 to 2 weeks, even in the case of mild presentations, followed by step-down therapy to azoles.

Alternative Antifungal Agents

Voriconazole and posaconazole have demonstrable in vitro activity against *B. dermatitidis*, and voriconazole is listed as a second-line therapy for mild to moderate blastomycosis in Infectious Diseases Society of America treatment guidelines.[206–209] Isavuconazole has in vitro activity against *B. dermatitidis* and has been used for the treatment of patients with blastomycosis, but data are very limited.[154] Although a case of successful treatment of chronic blastomycosis with caspofungin has been reported in a patient with severe allergy to azoles,[210] echinocandins have not been well evaluated for blastomycosis and are not recommended.

Duration of Therapy and Special Populations

Indefinite suppressive treatment may be required if immunosuppression cannot be reversed. For patients with HIV/AIDS, treatment with itraconazole for at least 1 year, CD4 cell counts of >150 cells/mm^3 for at least 6 months, undetectable HIV viral load on ART, and reduction of antigen levels to <2 ng/mL may be used as criteria to discontinue therapy for blastomycosis. Notably, however, these criteria are extrapolated from experience with patients with HIV/AIDS with histoplasmosis.[201] For recipients of solid organ transplantation, immunosuppression should be reduced concomitantly with antifungal treatment.[157] Suppressive therapy following successful treatment may be considered in transplant patients on significant immunosuppression.[157] For all manifestations of blastomycosis, treatment should continue until there is clinical and radiographic improvement or stabilization to residual healed lesions, as well as significant reduction or normalization of serum or urine antigen levels.

Prevention

Patients at high risk for dissemination should avoid activities that expose them to *B. dermatitidis*, such as caving, landscaping, or construction, particularly in areas endemic for blastomycosis. Screening for blastomycosis is not recommended prior to transplantation as the risk of reactivation post-transplant is extremely low.[157]

COCCIDIOIDOMYCOSIS

Coccidioidomycosis is the most serious of the endemic mycoses, with particular proclivity for reactivation, relapse, and treatment failure. An increasing population in the southwestern states, as well as climate-related and anthropomorphic land changes, have placed large numbers of persons at risk. Large outbreaks have been reported in Arizona and southern California in the last decade.[211] Increasing travel through these areas, along with expansion of traditional locations where the organism is considered endemic, have increased the global importance of coccidioidomycosis. *Coccidioides* is listed as a "select agent" of bioterrorism, complicating its use in the clinical and research laboratory.

Epidemiology

Coccidioidomycosis, often referred to as "Valley Fever" (from a San Joaquin Valley outbreak), occurs in a spotty distribution across the southwestern United States, northern Mexico, and Central America (Fig. 133-1). Counties of southern California and southern Arizona are perhaps the most recently well-studied and have experienced an increased incidence of disease.[212,213] Exposure to *Coccidioides* spores is heaviest in the late summer and fall when the soil is dry and conditions are windy. In Kern County, the incidence of coccidioidomycosis has a yearly cycle, with the number of cases generally increasing toward the late fall (17 per month per 100,000 population), decreasing in the winter, and reaching a minimum in the spring and summer.[214] Coccidioidomycosis is laboratory-reportable, and an abundance of information is available, for example, on the Arizona Department of Health website (*www.azdhs.gov/preparedness/epidemiology-disease-control/valley-fever/*).

Coccidioidomycosis is also a common cause of community-acquired pneumonia in the southwest endemic areas.[215,216] Cases are often identified in construction workers, archaeologists, or military personnel. Dust storms (haboobs) can carry the spores for miles, exposing persons with no direct contact with contaminated soil. Many cases occur in individuals with no clear exposure history. Cases are identified outside the endemic area in travelers or past residents of those regions, often years after exposure. Reports of coccidioidomycosis occurring in otherwise healthy young adults[217] and reports of acquisition of disease outside traditionally defined endemic areas contribute to delays in diagnosis.[218,219] Coccidioidomycosis also is a threat to laboratory personnel working with the organism outside of biosafety cabinets. Persons of Black race, Filipinos, and Hispanics experience a disproportionately higher frequency of disease in some studies, although it is not clear whether the predilection is related to genetics or socioeconomic status.[212,220] Notably, coccidioidomycosis is a serious opportunistic infection in immunosuppressed patients, including those with AIDS, transplant recipients, and those receiving immunosuppressive treatment.[221–223]

Mycology

Coccidioidomycosis is caused by the pathogenic fungus *Coccidioides,* which includes two species, *C. immitis* and *C. posadasii.* Except for different geographic locations (*immitis* in California and *posadasii* in Arizona), the laboratory properties, virulence factors, pathogenesis, clinical findings, diagnostic approach, and treatment are mostly identical. Hence, *Coccidioides* will be used to refer to both species in this section.

Coccidioides is highly virulent, causing infection upon exposure to only a few arthroconidia and severe disease with larger inocula. *Coccidioides* has been designated as a select agent by the Centers for Disease Control, requiring that it be ultimately destroyed upon identification in the laboratory except at facilities approved for handling select agents. *Coccidioides* grows as a mold with septate hyphae in the soil and on culture media at room temperature. Its arthroconidia are 2.5 to 4 × 3 to 6 µm in size and function as infectious particles. At body temperature and in clinical specimens, it exists as an endosporulating spherule.

When using special media. Coccidioides converts to an endosporulating spherule at 37° to 40°C. Spherules measure 30 to 60 µm in diameter and contain numerous 2- to 5-µm endospores (Figs. 133-3 and 133-5). In contrast with *H. capsulatum* and *B. dermatitidis*, growth on fungal media occurs rapidly, usually within 3 to 5 days.

Pathogenesis

Infection occurs following inhalation of arthroconidia of the mycelial phase of the fungus or reactivation of latent infection during immunosuppression. Person-to-person transmission does not occur, and direct inoculation of the skin is rare. Donor-derived transmission by transplantation of an infected organ allograft has been reported and causes rapidly progressive disease in the recipient.[224]

In the lungs, the arthroconidia enlarge to form thick-walled spherules, which contain multiple endospores. Spherules rupture releasing endospores, which spread locally and disseminate hematogenously. Cellular immunity and neutrophils are both involved in host defense in coccidioidomycosis.[225] Patients with deficient cellular immunity may experience severe progressive forms of coccidioidomycosis.

Coccidioides infection produces several mixed pyogranulomatous reactions in tissues, which often also contains eosinophils. The neutrophil response and caseous necrosis may lead to the development of large abscesses, which often require surgical drainage. Abscesses may also spontaneously rupture or produce fistulas. Tissue and blood eosinophilia can be prominent.[226]

Clinical Findings

Coccidioidomycosis is asymptomatic in more than one-half of cases. In symptomatic cases, a pulmonary illness is most common, with symptoms appearing 1 to 4 weeks following exposure. True coccidioidal primary infections are difficult to diagnose, since the symptoms of early infection overlap substantially with those of other respiratory infections. While most immunocompetent patients recover without treatment over a course of several weeks, many do receive treatment. Nevertheless, serious infections do occur; in one outbreak following an earthquake, 27% of patients who developed coccidioidomycosis were hospitalized and 1.5% died.[227]

Primary Pulmonary Infection

Symptoms develop within a few weeks following exposure, depending on the size of the inoculum and the immune status of the patient. Low inoculum exposure in the immunocompetent host usually results in a localized pneumonia that may be mistaken for bacterial community-acquired pneumonia. Symptoms include pleuritic or dull chest pain, nonproductive cough, headache, fever, and fatigue.[228] A macular rash, erythema nodosum, and erythema multiforme are common and help to distinguish the infection from bacterial pneumonia. The constellation of fever, arthralgia, and erythema nodosum is referred to as “desert rheumatism.” Infection is more severe in older persons, those with diabetes, and smokers. Diffuse bilateral pneumonia may be associated with an ARDS-type presentation and may occur in the absence of dissemination. A miliary appearance suggests dissemination or fungemia, more often in an immunosuppressed host.

Acute infection typically resolves, even in the absence of treatment, but can set the stage for chronic, progressive disease, which occurs more commonly in immunocompromised individuals, including diabetics. This may result in thick-walled cavities resembling tuberculosis or malignancy. In acute disease, chest radiographs demonstrate patchy infiltrates, often with mediastinal adenopathy. The main CT finding in acute disease is multiple nodules.[229] Typical patterns also include dense lobar consolidation and centrilobular nodules, often with a tree-in-bud pattern.[230] Chronic sequelae include pulmonary nodules in about 20% of cases and thin-walled cavities in 10%. These are usually asymptomatic and may clear without therapy (Fig. 133-7). Residual cavities, however, may become superinfected with bacterial or other fungal organisms or, when in proximity to the pleura, rupture resulting in a pneumothorax, pyopneumothorax, or bronchopleural fistula. When the diagnosis of coccidioidomycosis is not clear, residual and typically asymptomatic nodules are occasionally biopsied or surgically removed, as they mimic malignancy.[231]

Disseminated Disease

Approximately 1% of patients will have disseminated infection, with the most common extrathoracic sites including skin, soft tissue, bone, and meninges.[232] Progressive disseminated disease is, however, reported in nearly one-half of cases, occurring in patients with underlying immunosuppression.[233] Disseminated disease may be first recognized years following exposure. Risk factors for disseminated disease, in addition to immunosuppression, include non-white race, extremes of age, and pregnancy.[220,234,235] Pulmonary involvement is common in disseminated disease; chest imaging usually shows diffuse reticulonodular or miliary infiltrates, although focal pulmonary lesions, nodules, cavities, adenopathy, and pleural effusions also may be seen (Fig. 133-7).

Meningitis is the most common and severe manifestation of disseminated disease; approximately 300 cases are reported in endemic areas per year.[236,237] Patients complain of headache, nausea, vomiting, and confusion. Meningitis carries a poor prognosis and a tendency to relapse despite long-term maintenance therapy. Abscesses may develop in the brain or spinal cord. Hydrocephalus and vasculitis are serious, life-threatening complications of meningitis.

Less frequently involved extrapulmonary sites include liver, peritoneum, kidneys, epididymis, prostate, testes, retina, ears, larynx, heart, thyroid, adrenal, and pituitary gland, esophagus, and pancreas.

Diagnosis

Because the diagnosis of coccidioidomycosis based on clinical and radiographic parameters alone can be difficult, laboratory testing is usually required to establish a diagnosis. A battery of tests, including fungal stain, culture, antigen, and serology, are useful for the diagnosis of coccidioidomycosis (Table 133-9).[76–84,141–143,238–240] The sensitivity of these methods is affected by the extent of exposure, the immune status of the patient, and the type of infection.

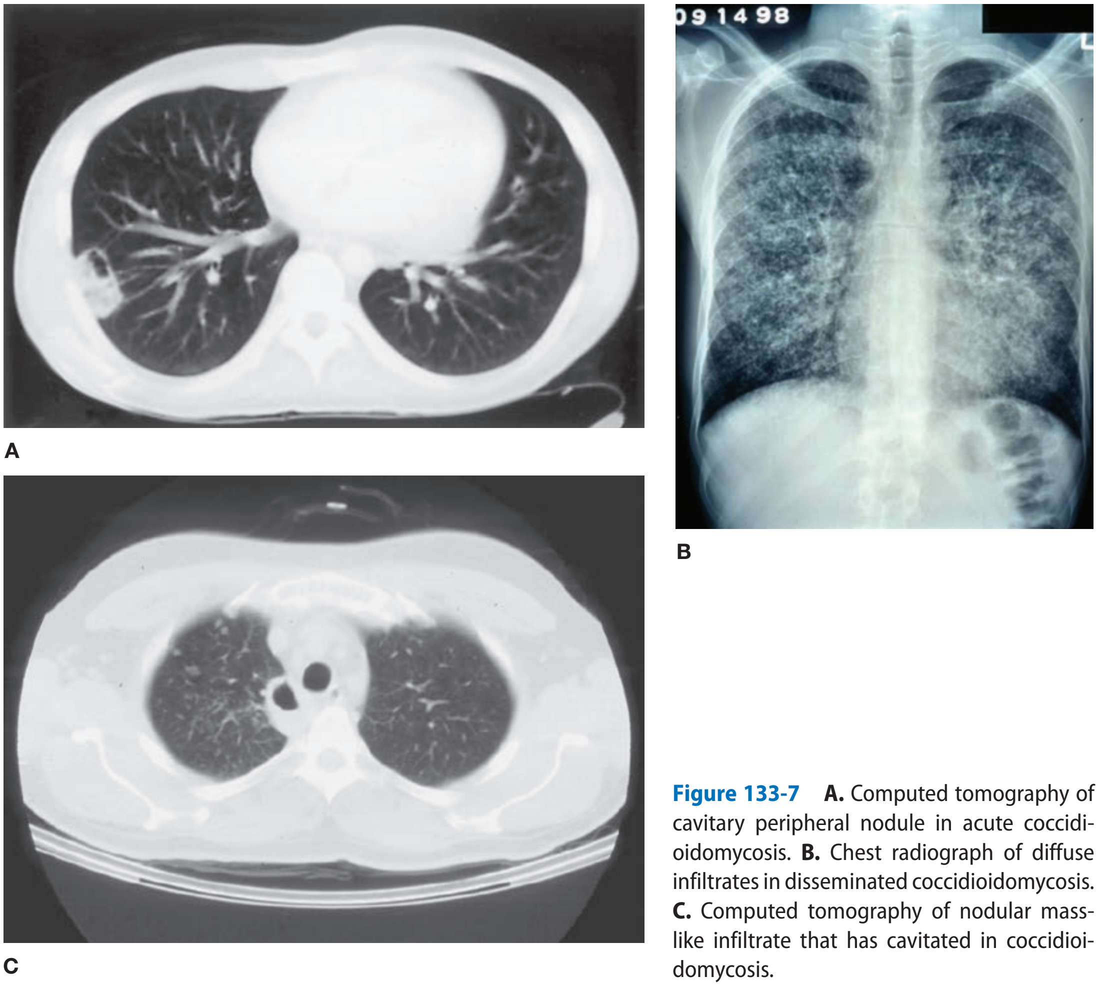


Figure 133-7 **A.** Computed tomography of cavitary peripheral nodule in acute coccidioidomycosis. **B.** Chest radiograph of diffuse infiltrates in disseminated coccidioidomycosis. **C.** Computed tomography of nodular mass-like infiltrate that has cavitated in coccidioidomycosis.

TABLE 133-9 Diagnostic Studies in Coccidioidomycosis (Percent Positive Assays)

Test	Acute Pneumonia, Focal	Acute Pneumonia, Diffuse	Nodule or Cavity	Chronic Fibrocavitary	Disseminated
Papanicolaou smear or histopathology	<25	64	50	35	>75
Culture	<10	86	10	95	39
Serology	90	54	<50	95	95
Antigen	70				

Imaging Studies

The radiologic findings of coccidioidomycosis are diverse (Fig. 133-7).[229,230] Pulmonary infiltrates are identified in the majority of patients, as well as pulmonary nodules and cavities. Pleural effusions and adenopathy are also commonly identified on chest radiographs. Immunosuppressed patients may manifest with a diffuse miliary pattern. CT scans of the chest are more sensitive than chest radiographs, identifying effusions, hilar lymph nodes, micronodular infiltrates, and multifocal ground-glass infiltrates more readily.[241] Pulmonary nodules as sequelae of past coccidioidomycosis infection are usually less than 5 cm in diameter in size but can be confused with malignancy. Nodules rarely calcify; rather, they may evolve into thin-walled cavities with spontaneous excavation of the nodule contents. These cavities may predispose to secondary infection, pneumothorax, hemoptysis, and mycetoma. Lymph nodes and nodules exhibit varying degrees of uptake on PET scans, limiting its utility in distinguishing them from malignancy.[242]

Serology

Serologic tests are the most widely used method of diagnosis for coccidioidomycosis.[232,238,243] Serology is positive in 90% of clinically recognized cases, and the magnitude of response correlates with the extent of infection. However, serology may be negative early in the course of infection, in asymptomatic cases, and in those with mild illness, including thin-walled cavities and solitary nodules. Additionally, immunocompromised patients may have negative serology due to inefficient antibody production.[244] Paired testing 2 to 4 weeks apart may improve sensitivity especially when early disease is suspected. Sensitivity may also be increased by concentrating the specimen, as is done in some reference laboratories.[239]

The immunoglobulin M (IgM) response can be measured by enzyme immunoassay (EIA), tube precipitation, or agar gel diffusion, and is positive in the majority of cases by the end of the first month of the illness, fading over the next 6 months.[239,245] EIA has emerged as the most commonly utilized initial test. False-positive results may occur, and an isolated positive EIA IgM warrants further clinical assessment and diagnostic testing.[246,247] Blair et al.[244] found that EIA was positive in 87% of healthy patients with coccidioidomycosis, compared with 67% of immunosuppressed patients. Sensitivity improved to 95% and 84%, respectively, when sequential and confirmatory tests were employed. Serology may be falsely negative in about one-quarter of solid-organ transplant patients with coccidioidomycosis, and two-thirds to three-quarters if positive EIA results alone are not considered diagnostic.[248]

The immunoglobulin G (IgG) response measured by EIA, complement fixation, or immunodiffusion follows the IgM and peaks during the fourth month of illness, and then slowly fades.[244] The commercial IgG EIA tests are commonly used and are generally highly sensitive and specific. However, the performance characteristics may vary depending on the test used and the performing laboratory.[243,249,250] In the proper clinical setting, a positive result is considered diagnostic. Otherwise, a positive IgG EIA may be sent to specialized reference laboratories for confirmation and quantification. Immunodiffusion quantitative testing or complement fixation testing is often performed as the confirmatory test and provides prognostic information with higher titers (>1:16) suggesting dissemination. However, this finding is neither sensitive nor specific for dissemination, especially in the setting of meningitis.[235] Antibody titers decline with treatment, assisting in monitoring therapy and identifying relapse. Serial testing is also useful in patients who are not receiving therapy, as rising titers suggest progressive infection and support evaluation to exclude dissemination. Detection of complement fixation antibody in CSF is useful for diagnosing meningitis.[237]

Antigen Detection

An enzyme immunoassay using antibodies against *Coccidioides* galactomannan, a cell wall component of *Coccidioides* spp., may be used in conjunction with serologic testing to aid diagnosis. A few studies have highlighted the clinical utility of testing *Coccidioides* galactomannan antigenemia and antigenuria in predominantly immunocompromised patients with moderately severe or disseminated disease. In this severely ill patient population, antigenemia can be detected in up to 71% of urine specimens and 73% of EDTA-treated serum samples.[251,252] Antigen detection in cerebrospinal fluid has been shown to be highly sensitive for the diagnosis of coccidioidal meningitis, with detectable antigen in 93% of cases in one study.[253] In a more recent study of 158 immunocompetent and immunocompromised patients with progressive (severe) coccidioidomycosis that evaluated the performance characteristics of antibody detection by immunodiffusion, as well as *Coccidioides* antigen detection in urine and serum, the sensitivity of urine *Coccidioides* antigen testing was 37% overall but increased to 57% when serum antigen testing was added to urine testing, compared with 84% for serology.[254] The sensitivity of combined antigen urine and serum antigen detection was 79% in disseminated disease, 42% in pulmonary disease, 75% in immunocompromised patients, and 40% in immunocompetent patients. The sensitivity of combined antigen and antibody testing was 93%, supporting the use of both diagnostic modalities for the diagnosis of severe pulmonary or extrapulmonary disease. In real-world settings, antigen testing is most useful in highly immunocompromised patients for whom the sensitivity of serology is suboptimal. Cross-reactivity with other endemic fungi, including histoplasmosis, can occur, and clinical context is needed for accurate diagnosis.[255,256]

Cytology, Histopathology, and Culture

Sputum can be useful for diagnosis, although other respiratory specimens may improve sensitivity. Cytology has been found to be positive in 35% of culture-positive bronchoscopy specimens from patients with pneumonia (specifically, in 46% with diffuse infiltrates and 26% with a focal infiltrate).[257–259] In a study of severe multifocal pneumonia in patients with AIDS, a Papanicolaou smear was positive in 9 of 14 BAL specimens, compared to KOH wet mount in only 3, calcofluor white stain in 2, and culture in 12.[257] Histopathology is positive on needle-biopsy specimens from lung nodules in about one-half of cases.[260] The sensitivity of histopathology in extrapulmonary lesions has not been reported but is presumably high, except for meningitis.

Interestingly, cultures of respiratory specimens are infrequently positive in patients with acute pneumonia. The sensitivity of culture for diagnosis is uncertain because culture positivity is often a basis for inclusion in the published studies. Nevertheless, culture of lung specimens is more sensitive than cytology.[259] Cultures of skin or bone lesions are positive in the majority of cases of disseminated coccidioidomycosis. However, blood, urine, and CSF cultures are frequently negative, complicating the diagnosis. As such, serology and antigen testing play an important complimentary role in the diagnosis of ill patients. Importantly, cultures of *Coccidioides* spp. pose a significant risk for infection to laboratory personnel. Laboratory personnel should be notified if this diagnosis is suspected, and cultures should be handled in a biosafety level 3 laboratory.[232,261]

Polymerase Chain Reaction (PCR)

Once *Coccidioides* is cultivated in the laboratory, confirmation typically occurs via chemiluminescent DNA probe or by DNA sequencing methods, thereby shortening the time to diagnosis. In addition, a few reference laboratories can apply PCR and real-time PCR methodologies directly to clinical samples. Binnicker et al.[262] applied real-time PCR to 66 fresh tissue specimens, yielding 93% sensitivity and 98% specificity when compared with culture. The assay was sensitive enough to be used on paraffin-embedded tissue. Subsequently, clinical sensitivity was shown to be 56% versus 44% for fungal culture, similar to the sensitivity of fungal culture in past studies.[262,263] More recently, Saubolle et al.[264] found that a new real-time PCR assay demonstrated high sensitivity and specificity when compared to culture of bronchial washings or bronchoalveolar lavage fluid. As clinical performance improves and becomes more reliable, molecular methods are likely to become more important for clinical diagnosis in the future.

Skin Test

Skin test reagents were historically used in diagnosis, but this method has fallen out of favor because of a lack of clinical availability and development of newer tests. *Coccidioides immitis* Spherule-Derived Skin Test Antigen (Spherusol) has been approved for the detection of a delayed-type hypersensitivity to *Coccidioides* in individuals with a history of pulmonary coccidioidomycosis. In a real-world assessment of the performance of this test in an endemic region, it was found to be positive in only 72% of proven or probable cases.[265]

Treatment

Guidelines for treatment are continually being updated (Table 133-10).[134,266] Most infections are asymptomatic or self-limited pulmonary infections and require no treatment in the absence of immunosuppression. Before withholding treatment, however, patients must be evaluated carefully for the extent of disease and evidence for extrapulmonary dissemination. Any evidence of dissemination, such as new or persistent headache, skin lesions, inflammatory arthritis, or pain suggestive of osseous involvement, should prompt further investigation and consideration of empiric therapy, pending definitive diagnosis. In patients in whom treatment is withheld, radiographic and clinical follow-up at 4 to 6 weeks and then at 3- to 6-month intervals for 2 years is recommended to identify progressive infection. Patients should be educated regarding the typical course and symptoms of coccidioidomycosis, including those associated with dissemination, and should be considered for reconditioning physical therapy to manage the associated fatigue and deconditioning.[266]

Acute Uncomplicated (Mild) Pneumonia

In minimally symptomatic patients, some physicians recommend treatment to prevent long-term complications, but most recommend observation without therapy. Circumstances warranting treatment include symptoms persisting for 4 to 6 weeks; immunosuppression; other chronic diseases or conditions affecting recovery from the acute infection, such as diabetes, COPD, pregnancy, age greater than 55 years, Black race, or Asians of Filipino descent; and higher severity of illness. Indicators of severe illness include weight

TABLE 133-10 Treatment Recommendations for Coccidioidomycosis Syndromes

Syndrome	Recommendation
Acute pulmonary coccidioidomycosis	
Uncomplicated (mild) infection	Observation
Complicated (moderate to severe) infection	Fluconazole 400 mg/day or itraconazole 400 mg/day for 3–6 months for moderate or prolonged symptoms, risk factors for severe disease
	ARDS/diffuse lung disease: liposomal amphotericin B 5 mg/kg/day until clinical improvement (usually 10–14 days), then fluconazole 400 mg/day or itraconazole 400 mg/day for at least 12 months
Chronic sequelae of coccidioidomycosis	
Pulmonary nodule	No treatment
Pulmonary cavity	No treatment in most cases
	Fluconazole 400 mg/day or itraconazole 400 mg/day for 3–6 months for chronic fibrocavitary disease until symptoms/cavity stabilize
	Surgical resection for persistent or massive hemoptysis, cavity rupture with pneumothorax
Disseminated coccidioidomycosis	
Nonmeningeal and mild–moderate	Fluconazole 400 mg/day or itraconazole 400 mg/day for at least 1 year until clinical stability/improvement
Nonmeningeal and severe	Liposomal amphotericin B 5 mg/kg/day for severe cases until clinical improvement (usually 10–14 days) followed by transition to oral azole therapy as above
Meningitis	Fluconazole 400–1000 mg/day or itraconazole 600 mg/day for life
	Intrathecal amphotericin B in rare cases
	CSF shunt for hydrocephalus

loss greater than 10% of body weight, intense night sweats for more than 3 weeks, infiltrates involving more than one-half of one lung or portions of both lungs, prominent or persistent hilar adenopathy, and inability to work.[134] Treatment is indicated in all patients with diffuse pulmonary or disseminated coccidioidomycosis.[134,266]

Acute Complicated (Moderate to Severe) Pneumonia

Fluconazole is used in the majority of outpatients and those with mild to moderate coccidioidal pneumonia. Consultation is warranted for patients with severe or extrapulmonary disease or with underlying immunosuppression. Liposomal amphotericin B (5 mg/kg/d), generally preferred over nonlipid formulations for its lower nephrotoxicity profile, is indicated as initial therapy in severe cases with subsequent transition to oral azole therapy.

Non-CNS Extrapulmonary Disease

Itraconazole and fluconazole are effective in milder nonmeningeal cases. In patients with bone disease, outcomes have been better with itraconazole.[267,268] Recommended dosages for fluconazole and itraconazole are 400 mg/day for nonmeningeal disease. Drug interactions and inadequate drug exposure occur more often with itraconazole than fluconazole. Patients with severe disease should receive induction with liposomal amphotericin B 5 mg/kg/day until clinical improvement (usually 10–14 days), followed by transition to oral azole therapy.

CNS Disease

Treatment for meningitis is less effective than for other forms of coccidioidomycosis. Fluconazole, 400 to 1000 mg per day (typically, 800 mg per day at initiation) is recommended because of excellent penetration into CNS.[134,269] Some physicians also administer amphotericin B intrathecally, although this is more commonly done for cases refractory to azole therapy.[270] For patients in whom hydrocephalus develops, administration via a ventricular Ommaya reservoir facilitates intrathecal therapy. Consultation with an infectious disease or pulmonary physician who specializes in coccidioidomycosis treatment is advised. Because the presence of CNS coccidioidomycosis is often associated with non-CNS extrapulmonary disease, many experts add intravenous liposomal amphotericin B to fluconazole. Treatment for coccidioidal meningitis requires lifelong suppressive therapy with fluconazole (or itraconazole) due to a high risk of recrudescent disease with cessation of therapy.[271,272] Response to therapy, including assessment of symptoms, imaging features, and CSF analysis, must be documented. In those with an inadequate response, escalating doses or intrathecal amphotericin B is recommended.[266]

Persistent Cavities or Nodules

Approximately 10% of patients with acute pulmonary coccidioidomycosis will develop residua of acute infection (nodules or cavities), which are often asymptomatic and require no therapy. However, these residua can lead to complications, including pain, cough, hemoptysis, and bacterial superinfection. Antifungal therapy is appropriate in patients with persistent symptoms or rising serologic titer. Treatment is also recommended in those with lesions contiguous with the pleura or exhibiting progressive enlargement, such as patients with chronic fibrocavitary disease. Biopsy of nodules may be required if a history of infection is not secure in order to exclude malignancy.

Alternative Antifungal Agents

The newer triazoles posaconazole, voriconazole, and isavuconazole exhibit in vitro and in vivo activity against *Coccidioides,* and there are several reports of successful treatment, including cases of meningitis.[152,273] Because of poor in vitro activity and inconsistent results, caspofungin and other echinocandins are not currently recommended.

Duration of Therapy and Special Populations

In patients with acute pulmonary coccidioidomycosis, up to 3 months of therapy may be sufficient. Patients should be re-evaluated before treatment is stopped to identify evidence for chronic infection or extrapulmonary dissemination, in which case treatment should be continued for 12 to 18 months or longer. Prolonged therapy may be considered in patients with underlying immunodeficiency, although duration of therapy in these populations is generally similar to that in immunocompetent patients.[134,157,266]

Immunocompromised patients, such as those with hematopoietic stem cell or solid organ transplant, those on biologic response modifiers, and individuals with HIV infection and CD4 counts less than 250 cells/mm^3, are at higher risk for severe and disseminated infection and should be treated regardless of severity at the time of diagnosis.[157] Treatment is generally similar for immunocompetent patients, with oral azole therapy considered first-line, with the exception of severe or refractory disease, for which liposomal amphotericin B is recommended as initial or rescue therapy, respectively.[266] In solid organ transplantation, maintenance immunosuppression should be reduced concomitantly with antifungal treatment.

There is also a real risk of relapse of coccidioidomycosis after discontinuation of antifungal therapy, so lifelong suppressive therapy with azoles (fluconazole 200–400 mg daily) is usually recommended unless complete withdrawal of immunosuppressive therapy is achievable.[157] Pregnant women are also at higher risk for severe disease, but the teratogenicity of azole therapy complicates treatment. For those who develop symptomatic disease during pregnancy, treatment should be strongly considered with a preference for amphotericin B during the first trimester and oral azole therapy thereafter. Coccidioidal meningitis during the first trimester of pregnancy is preferentially treated with intrathecal amphotericin.[266] As discussed above, treatment should be continued indefinitely for patients with meningitis or those with severe underlying immunodeficiency states, regardless of the underlying host.[134,266]

Adjunctive Surgical Therapy

Surgical debridement or resection of infected tissue often is necessary as an adjunct to antifungal therapy. Cavitary disease that results in persistent symptoms despite antifungal therapy should be considered for surgical resection, preferably by video-assisted thoracoscopic surgery. For cavities that rupture into the pleural space, drainage is required, preferably with decortication and surgical resection of the cavity rather than tube thoracostomy alone.[231,266,274] Hydrocephalus may require surgical intervention with placement of a shunt. Soft tissue, joint, or bony abscesses may require drainage or debridement.[268]

Adjunctive Steroid Therapy

Although not routinely used, corticosteroid therapy plays a limited role as adjunctive therapy in coccidioidomycosis. An intense eosinophilic pneumonia can occur resembling a hypersensitivity reaction and clinical improvement has been noted with concomitant steroid therapy.[226,275] Corticosteroids may also be of utility as adjunctive therapy in coccidioidal IRIS.

■ Prevention

Recommendations exist for the prevention of coccidioidomycosis in high-risk occupations.[276] Patients with diseases that impair cellular immunity probably should avoid activities involving dust or soil, areas experiencing active outbreaks, and the desert during dry and windy periods. Death from coccidioidomycosis was reduced by antifungal therapy used as secondary prophylaxis in solid-organ transplant patients with a history of symptomatic coccidioidomycosis up to 5 years before transplantation, supporting a recommendation for preventive treatment.[277] As such, primary antifungal prophylaxis is recommended for organ transplant recipients who have lived or are living in endemic areas in the first 6 to 12 months after transplantation.[266,278] Serologic screening for coccidioidomycosis prior to transplant is recommended, with seropositive patients receiving prophylaxis with fluconazole 400 mg daily, and seronegative patients (who continue to reside in endemic areas) receiving 200 mg daily. In lung transplant recipients, some experts recommend lifelong prophylaxis.[157,222,279] Solid-organ transplantation should be delayed in any patient with active coccidioidomycosis until the infection is well controlled or resolved. In persons with HIV/AIDS with a CD4 count less than 250 cells/mm^3 living in *Coccidioides*-endemic areas, serologies should be checked yearly. Those with positive IgG on initial testing or who seroconvert from negative to positive should be placed on primary prophylaxis with fluconazole.[266,279] Although prophylaxis is not generally recommended for patients on biologic immunomodulatory therapy, individuals in endemic regions should undergo screening for coccidioidomycosis by chest radiograph and serology prior to initiating therapy; treatment of those with positive results is recommended before starting biologic therapy.[280] Efforts to develop a vaccine to prevent coccidioidomycosis in humans have been unsuccessful to date, but are ongoing.[281]

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CHAPTER 134

Pneumocystis Pneumonia

Eliezer Zachary Nussbaum
Marwan M. Azar

INTRODUCTION

Pneumocystis is an opportunistic yeast-like fungus that is tropic to mammalian lung tissue and produces a clinical spectrum ranging from asymptomatic infection to subacute and acute interstitial pneumonia in susceptible hosts. The earliest descriptions of *Pneumocystis jiroveci* pneumonia (PCP) in humans came from reports of malnourished children and neonates with pneumonia in the 1940s, but the syndrome came into worldwide prominence during the HIV/AIDS pandemic in the 1980s where PCP accounted for more than one-fourth of community-acquired pneumonias in persons living with HIV/AIDS (PLWH). The subsequent introduction of combination antiretroviral therapy (ART) and institution of routine PCP prophylaxis for those at greatest risk of infection led to a decreased incidence of PCP among PLWH. In the developed world, HIV-negative patients with cell-mediated immune deficiencies have become the most common hosts for PCP, with 60% to 70% of new infections occurring in patients on prolonged high-dose corticosteroids and chemotherapeutic agents as well as those with autoimmune diseases or recipients of solid organ or hematopoietic stem cell transplantation.[1–3] Although it produces a characteristic interstitial pneumonia for which effective treatments are available, *Pneumocystis jiroveci* has remained a problematic pathogen due to an enlarging population of at-risk individuals, a propensity to colonize hosts for short periods of time without necessarily causing infection, an ability to produce fulminant infection despite low pathogen burdens, intrinsic resistance to the most common antifungal classes, and the inability to sustain and thus study the organism in vitro.

HISTORY AND BACKGROUND

The fungus *Pneumocystis,* a unicellular, host-specific yeast-like organism, is unusual among fungi in many respects including its history. First described by Carlos Chagas in 1909, *Pneumocystis* was mistakenly interpreted as a developmental stage of the protozoan *Trypanosoma cruzi* and classified as a parasite until years later when genetic analyses revealed the organism to be more closely related to fungi.[4] In 1912, the organism infecting rat lung tissue was understood by Delanoe and Delanoe to be separate from the trypanosome and named *Pneumocystis carinii*, but *Pneumocystis* was not recognized as a pathogen of humans until 1942 (Van der Meer and Brug).[5,6] The first descriptions of a syndrome consistent with PCP came from orphanages in Europe in the 1930s and following World War II and the Vietnam War where clusters of "plasma cell interstitial pneumonitis" were reported among disadvantaged children and neonates.[7] It was not until 1952 that a clear association with human disease was made by Vanek and Jírovec.[7] In addition to severe malnutrition, prolonged corticosteroids and chemotherapeutic agents were recognized as risk factors for PCP.

In the 1970s, the Centers for Disease Control and Prevention (CDC) undertook epidemiologic and therapeutic studies to better characterize the host–pathogen interaction and to broaden the antimicrobial armamentarium beyond pentamidine, which was the only available therapeutic option at the time. This investigation resulted in the development of pyrimethamine, sulfadoxine, trimethoprim (TMP), and sulfamethoxazole (SMX), agents that are highly effective in treatment and prevention of PCP. In the 1980s, the rise of the HIV/AIDS pandemic was accompanied by an explosion in the incidence of PCP presenting as an AIDS-defining opportunistic infection, with more than 200,000 cases since 1979. In 1976, Frenkel described serologic differences between organisms recovered from humans and rats suggestive of the existence of distinct species, and in 1988, rRNA analysis indicated that *Pneumocystis* was more closely related to fungi.[4] Currently, a unique species of *Pneumocystis* has been described as pathogenic for almost every mammal, although the basis for this specificity is as of yet unknown.[8] Although both *carinii* and *jirovecii* have been used interchangeably in the medical literature, *P. jiroveci* is now understood as the organism that infects humans while *P. carinii* is the pathogen of rats. Despite the change in nomenclature, PCP continues to be the preferred abbreviation for the pneumonia syndrome.[9]

PATHOGEN

Pneumocystis is an extracellular, obligate ascomycetous yeast-like fungus that is mostly restricted to lung tissues with rare exceptions of extrapulmonary infection, mainly in highly immunosuppressed hosts with structural lung disease and heavy organism burdens. Morphologic forms of the *Pneumocystis* life cycle continue to be designated in terms of cysts and trophozoites, a relic of the organism's taxonomic past. *Pneumocystis* organisms carry a variety of surface glycoproteins, some of which are unique to different species.[10] Unlike most fungi, *Pneumocystis* lacks ergosterol in its cell membrane, but is instead rich in cholesterol like mammalian cells. Commonly used antifungal medications that target ergosterol biosynthesis, such as azoles and the polyene amphotericin B, are therefore ineffective against this organism.[11] The cell wall of *Pneumocystis* is also characterized by low amounts of chitin and an abundance of other polysaccharides including glucose, mannose, and (1,3)-β-D glucan, a biologic feature that has been exploited for the development of highly sensitive peripheral antigenic testing in the setting of clinical infection (particularly targeting peripheral detection of [1,3]-β-D glucan) and as a therapeutic target for echinocandin antifungal agents (which bind [1,3]-β-D glucan). *Pneumocystis* species demonstrate high degrees of host specificity with *P. jirovecii* acting as a human pathogen, *P. carinii* a rat pathogen, and *P. murina* a mouse pathogen among many others with no cross-infection across mammalian species. Growth of *Pneumocystis* cannot be sustained in in vitro culture beyond a few replication cycles. As such, culture is not an available diagnostic tool for this fungus. Furthermore, lack of culture capability has hampered research on the organism's life cycle, metabolic functions, and potential targets for drug therapy.

MORPHOLOGIC FORMS AND LIFE CYCLE

Pneumocystis exists in three predominant morphologic forms: the trophozoite (2–5 μm in size), the mature cyst (3–8 μm in size), and the precyst (3–8 μm in size), although other intermediate developmental stages exist. Trophozoites are single-celled, thin-walled, and ameboid in shape, and they exhibit pseudopodia and filopodia used for limited motility and/or anchoring to host cells. Mature cysts are thick-walled and globular and contain up to eight sporozoite or intracystic bodies (1 μm in size), the majority of which are haploid. In the setting of *P. jirovecii* pulmonary infection, trophozoites are 10-fold more abundant than cyst forms in respiratory clinical specimens. Mature cysts likely allow *Pneumocystis* to subsist outside of

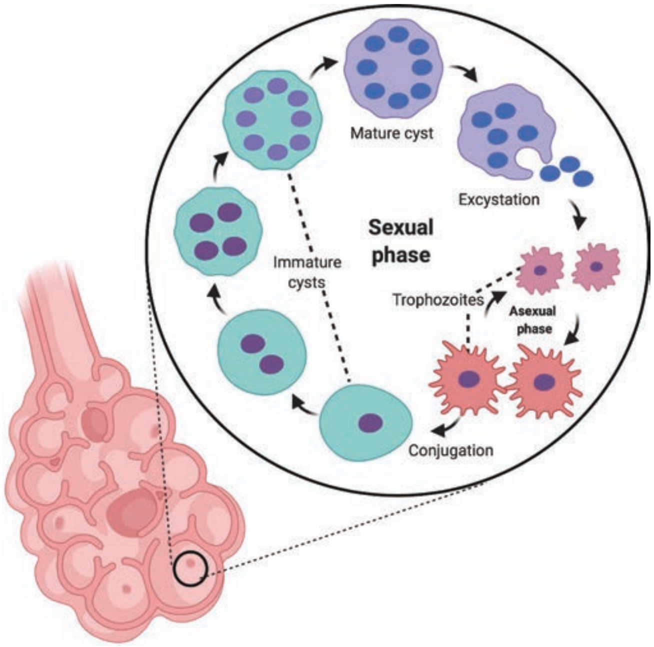

Figure 134-1 *Pneumocystis jirovecii* proposed life cycle within the human lung. Mature cysts undergo excystation to numerous sporozoites into lung tissue. Sporozoites then develop into trophozoites, which proliferate by binary fission to produce more trophozoites in an asexual cycle. Alternatively, two haploid trophozoites can undergo conjugation into an immature cyst (or precyst), which then progressively matures into a full cyst.

lung tissue and appear to be essential for transmission of infection to other hosts.[12,13] Precysts are immature cysts that contain up to eight developing sporozoites depending on the stage of maturation. Precysts do not have well-defined sporozoites, and their cell wall progressively thickens as they mature.[14] *Pneumocystis* organisms do not bud, which distinguishes them from most other yeasts and yeast-like organisms.

Owing to the inability to sustain continuous growth in culture, the *Pneumocystis* life cycle is incompletely understood and knowledge is derived from animal models of infection or microscopic analyses of clinical specimens, neither of which is fully representative of the entire human life cycle. Mammalian infection may begin when aerosolized mature cysts are inhaled into terminal alveoli. In a putative life cycle, the mature cysts then undergo excystation to release numerous sporozoites into lung tissue (Fig. 134-1). In the asexual phase, sporozoites develop into trophozoites that proliferate by binary fission to produce more trophozoites. Trophozoites can also attach to one another to form clumped trophic forms that are seen during infection. In a proposed alternate sexual phase, two haploid trophozoites undergo conjugation into a precyst diploid form, which then progressively matures into a full cyst (Fig. 134-1).[15]

EPIDEMIOLOGY AND RISK FACTORS

Pneumocystis is ubiquitous worldwide. The organism is likely acquired early in life based on the near universal seropositivity of humans by 2 to 4 years of age.[16,17] Primary infection either presents as a mild respiratory illness or is completely asymptomatic. In an early model of *Pneumocystis* infection, the organisms were thought to settle into quiescence for years to decades after primary infection, reactivating only in the event of T-cell immune compromise. Though instances of prolonged latency are possible, colonization with *Pneumocystis* appears to be more transient with frequent re-exposures leading to short-lived re-infections throughout life. Person-to-person transmission of *Pneumocystis* has been strongly suggested among normal and immunocompromised hosts. In the absence of a known epidemiologic niche, humans have themselves been proposed as the reservoir. The mode of transmission is thought to be airborne via close proximity with an infected host. Studies in animal models suggests that close contact for 24 h may be sufficient for transmission to other hosts, and studies of air samples from clinics, bronchoscopy suites, and hospital rooms of patients with PCP have identified genotypically identical aerosolized organisms by polymerase chain reaction (PCR).[18,19] Outbreaks of PCP have occurred among children and immunosuppressed patients, particularly liver, kidney, and heart transplant recipients, with *Pneumocystis* strain genotyping showing a common source of infection and suggesting either interhuman transmission or a common environmental source of infection.[20,21] Despite these concerns, there has been insufficient evidence to recommend isolation of all patients with documented PCP. CDC infection control guidelines recommend standard precautions with the added suggestion of avoiding placing an immunocompromised patient in the same hospital room as a patient with PCP.[22] Treatment of active infection and prophylaxis for those at risk remain the most effective prevention methods for PCP. Although neutropenia and hypogammaglobulinemia enhance the risk of PCP by contributing to the overall net state of immunosuppression, T-cell dysfunction is the primary risk factor for development of PCP. Susceptible individuals include PLWH, HIV-negative immunocompromised individuals with innate or acquired T-cell dysfunction, and malnourished infants or neonates.

In the early HIV/AIDS era, PCP became the most common AIDS-defining condition, affecting 75% of all PLWH.[23] Although the incidence has since decreased, PCP remains one of the most common opportunistic infections in this population.[24] Currently about 40% of patients who develop PCP have underlying HIV/AIDS.[1] In the absence of effective prophylaxis or ART, 66% to 85% of patients with AIDS are likely to develop PCP.[25,26] The main risk factor for development of PCP in the setting of HIV-infection is a peripheral CD4 T-cell count of <200 cells/μL, as progressive depletion of CD4+ T cells hinders an effective cellular response to the pathogen. The incidence of infection increases by 100% when peripheral CD4+ lymphocyte counts decrease from 100 to 200 cells/μL to below 100 cells/uL.[25,27] Additional risk factors include a CD4 T-cell percentage of <14%, as well as other indicators of poor cellular immunity including a previous history of PCP and oral candidiasis irrespective of CD4 count, higher HIV RNA levels in plasma, and malnutrition.[28,29] HIV viral load is a strong independent predictor of PCP, and evidence is mounting that patients with suppressed viral load are at very low risk of PCP even in the setting of CD4 counts of 100 to 200 cells/μL.[30] PCP can rarely occur with a CD4 T-cell count of >200 cells/μL. This may be a consequence of superimposed risk factors such as concurrent use of corticosteroids or immune senescence from advanced age but may also be reflective of subtle qualitative immune deficits as a result of impaired T-cell repertoires in patients with a history of profound AIDS and very low CD4 T-cell count nadirs.[31] Additionally, PCP may manifest with CD4 T-cell recovery after institution of ART as a part of the immune reconstitution syndrome.

In the current era, the majority of PCP cases occur in HIV-negative immunocompromised patients with impaired T-cell function. The highest incidences are in patients with HTLV-1 associated lymphoma (50%), severe combined immunodeficiency syndrome (27%–42%), acute lymphocytic leukemia (6%–45%), rhabdomyosarcoma (4%–25%), and non-Hodgkin lymphoma (0%–32%). Solid organ transplantation (0.4%–25%), allogeneic bone marrow transplantation (4.8%), and other conditions including non-cancer patients receiving prolonged courses of steroids in high doses also are at risk (Fig. 134-2).[32] For recipients of solid-organ transplantation, the risk is greatest within the first 6 months after transplantation, during periods of increased immune suppression, as with the use of pulse corticosteroids or lymphocyte depletion for graft rejection and with recent cytomegalovirus (CMV) infection.[33] Approximately 70% of PCP infections in solid-organ transplant recipients are associated with a CD4 T-cell count less than 200 cells/μL and an absolute lymphocyte count less than 500 × 10^6 cells/μL.[34,35] Solid-organ transplant recipients receiving sirolimus-based immunosuppression may rarely develop an idiosyncratic diffuse pneumonitis that mimics PCP.[36] Patients with primary immunodeficiencies including idiopathic CD4 T-cell lymphocytopenia also are at risk. The use of corticosteroids has been identified in up to 90% of HIV-negative patients with PCP.[37] In one study of HIV-negative patients with PCP, the median dose of prednisone was 30 mg/day for 12 weeks, although 25% received a prednisone dose of 16 mg for 8 weeks or fewer.[38] A lower peripheral lymphocyte count is associated with an increased risk for PCP in HIV-negative patients, but the correlation is weaker than for HIV positive patients. The use of corticosteroids and other immunosuppressive agents also confounds this relationship.[39] CD4 counts are most likely to be useful for risk prediction if they are low or low in comparison with baseline or previous values.

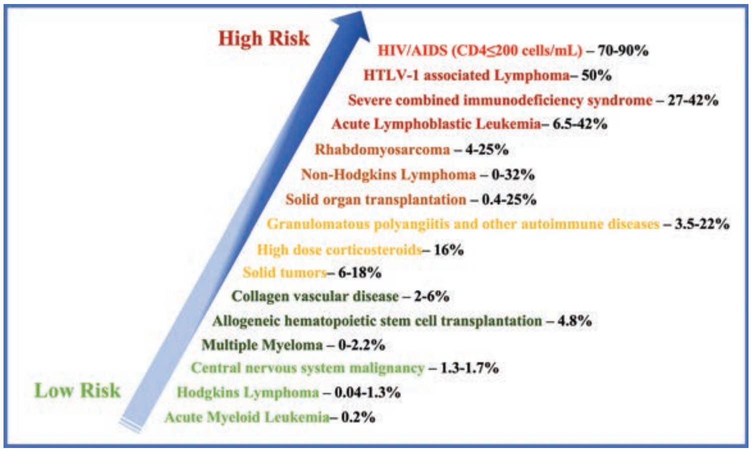
High Risk
HIV/AIDS (CD4≤200 cells/mL) – 70-90%
HTLV-1 associated Lymphoma– 50%
Severe combined immunodeficiency syndrome – 27-42%
Acute Lymphoblastic Leukemia– 6.5-42%
Rhabdomyosarcoma – 4-25%
Non-Hodgkins Lymphoma – 0-32%
Solid organ transplantation – 0.4-25%
Granulomatous polyangiitis and other autoimmune diseases – 3.5-22%
High dose corticosteroids– 16%
Solid tumors– 6-18%
Collagen vascular disease – 2-6%
Allogeneic hematopoietic stem cell transplantation – 4.8%
Multiple Myeloma – 0-2.2%
Central nervous system malignancy – 1.3-1.7%
Low Risk
Hodgkins Lymphoma – 0.04-1.3%
Acute Myeloid Leukemia– 0.2%

Figure 134-2 Incidence of PCP in HIV-positive and HIV-negative immunocompromised populations.

CLINICAL PRESENTATION

Infection with *P. jirovecii* most often presents as a pulmonary syndrome characterized by hypoxemia, dyspnea, and cough, commonly out of proportion to physical exam or radiologic findings. Notably, the clinical course often manifests differently in PLWH and HIV-negative patients, a clinical distinction that has become more apparent with the rise in prevalence of infection in HIV-negative immunocompromised hosts.

■ Persons Living with HIV

PLWH with PCP classically present with fever, cough, dyspnea, and hypoxemia. HIV-infected hosts characteristically experience subacute and insidious progression of symptoms over the course of several weeks.[40–43] Patients generally present to medical attention between 2 and 8 weeks after symptom onset with a median time to diagnosis of 21 days after symptom onset.[1,44] Fever is often low grade, cough is typically nonproductive, and frank tachypnea is present in just over half of patients. Hypoxemia is initially mild and may only be observed with exercise or exertion so an ambulatory oxygen saturation test may be revealing. Fewer than 10% of patients are completely asymptomatic. Physical exam findings can be subtle, and lung auscultation is often normal. Inspiratory crackles are the most commonly encountered abnormal pulmonary exam finding.[40]

■ HIV-negative Hosts

PCP among HIV-negative immunocompromised hosts often presents as a more severe respiratory illness, sometimes with fulminant disease. Clinical manifestations are still characterized by dyspnea, hypoxemia, fever, and minimally productive cough; however, the onset and progression of symptoms tends to be more rapid and severe compared with PLWH. The average time from symptom onset to presentation is less than 1 week. Patients often require higher levels of supplemental oxygen support, are more likely to necessitate mechanical ventilation and ICU admission, and are more likely to develop hemodynamic compromise.[42–46] Accordingly, reported mortality rates in this population have been higher than for the HIV-positive population.[43–45] However, with improvements in diagnostic techniques and increased awareness of PCP among HIV-negative patients, less severe and more indolent presentations are increasingly observed in this population, perhaps due to earlier recognition and diagnosis.

The discordance in clinical presentations among HIV-positive and -negative patients appears to be related to differing inflammatory responses to infection. Patients with HIV/AIDS typically have a higher burden of organisms, but an ineffective and/or less rigorous host immune response may dampen inflammation within the lungs and manifest with less aggressive symptomatology. Indeed, in one study, patients with AIDS and PCP had both lower BAL neutrophil counts and higher arterial oxygen tension than non-HIV immunocompromised patients with PCP, even in the absence of microorganisms other than *P. jiroveci.*[47] In non-HIV/AIDS patients, the inflammatory response tends to be more robust, leading to more severe clinical symptoms despite a smaller organism burden in the lungs.[41,44] In addition, the smaller inoculum makes diagnosis more challenging, which can lead to diagnostic and therapeutic delay. This immunologic interplay further informs our understanding of risks of disease acquisition among HIV-negative patients over time. In the organ transplant recipient, PCP most frequently occurs approximately 2 to 4 months after initiation of immune suppression as well as during periods of increased immune suppression (pulsed corticosteroids, antilymphocyte therapies). Severe presentations may also occur when immunosuppression is abruptly decreased, since immune reconstitution allows for a more robust inflammatory response to even a small organism burden.

In both populations, coinfection with other organisms may accelerate progression of disease and effect the clinical presentation. In particular, CMV, *Histoplasma capsulatum*, *Legionella* spp., and mycobacterial species may contribute to symptomatology and influence the clinical syndrome. Coinfection with CMV and other pathogens is detected in many *Pneumocystis*-infected patients and likely plays a role in the individual immune response of each patient.[38,48] In addition, the rate of development and severity of clinical infection is exacerbated by the presence of pre-existing lung disease (e.g., pulmonary fibrosis).

EXTRAPULMONARY PNEUMOCYSTOSIS

Extrapulmonary infection with *Pneumocystis* is rare. The incidence among PLWH has been estimated at 0.06% to 0.53%.[49,50] Risk factors for extrapulmonary spread of *Pneumocystis* infection have not been established, but use of inhaled pentamidine for prophylaxis was once considered a risk factor because of poor systemic absorption. However, the incidence of extrapulmonary infection among patients on aerosolized pentamidine for primary or secondary PCP prophylaxis appears to be low, with 6 reported cases in a total of 1099 combined patients from several published studies, for an overall incidence of 0.5%.[51] Conversely, cases of extrapulmonary *Pneumocystis* in patients receiving systemic prophylaxis have been reported, including in 2 patients on dapsone-pyrimethamine prophylaxis.[52,53] Although it is not clear from the available evidence that inhaled pentamidine prophylaxis is inadequate to prevent extrapulmonary spread, the low incidence of disease prevents an accurate measurement of risk or incidence so it continues to be a theoretical concern.

Extrapulmonary pneumocystosis has been described in both HIV-positive and HIV-negative individuals. Infection may occur concurrently with lung involvement or with minimal or absent respiratory disease. Sites of extrapulmonary infection include the liver, spleen, lymph nodes, thymus, thyroid, skin, eye, ear, mastoids, muscles, peritoneum, gastrointestinal tract, omentum, pleura, kidney, bone marrow, pancreas, adrenal glands, meninges, and cerebral cortex. Hematogenous dissemination was evident in several cases in which *Pneumocystis* was detected in the lumens of large blood vessels during autopsy.[51] *Pneumocystis* has also been associated with the development of venous thromboembolism and, rarely, with vasculitis leading to ischemic necrosis of the digits.[54] The most common disease presentation is that of a mass lesion or abscess along with fever and constitutional symptoms with the addition of organ-specific symptoms (such as visual loss with choroidal involvement), signs (ascites with peritoneal lesions), or laboratory abnormalities (transaminase elevations with liver impairment). In contrast with pulmonary infection, which tends to be more acute and symptomatic in HIV-negative patients, extrapulmonary infection appears to be more clinically evident in HIV-infected persons with symptoms associated with the involved organs. Additionally, disease restricted to the ear and eye has mainly been observed among HIV-infected individuals.[51]

Demonstration of *P. jirovecii* organisms in affected tissues confirms the diagnosis of extrapulmonary pneumocystosis. The presence of typical foamy eosinophilic material within extrapulmonary tissues is a clue to the diagnosis and should prompt additional investigation for pneumocystosis with special staining. Histopathology will often demonstrate granulomatous inflammation or the presence of cavities.[55] Calcifications may be seen in infected tissues, especially within the parenchyma of the liver and spleen but also in other sites such as the pleura or thyroid gland.[56] Computed tomographic (CT) scan findings include focal, nonenhancing lesions with low attenuation in various organs but most commonly the liver and spleen, often with rim-like or punctate calcification and/or necrosis and/or hemorrhage (Fig. 134-3). Based on published studies and expert opinion, medical treatment of extrapulmonary *Pneumocystis* infection is usually successful without the need for surgical drainage. There is no preferred systemic agent for extrapulmonary pneumocystosis, and treatment typically consists of the same regimens used for pulmonary disease.

RADIOLOGIC PATTERNS OF PNEUMOCYSTIS PNEUMONIA

Lung imaging plays an important role in the evaluation of patients with PCP. Chest x-rays and CT scans are the most frequently utilized imaging modalities. Typical radiologic features include diffuse, bilateral, interstitial infiltrates and ground-glass opacities. Less

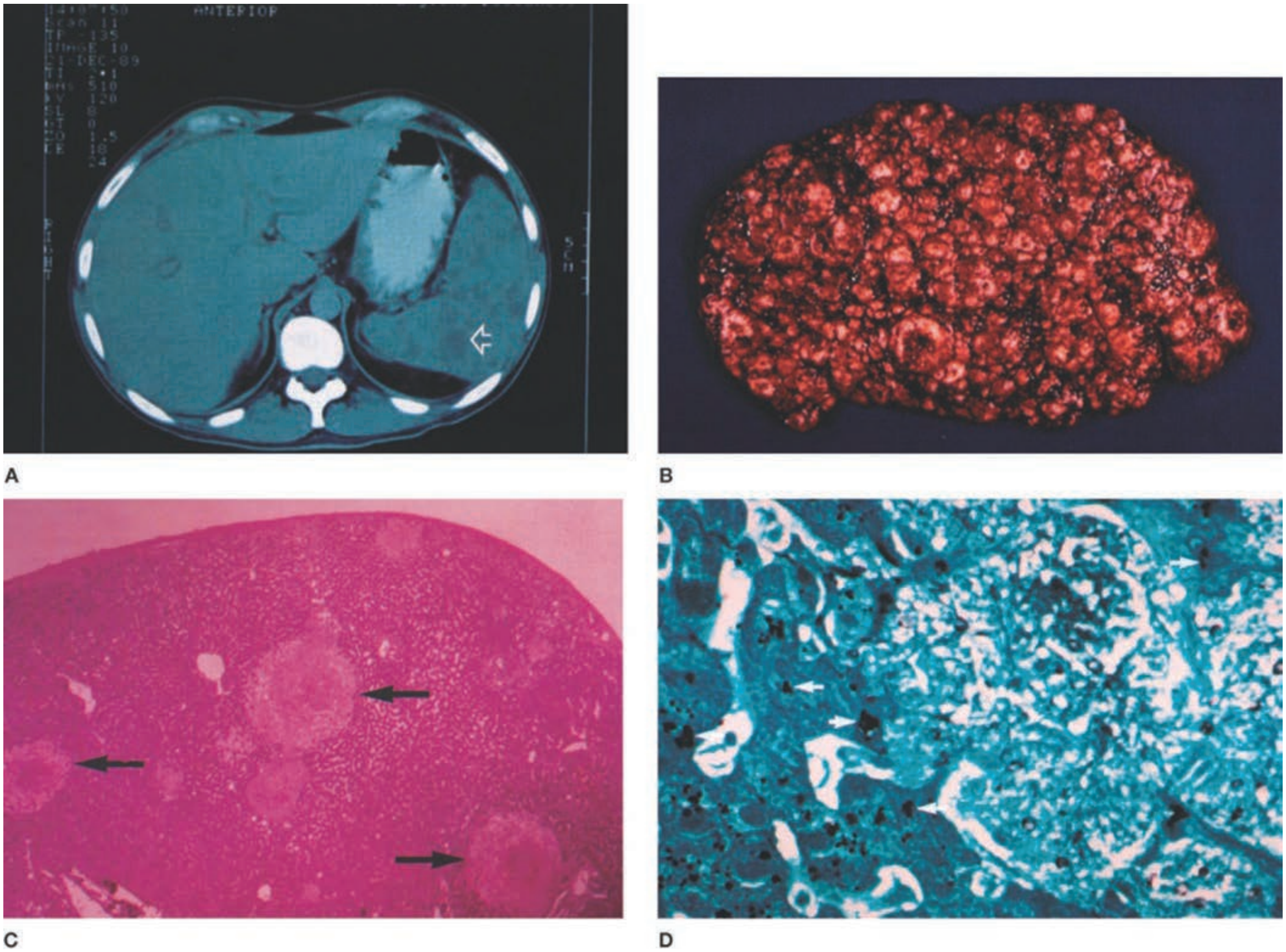

Figure 134-3 Extrapulmonary pneumocystosis in a patient with AIDS on aerosolized pentamidine prophylaxis presented as a splenic mass lesion with abdominal pain. The computerized body tomographic (CBT) scan reveals a mass lesion **(A)**, seen after splenectomy on gross pathology (**B**), and on microscopic examination (hematoxylin and eosin stain, **C**. Silver stain, **D**). *(Reproduced with permission from Dr. J. Davis Allen, Jr., New England Deaconess Hospital.)*

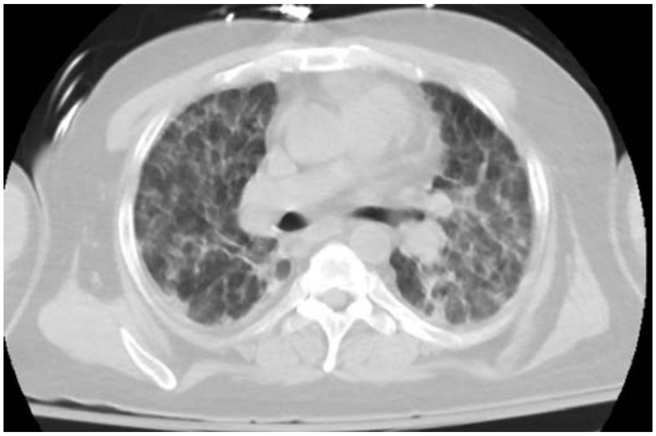

Figure 134-4 Bilateral diffuse ground-glass opacities and septal thickening in a patient with PCP.

common radiologic findings include pulmonary cysts, pneumothoraces, lobar consolidations, and pulmonary nodules.

Interstitial Pattern

The classic imaging finding in PCP is a bilateral interstitial pattern, characterized by extensive ground-glass opacities (Fig. 134-4). This appearance likely represents the accumulation of fibrin, debris, and organisms within alveoli as well as interstitial inflammation.[57] On conventional chest x-rays, this appears as fine, bilateral, perihilar, diffuse infiltrates that can progress to an interstitial alveolar butterfly pattern, characterized by a central predominance of opacities with a clear zone at the periphery of the lobes. Early in the course of disease and in patients with AIDS, chest x-rays are less sensitive and may demonstrate normal or only subtle findings.[57,58] Chest CT is a more sensitive imaging modality and is helpful when clinical suspicion remains high despite a normal chest x-ray. The classic chest CT finding is that of extensive ground-glass attenuation, which may be diffuse, mosaic, or predominantly central in distribution.[57–60] This interstitial pattern is also classically observed in patients who undergo nuclear imaging when chest CT cannot be obtained; however, this modality is rarely used in the current era.

Pulmonary Cysts

Pulmonary cysts can be seen in as many as many as one-third of patients with PCP and are more likely to develop in AIDS patients.[57] Lung cysts can vary in appearance, although they tend to have thin walls and may range from several millimeters to several centimeters in size (Fig. 134-5). When present, cysts are often numerous and occur in multiple lung segments. The pathogenesis of these cystic lesions is incompletely understood but is theorized to relate to bronchiolar obstruction, elastase release from macrophages, and direct tissue destruction from the organism itself.[61] Cysts typically resolve after successful treatment. Notably, cyst rupture may lead to spontaneous pneumothorax.

Pneumothorax

Pneumothorax is reported to occur in anywhere from 5% to 20% of patients with PCP and is more common in PLWH.[60,62] This finding is most frequently detected via either chest x-ray or CT of the chest (Fig. 134-6). Pneumothoraces most commonly occur spontaneously as sequelae of ruptured cysts; however, they may also develop even in the absence of identifiable cystic disease, as well as iatrogenically from barotrauma secondary to mechanical ventilation or from complications of other procedures such as thoracenteses. In addition, patients who receive aerosolized pentamidine as prophylaxis appear to be at greater risk for spontaneous pneumothorax. Breakthrough disease has been well described after use of inhaled pentamidine, and classically presents largely or solely in the upper lobes. Bullous or cystic changes may then develop in the lung apices, increasing the risk of spontaneous pneumothoraces.[60,63]

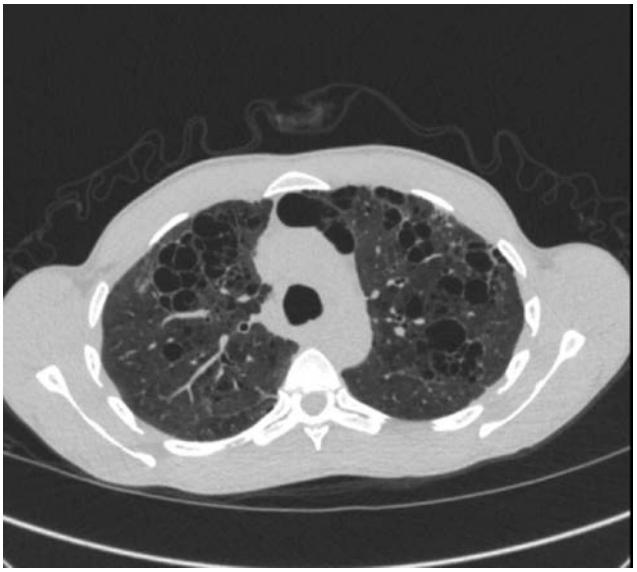

Figure 134-5 Numerous thinly walled cysts and diffuse interstitial ground-glass opacities in a patient with PCP.

Consolidation

Lung consolidation is infrequently encountered but may develop in more advanced disease, particularly in HIV-negative patients who are able to mount a more profound immune response. When present, consolidative changes with air bronchograms may be seen on

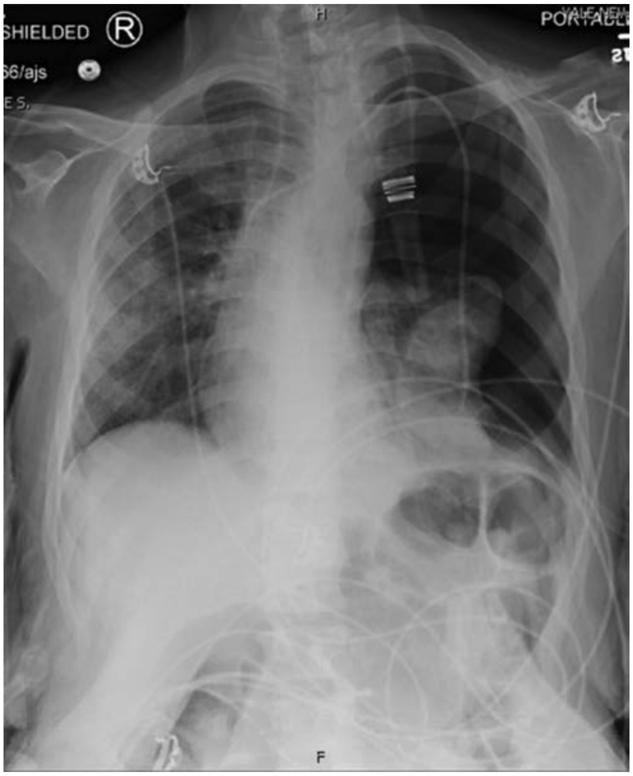

Figure 134-6 Large left pneumothorax with complete collapse of the lung and mediastinal shift toward the right with compression of the right lung in patient with PCP.

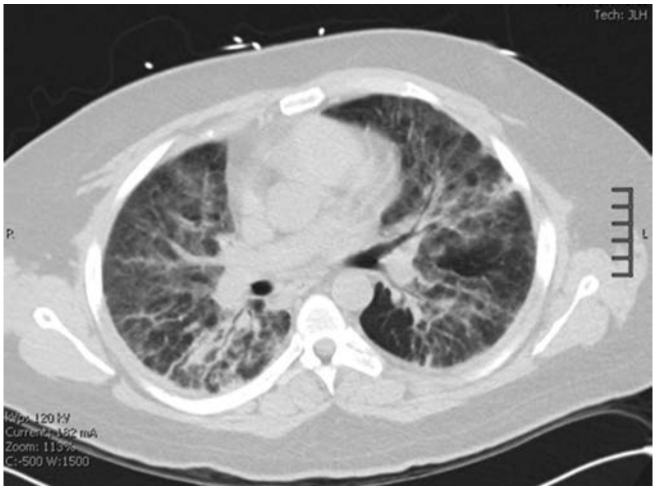

Figure 134-7 Diffuse lung disease affecting all five lobes with upper lobe–predominant ground-glass opacities and lower lobe–predominant peribronchovascular areas of consolidation in a patient with PCP.

both chest x-ray and chest CT, particularly in the setting of disease progression. Consolidations can be peribronchovascular, patchy, unilateral, or bilateral, and occur concurrently with interstitial infiltrates[57] (Fig. 134-7).

Pulmonary Nodules

PCP may rarely manifest as a predominantly nodular pattern on chest CT. This is thought to develop as a result of a granulomatous response to infection, known as granulomatous PCP.[64] Chest imaging in patients with granulomatous disease typically reveals solitary nodules, masses (3 cm or larger), or multiple randomly distributed nodules of varying sizes (Fig. 134-8). These findings may mimic lung carcinoma, metastatic disease, lymphoproliferative disorders, or other infectious etiologies frequently encountered in immunosuppressed patients such as fungal or mycobacterial disease. Granulomatous inflammation occurs in about 5% of cases and is more common in patients with hematologic malignancies than in those with AIDS.[57,64] Notably, diagnosis of granulomatous PCP is challenging since bronchoalveolar lavage may be negative due to encasement of the organism by granulomas.[64] Biopsy remains the cornerstone of diagnosis for this form of disease.

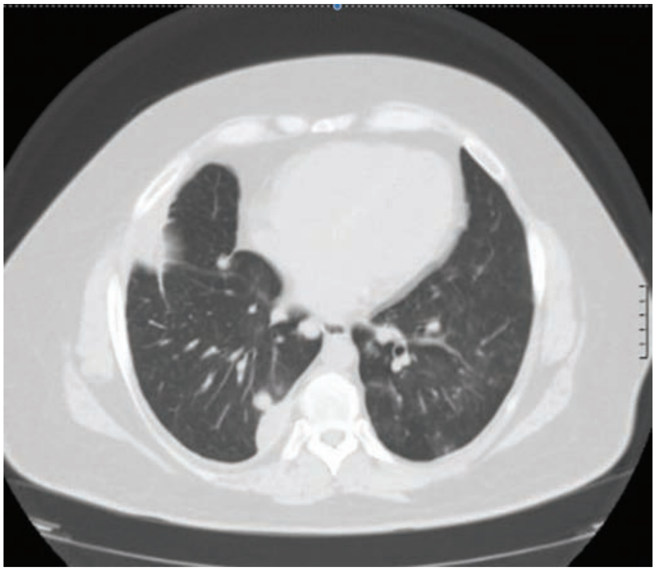

Figure 134-8 Scattered pulmonary nodules in a patient with biopsy-proven granulomatous PCP.

Other Imaging Findings

Pleural effusions may be encountered but are often secondary to a concurrent, alternative process. Patients with recurrent disease may develop residual interstitial fibrosis, with chronic interstitial markings or honeycombing on chest CT. Cavitation and calcification may infrequently occur with nodular disease.[60] However, these findings may be due to numerous alternative infectious and noninfectious etiologies in the immunocompromised host with multiple processes often occurring simultaneously.

LABORATORY FINDINGS

A number of nonspecific laboratory markers are frequently used to aid in the diagnosis of PCP. The most frequently utilized tests include CD4 and absolute lymphocyte counts, blood gas analysis, (1-3)-β-D-Glucan, lactate dehydrogenase (LDH), and other markers.

CD4 and Absolute Lymphocyte Counts

In PLWH, the incidence of PCP increases as the CD4 count decreases. Most cases occur with a CD4 count less than 200 cell/μL or a CD4 cell count percentage less than 14%. In fact, there is a 70% to 90% incidence of PCP in PLWH with a CD4 count of less than or equal to 200 cells/μL. In HIV-negative patients, low CD4 counts are also associated with an increased risk of developing PCP. In addition, low absolute lymphocyte counts have been associated with opportunistic infection in HIV-negative solid organ transplant (SOT) recipients. In one study, around 70% of SOT recipients with PCP had a CD4 count of less than or equal to 200 cells/μL and an absolute lymphocyte count of less than or equal to 500 cells/μL.[34,65] Similarly, both lymphopenia and decreased CD4 counts are risk factors for PCP in hematopoietic stem cell transplant (HSCT) recipients and patients with hematologic malignancies, autoimmune disorders, and solid tumors on chemotherapy.[35,66,67] Although CD4 and absolute lymphocyte counts may be useful to stratify the risk of PCP in HIV-negative patients, the relationship is not as clear as for PLWH, and lymphocyte counts are impacted by several other factors such as increased immunosuppression, CMV, or other viral coninfections.[68]

Blood Gas Analysis

In general, patients will have a PO_2 less than 75 mm Hg with a widened alveolar–arterial (A–a) oxygen gradient and a respiratory alkalosis.[69] More profound hypoxemia is often unmasked with exercise. In mild disease, the PO_2 is greater than 70 mm Hg with an A–a gradient less than 35 mm Hg while in severe disease, the PO_2 is less than 60 mm Hg with an A–a gradient greater than 45 mm Hg.[70]

(1,3)-β-D-Glucan

(1-3)-β-D-glucan is a cell wall component of *P. jirovecii* as well as many other pathogenic fungi and has gained acceptance as a useful but nonspecific marker of invasive fungal disease. Serum (1-3)-β-D-glucan values are almost always elevated in PCP but may also be elevated in a variety of other invasive fungal diseases such as candidiasis, aspergillosis, and fusariosis.[71] Other opportunistic fungi, like *Mucor* species and *Cryptococcus neoformans,* have little to no (1-3)-β-D-glucan in their cell walls and the assay has not been useful for these infections. Additionally, false-positive (1-3)-β-D-glucan results may occur after infusion of intravenous immune globulin, defibrotide, plasmalyte, and albumin, and with exposure to gauze.[72] Hemodialysis use with exposure to unmodified cellulose containing dialyzer membranes may also cause false positive (1-3)-β-D-glucan results.[73]

A number of studies have evaluated the utility of (1-3)-β-D-glucan for diagnosis of PCP. In general, the assay is very sensitive (>80%–100%) and has a high negative predictive value (>95%), indicating that patients with a negative (1-3)-β-D-glucan assay are very unlikely to have PCP.[74–81] These performance characteristics appear to be best in PLWH, likely because of increased organism burden in HIV/AIDS.[81] Because (1-3)-β-D-glucan can be elevated in other fungal infections, the specificity in an unselected population is relatively low. However, specificity is significantly increased in patients with a compatible clinical syndrome with higher (1-3)-β-D-glucan assay values. In a retrospective analysis of greater than 400 immunocompromised patients with a compatible clinical syndrome, a (1-3)-β-D-glucan value greater than 80 pg/mL yielded a specificity of 81% and positive predictive value (PPV) of 35%. In the same cohort, (1-3)-β-D-glucan values greater than 200 pg/mL yielded a specificity and PPV of 100%.[82] Thus, measurement of (1-3)-β-D-glucan is a very useful test, particularly for those in whom clinical suspicion for PCP is highest or those for whom a confirmatory bronchoscopy may be contraindicated since a positive (1-3)-β-D-glucan may serve as the basis for a probable diagnosis of PCP (see "Diagnosis: Consensus Definitions," below).

In small retrospective evaluations, persistently positive serum elevations of (1,3) β-D-glucan have been reported despite appropriate therapy and clinical improvement. The utility of this assay in determining prognosis or in therapeutic monitoring is unclear; however, it is generally accepted that serial measurements are unlikely to be clinically useful.[83,84]

■ LDH

Serum LDH is elevated (≥300 IU/mL) in almost all cases of PCP. Because LDH is a marker of underlying lung injury in PCP and other conditions, the degree of elevation correlates with underlying hypoxemia and may have prognostic value.[85] However, LDH may also be elevated in a variety of other pulmonary and extrapulmonary disorders, including malignancy, hemolysis, ischemia, and other infections such as toxoplasmosis and histoplasmosis among others.[86] Thus, LDH is a sensitive but nonspecific marker that should not be used in isolation for PCP diagnosis, particularly in the leukemic population where confounding etiologies of LDH elevation are more likely.

■ Additional Testing

There have been several case series suggesting that hypercalcemia is common in PCP, particularly among renal transplant recipients.[87,88] In one series, hypercalcemia (12.6 ± 1.6 mg/dl) was observed in 37% (18/49) of renal transplant recipients and regressed concomitantly with PCP treatment in all cases.[87] Hypercalcemia may precede the diagnosis of PCP in this cohort. While the etiology of hypercalcemia in this population is not entirely clear, it is thought to be associated with a 1 α-hydroxylase enzyme dependent mechanism, particularly in those with granulomatous disease. In the above study, serum levels of 1,25-dihydroxyvitamin D were elevated at the time of PCP diagnosis and decreased after PCP treatment while PTH serum levels increased, suggesting a granuloma-mediated mechanism for hypercalcemia.[87]

Another nonspecific indicator of lung injury in PCP is the angiotensin-converting enzyme (ACE) level, which can also be elevated by smoking and sarcoidosis, among other causes.[89] Krebs von den Lungen antigen (KL-6), a mucin-like glycoprotein expressed on pneumocytes and bronchiolar epithelial cells, can also be detected in the serum of patients with PCP, but once again is likely a nonspecific marker of pneumonitis in general.[85,90] These laboratory markers lack the specificity needed to be useful diagnostic tools in isolation but may be helpful adjuncts in the appropriate clinical setting.

DIAGNOSIS: HISTOPATHOLOGY, SPECIAL STAINS AND POLYMERASE CHAIN REACTION

The gold standard for the diagnosis of PCP remains the identification of characteristic organisms on examination of pulmonary specimens. Special stains must be used to highlight the morphology of *Pneumocystis* itself including cell wall stains, nuclear and cytoplasmic stains, and immunofluorescence stains. The presence of *Pneumocystis* in clinical specimens can also be detected using *Pneumocystis*-specific polymerase chain reaction (PCR) assays.

■ Lung Histopathology

The lung histopathology in the setting of PCP is characterized by typical features that have diagnostic value even when organisms are not initially seen. The hematoxylin and eosin stain, one of the most common stains used in the anatomic pathology laboratory, does not stain *Pneumocystis* organisms but instead reveals characteristic acellular foamy exudates. The infection is predominantly located in terminal alveoli with airspaces appearing honeycombed or vacuolated and filled with a foamy eosinophilic exudate that consists of organisms, surface glycoprotein, proteinaceous exudate from the lungs, and debris of macrophages and inflammatory cells while neutrophils and lymphocytes populate the alveolar interstitium. The disease can be patchy in distribution, making the characteristic histopathologic changes difficult to find. In malnourished children and HIV-negative adults, the interstitial component is more prominent. Using special stains on lung tissue, a large number of *Pneumocystis* organisms usually appear enmeshed with inflammatory cells within the alveolar exudate. Hyaline membrane formation may occur within alveoli as a result of denudement of the alveolar epithelium and deposition of cellular debris on the basement membrane.[91] This pattern of diffuse alveolar damage can be seen with oxygen toxicity, alveolar proteinosis, or acute respiratory distress syndrome (ARDS) and is not specific for either condition. A granulomatous response to *Pneumocystis* lung infection that includes nonnecrotizing or poorly necrotizing granulomas has been rarely described (Fig. 134-9A). These most often lack classic features of intra-alveolar foamy exudates and are more commonly seen among men with HIV/AIDS and hematopoietic or solid malignancies.[92]

■ Cell Wall Stains

Cell wall stains bind to components of the *Pneumocystis* cyst cell wall, but not those of other morphologic forms including the trophozoite. Since there are 10-fold more trophic forms than cystic forms in lung tissues during active infection, cell wall stains are insensitive for the diagnosis of PCP when the organism burden is low. This is especially true for HIV-negative immunocompromised individuals who harbor approximately 14 times fewer cysts per mL of BAL fluid than patients with HIV/AIDS.[47] Host cells including alveolar epithelial cells and macrophages are not stained, making detection of *Pneumocystis* organisms and stain interpretation easier. The methenamine silver stain (Grocott or Gomori variation) is one of the most commonly used in this category.[93,94] It stains *Pneumocystis* cysts black in a cup-shaped morphology against a green background (Fig. 134-9B). Focal thickenings in the *Pneumocystis* cyst cell walls stain more deeply and appear either as central black dots when the staining is confluent, or as thick "commas" or "parentheses" when the two distinct parallel areas are stained (Fig. 134-9C). Other cell wall stains include the toluidine blue, cresyl echt violet, and calcofluor stains. Toluidine blue and cresyl echt violet render a similar cyst appearance to the methenamine silver stain, but the organism color is purple against a light pink background. Calcofluor white stains the chitin in fungal cell walls and requires a fluorescence microscope for visualization of either apple-green fluorescent or blue–white cysts depending on the suppression filter used. Cell wall

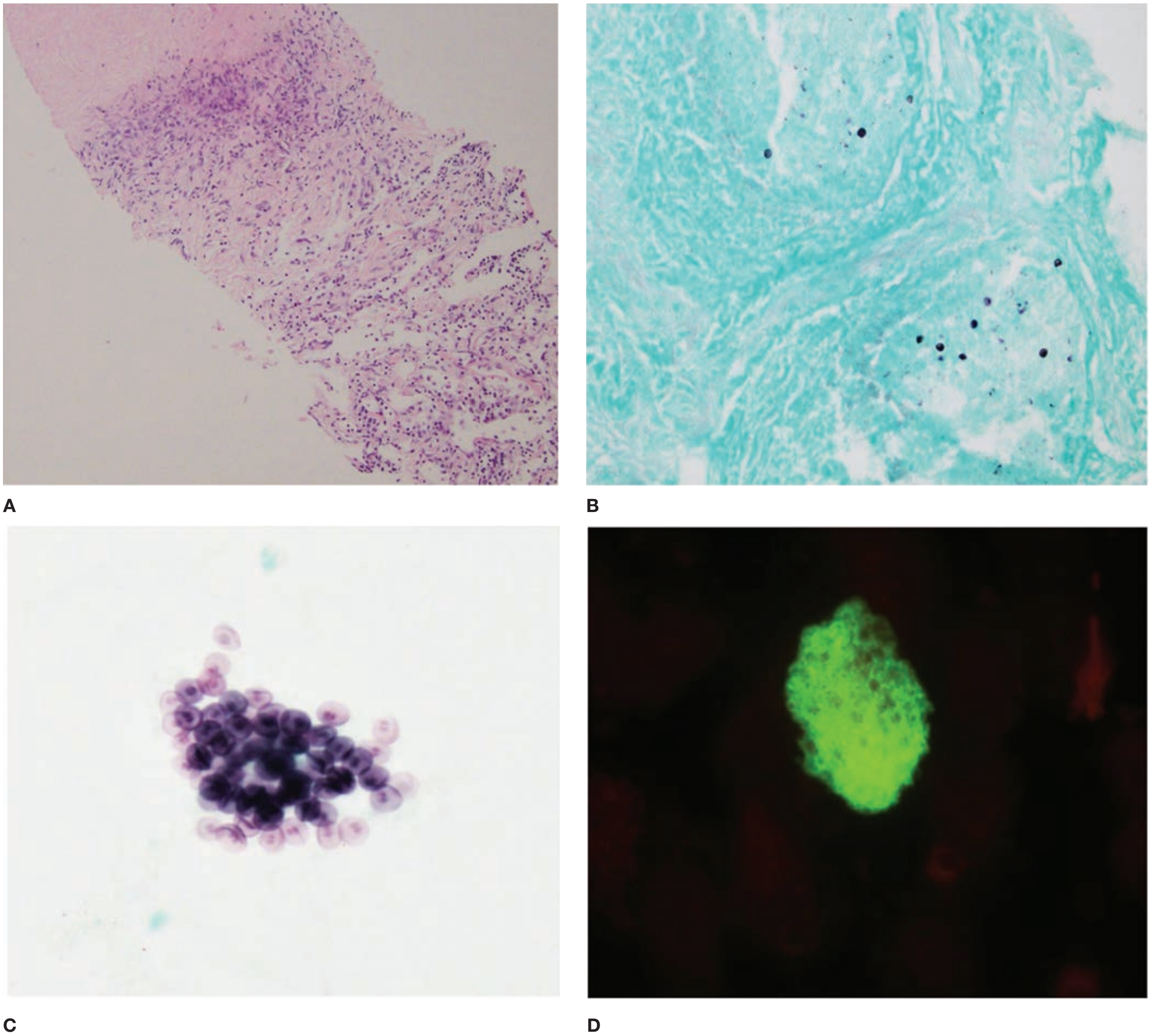

Figure 134-9 **A.** A large area of necrosis with surrounding histiocytes consistent with necrotizing granulomatous inflammation in a patient with PCP (H&E 100×). **B.** Grocott methenamine silver stain at 600× revealing *Pneumocystis* cysts stained black against a green background. **C.** Grocott methenamine silver stain of cytologic specimen showing multiple *Pneumocystis* cysts. **D.** Pneumocystis direct immunofluorescence stain.

stains are also useful to identify other pathogenic fungi including dimorphic fungi, molds, and yeasts. The sensitivity of cell wall stains for PCP is dependent on multiple factors that are discussed below and in Table 134-1.

■ Nuclear and Cytoplasmic Stains

Nuclear and cytoplasmic stains including the Giemsa, Wright-Giemsa, and Giemsa-like stains (such as the Diff-Quik) highlight the nuclei and cytoplasm of all *Pneumocystis* developmental stages. Trophozoite nuclei appear deep purple against a light blue cytoplasm, whereas the ghostly outlines of a cyst surrounds several (usually eight) internal deep purple–staining intracystic body nuclei. Modified Giemsa techniques have the advantage of faster turnaround time and lower cost and are usually preferred in clinical settings. Adequate interpretation of Giemsa-stained lung specimens requires experienced readers in order to distinguish between clumps of *Pneumocystis* organisms from the nuclei of host cells including alveolar and immune cells, which are larger in size. In the hands of an experienced laboratorian, Giemsa staining detects both cyst and trophozoite stages and so has increased sensitivity compared to cell wall stains. Additionally, since host cells are stained, demonstration of host alveolar macrophages can allow assessment of specimen adequacy. Nuclear and cytoplasmic stains will also identify other pulmonary fungal pathogens.

■ Immunofluorescence Stains

Fluorescein-conjugated monoclonal antibodies directed against *Pneumocystis* surface glycoproteins can be used to identify all *Pneumocystis* developmental stages in clinical specimens and have become a staple in the diagnosis of PCP. Both direct fluorescent antibody (DFA) and indirect fluorescent antibody (IFA) techniques are available.[95,96] DFA employs a chromophore-labelled antibody that binds directly to *Pneumocystis* antigens, while IFA consists of a two-step procedure in which a primary antibody that binds *Pneumocystis*-specific antigens is added, followed by layering with a secondary chromophore-labelled antibody that binds to the first antibody. Specimens are then examined under ultraviolet light for nuclear and/or cytoplasmic immunofluorescence. When the employed chromophore is fluorescein isothiocyanate, organisms and their surrounding matrix appear apple-green in color (Fig. 134-9D). Indirect immunofluorescence assays are more sensitive but less specific than DFA and require an additional staining step. Since commercially used IFA and DFA detect *Pneumocystis* cysts as well as the more abundant trophozoites, the sensitivity of immunologic techniques is superior to conventional staining and, when used on BAL fluid, approaches that of PCR testing. Immunofluorescent staining has the added advantage of allowing for visualization and quantification of the number of *Pneumocystis* organisms in a clinical specimen, enhancing the clinical specificity of the assay.

■ *Pneumocystis*-specific PCR Assays

Pneumocystis-specific nucleic acid amplification assays including PCR are highly sensitive for the detection of *Pneumocystis* in clinical specimens, superior even to immunofluorescence testing. A variety of commercial and laboratory-developed *Pneumocystis*-PCR assays are available, with the most sensitive employing either a multicopy gene target such as mitochondrial rRNA or major surface glycoprotein, or a nested PCR method that utilizes two amplification rounds.[32,97] Due to very low limits of detection, PCR assays maintain excellent performance in the setting of low organism burdens, such as with PCP in HIV-negative immunocompromised individuals. Conversely, because of high sensitivity, PCR assays suffer from decreased PPV for PCP because detection of low organism burdens in the absence of appropriate clinical, radiographic, and host factors more likely represents transient colonization rather than infection.[98] In studies performed among HIV-positive and HIV-negative individuals, the sensitivity of PCR was comparable to immunofluorescence testing but the PPV of PCR was lower once clinical and radiographic criteria were applied.[99,100] Combining serum (1-3)-β-D-glucan with PCR on respiratory samples can help discriminate *Pneumocystis* infection from colonization. In a study of high-risk oncology patients evaluated for PCP, a (1-3)-β-D-glucan level greater than or equal to 200 pg/mL with a positive PCR and a compatible clinical syndrome had a specificity of 100% and a PPV of 100% for proven or probable PCP versus a specificity of 97% and PPV of 75% for PCR alone.[82] Quantitative or semiquantitative PCR assays that provide a measure of organism burden may allow differentiation between colonization (a very low organism state) and infection (low to high organism state). The PCR assay cycle threshold (Ct, which is inversely proportional to fungal organism load) has been shown to be lowest for HIV-positive patients with confirmed PCP followed by HIV-negative patients with confirmed PCP and highest for patients with an alternative diagnosis, suggesting that Ct values may enhance clinical specificity and aid in differentiating infection from colonization.[95,101] Unfortunately, due to a lack of standardization, the performance of various commercially available PCR assays is variable and Ct thresholds cannot be extrapolated across different PCR assays, limiting the applicability of Ct cutoffs.[102] However, the Fungal PCR Initiative, a working group of the International Society for Human and Animal Mycology, is leading the effort to standardize *Pneumocystis* PCR assays. Recent multicenter studies have suggested that reverse transcriptase–qPCR assays targeting the mitochondrial small subunit gene provided the most precise and accurate Ct values and could serve as a basis for standardizing the *P. jirovecii* load.[103]

DIAGNOSIS: SPECIMEN TYPES

Several specimen types including induced sputum, bronchoalveolar lavage (BAL), oral washes, and lung biopsy can be examined in the diagnostic approach to PCP (Table 134-1). The sensitivity of different specimen types varies across the published literature and is reflective of heterogeneity in several important factors including (1) specimen adequacy, with suboptimal specimens commonly yielding false negative results, (2) the diagnostic method employed including cell wall or nuclear stains, immunofluorescence antibody testing, and PCR, (3) the reference method used as a comparator, (4) the population studied especially with regards to HIV-status, (5) the underlying burden of organisms, which is highest in profoundly lymphopenic HIV-positive persons and lowest in patients with mild disease and HIV-negative individuals, and (6) the use of prophylaxis or antecedent treatment.

■ Induced Sputum

Testing of induced sputum is a widely employed diagnostic tool for the diagnosis of PCP. Induced sputum samples are obtained by inhalation of aerosolized hypertonic saline using a nebulizer, after which specimens are most commonly stained with cell wall or nuclear stains to identify *Pneumocystis* organisms although immunofluorescence testing and PCR can be applied. The sensitivity of induced sputum for PCP ranges from 28% to 94% for people living with HIV and 0% to 88% for HIV-negative immunocompromised persons

TABLE 134-1 Sensitivity and Specificity of Various Specimen Types and Diagnostic Methods for PCP Diagnosis

	HIV-positive		HIV-negative[a]	
Specimen Type (Diagnostic Method)	**Sensitivity**	**Specificity[b]**	**Sensitivity**	**Specificity[b]**
Induced sputum (cell wall stain)	28%–94%[104,184–187]	100%[104,184–187]	35%–50%[188,189]	100%[188,189]
Induced sputum (immunofluorescence stain)	55%–89%[188,189]	98%–100%[99,188,189]	75%[190]	100%[190]
Induced sputum (PCR)	84%–98%[191]	71%–98%[99,191]	88%–100%[189,192]	81%–100%[189,192]
Oral wash (PCR)	44%–100%[110,193]	94%–100%[110,111,113–115,193]	100%[110,193]	100%[110,111,113–115,193]
Bronchoalveolar lavage (cell wall stain)	63%–100%[99,108]	100%[99,108]	46%–100%[108,189]	100%[108,189]
Bronchoalveolar lavage (immunofluorescence stain)	71%–100%[99]	100%[99]	16%–93%[100]	100%[100]
Bronchoalveolar lavage (PCR)	91%–100%[194,195]	83%–95%[194,195]	72%–100%[189,196,197]	90%–100%[189,196,197]
Transbronchial biopsy (cell wall stain)	43%–95%[116,118]	100%[116,118]	67%	100%[c]

[a] *Generally limited studies with small numbers of patients.*

[b] *Specificity definitions vary, with some studies reporting an analytical specificity and others clinical specificity, which distinguishes between colonization and infection.*

[c] *Unpublished data.*

when using cell wall staining but higher when immunofluorescence staining (55%–89%) or PCR (84%–98%) are used.[104] Although PCR specificity is often reported to be close to 100%, many studies report analytical sensitiivty (presence of *Pneumocystis* organisms) rather than clinical sensitivity (presence of *Pneumocystis* infection rather than just colonization). Induced sputum can be used as an initial screening method for PCP and, if negative, should be followed by invasive sampling with bronchoscopy and bronchoalveolar lavage, as repeat testing does not significantly increase diagnostic yield.[105] Expectorated sputum is generally considered inadequate for testing, especially since many patients with PCP do not have a productive cough. A retrospective comparison of expectorated and induced sputum yielded similar sensitivity of around 50% for both methods, although a direct fluorescent antibody screening was used rather than traditional staining.[106]

■ Bronchoalveolar Lavage

Testing of bronchoalveolar lavage (BAL) fluid for the presence of *Pneumocystis* organisms is considered the gold standard for PCP diagnosis and should be performed if noninvasive testing is negative in a patient with moderate to high pretest probability. Reported sensitivities for silver staining on BAL fluid have varied in published studies, ranging from 63% to 100% for HIV-positive patients and 46% to 100% for HIV-negative patients. Lavaging multiple lobes can increase the sensitivity and lavage should be performed from the upper lobes to improve the yield if diffuse disease is present.[107] However, BAL cell wall staining is generally considered inadequate for HIV-negative patients given the lower burden of infecting organisms and the potential for false negative results. In a recent study of 45 adult immunocompromised patients with proven or probable PCP by modified European Organization for Research and Treatment of Cancer (EORTC) criteria, the sensitivity of BAL silver staining was 100% in HIV positive versus 46% in HIV-negative patients.[108] Delayed or missed PCP diagnoses were seen in 3 cases in which BAL silver stain was negative. In HIV-negative patients, testing of BAL by PCR or immunofluorescence testing should be done if silver stain is negative. The sensitivity of BAL testing is higher when combined with immunofluorescence or PCR testing for both HIV-positive (71%–100% and 91%–100%, respectively) and HIV-negative patients (16%–93% and 72%–100%). The specificity of BAL immunofluorescence antibody testing may be higher, as PCR testing may confound infection with colonization.[99,100] Using a cycle threshold cutoff may improve the PPV of PCR assays.

■ Oral Wash

Testing of oral wash specimens using *Pneumocystis* PCR may be a more convenient and sensitive technique than induced sputum and a less invasive method than bronchoscopy.[109] Oral wash samples are obtained after patients gargle 50 mL of sterile saline for 10 to 30 s. The sensitivity of oral wash *Pneumocystis* PCR has varied in published studies, ranging from 54% to 100% for people living with HIV.[110–113] Among HIV-negative immunocompromised persons, the sensitivity was reported at 44% to 100%, but generalizability is limited by small numbers and use of different PCR assays.[114,115] As with other diagnostic methods, the clinical sensitivity of oral wash specimens is dependent on the underlying burden of organisms. In a study of 104 HIV-positive patients who underwent PCR and/or silver staining, only 50% of positive induced sputum specimens were positive by oral washes. Additionally, oral washes detected only 39% of patients with a low fungal burden compared to 63% of specimens with moderate to high load.[113] The results of this study are likely impacted by the use of cell wall staining, which is known to be an insensitive method when applied to oral specimens. When combined with a sensitive *Pneumocystis* PCR method, the sensitivity of oral washes is likely adequate for initial testing of HIV-positive patients with suspected PCP.

■ Lung Biopsy

The diagnosis of PCP can be made by examining lung biopsy specimens obtained through open thorax lung biopsies, a procedure rarely performed in the current era or during fiberoptic bronchoscopy. The most common diagnostic methods applied to lung biopsy tissue are cell wall or nuclear stains as part of general workup for fungal, parasitic, and bacterial organisms. The sensitivity of cell wall staining of transbronchial biopsy specimens ranges from 43% to 95% for HIV-positive patients and is likely lower for HIV-negative immunocompromised patients.[116] The added diagnostic value of transbronchial biopsy for the diagnosis of PCP when BAL testing is performed is unclear. In a study that included 95 patients with PCP for whom both transbronchial biopsy and BAL was performed, Giemsa staining of biopsy specimens identified only 2 cases of PCP that were missed by Giemsa-stained BAL alone.[117] However, in another study, the yield for PCP diagnosis was increased from 74% to 96% when examination of transbronchial biopsy specimens was combined with direct fluorescent antibody staining of BAL. In 26%, the diagnosis of PCP was obtained only by transbronchial biopsy.[118] The discrepant findings of these studies may be related to different methods applied to BAL and biopsy specimens as well as underlying population characteristics. In general, a lung biopsy specimen is no longer considered necessary for the diagnosis of PCP. In patients suspected of harboring multiple pathogens, obtaining a lung biopsy may be indicated. Bleeding complications after biopsy are common (25%) but rarely life-threatening if the coagulation parameters are normal.

DIAGNOSIS: CONSENSUS DEFINITIONS

Results of diagnostic tests for PCP must be taken within the context of all available host, clinical, radiographic, and microbiologic evidence in order to render an appropriate interpretation. In light of *Pneumocystis*' propensity to lead to transient pulmonary colonization without infection, highly sensitive tests, such as PCR, that may confound these two conditions should not be used as stand-alone evidence to diagnose PCP since doing so can lead to unnecessary antibiotic treatment and associated side effects with no clinical benefit. The EORTC and the Mycoses Study Group Education and Research Consortium (MSGERC) has established consensus definitions for the diagnosis of invasive fungal diseases. A recent update now includes criteria for pneumocystosis.[119] Although intended to guide clinical and epidemiologic studies, these definitions can be useful in a clinical context, especially when the diagnosis is in question. A proven diagnosis of PCP requires detection of the organism in BAL, sputum, or lung tissue using conventional or immunofluorescence staining while a probable diagnosis requires a constellation of factors including at least one host criterion (HIV/AIDS or other condition leading to a CD4 count of <200 cells/μL, T-cell depleting therapy, high-dose corticosteroids of ≥0.3 mg/kg for ≥2 weeks, or solid organ transplantation), clinical feature (includes respiratory symptoms and radiographic findings), and mycologic evidence [positive serum (1-3)-β-D-glucan on 2 consecutive serum samples or a positive *Pneumocystis* PCR assay on a respiratory tract specimen]. Cases that meet criteria for a host factor and a clinical feature but for which mycologic evidence has not been found are considered possible PCP, although a negative serum (1-3)-β-D-glucan has a very high negative predictive value for PCP and makes the diagnosis highly unlikely.[82] Notably, a positive *Pneumocystis* PCR test in the absence of host, clinical, and radiographic criteria and without detection of the organism using conventional or

TABLE 134-2 Treatment of *Pneumocystis jirovecii*[a]

Agent(s)(Route)[b]	Dose	Additional Considerations[b]
Trimethoprim-sulfamethoxazole (TMP-SMX) (IV/PO)	15–20 mg/kg/d TMP component	Treat through mild rash: reduce TMP or SMX by one-half; desensitize; first choice
Pentamidine isethionate (IV)	4 mg/kg/d 300 mg/d maximum	Nephrotoxicity, hypotension, electrolyte abnormalities, cardiac arrhythmias may be life threatening
Dapsone (PO) with TMP (PO/IV)	100 mg/d dapsone plus 5 mg/kg/d TMP	Methemoglobinemia, G6PD; *may* be tolerated in sulfadiazine allergy
Clindamycin (IV/PO) and primaquine	Clindamycin: PO 450–600 mg q6–8h; IV 900 mg q8h Primaquine 15–30 mg oral base qd	Methemoglobinemia, diarrhea (pyrimethamine for primaquine)
Atovaquone (PO) suspension	750 mg (PO) bid	Variable absorbance, improved with fatty food; rash, GI intolerance

IV, intravenous; PO, oral.

[a] *Adjunctive therapies (see text): Corticosteroids (high dose with rapid tapering), possibly interferon-γ, granulocyte-macrophage colony-stimulating factor.*

[b] *Based on clinical judgment of physician; some agents are not FDA-approved for this indication.*

immunofluorescence stains is consistent with neither proven, probable, nor possible PCP.

TREATMENT

If left untreated, PCP is almost uniformly fatal. Several effective therapeutic agents are available for the treatment of PCP (Table 134-2). Because of the potential for rapid clinical decline, treatment should be instituted as soon as PCP is considered based on epidemiologic, radiographic, and clinical grounds. Delay in therapy, more common among HIV-negative patients likely as a result of disease underrecognition, is a risk factor for increased mortality.[120,121] Based on several consensus guidelines, treatment should be continued for 21 days in HIV-positive individuals and for at least 14 days for HIV-negative immunocompromised patients.[122,123] Although data are lacking to guide duration of therapy for HIV-negative patients, practice recommendations for solid-organ transplant patients favor a 21-day course for PCP unless the clinical presentation and initial work support mild disease.[68] This is based on the significant risk of PCP recurrence among HIV-infected persons treated with shorter courses including those with lower burdens of disease.[124]

Clinical response to treatment initiation, including fever resolution and radiographic improvement, is variable but usually occurs sooner in HIV-negative (~5 days) than HIV-positive (~7–10 days) patients, likely because of lower burdens of organisms in the former group. Transient clinical deterioration may occur in the first 48 h after treatment initiation, especially in moderate to severe cases and among HIV-positive patients, likely as a consequence of a heightened inflammatory response to antigens released from dead organisms. A lack of response to therapy within a week is suggestive of another process, infectious or noninfectious, and should be investigated further with bronchoscopy and BAL and/or further chest imaging. Treatment options, many of which have been evaluated head-to-head in clinical trials (Table 134-3), include trimethoprim and sulfamethoxazole, trimethoprim and dapsone, pentamidine, clindamycin plus primaquine, and atovaquone. Combining medications does not lead to improved outcomes but increases the chance of adverse side effects.

■ Trimethoprim and Sulfamethoxazole

The treatment of choice in both HIV-positive and HIV-negative patients with PCP is the combination of the antifolate antibiotics trimethoprim and sulfamethoxazole (TMP-SMX). Sulfamethoxazole inhibits the folate biosynthetic enzyme dihydropteroate synthase (DHPS), which catalyzes the formation of dihydropteroate, but

TABLE 134-3 Head-to-head Comparisons of PCP Treatment Regimen Effectiveness and Side Effects Based on Clinical Trial Data[128–134]

Effectiveness/ Side Effects	TMP-SMX	Intravenous Pentamidine	Dapsone + TMP	Clindamycin/ Primaquine	Atovaquone
TMP-SMX	—	TMP-SMX more or equally effective	Equally effective	Equally effective	TMP-SMX more effective
Intravenous Pentamidine	Side effects less common with TMP-SMX	—	?	Clinda/prima more effective (salvage therapy)	Equally effective (mild disease)
Dapsone + TMP	Side effects less common with dapsone + TMP	?	—	Equally effective	?
Clindamycin/ primaquine	LFT elevation with TMP-SMX; hematologic toxicities with clinda/ prima	Sides effects less common with clinda/ prima	Side effects more common with clinda/prima	—	?
Atovaquone	Side effects less common with atovaquone	Side effects less common with atovaquone	?	?	—

TMP may be inactive against *Pneumocystis* based on data from animal models and the absence of polymorphisms in the gene coding for dihydrofolate reductase (the protein target of TMP), suggesting the absence of selective pressure in the presence of TMP.[125–127] Patients who have moderate to severe disease and those who cannot tolerate oral medications should receive the intravenous form. TMP-SMX benefits from wide availability, excellent tissue penetration, overall good tolerability, rapid clinical response (within 3–4 days), and both oral and intravenous formulations allowing for step-down therapy. In head-to-head randomized controlled trials, TMP-SMX was either more[128,129] or equally[130–132] effective compared with intravenous pentamidine for the treatment of PCP in HIV-positive[129,131,132] and HIV-negative[128] patients. These same trials showed that side effects were very common with both regimens (in up to 100% of patients) but TMP-SMX was less frequently associated with severe side effects including nephrotoxicity, hypotension, and hypoglycemia than pentamidine. Crossover trials also demonstrated that treatment changes from one agent to the other due to drug toxicity (in either direction) were associated with favorable outcomes, but changes made due to lack of treatment response were associated with high mortality.[130,131] The addition of pentamidine to TMP-SMX has not been associated with clinical benefit, and antagonism between these agents has been suggested in animal studies.[133] TMP-SMX was equally effective as clindamycin-primaquine and dapsone-trimethoprim for PCP in a multicenter randomized controlled trial. Elevation of liver enzymes to more than five times baseline levels was more common with TMP-SMX, while serious hematologic toxicities including neutropenia, anemia, thrombocytopenia, or methemoglobinemia occurred more frequently in the clindamycin-primaquine group.[134]

The recommended dose of TMP-SMX for the treatment of PCP is 15 to 20 mg/kg/day of the trimethoprim component divided in three to four daily doses for 21 days. In patients with moderate to severe disease, intravenous therapy is preferred up front; a switch to oral therapy can be done once there is clinical improvement. Patients with mild disease can be initiated on oral therapy, which benefits from a high oral bioavailability of approximately 85%. TMP-SMX requires dosing adjustment in the setting of renal impairment.

TMP-SMX is generally well tolerated, but minor toxicities including gastrointestinal disturbances, skin rashes (ranging from mild to severe), drug fever, hyperkalemia, and elevation of serum creatinine may occur (8% of HIV-negative patients).[135] Hyperkalemia results from blockade of distal nephron sodium channels by trimethoprim, whereas creatinine elevation is due to inhibition of creatinine secretion by trimethoprim, which leads to a reversible increase in serum creatinine independent of changes in glomerular filtration rates. The incidence of serious adverse events with TMP-SMX is greater in patients with HIV/AIDS (80% or more) and solid-organ and bone marrow transplant recipients. Treatment-limiting toxicities requiring a change of therapy (in ~50% of HIV/AIDS patients) usually occur around 7 to 10 days after treatment onset and include cytopenias, severe nausea and vomiting, hepatitis, pancreatitis, nephritis, metabolic acidosis, central nervous system manifestations, and severe drug allergy.[124,132,136,137] Solid-organ transplant recipients are particularly susceptible to nephrotoxicity (renal transplant recipients) and transaminase elevations (liver transplant recipients), while cytopenias are common in bone marrow transplant recipients. Dose reduction may reduce toxicities in some cases. Treatment continuation despite adverse side effects and with supportive management using antihistamines, antipyretics, corticosteroids, and/or therapeutic drug monitoring has been successful in published studies.[138]

In patients with immediate hypersensitivity reactions (type 1) or mild severe delayed hypersensitivity reactions (type 4) to TMP-SMX, oral and intravenous drug desensitization can be performed to allow use of the medication. When compared to re-introduction of TMP-SMX at a later date, desensitization resulted in fewer treatment discontinuations and adverse reactions in HIV-infected adult patients with a previous history of mild or moderate hypersensitivity to cotrimoxazole.[138]

■ Pentamidine

Pentamidine isethionate was first used to treat African trypanosomiasis due to *Trypanosoma gambiense* but also has activity against *Leishmania* and *Pneumocystis*. The drug interferes with microbial nucleic acids and protein synthesis, but the exact mechanism of action against *Pneumocystis* is unclear. Intravenous pentamidine is considered an alternative regimen for moderate to severe PCP, mainly due to the higher incidence of severe toxicities rather than decreased efficacy. Several randomized studies have shown that pentamidine is as or slightly less effective than TMP-SMX for PCP for HIV-positive and HIV-negative patients, although clinical response is faster with TMP-SMX.[128–132] Delayed response to pentamidine may be associated with high levels of extrapulmonary tissue drug deposition and a slow accumulation in the lungs over 5 to 7 days. Conversely, drug build-up in tissues and a long half-life of 12 days contribute to sustained elevated serum levels and a possible continued therapeutic effect after cessation of therapy. Pentamidine is associated with increased rates of failure and increased mortality when used as salvage therapy. In those cases, clindamycin and primaquine is preferred based on results from meta-analyses.[139] Pentamidine is administered intravenously at 4 mg/kg once a day via a slow infusion of 1 to 2 h. The inhaled form does not achieve sufficient systemic drug concentrations and should not be used for treatment.

Side effects are very common with intravenous pentamidine (in up to 80% of patients) and the main barrier to therapy. These include hypotension, tachycardia, arrhythmias (including torsade de pointes), hepatitis, pancreatitis, nephrotoxicity, hypo- and hyperglycemia, hypokalemia, hypomagnesemia, nausea and vomiting, facial flushing, pruritis, dysgeusia, hallucinations, and syncope. Side effects are exacerbated by intravenous administration and in the presence of decreased renal function. Hypoglycemia, which usually manifests early in the treatment course, is a result of damage to pancreatic β cells leading to increased release of insulin, whereas hyperglycemia, a later manifestation, results from destruction of pancreatic β cells and secondary diabetes mellitus.[140] Pentamidine should therefore be avoided in pancreas transplant recipients given the potential for islet cell necrosis. As with TMP-SMX, pentamidine induces hyperkalemia by interfering with urinary potassium excretion. Prolonged half-life contributes to lasting toxicities after cessation of therapy.

■ Clindamycin and Primaquine

The combination of clindamycin with primaquine is an alternative regimen for initial treatment of mild to moderate PCP. Although comparative data are lacking for the treatment of severe PCP, clindamycin and primaquine has advantages over intravenous pentamidine including good efficacy as primary and salvage therapy and a better side-effect profile. The mechanisms of action of clindamycin and primaquine are unknown but may be related to negative impacts on mitochondrial activity and nucleic acid synthesis, respectively.[141] Clindamycin and primaquine was equivalent to TMP-SMX and dapsone–TMP in one study, but toxicity was higher with the former regimen.[134] Clindamycin and primaquine is also the preferred regimen for salvage therapy in patients who do not respond to first-line treatment. In a meta-analysis of salvage therapy for PCP, 90% of patients who failed treatment with TMP-SMX or pentamidine or both had a good clinical response to clindamycin–primaquine.[142] In a more recent meta-analysis, the response rates for

TMP-SMX and clindamycin–primaquine as salvage therapy were 73% and 68% respectively, compared with 44% for pentamidine.[139] The recommended dose of clindamycin is 300–450 mg orally four times a day (or 600–900 mg IV every 6 to 8 h) and primaquine 15–30 mg of base daily. A G6PD level should always be checked prior to initiating primaquine, and the drug should be avoided in the setting of G6PD deficiency because of the potential for severe hemolysis. Common side effects include rash and gastrointestinal disturbances, including an increased risk of *Clostridioides difficile* diarrhea associated with clindamycin use.

Atovaquone

Atovaquone is an alternative treatment option for mild to moderate PCP. The mechanism of action against *Pneumocystis* is not clear but may be related to inhibition of cytochrome b within the electron transport chain, impairing metabolic function as is the case against *Plasmodium* species. Atovaquone is less effective than TMP-SMX for the initial treatment of PCP but leads to fewer treatment-limiting side effects.[143] In a randomized controlled trial of HIV-positive patients with mild to moderate PCP, the failure rate was greater with atovaquone compared with TMP-SMX (20% vs. 7%), and treatment with atovaquone was associated with a higher mortality rate at 4 weeks after treatment completion. Treatment-limiting toxicities requiring a change of therapy were more common with TMP-SMX.[144] Atovaquone showed similar efficacy to intravenous pentamidine for mild to moderate PCP treatment in patients with HIV, but treatment-limiting side effects were more common with pentamidine.[145] Taken together, these data highlight the main advantage of atovaquone, which is a favorable side-effect profile. Adverse reactions including rash, fever, diarrhea, and abnormal liver function tests typically are not severe enough to warrant discontinuation. The medication has a bitter taste that may impact adherence. Diarrhea and other gastrointestinal dysfunction may lead to poor absorption of atovaquone, decreased therapeutic drug levels, and worse clinical outcomes.[144] The recommended dose is 750 mg/5 mL via oral suspension, twice daily with food.

Dapsone and Trimethoprim

Dapsone is a folate synthesis inhibitor that can replace SMX and be combined with TMX for the treatment of mild to moderate disease. Dapsone plus TMX was equivalent to TMP-SMX and clindamycin–primaquine in terms of clinical efficacy and treatment limiting toxicities in a clinical trial. Serious hematologic disturbances and hepatitis were least common with the combination of dapsone and TMX.[134] As such, the regimen is an effective alternative treatment option. Although associated with fewer side effects than SMX, dapsone has a longer half-life (30 h), so toxicities may be longer-lasting. As with primaquine, dapsone can induce hemolysis in patients with G6PD deficiency. Other recognized hematologic toxicities include methemoglobinemia and anemia. Methemoglobinemia is thought to result from oxidation of the hemoglobin molecule by breakdown products of dapsone metabolism, leading to a decreased oxygen carrying capacity that can be fatal if methemoglobin levels exceed 70%.[146] Dapsone-induced methemoglobinemia may improve with discontinuation of therapy along with supportive treatment. Methylene blue can be administered for more severe cases and leads to conversion of methemoglobin to hemoglobin but should be avoided in the setting of G6PD deficiency where it may paradoxically induce hemolysis.[147] The recommended dose is dapsone (100 mg orally per day) in combination with oral TMP (15 mg/kg per day).

Adjunctive Therapies

Corticosteroids should be used in patients with moderate to severe infection, defined as having a Pa_{O_2} below 70 mm Hg at room air or an alveolar–arterial oxygen gradient of at least 35 mm Hg. Steroids have been demonstrated to reduce the likelihood of early deterioration of oxygenation, respiratory failure, need for mechanical ventilation, and death when combined with anti-*Pneumocystis* therapy for HIV-positive patients.[148] This is likely through blunting of an intensified immune response to dying organisms that would otherwise lead to uncontrolled lung damage. The evidence is less robust for HIV-negative immunocompromised patients. A meta-analysis showed no benefit of adjunctive corticosteroids in this population, but available studies were small and retrospective in nature.[149] Steroids continue to be recommended for non-HIV patients with PCP based on effectiveness in HIV-positive patients and expert opinion.[37] Steroids should ideally be administered prior to or within 72 h of initiation of PCP therapy, as corticosteroids initiated beyond 72 h have not been associated with any clinical benefit.[150,151] Corticosteroids may also be advantageous for patients with milder hypoxemia, but the benefit has not been confirmed. In HIV-positive patients with a high pretest probability for PCP and who meet oxygenation criteria, it is reasonable to initiate anti-PCP treatment with adjunctive steroids until the diagnosis is confirmed. The recommended regimen consists of oral prednisone in a dose of 40 mg twice daily for the first 5 days, followed by 40 mg daily for another 5 days, followed by 20 mg once daily for an additional 11 days for a total of 21 days of treatment. Other equivalent oral or intravenous steroid regimens including intravenous methylprednisolone can be used.[151] Tapering of steroids is thought to reduce the likelihood of a relapse of pulmonary inflammation.

In HIV-infected patients, treatment of the HIV infection with ART should be initiated within 2 weeks of the onset of PCP therapy. Randomized controlled trials have demonstrated that early initiation of ART in the setting of most opportunistic infections, including PCP, reduces the likelihood of AIDS progression and mortality by 50%.[152] For solid-organ transplant patients, a reduction of other immunosuppression is often pursued although such measures have not been evaluated in clinical trials. Colony-stimulating factors (CSF) including monocyte/macrophage (M-CSF) and granulocyte/macrophage (GM-CSF) lineages may enhance the clearance of *P. jiroveci* by alveolar macrophages without significantly increasing the inflammatory response in animal models, but there is little clinical evidence to support their use in PCP.[153]

Echinocandins

Echinocandins, antifungals most commonly used for the treatment of invasive candidiasis, have been increasingly explored as an experimental treatment option for *Pneumocystis* infection. Echinocandins exhibit antifungal activity via noncompetitive inhibition of the GSC1 subunit of the enzymatic complex involved in the synthesis of (1-3)-β-D-glucan, a key component of the *Pneumocystis* cell wall and much more abundant in cysts than trophozoites. Echinocandins have demonstrated activity against *Pneumocystis* in animal models, especially against cyst forms. Caspofungin rapidly depleted *Pneumocystis* cysts but not trophozoites in a murine model of infection, although it also appears to interfere with transport of surface glycoproteins and formation of tubular elements that are integral to the trophozoite stage.[13,154] Similarly, anidulafungin and rezafungin, a novel echinocandin, were effective against both *Pneumocystis* developmental stages.[155] Caspofungin was associated with increased survival in rodents with *Pneumocystis* infection. The question of lower efficacy against trophozoite forms has prompted evaluation of echinocandin in combination with other agents to enhance antifungal activity. Caspofungin plus TMP-SMX eradicated *Pneumocystis* from murine lungs, suggesting the possibility of synergism.[156] In human studies, echinocandin monotherapy or in combination with other agents has been effective for PCP as salvage therapy in HIV-positive[157] and HIV-negative patients,[158] but treatment failures have also been reported with monotherapy.[159,160] Based on these data, the 2016 6th European Conference on Infections in Leukemia (ECIL-6) guidelines cite the combination of TMP-SMX plus caspofungin as a salvage treatment option for HIV-negative patients with PCP but recommend against the use of echinocandin monotherapy.[123] Studies assessing the effectiveness of available and novel echinocandins for the treatment of PCP will be of continued interest given the considerable advantages afforded by this class of antifungals, which include minimal side effects and drug–drug interactions.[161] Glucan synthase inhibitors other than echinocandins, including the triterpenoid antifungal agent ibrexafungerp, have demonstrated in vitro and in vivo activity against *Pneumocystis* and represent a novel therapeutic class for the treatment of PCP.

■ Resistance

Drug resistance in *Pneumocystis* is difficult to ascertain because of the inability to perform in vitro susceptibility testing. However, the presence of mutations in key parts of the *Pneumocystis* genome, such as in genes that code for proteins targeted by antifungals, is suggestive of resistance. One such example is the DHPS gene, whose enzyme product is inhibited by SMX and dapsone. Sequencing of *P. jiroveci* clinical strains have revealed nonsynonymous polymorphisms in the DHPS gene that were much greater in frequency among patients who were exposed to sulfa drugs, suggesting that mutations arise from drug-induced selective pressure.[32,162] Mutations in DHPS have been associated with decreased survival and increased risk for treatment failure in patients receiving sulfa-based PCP therapy in some studies but not in others.[163–166] Taken together, these data suggest that long-term exposure to sulfa drugs may select for resistance but their impact on clinical outcomes appears to be limited. Although populations directly exposed to sulfa drugs are at increased risk for harboring *P. jiroveci* with mutated DHPS strains, adults with a first PCP episode in Chile had a high frequency of such mutations, suggesting that other factors such as interhuman transmission of resistant strains may impact resistance patterns.[167] *P. jiroveci* resistance to atovaquone is mediated by mutations in the cytochrome b gene within the mitochondrial genome. As with sulfa drugs, mutations to atovaquone are more common with prolonged drug exposure but because the rate of spontaneous mutations is significantly higher in the mitochondrial genome compared to the nucleus, resistance to atovaquone develops faster and mutated genes are much more diverse.[164]

PROPHYLAXIS

The use of appropriate prophylaxis is effective in preventing PCP. Several different prophylactic regimens exist, and strategies differ between persons living with HIV (PLWH) and HIV-negative immunosuppressed patients.

■ Indications

Below we consider indications for PCP prophylaxis in at-risk groups.

Persons Living with HIV

PCP is most likely to occur in patients who are not receiving antiretroviral therapy and whose CD4 cell counts are less than or equal to 200 cells/μL. Before widespread use of antimicrobial prophylaxis, PCP developed in 70% to 80% of people with AIDS.[168] Initiation of antiretroviral therapy to restore immune function is the most critical component of PCP prevention. However, PLWH benefit from PCP directed antimicrobial chemoprophylaxis until some measure of immune reconstitution is achieved. One of the earlier studies evaluating PCP prophylaxis showed that patients with CD4 counts less than 200 cells/μL who did not receive antimicrobial prophylaxis were nine times more likely to develop PCP than those who did receive prophylaxis.[25] Current guidelines recommend that primary PCP prophylaxis be administered to PLWH, including those on antiretroviral therapy, with CD4 counts less than 200 cells/μL or CD4 percentage less than 14%.[169] It may also be appropriate to administer prophylaxis when CD4 counts are between 200 and 250 cells/μL and frequent monitoring of CD4 counts is not feasible (i.e., at least every 3 months). After a course of therapy for PCP, patients with HIV/AIDS should continue to receive secondary prophylaxis to prevent infection recurrence. When patients achieve a CD4 count greater than or equal to 200 cells/μL or a CD4 count between 100 and 200 cells/μL with an undetectable HIV viral load for at least 6 months, secondary prophylaxis can be discontinued.[170] PCP occurring in an HIV-positive patient with a CD4 count greater than or equal to 200 cells/μL, especially while on antiretroviral therapy, suggests additional undefined qualitative cellular immune defects that predispose to disease recurrence. Therefore, such patients should be considered for lifelong prophylaxis unless a reversible host factor (such as chronic steroid use) can be identified and reversed.

HIV-negative Immunosuppressed Patients

Antimicrobial prophylaxis has been shown to be highly effective in preventing PCP in HIV-negative immunosuppressed hosts. In a meta-analysis of 12 randomized clinical trials involving HIV-negative immunosuppressed patients, TMP-SMX prophylaxis was associated with a 91% reduction in PCP occurrence and a significant reduction in PCP related mortality.[171] Prophylaxis is generally recommended for all solid-organ transplant recipients early after transplantation and lifelong for some organ types including lung allograft recipients. Risk of PCP is greatest within the first 6 months after transplant. With widespread use of prophylaxis and improved immunosuppressive regimens, the incidence of infection post-transplant has decreased to 0.3% to 2.5%.[37] Lung transplant recipients are particularly high risk. Routine prophylaxis is also recommended for all allogenic HSCT recipients and should be considered for select autologous HSCT recipients, particularly those with underlying lymphoma, myeloma, and leukemia, and in those who have received intensive treatment or conditioning regimens. In addition to transplant recipients, PCP prophylaxis is recommended for all patients with acute lymphoblastic leukemia as well as those receiving the monoclonal antibody alemtuzumab, phosphatidylinositol 3-kinsase inhibitors such as idelalisib, or a combination of radiotherapy and the alkylating agent temozolomide, and in patients with select primary immunodeficiencies such as idiopathic CD4 lymphopenia and severe combined immunodeficiency.[172]

One of the most common indications for PCP prophylaxis in HIV-negative hosts is the prolonged use of high-dose glucocorticoids. The 2020 Clinical Practice Guidelines for Prevention and Treatment of Cancer-Related Infections recommends consideration of PCP prophylaxis in cancer patients receiving the prednisone equivalent of 20 mg or more daily for 4 weeks.[172] Recent guidelines from the American Society of Transplantation suggest that PCP prophylaxis be considered in organ transplant recipients who receive the equivalent of 20 mg of prednisone daily for at least 2 weeks or for those receiving more intensive pulse-dose steroids for graft rejection.[37] While there are no guidelines for PCP prophylaxis for patients with rheumatologic diseases necessitating corticosteroid use, receipt of a prednisone equivalent of 20 mg daily for 4 weeks, especially in the setting of another cause of immunocompromise, is a generally accepted indication.

■ Regimens

Prophylactic regimens for PCP (Table 134-4) are summarized in the following sections.

TABLE 134-4 Regimens for *Pneumocystis jirovecii* Prophylaxis

Agent(s)	Dose	Common Adverse Reactions
Trimethoprim-sulfamethoxazole (TMP-SMX)	1 single-strength tablet daily *or* 1 double-strength tablet daily *or* 1 double-strength tablet 3 times weekly	Increased serum creatinine, hyperkalemia, bone marrow suppression[a]
Atovaquone oral suspension	1500 mg daily taken with food	Bitter taste, gastrointestinal upset
Pentamidine (inhaled)	300 mg monthly	Cough, bronchospasm, breakthrough disease particularly in upper lung zones
Dapsone	50 mg twice daily *or* 100 mg once daily	Hemolytic anemia in G6PD deficiency (required G6PD testing), methemoglobinemia, gastrointestinal upset

[a] *One double-strength tablet daily is preferred in patients with a coexisting indication for prophylaxis against toxoplasmosis (CD4 count < 100). Patients receiving treatment for toxoplasmosis with pyrimethamine/sulfadiazine do not require additional antimicrobial prophylaxis for PCP.*

Persons Living with HIV

TMP-SMX is the first-line agent for PCP prophylaxis. In a meta-analysis of 35 studies encompassing over 6500 patients, TMP-SMX was shown to be superior to both dapsone and aerosolized pentamidine.[173] TMP-SMX also provides protection against other clinically important pathogens including *Toxoplasma gondii*, *Listeria monocytogenes*, *Isosporabelli*, and susceptible bacteria, including some strains of *Streptococcus pneumoniae*, *Haemophilus influenzae*, community-acquired staphylococci, and some enteric Gram-negative rods. Infection with *Nocardia* spp., which are often sensitive to TMP-SMX, may also be prevented by prophylaxis. The optimal dosing strategy for PLWH differs based on the need to provide prophylaxis against toxoplasmosis. In patients with CD4 counts less than 100 cells/μL who are at high risk for toxoplasmosis, TMP-SMX is dosed at one double-strength tablet daily. In patients who do not require prophylaxis against toxoplasmosis, one single-strength tablet daily is the preferred dosing strategy, owing to better tolerability and equal efficacy compared with double-strength daily dosing. This is supported by a randomized trial that showed no difference in rates of PCP development in single-strength versus double-strength groups, but higher rates of adverse effects and treatment discontinuation in the double-strength group.[174] A dosing regimen consisting of one double-strength tablet three times weekly is an alternative option.

In patients who cannot tolerate TMP-SMX, alternative regimens include atovaquone 1500 mg daily, dapsone 50 mg twice daily or 100 mg daily, or aerosolized pentamidine. Aerosolized pentamidine is the least effective, and breakthrough disease has been well documented, particularly in the upper lung zones.[63,175] Dapsone and atovaquone have comparable efficacy, but both have drawbacks. In particular, dapsone may cause severe hemolytic anemia in patients who are G6PD deficient as well as methemoglobinemia. Patients must be screened for G6PD deficiency prior to initiation of therapy. Atovaquone may be prohibitively expensive and also causes gastrointestinal upset and must be taken with food.

HIV-negative Immunosuppressed Patients

Chemoprophylactic regimens are generally the same as those for PLWH. Guidelines recommend TMP-SMX as the first-line agent and can be administered as one single-strength tablet daily, one double-strength tablet daily, or one double-strength tablet three times weekly.[37,172] TMP-SMX–related adverse effects are particularly relevant in this population. In particular, TMP-SMX may cause mild bone marrow suppression. This tends to be overestimated but may be exacerbated when used in combination with other myelosuppressive agents. Some institutions avoid TMP-SMX in HSCT recipients at least through the time of engraftment, although data on this practice are limited. Trimethoprim also inhibits potassium and creatinine secretion, which can lead to elevations in serum potassium and creatinine, but this may not reflect a true decrease in glomerular filtration. This is reversible and more common during therapy than with prophylaxis. Some patients may not tolerate any dose of sulfa drugs, owing to significant rash (occasional Stevens–Johnson syndrome), hepatitis, interstitial nephritis, pancreatitis, or aseptic meningitis, although these complications are far less common. In the renal transplant population, thrice-weekly dosing with one double-strength tablet has been shown to limit these adverse effects and is likely as effective as daily dosing.[176,177]

Dapsone, atovaquone, and pentamidine remain second-line agents.[37,172] In a study of allogenic HSCT transplant recipients, breakthrough infection was shown to be more common in those receiving dapsone prophylaxis compared with TMP-SMX, although the dapsone dose used in this study may have been too low.[178] Atovaquone may provide comparable protection against PCP compared to TMP-SMX in this population, but it does not confer the same level of protection against other common opportunistic pathogens.[179]

■ Duration

The duration of PCP prophylaxis for HIV-infected persons and those with other immune-compromising disorders is considered below.

Persons Living with HIV

Primary prophylaxis may be safely discontinued in PLWH who have responded to antiretroviral therapy once CD4 counts are greater than 200 cells/μL for at least 3 months.[169] Primary prophylaxis can likely also be safely discontinued in patients with CD4 counts between 100 and 200 cells/μL if they are adherent to ART and have an undetectable viral load for a minimum of 3 to 6 months. This is supported by a large combined analysis of multiple European cohort studies that revealed an extremely low incidence of PCP in virologically suppressed patients with CD4 counts between 100 and 200 cells/μL.[180] Secondary prophylaxis can also be discontinued when either of these conditions are met.

HIV-negative Immunosuppressed Patients

Duration of chemoprophylaxis varies depending on the host and underlying immunosuppression. In general, PCP prophylaxis is recommended for all solid organ transplant recipients for at least 6 to 12 months post-transplant.[37] Lifelong prophylaxis is typically recommended for recipients of lung and small bowel transplants, and some cardiac, liver, and renal transplant programs also advocate for lifelong prophylaxis.[181] If immune suppression cannot be reduced after a course of treatment for PCP, prophylaxis should be maintained indefinitely. For recipients of allogeneic HSCT, prophylaxis is typically continued for at least 6 months and potentially longer if immunosuppression is unable to be tapered.[172] In both solid-organ and HSCT recipients, reinstitution of prophylaxis should be considered with increases in immune suppression, particularly pulse corticosteroids or antilymphocyte antibody therapies for treatment of organ rejection or graft-versus-host disease. For patients with acute lymphoblastic leukemia and for those treated with temozolomide or phosphatidylinositol 3-kinsase inhibitors, prophylaxis is generally continued for the duration of active therapy. In patients receiving alemtuzumab, prophylaxis is recommended for at least 2 months after completion of therapy, and until CD4 cell counts are greater than 200.[172] In patients receiving high-dose corticosteroids, prophylaxis should be continued at least through the completion of the steroid taper and/or for up to 6 weeks after cessation of therapy.[182]

Data regarding duration of prophylaxis in HIV-positive transplant recipients are relatively limited. In some instances, PCP prophylaxis is prescribed lifelong. However, in a recent study of 122 HIV-positive kidney transplant recipients, no patients developed PCP after prophylaxis was stopped at 6 months, suggesting that a 6-month regimen of PCP prophylaxis may be sufficient among HIV-positive recipients, similar to those without HIV.[183]

CONCLUSIONS

Pneumocystis jiroveci is an opportunistic pathogen that produces a clinical syndrome ranging from asymptomatic infection to subacute and acute interstitial pneumonia in susceptible hosts. While the syndrome of PCP came to worldwide prominence during the HIV/AIDS epidemic in the 1980s, the incidence of PCP is currently highest in HIV-negative immunocompromised patients owing to improvements in HIV treatments and increases in the number of HIV-negative patients receiving heavily immunosuppressive therapies. Established consensus definitions have recently been developed, with diagnosis requiring a combination of clinical, radiologic, and mycologic evidence. The treatment of choice in both HIV-positive and HIV-negative immunosuppressed patients is TMP-SMX, which has also proven to be a highly effective regimen for prevention of disease in vulnerable hosts.

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CHAPTER 135

Protozoan Infections of the Thorax

Louise C. Ivers
Edward T. Ryan

INTRODUCTION

Protozoan infections of the thorax are generally quite rare. Other infectious and noninfectious processes can mimic their presentation, and the clinician needs to be aware of the possibility of these more rare pathogens, especially in endemic regions. Diagnostics can be more challenging and may necessitate more invasive procedures to obtain the diagnosis. Treatment is not always straightforward and may require surgical intervention with some infections.

AMEBIASIS: *ENTAMOEBA HISTOLYTICA*

Entamoeba histolytica is a protozoan infection of humans that is found worldwide and is globally responsible for tens of thosands of deaths annually. It is endemic in most temperate and tropical areas of the world, particularly in areas with poor socioeconomic development and limited sanitation. Serologic evidence of prior or current infection with *E. histolytica* is present in 5% to 50% of individuals in impoverished populations. *E. histolytica* is infectious in the cyst form. Transmission usually occurs as a result of contamination of food or water, but may also occur by means of oral–anal contact. Infection is common in developing countries. In Europe and the United States, infection is most commonly seen in individuals who have lived in endemic areas of the world. Institutionalized individuals are also at increased risk of infection. Sexually active men who have sex with men are also at increased risk of infection. There does not appear to be an increased risk of invasive disease in persons with HIV infection.

A morphologically identical but nonpathogenic protozoan, *Entamoeba dispar*, also infects the human gastrointestinal tract. It can be distinguished from *E. histolytica* by antigenic, genetic, and immunologic methods. Infection is 10 times more prevalent with *E. dispar* than with *E. histolytica*; however, the former does not cause invasive disease. Many older epidemiologic studies relied on microscopic diagnosis alone, and inadvertently incorporated both pathogenic and nonpathogenic species in estimates of prevalence of infection.

E. histolytica has a simple life cycle involving an infectious cyst and an ameboid trophozoite phase. Cysts may survive in the external environment for several weeks to months, especially in damp conditions and temperatures between −5°C and 40°C. After ingestion by humans, cysts excyst in the small intestine, each forming eight daughter trophozoites. These motile trophozoites can adhere to the intestinal wall; it is in this form that they may invade the mucosa, causing symptomatic invasive disease. In the colon, trophozoites encyst to complete the life cycle and are excreted. Trophozoites do not survive outside the human host.

■ Clinical Manifestations

The incubation period for intestinal amebiasis is usually 1 to 4 weeks, but ranges from a few days to months. Infection with *E. histolytica* is asymptomatic in up to 90% of cases, but may cause a range of gastrointestinal symptoms from mild diarrhea to severe colitis with bloody diarrhea. Symptoms result from penetration of the trophozoites through the mucosal barrier with invasion of the colon wall. In the absence of frank blood, stool is usually positive for occult blood. Fever is present in less than half of cases. Fecal leukocytosis is usually less marked than in bacterial colitis. Rarely, progression of invasive intestinal disease may lead to severe colitis and bowel perforation. On occasion, granulation tissue formation surrounding a localized area of invasive disease may form an inflammatory mass (an "ameboma") and manifest as a tender abdominal mass.

Extraintestinal disease most commonly occurs in the liver, and manifests as a liver "abscess." In this instance, trophozoites migrate to the liver via the portal veins, and infection results in inflammation, necrosis, and ultimately a fluid collection. The collection is often referred to as an abscess; however, it does not contain polymorphonuclear cells like a true abscess, but only cellular debris. Eighty percent of amebic hepatic abscesses are solitary, and 80% occur in the right lobe of the liver. Extraintestinal disease may present years after residence in an endemic area and should be considered in all patients with an appropriate travel history and suggestive symptoms. Liver abscesses occur more frequently in men than women, and usually in the age range of 18 to 50 years.

Thoracic manifestations of *E. histolytica* infection are rare; they have been reported in 2% to 3% of cases of invasive amebiasis. They can be considered chiefly as either pleuropulmonary or pericardial. A case of *E. histolytica* osteomyelitis of the rib has been reported, as has a case of pulmonary amebiasis presenting as superior vena cava syndrome.[1]

■ Pleuropulmonary Disease

Amebic pulmonary disease may occur by a number of mechanisms.[1–3] It most often occurs as the result of a concomitant liver abscess. The abscess may result in an ipsilateral sympathetic pleural effusion that does not require specific therapy. A liver abscess may alternatively rupture through the diaphragm into the pleural space, causing respiratory distress, empyema, and subsequent parenchymal lung abscesses (Figs. 135-1 to 135-3). Pulmonary parenchymal disease in the form of lung abscesses and consolidation less often occurs in the absence of hepatic disease, but may occur if there has been hematogenous spread of trophozoites to the lung or infectious thrombophlebitis.[4]

Most patients with extraintestinal amebiasis have not had symptomatic intestinal disease, so the absence of preceding gastrointestinal symptoms does not exclude the diagnosis. Patients with liver abscess often present with insidious onset of fever, right upper quadrant pain, and hepatic tenderness on palpation. Pleuritis, respiratory symptoms such as cough, dyspnea, and/or physical examination consistent with pleural effusion further suggest involvement of the pleuropulmonary system. Sputum production may range from scant to copious, and sputum may contain purulent material, particularly if a hepatobronchial fistula has developed. Classically, the purulent material of amebic abscess is reddish "anchovy paste." Jaundice is uncommon. Leukocytosis may be present, but eosinophilia is not a feature of the disease.

■ Pericardial Disease

Pericardial disease can result from either sterile inflammation of the pericardium as a result of a contiguous liver abscess in the left lobe of the liver, or may be a purulent infection as a result of rupture of a hepatic amebic abscess into the pericardial space (Fig. 135-4). Chest pain, pericardial friction rub, and symptoms and signs of pericarditis may be presenting features. Presentation may be acute and severe, with symptoms and signs of pericardial tamponade.[5]

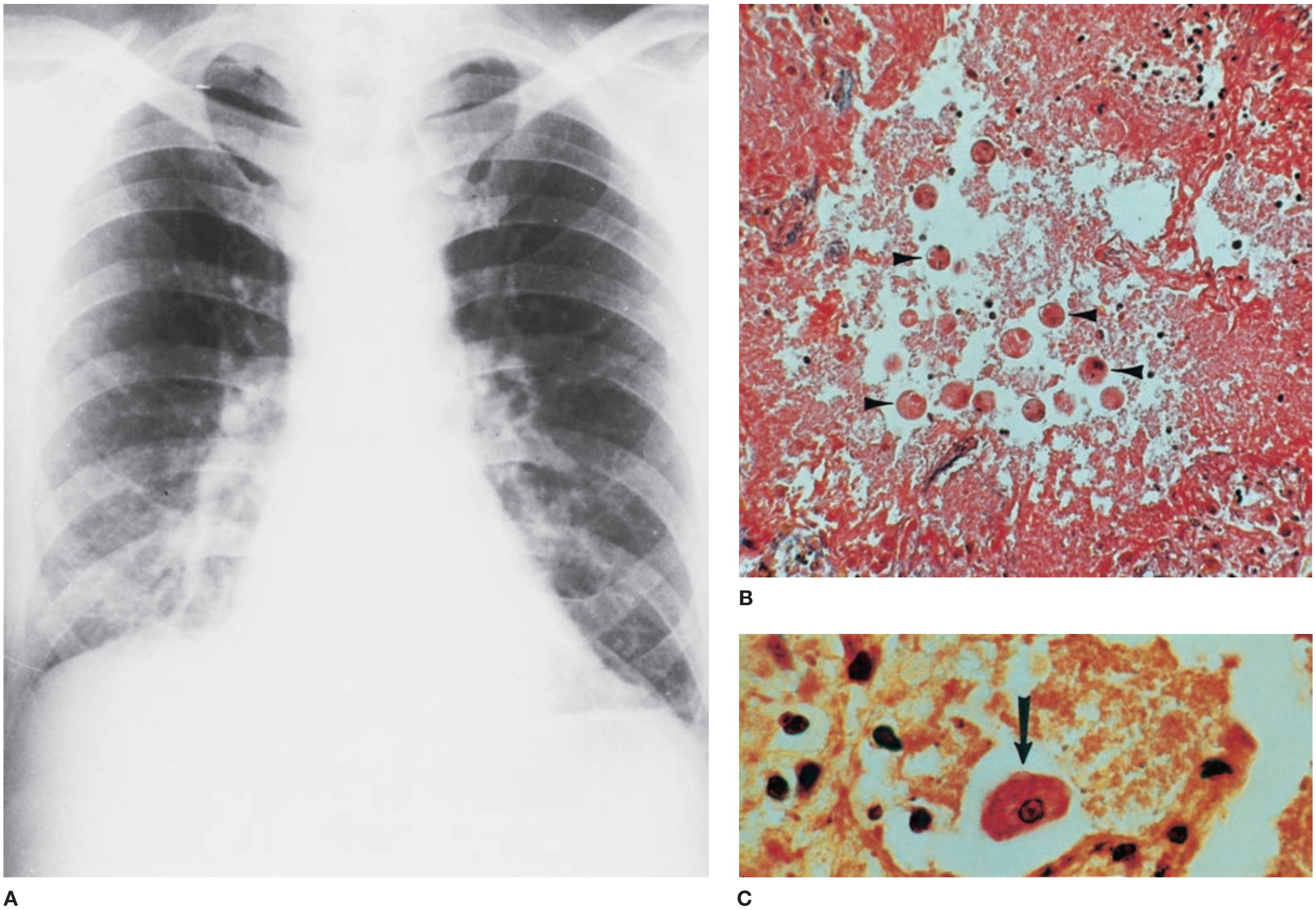

Figure 135-1 *Entamoeba histolytica* involving the right lung after rupture of a hepatic abscess through the right hemidiaphragm. **A.** Chest radiograph shows elevated right hemidiaphragm, right lower lobe infiltrate, and effusion. **B.** Alveolar spaces are filled with amebae *(arrowheads)*. (Iron hematoxylin stain, ×300). **C.** Trophozoite *(arrow)* and necrotic debris. *(**A.** Reproduced with permission from Armed Forces Institute of Pathology [AFIP]; **B.** Reproduced with permission from Dr. Y. Gutierrez.)*

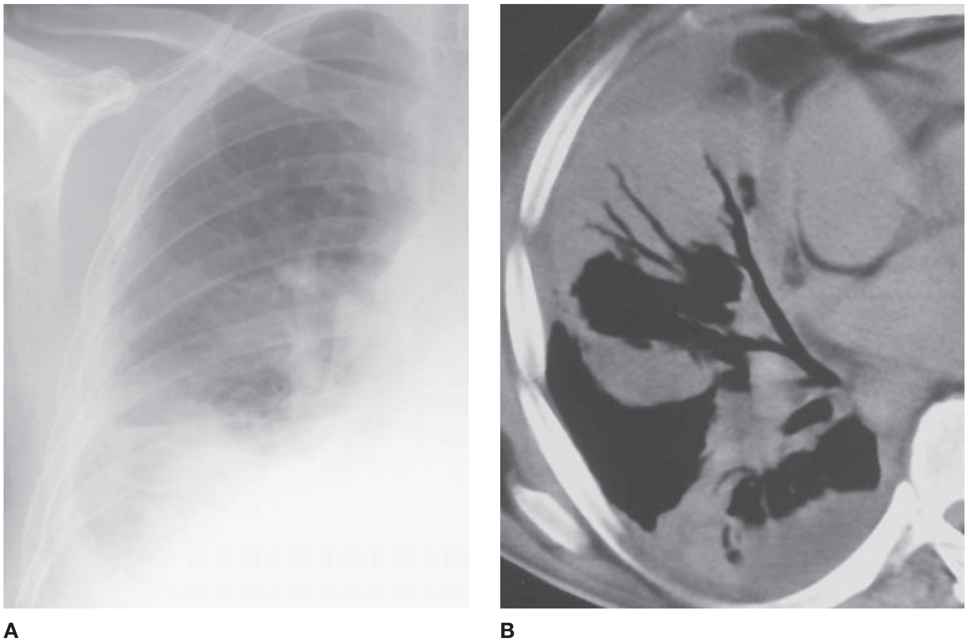

Figure 135-2 Right-sided amebic pleural empyema and pneumonia in a 43-year-old man with an abscess of the right hepatic lobe. **A.** Initial chest radiograph shows pleural effusion and right-sided basal consolidation. **B.** Chest CT scan helps confirm pleural involvement and right-sided basal alveolar infiltrates. Trophozoites of *E. histolytica* were obtained at bronchoalveolar lavage. *(Reproduced with permission from Martinez S, Restrepo CS, Carrillo JA, et al. Thoracic manifestations of tropical infections: a pictorial review. RadioGraphics. 2005;25(1):135–155.)*

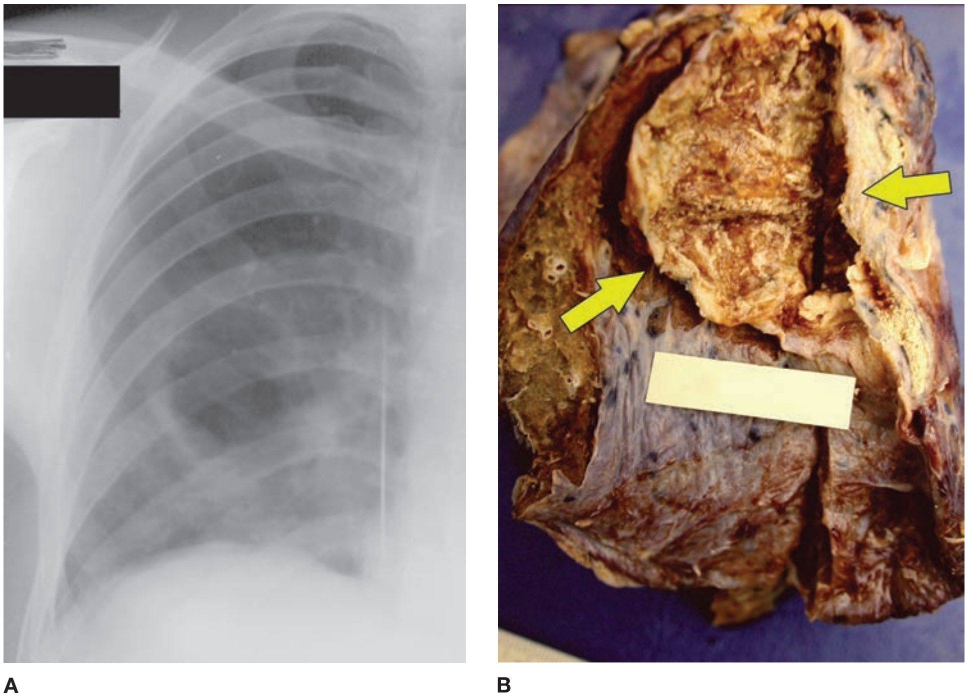

Figure 135-3 Right-sided amebic pneumonia in a 35-year-old man with a hepatic abscess. **A.** Chest radiograph shows elevation of the right hemidiaphragm and right-sided basal consolidation with cavitation. **B.** Photograph of the gross specimen demonstrates an irregular cavitary lesion *(arrows)*. Anchovy sauce content and trophozoites of *E. histolytica* (not shown) were found on the lesion wall. *(Reproduced with permission from Martinez S, Restrepo CS, Carrillo JA, et al. Thoracic manifestations of tropical infections: a pictorial review. RadioGraphics. 2005;25(1):135–155.)*

■ Diagnosis of Pleuropulmonary and Pericardial Disease

Stool microscopy may reveal the presence of *E. histolytica* trophozoites or cysts, but microscopy is neither a sensitive nor a specific method for the diagnosis of amebiasis. Microscopy is unable to distinguish *E. histolytica* from nonpathogenic *E. dispar*, and extraintestinal disease is associated with presence of the pathogen in stool in only a minority of cases. Stool may be concentrated and stained with iodine to evaluate for the presence of cysts. Trophozoites are best seen on a fresh smear with iron hematoxylin and trichrome stain. Microscopy of abscess fluid occasionally may

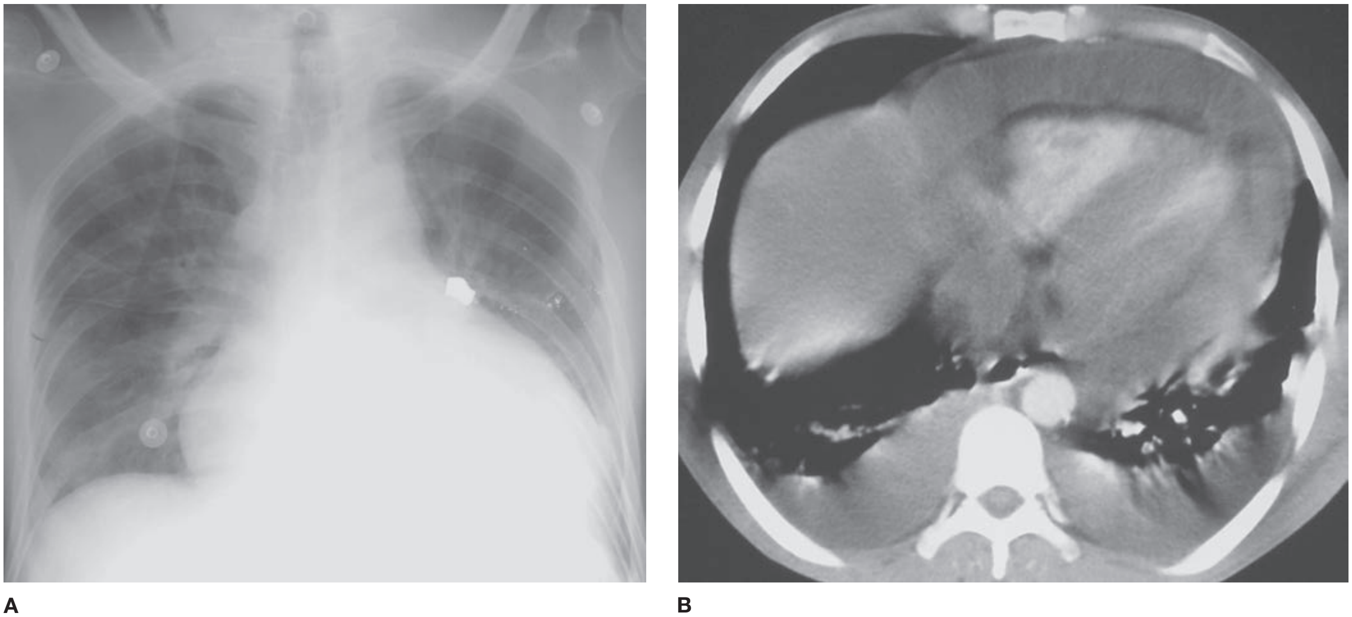

Figure 135-4 Amebic pericardial tamponade in a 27-year-old man with an abscess of the left hepatic lobe. The patient presented with pulsus paradoxus, fever, and chills. **A.** Chest radiograph shows enlargement of the cardiac silhouette. **B.** Chest CT scan shows extensive pericardial effusion that resulted from rupture of a left hepatic lobe abscess (not shown) into the pericardial space. *(Reproduced with permission from Martinez S, Restrepo CS, Carrillo JA, et al. Thoracic manifestations of tropical infections: a pictorial review. RadioGraphics. 2005;25(1):135–155.)*

reveal presence of trophozoites. Diagnosis of extraintestinal disease is best made by a combination of microscopic examination of samples, antigen detection, and serology tests.

Antigen Detection

Antigen detection methods detect *E. histolytica*. These tests are able to distinguish *E. dispar* from *E. histolytica*. Stool antigen tests are over 95% sensitive and specific for the diagnosis of intestinal disease. Antigen detection assays are also highly sensitive and specific when applied to abscess fluid.

Serology

Most patients infected with *E. histolytica*, but not *E. dispar*, develop a serum antibody response. Amebic serology is positive in over 90% of patients with extraintestinal disease. Serologic analysis may be negative in early infection. The presence of IgG antibodies does not always indicate active disease; IgG may persist for many years after active infection.

Treatment

Metronidazole or tinidazole is effective in the treatment of individuals with intestinal and extraintestinal amebiasis. To prevent a relapse, a luminal agent such as iodoquinol or paromomycin also should be administered. Sympathetic pleural effusions do not need specific therapy, other than treatment of the underlying liver abscess. Amebic empyema and amebic pericarditis are best treated with aspiration or percutaneous drainage, in combination with administration of antiamebic microbial therapy.

FREE-LIVING AMEBA: ACANTHAMOEBA

Free-living amebae are rarely associated with human infection; however, when infection does occur, disease tends to be progressive and difficult to treat.

Acanthamoeba spp. are ubiquitous, and have been isolated from a wide variety of locations, including the nasal passages of healthy adults, water sources, soil, and contact lens fluid. Infection in humans usually manifests as either keratitis or systemic disease. Systemic disease usually involves the central nervous system, manifesting as granulomatous amebic encephalitis. Amebic infection of skin also has been reported.

Clinical Features

Acanthamoeba sp. keratitis is usually a disease of healthy individuals, often contact lens wearers. Infection is thought to result from direct deposition of ameba into the eye. In contrast, systemic disease results from hematogenous dissemination of ameba, which are thought to first enter the human host via the respiratory tract or skin. Systemic disease is primarily a disease of immunocompromised or debilitated persons, including individuals with acquired immunodeficiency syndrome (AIDS), and those who have undergone bone marrow transplantation, organ transplantation, or are otherwise immunosuppressed. Pulmonary nodular infiltrates and pneumonitis have been reported in cases of systemic disease.[6]

Diagnosis

Diagnosis of systemic acanthamebiasis is usually made late in the clinical course, and unfortunately, very often at autopsy. Evaluation of cerebrospinal fluid from individuals with granulomatous amebic meningoencephalitis may disclose hypoglycorrhachia and elevated protein, but amebae are not usually seen. Evaluation of biopsies of lesions of skin or brain usually provides the definitive diagnosis. *Acanthamoeba* spp. can be identified on histopathology, and may be cultured on nutrient agar overlaid with *Escherichia coli*. Radiographic imaging of the central nervous system is often helpful.

Treatment

No single drug is effective against systemic *Acanthamoeba* spp. infection. Combinations of treatment with amphotericin B, miltefosine, azithromycin, voriconazole, posaconazole, isavuconazole, fluconazole, 5-fluorocytosine, pentamidine, metronidazole, rifampicin, sulfadiazine and other agents have been attempted, with success in some cases and failure in other cases that used similar regimens. Most individuals with systemic amebiasis do not survive, regardless of therapy. Individuals with acanthamebic keratitis are usually treated topically and may require corneal grafting.

SYSTEMIC COCCIDIOSIS: TOXOPLASMOSIS

Toxoplasmosis is caused by *Toxoplasma gondii*. Asymptomatic disease is common. Symptomatic disease usually occurs in persons with suppressed cell-mediated immunity and infants born with congenital infection.

Epidemiology and Life Cycle

Understanding the life cycle of *T. gondii* is important in understanding the disease process. The parasite is found worldwide. It has both sexual and asexual stages, the latter being the pathogenic stage in humans and other animals. Cats are the definitive host, and in the feline, oocysts develop after an intestinal intraepithelial sexual cycle. Oocysts are then passed in cat feces, and after 2 to 3 days become infectious. They may persist in soil. If ingested by humans or other animals (sheep, pigs, rodents, or cats), oocysts produce rapidly dividing tachyzoites. Tachyzoites invade varying cell types and result in cell death and tissue necrosis. Eventually the host immune response curtails this process, and tachyzoites give rise to slowly dividing bradyzoites, which encyst and persist indefinitely in host tissues. Bradyzoites are infectious if ingested, giving rise to tachyzoites in the new host. Bradyzoites may also revert to tachyzoites if a host becomes immunocompromised, leading to “reactivation” of disease. Humans and other animals may be infected, not only by ingestion of oocysts, but also by ingestion of tissue cysts, such as following the consumption of undercooked infected meat. Toxoplasma infection may also be acquired by transplacental passage of tachyzoites, resulting in congenital infection, or by organ transplantation.

Serologic studies demonstrate a wide geographic variation in prevalence of infection between 10% and 90%. In the United States, rates range from 3% in Denver, Colorado, to 17% in Massachusetts, and 30% in Birmingham, Alabama.

Clinical Features

Infection may be primary or due to reactivation. After ingestion of infectious oocysts or tissue cysts, tachyzoites disseminate and invade organs, replicating intracellularly. Acute infection may result in tachyzoites being found in all organs, especially muscle, lymphatic tissue, and the central nervous system. Primary infection may be subclinical or asymptomatic. If symptomatic, the most common manifestations of acute disease include fever, painless lymphadenopathy, and a mononucleosis-like syndrome. More rarely pneumonitis, myocarditis, and myositis may occur.

Congenital infection is usually the result of primary infection in the mother, with transplacental passage of tachyzoites resulting in infection of the fetus. Infected infants may be symptomatic at birth, or may have hepatosplenomegaly, pneumonitis, myocarditis, rash, or jaundice. Congenitally infected children may be asymptomatic initially, but may subsequently develop central nervous system or ocular manifestations.

Reactivation disease occurs in persons who are immunocompromised, particularly those with deficiency in cell-mediated immunity. Patients with organ or bone marrow transplants or who have HIV infection and CD4 cell counts less than 100 cells/mm^3

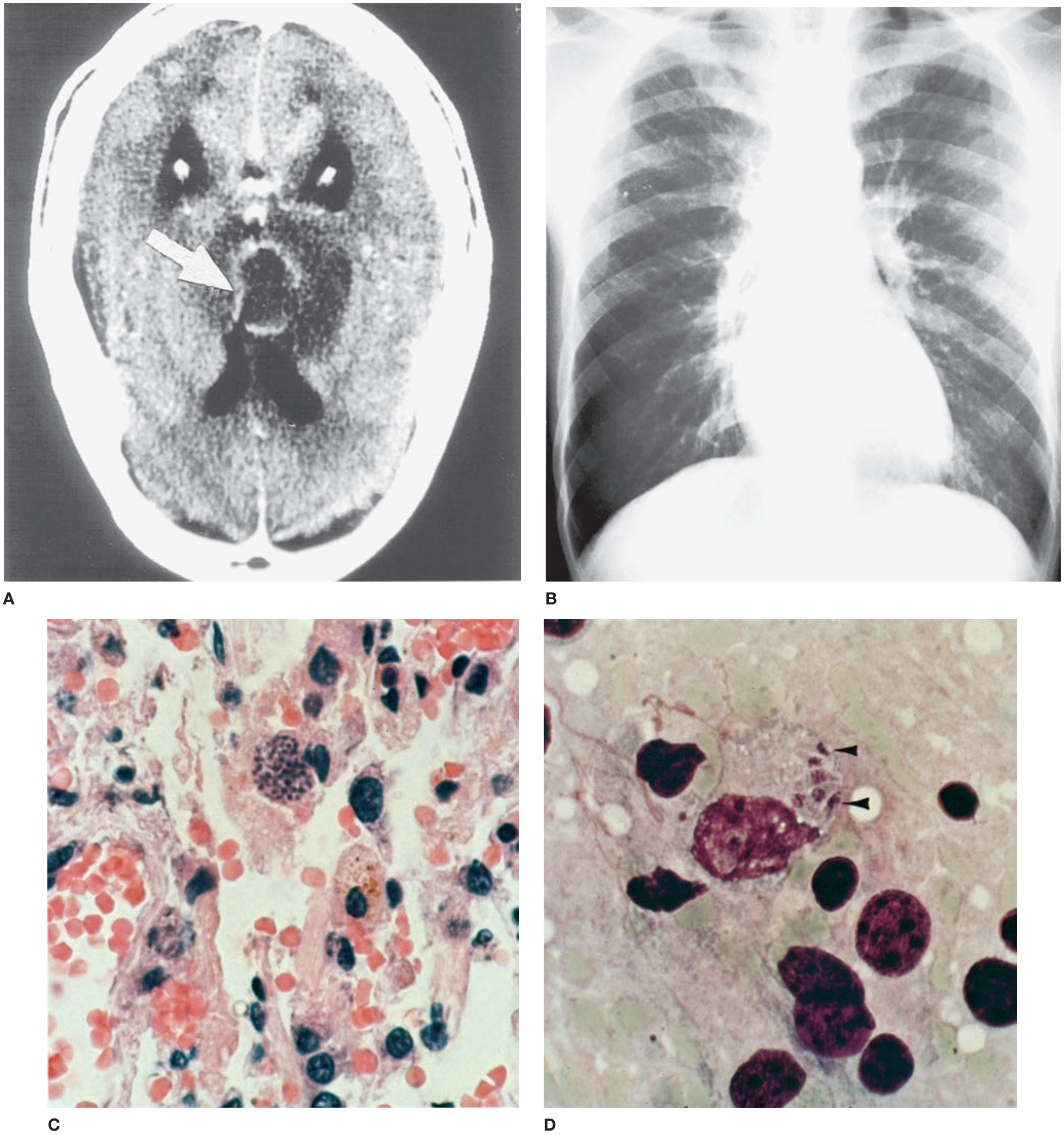

Figure 135-5 *Toxoplasma gondii* in the brain and lung of a patient with AIDS. **A.** Brain CT scan shows *Toxoplasma* abscess as a contrast-enhancing lesion *(arrow)*. **B.** Chest radiography. Diffuse bilateral infiltrates and hilar adenopathy. **C.** Lung biopsy shows *Toxoplasma* forms (arrow, cyst, hematoxylin & eosin stain, ×100). **D.** Impression smear of brain biopsy shows five intracellular tachyzoite (trophozoite) forms (*arrowheads*; Giemsa stain ×1500). *(C and D are Reproduced with permission from Dr. Y. Gutierrez.)*

are at particular risk of life-threatening disease. For those with HIV, although primary infection may occur in these individuals, reactivation disease is most common. Reactivation disease may be prevented in those at particular risk with the prophylactic use of trimethoprim–sulfamethoxazole. Necrotizing central nervous system disease is the most common manifestation of reactivation toxoplasmosis in AIDS patients. Affected individuals usually present with altered mental status, fever, headache, and clinical findings suggestive of focal CNS disease, and neuroimaging often reveals multifocal, ring-enhancing lesions.

■ Pulmonary Disease

Pulmonary involvement in toxoplasmosis is common, and is usually reported in patients with AIDS or in individuals who have undergone bone marrow or solid-organ transplantation (Fig. 135-5).[7–9]

Shortness of breath and cough are the most common presenting symptoms of pulmonary involvement during toxoplasmosis. In one review, immunocompetent patients with toxoplasmic pneumonitis were more likely than immunocompromised individuals to have evidence of hepatosplenomegaly at presentation, but clinical findings were otherwise similar. Bilateral interstitial pulmonary infiltrates are most often evident in radiography; however, a variety of other findings, from discrete pulmonary opacities to cavitary disease, also have been described. Severe disease or the acute respiratory distress syndrome (ARDS) may develop. *T. gondii* organisms can invade myocytes, and during acute or reactivation disease, myocarditis may occur and may be severe.

■ Diagnosis

In primary toxoplasmosis, the differential diagnosis is broad, but IgM-specific antibodies will usually be present. During reactivation of toxoplasmosis, IgM and IgG antitoxoplasma antibodies are usually present in serum. Absence of antitoxoplasma IgG antibodies makes the diagnosis of reactivation toxoplasmosis unlikely, but the presence of the antibody itself does not differentiate between latent and active diseases.

Biopsy can confirm the diagnosis. Polymerase chain reaction (PCR) analysis of blood, tissue samples, or cerebrospinal fluid is sensitive, and PCR analysis of amniotic fluid is particularly helpful in the antenatal diagnosis of congenital infection. PCR has been used to detect toxoplasma in sputum specimens, but the sensitivity of this method for diagnosing pulmonary toxoplasmosis has not yet been determined. In pulmonary disease, microscopic or molecular analysis of bronchoalveolar lavage fluid or open lung biopsy may be required for confirmation of the diagnosis.[10]

■ Treatment

Except in the case of pregnant women or individuals with severe or persistent symptoms, primary toxoplasmosis in immunocompetent individuals usually does not require treatment. Reactivation disease in immunocompromised individuals is usually treated for the duration of the period of immunosuppression, as therapy does not fully eradicate the parasite; this is often done with a combination of treatment followed by ongoing prophylaxis. Standard therapy is pyrimethamine and a sulfonamide, usually sulfadiazine. Leucovorin is added to overcome the bone marrow suppressive effects of pyrimethamine. Clindamycin or atovaquone may be used as an alternative in those intolerant of sulfonamides. Trimethoprim-sulfamethoxazole may also be used if sulfadiazine/pyrimethamine is not available. After acute disease has been controlled, secondary suppressive therapy should be continued for the duration of immunosuppression to prevent relapse. Unfortunately, mortality in immunocompromised patients with *Toxoplasma* pneumonia diagnosed antemortem has been as high as 40%.

INTESTINAL COCCIDIOSIS: CRYPTOSPORIDIOSIS

Cryptosporidium spp. *(C. hominis/parvum* and *C. muris)* are intracellular protozoans that mainly cause intestinal pathology (Fig. 135-6). Disease may occur in immunocompetent hosts but is more common and severe in immunocompromised individuals, particularly in patients with AIDS, in whom cryptosporidiosis may result in severe and persistent diarrhea. The organism also causes infection in a variety of animals, and fecal contamination of water or food is a common source of infection in humans, although person-to-person transmission also occurs.

The life cycle of *Cryptosporidium* spp. begins when the infectious oocyst is ingested. These organisms, which are 4 to 5 μm in diameter, may remain viable in the environment for months. After ingestion, they excyst in the small intestine and release four motile sporozoites, which invade epithelial cells of the intestinal wall. Asexual maturation then results in merozoites being released back into the intestinal lumen. These merozoites either result in reinvasion of epithelial cells or undergo maturation to become oocysts. The oocysts may then be excreted or may excyst while still in the lumen to "autoinfect" the host.

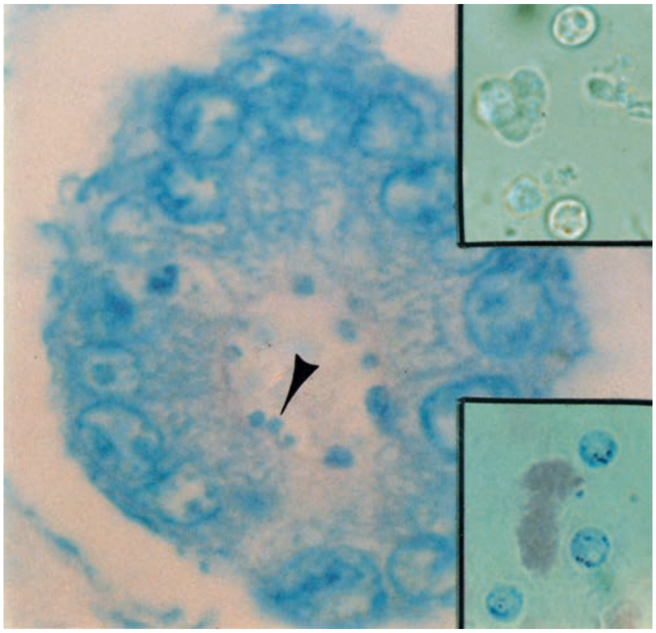

Figure 135-6 *Cryptosporidium parvum* infecting an intestinal crypt *(arrowhead)*. Parasites line the apical surface of the epithelial cells and are covered by host membranes. *Insets*: Oocysts isolated from feces. Upper, organisms isolated after a Sheather's sugar flotation, ×1360. Lower, Giemsa–Jenner stain, ×1360. *(Reproduced with permission from J.A. Fishman, Massachusetts General Hospital.)*

■ Clinical Features

Cryptosporidial infection may be asymptomatic, or it may be associated with a range of illness from mild diarrhea to severe gastroenteritis. Invasion of the intestinal epithelium results in secretory diarrhea. The biliary tree may be infected, causing cholangitis, and hepatitis and pancreatitis also have been described. Infection may be associated with systemic symptoms such as malaise, nausea, and abdominal cramps. In some patients, diarrhea is voluminous and has been described as "cholera-like." In patients with a normal immune system, cryptosporidial diarrhea usually resolves within 2 weeks. In immunocompromised individuals, especially those with HIV infection and CD4 cell counts less than 100 cells/mm^3, symptoms often continue until the immune status of the individual is restored. In such individuals, cryptosporidiosis may result in a severe wasting syndrome.

■ Pulmonary Cryptosporidiosis

Respiratory infection with *Cryptosporidium* spp. is rare but has been reported, usually in patients with AIDS (Fig. 135-7).[11] Pulmonary involvement, as with other extraintestinal manifestations of cryptosporidiosis, usually occurs in the setting of intestinal disease. At least one case of pulmonary infection, however, has been reported with no apparent evidence of intestinal infection. Pulmonary involvement may appear as an interstitial infiltrative process or as areas of focal consolidation. In a series of 47 organ transplant recipients with cryptosporidiosis, only 1 had pulmonary involvement.[12]

Some authors suggest that the prevalence of pulmonary cryptosporidiosis is underestimated, and one study reported a prevalence of 17% in HIV-positive patients with respiratory symptoms. Pulmonary cryptosporidiosis with *C. baileyi*, an avian parasite, has also been reported in a human with a pulmonary hamartoma.[13]

■ Diagnosis

Cryptosporidium may not be cultured in vitro, and diagnosis of cryptosporidiosis relies largely on demonstration of pathologic

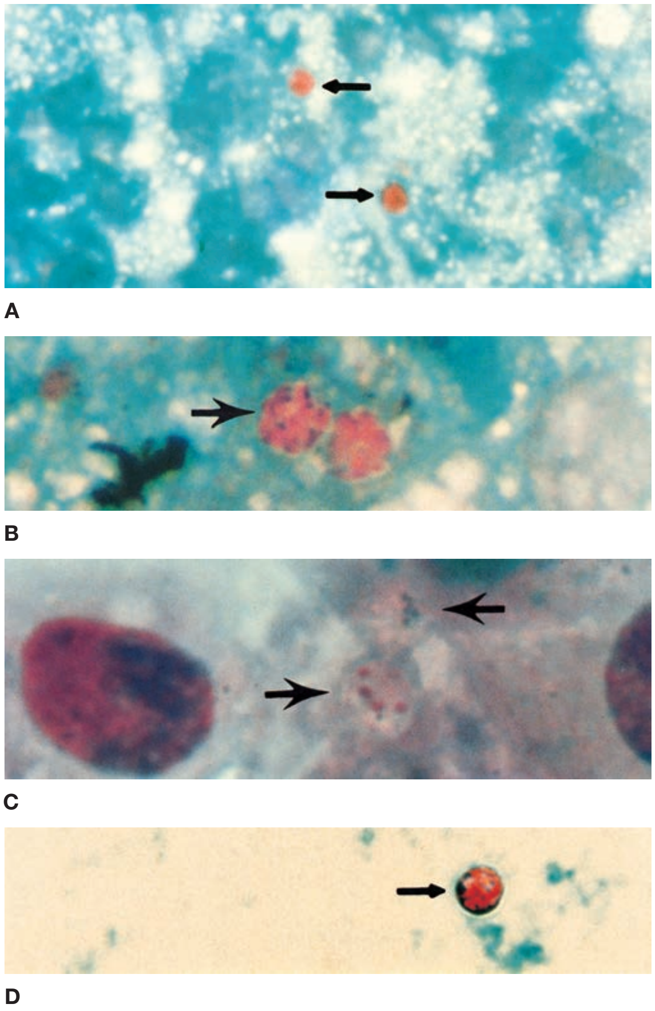

Figure 135-7 Pulmonary cryptosporidiosis. **A.** Touch preparation from a lung biopsy of a patient with AIDS. *Arrows* show organisms stained with a modified acid-fast stain (modified cold Kinyoun, MCK), which stains the organisms red (×880). **B.** Same preparation and stain as (**A**) showing internal red-black dense granules *(arrow)* characteristic of the organism. **C.** Same preparation as (**A**) showing similar morphology *(arrow)* using a rapid Giemsa Hemacolor stain. **D.** Sputum stained with MCK technique reveals organisms *(arrow)*. *(Reproduced with permission from Dr. P. Ma.)*

findings in tracheal or bronchial tissues, and visualization of cryptosporidial cysts by microscopy. The cysts may be best seen by acid-fast staining of specimens. Oocysts have been detected in bronchoalveolar lavage, open lung biopsy, and sputum specimens.

■ Treatment

Nitazoxanide decreases diarrhea in immunocompetent individuals with intestinal cryptosporidiosis. However, reliable efficacy has not been demonstrated in individuals with disseminated cryptosporidial disease, or those who are immunocompromised. Thus, in most individuals, treatment is predominantly supportive while attempts are made to restore immune function; in patients with AIDS, this is chiefly through the use of antiretroviral therapy. In addition to nitazoxanide, other agents have been administered to individuals with cryptosporidiosis, although efficacy has not been demonstrated. Administered agents have included paromomycin, trimethoprim–sulfamethoxazole, rifaximin, and metronidazole. Anecdotally, azithromycin has been successfully combined with paromomycin in the therapy of pulmonary infection.

CYCLOSPORIASIS

Cyclospora cayetanensis is a protozoan organism usually associated with diarrheal illness in humans. It is ubiquitous and transmitted usually as a result of contamination of food or water. The protozoan is usually detected as an approximately 10-μm organism on acid-fast stains of specimens. Infection usually responds to trimethoprim–sulfamethoxazole. There are rare case reports of possible pulmonary cyclosporiasis. A 60-year-old Brazilian man with a history of treated tuberculosis was found to have *C. cayetanensis* organisms in sputum specimens examined for evaluation of respiratory distress and pulmonary infiltrates. No other organisms were detected, and the patient's symptoms resolved following administration of trimethoprim–sulfamethoxazole (and treatment of concomitant intestinal parasitosis). A similar case report from Egypt demonstrated infection with *C. cayetanensis* after treatment for tuberculosis.[14]

SARCOCYSTIS

Sarcocystis spp. are intracellular protozoal coccidian two-host parasites. Humans can be a definitive host for *Sarcocystis hominis* and *Sarcocystis suihominis,* and following ingestion of tissue cysts in undercooked beef *(S. hominis)* or pork *(S. suihominis)*, can develop acute gastroenteritis and excrete oocysts. Alternatively, humans can ingest the oocysts of other predator animals and develop a vasculitis that can manifest as myositis or cardiomyositis, or may involve the lungs, kidneys, and liver. Eosinophilia is prominent. Eventually the parasites encyst in musculature, including cardiac tissue. Diagnosis is usually based on clinical recognition, myositis associated with eosinophilia and a negative trichinella serology, and/or biopsy of muscle. Treatment is usually supportive, often involving steroids. Cases are usually sporadic, although recurrent outbreaks have been associated with Tioman and nearby islands in Malaysia.[15,16]

MALARIA

Malaria in humans is the result of infection by one of five species of plasmodia: *Plasmodium falciparum*, *P. vivax*, *P. ovale*, *P. malariae*, and *P. knowlesi*. Human malaria is endemic in parts of sub-Saharan Africa, India, Southeast Asia, the Caribbean, and Central and South America. Hundreds of thousands of deaths annually are attributed to malaria, usually among pregnant women and children under the age of 5 years who live in endemic areas, especially in sub-Saharan Africa. The majority of malaria-related fatalities are a result of infection with *P. falciparum*.

Malaria is acquired by the bite of an infective female *Anopheles* sp. mosquito. In nonendemic areas, malaria cases are found largely in travelers who have returned from malaria-endemic areas, but the parasite also may be transmitted by contaminated blood products, in utero from mother to child, and by organ transplantation. Malaria infection in persons coinfected with HIV is associated with increased HIV viral load and increased symptoms in the setting of parasitemia.

■ Life Cycle

When bitten by an infective mosquito, malarial sporozoites enter the host and travel to the liver, where they invade hepatocytes and divide, forming tissue schizonts in an asymptomatic stage. These schizonts then rupture, releasing thousands of daughter merozoites into the bloodstream. These merozoites invade erythrocytes and develop to form mature ring forms and, ultimately, erythrocytic schizonts. A small percentage of merozoites develop into sexual forms called gametocytes. Gametocytes do not cause symptoms, but when another mosquito bites an infected human host, the gametocytes are ingested by the feeding mosquito, permitting the malarial life cycle to continue. *P. falciparum* may infect red blood cells of all ages, resulting in the potential for very high levels of parasitemia.

Infection with *P. vivax* and *P. ovale* may result in a dormant liver phase in which parasites remain in the liver in the form of hypnozoites, potentially causing relapse many months after first infection. *P. falciparum* and *P. malariae* do not have such a dormant stage, and do not cause late relapsing disease. *P. knowlesi* is a simian malarial parasite that has been diagnosed in humans in areas of Asia.

Pathogenesis

Malaria-related morbidity and mortality occurs predominantly in children and pregnant women. Most individuals who live in endemic areas develop partial immunity to symptomatic disease as they age. This immunity does not prevent infection, but it reduces the frequency of symptoms and severity of disease despite ongoing parasitemia. Infection with any of the five species of malaria causes hemolysis, resulting in anemia that may be severe.

Certain genetic traits associated with hemoglobin structure or erythrocyte surface antigens are associated with decreased infection rates or decreased symptomatic disease. For example, absence of the Duffy antigen on the surface of erythrocytes protects against *P. vivax* infection, and sickle cell trait is protective against severe *P. falciparum* infection. *P. falciparum* also causes the formation of "sticky knobs" on the surface of infected erythrocytes. These knobs comprise host cell and parasite antigens, and they mediate binding of infected erythrocytes to endothelial surfaces. This binding results in sequestration of infected erythrocytes, and may result in "sludging" of blood flow. This sequestration and sludging contributes to microvascular obstruction that can result in organ dysfunction.

Clinical Features

Patients with malaria typically present with fever and a constellation of other nonspecific symptoms such as headache, chills, and myalgias. Vomiting, nausea, diarrhea, and cough also may be present. Anemia, thrombocytopenia, and hepatosplenomegaly may be present. Sequestration of infected erythrocytes in the brain may cause cerebral malaria. Individuals with cerebral malaria may present with altered mental status, seizures, focal neurologic findings, or coma. Even with treatment in modern intensive care units, mortality during cerebral malaria is high. Other organ-specific complications of infection are also largely related to microvascular sequestration of parasitized red blood cells in specific tissues, and may manifest as placental, renal, or pulmonary dysfunction (Fig. 135-8).

Pulmonary Features

Pulmonary symptoms such as cough and increased respiratory rate are common during malaria.[17] In African children, malaria frequently presents with symptoms and signs suggestive of pneumonia. Metabolic acidosis is an important cause of respiratory distress in these children, but pneumonitis as a result of sequestered parasitized red blood cells is also responsible. In more severe disease, noncardiogenic pulmonary edema may develop. Initial acute lung injury may progress to ARDS (Fig. 135-9).[18] Tachypnea and dyspnea, followed by hypoxemia and respiratory failure, may develop. Studies have confirmed the development of impaired alveolar–capillary membrane function in patients with severe malaria. Lung injury in severe disease is postulated to be not only the result of pulmonary microvascular sequestration, but also a consequence of the inflammatory response to infection.

In a study of uncomplicated symptomatic malaria, altered pulmonary physiology, including increased airflow obstruction, decreased gas transfer, impaired ventilation, and increased pulmonary phagocytic activity were found in both *P. vivax*– and *P. falciparum*–associated infections, but were worse in cases of *P. falciparum* malaria.[19] ARDS has also been reported in cases of malaria caused by *P. vivax*, and one case of pulmonary edema has been reported complicating

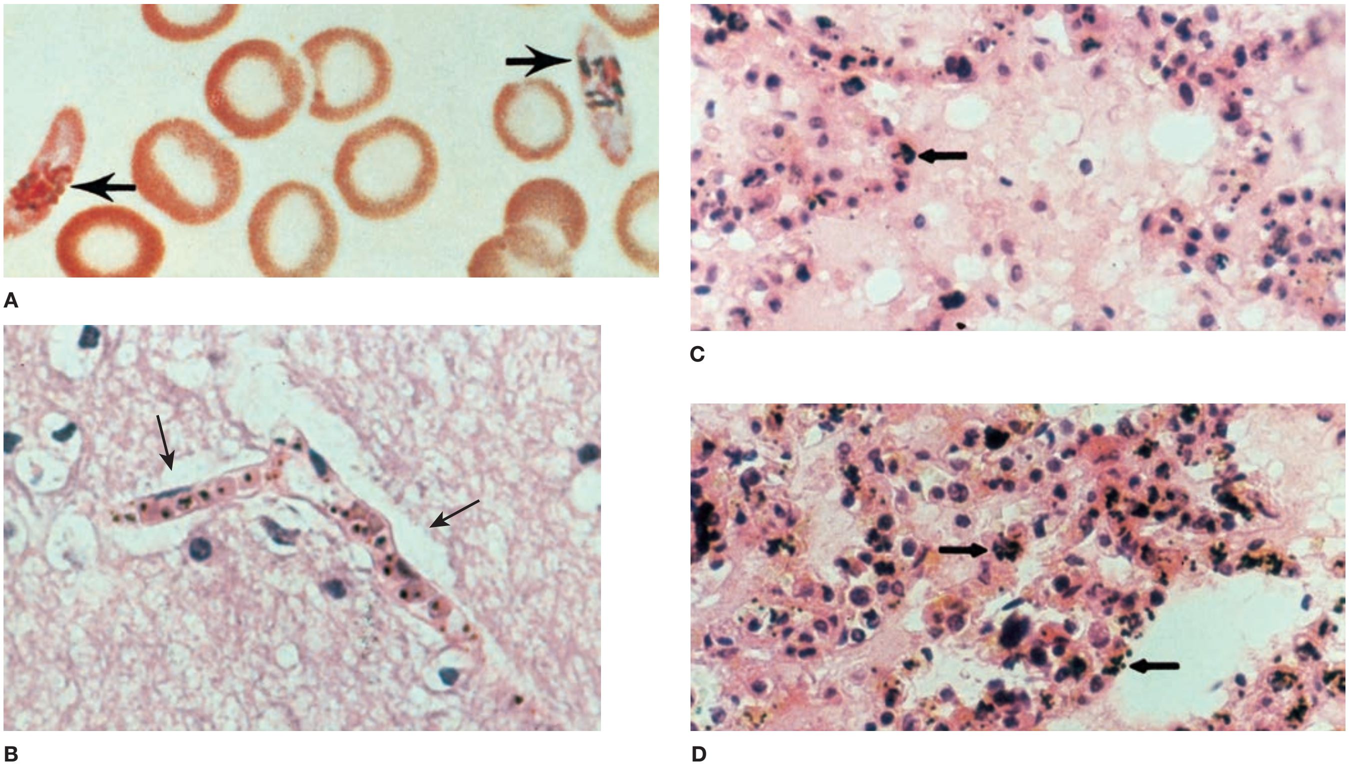

Figure 135-8 *Plasmodium falciparum*. **A.** Banana-shaped gametocytes on peripheral blood smear *(arrows)*. This form is only seen with falciparum malaria (Wright stain, ×1375). **B.** Cerebral vessels obstructed by parasitized red blood cells *(arrow)* with surrounding edema (hematoxylin and eosin stain, ×1375). **C.** Acute pulmonary edema due to pulmonary venular occlusion (organism at *arrow*; hematoxylin and eosin). **D.** Deposition of malarial pigment *(arrows)* in vicinity of occluded pulmonary vessels.

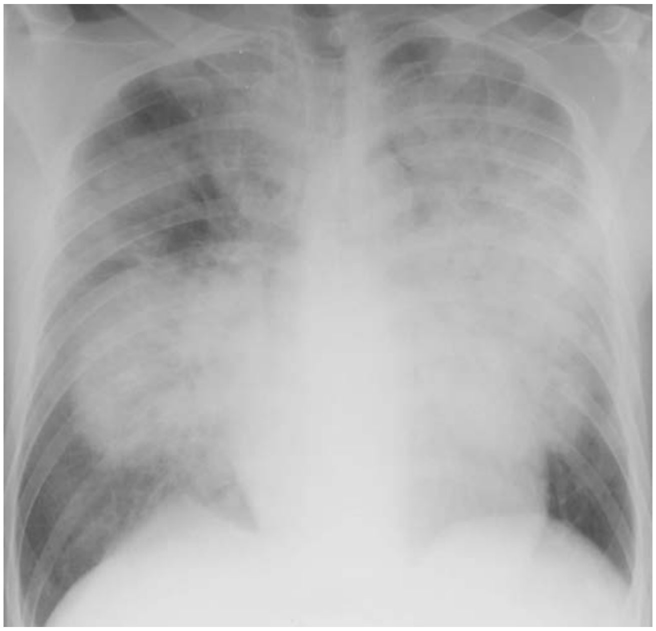

Figure 135-9 ARDS in a 31-year-old man with *P. falciparum* malaria. Chest radiograph demonstrates patchy bilateral areas of increased opacity. *P. falciparum* trophozoites were found in a thick blood smear. *(Reproduced with permission from Martinez S, Restrepo CS, Carrillo JA, et al. Thoracic manifestations of tropical infections: a pictorial review. RadioGraphics. 2005;25(1):135–155.)*

a case of *P. ovale* malaria.[20] Pulmonary involvement also occurs during *P. malariae* infection;[21] however, significant pulmonary morbidity is largely confined to infection by *P. falciparum* and usually occurs in the context of multisystem involvement. The principal differential diagnosis for pulmonary disease in malaria infection is metabolic acidosis and bacterial pneumonia.

■ Diagnosis

The diagnosis of malaria should be considered in any symptomatic patient who has had exposure to the parasite in a malaria-endemic area. Rare cases of transmission by blood products, organ transplantation, or congenital infection also have occurred. Individuals with malaria caused by *P. falciparum* usually develop symptoms within 3 months of the mosquito bite, and usually within 1 month. Since *P. vivax* and *P. ovale* have potentially dormant liver phases, individuals infected with these parasites may not develop symptoms for many months after exposure (usually within 1 year of the mosquito bite).

Malaria is usually diagnosed through microscopic examination of blood smears, or with antigen-based rapid diagnostic tests (RDTs).

■ Treatment

Appropriate treatment of individuals with malaria depends on the infecting species, severity of disease, age and pregnancy status, and the ability of the patient to take drugs by mouth. Non-falciparum malaria is generally susceptible to chloroquine phosphate, although to date, resistance has been reported in parts of Indonesia, Papua New Guinea, India, Myanmar, and Brazil. The World Health Organization now recommends that individuals with chloroquine-resistant *P. falciparum* malaria be treated with artemisinin-based combination therapies (ACTs) that include an artemisinin derivative with a second agent such as lumefantrine, amodiaquine, pyronaridine, piperaquine, or mefloquine. Less optimal alternatives include oral atovaquone–proguanil or mefloquine, or quinine sulfate in combination with either doxycycline or clindamycin. Individuals with severe disease can receive intravenous artesunate in the United States, followed by an oral combination therapy. Less optimal alternatives include parenteral quinine dihydrochloride or quinidine gluconate with a second agent.

Individuals with malaria caused by *P. vivax* or *P. ovale* also should be treated with primaquine to treat the hypnozoite form of disease. Primaquine should not be administered to individuals deficient in glucose-6-phosphate dehydrogenase or to pregnant women. Pulmonary manifestations and other organ-specific complications of severe infection are treated supportively. Mechanical ventilation may be required. Early institution of renal replacement therapy may prevent subsequent development of ARDS in severe malaria. Exchange transfusion has been used for patients with severe falciparum-associated disease with parasitemia levels over 5%, although data on efficacy are controversial.

BABESIOSIS

Babesiosis is a tick-borne infection usually caused by *Babesia microti* in the United States, and *Babesia divergens* in Europe. In the United States, the majority of cases occurs in New England, Mid-Atlantic and Upper Mid-West. Transmission also may occur as the result of infected blood transfusions.

Babesia parasites invade, multiply within, and lyse red blood cells. In immunocompetent hosts, disease is most commonly asymptomatic or relatively mild, and characterized by fever, flu-like illness, myalgias, and nausea. More severe manifestations may include thrombocytopenia, hemolytic anemia, jaundice, meningismus, noncardiogenic pulmonary edema, disseminated intravascular coagulation, hypotension, and shock. Severe disease is most common among the elderly or individuals with compromised immunity. Asplenic individuals are at particular risk of severe disease, and individuals infected with HIV or following organ transplantation are at particular risk of persistent disease. Pulmonary disease in babesiosis occurs in association with multisystem disease, and usually presents as ARDS or noncardiogenic pulmonary edema or ground-glass opacification.[22,23]

The diagnosis of babesiosis should be considered in any patient with appropriate exposure history who presents with fever or a sepsis syndrome. Diagnosis is usually confirmed by microscopic examination of peripheral blood. Atovaquone, azithromycin, quinine, and clindamycin all have anti-*Babesia* activity; combination therapy is usually administered; exchange transfusion can also be considered.

TRYPANOSOMIASIS

American and African trypanosomiasis are considered below.

■ American Trypanosomiasis (Chagas Disease)

Chagas disease is caused by infection with *Trypanosoma cruzi*, a protozoan parasite transmitted to humans most often via the feces of an infected reduviid bug. The disease is endemic in certain South and Central American countries. Infection has also occurred following solid organ transplantation including lung.[24]

Clinical manifestations may occur acutely after initial infection. More commonly, clinical manifestations may not become evident until years or decades after initial infection. When acute symptoms do occur, they may include fever, peripheral edema, hepatosplenomegaly, and myocarditis. Chronic sequelae may occur in up to one-third of infected individuals and usually involve the heart, esophagus, or large bowel (Fig. 135-10).

Cardiac disease usually manifests clinically as congestive-dilatory cardiomyopathy.[25] Chronic dilatation of the esophagus or colon resulting from denervation of the gut may result in Chagasic megaesophagus or megacolon. Acute myocarditis may result in pulmonary edema. Pulmonary involvement during Chagas disease is usually secondary to cardiac or intestinal disease, and may include pulmonary edema secondary to congestive heart failure, pulmonary hypertension secondary to right-sided dilatory cardiomyopathy, or aspiration pneumonia secondary to vomiting and regurgitation associated with megaesophagus or megacolon. Recurrent aspiration and pneumonitis may lead to lung abscesses, fibrosis, scarring, and bronchiectasis. The debilitation of chronic Chagas disease may lead to cachexia, and may be associated with a higher rate of tuberculosis. In an autopsy review of 69 adult cases of Chagasic megaesophagus in Brazil, 35% of patients had pneumonia, and 22% had pulmonary tuberculosis—rates that were higher than in a cohort of patients in the same study who had Chagasic cardiac disease but no megaesophagus.

Congenital Chagas disease has been associated with pneumonitis; in an autopsy review of 10 congenital cases, pathologic findings have included diffuse pulmonary interstitial edema and endothelial swelling in lung tissues.

Diagnosis in acute Chagas disease may be made by detecting parasites on blood smear. Culture of parasites from specimens is possible using specialized media, although the usefulness of this method is limited because culture may take several weeks.

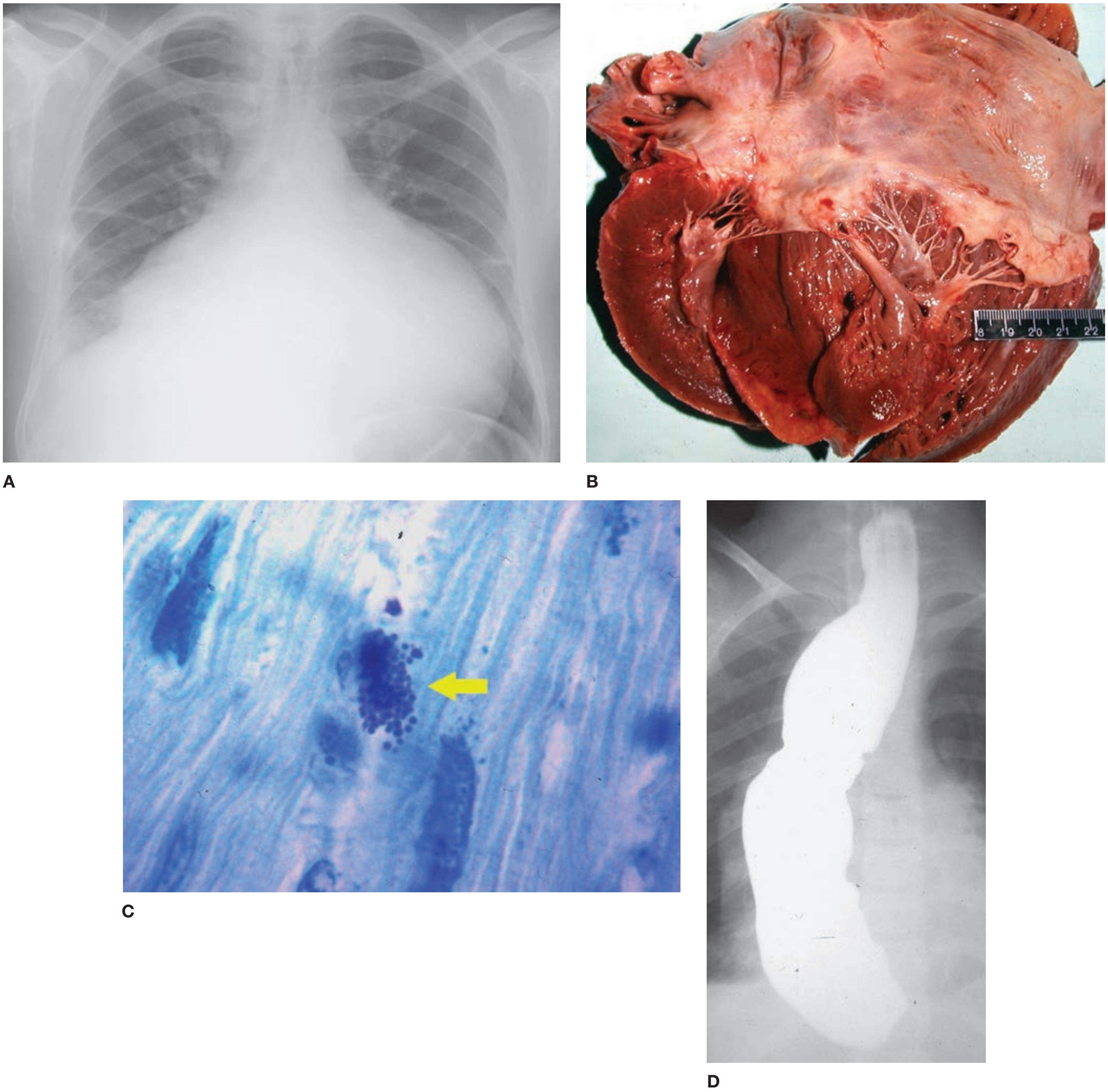

Figure 135-10 Chronic Chagas disease in a 39-year-old man with chronic dilated cardiomyopathy. **A.** Chest radiograph shows global cardiomegaly with pulmonary congestion. **B.** Photograph of the gross specimen demonstrates dilatation of the cardiac chambers with thickening of the ventricular myocardium. Scale is in centimeters. **C.** Low-power photomicrograph (original manifestation, ×10; Giemsa stain) shows *T. cruzi* amastigotes within a myofiber *(arrow)*. **D.** Chagasic achalasia in a 13-year-old girl with Chagas disease. Barium esophagogram shows diffuse and severe dilatation of the esophagus. Histologic analysis demonstrated *T. cruzi* amastigotes within the esophageal wall. *(Reproduced with permission from Martinez S, Restrepo CS, Carrillo JA, et al. Thoracic manifestations of tropical infections: a pictorial review. RadioGraphics. 2005;25(1):135–155.)*

In chronic disease, parasites are not usually visualized. Diagnosis is usually based on serologic analysis, suggestive radiology, PCR analysis, and, more rarely, pathologic examination of tissues. Treatment in acute disease and in patients with immunosuppression is warranted, and nifurtimox and benznidazole are the mainstays of therapy. The utility of treating individuals with established, chronic disease with antiparasitic agents is currently unclear.

African Trypanosomiasis (African Sleeping Sickness)

Trypanosoma brucei gambiense and *Trypanosoma brucei rhodesiense* are the causative agents of African trypanosomiasis (African sleeping sickness). African sleeping sickness is usually transmitted by the bite of an infective tsetse fly. East African trypanosomiasis is caused by *T.b. rhodesiense*. Individuals with East African trypanosomiasis are often acutely ill with fever, lymphadenopathy, headache, and myalgia. Disease may be fulminant, and individuals may develop disseminated intravascular coagulopathy, ARDS, hypotension, and shock. The most common pulmonary manifestations during acute disease are noncardiogenic pulmonary edema and ARDS. West African trypanosomiasis is caused by *T.b. gambiense*. Individuals with West African trypanosomiasis usually do not develop severe disease during the acute stage. Rather, months or years after initial infection, infected individuals present with mental status changes, personality changes, recurrent fever, lymphadenopathy, weight loss, and disorders of circadian rhythm. QTc prolongation can occur.[26]

The most common pulmonary manifestation during late-stage disease is pneumonitis second to recurrent aspirations associated with inanition and altered mentation. Direct pulmonary involvement is not common in West African trypanosomiasis. A single case report describes an African child who presented with severe respiratory symptoms and was later found to have African trypanosomiasis.

LEISHMANIASIS

Leishmaniasis is caused by an intracellular protozoa parasite in the *Leishmania* genus. The *Leishmania* parasites are widely distributed and are usually transmitted through the bite of an infective sand fly. Infection of humans may be asymptomatic or may involve the skin (cutaneous leishmaniasis), the mouth or nose (mucocutaneous leishmaniasis), or be systemic (visceral leishmaniasis). Human infection is most common in South and Central Asia, the Middle East, the Mediterranean, Balkans, North Africa, sub-Saharan Africa, and Central and South America. Specific organisms are often responsible for specific clinical syndromes, although overlap occurs. Disease is often considered as “New World” or “Old World,” based on geographic location. The parasite exists as an intracellular organism (amastigote) in host macrophages, and as an extracellular promastigote in the sandfly gut—being inoculated into the host’s skin during the bite of the fly.

Clinical Features

Cutaneous syndromes may range from localized disease, usually on exposed areas of skin, to widespread cutaneous involvement. In localized disease, painless ulcers develop and most often resolve spontaneously over months. Classically, “Old World” cutaneous leishmaniasis is caused by *L. major*, *L. tropica*, *L. aethiopica*, or *L. infantum*; “New World” cutaneous disease is usually caused by *L. braziliensis* or *L. mexicana* complex organisms. Some New World species are associated with the development of mucocutaneous disease months to years after resolution of the initial skin lesions. Severe destruction and disfiguration of the face with resultant aspiration pneumonitis may occur.

Visceral leishmaniasis is usually caused by *L. donovani*, *L. infantum*, or *L. chagasi*. Individuals with visceral leishmaniasis usually present with fever, hepatosplenomegaly, weight loss, pancytopenia, and hypergammaglobulinemia. Lymphadenopathy is commonly present. Gastrointestinal symptoms are common in advanced disease, and individuals with untreated visceral leishmaniasis develop a wasting syndrome. Pneumonia and tuberculosis may be the cause of death.

Pulmonary Disease

Pulmonary involvement from leishmaniasis in immunocompetent hosts is rare, but interstitial pneumonitis has been reported. However, immunosuppressed patients, particularly those with HIV infection, are at increased risk of atypical disease. In areas surrounding the Mediterranean, where seroprevalence for *L. infantum* in young adults may be as high as 30%, an increase in the incidence of HIV infection has caused an increase in the number of advanced cases of visceral leishmaniasis—a result either of new infections or reactivation of old infections. Patients with leishmaniasis and HIV infection may present with cough, dyspnea, hemoptysis, granulomatous mediastinal lymphadenopathy, solitary pulmonary nodules, or pleural effusions. Advanced visceral leishmaniasis may be complicated by suprainfecting pneumonia even in immunocompetent hosts.[27]

Treatment of leishmaniasis depends on type of disease (cutaneous vs. mucocutaneous vs. visceral), infecting species, parasite resistance patterns, severity of disease, and status of the host. Therapeutic options include liposomal preparations of amphotericin, amphotericin B, pentavalent antimony (sodium antimonylgluconate or N-methylglucamine antimonate), pentamidine, and miltefosine.[28]

CILIATE INFECTIONS: *BALANTIDIUM COLI*

Balantidium coli is the only ciliated protozoa that infects humans. Infection of humans usually occurs in individuals with contact with pigs, and human disease usually manifests as an infectious colitis very similar to amebiasis. Rare cases of pulmonary infection have been reported in humans: in a leukemic patient who presented with pulmonary lesions, in a 71-year-old woman with anal cancer and pneumonia, and in a patient with chronic colitis and an intrapulmonary mass.[29,30]

Diagnosis is usually made through histologic examination of tissue samples. Treatment with tetracycline, metronidazole, or iodoquinol is usually effective.

FLAGELLATES

Two flagellates are discussed briefly below: *Trichomonas* species and *Giardia lamblia*.

Trichomonas Sp.

Trichomonads are flagellated protozoa. Pulmonary disease has been attributed most commonly to *Trichomonas tenax*, an organism that is most often considered a commensal in the human oropharynx, especially in individuals with poor oral hygiene. In one study of symptomatic patients, prevalence of *T. tenax* by PCR among 100 immunocompromised and 100 patients with chronic pulmonary disease was 10%.[30]

Diagnosis is most often made by examination of a wet mount of sputum or bronchoalveolar lavage specimen. Chronic purulent, necrotic pulmonary disease, or pleural involvement has been described, often thought to be a result of aspiration.[31] Affected individuals have responded to metronidazole therapy.

Giardia Lamblia

Giardia lamblia is a pathogenic intestinal flagellate of humans. In humans, it usually causes chronic diarrhea and malabsorption. There is one case report of uncertain significance of recovery of *G. lamblia* trophozoites from bronchoalveolar lavage fluid.

MICROSPORIDIOSIS

Microsporidia is the name given to a group of spore-forming obligate intracellular organisms from the phylum *Microsporidia*. These organisms have been variously considered with the protozoa and fungi. More than 1400 microsporidia species occur worldwide, but the most common human pathogens are *Enterocytozoon*, *Encephalitozoon*, *Nosema*, *Pleistophora*, and *Septata* spp.

The microsporidia spore is the infective form of the organism, and when ingested or inhaled, it extends a polar tubule that infects the host cell. Within the host cell, replication occurs and more spores are formed. When spores sufficiently fill the cell, the cell membrane ruptures and spores are released; they may then proceed to infect nearby cells, or be passed into the environment in stool, urine, or respiratory secretions.

Most clinical cases of microsporidiosis in humans occur in immunocompromised hosts. In immunocompetent patients, infection with *Enterocytozoon bieneusi* can be asymptomatic or may cause acute and very rarely chronic diarrhea. In patients with HIV infection, symptomatic microsporidiosis tends to occur in advanced disease, such as when CD4 cell counts are less than 100 cells/mm^3. *E. bieneusi* and some species of *Encephalitozoon* (*E. hellem*, *E. cuniculi*, and *E. intestinalis*) have come to be recognized as major causes of diarrheal enteritis and disseminated infection in patients with AIDS. Disseminated disease caused by *Trachipleistophora* also has been described. Microsporidial species have been associated with disseminated disease including biliary tract disease, sinusitis, myositis, respiratory infection, and keratoconjunctivitis.

Pulmonary Disease

Microsporidial disease with specific pulmonary involvement has been described in cases of patients with HIV infection, and in individuals who have undergone bone marrow or organ transplantation (Fig. 135-11).[32]

Pulmonary disease usually occurs in the setting of concomitant intestinal infection. In one retrospective review of 42 patients with HIV and microsporidial infection, 24% had respiratory symptoms, and 4 of 6 patients who had specimens examined had sputum or bronchoalveolar lavage positive for microsporidia.[33]

Diagnosis

Diagnosis of microsporidiosis is based on identification of organisms in specimens of tissue or stool. Modified trichrome staining allows detection of organisms on light microscopy, but electron microscopy is currently the definitive diagnostic method. Tissue culture, serologic assays, and PCR testing are used in research settings but are not yet commercially available.

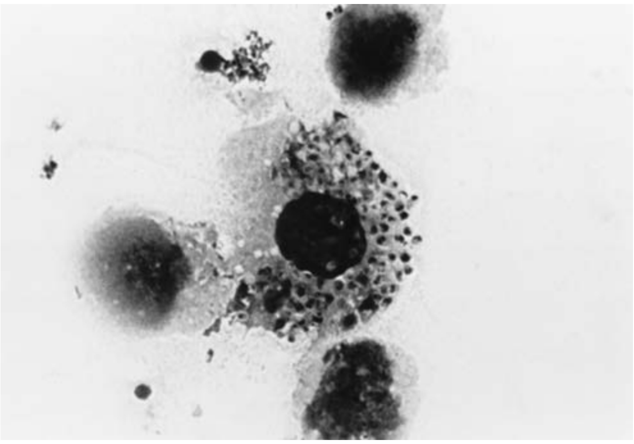

Figure 135-11 Pulmonary microsporidiosis. Tiny organisms (~1 μm) within a pulmonary macrophage obtained via bronchoalveolar lavage (Giemsa–Wright stain, ×1000). *(Reproduced with permission from Dr. C. Wanke.)*

Treatment

Albendazole has activity against *Encephalitozoon* species but is only partially effective against *E. bieneusi*. *E. bieneusi* should be treated with fumagillin. In immunocompromised individuals, treatment is directed at enhancing the immune status of the patient—that is, antiretroviral therapy in patients with HIV infection, and decreased immunosuppression in transplant recipients. Duration of therapy depends on the severity of illness.

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CHAPTER 136

Helminthic Diseases of the Lung

Ricardo M. La Hoz
James B. Cutrell

INTRODUCTION

Parasitic worms, also known as helminths, are a leading cause of global morbidity and mortality, particularly in low-income and resource constrained regions. More than 1 billion people in developing areas of sub-Saharan Africa, Asia, and the Americas are infected with one or more helminth species.[1] The helminths causing human disease include the nematodes (roundworms) and the platyhelminths (flatworms). The platyhelminths are further subdivided into the cestodes (tapeworms) and the trematodes (schistosomes and other flukes).

Individuals with helminthic infections of the lung often seek medical advice due to cough, chest pain, or shortness of breath. They may have unexplained laboratory abnormalities (eosinophilia) or imaging abnormalities (nodule or a mass). In nonendemic areas, they pose a diagnostic challenge given their overlap with other clinical syndromes. A thorough history that includes travel to or long-term residency in endemic areas as well as environmental or dietary exposure are key to the diagnosis. Helminthic infections of the lung may be categorized by their principal clinical presentation (Fig. 136-1). Once the diagnosis is suspected, clinicians must pursue appropriate diagnostic testing to direct therapeutic intervention (Table 136-1). Herein we outline a diagnostic approach to suspected pulmonary disease caused by helminths, followed by review of the most common helminths affecting the respiratory system.

APPROACH TO DIAGNOSIS OF SUSPECTED PULMONARY HELMINTHIC DISEASE

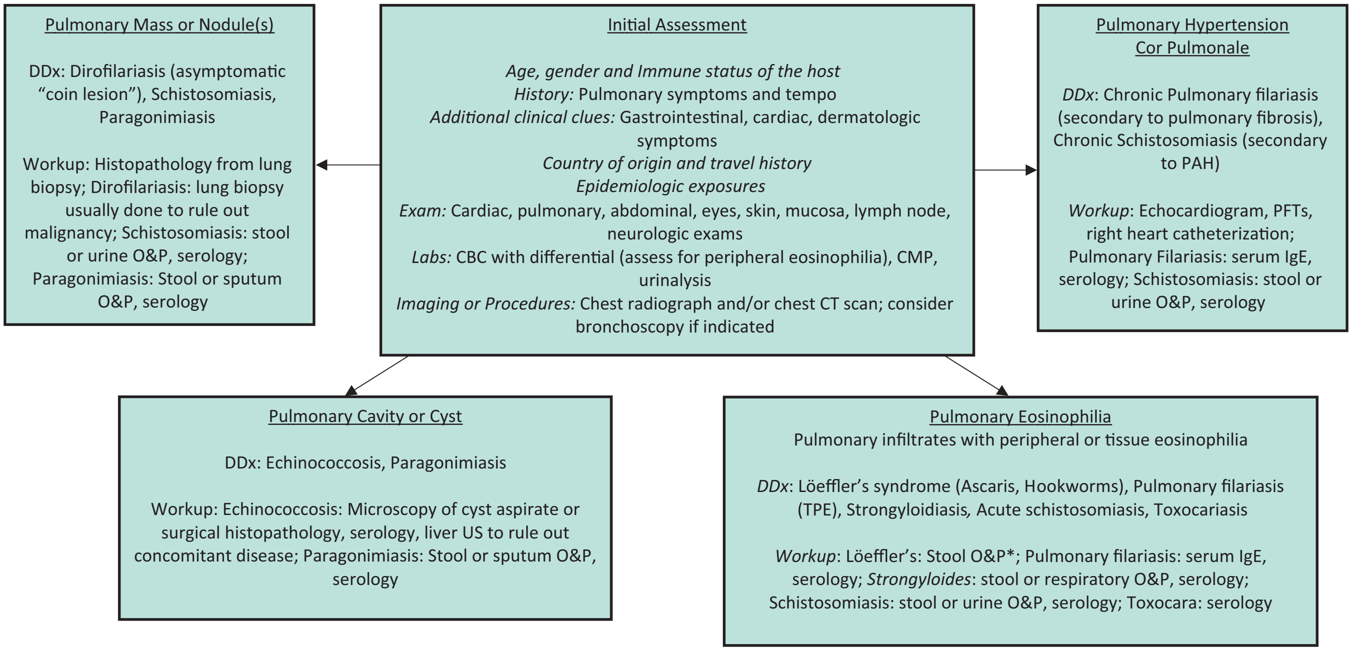
Given their nonspecific symptoms and overlap with other infectious and non-infectious etiologies, helminthic pulmonary infections require a high index of suspicion to prompt their diagnosis. A comprehensive history should characterize the cardiopulmonary symptoms, including their tempo and chronicity, and a detailed review of systems should evaluate for other concomitant sites of involvement such as the skin, eyes and gastrointestinal (GI) tract. Special attention to the immunologic status of the patient, particularly cellular immune defects and any immune-modifying therapies, such as corticosteroid use, may alert physicians to risk factors for disseminated disease or obscure typical diagnostic clues such as peripheral eosinophilia. A thorough social history should focus on the patient's country of origin, as well as recent and remote travel to endemic geographic regions and address any important epidemiologic clues, including dietary, occupational, recreational, animal, or insect vector exposures. Armed with this information, a targeted physical examination and initial laboratory and radiographic evaluation can assist in categorizing a patient's clinical syndrome and directing a focused diagnostic workup for potential helminth pathogens.

SPECIFIC PARASITES

In the sections that follow, we discuss each of the most commonly encountered parasites that affect the lung.

■ Ascariasis

Below we consider the etiology, pathogenesis, clinical manifestations, diagnosis, and treatment of ascariasis.



Initial Assessment

Age, gender and Immune status of the host
History: Pulmonary symptoms and tempo
Additional clinical clues: Gastrointestinal, cardiac, dermatologic symptoms
Country of origin and travel history
Epidemiologic exposures
Exam: Cardiac, pulmonary, abdominal, eyes, skin, mucosa, lymph node, neurologic exams
Labs: CBC with differential (assess for peripheral eosinophilia), CMP, urinalysis
Imaging or Procedures: Chest radiograph and/or chest CT scan; consider bronchoscopy if indicated

Pulmonary Mass or Nodule(s)

DDx: Dirofilariasis (asymptomatic "coin lesion"), Schistosomiasis, Paragonimiasis

Workup: Histopathology from lung biopsy; Dirofilariasis: lung biopsy usually done to rule out malignancy; Schistosomiasis: stool or urine O&P, serology; Paragonimiasis: Stool or sputum O&P, serology

Pulmonary Hypertension
Cor Pulmonale

DDx: Chronic Pulmonary filariasis (secondary to pulmonary fibrosis), Chronic Schistosomiasis (secondary to PAH)

Workup: Echocardiogram, PFTs, right heart catheterization; Pulmonary Filariasis: serum IgE, serology; Schistosomiasis: stool or urine O&P, serology

Pulmonary Cavity or Cyst

DDx: Echinococcosis, Paragonimiasis

Workup: Echinococcosis: Microscopy of cyst aspirate or surgical histopathology, serology, liver US to rule out concomitant disease; Paragonimiasis: Stool or sputum O&P, serology

Pulmonary Eosinophilia
Pulmonary infiltrates with peripheral or tissue eosinophilia

DDx: Löeffler's syndrome (Ascaris, Hookworms), Pulmonary filariasis (TPE), Strongyloidiasis, Acute schistosomiasis, Toxocariasis

Workup: Löeffler's: Stool O&P*; Pulmonary filariasis: serum IgE, serology; *Strongyloides*: stool or respiratory O&P, serology; Schistosomiasis: stool or urine O&P, serology; Toxocara: serology

**For Ascariasis and hookworms stool microscopy should be ordered 4 to 8 weeks after onset of pulmonary symptoms.*
Abbreviations: CBC, Complete blood count; CMP, Comprehensive metabolic panel; CT, Computed tomography; DDx, differential diagnosis; O&P, microscopy for ova and parasites; PAH, pulmonary arterial hypertension; PFTs, pulmonary function tests; TPE, tropical pulmonary eosinophilia; US, ultrasound.

Figure 136-1 Approach to the diagnosis of suspected pulmonary helminthic diseases.

TABLE 136-1 Treatments for Helminthic Pulmonary Diseases

Parasite	Therapies	Comments
Ascaris lumbricoides	Preferred: albendazole 400 mg orally as a single dose Alternate: mebendazole 500 mg orally as a single dose or 100 mg twice daily for three days	Antihelminthic treatment is only effective against adult worms in the intestinal phase.
Ancylostoma duodenale *Necator americanus*	Preferred: albendazole 400 mg orally as a single dose Alternate: mebendazole 500 mg orally as a single dose or 100 mg twice daily for three days	Antihelminthic treatment is only effective against adult worms in the intestinal phase.
Strongyloides stercoralis	A single dose of ivermectin (200 µg/kg orally) for patients with uncomplicated infection. Oral or parenteral formulations of ivermectin alone or in combination with albendazole have been used for patients with hyperinfection syndrome or disseminated disease.	Ivermectin is only effective against the intestinal stages of the parasite.
Wuchereria bancrofti *Brugia malayi*	Diethylcarbamazine (6 mg/kg divided in three daily doses for 21 days)	Corticosteroids have been used as adjunctive therapy, but clinical trials are lacking to define dose and duration.
Toxocara canis *Toxocara cati*	Visceral larva migrans: albendazole 400 mg orally twice daily for 5 days Ocular larva migrans: albendazole 400 mg orally twice daily for 14 days	Corticosteroids are recommended for ocular disease or severe visceral disease.
Echinococcus granulosus	The mainstay of treatment for pulmonary hydatid cyst is surgery. Albendazole 400 mg orally twice daily for 3 to 6 months is recommended for small cysts or when surgery is not feasible.	Use of albendazole postoperatively may be considered, but guidelines do not recommend treatment preoperatively for large pulmonary cysts.
Schistosoma haematobium *S. mansoni* *S. intercalatum*	Praziquantel 40 mg/kg orally in one or two divided doses for 1 day	Praziquantel prevents further oviposition of adult worms.
Schistosoma japonicum *S. mekongi*	Praziquantel 60 mg/kg orally in two divided doses for 1 day	Praziquantel prevents further oviposition of adult worms.
Paragonimus westermani, *P. kellicotti*	Preferred: praziquantel 25 mg/kg orally three times a day for 2 to 3 days Alternative: triclabendazole 5 mg/kg orally per day for 3 days or 20 mg/kg orally in two divided doses for 1 day	Corticosteroids should be given if concomitant central nervous system disease is present.

Etiology

Infection due to *Ascaris lumbricoides* occurs worldwide. Most individuals with ascariasis live in Asia, Africa, and South America.[2] People living in, travelling to, or coming from areas with poor sanitation are at higher risk for infection. This parasite most commonly infects children and adolescents, with decreasing prevalence in those over 15 years of age.[3] *Ascaris* also affects vulnerable populations in high-income countries. For example, the southeastern United States (US) has historically had the highest burden of *Ascaris*.[4]

Human ascariasis occurs by fecal-oral transmission when embryonated eggs found in the environment are ingested. The eggs hatch in the gastrointestinal (GI) tract, producing larvae that penetrate the enteric mucosa and subsequently gain access to the venous system. They eventually reach the lung via the right side of the heart and migrate to the alveoli through the pulmonary capillaries. Once in the alveoli, they ascend the bronchial tree and are eventually swallowed back into the GI tract where they become adults.

Pathogenesis and Pathology

In patients without prior *Ascaris* exposure, a type-1 hypersensitivity reaction, known as Löeffler's Syndrome, occurs when the larval stage passes through the lung parenchyma.[5] On pathology, portions of larvae are seen in the pulmonary parenchyma, surrounded by a patchy infiltrate of neutrophils and eosinophils.

The immune response to *A. lumbricoides* infection is polarized to a T-helper cell type 2 (Th2) response, characterized by high levels of interleukin (IL)-4, IL-5, IL-13, immunoglobulin E (IgE) as well as tissue eosinophilia and mastocytosis. This organized response stimulates the eosinophil-mediated destruction of migrating larvae and production of IgE against worm antigens. Indirect evidence of the importance of the Th2 response is provided by studies demonstrating an association between a weak Th2 response and susceptibility to reinfection.[6–8] *A. lumbricoides* also stimulates the production of IL-10. Its primary effect is to protect the host from the inflammatory response, but it may also allow the survival of the helminth.[7]

Clinical Manifestations

The symptoms of ascariasis depend on the phase of the disease. In the migratory phase, pulmonary symptoms predominate. Pulmonary ascariasis, the most common cause of Löeffler's syndrome. It predominantly occurs in individuals without prior *Ascaris* exposure and thus rare among people in endemic areas.[5] A study including 13,000 patients in Colombia, where prevalence ranges from 25% to 90%, found only 4 cases of Löeffler's syndrome.[9] The symptoms of cough, dyspnea, chest pain, bronchospasm and hemoptysis begin 1 to 2 weeks after the ingestion of eggs as the larvae migrate through the lungs and last for 5 to 10 days. In addition to the pulmonary manifestations during the migratory phase, some patients may also present with urticaria or peripheral eosinophilia. Analysis of sputum characteristically demonstrates eosinophils and Charcot-Leyden crystals.[10] Chest radiography may show oval or round infiltrates, while computed tomography (CT) of the chest demonstrates pulmonary nodules.[11–13] Chronic intestinal infection with the adult worm is usually either asymptomatic or associated with mild abdominal discomfort, lack of appetite, or changes in bowel habits.

Diagnosis

After ingestion of embryonated eggs, 40 days are required for the larvae to migrate and reach the intestine before maturing to an adult worm capable of producing eggs that can be detected in stool. Thus, although the diagnosis of the migratory phase of *Ascaris* can be suspected based on epidemiological risk factors and clinical presentation, its confirmation is often delayed for weeks. The chronic *Ascaris* intestinal phase is established by identifying *Ascaris* eggs in stool via microscopy. Methods for detection include Kato-Katz and FLOTAC techniques.[14–16] The former is recommended by the World Health Organization (WHO) due to its simplicity and low cost, making it the most commonly used technique. The drawback is that it is labor intensive. The FLOTAC technique is more sensitive but requires a centrifuge that may not be available in some settings.[16] In addition, polymerase chain reaction (PCR) has better diagnostic performance compared to microscopy.[17]

Treatment

Because the migratory phase of ascariasis is self-limited, specific therapy is usually not required. Prednisone use has been described in case series for those with severe disease.[18] Antihelminthic medication is reserved for those with eggs detectable in the stool, as the drugs are only active against the adult worm. The mainstay of treatment for chronic intestinal ascariasis in those older than 12 years of age are the benzimidazoles. Albendazole (400 mg orally as a single dose) or mebendazole (500 mg orally as a single dose or 100 mg orally twice daily for three days) achieve high cure rates with excellent safety profiles.[19–21]

■ *Ancylostoma duodenale* and *Necator americanus*

Below we consider the etiology, pathogenesis, clinical manifestations, diagnosis, and treatment of the hookworms, *Ancylostoma duodenale* and *Necator americanus.*

Etiology

Ancylostoma duodenale and *Necator americanus* are the primary hookworms that cause infection in humans. The term hookworm refers to attachment of the buccal cutting plates found in the mouth of these parasites to the intestinal mucosa of the host. Globally, approximately 450 million people are infected with hookworms.[22] *N. americanus* is the most common species, with predominance in sub-Saharan Africa, Southeast Asia, and the Americas. In contrast, *A. duodenale* has endemic foci in India, Pakistan and the Mediterranean region.[23] While *Ascaris* is a helminth affecting children, hookworms predominantly affect adults.[24] In the southern US, infection with *N. americanus* occurs in areas of extreme poverty.[25]

The predominant route of hookworm acquisition is through dermal penetration by the free-living larvae in the soil while walking barefoot. Once the larvae gain access to the venous system, they travel to the right heart and pulmonary circulation. From the pulmonary capillaries, they migrate to the alveoli, ascend through the bronchial tree, and are eventually swallowed. In the intestine, the larvae molt and develop to the adult worm.[26] *A. duodenale* can also be acquired orally, resulting in Wakana Disease, characterized by GI disturbances, cough, laryngeal irrigation and eosinophilia.[27]

Pathogenesis and Pathology

N. americanus and *A. duodenale* may cause a type 1 hypersensitivity reaction during the migratory phase in the lungs (Löeffler Syndrome). The adult worms use their buccal cutting plates to attach to the intestinal mucosa. Hookworms secrete factors Xa, XIa, and VIIa-tissue factor inhibitors that augment blood loss.[28] Intestinal hookworm infection is associated with a Th2 response (elevated IgE, IL-5 and eosinophilia).[29,30] In contrast with other helminth infections, exposure is not associated with resistance to infection due to the development of host tolerance.[31,32]

Clinical Manifestations

Although commonly asymptomatic, clinical manifestations of hookworm infection reflect different phases of the parasite life cycle. Penetration of the skin results in "ground itch," a pruritic erythematous or maculopapular rash which slowly migrates (1–2 cm/day) from common sites of entry on the hands and feet and lasts 2 weeks.[23,33] About 10 days after entering the skin and migrating through the venous system, the larvae reach the lung. Symptoms during this phase are less likely to occur with hookworms than *Ascaris*. As with Löeffler's syndrome caused by ascariasis, cough, chest discomfort, and wheezing are the predominant symptoms and can be accompanied by eosinophilia and pulmonary infiltrates. While the symptoms caused by *Ascaris* in this phase only last 5 to 10 days, they can last up to 30 days with hookworms.[34] The intestinal phase is characterized by abdominal pain, diarrhea, and chronic GI blood loss leading to severe microcytic anemia and its associated complications.

Diagnosis

Diagnosis is established by identifying eggs in stool. Morphologically, the eggs of *N. americanus* and *A. duodenale* are indistinguishable. In the case of *N. americanus*, eggs can be identified in the stool 8 weeks after dermal entry while it can take up to 38 weeks for *A. duodenale*. Thus, stool microscopic examination is unreliable to establish the diagnosis of "ground itch" and Löeffler's syndrome. The Kato-Katz and McMaster's techniques are most commonly used to diagnose the intestinal phase.[35,36] PCR based diagnostics are species specific and have superior sensitivity compared to microscopy.[37]

Treatment

Since antihelminthic treatment is only effective against the adult worm, it is not effective for hookworm-related Löeffler's Syndrome. Treatment is not usually required during this phase although corticosteroids have been used in severe cases. For intestinal infection, Albendazole (400 mg orally as a single dose) has the highest cure rate while mebendazole (500 mg orally as a single dose or 100 mg orally twice daily for three days) is an alternative.[20,21,38] Iron replacement is recommended for those with anemia.

■ Strongyloidiasis

Below we consider the etiology, pathogenesis, clinical manifestations, diagnosis, and treatment of strongyloidiasis.

Etiology

Strongyloidiasis affects 370 million people worldwide.[39] The causative parasite, *Strongyloides stercoralis*, is endemic throughout the tropics and subtropics with Africa, Asia, and Latin America being disproportionately affected.[40] In the US, strongyloidiasis is endemic to the Appalachian region.[4,41,42]

S. stercoralis can complete its life cycle both in the environment and in the human host. The primary reservoir of the parasite is soil contaminated with human feces. The filariform larvae penetrate the skin, gain access to the venous system, migrate to the lung, enter the alveoli, ascend the bronchial tree, and then are swallowed. In the intestine, the larvae molt to adult worms. Adult females reproduce sexually and asexually producing eggs that become rhabditiform larvae, which are then eliminated in stool. *Strongyloides* has an auto-infective cycle through which the rhabditiform larvae molt into filariform larvae that can penetrate the intestinal mucosa or perianal skin, re-initiating the cycle. This auto-infective cycle is accelerated in immunosuppressed hosts and is the basis for long-term persistent infections and the severe manifestations seen in those that are immunocompromised.[43]

Pathogenesis and Pathology

The small size of the *Strongyloides* larvae has been linked to the few symptoms observed during lung migration.[44] In the immunocompetent host, *Strongyloides* induces a Th2 response where IL-4 and IL-5 predominate.[45] Patients co-infected with human T-lymphotropic virus-1 (HTLV-1) and other immunocompromised hosts infected with *Strongyloides* have a Th1 skewed response.[46] This coinfection has been linked to lack of parasite control, increased risk of hyperinfection syndrome and disseminated disease, and a lack of eosinophilia in those with severe manifestations.[47]

Clinical Manifestations

The symptoms are dependent on the phase of infection. Edema or urticaria may occur at the site of inoculation. Symptoms during migration through the lung are mild and uncommon[34] while chronic intestinal infections are asymptomatic or have mild nausea, abdominal pain and diarrhea. The auto-infective cycle can cause the following manifestations: *larva currens*, hyperinfection syndrome, and disseminated disease. *Larva currens* occurs when the rhabditiform larvae migrate through the subcutaneous perianal, buttocks, and thighs, creating an urticarial band which migrates 5 to 15 cm per hour.[33]

Hyperinfection syndrome is characterized by an accelerated proliferation of rhabditiform larvae in the intestine that migrate through the intestinal mucosa, travel to the lungs and back to the intestine. In the hyperinfection syndrome, the parasite is restricted to the GI and pulmonary systems. The GI symptoms include anorexia, nausea, vomiting, abdominal pain, diarrhea, ileus, obstruction, and GI bleeding. The pulmonary symptoms include wheezing, dyspnea, hemoptysis, and acute respiratory distress syndrome. Frequent complications of hyperinfection syndrome include septic shock (50%) and bacteremia (40%) caused by translocation of intestinal flora carried by migrating larvae. Disseminated disease consists of hyperinfection syndrome coupled with spread of larvae to other organs. The mortality rate approaches 50% in hyperinfection syndrome and 70% in disseminated infection.[48–50]

Diagnosis

The diagnosis of strongyloidiasis is made by serological methods or by detecting larvae in a clinical specimen (Fig. 136-2). Serological methods are commonly used to diagnose chronic uncomplicated intestinal strongyloidiasis.[51] The sensitivity and specificity of serologies are 75–95% and 95–100%, respectively.[52] False positive results occur with other helminths while false negatives occur in immunocompromised hosts, particularly in those with hyperinfection syndrome or disseminated disease.[53,54]

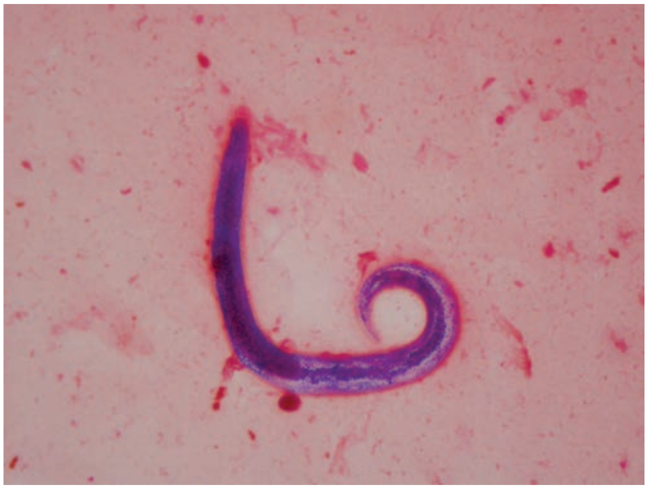


Figure 136-2 Gram stain of a bronchial wash demonstrating a rhabditiform larva of *Strongyloides* at 400× magnification. *(Reproduced with permission from Dr. Dominick Cavuoti.)*

Patients with chronic uncomplicated intestinal strongyloidiasis have a low parasitic burden with intermittent excretion of larvae. Thus, a single stool sample lacks adequate sensitivity, which can be increased with multiple samples.[43,55] The Agar Plate method is the most commonly used method to identify stool larvae and has the highest sensitivity.[42] In hyperinfection or disseminated disease, larvae can be found in respiratory secretions, cerebrospinal fluid, peritoneal and pleural fluid. Affected organs should be sampled to increase the diagnostic yield. Although patients with uncomplicated infection may have eosinophilia, those with hyperinfection syndrome or disseminated disease usually (70–100%) have normal eosinophil counts.[48,50,56,57] Patients diagnosed with *Strongyloides* should be screened for HTLV-1 since co-infection is associated with a high risk of relapse.[58,59] Although not widely available, PCR tests have been developed to detect *Strongyloides* in stool samples.[51] Different techniques have been used and the performance has varied.[56,60]

Treatment

Ivermectin is the treatment of choice for strongyloidiasis and can be administered via oral, rectal, and subcutaneous routes.[61–64] Ivermectin is only effective against the intestinal stages of the parasite.[65,66] Albendazole is considered second-line therapy based on a meta-analysis demonstrating that ivermectin is more effective than albendazole.[61,67–69] A single dose of ivermectin (200 μg/kg orally) was compared to multiple doses of ivermectin (200 μg/kg given on days 1, 2, 15, and 16), demonstrating similar efficacy and better tolerability with a single dose regimen.[70] Since immunocompromised hosts were excluded from the study, some experts still advocate for a multi-dose regimen in this population. Patients from west and central Africa should be screened for microfilarial disease with a blood smear because treatment with ivermectin in this scenario may trigger the Mazzotti reaction within 7 days.[71]

Limited data exist to guide the optimal management of *Strongyloides* hyperinfection syndrome and disseminated disease. In addition to antihelminthic therapy and supportive care, broad spectrum antimicrobials are also recommended given the high rate of concomitant bacterial sepsis. Ivermectin (200 mcg/kg orally daily) for two weeks after the last positive stool sample is recommended to cover for a complete autoinfection cycle. Combination therapy with albendazole has been used for those with hyperinfection syndrome and disseminated disease.[72] Subcutaneous ivermectin (200 mcg/kg/daily) is favored over rectal ivermectin for those unable to tolerate oral therapy.[73–76] In the US, use of the veterinary subcutaneous formulation requires an emergency investigational new drug application (eIND).[77]

■ Pulmonary Filariasis

Below we consider the etiology, pathogenesis, clinical manifestations, diagnosis, and treatment of filariasis.

Etiology

Pulmonary filariasis, referred to as tropical pulmonary eosinophilia (TPE), is a distinct clinical syndrome due to pulmonary immune hyperreactivity directed against the filarial nematodes *Wuchereria bancrofti* and *Brugia malayi*. Transmitted by mosquito vectors, filarial infections are endemic in the tropics and subtropics, including the Indian subcontinent, southeast Asia, South America, and Africa. While more than 120 million people are infected with lymphatic filariasis globally, fewer than 1% manifest pulmonary symptoms of

TPE.[78] For unclear reasons, most reported cases of TPE occur in adolescents or young adults from India with a strong male predilection.[79]

Following mosquito bite injection of the infective third-stage larvae, the nematodes develop into the adult male and female worms (macrofilaria) which take up residence in the lymphatics and lymph nodes. From here, microfilariae are released into the peripheral circulation to be picked up by mosquito vectors completing the life cycle. In lymphatic filariasis, microfilariae levels in the blood can peak at specific times of day (periodicity), which may be important diagnostically. However, in TPE, microfilariae are commonly absent from the peripheral blood although they have been detected in lung and lymph node biopsies.

Pathogenesis and Pathology

A clear explanation for the low percentage of those with lymphatic filariasis who develop TPE is lacking. Patients with TPE demonstrate marked humoral immune hyperresponsiveness, with elevated levels of total IgE and antifilarial IgM and IgE in both blood and lung epithelial lining fluid that decrease in response to antifilarial treatment.[79,80] A specific IgE-inducing filarial antigen also demonstrates homology with human gamma-glutaryl transpeptidase present in lung epithelium, suggesting molecular mimicry may induce an autoimmune response.[78] Exuberant eosinophil trafficking to the lungs driven by IL-4, IL-5 and eotaxin in response to microfilariae may also play a pathogenic role. Eosinophil degranulation products such as eosinophil-derived neurotoxin and major basic protein are hypothesized to contribute to TPE pathology although genetic polymorphism studies of these genes to date are inconclusive.[81,82]

The histopathologic lesions of early TPE demonstrate histiocytes in the pulmonary interstitium and alveoli.[78] However, as infection progresses, eosinophilic infiltrates develop throughout the lung tissue and can form abscesses or eosinophilic granuloma in severe cases.[79] Finally, chronic untreated disease can progress to fibrosing alveolitis and honeycombing.

Clinical Manifestations

The hallmark clinical syndrome of TPE is an insidious, nonproductive, paroxysmal cough that is worse at night. It can also be associated with fatigue, low grade fevers, shortness of breath, and wheezing, frequently leading to misdiagnosis as asthma especially in nonendemic areas.[83,84] Pulmonary function testing usually reveals a restrictive pattern with moderate concomitant airway obstruction and often reductions in diffusion capacity.[79] Chest radiographs may be normal or demonstrate reticulonodular opacities or miliary patterns in the mid to lower lung zones. End-stage disease can progress to pulmonary fibrosis and cor pulmonale. Prototypical laboratory testing demonstrates marked elevation in peripheral blood and bronchoalveolar lavage (BAL) fluid eosinophilia, elevated serum IgE levels (>1000 units/mL), and elevations in anti-filarial antibody levels.[78,83]

Diagnosis

The differential diagnosis for TPE includes other helminthic pulmonary syndromes (particularly strongyloidiasis or Löeffler's syndrome related to *Ascaris* or hookworms) and infectious and noninfectious eosinophilic pneumonias. Strongyloidiasis is important to exclude since corticosteroids can lead to dissemination with this infection. Since patients with TPE generally lack microfilariae or filarial antigens in their blood, a gold-standard diagnostic test is lacking to distinguish it from other mimics. However, diagnostic criteria have been proposed, including: (1) appropriate exposure history (mosquito bite) in an endemic region; (2) compatible clinical syndrome and radiographic findings; (3) elevated serum IgE levels and peripheral blood eosinophilia (>3000 cells/mm^3); and (4) elevated serum IgG and IgE antifilarial antibodies.[78] A clinical response to the recommended treatment of diethylcarbamazine (DEC) also supports the diagnosis.

Treatment

The recommended treatment for TPE by the WHO is DEC given orally 6 mg/kg divided in three daily doses for 21 days.[78] DEC rapidly kills both the microfilariae and adult worms, with rapid improvement in symptoms and lung function within 1 month of treatment initiation if given within the first few years of the disease. However, a persistent low-grade eosinophilic alveolitis can persist following treatment. Corticosteroids have been used as adjunctive therapy, but clinical trials have not been conducted to define the optimal dose and duration. Approximately 20% of cases will recur within 5 years necessitating a second course of DEC therapy.[79] Treatment is not successful at reversing pulmonary fibrosis or impaired lung function in later stage disease. DEC is not available currently in the US but can be obtained via eIND. Other treatments such as ivermectin, albendazole, or doxycycline to treat the symbiotic *Wolbachia* associated with filariasis are part of the WHO mass drug administration campaigns to eradicate global filarial disease, but these agents do not have an established role in TPE.[78,85]

■ Dirofilariasis

Below we consider the etiology, pathogenesis, clinical manifestations, diagnosis, and treatment of dirofilariasis.

Etiology

Dirofilariasis is caused by infection from the filarial nematodes in the genus *Dirofilaria* and is the most common zoonotic filariasis. Unlike other human filarial infections restricted to tropical and subtropical regions, it has a worldwide distribution.[86] While subcutaneous dirofilariasis is caused by other species, human pulmonary dirofilariasis (HPD) is primarily caused by infections with the dog heartworm, *Dirofilaria immitis*. Dirofilariasis is transmitted to humans by the bites of mosquito intermediate vectors, and the most important animal reservoir are dogs. Although the true incidence of disease is unknown, reported cases track with areas of canine hyperendemicity such as the southeastern US.[87]

Pathogenesis and Pathology

Developing adult worms reside in the canine right ventricle and pulmonary arteries and produce microfilariae, which are then taken up by mosquitoes in a blood meal. In the human accidental host, the developing worms pass through the right ventricle before lodging in small pulmonary arterial beds where they cause a local vasculitis and inflammatory response before dying.[87] Histopathology demonstrates a dead worm with a small pulmonary infarct and vasculitis within a background of granulomatous or eosinophilic inflammation (Fig. 136-3).[87] Mature adult worms and microfilariae are not typically detected in humans.

Clinical Manifestations

The classic presentation of HPD is an asymptomatic pulmonary nodule or coin lesion on routine chest imaging.[88] The lesions are typically solitary, round, 1–4 cm in size, with sharp borders located on the periphery of the lung, and often are mistaken for malignancy. When symptomatic, patients with HPD present with cough, chest pain, or hemoptysis. Eosinophilia is seen in less than 15% of cases.

Diagnosis and Treatment

Definitive diagnosis involves identification of the worm in a biopsy or autopsy specimen. Serology and tissue PCR are available but rarely needed. The only treatment is surgical removal of the worm, which is typically achieved during the diagnostic workup.

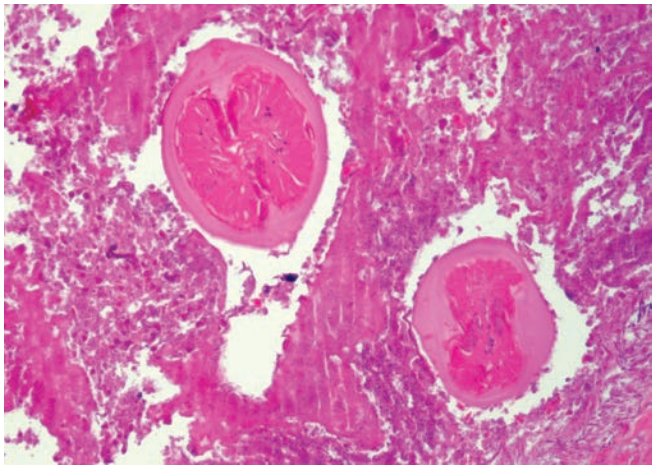


Figure 136-3 Lung biopsy of an isolated pulmonary nodule demonstrating a degenerating *Dirofilaria* helminth on hematoxylin eosin stain at 100× magnification. *(Reproduced with permission from Dr. Dominick Cavuoti.)*

Toxocariasis

Below we consider the etiology, pathogenesis, clinical manifestations, diagnosis, and treatment of toxocariasis.

Etiology

Toxocariasis occurs worldwide and is primarily caused by infection with *Toxocara canis*, and less frequently by *T. cati*.[89] In the US, the seroprevalence of toxocara is estimated at about 5%.[90] Infection is more common in those living in poverty.[90,91]

The life cycle of *T. canis* and *T. cati* occurs in the dog and cat, respectively. Eggs are shed in the stool of dogs and cats and become infective three weeks later. Humans are accidental hosts. The predominant route of infection is ingestion of infective eggs found in contaminated soil and fruits or vegetables.[92] A less common route of infection is ingestion of undercooked meat containing larvae from intermediate hosts like swine, cattle, rabbits, or chickens. Once the eggs reach the intestine, they release larvae, which penetrate the intestinal mucosa, gain access to the venous circulation and can be transported to virtually any organ.

Clinical Manifestations

Most infected individuals are asymptomatic. The damage caused by migrating larvae, eosinophilic infiltrates, and eosinophilic granulomas are responsible for the clinical manifestations. Two clinical entities encompass the clinical manifestations of toxocariasis: visceral larva migrans (VLM) and ocular larva migrans (OLM). These syndromes may occur simultaneously, sequentially, or independently. VLM predominantly affects children less than 5 years of age, and the lungs, liver, spleen, and central nervous system are the organs most commonly affected. It is characterized by fever, anorexia, chronic nonproductive cough, dyspnea, wheezing, hepatomegaly, splenomegaly, seizures, eosinophilia, and hypergammaglobulinemia. The most common chest radiograph findings are bilateral peribronchial and parenchymal infiltrates.[93] The described CT findings are multifocal pulmonary nodules with surrounding ground glass opacities.[13] OLM largely affects children 5 to 10 years of age. The most common presentation is unilateral decrease in visual acuity and strabismus; uveitis, scleritis, and endophthalmitis have also been described.[94–96]

Diagnosis

Enzyme linked immunosorbent assays (ELISA), using recombinant antigens, have the best diagnostic performance for toxocariasis. These assays cannot differentiate between infection with *T. canis* and *T. cati*. The sensitivity and specificity are about 78% and 92%, respectively.[89] Although the definitive diagnosis is made by detecting larvae in the affected tissue, this is rarely performed. The diagnosis of OLM relies on the ophthalmologic exam as the sensitivity of ELISA is lower in this setting, and the titers are often low or negative.[97,98]

Treatment

Most patients with mild symptoms due to VLM have a self-limited course and do not require antihelminthic therapy.[99] For patients with moderate to severe symptoms of VLM, albendazole (400 mg orally twice a day for 5 days) is recommended.[100] Some experts advocate for corticosteroids in those with severe manifestations to mitigate the immune response to dying larvae during therapy. For OLM, treatment with albendazole (400 mg oral twice day for 14 days) and corticosteroids are recommended. Patients with severe manifestations may require surgical intervention.[94,101,102]

Echinococcosis

Below we consider the etiology, pathogenesis, clinical manifestations, diagnosis, and treatment of echinococcosis.

Etiology

Echinococcosis is caused by human infections from the larvae of zoonotic cestodes in the genera *Echinococcus*. While four species cause human disease (*Echinococcus granulosus*, *E. multilocularis*, *E. vogeli*, and *E. oligarthus*), the most common etiology in pulmonary disease is the dog tapeworm *E. granulosus*, the causative agent of cystic echinococcosis (CE) or hydatid disease. It has recently been recognized that *E. granulosus* represents a complex of 10 distinct genotypes, some of which have been elevated to new distinct species.[103] With a worldwide distribution, it is endemic in the pastoral communities of South America, Australia, eastern Europe, north Africa, the Middle East, central Asia, and western China although there are reports of autochthonous disease in North America.[103,104]

The infection life cycle is maintained through ingestion by the definitive host (usually domestic dogs, foxes, wolves, or other canids) of the hydatid cyst form in the infected viscera of the intermediate host (e.g., sheep, pigs, cattle, goats). The cyst matures into the adult tapeworm in the canine intestine and then sheds its embryonated eggs in the feces. Humans become accidentally infected either from ingestion of eggs in contaminated food and water or close contact and handling of dogs.[105] In humans, the embryo oncospheres are released in the stomach, penetrate the intestines, and then spread through the bloodstream to the liver or other organs where they mature into the metacestode cysts (Fig. 136-4). The lungs are the second most common location (20%) in CE after the liver (80%).[104,106] Usually unilocular in the case of CE but multilocular in other species, the maturing cyst forms a space-occupying lesion with an inner germinal layer that produces protoscolices and daughter cysts, which can seed other tissues upon cyst rupture.

Pathogenesis and Pathology

While liver involvement is predominant in adults, lung disease is more frequently detected in children whose lungs accommodate faster cyst growth.[104] The cysts have three layers: an outer host-derived pericyst, which constitutes compressed lung and a granulomatous inflammatory response which progresses to fibrosis; a middle or laminated layer; and the inner endocyst or germinal layer (Fig. 136-5), which deposits both sediment (hydatid sand) and daughter cysts into the enlarging cyst. The cyst gradually grows over the course of years to decades until it causes symptoms due to mass effect. Eventually, the cyst may degenerate into a calcified mass lesion. On the other hand, a viable cyst may acutely rupture

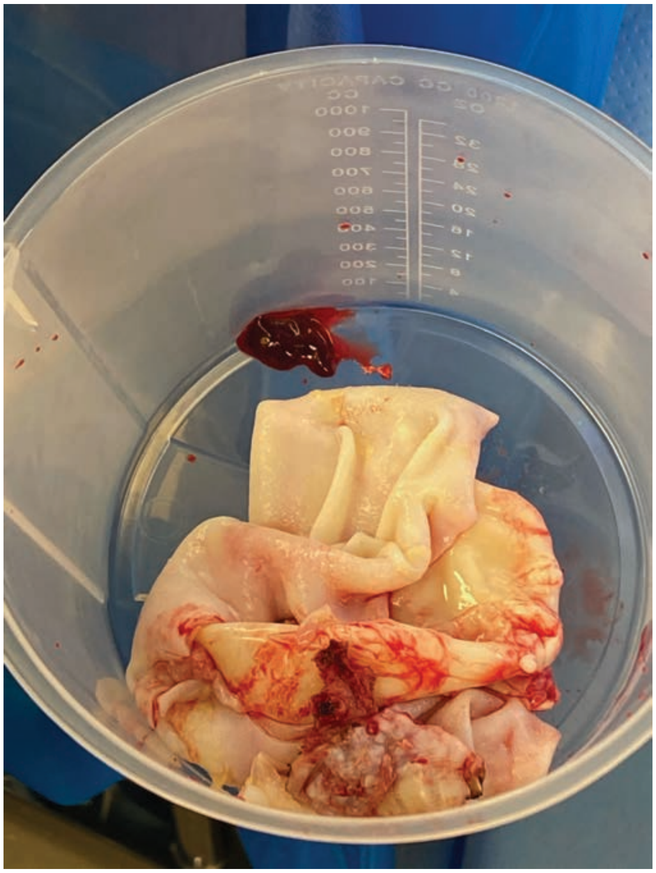


Figure 136-4 Pulmonary hydatic cyst. *(Reproduced with permission from Dr. John Waters.)*

either into the bronchial tree causing expectoration of cyst material in sputum or into the pleural space leading to pneumothorax, effusion, or secondary seeding of new daughter cysts. The cyst fluid is also highly immunogenic so rupture, either spontaneous or iatrogenic, can lead to acute hypersensitivity or anaphylactic reactions. Cysts may also become secondarily infected leading to lung abscess. Lung involvement with other species besides *E. granulosus* is much rarer but can occur with infiltration or spread from the primary hepatic site.[106]

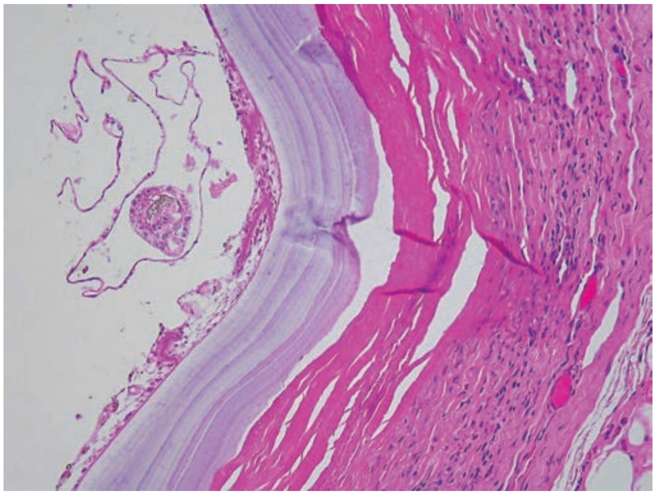


Figure 136-5 Lung biopsy of hydatid cyst from *Echinococcus granulosus* demonstrating outer compressed host tissue, middle laminated layer, and a protoscolex arising from the inner germinal layer on hematoxylin eosin stain at 100× magnification. *(Reproduced with permission from Dr. Dominick Cavuoti.)*

Clinical Manifestations

Pulmonary hydatid cysts often are asymptomatic and found incidentally on imaging. Children are more likely to be asymptomatic even with very large cysts, likely due to greater lung elasticity and weaker immune responses.[104] Commonly described symptoms include cough, chest pain, dyspnea, or less often hemoptysis. An abrupt change in symptoms usually heralds a cyst complication, either cyst rupture or secondary bacterial infection. Pulmonary cysts tend to be unilateral (50–80%), solitary (60%) and have a predilection for the lower lobes, with up to 35% of individuals having concomitant hepatic involvement.[107,108] Laboratory studies are generally non-specific with peripheral eosinophilia seen in less than 25% of cases.

Diagnosis

The primary diagnostic modality for pulmonary CE is compatible imaging in the appropriate epidemiologic and clinical context. On chest radiographs, cysts usually manifest as well defined, round masses of uniform density that range in size from 1 to 20 cm in diameter.[107] Less commonly, an air-fluid level in the cyst due to detachment of the endocyst can lead to a "water lily" or "meniscus" sign. Chest CT scan may be useful in complicated cysts to define secondary infection with contrast enhancement around the cyst wall, communication with the bronchial tree, or additional smaller cysts (Fig. 136-6).[104] Although commonly used in staging of hepatic disease, ultrasound is rarely used except for pleural disease or cysts adjacent to the thoracic wall.

Serologic testing by either ELISA, indirect hemagglutination, or latex agglutination can serve as adjunctive confirmation but generally has lower sensitivity in lung compared to hepatic disease (50–60% vs. 85–98%).[106] Positive tests should be confirmed using Western blot for purified antigens since specificity is limited by cross-reactivity with other helminth diseases, malignancies, and autoimmune disease. Cyst complications or multiorgan involvement are associated with higher seropositivity rates.[108] Direct microscopy of the protoscolices or other parasite features from aspirated cyst

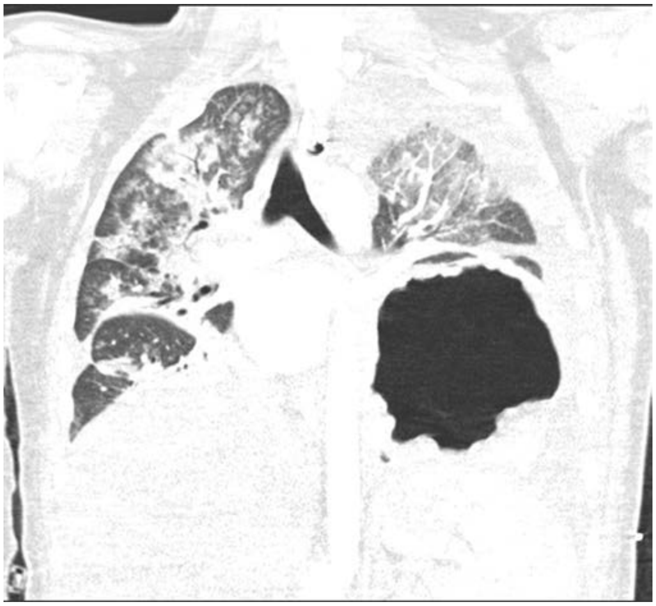


Figure 136-6 Computed tomography of the chest showing a well-defined cyst characteristic of pulmonary hydatic cyst. *(Reproduced with permission from Dr. Jorge Taboada.)*

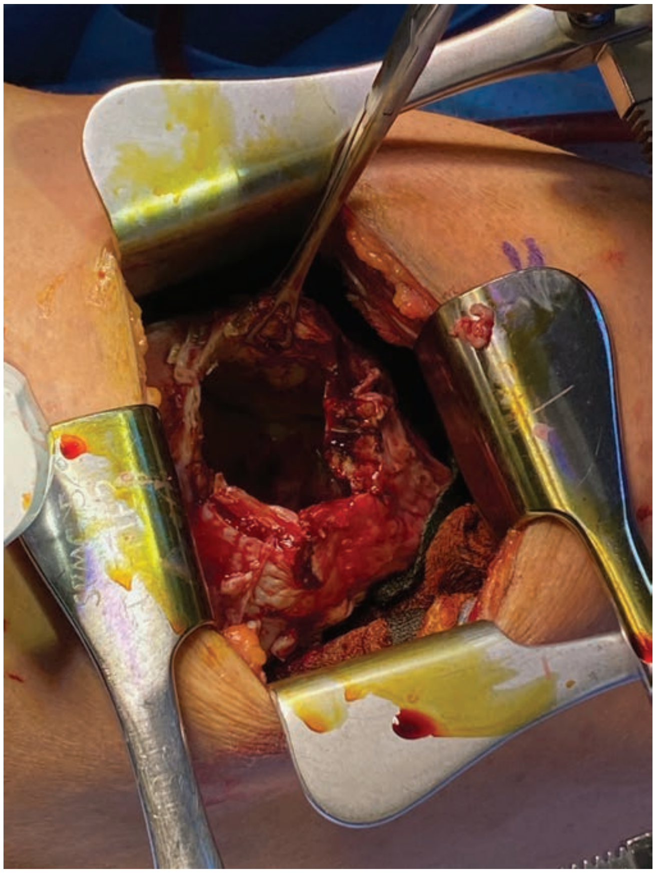


Figure 136-7 Thoracotomy and cystostomy of pulmonary echinococcosis. *(Reproduced with permission from Dr. John Waters.)*

fluid or surgical histopathology is also diagnostic. WHO expert consensus guidelines, last updated in 2009, summarize key diagnostic and management recommendations.[106]

Treatment

The mainstay of treatment for pulmonary hydatid disease is surgery, which can both confirm the diagnosis and treat local complications.[106] The primary goal of surgery is to remove as much of the cyst as possible while avoiding intraoperative spillage and dissemination. Current surgical approaches favor complete cyst excision either via enucleation, cystotomy (Fig. 136-7), or removal after aspiration while preserving as much of the lung parenchyma as possible, with low rates of recurrence seen at less than 2%.[109] More extensive resection is reserved for giant cysts or when complicated by secondary bacterial abscesses. Use of hypertonic saline-soaked surgical drapes to protect the operative field and cavity marsupialization or surgical drain placement after removal are often required.[104,110]

Chemotherapy with benzimidazoles is reserved for small cysts or when surgery is not feasible. While mebendazole was previously used, albendazole is currently the preferred agent due to improved bioavailability. A prolonged course of albendazole 400 mg twice daily for three to six months may be effective in small, uncomplicated cysts.[104] Key side effects include hepatotoxicity, leukopenia, hair loss, and GI distress. The use of albendazole in the perioperative and post-operative periods and its combination with praziquantel for synergy have shown promise of improved efficacy in hepatic disease, but data are limited in pulmonary disease.[111] The "PAIR procedure" (*P*ercutaneous *A*spiration, *I*njection of cysticidal agent, and *R*e-aspiration) often done for hepatic cysts is not recommended for pulmonary cysts due to higher complication rates.[106]

■ Schistosomiasis

Below we consider the etiology, pathogenesis, clinical manifestations, diagnosis, and treatment of schistosomiasis.

Etiology

Schistosomiasis is caused by the blood flukes (trematodes) from the genus *Schistosoma*, and represents one of the most common neglected tropical diseases, with more than 200 million infections worldwide. Endemic foci of disease exist in Africa, southeast Asia, the Middle East, and South America, with the majority of cases in Sub-Saharan Africa. Five major species, each with specific geographic distribution and tissue tropism, cause clinically significant human disease: *Schistosoma haematobium*, *S. mansoni*, *S. japonicum*, *S. mekongi*, and *S. intercalatum*.[112]

Human infection begins with the free-living cercariae, which are shed by freshwater snails, directly penetrating intact skin. The cercariae lose their tail to transform into schistosomula and remain in the subcutaneous tissue for about 48 hours before sequentially migrating through the blood to the heart, lungs and then liver. Here, they mature into the adult male or female worms before reaching their ultimate destination in the genitourinary (*S. haematobium*) or mesenteric (all other species) veins. Adult worms shed eggs through the urine or feces into the environment, where they hatch into miracidia that infect aquatic snails to complete the life cycle. However, the eggs may deposit in other human tissues leading to clinical disease.

Pathogenesis and Pathology

Schistosomiasis pathogenesis is typically divided into acute and chronic phases although the timing and distinctions of these phases are being reconsidered.[112,113] Acute schistosomiasis syndrome (often referred to as "Katayama fever") usually occurs 2 to 8 weeks after exposure and is related to a systemic hypersensitivity reaction to migrating schistosomula and/or circulating antigens and immune complexes prior to the onset of egg production and deposition (oviposition). Pathologic specimens from this phase are rarely collected but demonstrate eosinophilic infiltrates and abscesses in the airspaces and pulmonary capillaries without evidence of the eggs.[112]

In contrast, chronic schistosomiasis occurs following years of chronic or repeated infection and is directly related to the duration and burden of eggs trapped in the end organ tissue. Since *S. haematobium* adult worms reside in the urinary vesical veins, eggs can directly enter the inferior vena cava and embolize to the pulmonary vessels at any stage of infection. The other species, principally *S. mansoni*, produce hepatosplenic schistosomiasis, which leads to non-cirrhotic portal hypertension; pulmonary embolization is a later finding after portocaval shunting develops. Once the ova reach the pulmonary circulation, the pathologic hallmark are granuloma formations (Fig. 136-8) in the arterioles and airspaces, progressing to an obliterative arteritis and eventually fibrosis causing pulmonary arterial hypertension (PAH).[112] However, the inciting embolization can also trigger autonomous, ongoing inflammation, principally mediated by tissue growth factor-beta, leading to plexiform or angiomatoid vascular lesions reminiscent of those seen in idiopathic PAH (iPAH).[114]

Finally, a presentation of pulmonary nodules due to clusters of deposited eggs surrounded by granuloma formation in the lungs has recently been described, which occurs both in the acute and early chronic phases.[115,116] These lesions resolve with treatment and are not associated with fibrosis or PAH, suggesting an intermediate stage. It has also led to the hypothesis that adult worms may migrate through the lungs and other ectopic organs and shed eggs *in situ* more commonly than previously recognized.

Clinical Manifestations

Acute schistosomiasis syndrome manifests as acute onset fevers, fatigue, myalgias, non-productive cough, and bronchospasm and

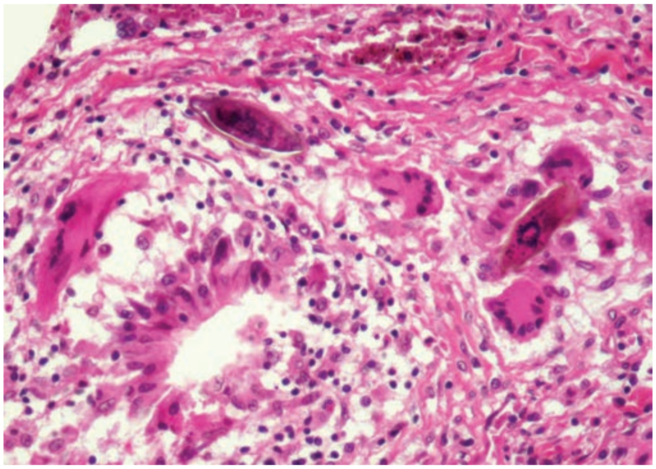


Figure 136-8 Lung biopsy demonstrating *Schistosoma japonicum* ova with surrounding granulomatous reaction on hematoxylin eosin stain at 20× magnification. *(Reproduced with permission from Dr. Dominick Cavuoti.)*

occurs almost exclusively in travelers or tourists coming from non-endemic regions.[112] Additionally, the pulmonary symptoms may become predominant several weeks after the febrile illness. With a compatible clinical syndrome and epidemiologic exposure, marked peripheral eosinophilia, elevated IgE levels, and patchy interstitial infiltrates or scattered micronodules with or without ground-glass, best seen on CT scan, are suggestive.[107] Radiographic findings may show up only after anti-helminthic treatment.

Often accompanied by the classic genitourinary or GI *Schistosoma* sequelae, the spectrum of chronic pulmonary schistosomiasis ranges from asymptomatic imaging abnormalities, chronic cough, chest pain or hemoptysis to end-stage PAH and cor pulmonale. A review of 10 cases of chronic pulmonary schistosomiasis described radiographic findings on high-resolution CT including lung consolidations, solid pulmonary nodules with peri-nodular halos, ground glass opacities, and hilar lymphadenopathy, all of which resolved with treatment.[117] Finally, chronic untreated or recurrent infection can lead to PAH and cor pulmonale which is indistinguishable clinically from other causes. Although limited by varying diagnostic criteria and lack of systematic screening in endemic areas, the current estimated prevalence of PAH in those with chronic hepatosplenic schistosomiasis is 5–10%.[114] The clinical presentation of those with schistosomiasis-related PAH appear similar to those with iPAH, but their hemodynamic profiles, response to vasodilator therapy and short-term survival appear more favorable based on a recent systematic review.[118]

Diagnosis

Diagnosis of active schistosomiasis involves microscopic identification in the urine or stool of the *Schistosoma* eggs, which can differentiate the various species.[119] However, sensitivity is poor even with serial testing in both acute and low burden infections. Serologies including ELISA and immunoelectrotransfer blot are primarily useful in returning travelers and non-endemic areas, and rapid antigen and molecular PCR-based diagnostics are becoming more widely available.[119] Demonstration of the ova in bronchoscopic samples or tissue biopsies are also confirmatory.

Treatment

The preferred treatment for active schistosomiasis is praziquantel, which targets the adult worms and prevents further oviposition.[120] The recommended dosages are either 40 mg/kg for one day (in one or two divided doses) for *S. haematobium*, *S. mansoni*, or *S. intercalatum* or 60 mg/kg for one day (in two divided doses) for *S. japonicum* or *S. mekongi*. Persistence of viable eggs on urine or stool microscopy at least 6 weeks after initial treatment would warrant retreatment with praziquantel. In acute schistosomiasis syndrome, corticosteroids are the primary treatment, with praziquantel given only after symptoms are fully resolved usually 4 to 6 weeks later. Antihelminthic therapy can reverse pulmonary nodules due to deposited eggs but not irreversible lung pathology in the later stage disease.

■ Paragonimiasis

Below we consider the etiology, pathogenesis, clinical manifestations, diagnosis, and treatment of paragonimiasis.

Etiology

Paragonimiasis is caused by lung flukes (trematodes) from the genus *Paragonimus*, with more than 15 species implicated in human disease. The disease is commonly acquired by consumption of raw, undercooked or pickled crustaceans (freshwater crabs and crayfish) infected with the metacercariae although infection from wild game meat such as boar and deer are reported.[121] It causes more than 20 million infections globally with the highest prevalence in southeast Asia where the predominant species is *Paragonimus westermani*; other species cause disease in Africa and South and Central America.[122] Autochthonous cases caused by *P. kellicotti* have been reported in North America associated with infected freshwater crayfish.[123]

Following human ingestion from infected food sources, the metacercariae excyst, penetrate the intestinal wall, and migrate from the abdominal cavity through the diaphragm into the pleural space and lungs. In the lungs, they mature into reddish-brown, hermaphroditic adult worms in cystic cavities, which produce golden-brown operculated eggs (~100 × 55 um in size) (Fig. 136-9) that are coughed up in sputum or swallowed and shed in the feces. Once in the environment, the eggs hatch and go on to complete the non-human life cycle in its two intermediate hosts, freshwater snails and crustaceans.

Pathogenesis and Pathology

The pathology of *Paragonimus* infection correlates with the three disease stages: (1) primary infection and migration; (2) encystation; and (3) death. Migration of the lung flukes through the pleural cavity and lungs induces inflammation, hemorrhage, and tissue necrosis as they "tunnel" from the periphery toward the bronchioles.

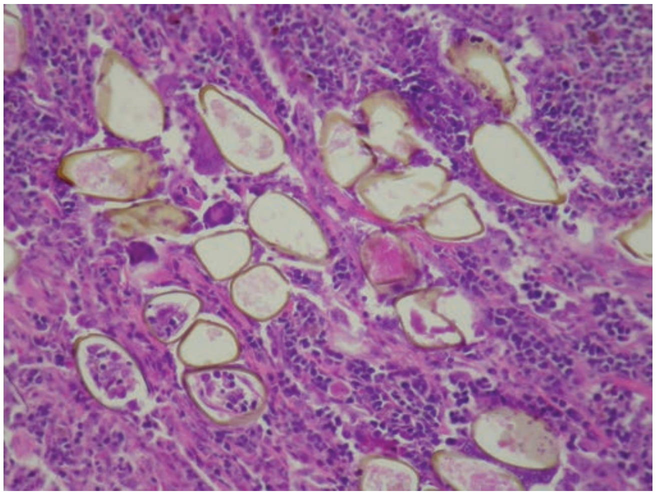


Figure 136-9 Lung biopsy demonstrating *Paragonimus westermani* operculated eggs on hematoxylin eosin stain at 100× magnification. *(Reproduced with permission from Dr. Dominick Cavuoti.)*

Surrounding neutrophilic and eosinophilic inflammation, with Charcot-Leyden crystals, can be seen along these tracks. The worms then encyst in the lungs, forming clusters of encapsulated cysts that communicate with each other or the bronchi and form fistula which allow eggs entry into the airways. Finally, with death of the worms, the cyst collapses leading to fibrosis or calcification. Ectopic migration of the flukes out of the lungs can spread to other areas, most commonly the central nervous system, abdominal viscera, and skin.

Clinical Manifestations

The clinical presentation varies based on the duration of infection and helminthic burden. Following a nonspecific prodrome of fever, diarrhea, abdominal pain, cough and urticaria a few weeks after infection, established pulmonary infection manifests after an incubation period of 2 to 16 weeks. The classic presentation involves fevers, cough, hemoptysis, and peripheral eosinophilia.[124] More chronically, the clinical presentation resembles chronic bronchitis or bronchiectasis marked by copious, rust brown, blood-tinged sputum which contains parasite eggs, necrotic material, and Charcot-Leyden crystals. The presence of peripheral eosinophilia, seen in 45–80% of cases, can be a key discriminating feature from other more common entities such as tuberculosis or malignancy.[124,125]

In early disease, chest radiographs demonstrate non-specific opacities from the migrating worms or may be normal in up to 20% of cases. In later disease, radiographic signs may include lobar consolidations, cystic or cavitary lesions, calcified nodules, hilar enlargement and pleural effusions.[126] Chest CT may demonstrate a classic "ring sign" of a subpleural nodule with central necrosis or surrounding ground glass, often accompanied by characteristic linear opacities to the pleural surface due to worm migration tracks.[126,127] Pleural fluid studies demonstrate an exudate with elevated eosinophilia, total protein and lactate dehydrogenase accompanied by low glucose and pH. Recognized in up to 25% of hospitalized patients with paragonimiasis, the most common extrapulmonary manifestation is neurologic disease, which can present as eosinophilic meningitis or ring-enhancing mass lesions presenting with headaches, vision changes and seizures.[122]

Diagnosis

Diagnostic microscopy can demonstrate the characteristic *Paragonimus* eggs in sputum, feces, BAL, or tissue biopsy. Multiple samples are needed since the yield of a single sputum or stool specimen is less than 40%.[122] For cases with negative microscopy, commercial ELISA serologies and a CDC-developed immunoblot are helpful with demonstrated high sensitivity (>90%) for *P. westermani*[128]; a Western blot specifically for the *P. kellicotti* antigens may be more useful for cases acquired in North America. Molecular diagnostics including PCR and multiplex protein microarrays are in development.

Treatment

The preferred treatment for paragonimiasis is praziquantel at a dose of 25 mg/kg three times daily for 2 to 3 days.[122] Symptoms improve rapidly while clearance of eggs from sputum and radiographic resolution may take weeks to months. Recurrent pleuropulmonary disease may require a second course of therapy.[129] An alternative regimen is triclabendazole at a dose of 5 mg/kg per day for 3 days or 20 mg/kg divided in two doses for one day.[130] In patients with concomitant CNS disease, corticosteroids are given to blunt the inflammatory response to the dying worms.

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CHAPTER 137

Nocardiosis and Actinomycosis

Daniel N. Maxwell
Reuben J. Arasaratnam
Alejandro Restrepo
Tara M. Babu

INTRODUCTION

Nocardia, a Gram-positive, filamentous bacteria, causes the rare infection known as nocardiosis and belongs to the *Nocardia* genus in the actinomycetes group. Ubiquitous in nature, *Nocardia* spp. are found worldwide in soil, water, and vegetation.[1] Actinomycosis is an indolent infection caused by anaerobic or microaerophilic bacteria primarily belonging to the genus *Actinomyces*. Each is discussed in detail below.

NOCARDIOSIS

The clinical spectrum of nocardiosis ranges from localized to disseminated disease in both animal and human hosts. It is an opportunistic pathogen, primarily infecting immunocompromised individuals. New molecular techniques have improved *Nocardia* spp. identification. Clinical manifestations mainly include cutaneous, pulmonary, and disseminated disease involving the brain. Treatment often requires regimens of multiple antibiotics for a prolonged duration of therapy.

■ History and Classification

In 1888, Edmon Nocard first isolated an aerobic actinomycetes, later named *Nocardia*, in cattle afflicted with bovine farcy, a lymphatic disease.[2] Two years later, Eppinger described the first human case of *Nocardia* infection in a man with both "pseudo tuberculous" pulmonary disease and central nervous system infection.[3] In 1921, Henrici and Gardner reviewed the world literature for every case of aerobic acid-fast actinomycosis and identified only 26 cases.[4] Despite the paucity of cases, they succeeded in describing aspects of nocardiosis that have influenced our current understanding; infection occurs via inhalation resulting in pulmonary disease, the occurrence of disseminated disease (i.e., the brain), and a disease course of approximately 6 months.

Molecular diagnostic techniques identifying key housekeeping genes such as 16S rRNA, gyrB, secA, hsp65, and/or rpoB have allowed a more comprehensive characterization of the taxonomy.[5] Consequently, *Nocardia* spp. have undergone significant taxonomic changes and species reclassification. The *Nocardia* genus consists of more than 80 species.[6] More than 40 species are associated with infections in humans.[6] Elucidation of further *Nocardia* species is ongoing. Commonly identified species responsible for infections in humans are *N. asteroides*, *N. nova*, *N. farcinica*, *N. otitidiscaviarum*, *N. transvalensis*, *N. brasiliensis*, *N. brevicatena*, *N. abscessus*, *N. cyriacigeorgica*, *N. veterana*, *N. paucivorans*, *N. wallacei*, *N. blacklockiae*, *N. elegans*, *N. concava*, and *N. cassostreae*.[7] Pulmonary infection is frequently caused by *N. cyriacigeorgica*, *N. nova* complex, and *N. farcinica*, while *Nocardia brasiliensis* is responsible for skin and soft tissue infections.[8]

■ Environmental Epidemiology

Nocardia spp. are not human commensals but are environmental saprophytes found widely in aquatic, vegetative, and soil-based environments.[1] Human infection occurs primarily from inhalation, direct skin/soft tissue inoculation, and rarely ingestion of bacteria. Nocardiosis occurs in men more than women. In the United States the primary route of *Nocardia* infection is secondary to inhalation. Some authors suggest a higher incidence of pulmonary nocardiosis in geographic regions such as the Southwest United States, where dry, windy and dust-laden climates potentiate aerosolization of *Nocardia*.[9] Nosocomial nocardiosis outbreaks are described in catheterized patients, postsurgical patients, and immunocompromised patient wards.[10–13] Sources of infection identified are proximal construction sites, fomites isolated from staff hands, contaminated air, and dust particles laden with bacteria.[13–15] In a nosocomial outbreak investigation of five cases of postoperative *N. farcinica* sternotomy infection, four of the patients had similar ribotype isolates as an isolate recovered from an anesthesiologist's hand.[14] *Nocardia* spp. infections are rarely implicated in intravascular catheter infections and peritoneal dialysis catheter infections in immunocompromised hosts.[10,16,17] Additionally, a cosmetic injection was responsible for an outbreak of *N. cyriacigeorgica* soft tissue infection (n = 8), confirmed by multilocus sequence typing.[18] Recently, two cutaneous nocardiosis cases occurred in immunocompetent hosts following intralesional steroid injections.[19]

■ Disease Pathogenesis

The current conceptual framework of *Nocardia* infection supports an initial immune response by macrophages and neutrophils that is able to suppress but not eliminate the bacteria.[20,21] IL-17 production by γδ T lymphocytes is important in neutrophil recruitment in nocardiosis.[22] Ultimately, clearance of the organism is dictated by T cell–mediated killing.[23] The integral role of neutrophils and T cells in the control and elimination of the disease is illustrated clinically by the higher incidence of disseminated disease in patients with neutrophil defects (e.g., chronic granulomatous disease). Impaired T-cell immunity is a known risk factor for *Nocardia* infection (discussed below). Humoral immunity is not believed to play a significant role in protection from *Nocardia* infections.

Nocardia is an opportunistic pathogen that primarily infects immunocompromised individuals. However, it does have the ability to infect immunocompetent hosts, including up to one-third of all cases in a retrospective study conducted from 1972 to 1974.[24] *Nocardia* virulence factors enable evasion of the host immune system. *Nocardia* is a facultative intracellular organism that inhibits phagosome–lysosome fusion,[25] resists phagosome acidification,[26] causes cell wall lipid induction of macrophages to produce proinflammatory cytokines (IL-1B, IL-6, and CCL-2), and suppresses microbicidal effects of macrophages and dendritic cells.[27] *Nocardia* bacteria undergoing log growth phase replication have the ability to evade phagocytosis.[28] Additionally, a critical virulence factor of *Nocardia* spp. is the production of superoxide dismutase and catalases enabling resistance to oxidative killing.[29]

As previously mentioned, *Nocardia* central line–associated bloodstream infections (CLABSI) are rare. In an in vitro biofilm model, *Nocardia* spp. form dense branching networks within a heavy biofilm matrix on the surface of central venous catheters (CVC).[10] The biofilm protects the bacteria from relatively low serum concentrations of antimicrobial drugs. Exposure to high concentrations of antimicrobials, lock therapy, and removal of CVCs may be effective methods for managing biofilm production in isolated CVC infections.[10]

■ Risk Factors for Disease

In the 1970s, a national survey among infectious disease practitioners in the United States estimated the incidence of *Nocardia* infection to be between 500 and 1000 cases per year.[24] The vast majority (>80%) of infections were classified as severe pulmonary or systemic infections, and 15% of cases had no identified underlying immunosuppressive condition.[24] Due to an increasing population of patients on immunomodulating medications, the incidence of nocardiosis is increasing. A study conducted in Quebec, Canada, confirmed a significant increase from 1997 to 2008 in the annual incidence of *Nocardia* spp. from 0.33 to 0.87 per 100,000 inhabitants.[30] The majority of nocardiosis cases occur in immunocompromised patients, most commonly in the setting of solid organ and hematologic stem cell transplantation, malignancy, immunosuppressive medications, and human immunodeficiency virus.

Solid-organ Transplantation

The incidence of *Nocardia* infections in solid-organ transplant recipients is estimated to be between 0.04% and 3.5%, with infection commonly occurring within the first 2 years post-transplantation.[31–33] In a case-control study of 35 SOT patients with nocardiosis, higher incidence of nocardiosis was found in heart (2.5%) and lung (3.5%) transplant recipients compared with liver (0.1%) and kidney (0.2%) transplant recipients.[32] Heart and lung transplantation require higher net states of immunosuppression to maintain the allograft. Impaired respiratory immune surveillance and increased pulmonary diagnostic surveillance (i.e., frequent bronchoscopies) also may contribute to the high incidence of nocardiosis in lung transplant recipients.

In a large, multicenter, retrospective study in Europe, the main risk factors identified for nocardiosis in a solid-organ transplant population included older age, elevated calcineurin trough level inhibitor in the month preceding diagnosis, use of tacrolimus or corticosteroids at the time of diagnosis, and longer duration of intensive care unit stay following transplantation.[33] History of preceding cytomegalovirus disease was identified as a risk factor for nocardiosis, although it is unclear if this finding represents the immunomodulatory potential of the virus or reflects a high net state of immunosuppression in the host.[32]

The 1-year mortality rate from nocardiosis in SOT recipients ranges from 11% to 17%.[32–34] One case-control study found a 10-fold higher all-cause mortality rate in SOT recipients with nocardiosis compared to those without.[35] In a case-control study of SOT recipients with nocardiosis (n = 117), independent risk factors associated with mortality were a history of malignancy, prior invasive fungal infection, and increased transplant donor age.[33] Acute rejection and consequent increased immunosuppression in the preceding year of nocardiosis diagnosis was associated with a decreased risk of mortality.[33] The authors attributed these paradoxical findings to increased surveillance and screening for infection or potential blunting of the inflammatory response secondary to *Nocardia* infection.

Hematopoietic Stem Cell Transplantation and Malignancy

Nocardiosis occurs more in allogeneic stem cell transplant (SCT) recipients than autologous stem cell recipients.[36,37] In allogeneic SCT recipients, the risk of *Nocardia* infection within the first 2 years post-transplant is estimated from 0.3% to 1.7%.[36–38] In small case series, late infections (>500 days post-transplant) are associated with the use of high-dose corticosteroids for graft-versus-host disease.[39] In single-center cohort studies, mortality rates are as high as 40% to 50%.[39,40] Several authors have noted a correlation between delayed lymphocyte recovery, particularly CD4 T lymphocytes, and nocardiosis in the allogeneic stem cell transplant population.[41,42]

Patients with solid tumor malignancies are also at risk for nocardiosis due to immunosuppressive chemotherapy regimens. In a retrospective review of admissions at a major cancer center in the United States, spanning 1988 to 2001, 43 episodes of nocardiosis were detected (constituting an incidence of 60 cases per 100,000 admissions).[43] Sixty-four percent had an underlying hematologic malignancy and 36% had an underlying solid tumor malignancy.[43] Pulmonary infection was the most common manifestation (70% of cases), with preceding chemotherapy or receipt of corticosteroids being documented risk factors.

HIV Infection

Nocardiosis is relatively rare in individuals infected with HIV. In a retrospective analysis from 1981 to 2000, in an 1100-bed teaching hospital in Madrid, Spain, only 8 cases of *Nocardia* infection were diagnosed in those with HIV, constituting an incidence of 0.38% among the HIV population.[44] The majority of patients were male, with an average age of 28 and median CD4 counts of 35 cells/μL.[44] Of the 8 patients in this series, 2 died from progressive pulmonary infection. In several case reports and case series of *Nocardia* infection in individuals living with HIV, identified risk factors were CD4 count less than 200 or advanced AIDS, preceding use of systemic corticosteroids,[45,46] and a delay in diagnosis leading to detection at a late stage of disease.[47]

Immunosuppressive Medications

In several large cohort studies, the chronic administration of systemic corticosteroids alone, or in combination with other immunosuppressive medications, remains the most consistent risk factor for development of nocardiosis.[32,43] It is imperative to consider *Nocardia* in the differential diagnosis of a patient presenting with pulmonary infection on chronic steroids, regardless of whether there is underlying lung disease.[48,49] While the risk of *Nocardia* infection is related to cumulative use (dose and duration) of corticosteroids, cases of *Nocardia* infection occur with daily doses of prednisone as low as 10 to 15 mg daily.[50,51] The association of nocardiosis and use of other immunosuppressive agents such as TNF-α inhibition,[52] IL-6 inhibition,[53] and anti-CD20 monoclonal antibody therapy[54,55] are described in patients with autoimmune inflammatory disease. However, due to the low incidence of *Nocardia* in these populations, the limited case reports published, and coadministration of other immunosuppressants (i.e., corticosteroids), no conclusions regarding causality for nocardiosis can be drawn for these agents.

Chronic Lung Disease

The presence of chronic lung disease is considered a risk factor for the development of nocardiosis. In a large retrospective analysis carried out at a tertiary medical center between 1996 and 2013, noncystic fibrosis bronchiectasis was common in both immunocompetent (38%) and immunocompromised (10%) patients.[56] The association of chronic lung disease with nocardiosis may be related mechanistically to abnormal bronchial architecture, anatomy, and mucociliary clearance that enables establishment and interference with clearance of the organism. In addition, concomitant use of systemic steroids for several chronic lung diseases (e.g., COPD, interstitial lung disease) is likely a major contributive risk factor.

Inherited Immunodeficiencies and Genetic Syndromes

Patients with chronic granulomatous disease (CGD) possess genetic mutations in the phagocytic NADPH oxidase system leading to impaired phagocytosis and increased risk for infections, including *Nocardia*.[57] In patients with CGD, prophylaxis with IFN-γ and a sulfonamide is recommended to prevent disseminated nocardiosis.[58]

Anticytokine antibodies are an emerging cause of immunodeficiency in adults.[59] In a case-control study of otherwise immunocompetent patients with CNS nocardiosis, anti–granulocyte-macrophage colony-stimulating factor (anti–GM-CSF) autoantibodies were detected in 5 of 7 patients with nocardiosis.[59] Anti–GM-CSF antibodies have also been associated with pulmonary alveolar proteinosis and other opportunistic infections.[60,61] Lastly, idiopathic CD4 T-lymphocytopenia is a rare condition that is defined as

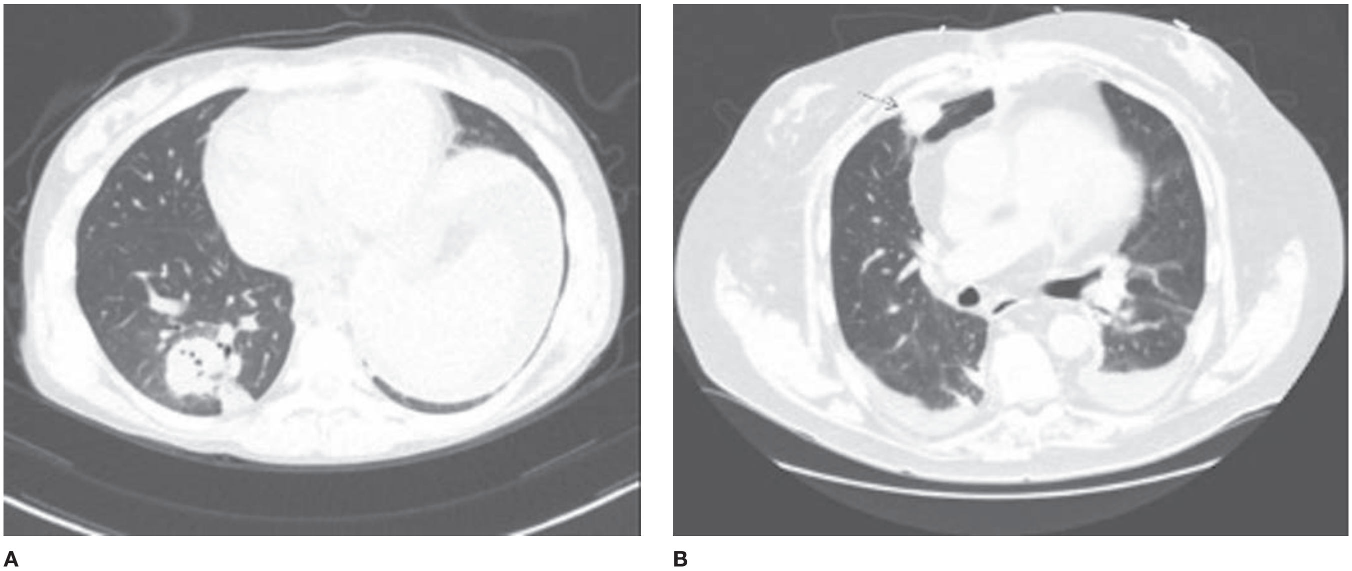


Figure 137-1 Pulmonary nocardiosis in a 17-year-old female with past medical history of a pediatric liver transplant developed a nonproductive cough. Her sputum culture was positive for *Nocardia* spp. Her brain MRI was negative for CNS infection. **A.** Axial CT image of the chest depicts a right lower lobe mass with internal foci of air. **B.** Axial CT image of the chest demonstrates a right upper lobe peripheral nodule[169] abutting the anterior chest wall pleura. *(Reproduced with permission from Sally Chuang, MD.)*

persistent CD4 T-cell lymphopenia without HIV or an alternative immunodeficiency diagnosis, which predisposes patients to opportunistic infections, such as *Nocardia* infection.[62]

■ Clinical Manifestations

Below we discuss the pulmonary and extrapulmonary manifestations of nocardiosis.

Pulmonary Nocardiosis: Clinical and Radiographic Findings

Pulmonary infection is the major clinical manifestation of nocardiosis, due to inhalation or aspiration of bacterial mycelia. Pulmonary infections represent around 50% to 70% of all nocardiosis cases.[7,45,63] The onset of nocardiosis is primarily subacute, but it may occur more acutely in immunocompromised hosts. Cough and fever are the most common symptoms described in pulmonary nocardiosis. Additionally, systemic symptoms are common, consisting of fever, chills, malaise, night sweats, fatigue, and unexpected weight loss. Chest pain, pleuritic pain, hemoptysis, and dyspnea are rare.

The spectrum of radiographic findings for pulmonary nocardiosis includes lung infiltrates, nodules, cavitation, and masses (Figs. 137-1 and 137-2). Infection can be isolated to a single lobe or present as multilobar pneumonia. The masslike appearance may be indistinguishable radiographically from malignancy. The differential diagnosis for pulmonary nocardiosis is broad and ranges

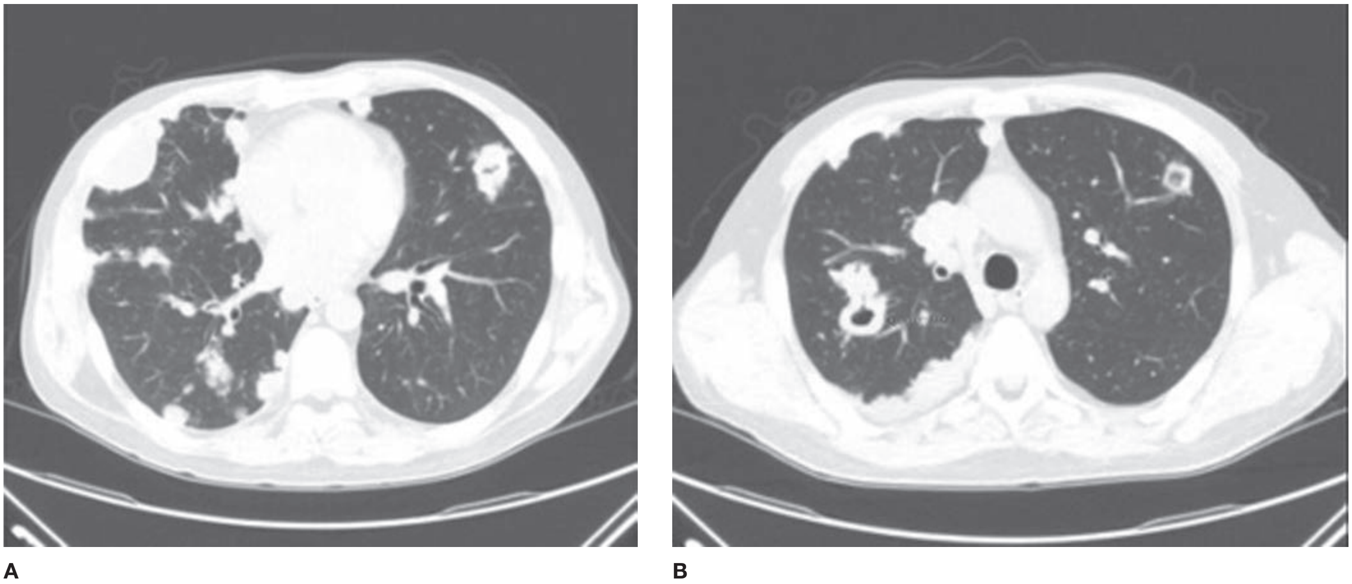


Figure 137-2 Pulmonary and CNS nocardiosis in a 36-year-old male with a past medical history of anaplastic B-cell lymphoma treated with chemotherapy (cyclophosphamide, doxorubicin, etoposide, vincristine, and prednisone) who presented to the hospital with productive cough and mild headache. **A.** Axial CT of the chest shows bilateral centrilobular nodules right > left, some of which contain foci of air. **B.** Axial CT of the chest demonstrates a large central cavitary lesion of the right upper lobe. *(continued)*

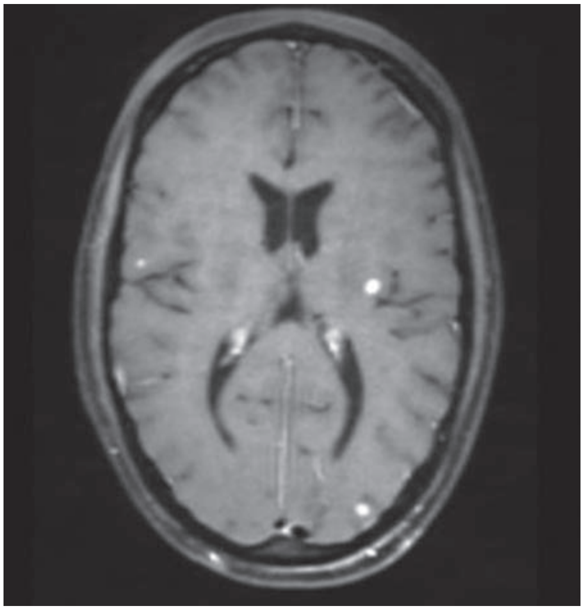


Figure 137-2 *(Continued)* **C.** MRI of the brain shows multiple, variable-sized, enhancing parenchymal lesions involving the supra- and infratentorial compartment bilaterally, the largest involving the left posterior subinsular region measuring 5 × 5 mm. *(Reproduced with permission from Sally Chuang, MD.)*

from bacterial and fungal pathogens to malignancy (Table 137-1). Pulmonary nodules are the most common radiographic presentation of pulmonary nocardiosis. In a large case-control study of 117 solid-organ transplant recipients, radiographic imaging demonstrated pulmonary nodules in 75% of cases, cavitation in 32% of cases, lung consolidation in 41% of cases, and pleural effusion in 26% of cases.[33] Fifty-six percent had multilobar involvement, and 51% had bilateral disease.[33] In a study of 25 immunocompromised and immunocompetent patients, the most common chest CT findings consisted of multiple pulmonary nodules (96%), consolidation (76%), and cavity (52%).[64] No difference was found in the CT findings between immunocompromised and immunocompetent patients.

The isolation of *Nocardia* from patients without evidence of lung infection has been shown in patients with underlying lung disease, that is, bronchiectasis or cystic fibrosis, and requires careful consideration. *Nocardia* isolation in an immunocompromised host should always be considered pathogenic, and treatment is indicated.

Extrapulmonary nocardiosis results from the hematogenous or contiguous spread of bacteria from the lung to other sites in the body. Infection may spread contiguously to the pleural space, mediastinum, pericardium, and/or vena cava. Empyema is present in one-third of cases. The central nervous system (CNS) is the most common site for extrapulmonary nocardiosis and is discussed below (Fig. 137-2). Other sites of disseminated disease are the skin and subcutaneous tissues, eyes (especially the retina), kidneys, joints, bones, and heart.[65]

Cutaneous Manifestations

Nocardia cutaneous infection often results from the direct inoculation of bacteria. Skin and soft tissue manifestations of nocardiosis are categorized into four classes: superficial soft tissue infection (cellulitis or abscess), lymphocutaneous infection, mycetoma, and manifestations secondary to disseminated disease (Figs. 137-3 and 137-4). Cutaneous lesions occur in both immunocompetent and immunocompromised hosts. Similar to *Nocardia* pneumonia, skin lesions have both acute and subacute onset, and manifest as indolent lesions, presenting days to months following inoculation.

TABLE 137-1 Selected Differential Diagnosis for Nocardiosis

Pulmonary Disease	
Fungal infection	*Aspergillus* *Mucormycosis* *Histoplasmosis* *Blastomycosis* *Cryptococcus* *Coccidioidomycosis*
Bacterial infection	Actinomycosis *Rhodococcus equi* *Burkholderia pseudomallei* Septic emboli secondary to bloodstream infection Other bacteria
Mycobacterial infection	*M. tuberculosis* Nontuberculous mycobacterial (NTM) infections
Malignancy	Primary and metastatic
Cutaneous Disease	
Lymphocutaneous disease	Sporotrichosis *Mycobacterium marinum*
Superficial cellulitis	Group A *Streptococcus* *Staphylococcus aureus* *Erysipelothrix* species *Francisella tularensis*
Mycetoma (late stage)	Actinomycosis Fungal infections • *Pseudallescheria* species • Other molds
Other	Cutaneous leishmaniasis Cryptococcosis Rapidly growing NTM (*Mycobacterium fortuitum, Mycobacterium chelonae)*
Central Nervous System Disease	
Malignancy	Primary and metastatic
Bacterial abscess	
Vascular infarction	
Other (depending on host risk factors)	Toxoplasmosis *M. tuberculosis* *Taenia solium*/cysticercosis Fungal infection • Cryptococcosis • Aspergillosis • Mucormycosis

Modified with permission from Wilson JW. Nocardiosis: updates and clinical overview. Mayo Clin Proc. 2012;87(4):403–407.

Mycetoma is a chronic, painless, progressive, and destructive bacterial or fungal infection of the skin, subcutaneous tissues, and fascia that may involve bone. Mycetoma occurs in rural, subtropical areas with a predilection for men.[66] The lesion initially presents as a nodule that can evolve a fistulous tract to the skin. Mycetoma forms following a trauma to an extremity, and pathology is consistent with suppurative granulomas, necrotizing lesions with fibrosis, and sinus formation.[66] Exudate may contain granules secondary

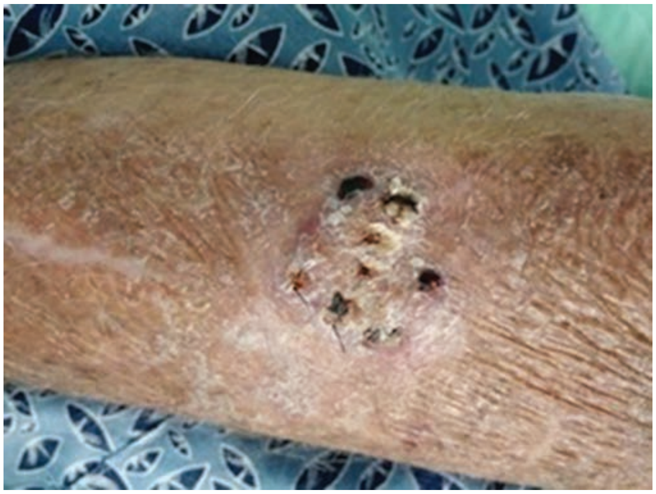


Figure 137-3 *Nocardia* skin and soft tissue infection in a 73-year-old male with a past medical history of kidney transplant who presented with skin lesions following a history of trauma related to working with wood. Skin biopsy was positive for *Nocardia otitidiscaviarum*. *(Reproduced with permission from Carolyn D. Alonso, MD, FIDSA.)*

to clumps of bacteria. In North America, South America, and Australia, *N. brasiliensis* is the *Nocardia* species primarily associated with mycetoma.[66]

In solid-organ transplant recipients, cutaneous infection represents approximately 10% of all *Nocardia* manifestations.[32,67] Cutaneous nocardiosis presents similarly to other opportunistic infections in immunocompromised hosts, and bacterial, fungal, and mycobacterial diseases should be considered. *Nocardia* cutaneous infections manifest as pustules, cellulitis, or pyoderma, often resembling typical bacterial skin and soft tissue infections due to *Streptococcus* and *Staphylococcus* species.[66] Biopsy and histopathology are diagnostic for *Nocardia* and other pathogens. Since *Nocardia* skin infection could represent sequelae of a disseminated process, we recommend imaging to evaluate for disseminated disease (i.e., pulmonary and CNS) in the immunocompromised host with a cutaneous infection.

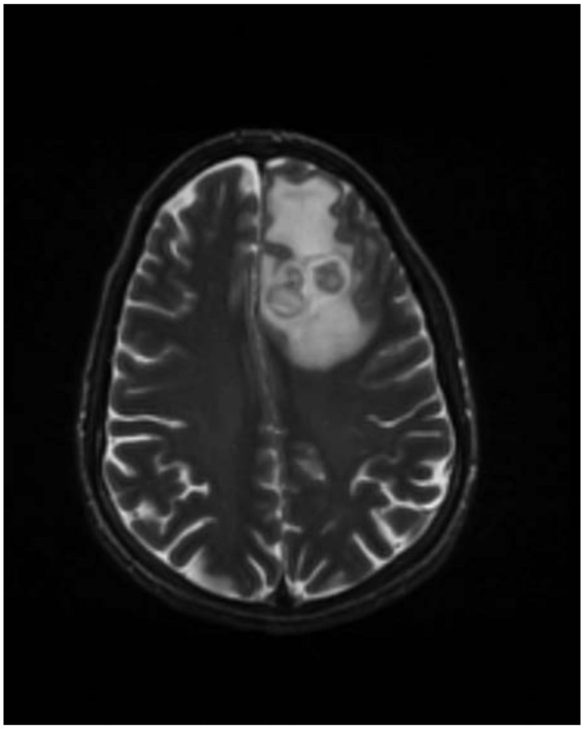
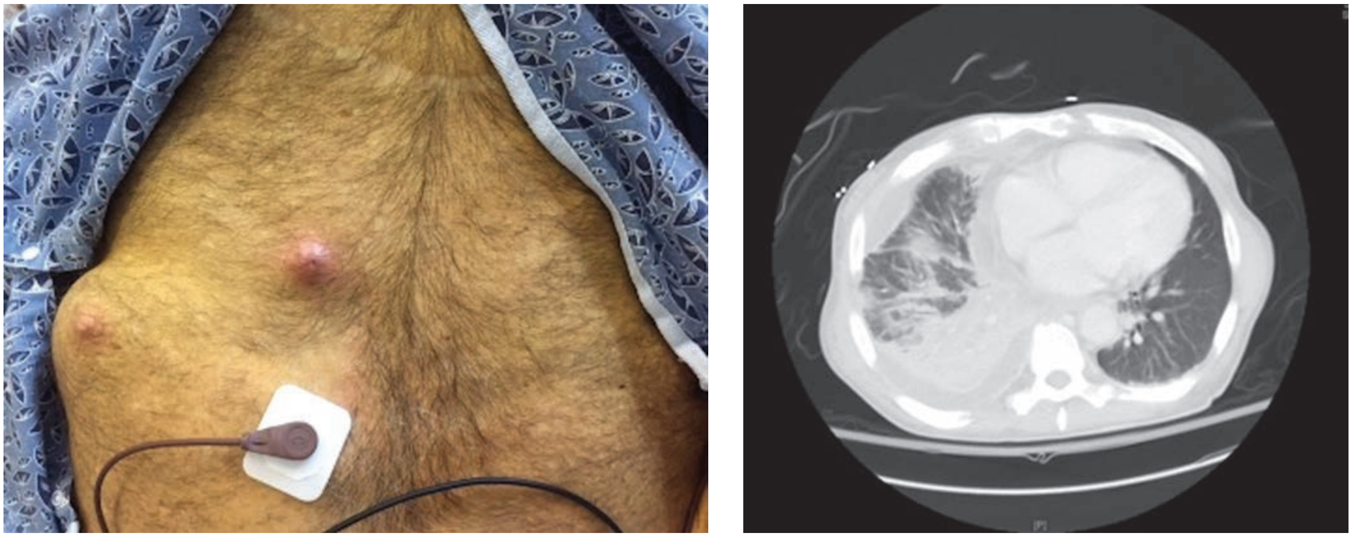


Figure 137-5 Fluid-sensitive MRI image demonstrates a left frontal brain abscess from *Nocardia asteroides* with surrounding edema in a middle-aged man with a history of amyloid treated by autologous bone marrow transplant and heart transplant. *(Reproduced with permission from Camille Kotton, MD, FIDSA.)*

Central Nervous System Manifestations

Central nervous system infection is insidious in nature and presents in one-third of nocardiosis cases and up to 44% of disseminated cases.[66] Radiographic findings, on CT or magnetic resonance imaging (MRI), consist of multiloculated, single or multiple brain abscesses within the supratentorial region (Figs. 137-2 and 137-5). Meningitis is less common. Asymptomatic brain lesions occur frequently in nocardiosis; CNS imaging (preferably MRI) should



A **B**

Figure 137-4 Cutaneous and pulmonary nocardiosis in a 60-year-old male with past medical history of a liver transplant who presented with dry cough and associated skin lesion. **A.** Erythematous cutaneous nodule on the chest. **B.** Axial CT of the chest is significant for a nodular and endobronchial infection with an associated pleural effusion in the right lung. *(Reproduced with permission from Carolyn D. Alonso, MD, FIDSA.)*

be considered in immunocompromised hosts and patients with pulmonary or disseminated disease. The CNS radiographic imaging of choice is MRI. Neurologic presentations in the CNS include headache, confusion, focal neurologic signs, seizures, and coma.[68] CNS infection is due primarily to hematogenous dissemination, but positive blood cultures are rarely detected.

Other Presentations of Nocardiosis

Disseminated nocardiosis is defined as the involvement of two noncontiguous organs. Disseminated disease has been associated with an all-cause mortality rate as high as 44%.[10,11] *Nocardia* bacteremia is rarely identified. Foreign materials as a prosthetic heart valve or central venous catheters are identified risk factors for *Nocardia* spp. bacteremia.[10,11]

Nocardia ocular infections are rare. Infections occur following eye trauma, ocular surgery, or ophthalmic infection secondary to hematogenous spread in the immunocompromised host.[69–71] Ocular nocardiosis manifests as uveitis, choroiditis, retinal abscess, retinal detachment, keratitis, and iritis.[8] *Nocardia* endophthalmitis can result in blindness and is associated with significant mortality.[8,69]

■ Diagnosis

The definitive diagnosis of nocardiosis is made by isolating the bacteria in culture from clinical samples. Blood cultures are positive in only 25% of patients (*Nocardia* grows in routine blood cultures, without need for fungal or mycobacterial isolators). Tissue biopsy or abscess drainage of infected sites is usually necessary. Bronchoalveolar lavage, pulmonary nodule biopsy, or skin tissue biopsies of infected sites are often performed for diagnosis. If *Nocardia* spp. is identified in pulmonary nocardiosis, it is reasonable to assume that the CNS radiographic abnormalities are due to the same process.[72] However, in the immunocompromised host there is a higher risk for concurrent pathogens and early brain tissue biopsy should be considered.

Historically, *Nocardia* is difficult to identify in the laboratory. *Nocardia* appears as a Gram-positive beaded or branching filamentous bacteria on Gram stain. The presence of *Nocardia* on Gram stain may allow for a presumptive diagnosis. Most strains of *Nocardia* possess weakly acid-fast staining properties, enabling differentiation from *Actinomyces*. In a study of 80 patients with *Nocardia*-positive cultures, 50 (64%) patients were positive by Gram stain and only 26 (51%) were also positive by modified acid-fast staining.[9]

The classic histologic finding of nocardiosis is an abscess with neutrophilic predominance and necrosis. Surrounding granulation tissue is present without extensive fibrous encapsulation. The Brown-Brenn and Gomori methenamine silver stains can be used to identify bacteria from tissue histopathologic samples[73] (Fig. 137-6).

Nocardia species identification aids in guiding therapy, as discussed below. Gene sequencing of *Nocardia* proteins (i.e., heat shock protein 65) or 16S rRNA are now the standard methodology

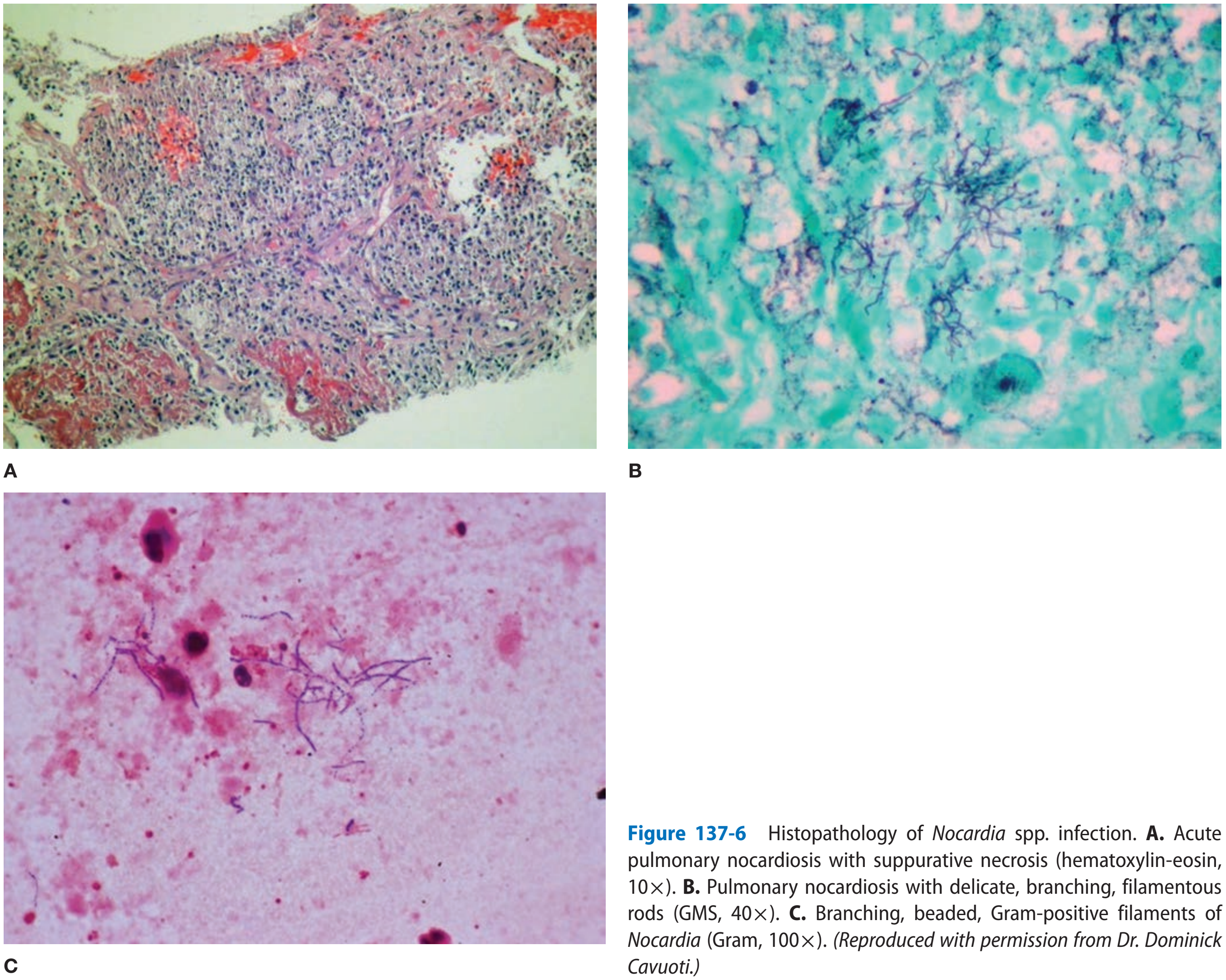


Figure 137-6 Histopathology of *Nocardia* spp. infection. **A.** Acute pulmonary nocardiosis with suppurative necrosis (hematoxylin-eosin, 10×). **B.** Pulmonary nocardiosis with delicate, branching, filamentous rods (GMS, 40×). **C.** Branching, beaded, Gram-positive filaments of *Nocardia* (Gram, 100×). *(Reproduced with permission from Dr. Dominick Cavuoti.)*

TABLE 137-2 Susceptibility Patterns for *Nocardia* Species

	TMP-SMX	IMI	AMK	MIN	CTX	CIP	AMOX-CLAV	LNZ	MOX	CAM/AZ	TIG[a]
N. abscessus	+	+/−	+	+/−	+	−	+	+	−	−	+
N. farcinica	+/−	+/−	+	+/−	−	+/−	+/−	+	+	−	−
N. nova complex	+	+	+	+/−	+	−	−	+	−	+	+/−
N. brasiliensis	+	−	+	+/−	+/−	−	+	+	+/−	−	+
N. transvalensis	+	+	+/−	+/−	+	+	+/−	+	+	−	ND
N. otitidiscaviarum	+	−	+	+/−	−	+/−	−	+	+/−	+/−	ND
N. cyriacigeorgica	+	+/−	+	+/−	+	−	+/−	+	+/−	−	+/−

TMP-SMX, trimethoprim-sulfamethoxazole; IMI, imipenem; AMK, amikacin; MIN, minocycline; CTX, ceftriaxone; CIP, ciprofloxacin; AMOX/CLAV, amoxicillin–clavulanic acid; LNZ, linezolid; MOX, moxifloxacin; CAM, clarithromycin; AZ, azithromycin; TIG, tigecycline.

+, susceptible; –, resistant, +/–, variable; ND, no substantial data for conclusion.

[a] *There are no established interpretive categories for susceptibility testing for tigecycline; a minimum inhibitory concentration ≤1 μg/mL was arbitrarily designated as susceptible.*

Data from Restrepo A, Clark NM; Infectious Diseases Community of Practice of the American Society of Transplantation. Nocardia infections in solid organ transplantation: Guidelines from the Infectious Diseases Community of Practice of the American Society of Transplantation. Clin Transplant. 2019;33(9):e13509.

for speciating *Nocardia*. Multilocus analysis may be indicated for distinguishing closely related *Nocardia* species. Additionally, matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF) is a rapid and cost-effective protein profiling methodology for identifying *Nocardia* spp. once bacterial growth is present.[74–76] However, MALDI-TOF relies on a prior validated protein profile database for the specific pathogen isolated. Uncommon bacteria species remain a challenge for MALDI-TOF MS identification.

■ Treatment

The standard treatment for nocardiosis is antibiotic therapy; adjunct surgical debridement is sometimes required. Due to the relatively low incidence and wide variability in the clinical presentation of nocardiosis, no prospective controlled clinical trials evaluating comparative treatments exist. *Nocardia* is variably resistant to different antibiotic classes. Empiric therapy consisting of two or three drugs is recommended for severe infection, particularly CNS disease, while awaiting antibiotic susceptibility testing (Table 137-2). Due to favorable susceptibility patterns, decreased *Nocardia*-associated mortality, lower infection relapse risk, and historic clinical experiences, sulfonamides are considered the drug of choice for nocardiosis (Table 137-3).

Historically, the most data and clinical experiences for nocardiosis treatment are with sulfonamides.[77,78] In the United States, trimethoprim-sulfamethoxazole (TMP-SMX) is the only parenteral sulfonamide and the preferred sulfonamide for nocardiosis. TMP-SMX has shown excellent clinical efficacy for nocardiosis treatment.[77,78] Most patients demonstrate clinical improvement from nocardiosis 7 to 10 days following initiation of empiric sulfonamide therapy.[6] Increasing sulfonamide resistance in *Nocardia* isolates highlights the need for species identification and antibiotic susceptibility data. Resistance rates range from 3% to 10% and are reported as high as 20% in certain *Nocardia* spp.[79] A cross-sectional surveillance study conducted in the United States found TMP-SMX and/or sulfamethoxazole resistance as low as 2% (n = 552).[80]

The recommended dose for TMP-SMX for isolated *Nocardia* cutaneous infection is 5 to 10 mg/kg/day (based on trimethoprim component) divided in 2 to 4 doses. Our recommended dosage of TMP-SMX for pulmonary, disseminated, and CNS nocardiosis is 10 to 15 mg/kg/day (based on trimethoprim component) divided in 2 to 4 doses. Renal dosing (for creatinine clearance of ~<30 mL/min) of sulfonamides is necessary and often indicated in transplant recipients. Clinical failures with sulfonamide therapy are rare; however, if TMP-SMX resistance is present alternative therapies should be considered, and this is why we often start with multiple agents. TMP-SMX intolerance is demonstrated in 20% to 50% of patients, and side effects include myelosuppression, renal failure, hepatitis, and in rare cases aseptic meningitis. In a retrospective study

TABLE 137-3 Empiric Therapy Recommendations for Nocardiosis

Treatment	Cutaneous	Mild Pulmonary Disease	Severe Pulmonary Disease[a]	Cerebral Disease[a]	Disseminated Infection[a]
Primary drugs	TMP-SMX	TMP-SMX	TMP-SMX + imipenem *or* Imipenem + amikacin	TMP-SMX + imipenem *or* TMP-SMX + imipenem + amikacin	TMP-SMX + imipenem *or* Imipenem + TMP-SMX + amikacin
Alternative drugs	Linezolid	Imipenem + linezolid	Imipenem + linezolid	Imipenem + amikacin and/or linezolid *or* TMP-SMX + imipenem and/or linezolid	Imipenem + amikacin and/or linezolid *or* TMP-SMX + imipenem and/or linezolid

IV, intravenous; PO, oral; TMP-SMX, trimethoprim-sulfamethoxazole; CTX ceftriaxone.

For severe disease, consider three-drug empiric therapy.

(n = 24) of patients with pulmonary nocardiosis, 11 of 21 (52%) patients who received TMP-SMX required antibiotic cessation due to adverse events.[81] Adverse events included pancytopenia 45.5%, gastrointestinal symptoms 18.2%, electrolyte imbalance 18.2%, renal failure 18.2%, drug fever 9.1%, and rash 9.1%. The median duration from the initiation of TMP-SMX treatment to adverse effects was 8.0 ± 5.4 days.[81] If a patient is allergic to sulfonamides, desensitization should be considered when possible.

Imipenem has variable activity in vitro and resistance is present in some *Nocardia* spp. (Table 137-2). Imipenem tends to have a better susceptibility profile than meropenem for *Nocardia* species.[82] However, meropenem is an alternative to imipenem, particularly if there is concern for imipenem lowering the seizure threshold.[83] Identified risk factors for seizure and imipenem use consist of renal dysfunction, epilepsy, and underlying CNS disease.[84] In a more recent meta-analysis, carbapenems posed a low overall risk of seizure, but the risk of seizure was higher with the use of carbapenems compared with noncarbapenem antibiotics.[85] Although imipenem was more epileptogenic than noncarbapenem antibiotics, imipenem was not more epileptogenic than meropenem in a head-to-head comparison.[85] Ertapenem should not be used for nocardiosis therapy, as it does not cover *Nocardia* well. In vitro amikacin has broad activity against *Nocardia* spp. (Table 137-2). Amikacin does not have adequate CNS penetration, and the side-effect profile of nephrotoxicity and hearing loss can be treatment-limiting. Amikacin levels require close monitoring. Imipenem and amikacin combination therapy is efficacious for the treatment of pulmonary and CNS nocardiosis in mouse models.[86] Additionally, the treatment of choice for *Nocardia* keratitis is topical amikacin.[87]

Linezolid is an oxazolidinone drug with a broad activity across *Nocardia* species (Table 137-2).[88] Linezolid has successfully treated nocardiosis alone or as part of combination therapy in case series of patients with TMP-SMX intolerance or allergy.[47,89] Due to its favorable in vitro susceptibility and high bioavailability, linezolid is a reasonable addition to empiric therapy while awaiting speciation and susceptibility data. Some clinicians prefer linezolid over amikacin in empiric therapy due to the more favorable side-effect profile of linezolid in the short term and its excellent CNS penetration. Use of linezolid (>2 weeks) can result in myelosuppression. Clinically, linezolid may be given twice a day then tapered to daily dosing due to the slow-growing nature of *Nocardia* and to minimize myelosuppression. In a retrospective review, linezolid-containing regimens (n = 20) and non-linezolid regimens (n = 8) were evaluated.[90] The median linezolid induction therapy duration was 28 days. The most common adverse effects in linezolid-containing regimens were thrombocytopenia (45%) and anemia (40%).[90] Adverse events prompting the discontinuation were more common due to TMP-SMX (40%) than linezolid (20%). There was no significant difference in 30-day mortality between the two treatment arms.[90] Other adverse events due to linezolid are serotonin syndrome with coadministration of selective serotonin reuptake inhibitors (SSRIs), peripheral neuropathy, and lactic acidosis. Tedizolid is a newer drug in the oxazolidinone class. In an in vitro susceptibility study, tedizolid had a MIC90 value two to three dilutions more active than linezolid for most *Nocardia* spp., with the exception of the *N. nova* complex and *N. brasiliensis*.[91] Tedizolid possesses a longer half-life, higher protein-binding capacity, and lower CNS penetration than linezolid. Tedizolid causes less myelosuppression and serotonin syndrome with coadministration of SSRIs compared with linezolid. A few case reports and a case series have demonstrated the effective use of tedizolid for nocardiosis treatment.[92–94]

Third-generation cephalosporins (ceftriaxone, cefotaxime, and cefuroxime) have variable activity against *Nocardia* species (Table 137-2) but a favorable side-effect profile and excellent CNS penetration. Several case reports have demonstrated successful combination therapy with ceftriaxone for the treatment of CNS nocardiosis.[95,96] Ceftriaxone, cefotaxime, and cefuroxime are reasonable therapies for *Nocardia* once susceptibility data are available.

Minocycline is the tetracycline with the best in vitro activity against *Nocardia* spp. Minocycline has been used in combination therapy.[45,97] However, treatment failure with minocycline has been described.[98] Minocycline is an option for cutaneous infection when TMP-SMX is not an option and susceptibility data are available. Minocycline toxicity includes photosensitivity, headache, nausea, dizziness, esophageal ulcerations, and skin changes with prolonged use.[99]

Amoxicillin-clavulanate provides moderate coverage against *Nocardia* spp., particularly *N. brasiliensis*. Amoxicillin-clavulanate is useful for the treatment of *Nocardia* spp. when susceptibilities are known.[100,101]

In vitro susceptibility of *Nocardia* spp. varies for tigecycline, fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin), and macrolides (azithromycin, clarithromycin) (Table 137-2).[82] A few case reports mention successful therapy, but these agents are not first-line empiric therapies.[102–104]

Following empiric therapy, targeted antibiotic therapy guided by susceptibility data is recommended. Patients may be transitioned from parenteral to oral therapy after 3 to 6 weeks based on clinical improvement and antimicrobial susceptibility results. However, undrained abscesses and persistent necrotic areas often require prolonged parenteral antibiotics with radiographic monitoring. Decreasing immunosuppression when possible is an important adjunct to antibiotic therapy for all *Nocardia* infections. Surgical drainage may be necessary in the treatment of nocardiosis, particularly in cerebral and soft tissue abscesses refractory to antibiotic therapy. Pericardial effusions, mediastinal collections, and empyema secondary to pulmonary nocardiosis require drainage and antibiotic therapy. The risks and benefits of abscess drainage need to be considered. If drainage of the abscess is deemed unsafe, radiographic monitoring for resolution on antibiotic therapy is indicated.

■ Duration of Treatment

The duration of therapy has not been well studied. Therapy duration is based on the site of infection, host net state of immunosuppression, and clinical response to therapy (Table 137-4). In cutaneous nocardiosis in an immunocompetent host, antimicrobial therapy is recommended for 1 to 3 months.[6] Uncomplicated pulmonary infection in an immunocompetent host without neurologic involvement is treated for a minimum of 6 months. Patients with disseminated nocardiosis, CNS disease, and immunocompromised hosts with

TABLE 137-4 Estimated Recommendations for Duration of Treatment for Nocardiosis

Clinical Manifestations	Estimated Duration of Therapy
Pulmonary or systemic	
Immunocompetent	6–12 months[a]
Immunocompromised	12 months[b]
CNS disease and disseminated disease	12 months
Cutaneous	3 months
Osteomyelitis, arthritis, laryngitis, sinusitis	4 months
Mycetoma	6–12 months after clinical resolution

[a] *Depending on clinical response; for severe pulmonary infection or disseminated disease would recommend at least 12 months of therapy.*

[b] *HIV and CGD patients may be placed on secondary prophylaxis indefinitely.*

pulmonary infection are treated for a minimum of 12 months.[6] Common practice is to place HIV and CGD patients on secondary prophylaxis following *Nocardia* infection.

ACTINOMYCOSIS

Actinomycosis is an indolent infection caused by anaerobic or microaerophilic bacteria primarily belonging to the genus *Actinomyces*. The disease is marked by the formation of sinus tracts, granulomatous inflammation, and suppuration. The spread of infection with actinomycosis across tissue planes results in tract formation, and suppuration is notable for small yellow granules reminiscent of elemental sulfur. Actinomycosis may manifest as dense, "woody" lesions with surrounding fibrosis suggestive of malignancy. In its pulmonary manifestations, actinomycosis mimics several pathogens, ranging from fungal to mycobacterial to bacterial. Diagnosis is further complicated by the diversity of infection sites. Agents of actinomycosis are part of the human microbiota, colonizing the mouth, colon, and vagina, and often spread following trauma or insult. Growth on culture can sometimes be misinterpreted as normal flora. Prolonged antibiotic therapy is often curative.

History and Classification

Similar to nocardiosis, the causative agent of actinomycosis was first identified in cattle. Bollinger discovered a pathogen, later identified as *Actinomyces bovis*, as the cause of "lumpy jaw."[105] In 1878, James Israel described a case of actinomycosis in a human host.[106,107] This first case involved thoracic disease, which accounts for approximately 15% of all actinomycosis cases.[79] Due to the branching filamentous appearance of the organism, Dr. Israel and those who followed him for more than 70 years would incorrectly attribute the infection to a fungal pathogen—hence the misnomer *actinomycosis*, meaning "ray fungus." Although a bacterial etiology was established by 1957, reference to a fungal infection persisted in publication until at least 1975.[108] Actinomycosis is caused primarily by members of the genus *Actinomyces*. *Pseudopropionibacterium propionicum* (formerly *Propionibacterium propionicum* and *Arachnia propionica*) is an additional agent of actinomycosis.[109–111] Similar to *Nocardia* spp., *Actinomyces* spp. has undergone taxonomic changes resulting in the reclassification of some *Actinomyces* spp. to *Trueperella* (*Arcanobacterium*), *Actinotignum* (*Actinobaculum*), or *Cellulomonas*.[111–113] Currently, there are 26 published *Actinomyces* species recovered from human samples. *Actinomyces israelii* is the most common *Actinomyces* species isolated in human infection.[114] *A. israelii*, *A. gerencseriae*, *A. graevenitzii*, *A. meyeri*, *A. odontolyticus*, *A. turicensis*, *A. cardiffensis*, *A. funkei*, and *A. naeslundii* are associated with thoracic disease.[115,116]

Epidemiology

Actinomycosis was likely more common prior to the advent of antibiotics. Cope, in his seminal 1938 treatise *Actinomycosis*, stated that it "existed wherever there was a microscope and a laboratory."[117] However, studies of the prevalence of actinomycosis in the latter half of the 20th century indicate that while human colonization is nearly universal, progression to human disease is rare. A review of 57 cases at the University of Iowa over 36 years demonstrated a decrease in incidence of actinomycosis from 1:14,800 in the mid-1930s to 1:63,118 by the 1970s.[117] The incidence of actinomycosis in Germany and the Netherlands in the 1960s was estimated to be 1:100,000.[79] Recently, 71 consultations for actinomycosis were noted by the Department of Health in the United Kingdom from 2002 to 2003—an estimated 0.0006% of all consultations.[114] Among patients with pulmonary opacities, one series of 2247 Italian patients identified pulmonary actinomycosis in only 13 patients (0.6%).[118] Limited data exist regarding the presence of actinomycosis in low- and middle-income countries.

Disease Pathogenesis

A variety of virulence factors and host immune responses play a role in the pathogenesis of actinomycosis.

Virulence Factors

Actinomycetes are commensals, known to produce biofilms and fimbriae for attachment to the host as well as other organisms. Most clinically relevant species of *Actinomyces* can produce biofilms using polysaccharides of levan, dextran, glycogen, and *N*-acetylglucosamine.[119] In addition, they have both type 1 and type 2 fimbriae, made largely of shaft proteins FimA and FimP and cap protein FimB, each type with a separate purpose. Type 1 fimbriae adhere to proline-rich proteins that are found on the mineral surface of teeth,[120] while type 2 fimbriae use the shaft protein FimA to adhere to oral streptococci and host red blood cells, and to aid in biofilm formation. Variations in the expression of these two fimbriae affect the specific niche of a species—for example, *A. naeslundii* possesses fewer type 1 fimbriae and adheres preferentially to epithelial cells rather than dental surfaces.[121]

Host Immune Responses

Fimbriae enable *Actinomyces* to form dense clumps of "mycelial" growth, conferring protection against phagocytosis by neutrophils.[122,123] Additionally, clumping protects against antibiotics.[124] A phosphatase-driven inflammatory host response occurs at the site of growth, leaving calcium phosphate in the center of this mass, thus a mineralized granule core. Histologically, these appear as rosettes of branching filaments, from 30 to 400 μm in size, with radial clubbing at the periphery, which results from filaments being covered in protein-polysaccharide complexes. Foamy macrophages play a role in host response, causing the yellow coloration of the "sulfur granule."[125] Actinomycosis commonly presents as a polymicrobial infection, believed to enhance pathogenesis.[116] As an example, *A. viscosus* alone produces inflammation through activation of Toll-like receptor 2, but it gains resistance to phagocytosis and killing by neutrophils when coaggregated with *Streptococcus mitis*.[126,127]

Risk Factors for Disease

Actinomycosis typically occurs in individuals 20 to 60 years of age and is three times more common in men than women.[114] Alcoholism is associated with actinomycosis, likely due to an increased aspiration risk.[128] Pulmonary actinomycosis is more prevalent in individuals with chronic lung diseases like bronchiectasis, chronic bronchitis, and emphysema.[128] Trauma, surgery, dental procedures, and dental sepsis disrupt the mucosal barrier and increase the risk of actinomycosis.[129] Additionally, osteoradionecrosis and bisphosphonate-related osteonecrosis of the jaw disrupt bone and tissues in the cervicofacial region and are associated with actinomycosis.[116] Several case reports describe the association with hereditary hemorrhagic telangiectasia and the occurrence of *Actinomyces* spp. and polymicrobial brain abscesses (Fig. 137-7).[116] Other risk factors for actinomycosis include diabetes, HIV, leukemia with chemotherapy, solid-organ transplantation, and corticosteroid use.[114,116]

Clinical Manifestations

Actinomycosis is divided by anatomic location: thoracic (15%–20%), cervicofacial (50%), and abdominopelvic (20%) are the most common presentations.[105] Less common infections involve the CNS, musculoskeletal system, prosthetic joints, ophthalmic infections, cutaneous infections, and disseminated disease.[114,128]

Thoracic Actinomycosis: Pathogenesis and Clinical Presentation

Aspiration of oropharyngeal secretions is considered the primary mechanism for thoracic actinomycosis. Thoracic disease due to

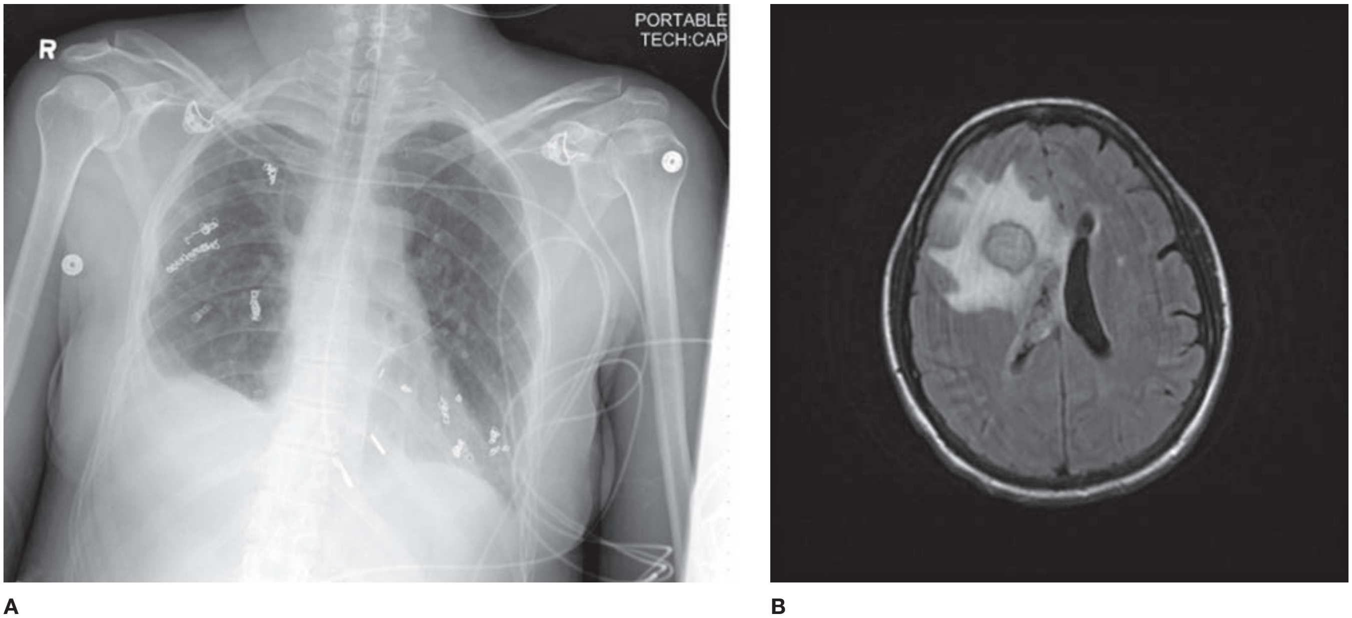


Figure 137-7 CNS polymicrobial abscess (including *Actinomyces* spp.) in a 53-year-old female with past medical history of hereditary hemorrhagic telangiectasia, right lung resection, and coiling of pulmonary arteriovenous malformations (AVMs), who presented with fever, altered mental status, and symptoms of meningismus. **A.** Chest x-ray shows evidence of a prior right lung resection and multiple bilateral coils over the chest representing sequelae of prior AVM procedures. **B.** Axial MRI FLAIR image of the brain demonstrates a right frontal lobe periventricular abscess with surrounding white-matter edema producing mass effect on the anterior horn of the right lateral ventricle. The patient underwent a craniectomy and external ventricular drain placement, and cultures grew *Actinomyces* spp., *Haemophilus aphrophilus*, and α-hemolytic *Streptococcus*.

direct spread of cervicofacial or abdominopelvic disease was more common prior to the advent of antibiotics but is rare in the modern era.[128] Thoracic actinomycosis is subdivided into pulmonary, pleural, mediastinal, chest wall, and mixed presentations. Pulmonary disease is the most common form of thoracic disease. Symptoms can mimic tuberculosis, malignancy, fungal infection, and other chronic pneumonias (Table 137-5). Symptoms of pulmonary actinomycosis include cough with or without sputum production, shortness of breath, chest pain, and hemoptysis, and may be associated with fever, night sweats, weight loss, and fatigue (Table 137-6). While these symptoms are common in many pulmonary infections, a hallmark of pulmonary actinomycosis is clinical improvement with standard community-acquired pneumonia treatment followed by recrudescence of infection days to weeks following cessation of antibiotics.

Actinomycosis can spread from the lung parenchyma contiguously to the pleura, mediastinum, and chest wall. Such intrathoracic spread should suggest the diagnosis of actinomycosis. Empyema necessitans, in which an empyema extends outward through the chest wall, is rare as antibiotics are often given prior to progression of infection. Esophageal perforation resulting in mediastinitis is a less common cause of thoracic disease.[114] Additionally, *Actinomyces* spp. are a rare cause of breast abscesses, as described in several case reports.[130,131]

Thoracic Actinomycosis: Radiographic Presentation

Parenchymal actinomycosis manifests as pulmonary consolidations (36%–100%) and masses or nodules (9%–48%) (Table 137-7).[132–135] In early stages of infection a small peripheral nodule occurs, which gradually progresses into a consolidation or mass (Fig. 137-8).[136] The consolidation often contains hypoattenuated areas with cavitation. Pleural thickening near the site of parenchymal infection is present in many patients (24%–100%).[132–135] On chest CT, bronchiectatic actinomycosis appears as a localized bronchiectasis, irregular bronchial wall thickening, and peribronchial consolidation.[137] Parenchymal and bronchiectatic actinomycosis may occur simultaneously in some patients. Endobronchial actinomycosis is rare and due to colonization of foreign bodies or obstructive broncholiths, formed by erosion of calcified lymph nodes into the airway due to a granulomatous process.[137] Endobronchial actinomycosis secondary to a broncholith appears on chest CT scan as a proximal obstructive calcified endobronchial nodule with distal obstructive pneumonia.[137] Fluorodeoxyglucose positron emission tomography (FDG-PET) imaging findings may be nonspecific, as actinomycosis can be hypermetabolic on this imaging modality.[79]

A fungus ball appearance is a well-documented but less common radiographic presentation. Actinomycosis in this form is often diagnosed invasively, by lobectomy, video-assisted thoracoscopic surgery, and bronchoalveolar lavage.[138]

The more specific and classically described finding of rib destruction is rare in the modern antibiotic era—occurring only 2 times in 94 patients among 4 case series dating from the 1970s to 2010,[133,135,139–141] with both occurrences in older series from 1974 and 1990.[139,140] Chest wall invasion, another classically described finding of actinomycosis, is uncommon.

Cervicofacial Actinomycosis

The loss of mucosal integrity following facial trauma, dental manipulation, poor dental hygiene, or necrosis following medications such as bisphosphonates transforms commensal agents of actinomycosis into opportunistic pathogens, resulting in cervicofacial disease (Fig. 137-9). Oral disease is predominated by *A. israelii*, *A. gerencseriae*, and *A. naeslundii/viscosus*, which were associated with 75% of cases in one large series.[142] Coinfection with other pathogens is common. Cervicofacial actinomycosis manifests as soft tissue swelling around the mandible and potential progression to dense "woody" induration, with or without pain. Oral actinomycosis presents as ulcerations, abscesses, and nodules resembling malignancy, and biopsy is often necessary for diagnosis.[143] Sinus tracts and

TABLE 137-5 Comparison of Actinomycosis and Nocardiosis with Some of Their Bacterial and Mycobacterial Mimics

	Nocardia	*Actinomyces*	*Burkholderia pseudomallei* (Melioidosis)	*Rhodococcus*	Tuberculosis	NTM
Clinical						
Environment/ exposure	Soil/environmental	Human commensal of many mucosae	Soil/water inhabitant from Southeast Asia, Australia, rainfall	Horses (severe IC—no exposure necessary)	Person-to-person transmission	Environmental (soil/water), *M. kansasii*—municipal water
Host risk factors	IC (SOT and BMT recipients)	Periodontal disease, loss of mucosal integrity, IC	Diabetes, alcoholism, CKD	IC (steroids, HIV, SOT)	Diabetes, silicosis, ESRD, and intestinal bypass	Bronchiectasis, COPD, smoking tobacco, CF
Salient symptoms	Cough, dyspnea, hemoptysis, fever	Cough ± sputum, hemoptysis, pleuritic pain; weight loss and malaise	High fever, dyspnea, cough with purulent sputum and hemoptysis	Fever, cough, dyspnea	Cough, fever, weight loss, dyspnea, hemoptysis, night sweats	Cough, dyspnea, fever
Time course	Subacute–chronic	Subacute–chronic	Acute–chronic	Subacute–chronic	Subacute–chronic	Subacute–chronic
Radiographic						
	Nodules, cavitation, diffuse infiltrates, pleural effusions	Consolidation, nodules, masses, cavities, across tissue planes (interlobar extension, empyema, mediastinitis, pericarditis)	Diffuse miliary nodules, eventual cavitation	Lobar infiltrates that can lead to nodules, cavitation, pleural effusion	Reactivation TB more common in upper lobes, cavitation	Cavitary upper lobe disease, nodules
Laboratory Diagnosis						
Gram stain	Gram-positive filamentous rods, weakly acid fast	Gram-positive filamentous rods, not acid fast	Gram-negative rod, sometimes bipolar staining	Gram-positive coccobacillus, slightly acid fast	Gram-neutral, acid fast	Gram-neutral, acid fast
Culture media	Standard media, BCYE media, selective media (Thayer–Martin)	Anaerobic (*A. meyeri* and *A. neuii* can grow aerobically)	Routine (e.g., blood agar, MacConkey)	Routine (e.g., blood agar) aerobic culture	Solid (e.g., Lowenstein–Jensen) or liquid media	Solid (e.g., Lowenstein–Jensen) or liquid media
Culture time	48 h–14 days	Usually 5–7 days, but may take 4 weeks	Usually within 48 h	Usually within 48 h	4–8 weeks on solid media, 6–10 days in liquid media	On solid media, 2–6 weeks
Other diagnostic methods	NAAT, MALDI-TOF	Sulfur granules 16S sequencing; MALDI-TOF databases still being optimized	Fluorescent antibody, agglutinin antibody, NAAT	Biochemical tests, NAAT	Tuberculin skin test, IFN-γ release assay, NAAT	NAAT
Treatment						
Pharmacologic	Sulfonamides first line, often require two agents	Penicillin first line, resistance very rare	Carbapenems, ceftazidime, trimethoprim-sulfamethoxazole	Vancomycin, fluoroquinolones, rifamycins, macrolides, sulfonamides, aminoglycosides	Rifampin, isoniazid, pyrazinamide, ethambutol (resistant strains require additional antibiotics)	NTM susceptibility–guided therapy MAI: rifampin + ethambutol + macrolide

NTM, nontuberculous mycobacterium; IC, immunocompromised; CKD, chronic kidney disease; ESRD, end-stage renal disease; COPD, chronic obstructive pulmonary disease; CF, cystic fibrosis; BCYE, buffered charcoal–yeast extract agar; MAI, Mycobacterium avium-intracellulare; NAAT, nucleic acid amplification test.

trismus can occur; infection can spread to local structures, resulting in periostitis or osteomyelitis, observed in 12% of patients in a review of 317 cases.[114] Newer radiographic techniques have been proposed to help differentiate actinomycosis from some of its mimics and monitor the response to therapy. F-alpha-methyl tyrosine PET/CT and quantitative light-induced fluorescence are both used in cervicofacial disease, but not widespread in clinical practice.[144,145]

Abdominopelvic Actinomycosis

Abdominal actinomycosis results from mucosal disruption due to abdominal surgery, trauma, neoplasm, ingestion of a foreign body, or perforated viscus (Fig. 137-10). Appendicitis is the most common presentation of abdominal actinomycosis, associated with 65% of cases. Dropped gallstones during cholecystectomy are another possible source of infection.[146] Despite the high incidence of diverticulitis, only a small

TABLE 137-6 Clinical Presentation of Pulmonary Actinomycosis from 10 Case Series

	Cumulative	Bates	Slade	Frank	Kinnear	Jensen	Kwong	Hsieh	Tastepe	Baik	Song
Number pts	223	85	7	6	19	9	8	17	7	25	40
Year published		1957	1974	1974	1990	1989	1992	1993	1998	1999	2010
Year of cases	1957–2008				1974–1990	1966–1987		1984–1990	1990–1997	1985–1997	2004–2008
Symptoms (thoracic)	No. of patients (%)										
Cough	95 / 138 (69%)		6 (86%)	4 (67%)	16 (84%)	8 (89%)	7 (88%)	8 (47%)	7 (100%)	17 (68%)	22 (55%)
Hemoptysis	68 / 138 (49%)		2 (29%)	1 (17%)	6 (32%)	2 (22%)	3 (38%)	9 (53%)	3 (43%)	18 (72%)	24 (60%)
Sputum	60 / 130 (46%)		2 (29%)	1 (17%)	14 (74%)	3 (33%)		1 (6%)	6 (86%)	15 (60%)	18 (45%)
Chest pain	93 / 216 (43%)	43 (51%)	1 (14%)	2 (33%)	13 (68%)	4 (44%)	6 (75%)	6 (35%)		11 (44%)	7 (18%)
Dyspnea	24 / 73 (33%)		3 (43%)	0 (0%)	9 (47%)	4 (44%)	6 (75%)	1 (6%)	1 (14%)		
Symptoms (systemic)											
Weight loss	20 / 65 (31%)		1 (14%)	1 (17%)	10 (53%)		4 (50%)			4 (16%)	
Malaise	9 / 32 (28%)		1 (14%)	0 (0%)	8 (42%)						
Fever	30 / 122 (25%)		4 (57%)	1 (17%)	4 (21%)		4 (50%)	3 (18%)		8 (32%)	6 (15%)
Night sweats	7 / 32 (22%)		0 (0%)	1 (17%)	6 (32%)						

TABLE 137-7 CT Findings with Pulmonary Actinomycosis from Four Case Series

	Cumulative	Kwong	Cheon	Baik	Song
Number pts	95	8	22	25	40
Year published		1992	1998	1999	2010
Year of cases	1992–2008			1985–1997	2004–2008
CT Findings	No. of patients (%)				
Consolidation	60 / 95 (63%)	8 (100%)	20 (91%)	9 (36%)	23 (58%)
Nodule/mass	28 / 95 (29%)	2 (25%)	2 (9%)	12 (48%)	12 (30%)
Central hypoattenuation	46 / 95 (48%)	3 (38%)	15 (68%)	7 (28%)	21 (53%)
Lymphadenopathy	31 / 95 (33%)	3 (38%)	3 (14%)	6 (24%)	19 (48%)
Pleural thickening	30 / 55 (55%)	8 (100%)	16 (73%)	6 (24%)	
Pleural effusion	7 / 30 (23%)	5 (63%)	2 (9%)		
Cavitation	19 / 95 (20%)	0 (0%)	8 (36%)	3 (12%)	8 (20%)
Chest wall invasion	0 / 22 (0%)		0 (0%)		
Rib destruction	0 / 22 (0%)		0 (0%)		

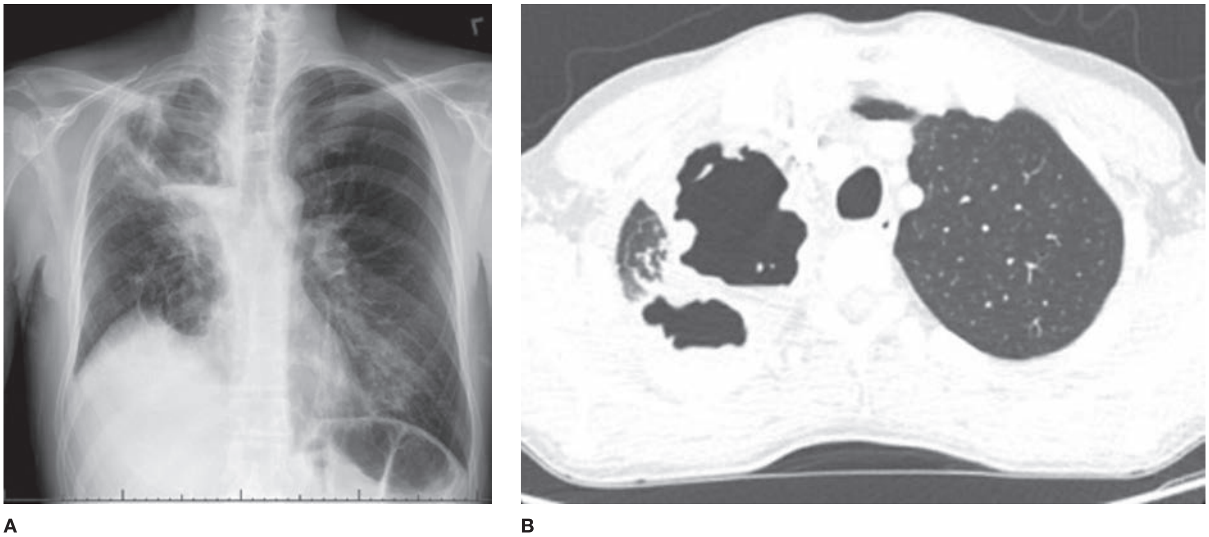


Figure 137-8 Pulmonary actinomycosis infection concurrent with squamous cell lung carcinoma in a 50-year-old male. **A.** Frontal chest x-ray shows right lung volume loss and a loculated hydropneumothorax suggesting recent lobectomy. The patient underwent right upper lobe lobectomy 4 weeks prior for a 10-cm mass shown to be squamous cell carcinoma. **B.** Axial CT of the chest confirms the presence of a loculated cavity with irregular thickened septations in the right apical lung. A right-sided chest tube drained 10 cc of pus, which grew *Actinomyces odontolyticus*.

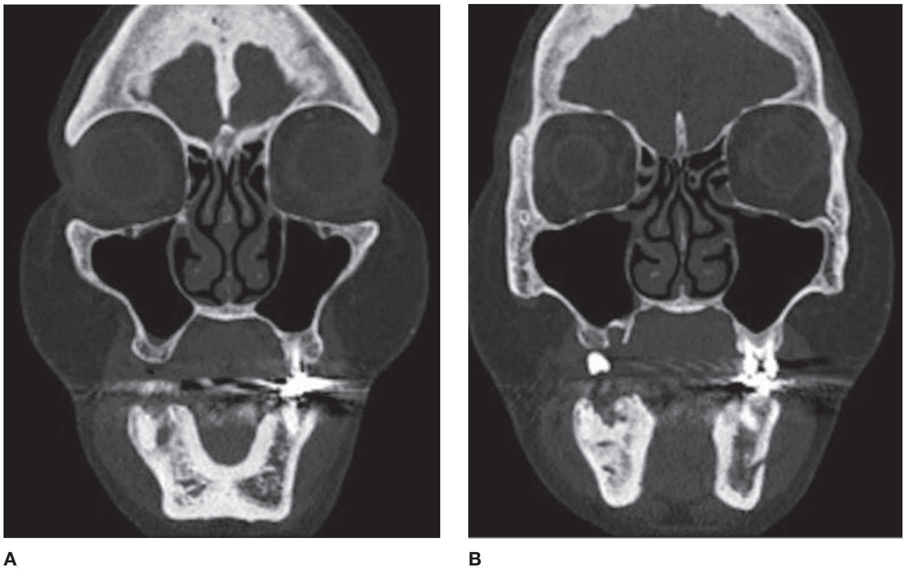


Figure 137-9 **A** and **B.** Mandibular osteomyelitis secondary to actinomycosis in a 76-year-old female with past medical history of diabetes mellitus who underwent extensive dental work prior to developing right mandibular pain. She underwent a bone biopsy with pathology consistent with osteomyelitis, and multiple cultures were significant for *Actinomyces* spp. and *Prevotella/Porphyromonas*. Coronal CT maxillofacial images show asymmetric cortical thickening and sclerosis of the right mandible and erosions in the visible tooth bed, suggesting a clinical diagnosis of osteomyelitis.

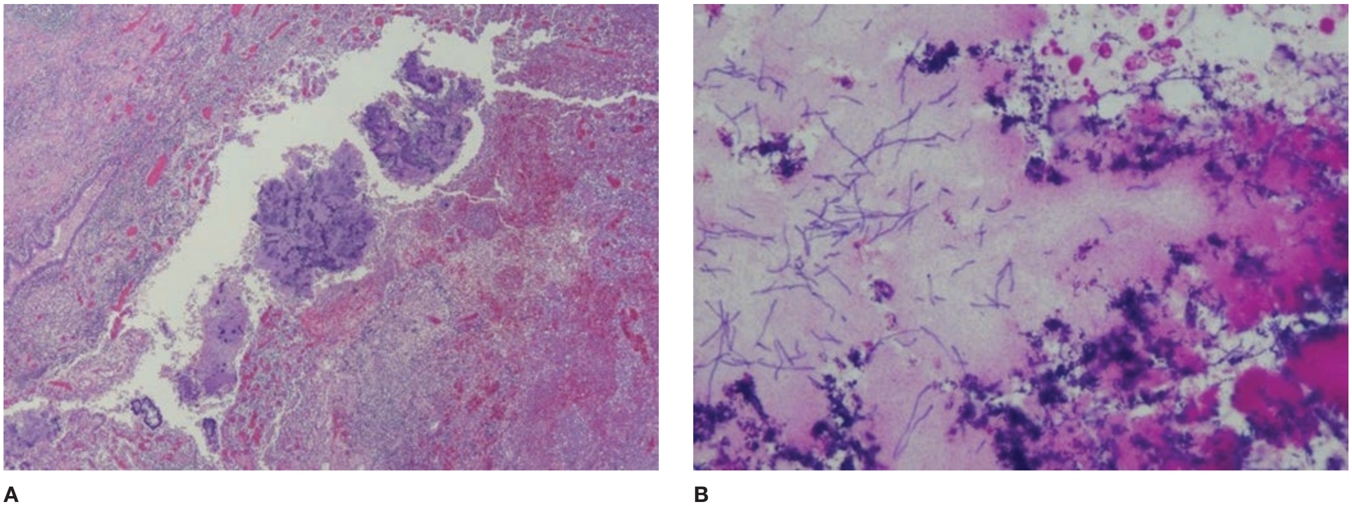


Figure 137-10 Histopathology of actinomycosis. **A.** Granules of thoracic actinomycosis (hematoxylin-eosin, 10×). **B.** Same thoracic granule showing mixed bacterial morphologies including *Actinomyces* spp. (Brown-Hopps, 100×). *(Reproduced with permission from Dr. Dominick Cavuoti.)*

number of cases result in abdominal actinomycosis. Diverticulitis and foreign body perforation between the distal colon and the hepatic flexure account for approximately 7% of cases. Sinus tract formation may occur through the abdominal wall and in the perirectal area. Anorectal disease presents as rectal strictures, perirectal abscess, and fistulous tracts.[129] Although gastric, hepatic, splenic, and renal disease are uncommon, actinomycosis spreads throughout the peritoneum and has the ability to seed any organ within the abdomen.[129]

Abdominal actinomycosis presents with fever, weight loss, constipation, and abdominal pain. The indolent nature of abdominal actinomycosis and vague symptomatology present a diagnostic challenge. In a review of abdominal actinomycosis (n = 406), diagnosis was obtained post-laparotomy in 91% of cases. The colon, abdominal wall, and appendix were the most involved structures, while the clinical presentation of a localized mass or malignant neoplasm occurred in 39% and 19% of cases, respectively. Despite frequent and early surgical intervention, average time to diagnosis for abdominopelvic actinomycosis was 10.6 days, even in a high-resource setting.[79,114,129,147]

Pelvic actinomycosis is most commonly associated with contraceptive intrauterine devices (IUDs), although any disruption of the uterine mucosa can serve as an inciting event, including pessaries, endometrial curettage, and surgical mesh placement. The risk increases with time from implantation of a foreign body; when actinomycosis arises in the setting of an IUD, it is on average at 8 years following IUD placement. In primary pelvic actinomycosis, infection spreads to the endometrium and ovaries. As with other forms of actinomycosis, patients present with indolent, nonspecific symptoms such as fever, localized pain, and weight loss. Abnormal vaginal bleeding is an additional symptom. If pelvic dissemination of infection occurs secondary to abdominal ileocecal disease, the ovary is the most commonly affected pelvic organ followed by the fallopian tubes, uterus, vulva, and cervix.[129] Differentiating colonization and infection is necessary, as *Actinomyces*-like organisms are found in 7% of Papanicolaou smears, and in the absence of infectious symptoms, these organisms should be considered as commensals in the female genitourinary tract.[79,114,129,148]

Other Forms of Actinomycosis: CNS infection, Otitis Media, Lacrimal, and Others

Central nervous system infections, while rare, can be fatal. The majority of CNS actinomycosis infections present as brain abscesses (75%) (Fig. 137-7), with a predilection for the frontal and temporal lobes.[131] CNS infection is typically associated with hematogenous spread from pulmonary, cervicofacial, and abdominal/pelvic infection. Consequently, headache and focal neurologic signs are the most common presenting symptoms. In a review of CNS actinomycosis cases (n = 70), the clinical manifestations reported were brain abscess (67%), meningitis and meningoencephalitis (13%), actinomycoma (space-occupying lesion) (7%), subdural empyema (6%), and epidural abscess (6%).[149] The primary foci of infection (n = 47) were identified as pulmonary (27%), cervicofacial (20%), abdominal pelvis (10%), and ear/mastoid and sinuses (10%).[149] Mixed bacterial infection was found in 34% of cases with available microbiologic culture data (n = 50).[149]

Lacrimal canaliculitis, musculoskeletal disease, and disseminated actinomycosis are other clinical manifestations of actinomycosis.[79,129,149]

■ Diagnosis: Microbiologic and Pathologic

Clinically and radiographically, actinomycosis is difficult to differentiate from more common pathogens. Traits of this pathogen are the indolent and refractory nature of the infection, failure to respond to shorter courses of antibiotics, and the anatomic progression across tissue planes and compartments. Consequently, regardless of the location, the key to management of actinomycosis is to consider the diagnosis and obtain microbiologic bacterial aerobic/anaerobic cultures from the infected site as well as consideration of tissue biopsy when possible. Microbiologic diagnosis is challenging, as agents of actinomycosis are highly sensitive to a wide variety of antibiotics and are commensals of the human respiratory, gastrointestinal, and genitourinary tracts, such that they may be considered and reported as normal flora by the laboratory. Evaluating a patient prior to antibiotic administration, if appropriate, increases the likelihood of obtaining a microbiologic diagnosis, as sputum samples and bronchial alveolar lavages can be rendered sterile with a single dose of antibiotics (although the underlying infection remains active).

Tissue biopsy with histopathologic diagnosis is often indicated and helpful, particularly if sulfur granules are found. A survey of 181 cases of actinomycosis found an average of 7 granules per specimen.[150] One to 3 granules were found in 56% of cases, while a single granule was identified in 26% of cases.[150] However, granules are not pathognomonic for actinomycosis, as they can be seen in nocardiosis, aspergillosis, and botryomycosis among others. To help differentiate, the agents of actinomycosis can be seen at the periphery of granules on hematoxylin-eosin stains as well as Grocott-Gomori methenamine silver or Giemsa stains, appearing as Gram-positive, filamentous, branching bacteria (Fig. 137-11).[79,114,129]

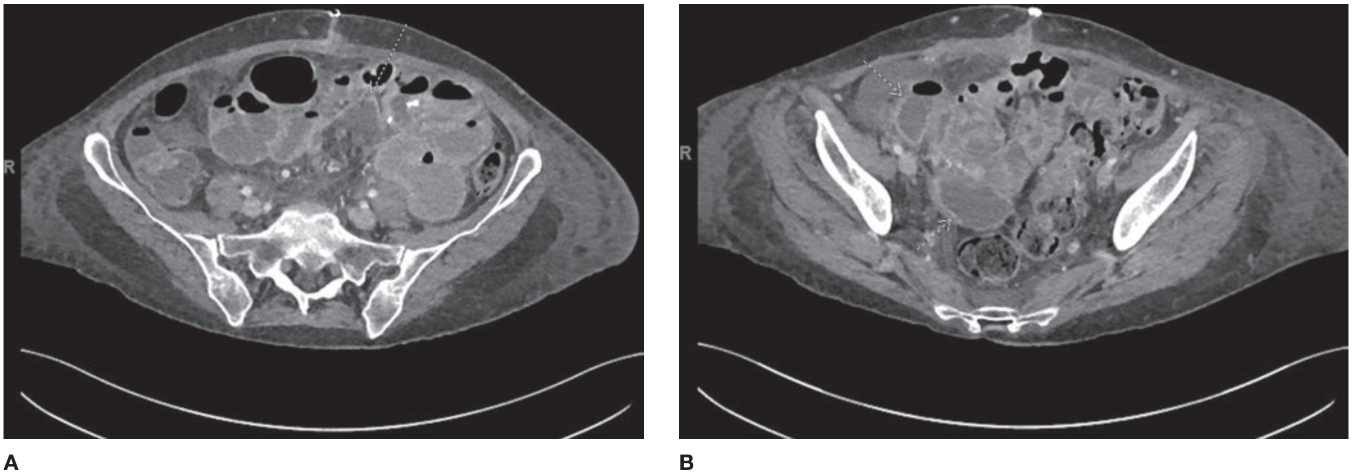


Figure 137-11 Abdominal actinomycosis in a 55-year-old female with a past medical history of diffuse large B-cell lymphoma refractory to chemotherapy, and history of multiple intra-abdominal surgeries, who presented with abdominal pain and underwent an open small bowel resection for bowel obstruction. Her course was further complicated by abdominal and pelvic abscesses. **A.** Axial CT of the abdomen shows a rim-enhancing 2.5-cm fluid collection with a collection of air between loops of bowel. **B.** Axial CT of the pelvis with multiple fluid collection; the largest is a 5 × 3 cm deep fluid collection with rim-enhancing walls. Her pelvic abscess was aspirated and grew *Actinomyces* spp. *(Reproduced with permission from Sally Chuang, MD.)*

Although low-yield in prior series,[151] larger and more recent case series have shown success with bronchoscopic biopsy and percutaneous thoracic needle biopsy/aspiration.[152]

An analysis of 11 case series from 1982 to 1999 demonstrated a gradual shift in diagnostic methodology. Prior to 1995, diagnosis of thoracic actinomycosis was 22% by nonsurgical means (fine-needle aspiration, bronchial biopsy) and 77% with surgical intervention. After 1995, this shifted to 47% by nonsurgical means and 53% by surgical means.[128] More recent cases demonstrate diagnosis via bronchial brush sampling,[153] transbronchial biopsy,[154] bronchoalveolar lavage,[155] bronchial alveolar lavage cytology in combination with transbronchial biopsy,[156] and transbronchial biopsy using a Wang needle for aspiration.[157]

16S rRNA nucleic acid amplification tests (NAAT) and MALDI-TOF are newer technologies that may enable detection of pathogens. However, their increased use has led to new challenges. Gram-positive rods in blood cultures that are true agents of actinomycosis but may previously have been considered as contaminants (i.e., presumed to be *Corynebacterium* spp. or *Propionibacterium* spp.) with NAAT and MALDI-TOF are now being identified on blood cultures. Although previously thought to always signal infection when found in sterile samples, a series of 60 patients with *Actinomyces* spp. found in blood culture showed no ill effect in withholding treatment for actinomycosis from 50 of those patients who were not felt to have risk factors for actinomycosis or symptoms.[158] What remains unknown is whether those isolates represented contamination (which might suggest a previously unknown dermatologic niche for *Actinomyces* spp. [via the site of puncture for blood cultures drawn through the skin]), or a transient, harmless bacteremia, which could be possible given that they are commensals in the oropharynx.[79,158]

■ Treatment

Penicillin is the treatment of choice for actinomycosis. Traditional therapy for actinomycosis is high-dose IV penicillin at 18 to 24 million units daily for 2 to 6 weeks, followed by oral penicillin or amoxicillin for a period of 6 to 12 months. In the setting of copathogens, many of which are anaerobic, the addition of a β-lactamase inhibitor to penicillin (e.g., ampicillin-sulbactam) is often used. If the patient is penicillin allergic, erythromycin, doxycycline, minocycline, and tetracycline are well-studied treatment options (Table 137-8). Clindamycin resistance is reported, with rates as high as 30% or greater.[159] Among other β-lactams, ceftriaxone, ertapenem, and imipenem-cilastatin have been used successfully although less frequently.[160–163] Metronidazole and moxifloxacin, both used for anaerobic infections, should not be used against actinomycosis due to high levels of resistance.[79,159,162,164]

Medical therapy is often curative. Adjunctive surgical interventions are dependent on the site, extent, and severity of infection. Surgery or percutaneous drainage is often indicated for infections within confined and critical spaces, such as the brain or epidural space, hemoptysis that cannot be managed otherwise, abscesses, extensive disease, or infection refractory to treatment. Medical failure occurs secondary to coincident pathology such as malignancy, tuberculosis, or aspergillosis. Drainable fluid collections should be aspirated and cultured, to expedite clinical improvement and identify copathogens for guidance of therapy. In the setting of an IUD infection, antimicrobial therapy and removal of the IUD are recommended.

TABLE 137-8 Treatment for Actinomycosis[a]

Extensive Clinical Experience and Success[a]	Anecdotal Experience and Success	Predicted Efficacy Based on In Vitro Activity
Penicillin	Ceftriaxone	Vancomycin
Amoxicillin	Ceftizoxime	Linezolid
Erythromycin	Imipenem-cilastatin	Quinupristin-dalfopristin
Tetracycline	Piperacillin-tazobactam	Rifampin
Doxycycline		Ertapenem
Minocycline		Tigecycline
Clindamycin[b]		Azithromycin

[a] *Additional coverage for concomitant bacteria may be indicated.*

[b] *Recent in vitro data demonstrated a >30% resistance rate.*

Data from Bennett JE, Dolin R, Blaser MJ: Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 9th ed. Philadelphia, PA: Elsevier/Saunders; 2020.

Duration of Treatment

Treatment duration should be individualized, and extension of therapy beyond 1 year may be indicated in complicated cases and immunocompromised hosts. Short courses of treatment have been used successfully with less extensive cervicofacial disease.[165,166] While some patients with complicated thoracic disease require longer courses, there are reports of shortened treatment courses. In a survey of 19 patients with thoracic actinomycosis, radiographically, pulmonary disease was reported as unilateral in 12 cases and bilateral in 1 case; cavitation occurred in 3 cases and pleural abnormalities were present in 7 cases. Two patients experienced extrapulmonary complications, including vertebral bone erosion and liver abscess.[140] All 19 cases were successfully treated with a median duration of 6 weeks (range, 1–24 weeks) of antibiotic therapy, and 7 patients underwent surgical resection.[140] In a series of 28 patients with thoracic actinomycosis, radiologic findings included consolidation (61%), nodular or masslike lesions (32%), and atelectasis (7%); 96% of these cases were successfully treated.[167] In solely medically managed individuals (n = 15), IV antibiotic therapy was administered for a median of 2 days (range, 0–18 days) and oral antibiotic therapy lasted a median of 167 days (range, 76–412 days). In patients who received a combination of antibiotic and surgical treatments (n = 13), IV antibiotic therapy was administered for a median of 8 days (range, 3–17 days) and oral antibiotic therapy lasted a median of 150 days (range, 0–534 days).[167] Shortened courses of antibiotic therapy should be approached with caution in patients with thoracic disease who have not had surgical debridement given the risk for relapse of infection.[168]

Conclusion

Nocardiosis and actinomycosis are rare infections often termed "the great masqueraders" due to their variable presentations and similar clinical manifestations to other infectious diseases. Microbiologic diagnoses are challenging, but with advances in molecular methodologies, the identification of these organisms is improving. Despite the low incidence of nocardiosis and actinomycosis, awareness of these infections, early diagnostic consideration, and initiation of appropriate treatment allow for more favorable outcomes. Due to the complexity of these infections and considerable duration of management, an infectious disease consultation, if available, is recommended.

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CHAPTER 138

Zoonotic and Environmental Bacterial Pneumonias

Camille Nelson Kotton
Howard M. Heller

INTRODUCTION

Many different microorganisms can infect the lung parenchyma; the focus in this chapter is pneumonias caused by zoonoses, environmental pathogens, and other unusual bacterial pathogens. Making a clinical diagnosis of pneumonia is relatively easy; defining the causative agent can be difficult. Routes of spread to the lungs are few, clinical presentations overlap, radiologic appearance often is nonspecific, and pathophysiologic mechanisms are limited. The search for the specific etiologic agent is driven by the desire to administer a specific antimicrobial drug as soon as possible, hopefully avoiding progressive functional impairment and containing spread to other individuals or to a community. Identifying a pathogen may, in turn, expand epidemiologic considerations and public health awareness.

In the decades that have passed since the epidemic of acute respiratory "Legionnaire's disease" due to *Legionella* erupted among delegates to the American Legion Convention in Philadelphia in 1976, physicians, microbiologists, and epidemiologists have become increasingly prepared for the diagnostic challenges of patients with unusual pneumonias. Some newer zoonotic pathogens with primarily pulmonary manifestations include Sin Nombre virus (hantavirus pulmonary syndrome) and certain coronaviruses (Chapter 126). Zoonotic viral pathogens that can be transmitted from animal to human, and then human to human, including influenza and the coronaviruses, have the greatest potential for rapid pandemic spread; it is likely that new viral respiratory pathogens will continue to emerge. Viral pathogens are discussed in detail elsewhere; the focus of this chapter is exclusively bacterial pathogens most often associated with animals, animal products, or the environment.

Global surveillance and cooperation have enabled more rapid recognition of new infectious syndromes, and the use of molecular techniques has allowed for rapid development of diagnostic tools that are critical for understanding the animal origin of pathogens and routes of transmission. Zoonotic infections can reflect an initial event, followed by person-to-person secondary cases, typical of viral diseases like the severe acute respiratory syndrome coronaviruses (SARS-CoV-1 and SARS-CoV-2) and occasionally observed with *Yersinia pestis*. While avian influenza virus (H5N1) primarily spread to individuals in proximity to chickens, the novel H1N1 influenza virus in 2009–2010 demonstrated an anthropocentric cycle that led to a worldwide pandemic, despite being of zoonotic origin. New zoonoses are always emerging: an outbreak in a monkey colony of deadly titi monkey adenovirus, not known to infect humans, was shown to infect a researcher and a family member, without further spread.[1] Similarly, *Streptococcus equi* subsp. zooepidemicus (*Streptococcus zooepidemicus*)[2] has been shown to cause pneumonia in humans after exposure to horses, dogs, and unpasteurized milk.

Companion animals have been the source of numerous zoonotic pneumonias, including *Pasteurella multocida*,[3,4] *Chlamydia psittaci*,[5] *Rhodococcus*, and *Bordetella bronchiseptica* hosts[6–9] (Tables 138-1 and 122-5). In a study in Spain, contact with pets was associated with an increased risk for community-acquired pneumonia, which tended to be more frequent as the number of pets increased; the relative risk was similar for bird, cat, and dog exposures.[10] There are multiple examples of animals serving as reservoirs of antibiotic-resistant bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA) (companion animals,[11,12] pigs[13]); some are seen in association with nosocomial ventilator-associated pneumonia[11] and highly resistant Enterobacteriaceae.[14] Nonetheless, experts usually permit companion animals for even immunocompromised hosts, balancing the risk of infection with benefit.[6,15] Wild and farm animals may also harbor zoonotic pneumonia pathogens. *Pasteurella multocida* has been associated with pneumonia in bighorn sheep,[16] lambs,[17] and pigs.[18] *Yersinia pestis* has been associated with numerous wild mammals; recent work suggests a correlation between seropositivity in coyotes and human disease.[19]

Many of the zoonotic bacteria discussed in this chapter are recognized as pathogens that can be weaponized for use by terrorist organizations. The global community is developing rapid diagnostics and countermeasures to warn, protect, and treat people exposed to a biologic weapon. Unfortunately, we have the experience of the "mailroom" anthrax event of September 2001 to illustrate the potential of an inhalational disease causing illness, casualties, public panic, and challenging diagnostic and therapeutic decisions, as well as the expenses of decontamination and task of criminal investigations.[20] Physicians need to become familiar with the typical and atypical spectrum of disease caused by these pathogens, including the impact and variable expression of a large inoculum aerosol release in a crowded urban area or building.

This chapter focuses on the epidemiologic and clinical features helpful in evaluating typical and atypical features of zoonotic and environmental bacterial pneumonias (Table 138-1). The unique properties of these bacteria exemplify how bacteriology, molecular biology, ecology, epidemiology, and pathogenesis serve as clues to earlier etiologic diagnosis and to initiation of specifically targeted therapies. The movements of immigrant populations, adventure and other forms of travel, the immune status of individuals, the latency of pathogens, and the legal and illegal transportation of live animals and animal products contribute to the importance of zoonotic pneumonias. Ultimately, the diagnosis is heavily dependent on a detailed history, along with appropriate diagnostic studies.

ZOONOTIC BACTERIAL PNEUMONIAS

Several important diseases are spread to humans predominantly from animal contact, including pasteurellosis, plague, tularemia, and *Rhodococcus*. The diagnosis usually depends on a careful animal exposure history. Once alerted, the clinician can request appropriate studies, as these diseases may be more elusive in their diagnosis.

■ *Pasteurella multocida*

P. multocida is a common commensal of the oral cavity of most felines and many dogs and a frequent respiratory pathogen in animals and birds.[3] The respiratory tract is the second most common site of *Pasteurella* infection, following skin and supporting tissues. Elderly people with structural lung diseases, such as emphysema, bronchiectasis, or malignancy, are at higher risk for pulmonary infection.[21,22] Immunocompromised patients, including those with AIDS, may be prone to infection without close contact or traumatic dog or cat exposures. Immunosuppressing medications, including TNF inhibitors and interleukin 6 blockers, also may increase risk.[23,24] Pneumonia caused by the closely related organism *Pasteurella canis* has been reported.[25]

TABLE 138-1 An Overview of Zoonotic and Other Unusual Pneumonias

Environmental Niche	Microorganism	Disease	Epidemiologic Associations	Distribution
Live animal contact or via arthropod	*Chlamydia psittaci*	Psittacosis	Inhalation of bird respiratory secretions or feces.	Worldwide
	Francisella tularensis	Tularemia	Contact with wild and pet animals, birds, or arthropods (ticks, deer fly)	North America, Europe, Asia
	Pasteurella multocida	Pasteurellosis	Feline and dog contact; chronic lung disease	Worldwide
	Rhodococcus equi	Rhodococcus pneumonia	Airborne droplets; contact with soil contaminated with horse, cow, or swine excrement	Worldwide
	Yersinia pestis	Plague	Contact with rodents, fleas; contact with plague pneumonia case	Worldwide, including Asia, southwest U.S.
Soil, stagnant water, and inert animal products	*Bacillus anthracis*	Inhalation anthrax or woolsorter's disease	Industrial; use of or contact with animal products in hobbies	Worldwide in warmer regions inhabited by grazing animals
	Brucella species	Brucellosis	Ingestion or contact with infected animal products, slaughterhouses	Worldwide
	Burkholderia pseudomallei	Melioidosis	Direct penetrating contact of wounds with soil, water	Latitude 20°N to 20°S, especially rural Asia, northern Australia
	Coxiella burnetii	Q fever	Contaminated birthing products, milk, meat, and wool, or inhalation of windblown dust from areas contaminated by placentae and other animal product	Worldwide

Bacteriology

P. multocida is a small, Gram-negative, bipolar-staining coccobacillary organism that resembles *Haemophilus* spp. and may form pairs and chains. Rapid growth on blood agar and inhibition by MacConkey medium separate this microorganism from other common components of the respiratory flora, including *Haemophilus* spp. Numerous virulence factors in *P. multocida* have been identified. These include the capsule in serogroups A and B (which interferes with phagocytosis), a toxin in strains causing atrophic rhinitis in pigs, lipopolysaccharide endotoxin, several iron acquisition proteins (e.g., TonB, ExbD, ExbB), and the putative filamentous hemagglutinins PfhB1 and PfhB2.

Ecology, Epidemiology, and Pathogenesis

In cats and other felines, the organism resides periodontally in the anterior regions of the mouth. Isolates from dogs are characteristically from the posterior pharynx. Many birds and domestic and wild animals worldwide harbor this organism as a commensal in oral or gastrointestinal areas. *P. multocida* is occasionally found in the secretions of persons with chronic lung disease, especially those with bronchiectasis and domestic animal contacts. Cooking and ingestion of pig trotters (feet) as well as occupational exposure in an abattoir worker with subsequent pneumonia have been described.[26,27] Human-to-human transmission has been documented from mother to newborn infant, resulting in neonatal pneumonia. The organism can survive in soil and water for more than 3 weeks and in animal carcasses for approximately 2 months. In about half of the cases of respiratory disease, no clue to airborne spread exists, but there are usually cats in the local environment.

Pathogenic strains have a polysaccharide capsule that inhibits phagocytosis, and an endotoxin is contained within the cell envelope. Exotoxins and other pathogenicity-promoting factors have not been specifically identified (see "Bacteriology," below). Almost all patients who develop respiratory infections have underlying chronic pulmonary disease. Aspiration probably initiates active infection. Necrosis and lung abscess, empyema, septicemia, and transbronchial spread to other lung segments have been described.

Clinical and Radiologic Features

The clinical features of *P. multocida* respiratory disease include worsening of the patient's baseline pulmonary function—especially when high fever, tenacious secretions, and pleural effusions develop. Radiologic changes include lobar, multilobar, or diffuse patchy infiltrates, usually sparing the upper lobes, superimposed on underlying chronic lung disease (Fig. 138-1). Pleural effusions and empyema have been noted in approximately 20% of cases. Bacteremia has been reported in up to 55% of patients with pneumonia, and endocarditis has occasionally complicated bloodstream invasion.[3,28]

Diagnosis and Differential Diagnosis

Diagnosis depends on isolation of the organism from sputum, pleural fluid, or blood. Usually, the pathogen can be identified with the routine methods of the diagnostic laboratory. The bipolar, Gram-negative–staining bacilli resemble *Brucella* spp., *Y. pestis*, *Francisella tularensis*, *Burkholderia pseudomallei*, and *Haemophilus* spp., but the clinical history of exposure to cats and/or dogs and bacteriologic characteristics can rapidly clarify identification.

Treatment

Most strains are exquisitely susceptible to penicillin or ampicillin. Third-generation cephalosporins are as active as penicillin and more potent than earlier-generation relatives. Oral preparations of cephalosporins and penicillins are not recommended for treating pneumonias caused by *P. multocida* due to reduced bioavailability. Fluoroquinolones, including moxifloxacin and levofloxacin, are very active in vitro against *P. multocida* and other *Pasteurella* spp., although published experience in humans is limited. Chloramphenicol, with consideration of its potential toxicities, and tetracycline are effective alternatives when a history of allergic reactions precludes use of a β-lactam agent or fluoroquinolone.

■ *Chlamydia psittaci*

The avian bacterium *Chlamydia psittaci* causes disease in birds and, when transmitted to humans, can cause systemic disease, psittacosis, and pneumonia. Psittacosis is also known as avian chlamydiosis, ornithosis, and "parrot fever." Although psittacine birds (parrots,

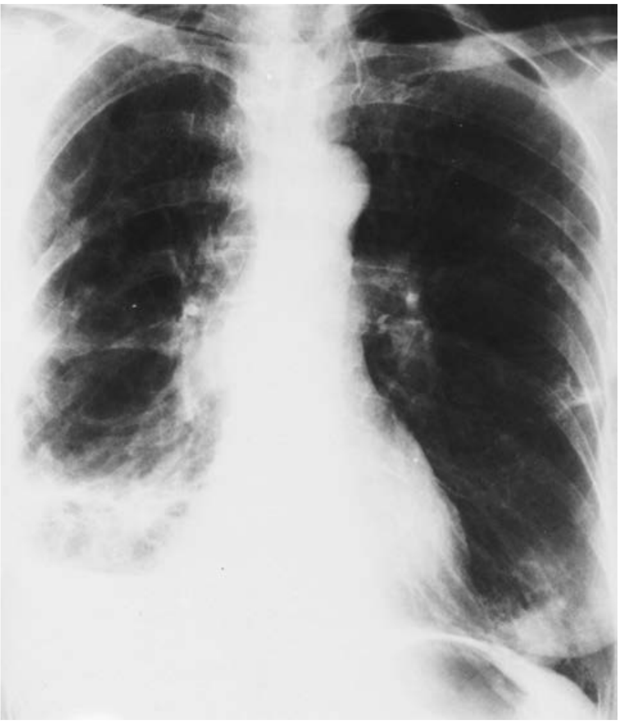

Figure 138-1 Bilateral pneumonia due to *Pasteurella multocida* in a 69-year-old woman suffering from chronic obstructive pulmonary disease and a prior right lower lobectomy for carcinoma. Infiltrates disappeared with penicillin therapy.

cockatiels, macaws, and parakeets) are commonly believed to be the associated risk factor, in fact, most humans contract psittacosis from poultry (especially turkeys) and other non-psittacine birds.

Bacteriology

C. psittaci is an obligate intracellular Gram-negative bacterium. It exists in two forms: elementary bodies and reticulate bodies. The metabolically inactive elementary bodies are ingested by host cells by receptor-mediated endocytosis and then differentiate into metabolically active, but noninfectious, reticulate bodies. The reticulate bodies divide and reorganize into new elementary bodies that then leave the host and can infect new hosts. Since it is an intracellular organism, it does not grow in standard culture medium.

Ecology, Epidemiology, and Pathogenesis

Infection of humans can occur after inhalation of aerosolized avian respiratory secretions, dried feces, or feather dust, and, less commonly, beak-to-mouth contact. Exposure to live poultry or pet birds or habitation in locations with many birds or bird droppings (e.g., under bridges) are epidemiologic clues to the possibility of psittacosis. Human-to-human transmission has not been reported, so isolation of patients is not needed. Outbreaks among poultry workers have occurred.[29] Infection is generally seen in owners of pet birds, pet shop employees, farmers, and workers in zoos, laboratories, and avian quarantine stations. *C. psittaci* infection is a disease reportable to public health departments.

After inhalation the elementary bodies are phagocytized, but they do not fuse with lysosomes and evade destruction, transforming into reticulate bodies and inducing a host response. Inclusion bodies can be seen in alveolar cells on histopathology.

Clinical and Radiologic Features

Symptoms appear 5 to 14 days after infection and include abrupt onset of fever and chills, headache, myalgias, and nonproductive cough. Less common findings include temperature–pulse dissociation, keratoconjunctivitis, and macular rash on the face or extremities. Severe complications include respiratory failure, endocarditis, hepatitis, encephalitis, and sepsis.

Chest radiographs typically reveal lobar infiltrates, commonly in the lower lobes. CT imaging has higher sensitivity and may show nodular infiltrates with surrounding ground-glass opacities.[30]

Diagnosis and Differential Diagnosis

C. psittaci infection can be diagnosed serologically, preferably with a microimmunofluorescent (MIF) antibody test. A titer greater than 1:16 suggests evidence of infection, and demonstration of a fourfold rise is diagnostic for recent infection. Complement fixation assays are available but can cross-react with other *Chlamydia* species. The organism can be cultured, but culture capability is not generally available. Molecular diagnostics of respiratory samples are emerging as a preferred method for diagnosing psittacosis. *C. psittaci* is not included in commercially available "respiratory panel" molecular diagnostic assays. It can be identified in metagenomic "next-generation" assays and at the Centers for Disease Control and Prevention.[29,31] Lower respiratory samples carry a higher yield than nasopharyngeal specimens. In some patients, the organism can also be identified in stool specimens.

The differential diagnosis of pneumonia with fever with no organisms seen on Gram stain of sputum and none isolated on routine culture media includes *Legionella*, *Mycoplasma*, *Chlamydophila pneumoniae*, *Coxiella burnetii*, and viral infections, including the respiratory viruses (SARS, MERS, COVID-19).

Treatment

The preferred treatment for psittacosis is doxycycline, 100 mg twice daily (oral or intravenous) for 7 to 10 days. Azithromycin, 250 to 500 mg once daily for 5 days is adequate alternative treatment for children, pregnant persons, and those who cannot tolerate doxycycline.[32]

■ *Yersinia pestis*

Yersinia pestis, the etiologic agent of the plague, left an indelible mark on humanity long before its late–nineteenth-century isolation and characterization. The organism caused three major pandemics from the sixth through the nineteenth centuries; pulmonary disease in a few victims led to aerosol spread to countless others, resulting in acute primary pneumonia and the "black death" of epidemic plague.

Familial Mediterranean fever has been shown to have mutations that confer heightened resistance to *Y. pestis* that were positively selected in Mediterranean populations.[33] During the period from 1932 through the end of World War II (1945), the Japanese biologic warfare program included use of aerosol drops of *Y. pestis,* as well as infected flea disseminations in occupied China and at the infamous experimental Unit 731. The effectiveness of the flea disseminations remains in question, but the aerosol disposal definitely led to clinical pneumonic plague.

A global scare emanated from India's Maharashtra state in 1994, with reports of suspected pneumonic and bubonic plague; interestingly, some suspected cases were subsequently found to be due to *Burkholderia pseudomallei.*[34] Madagascar accounts for 75% of global plague cases, with an annual incidence of 100 to 700 suspected cases (mainly bubonic plague).[35]

In the United States, fewer than 20 cases of plague are reported yearly, with no human-to-human transmission in the United States since the 1920s. If plague is diagnosed outside an endemic area, bioterrorism should be considered. When *Yersinia* pneumonia occurred in a couple that became ill in New York City, the event was investigated as a potential bioterrorism event until their travel from an endemic area of plague (Santa Fe County, New Mexico) was discovered.[36] Although the bacteria are difficult to process, handle, and disperse in an aerosol form, person-to-person airborne spread is very efficient, and laboratory accidents have occurred.[37]

Ecology, Epidemiology, and Pathogenesis

In the United States, *Y. pestis* is endemic, primarily in the Southwest, in rock squirrels, prairie dogs, rabbits, rats, and other small ground animals. Spread among animals occurs via several species of rodent fleas, especially *Xenopsylla cheopis*. Domestic animals that wander outdoors, like cats, can become infected by direct contact with sick rodents or via rodent flea bites. In addition, cats and dogs can inadvertently carry fleas into the home. Occasionally, rodent die-offs, called epizootics, occur, and many dead animals can be found with viable organisms in carcasses and in the soil surrounding ground dwellings.

Spread to humans occurs when an infected flea feeds on a susceptible person, through handling or ingestion of infected animal tissues, or via inhalation of infectious droplets. Living or working in proximity to local enzootic "hot spots" places certain groups (such as Native Americans, geologists, hikers, veterinarians, and pet owners) at risk. Bubonic and cutaneous plague are usually acquired on exposed areas by contact with infected fleas, but aerosols from ill animals or carcasses can lead to primary pneumonia, pharyngitis, or conjunctivitis. Several cases of cat-to-human aerosol spread have been associated with respiratory infection or submandibular abscesses in pets. Infection control is a concern of clinicians caring for patients with respiratory infection, given the potential for rapid airborne dissemination, especially during coughing and face-to-face contact, resulting in primary pneumonia and the rapid development of adult respiratory distress syndrome (ARDS).

After the organism gains access to human tissues at 37°C, rapid multiplication occurs. The polysaccharide capsule imparts virulence properties that include resisting phagocytosis and persistence of bacteria within nonsensitized monocytes. Virulence factors include a potent endotoxin and V and W antigens of the cell envelope, which influence intracellular survival. A mouse model has demonstrated a biphasic illness with an initial anti-inflammatory phase that rapidly progresses to a highly proinflammatory state by 48 h and death by 3 days. Microarray analysis demonstrates a change in the expression of about 10% of the bacterium's genes after it infects a host.

Clinical and Radiologic Features

Clinical presentations are highly varied and range from subclinical cases (positive serology without evidence of disease) to a chancriform skin lesion (pestis minor abortive bubonic plague), pharyngitis, bubonic plague (with tender, enlarged lymph nodes or "buboes" near the site of a flea bite), septicemic plague (sepsis sometimes complicated by hemorrhage and distal limb necrosis, often the sequelae of untreated bubonic plague), pneumonic plague, and meningitis. The clinical presentation of pneumonia in pneumonic plague depends on the mechanism of spread. In contemporary experience in the United States, cases have been secondary to bubonic plague or primary septicemic plague, rather than from pneumonic plague.[38] The onset of respiratory disease follows days to a week of a febrile illness and is ushered in by the gradual onset of cough, dyspnea, and increasing toxicity. Pink to hemorrhagic frothy sputum, pleurisy, and respiratory distress are additional symptoms. The unique feature in most cases of pneumonia is the epidemiologic association with classic bubonic plague, that is, occurrence in a person in or from an endemic area. From histories of primary inhalation pneumonia described previously, exposure to an index case with pneumonic plague may be followed by rapid development of a fulminating respiratory illness, with dyspnea, cyanosis, and thin, watery sputum that rapidly becomes hemorrhagic. The clinical picture is not unlike that of overwhelming pneumococcal pneumonia, with marked toxicity and mental torpor associated with progressive cyanosis.

The radiologic features of secondary pneumonia include basal segment nodular or hazy airspace infiltrates, hilar and mediastinal node enlargement, and, occasionally, pleural effusions.[39] In primary pneumonia, infiltrates may be minimal during the first 24 h but are followed by progressive airspace disease resembling ARDS or pulmonary edema.

Bacteriology, Diagnosis, and Differential Diagnosis

Y. pestis is a bipolar-staining, Gram-negative bacillus closely related to *Escherichia coli* and other Enterobacteriaceae. Other acute respiratory infections caused by microorganisms that appear as Gram-negative bacilli with bipolar staining must be considered, including *Francisella tularensis* and *P. multocida*. Cultures of blood, sputum, and lymph node aspirates often yield positive results. The organism grows well on blood or MacConkey agar and is identified definitively with differential biochemical tests, agglutination reactions, direct fluorescent antibody staining, and matrix-assisted laser desorption ionization–time of flight (MALDI-TOF) mass spectrometry.

Rapid assays for diagnosis of plague have been shown to be useful, such as that based on the antigen F1, which is highly sensitive for diagnosing either pneumonic or bubonic plague and could be useful in detecting plague in remote areas, although false-positive results indicate a need for culture or PCR confirmation; culture is still needed for additional information on antibiotic resistance and bacterial strains.[40] Concerns for laboratory safety have led to routine use of biosafety level 2 (BSL-2) procedures, as well as better communication between clinicians and microbiology laboratory personnel in suspected cases.[37] Postinfection confirmatory serologic studies can be done using passive hemagglutination testing on acute and convalescent sera at selected reference laboratories, such as the U.S. Centers for Diseases Control and Prevention (CDC).

The differential diagnosis for pneumonic plague includes infectious agents that cause community acquired pneumonia, such as pneumococcus, *Streptococcus*, *H. influenzae*, viruses, and unusual etiologies like anthrax or tularemia.

Treatment and Prevention

A review of published cases of treated plague from 1937 to 2019 found an overall case fatality rate of 20%.[41] Combination treatment with either streptomycin or gentamicin and doxycycline or tetracycline has been the treatment of choice for serious plague infections;[42] some experts recommend starting doxycycline whenever the disease is suspected.[43] Fluoroquinolones, such as ciprofloxacin, and chloramphenicol also are effective in treating pneumonia.[41,42] Multidrug-resistant plague has been reported, and clinicians should be aware of local trends, as well as the potential for terrorist-instigated modifications in antibiotic susceptibility.

Persons suspected of having plague pneumonia should be rapidly isolated and strict contact, respiratory, and conjunctival precautions instituted. Anyone exposed face-to-face with a coughing patient, including health care workers, should be given preventive doxycycline or ciprofloxacin (trimethoprim-sulfamethoxazole in pregnant women and children). Isolation procedures are continued until the productive cough resolves or sputum cultures are negative for *Y. pestis*.

An inactivated vaccine is available for laboratory workers and others with frequent exposure to the microorganisms or hyperendemic areas, although it is not commercially available in most countries and does not appear to protect against pneumonic plague.[44] Careful surveillance of ground rodent populations, posting warnings in endemic regions, watching for die-offs that indicate epizootic spread, and spraying for local flea control may also be effective preventive measures, along with public education.[38]

Francisella tularensis

Tularemia is a common animal disease in the United States as well as many other regions of the temperate globe. The causative agent, *F. tularensis*, is ubiquitous, distributed among many species of wild and domestic animals and birds. As with plague, the major clinical manifestations include skin lesions and swollen or draining regional lymph nodes. In addition to primary inhalation pneumonia, pulmonary invasion is seen following bacteremia in 10% to 15% of ulceroglandular cases and in more than 50% of patients with the typhoidal syndrome. Some 200 to 300 human cases are reported in the United States yearly, but this is probably an underestimate; approximately 50% of all tularemia cases each year in the United States occur in Arkansas, Kansas, Oklahoma, and Missouri.[45] In the summer of 2000, an outbreak of pneumonic tularemia occurred on Martha's Vineyard, Massachusetts, and 11 of 15 patients were diagnosed with primary pneumonic tularemia; lawn mowing and brush cutting were found to be risk factors for infection.[46] An epidemic of tularemic pharyngitis from ingestion of contaminated well water and food occurred in war-torn Western Kosovo primarily among young children originally suspected of having group A streptococcal pharyngitis, with no secondary pneumonias reported.[47]

Bacteriology

F. tularensis is a fragile-appearing Gram-negative coccobacillary organism that is quite fastidious and grows poorly on artificial media unless fortified with serum and cysteine (or sulfhydryl compounds). The potential for laboratory-acquired inhalation or ingestion-associated disease is great. Most routine laboratories do not attempt to culture the organism, leaving this to special reference centers. Identification is based on morphologic and biochemical determinants, but direct fluorescent staining or agglutination reactions with specific antisera also are useful.

Ecology, Epidemiology, and Pathogenesis

The organism is associated with more than 100 species of wild and domestic animals and birds, including aquatic mammals, but most clinical cases arise from contact with rabbits, squirrels, or arthropods. Of great concern is the recent fad for exotic pets; tularemia in prairie dogs has led to spread in holding pens and to human transmission. In cold weather the organism can persist in water and mud environments for weeks to months.

Fewer than half of human cases are acquired from contact with infected animals during hunting, trapping, and other outdoor pursuits, especially during colder months. In southern areas, or in the summer season in northern latitudes, gardening and lawn mowing without animal contact are becoming important methods of dissemination from disturbed soil. Bloodsucking arthropods constitute a significant and increasing mode of spread, especially in warmer seasons. Ingestion of contaminated food or water,[47] animal bites, conjunctival contact, and aerosol dissemination also are important mechanisms for acquiring the pathogen. In recent years, cases secondary to arthropods have been more frequent than those associated with direct animal contact, although domestic cat bites[48] and airborne spread appear to be increasing. Human-to-human transmission is rare, in contrast to the significant theoretical potential for spread of pneumonic plague. *F. tularensis* is a category A bioterrorism agent because of potential for aerosol release.[49] Aerosol release could lead to respiratory, as well as cutaneous, conjunctival, or pharyngeal disease.

F. tularensis contains a number of protein and polysaccharide antigens in the cell envelope, as well as an endotoxin component that is similar to endotoxins of other Gram-negative microorganisms. The organism is capable of remaining viable in reticuloendothelial cells of nonimmune subjects and in macrophages that have not been activated by recent exposure to other intracellular pathogens. As few as 10 to 50 organisms can initiate disease following cutaneous penetration or by inhalation, but a significant number are required when the challenge is through ingestion of contaminated water or foods. Local growth usually is followed by regional node suppuration and, occasionally, bacteremic dissemination to many organs, including the lungs. Primary pneumonia follows inhalation of organisms, resulting in numerous areas of inflammation, necrosis, a tendency to granuloma formation, hilar and mediastinal adenopathy, and pleural inflammation and effusion.

Clinical and Radiologic Features

Respiratory disease is heralded by the onset of a nonproductive cough, usually in a febrile patient ill with the ulceroglandular form of tularemia.[50] In the absence of a local chancriform lesion or a tender swollen lymph node (bubo), the disease may be dominated by constitutional symptoms, with high fever, severe headache, prominent myalgias, and shaking chills (typhoidal tularemia). Pneumonia following an inhalation exposure results in cough, dyspnea, and, occasionally, pleurisy. Respiratory disease can be subtle, and the diagnosis may be apparent only if a chest radiograph is done. Pleural effusions may be serosanguineous or frankly bloody, an uncommon finding with other pulmonary infections except anthrax.

Radiologic changes include evidence of parenchymal and pleural disease, which is often out of proportion to the findings on examination. Diffuse areas of bronchopneumonia occur, with hilar node enlargement and occasionally mediastinal widening, similar to the radiologic appearance of anthrax. Unilateral or bilateral pleural effusions are often noted (Fig. 138-2).

Diagnosis and Differential Diagnosis

Any febrile patient with animal, arthropod, or landscaping exposure in an endemic region, especially one presenting with a chancriform skin lesion and/or a tender lymph node, should be evaluated for tularemia. Cough, when present, is usually nonproductive, and blood cultures are seldom positive. Characteristic organisms are rarely seen in pleural fluid or aspirates of suppurating nodes. Direct fluorescent antibody staining of exudates can confirm the diagnosis, but this method is not widely available. Serologic testing remains the method of choice for confirming a diagnosis. ELISA and microagglutination methods may be more sensitive than tube agglutination testing. A single convalescent titer of 1:160 or greater is considered highly suspect for active disease, but a fourfold rise in titer between acute and convalescent (1–5 weeks) sera is more reliable since antibodies can persist for many years after infection. Polymerase chain reaction and other molecular biologic techniques have successfully diagnosed tularemia in human specimens. An elevated blood level of creatine phosphokinase may be a clue that tularemia-induced rhabdomyolysis is a response to the acute infection, especially in highly endemic areas.

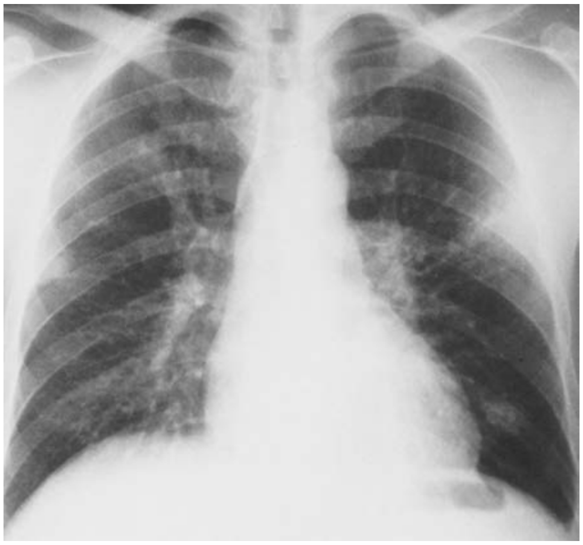

Figure 138-2 Patchy nodular and bronchopneumonia, hilar adenopathy, and left pleural effusion due to *Francisella tularensis* in a 38-year-old veterinarian exposed to a cat dying with a respiratory infection. All the findings resolved with tetracycline therapy.

F. tularensis can be cultured from blood, sputum, and other body tissues. If tularemia is suspected, it is important to notify the microbiology laboratory staff because of the high risk of aerosolizing the organism if the culture plate is opened outside of a biosafety containment hood.

Perplexing diseases that are also associated with outdoor and animal exposures, such as psittacosis and Q fever, may be confused with tularemia. Legionnaires' disease and *Mycoplasma* pneumonia can present with similar clinical courses, without diagnostic sputum. Plague, tuberculosis, and systemic fungal infections produce a spectrum of acute to chronic respiratory manifestations that can mimic pulmonary tularemia.

Treatment and Prevention

Streptomycin was the first effective antibiotic for treating all forms of tularemia, but it is not readily available.[50] Gentamicin appears to be equally potent and has the advantage of a broader spectrum of activity if one is initiating treatment when the etiologic diagnosis is less secure.[50] Additionally, it can be given intravenously, and blood levels can be monitored. Tobramycin, however, appears to be unreliable and, therefore, should not be substituted for other aminoglycosides. Recent experience confirms that results of therapy are optimal when an aminoglycoside is chosen early in the clinical illness. Tetracycline/doxycycline, ciprofloxacin, and chloramphenicol may be useful alternatives when an aminoglycoside is contraindicated. Relapse rates are higher with the bacteriostatic combination of tetracycline/doxycycline and chloramphenicol, especially when given for less than 2 weeks. β-Lactam antibiotics are not effective. The prognosis is excellent with appropriate antimicrobial therapy.

Cautious practices are required when one is dealing with animals and their carcasses. Using gloves, cooking wild animal meat thoroughly, and wearing protective clothing and repellants to avoid blood-sucking arthropods are helpful measures. An attenuated live vaccine strain (LVS) has been developed but is not commercially available. With the increase in concern in bioterrorism, the Tularemia Vaccine Study Group and others are working to develop an improved vaccine.[51]

■ *Rhodococcus equi*

Rhodococcus equi, formerly known as *Corynebacterium equi*, was first isolated in 1923 by Magnussen when it was identified as a cause of suppurative pneumonia in foals. It was later shown to be a frequent pathogen in horses, cattle, and swine. First described as a pathogen in humans in 1967, the majority of recognized cases in recent years have been in immunocompromised patients, especially individuals receiving corticosteroids, those infected with the human immunodeficiency virus,[52] or those who have undergone solid organ transplantation.[53,54] Pneumonia with the related bacteria *Rhodococcus defluvii* has been reported in a patient with AIDS.[55]

Bacteriology, Ecology, Epidemiology, and Pathogenesis

Rhodococcus is a pleomorphic Gram-positive bacillus in the order Actinomycetales. It grows well aerobically on most media, at 37°C, as mucoid pale-pink or salmon-pink colonies that are usually observed by 48 h of incubation. *R. equi* has a high cell wall mycolic acid content and is acid-fast, similar to *Nocardia* spp. and Mycobacteriaceae. Some strains ferment glucose, but the majority will not ferment carbohydrates. Most produce catalase and hydrogen sulfide. β-Lactamase is present in some strains.

Most reported cases occurring in humans without HIV infection have been in patients who had significant contact either with livestock or soil and environments that were heavily contaminated with livestock waste. In contrast, HIV-related *Rhodococcus* disease appears to occur in patients who do not have any particular environmental exposure history—implying a wider distribution of the organism.[52] There is no known geographic endemicity.

R. equi usually is inhaled, although soft-tissue infections after cutaneous inoculation can occur. As an intracellular pathogen it causes disease primarily in patients with impaired cell-mediated immunity and defects in phagocytic processing of organisms. Diseased tissues usually show a necrotizing granulomatous reaction, with histiocytes and macrophages frequently containing bacteria. In contrast to lesions associated with *Mycobacterium tuberculosis* and systemic fungi, there is also a prominent infiltration of neutrophils in the affected areas, a characteristic shared with other *Actinomyces* spp.

Clinical and Radiologic Features

Patients frequently complain of indolent symptoms, such as fever, nonproductive cough, and mild dyspnea.[53] Typically there is a paucity of findings on physical examination of the chest, but signs of consolidation and pleural friction rubs may be present. Patients with HIV infection generally present in a manner similar to patients without HIV infection, although pleuritic chest pain may be more common. In HIV-infected patients, *R. equi* disease tends to occur after there has been significant deterioration in their immune systems, with CD4 lymphocyte counts less than 200 cells/mm^3.[52] It is often found associated with other pulmonary infections. Extrapulmonary dissemination occurs in HIV-infected and non–HIV-infected patients, but there appears to be a significantly greater rate of recovery of the organism from blood cultures in HIV patients. The central nervous system is a recognized site of metastatic infection, as it is for *Nocardia* spp. The immune reconstitution inflammatory syndrome (IRIS) has been reported in patients with HIV after starting antiretroviral therapy.[56,57] *R. equi* has been reported as an opportunistic pathogen in patients with solid organ transplants.[58,59]

The most common radiographic abnormalities are lobar infiltrates, which usually evolve into nodular or cavitating lesions within weeks or months. There is no predilection for involvement of any particular lobe. Pleural effusions are common, occurring in up to 40% of HIV patients with pulmonary *R. equi* infection. Significant hilar adenopathy is unusual.

Diagnosis and Differential Diagnosis

R. equi can readily be cultured from sputum, bronchial lavage, pleural fluid, or other infected tissue and often from blood. Since the organisms stain as pleomorphic Gram-positive bacilli, grow readily on most media, and are usually catalase producers, they can be mistaken for "diphtheroid" or "Coryneform" contaminants unless further testing is done; therefore it is important for the clinician to alert the microbiology laboratory staff if the possibility of *R. equi* is entertained. *R. equi is* slightly acid-fast with modified Ziehl-Neelsen stain.

Rhodococci share many microbiologic features with mycobacteria and *Nocardia*, and this may account for similarities in the subacute to chronic evolution of the disease. The high mycolic acid content of their cell walls results in their acid-fast staining properties and may also play a role in their similar clinical and pathologic manifestations. *Nocardia* spp., *M. tuberculosis*, and nontuberculous mycobacteria also should be considered when acid-fast organisms are found in clinical specimens, especially in immunocompromised patients with nodular or cavitary pneumonia (Table 138-2).

Other considerations in the differential diagnosis of nodular or cavitating pulmonary lesions include malignancy, fungal infection such as *Cryptococcus neoformans*, anaerobic lung abscess, and necrotizing pneumonia caused by facultative bacteria such as *Staphylococcus aureus* or *Klebsiella pneumoniae*.

Treatment and Prevention

Antibiotic therapy alone is usually adequate to achieve cure.[53] As with mycobacterial infections, multidrug regimens and therapy of 2 to 6 months' duration may be needed, especially in immunocompromised patients. Because *R. equi* is an intracellular pathogen that multiplies in phagocytes, antibiotics capable of achieving

TABLE 138-2 Diagnosing *Rhodococcus equi* Respiratory Infection

History of exposure to horses, cattle, or their environment
Immunocompromised host: malignancy, steroids, HIV
Cavitary or nodular infiltrates on radiograph
Gram-positive pleomorphic bacilli
Modified acid fast
Pale-pink or salmon-pink mucoid colonies
Grows rapidly, aerobically on most media
Differential diagnosis includes *Nocardia* species, mycobacteria

high intracellular levels, such as rifampin or fluoroquinolones and macrolides, are preferred. Chloramphenicol, sulfonamides, and aminoglycosides are active against most isolates. In some patients, surgical resection of a nodular or cavitating lesion may be necessary to achieve cure. For prevention, we advise immunocompromised hosts to avoid contact with horses and their environments.

ENVIRONMENTAL AND ANIMAL PRODUCT PNEUMONIAS

This section focuses on diseases that are spread to humans predominantly from contact with contaminated soil, water, foods, or animal structural elements. The diagnosis usually depends on a careful history focused on epidemiologic and ecologic characteristics. Once alerted, the clinician can request studies that may reveal the cause of these often obscure diseases. It should be apparent that this distinction—an association with environmental contamination and animal products—can be somewhat arbitrary. For example, anthrax bacilli can spread directly from animals to humans, and *R. equi* contamination of soil could place it in this group, rather than in the group infected via direct animal exposure.

■ *Bacillus anthracis* (Anthrax)

Inhalation anthrax was a common enough disease in the nineteenth and early twentieth centuries to be referred to variously as Bradford's disease, after the English town, and woolsorter's disease for the epidemiologic association with the sheep industry. Fortunately, inhalation anthrax has become a rare spontaneously acquired disease, accounting for less than 5% of anthrax cases (95% are cutaneous, and gastrointestinal disease is very rare).[60] An epidemic of anthrax in 1979, following an accidental release at a bioweapons facility occurred in the area of Sverdlovsk (now renamed Ekaterinburg) in the former USSR, resulted in 42 deaths due to inhalational anthrax.[61] In 2001 there were 18 confirmed cases of inhalational and cutaneous anthrax and an additional 4 suspected cases of cutaneous anthrax in the United States; of the 22 cases, at least 20 were definitively related to mail contaminated with the same strain of *B. anthracis*. The potential zoonotic as well as terrorist-induced exposure of susceptible persons to *Bacillus anthracis* spores argues for including this devastating, often lethal, disease in this chapter.

Bacteriology, Ecology, Epidemiology, and Pathogenesis

B. anthracis is a large (red blood cell diameter), square-ended bacillus that stains Gram-positive and tends to form chains. Growth on sheep blood agar results in dull, sticky, irregularly shaped colonies within 24 h. The organism possesses a polyglutamic acid capsule, produces a complex potent trivalent exotoxin, and, under adverse conditions, forms highly refractile, centrally located spores that are very resistant to temperature and moisture extremes.

Anthrax is primarily a disease of herbivores. The resistant spores are present after animals dying of the disease contaminate the soil. Anthrax "hot spots" are found internationally, and in milder regions in the United States, such as Oklahoma, Texas, and California. Optimal conditions for germination of spores and multiplication of bacilli include alkaline soils containing adequate calcium and low areas that are wet for prolonged periods, termed incubator areas, with thick vegetation that produces heat with decay. Periods of extreme drought after a rainy season favor spore formation. Climate change has increased rates of anthrax in new regions. Animals grazing in these areas inhale, ingest, or pick up spores on their fur. The cycle is completed when an animal develops the disease, dies, and returns organisms to the soil for eventual sporulation.

Inhalation anthrax rarely occurs from contact with live infected animals, and there is no human-to-human transmission. The animal hide industry, exposure to bone meal fertilizer,[62] and use of imported goat skins and raw wool in home crafts can lead to inhalation of spores and clinical disease in susceptible persons.[63] Inhalation of spores from wind-disturbed soil can also cause infection.

Inhalation results in activation of bronchial clearing mechanisms and entrapment of spores in hilar and mediastinal nodes, where reversion to vegetative bacilli can occur. The polyglutamic acid capsule is antiphagocytic, and the extracellular microorganisms produce a trivalent protein exotoxin that leads acutely to profound local edema, accompanied by hemorrhage in the mediastinal and hilar areas, with compromise of airflow. The pathogenesis of this tripartite toxin consists of a protective antigen, an edema factor, and a lethal factor.

The protective antigen fragment of the toxin serves as the binding domain, essential for cell penetration by both the edema factor and the lethal portions of the molecule.

Edema factor is a potent adenylate cyclase; activation within mammalian cells stimulates production of cAMP, and the resultant flux of sodium, potassium, and water leads to abundant local edema. When this process takes place in hilar and mediastinal nodes and surrounding tissues, profound airway obstruction ensues, with pooling of secretions and if the patient survives, secondary bacterial pneumonia.

Lethal factor is a potent protease that acts primarily in macrophages, activating intracellular mitogen-activated protein kinase, leading to production of proinflammatory cytokines and reactive oxygen intermediates. The pathogen rarely invades lung tissue, as death from asphyxia occurs rapidly, usually associated with pleural effusions (secondary to lymphatic obstruction) and hemorrhagic septicemic lesions in many organs. In a large inoculum exposure, as occurred in the 2001 "mail room" criminal outbreak, patients can develop disease within the pulmonary parenchyma and the gastrointestinal tract.[60]

Clinical and Radiologic Features

In spontaneously occurring disease, the onset is insidious, usually resembling a nonspecific febrile influenza–like illness.[20,60] Malaise and muscle aches, low-grade fever, mild headache, coryza, mild and nonproductive cough, pharyngitis, and chest pains have been described as early symptoms. At this stage, it is hardly possible for the physician to entertain a presumptive or possible diagnosis of anthrax unless a history of industrial or craft-related exposure to imported animal hair or hides or to animal products, such as bone meal, is obtained. Watery nasal discharge can be indicative of nasal or paranasal sinus involvement. Cough may represent hilar and mediastinal node swelling, and careful auscultation may reveal prolonged expiratory wheezes or evidence of a pleural effusion. Chest pain may be the first clue that hilar and mediastinal inflammation is present.

Within hours to a few days, the mild complaints abruptly worsen, and acute airway obstructive features dominate the clinical picture. Any activity precipitates severe dyspnea, stridor, and wheezing. Impairment of the nervous system (hemorrhagic meningitis) and hypoxemia result in decreasing levels of consciousness. Edema of the pharynx, neck, and anterior chest may develop. Chest pain, fever, and cyanosis are progressive. Worsening airway obstruction can lead to intercostal space retraction, and pleural effusions are noted on examination. Death usually occurs within hours to a day once acute respiratory symptoms are present. In the 2001 exposures to significant spore burden, some patients had a biphasic illness with early upper respiratory and gastrointestinal symptoms, followed by respiratory distress days later.[60]

Inhalation anthrax is primarily a mediastinitis, and the radiologic features mostly reflect the pathologic findings.[64] Widening of the mediastinum or prominence of hilar nodes is the earliest radiologic finding, sometimes accompanied by pleural effusion; in advanced cases, the mediastinal width may be greater than 9 cm and sharply demarcated from surrounding lung tissue given the absence of airspace consolidation. There may be perihilar and peribronchial streaking from edema and hemorrhage.

Diagnosis and Differential Diagnosis

A physician alerted to the possibility of inhalation anthrax has few laboratory studies to rely on. Nasal secretions and sputum rarely reveal the characteristic bulky Gram-positive bacilli. Half of the reported cases of inhalation disease are complicated by meningitis, and hemorrhagic cerebrospinal fluid with observable organisms can confirm the diagnosis. There are no available data on examination of buffy-coat smears, and therapy must be instituted before blood culture results become available. Microscopic examination of pleural fluid may reveal the characteristic organisms. The most commonly recognized form of anthrax, the cutaneous chancriform necrotic lesion, does not usually accompany inhalation cases in naturally occurring disease.

Differential diagnosis includes other causes of acute mediastinitis, such as esophageal perforation. Tuberculosis, histoplasmosis, and tularemia rarely produce acute respiratory failure as part of hilar and mediastinal node involvement. Hantavirus pulmonary syndrome is associated with similar central pulmonary changes, including edema but should be separable from anthrax by epidemiologic data, the presence of air space disease, and absence of mediastinal involvement. Lymphoproliferative diseases that may have mediastinal involvement, like nodular sclerosing Hodgkin disease, evolve at a slower pace. Chest wall and neck edema, associated with acute breathing difficulties, can accompany diphtheria or *Streptococcus pyogenes* pneumonia, with bilateral pleural effusions, an early manifestation of streptococcal pneumonia. Acute epiglottitis caused by *Haemophilus influenzae* can mimic some manifestations of inhalation anthrax.

Treatment and Prevention

Combination therapy is currently recommended based upon the "mail room" epidemic of 2001.[20] Regimens with ciprofloxacin or doxycycline, plus clindamycin (to block toxin production) and rifampin (which penetrates CSF and intracellular sites) are favored. Monotherapy with penicillin should not be used in inhalation disease since multiple strains, including the 2001 "mail room" outbreak, produce an inducible β-lactamase. Treatment is recommended for 60 days to avoid activation of persistent spore forms.[20] Corticosteroids should be considered for treatment of significant mediastinal edema or meningitis. Early thoracentesis appears to be beneficial. Unfortunately, the airway obstructive manifestations are not reversible once acute respiratory manifestations have progressed. Assisted ventilation and use of diuretics are all reasonable support efforts, but they are generally not successful due to the continued effects of tissue-bound toxin. Before 2001, mortality in inhalation anthrax approached 100%. In the 2001 experience, mortality was 45% (5 of 13 respiratory cases); knowledge gained from that experience might prove helpful in future cases.[60]

In the animal hide industry, vaccination is the cornerstone of preventing anthrax. Plant workers and others in contact with potentially infected animal products should be immunized with the currently available vaccine: anthrax vaccine adsorbed.[65] Numerous new vaccines are under development, many based upon the protective antigen segment of the toxin. Animal products imported from endemic regions of the world (e.g., Africa, the Near East, the Indian subcontinent) are steam sterilized, and there is modern ventilation in the workplace. At-risk persons are those who are unlikely to be vaccinated, that is, those who service these plants, such as ventilation specialists and other transients. Bone meal should be treated by heat sterilization before packaging for use by commercial and home gardeners.[62] Those who import yarn from endemic areas are at special risk unless the rules for commercial hide sterilization are also imposed on casual animal hair imports.[63] A recent case of inhalation anthrax in a drum maker who carried goatskins into the United States emphasizes the need for appropriate education and importation controls.[63,66]

■ *Brucella* Species

Lung involvement is an uncommon presentation of brucellosis, yet respiratory symptoms can be prominent manifestations of the disease.[67,68] Brucellosis is often a prolonged and perplexing illness however, and in chronic cases pleurisy, hilar adenopathy, and nodular lung lesions can be encountered.[69] Exposure to animals, animal-based foods (cheeses or meats), or residence in an endemic region is usually found.

Bacteriology, Ecology, Epidemiology, and Pathogenesis

Brucellae are slow growing, small, coccobacillary, Gram-negative, nonmotile, aerobic, nonencapsulated organisms that are now classified with the Alphaproteobacteria, closely related to *Rochalimaea* and *Bartonella* spp. Carbon dioxide is essential for growth of *Brucella abortus*, and all four pathogenic species require growth medium enriched with vitamins and serum. With the aid of a battery of biochemical, metabolic, and immunologic criteria, Brucellae pathogenic for humans can be classified as *B. abortus*, *B. suis*, *B. melitensis*, and *B. canis*. In general, the species designation corresponds to the animal usually colonized or diseased.

Brucellae spp. are distributed worldwide. Infection and disease occur primarily in domestic animals in geographic regions such as the Mediterranean (*B. melitensis*), worldwide except in areas of Europe and Japan (*B. abortus*), the midwestern United States (*B. suis*), and North and Latin America (*B. canis*). Spread from one region to another occurs with live animal movements or when infected animal products are commercially or privately shipped.

The epidemiology of brucellosis is intimately related to the association of susceptible persons with infected animals and animal products. Abattoir workers (especially slaughterers) and others in the meat-processing industry, farmers, dairy workers, veterinarians, and bacteriology laboratory technicians account for most cases in the United States, with a general preponderance of male patients. Human brucellosis is rare in the United States, with 80 to 120 cases reported annually; most of these are associated with *Brucella* exposures abroad.[70] Worldwide approximately 500,000 cases are reported annually.[71] Also at risk are military personnel and travelers to endemic regions who eat local foods and persons who consume imported goat cheese, sausage, and other unpasteurized edibles from endemic areas. The organisms are usually acquired by ingestion, through skin abrasions and lacerations, or via conjunctival inoculation. Aerosol spread can be a route in abattoir workers;[72,73] inhalation of only 10 to 100 bacteria can cause disease in humans.[74] No human-to-human transmission has been reported.

Organisms invade the local reticuloendothelial system and lymph nodes, followed by bacteremic spread to many organs during the following weeks. There is increasing evidence that the aerosol route may be a rare but especially efficient portal of entry. The distribution of nodular lesions in lung tissue is primarily in basal segments, however, which argues for bacteremia rather than primarily an inhalation mechanism for most cases of pulmonary disease.

A race between bacterial growth and the development of cell-mediated immunity ensues, primarily in lymph nodes and the reticuloendothelial system. As with tuberculosis, the result is often containment within granulomas that eventually become fibrotic or calcify. Species and strain differences account for the wide variety of tissue reactions encountered, including granulomas, necrosis, and abscess formation. Smooth variants appear to be more virulent than rough forms, and many contain polysaccharide polymers in their superficial envelope that, like true capsules, inhibit phagocytosis and intracellular destruction. Lipopolysaccharide endotoxin is present in the cell envelope and may be responsible for profound metabolic and cardiovascular effects as organisms are killed during therapy, releasing endotoxin. *Brucella* spp. can survive within nonstimulated macrophages while escaping host antibodies and antibiotic therapy. As macrophages become activated, they develop the capacity to rapidly kill *Brucella* organisms. Host immunity appears to be primarily cell mediated. Impairment of cell-mediated immunity can lead to reactivation of latent *Brucella* or greater susceptibility and severity with primary infection.

Clinical and Radiologic Features

Clinical brucellosis is dominated by nonspecific flu-like constitutional manifestations, including fever and headache. Nonproductive cough has been described in 10% to 33% of cases, but other indicators of respiratory involvement are rarely or poorly described. In one review of 59 cases, dyspnea and pleuritic chest pain were present in 10% of the patients. Hoarseness, bronchitis, and, rarely, mucopurulent, purulent, or hemorrhagic sputum have been noted. Only one patient with verified pulmonary invasion was described in a review of 160 acute and subacute cases of brucellosis reported in 1974. In a recent description of 37 patients with *Brucella* respiratory disease, 32% had typical lobar pneumonia, 41% had an interstitial pattern on chest x-ray, and a honeycomb pattern was seen in 11%, with pleural effusion(s) in the same number.[75] Extrapulmonary disease was found in 76% of patients, with 22% having greater than one extrapulmonary complication. Unilateral hilar adenopathy and granulomas occur occasionally.

Diagnosis and Differential Diagnosis

During the acute illness or in relapse, blood cultures may be positive. In the presence of an infiltrate or pleural effusion, material for Gram stain and culture should be obtained, although the yield is small. A positive culture may be obtained from a lymph node or pulmonary granuloma biopsy. In most cases the diagnosis is made from a fourfold rise or a single value of at least 1:160 in the agglutination titer. Occasionally “inhibitory” or blocking antibodies are present in the serum, and a positive titer is discovered only if the serum is further diluted (so-called prozone phenomenon). The standard tube agglutination test utilizes *B. abortus* as the antigen and detects antibodies to *B. suis* and *B. melitensis*, but not to *B. canis*. Direct comparison of the clinical manifestations of *B. abortus* with *B. melitensis* reveals that the latter presents more acutely as fevers of unknown origin with statistically significant higher rates of abdominal tenderness, hepatomegaly, splenomegaly, thrombocytopenia, pancytopenia, and hepatic dysfunction. Acute disease can be confused with miliary tuberculosis, endocarditis, tularemia, disseminated histoplasmosis, and lymphoproliferative diseases. Subacute and chronic cases must be differentiated from subacute bacterial endocarditis, tuberculosis, histoplasmosis, other systemic fungal infections, and sarcoidosis.

Treatment and Prevention

The combination of doxycycline with rifampin for 4 to 6 weeks is one of the most effective and easiest oral antibiotic regimens.[67,76] Doxycycline combined with streptomycin or gentamicin, or trimethoprim-sulfamethoxazole also are effective alternative regimens. Fluoroquinolones are active in vitro, but they are associated with an unacceptably high relapse rate as monotherapy.

Rigorous control measures, such as herd inspections and vaccination procedures, have dramatically reduced enzootic and epizootic disease in many regions. Quarantine and inspection activities have diminished the risk of importing infected animals into the United States. The program for *B. suis* eradication has been ineffective, and human cases of *B. suis* now outnumber those due to *B. abortus*. Education programs for workers in abattoirs have been aimed at protecting and preventing skin lacerations and eye contamination.

■ *Burkholderia (Pseudomonas) pseudomallei*

Melioidosis ranges from an acute necrotizing to a chronic fibronodular cavitating process indistinguishable from tuberculosis.[77] It is a disease of tropical latitudes and is associated with rural settings.[78] Most cases are in the heavily endemic regions of Southeast Asia, including northeast Thailand, Malaysia, and Singapore, as well as northern Australia. A number of cases were noted in survivors of the 2004 tsunami[78] and after flooding in Puerto Rico.[79]

Sporadic cases have been reported among residents of or travelers to central and South America, and clusters have been reported in northeastern Brazil. Infection with *Burkholderia pseudomallei* has been seen in the United States almost exclusively after a latent period of months to years in military personnel returning from regions such as Vietnam and in refugees from endemic areas, and there are similar case reports from areas such as the Caribbean,[79] Africa, the Middle East, and Brazil. The mortality rate can reach 40%.[77] Cases have also been reported in nontravelers in the United States, possibly linked to imported products since the organism was not isolated from environmental sources.[80]

Bacteriology, Ecology, Epidemiology, and Pathogenesis

The organism is an aerobic, bipolar-staining, Gram-negative bacillus that is motile and lacks a well-defined capsule. Similar to *Pseudomonas*, *B. pseudomallei* grows well on minimal as well as enriched media, including blood and MacConkey agar used in most routine laboratories. Typical colonies are distinctive in appearance, rough or wrinkled, and cream to orange in color; they may resemble a flower with folds radiating from a central core. Colonies have the typical musty, fruity odor of the pseudomonads but lack pyocyanin and other pigments that characteristically color the surrounding medium. Identification rests on a battery of biochemical reactions, and confirmation is based on agglutination or fluorescent antibody studies.

B. pseudomallei occupies an environmental niche that includes moist soils, rice paddies, and other stagnant water in tropical and subtropical regions, approximately subtended by latitude 20 degrees north to 20 degrees south. Evidence of subclinical and clinical disease occurs in wild and domestic animal populations, as well as in humans living permanently or transiently in rural endemic areas, especially in southeast Asia and northeast Australia. As many as 10% to 30% of native populations have evidence of prior infection based on serologic data. Approximately 1% to 2% of healthy American military personnel who served in Southeast Asia have antibodies, and almost 9% of soldiers wounded in Vietnam have titers for *B. pseudomallei*. A significant number of the approximately 3 million U.S. soldiers who fought in the region constitute a reservoir of latent disease that, like tuberculosis, can become active even decades later, far removed from an endemic area. Refugees from Southeast Asia represent another important group of potential carriers.

Transmission is mainly by direct contact with contaminated soil or water through minor abrasions or major wounds. Ingestion and inhalation are probably less frequent modes of spread, but common source outbreaks occur in animals and humans. Animal-to-human disease is very rare, with only three cases reported from Australia. Human-to-human spread also has been exceptional, associated with breastfeeding or urinary catheter contamination, or occurring between siblings with cystic fibrosis. In endemic regions, lack of previous exposure and debilitating circumstances, including malnutrition and uncontrolled diabetes, may increase susceptibility to infection and disease. In a survey of 524 patients with melioidosis in northeast Thailand, coinfection with HIV was detected in only 8 of 524 adults (1.5%); clinical presentation and acute outcome were similar in HIV-positive and -negative patients. Although it is not clear if solid organ transplant alters the risk for melioidosis, pleuropulmonary melioidosis with septicemia has been reported in a renal transplant patient in Australia; although she was not from an endemic region, on revisiting her travel history, it was found that the patient had travelled to the endemic tropical northern Queensland part of Australia during the rainy season.[81]

Pathogenesis and Pathophysiology

The presence of potent endotoxin and the absence of an antiphagocytic capsule have been noted. Acute infections are associated with necrotic lesions containing polymorphonuclear neutrophils (PMNs) in lung and other tissues. Chronic infections, especially in the respiratory tract, resemble tuberculosis with granuloma formation, Langhans or foreign-body giant cells, central caseating necrosis, and occasionally a PMN response in the necrotic area. Activation of latent infection after a period of months or even decades occurs. This “awakening” can be in the wake of influenza and other acute infections, acute stress (trauma, thermal burn, surgery, etc.), and immunosuppressing illnesses or therapies, but spontaneous activation also occurs. The location of dormant microorganisms and the specific molecular events that stimulate recurrent disease are unknown but remain an area of active investigation.

An antecedent local infection in an area of broken skin can be followed by acute septicemia in nonimmune subjects. Initial pulmonary lesions occur predominantly in the better-vascularized basal segments, consistent with bacteremic spread to the lungs. Eventually, other areas of the lungs and other tissues are affected. Subacute and chronic disease may result from a subclinical primary focus, often localized in an apical segment, resembling tuberculosis in location and propensity for granuloma formation and cavitation. Subpleural invasion can result in empyema or sympathetic sterile effusions.

Clinical and Radiologic Features

Primary melioidosis occurs within a few days to 3 weeks of exposure, usually via a cutaneous wound in persons from (or with recent exposure to) an endemic area. The portal of entry may be present as a small necrotic skin lesion in an area of known trauma, with accompanying cellulitis or lymphangitis. Although the acute phase of melioidosis is the most common manifestation in endemic areas, it is very rarely seen in the United States. In addition to marked toxicity and high fevers, respiratory complaints include cough, dyspnea, pleuritic pain, and purulent sputum. Bibasilar rales may be heard, but objective physical findings are often minimal in the face of severe toxicity.

Milder types of subacute and chronic pneumonia are often seen. In addition to fever, productive cough, and pleuritic pain, many patients experience marked weight loss and a clinical picture resembling tuberculosis or fungal disease. Secondary skin manifestations are rarely seen unless bacteremia ensues. Physical changes are often subtle but can include localized rales, a pleural friction rub, signs of an effusion, and manifestations of disease localized to soft tissues, lymph nodes, bones, or joints.

Radiologic findings reflect the stage of disease present. In acute fulminant infections, airspace disease can be absent or miliary to larger nodular densities seen in basal segments. In subacute and chronic cases, fibronodular or cavitary apical lesions are found, similar to reactivation tuberculosis.

Diagnostic Features

Melioidosis should be seriously entertained in any febrile patient with a history of residence in a major endemic region such as Southeast Asia or northeast Australia. If sputum is available, the Gram-negative, bipolar-staining bacilli may be seen, and the organisms can be readily cultured and identified in the routine laboratory. Blood and urine cultures are frequently positive in acute cases. In more indolent infections, biopsy may be necessary. Polymerase chain reaction and MALDI-TOF mass spectrometry are increasingly used for diagnosis. Serologic studies can be helpful in active and recrudescent disease, especially in patients residing in nonendemic areas. A specific IgM immunofluorescence test is often positive in recent infections and recrudescent disease. Complement fixation and indirect hemagglutination tests are available and require testing of paired sera over several weeks to confirm active disease.

Differential Diagnosis

In patients from Southeast Asia, acute fulminating infections with pneumonia may be due to traditional bacteria and viruses but may also be caused by infection with *Y. pestis* (plague) and *F. tularensis* (tularemia) (see above). Chronic forms of melioidosis resemble tuberculosis and fungal infections such as histoplasmosis and blastomycosis. Occupation, travel, and history of respiratory illness should help to clarify the cause.

Treatment and Prevention

Recommendations for therapy of acute septicemic melioidosis must be couched in cautious statements. During the Vietnam War, mortality greater than 50% occurred, even with use of three-drug regimens in massive doses. In subacute and chronic pneumonias and recrudescent disease, cure rates approach 100%. Treatment must be prolonged and surgical intervention for drainage or removal of cavitary lesions is sometimes necessary to prevent relapse.

Imipenem, meropenem, or the third-generation cephalosporin ceftazidime in high doses are considered first-line therapy. Some centers add trimethoprim/sulfamethoxazole for better intracellular activity and as a means to potentially decrease the emergence of antimicrobial resistance with combination therapy. Once a good clinical response is seen—usually after at least 2 weeks, and longer if bacteremia or lobar pneumonias are present (3–4 weeks per the Darwin melioidosis treatment guideline[82])—oral therapy may be initiated; this subsequent eradication therapy is considered necessary for preventing recrudescence or later relapse of melioidosis. Eradication regimens are varied and include such agents as trimethoprim-sulfamethoxazole, doxycycline, chloramphenicol, and (less effective) azithromycin and ciprofloxacin. Amoxicillin–clavulanic acid may be used in children. A trial in 140 subjects in Thailand showed that trimethoprim-sulfamethoxazole alone is as effective as and better tolerated than cotrimoxazole plus doxycycline for the eradication treatment of melioidosis.[83] With the exception of kanamycin, other aminoglycosides are ineffective.

No prophylactic antimicrobial studies are available, and no vaccine has been developed. People traveling, living, or working in endemic regions should be advised of this soil- and water-dwelling organism. Traumatic injuries should be avoided, and wounds contaminated with soil or stagnant water should be assiduously cleaned.

■ *Coxiella burnetii* (Q fever)

Initially described in abattoir workers in Brisbane, Australia, in 1935 as Q (for query) fever, Q fever generally causes systemic symptoms, which can progress to atypical pneumonia, occasionally complicated by ARDS, as well as endocarditis and chronic Q fever. In temperate-zone countries, the prevalence of acute Q fever in patients with CAP ranges from 0% to 2.3%: 1.2% in the United Kingdom, 0.9% in the rest of Europe, and 2.3% in the United States.[84] Among endemic regions, rates vary; in the late 1960s in Riyadh, Saudi Arabia, 8.4% of residents greater than 5 years of age were seropositive,[85] while of those with pneumonia in Greece, the frequency of acute Q fever was 4.7% among 3686 patients with atypical pneumonia.[86] In Israel, a study conducted in 1995 among 346 inpatients with CAP showed that 20 (5.8%) had Q fever pneumonia,[87] and a study in the Spanish Basque region demonstrated a prevalence of 18.8% in patients with CAP.[88] Work in French Guiana showed a prevalence of 24%.[84] Although the Middle East is an endemic region, only 3 soldiers developed Q fever during operation Desert Storm, probably because most troops had very limited or no contact with herds of animals.[89]

Bacteriology, Ecology, Epidemiology, and Pathogenesis

C. burnetii has traditionally been grouped with the Rickettsiae, which also includes typhus and spotted fevers. Recent phylogenetic studies based on 16S rRNA sequence analysis have demonstrated that *C. burnetii* is more closely related to *Legionella*, *Francisella*, and *Rickettsiella*. The organism is now classified in the family Coxiellaceae and order Legionellales in the gamma subdivision of Proteobacteria.[90] *C.* burnetii is an acid-fast, pleomorphic, small coccoid or filamentous organism. It is an obligate intracellular pathogen. Although Gram negative, it is often not detected by Gram stains. *C. burnetii* forms spore-like structures that are highly resistant to even severe environmental conditions; it can survive like this for extended periods, especially in very arid soils.

Q fever exists worldwide, except for New Zealand. The largest outbreak ever described occurred in the Netherlands in 2007 to 2010. Large outbreaks have been reported in Switzerland, Great Britain, Germany, and southern France. In North America, Nova Scotia has been the location of a significant number of cases. There are case reports of Q fever in armed forces personnel returning from Iraq.[91] A series of 357 cases of atypical pneumonia from Chile found that 71 (20%) had Q fever; endemic disease had not previously been described there.[92]

Transmission occurs via contact with contaminated birthing products, unpasteurized milk, meat, and wool, or inhalation of windblown dust from areas contaminated by placentae and other animal products. Inhalation results in much more efficient transmission compared with oral intake. Ticks can facilitate transport to other animals. Transfer between humans has been very rarely described, primarily occurring during autopsies or to healthcare workers.[90] Risk factors for spread among animals include relatively closely located bulk milk small ruminant farms, spread from vermin and companion animals, imported straw, and use of artificial insemination.[93] A classic outbreak was described in 12 poker players in Nova Scotia after exposure to a parturient cat—an entity subsequently termed "poker player's pneumonia."[94]

C. burnetii has two distinct antigenic phases. Phase I and II cells are morphologically identical, although they differ in certain biochemical characteristics including their lipopolysaccharide composition. Organisms isolated from infected animals or humans express phase I antigens and are very infectious; the ID50 (number of bacilli needed to infect 50% of individuals) is considered to be 1 to 10, making it among the most infectious agents known.[95] Organisms expressing phase II antigens are less infectious and are recovered after the bacteria have been repeatedly passaged in cell cultures or eggs. Experimentally infected animals and humans first produce antibodies to phase II antigens and later produce antibodies to phase I antigens, which may be used to distinguish acute from chronic infections.

Monocytes and macrophages are the target cells for *C. burnetii* infection. Phagocytosis of *Coxiella* creates phagolysosomes in which the organisms can persist and multiply. The formation of pseudopodal extensions and transient reorganization of filamentous actin are stimulated by virulent (but not avirulent) bacteria. Cell-mediated immunity and granuloma formation is important for control of primary infection. Chronic Q fever is characterized by defective cellular immunity; lymphocytes from patients with Q fever endocarditis do not proliferate in response to *C. burnetii* antigen compared with lymphocytes from those with acute Q fever.[90] Severe inflammation is common with Q fever endocarditis, characterized by upregulated levels of TNF and IL-6 (two inflammatory cytokines), type II TNF receptors, and IL-1 receptor antagonist.[90]

Clinical and Radiologic Features

The incubation period can be as long as 2 to 3 weeks, stressing the importance of recent travel and exposure history. Acute symptomatic infection develops in 40% of patients, while 60% are asymptomatic.[90] Illness may present acutely, with fever, severe headache, arthralgias, myalgias, cough, and other influenza-like symptoms.[96] Q fever can cause endocarditis, hepatitis, and pneumonia. Unlike the other rickettsial diseases, Q fever primarily affects the lungs, with pneumonia in approximately half of cases. The combination of pneumonia and hepatitis should suggest Q fever. Rashes are rare, unlike in the other rickettsial diseases. There can be variation in the predominant symptoms, with pneumonia more common in some outbreaks, and hepatitis more common in others, perhaps due to strain variation or the method of inoculation (ingestion versus inhalation).[90]

Chest radiograph findings are nonspecific. Pleural effusion may be present, as may pericardial effusion. In the 1989 West Midlands outbreak, 10% of chest radiographs were normal, and the features seen on 62 abnormal films were varied; there were no specific aspects to help distinguish Q fever pneumonia from other pneumonias.[97] Complete radiographic resolution frequently took up to 6 months. In another series in the north of Spain, 87% of patients had a single lobar or segmental alveolar opacity, most commonly in the lower lobes, and chest radiographs returned to normal in 70% of patients within 2 months.[98]

Diagnosis and Differential Diagnosis

Sputum is infrequent and often nondiagnostic. Diagnosis of Q fever is most commonly made in patients with epidemiologic risk and confirmed by serology using an immunofluorescence assay against phase II (acute infection) and phase I (chronic infection) antigens, comparing acute and convalescent samples. Seroconversion usually occurs by 7 to 15 days after the onset of clinical symptoms, with roughly 90% of patients seropositive by 3 weeks.[96] A significant number of persons are exposed and never develop symptoms. In one series, sera of 268 people living or working on 111 dairy goat farms in the Netherlands were tested for *C. burnetii* IgG and IgM antibodies using immunofluorescence assay: the seroprevalence in asymptomatic farmers, spouses, and children (12–17 years) was 73%, 67%, and 57%, respectively.[99] In work done to develop models for disease prediction in the outbreak in the Netherlands, male sex, fever, and pneumonia were strong positive predictors of acute Q fever, while cough was a strong negative predictor.[100]

C. burnetii can be cultivated in embryonated eggs, laboratory animals, and in vitro cell culture systems. It must be cultured in biosafety level 3 laboratories due to its extreme infectivity; thus, culture is challenging and not readily available. Molecular diagnostics are increasingly useful, especially for early diagnosis of acute Q fever; *C. burnetii* DNA becomes undetectable in serum as the serologic response develops. With hepatitis, liver biopsy may show the classic granulomas with open space surrounded by a dense eosinophilic fibrin ring, called "doughnut granulomas" (which can also be seen with *Brucella*, *Salmonella*, CMV, Epstein-Barr virus, leishmaniasis, Hodgkin and non-Hodgkin lymphomas, and immune disorders).[101] In the placenta, organisms can be identified in exudates or areas of inflammation using a modified Ziehl–Neelsen, Gimenez, Stamp, Giemsa, or modified Koster stain.

The blood leukocyte count may be elevated in 25% of cases[96] but is less commonly elevated than with routine community acquired pneumonia.[84] Elevations in the erythrocyte sedimentation rate, liver enzymes, and creatine phosphokinase, as well as thrombocytopenia, may be seen.[96] Autoantibodies sometimes develop, including antimitochondrial and anti–smooth muscle antibodies and antibodies to phospholipids (i.e., anticardiolipin or lupus anticoagulant).

Given the relatively nonspecific findings with Q fever, the differential diagnosis is broad, appropriately narrowed based on epidemiology. For pneumonia, other diagnoses would include atypical pathogens such as *Chlamydophila pneumoniae*, *Chlamydia psittaci*, *Francisella tularensis*, *Legionella pneumophila*, and *Mycoplasma pneumoniae*. Viral etiologies also may mimic Q fever. A case report from Turkey describes Q fever mimicking Crimean-Congo hemorrhagic fever.[102]

Treatment and Prevention

Treatment usually involves the use of doxycycline, although fluoroquinolones or rifampin also are effective, and trimethoprim-sulfamethoxazole can be used in pregnant women and children.[90] In chronic Q fever, recommended treatment in adults is at least 18 months of doxycycline given with an alkalizing agent like hydroxychloroquine (added to neutralize the acid environment of the phagosome).

A whole-cell vaccine for Q fever (Q-Vax), developed in Australia, protects humans in occupational settings with a vaccine efficacy of 94%;[103] this vaccine is not commercially available in the United States. Prior to vaccination, patients should be tested for previous exposure to *C. burnetii*; those with previous exposure should not receive the vaccination because of severe local reactions. Vaccination of farm animals against Q fever is effective in curtailing spread.

CONCLUSIONS

Many of the infectious diseases that affect humans originate in animals and enter the human host directly from contact with the animal, from an animal intermediary, or from environmental material contaminated with animal parts or waste. Animals too can acquire infections from contact with humans: "anthroponoses." The crossover of microorganisms between species—pathogenic in some and nonpathogenic in others—highlights the importance of the relationships that humans have with domesticated and nondomesticated animals. Climate change, ecotourism, global transport of goods, and changes in areas of human habitation all contribute to the cross-species transmission of disease. New zoonotic diseases are frequently identified, and the key to recognizing new infectious syndromes requires a thorough understanding of patients' animal and environmental exposures. "One Health" is a global collaborative, multisectoral, and transdisciplinary approach to disease that recognizes the interconnection between people, animals, plants, and their shared environment.[104] We are only beginning to understand the role of animal contact on the human microbiome and the effect that alterations in the gut microbiome have on human disease. As tools for diagnosing infectious diseases caused by pathogens that cannot be seen microscopically or grown in vitro become more readily available and more sophisticated, we are bound to discover more zoonotic and anthroponotic diseases.

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CHAPTER 139

Respiratory Failure: An Overview

Michael A. Grippi

Respiratory failure is a condition in which the respiratory system fails in one or both of its gas-exchanging functions—that is, oxygenation of, and carbon dioxide elimination from, mixed venous (pulmonary arterial) blood. Hence, respiratory failure is a syndrome rather than a disease. Many diseases result in respiratory failure, as discussed elsewhere in this volume.

Respiratory failure may be acute or chronic. The clinical presentations of patients with acute and chronic respiratory failure usually are quite different. While acute respiratory failure is characterized by life-threatening derangements in arterial blood gases and acid–base status, the manifestations of chronic respiratory failure are more indolent and may be clinically inapparent.

Although the causes of respiratory failure are diverse, common underlying pathophysiologic mechanisms and management strategies merit a general discussion. This chapter begins with a focus on the definition of respiratory failure and underscores distinctions between acute and chronic varieties. Hypoxemic and hypercapnic respiratory failure are described, and the pathophysiologic underpinnings of each type are reviewed. The concepts of ventilatory supply and demand are considered before an overview of the many categories of disease that result in respiratory failure. Finally, an approach to clinical evaluation and management is outlined, followed by a summary of complications, comments on prognosis, and consideration of sites of care for survivors of respiratory failure who remain "chronically critically ill."

CLASSIFICATION OF RESPIRATORY FAILURE

As noted previously, respiratory failure is characterized by inadequate blood oxygenation or carbon dioxide removal. "Adequacy" is defined by tissue requirements for oxygen uptake and carbon dioxide elimination. In the absence of bedside techniques for direct measurement of these metabolic parameters, clinicians must rely on arterial blood gas values.

Respiratory failure may be classified as *hypercapnic* or *hypoxemic* (Fig. 139-1). *Hypercapnic respiratory failure* is defined as an arterial P_{CO_2} (Pa_{CO_2}) greater than 45 mm Hg. *Hypoxemic respiratory failure* is defined as an arterial P_{O_2} (Pa_{O_2}) less than 60 mm Hg. In many cases, hypercapnic and hypoxemic respiratory failure coexist. Disorders that initially cause hypoxemia may be complicated by respiratory pump failure (see below) and hypercapnia. Conversely, diseases that produce respiratory pump failure are frequently complicated by hypoxemia due to secondary pulmonary parenchymal processes (e.g., pneumonia or atelectasis) or vascular disorders (e.g., pulmonary embolism).

TABLE 139-1 Distinctions Between Acute and Chronic Respiratory Failure

Category	Characteristic
Hypercapnic respiratory failure	Pa_{CO_2} >45 mm Hg
Acute	Develops in minutes to hours
Chronic	Develops over several days or longer
Hypoxemic respiratory failure	Pa_{O_2} <60 mm Hg
Acute	Develops in minutes to hours
Chronic	Develops over several days or longer

Distinctions between *acute* and *chronic* respiratory failure are summarized in Table 139-1. In general, acute hypercapnic respiratory failure is defined as a Pa_{CO_2} greater than 45 mm Hg with accompanying acidemia (pH <7.30).[1] The physiologic effect of a sudden increment in Pa_{CO_2} depends on the prevailing level of serum bicarbonate anion. In patients with chronic hypercapnic respiratory failure—for example, due to chronic obstructive pulmonary disease (COPD)—a long-standing increase in Pa_{CO_2} results in renal "compensation" and an increased serum bicarbonate concentration. A superimposed acute increase in Pa_{CO_2} has a less dramatic effect than does a comparable increase in a patient with a normal bicarbonate level.

Distinction between acute and chronic hypoxemic respiratory failure may not be readily made on the basis of arterial blood gas values.[1] The presence of markers of chronic hypoxemia (e.g., polycythemia or cor pulmonale) provides clues to a long-standing disorder, whereas abrupt changes in mental status suggest an acute event.

An important fact to bear in mind is that even though the definition of hypoxemic respiratory failure rests on measurement of Pa_{O_2}, the major threat of arterial hypoxemia is inadequate tissue oxygenation, reflected in tissue *oxygen delivery.* Tissue oxygen delivery is determined by the product of cardiac output and blood *oxygen content* (Chapter 15); the latter, in turn, depends on hemoglobin concentration and oxygen saturation. Therefore, factors that lower cardiac output or hemoglobin concentration, or inhibit dissociation of oxygen from hemoglobin at the tissue level, may promote tissue hypoxia without technically producing respiratory failure.

PATHOPHYSIOLOGY

Respiratory failure can arise from an abnormality in any of the "effector" components of the respiratory system—central nervous

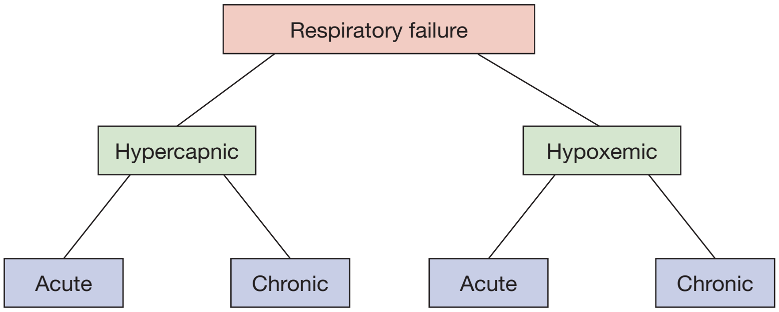


Figure 139-1 Classification of respiratory failure. Although depicted as distinct entities, hypercapnic and hypoxemic respiratory failure frequently coexist. Either may be acute or chronic.

system, peripheral nervous system, respiratory muscles and chest wall, airways, or alveoli (Fig. 139-2). A defect in any of the first four components, which constitute the "respiratory pump," may cause coexistent hypercapnia and hypoxemia; at least initially, disorders of the alveoli are more apt to result in hypoxemia.[2,3]

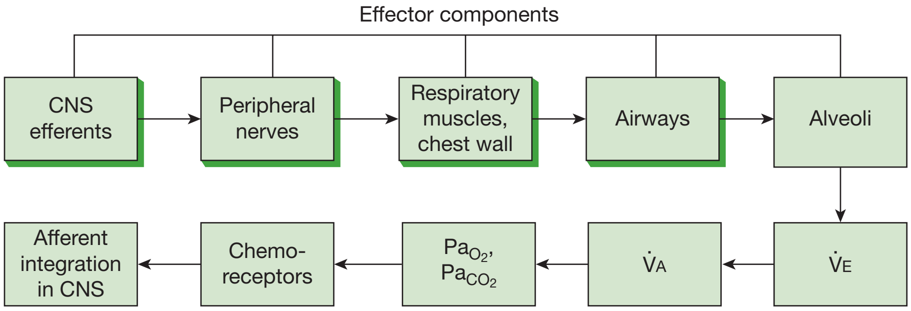


Figure 139-2 Functional components of the respiratory system and its controller. Abnormalities in any of the effector components can result in respiratory failure. The central and peripheral nervous systems, respiratory muscles and chest wall, and airways constitute the "respiratory pump" *(shaded boxes)*. Hypercapnia is the hallmark of respiratory pump failure, while hypoxemia constitutes the primary disturbance in alveolar disorders producing respiratory failure. *(Reproduced with permission from Grippi MA: Pulmonary Pathophysiology. Philadelphia. PA: JB Lippincott; 1995.)*

Hypoxemic Respiratory Failure

As described in Chapters 14–16, four pathophysiologic mechanisms account for the hypoxemia seen in a wide variety of diseases: alveolar hypoventilation, ventilation–perfusion mismatch, shunt, and diffusion limitation.[2] Alveolar hypoventilation occurs in neuromuscular disorders that affect the respiratory system. In the absence of underlying pulmonary disease, the hypoxemia accompanying alveolar hypoventilation is characterized by a normal alveolar–arterial oxygen gradient,[4] as defined by Equation 1:

$$\mathrm{PA_{O_2} - Pa_{O_2} = [PI_{O_2} - Pa_{CO_2}/R] - Pa_{O_2}} \qquad (1)$$

where

$\mathrm{PA_{O_2}}$ = alveolar $\mathrm{P_{O_2}}$
$\mathrm{Pa_{O_2}}$ = arterial $\mathrm{P_{O_2}}$
$\mathrm{PI_{O_2}}$ = inspired $\mathrm{P_{O_2}}$
$\mathrm{Pa_{CO_2}}$ = arterial $\mathrm{P_{CO_2}}$
R = respiratory exchange ratio

In contradistinction, disorders in which any of the other three mechanisms are operative are characterized by widening of the alveolar–arterial oxygen gradient, which is normally less than 20 mm Hg. With ventilation–perfusion mismatching, areas of low ventilation relative to perfusion contribute to the hypoxemia. Similarly, with shunt, either intrapulmonary or intracardiac, deoxygenated mixed venous blood bypasses ventilated alveoli, resulting in "venous admixture." Finally, diseases that increase the diffusion pathway for oxygen from the alveolar space to pulmonary capillary impair oxygen transport across the alveolar–capillary membrane.

Although changes in minute and alveolar ventilation can change $\mathrm{Pa_{CO_2}}$ considerably, this is not so for $\mathrm{Pa_{O_2}}$. Increases in minute ventilation and, secondarily, in alveolar ventilation modestly increase $\mathrm{Pa_{O_2}}$. Indeed, at a $\mathrm{Pa_{O_2}}$ above 55 to 60 mm Hg, the effect of increasing ventilation on oxygen content is minimal, since the oxyhemoglobin dissociation curve is flat in this range.

Hypercapnic Respiratory Failure

At a constant rate of CO_2 production ($\dot{V}_{CO_2}$), $\mathrm{Pa_{CO_2}}$ is determined by the level of alveolar ventilation.[5] The relationship between alveolar ventilation, rate of CO_2 production, and $\mathrm{Pa_{CO_2}}$ is described by Equation 2:

$$\dot{V}_A = K \cdot \dot{V}_{CO_2}/\mathrm{Pa_{CO_2}} \qquad (2)$$

where

$\dot{V}_A$ = minute alveolar ventilation
K = a constant
$\dot{V}_{CO_2}$ = rate of CO_2 production

When $\dot{V}_{CO_2}$ is constant, $\mathrm{Pa_{CO_2}}$ is determined by $\dot{V}_A$, which, in turn, is dictated by two factors: minute ventilation ($\dot{V}_E$) and the relationship between $\dot{V}_E$ and $\dot{V}_A$. The latter is determined by the proportion of $\dot{V}_E$ that constitutes dead space ventilation—that is, the dead space to tidal volume ratio (V_D/V_T):

$$\dot{V}_E = K\,(\dot{V}_{O_2} \cdot RQ)/(\mathrm{Pa_{CO_2}}/[1 - V_D/V_T]) \qquad (3)$$

where

$\dot{V}_{O_2}$ = rate of O_2 consumption
RQ = respiratory quotient (the respiratory exchange ratio in the steady state)
V_D = dead space volume
V_T = tidal volume

Inspection of Equation 3 indicates that disorders reducing $\dot{V}_E$ or increasing the proportion of dead space ventilation may result in hypercapnia.

Ventilatory Supply Versus Demand

A useful theoretical construct for understanding the pathophysiologic basis for hypercapnic respiratory failure is the relationship between ventilatory supply and ventilatory demand (Fig. 139-3).[1]

Ventilatory supply is the maximal spontaneous ventilation that can be maintained without development of respiratory muscle fatigue; ventilatory supply is also known as *maximal sustainable ventilation* (MSV).

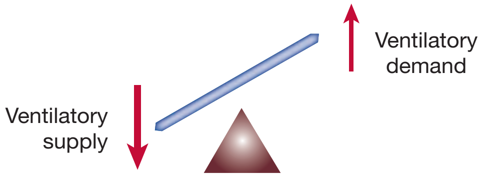
Ventilatory demand is the spontaneous minute ventilation, which, when maintained constant, results in a stable $\mathrm{Pa_{CO_2}}$ (assuming a fixed rate of CO_2 production).

Normally, ventilatory supply greatly exceeds ventilatory demand. Hence, major changes in minute ventilatory requirements (e.g., during exercise) may occur without hypercapnia. In lung disease, significant abnormalities may be present before ventilatory demand encroaches on MSV. Consequently, hypercapnia is a late finding. When ventilatory demand exceeds MSV, $\mathrm{Pa_{CO_2}}$ increases.

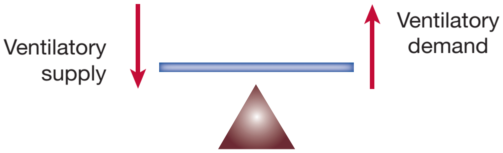
As a general rule, MSV is approximated as one-half the *maximal voluntary ventilation*, or MVV (Chapter 31). A 70-kg adult has an MVV of about 160 L/min, an MSV of 80 L/min, and, under basal conditions, a $\dot{V}_E$ of approximately 6 to 7 liters per minute (90 mL/kg/min). Normally, therefore, there is a 10- to 15-fold difference between resting $\dot{V}_E$ and MSV. In disease states, the $\dot{V}_E$ requirement may approach a markedly reduced MSV. Further reductions in MSV result in ventilatory demand exceeding supply, and hypercapnia occurs.

FACTORS THAT REDUCE VENTILATORY SUPPLY OR INCREASE VENTILATORY DEMAND

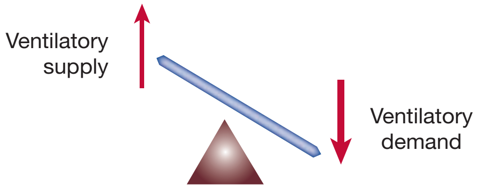
Disruption of any component of the efferent arm of the respiratory control system may diminish ventilatory supply (Table 139-2). While a variety of diseases produce specific abnormalities along the efferent pathway (e.g., phrenic nerve and respiratory muscle disorders), some result in respiratory muscle fatigue—the biochemical,



A Ventilatory supply exceeds ventilatory demand.



B Ventilatory supply equals ventilatory demand.



C Ventilatory demand exceeds ventilatory supply.

Figure 139-3 Relationship between ventilatory supply (maximal sustainable ventilation) and ventilatory demand (overall level of ventilation specified by the CNS controller). Relative size of the arrows indicates levels of supply and demand in each of the three circumstances illustrated. **A.** Normal. Ventilatory supply greatly exceeds ventilatory demand. Physiologic "reserve" is maintained. **B.** Ventilatory supply is decreased and ventilatory demand increased (e.g., acute asthma attack). "Borderline" respiratory failure exists. **C.** Ventilatory demand exceeds ventilatory supply (e.g., sepsis in a patient with COPD). Respiratory muscle fatigue develops, and hypercapnic respiratory failure ensues. See text for details. *(Reproduced with permission from Grippi MA: Pulmonary Pathophysiology. Philadelphia. PA: JB Lippincott; 1995.)*

cellular, and molecular mechanisms of which remain poorly understood.

As described previously, ventilatory demand can be assessed according to Equation 3:

$$\dot{V}_E = K \cdot (\dot{V}_{O_2} \cdot RQ)/(Pa_{CO_2}/[1 - V_D/V_T])$$

Any factor that affects terms on the right-hand side of the equation may result in ventilatory demand exceeding supply. Selected clinical examples are given in Table 139-3.

CATEGORIES OF RESPIRATORY FAILURE

Although many different diseases cause respiratory failure, they may be grouped conveniently according to primary abnormalities in the individual effector components of the respiratory system.[1,2]

Abnormalities of the Central Nervous System

A variety of pharmacologic, structural, and metabolic disorders of the CNS are characterized by suppression of the neural drive to breathe.[3] The resultant hypoventilation and hypercapnia may be acute or chronic.

An overdose of a narcotic or other drug with sedative properties is a common cause of respiratory failure. While the most striking clinical picture occurs with an acute overdose, longstanding use of some agents (e.g., methadone) may result in chronic hypercapnia.

TABLE 139-2 Factors That Diminish Ventilatory Supply

Factor	Clinical Examples
Decreased respiratory muscle strength	
Muscle fatigue	Recovery from acute respiratory failure, high respiratory rates, increased inspiratory time
Disuse atrophy	Prolonged mechanical ventilation, following phrenic nerve injury
Malnutrition	Protein–calorie starvation
Electrolyte abnormalities	Low serum phosphate or potassium concentrations
Arterial blood gas abnormalities	Low pH, low Pa_{O_2}, high Pa_{CO_2}
Fatty infiltration of diaphragm	Obesity
Unfavorable alteration in diaphragm length–tension relationship	Flattened domes of diaphragm caused by hyperinflation
Increased muscle energy requirement or decreased substrate supply	
High elastic work of breathing	Low lung or chest wall compliance, high respiratory rate
High resistive work of breathing	Airway obstruction
Reduced diaphragm perfusion	Shock, anemia
Decreased motor neuron function	
Decreased phrenic nerve output	Polyneuropathy, Guillain–Barré syndrome, phrenic nerve transection or injury, poliomyelitis
Decreased neuromuscular transmission	Myasthenia gravis, use of paralyzing agents
Abnormal respiratory mechanics	
Airflow limitation	Bronchospasm, upper airway obstruction, excessive airway secretions
Loss of lung volume	After lung resection, large pleural effusion
Other restrictive defects	Pain-limited inspiration; tense abdominal distention due to ileus, peritoneal dialysis fluid, or ascites

TABLE 139-3 Factors That Increase Ventilatory Demand

Factor	Clinical Examples
Increased V_D/V_T	Acute asthma, emphysema, late phase of acute respiratory distress syndrome, pulmonary emboli
Increased $\dot{V}_{O_2}$	Fever, sepsis, trauma, shivering, increased work of breathing, massive obesity
Increased RQ	Excessive carbohydrate feeding
Decreased Pa_{CO_2}	Hypoxemia, metabolic acidosis, anxiety, sepsis, renal failure, hepatic failure

Data from Grippi MA: Pulmonary Pathophysiology. Philadelphia. PA: JB Lippincott; 1995.

"Structural" CNS abnormalities producing hypercapnic respiratory failure include meningoencephalitis, localized tumors or vascular abnormalities of the medulla, and strokes affecting medullary control centers. Usually, respiratory failure is observed in the context of other neurologic findings.

A variety of metabolic derangements may produce hypercapnia through depression of respiratory control centers. Examples include severe myxedema, hepatic failure, and advanced uremia. In addition, elevation of P_{CO_2} in the CNS results in neural depression, further enhancing CO_2 retention. A common clinical setting in which elevation of Pa_{CO_2} is observed is chronic metabolic alkalosis (e.g., due to diuretic use), as detailed in Chapter 17.

Finally, obesity hypoventilation syndrome is characterized by hypercapnia due to hypoventilation on a central basis.[6]

■ Abnormalities of the Peripheral Nervous System or Chest Wall

A wide variety of disorders of the peripheral nerves, neuromuscular junction, and chest wall may be associated with hypercapnic and hypoxemic respiratory failure.[3,7–16] While the hallmark is an inability to maintain a level of $\dot{V}_E$ appropriate for the rate of CO_2 production, many of these disorders are complicated by impaired expiratory muscle strength, atelectasis, and aspiration. Through mechanisms outlined previously, hypoxemia develops in conjunction with the hypercapnia.

Among the most common neuromuscular causes of hypercapnic respiratory failure are Guillain–Barré syndrome,[17] myasthenia gravis,[18] polymyositis,[19] the muscular dystrophies, amyotrophic lateral sclerosis (ALS),[20] and a large number of metabolic muscle disorders. In addition, acute poliomyelitis and traumatic spinal cord injury are associated with hypercapnia. Development of respiratory muscle fatigue and atrophy[10,21–23] during prolonged weaning from mechanical ventilation may cause recurrent hypercapnia in the critical care setting.[10,21–25]

Pharmacologic causes of hypercapnia in the intensive care unit are frequently encountered. Early reports on use of depolarizing and nondepolarizing paralyzing agents,[26] particularly in conjunction with systemic corticosteroids (e.g., in management of status asthmaticus) have been well documented; cholinergic crisis during therapy of myasthenia gravis, and administration of aminoglycosides to patients with myasthenia gravis are additional examples.

Primary disorders of the chest wall constitute another important category of neuromuscular respiratory failure. The prototype is severe kyphoscoliosis. Additional examples include flail chest (Chapter 104), extensive thoracoplasty, morbid obesity, and massive abdominal distention due to ascites[27] or distended loops of bowel.

In each of these disorders, a common pathophysiologic sequence develops. Because of inadequate activation of inspiratory muscles or limited thoracic excursion, tidal volume falls. While an increase in respiratory rate compensates initially for the fall in $\dot{V}_E$ (and in $\dot{V}_A$), $\dot{V}_E$ eventually declines. In addition, the sigh mechanism is impaired, which, in conjunction with the low tidal volume, results in atelectasis and reduced lung compliance. Reduced lung compliance produces a further fall in tidal volume and an increase in the elastic work of breathing (Chapter 10). Hence, ventilatory supply becomes limited, while ventilatory demand increases due to a rise in V_D/V_T (as a result of atelectasis and other factors noted below). An imbalance between ventilatory supply and demand arises, and hypercapnia ensues. Furthermore, an impaired gag reflex in the setting of bulbar weakness, coupled with impaired cough due to respiratory muscle involvement, may result in aspiration pneumonia and secondary hypoxemia.

In addition to the pathophysiology described, structural abnormalities of the thoracic cage (e.g., severe kyphoscoliosis, ankylosing spondylitis, thoracoplasty, fibrothorax)[7,28,29] are characterized by an increase in the elastic component of the work of breathing. This results in a higher $\dot{V}_{O_2}$ and a higher proportion of total O_2 consumption by the respiratory muscles (normally, $<5\%$ of $\dot{V}_{O_2}$).

■ Abnormalities of the Airways

Obstructive diseases of the airways—either upper or lower—are common causes of acute and chronic hypercapnia. Examples in the upper airways include acute epiglottitis, aspirated foreign body, tracheal tumor, and narrowing of the trachea or glottis by fibrotic tissue. Disorders of the lower airways include COPD,[30] asthma, and advanced cystic fibrosis. Increasingly, the development of bronchiolitis obliterans, a manifestation of allograft rejection in patients who have undergone lung transplantation, has been recognized as an important cause of respiratory failure.[31]

The underlying mechanisms in airway abnormalities as causes of respiratory failure are multifaceted and variable. However, several common pathophysiologic pathways are operative.

Airway narrowing results in a greater transthoracic pressure gradient requirement for inspiratory airflow. The resistive component of the work of breathing is increased, and the increase is associated with an elevation in $\dot{V}_{O_2}$. In addition, tidal volume falls and dead space ventilation increases. Respiratory muscle fatigue may develop; the consequences of a shallow breathing pattern ensue.

Finally, in some disorders (e.g., acute asthma or an acute exacerbation of COPD), air trapping and lung hyperinflation occur, resulting in diaphragm flattening and worsening diaphragm mechanics (Chapter 10). The overall effect is a growing imbalance between ventilatory supply and demand.[1]

■ Abnormalities of the Alveoli

Although diseases characterized by diffuse alveolar filling frequently result in hypoxemic respiratory failure, hypercapnia may complicate the picture. Common clinical examples in this category include cardiogenic and noncardiogenic pulmonary edema,[32] diffuse pneumonia, extensive pulmonary hemorrhage, aspiration of stomach contents, and near drowning.

Diffuse alveolar filling creates a large right-to-left shunt as pulmonary blood flows through nonventilated or poorly ventilated regions of the lung. In addition, coexisting interstitial edema may impair diffusion across the alveolar–capillary membrane, further impairing oxygenation of mixed venous blood.

In extensive, acute pulmonary disease characterized by alveolar filling, ventilatory demand is high because of hypoxemia and increases in V_D/V_T, the elastic work of breathing (due to reduced lung compliance), the resistive work of breathing (due to airway narrowing and increased airway reactivity), and the neural drive to breathe (mediated by pulmonary parenchymal vagal fibers). In conjunction with heightened ventilatory demand, ventilatory supply is reduced because of alveolar flooding, reduced lung elasticity, respiratory muscle fatigue, and, possibly, reduced blood supply to the diaphragm secondary to shock. Once again, the imbalance between ventilatory supply and demand results in hypercapnia.

APPROACH TO THE PATIENT

The diagnosis of acute or chronic respiratory failure begins with clinical suspicion of its presence. Confirmation of the diagnosis is based on arterial blood gas analysis. Evaluation for an underlying cause must be initiated early, frequently in the presence of concurrent treatment for acute respiratory failure. While the diagnosis of chronic respiratory failure is usually easily established with clinical findings of chronic hypoxemia (with or without findings of hypercapnia), the diagnosis of acute respiratory failure requires more careful analysis.

Signs and symptoms in acute respiratory failure reflect the underlying disease process and associated hypoxemia or acidemia due to hypercapnia. Localized pulmonary findings reflecting the acute causes of hypoxemia (e.g., pneumonia, pulmonary edema, asthma, or COPD) may be readily apparent. Alternatively, the predominant findings may be systemic (e.g., hypotension due to sepsis). The principal manifestations may even be remote from the thorax—for example, abdominal pain in acute pancreatitis, or leg pain due to soft tissue infection complicated by sepsis—each associated with acute respiratory distress syndrome (Chapters 140 and 141). Frequently, neurologic or cardiovascular symptoms and signs predominate. Neurologic manifestations include restlessness, anxiety, confusion, seizures, or coma. Asterixis may be seen with severe hypercapnia. Common cardiovascular findings include tachycardia and a variety of arrhythmias. Finally, there may be few or no findings other than a complaint of dyspnea, as in some patients with hypoxemia due to pulmonary embolism.

Once respiratory failure is suspected on clinical grounds, arterial blood gas analysis is performed to confirm the diagnosis, to assist in the distinction between acute and chronic forms, to assess the magnitude and metabolic impact, and to help guide management (Table 139-4).

PRINCIPLES OF MANAGEMENT

The principles of management of patients in acute respiratory failure include those that are general[2,3,6–8,20,33] and those that are more cause-specific.[30] Triage of the patient to the proper clinical setting, airway maintenance, correction of hypoxemia and hypercapnia, and management of the underlying cause are of paramount importance.

Triage Decisions

The first step in management is to determine the appropriate setting for care—admission to a standard inpatient medical floor or to an intensive or "intermediate care" unit. Factors that constitute the basis for this decision include the acuity of the respiratory failure; the degree of hypoxemia, hypercapnia, and acidemia; the presence of comorbid conditions (e.g., cardiac disease or renal insufficiency); and the clinical direction that the patient takes over the first few minutes or hours of observation. At one end of the spectrum is the patient with fulminant hypoxemic respiratory failure, metabolic acidosis, and imminent cardiovascular collapse, who needs emergent intubation, mechanical ventilation, and admission to a critical care unit. At the other end of the spectrum is the patient with COPD and chronic, compensated hypercapnic respiratory failure, who requires observation in an intermediate care unit or general medical setting.

Airway Management

Assurance of an adequate airway is key in the patient with acute respiratory distress. Whether emergency intubation is required depends on the clinical circumstances described previously. For patients with chronic respiratory insufficiency, the need for intubation also depends on critical arterial blood gas values and the patient's early acute course. When progressive hypoxemia or hypercapnia is observed over the first few minutes or hours of care, intubation and mechanical ventilation are warranted.

However, in recent years, two approaches to acute respiratory failure that might delay or avoid intubation have been investigated: administration of high-flow oxygen (HFO_2) and noninvasive ventilation (NIV).[34–43] These techniques have been evaluated primarily in management of acute hypoxemic respiratory failure, but also in acute hypercapnic failure as well. Additionally, HFO_2 and NIV have been advocated as means of avoiding reintubation in patients with deteriorating respiratory status following surgical procedures.

Contraindications to a trial of noninvasive ventilation include respiratory arrest, ill-fitting face mask, hemodynamic or cardiac instability, patient agitation, swallowing difficulty, excessive respiratory secretions, inability to protect the airway, and recent upper airway or upper gastrointestinal surgery.

Correction of Hypoxemia and Hypercapnia

Once the airway is secured, the clinician must turn attention to the treatment of hypoxemia—the most life-threatening aspect of acute respiratory insufficiency. The goal is to assure adequate oxygen delivery to tissues, generally achieved with a Pa_{O_2} of about

TABLE 139-4 Changes in Arterial Blood Gases, $P_{A_{O_2}}$–Pa_{O_2}, and Ventilation in Acute Respiratory Failure

Failed Respiratory System Component	pH	Pa_{CO_2}	Pa_{O_2}	$P_{A_{O_2}}$–Pa_{O_2}	$\dot{V}_E$	$\dot{V}_A$
Central nervous system	↓	↑	↓[a]	NL or ↑[b]	↓	↓
Peripheral nervous system or chest bellows	↓	↑	↓[a]	NL or ↑[b]	↓	↓
Airways						
In acute asthma						
Early phase (before respiratory failure)	↑	↓	NL	↑	↑	↑
"Crossover point"	NL	NL	NL or ↓	↑	↑	NL
With development of respiratory muscle fatigue	↓	↑	↓	↑	↓[c]	↓
In COPD						
Non-CO_2 retainer	↓	NL or ↑[d]	↓	↑	↑	↓
CO_2 retainer						
Baseline	NL to ↓	↑	↓	↑	NL or ↑	↓
Flare	↓	↑↑	↓↓	↑	NL, ↑ or ↓[c]	↓
Alveoli						
Before respiratory muscle fatigue develops	↑	↓	↓↓	↑↑	↑	↑
After respiratory muscle fatigue develops	↓	↑	↓↓	↑↑	↓	↓

↑, increased; ↑↑, very increased; ↓, decreased; ↓↓, very decreased; NL, in normal range.

[a] *Pa_{O_2} may decrease when pneumonia or atelectasis occurs as a complication.*

[b] *($P_{A_{O_2}}$–Pa_{O_2}) widens when pneumonia or atelectasis occurs as a complication.*

[c] *$\dot{V}_E$ declines when frank respiratory muscle failure occurs.*

[d] *Pa_{CO_2} may increase during an exacerbation.*

Data from Grippi MA: Pulmonary Pathophysiology. Philadelphia. PA: JB Lippincott; 1995.

60 mm Hg (assuming an adequate hematocrit and cardiac output). In patients who have coronary or cerebrovascular disease, a slightly higher level of arterial oxygenation may be desirable in order to provide a "buffer" for any sudden, unpredictable changes in gas exchange.

The means by which supplemental oxygen is administered is determined by the clinical circumstances. While some patients may simply require nasal prongs or a face mask to achieve an adequate Pa_{O_2}, others are best treated with controlled-flow oxygen delivered via a Venturi mask—for example, the patient with COPD and chronic hypercapnia (Chapter 40). Generally, if an acceptable level of oxygenation, as judged by arterial blood gases, cannot be attained using a face mask, or if administration of supplemental O_2 causes hypercapnia to worsen significantly (e.g., in some patients with COPD), mechanical ventilation (invasive or noninvasive) is required.

While correcting hypoxemia, the clinician must also address any coexisting hypercapnia and respiratory acidosis. Once again, the immediacy of correction depends on the magnitude of the acidosis and its attendant effects (e.g., elevation of serum potassium). A partly compensated respiratory acidosis in a patient with COPD usually constitutes a less urgent clinical circumstance than does profound respiratory acidosis in a patient with a drug overdose.

Additional management strategies in addressing critically ill patients with acute hypoxemic respiratory failure, including, for example, low-stretch ventilation and prone positioning in ARDS, including that due to COVID-19 infection, and extracorporeal membrane oxygenation (ECMO) are discussed in Chapters 141 and 150, respectively.

■ Search for an Underlying Cause

Finally, as therapy is initiated to correct the hypoxemia, hypercapnia, and acidosis of respiratory failure, a search for the cause of the problem and its management must be undertaken. In some cases, the cause and management are straightforward (e.g., administration of a narcotic antagonist to the patient with a narcotic overdose). In others, a more protracted course may be in store (e.g., long-term ventilator management of fulminant acute respiratory distress syndrome due to sepsis).

In both brief and prolonged cases of respiratory failure, attention to details of management is important in order to minimize the risks of complications of therapy, as discussed in the following section.

MONITORING PATIENTS WITH ACUTE RESPIRATORY FAILURE

Repeated assessment of the patient with incipient or resolving respiratory failure, as well as the patient with frank hypoxemic or hypercapnic failure, is critical in formulating decisions about therapy. Monitoring methods range from routine bedside observations to use of invasive techniques (Chapter 147).

For many patients with acute respiratory failure, simple observation of respiratory rate, tidal volume, use of accessory muscles, and presence of paradoxical breathing movements provides evidence of worsening respiratory failure and the need for intubation and mechanical ventilation. The patient with asthma or an acute exacerbation of COPD will frequently manifest rapid, shallow breathing and paradoxical thoracoabdominal breathing movements as respiratory mechanics deteriorate.[15]

Once placed on mechanical ventilation, the patient must be carefully monitored for ventilator-associated complications (see below). In addition, placement of indwelling arterial and venous catheters, patient immobilization, and use of a broad range of pharmacologic agents present additional potential threats to the acutely ill patient.

While many monitoring techniques are routine and may be universally applicable to patients in a critical care setting (e.g., pulse oximetry), others may be of particular importance in selected clinical circumstances. For example, routine assessment of static respiratory system compliance in a mechanically ventilated patient with acute respiratory distress syndrome or pulmonary fibrosis may provide an early warning of changes in lung edema, atelectasis, or barotrauma.[44] In the patient with status asthmaticus requiring mechanical ventilation, development of hypotension due to intrinsic positive end-expiratory pressure (intrinsic PEEP or "auto-PEEP"),[45] as discussed in Chapter 148, may signal the need to alter ventilator settings or implement sedation or pharmacologic paralysis.

COMPLICATIONS OF ACUTE RESPIRATORY FAILURE

The respiratory patient in a critical care unit must navigate not only the obstacles presented by the underlying pulmonary process, but also the hazards associated with use of mechanical devices and pharmacologic agents. Complications of acute respiratory failure may be broadly categorized as pulmonary, cardiovascular, gastrointestinal, renal, infectious, nutritional, and other (Table 139-5). For details in each of these areas, the reader is referred to chapters elsewhere in this volume.

■ Pulmonary

Common pulmonary complications of acute respiratory failure include ventilator-associated pneumonia ("VAP"),[46–49] ventilator-induced diaphragmatic dysfunction,[23,50,51] critical illness polyneuropathy and myopathy,[52] pulmonary emboli, pulmonary barotrauma, pulmonary fibrosis, and complications directly related to use of mechanical devices.[53,54]

As noted below, pulmonary emboli have been reported in up to one-fourth of patients with respiratory failure in intensive care units. The diagnosis is difficult in this setting, since patients typically have diffuse underlying lung disease, abnormal gas exchange, and many coexisting potential causes for the clinical, radiographic, and physiologic consequences of pulmonary emboli.

Pulmonary barotrauma, identified as the presence of extra-alveolar air in structures that do not normally contain air, may occur in patients receiving mechanical ventilation for a variety of indications, including the acute respiratory distress syndrome.[53] Manifestations of barotrauma include pulmonary interstitial emphysema, pneumothorax, pneumomediastinum, pneumoperitoneum, subcutaneous emphysema, tension lung cysts, and subpleural air cysts.[54] Pulmonary fibrosis may follow acute lung injury associated with acute respiratory distress syndrome. In addition, use of high inspired concentrations of oxygen may enhance development of fibrosis in the presence of acute lung injury.

A strategy of low-stretch ventilation is currently the standard for managing patients with acute lung injury or ARDS and is aimed at minimizing the risks of ventilator-induced injury.[55,56] Use of such a strategy is outlined in the chapters on ARDS (Chapter 141) and mechanical ventilation (Chapter 148). More limited experience has been described using extracorporeal membrane oxygenation (Chapter 150).[57,58]

Common device-related complications include those due to pulmonary artery flotation catheters (Chapter 147), endotracheal intubation, and tracheostomy (Chapter 146).

Additionally, daily interruption of sedative infusions has been shown to reduce duration of mechanical ventilation and length of stay in the ICU.[59–62]

■ Neurologic

Increasingly, neurologic complications of prolonged respiratory failure and mechanical ventilation have been recognized. Two of the most notable are critical illness myopathy and neuropathy, as noted previously, and cognitive disorders. The incidence of cognitive impairment in survivors of ARDS has been reported as high as 70% to 100% at hospital discharge and 20% at 5 years post-discharge. Depression and posttraumatic stress disorder (PTSD) also are common.[63,64]

TABLE 139-5 Complications of Acute Respiratory Failure

- Pulmonary
  - Pulmonary emboli
  - Pulmonary barotrauma (interstitial emphysema, pneumothorax, subcutaneous emphysema, pneumoperitoneum, tension lung cyst, subpleural air cyst)
  - Pulmonary fibrosis
- Related to Use of Mechanical Devices
  - Complications of mechanical ventilation (infection, arterial desaturation, hypotension, barotrauma, others)
  - Complications of insertion and maintenance of pulmonary artery catheter (pneumothorax, air embolism, arrhythmias, infection, thrombosis, pulmonary artery rupture)
  - Complications of tracheal intubation
    - Related to prolonged intubation attempt (hypoxemic brain injury, cardiac arrest, seizures, others)
    - Related to right main bronchus intubation (hypoventilation, pneumothorax, atelectasis)
    - Self- or inadvertent extubation
    - Endotracheal tube dislodgment
    - Endotracheal tube cuff leak
    - Injury to pharynx, larynx, trachea
  - Complications of tracheotomy (pneumothorax, bleeding, tube dislodgment, tracheoinnominate fistula, tracheoesophageal fistula, tracheal stenosis)
- Gastrointestinal
  - Hemorrhage (including "stress" ulceration)
  - Ileus
  - Diarrhea
- Cardiovascular
  - Hypotension
  - Arrhythmias
  - Decreased cardiac output
  - Myocardial infarction
  - Pulmonary hypertension
- Renal
  - Acute renal failure
  - Fluid retention
- Infectious
  - Nosocomial pneumonia
  - Bacteremia
  - Sepsis
  - Paranasal sinusitis
- Nutritional
  - Complications of underlying malnutrition (decreased respiratory muscle strength, immune suppression, others)
  - Complications of enteral feeding (pneumothorax, pleural effusion, sinusitis, aspiration, diarrhea)
  - Complications of parenteral feeding (pneumothorax, sepsis, hyperglycemia, hyperosmolar coma, hypophosphatemia, liver function test abnormalities)
  - Complications of refeeding (hypercapnia)
- Other
  - Psychiatric (anxiety, depression, confusion, sleep dysfunction, psychosis)
  - Hematologic (anemia, thrombocytopenia)

■ Cardiovascular

Common cardiovascular complications in patients with acute respiratory failure include hypotension, reduced cardiac output, arrhythmias, pericarditis, and acute myocardial infarction. These complications may be related to the underlying disease process, mechanical ventilation, or use of pulmonary artery flotation catheters.

While venous and, less commonly, arterial thromboemboli are well-known complications of prolonged immobility in mechanically ventilated patients in an ICU, recent experience with an acquired coagulopathy in patients with ARDS due to COVID-19 infection has modified approaches to prophylaxis and treatment.[65,66]

■ Gastrointestinal

A variety of gastrointestinal complications of acute respiratory failure, particularly during mechanical ventilation, have been well described.[67] The major ones include hemorrhage, gastric distention, ileus, diarrhea, and pneumoperitoneum. "Stress" ulceration is extremely common in patients with acute respiratory failure. Associated risk factors include trauma, shock due to a variety of causes, sepsis, renal failure, and liver disease.

■ Infectious

Nosocomial infections are a frequent complication of acute respiratory failure. Principal among these are pneumonia, sepsis, and urinary tract infections. Each typically occurs with the use of mechanical devices, including endotracheal and tracheotomy tubes, indwelling central venous and pulmonary artery catheters, and urinary bladder catheters.

The incidences of VAP and ventilator-associated tracheobronchitis (VAT)[68–71] in the critically ill are significant. The incidence of VAP is estimated to be as high as 5.8 cases per 1000 ventilator days and is particularly prevalent in those with ARDS. The need for prolonged mechanical ventilation is a harbinger for development of VAP. Not unexpectedly, VAP occurring in the medical intensive care unit is associated with a significantly increased length of stay and higher mortality. Guidelines have been developed for treatment of patients with VAP.[72–76]

■ Renal

Acute kidney injury, previously referred to as acute renal failure, and abnormalities in electrolyte and water homeostasis are not uncommon in critically ill patients with acute respiratory failure; the former may be seen in up to 60% of patients in intensive care units. Development of acute kidney injury in a patient with acute respiratory failure carries a poor prognosis and a high mortality. The causes of acute kidney injury are numerous and include sepsis or septic shock, cardiogenic shock, hypovolemia, cardiac or extensive gastrointestinal surgery, administration of nephrotoxic drugs, hepatorenal syndrome, and urinary obstruction, among others.[77]

In the case of critical illness due to COVID-19, a high incidence of renal disease has been recognized.[78,79]

■ Nutritional

Nutritional complications of acute respiratory failure include the effects of malnutrition on respiratory performance and complications related to the administration of enteral or parenteral nutrition.[80–82] Complications of enteral nutritional support relate to initial insertion of the catheter (e.g., tracheal or pleural space penetration, pneumomediastinum, pneumothorax, pleural effusion) and its maintenance (e.g., paranasal sinusitis, aspiration). In addition, vomiting, abdominal distention, and diarrhea are common.

Complications of parenteral nutrition are mechanical (e.g., pneumothorax during catheter insertion), infectious (e.g., catheter-related sepsis), or metabolic (e.g., metabolic acidosis, hyperglycemia and hyperosmolar coma, hypophosphatemia). Hypercapnia, induced by enteral as well as parenteral nutrition, can complicate management of patients who have limited ventilatory reserve.

PROGNOSIS

Interpretation of studies addressing the prognosis of patients with acute respiratory failure is subject to a number of constraints, including marked clinical variability in the patients studied, predominance of studies from intensive care units in large university teaching hospitals, and variability in treatment methods employed over the time span of studies performed. In addition, many studies report only hospital mortality, not long-term survival or quality of life. Finally, findings from large-population studies are difficult to extrapolate to prediction of outcome in a single patient. Nonetheless, several generalizations can be made regarding the prognosis of patients hospitalized with acute respiratory failure.

■ Morbidity and Mortality in Acute Hypoxemic Respiratory Failure

As expected, mortality in hypoxemic respiratory failure depends on the underlying cause. A number of studies have addressed outcome in patients with ARDS.

Mortality in ARDS appears to have improved in recent years, but it remains high in the elderly; for those 85 years of age or older, mortality is 60%.[83] Patients who develop sepsis after trauma have a lower mortality than do patients with sepsis that complicates medical disorders. Notably, patients with pre-existing lung disease, higher $F_{I_{O_2}}$ or PEEP requirements, or a lower Pa_{O_2} may not necessarily have a poorer chance of survival. Early experience with ARDS due to COVID-19 suggested an extremely high mortality, but mortality rates seen later in the pandemic were not as high. The improvement may reflect use of better treatment strategies, including timing of intubation, application of prone positioning, and use of selected therapeutics, including corticosteroids.[84,85]

Although earlier studies indicated that many patients who survived an episode of ARDS manifested some impairment of pulmonary function, including obstructive and restrictive defects and reduction in diffusing capacity, 1 or more years after recovery,[86] more recent data show good preservation of lung function 5 years following survival from ARDS. In fact, lung function is usually normal or near normal, especially in young patients.

Despite recovery of pulmonary function, many survivors of ARDS have persistent functional disabilities after discharge, largely related to muscle wasting and weakness.[87] As noted previously, many survivors of ARDS have neurocognitive findings at hospital discharge, and in a significant number, the deficits persist long term.[87–91]

■ Morbidity and Mortality in Acute Hypercapnic Respiratory Failure

In general, several parameters presage a higher mortality in patients admitted with hypercapnic respiratory failure: (1) the patient's "physiologic reserve," as determined by concurrent cardiopulmonary, renal, hepatic, or neurologic disease and the patient's age; (2) the underlying cause of the acute deterioration; (3) the severity of the respiratory failure, as defined by arterial pH and P_{CO_2}; and (4) development of complications after onset of acute respiratory failure—for example, sepsis, pneumonia, renal failure, or gastrointestinal bleeding.

For patients hospitalized with an acute exacerbation of COPD, overall mortality is 8% to 12%, but it may be as high as 28% for those with significant comorbidities;[92,93] mortality for this group at 1 year is 43%.[93] For patients with an acute exacerbation of COPD who require mechanical ventilation, in-hospital mortality is high; 1-year mortality approaches 25%, and 5-year mortality 70%.[30,87–91]

■ Post-Acute Care Options for Survivors with Chronic Critical Illness

With increasing numbers of patients surviving acute, catastrophic illness or complications of advanced surgical procedures, long-term ventilator dependency and "chronic critical illness" have become challenging clinical issues. This group of patients requires complex medical management and generates considerable debate over medical ethics and healthcare costs. One relatively recent development related to management of chronically critically ill patients is the growth of long-term acute care hospitals—LTACHs.

LTACHs are either free-standing facilities or are based on the concept of a "hospital within a hospital." They focus on management of a wide variety of medically complex patients and typically include a significant cohort of those who are ventilator-dependent. Medicare provides a DRG payment to the LTACH that is separate from that to the acute care facility from which the patient is transferred. Fairly precise rules constitute admission and discharge criteria and, thereby, determine the average length of stay at the LTACH (25 days or greater).[94]

Data on long-term survival and functional status for ventilator-dependent patients discharged from LTACHs are striking. For those who are admitted and subsequently discharged with ventilator dependency (i.e., patients who are not successfully liberated), mean survival post-discharge is 100 days.[95] Furthermore, overall 1-year survival is 56%, with only 9% of patients reporting independent functioning 1 year after discharge.[96]

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SECTION 15 Lung Failure

CHAPTER 140

Acute Respiratory Distress Syndrome: Pathogenesis

Asha N. Chesnutt
Michael A. Matthay

INTRODUCTION

This chapter focuses on the pathogenesis of the acute respiratory distress syndrome (ARDS). Chapter 141 discusses clinical features and management of these disorders.

A 1994 consensus conference defined the spectrum of acute lung injury (ALI)/ARDS as follows: (1) ALI, defined as arterial hypoxemia with a $\text{Pa}_{\text{O}_2}/\text{FI}_{\text{O}_2}$ less than 300, and ARDS, defined as a $\text{Pa}_{\text{O}_2}/\text{FI}_{\text{O}_2}$ less than 200, accompanied by (2) bilateral pulmonary infiltrates, and (3) absence of left atrial hypertension.[1] A more recent report, based on the so-called Berlin definition, recommends identification of three categories of ARDS, based upon the degree of hypoxemia alone: (1) mild ARDS ($200 < \text{Pa}_{\text{O}_2}/\text{FI}_{\text{O}_2} \leq 300$ mm Hg), (2) moderate ARDS ($100 < \text{Pa}_{\text{O}_2}/\text{FI}_{\text{O}_2} \leq 200$ mm Hg), or (3) severe ARDS ($\text{Pa}_{\text{O}_2}/\text{FI}_{\text{O}_2} \leq 100$ mm Hg).[2] For the purposes of this chapter, both ALI and ARDS will be referred to as ARDS.

A recent comprehensive review of ARDS provides extensive references and illustrations relevant to epidemiology, definitions (including pediatric ARDS), pathogenesis based on experimental and clinical studies, management strategies, and long-term complications of ARDS.[3]

PATHOPHYSIOLOGY OF PULMONARY EDEMA IN ACUTE RESPIRATORY DISTRESS SYNDROME

Pulmonary edema occurs when fluid is filtered into the lungs faster than it can be removed. Accumulation of fluid may have major consequences on lung function because efficient gas exchange cannot occur in fluid-filled alveoli. Lung structure relevant to edema formation and the forces governing fluid and protein movement in the lungs have been the subject of classic and more recent reviews.[4,5]

Vascular Fluid and Protein Exchange

The essential factors that govern fluid exchange in the lungs are expressed in the Starling equation for the microvascular barrier:

$$\text{Jv} = \text{LpS}[(\text{Pc} - \text{Pi}) - \sigma\text{d}(\pi\text{c} - \pi\text{i})]$$

where

Jv = the net fluid-filtration rate (volume flow) across the microvascular barrier
Lp = the hydraulic conductivity (permeability) of the microvascular barrier to fluid filtration (a measure of how easy it is for water to cross the barrier)
S = the surface area of the barrier
Pc = the pulmonary capillary (microvascular) hydrostatic pressure
Pi = the interstitial (perimicrovascular) hydrostatic pressure
πc = the capillary (microvascular) plasma colloid osmotic (or oncotic) pressure
πi = the interstitial (perimicrovascular) fluid osmotic pressure
σd = the average osmotic reflection coefficient of the barrier (a measure of the effectiveness of the barrier in hindering the passage of solutes from one side of the barrier to the other)

The Starling equation predicts the development of two different kinds of pulmonary edema. *Increased pressure pulmonary edema* occurs when the balance of the driving forces increases, forcing fluid across the barrier at a rate that can no longer be accommodated by lymphatic drainage. *Increased permeability pulmonary edema* occurs in the presence of ARDS that damages the normal barriers to fluid filtration and allows increased flux of liquid and protein into the extravascular compartments of the lungs. Congestion, atelectasis, and pulmonary edema were features of the original description of the syndrome.[6]

Thus, pulmonary edema results from increases in either hydrostatic driving pressures (increased pressure edema) or barrier conductance (increased permeability edema), or both. What distinguishes the two types is barrier permeability, which is normal in increased pressure edema, but abnormal in increased permeability edema. Fluid flow into the lungs is driven across the barrier in both types of edema by the balance of pressures. ARDS results primarily from an increase in lung vascular permeability, although some cases may be made worse by the presence of elevated lung vascular hydrostatic pressures.

Increased Permeability Pulmonary Edema

Increased permeability pulmonary edema is caused by an increase in liquid and protein conductance across the barriers in the lungs. The essential feature is that the integrity of the barrier to fluid and protein flow into the lung interstitium and alveoli is altered. Increased permeability edema is sometimes called *noncardiogenic pulmonary edema*, and the resulting clinical syndrome is ARDS.

Accumulation of fluid and protein increases when the lung endothelial and epithelial barriers are injured. If the rate of fluid accumulation exceeds the rate at which it can be removed, increased permeability edema occurs. Large animal models employing measurements of hemodynamics and lung lymph flow demonstrate that clinically relevant causes of ARDS, including live bacteria, endotoxin, and microemboli, induce an increase in lung vascular permeability that causes protein-rich lung edema.[7–9] Because the barriers limiting fluid and protein flow into the lungs do not function normally when the lungs are injured, the lungs are not protected against edema by the usual safety factors. Although increases in fluid and protein filtration across the lung endothelium can be removed by lymphatics and drained away from the alveolar walls as in increased pressure edema, much more fluid and protein are filtered at any given sum of driving pressures, since the barriers to flow are much less restrictive than normal.

Edema formation in injured lungs is sensitive to hydrostatic driving pressures. Driving pressures are often increased when the lungs are injured because of the vasoconstrictive effects of inflammatory mediators, such as thromboxanes. Thromboxanes may shift the main site of vascular resistance to postcapillary venules, thus increasing hydrostatic pressure at the microvascular fluid exchange sites, or may exert cardiac effects. For example, elevated left atrial pressure, pulmonary venoconstriction, or an increase in cardiac output in sepsis may increase hydrostatic pressure at the microvascular fluid exchange sites. Although a primary event in ARDS is an increase in lung vascular permeability, the magnitude of lung edema formation in ARDS may be substantially increased when lung vascular pressures and volume are elevated, consistent with the effects of elevated hydrostatic pressure on transvascular flux of fluid and protein.

Because the lung endothelial and epithelial barriers are injured in ARDS, the protective effects of protein osmotic pressure differences across them are lost; driving pressure is unopposed by protein osmotic pressure, and even normal hydrostatic pressure results in significant fluid and protein extravasation into the interstitial and alveolar spaces. The ability of the lymphatics to pump the excess filtrate away is increased when the lungs are injured. If the alveolar epithelial barrier is damaged, edema may accumulate readily in alveoli, since most of the resistance to fluid and protein flow into the alveoli is in the epithelial barrier.

To summarize, the majority of patients with ARDS have normal or low hydrostatic pressures and increased alveolar-capillary permeability. However, up to 30% of patients with ARDS may have an elevated left atrial pressure.[10] Lung fluid balance is a dynamic concept that incorporates both formation and removal of edema fluid in the interstitium and airspaces.

Lung Physiology

The effects of increased permeability edema on lung mechanics and gas exchange depend, in part, on the magnitude of edema accumulation. As with increased pressure edema, the major effects on pulmonary mechanics occur with alveolar flooding.

About 20% to 30% of the extravascular water of the lungs is in the extravascular interstitial tissue. This volume can more than double before alveolar flooding occurs. In experimental lung injury, functional residual capacity (FRC) is decreased as a consequence of alveolar flooding; the loss of units that can be ventilated accounts for most of the decrease in static lung compliance.[11] Computed tomography has provided new insights into structure-function relationships in human ARDS. In the early stage of lung injury, when alveolar edema predominates, the lungs are characterized by a more homogeneous alteration of vascular permeability, and edema may accumulate evenly in all lung regions, with a nongravitational distribution. Later in the exudative phase of ARDS, the consolidation is more gravity-dependent. In the organizing phase, lung reticulation appears.

Measurements of pulmonary mechanics in mechanically ventilated patients with ARDS show a decrease in static lung compliance as a consequence of loss of ventilated lung units. In addition, airflow resistance is increased as a result of decreased lung volume.[12] Bronchospasm may add to the increase in airflow resistance and may be partially reversed in some patients by administration of inhaled bronchodilators. Chest wall compliance is reduced, probably because of alterations in the intrinsic mechanical properties of the chest wall by abdominal distention, chest wall edema, and pleural effusion. Respiratory mechanics and responses to positive end-expiratory pressure (PEEP) during mechanical ventilation in patients with ARDS originating from pulmonary disease (e.g., pneumonia and associated lung consolidation) and those arising from extrapulmonary disease may differ.[13]

The injured lung in ARDS may release biologically active substances that can interfere with the normal state of low surface tension in the alveoli. In addition, activated neutrophils may reduce surfactant function in vitro and degrade major surfactant apoproteins through a combination of proteolysis and oxidant radical-mediated mechanisms. Human lung surfactant obtained from bronchoalveolar lavage (BAL) fluid in patients at risk for ARDS and from those with established ARDS are abnormal in chemical composition and functional activity.[14] Abnormalities may also be caused by interactions between surfactant and edema proteins, since plasma proteins interfere with surfactant function.

Gas exchange is severely compromised in increased permeability edema, because of both intrapulmonary shunting of blood and ventilation–perfusion inequalities. Clinical evidence indicates that patients with early ARDS have a marked increase in pulmonary dead space fraction.[15] This finding indicates that many ventilated lung units are not well perfused, although intrapulmonary shunting may also contribute to the elevated dead space. Minute ventilation is typically twice normal (approximately 12 L/min) at the onset of ARDS. The subject of gas exchange in ARDS has been recently reviewed.[16]

Pathologic Findings

Based on several studies that included a preponderance of postmortem pathology, the light and electron microscopic appearances of human and animal lung tissue in ARDS have been described.[17] The earliest changes are marked by widespread alveolar and interstitial edema, inflammation, and hemorrhage. This phase is the exudative phase of ARDS. Hyaline membranes, composed of precipitated plasma proteins, fibrin, and necrotic debris, are frequently found and constitute the footprint of a pathologic finding termed diffuse alveolar damage (DAD), which pathologists use to define ARDS microscopically (Fig. 140-1).[18]

The alveolar epithelium may be more extensively damaged than is the vascular endothelium. Alveoli that demonstrate widespread destruction of type I alveolar epithelial cells may appear adjacent to normal alveoli. The injured alveolar epithelium is swollen, disorganized, and, frequently, detached from basement membranes. The alveolar surface may be covered by hyaline membranes. Type I cells are more severely damaged than type II cells. The thin cytoplasmic extensions of cells far from the nucleus, which cover the thin side of the alveolar-capillary barrier, may be most severely affected. The interstitium is widened by edema (especially in peribronchovascular cuffs) and may be filled with leukocytes, platelets, red blood cells, fibrin, and debris (especially near the alveolar walls). The microvascular endothelium may show cytoplasmic swelling or vacuoles and greater numbers of intraluminal leukocytes.

After about 5 to 10 days, the exudative phase of ARDS is followed by a proliferative phase. The relative contributions of the original insult, repair processes, and effects of therapies on this and subsequent phases are not well known. Some abnormalities occurring after the initial exudative phase are related to effects of traditional modes of mechanical ventilation that used tidal volumes between 12 and 15 mL/kg predicted body weight.

Reabsorption of some of the edema fluid characterizes the proliferative phase. Fibrin may be prominent in alveoli and interstitium, and infiltration with inflammatory cells and fibroblasts, which may have been activated very early in the course of lung injury, may be seen. The alveolar epithelium is often cuboidal and made up largely of proliferating type II cells. The air–blood barrier may be thickened by interstitial and epithelial enlargement. The pulmonary vascular bed may be partially or completely disrupted, and structural alterations may reduce its surface area.

In a study addressing the clinicopathologic correlation of the new Berlin definition of ARDS severity with historic autopsy data, a greater proportion of patients with severe ARDS demonstrated histopathologic findings of DAD compared with those with mild or moderate disease.[19] The final or fibrotic phase does not occur in all patients but has been linked to prolonged mechanical ventilation.

Experimental Studies

The most common clinical disorders associated with the development of ARDS are pneumonia, sepsis, gastric aspiration, and major

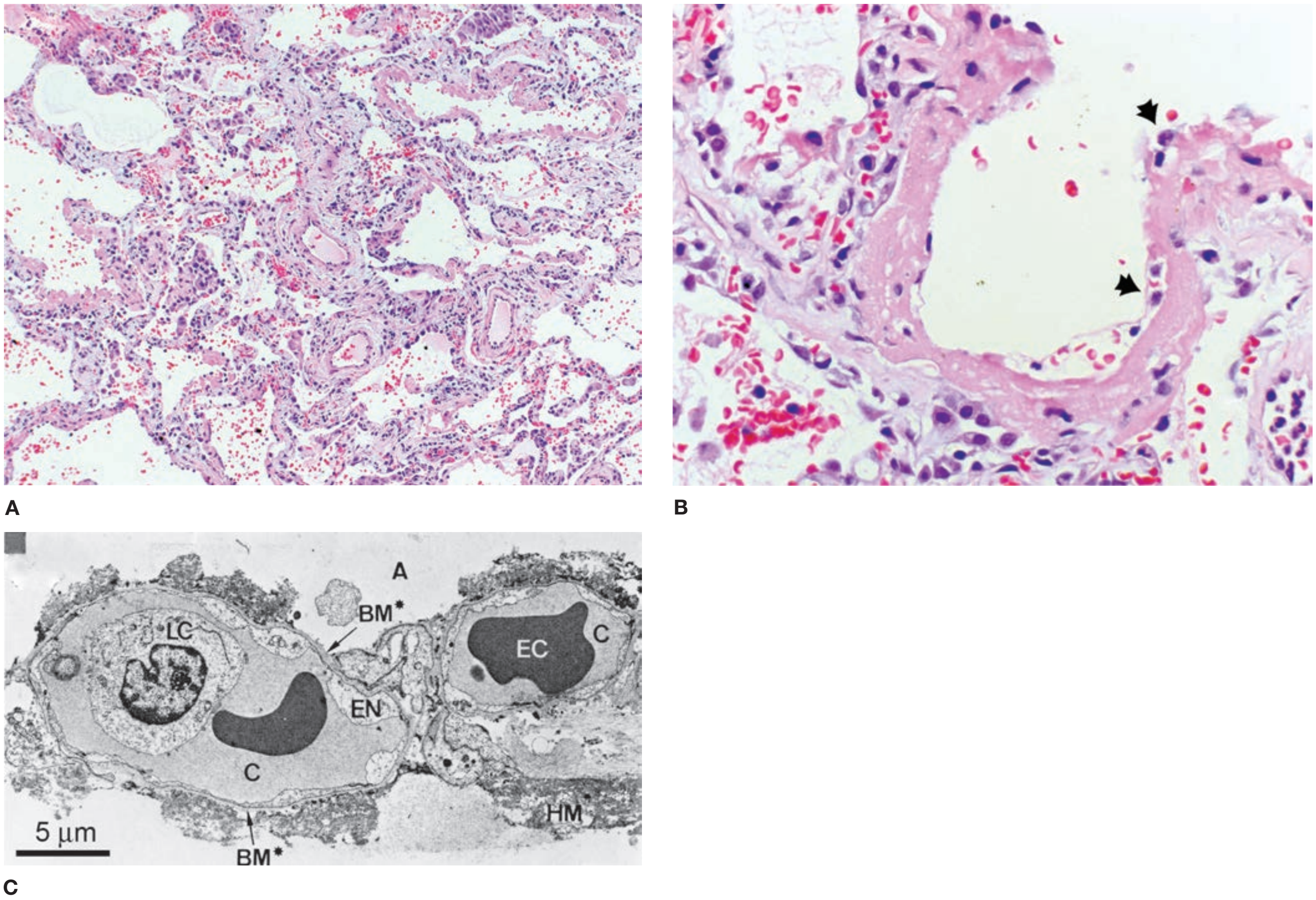

FIGURE 140-1 **A**. A low-power light micrograph of lung biopsy specimen collected 2 days after the onset of ALI/ARDS secondary to Gram-negative sepsis demonstrates key features of diffuse alveolar damage, including hyaline membranes, inflammation, intra-alveolar red blood cells and neutrophils, and thickening of the alveolar-capillary membrane. **B**. High-power view of a different field illustrates dense hyaline membrane and diffuse alveolar inflammation. Polymorphonuclear leukocytes are imbedded in the proteinaceous hyaline membrane structure *(black arrows)*. *(Histologic sections in A and B used with permission of Dr. K. Jones, University of California, San Francisco.)* **C**. Electron micrograph from a classic analysis of ALI/ARDS showing injury to capillary endothelium and alveolar epithelium. A, alveolar space; BM, exposed basement membrane where the epithelium has been denuded; C, capillary; EC, erythrocytes; EN, blebbing of the capillary endothelium; LC, leukocyte within capillary lumen. *(Reproduced with permission from Bachofen M, Weibel EAR. Structural alterations of lung parenchyma in the adult respiratory distress syndrome. Clin Chest Med. 1982;3(1):35–56.)*

trauma. Other, less common causes include transfusion-associated lung injury, drug overdose, severe acute pancreatitis, and near-drowning. The initiating insult to the lungs occurs via either the airways or the bloodstream.

The exact mechanisms by which the lungs are injured have been studied in humans, animals, and cellular systems. Human studies have provided descriptive data regarding the events that occur in the airspaces before and after the onset of lung injury. Studies using BAL or collection of pulmonary edema fluid in patients following the onset of ARDS have demonstrated a major acute inflammatory response, which begins prior to clinical recognition of ARDS.[20] The response peaks during the first 1 to 3 days of clinically defined ARDS and resolves slowly over 7 to 14 days in patients who remain intubated. These studies have shown the complexity of the evolving inflammatory responses, characterized by accumulation of acute response cytokines and their naturally occurring inhibitors, oxidants, proteinases and antiproteinases, lipid mediators, growth factors, and the collagen precursors involved in the repair process.

Hypotheses regarding the mechanisms of lung injury have been tested in animal models and in vitro studies, and several reviews have summarized the findings.[4,9] The existing animal models do not completely reproduce all of the aspects of ARDS in humans, in part because human ARDS evolves over a longer period of time than can be studied in the laboratory. In addition, the lungs of humans are exposed not only to the initial injurious insult, but also to the therapies that are used to treat ARDS, such as mechanical ventilation, fluid resuscitation, and antibiotics. Experiments using isolated cells have been helpful in testing specific concepts, but the complexity and redundancy of intact biologic systems are not reproduced in simplified experimental systems. By design, most experimental work limits study to one causative agent, thereby reducing actual clinical complexity to the simplicity of a single experimental pathway. Increased permeability edema in humans is likely to be caused by interactions among a number of different pathways acting in parallel or series, and modulated by process of care variables such as mechanical ventilation, fluid management, vasopressor use, and several comorbidities, including diabetes mellitus, alcohol and cigarette exposure, and renal and liver disease.[9]

Studies in isolated organs and small animals in which hemodynamic variables are not measured can be difficult to evaluate. Indices of lung injury, usually measured by the appearance of markers in lungs, lavage fluid, or perfusate, are not determined solely by the barrier function of the microvasculature. Indeed, when vascular endothelium is injured, fluid and protein movement from the vascular space into the lungs is sensitive to hydrostatic driving pressures and filtration surface area. Hence, the effects of experimental interventions may be caused by changes in these parameters and not by changes in microvascular barrier function.

The effects of microvascular driving pressures and surface area can be difficult to evaluate, even in large, instrumented animals. In sheep and goats, interpretation of lung lymph fluid and protein flow changes are further complicated by contributions of extrapulmonary lymphatics, physical forces acting on lymphatics, and possible intranodal modification of lymph. Data from experimental animal models suggest that at least two broad categories of mechanisms of ARDS are operative: (1) those that are *indirect* (i.e., require the participation of intermediary mechanisms, e.g., host defenses); and (2) those that are *direct* (i.e., do not require intermediary mechanisms; injury probably occurs as a result of contact between an offending substance and lung tissue). These categories overlap, since once the lungs are injured, inflammatory responses occur, which may compound the primary mechanism of injury.

MECHANISMS OF ACUTE RESPIRATORY DISTRESS SYNDROME

The following themes regarding the mechanisms of ARDS are discussed below: infection, inflammation, and direct toxicity. Although discussed separately, they are all interrelated.

■ Role of Infection

ARDS develops in 20% to 45% of patients with severe sepsis. Increased microvascular permeability to albumin has been shown to accompany human sepsis, and infection and the sepsis syndrome are major causes of ARDS in humans. Patients who develop shock in response to known or suspected infection have a particularly high incidence of ARDS, and the mortality of patients with ARDS associated with infection (i.e., sepsis syndrome) is increased. ARDS also appears to predispose the lungs to infection, and delayed infection is an important cause of morbidity in patients who survive the initial lung insult.

The mechanisms by which infection and sepsis syndrome injure the lungs are only partially understood. The lung injury is likely related to factors other than direct damage by bacteria or other microorganisms, since the prognosis appears unrelated to documented bacteremia or pneumonia. In experimental animals, intravenous infusions of live *Pseudomonas aeruginosa*, or endotoxins from *Escherichia coli*, or surgically induced peritonitis result in increased permeability pulmonary edema.[21] ARDS caused by endotoxin in sheep is thought to be an inflammatory response mediated, at least in part, by neutrophils and tumor necrosis factor (TNF). Endotoxin may also affect the clotting system and metabolic functions of the lungs, as well as predispose the lungs to the development of pulmonary infections by increasing adherence of bacteria to injured endothelium. Exoproducts of bacteria, such as elastase and *Pseudomonas* exoenzyme U, also have been shown to injure the lungs.[7] Current evidence supports a primary role of the microcirculation in the pathogenesis of ARDS after sepsis.[3]

Bacterial products may also play a role in pathogenesis of ARDS by sensitizing the lungs to the effects of mechanical stretch. Gram-negative lipopolysaccharide causes an acute inflammatory response in the lungs of humans. Bacterial endotoxin enhances the responses of human alveolar macrophages to positive-pressure ventilation; pretreatment of rats with intravenous endotoxin enhances cytokine production in the lungs during mechanical ventilation ex vivo. Furthermore, mechanical ventilation using moderate or large tidal volumes increases the sensitivity of lung macrophages to endotoxin in vitro and the expression of the endotoxin recognition molecule, CD14, on lung cells in vivo. Endotoxin recognition pathways are increased in the lungs of patients with ARDS, and the biologic effects of endotoxin are amplified in the lungs of patients with lung injury. The synergism between bacterial products and mechanical stretch suggests that interrupting these pathways might limit some forms of ARDS in humans.[22]

Increased permeability edema is associated with impaired antibacterial defenses. In animal models, bacterial infections worsen ARDS. The cause of impaired bacterial defenses in ARDS is not known. Genetic polymorphisms that predispose individuals to the injurious effects of specific bacteria or viruses may influence the development of ARDS. Several polymorphisms are associated with more severe pneumococcal, *Legionella*, and viral lung infections.[23] The genetic factors that regulate the virulence of infecting pathogens also require more research to relate the severity of clinical lung injury to specific microbiologic variables that contribute to severe pneumonia and ARDS.[24]

■ Role of Inflammation

Substantial evidence implicates host defenses and inflammatory responses in the underlying mechanism of ARDS. The balance between protective and injurious innate and adaptive immune responses and hemostatic pathways may determine whether alveolar injury can be repaired and resolved. For example, in lung infection, acute inflammatory responses to pathogens and their toxins cause ARDS through leukocyte protease release, generation of reactive oxygen species, synthesis of chemokines and cytokines, Toll-like receptor engagement, and actions of lipid mediators. However, these same inflammatory mechanisms, when controlled, rather than excessive, are requisite in pathogen containment and clearance.[25–27]

Normally, the pulmonary circulation contains a large pool of marginated neutrophils that change shape in order to squeeze through the lung capillaries. When neutrophils are activated, they stiffen and become less distensible. These neutrophils are retained for longer periods of time in the pulmonary microcirculation. Endothelial activation leads to increased expression of leukocyte adhesion molecules, providing a second mechanism to slow the transit of neutrophils. Trapped neutrophils respond to chemotactic gradients generated by chemokines produced by alveolar macrophages and mesenchymal cells and migrate into the airspaces. Activated neutrophils generate and release toxic substances (e.g., oxygen metabolites and granular constituents, such as proteases, and cationic lysosomal enzymes) that disrupt the function of the microvascular and epithelial barriers. Normally, these barriers limit liquid and protein flow out of the vascular space and into the alveolar spaces, mitigating the development of permeability edema.[22]

Inflammatory responses also have the potential to induce lung cell injury by activating cell death pathways, leading to apoptosis. Bacterial products, such as *Pseudomonas* exoenzyme U and mechanical stretch, may lead to direct cellular necrosis. Apoptosis is mediated by a family of death receptors, including TNF and Fas receptors. The Fas ligand (FasL) is a 45-kDa peptide that is shed from the cell surface by the action of metalloproteinases.[28] Biologically active soluble FasL (sFasL) accumulates in the lungs of patients with ARDS, inducing apoptotic death of human lung epithelial cells in vitro. Human sFasL induces epithelial cell death in the lungs of rabbits; a monoclonal antibody that activates membrane Fas causes alveolar wall apoptosis and fibrosis in the lungs of mice.[28]

Apoptosis and inflammation pathways intersect, as stimulation of membrane Fas induces cytokine production in human macrophages and inflammation in the lungs of rabbits and mice. In addition, lung injury may be able to trigger apoptosis pathways in distant organs, such as the kidney, perhaps by increasing the concentrations of circulating sFasL. Thus, inflammatory responses may trigger cell death pathways, and cell death pathways triggered by sFasL may induce inflammation in the lung alveolar environment. Recent human studies implicate apoptosis as an important mechanism in human lung injury.[29]

Precision medicine has transformed approaches to many disease states including ARDS. Latent class analysis has identified a hyperinflammatory and hypoinflammatory subphenotypes in ARDS. The hyperinflammatory subphenotype is characterized by higher plasma concentrations of inflammatory biomarkers, and some clinical variables including lower platelet counts and lower serum bicarbonate concentrations. Secondary analysis of the NHLBI, ARDS, NET, ALVEOLI, ARMA, and FACTT trials have shown that these subphenotypes respond differently to randomly assigned fluid management.[30,31] The hyperinflammatory subphenotype has elevated levels of interleukin 6 (IL-6), IL-8, and soluble TNFR1. Sepsis and vasopressor use have been more common, and mortality has been higher in the hyperinflammatory subphenotype. A study showed that application of the latent class analysis to a trial of simvastatin for ARDS, which was carried out in the United Kingdom, revealed again that patients segregated into a hyper- or hypoinflammatory subphenotype, with approximately 35% of patients in the hyperinflammatory group.[32] In addition, although the overall results of the trial showed no effect of simvastatin on mortality, this secondary analysis showed that patients in the hyperinflammatory group benefited from simvastatin with a greater 28-day survival—thus raising the possibility that identifying subphenotypes in ARDS might lead to effective pharmacologic therapies.

■ Role of Direct Toxicity

Inflammation is not required for all forms of ARDS. ARDS may develop in neutropenic patients. A clinical trial using granulocyte colony–stimulating factor to increase the number and activation state of circulating neutrophils in patients with severe pneumonia did not reveal an increased incidence of ARDS.[33] Lung injuries that do not require the participation of neutrophils have been described in animal models.

Direct lung injury is also thought to occur in humans. Putative agents that directly injure the lungs include mechanical forces during mechanical ventilation, toxic and corrosive chemicals and gases (e.g., hydrochloric acid, chlorine gas, phosgene), and aspiration of fresh or salt water (near-drowning). Many of these injuries develop rapidly, supporting the idea that injury is caused directly by contact with the respiratory epithelium in the airways or alveolar walls.

ARDS develops in approximately 10% to 30% of critically ill trauma patients. Many investigators have studied air pollution as a risk factor. A recent study showed that among a cohort of patients presenting to a level 1 trauma center, long-term exposures to NO_2, SO_2, CO, and PM 2.5 and ozone were associated with the subsequent development of ARDS.[34] Another study showed that cigarette smoking contributes to ARDS development after trauma by altering community composition of lung microbiotica.[35]

Inflammatory pathways are likely to be rapidly activated following many types of direct lung injury, as probably occurs following aspiration of gastric secretions—one of the most common clinical causes of ARDS. Lung injury occurs rapidly, especially to the epithelium. The injury is probably related, in part, to the low pH of the aspirated stomach contents. Aspirated acid is almost immediately neutralized. However, within hours, proinflammatory mediators are released, the injured lung is infiltrated with neutrophils, fibrin accumulates in the alveolar spaces, and further structural damage is seen on histologic examination. Thus, even direct toxic injuries damage the lung in part through activation of inflammatory pathways.

■ Biologic Markers

Considerable interest exists in finding a simple test of blood, urine, or BAL fluid that would identify patients at risk for, or in the earliest stages of, ARDS, or that might predict clinical outcome.

Although products of complement activation have been proposed as markers, their serum levels correlate poorly with lung injury. Measurement of circulating endotoxin is not appropriately sensitive or specific for the presence or risk of developing lung injury. The same is true for measurements of release or activity of angiotensin-converting enzyme.[36] von Willebrand factor (VWF) antigen may be useful as a plasma marker of impending ARDS in patients with nonpulmonary sepsis.[37] VWF levels are elevated in the edema fluid and plasma of patients with ARDS and correlate with poor clinical outcomes.[38] Also, work has indicated that elevated levels of plasma angiopoietin 2 predict the development of ALI in patients with sepsis identified in the emergency department.[39] While increases in other biochemical and inflammatory markers, including surfactant protein D and IL-6, correlate somewhat with lung injury and mortality, no simple biologic marker currently serves in the same diagnostic capacity, as do cardiac enzymes in evaluation of suspected acute myocardial infarction.[40]

Other mediators of inflammation in ARDS have been studied. For example, increased levels of TNF are detected in blood and BAL fluid in lung injury, but an association between TNF levels and the development of ARDS has not been found.

Furthermore, elevated TNF levels are found in patients with severe congestive heart failure. Lipoxygenase products of arachidonic acid metabolism have been detected in pulmonary edema fluid, BAL fluid, plasma, and urine, and elastase has been detected in BAL fluid in the setting of lung injury.

ARDS follows a wide variety of insults of varying severity. In a study of injured patients with ARDS, investigators found increased levels of IL-6 and thrombomodulin in those who had fewer ventilator-free days.[41] However, since ARDS is such a heterogeneous disorder, with so many possible mechanisms, it is unlikely that any single marker that unequivocally identifies the risk or the presence of ARDS will be found. An investigative focus on particular subgroups of patients with common causes of lung injury, coupled with study of much larger groups of more precisely diagnosed patients, may be a better pathway for future research.

Figure 140-2 depicts multiple pathways involved in the pathogenesis of ARDS in the context of normal and injured alveoli. The depictions place emphasis on potential pathways for injury across the vascular endothelium and alveolar epithelium.

VENTILATOR-INDUCED LUNG INJURY

The most important development of the last 10 years in our understanding of the pathogenesis and treatment of ARDS is recognition that the long-standing practice of mechanically ventilating affected patients using high tidal volumes and airway pressures worsens the injury. Animal studies first suggested the potential contributory role of high tidal volumes and elevated airway pressures in the pathogenesis of lung injury; subsequently, clinical trials confirmed the findings.[4]

■ Animal Studies

Experimental studies have shown that ventilation using high tidal volumes may increase vascular filtration pressures; produce stress fractures of microvascular endothelium, alveolar epithelium, and basement membranes; and cause lung rupture (so-called ventilation-induced lung injury).[42] The injury appears to be due to increased lung excursions at high volumes (volutrauma), rather than the high-airway pressure, per se, since it can be prevented by limiting thoracic motion (e.g., by placing the chest in a cast).

The concept of volutrauma was first established in 1974 when investigators found that modestly elevated tidal volumes, especially in the absence of PEEP, caused lung edema in rats.[43] Several years later, additional animal studies further demonstrated the potential

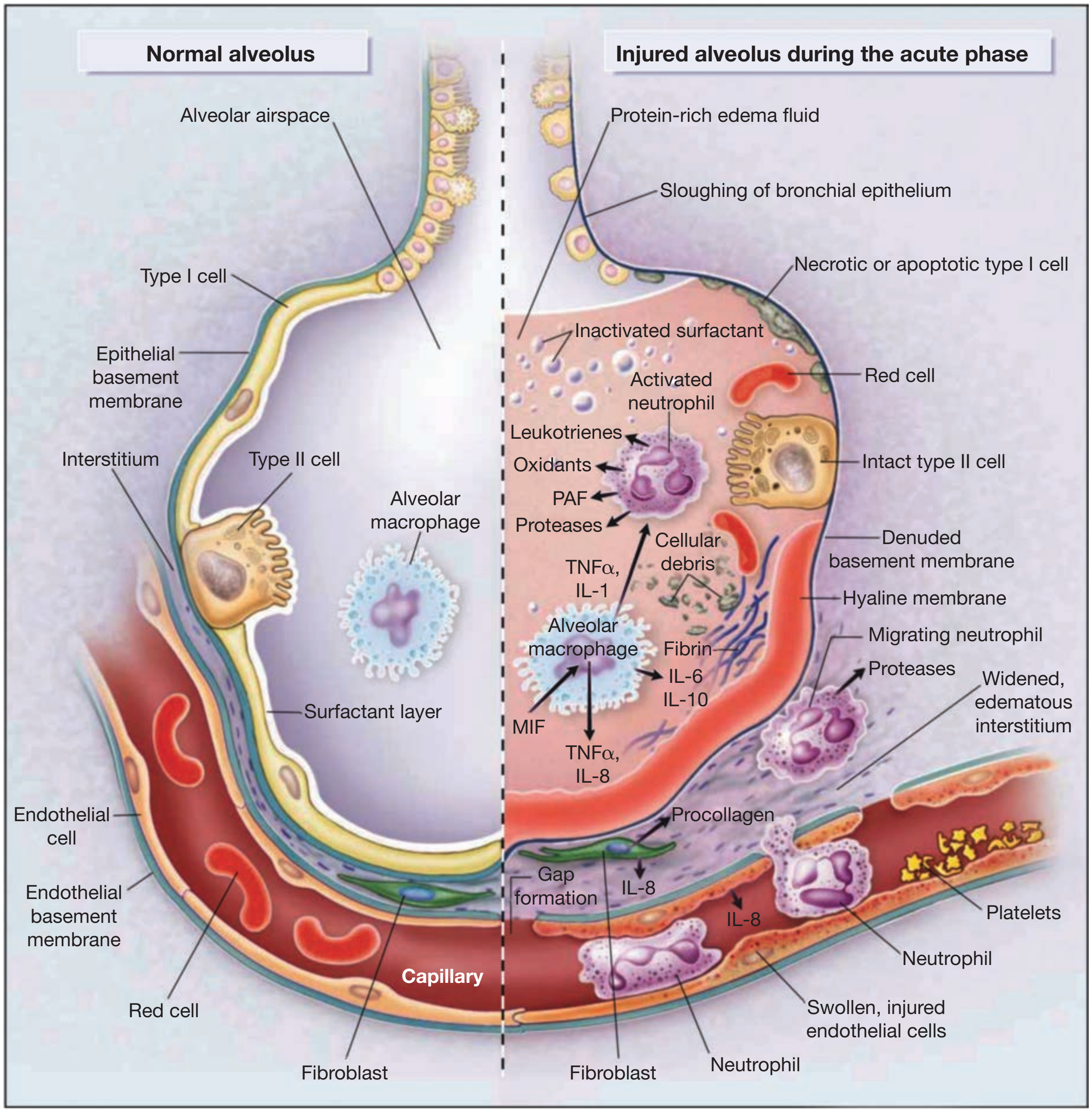
Normal alveolus
Injured alveolus during the acute phase
Alveolar airspace
Type I cell
Epithelial basement membrane
Interstitium
Type II cell
Alveolar macrophage
Surfactant layer
Endothelial cell
Endothelial basement membrane
Red cell
Capillary
Fibroblast
Protein-rich edema fluid
Sloughing of bronchial epithelium
Necrotic or apoptotic type I cell
Inactivated surfactant
Activated neutrophil
Red cell
Leukotrienes
Oxidants
PAF
Proteases
Intact type II cell
Cellular debris
TNFα, IL-1
Denuded basement membrane
Hyaline membrane
Alveolar macrophage
Fibrin
IL-6
IL-10
Migrating neutrophil
Proteases
Widened, edematous interstitium
MIF
TNFα, IL-8
Procollagen
Gap formation
IL-8
IL-8
Platelets
Neutrophil
Swollen, injured endothelial cells
Fibroblast
Neutrophil

FIGURE 140-2 Multiple cellular responses and mediators contribute to alveolar-capillary membrane injury *(right-hand side)* and the transition from normal alveolar structure and function *(left-hand side)* in the acute phase of ALI/ARDS. Original investigations of the pathogenesis of ALI/ARDS searched for single mediators that provided final common pathways to inflammation and alveolar edema. Current concepts of pathogenesis involve multiple molecular factors of several classes, a variety of responding cells, and an imbalance between injurious and reparative signals and pathways. See text and Ware & Matthay (2000). *(Reproduced with permission from Ware LB, Matthay MA. The acute respiratory distress syndrome. N Engl J Med. 2000;342(18):1334–1349.)*

injurious role of high tidal volumes and elevated airway pressures, an effect termed *ventilator-induced lung injury* (VILI).[44] Subsequent experiments demonstrated that VILI could also induce release of several proinflammatory cytokines, injuring the lung and other organs—a process referred to as "biotrauma."[45] These animal studies stimulated clinical investigation that revolutionized the care of patients with ARDS.[44]

■ Clinical Studies

The compelling evidence from animal experiments and small clinical trials prompted clinical studies aimed at testing the potential benefit of lower tidal volumes and reduced airway pressures during mechanical ventilation in management of ARDS. In a large, multicenter, National Heart, Lung, and Blood Institute–sponsored trial of 861 patients, mortality was reduced from 40% to 31% using a tidal volume of 6 mL/kg of ideal body weight and a limited plateau airway pressure of less than 30 cm H_2O.[46] In this trial, use of small tidal volumes was associated with a lower incidence of nonpulmonary organ failure. The protocol for carrying out the lung protective ventilatory strategy is described in detail in Table 140-1. The results of the trial transformed the management of patients with ARDS. Notably, a follow-up clinical trial demonstrated that ventilation using the limited tidal volumes and plateau pressure of the original study is associated with an overall reduction of mortality to 26%. In the follow-up trial, although elevated levels of PEEP did not decrease mortality, the basic lung protective strategy was validated as effective.

The beneficial mechanism underlying the low tidal volume strategy has been well studied. An Italian study reported that use of low tidal volumes in patients with ARDS attenuates the inflammatory response in both lungs and bloodstream, as measured by reductions

TABLE 140-1 National Institute of Heart, Lung, and Blood, ARDS Network: Lung Protective Ventilatory Strategy

Ventilator mode	Volume assist–control
Tidal volume	$\leq$6 mL/kg PBW
Plateau pressure	$\leq$30 cm H_2O
Ventilation set rate, pH goal	6–35, adjusted to achieve arterial pH $\geq$7.30, if possible
Inspiratory flow, I:E	Adjust flow to achieve I:E = 1:1–1:3
Oxygenation goal	$55 \leq Pa_{O_2} \leq 80$ mm Hg or $88 \leq SP_{O_2} \leq 95\%$
F_{IO_2}/PEEP Combinations	

F_{IO_2}	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7	0.7	0.8	0.9	0.9	0.9	1.0
PEEP, cmH_2O	5	5	8	8	10	10	10	12	14	14	14	16	18	18, 22, 24

(Further increases in PEEP to 34 cm H_2O allowed, but not required)

Weaning	Attempts to wean by pressure support required when F_{IO_2}/PEEP $\leq$0.40/8

$Jv = LpS[(Pc - Pi) - \sigma d(\pi c - \pi i)]$

I:E, ratio of inspiratory to expiratory duration; Pa_{O_2}, partial pressure of oxygen in arterial blood; Sp_{O_2}, oxyhemoglobin saturation measured by pulse oximetry.

Data from Kraus PA, Lipman J, Lee CC, et al. Acute lung injury at Baragwanath ICU. An eight-month audit and call for consensus for other organ failure in the adult respiratory distress syndrome. Chest. 1993;103(6):1832–1836.

in neutrophil and cytokine concentrations in BAL and cytokines in circulating blood.[47] Other studies have confirmed a number of these findings. In addition, a reduction in alveolar epithelial injury appears likely, based on a decline in plasma surfactant protein D levels. Additional clinical and experimental studies are underway. A reduction in lung endothelial and epithelial injury, attenuated inflammatory responses, reduced edema formation, and more rapid resolution of lung edema are likely part of the mechanism(s).[4] Figure 140-3 summarizes current knowledge of the mechanisms of VILI.

There has not been an accurate method to estimate the extent of pulmonary edema in a patient with ARDS. However, the Radiographic Assessment of Lung Edema (RALE) score is a simple, noninvasive way to assess the extent and density of alveolar opacities on the chest radiograph, using a scoring system based on the density and extent of infiltrates in each of the four quadrants on the chest radiograph.[48] An earlier version of the RALE score correlated with direct gravimetric assessment of pulmonary edema in donor lungs.[48] In addition, higher RALE scores identified patients with higher mortality in a subset of patients in the FACTT trial. In addition, patients who were treated with a conservative fluid therapy had a significantly reduced RALE score compared with those treated with a fluid-liberal strategy.

■ Resolution of Acute Lung Injury

In the last three decades, notable progress has occurred in elucidating the mechanisms responsible for resolution of lung edema.[49] More limited progress characterizes our understanding of the resolution of lung inflammation.

Considerable advances have been made in our understanding of the clearance of fluid and solute from alveoli. Edema can be cleared via five routes: lymphatics, airways, blood vessels, the pleural space, and the mediastinum. Active sodium and chloride transport across the alveolar and distal airway epithelial barriers into the interstitium drives edema fluid removal from the airspaces.[50] The uninjured alveolar epithelium has a remarkable ability to rapidly clear fluid from the airspaces. Even when mild to moderate alveolar injury occurs, salt and water transport capacity is often preserved. In severe injury, when the barrier is disrupted, the capacity to clear edema is lost. The vascular endothelium becomes the limiting barrier between the vascular space and airspace. Clinically, the capacity to remove some alveolar edema fluid in the first 4 to 12 h following ARDS is a favorable prognostic finding; the associated mortality rate is only 20%. In contrast, an inability to resorb alveolar edema fluid early in the course of injury is associated with a mortality of nearly 80%. Thus, the function of the alveolar epithelial barrier early in the course of ARDS may be a useful prognostic index, serving as a marker of the severity and extent of injury.[51]

Resolution of ARDS requires effective: (1) reabsorption of alveolar edema, (2) repair of the epithelial and endothelial barriers, and (3) removal of inflammatory cells and exudates from the distal airspaces. Reabsorption of alveolar edema occurs through vectorial transport of sodium and chloride across alveolar epithelial type I and II cells to create a mini-osmotic gradient to reabsorb water.[52–54] This process is impaired in ARDS, in part because of apoptosis and necrosis of alveolar epithelium and defects in transcellular ion transport induced by proinflammatory cytokines, oxidants, and hypoxia.[29,52,55–58]

In uninjured, ex vivo human lungs, alveolar fluid clearance (AFC) is increased by administration of the β2 agonist salmeterol.[59] However, the β-adrenergic-mediated effect by augmentation of intracellular cAMP works primarily when the alveolar epithelium is not injured, as in hydrostatic edema. Aerosolized or intravenous β2 agonist therapy does not appear to improve clinical outcomes.[60,61]

Clearance of protein from flooded alveoli is much slower (1%–2% per hour) than clearance of fluid (10%–20% per hour), resulting in an increased concentration of protein in the airspaces. If alveolar edema formed during increased lung vascular permeability clots, its removal from flooded alveoli may be slowed. Clotting may occur because extravasation of plasma into airspaces may lead to clotting system activation by surfactant or macrophage-derived procoagulants.

Most of the interstitial water in pulmonary edema lies in the peribronchovascular loose connective-tissue spaces, rather than in alveolar walls. Because the lymphatic capillaries are arranged to drain only the alveolar wall interstitium, this route for edema removal is not significant for most interstitial edema. Some fluid from the loose peribronchovascular interstitium may drain directly into the bloodstream by crossing the walls of blood vessels in the lungs. Edema may also drain into the pleural space.

Pleural effusions are more common in increased pressure pulmonary edema (25%–50% of patients; if unilateral, usually on the right). However, pleural effusions occur in ARDS as well (35% of patients). As much as 25% to 30% of edema fluid may leave the lungs through the pleural space. A significant portion of interstitial

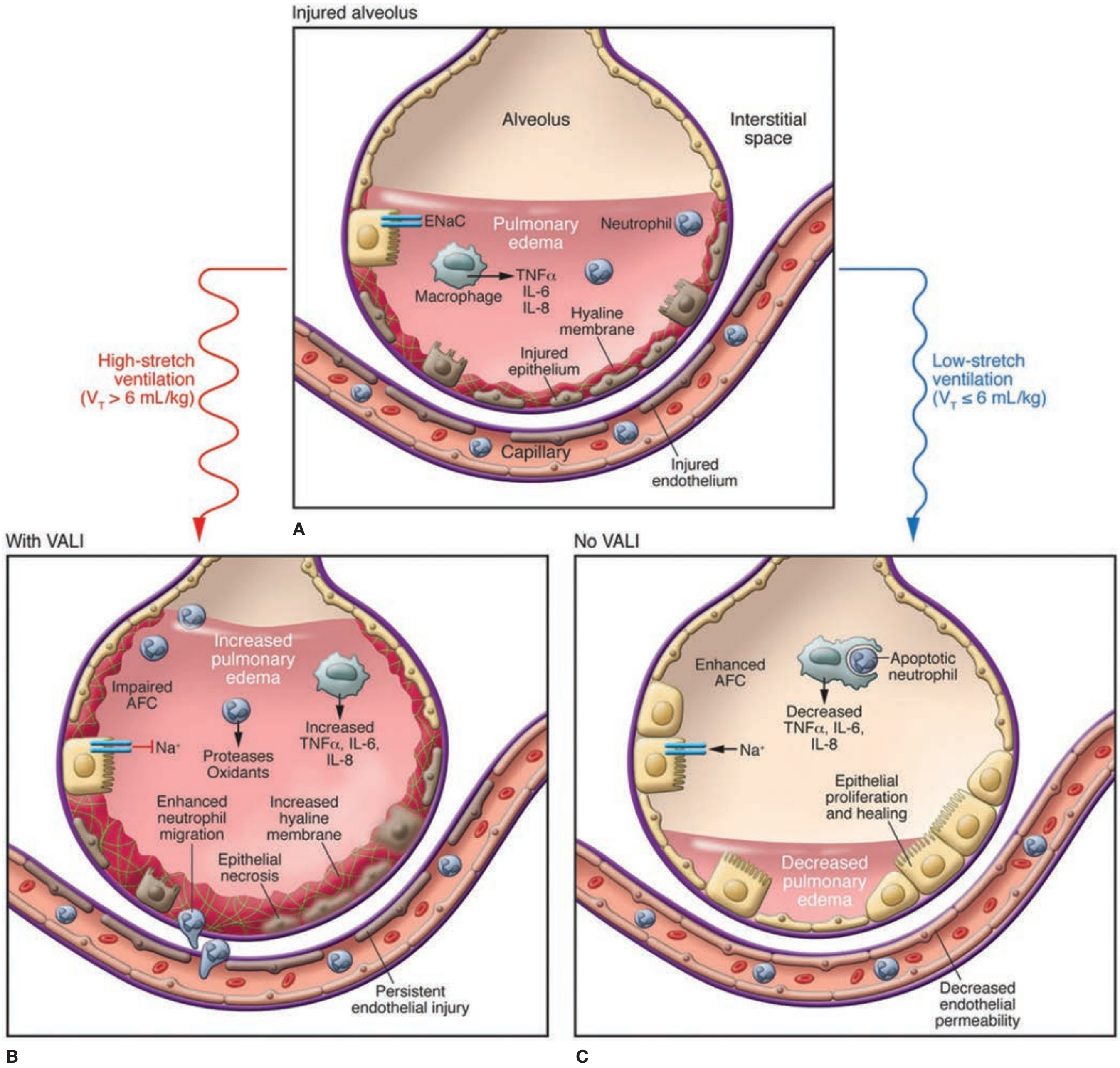
Injured alveolus
Alveolus
Interstitial space
ENaC
Pulmonary edema
Neutrophil
Macrophage
TNFα
IL-6
IL-8
Hyaline membrane
Injured epithelium
Capillary
Injured endothelium
A
High-stretch ventilation (V$_T$ > 6 mL/kg)
Low-stretch ventilation (V$_T$ ≤ 6 mL/kg)
With VALI
Increased pulmonary edema
Impaired AFC
Na$^+$
Proteases
Oxidants
Increased TNFα, IL-6, IL-8
Enhanced neutrophil migration
Increased hyaline membrane
Epithelial necrosis
Persistent endothelial injury
B
No VALI
Enhanced AFC
Apoptotic neutrophil
Decreased TNFα, IL-6, IL-8
Na$^+$
Epithelial proliferation and healing
Decreased pulmonary edema
Decreased endothelial permeability
C

FIGURE 140-3 Mechanisms of ventilator-associated lung injury (VALI). **A**. Acute lung injury leads to lung endothelial and epithelial injury, increased permeability of the alveolar-capillary barrier, flooding of the airspace with protein-rich pulmonary edema fluid, activation of alveolar macrophages with release of proinflammatory chemokines and cytokines, neutrophil margination and activation, and fibrin deposition (hyaline membranes). **B**. If the injured lung is ventilated with high tidal volumes and high inflation pressures (high-stretch ventilation), then lung injury is exacerbated, with increased lung endothelial and epithelial injury and/or necrosis, enhanced neutrophil margination, release of injurious neutrophil products such as proteases and oxidants, increased release of proinflammatory cytokines from alveolar macrophages and the lung epithelium, increased fibrin deposition, and increased hyaline membrane formation. Injurious mechanical ventilation can also impair alveolar fluid clearance (AFC) mechanisms. **C**. In contrast, a protective ventilatory strategy (low-stretch ventilation) can limit further lung endothelial and epithelial injury, reduce the release of proinflammatory cytokines, and enhance AFC through the active transport of sodium and chloride across the alveolar epithelium, thereby reducing the quantity of pulmonary edema and allowing endothelial and epithelial repair to occur. Epithelial repair occurs through migration, proliferation, and differentiation of alveolar epithelial type II cells to repopulate the denuded basement membrane. *(Reproduced with permission from Matthay MA, Ware LB, Zimmerman GA. The acute respiratory distress syndrome. J Clin Invest. 2012;122(8):2731–2740.)*

edema probably follows the prevailing pressure gradient in the lungs to drain into the mediastinum, where it may be picked up by the lymphatics.

Short-term alveolar protein clearance appears to proceed primarily by paracellular diffusion. The process depends on the size of the proteins. Most proteins are cleared intact, rather than as degraded, smaller fragments. However, a few specific proteins (e.g., vasoactive intestinal peptide and gastrin) are degraded before being cleared.

Finally, the general consensus is that transcytosis (transport via vesicles) is not a major mechanism for clearing bulk quantities of albumin or other proteins from the alveolar space. Over the long term, phagocytosis and catabolism by macrophages account for most protein clearance from the alveolar spaces. All insoluble, precipitated proteins are removed in this way. Macrophages are also ultimately responsible for removing senescent and dead neutrophils and other debris. The presence of a small, ciliated surface area of the distal airspaces suggests that the mucociliary route accounts for only a minor fraction of alveolar protein clearance. Complete clearance of alveolar protein from pulmonary edema by any route is slow.

AFC appears to be clinically important. In a study of 116 patients with ARDS, the rate of AFC in patients with shock was significantly slower than in those without shock. AFC also decreased significantly as the number of vasopressors required increased. The findings suggest that vasopressor use may be a marker for impaired alveolar epithelial barrier integrity in patients with ARDS and shock.[62]

E-CIGARETTE AND VAPING-ASSOCIATED LUNG INJURY

Early in 2020, the CDC reported 2558 cases in the United States of patients hospitalized due to e-cigarette and vaping associated lung injury (EVALI), along with 60 fatalities. All of these cases of acute lung injury in young adults had one common finding: use of electronic cigarette products.[63]

The diagnosis of EVALI requires reported use of e-cigarette or vaping products within 3 months of symptom onset, compatible chest imaging findings, and an evaluation that excludes infectious etiologies. Although the etiologic agents initially were unclear, as cases mounted, tetrahydrocannabinol (THC) products in electronic devices were implicated, including many from black market sources. Furthermore, discovery that vitamin E acetate (VEA) is used in the extraction of THC liquid, and is an additive in THC-containing products, led to further research of this substance as the primary causative agent. The largest study of 82 patients that incorporated use of bronchoalveolar lavage (BAL) showed that 94% had VEA in the BAL fluid compared to none in healthy controls.[64]

Finally, a study in laboratory mice using cell cultures demonstrated that aerosolized VEA causes dose-dependent pulmonary edema, increased alveolar–capillary barrier permeability to protein, and a bronchiolocentric pattern of inflammation, including lipid-laden and multinucleated macrophages. The investigators also showed that VEA aerosol causes direct injury to alveolar type II cells, including secretion of inflammatory cytokines.[65]

SARS-COV2 ARDS

The SARS-CoV2 pandemic has accelerated ARDS research, providing insight into COVID-19–related lung injury. A large, systematic, multicenter study has demonstrated that patients with COVID-19–related ARDS have lung morphology and respiratory mechanics that largely match those of classic ARDS.[66] In both types of ARDS, there is marked upregulation of proinflammatory biomarkers, an increase in capillary endothelial permeability, and an increase in inflammatory cells (neutrophils, monocytes/macrophages) in the vascular and alveolar compartments.[67] Furthermore, previously identified hyperinflammatory and hypoinflammatory phenotypes have been prospectively validated in COVID-19–related ARDS.[68] However, significantly fewer hyperinflammatory phenotypes have been identified than in other etiologies of ARDS. This is surprising, given that the term *cytokine storm* is often used to describe COVID-19–related ARDS. While many authors have used the term in describing the hyperinflammatory response in COVID-19, median IL-6 levels in patients with the hyperinflammatory phenotype of non–COVID-related ARDS are 10- to 200-fold higher than levels in patients with severe COVID-19.[69] These studies demonstrate that COVID-19–related ARDS is a heterogenous entity that is similar to ARDS due to other etiologies, including both epithelial and endothelial damage. Treatment should follow evidence-based guidelines.[70]

Immunophenotyping of neutrophils, lymphocytes, and monocytes has demonstrated that in BAL the neutrophil-to-lymphocyte ratio, especially in the context of a reduction in CD8+ T cells, is a marker of COVID-19–related disease severity. Interferons play an important role in early host defense, and several studies suggest impaired interferon response in some patients with COVID-19–related injury who develop severe disease.[71]

Relative to milder forms of COVID-19–related ARDS, significant alterations in severe COVID-19–related ARDS include (1) a higher SARS-CoV-2 viral load in both the upper airways (nasal lumen) and in the circulation, (2) a higher neutrophil count and activity (i.e., neutrophil extracellular trap [NET] formation), (3) an increase in inflammatory biomarkers and thrombosis, (4) greater monocyte HLA-DR expression and lymphocyte activation (CD8+ T cell CD38 expression), and (5) more damage to the alveolar–interstitial–capillary unit. Neutrophils produce NETS through a cell death process called NETosis. Extracellular chromatin and histones are released upon stimulation from pathogens, such as viruses. NETS trap and kill pathogens, but upon dysregulation, they may lead to tissue damage and thrombosis.[72]

Vascular injury and thromboses of pulmonary capillaries, as well as small and even larger pulmonary vessels, are more common COVID-19–related ARDS.[73] Additionally, evidence has arisen that patients with severe COVID-19–related ARDS have higher pulmonary dead space, decreased lung perfusion, and elevated D-dimer levels.[74] Several candidate pathways may account for lung and systemic vascular injury, including neutrophil extracellular traps and hyperfibrinolysis that contributes to the elevated D-dimer levels. A pathologic study comparing COVID-19–related ARDS with other causes of ARDS demonstrated nine times more alveolar capillary thrombi in COVID-19–related cases than in historic autopsies from patients with influenza-induced ARDS.

Treatment for COVID-19–related ARDS (Chapter 141) should follow well-established, evidence-based guidelines. While use of steroids in the treatment of ARDS has been controversial for the past four decades, the large UK RECOVERY trial showed a mortality benefit of dexamethasone in hospitalized patients with COVID-19 who require supplemental oxygen or mechanical ventilation.[75] Although there are still many open questions about trial design,[76] these findings support those in another recent non-COVID trial. In a Spanish, open-label, randomized, multicenter trial of 277 patients with moderate to severe non–COVID-19–related ARDS, a 15% absolute reduction in 60-day mortality (36% to 21%; $p = 0.0047$) in dexamethasone-treated patients was observed.[77]

Finally, ongoing trials are addressing use of monoclonal antibodies, low-dose versus full-dose anticoagulation, and mesenchymal stem cells.

CONCLUSIONS

Among the major advances in respiratory medicine and physiology over the last three decades has been the acquisition of important new knowledge on the physiology of fluid, solute, and protein transport in healthy and diseased lungs. Pulmonary edema, defined as the abnormal accumulation of extravascular lung fluid, is a pathologic state that occurs when fluid is filtered into the lungs faster than it can be removed.

The many causes of pulmonary edema are grouped into two main pathophysiologic categories: (1) increased pressure edema, which results from an increase in hydrostatic or protein osmotic forces (or both) that act across the barriers that normally restrict movement of fluid and solutes in the lungs; and (2) increased permeability edema, which is seen in ARDS, and in which a breakdown of the normal barrier properties of lung endothelium or epithelium develops. Although these two different types of pulmonary edema share many features, usually they can be distinguished by careful clinical, radiologic, and physiologic evaluation. They also differ in treatment and prognosis.

Major advances in the treatment of ARDS have occurred because of the successful application of lung protective ventilatory strategies early in the course of the illness (Table 140-1). Use of a low tidal volume (6 mL/kg of ideal body weight), coupled with a plateau pressure limit (<30 cm H_2O) has resulted in the first therapy demonstrated to reduce mortality in patients with ARDS.[46]

Another major advance in the treatment of ARDS was triggered by findings from the Fluid and Catheter Treatment Trial (FACTT), a large randomized trial comparing liberal and conservative fluid management strategies in affected patients.[10] A marked difference in outcome was reported, with patients in the conservative fluid management arm having 2.5 more ventilator-free days (and improved physiology) than those in the liberal fluid management arm. In addition, although not statistically significant, a 2.9% reduction in the 60-day mortality rate was noted in the conservative fluid management arm. Patients were also randomized to receive either a pulmonary arterial catheter or a central venous catheter for monitoring and fluid management. No differences were noted in clinical outcomes between the two groups.[77]

New insights into the pathogenesis of ARDS suggest that other therapies may also prove efficacious in reducing mortality in this common form of severe acute respiratory failure. A major development has been the ability to conduct large, prospective, randomized clinical trials (e.g., those sponsored by the National Heart, Lung, and Blood Institute) to test a variety of therapies important in supportive patient care, including use of mechanical ventilation, intravenous fluids, and a variety of pharmacologic agents.

Interest exists in the possibility that cell-based therapy using bone marrow–derived mesenchymal stem cells may be effective for more severe ARDS.[4,78] Such trials have led to a better understanding of the pathogenesis of human ARDS and have confirmed the importance of VILI. In addition, ancillary pathogenetic studies carried out on biologic samples from clinical trials have advanced our understanding of underlying mechanisms, especially leading to a new era potentially to subphenotype ARDS patients based on plasma biologic markers and selected clinical data. In the future, clinical studies will be needed to test new therapeutic strategies suggested by basic investigation conducted in animal models of ALI, including efforts to treat patients at an early phase of acute respiratory failure, prior to the need for positive pressure ventilation.[4,79]

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CHAPTER 141

Acute Respiratory Distress Syndrome: Clinical Features, Management, and Outcomes

John P. Reilly
Jason D. Christie

DESCRIPTION AND DEFINITIONS

In 1967, Ashbaugh et al.[1] described a syndrome characterized by the acute onset of dyspnea, severe hypoxemia, diffuse lung infiltrates, and decreased respiratory system compliance in the absence of evidence for congestive heart failure (CHF). The syndrome, initially called acute respiratory distress in adults (to contrast it with acute respiratory distress in neonates), is now known as the acute respiratory distress syndrome (ARDS). Following the initial report, other authors utilized various definitions that incorporated elements related to time of onset, presence of hypoxemia and radiographic infiltrates, and absence of overt CHF.

In 1988, Murray and others introduced the Lung Injury Score (LIS), an assessment tool for ARDS that reflects the extent of radiographic infiltrates, severity of hypoxemia and reduced respiratory system compliance, and level of positive end-expiratory pressure (PEEP) used in mechanically ventilating affected patients.[2] The LIS incorporates four parameters that are graded on a scale of 0 to 4: (1) ratio of Pa_{O_2} to FI_{O_2} (Pa_{O_2}/FI_{O_2}); (2) total respiratory compliance; (3) level of PEEP; and (4) extent of radiographic infiltrates (assessed by noting the number of quadrants in the chest radiograph demonstrating infiltrates). The LIS equals the sum of the scores for the four variables divided by 4. In clinical studies, a score of 2.5 or more was generally used as a threshold for severe disease.

Consensus Definitions of Acute Lung Injury and ARDS

Prior to 1994, published studies used nonuniform definitions of ARDS, prompting an American European Consensus Conference (AECC) to develop standardized definitions for ARDS and acute lung injury (ALI)—a broader category that encompassed ARDS.[3] The AECC definitions included the acute onset of illness, bilateral chest radiographic infiltrates consistent with pulmonary edema, poor systemic oxygenation, and absence of evidence for left atrial hypertension (Table 141-1A). The syndrome was referred to as ALI when the ratio of Pa_{O_2} to FI_{O_2} (Pa_{O_2}/FI_{O_2}) was ≤ 300, and ARDS when the ratio was ≤ 200. The AECC definitions of ALI and ARDS were intentionally broad in order to encompass different types of acute hypoxemic respiratory failure occurring in a wide variety of settings.

Development of the Berlin Definition of ARDS

The standardization of definitions of ALI and ARDS led to significant advances in the understanding of the syndrome and allowed researchers and clinicians to communicate findings using common criteria. The AECC definitions were widely used in clinical trials, including those that demonstrated therapeutic benefit.[4,5] In addition, they added important validity to the definition, allowing clinicians to generalize trial results to clinical decisions involving their own patients. Despite this standardization, few data were available to support the reliability and validity of ARDS definitions. In fact, several components of the AECC definition have been recognized as problematic: (1) Acute onset is not defined within a specific time frame. (2) The chest radiograph is subject to variability in interpretation.[6,7] (3) Pa_{O_2}/FI_{O_2} may vary according to ventilator parameters, for example, PEEP, and at extremes of FI_{O_2}. (4) Accuracy in excluding the presence of heart failure may be influenced by measurement methodology and timing, as discussed below.[8]

Given these limitations, an international expert panel was convened in Berlin in 2012 to revise the definition of ARDS. The resultant "Berlin definition" of ARDS addresses ambiguities in the prior AECC definition. The authors of the Berlin definition also applied proposed criteria for the syndrome to existing databases of patients with ARDS to specifically address the predictive validity of a new ARDS definition.[9] According to the Berlin definition, ARDS is defined as a syndrome characterized by (1) onset within 1 week of a known clinical insult, (2) bilateral radiographic opacities not fully explained by pleural effusions, atelectasis, or nodules, (3) respiratory failure not fully explained by cardiac failure or fluid overload, and (4) poor systemic oxygenation, with a $Pa_{O_2}/FI_{O_2} \leq 300$ and a PEEP or CPAP ≥ 5 cm H_2O. The definition also categorizes syndrome severity as mild, moderate, or severe, based on Pa_{O_2}/FI_{O_2}. According to the Berlin definition, patients who previously were diagnosed with ALI, but not ARDS (i.e., $Pa_{O_2}/FI_{O_2} \leq 300$, but >200), are referred to as having mild ARDS, with ALI now an obsolete term. Moderate ARDS is defined as $Pa_{O_2}/FI_{O_2} \leq 200$, but >100, and severe ARDS is defined as $Pa_{O_2}/FI_{O_2} \leq 100$ (Table 141-1B).

While the Berlin definition leaves the AECC definition of ARDS largely unchanged, the new definition addresses several specific ambiguities of the prior diagnostic criteria. First, the definition

TABLE 141-1A American European Consensus Conference Criteria for Acute Lung Injury (ALI) and the Acute Respiratory Distress Syndrome (ARDS)

Clinical Variable	Acute Lung Injury	Acute Respiratory Distress Syndrome
Onset	Acute	Acute
Hypoxemia	$Pa_{O_2}/FI_{O_2} \leq 300$ mm Hg	$Pa_{O_2}/FI_{O_2} \leq 200$ mm Hg
Chest radiograph	Bilateral infiltrates consistent with pulmonary edema	Bilateral infiltrates consistent with pulmonary edema
Noncardiac etiology	No clinical evidence of left atrial hypertension or, if measured, pulmonary artery wedge pressure ≤ 18 mm Hg	No clinical evidence of left atrial hypertension or, if measured, pulmonary artery wedge pressure ≤ 18 mm Hg

Adapted with permission from Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference of ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med. 1994;149(3 Pt 1):818–824.

TABLE 141-1B Berlin Definition of Mild, Moderate, and Severe Acute Respiratory Distress Syndrome (ARDS)

Clinical Variable	Mild ARDS	Moderate ARDS	Severe ARDS
Onset	Onset within 1 week of clinical insult known to result in ARDS		
Hypoxemia	$Pa_{O_2}/FI_{O_2} \leq 300$ mm Hg PEEP or CPAP ≥ 5 cm H_2O	$Pa_{O_2}/FI_{O_2} \leq 200$ mm Hg PEEP ≥ 5 cm H_2O	$Pa_{O_2}/FI_{O_2} \leq 100$ mm Hg PEEP ≥ 5 cm H_2O
Chest radiograph	Bilateral opacities, not explained by effusions, atelectasis, or nodules		
Noncardiac etiology	Respiratory failure, not fully explained by cardiogenic pulmonary edema; exclude hydrostatic edema if no clinical risk factor present		

Data from ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA. 2012;307(23):2526–2533.

defines “acute onset” and attempts to clarify chest radiograph criteria. In addition, the Pa_{O_2}/FI_{O_2} criterion is influenced by the level of PEEP and other transient factors, including the presence or absence of airway secretions or inadequate sedation. Increasing PEEP generally increases Pa_{O_2} at a given FI_{O_2}. The consequent increase in Pa_{O_2}/FI_{O_2} may result in a value that no longer meets criteria for ARDS. Conversely, without any PEEP, values of $Pa_{O_2}/FI_{O_2} < 300$ may reflect simple atelectasis, rather than ARDS. Adding PEEP may recruit sufficient atelectatic lung to raise $Pa_{O_2}/FI_{O_2} > 300$, thereby excluding such patients from meeting this criterion for ARDS. The Berlin definition addresses this concern directly by requiring a minimum level of PEEP when a determination of Pa_{O_2}/FI_{O_2} ratio is made.

Finally, given the declining use of pulmonary artery catheters (PACs),[10] potential inaccuracies of pulmonary artery occlusion pressure (PAOP) measurements, and the now recognized possibility of concomitant hydrostatic edema and ARDS, the Berlin definition no longer specifies PAOP requirements.[11,12] PAOP in ARDS may be higher than 18 mm Hg due to intravascular volume loading. Conversely, some patients with pulmonary edema due to CHF and high left atrial pressures have a normal PAOP by the time the catheter is inserted and PAOP is measured. The Berlin definition specifies that the respiratory failure of ARDS is not fully explained by cardiac failure or fluid overload and requires objective assessment to exclude hydrostatic edema (e.g., an echocardiogram) if no risk factor for ARDS is present.

The predictive validity of the Berlin ARDS definition was assessed in several large cohorts of patients with ALI, as defined by AECC. Compared with the AECC definition, the Berlin definition had marginally better predictive validity for mortality. The identified categories of mild, moderate, and severe ARDS corresponded with progressive increases in mortality. Proposed ancillary variables in the definition of severe ARDS, including a chest radiograph with three or four quadrants demonstrating opacities, PEEP ≥ 10 cm H_2O, and either a respiratory system static compliance ≤ 40 mL/cm H_2O or a corrected expired volume per minute of at least 10 L/min did not improve the predictive validity of the definition of severe ARDS. Therefore, the final definition did not include any of these ancillary variables.

While the Berlin definition has been accepted by major professional organizations, it is important to note that many of the studies referred to in this chapter were performed prior to its development and, therefore, utilize the older AECC definition of ALI and ARDS. Additionally, problems remain in consistently identifying ARDS including interobserver variability in chest radiograph interpretation and continued challenges in distinguishing cardiogenic from noncardiogenic edema.[13,14] The Berlin criteria are also difficult to use in resource-limited settings, potentially resulting in ARDS under recognition in much of the world. The proposed Kigali modification of the Berlin criteria attempts to overcome this limitation by allowing for ARDS to be diagnosed in the absence of chest radiography, mechanical ventilation, and/or blood gas measurements.[15] Further refinements in the reliability and validity of definitions of ARDS constitute important future directions for clinical studies, and may potentially be improved by the integration of new technologies, such as lung ultrasound or measurements of extravascular lung water,[16,17] as well as molecular markers reflecting the underlying biology of ARDS.[18] In addition, attempts at understanding the heterogeneity underlying the syndrome may allow for identification of ARDS subgroups with potential diverse risk factors and pathogenesis. More reliable definitions will not only improve estimates of the public health impact of these syndromes, but also will decrease misclassification errors, which can be especially problematic for research aimed at clarifying underlying mechanisms.

EPIDEMIOLOGY

Over the last several decades, the epidemiology of ARDS has become more clearly delineated.

■ Incidence and Mortality Rate

A landmark epidemiologic study of the incidence of ARDS in the United States between 1999 and 2000—the King County Lung Injury Project (conducted in King County, Washington)—represents the first broad, population-based epidemiologic study of ARDS in the United States using the standardized AECC definitions.[19] Study results included an estimated incidence of ARDS based on a $Pa_{O_2}/FI_{O_2} \leq 300$ of 78.9 per 100,000 person-years and an age-adjusted incidence of 86.2 per 100,000 person-years. The incidence of what is now called moderate or severe ARDS was estimated as 58.7 per 100,000 person-years, with an age-adjusted incidence of 64.0 per 100,000 person-years. The incidence of ARDS increased dramatically with age, with an incidence of 306 per 100,000 person-years for ages 75 through 84 years. By extrapolation, an estimated 190,600 cases of ARDS occur each year in the United States (Table 141-2).

Although prior estimates of the incidence of ARDS had been lower, the studies were limited by incomplete and nonvalidated data, inaccuracies in the definition of the syndrome, and use of administrative coding.[19–25] Thus, the estimates from King County Lung Injury Project serve as the best indicator of the public health impact of ARDS in the United States. Additionally, the incidence of ARDS over time may be decreasing. In a retrospective cohort study of all patients admitted to the ICU at the Mayo Clinic from 2001 to 2008, the incidence of ARDS declined significantly during the period of observation.[26] Since the Mayo Clinic provides all ICU-level care to the population of Olmsted County, Minnesota, the authors could estimate the incidence trends of ARDS over time. The age and sex

TABLE 141-2 Estimated Incidence, Hospital Days and Intensive Care Unit (ICU) Days for Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS) in the United States Based on American European Consensus Criteria for ALI and ARDS

Variable	ALI	ARDS
Crude incidence, per 100,000 person-years	78.9	58.7
Age-adjusted incidence, per 100,000 person-years	86.2	64.0
Estimated annual number of cases in United States	190,600	141,500
Estimated annual number of hospital days in United States	3,622,00	2,746,000
Estimated annual number of days in ICU in United States	2,154,000	1,642,000

Reproduced with permission from Rubenfeld GD, Caldwell E, Peabody E, et al. Incidence and outcomes of acute lung injury. N Engl J Med. 2005;353(16):1685–1693.

adjusted incidence of moderate and severe ARDS ($\text{Pa}_{\text{O}_2}/\text{FI}_{\text{O}_2} \leq 200$) declined from 81 cases per 100,000 person-years in 2001 to 38.3 cases per 100,000 person years in 2008. This trend appeared to be driven by declining hospital-acquired ARDS, perhaps the result of improvements is overall ICU care and the increasing use of lower tidal volume ventilation (see "Approach to Treatment," below).

Previous reports of ARDS epidemiology utilized the AECC definition of ARDS and largely focused on a single country or region until the publication of The Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG SAFE).[27] The LUNG SAFE study was a multicenter, prospective cohort study of patients undergoing invasive and noninvasive ventilation conducted over 4 consecutive weeks of 2014 in 459 ICUs from 50 countries across 5 continents. The authors aimed to determine the ICU incidence of ARDS according to the Berlin definition, as well as, clinician recognition of ARDS and application of specific interventions. ARDS occurred in 10.4% of all ICU admissions and 23.4% of all patients requiring mechanical ventilation. The authors were unable to calculate the population incidence of ARDS because they could not estimate the population served by ICUs included in the study. The LUNG SAFE study also provided evidence that ARDS is under recognized as only 60% of ARDS cases identified by research were documented by treating clinicians.

During the time of observation in the King County Lung Injury Project study, the mortality from ARDS was 38.5%, translating into an estimated 74,500 annual deaths from ARDS in the United States.[19] Despite being conducted over a decade later, the LUNG SAFE study reported a similar hospital mortality of 40.0%.[27] Reported mortality estimates have ranged from 26% to 58%.[24–30] To put these figures into perspective, more people die annually with ARDS than from AIDS, asthma, and breast cancer combined.[31] Other than lung cancer, ARDS leads to more annual deaths than any type of cancer, including lymphoma, leukemia, and breast, prostate, colon, ovarian, and pancreatic cancers (Table 141-3). The most common causes of death among patients with ARDS arise from the underlying insult or subsequent nosocomial pneumonia and sepsis.[32,33] Only rarely do patients die from progressive hypoxia and respiratory failure.

TABLE 141-3 Estimated Annual Number of Deaths in the United States from Selected Causes

Cause	Number of Deaths
ARDS	59,000
Asthma	3311
HIV/AIDS	7638
Breast cancer	41,271
Leukemia	22,982
Lung cancer	156,614
Lymphoma	21,393
Ovarian cancer	14,312
Pancreatic cancer	37,371
Prostate cancer	27,929

Data for ARDS from Rubenfeld GD, Caldwell E, Peabody E, et al. Incidence and outcomes of acute lung injury. N Engl J Med. 2005;353(16):1685–1693; all other are from CDC National Center for Health Statistics estimated number of deaths in 2011.

Several studies have suggested that ARDS mortality has decreased over time.[33–36] In one hospital using the same definition of ARDS throughout the period analyzed, the mortality rate was 68% in 1982, 29% in 1996, and in the mid-30% range in 1997 and 1998.[32] Obviously, the decrease cannot be ascribed to widespread application of low tidal volume ventilation strategies, since the decline was observed prior to publication of the study reporting the value of using a "low stretch" ventilator protocol in 2000.[4] The improvement is likely attributable to enhancements in general ICU care, including prevention of nosocomial pneumonias and other infections, earlier institution of enteral nutrition, routine use of stress ulcer prophylaxis, and improved teamwork in the ICU.

Interestingly, the case fatality rate for patients with ARDS due to sepsis remained the same over the same time frame noted earlier, while that for patients with ARDS due to trauma or other causes decreased significantly. Mortality rates among subjects enrolled in ARDS Network trials[4,37–40] appear to have decreased from 35% (1996–1997) to 26% (2004–2005).[34,41] These findings were robust in adjusting for covariates, including severity of illness and use of low tidal volume ventilation. However, these rates were obtained from clinical trials in specialized centers, excluding large numbers of patients with high-risk comorbidities. Recent systematic reviews of clinical trials and more inclusive prospective cohort studies have drawn opposing conclusions.[35,42] Also, the previously noted study from the Mayo Clinic demonstrated a reduction in ARDS incidence, but it failed to show a change in mortality.[26] While it is unclear whether or not survival from ARDS is improving, the mortality rate remains unacceptably high and represents a major public health problem. Furthermore, as the population of the United States becomes older, the incidence of those at risk for ARDS and ARDS-related death can be expected to rise.

■ Precipitating Causes

The severe, extensive lung inflammation characteristic of ARDS represents the common final pathogenic process in response to a large variety of precipitating causes,[43–46] resulting in either direct or indirect (systemic) lung injury.[47,48] In general, *direct* causes of ARDS include those that originate within the lung, such as aspiration of gastric contents or viral pneumonia. Examples of *indirect* causes include sepsis, ingested toxins, hypotension, and ischemia–reperfusion injury. Although some causes of ARDS may fit into either

TABLE 141-4 Common Direct and Indirect (Systemic) Precipitating Causes of ARDS

Direct Precipitating Causes	Indirect (Systemic) Precipitating Causes[a]
Aspiration of gastric fluids	Acute pancreatitis
Bacterial pneumonia (diffuse), e.g., Legionnaires' disease	Blood transfusions with transfusion-related acute lung injury (TRALI)
Chest trauma with lung contusion	Post–cardiopulmonary bypass
Near drowning	Primary graft failure of lung transplantation
Pneumonia due to *Pneumocystis carinii*	Severe sepsis and septic shock
Toxic inhalations, e.g., smoke inhalation, inhaled crack cocaine	Toxic ingestions, e.g., aspirin, tricyclic antidepressants
Viral pneumonia, e.g., influenza, severe acute respiratory syndrome (SARS)	Trauma with multiple fractures and the fat-emboli syndrome

[a] *In indirect or systemic mechanism of lung injury, the lung injury results from deleterious effects on the alveolar epithelium by inflammatory or other mediators delivered via the pulmonary circulation.*

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category (e.g., multilobar pneumonia with septic shock), this simple classification scheme is useful both for considering the many predisposing causes of ARDS and their varying mechanisms of lung injury and for future development of therapies aimed at different categories of ARDS. Table 141-4 lists precipitating causes of ARDS according to this construct.

■ Factors Influencing Risk of ARDS

Not all patients with an underlying cause of ARDS (e.g., sepsis) develop the syndrome. In addition to inherent risk differences within at-risk populations, specific clinical variables may be important.

Clinical variables found to be associated with an increased risk of ARDS include chronic alcohol abuse,[49] hypoproteinemia,[50] advanced age,[19] increased severity, and extent of injury or illness as measured by injury severity score (ISS) or APACHE score, transfusion of blood products,[45,51] cigarette smoking,[52,53] ABO histo-blood type A,[54,55] and ambient air pollution.[56,57] Diabetes mellitus and prehospitalization antiplatelet therapy appear to decrease the risk of ARDS.[58–60] The role of obesity in modifying ARDS risk is unclear, as excess soft tissue can render chest x-ray interpretation difficult; the potential role of obesity remains the subject of ongoing research. A higher body mass index has been associated with an increased incidence of ARDS; however, obesity has not been associated with a consistent change in mortality.[61–64] Since many studies of risk factors for ARDS have been retrospective or based on a single center's experience, the consistency and generalizability of identified risk factors have not been confirmed. Nonetheless, the mechanistic underpinnings and potential therapeutic implications of these probable associations are the subject of ongoing research.

In addition to clinical variables, several genetic variants have also been reported to influence ARDS risk.[65] Despite requiring a significant environmental insult such as sepsis or pneumonia, genetic heterogeneity resulting from evolutionary pressures likely contribute to the risk of developing ARDS. Initial studies based on a candidate gene approach identified functional variation in the gene encoding angiotensin-converting enzyme (*ACE*) and the surfactant protein B (*SFTPB*) gene, among many others, associated with ARDS risk.[66,67] More recently, larger scale genome-wide or near genome-wide approaches have identified variation in genes including *ANGPT2*, *PPFIA1*, *SELPLG*, and *FLT1* as associated with ARDS risk.[68–71] While many of the identified variants require further replication, the potential for genetics to impact our understanding and treatment of ARDS remains.

■ Factors Influencing Mortality from ARDS

Clinical variables at the onset of ARDS that are associated with increased mortality include advanced age, lower $\text{Pa}_{\text{O}_2}/\text{FI}_{\text{O}_2}$, high plateau pressure (i.e., low respiratory system compliance),[72] greater extent of pulmonary infiltrates, sepsis, chronic liver disease, nonpulmonary organ dysfunction, increased global severity of illness, hypoproteinemia, and greater length of hospitalization prior to onset of ARDS.[19,50,72–77] In addition, an increased dead-space fraction has been identified as a risk factor for increased mortality, possibly indicating the importance of early loss of the pulmonary vascular bed as a sign of greater disease severity.[78,79] Although various precipitating causes of ARDS carry somewhat different prognoses, the strategy of low tidal volume ventilation utilized by the National Institutes of Health (NIH), National Heart, Lung, and Blood Institute (NHLBI)–sponsored ARDS Clinical Trials Network (ARDSNet) as part of its clinical trials appears to be equally efficacious in all subgroups.[4]

■ Predicting ARDS

Using the identified precipitating causes and modifying risk factors, investigators developed and validated a lung injury prediction score (LIPS) aimed at identifying those at highest risk of developing ARDS early.[80,81] The LIPS was developed in a multicenter cohort of 5584 hospitalized patients at risk for ARDS, among whom 7% eventually developed the syndrome. The LIPS is generated from the sum of points assigned for each of 6 predisposing conditions (shock, aspiration, sepsis, pneumonia, high-risk surgery, and high-risk trauma) and 9 risk modifiers (alcohol abuse, obesity, hypoalbuminemia, chemotherapy, need for oxygen, tachypnea, hypoxia, academia, and diabetes mellitus). The negative predictive value for a score <4 was 97%, while the sensitivity and specificity for ARDS of a score >4 were 69% and 78%, respectively. While not perfect, the LIPS allows for the identification of a higher-risk population and may prove useful for studies of preventative interventions. The LIPS-A study of aspirin to prevent ARDS utilized the LIPS to enroll patients at high risk of developing ARDS.[82] Although aspirin showed no benefit, the LIPS-A trial demonstrated the potential usefulness of an ARDS prediction tool and the goal to shift the syndrome's treatment paradigm to strategies aimed at prevention and treatment at the earliest phases of development.

■ ARDS Heterogeneity and Subtypes

The current clinical definition of ARDS is intentionally broad and encompasses patients with a marked degree of clinical, radiographic, pathologic, and biologic heterogeneity.[83] This heterogeneity is hypothesized to explain the inability to successfully translate promising preclinical therapeutics to critically ill patients. Subtypes of ARDS with unique clinical and biological features, as well as potentially heterogeneous treatment responses have increasingly been reported in the literature. Traditionally, ARDS subtypes have been distinguished based on the precipitating risk factor (e.g., sepsis, trauma) and direct/pulmonary versus indirect/extrapulmonary ARDS.[75,84,85] Direct lung injury precipitated by insults including pneumonia, aspiration, and pulmonary contusion is characterized by more radiographic heterogeneity, lower lung compliance, and potentially less response to PEEP.[86–89] Conversely, indirect lung injury precipitated by insults including nonpulmonary sepsis, nonthoracic trauma, and transfusion is characterized by radiographic homogeneity, higher lung compliance, and a higher likelihood of PEEP responsiveness. Biologically, direct ARDS is associated with higher plasma concentrations of biomarkers of epithelial injury, while indirect ARDS is associated with higher plasma concentrations of biomarkers of endothelial injury.[90] Other researchers have reported clinical heterogeneity based on timing of ARDS onset, severity of ARDS, and radiographic features of ARDS.[91–93]

More recently, unbiased approaches to identify endotypes (i.e., subtypes based on biology) of ARDS have been employed. Specifically, latent class analysis was applied to clinical and plasma biomarker data and identified two unobserved (latent) endotypes of ARDS within a heterogeneous population of ARDS patients enrolled in several ARDS Network Trials.[94–97] The first endotype was characterized by a hyperinflammatory phenotype and was associated with a higher mortality and worse shock compared to a second endotype without a hyperinflammatory response. Importantly, clinical features alone could not predict endotype classification. The authors also reported heterogeneous treatment effects based on PEEP strategy, fluid strategy, and statin therapy in a post-hoc analysis of ARDS clinical trials. Other investigators have applied clustering analysis techniques to observational ARDS cohorts and again identified reactive/hyperinflamed and uninflamed endotypes.[98]

CLINICAL PRESENTATION AND DIAGNOSIS

The clinical presentation and diagnosis of ARDS are fundamentally related to the syndrome's pathophysiologic changes, regardless of the underlying etiology. A brief description of the pathology and pathophysiology is provided before a detailed discussion of clinical aspects of the disorder. The reader is also referred to Chapter 140 for additional details on disease mechanisms.

Pathology and Pathophysiology

A number of interrelated mechanisms contribute to the development and clinical course of ARDS. Inflammatory cytokines, oxygen radicals, activation of coagulation and complement, platelet and immune cell activation, generation of proteases, and abnormal fluid fluxes resulting in edema fluid generation and defective epithelial alveolar fluid clearance have all been hypothesized to play a role in the early stages.[99,100] In addition, factors specific to apoptosis, edema fluid resolution, and fibrosis and repair, as well as the response to mechanical ventilation are likely to play a role in the pathophysiology of the later phases of ARDS.

Pathologically and clinically, ARDS can be divided into *early* and *late phases* of lung injury (Fig. 141-1).[101–104] In the early phase (first few hours or days), light microscopy shows interstitial and alveolar edema, capillary congestion, and intra-alveolar hemorrhage with minimal evidence of cellular injury. Electron microscopy reveals changes of endothelial cell swelling, widening of intercellular junctions, increased numbers of pinocytotic vesicles, and disruption and denudation of the basement membrane. Inflammatory cell infiltration of the lung interstitium may also be seen. Protein-rich pulmonary edema and its clinical effects are most pronounced in the early exudative phase. Hyaline membranes containing condensed fibrin and plasma proteins form over the next several days. Later, in the exudative phase, inflammatory cells become more numerous within the lung interstitium, and extensive necrosis of type I alveolar epithelial cells is present. Pathologists refer to this constellation of findings as *diffuse alveolar damage* (DAD). While DAD is considered the pathologic correlate of the clinical syndrome ARDS, not all patients meeting the clinical criteria for ARDS have DAD on pathology.[105] In an autopsy study of 356 patients with ARDS, DAD was found in 45%, and was more common in patients with severe ARDS and patients who met clinical criteria for more than 72 h, demonstrating the pathologic heterogeneity of the clinical syndrome.

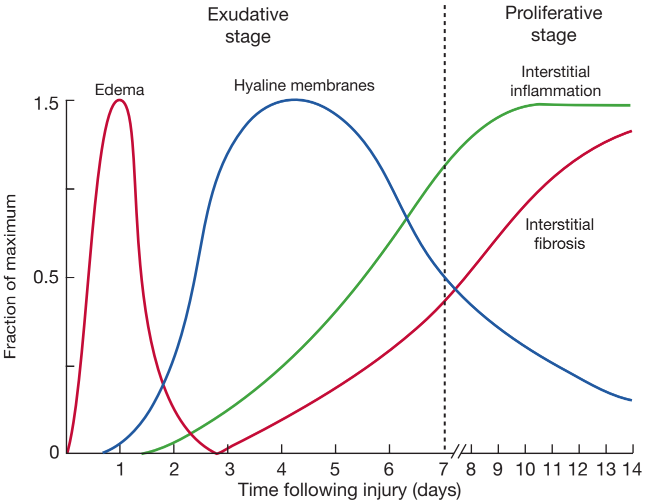

Figure 141-1 Schematic representation showing time course of evolution of the acute respiratory distress syndrome (ARDS). The early or exudative phase is characterized by a pulmonary capillary leak with interstitial and alveolar edema and hemorrhage followed by hyaline membrane formation. Within as short a period of time as 7 to 10 days, a proliferative phase may appear with marked interstitial and alveolar inflammation and cellular proliferation, followed by fibrosis and disordered healing (see text for discussion). *(Reproduced with permission from Katzenstein AA, Askin FB. Surgical Pathology of Non-Neoplastic Lung Diseases. 2nd ed. Philadelphia, PA: Saunders; 1990.)*

Pathophysiologically, in the exudative phase, alveolar edema and alveolar collapse, that is, atelectasis due to loss of normal surfactant-related stabilization of alveoli, interfere with oxygenation.[106,107] Surfactant is washed out of alveoli and inactivated by the alveolar edema. The hypoxemia in ARDS is typically resistant to supplemental oxygen, reflecting an increased right-to-left shunt (Fig. 141-2). Continued perfusion of alveoli that lack ventilation because of alveolar edema results in ventilation–perfusion ratios of zero, thereby defining physiologic shunt. Furthermore, the effects of this type of shunt are exacerbated by shunt-like contributions from alveoli with very low ventilation–perfusion ratios.

Disordered healing and proliferation of fibrous tissue dominate the late phase of ARDS or persistent ARDS, that is, the *proliferative or fibroproliferative* phase. Type II alveolar cells, fibroblasts, and myofibroblasts proliferate in this phase, which can occur as early as 7 to 10 days after initial injury. The late phase of ARDS is characterized by an increased dead-space fraction, high minute ventilation requirement, pulmonary hypertension, and further reduction in lung compliance.[108,109]

Clinical Presentation

The development of ARDS usually follows a rapid course, occurring most often within 12 to 72 h of the predisposing event.[45] At its onset, patients with ARDS often become anxious, agitated, and dyspneic. Inflammatory changes in the lung decrease lung compliance, which, in turn, leads to an increased work of breathing, small tidal volumes, and tachypnea. If breathing ambient air or low-flow supplementary oxygen, patients with ARDS typically have initial arterial blood gas results showing a Pa_{O_2} less than 50 to 55 mm Hg and pulse oximetry recordings of less than 85% arterial O_2 saturation. The hallmark of ARDS is hypoxemia that is resistant to oxygen therapy because

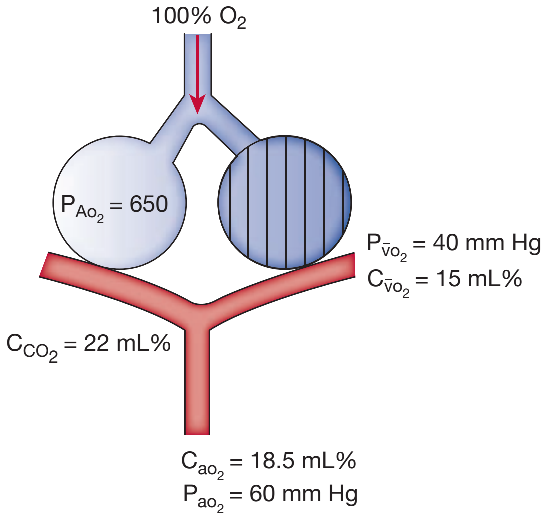

Figure 141-2 Diagram of a two-compartment model of lung perfusion and ventilation demonstrating basis for failure of oxygenation in ARDS. When large portions of the lung are nonventilated due to alveolar collapse or flooding (hatched area), blood flow to these units with mixed venous P_{O_2} ($P\bar{v}_{O_2}$) of 40 mm Hg and content of 15 vol. percent is effectively "shunted" through the lungs without being resaturated. Thus, despite a high concentration of supplemental oxygen (100% in this example) and high alveolar P_{O_2} in ventilated unit, these blood flows mix in accord with their oxygen contents, that is, the resulting left atrial blood has an oxygen content that is the weighted mean of the oxygen content of the shunted and nonshunted blood. In this example of a 50% shunt, the left atrial and systemic arteries have an arterial P_{O_2} of 60 mm Hg. Ca_{O_2}, arterial oxygen content; C_{CO_2}, capillary oxygen content; $C\bar{v}_{O_2}$, mixed venous oxygen content; PA, alveolar pressure; Pa_{O_2}, arterial P_{O_2}; $P\bar{v}_{O_2}$, partial pressure of oxygen in the mixed venous blood. *(Reproduced with permission from Hall JB, Schmidt GA, Wood LDH: Principles of Critical Care, 3rd ed. New York, NY: McGraw Hill; 2005.)*

of the large right-to-left shunt (Fig. 141-2). Initially, patients may be able to compensate by hyperventilating, thereby maintaining an acceptable Pa_{O_2} with an acute respiratory alkalosis. Typically, patients deteriorate over several hours, requiring endotracheal intubation and mechanical ventilation.

Differential Diagnosis

The differential diagnoses for acute hypoxemic respiratory failure, in general (Table 141-5), and for ARDS, in particular (Table 141-6), are extensive.[110,111] Identifying the specific etiology of the diffuse infiltrates in ARDS is important because several causes, for example, acute eosinophilic pneumonia or diffuse alveolar hemorrhage, have specific therapies. Table 141-6 lists the major clinical and diagnostic characteristics of these disorders.

The setting in which respiratory failure occurs usually provides important diagnostic information. ARDS commonly arise following development of a typical predisposing factor (Table 141-4). Sepsis, pneumonia, trauma, transfusion of blood products, and gastric aspiration account for the majority of cases.[44] When an inciting event is obvious and diagnostic criteria (Tables 141-1A and 141-1B) are met, establishment of a clinical diagnosis of ARDS is not difficult. Under such circumstances, management can be instituted immediately. However, in the absence of a clear predisposing event, or when conflicting or ambiguous information exists, the other causes listed in Table 141-6 should be considered, and relevant clues from the history and physical examination sought. For example, cardiogenic edema is most often accompanied by systolic left ventricular or valvular dysfunction, and the appropriate history and physical findings (e.g., a heart murmur or ventricular gallop) are often present. Electrocardiographic and laboratory-based evidence (e.g., serum troponin I levels) of cardiac ischemia suggest cardiogenic edema as a likely cause. Additional important tests that help to differentiate ARDS from other causes of acute hypoxemic respiratory failure are discussed subsequently.

TABLE 141-5 Differential Diagnosis of Acute Hypoxemic Respiratory Failure (AHRF)

1. ARDS
2. Acute cardiogenic pulmonary edema
3. Bilateral aspiration pneumonia
4. Lobar atelectasis
5. Acute loss of ventilation to one lung due to complete or near-complete obstruction of its mainstem bronchus, e.g., due to a mucus plug or blood clot
6. Loss of ventilation to one or both lungs due to large pneumothorax/pneumothoraces
7. Loss of ventilation to one or both lungs due to large pleural effusion(s)
8. Diffuse alveolar hemorrhage
9. Massive pulmonary embolus
10. Acute opening of a right to left intracardiac shunt resulting in shunting of venous blood to the arterial system without being oxygenated in the lung

ARDS, acute respiratory distress syndrome.

Approach to Clinical Diagnosis

A number of diagnostic methods are extremely valuable in evaluating suspected ARDS. Each is briefly described.

Chest Imaging

The chest radiograph is a simple and widely available test used to assess patients with acute hypoxic respiratory failure. In cases of *established* ARDS, the chest radiograph typically demonstrates findings of diffuse, bilateral alveolar infiltrates consistent with pulmonary edema (Fig. 141-3). However, especially early in the course of the disorder, the infiltrates associated with ARDS may be variable: mild or dense, interstitial or alveolar, patchy or confluent.[7] In addition, the radiographic infiltrates may not correlate well with the degree of hypoxemia. For example, a patient with early ARDS may have profound hypoxemia in the setting of patchy asymmetrical infiltrates that may be interpreted as pneumonia or segmental atelectasis.

Routine chest radiographs cannot reliably distinguish hydrostatic edema, that is, cardiogenic edema, from ARDS. Nonetheless, several criteria suggest *cardiogenic* edema: increased heart size, increased width of the vascular pedicle, vascular redistribution toward upper lobes, the presence of septal lines, or a perihilar (bat's wing) distribution of the edema.[112] Lack of these findings, in conjunction with patchy peripheral infiltrates that extend to the lateral lung margins, suggests ARDS. In the proper clinical setting, despite a variable radiographic appearance, the presence of bilateral infiltrates and moderate or severe hypoxemia ($Pa_{O_2}/FI_{O_2} \leq 300$ mm Hg) should raise the possibility of ARDS. Additionally, computed tomography (CT) scans of the chest tend to demonstrate widespread patchy or coalescent airspace opacities often more apparent in the dependent lung zones.[113] CT scans can augment chest radiograph to further diagnosis of underlying syndromes resulting in ARDS but are often

TABLE 141-6 Differential Diagnosis of ARDS

Disorder	Characteristics	Comments
Pulmonary edema due to left heart failure	History of cardiac disease, enlarged heart on chest radiograph, third heart sound.	Rapid improvement with diuresis and/or afterload reduction.
Noncardiogenic pulmonary edema	History of one or more precipitating causes (Table 141-4), crackles absent or not prominent, normal cardiac size on chest radiograph.	Usual etiology for ARDS. Rarely some patients with ARDS have no obvious precipitating cause.
DAH	Often associated with autoimmune diseases (e.g., vasculitis) or following bone marrow transplantation. Often patients do not have bloody sputum. Renal disease or other evidence of systemic vasculitis may be present. Hemosiderin-laden macrophages in bronchoalveolar lavage fluid can confirm diagnosis of DAH. May respond to apheresis, corticosteroids, or cyclophosphamide, depending on etiology.	May meet diagnostic criteria for ARDS (Tables 141-1A and 141-1B), but has different pathophysiology and management.
Acute eosinophilic pneumonia	Cough, fever, pleuritic chest pain, and myalgia are often present. Patients often do not have peripheral blood eosinophilia, but generally have >15% eosinophils in bronchoalveolar lavage fluid. Usually responds rapidly to high-dose corticosteroid therapy.	May meet diagnostic criteria for ARDS (Tables 141-1A and 141-1B), but has different pathophysiology and management.
Lupus pneumonitis	Usually associated with active lupus. May respond to high-dose corticosteroid therapy or cyclophosphamide.	May meet diagnostic criteria for ARDS, but has different pathophysiology and management.
AIP	Slower onset than ARDS (over 4–6 weeks) with progressive course. However it may present in advanced state, mimicking ARDS.	Associated with >90% mortality. AIP includes Hamman–Rich syndrome.
Pulmonary alveolar proteinosis (PAP)	Slower onset than ARDS (over 2–12 months) with progressive course. Can be treated with whole lung lavage.	Characteristic "crazy paving" pattern on high-resolution CT scan of chest.
Bronchiolitis obliterans with organizing pneumonia (BOOP) or cryptogenic organizing pneumonia	May be precipitated by viral syndrome. Slower onset than ARDS (over >2 weeks) with progressive course. However it may present in advanced state, mimicking ARDS. May respond to high-dose corticosteroid therapy.	
Hypersensitivity pneumonitis	Typically slower onset than ARDS (over weeks) with progressive course. However, it may present in advanced state, mimicking ARDS. May respond to high-dose corticosteroid therapy and removal from offending agent.	
Leukemic infiltration	May be rapid in onset during active disease states. Usually leukemia is clinically apparent.	
Drug-induced pulmonary edema and pneumonitis	May follow use of heroin, other opioids, overdose of aspirin, tricyclic antidepressants, or exposure to paraquat.	May progress to overt ARDS.
Acute major pulmonary embolus (PE)	Occurs acutely, occasionally accompanied by severe hypoxemia that may be resistant to O_2 therapy like ARDS, and by hypotension, requiring pressors, mimicking ARDS with sepsis. Patients typically have risk factors for acute PE and may not have common precipitating causes of ARDS.	Chest radiograph in ARDS should have bilateral infiltrates consistent with pulmonary edema. Chest radiograph in acute major PE may have unilateral or no infiltrates. Acute major PE needs a confirmatory study, e.g., CT scan with pulmonary embolism protocol.
Sarcoidosis	The onset is not acute, but its clinical recognition may be. Oxygenation is often impaired and the chest radiograph can be diffusely abnormal.	Historical features and the frequent presence of hilar adenopathy in sarcoidosis usually eliminate confusion with ARDS.
Interstitial pulmonary fibrosis	The onset is not acute, but its clinical recognition may be. Oxygenation is often impaired and the chest radiograph can be diffusely abnormal.	Prior chest radiographs and a history of chronic and progressive dyspnea characterize the collection of diseases causing interstitial pulmonary fibrosis.

AIP, acute interstitial pneumonia; ARDS, acute respiratory distress syndrome; CT, computed tomography; DAH, diffuse alveolar hemorrhage.
Reproduced with permission from Christie JD, Schmidt G, Lanken PN. Acute respiratory distress syndrome, ACP Smart Medicine. Philadelphia: American College of Physicians; 2004.

unavailable due to a patients instability or are unnecessary. Findings on lung ultrasound may also assist in the diagnosis of ARDS, particularly when chest radiography and CT scans are unavailable.[114] On lung ultrasound, ARDS is described as multiple B lines, typically with a nonhomogeneous distribution, subpleural consolidations, and variable lung sliding.[115,116]

Laboratory Studies

Although no laboratory test is specific for the diagnosis of ARDS, arterial blood gas analysis is important for confirming the diagnosis.[9] Pa_{O_2}/FI_{O_2} is markedly abnormal in patients with ARDS (Tables 141-1A and 141-1B). In addition to the profound oxygen therapy–resistant hypoxemia that is the hallmark of ARDS, acute respiratory

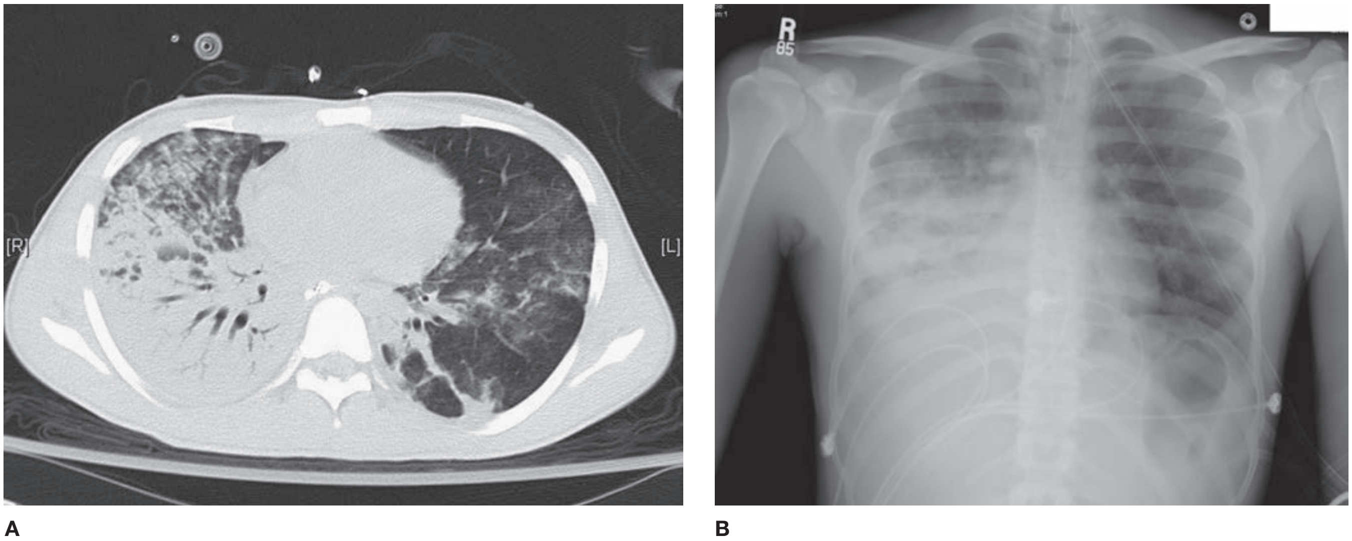

Figure 141-3 Chest CT and plain radiograph in ARDS. **A.** Chest CT scan reveals asymmetric lung injury, with dense consolidation at the right base, patchy alveolar infiltrates in the right anterior lung field, and patchy ground-glass infiltrates throughout the right lung. **B.** Chest radiograph obtained concurrently with chest CT scan shown in panel (**A**). Dense infiltrates at right base, patchy infiltrates in the right upper lung zone, and more subtle infiltrates in the left lung are demonstrated. The panels illustrate the subtle findings of lung injury that are more apparent on the CT scan than on the chest radiograph.

alkalosis may also occur in the early stage. If a patient with ARDS then develops respiratory muscle fatigue, hypercapnia results. In late-stage ARDS, patients typically have increased minute ventilation requirements due to an increasing dead-space fraction, despite possible improvement in oxygen exchange.

In addition to arterial blood gas measurements, several other laboratory studies may be helpful in investigating other causes of respiratory failure and evaluating additional aspects of critical illness associated with ARDS. For example, cardiac enzymes (creatine phosphokinase and troponins) are useful for evaluating the presence of myocardial infarction or cardiac ischemia in patients at risk because of increased age or other factors. The results should be interpreted in conjunction with electrocardiographic findings, since elevations in cardiac enzymes, especially troponins, have been reported in patients with sepsis or septic shock in the absence of coronary artery disease.[117–119]

Another cardiac-related laboratory test that may be useful in this clinical context is plasma brain natriuretic peptide (BNP), which is secreted by the cardiac ventricles, and, to a lesser extent, the atria. BNP measurements are often utilized in the evaluation of acute shortness of breath in patients presenting to an emergency department.[120] In this group, a BNP greater than 500 pg/mL indicates that CHF is likely with a positive predictive value greater than 90%. In the same group, a BNP less than 100 pg/mL suggests that congestive heart is unlikely with a negative predictive value greater than 90%. However, interpretation of an elevated BNP in patients who are critically ill is problematic. Reports indicate that BNP increases with renal failure, and that elevations of BNP greater than 500 pg/mL may occur in patients with sepsis and normal left ventricular function.[121] Nonetheless, one can reasonably exclude a cardiac cause for acute pulmonary edema in patients in the intensive care unit if BNP is less than 100 pg/mL.

Echocardiography

Echocardiography is a useful noninvasive method to evaluate potential cardiac causes of acute hypoxemic respiratory failure.[122] Cardiogenic pulmonary edema is suggested by echocardiographic findings of mitral valve stenosis or regurgitation, left ventricular dilatation and systolic dysfunction, or regional left ventricular wall motion abnormalities. Although these findings do not rule out coexisting lung injury, they are helpful in the initial evaluation and management, even in the presence of ARDS.

Invasive Hemodynamic Monitoring

Although pulmonary artery catheterization was previously performed often in patients with pulmonary edema, the benefits of the procedure are unproven and the risks non-trivial (Chapter 147).[11,123] Several studies have demonstrated that physician interpretation of data obtained from PACs is inconsistent and often erroneous.[124,125] Previous definitions of ARDS have suggested the measurement of PAOP to distinguish ARDS from cardiogenic pulmonary edema;[3] however, the currently accepted Berlin definition of ARDS eliminates such suggestions, recognizing the problems inherent in use of PACs.[9] Studies have demonstrated that many patients who originally met AECC criteria for ARDS (i.e., had a PAOP $\leq$18 mm Hg) often have subsequent measurements with a PAOP $>$18 mm Hg.[12] Furthermore, the Berlin definition recognizes the possibility of concomitant ARDS and cardiogenic edema.

Results of the ARDSNet Fluid and Catheter Treatment Trial (FACCT) support the removal of PAOP criteria from the definition of ARDS, acknowledging that a threshold of 18 mm Hg is arbitrary.[11] FACTT was a large, randomized clinical trial that used a two-by-two factorial design to test a fluid-conservative management strategy against a fluid-liberal management strategy in ARDS. The study also assessed safety and efficacy of a central venous catheter (CVC) or PAC to guide fluid management. In FACTT, 29% of 513 patients enrolled in the PAC arm of the trial were found to have a PAOP greater than 18 mm Hg at the time of initial measurement (following passage of the catheter shortly after enrollment and randomization). Before enrollment, FACTT investigators believed that these patients lacked a primary cardiogenic cause for their pulmonary edema. Approximately one-half of the patients had PAOPs of 19 or 20 mm Hg. Since the vast majority (97%) of this group had a normal cardiac index ($\geq$2.5 L/m^2/min) and a mortality similar to other subjects in FACTT, the elevated PAOP ($>$18 mm Hg) likely reflected intravascular volume loading, rather than cardiogenic pulmonary edema.

Bronchoalveolar Lavage

Bronchoscopy with bronchoalveolar lavage (BAL) is an important tool in the evaluation of patients who have ARDS of unclear origin. In general, BAL can be performed safely in patients with ARDS, except in those with a very low Pa_{O_2} or those requiring high levels of PEEP. The principal reason for performing bronchoscopy in ARDS is to rule in or rule out acute processes that may have specific therapies.

For example, acute eosinophilic pneumonia is a rare disorder characterized by diffuse eosinophilic infiltrates in the lungs (Table 141-6).[126] When the precipitating cause for ARDS is uncertain, performance of BAL and measurement of the percent of eosinophil count in the lavage fluid is helpful in establishing a diagnosis of this corticosteroid-responsive disorder.

Likewise, BAL may be diagnostic for diffuse alveolar hemorrhage (Chapter 68).[127] In this case, the bronchoscopy may or may not reveal fresh blood in the trachea and major bronchi. However, BAL generally demonstrates blood-tinged fluid, which contains red blood cells and hemosiderin-laden macrophages. Diffuse alveolar hemorrhage may occur following bone marrow transplantation or as a result of rheumatologic or other immunologic disorders, including Goodpasture syndrome, granulomatosis with polyangiitis (formerly known as Wegener granulomatosis), systemic lupus erythematosus, or antiphospholipid antibody syndrome.

Lung Biopsy

Routine lung biopsy is not recommended in ARDS; however, lung biopsy should be considered if alternative etiologies of respiratory failure cannot be adequately excluded. While many patients with ARDS are not sufficiently stable to undergo a lung biopsy, the safety of a surgical lung biopsy has been demonstrated in a highly selective group of patients with hypoxic respiratory failure.[128,129] In general, lung biopsy should be reserved for a highly selective group of patients where alternative diagnoses are possible and would significantly change management and prognosis.

APPROACH TO TREATMENT

The general approach to treatment of ARDS includes addressing precipitating causes and other concurrent clinical issues, ensuring adequate oxygenation, careful implementation of a lung-protective ventilator strategy, prudent fluid and hemodynamic management, special patient positioning, and a multitude of other measures, including pharmacologic considerations. Each is discussed subsequently.

■ Goals of Management

Management of patients with ARDS can be complicated and challenging because clinicians are often faced with simultaneous failure of both respiratory and nonrespiratory organ systems (Table 141-7). Unfortunately, only a limited set of controlled clinical trials are available to support an evidence-based approach. For example, even large, multicenter, randomized clinical trials, such as those done by ARDSNet, are limited in the number of variables that can be tested. As a result, patient management rests on a combination of relevant evidence-based medicine, extrapolations from basic and clinical research, and experience-based approaches.

■ Diagnosis and Treatment of Precipitating Causes and Other Comorbidities

The first step in the therapy of ARDS is identification and treatment of the precipitating cause(s) and any other life-threatening medical or surgical issues (Fig. 141-4).

Since ARDS is a *syndrome* based on nonspecific radiographic and physiologic criteria, establishing a diagnosis of ARDS is *not*

TABLE 141-7 Goals of Management of Patients with ARDS

- Treatment of respiratory system abnormalities
  - Diagnose and treat the precipitating cause of ARDS, if possible (Table 141-8)
  - Maintain oxygenation, preferably using nontoxic $F_{I_{O_2}}$ (<0.7), PEEP, or mechanical ventilation
  - Prevent ventilator-induced lung injury (VILI) by using a low tidal volume ventilatory strategy (Table 141-9) with a limit (≤30 cm H_2O) on static end-inspiratory airway pressure (plateau pressure)
  - Keep pH in normal range without compromising goal to prevent VILI (but reverse a life-threatening acidosis, even if it prevents meeting goal to prevent VILI)
  - Enhance patient–ventilator synchrony and patient comfort by use of sedation, amnesia, opioid analgesia, and pharmacologic paralysis, if necessary
  - Liberate or wean from mechanical ventilation when patient can breathe without assisted ventilation
- Treatment of nonrespiratory system abnormalities
  - Support or treat other organ system dysfunction or failure
  - General critical care (preventive and homeostatic measures)
  - Adequate early nutritional support

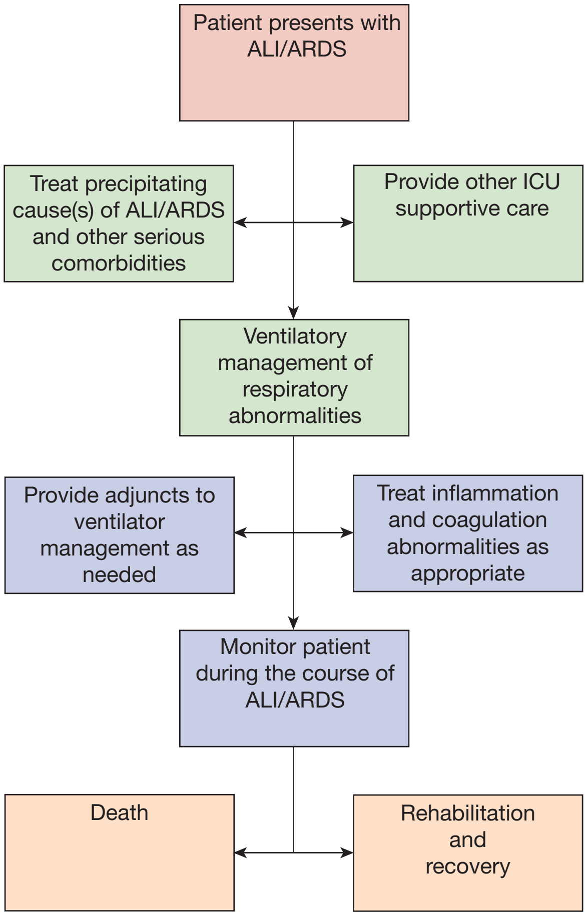
Patient presents with ALI/ARDS
Treat precipitating cause(s) of ALI/ARDS and other serious comorbidities
Provide other ICU supportive care
Ventilatory management of respiratory abnormalities
Provide adjuncts to ventilator management as needed
Treat inflammation and coagulation abnormalities as appropriate
Monitor patient during the course of ALI/ARDS
Death
Rehabilitation and recovery

Figure 141-4 Summary of treatment approach to ARDS. Note that, "Treat inflammation and coagulation abnormalities as appropriate," is currently limited. *(Reproduced with permission from Hall JB, Schmidt GA, Wood LDH: Principles of Critical Care, 3rd ed. New York, NY: McGraw Hill; 2005.)*

TABLE 141-8 Treatable Inciting Causes of ARDS

- Infectious etiologies
  - Bacterial or other sepsis, e.g., fungemia, responsive to antimicrobial therapy
  - Diffuse bacterial pneumonias, e.g., *Legionella* species
  - Diffuse viral pneumonias, e.g., cytomegalovirus, influenza A
  - Diffuse fungal pneumonias, e.g., *Candida* species, *Cryptococcus*
  - *Pneumocystis jiroveci* pneumonia
- SARS-CoV2 pneumonia
  - Other diffuse lung infections, e.g., military tuberculosis
- Noninfectious etiologies
  - Diffuse alveolar hemorrhage post–bone marrow transplantation
  - Diffuse alveolar hemorrhage due to vasculitis, e.g., Goodpasture syndrome
  - Acute eosinophilic pneumonia
  - Lupus pneumonitis
  - Toxic drug reactions, e.g., aspirin

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equivalent to diagnosing the precipitating cause. The fact that early identification and treatment directed at the inciting cause(s) of ARDS are imperative for the resolution of lung injury and respiratory failure cannot be overemphasized. Treatable inciting causes of ARDS include a variety of infectious and noninfectious disorders (Table 141-8).

■ Management of Respiratory Failure

Management of respiratory failure in ARDS rests on assurance of adequate oxygenation and carefully crafted ventilatory strategies, as outlined in the following sections.

Maintaining Adequate Oxygenation

As noted, the pathophysiologic hallmark of ARDS is hypoxemia that is resistant to oxygen therapy. Maintaining adequate arterial oxygenation is the primary goal of both traditional and newer ("lung-protective") approaches to assisted ventilation.

As expected with shunt physiology, administration of supplemental oxygen provided by high-flow oxygenation systems, for example, a nonrebreather facemask or high flow oxygen via nasal cannula, is generally ineffective in reversing the oxygenation deficit. Additionally, concomitant hypercapnic respiratory failure and shock may also lead to the failure of noninvasive oxygenation techniques. Exceptions to this rule are some patients with mild or transient cases of ARDS that are otherwise uncomplicated by other organ system failures. In a randomized controlled trial of 310 nonintubated patients with acute hypoxemic respiratory failure without hypercapnia, altered mental status, or shock, the use of high-flow oxygen through a nasal cannula resulted in a lower hazard ratio for death at 90 days compared with noninvasive ventilation via face mask or standard oxygen therapy.[130] Since many of these hypoxic patients had bilateral infiltrates consistent with ARDS, high-flow oxygen via nasal cannula represents a reasonable first step in this select patient group. This study suggests, however, that the use of noninvasive ventilation via face mask for patients with ARDS should generally be avoided. Another noninvasive alternative to intubation is noninvasive helmet ventilation. While the evidence for helmet ventilation is limited, a small single center randomized controlled trial of 83 nonintubated patients with ARDS demonstrated reduced requirements for invasive ventilation and reduced mortality with noninvasive ventilation via helmet relative to face mask.[131]

Upon intubation, most patients with ARDS require high levels of $\mathrm{FI}_{\mathrm{O}_2}$ to maintain oxygenation; however, high concentrations of oxygen may potentially be toxic. While not studied adequately in patients with ARDS, studies of animals and healthy humans have demonstrated the toxic effects of oxygen therapy within hours of its initiation.[132,133] Given the theoretical concern for oxygen toxicity, PEEP is employed to improve oxygenation by reducing physiologic shunt. When utilized in sufficient amounts, PEEP generally results in some degree of correction of the hypoxemia in patients with ARDS, thereby allowing $\mathrm{FI}_{\mathrm{O}_2}$ to be lowered from high, potentially toxic concentrations. The effect of PEEP-induced improvement in arterial oxygenation is attributed predominantly to recruitment of collapsed alveoli. However, application of PEEP may also mediate a redistribution of alveolar fluid into the interstitium and decrease the absolute magnitude of shunt by reducing cardiac output.

Lung-Protective Mechanical Ventilation

As described in Chapter 140, over the past several decades investigators have convincingly shown that large tidal volumes delivered during mechanical ventilation can injure lungs of normal animals, producing a pathologic pattern resembling ARDS in humans.[134,135]

In animal models of ALI, use of large tidal volume ventilation has been found to augment pre-existing injury. In addition, repetitive opening and closing of alveoli during inspiration and expiration induces ALI in normal animals.[136,137] The injury can be prevented by application of sufficient PEEP. Finally, overexpansion of alveoli in normal lungs of sheep induces multiorgan failure,[138] with studies in other species showing that lung overexpansion results in systemic release of proinflammatory cytokines—providing a likely mechanism for these remote deleterious effects.[139–141] These observations support the concept that the lung is an "engine of inflammation."

Concurrent with the previously described observations, clinical investigators studying patients with ARDS using computed tomography observed that, in contrast to the typical diffuse-appearing pattern noted on plain chest radiographs, the pattern of consolidation, atelectasis, and normal alveoli is actually heterogeneous (Fig. 141-3).[142] The key physiologic implication of these observations is that a ventilator-delivered tidal volume is preferentially distributed to the open alveoli, which represent only a small fraction of the entire lung.[143] In referring to this lung fraction as "the baby lung," investigators emphasized the potential danger of delivering traditional tidal volumes of 10 to 15 mL/kg actual body weight and the associated risk for alveolar overexpansion and lung injury. Notably, tidal volumes of 10 to 15 mL/kg actual body weight (equivalent to approximately 12 to >15 mL/kg predicted body weight) were used originally in critically ill patients with ARDS as a complementary strategy to PEEP in recruiting atelectatic alveoli.

These productive lines of basic and clinical research strongly support the hypothesis that mechanical ventilation using limited tidal volumes should be less injurious to the lungs of patients with ARDS and should result in better outcomes (i.e., decreased mortality) compared with use of traditional, large tidal volume ventilation. Several randomized controlled trials have been conducted to address the role of low tidal volume ventilation in ARDS, including the landmark ARDSNet trial, ARMA, discussed in detail below.[4,144] Meta-analyses of multiple trials support a low tidal volume ventilation approach to reduce mortality in ARDS.[145,146]

In summary, the goals of lung-protective ventilation are to avoid injury due to overexpansion of alveoli during inspiration ("volutrauma") and injury due to repetitive opening and closing of alveoli during inspiration and expiration ("atelecta-trauma") (Fig. 141-5). The injurious effects of mechanical ventilation on the lung have been referred to as ventilator-induced lung injury or "VILI." The

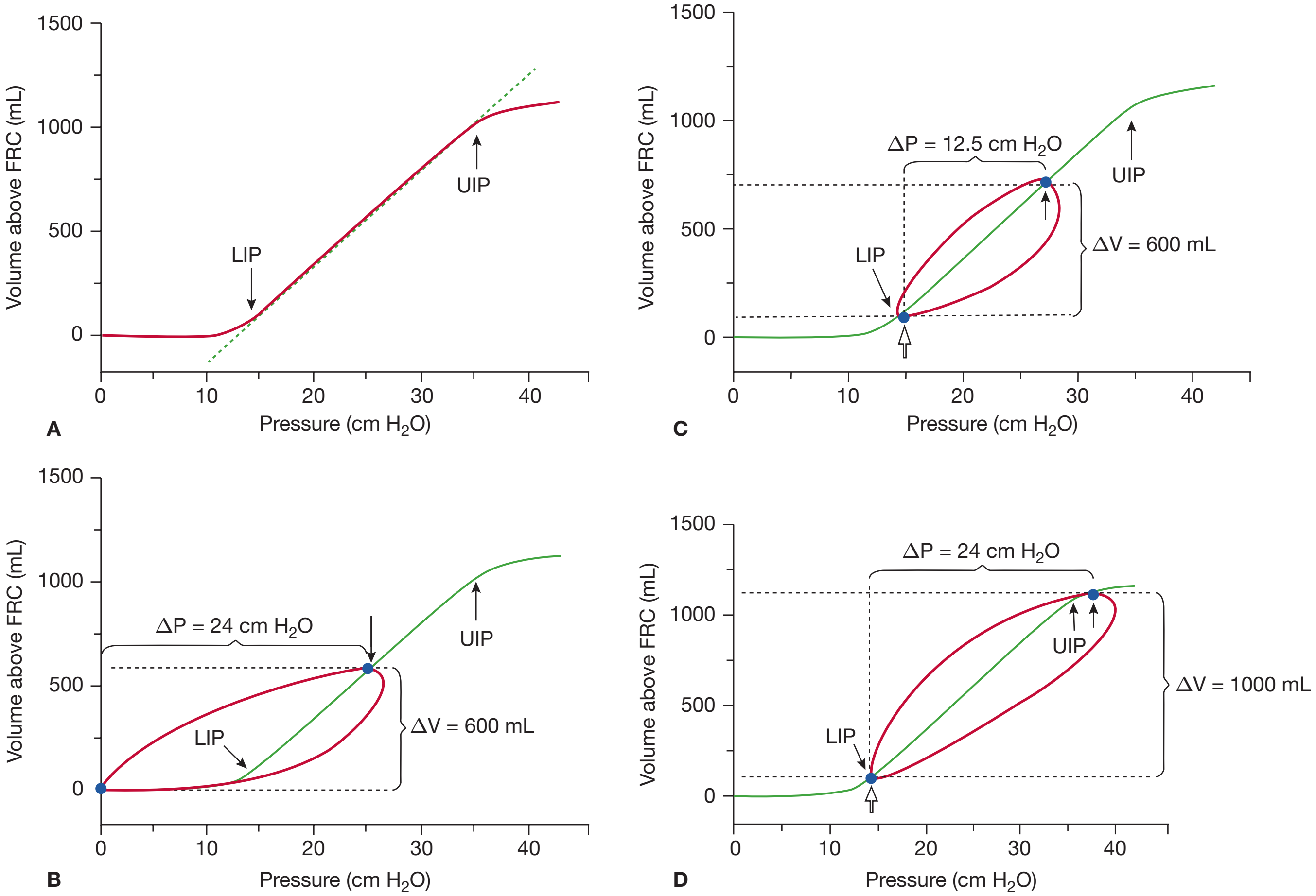

Figure 141-5 **A.** Schematic inspiratory static pressure–volume (P–V) curve of the respiratory system (lung and chest wall combined) in ARDS. Lower inflection point (LIP) is approximately 14 cm H_2O, and upper inflection point (UIP) is approximately 35 cm H_2O. Abscissa is respiratory system recoil pressure; ordinate is lung volume above functional residual capacity (FRC). **B.** Same static P–V curve as (**A**), plus dynamic P–V curve of 600 mL tidal volume starting below the LIP (PEEP = 0). This tidal volume results in a plateau pressure *(closed arrow)* below the UIP (24 cm H_2O). Static compliance (Cstat = ΔV/ΔP = 600 mL/24 cm H_2O) is 25 mL/cm H_2O. **C.** PEEP of 15 cm H_2O has moved the starting point for the 600 mL tidal volume up the static P–V curve to a new FRC *(open arrow)*, which is at the LIP. The tidal volume results in a plateau pressure of 27.5 cm H_2O *(closed arrow)*, which is well below the UIP. Cstat (ΔV/ΔP = 600 mL/12.5 cm H_2O) is increased to 48 mL/cm H_2O. **D.** Dynamic P–V curve of a 1000 mL tidal volume, starting at 14 cm H_2O PEEP, results in a plateau pressure of 37.5 cm H_2O *(closed arrow)*. Despite an increase in Cstat (ΔV/ΔP = 1000 mL/24 cm H_2O = 41.5 mL/cm H_2O), compared with Cstat derived from the 600 mL tidal volume in (**B**), the plateau pressure associated with the 1000 mL tidal volume exceeds the UIP. Delivery of an inflation volume that results in a plateau pressure exceeding the UIP implies alveolar overdistension and is believed to put the lung at risk for ventilator-induced lung injury (see text). *(Reproduced with permission from Lanken PN, Hanson CW III, Manaker S: The Intensive Care Unit Manual. Philadelphia, PA: Saunders; 2001.)*

term “bio-trauma” encompasses the direct lung injury and the concomitant release of inflammatory cytokines that produce remote cell death or organ injury.[147] Clinical strategies underlying contemporary applications of mechanical ventilation in treatment of ARDS are described subsequently.

ARDSNet Ventilator Strategies: Low Versus Traditional Tidal Volumes Based on the aforementioned considerations, the ARDSNet conducted a randomized trial (ARMA) in the mid-to-late 1990s to test the hypothesis that low tidal volume ventilation, combined with limited end-inspiratory (plateau) pressure, would lower mortality and ventilator days among survivors of ARDS compared with use of traditional tidal volumes.[4] The trial included 861 subjects. The low tidal volume arm consisted of a tidal volume of 6 mL/kg predicted body weight, as long as the end-inspiratory pressure (Pplat) was ≤30 cm H_2O; if Pplat exceeded 30 cm H_2O, the tidal volume could be decreased to as low as 4 mL/kg. The traditional tidal volume arm used a tidal volume of 12 mL/kg predicted body weight, as long as the Pplat remained <50 cm H_2O. Both arms included explicit goals and protocols as the bases for ventilator adjustments and determination of the time and means of weaning (Table 141-9).

Important results of the ARMA trial are summarized in Table 141-10. The difference in actual tidal volumes resulted from protocol-driven target tidal volumes in each study arm. As expected, the mean plateau pressure for the lower tidal volume group was <30 cm H_2O (25 cm H_2O), since the protocol required decreasing the tidal volume from 6 mL/kg predicted body weight to as low as 4 mL/kg if Pplat exceeded 30 cm H_2O. Of note, the traditional tidal volume group had a mean Pplat of 33 cm H_2O on study day 1—a value less than the threshold of 35 cm H_2O that some clinicians had believed represented a safe threshold.

Despite the fact that the ARMA clinical trial used an arbitrary threshold of 30 cm H_2O for Pplat in the lower tidal volume arm, it should not be assumed that any Pplat ≤30 cm H_2O is safe. If a “safe” upper limit of Pplat exists, its value is unknown. Lack of such a safe threshold is supported by the finding of an absence of any significant

TABLE 141-9 NIH NHLBI ARDS Clinical Trials Network Low Tidal Volume Ventilation Strategy

Part I: Ventilator Setup and Adjustment

1. Calculate ideal body weight (IBW)[a] (also known as predicted body weight [PBW])
2. Use Assist/Control mode and set initial TV to 8 mL/kg IBW (if baseline TV >8 mL/kg)
3. Reduce TV by 1 mL/kg at intervals ≤2 h until TV = 6 mL/kg IBW
4. Set initial rate to approximate baseline $\dot{V}_E$ (but not >35 bpm)
5. Adjust TV and RR to achieve pH and plateau pressure (Pplat) goals below.
6. Set inspiratory flow rate above patient demand (usually >80 L/min); adjust flow rate to achieve goal of I:E ratio of 1:1.0–1.3

Part II: Oxygenation Goal: Pa_{O_2} = 55–80 mm Hg or Sp_{O_2} = 88–95%

1. Use these incremental $F_{I_{O_2}}$–PEEP combinations to achieve oxygenation goal:

$F_{I_{O_2}}$	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7
PEEP	5	5	8	8	10	10	10	12
$F_{I_{O_2}}$	0.7	0.8	0.9	0.9	0.9	1.0	1.0	1.0
PEEP	14	14	14	16	18	20	22	24

Part III: Plateau Pressure (Pplat) Goal: ≤30 cm H_2O

1. Check Pplat (use 0.5-s inspiratory pause), Sp_{O_2}, total RR, TV, and ABG (if available) at least every 4 h and after each change in PEEP or TV.
2. If Pplat >30 cm H_2O, decrease TV by 1 mL/kg steps (minimum 4 mL/kg IBW)
3. If Pplat <25 cm H_2O and TV <6 mL/kg, increase TV by 1 mL/kg until Pplat >25 cm H_2O or TV = 6 mL/kg.
4. If Pplat <20 cm H_2O and breath stacking occurs, one may increase TV in 1 mL/kg increments (to a maximum of 8 mL/kg)

Part IV: pH Goal: 7.30–7.45

Acidosis management: pH <7.30

1. If pH = 7.15–7.30, increase RR until pH >7.30 or Pa_{O_2} <25 mm Hg (maximum RR = 35); if RR = 35 and Pa_{CO_2} <25 mm Hg, may give NaH_{CO_3}
2. If pH <7.15 and NaH_{CO_3} considered or infused, TV may be increased in 1 mL/kg steps until pH >7.15 (Pplat goal may be exceeded) Alkalosis management: pH >7.45: decrease RR, if possible

ABG, arterial blood gas; RR, respiratory rate on ventilator; Sp_{O_2}, Oxygen saturation by pulse oximetry; TV, tidal volume; $\dot{V}_E$, minute ventilation.

[a] *Male IBW, 50 +2.3 (height [inches] – 60); female IBW, 45.5+2.3 (height [inches] — 60).*

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interaction between differences in mortality and quartiles of static respiratory compliance or quartiles of plateau pressures (Fig. 141-6). These results suggest that the lower tidal volume ventilatory strategy tends to be effective across a wide range of baseline static compliances and plateau pressures. Likewise, a statistical model of mortality proportion versus day 1 Pplat which combined data from both arms of this clinical trial suggests that, in general, the lower the Pplat, the lower the associated mortality (Fig. 141-7).[148]

These considerations are important, since some clinicians may believe that they can achieve the improved mortality rate simply by

TABLE 141-10 Results of NIH NHLBI ARDS Clinical Trials Network Low Tidal Volume Versus Traditional Tidal Volume Clinical Trial ("ARMA")

Variable or Outcome	Units	Low Tidal Volume Ventilatory Strategy Mean ± SD	Traditional Tidal Volume Ventilatory Strategy Mean ± SD	*p* Value
Tidal volume on day 1	mL/kg PBW	6.2 ± 0.9	11.8 ± 0.8	<0.05
Plateau pressure on day 1	cm H_2O	25 ± 7	33 ± 9	<0.05
PEEP on day 1	cm H_2O	9.4 ± 3.6	8.6 ± 3.6	<0.05
Pa_{CO_2}: $F_{I_{O_2}}$ on day 1		158 ± 73	176 ± 76	<0.05
Pa_{CO_2} on day 1	mm Hg	40 ± 10	35 ± 8	<0.05
Death before discharge or 180 days	%	31.0	39.8	0.007
Breathing without assistance at day 28	%	65.7	55.0	<0.001
No. of ventilator-free days by day 28		12 ± 11	10 ± 11	0.007
No. of days without failure of nonpulmonary systems by day 28		15 ± 11	12 ± 11	0.006

PBW, predicted body weight (see footnote of Table 141-9 for details); PEEP, positive end expiratory pressure; SD, standard deviation; ventilator-free days by day 28, number of days alive and not receiving assisted ventilation between days 1 and 28.

Data from Acute Respiratory Distress Syndrome Network, Brower RG, Matthay MA,et al. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med. 2000;342(18):1301–1308.

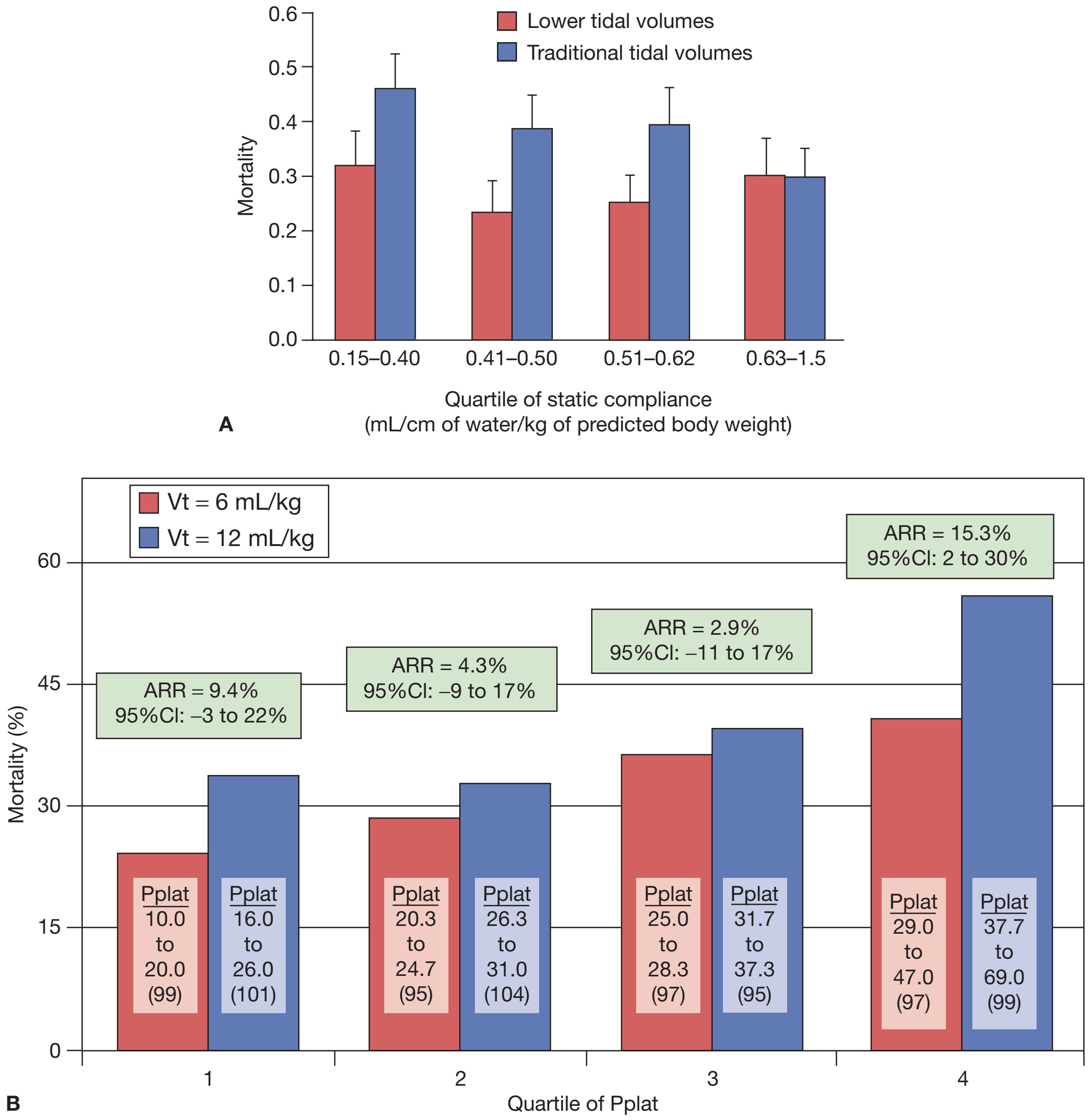

Figure 141-6 ARDSNet ARMA study. Mortality according to quartiles of treatment group (**A**) and end-inspiratory pressure (plateau pressure, Pplat) (**B**) on day 1 in 787 subjects for whom Pplat data are available. Pplat was measured using protocol-dictated tidal volumes. Subjects with the stiffest lungs are likely to have Pplat in the fourth quartile (far right). Range of Pplat (cm H_2O) and number of subjects (parentheses) are shown in each bar of the graph (ARR, absolute risk reduction; CI, confidence interval). Lower tidal volume ventilation appears to benefit patients with ARDS across a range of Pplat. The hypothesis that a "safe" upper limit exists for Pplat, below which ventilator-induced lung injury does not occur, is *not* supported by the data. *(Reproduced with permission from Hager DN, Krishnan JA, Hayden DL, et al. Tidal volume reduction in patients with acute lung injury when plateau pressures are not high. Am J Respir Crit Care Med. 2005;172(10):1241–1245.)*

lowering tidal volumes to the point where Pplat is at or slightly less than 30 cm H_2O, instead of following the ARDSNet low tidal volume strategy of using a tidal volume of 6 mL/kg predicted body weight. In addition, recognition of the need to use predicted, rather than actual, body weight is important, since the latter has been estimated to be about 20% greater than the former (due to fat and extravascular fluid). In summary, clinicians should employ the *entire* ARDSNet protocol (Table 141-9), rather than selected parts in attempting to achieve comparably favorable mortality results.

Lung Protection Due to Higher PEEP The initial ARDSNet trial (ARMA) described earlier did not address the question of whether application of higher levels of PEEP than used traditionally is beneficial.[4] The possibility of improved outcomes using higher levels of PEEP was suggested by both basic and clinical studies conducted in the early 1990s.[5] To address whether higher levels of PEEP combined with low tidal volumes decrease mortality, the ARDSNet conducted a second ventilator clinical trial (ALVEOLI) in which each of two groups received the same low tidal volume ventilatory strategy, but one group was treated using an additional 4 to 5 cm H_2O of PEEP.[37] Mortality rates at day 60 were below 30% for both groups and were not significantly different, even after adjustment for imbalances in baseline variables. Similarly, ventilator-free days were not significantly different.

Subsequently, two further trials were conducted to address the role of a high PEEP strategy, the Lung Open Ventilation to Decrease Mortality in ARDS (LOVS) trial and the Expiratory Pressure Study (EXPRESS).[149,150] Neither study demonstrated a difference in the primary mortality outcomes between the control and intervention groups. However, the high PEEP strategy improved secondary endpoints, including use of rescue therapies in LOVS and duration of mechanical ventilation and organ failure in EXPRESS. More recently, a meta-analysis combined the data from AVEOLI, LOVS, and EXPRESS.[151] Treatment with higher levels of PEEP was not

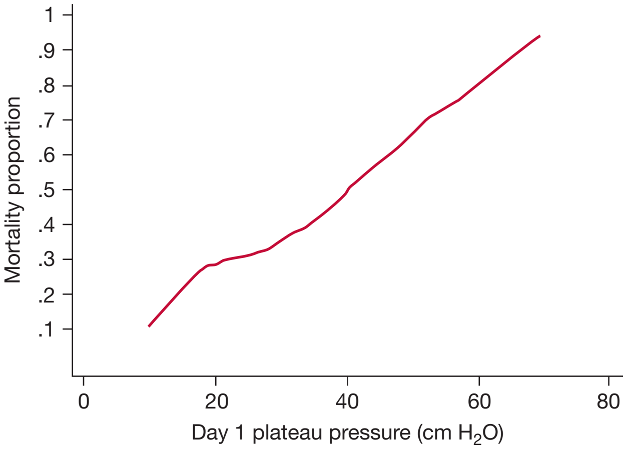

Figure 141-7 Lowess (locally weighted regression and smoothing) plot (bandwidth, 0.4) of mortality proportion and day 1 plateau pressure (Pplat, cm H_2O) for 787 patients enrolled in the ARDSNet ARMA study. Plot includes same subjects and Pplat shown in Figure 141-6. When expressed using this estimating method, the data do not support a safe upper limit for Pplat, the presence of which would be suggested by a leveling in mortality proportion, rather than a further decrease, as the plot demonstrates. The Lowess method is a nonparametric smoother that uses overlapping neighborhoods of data to estimate a local effect. A bandwidth of 0.4 means that 20% of the data on either side of a given Pplat contribute to a local estimate of mortality at that Pplat; data at the high and low ends of the curve represent fewer observations. As data are smoothed using a tricubic weight function, points furthest from the Pplat of interest are assigned the least weight and approach zero. *(Reproduced with permission from Hager DN, Krishnan JA, Hayden DL, et al. Tidal volume reduction in patients with acute lung injury when plateau pressures are not high. Am J Respir Crit Care Med. 2005;172(10):1241–1245.)*

associated with an in-hospital mortality benefit, but among patients with a Pa_{O_2}/FI_{O_2} <200 there appeared to be a reduction in mortality. In addition, other studies have demonstrated that while some patients with ARDS have little or no alveolar recruitment (i.e., opening previously collapsed or fluid filled airspaces) with increased levels of PEEP, others PEEP show marked recruitment.[113] This suggests that future clinical trials using higher PEEP be restricted to subjects with ARDS in whom PEEP increments can reliably result in recruitment.

Amato et al. conducted a retrospective post-hoc analysis of nine previously reported randomized trials evaluating lung protective mechanical ventilation to determine the components of lung protection, such as lower tidal volume, lower plateau pressure, and higher PEEP, that most strongly mediate the reduced mortality.[152] The authors hypothesized that normalizing the tidal volume to the respiratory-system compliance using the driving pressure would better reflect the "functional" size of the lung and therefore be associated with outcomes. The driving pressure represents the tidal volume divided by the respiratory-system static compliance and can easily be calculated on the vent by subtracting plateau pressure minus PEEP. The authors found that of the ventilator variables collected, the driving pressure most strongly associated with survival. Given these data, some have suggested PEEP and tidal volume titration strategies should be aimed at reducing driving pressure. These approaches are currently being evaluated in prospective randomized control trials.[153]

Recommended Core Ventilator Management We recommend that as the core ventilator management in ARDS, clinicians follow the ARDSNet low tidal volume ventilatory strategy (Table 141-9).[4] This strategy includes permissive hypercapnia defined as clinician-allowed hypercapnia during assisted ventilation, despite an ability to achieve a level of minute ventilation sufficient to maintain a normal Pa_{CO_2} with higher tidal volumes. Because higher levels of PEEP have not yet been found to improve outcomes, unless new evidence arises to the contrary, we also recommend that clinicians follow the same combinations of FI_{O_2} and PEEP used in the first ARDSNet trial, ARMA (Table 141-9). Alternatively, clinicians can consider assessing PEEP responsiveness and increasing PEEP in those that demonstrate significant improvements in oxygenation or reductions in driving pressure with the addition of higher levels of PEEP.

Because of constraints of sample size, the ARMA trial tested the low-volume strategy only against use of tidal volumes of 12 mL/kg predicted body weight. Notably, a strategy using 6 mL/kg has not been shown to be superior to a strategy using tidal volumes of 8 to 10 mL/kg. However, based on the previous descriptions of ventilator-induced lung injury (VILI) and biotrauma, we believe it is prudent for clinicians to strictly follow the ARDSNet protocol as their core management strategy in ARDS. Modifications should be considered only in special cases, for example, when contraindications for permissive hypercapnia exist (Table 141-11).

Other Approaches to Ventilator Management

In addition to the low-volume protocol described, several additional approaches may be used in the management of ARDS but lack the level of evidence of the ARDSNet ARMA strategy. These approaches are discussed briefly subsequently.

Pressure Control Mode The ARDSNet low tidal volume strategy used the volume-assist-control mode—a familiar device setting and the only ventilator intervention that has been shown thus far to improve long-term survival in patients with ARDS.[4] However, other modes of ventilation can also provide low tidal volume ventilation, including pressure control ventilation (PCV).

PCV can limit maximal peak airway pressure as well as end-inspiratory pressure (Fig. 141-8A) and, hence, is favored by some clinicians. However, the end-inspiratory pressure in PCV can be underestimated. For example, using PCV with an inspiratory pressure of 30 cm H_2O and a PEEP of 10 cm H_2O, the end-inspiratory pressure is 40 cm H_2O (the sum of the two pressures). Some may misinterpret this combination as equivalent to a Pplat of 30 cm

TABLE 141-11 Contraindications to Permissive Hypercapnia and Acute Respiratory Acidosis

Increased intracranial pressure from any cause (trauma, mass lesion, malignant hypertension)
Acute cerebrovascular disorders, e.g., stroke
Acute or chronic myocardial ischemia
Severe pulmonary hypertension
Right ventricular failure
Uncorrected severe metabolic acidosis
Sickle cell anemia
Tricyclic antidepressant overdose
Patients taking beta-blockers
Pregnancy (due to potential for decreased fetal blood flow from vasodilation-induced steal syndrome; in addition, shift to the right of the O_2 dissociation curve decreases the maternal-fetal gradient for O_2)

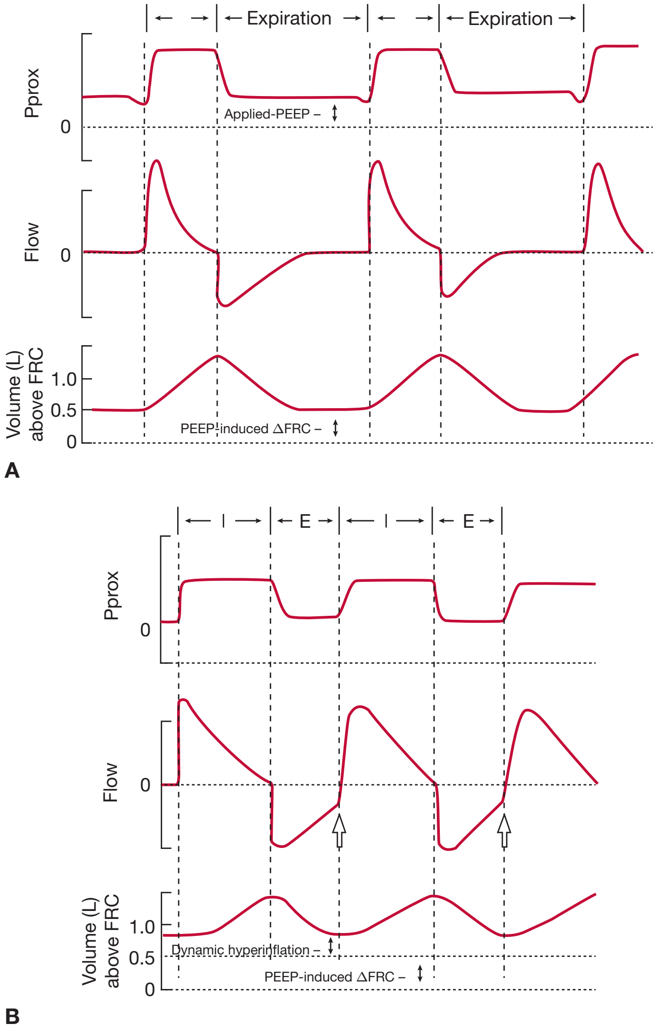

Figure 141-8 Schematic depiction of pressure, flow, and volume waveforms during pressure control ventilation (PCV) with applied PEEP. The x-axis is time and y-axes (from top to bottom) are proximal airway pressure (P_{prose}), inspiratory flow, and volume above functional residual capacity (FRC). Other abbreviations: I, inspiration; ΔFRC, change in FRC. **A.** The inspiratory-to-expiratory (I:E) time is about 1:2. The pressure waveform resembles pressure support ventilation, and the flow pattern is characterized by marked deceleration. Applied PEEP increases FRC (PEEP effect). **B.** I:E time is reversed (I > E), representing pressure-controlled inverse ratio ventilation (PC-IRV). As a result, the next breath starts before expiratory flow has returned to zero *(open arrows)*, resulting in auto-PEEP and dynamic hyperinflation. The latter is superimposed on the increased FRC due to the applied PEEP. *(Reproduced with permission from Lanken PN, Hanson CW III, Manaker S: The Intensive Care Unit Manual. Philadelphia, PA: Saunders; 2001.)*

H_2O and assume that it is a “safe” value according to interpretation of ARDSNet results. As discussed previously, however, no Pplat is known to be safe, even when end-inspiratory pressure is calculated correctly. Furthermore, use of PCV to mimic both tidal volume and Pplat used in the ARDSNet trial remains problematic. The tidal volume delivered at a set pressure in PCV is dependent on the compliance of the respiratory system and is, therefore, variable, particularly in ARDS. The benefit seen from using the ARDSNet strategy may have been due as much to the use of low tidal volume as to lower Pplat. It may be difficult in PCV to ensure tidal volumes are limited, particularly as compliance improves as ARDS improves, which will result in larger tidal volumes at the same set pressure.

TABLE 141-12 “Rescue” or “Salvage” Interventions Used in Patients with ARDS and Severe Hypoxemia Resistant to Conventional Mechanical Ventilation and PEEP

Corticosteroids
Extracorporeal CO_2 removal ($ECCO_2R$)
Extracorporeal membrane oxygenation (ECMO)
High-frequency oscillatory ventilation (HFOV)
Inhaled nitric oxide (NO) or inhaled prostacyclin (epoprostenol/iloprost)
Pressure-controlled inverse ratio ventilation (PC-IRV)
Prone positioning
Recruitment maneuvers

Inverse ratio ventilation (IRV) with PCV is based upon an inspiratory time (I) greater than expiratory time (E), that is, I:E >1 (Fig. 141-8B). Lengthening the inspiratory time increases mean airway pressure because more of the respiratory cycle is spent in inspiration, which may translate into improvements in oxygenation. However, IRV also limits the time for exhalation, potentially resulting in dynamic hyperinflation and auto-PEEP. While increasing auto-PEEP may translate to improved oxygenation, it also results in high pulmonary pressures that may not be lung-protective. IRV with auto-PEEP plus applied PEEP may also compromise cardiac output and increase the risk of nonpulmonary organ dysfunction. Clinicians should consider using PCV–IRV only as a “salvage” mode of ventilation (Table 141-12).

Modes That Allow Spontaneous Breathing During Positive Pressure Ventilation Two ventilatory modes of modern, microprocessor-based devices that permit spontaneous breathing to occur at any phase of the respiratory cycle during assisted ventilation include biphasic airway pressure (BIPAP) and airway pressure release ventilation (APRV). In each, airway pressure cycles between higher and lower levels of PEEP at preset time intervals. APRV represents the extreme of BIPAP whereby patients are given a high level of PEEP to promote alveolar recruitment with a brief release to allow for carbon dioxide removal without allowing alveolar derecruitment. Controlled studies using these ventilator modalities are limited. One report found that the use of APRV in patients with ARDS decreased intrathoracic pressure, improved ventilation–perfusion mismatch and cardiac output, and decreased shunt and dead-space fractions compared with pressure support ventilation (matched for the same airway pressure limits or minute ventilation).[154] However, clinically important outcomes were not compared. Another study performed at a single center in China randomized 138 patients to APRV or lung protective mechanical ventilation.[155] Patients randomized to APRV had more ventilator-free days, a shorter ICU duration, and received less sedation. It is unclear, however, if the study’s findings are generalizable and if they are the result of the application of APRV or an APRV protocol that may have resulted in closer attention being paid to subjects in the intervention arm.

BIPAP and APRV may decrease the use of neuromuscular blocking agents and possibly sedation in patients with ARDS, since both allow spontaneous breathing and potentially less patient-ventilator dyssynchrony. However, whether such modes of ventilation are better than, equal to, or worse than the ARDSNet lower tidal volume ventilatory strategy remains unknown. Until more multicenter clinical evidence supports their superiority or equivalency, their routine use cannot be recommended.

High-Frequency Oscillatory Ventilation High-frequency oscillatory ventilation (HFOV) is a mode of ventilation in which patients are supported with rapid pressure oscillations that generate very small tidal volumes. Theoretically, HFOV may be regarded as the ultimate low-tidal-volume ventilator, with a capacity to ventilate a patient using a very small tidal volume, which lies midway between the upper and lower inflection points of the pressure–volume curve (Fig. 141-5). While commonly used in respiratory distress of the newborn, the use of HFOV in ARDS had previously been limited to centers with necessary ventilatory equipment and technical expertise. Two large, multicenter, randomized controlled trials of moderate to severe ARDS comparing HFOV and traditional care are noteworthy. The trial conducted by the Oscillation in ARDS (OSCAR) study group demonstrated no significant mortality benefit of HFOV compared with usual care, as determined by local practice of participating ICUs.[156] The Oscillation for ARDS Treated Early (OSCILLATE) Trial was stopped early by the Data Safety and Monitoring Committee, as the HFOV group appeared to have a higher in-hospital mortality compared with a low tidal volume, high PEEP control group.[157] While some clinicians previously used high-frequency ventilation as a “salvage” mode (Table 141-12), its use, even in those circumstances, is not supported by controlled clinical trials.

Adjuncts to Lung-Protective Mechanical Ventilation

A number of adjunctive measures to mechanical ventilation have assumed importance in the management of patients with ARDS. In some cases, the physiologic or pharmacologic basis for the measure’s beneficial effect is apparent; in others, the mechanism is unknown.

Overview The use of many adjuncts to lung-protective ventilation is based on extrapolations from animal studies, or from clinical studies using physiologic markers as surrogates for clinically meaningful endpoints, for example, mortality or ICU length of stay or ventilator-free days. However, extrapolation from such studies to clinical practice is problematic. For example, the ARDSNet low tidal volume ventilatory strategy has a demonstrated mortality benefit but also resulted in patients in the low-volume group having significantly lower Pa_{O_2}/FI_{O_2} after enrollment compared with those receiving traditional tidal volume ventilation (Table 141-10).[4] If the trial had used improvement in Pa_{O_2}/FI_{O_2} as a surrogate marker for better survival, the results would have been interpreted as showing that low tidal volume ventilation results in *higher*, rather than *lower*, mortality.

While several adjunctive therapies are employed in ARDS, the most common therapies applied to select patients are prone positioning, neuromuscular blockade, corticosteroids, and conservative fluid management.[38,158–161] The data supporting each of these therapies range from strong to controversial and are discussed further below. Additionally, extracorporeal oxygenation (ECMO) is increasingly being employed at specialized centers for patients with the most severe forms of ARDS.[162,163] Data supporting the use of other adjunctive therapies in ARDS is lacking and thus, these interventions should be used cautiously, if at all.

Prone Positioning It has long been recognized that placing patients in a prone position improves oxygenation in a majority of patients with ARDS.[164] However, managing critically ill patients in the prone position is challenging and requires special attention to prevent pressure necrosis of the nose, face, and ears. Extra care is also needed to ensure security and patency of the endotracheal tube, central lines, and arterial lines. Pressure on the eye may result in retinal ischemia, especially in hypotensive patients. Others may experience cardiac arrhythmias or hemodynamic instability when turned prone mandating close monitoring by experienced clinicians during patient positioning.

In the past, prone positioning was largely reserved for the emergency management of severe hypoxemia, and despite clinical trials that demonstrated improved oxygenation in the prone position, older trials failed to demonstrate a mortality benefit.[165] More recently, a meta-analysis examined the effects of prone positioning on all patients with ARDS and a prespecified subgroup with severe ARDS ($Pa_{O_2}/FI_{O_2} < 100$ mm Hg).[166] Prone positioning failed to demonstrate a mortality benefit among all patients with ARDS, but findings suggested a mortality benefit among those with severe ARDS. In 2013, a prospective, randomized, controlled trial comparing prone positioning for at least 16 hours a day to supine positioning in 466 patients with ARDS and $Pa_{O_2}/FI_{O_2} < 150$ mm Hg was published.[160] All patients were enrolled within 36 h of initiation of mechanical ventilation for ARDS and were managed with a low tidal volume ventilation strategy. The large majority of the patients in the prone and supine arms were also managed with heavy sedation, vasopressors for shock, and neuromuscular blockade. The primary outcome, 28-day mortality, was 16% in the prone group and 32.8% in the control group, a statistically significant reduction in mortality.

The mechanisms by which prone position may confer a survival advantage in ARDS are not definitely known; however, there is significant experimental evidence that placing a patient in the prone position results in improvements in ventilation-perfusion relationships and reduction in ventilator induced lung injury.[167] Computed tomography studies have demonstrated that patients placed in the prone position have lung inflation that is more homogeneous from dorsal to ventral than in the supine position. This homogeneously distributed ventilation distributes stress and strain and reduces both over-distention and atelectasis limiting ventilator induced lung injury. It is hypothesized that this mechanism among others contributes to the benefits of prone positioning in moderate to severe ARDS. In the past several years, the use of prone positioning in moderate to severe ARDS has becoming increasingly routine and should be considered in all ARDS patients with a $Pa_{O_2}/FI_{O_2} < 150$ mm Hg, at centers with the necessary staff and expertise.

Neuromuscular Blocking Agents Significant controversy exists regarding the role of neuromuscular blocking agents in ARDS with the two largest randomized controlled trials producing conflicting results.[158,159] These agents are frequently used to promote ventilator synchrony and improve oxygenation in moderate to severe cases of ARDS; however, they have been associated with prolonged neuromuscular weakness in survivors of ARDS.

In a multicenter study, 340 heavily sedated patients with ARDS and a $Pa_{O_2}/FI_{O_2} < 150$ were randomized to 48 h of cisatracurium or placebo early after ARDS onset.[158] The 90-day mortality rate was 31.6% in the cisatracurium group and 40.7% in the placebo group, a finding that was only statistically significant after adjustment for baseline Pa_{O_2}/FI_{O_2}, baseline plateau pressure, and the Simplified Acute Physiology II score. Although not powered for this outcome, ICU-acquired neuromuscular weakness was not different between the groups. Unlike other paralytics, cisatracurium is largely metabolized by Hofmann elimination and is mostly independent of liver and renal dysfunction, both of which are common in ARDS. One significant limitation to this study was both the intervention and control arms were heavily sedated. The Reevaluation of Systemic Early neuromuscular blockade (ROSE) trial, published in 2019, sought to address this limitation by comparing early neuromuscular blockade with cisatracurium to a usual care strategy that attempted to limit sedation as much as possible.[159] The study included 1006 patients with ARDS and a $Pa_{O_2}/FI_{O_2} < 150$ randomized to heavy sedation and cisatracurium for 48 h versus usual care including limited sedation. The lung protective ventilator strategies were the same in both arms. Mortality at 90 days was nearly identical in the two arms (42.5% in the intervention arm versus 42.8% in the control arm), suggesting neuromuscular blockade does not benefit ARDS patients over usual care and reduced sedation. A significant limitation to the ROSE study was that less than 15% of patients underwent prone positioning despite the evidence for its use.[160] Based on the current available evidence, neuromuscular blockade should not be used routinely in all patients with moderate to severe ARDS. It may, however, be beneficial in select patients, such as those with severe ventilator dyssynchrony, or to facilitate placing and maintaining a patient safely in prone position.

Corticosteroids The use of corticosteroids in ARDS remains controversial despite being the subject of clinical research for over 30 years. The theoretical benefits of corticosteroids include reducing inflammation and fibrosis, key components of both the acute and proliferative phases of ARDS.[168] Despite these theoretical benefits, corticosteroids also have potential downsides, including increased secondary infections, hyperglycemia, delirium, and long-term neuromuscular weakness. There is increasing evidence, however, for the use of corticosteroids in critically ill populations that overlap with ARDS, including severe community acquired pneumonia and septic shock.[169,170] Therefore, corticosteroids use in ARDS has increased over time with unclear benefit.

Initial studies of high dose methylprednisolone failed to demonstrate a consistent benefit early in ARDS, leading researchers to hypothesize that moderate dose methylprednisolone may benefit patients with persistent ARDS.[171] In 2006, the ARDSNet investigators published results of a double blind, randomized, controlled clinical trial (Late Steroid Rescue Study or LaSRS) designed to evaluate benefits and risks of moderate doses of methylprednisolone in 180 patients with persistent ARDS (ARDS lasting 7–21 days).[172] The study revealed no differences in 60- or 180-day mortality rates. Although parameters of respiratory function and time to liberation from mechanical ventilation improved after corticosteroid administration, the corticosteroid treated group included more patients who required re-intubation. Furthermore, no statistically significant differences between treated and untreated groups in ICU or hospital days by 180 days were observed. In addition, more adverse events related to weakness occurred in the treated group than in those receiving placebo. Finally, patients treated with corticosteroids after 14 days of persistent ARDS had a significantly increased mortality. Hence, the results of this study do not support the routine use of steroids for late-phase ARDS in general, and they argue against their use if ARDS has been present for 14 days or longer.

More recently, investigators published the results of a randomized controlled trial of high dose dexamethasone in patients with moderate or severe ARDS ($Pa_{O_2}/FI_{O_2} < 200$).[161] In total, 277 patients enrolled at 17 ICUs in Spain were randomized to dexamethasone 20 mg intravenously daily for 5 days followed by five days of 10 mg daily or usual care. Importantly, the dexamethasone was administered unblinded with no placebo administered in the usual care group. The 60-day mortality was 21% in the interventional group and 36% in the control group ($p = 0.005$), suggesting a mortality benefit to the steroid regimen. It remains unclear, however, if the study results were impacted by the un-blinding of treating clinicians.

Several questions remain regarding the usefulness of corticosteroids in the routine care of ARDS. The benefit of a particular corticosteroid over another or a particular dosing regimen over another remains unknown. Additionally, the long-term impact of corticosteroid use is unclear. Based on the available evidence, it is reasonable to consider corticosteroids in patients with moderate or severe ARDS, early in their course, who have not responded to initial therapies. Corticosteroids should also be administered to patients with non-ARDS indications, such as *Pneumocystis carinii* pneumonia or acute eosinophilic pneumonia. Lastly, corticosteroids should be avoided in patients who have met ARDS criteria for greater than 14 days.

Fluid Management The ARDSNet Fluid and Catheter Treatment Trial (FACTT), noted previously, used a two-by-two factorial design to test the hypothesis that a management strategy of fluid restriction (conservative fluid management) would improve clinically important outcomes in ARDS compared with more generous fluid management strategy (liberal fluid management).[38] Although the strategy of liberal fluid management was based upon a protocol to determine fluid balance, patients' net fluid balance during the first 7 days of the trial resembled that resulting from the non-protocol-directed care in the first two ARDSNet clinical trials (ARMA and ALVEOLI).[4,37]

FACTT investigators developed a detailed fluid management protocol that, except for patients in shock (mean arterial pressure [MAP] <60 mm Hg or on vasopressors for hypotension), used four basic input variables (assessed every 1–4 h) to determine the fluid management instructions: (1) MAP; (2) urine output; (3) effectiveness of circulation; and (4) intravascular pressure (central venous pressure [CVP] or PAOP). In both arms of the study, the protocol goals were MAP greater than 60 mm Hg (or vasopressor independence); urine output greater than 0.5 mL/kg predicted body weight/hour; and evidence for effective circulation, including a cardiac index of at least 2.5 L/min/m^2 in patients with PACs or, in those with CVCs, absence of physical examination findings indicating hypoperfusion of extremities. In the group randomized to conservative fluid strategy, the target intravascular pressure was a CVP less than 4 mm Hg or PAOP less than 8 mm Hg. In contrast, for those randomized to the liberal fluid strategy, targets were a CVP of 4 to 8 mm Hg or PAOP of 8 to 12 mm Hg.

Despite marked differences in cumulative net fluid balance between the conservatively and liberally managed groups, the two showed no statistically significant difference in mortality at 60 days, which was the study's primary outcome (Table 141-13). Nonetheless, compared with the liberal strategy, the conservative strategy resulted in statistically significant improvements in several clinically important outcomes, including decreased duration of assisted ventilation and length of stay in the intensive care unit (Table 141-13). Moreover, the conservative strategy did not worsen the incidence of shock, number of days in shock, frequency or extent of other organ system failures, or rate of use of dialysis. In a long-term follow-up study of some of the survivors of the FACTT trial, randomization to a conservative fluid-management strategy was associated with increased cognitive impairment.[173] While not definitive, these findings highlight the lack of long-term outcomes in the majority of published clinical trials in ARDS. The results of the FACTT trial supports the use of a conservative fluid strategy in managing patients with ARDS who are not in shock; however, the impact on long-term outcomes is unknown.

Hemodynamic Management Using the trial's two-by-two factorial design, the ARDSNet FACTT investigators also compared the safety and efficacy of PACs with CVCs in directing fluid and hemodynamic protocols, as described.[11] Mortality and other important clinical outcomes, such as ventilator-free days, ICU-free days, and organ failure–free days by study day 28 were no different in patients managed with a PAC versus a CVC (Table 141-14). However, use of a PAC was associated with a significantly higher complication rate during catheter insertion—primarily, cardiac arrhythmias. The excess events were attributed principally to the need for passing both a sheath and catheter; none of the adverse events was fatal.

Based on the results, the FACTT investigators recommend using a CVC to guide a hemodynamic and fluid management. The use of

TABLE 141-13 Results of ARDSNet FACTT (Fluids and Catheter Treatment Trial): Conservative Fluid Management Strategy Versus Liberal Fluid Management Strategy

Result	Conservative Strategy (*n* = 503)	Liberal Strategy (*n* = 497)	*p* Value
Cumulative net fluid balance from day 1 to day 7 (mL)			
All patients	−139 ± 491	6992 ± 502	<0.001
Patients in shock at entry	2904 ± 1008	10, 138 ± 922	<0.001
Patients not in shock at entry	−1576 ± 519	5287 ± 576	<0.001
Death at 60 d (%)	25.5	28.4	0.30
Ventilator-free days from day 1 to day 28[a]	14.6 ± 0.5	12.1 ± 0.5	<0.001
ICU-free days from day 1 to day 28[a]	13.4 ± 0.4	11.2 ± 0.4	<0.001
Organ failure-free days from day 1 to day 7[a,b]			
Cardiovascular failure[c]	3.9 ± 0.1	4.2 ± 0.1	0.04
CNS failure[d]	3.4 ± 0.2	2.9 ± 0.2	0.02
Renal failure[c]	5.5 ± 0.1	5.6 ± 0.1	0.45
Hepatic failure[c]	5.7 ± 0.1	5.5 ± 0.1	0.12
Coagulation abnormalities[c]	5.6 ± 0.1	5.37 ± 0.1	0.23
Dialysis to day 60			
Patients (%)	10	14	0.06
Days of dialysis	11.0 ± 1.7	10.9 ± 1.4	0.96

CNS, central nervous system.

Plus–minus values are means ± SE.

[a] *This was an a priori secondary outcome. Death at 60 d was the primary outcome.*

[b] *Cardiovascular failure, systolic blood pressure <90 mm Hg, or receiving a vasopressor other than dopamine at 5 μg/kg/min or less; CNS failure, Glasgow Coma Scale of 12 or less; renal failure, serum creatinine ≥mg/dL (177 μmol/L); hepatic failure, serum bilirubin ≥2 mg/dL (34 μmol/L); coagulation abnormalities, platelet count of 80,000/μL or less. Number of days without organ failure is determined by subtracting the number of days with organ failure from the lesser of 28 or from number of days until death.*

[c] *This difference was not significant from day 1 to day 28.*

[d] *This difference was still statistically significant from day 1 to day 28.*

Data from National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network, Wiedemann HP, Wheeler AP, et al. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med. 2006;354(24):2564–2575.

the PAC in the United States had been declining, even prior to the publication of the FACTT trial, as evidence had been accumulating against routine use.[10] However, clinicians may elect to use a PAC in selected circumstances, for example, determining the adequacy of cardiac output in mixed shock, measuring the oxygen saturation of mixed venous blood, calculating the degree of intrapulmonary shunt, or searching for equalization of diastolic pressures during suspected cardiac tamponade.

Recruitment Maneuvers Lung recruitment maneuvers are defined as the application of CPAP aimed at "recruiting" or opening totally or partially collapsed alveoli. The alveoli are then kept inflated during expiration using an appropriately high level of PEEP. In one study of a "lung-protective" strategy utilizing low tidal volume ventilation and extra-high PEEP, recruitment maneuvers were performed by maintaining a CPAP level of 35 to 40 cm H_2O for 30 s.[149] Others advocate application of equivalent or higher pressures for longer periods.

No controlled clinical trial supports the efficacy of recruitment maneuvers alone to improve clinically important outcomes, such as mortality or ventilator-free days. Studies of recruitment maneuvers have generally used physiologic end points, for example, improvement in oxygenation.[174,175] In a subset of patients treated with high levels of PEEP in the ARDSNet trial comparing high versus low PEEP in ARDS, no clinically relevant improvements in arterial saturation were noted.[176] However, complications, such as transient hypotension and slight drops in arterial saturation during the maneuver, were reported. On the other hand, other clinical studies have reported that recruitment maneuvers improve oxygenation in patients on relatively low levels of PEEP, receiving large tidal volumes, or maintained on paralytics.

The Alveolar recruitment in ARDS (ART) trial, published in 2017, tested a ventilator management strategy that paired a lung recruitment maneuver with aggressive PEEP titration according to the best respiratory-system compliance against a conventional low-PEEP strategy.[177] The 28-day mortality was statistically higher in the experimental group (55.3%) when compared to the control group (49.3%). Additionally, the experimental lung recruitment strategy increased the risk of barotrauma and the need for vasopressors or hypotension in the first hour, raising significant concerns regarding the safety of such a strategy. Because no controlled clinical trials demonstrate efficacy in clinically relevant end points, and because there are potentially harmful adverse effects, routine use of recruitment maneuvers is not recommended in ARDS. Likewise, in the absence of data showing efficacy, routine use of ventilator "sighs" exceeding peak pressures of 30 cm H_2O (the threshold used in the ARDSNet clinical trial that showed improved survival) is also not recommended. Some clinicians may use recruitment maneuvers with higher pressures as part of salvage therapy for patients with severe refractory hypoxemia (Table 141-12).

Inhaled Nitric Oxide In 1993, Roissant et al. published a study of inhaled nitric oxide (NO) as a novel therapy for ARDS.[178] Given via inhalation, NO selectively vasodilates pulmonary capillaries and arterioles that serve *ventilated* alveoli, diverting blood flow to these alveoli and away from areas of shunt. Lowering of the pulmonary vascular resistance, accompanied by lowering of the pulmonary

TABLE 141-14 Results of ARDSNet FACTT (Fluids and Catheter Treatment Trial): Use of Pulmonary Arterial Catheter (PAC) Versus Use of Central Venous Catheter (CVC) to Direct Fluid and Hemodynamic Management Protocols

Result	Pulmonary Artery Catheter Group ($n = 13$)	Central Venous Catheter Group ($n = 87$)	p Value
Death at 60 d (%)	27.4	26.3	0.69
Ventilator-free days from day 1 to day 28[a]	13.2 ± 0.5	13.5 ± 0.5	0.58
ICU-free days from day 1 to day 28[a]	12.5 ± 0.5	12.0 ± 0.4	0.4
Number of catheters inserted[b]	2.47 ± 0.05	1.64 ± 0.04	<0.001
Number of complications per catheter	0.08 ± 0.01	0.06 ± 0.01	0.35
Total number of catheter-related complications per group[b]	100	41	

Plus–minus values are means ± SE.

[a] *This was an a priori secondary outcome. Death at 60 d was the primary outcome.*

[b] *This includes the sheath for PAC, PAC, and CVC for subjects in the PAC group and sheath (n = 6) and CVC for subjects in the CVC group.*

Data from National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network, Wheeler AP, Bernard GR, et al. Pulmonary-artery versus central venous catheter to guide treatment of acute lung injury. N Engl J Med. 2006;354(21):2213–2224.

artery pressure, appears maximal at very low concentrations (0.1 ppm) in patients with ARDS. Beneficial effects on oxygenation take place at somewhat higher inspired concentrations of NO (1–10 ppm). Rapid inactivation of NO by hemoglobin prevents unwanted systemic hemodynamic side effects, but also requires continuous delivery of gas through the ventilator circuit. Thus, if continuous delivery of NO is interrupted (e.g., during patient transport or due to NO supply exhaustion), precipitous and life-threatening hypoxemia and right-sided heart failure may occur.

Inhaled NO has been studied in several controlled clinical trials in patients with ARDS.[179–181] While demonstrating improvements in oxygenation in some patients, inhaled NO did not improve survival in any of the trials. Based on these trials, the routine use of inhaled NO in ARDS is not recommended. Some clinicians may consider using inhaled NO as a salvage intervention (Table 141-12). However, a much less costly alternative, inhaled prostacyclin (epoprostenol/iloprost), is available. Although less well studied than inhaled NO, inhaled prostacyclin seems to improve oxygenation to the same degree in many patients with ARDS.[182]

Extracorporeal Life Support Extracorporeal Life Support (ECLS) is a therapy that utilizes an external artificial membrane and a mechanical pump to provide gas exchange and systemic perfusion in patients with failure of lung and/or heart function. The use of extracorporeal gas exchange, such as extracorporeal membrane oxygenation (ECMO) or extracorporeal CO$_2$ removal (ECCO$_2$R), is based on the hypothesis that more patients will survive if the lung is allowed to recover from its injury by "resting" using extracorporeal gas exchange temporarily. Although this hypothesis was initially stimulated by the desire to decrease the risk of pulmonary oxygen toxicity, its assessment can now be justified in regard to the techniques' potential roles in reducing VILI.

In the 1970s, a large-scale study on use of ECMO in patients with severe ARDS demonstrated that it offered no survival benefit to patients whose mortality was extremely high (approximately 90%).[183] Similarly, a randomized controlled trial in severely ill patients with ARDS reported in 1994 did not find improved survival using ECCO$_2$R.[184] The therapy received renewed attention during the H1N1 influenza pandemic of 2009.[185] Significant technologic advances, along with a population of previously healthy patients infected with influenza and suffering from severe ARDS, prompted the increased use of ECLS.

More recently, two large contemporary trials examining the utility of ECMO in ARDS have been published.[162,163] The first, the Conventional Ventilatory Support versus Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure (CESAR) Trial randomized 180 patients with severe, but potentially reversible, respiratory failure to conventional therapy or referral to a single, specialized ECMO center for consideration for ECMO.[162] Death or severe disability, the study's primary outcome, occurred in 53% of the conventional arm versus 37% of those referred to the ECMO center. Among those referred to the ECMO center, 76% received ECMO. While the study demonstrated a statistically significant finding, the study design makes it impossible to distinguish the effects of the ECMO therapy from those of a specialized referral center. The second trial, the ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial randomized 124 ARDS patients receiving mechanical ventilation for less than 7 days and met one of three criteria to receive immediate veno-venous ECMO or continued conventional treatment.[163] The three criteria for enrolment were a $\text{Pa}_{\text{O}_2}/\text{FI}_{\text{O}_2}$ <50 mm Hg for more than 3 hours, a $\text{Pa}_{\text{O}_2}/\text{FI}_{\text{O}_2}$ <80 mm Hg for more than 6 hours, or an arterial blood pH <7.25 with a Pa_{CO_2} >60 mm Hg for more than 6 hours despite optimal ventilator management. The patients were managed with lung protective ventilation and physicians were strongly encouraged to use neuromuscular blocking agents and prone positioning before randomization. The primary outcome of 60-day mortality occurred in 35% in the ECMO group and 46% in the control group with a relative risk of 0.76, 95% confidence interval 0.55 to 1.04, and $p = 0.09$. Despite an 11% absolute mortality difference, the results did not achieve the pre-specified statistical threshold of 0.05. Crossover to ECMO occurred in 28% of patients in the control group, possibly impacting the results. Given these results, some specialized centers offer ECLS to a highly selective group of adults with severe ARDS and consider the technique as a safe life-saving salvage intervention (Table 141-12).[186]

Other Therapies Several other therapies have been the subject of ongoing research in ARDS, including statins, beta agonists, macrolide antibiotics, mesenchymal stem cells (MSCs), and aspirin.

Given their effects on inflammatory cytokines, statins were investigated as a therapeutic in ARDS, but in several large trials failed to demonstrate a benefit.[187–189]

Beta-agonists stimulate removal of fluid from flooded alveoli by stimulating the epithelial sodium pump and promoting active transport of sodium out of the alveoli (with water following passively according to osmotic gradients) and therefore, were considered as a therapy for ARDS. However, two large, randomized controlled trials failed to demonstrate a mortality benefit from beta agonist.[39,190] One of these trials was actually stopped early for increased mortality among the beta-agonist arm.

Animal studies and an observational cohort study of macrolide antibiotics have suggested they may have a positive effect in

ARDS.[191,192] This evidence requires a prospective clinical trial prior to routine use of macrolides in ARDS.

Preclinical studies have demonstrated promising results with exogenous administration of MSCs resulting in attenuated lung injury and improved tissue repair.[193] Phase 1 and 2 randomized controlled trials have demonstrated safety and feasibility of MSC infusions.[194,195] Several larger trials are planned or ongoing testing the role of MSCs in ARDS.

Both preclinical and observational studies have suggested the antiplatelet and anti-inflammatory drug, aspirin, may prevent the development of ARDS in those at risk.[196,197] However, in the LIPS-A trial, aspirin provided no benefit in preventing ARDS.[81]

CLINICAL COURSE, OUTCOME, AND LONG-TERM SEQUELAE

The clinical course and outcomes of ARDS have been better delineated in recent years. Both pulmonary and nonpulmonary outcomes have been investigated.

Clinical Course and Duration

The course of illness varies considerably in severity and duration among patients. ARDS may last for a few days or even less (e.g., ARDS from opioid exposure, with the patient recovering rapidly after the initial insult). Alternately, ARDS from other causes may last several months and involve a prolonged ICU course. Patients can recover or die at any point in the course of ARDS. Using the new Berlin definition of ARDS, the median duration of mechanical ventilation is approximately 5 days, 7 days, and 9 days for mild, moderate, and severe ARDS, respectively.[9] Up to 25% of patients remain on mechanical ventilation for longer than approximately 2 weeks, many for much longer. Most ARDS-related deaths occur within the first 2 weeks, with one-third occurring by day 7, two-thirds by day 14, and three-fourths to four-fifths by day 28.[33]

The mortality rate of patients on mechanical ventilation after 2 to 4 weeks of persistent ARDS is about 30% over the ensuing 2 to 6 months. These rates are similar to the overall mortality rate (at 180 days) for patients enrolled in ARDSNet clinical trials in which low tidal volume ventilation was used. The findings highlight the importance of continued supportive care in the ICU and vigilance aimed at reducing nosocomial complications.

Causes of Death

Approximately one-third of ARDS-related deaths occur in the first 7 days.[33] Most are related to the underlying disease or injury, that is, to events occurring before the onset of ARDS. The majority of patients who die succumb after 7 days, with these late deaths also commonly due to the underlying injury or illness. Other causes include complications occurring contemporaneously with, or after the onset of, ARDS. The most common cause of death in this group of patients is sepsis, with associated multiple organ system failure. Of note, only a relatively small fraction of patients—10% to 20% of all patients with ARDS—die a respiratory death due to irreversible hypoxemia or refractory respiratory acidosis. Therefore, not surprisingly, clinical trials of interventions aimed selectively at improving gas exchange (e.g., use of inhaled nitric oxide or exogenous surfactant) have not demonstrated improved survival.

Long-Term Sequelae

Recent studies indicate that many survivors of ARDS have medical problems and a compromised quality of life, both of which persist well beyond their initial ICU stay.[198–200] Impaired pulmonary, neurologic, musculoskeletal, cognitive, and psychosocial functions have been documented in survivors of ARDS. Furthermore, survivors have a poorer quality-adjusted survival than do critically ill subjects without ARDS.

Research into these disorders is in the early stages; the etiology and pathophysiology of are incompletely understood. Recognition of the problems affecting survivors of ARDS and referral for appropriate evaluation and therapy constitute important components of overall care. With improved therapy of ARDS resulting in greater survival rates, clinicians should anticipate an increase in the prevalence of long-term sequelae.

Health-Related Quality of Life

Health-related quality of life (HRQL) has become increasingly recognized as important in the evaluation of patient-centered outcomes in recovery from a variety of illnesses. A number of studies have evaluated HRQL in ARDS survivors.[198–205] Tools used to assess HRQL include the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36), St. George's Respiratory Questionnaire, Quality of Well-Being Scale, and Sickness Impact Profile. Each has illustrated impaired quality of life in survivors of ARDS compared with various control populations, including critically ill subjects without ARDS, and patients with chronic diseases (including cystic fibrosis). In general, impairments in HRQL improve over the first 3 months following discharge from the ICU and appear to plateau by 1 year. Studies of interventions to improve HRQL are under way.

Pulmonary Sequelae

Studies of pulmonary function following ARDS are affected by inconsistent disease definitions, methodologic problems due to lack of patient follow-up, and heterogeneity of pre-existing pulmonary diseases. Consequently, a range of lung function impairments has been reported following recovery.[199,200,203,206,207] Although a proportion of survivors of ARDS may have impaired diffusion capacity or restrictive or obstructive abnormalities, restoration of normal lung function occurs in a substantial proportion. In the Toronto ARDS Outcomes study, spirometry and lung volumes improved rapidly among survivors, reaching normal in most subjects by 6 months.[199] Diffusion capacity is mildly impaired in many patients after ARDS, but it may return to normal by 2 to 5 years among survivors.[199,200] Given the severely impaired physical function domains reported in HRQL surveys and the relatively mild pulmonary impairment, investigation has more recently focused on other limitations and causes of symptoms in survivors of ARDS.

Physical and Neuromuscular Sequelae

In the previously noted Toronto ARDS Outcomes study, persistent physical impairment in survivors of ARDS was assessed.[199,200] Despite improvement in pulmonary function at 1 year following their ICU stay, this cohort had low exercise capacity, weakness, and decreased physical quality of life as far as 5 years after their acute illness. Risk factors for these findings included multiorgan dysfunction in the ICU, prolonged duration of ARDS, treatment with corticosteroids during the ICU stay, and increased comorbid disease burden. Although the basis for many of the abnormalities is not clear, a number of patients demonstrated a range of abnormalities, including critical illness polyneuropathy, ICU-acquired myopathy (critical illness myopathy), entrapment neuropathy, and heterotopic ossification.

Cognitive and Psychological Sequelae

Cognitive impairments can cause major limitations in the ability to return to work, affect mood, and lead to increased healthcare expenditures. Study of long-term cognitive function in survivors of ARDS indicates that many have impaired memory, reduced attention, and decreased concentration and processing speed.[173,198–200,208] The abnormalities appear to be associated with the number and severity of hypoxemic episodes in the ICU. Similar to physical abnormalities, cognitive dysfunction appears to be worse in the first 3 months following hospital discharge; it may improve for up to 1 year and then reach a plateau.

Depression and anxiety are frequent following ARDS. Several studies indicate that the prevalence of depression is over 25% following recovery.[209,210] These emotional problems are likely multifactorial, including prior hypoxic brain injury and delirium and subsequent limitation of physical function. In addition, some authors have suggested the presence of a major component of posttraumatic stress disorder (PTSD) in survivors of ARDS.[211] Because these disorders are potentially treatable using pharmacologic, behavioral, and cognitive therapies, clinicians should ask survivors about possible depression and anxiety, which, in turn, may improve HRQL.

Finally, in accord with the concept that the ICU team treats patients, as well as their families, clinicians need to be aware that familial caregivers of patients who are survivors of ARDS experience long-term health effects.[212] In particular, they are at increased risk for emotional distress (associated with various factors, including patient depression) and a lower HRQL over all domains tested on the Medical Outcomes Short Form 36. Clinicians providing long-term follow-up care for patients with ARDS should aim to ensure adequate social and other support for their familial caregivers.

SPECIAL CONSIDERATION: CORONAVIRUS DISEASE 2019 (COVID-19) – RELATED ARDS

In the last months of 2019, a novel coronavirus, designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), was identified as the cause of a cluster of severe pneumonia cases in Wuhan, China.[213] Subsequently, SARS-CoV2 spread throughout the world resulting in the ongoing global pandemic that claimed the lives of an estimated 1.8 million persons in 2020, straining health care systems in dozens of countries.[214] The World Health Organization designated the disease resulting from SARS-CoV2 infection Coronavirus Disease 2019 (COVID-19). While the majority of patients who are infected with SARS-CoV2 develop a relatively mild course of disease with mild or no symptoms, many patients develop severe disease, characterized by bilateral infiltrates, profound hypoxia, and acute respiratory failure consistent with ARDS, often followed by septic shock and multisystem organ failure.[213,215–218] The major morbidity and mortality in COVID-19, therefore, is thought to be attributed to acute viral pneumonia that progresses to acute hypoxic respiratory failure and ARDS.

Estimates of the prevalence of severe COVID-19 among SARS-CoV2–infected individuals varies across epidemiologic studies; however, early in the pandemic it was estimated that as many as 20% of patients infected with SARS-CoV2 required hospitalization, and up to 25% of hospitalized patients required intensive care.[213,214,219,220] Among critically ill patients with COVID-19, ARDS is common and the Berlin criteria are met in nearly all patients requiring invasive mechanical ventilation. Observational studies have identified several important risk factors for severe illness driven predominately by advanced age and medical comorbidities.[219–222] While COVID-19–related ARDS have been observed across individuals from all age groups, older age is strongly associated with severity of illness and mortality. Comorbidities associated with worse outcomes include cardiovascular disease, hypertension, chronic lung disease, diabetes mellitus, cancer, chronic kidney disease, and obesity.[213,219–225] Additionally, cigarette smoking and chronic exposure to elevated air pollution are also associated with COVID-19 outcomes similar to non–COVID-19–related ARDS.[53,56,57,226,227] In multiple patient cohorts, male sex has also been associated with severity and mortality of COVID-19.[220,223] In the United States, Black, Hispanic, and Native American individuals have constituted a disproportionally high number of severe cases and deaths attributed to COVID-19 compared to non-Hispanic Whites.[228,229] While the exact reason for this disparity is unknown, it is hypothesized that long-standing racial and ethnic disparities in American society in general and healthcare in particularly account for much of these findings.[230]

The presentation of ARDS in COVID-19 is similar to that of non–COVID-19–related ARDS. It is characterized by the acute onset of bilateral noncardiogenic pulmonary infiltrates and severe hypoxemia. However, early in the pandemic several clinicians reported unique aspects of ARDS in COVID-19. First, investigators described a dissociation between the severity of hypoxemia and relatively well-preserved lung mechanics in some patients with COVID-19–related ARDS.[216,231] This observation led to a debate as to whether COVID-19–related ARDS is "typical" ARDS and if it requires distinct management strategies.[232,233] In a study of 301 patients with COVID-19–related ARDS, median static compliance was 28% higher compared with a historic control population of ARDS unrelated to COVID-19; however, the large majority of static compliances measured in the COVID-19 population were well within the range of those observed in classic ARDS cohorts.[234] Second, while pulmonary microthrombosis is common in ARDS unrelated to COVID-19, coagulation dysfunction has been reported to be particularly common in COVID-19–related ARDS.[234,235] In an autopsy series, lungs from patients who died of COVID-19–related ARDS demonstrate classic diffuse alveolar damage with immune cell infiltration, in addition to widespread endothelial injury and microthrombosis.[236] While endothelial and coagulation dysfunction are common in sepsis-associated ARDS, the microthrombi observed in autopsies of COVID-19 patients were significantly more prevalent when compared with patients who died from influenza-associated respiratory failure. While ongoing research may identify further distinct characteristics of COVID-19–related ARDS, current evidence supports the conclusion that COVID-19–related ARDS largely fits within the heterogenous umbrella of "classic" ARDS.

Given the novelty of the SARS-CoV2 virus, treatment strategies employed for COVID-19–related ARDS are mostly extrapolated from evidence in ARDS prior to the COVID-19 pandemic and include best supportive care measures typical of critical care delivery.[237] Current expert opinion supports the use of a lung-protective mechanical ventilation strategy in all COVID-19–related ARDS patients requiring invasive mechanical ventilation, as well as prone positioning in patients with a $\mathrm{Pa_{O_2}/F{\scriptstyle I}_{O_2}}$ <150 mm Hg at institutions with necessary expertise. In patients with moderate to severe COVID-19–related ARDS, prone positioning has been demonstrated to increases lung recruitment and improve oxygenation, suggesting the findings in the PROSEVA trial can be extrapolated to COVID-19.[160,238] Early in the pandemic, experts disagreed over the role of corticosteroids in COVID-19 leading to multiple, large, well-conducted clinical trials of corticosteroids.[239,240] The largest trial, the Randomized Evaluation of Covid-19 Therapy (RECOVERY trial), randomized 6425 patients hospitalized with COVID-19 to dexamethasone, 6 mg daily for up to 10 days, versus usual care.[239] Overall, dexamethasone reduced 28-day mortality by 2.8% (22.9% in the steroid group vs. 25.7% in the usual care group). Among patients requiring invasive mechanical ventilation at the time of randomization the mortality was even more significantly reduced in the steroid treatment group (29.3% vs. 41.4% for usual care). Subsequently, a meta-analysis of 7 randomized clinical trials, including RECOVERY, evaluating the efficacy of corticosteroids in critically ill patients with COVID-19 also demonstrated a statistically significant reduction in 28-day mortality and did not identify an increase in serious adverse events with corticosteroid treatment.[240] The studies included in the meta-analysis randomized patients to various corticosteroids at various dosages including the higher dose dexamethasone previous used in DEXA-ARDS; however, the optimal corticosteroid, dose, and duration could not be assessed due to the small size of several trials.[161] There was no evidence, however, suggesting that a higher dose of corticosteroids was associated with a greater benefit than a the lower dose employed in the RECOVERY trial. Many other therapeutics aimed at viral replication or the host immune response have been studied in COVID-19, with some demonstrating a potential benefit, including the antiviral remdesivir,[241,242] Janus kinase inhibitor baricitinib,[243] and interleukin 6 inhibitor tocilizumab;[244,245] Other therapies of unknown benefit that are frequently employed in the sickest patients with COVID-19–related ARDS include neuromuscular blockade, inhaled pulmonary vasodilators, and extracorporeal membrane oxygenation.[237,246] With the advent of effective and safe SARS-CoV2 vaccines, the incidence of COVID-19–related ARDS will hopefully continue to drop;[247,248] however, COVID-19 has brought renewed attention to ARDS and a recognition that therapies are sorely needed to prevent and treat critically ill patients impacted by ARDS both during and after the global pandemic.

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CHAPTER 142

Chronic Hypercapnic Respiratory Failure: Pathogenesis and Management

Jennifer J. Dorsch
Jorge I. Mora

INTRODUCTION

The respiratory control system is made up of three main components: (1) the central neural respiratory generator, (2) the sensory input system, and (3) the neuromuscular effector system.[1] These three systems work in unison for the purpose of carbon dioxide (CO_2) elimination and oxygen (O_2) uptake. By incorporating sensory and chemosensory input, a ventilatory response to physiologic or neuromuscular stress arises, the goal of which is to produce steady alveolar ventilation, while expending minimal energy to meet a person's metabolic needs.

The alveolar–capillary CO_2 gradient is small. Effective elimination of CO_2 requires an active pump mechanism that preserves this diffusion gradient. This is physiologically achieved by the respiratory system but often requires extrinsic mechanical support in disease states. A large diffusion gradient for O_2 makes O_2 transport simpler and explains why supplemental oxygen administration without pump support is often sufficient.

Disease states that affect neuronal stimulation of the muscles of respiration (e.g., congenital central hypoventilation), muscular function (e.g., neuromuscular disease), respiratory mechanics (e.g., kyphoscoliosis, morbid obesity), or dead space ventilation and respiratory pump efficiency (e.g., chronic obstructive pulmonary disease [COPD]) potentially decrease alveolar ventilation and, correspondingly, impair CO_2 elimination. As a compensatory mechanism in disease states, the body may turn to maladaptive respiratory mechanics or breathing patterns which are inefficient and nonsustainable, ultimately resulting in chronic hypercapnic respiratory failure.

Chronic hypercapnic respiratory failure is defined as a steady state partial arterial CO_2 pressure (Pa_{CO_2}) larger than >45 mm Hg during wakefulness. This value is arbitrary, but it is useful in clinical practice, as it allows for standardization of clinical outcomes. In most patients, rather marked abnormalities in the respiratory control system are required before chronic hypercapnic respiratory failure ensues.

Oftentimes hypercapnia first transiently appears during rapid eye movement (REM) sleep, heralding the forthcoming development of chronic hypercapnic respiratory failure and daytime hypercarbia. Mechanical ventilatory support during sleep, both invasive and noninvasive, may delay and, often, reverse this process by enhancing ventilation, achieving eucapnia, and by unloading respiratory muscles during sleep, leading to increased diurnal ventilatory reserve.

This chapter deals with the pathogenic mechanisms at work in the development of CO_2 retention in diseases characterized by increased pulmonary dead space, neuromuscular derangements, or restrictive processes of the lung and chest wall. The compensatory or adaptive mechanisms that help preserve ventilation (e.g., respiratory chemosensitivity, motor responses to alterations in the mechanics of breathing, intrinsic changes in respiratory muscle strength and endurance) and the decompensating, maladaptive responses that predispose to CO_2 retention (e.g., respiratory muscle wasting and fatigue, a rapid, shallow pattern of breathing) will be discussed, as will the concepts involved and technologies utilized in managing chronic hypercapnia.

PATHOPHYSIOLOGY AND MECHANICS OF VENTILATION

In considering hypercapnic respiratory failure, an understanding of respiratory control mechanisms and mechanics, both normal and abnormal, is paramount.

Neuronal Drive to Breathe

Breathing occurs via both automatic and volitional mechanisms. Breathing pattern, amplitude, and rhythmicity are controlled by the respiratory control center in the ventrolateral medulla, which is composed of the pre-Bötzinger complex (pre-BötC), the Bötzinger complex (BötC), and the rostral ventral respiratory group (rVRG).

While eupneic exhalation in normal states of health is passive, BötC, located in the parafacial respiratory group (pRFG), controls active exhalation during states of increased metabolic demand or blood gas derangements (e.g., exercise, hypercapnia, hypoxia). It does this through the recruitment of expiratory abdominal muscles.[2,3] Nearly spatially indistinct from the pRFG is the retrotrapezoid nucleus (RTN), which receives inputs from carotid chemoreceptors, pulmonary stretch receptors, and the hypothalamus.[4,5] The RTN integrates these stimuli and sends projections to the pre-BötC, thus allowing for alterations in respiratory pattern based on sensory inputs.[6] Interestingly the homeobox transcription factor *PHOX2B*, whose mutations cause congenital central hypoventilation syndrome (see below), which is characterized by the loss of automatic responsiveness to hypercarbia during sleep, is located in the RTN.[7]

The pre-BötC is responsible for automatic inhalation through its intrinsic rhythmogenic properties.[2,6,8] Pre-BötC may be influenced by neuronal inputs from mechanoreceptors and chemoreceptors, thus altering the respiratory pattern; however, this input is not necessary for maintenance of respiration. In addition to sensory inputs, µ-opioid receptors are present on pre-BötC neurons, which are responsible for opiate-induced respiratory depression.[4,9]

The rVRG receives and integrates excitatory impulses from the pre-BötC neuronal network supporting inhalation efforts, inhibitory impulses from the BötC neuronal projections which support exhalation, and inputs from the pontine respiratory group (PRG) which analyze input from the hypothalamus, cortex, and nucleus tractus solitarius[10] prior to emitting an impulse to the spinal phrenic and intercostal inspiratory motoneurons, shaping the inspiratory and expiratory pattern.[6] The neuronal impulse generated in the rVRG travels through cranial and spinal motoneurons to effector muscles. The former tract innervates cranial nerves 3, 4, and 5 which control the diaphragm. Additionally, it contributes to airway dilator functions of the larynx, pharynx and tongue which, when activated, maintain a patent airway and decrease resistance to airflow.[10] The latter tract innervates accessory muscles, including scalene, sternocleidomastoid, pectoralis major, trapezius, and intercostal muscles.[11] Through the PRG's input to the rVRG, respiration is further influenced by cortical control, peripheral sensory information (odor, temperature), and visceral/cardiovascular inputs.[10]

Conditions of Altered Neuronal Functioning

Neuromuscular disease, most commonly amyopathic lateral sclerosis (ALS), causes alterations in the neuronal circuitry affecting respiration. Respiratory failure in ALS is multifactorial. Degeneration of upper and lower motor neurons effectively reduces the transmission of the signal to breathe from the medulla to effector muscles. Additionally, lack of stimulation to the muscles of respiration, particularly the diaphragm, causes muscular weakness and atrophy. Respiratory function remains somewhat intact as the disease progresses due to compensatory mechanisms. A number of hypotheses have been proposed as to how this adaptation occurs, including (1) increased central respiratory output from the medulla, (2) augmentation of intact respiratory motor neurons, (3) increase in size of motor unit through neuromuscular junction plasticity, and (4) greater activation of accessory muscles.[12] However, more research needs to be done to characterize the complex interplay of these mechanisms.

In patients with COPD, regardless of the presence or absence of hypercapnia, neuronal output to the diaphragm and accessory muscles of respiration is increased compared with controls.[13] On average patients with COPD have a respiratory drive that is three times that of healthy subjects, which contributed to the previous proposition that COPD—induced hypercapnia was due to respiratory muscle fatigue.[14] Oxidative stress and sarcomeric injury lead to contractile protein wasting and loss of force generating capacity of diaphragm fibers in patients with COPD, in addition to altered peripheral sensory and chemoreceptor input, resulting in altered neuronal output and further adaptive dysfunction. Hypercapnia is now believed to be ultimately due to the mechanical limitations created by chest wall geometric distortions and respiratory muscle remodeling as muscle fails to compensate for higher end-expiratory volumes. Ultimately, decreased minute ventilation arises.

Respiratory Chemosensitivity

Peripheral chemoreceptors are sensory cells in the arterial circulation that monitor the environment outside of the central nervous system (CNS) for changes in pH, O_2, and CO_2, among other parameters. Two of the best-known chemoreceptors are the carotid bodies, located at the bifurcation of the internal and external carotid arteries, and the aortic bodies, located in the aortic arch. Together, these receptors relay information to the CNS which, in turn, increases inspiratory and expiratory muscle activity in proportion to the severity of blood–gas tension fluctuations. The goal is restoration of blood–gas tensions toward normal by modifying alveolar ventilation.

When adjusted for size, the carotid bodies receive the highest blow flow rate of any organ in the body, which allows for nearly continuous sensing of changes in arterial oxygen (Pa_{O_2}), arterial carbon dioxide (Pa_{CO_2}), pH, and temperature.[5] Carotid bodies are most sensitive to changes in Pa_{O_2}. Aortic bodies, on the other hand, operate under a lower blood flow state and respond mainly to changes in Pa_{CO_2}. Peripheral chemoreceptors register and respond rapidly to changes in arterial pH. For example, up to 50% of the acute hypercapnia-induced increase in respiratory drive is due to peripheral chemoreceptor stimulation; the remaining portion of ventilatory augmentation to hypercapnia is accomplished through direct effects of hypercarbia on central chemoreceptors.[15] Peripheral chemoreceptors transmit this information to the central nervous system where it is integrated and relayed to muscles of respiration, causing an increase tidal volume as well as respiratory rate. Alveolar ventilation is augmented in an effort to return Pa_{CO_2} to steady state levels. Central chemoreceptors located in the RTN monitor extracellular pH and thus, function under steady state conditions, rather than during acute fluctuations, thereby constituting the main central site of CO_2 responsiveness.[4,10]

Alterations in Pa_{CO_2} and Pa_{O_2} both result in increased respiratory drive by affecting timing of respiratory motor activity, as well as respiratory muscle activation. Inspiratory muscles increase the rate of change and peak inspiratory intrathoracic pressure, inspiratory airflow, and tidal volume. Expiratory muscles enhance the rate of expiratory airflow; resistance to inspiratory airflow is reduced in the upper airway muscles.[16–18] Additionally, hypoxia and hypercapnia lead to decreased inspiratory time (T_I) and expiratory time (T_E), thus increasing respiratory rate.[19,20] Reductions in T_E are generally out of proportion to the reduction in T_I, thereby increasing the fraction of the respiratory cycle spent in inspiration.

Hypoxia and hypercapnia differ in their effects on the activity of the inspiratory muscles after cessation of inspiratory airflow—so-called post-inspiratory inspiratory activity (PIIA).[11] Hypoxia increases PIIA in both chest wall inspiratory muscles and muscles that constrict the laryngeal aperture. Accordingly, hypoxia has a braking effect on the rate of expiratory airflow. As T_E decreases with increasing hypoxic drive, end-expiratory lung volume increases. PIIA-induced increases in lung volume increase the caliber of the intrathoracic airways and the O_2 content of the lung. Hypoxia-induced PIIA affects the load on the respiratory muscles in complex fashion; PIIA reduces the inspiratory resistive work of breathing, but increases the inspiratory elastic and expiratory resistive work of breathing. It has been suggested, however, that the net effect of hypoxia-induced PIIA is a reduction in overall energy expenditure during breathing. In contrast, hypercapnia diminishes the PIIA.

Role of Blunted Chemosensitivity in Development of Respiratory Failure

The ventilatory response to chemical stimuli (e.g., changes in arterial pH, CO_2, or O_2) is impaired in patients with COPD due to mechanical limitations: hyperinflation, diaphragmatic flattening, chest wall alterations. Additionally, the physiologic response to derangements in oxygen and carbon dioxide is blunted in these patients. For example, patients with COPD who are chronically hypoxic or hypercapnic were found to have a decreased ventilatory response to either increased hypoxia[21] or hypercapnia.[22]

Blunted chemosensitivity to hypoxia and hypercapnia has been proposed as a premorbid and, perhaps, inherited feature of hypercapnic patients with COPD that contributes to the development of respiratory failure. A study comparing subjects with COPD, with and without hypercapnia, to family members without COPD demonstrated that healthy relatives of hypercapnic patients with COPD have a blunted ventilatory response to hypoxia and hypercapnia as compared to normal relatives of eucapnic patients with COPD.[23] These findings may explain the, at times, perplexing lack of correlation between the extent of lung parenchymal distortion and ventilation (Pa_{CO_2}) (Fig. 142-1).

A long-held belief is that when patients with COPD are exposed to hyperoxia, as with inappropriately high supplemental oxygen administration, their respiratory drive will decrease, resulting in an acute rise in Pa_{CO_2} (hyperoxic hypercapnia). This makes theoretical sense since chronically hypercapnic patients are less responsive to increasing CO_2 levels and, thus, are dependent on relative hypoxia spurring their drive to breath, and in part explains hyperoxic hypercarbia. In addition, and more importantly, hypoxemia causes bronchoconstriction via increases in parasympathetic outflow to airway smooth muscle. Accordingly, relief of hypoxemia causes bronchodilation and increased dead space volume. Increased CO_2 in the setting of hyperoxia is largely due to the loss of this hypoxic vasoconstriction, generating ventilation–perfusion distortion that, in turn, leads to an increase in dead space ventilation at the expense of alveolar ventilation (and unchanged minute ventilation), rather than alterations in ventilatory drive[24] (Fig. 142-2).

Respiratory chemosensitivity to both hypoxemia and hypercapnia declines with age.[25] The decline in chemosensitivity with aging

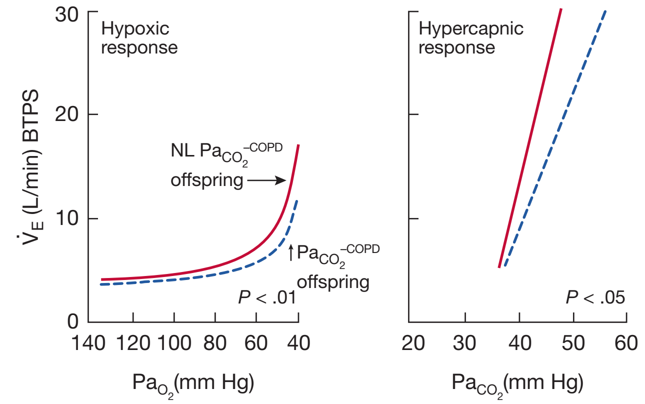

Figure 142-1 Mean isocapnic hypoxia and hyperoxic hypercapnic ventilatory response curves of 12 offspring of hypoventilating patients with COPD *(solid line)* and 10 offspring of eucapnic COPD patients *(dashed line)*. Ventilatory responses to hypoxia and hypercapnia are significantly lower in the offspring of hypercapnic COPD than in the offspring of eucapnic patients with COPD. *(Data from Mountain R, Zwillich C, Weil J. Hypoventilation in obstructive lung disease. The role of familial factors. N Engl J Med. 1978;298(10):521–525.)*

may explain why elderly subjects with lung disease (e.g., COPD) or chest wall disease (e.g., kyphoscoliosis) develop hypercapnic respiratory failure more frequently than young adults. Subjects with the greatest respiratory effort response to changes in Pa_{CO_2} have arterial Pa_{CO_2} values closer to normal than subjects with blunted responses to CO_2, despite the same severity of lung dysfunction. Accordingly, when chemosensitivity is low, subjects with diseases of the ventilatory pump are predisposed to develop hypercapnic respiratory failure. However, since CO_2 retention per se may blunt the response to acute hypercapnia, studies in patients in respiratory failure have not been able to determine whether blunted CO_2 responses are a *cause* or *consequence* of respiratory failure.[26] The important point is that when chemosensitivity is low, subjects are predisposed to develop chronic hypercapnic respiratory failure.[23,27,28]

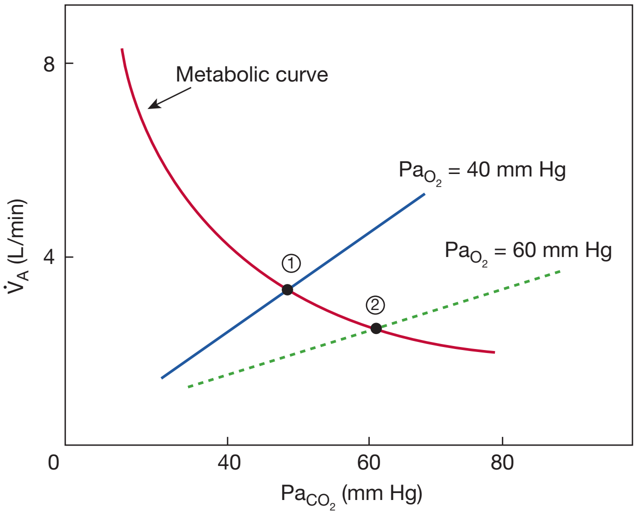

Figure 142-2 Theoretical effects of supplemental O_2 on the ventilatory response to CO_2 and steady-state arterial Pa_{O_2} in subjects with COPD in hypercapnic respiratory failure. Increasing Pa_{O_2} decreases alveolar ventilation and increases Pa_{CO_2} as dictated by effects of O_2 on the CO_2 ventilatory response. The two straight lines represent hypercapnic ventilatory response curves at Pa_{O_2} of 40 and 60 mm Hg. As may be seen, increasing Pa_{O_2} produces a downward, rightward shift of the ventilatory response. In contrast, the hyperbolic line intersecting the ventilatory response lines is the metabolic CO_2–ventilation curve, which represents the effect of increasing alveolar ventilation (independent variable) on Pa_{CO_2} (the dependent variable) when CO_2 production is normal (~200 mL/min). Steady-state alveolar ventilation and Pa_{CO_2} at rest are dictated by intersection of the ventilatory response curves with the metabolic curve (points 1 and 2). Note the increase in Pa_{CO_2} as the ventilatory response with Pa_{O_2} 60 mm Hg intersects at a lower alveolar ventilation and higher Pa_{CO_2} (point 2) compared to the higher ventilatory response when Pa_{O_2} was 40 mm Hg (point 1).

■ Respiratory Muscle Function

The mechanics of breathing require timed, coordinated activation of a number of muscle groups. The primary muscle of respiration is the diaphragm; however, accessory muscles, including the scalenes, intercostals, paraspinals, and sternocleidomastoids, also are recruited under situations of increased respiratory load (e.g., exercise, changes in elastance or compliance of the lung or chest wall, or altered CO_2 or O_2 tension) and contribute to respiratory effort.[29] Contraction of the muscles of the upper airway (genioglossus, alae nasi, posterior arytenoids, pharyngeal dilators, sternohyoid, etc.) increases the caliber of the upper airway and diminishes its susceptibility to collapse during inspiration.[16] Contraction of the muscles of the chest wall (e.g., diaphragm, intercostals, abdominals, and neck muscles) transiently reshapes the thoracic geometry, which allows it to generate negative pressure, resulting in inhalation or inspiration.[16] In patients with normal neuromuscular function and dead space fraction, the diaphragm alone can produce adequate ventilation, as evidenced by normal gas exchange during rapid eye movement (REM) sleep when all muscles of respiration, other than the diaphragm, are paralyzed. However, disease states that affect the strength and endurance of respiratory muscles may result in hypoventilation. Although hypoventilation typically arises first during REM sleep for the reason noted above, over time, it may progress to daytime hypercapnia.

A complex array of mechanoreceptors and proprioceptors whose afferents project to respiratory neurons in the brain stem and higher CNS structures provides the respiratory controller with information about the mechanics of breathing and performance of the ventilatory pump.[16] The sensory receptors providing this afferent feedback and the CNS structures that integrate the feedback into a coordinated respiratory response are not perfectly understood. However, mechanoreceptors in the intercostal muscles that sense muscle tension and length (Golgi tendon receptors and spindle organs, respectively) and pressure and flow sensors in the lower (vagal irritant receptors) and upper airway (larynx and mouth) clearly play a role in shaping the neuromuscular response to alterations in the mechanics of breathing.

■ Alterations in Respiratory Muscle Function and Compensatory Mechanisms

Individuals with decreased lung compliance, as seen in either conditions of increased resistive loading such as obesity, or restrictive diseases such as kyphoscoliosis or pulmonary fibrosis, require increased transpulmonary pressures to produce changes in lung volume as compared to individuals with normal compliance.[30] Their work of breathing is increased, putting them at risk for respiratory muscle fatigue and resultant hypercapnia.

A study evaluating patients with restrictive lung physiology secondary to interstitial lung disease (ILD) showed that such patients have a shorter inspiratory time as well as higher respiratory and lower tidal volume compared with matched controls. Additionally, a higher degree of diaphragmatic and intercostal neuronal stimulation was noted; however, evidence for decreased neuromuscular coupling was noted, as seen in reduced mouth occlusion pressure

($P_{0.1}$) compared to diaphragmatic electromyography (EMG) in patients with ILD compared to controls. These findings could be explained by reduced inspiratory muscle strength.[31] Research on subjects with intact neuromuscular function, as well as normal lung and chest wall mechanics, demonstrated that their respiratory pattern was altered as muscles fatigued. Rapid, shallow breathing was adopted by subjects experiencing respiratory muscle and isolated diaphragmatic muscle fatigue.[32]

In obstructive lung disease such as COPD, respiratory pump function is altered due to extrinsic and intrinsic changes occurring as a function of the disease process. Extrinsic changes refer to alterations in chest wall shape, lung volumes, and systemic metabolism, whereas intrinsic factors relate to respiratory muscle fiber size, composition, and muscle metabolism.[33]

COPD is characterized by increased resistance to expiratory flow and increased end-expiratory volume resulting in hyperinflation. Hyperinflation alters the overall shape of the diaphragm and the length and size of muscle fibers due to the increased diameter of chest wall, putting it at a mechanical disadvantage. Patients with COPD often develop a rapid, shallow breathing pattern in the absence of impending respiratory failure in order to reduce work of breathing by limiting tidal volumes and decrease perceived dyspnea.[34] Increased respiratory rate is required to maintain appropriate alveolar ventilation; however, due to the previously described mechanical limitations, respiratory rate augmentation is limited and hypercapnia often ensues.

In an effort to maintain eucapnia and normoxia, increased neuronal stimulation to the diaphragm and accessory muscles arises in COPD; however, diaphragmatic fatigue is uncommon. For example, even in states of increased phrenic nerve stimulation[35] or exhaustive exercise,[36] a decrease in transdiaphragmatic pressure may not be noted. This is likely due to alteration of the skeletal muscle to compensate for a chronically elevated resistive load. Specific alterations to decrease respiratory fatigue include increased mitochondrial activity, increased ATP generation relative to ATP consumption, and a transition from type II fast-twitch to less fatigable type I slow-twitch muscle fibers.[37,38] Despite these adaptive changes, respiratory muscle fatigue may occur. Contractions producing large increases in intra-abdominal pressure, as seen with forced expiration, produce more diaphragmatic fatigue than muscle activation required to generate large increases in negative intrathoracic pressures, such as maximum inspiratory efforts.[39] This can explain the increased incidence in diaphragmatic fatigue in patients with advanced COPD who rely on accessory muscles of respiration to aid in maintenance of alveolar ventilation. Diaphragm fatigue is presumed to result from compromised blood flow to the muscle during the periods of increased intra-abdominal pressure required for expulsive efforts.[39]

■ Effects of Sleep

Chemoreceptor responses to chemical stimuli to breathing are deeply influenced by sleep. O_2 and CO_2 chemosensitivity are depressed during slow-wave and REM sleep. During wakefulness ventilation is largely independent of changes in Pa_{CO_2}: ventilation persists even when Pa_{CO_2} is less than about 30 to 35 mm Hg. Persistence of ventilation in the setting of hypocapnia (the so-called wakefulness drive to breathe) probably represents the effects on medullary neurons of inputs activated by auditory, visual, and tactile stimuli. In contrast, in the sleeping state, the ventilatory response to CO_2 extrapolates to zero ventilation in the hypocapnic range. In fact, apnea occurs when Pa_{CO_2} falls only 4 to 6 mm Hg below waking eucapnic levels. Sleep-related changes in chemosensitivity, therefore, underlie the recurrent periods of apnea and hyperpnea and exaggerated hypercapnia that occur in some patients with diseases of the lung and chest wall.

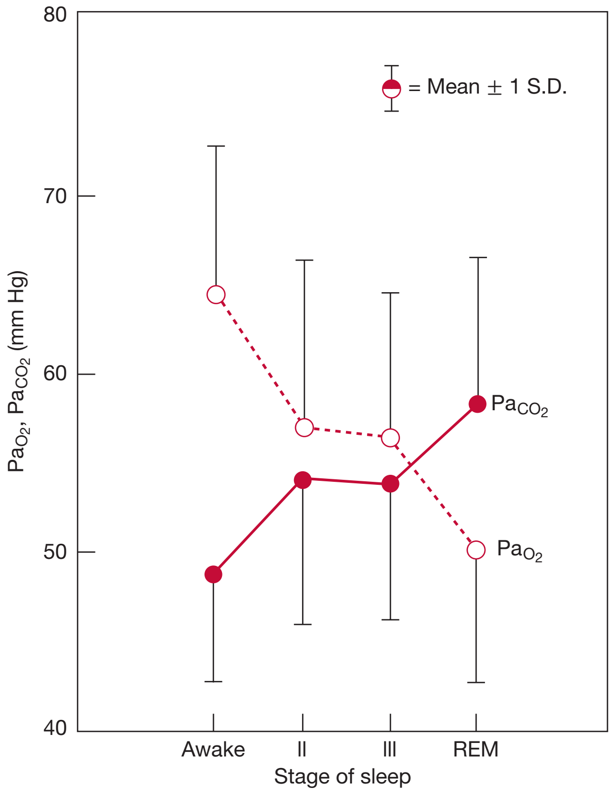

Figure 142-3 Changes in steady-state arterial P_{CO_2} during sleep in eight patients with stable COPD. Note that arterial P_{CO_2} increases and arterial P_{O_2} decreases during sleep. Greatest changes occur during REM sleep. For Pa_{CO_2}, average increase is 10 mm Hg. *(Data from Koo KW, Sax DS, Snider GL. Arterial blood gases and pH during sleep in chronic obstructive pulmonary disease. Am J Med. 1975;58(5):663–670.)*

The increase in respiratory motor activity induced by derangements in respiratory mechanics is also state-dependent—that is, heightened activity in awake subjects is absent in sleeping or anesthetized subjects. REM sleep, in particular, impairs the "load" response and causes collapse of the upper rib cage during inspiration, which adversely affects the level of ventilation as well as its distribution. Descending inhibitory drives to spinal α- and spindle γ-motor neurons in REM sleep cause atonia of all the respiratory muscles except the diaphragm. The diminished or absent load response during sleep explains the exaggerated increases in Pa_{CO_2} that occur during these periods in patients with lung and chest wall disorders. In fact, REM sleep is the period in which Pa_{CO_2} is highest and Pa_{O_2} lowest in patients with stable COPD (Fig. 142-3).

USE OF NONINVASIVE POSITIVE PRESSURE VENTILATION (NIPPV) IN HYPOVENTILATION

NIPPV for hypoventilatory syndromes of any nature rely on the use of home-based portable, battery-capable, and alarm-equipped life-support ventilators. NIV is provided using pressure-cycled ventilatory modes: bilevel pressure support (PS) with spontaneous and timed breaths (bilevel/BPAP S and S/T) or bilevel pressure control (PC). BPAP S/T allows for both patient-triggered (flow or pressure) breaths as well as time-triggered breaths. With PC all breaths are supported.

For BPAP S/T and PC modes, a backup rate is set as well as an inspiratory time (Ti). The inspiratory pressure (IPAP) and expiratory pressure (EPAP) are set and do not vary in PS or PC. Spontaneous/patient-triggered breaths are supported until the patient-generated inspiratory flow reaches a preset decline from its peak which induces ventilator cycling (transition from inspiration to expiration). Timed breaths are supported for the entire preset Ti. Consequently, tidal volume (Vt) will be defined by intrinsically variable respiratory system mechanics (e.g., lung compliance, thoracic recoil) and Ti. This translates into almost minute-to-minute variability in minute ventilation (MV) and, likely, a decrease in ventilation as NMD progresses.

Either PS or PC can be coupled with software modifications designed to provide a steady Vt and MV (volume-assured pressure support or VAPS). Note that VAPS is not a ventilatory mode in itself, but rather, an algorithmic manipulation in which the ventilator can sense real-time instantaneous variations in Vt or MV and bidirectionally adjust the level of pressure support (IPAP–EPAP) within an operator-defined range and rate, to reach a target tidal volume. This "adaptive" feature allows maintenance of a steady or "assured" ventilation and enables automatic compensation or "autotitration" for episodic changes in respiratory mechanics (dynamic lung compliance changes due to position, volume status), sleep stages (REM-related hypoventilation), and changes related to progressive ventilatory compromise inherent to NMD.

The ability to control and set a minimum and maximum inspiratory time (Ti min, Ti max) blurs the line between PS and PC. Initially, the breath is fully supported until Ti min is reached (both spontaneous and timed breaths), but once the breath reaches Ti min the rate of flow decline determines the ultimate duration of inspiration beyond Ti min. If flow has not reached the cycling threshold by Ti max, the ventilator will then cycle, effectively terminating inspiration. This algorithm practically makes the interval between the onset of inspiration and Ti min function as pressure control, and the interval between Ti min to Ti max as pressure support.

Current home ventilators with VAPS features can also autotitrate EPAP (VAPS-AE), mirroring auto-CPAPs and providing effective and variable upper airway stenting in patients with overlapping obstructive sleep apnea and nocturnal alveolar hypoventilation. These features are summarized in Fig. 142-4.

SPECIFIC HYPOVENTILATORY SYNDROMES

The vast majority of clinical conditions leading to hypoventilation can be encompassed into four major groups: neuromuscular or thoracic cage diseases, obesity–hypoventilation, chronic obstructive pulmonary disease, and central hypoventilation.

Neuromuscular Disease

A variety of neuromuscular diseases may be complicated by hypercapnic respiratory failure, as discussed below.

Pathophysiology, Disease Progression, and Diagnosis of Hypercapnic Respiratory Failure in Patients with Neuromuscular Disease

The neuromuscular effector component of the respiratory pump is effectively compromised by a variety of conditions generically known as neuromuscular diseases (NMD). The diverse pathophysiologic mechanisms involved, some unique to each entity, affect ventilation in different ways and degrees, but they all converge in producing pulmonary restriction, decreased forced vital capacity (FVC), normal or elevated FEV_1/FVC, low total lung capacity (TLC) and functional residual capacity (FRC), and decreased inspiratory and expiratory forces (MIP and MEP, respectively). What is also unique about NMD is that patients demonstrate an impaired ability to sigh (i.e., a greater than twofold increase in the tidal volume) because of inspiratory muscle weakness. Inability to sigh decreases lung compliance by interfering with the redistribution of surfactant within the alveolar space. Progressive stiffening of the lung leads to microatelectasis and, ultimately, to lobar atelectasis. In addition, expiratory muscle weakness impairs the cough mechanism and causes retention of secretions, contributing to regional atelectasis and reduced FRC and ventilatory reserve.

NMD includes neuropathic and myopathic disorders, such as amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA), muscular dystrophies (MD), myasthenia gravis, poliomyelitis including postpolio syndrome, and glycogen storage and mitochondrial diseases. These conditions affect various components of the nervous system (afferent and efferent conduction, neuromuscular junction, and muscles), potentially leading to chronic hypercapnic respiratory failure.

Congenital or acquired abnormalities of the thoracic cage (e.g., kyphoscoliosis) impair the mechanical coupling generated by muscle contraction and make the thoracic cage–lung apparatus ineffective. These disorders physiologically mirror NMD. The elastic work of breathing is markedly increased. In addition, the mechanical action of the respiratory muscles may be impaired by changes in configuration of the bony structures on which the respiratory

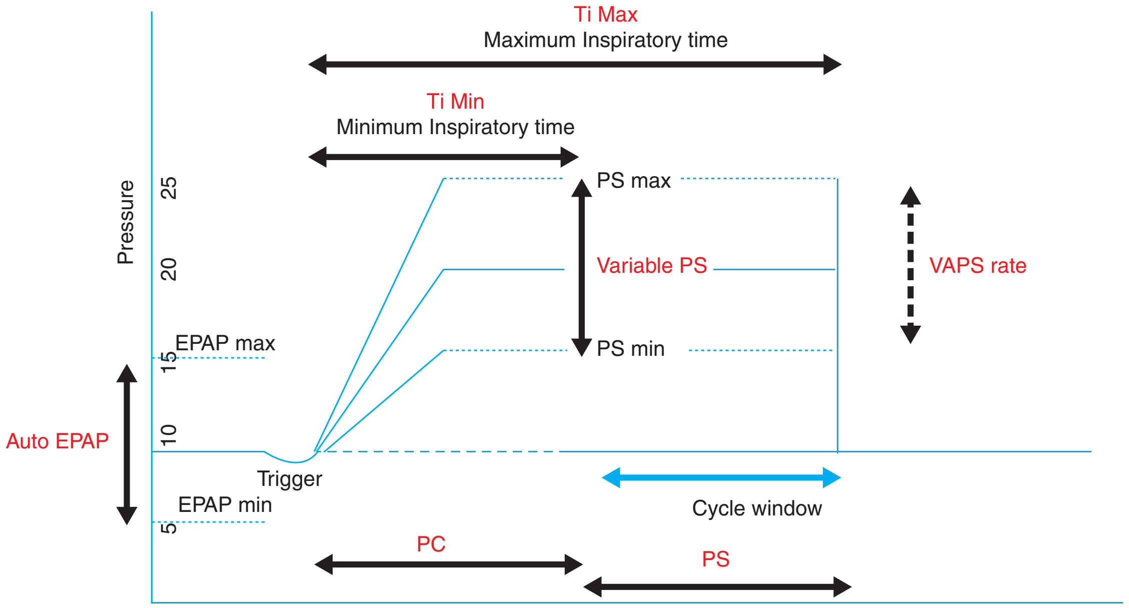

Figure 142-4 Volume-assured pressure support (VAPS). See text for explanation.

muscles insert. Ventilation–perfusion mismatch and increases in the alveolar–arterial O_2 gradient are common. As expected in patients with diminished respiratory compliance, subjects with kyphoscoliosis breathe rapidly and shallowly. The tendency to develop CO_2 retention is a function of the severity of the restrictive process in kyphoscoliosis, as reflected in the Cobb angles, and is predicted separately for the magnitude of scoliosis and kyphosis.

Hypercapnic respiratory failure tends to develop late in life, even if the severity of the spinal deformity has not changed since childhood—that is, stability of the Cobb angles of kyphosis and scoliosis does not preclude development of hypercapnic respiratory failure. It is not clear why respiratory failure ensues late in life. However, several possibilities may be considered. Aging adversely affects compliance of the chest wall, leading to an increase in the elastic work of breathing. In addition, aging diminishes respiratory muscle strength. Finally, chemosensitivity to O_2 and CO_2 declines with advancing age, and it seems likely that the subject's ability to compensate for derangements in blood-gas tensions is progressively impaired.

Patients with ALS, SMA, and some muscular dystrophies tend to develop rapidly progressive respiratory failure, whereas patients with myopathies have a slower, chronic decline in respiratory function. Elevated serum bicarbonate levels greater than 28 mEq/L or elevated arterial carbon dioxide (Pa_{CO_2}) levels above 45 mm Hg tend to be late manifestations of hypoventilation in patients with NMD and no other underlying pulmonary insufficiency.

Hypoventilation generally occurs as a result of inspiratory muscle weakness, with nocturnal hypoventilation being the heralding sign of overt respiratory failure. Since ventilation depends almost exclusively on the diaphragm during REM sleep, transient REM-related hypercapnia may be seen early in NMD, often before sustained diurnal hypercapnia occurs. Polysomnography (PSG) with end-tidal CO_2 ($ETCO_2$) or transcutaneous carbon dioxide monitoring ($PtcCO_2$) , both surrogate markers for Pa_{CO_2}, is useful in diagnosing nocturnal alveolar hypoventilation (Fig. 142-5).

Nocturnal hypoventilation can be diagnosed if Pa_{CO_2} (or a surrogate) is >55 mm Hg during sleep for ≥ 10 min, or Pa_{CO_2} (or its surrogate) increases ≥ 10 mm Hg from wake levels for ≥ 10 min.[40] These definitions are rather arbitrary. Additionally, patients with hypoventilation may also have concomitant OSA that manifests with symptoms of snoring, choking, gasping, witnessed apneas, and daytime somnolence. Important to note is that treatment should include a combination of ventilatory support as well as upper airway stabilization, as repetitive obstructive apneas, if present, can exacerbate underlying nocturnal hypercapnia.

ALS-related respiratory failure represents as good model for explaining how ventilatory failure presents and progresses in NMD and how ventilatory support can be provided. Patients newly diagnosed with ALS should undergo baseline pulmonary testing, including spirometry (particularly vital capacity) and periodic retesting for disease progression. Once FVC is $<80\%$ predicted, negative inspiratory force <60 mm H_2O,[41] peak cough expiratory flow <270 L/min,[42] or nocturnal hypoxia is detected, an evaluation for nocturnal hypoventilation should be considered, even in absence of symptoms. The best indicators of a tendency to develop CO_2 retention in patients with neuromuscular disease are reductions in inspiratory muscle strength (Pi_{max}) and FVC. Reductions in Pi_{max} and FVC to $<30\%$ and 25% of predicted, respectively, are associated with CO_2 retention. Overt symptoms of hypercapnia include daytime somnolence, morning headaches, and decreased cognition or attention.

Treatment of Hypoventilation

Treatment of hypoventilation in the setting of neuromuscular disease entails consideration of a variety of mechanical ventilation modalities, as well as adjunctive measures.

Noninvasive Positive Pressure Ventilation (NIPPV) ALS is the NMD for which NIPPV is most commonly prescribed; however, a consensus for timing of institution of NIPPV in this patient population does not

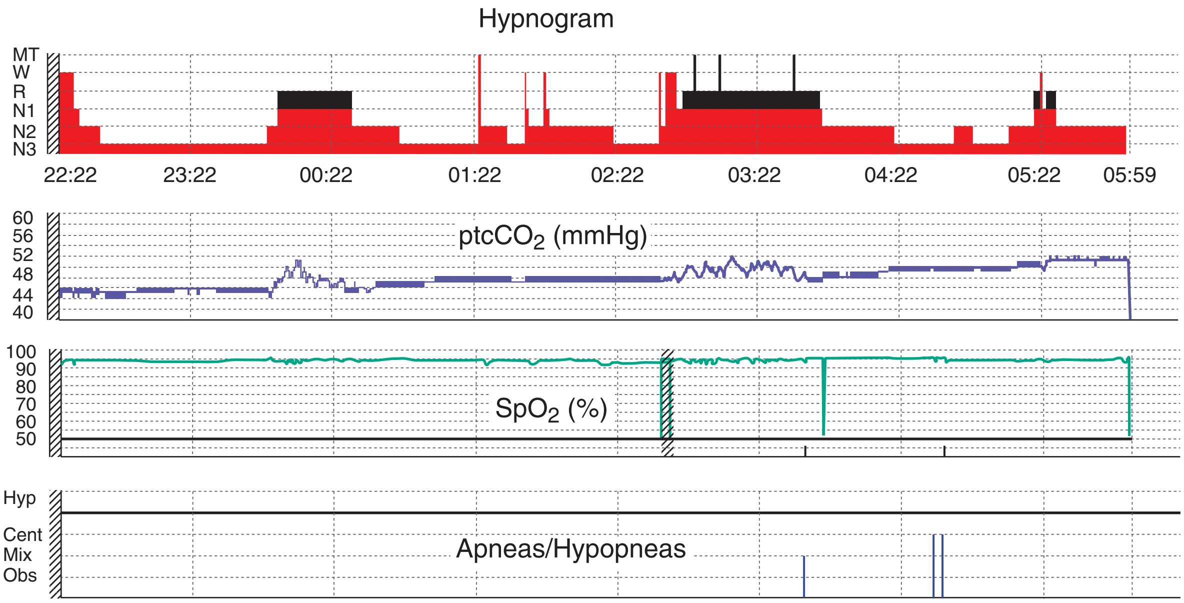

Figure 142-5 Polysomnography synopsis from a 67-year-old non-ventilated male patient with spinal-onset ALS. The figure depicts four tracings representing hypnogram, transcutaneous capnometry, pulse oximetry, and graphical presentation of apneas or hypopneas *(from top to bottom)*. Whereas capnometry shows hypercapnia, which begins during REM and persists during the last third of the night, peripheral oxygen saturation is normal throughout the entire recording. ALS, amyotrophic lateral sclerosis; Cent/Mix/Obs, central/mixed/obstructive apneas; Hyp, hypopneas; N1–N3, non-REM sleep stages; ptcCO_2, transcutaneous carbon dioxide tension; REM/R, rapid eye movement sleep; SpO_2, peripheral oxygen saturation; W, wake. *(Nature and Science of Sleep. 2019:11 97–111. Originally published by and used with permission from Dove Medical Press Ltd.)*

exist.[41] Conflicting data exist regarding the value for FVC at which NIPPV should be initiated; the general consensus recommends starting nocturnal NIPPV once FVC drops to <50% of predicted;[42] however, some investigators have found that initiation of NIPPV once FVC is <75% of predicted reduces mortality in ALS patients.[43] What is clear is that NIPPV consistently prolongs survival in ALS (Fig. 142-6).

In addition to FVC decline, initiation of nocturnal ventilatory support should be considered once one of the following criteria are met: maximal inspiratory pressure (MIP) ≤60 cm H_2O or sniff nasal pressure <40 cm H_2O, or overnight oxyhemoglobin desaturation below 88% for over 5 min.[44]

NIPPV is recommended for patients with ALS in the absence of significant bulbar symptoms, as this group has been demonstrated to have improved morbidity and mortality with NIPPV therapy.[45,46] Nocturnal hypoventilation is often the heralding sign of overt respiratory failure; therefore, ventilatory support should be initiated at the first sign of diurnal hypercapnia.

NIPPV is acceptable in patients without bulbar dysfunction, who are able to protect their airway from aspiration of oral secretions, and whose respiratory muscles are able to sustain the effort of respiration without continuous support. Additionally, NIPPV is appropriate for patients who wish to avoid early tracheostomy.

As NMD progresses and respiratory muscles are no longer able to generate and sustain consistent and effective inspiratory flow, the level of nocturnal NIPPV can be progressively modified to match the patient's needs by taking advantage of proprietary-brand algorithms embedded in Respiratory Assist Devices (RADs) and home ventilators. Such modifications may be effected by cleverly modifying ventilatory parameters and pressure-cycled modes—for example, by transitioning to VAPS pressure-control or lengthening Ti minimum to support the entirety of the breath while keeping the patient on pressure-support or bilevel VAPS (i.e., Ti min = Ti max) and making breaths the same as pressure control breaths.

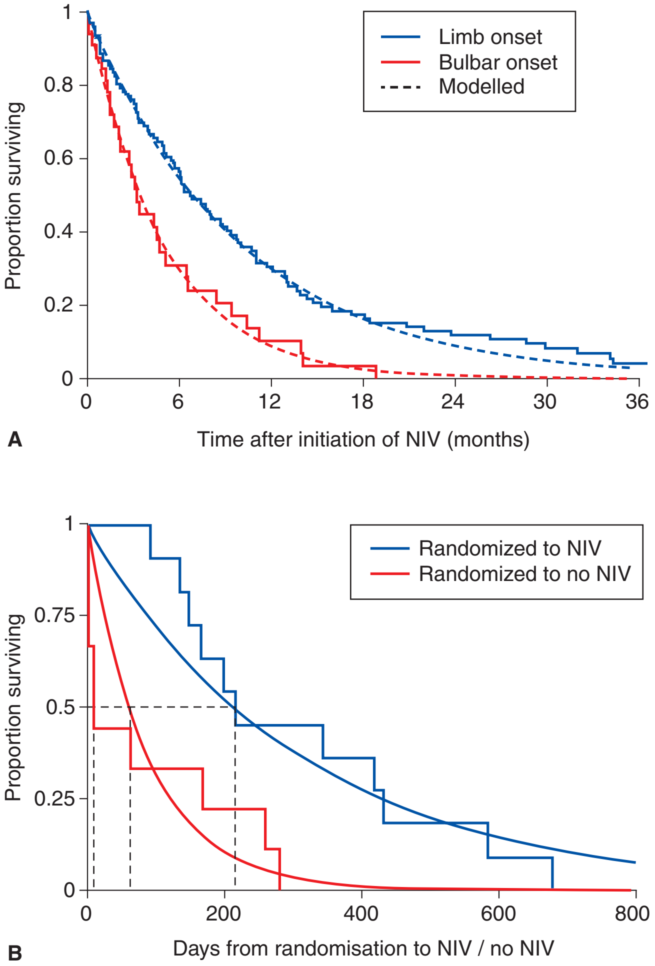

Figure 142-6 **A.** Limb-onset ALS has a better overall survival compared with bulbar-onset. **B.** Institution of NIV in ALS results is a significantly delayed death. *(Reproduced with permission from Knibb JA, Keren N, Kulka A, et al. A clinical tool for predicting survival in ALS. J Neurol Neurosurg Psychiatry. 2016;87(12):1361–1367.)*

Patients with NMD are typically "air hungry" and are often unable to generate an inspiratory flow capable of triggering the ventilator. Effective ventilation and perceived comfort require longer inspiratory times and ventilator-triggered breaths. PC ventilation is sometimes preferred since it assures a Ti for any given level of PS as spontaneous breaths become more ineffective with disease progression (diminished inspiratory effort and inability to sustain flow due to inspiratory muscle weakness).

In NMD, mean pressure support and IPAP are lower in the VAPS algorithm compared with pressure support (PS) for any given tidal volume,[47–49] although studies differ in comparability of respiratory rate and tidal volume. Investigators have reported preserved minute ventilation in both VAPS and PS groups;[49] however, VAPS appears to generate greater, more consistent tidal volumes and lower respiratory rates compared to the rapid shallow breathing seen with PS. This may be related to decreasing tidal volumes when fixed PS settings are used as NMD progresses, resulting in increased rapid shallow breathing. Tidal volume depends on lung mechanics and the ability to sustain and inspiratory flow; the latter decreases as respiratory muscle weakness progresses. The differences in respiratory rate and tidal volume between the VAPS and PS are largely due to the fact that in ALS, breath triggering remains relatively preserved; however, breath cycling decreases with increasing respiratory muscle weakness.[49] Therefore, it is imperative that these patients are treated with a ventilator mode or algorithm that allows for set inspiratory time in order to support an entire breath independently from effort and flow-cycling as the disease progresses.

VAPS and appropriately monitored PS are largely comparable with regard to diurnal oxygenation, CO_2 levels[48] and patient compliance,[49] although some have reported a patient preference of VAPS over PS.[47] A significant benefit of using VAPS is that it can automatically account and compensate for unintentional air leak and adjust pressure support to maintain target tidal volume. This feature can be used to overcome large leaks when VAPS is used invasively in tracheostomy patients the cuff is deflated or an uncuffed tracheostomy tube is placed, thus providing continued ventilatory support while allowing for patient phonation and decreasing local tracheal complications.

Regardless of the ventilatory mode chosen mode, initial settings are generally a minimum tidal volume of 8 cc/kg predicted body weight. Additionally, a highly sensitive trigger should be set to allow for patient-initiated breaths in advanced NMD. Lastly, for flow-cycled breaths based on percentage of peak flow, values must be very low (in the 8%–15% range) to allow for ventilator support through the majority of the breath[48] to ensure adequate respiratory muscle rest. This is confirmed by a decrease in diaphragmatic electromyographic (EMG) activity during sleep, or by an increased inspiratory transpulmonary pressures measured using an intraesophageal balloon in controlled sleep laboratory conditions. Modern home ventilators are able to analyze and report percentage of triggered breaths allowing fine tuning to decrease respiratory muscle load during sleep. As disease progresses, it is common to transition from flow-cycled breaths to Ti-cycled breaths in order to maintain ventilation in the face of weakening inspiratory muscles. Longer Ti equates to larger tidal volumes and recruitment of microatelectatic regions of the lung. Lastly, setting an appropriate back up rate to deliver the majority of breaths is necessary to allow for respiratory muscle rest.

Tracheostomy For patients with bulbar-onset ALS who are severely symptomatic, are unable to clear secretions, and desire to live as long as possible, tracheostomy and invasive ventilatory support are the mainstays of treatment. Important to consider are the potential repercussions of tracheostomy placement, as it complicates care and may require hiring of skilled caretakers or transition to a long-term care facility. The need for continuous, 24-h ventilatory support does not necessarily translate into tracheostomy, as studies have demonstrated success with long-term, continuous use of NIPPV in the absence of significant bulbar symptoms.[45] However, interface (mask)-related skin abrasions and pressure damage, along with altered respiratory secretion clearance, eventually results in transitioning to tracheostomy for continued ventilatory support.

Adjunctive Treatments Coughing helps to mobilize and clear secretions from the airway, thus decreasing risk of atelectasis and subsequent restrictive pulmonary physiology, as well as pneumonia. Coughing requires coordinated activation of a number of muscles to be successful. First, the patient must be able to take in a sufficiently large volume of air and then close the glottis briefly, thereby raising intrathoracic pressure. Thereafter, opening the glottis in conjunction with contraction of abdominal muscles results in forceful expulsion of air, leading to a cough.[50] All of these steps can be compromised in patients with advanced neuromuscular disease, especially if bulbar dysfunction is present, leading to poor secretion clearance and its negative sequelae. Secretion expectoration with coughing requires a minimum peak cough flow of 180 L/min, as measured using a handheld flow meter.[51] If a patient is unable to produce this flow, adjunctive treatments should be implemented in the form of cough assist devices, which can be considered in two categories: those that assist with cough augmentation, and those that facilitate secretion mobilization.

Cough augmentation can be achieved through improvement in exhalation, as well as through support of inhalation. Exhalation support can be achieved via manually assisted cough (MAC) techniques, including costophrenic compression or Heimlich-type abdominal thrusts, which displace the diaphragm up, leading to air expulsion.[52]

In addition, negative pressure can be applied via facemask—a technique called *exsufflation*. Assisted inspiration allows for a patient with NMD to take in an increased volume of air on inspiration, allowing more air to be exhaled and raising peak cough flow in patients with intact glottic function. Assisted inspiration can be used through delivery of breaths via noninvasive ventilation or intermittent positive pressure breathing through the use of a bag-valve mask.[52] These delivery systems can either deliver a single breath or multiple, stacked breaths.

Mechanical insufflation–exsufflation (MI-E) devices function via facemask or are attached to tracheostomy tube and provide positive pressure ventilation, followed by a rapid switch to negative pressure, thereby generating a cough.[53] Modes of assisted inspiration can also be combined with manually assisted cough techniques. MI-E, when used in conjunction with MAC, appears to produce the greatest peak cough flow when compared to MI-E alone or assisted inspiration followed by MAC.[54] In a small pilot study evaluating traditional tracheal suctioning compared with MI-E via a cuffed tracheostomy tube with the cuff deflated, investigators found that MI-E was more effective and better tolerated.[55] To our knowledge, there have been no long-term studies regarding morbidity or mortality outcomes specifically for MI-E devices.[56]

Secretion mobilization techniques include manual chest wall percussion, high-frequency chest wall oscillations (HFCWO), high-frequency chest wall compression (HFCWC), and intrapulmonary percussive ventilation (IPV). Manual percussion, with or without postural drainage, involves percussing a patient's back to loosen and mobilize secretions. HFCWO and HFCWC involve compression of the chest via a pneumatic vest encasing the thorax. The vest inflates and transmits high frequency oscillations to the chest, producing oscillations in airflow and mobilizing secretions. HFWCO repeatedly inflates and deflates, whereas HFWCC tonically inflates and provides superimposed oscillations.[57] IPV involves intermittent positive pressure breathing with high-frequency bursts of airflow that provide internal percussion to the bronchial tree and promote secretion clearance.[52]

OBESITY HYPOVENTILATION SYNDROME (OHS)

Obesity hypoventilation syndrome is a common and important entity, a hallmark of which is hypercapnia. In addition to the discussion below, the reader is referred to Chapter 99, Sleep-Related Hypoventilation Syndromes.

Diagnosis and Pathophysiology

Obesity imposes a mechanical stress and added load on the respiratory system by altering lung mechanics and the work of breathing. The mass loads applied to the thorax and abdomen by excess adipose tissue decrease chest wall compliance and end-expiratory lung volumes, resulting in increases in the elastic and resistive work of breathing. Furthermore, by diminishing airway caliber, obesity predisposes to premature airway closure and atelectasis. This results in areas with low ventilation–perfusion ratios (V/Q) resulting in an increased alveolar–arterial O_2 gradient and arterial hypoxemia.

The excessive body mass also results in increased CO_2 production and O_2 consumption. Increases in metabolism may be two to three times normal in morbidly obese subjects.[58] For example, a doubling in CO_2 production requires a doubling in alveolar ventilation to maintain eucapnia. These metabolic changes require significant increases in minute and alveolar ventilation to maintain eucapnia, dramatically increasing ventilatory demands in a mechanically overloaded system, with inherently diminished ventilatory reserve. Finally, arterial hypoxemia, which is common, induces a further increase in ventilation. Given these stresses, the maintenance of normal blood–gas tensions requires a considerable increase in respiratory motor output and the work of breathing. Increased work of breathing appears to explain the common occurrence of dyspnea in the morbidly obese person.

Not all morbidly obese subjects develop hypercapnic respiratory failure, however. Although body weight alone does not predict the development of hypercapnia, approximately 30% of severely obese subjects with a body mass index (BMI) >35 kg/m^2, and almost 50% with a BMI ≥ 50 kg/m^2, have unexplained daytime hypercapnia. Observations of eucapnic and hypercapnic obese subjects demonstrate that eucapnic subjects have greater increases in diaphragm electrical activity with increases in CO_2 than do hypercapnic subjects. Obese subjects with hypercapnic respiratory failure may have impaired chemosensitivity to hypercapnia and hypoxemia. The sustained gas exchange abnormalities often result in a subset of obese, hypercapnic subjects developing polycythemia, pulmonary hypertension, and cor pulmonale (Fig. 142-7).

The diagnosis of obesity hypoventilation syndrome (OHS) is made in a patient who has a body mass index (BMI) ≥ 30 kg/m^2 in conjunction with daytime hypercapnia, with $Pa_{CO_2} > 45$ mm Hg, in the absence of other causes of alveolar hypoventilation.[59] OSA is present in the vast majority of patients with OHS, but it is not a requisite to make the diagnosis.

Sleep-related hypoventilation is defined as an increase in $PaCO_2$ or a surrogate marker (e.g., $ETCO_2$, $PtcCO_2$) of >10 mm Hg during sleep (compared with wake supine levels) and to >50 mm Hg for >10 min.[40] This is a rather arbitrary definition, with clinical outcomes more precisely described in the pediatric population. The clinical implications

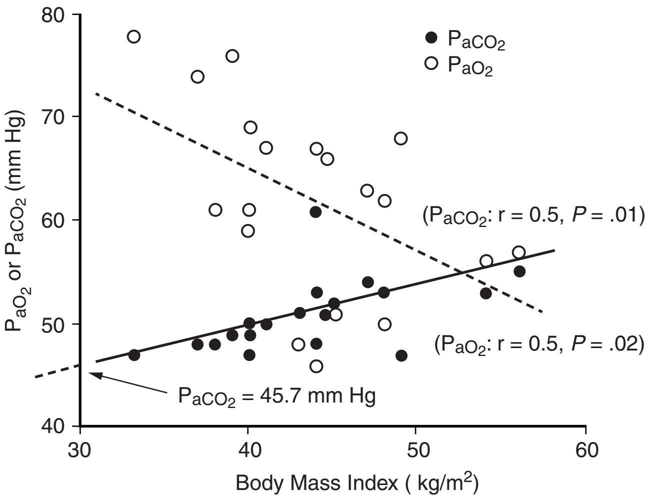

Figure 142-7 As BMI increases, so do gas exchange abnormalities: Pa_{CO_2} steadily increases as Pa_{O_2} decreases for any given BMI above 30 kg/m^2. *(Data from Mokhlesi B, Tulaimat A, Faibussowitsch I, et al. Obesity hypoventilation syndrome: prevalence and predictors in patients with obstructive sleep apnea. Sleep Breath. 2007;11(2):117–124.)*

of fluctuating Pa_{CO_2} during sleep, and whether a variation of 10 mm Hg is more clinically significant than a change of 5 or 15 mm Hg, is speculative at best. If CO_2 fluctuations do not result in hypercapnia during wakefulness, then it is unclear that, aside from heralding diurnal hypercarbia, they have any true clinical significance.

Consideration for OHS should be given to obese patients who are at an elevated risk for OSA, as defined by at least an intermediate pretest probability based on validated-standardized clinical screening tools and questionnaires, a serum bicarbonate ≥27 mmol/L, or significant oxyhemoglobin desaturations unexplained by obstructive events (nonobstructive desaturations) on overnight pulse oximetry.[60,61] A good patient history, pulmonary function tests, and, possibly, a computed tomography (CT) scan of the chest should be obtained to rule out other causes of hypoventilation. Pulmonary function tests may be normal, but they typically demonstrate mild to moderate restrictive physiology. Chest CT should not show evidence of significant parenchymal or pleural disease, thoracic cage malformation, or other causes of restriction.

The mechanism by which OHS leads to chronic hypercapnic respiratory failure is incompletely understood. Various theories include altered chemosensitivity to hypercapnia and hypoxia; leptin resistance; abnormal respiratory mechanics, such as decreased lung compliance and increased restrictive physiology; increased work of breathing leading to muscle fatigue; and obstructive apneas. Fewer than one-third of patients who are obese develop chronic hypercapnia, arguing against altered respiratory mechanics in isolation as the main cause of hypercapnia.[60]

Typically, hypoventilation first develops during REM sleep. This is due to REM-induced paralysis of the accessory muscles of respiration, in conjunction with decreased diaphragmatic excursion from abdominal adiposity and exaggerated upward displacement of the diaphragm when supine. Furthermore, respiratory muscles fatigue due to the increased work of breathing from body habitus, as well as need for increased respiratory rate in response to decreased functional vital capacity and increased resistance seen in obesity,[62] leading to CO_2 retention. As a response to cyclically elevated CO_2 levels, over time, central chemoreceptors develop decreased CO_2 sensitivity,[63] leading to continuous hypercapnia. Additionally, patients with OHS tend to have increased leptin levels and leptin resistance, thus reducing respiratory drive, as leptin is a potent respiratory stimulant.[63]

■ OHS Phenotypes and Their Management

Most patients diagnosed with OHS demonstrate some sleep-related breathing disturbance; however different phenotypes involve varying sleep disturbances. OSA encompasses approximately 90% of the sleep-disordered breathing in OHS; however, 10% have sleep-related hypoventilation in the absence of obstructive events.[64]

Approximately 70% of patients with OHS have severe OSA, defined as an apnea-hypopnea index (AHI)—the average of obstructive, hypopneic, and central events per hour of sleep—of ≥30 events/h; 30% have mild OSA (an AHI of 5–14 events/h) or moderate OSA (an AHI of 15–29 events/h) or a lack of significant obstructive or hypopnea events with continued nocturnal hypoventilation.[64] This distinction leads to differing modes of treatment based on the predominant underlying disturbed breathing pattern during sleep.

OHS with Severe Obstructive Sleep Apnea

Patients with OHS with an AHI >30 tend to be younger and male and to have higher BMI and daytime sleepiness scores compared with patients with OHS without severe OSA. Surprisingly, this phenotype also tends to have less cardiovascular morbidity and mortality.[65] Oxyhemoglobin desaturations are likely to be more pronounced and slower to resolve, due to reduced functional vital capacity in these patients. Additionally, obstructions are longer in duration, leading to hypercapnia. Computer models demonstrate that when periods of apnea are more than three times as long as the terminating hyperventilation, hypercapnia may ensue.[66] By solely decreasing obstructive events, many of these patients are able to achieve eucapnia. Consequently, a large percentage of these patients can be successfully treated with CPAP alone.

OHS without Severe Sleep Apnea

In patients with OHS who lack evidence of severe sleep apnea, but who still demonstrate nocturnal hypoventilation, CPAP is usually an ineffective treatment. This subset of patients often requires NIPPV. A study demonstrated significant reductions in Pa_{CO_2}, serum bicarbonate, and Epworth Sleepiness Scores (ESS) in patients with OHS treated with VAPS compared with lifestyle modification alone.[67] All subjects included were required to use VAPS ≥4 h per day. Additionally, time to emergency department visit was longer in patients treated with NIPPV compared with controls.[68]

Malignant OHS

Malignant obesity–hypoventilation syndrome has been described in a small, observational study as a subset of patients who meet criteria for OHS, whose BMI >40 kg/m^2, and who are admitted to an ICU with evidence of multisystem organ dysfunction.[69] The majority of patients had evidence of left ventricular hypertrophy, left ventricular diastolic dysfunction, and pulmonary hypertension. Since these patients commonly have some degree of pulmonary hypertension, BPAP is the treatment modality of choice, as NIPPV has been shown to impart a positive effect on cardiac structure and function.[70] The American Thoracic Society recommends that patients with OHS hospitalized with respiratory failure be started on NIV treatment during the hospitalization, and that NIV be continued upon discharge. Plans should be undertaken for formal polysomnography and ventilator titration within 3 months of discharge.[61]

Providing ventilatory support (mechanical ventilation, both invasive and noninvasive) to patients with OHS and severe pulmonary hypertension or right ventricular dysfunction, can be challenging at times. Positive pressure ventilation may result in increased right ventricular afterload and acute right ventricular failure and complicate already taxing volume management. NIPPV may also result in worsened V/Q mismatch, producing further hypoxemia despite increases in minute ventilation.

Natural Progression of OHS and Diagnosis of Hypercapnic Respiratory Failure

The diagnosis of OHS often lags behind patient complications from the disease. In fact, patients who are ultimately diagnosed with OHS tend to have increased health care utilization and ICU visits up to 5 years before their diagnosis compared with BMI-matched counterparts without hypoventilation. In order to capture patients at an earlier phase of their disease process, investigators have recommended evaluating base excess in addition to serum bicarbonate levels.[71] Patients with a base excess >2 mmol/L and normal serum bicarbonate level responded to hypercarbic and hypoxic insults more similarly to patients with OHS, raising the concern that OHS may represent a spectrum of disease. Also, patients with OHS are more likely to develop pulmonary hypertension[72] and resultant cor pulmonale compared to BMI-matched patients with OSA alone.[73]

Mortality is elevated for patients with OHS compared with BMI-matched patients with OSA. In one study, a 2-year all-cause mortality in previously hospitalized patients with OSA of 23% was reported, compared with 9% in previously hospitalized patients with simple obesity.[74] Of note, hypercarbia was defined as $Pa_{CO_2} \geq 43$ mm Hg, and the majority of patients with OHS were not discharged with CPAP or NIV treatment. Additionally, in an observational study of patients with OHS who were admitted to the hospital with acute-on-chronic hypercapnic respiratory failure, a 1-year mortality of 18% was reported[75] (Fig. 142-8).

Treatment of OHS: Phenotypic Considerations in NIPPV and Other Forms of Therapy

The clinical management of OHS requires an understanding of how different phenotypes respond to therapy; indeed, different modes of NIPPV can be equally effective. Furthermore, escalation of therapy is not always required to achieve eucapnia. A subset of patients may benefit from additional therapeutic interventions that either facilitate a safe mode of ventilatory support (e.g., tracheostomy) or provide additional clinical benefits when combined with NIPPV.

NIPPV in Low-AHI and Malignant OHS

Noninvasive positive pressure ventilation is a cornerstone of treatment for patients with OHS. The majority of patients can be treated with CPAP; however, in malignant OHS and low AHI groups, bilevel PS, with or without VAPS, should be first-line therapy. For patients who are started on CPAP, but who demonstrate continued hypercarbia three months after starting therapy, despite adequate CPAP settings and patient adherence, NIPPV should be transitioned to bilevel PAP (PS, S or S/T) or VAPS-AE (see “Use of Noninvasive Positive Pressure Ventilation (NIPPV) in Hypoventilation,” above, for details).

These patients often require high levels of PS to overcome the mass load and mechanical stress that overweight exerts over the respiratory system. In addition, recumbency during sleep displaces the abdominal contents rostrally, resulting in ineffective diaphragmatic contraction and basilar atelectasis. For this driving force (PS) to be effectively and homogenously applied across the lungs, a prolonged inspiratory time (Ti) is often needed. A short Ti is likely to result in preferential overdistension of viable, non-atelectatic lung segments (in nondependent apical areas). In contrast, a longer Ti will allow progressive recruitment of atelectatic and microatelectatic segments, resulting in a homogenous distribution of Vt and optimized V/Q.

Studies evaluating modes of ventilation have historically not distinguished between phenotypes and their response to specific modes of mechanical ventilation.

For the majority of patients with the high AHI phenotype of OHS, treatment with CPAP alone resolves apneas and hypoventilation. Average CPAP settings for this group are expiratory positive airway pressures of 12 to 14 cm H_2O with treatment for more than 4.5 h per day.[76] Pa_{CO_2} levels should be reassessed after 2 to 3 months of CPAP adherence to ensure resolution of hypercapnia. If, despite this treatment, Pa_{CO_2} remains elevated (≥45 mm Hg), the patient should be transitioned to noninvasive ventilation with use of bilevel PAP. One investigation demonstrated that patients with OHS whose pretreatment Pa_{CO_2} was >62 mm Hg had more than an eightfold increased risk of persistent ventilatory failure compared with those with a $Pa_{CO_2} \leq 50$ mm Hg, despite treatment with CPAP.[77]

When patients with high AHI–OHS are compared with patients with “lower” AHI–OHS with regard to treatment with CPAP versus NIPPV versus lifestyle modification, NIPPV has been found to significantly reduce Pa_{CO_2} levels compared with the other interventions. However, no significant difference has been observed between serum bicarbonate reduction with CPAP (at mean airway pressure of 11 cm H_2O) compared with NIPPV (average bilevel ST: IPAP 20 cm H_2O, EPAP 8 cm H_2O, rate 14). Both CPAP and NIPPV have been demonstrated to be superior in reducing serum bicarbonate when compared with lifestyle modifications alone.[64]

In patients requiring NIPPV support, AVAPS versus BPAP S/T modes of ventilation have been shown to have similar degrees of patient adherence and to produce equivalent reductions in Pa_{CO_2}. Improvements in daytime sleepiness and quality of life metrics also are similar between the groups.[78,79] The AVAPS-AE algorithm produces lower respiratory rates.[79] Additionally, increased tidal volume, IPAP, and total ventilation have been reported with the AVAPS

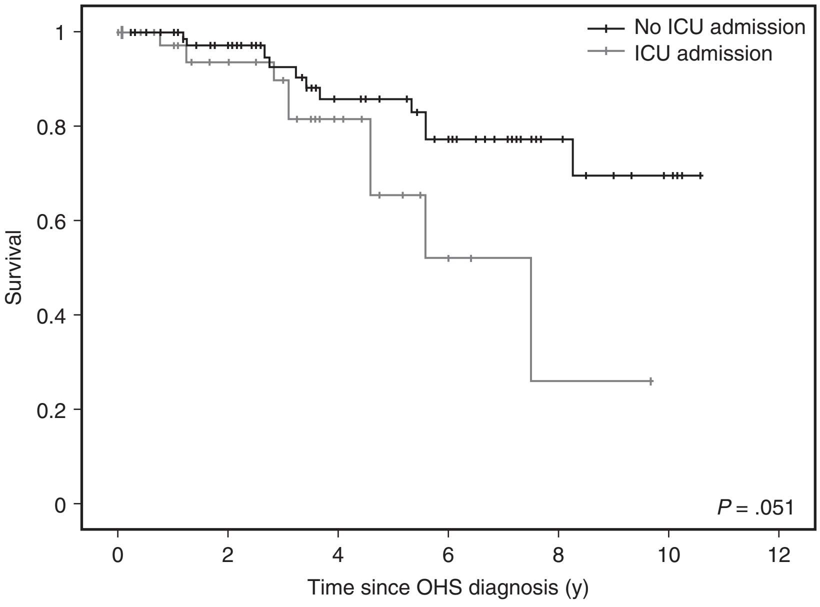

Figure 142-8 Survival of patients with OHS is significantly diminished if the initial diagnosis coincides with admission to ICU with acute hypoxemic respiratory failure. This highlights the importance of early recognition and treatment of this syndrome. *(Reproduced with permission from Chebib N, Nesme P, Freymond N, et al. Acute Respiratory Failure in Obesity-Hypoventilation Syndrome Managed in the ICU. Respir Care. 2019;64(12):1545–1554.)*

algorithm compared with BPAP S/T alone;[80] however, worsened objective and subjective sleep quality were noted with AVAPS compared to S/T, despite improved values for $PtcCO_2$.

Additional studies comparing BPAP with AVAPS to BPAP S/T modes are needed to determine which modality is best tolerated, produces the greatest reductions in CO_2 and mortality, and yields the largest improvement in quality of life. At present, both BPAP with AVAPS and BPAP S/T modes are considered appropriate for use in patients with OHS, given the fact that OHS is not a progressive disease. Therefore, with appropriately titrated EPAP, pressure support, and backup rate settings, adequate minute ventilation can be reliably achieved without the addition of the AVAPS algorithm.

When choosing ventilatory settings for patients with OHS it is important to realize that high levels of pressure support (e.g., in the range of 12–25 cm H_2O) will likely be needed to overcome increased chest wall resistance. The goal for tidal volume is 8 to 10 mL/kg of ideal body weight. EPAP should be initiated at 4 to 8 cm H_2O, but if AVAPS-AE algorithm is used, the level of EPAP will depend on a variety of patient factors. As with patients with neuromuscular disease, patients with OHS benefit from a longer inspiratory time in order to recruit atelectatic regions of lung. We recommend a Ti of 1.2 to 1.6 s in the absence of any obstructive lung disease. Also, to allow for maximal recruitment and to minimize risk of overdistention of non-atelectatic lung, the rise time should be between 400 and 600 ms. If Ti or rise time is too short, patients are put at risk for volutrauma, as the inflation volume is delivered over a short period of time and may over-distend non-atelectatic lung, rather than recruit atelectatic regions.

Tracheostomy

Patients may be intolerant of NIPPV due to discomfort, high pressure requirements needed to overcome obstruction or to provide adequate ventilation, an inability to grasp the severity of illness, or reticence to comply with recommended therapy. Oftentimes, these patients are hospitalized due to malignant OHS and right heart failure. In these patients, tracheostomy should be considered for facilitation of adherence to treatment, to provide a stable airway in lieu of need for intubation, and, often, to serve as a therapeutic bridge that allows safe ventilation if bariatric weight loss surgery is pursued.

Bariatric Surgery

Based on expert opinion by the American Thoracic Society, sustained weight reduction of 25% to 30% of actual body weight is required for resolution of hypoventilation. Bariatric surgery is the most effective and durable manner to accomplish this weight loss, since lifestyle interventions alone only yield an average weight loss of 10 to 12 kg.[81] In one study, statistically significant weight reduction at 3 months was noted when an intensive nutrition program was combined with NIPPV compared with NIPPV alone; however, the effect was lost at 12 months.[82] Bariatric surgery has been shown to produce significant weight loss over the first year following surgery, leading to improvements in hypoxemia and restrictive pulmonary physiology.[83] Patients followed 5 years after bariatric surgery may demonstrate normalization of Pa_{CO_2} and Pa_{O_2}.[84]

Oxygen Therapy

In stable patients with OHS without daytime hypoxia, oxygen therapy has been shown to acutely decrease minute ventilation through decreased tidal volume, resulting in worsening hypercapnia.[85,86] However, when used long-term and titrated to an awake pulse oximetry value of 88% to 92%, oxygen therapy has been shown to increase compensatory metabolic alkalosis.[87,88] As a result, hyperoxia should be avoided in this patient population, and goal oxygen levels measured with pulse oximetry should be between 88% and 92%.

Medications

Multiple medications have been considered as adjunctive treatments of OHS on the basis of respiratory stimulation. Data do not support the routine use of these medications in treatment of OHS.[89,90] The authors recommend against the use of respiratory stimulants outside clinical trials.

Congenital Central Hypoventilation Syndrome

Another important disorder characterized by hypoventilation and hypercapnia is the congenital central hypoventilation syndrome, diagnosis and management of which is discussed below.

Diagnosis and Pathophysiology

Congenital Central Hypoventilation Syndrome (CCHS) is colloquially known as "Ondine's Curse," based on the fable of a jilted water nymph, Ondine, who cursed her unfaithful mortal lover with the ability to breathe only when awake.[91] Scientifically, CCHS is defined as alveolar hypoventilation due to a failure of automatic control of ventilation by the central nervous system which is unrelated to pulmonary, cardiovascular, neurologic, or muscular anomalies.[92,93] Hypoventilation occurs predominantly during sleep; however up to one-third of patients will require ventilatory support 24 h per day.[94] Decreased tidal volume with maintained respiratory rate, impaired ventilatory response to hypercapnia and hypoxia, and absent arousal response to these insults result in excess mortality in untreated CCHS.[95]

A polyalanine expansion mutation in the paired-like homeobox 2B (*PHOX2B*) gene on chromosome 4p12 is found in 90% of patients diagnosed with CCHS.[96] *PHOX2B* is predominantly expressed in the RTN, which is the primary area of chemosensitivity in the CNS. Its inheritance pattern is autosomal dominant; however, de novo mutations account for 90% of cases.[93] The majority of cases are diagnosed in the neonatal period; however, depending on the *PHOX2B* genotype, symptoms may become evident after infancy, which is termed late-onset CCHS (LO-CCHS). Increased polyalanine repeat expansions in the *PHOX2B* gene are correlated with increased severity of the respiratory phenotype, associated symptoms, and age of onset.[97] For example, patients with 20/27 and 20/33 genotypes, indicating the presence of 7 to 13 extra alanine nucleotides above the baseline 20 present in normal *PHOX2B* genes, often require ventilatory support during both sleep and wakefulness.[98] Patients with the genotype *PHOX2B* 20/25 have less severe disease and are more likely to present during adulthood.[99,100] It is thought that children's respiratory rate is elevated compared to adults, and as children age their respiratory rate decreases, which may unmask hypoventilation due to decreased tidal volume breaths.[101] Initial screening is done using gel electrophoresis which evaluates for polyalanine repeats and other common non-polyalanine repeat mutations associated with CCHS. A confirmatory *PHOX2B* gene sequencing test can be done if the screen is negative but the suspicion for CCHS remains high.[98]

When diagnosed in the neonatal period, symptoms include oxyhemoglobin desaturations, cyanosis, apneas most prevalent during sleep, and, possibly, cardiopulmonary arrest. Alveolar hypoventilation is most severe during NREM sleep.[102] Additionally, decreased body temperature, developmental delays, ability to breath hold for prolonged time period, constipation, esophageal dysmotility, and pupillary abnormalities are seen.[101] Phenotypically, children typically have flat forehead, box-like face shape, deep philtrum, and downturned lips.[103] Patients presenting after infancy may have evidence of right heart failure, developmental delay, or seizure disorder.[98] If presenting in adulthood, often evidence of right heart failure, polycythemia, and chronic, hypercarbic respiratory failure are seen. Respiratory decompensation typically occurs with respiratory illness, after receiving general anesthesia, during pregnancy, or with alcohol consumption.[100,104]

Awake manifestations of CCHS include decreased ventilatory response to exertion or increased metabolic demand, resulting in severe hypoxia and hypercarbia during exercise and illness. Affected persons may exhibit autonomic dysregulation, manifesting as bradycardia, sinus pauses, decreased heart rate variation in response to exercise or exertion, attenuated positional blood pressure fluctuations, and abnormalities of pupillary constriction.[101,105] There are also known associations with Hirschsprung disease and neural crest tumors, including neuroblastomas and ganglioneuroblastomas.[106,107]

Unrelated to a mutation in the *PHOX2B* gene, there are acquired forms of central hypoventilation resulting from neurologic injury, including trauma, ischemia,[108] infection, mass lesions, Chiari malformation with tonsillar herniation,[109] or demyelinating disease.

■ Special Circumstances

Important to consider clinically are special circumstances that impact CCHS, including illness, air travel, pregnancy, and use of centrally acting substances.

Illness

Due to an inability to augment ventilatory in response to increased metabolic demand, affected individuals may require nocturnal ventilation or continuous (24 h/day) ventilation during illness.[93]

Air Travel

In patients with intact chemoreceptors, as partial pressure of oxygen decreases during air travel or in high-altitude environments, respiratory rate increases. In those with CCHS, this respiratory augmentation does not occur; therefore, they should have preflight assessment to determine if supplemental oxygen is needed. Additionally, ventilators or pacing transmitters, supplemental oxygen, and oxygen monitors should be available for use on the aircraft.[93,110]

Pregnancy

Pregnancy and delivery are associated with increased metabolic demand that cannot be met in patients with CCHS. Some pregnant women require increased ventilatory support during their pregnancies; however, many are stable on their pre pregnancy treatment regimens.[111] For women with diaphragmatic pacers (DP) in place prior to pregnancy, the device has been shown to effectively treat hypoventilation during pregnancy and vaginal delivery. Some women experience discomfort with DP during the third trimester. With cesarean delivery, noninvasive positive pressure ventilation should be utilized due to pain associated with DP use following abdominal surgery.[112]

Centrally Acting Substances

Central depressants may exacerbate existing nocturnal hypoventilation; as a result, patients should be carefully monitored when these agents are administered. Commonly, patients with CCHS require close monitoring in the postprocedural period, as they will not demonstrate respiratory distress, despite inadequate oxygenation or ventilation due to blunted or absent chemosensitivity and ventilatory response.[113] Ventilatory support is often needed in the postprocedural period, even if the patient is awake.[93] Additionally, patients should be counseled against the use of alcohol, as it may lead to adverse events, such as coma or fatal nocturnal hypoventilation.[104,114]

■ Treatment Modalities for CCHS

By definition, patients afflicted with CCHS require nocturnal ventilatory support; however, they may require 24-h support during periods of illness, or even when well, depending on their genotype and respiratory phenotype. Goal values for gas exchange are an oxygen saturation of at least 95% measured by pulse oximetry, and Pa_{CO_2} of 35 to 45 mm Hg or $ETCO_2$ values between 30 and 35 mm Hg.[115] Regardless of the form of ventilatory support, continuous overnight pulse oximetry is recommended, and periodic CO_2 monitoring should be done to ensure adequacy of ventilation. Ventilatory support may be given either via IMV via tracheostomy or by NIPPV. Diaphragmatic pacing is another permanent, invasive option for ventilatory support. Less commonly used, negative pressure ventilation has documented efficacy in treating this condition.[116]

Invasive Mechanical Ventilation

The majority of infants who are diagnosed with CCHS require tracheostomy placement due to their immature respiratory system and lack of circadian rhythm, making timing of implementation of NIPPV challenging and potentially dangerous.[98,101] Additionally, young children may dislodge their NIPPV mask, which could be potentially fatal. Lastly, for children requiring prolonged ventilatory support there is a concern of midface hypoplasia due to pressure that the NPPV mask exerts on the midface. The American Thoracic Society recommends use of invasive ventilation via tracheostomy until the child is 6 to 8 years of age, as this mode of ventilation is associated with higher oxygen levels and less risk of adverse neurocognitive sequalea.[117] A retrospective review evaluating neurodevelopmental outcomes of patients with CCHS found that infants treated with tracheostomy and IMV before 3 months of age had improved cognitive outcomes compared with infants undergoing tracheostomy after 3 months of age, as well as those exclusively treated with NIPPV.[118]

Uncuffed, small-diameter tracheostomy tubes are recommended due to the decreased the risk of tracheomalacia and the opportunity to maintain phonation; however, the tradeoff is that due to the small lumen, the tubes are prone to obstruction by secretions; in addition, leak occurs as the tracheostomy tube is uncuffed and fails to form a seal with the tracheal wall. As a result, tracheostomy care must be routine, and ventilator settings need to be adjusted to overcome intrinsic air leak.

As children reach school age, a social stigma in response to tracheostomy tubes is often encountered. As a result, families and patients are likely to inquire about alternative methods of ventilation. A decannulation algorithm for children has been reported.[119] The process was started if the child was conscious, could manage his or her secretions with suction requirements <1 time per day, demonstrated no airway anomalies on bronchoscopy, and required only nocturnal IMV, and if the patient and family were motivated to transition to NIPPV. Patients were able to transition to nocturnal ventilation only if they could keep their end-tidal CO_2 <45 mm Hg and oxygen saturation >93% while awake and spontaneously breathing.[94] The protocol was used in four children with an average age of 8.9 years. Progressive increases in the duration of tracheostomy capping, while also increasing the duration of nocturnal NIPPV was the basis for the transition. Children achieved decannulation approximately 1 year after initiation of the protocol. Tracheocutaneous fistula was surgically closed 12 months after decannulation. In a separate study, adjustment to NIPPV was achieved within as little of a week for most children.[120] Other potential methods of decannulation include sequential downsizing of tracheostomy tube prior to capping.[94,121]

Noninvasive Positive Pressure Ventilation

Although IMV is the recommended ventilatory modality for young children,[117] cases in which infants have been treated solely with NIPPV for years have been reported.[120,122–124]

Bilevel positive airway pressure (BPAP) is the NIPPV modality of choice. As patients with CCHS have periods of apnea, a mandatory timed mode is needed; however, a straight timed mode can be uncomfortable; hence, the spontaneous/timed (S/T) mode is most commonly employed.[125] In order to provide a stable tidal volume (assuming lung mechanics are constant), fixed levels of EPAP and IPAP are chosen. However, since lung mechanics and airway resistance are not constant over time, a trend has developed toward greater use of adaptive algorithms for ventilation, including average volume-assured pressure support (AVAPS)/intelligent volume-assured pressure support (iVAPS).

In a head-to-head comparison of BPAP S/T with iVAPS in eight children with CCHS, the NREM peak PtcCO$_2$ median was significantly lower in the iVAPS group compared with fixed BPAP S/T. No difference in PtcCO$_2$ during REM sleep or in sleep quality or sleep architecture was noted between the two groups. However, sleep efficiency trended toward improvement in the iVAPS algorithm. Interestingly, no difference was observed in tidal volume, minute ventilation, or adherence rates. It is unclear whether this peak PtcCO$_2$ reduction equates to long-term improvements in neurocognitive function, since peak PtcCO$_2$ was below 50 mm Hg in all patients except one during a BPAP therapy S/T mode titration.[126] Another case study documented improvement in PtcCO$_2$ variability after transitioning a 10-month-old infant from BPAP S/T to VAPS.[123] Use of VAPS algorithm is limited in infants as it has a minimum tidal volume requirement of 50 mL.

Negative Extrathoracic Pressure Ventilation

Negative extrathoracic pressure ventilation (NPV) has been successfully used in patients with CCHS. NPV involves generating subatmospheric pressure around the patient's chest, which causes chest wall and upper abdominal expansion, as well as downward diaphragmatic movement, resulting in inspiration. The negative pressure generated is proportional to the tidal volume delivered. Devices that accomplish this are the chest shell (cuirass) ventilator, wrap ventilator, and Port-a-lung.[113] This mode of ventilation was made popular during the polio epidemic, but it hasn't gained widespread use due to its lack of portability, requirement of supine sleep, and risk of vocal cord opening and inspiratory effort asynchrony, resulting in obstructive apneas.[98,127]

Diaphragmatic Pacing

Diaphragmatic pacing involves insertion of electrodes into the phrenic nerve that, when activated, cause diaphragmatic contraction resulting in inspiration. Lead wires connect the phrenic nerve electrodes to receivers located under the patient's skin. External antennas placed on top of the skin over the receivers interact with a battery-powered transmitter worn by the patient, which serves as the impulse driving electrode stimulation and regulating breathing. The receiver converts the transmitter impulse to electrical current, and the voltage is proportional to diaphragmatic contraction and tidal volume.[94] The duration of the impulse equates to inspiratory time. Pediatric patients generally need bilateral phrenic nerve electrode placement for adequate ventilatory support.

These pacers can be used as the sole method of ventilation in patients requiring nocturnal support. Alternatively, in patients requiring 24-h ventilatory support, diaphragmatic pacers can be used during the day to allow for increased mobility and functional independence. Patients will still require either NPPV or negative pressure ventilation at night, as pacing for more than 12 to 16 h/day is not recommended due to risk of diaphragmatic fatigue.[93,94] Initially, the diaphragm fatigues easily and requires a slow increase in duration of stimulation to enable the patient to tolerate 12 to 16 h of stimulation daily. During this time, backup methods of ventilation should be employed.[113] Pacing may begin 4 to 6 weeks after electrode implantation and, on average, takes 6 months to reach a pacing duration of 12 to 16 h.[128]

Toddlers and children with diaphragmatic pacers should be evaluated every 6 months for adequacy of inspiratory time and tidal volume generated by the device, whereas older children and adults can be evaluated annually.[98] Additionally, patients with DP may develop upper airway obstruction and should be evaluated for possible obstructive apneas and hypopneas prior to decannulation if a tracheostomy is in place.[129] If diaphragmatic pacers are used during pregnancy, the recommendation is that the woman undergo PSG with oxygen and carbon dioxide monitoring to ensure adequacy of ventilatory support.[112] There have been no identified diaphragmatic or phrenic nerve complications of long-term DP in patients using this mode of ventilation for up to 30 years.[113]

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

Given the prevalence of COPD, an appreciation of the significance of hypercapnia in this disorder, as well as its management is of paramount importance.

Chronic Hypercapnia in COPD: Pathophysiology

COPD may cause both hypoxemic and hypercapnic chronic respiratory failure. The development of diurnal hypercapnia in patients with COPD is a combination of gas exchange and diffusion abnormalities, parenchymal distortions leading to an increased dead-space ventilation (Vds) fraction, mechanical impartment of the respiratory system, and a primary or acquired blunted ventilatory response to hypercapnia. Pa$_{CO_2}$ does not usually increase above normal until the FEV$_1$ decreases to about 20% to 25% of predicted normal values. However, the CO$_2$ chemoreceptor response may affect this curvilinear relation.

As discussed previously in this chapter, increases in lung dead space and abnormalities in ventilation/perfusion relationships impair CO$_2$ elimination and O$_2$ uptake. Increases in physiologic dead space require greater than normal levels of ventilation and tidal volume to maintain eucapnia. Maintenance of "normal tidal volume" in the setting of increased dead space predisposes to CO$_2$ retention because of an unfavorable Vds/VT. Minute ventilation is increased still further by hypoxemia.

Increases in ventilation require increases in airflow, tidal volume, and respiratory rate. This process often results in dynamic hyperinflation and increased TLC and FRC. These changes are multifactorial in origin: decreased elastic recoil secondary to emphysema, increased transpulmonary pressures due to tonic inspiratory muscle activation, increased laryngeal resistance, and the shift of tidal breathing to the upper portion of the flow–volume curve, which results in insufficient time to achieve passive exhalation to FRC, ultimately producing dynamic hyperinflation.

In presence of hyperinflation due to COPD, the diaphragm is able to generate pressures better than expected on the basis of hyperinflation alone. However, the diaphragm in these patients is also lower in the chest cavity and, despite a supraphysiologic neural drive, the diaphragm's ability to descend during inspiration is reduced, as is rib cage expansion. As hyperinflation progresses, diaphragmatic contraction may result in paradoxical deflation, rather than expansion of the rib cage, reducing the ability of the diaphragm to increase lung volumes and, ultimately, making inspiration dependent on other inspiratory muscles.[130] The effects of diaphragmatic dysfunction on ventilation are most evident during REM sleep (Fig. 142-9).

In addition to this mechanical disadvantage, the diaphragmatic muscle fibers in patients with COPD show reduced force generation per cross-sectional area, reduced myosin heavy chain content per half sarcomere, decreased Ca^{2+} sensitivity of force generation, and slower cross-bridge cycling kinetics. Inspiratory muscle weakness is a major determinant of chronic hypercapnia in COPD.[131]

Chronic hypercapnia occurs in some patients with COPD, but not in all.[132,133] Some patients admitted to the hospital with acute hypercapnia revert to normocapnia following recovery, while others remain hypercarbic in absence of nocturnal NIPPV. Data support

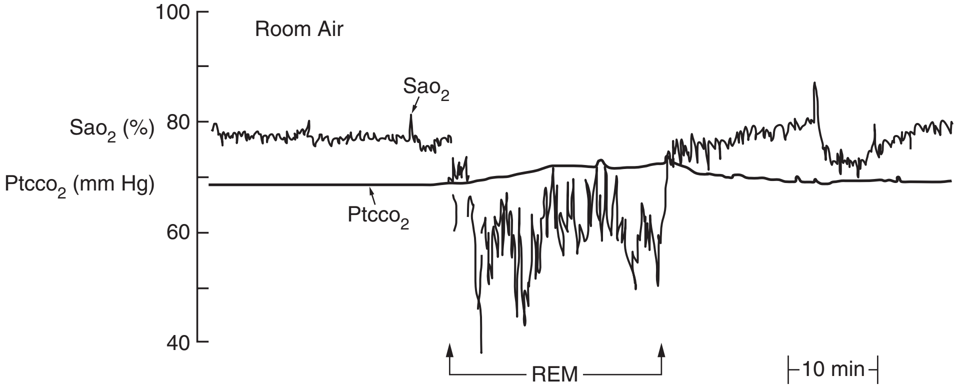

Figure 142-9 SpO_2 is reduced predominantly during REM sleep, mirroring an elevation in $PtcCO_2$ in patients with COPD. This desaturation pattern is typically seen in hypoventilatory states. *(Reproduced with permission from McNicholas WT. Chronic obstructive pulmonary disease and obstructive sleep apnoea-the overlap syndrome. J Thorac Dis. 2016;8(2):236–242.)*

the notion that persistent hypercapnia is a poor prognostic indicator for patients with COPD, and that survival in patients with hypercapnic COPD is shorter than in those with normocapnia or reversible hypercapnia.[134] Persistent hypercapnia after an exacerbation is associated with excess mortality[135] and early rehospitalization.[136]

Noninvasive Positive Pressure Ventilation in COPD

Long-term oxygen therapy (LTOT) is well recognized as the standard of care in patients with COPD with chronic hypoxemic respiratory failure and is associated with improved survival. Notably, chronic hypercapnia is a determinant of mortality in COPD.[137,138] Patients with COPD with chronic hypercapnia are more likely to be hospitalized than those without hypercapnia; the admissions are often followed by an accelerated clinical decline.[139,140] Hospital admissions for exacerbations of COPD carry a 5-year mortality near 50%.[141]

Correcting hypercapnia is a plausible intervention to improve the prognosis in this group of patients. In hypercapnic patients with COPD, NIPPV results in reduced lung hyperinflation and expiratory muscle load, in addition to increased chemosensitivity to CO_2; these findings suggest NIPPV may result in improved ventilatory performance and, ultimately, in reduced Pa_{CO_2}.[142,143]

Several trials support the observation that NIV and LTOT reduce COPD-related hospital admissions.[144,145] A pivotal study[146] supports the use of home noninvasive ventilation in patients with persistent hypercapnia for 2 to 4 weeks after resolution of an acute exacerbation of COPD that resulted in acute hypercarbia requiring acute noninvasive ventilation. This randomized trial showed improvement in time to readmission or death when home NIPPV was added to LTOT in patients with persistent hypercapnia following an admission for an acute exacerbation of COPD (Fig. 142-10).

Screening patients with COPD for persistent hypercapnia with a Pa_{CO_2} of at least 52 mm Hg after they have received NIV in the acute setting, and introducing home NIPPV, results in reduced readmissions. The number needed to treat (NNT) is six patients to avoid one readmission.[146]

Home NIPPV in patients with severe COPD improves ventilatory response to hypercapnia,[147] resulting in an improved adaptive response to acute hypercapnia during an exacerbation. Data also suggest that high-pressure noninvasive ventilation (PS or IPAP-EPAP $\geq$ 15 cm H_2O) may result in airway remodeling, decreased dynamic hyperinflation, and improved V/Q ratios.[148] The resultant reduction in Pa_{CO_2} and exacerbation frequency may also be supported by increased secretion of IL-6 and TNF in the lungs, leading to improved lung neutrophil function.[149]

Pressure support (bilevel S/T) is the preferred noninvasive ventilatory mode in COPD. As mentioned previously, high-intensity BiPAP should be used (IPAP-EPAP or pressure support > 15 cm H_2O). The use of a rather short Ti and the avoidance of high set respiratory rates decreases the possibility of dynamic hyperinflation by promoting a shorter inspiratory phase and a longer expiratory time, resulting in a low I:E ratio. Pressure control (PC) should be avoided, as patient-generated tachypnea may result in dynamic hyperinflation, as all breaths (spontaneous and timed) will be supported throughout the set Ti.

The addition of VAPS may prove beneficial in this group of patients. The ability to set a target Vt or MV assures a steady

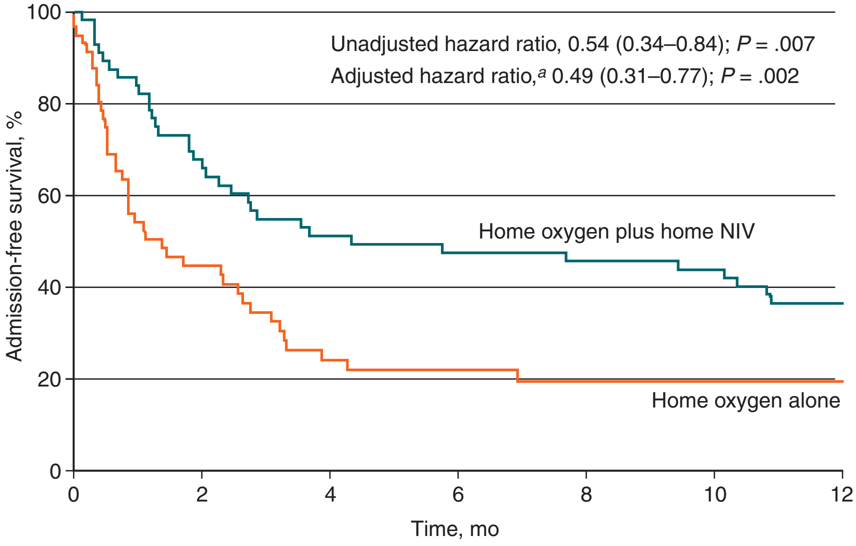

Figure 142-10 Kaplan-Meier survival plot of time to readmission or death from randomization to the end of trial showing a significant improvement in admission-free survival in the NIPPV group.[146]

ventilation, even in the setting of disease progression or clinical fluctuations, allowing theoretically for more precise control of Pa_{CO_2} toward eucapnia.

Some data suggest that BIPAP with AVAPS mode facilitates rapid recovery in pH, Pa_{CO_2}, and reduction in length of stay (LOS) compared with BIPAP S/T mode[150] AVAPS has also found to improve exercise tolerance and multiple domains of health-related quality of life when randomized versus BPAP S/T.

The addition of autotitrating EPAP to AVAPS (AVAPS AE) also provides additional benefit in overlapping COPD-OSA.

DEDICATIONS

Jennifer J. Dorsch:

This chapter is dedicated to the memory of my parents, Mike and Teri Dorsch.

Jorge I. Mora:

To my daughters, Ana and Isabel, my infinite source of inspiration.

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CHAPTER 143

Oxygen Therapy and Toxicity

Matthew Wemple
Erik R. Swenson

INTRODUCTION

Oxygen was discovered in the late 18th century chiefly through the work of three scientists. Joseph Priestley, a minister in England, made his discovery after attempting to melt mercuric oxide using a magnifying glass and the sun's rays. The vapor that was produced by this melting allowed a candle to burn brighter, and Priestley later discovered the vapor could be used in place of air to keep a mouse alive. He first published his findings in 1775. In a similar way to Priestley (i.e., by burning mercuric oxide), Carl Scheele, a pharmacist in Sweden, independently made the same discovery earlier in 1772, but did not publish his results until 1777.[1] After being told about this new vapor during a 1774 visit to Paris by Joseph Priestley, the French chemist Antoine Lavoisier devised quantitative experiments that he used to prove the existence of this element and its role in combustion. He named the element "oxygen," meaning "sharp-begetter"—"oxy" meaning sharp, "gen" meaning begetter—as he believed the element was a necessary element to form acids and published his research in 1777. Scheele beat Priestley by several years but was deprived of priority because Lavoisier denied receiving a letter Scheele later claimed to have sent in September 1774 describing his 1772 discovery of what he called "fire air." Scheele's claim of priority remained unconfirmed, until his missing letter (received on October 15, 1774) was finally made public in 1992 in Paris, 218 years later. It now resides at the French Academie de Sciences. Lavoisier's guilt was kept secret in the effects of his wife and scientific assistant, Madame Lavoisier. Lavoisier failed on several occasions to credit either Priestley or Scheele for contributing to the one of the most important discoveries in the history of medicine and science.[1]

Soon after its discovery, oxygen began to be used as a medicine and cure-all for many respiratory diseases, including "dropsy," "consumption," and asthma. However, suspicions about the safety of oxygen therapy were raised almost as soon as it was discovered and even before the element was named. In 1775, Joseph Priestley wrote of oxygen: "A moralist, at least, may say that the air which nature has provided for us is as good as we deserve."[2]

Rigorous scientific evaluation of the potential toxicities of oxygen did not occur until the work of James Lorrain Smith, an Edinburgh pathologist, who first published the pulmonary pathologic alterations associated with oxygen exposure in 1899. It was also recognized around this time that under ambient air, the arterial blood was already at near-maximal oxygen-carrying capacity, putting into doubt the utility of further increasing the fraction of inspired oxygen. Following these observations, the use of therapeutic oxygen fell into some disrepute.

In the early 1920s, supplemental oxygen therapy was reevaluated. This was occurring as the detrimental effects of tissue hypoxia were being recognized, along with their reversibility with supplemental oxygen. Since the mid-20th century, especially with the advent of improved oxygen delivery systems, mechanical ventilation, and the modern intensive care unit, the use of oxygen has become a standard prescribed therapy for a multitude of cardiac and respiratory diseases. Oxygen therapy is now common in the outpatient setting. As of 2005 in the United States, approximately 1 million people receive long-term oxygen therapy (LTOT) from the Medicare Program, with total reimbursement costs related to LTOT exceeding 2 billion dollars per year.[3]

In this chapter, the physiology of hypoxia at the tissue level and mechanisms of arterial hypoxemia are discussed. In addition, various clinical assessments of hypoxemia, indications for acute and LTOT, and available methods of noninvasive oxygen administration are considered. Finally, the pathophysiology and clinical manifestations of pulmonary oxygen toxicity are addressed, along with the increasingly recognized potential for oxygen toxicity in other organ systems.

TISSUE OXYGENATION

Ultimately, the primary goal of supplemental oxygen therapy is to ensure sufficient oxygen delivery to all organs and tissues. Therefore, one must understand the causes, consequences, and mechanisms of tissue hypoxia to understand the indications for supplemental oxygen in patient care.

Tissue hypoxia is governed by the balance between oxygen delivery and oxygen utilization. Generally, failures in oxygen delivery to the mitochondria lead to most instances of tissue hypoxia. Oxygen delivery is determined by the cardiac output (Q) and the oxygen content of arterial blood, as described by the formula:

$$\mathrm{D}_{\mathrm{O}_2}\ \text{(oxygen delivery)} = \mathrm{Q}\ \text{(cardiac output)} \times \mathrm{Ca}_{\mathrm{O}_2}\ \text{(oxygen content of arterial blood)} \tag{1}$$

where $\mathrm{Ca}_{\mathrm{O}_2}$ is calculated by the formula:

$$\mathrm{Ca}_{\mathrm{O}_2}\ (\text{ml } \mathrm{O}_2/\text{dL}) = (1.34 \times \text{hemoglobin concentration} \times \mathrm{Sa}_{\mathrm{O}_2}) + (0.0031 \times \mathrm{Pa}_{\mathrm{O}_2}) \tag{2}$$

where $\mathrm{Sa}_{\mathrm{O}_2}$, is the arterial hemoglobin oxygen saturation (in the equation a fraction rather than percentage) and $\mathrm{Pa}_{\mathrm{O}_2}$ is the oxygen tension or partial pressure of arterial blood.

From this formula, the causes of poor oxygen delivery can be narrowed to three categories: low cardiac output states (i.e., various forms of shock), low hemoglobin concentration states (i.e., anemia), and low $\mathrm{Sa}_{\mathrm{O}_2}$ states (i.e., arterial hypoxemia and genetic or acquired hemoglobinopathies). Note that a low oxygen tension, although often leading to low arterial hemoglobin saturation, does not contribute appreciably to oxygen delivery. This can be seen numerically in the above formula for $\mathrm{Ca}_{\mathrm{O}_2}$, where the $\mathrm{Pa}_{\mathrm{O}_2}$ is multiplied by 0.0031 (reflecting a very low solubility) and, therefore, contributes little to the final total blood oxygen concentration. It is important to point out that supplemental oxygen therapy addresses only arterial hypoxemia. For other causes of tissue hypoxia, more specific therapies are generally required, such as vasoactive agents or intravenous fluid administration to reverse distributive and hypovolemic shock, and blood transfusions for anemia.

Along with the primary basis of poor oxygen delivery, tissue hypoxia can also occur in the setting of histotoxic hypoxia, which occurs when cells, for a variety of reasons, are unable to utilize oxygen for aerobic metabolic respiration. This is classically seen in cyanide poisoning, in which the cyanide molecule inhibits the mitochondrial enzyme cytochrome c oxidase, and the cell is subsequently unable to use oxygen in the Krebs cycle to produce adenosine triphosphate (ATP) via the mitochondrial electron transport chain. This leads to far greater amounts of glycolysis in the effort to produce sufficient ATP anaerobically, profound lactic acidosis, and cell and tissue death. Administration of oxygen is indicated if arterial P_{O_2} is low, but it will not, by itself, reverse the toxicity of cyanide or other mitochondrial poisons; other antidotes must be given (generally, sodium nitrite, amyl nitrite, and sodium thiosulfate).[4]

Another cause of decreased oxygen utilization may occur in the setting of sepsis. In this case, oxygen is not utilized by tissues due to both mitochondrial damage and abnormal shunting of blood from a variety of insults at the endothelial and microvascular levels.

Finally, oxygen may be excessively utilized by tissues relative to oxygen delivery. This may occur in hypermetabolic states, such as thyrotoxicosis[5] and fever,[6] and certain exogenous poisons such as in salicylate overdose.

ARTERIAL HYPOXEMIA

It is important to distinguish the terms *hypoxia* and *hypoxemia*. Hypoxia may be thought of as the functional equivalent of ischemia. It is not associated with acidosis from CO_2 retention and failure to clear other metabolites and refers to a lack of or misuse of oxygen at the tissue level. Hypoxemia refers to the blood's oxygen content and can be more formally defined as a validated lower oxygen tension in the blood. In other words, when a patient's Pa_{O_2} and, therefore, Sa_{O_2} are low, the patient is hypoxemic. Since arterial hypoxemia is a major cause of tissue hypoxia, the cause of which is most likely to be reversed or improved with oxygen therapy, its major etiologies are discussed below.

The driving force of oxygen diffusion across the alveolar–capillary barrier into the blood depends on the partial pressure of oxygen in the alveolus (PA_{O_2}). Thus, arterial hypoxemia results from either reduction of the inspired oxygen tension or dysfunction of the respiratory system leading to regions of the lung with lower PA_{O_2}. Along with the reduction of inspired oxygen tension (such as at altitude), there are four other pathophysiologic causes of arterial hypoxemia (Table 143-1).

Alveolar hypoventilation leads to a diminished PA_{O_2} and resultant decrease in Pa_{O_2} and Sa_{O_2}. It may constitute the final common pathophysiologic denominator for a variety of pulmonary and nonpulmonary disorders leading to hypercapnia and hypoxemia. Examples of nonpulmonary disorders leading to these derangements include narcotic overdose, which reduces the central drive to breathe; abdominal compartment syndrome, which can mechanically reduce ventilation due to abdominal distension; and control of ventilation disorders such as obstructive sleep apnea and the obesity–hypoventilation syndrome.

Another pathophysiologic cause of hypoxemia arises with defects in diffusion of oxygen across the alveolar–capillary membrane, as, for example, in fibrotic lung diseases and interstitial pneumonias. The increased barrier to oxygen diffusion is detected as a reduced diffusing capacity of carbon monoxide (DL_{CO}), although many other conditions lead to reductions in diffusing capacity. Diffusion limitation generally coexists with ventilation–perfusion mismatch. Its effects on oxygenation often become clinically prominent in states of increased cardiac output and greater tissue oxygen extraction (such as exercise) in the setting of high altitude and fibrotic or interstitial lung disease.[6] These higher-output states lead to reduced red cell capillary transit times and thus less time for complete diffusional equilibration of oxygen between alveolar gas and capillary blood with resultant hypoxemia.

Clinically, besides hypoventilation, most frequently observed pathophysiologic mechanisms of hypoxemia are ventilation–perfusion mismatch and shunt. Ventilation–perfusion mismatch generally results when focal (or sometimes diffuse) areas of diminished ventilation arise relative to persistent pulmonary blood flow. Clinical examples include obstructive lung diseases such as COPD and asthma, and interstitial edema leading to reduced ventilation, but continued perfusion. The hypoxemia resulting from a relative lack of ventilation to these areas can generally be overcome simply by increasing the fraction of inspired oxygen (FI_{O_2}); that is, with the use of supplemental oxygen. In the setting of ventilation–perfusion mismatch, without oxygen supplementation, reflex hypoxic pulmonary vasoconstriction (HPV) occurs helping to reduce the mismatch. HPV, when extensive throughout the lung, may ultimately lead to increased pulmonary artery pressure and, if severe and prolonged, cor pulmonale.

Shunt occurs when a fraction of pulmonary blood flow effectively bypasses ventilated alveolar regions or flows through unventilated regions. Examples of the latter include alveolar filling processes, such as cardiogenic alveolar edema, pneumonia, drowning, and atelectatic lung in which ventilation is absent, but perfusion maintained (at least in part, as it is often blunted by HPV). Examples of the former include right-to-left lung shunting processes such as atrial septal defect and large vessel intrapulmonary arteriovenous malformations. Compared with ventilation–perfusion mismatch, increasing the alveolar concentration of oxygen in the setting of shunt has less of an effect on improving arterial oxygenation. In other words, as shunt fraction is increased, the resulting hypoxemia will become increasingly refractory to increases in FI_{O_2}.

Finally, when tissue hypoxia is severe, or when increased tissue oxygen utilization is present, the oxygen content of venous blood returning to the right heart may be profoundly reduced—detected as a low oxygen saturation of venous blood (Sv_{O_2}). A low Sv_{O_2}, in combination with hypoventilation, ventilation–perfusion mismatch, or shunt, will also lead to worsening arterial hypoxemia. This pathophysiologic constellation may be observed when patients with severe lung disease and poor oxygen delivery are physically active, anemic, or have high metabolic demands due to critical illness. Hemoglobin desaturation can then be seen.

CLINICAL ASSESSMENT OF TISSUE HYPOXIA

To use oxygen therapy correctly, clinicians must recognize the presence of tissue hypoxia and its etiology. With this knowledge,

TABLE 143-1 Causes of Arterial Hypoxemia and Response to Oxygen Therapy

Cause	Clinical Examples	Response (Dependent on Magnitude of F_{IO_2})
Decreased inspired oxygen	Altitude (reduced P_{IO_2})	Appreciable rapid increase in Pa_{O_2}
Alveolar hypoventilation	COPD, obesity hypoventilation	Increase in Pa_{O_2}, may depress ventilation, however, and cause or worsen hypercapnia
Diffusion defect	Interstitial pneumonitis	Moderately rapid increase in Pa_{O_2}
Ventilation–perfusion mismatch	COPD, asthma	Moderately rapid increase in Pa_{O_2}
Shunt	Atrial septal defect, with right-to-left shunting, pulmonary AVMs	Variable increase in Pa_{O_2}, depending on size of shunt

TABLE 143-2 Signs and Symptoms of Acute Hypoxia

System	Signs and Symptoms
Respiratory	Tachypnea, dyspnea, cyanosis, pulmonary hypertension
Cardiovascular	Increased cardiac output, palpitations, tachycardia, bradycardia, arrhythmias, hypotension, angina, vasodilation, diaphoresis, shock
Central nervous	Headache, impaired judgment, inappropriate behavior, confusion, euphoria, delirium, restlessness, papilledema, seizures, obtundation, coma
Neuromuscular	Weakness, tremor, asterixis, hyperreflexia, incoordination
Metabolic/renal	Sodium and water retention, lactic acidosis, acute tubular necrosis

the clinician can determine who may benefit from supplemental oxygen. Furthermore, the degree of hypoxia must be assessed to determine the optimal dosage of oxygen. In this way, one can balance oxygen's benefits and potential toxicities. Unfortunately, tissue hypoxia is not directly measured by any one test. Instead, a combination of clinical and laboratory parameters is used to determine its severity. In the case of tissue hypoxia caused by isolated arterial hypoxemia, measurement of arterial oxygen saturation can be an excellent guide to appropriate oxygen therapy.

Clinical Manifestations

Clinical manifestations of tissue hypoxia are variable and nonspecific. Whether hypoxia develops acutely or is chronic influences a patient's presentation. Patients with chronic hypoxia often have minimal symptoms. Symptoms and signs of acute hypoxia are outlined in Table 143-2. The most prominent findings are dyspnea, tachypnea, tachycardia, and respiratory distress. A frequently observed finding is an acute change in mental status, ranging from agitation to delirium to coma. Cardiac arrhythmias are common. Cyanosis is generally a late finding and is often unreliable in diagnosing hypoxia, as it may be absent in the setting of anemia and with poor peripheral perfusion.

Laboratory Assessment

Distinction between tissue hypoxia and arterial hypoxemia is important in applying various laboratory studies in the clinical evaluation. To determine if tissue hypoxia, that is, hypoxia in end-organs, is present, measures such as serum lactate (elevated in ischemia) and Sv_{O_2} (reduced in ischemia or low cardiac output states) are generally used. Evaluation for anemia by measuring hemoglobin or hematocrit is also important in this context.

When the cause of tissue hypoxia is isolated arterial hypoxemia, measurements of Pa_{O_2} and Sa_{O_2} provide appropriate surrogates of oxygen delivery and, therefore, tissue hypoxia. Values are derived from arterial blood–gas measurements. Since Sa_{O_2} and Pa_{O_2} have a generally predictable relationship according to the oxygen–hemoglobin dissociation curve, measuring Sa_{O_2} may alone be sufficient to assess arterial hypoxemia. This is done noninvasively using pulse oximetry; the estimated Sa_{O_2} is designated as Sp_{O_2}. Importantly, various toxins, such as carbon monoxide (CO) and those that result in methemoglobinemia will disrupt the predictable relationship between Sa_{O_2} and Pa_{O_2} as measured by pulse oximetry (see next section). Under these circumstances, pulse oximetry cannot be relied upon to evaluate arterial hypoxemia. This can only be done by co-oximetry that utilizes four wavelengths of light rather than two as with pulse oximetry.

Pulse Oximetry

Pulse oximetry is an important diagnostic tool that is now widely utilized in hospitals, in outpatient settings, and at home. The general principles of this technology are useful to understand, as are its limitations.

First proposed conceptually in the 1930s and developed further in the mid-20th century, the underlying principle of oximetry is Beer's law, which states that concentration of an unknown substance dissolved in a solvent can be determined by its light absorption:[8]

$$L_{out} = (L_{in} \times e) - (D \times C \times a) \tag{3}$$

where

L_{out} is the intensity of transmitted light through the substance
L_{in} is the incident light
D is the distance the light travels
C is the concentration of the substance (in this case, oxyhemoglobin or reduced hemoglobin)
a is the absorption coefficient

When light is passed through a finger, ear lobe, or other tissue, most of it is absorbed by connective tissue, skin, bone, and venous blood, and the amount absorbed is constant. However, with each heartbeat, pulsatile flow of arterial blood occurs, allowing the pulse oximeter to detect changes in light absorbance at two wavelengths, 660 nm (red) and 940 nm (infrared). Since reduced hemoglobin and oxyhemoglobin have different absorptions at these two wavelengths, the concentration of oxyhemoglobin relative to total hemoglobin can be deduced.

Several limitations to pulse oximetry exist, which can be inferred from its basic principles.[9] Any substance in the blood with similar absorption at the two wavelengths employed will interfere with accuracy. This is clinically important in the evaluation of two acquired hemoglobinopathies—carboxyhemoglobinemia and methemoglobinemia, and any genetic hemoglobin variants.

Carboxyhemoglobin has a very similar absorption coefficient at 660 nm as oxyhemoglobin; at 940 nm, it has minimal light absorption. Therefore, no matter what the relative concentrations of hemoglobin molecules saturated with CO versus O_2, Sp_{O_2} will be constant (generally about 90%–95%).

In methemoglobinemia, a condition in which the iron moiety of hemoglobin is reduced to the ferric state, methemoglobin is characterized by equalization of absorption coefficients at 660 nm and 940 nm. Equal absorption at these two wavelengths translates into an Sa_{O_2} ranging from 83% to 87%, which is what the pulse oximeter inevitably reads as methemoglobin concentration increases. Furthermore, methylene blue, an antidote for methemoglobinemia and used also in other clinical conditions, also affects absorption of light at 660 nm and may falsely lower Sp_{O_2}.

Given that pulse oximetry relies upon pulsatile flow, the technology cannot be used in conditions of low flow, such as cardiac arrest, profound shock, or in patients treated with nonpulsatile cardiac support such as with extracorporeal membrane oxygenators or ventricular assist devices. Errors also occur when venous pulsatility is prominent, such as in severe tricuspid regurgitation. In this case, the pulsatility of venous blood, with its higher concentration of deoxyhemoglobin, may result in artificially low readings of oxygen saturation. When profound arterial hypoxemia exists, for example, Sa_{O_2} <70%, the accuracy of pulse oximetry declines, as the technology was never validated for humans at lower saturations.

Other Assessments of Hypoxemia

Several other calculated assessments of hypoxemia are useful in assessing the degree of respiratory dysfunction.

$\mathrm{Pa}_{\mathrm{O}_2}/\mathrm{FI}_{\mathrm{O}_2}$

$\mathrm{Pa}_{\mathrm{O}_2}/\mathrm{FI}_{\mathrm{O}_2}$ (P/F ratio) requires an arterial blood gas specimen. For example, consider a patient breathing gas with an $\mathrm{FI}_{\mathrm{O}_2}$ of 0.80, who has a $\mathrm{Pa}_{\mathrm{O}_2}$ 240 mmHg. The P/F ratio is 240/0.8 or 300. The ratio, considered to reflect the magnitude of derangement in O_2 transfer across the lung and thought to be relatively unaffected by differences in $\mathrm{FI}_{\mathrm{O}_2}$ among measurements, is most useful in mechanical ventilation, when accurate determination of $\mathrm{FI}_{\mathrm{O}_2}$ is possible. In the setting of acute hypoxemia, a P/F ratio of <300 indicates clinically important abnormal gas exchange, and a P/F ratio <200 indicates severe hypoxemia.

Alveolar–Arterial (A–a) Difference

The A–a difference (also called somewhat imprecisely the A–a gradient) measures the difference in alveolar oxygen tension and arterial oxygen tension. This measurement, which requires an arterial blood gas, is determined as:

$$\text{A-a difference} = \mathrm{PA}_{\mathrm{O}_2} - \mathrm{Pa}_{\mathrm{O}_2} \tag{4}$$

$\mathrm{PA}_{\mathrm{O}_2}$ is calculated using the alveolar air equation:

$$\mathrm{PA}_{\mathrm{O}_2} = (\mathrm{FI}_{\mathrm{O}_2} \times [\mathrm{P}_{\mathrm{atm}} - \mathrm{PH_2O}]) - (\mathrm{Pa}_{\mathrm{CO}_2}/\mathrm{R}) \tag{5}$$

where

$\mathrm{FI}_{\mathrm{O}_2}$ is the fraction of inspired oxygen
$\mathrm{P}_{\mathrm{atm}}$ is the atmospheric pressure (760 mmHg at sea level)
$\mathrm{PH_2O}$ is the partial pressure of water (47 mmHg at 37 degrees C)
$\mathrm{Pa}_{\mathrm{CO}_2}$ is the arterial carbon dioxide partial pressure
R is the respiratory quotient (which, in a normal resting steady state, is usually 0.8, depending on the patient's nutritional intake, but may approach 1.0 with critical illness and high sympathetic tone)

A "normal" A–a difference on room air is often considered to be 10 mmHg. However, two important factors affect the "normal" value. The first is patient's age, the influence of which can be expressed numerically according to the formula:

$$\begin{aligned}&\text{Normal A–a difference breathing ambient air}\\ &\quad = 2.5 + 0.21 \times \text{age in years}\end{aligned} \tag{6}$$

The second is $\mathrm{FI}_{\mathrm{O}_2}$: The higher the $\mathrm{FI}_{\mathrm{O}_2}$ and resultant $\mathrm{PA}_{\mathrm{O}_2}$, the larger is the A-a PO_2 difference and vice versa. This is because for any extent of venous admixture the shallower the slope of the hemoglobin dissociation curve over which gas exchange occurs (from mixed venous PO_2 to alveolar PO_2), the larger is the A-aPO2 difference. In contrast if the mean alveolar PO_2 is low due to hypoventilation or being at high altitude, the A–a difference falls below normal and may underestimate or obscure the diagnosis of lung dysfunction.[10] Note the distinction in this regard also with respect to the P/F ratio described previously.

INDICATIONS FOR OXYGEN THERAPY

Supplemental oxygen is a drug with indications, contraindications, and a therapeutic window. Oxygen dosage should be titrated as precisely as possible and oxygen administration monitored closely with respect to clinical benefits and potential toxicities. Indications for oxygen therapy may be considered in both acute and chronic settings. In addition, special circumstances under which oxygen is used therapeutically warrant special discussion, including hyperbaric administration (oxygen delivered at 2–3 atmospheres of pressure) and oxygen therapy during air travel.

■ Acute Indications for Oxygen Therapy

Indications for acute, short-term supplemental oxygen therapy, listed in Table 143-3, are based upon guidelines established by the American Association of Respiratory Care and other organizations.[11–13]

Usually, when a patient presents with respiratory distress, supplemental oxygen is administered until an assessment of hypoxemia is made. The clearest indication for oxygen therapy is arterial hypoxemia, and supplemental oxygen is generally administered when the $\mathrm{Pa}_{\mathrm{O}_2}$ is <60 mmHg, which normally corresponds to an $\mathrm{Sa}_{\mathrm{O}_2}$ or $\mathrm{Sp}_{\mathrm{O}_2}$ of 89% to 90%. When the $\mathrm{Pa}_{\mathrm{O}_2}$ drops below 60 mmHg, oxygen saturation may drop precipitously, leading to a much lower arterial oxygen content and resultant possible tissue hypoxia.

TABLE 143-3 Guidelines for Acute Oxygen Therapy

Accepted Indications
• Documented hypoxemia, defined as $\mathrm{Pa}_{\mathrm{O}_2}$ below the normal range. Usually $\mathrm{Pa}_{\mathrm{O}_2}$ <60 mmHg or $\mathrm{Sa}_{\mathrm{O}_2}$ <90%.
• Acute care situation in which hypoxemia is suspected, such as respiratory distress. Requires substantiation of hypoxemia (by $\mathrm{Sa}_{\mathrm{O}_2}$ or $\mathrm{Pa}_{\mathrm{O}_2}$) in a reasonable time.
• Severe trauma
• Severe acute anemia
• Acute myocardial infarction with hypoxemia
• Low cardiac output with metabolic acidosis
• Hypotension (systolic blood pressure <100 mmHg)
Questionable Indications
• Acute myocardial infarction without hypoxemia
• Dyspnea without hypoxemia (palliative)
• Sickle cell pain crisis
• Pneumothorax

Data from Kallstrom TJ, American Association for Respiratory Care (AARC). AARC Clinical Practice Guideline: oxygen therapy for adults in the acute care facility—2002 revision & update. Respir Care. 2002;47(6):717–720; O'Driscoll BR, Howard LS, Davison AG; British Thoracic Society. BTS guideline for emergency oxygen use in adult patients. Thorax. 2008;63 Suppl 6:vi1–vi68; Fulmer JD, Snider GL. American College of Chest Physicians (ACCP)–National Heart, Lung, and Blood Institute (NHLBI) Conference on oxygen therapy. Arch Intern Med. 1984;144(8):1645–1655.

As noted previously, the common pathophysiologic causes of hypoxemia, ventilation–perfusion mismatch, and hypoventilation respond readily to supplemental oxygen. Hypoxemia secondary to right-to-left shunt is less responsive to supplemental oxygen; when the shunt fraction exceeds 20% to 25%, hypoxemia persists, despite administration of inspired gas with $\mathrm{FI}_{\mathrm{O}_2}$ of 1.0. In the case of hypoxemia due to alveolar hypoventilation, oxygen therapy often improves $\mathrm{Sa}_{\mathrm{O}_2}$ and oxygen delivery, but it does not correct the hypercapnia and underlying cause of respiratory dysfunction; restoration of ventilation must be pursued.

An oxygen saturation target of 92% to 96% is reasonable for patients at sea level who are hypoxemic and who have normal baseline lung function.[12] In certain circumstances, such as profound anemia, the target may be higher in an attempt to maximize the oxygen content of arterial blood before blood transfusion can be accomplished. Conversely, in patients who have abnormal control of respiration, such as those with chronic hypercapnia, a lower $\mathrm{Pa}_{\mathrm{O}_2}$ goal may be more appropriate (as discussed later in this chapter).

Use of supplemental oxygen may be indicated in a few clinical scenarios other than arterial hypoxemia. As discussed earlier, patients with severe anemia may benefit from enhanced arterial oxygen content and delivery, as may patients in cardiac and respiratory arrest. Similarly, trauma victims and critically ill surgical patients may benefit from early oxygen therapy to improve tissue hypoxia and for its hypertensive effects in hypovolemic shock. In patients with carbon monoxide poisoning, in whom pulse oximetry readings are unreliable, supplemental oxygen increases $\mathrm{Pa}_{\mathrm{O}_2}$ and blood oxygen content by both increasing the dissolved oxygen content and immediately displacing some of the CO bound to hemoglobin to increase the percentage of oxyhemoglobin. More importantly, it shortens the half-life of carboxyhemoglobin and hastens the clearance of CO. With administration of pure oxygen, the half-life of carboxyhemoglobin is 70 to 80 min,[14] compared with a half-life of 320 min when a patient breathes ambient air.[14] Under hyperbaric conditions, when pure oxygen is delivered at higher atmospheric pressure, the half-life is shortened even further to under 10 minutes. Hyperbaric oxygen is generally employed when carboxyhemoglobin levels are high (>25%) and there is evidence of end-organ damage, such as cardiac ischemia or alterations in sensorium,[16] although use of hyperbaric oxygen in this setting is currently controversial.

Several other disorders may benefit from administration of supplemental oxygen, although supportive data in these settings are lacking or equivocal. Oxygen therapy is often used in cluster headaches,[17] sickle cell pain crises (although this is falling out of favor),[18] palliative relief of dyspnea without hypoxemia,[19] and pneumothorax in patients who do not have a chest tube (in an effort to facilitate resorption of pleural air).[20,21] Administration of supplemental oxygen has also been proposed to reduce postoperative nausea and vomiting and to alleviate nausea associated with medical transport in ambulances.[22] Use of supplemental oxygen in uncomplicated myocardial infarction and stroke is common but controversial; the topic is discussed in more detail below. Finally, hyperbaric oxygen is sometimes used in an effort to accelerate healing of complicated, chronic wounds arising in the setting of peripheral or microvascular disease.[23] Hyperbaric oxygen therapy is widely accepted as the therapy of choice in decompression sickness (Chapter 93).[24]

Indications for Long-Term Oxygen Therapy

The use of LTOT has been growing as our ability to deliver oxygen in outpatient settings has improved. Criteria for administering LTOT have become well established, generally in the context of chronic obstructive pulmonary disease (COPD). Table 143-4 outlines the guidelines of the American Thoracic Society (ATS) for LTOT in Chronic Lung Disease.[25] The guidelines are largely based on the data derived from two major trials.

TABLE 143-4 Physiologic Indications for Long-Term Oxygen Therapy (LTOT) in COPD[a]

Pa_{O_2}	Sa_{O_2}	LTOT Indication	Qualifier
<55 mmHg	≤88%	Absolute	None needed
55–59 mm Hg	89%	Relative with qualifier	Presence of any of the following signs of cor pulmonale: • History of dependent edema • Polycythemia (Hematocrit >55%) • P pulmonale on ECG (P wave >3 mm in leads II, III, or aVF)
≥60 mmHg	≥90%	None unless qualifier	• Severe exercise desaturation (ambulatory use only)

[a] *Generally used in other conditions as well.*

Data from Jacobs SS, Krishnan JA, Lederer DJ. Home oxygen therapy for adults with chronic lung disease. An official American Thoracic Society clinical practice guideline. Am J Respir Crit Care Med. 2020;202(10):1345–1359; Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Nocturnal Oxygen Therapy Trial Group. Ann Intern Med. 1980;93(3):391–398; Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Report of the Medical Research Council Working Party. Lancet. 1981;1(8222):681–686.

The first trial, published in 1980, is the Nocturnal Oxygen Therapy Trial (NOTT).[26] In NOTT, 203 hypoxemic patients with COPD were randomized to the treatment with either nocturnal (at least 12 h) or continuous oxygen. Patients who received nocturnal oxygen therapy alone had a higher mortality at both 12 and 24 months (40.8% at 24 months) compared with those who received continuous oxygen therapy (22.4% at 24 months).

The second trial, published in 1981, is the British Medical Research Council Domiciliary (BMRCD) trial.[27] In this trial, 87 patients with hypoxemia and COPD were randomized to receive either no oxygen therapy or at least 15 h/day of supplemental oxygen. Similar to the NOTT trial, mortality was significantly higher in the no-oxygen group. Both trials studied patients in a stable medical state on maximal therapy and nonsmoking, who had Pa_{O_2} <55 mmHg or <60 mmHg if they had polycythemia or cor pulmonale. Currently, Sp_{O_2} <88% can also serve in lieu of an arterial blood gas measurement.

From these two trials, in patients with COPD and hypoxemia, we can infer that supplemental oxygen for >15 h/day is better than no oxygen at all, and that continuous supplemental oxygen is better than nocturnal-only therapy. The entry criteria for these trials form the basis of the current Medicare criteria and ATS guidelines for LTOT. Based on the BMRCD trial, most prescriptions for oxygen are written for at least 15 h/day. The data from the two trials have been extrapolated to other cardiopulmonary diseases complicated by chronic hypoxemia for which data from large trials are lacking, including cystic fibrosis, restrictive lung diseases, and chronic cardiac diseases.

In patients with COPD whose hypoxemia does not meet resting criteria or who have exercise induced hypoxemia, a recent multicenter trial did not support long term oxygen therapy. The 2016 Long Term Oxygen Therapy Trial (LOTT) randomized 738 patients with a resting desaturation of 89% to 93% or exercise-induced desaturation (defined by desaturation during the 6-min walk test) to either LTOT versus no LTOT. In the intervention arm, LTOT was delivered as either continuous oxygen therapy, for those patients with moderate resting desaturation, or oxygen therapy only during sleep and exercise, for those with exercise-induced desaturation. Patients randomized to the intervention arm did not experience life extension, lower rates of first hospitalization, or improvement in quality of life compared with controls.[28]

Finally, nocturnal supplemental oxygen is sometimes prescribed in patients with significant desaturation while sleeping. There is currently no clear evidence to support this practice in COPD.[29,30] Patients with nocturnal desaturation in the absence of underlying lung disease will often have obstructive sleep apnea or obesity hypoventilation syndrome, for which noninvasive positive pressure ventilation, rather than supplemental oxygen, constitutes primary and more effective therapy.[31]

Indications for Oxygen Therapy in Air Travel

An important consideration for clinicians who manage patients with lung disease is determining the need for supplemental oxygen during air travel.

Most commercial aircraft fly at cruising altitudes between 25,000 and 45,000 ft, which would normally result in a very low inspired oxygen tension (PI_{O_2}). Airplane cabins, however, are generally pressurized to an equivalent altitude of 8,000 ft, which results in an oxygen tension of approximately 108 mmHg (the PI_{O_2} at sea level is 149 mmHg). In patients with lung disease, this reduced PI_{O_2} may result in marked reductions in PA_{O_2} and Pa_{O_2}, placing the patient at risk for hypoxemia.

Prior to travel, the patient should have a thorough medical evaluation, with consideration for reevaluating pulmonary function tests, specifically spirometry and DL_{CO}, and obtaining an arterial blood gas. For patients whose Pa_{O_2} ≥70 mmHg (Sp_{O_2} >95%) at ground level, their in-flight Pa_{O_2} will likely exceed 50 mmHg, which is generally considered adequate for rest and minimal physical activity. For patients with a more marginal Sp_{O_2} or Pa_{O_2} and other risk factors, a 6-min walk test or other evaluation may be considered.[32]

The 6-min walk test may be a reliable and practical way of estimating the cardiopulmonary reserve that patients require to deal with the physiologic demands of a reduced PI_{O_2} during flight. Although the entire medical evaluation must be taken into account, if a patient has an abnormally low 6-min walk distance, has significant dyspnea during the test, or experiences a decline in Sp_{O_2} to <85%, the patient will likely need supplemental oxygen during air travel.

Finally, in anticipation of air travel, a hypoxia altitude simulation test (HAST) may be performed (Chapter 31).[33] In this test, an arterial blood gas is drawn just prior to administration of a gas mixture with an FI_{O_2} of 15.1%. Another arterial blood gas is drawn 20 min later, while the patient breathes the hypoxic gas mixture. If the Pa_{O_2} is <50 mmHg, administration of supplemental oxygen during flight is recommended. If the Pa_{O_2} is between 50 and 55 mmHg, further testing should be considered, including a 6-min walk test. Reviews are available that address oxygen therapy and air travel including testing options and recommended liter flow rates to achieve adequate oxygenation.[34]

TECHNIQUES OF OXYGEN ADMINISTRATION

When choosing an oxygen delivery device for a given patient, the clinician must consider the degree of hypoxemia, the specificity required with regard to setting the FI_{O_2} (which depends on the patient's ventilatory control), and the patient's minute ventilation. The oxygen flow that the device can deliver, the adjustability and precision of that delivery, and the comfort and cost of the device are additional considerations.

Oxygen delivery devices utilized in the acute setting may be divided into low-flow and high-flow delivery systems. The required flow depends on the patient's degree of hypoxemia and minute ventilation. Patients with a high minute ventilation or who are profoundly hypoxemic require high-flow devices, if they do not require mechanical ventilation. Patients with more moderate degrees of hypoxemia may only need low-flow systems, which are generally more comfortable.

■ Low-flow and Variable Performance Oxygen Devices

Low-flow systems deliver only a fraction of the patient's minute ventilation as pure oxygen. The maximum flow in these systems is 15 L/min. Since a patient's tidal volume and inspiratory flow rate usually vary from breath to breath, and the delivered flow of oxygen from the device is constant, the fraction of inspired oxygen for any given breath is impossible to predict. For example, when a patient takes very deep breaths, more ambient air is entrained, but the flow of pure oxygen is constant, thereby diluting the administered FI_{O_2}. Conversely, when a patient has a reduced minute ventilation or is taking very shallow breaths, the amount of entrained ambient air is minimal, and the FI_{O_2} inspired may be far greater than what might be expected. Table 143-5 illustrates this important principle mathematically. The variation in FI_{O_2} with minute ventilation must be considered when administering oxygen to patients with chronic CO_2 retention who are at risk for worsening hypercapnia with excessive oxygen therapy. Because of the uncertainty of the FI_{O_2} delivered by low-flow devices, they are sometimes referred to as "variable performance devices."

Nasal Cannulae

Nasal cannulae allow comfortable delivery of oxygen and unimpeded communication and access to oral intake. The cannula rests just below the nares (Fig. 143-1) and delivers a constant flow of pure oxygen, generally ranging from 2 to 6 L/min. At 6 L/min or higher, the patient may experience discomfort, excessive mucosal dryness, and epistaxis. The continuous flow creates an anatomic reservoir of oxygen in the nasopharynx from which the patient draws during inspiration. Contrary to popular belief, even if a patient is a "mouth-breather," the gas inhaled is oxygen enriched because of the effect of the nasopharyngeal reservoir. In certain disease states, such as chronic obstructive pulmonary disease (COPD), with a prolonged expiratory phase, end-expiratory flow may be present, which limits the creation of the anatomic reservoir and "mouth-breathing" effects may be present.[35] Although FI_{O_2} varies widely with nasal cannulae (as described above), an approximation of FI_{O_2} based on oxygen flow rate can be derived (Table 143-6). Typically, FI_{O_2} increases by 0.03 to 0.04 with each 1-L increment in flow.

Several variations in nasal cannulae design may reduce oxygen waste. The moustache-style reservoir (Fig. 143-1C) contains a soft, inflatable reservoir with a volume of approximately 20 ml. During exhalation, the reservoir fills with oxygen. During inspiration, the patient initially draws from the reservoir and then, when the reservoir is depleted, from the continuous flow of the cannula. This acts to deliver a bolus of oxygen early in the course of the inspiration, while reducing wasted oxygen during expiration. Generally, patients can be maintained at a slightly lower flow rate using the moustache-style cannula compared with a regular nasal cannula.

Another modification is the pendant reservoir cannula (Fig. 143-1B). This device consists of a reservoir worn on the chest like a pendant. The reservoir is attached to a nasal cannula with tubing of

TABLE 143-5 Effects of Minute Ventilation on FI_{O_2} in Low-flow Systems

	Respiratory Distress	Relief of Respiratory Distress
Minute ventilation	30 L/min (40 breaths/min × 750 ml/breath)	5 L/min (10 breaths/min × 500 ml/breath)
O_2 flow rate	2 L/min	2 L/min
Calculation of inspired O_2 concentration (FI_{O_2})	2 L/min of 100% oxygen + 28 L/min of 21% oxygen (room air drawn into mask) = 30 L/min minute ventilation Thus, $FI_{O_2} = \frac{(1.0 \times 2) + (0.21 \times 28)}{30} = 0.26$ (**26%** FI_{O_2})	2 L/min of 100% oxygen + 3 L/min of 21% oxygen (room air drawn into mask) = 5 L/min minute volume Thus, $FI_{O_2} = \frac{(1.0 \times 2) + (0.21 \times 3)}{5} = 0.53$ (**53%** FI_{O_2})

Modified with permission from Bateman NT, Leach RM. ABC of oxygen. Acute oxygen therapy. BMJ. 1998;317(7161):798–780.

slightly greater diameter than normal. The pendant reservoir cannula provides a similar function to the moustache-style cannula.

Simple Oxygen Masks

Oxygen masks can deliver higher oxygen flow rates than nasal cannulae; they entrain less ambient air and, therefore, can generate a higher FI_{O_2}. In addition, the configuration of simple masks (Fig. 143-2A) enables an enlarged reservoir of oxygen for inhalation. With nasal cannulae, the reservoir comprises anatomic dead space in the airway, such as the nasopharynx. With a well-fitting oxygen mask, the reservoir is expanded to include the volume within the mask. Generally, flow rates for simple masks range from 5 to 12 L/min, which usually requires some ambient air to be entrained via the side ports of the mask to meet the patient's minute ventilatory needs. Given the higher flow rates delivered using face masks, a humidifier is also often required. The flow rate of a simple mask should never be <5 L/min; below this level, carbon dioxide rebreathing may occur, along with an increased resistance to inspiration.

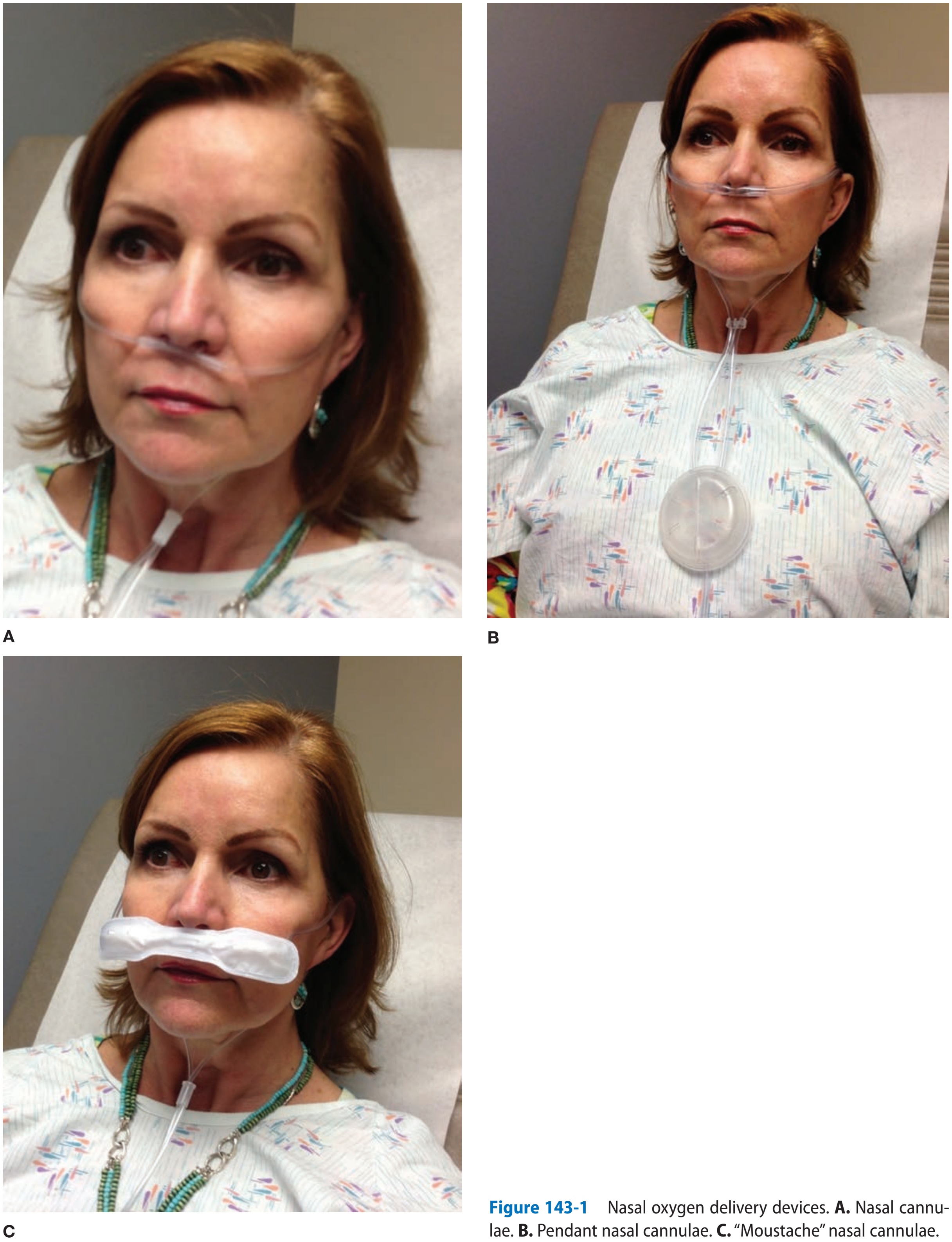

Figure 143-1 Nasal oxygen delivery devices. **A.** Nasal cannulae. **B.** Pendant nasal cannulae. **C.** "Moustache" nasal cannulae.

TABLE 143-6 Approximate F_{IO_2} Using Various Oxygen Devices (Assumes Perfect Fit of Mask)

100% O_2 Flow Rate (L/min)	F_{IO_2}
Nasal Cannula	
1	0.24
2	0.28
3	0.32
4	0.36
5	0.40
6	0.44
Oxygen Mask	
5–6	0.40
6–7	0.50
7–8	0.60
Mask with Reservoir Bag	
6	0.60
7	0.70
8	0.80
9	0.90
10	0.99
Nonrebreathing Mask	
4–10	0.60–1.0
Venturi Mask[a]	
3 (80)	0.24
6 (68)	0.28
9 (50)	0.35
12 (50)	0.40
15 (41)	0.50

[a] *Number in parentheses indicates total flow of entrained ambient air with Venturi mixture.*

As is the case with nasal cannulae, predicting the actual F_{IO_2} delivered by simple oxygen masks is difficult, since the F_{IO_2} varies with the size of the patient's tidal volumes, inspiratory flow rate, and minute ventilation. Simple masks are also more uncomfortable, making eating and communicating challenging. Because they cover the mouth, aspiration is a risk with any mask.

Reservoir Masks

A reservoir mask is similar to a simple mask but has an attached reservoir of 600 to 800 ml, resting below the patient's chin. Generally, the mask provides flow between 8 and 15 L/min, which keeps the reservoir bag at least half full. Reservoir masks include partial rebreather and nonrebreather types (Fig. 143-3).

When using a partial rebreather mask, the patient exhales approximately the first one-third of the expired tidal volume into the reservoir. That volume is derived predominantly from anatomic dead space and, consequently, its O_2 content is high and CO_2 content low. The reservoir bag is filled with the exhaled volume and continued oxygen inflow, while the remainder of the patient's tidal volume is exhaled via the mask's side ports and edges. A patient with a high minute ventilation can sometimes deflate the reservoir. As with simple oxygen masks and nasal cannulae, the F_{IO_2} the patient is receiving cannot be determined precisely at any point in time.

The nonrebreathing reservoir mask (Fig. 143-2B) is similar to the partial rebreather, with the exception of a one-way valve at the exit of the reservoir bag. The valve ensures that no exhaled air enters the reservoir (i.e., air can travel only in an inward direction), enabling delivery of 100% oxygen. The mask also incorporates one-way valves on its side ports to minimize the inhalation of ambient air. When using a nonrebreathing reservoir mask, oxygen flow should be set high enough to prevent deflation of the reservoir bag—usually about 15 L/min. Currently available masks do not fit securely enough to ensure a delivered F_{IO_2} of 1.0. Typically, these masks provide a maximum F_{IO_2} of 0.8 to 0.9; the F_{IO_2} may be even lower (0.60–0.8) in the setting of very high minute ventilation.[36]

■ High-flow or Fixed-Performance Oxygen Devices

High-flow oxygen devices deliver a constant F_{IO_2} and are, therefore, sometimes referred to as "fixed performance devices." The devices allow for a fixed F_{IO_2} by providing very high flows of pure oxygen that exceed the patient's minute ventilation, sometimes by a factor of four. Along with very high flow rates, the devices incorporate oxygen reservoirs whose volumes exceed the patient's anatomic dead space. Since the F_{IO_2} is predictable, high-flow devices are ideal for patients who have precise oxygen needs that should be neither exceeded nor unmet. Patients for whom high-flow devices are prescribed may be severely hypoxemic and must be monitored closely for the possible need for noninvasive or invasive mechanical ventilation.

Air-entrainment Masks (Venturi Masks)

The Venturi mask consists of a mask, a jet nozzle, and entrainment ports (Fig. 143-2D). Oxygen is delivered under pressure via the jet nozzle, which acts to dramatically increase the velocity of the gas. The high-velocity gas entrains ambient air via the entrainment ports. Depending upon the size of entrainment ports, size of the jet nozzle, and flow rate of oxygen, a predictable F_{IO_2} can be delivered.

Typically, the Venturi mask has interchangeable or adjustable valves that enable the clinician or respiratory therapist to better titrate the F_{IO_2} to the patient's needs. Humidification is sometimes difficult to ensure and requires the use of an aerosol-entrainment collar over the jet orifice and entrainment port. Humidification increases the density of the entrained air, slows the speed of entrainment, and thereby reduces the amount of room air entrained, resulting in a higher F_{IO_2}. Although described as a high-flow device, air-entrainment masks generally can only ensure a high-flow rate when the F_{IO_2} is <0.3.[36] As the F_{IO_2} increases above 0.3, the devices are unable to deliver flow rates of 40 L/min (as less ambient air is entrained) and are considered variable performance devices. However, the ability of these masks to deliver an exact F_{IO_2} at lower levels of F_{IO_2} makes them ideal for patients with chronic lung disease who require a specific F_{IO_2} due to the risk of hypercapnia from hyperoxia. In fact, for treatment of patients with COPD in emergency departments, the British Thoracic Society recommends oxygen administration using a Venturi mask to ensure an appropriate F_{IO_2}.[12]

High-flow Generators

High-flow generators are used to ensure noninvasive delivery of a constant, high concentration of inspired oxygen. High-flow generators are capable of delivering gas in excess of 40 to 60 L/min. From the generator, gas is routed through a heated humidifier, similar to that used for mechanical ventilators. A large reservoir is often placed in line between the humidifier and aerosol face mask. The face mask may incorporate valves that ensure that no rebreathing occurs. Given the high flows delivered, a constant F_{IO_2} is achieved, regardless of the patient's minute ventilation and fit of the mask. When precise oxygen titration is required, air–oxygen blenders are used. The blenders are metering devices that use compressed oxygen and air from a high-pressure wall source (50 psi) to generate a gas mixture that can be delivered at high flow (e.g., 100 L/min) and precise

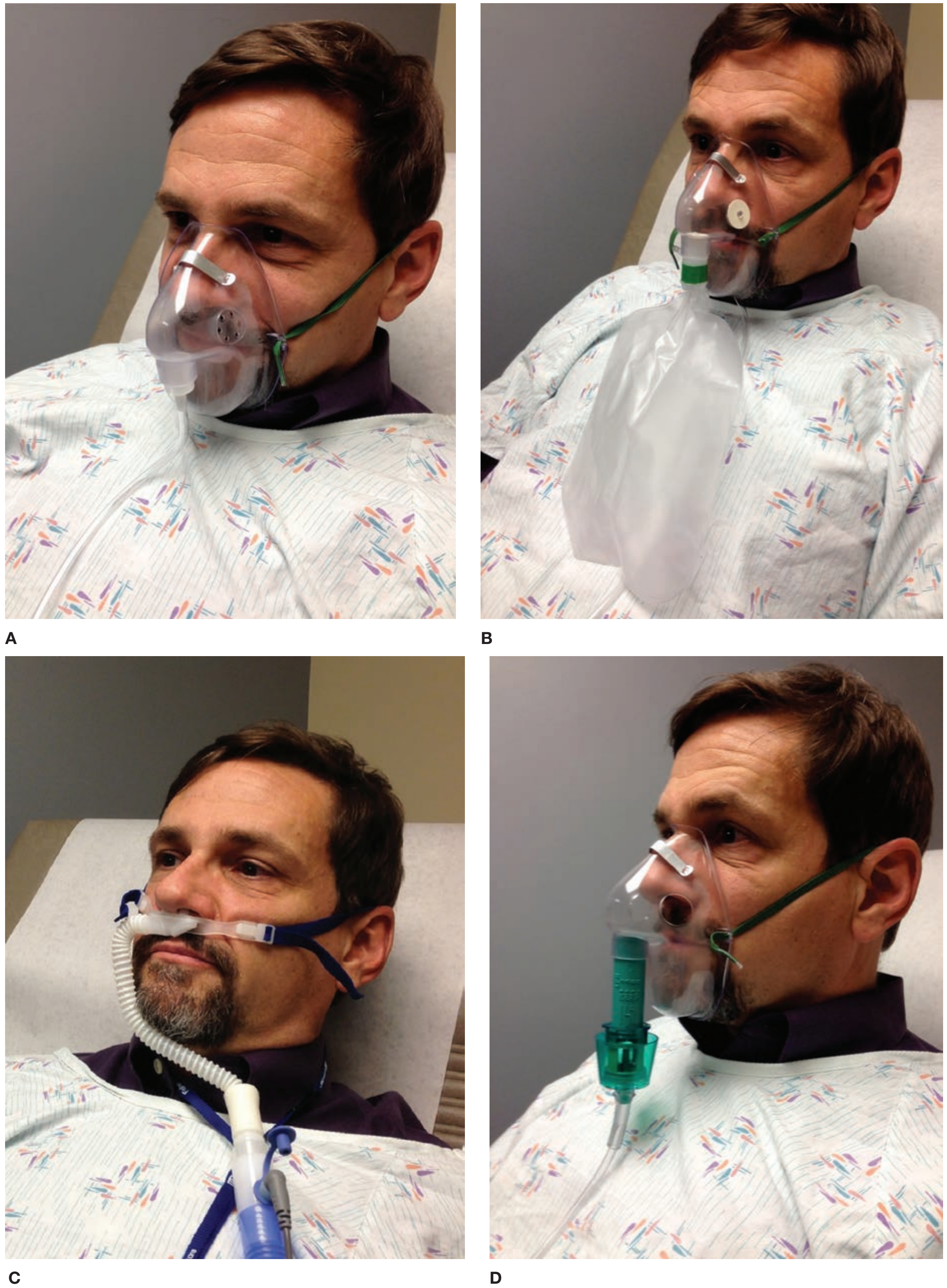

Figure 143-2 Mask oxygen delivery devices. **A.** Simple face mask. **B.** Nonrebreather mask. **C.** High-flow nasal cannulae. **D.** Venturi mask.

$\mathrm{FI}_{\mathrm{O}_2}$. The devices are noisy and require specialized personnel to set up and monitor, limiting their usage to intensive care settings.[37]

High-flow Nasal Cannulae (HFNC)

Over the past 10 years, nasal cannulae that can deliver much higher rates of flow than simple nasal cannulae have been developed (e.g., Optiflow or Vapotherm). These can be used with the same type of high-flow generators discussed above, allowing delivery of up to 60 L/min of heated, humidified oxygen. The high-flow nasal cannula interface (often abbreviated HFNC) can be more comfortable than a facemask. Physiologic benefits of HFNC compared with face mask delivery include elimination of interface dead space, washout of

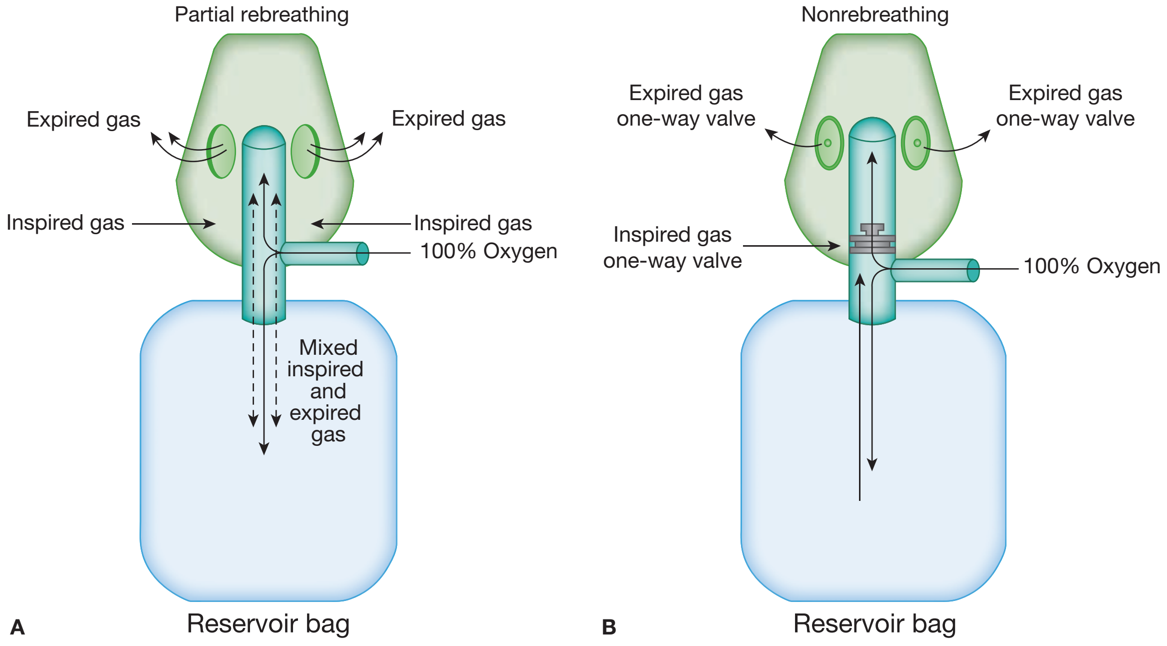

Figure 143-3 Mask reservoir bag systems, illustrating airflows with partial rebreathing (**A**) and nonrebreathing (**B**) masks. *Arrows* indicate direction of airflow.

carbon dioxide from the nasopharynx, improved thoracoabdominal synchrony and improved work of breathing, and increased positive end-expiratory pressures, up to 4 cmH_2O.[38] Use of HFNC has been studied in a number of clinical settings, including hypoxemic respiratory failure, hypercarbic respiratory failure, postoperative respiratory failure, preoxygenation for intubation, and prevention of reintubation following extubation.[39] In hypoxemic respiratory failure, randomized controlled trials have shown a lower rate of intubation compared with conventional supplemental oxygen[40,41] and noninvasive positive pressure ventilation.[40] Studies looking at prevention of reintubation have shown comparable rates of reintubation in high-risk patients compared with noninvasive positive-pressure ventilation and lower rates of reintubation compared with conventional oxygen therapy.[42]

■ Long-Term Oxygen Therapy

As noted previously, LTOT has a significant beneficial effect on survival in patients with COPD and chronic hypoxemia. However, initiation of chronic home oxygen therapy can be a substantial burden for patients. Like any therapy, LTOT requires patient adherence. Various studies have noted adherence to LTOT in only 45% to 70% of patients.[43] The barriers to adherence are many and include patient concerns of addiction and dependency, embarrassment from the "stigma" that an oxygen delivery device represents a smoking-related disease, and the associated limitations on physical activity arising from bulky ambulatory oxygen sources.[43] Therefore, appropriate counseling about the benefits (life extension, improved exercise capacity and quality of life) and demands of oxygen therapy is necessary before beginning treatment. Furthermore when considering LTOT, the clinician should consider oxygen source portability, available social and home support (e.g., friends, family, visiting nurses), and patient attitudes and beliefs, especially regarding smoking cessation. Finally, the prescribing clinician needs to facilitate sufficiently close patient monitoring to ensure long-term benefit from therapy. In the United States, oxygen therapy requires a Certificate of Medical Necessity (CMN). Continued need for LTOT must be recertified annually.

Oxygen Concentrators

Oxygen concentrators use specialized filters to eliminate other gases from ambient air, thus "concentrating" oxygen for delivery to the patient. Concentrators accomplish this by (1) using a compressor to draw ambient air into the system, (2) cooling the air (which has been heated up from the compression) using a heat exchanger, and (3) passing the air into molecular sieve beds where oxygen is concentrated. Sieve beds contain granular zeolite crystal composed of an array of small particles that separate gases according to size. Air cycles through two separate sieve beds; the cycling gradually removes nitrogen as waste and isolates oxygen, which is diverted to a product tank. The oxygen in the product tank is pressurized at 10 psi and, prior to patient delivery, is passed through a bacteria filter and flow meter. Concentrators usually can produce oxygen concentrations of 95% to 97% at 2 L/min flow; the concentration falls to 86% to 93% at 3 to 5 L/min flow (note that pure oxygen tanks provide 100% oxygen at any flow rate up to 6 L/min).[37] Oxygen concentrators include large devices (weighing about 35 lb) intended for stationary use in the home and smaller portable devices, designed for use outside the home. The larger concentrators can produce high flows (up to 10 L/min) but are often tethered by power cords. High flow rates also demand humidification, which can also be provided by most large concentrators. Portable oxygen concentrators permit patient mobility; their use is increasingly being approved for air travel.[44] They usually weigh between 5 and 10 lb. Battery life is variable, typically on the order of 2.5 h.

Liquid Oxygen

Although compressed gas oxygen is still utilized, often as an emergency supply in the home, liquid oxygen (LOx) has become standard in domiciliary systems. LOx has advantages of being more compact, requiring fewer refills, and operating at lower pressures than gaseous oxygen.

A home system of LOx typically consists of a large stationary reservoir that can hold up to 100 lb of LOx, and a smaller portable system for ambulation. The portable system can be refilled by the patient and may weigh as little as 5 lb. LOx is stored in tanks called dewars, which generally resemble a thermos bottle. The dewar consists of inner and outer containers and interposed insulating material and vacuum to maintain low temperatures.[37] Generally, LOx is more expensive than compressed gas and requires pressure-relief venting. However, LOx delivery systems consume less electricity and enable longer periods of high-flow oxygen administration.

Oxygen-conserving Devices

LTOT is expensive, and oxygen-conserving devices have been designed to limit oxygen waste. Simple oxygen-conserving devices were discussed earlier. In addition to these simple devices, electronic oxygen-conserving devices are available.

Electronic oxygen-conserving devices are triggered by the onset of inspiration and deliver oxygen in boluses, the volume of which depends on device settings. For *pulse-type devices*, a fixed volume of oxygen is delivered (based on the flow setting) each time a breath is initiated. Some pulse-type devices deliver the volume with alternating breaths, rather than with every breath. For *demand-type devices*, the volume of oxygen is delivered throughout the whole inspiratory cycle; consequently, the volume varies according to the length of the cycle. For demand-type devices, as respiratory rate decreases, the amount of oxygen conserved also decreases. In fact, demand-type devices commonly deliver an equal or greater volume of oxygen than a continuous-flow device. In the event of an electronic-conserving device malfunction, the delivery system defaults to continuous flow, often without the patient being aware.

Transtracheal Catheters

Transtracheal catheters, also considered oxygen-conserving devices, are considerably more invasive than other forms of LTOT. Transtracheal catheters require insertion directly into the trachea. Usually, this is accomplished percutaneously, using a modified Seldinger technique (similar to that used for placement of a percutaneous tracheostomy), or surgically, using a Lipkin procedure or minitracheotomy.[45]

The benefit of a transtracheal catheter is that it delivers oxygen that bypasses much of the anatomic dead space and utilizes the natural oxygen reservoir of the upper airway. Oxygen usage may be reduced by 50% to 75% with the use of a transtracheal catheter. In addition, nasal or facial irritation is minimal. Unfortunately, the catheter can be a nidus for infection and formation of "mucus balls," which rarely are fatal.[46]

OXYGEN TOXICITY

Concerns about oxygen toxicity have existed essentially since its discovery. Soon after his discovery in 1775, Joseph Priestley wrote that oxygen "might not be so proper for us in the usual healthy state of the body …" The modern study of oxygen toxicity largely focused on pulmonary oxygen toxicity and began with J. Lorrain Smith in 1899. Smith described pathologic changes of oxygen toxicity in small animals exposed to the gas at a fractional concentration of 0.4 at 4.5 atmospheres (hyperbaric oxygen).[47] He noted that with high levels of oxygen exposure in mice, "the effect was uniformly fatal, and the immediate cause of death was inflammation of the lungs … and the lungs were found postmortem to be extremely congested … the alveoli were to a great extent filled with an exudate, which was granular and fibrillated in appearance…."

Further studies were conducted in animals to confirm Smith's findings. In the late 1930s, Becker-Freysang et al. studied oxygen exposure in humans and found that with 65 h of exposure to O_2 at 730 mmHg, paresthesias, nausea, and significant decreases in vital capacity occurred.[46] In the early 1960s, a healthy volunteer exposed to 110 h of continuous high oxygen exposure experienced profound alterations in vital capacity, minute ventilation, pH, and Pa_{O_2}.[48] However, in general, the study of oxygen toxicity in humans has proved challenging. Based on animal models, information has been generated on the underlying cellular mechanisms.

■ Biochemical Basis of Oxygen Toxicity

In considering the biochemical basis of oxygen toxicity to the lungs and body, the roles of free radicals in the production of tissue damage and the protective cellular antioxidant defenses should be noted.

Free Radicals

Descriptions of the mechanisms of oxygen toxicity invariably begin with the concept of highly reactive oxygen-derived free radicals, specifically, superoxide (O_2^-), hydrogen peroxide (H_2O_2), and the hydroxyl radical (OH^-). By definition, free radicals have an unpaired orbital electron that causes oxidation of a surrounding molecule. Free radicals are ubiquitously produced during cellular oxidative metabolism; however, cells normally have the capability of neutralizing them quickly. Invariably, in hyperoxic conditions, generation of free radicals overcomes the cell's natural defenses.[49] Once formed in excess, free radicals are responsible for a cascade of effects, including lipid damage, leading to membrane dysfunction; disruption of enzymatic protein function; and nucleic acid damage.[50] Ultimately, these effects may result in cell death. In the case of nucleic acid damage, mutagenesis may occur.

Cellular Antioxidant Defenses

Various enzymes and cofactors in cells neutralize free radicals produced normally as a byproduct of mitochondrial metabolism. These neutralizing enzymes are ubiquitous in eukaryotes.[51] The prototype is the metalloprotein superoxide dismutase, which converts superoxide to hydrogen peroxide. Hydrogen peroxide so-generated is converted intracellularly to H_2O and O_2 through the actions of catalase (found in peroxisomes) and glutathione peroxidase (found in the cytoplasm). Glutathione peroxidase also repairs damaged lipids. Glutathione reductase and glucose-6-phosphate dehydrogenase regenerate glutathione, enabling its recycling as an antioxidant.

Nonenzymatic antioxidants, which are present within cells, include the vitamins α-tocopherol (vitamin E) and ascorbate (vitamin C). Other antioxidants, such as ceruloplasmin and cysteine, also are normally present in cells and the extracellular fluid. In fact, human lung tissue contains a high concentration of extracellular antioxidants and superoxide dismutase isoforms, which allow exposure to higher-concentration oxygen without development of toxicity.[52–54]

Tissue Damage in the Lungs

The cascade of reactions leading to hyperoxia-induced pulmonary tissue damage can be described in two phases.[55] Three to four days following hyperoxic exposure and generation of free radicals, an *exudative* phase commences, characterized by death of alveolar type 1 and endothelial cells. Interstitial edema is seen along with exudative alveolar filling. Neutrophil recruitment into the capillaries and interstitium is present. Alveolar epithelial damage then occurs, as neutrophils enter the alveoli, as seen in bronchoalveolar lavage specimens. A second, *proliferative* phase follows, characterized by proliferation of endothelial cells and type 2 pneumocytes. The pneumocytes cover the previously exposed basement membrane. Fibroblast proliferation also occurs in this phase. Recovery from oxygen injury is characterized by interstitial scarring and fairly normal-appearing capillary endothelium and alveolar epithelium.

■ Clinical Manifestations of Pulmonary Oxygen Toxicity

The exposure level at which oxygen toxicity occurs has not been clearly identified, although a higher FI_{O_2} experienced for a longer period of time is associated with an increased risk. Clinical oxygen toxicity is manifest in several ways. Normal subjects experience a decrease in vital capacity and fall in DL_{CO}.[56] Lung compliance is diminished.[57] Tracheobronchitis, which produces substernal chest pain and cough, also may occur.[57] Clinical toxicity is generally absent when the FI_{O_2} is <0.5. Most clinically relevant concerns over oxygen toxicity center around (1) absorption atelectasis; (2) hypercapnic respiratory failure in at-risk individuals; (3) acute respiratory distress syndrome (ARDS); and (4) hyaline membrane disease, leading to bronchopulmonary dysplasia (BPD) in newborns.[58–60]

Absorption Atelectasis

When a human breathes ambient air, oxygen in the lung passes freely from the alveoli into the capillaries and is bound to hemoglobin or dissolved in plasma. Nitrogen, however, being an inert gas, does not diffuse into the blood at any appreciable rate and thus acts to stent open the alveoli and maintain patency. For a patient breathing pure oxygen, the absence of nitrogen promotes alveolar collapse.

In a study based on mathematical modeling of alveolar collapse, the time from airway occlusion and cessation of ventilation into that region to alveolar collapse was 37 min using 3 min of ventilation with ambient air, compared with 8.7 min using preoxygenation with 100% oxygen (taking into account HPV).[61] In a clinical context, patients who received 40% oxygen just prior to extubation were shown to have less atelectasis on CT imaging compared with those who received 100% oxygen.[62] Absorption atelectasis can be observed with induction of anesthesia. Preoxygenation and resulting nitrogen washout particularly in lungs with areas of low ventilation to perfusion ratios, along with a decrease in FRC from chest wall and diaphragmatic paralysis that occurs with the use of anesthetics and neuromuscular blockade, lead to small airway and alveolar collapse.[63]

Hypercapnia in the Setting of Chronic CO_2 Retention and Hyperoxia

Patients with chronic CO_2 retention, usually in the setting of COPD, are at risk of worsening hypercapnia when exposed to high levels of inspired oxygen. Classically, this worsening of hypercapnia during excessive supplemental oxygen administration has been attributed to the suppression of hypoxic drive to breathe in the setting of a blunted hypercapnic drive. This formulation was first proposed in a case report published in the middle of the 20th century.[64] However, three other mechanisms have been proposed,[12] as discussed below.

Ventilation–perfusion mismatch is an important cause of hypoxemia in patients with COPD. As discussed previously, HPV blunts the adverse effects of a low $P_{A_{O_2}}$ due to reduced ventilation on both Pa_{O_2} and Pa_{CO_2}. When $P_{A_{O_2}}$ is increased through administration of supplemental oxygen, HPV is abolished, increasing perfusion to alveolar units that remain underventilated. In fact, they become units with even lower V_A/Q and, now, oxygen enriched. Alveolar oxygen diffuses across the alveolar–capillary membrane with a higher driving partial pressure, but because ventilation is still reduced, the gradient for CO_2 is not enhanced. The increase in perfusion comes at the expense of better ventilated units, which now do not eliminate as much CO_2 as before and as a result, $P_{A_{CO_2}}$ and thus Pa_{CO_2} increases.

An additional consideration is the *Haldane effect*—the increased capacity of deoxygenated blood over oxygenated blood for CO_2 binding. As hemoglobin molecules become deoxygenated (i.e., reduced), they more readily accept protons (H^+). Removal of dissolved protons from plasma drives formation of bicarbonate, which, in turn, is catalyzed by carbonic anhydrase:

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow HCO_3^- + H^+ \tag{8}$$

Bicarbonate is the primary form in which CO_2 is transported and eliminated from the body. Furthermore, deoxygenated hemoglobin binds CO_2 directly, forming carbaminohemoglobin. As $P_{A_{O_2}}$ and, consequently, Pa_{O_2} increase with oxygen therapy, the concentration of oxyhemoglobin increases while that of deoxyhemoglobin decreases. As a result, CO_2 and H^+ buffering capacity are depleted, diminishing venous blood's transport capacity for tissue-generated CO_2. Loss of this capacity to transport CO_2 results in a rise in Pa_{CO_2}.

Finally, since pure oxygen is of higher density than air, the increased density of oxygen-enriched mixtures may contribute to increased work of breathing in an already compromised patient.[65]

Regardless of the underlying mechanism(s), clinicians must be vigilant when administering supplemental oxygen to those with chronic CO_2 retention, especially when they are very hypoxemic and exhausted. Unfortunately, the worsening of hypercapnia with oxygen administration is unpredictable; some patients with COPD do not develop hypercapnia with hyperoxia, while others may develop frank ventilatory failure. Use of a high-performance oxygen delivery device (e.g., Venturi mask) and titration of $F_{I_{O_2}}$ to achieve a goal Sp_{O_2} of 88% to 90% in selected populations is the preferred management strategy. Isolated case reports over the years have reported poor outcomes with unregulated $F_{I_{O_2}}$, but this was incontrovertibly shown in a randomized out-of-hospital study in patients with acute exacerbation of COPD transported to hospital randomized to either high-flow O_2 or supplemental O_2 titrated to achieve Sp_{O_2} in the range of 88% to 92% with a mortality difference of 7% versus 2%.[66]

Acute Respiratory Distress Syndrome (ARDS) and Bronchopulmonary Dysplasia (BPD)

Oxygen toxicity has been implicated in the pathophysiology of ARDS, although this subject is controversial. In almost all nonhuman mammals, prolonged exposure to 100% oxygen leads to diffuse alveolar damage and, eventually, death. In humans, replicating these findings has been challenging. Conducting studies on oxygen toxicity presents ethical considerations of testing healthy human subjects. In addition, when oxygen toxicity is studied in the setting of pulmonary disease, differentiation between damage caused by the underlying lung disease and that caused by excessive oxygen exposure may be impossible. Furthermore, the situation is complicated by the fact that many inflammatory diseases evoke upregulation of antioxidant defenses. Thus, many human studies have failed to show an association between excessive oxygen exposure and development of acute lung injury or ARDS.

In a study of brain-dead patients whose normal lungs were exposed for 24 h to 100% oxygen delivered via a mechanical ventilator, only mild increases in alveolar capillary permeability were demonstrated; several more days of oxygen exposure failed to produce pathologic evidence of lung injury.[67] Similarly, another trial in postoperative cardiac patients failed to show any clinical differences between those ventilated with 100% oxygen and those ventilated with the minimal amount of oxygen needed (mean $F_{I_{O_2}}$ of 0.32).[68] Notably, an acute lung injury pattern due to oxygen toxicity may be seen in humans with prior drug exposure, as discussed below.

Premature newborns often require high levels of oxygen therapy in the setting of hyaline membrane disease—a disorder caused by surfactant deficiency and characterized by alveolar collapse and inflammation.[69] In survivors, chronic lung disease in the form of BPD is often seen. Oxygen toxicity is considered a major factor in the pathogenesis of BPD. BPD has been described in infants administered a high concentration of oxygen but not mechanically ventilated.[58] Newborns are particularly prone to damage by hyperoxia, as their cellular antioxidant defenses are not fully developed. The initial pathologic lesions of BPD resemble diffuse alveolar damage. As BPD evolves, pathologic findings include alternating areas of collapse and emphysema, hyaline eosinophilic material lining distended terminal airways, marked epithelial hyperplasia or metaplasia, peribronchial fibrosis, and elastic fibers around air sacs and lobules. Clinically, the condition presents as a persistent requirement for supplemental oxygen or mechanical ventilation following hyaline membrane disease, along with poor lung compliance and pulmonary hypertension. Most infants gradually improve after 2 to 4 months. In more severe cases, infants require prolonged mechanical ventilation and may develop cor pulmonale from severe pulmonary hypertension.

■ Potentiation of Pulmonary Oxygen Toxicity

Several drugs have well-known pulmonary toxicity and may potentiate the toxicity of oxygen. Bleomycin, an antibiotic agent first isolated from the fungus *Streptomyces verticillus* in the late 1960s,[70] has been used as a chemotherapeutic agent in the treatment of lymphomas, germ cell tumors, Kaposi sarcoma, cervical cancer, and squamous cell carcinomas of the head and neck. One mechanism by which bleomycin exerts its antitumor effect is through induction of cytotoxicity via generation of free radicals. Bleomycin forms a complex with Fe^{2+}, which is oxidized to Fe^{3+}, resulting in reduction of oxygen to free radicals. Bleomycin is also thought to exert direct effects on DNA. Along with its elimination by the kidneys, bleomycin can be deactivated by the enzyme bleomycin hydrolase, which is found in most tissues (especially the liver). However, two notable organs lack the enzyme: lung and skin.

In the lungs, bleomycin toxicity is manifested in three ways: organizing pneumonia, eosinophilic hypersensitivity, and interstitial pneumonitis, which all may progress to fibrosis. An experiment in the hamster demonstrated that high doses of oxygen may work synergistically with bleomycin to cause worsening lung injury.[71] In humans, several case reports describe ARDS in patients previously treated with bleomycin who had exposure to a high FI_{O_2} perioperatively.[72,73] However, one prospective trial failed to show an association between high levels of oxygen exposure, past bleomycin exposure, and significant postoperative pulmonary dysfunction.[74]

Another well-known potentiator of pulmonary oxygen toxicity is paraquat. Paraquat is a commercial herbicide commonly used in the United States. It is associated with considerable toxicity and mortality when ingested orally, often in suicide attempts.[75] Like bleomycin, paraquat-induced pulmonary toxicity is the result of oxidative stress arising from the generation of free radicals, leading to pneumonitis and pulmonary fibrosis. Similar to models of bleomycin toxicity, animal studies suggest worsening toxicity in the setting of higher levels of inspired oxygen.[76,77] Therefore, in managing patients with paraquat poisoning, FI_{O_2} should be minimized as much as clinically possible. Use of paraquat is banned in the European Union and in several other countries, but the herbicide is still available for agricultural use in the United States. Fulminant poisonings carry a mortality that well exceeds 50%.[78]

Other drugs studied with regard to potentiation of oxygen toxicity include disulfiram and nitrofurantoin. Disulfiram is converted in vivo to diethyldithiocarbamate, which inhibits cytosolic superoxide dismutase.[79] Metabolism of nitrofurantoin results in the production of superoxide in a similar way to paraquat. The final pathway in both cases is an accumulation of oxygen-free radicals.[80]

Finally, elements of dietary intake are also associated with potentiation of oxygen toxicity, at least in animal models.[81] Protein deficiency leads to hyperoxic damage, possibly through a lack of sulfur-containing amino acids, which are crucial to glutathione synthesis. Deficiencies in the antioxidants vitamin A and vitamin E have also been implicated in the potentiation of oxygen toxicity.[82,83]

Oxygen Toxicity in Other Organ Systems

Hyperoxia has the potential for producing toxicity in other organ systems. For example, an association between increased mortality and hyperoxia in the setting of return of spontaneous circulation (ROSC) following cardiac arrest has been reported.[84] In this large, multicenter, retrospective cohort study, patients who had a Pa_{O_2} >300 mmHg following ROSC had an odds ratio for in-hospital death of 1.8 (95% confidence interval [CI], 1.8–2.2), based on a model controlling for potential confounders. The increased mortality seen in this study was attributed to hyperoxic reperfusion injury leading to oxidative stress—specifically worsening postarrest functioning of the central nervous system. Based on the results of this study, the American Heart Association has adjusted its postarrest guidelines to emphasize titration of FI_{O_2} to maintain an oxygen saturation no greater than 94%. Prospective data are not currently available to prove causation. A recent study also described increased mortality in patients with hyperoxemia immediately following emergency department intubation, which correlated strikingly with the degree in elevation of Pa_{O_2}.[85]

In a retrospective study conducted at a single trauma center, higher mortality was noted in patients with traumatic brain injuries exposed to hyperoxia (Pa_{O_2} >200 mmHg) compared to normoxia.[86] Patients with hyperoxic exposure were more likely to have low Glasgow coma scores (3–8) on discharge than those who were normoxic. In the same study, patients with hypoxemia also had worse outcomes compared to those who were normoxic, emphasizing the importance of close and continued monitoring using pulse oximetry. Another study of patients treated with hyperbaric oxygen showed worse neurological outcomes.[87]

In the case of acute myocardial infarction (AMI), controversy exists regarding oxygen therapy. When treating patients with myocardial ischemia who are hypoxemic, oxygen is absolutely indicated, as it can be life-saving. However, when a patient with AMI is not hypoxemic, whether supplemental oxygen is beneficial is unclear. A double-blind randomized trial conducted in the late 1970s compared oxygen therapy (6 L/min) with no oxygen therapy in 157 patients with uncomplicated AMI.[88] In patients who received oxygen, higher rates of sinus tachycardia and a greater rise in myocardial enzymes were noted, along with no difference in mortality (actually, a trend toward improved mortality was seen in the no-oxygen arm). Several reasons for the potential deleterious effects of hyperoxia in an AMI have been proposed. In healthy humans, hyperoxia has been shown to induce coronary vasoconstriction. Furthermore, in critically ill patients, high-flow oxygen therapy may lead to maldistribution of microcirculatory blood flow, increased functional O_2 shunting, a reduction in total body oxygen consumption[89] and more reactive oxygen species damage in areas undergoing successful reperfusion. Although data supporting the use of supplemental oxygen in uncomplicated AMI remains absent, the practice remains nearly universal.

Finally, clinical trials and meta-analyses have examined the appropriate Sp_{O_2} target for acute care and critically ill inpatients. A single-center, open-label randomized trial was conducted over 2 years in 434 ICU patients, comparing conservative oxygen therapy (goal Sp_{O_2} 94%–98%) versus conventional oxygen therapy (accepting Sp_{O_2} to 97% to 100%). Patients randomized to conservative oxygen therapy had improved ICU mortality and a lower rate of shock, liver failure and bacteremia.[90] A subsequent meta-analysis examined results from 25 clinical trials which enrolled a total of 16,037 inpatients, with varying diagnoses including stroke, trauma, sepsis, myocardial infarction and emergency surgery. Results showed an increased hospital mortality in patients receiving a liberal oxygen strategy (relative risk, 1.21; 95% CI, 1.03–1.43).[91] However, two trials published in 2020 failed to show an effect of a conservative oxygenation strategy on ventilator-free days in mechanically ventilated patients with lung disease[92] or 28-day survival in patients with ARDS.[93] Current British Thoracic Society Guidelines advocate for a target Sp_{O_2} range of 94% to 98% in most adult inpatients, and 88% to 92% in patients at risk of hypercapnic respiratory failure.[94]

CONCLUSION

Since its discovery, oxygen has been successfully utilized in medicine, revolutionizing the field in the early half of the 20th century. Supplemental oxygen remains among the most common therapies provided in the inpatient setting. Oxygen therapy may improve oxygen delivery and reverse tissue ischemia. The role of supplemental oxygen in management of outpatients with chronic, severe, pulmonary, and cardiac diseases is broad. In the outpatient setting, supplemental oxygen may considerably improve quality of life in those patients willing to adapt to its use. Despite the widespread availability of supplemental oxygen and its relative ease of use, oxygen must be considered a drug with a therapeutic window, above which the potential for significant toxicity exists.

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CHAPTER 144

Pulmonary Pharmacotherapy

Karen J. Tietze

Scott Manaker

A wide spectrum of therapeutic agents is currently employed in the treatment of respiratory disorders, including obstructive lung diseases. This chapter reviews the rationale for, and clinical use of, these agents in current clinical practice.

DRUG DELIVERY

Inhaled drug administration is preferred for many medical conditions. Advantages of inhaled drug administration include rapid onset of action and the ability to deliver small drug doses directly to the lungs, minimizing systemic drug exposure. Compressed air nebulizers have been in use for more than 150 years; the first metered-dose inhaler (MDI) became available in the 1950s, followed by the first dry powder inhaler (DPI) in the 1960s.[1] Many new and innovative devices have been marketed as the result of the phase-out of chlorofluorocarbon-containing MDIs.[2]

Device selection depends on drug–device availability, patient characteristics (e.g., age, cognitive function, manual dexterity), and patient preference (Tables 144-1 and 144-2).[3,4] MDIs and nebulizers share universal designs; other drug delivery devices are unique, individually patented devices.

MDIs are small portable devices that protect the medication from contamination; they are difficult to use correctly. Common drug administration errors include improper timing of actuation and inspiration and failure to inspire slowly and deeply. MDI accessory devices (e.g., spacers, valved holding chambers) decrease oropharyngeal drug deposition and reduce the need for precise "press and breathe" timing, but they are bulky, add to the cost of therapy, and must be regularly cleaned to reduce bacterial contamination and electrostatic charges within the chamber. The Respimat device is a unique, multidose liquid inhaler that uses spring-loaded energy to generate a fine aerosol mist.

DPIs are available as single-dose devices, multidose premetered devices, and multidose reservoir devices. DPIs are breath actuated, requiring rapid and forcible inhalation to aerosolize and deliver the dose; most require inspiratory flow rates of 30 to 60 L/min. Young children, the elderly, and patients with reduced lung function (e.g., during an acute exacerbation) may be unable to generate adequate inspiratory flow rates.

Nebulizers aerosolize a solution or suspension by one of the three mechanisms: compressed air or oxygen (jet nebulizers), high-frequency ultrasonic energy (ultrasonic nebulizers), and vibrating mesh. Suspensions can only be aerosolized with jet nebulizers. Nebulizers are more expensive, require more dose preparation, and take more time to deliver a dose than other drug delivery devices. However, they require less patient cooperation and may be used by patients of all ages and abilities.

TABLE 144-1 Inhaled Drug–Device Availability

Drug Class	pMDI	DPI	SMI	Nebulizer
SABA	X	X		X
SAMA	X			X
SABA + SAMA			X	X
LABA		X	X	X
LAMA		X	X	X
LABA + LAMA	X	X	X	
ICS	X	X		X
ICS + LABA	X	X		
ICS + LABA + LAMA	X	X		
MCS				X

pMDI, metered-dose inhaler; DPI, dry powder inhaler; SMI, soft-mist inhaler; SABA, short-acting β-agonist; SAMA, short-acting muscarinic antagonist; LABA, long-acting β-agonist; LAMA, long-acting muscarinic antagonist; ICS, inhaled corticosteroid; MCS, mast cell stabilizer.

BRONCHODILATORS

Bronchodilation produced by β-adrenergic agonists, muscarinic antagonists, and methylxanthines is a major component of the pharmacologic management of obstructive airway diseases. Other drugs (e.g., magnesium) have been used clinically for bronchodilation.

β-Adrenergic Agonists

The β-adrenergic agonists mimic the actions of norepinephrine at neuroeffector and synaptic junctions. Norepinephrine is the major neurotransmitter in the sympathetic nervous system; therefore, this class of drugs is referred to as *adrenergic agonists* or *sympathomimetics*. The two major types of adrenergic receptors are the α and β receptors; at least two α and three β receptor subtypes have been identified.

β-Adrenoceptor stimulation relaxes smooth muscles via cyclic-3′5′-adenosine monophosphate (cAMP)-dependent and cAMP-independent mechanisms.[5] Adrenergic receptor stimulation catalyzes the conversion of adenosine triphosphate (ATP) to cAMP by activating adenyl cyclase, a cofactor in the production of cAMP. The increase in cAMP triggers the intracellular events that mediate

TABLE 144-2 Age–Device Guidelines

Device	Age
pMDI	≥5 years <5 years, spacer or VHC with face mask
DPI	≥4 years
Spacer or VHC	≥4 years <4 years, VHC with face mask
Nebulizer	Infants: SVN with face mask or hood ≤3 years: SVN with face mask ≥3 years: SVN with mouthpiece ≥5 years: Breath-actuated nebulizer All ages unable to use pMDI with VHC and face mask

pMDI, metered-dose inhaler; DPI, dry powder inhaler; VHC, valved holding chamber; SVN, small-volume nebulizer.

Data from National Asthma Education and Prevention Program. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Report No. 07–4051. www.ncbi.nlm.nih.gov/books/NBK7232/pdf/Bookshelf_NBK7232.pdf.

TABLE 144-3 Adrenergic Agonists

	Receptor Activity			Dosage Forms						
Agent	α	β_1	β_2	Duration[a]	pMDI	DPI	Neb	SC	SMI	Oral
Albuterol		Slight	+	Short	√	√	√			√
Arformoterol		Slight	+	Long			√			
Epinephrine	+	+	+	Short				√		
Formoterol		Slight	+	Long			√			
Indacaterol		Slight	+	Very long		√				
Levalbuterol		Slight	+	Short	√		√			
Metaproterenol		Slight	+	Short						√
Olodaterol		Slight	+	Very long					√	
Pirbuterol[b]		Slight	+	Short	√					
Racepinephrine[c]	+	+	+	Short			√			
Salmeterol		Slight	+	Long		√				
Terbutaline		Slight	+	Short				√		√
Vilanterol		Slight	+	Very long		√				

pMDI, metered-dose inhaler; DPI, dry powder inhaler; Neb, nebulizer solution; SC, subcutaneous.

[a] Duration: short, 1–6 h; long, 8–12 h; very long, 24 h.

[b] Breath-activated autohaler; contains chlorofluorocarbons; last date for sale in the United States was December 31, 2012.

[c] Nonprescription product.

pulmonary and extrapulmonary responses. β-Adrenoceptor stimulation also activates large-conductance, calcium-activated potassium channels in plasma membranes independent of cAMP.

The β-adrenergic agonists (Table 144-3) are indicated in the treatment of bronchospasm associated with acute and chronic asthma, bronchitis, emphysema, exercise, and other obstructive pulmonary diseases. Selection of a specific agent and route of administration depends on underlying patient risk factors and the receptor specificity of the drug.

Pharmacology

Adrenergic receptors are G-protein cell surface receptors. Adrenergic agonist binding to the β_2-adrenergic receptor activates Gs subtype proteins.[6] Gs subtype proteins stimulate adenylyl cyclase and activate cAMP-dependent protein kinase (PKA). PKA phosphorylates proteins involved in intracellular calcium regulation and sensitivity. Adrenergic receptor stimulation produces a wide range of functional responses, depending on the effector organ and the specific receptor.[7] Although bronchial smooth-muscle relaxation results from β_2-adrenergic receptor stimulation, none of the currently marketed agonists is completely specific for β_2-adrenergic receptors. The α-adrenergic receptor is generally associated with constrictor/contractor responses, including constriction of arteries and veins and contraction of the uterus, radial and sphincter muscles of the iris, urinary bladder, and stomach sphincters. β_1-Adrenergic receptor stimulation increases heart rate, atrial and ventricular contractility, and cardiac conduction velocity. Effects from β_2-adrenergic receptor stimulation include relaxation of bronchial and uterine smooth muscle, dilatation of arteries and veins, and several metabolic effects, including glycogenolysis, gluconeogenesis, and induction of hepatic pancreatic β-cell secretion.

Structure–Activity Relationships

The parent compound for the adrenergic agonists, phenylethylamine, consists of a benzene ring and an ethylamine side chain. Substituents can be added to the α or β carbons of the ethylamine side chain, the terminal amine group, or one or more of the carbons in the aromatic ring.[8] The addition of hydroxyls at positions 3 and 5 of the aromatic ring (e.g., metaproterenol and terbutaline) promotes oral bioavailability. Large substituents added to the amino group promotes β_2-adrenergic receptor selectivity and favors a long duration of action (e.g., arformoterol, formoterol, indacaterol, olodaterol, salmeterol, vilanterol).

At least two theories have been proposed to explain the long duration of action of the long-acting and ultra-long-acting β_2-adrenergic agonists (LABAs).[9,10] The *exosite theory* states that a portion of the large side chain on the terminal amine binds to a site separate from, but close to, the β_2-adrenergic receptor, keeping the active portion of the structure available for binding and rebinding to the β_2-adrenergic receptor. The *diffusion mucokinetic model* states that the plasma membrane serves as a drug reservoir. However, neither theory fully explains the long duration of action of the long- and ultra-long-acting β_2-adrenergic agonists, suggesting additional mechanisms.

Enantiomers

Albuterol and formoterol are 1:1 mixtures of (R)- and (S)-enantiomers. The therapeutic effect of albuterol comes from the (R)-enantiomer; the (R)-enantiomer is marketed separately as levalbuterol. Early in vitro studies suggested that (S)-albuterol might antagonize the effects of (R)-albuterol, but levalbuterol has not been demonstrated to be clinically superior to racemic albuterol.[11] The (R)-formoterol enantiomer, marketed as arformoterol, is 1000-fold more potent in β_2-receptor binding affinity than the (S)-enantiomer.[12] The racemic mixture is marketed as formoterol. Formoterol and arformoterol are equally effective bronchodilators with similar side effect profiles.[13]

Drug Delivery

The β-adrenergic agonists may be administered systemically or by inhalation; however, not all drugs are marketed in every dosage form (Table 144-1). Systemic dosage forms include oral (i.e., tablets, syrups), subcutaneous, and intravenous preparations. Systemic administration decreases the β_2-adrenergic receptor selectivity of the drug due to exposure to various metabolic enzymes, including catechol-o-methyl transferase, monoamine oxidase, and sulfatase. These enzymes change the chemical structure of the drug, decreasing the β_2-adrenergic receptor selectivity.

Inhaled β-adrenergic agonists are available in several dosage forms, including wet aerosols, aerosols from MDIs, and dry powder forms. Historically, nebulized drug delivery was standard practice for children and for emergency treatment of asthma exacerbations, hospitalized patients, and severely obstructed patients. Comparative data are limited, but outcomes are similar for drug delivery with MDI plus spacer drug delivery and nebulization.[14,15] Nebulized drug delivery is labor intensive; significant cost savings can be realized, without sacrificing efficacy, by using MDIs coupled with spacer devices.

Clinical Use

The β_2-adrenergic agonists remain first-line drugs in the treatment of both asthma and chronic obstructive pulmonary disease (COPD).[16,17] In asthma, the short-acting inhaled β_2-adrenergic agonists are preferred for treating acute symptoms and for preventing exercise-induced bronchospasm. The subcutaneous route of administration is generally reserved for patients unresponsive to frequent, high-dose, inhaled β_2-adrenergic agonists; uncooperative patients; or patients too severely dyspneic to inhale the dose. Subcutaneous or parenteral administration should not be used in patients with angina or a recent history of myocardial infarction. Oral adrenergic agonists may be appropriate for children too young to cooperate with inhaled drug administration; sustained-release, oral adrenergic agonists decrease nocturnal symptoms, but they are less effective than LABAs.

In COPD, β_2-adrenergic agonists provide modest symptomatic relief and improvement in pulmonary function. LABAs are standard bronchodilator therapy for patients with moderate and severe COPD. The value of subcutaneous drugs and high-dose, short-acting bronchodilators in the management of COPD remains indeterminate.

The intensity and duration of response to β_2-adrenergic agonists is dose and frequency dependent. For patients with asthma, higher doses result in incrementally greater bronchodilation. The dose–response relationships are less well defined for COPD.

The dose–response curve in asthma led to the development of intensive inhaled β_2-adrenergic agonist drug regimens for the treatment of severe, acute exacerbations. Typically, the nebulized drug is administered every 20 min for three to six doses; some patients respond better to continuous nebulized drug delivery. These regimens are generally well tolerated, although cardiac stimulation is common.

The LABAs are add-on agents for patients with moderate or severe asthma when usual doses of inhaled corticosteroids are inadequate and for patients with moderate or severe COPD. The LABAs are also alternate add-on agents for patients with symptoms of nocturnal asthma. The LABAs play no role in the treatment of an acute asthma or COPD exacerbation; all patients should have a short-acting inhaler and should be instructed on how and when to use each type of β_2-adrenergic agonist. International guidelines recommend single maintenance and reliever therapy (SMART) with a combination of a quick onset long duration LABA and inhaled corticosteroid for management of patients with moderate to severe asthma.[18] The combination of formoterol, a long-acting β-adrenergic agonist with a rapid onset of action and long duration of action and inhaled corticosteroid has been documented to lower the risk of asthma exacerbations.[19,20]

Tolerance, that is, receptor subsensitivity or tachyphylaxis, is a decreased response to receptor stimulation. Regular use of either short- or long-acting β_2-adrenergic agonists leads to tolerance of both the nonbronchodilator and bronchodilator effects of the β_2-adrenergic agonist.[21] Tolerance to the nonbronchodilator effects of the β_2-adrenergic agonists, including tremor, tachycardia, QT_c prolongation, hypoglycemia, hypokalemia, and vasodilation, has been recognized for many years. Tolerance to the bronchodilator effects of the β_2-adrenergic agonists develop rapidly with quick recovery following discontinuation of the drug.[22] Receptor downregulation mediated by β-arrestin and G protein–coupled regulatory kinase likely mediates tolerance to the β_2-adrenergic agonists.[23]

Safety

The β_2-selective adrenergic agonists produce less cardiovascular toxicity than do the nonselective agents, but because β_2-adrenergic receptors are expressed in cardiac tissues and some innate immune cells (e.g., eosinophils, mast cells), β_2-selectivity does not protect from all adverse events.[6]

Biochemical abnormalities associated with the β_2-adrenergic agonists include hyperglycemia, hyperinsulinemia, lipolysis, hypokalemia, hypomagnesemia, and lactic acidosis.[7] These side effects are most pronounced with parenteral and oral drug administration; they are minimal with usual doses of inhaled agents.

β_2-Adrenergic agonists cause dose- and route-dependent hyperglycemia by stimulating glycogenolysis and gluconeogenesis and suppressing glucose clearance.[24] Hyperglycemia may be clinically most important in asthmatic patients with diabetes mellitus or during pregnancy. β_2-Adrenergic agonists increase plasma insulin by directly stimulating pancreatic islet cells; indirect increases occur secondary to the hyperglycemic response. β_2-Adrenergic agonists induce the release of free fatty acids from adipose tissue. Although hyperinsulinemia and high concentrations of free fatty acids have been linked with cardiovascular morbidity and mortality, tolerance minimizes these effects. β_2-Adrenergic receptor stimulation also induces muscle glycogenolysis, increasing lactate production.

The β_2-Adrenergic agonists induce hypokalemia by increasing cellular uptake of potassium via direct stimulation of cell membrane Na^+/P^+-ATPase.[25] β_2-Adrenergic receptor stimulation induces the cellular uptake of magnesium; hypomagnesemia may induce arrhythmias or worsen symptoms of coronary artery disease. Other adverse β_2-adrenergic agonist effects include (1) an increased baseline tremor by creating an imbalance in fast- and slow-twitch muscle groups; (2) tachycardia by direct chronotropy and through reflex peripheral vasodilatation and decreased venous return; and (3) central nervous symptoms, such as appetite suppression, headache, nausea, and sleep disturbances.[7] The nervousness reported by many patients is probably a response to the peripheral tremors, rather than a result of direct stimulation of the central nervous system.

β-Adrenergic agonist use has increased coincident with the increase in asthma morbidity and mortality in the United States and other countries. The first linkage between β-adrenergic agonists and asthma mortality was identified during the 1960s when the newly marketed, nonselective, short-acting β-adrenergic agonist isoproterenol was associated with an increase in asthma morbidity and mortality in the United Kingdom. In 2006, two studies associated LABA use with an increased risk of death in patients with asthma.[26,27] In 2005, the U.S. Food and Drug Administration (FDA) began requiring that labeling for all LABAs include a black box warning regarding the increased risk of asthma-related death. In 2010, the FDA released new safe-use requirements for LABAs.[28] The FDA requires (1) that LABAs be used in combination with an asthma controller medication, and only in patients whose asthma is poorly controlled despite controller medications; (2) that LABAs be used for the shortest duration of time needed to achieve control and then be discontinued, if possible; and (3) that combination inhaled corticosteroid–LABA products be used for children and adolescents.[28] In 2011 the FDA required manufacturers of LABAs to conduct postmarketing safety trials for LABAs in the treatment of asthma.[29] Combined analysis of these safety trials found no significant increase in risk with combined LABA and corticosteroid therapy.[30] In 2017 the FDA removed the black box warning for combination LABA-corticosteroid medications; the black box warning for single-entity LABA medications remains.[3] The mechanism of increased risk of LABAs as single-entity treatment of asthma is unclear, although it may be related to β_2-adrenergic receptor downregulation and desensitization.

Anticholinergics

Atropine, scopolamine, and other naturally occurring antimuscarinic alkaloids from plant extracts have been used for thousands of years to relieve respiratory symptoms in humans with airway diseases. Historically, clinical use of atropine and atropine-like agents has been limited by side effects, including dry mouth and skin, tachycardia, meiosis, and difficulty urinating and mentating. Six synthetic atropine derivatives (ipratropium, tiotropium, aclidinium, umeclidinium, glycopyrrolate, and revefenacin), which have more favorable side effect profiles, are available for management of COPD.

Pharmacology

Anticholinergics, also known as parasympatholytics or antimuscarinics, reversibly compete with acetylcholine at muscarinic receptors. Acetylcholine is the predominant airway parasympathetic neurotransmitter. Three of the five known muscarinic receptor subtypes (M_1, M_2, and M_3) are located on airway smooth muscle, nerves, glands, and innate lymphoid cells (eosinophils, macrophages, lymphocytes, neutrophils).[32] Acetylcholine receptor binding activates adenylyl cyclase and phospholipase C and opens potassium channels, effecting bronchoconstriction, goblet cell metaplasia and increased mucus secretion, airway hyperreactivity, inflammation, airway smooth muscle thickening, and extracellular matrix deposition.[33] M_1 and M_3 muscarinic receptors are excitatory; airway M_2 receptors are inhibitory though with minimal effect on airway smooth muscle contraction. M_1 muscarinic receptors, located in airway epithelial cells and ganglia, regulate epithelial cell electrolyte and water secretion. M_3 muscarinic receptors, the primary receptor subtype in airway smooth muscle and submucosal glands, regulate airway smooth muscle and mucus secretion.[33]

Five of the six currently FDA-approved anticholinergic medications for management of obstructive lung diseases (ipratropium bromide, tiotropium bromide, aclidinium bromide, umeclidinium bromide, and glycopyrrolate) are quaternary ammonium compounds. Revefenacin, the newest anticholinergic, is a biphenyl carbamate tertiary amine. Shared properties include minimal absorption following oral inhalation, inability to penetrate the blood–brain barrier, similar binding affinities for M_1, M_2, and M_3 muscarinic receptors, and longer M_3-drug complex dissociation half-lives than M_1-drug complex and M_2-drug complex dissociation half-lives.

Ipratropium bromide, the only marketed short-acting anticholinergic, has a shorter M_3-drug complex dissociation half-life than the long-acting anticholinergics.[34–36] Bronchodilation following inhalation of ipratropium bromide occurs within 15 min with peak effect in 1 to 2 h.[37] Inhalation of the long-acting anticholinergics typically produces bronchodilation within 1 h with prolonged duration of action.[37–41] Tiotropium bromide, umeclidinium bromide, and revefenacin are approved for once-daily administration. Aclidinium bromide and glycopyrrolate are approved for twice-daily administration. Differences among the long-action anticholinergics in terms of muscarinic subreceptor affinities and receptor–drug complex dissociations are measurable, although the clinical relevance is not well described.

Drug Delivery

Ipratropium bromide is available in the United States as a HFA MDI. Tiotropium bromide, aclidinium bromide, umeclidinium bromide, and glycopyrrolate are available in the United States as DPIs. Additional dosage formulations include soft-mist aerosol inhaler (tiotropium bromide) and solutions for nebulization (ipratropium bromide, revefenacin, and glycopyrrolate). Various combination products with short-acting and long-acting bronchodilators and corticosteroids are marketed in multiple dosage formulations.

Clinical Use

Ipratropium bromide, tiotropium bromide, aclidinium bromide, umeclidinium bromide, glycopyrrolate, and revefenacin are FDA-approved for the management of patients with COPD. The long-acting anticholinergics improve quality of life and reduce hospitalizations due to COPD exacerbations. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2022 Report recommends monotherapy with long-acting anticholinergics for the initial management of patients with fewer symptoms and greater exacerbation risks, and as monotherapy or combination therapy with long-acting β-adrenergic agonists for patients with more symptoms, regardless of the exacerbation risk.[17] The GOLD 2022 Report recommends long-acting anticholinergics for follow-up pharmacologic therapy as alternative or add-on therapy.[17]

Tiotropium bromide as the soft mist inhaler Spiriva was approved by the FDA in 2015 for maintenance therapy of asthma in adults and children 12 years of age and older; the approved age range was subsequently lowered to 6 years of age and older. No other drug delivery system or anticholinergic drug is FDA-approved for the management of asthma. A systematic review concluded that the addition of tiotropium bromide to a combination of long-acting β_2-adrenergic agonists and inhaled corticosteroids reduced the need for rescue oral corticosteroids.[42]

International guidelines recommend the addition of the short-acting anticholinergic ipratropium bromide to short-acting β-adrenergic agonists in the emergency management of adults with moderate to severe asthma exacerbations.[18] Compared with the β-adrenergic agonists, anticholinergics have a slower onset of action and less effect on lung function and should not be used in place of short-acting bronchodilators.[43] A systematic review concluded that patients with severe asthma exacerbations treated with a combination of β-adrenergic agonist and anticholinergic were less likely to be admitted to the hospital; the effect was less in patients with mild to moderate asthma exacerbations.[44] Any such use of an anticholinergic in the United States is off-label and not FDA-approved.

Safety

Consistent with their very low systemic bioavailability, the inhaled anticholinergics are remarkably free of side effects. Class effects with inhaled anticholinergics include mild dry mouth, constipation, and throat irritation. The inhaled anticholinergics do not change mucus viscosity or transport, pulmonary hemodynamics, ventilation–perfusion matching, oxyhemoglobin saturation, heart rate, or urinary flow; however, blurred vision and pupillary dilation may occur if any drug inadvertently contacts the eye. Anticholinergics should be used with caution in patients with narrow-angle glaucoma, prostatic hyperplasia, or bladder neck obstruction.

Dose modifications for renal or hepatic impairment are not required for ipratropium bromide, tiotropium bromide, and aclidinium bromide. Ipratropium bromide is partially metabolized to inactive ester hydrolysis products. Tiotropium bromide undergoes minimal hepatic metabolism via CYP2DC and CYP3A4. Plasma esterases rapidly hydrolyze aclidinium bromide to inactive metabolites. Glycopyrrolate, excreted in the urine and bile, should be used with caution in patients with renal impairment (Clcr <30 mL/min/1.73 m^2). Revefenacin, hepatically metabolized to an active carboxylic acid, should not be used in patients with any degree of hepatic impairment.

Cardiovascular risks with inhaled anticholinergics in patients with COPD have been identified, but absent quality long-term data, the issue remains unresolved.[45] A 2011 meta-analysis of 17 randomized controlled trials of tiotropium bromide delivered with the Respimat soft-mist inhaler identified a statistically significant increase in cardiovascular events, including stroke, myocardial infarction, and death with long-term (≥30 days) tiotropium bromide.[46] Tiotropium bromide delivered with the Respimat soft-mist inhaler appears to be safe in patients with asthma.[47] A trial directly comparing tiotropium dry powder and fine-mist inhaler safety in patients with COPD revealed no significant differences in either safety or efficacy.[48] No increased risk for major cardiovascular events in patients with COPD has been identified for aclidinium bromide, umeclidinium bromide, glycopyrrolate, or revefenacin.[49–52] However, until adequate long-term safety data are available, long-acting anticholinergics should be used with caution in patients with unstable ischemic heart disease, history of myocardial infarction, left ventricular failure, history of arrhythmias including long QT syndrome, narrow-angle glaucoma, prostatic hyperplasia, and bladder-neck obstruction.

Drugs with anticholinergic properties are used to manage a wide range of medical conditions including allergies, arrhythmias, depression, diarrhea, emesis, muscle spasms, Parkinson disease, and psychosis. Concomitant use of drugs with anticholinergic properties and anticholinergic bronchodilators may increase the risk of anticholinergic side effects.

■ Methylxanthines

Methylxanthines have been used to treat pulmonary disease for more than 100 years.[53] General use of methylxanthines became widespread in the 1930s; contemporary use is more limited due to the availability of more effective and safer medications. Theophylline and aminophylline, the ethylenediamine salt of theophylline, are used to treat asthma and COPD. Theophylline may also have a role in therapy of obstructive sleep apnea, apnea of prematurity, and airway obstruction secondary to pulmonary edema.

Pharmacology

Potentially beneficial therapeutic effects of theophylline include bronchial smooth-muscle relaxation, enhanced mucociliary transport, inhibition of mediator release, suppression of permeability edema, decreased pulmonary hypertension, increased right ventricular ejection fraction, improved diaphragmatic contractility, and central stimulation of ventilation.

Methylxanthines have direct bronchodilator and immunomodulatory properties; however, despite having been marketed and studied for decades, the precise molecular mechanism of action is not known. Multiple molecular mechanisms have been proposed, including competitive adenosine receptor inhibition (A_1, A_2, and A_3 receptors), nonselective phosphodiesterase (PDE) inhibition, GABA receptor modulation, activation of ryanodine-sensitive calcium channels, activation of histone deacetylases (HDACs), reduced expression of inflammatory genes, promotion of neutrophil and T-lymphocyte apoptosis, and inhibition of poly(ADP-ribose)polymerase-1 (PARP-1).[54,55] Nonselective PDE inhibition and adenosine receptor antagonism are the most established of the proposed molecular mechanisms of action at clinically relevant plasma drug concentrations.[54,55]

PDEs hydrolyze cAMP and cyclic guanine monophosphate (cGMP) to inactive 5′ monophosphates; inhibition of PDE increases intracellular concentrations and, therefore, the activity of these secondary messengers, resulting in airway smooth-muscle relaxation and bronchodilation. However, methylxanthine PDE inhibition is weak and concentration dependent, with minimum inhibition seen at clinically relevant serum concentrations.[54] Adenosine is a nucleoside signaling molecule. Adenosine receptor antagonism regulates airway smooth muscle, blocks adenosine-induced mast cell degranulation, and activates HDAC enzymatic activity, inhibiting transcription of proinflammatory cytokines. These anti-inflammatory and immunomodulatory effects are observed at clinically achievable serum drug concentrations.[54]

The anti-inflammatory effect of methylxanthines appears to be qualitatively different than that of corticosteroids. Corticosteroids recruit HDACs to sites of active inflammatory gene transcription. The HDACs then inhibit histones, inhibiting inflammatory gene transcription.[56] Methylxanthines, independent of phosphodiesterase and adenosine activity, induce HDAC epithelial cell and macrophage activity.[56] The combination of corticosteroids and methylxanthines may be synergistic.

Structure–Activity Relationships

Xanthine structure substituents determine methylxanthine pharmacology.[57] Theophylline and aminophylline are 1,3-dimethylxanthines. Other methylxanthines, including theobromine (3,7-dimethylxanthine) and caffeine (1,3,7-trimethylxanthine), differ in the positions of the methyl substituents on the xanthine molecule. Dyphylline is a synthetic 7-(2,3-dihydroxypropyl)-theophylline. N-1 substituents are important for adenosine antagonism, whereas N-3 substituents augment bronchodilator activity. Substituents at N-7 decrease bronchodilator potency; substituents at N-9 decrease the potency of the xanthine. C-8 substituents determine adenosine receptor subselectivity.

Drug Delivery

Three methylxanthines are available in the United States: theophylline, aminophylline, and dyphylline. Dosage forms for theophylline include extended-release tablets and capsules, oral solution, oral elixir, and intravenous solution. Aminophylline, the ethylenediamine salt of theophylline, is available as an intravenous solution. Dyphylline is available as immediate release tablets and oral solution.

Clinical Use

Methylxanthines are FDA approved for the treatment of reversible airway obstruction associated with chronic asthma or other chronic lung disease. Concerns regarding the relative efficacy and safety of the methylxanthines in comparison to other bronchodilators and long-term control medications have relegated methylxanthines to alternative therapy status for both asthma and COPD. Caffeine is the preferred methylxanthine for the treatment of apnea of prematurity.[58]

The GOLD guidelines identify oral theophylline as an alternative maintenance bronchodilator.[17] The current Global Initiative for Asthma (GINA) guidelines recommend low-dose theophylline as an add-on controller medication for adolescents and adults with step 3 and step 4 asthma inadequately controlled on inhaled glucocorticoids alone and as an add-on controller for adolescents and adults with step 5 asthma inadequately controlled on dual therapy.[18] The current National Asthma Education and Prevention Program (NAEPP) guidelines recommend theophylline as an alternate medication for patients with mild persistent asthma, or as an alternate adjunctive therapy in combination with inhaled corticosteroids.[16] Neither the GINA nor the NAEPP guidelines recommended theophylline for the treatment of acute asthma exacerbations.[16,18] The previously accepted therapeutic range for theophylline (10–20 mg/L) was based on early dose–bronchodilator response studies and is no longer considered state of the art.[55,59] The current NAEPP asthma guidelines recommend a lower target therapeutic range for theophylline (5–15 mg/L).[16] The rationale for lowering the target serum theophylline range includes improved understanding of the dose–bronchodilator response and recognition of the greater risk of adverse drug reactions at serum theophylline concentrations greater than 15 mg/L. Nonbronchodilator effects, including immunomodulatory effects and effects on diaphragmatic activity are associated with lower serum concentrations (<10 mg/L).[60,61]

Safety

Adverse effects of methylxanthines are generally attributed to PDE inhibition (nausea, vomiting, diarrhea, headache, and increased acid secretion and gastrointestinal reflux) and adenosine receptor antagonism (diuresis, cardiac arrhythmias and seizures).[55] Other adverse effects include irritability and insomnia. The caffeine-like adverse effects (nausea, vomiting, diarrhea, nervousness, insomnia, headache) are generally associated with serum theophylline concentrations greater than 15 mg/L.[62] The more life-threatening adverse effects (ventricular arrhythmias and seizures) are generally associated with serum theophylline concentrations greater than 40 mg/L, although these adverse effects may occur at much lower serum concentrations.[62]

Theophylline is metabolized primarily by cytochrome P450 (CYP1A2) enzymes, making it susceptible to numerous drug–disease and drug–drug interactions.[63] Hyperthyroidism and cystic fibrosis decrease serum theophylline concentrations by unknown mechanisms. Polycyclic aromatic hydrocarbons in tobacco smoke, and medications such as rifampin, phenytoin, antivirals, and barbiturates, induce cytochrome P450 enzymes, reducing serum theophylline concentrations. Macrolide and quinolone antibacterials, fluvoxamine, fluconazole, ketoconazole, and cimetidine inhibit cytochrome P450 enzymes, increasing serum theophylline concentrations.

Medical conditions that directly impair hepatic function (e.g., cirrhosis, viral hepatitis), cause passive hepatic congestion (e.g., congestive heart failure, cor pulmonale), or induce interferon (e.g., acute viral illness or pneumonia) result in increased serum theophylline concentrations.[62] CYP1A2 single polymorphisms may influence methylxanthine metabolism but are not well described. Methylxanthine metabolism is markedly reduced in neonates, increased in children and adolescents, and reduced in adults 65 years of age and older.[63]

Given the narrow therapeutic window, multitude of drug and disease interactions, and wide interpatient variability, it is important to routinely monitor serum theophylline concentrations. The mid-dosing interval serum concentration should be assessed 3 to 5 days after initiating theophylline or modifying the dose and any time theophylline toxicity is suspected.[16]

■ Other Bronchodilators

Ancillary drugs sometimes used as bronchodilators include magnesium sulfate and inhaled diuretics.

Magnesium Sulfate

The bronchodilatory mechanism of action of magnesium has not been definitively identified. Several actions have been proposed, including transient blockade of N-methyl-D-aspartate–gated calcium channels, decreasing smooth-muscle intracellular calcium, and inhibition of mast cell degranulation and acetylcholine release.[64]

Several systematic reviews of trials of inhaled and intravenous magnesium sulfate in the management of adults and children presenting to emergency departments with severe acute exacerbations of asthma have been published.[65–69] In general, patients with severe exacerbations demonstrate small improvements in pulmonary function following administration of inhaled or intravenous magnesium sulfate when added to standard therapy. However, the small numbers of patients studied, differences with exacerbation severity, patient age, dosage, primary outcomes, and concurrent therapy make the data difficult to interpret. The most recent, well-done clinical trial failed to demonstrate any salutary effect of inhaled magnesium on the need for admission or any secondary outcome measures in children with asthma.[70] Potential adverse effects include hypotension with rapid infusion, muscle weakness, respiratory depression, and cardiac conduction abnormalities. The current GINA guidelines recommend considering intravenous magnesium sulfate in the management of severe acute asthma exacerbations in adults not responding to initial treatment and nebulized isotonic magnesium sulfate in the first hour of treatment of acute severe asthma exacerbations in children 2 and older.[18]

Inhaled Diuretics

Inhaled diuretics (e.g., furosemide) may act upon the airways through a variety of mechanisms to achieve bronchodilation, reduce mucosal inflammation, or interrupt sensory nerve reflex responses to irritants.[71] Data regarding the clinical efficacy of inhaled diuretics in the treatment of acute and chronic asthma are limited. A meta-analysis of six randomized controlled trials (with only 78 total patients) found that adjunctive inhaled furosemide in doses of 20 to 40 mg in adults and 1 mg/kg or 10 mg/m^2 in children significantly improved airflow obstruction with no adverse effects.[72] Additional information from well-designed clinical trials is needed before use of inhaled diuretics can be recommended for the treatment of acute exacerbations or chronic management of asthma.

ANTI-INFLAMMATORY AGENTS

Corticosteroids are the mainstay of current anti-inflammatory regimens; other agents in clinical use include mast cell stabilizers, leukotriene receptor antagonists, and leukotriene formation inhibitors.

■ Corticosteroids

Corticosteroids are cortisol-like drugs that influence metabolic pathways and have an anti-inflammatory effect. By reducing airway inflammation, corticosteroids have long been known to be useful in the management of asthma; their role in the management of COPD has been increasingly recognized.

Pharmacology

Cortisol is produced by the adrenal cortex and regulated via the hypothalamic–pituitary axis in response to physical and emotional distress. The usual daily secretion of cortisol is approximately 7 mg/m^2/d in men and 5 to 6 mg/m^2/d in women; up to 500 mg/d can be secreted during periods of severe stress.[73,74] Corticosteroids stimulate and inhibit DNA transcription in cells with glucocorticoid receptors, which are widespread throughout the body.

Glucocorticoids diffuse across cellular membranes to bind inactive glucocorticoid cytoplasmic receptors; these activated glucocorticoid-receptor complexes translocate to the nucleus and bind to specific glucocorticoid response elements of the gene, influencing gene transcription.[75] Increased gene transcription increases expression of β_2-adrenergic receptors, increases the production of anti-inflammatory mediators, and decreases the production of inflammatory mediators. The clinical effects of glucocorticosteroids are delayed for several hours following administration, reflecting the time needed to influence gene transcription. In the airways, glucocorticosteroids increase the number and responsiveness of β_2-adrenergic receptors, decrease mucus production, decrease bronchial hyperresponsiveness, decrease the number of mucosal mast cells, enhance eosinophil apoptosis, and decrease airway edema. Glucocorticosteroids are inactivated by hepatic metabolism, with a clearance rate approximately the same as liver blood flow; beclomethasone dipropionate, ciclesonide, and their metabolites are also inactivated by blood esterases.

The inhaled glucocorticoids (beclomethasone dipropionate, budesonide, ciclesonide, fluticasone furoate, fluticasone propionate, mometasone furoate) have different physicochemical properties (potency, receptor-binding affinity, protein binding, lipophilicity, oral bioavailability, pulmonary bioavailability, systemic clearance, volume of distribution, and half-life).[76] Physicochemical properties that enhance inhaled glucocorticosteroid efficacy include high receptor-binding affinity, high pulmonary bioavailability, and long pulmonary retention time. Physicochemical properties that enhance safety include low oropharyngeal deposition, high protein binding, rapid systemic clearance, and conversion of inactive prodrug to active drug in the lungs. Since inhaled glucocorticosteroids are marketed and prescribed in relatively equipotent doses, potency is not an important differentiating characteristic as other physicochemical characteristics.

Data regarding the relative clinical benefits of inhaled corticosteroids with different physicochemical characteristics are limited. However, physicochemical characteristics may influence drug safety. For example, oropharyngeal side effects (dysphonia, oral candidiasis) may be minimized by using drug delivery systems that generate a greater proportion of small particles (<5 μm) and with administration of prodrugs that are converted in the lungs to the active drug.[77] DPI particle size depends on the specific device and the patient-generated inhalation flow rate; hydrofluoroalkane MDIs tend to generate a greater proportion of smaller particles. Beclomethasone 17,21-dipropionate is hydrolyzed in the lungs to the more active drug, beclomethasone 17-monopropionate. Ciclesonide is hydrolyzed in the lungs from the inactive parent drug to the active drug, desisobutyryl-ciclesonide.

The risk of systemic adverse effects may be minimized by using inhaled corticosteroids with low systemic bioavailability, high protein binding, rapid systemic clearance, and increased pulmonary residence time. Ciclesonide, fluticasone, and mometasone undergo rapid first-pass hepatic metabolism, resulting in very low ($<1\%$) oral bioavailability. Ciclesonide and mometasone are highly protein bound (99%). Drugs with a higher lipophilicity and drugs that undergo lipid conjugation have a longer pulmonary residence time. Mometasone furoate, beclomethasone dipropionate, fluticasone furoate, and fluticasone propionate have higher lipophilicity than fluticasone propionate, ciclesonide, and budesonide.[76]

Clinical Use

Corticosteroids are the cornerstone of therapy in the treatment of asthma. The role of glucocorticoid therapy in COPD is more limited.

Asthma The role of airway inflammation in asthma is well established, and high-dose systemic (parenteral or oral) corticosteroids are standard therapy for patients experiencing severe acute exacerbations of asthma.[16,18,78] Parenteral administration of corticosteroids is often used preferentially due to the inability of some patients to swallow medications while in respiratory distress or because of lack of oral access after intubation. The time to initial response, as evidenced by augmentation of FEV_1 with bronchodilator administration, begins as early as 1 hour after corticosteroid administration; maximal response is achieved in 8 to 12 h. Parenteral methylprednisolone is the corticosteroid of choice, due to its lower mineralocorticoid and greater glucocorticoid effects than hydrocortisone.

The combination of an inhaled corticosteroid and a long-acting bronchodilator is better than either agent alone at improving lung function and preventing asthma exacerbations; in patients with moderate to severe asthma, such a combination of low-dose inhaled corticosteroid with a LABA appears equally effective as high-dose inhaled corticosteroid alone.[16,18] Given the concerns regarding the safety of LABAs (see above) as monotherapy in asthma, the FDA recommends that an inhaled corticosteroid always accompany a LABA in asthma therapy.[28]

Beclomethasone dipropionate, budesonide, ciclesonide, and fluticasone propionate are FDA approved for twice-daily administration. Mometasone furoate is FDA approved for once- or twice-daily administration. Fluticasone furoate is FDA approved for once-daily administration. Poor adherence with inhaled corticosteroid regimens is an ongoing issue. Although data are limited, patients with stable, mild persistent asthma might benefit from once-daily inhaled corticosteroids.[16] Twice-daily dosage regimens are more effective for patients with moderate persistent or severe persistent asthma.[16]

Chronic Obstructive Pulmonary Disease The mechanism underlying the beneficial effects of corticosteroids in COPD is not fully known, but changes in inflammatory gene transcription and modulation of β_2-adrenergic receptor function appear to play a role. The blood eosinophil count is a potentially useful prognostic and theragnostic biomarker in COPD.[79] Thresholds, rather than specific target blood eosinophil counts, are associated with beneficial effect.[80] The GOLD guidelines recommend initial treatment of patients with more symptoms and exacerbations (GOLD grade D) with a combination of inhaled corticosteroid and long-acting β_2-adrenergic agonist if the blood eosinophils are at least 300 cells/μL.[17] For follow-up therapy of patients experiencing exacerbations, the GOLD guidelines recommend a combination of long-acting β_2-adrenergic agonist plus inhaled corticosteroid if the blood eosinophil count is at least 300 cells/μL; or with at least 100 cells/μL if at least two moderate exacerbations or one severe exacerbation requiring hospitalization.[17]

Treatment of patients hospitalized for management of acute COPD exacerbations treated with short-course (5–7 days) systemic corticosteroids is associated with fewer treatment failures, shorter duration of hospitalization, improved lung function (FEV_1), and improved breathlessness.[81] Five-day regimens are as effective as longer regimens (10–14 days) with less risk for significant adverse effects (e.g., hyperglycemia).[82] For hospitalized patients, the GOLD guidelines recommend consideration of short-course oral corticosteroids (prednisone 40 mg daily for 5 days).[17] Oral corticosteroids in the management of acute COPD exacerbations in nonhospitalized patients appear to be effective based although are not currently recommended in some guidelines.[17,83]

Safety

Short-term use (<14 days) of systemic corticosteroids is associated with mild glucose intolerance, fluid retention that may progress to edema and hypertension, proximal muscle weakness (especially with large parenteral doses), and mood alteration. Long-term systemic corticosteroids prolong the short-term effects; in addition, peptic ulcer disease, cataracts, increased risk of infection, and impaired wound healing occur. Truncal obesity, hirsutism, acne, moon-shaped facies, striae, and ecchymoses contribute to a cushingoid appearance. Disruption of bone metabolism predisposes patients to osteoporosis and resultant vertebral and long-bone fractures; inhibition of long-bone growth is the major complication in children receiving systemic corticosteroids. Suppression of the hypothalamic–pituitary–adrenal axis diminishes body cortisol stores, reducing the response to stresses such as trauma, surgery, or infection.

Inhaled corticosteroids are less systemically bioavailable due to poor absorption from the tracheobronchial tree. The most common adverse effect is local irritation of the oropharynx, cough, and bronchospasm. Dysphonia may arise from vocal cord myopathy induced by the corticosteroid, and oral candidiasis (thrush) may occur secondary to suppression of normal oral flora. The risk of dysphonia and thrush are reduced by rinsing the mouth, gargling, and spitting out the rinse water after each use of a corticosteroid inhaler; using a spacer device to decrease deposition of drug particles in the mouth; and keeping the inhaler mouthpiece clean. Inhaled corticosteroids increase the risk of pneumonia in patients with COPD although the absolute risk is low and may depend on the lipophilicity and lung retention properties of the inhaled corticosteroid.[80] The benefits of reduced COPD exacerbations from combined single-inhaler triple therapy (with a LABA, LAMA, and ICS) appear to outweigh this small absolute risk of community-acquired pneumonia.[84,85]

Depending on the bioavailability, dose, and duration of use, inhaled corticosteroids may be associated with the systemic adverse effects typically associated with oral corticosteroids, including adrenal suppression, particularly in children. Inhaled corticosteroids slow bone growth velocity in prepubertal children and reduce ultimate adult height by about 1 to 1.5 cm.[86] High-dose inhaled corticosteroids decrease bone mineral density and increase bone fracture risk, especially in older and postmenopausal women.[86]

Steroid Resistance

Patients with asthma unresponsive to usually sufficient doses of corticosteroids are described as *steroid resistant.* Varying definitions of steroid resistance exist, such as a less than 15% increase in FEV_1 after either oral prednisolone administered for 7 days at a dose of 20 mg daily, or 14 days at a dose of 15 mg daily; or a 2-week trial of 40 mg/d prednisone in bronchodilator-responsive asthmatics.[87,88] Steroid resistance has been associated with bacterial and viral respiratory infections, exacerbations associated with infections, and a high-fat diet and obesity.[89] Steroid resistance must be distinguished from steroid dependency, which is usually defined as the need for systemic corticosteroids to maintain control of asthma.

Steroid resistance may involve reduced metabolism of oral corticosteroids to the active compound or accelerated drug clearance. An impaired cellular response to corticosteroids has been observed in steroid-resistant asthmatics, and altered receptor binding or the presence of antilipocortin antibodies may contribute to the phenomenon. Aberrant microRNA 21 (miR-21) and interleukin 1β responses may contribute to steroid-resistant airway inflammation.[89]

■ Corticosteroid-sparing Agents

Chronic systemic corticosteroid therapy required for the treatment of severe airflow obstruction often results in numerous side effects. Therefore, many anti-inflammatory agents have been evaluated in an effort to identify alternatives to systemic corticosteroid therapy.[90,91] However, wide variability exists among studies in their assurances of proper inhaler technique, dose and frequency of baseline inhaler regimens, and minimization of exposure to known antigens. In addition, most studies have not systematically evaluated and excluded (or otherwise controlled for) the concomitant presence of disorders known to mimic or exacerbate asthma, including vocal cord dysfunction, gastroesophageal reflux, and rhinosinusitis. These methodologic considerations further restrict the limited conclusions to be drawn from these studies.

Methotrexate

From initial observations in patients with rheumatoid arthritis and coexistent asthma, methotrexate therapy appeared to ameliorate both asthmatic and arthritic symptoms. A small number of older studies offer no clear documentation of the clinical efficacy of methotrexate administration in severe, steroid-dependent asthma. Several more recent meta-analyses suggest a small benefit may exist, but use is associated with a significant risk of toxicity. Due to significant side effects, potentially fatal complications, and long-term toxicity concerns, prudence argues for limiting methotrexate administration in severe, steroid-dependent asthmatics to empiric trials in individual patients or investigations in large-scale, controlled clinical trials.

Cyclosporine

Used widely in organ transplantation, cyclosporine inhibits lymphokine synthesis, thereby blocking the activation of T cells. The absence of significant drug interactions with β-adrenergic agonists, corticosteroids, or theophylline makes cyclosporine particularly attractive as an anti-inflammatory agent for use in asthma. However, only one of the three small, double-blind, placebo-controlled studies suggested that cyclosporine increased peak expiratory flow and FEV_1, reduced exacerbations of airway obstruction, or reduced oral prednisolone dosage by more than 60%. Hypertrichosis, hypertension, reversible nephrotoxicity, and a large number of nonspecific side effects limit widespread use of cyclosporine in the management of asthma.

Other Agents

The search continues for anti-inflammatory agents with potential efficacy in asthma. Historically, a broad spectrum of agents has been touted, including gold salts, pooled immunoglobulins, azathioprine, colchicine, dapsone, hydroxychloroquine, ketotifen, nonsteroidal anti-inflammatory agents, inhaled heparin, and anti–tumor necrosis factor agents (both etanercept and infliximab). The original studies purporting the efficacy of these various agents are mainly anecdotal reports, small case series, or early phase studies demonstrating little clinical efficacy. Use of these drugs in obstructive airway disease should be restricted to well-designed, controlled clinical trials.

■ Antibiotic Macrolides

Recently, the role of macrolide antibiotics as anti-inflammatory agents has been recognized and their potential utility in management of a number of pulmonary disorders examined.

Pharmacology

Erythromycin comprises a 14-membered lactone ring, with two attached sugars (cladinose and desosamine). As the first macrolide antibiotic discovered, erythromycin has served as the base compound for this class of drugs.[92,93] Azithromycin (9-deoxo-9 a-aza-9 a-methyl-9 a-homoerythromycin) is formed by substituting a methyl-substituted nitrogen for the position 9a carbonyl group of the aglycone ring, producing an azalide. Substituting a methoxy group for the C-6 hydroxyl group of erythromycin creates clarithromycin (6-O-methylerythromycin). Compared with erythromycin, both of these macrolide derivatives have superior pharmacokinetic and pharmacodynamic properties, including a longer serum half-life, increased tissue penetration and persistence, increased oral bioavailability, and greater Gram-negative antibacterial activity. Tissue concentrations of clarithromycin and azithromycin can exceed serum concentrations by 100-fold.

In the liver, cytochrome P450 3A4 (CYP3A4) metabolizes clarithromycin to an active 14-hydroxy form and six additional products. Clarithromycin and its metabolites are mostly excreted in the bile. However, since about one-third is excreted in the urine, doses should be reduced in patients with creatinine clearances <30 mL/min. In contrast, with hepatic impairment and normal renal function, the consequent reduced metabolism of clarithromycin to the active 14-hydroxy form allows for increased renal excretion of native clarithromycin and obviates dosing modifications. Since azithromycin elimination occurs primarily in the feces as the unchanged drug, with minimal urinary excretion, dosing modifications are unnecessary in renal or hepatic dysfunction.

Traditionally, antibiotic macrolides are prescribed for infections from a variety of Gram-positive bacteria (β-hemolytic streptococci, pneumococci, staphylococci, enterococci), *Haemophilus influenzae*, *Legionella pneumophila*, *Mycoplasma*, mycobacteria, *Chlamydia*, and some rickettsias. Macrolides rarely cause allergic reactions and, therefore, are a common alternative for penicillin-allergic patients.

Macrolides reversibly bind to ribosomes, where they inhibit protein synthesis in several ways.[92,93] They block peptidyl transferase from adding the peptidyl attached to transfer-RNA to the next amino acid, analogous to the activity of chloramphenicol. Macrolides accelerate dissociation of peptidyl-transfer-RNA from ribosomes and also inhibit ribosomal translocation. Since macrolides accumulate within cells, in addition to their antibacterial actions, they can exert numerous anti-inflammatory effects within the respiratory tract, including increasing mucus clearance, inhibiting neutrophil recruitment and activation, promoting neutrophil apoptosis, and decreasing the production of reactive oxygen species and elaboration of cytokines, including interleukins (IL-4, IL-5, IL-8, IL-13) and chemokines (C-X-C motif ligand 2 [CXCL2], and ligand 2 [CCL2], 3 [CCL3], and 4 [CCL4]). These anti-inflammatory actions are believed to mediate the efficacy of macrolides in controlling exacerbations of underlying respiratory diseases.

Clinical Use

Since the first clinical use of erythromycin as an anti-infective agent in the 1950s, over the past decade a new role has emerged for macrolide antibiotics as anti-inflammatory agents, mainly in treatment of chronic suppurative respiratory disorders. In randomized, double-blind, placebo-controlled trials in adults with either non–cystic fibrosis bronchiectasis or COPD, azithromycin (250 mg daily) or erythromycin (400 mg twice daily in bronchiectasis, 250 mg twice daily in COPD) reduced clinical exacerbations and yielded modest improvements in FEV_1 and quality of life.[94,95]

Retrospective analysis of the Acute Respiratory Distress Syndrome Network dataset revealed increased survival and decreased time to successful discontinuation of mechanical ventilation associated with use of a macrolide early in the clinical course of respiratory failure.[96] However, no randomized trials have expressly tested the efficacy of macrolides in acute lung injury. Azithromycin effectively reduces exacerbations and improves FEV_1 in children with cystic fibrosis, although this effect is attributed to antipseudomonal, rather than anti-inflammatory, effects.[97] Macrolides have not been proven effective in infants with viral bronchiolitis.[98,99]

Safety

Since larger macrolide doses produce higher serum concentrations, the incidence of adverse effects increases with increasing doses. Most common are gastrointestinal side effects, specifically abdominal pain and diarrhea, which are usually tolerable. These side effects appear to represent luminal phenomena, while auditory side effects have been attributed to tissue accumulation. Nonetheless, drug-induced, bilateral, sensorineural hearing loss accentuated at the lower frequencies is usually transient and reverses with discontinuation of the macrolide.

Most clinical trials of chronic macrolide therapy that address resistance demonstrate emergence of macrolide-resistant flora. Hepatotoxicity may occur, as manifested by an increase in liver enzymes or cholestasis—findings that should prompt immediate discontinuation of chronic macrolide therapy.

All macrolides may prolong the QT interval, primarily by blocking the outward delayed rectifier potassium channel encoded by the hERG gene. Indirectly, macrolides may also prolong the QT interval by inhibiting the metabolism of other arrhythmogenic drugs metabolized by CYP3A4. The increase in sudden cardiac death associated with erythromycin administration has led to a marked reduction in use of this drug, particularly in the elderly and patients with heart failure. Electrocardiograms to monitor QT prolongation should be considered during chronic macrolide administration.

Clarithromycin, when oxidized by CYP3A4, forms an inactive metabolite/enzyme complex. Clarithromycin is less potent than erythromycin at inhibiting CYP3A4, and azithromycin minimally inhibits CYP3A4. Therefore, dose reductions, clinical assessments, and therapeutic drug level monitoring (when practicable) are necessary with simultaneous administration of drugs metabolized by the CYP3A4, particularly with clarithromycin or erythromycin therapy. The concurrent use of cisapride, pimozide, terfenadine, and astemizole with clarithromycin or erythromycin is contraindicated because of QT prolongation and reported cases of torsades de pointes. Simultaneous therapy with clarithromycin and ergot compounds risks acute ergot toxicity. Numerous other medications metabolized by CYP3A4 (e.g., benzodiazepines, statins, class 1A antiarrhythmic agents, theophylline, carbamazepine, warfarin, sildenafil, colchicine, cyclosporine) should be used cautiously when given with clarithromycin. Furthermore, although these drug–drug interactions are less likely to occur with azithromycin because of less efficacious inhibition of CYP3A4, high doses may, nonetheless, produce clinically significant side effects. Similarly, respiratory patients with hepatic dysfunction, concurrent congestive heart failure, or cor pulmonale may require dose adjustments. Finally, combination of macrolides with statins has been linked to rhabdomyolysis.[93]

Troleandomycin

Since the 1960s, anecdotal clinical observations suggested that the macrolide antibiotic troleandomycin might reduce corticosteroid requirements in patients with severe asthma by decreasing steroid metabolism. However, results from double-blind, randomized trials were mixed, and the weight of evidence suggests that troleandomycin has no clinical effect at relieving airway obstruction or inflammation independent of its effects on corticosteroid metabolism. Troleandomycin has no role in the current therapy of severe, steroid-dependent asthma.

■ Mast Cell Stabilizers

Cromolyn sodium and nedocromil exert anti-inflammatory actions by stabilizing mast cells. This blockade of mast cell degranulation prevents inflammatory mediator release, which is partially responsible for the bronchoconstriction and epithelial injury that are characteristic of asthma. However, these agents remain inferior to inhaled steroids for controlling asthma.[100] In addition, limited commercial availability of these agents hampers current usage, largely supplanted by the oral leukotriene formation inhibitors and receptor antagonists.

Cromolyn Sodium

Cromolyn sodium was the first mast cell stabilizer to be approved for clinical use in asthma and remains in use as a nebulized agent in pediatric asthmatics. MDI formulations are no longer available in the United States and Canada.

Pharmacology Cromolyn sodium potently inhibits inflammatory responses. Cromolyn sodium diminishes early-phase reactions in asthma by blocking the release of intracellular calcium and inhibiting enzymes responsible for mast cell degranulation; cromolyn reduces late phase reactions in asthma by inhibiting production of the enzymes necessary for superoxide generation. Cromolyn sodium may also exhibit tachykinin antagonism, accounting for some of its anti-inflammatory properties. In vitro, cromolyn sodium potentially inhibits the activation of inflammatory cells, antibody-induced granulocyte cytotoxicity, IgE production by atopic cells, and monocyte IgG production.

Clinical Use Nebulized cromolyn sodium (20-mg dose) is a second-line agent for the management of asthma in children 2 to 5 years of age.[16] Cromolyn sodium, alone or in combination with β_2-adrenergic agonists, reportedly improved exercise tolerance, enhanced sleep quality, and reduced asthma exacerbations. Cromolyn sodium prophylaxes against exercise-induced asthma in children, although less efficaciously than β_2-agonists alone.

Safety Cromolyn sodium causes few adverse effects, even after long-term use. Although the efficacy of cromolyn sodium in preventing childhood asthma symptoms remains unclear, its safety record leads to continued use as a second-line agent, in conjunction with β_2-adrenergic agonists, in management of asthma in children.[100]

Nedocromil

Nedocromil also stabilizes mast cells in the bronchial mucosa, but with a broader anti-inflammatory spectrum than cromolyn sodium. Although useful as prophylaxis against asthma exacerbations, nedocromil is not therapeutically efficacious for acute bronchospasm and is currently available only as a DPI in a small number of countries.

Antileukotriene Agents

Leukotrienes are synthesized from arachidonic acid, a fatty acid stored in phospholipids of cell walls. Numerous stimuli, including IgE receptor activation, antigen–antibody interactions, and activation of phospholipase A_2, induce release of arachidonic acid from phospholipids. Arachidonic acid is converted to a variety of products via several unrelated pathways; the 5-lipoxygenase (5-LO) pathway is the pathway of importance in asthma. Leukotriene A_4 (LTA_4) is metabolized by two different pathways to either the nonpeptide LTB_4 or the cysteinyl leukotrienes (LTC_4, LTD_4, and LTE_4). LTB_4 recruits and activates inflammatory cells but has no effect on bronchial tone or reactivity. The cysteinyl leukotrienes stimulate smooth-muscle contraction, increase vascular permeability, and enhance bronchial hyperresponsiveness; thus, they have a role in the pathogenesis of asthma.

Leukotriene action may be inhibited by either selective receptor blockade or interference with synthesis. Most clinical experience has been with the LTD_4 receptor antagonists, since LTC_4, LTD_4, and LTE_4 interact with a common family of cysteinyl leukotriene receptors.[101] Inhibition of 5-LO reduces the generation of all leukotrienes.

Clinical Use

Two LTD4 receptor antagonists (montelukast and zafirlukast) and one 5-LO inhibitor (zileuton) are FDA approved and marketed in the United States. The receptor antagonist pranlukast is available only in Japan; zafirlukast is unavailable in Europe. The antileukotriene agents are alternate anti-inflammatory medications for long-term use in children and adults with mild or moderate asthma, including aspirin- or exercise-induced asthma and asthma associated with concomitant allergic rhinitis.[16] Montelukast is FDA approved for children beginning at age 2 years; zafirlukast for children beginning at age 6 years; and zileuton for teenagers beginning at age 12 years and adults. Although less effective than inhaled steroids or LABAs at improving asthma control, antileukotriene agents have fewer side effects and can provide incremental clinical benefit through bronchodilation and symptom reduction.[102] Acute administration of antileukotriene agents has no role in the management of acute asthma exacerbations.[103] Antileukotriene agents have modest salutary effects on airway obstruction, symptoms, and quality of life in patients with COPD, but administration of zileuton does not reduce length of stay in acute exacerbations of COPD.[104,105]

Safety

Montelukast has a black box warning for serious neuropsychiatric events. Montelukast chewable tablets contain phenylalanine and, therefore, are contraindicated in patients with phenylketonuria. The leukotriene receptor antagonists have numerous drug interactions.

Hepatotoxicity has been reported with zileuton, which is contraindicated in patients with active liver disease and in patients with serum transaminase levels exceeding three times the upper limit of normal. Baseline liver function tests should be obtained prior to initiating therapy with zileuton, and patients should be monitored closely for the duration of therapy. Zileuton must be discontinued if serum transaminase levels exceed five times the upper limit of normal.

Immunoglobulin E Antibody

Administration of antibodies directed against immunoglobulin E (IgE) has a role in management of pulmonary disorders with an allergic basis.

Pharmacology

Omalizumab is a recombinant humanized antibody developed for therapy of allergic diseases that has significant efficacy in severe atopic asthmatics.[106] By specifically binding with high affinity to free IgE, but not to other immunoglobulins, omalizumab does not activate mast cells or basophils. Clinical efficacy depends upon near total elimination of circulating IgE; therefore, the role of omalizumab is limited to those asthmatics with elevated serum IgE levels. Subcutaneous administration of omalizumab produces rapid binding of circulating IgE, with serum levels slowly rebounding over the subsequent 4 to 6 weeks.

Randomized, double-blind, placebo-controlled studies of omalizumab have been completed in patients more than 12 years of age who have moderate or severe atopic asthma refractory to high-dose inhaled corticosteroids alone. Studies have also been conducted in patients with severe asthma ages 6 to 12 years and greater than 12 years who were also receiving inhaled, long-acting β-agonists and oral leukotriene antagonists.[107] Use of omalizumab reproducibly decreased the frequency of asthmatic flares, reduced inhaled and oral steroid dosage, and improved quality of life scores. Although not approved for use in pregnant women, long-term observational registry data provide no evidence of an increased risk of major congenital anomalies among pregnant women exposed to omalizumab when compared with a disease-matched unexposed cohort.[108]

Ligelizumab, a fully humanized monoclonal antibody that binds human IgE with higher affinity than omalizumab, is currently under investigation in clinical trials. In patients with mild allergic asthma, ligelizumab had greater efficacy than omalizumab in blunting bronchoprovocation responses.[109]

Clinical Use

Omalizumab therapy is indicated for moderate or severe asthmatics who have serum IgE levels exceeding 30 IU/mL (75 ng/mL) and an allergic basis for their asthma, as demonstrated by positive skin testing or radioallergosorbent tests (RASTs) to common antigens. Although several early trials demonstrated efficacy of omalizumab when added to monotherapy with inhaled corticosteroids alone, current guidelines recommend addition of omalizumab to combined therapy using both inhaled corticosteroids and inhaled, long-acting β-agonists.[16] As a chronic therapy, omalizumab treatment should not be initiated in the setting of an acute asthma flare. Subcutaneous administration of omalizumab every 2 to 4 weeks is required to maintain reductions in circulating IgE, with the required dose and frequency dependent upon body weight and initial serum IgE level. Up to three separate subcutaneous injections, each not exceeding 150 mg at a single site, may be required at each administration. When pretreatment serum IgE levels exceed 300 IU/mL, omalizumab should not be administered to patients whose body weight exceeds

90 kg; with high pretreatment serum IgE levels, for example, levels approaching 700 IU/mL, omalizumab should not be administered, even to individuals of normal weight. Subsequent serum IgE measurements are unnecessary, as levels plummet to negligible levels and slowly rebound after each administration of the drug.

The total duration of necessary therapy is unclear, although a review every 6 to 12 months is commonly employed to assess whether improved asthma control has been achieved (as indicated by reduced inhaled and oral steroid usage, fewer emergency medical encounters and hospitalizations, and decreased overall medical costs).[110] In addition, withdrawal of omalizumab can be associated with increased asthma exacerbations.[111] Because of high acquisition costs, the cost-effectiveness of omalizumab remains controversial.[112]

Safety

Minor local skin reactions at the injection sites occur in almost one-half of patients. A diffuse urticarial rash has been reported, but it is extremely uncommon. Severe hypersensitivity reactions, including anaphylaxis, are rarely observed (rate of 1–2 per 1000 patients receiving omalizumab).[113] Therefore, close observation, including frequent assessment of vital signs, is recommended for at least 2 h following initial drug administration; similar monitoring is warranted for at least 1 h following each subsequent administration. Omalizumab should not be self-administered, although self-administration was allowed during the recent coronavirus pandemic.[114,115]

RECENT ANTI-INTERLEUKIN AGENTS

Recognition of the role of interleukins in mediating inflammation has led to development of a variety of anti-interleukin agents.

■ Mepolizumab

Mepolizumab is a humanized, mouse monoclonal antibody directed against human IL-5. Intermittent intravenous of the agent reduces peripheral blood and sputum eosinophil counts.

Pharmacology

Eosinophils play a role in the development of diverse inflammatory responses and have long been thought to play a pathogenetic role in the inflammation of asthma. Eosinophils migrate from the bloodstream to sites of inflammation, including the tracheobronchial epithelium, where they participate in antigen presentation and release of other inflammatory cytokines, as well as disgorge their own cytotoxic granules. Although IL-3 and GM-CSF have important stimulatory effects upon eosinophils, IL-5 is the most specific stimulant of eosinophil growth and activity, mediated through the IL-5 receptor complex expressed on the surface of eosinophils.

Clinical Use

Monoclonal antibodies directed against IL-5 failed to demonstrate efficacy in initial clinical trials performed in patients with asthma, in contrast to clear effectiveness in patients with hypereosinophilic syndromes. Subsequently, in a large, international, multicenter, double-blind, placebo-controlled trial, patients with eosinophilic asthma were randomized to receive monthly intravenous mepolizumab (75 mg, 250 mg, or 750 mg) infusions or placebo for 1 year.[116] In a dose-dependent manner, mepolizumab reduced clinically significant asthma exacerbations, along with both blood and sputum eosinophil counts. The efficacious effects of mepolizumab, including reduced hospitalizations, seem to be limited to patients with severe, eosinophilic asthma accompanied by peripheral eosinophilia, who often require concurrent oral and high-dose inhaled corticosteroids.[117–119]

Mepolizumab is also effective in eosinophilic granulomatosis with polyangiitis, and under investigation for patients with an eosinophilic phenotype of COPD.

Safety

Mepolizumab appears to be well tolerated, with relatively few significant adverse reactions equally reported in both treatment and placebo groups. The most frequently reported adverse events are headache and symptoms of respiratory infections; no serious life-threatening or anaphylactic reactions related to mepolizumab have been reported.[120]

■ Dupilumab

IL-4 and IL-13 have been implicated in the pathogenesis of asthma and atopic diseases, with inflammatory activity from these cytokines present in almost half of the patients with asthma. IL-4 and IL-13 signal inflammatory cells through two distinct receptors, although both receptors contain an α subunit of the IL-4 receptor. Dupilumab, a human monoclonal antibody to the IL-4 receptor α subunit, inhibits both IL-4 and IL-13 signaling.

A double-blind, placebo-controlled trial assessed the efficacy and safety of dupilumab in adults with persistent, moderate-to-severe asthma and elevated blood or sputum eosinophil levels, despite appropriate use of LABAs and inhaled corticosteroids.[121] After initiating administration of dupilumab or placebo subcutaneously once weekly, both LABAs and inhaled corticosteroids were withdrawn. Significant improvements were observed in spirometric values and asthma control, and withdrawal of LABAs and inhaled corticosteroids precipitated fewer asthma exacerbations in patients receiving dupilumab. However, only a minority of asthmatics have blood or sputum eosinophilia, and whether dupilumab will add incremental value to standard therapy with LABAs and inhaled corticosteroids remains to be seen.

■ Daclizumab

Airway inflammation in asthma includes activation of T cells and, consequently, increased levels of IL-2 and soluble IL-2 receptor (IL2R), all of which contribute to airway inflammation. Daclizumab is a humanized, monoclonal murine antibody that specifically binds to the α subunit of the high-affinity IL2R, thereby inhibiting IL-2 binding and subsequent activity.[122] Initially, the agent received FDA approval for induction immunosuppression and rejection prophylaxis of patients receiving renal transplantation. Daclizumab has limited availability due to market competition from basiliximab, used for immunosuppression in the setting of renal transplantation.

In a double-blind, placebo-controlled study, 116 patients with moderate or severe persistent asthma on stable doses of inhaled triamcinolone were randomized to receive intravenous infusions of daclizumab or placebo every 2 weeks for 5 months. Daclizumab improved FEV_1, reduced asthma symptoms, and delayed exacerbations.[122] However, an excess number of serious adverse events occurred in those treated with daclizumab, including an episode of severe anaphylaxis. In contrast, prior to withdrawal from the marketplace, daclizumab appeared to be generally well tolerated, in both renal transplant patients and those with inflammatory diseases receiving the drug off-label.

PHOSPHODIESTERASE 4 INHIBITORS

A new area of interest has evolved in the development of phosphodiesterase 4 (PDE4) inhibitors in the management of airways diseases.

■ Pharmacology

Roflumilast is the first-in-class isozyme-selective PDE4 inhibitor to be marketed in the United States. Although nonselective PDE inhibitors (i.e., theophylline, aminophylline) have been used for decades to treat obstructive lung diseases, roflumilast represents a markedly different type of medication.

PDEs hydrolyze cAMP and cGMP to inactive 5′ monophosphates; inhibition of PDE increases intracellular concentrations and, therefore, the activity of these secondary messengers.[123] Intracellular cAMP regulates cytokine and chemokine release from inflammatory cells and cell trafficking.

There are 11 known isoenzymes in the PDE superfamily (PDE 1–11).[124] The PDE 4 isoenzyme is expressed in lung inflammatory (neutrophils, monocytes, macrophages, and CD4+ and CD8+ T lymphocytes) and structural (sensory nerves, smooth muscle cells, fibroblasts, endothelial cells, epithelial cells) cells; PDE 4 inhibition reduces lung inflammation and remodeling.[123,124]

Roflumilast is well absorbed following oral administration and has an absolute bioavailability of about 80%.[125] The drug is rapidly metabolized by cytochrome P450 (CYP450) isoenzymes to roflumilast N-oxide, the major active metabolite that accounts for approximately 90% of the PDE 4 inhibitory activity. Roflumilast N-oxide is metabolized by CYP450 isoenzymes to inactive metabolites. Both roflumilast and its metabolites are excreted in the urine. The long plasma half-lives of roflumilast (approximately 20 h) and roflumilast N-oxide (30 h) allow the medication to be administered once daily.

Drug Delivery

Roflumilast is marketed as a 500-μg tablet. Food does not affect absorption; patients may take it with or without food, although given the pharmacokinetic and pharmacodynamics profile, patients should take the dose at the same time every day.

Clinical Use

Roflumilast is FDA approved for the treatment of patients with severe COPD associated with chronic bronchitis and a history of exacerbations. The current GOLD guidelines recommend roflumilast as add-on therapy for two clinical situations: (1) patients experiencing exacerbations despite dual therapy with LABA/LAMA if blood eosinophils are less than 100 cells/μL, and (2) patients experiencing exacerbations with chronic bronchitis, FEV_1 less than 50%, and at least one hospitalization for an exacerbation while on triple therapy with LABA/LAMA/ICS.[17] A systematic review of 28 randomized controlled trials concluded that patients with moderate to very severe COPD treated with roflumilast had small, but clinically insignificant, improvements in FEV_1, improved quality of life, and reduced likelihood of COPD exacerbations with no effect on mortality.[126]

Safety

Concerns regarding the relative risks and small benefits of roflumilast resulted in the FDA's Pulmonary-Allergy Drugs Advisor Committee's vote against approval of the drug.[127] Although generally well tolerated, roflumilast has PDE 4 inhibitor class-specific gastrointestinal (diarrhea, nausea, decreased appetite) and neuropsychiatric (insomnia, anxiety, depression, mood changes, suicidality) adverse effects.[126] Unexplained weight loss, typically <3% of baseline body weight, has been reported with roflumilast. Patients should be advised of the possibility of these adverse effects and monitored closely during treatment with roflumilast. Roflumilast is contraindicated in Child–Pugh B or C liver impairment.

Many drugs interact with roflumilast.[128] Strong inducers of CYP450 (e.g., carbamazepine, phenobarbital, phenytoin, rifampin) reduce the effect of roflumilast and should be avoided. CYP3A4 or dual CYP3A4/CYP1A2 inhibitors (e.g., cimetidine, enoxacin, erythromycin, fluvoxamine, ketoconazole) increase the effect of roflumilast and also should be avoided.

Clinical experience with roflumilast in patients with immunologic disorders and serious infections is limited. Until more data are available, roflumilast should not be used in patients with severe immunologic disorders, severe acute infections, or latent infections (e.g., tuberculosis, herpes viral infections, viral hepatitis).[128] Concurrent use of roflumilast with immunosuppressants, including long-term systemic corticosteroids, is not recommended.[128]

MUCOACTIVE AGENTS

Chronic sputum production or inspissated airway secretions trouble most patients with obstructive lung disease. Mucus, which consists of a tangled network of mucin glycoproteins, oligosaccharide side chains, water, and electrolytes, is produced by goblet cells and submucosal glands and is cleared by ciliary action; sputum (expectorated mucus) is cleared by cough. Inflammatory-derived substances (neutrophil-derived DNA, filamentous actin, cells and cellular debris, and bacteria) alter the physical characteristics of mucus.

Mucoactive drugs (expectorants, mucolytics, mucoregulators, mucokinetics) modify mucus viscoelastic properties and enhance mucus clearance.[129] Expectorants increase mucus secretion or increase airway water to facilitate mucus expulsion from the airways. Mucolytics directly decrease mucus viscosity. Mucoregulator drugs, such as the anticholinergics and glucocorticoids, decrease mucus secretion and improve mucociliary clearance, respectively. Mucokinetic drugs (e.g., β_2-adrenergic agonists) enhance ciliary activity.

Expectorants

FDA-approved expectorants include guaifenesin, available in multiple nonprescription and prescription products, and potassium iodide. The mechanism of action of guaifenesin (glyceryl guaiacolate) is unclear. Guaifenesin may suppress mucin production, stimulate gastric vagal receptors triggering cholinergic parasympathetic reflexes, alter mucus adhesiveness and surface tension, and increase mucus hydration.[130] Guaifenesin is not recommended in the current American College of Chest Physicians evidence-based cough guidelines.[131,132] Despite a lack of proven efficacy, guaifenesin, with few adverse effects or drug interactions, is a common component in numerous nonprescription cough medications.

Aerosolized hypertonic saline is used in the management of cystic fibrosis and non–cystic fibrosis bronchiectasis and to induce sputum for diagnostic and research purposes. The mechanism of action is unclear, but aerosolized hypertonic saline may increase airway surface liquid layer volume and decrease bronchial epithelial cell volume.[133] Although evidence is limited, regular use of hypertonic saline by adolescents greater than 12 years of age and adults with cystic fibrosis may improve lung function, reduce exacerbations, and improve quality of life.[134] Adverse reactions to aerosolized hypertonic saline include bronchospasm, cough, and breathlessness.[135] The mechanism of action of potassium iodide as an expectorant is not known. Efficacy data are limited.[131] Potassium iodide may cause significant adverse effects (hypersensitivity, dermatitis, hypothyroidism, chronic iodide poisoning) and must be used with caution in patients with Addison disease, cardiac disease, and renal impairment. Potassium iodide is contraindicated during pregnancy.

Mucolytics

Drugs that directly reduce mucus viscosity are classified as classic (e.g., N-acetylcysteine [NAC]) or peptide (e.g., dornase alfa) mucolytics. When administered as an aerosol, the NAC free thiol sulfhydryl group hydrolyzes the disulfide bonds that link mucin strands, resulting in less viscid mucus.[136] Evidence for efficacy of aerosolized or oral thiols in the treatment of cystic fibrosis is limited.[137] Aerosolized NAC is acidic (pH 2.2); pretreatment with inhaled bronchodilators is necessary to reduce NAC-associated cough and bronchospasm.[137]

Dornase alfa, purified recombinant human deoxyribonuclease, depolymerizes DNA and F-actin polymers, reducing sputum adhesiveness. FDA approved for the management of cystic fibrosis, dornase alfa improves lung function and reduces exacerbations.[138] Dornase alfa is administered by nebulizer once daily. Limited data suggest that timing of administration (time of day or before or after airway clearance) has no impact on clinical outcomes.[139]

ANTITUSSIVES

Antitussives (cough suppressants) are used for the symptomatic treatment of cough associated with a variety of acute and chronic medical conditions. The number of FDA-approved antitussives is limited; no new antitussives have been approved for decades. Data regarding efficacy and comparative efficacy in specific medical conditions are limited.

■ Pharmacology

Cough is a complex coordinated neuromuscular response to mechanical and sensory stimuli in the larynx, trachea, and bronchi.[140] The medullary brainstem cough center controls involuntary cough in response to mechanical and chemical stimulation and is interconnected with suprapontine voluntary control of cough.[141]

Antitussives are classified as centrally acting or peripherally acting, depending on the site of action. Centrally acting opioid (codeine, hydrocodone, and morphine) and nonopioid (dextromethorphan, diphenhydramine, and chlophedianol) antitussives suppress cough by acting on the medullary cough center. Benzonatate, a procaine derivative, inhibits peripheral pulmonary stretch receptors. Levodropropizine and moguisteine (neither available in the United States) may modulate peripheral sensory neuropeptide levels throughout the respiratory tract.[142,143] Guaifenesin may have antitussive effects in acute viral cough, although the evidence is limited and contradictory.[144]

Drug Delivery

Antitussive medications are available in a variety of product-specific formulations, including solutions (liquids, extended-release liquids, syrups, elixirs, and gels) and solid dosage forms (lozenges, capsules, tablets, chewable tablets, and oral disintegrating strips). Alcohol-, sugar-, dye-, and gluten-free and single-ingredient antitussive products are available, although most products contain multiple additional active ingredients (e.g., expectorants, decongestants, analgesics, antihistamines). The majority of states allow codeine-containing antitussives to be sold as nonprescription medications if the products contain one or more non-codeine active ingredients and a maximum of 200 mg of codeine per 100 mL.[145]

Clinical Use

The ACCP Evidence-Based Clinical Practice Guidelines recommend codeine or dextromethorphan for short-term symptomatic relief of cough associated with acute and chronic bronchitis and postinfectious cough, and centrally acting antitussives, such as dihydrocodeine and hydrocodone, for chronic cough associated with lung tumors.[131] Evidence for the efficacy of antitussives in the management of other medical conditions, including cough due to viral upper respiratory tract infections, is lacking.[146–149]

Safety

Questions regarding the safety of opioid-containing cough medications prompted the FDA to limit the use of prescription codeine and hydrocodone cough medications to adults 18 years of age and older.[150] Although the FDA has not taken action on opioid or nonopioid nonprescription cough and cold medications, manufacturers voluntarily restricted labeling to state "do not use" in children under 4 years of age.[151]

Common side effects associated with opioid antitussives include sedation, constipation, nausea, and vomiting. At antitussive dosages, dextromethorphan has a wide margin of safety; side effects similar to codeine occur infrequently. Side effects of chlophedianol include excitation, hyperirritability, and hallucinations. Benzonatate may cause drowsiness or dizziness; capsules should be swallowed whole to avoid the local anesthetic effect of the liquid capsule contents.

Codeine and dextromethorphan are abused for the CNS effects associated with high doses. Robotripping, intentional abuse of dextromethorphan-containing cough medications for the dissociative hallucinogenic effects, is well known, especially among adolescents. At higher than approved doses, dextromethorphan is associated with dose-dependent symptoms ranging from mild motor and cognitive impairment at low doses (1.5–2.5 mg/kg) to complete psychophysical dissociation at high doses (>15 mg/kg).[152] In 2010, an FDA advisory panel considered, but voted against, recommending that dextromethorphan be scheduled in the Controlled Substance Act.[153]

PHYSIOLOGIC REPLACEMENTS

Replacement therapy comprises a novel class of agents to replace deficient, or augment existing, endogenous substances. To date, replacement therapy has been employed only in adults with α_1-antitrypsin deficiency or neonates with respiratory distress syndrome. However, clinical studies of replacement therapy are ongoing in patients with a wide spectrum of obstructive and other lung diseases.

■ α_1-Antitrypsin

α_1-Antitrypsin is a glycoprotein synthesized and secreted largely by hepatocytes. A protease inhibitor, α_1-antitrypsin blocks the actions of neutrophil-derived elastase in the lung. Inherited deficiency of α_1-antitrypsin promotes development of emphysema in adulthood; tobacco smoking rapidly accelerates the clinical presentation and severity of the emphysema. Since 1987, α_1-antitrypsin replacement therapy has been available for intravenous administration as a purified product derived from pooled human plasma.

Clinical Use

Weekly or monthly intravenous infusion of α_1-antitrypsin to deficient patients increases α_1-antitrypsin levels in serum and bronchoalveolar lavage specimens and restores antielastase activity in serum and alveolar lining fluid. Numerous case reports and small series dispute whether α_1-antitrypsin replacement reduces the accelerated rate of decline in pulmonary function, CT-measured lung density, or mortality associated with α_1-antitrypsin deficiency.[154–156] The absence of clear efficacy data and high cost have prevented governmental approval for administration of replacement therapy in many countries. However, the withdrawal of governmental financing of replacement therapy led to an extremely rapid and prevalent increase in exacerbations, leading to reinstitution of financing.[157]

Currently, weekly α_1-antitrypsin replacement infusions of 60 mg/kg are recommended for patients with α_1-antitrypsin deficiency who are older than 18 years of age, maintain complete tobacco abstinence, and have both abnormal pulmonary function tests and a serum α_1-antitrypsin level less than 11 mM.[17,158,159] Replacement therapy for α_1-antitrypsin deficient patients is not recommended following lung transplantation.

Side Effects

α_1-Antitrypsin replacement therapy is remarkably nontoxic, and current preparations have few side effects, other than mild fever, headache, dyspnea, or dizziness. Repeated administration of α_1-antitrypsin does not shorten the serum half-life, suggesting that α_1-antitrypsin antibodies do not develop, even in patients with complete deficiency.

Pulmonary Surfactant

The administration of pulmonary surfactant to premature infants with, or at risk for, respiratory distress syndrome remains in practice as an alternative or supplement to nasal continuous positive airway pressure.[160] Surfactant administration decreases mortality from respiratory distress syndrome by 30% to 40% and reduces morbidity due to pneumothoraces, interstitial emphysema, bronchopulmonary dysplasia, and intraventricular hemorrhage. Traditionally administered intratracheally via intubation, newer methods including nebulized administration or a thin, endotracheal catheter transiently placed during nasal continuous positive-pressure ventilation are in clinical trials.[161,162] In addition, surfactant administration may have a role in neonates with meconium aspiration syndrome and respiratory failure, reducing the need for mechanical ventilation or extracorporeal membrane oxygenation, and hospital length of stay but not mortality.[163]

Endogenous pulmonary surfactant is an emulsion of phospholipids, cholesterol, and apoproteins that reduces surface tension within alveoli. Natural surfactant is commercially available and is prepared from bovine or porcine lung tissue or lavages. Synthetic surfactant was initially available from a number of commercial sources, but it was withdrawn from the market due to superiority of natural surfactant. However, newer-generation synthetic surfactants, enriched in peptide analogues of the human surfactant proteins B and C, are currently in clinical trials.[164]

Pulmonary surfactants reduce oxygen toxicity by scavenging free radicals, and the surfactants may be cytoprotective for alveolar cell surfaces. Pulmonary surfactants suppress mediator release by inflammatory cells and may deactivate inflammatory mediators upon release. In vitro studies indicate that surfactant suppresses lymphocyte mitogenic responses, leading to a decrease in inflammatory cell influx. Pulmonary surfactant has both antibacterial and antiviral properties that are mediated by an increase in alveolar macrophage phagocytosis. Surfactant may promote airway clearance by changing the physical properties of mucus, as well as by increasing ciliary beat frequency. Finally, pulmonary surfactant may directly relax airway smooth muscle. This spectrum of putative biologic activities may directly interrupt the pathogenesis of airway inflammation, chronic infection, and bronchoconstriction seen in most obstructive lung diseases.

In adults with respiratory failure, multiple placebo-controlled trials showed that administration of synthetic surfactant yielded no demonstrable physiologic benefit and no significant decrease in mortality rate. Similarly, the most recent trial using bovine surfactant yielded no significant improvements in oxygenation, length of stay, or survival at the first interim analysis and was discontinued.[165]

RESPIRATORY STIMULANTS

Respiratory stimulants are a group of pharmacologically unrelated agents used to treat diverse pathophysiologic conditions, including COPD, postanesthesia respiratory depression, apnea of prematurity, acute mountain sickness, and obstructive or central sleep apnea.

Acetazolamide

Acetazolamide is a noncompetitive inhibitor of carbonic anhydrase that induces a weak diuresis and mild metabolic acidosis. FDA-approved indications include acute mountain sickness (prophylaxis and adjunctive treatment), edema, epilepsy, and glaucoma.

Acetazolamide may have both indirect and direct respiratory stimulant properties.[166] The increased hydrogen concentration indirectly stimulates respiration via peripheral and medullary chemoreceptor stimulation. Acetazolamide may also directly stimulate respiration by increasing cerebral blood flow through mechanisms unrelated to the metabolic acidosis.[167] In one small clinical trial, the combination of acetazolamide and auto-continuous positive-airway pressure improved nocturnal oxygen saturation and reduced the apnea/hypopnea index in patients with obstructive sleep apnea at altitude.[168] In a large, randomized, double-blind, multicenter trial in patients with COPD receiving invasive mechanical ventilation, acetazolamide did produce a statistically significant reduction in the duration of invasive mechanical ventilation.[169]

Side effects include drowsiness, numbness or tingling of the face and extremities, tinnitus, hypokalemia, and gastrointestinal upset. Long-term safety and efficacy data for use as a respiratory stimulant are unavailable.

Almitrine

Almitrine bismesylate increases alveolar ventilation and improves ventilation–perfusion mismatching by stimulating peripheral aortic and carotid chemoreceptors and enhancing hypoxic pulmonary vasoconstriction.[170,171] Small clinical trials of sequential treatment in patients with moderate or severe COPD and hypoxemia demonstrate a small, dose-dependent improvement in oxygenation.[172,173] Investigational in the United States, but approved as a respiratory stimulant in Europe, side effects, including peripheral neuropathy[174] and weight loss, limit the clinical usefulness of the drug.

Doxapram

Doxapram is a short-acting, parenterally administered respiratory stimulant. FDA-approved indications include respiratory depression following anesthesia, acute hypercapnia secondary to COPD, and drug-induced respiratory depression; off-label uses include treatment for apnea in premature infants, weaning from mechanical ventilation, and obstructive sleep apnea.[175,176] Doxapram exhibits dose-dependent peripheral chemoreceptor agonist and central respiratory stimulant properties.[175] Limited case reports and small studies describe use of doxapram as a respiratory stimulant in COPD complicated by acute respiratory failure.[177] Benzyl alcohol–containing solutions may cause significant adverse effects in infants, including metabolic acidosis, hypotension, and the “gasping syndrome.”[175] Doxapram-associated side effects include flushing, sweating, elevated blood pressure, and muscle spasticity.

Medroxyprogesterone

Medroxyprogesterone acetate is a synthetic progesterone hormone with central and peripheral respiratory stimulant properties.[178,179] Although the mechanism of action is unclear, medroxyprogesterone increases minute ventilation and produces hypocapnia in normal subjects. However, it does not improve breathing disturbances during sleep in patients with obstructive sleep apnea.[180] Limited data show that medroxyprogesterone improves oxygenation and hypercapnia in patients with hypercapnic obstructive lung disease.[168,181] Medroxyprogesterone side effects include thromboembolic disorders, elevated liver function tests, visual disturbances, breast tenderness, reduced bone mineral density, edema, and gastrointestinal upset.

Methylxanthines

Caffeine, theophylline, and aminophylline are structurally related methylxanthines with bronchodilatory and respiratory stimulatory properties (see above). Caffeine is FDA approved for the treatment of apnea of prematurity and respiratory depression in adults. The mechanism of respiratory stimulation is not known, but it may include enhanced medullary respiratory center chemoreceptor responsiveness to carbon dioxide, improved diaphragmatic contractility, and competitive adenosine inhibition.[182,183] Caffeine is the most effective methylxanthine for the treatment of apnea of prematurity, and it may protect against acute kidney injury.[184,185] Common side effects include tachycardia, jitteriness, and increased gastric aspiration.[187] Caffeine inhibits adenosine receptors, creating a theoretical risk of cerebral damage and impaired neuronal development.[187] No neurodevelopmental disability was reported 18 to 21 months post-treatment in very low-birth-weight infants.[188] When compared with placebo-treated controls, 11 years following caffeine therapy for the apnea of prematurity, children have improved expiratory airflows, neurobehavioral outcomes, and motor impairments without adverse changes to self-reported health-related quality of life.[189–192]

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CHAPTER 145

Intubation and Upper Airway Management

Joshua H. Atkins
Christopher H. Rassekh

INTRODUCTION

Management of the upper airway, in both acute and elective settings, requires significant expertise, proper equipment, and organizational structure. Airway management is generally an interprofessional and interdisciplinary team effort that is enhanced by coordination and planning. Complications from a difficult intubation or problems from tracheostomy create may lead to considerable morbidity and mortality. Closed-claims analysis of medicolegal cases in anesthesiology reveals that litigation for patient harm related to airway management is generally associated with severe morbidity related to intubation and tracheostomy.[1,2] Multidisciplinary management of the airway, operator preparedness, and team communication are critical to preventing such complications.[3]

This chapter reviews anatomic considerations, clinical airway assessment in both the emergent and elective settings, and multidisciplinary considerations in airway management. The narrative specifically addresses refinements in equipment and techniques that allow for safer patient care. In addition, as systems-based initiatives and practice-based learning are critical, we highlight some of the concepts that allow members of the airway team to improve their fund of knowledge and technical skills related to airway management.

UPPER AIRWAY ANATOMY AND CLINICAL RELEVANCE

The approach to any clinical problem begins with a solid understanding of both normal anatomy and alterations associated with disease-specific pathophysiology. Knowledge of the types of anatomic variations and specific pathologic entities that can alter the anatomy are fundamental to safe and effective airway management.

The "upper" airway is defined as the portion of the head and neck where there is airflow. Thus, the nasal cavity, oral cavity, pharynx, larynx, and upper trachea constitute the upper airway. Each of these anatomic sites has several subsites. The nasal cavity is divided into left and right sides by the nasal septum and includes the superior, middle, and inferior turbinates. The choana is the boundary between the nasal cavity and the nasopharynx. The oral cavity includes the teeth, mandible, and oral tongue; the oropharynx includes the base of tongue, tonsillar structures, posterior oropharynx, and soft palate. The area at the junction of the oropharynx and the nasopharynx is particularly important. As there is minimal cartilaginous support in this area, collapse of the pharyngeal wall is common with induction of anesthesia and may impair mask ventilation.

The larynx (Fig. 145-1) consists of supraglottic structures (the epiglottis, false vocal cords, and aryepiglottic folds) and the glottis (the true vocal cords). Below the glottis is the subglottis, which transitions to the trachea below the cricoid cartilage. The vallecula is considered part of the pharynx and constitutes a depression between the lingual surface of the epiglottis and the root of the base of the tongue. It is an important landmark for intubation, since Macintosh-style laryngoscope blades are designed to fit into the area, to lift the larynx, and to expose the glottis region. The epiglottis can also be lifted on the laryngeal surface, as is typically done using straight-blade and tubular (surgical) laryngoscopes. The hypopharynx is the area of the pharynx inferior to the epiglottis; it includes the pyriform sinuses (with anterior, medial, and lateral walls) bilaterally, and the posterior hypopharynx (which is the continuation of the oropharyngeal posterior wall to the entrance of the cervical esophagus and the postcricoid area). The length of the cervical trachea and cervical esophagus are variable, depending on the patient's neck length and body habitus; the distance between the bottom of the cricoid and the sternal notch defines these lengths. These dimensions are important because patients who have longer cervical tracheas provide easy access to the cricothyroid membrane and trachea, making both emergent and elective surgical airway

1) True vocal cord
2) False vocal cord
3) Laryngeal surface of epiglottis (lingual surface out of view)
4) Left arytenoid
5) Right aryepiglottic fold
6) Left pharyngoepiglottic Fold
7) Left vallecula (oropharynx)
8) Base of tongue (oropharynx)
9) Subglottic airway
10) Right pyriform sinus (hypopharynx)
11) Posterior hypopharyngeal wall
12) Interarytenoid region (larynx)
13) Postcricoid area (hypopharynx)

Note: Esophageal inlet is between #11 and #13.

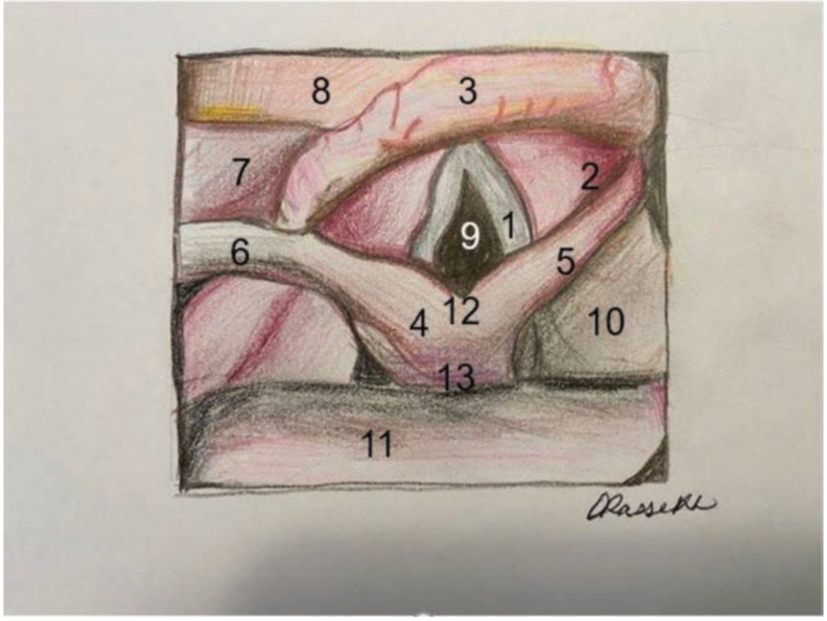

Figure 145-1 "Portrait of a telescopic endoscopy." Direct laryngoscopy view of larynx and pharynx. *(Reproduced with permission from Chamonix Helene Rassekh.)*

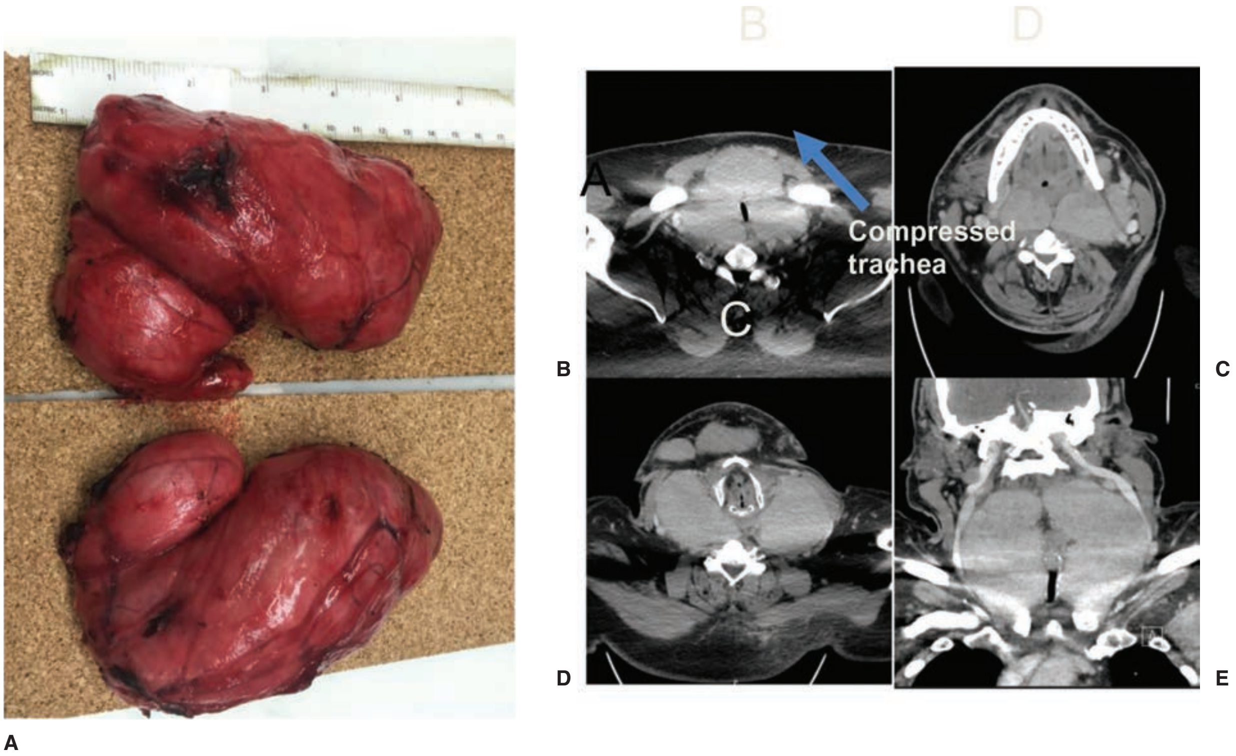

Figure 145-2 **A.** Gross thyroidectomy specimen from patient with sclerosing thyroiditis. Femoral wires were placed prior to sedation due to concerns about inability to ventilate or intubate. However, the patient was able to be ventilated and intubated and was extubated after the goiter was removed. **B.** Axial CT scan at level of trachea showing marked tracheal compression. **C.** Axial CT scan at level of larynx. **D.** Axial CT scan at level of oropharynx showing retropharyngeal extension. **E.** Coronal CT scan. *(Reproduced with permission from the personal collection of Christopher H. Rassekh.)*

access much more straightforward. Patients in whom the cricoid is not easily palpated, due to a short distance to the sternal notch, obesity, or limited neck mobility, should be identified as posing difficult surgical access.

The thyroid gland isthmus generally lies over the trachea, near the level of the cricoid cartilage. Since the thyroid is a very vascular organ, the preferred emergency surgical airway is usually a cricothyroidotomy, rather than a tracheostomy. However, if the clinical issue necessitating emergency airway access is subglottic, tracheostomy has to be considered, since a cricothyroidotomy may not bypass a proximal obstruction. If the thyroid is enlarged due to a massive goiter or malignancy overlying the airway, establishing an emergency surgical airway may be very difficult (Fig. 145-2).

Transnasal intubation is a good alternative for patients with limited mouth opening, prior head and neck irradiation, or oropharyngeal pathology. Important to note is that the anatomy of the nasal cavity may be altered by prior nasal surgery, a deviated septum, pathology of the lateral nasal wall, or hypertrophic turbinates. These conditions should be noted if nasal intubation is considered. In addition, the mucosa of the nasopharynx is highly vascular, and the risk of bleeding during transit of an endotracheal tube through the nasopharynx may be significant. Flexible fiber-optic nasopharyngolaryngoscopy (NPL) by an experienced clinician should be considered prior to elective nasotracheal intubation for anatomic assessment. Nasal intubation may be done under local anesthesia with maintenance of spontaneous respiration for patients deemed difficult candidates for oral intubation. Risk factors for difficult oral intubation are explored later in this chapter.

There are important differences between the normal adult and pediatric airways. One major difference is the stiffness, shape, and relative thickness of the epiglottis. This is relevant for oral intubation; the thinner, and relatively stiffer, adult epiglottis, with its wider arc and ligamentous attachments, can be lifted by placing a curved laryngoscope blade into the vallecula. In contrast, the more "omega-shaped" epiglottis in children, which is also longer and not as stiff, often requires lifting with a straight blade or a surgical-style laryngoscope to enable visualization of the glottis. Additionally, in adults, the diameter of the airway is smallest at the level of the vocal cords, whereas the tightest dimension in infants is the subglottic airway at the level of the cricoid cartilage. Of course, the pediatric larynx is smaller, and the vocal cords are a smaller proportion of the glottic length. The adult larynx is adjacent to the fourth to sixth cervical vertebrae, whereas the infant larynx is between C2 and C3; in addition, the superior portion of the pediatric larynx is angulated anteriorly, causing the plane of the glottis to be less parallel to the horizontal plane. Finally, the thyroid cartilage becomes ossified as patients age. Rare congenital syndromes may include substantial alteration of normal airway anatomy. Examples include Treacher Collins, Pierre Robin, Klippel–Feil, Goldenhar, Beckwith–Wiedemann, and Crouzon Syndromes, as well as mucopolysaccharidoses.

Infections, tumors, anatomic deformities, trauma, congenital anomalies, and other causes of swelling, such as angioedema, may markedly distort normal anatomy; different parts of the nasal, oral, pharyngeal, laryngeal, and tracheal airways are affected. A careful history and physical examination, even in the emergent setting, are important. When two or more of the issues noted are present, having a backup plan available that includes additional airway expertise is critical.

AIRWAY ASSESSMENT

Airway assessment and risk stratification prior to interventions are mandatory in order to devise an airway strategy and plan for potential challenges with mask ventilation, intubation, or both. Assessment includes physical examination and review of prior airway management, flexible fiberoptic procedure notes, radiology studies, and laboratory testing to assess for abnormalities in coagulation, platelet count, and serum potassium level. A rigorous approach to airway assessment may alert the clinician to warning signs that warrant a specialized approach. For example, someone who has tracheal stenosis and is predicted to have challenges with mask ventilation, as well as laryngoscopy, and who also has a cricoid cartilage that is difficult to palpate, should be considered for urgent transfer to the operating room for airway management. In extreme situations, consideration of the management of "can't ventilate, can't intubate, can't do surgical airway" may rarely require consideration of extracorporeal membrane oxygenation (ECMO).[4]

No foolproof strategy exists for predicting a challenging or impossible intubation. Backup plans and equipment should be in place for all airway management, since most challenging airways are unanticipated.[5] Considered in isolation, no component of airway assessment is 100% sensitive or specific in ruling in or out a difficult intubation. The combination of results from different assessments may be helpful in predicting a potentially difficult intubation.

A structured approach to airway assessment should include determination of a Mallampati score, measurement of mento-hyoid or mento-thyroid distance, approximation of the extent of mouth opening (as approximated by number of finger breaths), evaluation of jaw subluxation and neck range of motion, and identification of the cricoid cartilage.

The Mallampati score (Fig. 145-3) is most referenced; scores of 3 and 4 indicate greater concern for a difficult intubation. The upper lip bite test (Fig. 145-4) is an evaluation that is relatively specific (96%). In one study, 60% of patients with a class 3 finding in the upper lip bite test had a difficult airway. The test has been used increasingly.[6]

Some integrated scoring systems, such as the Wilson score (which incorporates metrics including weight, neck and jaw mobility, retrognathia, and prominent incisors), have been investigated and have demonstrated only modest predictive utility.[7] Obesity, neck circumference, presence of a beard are associated with difficult mask ventilation.[8] These features are also found frequently in patients with obstructive sleep apnea—a diagnosis that, itself, should raise concerns about mask ventilation.

A thorough inspection of the dentition may reveal loose or otherwise fragile teeth that could be displaced into the airway during intubation. Angulation of the dentition and length of the incisors should be inspected, as they may make intubation more difficult. Overlapping or crowded lower incisors may suggest a smaller mandible and anteriorly displaced larynx. Maryland bridges, in which the bridge is fixed into place by bonding to adjacent dentition, may be particularly susceptible to pressure-related injury from contact with the laryngoscope. Neck range of motion also is an important element of airway assessment, as it relates to the ability to align the axes during laryngoscopy.

Perhaps the most informative source of information about the airway is a prior airway management note. If a systemic process

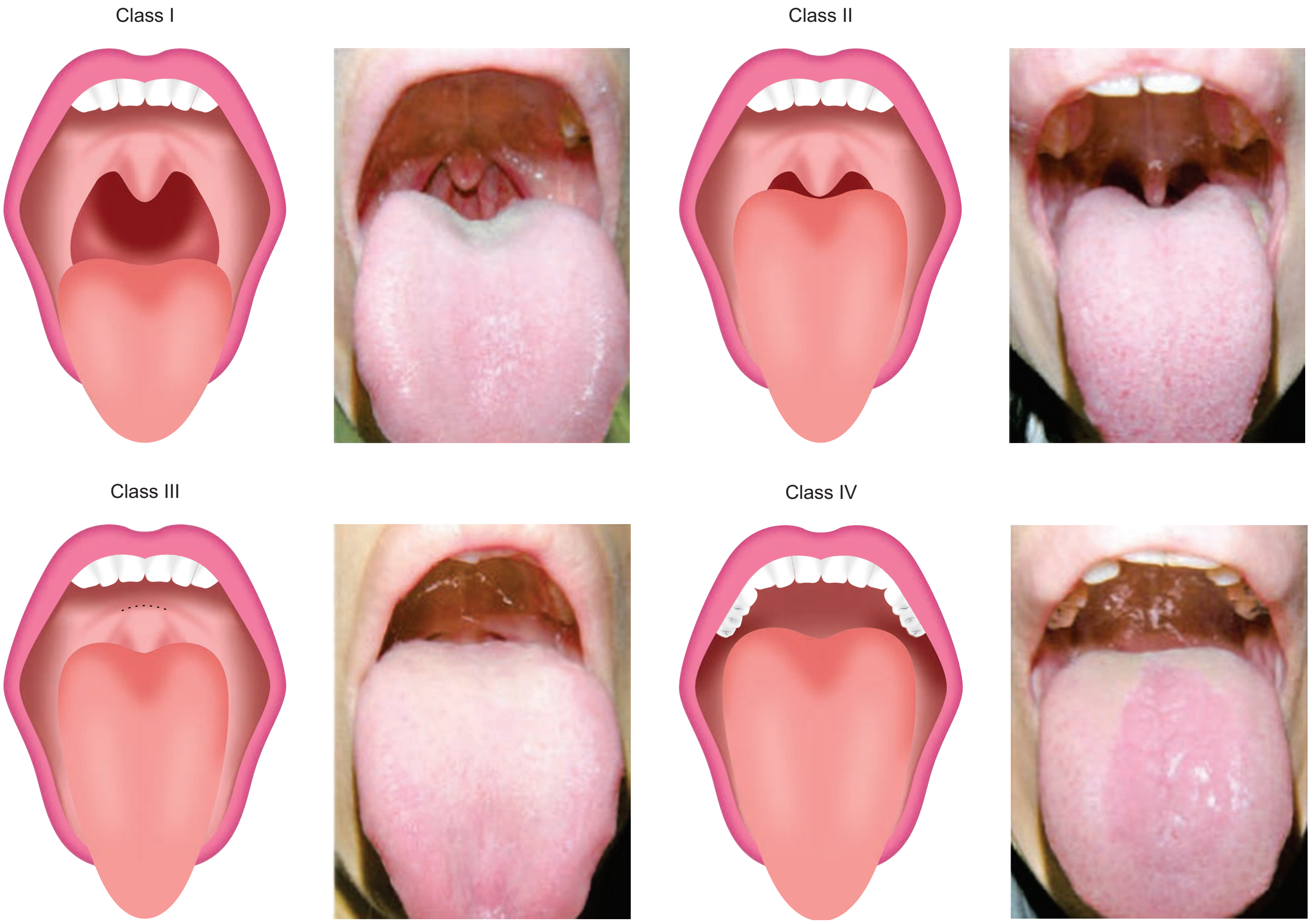

Figure 145-3 Mallampati scoring performed in the sitting position, with mouth maximally open, tongue maximally protruded, and, usually, without phonation. The Mallampati classification assesses the visibility of oropharyngeal structures when the mouth is maximally opened and the tongue protruded: class I, soft palate, fauces, uvula, pillars; class II, soft palate, fauces, uvula; class III, soft palate, base of uvula; and class IV, soft palate not visible. *(Modified with permission from Ouchi K, Hosokawa R, Yamanaka H, et al. Mallampati test with phonation, tongue protrusion and supine position is most correlated with Cormack-Lehane test. Odontology. 2020;108(4):617–625.)*

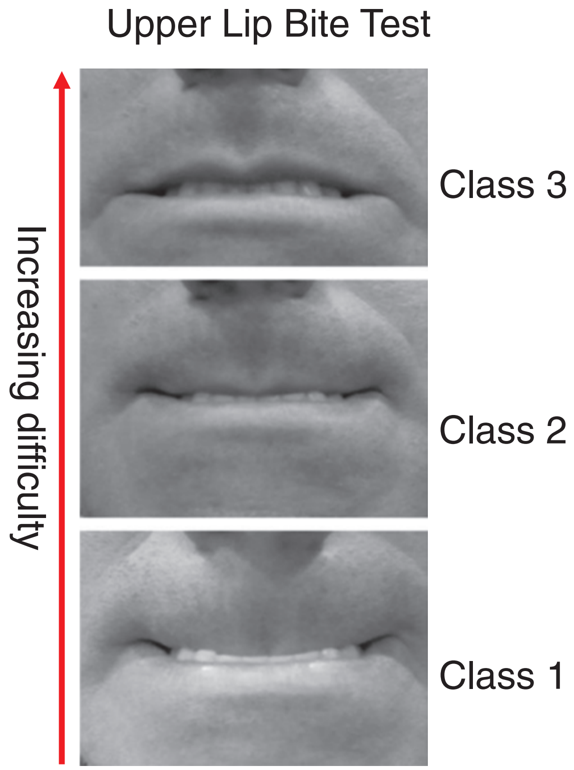

Figure 145-4 The upper-lip bite test is a commonly used adjunct to the Mallampati score. It assesses jaw mobility and has reasonable sensitivity in predicting difficult laryngoscopy. *(From Joffe AM, Deem S. Airway management. In: Tobin MJ, ed. Principles and Practice of Mechanical Ventilation. 3rd ed. New York, NY: McGraw-Hill; 2013. Reproduced with permission from Dr. Aaron M. Joffe.)*

(e.g., angioedema, SVC syndrome) or therapy (e.g., neck irradiation) has arisen since the last airway intervention, prior notes may not be applicable. Neck irradiation immobilizes tissues, such as the epiglottis and tongue, and may contribute to necrosis of the temporomandibular joint, resulting in limited mouth opening.

Also important to know is whether the patient has abnormalities in coagulation, including quantitative or qualitative platelet abnormalities, since contact of the relatively fragile oropharyngeal mucosa with the rigid laryngoscope may result in significant bleeding. This is particularly true when considering nasal intubation.

For cases involving known or suspected airway pathology (e.g., stenosis, tumor, or edema), it is important to consider a preintubation fiberoptic evaluation of the pharynx and larynx. If nasal intubation is planned, examination of the nasal cavity for any obstructive anatomy (e.g., deviated septum, or large turbinates or adenoids) or pathology (e.g., polyps, tumors) is also important. Occluding alternating sides of the nose may help predict nasal obstruction prior to placing a nasal airway. Nasal intubation may be used in the urgent setting when oral intubation is deemed to be difficult or hazardous (e.g., angioedema); it may also be helpful when addressing specific pathology of the oral cavity and oropharynx, where an oral tube may make access to pathology more difficult.

CLINICAL SETTING

The clinical setting is an important consideration with regard to upper airway management. Conditions in the operating room or procedural suite differ markedly from the general inpatient or intensive care (ICU) setting. Likewise, elective and emergent airway interventions are fundamentally different procedures. Most airway management on the general hospital floor or in the ICU is urgent or emergent and is performed on patients with significant respiratory compromise and physiologic frailty. Few parameters can be readily optimized, and physiologic reserve is minimal. These include issues related to volume status, oxygenation, cardiovascular function, and patient position, due to the limitations of the hospital bed and the unit's monitoring capabilities. In general, the equipment and airway expertise available on a general patient floor or in a remote location, such as radiology, will be limited, and support staff may have less working familiarity with less frequently used airway equipment. Overall, difficult intubating conditions are most likely to be encountered in the ICU or remote locations.[9] These factors all enhance the need for careful planning, acknowledgement of limitations, and robust systems for emergency backup. Fortunately, technologic advances in respiratory support and airway management equipment provide the clinician with a substantial armamentarium to aid in managing complex situations.

OXYGENATION, DENITROGENATION, AND RAPID SEQUENCE INDUCTION

The majority of intubations are performed with the patient asleep and following pharmacologically induced ablation of spontaneous ventilation; however, intubation with maintenance of spontaneous ventilation can and should be considered if difficult laryngoscopy is anticipated. Denitrogenation (colloquially referred to as "preoxygenation") of the lungs prior to intubation fills the functional residual capacity (FRC) of the lungs with oxygen and generally decreases the rate and extent of desaturation during intubation-associated apnea.[10] Denitrogenation is one of the most important steps in upper airway management and is challenging in critically ill patients with respiratory compromise and delirium.

The most common strategy for denitrogenation is use of a self-inflating bag-valve-mask (BVM) and 100% oxygen administered at a flow rate sufficient to wash out carbon dioxide and prevent rebreathing. An oxygen reservoir can be attached to the apparatus to increase the inspired Fi_{O_2}; a PEEP valve can be used if indicated. Imperative is maintenance of a good mask-to-face seal, which frequently requires two hands. An alternative to the self-inflating bag is a free-flowing bag (e.g., Mapleson C Circuit), which is preferred by some clinicians, as it more readily facilitates detection of patient breathing and always provides 100% oxygen, even at high minute ventilation, in the absence of a reservoir. A perceived advantage of the self-inflating bag is that it enables the operator to provide positive pressure ventilation if there is no oxygen source available. However, because of the self-inflating feature, risk of unnoticed disconnect of the oxygen during the denitrogenation phase is possible. In contrast, a disconnect in a free-flowing bag will be immediately noticed. Maintenance of team situational awareness and proactive monitoring can minimize the possibility of a disconnect.

The one-way valve that prevents rebreathing of exhaled gases on the self-inflating bag should be held open during denitrogenation if low oxygen flows are used, as they may be during resuscitation of a patient with COVID-19.[11,12] Generally, flows higher than the patient's minute ventilation are recommended to prevent rebreathing of exhaled gases. An adequate mask seal is imperative and can be confirmed using bedside end-tidal capnography, which has become commonplace in many centers (see below).

Critically ill patients requiring intubation frequently demonstrate reduced minute ventilation and FRC, impaired baseline oxygenation, or increased metabolic rate. In these circumstances, even robust denitrogenation may not provide much of a safeguard against rapid desaturation during apnea. A reduced functional residual capacity (FRC) accentuates the problem in patients who are obese, recumbent, or pregnant, or who have atelectasis or splinting with pain.

High-flow nasal oxygenation (HFNO) and high-velocity nasal insufflation (HVNI) are two similar modes of oxygen delivery that have gained extensive use in recent years as a strategy to enhance respiratory mechanics in an effort to prevent the need for intubation and mechanical ventilation. These modes deliver humidified oxygen at flow rates up to 70 L/min and are generally well tolerated by awake patients. Use of HFNO during intubation has been evaluated as a strategy to reduce hypoxemia around the time of apnea and intubation in critically ill patients. A meta-analysis of seven studies, including six randomized controlled trials, demonstrated noninferiority of HFNO and a distinct benefit in patients will mild hypoxemia prior to intubation.[13] HFNO may reduce hypoxemia by a variety of mechanisms, including washout of dead space and stenting open of airways to facilitate apneic oxygenation. Patients with respiratory compromise are also frequently placed on noninvasive ventilation (NIV) modes such as Bi-PAP or CPAP. In these patients, the respiratory mechanics for denitrogenation prior to intubation are likely to be better if the noninvasive ventilation is maintained using 100% oxygen, rather than shifting to an alternative mode of ventilation, such as the self-inflating bag.[3]

Each of the above denitrogenation strategies frequently improves respiratory dynamics, decreases work of breathing, and, likely, reduces atelectasis. These effects reduce the extent of hypoxemia or hypercarbia prior to induction of apnea for intubation. The approach may be especially important in obese patients or challenging intubations. Use of HFNO and NIV in combination in selected patients can be efficacious.[14]

Patients in need of urgent or emergent airway management usually have not been fasting, and maintaining oxygenation using bag mask ventilation may be difficult due to the host of factors discussed above. Under these circumstances, rapid sequence induction (RSI) is most often utilized. The technique is designed to achieve conditions for intubation as quickly as possible and to reduce both aspiration risk and desaturation. The precise details of RSI may vary by institution, clinical setting, and local experience. The key features of RSI include administration of a rapidly acting sedative–hypnotic and muscle relaxant, elevation of the head of the bed, rapid achievement of intubating conditions in an effort to avoid the need for positive-pressure mask ventilation, and consideration of cricoid pressure to obstruct the reflux of gastric contents into the oropharynx. It is critical to be prepared to provide effective mask ventilation when indicated—typically in the setting of unanticipated difficult intubation or rapid desaturation after administration of sedative–hypnotic agents, before intubation can be accomplished.

MASK VENTILATION

Delivery of effective mask ventilation can be challenging, but it is a life-sustaining skill and intervention. When required, effective mask ventilation can be most reliably accomplished in most patients and clinical circumstances using a two-handed technique and the "triple maneuver."[15,16] This is particularly true given the high prevalence of obesity and obstructive sleep apnea. The triple maneuver (Fig. 145-5) employs mouth opening and mandibular advancement, combined with caudad tension on the mental protuberance and firm inward (not downward) pressure on the mask to achieve a seal. Transoral ventilation is more reliable in the sleeping or sedated patient than is transnasal intubation.

The velopharyngeal sphincter is a three-dimensional structure, located between the oral and nasal cavities, consisting of lateral and posterior pharyngeal walls and the soft palate. It is unsupported by cartilage. This area readily collapses with administration of sedative agents or muscle relaxants and may require substantial pressure to effectively re-expand. The lowest inflating pressures that can be used to achieve adequate tidal volumes should be employed so as to decrease air entry into the stomach. When mask ventilation is necessary during a rapid sequence intubation, cricoid pressure can be maintained if it allows effective ventilation. PEEP can be added as needed, but it will not be as effective as PEEP in the intubated patient. Factors contributing to difficult mask ventilation include facial hair, operator inexperience, use of one hand in critical settings, large neck circumference, history of sleep apnea, and lack of muscle relaxation or adequate sedation.

MASK VENTILATION ADJUNCTS

Challenging mask ventilation can often be overcome with use of an oral or nasal airway and, often, addition of muscle relaxants and paralytics, if not already administered. Oral and nasal airways can displace the tongue (oral airway) or nasal–oropharyngeal junction (nasal airway) from the airway. Artificial airways come in a variety of sizes and frequently, but not invariably, enhance the effectiveness of mask ventilation (Fig. 145-6). Artificial airways may cause significant injuries, such as bleeding, dental damage, or soft tissue trauma. In the unparalyzed or inadequately sedated patient, placement of an oral airway may induce vomiting and result in aspiration of gastric contents. Placement of a nasal airway along the floor of the nasal passage, on the side where the nasal septum is less obstructive, is useful in providing a passageway for both mask ventilation and nasal intubation, thereby avoiding trauma to the turbinates from the tip or cuff of the balloon or artificial airway. Once the choana is navigated, gentle passage through the nasopharynx should be feasible.

DIRECT LARYNGOSCOPY, VIDEOLARYNGOSCOPY, AND TRACHEAL INTUBATION

Chevalier Jackson, an otolaryngologist, is considered the father of bronchoscopy and laryngoscopy. He designed the first direct laryngoscope in 1903 (Fig. 145-7).[17] Traditional direct laryngoscopy

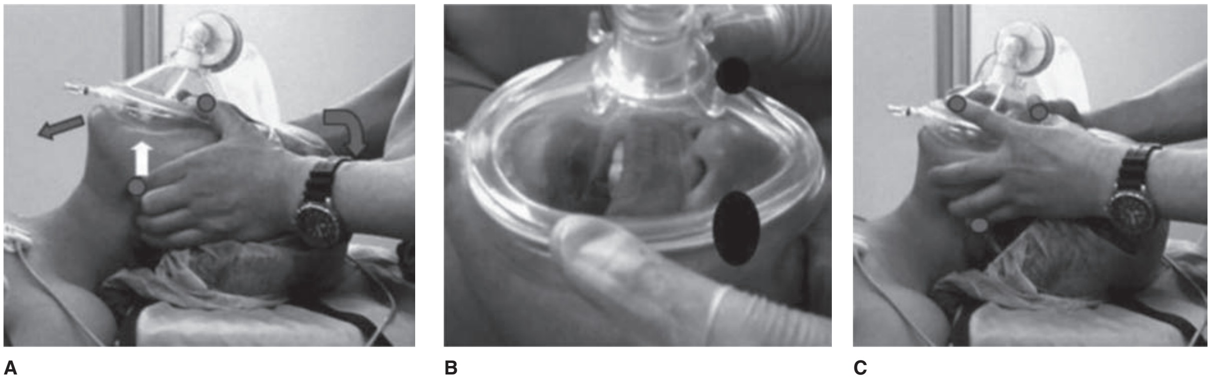

Figure 145-5 Triple airway maneuvers (mandible advancement, neck extension, and mouth opening) with two hands in the sniffing position. **A.** Only thumbs and forefingers are used for the triple airway maneuvers. **B.** Mouth opening is easily maintained in the triple maneuver approach. Mask is sealed with inward pressure toward the nose and gentle lifting into the mask. **C.** Mouth opening is often difficult using the common, two-hand clamshell technique. *(Reproduced with permission from Sato Y, Ikeda A, Ishikawa T, et al. How can we improve mask ventilation in patients with obstructive sleep apnea during anesthesia induction? J Anesth. 2013;27(1):152–156)*

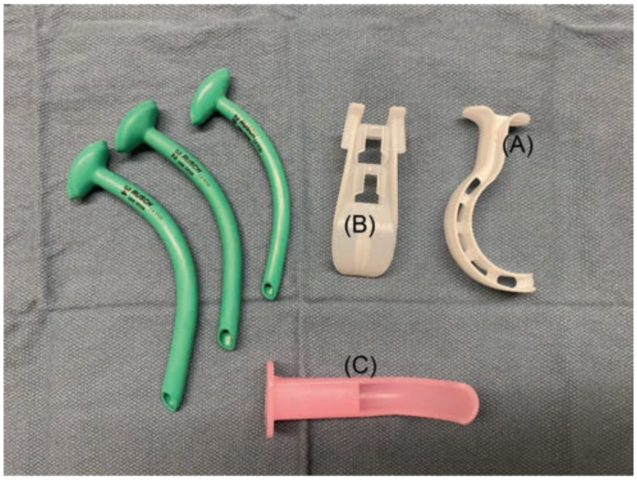

Figure 145-6 Nasal airways *(green)* in three sizes (28F, 32F, 34F). **A.** ventilating oral airway. Intubating oral airways through which ventilation and flexible fiberoptic intubation can be achieved, including Ovassapian breakaway airway (**B**) and Williams airway (**C**).

employs laryngoscope blades invented in the 1940s by Robert Miller, a Texas clinician, and Robert Macintosh, an Oxford professor. The curved Macintosh blade differed from previous models and was designed for insertion between the epiglottis and tongue. The Miller blade was an advance over similar straight blades; it was designed to pick up the epiglottis and expose the vocal cords (Fig. 145-1). Although many variants of the two blades are available today, including those with different angulations, prisms, and fiberoptic bundles, the Miller and Macintosh blades remain mainstays in the armamentarium for intubation (Fig. 145-8).

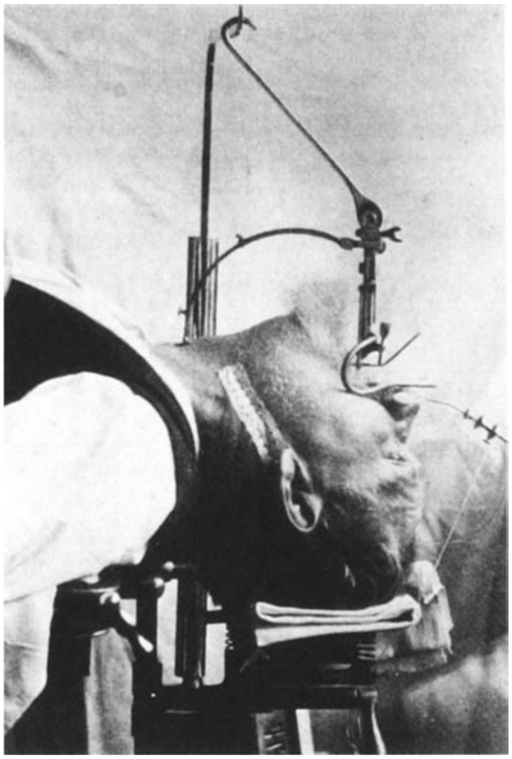

Figure 145-7 Killian's suspension microscope with a retrofitted, external, laryngeal counterpressure device. The head and neck position are incorrect; the occiput is below the shoulders. *(Reproduced with permission from Zeitels SM. Chevalier Jackson's contributions to direct laryngoscopy. J Voice. 1998;12(1):1–6.)*

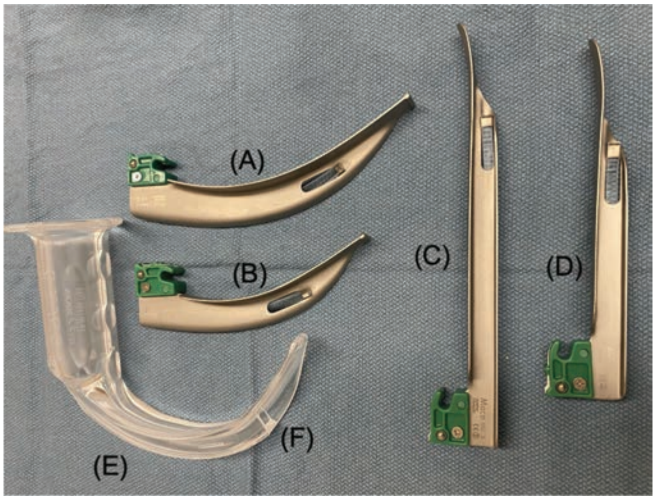

Figure 145-8 Commonly used laryngoscope blades. The curved MacIntosh blades in sizes 4 (**A**) and 3 (**B**) are placed into the vallecula. The straight Miller blades in sizes 3 (**C**) and 2 (**D**) are placed under the epiglottis. The hyperangulated blade **E** is used with a videolaryngoscope, usually in a difficult intubation scenario. The camera is positioned at point **F**. All blades shown come in single-use and re-usable formats.

Direct laryngoscopy applies perpendicularly oriented forces, along with tissue forces, to a laryngoscope blade in order to displace the tongue, epiglottis, and other soft tissues, and to facilitate alignment of the mouth, pharyngeal, and laryngeal axes (the "three axes") with the eye (Fig. 145-9). Head position likely plays an important role in the ability to achieve alignment, and various head elevation (see above)

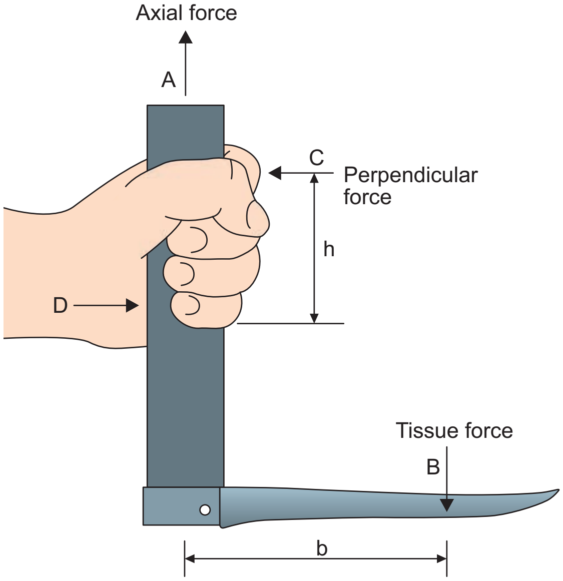

Figure 145-9 Laryngoscope in hand and straight blade attached, showing the lever arms and forces applied in direct laryngoscopy to visualize the glottis. Upward lift on the handle (**A**). This external force is resisted by a normal force from the patient's tongue. The two forces perpendicular to the handle are also separated by a moment arm (**h**). The two forces parallel to the handle do not act on the same point on the laryngoscope, but are separated by a moment arm (**b**). Force acting around a moment arm results in torque. The laryngoscopist's upper fingers pull back on the handle with force that is resisted by the palm (**D**). *(Reproduced with permission from Hastings RH, Hon ED, Nghiem C, et al. Force, torque, and stress relaxation with direct laryngoscopy. Anesth Analg. 1996;82(3):456–461.)*

or “sniffing” positions have been described to optimize chances of success.

MRI studies in awake subjects in the sniffing position (Fig. 145-10) suggest that the hypothetical axis alignment is actually difficult to achieve.[17] Once the mouth is scissored open, using a curved Macintosh blade the tongue is displaced laterally with the flange as the blade is gradually advanced into the vallecula. A straight Miller or tubular surgical laryngoscope is advanced over the tongue and under the epiglottis. Blade choice is often related to the comfort and experience of the intubator, but straight blades can be particularly helpful with a large, floppy epiglottis or an anteriorly located glottis. A standard grading system (modified Cormack–Lehane system) is used to describe the degree to which the glottic structures can be visualized during laryngoscopy and is a critical component of the airway procedure note (Fig. 145-11). This system is not ideal, as it is subject to interpretation and has led to modifications of grade 2 in the Cormack–Lehane classification system. An alternative and more descriptive score, percentage of glottic opening (POGO) visualized, has been advocated and validated, but it is not widely adopted.[18]

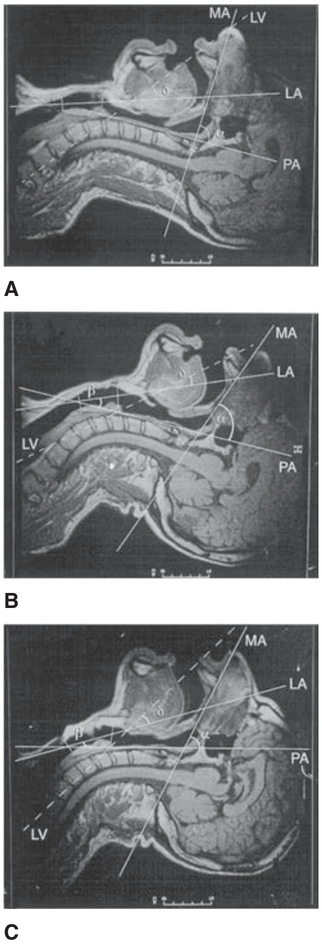

Figure 145-10 Evolution of the four axes that hypothetically need to be aligned for successful visualization of the glottis by direct laryngoscopy (mouth axis **[MA]**, pharyngeal axis **[PA]**, laryngeal axis **[LA]**, line of vision **[LV]**), and the α, β, and δ angles in the three head positions. Magnetic resonance images are shown for a single patient. **A.** Neutral position. **B.** Simple head extension. **C.** “Sniffing” position—a combination of flexion of the neck and extension of the head. *(Reproduced with permission from Adnet F, Borron SW, Dumas JL, et al. Study of the “sniffing position” by magnetic resonance imaging. Anesthesiology. 2001;94(1):83–86.)*

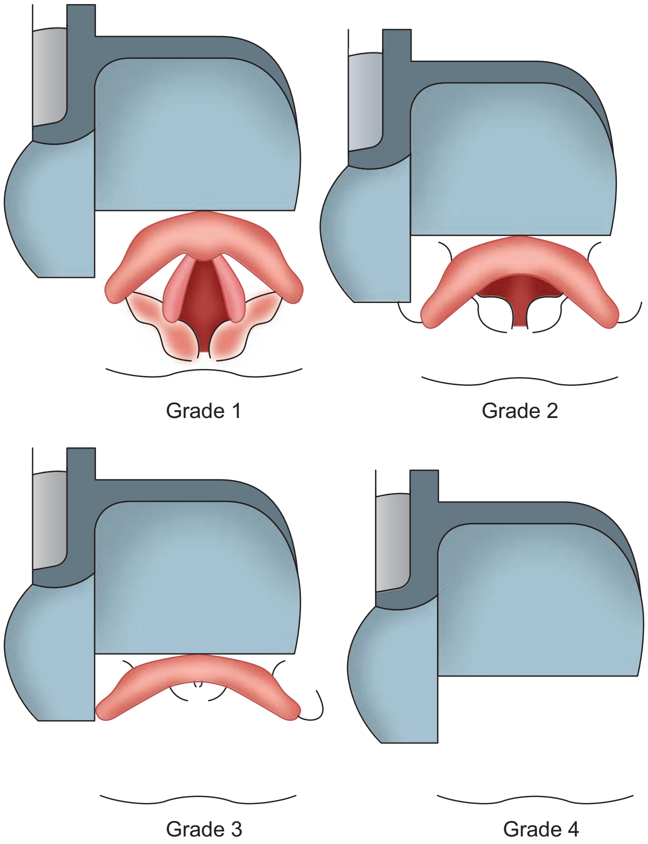

Figure 145-11 Modified Cormack–Lehane score. Laryngoscopic views of the Cormack–Lehane grades. Grade 1: 100% of vocal cords completely visualized. Grade 2: Less than 100% of vocal cords visualized. Some divide this into 2a with full arytenoids visible, and 2b with only the base of the arytenoids visible. Grade 3: Only epiglottis visualized. Grade 4: Epiglottis not visualized. This score can be compared with the POGO score referenced in the text.

Mastery of technique in traditional laryngoscopy is important as a foundational skill. However, the approach is fraught with challenges that are made even more complicated in emergent settings by the presence of secretions, coagulopathy, episodes of rapid desaturation, and highly variable patient anatomy. A fraction of patients will have upper airways difficult or impossible to visualize using direct laryngoscopy, thereby necessitating rapid transition to alternative approaches. Small mouth opening, radiation-induced fibrosis, disease of the temporomandibular joint, excess soft tissue, short mentohyoid distance, airway edema, crowded or prominent incisors, and oropharyngeal pathology may all contribute to the difficulty. For these reasons, intubation technique has rapidly shifted away from direct laryngoscopy using Miller and Macintosh blades to video-assisted indirect laryngoscopy (VAL). Ironically, this is a modern, “high-tech” approach to the indirect mirror-and-candle approach to visualizing the vocal cords taken by some of the earliest innovators. In highly resourced environments, use of VAL for emergency intubation has become routine, and this trend is certain to continue.

VAL uses a recessed light source and camera to produce an indirect view of the larynx. The view is panoramic and visible on a screen.[18] This can be advantageous to the operator in identifying anatomic landmarks and anatomic variants, or pathology that may encumber intubation. VAL also allows the entire clinical team to view the intubation and provide clinical assessment, advice, and assistance, if needed. With most devices the procedure can be video recorded for later reference or for permanently capturing airway anatomy in the patient record. VAL has been associated with fewer attempts to achieve successful intubation, but in some studies has been associated with a longer time to achieve intubation. VAL may enhance the glottic view, especially in more challenging circumstances, such as in patients with limited mouth opening or decreased cervical mobility. Many varieties of VAL technology are commercially available, and different devices may lead to variations in practitioner success rates in the absence of structured training and practice.

Two general classes of VAL scope blades are available: (1) blades with an integrated channel for passage of the endotracheal tube, and (2) unchanneled blades that allow free mobility of the tube in the oropharynx.[18] Many devices offer a variety of blades including, for example, a hyperangulated blade able to enable visualization of an anteriorly positioned glottic inlet. A hyperangulated blade (Fig. 145-8E) is frequently used to rescue failed traditional laryngoscopy. Currently, many VAL laryngoscopes are also equipped with blades that mimic traditional Macintosh or Miller blades. These scopes can be used for teaching and practicing direct laryngoscopy; the screen can be turned off or away from the intubator, while still allowing transition to the video approach, if needed, without delay or need for repeat laryngoscopy.

VAL is not a panacea; difficult and failed intubations are a present-day reality. For example, VAL is challenging in the bloody or secretion-filled airway. Tube passage or alignment, despite excellent glottic view, has been noted as a significant problem encountered infrequently with direct laryngoscopy. The operator's status as a novice or expert when using a specific device can be crucial.[19] Hybrid techniques that employ flexible fiberoptic bronchoscopy and VAL can also be of utility in these situations. Likewise, a gum elastic bougie with an angulated tip can sometimes be placed into the trachea and used as a guide to VAL-assisted intubation. Use of the bougie can also be considered when a "blind" intubation is needed due to inadequate view of the glottic structures.

Pharyngeal soft-tissue injury by the blade or tube due to fixation of the operator on the screen, instead of the mouth, may occur and can be severe.[20] Care must be taken to advance the tube into the oropharynx under direct vision, and then to look at the screen as the tube approaches the glottic opening. Disposable and reusable versions of a blade can have different properties, including size and thickness, that contribute to challenges in switching from one to the other. As was learned during the COVID-19 pandemic, supply chains can be unexpectedly disrupted, and reliance on a single platform can be problematic under these circumstances. Use of a single type of VAL throughout all clinical areas of a hospital may be of benefit, providing for universal familiarity, equipment exchangeability, and ease of maintenance.

Most intubations use a standard endotracheal tube with a high-volume, low-pressure cuff. All single-lumen tubes can connect to any standard ventilation device. Tubes come in a wide range of sizes. Single-lumen tubes are described by the size of the inner diameter (in mm). A larger-diameter tube will be necessary for therapeutic bronchoscopy, and a smaller-diameter tube might be used for patients with airway pathology or narrowing. Most also have a radio-opaque stripe that permits tube localization on a chest radiograph. Specialized tubes, including wire-reinforced, double-lumen, and metal laser tubes, can be considered in certain special situations. Importantly, use of special-purpose endotracheal tubes should be limited in the intensive care setting. Lack of staff familiarity with such tubes poses a significant latent safety threat. Tubes with tapered cuffs or subglottic suction (e.g., Hi-Lo tubes) are endorsed by some clinicians for prolonged intubation, as they may decrease the risk of ventilator-associated pneumonia. The Parker Flex-Tip tube is a good alternative to a flexible fiberoptic or blind intubation, as the curved bevel is designed to decrease impingement of the tube on the right arytenoid during blind passage over the scope.[21]

Proper location of the tube in the trachea must be confirmed after intubation by measurement of end-tidal carbon dioxide (using a colorimetric, in-line, or portable handheld device) or direct inspection of the endotracheal tube by fiberoptic inspection when carbon dioxide detection is not feasible. Auscultation of both lungs should be performed to rule out mainstem intubation. The high-volume, low-pressure cuff should be inflated with the minimum pressure required to eliminate a leak, and the pressure should be monitored periodically. An overinflated cuff produces ischemic injury to adjacent tissues. Ideally, the cuff should not be inflated high in the airway, since this can lead to significant tracheal injury resulting in stenosis or unintended extubation during patient movement. Optimal tube position within the trachea can be further confirmed with a chest radiograph—the best way to confirm that the endotracheal tube is not too shallow. Prolonged intubation with a cuff inflated too high in the airway can contribute to tracheal stenosis, long-term morbidity, and inadvertent tube dislodgement during repositioning for clinical examinations or procedures.

In cases where intubation is predicted to be difficult, based on history or factors previously discussed, awake or sedated flexible bronchoscopic intubation may provide a measure of safety. Spontaneous respiration and airway tone are largely maintained with this approach. Depending on the level of concern, this may be done with minimal or moderate sedation, administration of an antisialagogue, and application of topical lidocaine to blunt airway reflexes. If the patient already demonstrates airway obstruction, the procedure may need to be done using no sedation and only topical, local anesthesia to maintain spontaneous ventilation. In such cases, intubation by clinicians with advanced airway expertise should be considered. Rapid access to an intubating flexible fiberoptic bronchoscope is an important backup for all intubations.

In rare cases, intubation may be impractical, and ventilation may be compromised, for example in the presence of distal tracheal obstructions or compressive, low-midline neck masses, such as massive thyroid goiters (Fig. 145-2). When the possibility of a difficult airway is entertained, the potential anatomic difficulty of surgical front-of-neck access must also be evaluated, since a surgical airway is also not a guaranteed salvage option. In such cases, interim use

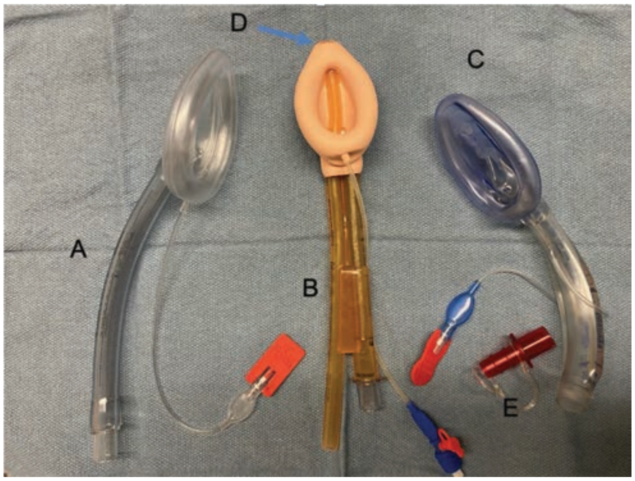

Figure 145-12 Different varieties of supraglottic airways. **A.** Classic disposable LMA 5 with non-removable connector. **B.** Second-generation reusable LMA Proseal. The second lumen transits to the tip of the cuff (**D**), which is placed into the proximal esophagus and can be used to evacuate gastric contents with an orogastric tube. Higher ventilating pressures can also be achieved due to the larger cuff. **C.** Air-Q LMA with a removable connector (**E**). The curve is designed to facilitate placement, and the removable cuff and other features allow for trans-LMA flexible fiberoptic intubation.

of heliox and proactive planning for establishing an airway in the operating room, using rigid bronchoscopy and possibly ECMO, may be required. When intubation fails due to an inadequate view or difficulty with tube passage, rapid transition to a supraglottic airway as a temporary or definitive ventilation conduit is indicated.

SUPRAGLOTTIC AIRWAYS

In recent decades an entire class of airway devices, known as supraglottic airways (SGAs), has revolutionized airway management and airway safety. These devices come in many varieties; the most common class is the laryngeal mask airway (LMA) (Fig. 145-12).[22] The distal tip of the LMA sits in the proximal esophagus, while the LMA cuff forms a supraglottic seal with the arytenoids. Placement is relatively straightforward and involves advancing the lubricated cuff into the back of the oropharynx and then applying gentle pressure to the tube to advance to the upper end of the esophagus (Fig. 145-13).

Different types of SGA may require slightly different placement technique. SGAs are extremely valuable for a number of reasons:

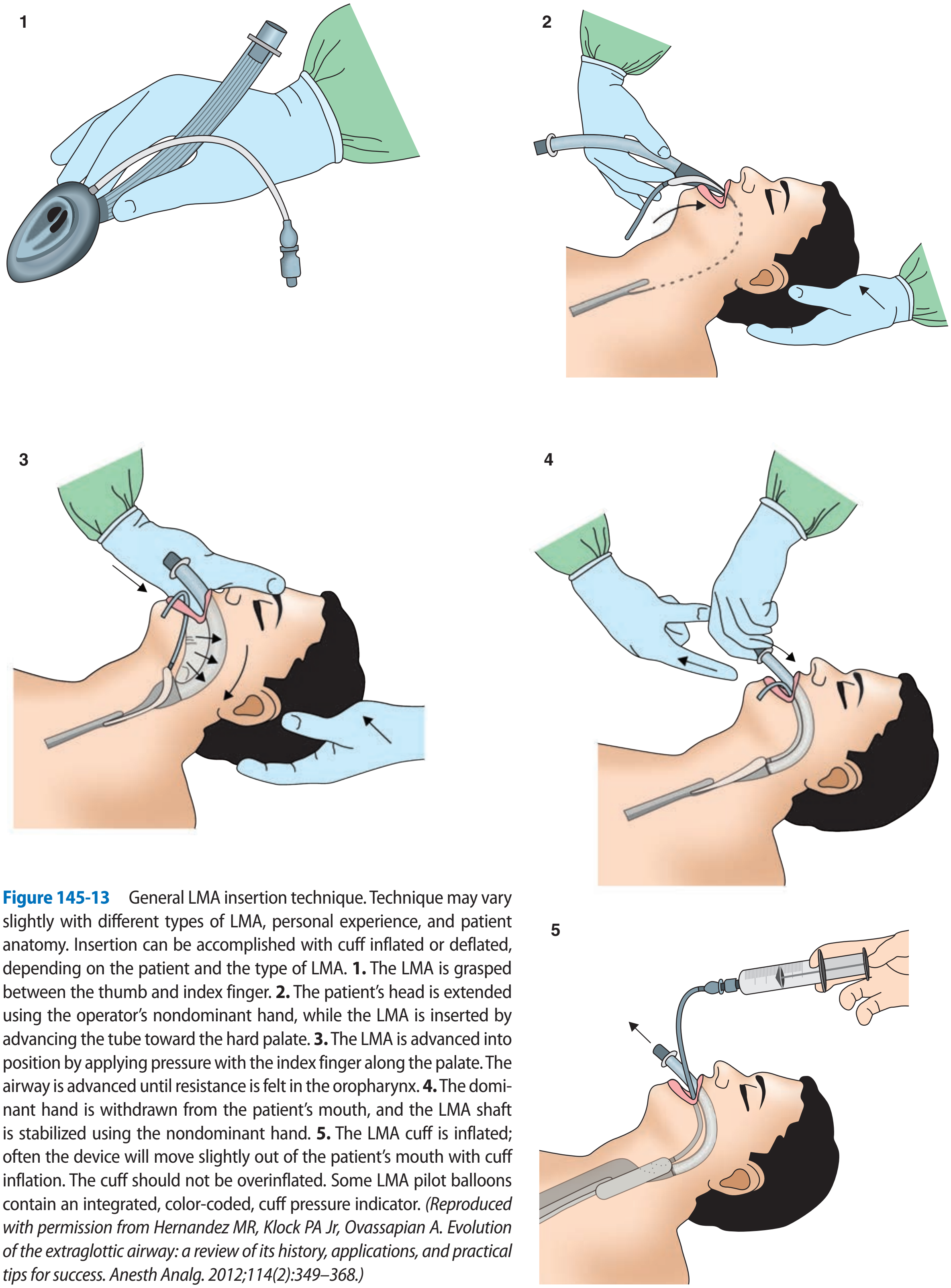

Figure 145-13 General LMA insertion technique. Technique may vary slightly with different types of LMA, personal experience, and patient anatomy. Insertion can be accomplished with cuff inflated or deflated, depending on the patient and the type of LMA. **1.** The LMA is grasped between the thumb and index finger. **2.** The patient's head is extended using the operator's nondominant hand, while the LMA is inserted by advancing the tube toward the hard palate. **3.** The LMA is advanced into position by applying pressure with the index finger along the palate. The airway is advanced until resistance is felt in the oropharynx. **4.** The dominant hand is withdrawn from the patient's mouth, and the LMA shaft is stabilized using the nondominant hand. **5.** The LMA cuff is inflated; often the device will move slightly out of the patient's mouth with cuff inflation. The cuff should not be overinflated. Some LMA pilot balloons contain an integrated, color-coded, cuff pressure indicator. *(Reproduced with permission from Hernandez MR, Klock PA Jr, Ovassapian A. Evolution of the extraglottic airway: a review of its history, applications, and practical tips for success. Anesth Analg. 2012;114(2):349–368.)*

(1) they are placed blindly (i.e., no need to visualize the glottis) and can be used in emergencies, with operators having limited training; (2) they seat well enough to oxygenate the vast majority of patients, even those having difficult intubations; (3) they are disposable; and (4) they may serve as a conduit for positive-pressure ventilation, intubation, evacuation of gastric contents, airway suctioning, and bronchoscopy.

SGAs are used as the primary airway for general anesthesia in a large range of procedures, including bronchoscopy, because they are safe, are generally easy to place, and provide an excellent conduit for bronchoscope passage. The primary limitations of SGAs are that they do not protect against aspiration or laryngospasm. Positive-pressure ventilation is possible (generally at pressures <25 cm H_2O); in difficult mask ventilation settings, rapid transition to an SGA for oxygenation and ventilation may be life-sustaining until definitive airway management is possible. Many variants of the LMA can also serve as a conduit for blind or fiber-optically guided intubation. So-called second-generation SGAs, such as the LMA Pro-seal, LMA supreme, Air-Q, Gastro, and I-Gel, include a variety of features, such as enhanced cuffs for improved airway protection and higher-pressure ventilation. They also include a second esophageal lumen at the distal tip of the cuff for evacuation of gastric contents. In the past, devices such as the Combitube and the King Airway were used to facilitate blind airway management in the field or in other emergent circumstances. The LMA has largely replaced these alternatives due to its ease of use and demonstrated effectiveness.

THE DIFFICULT AIRWAY

The definition of a difficult airway is often context- and provider-dependent. Widespread adoption of VAL has complicated the definition. Generally, difficulty keeping the patient's saturation at or above about 90% using mask ventilation (assuming the patient has normal pulmonary function), the need for more than three intubation attempts, or the need to use a specialized intubation technique or advanced equipment warrants designation as a difficult airway. The Difficult Airway Society (DAS)[23] and the American Society of Anesthesiologists[24] have each published difficult airway guidelines, including embedded algorithms and checklists (Fig. 145-14) that are

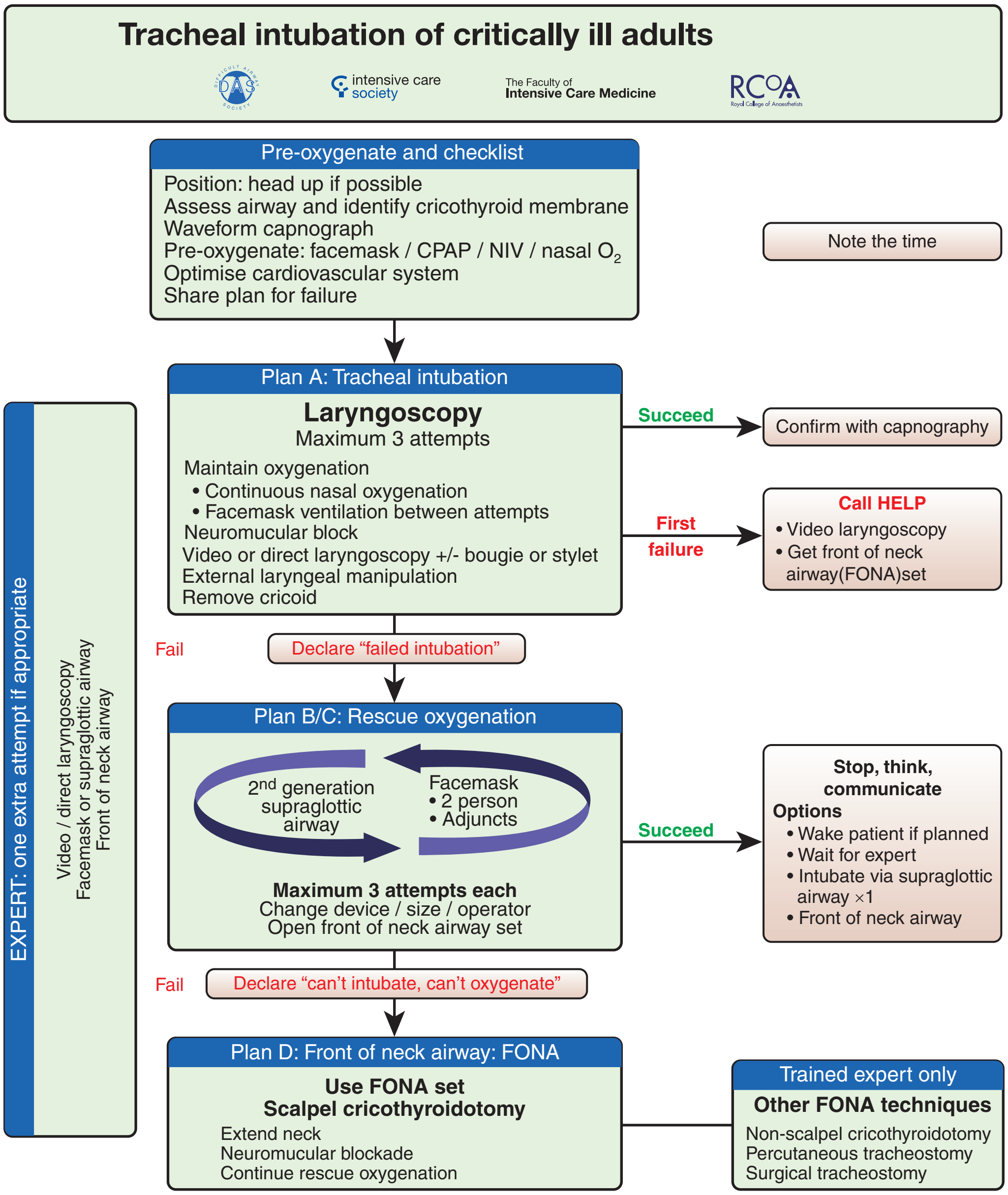
Tracheal intubation of critically ill adults
DAS
intensive care society
The Faculty of Intensive Care Medicine
RCoA
Pre-oxygenate and checklist
Position: head up if possible
Assess airway and identify cricothyroid membrane
Waveform capnograph
Pre-oxygenate: facemask / CPAP / NIV / nasal O2
Optimise cardiovascular system
Share plan for failure
Note the time
Plan A: Tracheal intubation
Laryngoscopy
Maximum 3 attempts
Maintain oxygenation
• Continuous nasal oxygenation
• Facemask ventilation between attempts
Neuromucular block
Video or direct laryngoscopy +/- bougie or stylet
External laryngeal manipulation
Remove cricoid
Succeed
Confirm with capnography
First failure
Call HELP
• Video laryngoscopy
• Get front of neck airway(FONA)set
Fail
Declare "failed intubation"
Plan B/C: Rescue oxygenation
2nd generation supraglottic airway
Facemask
• 2 person
• Adjuncts
Maximum 3 attempts each
Change device / size / operator
Open front of neck airway set
Succeed
Stop, think, communicate
Options
• Wake patient if planned
• Wait for expert
• Intubate via supraglottic airway ×1
• Front of neck airway
Fail
Declare "can't intubate, can't oxygenate"
Plan D: Front of neck airway: FONA
Use FONA set
Scalpel cricothyroidotomy
Extend neck
Neuromucular blockade
Continue rescue oxygenation
Trained expert only
Other FONA techniques
Non-scalpel cricothyroidotomy
Percutaneous tracheostomy
Surgical tracheostomy
EXPERT: one extra attempt if appropriate
Video / direct laryngoscopy
Facemask or supraglottic airway
Front of neck airway

Figure 145-14 Difficult Airway Society guidelines for management of unanticipated difficult tracheal intubation in adults. *(Reproduced with permission from Price TM, McCoy EP. Emergency front of neck access in airway management. BJA Educ. 2019;19(8):246–253.)*

periodically reviewed and updated. The DAS has gone one step farther and developed guidelines focused on intubation of the critically ill patient, acknowledging the unique patient characteristics, setting, and teams in the intensive care unit.[25] The use of difficult airway alerts in the electronic health record, patient bracelets, and identification of response clinical teams (see below) have become common.

Anyone participating in upper airway management should be familiar with these guidelines, have the necessary skill and equipment to implement them as necessary, and reference them explicitly when difficulty is anticipated or encountered. Difficult airway guidelines and national audits, such as the UK NAP4, reflect the critical aspects of planning, appropriate staffing, equipment availability, and human factors (i.e., communication, situation monitoring, and teamwork) contributing to success or failure of establishing an airway.[26] Human factors, for example, come into play when one member of the team suggests a surgical front-of-neck access after several failed intubation attempts, but the intubators are so focused on successfully managing the airway that they are unable to hear, process, or endorse the suggestion.

The Vortex is one structured approach that brings together difficult airway technique, cognitive aids, and teamwork (Fig. 145-15).[27] The Vortex visual "cone" is designed to reinforce that mask ventilation, supraglottic devices, and endotracheal tubes should all be considered for patient oxygenation during the course of airway management, particularly as challenges occur with the primary strategy. Fixation errors in which teams struggle to adjust a plan—for example, failure to intubate using an 8.0-mm endotracheal tube for bronchoscopy when a 6.0-mm tube would have worked—may lead to poor outcomes. Human factors are as relevant as technical skills in airway management, including open team communication before, during, and after upper airway management, especially in the critical care setting. This can be accomplished in a variety of ways, including use of periprocedural huddles, checklists, patient simulation, and readily accessible electronic documentation by all clinicians.

DIFFICULT AIRWAY EQUIPMENT

Availability of advanced equipment for difficult airways is essential. Difficult airway carts centralize specialized airway equipment in one location and can be rapidly mobilized to other areas as needed. The specific equipment on the cart is customized to local provider and patient needs, but it generally includes a fiber-optic scope and screen, a range of tube sizes and types, intubating oral airways, ventilating airways, exchange catheters and bougies, forceps, alternative laryngoscopes, supraglottic airways, sets for emergent scalpel use and percutaneous front-of-neck access, and cognitive aids such as difficult airway algorithms.[28] Operationalizing difficult airway trolleys requires careful planning with regard to the equipment, a process to check and maintain the supplies, a system to deliver the equipment quickly when needed, and working familiarity of staff with the process.

Difficult or surgical airway response systems are another potential resource to be considered in high-acuity centers. These systems involve an integrated alert call to bring difficult airway equipment, support staff, and a surgeon capable of front-of-neck access quickly to the bedside through an integrated activation process.[29] Such a system can be useful not only for failed intubation, but also for urgent interdisciplinary, interprofessional consultation on "at-risk" airways.

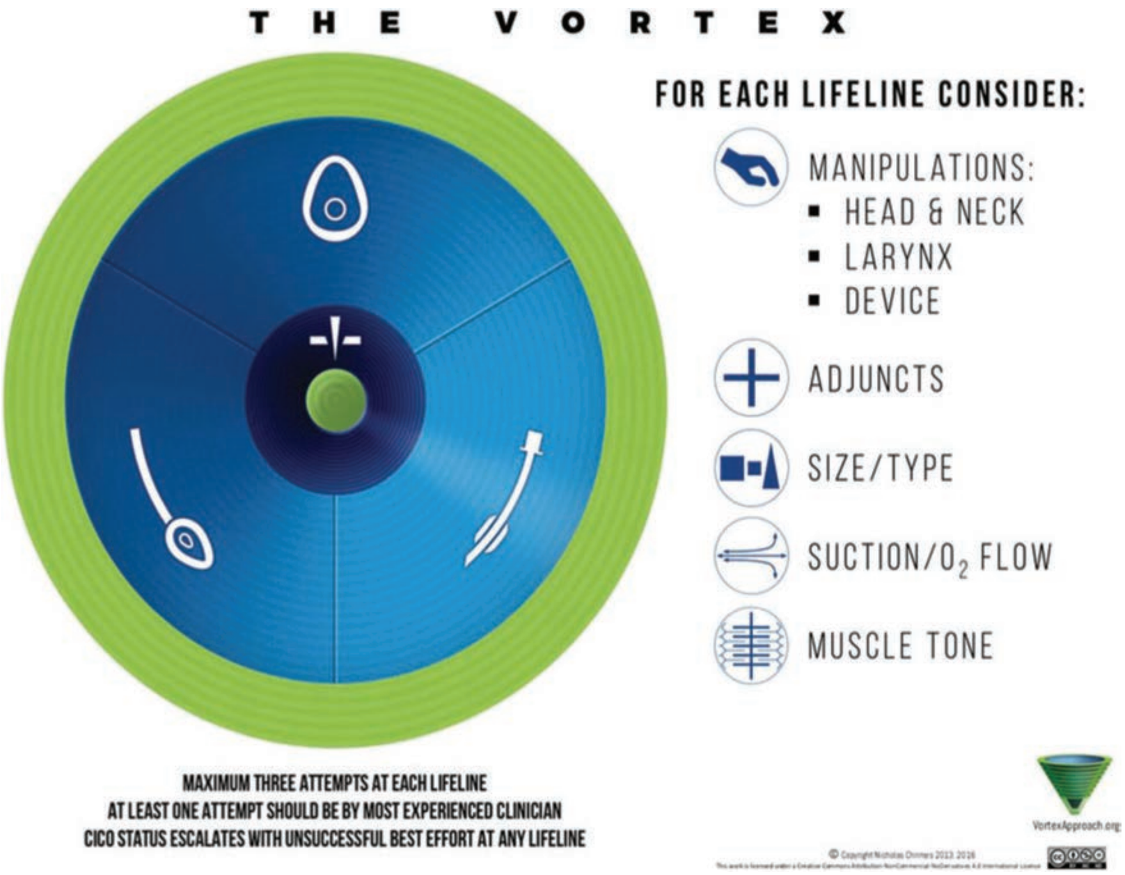
THE VORTEX
FOR EACH LIFELINE CONSIDER:
MANIPULATIONS:
HEAD & NECK
LARYNX
DEVICE
ADJUNCTS
SIZE/TYPE
SUCTION/O2 FLOW
MUSCLE TONE
MAXIMUM THREE ATTEMPTS AT EACH LIFELINE
AT LEAST ONE ATTEMPT SHOULD BE BY MOST EXPERIENCED CLINICIAN
CICO STATUS ESCALATES WITH UNSUCCESSFUL BEST EFFORT AT ANY LIFELINE
VortexApproach.org
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Figure 145-15 The VORTEX approach to intubation. The approach is designed to help teams maintain situational awareness when a difficult intubation is encountered. It also provides visual cues for continued advancement along the difficult airway algorithm, using adjuncts like the LMA. *(Reproduced with permission Chrimes N. The Vortex: a universal 'high-acuity implementation tool' for emergency airway management. Br J Anaesth. 2016;117 Suppl 1:i20–i27.)*

A patient with a prior difficult intubation should be labelled as such using a bracelet identifier, an alert in the electronic health record, and notation in a discharge summary provided to the patient for future reference. Ideally, the information necessary to manage the airway is readily available to emergency response teams.

As discussed, airway challenges create great stress in the clinical environment. The wide range of pathology and situations requires a multidisciplinary approach to management. Airway crises may arise de novo or in patients with existing airways, including tracheostomies. Many centers have organized difficult airway teams that bring the key players in the hospital together to address complex scenarios.[30,31]

Discussion of some of the system initiatives that can be beneficial in managing planned and unplanned airway scenarios that may challenge the members of a multidisciplinary team is worthwhile. Such programs include, for example, the "Multidisciplinary Airway Rapid Response Team" (MAART), which, when activated, brings personnel with requisite expertise and special equipment to the scene of an airway emergency. This higher level of emergency response is beneficial for patients who have been previously identified as having a difficult airway. Patients who have been deemed "difficult" receive a special bracelet and are specifically identified in the electronic medical record. In addition, the "MAART" can be activated whenever there is difficulty securing an airway, even when the difficult airway designation has not been made previously. Furthermore, patients who are deemed high risk are so labeled following intubation, creating an opportunity for planning an "extubation" protocol. These patients have a sticker placed on their ET tube pilot balloon, and chart documentation defines the circumstances, personnel, and protocols needed for extubation.

Finally, since tracheostomy is such a frequent trigger of airway emergencies, use of tracheostomy "cards" should be considered as a way of indicating the type and timing of tracheostomy (open or percutaneous) or laryngectomy. This approach was pioneered in the United Kingdom and incorporates a first- and expert-responder algorithm to help manage acute emergencies.[32,33]

FAILED AIRWAY MANAGEMENT AND EMERGENCY FRONT-OF-NECK ACCESS

The first-line surgical airway for the "cannot oxygenate/ventilate, cannot intubate" scenario is to perform a cricothyroidotomy. The procedure is faster and safer than emergent tracheostomy, as long as the patient's pathology is not subglottic in location. Cricothyroidotomy also has a lower complication rate than emergent tracheotomy.[34] Ideally, if the procedure becomes necessary, the airway team has already been activated. Oxygenation should be given at 100% concentration and placement of an LMA attempted while front-of-neck access is being secured. The neck is extended, and the cricothyroid membrane is palpated using a laryngeal "handshake" (Fig. 145-16 Upper Panel). When the anatomy is not clear, a vertical incision is made over the membrane down to the larynx to avoid anterior jugular veins; care must be exercised to avoid incising thyroid tissue. A horizontal incision is then made through the cricothyroid membrane, and the scalpel is rotated 90 degrees so the tip of the blade is toward the patient's feet (Fig. 145-16 Lower Panel).[35] Bleeding may occur from the cricothyroid artery, but it should not prevent airway entry. The incision is then held open, which may facilitate tamponade of any bleeding that does occur, and an endotracheal tube is placed, ideally over a bougie or tube exchange catheter, if available. The cuff is inflated, and ET tube placement is confirmed with auscultation, capnography, and observation of patient chest rise. Bronchoscopy should be considered in assuring that the tube is situated just above the carina. If the cricothyroid membrane is not easily palpable, the vertical skin incision should be longer, and palpation of the membrane repeated, once it is exposed.

Ultrasound provides a quick, portable way to evaluate the airway, and it may be helpful in guiding difficult surgical airway access.[36,37] In cases of large laryngeal masses, where there may also be obstruction at the subglottic or tracheal levels, the preferred emergency surgical airway may be tracheostomy. Additionally, relative contraindications to cricothyroidotomy include age younger than 10 years, severe neck trauma, expanding hematoma, and preexisting laryngeal disease, such as cancer with subglottic extension. Under these circumstances, a planned urgent, rather than emergent, tracheostomy is preferred. Emergency tracheostomy has a high incidence of complications. For patients who have had prior tracheostomy, incision through the scar and use of a Kerrison rongeur to enlarge the tracheal opening may be safer than uncontrolled lateral dissection in scar tissue, which may cause excessive bleeding.

In general, emergency cricothyroidotomy should be converted to a tracheostomy as soon as the patient is stable enough for transfer to the operating room. While there may be a role for decannulation in some patients (if it can be done within a few days), rather than conversion (assuming reasonable confidence that the procedure was done correctly), there is some risk of laryngeal complications from this approach. This is especially true if the original procedure was done emergently and performed by a less experienced operator.[38] Notably, elective cricothyroidotomy for oral, pharyngeal, and laryngeal procedures and for head and neck trauma has been largely abandoned in favor of elective tracheostomy.

TRACHEOSTOMY: HISTORY AND INDICATIONS

The standard of care for establishing an elective surgical airway is tracheostomy. The procedure is indicated for patients who have the need for prolonged mechanical ventilation or in whom upper airway obstruction is anticipated for at least 7 to 10 days. Classic examples of its use for airway obstruction include supraglottic infection or tumor, obstructive sleep apnea, angioedema, and bilateral vocal cord paralysis; however, many of these conditions can be managed without tracheostomy. The procedure is also used in facial trauma when surgery is required and where neither oral nor nasal tubes can be safely secured. Finally, tracheostomy is sometimes used to manage chronic aspiration.

Practically speaking, the terms *tracheostomy* and *tracheotomy* are interchangeable. However, strictly speaking, distinction arises with procedures that intentionally create more permanent stomas. While tracheostomy is performed during partial laryngectomy, the preferred term for tracheal access performed during a total laryngectomy is tracheostomy or *laryngectomy stoma*. Important to note is that patients who have a total laryngectomy stoma cannot be ventilated, oxygenated, or intubated through the mouth or nose, since the trachea is sutured directly to the skin. This represents a critical issue that must be recognized during airway emergencies.

Tracheostomy, although recognized as far back as the time of the ancient Egyptians, did not become a routine surgical procedure until the late 19th century. In 1909, Chevalier Jackson published a landmark work that defined what we know as the current indications for the technique and postoperative management.[39] Most tracheostomies are performed on critically ill, intubated patients. Tracheostomy and removal of the endotracheal tube decreases the risk of long-term laryngeal complications, decreases the need for sedation in mechanically ventilated patients, aids patient liberation from mechanical ventilation, and facilitates initiation of oral intake and phonation. Percutaneous tracheostomy has rapidly become the method of choice in the intensive care unit and is associated with acceptable intraoperative and postoperative complication rates when performed by experienced individuals in the correct context. While open tracheostomy at the bedside is feasible, percutaneous tracheostomy is the most commonly utilized technique in most institutions. Its major benefit is elimination of the need to transport critically ill patients to the operating room.

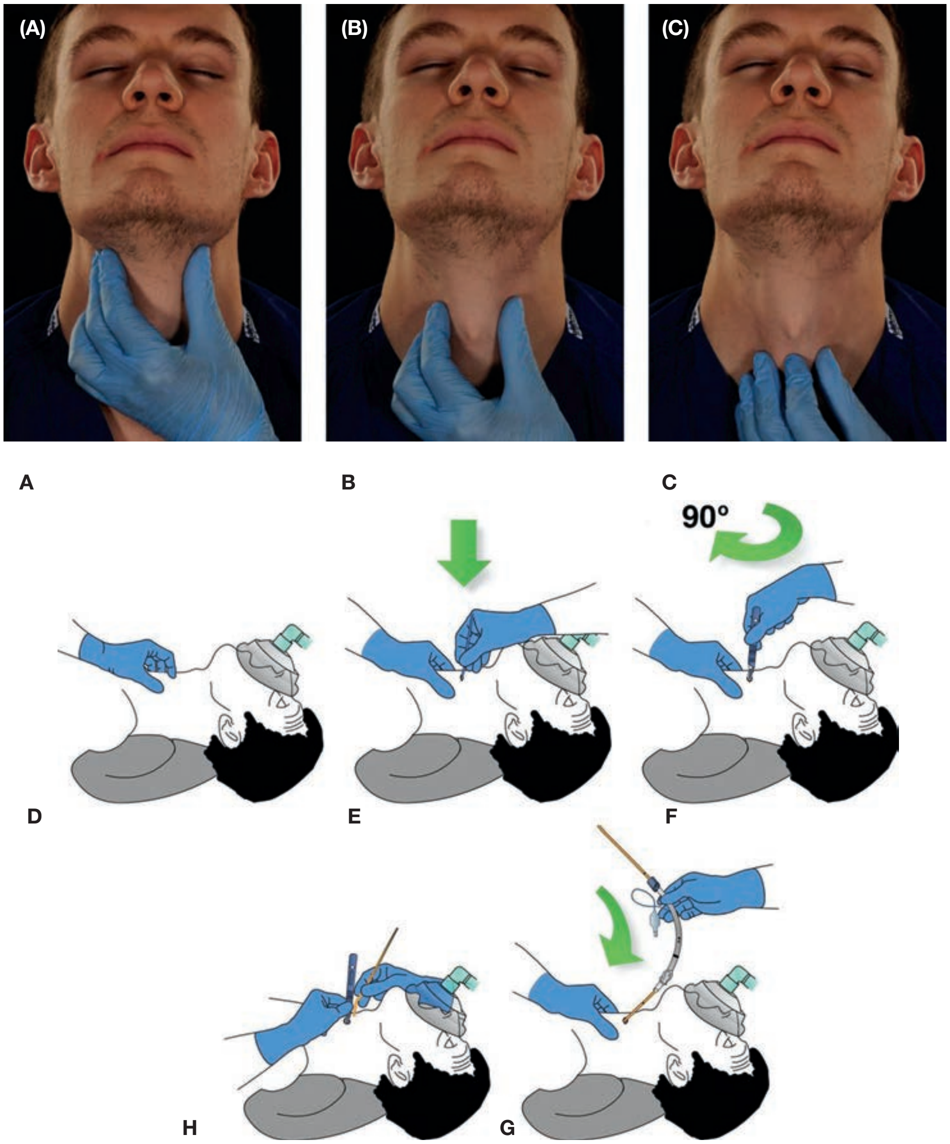

Figure 145-16 **Upper Panel.** The laryngeal handshake. **A.** The index finger and thumb of the nondominant hand grasp the top of the larynx and roll it from side to side. **B.** The fingers and thumb slide down over the thyroid laminae. **C.** Middle finger and thumb rest on the cricoid cartilage, with the index finger palpating the cricothyroid membrane. **Lower Panel.** Cricothyroidotomy technique. **D.** If the cricothyroid membrane can be palpated as in the upper panel: **E.** A horizontal scalpel incision is made through skin and cricothyroid membrane with blade facing towards operator. **F.** Scalpel is rotated 90 degrees towards the feet. **G.** The belly of the blade is used to stent the incision open by pulling towards operator to allow the bougie to slide along the medial aspect of the blade into the trachea. **H.** The tube is inserted into the trachea over the bougie. Note: If the cricothyroid *cannot* be palpated, as shown in the upper panel, an 8- to 10-cm incision is made in the midline and the laryngeal handshake performed after blunt dissection in order to identify the larynx. *(Reproduced with permission from Frerk C, Mitchell VS, McNarry AF, et al. Difficult Airway Society 2015 guidelines for management of unanticipated difficult intubation in adults. Br J Anaesth. 2015;115(6):827–848.)*

In December 2011, the American Academy of Otolaryngology–Head and Neck Surgery developed a series of consensus statements regarding tracheostomy, to which the reader is referred. Many are described below. A great deal of work is yet to be done in standardizing the perioperative care of patients with tracheostomies.

OPEN TRACHEOSTOMY

Open tracheostomy is defined as a tracheostomy in which the incision is made as the initial step. The incision may be vertical or horizontal, and it may require modification if done in a patient with an existing scar from prior surgery, including prior tracheostomy. The patient's neck should be extended, and the major landmarks palpated (including thyroid cartilage, cricoid cartilage, and sternal notch). A horizontal incision is preferred if the procedure is not urgent. In general, the incision should be approximately 5 mm to 1 cm below the level of the cricoid cartilage and approximately 2 cm above the sternal notch. The length is determined by the estimated depth of the cricoid, but it usually is about 2 to 3 cm.

Most of the time, the procedure is performed with the patient intubated and under general anesthesia. The skin and subcutaneous tissues are divided, and then the fascia dividing the strap muscles is incised vertically to expose the cricoid cartilage. Care should be taken to avoid the anterior jugular veins, which may sometimes be quite close to the midline. Often the thyroid isthmus lies in close proximity; most prefer to divide it with cautery to avoid subsequent obstruction of the airway if accidental decannulation occurs. A cricoid hook may be used to elevate the larynx. The soft tissue in the pretracheal area is divided and then bluntly dissected using a

Kittner. Bleeding is controlled using cautery, as needed. Ideally, the first three tracheal rings are exposed. Our preference is to perform a Bjork-style flap in most cases of open tracheostomy.

Once we are prepared to enter the airway, we alert the anesthesiology team. The tape or suture that secures the endotracheal tube is divided and the cuff is deflated. It is preferable to decrease the flow of oxygen in the event cautery is required again after the airway is entered. The tube may be advanced beyond the site of entry, or the incision may be made with the cuff deflated to avoid injuring the cuff. By pushing the tube cuff distal to the tracheostomy site, the cuff may be reinflated so that ventilation may resume during preparation of the Bjork flap. The Bjork flap is created by incising between the second and third tracheal rings; the inferiorly based tracheal ring flap of the third ring is created by making lateral cuts. Care should be taken to avoid going too far laterally with the lateral cuts to avoid an unstable trachea and, potentially, creation of an "A-frame" deformity that can lead to tracheal stenosis. The inferiorly based tracheal ring flap is then secured to the inferior skin using a single absorbable suture. This reduces the risk of a false passage in the event of accidental decannulation postoperatively, requiring urgent tube reinsertion. In our experience, the risk of tracheocutaneous fistula is very low, and most stomas heal after decannulation unless the stoma has been irradiated.

Subsequently, the cuff is again deflated, the tube is pulled back so that the tip is just visible above the tracheostomy site, and a cuffed tracheostomy tube is placed. The inner cannula is inserted, the tracheostomy cuff inflated, the ventilator connected, and adequate ventilation confirmed before the endotracheal tube is removed from the larynx. Finally, the tube is secured bilaterally, both superiorly and inferiorly, with permanent sutures from the skin to the tracheal tube flange; a tracheostomy tie is placed.

In case of prior tracheostomy, surgical identification of the cricoid may be difficult, and creation of a Bjork flap may be challenging. However, the scar over the trachea generally leads directly to the airway, so one useful technique is performing the procedure as technically similar to what was described above. If the trachea is entered at the site of prior tracheostomy and further dissection is difficult, a Kerrison rongeur can be used to safely enlarge the opening to allow insertion of the tube, without risking extensive dissection into scar tissue.

If the procedure is performed under local anesthesia, for example, in the setting of a marginal airway, use of a clear head frame to preclude the surgical drape from directly covering the patient's head allows the anesthesiologist to communicate with the patient, to titrate sedation safely, and to provide feedback to the surgeon. Local injection of lidocaine with epinephrine is employed for the procedure (which may also be done under general anesthesia in order to minimize oozing); the injection may need to be repeated once deeper dissection is performed, so additional local anesthesia should be on the surgical field. Use of topical transtracheal anesthesia greatly facilitates the procedure by suppressing excessive coughing. In children, a Bjork flap should be avoided to minimize the tracheal incision. In general, a small incision should be made and stay sutures used instead. The size of the tracheostomy tube varies and is circumstance-dependent. In most cases, we utilize a #6 cuffed tube in adults.

PERCUTANEOUS TRACHEOSTOMY

Percutaneous technique for tracheostomy is an alternative for adults. The procedure should be performed by experienced practitioners using bronchoscopic guidance. The main contraindication for the procedure is severe clinical instability, when bronchoscopy is not tolerated. In patients with coagulopathy, open tracheostomy is usually favored. Morbid obesity is considered by many as a relative contraindication for percutaneous tracheostomy, as is suspicion of cervical spine instability. In such cases, concern about eventual accidental decannulation may lead the team to choose an open technique and a more secure airway, such as a Bjork flap or an "epithelial-lined" tracheostomy.

POSTTRACHEOSTOMY COMPLICATIONS AND MANAGEMENT

In a survey of the American Academy of Otolaryngology–Head and Neck Surgery, 478 members responded to inquiries regarding 4 specific complications of tracheostomy. In all, 66% of "catastrophic" events involved loss of airway or bleeding; 34% were specifically related to loss of the airway. Accidental decannulation occurred much more frequently than loss of airway during planned tracheostomy change (nearly 90% were the former). A total of 32% were related to major bleeding, and more than 90% of these were specified as tracheoinnominate fistulae (TIF). TIF was more common in the pediatric population. Fourteen percent of the events involved obstruction of the tube. Authors of the study reported a "very approximate" annual estimate of 1000 such events, with about half of these causing death or permanent morbidity. The overwhelming majority of events occurred more than 7 days following tracheostomy.

Other complications should be noted, although they are less frequently "catastrophic."[40] For example, pneumothorax is rare, but a postprocedure chest radiograph should be performed in all patients. Many airway occlusive events can be managed with suctioning, and such events are the most frequent cause of tracheostomy-related emergencies. In our experience, most bleeding events are self-limited. However, worth noting is the role of CT angiography based on the findings from a flexible fiberoptic examination. False passage and decannulation also occur, particular in obese patients; prevention is better than management. Esophageal injury (i.e., tracheoesophageal fistula) is a rare but catastrophic complication that should be considered in patients who have postoperative dysphagia or aspiration. Tracheostomy, itself, may promote aspiration by tethering the larynx or decreasing the cough reflex by limiting subglottic pressure, especially when associated with laryngeal injury, tracheal stenosis, or recurrent laryngeal nerve paralysis. Tracheocutaneous fistula is a long-term complication that can usually be avoided by using a meticulous decannulation technique: downsizing the tracheostomy tube, capping the tube, taping the tracheostomy stoma, and instructing the patient on tracheostomy tube occlusion during speech and coughing while the stoma is healing. When tracheocutaneous fistula is persistent, repair can usually be done with local tissue and, if possible, a staggered three-layer repair technique.

AEROSOL-GENERATING PROCEDURES AND CONTAGION

Experience with virus outbreaks such as MERS, SARS, and COVID-19 have demonstrated that aerosol-generating procedures (AGPs) carry a high risk of viral transmission to clinicians. Fiberoptic inspection of the airway, mask ventilation, intubation, and creation of a surgical airway all constitute AGPs.[41] Best practices with regard to AGP and virus transmission continue to evolve from the lessons learned during the COVID-19 global pandemic.[42] Important considerations include use of personal protective equipment, proper patient room ventilation (e.g., negative pressure), limitation of the number of staff in the room, communication strategies employed during emergencies, and efforts at minimization of potential aerosol dispersion that can occur during laryngoscopy, mask ventilation, or ventilator circuit disconnects.[42] Critically important is that clinicians have the opportunity to become familiar with new processes, protocols, and equipment through dress rehearsals and simulation. Of course, the best practice for a given environment will need to be tailored to local resources and experience.

CONCLUSIONS

Many considerations are important to effective upper airway management. The astute clinician has a foundational knowledge of upper airway anatomy, airway assessment rubrics to predict management difficulty, access to the latest technology to facilitate intubation, and a willingness to endorse a team approach to safety. Communication effectiveness is as crucial to safe airway management as are equipment readiness and technical skills. A rigorous approach to chart review and airway planning is also critical to success.

A range of effective approaches to upper airway management exists, and the expert will have sufficient familiarity and experience with each to allow for adaptation to the unique clinical circumstances of the patient. At times, airway consultants may be needed to provide unique skills and equipment in airway assessment, management, or rescue. These skills include familiarity with emergency front-of-neck access, as well as an ability to assess and rescue the patient with an in-situ tracheostomy or laryngectomy. A well-defined, systems-based approach to activate additional expertise and specialized equipment, when needed, is preferred to an ad-hoc system.

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CHAPTER 146

Hemodynamic and Respiratory Monitoring in Acute Respiratory Failure

Hari M. Shankar
Brian J. Anderson

INTRODUCTION

Acute respiratory failure (ARF) accounts for a substantial portion of intensive care unit (ICU) admissions. Patients receiving invasive mechanical ventilation, as well as those receiving noninvasive respiratory support, such as high-flow nasal cannula and noninvasive positive-pressure ventilation, are at risk for hemodynamic and further respiratory decompensation. Therefore, close monitoring is necessary to identify early signs of instability and to allow for prompt intervention to prevent morbidity and mortality.

The primary goals of monitoring include ensuring adequate circulatory function, ensuring adequate ventilation and oxygenation, detecting the mechanisms of circulatory or respiratory decompensation when they occur, providing surveillance for common complications associated with noninvasive and invasive respiratory support, evaluating hemodynamic and respiratory responses to therapeutic interventions, and watching the trajectories of hemodynamic and respiratory disorders over time to gain insight into a patient's prognosis.

Given the myriad forms of physiologic monitoring available to the modern clinician, many considerations should be taken into account when deciding which monitoring parameter and system to use. First, clinicians should select parameters and systems that have proven accuracy for the specific patient and clinical scenario. Second, clinicians should take into consideration the level of comfort and expertise that the entire clinical team has with the chosen monitoring system. Even the most precise and advanced monitoring system can lead clinical teams astray if they lack the expertise to appropriately interpret and act upon the data it provides. Third, and most important, physiologic monitoring data should not be evaluated in isolation, as reliable interpretation of data necessitates review of multiple data sources in a collective fashion at a single time point, as well as review of trends in data over time.

This chapter reviews the various parameters and methods available for hemodynamic and respiratory monitoring in patients with ARF.

HEMODYNAMIC MONITORING

In this section, we review noninvasive and invasive methods for hemodynamic monitoring in patients with ARF. Respiratory monitoring is detailed in a subsequent section of this chapter.

Hemodynamic assessment is a vital component of caring for critically ill patients. In addition to alerting clinicians to early signs of hemodynamic decompensation, it can provide important diagnostic information on the cause of the patient's respiratory failure, including differentiation between cardiogenic and noncardiogenic pulmonary edema—a distinction that has clear therapeutic implications.

Hemodynamic monitoring is also vital in identifying untoward effects of positive-pressure ventilation on the cardiovascular system. Positive-pressure ventilation increases intrathoracic pressure, decreases venous return, and increases pulmonary vascular resistance, thereby potentially reducing right ventricular cardiac output and causing right ventricular dilatation. In certain patients, these effects can impair left ventricular filling if the impaired right ventricular function and cavity dilatation cause the interventricular septum to impinge on the left ventricle due to ventricular interdependence. Positive-pressure ventilation may lead to an overall summative reduction in cardiac output and, in rare circumstances, such as in patients with severe pre-existing right ventricular dysfunction or pulmonary hypertension, may lead to cardiovascular collapse.

Below we discuss electrocardiogram monitoring, noninvasive and invasive blood pressure monitoring, invasive central venous monitoring, cardiac and thoracic echocardiography, and novel cardiac output monitoring systems.

Electrocardiogram Monitoring

A continuous bedside electrocardiogram (ECG) is a common function of bedside monitors in the intensive care unit. The bedside ECG generally involves 3 to 5 leads, as opposed to the standard 12 leads, and provides a method for measuring heart rate and assessing heart rhythm.

Heart rate (HR) is, perhaps, the simplest hemodynamic parameter to monitor. However, despite its simplicity, its relationship to cardiac output mandates that it not be overlooked. Tachycardia is one of the earliest compensatory responses to volume depletion and can alert clinicians to hypovolemia well in advance of a change in blood pressure. Bradycardia may occur as a result of medications commonly used in patients with ARF, most notably propofol and dexmedetomidine; clinicians need to ensure an adequate cardiac output is maintained when patients develop bradycardia while these medications are administered. Similar assurance must be sought in patients with elevated HR, as tachycardia may impair cardiac filling and compromise cardiac output. Unfortunately, most bedside monitors do not display trends in HR. Therefore, clinicians should use electronic or bedside flow sheets to assess for changes in HR over time.

The continuous ECG also provides a method to monitor heart rhythm and can alert bedside clinicians to arrhythmias. Atrial fibrillation is the most common arrhythmia in critically ill patients, occurring in an estimated 10% to 40% of patients during their ICU stay.[1–4] Although most cases occur in patients with preexisting atrial fibrillation, approximately 5% to 25% of patients develop new onset of the arrhythmia as part of their critical illness.[1,2,4–6] Risk factors for new-onset atrial fibrillation include increased age, underlying cardiovascular disease, sepsis, shock, use of vasopressors or inotropes, severe illness, and heart failure.[2–7] Patients with new-onset atrial fibrillation have higher rates of renal replacement therapy (RRT) and mechanical ventilation, longer ICU and hospital lengths of stay, and higher mortality.[1,3–6,8] In critically ill patients with sepsis, new-onset atrial fibrillation has also been linked to a higher rate of in-hospital stroke and subsequent heart failure.[8,9]

Blood Pressure Monitoring

Blood pressure (BP) is a core hemodynamic parameter monitored in critically ill patients.

General Principles

Mean arterial pressure (MAP) is the most commonly used blood pressure variable in managing critically ill patients. A target MAP goal >60 to 65 mm Hg has historically been suggested and is recommended by societal guidelines.[10,11] Below this target, autoregulatory mechanisms that protect regional perfusion may fail, and blood flow becomes entirely dependent on pressure. Observational studies have similarly linked the amount of time spent below a MAP of 60 to 65 mm Hg with worse outcomes, including higher mortality and need for RRT.[12–15] However, arterial hypertension has been shown to shift the autoregulatory curve higher,[16] and some observational studies have suggested that higher MAP targets (75–85 mm Hg) are necessary to avoid kidney injury.[14,17] Prospective studies targeting higher MAP targets have been mixed.

Nonrandomized studies targeting a MAP of 75 to 85 mm Hg using higher doses of vasopressors demonstrated an increase in cardiac output and oxygen delivery but did not demonstrate improvements in tissue perfusion as measured by serum lactate, capillary blood flow, urinary output, or renal function.[18–20] More recently, two randomized controlled trials evaluated higher MAP goals (75–85 mm Hg) primarily in patients with septic shock.[21–23] Overall, there was no difference in mortality, and patients randomized to the higher MAP target had a greater rate of new-onset atrial fibrillation and a longer duration of vasopressor use; notably, they did not appear to have a longer ICU length of stay.[21–23] Interestingly, both studies and a subsequent patient-level pooled analysis revealed significant differences in specific subgroups. Among patients with chronic hypertension, the higher MAP target was associated with a lower risk of acute kidney injury and RRT.[21] Alternatively, mortality was higher in patients receiving vasopressors for >6 h prior to enrollment and in older patients randomized to the higher MAP target.[22,23]

Based on these data and consensus guidelines, an initial MAP of 65 mm Hg or higher should be targeted for most patients with ARF. Patients with chronic hypertension can be considered for a higher MAP goal, particularly if there is concern for concurrent renal injury. Although data are sparse, patients with cirrhosis with a baseline low MAP may achieve adequate perfusion at a lower MAP goal.[24]

Methods of Blood Pressure Measurement

Four methods for BP measurement are used primarily, including three intermittent, noninvasive methods and one invasive continuous method. Intermittent methods utilize an inflatable cuff and can be performed manually using the palpatory or auscultatory methods, or with an automated oscillometric device. Continuous BP measurement involves an intra-arterial catheter that provides beat-by-beat measurement as well as arterial blood sampling capabilities.

With the palpatory method, only a BP cuff with a sphygmomanometer is required. The cuff is inflated while the radial pulse is palpated, and when the pulse can no longer be palpated the cuff is slowly deflated until the pulse can again be palpated. The pressure at which the radial pulse returns corresponds to the systolic blood pressure (SBP). Despite providing only SBP, the palpatory method may be useful in emergencies when equipment is limited, or in noisy environments when the auscultatory method can be challenging.

For the auscultatory method, both a BP cuff with a sphygmomanometer and a stethoscope to detect the characteristic Korotkoff sounds are required. The cuff is inflated above the anticipated SBP, confirmed by an inability to palpate the radial pulse, and the stethoscope is placed distal to the cuff on the upper arm over the brachial artery while the cuff is slowly deflated. The onset of Korotkoff sounds corresponds to the SBP and the disappearance of the sounds corresponds to the diastolic blood pressure (DBP). The auscultatory method is preferred over the palpatory method, given that it provides both systolic and diastolic pressures and thus provides the possibility of calculating the MAP using the formula:

$$MAP = (1/3 \times SBP) + (2/3 \times DBP)$$

Although manual BP measurement is still used in clinical practice, automated BP measurement has become the norm due to the frequency of measurement required in critically ill patients and the widespread availability of oscillometric devices. Similar to the manual methods, oscillometric devices utilize a cuff that is inflated until it exceeds the SBP and is then slowly deflated while sensing the return of blood flow. These devices detect oscillations that occur with the return of flow, and the maximum amplitude of these oscillations corresponds to the MAP.[25] SBP and DBP are subsequently calculated using algorithms that are generally proprietary for each device.[25] Oscillometric devices are time-saving, and in most circumstances, provide an accurate and reproducible measurement of MAP. Although uncommon, excessively frequent measurements using an automated device may lead to complications, including bruising, petechiae, pain, limb edema, or peripheral neuropathy.

BP measurement using an intra-arterial catheter (commonly referred to as an "arterial line" or "a-line") is considered the gold standard for determining arterial blood pressure. The radial artery is the most common site for catheter placement, followed by the femoral artery. Less common sites include the brachial, ulnar, and dorsalis pedis arteries. Once inserted, the arterial catheter is connected to fluid filled tubing, which is connected to a pressure transducer that converts pressure changes in the tubing into an electrical signal from which a pressure waveform is generated. Arterial lines provide direct measurement of SBP and DBP, whereas MAP is calculated by integrating the area under the pressure waveform during a single beat and is usually averaged over a specific time period.

Indications for continuous invasive BP monitoring include difficulty with obtaining accurate noninvasive measurements; shock or need for titration of vasopressor medications, especially when patients do not respond to initial therapy; and a requirement for frequent laboratory testing, including frequent arterial blood gas sampling. Although invasive BP monitoring was shown to increase detection of hypotension and resulted in more frequent intervention for hypotension in one intraoperative study, a paucity of data exists linking invasive BP monitoring with clinical outcomes. In addition, arterial lines are not without risk.[26]

Common complications of arterial lines include pain, swelling, bruising, hematoma formation, and minor bleeding. Thrombosis is uncommon in the femoral artery, but relatively common in peripheral arteries, with nonocclusive thrombosis occurring in up to 60% of radial arterial lines and occlusive thrombosis in 15% to 30% of radial arterial lines.[27–30] Although usually not clinically significant, thrombosis can lead to limb ischemia in rare cases. Risk factors for thrombosis include arterial spasm at the time of catheterization, larger catheters, smaller vessels, peripheral vascular disease, and longer duration of arterial cannulation.[27–29,31–33] The rate of arterial catheter-related blood stream infection has been reported to range from 1.0 to 1.7 per 1000 catheter-days, a rate that is similar to antimicrobial-coated short-term central venous catheters commonly used in critically ill patients.[34–36] Higher infection rates have historically been reported with femoral artery catheters, although recent studies have shown higher rates of colonization but not infection, suggesting that modern infection-prevention practices may have improved infection rates for femoral arterial lines.[35,37,38] Rare but severe complications of arterial lines include air embolism, pseudoaneurysm, arteriovenous fistula formation, and retroperitoneal hemorrhage (with femoral site cannulation).

Accuracy of Blood Pressure Measurement Methods

The two most common methods for BP measurement in critically ill patients, oscillometric and intra-arterial, are both prone to measurement error that may have a clinically significant impact.

The most common source of error with oscillometric BP measurement is an inappropriate cuff size. Cuffs that are too large will produce falsely low oscillometric readings and thus underestimate the MAP, whereas cuffs that are too small will produce falsely high readings and overestimate MAP. Oscillometric measurement can also be impacted by a shivering patient, arrhythmias, or severe hypotension. The accuracy of oscillometric BP measurements when measured at sites other than the upper arm is poor in critically ill patients and should be interpreted with caution.[39]

For intra-arterial BP measurement, improper leveling of the transducer may introduce error, and clinicians must ensure the catheter has been correctly "zeroed" before interpreting values. Assessment of the quality of the arterial waveform is also critical prior to interpreting values. The two main artifacts that can alter the arterial wave form are underdamping and overdamping (Fig. 146-1).[40] With underdamping, the arterial waveform overestimates SBP, underestimates DBP, and overestimates pulse pressure (PP). Causes of underdamping include overly stiff tubing, excessive tubing length, tubing connected with multiple stopcocks, or a defective transducer. Alternatively, overdamping results in underestimation of SBP, overestimation of DBP, and underestimation of PP. Overdamping can occur due to air bubbles or clots in the tubing, loose connections, kinked tubing, and low pressure in the infusion bag. The degree of damping can be assessed using the *fast-flush test* and calculating the damping coefficient, although in clinical practice the fast-flush test is usually simply inspected visually. Normally, with a "snap" flush of the arterial line, a square wave tracing is generated, followed by a single oscillatory wave; more than one oscillation indicates underdamping, while the absence of any oscillations indicates overdamping. Underdamping is the most common in clinical practice, occurring in up to 30% of patients, and is particularly common in patients with hypertension or chronic obstructive pulmonary disease.[41]

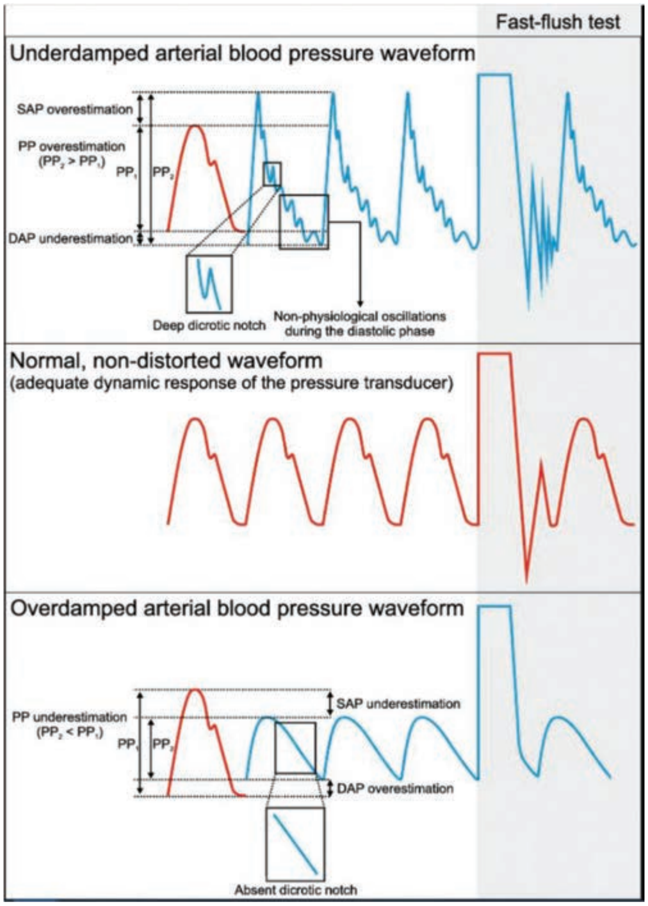
Fast-flush test
Underdamped arterial blood pressure waveform
SAP overestimation
PP overestimation
($PP_2 > PP_1$)
PP_1
PP_2
DAP underestimation
Deep dicrotic notch
Non-physiological oscillations during the diastolic phase
Normal, non-distorted waveform
(adequate dynamic response of the pressure transducer)
Overdamped arterial blood pressure waveform
SAP underestimation
PP underestimation
($PP_2 < PP_1$)
PP_1
PP_2
DAP overestimation
Absent dicrotic notch

Figure 146-1 Arterial waveforms and flush test for a normal arterial waveform *(middle)*, underdamped arterial waveform *(top)*, and overdamped arterial waveform *(bottom)*. Underdamping may be suggested by a deep dicrotic notch or nonphysiologic oscillations in the diastolic runoff phase. Underdamped waveforms overestimate systolic blood pressure, underestimate diastolic blood pressure, and overestimate pulse pressure. Overdamping may be suggested by a slurred systolic upstroke and absence of the dicrotic notch. Overdamped arterial waveforms underestimate systolic blood pressure, overestimate diastolic blood pressure, and underestimate pulse pressure. *(Reproduced with permission from Saugel B, Kouz K, Meidert AS, et al. How to measure blood pressure using an arterial catheter: a systematic 5-step approach. Crit Care. 2020;24(1):172.)*

In general, when performed correctly, MAP correlates well between oscillometric and intra-arterial measurements across a relatively wide range of pressures. However, oscillometric devices tend to overestimate SBP at low values and underestimate SBP at high values when compared to intra-arterial measurement,[42–47] and the difference may be greater than 10 mm Hg up to 50% of the time.[43] Importantly, the overestimation of SBP is more pronounced in hypotensive patients and in patients receiving vasopressors, which may falsely reassure clinicians.[42,43,45] Lastly, small studies have suggested that oscillometric devices may significantly underestimate both MAP and SBP in obese patients.[47,48]

In summary, routine noninvasive monitoring of MAP using an oscillometric device is appropriate for most hemodynamically stable patients, and invasive BP monitoring should be considered in patients with severe hypotension or severe hypertension; in patients receiving vasopressors, especially if they are not responding to initial therapy; and in obese patients.

■ Invasive Central Venous Monitoring

Central venous catheters (CVCs) are frequently inserted in critically ill patients, particularly in patients with concurrent shock. CVCs are used for vasopressor infusion, central venous pressure measurement, and measurement of central venous oxygen saturation. In select circumstances, pulmonary artery catheters may be used to measure mixed venous oxygen saturation, pulmonary artery pressures, and pulmonary occlusion (wedge) pressure.

Central Venous Pressure

Central venous pressure (CVP) represents the blood pressure in the vena cava and is a good approximation of right atrial pressure; hence, it can be used to estimate right ventricular preload. CVP can be measured by connecting one of the CVC lumens to a pressure transducer and, similar to arterial lines, the transducer must be appropriately leveled and zeroed. Clinicians must also have experience interpreting the CVP waveform, as CVP should generally be measured at the base of the *c* wave at end-expiration (Fig. 146-2).

In patients with shock, CVP may be helpful in differentiating the underlying pathophysiology. Distributive and hypovolemic shock may be associated with a low CVP, whereas obstructive shock may be associated with a high CVP. However, these are generalizations, and clinicians need to interpret the CVP in the broad context of the patient's presentation. The CVP waveform may also be useful for identifying specific cardiac disorders. A large *v* wave is suggestive of tricuspid regurgitation and may be seen in patients with right ventricular failure. An attenuated *y* wave descent may be seen in cardiac tamponade, whereas a prominent *y* wave descent may be seen in pericardial restriction or right ventricular overload.

CVP has historically been used to guide fluid resuscitation; however, numerous studies have demonstrated that CVP is a poor marker of fluid responsiveness, and consensus guidelines recommend against using static measures like CVP to assess the likelihood of fluid responsiveness, favoring use of dynamic variables.[10,11] Although CVP can be elevated in patients with left ventricular failure and pulmonary edema, ARF and positive-pressure ventilation (and, especially, positive end-expiratory pressure) may increase pulmonary vascular resistance and impair right ventricular function,

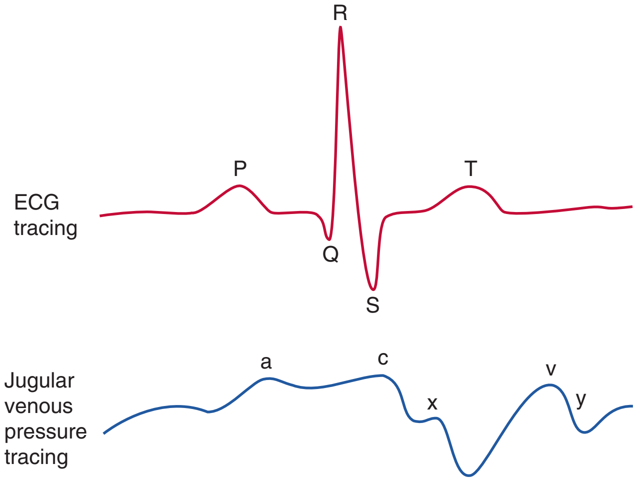

Figure 146-2 CVP waveforms. Since there are no valves between the vena cava and the right atrium, central venous pressure waveform reflects the events of cardiac contraction. Simultaneous display of the ECG allows one to identify and time the CVP waveform. **a wave.** Increased atrial pressure during right atrial contraction. It occurs following the P wave on an ECG. **c wave.** During early ventricular contraction the tricuspid valve bulges into the right atrium. It occurs at the end of the QRS segment on an ECG. **x descent.** Atrial relaxation. It occurs before the T wave on an ECG. **v wave.** Atrial filling—the right atrium progressively fills while the tricuspid valve is closed. It occurs at the end of the T wave on an EKG. **y descent.** Following opening of the tricuspid valve in diastole, the atrium empties as blood flows into the right ventricle. It occurs before the P wave on an ECG.

resulting in a high CVP and making CVP by itself insufficient to differentiate cardiogenic from noncardiogenic pulmonary edema.

Venous Oxygen Saturation

Shock is defined as global tissue hypoxia and occurs as a result of an imbalance between oxygen delivery and oxygen demand. Under normal physiologic conditions, oxygen demand and oxygen delivery are well matched. When oxygen demand increases, the higher demand is first mitigated by an increase in cardiac output. When the oxygen demand cannot be met by an increase in cardiac output, an increase in oxygen extraction occurs at the tissue level. Once these compensatory mechanisms are overwhelmed, shock and anaerobic metabolism ensues.

Because most of blood oxygen is bound to hemoglobin, the oxygen saturation of blood returning to the lungs provides a surrogate measure for the adequacy of global oxygen delivery. The oxygen saturation of blood in the pulmonary artery is referred to as the mixed venous oxygen saturation (Sv_{O_2}) and, under normal circumstances, ranges from 65% to 75%. Lower Sv_{O_2} values, particularly values below 50%, suggest inadequate oxygen delivery compared to oxygen demand (i.e., shock). High Sv_{O_2} values can be seen in patients with poor oxygen extraction, including patients with septic shock, or in high cardiac output states.

In addition to providing an assessment of global oxygen adequacy, Sv_{O_2} can be used to estimate cardiac output and cardiac index, using the Fick equation:

$$CO = V_{O_2}/(Ca_{O_2} - Cv_{O_2})$$

where CO is cardiac output, V_{O_2} is oxygen consumption, Ca_{O_2} is arterial oxygen content and Cv_{O_2} is venous oxygen content. Oxygen content is calculated as:

$$C_{O_2} = (1.34 \times [Hgb] \times \%\ Hgb\ saturation) + 0.003 \times P_{O_2}$$

where $[Hgb]$ is the hemoglobin concentration and P_{O_2} is the partial pressure of oxygen. Once calculated, cardiac index can be calculated using the formula:

$$CI = CO/BSA$$

where BSA is the patient's body surface area.

In general, monitoring Sv_{O_2} is superior to monitoring cardiac output because inadequate oxygen delivery can occur despite a normal or elevated cardiac output. A major barrier to Sv_{O_2} monitoring is that it requires use of a pulmonary artery catheter—a device that has fallen out of favor and is generally reserved for select circumstances, as discussed in the next section. Fortunately, the central venous oxygen saturation (Scv_{O_2}) can often be used as a surrogate for Sv_{O_2} and can be easily measured using a routine CVC in both ICU and non-ICU environments.

Scv_{O_2} measured from the superior vena cava (SVC) has been shown to strongly correlate with Sv_{O_2}, but, on average, is approximately 2% to 8% higher than Sv_{O_2}, thus slightly overestimating global oxygen adequacy.[49–60] Although the Sv_{O_2} – Scv_{O_2} difference is less than 10% in most patients, it can be greater than 10% in up to 30% of patients, with differences as high as 15% to 20% in some cases.[49,55–57,60] A normal Scv_{O_2} (≥70%) is almost always reassuring, with a negative predictive value for a low Sv_{O_2} of 94% to 96%.[51,56] An important limitation of using the SVC Scv_{O_2} is that the Scv_{O_2} – Sv_{O_2} difference may be greater at lower Sv_{O_2} levels when accuracy is most relevant, in patients with hypocapnia, and in patients with elevated intracranial pressure.[55,57,59,61,62] Venous oxygen saturation measured in the right atrium, sometimes denoted Sra_{O_2}, is generally more accurate and has been reported to differ from Sv_{O_2} by only 1% to 3% on average.[49,52,53,58,62]

Pulmonary Artery Catheterization

Historically, pulmonary artery catheters (PACs) were inserted routinely for hemodynamic monitoring in critically ill patients and patients undergoing high-risk surgery.[63] The PAC can provide direct measurements of CVP, right atrial pressure, right ventricular pressure, pulmonary artery pressure, and pulmonary capillary occlusion pressure (PAOP, also referred to as the pulmonary capillary wedge pressure [PCWP]). PACs can also be used to measure cardiac output and mixed venous oxygen saturation, as well as to determine systemic and pulmonary vascular resistances, which can be helpful in differentiating types of shock.

Over the past 20 to 30 years, the use of PACs has become far less common due to higher rates of complications compared with CVCs and numerous clinical trials that failed to demonstrate a clear improvement in outcomes among patients managed with PACs.[64–71] Currently, PACs are mostly reserved for patients with unexplained shock, refractory cardiogenic shock, decompensated pulmonary hypertension, and select patients undergoing high-risk surgery.

When performed, pressures obtained from a PAC may be helpful in differentiating the cause of a patient's respiratory failure if not determined through other means. Elevated right-sided pressures are seen in patients with pulmonary embolism, acute respiratory distress syndrome (ARDS) as a result of hypoxic vasoconstriction, chronic pulmonary hypertension, hypervolemia, and left-sided heart failure. In patients for whom cardiogenic versus noncardiogenic pulmonary edema is being considered, the pulmonary capillary occlusion pressure may be helpful as an estimate of the left atrial pressure, with higher values (>15 to 18 mm Hg) generally suggestive of hydrostatic pulmonary edema.

■ Ultrasonography

Ultrasonography is an essential tool for hemodynamic assessment in patients with respiratory failure and, particularly, patients with concurrent shock. In addition to formal echocardiography, focused bedside cardiac and thoracic ultrasound is increasingly recognized as a valuable tool due to its widespread availability and increasing experience among clinicians. Both echocardiography and thoracic ultrasound can provide diagnostic information to help categorize shock and respiratory failure and can be used to assess for complications of therapy.

Echocardiography

Transthoracic echocardiography (TTE) is generally rapidly available, reliable, provides adequate images for the vast majority of critically ill patients, and is highly sensitive and specific for cardiac causes of shock.[72] A transesophageal echocardiogram (TEE) is generally reserved for patients in whom TTE images were inadequate for the diagnostic question at hand, such as evaluation for atrial thrombus or endocarditis.

Basic critical care echocardiography involves a limited number of standard echocardiographic views, including the parasternal long axis, parasternal short axis, apical four chamber, and subcostal long axis. Although useful as a standalone tool, focused critical care echocardiography does not eliminate the need for standard echocardiography, especially in patients in whom image quality is poor, when confirmation of a diagnosis is required, or when significant valvular disease is under consideration. Common indications for echocardiography in patients with ARF include assessment of left ventricular (LV) function, assessment of right ventricular (RV) function, assessment of fluid status, and evaluation for right-to-left shunting.

LV function and LV size are commonly measured or qualitatively evaluated as part of an echocardiogram. LV systolic and diastolic dysfunction can be seen in patients with ARF due to decompensated left-sided heart failure, and LV systolic dysfunction can also be seen as a result of ischemia, as well as sepsis- or stress-induced cardiomyopathy. Thus, echocardiography can be useful in differentiating the cause of ARF, as well as in assessment for cardiac complications of common forms of critical illness.

RV dysfunction is common in critically ill patients, especially in patients with pulmonary embolism or ARDS.[73] Importantly, RV dysfunction can also be caused by excessive mean airway pressure, as seen in patients treated with high PEEP. In addition to assessing RV function, echocardiography can assess RV dilation and tricuspid regurgitation, which are additional signs of RV overload. Early recognition of RV failure is paramount in critically ill patients, as overresuscitation of a failing RV can lead to further hemodynamic deterioration.

New-onset right-to-left shunting is common in critically ill patients due to the relatively high prevalence of patent foramen ovale in the general population (25% to 30%) and the frequent occurrence of RV dysfunction in critical illness that can ultimately increase right atrial pressure to the point it exceeds left atrial pressure.[74,75] Shunting should be suspected in patients with hypoxemia out of proportion to imaging findings, when hypoxemia fails to respond to higher $\mathrm{Fi}_{\mathrm{O}_2}$, and when hypoxemia fails to improve or worsens with increased PEEP. A right-to-left shunt can be detected by injecting agitated saline through a peripheral or central vein during echocardiography and is commonly referred to as a "bubble study." The appearance of microbubbles in the left atrium within the first three cycles is seen in intracardiac right-to-left shunts, whereas the presence of microbubbles in later cycles is seen in intrapulmonary shunts.

Echocardiography may also be helpful in estimating volume status. The inferior vena cava expiratory diameter and the *inferior vena cava collapsibility index* have been studied as tools to determine fluid responsiveness, as well as to identify patients with heart failure.[76–78] In spontaneously breathing patients, the IVC collapsibility index is calculated as maximum IVC diameter on expiration − (minimum diameter on inspiration/maximum diameter on expiration); in mechanically ventilated patients, the index is known as the *IVC distensibility index* and is calculated as (IVC maximum diameter on inspiration − minimum diameter on expiration)/minimum diameter on expiration. Although studies have shown consistent differences in these metrics according to volume responsiveness and presence of heart failure, specific cut-points of each metric have been shown to be only moderately predictive.[76–78] Therefore, they should not be used in isolation but may be valuable as part of a comprehensive assessment of volume status.

Thoracic Ultrasound

Thoracic ultrasonography is a powerful tool in patients with ARF and can be used to diagnose pulmonary edema, pleural effusions, and pneumothorax. Importantly, simple systematic approaches are available to ensure a thorough examination, and interpretation of thoracic ultrasound requires knowledge of only a handful of characteristic findings.[79,80]

Ribs can be identified as round, hyperechoic structures with distal acoustic shadowing. Just below the rib line, the *pleural line* can be identified as a hyperechoic and sliding, or shimmering, line that represents the movement of the visceral pleura against the parietal pleura during the respiratory cycle. Below the pleural line, *A lines* can be identified as motionless horizontal lines spaced at regular intervals from the pleural line and represent reverberation artifacts created by the ultrasound beam and the pleural line. The presence of a normal sliding pleural line (often referred to as "*lung sliding*") and A lines represent the normal lung pattern.

B lines or "comet tails" are vertical artifacts that arise from the pleural line and extend the entire depth of the ultrasound beam, interrupting A lines that may be present. B lines are reverberating artifacts resulting from interlobular septal thickening and alveolar fluid and represent the so-called alveolar-interstitial syndrome.[81] A small number (<3) of B lines in any given zone of the lung is considered normal. B lines are not specific to alveolar edema and may result from other processes that thicken the interstitium or cause interstitial inflammation, such as lung fibrosis or pneumonitis. B lines that are 7 mm or more apart are caused by interlobular septal thickening characteristic of interstitial edema, whereas B lines ≤3 mm apart are caused by alveolar edema. With additional findings, lung ultrasound may help differentiate cardiogenic from noncardiogenic pulmonary edema (i.e., ARDS). Focal B lines with a nonhomogenous distribution with spared areas, subpleural consolidations, an irregular pleural line, and reduced pleural motion are characteristic findings in ARDS.[82] Alternatively, diffuse bilateral B lines in a homogenous distribution and a smooth pleural line are characteristic of cardiogenic pulmonary edema.[82]

Thoracic ultrasound can also be used to assess for pneumothorax, which can occur as the result of common procedures in critically ill patients, such as thoracentesis, CVC insertion, and barotrauma from positive-pressure ventilation. Because a pneumothorax can rapidly progress and cause tension physiology, thoracic ultrasound for rapid diagnosis of a pneumothorax should be considered in patients who develop hemodynamic instability in relation to these procedures. When evaluating for a pneumothorax, multiple adjacent rib spaces should be evaluated in a short period of time. The presence of lung sliding or B lines are definitive findings that exclude pneumothorax, but notably, *only at that particular rib space*, highlighting the importance of scanning multiple rib spaces to fully evaluate the thorax. A pneumothorax is suggested by the absence of a lung sliding; however, the absence of lung sliding is not diagnostic and can be seen in conditions that eliminate movement between the visceral and parietal pleura, such as malignant processes, parapneumonic processes, or prior pleurodesis. Alternatively, the presence of a *lung point*, an intermittent respirophasic appearance of lung sliding that represents the boundary between the pneumothorax and an area of lung that still has apposition of the two parietal surfaces, is diagnostic of a pneumothorax.

The reader is referred to Chapter 29 for additional discussion of thoracic ultrasound.

Novel Hemodynamic Monitoring Tools

In most patients with ARF, the history, physical examination, laboratory testing, bedside ultrasonography, and basic bedside monitoring are adequate for hemodynamic monitoring and to diagnose causes of hemodynamic decompensation. In patients with unclassified shock or in patients who don't respond to initial therapy, the addition of cardiac output monitoring may be helpful. Although measurement of cardiac output from a PAC using thermodilution is considered the gold standard, the inherent issues with PACs have led to the development of numerous, less invasive methods for monitoring cardiac output. Although potentially useful in a variety of settings, data from randomized trials are insufficient to support their routine use.

Arterial Pulse Contour Analysis

Arterial pulse contour analysis or arterial pulse wave analysis relies on the relationship of the arterial pressure waveform to stroke volume and the elastic properties of the arterial wall. The area under the arterial waveform is reflective of stroke volume and, therefore, along with heart rate can be used to estimate cardiac output. To account for the elastic properties of the arterial wall, calibration of the pressure signal with an alternative method for measuring cardiac output or algorithms using preexisting patient data is required.

The PiCCO system (Getinge, Sweden) is based on pulse contour analysis of the systolic portion of the arterial waveform and is calibrated using transpulmonary thermodilution, in which a cold bolus of saline is injected into a central vein and changes in blood temperature are measured at a thermistor in an arterial catheter. For the PiCCO system, both a CVC and a separate arterial catheter (usually femoral) are required.

LiDCOplus (LiDCO, England) is similar to PiCCO except that it is based on pulse power analysis of the entire arterial waveform and is calibrated using lithium dilution instead of thermodilution. Benefits of LiDCO include its ability to be used with a radial arterial catheter and that its calibration does not require a CVC. Although calibrated pulse contour devices show good agreement with PAC thermodilution, frequent recalibration is necessary, particularly with changes in clinical status.[83,84]

Flotrac (Edwards Lifesciences, United States) uses pulse contour analysis, along with a proprietary algorithm built from demographic data (age, gender, height, etc.) from an expansive patient database to estimate cardiac output. The accuracy of uncalibrated devices has been challenged, especially in patients with shock. Further study is needed, given continued improvement in the technology.[83,84]

Esophageal Doppler

Esophageal doppler technology takes advantage of the proximity of the esophagus to the descending aorta. Insertion of a doppler probe allows for measurement of blood flow velocity in the aorta, which can then be used to estimate cardiac output. These calculations must take into account the diameter of the aorta, which in most cases is estimated from demographic data, rather than measured, and which may not be static in patients with shock undergoing resuscitation. Widespread use in critically ill patients is limited by the need to frequently reposition the probe and the limitation that it can be used only in deeply sedated patients.

Bioimpedance and Bioreactance

Bioimpedance uses the principle of electrical impedance (opposition to flow of electrical current) to estimate cardiac output. Blood is conductive of electricity and, therefore, changes in the blood content of the thorax that occur with cardiac contraction result in small changes in impedance that can be extrapolated to stroke volume and cardiac output. Bioreactance, the technology upon which the Starling system (Baxter, United States) is based, uses a related concept termed the "phase shift." These devices apply a low-frequency, high-amplitude electrical current that transverses the thorax and is recorded by other electrodes. The time delay between the application and measurement is the phase shift and is related to the amount of pulsatile blood flow in the thorax, allowing it to be used to estimate cardiac output. Studies on the accuracy of bioreactance-measured cardiac output have yielded inconsistent results, particularly in critically ill patients; their use is not widespread.[83,84]

RESPIRATORY MONITORING

Monitoring the respiratory system is a fundamental part of caring for patients with ARF. Regardless of the form of respiratory support, clinicians need to that ensure patients have adequate oxygenation and ventilation and must remain vigilant for respiratory decompensations that can occur as a result of acute events, such as mucus plugging, sepsis, pneumothorax, or new thromboembolic disease. Trending respiratory mechanics is also a critical component of respiratory monitoring and is used to minimize ventilator-induced lung injury, providing valuable prognostic information.

Specific topics discussed in this section focus on monitoring of oxygenation, ventilation, respiratory mechanics, ventilator waveforms, and respiratory muscle strength.

Oxygenation

Below we consider use of pulse oximetry, arterial and venous blood gases, and calculation of $\mathrm{Pa_{O_2}/Fi_{O_2}}$ and $\mathrm{Sp_{O_2}/Fi_{O_2}}$ ratios.

Pulse Oximetry

Oxygenation is routinely measured in hospital wards and ICUs using pulse oximeters. Pulse oximetry measures blood oxygen saturation by illuminating the skin with two wavelengths of light: 660 nm (red) and 940 nm (infrared). By measuring the ratio of absorbance at these wavelengths by oxygenated (oxyhemoglobin) and deoxygenated (deoxyhemoglobin) hemoglobin, the device generates an oxygen saturation and waveform. Routine pulse oximetry has proved advantageous in the acute care setting, even though studies have not demonstrated differences in clinical outcomes.[85]

Major advantages of pulse oximetry include its speed, noninvasive nature, limited adverse effects, and capacity to provide continuous data. However, the technique does have certain limitations.

In critically ill patients, the accuracy of measurements of pulse oximetry oxygen saturation ($\mathrm{SP_{O_2}}$) when compared with co-oximetry oxygen saturation ($\mathrm{Sa_{O_2}}$) as a reference standard is greatest at high oxyhemoglobin saturations.[86] When $\mathrm{Sa_{O_2}}$ is greater than 90%, the average difference between $\mathrm{Sa_{O_2}}$ and $\mathrm{Sp_{O_2}}$ is less than 2%; however, that difference increases when $\mathrm{Sa_{O_2}}$ drops below 90%, thus making pulse oximetry less reliable in hypoxemic states.[87]

Concerns have recently arisen regarding the accuracy of pulse oximetry in Black patients. A number of studies have reported that $\mathrm{Sp_{O_2}}$ frequently overestimates $\mathrm{Sa_{O_2}}$ in Black patients, potentially resulting in occult or unrecognized hypoxemia.[88,89] One study revealed that in patients with an $\mathrm{Sp_{O_2}}$ of 92% to 96%, occult hypoxemia ($\mathrm{Sa_{O_2}} < 88\%$) was three times more frequent in Black patients compared with white patients.[89] While further study is needed, it is clear that racial differences in pulse oximetry need to be recognized and incorporated into clinical care.

Since pulse oximetry does not measure $\mathrm{Pa_{O_2}}$ (arterial oxygen tension), large falls in $\mathrm{Pa_{O_2}}$ may go undetected until it reaches 60 to 70 mm Hg, the steep portion of the oxyhemoglobin dissociation curve.[90]

Pulse oximeters are also unable to account for measurement error in the presence of dyshemoglobins, such as methemoglobin, carboxyhemoglobin, or sulfhemoglobin. Thus, co-oximetry is necessary in situations where clinical suspicion for a dyshemoglobinemia is suspected.

Additional sources of potential error include hypotension, hypothermia, vasoconstriction, patient movement, and venous congestion (such as that due to tricuspid regurgitation).[91]

Arterial Blood Gas

Arterial blood gas (ABG) measurement is commonly performed in acutely ill patients to measure Pa_{O_2}, P_{CO_2}, pH, Sa_{O_2}, serum bicarbonate, and other variables, such as dyshemoglobins and electrolytes—information that is crucial to the management of critically ill patients.[92] ABG analysis is also used to accurately assess arterial oxygenation, by calculating the alveolar–arterial oxygen gradient or the Pa_{O_2}/Fi_{O_2} (P/F) ratio, both of which are essential to the management of patients with hypoxemic respiratory failure.[93]

Venous Blood Gas

Venous blood gas (VBG) analysis has become widespread and can be useful for respiratory monitoring in critical care settings. VBGs are easier and less painful to obtain than ABGs and can provide important information, including venous pH, P_{CO_2}, bicarbonate, and other data that may aid in the management of critically ill patients.[94] Many studies have focused on the generally good correlation between ABGs and VBGs in specific disease processes, such as diabetic ketoacidosis,[95] or in specific settings such as the emergency department.[96,97] A study done in ICU patients found excellent agreement between central VBGs and simultaneous ABGs for the detection of acid–base disorders, including in patients in shock.[98]

Pa_{O_2}/Fi_{O_2} and Sp_{O_2}/Fi_{O_2}

The Pa_{O_2}/Fi_{O_2} (P/F) ratio is a diagnostic criterion, as well as a criterion for stratifying the severity of ARDS. A P/F >200 but <300 mm Hg denotes mild ARDS; a P/F >100 but <200 mm Hg denotes moderate ARDS; and a P/F <100 mm Hg denotes severe ARDS.[93,99] However, the need for an arterial blood gas to calculate the P/F ratio can limit the diagnosis of ARDS in situations when the test is not readily available. Consequently, several studies have examined the potential role of the Sp_{O_2}/Fi_{O_2} (S/F) ratio as a surrogate for the P/F ratio. A 2007 analysis of ARDSnet data showed that the S/F ratio strongly correlated with a simultaneously drawn P/F ratio, and that an S/F ratio of 315 corresponded to P/F ratios of 300, the diagnostic cutoff for ARDS.[100] A more recent analysis investigated the use of a nonlinear imputation method to estimate the P/F ratio from the S/F ratio and found that the nonlinear method had reasonable accuracy among mechanically ventilated patients, particularly when Sp_{O_2} was $\leq 96\%$.[101]

■ Ventilation

Assessment of CO_2 metabolism requires knowledge of the concentrations of CO_2 present in plasma (PC_{O_2}) and in exhaled tidal volume (P_{ECO_2}), as well as the amount of CO_2 in the extracellular compartment (total CO_2 or bicarbonate concentration). These measurements can be used to determine the amount of dead space ventilation, diagnose acid–base disturbances, assess the adequacy of ventilation, and help confirm correct endotracheal tube (ETT) or tracheostomy tube placement. Values of CO_2 from these different compartments are commonly measured using blood gas analysis, capnography, or transcutaneous devices.

Dead Space Fraction

Understanding the fraction of dead space ventilation is important in gauging the severity of underlying lung disease in ARF. Dead space ventilation, which is made up of the sum of anatomic and physiologic dead space, is defined as the fraction of tidal volume that does not participate in gas exchange. The modified Bohr equation allows calculation of the dead space to tidal volume (V_D/V_T) ratio using the formula:

$$V_D/V_T = (Pa_{CO_2} - P_{ECO_2})/Pa_{CO_2}$$

where Pa_{CO_2} is the arterial partial pressure of CO_2 and P_{ECO_2} is the mean expired partial pressure of CO_2. The latter can be measured using a metabolic monitor that collects expired gas or using capnography in mechanically ventilated patients.[102]

End-tidal CO_2

Under normal physiologic conditions, alveolar P_{CO_2} is the same as Pa_{CO_2} and can be estimated by measuring end-tidal CO_2 (P_{ETCO_2}). However, this relationship does not hold true in states with significant physiologic dead space, such as ARF, pulmonary embolism, pulmonary vascular disease, or low cardiac output states, during which P_{ETCO_2} may underestimate Pa_{CO_2}. Even with this limitation, evidence exists to support the use of P_{ETCO_2} in cardiac arrest, as a measure of cardiopulmonary resuscitation (CPR) quality, to identify return of spontaneous circulation (ROSC), and to help guide prognosis.[103] There has also been interest in using capnography to predict fluid responsiveness and measure changes in cardiac output.[104] Although there has been significant interest in using capnography as an alternative to ABG analysis, P_{ETCO_2} correlates poorly with Pa_{CO_2} in critical illness due to the number of factors that impact P_{ETCO_2}, including ventilator settings, underlying lung disease, and cardiac output.[102]

Transcutaneous CO_2 Monitoring

Transcutaneous CO_2 (TC_{CO_2}) monitoring technology was first developed in the 1980s and is based on the understanding that CO_2 diffuses easily throughout the body. CO_2 can be measured indirectly by determining changes in the pH of an electrolyte solution applied to a heated skin sensor, usually placed on the earlobe or forehead. Conceptually, TC_{CO_2} monitoring can be used to measure arterial P_{CO_2} in respiratory failure and to estimate tissue perfusion in shock states. Although TC_{CO_2} monitoring is considered valid in routine respiratory care, its validity in critically ill patients has been challenged because poor perfusion, peripheral vascular disease, or vasopressors may confound measurements.[105] Technology has improved in recent years with better accuracy in critically ill patients, including patients with very high P_{CO_2} and patients on vasopressors;[106,107] however, lingering uncertainties about its accuracy have led to inconsistent and patchy use.

Endotracheal Tube Positioning and Cuff Monitoring

Verification of ETT placement is of vital importance. Misplacement of the ETT is common, particularly accidental intubation of the esophagus or the right mainstem bronchus. ETT placement can be confirmed in several ways, including auscultation of bilateral breath sounds, palpation of the ETT cuff in the jugular notch, fiberoptic bronchoscopy, chest radiography, and by determining the presence of P_{ETCO_2} using capnography or capnometry.[108]

The ETT cuff is an important component of the ETT that requires diligent and frequent monitoring. The inflated cuff functions to create a seal between the outer surface of ETT and the tracheal wall, permitting delivery of the tidal volume and preventing aspiration of nasopharyngeal secretions. Regular monitoring of the cuff is required to ensure that the pressure inside the cuff is kept below 20 to 25 cm H_2O, as the capillary perfusion pressure of the tracheal mucosa is approximately 25 cm H_2O and cuff pressures above this may lead to mucosal injury, ischemia, and eventually, tracheal stenosis or malacia.[108]

Following intubation and positioning of the ETT, the cuff balloon should be progressively inflated just until the gas leak that occurs during ventilation ceases. Measurement of cuff pressure requires connection of a manometer to the tubing leading to the cuff's pilot balloon. Excessively high cuff pressures may indicate either an undersized ETT for the patient's tracheal size or tracheal stenosis. Alternately, low cuff pressures, in addition to other signs such as audible noise during inspiration, frothy oral secretions with each breath, discrepancies between set and exhaled tidal volumes, and hypoxemia may suggest a cuff leak. Identification of a leak from the cuff mandates replacement of the endotracheal tube.[109]

■ Respiratory Mechanics

Characterization of respiratory system mechanics is fundamental to understanding the physiology of mechanically ventilated patients. Vital information can be gleaned, including respiratory system compliance, airway resistance, and the presence of restrictive or obstructive lung disease. Respiratory mechanics can also be helpful in identifying the etiology of episodes of clinical instability and monitoring the response to therapeutic interventions, such as diuresis or ventilator changes. Trending respiratory mechanics is also important to minimize ventilator-induced lung injury. Measurements should ideally be taken when the patient is passive with the ventilator, such as immediately after intubation or while otherwise sedated or paralyzed.

Airway Pressures

Airway pressures are routinely measured during mechanical ventilation and provide a plethora of useful information. The electromechanical transducers that convert pressure to electrical current are often located either in the ventilator circuit or, sometimes, the esophagus. The term *airway pressure* (P_{AW}) refers to pressure measured within the ventilator circuit, while pressure measured within the esophagus is referral to as *esophageal pressure* (P_{ES}). P_{ES} is thought of as a surrogate for pleural pressure, which is difficult to directly measure in routine practice.[110]

A number of pressure measurements are commonly made during the respiratory cycle, including peak airway pressure (Ppeak), plateau pressure (Pplat), mean airway pressure (Pmean), driving pressure (ΔP), positive end-expiratory pressure (PEEP), and autoPEEP or intrinsic PEEP.[111]

Ppeak (Fig. 146-3) represents the total pressure the ventilator must generate to overcome the impedance of the respiratory system, including airflow resistance, load imposed by distention of the lung and chest wall, and any load imposed by other factors, such as dynamic hyperinflation or increased intra-abdominal pressure. Ppeak is governed by several factors, including inspiratory flow rate, the inspiratory waveform (ramp versus square), and the tidal volume.

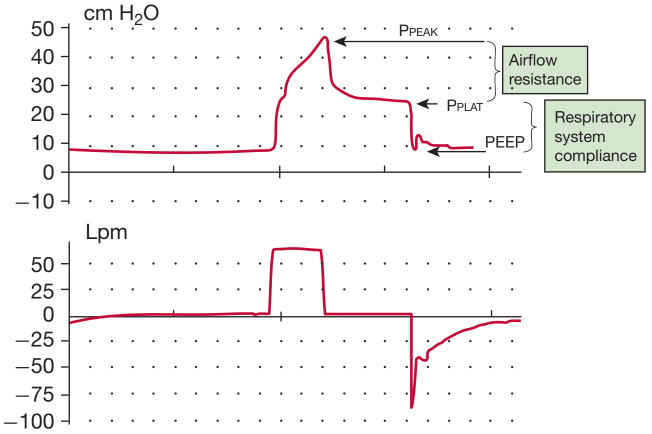

Figure 146-3 Inspiratory hold maneuver during constant flow in a volume-controlled breath. Note the significant difference between the patient's peak airway pressure (48 cm H_2O) and plateau pressure (26 cm H_2O), indicative of increased airway resistance.

Pplat (Fig. 146-3) is a measure of end-inspiratory alveolar pressure and is measured by applying an end-inspiratory breath hold that allows pressure to equilibrate throughout the respiratory system once flow has ceased. Pplat should always be lower than Ppeak, and the pressure difference between the two reflects the pressure needed to drive airflow through the respiratory tree into the alveoli. Relatedly, the driving pressure (ΔP) is calculated as Pplat − PEEP and is reflective of the respiratory system compliance.[112]

In patients with high airway pressures, the problem could be either resistive (due to high airway resistance) or elastic (lung and chest wall apparatus) issues. This can be quickly characterized by determining the difference between Ppeak and Pplat, as well as the driving pressure (Fig. 146-3). If Ppeak − Pplat increases while the driving pressure remains unchanged, it strongly suggests an issue with airflow resistance, such as mucus plugging, bronchospasm, or otherwise obstructed ETT. In contrast, an increase in driving pressure suggests decreased lung or chest wall compliance, which can stem from a variety of issues including pleural effusion, pneumothorax, alveolar filling processes, single mainstem bronchus intubation, or increases in intra-abdominal pressure.[111] Attempts to correct a high Ppeak in a patient with obstructive lung disease by reducing the inspiratory flow may paradoxically result in increased auto PEEP and Ppeak due to insufficient expiratory time.[111] The resulting increase in Pplat may heighten the risk of barotrauma.

AutoPEEP, also known as intrinsic PEEP, refers to the pressure exerted by gas that is left over in the alveoli at the end of expiration. There are three common situations in which autoPEEP develops, including high minute ventilation, expiratory flow limitation, and expiratory resistance. High minute ventilation can be caused by either large tidal volumes, high respiratory rates, or both; both situations can make it more difficult for the patient to fully exhale the entirety of the tidal volume.[113] Expiratory flow limitation is usually the result of airway narrowing due to bronchospasm, inflammation, or scarring, and is a common cause of autoPEEP in patients with chronic obstructive pulmonary disease. Expiratory resistance is a similar concept, except that it is unrelated to the airways and generally refers to the rest of the respiratory apparatus, such as a narrow or kinked ETT, the presence of a PEEP valve, or tenacious ETT secretions.[114]

In mechanically ventilated patients, autoPEEP is generally identified by examining the flow–time waveform to verify that the expiratory flow curve returns to baseline before the next breath is delivered (Fig. 146-4). The magnitude of autoPEEP can be quantified

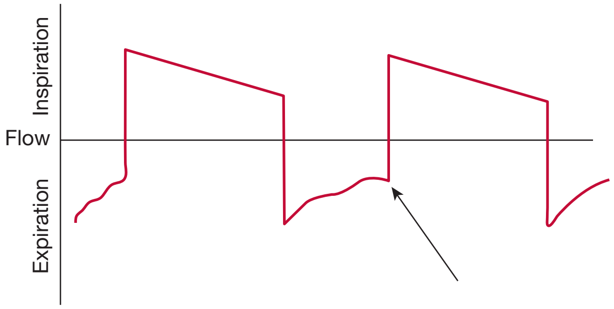

Figure 146-4 The presence of auto-PEEP is identified from the flow waveform. The next breath commences before expiratory flow returns to zero.

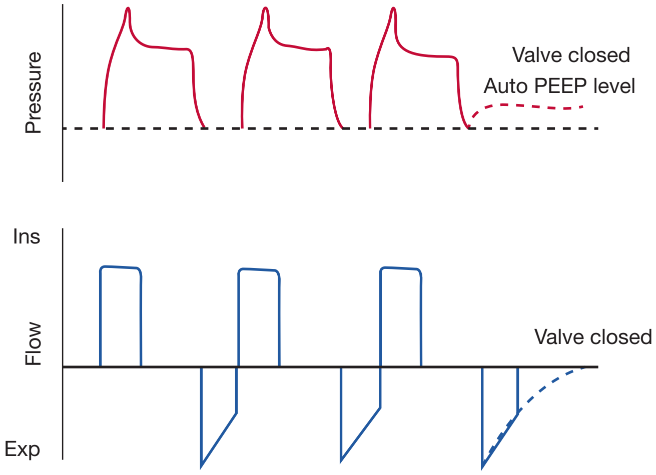

Figure 146-5 Expiratory hold technique to quantify auto-PEEP. The expiratory valve is closed during an expiratory "hold" at the end of a set expiratory time. When flow equals zero, airway pressure rises to the auto-PEEP level.

by doing an expiratory hold maneuver, which allows pressures to equilibrate throughout the respiratory system (Fig. 146-5). The total PEEP "experienced" by the alveoli is then calculated as the sum of the measured autoPEEP and the PEEP applied by the ventilator.[115] While measurement of autoPEEP is generally easily accomplished, active respiratory efforts by the patient may preclude accurate measurement of autoPEEP, which may necessitate heavy sedation or paralysis if measurements are needed.[114]

Calculation of the aforementioned pressures facilitates an understanding of other important measures of respiratory mechanics, particularly respiratory system compliance (Crs), elastance, and airway resistance (Raw). Compliance is defined as the change in lung volume (tidal volume) divided by the driving pressure (the difference between Pplat and total PEEP). Normal Crs is generally >60 mL/cm H_2O. Elastance is defined as the inverse of compliance (1/compliance).[111]

Lung-protective ventilation aims to reduce ventilator-induced lung injury (VILI) by setting low tidal volumes and targeting a Pplat less than 30 cm H_2O.[116–119] This is predicated on the idea that such practices reduce mechanical end-expiratory lung stress, strain, and atelectrauma in patients with ARDS.[120] However, even reduced tidal volumes based on ideal body weight may generate lung injury due to the reduced volume of lung available for ventilation (i.e., the "baby lung" concept).[121] Recent studies have suggested that among ventilation variables, including tidal volume and plateau pressure, driving pressure is the variable that best stratifies risk of mortality.[122] Although it has been suggested that titrating PEEP to target a driving pressure of 15 cm H_2O or less could lead to improved patient outcomes, only observational studies exist supporting the effects of driving pressure optimization on outcomes; prospective randomized controlled trials may be needed.[121–124]

Esophageal Pressure

Quantification of the pleural pressure can be useful, as it permits calculation of the transmural distending pressure of the lung and allows characterization of the compliance of the entire lung and chest wall apparatus. Pleural pressure is difficult to routinely measure but may be useful in certain patients where the underlying etiology of respiratory failure is difficult to determine. Esophageal pressure (P_{ES}) is considered a surrogate for pleural pressure and can be estimated using a balloon-tipped esophageal catheter, typically inserted to a depth of approximately 40 cm in order to minimize artifact from cardiac oscillations.[110] While a small study suggested improved outcomes with the use of esophageal catheters to titrate PEEP in patients with ARDS, a larger, randomized, controlled trial (EPVENT2) suggested that a P_{ES}-guided PEEP strategy (compared with empiric PEEP titration) did not improve outcomes in patients with moderate to severe ARDS.[120] Therefore, given the complexities involved in its use, esophageal pressure remains predominantly a research tool.

■ Ventilator Waveforms

All mechanical ventilators are equipped with a spirometer that enables monitoring of flow and volume of gas being exchanged during the respiratory cycle. These data are graphically represented on the ventilator screen as waveforms, most commonly flow, pressure, and volume plotted over time. A keen understanding of these waveforms is crucial to detecting development of autoPEEP, patient-ventilator dyssynchrony, airway obstruction, worsening compliance, and a variety of other issues.

Pressure–Time Waveform

The pressure waveform graphed over time is particularly useful in volume-cycled modes of ventilation, as pressure is the dependent variable. Examination of the waveform can yield important information, such as whether the patient is initiating breaths (negative deflection before delivery of tidal volume), the amount of work needed to trigger inspiration (the amplitude of the negative deflection), whether inspiratory flow is sufficient to meet the patient's needs (Fig. 146-6, demonstrating downward deflection during inspiration), and whether the set inspiratory time is too long or too short compared with the patient's "neural" inspiratory time. An inspiratory and expiratory hold can also be performed at the bedside and help determine compliance, resistance, and autoPEEP.

Flow–Time Waveform

In volume-cycled modes of ventilation the flow rate and pattern are set by the clinician, so examination of the flow waveform is most useful in pressure-cycled modes. In pressure-control ventilation, inspiratory time is set and thus governs inspiratory flow, which should cease prior to onset of exhalation. If this does not happen, inspiratory time should be adjusted. In pressure support ventilation, where inspiratory time may vary, flow is important in determining when exhalation is triggered; typically, exhalation begins when inspiratory flow reaches 25% of the peak flow. This threshold may need to be altered in patients with obstructive lung disease due to high lung compliance in that population. The expiratory limb of the flow waveform can also be scrutinized to help detect autoPEEP. Expiratory flow that fails to cease before the next breath is delivered suggests the presence of autoPEEP (assuming no active respiratory effort), which can be quantified with an expiratory hold.

■ Respiratory Muscle Strength

Measurements of respiratory muscle strength can be important to identify neuromuscular weakness as a cause of respiratory failure; recent technology may be helpful to monitor for development of diaphragmatic weakness as occurs with critical illness myopathy.

Inspiratory and Expiratory Pressure

Assessment of respiratory muscle strength generally involves measuring maximal inspiratory pressure (MIP), also known as negative inspiratory force (NIF) and, less commonly, maximal expiratory pressure (MEP). Each measurement is compared with reference ranges according to a patient's age and sex. MIP is measured at functional residual capacity and is generally performed while the patient is connected to the ventilator by performing an expiratory hold and measuring the magnitude of the negative pressure deflections over

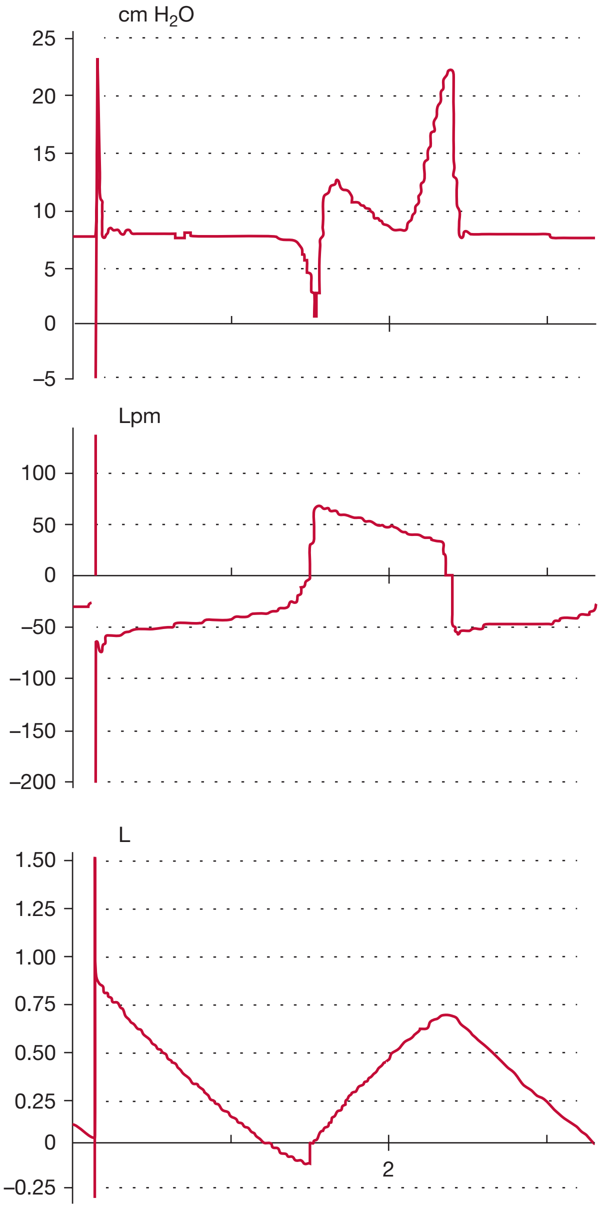

Figure 146-6 Patient-ventilator dyssynchrony during volume-controlled ventilation, secondary to inadequate flow.

10 consecutive inspirations or 30 s. MEP is measured at total lung capacity, but it is not routinely used in clinical practice except in certain patient populations.[125]

Diaphragm Ultrasound

In recent years, there has been growing interest in using ultrasound to evaluate diaphragm function. In general, diaphragm ultrasound (DUS) can be used in two ways: to measure changes in diaphragm thickness or to quantify diaphragm excursion. Diaphragm thickness can be measured by placing a high-frequency linear probe at the *zone of apposition*—the vertical regions of the hemidiaphragms that are directly apposed to the ribs of the lower chest wall. Thickness at end-inspiration and end-expiration are used to calculate a "thickening fraction." Although several studies have shown that the diaphragm undergoes changes in thickness during mechanical ventilation detectable by ultrasound, it is not clear that this correlates to diaphragmatic weakness or differences in outcome. Measurement of diaphragm excursion can be performed by placing a phased-array or curvilinear probe in an anterior subcostal position and identifying the diaphragm. Movement of the diaphragm toward and away from the probe is then quantified, with less than a normal amplitude of diaphragm excursion suggesting weakness, and absent or paradoxical motion suggesting diaphragm paralysis.[126] Diaphragm ultrasound may have a role in patients with ARF, including estimating work of breathing in patients undergoing noninvasive ventilation,[127] detecting diaphragm weakness or paralysis,[128] and assessing probability of success weaning from mechanical ventilation.[129]

Diaphragm Electromyography

Electromyography (EMG) is a spatiotemporal summation of neural impulses that are transformed into muscle action potentials. Diaphragm EMG has garnered increasing interest over recent years due to growing recognition of the diaphragm's role in respiratory failure, particularly in patients with prolonged mechanical ventilation and difficulty weaning from the ventilator. Diaphragm EMG is best recorded using an esophageal catheter with multiple electrodes; the processed signal is referred to as the *amplitude of the electrical activity of the diaphragm* (EADi). There is great interest in using EADi to detect patient–ventilator asynchrony, to monitor respiratory muscle unloading during mechanical ventilation, and to assess efficacy of breathing in critically ill patients, including those on ECMO.[130] However, this technology is still making the transition to the bedside and requires further study before it is ready for widespread use in clinical practice.

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CHAPTER 147

Principles of Mechanical Ventilation

Martin J. Tobin

INTRODUCTION

The pivotal importance of mechanical ventilation was highlighted in the early days of the COVID-19 pandemic when scientific societies issued guidelines on how to connect four patients to a single machine, and politicians pleaded with automakers to branch into the manufacture of ventilators.[1]

Given the panic and pandemonium, the prediction that patients were being inappropriately intubated and ventilated was quickly borne out, as 90% or more of patients were intubated in some intensive care units.[2,3] The number of deaths that resulted from unnecessary use of invasive mechanical ventilation will never be known, but it is likely to have been very high.[4] A sound understanding of the principles of mechanical ventilation is vitally important for every pulmonary and critical care physician.

OBJECTIVES AND INDICATIONS FOR MECHANICAL VENTILATION

The objectives of mechanical ventilation are listed in Table 147-1.[5] Authors have listed criteria to guide intubation, but none has stood the test of rigorous investigation.[1,6] Measurements such as oxygen saturation help, but it is not possible to pick a saturation breakpoint at which the benefits of mechanical ventilation will decidedly outweigh its hazards across all patients.[2] The decision to insert an endotracheal tube is, instead, based on clinical judgment, gestalt, and tacit knowledge individualized to each particular patient.[1,6]

Increased work of breathing is the most common reason for intubation.[6] Accurate measurement of work of breathing involves inserting an esophageal balloon to measure inspiratory effort, which requires a certain technical skill.[7] More practical is estimation of work of breathing based on meticulous physical examination. The key step is gently touching the sternomastoid muscle with the index finger, checking for phasic—not tonic—contraction, and then judging its magnitude qualitatively (Fig. 147-1).[8] Next is placing the index finger on the cricoid cartilage and judging the presence and degree of tracheal tug (Fig. 147-2). Then, inspecting the suprasternal fossa and the intercostal spaces for recession is performed (Figs. 147-3 and 147-4). The physician integrates these physical signs into the clinical context and judges if respiratory work is sustainable, or if assisted ventilation (invasive or noninvasive) is more prudent.[1,6,8]

Increased respiratory work increases the oxygen cost of breathing to as much as 50% of total oxygen consumption.[9] By decreasing respiratory work, mechanical ventilation allows precious oxygen stores to be rerouted to other vulnerable tissue beds. To substantially reduce patient effort, the ventilator must cycle in unison with

TABLE 147-1 Objectives of Mechanical Ventilation

Improve pulmonary gas exchange
Reverse hypoxemia
Relieve acute respiratory acidosis
Relieve respiratory distress
Decrease oxygen cost of breathing
Reverse respiratory muscle fatigue
Alter pressure–volume relationships
Prevent or reverse atelectasis
Improve lung compliance
Prevent further lung injury
Permit lung and airway healing
Avoid complications

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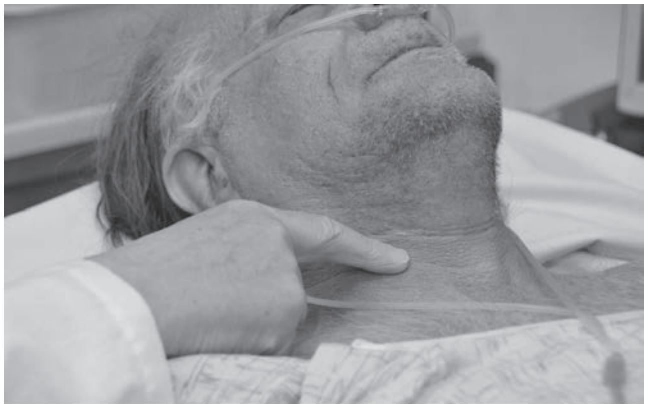

Figure 147-1 Placement of the index finger (gently, barely touching) on the body of the sternomastoid muscle to judge the presence of phasic contraction and qualitatively determine its magnitude (mild, moderate, marked). *(Reproduced with permission from Tobin MJ. Why Physiology Is Critical to the Practice of Medicine: A 40-year Personal Perspective. Clin Chest Med. 2019;40(2):243–257.)*

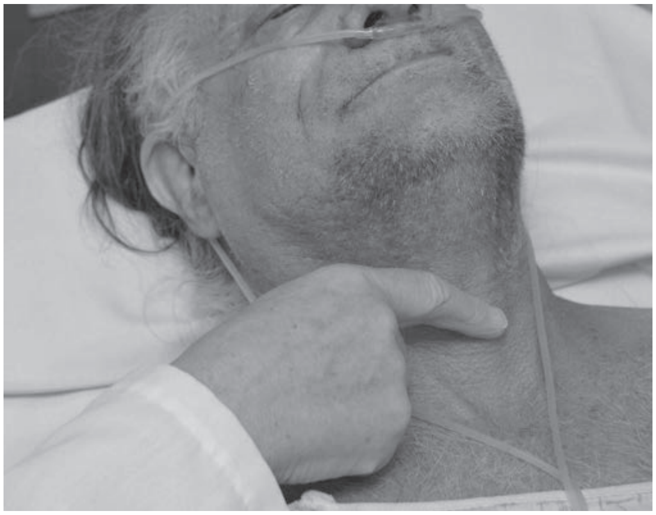

Figure 147-2 Placement of the index finger on the cricoid cartilage to judge the presence of tracheal tug and qualitatively determine its magnitude (mild, moderate, marked). *(Reproduced with permission from Tobin MJ. Why Physiology Is Critical to the Practice of Medicine: A 40-year Personal Perspective. Clin Chest Med. 2019;40(2):243–257.)*

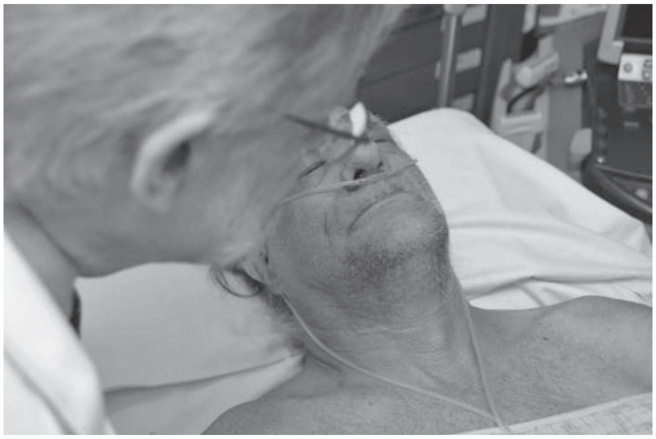

Figure 147-3 Inspection of the suprasternal fossa to judge the presence of recession with each inspiration and qualitatively determine its magnitude (mild, moderate, marked). *(Reproduced with permission from Tobin MJ. Why Physiology Is Critical to the Practice of Medicine: A 40-year Personal Perspective. Clin Chest Med. 2019;40(2):243–257.)*

the patient's central respiratory rhythm (Fig. 147-5).[10] For perfect synchronization, the period of mechanical inflation must match the period of neural inspiratory time (the duration of inspiratory effort), and the period of mechanical inactivity must match the neural expiratory time.[11] Work of breathing is increased in patients with atelectasis or acute lung injury because breathing occurs on the low, flat portion of the pressure–volume curve. By shifting tidal ventilation to the steep, compliant portion of the curve, mechanical ventilation can decrease respiratory work.

Acute progressive respiratory acidosis is a classic indication for mechanical ventilation, although simpler measures can sometimes reverse the process.[7] For example, among patients with acute severe asthma and hypercapnia, hypercapnia resolves with standard bronchodilator therapy, without the need for mechanical ventilation, in more than 90% of patients.[12] If a patient has severe respiratory depression that is expected to be slow in resolving (e.g., in certain drug overdoses), intubation and mechanical ventilation should be instituted without delay.

Hypoxemia is not a common reason for intubation and mechanical ventilation. In critically ill patients, hypoxemia is usually caused by an amalgam of ventilation–perfusion mismatch and shunt physiology. When ventilation–perfusion mismatch prevails, arterial oxygen tension ($\mathrm{Pa}_{\mathrm{O}_2}$) increases substantially in response to supplemental oxygen; a satisfactory level of arterial oxygenation is usually sustained in these patients without recourse to intubation (and mechanical ventilation).[1] When intrapulmonary shunt is dominant, the increase in $\mathrm{Pa}_{\mathrm{O}_2}$ with supplemental oxygen is modest or absent. Intubation helps by ensuring delivery of a high fractional inspired oxygen concentration ($\mathrm{FI}_{\mathrm{O}_2}$), and positive-pressure ventilation helps by recruiting collapsed lung units, leading to improved matching of ventilation and perfusion.[6]

Patient self-inflicted lung injury (P-SILI) is a new condition postulated to justify pre-emptive endotracheal intubation in patients breathing vigorously; P-SILI attracted considerable coverage in the context of COVID-19.[2] Studies put forward to support the existence of P-SILI are circumstantial and weak, and there is no robust experimental evidence to prove that P-SILI actually occurs in patients.[3] Several studies have now revealed that alacrity in intubation of COVID-19 patients is associated with higher mortality. In one series, mortality decreased from 44% in February and March to 34% in April and May of 2020 in conjunction with a decrease in the rate of intubation from 76% in the first time frame to 44% in the second.[13]

Commonly listed indications for mechanical ventilation include acute respiratory failure, exacerbation of chronic respiratory failure (secondary to infection, bronchoconstriction, or heart failure), coma, and neuromuscular disease. Many patients with these same conditions, however, are managed without ventilator assistance. Indeed, the most common, and honest, reason that mechanical ventilation is instituted is a tautology: A physician thinks that "the patient looks like he (or she) needs to be placed on the ventilator."[6] Mechanical ventilation is most commonly instituted based on a physician's clinical gestalt, formed through assessing a patient's signs and symptoms, rather than because a patient satisfies a certain set of criteria on a checklist. It is important to ground this decision on solid knowledge of pulmonary pathophysiology.

MODES OF MECHANICAL VENTILATION

The term *mode* refers to the relationship among various breath types (mandatory, assisted, supported, and spontaneous), as well as inspiratory phase variables.

■ Controlled Mechanical Ventilation

In controlled mechanical ventilation, the ventilator delivers all breaths at a preset rate, and the patient cannot trigger the machine.

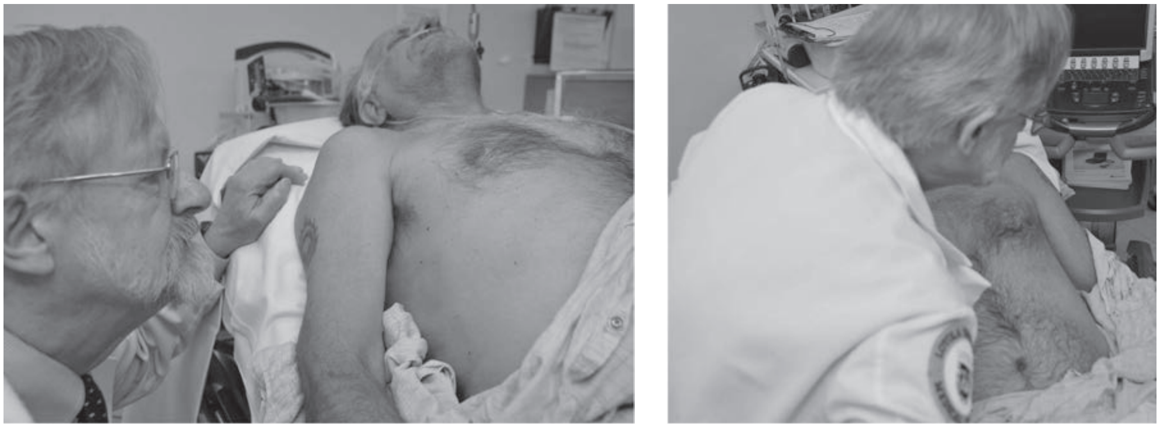

Figure 147-4 Inspecting the ipsilateral intercostal spaces to judge for the presence of inspiratory recession *(left)*. Sometimes recession is easier to detect upon inspecting the profile of the contralateral hemithorax *(right)*. When inspecting each hemithorax, the clinician should also check for Hoover sign, a paradoxical inward motion of the lower rib cage during inspiration, signifying a flattened and disadvantaged diaphragm. *(Reproduced with permission from Tobin MJ. Why Physiology Is Critical to the Practice of Medicine: A 40-year Personal Perspective. Clin Chest Med. 2019;40(2):243–257.)*

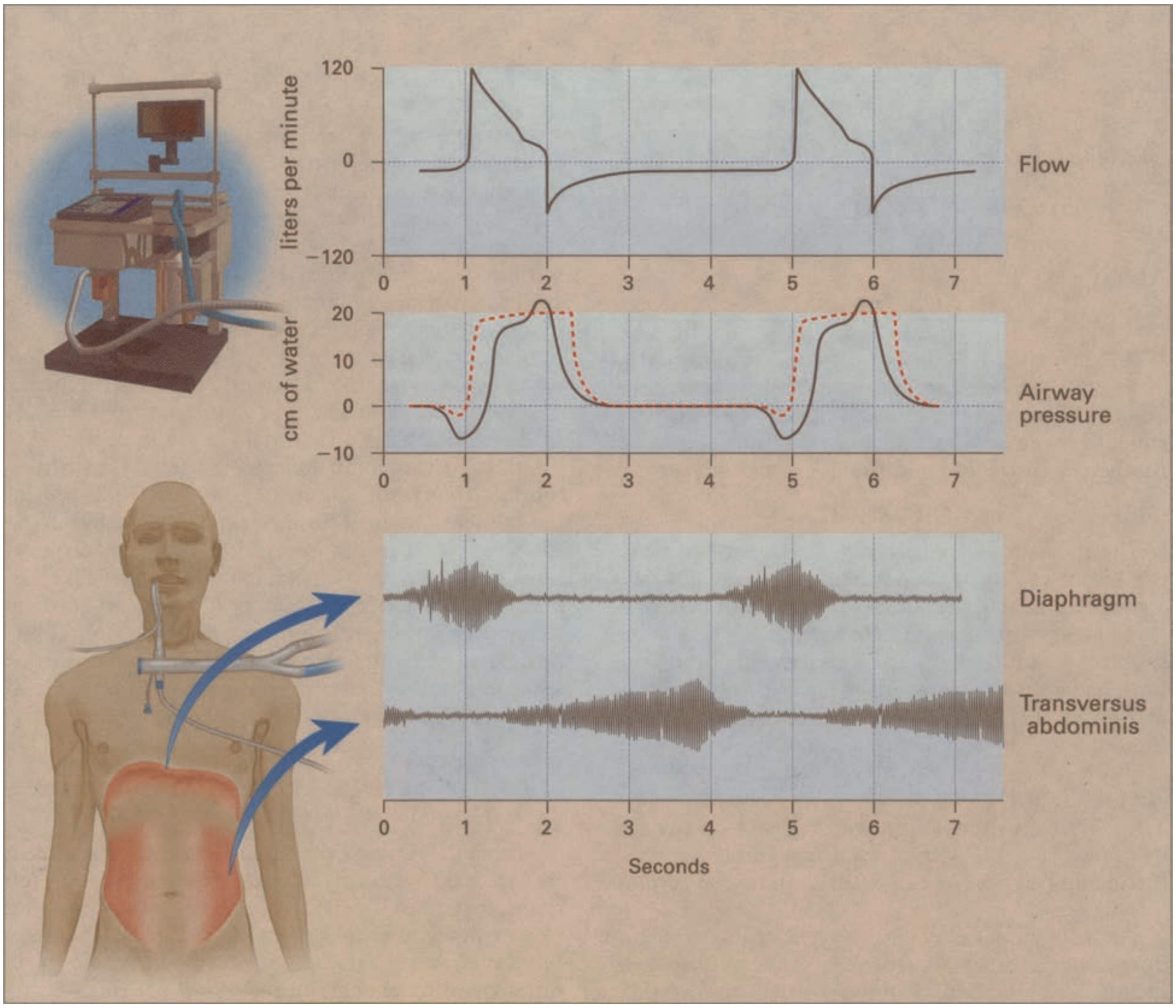

Figure 147-5 Flow, airway pressure, and inspiratory and expiratory muscle activity in a patient with chronic obstructive pulmonary disease who received pressure-support ventilation at an airway pressure of 20 cm H_2O. The electromyograms in the *lower portion* of the figure show inspiratory muscle activity in the patient's diaphragm and expiratory muscle activity in the transversus abdominis. The patient's increased inspiratory effort caused the airway pressure to fall below the set sensitivity (−2 cm H_2O), and inadequate delivery of flow by the ventilator resulted in a scooped contour on the airway–pressure curve during inspiration. While the ventilator was still pumping gas into the patient, his expiratory muscles were recruited, causing a bump in the airway–pressure curve. That the flow never returned to zero throughout expiration reflected the presence of PEEPi. The *broken red line* shows airway pressure in another patient, who generated just enough effort to trigger the ventilator and in whom there was adequate delivery of gas by the ventilator. *(Reproduced with permission from Tobin MJ. Advances in mechanical ventilation. N Engl J Med. 2001;344(26):1986–1996. Data from Jubran A, Van de Graaff WB, Tobin MJ. Variability of patient-ventilator interaction with pressure support ventilation in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1995;152: 129–136; Parthasarathy S, Jubran A, Tobin MJ. Cycling of inspiratory and expiratory muscle groups with the ventilator in airflow limitation. Am J Respir Crit Care Med. 1998;158:1471–1478.)*

In the volume-targeted mode, the breaths have a preset volume—so-called volume-controlled ventilation. When the breaths are pressure limited and time cycled, the mode is termed *pressure-controlled* ventilation. Use of volume-controlled ventilation is largely restricted to patients who are apneic as a result of brain damage, sedation, or paralysis.

■ Assist-control Ventilation

In the assist-control mode, the ventilator delivers a breath either when triggered by the patient's inspiratory effort (pressure or flow triggered) or, independently, if such an effort does not occur within a preselected time period.[14] All breaths are delivered under positive pressure by the machine, but unlike controlled mechanical ventilation, the patient's triggering effort can exceed the preset rate. If the patient's spontaneous rate drops below the preset back-up rate, controlled ventilation is provided. The breath delivered by the ventilator may have a predetermined volume (volume-cycled form of assist-control ventilation) or a predetermined inflation pressure that is applied for a predetermined inflation time (pressure control form of assist-control ventilation). By design, delivered tidal volume (V_T) is not influenced by patient effort. The greater the inspiratory effort made by the patient, the lower will be the airway pressure during the volume-cycled form of assist-control ventilation, such that the overall airway pressure on the ventilator monitor bears an inverse relationship to patient-generated pressure.

The ventilator cycles off when the preset V_T is reached, and machine inspiratory time may be shorter or longer than the patient's intrinsic (neural) inspiratory time.[11] If the set V_T is reached before the end of neural inspiratory time, the machine cycles off while the patient's inspiratory effort continues. If the patient's inspiratory effort ceases before the set V_T is reached, the machine increases pressure to provide continued inspiratory flow. The amount of active work performed by a patient ventilated in the assist-control mode is critically dependent on the trigger sensitivity and inspiratory flow settings. Even when these settings are selected appropriately, patients actively perform about one-third of the work performed by the ventilator during passive conditions.[15]

Intermittent Mandatory Ventilation

With intermittent mandatory ventilation (IMV), the patient receives periodic positive-pressure breaths from the ventilator at a preset volume and rate, but the patient can also breathe spontaneously between these mandatory breaths.[16] A problem unforeseen at the time IMV was introduced is the difficulty that patients encounter in trying to adapt to the intermittent nature of ventilator assistance. It had been assumed that the degree of respiratory muscle rest achieved by IMV would be proportional to the number of mandatory breaths delivered. Studies, however, have demonstrated that inspiratory effort is equivalent for spontaneous and assisted breaths during IMV (Fig. 147-6).[17,18] Indeed, the tension–time index for both spontaneous and assisted breaths is above the threshold associated with respiratory muscle fatigue at IMV rates of 14 breaths/min or less.[17] At a moderate level of machine assistance (at which the ventilator accounts for 20% to 50% of total ventilation), electromyographic activity of the diaphragm and sternocleidomastoid muscles is equivalent for assisted and spontaneous breaths.[18] These findings suggest that respiratory center output is preprogrammed and does not adjust to breath-to-breath changes in load, as occurs during IMV. As a result, IMV may contribute to development of respiratory muscle fatigue or prevent its recovery.

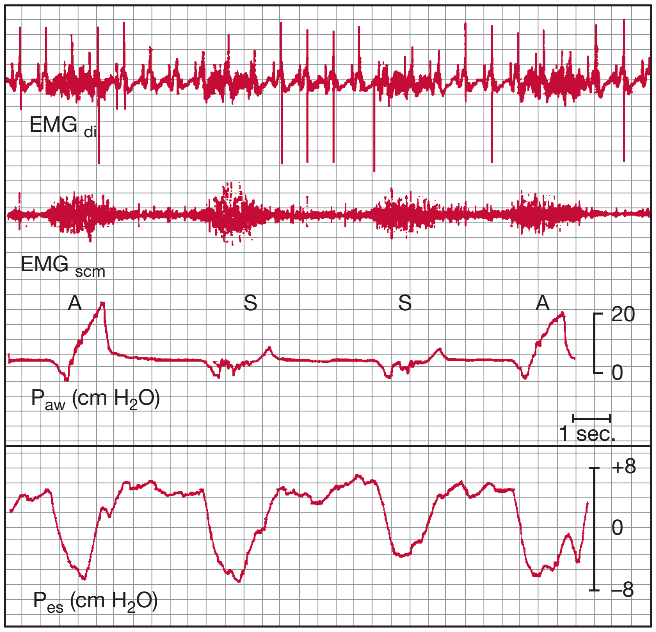

Figure 147-6 Electromyograms of the diaphragm (EMGdi) and sternocleidomastoid muscles (EMGscm) in a patient receiving synchronized intermittent mandatory ventilation. Similar intensity and duration of electrical activity during assisted (**A**) and spontaneous (**S**) cycles are demonstrated. P_{aw}, airway pressure; P_{es}, esophageal pressure. *(Reproduced with permission from Imsand C, Feihl F, Perret C, et al. Regulation of inspiratory neuromuscular output during synchronized intermittent mechanical ventilation. Anesthesiology. 1994;80(1):13–22.)*

Pressure-support Ventilation

Pressure-support ventilation is patient triggered, like assist-control ventilation and IMV, but it differs in that it is pressure targeted and flow cycled.[19] The physician sets a level of pressure that augments every spontaneous effort, and the patient may alter respiratory frequency, inspiratory time, and V_T. V_T is determined by the pressure setting, the patient's effort, and pulmonary mechanics, in contrast to assist-control ventilation and IMV, in which a guaranteed volume is delivered. With volume-targeted ventilation, the inspiratory flow setting is a crucial determinant of patient work. There is no flow setting with pressure-support ventilation, although the initial peak flow determines the speed of pressurization and the initial pressure ramp profile.

Pressure support can be very effective in decreasing the work of inspiration. The degree of inspiratory muscle unloading, however, is variable, with a coefficient of variation of up to 96% among patients.[20] The level of pressure delivered by the ventilator is usually adjusted in accordance with changes in the patient's respiratory frequency. The respiratory frequency, however, that signals a satisfactory level of respiratory muscle rest has never been well defined, and recommendations range from 16 to 30 breaths/min.[20]

Cycling to exhalation is triggered by a decrease in inspiratory flow to a preset level, such as 5 L/min or 25% of peak inspiratory flow, depending on the manufacturer's algorithm (Fig. 147-7). The algorithm for "cycling off" of mechanical inflation causes problems in patients with COPD because increases in resistance and compliance produce a slow time constant (of the respiratory system). The longer time needed for flow to fall to the threshold value may cause mechanical inflation to persist into neural expiration.

In 12 patients with COPD receiving pressure support of 20 cm H_2O, Jubran et al.[20] found that 5 recruited their expiratory muscles while the machine was still inflating the thorax. The patients who recruited their expiratory muscles during mechanical inflation had an average time constant of 0.54 s, compared with an average of 0.38 s in patients who did not exhibit expiratory muscle activity. The persistence of mechanical inflation into neural expiration is very

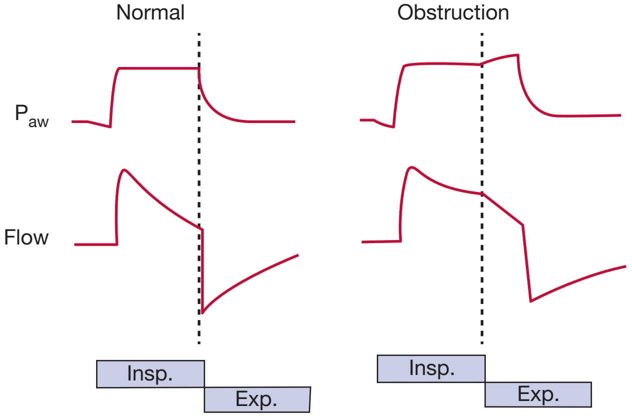

Figure 147-7 Airway pressure (P_{aw}) and inspiratory (Insp) and expiratory (Exp) flow during pressure-support ventilation in patients with normal and obstructed airways. Patient effort triggers the ventilator to deliver a preset pressure, and inspiratory assistance continues until the flow rate falls to 25% of the peak inspiratory flow. In patients with airway obstruction, who have a prolonged time constant, more time is required for flow to decrease to this threshold value, so that neural expiration commences before the termination of mechanical inflation. The resulting activation of the expiratory muscles hastens the fall in flow, but it also results in dyssynchrony between the patient's neuromuscular activity and the mechanical phase of the ventilator—so-called "fighting the ventilator."

uncomfortable, as well recognized with use of inverse-ratio ventilation (where, contrary to the normal pattern, inflation lasts longer than exhalation).

New Modes

New modes of mechanical ventilation are frequently introduced. Each has an acronym, and the jargon is inhibiting to those unfamiliar with it. Yet each new mode involves nothing more than a modification of the manner in which positive pressure is delivered to the airway and of the interplay between mechanical assistance and the patient's respiratory effort.[10] The purpose of a new mode may be to enhance respiratory muscle rest, prevent deconditioning, improve gas exchange, prevent lung damage, enhance coordination between ventilator assistance and patient respiratory effort, and foster lung healing. The priority given to each goal varies.

VENTILATOR SETTINGS

Ventilator settings are based on the patient's size and clinical condition. Determination of the settings is a dynamic process, based on a patient's physiologic response, rather than on a fixed set of numbers.[21] The settings require repeated readjustment over the period of ventilator dependency. Such an iterative process requires careful respiratory monitoring.

Triggering

Many ventilators employ pressure triggering, whereby a decrease in circuit pressure is required to initiate ventilator assistance. Patients reach the set sensitivity by activating their inspiratory muscles. When the threshold is reached, however, inspiratory neurons do not simply switch off.[7] Consequently, the patient may expend considerable inspiratory effort throughout a machine-cycled inflation. The level of patient effort during this post-trigger phase is closely related to a patient's respiratory motor output at the point of triggering.[22] As such, measures that decrease respiratory drive may enhance respiratory muscle rest during mechanical ventilation.

If respiratory motor output at the point of triggering is important, one might expect that effort during the time of triggering would determine patient effort during the remainder of inspiration. To elucidate this issue, Leung et al.[22] applied graded levels of pressure support in 11 critically ill patients. They achieved a fourfold reduction in overall patient effort. Yet patient effort during the time of triggering did not change. The constancy of effort during the trigger phase was probably secondary to different factors becoming operational as the level of ventilator assistance was varied (Fig. 147-8). Thus, increases in the level of ventilator assistance do not substantially decrease patient effort during the time of triggering.

The display of airway pressure and flow tracings on ventilator screens has increased awareness that inspiratory effort is frequently insufficient to trigger the ventilator.[10,11] At high levels of mechanical assistance, up to one-third of a patient's inspiratory efforts may fail to trigger the machine (Fig. 147-9). The number of ineffective triggering attempts increases in direct proportion to the level of ventilator assistance. Surprisingly, unsuccessful triggering is not the result of poor inspiratory effort.

In a study of factors contributing to ineffective triggering, effort was noted to be more than one-third greater when the threshold for triggering the ventilator was not reached than when it was.[22] Breaths that do not reach the threshold for triggering the ventilator have higher V_T and shorter expiratory time than do breaths that do trigger the ventilator. Consequently, elastic recoil pressure builds up within the thorax in the form of PEEPi. To trigger the ventilator, the patient's inspiratory effort has to first generate a negative intrathoracic pressure in order to counterbalance the elastic recoil; it then must reach the set sensitivity.

The time at which a patient initiates an expiratory effort (in relation to the cycling of the ventilator) partly determines the success of the ensuing inspiratory effort in triggering the machine. The relationship between the onset of expiratory muscle activity and termination of mechanical inflation by the ventilator has been quantified.[23] At a pressure support of 20 cm H_2O, mechanical

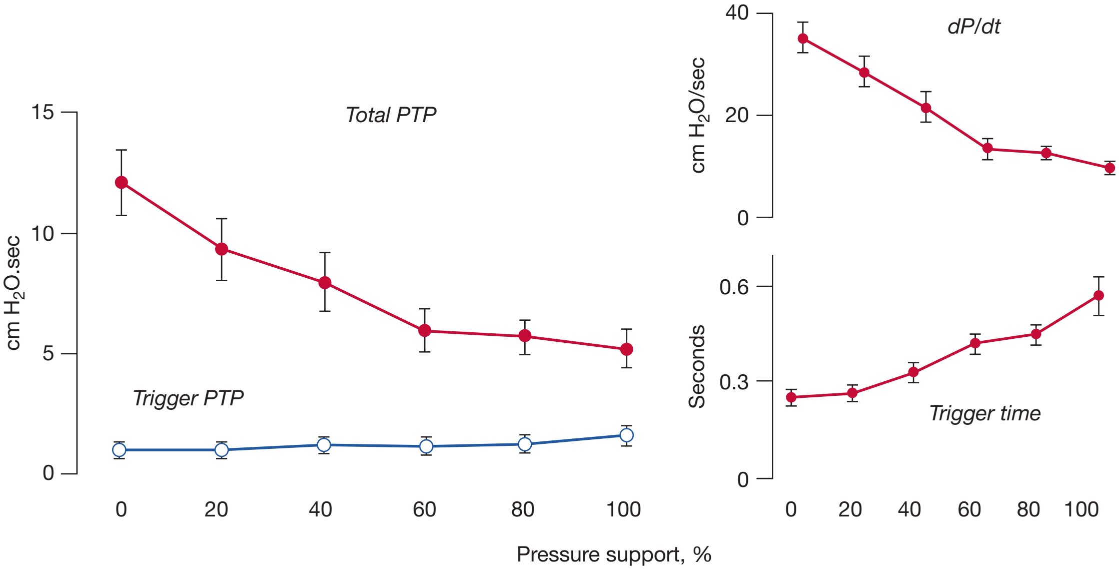

Figure 147-8 Graded increases in pressure support produced a decrease in total pressure–time product (PTP) per breath *(closed symbols)*, although PTP during the trigger phase *(open symbols)* did not change *(left panel)*. The constancy of PTP during triggering probably resulted from different factors becoming operational at different levels of assistance *(right panel)*. At low levels of pressure support, respiratory drive (dP/dt) and PEEPi were high, but triggering time was short, resulting in a large change in pleural pressure over a brief interval. At high levels of pressure support, dP/dt and PEEPi were low, but triggering time was long, resulting in a smaller change in pleural pressure over a longer time. *(Data from Leung P, Jubran A, Tobin MJ. Comparison of assisted ventilator modes on triggering, patient effort, and dyspnea. Am J Respir Crit Care Med. 1997;155:1940–1948; Tobin MJ, Jubran A, Laghi F. Patient ventilator interaction. Am J Respir Crit Care Med. 2001;163:1059–1063.)*

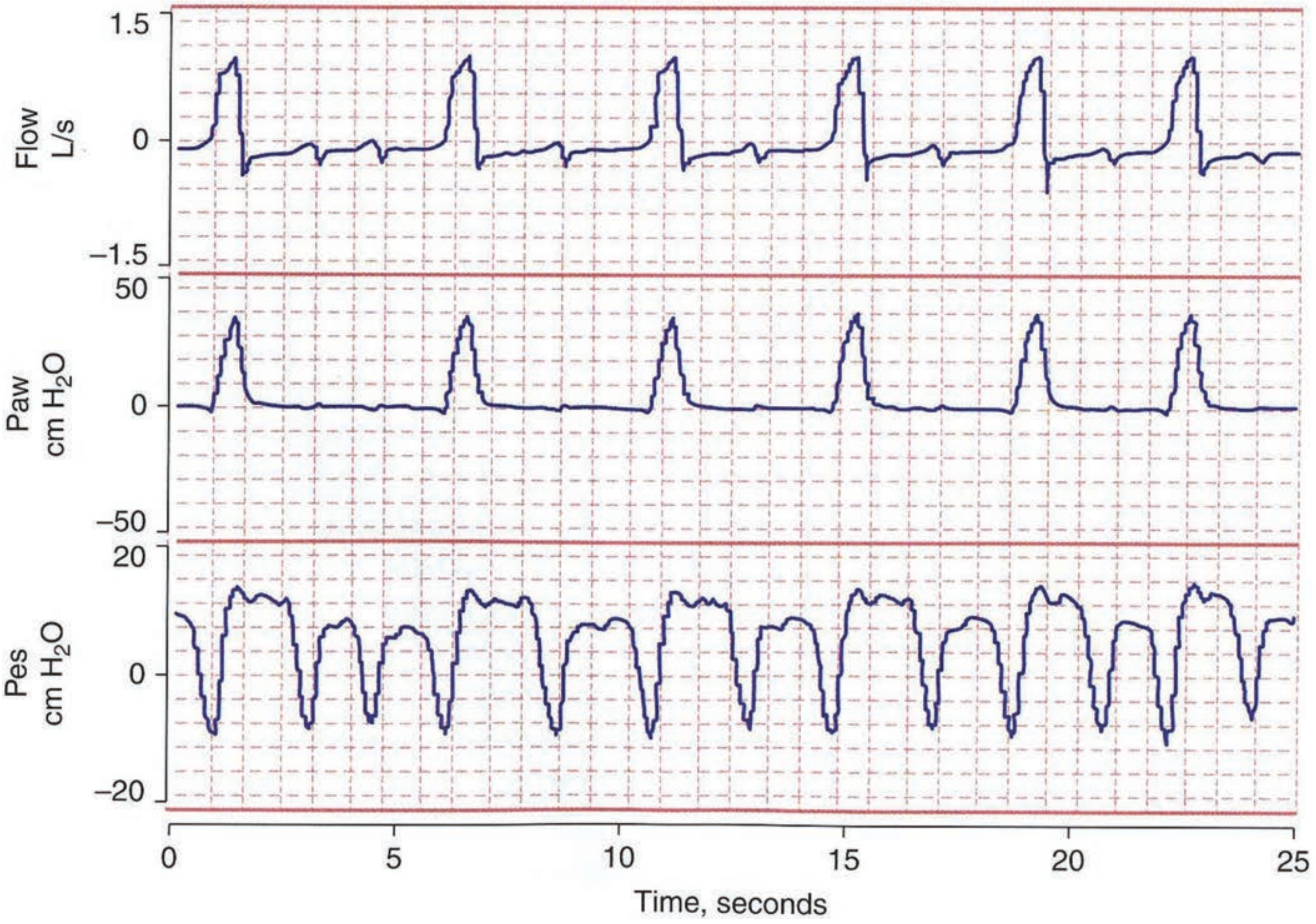

Figure 147-9 Failure to trigger the ventilator. Flow, airway pressure (Paw), and esophageal pressure (Pes) in a patient with COPD who is receiving assist-control ventilation at the following settings: tidal volume 600 mL, inspiratory flow 60 L/min, trigger sensitivity −2 cm H_2O, and positive end-expiratory pressure 0 cm H_2O. The patient's intrinsic respiratory rate is 28 breaths/min, whereas the number of breaths delivered by the ventilator is 16 breaths/min. That is, 43% of the patient's inspiratory efforts fail to trigger ventilator assistance. Contractions of the inspiratory muscles during the failed triggering attempts cause a temporary deceleration of expiratory flow and much less obvious decreases in airway pressure. The temporary decelerations in expiratory flow are followed by temporary accelerations of expiratory flow that coincide with the termination of the unsuccessful inspiratory effort. *(Reproduced with permission from Tobin MJ, Laghi F, Jubran A. Ventilatory failure, ventilator support, and ventilator weaning. Compr Physiol. 2012;2(4):2871–2921.)*

inflation continues for a longer time into neural expiration in the breaths preceding nontriggering attempts. Continuation of mechanical inflation into neural expiration counters expiratory flow, and it also decreases the time available for unopposed exhalation. Consequently, elastic recoil increases. In turn, a greater inspiratory effort will be needed to achieve effective triggering. In this way, the time at which a patient commences an expiratory effort (in relation to cycling off of mechanical inflation) partly determines the success of the ensuing inspiratory effort in triggering the ventilator.

■ Tidal Volume

Tidal volume (V_T) has become the most misunderstood ventilator setting and a source of considerable torment to patients. V_T of 12 mL/kg is the only ventilator setting proven to influence patient mortality in randomized clinical trials (RCTs).[24–26] Because the RCTs involved a comparison of V_T of 12 mL/kg versus 6 mL/kg, guidelines promoted 6 mL/kg as the ideal V_T—not only in patients with acute respiratory distress syndrome (ARDS) but extrapolated (irrationally) to all ventilated patients. In reality, V_T of 6 mL/kg has not been proven superior to 11 mL/kg (or anything in between).[26]

In five RCTs of V_T in patients with ARDS, the sole physiologic variable that discriminated between the two positive RCTs[24,25] and the three negative RCTs[27–29] was the average airway plateau pressure. Patients with significantly increased mortality had plateau pressures greater than 32 cm H_2O.[30] It never made sense physiologically to advocate setting V_T in terms of mL per kg because it ignores the physiologic variable (plateau pressure) that signals alveolar injury.[7,10] This is analogous to basing pharmacotherapy in a patient with a hypertensive emergency on milligram dosage and ignoring changes in arterial blood pressure.[30] The most recent reanalyses of data from the five RCTs of high versus low V_T have finally come around to stating that V_T should not be based on mL per kg.[31,32]

Critically ill patients have inflamed lungs, and stimulation of sensory receptors produces heightened respiratory drive and dyspnea.[1,33] Dyspneic patients react by attempting deeper inspirations. When a low V_T setting impedes this response, intense dyspnea is guaranteed through corollary discharge from the medulla oblongata to the cerebral cortex.[34] Dyspnea is amplified by hypercapnia that is axiomatic with hypoventilation; an increase in Pa_{CO_2} from 45 to 50 mm Hg induces an increase in minute ventilation of 25 L/min and tremendous air hunger.[33] Patients rebel against the racking constraint—air hunger—and buck the ventilator.[35] Caregivers use sedative and paralyzing agents to combat recalcitrant patients and restrain them on the Procrustean bed of 6 mL/kg.[32] Sedative agents

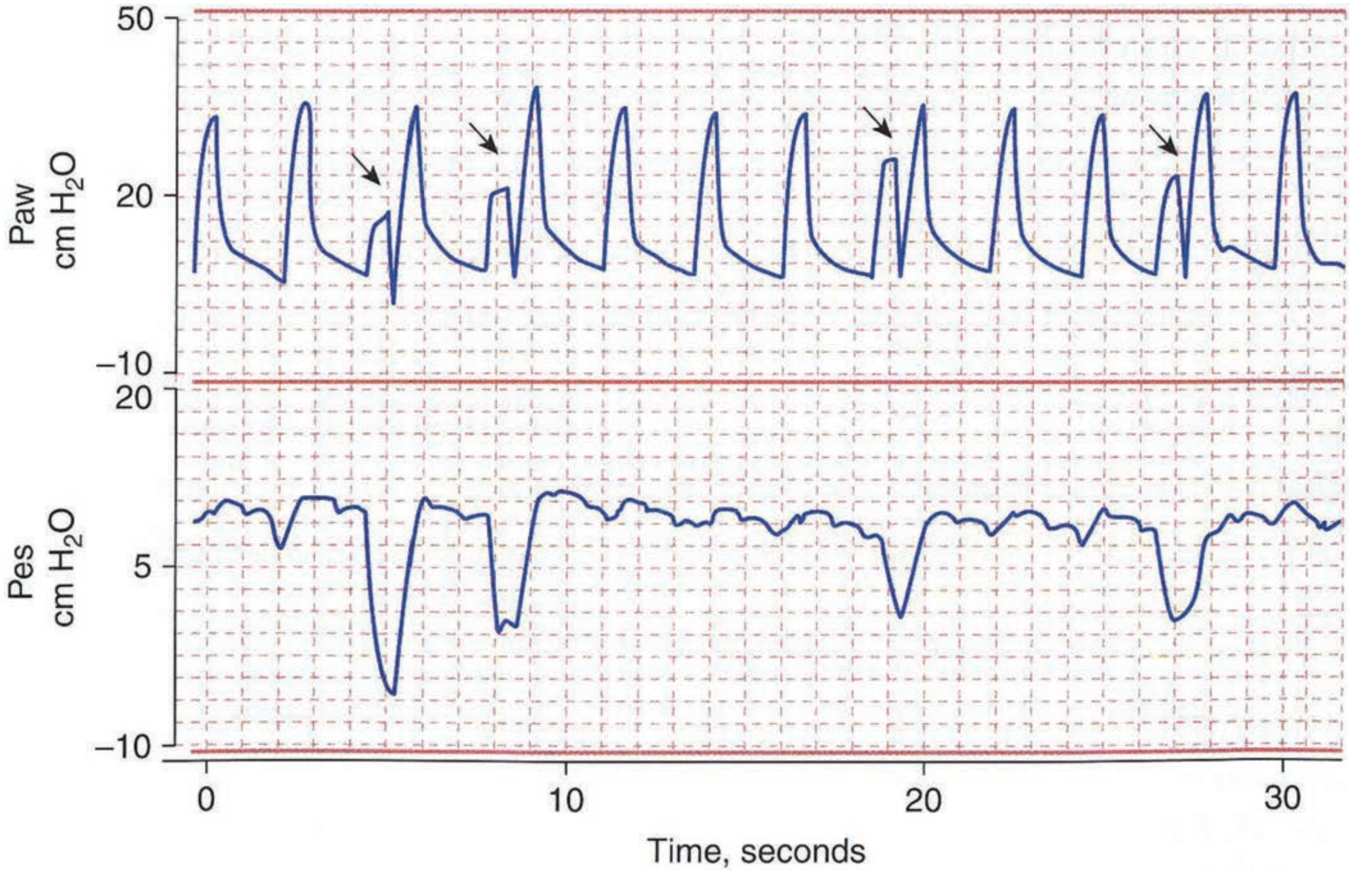

Figure 147-10 Four incidents of double triggering, each indicated by an arrowhead symbol *(↑)*. Airway pressure (Paw) and esophageal pressure (Pes) in a patient with COPD and pneumonia who was receiving assist-control ventilation at the following settings: tidal volume 600 mL, inspiratory flow 60 L/min, trigger sensitivity −2 cm H_2O, and positive end-expiratory pressure 5 cm H_2O. The duration of neural inhalation of the double-triggered breaths, roughly equivalent to the width of the associated swings in esophageal pressure, was substantially longer than the neural inhalation of the normally triggered breaths. *(Reproduced with permission from Tobin MJ, Laghi F, Jubran A. Ventilatory failure, ventilator support, and ventilator weaning. Compr Physiol. 2012;2(4):2871–2921.)*

do not relieve air hunger.[36] Neuromuscular blockers do not relieve dyspnea; indeed, they aggravate dyspnea by removing behavioral clues that alert caregivers to patient discomfort.[34]

V_T needs to be customized for each patient based on physiology and comfort. If plateau pressure is above 30 cm H_2O, it is prudent to decrease V_T to bring plateau pressure as low as possible while avoiding double triggering; a plateau pressure of less than 28 cm H_2O is a reasonable target. If plateau pressure is in the low 20s (the case for most ventilated patients), the use of unnaturally low V_T contravenes every principle of physiology.[32]

Many hospital administrators advocate the use of protocolized V_T in ventilated patients. Ungrounded in physiology, protocol advocates do not recognize that low V_T is necessarily accompanied by shortening of mechanical inspiratory time;[7] once mechanical inspiratory time becomes less than neural inspiratory time, double triggering is inevitable (Fig. 147-10). Protocol enthusiasts believe they are delivering V_T 6 mL/kg, but the patient is actually receiving 12 mL/kg—a setting proven to increase mortality.[24–26]

Respiratory Rate

Correct setting of the ventilator rate depends on the mode of ventilation employed.[21] With assist-control ventilation, the ventilator supplies a breath in response to each patient effort. With this mode, physicians commonly pay little attention to the machine rate, which may be set much lower than the patient's spontaneous rate. This gap results in two problems: (1) If the patient has a sudden decrease in respiratory center output, a low machine rate results in serious hypoventilation.[7] (2) A large discrepancy between the patient's spontaneous rate and the machine's backup rate results in a respiratory cycle with an inverse inspiratory-to-expiratory time (I:E) ratio.

Development of an inverse I:E ratio arises because inspiratory time (T_I) on the machine remains fixed at the initial setting and does not change in response to increases in the patient's spontaneous rate (Fig. 147-11).[21] For example, if the machine rate is initially set at 12

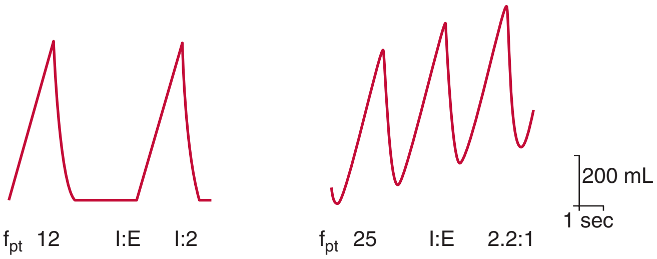

Figure 147-11 Effect of interaction between a patient's respiratory rate and the ventilator backup rate on inspiratory time–expiratory time ratio (I:E) during assist-control ventilation. Ventilator backup rate is 12 breaths/min and inspiratory time (T_I) 1.65 s. *Left panel.* If the patient's intrinsic respiratory (fpt) rate is also 12 breaths/min, the total respiratory cycle time (T_{TOT}) is 5.0 s, the expiratory time (T_E) is 3.35 s, and the I:E ratio is 1:2. *Right panel.* If the patient's respiratory rate increases to 25 breaths per minute, the new T_{TOT} is 2.4 s, T_E is 0.75 s, and I:E is 1:0.45 (or, as more conventionally noted, 2.2:1).

breaths/min (T_{TOT} of 5 s) and T_I set at 1.65 s (either set directly or indirectly as a consequence of the volume and flow settings), then expiratory time (T_E) will be 3.35 seconds. The I:E ratio will be 1:2. If the patient's spontaneous respiratory rate is increased to 25 breaths/min, T_{TOT} will be 2.4 s. Because T_I remains fixed at 1.65 s, T_E will be 0.75 s, and the I:E ratio will be 2:1. Such inverse-ratio ventilation is very uncomfortable and may lead to increased sedative use, or even to use of neuromuscular blockade, simply because of inappropriate setting of the backup rate.

Based on the above considerations, the backup rate during assist-control ventilation should be set at approximately four breaths less than the patient's spontaneous rate.[5]

■ Inspiratory Flow Rate

When patients are initially connected to a ventilator in the volume-control mode, inspiratory flow is typically set at some default value, such as 60 L/min.[5,10] Many critically ill patients have an elevated respiratory center output, and the flow setting may not be sufficient to meet the patient's flow demands. Consequently, patients will struggle against their own respiratory impedance and that of the ventilator, with consequent increase in the work of breathing.[35] This problem is usually detectable by observing a scalloped contour on the airway pressure tracing (signifying an increased level of patient work) (Fig. 147-12).[5]

Frequently, an increase in inspiratory flow will achieve a more favorable airway pressure contour (becoming more convex or outward). In some patients, however, an increase in flow causes immediate and persistent tachypnea,[37] with consequent shortening of expiratory time and increase in intrinsic positive end-expiratory pressure (PEEPi). The response to such adjustments is influenced by the Hering–Breuer reflex and is variable from patient to patient.[38]

Based on the above considerations, the clinician needs to adopt a "trial-and-error" approach, adjusting ventilator flow and observing the contour of the airway pressure tracing. No algorithm can substitute for bedside iterative adjustments.[35]

■ Fractional Inspired Oxygen Concentration (FI_{O_2})

Correction of hypoxemia is a classic goal of mechanically ventilation. Many predictive equations have been published to aid in selecting an appropriate FI_{O_2}, but none is sufficiently accurate to substitute for a trial-and-error approach.[39] Initially, FI_{O_2} is set at a high value (often 1.0) to ensure adequate oxygenation. Thereafter, the lowest FI_{O_2} that achieves satisfactory arterial oxygenation should be selected. The usual target is Pa_{O_2} 60 mm Hg or arterial saturation (Sa_{O_2}) 90%; higher values do not substantially enhance tissue oxygenation. Although it is customary to wait 30 min to assess the response to a change in FI_{O_2}, the effect is usually well defined within 10 min. When using arterial blood samples to assess oxygenation, a target of 90% for Sa_{O_2} is appropriate. If pulse oximetry is employed, an Sp_{O_2} target may result in Pa_{O_2} as low as 41 mm Hg. In white patients, a target of 92% for Sp_{O_2} indicates satisfactory oxygenation. In Black patients, however, this target may still result in significant hypoxemia.[40]

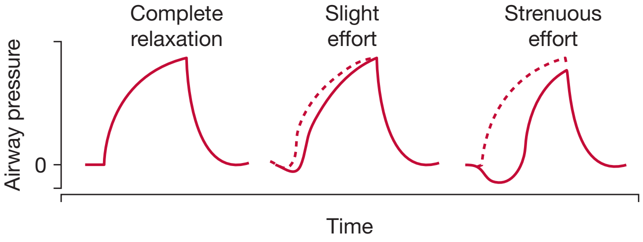

Figure 147-12 Airway-pressure waveforms recorded during assist-control ventilation. The tracings represent changes in airway pressure during inspiration in a completely relaxed patient, and in patients making slight *(center tracing)* and strenuous efforts *(tracing on right)* to breathe. The distance between the *dashed line* (representing controlled ventilation) and the *solid line* (representing spontaneous breathing) is proportional to the patient's work of breathing. *(Reproduced with permission from Tobin MJ. Mechanical ventilation. N Engl J Med. 1994;330(15):1056–1061.)*

In experimental animals, hyperoxia produces diffuse alveolar damage, with histologic changes that are indistinguishable from ARDS resulting from any other cause. No diagnostic tests distinguish oxygen-induced injury from progression of the underlying disease. Thus, the possibility of oxygen toxicity should be considered in any patient receiving an FI_{O_2} of more than 0.50 for 24 to 48 h or longer. In the face of potential oxygen toxicity, the sensible strategy is to reduce the FI_{O_2} to the lowest level compatible with adequate systemic oxygenation.

■ Positive End-expiratory Pressure

The beneficial effects of PEEP include improvement in arterial oxygenation, improvement in lung compliance, alleviation of excessive respiratory work secondary to PEEPi in patients with airflow limitation, and, possibly, a decrease in lung injury resulting from repeated alveolar collapse and reopening.[10] The principal beneficial effect of PEEP is an increase in Pa_{O_2}, which permits a decrease in FI_{O_2} and a reduction in the risk of oxygen toxicity. The major mechanism for the increase in Pa_{O_2} with PEEP is an increase in end-expiratory lung volume (Table 147-2).

Patients with ARDS develop alveolar instability and collapse. Consequently, functional residual capacity falls below closing volume, and small airways close during tidal breathing, leading to intrapulmonary shunt and hypoxemia. PEEP increases end-inspiratory lung volume by distending lung units that are already open, preventing collapse of unstable alveoli at end expiration, recruiting collapsed lung units, and redistributing liquid within the lung.[41–43] The decrease in venous admixture with PEEP is proportional to alveolar recruitment. It had been thought that the decrease in venous admixture with PEEP resulted largely from a decrease in cardiac output. This view has been shown to be erroneous.[44]

At one time PEEP was thought to decrease extravascular lung water by "pushing" alveolar fluid back into the circulation. On the contrary, PEEP can actually increase lung water.[45] As alveoli expand with application of PEEP, interstitial pressure in the extra-alveolar space decreases, leading to an increase in transmural pressure across the vessel wall. If intravascular pressures remain the same or increase, the filtration of fluid across the vessel wall increases, causing an increase in pulmonary edema; if PEEP causes a decrease in cardiac output and vascular pressures, lung water does not change. The beneficial action of PEEP in pulmonary edema is produced by redistribution of edema fluid from the alveolar space into the

TABLE 147-2 Mechanisms of Increased Pa_{O_2} with PEEP

Increase in end-expiratory lung volume	
	Distention of patent lung units
	Recruitment of collapsed lung units
	Redistribution of fluid within the lung
Decrease in shunt	
	Increase in end-expiratory lung volume
	Decrease in cardiac output

perivascular cuffs. This redistribution of lung water, in association with an increase in end-expiratory lung volume, is the major mechanism underlying the increase in Pa_{O_2} with PEEP.

In patients with ARDS, PEEP is often used for the purpose of recruiting previously nonfunctioning lung tissue. Selecting the right level of PEEP for a given patient is difficult because the severity of injury varies throughout the lungs. PEEP can recruit atelectatic areas, but it may also overdistend normally aerated areas.[43]

The addition of PEEP also influences lung mechanics. Patients with acute lung injury commonly have a decreased end-expiratory lung volume and, thus, tidal breathing occurs on the low, flat portion of the pressure–volume curve (Fig. 147-13). By shifting tidal breathing to a more compliant portion of the curve, PEEP may reduce the work of breathing.[46] In patients with an airflow limitation and PEEPi who have difficulty triggering the ventilator, the addition of external PEEP (to a level not exceeding the level of PEEPi) can help to counteract this problem, because to trigger the ventilator the alveolar pressure needs to be decreased only below the level of external PEEP, rather than below zero.[47] In addition to the injury induced by high inflation pressures, mechanical ventilation at a low end-expiratory lung volume aggravates lung injury in laboratory animals, possibly because of shear stresses associated with the repeated closing and opening of alveolar units.[48]

Overall, about 30% of patients with acute lung injury either do not benefit from PEEP or experience a fall in Pa_{O_2}.[49,50] With the patient in the supine posture, PEEP generally recruits the regions of the lung closest to the apex and sternum. Conversely, PEEP can increase the amount of nonaerated tissue in the regions close to the spine and diaphragm. Among patients in the early stages of ARDS, those with pulmonary causes, such as pneumonia, are less likely to benefit from PEEP than patients with nonpulmonary causes, such as intra-abdominal sepsis or extrathoracic trauma.[51] This distinction may be related to the type of morphologic involvement: Pulmonary causes of ARDS are characterized by alveolar filling, whereas nonpulmonary causes are characterized by interstitial edema and alveolar collapse. In the later stages of ARDS, remodeling and fibrosis may eliminate this distinction between pulmonary and nonpulmonary causes.

Three randomized trials on the effect of PEEP on survival in patients with ARDS have been undertaken: the ALVEOLI trial, the LOV trial, and the Express trial.[52–54] The results of all three trials revealed no improvement in patient survival. The ALVEOLI investigators employed a complex sliding scale for adjusting PEEP and FI_{O_2}.[52] When patients were receiving FI_{O_2} 0.60, the design mandated that patients receive either PEEP 10 or 20 cm H_2O, with no other options. At FI_{O_2} 0.80, patients were mandated to receive either PEEP 14 or 22 cm H_2O, with no other options. Such a nonscientific design robs the ALVEOLI trial of any clinical relevance. The investigators of the LOV trial employed the exact same flawed PEEP-FI_{O_2} table,[53] again depriving the LOV trial of any scientific credibility.

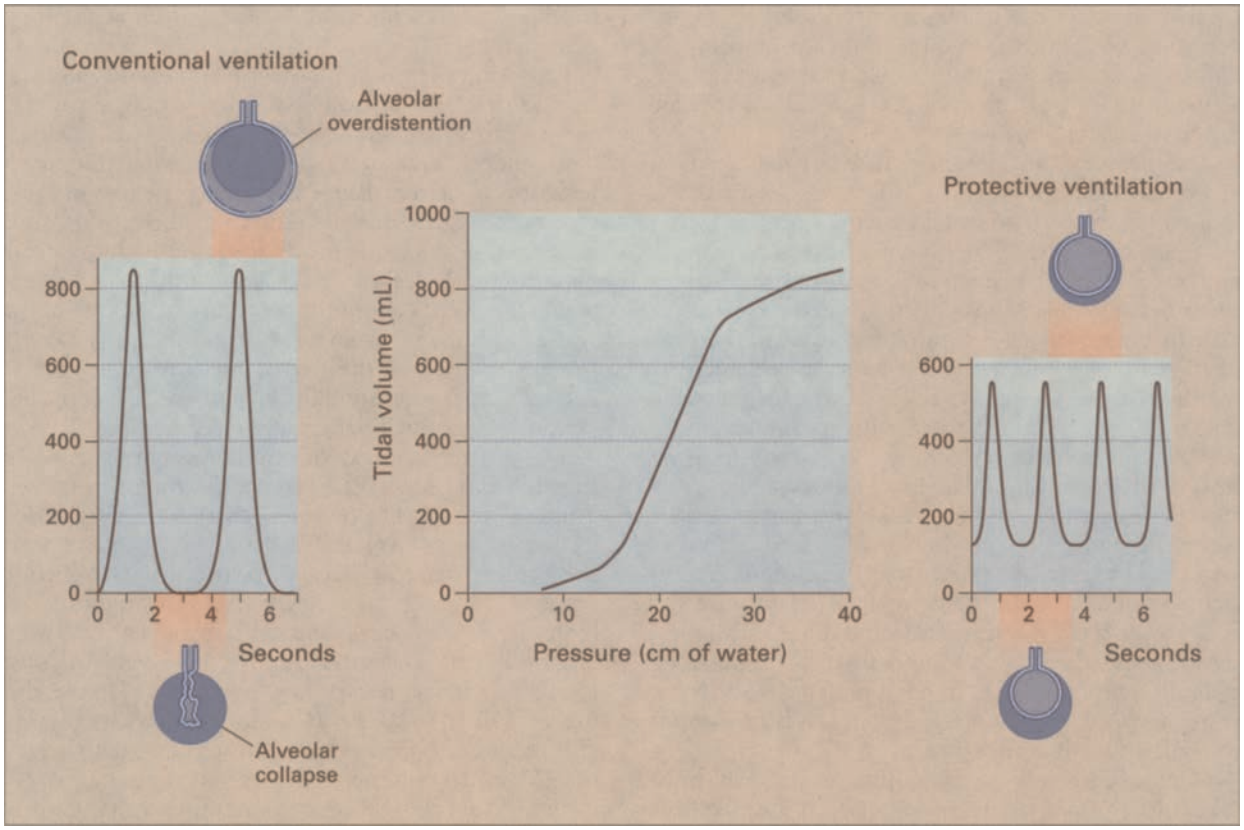

Figure 147-13 Respiratory pressure–volume curve and the effects of traditional versus protective ventilation in a 70-kg patient with acute respiratory distress syndrome. The lower and upper inflection points of the inspiratory pressure–volume curve *(center panel)* are at 14 and 26 cm H_2O, respectively. With conventional ventilation at a tidal volume of 12 mL/kg and zero end-expiratory pressure *(left panel)*, alveoli collapse at the end of expiration. The generation of shear forces during the subsequent mechanical inflation may tear the alveolar lining, and attaining an end-inspiratory volume higher than the upper inflection point causes alveolar overdistention. With protective ventilation at a tidal volume of 6 mL/kg (*right panel*), the end-inspiratory volume remains below the upper inflection point; the addition of PEEP at 2 cm H_2O above the lower inflection point may prevent alveolar collapse at the end of expiration and provide protection against the development of shear forces during mechanical inflation. *(Reproduced with permission from Tobin MJ. Advances in mechanical ventilation. N Engl J Med. 2001;344(26):1986–1996.)*

It is long recognized that the response to PEEP is very variable in ARDS. Some patients develop overdistention with PEEP 10 cm H_2O, whereas other patients show little aeration despite airway pressure of 45 cm H_2O.[43] The investigators made no attempt to determine the individual characteristics of patients; instead, every patient was treated the same in each arm of the trial.[52–54]

Talmor et al.[55] hypothesized that setting PEEP based on transpulmonary pressure might achieve a better physiologic result. They randomized 61 patients with acute lung injury or ARDS to two study arms, one where PEEP was adjusted to maintain a transpulmonary pressure between 0 and 10 cm H_2O at end expiration; in the second arm, PEEP was adjusted according to airway pressure. A trend, although not statistically significant, toward lower mortality at 28 days was observed in the esophageal catheter group. When estimating absolute pleural pressure, Talmor et al.[55] employed a correction factor of 5 cm H_2O in all patients, which constitutes a major assumption. The advantage of setting PEEP based on transpulmonary pressure has not been replicated or adopted.

BRONCHODILATOR THERAPY

Several obstacles are encountered when inhaled drugs are administered to ventilated patients. As a result, drug deposition to the lower respiratory tract is less than that in ambulatory patients. Determinants of aerosol deposition include the configuration of the endotracheal tube and ventilator circuit, ventilator mode and settings, and patient-related factors.[56]

Nebulizers have been used traditionally for the delivery of bronchodilators, but they have a number of disadvantages.[56] Nebulizer contamination causes aerosolization of bacteria, and lack of attention to this matter by healthcare providers has led to epidemics of nosocomial pneumonia.

Tidal volume and inspiratory flow must be adjusted to compensate for nebulizer flow. This factor is inconsequential in most adults, but instances of hypoventilation have occurred in patients who are unable to trigger the ventilator. Another shortcoming of nebulizers is the considerable variation in efficiency of different commercial brands, as well as among various batches of the same brand.

In contrast, metered-dose inhalers (MDIs) are easy to administer, involve less personnel time, and provide reliable dosing. Moreover, when MDIs are used with a collapsible cylindrical spacer, it is not necessary to disconnect the ventilator circuit for each treatment. Thus, risk of ventilator-associated pneumonia is decreased. Using MDIs instead of nebulizers results in substantial cost savings. The combination of an MDI and a chamber device achieves a four- to sixfold greater delivery of aerosol than MDI actuation into a connector attached directly to the endotracheal tube or into an inline device that lacks a chamber.[56] Delivery is increased with use of a higher V_T and longer fractional inspiratory time (T_I/T_{TOT}). Aerosol delivery is decreased by a high inspiratory flow rate; heating and humidification of inhaled gas reduce aerosol deposition by about 40%. When an aerosol is carried by a low-density gas, such as an 80:20 helium–oxygen mixture, aerosol delivery from an MDI is increased by more than 50%.

A dose–response study of 4, 8, and 16 puffs of albuterol (administered with an MDI and cylindrical spacer) conducted in ventilated patients with COPD (Fig. 147-14) demonstrated a decrease in airway resistance after 4 puffs of albuterol; no additional effects were noted after cumulative doses of 12 and 28 puffs.[57] In another study in ventilated patients with COPD, the bronchodilator effect of a single dose of 4 puffs of albuterol was sustained for at least 60 min. The bronchodilator effect obtained with 4 puffs of albuterol from an MDI was comparable with that obtained with 6 to 12 times the same dose given by a nebulizer.

Steps to achieve maximum bronchodilator effect with use of MDIs in ventilated patients are listed in Table 147-3.[56] Therapy

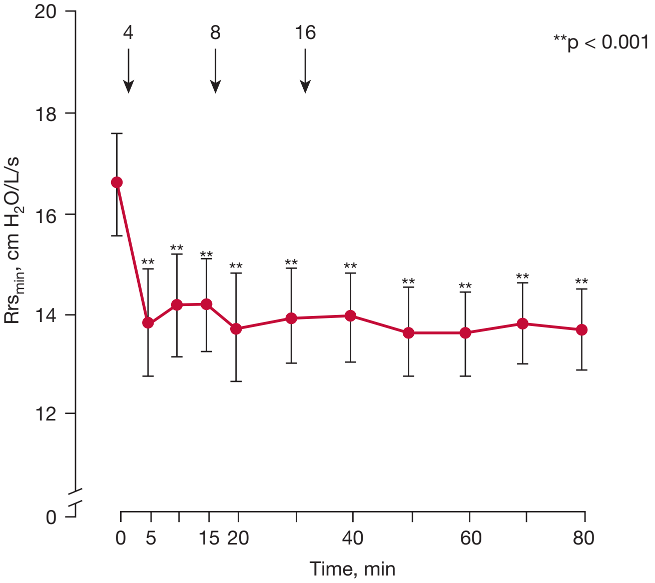

Figure 147-14 Effect of albuterol on minimal inspiratory resistance (Rrsmin) in 12 stable mechanically ventilated patients with chronic obstructive pulmonary disease. Significant decreases in resistance occurred within 5 min of administration of 4 puffs of albuterol. The addition of 8 and 16 puffs (cumulative doses of 12 and 28 puffs, respectively) did not achieve a significantly greater effect than that with 4 puffs ($p > 0.05$). *Bars* represent SE. **$p < 0.001$. *(Modifed with permission from Dhand R, Duarte AG, Jubran A, et al. Dose-response to bronchodilator delivered by metered-dose inhaler in ventilator-supported patients. Am J Respir Crit Care Med. 1996;154(2 Pt 1):388–393.)*

TABLE 147-3 Technique for Using Metered-Dose Inhalers in Mechanically Ventilated Patients

1. Assure $V_T > 500$ mL (in adults) during assisted ventilation
2. Aim for an inspiratory time (excluding the inspiratory pause) >0.30 of total breath duration
3. Ensure that the ventilator breath is synchronized with the patient's inspiration
4. Shake the metered-dose inhalers vigorously
5. Place canister in actuator of a cylindrical spacer situated in inspiratory limb of ventilator circuit[a]
6. Actuate metered-dose inhalers to synchronize with precise onset of inspiration by the ventilator[b]
7. Allow a breath hold at end-inspiration for 3–5 s
8. Allow passive exhalation
9. Repeat actuations after 20–30 s until total dose is delivered[c]

[a] *With metered-dose inhalers, it is preferable to use a spacer that remains in the ventilator circuit to avoid disconnecting the ventilator circuit for each bronchodilator treatment. Although bypassing the humidifier can increase aerosol delivery, it prolongs each treatment and requires disconnecting the ventilator circuit.*

[b] *In ambulatory patients with metered-dose inhalers placed inside the mouth, actuation is recommended briefly after initiation of inspiratory airflow. In mechanically ventilated patients using a metered-dose inhaler and spacer combination, actuation should be synchronized with onset of inspiration.*

[c] *The manufacturer recommends repeating the dose after 1 min. Metered-dose inhalers' actuation within 20–30 s after the previous dose does not compromise drug delivery.*

Modified with permission from Dhand R, Tobin MJ. Inhaled bronchodilator therapy in mechanically ventilated patients. Am J Respir Crit Care Med. 1997;156(1):3–10.

may be given in combination with either controlled or assisted ventilation, provided aerosol administration is synchronized with inspiratory flow. Based on the recommended technique for use of an MDI in ambulatory patients, some authors recommend use of a post-inspiratory breath hold; with optimal technique, however, this maneuver does not influence bronchodilator response in ventilated patients. Although humidification of the circuit reduces aerosol deposition, it is advisable not to bypass the humidifier. Even with a humidified circuit, significant bronchodilation can be achieved with as few as four puffs of a bronchodilator aerosol when the MDI technique is carefully executed.

MONITORING AND COMPLICATIONS

Several devices can be used to monitor pulmonary gas exchange, respiratory neuromuscular function, respiratory mechanics, and patient–ventilator interaction. Use of the derived information permits the physician to better tailor ventilator settings to an individual patient's physiologic characteristics, with the intent of enhancing patient comfort.[58] Monitoring of key variables helps to minimize the risk of iatrogenic complications and alerts the physician to the likelihood of an impending catastrophe, allowing sufficient time for the institution of lifesaving measures.

Patients receiving mechanical ventilation are at risk of numerous complications, including oxygen toxicity, volutrauma, air leaks, decreased cardiac output, and endotracheal tube–related problems.

WEANING

The term *weaning* literally means a slow, gradual decrease in the amount of ventilator support. The term, however, is used more commonly to refer to all methods of discontinuing mechanical ventilation.[59]

Causes of Weaning Failure

After discontinuation of mechanical ventilation, up to 25% of patients experience respiratory distress severe enough to necessitate the reinstitution of ventilator support. Among patients who cannot be weaned, disconnection from the ventilator is followed almost immediately by an increase in respiratory frequency and fall in tidal volume—that is, rapid, shallow breathing (Fig. 147-15).[60] As a trial of spontaneous breathing is continued over the next 30 to 60 min, respiratory effort increases considerably, reaching more than four times the normal value at the end of this period (Fig. 147-16).[61] The increased effort is caused mainly by worsening respiratory mechanics.[62] Respiratory resistance increases progressively, reaching about seven times the normal value at the end of a failed weaning trial; lung stiffness also increases, reaching five times the normal value; and gas trapping, measured as PEEPi, more than doubles over the course of the trial.[61] Before weaning is started, however, respiratory mechanics in such patients are similar to patients in whom subsequent weaning is successful. Thus, unknown mechanisms associated with the act of spontaneous breathing cause the worsening of respiratory mechanics in patients who are weaning failures.

In addition to the increase in respiratory effort, an unsuccessful attempt at spontaneous breathing causes considerable cardiovascular stress. Patients may experience substantial increases in right- and left-ventricular afterload during a trial of spontaneous breathing, with increases of 39% and 27% in pulmonary and systemic arterial pressures, respectively.[63] The changes are most likely attributable to the extreme negative swings in intrathoracic pressure. At the completion of a weaning trial, the level of oxygen consumption is equivalent in patients who can be weaned and in those who cannot. How the cardiovascular system meets the oxygen demand differs in the two groups of patients.

In patients who are successfully weaned, oxygen demand is met through an increase in oxygen delivery, mediated by the expected increase in cardiac output on discontinuation of positive-pressure ventilation. In patients who cannot be weaned, oxygen demand is met through an increase in oxygen extraction; these patients have a relative decrease in oxygen delivery. The greater oxygen extraction causes a substantial decrease in mixed venous oxygen saturation, contributing to the arterial hypoxemia that occurs in some patients.[63]

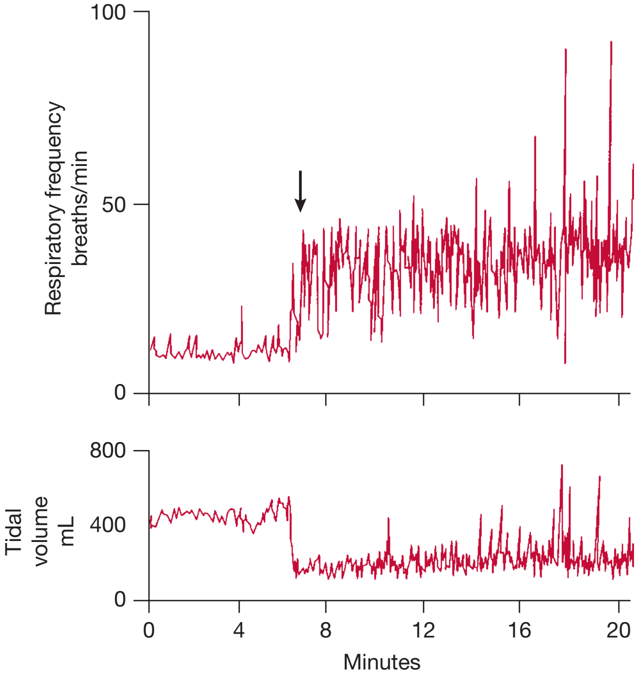

Figure 147-15 A time-series, breath-by-breath plot of respiratory frequency and tidal volume in a patient who failed a weaning trial. The *arrow* indicates the point of resuming spontaneous breathing. Rapid, shallow breathing developed almost immediately after discontinuation of the ventilator. *(Reproduced with permission from Tobin MJ, Perez W, Guenther SM, et al. The pattern of breathing during successful and unsuccessful trials of weaning from mechanical ventilation. Am Rev Respir Dis. 1986;134(6):1111–1118.)*

Over the course of a trial of spontaneous breathing, about half of the patients in whom the trial fails have an increase in Pa_{CO_2} of 10 mm Hg or more. The hypercapnia is not usually a consequence of a decrease in minute ventilation. Instead, hypercapnia results from rapid, shallow breathing, which causes an increase in dead-space ventilation.[60] In a small proportion of patients who cannot be weaned, primary depression of respiratory center output may be responsible for the hypercapnia.

Timing of the Weaning Process

One of the major challenges in the management of ventilator-supported patients is deciding on the right time to discontinue mechanical ventilation. If the physician is too conservative and postpones weaning onset, the patient is placed at an increased risk of life-threatening, ventilator-induced complications. Conversely, if weaning is begun prematurely, the patient may suffer cardiopulmonary or psychological decompensation of sufficient severity to set back a patient's clinical course.[59]

In randomized trials of different weaning techniques, most patients who had received mechanical ventilation for a week or longer were able to tolerate ventilator discontinuation on the first day that weaning-predictor tests were measured.[64,65] Many of these patients would have tolerated extubation a day or so earlier. As such, one of the main sources of weaning delay is the failure of the physician to *think* that the patient *just might* come off the ventilator. Psychological research suggests that much of this delay in ventilator weaning results from clinicians being overconfident in their intuition

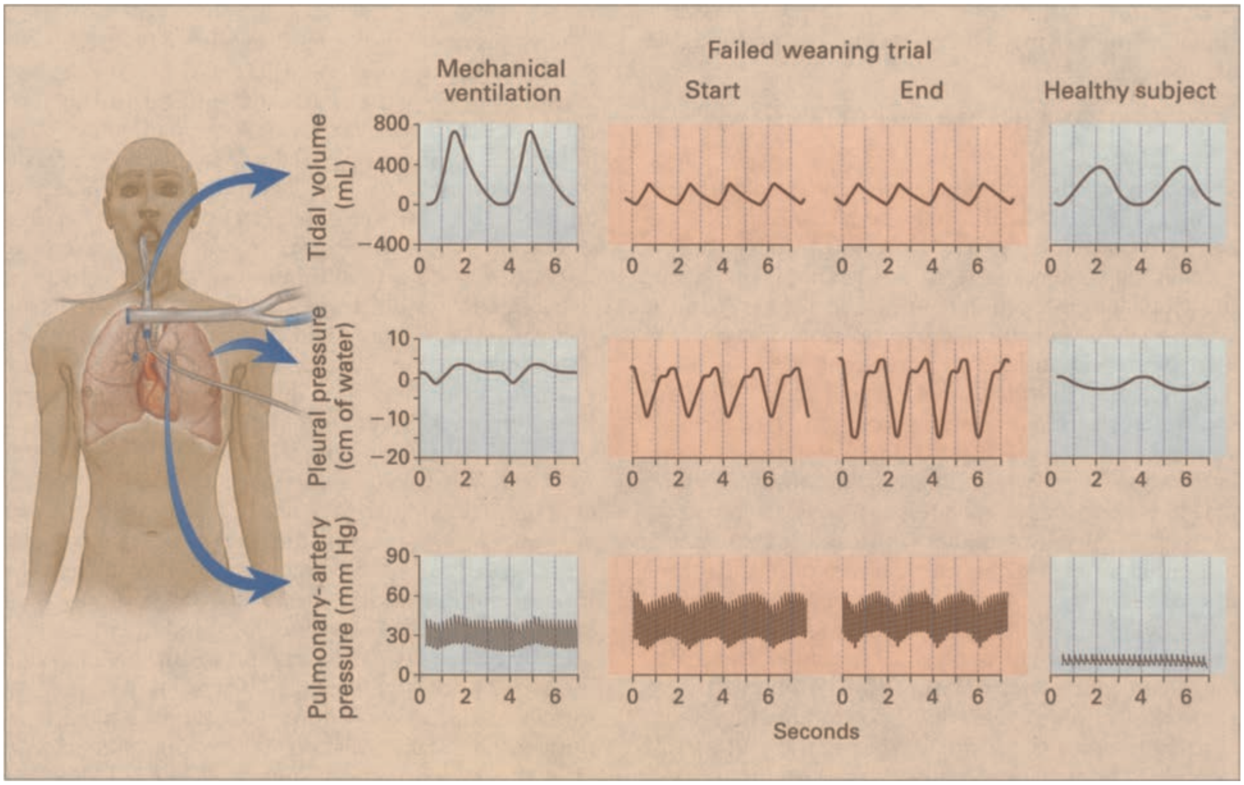

Figure 147-16 Tidal volume, pleural pressure, and pulmonary-artery pressure during assist-control ventilation and at the start and end of a failed weaning trial. During mechanical ventilation, the patient's inspiratory effort is in the normal range, and the pulmonary-artery pressure is 45/22 mm Hg. At the start of the weaning trial, tidal volume falls to 200 mL, respiratory frequency increases to 33 breaths per minute, and a swing of 11 cm H_2O in pleural pressure is noted; the pulmonary-artery pressure at the end of expiration is 60/28 mm Hg. At the end of the trial, 45 min later, the tidal volume and respiratory frequency are unchanged, a swing in pleural pressure of 19 cm H_2O is evident, and PEEPi is 4 cm H_2O; pulmonary artery pressure is 60/31 mm Hg. The values in a healthy subject are tidal volume, 380 mL; respiratory frequency, 17 breaths per minute; pleural-pressure swing, 3 cm H_2O; and pulmonary artery pressure, 18/8 mm Hg. *(Reproduced with permission from Tobin MJ. Advances in mechanical ventilation. N Engl J Med. 2001;344(26):1986–1996. Data from Tobin MJ, Perez W, Guenther SM, et al. The pattern of breathing during successful and unsuccessful trials of weaning from mechanical ventilation. Am Rev Respir Dis. 1986;134:1111–1118; Jubran A, Mathru M, Dries D, et al. Continuous recordings of mixed venous oxygen saturation during weaning from mechanical ventilation and the ramifications thereof. Am J Respir Crit Care Med. 1998;158:1763–1769; Jubran A, Tobin MJ. Pathophysiologic basis of acute respiratory distress in patients who fail a trial of weaning from mechanical ventilation. Am J Respir Crit Care Med. 1997;155:906–915.)*

that a patient is not ready for a weaning trial.[59] Another source of error is the failure of clinicians to pay close attention to pretest probability—they fail to recognize the importance of Bayesian principles in clinical decision-making. When taking care of a ventilator-supported patient, physicians should be mindful of these cognitive processes and employ compensatory tactics, specifically the use of screening tests, to spot a patient's readiness for weaning. By alerting an unsuspecting physician to a patient's readiness to tolerate unassisted ventilation—hours or days before he or she would otherwise order a spontaneous breathing trial—weaning-predictor tests circumvent the cognitive errors inherent in clinical decision-making.[59]

Physicians commonly view diagnostic testing in monolithic terms: a test is a test is a test. In reality, diagnostic testing has to satisfy two very different tasks: one is screening, the other is confirmation.[66] The characteristics of these test types differ, and a single diagnostic test rarely fulfills both functions.[66]

The fundamental job of a weaning-predictor test is screening. Because the goal is to not miss anyone with the condition under consideration, a good screening test has a very low rate of false-negative results; to achieve this goal, a higher false-positive rate is acceptable. Thus, an ideal screening test has a very high sensitivity. The ratio of respiratory frequency to tidal volume (f/V_T) meets this requirement; numerous studies have documented that its sensitivity is 0.90 or higher.[67,68]

The f/V_T ratio must be calculated during spontaneous breathing. Measurements of f/V_T in the presence of pressure support or CPAP will result in inaccurate predictions of weaning outcome.[59] The higher the f/V_T ratio, the more rapid and shallow the breathing and the greater the likelihood of unsuccessful weaning. A ratio of 100 discriminates between successful (<100) and unsuccessful (>100) attempts at weaning.[67]

Because the results of screening tests are often negative, an ideal screening test should be simple, expeditious, and safe.[66] Measurement of f/V_T takes a minute or so to perform. In contrast, a trial of spontaneous breathing takes 0.5 to 2 h to perform, during which time attendants commonly leave the patient's room. Accordingly, a spontaneous breathing trial does not satisfy the criteria for a desirable screening test, and commencing weaning with such a trial is likely to prolong the weaning process.[59]

If clinicians obtain weaning-predictor tests at the earliest point that a patient might tolerate extubation, the results will be negative at least half the time. In studies of weaning-predictor tests, however, positive results have been obtained at least 75% of time.[68] Such a high rate of positive test results indicates that clinicians were being too slow in initiating the weaning process.

When a screening test is positive, the diagnostician proceeds to a confirmatory test.[66] A positive confirmatory test result essentially rules in a condition: the likelihood of a patient tolerating a trial of extubation is very high. An ideal confirmatory test has a very low rate of false-positive results, that is, a high specificity. The specificity of a weaning trial is not known and will never be known because its determination would involve an unethical experiment—extubating all patients who fail a weaning trial and counting how many are reintubated.[59]

Weaning Trials

Four methods can be used for conducting a weaning trial. The oldest is to perform trials of spontaneous breathing several times a day, using a T-tube circuit that contains an enriched supply of oxygen.[59] Initially, 5 to 10 min in duration, T-tube trials are extended and repeated several times a day until the patient can sustain spontaneous ventilation for several hours. This approach has become unpopular because it involves considerable time on the part of ICU staff.

For many years, IMV was the most popular methods of weaning.[59] With IMV, the mandatory rate from the ventilator is reduced in steps of 1 to 2 breaths/min, and an arterial blood gas is obtained about 30 min after each rate change.[16] Unfortunately, titrating the number of breaths from the ventilator in accordance with the results of arterial blood gases can produce a false sense of security. As few as two to three positive-pressure breaths per minute can achieve acceptable blood gases, but these values provide no information regarding the patient's work of breathing (which may be excessive). At IMV rates of 14 breaths/min or less, patient inspiratory efforts are increased to a level likely to cause respiratory muscle fatigue.[17,18] Moreover, this occurs not only with the intervening spontaneous breaths, but also with ventilator-assisted breaths. Consequently, use of IMV may actually contribute to the development of respiratory muscle fatigue or prevent its recovery.

When pressure support is used for weaning, the level of pressure is reduced gradually (decrements of 3–6 cm H_2O) and titrated based on the patient's respiratory frequency.[19,64] When the patient tolerates a minimal level of pressure support, he or she is extubated. What exactly constitutes a "minimal level of pressure support" has never been defined.[20]

The fourth method of weaning is to perform a single, daily T-tube trial, lasting for 30 to 120 min.[59,65] If this trial is successful, the patient is extubated. If the trial is unsuccessful, the patient is given at least 24 h of respiratory muscle rest with full ventilator support before another trial is performed.[62]

Two randomized trials have revealed that weaning time was three times longer with IMV than it was with the use of T-tube trials.[64,65] In a study involving patients with respiratory difficulties on attempted weaning, T-tube trials halved the weaning time as compared with pressure support;[65] in another study, the weaning time was similar with the two methods.[64] Performing trials of spontaneous breathing once a day is as effective as performing such trials several times a day, but much simpler.[65] In patients not expecting to pose any particular difficulty with weaning, a half-hour trial of spontaneous breathing is as effective as a 2-h trial.[69] In a study of patients receiving prolonged mechanical ventilation at a long-term acute care hospital, the rate of successful weaning was more than 40% higher with trials involving unassisted breathing through a tracheostomy than with use of pressure support.[70]

In conclusion, to minimize the likelihood of either delayed weaning or premature extubation, a two-step diagnostic strategy is recommended: measurement of weaning predictors followed by a weaning trial. The critical step is for the physician to contemplate the possibility that a patient just might be able to tolerate weaning. Such diagnostic triggering is facilitated through use of a screening test, which is the rationale for measurement of weaning-predictor tests. It is important not to postpone this first step by waiting for a more complex diagnostic test, such as a T-tube trial.

EXTUBATION

Decisions about weaning and extubation are commonly conflated. When a patient tolerates a weaning trial without distress, a clinician feels reasonably confident that the patient will be able to sustain spontaneous ventilation after extubation. Before removing the endotracheal tube, however, the clinician also has to judge whether the patient will be able to maintain a patent upper airway after extubation.[59,71]

Among patients who are expected to tolerate extubation without difficulty, about 10% to 20% fail and are reintubated.[64] Mortality among reintubated patients is more than six times as high as mortality among patients who tolerate extubation.[69] The reason for the higher mortality is unknown. It might be related to the development of new problems after extubation or complications associated with reinsertion of a new tube. A more likely explanation is that the need for reintubation reflects greater severity of the underlying illness.[71]

Because of the high mortality associated with reintubation, clinicians are eager to avoid this problem. The major diagnostic test used to predict the success of an extubation attempt is a weaning trial. In contrast to the many studies that have evaluated the reliability of diagnostic tests that predict the outcome of a trial of weaning, the diagnostic accuracy of weaning trials in predicting the outcome of a trial of extubation is unknown. Moreover, the accuracy is impossible to determine because the experiments necessary to measure the sensitivity and specificity of a weaning trial (for predicting extubation outcome) are unethical.

Many physicians find it convenient to extubate a patient once he or she can breathe comfortably on a pressure support of about 7 cm H_2O and PEEP 5 cm H_2O based on the belief that such "minimal ventilator settings" are simply overcoming the resistance engendered by an endotracheal tube.[72] This claim ignores the inflammation and edema that develops in the upper airways after an endotracheal tube has been in place for a day or more. On removal of the tube, the mucosal swelling produces an increase in upper airway resistance.

Straus et al.[73] demonstrated experimentally that the respiratory work dissipated against the supraglottic airway after extubation is almost identical to the work dissipated against an endotracheal tube before extubation. Thus, applying any level of pressure support causes physicians to underestimate the respiratory resistance a patient will encounter after extubation.

The addition of a small amount of pressure support produces surprisingly large reductions in inspiratory work in ventilated patients: 5 cm H_2O decreases inspiratory work by 31% to 38%, and 10 cm H_2O decreases work by 46% to 60%.[20,74] Independently, addition of 5 cm H_2O of PEEP can decrease work of breathing by as much as 40% in ventilated patients.[74] In the case of a patient who might experience cardiorespiratory difficulties after extubation, it is incumbent on a physician to ensure that the patient is able to breathe comfortably for about 30 minutes in the complete absence of pressure support or PEEP before removal of the endotracheal tube.[72]

CONCLUSION

Although the ventilator is a machine, the greatest challenge in its operation is cognitive, not technical. This distinction was highlighted during the COVID-19 pandemic. A generation of physicians nurtured on protocols and guidelines were left in the lurch when they faced an onslaught of patients requiring decisions based on clinical judgment. Employing protocols that cautioned against noninvasive strategies and advocated liberal use of intubation contributed to the high mortality of COVID-19 patients in many hospitals. No algorithm can substitute for trial and error (also known as the scientific method: hypothesis and experimentation), interpreting the patient's response in a physiologic framework, and making iterative adjustments.

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CHAPTER 148

Principles of Noninvasive Pressure-targeted Ventilation

Bernardo Selim
Janet Hilbert
Henry K. Yaggi

INTRODUCTION

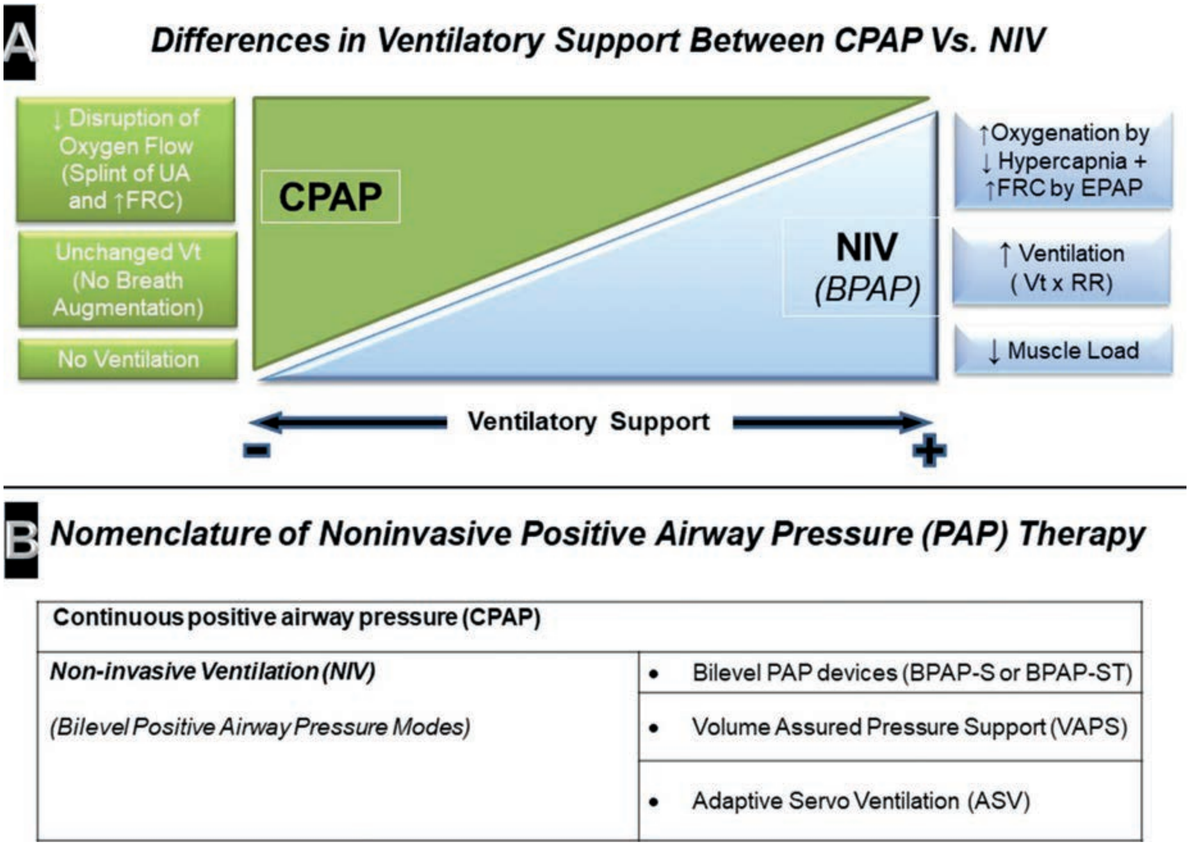
Emergent technologies have provided a wide variety of noninvasive ventilation (NIV) devices and modes to deliver treatment for respiratory failure through a mask or tracheotomy, both in the acute care setting and at home. An in-depth understanding of NIV indications, modes, and settings is crucial to guarantee delivery of effective therapy. However, knowledge gaps exist in most practitioners regarding matching advanced NIV modes and settings to a patient's unique respiratory failure pathophysiology. In this chapter we review the principles of NIV devices and modes, assess indications for its use (e.g., neuromuscular and chest wall disease, obstructive airway diseases, obesity-related respiratory failure), and review the most recent published literature, including guidelines in the application (and adjustment) of these devices during hospitalization and at home. For additional information, the reader is referred to Chapters 98, 99, and 142, in which the use of noninvasive ventilation in management of sleep-disordered breathing and the pathogenesis of hypoventilatory disorders are discussed.

PRINCIPLES OF PRESSURE-TARGETED NONINVASIVE VENTILATION

Before considering the details of a noninvasive mechanical ventilator circuit and important underlying physiologic principles, we provide a brief review of the history of the modality.

Brief Historic Perspective of Noninvasive Positive Airway Pressure Modes

In 1981, Sullivan published his seminal paper describing a novel therapeutic modality to successfully treat obstructive sleep apnea (OSA). By applying a mask ("soft plastic tubes shaped to fit each naris"), hoses, and a "vacuum cleaner–blower motor with variable speed control," he was able to deliver pressurized air to a patient's upper airway. He coined the term *continuous positive airway pressure* (CPAP) to describe the delivery of constant pressure throughout the respiratory cycle.[1] Today, CPAP is a commonly prescribed noninvasive positive airway pressure mode that provides a pneumatic splint to the pharyngeal airway (preventing it from collapsing during sleep), along with improvement in end-expiratory lung volumes and oxygenation (improvement of ventilation–perfusion matching). However, by providing the same single (constant) pressure during inhalation and exhalation, CPAP does not support or augment a patient's tidal volume and, therefore, minute ventilation (Fig. 148-1A).


A
Differences in Ventilatory Support Between CPAP Vs. NIV
↓ Disruption of Oxygen Flow (Splint of UA and ↑FRC)
Unchanged Vt (No Breath Augmentation)
No Ventilation
CPAP
NIV (BPAP)
↑Oxygenation by ↓ Hypercapnia + ↑FRC by EPAP
↑ Ventilation (Vt x RR)
↓ Muscle Load
Ventilatory Support
-
+
B
Nomenclature of Noninvasive Positive Airway Pressure (PAP) Therapy

Continuous positive airway pressure (CPAP)	
Non-invasive Ventilation (NIV) *(Bilevel Positive Airway Pressure Modes)*	• Bilevel PAP devices (BPAP-S or BPAP-ST) • Volume Assured Pressure Support (VAPS) • Adaptive Servo Ventilation (ASV)

Figure 148-1 Differences between CPAP and NIV in respiratory support. **A.** CPAP versus NIV in respiratory support. **B.** Types of positive airway pressure modes: BPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; FRC, functional residual capacity; NIV, noninvasive ventilation; RR, respiration rate; ST, spontaneous-timed; UA, upper airway; Vt, tidal volume.

In 1990, almost 10 years after the introduction of CPAP, Sanders and Kern published a novel research article describing the treatment of OSA by "independently adjusted inspiratory and expiratory positive airway pressures" via a nasal mask.[2] By installing a flow sensor (input), the device was able to correctly detect (and differentiate) the patient's breath phase to deliver a different therapeutic pressure during inhalation—inspiratory positive airway pressure (IPAP)—and during exhalation—expiratory positive airway pressure (EPAP). This research introduced for the first time the principles of bilevel positive airway pressure ventilation (BPAP). With the introduction of digital algorithmic analysis of the flow signal (input), advanced bilevel devices have developed the capability to self-modulate IPAP and/or EPAP as well as to "time" the initiation (trigger) and/or termination (cycle) of each breath. Different from CPAP, these advanced modes of BPAP, collectively known as *noninvasive ventilation* (NIV), have been applied either invasively through a tracheotomy tube or noninvasively via a mask for long-term management of patients with respiratory failure in need of minute ventilation augmentation and/or muscle load reduction (Fig. 148-1A,B).

Pathophysiology: Decision Framework in Selecting NIV Modes

A practical approach to NIV selection is based on analysis of arterial blood gases.

Respiratory Failure Related to CO_2 Imbalance

Respiratory failure encompasses a heterogeneous group of breathing disorders with diverse pathophysiologic mechanisms, impacting carbon dioxide (CO_2) balance, oxygenation levels, or both (Table 148-1).

In practical terms, respiratory failure associated primarily with changes in CO_2 balance may be divided into two main groups as reflected in arterial carbon dioxide tension (Pa_{CO_2}) obtained by arterial blood gas (ABG). In one group, alveolar hypoventilation disorders ("pump failure") are associated with hypercapnia (Pa_{CO_2} $\geq$45 mm Hg) as a result of increased respiratory system load (chest wall and lung loads, e.g., kyphoscoliosis or chronic obstructive pulmonary disease), decreased respiratory drive (ventilation control abnormalities, e.g., opioid overdose), and/or inadequate respiratory muscle strength/endurance (e.g., neuromuscular disorders), or a combination of them (Fig. 148-2A,B).

In contrast, the Central Sleep Apnea Syndrome (CSAS) group consists of eucapnic (Pa_{CO_2} $\leq$45 mm Hg) or even hypocapnic (Pa_{CO_2} <40 mm Hg) breathing disorders characterized by intermittent reduction (or absence) of respiratory efforts (e.g., heart failure–related Cheyne–Stokes respiration [CSR]). CSAS is most often the result of unstable breathing caused by high loop gain. Loop gain is an engineering term that describes in pulmonary physiology the degree of response, in this case, of the respiratory control system, after a ventilatory disturbance results in minimal changes of nocturnal Pa_{CO_2}.[3] The higher the loop gain, the higher the respiratory instability. Loop gain has three components: circulatory time, plant gain, and controller gain. The prolonged lung-to-brain circulatory delay is commonly seen in heart failure (HF) due to reduced cardiac output. In HF, the circulatory delay is doubled (10–20 s). Controller gain is related to chemosensitivity

TABLE 148-1 Pathophysiology of Hypoventilation Disorders and Central Sleep Apnea Syndromes

Pathophysiology	Disorders	Notes
High Arterial Carbon Dioxide Tension ***(Alveolar Hypoventilation Disorders)***	*Ventilatory control abnormalities:* • E.g., congenital or acquired central alveolar hypoventilation	Ventilatory control is affected by mutations in the PHOX2B gene (congenital central alveolar hypoventilation syndrome) or secondary (acquired) compromise of the hindbrain (brainstem and cerebellum) by infections, autoimmune diseases, or paraneoplastic syndromes
	Neuromuscular disorders: • E.g., amyotrophic lateral sclerosis (ALS)	Inability to translate ventilatory center output into appropriate output by the neuromuscular apparatus, thus rendering ventilatory control ineffective
	Chest wall abnormalities: • E.g., kyphoscoliosis or obesity hypoventilation syndrome (OHS)	Increased work of breathing and limited lung expansion due to thoracic cage abnormalities, such as skeletal rigidity or excessive load from adipose tissue, blunts the intended response to CO_2
	Lung disorders: • E.g., chronic obstructive pulmonary disease (COPD)	Mechanical effectiveness of ventilation is compromised by ventilation–perfusion inequality, respiratory muscle dysfunction, and changes in chemosensitivity of the respiratory centers; during sleep, ventilation failure is particularly evident in REM sleep, when persistence of ventilation is primarily dependent on diaphragm activity and central (nonmetabolic) respiratory drive
Normal or Reduced Carbon Dioxide Tension ***(Central Sleep Apnea Syndromes)***	*Treatment-emergent central sleep apnea*	High loop gain induced by CPAP therapy for obstructive sleep apnea syndrome; OSA phenotype characterized by ventilatory control center instability in response to minor CO_2 fluctuations induced by CPAP therapy
	Central sleep apnea with Cheyne–Stokes respiration	Primarily seen in patients with congestive heart failure with reduced or preserved ejection fraction; high loop gain with feedback delays induced by poor cardiac output; patients exhibit enhanced ventilatory drive leading to cyclic over- and undershoot of ventilation (crescendo and decrescendo breathing pattern interspaced by central apneic events)
	Central sleep apnea due to high-altitude periodic breathing	High loop gain–induced CSA by hypoxemia as a result of decreased fractional oxygen concentration at high altitude
	Central sleep apnea due to medications or substances: • E.g., opioids	Loop gain is variable, and opioid effects on the pre-Bötzinger complex (respiratory rhythm generator) result in reduction of respiratory rate

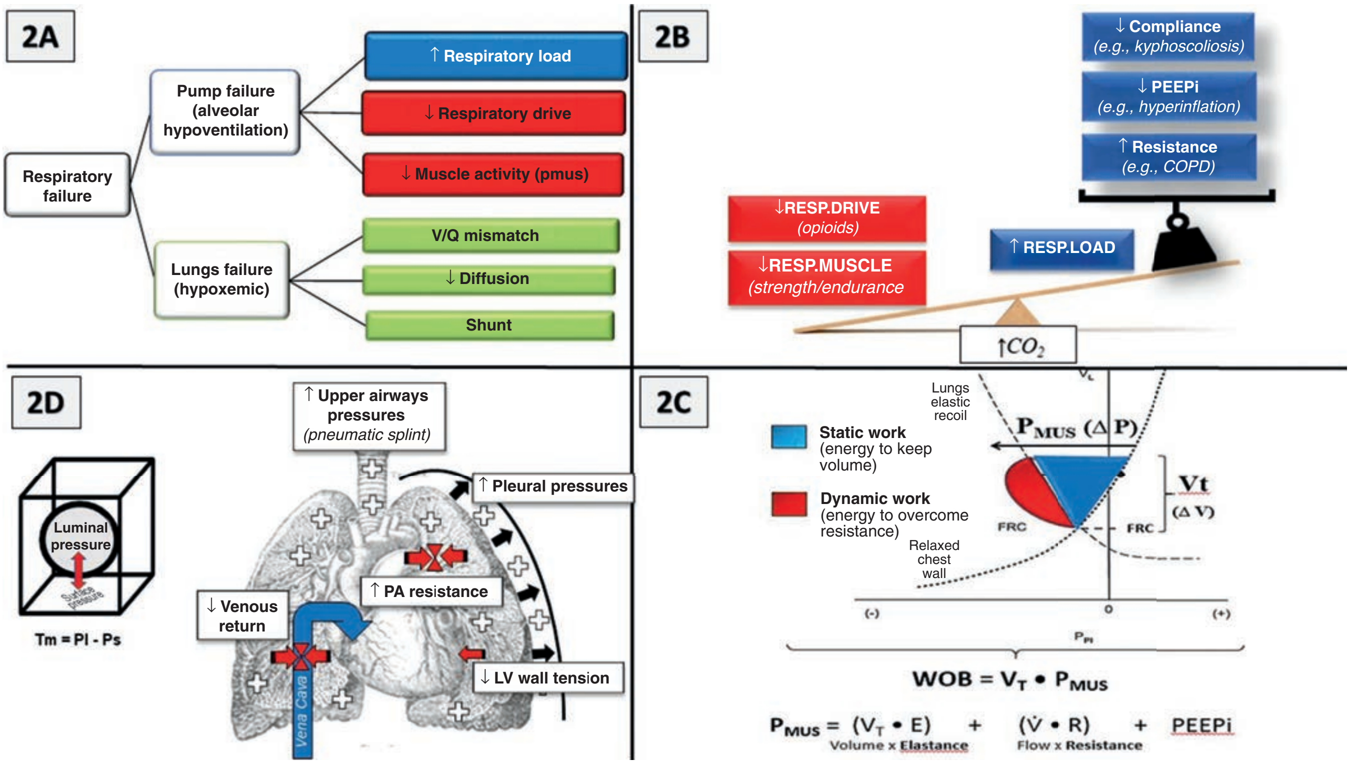

2A
Respiratory failure
Pump failure (alveolar hypoventilation)
↑ Respiratory load
↓ Respiratory drive
↓ Muscle activity (pmus)
Lungs failure (hypoxemic)
V/Q mismatch
↓ Diffusion
Shunt
2B
↓ Compliance (e.g., kyphoscoliosis)
↓ PEEPi (e.g., hyperinflation)
↑ Resistance (e.g., COPD)
↓RESP.DRIVE (opioids)
↓RESP.MUSCLE (strength/endurance
↑ RESP.LOAD
↑CO2
2D
Luminal pressure
Surface pressure
Tm = Pl - Ps
↑ Upper airways pressures (pneumatic splint)
↑ Pleural pressures
↑ PA resistance
↓ Venous return
↓ LV wall tension
Vena Cava
2C
Lungs elastic recoil
Static work (energy to keep volume)
Dynamic work (energy to overcome resistance)
Relaxed chest wall
PMUS (Δ P)
Vt (Δ V)
FRC
FRC
VL
(-)
0
(+)
Ppl
WOB = VT • PMUS
PMUS = (VT • E) + (V̇ • R) + PEEPi
Volume x Elastance
Flow x Resistance

Figure 148-2 Pathophysiology of respiratory failure. **A.** Etiology of respiratory failure. **B.** Alveolar hypoventilation. **C.** Campbell diagram with representation of work of breathing (WOB). Work of breathing is the result of delta volume (tidal volume, Vt) × pressure from muscle contraction (Pmus) needed to overcome the respiratory load from the respiratory system (equation of motion defined by compliance, resistance, and intrinsic positive end-expiratory pressure (PEEPi). Pmus is the pressure change generated by contraction of inspiratory muscles (shown by the length of the *horizontal arrow*). The *diagonally hatched area* is work done against resistance, and the *stippled area* is work done against elastance of lung and chest wall. Work of breathing is the summation of static work (energy required to maintain volume) and dynamic work (energy necessary to keep flow and overcome resistance). **D.** Transmural pressures. The transmural pressure (Tm) is equal to the luminal pressure (Pl) − surface pressure (Ps). This relationship defines the working pressure of the heart chambers and blood vessels within the intrathoracic cavity. The same principle applies for the transpulmonary pressures (alveolar pressure minus pleural pressure) that define the lung volumes and the perialveolar capillary vascular resistance. CO_2, carbon dioxide; E, elastance; LV, left ventricle; PA, pulmonary artery; PEEPi, intrinsic positive end expiratory pressure; Pmus, pressure from muscle contraction; R, resistance; Tm, transmural pressure; V, flow; V/Q, ventilation to perfusion ratio; Vt, tidal volume; WOB, work of breathing.

(heightened ventilatory response to minor CO_2 fluctuations), while plant gain is related to the modification in carbon dioxide tension (Pa_{CO_2}) resulting from a given change in ventilation. High loop gain predisposes to hyperventilation (overshoot) and subsequent lowering of Pa_{CO_2} below the apneic threshold, which is elevated during sleep. When CO_2 drops below the apneic threshold, a central apnea event (undershoot) occurs and lasts until the CO_2 increases above the threshold.[4] Therefore, Pa_{CO_2} levels oscillate above and below the apneic threshold, thereby causing the typical cyclical hyperventilation followed by central apnea pattern that defines CSR[5] (Fig. 148-3).

Treatment of these diverse Pa_{CO_2} disorders shares some common basic principles. In general, if the disorder is associated with underlying medical illnesses or medications, treatment of the underlying condition may improve the breathing disorder (e.g., downtitration of opioid doses in chronic opioid users or optimization of guideline-directed congestive heart failure therapy in CSR). When correction of the underlying problem is not achievable, the most frequently applied treatments are based on NIV therapy. In general, BPAP and volume-assured pressure support (VAPS) are modes usually recommended for patients with predominant alveolar hypoventilation in need of ventilatory support, while adaptive servo-ventilation (ASV) mode is indicated for patients with CSAS and preserved ventilation. However, phenotypic variance in breathing disorders and the individual response to NIV should be considered in the final decision of the optimal mode and settings (precision sleep medicine)[6,7] (Table 148-2).

Respiratory Failure Related to Hypoxemia Without Hypercapnia

Patients with hypoxemic (nonhypercapnic) respiratory failure are less likely to benefit from NIV. In these patients, hypoxemia is mainly the result of shunt, diffusion barrier, ventilation/perfusion (V/Q) mismatch, or a combination of these mechanisms (Fig. 148-2A). In these patients, systemic oxygen content depends mainly on hemoglobin and V/Q matching, and tends to plateau as minute ventilation (MV) or alveolar ventilation (V_A) are increased with bilevel PAP therapy. Therefore, choosing NIV in this population should take into consideration the etiology of hypoxemic respiratory failure and whether other forms of oxygen delivery (e.g., high-flow nasal cannula) may provide the oxygen support needed.[8]

■ Physiologic Effects of Pressure-targeted Noninvasive Ventilation

Below we discuss the cardiopulmonary effects of NIV, including potential adverse effects and contraindications to its use.

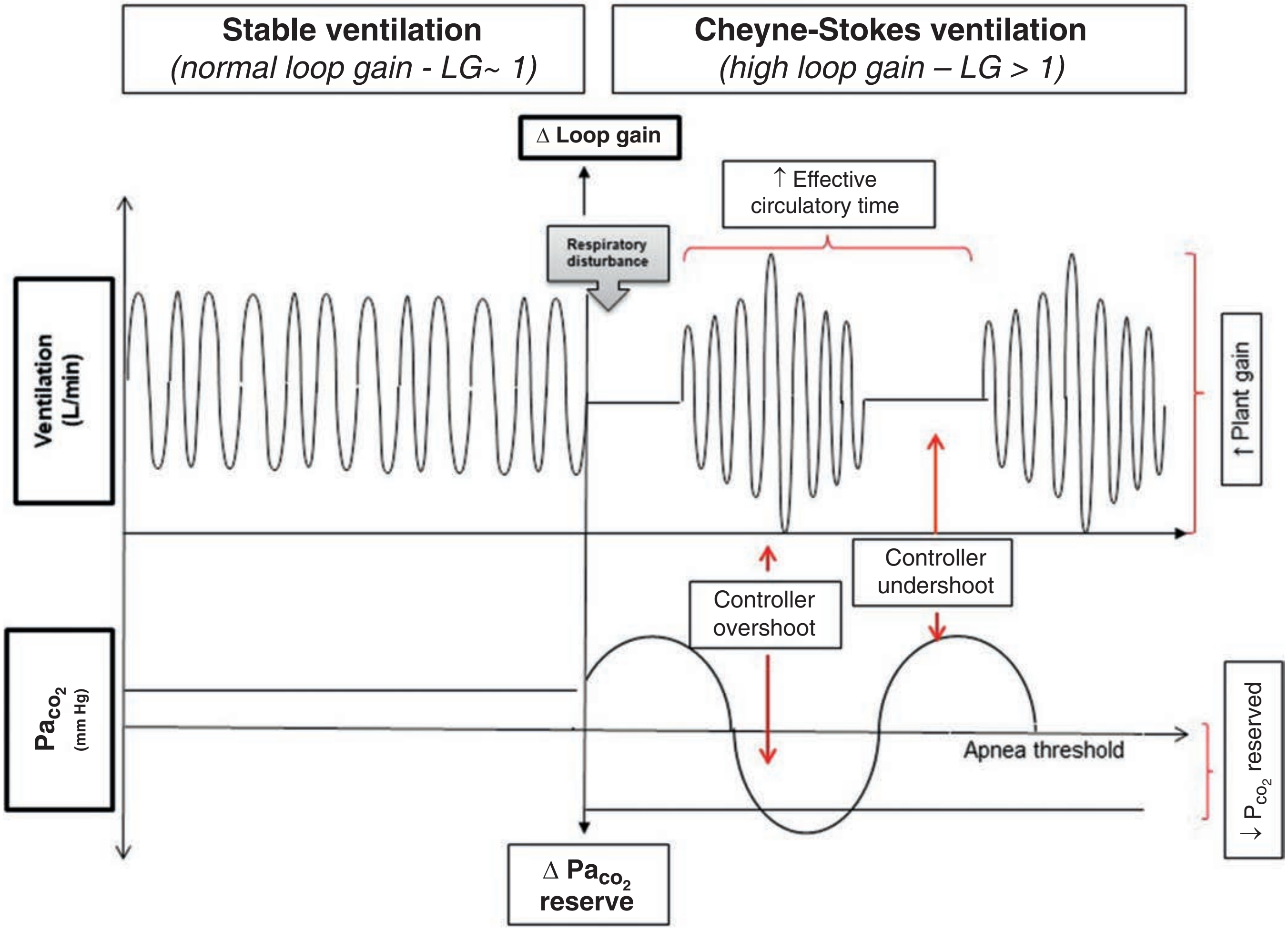


Figure 148-3 Hypocapnic respiratory failure—CSAS related to HF-CSR. CSAS, central sleep apnea syndrome; CSR, Cheyne-Stokes respiration; HF, heart failure; LG, loop gain; Pa_{CO_2}, tension of carbon dioxide.

Cardiopulmonary Effects of Positive Airway Pressure (PAP) Therapy

The pulmonary and cardiac systems are pressure chambers embedded into the thoracic cavity. By influencing each other as biologic pumps, they result in a direct mechanical interdependence. When PAP therapy is applied to an "active" breathing patient, the positive airway pressure will transmit along airways and alveoli into the pleural cavity resulting in increased (less negative) intrapleural pressure. This change will affect the transmural pressures of intrathoracic chambers such as the pericardial compartment, cardiac cavities, and blood vessels (e.g., vena cava).

Following a Starling resistor model in the upper airways, PAP therapy increases the intraluminal pharyngeal pressure resulting in a pneumatic splinting of those regions with propensity to collapse in OSA (e.g., retropalatal and retroglossal area).[1] Transmitted to distal airways and alveoli, positive airway pressure may facilitate a larger end-expiratory lung volume (prevent alveolar derecruitment), resulting in a higher oxygen reservoir and distal traction of the trachea with subsequent improvement of upper airway stability.[9,10]

During stable (unassisted) inhalation in a healthy individual, the resulting tidal volume will depend on the force generated by the respiratory muscle contraction (Pmus) to overcome the respiratory system load (respiratory system compliance, resistance, and intrinsic positive end-expiratory pressure [iPEEP]). This "work of breathing" is the summation of static work (energy required to maintain volume) and dynamic work (energy necessary to maintain flow and overcome resistance). When bilevel PAP therapy is implemented (assisted inhalation), the support and/or augmentation of the tidal volume and minute ventilation may unload the "work" of respiratory muscles and therefore decrease the work of breathing[11] (Fig. 148-2C).

The hemodynamic effects of positive intrathoracic pressure are complex and will depend on the interplay between several factors that regulate venous return and cardiac function. In general, the increase in intrathoracic pressure as a consequence of positive airway pressure therapy will affect the following four primary components of the circulatory system: (1) systemic venous return, (2) right ventricular output, (3) left ventricular filling, and (4) left ventricular cardiac output. The increase in intrathoracic pressure may result in an increase in vena cava resistance with subsequent reduction of venous return to the right atrium (decrease in right ventricular preload), an increase in pulmonary arterial resistance (increase in right ventricular afterload), and a reduction of venous return to the left atrium (decrease in left ventricular preload). Finally, the transmission of a more positive pleural pressure to the pericardial cavity will decrease the transmural pressure across the left ventricle, resulting in a reduction of left ventricular wall tension (decrease in left ventricular afterload)[12,13] (Fig. 148-2D). The consequences of these hemodynamic changes in clinical practice depend on the patient's cardiac function and volume status. Although homeostatic adaptation (e.g., decrease in vascular capacitance) to the application of PAP therapy will prevent hypotension in most euvolemic patients,

TABLE 148-2 Matching Noninvasive Ventilation (NIV) Modes to Pathophysiology: Indications

NIV Devices	NIV Action(s)	Pathophysiology Match—Indications
Bilevel positive airway pressure (BPAP) **Device that delivers a higher inspiratory pressure (IPAP) and a lower expiratory pressure (EPAP), potentially increasing tidal volumes, and hence, alveolar ventilation** - ***S: Spontaneous (no backup rate)*** - ***ST: Spontaneous-timed (backup rate)***	• Support/augment ventilation • Pneumatic splinting of upper airways • Backup rate is set when minimal minute ventilation is needed, or a mechanical breath is required during central apnea	**Hypercapnic respiratory failure with/without upper airways instability** • Alveolar hypoventilation *(BPAP-S or BPAP-ST mode to support minute ventilation)* **Central sleep apnea (CSA)** • Primary central sleep apnea *(BPAP-ST mode)* • Second-line treatment for CSA related to CHF *(CSR-CHF) (generally BPAP-ST mode)*
Volume-assured pressure support (VAPS) **Feedback control system with self-adjustable pressure support to target:** - ***Expiratory tidal volume (eVt)*** ***or*** - ***Target alveolar ventilation (VA)***	• Support/augment ventilation • Pneumatic splinting of upper airways • Backup rate is set when minimal minute ventilation is needed	**Hypercapnic respiratory failure with/without upper airways instability** • Alveolar hypoventilation *(neuromuscular or restrictive lung disease)* • OHS with failure to CPAP and/or BPAP-S or OHS without predominant OSA
Adaptive servo ventilation (ASV) **Feedback control system with self-adjustable pressures that target an average ventilation or inspiratory flow**	• Breathing pattern correction Note: avoid if hypoventilation syndrome is suspected or present	**Hypocapnic or normocapnic respiratory failure** • Systolic (EF ≥45%) or diastolic CSR-HF • Treatment of emergent central sleep apnea unresponsive to CPAP • CSAS due to long-acting opioids without carbon dioxide retention

CPAP, continuous positive airway pressure; CSAS, central sleep apnea syndrome; CSR, Cheyne–Stokes respiration; EF, ejection fraction; HF, heart failure; NIV, noninvasive ventilation; OHS, obesity hypoventilation syndrome; OSA, obstructive sleep apnea.

elevated intrathoracic pressure may improve cardiac function in those with decompensated left heart failure.[14–16]

Potential Detrimental Effects of NIV

Acceptance of NIV is a complex process, and adaptation to the NIV machine can be challenging. Difficulties in becoming accustomed to the device may range from mild (air leak, claustrophobia, eye redness, rhinorrhea, mouth dryness, aerophagia, skin break at mask contact) to more serious side effects such as laryngeal spasm and patient–ventilator asynchronies, all of which can impair quality of life and affect compliance.

Asynchrony in the patient–ventilator interaction may have a profound impact on patient's compliance with therapy (e.g., intolerance, dyspnea) as well as detrimental effects on cardiorespiratory system mechanics. For example, an excess of inspiratory pressure may lead to overventilation (risk of volutrauma), overdistention (risk of barotrauma), and muscle overload (decreased neural inspiratory time with activation of expiratory muscles); excess expiratory pressure may compromise patient's hemodynamics (see "Pathophysiology: Decision Framework in Selecting NIV Modes," below). Furthermore, asynchronies in crucial points of pressure transitions from EPAP to IPAP (triggering) and back to EPAP (cycling) may also be detrimental (see "Advanced Settings and Dyssynchrony in NIV," below). Delayed (or missed) triggers may translate into pronounced dyspnea because of inappropriate isometric muscle load. In addition, early or premature mechanical breath termination (mismatch with neural inspiratory time) may result in excess muscle load and large tidal volumes as a result of double breaths (double triggering). In contrast, when breath termination is delayed, expiratory muscles may be recruited to terminate the inhalation.

Contraindications to NIV

There are few absolute contraindications for NIV use; important ones include (1) respiratory arrest or unstable cardiorespiratory status; (2) reduced consciousness and inability to protect the airway; (3) an uncooperative patient; (4) copious respiratory secretions; (5) severe nausea with vomiting; (6) facial trauma, burns, or craniofacial malformation; (7) certain head and neck–related surgeries or neurosurgeries; and (8) an air leak syndrome (e.g., pneumothorax with bronchopleural fistula).

■ Mechanical Anatomy of a Positive Airway Pressure Device (Hardware)

Positive airway pressure (PAP) devices (hardware) are portable flow generators capable of delivering positive air pressure to a patient via an interface (mask) or a tracheotomy tube. PAP devices are basically composed of a turbine ("dynamic blower system"—DC brushless motors), a respiratory circuit (a single or double hose), and a mask. Based on flow and pressure sensors (pneumotachograph) located in the device (device input), a microprocessor-based controller (governed by propriety algorithms) is constantly adjusting the turbine speed in order to reach a preset positive pressure (device output) stipulated by the provider. Because the pressure and flow sensor are within the device and not in the mask, the device must calculate the predicted pressure at the mask based on flow equations, adjusting the turbine speed in response to deviations in pressure that occur from leak or normal swings in air pressure as a result of the respiratory cycle.

PAP devices deliver positive pressure to the patient by hose(s) as part of respiratory circuits. There are two types of circuits: single-limb (one hose) or double-limb (two hoses). The single-limb circuit is a single tube for both inhalation and exhalation. To avoid carbon dioxide rebreathing, this system has a continuous exhaust port (intentional or controlled pressure leak) located either in the mask shell (vented mask) or in the swivel connector joining the hose to the mask (passive circuit). In contrast, the double-limb circuit is composed of separate inspiratory and expiratory limbs, and is generally used with an unvented mask (without an exhaust port) as carbon dioxide is directly expelled through the expiratory limb into the expiratory valve of the ventilator (active circuit). Most devices

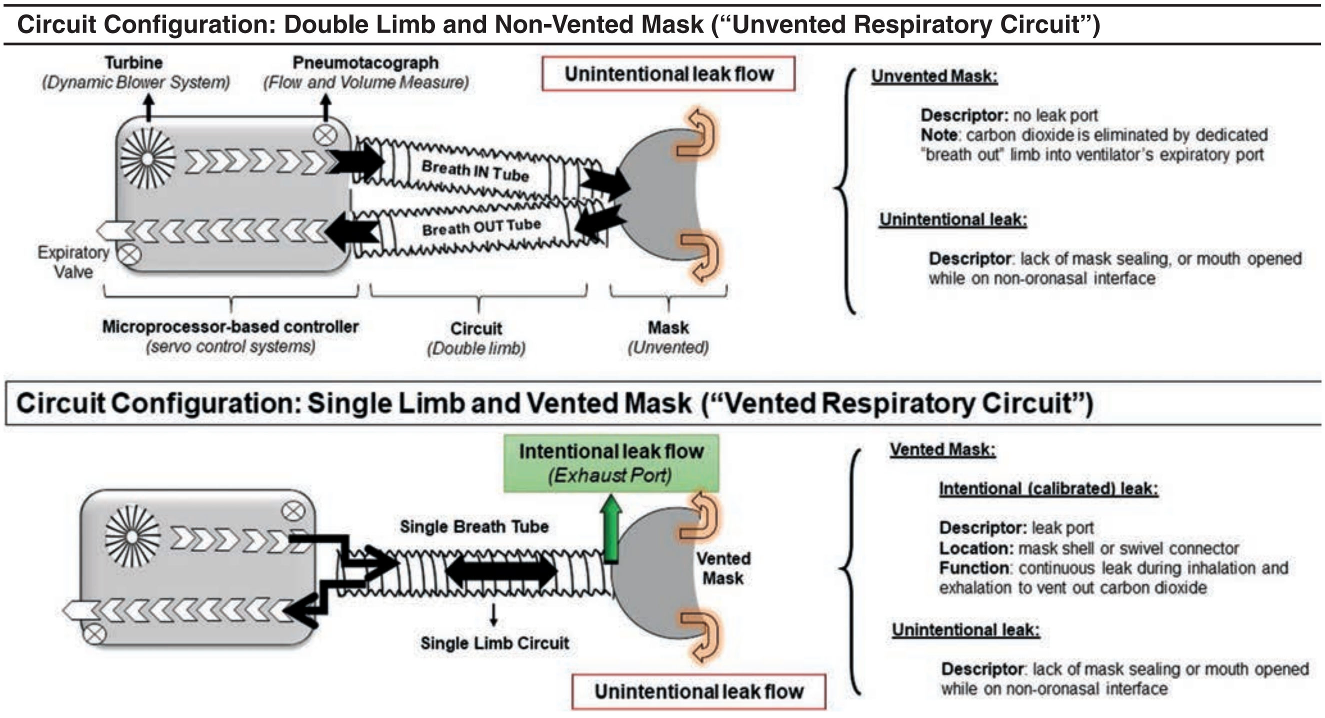

Circuit Configuration: Double Limb and Non-Vented Mask ("Unvented Respiratory Circuit")
Turbine
(Dynamic Blower System)
Pneumotacograph
(Flow and Volume Measure)
Unintentional leak flow
Breath IN Tube
Breath OUT Tube
Expiratory Valve
Microprocessor-based controller
(servo control systems)
Circuit
(Double limb)
Mask
(Unvented)
Unvented Mask:
Descriptor: no leak port
Note: carbon dioxide is eliminated by dedicated "breath out" limb into ventilator's expiratory port
Unintentional leak:
Descriptor: lack of mask sealing, or mouth opened while on non-oronasal interface
Circuit Configuration: Single Limb and Vented Mask ("Vented Respiratory Circuit")
Intentional leak flow
(Exhaust Port)
Single Breath Tube
Vented Mask
Single Limb Circuit
Unintentional leak flow
Vented Mask:
Intentional (calibrated) leak:
Descriptor: leak port
Location: mask shell or swivel connector
Function: continuous leak during inhalation and exhalation to vent out carbon dioxide
Unintentional leak:
Descriptor: lack of mask sealing or mouth opened while on non-oronasal interface

Figure 148-4 Circuit and mask configuration.

undergo automatic compensation for circuit compliance (drop pressure) and gas compressibility after setting the type of mask and the tube's length in the device's clinical menu[17] (Fig. 148-4).

The Basics: Modes (Software)

Based on their settings (mode), PAP devices may either deliver a single, continuous pressure (CPAP) during the respiratory cycle, or a higher inspiratory pressure (IPAP) and a lower expiratory pressure (EPAP) in the form of bilevel positive airway pressure (BPAP) mode, supporting and/or augmenting the patient's breath (tidal volumes), and hence, minute ventilation. Depending on the type of software, BPAP modes may interact differently with the breathing pattern, adjusting pressure accordingly using propriety algorithms (decision paths) designed to achieve a specific respiratory assistance (e.g., ventilation support in alveolar hypoventilation, or counterbalance compensatory respiratory support in Cheyne–Stokes respiration).

Bilevel PAP Modes (BPAP): Spontaneous (BPAP-S) and Spontaneous-timed (BPAP-ST)

The BPAP mode may cycle between two pressures, a higher IPAP and a lower EPAP, in response to the patient's respiratory effort (effort-triggered breath) or time to breath (time-triggered breath). While the IPAP augments inspiration, the EPAP (similar to CPAP) provides a pneumatic airway splint to maintain upper airway patency proximally and stable expiratory residual volume distally. The difference of the two pressures, called pressure support or delta pressure, contributes to improved ventilation through tidal breath support or augmentation. The larger the pressure support is, the larger the tidal volume generated with subsequent washout of Pa_{CO_2} (assuming a constant dead space). However, for a given patient, the tidal volume generated by BPAP is not fixed (nor guaranteed) and depends on the interplay of many important factors: preset settings in the device, patient's inspiratory time and effort, the dynamic characteristic of patient's respiratory system (resistance and compliance of the respiratory system), and the device's circuit (nonhermetic circuit, potential pressure leak) among others.

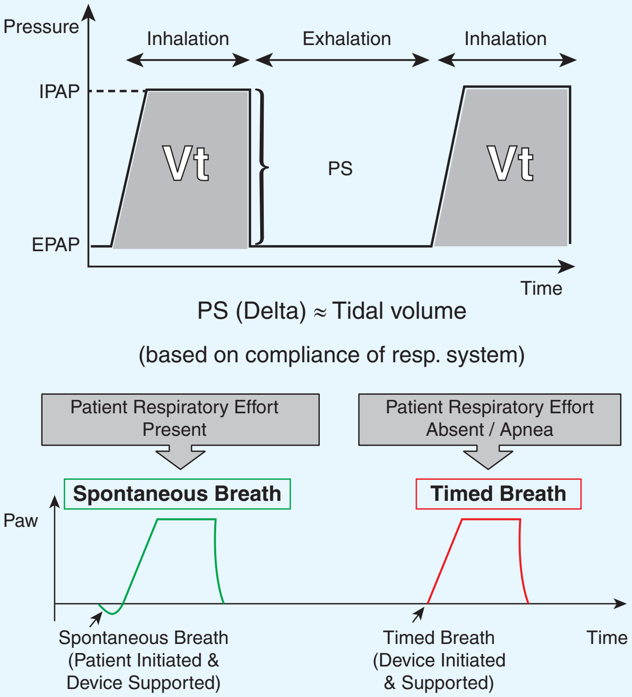
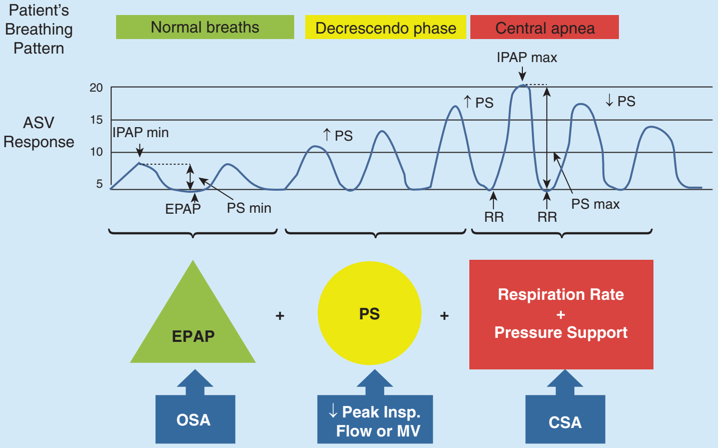
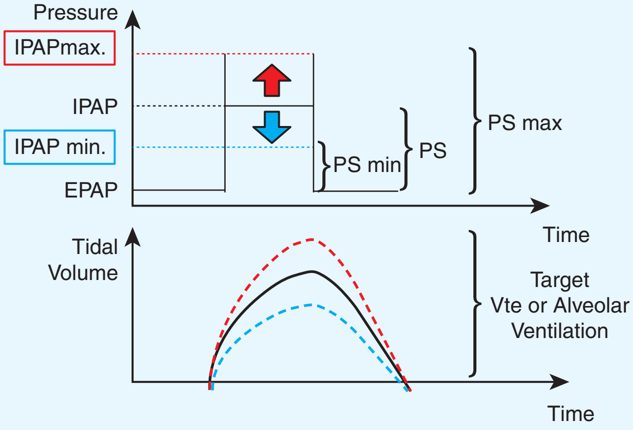
Based on the level of interaction with the patient's spontaneous respiratory effort, BPAP may be delivered in S (Spontaneous), ST (Spontaneous/Timed), and T (Timed) mode. In "spontaneous mode," the device senses when the patient is inhaling and exhaling and supplies the IPAP and EPAP accordingly. In "spontaneous/timed mode," the device will support and/or augment breaths initiated by the patient and supply additional breaths if patient's breath rate falls below a preset backup respiratory rate (RR). Although rarely used, the "T mode" delivers a fixed breath rate and duration and is a mode almost exclusively selected for those patients without (or with severely diminished) respiratory drive (Table 148-3, Fig. 148-5B).

Volume-Assured Pressure Support (VAPS) Mode

VAPS mode tracks a patient's spontaneous respiratory breath, proportionally adjusting IPAP and thus pressure support to augment breathing when needed to reach a respiratory target set by the provider. This respiratory target may be either expiratory tidal volume (eVt) or alveolar ventilation (V_A). In those cases where inadequate ventilation is due to (or exacerbated by) a decrease in respiratory rate (decreased respiratory drive), a backup respiratory rate will supply additional breaths to reach an adequate minute ventilation. An auto-EPAP function is also available in more recent device models to self-adjust to upper airway resistance (Table 148-3).

Manufacturer Differences in VAPS Modes by Respiratory Targets The VAPS algorithm patented in the "Average" Volume-Assured Pressure Support trademark (AVAPS, Philips) adjusts PS by varying the IPAP or PS level between a minimum (IPAP Min or PS Min) and a maximum (IPAP Max or PS Max) setting to match a target expiratory tidal volume (eVt) preset by the provider. The rate at which IPAP self-adjusts to achieve this targeted volume may be slow (by 1 cm H_2O/min) or fast (by up to 5 cm H_2O/min), and can be set in certain devices by the provider (VAPS rate). This proprietary algorithm analyzes the patient's spontaneous airflow to calculate the expiratory tidal volume (Vte), automatically adjusting trigger, cycle sensitivities, and pressure leak compensation (Auto-TRAK). In

TABLE 148-3 Advanced Modes of Noninvasive Ventilation (NIV)

Mode	Settings	Clinical Indications	Waveforms in NIV
Bilevel PAP (BPAP) **Spontaneous (S) mode:** the device senses patient's inhaling and exhaling flow and supplies the IPAP and EPAP respectively **Spontaneous-timed (ST) mode:** the device will support and/or augment breaths initiated by the patient and supply additional breaths should the patient's breath rate fall below the preset backup rate	Inspiratory pressure (IPAP) Expiratory pressure (EPAP) Spontaneous (S) mode: no backup rate Spontaneous-timed (ST) mode: backup respiratory rate; this ensures that the patient receives a minimum number of breaths per minute	Spontaneous (S) mode: to support and/or augment breaths in patients with intact respiratory drive and respiratory muscle strength Spontaneous-timed (ST) mode for patients with impaired respiratory drive or neuromuscular disease with insufficient triggering of IPAP	 Pressure Inhalation Exhalation Inhalation IPAP Vt PS Vt EPAP Time PS (Delta) ≈ Tidal volume (based on compliance of resp. system) Patient Respiratory Effort Present Patient Respiratory Effort Absent / Apnea Spontaneous Breath Timed Breath Paw Spontaneous Breath (Patient Initiated & Device Supported) Timed Breath (Device Initiated & Supported) Time
Adaptive Servo-Ventilation (ASV) ASV mode self-adjusts pressures to deliver anticyclical respiratory support to patient's breathing pattern	Maximum and minimum inspiratory pressures End-expiratory pressure (EEP). Backup ventilatory rate and flow characteristics may be adjusted or set to default factory settings	Treatment-emergent central sleep apnea Opioid induced central sleep apnea *without* hypoventilation	 Patient's Breathing Pattern Normal breaths Decrescendo phase Central apnea IPAP max 20 15 10 5 ASV Response IPAP min ↑ PS ↑ PS ↓ PS EPAP PS min RR RR PS max EPAP + PS + Respiration Rate + Pressure Support OSA ↓ Peak Insp. Flow or MV CSA
Volume-assured Pressure Support (VAPS) Feedback loop system that adjusts its pressures to deliver a set tidal volume or alveolar ventilation, guaranteeing a minute ventilation	Target tidal volume or alveolar ventilation Expiratory positive airway pressure (EEP) Min. inspiratory pressure Max. inspiratory pressure Respiratory rate Flow characteristics also may be set, but default values are provided by factory	In OHS patients who failed CPAP therapy In OHS with predominant reduced respiratory drive ("true Pickwickian syndrome")	 Pressure IPAPmax. IPAP IPAP min. EPAP PS min PS PS max Time Tidal Volume Target Vte or Alveolar Ventilation Time

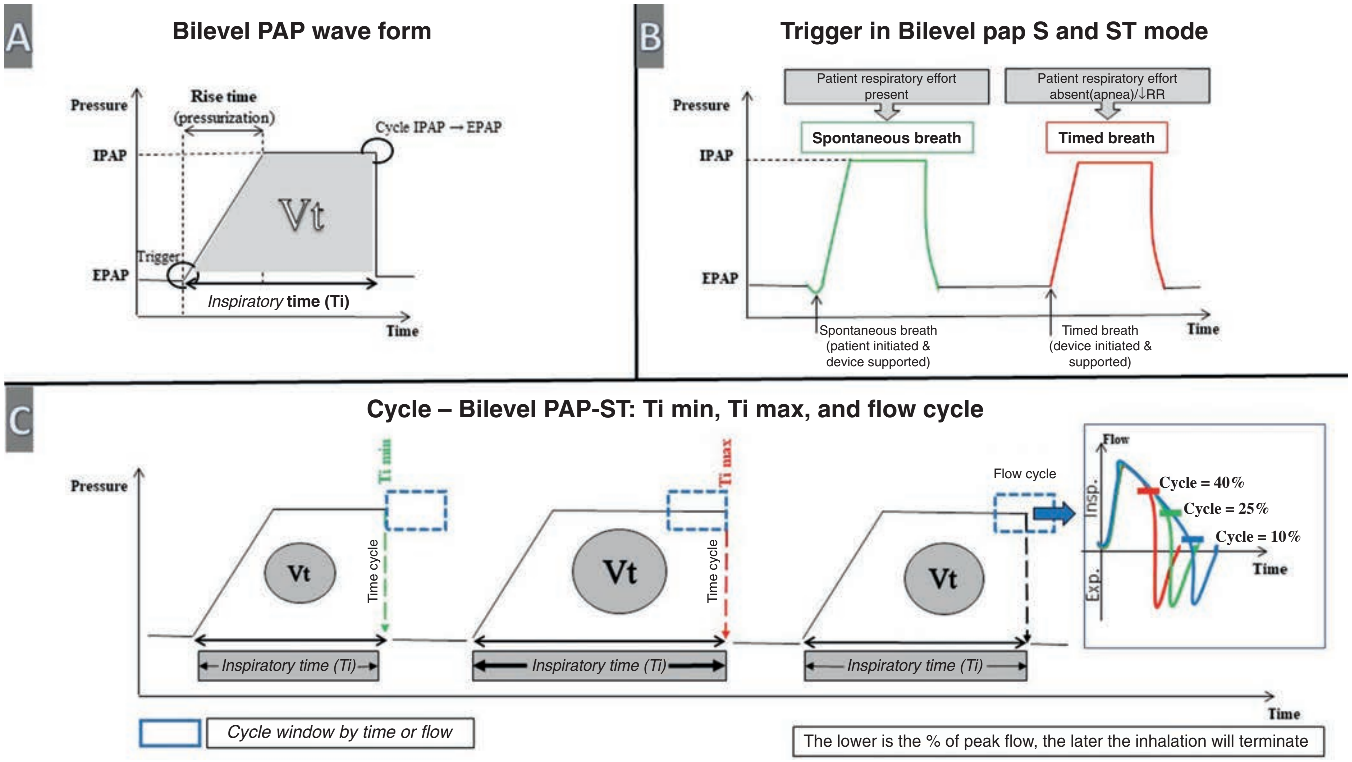

A
Bilevel PAP wave form
Pressure
Rise time
(pressurization)
Cycle IPAP → EPAP
IPAP
Vt
Trigger
EPAP
Inspiratory time (Ti)
Time
B
Trigger in Bilevel pap S and ST mode
Patient respiratory effort present
Patient respiratory effort absent(apnea)/↓RR
Pressure
Spontaneous breath
Timed breath
IPAP
EPAP
Spontaneous breath (patient initiated & device supported)
Timed breath (device initiated & supported)
Time
C
Cycle – Bilevel PAP-ST: Ti min, Ti max, and flow cycle
Pressure
Ti min
Ti max
Flow cycle
Flow
Insp.
Exp.
Cycle = 40%
Cycle = 25%
Cycle = 10%
Time
Vt
Time cycle
Vt
Time cycle
Vt
Inspiratory time (Ti)
Inspiratory time (Ti)
Inspiratory time (Ti)
Time
Cycle window by time or flow
The lower is the % of peak flow, the later the inhalation will terminate

Figure 148-5 Bilevel waveform trigger cycle. EPAP, expiratory positive airway pressure; Exp, expiratory; Insp, inspiratory; IPAP, inspiratory positive airway pressure; PAP, positive airway pressure; RR, respiratory rate; S, spontaneous breath; ST, spontaneous-timed breath; Ti, inspiratory time; Ti max, maximal inspiratory time; Ti min, minimal inspiratory time; Vt, tidal volume.

some devices, Auto-TRAK is optional, allowing manual adjustment of trigger, rise time, and cycle (please refer to advanced settings in this chapter). In VAPS mode with auto-adjusting EPAP capability, the device also monitors the patient's upper airway resistance and automatically regulates the EPAP required to maintain upper airway patency. When the breath rate is set to Auto, the device will adjust the backup breath rate based on the patient's spontaneous respiratory rate, remaining two breaths below detected average spontaneous breathing until a higher backup rate is needed to maintain minute ventilation.

Different from Vte target by AVAPS, the "Intelligent" iVAPS (Resmed) targets a preset alveolar ventilation (V_A), adjusting for anatomic dead space calculated from the patient's height. By analyzing the patient's actual ventilation and respiratory rate, PS and the backup rate are continuously and proportionally self-adjusted to achieve and maintain the target V_A. In this mode, the backup rate is a factor in the V_A calculation, and is designed to be at two-thirds of the "baseline spontaneous patient's rate" (target patient rate) during spontaneous ventilation. However, during apneic events or decreased MV, the backup rate may escalate to "target patient rate." In VAPS mode with autoadjusting EPAP capability, the device will automatically regulate the EPAP required to maintain upper airway patency. The device may also contain a "Learn Target" feature, which allows the device to identify the patient's alveolar ventilation and spontaneous respiratory rate, and automatically uses these data as input in the device settings.

In general, VAPS mode can be activated in ST or Pressure Assist–Controlled (PAC) mode. Like in ST mode, inhalation in PAC mode is either initiated by the ventilator at a set rate (time-triggered breath) or the patient (spontaneous-triggered breath). However, different from ST mode, there is no spontaneous/flow cycling determined by the patient. The end of inspiration is controlled by the ventilator (time-cycled breath) by applying a fixed inspiratory time (Ti).

Adaptive Servo-ventilation (ASV) Mode

The ASV device supports breathing in a counterbalance proportional to the patient's breathing. When a patient's ventilation decreases, the ASV mode may provide higher respiratory support (i.e., minute ventilation or peak flow) by increasing inspiratory pressure support and/or respiratory rate. When ventilation returns to a more stable breathing pattern, this mode lowers support to a minimum. As the device detects a stronger breath, it automatically lowers the pressure support provided. This "on demand" breathing support allows a dampening effect on respiratory drive fluctuations, and is particularly useful in periodic breathing secondary to a highly unstable respiratory drive system (high loop gain) like CSR[18,19] (Table 148-3).

■ Advanced Settings and Dyssynchrony in NIV

If properly adjusted, NIV unloads ventilatory muscles and reduces the work of breathing by delivering pressure-supported breaths. For this to occur, the patient–ventilator interaction should achieve synchrony by aligning the device's settings with the patient's neural time (respiratory drive) and respiratory system mechanics (compliance and resistance). For this to happen, the NIV's flow and pressure delivery must synchronize with patient effort during all three mechanical phases of breath delivery: trigger (breath initiation), rise time and inspiratory time (flow/duration of flow), and cycling (breath termination).

Advanced Settings

A variety of advanced settings in use of NIV should be considered and are discussed below.

Trigger Sensitivity "Trigger sensitivity" sets the level of inspiratory flow change generated by the patient's initial inhalation effort, above which the device switches from EPAP (exhalation) to IPAP (inhalation). Changes in trigger sensitivity should be customized to a patient's pathophysiology and assessed at the bedside. In some devices, a proprietary algorithm continuously analyzes the flow waveform to determine the best trigger without the physician needing to adjust the setting manually (e.g., Auto-Trak, Respironics). However, the use of standard Auto-Trak assumes normal diaphragmatic strength. Therefore, it may be associated with asynchronies in COPD and neuromuscular disease patients (Fig. 148-5A).

Rise Time "Rise Time" sets the time (ms) it takes the device to transition from EPAP to IPAP (pressurization time). The shorter the rise time, the higher the flow generated. Therefore, a faster rise time may be helpful to improve comfort in those with "air hunger," while a slower rise can be helpful in those with bulbar disease or chest wall stiffness (Fig. 148-5A).

Inspiratory Time "Inspiratory time" (Ti) sets the time limit spent on IPAP (s). Together with PS, Ti is the main setting to determine Vt. The longer the time spent in inhalation, the larger the Vt (assuming constant pulmonary mechanics). Ti will also affect the expiratory time and therefore expiratory Vt in a respiratory cycle. Depending on the manufacturer and device's model, Ti may either apply to mandatory breaths (Respironics), or to spontaneous as well as to mandatory breaths (ResMed) in ST mode. In PC mode, all manufactures will deliver a fixed Ti in response to all breaths (Fig. 148-5A).

Cycle Sensitivity "Cycle sensitivity" sets the cycle out of IPAP into EPAP based on flow decay at the end of inhalation. Therefore, termination of inhalation support may be determined by either flow decay (percentage of decrement in flow as compared to the peak inspiratory flow noted at the initiation of inhalation) or by time (Ti). When the cycle is determined by the percentage of peak flow, the lower it is set, the later IPAP support will terminate. For example, in neuromuscular disease it may be set "low" to allow longer inhalation, while COPD patients may benefit from a "high" cycle sensitivity (Fig. 148-5A,C).

Manufacturer Differences in Advanced Settings

Manufacturer differences regarding cycling parameters may exist. For example, Resmed devices cycle out of IPAP in a "time window period." This cycle window is defined by a Ti min., which guarantees a minimal time in inhalation, so that a short, shallow breathing pattern does not develop in those with neuromuscular disorders. Ti max limits the maximal time in IPAP providing protection against hyperinflation in those with COPD or against late cycling in those with a large unintentional pressure leak from the mask. Between these two "time limit parameters" (or time window), the patient's spontaneous breath may cycle by flow decay.

In some NIV modes, the trigger and the cycle are automatically adjusted by the device (based on proprietary flow shape signal analysis) to reach maximal synchrony with the patient. In other NIV modes, manual adjustment of the trigger is possible by adjusting the "trigger sensitivity," which is the inspiratory flow set above which the device triggers in spontaneous mode. In the case of flow cycled breath, "cycle sensitivity" can also be manually set in the device by assigning a level of inhaled flow below which the device changes out of IPAP (Fig. 148-5C).

Patient–Ventilator Dyssynchrony

Patient–ventilator dyssynchrony occurs when the trigger, flow, and/or cycling of a mechanical breath is not in time agreement with the initiation and termination of a patient's neural inspiration, respectively, or if the magnitude of mechanical assist does not respond to the patient's respiratory demand. Dyssynchrony between the patient and the NIV mode may overload ventilatory muscles (respiratory load), compromise respiratory ventilation, disrupt sleep patterns, and cause patient discomfort with subsequent poor compliance. The most frequent asynchrony results from pressure leak from the mask, compromising triggering (delayed, missed, or auto-triggering), rise time, and Ti (flow), as well as cycling (premature or delayed). Once the mask pressure leak is resolved, if residual trigger asynchrony is identified, adjustment of the sensitivity setting should be a compromise between trigger difficulty and auto-triggering. Similarly, cycle asynchrony can occur if the inspiratory time is set too short (double triggering) or too long (active exhalation). This asynchrony can be addressed by appropriately setting the Ti and/or the cycle sensitivity[18,20,21] (Table 148-4).

Another respiratory support failure may be the result of increased resistance in the upper airway (e.g., OSA or glottic closure induced

TABLE 148-4 Troubleshooting Asynchronies

Asynchrony	Definition	Types	Action
Inspiratory triggering Industry default to *medium* sensitivity or Auto-Trak[a]	Mismatch between patient's inspiratory effort and ventilator triggering	Ineffective inspiratory effort	First: Minimize mask leak Second: Minimize UA resistance (OSA) Third: Set trigger sensitivity to *High* for very weak muscular effort (e.g., NMD or high PEEPi) or Auto-Trak sensitive
		Double triggering	Increase PS and/or decrease cycle sensitivity Extend Ti time in PC mode
		Autotriggering	Set trigger sensitivity to *Low* if device's inhalation starts before patient's inhalation
Cycling[a] Industry default to *medium* sensitivity or Auto-Trak[a]	Ventilator cycling does not coincide with end of patient's effort	Premature cycling (cycle before patient ends inhalation, long neuronal insp. time)	First: Minimize mask leak Second: Review Ti (or Ti max) Third: Set cycle sensitivity to *Low* (low % of peak flow) • Trial of Auto-Trak sensitive • Consider change to PC mode so that spontaneous triggered breaths will be fully supported
		Late cycling (cycle after patient ends inhalation, short neuronal insp. time)	First: Minimize mask leak Second: Review Ti (or Ti min) Third: Set cycle sensitivity to *High* (high % of peak flow)

[a] *Respironics program is based on automatic adjustments of trigger and cycle sensitivity called Auto-Trak sensitivity (this function also adjusts for mask leak).*

by hyperventilation). This may act as a barrier to effectively delivery of the required pressure support. Therefore, increasing the delivered inspiratory pressure or Ti during NIV will not necessarily result in increased effective ventilation reaching the lungs until an appropriate EPAP is set to maintain upper airway patency.

Differences Between Respiratory Assist Devices (RADs) and Ventilators

National and local coverage determination (NCD and LCD) reimbursement criteria for PAP devices, durable medical equipment (DME) coding, and current procedural terminology (CPT) coding are complex and governed by intricate national and local reimbursement policies. Historically, and based on criteria of cost and safety features offered by the device, coverage qualification criteria for NIV devices have traditionally differentiated between respiratory assist devices (RADs) and home mechanical ventilators (HMVs) (Table 148-5). RADs are, in general, portable, home-based, single-limb circuit bilevel PAP devices designed for noninvasive ventilation through a vented interface. In contrast, HMVs are, in general, devices that may deliver volume or pressure modes by single- or double-limb circuits designed for noninvasive ventilation through a mask or invasive ventilation through tracheotomy tube. Because

TABLE 148-5 Respiratory Assist Devices (RADs) and Ventilators: Centers for Medicare and Medicaid (CMS) Services Qualifying Guidelines in Different Diseases

Diagnosis/Test Needed	Device	PSG Needed?	Diagnostic Criterion
Respiratory Assist Devices (RADS)			
Obstructive sleep apnea[a] (OSA)	CPAP (E0601)	Yes (type I or III)	AHI ≥15 or AHI ≥5 plus symptoms and/or comorbidities
	Bilevel (S) (E0470)	Yes (type I or III)	If CPAP failure (e.g., low Sp_{O_2}, persistent high AHI, CPAP intolerance)
Central sleep apnea[b] (CSA)	Bilevel (ST) (E0471)	Yes (type I or III)	AHI and CAI ≥5 *and* CAI >50% of the total AHI
COPD[b] Test: ABG and sleep oximetry	Bilevel (S) (E0470)	No	*All of*: • Pa_{CO_2} ≥52 mm Hg *and* • Sp_{O_2} <88% for cumulative >5 min while on usual O_2 or O_2 at 2 L/min (whichever is higher) *and* • OSA considered and ruled out clinically
	Bilevel (ST) (E0471)	Sometimes (type I)	Situation 1: If both of the following occur on an E0470 device: • Pa_{CO_2} ↑ ≥7 mm Hg *and* • Facility-based PSG shows Sp_{O_2} <88% for cumulative >5 min while on usual O_2 or O_2 at 2 L/min (whichever is higher) Situation 2: If both of the following occur on an E0470 device no sooner than 61 days: • Pa_{CO_2} ≥52 mm Hg *and* • Sleep oximetry shows Sp_{O_2} ≤88% for cumulative >5 min while on usual O_2 or O_2 at 2 L/min (whichever is higher)
Restrictive thoracic disease[b] (RTD) Scoliosis Test: ABG or sleep oximetry NMD Test: ABG or sleep oximetry or FVC or MIP	Bilevel (S) (E0470) or bilevel (ST) (E0471)	No	*Any one of*: • Pa_{CO_2} ≥45 mm Hg *or* • Sleep oximetry shows Sp_{O_2} ≤88% for cumulative >5 min while on usual O_2 *or* • NMD only FVC <50 OR MIP <60
Hypoventilation[b]	Bilevel (S) (E0470)	Sometimes (type I or III)	*All of*: • Pa_{CO_2} ≥45 mm Hg *and* • FEV_1/FVC ≥70% *and* • Facility-based PSG or HST with Sp_{O_2} ≤88% for ≥5 min not due to obstruction (AHI <5) *or* Pa_{CO_2} ↑ ≥7 mm Hg during sleep or upon awakening
	Bilevel (ST) (E0471)	Sometimes (type I or III)	If both of the following occur on an E0470 device: • FEV_1/FVC ≥70% *and* • Facility-based PSG or HST shows Sp_{O_2} ≤88% for ≥5 min not due to obstruction (AHI <5) *or* Pa_{CO_2} ↑ ≥7 mm Hg (compared with qualifying ABG) during sleep or upon awakening

(*continued*)

TABLE 148-5 Respiratory Assist Devices (RADs) and Ventilators: Centers for Medicare and Medicaid (CMS) Services Qualifying Guidelines in Different Diseases (*Continued*)

Diagnosis/Test Needed	Device	PSG Needed?	Diagnostic Criterion
Home Mechanical Ventilation			
Life support or life-sustaining ventilation	Invasive home ventilator (E0465)	No	Home ventilator, any type, used with invasive interface (e.g., tracheostomy tube) Medical necessity to support a ventilator over a bilevel RAD device for therapy can be established in several ways that include but are not limited to: 1. Elevated Pa$_{CO_2}$ 2. Prolonged use of device (>8–12 h/day) 3. High pressure requirement needed for daytime support and portability
	Noninvasive home ventilator (E0466)	No	Home ventilator, any type, used with noninvasive interface (e.g., mask, chest shell) Medical necessity to support a ventilator over a bilevel PAP RAD device for therapy can be established in several ways that include but are not limited to: 1. Elevated Pa$_{CO_2}$ 2. Prolonged use of device (>8–12 h/day) 3. High pressure requirement needed for daytime support and portability

ABG, arterial blood gas; AHI, apnea–hypopnea index; Bilevel (S), bilevel positive airway pressure in spontaneous mode; Bilevel (S), bilevel positive airway pressure in spontaneous mode; CAI, central apnea index; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; FEV$_1$, forced expiratory volume in 1 s; FVC, forced vital capacity; HST, home sleep test; MIP, maximal inspiratory pressure; NMD, neuromuscular disease; OHS, obesity hypoventilation syndrome; OSA, obstructive sleep apnea; Pa$_{CO_2}$, partial pressure of carbon dioxide in arterial blood; PSG, polysomnography; Sp$_{O_2}$, pulse oximetry.

[a] *LCD L33718 CPAP for OSA: www.cms.gov/medicare-coverage-database/view/lcd.aspx?LCDId =33718*

[b] *LCD L33800 RAD criteria: www.cms.gov/medicare-coverage-database/view/lcd.aspx?LCDId =33800*

HMV devices are used in advanced respiratory failure ("life support"), they are usually set with safety alarms (e.g., for disconnection or critical volume and/or respiratory rate values) and batteries for autonomous function.

Although traditionally RADs and HMV varied in the features offered (modes, alarms, batteries), technologic developments have blurred the distinction between these two classes as RADS are becoming gradually more sophisticated, and HMV are becoming increasingly applied for chronic hypercapnic respiratory failure in need of NIV. Therefore, the practice of associating the type of NIV device to the degree of ventilator dependence, type of interface, or other feature may soon no longer be applicable based on technologic progress.

NONINVASIVE VENTILATION IN THE ACUTE CARE SETTING

Increasingly, NIV has come into widespread use in the acute care setting. A variety of applications are considered below.

Acute Cardiogenic Pulmonary Edema

Despite the use of supplemental oxygen and medications that decrease pulmonary edema and improve myocardial performance, many patients develop severe respiratory failure. The use of noninvasive positive airway pressure in patients with cardiogenic pulmonary edema was originally described nearly 85 years ago, and it was one of the first described indications for noninvasive mechanical ventilation in the acute setting.[22] When 39 consecutive patients with respiratory failure due to severe cardiogenic pulmonary edema were randomized to CPAP versus usual care, the use of NIV resulted in a significant decrease in the subsequent requirement for intubation and mechanical ventilation.[23] The physiologic benefits of continuous positive airway pressure among patients with acute cardiogenic pulmonary edema include preventing alveolar collapse at end-expiration, increasing hydrostatic pressure and forcing fluid out of the alveolar space and into the interstitial space, improving oxygenation, reducing preload, and decreasing left ventricular afterload. More recent data, including a meta-analysis of randomized, controlled trials in patients with acute cardiogenic pulmonary edema, demonstrated that NIV, usually in the form of CPAP, decreased the need for intubation, improved clinical and laboratory indices of respiratory failure, and improved mortality.[24–26] The effect was more prominent in trials that included patients in which myocardial ischemia or infarction caused the acute pulmonary edema. No differences were detected between CPAP and bilevel ventilation and any clinical outcomes for which they were directly compared.[27]

Acute Exacerbation of COPD

NIV is the preferred initial mode of ventilatory support for patients with acute exacerbations of COPD, if no contraindications exist. Usual indications include severe dyspnea, increased work of breathing, and respiratory acidosis. The use of NIV in patients with acute exacerbations of COPD is associated with a decreased respiratory rate, increased tidal volume, increased minute ventilation, decreased mortality, decreased intubation rates, and decreased length of stay.[27–29] The mechanisms by which bilevel NIV improves hypercapnic respiratory failure and acute exacerbations of COPD include improved alveolar ventilation through improved respiratory mechanics and improved gas exchange.[30,31]

Acute Exacerbation of Asthma

Unlike acute exacerbations of COPD, there is less evidence of benefit for the use of NIV among patients with acute asthma exacerbations.

Bilevel NIV is commonly used in patients with severe asthma exacerbation; however, data are limited to small randomized controlled trials[27] and two large retrospective studies[32,33] that have not documented a clear benefit on mortality or intubation rates. Larger randomized controlled trials are clearly needed in this domain. In this context, despite inconclusive data, short trials of NIV (usually with BPAP) could be considered in acute asthma exacerbation, especially among those not responding to medical therapy. Close observation and a low threshold to intubate if no improvement with NIV is recommended. In support of this approach is a randomized controlled trial that compared conventional asthma treatment with BPAP among 300 patients with severe asthmatic exacerbations admitted to the emergency department. The addition of BPAP to conventional treatment improves lung function, alleviated the exacerbation faster, and significantly reduced the need for hospitalization.[34]

■ Hypoxemic, Nonhypercapnic Respiratory Failure

In general, data are not as supportive of the use of NIV in this population compared to those with acute hypercapnic respiratory failure. The benefit from NIV likely varies in this nonhypercapnic phenotype due to the heterogeneity of this group. The most robust mortality benefit and reduction in intubation rates associated with NIV are driven by the subgroup of patients with pneumonia as the underlying cause of hypoxemia.[35] In contrast, most patients with ARDS require invasive mechanical ventilation, particularly for those with moderate to severe ARDS defined as Pa_{O_2}/Fi_{O_2} ratio of <200 mm Hg. Limited data indicate a high failure rate NIV in patients with Middle East respiratory syndrome (MERS)[36] and influenza.[37] Despite this, in several retrospective cohorts of COVID-19 patients, 11% to 56% of patients were treated with NIV.[38,39] On balance, in hypoxemic respiratory failure due to COVID-19, high-flow nasal cannula (HFNC) is favored over NIV based more on indirect data among non–COVID-19 patients with hypoxemic respiratory and the fact that it is a more practical mode of support, which allows patients to converse and eat, compared to NIV.[40]

■ NIV in Postoperative Care

Hypoxemia from atelectasis is a common postoperative pulmonary complication, particularly after thoracoabdominal procedures. Among patients with hypoxemia without significant secretions, CPAP may be of benefit. This was demonstrated in one multicenter, randomized, controlled trial that enrolled 209 consecutive patients with hypoxemia after major elective abdominal surgery.[41] In this study, patients were randomly assigned to receive either oxygen or oxygen plus CPAP. The group that received oxygen plus CPAP had a lower intubation rate, lower rate of pneumonia, lower infection rate, and lower rate of sepsis compared with those treated with oxygen alone. Although these findings have not been consistent across all studies,[42] it is likely that the benefits of CPAP in hypoxic patients with atelectasis and low secretion burden outweigh the risks as long as close monitoring is performed to assess the need for reintubation. Among patients unable to participate in incentive spirometry maneuvers, CPAP may also be of benefit as a lung expansion technique. In one trial, 500 patients scheduled for elective cardiac surgery were randomized to either 10 min of intermittent CPAP at 10 cm H_2O pressure every 4 h or continuous CPAP for at least 6 h. The continuous CPAP arm had significantly improved oxygenation, reduced pneumonia rates, reduced reintubation rates, and reduced admissions to the ICU.[43] More studies are needed to better determine the role of CPAP among postoperative patients, particularly in patients with obesity and underlying sleep-disordered breathing.

■ NIV in Extubation Management

In a meta-analysis of 16 trials involving 994 patients, the majority with chronic obstructive pulmonary disease (COPD), the use of extubation to NIV, compared with invasive positive pressure mechanical ventilation weaning, significantly decreased mortality. The mortality benefits were significantly greater in trials primarily enrolling participants with COPD (relative risk [RR] 0.36; 95% confidence interval [CI], 0.42–0.98) compared with mixed populations. Additional benefits to NIV included a reduction in weaning failure, reduction in ventilator-associated pneumonia, shorter length of stay in the ICU, a decrease in the total duration of ventilation, and a decrease in the duration of endotracheal mechanical ventilation. NIV also significantly reduced tracheostomy and reintubation rates.[44]

In one study, 97 patients requiring >48 h of mechanical ventilation and at risk of developing postextubation respiratory failure (i.e., patients who had hypercapnia, congestive heart failure, ineffective cough, excessive tracheobronchial secretions, more than one failure of a weaning trial, more than one comorbid condition, and upper airway obstruction) were randomized after a successful weaning trial to receive NIV for >8 h a day in the first 48 h or standard medical therapy.[45] Compared with standard medical therapy, the NIV group had a significantly lower rate of reintubation, and the need for reintubation was associated with a higher risk of mortality. Use of NIV was also associated with a reduction in intensive care unit mortality, which was mediated by the reduction in the need for reintubation.

CHRONIC DISEASE-DRIVEN USE OF NONINVASIVE MECHANICAL VENTILATION

Below we consider application of NIV in a variety of common clinical disorders that may be accompanied by hypercapnia.

■ Stable Hypercapnic Chronic Obstructive Pulmonary Disease

Hypercapnia is associated with a poor prognosis in COPD.[46] Studies dating back to the 1990s showed that nocturnal ventilation with either cuirass ventilation[47] or positive-pressure ventilation[48] reduced diurnal hypercapnia. However, early clinical studies of NIV showed little improvement or conflicting data in important clinical outcomes.[49] A 2013 Cochrane review (including 7 studies and 245 patients) found no improvement in gas exchange, 6-min walk distance, health-related quality of life (HRQOL), lung function, respiratory muscle strength, or sleep efficiency.[50] In subgroup analyses, significant differences in change in Pa_{CO_2} after 3 months were found in patients ventilated with IPAP of at least 18 cm H_2O, in patients who used NIV at least 5 h per night, and in patients with baseline Pa_{CO_2} at least 55 mm Hg.

Early studies of NIV in stable hypercapnic COPD mostly used BPAP therapy with low levels of pressure support (PS).[49] However, higher PS has been shown to reduce diaphragm activity to a greater extent than lower PS in COPD.[11] In a prospective randomized trial of "high intensity" NIV (targeted to reduce Pa_{CO_2} by ≥20% or <48.1 mm Hg) in patients with advanced COPD and Pa_{CO_2} at least 51.9 mm Hg, compared with no NIV, survival was significantly improved (1-year mortality 12% in the treated group and 33% in the control group). BPAP-ST was used with a mean IPAP of 21.6 cm H_2O, mean EPAP of 4.8 cm H_2O, and mean backup rate of 16.1 breaths per minute. Similarly, in the HOT-HMV trial, high-intensity NIV was associated with a reduction in a composite outcome of time to hospital readmission or death (driven primarily by hospital readmission) in patients with persistent hypoxemia and hypercapnia 2 to 4 weeks following an acute exacerbation.[51] In contrast, in the RESCUE trial, in which patients with advanced COPD were treated with high-intensity NIV (or no NIV) if Pa_{CO_2} remained >48 mm Hg 48 h after liberation from mechanical ventilation for COPD exacerbation, there was no difference in time to readmission or death.[52] A possible reason for this discrepancy may be that the patients in the RESCUE trial may not have been at baseline when

NIV was initiated. In the HOT-HMV trial, of 2021 potentially eligible patients, 419 (21%) were excluded because ABG no longer met eligibility criteria. These studies were conducted in Europe and may not be generalizable to a U.S. population.[53]

In a recent meta-analysis of NIV in stable hypercapnic COPD (21 randomized controlled trials and 12 observational studies; n = 51,085) NIV (delivered with a bilevel positive airway pressure device or mechanical ventilator) was associated with improvements in mortality and all-cause admission. Outcomes were not stratified by specific NIV mode or settings used.[54]

Guidelines for Use

A multicenter consensus conference (with representatives from the American Academy of Home Care Physicians, American Association for Respiratory Care [AARC], American College of Chest Physicians [ACCP], American College of Physicians, American Sleep Disorders Association, American Thoracic Society [ATS], and National Association for Medical Direction of Respiratory Care [NAMDRC]) held in 1999 recommended initiation of NIV in COPD in the presence of symptoms (e.g., fatigue, dyspnea, morning headache) and one of the following physiologic criteria: (1) Pa_{CO_2} $\geq$55 mm Hg, (2) Pa_{CO_2} of 50 to 54 mm Hg and nocturnal desaturation (Sp_{O_2} $\leq$88% for 5 continuous minutes on oxygen $\geq$2 L/min), or (3) Pa_{CO_2} of 50 to 54 mm Hg and hospitalization related to recurrent ($\geq$2 in a 12-month period) episodes of hypercapnic respiratory failure.[54] These ultimately informed the current Centers for Medicare and Medicaid (CMS) coverage decisions in place today. Note that CMS qualifying guidelines cover devices rather than modes. There are separate coverage determinations for (1) CPAP and less commonly used bilevel devices for OSA, (2) RADs for non-OSA ventilatory disorders, which are further divided into those without a backup rate (E0470) and those with a backup rate (E0471) and home mechanical ventilators delivered with a noninvasive interface (E0465) for chronic respiratory failure (Table 148-5).

Both the recent European Respiratory Society (ERS) guideline[56] and the recent ATS guideline[57] endorse NIV in chronic hypercapnic COPD (conditional recommendation, low-certainty evidence and conditional recommendation, moderate-certainty evidence, respectively). In light of emerging data, advances in NIV technology, and payer issues, a Technical Expert Panel with representatives from the American Academy of Sleep Medicine (AASM), AARC, ACCP and ATS has proposed new updated recommendations for initiation of NIV in COPD.[58,59]

Modes and Settings

Most studies of NIV in COPD have used BPAP-S or BPAP-ST. VAPS has been used in small studies with similar improvements in gas exchange, lung function, HRQOL, and sleep compared with BPAP-ST.[60,61] The ERS guideline suggests a fixed PS mode as the first-choice ventilator mode in COPD (conditional recommendation, very low-certainty evidence).[56] Mode is not addressed in the ATS guideline. Both the ERS guideline[56] and the ATS guideline[57] suggest a NIV titration strategy targeted to reduce or normalize Pa_{CO_2} (conditional recommendation, very low-certainty evidence and conditional recommendation, low-certainty evidence, respectively). An initial target tidal volume of 8 cc/kg ideal body weight has been suggested to be achieved by adjusting PS on BPAP-S, BPAP-ST, or VAPS, depending on the device available. A backup rate may better allow target Pa_{CO_2} to be achieved, but current CMS guidelines may preclude this, at least initially. EPAP is generally kept low unless upper airway obstruction. The authors suggest matching NIV settings to underlying pathophysiology (e.g., medium trigger sensitivity, fast rise time, short inspiratory time, and high cycle sensitivity)[7] (Table 148-6).

Initiation and Titration

Acute exacerbations of COPD (AECOPD) are associated with significant morbidity, mortality, and healthcare costs. The degree of hypercapnia and the timing of initiation of NIV in relation to AECOPD are likely important as evidenced by the contradictory results of the RESCUE trial (NIV initiated if Pa_{CO_2} >48 mm Hg 48 h after AECOPD)[52] and the HOT-HMV trial (NIV initiated if Pa_{CO_2} >53 mm Hg 2–4 weeks after AECOPD).[51] Those who remain significantly hypercapnic over time appear to be more likely to benefit from NIV. The ERS guideline suggests that “NIV be used in patients with COPD following a life-threatening episode of acute hypercapnic respiratory failure requiring acute NIV, if hypercapnia persists following the episode” (conditional recommendation, very low-certainty evidence).[56] The ATS guideline suggests “not initiating long-term NIV during an admission for acute-on-chronic respiratory failure, favoring reassessment for NIV at 2–4 weeks after resolution” (conditional recommendation, low-certainty evidence).[57]

In non-U.S. trials, long-term NIV is often initiated in the hospital or specialized home ventilation centers, sometimes with multiple admissions for acclimatization and serial adjustments.[51,62] This approach is not utilized in the United States. In-laboratory titration polysomnography (PSG) has been used clinically and can potentially optimize titration endpoints (e.g., target tidal volume, transcutaneous CO_2) and reduce patient–ventilator asynchrony. The AASM NIV Task Force recommends attended PSG for NIV titration in chronic alveolar hypoventilation syndromes,[63] but stable hypercapnic COPD was not specifically discussed. A recent randomized controlled trial showed noninferiority of a home-based approach (using trained nurses and telemedicine monitoring) compared

TABLE 148-6 Matching Noninvasive Ventilation Settings to Respiratory Pathophysiology

Advanced Settings	Chronic OHS	Chronic COPD	Chronic NMD
Trigger sensitivity	Default trigger sensitivity	Default trigger sensitivity	High trigger sensitivity (to support a weak respiratory muscular effort)
Rise time	Default or slow rise time	Fast rise time	Default or slow rise time
Inspiratory time (Ti)	Long Ti (to maximize Vt and gas exchange by ↑ I:E)	Short Ti (to increase expiratory time and minimize iPEEP by ↓ I:E)	Long Ti (to maximize Vt and gas exchange by ↑ I:E)
Cycle sensitivity	Default to low cycle sensitivity	Default to high cycle sensitivity (early cycle to provide a longer exhalation time (↓ I:E))	Default to low cycle sensitivity (late cycle) to provide a longer inhalation time (maximize Vt and gas exchange by ↑ I:E)

COPD, chronic obstructive pulmonary disease; I:E, inspiratory to expiratory ratio; iPEEP, intrinsic PEEP; NMD, neuromuscular disease; OHS, obesity hypoventilation syndrome; Ti, inspiratory time; Vt, tidal volume.

with a hospital approach.[64] There are minimal data on the utility of titration PSG compared with home initiation of NIV. In a small case series, titration PSG was beneficial in improving asynchrony and comfort in patients with dyspnea on therapy.[65] The ATS NIV in COPD guideline suggests "not using an in-laboratory overnight PSG to titrate NIV in patients with chronic stable hypercapnic COPD who are initiating NIV" (conditional recommendation, low-certainty evidence).[57]

■ Overlap Syndrome (Chronic Obstructive Pulmonary Disease and Obstructive Sleep Apnea)

Overlap syndrome (coexistent OSA and COPD)[66] is associated with a more severe nocturnal hypoxemia than either COPD or OSA alone.[67] Adverse cardiovascular outcomes, including pulmonary hypertension and right ventricular dysfunction, are more frequent.[68,69] Individuals with COPD with predominant chronic bronchitis phenotype may be at higher risk for coexistent OSA than those with predominant emphysema phenotype.[70] There are limited data on the utility of screening questionnaires for OSA in COPD,[71,72] and a high index of suspicion is needed. Despite imperfect screening tools, the ATS guideline does suggest screening for OSA in COPD (conditional recommendation, very low certainty),[57] in part because knowledge of the presence of OSA may lead to better titration (e.g., CPAP alone may be adequate; if bilevel modes used, EPAP will need to be adjusted for upper airway obstruction).

CPAP is the mainstay of therapy in OSA and is recommended as first-line therapy in moderate to severe disease.[73] In a long-term prospective study of patients with overlap syndrome,[74] those who were not treated with CPAP had higher mortality and were more likely to experience an AECOPD leading to hospitalization. Those with overlap syndrome treated with CPAP had similar mortality and AECOPD risk as those with COPD alone. In an observational, post-hoc analysis, greater time on CPAP was associated with reduced mortality in overlap syndrome.[75] BPAP has been used with success in individuals with overlap syndrome who fail CPAP due to residual respiratory disturbances, residual hypoxemia, or intolerance.[76] Auto-CPAP results in similar outcomes as CPAP in straightforward OSA,[77] but it has not been studied in patients with comorbid pulmonary disease.[78] There are no published randomized controlled trials comparing different positive airways pressure modes for overlap syndrome.

Guidelines for Use

The ATS NIV in chronic stable hypercapnic COPD guideline suggests clinical screening for OSA in COPD before initiating NIV (conditional recommendation, very low-certainty evidence).[57] There are multiple published guidelines on the evaluation and management of OSA[73,78,79] and on the titration of positive airway pressure therapy in OSA,[80] but none on the management of the overlap syndrome.

CMS has specific guidelines for initial coverage of CPAP for OSA including at least moderate OSA, as defined by apnea–hypopnea index (AHI) or respiratory event index (REI) ≥15 or mild OSA (defined by AHI or REI ≥5), plus qualifying symptoms (insomnia, excessive daytime sleepiness) and/or comorbidities (hypertension, ischemic heart disease, stroke, mood disorder). CMS covers BPAP-S for OSA in situations of documented CPAP failure (e.g., intolerance, residual sleep-disordered breathing).

Modes and Settings

Current practice supports CPAP as primary therapy for overlap syndrome. BPAP is reserved for those who fail CPAP (as defined by residual respiratory disturbances, residual hypoxemia, or intolerance). If BPAP is indicated, EPAP is adjusted to alleviate upper airway obstruction, and PS is adjusted to optimize ventilation.

Initiation and Titration

Sleep testing is indicated for the diagnosis of OSA.[81] The gold standard test is diagnostic PSG. If OSA is identified early in the night, a "split-night study" with the initiation of CPAP on the same night can be performed. Home sleep apnea testing is appropriate for the diagnosis of OSA in those with a high probability of moderate to severe OSA, but it is not recommended if significant pulmonary disease is present.[81] In individuals with underlying pulmonary disease, titration PSG is indicated to ensure resolution of obstructive events and correction of residual hypoxemia. CPAP alone may be adequate, but conversion to BPAP or addition of supplemental oxygen may be needed. Auto-CPAP has not been studied in overlap syndrome, and the authors suggest that this mode should be used cautiously if at all (e.g., with close monitoring of clinical status, PAP device data, and nocturnal oximetry), with a low threshold to perform titration PSG if suboptimal outcomes.

■ Obesity Hypoventilation Syndrome

Obesity hypoventilation syndrome (OHS) is defined by the presence of obesity (body mass index [BMI] ≥30 kg/m^2), sleep-disordered breathing (which may be obstructive or nonobstructive), Pa_{CO_2} ≥45 mm Hg, and the absence of other etiologies to explain hypoventilation.[82] In approximately 90% of individuals with OHS, the sleep-disordered breathing pattern is OSA, with 70% of these having severe OSA.[83] Although the pathophysiology of OHS is complex (Chapters 98–100), the repetitive, prolonged respiratory disturbances associated with cyclic hypoxemia and hypercapnia and relatively short inter-apneic intervals are thought to contribute to the development of diurnal hypercapnia.[84] The remaining 10% of individuals with OHS have nonobstructive sleep hypoventilation without (or with mild) OSA. OHS is associated with increased risk of pulmonary hypertension, cardiovascular and metabolic morbidity, hospitalization, intensive care admission, mortality, and health care utilization.[85–87]

The correction of diurnal hypoxemia and hypercapnia and improvement in symptoms with CPAP in OHS associated with severe OSA was first described in 1982.[88] Since then, multiple studies have been performed demonstrating the efficacy of positive airway pressure therapy in improving gas exchange, daytime sleepiness, sleep quality, quality of life, emergency department visits, and mortality.[89,90] In the largest randomized controlled study to date of OHS associated with severe OSA (n = 221), CPAP and NIV (delivered with VAPS) improved clinical symptoms and polysomnographic parameters better than lifestyle modifications at 2 months. Some HRQOL measurements, spirometry, and 6-min walk distance improved more with NIV than CPAP, but long-term implications of this finding are unknown.[83] In a randomized controlled trial of OHS without severe OSA (n = 98), NIV delivered with VAPS (compared with lifestyle intervention) was associated with improved gas exchange, quality of life, and daytime sleepiness but no change in hospital days/year over a median follow-up of 4.98 years.[91] In a systematic review of studies examining NIV versus CPAP as initial treatment in OHS (2994 potential articles found, 5 selected with sample sizes ranging from 36 to 225 subjects),[92] outcomes were similar between NIV and CPAP. The authors made a conditional recommendation that CPAP be offered as the first-line treatment in stable ambulatory patients with OHS and severe OSA.

In the minority of patients with OHS without significant OSA, NIV is typically used rather than CPAP. Additionally, NIV is also typically used in OHS in the inpatient setting when patients present with acute-on-chronic respiratory failure. Observational studies suggest higher mortality for patients discharged from the hospital without therapy (while awaiting further sleep evaluation) versus those discharged on NIV.[93]

Guidelines for Use

The ATS guideline on the evaluation and management of OHS endorses positive airway pressure therapy (CPAP or NIV) versus no therapy for stable ambulatory patients with OHS (conditional recommendation, very low level of certainty). Additionally, for those stable ambulatory patients with OHS with severe OSA, CPAP is recommended (rather than NIV) as first-line therapy (conditional recommendation, very low level of certainty). However, for hospitalized patients with respiratory failure and suspected OHS, NIV is recommended at discharge until outpatient workup and titration of positive airway pressure therapy can be performed, ideally within three months (conditional recommendation, very low level of certainty).[94] Other relevant published guidelines include those on the evaluation and management of OSA,[73,78,79] on titration of positive airway pressure therapy in OSA[80] and on titration of NIV in chronic alveolar hypoventilation syndromes including OHS.[63]

From a practical standpoint, CMS covers CPAP for OSA if (1) at least moderate OSA as defined by AHI or REI ≥15 or (2) mild OSA (defined by AHI or REI ≥5) plus qualifying symptoms (i.e., insomnia, excessive daytime sleepiness) and/or comorbidities (i.e., hypertension, ischemic heart disease, stroke, mood disorder). CMS covers BPAP-S for OSA in situations of documented CPAP failure (e.g., intolerance, residual sleep-disordered breathing). CMS coverage determination for respiratory assist devices for hypoventilation not associated with OSA is shown in Table 148-5, that is, starting with BPAP-S with a later option of transitioning to a device with a backup rate if failure of BPAP-S based on stringent criteria. The Technical Expert Panel has proposed new recommendations for initiation of NIV in OHS.[58,95]

Modes and Settings

Per ATS guideline on OHS,[94] CPAP is recommended (rather than NIV) as first-line therapy for stable ambulatory patients with OHS. BPAP-S may be required if intolerance at high pressures or persistent hypoxemia or hypercapnia. A backup rate is indicated in those with persistent hypoventilation (either due to inadequate respiratory rate or low tidal volume despite moderate to high pressure).

NIV with a backup rate (BPAP-ST and VAPS) is generally used in patients with OHS without significant OSA and in patients with respiratory failure. In a small, randomized crossover trial of VAPS versus BPAP-ST in OHS after failure of CPAP, VAPS and BPAP-ST resulted in similar improvements in oxygenation, sleep quality, and HRQOL. Transcutaneous CO_2 was lower with VAPS.[96] In another small study of VAPS versus BPAP-ST, VAPS was associated with a lower transcutaneous CO_2 but also objective and subjective impairment of sleep quality.[97] In a larger randomized controlled trial of VAPS versus fixed pressure support in OHS, there were no significant differences in gas exchange, somnolence, HRQOL, or sleep.[98] For empiric therapy in patients with suspected OHS with recent respiratory failure, VAPS with autoadjusting EPAP is theoretically advantageous while awaiting evaluation and titration. In a randomized controlled trial of a single night of VAPS with manual EPAP versus VAPS with autoadjusting EPAP in a mixed group of patients with chronic respiratory failure of diverse etiologies, VAPS with autoadjusting EPAP was noninferior.[99]

In OHS, EPAP is typically high (adjusted to eliminate upper airway obstruction), while PS is adjusted for an initial target tidal volume of 8 cc/kg ideal body weight and adjusted for ventilation. Prolonging the inspiratory time (Ti) may help optimize ventilation. The authors suggest matching NIV settings to underlying pathophysiology (e.g., low to medium trigger sensitivity, slow rise time, long inspiratory time, and low to medium cycle sensitivity)[17] as shown in Table 148-6.

Initiation and Titration

For stable ambulatory patients with obesity, Pa_{CO_2} ≥45 mm Hg, and the absence of other etiologies to explain hypoventilation, CPAP or NIV is initiated after the diagnosis of OSA[81] or non-OSA hypoventilation, respectively. Titration PSG (ideally with continuous CO_2 monitoring) is indicated to ensure resolution of obstructive events and correction of residual hypoxemia and hypercapnia.[63]

For patients who present with acute-on-chronic respiratory failure and suspected OHS, ATS OHS guidelines recommend discharge on NIV (settings based on clinical judgment) until outpatient evaluation and titration, ideally within 3 months. At that point, some patients may be able to be adequately titrated on CPAP while others may need to continue NIV.[100]

■ Neuromuscular Disease and Progressive Restrictive Thoracic Disorders

Neuromuscular and chest wall disorders constitute a diverse group of conditions that vary based on neuromuscular involvement, underlying cause, clinical presentation, and rate of progression, but are commonly associated with sleep-related alveolar hypoventilation and progression to hypercapnic respiratory failure.[101,102] Most studies have been done in amyotrophic lateral sclerosis (ALS) and Duchenne muscular dystrophy (DMD). NIV is associated with improvements in nocturnal and diurnal gas exchange, sleep quality, mortality, rate of lung function decline, quality of life, and symptoms.[103–110]

Guidelines for Use

There are multiple guidelines addressing NIV in patients with neuromuscular disease (NMD) and restrictive thoracic disorders (RTDs), some specific for ALS[105,108] or DMD,[111,112] while others cover a range of disorders.[55,109,113,114] In general, NIV is indicated for symptoms and signs of hypoventilation (e.g., orthopnea, disturbed sleep, reduced lung function, nocturnal hypoxemia, daytime hypercapnia).

Respiratory assist devices (with or without a backup rate) are covered by CMS in neuromuscular and chest wall disorders if criteria are met (Table 148-5). The Technical Expert Panel has proposed new recommendations for initiation of NIV.[58,115]

Modes and Settings

BPAP-ST is commonly used based on clinical experience, but VAPS is also acceptable.[17] Studies of VAPS versus fixed pressure support have been conflicting, but most studies were small and specific settings rather than modes may have explained results. In a case-crossover study of VAPS versus BPAP-ST in NMD/RTD, VAPS was associated with similar nocturnal oxygenation and sleep efficiency but increased nocturnal transcutaneous carbon dioxide tension.[116] This same group later studied VAPS with a modified VAPS algorithm versus BPAP-ST in a mixed group of NMD/RTD/COPD and found equivalent nocturnal oxygenation and ventilation at a lower median pressure support compared with BPAP-ST. Adherence was higher in the VAPS group.[117] In a retrospective chart review of VAPS versus fixed pressure support in ALS, VAPS was associated with a higher achieved tidal volume and a lower rapid shallow breathing index.[118]

With progression of neuromuscular weakness, there may be a need to transition to pressure control mode to better support ventilation or to use home mechanical ventilation to allow for mouthpiece ventilation during the day. Bulbar weakness may limit NIV tolerance. The initial target tidal volume is 6 to 8 cc/kg ideal body weight,[63] adjusted over time for ventilation. EPAP is generally kept low (unless coexistent upper airway obstruction), and IPAP is generally moderate (in the absence of parenchymal lung disease or significant load, e.g., obesity). The authors suggest matching NIV settings to underlying pathophysiology (e.g., high trigger sensitivity, slow rise time, long inspiratory time, and low cycle sensitivity)[17] as shown in Table 148-6.

Initiation and Titration

Given logistical difficulties, NIV is often initiated empirically in patients with neuromuscular disease. The AASM 2010 best clinical practices guideline for NIV in chronic alveolar hypoventilation recommends titration PSG, if possible, to optimize NIV settings and minimize patient–ventilator asynchrony.[63] Data are lacking, but a prospective observational study showed improvements in ventilation, sleep quality, quality of life, and adherence with an intensive NIV titration approach.[110]

■ Central Sleep Apnea

Central sleep apnea (CSA) is not one diagnosis and whether to treat and how to treat depends on the underlying etiology (Chapter 98). CSA may be primary or may be secondary to other disorders. CSA may also be divided into CSA associated with hypoventilation and CSA associated with hyperventilation.

CSA may be seen in severe hypoventilation disorders, including central hypoventilation disorders (e.g., congenital hypoventilation syndromes) or as a component of hypoventilation in other disorders (e.g., "pseudocentral" apneas in neuromuscular disease).[119] By definition, these disorders are associated with wake or sleep hypercapnia, and NIV is generally indicated. More commonly, CSA is associated with hyperventilation (i.e., hypocapnia) and high loop gain. Examples include primary (idiopathic) CSA, high altitude periodic breathing, and CSA associated with Cheyne–Stokes respiration in heart failure or stroke. CSA associated with medications (e.g., opiates) may have features of both hypoventilation and hyperventilation.

CSA may be associated with sleep disruption and daytime consequences. Repetitive desaturations may occur, which in turn may have physiologic consequences. However, whether CSA, per se, is responsible for excess mortality in Cheyne–Stokes respiration in heart failure, high-altitude periodic breathing, primary CSA, or opiate-induced CSA is not clear.[120] Often the treatment of CSA involves treating the underlying disorder (e.g., managing heart failure or reducing opiates). Therapies other than positive airway pressure therapy (e.g., oxygen, acetazolamide) may have benefits in some cases, and CPAP and other modes of positive airway pressure therapy may have a role in stabilizing breathing.[121] Most of the data on positive airway pressure for treatment of CSA comes from studies of Cheyne–Stokes respiration in heart failure.

CPAP has been shown to reduce central apneas in heart failure in several studies, the largest of which is the Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure (CANPAP) trial ($n = 258$). In comparison with no CPAP, CPAP-treated patients had improvements in respiratory disturbances, oxygenation, ejection fraction, and 6-min walk distance at 3 months.[122] However, followed over 2 years, there was no difference in transplant-free survival. In a posthoc analysis, those who were effectively treated with CPAP had better transplant-free survival.[123]

ASV improves central apnea in heart failure.[121] However, in the largest trial to date of CSA in symptomatic heart failure with reduced ejection fraction ($\leq 45\%$) (SERVE-HF, $n = 1325$), ASV was associated with increased mortality.[124] Opioid-related CSA may respond to ASV.[125,126]

Only a few small studies have evaluated BPAP-ST for treatment of CSA in heart failure.[121]

Guidelines for Use

The 2012 AASM practice parameters[121] on the treatment of CSA in adults recommended CPAP therapy for the initial treatment of CSA related to congestive heart failure. ASV was also indicated at that time for the treatment of CSA, but this recommendation was modified in the 2016 update following the publication of the SERVE-HF trial.[127] The update recommended against the use of ASV in patients with moderate-severe CSA and left ventricular ejection fraction $\leq 45\%$ and recommended ASV as an option in patients with CSA with ejection fraction $>45\%$ or mild CSA. Finally, the 2012 guideline stated that BPAP-ST might be considered for the treatment of CSA related to congestive heart failure if there is no response to adequate trials of CPAP, ASV, and oxygen therapies.

Modes and Settings

Studies directly comparing different modes of positive airway pressure therapy in CSA are lacking.[128] CPAP targeted to reduce respiratory disturbances is currently recommended first-line, with ASV as an option for those heart failure patients with reduced ejection fraction above 45% or those with preserved ejection fraction. BPAP-S often worsens CSA due to hyperventilation. However, BPAP-ST can theoretically improve CSA. In one small study comparing CPAP and BPAP-ST, outcomes at 2 weeks were similar.[129]

Initiation and Titration

Treatment of CSA with positive airway pressure therapy may be considered after the diagnosis is established by sleep testing. Not all patients require positive airway pressure therapy. If a decision is made to treat with positive airway pressure therapy, a titration study is indicated. A not-uncommon form of CSA is CPAP-emergent central apneas (i.e., central apneas that "emerge" in patients with OSA during CPAP titration). These may resolve over time on CPAP but may be less likely to resolve in the setting of cardiomyopathy or in patients who are older, have higher residual device-detected respiratory disturbances, or who have leaks,[130] and other PAP modes may need to be considered.

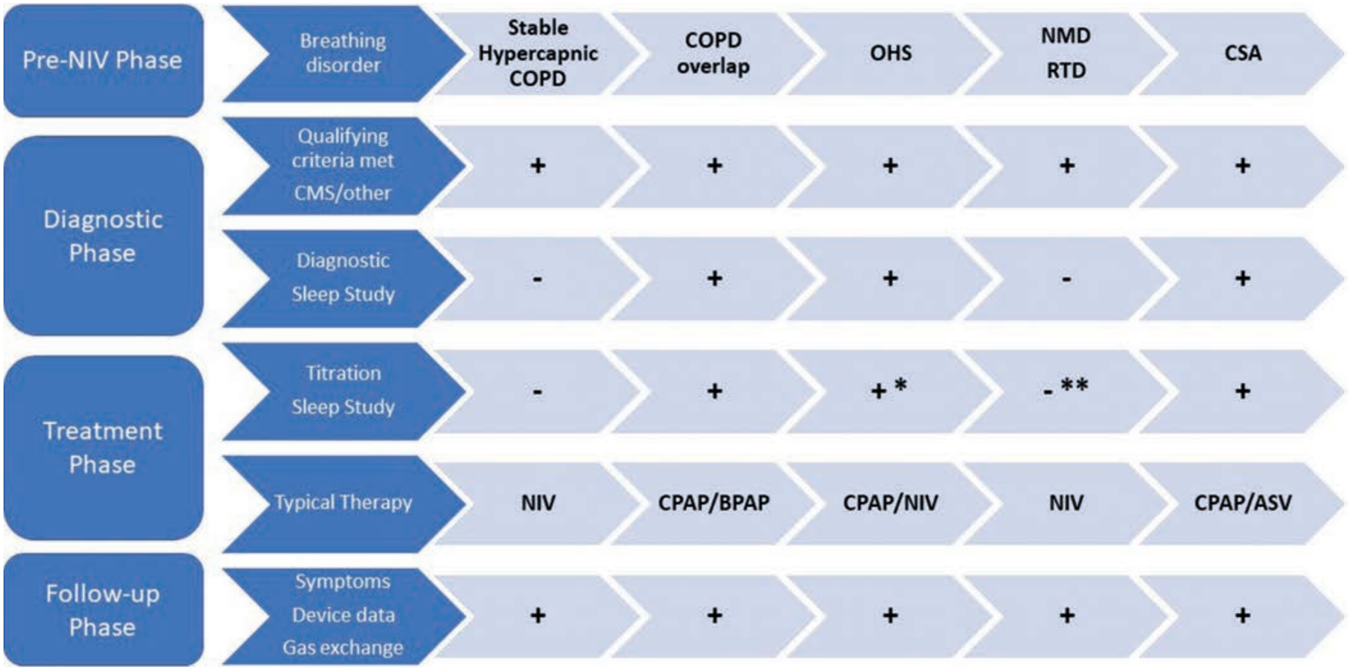
LONG-TERM MANAGEMENT OF NONINVASIVE MECHANICAL VENTILATION

Management of patients treated with NIV does not stop with the initiation of therapy. Instead, follow-up is part of the care continuum for such patients (Fig. 148-6). As noted above, therapy may be initiated empirically. Even if therapeutic PSG is used to guide initial therapy, not all goals of titration may be met on a single study night. For example, achieving a 20% fall in Pa_{CO_2} in one night of titration in severe stable hypercapnic COPD is often not feasible.[57] Respiratory status may improve or decline from the time NIV is initiated. AASM best clinical practice guideline for NIV in chronic alveolar hypoventilation syndromes recommends close follow-up after initiation of NIV to establish effective utilization patterns (ideally using objective data), remediate potential problems, and assess measures of ventilation and oxygenation to determine if adjustment to NIV is indicated.[63] CMS guidelines currently require follow-up including objective assessments of adherence for ongoing coverage of positive airway pressure devices.

■ Noninvasive Ventilation Device Downloads

Current NIV devices monitor usage, leak, and efficacy.[131] Usage data include the number of hours used per night as well as the clock times on and off the mask. Low use or variable use with frequent interruptions per night may indicate problems with asynchrony or intolerance and warrant further investigation. On a practical note, for OSA, CMS requires usage at least 4 h per night on at least 70% of nights to qualify for ongoing CPAP therapy coverage. Documentation of device usage is also required for RADs.

Leak includes intentional leak as well as unintentional leak. High unintentional leak is an indication of a problem with the interface or the circuit and needs to be addressed. Leak affects the performance of the device, including pressure delivered, cycle and trigger



Pre-NIV Phase	Breathing disorder	Stable Hypercapnic COPD	COPD overlap	OHS	NMD RTD	CSA
Diagnostic Phase	Qualifying criteria met CMS/other	+	+	+	+	+
	Diagnostic Sleep Study	-	+	+	-	+
Treatment Phase	Titration Sleep Study	-	+	+*	-**	+
	Typical Therapy	NIV	CPAP/BPAP	CPAP/NIV	NIV	CPAP/ASV
Follow-up Phase	Symptoms Device data Gas exchange	+	+	+	+	+

Figure 148-6 Phases of care continuum in sleep-related breathing disorders treated with positive airway pressure therapy. ASV, adaptive servo ventilation; BPAP, bilevel positive airway pressure; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; CSA, central sleep apnea; NIV, noninvasive ventilation; NMD, neuromuscular disease; OHS, obesity hypoventilation syndrome; RTD, restrictive thoracic disorder; +, indicated; -, not necessary. *Titration study is indicated in stable ambulatory OHS, but may be deferred for several months in favor of empiric therapy in patients with respiratory failure **Titration study is not required in neuromuscular disease, but is recommended if possible.

thresholds, and respiratory event determination.[132] Not only is leak associated with poor tolerance of therapy, but high leaks may also make therapy less effective. Device algorithms do not function optimally in the presence of high leak.

Efficacy of therapy may be determined by review of the synthesis report, which includes device-detected apnea–hypopnea index (AHI), exhaled tidal volume, respiratory rate, minute ventilation, and respiratory cycles triggered by the patient. The AHI is determined by the device algorithm, which is similar to but not the same as the AHI detected on PSG. AHI detected by NIV correlates well with AHI detected by PSG in OHS, assuming low leak and low asynchrony index.[133] Exhaled tidal volume (on noninvasive bilevel devices) is estimated rather than measured, and accuracy varies between devices.[134] Device-detected respiratory rate and rapid shallow breathing index (respiratory rate/tidal volume ratio) may be useful in assessing respiratory muscle rest versus fatigue.[118] Depending on the device and manufacturer, detailed data (e.g., tidal volume, minute ventilation, respiratory rate, flow, pressure, AHI) may be available to review cycle by cycle.[131] Some devices accommodate an external module that allows simultaneous recording of oximetry and heart rate.

Respiratory Monitoring

For disorders associated with alveolar hypoventilation (COPD, OHS, NMD, RTD), periodic measurement of Pa_{CO_2} is indicated to ensure that goals of treatment are being met. However, arterial blood gas testing during daytime, while important to assess diurnal ventilation, does not ensure that nocturnal ventilation is adequate.

Nocturnal CO_2 monitoring is preferred to diurnal testing for the measurement of sleep-related hypoventilation.[135] Transcutaneous CO_2 monitoring shows good agreement with Pa_{CO_2}[136,137] and is preferred to end-tidal CO_2 monitoring in patients using NIV.[131] Home-based transcutaneous CO_2 monitoring is feasible[138] but is not yet widely available in the United States.

Continuous nocturnal pulse oximetry is readily available and recommended to assess oxygenation on NIV.[63] However, there are some limitations.[131] Oximeter features (e.g., sampling frequency, signal averaging time) and motion artifacts affect results. Variations in pulse oximetry on NIV may be due to residual obstructive or central respiratory disturbances, decreases in ventilation, or pressure leaks. Prolonged desaturations may reflect periods of ventilation–perfusion mismatch, hypoventilation, leaks, or inadequate pressure support. In the presence of supplemental oxygen use, pulse oximetry is not sensitive for the detection of partial obstruction of upper airways (e.g., hypopneas) or hypoventilation. Guidelines for optimal oxygen saturation on NIV are not available; a suggested goal is a mean nocturnal oxygen saturation $\geq$90% with $<$10% time with oxygen saturation $<$90% after correction of leaks.[131]

Indications for Sleep Testing

As noted above and shown in Fig. 148-6, diagnostic sleep testing is indicated prior to initiation of CPAP or NIV in disorders in which obstructive or central apnea is a major component (i.e., COPD-overlap, OHS, or CSA). Diagnostic sleep testing is not necessary in stable hypercapnic COPD, NMD, or RTD in the absence of symptoms or signs of OSA.

Titration PSG could be helpful in stable hypercapnic COPD but is not recommended based on recent ATS guidelines.[57] Titration PSG is indicated in COPD-overlap syndrome. Titration PSG is also indicated in OHS, with the exception that it can be delayed in favor of empiric NIV for those being discharged from acute care for acute-on-chronic respiratory failure.[94] Titration PSG is not necessary and is often not practical in NMD, but it is recommended if possible.[63] Titration PSG is indicated in CSA.

Once established on CPAP or NIV therapy, follow-up includes clinical and objective reassessment, as noted above. One algorithm for monitoring NIV proposes targets, including (1) reduction in diurnal Pa_{CO_2} or nocturnal transcutaneous CO_2, (2) mean nocturnal oxygen saturation >90% for more than 90% of recording time, and (3) adequate use of at least 4 h per night without periods of fragmented use. If targets are not being met, the first step is an assessment of pressure leaks (to be corrected with mask assessment/refitting) followed by targeted adjustments in device settings if needed (e.g., increasing EPAP if upper airway instability, increase in pressure support if hypoventilation). If these fail to alleviate problems, repeat titration PSG may be indicated to optimize therapy.[139]

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CHAPTER 149

Extracorporeal Membrane Oxygenation (ECMO) in Acute Respiratory Failure

Asad Ali Usman
Jacob Gutsche

INTRODUCTION

Extracorporeal membrane oxygenation (ECMO), used synonymously with the term *extracorporeal life support*, can be traced back to the extracorporeal circuit invented by Gibbon first used successfully for cardiopulmonary bypass in 1953.[1] More recent advances in cannula, pump, and oxygenator design have improved the durability and availability of ECMO devices, making them available for widespread use.

Generally, an ECMO circuit consists of an inflow cannula that drains blood from the patient into the circuit, a pump to maintain flow, a membrane oxygenator, and an outflow cannula to return blood to the patient (Fig. 149-1). Two types of circuits are in use: veno-arterial (VA) ECMO for support of the heart and lungs, and veno-venous (VV) ECMO for support of the lungs. ECMO proceduralists have introduced multiple variations of these basic circuits to tailor the circuit design to specific types of cardiopulmonary failure. The circuits may be used as a bridge to recovery in patients with cardiopulmonary failure, and they have been used for weeks to months as a bridge to other options, such as a durable ventricular assist device or organ transplant.

In this chapter, we review the history and evolution of ECMO, the basics of circuit design and management, indications and criteria for use of ECMO, and the most common problems encountered. Although we focus on use of ECMO for pulmonary support, it is important for the clinician to understand use of ECMO for *cardiopulmonary* support, since there is overlap in use.

EVOLUTION OF ECMO

The use of ECMO as therapy for acute respiratory distress syndrome (ARDS) and acute respiratory failure (ARF) has evolved over the past 50 years in the context of a complex interplay among improvements in intensive care unit (ICU) therapies (e.g., paralysis, prone positioning, and low stretch ventilation), ICU systems (e.g., delivery of care; automation; electronic medical records; systems improvements, including better patient transport and care team dynamics), and ECMO technology.

ECMO developed as a natural progression from the traditional cardiopulmonary bypass circuit initially used in 1953 to perform the first successful open-heart surgery on an 18-year-old woman with an atrial septal defect.[1] The original circuit was only able to support patients for a very limited time due to the high rate of trauma

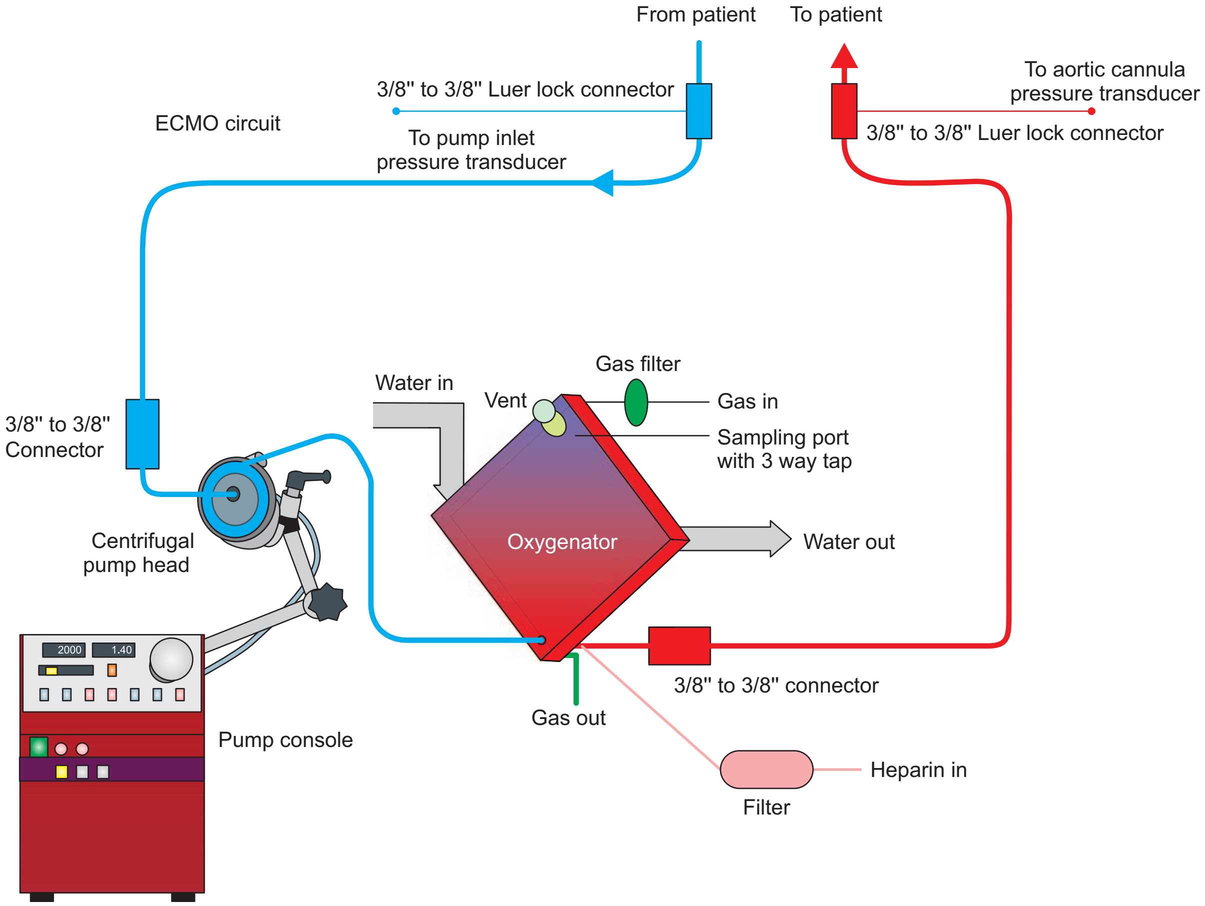

From patient
To patient
3/8" to 3/8" Luer lock connector
To aortic cannula pressure transducer
ECMO circuit
To pump inlet pressure transducer
3/8" to 3/8" Luer lock connector
Water in
Gas filter
Vent
Gas in
Sampling port with 3 way tap
3/8" to 3/8" Connector
Oxygenator
Water out
Centrifugal pump head
2000
1.40
3/8" to 3/8" connector
Gas out
Pump console
Heparin in
Filter

Figure 149-1 Basic ECMO circuit.

of blood components caused by their direct exposure to machine surfaces and oxygen.[2,3] Early challenges encountered with ECMO included poor gas permeability of the oxygenator (see below), weak structural integrity of the circuit, and poor biocompatibility of materials, resulting in sluggish blood flow. As material sciences progressed, new biopolymers were used as conduits for oxygen and carbon dioxide exchange, including Teflon, silicone dimethylpolysiloxane, and nylon. Another breakthrough occurred with development of a new capillary model for the blood–gas interface membrane that utilized a thin-lattice matrix (channels separated by 100–500 μm).[4,5]

The biophysics of extracorporeal membrane gas exchange is similar to that of gas exchange in mitochondria. In mitochondria, oxygen diffuses down a differential gradient from hemoglobin into the mitochondria, and CO_2 diffuses from mitochondria into the blood.[6,7] In ECMO oxygenators, the membrane consists of a lattice structure with a high surface area, and gas is introduced into a capillary-like tubing system—essentially opposite to what is found in the human circulation, where *blood* flows through the capillaries.

In modern-day ECMO oxygenators, blood circulates freely between the hollow fiber tubing carrying fresh gas, and oxygen diffuses through the membrane into the blood, which is propelled by a centrifugal pump. Hence, the gas tubing is akin to an alveolus. A typical red blood cell diameter is 8 μm, while the membrane pore size is <1 μm. The distance from the gas tubule to the blood (the *diffusion path*) is approximately 75 linear μm; however, the path from the fresh gas flow tube to the blood boundary layer is nonlinear due to the lattice matrix and is approximately 100 μm in length.[5]

In 1972 the first successful use of ECMO in a patient with trauma-induced ARDS was reported.[8] The patient was placed on VA ECMO for 75 h for refractory hypoxemia.[8] Importantly, at the time, standard ventilator settings included extremely high tidal volumes (>10 mL/kg) and lower levels of positive end-expiratory pressure (PEEP) than are commonly used today. This and subsequent reports in the literature prompted physicians to consider ECMO as possible salvage therapy for severe ARDS.[9–11]

The first multicenter clinical trial studying VA ECMO in patients with ARDS was completed in 1979.[12] Unfortunately, the study reported dismal results and was terminated early. Only 4 of 42 patients survived the interventional ECMO arm (although only 4 of the 48 patients survived the non-ECMO arm). Although a diagnosis of severe ARDS, irrespective of the treatment, portended a death sentence in the 1970s, the results from this trial demonstrated that VA ECMO did not improve outcomes. Many investigators now acknowledge that the trial was poorly constructed and, perhaps, executed too early in the technologic arc of ECMO and in the absence of institutional best practices. Furthermore, several other key aspects of ARDS care were yet to be established, such as prone positioning, low-stretch ventilation, and routine use of paralytic agents. Nonetheless, study results led to a strong aversion to the use of ECMO in ARDS, setting back development and application of ECMO by several years.

Subsequent studies on ECMO were based on the hypothesis that, perhaps, *CO_2 removal alone*, without targeting optimal oxygenation, might result in improved outcomes in ARDS. Gattinoni et al. suggested a paradigm based on the concept of "lung rest," in which ventilator settings (e.g., inflation volume) are minimized to avoid ventilator-induced lung injury.[13] In this model, the ECMO circuit is set to run at low rates of blood flow (0.5–2 LPM), targeting CO_2 removal only, and the ventilator is adjusted to low-frequency, positive-pressure ventilation to provide oxygenation.

A randomized controlled trial, published in 1994, compared use of ECMO for CO_2 removal versus standard care for patients with ARDS. Unfortunately, the trial was terminated due to lower survival in the ECMO group.[14] In addition, a second study was conducted, but was poorly designed to assess Extracorporeal carbon dioxide removal ($ECCO_2R$) because it encompassed two different experimental modalities. The protocol included use of pressure-controlled, inverse ratio ventilation in addition to low-frequency, positive-pressure ventilation; therefore, $ECCO_2R$ was implemented using two different ventilator settings. Ultimately, the investigators found improved oxygenation with $ECCO_2R$, demonstrated by higher ratio of Pa_{O_2} to F_{IO_2} (P/F ratio), but no difference in mortality (42% in the conventional arm with mechanical ventilation alone vs. 33% in the pressure-controlled, inverse ratio ventilation plus low-frequency, positive-pressure ventilation–$ECCO_2R$ group).[13] Notably, when compared with the absolute survival rate of ARDS in 1979, the 1994 study revealed a marked improvement with conventional management, that is, without using ECMO (survival increase from 8.3% to 58%).

In contrast, in neonatal and pediatric populations, ECMO found a home, prompting additional research and further advancements.[15] One example includes development of hollow-bore fiber tubing that is non-microporous and incorporates use of poly-4-methyl-1-pentene–based materials.[16] Poly-4-methyl-1-pentene oxygenators outperform older silicone dimethylpolysiloxane oxygenators due to lower platelet consumption, better gas exchange, and improved pressure drop requirements.[17,18]

Additional technologic developments in the past 10 years have produced devices designed to facilitate percutaneous cannula insertion.[19] Examples include a multitude of wires, catheters, and ultrasound techniques that have made percutaneous access the preferred choice for ECMO cannulation, resulting in reduced infection rates and bleeding risk.[19–21] Heparin-bonded cannulas and wire reinforcement allow peripherally inserted percutaneous catheters to remain in place without malfunction for weeks to months.[22–24] Wire reinforcement prevents kinking and collapse when negative pressure is applied to the catheter.[25] Additionally, bio-coated catheters and tubing which have a hydrophilic outer layer and contain negatively charged groups to repel negatively charged proteins and platelets have been developed, thereby creating a layer between blood and the artificial surface.[26] Development of dual-lumen, single-access cannulas has further decreased the vascular access burden faced by patients with ARF requiring extracorporeal support. Complications and iatrogenic effects of ECMO have been diminished with use of coated tubing; improved monitoring for anticoagulation; improved medication regimens, ICU management, and nursing care; and increased experience in tertiary centers.

Finally, during the last 25 years, as the definition of ARDS has evolved, considerations regarding the clinical application of ECMO have as well. In 1994 the American Thoracic Society and the European Society of Intensive Care Medicine, with the support of the NHLBI, published the American-European Consensus Conference (AECC) definition for ARDS.[14] AECC criteria were used in the pivotal studies on low-stretch ventilation. The AECC definition standardized the P/F ratio, application of chest radiography, and use of mild, moderate, and severe categories of disease, leading to the Berlin definition of ARDS.[27] By better defining the problem, further clinical trials could be conducted and compared. Against this backdrop, new studies of ECMO in ARDS were initiated. Several important examples are considered below.

■ CESAR Trial

The first major positive ECMO clinical trial was conducted in 2009. Called the Conventional Ventilation or ECMO for Severe Adult Respiratory Failure (CESAR) trial,[28] the trial was a prospective, randomized controlled study of 180 subjects. Patients were randomized to either conventional management or transfer to a quaternary center with ECMO capability for consideration for VV ECMO. Patients on mechanical ventilation >7 days and with inspiratory pressures >30 cm H_2O or F_{IO_2} >80% were excluded. Only 76% of patients randomized to transfer for ECMO consideration were actually placed on ECMO. The other 24% were further medically optimized.

The primary outcome was death or severe disability at 6 months. The study outcome favored ECMO intervention, with 37% mortality at 6 months in the ECMO group versus 53% in the conventional management group. The CESAR trial helped support development of ECMO centers of clinical excellence.

ECMO During the H1N1 Pandemic

In 2009 the H1N1 influenza pandemic led to several seminal publications which described the experience with ECMO in viral pneumonia with ARDS, thereby spurring further interest in expanding ECMO access.[29–33] The largest H1N1 series reported 68 subjects treated with ECMO in 15 ICUs. The average P/F ratio was 56, the initial pH 7.2, and the average PEEP 18 cm H_2O. Patients placed on VV ECMO had a survival rate of 78%.[29] The international impact of H1N1 and the success of VV ECMO led to an inflection point in VV ECMO use.[34]

EOLIA Trial

The Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome (EOLIA) trial, published in 2018, was a prospective, multicenter trial which randomized patients with ARDS to VV ECMO versus conventional treatment.[35] The target sample size of 331 patients was powered to detect an absolute risk reduction of 20% based on an expected 60-day mortality of 60% in the conventional arm and 40% mortality in the ECMO arm. Conducted at 64 centers, trial inclusion criteria were mechanical ventilation <7 days, P/F ratio <50 for >3 h or <80 for >6 h, and an arterial blood pH ≤ 7.2. Exclusion criteria included pregnancy, morbid obesity, underlying irreversible chronic respiratory insufficiency, cardiac failure requiring VA ECMO, cancer with short life expectancy, prior cardiac arrest, do-not-resuscitate status or withdrawal of care orders, or difficult vascular access. No statistically significant difference in mortality at 60 days was noted between the ECMO group (44/124, 35%) versus the control group (57/125, 46%) on interim analysis. The study found that the ECMO group did have lower risk of treatment failure, lower risk of renal replacement, and decreased requirement for prone positioning. Investigators also found that 35 of 125 patients crossed over into the ECMO group, which occurred at a median of 4 days. Mortality was higher in the crossover group. ECMO was associated with severe thrombocytopenia, more bleeding events, and fewer ischemic strokes. Based on predefined stopping rules, the data safety and monitoring board stopped the EOLIA trial early due to futility, noting no difference in survival between the ECMO and conventional therapy groups.

Notable is that there were several serious statistical limitations to the EOLIA trial, including the implausible power calculation performed prior to the study, which eventually resulted in early termination of the trial. The trial assumed a mortality of 60% in the conventional group, but the study's own conventional treatment group had a mortality of only 46%. As mentioned previously for the CESAR trial, the mortality from ARDS in the conventional management (mechanical ventilation) group was 53%. Furthermore, the absolute risk reduction to reject the null hypothesis in the EOLIA trial was set at 20% less in the ECMO group compared to the conventional management group.

As for the CESAR trial, and as in clinical practice, when faced with extreme ARDS and a high risk of mortality, withholding ECMO in the EOLIA trial was considered unethical; therefore, the crossover rate was high. This approach would be especially true if the clinician has a positive prior opinion on the benefits of ECMO and the patient is at an ECMO center. Due to the high degree of crossover, the final study results are biased against ECMO treatment because the crossover occurred after a period of conventional management, exposing the ECMO-delayed group to a longer duration of MV, lack of lung-rest, and delayed treatment. Additionally, this subgroup of "delayed ECMO" might represent an ARDS phenotype that should have received *early* ECMO and, therefore, carried a higher mortality.

Secondary limiting factors for the generalizability of the EOLIA trial include the duration of the trial, which lasted 6 years and entailed slow recruitment; inclusion of both VA and VV ECMO in the study analysis, suggesting a broad patient population, including combined cardiac failure; and lack of synchronization of institutional guidelines and protocols for ECMO management across 52 centers.

Goligher et al. reanalyzed the EOLIA trial data in favor of ECMO based on a Bayesian approach.[36] The analysis demonstrated that the trial was statistically flawed, and that by using Bayesian statistical analysis, a more nuanced understanding of the data was evident.

MECHANICS OF ECMO: CIRCUITS

ECMO includes insertion of peripheral and central cannulas. Central cannulation requires an incision in the chest, usually via sternotomy, to place the cannula in large central vessels. Usually, central cannulation is reserved for patients who are already cannulated for cardiopulmonary bypass for heart surgery and who fail to wean from bypass. The surgeon exchanges the cardiopulmonary bypass machine for an ECMO machine, utilizing the pre-existing cannula. Cannulating large central vessels allows the surgeon to insert very large device, allowing for higher flows.

Peripheral cannulation, which can be undertaken by non-surgeons, utilizes peripheral vessels for the ECMO cannula. Rarely, patients who require extremely high rates of flow may be switched from peripheral to central cannulation, but this is considered a highly morbid procedure due to higher bleeding and infection rates associated with central cannulation.[37,38]

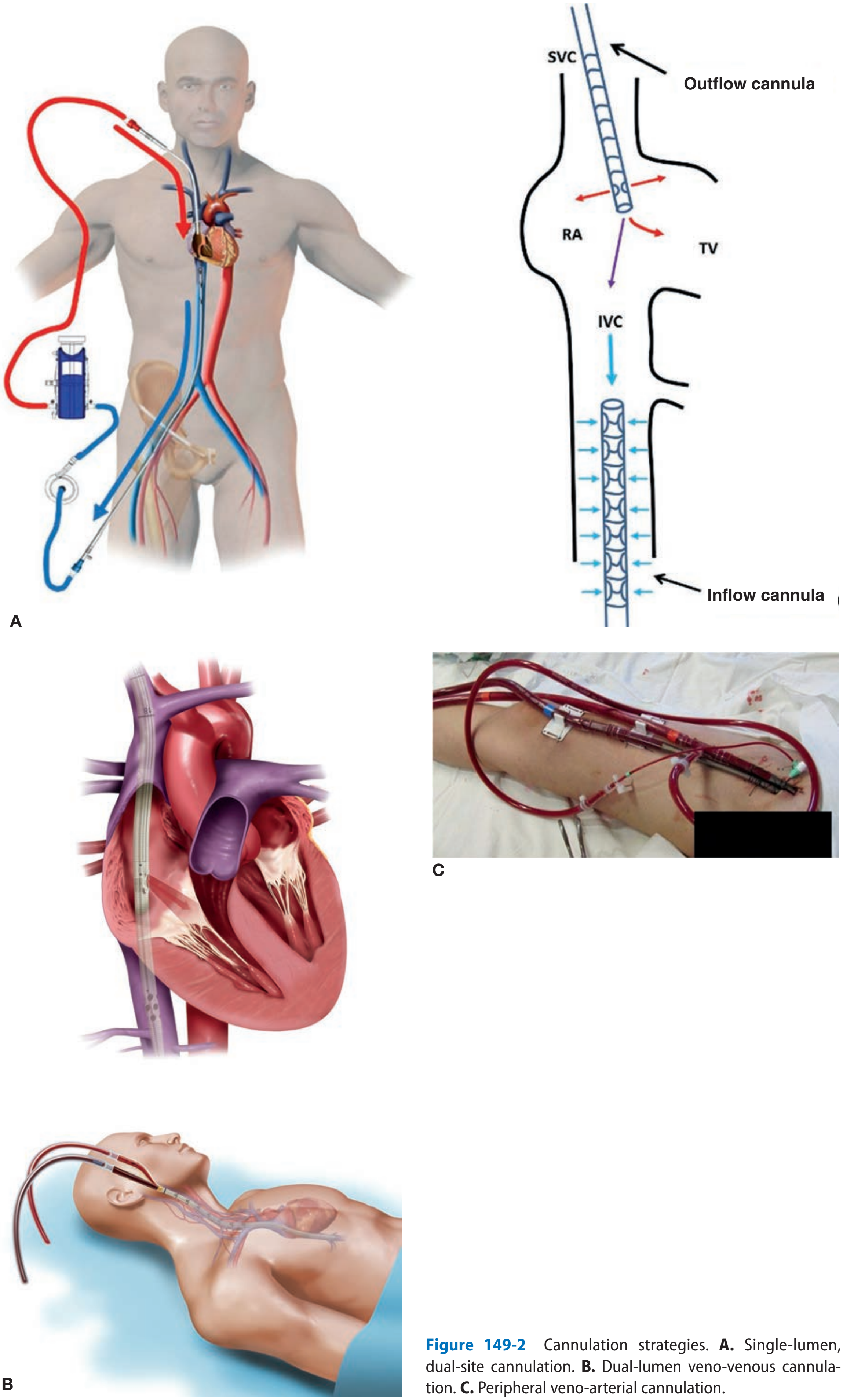
Cannulas are named in relation to the ECMO machine. An *inflow cannula* drains venous blood *to the machine*, and an *outflow cannula* returns blood *to the patient* from the machine. As described below, outflow cannulas may return to an artery, vein, or both.

CHOICE OF ECMO PLATFORM

VV ECMO is the most common ECMO platform used for primary pulmonary failure.[39] One of the most common configurations for cannulation for ARF and ARDS is single-lumen, dual-site cannulation, with femoral vein inflow and right internal jugular (IJ) outflow (Fig. 149-2A).

The right common femoral vein (CFV) is the most commonly used access site for venous inflow due to the direct and linear anatomic configuration of the right common femoral vein as it transitions to the inferior vena cava towards the heart; however, the left common femoral vein may be accessed if the right common femoral vein cannot due to anatomic or structural abnormalities. The right IJ is suggested as the venous return location due to the short and linear approach to the right atrium. The left IJ is not ideal for venous outflow return because the left IJ turns acutely at the innominate confluence. The optimal position of the tip of the inflow cannula is at the inferior vena cava–atrial junction, which decreases risk of recirculation but allows for adequate drainage. The venous inflow drainage cannula is multi-orifice and, therefore, does not depend on rotational positioning to facilitate drainage. The venous outflow return cannula is usually an end-hole cannula. If placed near the orifice of the venous inflow cannula, recirculation can occur, particularly with higher rates of flow.[40]

A second approach to VV ECMO is insertion of a dual-lumen cannula via the right IJ vein. The dual-lumen single cannula (DLSC) encompasses three areas of blood flow: proximal, middle, and distal (Fig. 149-2B). The proximal and distal aspects of the cannula are multi-orifice drainage sites connected via a common blood-flow channel. The channel constitutes the venous drainage inflow component of the DLSC. The distal tip of the DLSC is strategically


SVC
Outflow cannula
RA
TV
IVC
Inflow cannula
A
C
B

[redacted]

Figure 149-2 Cannulation strategies. **A.** Single-lumen, dual-site cannulation. **B.** Dual-lumen veno-venous cannulation. **C.** Peripheral veno-arterial cannulation.

placed into the inferior vena cava (IVC), and the proximal section of the DLSC is placed in the superior vena cava. The middle channel serves as the return outflow channel and rests in the right atrium facing the tricuspid valve.

The DLSC catheter should be placed using transesophageal echocardiography with assistance of fluoroscopic guidance to reduce the risk of right ventricle perforation.[41–43] Echocardiographic positioning is helpful in positioning the cannula so that the return outflow jet is directed towards the tricuspid valve.[44] Newer cannula designs are less dependent on rotational positioning for the outflow limb due to multi-orifice return channeling. Regardless, correct directionality of blood flow can be demonstrated on color doppler imaging of the bicaval or modified bicaval view on TEE.[45,46] The dual-lumen cannula keeps the groin vessels free of cannulas and enables the patient's participation in ambulation and physical therapy. Additionally, it does not sacrifice two venous access points, which are often scarce in critically ill patients in the ICU who need access for administration of vasoactive medications and, potentially, hemodialysis. Specific complications of this catheter strategy include difficulty in placement, lower potential flow range, cannula movement, cerebral venous congestion, and air embolism.

A third cannulation strategy is bifemoral (Fem–Fem) venous cannulation. This is usually considered a bridging or salvage cannulation configuration. If a patient is on femoral–IJ cannulation and needs to be transitioned to a dual-lumen cannula, femoral–femoral VV ECMO can be implemented so that a IJ cannula can be replaced with the dual-lumen cannula in the IJ position. Alternatively, a Fem–Fem strategy can be employed when femoral–IJ cannulation is not possible due to line infection, necessitating movement of catheters to new locations, or when no alternative venous access options remain. This strategy makes it challenging to mobilize the patient for physical therapy and carries a very high rate of lower extremity edema and DVT.[47,48] Furthermore, patients managed with a Fem–Fem cannulation strategy also have a high incidence of recirculation due to the proximity of the inflow and outflow cannula orifices.[49]

An advanced VV ECMO modality that can be considered in the setting of right heart failure with pulmonary failure is an oxygenated RVAD. Recently, a new catheter has been introduced that is effectively a percutaneous right ventricular assist device that can be oxygenated[50] (Fig. 149-3). This catheter-based approach is, in design, very similar to the DLSC; however, instead of having the inflow drainage positioned in the SVC and IVC, this cannula has a series of inflow orifices that are positioned in the superior vena cava and right atrium. The oxygenated outflow blood is then introduced distally in the pulmonary artery through a separate lumen.

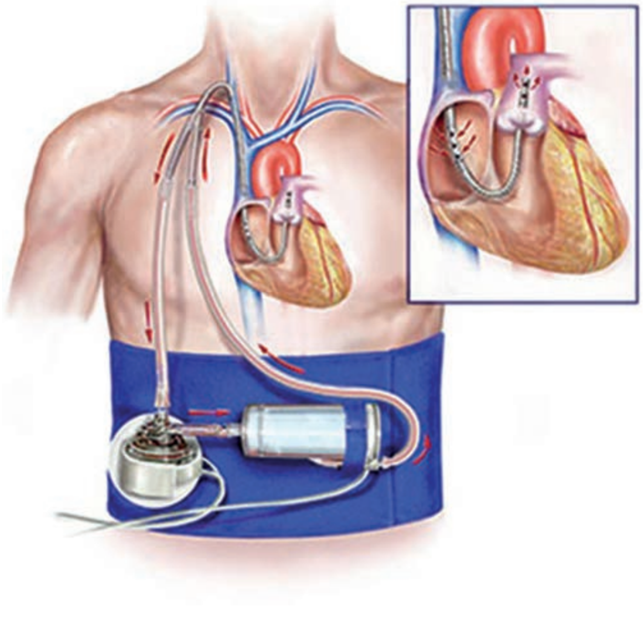


Figure 149-3 RVAD ECMO-Protek Duo.

To place this cannula, a pulmonary artery flotation (Swan-Ganz) catheter is first inserted into the main pulmonary artery (PA). A wire is exchanged through the catheter, and a DLSC Protek cannula is placed. The catheter is located in the same trajectory as a typical pulmonary artery catheter; however, it terminates in the main PA. Echocardiographic guidance is essential for ensuring placement of the catheter tip in the main pulmonary artery, as opposed to the right or left PA. Fluoroscopy is also essential for safety purposes, and placement of a stiff guidewire, into the middle or lower lobar pulmonary arteries is necessary to guide the catheter into place. The final location of the catheter tip is the distal main PA. Deep placement of the catheter into the right or left PA will result in severe ventilation–perfusion mismatching, hyperemia of one lung, and, possibly, pulmonary overcirculation.[51,52]

This cannula traverses both the tricuspid valve and pulmonic valves. The venous inflow drainage orifice drains blood from the SVC and right atrium, and the return outflow terminates as an end-hole at the tip of the cannula in the PA. This cannula is not always used with an ECMO circuit; originally, it was designed to be a percutaneous right ventricular assist device used with a centrifugal pump for isolated RV systolic failure. However, more common now is introduction of an oxygenator after the pump head to convert the cannula into an oxygenated RVAD.[53,54] This configuration not only provides oxygenation support, but also provides critical right ventricular support in a subset of patients with ARDS and RV systolic failure. In ARDS-induced cardiac failure, patients may have isolated RV systolic failure due to a myriad of causes, including ventilator-induced lung injury and cardiac dysfunction due to hypoxia, which often goes together with ARF.[54–56]

Although not considered a conventional ARDS and ARF modality, VA ECMO is also a platform that can be used for ARF (Fig. 149-2C). This modality is often considered when acute decompensated heart failure accompanies ARF.[55,57] Point-of-care transesophageal echocardiography is helpful in decision-making during evaluation for ECMO cannulation for ARF.[58] Prior to ECMO, a comprehensive echocardiographic examination can help diagnose a reversible etiology, as well as guide the cannulation strategy. If echocardiography demonstrates cor pulmonale, then VA ECMO or VAV ECMO might be indicated. Furthermore, pericardial effusions and LV function can be assessed, as well as valvular pathology, which may preclude VV ECMO cannulation.

Sepsis-induced heart failure in pneumonia with ARDS is a known phenomenon and occurs in up to 15% to 20% of patients.[59,60] When a patient is cannulated for ARF, a TEE examination can be used to predict the likelihood of success with isolated pulmonary support through VV ECMO.[45,58,61] If there is evidence of RV dysfunction, an oxygenated RVAD can be considered. If there is evidence of LV failure or biventricular failure with ARF and hypoxemia, then a VA ECMO or VAV ECMO cannulation strategy may be considered (Fig. 149-4). Additionally, in rare situations, patients who are on the brink of cardiovascular collapse may not tolerate VV ECMO cannulation; VA ECMO can be used as a rescue maneuver for concurrent heart failure and acute respiratory failure.[62,63] A VA ECMO system will help unload the RV and provide LV support and systemic oxygenation and may need to be used as a temporizing measure.

Once VA ECMO is established and the cardiac function starts to recover, a transition to VAV ECMO to partially support the heart, can be used in order to bridge the patient back to VV ECMO.[62] VAV ECMO is configured with an oxygenated venous outflow limb can be added to the right IJ, thereby splitting flow back to the patient

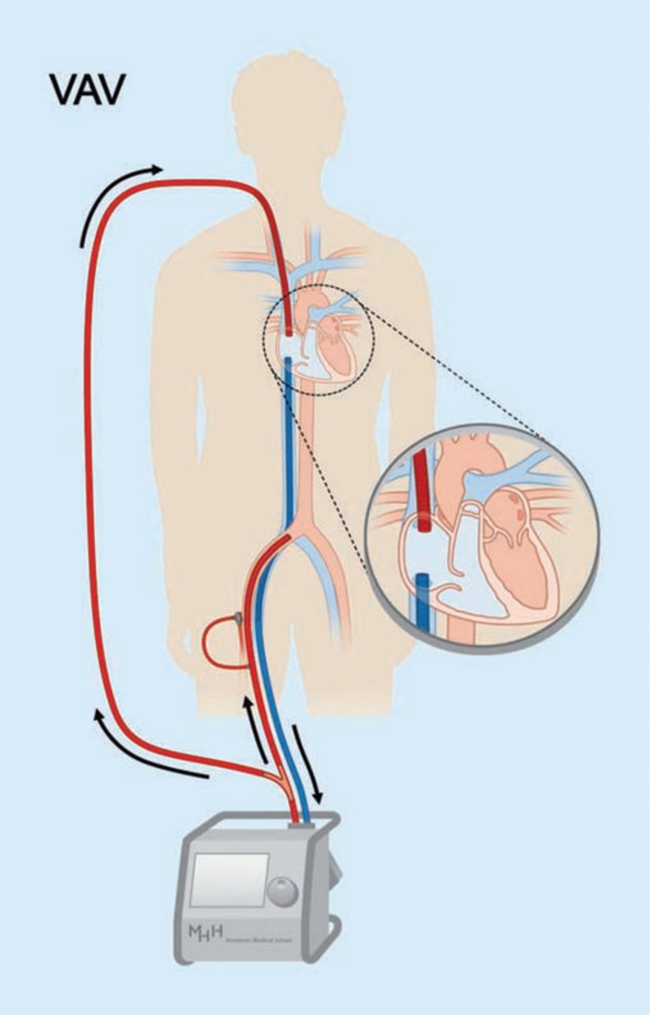


Figure 149-4 Veno-arterio-venous cannulation.

between the arterial and venous systems, which must be regulated by partially clamping the venous outflow limb. As LV support requirements decrease, more flow can be shunted toward the right IJ, and the arterial limb can eventually be clamped and decannulated while the patient recovers from respiratory failure; the patient can be converted to a traditional IJ/Femoral VV ECMO setup.

Patients with severe ARDS placed on peripheral veno-arterial ECMO are at high risk for continued hypoxia. The cannula do not completely empty the heart; thus hypoxic blood is usually ejected and delivers hypoxic blood to the coronary circulation and potentially the aortic arch (Fig. 149-5). If a patient with severe ARDS is placed on peripheral veno-arterial ECMO, every effort should be made to optimize pulmonary gas exchange to prevent differential hypoxia. Other maneuvers to prevent differential hypoxia include conversion to VAV ECMO to oxygenate blood that circulates through the heart or converting to central VA ECMO platforms such as the so-called sport model (Fig. 149-6).

Inclusion and Exclusion Criteria for ECMO

ECMO remains a limited resource that is associated with high costs and resource utilization.[28,64] It is prudent for hospitals and health systems performing ECMO to develop inclusion and exclusion criteria, which should be regularly reviewed.[33,65,66] Criteria for patients considered as a bridge to transplant may be more conservative than patients considered for ECMO as a bridge to survival.[67,68] Criteria have been published and utilized by the Extracorporeal Life Support Organization and by various ECMO programs (Table 149-1).[69,70]

RISKS OF ECMO

ECMO is a support tool, not a therapeutic tool. The technique carries several drawbacks, including need for large-bore vessel cannulation, infection associated with the cannulas, variable and erratic pharmacodynamics and kinetics of drugs (in particular, antibiotics), and need for anticoagulation.[71–73] Due to these risks, patients may experience severe complications, including strokes, severe bleeding, disseminated intravascular coagulation, deep venous thrombosis,

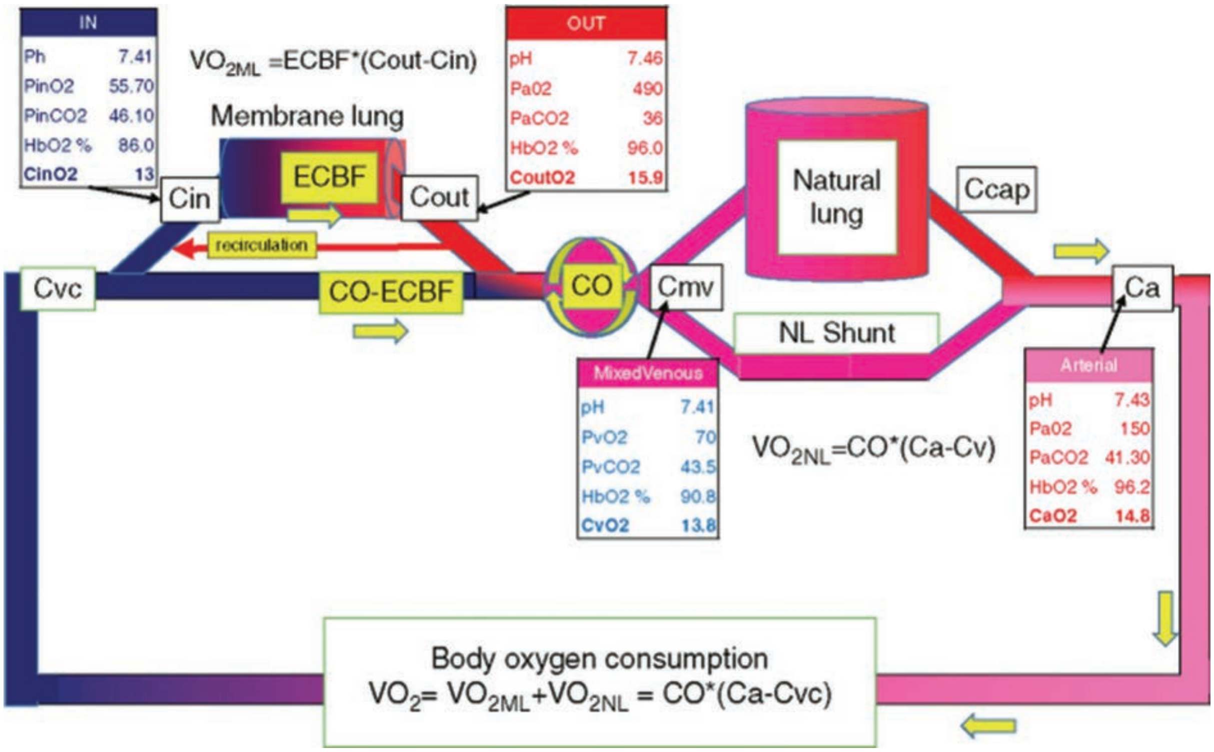
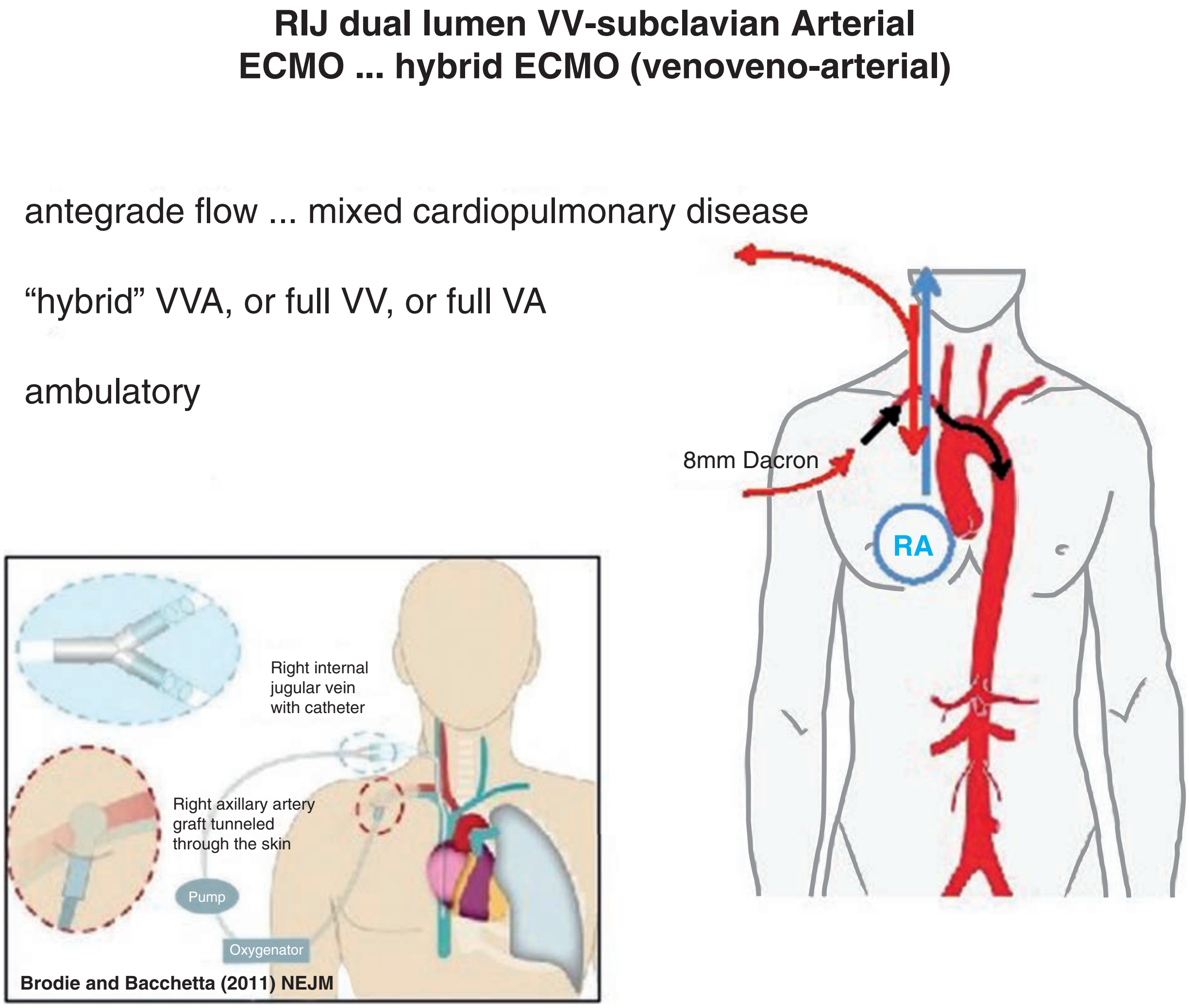

IN
Ph 7.41
PinO2 55.70
PinCO2 46.10
HbO2 % 86.0
CinO2 13
VO2ML =ECBF*(Cout-Cin)
Membrane lung
OUT
pH 7.46
Pa02 490
PaCO2 36
HbO2 % 96.0
CoutO2 15.9
Cin
ECBF
Cout
Natural lung
Ccap
recirculation
Cvc
CO-ECBF
CO
Cmv
Ca
NL Shunt
MixedVenous
pH 7.41
PvO2 70
PvCO2 43.5
HbO2 % 90.8
CvO2 13.8
VO2NL=CO*(Ca-Cv)
Arterial
pH 7.43
Pa02 150
PaCO2 41.30
HbO2 % 96.2
CaO2 14.8
Body oxygen consumption
VO2= VO2ML+VO2NL = CO*(Ca-Cvc)

Figure 149-5 Differential hypoxia.



RIJ dual lumen VV-subclavian Arterial ECMO ... hybrid ECMO (venoveno-arterial)

antegrade flow ... mixed cardiopulmonary disease

“hybrid” VVA, or full VV, or full VA

ambulatory

Brodie and Bacchetta (2011) NEJM

8mm Dacron
RA
Right internal jugular vein with catheter
Right axillary artery graft tunneled through the skin
Pump
Oxygenator

Figure 149-6 Central veno-arterial ECMO “sport model.”

TABLE 149-1 Veno-Venous ECMO Criteria Example

Veno-Venous (VV) ECMO Indications	VV-ECMO Contraindications	VV-ECMO Relative Contraindications
$\mathrm{Pa}_{\mathrm{O}_2}$ <80 on $\mathrm{F}_{\mathrm{IO}_2}$ 100% *or* pH <7.2 with hypercarbia unresponsive to conventional management	Age >70 (except s/p lung transplant)	Weight >140 kg
Severe pneumonia	Severe cardiac insufficiency or cardiac arrest	Severe baseline disability (significant dementia, quadriplegia, etc.) that would inhibit ventilator weaning/rehabilitation
Acute respiratory distress syndrome	Nonrecoverable neurologic injury (ischemic, hemorrhagic, or anoxic)	
Graft failure following lung transplantation	Active malignancy with predicted survival <1 year	
Pulmonary contusion	Graft-vs.-host disease (post-allogeneic transplant ARF)	
Alveolar proteinosis	Severe pulmonary hypertension with severe right ventricular dysfunction	
Airway trauma		Ventilator dependent >10 days
Status asthmaticus	Severe baseline disability (end-stage, which would inhibit ventilator weaning/rehabilitation)	
Airway obstruction		
Aspiration syndrome	Age >70 (except s/p lung transplant)	
Postoperative hypoxemia		

and right ventricular failure.[74–76] Therefore, ECMO should be considered as a rescue treatment when conventional therapy would likely lead to death. The three main indications for ECMO in respiratory failure are refractory hypoxemia, refractory hypercarbia, and need for rescue from injurious mechanical ventilation.

INITIATION OF ECMO

A number of factors must be considered in initiating ECMO, including the decision to perform cannulation; a variety of technical considerations; specifics regarding choice of cannulas, oxygenators, tubing, and pumps; and subsequent monitoring of patients, as discussed below.

■ Decision to Cannulate

Several factors should be assessed when deciding to place a patient on ECMO support. The potential risks and benefits should be weighed for each individual patient. The three key elements include timing, presence of reversible lung pathology, and lack of contraindications. Timing of ECMO is critical, as highlighted in each of the aforementioned clinical trials.[12,28,35,77] A strict cutoff of 7 days of MV was used in all of these studies.[28,35]

Little literature exists regarding the optimal timing for initiation of ECMO since, historically, ECMO has been considered a salvage therapy. As ECMO has become more commonplace, early intervention has played a key role in improved outcomes and survival. Importantly, however, evidence-based practice and utilization of the full armamentarium of ICU treatment modalities should be exhausted prior to instituting ECMO; these modalities include complete pharmacologic paralysis, early and targeted antibiotic usage, low-stretch lung protective ventilation, and prone positioning.[78]

Early intervention is essential in ARF, and identification of reversible causes paramount for achieving good outcomes in ARDS and ARF. In addition, differentiation among acute causes of respiratory failure, chronic irreversible lung disease, and acute-on-chronic pulmonary disease is essential when selecting appropriate candidates for ECMO. Typically, specialized centers have developed strict inclusion and exclusion criteria based on the Extracorporeal Life Support Organization (ELSO) recommendations.[69,70] Strict exclusion criteria include extreme age, nonreversible neurologic injury, active malignancy with predicted survival less than 1 year, prolonged ventilator dependency, lung disease not amenable to reversal that will prevent successful weaning, extreme obesity, and high risk for anticoagulation, including active intracranial hemorrhage. A few specific etiologies that are considered common indications for VV ECMO include ARDS secondary to infection, trauma, pancreatitis, primary graft dysfunction after lung transplant, pre–lung transplant ARF, acute pulmonary embolism, acute eosinophilic pneumonia, alveolar hemorrhage, chronic obstructive pulmonary disease exacerbation, severe asthmatic exacerbation, large bronchopleural fistula, and extremely difficult, high-risk airway for planned operative intervention.

Clinical parameters to consider prior to cannulation include vital signs; hemodynamic metrics; vasopressor requirements; ventilator settings; presence or absence of active infections; baseline imaging, including CT imaging of the chest and cardiac echocardiography; immunosuppression; and etiology of ARF. Ethical considerations include do-not-resuscitate and do-not-intubate orders, as well as planned use of ECMO as a bridge to recovery, bridge to transplant, bridge to decision, and bridge to palliation.

When evaluating ventilator use for patients being considered for ECMO therapy, the guiding principles include restoring adequate systemic oxygen by matching ventilation and perfusion and maintaining cardiac output. Use of pulmonary vasodilators, including nitric oxide or inhaled epoprostenol, and use of PEEP for recruitment are essential.[79–82] PEEP adjustment and recruitment maneuvers help improve V/Q matching. Unfortunately, both hypoxemia and extreme ventilator settings can lead to cardiac dysfunction.[83] ARDS also can independently cause cardiac dysfunction as well, in particular cor pulmonale and RV failure due to severe increases in PA pressures.[84] Particular attention in candidate selection should be direct toward right ventricular function and volume status. Patient positioning, presence of anemia, and metabolic rate of oxygen consumption also play important roles when deciding to place a patient on ECMO.

ARDS-associated cardiac dysfunction is similar to that found in septic shock. Often times the cause of ARDS is pneumonia, which can cause septic shock and lead to cardiac dysfunction; furthermore, ARDS is a contributor to inadequate myocardial oxygen delivery.[85] In spite of fully maximizing ventilation and perfusion to the lung, inadequate cardiac dysfunction leads to decreased oxygen delivery at the tissue level. Both Swan-Ganz catheter use and point-of-care transthoracic and transesophageal echocardiography can be used to assess and monitor cardiac function. Clinical trials using Swan-Ganz catheters in the ICU have demonstrated no significant benefit for morbidity or mortality; however, newer European guidelines suggest use of a thermodilution pulmonary artery catheter in patients with ARDS can improve fluid management and estimation of extravascular lung water.[86–88]

Due to the equivocal data surrounding Swan-Ganz catheters, their use has fallen out of favor in many ICUs; however, newer, continuous monitoring catheters can provide better more detailed information. These catheters are now being increasingly used.[88]

Vasopressor and inotropic support should be added or titrated to support cardiac function, as well as peripheral vasomotor tone. In addition, fluid management remains difficult prior to initiation of ECMO, as well as in management of ARF in general. The competing clinical goals of decreasing pulmonary edema while maintaining optimal cardiac output are challenging. Echocardiography-guided fluid management and inotropic support can improve overall mortality.[89] Furthermore, carefully considered antibiotic choices, inotropic support, ventilator management, and fluid management can lessen lung and cardiac injury.

Broadly, indications for ECMO include hypoxemia and hypercapnia. Further delineation of the ECMO modality best suited for the patient can be achieved by evaluating cardiac function. If a patient with normal cardiac function has hypercapnia without hypoxemia, or hypercapnia with hypoxemia that is manageable using low-stretch, conventional ventilator settings, consideration should be given to low-flow venovenous ECMO. Alternatively, in the era of COVID-19 ARDS some physicians are utilizing minimally invasive ECCO$_2$R devices, which can remove carbon dioxide. These machines function with low blood flows and cannot improve oxygenation. If a patient has hypoxemia with normal cardiac function, the primary cannulation strategy is VV ECMO; however, if a TEE exam demonstrates RV, LV, or biventricular failure, cardiopulmonary support using advanced mechanical circulatory support should be considered, for example, oxygenated RVAD or VA ECMO (Fig. 149-7).

■ Technical Considerations

Both anatomic and physiologic principles are considered in determining cannulation location, configuration, and sizing. Additionally, consideration must be given to whether a patient needs to be stabilized with VV ECMO prior to, or after, transportation to higher level of care.[90]

VV ECMO flows are limited by venous cannula size, transmembrane pressure levels (knows as the *pressure drop*), and outflow cannula size. Insufficient cannula size may result in inadvertent

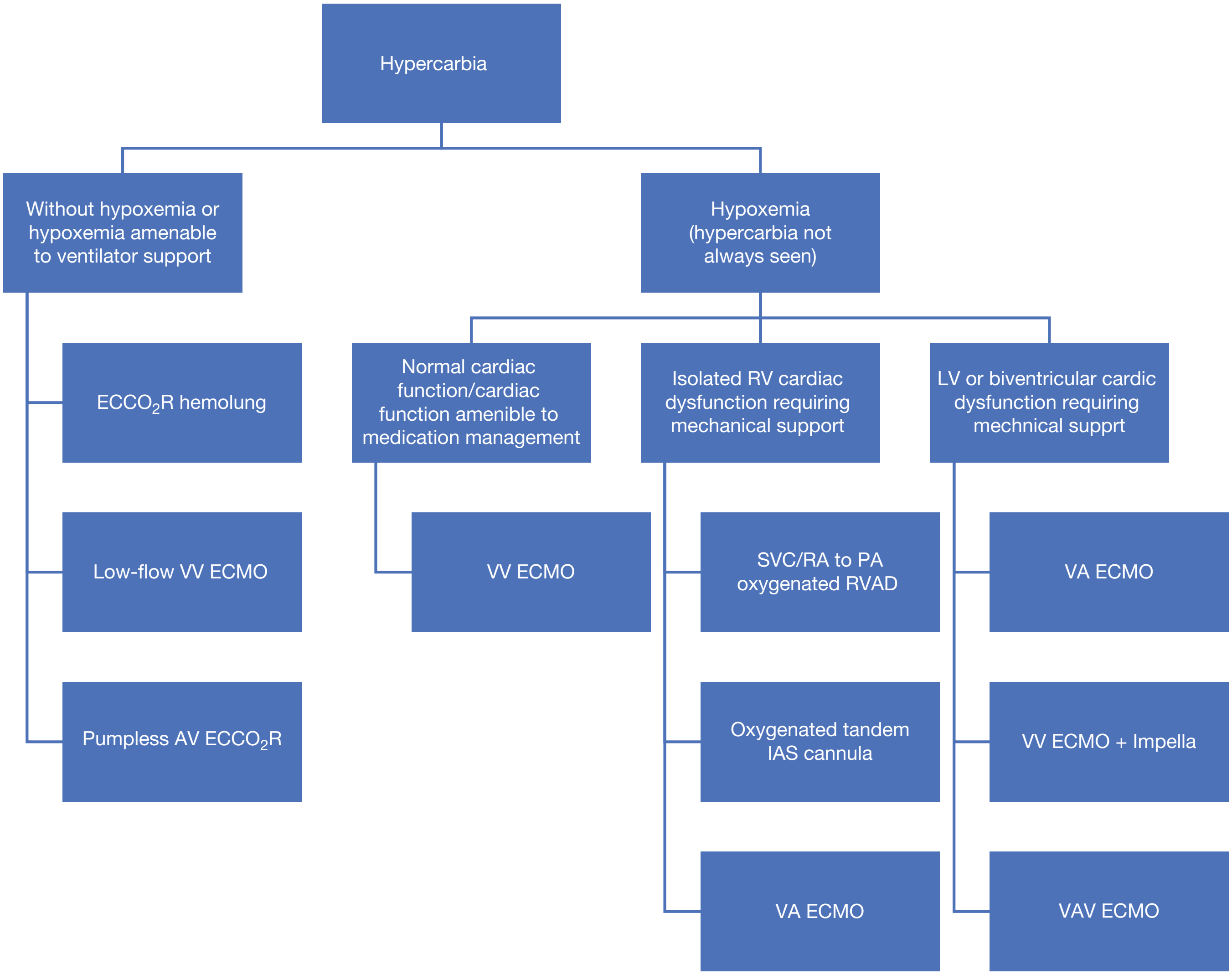

Hypercarbia
Without hypoxemia or hypoxemia amenable to ventilator support
Hypoxemia (hypercarbia not always seen)
ECCO2R hemolung
Low-flow VV ECMO
Pumpless AV ECCO2R
Normal cardiac function/cardiac function amenible to medication management
VV ECMO
Isolated RV cardiac dysfunction requiring mechanical support
SVC/RA to PA oxygenated RVAD
Oxygenated tandem IAS cannula
VA ECMO
LV or biventricular cardic dysfunction requiring mechnical supprt
VA ECMO
VV ECMO + Impella
VAV ECMO

Figure 149-7 Decision algorithm for cannulation type.

hypoxemia if the ECMO circuit is unable to keep up with the native cardiac output[25,50] (Fig. 149-8). Flow limitation is often due to insufficient uptake of venous blood into the ECMO circuit; under these circumstances, a second drainage cannula can be placed. An additional consideration when choosing cannula sizing is minimization of the shearing effects on blood due to turbulence.[91] Use of larger cannulae, fewer connections, and less reliance on Luer lock connections result in less hemolysis.[25] Finally, cannulas with coated surfaces have been designed to prevent clotting and minimize activation of the coagulation cascade.

Patient height and weight should be used to calculate the body surface area (BSA) and estimate flow rates needed to provide

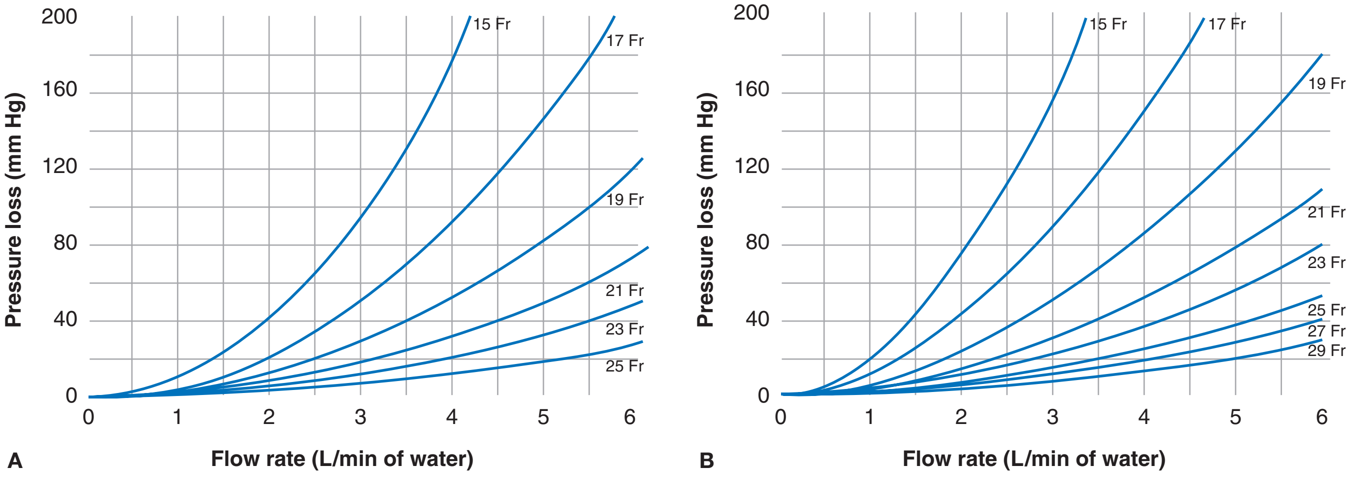


Figure 149-8 Example flow diagram for flow characteristics of cannula.

adequate oxygenation. An important anatomic consideration is body habitus, which may preclude patients from undergoing VV ECMO. Large pannus, excessive abdominal hypertension, or obesity may cause venous inflow obstruction and inadequate flow. Abdominal compartment syndrome is a relative contraindication for venous drainage cannulation.

The venous architecture and anatomy also should be considered when cannulating the patient. Patients often have limited venous access due to deep venous thrombosis or infection, further limiting options for VV ECMO cannulation. Cannulation configurations and tools are available to help address these constraints.

It is imperative to know the venous anatomy prior to cannulation, including whether an IVC filter is present; additionally, a persistent left superior vena cava or, rarely, a duplicated IVC should be considered.

A special subpopulation includes pregnant women. A large gravid uterus necessitates extra care in cannulating; a 10-degree left lateral tilt can be employed to free up the right femoral vein to iliac vein system.[92]

In order to select the correct cannula size, first priority should be given to titrating cannula size to estimated cardiac output requirements.[91] Peak flow through a cannula can be ascertained using information provided by the manufacturer in the instructions for use (IFU). An alternative method is to place maximum-sized cannulas based on vessel diameter measured on ultrasound during precannulation imaging. A balanced approach needs to be struck between the anticipated physiologic cardiac output through the course of the ECMO run (which is difficult to predict) and duration of ECMO (which can last days to weeks), and cannula oversizing (which can result in venous congestion, deep vein thrombosis, and vessel injury).

Several different cannulas are available for VV ECMO. VV cannulas are typically wire-reinforced with biocompatible polyurethane. Occasionally, the surface is coated with heparin to prevent clotting.[22–24,26] Currently, research is being conducted on use of nitric oxide released from ECMO tubing, circuit components, and cannulae to prevent or severely limit clotting.[93] Venous inflow cannula sizes range from 13 to 31 French, while venous outflow cannula sizes range from 13 to 21 French. The venous outflow cannula is typically an end-hole catheter.

■ Cannulas, Oxygenators, Tubing, and Pumps

The most important feature of a good ECMO circuit is simplicity, which makes ECMO easy to deploy at the bedside and defines the most powerful attribute of ECMO as a clinical tool.

The ECMO circuit is typically made of polyvinyl chloride plastic tubing with various connections, including a pump and oxygenator.[94] Connections, entry, and exit points are kept to a minimum to ensure sterility, to decrease the risk of air embolism, and to reduce the drag effect and thrombotic risk of edges and eddy currents. All ECMO circuits should be designed to minimize tubing length and transition points. The sizing of ECMO tubing determines the blood flow rate that can traverse a distance of 1 m with a pressure gradient of 100 mm Hg: 3/16-inch tubing accommodates flow at 1.2 L/min, 1/4-inch tubing at 2.5 L/min, 3/8-inch tubing at 5 L/min, and 1/2-inch tubing at 10 L/min.[95] Typically, 3/8-inch tubing is used.[91]

Not only does tubing diameter play a role in determining flow rates, but tubing length and size are important due to the biologic and pharmacologic effects of the tubing. Long tubing length exposes the blood stream to a large foreign surface, activating the inflammatory cascade and consuming vital clotting factors, while paradoxically increasing the thrombotic risk.[96–98] The large surface area of the tubing also alters the pharmacokinetics of several antibiotics, narcotics, and sedatives. As mentioned previously, during initiation of VV ECMO, the large prime volume can also contribute to acute hemodilution when the fluid is circulated during initiation. Blood priming can help augment those effects; however, blood priming may come with a risk of allosensitization if a patient with a high lung allocation score is placed on VV ECMO as a bridge to transplant.[99,100]

Typical ECMO pumps are driven by centrifugal force (Fig. 149-9). Centrifugal pumps use a magnetically levitated disc with inlet holes for blood and a common outlet for egress of blood. An external magnetic force is applied, causing the internal disc to rotate, raising the velocity, and creating a vortex of blood.[101,102] The centrifugal pump, much like an LVAD, is preload-dependent and afterload-sensitive. Flows fluctuate based on these two parameters and, therefore, no specific RPM provides the same amount of flow.

After leaving the centrifugal pump, blood enters an oxygenator. As described previously, the oxygenator is constructed using thousands of highly permeable tubes through which oxygen flows. Blood enters an interstitial-like space in which red blood cells float between the microtubules of gas. Oxygen enters blood plasma and red blood cells by diffusing down a concentration gradient. In a human lung, alveolar surface area is about 143 m^2, and capillary surface area is approximately 91 to 118 m^2. In a typical ECMO oxygenator, the surface area for gas exchange is 2 m^2.[103,104] Furthermore, the diffusion thickness from gas flow to blood surface is typically 100 μm, while in the human lung it is 2.2 μm[104] (Fig. 149-10).

A membrane oxygenator has functional limitations. The oxygenator is very efficient at CO_2 removal, and complete CO_2 removal can be accomplished using high-sweep gas flows and blood flow rates below 1 L/min. The addition of O_2 into the red blood cell, however, requires larger ECMO flow rates.[105–107] In order to achieve the O_2 delivery (DO_2) requirements for a typical patient (generally estimated to be 260 mL O_2/min) and a post-oxygenator O_2 gas tension >300 mm Hg, approximately 4 L/min flow must be maintained.[91] While blood traverses the oxygenator membrane, a large amount of heat loss occurs. Therefore, ECMO oxygenators also are required to provide heat exchange as blood crosses the membrane.[91]

Pre- and postmembrane pressure sensors allow for monitoring of oxygenator function, in addition to monitoring post-oxygenator gas values. A typical pressure drop across an oxygenator should not be >30 mm Hg, with an inlet pressure of 250 mm Hg and outlet pressure of 220 mm Hg.[108] Flow monitoring, as well as calculation of transmembrane pressure drop, is considered standard of care. Flow monitoring has been shown to be effective in identifying complications in the ECMO circuit and is easily incorporated in current ECMO practice. Since flow monitoring is continuous, it has the potential to serve as a nonspecific initial warning of elevated distal resistance.[108]

■ Spectrum Monitoring of ECMO Circuits

Future directions in ECMO circuit technology include advanced monitoring, such as that provided by integrated EMR systems like Spectrum (Spectrum Medical, Cheltenham, England).[109] Spectrum monitoring includes monitoring for continuous DO_2 and VO_2 by sampling pre- and post-oxygenator gas, monitoring for pressure drops, and subsequent integration of the information over time to synchronize with EMR systems. This capacity has not yet been fully integrated in all hospital systems. However, spectrum monitoring may provide real-time information and the potential to close loop circuits, thereby enabling automatic titration of flows and RPMs based on patient preload, afterload, and desired Pa_{O_2}.[110,111]

MAINTENANCE OF ECMO

Once initiated, the patient on ECMO must be carefully monitored using a variety of clinical approaches, as discussed below.

■ Machine and Cannula Maintenance

The ideal ECMO system provides a platform for CO_2 removal, addition of O_2 to the blood stream, minimal flow rates, and minimal risk

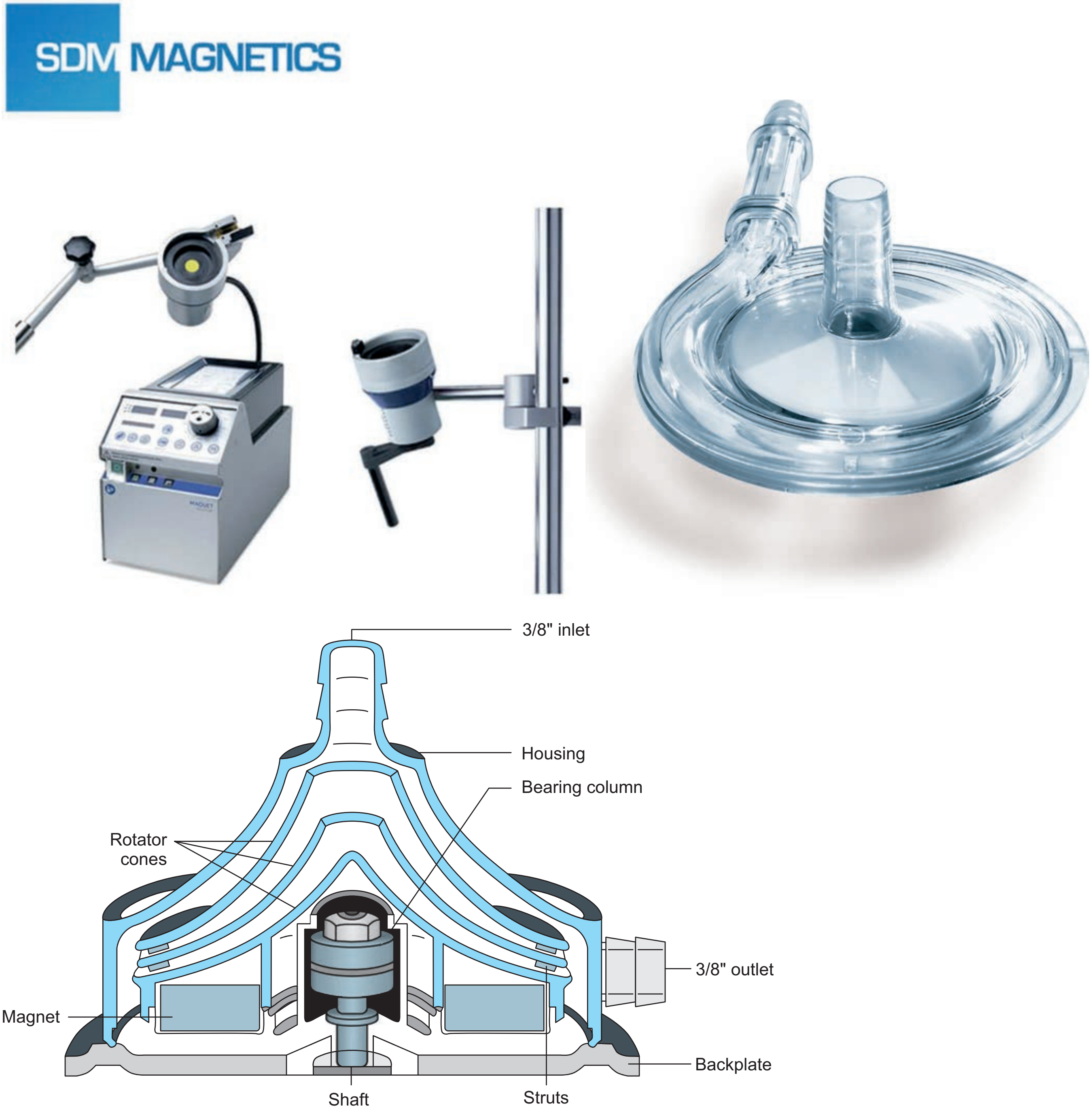


Figure 149-9 ECMO centrifugal pump. *(Top images only: Reproduced with permission from Getinge USA Sales, LLC, Wayne NJ.)*

of bleeding or thrombosis. Additional extracorporeal components can be added, including continuous renal replacement and temperature management (heater/cooler) devices.

Several iterations of the oxygenators have been developed, including a silicone rubber membrane with molecular diffusion, as well as the PMP membrane oxygenator. Oxygenator lifespan and maintenance include provision of adequate anticoagulation and daily assessment of clot burden on pre- and post-oxygenator surfaces. The assessment can be performed with daily transillumination, as well as physical inspection of the oxygenator.

Optimally, standard ECMO configurations include transmembrane pressure monitors. If transmembrane pressures are noted to rise along with hemolysis laboratory values (e.g., lactate dehydrogenase, plasma free hemoglobin, fibrin split products), or if fibrinogen levels fall and platelets consumed, oxygenator or circuit exchanges may be necessary. Commonly, oxygenators are changed on a weekly or monthly timeframe, consistent with the natural lifespan of the device.

Routine arterial and venous blood gas monitoring is mandatory for patients on VV ECMO. Patients on VV ECMO should have an arterial line in place for frequent hemodynamic and laboratory monitoring, as well as central line for vasoactive medication administration. Post-oxygenator Pa_{O_2} blood gas monitoring can help identify failing oxygenators. Establishing institutional practice guidelines for thresholds in oxygenator exchanges based on tolerated post-oxygenator Pa_{O_2} levels should be done. Post-oxygenator Pa_{O_2} should be checked at 100% ECMO FI_{O_2} and can be done at other FI_{O_2} settings as well. "ΔCO_2" levels should be calculated by comparing venous gas P_{CO_2} with post-oxygenator gas P_{CO_2}. ΔCO_2 levels can be used to assess the status of the oxygenator's CO_2 removal capacity,

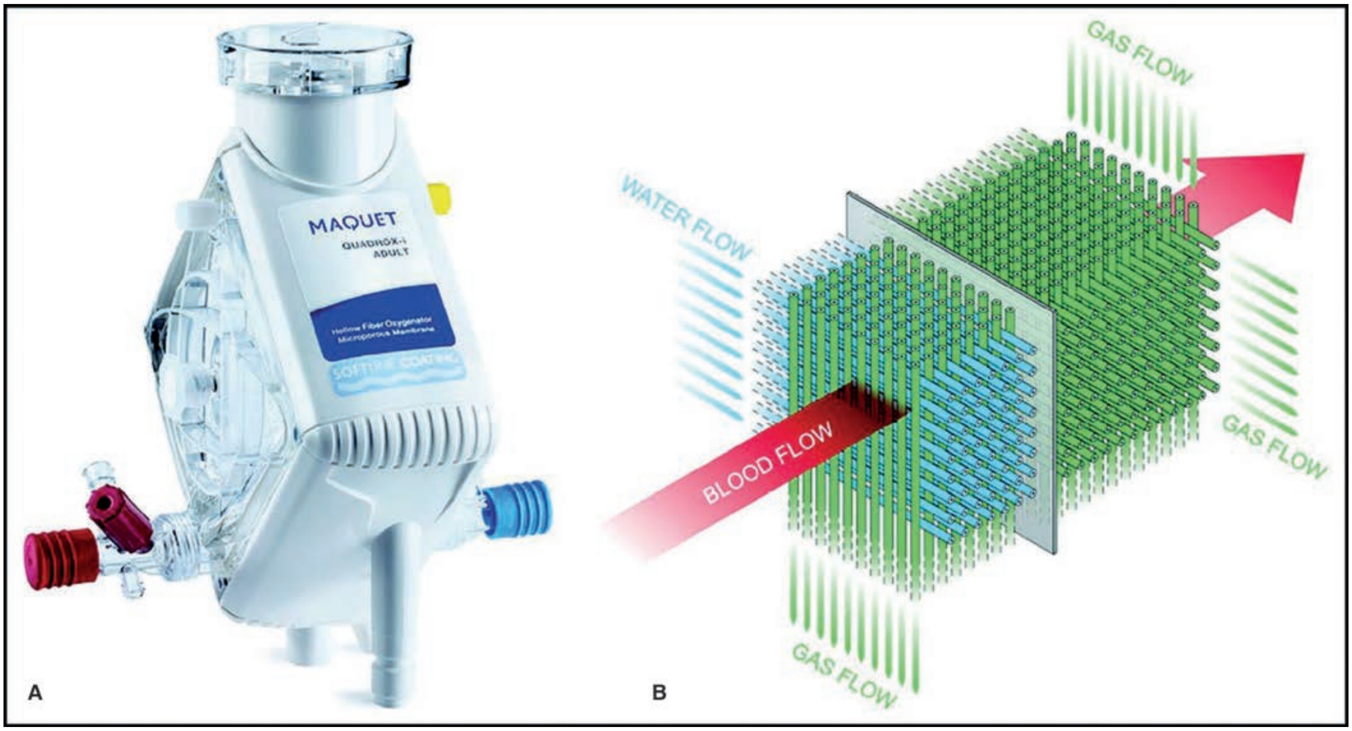


Figure 149-10 ECMO oxygenator. *(Reproduced with permission from Getinge USA Sales, LLC, Wayne NJ.)*

as well as patient readiness for decannulation or need to transition to $ECCO_2R$ devices if available.

The pump head and cannulas should be assessed for function and presence of clot daily. A spare manual, hand crank–driven centrifugal pump should be available on the ECMO cart in case of acute pump thrombosis or failure. Daily chest radiographs are mandatory to confirm cannula position. Cannulas often can migrate, especially during patient transport or prone positioning, and inadvertent decannulation can be catastrophic. Cannulation sites should be checked for induration, erythema, and evidence of infection, as well as wound development. Daily management of the ECMO machine and circuit is an essential aspect in the care of patients.

■ Ventilator Management

Very little definitive literature has been published regarding ventilator management for patients on VV ECMO. There is a complex interplay among the patient, the ECMO circuit, and the ventilator. Generally, lung protective ventilation using low tidal volumes is a cornerstone of management in ARDS.[112,113] This was demonstrated by Amato et al., who detailed the effects of a protective-ventilation strategy on mortality. They demonstrated that massive alveolar collapse, cyclical lung reopening, and overdistention during mechanical ventilation perpetuates alveolar injury: so-called ventilator-induced lung injury. This randomized control trial demonstrated improved survival at 28 days using protective tidal volumes of 6 mL/kg and driving pressures $<$20 cm H_2O.[114]

When a strategy of protective ventilation of 6 mL/kg is impossible due to the severity of lung disease and refractory hypoxemia, VV ECMO can be used to avoid ventilator-induced lung injury.[115,116] By using ECMO as a bridge, ventilator settings can be adjusted to avoid volutrauma, decrease set ventilator respiratory rate, decreasing repetitive inflation–deflation injury, and improve oxygenation, thereby improving cardiac and other organ functions. This strategy is known as "ECMO lung rest."[115,117] Unfortunately, the optimal ventilator strategy in patients with severe acute ARDS supported with VV ECMO has not been delineated.[118,119] Further complicating the complexity of ventilator management during VV ECMO is the fact that the terminology is not standardized. The question remains: to which new ventilator lung protective settings should the patient on VV ECMO be transitioned?

Individual elements of the ventilator can be modified during VV ECMO, including tidal volume, respiratory rate, FI_{O_2}, and level of PEEP. Pressure control ventilation (PCV) and volume control ventilation (VCV) settings have been used for patients on VV ECMO, as have spontaneous modes, such as pressure support ventilation (PSV).[120] While on VV ECMO, a tidal volume below 6 mL/kg can be achieved, resulting in near-absent tidal stress and strain. As noted previously, decreasing the intensity of mechanical ventilation beyond simply achieving tidal volumes 4 to 6 mL/kg predicted body weight (PBW) is associated with improved survival in patients with ARDS.[30] Depending on the severity of the underlying lung injury and subsequent impairment in respiratory system compliance, the tidal volume achieved using PCV may be very small. With high-flow VV ECMO, tidal volumes can potentially be brought to zero, constituting a strategy called "total lung rest."[115,121]

One potential benefit of using PCV during VV ECMO is that with a constant driving pressure, larger tidal volumes may be observed as the patient's condition and respiratory system compliance improves. This may signal a readiness for sedation weaning and decannulation.

The ventilator settings used in the CESAR trial were PCV with a peak inspiratory pressure limited to 20 cm H_2O, a PEEP of 10 cm H_2O, a respiratory rate of 10 breaths per minute, and an FI_{O_2} 30%.[28] In the EOLIA trial the ventilator settings were a plateau pressure $\leq$24 cm H_2O, PEEP $\geq$10 cm H_2O, respiratory rate of 10 to 30, and FI_{O_2} of 30% to 50%.[35] This lung rest strategy targets decreased respiratory rate, decreased tidal volume, and fixed PEEP and driving pressures. The drawbacks of this strategy remain severe alveolar derecruitment and irreversible lung consolidation. Complete atelectasis and fibrosis of lungs may occur. However, this remains the most commonly used MV strategy during VV ECMO.[118]

While data from large clinical trials supporting "ultraprotective" ventilatory settings are lacking, these settings are a logical extrapolation from established principles aimed at minimizing ventilator-induced lung injury and maximizing survival and are of increasing research interest. Further research is needed to determine whether putting the lung completely at rest could be a better solution than providing any ventilation on top of a continuous pressure. Likewise, extubation to spontaneous breathing, or the use of noninvasive ventilation such as BiPAP, CPAP, or high-flow nasal cannula (HFNC), while the patient is receiving VV ECMO for ARDS, is also an area of uncertainty at present.[122–124]

The optimal settings for PEEP for a patient on VV ECMO are also a matter of debate. Some groups use a higher PEEP (>10 cm H_2O), leveraging a strategy that keeps alveoli open and prevents atelectasis, while other groups use a strategy that includes no PEEP and negative-pressure ventilation.[118] Excessive use of PEEP may result in alveolar overdistention with increased plateau pressure and driving pressures. If no alveolar recruitment occurs, then the patient does not benefit (no improvement in oxygenation). Additionally, high levels of PEEP can result in cardiac dysfunction and decreased venous return.[125]

Investigators have demonstrated that high levels of PEEP may be associated with improved survival.[66] A high-PEEP/low-tidal-volume strategy while using VV ECMO is called the "open-lung approach."[126] The open-lung approach has not been clinically validated to produce better outcomes; rather, the strategy is based on mitigation of known causes of secondary lung injury in ARF and ventilator-induced injury, in particular, alveolar collapse and strain.[127–129] Generally, in VV ECMO, PEEP-related alveolar recruitment is less frequently required to improve oxygenation or to reduce the impact of regional alveolar stress and strain; however, when combined with an open-lung strategy, recruitment maneuvers have failed to demonstrate survival benefit.[130]

Nonpulmonary gas exchange provided by the ECMO circuit must be sufficient to enable avoidance of injurious levels of mechanical ventilation. At a minimum, the MV settings should not exceed evidence-based guidelines. Generally, clinicians should target a plateau pressure ≤ 30 cm H_2O and tidal volume of 4 to 6 mL/kg predicted body weight, as used in patients with ARDS who are not supported with VV ECMO.[131,132] However, in many cases of VV ECMO, ventilatory settings can and, likely, should be set considerably lower than these thresholds, particularly driving pressure (e.g., <15 cm H_2O, keeping inspiratory Pplat <25 cm H_2O) and respiratory rate (e.g., 4–15 breaths/min). Any mode that can achieve lung-protective ventilation (e.g., PCV, VCV, APRV, neurally adjusted ventilatory assist [NAVA]) can be used. Once the patient stabilizes and sedation is lightened, transitioning to spontaneous breathing on partial-assist modes (e.g., pressure support ventilation) should be considered.

In a recent, large observational study involving patients treated with VV ECMO for H1N1-associated ARDS, the plateau pressure observed during mechanical ventilation while the patient was supported with VV ECMO was found to be a significant prognostic factor.[30] Plateau pressure and compliance before initiation of VV ECMO were not significantly correlated with prognosis, suggesting that plateau pressure while on VV ECMO was nothing more than a simple marker of severity. These data were used to design the ventilatory strategy used in the EOLIA trial, using a plateau pressure strictly <25 cm H_2O while the patient was supported with VV ECMO.[35,125] Finally, because lung protection remains an important objective during VV ECMO, not only a low plateau pressure, but also a low respiratory rate, may be recommended.

■ ECMO Management

VV ECMO provides the patient with a fixed quantity of oxygen, based on circuit flow and blood oxygen content. The total oxygen content of blood (Ca_{O_2}) is determined as $Ca_{O_2} = [\text{Hemoglobin}] \times 1.36[Sa_{O_2}] + 0.0034[Pa_{O_2}]$. Since the vast majority of oxygen in blood is bound to hemoglobin, the final arterial oxygen saturation of blood returning from the ECMO circuit has an oxygen saturation of 100%. However, ECMO does not drain all venous return to the heart, so a percentage of the patient's cardiac output shunts past the ECMO circuit (e.g., that coming from the coronary sinus). The concentration of oxygen in the pulmonary artery is dependent on the weighted average of the saturations of venous blood bypassing the ECMO circuit and the fully saturated ECMO blood flow. This can be defined as the ratio of ECMO blood flow to cardiac output (ECMOBF/CO).

Once the blood enters the pulmonary artery, it passes through the pulmonary circulation, and based on the injured lung's ability to oxygenate and remove CO_2, the final P_{O_2} in arterial blood is determined. If any native lung function remains, the Pa_{O_2} rises. If there is a complete shunt, the final Pa_{O_2} will be equivalent to the Pa_{O_2} in the PA. Once blood enters the systemic arteries, hemoglobin concentration and cardiac output determine O_2 delivery, as described by the previously noted equation for Ca_{O_2}. Therefore, a balance between HR and RV filling, and ECMOBF/CO and left sided cardiac output and O_2 delivery, is important in determining tissue oxygenation.[133]

Two important clinical considerations should be anticipated during the initiation and maintenance phases of VV ECMO. First, during the initial circulation of VV ECMO, exposure to the plastic tubing, oxygenator, and machinery causes a profound vasodilation that can increase the cardiac output by reducing the afterload.[134] Second, the ECMO circuit prime volume, which can vary based on tubing length, results in acute hemodilution. When the ECMO circuit initially starts to circulate, it can cause a decrease in oxygen saturation if the VV ECMO flow rate is kept static.[135] In order to counteract this initial vasodilation, an increase flow rate is recommended to maintain saturations greater than 92%. Additionally, liberal use of vasopressors should be considered. Pretreatment with vasopressors or push-dose vasopressors should be on hand when initiating VV ECMO. Additionally, the temperature difference between the blood and crystalloid prime can cause profound bradycardia.

If the initial indication for VV ECMO is acute respiratory failure secondary to infection, sepsis, pneumonia, or shock, and cardiac output is high, setting the ECMO flow rate to a normal cardiac output may cause hypoxemia due to a reduced ECMOBF/CO ratio. Likewise, during a long ECMO run, if the cardiac output increases due to any cause (e.g., infection, sepsis, sedation weaning) and lung function remains compromised, the patient may experience hypoxemia due to shunt. For example, consider circumstances in which the VV ECMO flow rate is set at 5 L/min and the native CO increases to 10 L/min. If the ability of the damaged lung to oxygenate remains unchanged, then even in the setting of 100% saturation from the ECMO circuit, the native lung needs to provide $>80\%$ saturation to maintain a final saturation of 90% in the systemic circulation (barring any shunts or venous admixture). V/Q mismatch and shunts will further decrease the final systemic saturation. Therefore, preload, cardiac output, ECMO flow rate, and hemoglobin levels need to be managed closely during VV ECMO.

After patient stabilization on VV ECMO, and with recovery of cardiac function and improvement in tissue oxygenation and waste removal, vasoactive support can often be reduced significantly. Hemodynamic goals should be reviewed daily and adjusted, if necessary. In general, a fluid-restrictive approach to volume resuscitation is promoted after the acute phase of critical illness to avoid excessive capillary leak and improve pulmonary function. A restrictive transfusion practice also may be considered, targeting a hemoglobin threshold >7 g/dL.[136,137] In patients with a high cardiac output due to sepsis or other cause, significant hypoxemia can occur due to excessive blood flow through the native lungs.[138] A trial of short-acting beta-blocker infusion may be an effective method to improve oxygenation by reducing the patient's native cardiac output, reducing pulmonary shunt, and increasing the fraction of blood flow through the ECMO circuit.[133]

Fluid Management

Many patients undergoing invasive mechanical ventilation for severe respiratory failure are in a vasoconstricted state and demonstrate impaired peripheral perfusion. Fluid administration frequently causes some pulmonary edema, especially during inflammatory states, which then impairs gas exchange. Thus, many patients with severe respiratory failure are managed with a fluid-restrictive strategy before initiation of VV ECMO, in part because a conservative fluid strategy in patients with ARDS is associated with improved outcomes.[139]

ECMO, like any mechanical circulatory support device, is preload dependent; therefore, the ability of the ECMO circuit to oxygenate blood is dependent on the ECMO blood flow through it. Increasing blood flow during VV ECMO predictably increases systemic oxygen delivery. When patients are initially placed on ECMO, the goals for fluid resuscitation should be targeted toward maintaining adequate flows, appropriate preload, and sufficient volume for the ECMO circuit to run effectively. This initial phase of fluid administration may result in an increase in pulmonary edema. During this resuscitative phase, lung compliance decreases; at stable inspiratory pressures, tidal volumes rapidly and predictably fall. There is evidence to suggest that MV changes to overcome this decrease in tidal volume should not be undertaken. Increases in ventilatory intensity to overcome the decreased compliance seem more injurious than beneficial, assuming adequate ECMO flow and systemic oxygen delivery.[140] This is especially true with ECMO initiated for SARS-CoV-2–related ARDS. Therefore, decreases in ventilation and tidal volume with increasing lung water during the resuscitative phase of VV ECMO should be tolerated by using ECMO flow to enable sufficient gas exchange.

Predictably, as the inflammatory process improves over the first few days and the lungs are not subjected to injurious ventilatory forces in an effort to "overcome" the pulmonary edema, the fluid is redistributed back into the vasculature. As tissue oxygenation improves and the inflammatory response abates, fluid removal and improvement in EVLW can be targeted. Over the maintenance phase of ECMO, negative fluid balance results in better lung compliance, while increased fluid balance results in increased mortality.[141–143]

Chatter and Suck-down

The venous drainage inflow cannula, typically positioned in the femoral vein, extends into the inferior vena cava, terminating at the cavoatrial junction. The cannula is usually fenestrated, with multiple side holes to optimize drainage. The centrifugal pump in the ECMO circuit creates negative pressures, ranging from 200 mm Hg to 250 mm Hg ("premembrane" pressure). Fluid balance during the ECMO run changes, depending on the goals of ICU management, for example, diuresis for the volume-overloaded patient versus provision of sufficient vascular volume to ensure adequate flow on ECMO. Intravascular venous volume, patient position, intrathoracic pressures, and cannula type all influence the tendency of the vein to collapse around the pre-pump cannula. This can be as minor as "chugging," during which the pre-pump limb demonstrates a low-frequency rhythmic "chatter," or more severe collapse, leading to deceasing ECMO flow or "suck-down." Excessive fluid administration to decrease suck-down events often leads to harmful fluid overload. Fluid management should be guided by the patient's condition and degree of pulmonary edema. The ideal treatment for persistent suck-down and severe chatter is to turn the ECMO flows down if the patient's oxygenation and ventilation status allow.

The DLSC has many of its return fenestrations on the sides; hence, the catheter typically is associated with more instances of intermittent flow limitation compared to a nonfenestrated cannula or one located in a dependent position, such as the femoral vein. In general, the flow limitations are more dramatic during rapid shifts of intrathoracic pressure, such as during coughing or when the patient is sitting up or ambulating.

As the patient improves, increases in intravascular volume are expected; resolution of capillary leak leads to fluid redistribution back into the vasculature, thereby facilitating diuresis. Under these circumstances, alternative causes of intravascular volume depletion should be considered, such as bleeding, which commonly occurs in patients on ECMO, and septic shock.

Systemic Inflammation and Fluid Resuscitation

Administration of intravenous fluid to patients experiencing an initial inflammatory vasodilatory state results in increases in systemic blood flow.[96] While the ECMO circuit provides a fixed quantity of oxygen to the body at a given level of ECMO blood flow, arterial saturation during ECMO is dependent upon the ratio of ECMO flow to systemic blood flow, which incorporates native lung function. Predictably, within the first few hours after initiation of ECMO, systemic saturation decreases. The decrease is likely related both to increases in lung water with fluid administration and corresponding impairment of gas exchange. Additionally, decreases in the ECMOBF/CO ratio, as systemic cardiac output increases with improved oxygenation, may contribute. To the extent that decreases in systemic saturation are due to changing flow ratios, peripheral oxygen delivery often remains unchanged or increases. It is critically important to ground assessments of adequate oxygenation on objective measures of tissue perfusion, rather than the percent saturation of arterial blood.

With improvement in the initial inflammatory state, increases in blood flow and oxygen delivery often lead to improvement in organ function and, in cases of preserved renal function, an autodiuresis.[96] Limited data are available in ECMO populations to guide fluid management after the initial resuscitative phase. Since a conservative fluid management strategy has shown benefit in patients with ARDS without ECMO, in the absence of data, it is reasonable to assume that following initial fluid resuscitation the same holds true for critically ill patients managed with ECMO.

In many of the studies that demonstrated a benefit with conservative fluid management in ARDS, fluid minimization commenced only during days 1 to 4, following an initial resuscitative phase. In some studies, diuretics were also administered to achieve this conservative fluid status.[144,145]

Evidence suggests that a negative fluid balance, including that attributed to deresuscitation, is associated with reduced mortality and shorter duration of mechanical ventilation for patients with ARDS, including patients on ECMO.[141,143] In two other studies of VA ECMO for shock, the highest quartiles of positive fluid balance were associated with increased mortality; patients with negative fluid balance demonstrated improved survival.[146,147] Increasingly, data from ECMO and non-ECMO patients suggest harm from excessive fluid administration and positive fluid balance. Thus, the best available data at this time suggests that after the initial resuscitative phase of VV ECMO, patients should undergo de-resuscitation to achieve negative fluid balance.

Anticoagulation and Bleeding in ECMO

Exposure of blood to the polyvinyl chloride, PMP, and oxygenator surfaces actives the thrombotic and inflammatory response systems. When blood proteins are exposed to the foreign surface of the polyvinyl chloride and PMP in the oxygenator, several activating factors, including von Willebrand factor (vWF), bind to the surfaces; platelets are activated, and fibrinogen is converted to fibrin that binds to the surface. Thrombin formation also creates a mesh network that consumes coagulation factors. Coagulation factors leak from plasma as blood is moved through the oxygenator, and proteins leak in a retrograde direction through the pores of the microtubules carrying oxygenated gas.

In addition, proinflammatory mechanisms that include neutrophils, monocytes, and leukocytes are activated—a process that occasionally becomes deranged, constituting "cytokine storm."

Anticoagulation at the time of initiation and maintenance is usually required during VV ECMO. Due to the anticoagulation requirement, as well as thrombocytopenia, mechanical destruction of platelets, and loss of clotting factors, patients on ECMO are at increased risk of bleeding. Additionally, heparin is used to bind to antithrombin III, which leads to decreased thrombin formation and decreased clot formation. Antithrombin III levels may also decline due to critical illness and losses during ECMO.[148] Hemorrhage also may be attributed to direct injuries during cannulation. However, with vascular access ultrasound, improved cannula design, better wire placement, and echocardiography guidance, hemorrhagic complications have been mitigated significantly.

In patients on ECMO, common sources of bleeding include epistaxis and gastrointestinal sources; rare sources include intracranial or pulmonary sources.[149] Anticoagulation protocols typically include intravenous unfractionated heparin; however, some institutions select bivalirudin or argatroban more often. The advantages of heparin include ease and familiarity of use, easy reversal, and easy monitoring with PTT and activated clotting time levels. The drawbacks include variable anticoagulant effects, heparin resistance, and heparin-induced thrombocytopenia. Direct thrombin inhibitors, including argatroban and bivalirudin, carry a lower risk of heparin-induced thrombocytopenia (HIT) and function independently of antithrombin III. However, they are renally and hepatically cleared and require adequate end-organ function. Unfortunately, there are no U.S. Food and Drug Administration–approved reversal agents for these intravenous direct thrombin inhibitors. Hemodialysis and activated factor VII are options. With normal renal and hepatic function, the half-lives range from 25 min for bivalirudin to 45 to 50 min for argatroban.

Recently, investigators performed a retrospective, single-center cohort study of patients on VV ECMO, 162 of whom received unfractionated heparin and 133 of whom received bivalirudin.[150] Patients on bivalirudin had decreased circuit thrombosis, increased time to circuit thrombosis, and decreased transfusion requirements for packed red blood cells, plasma, and platelets. Most importantly, they found. fewer major bleeding events for patients treated with bivalirudin than those treated with heparin (40.7% for patients receiving heparin vs. 11.7% for those receiving bivalirudin).[150]

Imaging

As with any invasive procedure, there are risks in establishing the ECMO circuit, including vascular injury. Common pitfalls include pneumothorax and arterial puncture or injury.

Percutaneous vascular access should be guided using linear surface ultrasound. Once vascular access is obtained, cardiac transesophageal echocardiography (TEE) should be performed prior to, and during, cannulation. TEE examination should include assessment of right and left ventricular function. Particular attention should be paid to the presence of a patent foramen ovale, atrial septal defect, or ventricular septal defect. The presence or absence of a pericardial effusion (likely transudative) should be noted.

Once cannulation is commenced, several passes of large, stiff wires may result in injury to the cardiac structures. The presence of a postprocedural pericardial fluid may suggest hemopericardium.[87] Other pathologies should not be ignored, including large pleural effusions, which can be readily seen on TEE. Finally, TEE should be done at the time of cannulation, as undiagnosed cardiac dysfunction may occur concurrently with ARF, prompting a change in cannulation strategy from VV ECMO to VA ECMO.

Although fluoroscopy and TEE can each be used to guide ECMO cannulation, since many cannulations have moved to the ICU setting, for both VA and VV ECMO, TEE, at a minimum, is required for cannulation. When necessary, fluoroscopy can be used when available in the cardiac catheterization laboratory or in the operating room.

Imaging using TEE is mandatory when placing the dual-lumen, bicaval Avalon cannula because the outflow jet should be directed towards the tricuspid valve. This can be determined using color doppler through the cannula orifice. TEE also should be used to confirm the distal positioning for a RA/PA Protek Duo cannula; the tip of the cannula should be situated in the main pulmonary artery, and color doppler should be directed bidirectionally into branch pulmonary arteries. Distal migration may result in V/Q mismatch.

Particular attention should be directed to the TEE when starting the circulation during ECMO. Initial exposure to the large volume of cold saline may result in cardiac bradyarrhythmias. During VV ECMO blood is taken from, and returned to, the right heart with no significant change in RV preload and no adverse effects on left-heart hemodynamics. VV ECMO also increases mixed venous oxygen saturation, leading to a decrease in pulmonary vascular resistance and a lower RV afterload. The increased oxygenation of the LV indirectly improves the LV function and increases oxygen delivery to the coronary artery circulation. During the ECMO run, patients should have frequent chest imaging, not only to monitor ARDS progress but also to closely monitor cannula positioning; daily chest radiographs are recommended. Furthermore, serial, lower extremity duplex venous scanning is essential to evaluate for DVTs.

Physical Therapy

Patients on ECMO may be safely mobilized for physical therapy (PT) and benefit from both PT and occupational therapy (OT). In a retrospective cohort study of 100 patients on ECMO, 35% participated in active physical therapy;[151] 19% of patients were on ECMO as a bridge to transplant and 16% as a bridge to recovery for ARDS. Patients were on ECMO for an average of 14 days and received an average of 7 PT sessions. During PT sessions, 51% of patients ambulated.[151]

Particular attention should be paid to the cannulation strategy when patient ambulation is anticipated. DLSC IJ cannulation is the ideal platform for ambulation, with or without mechanical ventilation. Furthermore, a portable ECMO machine, such as the Cardiohelp system by Marquet, constitutes a low-profile device with combined pump and oxygenator and is amenable to both patient transport and mobilization with PT.

DECANNULATION

Careful planning should be undertaken for patients who have clinically improved and are ready for decannulation, as described in the following sections.

Weaning ECMO

As with all ICU therapies, weaning and liberation from ECMO are clinically challenging and poorly studied. No gold standard approach exists; rather, several physiologically sound strategies have been advocated.

As a patient's lung function improves, typically compliance also improves while on low-stretch ventilation. The P/F ratio rises. Patients on ECMO for lung rest, who are on pressure control ventilation and have unchanged driving pressures, begin to manifest larger tidal volumes as lung healing occurs. During the recovery phase, sweep gas flow and F_{IO_2} on the VV ECMO circuit are independently weaned. If the patient presented has concurrent hypercarbia or demonstrates difficulty with CO_2 removal in the setting of stable oxygenation, then transition to $ECCO_2R$ can be undertaken. If the initial indication for VV ECMO was hypoxemic respiratory failure, then every attempt should be made to wean the ventilator first.

Patients can be extubated while on VV ECMO if mechanical ventilation is no longer necessary. Reaching the point of extubation is, however, not the most common scenario. Extubating patients while on VV ECMO is a challenge because the clinician needs to strike a balance between wakefulness and sedation/analgesia, allowing for appropriate respiratory drive in the setting of damaged neuropulmonary feedback due to ARDS. Awake patients on ECMO often demonstrate extreme tachypnea and coughing, which can cause a decrease in ECMO flow rates. However, awake, ambulatory, negative pressure–based ventilation while on VV ECMO is an ideal platform for lung rest and minimization of ventilator-induced lung injury.[152]

Frequently, patients require mechanical ventilation for longer periods than they require ECMO support. The risks and benefits of prolonged ECMO support versus decannulation must be considered in the setting of achieving minimal mechanical ventilatory support necessary to maintain oxygenation adequate for end-organ function. This is often the most common scenario in transitioning from ECMO. When the patient's ventilatory requirements can be met with MV alone, ECMO can be discontinued.

Basic weaning thresholds for decannulation include $\mathrm{FI_{O_2}}<50\%$, PEEP <10 cm H_2O, respiratory compliance >50 mL/cm H_2O, and respiratory rate <20 breaths per minute. Patients should be able to sustain these settings for at least 48 h. The airway should be cleared of all secretions and mucolytic therapies continued following decannulation. Patients should not have active pneumonia or other infections that would portend post-decannulation failure. Frequently, patients have had a tracheostomy and are debilitated from paralysis, immobilization, and fluid administration associated with treatments common in ARDS. Diaphragmatic failure can also result in post-decannulation respiratory failure. Anticipated increases in metabolic oxygen requirements, such as those due to fever, lightening sedation, and infection should be considered when deciding to decannulate.

Decannulation may result in a systemic inflammatory response syndrome (SIRS) as indwelling catheters are removed, as well as showering of clot and thromboembolism which can compromise lung function. If these effects are not anticipated, a decannulated patient may not be able to achieve adequate oxygenation or CO_2 removal with mechanical ventilation alone, thereby necessitating recannulation or patient/family discussion regarding failure of therapy and palliation.

Finally, the underlying lung pathology should be considered. An appropriate decannulation strategy should incorporate the ARDS pathology arc and the timing from onset of critical illness. Patients with acute-on-chronic lung failure, baseline interstitial lung disease or pulmonary fibrosis, or chronic obstructive pulmonary disease are extremely challenging and can pose difficulty in liberating from ECMO, necessitating a bridge to transplant or to palliation.

Stepwise reduction in $\mathrm{FI_{O_2}}$ on both the ventilator and VV ECMO circuit should take place incrementally. The VV ECMO circuit should be reduced to 21% O_2 concentration prior to decannulation for a period of 24 h or more. The patient should maintain a $\mathrm{Sa_{O_2}}$ $>92\%$ on this setting with a ventilator $\mathrm{FI_{O_2}}<50\%$. Similarly, the sweep gas should be reduced to 0.5 to 1 LPM. The $\mathrm{Pa_{CO_2}}$ should be <60 mm Hg, and a normal pH should be maintained for at least 24 h. Simultaneously, consideration should be taken for any metabolic alkalosis or acidosis that would require acute compensation by pulmonary mechanisms.

Respiratory failure after decannulation may occur if the patient requires an acute increase in minute ventilation due to metabolic acidosis that was unaccounted for at the time of decannulation. Some groups in Europe have described introduction of CO_2 into the circuit to challenge the respiratory system in CO_2 removal. However, this is not recommended, especially in critically ill patients. Weaning to hemolung may be a feasible option and is ideal when the sweep has reached 1 LPM and maximum flows of 0.5 LPM are required.

Particular attention around the time of decannulation should be directed to cannula-induced thrombus and acute pulmonary embolism during cannula removal. Anticoagulation should be stopped prior to decannulation, and serial arterial blood gases followed for 24 h post-decannulation.

Outcomes and Long-term Effects

The most recent international report (January 2018) from the Extracorporeal Life Support Organization (ELSO) Registry documented 15,686 ECMO runs in adults with respiratory failure; 66% survived the ECMO run and 59% survived to hospital discharge.[153] This report found that the most common diagnoses requiring VV ECMO support included ARDS due to viral pneumonia, bacterial pneumonia, other medical causes of ARDS, postoperative ARDS, and trauma-related ARDS.

In the prior 2016 ELSO Registry report, the ECMO average run duration for adult respiratory failure was 256 h for postoperative or trauma-related ARDS, 313 h for non-postoperative or non-trauma-related ARDS, 275 h for acute respiratory failure (non-ARDS), 261 h for bacterial pneumonia, and 325 h for viral pneumonia. Many patients required prolonged ECMO, defined as >14 days.

VV ECMO for adults with ARF represents the fastest growing use for any type of mechanical circulatory support or ECMO platform.[154] A small percentage of patients may not be successfully weaned and die on ECMO support, while an even smaller number go on to lung transplantation.[155]

Complications

As described previously, a number of complications are explicitly associated with ECMO, including bleeding, thromboembolism, infection, hemolysis, wound formation, and malnutrition. However, critically ill patients with ARDS receiving ECMO also undergo additional therapies such as prone positioning, which may be associated with complications, and long-duration paralytics, which may contribute to poor long-term quality of life.[156]

Survivors of ARDS experience limited functional capacity, decline in pulmonary function test results, and decreased 6-min walk testing at 6 months.[157] ARDS survivors at 1 year have been reported to have lost 18% of their baseline body weight at the time of ICU discharge.[158] Additionally, although lung and spirometric measures may be normal by 6 months, $\mathrm{DL_{CO}}$ is decreased, and distanced walked is reduced compared with predicted at both 3 months and 6 months.[158]

Not many long-term studies have been published in the setting of VV ECMO for ARDS post–ICU discharge. The assumption is that patients with ARDS managed with ECMO had worse baseline disease necessitating the use of ECMO and, therefore, survivors would be expected to have generally worse functional status compared to patients who survived ARDS who were not treated with ECMO.

In one study of a limited group of patients, 28% of ECMO survivors reported anxiety and 56% reported depression. These patients had a posttraumatic stress disorder response and a quality of life, when matched for age and gender, that was lower than that of conventional ARDS survivors.[169]

One of the most comprehensive follow-up studies of patients with ARDS managed with ECMO described the PRedicting dEath for SEvere ARDS on VV–ECMO (PRESERVE) score, which is a practical mortality tool to assess patients in the ICU. The investigators assessed 140 patients with ARDS who were treated with ECMO at 6 months. They found that 60% were alive. The PRESERVE class defined parameters of age, BMI, immunocompromised state, prone positioning, days of mechanical ventilation, sepsis-related organ failure, plateau pressure, and PEEP. Six-month survival was scored as 97% for patients with 0 to 2 factors, 79% for those with 3 or 4 factors, and 54% for those with 5 or 6 factors. Anxiety, depression, and PTSD were reported in 34%, 25% and 16% of patients, respectively.[160]

Wound Care

Vascular complications from large bore cannulation result from a long duration of cannulation, the high risk of infection, and obstruction to native blood flow which promotes stasis and thrombosis.

Following decannulation, patients should undergo routine duplex imaging for deep venous thrombosis assessment.

Limb ischemia also is a devastating complication that is not infrequent. The proximity of the femoral cannulas to the femoral nerve can lead to pressure ischemia on the femoral nerve and subsequent foot drop. Local wound infections and skin breakdown are common. Plastic surgery and wound care management are mandatory in any robust ECMO program that performs a large volume of cannulations.

Long-term physical therapy is mandatory after ECMO therapy, not only for the chronic effects of pulmonary scarring after severe ARDS, but also for the additional effects of ECMO cannulation.

Pre-cannulation history of peripheral vascular disease is considered a risk factor for post-ECMO limb ischemia.[161]

Most ICU patients are not routinely followed up in post-ICU clinics; however, the degree of limb, skin, wound, cardiopulmonary disability, and psychological setbacks from long-duration ECMO for ARF ideally should prompt consideration for following these patients in a post-ICU ECMO clinic.[162] These developments represent the next opportunity for maximizing care for patients treated with any mechanical circulatory support device in the ICU.

Deep Venous Thrombosis and Pulmonary Embolism

Due to the large cannula size required for stable ECMO flows, venous and arterial thrombosis can develop downstream to the access sites. Thrombosis is also associated with the prothrombotic state that occurs with ECMO.[149] On average, deep venous thromboses (DVTs) are found at a rate of 8.1 per 1000 cannula-days.[163] Cannula-associated DVT was identified in 18% of ECMO survivors, with dual-lumen jugular cannulation having a higher observed rate of thrombosis compared with single-lumen femoral cannulation.[163]

Menaker et al. assessed the prevalence of cannula associated DVT in 70 patients undergoing VV ECMO for severe ARDS; 85% of patients demonstrated venous thrombosis on routine ultrasound 24 h after decannulation.[164] A separate study that assessed the utility of CT scanning for DVTs after decannulation demonstrated that cannula-associated DVT was found in 75 of 105 patients (71.4%).[48] These investigators found that Fem–Fem cannulation induced cannula-associated DVT more frequently than Fem–IJ cannulation (69.2% vs. 63.1%), and that 17 of the 105 patients (16.2%) had a pulmonary embolism.[48] This finding is particularly important because patients who are cannulated for ARF already have compromised pulmonary function, and the pulmonary embolism burden further contributes to long-term chronic respiratory failure.

SPECIAL POPULATIONS

Three populations of patients undergoing treatment with ECMO warrant special consideration: those with SARS-CoV-19, those on hemodialysis, and patients being considered for lung transplantation.

SARS-CoV-19

Based on the favorable clinical outcomes of VV ECMO in the H1N1 pandemic, many clinicians and centers have used the same strategy in SARS-CoV-19–related ARDS. In contradistinction to H1N1, SARS-CoV-19 presented with several challenges, including system-wide capacity problems, population-level resource utilization, and manufacture/supply issues. ECMO is a scarce and time-consuming resource. Therefore, when hospital systems are overloaded, ECMO is not the most ideal treatment choice.

Patients with SARS-CoV-19 presented with both thrombotic and hemorrhagic complications in the lung, system vasculature, and brain,[163] leading to some reports of intracranial hemorrhage and thrombosis associated with ECMO.[165] Early reports suggested a 90% mortality rate for patients with SARS-CoV-19–related ARDS treated with ECMO,[166] prompting caution at several centers in employing VV ECMO in treatment of ARDS due to SARS-CoV-19. Eventually, the Extracorporeal Life Support Organization (ELSO) produced a data registry report of 1093 patients with ARDS due to SARS-CoV-19 who were treated with ECMO and had an average P/F ratio of 72. The median time from initiation of MV to VV ECMO support was 4 days; 94% of patients were cannulated to VV ECMO. Renal replacement was required in up to 44% of patients, which is higher than non–SARS-Cov-19 patients treated with ECMO.[167] CNS hemorrhage and thrombosis occurred 6% and 0.7% of patients, respectively; 57% of patients were discharged alive and 39% died.[167] The estimated cumulative mortality was 38% after initiation of VV ECMO for ARDS, consistent with results for non–SARS-Cov-19–related ARDS treated with ECMO.

As highlighted previously, in the EOLIA trial, the mortality rate for patients with ARDS managed with ECMO was 35%, while mortality for patients in the conventional arm (treated with MV) was 46%.[35] One of the challenges with SARS-CoV-19–related ARDS is that it does not fit the typical Berlin criteria for ARDS. Consequently, patients may present with hypoxemic respiratory failure and normal compliance. As noted during the H1N1 pandemic, several other registry and retrospective publications have corroborated evidence from the ELSO registry for use of VV ECMO in managing patients with SARS-CoV-19.[168] Average mortality is approximately 50% for severe SARS-CoV-19-related ARDS managed with VV ECMO. Therefore, use of VV ECMO in treatment of SARS-Cov-19, depending on the level of surge, hospital capacity, and resource availability, remains a good option in the armamentarium to manage ARF.

Dialysis and Renal Failure

As highlighted previously, fluid management and fluid balance are critically important in maintaining the ECMO circuit and optimizing lung function. Pulmonary edema and interstitial fluid accumulation hinder optimal lung ventilation and oxygenation. The inflammation associated with ARDS should be managed both with fluid restriction and diuretics.

Concurrent acute kidney injury commonly exists with ARF.[169] Renal replacement therapy is often necessary with ECMO. Performing CRRT during ECMO can be considered in three major configurations: (1) RRT through venous access independent of the ECMO circuit, (2) introduction of a hemofiltration filter into the ECMO circuit using intravenous infusion pumps to control the ultrafiltrate volume, and (3) inclusion of a CRRT device in the ECMO circuit.[170] Patients who require any type of ECMO and CRRT have an increased in-hospital mortality odds ratio of 6.5; however, patients with ECMO with CRRT have better fluid balance for the duration of the ECMO run.[170,171] Unfortunately, hemolysis increases exponentially with introduction of a second extracorporeal circuit.[172]

Pre–Lung Transplant

Lung transplantation is a curative treatment for end-stage lung disease. Allocation for lung transplantation is determined by the lung allocation score (LAS). The LAS prioritizes patients who are critically ill, and implementation of the LAS has led decreased wait times for those patients.[173]

Pretransplant mechanical ventilation is considered a risk factor for increased posttransplant mortality.[174] Due to the limited supply of donors and the large volume of patients on the transplant list, many patients die while awaiting transplantation.[173] VV ECMO can help bridge patients with complete lung failure to lung transplantation. A typical cannulation strategy includes awake, ambulatory IJ DLSC cannulation, as well as IJ–Fem cannulation. Challenges with awake cannulation include air embolism during cannulation and the inability of the patient to lie supine during vascular access. Technical expertise is required for awake IJ cannulation. Patients who are awake on VV ECMO can participate in physical therapy. However, challenges include refractory coughing, tracheostomy bleeding, changes in intrathoracic pressure, and volume shifts, which can result in suck-down and flow limitations. Blood transfusion should be limited in the pretransplant setting in order to avoid alloimmunization and crossmatching difficulties. Therefore, fluid management and blood administration remain challenges, and utmost care is needed for patients cannulated pretransplantation.

Future technologic advances that are currently in development include implantable lung assist devices, much like left ventricular assist devices, that can provide continuous support while patients await bridge to transplantation or bridge to destination.[175,176] These devices are implanted in the right chest after a right pneumonectomy of the diseased lung. Inflow is from a graft sewn to the right pulmonary artery, and outflow is from a graft sewn into the pulmonary vein. These devices are “pumpless,” utilizing the native RV cardiac function for forward flow.

Initially there was reluctance to use VV ECMO as bridge to transplantation. Data were limited, and one of the largest studies included only 17 VV ECMO cases in 1305 lung transplant patients. In this report, Bermudez et al. demonstrated that 30-day, 1-year, and 3-year mortality were 81%, 74%, and 65%, respectively, for VV ECMO support as a bridge to transplantation, versus 93%, 78%, and 62%, respectively, for patients on mechanical ventilation prior to transplant without ECMO support.[177]

As technology has improved, VV ECMO has become much more prevalent in patients awaiting lung transplantation. As of 2017, approximately 5% of lung transplants occur in patients receiving ambulatory VV ECMO or who are mechanically ventilated while on VV ECMO; the number has been rising exponentially.[155,178] With increased frequency of VV ECMO as a bridge to transplant, and in parallel with growing experience, mortality in the pre–lung transplant VV ECMO group has declined.[179]

Tipograf et al. analyzed 121 pre–lung transplant patients who were listed for transplantation on VV ECMO as a bridge to transplantation. Of these, 70 patients were successfully transplanted. Of the 70, 64 survived to hospital discharge, and 88% of those who survived to discharge were alive at 1 year; 83% were alive at 5 years.[180] Propensity matching between bridge-to-transplant versus non-bridge-to-transplant did not show a significant difference in survival, despite differences in lung allocation score.[180]

Avoidance of mechanical ventilation and use of awake VV ECMO is the preferred strategy for patients who require ECMO prior to transplantation. Such an approach is associated with a 30% survival benefit.[181] A retrospective analysis reported an 80% 6-month survival post-transplant for patients bridged with ECMO compared with a 50% survival for patients bridged with preoperative mechanical ventilation.[181]

EXTRACORPOREAL CARBON DIOXIDE REMOVAL

An extracorporeal membrane can be used for CO_2 removal, as well as oxygenation, as described briefly below.

Acute Respiratory Distress Syndrome with Hypercarbic Failure

The extracorporeal membrane is much more efficient at removing CO_2 than adding oxygen. CO_2 removal requires less blood flow through the circuit and membrane and is associated with fewer thrombotic and bleeding effects due to smaller cannula size, lower dose requirements for anticoagulation, and design as a dual-lumen, single-vessel access catheter.

After the initial unsuccessful trial for VA ECMO in ARDS, Gattinoni and Kolobow used low-flow $ECCO_2R$ to accomplish extremely low-tidal volume, low-stretch mechanical ventilation.[13,182,183] They hypothesized that they could divorce the ventilator oxygenation function from the ventilator CO_2 removal function. In order to accomplish this, an extracorporeal device was conceptualized that removed CO_2 and provided “lung rest” by limiting mechanical ventilation through decreased tidal volumes and decreased respiratory rates.[13] Oxygenation was envisioned as occurring with passive or ultralow-tidal-volume settings. The investigators published a trial of patients with ARDS who had isolated hypercarbic respiratory acidosis and were already being treated with tidal volumes of 6 mL/kg tidal.[117] Patients were cannulated with a 14F dual-lumen catheter. They were ventilated using a low-stretch/ultralow-tidal-volume ventilator setting, and $ECCO_2R$ with a hemofilter was implemented. A total of 32 patients were enrolled. Results demonstrated that the low-stretch protocol with $ECCO_2R$ hemolung reduced lung cytokine production in ARDS, suggesting less ventilator-induced lung injury.[184]

$ECCO_2R$ can be used as an adjunct to mechanical ventilation to reduce the level of support required of the ventilator and, potentially, to delay impending respiratory failure and need for intubation. Most patients with severe ARDS have hypercarbic, as well as hypoxic, respiratory failure; however, prior to severe ARDS disease progression, in patients with mild or moderate ARDS, $ECCO_2R$ can facilitate application of very low tidal volumes by correcting acidosis and hypercarbic failure while the ventilator is used for oxygenation. Investigators have demonstrated that this strategy can reduce inflammatory markers by using $ECCO_2R$-supported reductions in plateau pressures. However, one study failed to demonstrate a reduction in overall ventilator days.[117] Using a decision tree to appropriately select configuration strategy is useful.

Chronic Obstructive Pulmonary Disease

Acute-on-chronic respiratory failure, particularly that due to chronic obstructive pulmonary disease, represents the most common indication for $ECCO_2R$. Several case series have demonstrated use of $ECCO_2R$ to correct severe hypercarbic respiratory acidosis.[185–187] Other cases have demonstrated that $ECCO_2R$ may be used to avoid mechanical ventilation and intubation for acute exacerbations of chronic obstructive pulmonary disease exacerbations requiring noninvasive ventilation (e.g., using BiPAP).[188]

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CHAPTER 150

Nutrition in Pulmonary Disease

Tachira Tavarez
David S. Seres

INTRODUCTION

The practice of clinical nutrition, particularly in the setting of acute illness, is somewhat complex due to the multiple interactions between disease and the ability to nourish patients. Much of clinical practice is based on observation or on flawed, biased, or severely underpowered studies. Furthermore, terminology related to malnutrition is extremely confusing: terms referring to problems attributable to alterations in nutritional intake are intermixed with those phenomena secondary to inflammatory illness, such as disease-related muscle wasting, which are not responsive to changes in nutrition intake.

Many excellent clinical publications[1,2] review general and specific nutritional concepts. This chapter introduces newly adopted definitions for malnutrition and their clinical utility, and reviews approaches to the clinical challenges specific to selected pulmonary diseases, acute respiratory failure, and the critical care setting. Chronic obstructive pulmonary disease (COPD) and cystic fibrosis (CF) serve as the prototypes for nutrition-related issues encountered in chronic pulmonary disease.

MALNUTRITION REDEFINED

Malnutrition has long been known to be associated with poor outcomes in medical and surgical patients.[3] However, for decades, the terminology describing malnutrition has created great confusion, incorporating biomarkers, such as albumin, which have since been disproven as reflective of dietary intake. While new efforts focus on defining malnutrition based on etiology,[4] the use of clinical parameters unrelated and unresponsive to nutrient intake[5] remain entrenched. The new definition of malnutrition (Table 150-1), adopted by major nutrition organizations in the United States, describes two forms: malnutrition due to nutrient imbalance or malnourishment (e.g., starvation, marasmus, obesity), and that which occurs due to systemic illness (e.g., catabolism, cachexia).[6] Only malnutrition due to nutrient imbalance resulting from alterations in intake or uptake can be treated by alterations in nourishment. It remains challenging, however, to decipher whether alterations in body habitus are due to illness, or due to altered intake, or both, and even whether and when changes in intake or nutrient levels represent deficiency or disease epiphenomena. While the new definitions have not been validated to predict which patients will respond to nutritional interventions, they are highly predictive of overall outcomes.[7]

TABLE 150-1 Findings in the New Definition of Malnutrition

	Starvation-related Malnutrition (Malnourishment)	Disease-related Malnutrition
Starvation	X	X
Fat wasting	X	+/−
Muscle wasting	X	X
Hypoproteinemia		X
Elevated inflammatory markers		X

Inflammatory markers, such as C-reactive protein, and serum albumin and prealbumin, do not correlate with nutrient intake, and the belief that most traditional markers of malnutrition (e.g., albumin, prealbumin [transthyretin], measures of immune function) reflect adequacy of nourishment has been disproved.[5] Despite this, not all of these markers have been removed from the new definition.[4] While it still may be surprising to many clinicians that many so-called nutritional markers are, in truth, markers of systemic inflammation, this is far from a new finding.[8,9] Discussion of alterations in serum albumin and other parameters as arising from systemic inflammation has appeared in physiology and biology texts for decades.[10] However, these "nutritional" markers have long been known to identify patients at high risk for untoward outcomes and to reflect severity of illness.[9] Moreover, nutritional assessments that incorporate the markers, such as the Prognostic Inflammatory and Nutritional Index (PINI),[11] are highly validated to predict poor outcomes. Importantly, recent research has shown that the level of systemic inflammatory response (e.g., elevated CRP) is predictive of response to nutritional interventions.[12]

Confusion surrounding how to define malnutrition will likely continue because clinical findings, which may be caused by starvation, systemic inflammation, or both, remain as diagnostic criteria. The etiology of these signs may be difficult, if not impossible, to distinguish clinically. Lean body mass loss due to inflammation, for example, does not respond to stand-alone nourishment strategies when inflammation is present. In other words, patients diagnosed with "malnutrition" may or may not actually be "malnourished." Well-nourished patients (e.g., those receiving tube feeding or eating well) with disease-related muscle wasting are "cachectic," but not malnourished. Weight maintenance or gain, especially related to maintenance or increase in lean mass, is considered desirable because of the association between low weight and morbidity and mortality.[13] However, weight loss is not, by itself, an adverse outcome due to poor nourishment in sick patients. Rather, it is more likely an epiphenomenon and a marker of disease severity.

For example, until systemic inflammation is resolved, serum albumin levels and muscle mass will not normalize, despite protein supplementation. Conversely, normalization of serum albumin may occur despite starvation, once systemic inflammation has resolved.[14] Prealbumin, properly referred to as transthyretin, normalizes more quickly than albumin with resolution of systemic inflammation, but it is no more reflective of adequacy of nutritional intake than is albumin. Moreover, nutritional supplementation has not proved to slow the decrements seen in these markers.

Traditional nutritional markers, such as serum proteins and muscle mass, should be considered surrogates for systemic inflammation and not markers for adequacy of nourishment. Nor should they be seen as an indication for nutrition support. For example, administration of parenteral nutrition in response to finding a low serum albumin in a patient who is eating and absorbing nutrients normally exposes the patient to potential harm without potential benefit.

Defining ideal nourishment for an individual patient is extraordinarily difficult due to a lack of granular clinical research. Moreover, much nutrition research reports impact on surrogate markers, such as lean mass, immunologic and inflammatory makers, and serum proteins, rather than appropriate clinical outcomes. Meaningful outcomes resulting from nutrition support include a reduction in morbidity, cost of care, and mortality.[15] These, however, require larger, costlier, and more complex randomized trials than are often performed.

Given the complexity of malnutrition, the work of nutrition practitioners conducting clinical assessments is particularly important in identifying high-risk patients. Insurers have recognized that patients with "malnutrition" are more complex than those who are not and have increased their reimbursement to hospitals for these patients. The authors contend that dietitians should be renamed "riskologists" to acknowledge this added value, and that patients identified as "at risk for nutritional complications" be relabeled "very sick and at risk for morbidity and mortality." In addition, patients so identified should receive intensive oversight by a multidisciplinary team of highly qualified clinicians.

TERMINOLOGY

The two previously noted forms of malnutrition often coexist. Sick patients often exhibit anorexia and decreased nutritional intake. In this instance, loss of muscle mass is due to both systemic inflammation and lack of nutritional intake. Distinguishing between the two forms is difficult. Recognizing a component of caloric deficit provides an opportunity to intervene.

In distinguishing between the two types of malnutrition, the terminology employed should be very specific.[4] As mentioned, patients with *disease-related malnutrition* who are well fed are not *malnourished*. Undernourishment, starvation, nutritional deficiency, nutritional imbalance, obesity, and nutritional excess are terms that may be used to describe imbalance-related malnutrition. Conversely, catabolism and disease-related malnutrition are used synonymously with malnutrition due to inflammation. *Marasmus* is an older term that refers to pure starvation. *Kwashiorkor*, an endemic disease in children, is likely due to systemic inflammatory response, but the term is no longer applied to hospitalized patients, especially adults, in nonendemic areas.[16] *Cachexia* is the syndrome resulting from severe chronic malnutrition, which contains a component of inflammation-related malnutrition.[17] It results, at least in part, from catabolism. Cachexia may be predominantly due to inflammation, with a smaller component of starvation, or alternatively, from starvation with a smaller component of inflammation.

ETIOLOGY AND MECHANISMS

Imbalance-related malnutrition is a result of inadequate nutrition, and it is treatable by feeding or supplementation. On the other hand, disease-related malnutrition is neither due to, nor responsive to, changes in calorie or protein intake.[15] The mechanism for inflammation-related muscle wasting that occurs despite adequate or supplemental nutrition is poorly understood, but it is clearly related to production of inflammatory cytokines.[18] One proposed mechanism is that muscle breakdown supports uncontrolled hepatic gluconeogenesis resulting from the insulin resistance observed in this setting. The decrement in serum albumin, as well as in other carrier proteins, is likely due to its extravasation from capillaries, along with other macromolecules, due to increases in capillary permeability arising with inflammation. With maintenance of vascular volume, plasma protein concentrations are diluted. In addition, plasma protein oncotic pressure falls, or becomes nonexistent, and plays a diminished role in minimizing fluid flux across capillary membranes into soft tissues, once normally semipermeable capillary membranes become permeable.

UTILITY

Diagnosing malnutrition certainly identifies patients at highest risk for poor outcomes,[7] and nutritional assessment will identify patients with, or at risk for, poor intake for whom nutritional interventions may be necessary. Understanding the etiology of malnutrition in the individual patient determines the utility of nutritional assessment. Recognizing ongoing inflammation by "nutritional" assessment may lead to recognition of a medical or surgical condition that may require medical or surgical, rather than nutritional, intervention or help to guide ethical decision-making. Prolonged, untreatable catabolism may predict incurable or fatal illness, and inflammatory markers have been shown to predict whether nutrition interventions will have benefit.[12] Low muscle mass may be hidden in an obese patient with preserved adiposity, but it can be discerned with careful physical examination and may help explain a delay in physical recovery. Muscle mass is an important determinate of serum creatinine concentrations. Physical assessment of muscle mass may also be important in explaining whether a widening of the ratio of blood urea nitrogen (BUN) to creatinine represents hypoperfusion or hypovolemia on the one hand, or severe muscle loss with renal impairment on the other.

Albumin levels require approximately 6 weeks to normalize once inflammation resolves. Consequently, direct markers of inflammation (e.g., C-reactive protein and cytokines) may provide a more accurate measure of inflammation in the presence of persistent hypoalbuminemia. Reversal of hypoalbuminemia is a helpful sign in tracking resolution of inflammation and may indicate a better prognosis; however, trending in albumin levels over weeks is required for the measurements to be useful in this regard.

Consequently, the work of nutrition practitioners conducting clinical assessments is very important and adds value by identifying patients at high risk for overall poor outcomes and complications, irrespective of whether a nutritional intervention is indicated. Patients so identified should receive intensive oversight by a multidisciplinary team of highly qualified clinicians. Further, insurers have recognized that patients with "malnutrition" are more complex than those without and accept malnutrition as a comorbid condition to adjust reimbursement to hospitals.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

COPD is an extremely common form of chronic lung disease. Nutritional management of patients with COPD may be challenging and frequently entails consideration of both starvation and disease-related malnutrition.

■ Malnutrition in COPD

COPD encompasses several systemic manifestations, including malnutrition, and should, therefore, not be considered solely a pulmonary disease. Muscle dysfunction and wasting are both common manifestations, and cachexia is common in COPD. Muscle wasting is reflected by a decrease in fat-free mass, which is a known predictor of mortality in patients with COPD.[19]

The underlying mechanisms of muscle wasting and dysfunction are complex and difficult to ascertain from existing epidemiologic and observational studies. Evidence suggests cachexia in COPD is partly related to systemic inflammation and increased oxidative stress.[20–22] It has long been known that weight loss in COPD is associated with an increase in inflammatory markers such as TNF-α.[23]

Given the systemic nature of cachexia and muscle dysfunction in COPD, purely nutritional strategies would be expected to have little impact on outcomes. Notably, and as discussed previously, weight gain is solely a surrogate marker and not a meaningful clinical outcome. While weight gain may be desirable, it may not be associated with improvement in quality or quantity of life or a decrease in the cost of care. In fact, until recently, whether nutrition support had any clinical outcome benefits was unclear, even though patients given such support gained weight.[17] Recent studies, which reassessed data in patients with COPD who received nutrition support compared with those who did not, demonstrated weight gain in the treated group, as well as improvements in both skeletal and pulmonary muscle function and fat mass. In addition, improvement in health-related quality of life (HRQOL) was observed when data using the St. George's Respiratory Questionnaire (SGRQ) were analyzed, although not when data from SGRQ were pooled with data from the Chronic Respiratory Questionnaire (CRQ).[18] Although this is low-quality evidence, it is reasonable to continue to recommend that patients with COPD who are undernourished receive nutrition support. That said, failure to gain weight, or to stem weight loss, should be contextualized in terms of disease process rather than patient adherence.

Macronutrients in COPD

A great deal of attention has been paid to concerns about the impact of macronutrients in COPD. Because carbohydrates are metabolized to CO_2 and water, concern exists that a diet or tube feeding high in carbohydrate content may result in increases in work of respiration or Pa_{CO_2} and, consequently, adverse outcomes. While initial studies seemed to support this concern, recent investigations suggest the opposite. In one study, nutritional supplementation using a high-fat product resulted in more dyspnea with exercise than did a high-carbohydrate product.[24] While the respiratory quotient (RQ)—the ratio of carbon dioxide produced to oxygen consumed per minute ($\dot{V}_{CO_2}/\dot{V}_{O_2}$)—increases more with a high-carbohydrate supplement, oxygen consumption is lower than that seen using a high-fat supplement.

While these findings are counterintuitive, they are consistent with studies of skeletal muscle in patients with COPD, which suggest impaired fat metabolism and an increase in carbohydrate metabolism. In these patients, studies have shown a decrease in oxidative function[25] and expression of peroxisome proliferator-activated receptors (PPAR),[26] which have an extremely important role in upregulating lipid uptake and metabolism in cells. In addition, in COPD, a shift from oxidative to glycolytic muscle fibers occurs in skeletal muscle, the degree to which is directly correlated with disease severity.[23] In theory, fat causes a delay of gastric emptying, so a full stomach may be responsible for the increase in dyspnea.

Amino acids, specifically branched amino acids (BCAAs), serve as alternate sources of fuel via their conversion into glutamine in muscle.[27] Serum BCAAs are low in patients with COPD compared with matched controls, and more so in underweight patients with COPD.[28] These serum levels were shown to correlate with anthropometric measures like ideal body weight and percentage arm muscle circumference. In one study, plasma concentrations of BCAAs correlated with muscle energy metabolism in patients with COPD, indicating that low BCAA levels are associated with alterations in muscle energy metabolism in these patients.[29] The hypothesis is that supplementation with BCAAs should improve exercise capacity. There have only been small studies involving BCAA and protein supplementation,[30,31] and there are currently no specific guidelines BCAA supplementation.[32]

Macronutrient mix in COPD may be far less important than previously thought, but total calories may play an important role. In a nutritional supplementation study, provision of excess calories to subjects with COPD was shown to cause a decrease in exercise performance. This was most profound in patients with more advanced disease and cachexia.[33]

Other Nutrition-related Considerations in COPD

Anabolic steroids have been demonstrated to increase fat-free mass in patients with COPD but have been proven to have minimal benefit in clinical outcomes. In a study of patients with COPD enrolled in a pulmonary rehabilitation program, those who received an anabolic steroid had a higher fat-free mass than those who did not, but improvements in muscle function, exercise capacity, and health status were not different between the two groups. Patients who received corticosteroids demonstrated less response to the rehabilitation. Maximal inspiratory mouth pressure and peak workload were improved in patients receiving both chronic corticosteroids and anabolic steroids compared with those given placebo; this was the only positive outcome.[34]

Appetite stimulants have not proved effective in improving outcomes in COPD. In a study of patients receiving megestrol acetate versus those receiving placebo, the treated group demonstrated a lower 6-min walk distance, despite having a decreased Pa_{CO_2} and increased Pa_{O_2}. Megestrol increased weight, but it did so by increasing fat mass.[35] No studies on use of cannabinoid appetite stimulants in COPD are available.

Recommendations

Patients with COPD should be screened for malnutrition and referred to a nutrition practitioner when any sign of diminished nutritional intake or weight loss is found. Similarly, obesity or excess weight gain in an individual previously of normal weight should serve as indications for nutritional intervention.

The authors' opinion is that as an initial goal, it is reasonable to choose a nutritional prescription based on either an estimate of basal requirements at ideal weight, or calorimetric measurement of basal metabolic rate, and increases aimed at slow (1–2 lb per week or 3600–7200 kcal excess per week) weight gain. Consultation with a nutrition clinician is recommended, and care should be taken to avoid overfeeding.

Because of difficulties in distinguishing malnourishment from disease-related changes, along with the inability of nutrition support to impact the latter, failure of nutritional interventions should be viewed as evidence of disease progression and factored into prognostic assessments. Strategies such as appetite stimulation and use of anabolic steroids may impact selected metrics, but they have not been demonstrated to impact outcomes. Measuring and monitoring markers, such as serum albumin, should be considered, but the results should be viewed as reflective of an underlying inflammatory state. In this regard, they may be prognostic but not reflective of nutritional adequacy.[14,15]

CYSTIC FIBROSIS

Cystic fibrosis (CF) is associated with nutritional issues that are far more complex than in most other pulmonary diseases. Patients with CF are prone to significant chronic inflammation, with acute worsening in the presence of infection. As in other inflammatory disorders, disease-related muscle wasting may be noted, and although not necessarily obvious, it may be evident even at an early age.[36]

Patients with CF are at high risk for malnutrition arising from a both systemic and local, gastrointestinal (GI) impairments. There is inflammation-mediated anorexia, increased energy expenditure, and essential fatty acid turnover. GI issues include malabsorption due to exocrine pancreatic insufficiency, dysphagia due to gastroesophageal reflux disease, issues with motility due to both delayed gastric emptying and small bowel transit time, and CF-related liver disease.[37]

Macronutrients and Micronutrients in Cystic Fibrosis

No properly designed, prospective, randomized controlled trials comparing enteral feeding to no intervention have been conducted in CF to determine whether enteral feeding improves outcomes.[38] Such studies are nearly impossible to perform because of the ethical dilemmas posed by not providing supplemental or artificial feeding to patients who are, as best as we can determine, chronically starved.

Regarding the macronutrients, a current pediatric consensus statement emphasizes the importance of a higher proportion of dietary fat intake compared to that of the general population.[39] According to the recommendation, dietary fat should compose 35% to 40% of total caloric intake. A high-fat diet has been implemented for patients with CF since a study in the 1980s comparing a cohort of CF patients in Toronto with a similar cohort in Boston suggested improved survival due to a higher-fat diet.[40] Supplementation with fatty acids, such as omega-3 fatty acids, also has been considered, given the evidence of fatty acid malabsorption and inflammation-induced increased catabolism in patients with CF.[37] However, evidence for the use of omega-3 fatty acids is limited to small studies that only suggest a possible benefit.[41]

Various vitamins and minerals have been considered in CF. CF patients with pancreatic insufficiency are particularly at risk for deficiencies in fat-soluble vitamins A, D, E, and K. Supplementation is recommended in most current adult and pediatric consensus statements[39,42] despite low-quality evidence.[43,44] Among the minerals considered in CF—a disorder characterized by immune dysfunction—zinc has long been of interest. Zinc deficiency may cause untoward immunologic changes, but zinc supplementation in the setting of normal levels generally has no beneficial effect and may be harmful. Zinc supplementation lowers copper levels,[45] and copper deficiency caused by excessive zinc ingestion may result in mortality.[46,47] Only a few trials, with small number of subjects, have assessed the efficacy of wholesale zinc supplementation for CF. Not surprisingly, zinc supplementation in patients with CF who have normal zinc levels has demonstrated no significant benefit, while supplementation in those with low zinc levels results in fewer days on antibiotics.[48]

■ Feeding and Pancreatic Insufficiency

Multiple approaches have been employed to overcome the complex feeding issues encountered in CF, including use of special, predigested tube feeding mixes and supplementation of nutrients thought to be supportive of immune function. Given difficulties with maldigestion due to pancreatic insufficiency and resulting malabsorption in patients with CF, the concept has arisen that providing partially predigested feedings may enhance absorption. However, in small studies, provision of predigested feedings appears not to improve absorption over use of enzyme replacement therapy.[49] Our approach is to feed patients concentrated, high-fat tube-feed products, enabling provision of goal calories in the face of small bowel dysmotility.

In recent years, the production of powdered pancreatic enzyme replacements has ceased. Currently, the primary form of pancreatic enzyme replacement is an enteric-coated product. Administration of the product through a gastric tube requires that the outer capsule be opened, exposing coated spherules that require suspension prior to administration. However, the spherules tend to coalesce and may clog the tube. One proposed method to avoid this problem is to mix the spherules into a viscous solution prior to administration,[35] thereby keeping them suspended and preventing settling and coalescence. Others recommend dissolution of the spherules in an alkaline solution, which is then added to the feed product and allowed to sit prior to administration, resulting in feed predigestion. While addition of enzymes to the feed may facilitate predigestion, concern exists that any manipulation of feed products prior to feeding tube installation may increase the risk of bacterial contamination.[50] The data supporting this concern, however, relate primarily to bacterial counts, rather than clinical outcomes. However, an inline device that contains lipase was developed for CF patients who receive tube-feeds. This device was shown to increase the absorption of fatty acids and was also deemed safe and well tolerated.[51] Other small retrospective studies providing evidence of its ability support weight gain were presented in a recent editorial by several physicians and dieticians who work with patients with CF.[52]

■ Strategies and Recommendations

In an effort to improve patient education and clinical outcomes, multidisciplinary care, including early involvement by nutrition practitioners, is recommended for all patients with CF.[39,42] Nutrition practitioners should have specialized knowledge of CF, as the feeding and nutritional problems can be quite complex. Malabsorption may be particularly challenging when patients require tube feeding, especially jejunal tube feeding.

ACUTE RESPIRATORY FAILURE

The importance of adequate nutrition in patients with acute respiratory failure who are admitted to critical care units has been recognized for some time. Several practical considerations in administration of nutrition in this setting are outlined subsequently.

■ Specific Nutrients

Much has been written about the role of specific macro- and micronutrients in patients with acute respiratory failure. As discussed previously, attempts at manipulating the composition of the feedings administered—for example, the ratio of carbohydrate to fat—have been shown to be without benefit. Use of specific fats, especially oils containing omega-3 fats or their precursors, has been studied in the acute respiratory distress syndrome (ARDS), but the results are still debated.

Ten prospective clinical trials implementing omega-3 fatty acid based formulas or supplements were included in a recent Cochrane systematic review of immunonutrition.[53] In this review, 4 of the 10 studies used similar enteral formulas and high-fat, low carbohydrate, feeding strategies.[54–57] These four studies found that the use of the omega-3 formula resulted in decreases in the development of new organ failure, time on mechanical ventilation, and time in the ICU. However, results from the Cochrane systematic review found insufficient evidence for these outcomes, largely due to the heterogeneity between studies.

■ Timing and Route of Administration of Artificial Nutrition

The timing of initiation of enteral or parenteral feeding in critically ill patients appears to be clinically important.[58] Early enteral feeding has become standard of care in the critically ill.[59] However, studies of this practice have limitations and risks for bias.[60,61] While early enteral feeding does not stand up to the strictest requirements for evidence-based practice and garners a low grade in evidence-based guidelines,[59] a large body of evidence indicates that food in the gut may play an important role in modulating systemic inflammatory response,[62] which theoretically may lead to preservation of immune function, less catabolism, and fewer complications. Indeed, in many cases the physiologic basis for septic shock may be related to interactions between gut pathogens and mucosal cells, with or without actual septicemia.[62]

Enteral nutrition (Tables 150-2 to 150-4), except in the face of severe prolonged gut failure, is almost always preferred over parenteral nutrition.[59] Early parenteral nutrition, whether the sole source of calories,[63] or as a means of augmenting enteral nutrition,[64] has not proved beneficial in critically ill patients and may, in fact, be harmful (Table 150-5). The time point at which the risks of starvation exceed the risks of parenteral nutrition is unknown, since most studies have excluded patients already suffering from malnutrition.[48] American guidelines recommend withholding parenteral nutrition during the first week of critical illness when enteral feeding is not possible.[59] Multiple randomized trials showed an increase in *morbidity* when parenteral nutrition was added to early enteral feeding, including a large trial with more than 2000 subjects.[64,65]

TABLE 150-2 Choice of Route for Administration of Enteral Nutrition

Large-bore nasogastric sump tube
Short-term (several days) feeding
Transition from gastric drainage to gastric feeding
Small-bore nasogastric feeding tube
Primary choice for nasal tubes
Short-term (up to 30–90 d)
Small-bore nasoenteric (nasoduodenal, nasojejunal)[a]
Gastric dysmotility[b]
Very high aspiration risk[c]
Gastrostomy (percutaneous endoscopic, surgical)
Long-term (>30–90 d)
Technical issues with nasal tube[d]
Jejunostomy (percutaneous endoscopic, surgical)
Gastric dysfunction[a]
Long-term access when gastric surgery anticipated[e]
Long-term access when gastric tube not possible[e]

[a] *Usually 6–10 French in adults.*

[b] *Concomitant gastric drainage is likely to be required or vomiting can occur. Short term, a second (nasogastric sump) draining tube or use of a combined dual-lumen nasogastrojejunal (draining nasogastric, feeding nasojejunal) tube may be useful. Combined dual-tube draining gastrostomy–feeding jejunostomy may be useful longer term.*

[c] *This recommendation appears in guidelines but is not supported by prospective randomized data. While jejunal placement may result in better calorie delivery, there are no outcome data to support routine choice of jejunal, over gastric, placement of feeding tubes.*

[d] *With the availability of techniques, such as the nasal bridle for securing nasal tubes, security of the tube is less commonly an indication for percutaneous feeding tubes.*

[e] *For example, patients with gastric cancer, or esophageal cancer and planned esophagectomy and gastric pull-up.*

■ Total Calories Provided

Whether critically ill patients should receive 100% of estimated or measured calorie needs, especially early in the course of their critical illness, is the subject of great debate. Failure of current practice to deliver "adequate" calories to critically ill patients has also received a great deal of attention. A recent study suggests that patients admitted to ICUs receive only about 35% of prescribed calories and 42% of their prescribed protein requirements during the first few days of their stay.[66] As a consequence, significant efforts have been made to increase calorie delivery through protocol development and quality improvement initiatives,[67] as well as through immediate initiation of parenteral nutrition to "top off" the calories that early enteral nutrition cannot provide.[68] However, the outcome benefits of these approaches have not been proven.

In the absence of high-quality, prospective, randomized studies, we do not know how to determine the individual caloric needs of critically ill patients. Indirect calorimetry has the potential to lead us completely astray. No currently available marker, assessment tool, or nutritional score can help discern what calorie and protein prescriptions will result in the best clinical outcomes.[5] In addition, high-quality studies in which calorie top-off was achieved enterally[69] or parenterally[64] have showed no benefit. Moreover, complications such as gastrointestinal intolerance with full enteral feeding[69,70] and prolonged length of stay may occur with a parenteral top-off approach.[64] The findings from the studies using parenteral nutrition have been criticized by proponents of early achievement of calorie goals on the basis that the investigators used a parenteral nutrition practice different from that employed in North America; in fact, two small studies suggest a benefit.[68,71] However, these smaller studies have significant limitations, and given the rigor of the larger parenteral study, its findings cannot be dismissed.

■ Position and Timing of Feeding Tube Placement

The choice of enteral feeding tube location has been a focus of discussion in the critical care setting: gastric versus duodenal or jejunal. A related center of debate is the incidence of pneumonia with each choice. Overall, studies have shown an increase in calorie delivery using nasoenteric tubes compared with nasogastric tubes.[72] However, current investigations using more stringent feeding protocols do not demonstrate a benefit with nasoenteric tube placement, and neither mortality nor the incidence of pneumonia is affected by tube placement.[72,73]

In the setting of pancreatitis, when artificial feeding is needed, enteral feeding is the standard of care.[74] One would expect in the setting of severe pancreatitis that postpyloric tube placement is advantageous over gastric placement. However, whether the tube should be placed in the stomach or jejunum is still a subject of debate; comparative studies have failed to show any differences in outcomes between these methods.[75]

In recent times, the practice of simultaneous insertion of tracheostomy and PEG tubes (PEG-TRACH) has gained some traction.[59] In certain institutions, interventional pulmonologists or surgeons perform both procedures in the same setting, alone or in collaboration with a gastroenterologist. Tracheostomy is an important and beneficial adjunct in the management of the critically ill (Chapter 145). It is used when clinicians predict that a patient will need a prolonged period of mechanical ventilation. The procedure is well tolerated and may be performed at the bedside. Tracheostomy insertion has been associated with a faster wean from mechanical ventilation, reduced incidence of pneumonia, and, ultimately, shorter hospital stay.[60] Timing of tracheostomy insertion has been debated; a move toward earlier performance has been observed because of a suggestion of improved outcomes reported in meta-analysis.[61] However, recent trials have suggested lack of real benefit from early tracheostomy. Consequently, this practice is liable to change.[62,63] Nevertheless, at present, the combination procedure of PEG-TRACH has been advocated by some and has resulted in simultaneous, early PEG insertions (in some cases within 4 days of admission to ICU).[59] Historic observational data on the feasibility of this approach are available, although the effectiveness and safety of this approach have not been studied.[64,65]

We postulate, based on discussions with critical care colleagues throughout the country, that a large portion of the drive for simultaneous PEG-TRACH is based on refusal by nursing homes in some parts of the United States to accept patients with nasal feeding tubes, coupled with the push for shorter lengths of stay. In a phone survey of the 127 nursing homes (participation rate, 85%) in New York City, 88 (81.5% of respondents) indicated that they have policies prohibiting nasal feeding tubes. Twenty nursing homes (18.5% of respondents) indicated they would accept nasal tubes, but most had not in the past 6 to 12 months.

Gastroenterologists and interventional radiologists at our institution have estimated that a large percentage of the gastrostomies placed were done solely because of anticipated discharge of the patient to a nursing home. Most nursing homes reported that their refusal of nasal feeding tubes is based on the perception of high risk of aspiration and tube dislodgement.[66] This concern is unsubstantiated in the literature. Indeed, only a total of 686 patients have

TABLE 150-3 Usual Characteristics and Indications for Enteral Feeding Formulas

	Standard	Standard Concentrated	Standard High Protein	Renal	Diabetic	Predigested[a]	Pulmonary[b]	Immune/ Inflammation Modulating
Use	First choice[c]	Fluid restriction/ bolus feeding[d]	Highly catabolic/ wound healing	Fluid and electrolyte restriction[e]	Bolus feeding diabetics[f]	Maldigestion or severe tube-feed intolerance[a]	See footnote[b]	See footnote[g]
Calories per mL	1–1.25	1.5–2.0	1.0–1.5	1.8–2.0	1.0–1.5	1.0–1.5	2.0	1.0–2.0
Protein g/ 1000 kcal	40–44	40–44	62.5	40–44	40–44	40–62.5	40–44	40–62.5
Electrolytes	Standard	Standard	Standard	Restricted[e]	Standard	Standard or restricted	Standard	Standard or restricted
Fiber[h]	+/−	+/−	+/−	+/−	+	+/−	−	+/−
Fat		High			Somewhat increased	See footnote[i]	High	See footnote[j]
Osmolarity[k]	Iso	Up to ∼700 mOsm/L	Iso or slightly increased	∼700 mOsm/L	Iso or slightly increased	Iso up to ∼700 mOsm/L	Increased	Iso or slightly increased

[a] *Predigested feeding products may be made up of simple sugars and individual amino acids (e.g., Vivonex) or of oligosaccharides and oligopeptides (e.g., Vital, Peptamen). These are marketed as providing superior tolerance and better absorption in states such as maldigestion and hypoproteinemia. Most of the data on these are preclinical, and there are no outcome data supporting their superiority. Very low-fat feeding has been promoted as an alternative to parenteral nutrition in patients with chyle leakage. Randomized studies are lacking.*

[b] *These products have not been shown to have any benefit in randomized trials. The principle on which they were created is that dietary fat produces less CO_2 than does carbohydrate. While this effect can be measured on calorimetry, patients are not extubated sooner. Certainly, these products are not indicated for patients on long-term ventilatory support.*

[c] *Most patients can be fed with a standard feeding product. The cost differential between a standard product and the disease-specific feeds can be as much as 15-fold.*

[d] *An increase in calorie density, from 1.0 to 1.5 kcal/mL, will not substantially increase viscosity and decreases the volume of tube feeding product required to meet calorie goals. The remainder of the volume requirements may be given as water boluses. This decreases overall feeding time and increases convenience for ambulatory patients.*

[e] *Patients with renal insufficiency and/or on hemodialysis, but not continuous renal replacement, require restriction of dietary sodium, potassium, and phosphorus. In addition, these products are fluid restricted.*

[f] *Glycemic index is the area under the curve of the rise in blood glucose after a bolus or meal, compared with a standard. This concept does not apply to patients receiving continuous feeding, as rate of appearance of glucose will be equal to rate of delivery plus rate of gluconeogenesis in these patients. Glycemic control formulas improve glycemic control only in patients fed intermittently.*

[g] *Because of the biochemical derangements that occur in critical illness, nutrient levels and consumption are altered. These alterations have led to a great interest in supplementation of specific nutrients to reverse these derangements. There is no strong evidence that these approaches result in improved outcomes. The author believes this may be due to these derangements being adaptive, or epiphenomena.*

[h] *Insoluble fiber, while favored in long-term tube feeding, should be avoided in critically ill patients, especially while on pressor agents. Bezoar may form when peristalsis is diminished.*

[i] *Fat content in these products varies. In some, it is highly restricted to 10% of calories (long-chain fat, Vivonex). In others, fat has been engineered to provide theoretical improvements in absorption and may contain mixtures of medium-chain, long-chain omega-3, and long-chain omega-6 fats.*

[j] *Fat content in these products varies widely. Products focused on inflammation may have a large amount of omega-3 and other putatively anti-inflammatory fats. Other products provide engineered triglycerides, with a mixture of long-chain omega-3 and omega-6 plus medium-chain fats. Discussed more fully in Acute Respiratory Failure/ Specific Nutrients section in text.*

[k] *Osmolarity of tube feeds ranges from isotonic to approximately two times isotonic. The osmolarity of many medications and electrolytes is orders of magnitude higher. The latter is a far more important concern when evaluation patients with diarrhea. It is unlikely the osmolarity of current tube feeding products will be the cause.*

been randomized in 9 trials comparing nasogastric feeding tube to PEG. PEG has been associated with fewer episodes of feeding interruption, tube blockage, tube leakage, or lack of adherence to treatment in a subset of 7 of these studies, which included only 314 patients. In aggregate, no differences were observed in the incidence of pneumonia or complication rates between the two feeding methods.[67]

Consensus guidelines suggest that PEG should be considered for patients likely to require enteral nutrition >30 days.[68] New York State Department of Health policy allows for nasal feeding tubes for up to 96 days[69] before considering PEG, but not placement, is required. PEG, while safe and reasonably well tolerated, is not a frivolous procedure. Mortality post–PEG insertion has been reported to be 26% at 30 days,[70] and as high as 43% at *1 week*.[71] These high rates are likely largely driven by poor patient selection. Based on these data, selection of critically ill patients undergoing tracheostomy for concurrent PEG insertion needs to be questioned. By virtue of their complex critical illness, patients undergoing tracheostomy are not at low risk for the procedure. The 30-day mortality post-tracheostomy has been variously reported at approximately 30%.[60,62] By extension, one may conclude that selection criteria for combined PEG-TRACH in these series resulted in an excess PEG insertion rate of at least 30%, without demonstrable outcome benefit.

In one series of patients undergoing simultaneous PEG-TRACH, the mortality at 30 days was 11%.[59] In the surviving patients, PEG tubes were removed in 73%, with a median of 76 days (range, 24–611 days). Thus, it seems likely that PEG insertion may have been avoided in many of these patients by deferring simultaneous insertion until the prognosis for resumption of oral diet and prognosis overall were clearer and the patient more medically stable.

In summary, nasogastric feeding tubes are widely regarded as safe and are the preferred option for short-term (30–90 days) delivery of nutrition. While the risks of simultaneous PEG-TRACH insertion appear to be tolerable, based mostly on anecdotal evidence, the procedure has not been proven to be superior to a “watch and wait” approach of continuing with nasogastric feeding. Patients undergoing simultaneous PEG-TRACH should be carefully chosen for procedural risk and likelihood of long-term requirement for a tube feeding.

TABLE 150-4 Challenges and Complications of Enteral Nourishment[a]

- Gastrointestinal intolerance
  - Abdominal distension
  - Nausea and vomiting
  - Diarrhea
    - Maldigestion/malabsorption
    - Contamination of enteral feeding solution
    - Infusion of hypertonic medications and solutions
    - Medication side effects
    - Gastrointestinal diseases
- Constipation
- Intestinal ischemia
- Gastroparesis and ileus
- Metabolic derangements
  - Hyperglycemia
  - Refeeding syndrome
    - Hypokalemia
    - Hypophosphatemia
    - Hypomagnesemia
    - Wernicke encephalopathy
- Dehydration
- Complications of tube access

[a] *Note that while aspiration and pneumonia are associated with use of enteral nutrition, recent studies have demonstrated a lack of relationship between even vomiting and pneumonia in patients receiving enteral nutrition.[76] Furthermore, the incidence of pneumonia does not appear to be decreased by positioning tubes in the jejunum.[57]*

TABLE 150-5 Complications of Parenteral Nutrition

- Complications of access
  - Bleeding
  - Infections
  - Venous thrombosis
- Metabolic complications
  - Refeeding syndrome
  - Hyperglycemia
  - Vitamin and mineral deficiencies due to shortages
- Systemic complications
  - Bacteremia/central line–associated blood stream infections (CLABSI)
  - Overall increased incidence of infections
  - Hepatic dysfunction
  - Prolonged ICU and hospital stays

■ Aspiration and Gastric Residual Volumes

Aspiration of gastric contents is a serious concern in the critically ill. But aspiration, by itself, should not be considered an adverse outcome unless it leads to a clinically significant event, such as ventilator-associated pneumonia. Aspiration is common in a variety of settings, such as intubation for routine surgery[72] and during sleep.[73,74] In a study published more than 40 years ago, aspiration was demonstrated in 50% of normal volunteers and in 75% of subjects with depressed consciousness.[74]

Based on the belief that the risk of aspiration is related to the volume of gastric contents, measurement of gastric residual volumes has become common practice in patients receiving enteral feeding. Many protocols and guidelines have been developed for managing tube feedings based on gastric residual volumes. Increasingly, however, this practice has been challenged. High gastric residual volumes are not associated with increases in ventilator-associated pneumonia. In fact, recent studies have questioned the value of checking gastric residuals at all. In a before–after study[75] and in a prospective randomized study,[76] checking gastric residual volumes had no impact on the incidence of pneumonia. In fact, in the randomized trial, vomiting was increased in the group of patients in whom gastric residual volumes were not assessed, but this did not result in an increase in the incidence of pneumonia.[76]

■ Strategies and Recommendations

Critically ill patients, whose prognosis warrants the intervention, should receive enteral nutrition early in their course if they are malnourished and are expected to be without nourishment for some time. Parenteral nutrition should only be used for patients with chronic gut failure, and it should not be used early. Our practice is to wait for up to 2 weeks to start parenteral nutrition in patients without preexistent malnourishment who do not respond to efforts at enteral feeding. The practice of routinely measuring gastric residual volumes has been shown to have no clinical benefit and may decrease calorie delivery.

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CHAPTER 151

Diagnosis and Treatment of Pain, Agitation, and Delirium in the Intensive Care Unit

Niall T. Prendergast
Timothy D. Girard
Nathan E. Brummel

INTRODUCTION

Most patients in intensive care units (ICUs) experience pain, agitation, or delirium at some point during their critical illness. During the last two decades, tremendous growth in knowledge regarding the assessment and management of these syndromes in the ICU has prompted important changes in the practice of intensive care medicine. Validated tools now allow clinicians to quickly and reliably evaluate patients for pain, assess their level of consciousness, and detect delirium. These assessments, in turn, guide clinicians as they choose and titrate therapies targeted to best manage a patient's symptoms. Novel strategies to address pain, agitation, and delirium have recently been investigated. The use of validated tools to diagnose these important clinical syndromes and the use of evidence-based management strategies improve both short- and long-term outcomes. This chapter reviews these assessment tools and describes best practices for management of pain, agitation, and delirium in patients with critical illness.

PAIN IN THE CRITICALLY ILL

Patients with critical illness frequently suffer from pain.[1,2] Because pain is nearly ubiquitous in the ICU and is a common source of agitation in patients with critical illness, clinicians should seek to treat pain first as a means by which to ensure patients are able to maintain an alert and calm state.[3–5] Nevertheless, although effective treatments for pain are widely available, detecting pain in those critically ill patients who are unable to report it is challenging. Prolonged pain in the critically ill is associated with adverse physiologic effects.[6] Because analgesia is most effective when pain is identified and treated early, clinicians should frequently assess patients for pain and treat it when identified.[7]

Assessing Pain in the Critically Ill

Pain is subjective by nature; therefore, a patient's self-report (using a numeric scale or a visual analog scale) is an easy and reliable method to determine its presence. In fact, the Society of Critical Care Medicine (SCCM) recommends that the numeric rating scale be used to assess pain when patients can self-report.[4] Among the critically ill, however, self-reporting is not always possible due to sedation or delirium. In cases where patients cannot self-report their pain, clinicians may view vital signs as indicators of pain, but multiple studies show that vital signs are poor correlates of pain in patients with critical illness.[8–10] Therefore, several instruments have been developed and validated to help clinicians identify and quantify pain in critically ill patients.

The two most widely studied pain assessment tools for use with ICU patients who are unable to report pain are the Behavioral Pain Scale (BPS) and the Critical Care Pain Observation Tool (CPOT).[11,12] Both the BPS and CPOT use nonverbal cues and patient behaviors to establish the presence of pain; these include facial expressions, body movements, and compliance with mechanical ventilation (Table 151-1A,B). Alternatively, a patient's surrogate (e.g., a spouse) may be able to describe behaviors indicative of pain in a particular patient based on the surrogate's prior knowledge of the patient.[13] Finally, in the case where the clinician is unsure if a patient is having pain, a trial of an analgesic medication can be used to assess for a decrease in the suspected pain-related behaviors.[13] Regardless of the assessment method used, it is important to note that assessing for pain among the critically ill is associated with improved clinical outcomes, including optimized analgesic and sedative administration and reduced duration of mechanical ventilation and ICU stay.[14–16]

Treating Pain in the Critically Ill

Comprehensive pain management in the critically ill consists of multimodal pharmacologic therapies (e.g., opioid and nonopioid medications) in combination with nonpharmacologic approaches to ensure adequate analgesia.[5,7]

TABLE 151-1A Critical Illness Pain Observation Tool (CPOT)

Clinical Indicator	Description	Score
Facial expression	Relaxed; no muscular tension observed	0
	Tense; frowning, brow lowering, eye tightening, neck contraction	1
	Grimacing; all previous facial movements plus eye lids tightly closed	2
Body movements	Absence of movements or normal position	0
	Protection; cautious movements, touching/rubbing site of pain, seeking attention through movements	1
	Restlessness/agitation; pulling tube, attempting to sit up, thrashing, not following commands, striking at staff, trying to climb out of bed	2
Muscle tension	Relaxed; no resistance to passive movements	0
	Tense/rigid; resistance to passive movements	1
	Very tense/rigid; strong resistance to passive movements	2
Intubated patients: compliance with the ventilator	Tolerating vent/movement; alarms not activated, easy ventilation	0
	Cough but tolerating; alarms stop spontaneously	1
	Fighting ventilator; blocking ventilation, alarms frequently activated	2
Nonintubated patients: verbalization	Talking in normal tone or no sound	0
	Sighing, moaning	1
	Crying out, sobbing	2

Higher scores indicate greater pain.
Data from Gélinas C1, Fillion L, Puntillo KA, et al. Validation of the critical-care pain observation tool in adult patients. Am J Crit Care. 2006;15(4):420–427 and Payen JF1, Bru O, Bosson JL, et al. Assessing pain in critically ill sedated patients by using a behavioral pain scale. Crit Care Med. 2001;29(12):2258–2263.

TABLE 151-1B Behavioral Pain Scale (BPS)

Item	Description	Score
Facial expression	Relaxed	1
	Partially tightened (e.g., brow lowering)	2
	Fully tightened (e.g., eyelid closing)	3
	Grimacing	4
Upper limb movements	No movement	1
	Partially bent	2
	Fully bent with finger flexion	3
	Permanently retracted	4
Compliance with mechanical ventilation	Tolerating movement	1
	Coughing but tolerating ventilation for most of the time	2
	Fighting ventilator	3
	Unable to control ventilation	4

Higher scores indicate greater pain.
Data from Gélinas C1, Fillion L, Puntillo KA, et al. Validation of the critical-care pain observation tool in adult patients. Am J Crit Care. 2006;15(4):420–427 and Payen JF1, Bru O, Bosson JL, et al. Assessing pain in critically ill sedated patients by using a behavioral pain scale. Crit Care Med. 2001;29(12):2258–2263.

Intravenous opioid analgesics, such as fentanyl, morphine, hydromorphone, methadone, and remifentanil, are recommended first-line treatments for acute, nonneuropathic pain among the critically ill. The specific drug choice and dose are determined by the severity of the pain, patient characteristics (e.g., age, renal, and hepatic function), the patient's clinical status, and the properties of the drug (e.g., pharmacokinetics and pharmacodynamics) (Table 151-2).

Nonopioid analgesics (e.g., acetaminophen, ibuprofen, ketamine) may be administered as adjuvant therapies to reduce pain intensity and decrease the overall dose of opioids.[5] Nonpharmacologic interventions such as massage, relaxation techniques, heat or ice application, and music therapy may provide additional analgesic effect.[7] For patients experiencing neuropathic pain, use of gabapentin, carbamazepine, or pregabalin may be added to opioid and nonopioid analgesics.[5]

AGITATION IN THE CRITICALLY ILL

Agitation in critically ill patients is associated with adverse outcomes, such as the removal of life-support devices and danger to the patient or beside staff. Commonly, agitated patients are given sedatives to reduce agitation and prevent harm.[17] It is important to remember, however, that agitation does not equate to "sedation deficiency." Rather, the presence of agitation should prompt the clinician to search for—and treat—an underlying cause, such as pain, hypoxemia, metabolic derangements, developing sepsis, delirium, or withdrawal from alcohol or other drugs. Agitation exists at one extreme of the continuum of consciousness that also includes calm states and states of decreased arousal, such as stupor and coma. This section reviews methods to assess level of consciousness as well as best practices for the treatment of agitation, primarily through the judicious use of sedative medications.

■ Assessing Agitation and Level of Consciousness in the Critically Ill

Several standardized measures can be used to determine level of consciousness in the critically ill. Although these tools are commonly referred to as "sedation-agitation scales," they should be used to evaluate all patients in the ICU, regardless of whether they are receiving sedatives, as they assess patient behaviors and response to verbal or physical stimuli to determine the patient's level of consciousness. The Richmond Agitation-Sedation Scale (RASS) and Riker Sedation-Agitation Scale (SAS) are the most valid and reliable for determining level of consciousness during critical illness (Table 151-3).[4] Unlike the Glasgow Coma Scale (GCS), the RASS and SAS have been validated for use in the setting of ongoing critical illness, even when patients are sedated and/or nonverbal due to placement of an endotracheal tube.[18–20] Regular assessments of level of consciousness can improve detection of changes in neurologic status as well as facilitate and guide delivery of sedatives and other psychoactive medications.

■ Treating Agitation in the Critically Ill

The first step in treating agitation should be to seek out the underlying (and potentially reversible) cause(s). Providing adequate analgesia, treating hypoxemia with supplemental oxygen, correcting electrolyte abnormalities, treating infection, providing reorientation, ensuring an environment conducive to sleep, early mobilization, and treating alcohol and drug withdrawal may eliminate agitation in the appropriate situation. If agitation persists despite measures aimed at addressing the underlying cause, consideration should be given to administration of sedatives.

Recent years have seen a dramatic shift in the strategies used to sedate patients in the ICU. As a result of numerous trials reporting better outcomes among patients managed using protocol-based administration of sedatives compared with those managed without the guidance of a protocol,[21–24] an increasing number of ICUs are adopting algorithmic approaches to the delivery of sedatives to critically ill patients. While many protocols exist, common threads present in each include objective assessment of level of consciousness using a validated tool; prioritization of analgesia over administration of sedatives; targeting lighter (e.g., alert, calm, and comfortable states) rather than moderate or heavy sedation; using intermittent

TABLE 151-2 Pharmacology of Selected Opioid Analgesics

Drug	Equianalgesic Dose	Half-life	Intermittent Dose	Infusion Dose	Adverse Effects/Other Information
Morphine	10 mg	2–3 h	0.01–0.15 mg/kg every 1–2 h	0.07–0.5 mg/kg/h	Accumulates in renal and hepatic failure; hypotension (due to histamine release)
Fentanyl	100 μg	1.5–6 h	0.35–1.5 μg/kg every 0.5–1 h	0.7–10 μg/kg/h	Less hypotension than morphine; accumulates in hepatic failure
Hydromorphone	1.5 mg	3–7 h	10–30 μg/kg every 1–2 h	7–15 μg/kg/h	Accumulates in renal and hepatic failure; use in patients intolerant of morphine or fentanyl
Remifentanil	—	3–10 min	—	Loading dose: 1.5 μg/kg Maintenance dose: 0.6–15 μg/kg/h	No accumulation in hepatic or renal failure

TABLE 151-3 Level of Consciousness Scales: Richmond Agitation-Sedation Scale (RASS) and Riker Sedation-Agitation Scale (SAS)

RASS Level	Label	Description	Label	SAS Score
+4	Combative	Combative, violent, immediate danger to staff, climbing over bedrail, thrashing side to side	Dangerous agitation	7
+3	Very agitated	Pulls to remove tubes or catheters, aggressive, requiring restraint and frequent reminder of limits	Very agitated	6
+2	Agitated	Frequent nonpurposeful movement; fights ventilator	Agitated	5
+1	Restless	Anxious, apprehensive, movements not aggressive; follows commands		
0	Alert and calm	Spontaneously pays attention to caregiver; follows commands	Calm and cooperative	4
−1	Drowsy	Not fully alert, but has sustained awakening to voice (eye opening and contact for >10 s)	Sedated	3
−2	Light sedation	Briefly awakens to voice (eyes open and contact for <10 s)		
−3	Moderate sedation	Movement or eye opening to voice (no eye contact)		
−4	Deep sedation	No response to voice, but movement or eye opening to physical stimuli	Very sedated	2
−5	Unarousable	No response to voice, physical or noxious stimulation	Unarousable	1

Higher (more positive) scores indicate greater agitation.

RASS, Richmond Agitation-Sedation Scale; SAS, Riker Sedation-Agitation Scale.

Data from Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med. 2002;166(10):1338–1344; Ely EW, Truman B, Shintani A, et al. Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). JAMA. 2003;289(22):2983–2991; Riker RR, Picard JT, Fraser GL. Prospective evaluation of the Sedation-Agitation Scale for adult critically ill patients. Crit Care Med. 1999;27(7):1325–1329.

dosing of medications or daily interruption of sedatives; and relying on nonbenzodiazepine regimens.

Prioritizing Analgesia

As discussed earlier in this chapter, pain is pervasive among critically ill patients and is a frequent reason for agitation. Thus, evaluation and treatment of pain using the techniques described earlier may be sufficient to restore a patient to a calm and alert state. Several studies of sedation protocols that preferentially treated pain before administering sedatives have demonstrated improved patient outcomes,[21,25,26] and current guidelines recommend treatment of pain prior to administration of sedatives.[5]

A dramatic example of the value of pain management prior to administration of sedatives was provided in a randomized trial comparing a control group (sedated primarily with propofol) to patients managed using a strategy of "no sedation."[27] Patients in the intervention arm received morphine for pain first, then haloperidol for agitation, then, if needed, intermittent short-course (i.e., 6-h) administration of propofol. Only after failing this regimen (as indicated by ongoing agitation) did patients in the intervention group receive sedation using a more conventional propofol- and midazolam-based sedation strategy. Patients managed with the "no sedation" strategy had significantly better outcomes than those in the control group, spending more time off mechanical ventilation and experiencing earlier discharge from the ICU and hospital.

A larger multicenter trial, which sought to determine if the "no sedation," analgesia-first strategy improves survival did not find significant differences in mortality, ICU length of stay, or ventilator-free days in treatment groups but did find that some secondary endpoints, including days without delirium or coma and major thromboembolic events at 90 days, were improved for those in the "no sedation" group.[28] Whereas some of the results of this multicenter trial do not corroborate those from the single-center study, several key points should be noted. First, challenging the notion that all patients on mechanical ventilation need sedation is that only around 20% of patients in the "no sedation" groups of both trials required treatment with continuous sedatives. Second, the need for sedation can be assessed multiple times daily, as was the case in this study where the need for sedation in the intervention group was assessed every 6 h.

Intermittent Versus Continuous Dosing of Sedatives

As demonstrated in the aforementioned trials of "no sedation" strategies, which prioritized use of intermittent morphine and haloperidol, many analgesic and sedative medications can be delivered intermittently (via bolus) rather than continuously (via infusions). The latter has been the most common method of sedation used in ICUs,[16] with routine use of continuous infusions reflecting the fact that most early studies of sedation in the ICU utilized continuous infusion strategies. Nevertheless, continuous infusion of analgesics and sedatives can lead to accumulation of the infused drug, resulting in delayed clearance and prolonged effects. Moreover, continuously infused medications are readily titrated to higher doses to treat agitation, but often the infusion may not be rapidly titrated to lower doses once the acute agitation has been controlled. These factors may combine to lead to adverse outcomes, including prolongation of mechanical ventilation and ICU and hospital stays. For example, one study showed that patients who were managed using intermittent doses of benzodiazepines rather than benzodiazepine infusions were extubated sooner, were discharged from the ICU and hospital earlier, and had lower rates of reintubation compared with those who received continuous sedation.[29] Based on these findings, the same group developed a sedation protocol that prioritized analgesia first, then intermittent bolus sedatives, before allowing continuous infusions of sedatives. In a randomized controlled trial, this sedation protocol resulted in earlier extubation and discharge from the ICU and hospital compared with management without a sedation protocol.[21]

When considering the evidence regarding intermittent versus continuous dosing of sedatives in the ICU, it should be noted that not all trials favored intermittent dosing. The choice of drug is also an important determinant of outcomes. Although intermittent dosing of benzodiazepines results in better outcomes than continuous benzodiazepine infusions, avoidance of benzodiazepines altogether, even if this means using continuous propofol, will improve outcomes further, as evidenced by trials comparing benzodiazepine sedation with nonbenzodiazepine alternatives.[30]

■ Avoiding Benzodiazepines

Although early trials of sedation protocols[21] utilized benzodiazepines as the sedative of choice (when an analgesia-only approach did not adequately treat agitation), more recent trials have consistently shown that benzodiazepines lead to worse outcomes than alternative sedative agents. As the result of these studies, nonbenzodiazepine sedatives are preferred over benzodiazepines for sedation in patients with critical illness.[5]

In the late 1980s and 1990s, more than a dozen randomized trials found that sedation with propofol led to better outcomes than sedation with benzodiazepines.[31] However, the results did not lead to changes in standard of care, in part because control groups used continuously infused midazolam rather than intermittent boluses. In fact, clinical guidelines published in 2002 recommended lorazepam as the drug of choice for sedating patients in the ICU.[32] Therefore, a key randomized trial was conducted to compare intermittent lorazepam with continuous propofol for the sedation of mechanically ventilated patients in the ICU.[30]

Patients in both groups were managed using daily interruption of sedatives. Despite the avoidance of continuous infusions in only the lorazepam group (since propofol generally requires delivery by continuous infusion when used in the ICU), patients sedated with propofol spent on average 5 days fewer days on mechanical ventilation. These findings were consistent with nearly every other trial comparing propofol with benzodiazepines, suggesting that continuous sedation with shorter-acting agents, such as propofol, when interrupted daily, improves outcomes compared with intermittent doses of benzodiazepines.

Benzodiazepine-based sedation has been compared with other sedative agents; the alternatives to benzodiazepines have been found superior. Numerous randomized trials have compared sedation with benzodiazepines with dexmedetomidine among mechanically ventilated patients in the ICU; all found that patients randomized to sedation with dexmedetomidine had better outcomes—for example, less delirium and earlier extubation—than those sedated with benzodiazepines.[33–39]

Similarly, in three trials randomizing mechanically ventilated patients to remifentanil-based sedation versus benzodiazepine-based sedation, those sedated with benzodiazepines had worse outcomes.[31–33] The pharmacologic properties of these and other agents commonly used for sedation in the ICU are presented in Table 151-4.

■ Choice of Sedative

As a result of the data presented above, first-line use of benzodiazepines for sedation is no longer recommended; guidelines recommend either propofol or dexmedetomidine.[5] The choice between those two agents has largely been a matter of clinician preference. Three trials, including two published since the 2018 PADIS guidelines, have shed additional light on this question.

The DahLIA study, published in 2016, randomized 74 patients in whom extubation was considered inappropriate due to agitation and delirium to either dexmedetomidine or placebo. Dexmedetomidine was found to increase the number of hours alive and off of mechanical ventilation at 7 days, as compared with placebo.[40]

The 2019 SPICE-III study analyzed 3904 mechanically ventilated patients randomized to either dexmedetomidine as a primary sedative or to usual care (primarily propofol, although midazolam and the combination of midazolam and propofol also were used). There was no difference in mortality, which was the primary outcome, but the dexmedetomidine group had a significantly greater number of days alive and free of delirium or coma.[41]

Most recently, the 2021 MENDS2 study randomized 422 mechanically ventilated patients with sepsis to sedation with either propofol or dexmedetomidine. The study found no difference in any of its endpoints, including mortality, days free of delirium or coma, and long-term neurocognitive dysfunction, between the two groups.[42] Evidence thus suggests that while dexmedetomidine may be useful in particular situations, for example when agitated delirium is a barrier to extubation, outcomes associated with these two drugs are similar.

■ Targeting Light Sedation and Daily Interruption of Sedatives

Regardless of which medications are used to provide analgesia and sedation, they should be given in the smallest doses necessary to treat pain and agitation while allowing patients to maintain wakefulness—that is, light, rather than heavy, sedation should be the goal. Sedation protocols not only prioritize analgesics and intermittent sedatives over continuous infusions, they may also target light sedation (measured using a sedation scale) over moderate or heavy sedation.[21] Evidence in support of targeting lighter sedation stems from both observational and clinical trial data showing those patients who are treated with light sedation have better outcomes. Three multinational, observational cohort studies show that patients who were maintained at a level of consciousness that was RASS −2 or more alert during the first 48 h of an ICU admission had greater 6-month survival than those who were maintained at deeper levels (e.g., RASS −3 or more sedated), regardless of the sedative medication(s) used.[43–45] Other studies of patients receiving mechanical ventilation

TABLE 151-4 Selected Sedative Agents

Drug	Mechanism of Action	Half-life	Intermittent Dose	Infusion Dose	Adverse Effects
Propofol	GABA$_a$ agonist	40 min	0.2–0.6 mg/kg	5–80 μg/kg/min	Hypotension, respiratory depression, pancreatitis, hypertriglyceridemia, PRIS
Dexmedetomidine	CNS α-2 agonist	$T_{1/2}$ a = 6 min $T_{1/2}$ b = 2 h	—	0.2–1.5 μg/kg/h	Hypotension and bradycardia (with loading dose); loss of airway reflexes
Haloperidol	CNS D_1 and D_2	18 h	2–10 mg	0.04–0.15 mg/kg/h	QTc prolongation; extrapyramidal symptoms; dystonia
Midazolam	GABA$_a$ agonist	3 h	0.02–0.08 mg/kg	0.04–0.2 mg/kg/h	Respiratory depression; hypotension; accumulates in renal and hepatic failure
Lorazepam	GABA$_a$ agonist	8 h	0.02–0.04 mg/kg	0.01–0.1 mg/kg/h	Respiratory depression; hypotension; propylene glycol–related acidosis; nephrotoxicity

PRIS, propofol-related infusion syndrome; $T_{1/2}$ a, distribution half-life; $T_{1/2}$ b, elimination half-life; QTc, corrected QT interval.

who were randomized to light versus moderate or heavy sedation also found that those managed with light sedation were extubated sooner, had shorter ICU stays, and had fewer disturbing memories of the ICU, compared with those managed with heavier sedation.[46]

Whenever given, sedatives should be held each day that basic safety criteria are met so that the clinician may assess the need for and optimal doses of analgesic and sedative medications required to maintain patient comfort and alert mental status. This period of daily interruption of sedatives, also referred to as a daily "wake-up," "sedation holiday," or "spontaneous awakening trial," led to significantly better outcomes in two seminal randomized trials. In one trial,[23] patients managed with daily interruption of sedatives had shorter durations of mechanical ventilation and shorter stays in the ICU. In another,[22] those managed using this strategy not only were extubated earlier than those in the control group, they also were discharged earlier from the ICU and hospital; furthermore, their 1-year mortality was 14% lower than that observed in the control group. The latter trial paired daily interruption of sedatives or daily spontaneous awakening trials with daily spontaneous breathing trials as part of a strategy referred to as "Wake-up and Breathe" (Fig. 151-1).

Although most sedation trials have examined either targeted light sedation or daily interruption of sedatives, the SLEAP randomized trial studied whether combining the two strategies yielded improved

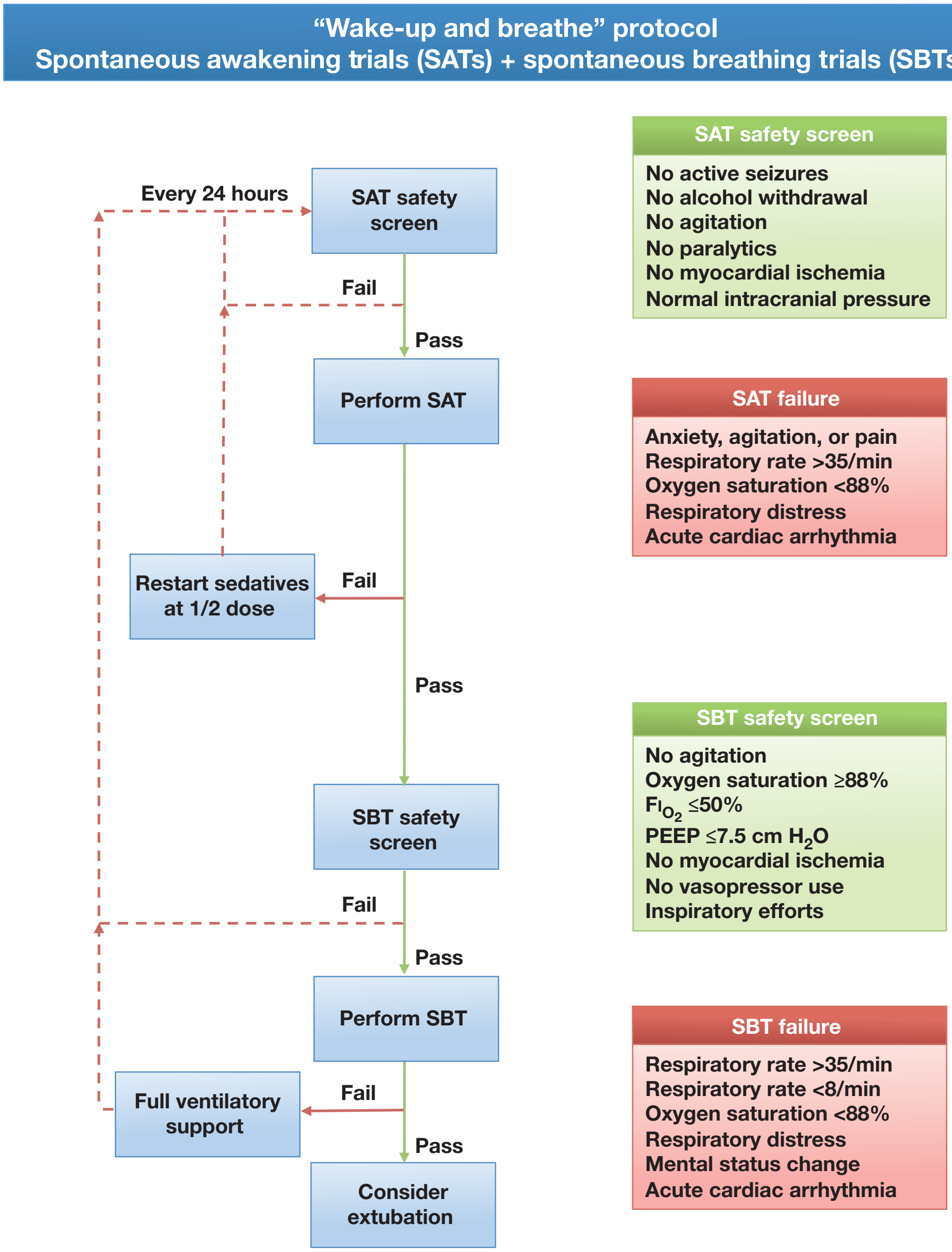

"Wake-up and breathe" protocol
Spontaneous awakening trials (SATs) + spontaneous breathing trials (SBTs)
Every 24 hours
SAT safety screen
Fail
Pass
Perform SAT
Restart sedatives at 1/2 dose
Fail
Pass
SBT safety screen
Fail
Pass
Perform SBT
Full ventilatory support
Fail
Pass
Consider extubation
SAT safety screen
No active seizures
No alcohol withdrawal
No agitation
No paralytics
No myocardial ischemia
Normal intracranial pressure
SAT failure
Anxiety, agitation, or pain
Respiratory rate >35/min
Oxygen saturation <88%
Respiratory distress
Acute cardiac arrhythmia
SBT safety screen
No agitation
Oxygen saturation ≥88%
FI_{O_2} ≤50%
PEEP ≤7.5 cm H_2O
No myocardial ischemia
No vasopressor use
Inspiratory efforts
SBT failure
Respiratory rate >35/min
Respiratory rate <8/min
Oxygen saturation <88%
Respiratory distress
Mental status change
Acute cardiac arrhythmia

Figure 151-1 Wake-up and breathe flowchart. Each day patients should be assessed for safety criteria to perform a spontaneous awakening trial (SAT). If the safety screen is passed, all sedating medications are held until the patient is RASS –3/SAS 3 or more alert. The patient is then screened for the presence of safety criteria to undergo a spontaneous breathing trial (SBT). As with the SAT, if the SBT safety screen is passed, the patient should undergo an SBT. If the patient meets any of the failure criteria, either sedation or ventilatory support is resumed and the trial begins anew the next day. Combining daily SATs with daily SBTs is associated with shorter duration of mechanical ventilation, ICU length of stay, and a 14% improvement in mortality 1 year following critical illness. *(Reproduced with permission from © icudelirium.org and Vanderbilt University, all rights reserved.)*

outcomes over using only targeted light sedation.[47] Patients randomized to targeted light sedation with daily interruption had similar outcomes to those managed with targeted light sedation alone. While these data suggest that there is no difference between these two sedation strategies, it is important to note that those in the daily interruption group were exposed to higher doses of benzodiazepines and opiates than those in the targeted light sedation group. This result is counter to prior studies of daily sedation interruption, which found this strategy reduced overall exposure to sedatives and showed improved outcomes. Although the SLEAP trial does not rule out the possibility that daily interruption of sedatives plus targeted light sedation is equivalent to a targeted light sedation strategy alone, further study is needed comparing daily sedative interruption in a way that lowers exposure to sedatives to targeted light sedation. Nevertheless, a key take-home message from the SLEAP study is that if sedation strategies do not reduce overall exposure to sedatives, patients are less likely to benefit.

In summary, modern sedation practices (1) place an emphasis on targeted light sedation, as assessed using a validated tool for determining level of consciousness; (2) prioritize treating pain first using intravenous opiates and then, if the patient requires additional sedation, intermittent and sometimes continuous doses of a nonbenzodiazepine sedative; and (3) routinely incorporate daily interruption of drugs, maintaining a “light” level of sedation (Fig. 151-2).

DELIRIUM IN THE CRITICALLY ILL

Delirium during critical illness represents an acute form of brain dysfunction. Because it is frequently observed in the ICU, this

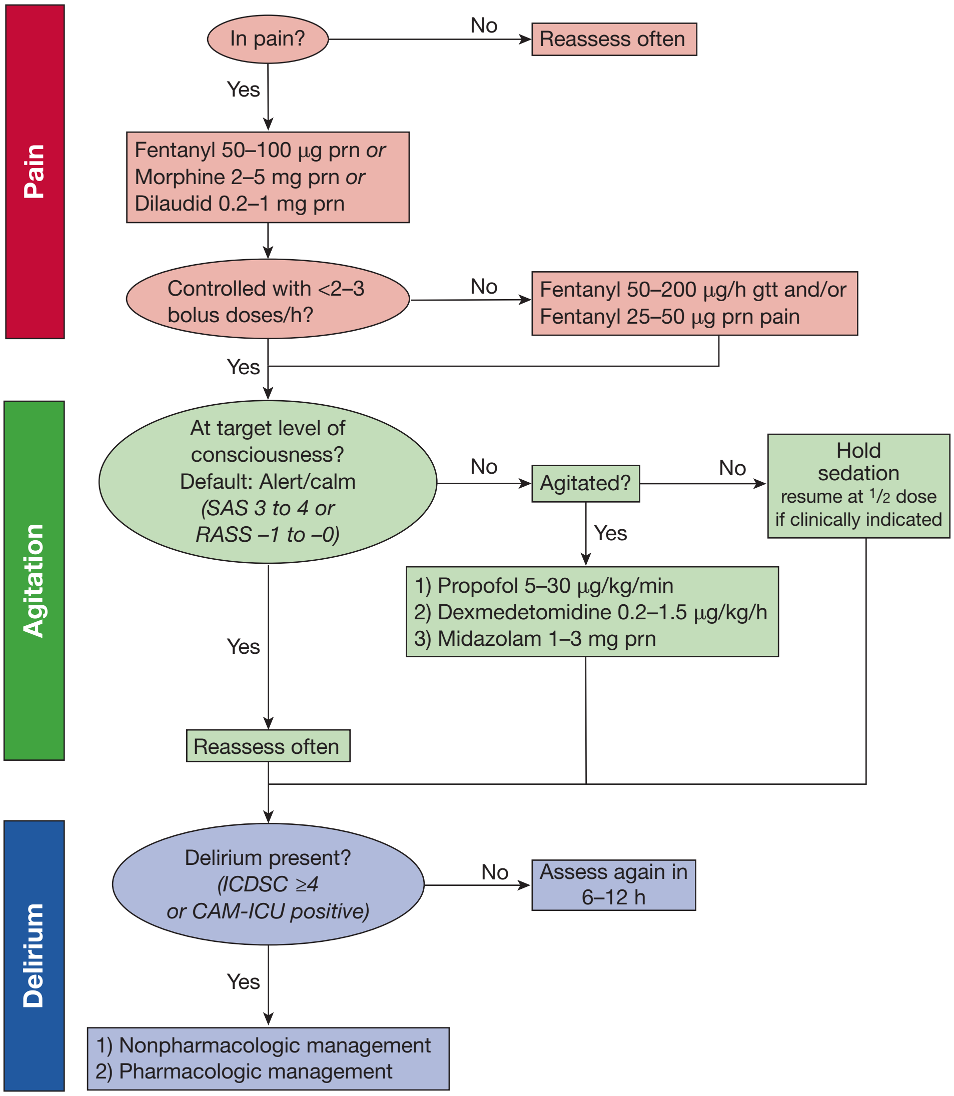

Pain
In pain?
No
Reassess often
Yes
Fentanyl 50–100 μg prn *or*
Morphine 2–5 mg prn *or*
Dilaudid 0.2–1 mg prn
Controlled with <2–3 bolus doses/h?
No
Fentanyl 50–200 μg/h gtt and/or
Fentanyl 25–50 μg prn pain
Yes
Agitation
At target level of consciousness?
Default: Alert/calm
(SAS 3 to 4 or RASS −1 to −0)
No
Agitated?
No
Hold sedation
resume at 1/2 dose if clinically indicated
Yes
1) Propofol 5–30 μg/kg/min
2) Dexmedetomidine 0.2–1.5 μg/kg/h
3) Midazolam 1–3 mg prn
Yes
Reassess often
Delirium
Delirium present?
(ICDSC ≥4 or CAM-ICU positive)
No
Assess again in 6–12 h
Yes
1) Nonpharmacologic management
2) Pharmacologic management

Figure 151-2 Example pain, agitation, and delirium protocol. In this example protocol, pain is first assessed, and if present, IV analgesia is given first with intermittent dosing. If more than three boluses are needed in an hour, an infusion of fentanyl is started. The patient’s level of consciousness is monitored using the Richmond Agitation-Sedation Scale (RASS) or the Sedation-Agitation Scale (SAS), with a default of alert/calm or drowsy (RASS –0 to –1 or SAS 4). If the patient is agitated despite adequate pain control, an infusion of either propofol or dexmedetomidine is preferentially used. Midazolam is begun only if the patient is withdrawing from alcohol, has a propofol intolerance, or has received propofol for >96 h. If the patient is more deeply sedated than RASS –1 or SAS 3, sedatives and analgesics are held until the patient is again alert and calm. If needed, analgesics and sedatives are resumed at half (or less) of the previous infusing dose. Each day patients undergo coordinated spontaneous awakening and breathing trials (SAT + SBT). Finally, patients are screened for delirium using either the Intensive Care Delirium Screening Checklist (ICDSC) or the Confusion Assessment Method for the ICU (CAM-ICU), and if delirium is present a cause is first sought with nonpharmacologic and pharmacologic interventions begun if no reversible cause is identified. *(Reproduced with permission from © icudelirium.org and Vanderbilt University, all rights reserved.)*

syndrome was previously considered by many to be an expected, inconsequential complication of critical illness, often referred to as "ICU syndrome."[48] Multiple studies have shown, however, that delirium is associated with numerous adverse short- and long-term outcomes. Yet it often goes unrecognized, in part because the most common presentation is that of hypoactive (quiet) delirium. This section reviews the definition of delirium, key features and differences from other forms of altered mental status, the current understanding of delirium's pathophysiologic basis, risk factors for development, bedside tools specifically designed to assess delirium in the ICU, the short- and long-term consequences associated with delirium, and methods for preventing and treating delirium.

■ Definition of Delirium

The American Psychiatric Association *Diagnostic and Statistical Manual of Mental Disorders* fifth edition (DSM-5)[49] diagnostic criteria for delirium are (1) a disturbance in attention (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment); (2) development of the disturbance over a short period of time (usually hours to a few days), in which the development represents a change from baseline in attention and awareness and which tends to fluctuate in severity during the course of a day; (3) an additional disturbance in cognition (e.g., memory deficit, disorientation, language, visual–spatial ability, or perception); (4) the disturbances in criteria (1) and (2) are not better explained by another pre-existing, established, or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal, such as coma; and (5) there is evidence from the history, physical examination, or laboratory findings that the disturbance is a direct physiologic consequence of another medical condition, substance intoxication or withdrawal (i.e., due to a drug of abuse or to a medication), or exposure to a toxin, or is due to multiple etiologies.

Many signs and symptoms commonly observed in delirium, such as disturbance in the sleep–wake cycle, psychomotor agitation or decreased psychomotor activity, hallucinations, delusions, and perceptual disturbances, support the diagnosis but are neither sufficient nor required to make the diagnosis. Because these symptoms may be caused by other neurocognitive disorders, delirium is sometimes mistaken for other disorders, particularly dementia. Table 151-5 summarizes differences between delirium and dementia.

Historically, a large number of terms have been used to describe delirium in ICU patients, including encephalopathy, ICU psychosis, ICU syndrome, toxic confusional state, brain failure, subacute befuddlement, postoperative psychosis, and septic encephalopathy.[50] Use of these terms can lead to misunderstanding by practitioners, and certain terms, including ICU syndrome and ICU psychosis, can imply that the syndrome is an expected part of an ICU stay.[48,50,51] Therefore, regardless of the underlying etiology, the standardized term *delirium* should be used to describe a patient who meets the DSM criteria for delirium, with the suspected underlying etiology then used to describe the delirium (e.g., use the term "delirium due to sepsis" rather than "septic encephalopathy").[48,50,51]

■ Prevalence and Subtypes of Delirium

Delirium is highly prevalent among mechanically ventilated patients in ICUs (60%–80% develop delirium at some point during their ICU stay),[22,33,34,52–54] and also commonly affects nonventilated patients in the ICU setting (20%–40% are affected).[55–58] Delirium can be classified into subtypes according to the motor activity of the patient; these subtypes include *hyperactive, hypoactive*, and *mixed delirium*. Patients with hyperactive delirium are agitated and restless, and they may describe or respond to hallucinations and/or delusions. Those with the hypoactive subtype are calm and lethargic, and they often have decreased spontaneous movements. Finally, the mixed delirium subtype presents at different times with features of both hyperactive and hypoactive delirium. The most common motor subtypes observed in the ICU are mixed and hypoactive, with purely hyperactive delirium accounting for only a small percentage of cases of delirium.[59,60]

Not only is hypoactive delirium a common presentation of delirium, but preliminary data also suggest that those with hypoactive delirium may have worse outcomes. In a prospective cohort study of 582 survivors of critical illness, those with a longer duration of hypoactive delirium had worse global cognition and worse executive function following their critical illness.[61] In contrast, the duration of hyperactive delirium showed no such association, although the small number of patients experiencing hyperactive delirium means that an association with adverse long-term outcomes cannot be ruled out. As data continue to accumulate that the length of time a patient is delirious is associated with worse clinical outcomes, the fact that a majority of delirious patients in the ICU have mixed or

TABLE 151-5 Distinguishing Delirium from Dementia

Syndrome	Onset	Course	Diagnostic Features	Associated Features	Common Causes
Delirium	Acute (hours to days)	Fluctuating	Disturbance in attention and awareness Memory impairment, disorientation, or language impairment	Sleep/wake disturbances Extremes in psychomotor activity Emotional disturbances (e.g., fear, anxiety, depression, irritability, euphoria, apathy)	Acute medical illnesses Medications Substance intoxication or withdrawal Multifactorial
Dementia	Insidious (months to years)	Progressive	Memory impairment, plus one of the following: – Aphasia – Apraxia – Agnosia – Impaired executive functioning Impairments must be severe enough to cause impairments in social or occupational functioning and represent a decline from baseline	Visuospatial impairment Little/no awareness of memory impairment Gait disturbance Anxiety/mood/sleep disturbances	Dementia of Alzheimer type Vascular dementia Chronic medical conditions (Pick disease, HIV, stroke, head injury)

Data from American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th Edition. Washington, DC: American Psychiatric Association; 2013.

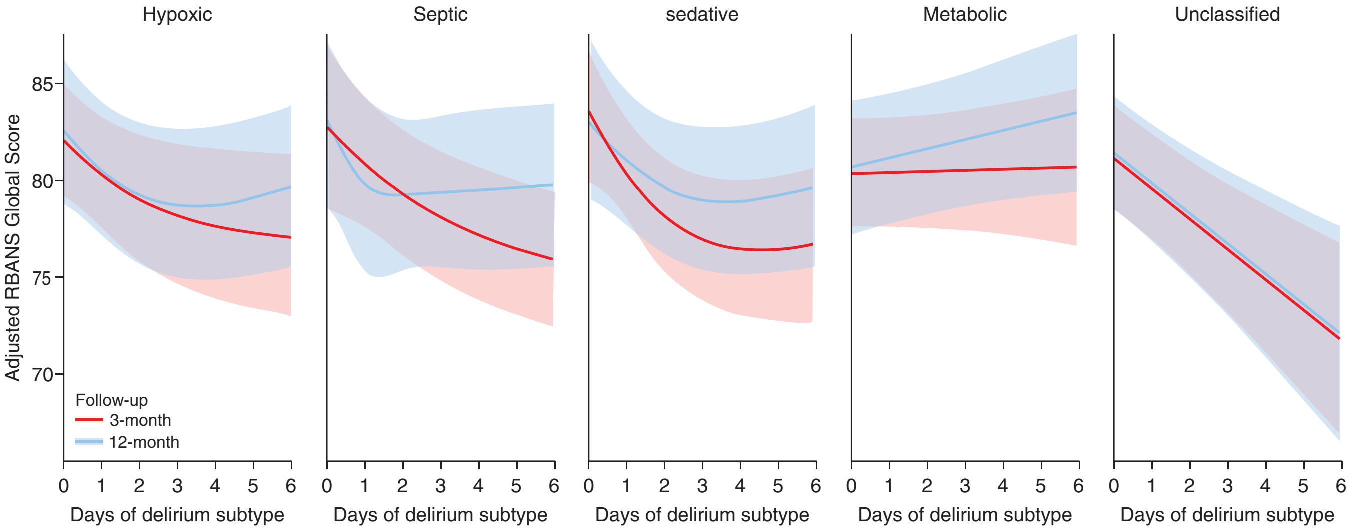


Figure 151-3 Associations between delirium phenotypes and long-term cognitive function. These figures show the associations between the number of days of different delirium phenotypes characterized by hypoxemia, sepsis, sedation exposure, metabolic abnormalities (e.g., renal failure or hepatic failure), or delirium characterized by none of these. With the exception of metabolic delirium, the duration of all phenotypes of delirium were associated with worse cognitive function at 3 months *(red lines)* and 12 months *(blue lines)*. *Solid lines* represent the association, and *shading* represents the 95% confidence interval of the association. *(Reproduced with permission from Girard TD, Thompson JL, Pandharipande PP, et al. Clinical phenotypes of delirium during critical illness and severity of subsequent long-term cognitive impairment: a prospective cohort study. Lancet Respir Med. 2018;6(3):213–222.)*

hypoactive subtypes is an important point for clinicians, as the presence of these subtypes of delirium is frequently overlooked.[62]

Delirium can also be classified into subtypes by its presumptive cause. One study divided 740 delirious patients into hypoxic (those patients with hypoxemia or shock), septic (those meeting criteria for sepsis), metabolic (those with uremia, hypoglycemia, hepatic dysfunction, or hyper/hyponatremia), sedative-associated (those who had received a sedative in the preceding 24 h), or unclassified (none of the above) delirium.[63] This study found that all delirium phenotypes except for metabolic delirium were associated with worse cognitive function at 12 months after discharge (Fig. 151-3). These data suggest that there are few benign causes of delirium and that even delirium that occurs in response to sedation, which is intended to reduce level of consciousness, is associated with adverse outcomes and should therefore be avoided whenever possible.

■ Risk Factors for Delirium

Delirium during critical illness is most often a multifactorial syndrome that develops when a vulnerable patient encounters a sufficiently strong insult or insults to precipitate onset of the syndrome,[64] although it is possible for a patient without preexisting vulnerabilities to become delirious during a critical illness. Typically, a patient with high baseline vulnerability, such as an elderly patient with underlying dementia, may require only a mild insult, such as pneumonia, but a younger patient without pre-existing cognitive impairment, that is, low baseline vulnerability, may require multiple strong insults, such as sepsis, mechanical ventilation, sedation with benzodiazepines, and immobilization. This scenario is not uncommon, given that critically ill patients are exposed on average to 11 risk factors for delirium.[65]

Risk factors for delirium can be thought of as predisposing factors, including baseline patient characteristics and premorbid conditions, and precipitating factors, such as those related to critical illness and treatments in an ICU. Baseline risk factors include older age, pre-existing cognitive impairment or dementia, use of alcohol or tobacco, hypertension, visual or hearing impairment, and APOE4 genotype.[53,66–70]

A number of precipitating factors are linked to development of delirium during critical illness, including high severity of illness, admission to an ICU for a medical illness (as opposed to a surgically treated condition), receipt of mechanical ventilation, high number of infusing medications, hypotension, acidosis, fevers, sepsis, electrolyte abnormalities, liver function test abnormalities, blood transfusion, and anemia.[54,66–69,71,72] Whereas each of these risk factors results from a patient's critical illness, factors associated with treatment may also increase risk. Precipitating risk factors associated with treatment in an ICU include immobility, presence of gastric tubes, bladder catheters, arterial lines, sedative and analgesic medications, particularly benzodiazepines, and those factors related to the overall ICU environment, including lack of daylight, isolation, lack of visitors, and sleep disturbances.[72,73]

■ Pathophysiology of Delirium

Delirium pathophysiology, although incompletely understood, likely represents a final common pathway from many different—perhaps interrelated—pathophysiologic mechanisms, including neurotransmitter imbalances, inflammation, aberrant stress responses, and impaired cerebral perfusion. It is thought that imbalances in the neurotransmitters that maintain arousal and sleep–wake cycles—notably acetylcholine and dopamine—are primary drivers of delirium.[74,75] Impaired central cholinergic functioning can result from derangements occurring anywhere along the pathway from acetylcholine production to its release and action on postsynaptic receptors. Acetylcholine deficiency or blockade has been associated with delirium, as has dopamine excess, likely through dopamine receptor regulation of acetylcholine activity.[75–77] Other neurotransmitters, such as gamma-aminobutyric acid (GABA), norepinephrine, serotonin, glutamate, and melatonin, also have been hypothesized to play a role in delirium, although the contribution of these neurotransmitters in the development of delirium is not well understood.[74–79]

Alterations in precursor molecules to neurotransmitters, such as dopamine, norepinephrine, serotonin, and melatonin—in particular, the large neutral amino acids (LNAAs)—also have been hypothesized to be involved in the pathogenesis of delirium.[80] LNAAs, which include leucine, valine, tryptophan, tyrosine, and phenylalanine, compete for transfer across the blood–brain barrier via a single transport receptor, such that increased transport of one LNAA results in decreased transport of others. Thus, the concentration of neurotransmitters in the CNS is related to changes in serum concentrations of LNAAs, and changes in these concentrations have been associated with delirium during critical illness.[81–83]

Systemic inflammation, which is very common during critical illness, also is thought to play a role in development of delirium. Inflammatory molecules such as interleukin-1β (IL-1β), IL-6, IL-8, TNF-α, and prostaglandins, and blood-borne molecules such as lipopolysaccharide, are released in response to infection, tissue damage, and surgery. These molecules interact with the brain via direct autonomic neural pathways, second-messenger systems, and active transport across the blood–brain barrier, and through disruptions in the blood–brain barrier, resulting in neuroinflammation.[84–87] Neuroinflammation triggers CNS production of additional inflammatory cytokines and metalloproteinases, release of reactive oxygen species, and expansion and activation of microglia, resulting in alterations in CNS perfusion, impaired neurotransmitter production, and derangements in oxidative metabolism, ultimately leading to neuronal damage and cell death.[85–87] Neuronal death results in a functional disconnect between neuroanatomic structures, culminating in the neurobehavioral changes observed in delirium.[79,85]

■ Screening Tools for Delirium

Since many delirious patients are lethargic or calm, rather than agitated, delirium in the ICU is overlooked nearly 70% of the time.[62] Thus, expert guidelines recommend that all patients in an ICU be routinely monitored using a well-validated delirium-screening tool.[5]

Two screening tools that were developed specifically for assessment of critically ill adult patients, the Confusion Assessment Method for the ICU (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC), have been the most rigorously validated and widely implemented and, thus, are recommended in expert guidelines.[5] Validated before the release of DSM-5[49] criteria, both the CAM-ICU and the ICDSC were compared in validation studies with expert psychiatric examinations applying the DSM-IV[88] criteria for delirium and were found to have high sensitivity and specificity, as well as excellent interrater reliability when performed by ICU physicians and nurses.[52,57,89–93] Both screening tools identify features of delirium that remain part of the DSM-5 definition, such that the tools are considered current and valid in the DSM-5 era.

With either the CAM-ICU or the ICDSC, the first step when assessing for delirium is to assess the patient's level of arousal/consciousness (see "Assessing Agitation and Level of Consciousness in the Critically Ill," above); as stated in the DSM-5, a patient cannot be assessed for delirium when comatose. In validation studies of the CAM-ICU, this was operationalized by determining that patients were arousable to voice (e.g., RASS −3 or more awake) before proceeding with the CAM-ICU assessment. Similarly, the ICDSC excludes patients in coma or stupor from delirium assessment. Once level of consciousness is assessed, the second step in the delirium evaluation is to assess the content of consciousness using either the ICDSC or the CAM-ICU.

The CAM-ICU was developed based on the full Confusion Assessment Method[94] but tailored to the specific needs of patients in the ICU (e.g., it can be performed in both nonintubated and intubated patients, even in the setting of sedation, as long as the patient is not comatose). During what is typically a 1- to 2-min evaluation, the CAM-ICU assesses four key features of delirium: (1) acute change or fluctuation in mental status, (2) inattention, (3) altered level of consciousness, and (4) disorganized thinking.[52,90] The CAM-ICU is positive—that is, the patient is considered to have delirium—if features 1 and 2 are present and *at least* feature 3 or 4 is present. See Fig. 151-4 for instructions on how to assess each feature in the CAM-ICU. This tool has been translated into more than 30 different languages, and many of these translated versions have been validated.[95]

The ICDSC is an eight-item checklist of delirium symptoms assessed over an 8- to 24-h period. Providers (typically the bedside nurse) monitor patients for the symptoms on the checklist during that period of time (e.g., during a nursing shift) and mark items on the checklist as they are observed. The symptoms include altered level of consciousness, inattention, disorientation, hallucinations/delusions/psychosis, psychomotor agitation or retardation, inappropriate speech or mood, sleep/wake disturbances, and fluctuation of symptoms. One point is given for each symptom observed; a score of four or greater indicates delirium (Table 151-6).

■ Outcomes Associated with Delirium

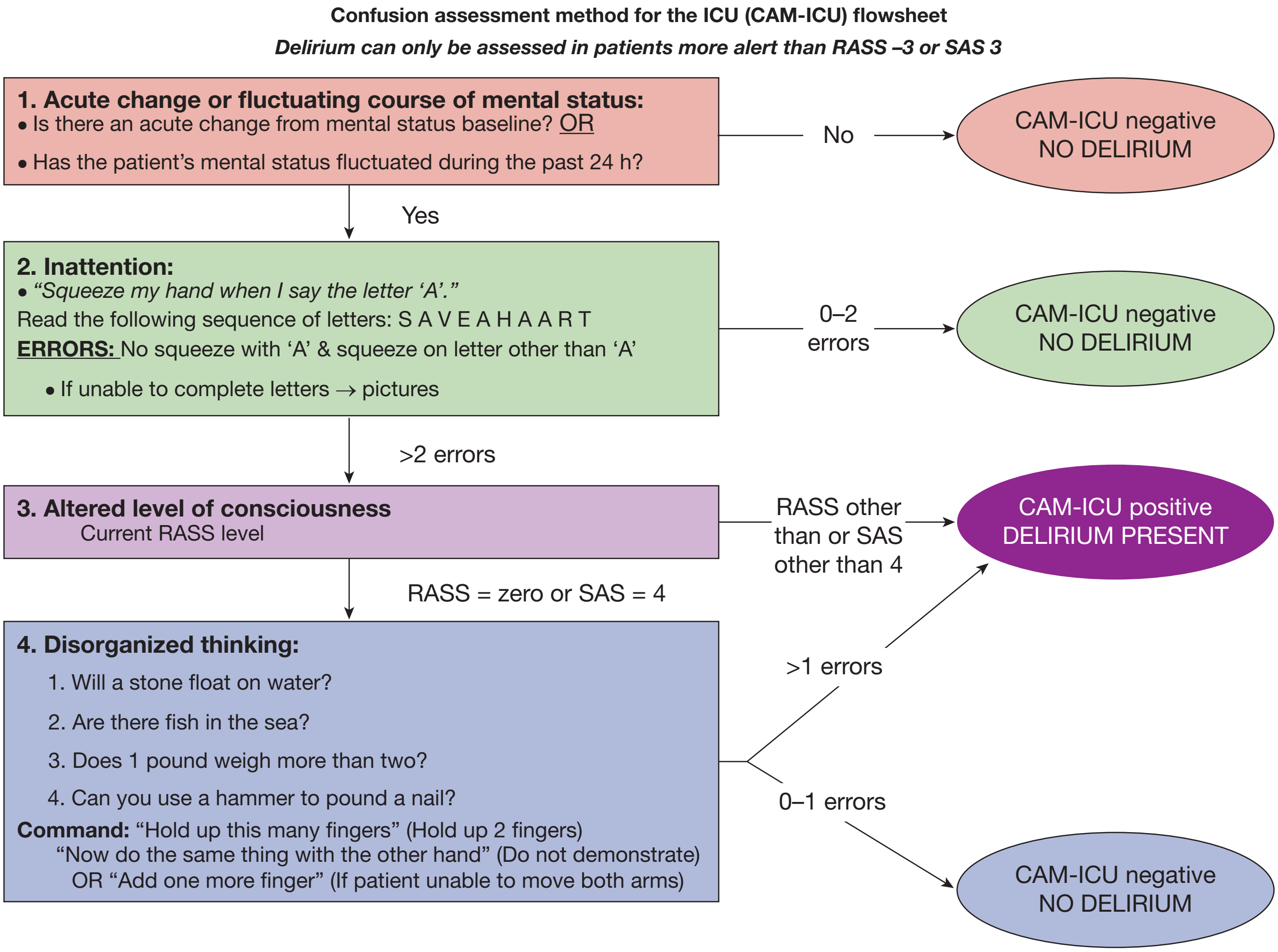
In both the short and long term, patients who suffer from delirium are at risk for several adverse outcomes. Within the context of the acute critical illness, patients who are delirious are more likely to remove catheters and endotracheal tubes, require physical restraints, and have prolonged mechanical ventilation.[66,96,97] In addition, compared with those who do not become delirious, these patients are at higher risk for longer stays in the ICU and hospital, higher healthcare costs, and discharge to locations other than home.[52,69,97–101]

The adverse outcomes associated with delirium do not end at the time of hospital discharge. In two separate prospective cohort studies, each additional day a patient was delirious in the ICU was associated with a 10% increase in the hazard of death at 6 or 12 months following hospital discharge.[102,103] A meta-analysis of 42 different ICU studies similarly found that ICU delirium was associated with a roughly twofold increase in the odds of mortality.[104] In addition, two separate cohort studies have identified duration of delirium as a strong independent predictor of long-term cognitive impairment, with longer delirium durations in the ICU associated with poorer cognitive performance a full year after discharge.[105,106] Additionally, longer durations of multiple delirium phenotypes (including septic, hypoxic, and sedative-associated delirium) were associated with worse long-term cognitive outcomes.[63] Finally, one additional study noted that duration of delirium during critical illness was also associated with activities of daily living among survivors of critical illness, with prolonged delirium predicting disability during long-term follow-up.[107]

■ Preventing Delirium

Preventing delirium from developing during a patient's ICU stay can be difficult because at the time of the patient's ICU admission, acute organ failures (often including delirium) are already present. Nevertheless, preventative measures may be beneficial, since some patients do not develop delirium until several days into their ICU stay. Additionally, because the duration of delirium is also associated with adverse outcomes, including cognitive impairment, physical disability, and death, measures that may shorten the duration of delirium should be implemented. Although not all risk factors for delirium can be avoided, three risk factors common in the ICU—exposure to sedative and analgesic medications, immobility, and sleep deprivation—have been targeted by interventions designed to prevent delirium; a number of studies have shown that these interventions are associated with reductions in delirium.

Benzodiazepines are consistently associated with the development of delirium in patients in the ICU and, therefore, serve as an easily modifiable risk factor. In studies of medical, surgical, cardiac, trauma, and burn patients, higher doses of benzodiazepines have been independently associated with higher risk for delirium.[33,67,108,109] Based on these data, a number of interventions



Confusion assessment method for the ICU (CAM-ICU) flowsheet

Delirium can only be assessed in patients more alert than RASS –3 or SAS 3

1. Acute change or fluctuating course of mental status:
- Is there an acute change from mental status baseline? OR
- Has the patient's mental status fluctuated during the past 24 h?

2. Inattention:
- *"Squeeze my hand when I say the letter 'A'."*

Read the following sequence of letters: S A V E A H A A R T

ERRORS: No squeeze with 'A' & squeeze on letter other than 'A'
- If unable to complete letters → pictures

3. Altered level of consciousness
Current RASS level

4. Disorganized thinking:
1. Will a stone float on water?
2. Are there fish in the sea?
3. Does 1 pound weigh more than two?
4. Can you use a hammer to pound a nail?

Command: "Hold up this many fingers" (Hold up 2 fingers)
"Now do the same thing with the other hand" (Do not demonstrate)
OR "Add one more finger" (If patient unable to move both arms)

No
CAM-ICU negative NO DELIRIUM
Yes
0–2 errors
CAM-ICU negative NO DELIRIUM
>2 errors
RASS other than or SAS other than 4
CAM-ICU positive DELIRIUM PRESENT
RASS = zero or SAS = 4
>1 errors
0–1 errors
CAM-ICU negative NO DELIRIUM

Figure 151-4 The Confusion Assessment Method for the ICU (CAM-ICU). The CAM-ICU assesses for the four features of delirium. Feature 1 is an acute change in mental status or a fluctuating mental status *(orange box)*, feature 2 is inattention *(green box)*, feature 3 is altered level of consciousness *(purple box)*, and feature 4 is disorganized thinking *(blue box)*. A patient screens positive for delirium if features 1 and 2 and either feature 3 or feature 4 are present. *(Reproduced with permission from copyright © 2002, E. Wesley Ely, MD and Vanderbilt University.)*

intended to reduce exposure to benzodiazepines have been investigated. Sedation of mechanically ventilated patients using dexmedetomidine, for example, rather than benzodiazepines, reduced daily risk of delirium in three major randomized trials.[33,34,41] In addition, in one study addressing avoidance of benzodiazepines as one part of a multicomponent quality-improvement program designed to reduce delirium risk, researchers found a significant increase in days patients spent without delirium.[110]

Opioid analgesic medications have also been associated with development of delirium in some studies, but the relationship between opioids and delirium is not as straightforward as the one between benzodiazepines and delirium. This difference likely relates to the dual effects of opioids. For example, when opioids are used to heavily sedate patients, their use is associated with an increased risk of delirium.[68,69,71] When opioids are used primarily to relieve pain rather than to sedate, such as in patients with trauma or burns, the risk of delirium is reduced.[54,108,111] A recent large observational study, however, found that opioid use was associated with a higher risk of developing delirium, even in the presence of pain.[112] Further study of whether opioid-sparing analgesic regimens can be used to prevent delirium are needed to definitively answer this important question.

Immobility, particularly due to the use of physical restraints, is a strong risk factor for the development of delirium among both non-ICU hospitalized and critically ill patients.[64,72] Studies in which early mobilization is promoted among critically ill patients have found that it reduces delirium.[113–116] For example, a 104-patient multicenter randomized trial of mechanically ventilated patients in the medical ICU who were randomized to early physical and occupational therapy or usual care (i.e., delayed physical therapy) found that those who received early physical and occupational therapy spent, on average, 2 fewer days in delirium than those in the control group.[113] A second 200-patient, multicenter randomized trial of surgical ICU patients that compared an early, goal-directed mobility intervention to usual care found that those in the early mobility group experienced 3 more days alive without delirium.[117]

Critically ill patients frequently suffer sleep deprivation. In fact, studies suggest that normal sleep rarely, if ever, occurs during acute respiratory failure requiring mechanical ventilation in the ICU; in one study, only a small percentage of the sleep observed was restorative (REM) sleep, and nearly half occurred during daytime hours.[118] In light of these data and the connection between sleep deprivation and delirium outside the ICU, investigators studied the effect of earplugs in a randomized trial of patients in ICUs and found significant reductions in incidence of delirium.[119] Using a multicomponent intervention that reduced nocturnal lights and noises and provided eye masks, earplugs, and pharmacologic sleep aids, others observed an increase in the number of days free from delirium or coma.[120,121]

Pharmacologic prevention of delirium has generally been shown not to be effective. For example, among nearly 1800 ICU patients at high risk of delirium who were randomized to receive either

TABLE 151-6 The Intensive Care Unit Delirium Screening Checklist (ICDSC)

1. **Altered level of consciousness** Choose **ONE** from A–E

Note: May need to reassess patient if recent administration of sedation therapy

- A. Exaggerated response to normal stimulation SAS = 5, 6, or 7 Score 1 point
- B. Normal wakefulness SAS = 4 Score 0 points
- C. Response to mild or moderate stimulation SAS = 3 Score 1 point
  (follows commands) **Score 0 if LOC related to recent sedation/analgesia**
- D. Response only to intense and repeated stimulation (e.g., loud voice and pain) SAS = 2 **Stop assessment**
- E. No response SAS = 1 **Stop assessment**

2. **Inattention** Score 1 point for any of the following abnormalities:

- A. Difficulty in following commands OR
- B. Easily distracted by external stimuli OR
- C. Difficulty in shifting focus

Does the patient follow you with their eyes?

3. **Disorientation** Score 1 point for any one obvious abnormality:

- A. Mistake in either time, place, or person

Does the patient recognize ICU caregivers who have cared for him/her and not recognize those that have not? What kind of place are you in? (list examples)

4. **Hallucinations or delusions** Score 1 point for either:

- A. Equivocal evidence of hallucinations or a behavior due to hallucinations (Hallucination = perception of something that is not there with NO stimulus) OR
- B. Delusions or gross impairment of reality testing (Delusion = false belief that is fixed/unchanging)

Any hallucinations now or over past 24 h? Are you afraid of the people or things around you?

(fear that is inappropriate to clinical situation)

5. **Psychomotor agitation or retardation** Score 1 point for either:

- A. Hyperactivity requiring the use of additional sedative drugs or restraints to control potential danger (e.g., pulling IV lines out or hitting staff) OR
- B. Hypoactive or clinically noticeable psychomotor slowing or retardation

Based on documentation and observation over shift by primary caregiver

6. **Inappropriate speech or mood Score 1 point for either:**

- A. Inappropriate, disorganized, or incoherent speech OR
- B. Inappropriate mood related to events or situation

Is the patient apathetic to current clinical situation (i.e., lack of emotion)?

Any gross abnormalities in speech or mood? Is patient inappropriately demanding?

7. **Sleep/wake cycle disturbance Score 1 point for:**

- A. Sleeping less than 4 h at night OR
- B. Waking frequently at night (do not include wakefulness initiated by medical staff or loud environment) OR
- C. Sleep ≥4 h during day based on primary caregiver assessment

8. **Symptom fluctuation Score 1 point for:**

Fluctuation of any of the above items (i.e., 1–7) over 24 h (e.g., from one shift to another) **based on primary caregiver assessment**

TOTAL ICSDC SCORE (Add 1–8)

This 8-item checklist should be completed using clinical information gathered over the last 8 or 24 h. First assess level of consciousness. If level of consciousness is C, D, or E proceed with the remaining items. Patients are given 1 point for having an obvious manifestation of the item. A score of 4 or greater is considered a positive delirium screen.

SAS, Riker Sedation-Agitation Scale; LOC, level of consciousness.

Adapted with permission from Morris PE1, Goad A, Thompson C et al. Early intensive care unit mobility therapy in the treatment of acute respiratory failure. Crit Care Med. 2008;36(8):2238–2243.

haloperidol or placebo, there was no difference in the incidence of delirium or the number of days alive without delirium.[122] A second smaller study of 68 patients with subsyndromal delirium (i.e. delirium symptoms that do not meet the full diagnostic criteria for delirium) who were randomized to haloperidol or placebo found no significant differences in the number of patients who subsequently developed delirium.[123] The findings of these trials are supported by a meta-analysis.[124] In contrast to these negative studies of antipsychotics, nocturnal (i.e., given between 9:30 P.M. and 6:00 A.M.) dexmedetomidine was found to reduce the risk of developing delirium. Among 100 mechanically ventilated patients who were receiving sedation and who were not delirious, those who were randomized to receive dexmedetomidine had a 44% greater chance of never developing delirium.[125]

■ Treating Delirium

After implementing the preventative measures, practitioners will likely continue to observe delirium in the ICU. Because delirium often serves as the "canary in the coal mine," heralding the onset of a new or exacerbated underlying pathology (e.g., infection, shock, metabolic abnormality) or a response to a deliriogenic medication, a positive screen for delirium should prompt an immediate search for, and correction of, an underlying etiology and any modifiable risk factors. After addressing potentially modifiable causes of delirium, pharmacologic therapies can be considered.

For many years, antipsychotics were the mainstay of treatment for delirium in the ICU.[126] Data from two placebo-controlled trials, however, suggest that these drugs have no effect on delirium. In a single-center trial, Page et al. randomized 142 mechanically ventilated patients to receive either haloperidol or placebo for up to 14 days.[127] There were no differences between groups in the number of days alive with normal brain function (i.e., the number of delirium/coma-free days) between groups. Patients randomized to treatment with haloperidol had less overall agitation (less time spent at a RASS +2 or more agitated), suggesting that this agent could serve as a sedative-sparing agent even though it did not alter the duration of delirium. A second trial, which was much larger and recruited patients in multiple hospitals throughout the United States, compared treatment of delirium with haloperidol versus ziprasidone versus placebo in 566 patients being treated for respiratory failure or shock.[128] The primary outcome—the number of days alive without delirium or coma during the 14-day study period—did not differ between groups. Likewise, there were no significant differences between groups in duration of hypoactive or hyperactive delirium or in 30- or 90-day mortality. Combined, these trials provide strong evidence that neither haloperidol nor ziprasidone should be used to treat delirium during critical illness. Based on these data, clinical practice guidelines recommend against the use of antipsychotics for the treatment of delirium.[5]

Given the recent data suggesting that pharmacologic therapy is ineffective for the treatment of delirium, the clinician may wonder how to reduce the burdens of this syndrome. Emerging data suggest that an evidence-based multicomponent strategy known as the “ABCDEF” bundle is effective in reducing both the presence and duration of delirium in the ICU. Components of the bundle include Assessment, prevention, and management of pain; Both spontaneous awakening and breathing trials: careful Choice of analgesia and sedation; Delirium assessment, prevention, and management; Early mobility and exercise; and Family engagement/empowerment.

Implementation of this strategy has been shown to be effective in reducing delirium and improving other clinical outcomes across individual hospitals, health systems, and a multicenter collaborative that included community, federal, and academic centers across the United States. Balas et al. compared outcomes before and after bundle implementation.[129] Following implementation, the proportion of patients who ever developed delirium was reduced by 13%, and the proportion of days patients spent in the ICU with delirium was reduced from 50% to 33%. Building on these findings, Barnes-Daly et al. implemented the bundle across ICUs at 7 community hospitals in Northern California over the course of a year.[130] In more than 6000 patients, increasing bundle performance (both in the number of days and amount of bundle elements performed) was associated with a significant increase in the number of days alive and without delirium

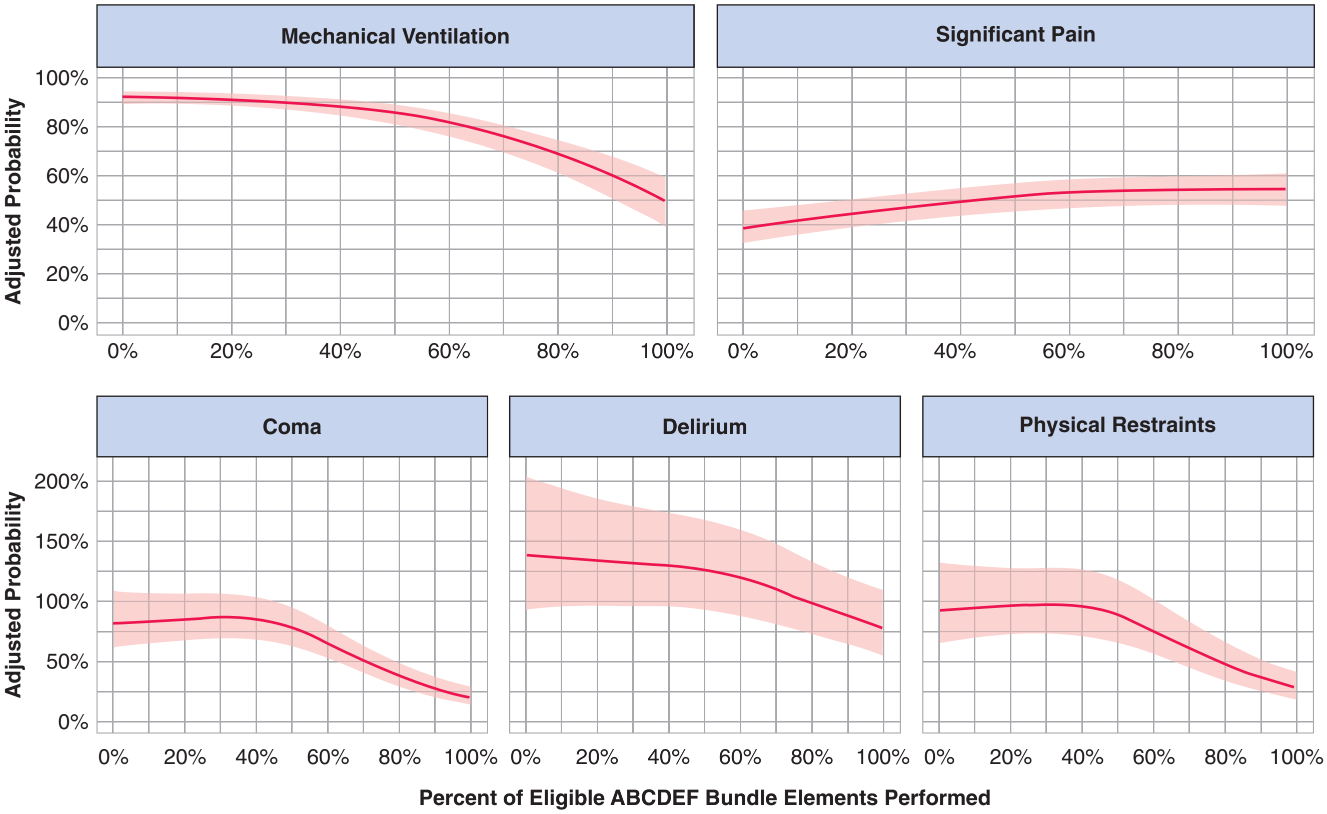


Figure 151-5 Clinical Outcomes associated with the ABCDEF Bundle. These figures show the relationship between the proportion of ABCDEF bundle elements performed *(x-axis)* and the adjusted probability of the clinical outcome the following day *(y-axis)*. The *solid lines* represent the association, and *shading* represents the 95% confidence interval. The top left panel shows a reduction in the probably of being treated with mechanical ventilation. The top right panel shows an increase in patient-reported pain. The bottom left panel shows lower probability of being comatose, the bottom center panel shows a lower probability of being delirious, and the bottom right panel shows a lower probability of being treated with physical restraints. *(Reproduced with permission from Pun BT, Balas MC, Barnes-Daly MA, et al. Caring for Critically Ill Patients with the ABCDEF Bundle: Results of the ICU Liberation Collaborative in Over 15,000 Adults, Crit Care Med. 2019;47(1):3–14.)*

or coma. Furthermore, more days of bundle performance and more elements performed were associated with greater hospital survival.

A large multicenter collaborative implemented the ABCDEF bundle in more than 68 centers across the United States during a 20-month cohort study.[131] Among more than 15,000 patients with at least 1 full day in the ICU, implementation of the bundle was associated with improved clinical outcomes such that as more of the bundle elements were performed, the chances of a patient having delirium the following day were reduced (Fig. 151-5). Similar dose-dependent relationships were seen between greater bundle performance and improved clinical outcomes such as a lower probability of being treated with mechanical ventilation, being comatose, and being treated with physical restraints. The only clinical outcome that worsened with implementation of the ABCDEF bundle was an increase in patient-reported pain, likely because patients were more alert and therefore able to communicate pain.

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CHAPTER 152

Ethics and Palliative Care in Critical Care Units

Joshua B. Kayser

Horace M. DeLisser

INTRODUCTION

Death is common in the intensive care unit (ICU), with approximately 20% of deaths in the United States occurring during or shortly after a stay in an ICU.[1] Many of these deaths involve the withholding or withdrawal of life-sustaining therapy, with considerable site variability.[2,3] Therefore, the ICU represents a particularly distinct clinical setting where the thoughtful and considered application of ethical concepts is required. A proper understanding of the basic principles of bioethics as well as the principles of providing comfort-focused, end-of-life care are essential elements in the competent practice of intensive care medicine.

A number of common ethical themes arise in the ICU. Technologic advancements have allowed healthcare providers to keep patients alive for prolonged periods in the context of diseases that, in the past, would have resulted in death. However, the capacity for delivering life-sustaining care has not been completely matched by efforts to align treatments with the care individual patients wish to receive at end of life, resulting in a potential discordance between care wanted and care received.[4–6] Compounding this problem is the reality that many patients dying in the ICU, prior to death, lack the capacity to make decisions regarding end-of-life care[7] and have not completed an advance directive that might aid surrogates and physicians in the decision-making process.[8] Many decisions about end-of-life care in the ICU are, therefore, made without the involvement or input of the patient.[7] The resulting uncertainty means that many patients frequently receive far more aggressive interventions than they would have otherwise chosen for themselves, or they receive care that has a low likelihood of restoring health, enabling discharge from the ICU, and having the potential for providing a meaningful quality of life.[6]

Ethical dilemmas that characterize critical care medicine often arise from this interface between the ability to prolong life by expensive and sometimes scarce technology and an inability to cure patients or restore them to their baseline. The relevant ethical question often is whether technology is being used wisely—that is, should the patient's life be prolonged? The question becomes even more complex for practitioners and patients' families when different ethical principles suggest conflicting answers.

Although the practice of critical care medicine encompasses a broad range of bioethical issues, several are particularly common, including palliative and end-of-life care, surrogate decision-making, medical futility, communication, and professionalism. These issues are among the most challenging for critical care practitioners and constitute the focus of this chapter.

FUNDAMENTAL PRINCIPLES OF BIOETHICS

Several fundamental principles of bioethics are at the core of the practice of critical care medicine: respect for patient autonomy, beneficence, nonmaleficence, and distributive justice.[9] Ethical dilemmas in the ICU arise when two or more of the principles are in conflict. An understanding of these areas provides a basis for addressing conflict and is imperative in providing high-quality palliative care at the end of life.

Respect for Patient Autonomy

The principle of patient *autonomy* refers to the concept of self-determination, which asserts that a competent and informed adult patient possessing adequate decision-making capacity has the right to determine what will be done to his or her body.[9] According to this principle, the patient has the ethical right to accept or refuse medical interventions, including those that might sustain life. In addition, the principle of autonomy encompasses the right to privacy and the requirement for informed consent. As such, except in an emergency, a competent adult must give informed consent before receiving medical care, especially interventions that have the potential to cause further harm or death. Under emergency conditions, consent is presumed. Respect for patient autonomy is applicable with respect not only to patients, but also to their families and surrogate decision makers or proxies—that is, individuals who speak on behalf of patients who lack the capacity to make medical care decisions.

In the United States, societal and professional consensus, as well as statutory law and judicial precedents, support the principle of patient autonomy. Absent countervailing obligations, healthcare providers are required to respect a competent and informed patient's decision to forgo life-sustaining care. Important to note, however, is that autonomy does not provide patients or their surrogates with the right to demand and receive any desired treatment. Rather, patients or their surrogates are permitted to accept or forgo medical interventions that fall within the standard of medical care.

Beneficence and Nonmaleficence

The principle of *beneficence* obligates healthcare providers to promote the well-being of their patient and provide services that benefit the patient.[9] *Nonmaleficence* is the duty to minimize pain and suffering.[9] The Hippocratic maxim *primum non nocere,* which can be translated as "first, do no harm," reflects the fundamental importance of this principle for physicians. Both principles relate to the provision of care that maximizes each individual's dignity and worth as a human being. However, a constant tension exists between these two principles: efforts to cure medical illness often come with substantial suffering. Provided the benefits outweigh the harms, administration of life-sustaining therapies is appropriate. However, once the physician believes the attendant harms may be greater than the foreseen benefits, the physician is obligated to communicate his or her concerns to patients and/or their families. A common example of this tension is provision of cardiopulmonary resuscitation (CPR) to patients who have refractory sepsis despite aggressive medical intervention. The medical literature indicates that offering CPR in this setting is unlikely to restore spontaneous circulation, or at the very best, delay the dying process.[10,11] Consequently, offering CPR in this context could constitute a harm that outweighs the benefits. Despite this ethical construct, the proportion of patients receiving CPR prior to death continues to rise, particularly among minority groups.[10]

Distributive Justice

Justice refers to fairness in the distribution of limited resources, that is, *distributive justice*.[9] Ethically, this principle holds that equals should be treated equally, and unequals treated unequally. In practice, the principle of distributive justice pertains to defining fairness in allocating resources among individuals when not all can receive the resources. The principle is applicable on two levels in health care: macroallocation and microallocation of resources.

Macroallocation entails the distribution of resources among various goods and services at a governmental or institutional level. In contrast, *microallocation* refers to decision-making about an individual patient or small group of patients within, for example, an individual ICU or hospital. A single formulation for the application of this principle in patient care is not available because widely accepted criteria are lacking. Various ethical theories (e.g., deontology, utilitarianism, egalitarianism, among others) define different values as the most relevant criteria for making such judgments. In general, determinations of how to allocate resources and treat patients are best left to institutional or governmental authorities, while physicians provide reasonable and appropriate care on an individual patient basis. Issues of distributive justice have been the subject of significant attention during the recent COVID-19 pandemic.[12]

CONSIDERATIONS IN END-OF-LIFE CARE IN THE ICU

A number of considerations constitute the core practice of bioethics in the ICU. Included are the withdrawal and withholding of life-sustaining therapies, surrogate decision-making, trust and communication, provision of good palliative care, and medical futility. In this regard, bioethics in the ICU should not be viewed as a fixed body of knowledge, but rather as a continually evolving field, similar to the rest of clinical medicine.

Withdrawal and Withholding of Life-sustaining Therapy

Over the last several decades, a broad societal consensus has developed in addressing the ethics of withholding or withdrawing life-sustaining therapies or "life support." Landmark judicial cases, such as the 1976 New Jersey Supreme Court decision regarding Karen Ann Quinlan[13] and the 1990 U.S. Supreme Court decision regarding Nancy Cruzan,[14] played substantial roles in defining both ethical and legal standards. Based on the principle of autonomy, the current societal and legal standard is that adequately informed adults possessing decision-making capacity have the right to refuse any life-sustaining medical therapy, even if the decision results in death. *Capacity* requires that the patient have the ability to comprehend relevant information, understand their condition, compare and contrast treatment options, and communicate wishes consistently.[15]

In practice, no meaningful legal or ethical difference exists between withdrawing and withholding life-sustaining therapy. In addition, legal precedent has established that artificial nutrition and hydration are considered medical interventions that are no different than CPR or mechanical ventilation. The legal issue of whether artificial nutrition and hydration provided by a feeding tube constitutes medical care was decided when the U.S. Supreme Court deemed it so in its 1990 decision on Nancy Cruzan.[14] This decision established a constitutionally protected legal right to refuse any medical care by a competent adult or appropriate surrogate decision-maker acting in accord with the patient's previously expressed preferences or values, including artificial nutrition and hydration. Of note, despite the legal and moral equivalence between withdrawal and withholding of life-sustaining therapy, many patients, families, and healthcare providers often perceive differences between the two.

Morally, controversy continues to exist over the distinction between actions and omissions leading to a patient's death.[16,17] Although the debate is ongoing in the United States, currently, withdrawal and withholding of life-sustaining therapies (sometimes referred to as passive euthanasia) are permissible. In contrast, active euthanasia, where a physician administers an intervention with the intent of hastening death, is neither morally nor legally permissible. This is in direct contradiction to attitudes in many other countries, including parts of Western Europe, where active euthanasia is currently practiced.[18]

Relief of Pain and Suffering

A key ethical principle in end-of-life care is that physicians are obligated, whenever possible, to provide relief of pain and suffering and ensure a dignified death for the dying patient. *Dignity* can be defined in various ways, but at its core is the idea that patients should be treated respectfully and humanely. This includes efforts to keep the patient clean and comfortable, with as little distress as possible. Control of pain is particularly important in the ICU, where significant doses of sedatives may be required to relieve suffering. For some healthcare providers, fear exists that administration of high doses of sedating medications could suppress respiration or cause hemodynamic instability, thus accelerating the dying process. Consequently, they may underdose patients to prevent potential side effects. Unfortunately, this approach carries the unintended consequence of incompletely or ineffectively controlling pain and suffering, thereby diminishing the quality of the dying experience for both the patient and their loved ones.

The *doctrine of double effect* is a key ethical principle that guides the practice of end-of-life care and informs our understanding of how we can effectively relieve pain and suffering. It holds that if, in the process of treating pain or distress of a dying patient, an intervention has the unintended consequence of hastening death, it is ethically and morally permissible.[9] In other words, as long as the intent is not to hasten death, aggressive treatment of symptoms to achieve comfort for the dying patient is acceptable and encouraged and is consistent with the ethical principle of beneficence. This should not be confused with active euthanasia or assisted suicide. The intention of active euthanasia or physician-assisted suicide is specifically to *cause* the patient's death. Based on current societal norms and judicial precedent, active euthanasia is ethically and legally distinct from withdrawal and withholding of life-sustaining therapies, which are intended to allow patients to die from their underlying disease.

Surrogate Decision-making

As noted previously, a majority of patients in the ICU lack the capacity to provide either informed consent for, or refusal of, a medical intervention.[7] Many factors may compromise decision-making capacity, including pain, anxiety, disorientation, fear, sleep deprivation, effects of the underlying disease, and the use of sedatives and narcotics. Unfortunately, most patients have not previously discussed their wishes with family and friends or outpatient medical providers, and they often have not completed an advance directive to articulate their wishes.[8]

When patients lack adequate decision-making capacity, surrogate decision makers are often involved in decisions to limit life-sustaining therapy. The current approach for decision-making in the ICU is a shared decision-making model, in which providers offer information about medical issues, anticipated benefits, and the patient's prognosis, while families provide an understanding of the patient's values and preferences.[19–21] Some patients may have previously explicitly identified a surrogate decision-maker. In the absence of an identified individual, standards for identifying someone to fill that role vary from state to state.

Under ideal circumstances, the surrogate is an individual who knows the patient well and has a good understanding of the patient's values and preferences, allowing them to advocate for the patient based on the *substituted judgment standard*. This standard holds that the surrogate must have knowledge about the patient's wishes, as expressed orally or in writing, or about the patient's values and life goals, from which valid inferences can be made. In situations in which the patient's explicit wishes are unknown, the healthcare team and the patient's loved ones should work collaboratively to make decisions based on the *best interest standard*, taking into consideration the patient's values, preferences, life goals, prior medical decisions, current condition, and prognosis. Under this standard, the surrogate, along with the caregivers, must base their decision on a weighing of the benefits and burdens of life-sustaining therapy—for example, the benefits of life, chance of survival, and chance of full recovery with a high quality of life, compared with the burdens of pain, additional suffering, and poor quality of life.

For a small subset of patients, a surrogate decision-maker cannot be identified.[22] Uniform standards for managing patients in this situation are lacking. In general, the manner in which this circumstance is handled varies by institution and may include multiple physician opinions, chief medical officer concurrence, and/or hospital ethics committee review. Institutions are encouraged to establish a written policy for this practice. Recently, some guidance has been issued to better standardize care for unrepresented patients.[23]

■ Medical Futility

An example of when ethical principles may conflict is in the ongoing debate over the use of medical futility to guide care of critically ill patients. While there are various conceptions of futility in health care, broadly, an intervention may be considered *futile* when it is incapable of accomplishing the result for which it is intended.[24] In the ICU, this goal is typically understood to be meaningful recovery from critical illness, where *meaningful* refers to a survival that the patient can value and appreciate.

An important distinction exists between *physiologic futility* and *medical futility*. An intervention that is judged to be *physiologically futile* is one that is not expected to, or does not achieve, the relevant physiologic function as an endpoint. There is both an ethical and professional consensus that healthcare providers are not required to provide such interventions.[25] As described previously, CPR may be judged to be physiologically futile in a patient with refractory septic shock complicated by cardiac arrest after progressively worsening hypotension, despite maximal therapy. Under these circumstances, the conclusion that CPR would have extremely little or no chance of success (beyond, possibly, a brief time period) is well supported by published literature and clinical experience. Further, an attempt at CPR would not only prolong the patient's dying but could also do physical harm by fracturing ribs and burning the skin. Prolonging dying is not one of the goals of medicine, and under these circumstances, CPR would violate the principle of nonmaleficence. Moreover, an argument has been made that forcing healthcare providers to perform CPR when there is virtually no prospect of success undermines the ethical integrity of the medical profession.[25]

Medical futility is more difficult to define than physiologic futility and is, therefore, less well supported in its application. Some of the older literature describes qualitative approaches, in which experience suggests an intervention will not result in a meaningful survival,[26] as well as quantitative approaches, in which the success of interventions is measured in a more standardized way.[27] However, it is important to recognize that physicians may be limited in their ability to accurately determine the prognosis of a patient.[28] Furthermore, what constitutes meaningful survival or good quality of life is inherently unique to a particular individual and, therefore, is difficult to measure. Consequently, employing a medical futility standard, rather than a physiologic standard, is more challenging. In recent years, professional societies have developed and recommended standards for responding to requests by patients and surrogates for potentially inappropriate treatments in the ICU. This includes avoidance of term "futile" to address interventions that are not physiologically futile but for which there is a competing ethical rationale not to offer the intervention. Included in these standards is a strong recommendation not to offer physiologically futile interventions.[24]

Not uncommonly, patients or their families request continuation of treatments that physicians believe are incapable of producing meaningful survival, based on the principle of autonomy. This tension between the rights of patients as autonomous beings and the obligation of physicians to honor the principles of beneficence and nonmaleficence may result in conflict between the parties. In this setting, the current ethical norm is that potentially inappropriate treatments should not be unilaterally withheld to circumvent patient or surrogate wishes when conflict exists with regard to the value of an intervention. Specifically, in the absence of predetermined, institutionally based criteria, individual physicians should not attempt to unilaterally withhold or withdraw life-sustaining therapies against the wishes of patients and surrogates on this basis. Instead, if a physiologic futility standard is to be used, it should be applied based on an explicitly defined institutional policy that is transparent, is inclusive of patients and their families, ensures effective communication, and incorporates an appeal process. Ultimately, conflict that is mediated by parties to achieve a mutually agreeable solution is preferable to invoking "futility."[24]

■ Communication and Professionalism

As noted previously, disagreements regarding the plans and goals of care arise at times between medical providers and patients or their surrogates. Frequently, disagreements are a consequence of a breakdown in communication or a loss of trust by the patient or the patient's surrogate for the medical team.

Recognizing the value of good communication and trust in the ICU serves to enhance the quality of care, promote the autonomy of the patient, and increase the likelihood of a patient-centered outcome. Rather than being assumed, trust should be viewed as something that must be earned from each patient and their family. Trust can be earned by providing compassionate care, communicating with patients and their families on a regular basis, encouraging dialogue, and listening empathically.

Good communication starts with a determination to uniquely understand each patient and to engage patients and families in a culturally sensitive and transparent manner. Information should be presented in a language, and at a level of detail, such that patients and their surrogates feel well informed. This is particularly important in light of studies that have found that a large proportion of patients and surrogates are unable to clearly express an understanding of medical facts, diagnoses, and prognosis after meeting with physicians[29] and that many surrogates are overly optimistic about their loved ones' predicted outcomes.[30] In addition, the proportion of time families are allowed to speak during family meetings correlates with the degree of their satisfaction with the care.[31] Despite these data, studies have shown that physicians typically do the majority of the talking and rarely initiate discussions about values and goals.[32,33]

The timing and manner of discussions with patients and families may vary, ranging from informal discussions on daily rounds to more formal family meetings to discuss changes in the goals of care. Efforts should be made to engage families initially at the time of admission, followed by a more formal discussion after 24 to 48 h to review events related to ICU care. This meeting should be less about goals of care or prognosis, and more about providing support for the family, while describing expectations for recovery and establishing benchmarks for recovery or decline. Following the meeting, short daily debriefings should occur to provide updates on the clinical status of the patient and the care being provided. If the patient declines clinically and it becomes clear that chances of recovery are limited, honest and open discussions should occur to provide truthful assessments of the patient's prognosis. Transparent communication enhances patient autonomy and allows families to make more informed decisions about the care of their loved one. This does not mean that all medically available options can, or even should, be discussed with each patient and family. The decision to offer specific treatments should be based on the medical judgment that the treatments in question are beneficial to the patient; they should be informed by a clear understanding of the patient's values and known wishes—what some have referred to as *authentic decisions*.[34]

Each family will vary in its comfort with the responsibilities of being surrogate decision-makers and the amount of information needed to make decisions.[35–37] While some families may prefer greater detail and more autonomy to make care decisions, others may lack the ability to process significant amounts of medical information, or they might prefer to take a lesser role in decision-making, deferring to the medical judgment of the physician. Evidence suggests that discordance in decision-making roles may substantially increase the incidence of anxiety and posttraumatic stress disorder (PTSD) among surrogates.[38] Consequently, identifying the category into which each family or members of families fit is essential for successful engagement and provision of adequate support.

Finally, the ICU and critical illness can be potentially overwhelming to patients and families.[39] The ICU experience can evoke powerful emotions, including fear, anger, frustration, guilt, and intense grief—emotions that are as important as physical symptoms and that need to be addressed by clinicians with empathy, patience, and understanding. At times, physicians may need to take time out from direct patient care to actively listen and allow patients and families to express their concerns and discuss the emotional burden of having a loved one in an ICU. These opportunities for empathic discussion provide for not only a catharsis for the patient or family but also a chance for the physician to obtain further insight into the patient's life, goals, and wishes, further enhancing trust. In addition, offering opportunities for family members to be involved in participating in the care of their loved one at high risk for dying in the ICU may reduce symptoms of posttraumatic stress disorder in family members.[40]

Discussing Goals of Care for the Dying Patient

Many patients fail to improve and will die in the ICU. As such, end-of-life discussions have a prominent role in the management of critically ill patients. One of the most difficult and important roles of the ICU physician is to engage in end-of-life discussions with patients and surrogates when it becomes evident the patient will not survive. Included in these discussions are efforts to reach consensus regarding the goals, and the subsequent plan, of care. Agreement is most likely to be reached when trust has been established through good communication. Although each circumstance is unique, basic communication skills and techniques can enhance the quality and success of these meetings.

Critical to the success of these discussions is advance preparation by the medical team, development of a clear understanding of the facts at hand, and establishment of a consensus regarding the best course of action before meeting with the family. Consideration of which team members should be present at the meeting is necessary to facilitate a patient-centered discussion and to reduce the likelihood of overwhelming the family. Ideally, the medical team members should not outnumber the family. At a minimum, the primary ICU physician and bedside nurse should be present. Other participants might include staff from pastoral care, social work, palliative care services, and, when appropriate, the patient's outpatient primary provider. Family members should be made aware of the purpose of the meeting in advance and should be offered the opportunity to meet at a time and place that allows for as many members as appropriate to participate. Determining the size or number of family members should be based on each unique case, but the meeting should incorporate essential members, including those directly involved in decision-making. Table 152-1 outlines recommendations for facilitating the goals of care meeting. While these recommendations are not proscriptive, they summarize the current published literature on the best practice for approaching these discussions.[19,34,41,42]

TABLE 152-1 A Recommended Approach for Facilitating the Goals of Care Meeting

- I. Preparation phase
  - (i) Notify family and friends of the time and location of the meeting
  - (ii) Hold a premeeting huddle
    - a) Confirm understanding of medical facts, prognosis, and direction of care and ensure team agreement about proposed changes to the goals and plan
    - b) Consider who should be present at the meeting and how to approach potential issues that may arise during conversation
  - (iii) Establish conditions for a productive conversation
    - a) Designate a quiet space for the meeting
    - b) Silence pagers and phones
    - c) Provide boxes of tissue
    - d) Disperse team members throughout the room
- II. Discussion phase
  - (i) Describe the purpose and goal of the meeting
  - (ii) Have everyone introduce themselves and state their relationship to the patient
  - (iii) Express appreciation for everyone's willingness to participate in the meeting
  - (iv) Determine and clarify the family's understanding of medical facts
  - (v) Provide additional information about anticipated prognosis and trajectory
  - (vi) Elicit fears, concerns, expectations, hopes, etc. from family and friends
  - (vii) Ask about the patient's life, values, and goals
- III. Negotiation phase
  - (i) Recommend treatments and options consistent with the patient's goals
  - (ii) Develop explicit consensus about the plan of care
  - (iii) Ensure all voices have been heard
- IV. Debriefing phase
  - (i) Summarize agreed upon plan of care
  - (ii) Describe next steps for patient care
  - (iii) Respond to unanswered questions
  - (iv) Attend to emotions
  - (v) Invite the family to share personal stories or experiences about the patient
  - (vi) If appropriate, invite prayer by a family member, their clergy, or a hospital chaplain
  - (vii) Acknowledge the difficulty of the conversation and decisions made
  - (viii) Assure ongoing care for the patient
  - (ix) Thank the family for their involvement

The goals of care meeting can be divided into four phases: preparation, discussion, negotiation, and debriefing. The preparation phase is a premeeting opportunity for the medical team to assemble and agree on what will be discussed, as described previously. The discussion phase is the early portion of the meeting, during which the medical team has an opportunity to describe current medical facts and prognosis, and the family has an opportunity to express fears, concerns, and expectations. The negotiation phase is an opportunity for the entire group to develop a mutually agreeable plan of care and to establish boundaries and limitations on care based on the patient's values, the family's individual hopes and wishes, and the medical realities of the patient's condition. Finally, the debriefing phase allows the medical team to provide emotional support to the family and to come together after the meeting to prepare to implement the agreed-upon plan of care.

Providing Palliative and End-of-life Care in the ICU

Palliative care is an essential component of good patient care in the ICU and has been strongly advocated as a core competency at an international level.[43] Good palliative care matches the care patients desire at end of life with that which they receive and can increase quality of life for patients prior to death. In addition, palliative care can enhance the perception of quality of death among family members and reduce instances of complicated bereavement, including caregiver depression, anxiety, and PTSD.[4] The vast majority of deaths in the ICU are preceded by a change in goals of care toward an approach that emphasizes comfort over cure. As such, a strong foundation and comfort with principles of hospice and palliative medicine is essential to the comprehensive care of critically ill patients. In addition, standardized policies are critical to ensuring effective and efficient relief of pain and suffering in the terminally ill.

The fundamental goal of palliative care is to restore or maintain quality of life and prevent needless physical or emotional suffering for patients and their loved ones. This includes not only administering analgesics and other medications to relieve symptoms of the dying process, but also providing other compassionate care. In fact, it is important to explicitly state that while palliative care encompasses limiting or discontinuing various life-sustaining interventions, it does not mean we are limiting "care" for our patients and their loved ones. In addition to symptom control, "care" also means providing general patient hygiene and attending to the spiritual, emotional, and psychological distress of the patient and the family of a dying patient. As an example of a simple, yet successful, intervention, use of empathic statements about the difficulty of making decisions to withhold or withdraw life-sustaining therapy and losing a loved one have been associated with increased ratings of family satisfaction and bereavement among surrogates.[44]

Once the decision is made to focus exclusively on care that promotes comfort, only treatments and interventions that achieve this goal should be employed. As appropriate, opiates and sedatives should be titrated to prevent pain, dyspnea, or anxiety before withdrawing life-sustaining therapies. When the patient is perceived to be comfortable by the medical staff and family, all life-sustaining interventions should be withdrawn or withheld so as to not prolong the dying process. While care should be tailored to the wishes and values of each family, some basic guidelines should be followed.

First, a clear explanation should be provided to the patient's loved ones before initiating comfort care interventions. Families should understand that comfort care will be provided throughout the dying process, and that time to death is variable. In addition, family should be offered the opportunity to be present at the time of death, understanding that for some, presence is associated with increased incidence of PTSD.[45] Second, withdrawal of all agreed-upon life-sustaining therapies should occur at one time, rather than in a sequential fashion, to minimize discomfort to the patient and disruption to the family. Third, any evidence of recurring pain, anxiety, or discomfort, as witnessed by a team member or family, should be aggressively treated. This includes any spiritual or existential suffering, which should be addressed with the support of palliative and pastoral care services. Fourth, when possible, in-room physiologic monitoring should be discontinued, as well as unnecessary medications, tests, devices, vascular access, and catheters. Finally, members of the medical team should be in close proximity and readily available to quickly address any issues that arise.

As a general rule, actively dying patients should not be transferred out of the ICU unless the bed is needed for a new critically ill patient. These patients often require high levels of nursing and physician support and typically die relatively quickly after life-sustaining therapies are withdrawn. In addition, leaving the patient in the ICU allows for continuity of care, which can be immensely helpful to grieving families. However, for patients whose needs for palliative care can be met by a less intense level of nursing and medical care, or for patients whose death may not be imminent, consideration should be given to transferring that patient to another room outside of the ICU, where there is more privacy and quiet during the dying process. Some hospitals have hospice units with specially trained nursing and medical staff and pleasant, private surroundings for patients and families. It is customary for hospital visiting hours to be suspended for dying patients.

CONFLICT RESOLUTION IN THE ICU

As a rule, good communication and sustaining of trust in the ICU significantly lessen the likelihood of conflict between healthcare staff and patients and their families. Unfortunately, conflict does arise at times. Although some disagreements may be based on ethical issues (e.g., autonomy vs. beneficence), in most instances conflict occurs due to breakdowns in communication, a loss of trust, or both. At these moments of conflict, it is important to recognize that individuals each have their own sets of values and beliefs that may inform their opinion about a plan of care. This applies not only to patients and their families, but also to medical staff as well. In addition, the ICU is a challenging environment. ICU staff are busy, patient conditions rapidly change, and families suffer from varying degrees of emotional distress. Recognizing and acknowledging these challenges is important in achieving resolution of conflict.

Conflict resolution begins with open communication among all parties. Usually, patient and honest negotiation between parties will result in resolution. In particular, attempting to understand the values and perspective of patients and their families can improve the communication process and diffuse difficult situations. However, at times further discussion may not resolve the dispute. At that point, a number of additional strategies may be considered.

Palliative Care Consultation

Palliative care services are an excellent resource for providing additional support in the end-of-life process. In addition to expertise in symptom control, palliative care teams can provide supportive counseling to patients and families, improve communication with the medical team, and aid in conflict resolution. Various studies of the effectiveness of palliative care consultation in the ICU suggest the potential for improved quality of death and dying, increased advance directive completion rates and hospice discharge rates, reductions in utilization of nonbeneficial life-sustaining therapies, and reductions in hospital and ICU length of stay.[46,47] In the absence of dedicated palliative care consultative services, social work and pastoral care (two common members of the palliative care multidisciplinary team) may be able to provide support.

Ethics Consultation and Bioethics Mediation

Another potential option for dealing with conflict resolution is the hospital ethics committee. Ethics consultants are excellent resources for clarifying ethical uncertainty when it arises. However, much of the conflict occurring in the ICU is not truly of an ethical nature. In this context, ethics consultation may not necessarily be helpful. In general, use of ethics consultation has produced similar outcomes as the palliative care interventions described earlier.[48]

When not employed appropriately, ethics consults may be viewed as arbitrary and biased in favor of the hospital and medical team. Rendering a decision runs the risk of not meeting the needs of the patient and family and increasing conflict. Given these reservations, it is imperative that hospital ethics committees have sufficient community representation and seek out the involved patients and their families directly to enable a complete understanding of their values, perceptions, and goals when conflict exists.

More recently, bioethics mediation has emerged as another potential approach for resolving conflicts in the ICU. Mediation has been practiced in legal and business settings for decades. Although new to health care, mediation offers an alternative means of handling disputes by focusing on a shared decision-making model, rather than the win–lose scenario of the healthcare team versus the patient and family.

Mediation operates under the premise that mutually agreeable solutions can be negotiated when conflict arises between multiple parties involved in the care of a patient. Unlike legal and business settings, healthcare mediation is nonbinding and, therefore, might be more akin to marriage counseling than true legal mediation. In this sense, it is perhaps better termed "facilitation." The goal of mediation is to create a neutral environment for all parties to come together and share perspectives and concerns. Although promising, bioethics mediation in the healthcare setting remains untested. Furthermore, there are few individuals currently trained in bioethics mediation to make its practice widely applicable at this time. There is, however, a growing sentiment that ICU clinicians should have some knowledge or training in principles of mediation to effectively negotiate conflict.[49,50]

■ Strategies When Conflicts Persist

Even with the previously noted resources, times will arise when the relationship between providers and patient or family is irrevocably damaged, and further communication and negotiation will not successfully resolve the conflict. In these settings, healthcare providers may find themselves providing care they believe to be ineffective or even harmful. This can have unfortunate consequences of burnout and cynicism, both of which can result in erosion of professionalism and poor quality of care for current and future patients.[51] If a provider feels strongly that he or she cannot, in good conscience, offer the care that the patient or family is requesting, the provider may transfer the care to another provider within the same institution or offer to transfer to another hospital. However, if another provider or hospital cannot be identified, it is vital that the medical staff support each other while continuing to provide good care to their patients. One effective approach that is being adopted in many ICUs to minimize emotional and moral distress is "death" or "grief" rounds, during which ICU staff come together to debrief and discuss difficult cases. Grief rounds allow staff to decompress and avoid burnout that could otherwise negatively impact job satisfaction and patient interaction.[52]

CONCLUSION

In today's critical care environment, death in the ICU is common and usually occurs after life-sustaining therapy is withheld or withdrawn. Many ethical considerations arise from the frequency and complexity of this process. Consequently, healthcare providers face challenging ethical dilemmas in weighing these considerations while providing care for their patients.

There is broad legal, ethical, societal, and professional support for limiting life-sustaining therapy at the end of life. As a general rule, the overriding principle is respect for patient autonomy. However, physicians must engage patients and their families to create a shared decision-making environment in which medical facts are matched by a desire to understand the values and wishes of patients with critical illness and terminal disease. Ultimately, effective communication enhances the quality of patient care and family satisfaction and is likely to result in patients getting the care they wish to receive.

Conflicts occur, although they can usually be resolved by good communication and honest, respectful engagement. In situations in which communication strategies fail, additional resources (e.g., palliative care, ethics committees, bioethics mediation) may prove helpful to resolve conflict. Only in very rare cases should providers find themselves in situations where they are morally distressed by the care they are required to provide. In these situations, the conflict can be resolved by transferring the patient to another provider or hospital and by supporting each other while continuing to provide high-quality critical care.

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APPENDIXES

Appendix A Terms and Symbols in Respiratory Physiology A-2

Appendix B Normal Values for a Healthy 20-Year Old Seated Man A-5

APPENDIX A

Terms and Symbols in Respiratory Physiology

GENERAL SYMBOLS

P	Partial pressure in blood or gas P_{O_2} = partial pressure of O_2
$\bar{X}$	A bar over the symbol indicates a mean value. $\bar{P}$ = mean pressure, as distinct from instantaneous pressure
$\dot{X}$	A time derivative (rate) is indicated by a dot above the symbol $\dot{V}_{O_2}$ = oxygen consumption per minute, mL $\dot{V}_{CO_2}$ = CO_2 production per minute, mL
% X	Percent sign preceding a symbol indicates percentage of the predicted normal value
X/Y%	Percent sign following a symbol indicates a ratio function with the ratio expressed as a percentage. Both components of the ratio must be designated FEV_1/FVC, % = 100 × FEV_1/FVC
XA, Xa	A small capital letter or a lower-case letter on the same line following a primary symbol is a qualifier to further define the primary symbol. Alternatively, subscript letters may be used XA = X_A, Xa = X_a Additional qualifiers of the primary symbol may be identified as shown PE_{O_2} = Pressure of CO_2 in the expired air, mm Hg

GAS PHASE SYMBOLS

Primary Symbols

V	Volume of gas
$\dot{V}$	Flow of gas
F	Fractional concentration of a gas

Qualifying Symbols

I	Inspired VI = inspired volume
E	Expired VE = expired volume $\dot{V}$E = expired volume per minute
A	Alveolar VA = alveolar volume $\dot{V}$ = alveolar ventilation per minute
T	Tidal VT = tidal volume
D	Dead space VD = volume of dead space $\dot{V}$D = dead-space ventilation per minute
B	Barometric PB = barometric pressure
STPD	Standard conditions: temperature 0°C, pressure 760 mm Hg, and dry (0 mm Hg water vapor)
BTPS	Body conditions: body temperature and ambient pressure, saturated with water vapor at these conditions
ATPD	Ambient temperature and pressure, dry
ATPS	Ambient temperature and pressure, saturated with water vapor at these conditions
an	Anatomic
p	Physiological
f	Respiratory frequency, per minute
max	Maximum
t	Time

BLOOD PHASE SYMBOLS

Primary Symbols

Q	Volume of blood
$\dot{Q}$	Blood flow $\dot{Q}$ = cardiac output, L/min
C	Concentration in the blood phase C_{O_2} = concentration of oxygen in blood, mL of O_2 per 100 mL of blood
S	Saturation in the blood phase S_{O_2} = Saturation of hemoglobin with O_2, percent

Qualifying Symbols

a	Arterial Ca_{O_2} = concentration of O_2 in arterial blood, mL of O_2 per 100 mL of blood
c	Capillary Cc_{O_2} = concentration of O_2 in capillary blood, mL of O_2 per 100 mL of blood
C′	Pulmonary end-capillary Pc'_{O_2} = partial pressure of O_2 in end-capillary blood, mm Hg
v	Venous Cv_{O_2} = concentration of O_2 in venous blood, mL of O_2 per 100 mL of blood
$\bar{v}$	Mixed venous $C\bar{v}_{O_2}$ = concentration of O_2 in mixed venous blood, mL of O_2 per 100 mL of blood

VENTILATION AND LUNG MECHANICS TESTS AND SYMBOLS

Static Lung Volumes*

RV	Residual volume. Volume of air remaining in the lungs after maximum expiration.
CV	Closing volume. Volume of air expired from the onset of airways closure to residual volume. May be expressed as a fraction of VC: CV/VC,%.
ERV	Expiratory reserve volume. Maximum volume of air expired from the resting end-expiratory level.
V_T	Tidal volume. Volume of air inspired or expired with each breath during quiet breathing. When tidal volume is used in gas-exchange formulations, this symbol is used.
IRV	Inspiratory reserve volume. Maximum volume of air inspired from the end-tidal inspiratory level.

Lung Capacities**

IC	Inspiratory capacity. The sum of IRV and TV.
IVC	Inspiratory vital capacity. Maximum volume of air inspired from the point of maximum expiration, i.e., from RV.
VC	Vital capacity. Maximum volume of air expired from the point of maximum inspiration, i.e., from TLC.
FRC	Functional residual capacity. Sum of RV and ERV. FRC is the volume of air remaining in the lungs at the resting end-expiratory position.
TLC	Total lung capacity. Volume of air in the lungs after maximum inspiration. Also, the sum of all volume compartments of the lungs.
RV/TLC,%	Residual volume to total lung capacity ratio, expressed as a percentage.
CC	Closing capacity. Closing volume plus residual volume, may be expressed as a percentage of TLC: CC/TLC, %.

Forced Respiratory Maneuvers During Spirometry†

FVC	Forced vital capacity. The maximum volume of air forcibly expired from total lung capacity
FIVC	Forced inspiratory vital capacity. Maximum volume of air forcibly inspired starting from residual volume.
FEV*t*	Timed forced expiratory volume. Volume of air expired in a specified time in the course of the forced vital capacity maneuver. FEV_1 = volume of air expired during the first second of the FVC.
FEV*t*/FVC,%	Ratio of timed forced expiratory volume to forced vital capacity, expressed in percentage.
FEF*x*	Forced expiratory flow, related to some portion of the FVC curve. Modifiers refer to the amount of the FVC that has been expired at the time of measurement.
$FEF_{200-1200}$	Forced expiratory flow between 200 and 1200 mL of the FVC (formerly called the maximum expiratory flow rate).
FEF_{25-75}	Forced expiratory flow during middle half of the FVC (formerly called the maximum midexpiratory flow rate or MMEF)
PEF	Peak expiratory flow. Highest value for expiratory flow.
$\dot{V}_{max_x}$	Maximum flow when *x* percent of the FVC has been expired. $\dot{V}_{max\,75}$ = flow (instantaneous) when 75% of the FVC has been expired.
FIF*x*	Forced inspiratory flow. As in the case of the FEF, appropriate modifiers designate the volume at which flow is being measured. Unless otherwise specified, the volume qualifiers indicate the volume inspired from RV at the point of measurement. FIF_{25-75} = forced inspiratory flow during the middle half of the FIVC.
MVV	Maximum voluntary ventilation. Volume of air exhaled during maximum breathing efforts within a specified time period. Formerly called the maximum breathing capacity (MBC) MVV_{60} = MVV at a breathing frequency of 60 per minute.
PImax	Maximum inspiratory pressure. The maximum pressure generated during a maximal inspiratory effort made at RV.
PEmax	Maximum expiratory pressure. The maximum pressure generated during a maximal expiratory effort made at TLC.

Measurements Related to Ventilation

$\dot{V}_E$	Expired volume per minute (BTPS)
$\dot{V}_I$	Inspired volume per minute (BTPS)
$\dot{V}_{CO_2}$	Carbon dioxide production per minute (STPD)
$\dot{V}_{O_2}$	Oxygen consumption per minute (STPD)
R	Respiratory exchange ratio, the ratio of CO_2 output to O_2 intake in the lungs
$\dot{V}_A$	Alveolar ventilation per minute (BTPS)
$\dot{V}_D$	Ventilation per minute of the physiological dead space (BTPS) defined by the equation $\dot{V} = \dot{V}_E \dfrac{Pa_{CO_2} - P_{A_{CO_2}}}{Pa_{CO_2} - P_{I_{CO_2}}}$
V_D	Volume of the physiological dead space, calculated as $\dot{V}_D/f$.
V_D/V_T	Ratio of dead space to tidal volume. The fraction, usually expressed as a percentage, of each breath that does not contribute to CO_2 elimination.

Mechanics of Breathing*

Pressure Terms

Paw	Pressure at any point along the airways
Pao	Pressure at the airway opening
Ppl	Pleural pressure
P_A	Alveolar pressure

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*Expressed as BTPS.

**Combinations of volumes for practical purposes.

†All values at BTPS.

*All pressures expressed relative to ambient pressure unless otherwise specified.

Pbs	Pressure at the body surface
Pes	Esophageal pressure: used to estimate Ppl
PA–Pbs	Transthoracic pressure
PA–Ppl	Transpulmonary pressure
Ppl–Pbs	Pressure difference across the chest wall
Paw–Ppl	Transbronchial pressure, estimated as difference between airway and pleural pressures.

Flow–Pressure Relationships[†]

R	General symbol for frictional resistance, defined as the ratio of pressure difference to flow.
Raw	Airway resistance, calculated from pressure difference between airway opening (Pa_o) and alveoli (Pa) divided by the airflow, cm H_2O/L/s.
Rl	Total pulmonary resistance, measured by relating flow-dependent transpulmonary pressure to airflow at the mouth.
Rti	Tissue resistance (viscous resistance of lung tissue), calculated as difference between Rl and Raw.
Rus	Resistance of the airways on the upstream (alveolar) side of the point in the airways where intraluminal pressure equals Ppl, i.e., equal pressure point. Measured during a forced expiration.
Rds	Resistance of the airways on the downstream (mouth) side of the point in the airways where intraluminal pressure equals Ppl, i.e., equal pressure point. Measured during a forced expiration.
Gaw	Airway conductance, reciprocal of Raw.
Gaw/Vl	Specific conductance, airway conductance, expressed per liter of lung volume at which Gaw is measured.

Volume–Pressure Relationships

C	General symbol for compliance of the lungs, chest wall, or total respiratory system. Volume change per unit change in applied pressure. For the lungs, the applied pressure is the pressure difference across the lungs, or transpulmonary pressure, Pao–Ppl; for the chest wall, the applied pressure is the transthoracic pressure, Ppl–Pbs; for the entire respiratory system, the applied pressure is Pao–Pbs.
Cl	Lung compliance. Value for the volume change divided by the transpulmonary pressure.
Cw	Chest wall compliance. Value for the volume change divided by the transthoracic pressure.
Cdyn	Dynamic compliance. Value for compliance determined at time of zero gas flow at the mouth during uninterrupted breathing. The respiratory frequency appears as a qualifier. $Cdyn_{40}$ = dynamic compliance at a respiratory frequency of 40 per minute.
Cst	Static compliance, value for compliance determined on the basis of measurements made during a period of zero airflow.
C/Vl	Specific compliance. Compliance divided by the lung volume at which it is determined, usually FRC.

Pst	Static pulmonary pressure at a specified lung volume. PST_{TLC} = static recoil pressure of the lung measured at TLC (maximum recoil pressure)

Diffusing Capacity Tests And Symbols

DL*x*	Diffusing capacity of the lung expressed as volume (STPD) of gas (*x*) uptake per minute per unit alveolar-capillary pressure difference for the gas used. A modifier can be used to designate the technique: DL_{CO}/SB = Single-breath CO diffusing capacity DL_{CO}/SS = Steady-state CO diffusing capacity
DM	Diffusing capacity of the alveolar-capillary membrane (STPD).
θ	Reaction rate coefficient for red blood cells. Determined as the volume of gas (STPD) that will combine per minute with 1 unit volume of blood per unit of gas tension. If the specific gas is not stated, θ is assumed to refer to CO and is a function of existing O_2 tension.
VC	Pulmonary capillary blood volume. This should be QC for consistency with other symbols, but VC is entrenched in the literature. In the equation that follows for 1/DL, VC represents the effective pulmonary capillary blood volume, i.e., capillary blood volume in intimate association with alveolar gas.
1/DL	Total resistance to diffusion, including resistance to diffusion of test gas across the alveolar-capillary membrane, through plasma in the capillary, and across the red blood cell membrane (1/Dm), with the resistance to diffusion within the red blood cell arising from the chemical reaction of the test gas and hemoglobin (1/θVC), according to the formulation $\frac{1}{DL} = \frac{1}{DM} + \frac{1}{\theta VC}$
DL/VA	Diffusing capacity per unit of alveolar volume. DL is expressed STPD, and VA is expressed in liters, BTPS.

BLOOD GAS SYMBOLS

Symbols for these values are readily composed by combining general symbols. Some examples include the following:

Pa_{CO_2}	Arterial CO_2 tension, mm Hg
Sa_{O_2}	Arterial O_2 saturation, percent
CcO_2	Oxygen content of pulmonary end-capillary blood, mL of O_2 per 100 mL of blood
$(A\text{-}a)Po_2$	Alveolar–arterial difference in the partial pressure of O_2, mm Hg
$Ca_{O_2} - C\bar{v}_{O_2}$	O_2 content difference between arterial and mixed venous blood (arteriovenous O_2 difference), mL of O_2 per 100 mL of blood

PULMONARY SHUNT SYMBOLS

$\dot{Q}s$	Flow of blood via shunts. This is usually determined as percent of cardiac output ($\dot{Q}$) while breathing 100% O_2, according to the equation $\frac{\dot{Q}s}{\dot{Q}} = \frac{CcO_2 - Ca_{O_2}}{Ca_{O_2} - C\bar{v}_{O_2}} \times 100$ Where CcO_2 = O_2 content of end-capillary blood CaO_2 = O_2 content of arterial blood $C\bar{v}_{O_2}$ = O_2 content of mixed venous blood

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[†] Unless otherwise specified, resistance measurements are assumed to be made at FRC.

APPENDIX B

Normal Values for a Healthy 20-Year Old Seated Man

Ventilation (BTPS)

Tidal volume (V_T), L	0.6
Frequency (f), breaths/min	12
Minute ventilation (V_E), L/min	7.2
Respiratory dead space (V_D), mL	150
Alveolar ventilation, V_A, L/min	5.4

Lung Volumes and Capacities (BTPS)

Inspiratory capacity (IC), L	3.0
Expiratory reserve volume (ERV), L	1.9
Vital capacity (VC), L	4.9
Residual volume (RV), L	1.4
Functional residual capacity (FRC), L	3.2
Total lung capacity (TLC), L	6.3
Residual volume/total lung capacity × 100 (RV/TLC), %	22

Mechanics of Breathing

Forced vital capacity (FVC), L	4.9
Forced expiratory volume, first second (FEV_1), L	4.0
Maximum voluntary ventilation (MVV), L/min	170
Forced expiratory volume in 1 s/forced vital capacity × 100 (FEV_1/FVC), %	83
Forced expiratory volume in 3 s/forced vital capacity × 100 (FEV_3/FVC), %	97
Forced expiratory flow during middle half of FVC (FEF_{25-75}), L/s	4.7
Forced inspiratory flow at the middle of forced inspiratory capacity (FIF_{50}), L/s	5.0
Static compliance of the lungs (Cst, l), L/cm H_2O	0.2
Compliance of lungs and thoracic cage (CRS, respiratory system compliance) L/cm H_2O	0.1
Airway resistance at FRC (Raw), cm H_2O/L/s	1.5
Pulmonary resistance at FRC, cm H_2O/L/s	2.0
Airway conductance at FRC (G_{aw}), L/s/cm H_2O	0.66
Specific conductance (G_{aw}/V_1)	0.22
Maximum inspiratory pressure, mm Hg	– 75
Maximum expiratory pressure, mm Hg	120

Distribution of Inspired Gas

Single-breath N_2 test (ΔN_2 from 750 to 1250 mL in expired gas), % N_2	<1.5
Alveolar N_2 after 7 min of breathing O_2, % N_2	<2.5
Closing volume (CV), mL	400
CV/VC × 100, %	8
Closing capacity (CC), mL	1900
CC/TLC × 100,%	30
Slope of phase III in single-breath N_2 test, % N_2/L	<2

Gas Exchange

O_2 consumption at rest (STPD), mL/min	240
CO_2 output at rest (STPD), mL/min	192
Respiratory exchange ratio (R), CO_2 output/O_2 uptake	0.8
ALVEOLAR GAS	
PA_{O_2}, mm Hg	105
PA_{CO_2}, mm Hg	40
ARTERIAL BLOOD	
Pa_{O_2}, mm Hg	95
Sa_{O_2}, %	98
pH	7.40
Pa_{CO_2}, mm Hg	40
Pa_{O_2}, while breathing 100% O_2, mm Hg	640

Alveolar Ventilation and Gas Exchange

Alveolar ventilation, L/min	4.2
Physiological dead space/tidal volume × 100 (V_D/V_T), %	<30
Alveolar–arterial oxygen-gradient, (A-a) P_{O_2}, mm Hg	10

Diffusing Capacity

Diffusing capacity at rest for CO, single-breath ($D_{L_{COsb}}$), mL CO/min/mm Hg	29
Diffusing capacity per unit alveolar volume (D_L/V_A)	4.8

Control of Ventilation

Ventilatory response to hypercapnia, L/min/per ΔPa_{CO_2} mm Hg	>1.5

Pulmonary Hemodynamics

Pulmonary blood flow (cardiac output), L/min	5.4
Pulmonary artery systolic/diastolic pressure, mm Hg	25/8
Pulmonary capillary blood volume, mL	100
Pulmonary “capillary” (wedge) blood pressure, mm Hg	<10

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